63-70°) showed some promise but was not explored further.

Reaction of epichlorohydrin and benzyltrimethylammonium chloride. Epichlorohydrin (222.0 g., 2.4 moles) and benzyltrimethylammonium chloride (3.8 g., 0.02 mole) were heated at reflux for 6 hr., and the reaction mixture was cooled and agitated vigorously with water (150 ml.) for 1 hr. Unchanged epichlorohydrin was removed, as previously described, by distillation at reduced pressure under nitrogen. A liquid residue, nonvolatile under these conditions, remained (8.2 g.; oxirane oxygen, 5.6%) (qualitative test for chlorine-positive).

Reaction of hydrogen chloride and glycidyl stearate. To an anhydrous solution of hydrogen chloride in ether (500 ml., hydrogen chloride concentration—0.40*N*), prepared by the method of Swern *et al.*[25] was added a solution of glycidyl stearate (34.0 g; oxirane oxygen, 4.47%) in ether (250 ml.) The resulting solution was allowed to stand at room temperature for 16 hr. and was then washed successively with water, dilute aqueous bicarbonate, and again water until the water washes were neutral to *p*H paper. The ether solution was then distilled on a steam bath and the oily residue (38.6 g.; oxirane oxygen, 0) was allowed to solidify at room temperature. The residue precipitated as a gelatinous solid on recrystallization from aqueous methanol at room temperature. Recrystallization from an ether–petroleum ether (b.p. 30–60°) mixture at −25° gave a crystalline solid which was dried to give "chlorohydrin ester" (presumably a mixture of 3-chloro-2-hydroxypropyl stearate and 2-chloro-3-hydroxypropyl stearate) (n_D^{55} 1.4500).

Anal. Calcd. for $C_{21}H_{41}O_3Cl$: C, 66.90; H, 10.96; Cl, 9.40; OH, 4.51. Found: C, 66.90; H, 10.94; Cl, 9.95; OH, 4.60.

Identification of some by-products in the preparation of glycidyl stearate. (a) *By-products in the reaction of stearic acid and epichlorohydrin.* Stearic acid (142.0 g., 0.5 mole) and epichlorohydrin (370.0 g., 4.0 mole) were heated to 105° and benzyltrimethylammonium chloride (4.1 g., 0.022 mole) was added. The mixture was heated at reflux for 22 min. (no remaining acidity), cooled, and washed twice with water (250 ml.). The epichlorohydrin solution was cooled at 2° overnight and filtered. The filtrate was reserved and the cake slurried twice with methanol (400 ml.) at room temperature, and each time the slurry was cooled at 2° and filtered.

The epichlorohydrin filtrate and the combined methanol filtrates were distilled separately at reduced pressure under nitrogen, and each residue was freed of epichlorohydrin completely by addition of toluene (50-ml. portions) and distillation at reduced pressure. The liquid residues were combined to give mixture (C) (49.6 g.; oxirane oxygen, 0.93%; sap. no., 507; Cl, 27.2%).

Mixture C (32.0 g.) was heated at 40–85° and 0.06–0.07 mm. pressure, and a liquid (D), distilling at 27–30.5° at 0.06 mm., was collected (10.7 g.; $n_D^{35.5}$ 1.4754; oxirane oxygen, 0.21%). D was identified as impure glycerol α-dichlorohydrin from its infrared spectrum and from its phenylurethan (m.p. 72–73°).

The still residue from C, after cooling, was a solid (E). A portion of E was dissolved in warm petroleum ether (b.p. 63–70°), and the solution was allowed to cool to room temperature, giving a second solid which, after two recrystallizations from petroleum ether (b.p. 63–70°) was identified as glycerol monostearate (m.p. 73.5–74.3°).

Anal. Calcd. for $C_{21}H_{42}O_4$: C, 70.34; H, 11.81; OH, 9.48. Found: C, 70.32; H, 11.91; OH, 9.09.

Another portion of E dissolved in petroleum ether (b.p. 63–70°) the cooled mixture filtered, and the filtrate evaporated to dryness gave a solid which was recrystallized from methanol. The infrared spectrum of this solid was identical with that of authentic "chlorohydrin ester" prepared by reaction of hydrogen chloride and the glycidyl stearate.

(b) *By-products in the reaction of sodium stearate and epichlorohydrin.* Sodium stearate (153.0 g., 0.5 mole) and epichlorohydrin (740.0 g., 8.0 mole) were heated to reflux, and benzyltrimethylammonium chloride (9.3 g., 0.05 mole) was added in one batch. The mixture was heated at reflux for 5 min., cooled to 90°, and stirred vigorously with water (500 ml.) for 30 min. The mixture was filtered to remove unchanged sodium stearate (1.5 g.), the phases of the filtrate were separated, and the epichlorohydrin layer was again agitated with water (500 ml.) The washed epichlorohydrin solution was cooled at 2° and filtered. The epichlorohydrin filtrate was reserved, and the cake (144.9 g.) was recrystallized from methanol at 10° to give recrystallized glycidyl stearate (139.1 g.). The methanol mother liquor was distilled at reduced pressure to remove the solvent. The residue, after addition of toluene (50 ml.), was heated to 60° at 15 mm. to remove traces of epichlorohydrin. The resulting solid (2.7 g.) was recrystallized from ether–petroleum ether (b.p. 63–70°) to give a white solid material (oxirane oxygen, 1.58%) which, according to its infrared spectrum, was a mixture of glycidyl stearate and "chlorohydrin ester."

PHILADELPHIA 18, PA.

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[25] D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Synthesis of Arachidonic Acid

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Arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) has been synthesized from acetylenic intermediates. The properties of the methyl ester were found to be practically identical with those of the methyl ester of naturally occurring arachidonic acid.

Linoleic acid (I,$x = 4, y = 2, z = 6$), γ-linolenic acid (I,$x = 4, y = 3, z = 3$) and arachidonic acid (I,$x = 4, y = 4, z = 2$) belong to a group known as

$$CH_3(CH_2)_x(CH{=}CH{-}CH_2)_y(CH_2)_zCOOH$$

I

the essential fatty acids (EFA).[1] It is generally accepted that the all *cis* geometric isomers of these unsaturated fatty acids are the biologically active forms.

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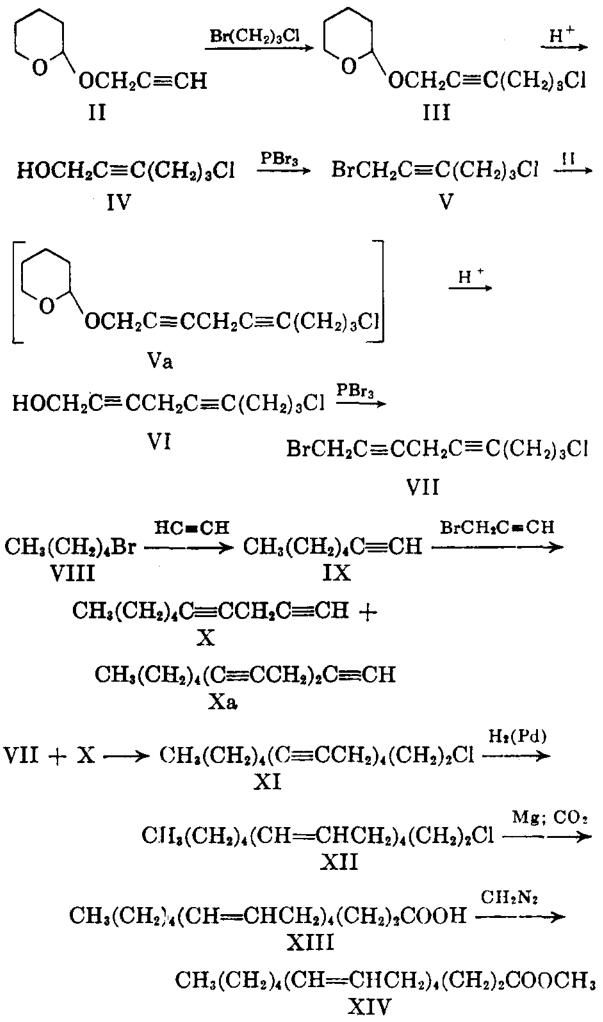
[1] For comprehensive reviews see (a) *The Vitamins,* W. H. Sebrell, Editor, Academic Press Inc., New York, N. Y., 1954, Vol. II, Chapter 7, pp. 267-319; (b) H. J. Deuel and R. Reiser in *Vitamins and Hormones,* Academic Press Inc., New York, N. Y., 1955, Vol. XIII, pp. 29-70; (c) *Essential Fatty Acids,* H. M. Sinclair, Editor, Academic Press Inc., New York, N. Y., 1958.

While linoleic acid is readily available from certain vegetable fats, there is no known comparable source of arachidonic acid. In the animal body arachidonic acid is synthesized mainly from linoleic acid.[2] In serum, arachidonic acid forms part of the cholesterol ester fraction. The amount present seems to be species specific, and has been inversely related to the susceptibility of the species to artificially induced atherosclerosis.[3] This tends to support the earlier suggestion of Sinclair,[4] that a deficiency of the essential fatty acids in the diet may be one of the factors in the etiology of atherosclerosis. Arachidonic acid is thus possibly the most important essential fatty acid for man.

Pure arachidonic acid can be isolated in limited amounts (in the form of its methyl ester) from animal lipids.[5] However, animal lipids are not a practical starting material for the preparation of the large quantities of pure arachidonic acid, which are required for comprehensive biological and nutritional investigations. A synthetic method was desirable for this purpose, and we decided therefore to develop one. At the time our work was started, arachidonic acid had not yet been synthesized. However, in the meantime, a synthesis, which differs from ours, has been described.[6]

The most convenient synthetic route to compounds containing a system of unconjugated double bonds, the structural feature common to the essential fatty acids, is *via* the corresponding acetylenic intermediates. This is the basis of all the known successful efforts in this area, namely the recently reported syntheses of arachidonic and some of the other essential fatty acids,[6] the older published syntheses of linoleic acid[7] and the formal synthesis of linolenic acid as the hexabromide.[8] With the exception of the recently published work on the preparation and properties of "skipped" polyynes,[9] there is no other pertinent literature on the synthetic aspects of these compounds.

Essentially, the synthesis of arachidonic acid developed by us, involved the preparation of two properly constituted diynes: a C_{10} hydrocarbon fragment (X) and a C_9 bromo-chloro fragment (VII). Coupling of these two entities resulted in a C_{19} unconjugated tetrayne (XI), carrying a terminal chlorine atom, which was used as a lever for introducing the twentieth carbon atom in the form of a carboxyl group. This was carried out *via* the corresponding tetraene (XII), as indicated in the following reaction scheme.



$$\text{II} \xrightarrow{Br(CH_2)_3Cl} \text{III} \xrightarrow{H^+}$$

$$\underset{\text{IV}}{HOCH_2C\equiv C(CH_2)_3Cl} \xrightarrow{PBr_3} \underset{\text{V}}{BrCH_2C\equiv C(CH_2)_3Cl} \xrightarrow{II}$$

$$\text{Va} \xrightarrow{H^+}$$

$$\underset{\text{VI}}{HOCH_2C\equiv CCH_2C\equiv C(CH_2)_3Cl} \xrightarrow{PBr_3} \underset{\text{VII}}{BrCH_2C\equiv CCH_2C\equiv C(CH_2)_3Cl}$$

$$\underset{\text{VIII}}{CH_3(CH_2)_4Br} \xrightarrow{HC\equiv CH} \underset{\text{IX}}{CH_3(CH_2)_4C\equiv CH} \xrightarrow{BrCH_2C\equiv CH}$$

$$\underset{\text{X}}{CH_3(CH_2)_4C\equiv CCH_2C\equiv CH} + \underset{\text{Xa}}{CH_3(CH_2)_4(C\equiv CCH_2)_2C\equiv CH}$$

$$\text{VII} + \text{X} \longrightarrow \underset{\text{XI}}{CH_3(CH_2)_4(C\equiv CCH_2)_4(CH_2)_2Cl} \xrightarrow{H_2(Pd)}$$

$$\underset{\text{XII}}{CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2Cl} \xrightarrow{Mg;\ CO_2}$$

$$\underset{\text{XIII}}{CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH} \xrightarrow{CH_2N_2}$$

$$\underset{\text{XIV}}{CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOCH_3}$$

Propargyl alcohol, in the form of 2-propargyloxytetrahydropyran (II), was coupled (lithium in liquid ammonia) with 1-bromo-3-chloropropane to give 1-(tetrahydro-2-pyranoxy)-6-chloro-2-hexyne (III) in 51% yield. Removal of the protecting group by acid catalyzed alcoholysis gave a 49% yield of 6-chloro-2-hexyn-1-ol (IV) which, by reaction with phosphorus tribromide, was converted in 70% yield to 1-bromo-6-chloro-2-hexyne (V). The carbon

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[2] J. F. Mead and D. R. Howton, *J. Biol. Chem.*, **229**, 575 (1957), have demonstrated that in the rat, linoleic acid is converted to arachidonic acid *via* γ-linolenic acid.

[3] L. Swell, H. Field, Jr., and C. R. Treadwell, *Proc. Soc. Expt. Biol. Med.*, **104**, 325 (1960).

[4] H. M. Sinclair, *Lancet*, (1), 381 (1956).

[5] S. F. Herb, R. W. Riemenschneider, and J. Donaldson, *J. Am. Oil Chem. Soc.*, **28**, 55 (1951).

[6] J. M. Osbond and J. C. Wickens, *Chemistry and Industry* (*London*), 1288 (1959).

[7] (a) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950); (b) H. M. Walborsky, R. H. Davis, and D. R. Howton, *J. Am. Chem. Soc.*, **73**, 2590 (1951); (c) W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951).

[8] S. S. Nigam and B. C. L. Weedon, *J. Chem. Soc.*, 4049 (1956).

[9] (a) W. J. Gensler and A. P. Mahadevan, *J. Am. Chem. Soc.*, **77**, 3076 (1955); (b) W. J. Gensler, A. P. Mahadevan, and J. Casella, Jr., *J. Am. Chem. Soc.*, **78**, 163 (1956); (c) W. J. Gensler and A. P. Mahadevan, *J. Am. Chem. Soc.*, **78**, 167 (1956); (d) W. J. Gensler and J. Casella, Jr., *J. Am. Chem. Soc.*, **80**, 1376 (1958); (e) S. S. Nigam and B. C. L. Weedon, *J. Chem. Soc.*, 3868 (1957).

The terminology "skipped" was suggested by Gensler and Mahadevan, (a), to describe unsaturations separated by a single saturated carbon atom. They propose that this word be used in the same way that "conjugated" is used for unsaturations separated by a single bond.

chain was extended to nine carbon atoms by repeating the process. For this purpose, the magnesium derivative of the protected propargyl alcohol (II) was coupled with (V) in a cuprous chloride catalyzed reaction in tetrahydrofuran to give, after alcoholysis of the blocking group of the unpurified intermediate (Va), 9-chloro-2,5-nonadiyn-1-ol (VI) in 62% yield. In a single experiment using unblocked propargyl alcohol[6] this material was obtained in 52% yield. Bromination with phosphorus tribromide gave a 54% yield of 1-bromo-9-chloro-2,5-nonadiyne (VII).

The C_{10} diyne (X) was prepared in two steps. 1-Bromopentane (VIII) and sodium acetylide in liquid ammonia gave a 62% yield of pure 1-heptyne (IX). This material, as the magnesium derivative, was coupled with propargyl bromide in a cuprous chloride catalyzed reaction in ether to give a 64.5% yield of 1,4-decadiyne (X), along with 1,4,7-tridecatriyne (Xa), isolated in 10% yield.

The cuprous chloride catalyzed coupling of 1,4-decadiyne (X), as the magnesium derivative, and 1-bromo-9-chloro-2,5-nonadiyne (VII) proceeded, in ether, to give 26–34% yields of 1-chloro-4,7,10-13-nonadecatetrayne (XI). The reaction also takes place in tetrahydrofuran, but use of this solvent is of no particular advantage. One attempt to obtain the C_{19} tetrayne (XI) by coupling 1,4,7-tridecatriyne (Xa) with 1-bromo-6-chloro-2-hexyne (V) failed. The linearity of the carbon chain of (XI) was confirmed by complete hydrogenation of (XI) to nonadecyl chloride and carboxylation of the latter (*via* the nitrile) to arachidic acid.

We had originally planned to carboxylate the C_{19} tetrayne (XI) *via* the corresponding Grignard compound with CO_2. However, this method proved to be unsuccessful, as was also the attempt to introduce the carboxyl group by way of the nitrile. We decided, therefore, to semihydrogenate the tetrayne (XI) to the corresponding tetraene (XII), and then to introduce the carboxyl group *via* the Grignard compound.[10] Hydrogenation of (XI) in purified petroleum ether proceeded smoothly in the presence of Lindlar's catalyst[11] to give 1-chloro-4,7,10,13-nonadecatetraene (XII), which was converted to the corresponding Grignard reagent without purification (a sample of 1-chloro-4,7,10-13-nonadecatetraene was purified and analyzed later). Carbonation with solid carbon dioxide yielded arachidonic acid (XIII) which, after reaction with diazomethane, was isolated and purified as the methyl ester (XIV). Based on 1-chloro-4,7,10,13-nonadecatetrayne (XI), the yield of the ester (XIV) was 45%.

On complete hydrogenation of the synthetic product, slightly more than the theoretical amount of hydrogen was consumed and methyl arachidate was isolated. The ultraviolet absorption spectrum of XIV showed that a minor percentage of conjugation was present. The infrared spectrum was virtually identical with that shown by a specimen of pure natural methyl arachidonate,[12] the only important deviation being a small peak at 10.3 μ, which is indicative of the presence of some *trans* isomer.

EXPERIMENTAL

Boiling points are uncorrected. Melting points are corrected. The infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer.

All compounds containing more than one unsaturated linkage are extremely unstable in air and, when possible, all transfers, etc., involving these compounds were carried out in an atmosphere of nitrogen. This was facilitated by using a specially constructed clear plastic box equipped with hand-holes fitted with tight-fitting rubber sleeves. An inert atmosphere was maintained by keeping the box under a slight positive pressure of nitrogen after an initial purge of about 15 min.

All reactions and distillations were carried out in a nitrogen atmosphere.

Intermediates were stored in glass-stoppered containers (flushed with nitrogen), which were kept at Dry Ice temperature.

1-Heptyne (IX). This material, b.p. 98–100° (10-inch helix-packed column), n_D^{20} 1.4090, was obtained in 62% yield from 1-bromopentane and sodium acetylide using the procedure described in *Organic Syntheses* for the preparation of 1-hexyne.[13]

1,4-Decadiyne (X). This material was prepared by the method described by Gensler, Mahadevan, and Casella[9b] for the preparation of 1,4-nonadiyne. From 94.0 g. (0.98 mole) of 1-heptyne and 77.0 g. (0.65 mole) of propargyl bromide[14] there was obtained 56 g. (64.5%) of product boiling at 75–77° (12 mm.) as a colorless, mobile liquid; $n_D^{24.5}$ 1.4532. The material became yellow immediately on exposure to air.

The analytical sample distilled at 104° (50 mm.); $n_D^{24.5}$ 1.4515.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.54; H, 10.21.

Infrared (film): 3.05 μ (—C≡CH); cluster of peaks around 4.5 μ (—C≡C—); small peak at 5.15 μ (allenic impurity). Redistillation of a sample after heating at 180° resulted in a 70% recovery of material free of allenic impurity.[9d]

1,4,7-Tridecatriyne (Xa). In one preparation of 1,4-decadiyne from 23.3 g. (0.23 mole) of propargyl bromide and 33.6 g. (0.35 mole) of 1-heptynylmagnesium bromide, after removal of the 1,4-decadiyne, the distillation was continued at a lower pressure. The product, 4.0 g. (10%), was obtained as a colorless liquid which became colored immediately on exposure to air; b.p. 130–132° (8 mm.).

The analytical sample, distilled through a 4-inch Vigreux column, boiled at 65° (0.05 mm.); n_D^{25} 1.4930; infrared (film): 3.05 μ (—C≡CH); cluster of peaks around 4.5 μ (—C≡C); small peak at 5.15 μ (allenic impurity).

Anal. Calcd. for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.20; H, 9.03.

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(10) J. C. Nevenzel and D. R. Howton, *J. Org. Chem.*, **23**, 933 (1958) prepared C^{14} labeled α- and γ-linolenic acids by this method.

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(12) Prepared by Dr. E. Kyburz, F. Hoffmann-LaRoche & Co., Basle, Switzerland.

(13) K. N. Campbell and Barbara K. Campbell, *Org. Syntheses*, **30**, 15 (1950).

(14) Freshly distilled. B.p. 82–83°; n_D^{20} 1.4901.

1-(Tetrahydro-2-pyranoxy)-6-chloro-2-hexyne (III). Lithium amide was prepared in the usual manner[15] by adding 10.5 g. (1.52 moles) of lithium wire to 1500 ml. of liquid ammonia in a 3-l. flask fitted with an air-driven stirrer and a Dry Ice reflux condenser. 2-Propargyloxytetrahydropyran[16] (210 g., 1.5 moles) was added over 30 min. with no external cooling. After stirring for an additional 15 min. at reflux temperature, the reaction mixture was cooled with a Dry Ice–acetone bath (−50°) and 236.5 g. (145 ml., 1.5 moles) of 1-bromo-3-chloropropane was added dropwise over 45 min. The cooling bath was removed, and stirring and refluxing were continued for 4 hr., after which time 75 g. of solid ammonium chloride was added. The Dry Ice condenser was removed and the ammonia was allowed to evaporate into the hood. Water (625 ml.) and then 750 ml. of ether was added, and the mixture was stirred vigorously for 10 min. It was then filtered through a coarse sintered glass funnel covered with a mat of filter aid (Hyflo), and the solid matter was washed with ether. The two phase mixture was separated, the aqueous layer was extracted with 500 ml. of ether which was combined with the original organic phase and, after drying over sodium sulfate, the ether was evaporated *in vacuo*. The dark orange-colored oil was dissolved in 750 ml. of petroleum ether (b.p. 30–60°), and the resulting turbid solution was passed through a large column packed with a slurry of 600 g. of Woelm alumina (neutral grade) in petroleum ether. The column was washed with 1500 ml. of fresh petroleum ether and was allowed to drain completely. The combined eluates were evaporated *in vacuo* and the residual pale yellow oil was stripped under nitrogen through a 6-inch Vigreux column, using a water pump. This operation was stopped when the vapor temperature, which reached a maximum of 80° (18 mm.), started to fall and the distillation rate had decreased markedly. The receivers were changed, and the distillation was continued in higher vacuum to give 166 g. (51%) of the product, a colorless liquid boiling at 110–114° (0.14 mm.); n_{D}^{25} 1.4842.

The analytical sample distilled at 79° (0.025 mm.); n_{D}^{26} 1.4839.

Anal. Calcd. for $C_{11}H_{17}ClO_2$: C, 60.96; H, 7.91. Found: C, 60.71, H, 7.75.

6-Chloro-2-hexyn-1-ol (IV). The combined eluates (after the alumina treatment) referred to above, were stripped of solvent *in vacuo*. The residual crude 1-(tetrahydro-2-pyranoxy)-6-chloro-2-hexyne thus obtained was dissolved in 1000 ml. of methanol, 10 g. of *p*-toluenesulfonic acid monohydrate was added, and the solution refluxed for 2 hr. After cooling below 50°, 10 g. of sodium carbonate was added, the mixture was stirred for 10 min., and the volatile matter distilled *in vacuo* while heat was applied with an 80° water bath. The residue was partitioned between 800 ml. of ether and 800 ml. of water, the ether layer was washed with three 500-ml. portions of water, and then it was dried over sodium sulfate and activated charcoal (Norite A). After evaporating the ether, the residue was distilled from a Claisen flask to give 115 g. of liquid boiling from 52–91° (0.04 mm.). This material was treated again for 2 hr. with 600 ml. of methanol and 5 g. of *p*-toluenesulfonic acid monohydrate and worked up as before. Distillation through a 6-inch Vigreux column gave 97.1 g. (48.8%) of pure product; b.p. 72–74° (0.04 mm.); n_{D}^{26} 1.4870.

The analytical sample distilled at 54° (0.025 mm.); n_{D}^{26} 1.4868.

Anal. Calcd. for C_6H_9ClO: C, 54.35; N, 6.84. Found: C, 54.82; H, 6.97.

1-Bromo-6-chloro-2-hexyne (V). A 1-l. flask equipped with a stirrer, thermometer, dropping funnel, and a vent, protected with a calcium chloride tube, was charged with a solution of 81.7 g. (0.62 mole) of 6-chloro-2-hexyn-1-ol in 250 ml. of anhydrous ether, containing 9.4 ml. of pyridine. The solution was cooled to 0° and, over a 20-min. period, 61.7 g. (21.7 ml., 0.23 mole) of phosphorus tribromide was added. A white precipitate formed. The temperature was maintained at 0° during the addition and also for 1 hr. longer. Then the temperature was allowed to rise to 20° over a 30-min. period and was maintained for 1.5 hr., after which time it was dropped to 0°. Cold hydrochloric acid (100 ml., 2*N*) was added, the layers were separated, and the ether layer was washed successively with 100 ml. of 2*N* hydrochloric acid, 100 ml. of water, 100 ml. of 5% sodium carbonate solution, and finally 100 ml. of water. After drying over sodium sulfate, the ether was stripped off *in vacuo* and the residue was distilled through a 6-inch Vigreux column. The product distilled as a colorless liquid; b.p. 40–43° (0.09 mm.); yield 84.9 g. (70%); n_{D}^{26} 1.5234.

The analytical sample distilled at 38° (0.08 mm.); n_{D}^{26} 1.5230.

Anal. Calcd. for C_6H_8ClBr: C, 36.68; H, 4.12. Found: C, 37.00; H, 4.33.

9-Chloro-2,5-nonadiyn-1-ol (VI). (A) *From 2-propargyloxytetrahydropyran.* Ethylmagnesium bromide, prepared from 10.1 g. (0.42 mole) of magnesium turnings and 47.2 g. (33.3 ml., 0.43 mole) of ethyl bromide in 250 ml. of anhydrous ether, was decanted in a nitrogen atmosphere through a loose plug of glass wool directly into a 2-l. reaction flask. The reaction mixture was diluted with 250 ml. of freshly prepared tetrahydrofuran,[17] which was added from a dropping funnel, and then over 30 min., a solution of 53.6 g. (0.38 mole) of 2-propargyloxytetrahydropyran in 125 ml. of tetrahydrofuran was added. Some heat was liberated. The reaction mixture was stirred and refluxed for 2 hr. It was then cooled to 30°, 0.77 g. of cuprous chloride was added, and refluxing was resumed for 15 min. longer. Finally, a solution of 69.9 g. (0.36 mole) of 1-bromo-6-chloro-2-hexyne in 125 ml. of tetrahydrofuran was added over 15 min., and the mixture was stirred and refluxed for 18 hr. After cooling 250 ml. of saturated ammonium chloride solution and 350 ml. of ether was added. The mixture was vacuum filtered through a mat of filter aid (Hyflo) supported on a coarse sintered glass funnel, the organic layer was washed with three 200-ml. portions of saturated sodium chloride solution and finally, after drying over sodium sulfate, the solvent was stripped *in vacuo*.

The residual oil, crude 1-(tetrahydro-2-pyranoxy)-9-chloro-2,5-nonadiyne, was dissolved in 375 ml. of ethanol, 4.5 g. of *p*-toluenesulfonic acid monohydrate was added, and the dark solution was refluxed for 2 hr. The solvent was stripped *in vacuo*, water and ether (150 ml. of each) were added, and the ether layer was washed with 140 ml. of 5% sodium bicarbonate solution, followed by two 140-ml. portions of 10% sodium chloride solution. After drying over sodium sulfate, the ether was stripped *in vacuo* and the product, 37.8 g. (62%), was distilled through a 4-inch Vigreux column; b.p. 115–118° (0.04 mm.); n_{D}^{26} 1.5101. 9-Chloro-2,5-nonadiyn-1-ol is a colorless liquid which colors rapidly on exposure to air.

The analytical sample distilled at 114° (0.03 mm.); n_{D}^{26} 1.5098; infrared (film): 3.1 μ (OH), cluster of peaks around 4.5 μ (—C≡C—), small peak at 5.15 (allenic impurity).

Anal. Calcd. for $C_9H_{11}ClO$: C, 63.35; H, 6.50. Found: C, 63.67; H, 6.92.

(B) *From propargyl alcohol.* A 2-l. reaction flask was charged with 140 ml. of preformed 3*M* ethylmagnesium bromide[18] solution in ether (0.42 mole of reagent). After dilution by the

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(15) R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, Butterworth's Scientific Publications, London, 1955, p. 193.

(16) R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.*, **75**, 4050 (1953).

(17) The tetrahydrofuran used in all of this work was purified prior to use by passing the material, as received from the vendor, through a column of dry, neutral Woelm alumina (125 ml. of loosely packed alumina per 700 ml. of tetrahydrofuran).

(18) Purchased from Arapahoe Special Products, Inc., Boulder, Colo.

careful addition of 135 ml. of tetrahydrofuran, the solution was cooled in an ice bath, and a solution of 11.2 g. (0.2 mole) of propargyl alcohol in 140 ml. of tetrahydrofuran was added over 35 min. The reaction was vigorous. Additional tetrahydrofuran (70 ml.) was added and the mixture was stirred and refluxed for 2 hr. The resulting clear solution was cooled and 0.4 g. of cuprous chloride was added. After stirring and refluxing for 15 min., a solution of 37 g. (0.19 mole) of 1-bromo-6-chloro-2-hexyne in 70 ml. of tetrahydrofuran was added to the warm solution over 20 min. The mixture was stirred and refluxed for a total of 44 hr. (an extra 0.4-g. portion of cuprous chloride was added after 19 hr.). After cooling, the reaction mixture was diluted with 270 ml. of saturated ammonium chloride solution and then with 350 ml. of ether. The mixture was filtered through a mat of filter aid (Hyflo) supported on a coarse sintered glass funnel, the organic layer was washed with three 150-ml. portions of saturated sodium chloride solution and finally, after drying over sodium sulfate, the solvent was stripped *in vacuo*. Distillation *in vacuo* through a 4-inch Vigreux column gave a main cut of material boiling at 111–114° (0.04 mm.); yield 16.7 g. (52%); n_D^{26} 1.5120.

1-Bromo-9-chloro-2,5-nonadiyne (VII). This material was prepared by the method described for 1-bromo-6-chloro-2-hexyne (V). From 40.7 g. (0.24 mole) of 9-chloro-2,5-nonadiyn-1-ol in 110 ml. of anhydrous ether, containing 3.6 ml. of pyridine, and 23.9 g. (0.089 mole) of phosphorus tribromide, there was obtained 30.1 g. (54%) of the bromide as a pale yellowish oil, after distillation through a 6-inch Vigreux column; b.p. 93–96° (0.06 mm.); n_D^{26} 1.5381. The material darkens rapidly on exposure to air.

The analytical sample distilled at 84° (0.04 mm.); n_D^{26} 1.5381. Infrared (film); cluster of peaks at about 4.5 μ; no allenic absorption at 5.15 μ.

Anal. Calcd. for $C_9H_{10}ClBr$: C, 46.28; H, 4.32. Found: C, 46.58; H, 4.28.

1-Chloro-4,7,10,13-nonadecatetrayne (XI). Ethylmagnesium bromide solution prepared from 1.41 g. (0.058 g.-atom) of magnesium turnings and 7.4 g. (5.2 ml.), of ethyl bromide in 50 ml. of anhydrous ether, was decanted, in a nitrogen atmosphere, through a loose plug of glass wool directly into a 500-ml. reaction flask. A solution of 8.7 g. (0.065 mole) of 1,4-decadiyne in 25 ml. of anhydrous ether was added over 30 min. and the mixture was stirred and refluxed for 1 hr. Cuprous chloride (0.25 g.) was then added. After 15 min., a solution of 10.2. g. (0.044 mole) of 1-bromo-9-chloro-2,5-nonadiyne in 26 ml. of anhydrous ether was added to the refluxing reaction mixture over 10 min. Stirring and refluxing were continued for 69 hr., during which time a heavy yellow precipitate had formed. After cooling with an ice bath, 75 ml. of cold 2*N* sulfuric acid was added, and the mixture was stirred until the two phases were clear. The ether layer was washed twice with 50 ml. of water, then with 25 ml. of a 5% sodium bicarbonate solution and, finally, twice with 50 ml. of water. After drying over sodium sulfate, the ether was stripped off, and the residue was distilled through a short distilling head without a capillary. When full water pump vacuum could be applied, 2.7 g. of colorless liquid (recovered 1,4-decadiyne) distilled at 68–70° (12 mm.), n_D^{26} 1.4531, and was collected in a receiver which was packed in Dry Ice. The distillation was then continued in high vacuum and, after taking a short forerun, the main cut distilled as a tan colored oil from 140–160° (<0.001 mm.). This oil, dissolved in 20 ml. of petroleum ether (30–60°), was filtered through 40 g. of Woelm alumina (neutral), which was packed dry in a 4-inch column, and washed through with 200 ml. of fresh petroleum ether.[19]

The solvent was stripped *in vacuo* and the crude product was distilled first in high vacuum through a short-path, wide-bore distilling flask. The distillate was then redistilled through a 4-inch Vigreux column, giving a pale yellow oil; b.p. 130–137° (<0.001 mm.); yield 3.8 g. (30%); n_D^{25} 1.5084. The analytical sample distilled at 135° (<0.001 mm.); n_D^{25} 1.5053; ultraviolet (isopropyl alcohol) maximum at 270 mμ (ϵ 724); infrared cluster of peaks around 4.5 μ (—C≡C—), no peak at 5.15 μ (allene). The material darkens rapidly on exposure to air and soon resinifies. Material stored in a glass stoppered flask, packed in Dry Ice for 4 months (crystalline at this temperature), was distilled to give a 70% recovery.

Anal. Calcd. for $C_{19}H_{23}Cl$: C, 79.56; H, 8.08. Found: C, 79.36; H, 8.52.

Arachidic acid from 1-chloro-4,7,10,13-nonadecatetrayne. A solution of 2.6 g. (0.009 mole) of 1-chloro-4,7,10,13-nonadecatetrayne in 50 ml. of ethyl acetate was hydrogenated in a Parr low-pressure hydrogenation apparatus over 100 mg. of platinum oxide catalyst. Hydrogen uptake ceased after 15 min., and a pressure drop of 5.0 p.s.i. was observed. (Theory for 4—C≡C—, 5.1 p.s.i.) After work-up, the crude waxy product (2.6 g.) was dissolved in 50 ml. of petroleum ether (b.p. 30–60°), the solution was passed through a column of 30 g. of Woelm alumina (neutral) and the column was eluted with petroleum ether (b.p. 30–60°). The eluates gave, after evaporation of the solvent, 2.1 g. (76%) of 1-chlorononadecane as a colorless oil, which crystallized at room temperature. This material was not analyzed.

A solution of 1.0 g. (0.003 mole) of the above-mentioned 1-chlorononadecane, 0.59 g. (0.0039 mole) of sodium iodide and 0.59 g. (0.012 mole) of sodium cyanide in a mixture of 15 ml. of ethanol, 1 ml. of water and 2 ml. of dimethylformamide was stirred and refluxed for 20 hr. The solvent was evaporated *in vacuo*, and the residue was partitioned between ether and water. The ether layer was evaporated, and the crude crystalline residue (0.74 g.) was dissolved in 20 ml. of ethanol. A solution of 3.5 g. of potassium hydroxide in 3 ml. of water was added, and the mixture was refluxed for 44 hr. Ammonia was liberated from the hot solution. Work-up yielded 0.55 g. (59%) of crude acid. Recrystallized from 3.5 ml. of ethanol, the material melted at 74–75° and gave no depression when mixed with a sample of arachidic acid (synthetic) purchased from Distillation Products Industries, Rochester, N.Y. The infrared spectra (potassium bromide) of the two substances were identical in all respects.

1-Chloro-4,7,10,13-nonadecatetraene (XII). A solution of 1.41 g. (0.0049 mole) of 1-chloro-4,7,10,13-nonadecatetrayne in 60 ml. of purified petroleum ether (b.p. 69–70°)[20] containing a suspension of 1.5 g. of Lindlar's catalyst,[11] was shaken with hydrogen at room temperature. When the reaction was interrupted after 25 min., 460 ml. of hydrogen at 25° (760 mm.) had been absorbed (96% of theory for the formation of 4 double bonds) and the rate had diminished greatly. After filtering the catalyst and stripping the solvent, the product was distilled through a 4-inch Vigreux column to give 1.0 g. (69%) of pure product as a very pale yellow oil; b.p. 96-98° (<0.001 mm.); n_D^{20} 1.4871. Infrared (film); no—C≡C— and a small peak at 10.3 μ (trace of *trans* double bonds). Ultraviolet (isopropyl alcohol); a shoulder from 225–230 mμ (ϵ 380) and an inflection at 260–270 mμ (ϵ 100).

Anal. Calcd. for $C_{19}H_{31}Cl$: C, 77.38; H, 10.70. Found: C, 77.56; H, 11.14.

Methyl eicosa-5,8,11,14-tetraenoate (*methyl arachidinoate*) (XIV). Ethylmagnesium bromide was prepared in a 100-ml. flask from 1.09 g. (0.01 mole) of ethyl bromide, 0.47 g.

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(19) The alumina treatment was introduced to eliminate a small amount of solid matter which codistills with the product. The alumina was packed in a 4-inch jacketed column, which was heated for 2 hr. with steam while a slow stream of nitrogen was passed through the bed during the heating and subsequent cooling periods, to eliminate adsorbed air.

(20) Commercial petroleum ether (63–69°) was purified by shaking four times with concentrated sulfuric acid and then washing with water, sodium carbonate solution, and finally water. It was dried over sodium sulfate and distilled. After a short turbid forerun, the main cut distilled at 69–70° as a clear, colorless liquid.

(0.0194 g.-atom) of magnesium turnings, and 25 ml. of anhydrous ether. Then a solution of 2.5 g. (0.0085 mole) of crude 1-chloro-4,7,10,13-nonadecatetraene in 20 ml. of anhydrous ether was added over 15 min. to the ethylmagnesium bromide and the remaining magnesium. The reaction mixture was stirred and refluxed for 18 hr., after which time only a small amount of magnesium remained, and then it was poured onto a slurry of 75 g. of powdered Dry Ice in 100 ml. of ether.[21] When the temperature had reached about 10°, 50 ml. of saturated ammonium chloride solution was added, and the mixture was shaken with just enough water to dissolve the solids and give two clear phases. The ether layer was washed with four 30-ml. portions of ice water, dried over sodium sulfate, and stripped *in vacuo*. The product, crude arachidonic acid (XIII), was obtained as an orange, unpleasant-smelling oil.

The crude arachidonic acid, dissolved in 50 ml. of ether, was added to 60 ml. of 0.34*M* diazomethane in ether (0.02 moles of diazomethane) and the solution was allowed to stand at 0° for 20 hr. A small amount of gelatinous matter was filtered, and, after stripping the solvent *in vacuo*, the residue was distilled through a 4-inch Vigreux column at <0.001 mm. pressure. The ester, total yield 1.5 g. (45% based on 1-chloro-4,7,10,13-nonadecatetrayne), was obtained as a series of cuts, which boiled from 113–118°, and had refractive indices which ranged from 1.4797 to 1.4810 at 20°. The tail fraction, consisting of about 10% of the total, distilled at 126° (a reflection of the higher bath temperature) and had n_D^{20} 1.4797. All the cuts were only faintly yellow and had an unpleasant odor.

The cut, b.p. 116–118° (<0.001 mm.), n_D^{20} 1.4806,[22] was selected for microanalysis, spectral examination and hydrogenation with the following results:

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.60; H, 11.17. Infrared (Film): peak at 5.76 μ (ester); peak at 6.05 μ (isolated —CH═CH—); small peak at 10.3 μ (some *trans* —CH═CH—). Except for the small peak at 10.3 μ the infrared spectrum of the liquid was essentially identical with that of natural material prepared by Dr. E. Kyburz.[12] Ultraviolet (in isopropyl alcohol): max. at 233–234 mμ (ε 815) and poorly defined maxima or inflections at 264–265 mμ (ε 235), 273–274 mμ (ε 230), and 318 mμ (ε 0.60).

Hydrogenation (platinum, methanol): 240 mg. (mol. wt. 318.6) requires 73.6 ml. at 25° (760 mm.) for four double bonds. Actual uptake 74.2 ml. at 25° (760 mm.). M.p. of hydrogenation product (A), 42°. M.p. of methyl arachidate (B),[23] 45°. Mixed m.p. A + B, 42–45°.

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[21] A. S. Hussey, *J. Am. Chem. Soc.*, **73**, 1364 (1951).

[22] Material isolated from natural sources has been reported to have n_D^{20} 1.47986 (S. F. Herb, R. W. Riemenschneider, and J. Donaldson, footnote 5) and n_D^{20} 1.4786 (Private communication from Dr. E. Kyburz, F. Hoffmann-LaRoche & Co., Basle, Switzerland, footnote 12).

[23] Prepared by esterifying pure synthetic arachidic acid (m.p. 74–75°), purchased from Distillation Products Industries, Rochester, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BARNARD COLLEGE]

Benzylidenepyruvic Acids. IV.[1a] *o*-Nitrobenzylidenepyruvic Acid and Its Enol-Lactone Tautomer

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Acid-catalyzed condensation of *o*-nitrobenzaldehyde with pyruvic acid produces a stable enol-lactone, 2,4-dihydroxy-4-(*o*-nitrophenyl)crotonic acid, γ-lactone (Ia) which is a weak acid. With diazomethane this forms the lactone ether (III) but with methanolic hydrogen chloride, Ia is methylated and tautomerized to the keto ester (IV). Alkaline hydrolysis of IV forms *o*-nitrobenzylidenepyruvic acid (V), a strong acid. Reactions of Ia and V with bromine and with phenylhydrazine are described.

In a recent publication[2a] we reported the determination of a reaction constant *rho*, for the dissociation of a series of benzylidenepyruvic acids with substituents on the benzene ring. The corresponding methyl esters were used to determine a *rho* value for the hydrolysis reaction in alkaline medium. Rate constants were determined spectrophotometrically in weakly alkaline buffers.

In the course of the preparation of the required *o*-nitrobenzylidenepyruvic acid (V) and ester, we found a further example of the lacto-enoic tautomerism recently uncovered for *p*-bromo- and *p*-ethoxy-β-bromobenzylidenepyruvic acids.[2b] When *o*-nitrobenzaldehyde was condensed with pyruvic acid using dry hydrogen chloride as the catalyst, the only product was 2,4-dihydroxy-4-(*o*-nitrophenyl)crotonic acid, γ lactone (Ia), m.p. 138–139°. This is the method described by Baeyer and Drewson,[3] by Heller[4] (m. p. 135–136°) and by Ciusa[4] (m.p. 135–136°). They all believed their product

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[2] (a) E. D. Stecher, F. Dunn, and E. Gelblum, *J. Am. Chem. Soc.*, **79**, 4748 (1957). (b) E. D. Stecher and A. Clements, *J. Am. Chem. Soc.*, **76**, 503 (1954).

[3] A. Baeyer and V. Drewson, *Ber.*, **15**, 2862 (1882); D.R.P. **19768**, Feb. 24, 1882; Frdl. 1, 140.

[4] G. Heller, *Ber.*, **43**, 1924 (1910). R. Ciusa, *Gazz.*, **49**, 168 (1919).