related to histamine and two 4-(2-aryloxyethyl)-imidazoles have been prepared from 4-(2-chloroethyl)-imidazole hydrochloride. A few of these substances resembled histamine in their pharmacodynamic actions but all were less active. Weak antihistaminic activity was shown by 4-(2-dibenzylaminoethyl)-imidazole.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, GENERAL MILLS, INC.]

Polyglycerols. III.[1] Synthesis of Triglycerol[2]

BY J. ROBERT ROACH AND HAROLD WITTCOFF

The synthesis of a crystalline isomer of linear triglycerol[3] is described in this paper.

Probably the first reference to triglycerol was made by Lourenco[4] who reported it as a distillable reaction product from the interaction of glycerol and gaseous hydrogen chloride. Levene and Walti[5] hydrolyzed the reaction products resulting from the action of potassium acetate on epichlorohydrin to obtain several distillable products including a small quantity of triglycerol (b. p. 200–205° (0.1 mm.)). The same boiling range was reported by Istin[6] who distilled triglycerol directly from a polyglycerol mixture. Isolation of crude triglycerol from a polyglycerol mixture by distillation of the acetates[7,8] and the allyl ethers[3] has also been reported. In none of this work has the crystalline pentahydric triglycerol been isolated.

The present synthesis involves the hydroxylation of O-α,α'-diallylglycerol[9] by action of either performic acid or potassium permanganate. The requisite diallylglycerol was prepared by the interaction of allyl alcohol and glycerol-α,α'-dichlorohydrin in the presence of sodium hydroxide. The homogeneity of this product, on which depends the linear structure of the triglycerol, follows from the oft-recorded observation that chlorohydrins such as glycerol dichlorohydrin are dehydrohalogenated in strong basic medium to epoxides. These, in turn, react with alcohols to yield ethers in which the ether linkage is primary.[10] Furthermore, it was not possible by careful fractional distillation to detect the presence of any isomeric substance.

Since the triglycerol could not be readily distilled from the reaction mixtures in which it was formed, acetonation was employed. On treatment of the crude mixtures with acidic acetone, there resulted a mixture of isopropylidenetriglycerol and diisopropylidenetriglycerol which on hydrolysis yielded the pure triglycerol.

Separation of isopropylidenetriglycerol and diisopropylidenetriglycerol was difficult. By careful fractional distillation, however, samples which analyzed properly were obtained.

The triglycerol obtained by hydrolysis of the isopropylidene derivatives was probably a sirupy mixture of stereoisomers. Crystallization from anhydrous *n*-butanol of the product resulting from performic acid hydroxylation yielded 25–33% of a crystalline isomer of melting point 98–99°. The sirup from the mother liquor could not be induced to crystallize. For linear triglycerol there are theoretically possible a *dl*-mixture and two *meso*-forms. The presence of isomers was perhaps indicated by the fact that the sirupy triglycerol from the performic acid hydroxylation demonstrated proper elementary analyses. That permanganate hydroxylation provided a different ratio of isomers was inferred from the observation that the sirupy triglycerol yielded, on crystallization, 50% of crystalline isomer of identical melting point.

The solid triglycerol was converted to the penta-(*p*-nitrobenzoate) derivative. Attempts to prepare similar derivatives of the sirupy isomers from which the crystalline triglycerol had been removed led only to uncrystallizable oils.

Experimental

O-α,α'-Diallylglycerol.—Allyl alcohol (1161 g., 20 moles) was added, with stirring, to 50% aqueous sodium hydroxide (880 g., 11 moles) whereupon the temperature rose spontaneously to 52°. Glycerol dichlorohydrin (644.8 g., 5 moles) was added dropwise over a period of three and one-fourth hours, while the temperature was maintained at 70–80° by the exothermic reaction. After completion of the addition, stirring was continued at 70–80° for one and one-fourth hours, whereupon the excess allyl alcohol was removed by distillation *in vacuo*. The product was washed successively with water, dilute acetic acid, and again with water until the washings were neutral. All of the aqueous solutions were combined and extracted with ether, after which the ether solution was washed with water and was combined with the product. The mixture was dried (sodium sulfate) and after removal of the ether, the product was distilled through a 15-inch Vigreux column. No forerun was obtained. The material of constant refractive index ($n^{25}\text{D}$ 1.4520, d^{25}_{4} 0.9810) distilled at 112–113° (14 mm.) and weighed 524.4 g. (60.8%). Redistillation at high reflux ratio through a 12-inch column packed with stainless steel helices gave a series of

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[1] Paper II, THIS JOURNAL, 71, 2666 (1949).

[2] Paper No. 100, Journal Series, Research Laboratories, General Mills, Inc.

[3] For a discussion of nomenclature *cf.* H. Wittcoff, J. R. Roach and S. E. Miller, THIS JOURNAL, 69, 2655 (1947), footnote 2.

[4] A. V. Lourenço, *Ann. chim. phys.*, [3] 67, 257 (1863).

[5] P. A. Levene and A. Walti, *J. Biol. Chem.*, 77, 685 (1928).

[6] M. Istin, *Ann. faculté sci. Marseille*, 13, 5 (1940); *C. A.*, 41, 2392 (1947).

[7] M. Rangier, *Compt. rend.*, 187, 345 (1928); *C. A.*, 22, 4468 (1928).

[8] H. J. Wright and R. N. DuPuis, THIS JOURNAL, 68, 446 (1946).

[9] N. Kishner, *J. Russ. Phys.-Chem. Soc.*, [1] 31 (1892); Beilstein, "Handbuch der organische Chemie," 4th ed., J. Springer, Berlin, 1918, Vol. I, p. 513.

[10] A. Fairbourne, G. P. Gibson and D. W. Stephens, *J. Chem. Soc.*, 1965 (1932).

fractions, all of which boiled at 68–69° (0.9–1.0 mm.) and 93% of which possessed a $n^{25}\mathrm{D}$ of 1.4510.

Anal. Calcd. for $C_9H_{16}O_3$: I_2 number, 294.8; hydroxyl %, 9.87. Found: I_2 number, 293.9; hydroxyl %, 9.7.

In addition of the diallylglycerol there was obtained an unidentified higher boiling product (93 g.) which distilled at approximately 135° (0.6 mm.).

Isopropylidenetriglycerol and Diisopropylidenetriglycerol from the Oxidation of O-α,α'-Diallylglycerol with Performic Acid.—A mixture of O-α,α'-diallylglycerol (172 g., 1 mole), formic acid (87%, 700 cc.) and hydrogen peroxide (28%, 229 g., 2 moles) was stirred mechanically (safety glass shield). The temperature rose to 40° in twenty minutes and was maintained there first by external cooling and then by heating for a total time of five hours. The mixture was allowed to stand overnight whereupon titration of a test sample indicated the presence of about 0.5 g. of hydrogen peroxide. This was destroyed with sodium bisulfite (20 g.) and the mixture was evaporated *in vacuo* to a thick sirup. A methanol solution of the sirup was filtered and evaporated, and the sirup was dissolved in absolute ethanol (300 cc.). The solution was made slightly alkaline with alcoholic sodium hydroxide and the ethyl alcohol and ethyl formate were removed by slow distillation. The residue was dissolved in methanol (200 cc.) which contained sodium hydroxide (15 g.), and the solution was heated on the steam-bath for one hour to saponify any formate groups not removed by the alcoholysis. The mixture was made slightly acid with concentrated hydrochloric acid, after which it was concentrated. Most of the sodium chloride was removed by dissolving the residue in methanol, filtering and removing the solvent under reduced pressure. This sequence of operations was carried out twice. Thereupon the residue was dissolved in absolute ethanol (200 cc.) and the solution was allowed to stand twelve hours over sodium sulfate. Concentration of the ethanol solution yielded a theoretical quantity (240 g.) of sirup.

The hydroxylation product (240 g.) together with a solution of hydrogen chloride (9.0 g.) in acetone (1500 cc.) was stirred overnight with anhydrous sodium sulfate (90 g.). After the reaction mixture was made slightly basic with alcoholic sodium hydroxide, it was filtered and concentrated. The acetonated product (113 g.) was obtained in low yield, indicating that much of the original product had not been acetonated. Accordingly, the sodium sulfate was extracted well with methanol, and from the alcohol solution there was obtained 90 g. of sirup. This was subjected to acetonation as above (500 cc. of acetone, 9 g. of hydrogen chloride, 100 g. of sodium sulfate) to obtain more product (98 g.). The total yield of acetonated derivative was thus 211 g. (approximately 70% overall yield). This was a mixture of isopropylidene- and diisopropylidenetriglycerol. For purposes of preparing triglycerol, the distilled product was hydrolyzed directly according to the procedure indicated below.

In order to separate the isopropylidene derivatives, 70 g. of the mixture was distilled through a short column, and the course of the distillation was followed by refractive index measurements.

Sixty-three grams of distillate was obtained in two fractions. The second fraction will be discussed below. The first fraction (47 g.) distilled at 146–196° (0.3 mm.) (major portion 150–165° (0.3 mm.)). As already indicated, it was difficult to separate pure diisopropylidenetriglycerol from small amounts of isopropylidenetriglycerol by fractional distillation.

In one experiment a material which analyzed properly was obtained by distilling the diisopropylidene fraction several times, at high reflux ratio, through a 12-inch, monel metal helices-packed column. The product distilled at 157–158° (0.6 mm.) and had a $n^{25}\mathrm{D}$ of 1.4530.

Anal.[11] Calcd. for $C_{15}H_{28}O_7$: C, 56.24; H, 8.75. Found: C, 55.9, 55.9; H, 8.7, 9.0.

The second fraction (16 g.) referred to above, distilling at 196–240° (0.3 mm.), was fractionally distilled to yield isopropylidenetriglycerol of boiling point 172–175° (0.25 mm.) and $n^{25}\mathrm{D}$ of 1.4691.

Anal. Calcd. for $C_{12}H_{24}O_7$: C, 51.41; H, 8.63. Found: C, 51.6, 51.4; H, 8.6, 8.9.

Sirupy Triglycerols from Isopropylidene- and Diisopropylidenetriglycerol.—The first fraction of the preceding experiment (30 g.) was dissolved in water (30 cc.) and concentrated hydrochloric acid (3 cc.). The solution was heated on the steam-bath for one-half hour. During this time acetone (12 cc. of the theoretical 13.5 cc.) distilled. The solution was then concentrated *in vacuo* to obtain a theoretical quantity (22.5 g.) of sirup. This was distilled to yield sirupy triglycerol (20 g.) which collected over a range of 190–230° (0.1 mm.), although most of the product distilled at 215–220° (0.1 mm.). The product had a $n^{25}\mathrm{D}$ of 1.4902. This value varies with the ratio of isomers obtained by the different preparative procedures used, as shown by subsequent data.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.7, 8.7.

Crystalline Triglycerol from the Performic Acid Hydroxylation.—The sirupy triglycerol described above (8 g.) was dissolved in warm anhydrous *n*-butanol (8 cc.). After several days of refrigeration there resulted 2 g. of crystalline triglycerol which, after three crystallizations from butanol, melted at 98–99°. Accordingly, from this and other experiments it appears that 25–33% of the crystalline isomer is present in the triglycerol which results from the hydroxylation of O-α,α'-diallylglycerol with performic acid.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.1, 8.3.

The sirup remaining in the mother liquor, when distilled at about 225° (0.3 mm.), yielded fractions varying in $n^{25}\mathrm{D}$ from 1.4758 to 1.4870. These values are considerably lower than the value of 1.4902 demonstrated by the original mixture from which the crystalline triglycerol was removed. None of these fractions could be crystallized, nor could they be converted to crystalline *p*-nitrobenzoates.

In an attempt to gain further insight into the composition of the unfractionated sirupy triglycerol, a quantity of it was separated by distillation at 206–275° (1 mm.) into 4 fractions. The first, second and fourth fractions weighed 4.0 g. each and had $n^{25}\mathrm{D}$ of 1.4855, 1.4899 and 1.4935, respectively. The third fraction weighed 21.5 g. and had a $n^{25}\mathrm{D}$ of 1.4920. The last two fractions crystallized readily to yield a total of 13 g. of crystalline product. The first two fractions and the sirupy portions of the last two could be induced neither to crystallize nor to yield solid *p*-nitrobenzoates. The crystalline triglycerol, on the other hand, could be converted to a solid *p*-nitrobenzoate. These data show that it is possible to obtain partial separation of the diastereoisomers of triglycerol by fractional distillation.

Penta-(*p*-nitrobenzoate) of the Crystalline Isomer of Triglycerol.—This derivative could be prepared either from crystalline triglycerol or from the unfractionated sirupy mixture of triglycerols. The melting point of the product was 134–134.5° regardless of its source, although the yield from the sirupy mixture was considerably lower and the product was purified with greater difficulty, as would be expected. Mixed melting points of the samples of *p*-nitrobenzoate derivative prepared from sirupy or crystalline triglycerol demonstrated no depression.

The unfractionated sirupy triglycerol was converted to the *p*-nitrobenzoate derivative by the conventional procedure employing anhydrous pyridine. The amorphous solid obtained by precipitation from water was crystallized from acetone to obtain the impure derivative melting at 95–102°. The product was crystallized once more from acetone, three times from mixtures of acetone and absolute ethanol (1:1) and twice from ethyl acetate. The resulting white needles melted sharply at 134–134.5°.

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(11) The authors are indebted to Mr. James Kerns for micro carbon and hydrogen analyses.

Anal. Calcd. for $C_{44}H_{35}O_{22}N_6$: C, 53.60; H, 3.57; N, 7.10. Found: C, 53.6, 53.7; H, 3.6, 3.6; N, 7.4, 7.5.

Triglycerol from the Oxidation of O-α,α′-Diallylglycerol with Potassium Permanganate.—To a mixture of O-α,α′-diallylglycerol (86.0 g., 0.5 mole) and water (600 cc.) cooled to 3° was added, with stirring, a solution of potassium permanganate (160 g., 1.01 mole) in water (3200 cc.) over a period of five hours. The temperature was kept at 3–5°. At the end of the addition the mixture was allowed to stand at room temperature for one and one-half hours, during which time the reaction temperature rose to 10°. The mixture was subsequently warmed to 25° and allowed to stand one hour longer after which the manganese dioxide was removed and the filtrate and washings were neutralized with concentrated hydrochloric acid (21.8 cc.). The aqueous solution was evaporated *in vacuo* to dryness and the residue was extracted with methanol. Removal of the methanol yielded a viscous sirup which was dissolved in ethyl alcohol. Benzene was added and the solvents were distilled in an attempt to remove the last trace of water azeotropically. A solution of the resulting sirup in absolute methanol was dried over anhydrous sodium sulfate. Filtration and removal of the methanol from the filtrate yielded 126.1 g. of a viscous water-white sirup (theoretical yield 121.1 g.). Undoubtedly impurities such as higher oxidation products were present as evidenced by the yield of isopropylidene derivatives.

The crude triglycerol (90 g.) was acetonated according to the procedure described above (750 cc. of acetone, 7.5 g. of anhydrous hydrogen chloride, 100 g. of anhydrous sodium sulfate). There resulted 75 g. (65.6% over-all yield based on diallylglycerol) of crude material which on distillation yielded 54 g. (approximately 47.2%) of a mixture of isopropylidene- and diisopropylidenetriglycerols. The mixture of isopropylidene derivatives was separated by fractional distillation into one fraction which was chiefly diisopropylidenetriglycerol (b. p. 162° (2 mm.)) and a higher boiling fraction (distillation range 190–220° (4–9 mm.)) which was primarily isopropylidenetriglycerol.

The first fraction (29 g.) was hydrolyzed to triglycerol as described above, yielding a viscous liquid (21.7 g., 100%) which on distillation gave 16.2 g. of sirupy triglycerol having a $n^{25}D$ of 1.4931. This value was higher than that shown by the sirupy triglycerol from the performic acid hydroxylation, probably because the proportion of isomers present was different, as shown by the following crystallization studies. The isolation of the crystalline isomer was effected as detailed above. Approximately 50% of the triglycerol prepared by this procedure was isolated as crystalline material as compared to 25–33% isolated from the sirupy triglycerol mixture resulting from the performic acid hydroxylation. The crystalline triglycerol prepared by the two methods had identical melting points (98–99°) which were not depressed on admixture. In this preparation, as in the previous one, the sirupy residue isolated from the mother liquor ($n^{25}D$ 1.4800) could not be induced to crystallize, nor could it be converted to a crystalline derivative.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.1, 8.2.

Summary

1. Triglycerol has been synthesized by the hydroxylation of O-α,α′-diallylglycerol by the action of performic acid and by the action of permanganate.

2. Crystalline triglycerol of melting point 98–99° has been isolated and identified.

3. Triglycerol was isolated from the reaction mixtures by conversion to its isopropylidene derivatives and subsequent distillation.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. I. The Synthesis of 6-Cyclohexyl-Δ^{1-9}-octalone-2 by the Robinson–Mannich Base Method

BY CLIFFORD H. SHUNK[1,2] AND A. L. WILDS

For some time we have been interested in the synthesis of certain analogs of the steroid hormones progesterone, desoxycorticosterone and testosterone lacking ring C. The first stage in this work, started in 1941 and interrupted during the war, has been to apply the Robinson–Mannich base synthesis[3] of cyclic α,β-unsaturated ketones to 4-cyclohexylcyclohexanone (I), obtaining 6-cyclohexyl-Δ^{1-9}-octalone-2 (VIII). Since we were interested in extending the reactions to less readily available derivatives of the ketone I, we have looked in some detail into several methods of applying this synthesis.

The best yields in the Robinson–Mannich base synthesis have been obtained with ketones having the adjacent methylene group activated, and accordingly we first investigated the carbomethoxy derivative III, as in our previous work in the chrysene series.[4] This was prepared from the ketone I *via* the glyoxylate II, although in poor yield (*ca.* 12%) primarily because of the decarbonylation step. The next reaction with the methiodide of 1-diethylaminobutanone-3 proceeded in good yield to the diketo ester IV, and the latter could be cyclized to 6-cyclohexyl-Δ^{1-9} octalone-2 (VIII) in fair yield (48%) with aqueous alkali or acid. With sodium methoxide the carbomethoxy group was retained giving IX.

Because of the poor over-all yields by this method, and particularly in the decarbonylation of the glyoxylate II, the latter derivative itself was used for condensation with the Mannich base methiodide. However, cyclization of the resulting product gave the octalone VIII in less than 20% yield.

It seemed attractive to try the hydroxymethyl-

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(3) *Cf.* du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and subsequent papers.

(4) Wilds and Shunk, THIS JOURNAL, **65**, 469 (1943).