α,α-Diphenyldiethylene glycol, Ia. To the Grignard solution resulting from the treatment of 12.2 g. (0.5 mole) of magnesium with 78.5 g. (0.5 mole) of bromobenzene in 200 cc. of ether was added with vigorous stirring, 15.2 g. (0.15 mole) of monomeric *p*-dioxanone dissolved in 50 cc. of dry benzene. The rate of addition was such as to cause gentle reflux. The reaction mixture was hydrolyzed with ice and aqueous ammonium chloride, and the product extracted with ether which was evaporated to yield 40.9 g. of crude product. Repeated recrystallization from water-ethanol gave 19.9 g. (51% yield) of a pure product, m.p. 109.0–109.2°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02; mol. wt. 258. Found: C, 74.63; H, 7.29; mol. wt., ebullioscopic in benzene, 250.

α,α-Di-p-chlorophenyldiethylene glycol, Ib. Prepared as above from Grignard reagent from 0.15 mole of *p*-bromochlorobenzene and 0.07 mole of *p*-dioxanone. Product recrystallized from ethanol-water weighed 6.2 g. (0.019 mole), yield 27%, m.p. 108.5–109°.

Anal. Calcd. for $C_{16}H_{16}O_3Cl_2$: C, 58.73; H, 4.93. Found: C, 58.95; H, 4.80.

α,α-Di-p-tolyldiethylene glycol, Ic. Use of the Grignard reagent from *p*-bromotoluene as above gave a 26% yield of product recrystallized from water-ethanol, then from petroleum ether, m.p. 91–91.5°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.51; H, 7.74. Found: C, 75.48; H, 7.88.

2,2-Diphenyl-p-dioxane, IIIa. A solution of 0.903 g. (0.0035 mole) of Ia dissolved in 50 cc. of dry benzene to which 3 g. of anhydrous calcium chloride had been added was saturated with anhydrous hydrogen chloride and allowed to stand for 24 hr. The solvent was removed by aspirator and the product recrystallized from petroleum ether to give 0.251 g. (0.00105 mole) of white crystals, m.p. 119.5–120. Yield 30%.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.77; H, 6.65.

A melting point of 121° has been reported for 1,1-diphenylethylene glycol,[8] a conceivable product of this reaction. The latter was prepared and shown to be different from IIIa by mixed melting point.

2,2-Di-p-chlorophenyl-p-dioxane, IIIb. The product was recrystallized from absolute ethanol, m.p., 78–79°. Yield, 12%. Unchanged starting material recovered by evaporation of the solvent amounted to 77%.

Anal. Calcd. for $C_{16}H_{14}O_2Cl_2$: C, 62.2; H, 4.53. Found: C, 61.49; H, 4.77.

2,2-Di-p-tolyl-p-dioxane, IIIc. M.p., 94.2–95.5; yield, 30%.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.46. Found: C, 80.42; H, 7.55.

2,2-Di-p-anisyl-p-dioxane, IIId. When the preparation of 2,2-di-*p*-anisyldiethylene glycol from *p*-dioxanone and *p*-anisylmagnesium bromide was attempted, the product had a carbon content quite different from that of the glycol, but close to that of the corresponding dioxane. The yield was 54%. Repeated crystallization from ethanol, methanol, and petroleum ether gave a product of fair purity. A satisfactory analytical sample, obtained by sublimation, melted at 106.5–107.2°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.67. Found: C, 72.30; H, 6.90.

Acknowledgment. Thanks are given to the Abbott Foundation of Northwestern University for financial aid and to Union Carbide Chemicals Corp. for a small sample of *p*-dioxanone.

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Unsaturated Fatty Acids. V. Preparation of α- and γ-Linolenic-1-C^{14} Acids[1]

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Received January 13, 1958

The decarboxylation-reconstitution technique developed[2] in this laboratory and employed[3,4] in the synthesis of oleic- and linoleic-1-C^{14} acids has now been applied to the problem of labeling two trienoic acids, α- (or the common) linolenic (all-*cis*-9,12,15-octadecatrienoic) and γ-linolenic (all-*cis*-6,9,12-octadecatrienoic), with C^{14} in the carboxyl group. Use of these labeled substances in studies of *in vivo* interconversions of polyunsaturated fatty acids has been described elsewhere.[5]

EXPERIMENTAL

All melting points are corrected. Reported *trans*-contents of olefinic substances, based on infrared absorption at 10.3μ, are considered to be within 5% of actual values.

Ultimate analyses were performed by Dr. A. Elek (Elek Micro Analytical Laboratories, Los Angeles) and infrared absorption analyses by Mr. Paul Kratz. Radioactivities were determined by Dr. J. F. Mead and by Mr. W. H. Slaton, Jr.

9,10,12,13,15,16-Hexabromostearic acid (α-I), m.p. 182.8–183.4°, was prepared by bromination of linseed oil fatty acids (kindly supplied by the Archer-Daniels-Midland Co.) essentially as described by McCutcheon,[6] except that butanone (16.5 ml. per g.) was found to be superior to dioxane as a crystallization solvent. Treating α-I in tetrahydrofuran with diazomethane in benzene gave *methyl 9,10,12,13,15,16-hexabromostearate,* m.p. 154.2–155.3° (recrystallized from butanone).

Anal. Calcd. for $C_{19}H_{32}Br_6O_2$: C, 29.56; H, 4.18; Br, 62.12. Found: C, 29.68; H, 4.16; Br, 62.18.

6,7,9,10,12,13-Hexabromostearic acid (γ-I) was obtained by bromination of the mixture of fatty acids produced by saponification of the oil extracted from seeds of the evening primrose, *Oenothera Lamarckiana*,[7] using a procedure developed by Dr. James F. Mead. In batches of about 300 g. each, 5 lbs. of dry seed (Vaughan Seed Co., Chicago) was crushed by shaking mechanically with porcelain balls (0.5–1 inch dia.) in 3 (dia.) by 10 inch tin cans for 3 hr. (Ball-mill treatment of the seeds was ineffective.) The crushed seeds were then steeped 48 hr. in 4 l. of light petroleum ether (30–60° or 60–70°), the mixture was filtered, and the dried filter cake was recrushed and reextracted twice. Evaporation of the combined yellow extracts (*in vacuo* under nitrogen) left 541 g. (23.8% by weight) of oil, which was refluxed

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[1] This paper is based on work performed under Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

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40 min. in 2.8 l. of methanol (in which 1.6 g. of sodium had previously been dissolved), diluted with a solution of 250 g. of potassium hydroxide in 1.7 l. of methanol and 500 ml. of water, and let stand overnight under nitrogen at room temperature. Diluted with an equal volume of water and extracted with petroleum ether, the mixture yielded 2.65 g. (0.49% by weight) of unsaponified material. The aqueous phase was acidified and re-extracted with petroleum ether and the extracts washed with water, dried over magnesium sulfate, and freed of solvent *in vacuo* at 60–70°, giving 503.5 g. of mixed fatty acids, brown-orange semisolid at 4°. (Concentration of the more highly unsaturated fatty acids at this point by crystallization of the more saturated components from a 10% solution in acetone at −65°[8] resulted in somewhat lower yields of γ-I and no apparent advantage from the standpoint of purity of the product.) In two approximately equal batches, the mixed fatty acids were dissolved in 3 l. of dry ether containing 0.5 g. of 2,6-di-*tert*-butyl-*p*-cresol, cooled to 0°, treated with bromine until color persisted (about 85 ml. was required), and let stand in a refrigerator overnight. Filtered off, washed thoroughly with ether, and air-dried, the crude γ-I weighed 63.15 g. and melted at 192–196°; recrystallization from 1.4 l. of butanone gave 36.24 g. of pure γ-I, m.p. 200.0–200.8° (lit.[7,8] m.p. 196°).

The yield of this most insoluble of the four diastereoisomeric hexabromides produced in unknown relative amounts by *trans*-addition of bromine to γ-linolenic acid was 38.8%; reversed-phase-chromatographic analysis[9] of *Oe. Lamarckiana* seed oil fatty acids showed the presence of 1.4% stearic, 15.7% oleic and palmitic (unresolved), 75.7% linoleic, and 6.8% γ-linolenic acids.

A small sample of γ-I in tetrahydrofuran was treated with ethereal diazomethane to give *methyl 6,7,9,10,12,13-hexabromostearate*, small prisms from acetone, m.p. 170.5–171.5° (melt brown).

Silver hexabromostearates (II). The low solubility of the hexabromostearic acids necessitated use of special solvents in order to obtain high yields of silver salts of satisfactory purity. In a typical preparation of α-II, 15.16 g. (0.02 mole) of α-I was dissolved in 200 ml. of redistilled tetrahydrofuran and treated dropwise during 5–10 min. with a solution of ammoniacal silver nitrate prepared by diluting a solution of 3.40 g. (0.02 mole) of silver nitrate in 5 ml. of redistilled acetonitrile with 10 ml. of methanol and adding another of 0.02 mole of anhydrous ammonia in 13.7 ml. of methanol. The resulting white paste was stirred 30 min. and the solid filtered off, washed with 50 ml. each of tetrahydrofuran and methanol, and dried *in vacuo*, giving 16.67 g. (96.4%) of α-II of purity adequate for use in the Borodin degradation. Analyses of a number of such products indicated some coprecipitation of the free acid with the desired silver salt.

Anal. Calcd. for $C_{18}H_{29}AgBr_6O_2$: Ag, 12.47. Found: Ag, 11.48, 11.75, 11.59.

Similarly, 25.21 g. (33.3 mmol.) of γ-I gave a 98.5% yield of white γ-II containing 11.18% Ag.

Heptabromoheptadecanes (III). A stirred slurry of 24.93 g. (0.02883 mole) of α-II (dried *in vacuo* over P_2O_5) in 500 ml. of dry carbon tetrachloride was treated during about 30 min. under reflux with bromine until a slight excess was indicated by persistent color; 650 ml. of carbon dioxide was evolved (theory 646 ml.). After cooling, the mixture was filtered and the filter cake triturated with three 50-ml. portions of tetrahydrofuran to give 7.61 g. of soluble regenerated crude α-I and 6.1 g. (88%) of insoluble silver bromide. The reaction mixture filtrate was decolorized with aqueous sodium sulfite, washed free of mineral acid with water, dried over magnesium sulfate, and freed of solvent, leaving 13.0 g. of white semisolid residue which was taken up in 300 ml. of warm carbon tetrachloride and chromatographically resolved (in two batches) by passage through a 7.4 (dia.) × 26.0 cm. column of silicic acid. Carbon tetrachloride eluted a total of 9.29 g. (40.6%) of crude α-III. The more polar components of the mixture were eluted with acetone and titrated (in tetrahydrofuran) to estimate content of regenerated α-I. Semiquantitative analyses indicated formation of 9.5% (from α-II) of Simonini ester and of 41.8% of α-I. Recrystallization of the crude α-III from 125 ml. of acetone gave 4.87 g. of α-III, m.p., 154.6–155.6° which was recrystallized again (from 100 ml. of acetone) to give 4.095 g. of pure 1,8,9,11,12,14,15-(α)-III, m.p. 155.0–156.0°.

Anal. Calcd. for $C_{17}H_{29}Br_7$: C, 25.75; H, 3.69; Br, 7056. Found: C, 25.98; H, 3.66; Br, 70.30.

Exhaustive crystallization of a similarly prepared 4.39-g. sample of crude (CCl_4-eluted) α-III (shown by infrared examination to be free of C=O-group-containing components) left 1.69 g. (38.5%) of viscous yellow oil, about 1.5 g. of which was soluble in 25 ml. of boiling pentane. Chromatography of 0.51 g. of this pentane-soluble material on silicic acid gave 0.44 g. of oil (eluted readily by carbon tetrachloride, but not by at least 4.5 column volumes of pentane) which probably contains lower-melting stereoisomers of α-III but also (as shown by the following analyses) significant amounts of higher bromides presumably arising *via* substitution during the Borodin reaction.

Anal. Found: C, 24.57; H, 3.29; Br, 73.74.

In the preparation of 1,5,6,8,9,11,12-(γ)-III, attempts were made to avoid vexing solubility problems by use of the modified Borodin reaction of Rottenberg[10] in which a mixture of the *free* fatty acid and silver trifluoroacetate is used instead of the silver salt of the fatty acid. However, as will be discussed in greater detail elsewhere, this technique involves rather extensive and previously unrecognized side reactions. Essentially as described above in the preparation of α-III, 28.36 g. of γ-II (89.5% by Ag analysis) in 700 ml. of carbon tetrachloride was treated with bromine, permanent color being obtained when only about 60% of a molecular-equivalent amount had been added. Of the 21.4 g. of carbon tetrachloride–insoluble solid filtered from the reaction mixture, 15.5 g. was soluble in hot tetrahydrofuran and presumed to be regenerated γ-I. After it had been decolorized by shaking with aqueous sodium bisulfite, washed free of acid with water, and dried, the carbon tetrachloride solution of the other reaction products was chromatographed to give 7.25 g. (31.1% based on γ-II) of crude γ-III eluted from silicic acid with carbon tetrachloride; recrystallization from about 300 ml. of acetone gave 3.205 g. of γ-III, m.p. 184.0–184.6°. An analytical sample melted at 186.4–187.6°.

Anal. Calcd. for $C_{17}H_{29}Br_7$: C, 25.75; H, 3.69; Br, 70.56. Found: C, 25.84; H, 3.71; Br, 70.43.

In another experiment, after γ-III and related polybromohydrocarbons had been eluted from the silicic acid column with carbon tetrachloride, 3% tetrahydrofuran in carbon tetrachloride eluted a viscous oil, analysis of which approached consistency with that expected for the Simonini ester, 5,6,8,9,11,12-hexabromoheptadecyl 6,7,9,10,12,13-hexabromostearate.

Anal. Calcd. for $C_{35}H_{58}Br_{12}O_2$: Br, 65.25. Found: Br, 69.77.

Mother liquors from crystallization of various preparations of γ-III were combined, freed of solvent, extracted with pentane, and the pentane-soluble material chromatographed on silicic acid to give an oil eluted slowly by petroleum ether and rapidly by 20% carbon tetrachloride in petroleum ether. The infrared spectrum of the oil (in carbon tetrachloride) agreed well with another of crystalline γ-III (in potassium bromide pellet) and its analysis supported designation as isomeric γ-III (in contrast to evident over-bromination of similar material isolated in the α-series studies).

Anal. Calcd. for $C_{17}H_{29}Br_7$: Br, 70.56. Found: Br, 70.09.

1-Bromoheptadecatrienes (IV). A suspension of 5.0 g. of

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(8) *Cf.* J. P. Riley, *J. Chem. Soc.*, 2728 (1949).

(9) *Cf.* J. F. Mead, *J. Biol. Chem.*, **227**, 1025 (1957).

(10) M. Rottenberg, *Helv. Chim. Acta*, **36**, 1115 (1953).

20-mesh zinc (preactivated by treating with concentrated aqueous hydrobromic acid) and 6.85 g. (8.64 mmol.) of α-III in 70 ml. of absolute ethanol was refluxed for 7 hr. (Remaining chunks of white solid were crushed after 50 min. of refluxing, and all α-III had dissolved in 90 min.; continued refluxing with zinc is probably responsible for the conversion of IV to bromine-free material and should therefore be avoided.) Isolated as described earlier in detail,[3] the product was distilled (short-path apparatus, at 0.01μ) to give 2.55 g. of oil, b.p. (bath temperature) 80–110°; from analysis of another product prepared in the same way and thus indicated to be contaminated with about 6.5% of bromine-free material, the yield of crude α-IV is estimated to be about 88%. Assuming the bromine-free contaminant to be heptadecatriene (produced by zinc reduction of IV) and hence more volatile than the desired product, the crude α-IV was freed of a small fraction, b.p. up to 116° (bath temperature) at 0.03μ, and the residue, predominantly all-*cis*-8,11,14-(α)-IV, n_D^{25} 1.4885, d^{25} 1.0134, analyzed and used in the preparation of α-linolenic-1-C^{14} acid.

Anal. Calcd. for $C_{17}H_{29}Br$: C, 65.17; H, 9.33; Br, 25.50. Found: C, 65.87; H, 9.34; Br, 24.80.

Infrared examination of a similar preparation of α-IV indicated the presence of 12% *trans* olefin (*i.e.*, on the average, one of the three double bonds in 12% of the material has the *trans* configuration), while ultraviolet absorption revealed 1.4% conjugated diene and 0.6% conjugated triene. The extent of double bond isomerization indicated by these analyses is typical of polyenes of this kind submitted to bromination-zinc-debromination.[11]

Similarly, refluxing 6.59 g. (8.31 mmol.) of γ-III with zinc in ethanol for 8.67 hr. (probably overly long—all γ-III had dissolved in 3.17 hr.) gave 2.1 g. of crude γ-IV; b.p. 120–135° (bath temperature) at 0.1μ. Analysis of the oil indicated the presence of 11.3% bromine-free material; yield of γ-IV is thus estimated to be 72%. Ultraviolet examination of this predominantly all-*cis*-5,8,11-(γ)-IV revealed the presence of 0.75% conjugated diene and 0.025% conjugated triene. Inasmuch as the bromine-free contaminant was expected to be inert in subsequent operations and to be easily and cleanly separable by chromatography from the ultimate fatty acid ester, no further effort was expended on purification of these samples of IV.

Zinc-debromination of a 350-mg. sample of chromatographically purified "*isomeric*" (oily) γ-III (see above) gave a product (twice distilled, but without fractionation) containing 96% γ-IV (by bromine analysis), possibly reflecting the benefit of a shorter reaction (5.5 hr.). The origin of this non-crystalline γ-III is perhaps most evidently explained on the basis of racemization (during the Borodin reaction) to give *erythro* vicinal dibromide groups which, with zinc, would yield *trans* double-bonds. It is therefore surprising that the sample of γ-IV prepared from this oily γ-III contained but 8–10% *trans* material. Conjugated polyenes were, however, present in comparatively large amounts (0.76% diene, 0.48% triene, and 0.21% tetraene).

In confirmation of the 5,8,11-structure of γ-IV, the material obtained by debromination of the oily γ-III was ozonized and the monocarboxylic acid fraction of the products shown by paper chromatography to consist solely of *n*-hexanoic acid. (The presence of small amounts of *n*-valeric acid would not have been detected under the conditions employed.)

Linolenic-1-C^{14} acids and methyl linolenates-1-C^{14}. Using techniques described in detail before,[3,4] 1.0783 g. (3.34 mmol.) of α-IV (97.2% by bromine analysis) was converted in 63% yield to the corresponding Grignard reagent, which was treated with 2.90 mmol. of carbon dioxide containing 1.993 mc. of C^{14}. By titration of an aliquot of the crude reaction product, formation of a 64% yield (based on Grignard) of acidic material was indicated. The ether-soluble fraction of the product was treated with excess diazomethane and the resulting material chromatographed on silicic acid–Celite (3:1 by weight), using a 3.4 (dia.) × 14.0 cm. column; successive column volumes of petroleum ether eluted 340 mg., 5 mg., and a trace of very weakly adsorbed material (heptadecatriene present in the α-IV and C_{34} hydrocarbon formed by Wurtz coupling during the formation of the Grignard reagent); 3% ether in petroleum ether eluted 10 mg., 320 mg., 80 mg., 10 mg., and a trace more of the desired ester; negligible amounts of material were eluted by 10% ether in petroleum ether; and acetone (two column volumes) eluted 70 mg. of strongly adsorbed material. The chromatographically pure ester, *methyl α-linolenate-1-C^{14}*, was obtained in 91% yield (based on acid determined by titration of the crude Grignard product) and found by spectroscopic examination to contain 8–12% *trans* material, 3.3% conjugated diene, 0.25% conjugated triene, and 0.5% conjugated tetraene; the ester is thus about 84% all-*cis*-9,12,15-linolenate. A 10.2-mg. sample of the substance was diluted with 849 mg. of corn oil, plated on lens paper, and counted (thin-window G.M. tube) to establish an activity of 2.01 mc./g. of the undiluted ester.

In the same way, 1.0519 g. (2.98 mmol.) of γ-IV (88.7% by bromine analysis) gave a 66% yield of Grignard, 1.83 mmol. of which was treated with 2.56 mmol. of active carbon dioxide (1.945 mc.) to give crude γ-linolenic-1-C^{14} acid (about 82% from Grignard by titration of an aliquot of the mixed products), converted with diazomethane in ether to the corresponding *methyl ester* (0.40 g. or 90% based on the acid, assay 3.55 mc./g.).

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Synthesis and Reactions of *p*-Vinylphenylmagnesium Chloride

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Received January 13, 1958

p-Chlorostyrene in tetrahydrofuran reacts smoothly with magnesium to form *p*-vinylphenylmagnesium chloride. The absence of polymer in the reaction may be attributed to controlled addition, the relative rapidity of the reaction with magnesium or to the stability of the coordination complex formed with the solvent. Under these conditions, monomer concentration remains low throughout the course of the reaction. The organometallic compound has been found to undergo typical Grignard reactions and thus provides a practical method for introducing the *p*-vinylphenyl group into a great variety of nuclei.

Carbonation of *p*-vinylphenylmagnesium chloride gave *p*-vinylbenzoic acid in 80% yield. *p*-Vinylbenzoic acid has been prepared from *p*-cyanostyrene[1] and from *p*-bromostyrene.[2] In the latter case, reaction of *p*-bromostyrene with magnesium

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(11) *Cf.* N. L. Matthews, W. R. Brode, and J. B. Brown, *J. Am. Chem. Soc.*, **63**, 1064 (1941); and J. S. Frankel and J. B. Brown, *J. Am. Chem. Soc.*, **65**, 415 (1943).

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