# 590. *Fatty Acids. Part VII.** *The Synthesis of Hexadeca-*8,10-*dienoic, Octadeca*-7,11-*dienoic, and Eicosa*-7,13-*dienoic Acid.*

By F. D. Gunstone and P. J. Sykes.

The *cis,cis*-isomers of the three dienoic acids named in the title and the corresponding diynoic acids have been synthesised.

Natural long-chain polyethenoid acids of lipid origin are mainly of the methylene-interrupted type, *i.e.*, acids such as linoleic, linolenic, and arachidonic, having one methylene group between each pair of olefinic centres. In connection with some oxidation studies,[1] dienoic acids containing the system $-CH{:}CH{\cdot}[CH_2]_n{\cdot}CH{:}CH-$ with $n = 0$, 2, and 4 were required and these have been obtained by synthesis through acetylenic intermediates.

1-Bromohept-1-yne (I) couples with non-8-ynoic acid (II) to give the $C_{16}$ diynoic acid (III) which may be partially reduced to the *cis,cis*-dienoic acid (IV). This coupling is more

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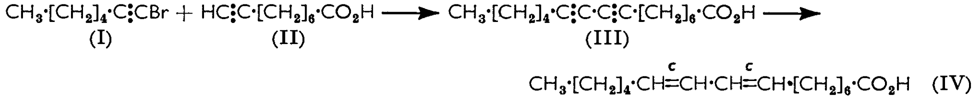
* Part VI, *J.*, 1959, 2137.

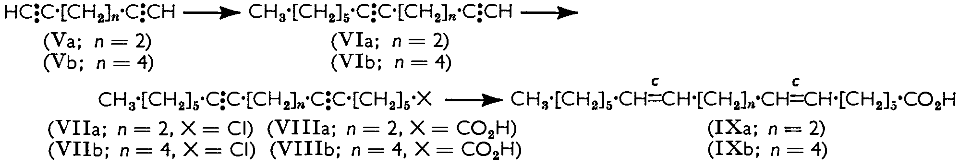
[1] Gunstone and Sykes, (*a*) Part VIII, (*b*) Part IX, the following two papers.

satisfactory [2] than crossed " Glaser " coupling of the two free ethynyl compounds, a procedure much used in the past. In common with other conjugated diynes [3] hexadecadiynoic acid is photolabile in the crystalline state, developing an intense red colour when exposed to light.



$$\underset{\text{(I)}}{CH_3\cdot[CH_2]_4\cdot C{:}CBr} + \underset{\text{(II)}}{HC{:}C\cdot[CH_2]_6\cdot CO_2H} \longrightarrow \underset{\text{(III)}}{CH_3\cdot[CH_2]_4\cdot C{:}C\cdot C{:}C\cdot[CH_2]_6\cdot CO_2H} \longrightarrow CH_3\cdot[CH_2]_4\cdot CH\overset{c}{=}CH\cdot CH\overset{c}{=}CH\cdot[CH_2]_6\cdot CO_2H \text{ (IV)}$$

The $C_{18}$ and $C_{20}$ acids have been prepared from hexa-1,5-diyne (Va) and octa-1,7-diyne (Vb), respectively. The diynes are alkylated, first with a hexyl halide and then with 1-chloro-5-iodopentane, to give the $C_{17}$ and $C_{19}$ diyne chlorides (VII), and these chlorides are converted into diynoic acids (VIII) by the usual sequence of reactions with sodium iodide, sodium cyanide, and potassium hydroxide. Partial hydrogenation in the presence of Lindlar's catalyst then gives the *cis,cis*-dienoic acids.



$$\underset{\substack{\text{(Va; } n = 2)\\ \text{(Vb; } n = 4)}}{HC{:}C\cdot[CH_2]_n\cdot C{:}CH} \longrightarrow \underset{\substack{\text{(VIa; } n = 2)\\ \text{(VIb; } n = 4)}}{CH_3\cdot[CH_2]_5\cdot C{:}C\cdot[CH_2]_n\cdot C{:}CH} \longrightarrow$$

$$\underset{\substack{\text{(VIIa; } n = 2,\ X = Cl)\ \text{(VIIIa; } n = 2,\ X = CO_2H)\\ \text{(VIIb; } n = 4,\ X = Cl)\ \text{(VIIIb; } n = 4,\ X = CO_2H)}}{CH_3\cdot[CH_2]_5\cdot C{:}C\cdot[CH_2]_n\cdot C{:}C\cdot[CH_2]_5\cdot X} \longrightarrow \underset{\substack{\text{(IXa; } n = 2)\\ \text{(IXb; } n = 4)}}{CH_3\cdot[CH_2]_5\cdot CH\overset{c}{=}CH\cdot[CH_2]_n\cdot CH\overset{c}{=}CH\cdot[CH_2]_5\cdot CO_2H}$$

## EXPERIMENTAL

Light petroleum is the fraction of boiling range 40—60°. Gas–liquid chromatography was carried out with a Pye Argon Chromatograph and an Apiezon L column.

1-*Chloro*-5-*iodopentane and* 1-*Chloro*-6-*iodohexane*.—These αω-dihalides were prepared from the corresponding diols by reaction with thionyl chloride to give the dichloride, followed by reaction with sodium iodide as described by Raphael and Sondheimer.[4]

Bromoheptyne was prepared by the method of Strauss, Kollek, and Heyn: [5] 10N-sodium hydroxide (25 ml.) and bromine (5·5 ml.), followed by heptyne [6] (9·6 g.) and stearic acid (300 mg.), were added to ice (50 g.), and the mixture was stirred for 18 hr. Organic material was then extracted with ether and fractionally distilled, to give 1-bromohept-1-yne (16·6 g., 95%), b. p. 55°/10·5 mm., $n_D^{20}$ 1·4598 (lit.,[7] 54·5°/10·5 mm., $n$ 1·4625).

*Non*-8-*ynoic Acid* (II).—A stream of acetylene, purified by passage through a solid-carbon-dioxide trap and two wash-bottles containing concentrated sulphuric acid, was bubbled through liquid ammonia (250 ml.) contained in a three-necked flask. After addition of sodium (5·5 g.), according to the method of Campbell and Campbell,[6] at such a rate that the solution did not become blue, the acetylene was shut off and 1-chloro-6-iodohexane (59·1 g.) was added during 0·5 hr. After a further 4 hours' stirring the mixture was treated with ammonium chloride solution and ether, and 8-chloro-oct-1-yne recovered (28·5 g., 83%), b. p. 73—76°/10 mm., $n_D^{20}$ 1·4560 (lit.,[4] 73—76°/10 mm., $n_D^{12}$ 1·4590).

The chloro-compound (28·5 g.), sodium iodide (30 g.), sodium cyanide (30 g.), and 1 : 4 v/v aqueous ethanol (300 ml.) were refluxed for 48 hr. and then for a similar period after addition of potassium hydroxide (100 g.) and water (150 ml.). Neutral compounds were removed by extraction with light petroleum, and the remaining alkaline solution, after acidification with 30% sulphuric acid at a temperature not exceeding 25°, was re-extracted with light petroleum. Nonynoic acid (28·5 g., 98%) crystallised in large needles, m. p. 18—20° (lit.,[8] 19°).

*Hexadeca*-8,10-*diynoic Acid* (III).—A methanolic solution of 1-bromohept-1-yne (1·75 g.) was added during 15 min. to a solution of nonynoic acid (1·54 g.) and cuprous chloride (60 mg.)

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[2] Chodkiewicz, *Ann. Chim.* (*France*), 1957, II, 852.
[3] Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998.
[4] Raphael and Sondheimer, *J.*, 1950, 2100.
[5] Strauss, Kollek, and Heyn, *Ber.*, 1930, **63**, 1879.
[6] Campbell and Campbell, *Org. Synth.*, 1950, **30**, 15.
[7] Pflaum and Wenzke, *J. Amer. Chem. Soc.*, 1934, **56**, 1106.
[8] Wotiz and Hudak, *J. Org. Chem.*, 1954, **19**, 1580.

in 30% aqueous methylamine (25 ml.) under nitrogen. Hydroxylamine hydrochloride was added in small portions as the reaction proceeded, to keep the copper salt in its reduced form. Stirring was continued for 5 min. after addition was complete, then aqueous potassium cyanide was introduced and unwanted neutral material was extracted with ether. After acidification with 2N-sulphuric acid the $C_{16}$ acid was extracted with ether. The distilled acid (2·48 g., 81% before distillation) melted at 32—34° and became red on exposure to daylight. Microhydrogenation required 3·85 mol. of hydrogen and a gas chromatogram of the reduced product after esterification showed methyl palmitate contaminated only with a little methyl nonanoate (3%). Absorption max. were at 2150 (log ε 2·55), 2260 (2·62), 2390 (2·62), and 2540 Å (2·38) in cyclohexane; Meisters and Wailes [9] report $\lambda_{max.}$ 2135 (log ε 2·70), 2245 (2·69), 2380 (2·60), and 2525 (2·36) for dodeca-4,6-diynoic acid in alcohol. After crystallisation the *diynoic acid* was analysed (Found: C, 77·2; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%).

*Hexadeca*-cis-8,cis-10-*dienoic Acid* (IV).—The diynoic acid (297 mg.) in ethyl acetate (10 ml.) containing a little quinoline (50 mg.) was semihydrogenated (2·02 mol.) by shaking it in an atmosphere of hydrogen with Lindlar's catalyst [10] (300 mg.). Removal of the solvent and catalyst left the diene acid as a low-melting solid, $\lambda_{max.}$ 2340 Å (log ε 4·51 in methanol). Partial oxidation [1a] gave only the expected products apart from a trace of nonanoic acid. The dienoic acid gave a 4-*bromophenacyl ester*, m. p. 74—75° (Found: C, 64·0; H, 7·2; Br, 17·7. $C_{24}H_{33}BrO_3$ requires C, 64·2; H, 7·4; Br, 17·8%).

*Hexa*-1,5-*diyne* (Va).—1,2,5,6-Tetrabromohexane (m. p. 51—52°; lit.,[11] 53—54°) was prepared in 96% yield by the method of Raphael and Sondheimer [12] and was converted into hexa-1,5-diyne (58%; b. p. 86—88°, $n_D^{20}$ 1·4385; lit.,[12] b. p. 87·5—88·5°, $n_D^{23}$ 1·4380—1·4382) by using their directions.

*Dodeca*-1,5-*diyne* (VIa).—Hexadiyne (13·6 g.) in dry ether (15 ml.) was slowly added to a cooled and stirred suspension of sodamide in liquid ammonia (250 ml.) prepared from sodium (4·4 g.) in the presence of ferric nitrate.[13] The mixture was stirred for 1 hr., 1-bromohexane (39 g.) in ether (40 ml.) was then added during 0·5 hr., and the mixture was stirred for a further 6 hr. After addition of ammonium chloride and evaporation of the ammonia the product was extracted and the dodeca-1,5-diyne (6·81 g., 25%), b. p. 100°/20 mm., $n_D^{20}$ 1·4545, was distilled as a pleasant-smelling mobile liquid.

1-*Chloroheptadeca*-6,10-*diyne* (VIIa).—Dodecadiyne (6·81 g.) in dry ether (10 ml.), similarly converted into its sodium derivative and condensed with 1-chloro-5-iodopentane (10 g.), gave 1-chloroheptadeca-6,10-diyne (2·2 g., 20%), b. p. 140—142°/0·5 mm., $n_D^{20}$ 1·4725.

*Octadeca*-7,11-*diynoic Acid* (VIIIa).—The chlorodiyne (VIIa) (2·2 g.) was treated with sodium iodide and sodium cyanide, and then with potassium hydroxide, as described for the preparation of nonynoic acid. The crude diynoic acid (1·65 g., 72%) was purified by distillation (b. p. 158—160°/$10^{-4}$ mm.); the pure *acid* (1·46 g., 64%) melted at 48—48·5° (Found: C, 78·1; H, 10·1. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%). Microhydrogenation required 4·05 mol. of hydrogen and gas chromatography of the product after esterification gave only a single peak corresponding to methyl stearate.

*Octadeca*-cis-7,cis-11-*dienoic Acid* (IXa).—Partial hydrogenation under conditions described above occurred with absorption of 1·95 mol. of hydrogen and furnished the *cis,cis*-dienoic acid (I value 179. Calc., 181) as a low-melting solid. Partial oxidation gave only the expected products.[1a] Bromination gave 7,8,11,12-*tetrabromostearic acid*, m. p. 120—122° (Found: C, 36·1; H, 5·2; Br, 53·1. $C_{18}H_{32}Br_4O_2$ requires C, 36·0; H, 5·4; Br, 53·4%).

*Octa*-1,7-*diyne* (Vb).—Redistilled thionyl chloride (320 ml.) was slowly added to a cooled mixture of tetramethylene glycol (100 g.) and dry pyridine (150 ml.) at such a rate that the temperature of the mixture remained at 25°. The mixture was then heated on a steam-bath for 2 hr., whereafter ice and water were added. The product was extracted with ether and washed with 50% sulphuric acid and with sodium hydrogen carbonate solution, and the 1,4-dichlorobutane (128 g., 91%), b. p. 53—55°/12 mm. (lit.,[14] 54°/12 mm.), distilled.

This dichloride (63·5 g.) was refluxed for 6 hr. with a solution of sodium iodide (150 g.) in

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[9] Meisters and Wailes, *Austral. J. Chem.*, 1960, **13**, 347.
[10] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[11] Ciamician and Anderlini, *Ber.*, 1889, **22**, 2498.
[12] Raphael and Sondheimer, *J.*, 1950, 120.
[13] Vaughn, Vogt, and Niewland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120.
[14] von Braun and Beschke, *Ber.*, 1906, **39**, 4124.

dry acetone (800 ml.). Sodium chloride was precipitated and violent bumping occurred towards the end of the reaction. After addition of water the organic product was extracted with light petroleum and distilled, to give 1,4-di-iodobutane (136 g., 88%), b. p. 120—121°/12 mm., $n_D^{20}$ 1·6140 (lit.,[15] 108—110°/10 mm., $n_D^{20}$ 1·615).

Sodium acetylide was prepared from sodium (30 g.), acetylene, and liquid ammonia and then treated with 1,4-di-iodobutane (136 g.), as described for non-8-ynoic acid. The reaction mixture was subsequently stirred for 9 hr. and set aside overnight before being extracted and distilled, to yield the octadiyne (42 g., 90%), b. p. 94—96°/190 mm., $n_D^{20}$ 1·4465 (lit.,[16] b. p. 93—95°/190 mm., $n_D^{18}$ 1·4521).

*Tetradeca-*1,7*-diyne* (VIb) *and* 1*-Chlorononadeca-*6,12*-diyne* (VIIb).—These were prepared from the octadiyne by condensation with 1-iodohexane and then with 1-chloro-5-iodopentane as described for the conversion of the hexadiyne (Va) into (VIa) and (VIIa). Tetradeca-1,7-diyne (VIb) was obtained in 55% yield as a pleasant-smelling liquid, b. p. 144—146°/23 mm., $n_D^{20}$ 1·4600, and 1-chlorononadeca-6,12-diyne (VIIb), obtained in 70% yield, was also a liquid (b. p. 155—157°/0·5 mm.).

*Eicosa-*7,13*-diynoic Acid* (VIIIb) *and Eicosa-*cis-7,cis-13*-dienoic Acid* (IXb).—The diacetylenic $C_{19}$ chloride gave the diacetylenic $C_{20}$ *acid* when treated with sodium cyanide and potassium hydroxide as already described. The acid (51%) was purified by crystallisation from ethanol and then had m. p. 45·5—46° (Found: C, 78·8; H, 10·5. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%). It absorbed 4·00 mol. on microhydrogenation, and gas chromatography of the product after esterification showed only a single peak, corresponding to methyl arachidate.

Semihydrogenation of the diynoic acid was effected in the presence of Lindlar's catalyst with absorption of 2·02 mol. of hydrogen. The *cis,cis*-dienoic acid was obtained as a low-melting solid, partial oxidation of which gave only the expected products.[1a] Bromination gave 7,8,13,14*-tetrabromoeicosanoic acid*, m. p. 132—134° (Found: C, 38·0; H, 5·9; Br, 51·2. $C_{20}H_{36}Br_4O_2$ requires C, 38·2; H, 5·8; Br, 51·0%).

Infrared absorption at 10·3 mμ showed the three *cis,cis*-dienoic acids (IV, IXa and b) to contain less than 2% of *trans*-olefin.[17]

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[15] Stone and Schechter, *Org. Synth.*, 1950, **30**, 33.
[16] Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619.
[17] O'Connor, *J. Amer. Oil Chemists' Soc.*, 1959, **36**, 627.