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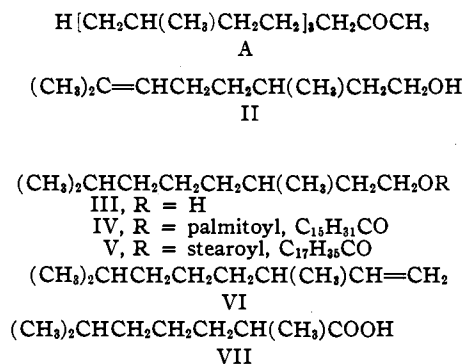
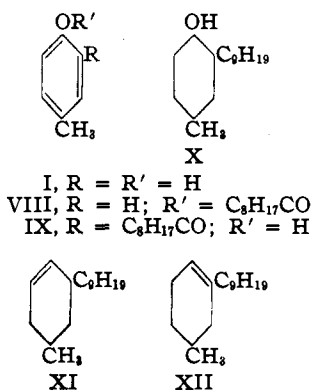
Vitamin E. XLII. Long Chain Aliphatic Compounds with Recurring "Isoprene" Units¹

BY LEE IRVIN SMITH AND GEORGE F. ROUAULT²

The synthesis in quantity of long chain compounds, particularly those carrying substituents on the chain, is a matter of considerable difficulty. The number of steps is usually large, and only too often some one or two steps in the synthesis give very poor yields so that, from the point of view of quantity production of these complicated compounds, most of the known syntheses are not very satisfactory. In a previous paper,¹ a synthesis of "phytol ketone" (A) from citral has been reported; each step in this synthesis proceeds well and the over-all yields of the ketone are quite acceptable. This paper reports another such synthesis, involving a different route and different intermediates.

It was obvious, of course, that in any synthesis of A, the chances of success would be just so much better the larger the fragments which were to be combined in order to produce A. *p*-Cresol (I), containing seven carbon atoms, appeared to be a promising substance for use as one of the building stones, for it contains a methyl group at-

tached to the ring, and it is a perfectly symmetrical substance with orienting groups that would direct any entering substituent into a position ortho to the hydroxyl group. The general sequence from *p*-cresol to the open-chained compound would then involve substances typified by



I, VIII, IX, X, XI, and XIII. For the aliphatic starting material necessary to prepare A, citronellol (II) had many advantages, for it was a substance that was available and relatively cheap, and it already contained two "isoprene" units in place. However, in these "isoprene" units, the methyl group is attached to the second carbon atom, and since *p*-cresol has the methyl group attached to a carbon atom twice removed from the position to be occupied by the entering group, it was necessary to transform citronellol into the next lower saturated acid before

(1) XLI, THIS JOURNAL, 65, in press (1943).

(2) Abstracted from a thesis by G. F. Rouault, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1942.

the combination with *p*-cresol could be made.

Citronellol (II) was reduced catalytically³ to perhydrogeraniol (III) in 95% yield. It was expected that dehydration of III by action of sulfuric acid would produce a mixture contaminated with much tar, and a trial experiment showed that this was indeed the case. Recent work⁴ has shown that the product obtained when III is dehydrated with phosphorus pentoxide does not have a terminal double bond. Decomposition of the quaternary ammonium base derived from III does result in a product having a terminal double bond (VI), but the yield leaves much to be desired.⁵ Welt⁶ reported that the only satisfactory method, in his hands, for converting 1-heptanol into 1-heptene involved pyrolysis of the palmitate of the alcohol according to the method of Krafft.⁷ Perhydrogeranyl palmitate (IV), pyrolyzed by the procedure of Dover and Hensley⁸ gave 3,7-dimethyloctene-1 (VI) in 27% yield; much IV remained undecomposed after the distillation at 310°. But the stearate (V), b. p. 360°, when pyrolyzed by slow distillation through a short packed column gave the desired olefin VI in 85% yield.

Oxidation of the olefin VI by action of potassium permanganate in acetone solution gave 2,6-dimethylheptanoic acid (VII) in 45% yield. Since oxidation by ozone gave excellent results in a later step in the synthesis, it is likely that ozonolysis of VI would have produced VII in much better yields, but the experiment was not tried. The acid VII gave a well-defined S-benzylthiuronium salt⁹ which melted at 141–143.5°. A solid toluide of VII could not be prepared.

The acid VII was converted into the acid chloride by action of phosphorus pentachloride. The chloride could not be distilled without almost complete decomposition; accordingly, the phosphorus oxychloride was removed under reduced pressure and the crude residue was used for acylation of *p*-cresol. This acylation, carried out by a modification of the procedure of Sandulesco and Girard¹⁰ gave the 2-acyl-*p*-cresol IX in 70% yield, doubtless via the (not isolated) ester VIII.

(3) Smith, Ungnade, Austin, Prichard and Opie, *J. Org. Chem.*, **4**, 334 (1939).

(4) Natelson, Gottfried and Kornblau, *THIS JOURNAL*, **64**, 1484 (1942).

(5) v. Braun and Teuffert, *Ber.*, **62**, 235 (1929).

(6) Welt, *ibid.*, **30**, 1495 (1897).

(7) Krafft, *ibid.*, **16**, 3019 (1883).

(8) Dover and Hensley, *Ind. Eng. Chem.*, **27**, 337 (1935).

(9) Donleavy, *THIS JOURNAL*, **58**, 1004 (1936).

(10) Sandulesco and Girard, *Bull. soc. chim.*, [4] **47**, 1300 (1930).

The acylcresol IX could not be converted into a solid α -naphthylurethan or dinitrophenylurethan¹¹ by the standard procedures.

Hydrogenation of the acylcresol IX to the alkyl cyclohexanol X was accomplished in practically quantitative yields by a two-stage reduction under 1800–2500 lb. and in the presence of Raney nickel, first at 175° and then at 225°. The reduction proceeded equally well in the absence of a solvent or in the presence of alcohol, but prolonged reaction times and high temperatures had to be avoided because these resulted in much hydrogenolysis and production of the disubstituted cyclohexane. The dinitrophenylurethan of X was a viscous oil.

Two paths were possible for the dehydration of X. One of these would produce 5-methyl-3-nonyl-1-cyclohexene (XI), a useless product for synthesis of A, and the other would produce 5-methyl-1-nonyl-1-cyclohexene (XII), the intermediate necessary for further use in the synthesis. Although Schneider and Spielman¹² as well as Collaud¹³ have recently prepared and dehydrated various 1-alkyl-1-cyclohexanols, the substances studied by these authors were perfectly symmetrical and the dehydrations could occur in only one way. Harper, Kon and Ruzicka¹⁴ have dehydrated a 1-cyclopentanol substituted in the 1- and 2-positions by alkyl groups; they found that the secondary hydrogen atom was removed entirely and that there was formed none of the isomeric product resulting by removal of the primary hydrogen atom. It appeared likely, then, that dehydration of X would produce XII and this was found to be the case. To bring about this dehydration, catalytic amounts of *p*-toluenesulfonic acid were used, and the product XII was formed in 85–90% yields. Dehydration of X by action of phosphoric acid¹⁵ was not successful.

Ozonolysis of the cyclohexene XII in ethyl bromide, followed by decomposition of the ozonide by action of hydrogen peroxide in acetic acid, produced the keto acid XIII in 90% yield.¹⁶ Use of aqueous hydrogen peroxide, in the absence of acetic acid, produced a poor yield of XIII. The acid XIII was reduced to the saturated acid and simultaneously esterified by a Clemmensen re-

(11) Smith and Sprung, *THIS JOURNAL*, **64**, 434 (1942).

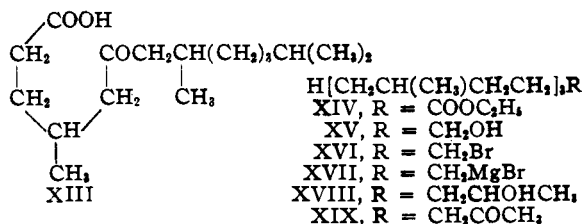
(12) Schneider and Spielman, *J. Biol. Chem.*, **142**, 345 (1942).

(13) Collaud, *Helv. Chim. Acta*, **25**, 965 (1942).

(14) Harper, Kon and Ruzicka, *J. Chem. Soc.*, 124 (1934).

(15) Price and Karabinos, *THIS JOURNAL*, **62**, 1161 (1940).

(16) Riebsomer and Tallman, *Proc. Indiana Acad. Sci.* **43**, 130 (1934) [*Chem. Abs.*, **29**, 118 (1935)].



duction in the presence of alcohol, according to the procedure of Schneider and Spielman.¹² The yield of ester XIV was 65%. Further hydrogenation of XIV at 250°, under a pressure of 2800 lb., and in the presence of a copper chromite catalyst, produced the alcohol XV in 85% yield.

Conversion of the alcohol XV to the bromide XVI by action of hydrobromic and sulfuric acids was not satisfactory, but action of dry hydrogen bromide¹⁷ at 120° produced the bromide XVI in 57% yield. This experiment was performed only once, and the low yield is probably due to loss of material by entrainment in the current of gas. The bromide XVI was converted into the carbinol XVIII in 78% yield via a reaction between the Grignard reagent XVII and acetaldehyde. Action of hot chromic acid upon a solution of the carbinol XVIII in a mixture of acetic acid and benzene produced crude "phytol ketone," 6,10,14-trimethyl-2-pentadecanone (A, XIX), in about 90% yield.

In the model experiments, performed before the above synthesis was undertaken, the readily available lauric acid, C₁₁H₂₃COOH, was used in place of the acid VII. Lauric acid was converted into lauroyl chloride by action of phosphorus pentachloride, and the crude chloride was used to acylate *p*-cresol. 2-Lauroyl-4-methylphenol was obtained in 75–80% yield, based upon lauric acid. The phenol was reduced to 2-dodecyl-4-methylcyclohexanol in 85% yield using the procedure outlined above and alcohol as the solvent. In one experiment, in which no solvent was used, 1-dodecyl-3-methylcyclohexane was produced in 65% yield. The cyclohexanol was dehydrated to 5-methyl-1-dodecyl-1-cyclohexene in 60% yield by action of potassium acid sulfate at 320°, and in 75% yield by action of *p*-toluenesulfonic acid at 180° for fifteen minutes. Action of phosphoric acid failed to dehydrate the cyclohexanol. Oxidation of the cyclohexene by action of potassium permanganate gave a product which was extremely difficult to purify and from which no analytical sample could be prepared; action of

(17) Reid, Ruhoff and Burnett, *Org. Syn.*, **18**, 24 (1935).

chromic acid in acetic acid, according to the procedure of Schneider and Spielman¹² failed to produce the keto acid, but action of ozone, followed by oxidative decomposition of the ozonide in acetic acid, produced 4-methyl-6-ketostearic acid in 90–95% yield. The cyclohexanol was oxidized to 2-dodecyl-4-methylcyclohexanone in 86% yield by action of sodium dichromate, but the cyclohexanone could not be converted into an open-chained compound by action of chromic acid¹⁸ or by action of sodamide.¹⁹ Clemmensen reduction of 4-methyl-6-ketostearic acid in alcohol¹² gave ethyl 4-methylstearate in 56% yield, and hydrogenation of this ester gave 4-methyl-1-octadecanol in 60% yield.

p-Cresol was also acylated with isobutyryl chloride to determine whether or not the procedure of Sandulesco and Girard¹⁰ was applicable to branched chained acid chlorides. 2-Isobutyryl-4-methylphenol was obtained, but the yield was poor (25%) because much of the isobutyryl chloride (b. p. 100°) escaped through the condenser during the reaction.

Experimental Part²⁰

3,7-Dimethyl-1-octene (VI).—Phosphorus pentachloride (pulverized, 242.3 g., 1.164 moles) was rapidly (five minutes) added to melted stearic acid (330.5 g., 1.164 moles). Phosphorus oxychloride was removed from the mixture by distillation under 20 mm. pressure until the temperature reached 150°. Perhydrogeraniol³ (158 g., 190 cc., 1.0 mole) was added (five minutes) to the warm residue of stearoyl chloride (350 g.). The reaction was completed by heating the mixture at 150° for ten minutes. The crude perhydrogeranyl stearate was pyrolyzed by slow (two and one-half hours) distillation at 360° (temperature of the liquid) through a 7-in. column packed with glass helices and wrapped with asbestos cord. The distillate was washed with water, dried (calcium chloride), and fractionated. The hydrocarbon VI (117.5 g., 84%) boiled at 152° (740 mm.).²¹

2,6-Dimethylheptanoic Acid (VII).—Powdered sodium bicarbonate (37 g.) was added to a solution of the olefin VI (165.5 g.) in acetone (1.3 l.) in an apparatus equipped with a Hershberg stirrer.²² The mixture was cooled to 7° and vigorously stirred while powdered potassium permanganate (700 g.) was slowly (four hours) added, in portions. Acetone was removed by distillation and the residue was diluted with water (2 l.). Dilute sulfuric acid and solid sodium bisulfite (about 400 g.) were added alternately until the mixture became clear. The product was removed by ether extraction (about 500 cc.); the ether was evaporated

(18) Schwenk and Prieue, *THIS JOURNAL*, **56**, 2102 (1934).

(19) Wash, Shive and Lochte, *ibid.*, **63**, 2975 (1941).

(20) Microanalyses by E. E. Renfrew, Stanley Rolison and C. H. Stratton.

(21) The boiling point given in the literature is 154° (ref. 5).

(22) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **6**, 313 (1936).

and the residue (200 cc.) was fractionated. The acid VII (83.5 g., 45%) boiled at 115° (3 mm.).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 67.71; H, 11.68. The S-benzylthiuronium salt melted at 141–143.5°.

Anal. Calcd. for $C_{17}H_{23}O_2N_2S$: C, 62.92; H, 8.70. Found: C, 62.69; H, 8.67.

2-[2',6'-Dimethylheptanoyl]-4-methylphenol (IX).—Phosphorus pentachloride (110 g., 0.528 mole) was added (ten minutes) to the acid VII (83.5 g., 0.528 mole), and the phosphorus oxychloride was removed by distillation under 20 mm. from a water-bath at 65°. The residue of crude acid chloride weighed 93 g. (100%). *p*-Cresol (68.6 g., freshly distilled) was placed in a 1-l. 3-necked flask fitted with a Hershberg stirrer, a dropping funnel, and an outlet tube. Aluminum chloride (77.5 g.) was added to the cresol and the mixture was heated for two hours at 130–140° (oil-bath). The above crude acid chloride (93 g.) was rapidly (ten minutes) added to the vigorously stirred mixture; the temperature was maintained at 145°, and stirring was continued, for one and one-quarter hours. The cooled mixture was decomposed by action of boiling hydrochloric acid (400 cc., 18%). The oil was removed and fractionated. After a small fore-run (5.3 g., b. p. 104° (3 mm.)), the phenol IX (90.8 g., 69%) boiled at 144° (3 mm.).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.53; H, 9.89.

2-[2',6'-Dimethylheptyl]-4-methylcyclohexanol (X).—A mixture of the acyl cresol IX (79.5 g.), dry ethanol (85 cc.), and Raney nickel catalyst (21 g.) was heated at 195° for two hours under a hydrogen pressure of 1700–3700 lb. The cooled mixture was filtered and the alcohol was removed from the filtrate by distillation under slightly reduced pressure. The residue was heated with Raney nickel catalyst (9 g.) for four hours at 175° under a hydrogen pressure of 1700–2400 lb. The catalyst was removed and the product was distilled. The cyclohexanol X (74.0 g., 96%) boiled at 133° (3 mm.).

Anal. Calcd. for $C_{16}H_{22}O$: C, 79.93; H, 13.42. Found: C, 80.08; H, 13.38.

5-Methyl-1-[2',6'-dimethylheptyl]-1-cyclohexene (XII).—A mixture of the cyclohexanol X (22.3 g.) and *p*-toluenesulfonic acid (2.3 g.) was heated for fifteen minutes at 180° in a metal-bath. The cooled mixture was dissolved in ether and the ethereal solution was washed successively with water, sodium hydroxide (10%) and again with water. The solvent was removed and the residue was distilled. The cyclohexene XII (18 g., 87%) boiled at 141° (15 mm.).

Anal. Calcd. for $C_{18}H_{30}$: C, 86.40; H, 13.60. Found: C, 86.27; H, 13.40.

4,8,12-Trimethyl-6-ketotridecanoic Acid (XIII).—A solution of the cyclohexene XII (13.9 g.) in ethyl bromide (300 cc.) was subjected for five hours to the action of a rapid (5 l. per hour) stream of ozonized oxygen (6% O_3). Acetic acid (200 cc.) was added to the mixture and the ethyl bromide was removed by distillation from a steam-bath. Hydrogen peroxide (30 cc., 30%) was added and the mixture was heated for two hours on the steam-bath. The solution was diluted with water (600 cc.) and extracted with two 100-cc. portions of ether. The combined ex-

tracts were washed with water, acidified ferrous sulfate solution (2%) and again with water. The solvent was removed and the residue was distilled. The acid XIII (15.6 g., 92%) boiled at 170° (4 mm.).

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 70.94; H, 11.08.

Ethyl 4,8,12-Trimethyltridecanoate (XIV).—The keto acid XIII (4.8 g.) was dissolved in dry ethanol (110 cc.) which had been saturated with hydrogen chloride. This solution was refluxed for forty hours with amalgamated zinc (100 g.); twice during this period hydrogen chloride was passed into the mixture until it was saturated. The mixture was poured into water (600 cc.) and the oil was removed, washed with water, and distilled. The ester XIV (3.6 g., 71%) boiled at 160° (3 mm.).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 75.99; H, 12.76. Found: C, 76.30; H, 12.54.

4,8,12-Trimethyl-1-tridecanol (XV).—The ester XIV (10.55 g.) and copper chromite catalyst (2.0 g.) were heated at 250° for five hours under a hydrogen pressure of 2800 lb. The mixture was washed out of the bomb with alcohol (50 cc.), filtered, and the alcohol was distilled from the filtrate under reduced pressure (15 mm.). The alcohol XV (7.4 g., 85%) boiled at 140° (3 mm.).

Anal. Calcd. for $C_{18}H_{34}O$: C, 79.26; H, 14.14. Found: C, 79.60; H, 13.76.

1-Bromo-4,8,12-trimethyltridecane (XVI).—Dry hydrogen bromide (from a 1-mm. orifice, 4 bubbles per second) was passed through the alcohol XV (7.7 g.) at 120° for one and one-quarter hours. The product was washed successively with sulfuric acid (4 cc.), aqueous methanol (50 cc.), and water and was dried (calcium chloride) and fractionated. The bromide XVI (5.5 g., 57%) boiled at 135° (2–3 mm.) and had n_D^{25} 1.4560.²³

6,10,14-Trimethyl-2-pentadecanol (XVIII).—Acetaldehyde (4 cc.) in ether (12 cc.) was added to a Grignard reagent prepared from the bromide XVI (5.5 g.), magnesium (0.5 g.) and ether (5 cc.). The mixture was filtered to remove unchanged magnesium, and the filtrate was shaken successively with hydrochloric acid (10%) and water. The ether was removed and the residual alcohol XVIII (3.8 g., 78%) was oxidized directly to the ketone XIX.²⁴

6,10,14-Trimethyl-2-pentadecanone (XIX) "Phytol Ketone."—A solution of the crude alcohol XVIII (3.8 g.) in benzene (4.6 cc.) was added, with stirring, to a solution of sodium dichromate dihydrate (3.2 g.) in a mixture of acetic acid (4.6 cc.), sulfuric acid (1.2 cc.), and water (10 cc.). The mixture was stirred for one and one-half hours, and was then diluted with water (80 cc.) and extracted with ether (100 cc.). The extract was washed thoroughly with water and the solvent was evaporated. Distillation of the residue (3.6 g., 95%) gave "phytol ketone" (XIX) boiling at about 150° (7 mm.) and having n_D^{25} 1.4436.²⁵ The semicarbazone, prepared in the usual way and crystallized from methanol, melted at 62–64° alone or when mixed with an authentic specimen.

(23) Ref. 1. The pure bromide boils at 138–140° (3 mm.) and has n_D^{25} 1.4598.

(24) Ref. 1. The alcohol boils at 150–155° (3 mm.) and has n_D^{25} 1.4448.

(25) Ref. 1. The pure ketone boils at 150–152° (3 mm.) and has n_D^{25} 1.4433.

2-Lauroyl-4-methylphenol.—Phosphorus pentachloride (208 g.) was added (ten minutes) to melted lauric acid (200 g.); the mixture was allowed to stand, with occasional shaking, for thirty minutes and then the phosphorus oxychloride was removed by distillation (bath temperature 90°) under 15 mm. The residue of crude lauroyl chloride (218 g., 100%), was converted into lauroyl-*p*-cresol (224 g., 77%) by reaction with *p*-cresol (119 g., 1.1 moles) and aluminum chloride (147 g., 1.1 moles) exactly as described for the preparation of IX. 2-Lauroyl-4-methylphenol boiled at 190° (3 mm.) and solidified to a light yellow solid which melted at 43–45°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.58; H, 10.78.

2-Dodecyl-4-methylcyclohexanol.—The above lauroyl-cresol (25 g.) was dissolved in dry ethanol (37 cc.) and hydrogenated over Raney nickel catalyst (3 g.) under an initial hydrogen pressure of 1700 lb. The bomb temperatures were as follows: 150° for one hour; 165° for two hours; 185° for thirty minutes; and 200° for one hour (maximum pressure, 2800 lb.). The theoretical amount of hydrogen (5 moles per mole of lauroylcresol) was absorbed. The catalyst was removed by filtration through Hyflo, and the solvent was removed by distillation under reduced pressure. Fractionation of the residue (21 g.) gave 2-dodecyl-4-methylcyclohexanol (19 g., 78%) boiling at 178° (2 mm.) and freezing at about 28° to a pasty white solid.

Anal. Calcd. for $C_{19}H_{30}O$: C, 80.78; H, 13.56. Found: C, 80.80; H, 13.22.

1-Dodecyl-3-methylcyclohexane.—The lauroylcresol (215 g.) was heated with Raney nickel catalyst (12 g.) for three hours at 175° under a hydrogen pressure of 2200 lb., after which the spent catalyst was removed, replaced by fresh catalyst (12 g.), and the hydrogenation was continued for seven hours at 225° as follows: after three hours, the catalyst was replaced by 10 g. of fresh catalyst; after another three hours, by 15 g. of fresh catalyst. The product (129 g., 65%) was fractionated and the 1-dodecyl-3-methylcyclohexane (109 g., 55%) was collected at 148° (2 mm.).

Anal. Calcd. for $C_{19}H_{38}$: C, 85.63; H, 14.37. Found: C, 85.71; H, 14.25.

2-Dodecyl-4-methyl-1-cyclohexanone.—2-Dodecyl-4-methyl-1-cyclohexanol (47.5 g.) was added to a stirred solution of sodium dichromate dihydrate (40 g.) in sulfuric acid (15.1 cc.), acetic acid (57 cc.) and water (124 cc.). The mixture was stirred for two hours and then was poured into water (300 cc.) and extracted with ether (150 cc.). The ethereal solution was washed with water and the solvent was removed by distillation. Fractionation of the residue gave the ketone (40.5 g., 86%) boiling at 170–171° (3 mm.).

Anal. Calcd. for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 82.04; H, 13.04.

The ketone formed a semicarbazone which melted at 86–89°, and a 2,4-dinitrophenylhydrazone which melted at 68–72°.

1-Dodecyl-5-methyl-1-cyclohexene.—The cyclohexanol (28.25 g., 0.1 mole) was heated with *p*-toluenesulfonic acid (3 g.) for twenty minutes in a metal-bath at 180°. The

cooled mixture was washed successively with warm water, sodium hydroxide (5%) and finally with water, and the residue was fractionated. The cyclohexene (19.5 g., 74%) boiled at 190° (3 mm.).

Anal. Calcd. for $C_{19}H_{36}$: C, 86.28; H, 13.72. Found: C, 86.20; H, 13.97.

4-Methyl-6-ketostearic Acid.—The above cyclohexene (11.4 g.) in ethyl bromide (250 cc.) was ozonized for four hours exactly as described for the preparation of XIII, but with the following amounts of materials: acetic acid, 300 cc.; hydrogen peroxide, 30 cc., 30%; water for dilution, 1.8 l.; ether for extraction, two 200-cc. portions. Fractionation of the residue gave the keto acid (12.6 g., 93%) boiling at 190° (3 mm.).

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 73.03; H, 11.61. Found: C, 72.74; H, 11.87.

Ethyl 4-Methylstearate.—A solution of the keto acid (9.2 g.) in dry ethanol (200 cc.) which had been saturated with hydrogen chloride, was refluxed with amalgamated zinc (100 g.) for forty hours. The mixture was processed as described for preparation of XIV; this included the two "resaturations" with hydrogen chloride during the reduction. The ester (6.2 g., 65%) boiled at 175° (3 mm.).

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.24; H, 12.87. Found: C, 77.57; H, 13.26.

4-Methyl-1-octadecanol.—The above ester (2.8 g.) was hydrogenated in the presence of copper chromite catalyst (0.5 g.) exactly as described for the preparation of XV. The alcohol (1.4 g., 58%) boiled at 170° (3 mm.).

Anal. Calcd. for $C_{19}H_{40}O$: C, 80.20; H, 14.17. Found: C, 80.38; H, 14.42.

Summary

1. A method of inserting "isoprene" units into aliphatic carbon chains is described. The seven carbon atoms in *p*-cresol are utilized, and, starting with *p*-cresol and the appropriate acid chloride, the synthesis gives an over-all yield of about 30%. The sequence of intermediates is as follows: 2-acyl-*p*-cresol IX, 2-alkyl-*p*-cyclohexanol X, 5-methyl-1-alkyl-1-cyclohexene XII, keto acid XIII, and saturated ester XIV.

2. A method for converting an unsaturated primary alcohol into the next lower saturated acid is described. The synthesis involves three steps, via the saturated alcohol and 1-alkene VI. By application of this synthesis, citronellol has been converted into 2,6-dimethylheptanoic acid (VII) in over-all yields of about 36%.

3. By a combination of these two syntheses, and starting with citronellol and *p*-cresol, "phytol ketone" XIX has been synthesized in about 4% over-all yield.

4. Starting with lauric acid and *p*-cresol, 4-methyl-6-ketostearic acid has been synthesized in 23% over-all yield. The keto acid

was then converted into ethyl 4-methylstearate in 65% yield, and the latter into 4-methyl-1-

octadecanol in 58% yield.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Sorbityl Glycosides and 2,3,4,5,6-O-Pentamethyl Sorbitol

BY M. L. WOLFROM AND THOMAS S. GARDNER

The preparation of disaccharide sugar alcohols by the reducing action of amalgams on the reducing sugars has been unsatisfactory as the conditions employed tended to degrade the sugars and gave impure products that were difficult to crystallize. More efficient, catalytic reduction methods at high pressure and temperature were introduced by Ipatieff.¹ Improvements in equipment and technique have made it possible for several disaccharide alcohols to be so synthesized in crystalline form. Thus, lactitol,² cellobiotol,³ melibiotol⁴ and 6-(β -*d*-glucosido)-dulcitol⁵ were obtained in the crystalline state by the reduction of the corresponding sugars, and maltitol^{4,6} was prepared as an amorphous substance but characterized as a crystalline nonaacetate. Pacsu and Rich⁷ used a platinum catalyst at room temperature and low pressure to reduce *keto*-turanose octaacetate to a mixture of 3-(α -*d*-glucosido)-(*levo*)⁸-sorbitol and 3-(α -*d*-glucosido)-*d*-mannitol octaacetates. The mixture was resolved by the fractional crystallization of the nonaacetates obtained on further acetylation. No attempts to crystallize the free alcohols were recorded.

In the work herein reported we wish to add another disaccharide alcohol to the above list. The high temperature and high pressure catalytic reduction of gentiobiose yielded gentiobiotol (6-(β -*d*-glucosido)-(*levo*)-sorbitol) as an amorphous material characterized as its crystalline nonaacetate. The structure of gentiobiotol was verified by its lack of Fehling reduction and by its hy-

drolisis to (*levo*)-sorbitol, characterized as its tri-benzylidene derivative, and to *d*-glucose, identified as its diethyl mercaptal.

The methylated disaccharide alcohols and the hydrolytic products of such ethers promise to be useful in the further determination of carbohydrate structure. Levene and Kuna³ prepared a sirupy O-nonamethyl-4-(β -*d*-glucosido)-(*levo*)-sorbitol by the methylation of cellobiotol and hydrolyzed this to the sirupy 1,2,3,5,6-O-pentamethyl-(*levo*)-sorbitol, the latter substance being described as a desirable reference compound for the study of the position of glycosidic union in a disaccharide. A derivative of this partially methylated hexitol was not recorded. In the present work we have prepared, as distilled sirups, the nonamethyl ethers of two other disaccharide alcohols, maltitol and lactitol.

We also wish to report a crystalline derivative of one of the isomeric pentamethyl ethers of (*levo*)-sorbitol. This substance is the 1-N- α -naphthylcarbamate of 2,3,4,5,6-O-pentamethyl-(*levo*)-sorbitol. This ether of sorbitol was prepared as a distilled sirup by the high pressure, high temperature, catalytic reduction of the *aldehydo-d*-glucose pentamethyl ether of Levene and Meyer.⁹ This crystalline carbamate of a sugar structure illustrates the possible usefulness of such an ester, hitherto little used in the sugar series.¹⁰

Experimental

Gentiobiotol (6-(β -*d*-Glucosido)-(*levo*)-sorbitol).—The gentiobiose used in this work was prepared through the octaacetate synthesized according to the Reynolds and Evans¹¹ modification of the procedure of Helferich and Klein.¹² Gentiobiose methyl alcoholate (5 g., m. p. 85°) was dissolved in 100 cc. of water containing 5 g. of a nickel catalyst supported on kieselguhr. The solution was reduced in a steel shaking autoclave (American Instrument

(1) V. N. Ipatieff, *Ber.*, **45**, 3218 (1912).
 (2) J. B. Senderens, *Compt. rend.*, **170**, 47 (1920); M. L. Wolfrom, W. J. Burke, K. R. Brown and R. S. Rose, Jr., *THIS JOURNAL*, **60**, 571 (1938).
 (3) P. A. Levene and M. Kuna, *Science*, **85**, 550 (1937); *J. Biol. Chem.*, **127**, 49 (1939).
 (4) M. L. Wolfrom and T. S. Gardner, *THIS JOURNAL*, **62**, 2553 (1940).
 (5) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **125**, 355 (1938).
 (6) P. Karrer and J. Büchi, *Helv. Chim. Acta*, **20**, 86 (1937).
 (7) E. Pacsu and F. V. Rich, *THIS JOURNAL*, **55**, 3018 (1933).
 (8) This denotes the ordinary form of sorbitol, which is slightly levorotatory in aqueous solution.

(9) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **69**, 175 (1926).
 (10) M. R. Salmon and G. Powell, *THIS JOURNAL*, **61**, 3507 (1939); M. L. Wolfrom and D. E. Fletcher, *ibid.*, **62**, 1151 (1940).
 (11) D. D. Reynolds and W. L. Evans, *ibid.*, **60**, 2559 (1938).
 (12) B. Helferich and W. Klein, *Ann.*, **450**, 219 (1926).