

Ethyl α -(*p*-iodobenzyl)-*n*-caproate was obtained in 68% yield as a colorless oil, b. p. 156° (2 mm.); sp. gr.²⁰₄ 1.352; *n*²⁵_D 1.5333.

Anal. Calcd. for C₁₈H₂₁O₂I: I, 35.2. Found: I, 35.4.

Hydrolysis and decarboxylation of ethyl ethyl-(γ -phenyl-*n*-propyl)-malonate gave α -ethyl- δ -phenyl-*n*-valeric acid in 80% yield, b. p. 189–190° (14 mm.); *n*²⁵_D 1.5033.

Anal. Calcd. for C₁₈H₁₈O₂: C, 75.7; H, 8.79; neut. equiv., 206. Found: C, 75.6; H, 8.62; neut. equiv., 207.

Ethyl α -Ethyl- δ -(α -iodophenyl)-*n*-valerate.—The iodination of α -ethyl- δ -phenyl-*n*-valeric acid was carried out in the presence of sodium nitrite. The iodinated acid was obtained as a heavy oil, which was converted to the ethyl ester without purification. A 61% yield of ethyl α -ethyl- δ -(α -iodophenyl)-*n*-valerate was obtained as a viscous oil, b. p. 162–164° (2 mm.); sp. gr. ²⁰₄ 1.362; *n*²⁵_D 1.5352. The position of the iodine atom was not determined.

Anal. Calcd. for C₁₈H₂₁O₂I: I, 35.2. Found: I, 35.2.

Summary

For study as absorbable liquid contrast media in radiographic diagnoses, the ethyl esters of the ω -(*p*-iodophenyl)-*n*-fatty acids from *p*-iodophenyl-acetic to ζ -(*p*-iodophenyl)-*n*-heptoic acids have been prepared from the corresponding uniodinated phenyl-*n*-fatty acids by direct iodination in the presence of sodium nitrite-sulfuric acid. Several branched chain iodophenyl fatty acids and their ethyl esters have been prepared, also. Of these various esters, ethyl δ -(*p*-iodophenyl)-*n*-valerate seems to be suitable for restricted use as a contrast medium. In the course of the work an improved synthesis of δ -phenyl-*n*-valeric acid has been developed.

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Vitamin E. XLI. Synthesis of 1-Chloro-3,7,11,15-tetramethylhexadecanol-3, and its Condensation with Trimethylhydroquinone to Form α -Tocopherol¹

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As is well known, tocopherols are synthesized by condensation of an appropriate hydroquinone with phytol or one of its derivatives—a phytyl halide or phytadiene. Since all of the derivatives are made from phytol itself, these syntheses all require an adequate source of phytol. Although enough phytol is available for relatively small scale operations, the supply of phytol would be a limiting factor in the manufacture of α -tocopherol on a scale comparable to that involved in the manufacture of some of the other vitamins, and for this purpose, a synthetic substitute would be desirable. The synthesis of phytol from hexahydropseudoionone by Fischer and Löwenberg² is well known, and, although this synthesis has recently been modified and improved,³ it still leaves much to be desired in its adaptability to large scale operations.

Citral is the most readily available commercial material whose structure contains repeating "isoprene" units; this C₁₀-compound therefore was chosen as the most promising starting material for

(1) XL, THIS JOURNAL, 65, 441 (1943). This work was made possible by financial aid, through the Graduate School, from the General Research Fund of the University of Minnesota, for which the authors make grateful acknowledgment.

(2) (a) Fischer and Löwenberg, *Ann.*, 464, 69 (1928); (b) 475, 183 (1929).

(3) Karrer and Ringier, *Helv. Chim. Acta*, 22, 810 (1939).

the synthesis of any substance containing twenty carbon atoms with a regular sequence of "isoprene" units. Moreover, in view of results previously obtained on the condensation of "potential dienes" with hydroquinones to give chromans⁴ it was known to be unnecessary to synthesize an unsaturated substance; any compound, having the requisite carbon chain ending with two functional groups—halogen and/or hydroxyl, in the 1,3-positions, would suffice. With these facts in mind, a synthesis of 1-chloro-3,7,11,15-tetramethylhexadecanol-3 (X) was undertaken; the synthesis is outlined in the chart. Several of the reactions in the chart required a considerable amount of study before the proper conditions were found.

In order to use trimethylene glycol, it was first necessary to convert it into a mono ether (I). The group R in this ether had to be one which (a) could be introduced in good yield, (b) would not be extensively cleaved when the halide II or Grignard reagent was formed, and (c) would cleave fairly readily from VI under the proper condition. Three ethers were prepared; those in which R in I was methyl, ethyl and benzyl. Of these, the ethyl

(4) Smith, Ungnade, Stevens and Christman, THIS JOURNAL, 61, 2615 (1939).

of Grignard reagents obtained from the alkoxy halides II. The over-all yields from IV to V were about 50%. No particular difficulty was experienced in carrying out the Grignard reactions; the intermediate carbinols were not isolated but were converted upon distillation into the unsaturated ethers V which were easily separated and which had sharp boiling points when purified pseudo-ionone had been used. These unsaturated ethers were yellow oils which, on exposure to air, slowly polymerized to sticky, glassy solids. They were, therefore, used soon after they had been prepared.

In the early experiments, γ -bromopropyl acetate, prepared from trimethylene bromohydrin and acetyl chloride, was substituted for the bromide II, but this material could not be converted into a Grignard reagent.

Reduction of the unsaturated ethers V to saturated ethers VI was usually quite smooth and nearly quantitative in the presence of Raney nickel catalyst at 125°, under a pressure of about 2000 lb. of hydrogen, and in the absence of any solvent. Very little, if any, hydrogenolysis occurred except with the benzyl ether, where it was quite noticeable. But the reduction was quite sensitive to impurities in the ethers V and was very sluggish if the bomb had been in contact with nitrogenous compounds previously. In a good reduction, complete absorption of three moles of hydrogen occurred during the first hour, but in the sluggish reductions no hydrogen was absorbed until the temperature reached 100°; then two to three hours was required for absorption of three moles of hydrogen and the fourth mole (complete saturation) was not absorbed at all. In these cases it was necessary to remove the material from the bomb, filter it and introduce fresh catalyst before the reduction could be completed. The saturated ethers VI were colorless, stable oils.

Cleavage of the saturated ethers VI to the bromide VII was very slow and incomplete when carried out in open vessels. When dry hydrogen bromide was passed through the ethyl ether VI ($R = C_2H_5$) at 135° for six hours (reflux condenser), cleavage to the extent of 27% occurred. Action of 48% aqueous hydrobromic acid was much slower; addition of a great excess of acetic acid to the mixture accelerated the reaction but action for twelve hours at 115° was required to produce 85% cleavage to VII. When the cleavage was carried out under pressure, in acetic acid

containing 3 moles of dry hydrogen bromide per mole of VI, the reaction was complete (96%) in six hours at 150°. In all these reactions, the extent of cleavage was followed by determining the refractive indices and (occasionally) by carbon-hydrogen analyses of the products. Of the three ethers VI studied, the methyl ether cleaved more readily (95% in four hours at 180°) than the ethyl ether, and the benzyl ether most readily of all (five hours at reflux temperature in acetic and hydrobromic acids). Unchanged ether VI could be removed from the products by extraction with sulfuric acid.

Judging from the over-all yields of later products, the bromide VII reacted with magnesium to produce a good yield of the Grignard reagent. The latter was added to acetaldehyde; there resulted a 70% (based on VII) yield of the alcohol VIII, which was identified by oxidation to the ketone IX and comparison of the semicarbazone of the ketone with an authentic specimen prepared from IX obtained by oxidation of phytol. This reaction showed that the structures of all the products involved had been correctly assigned. Moreover, these reactions constitute an excellent synthesis for this "phytol ketone" independent of phytol itself and this, in turn, eliminates from the tocopherol synthesis of Smith and Miller⁶ any dependency upon phytol.

The Grignard reagents from VII and two other bromides—ethyl and lauryl—were added to the chloroketone XII. The halohydrins X were obtained in about 50% yields. The model experiments showed that, for good results, it was necessary to use no more than one gram atom of magnesium per mole of the halide, or else to remove unchanged magnesium from the Grignard solution, since the chloroketone XII reacted with magnesium. Moreover, excess chloroketone was detrimental since it was decomposed during processing of the reaction into products which were difficult to remove later. Finally it was necessary to add the solution of the chloroketone slowly to the Grignard reagent, and to decompose the intermediate metallic derivative with iced saturated ammonium chloride solution, and not with hydrochloric acid. When methylethyl- β -chloroethylcarbinol was subjected to the action of quinoline or alcoholic potassium hydroxide, both water and hydrochloric acid were eliminated and the product was a mixture of pentadienes.

(6) Smith and Miller, *THIS JOURNAL*, **66**, 443 (1942).

Two halohydrins were condensed with trimethylhydroquinone. The reaction was smooth, the products were formed in good yield (70%), and were readily purified. Methylene- β -chloroethylcarbinol and the hydroquinone gave 2-ethyl-2,5,7,8-tetramethyl-6-hydroxychroman⁶ which had a melting point and mixed melting point of 60–61°. The halohydrin X and the hydroquinone gave α -tocopherol in 70% yield, and the product required much less processing for complete purification than did α -tocopherol prepared by condensation of the hydroquinone with phytol. The tocopherol was identified by analysis, melting point and analysis of its 3,5-dinitrophenylurethan, gold chloride titration,⁷ absorption spectrum,⁷ Furter–Meyer assay⁷ and by a bioassay⁸ which showed it to have the full vitamin E activity of natural α -tocopherol.

In one series of reactions, 74 g. (0.385 mole) of pseudoionone was converted into 9.2 g. (0.0214 mole) of pure α -tocopherol. This over-all yield, 5.5%, represents a minimum value because in this preparation the pseudoionone had not been purified via the bisulfite compound, nor was complete cleavage of the ether VI achieved. The over-all yield from pure pseudoionone and including a complete cleavage of the ether VI would be 8–10% (4–5% based upon citral).

Experimental Part⁹

γ -Ethoxypropanol (I, R = C₂H₅).¹⁰—Sodium (25 g., 1.08 gram atoms, cut into small pieces) was added, in portions, to a hot (115–120°) and vigorously stirred solution of trimethylene glycol (250 g., freshly distilled, b. p. 115–119° (9 mm.)) in dry xylene (100 cc.). External heating was not necessary until near the end of the reaction. Ethyl bromide (120 g., 1.2 moles) was slowly added, with stirring, to the hot (120°) solution of the sodium derivative. As soon as sodium bromide began to precipitate, further external heating was not necessary. The mixture was heated (120°) and stirred for one hour after all the ethyl bromide had been added. The mixture was cooled, the precipitate was removed, and the filtrate was distilled through a packed column. After a fore-run of xylene and diethoxypropane, the γ -ethoxypropanol boiled at 157–163°. The yields ranged from 58 to 62%. This substance was also prepared from trimethylene chlorhydrin and sodium ethoxide,¹¹ but the yield was only 38%.

γ -Methoxypropanol¹² (I, R = CH₃) was prepared in a similar manner, but with omission of the xylene, from the

glycol (254 g.), sodium (25.3 g.), and methyl iodide (158 g.). The temperature was difficult to control during the first part of the reaction, and the mixture was cooled to 20° before addition of the methyl iodide. The product (64 g., 64%) boiled at 148–149°.

γ -Benzyloxypropanol (I, R = C₆H₅CH₂)¹³ was prepared as described for the ethoxy compound from the glycol (240 g.), sodium (25 g.) and benzyl chloride (150 g.). The product (133 g., 73%) boiled at 145–150° (13 mm.).

γ -Ethoxypropyl Bromide (II, R = C₂H₅; X = Br).¹⁰—Phosphorus tribromide (108 g., 0.4 mole) was slowly (one hour) dropped, with stirring, into the ether I (104 g., 1 mole) in an apparatus protected from moisture. At room temperature a slow reaction began, with evolution of hydrogen bromide; the temperature was maintained below 60° by external cooling. Finally the mixture was warmed to 60° for one hour and then poured into water. The organic layer was removed, washed several times with water, dried (sodium sulfate), and distilled through a packed column. The yields ranged from 55 to 65% and the product boiled at 147–150° (86–87° (100 mm.)), but it was necessary to collect it in a cooled receiver to avoid loss.

γ -Methoxypropyl bromide (II, R = CH₃; X = Br)¹² was prepared from the corresponding ether (59 g.) and phosphorus tribromide (70 g.) as described above. The product (27 g., 27%) boiled at 131–133°. Apparently the methoxyl group was extensively cleaved during the reaction.

γ -Benzyloxypropyl Bromide (II, R = C₆H₅CH₂; X = Br).—Phosphorus tribromide (32.5 g., 0.12 mole) was slowly added to a cold (0°) and stirred solution of γ -benzyloxypropanol (50 g., 0.30 mole) in dimethylaniline (15 cc., 0.12 mole). The mixture was then heated to 50° until solution was complete. The material was poured into excess cold dilute hydrochloric acid and extracted with chloroform. The extract was washed thoroughly with dilute hydrochloric acid, then with water, and dried (sodium sulfate). The solvent was removed and the residue was distilled. The fraction boiling at 130–132° (8 mm.) weighed 23.3 g. (34%).

Anal. Calcd. for C₁₀H₁₃OBr: C, 52.40; H, 5.72. Found: C, 52.85; H, 5.76.

γ -Ethoxypropyl Chloride (II, R = C₂H₅; X = Cl).^{10, 14}—A mixture of γ -ethoxypropanol (68 g., 0.65 mole) and pyridine (11.5 g., 0.145 mole) was slowly added, with stirring, to cold (0°) phosphorus trichloride (36 g., 0.26 mole). The solution was heated at 75° for one hour and the product was then distilled directly from the reaction mixture. The halide boiled at 125–128° and weighed 53 g. (67%).

4-Chlorobutanone-2 (XII).—Freshly distilled methyl vinyl ketone (104 g., b. p. 78–82°) was saturated at 0° with a rapid stream of dry hydrogen chloride. The solution was allowed to stand at room temperature for one hour and was then poured into ice-water, neutralized with dilute sodium hydroxide and extracted thoroughly with ether. The colorless extract was washed with water, dried (sodium sulfate), the solvent was removed and the rather dark residue was distilled. The product (106 g., 67%) boiled at 48–50° (15 mm.).¹⁵ When this chloroketone

(7) We are indebted to Dr. T. J. Webb of the Research Laboratories, Merck and Co., Inc., Rahway, New Jersey, for these determinations.

(8) We are indebted to Dr. L. S. Palmer of the Division of Agricultural Biochemistry, University of Minnesota, for this assay.

(9) Micro analyses by E. E. Renfrew and C. H. Stratton.

(10) Noyes, *Am. Chem. J.*, **19**, 766 (1897).

(11) Rojahn and Lemme, *Arch. Pharm.*, **263**, 617 (1925).

(12) Pummerer and Schönamsgruber, *Ber.*, **72**, 1838 (1939).

(13) Bennett and Hock, *J. Chem. Soc.*, 472 (1927).

(14) Palomaa and Kenetti, *Ber.*, **64**, 798 (1931).

(15) Blaise and Maire, *Bull. soc. chim.*, [4] **3**, 268 (1908).

XII was warmed with either quinoline or alcoholic potassium hydroxide, the elements of both water and hydrogen chloride were eliminated and a mixture of dienes (b. p. 65–75°) resulted. Satisfactory analytical values could not be obtained because of the extreme volatility of the mixture. An attempt was made to condense the crude mixture with trimethylhydroquinone in the hope of obtaining the known 2-ethyl-2,5,7,8-tetramethyl-6-hydroxychroman, but no solid product could be isolated.

Pseudoionone (IV) was prepared from purified citral (203 g., b. p. 110–112° (8 mm.)), via the bisulfite compound and acetone (1 l., dried over potassium carbonate) exactly as described by Russell and Kenyon.⁵ The pseudoionone, when purified via the bisulfite addition compound, boiled at 127–129° (4 mm.) and had n_D^{25} 1.5310. The yield was 118 g. (45%). When the citral and the product were not purified via the bisulfite compounds, the yield was 56% of a material which boiled at 130–137° (5 mm.) and which had n_D^{25} 1.5280.

Ethers (V) of 4,8,12-Trimethyltrideca-3,5,7,11-tetraene-1-ol. Ethyl Ether, V, R = C₂H₅.—A small portion of a solution of pure pseudoionone (96 g., 0.5 mole) and γ -ethoxypropyl bromide (100 g., 0.6 mole) in dry ether (375 cc.) was dropped on to magnesium (15.2 g., 0.625 mole). The reaction was started by application of heat, or by addition of a crystal of iodine or a few drops of ethyl bromide, and when it was well under way, the remainder of the solution was added in a rapid stream. The reaction was completed by heating the mixture for thirty minutes. The ether solution was decanted from the magnesium, shaken with cold, dilute, hydrochloric acid, washed with water and dried (sodium sulfate). Water began to cleave from the product as the solvent was removed on the steam-bath; elimination of water was completed by heating the residue at 90–95° for thirty minutes. The product was dissolved in a little ether and dried (sodium sulfate). After removal of the solvent, the orange residue was distilled in an atmosphere of nitrogen. The distillate (52%) a lemon-yellow oil, boiled at 163–165° (3 mm.), had n_D^{25} 1.5242, and slowly set to a sticky, glassy solid on exposure to air.

Anal. Calcd. for C₁₅H₃₀O: C, 82.38; H, 11.51. Found: C, 82.09; H, 11.25.

When γ -ethoxypropyl chloride was substituted for the bromide in a reaction with pseudoionone that had not been carefully purified, the yield of the above ether was 46% and the reaction occurred much more slowly.

Methyl Ether, V, R = CH₃.—This was prepared by the above procedure from pseudoionone (28.8 g. not purified), γ -methoxypropyl bromide (25 g.) and magnesium (4.4 g.). The product (19.9 g., 53.5%) boiled at 150–160° (3 mm.)—a typical boiling range from these products when impure pseudoionone was used.

Benzyl Ether, V, R = C₆H₅CH₂.—This was prepared as above from pseudoionone (15.6 g.), γ -benzyloxypropyl bromide (32.9 g.), and magnesium (2.7 g.). The product (12.8 g., 49%) boiled at 210–220° (3 mm.) with some decomposition.

γ -Bromopropyl acetate (123 g., 68%, b. p. 103–108° (50 mm.)) was prepared from trimethylene bromohydrin (139 g., redistilled, b. p., 100–108° (50 mm.)) and acetyl chloride (157 g.) according to the procedure of Bogert

and Slocum.¹⁶ A solution of this acetate (20.9 g.) and pseudoionone (19.2 g.) in ether (75 cc.) was warmed with magnesium (2.9 g.) according to the procedure described above for preparation of V. The reaction was extremely difficult to start, and proceeded very slowly. Only after the mixture was refluxed for eight hours had an appreciable amount of magnesium dissolved. The mixture was processed as described above; a portion of the reactants was recovered, but the only product was polymeric material which could not be distilled.

Ethers (VI) of 4,8,12-Trimethyl-1-tridecanol: Ethyl Ether, VI, R = C₂H₅.—The unsaturated ether V, R = C₂H₅, was subjected to the action of hydrogen at 125° under 2000 lb. Reduction began at 50° and during the first hour three moles of hydrogen was absorbed. Reduction was completed by heating the bomb at 125° for one hour after all apparent absorption of gas had ceased. Usually the reductions were rapid and complete, but occasionally they were sluggish and no hydrogen was absorbed until the temperature reached 100°. In these cases the fourth mole of hydrogen was not absorbed even after prolonged heating at 150° and it was necessary to remove the catalyst from the material, add fresh catalyst and continue the reduction. The product was a colorless oil which boiled at 138–140° (3 mm.) and which had n_D^{25} 1.4370. The average yield for a large number of preparations was 82%.

Anal. Calcd. for C₁₅H₃₀O: C, 79.91; H, 14.17. Found: C, 80.16; H, 14.11.

Methyl Ether, VI, R = CH₃, and Benzyl Ether, VI, R = C₆H₅CH₂.—These were prepared from the respective unsaturated ethers as described above, but they were not characterized.

1-Bromo-4,8,12-trimethyltridecane (VII). A.—The ethyl ether VI was placed in a three-necked flask equipped with a thermometer, a short upright condenser, and an inlet tube which ended in a bulb with several perforations. A rapid stream of dry hydrogen bromide was passed through the ether VI for six hours at 135–140°. Most of the water formed in the cleavage dropped back into the reaction mixture, although no water was passed through the condenser. The material was poured into water, extracted with ether, and dried (sodium sulfate). The product boiled at 140–145° and had n_D^{25} 1.4431. Analysis indicated that cleavage had occurred to the extent of about 26%.

Anal. Calcd. for C₁₅H₃₃Br: C, 62.88; H, 10.89. Calcd. for C₁₅H₃₃O: C, 79.91; H, 14.17. Found: C, 75.45; H, 13.26.

B. This product (27 g.) was refluxed with aqueous hydrobromic acid (48%) for one and one-half hours. No noticeable evolution of ethyl bromide occurred during this time. Acetic acid (50 cc.) was then added and refluxing was continued for an additional seven hours, after which the material was processed as in A. Very little change had occurred; the boiling point and refractive index were practically the same as before, but the analysis indicated 34% of cleavage.

C. The product from B (24 g.) was refluxed for twenty-four hours with acetic acid (100 cc.) and hydrobromic acid

(16) Bogert and Slocum, *THIS JOURNAL*, **46**, 766 (1924).

(50 cc., 48%). The material, processed as in A, gave a product which had n_D^{25} 1.4559 and C, 66.28; H, 11.76. The analysis indicated that cleavage had occurred to the extent of 80%.

D. The same procedure used in A was employed except that the condenser was set downward to deliver into a cooled trap. The ethyl ether VI was subjected to the action of a rapid stream of hydrogen bromide at 185–200° for eight hours. The upper layer of the distillate in the trap was returned to the reaction mixture from time to time. The products from two such experiments had n_D^{25} 1.4555 and 1.4568, respectively, indicating 75–85% cleavage.

E. Apparatus as in A, with a water cooled reflux condenser. The ethyl ether VI (50 g. n_D^{25} 1.4370) was dissolved in acetic acid (50 cc.) and hydrogen bromide was passed into the solution at 115° for twelve hours. Two layers were formed; the cooled mixture was neutralized with solid sodium carbonate and extracted with ether. The extract was washed with water, dried (sodium sulfate), and the solvent was removed. The residue boiled at 135–140° (3 mm.), weighed 51 g. and had n_D^{25} 1.4568 (85% cleavage).

F. The ethyl ether VI (10 g.) was dissolved in acetic acid (25 cc.) in which hydrogen bromide (11 g.) had been absorbed at 0°. The solution was heated in a Carius tube at 150° for six hours. The product (two layers) was processed as in E. The material boiled at 135–138° (3 mm.) and had n_D^{25} 1.4598. The analytical values (C, 63.49; H, 11.23) indicated that the ether had been cleaved to the extent of 96%. The yield, however, was only 8.5 g. (75%), largely due to mechanical losses.

G. The pure bromide VII was prepared as follows: the product from E (47 g.) was shaken with sulfuric acid (15 cc.) and the mixture was allowed to stand overnight. The upper layer was removed, dissolved in ether, washed with dilute carbonate solution, and dried. The pure bromide boiled at 138–140° (3 mm.), weighed 30 g., and had n_D^{25} 1.4598.

Anal. Calcd. for $C_{18}H_{38}Br$: C, 62.88; H, 10.89. Found: C, 63.04; H, 11.17.

H. The methyl ether VI was subjected to the action of hydrogen bromide at 180° for four hours, according to procedure D. The bromide had n_D^{25} 1.4595 (95% cleavage).

I. The benzyl ether VI was completely cleaved by procedure C in five and one-half hours. The product was fractionated, the first fraction (benzyl bromide, b. p. 75–80° (10 mm.)) was followed by a fraction consisting of the pure bromide VII boiling at 140–145° (3.5 mm.) and having n_D^{25} 1.4600.

6,10,14-Trimethyl-2-pentadecanol (VIII).—A Grignard reagent was prepared in the usual way from the pure bromo compound VII (41 g., 0.135 mole), magnesium (4.85 g., 0.2 mole), and dry ether (75 cc.). Acetaldehyde (20 cc.) in ether (50 cc.) was slowly added to the cooled (0°) and stirred Grignard reagent. The mixture was refluxed for thirty minutes and was then decomposed by action of dilute hydrochloric acid and processed in the usual way. The alcohol (25.5 g., 70%) boiled at 150–155° (3 mm.) and had n_D^{25} 1.4448.

Anal. Calcd. for $C_{18}H_{38}O$: C, 79.91; H, 14.17. Found: C, 80.39; H, 13.88.

6,10,14-Trimethyl-2-pentadecanone (IX, "Phytol Ketone").—A solution of the above alcohol VIII (25 g., 0.0925 mole) in benzene (30 cc.) was slowly added to a well stirred solution of sodium dichromate dihydrate (21 g., 0.07 mole) in water (65 cc.) containing acetic acid (30 cc.) and sulfuric acid (8 cc., 0.14 mole). Stirring was continued, and the temperature (which rose to 50° during the reaction) was maintained at 40° for one hour after it had fallen to that point. The solution was extracted thoroughly with ether and the extract was washed with water, then with sodium hydroxide (5%), and dried (sodium sulfate). The ketone boiled at 150–152° (3 mm.), weighed 18.7 g. (75%) and had n_D^{25} 1.4433.¹⁷

Anal. Calcd. for $C_{18}H_{36}O$: C, 80.50; H, 13.53. Found: C, 80.75; H, 13.30.

The semicarbazone melted at 70–70.5 (in agreement with Heilbron's report),^{17a} alone or when mixed with an authentic specimen of the semicarbazone prepared from ketone obtained by oxidation of phytol.

1-Chloro-3-methyl-3-pentanol.—A Grignard reagent was prepared from ethyl bromide (32.7 g., 0.3 mole), magnesium (7.3 g., 0.3 mole), and ether (75 cc.) and to the cooled (0°) and stirred solution, 4-chloro-2-butanone (XII, 31.5 g., 0.3 mole) was slowly added. The metallic derivative was decomposed with cold dilute hydrochloric acid and processed in the usual way. The ether solution was colorless, but considerable darkening occurred as the solvent was removed. The alcohol boiled at 104–105° (50 mm.), weighed 21.5 g. (51%), and had an odor somewhat like that of camphor.

Anal. Calcd. for $C_8H_{18}OCl$: C, 52.70; H, 9.59. Found: C, 52.61; H, 9.81.

2-Ethyl-2,5,7,8-tetramethyl-6-hydroxychroman.—Trimethylhydroquinone (4 g.), zinc chloride (freshly fused, 4 g.) and the above chloropentanol (3.7 g.) were dissolved in acetic acid (15 cc.) and the solution was refluxed for one hour. The dark brown solution was poured into water and extracted with petroleum ether (b. p. 60–68°). The extract was evaporated and the residual oil was refluxed for thirty minutes with a solution of potassium hydroxide (2.5 g.) in methanol (10 cc.). The solution was extracted with petroleum ether (extract discarded) and then was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with carbonate, dried (sodium sulfate) and evaporated. The residual red oil was distilled (b. p. 135–140° (2 mm.)) and the orange distillate was crystallized from petroleum ether (b. p. 60–68°). The product formed colorless needles which melted at 60–61°, alone or when mixed with a specimen (m. p. 60.5–62.5°) prepared by a different method.⁸

Anal. Calcd. for $C_{18}H_{32}O_2$: C, 76.86; H, 9.48. Found: C, 76.72; H, 9.67.

The 3,5-dinitrophenylurethan¹⁸ melted at 200–201.5° alone or when mixed with an authentic specimen.⁸

1-Chloro-3-methyl-3-pentadecanol.—The above procedure for the chloropentanol was used, substituting lauryl-magnesium bromide (from lauryl bromide, 25 g., mag-

(17) The reported values are (a) 1.4432 (ref. 2a, p. 81); (b) 1.4434 (ref. 2b, p. 195); and (c) 1.4435 (20°). Heilbron, *J. Chem. Soc.* **117**, 884 (1920).

(18) Smith and Sprung, *THIS JOURNAL*, **64**, 433 (1942).

nesium, 2.5 g., and ether, 75 cc.) for ethylmagnesium bromide and using 8.5 g. of the ketone. The alcohol (9.5 g., 34.5%) boiled at 165–170° (3 mm.) but it contained small amounts of dilauryl.

Anal. Calcd. for $C_{16}H_{33}OCl$: C, 69.39; H, 12.02. Found: C, 70.03; H, 11.43.

A portion of a solution of lauryl bromide (25 g.) and methyl vinyl ketone (7 g.) in ether (75 cc.) was added to magnesium (2.5 g.). The reaction was very difficult to start, and when the remainder of the reactants was added, the reaction ceased completely and the mixture gradually set to a white gel from which no pure products could be obtained. When laurylmagnesium bromide (25 g. of bromide, 2.5 g. of magnesium, 75 cc. of ether) was prepared separately and added to methyl vinyl ketone (7 g.), a reaction apparently occurred, but the only product was a waxy yellow solid (13 g.) which could not be distilled or crystallized.

1-Chloro-3,7,11,15-tetramethyl-3-hexadecanol (X, "Isophytol Hydrochloride").—Impure bromo compound VII (66 g., mixture containing 75%, 0.162 mole, of VII and 25% of VI), magnesium (4.85 g., 0.2 mole) and ether (100 cc.) was converted into the Grignard reagent, and to it the ketone XII (21 g., 0.2 mole) in ether (50 cc.) was slowly added at 0°. The mixture was refluxed for thirty minutes and was then decomposed with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried (sodium sulfate), and the solvent was removed. The residue was distilled in an atmosphere of nitrogen. The first fraction consisted of unchanged ketone XII which partially decomposed during the distillation, giving a solid decomposition product which was deposited in the condenser. After this first fraction and the decomposition products were removed, the distillation proceeded smoothly. The second fraction (29.3 g.) boiled at 120–165° (2 mm.). The third fraction (21 g., 38%) boiled at 165–175° (2 mm.) and was a faintly yellow-green viscous oil. Fractions II and III were redistilled. Fraction II gave 19 g. of a product boiling at 120–128° (2 mm.) which was largely the ether VI present in the starting material, although it contained some other material—probably the hydrocarbon corresponding to the bromide VII. Almost all of fraction III, on redistillation, boiled at 173–175° (2 mm.), and had n_D^{20} 1.4620.

Anal. Calcd. for $C_{20}H_{41}OCl$: C, 72.12; H, 12.42. Found: C, 72.22; H, 12.23.

α -Tocopherol (XI).—The above halohydrin X (12 g., 0.036 mole) was added to a hot (115°) and stirred solution of trimethylhydroquinone (5 g., 0.033 mole) and zinc chloride (2.5 g., freshly fused) in acetic acid (20 cc.). The mixture was refluxed for one and one-half hours; hydrogen chloride was evolved throughout the course of the reaction. The dark brown liquid was poured into water (100 cc.) containing a small amount of sodium hydrosulfite, and the mixture was extracted with petroleum ether (50 cc., b. p. 60–68°). The extract was washed with water and then twice with a solution of potassium hydroxide in 50% aqueous methanol (5%, 50 cc. and 25 cc.) and finally with aqueous methanol (25 cc., 50%). Each of the wash liquids was extracted once with petroleum ether. All the petroleum ether solutions were combined, dried (sodium sulfate), and the solvent was removed. The residual red

oil was refluxed for one and one-half hours with a solution of potassium hydroxide (1.5 g.) in methanol (50 cc.), then poured into water and extracted with petroleum ether. The solvent was removed from the dried extract and the residue was again refluxed with alkali. The final petroleum ether extract was washed once with aqueous methanol (50%), dried, concentrated to a small volume and transferred to a high-vacuum still. The remainder of the solvent was removed, and the residue (13.7 g.) was degassed at 100° under 10 mm. and then distilled at a bath temperature of 185–190° and a pressure of approximately 10^{-5} mm. The distillate of α -tocopherol weighed 10.1 g. (70%).

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.85; H, 11.71. Found: C, 81.14; H, 11.69.

The 3,5-dinitrophenylurethan melted at 145–146°, alone or when mixed with an authentic specimen.¹⁸ The gold chloride titration gave a value 93.1%; the Furter-Meyer assay¹⁹ gave a value of 97.5%. The extinction coefficient for the wave length of maximum absorption was 2.7 ± 0.1 (1 millimole per liter as the unit of concentration; solvent, 95% alcohol). The accepted value for α -tocopherol is 3.05 ± 0.5 . The bio-assay (rats) showed the substance to have a full vitamin E activity with a median dose of between 1 and 3 mg.

Summary

1. This paper describes a synthesis of α -tocopherol from citral in which phytol is not an intermediate. An over-all yield of 4–5% of α -tocopherol can be obtained from citral.

2. Two "isoprene" units are built onto citral in six steps: (a) conversion of citral to pseudionone, (b) a Grignard reaction between pseudionone and a γ -alkoxypropyl halide, (c) reduction of the resulting unsaturated ether to a saturated ether, (d) cleavage of the saturated ether to a saturated C_{16} -bromide, (e) reaction between the Grignard reagent of the C_{16} -bromide and β -chloroethyl methyl ketone to produce a C_{20} -halohydrin structurally comprised of four "isoprene" units with a chlorine atom in the 1-position and a hydroxyl group in the 3-position, (f) condensation of this halohydrin with trimethylhydroquinone to produce α -tocopherol.

3. Each step in the synthesis has been examined and studied in some detail.

4. The synthesis is a general one for 1,3-halohydrins, and the condensation between these halohydrins and hydroquinones is also general, thus opening the way to the synthesis of a great variety of 2,2-dialkyl-6-hydroxychromans.

5. "Phytol ketone" has also been prepared, in excellent yield, from the C_{16} -bromide and acetaldehyde. This ketone can be converted

(19) Furter and Meyer, *Helv. Chim. Acta*, **22**, 249 (1939).

into phytol itself, so that these reactions may constitute the basis for a new synthesis of this alcohol.

6. With "phytol ketone" available, the toco-

pherol synthesis of Smith and Miller⁶ becomes practicable, since it is no longer dependent upon a source of phytol.

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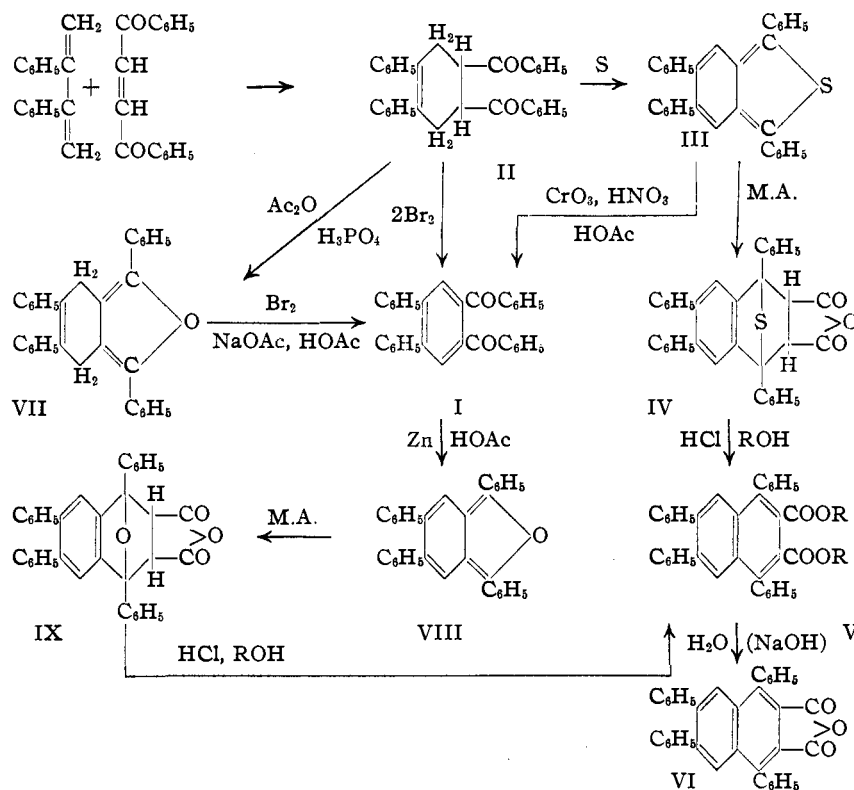
An Instance of the Diene Synthesis with an Isobenzothiophene

BY C. F. H. ALLEN AND J. W. GATES, JR.

4,5-Diphenyl-1,2-dibenzoylbenzene I was needed for use as a reference compound in some other work. The obvious way to secure this substance was by means of the diene synthesis, adding dibenzoyl ethylene to 2,3-diphenylbutadiene, and dehydrogenating; it is known that dibenzoyl ethylene can be added to dienes.^{1,2} The desired addition compound II was readily obtained, but when it was heated with sulfur for dehydrogenation, the product was bright yellow, with a strong greenish fluorescence. It was subsequently found to contain an atom of sulfur, which fact at once suggested that it was an isobenzothiophene III, by analogy with similar properties of isobenzofurans.^{3,4,5}

Like other thiophenes it fails to add methyl iodide nor is it oxidized to a sulfone, but it does add maleic anhydride. The new addition product IV is the first instance of the isolation of a substance containing a sulfur atom as a bridge across a six-membered ring. Other attempts to employ thiophenes in the diene synthesis have been unsuccessful⁶ or the sulfur has been eliminated as hydrogen sulfide⁷ during the reaction.

The sulfur-bridged substance dissociates into its components at its melting point (245°). It is very sparingly soluble in most solvents. When an alcoholic suspension is saturated with hydrogen chloride and heated for four hours, hydrogen sulfide is evolved and the anhydride is converted to



an ester; without isolation, the ester V was hydrolyzed by sodium hydroxide, and, upon acidification, the anhydride VI of 1,4,6,7-tetraphenylnaphthalene-2,3-dicarboxylic acid resulted. The sulfur bridge was not removed by lead salts, nor did it add methyl iodide or methyl *p*-toluenesulfonate under any conditions.

In contrast to the 4,5-dialkylated addition products, the diphenyl analog does not add bro-

- (1) Adams and Geissman, *THIS JOURNAL*, **61**, 2083 (1939).
- (2) Adams and Gold, *ibid.*, **62**, 56 (1940).
- (3) Dufraisse and Priore, *Bull. soc. chim.*, [5] **5**, 502 (1938).
- (4) Barnett, *J. Chem. Soc.*, 1326 (1935).
- (5) Norton, *Chem. Rev.*, **31**, 474 (1942).
- (6) Dufraisse and Daniel, *Bull. soc. chim.*, [5] **4**, 2063 (1937).
- (7) Clapp, *THIS JOURNAL*, **61**, 2733 (1939).