542. *Essential Fatty Acids. Part I. Synthesis of Linoleic, γ-Linolenic, Arachidonic, and Docosa-4,7,10,13,16-pentaenoic Acid.*

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The acids named in the title have been prepared by stereospecific partial reduction of the corresponding polyacetylenic acids. The latter were prepared by the condensation of various propargyl bromides with the di-Grignard derivatives of ω-acetylenic acids. This is a new, general, and flexible approach to this type of " skipped " polyenoic acid.

The important group of polyunsaturated fatty acids containing *cis*-ethylenic bonds separated by a methylene group (" skipped " or " methylene interrupted " unsaturation) can be classified into three main groups: those based on (1) linoleic, (2) linolenic, and (3) oleic acid. The first series have the general structure exemplified by (XVIII—XXII) and constitute the " essential fatty acid group." In addition to their nutritional importance[1] they have the property of lowering serum-cholesterol levels[2] and there is evidence[3] that the greater the unsaturation of the acid the more effective it becomes. In this connexion they may have value in the treatment of atherosclerosis. Four representatives of this group have been synthesised by a new and flexible method; they are linoleic acid (XIX); γ-linolenic (octadeca-6,9,12-trienoic) acid (XX), a rare triethenoid acid, isolated only from the seed oil of *Oenothera biennis*[4] and having importance in the biological transformation of linoleic acid into arachidonic acid;[5] arachidonic acid[6] (XXI), probably the most important animal unsaturated acid; and docosa-4,7,10,13,16-pentaenoic acid (XXII), a constituent of brain lipids.[7]

Previous syntheses of linoleic[8] and linolenic[9] (octadeca-9,12,15-trienoic) acid were not entirely satisfactory; a single-step attachment of the carboxyl group to the sensitive

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[1] Deuel and Reiser, *Vitamins and Hormones*, 1955, **13**, 29.

[2] Kinsell *et al.*, in " Essential Fatty Acids," ed. Sinclair, Butterworths, London, 1958, p. 125; Bronte-Stewart, *Brit. Med. Bull.*, 1958, **14**, 243; Hegsted, Gotsis, Stare, and Worcester, *Amer. J. Nutrition*, 1959, **7**, 5.

[3] Worne and Smith, *Amer. J. Med. Sci.*, 1959, **237**, 710.

[4] Eibner, Widenmeyer, and Schild, *Chem. Umschau*, 1927, **34**, 312; Riley, *J.*, 1949, 2728; Nevenzel and Howton, *J. Org. Chem.*, 1958, **23**, 933.

[5] Mead and Howton, *J. Biol. Chem.*, 1957, **229**, 575.

[6] Mowry, Brode, and Brown, *J. Biol. Chem.*, 1942, **142**, 671, 679; Arcus and Smedley-Maclean, *Biochem. J.*, 1943, **37**, 1.

[7] Klenk and Lindlar, *Z. physiol. Chem.*, 1955, **299**, 74; Klenk and Montag, *J. Neurochem.*, 1958, **2**, 233; Herb, Witnauer, and Riemenschneider, *J. Amer. Oil Chemists' Soc.*, 1951, **28**, 505.

[8] Raphael and Sondheimer, *J.*, 1950, 2100; Gensler and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 4601; Walborsky, David, and Howton, *ibid.*, 1951, **73**, 2590.

[9] Nigam and Weedon, *J.*, 1956, 4052.

polyacetylenic chain is required. In a preliminary note[10] we described the condensation of various ω-acetylenic acids, through their di-Grignard complexes, with propargyl halide derivatives; shortly after this, Sarycheva and her co-workers[11] described a similar synthesis of linoleic acid by means of the appropriate ω-acetylenic ester.

In preliminary work undeca-2,5-diyn-1-ol (V) was prepared by the method of Nigam and Weedon.[9] 1-Bromo-oct-2-yne[12] (I) with the Grignard derivative of tetrahydro-2-prop-2′-ynyloxypyran[13] gave the alcohol (V) in moderate yield after acid-hydrolysis. More conveniently, and in high yield, reaction of the di-Grignard complex of propargyl alcohol and the bromide (I) in tetrahydrofuran with cuprous chloride as catalyst gave the same alcohol. Bromination with phosphorus tribromide gave 1-bromoundeca-2,5-diyne (II). This sequence was repeated twice by the second of the two methods just mentioned and the chain extended to give crystalline but unstable alcohols (VI) and (VII) and the corresponding bromides (III) and (IV). The alcohols (V, VI, and VII) were obtained in 83, 69, and 74% yield respectively, and the bromides in 77, 77, 36% yield, respectively; the low yield of the bromide (IV) being due to polymerisation. Purification of the alcohols (VI) and (VII) by crystallisation was important and led to pure bromides; these six products were examined spectroscopically and only traces of conjugated and allenic material were detected. Similarly the bromide (III) and 5-hexyn-1-ol gave eicosa-5,8,11,14-tetrayn-1-ol in 86% yield, identical with the product obtained by reduction of the acid (XVI) with lithium aluminium hydride. Complete catalytic reduction of the alcohols (V) and (VI) and of eicosa-5,8,11,14-tetrayn-1-ol gave undecyl, tetradecyl, and eicosyl alcohol in good yield. After considerable experimentation it was found that condensation of the bromides (I—IV) with the di-Grignard derivatives of various ω-acetylenic acids (VIII—XII) (see Experimental section) was effected most efficiently in tetrahydrofuran at 20° with cuprous cyanide as catalyst. Other solvents, *e.g.*, ether, benzene, and methylene chloride, other catalysts, *e.g.*, cuprous chloride and copper, and different temperatures gave poorer yields. Thus the pairs (I) + (VIII), (I) + (IX), (II) + (X), (III) + (XI), and (IV) + (XII) gave the highly crystalline pure polyacetylenic acids (XIII—XVII) in 50—75% yields. Complete catalytic reduction of each acid (XIII—XVII) gave the saturated acids in 80—95% yield, after a theoretical uptake of hydrogen, thus showing the linearity of the product. The ultraviolet absorption spectra of the acids showed little or no conjugated material, and the infrared absorption showed the expected bands with no allene contaminant. An alternative route to the acid (XVI) was to condense

$CH_3\cdot[CH_2]_4\cdot[C\equiv C\cdot CH_2]_x\cdot Br$

(I) $x = 1$
(II) $x = 2$
(III) $x = 3$; m. p. 5·5—7·5°
(IV) $x = 4$; m. p. 26·5—28°

$CH_3\cdot[CH_2]_4\cdot[C\equiv C\cdot CH_2]_x\cdot OH$

(V) $x = 2$; m. p. 1·2—1·5°
(VI) $x = 3$; m. p. 28—30°
(VII) $x = 4$; m. p. 56—57°

$CH\equiv C\cdot CH_2\cdot[CH_2]_y\cdot CO_2H$

(VIII) $y = 7$
(IX) $y = 6$
(X) $y = 3$
(XI) $y = 2$
(XII) $y = 1$

$CH_3\cdot[CH_2]_4\cdot[C\equiv C\cdot CH_2]_x\cdot[CH_2]_y\cdot CO_2H$

(XIII) $x = 2, y = 7$; m. p. 39·5—41·5°
(XIV) $x = 2, y = 6$; m. p. 45—46°
(XV) $x = 3, y = 3$; m. p. 53—54°
(XVI) $x = 4, y = 2$; m. p. 81—82°
(XVII) $x = 5, y = 1$; m. p. 100—101·5°

$CH_3\cdot[CH_2]_4\cdot[CH{=}CH\cdot CH_2]_x\cdot[CH_2]_y\cdot CO_2H$

(XVIII) $x = 2, y = 7$
(XIX) $x = 2, y = 6$
(XX) $x = 3, y = 3$
(XXI) $x = 4, y = 2$
(XXII) $x = 5, y = 1$

$CH_3\cdot[CH_2]_4\cdot[CHBr\cdot CHBr\cdot CH_2]_x\cdot[CH_2]_y\cdot CO_2R$

(XXIII) $x = 2, y = 6$; R = H, m. p. 114·5—116°; R = Me, m. p. 58—59°
(XXIV) $x = 3, y = 3$; R = H, m. p. 199·5—200°; R = Me, m. p. 175—177°
(XXV) $x = 4, y = 2$; R = H, m. p. 234—235°; R = Me, m. p. 228—229°

$CH\equiv C\cdot CH_2\cdot C\equiv C\cdot[CH_2]_3\cdot CO_2H$

(XXVI) m. p. 18°

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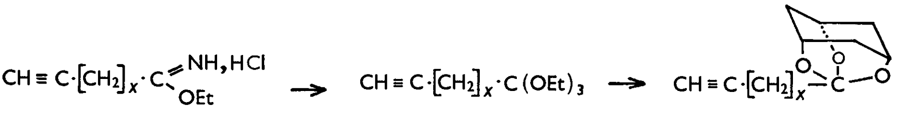
[10] Osbond and Wickens, *Chem. and Ind.*, **1959**, 1288.

[11] Sarycheva, Myagkova, and Preobrazhenskii, *Zhur. obschei Khim.*, 1959, **29**, 2318.

[12] Tchao Yin Lai, *Bull. Soc. chim. France*, 1933, **53**, 682; Wotiz and Webster, *J. Org. Chem.*, 1956, **21**, 1536; Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4263.

[13] Henbest, Jones, and Walls, *J.*, 1950, 3646.

5-hexynoic acid (XI) with propargyl bromide, giving nona-5,8-diynoic acid (XXVI) in 45% yield. The structure of this unstable acid was supported by infrared and ultraviolet absorption spectra and by reduction to nonanoic acid. The di-Grignard derivative of acid (XXVI) with 1-bromoundeca-2,5-diyne (II) under the usual conditions gave the acid (XVI) in 54% yield. The whole process could also be carried out, without isolation of the acid (XXVI), to give the product (XVI) in 55% overall yield [based on bromide (II)].



(XXVII) $x = 3$
m. p. 113° (decomp.)
(XXVIII) $x = 4$
m. p. 97—98° (decomp.)

(XXIX) $x = 3$

(XXX) $x = 4$

(XXXI) $x = 3$
m. p. 53—54°
(XXXII) $x = 4$
m. p. 47—49°

Before the conditions for these condensations had been fully worked out an alternative method of protecting carboxyl groups from Grignard attack, described by Stetter and Steinacker,[14] was investigated. Treatment of 5-cyanopent-1-yne and 6-cyanohex-1-yne in ethanol with hydrogen chloride gave the two imidoyl ester hydrochlorides (XXVII) and (XXVIII), respectively, in good yield. Conversion into the ortho-esters (XXIX) and (XXX) was effected with boiling ethanol–ether or with ethanol at 20°. Transesterification with *cis*-cyclohexane-1,3,5-triol in ethanol was then rapidly achieved with boron trifluoride, or less effectively with hydrogen chloride, to give the crystalline 2,8,9-trioxa-adamantanyl derivatives (XXXI) and (XXXII) in 84% yield. The mono-Grignard derivative from these, reacting with the bromides (III) and (II), gave the protected ortho-esters of the acids (XVI) and (XV) respectively. The protecting group was then removed by acid in tetrahydrofuran–ethanol, to give in low yield the acids (XVI) and (XV) identical with samples prepared by the first method.

Partial hydrogenation of the polyacetylenic acids (XIII—XVII) was fairly extensively examined.* In all cases Lindlar's catalyst [15] was used; it was particularly suitable for obtaining almost pure polyenoic acids with the *cis*-configuration. Different solvents were employed, *e.g.*, light petroleum, benzene and ethanol. It was necessary to have conditions which allowed a rapid uptake of hydrogen at 20° to just over the theoretical value, for the hydrogenation to stop completely, and then to shake the mixture for a further period. The amount of catalyst poison (quinoline) added had to be determined for each reduction. The rate and specificity depend on the type of solvent used, the age of the catalyst (the activity of Lindlar catalyst declines with time), the purity of the substrate (old samples which are slightly oxidised are more difficult to reduce), and the temperature. The polyenoic acids (XVIII—XXII) thus obtained were converted into their methyl and ethyl esters in *ca.* 80% yield for the two steps. The purity of the esters was determined by analysis, iodine value, infrared and ultraviolet spectroscopy, alkali-isomerisation and gas-phase chromatography, the last two techniques being the most valuable and critical. Alkali-isomerisation was particularly useful in detecting small amounts of acetylenic impurity. Details are given in the Experimental section but in all cases the polyene-esters were at least 85—90% pure with little or no conjugated material and only traces of *trans*-isomer. Partial reduction of the corresponding polyacetylenic esters gave slightly more *trans*-isomer under the same conditions. Similarly, partial reduction of eicosa-5,8,11,14-tetrayn-1-ol gave eicosa-5,8,11,14-tetraen-1-ol (arachidonyl alcohol). Bromination of linoleic (XIX), γ-linolenic (XX), and arachidonic acid (XXI) and their methyl

* We acknowledge valuable advice given by Drs. H. Lindlar and S. Shaeren on this stage.

[14] Stetter and Steinacker, *Chem. Ber.*, 1952, **85**, 453; 1954, **87**, 205.
[15] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.

esters gave the known characteristic tetra- and hexa-bromostearic and octabromoarachidic acid and their methyl esters (XXIII—XXV) with melting points in agreement with recorded values.

EXPERIMENTAL

The ultraviolet absorptions were measured for solutions in spectroscopic ethanol. The infrared measurements were carried out on Nujol mulls or liquid films, unless otherwise stated, by Dr. A. Wagland. The method of Herb and Riemenschneider [16] was used for the alkali-isomerisation of the polyenoic esters, unless otherwise stated; some of these determinations were carried out by Dr. S. Weber. Gas-phase chromatography was carried out by Drs. A. R. Moss and J. Würsch on a column of 20% polyethylene glycol adipate (1500) on Celite; temperature 200°; argon 50 c.c./min. at 1 atmosphere; quantity 0·025—0·10 μl.; theoretical plates 3000—4000; a Pye Argon chromatograph was used as a detector.

All reactions and the general handling of all compounds containing more than one triple or double bond were conducted in a nitrogen atmosphere. Distillation residues of polyacetylenic compounds could be thermally unstable and precautions are necessary.

Undeca-2,5-*diyn*-1-*ol* (V).—(*a*) A solution of ethyl bromide (381·5 g., 3·5 moles) in dry tetrahydrofuran (300 c.c.) was added to a stirred suspension of magnesium (76·5 g., 3·15 g.-atom) under tetrahydrofuran (700 c.c.) at 0°; the internal temperature was kept at ~5°. To the Grignard reagent was added propargyl alcohol (89·6 g., 1·6 moles) in tetrahydrofuran (80 c.c.) with stirring at 3—5° during 30—45 min. and then at 20° for 2 hr. The solution was cooled to 5°, cuprous chloride (3·6 g.) was added and, after 15 min., 1-bromo-oct-2-yne [12] (18·9 g., 1·0 mole) in tetrahydrofuran dropwise during 20—30 min. The solution was heated under reflux for 24 hr., more cuprous chloride (2 g.) being added after 16 hr. The solution was added to 2N-sulphuric acid (1·5 l.) and ice, extracted with ether (3 × 400 c.c.), washed with 2N-sodium carbonate (200 c.c.) and water (2 × 200 c.c.), and dried (Na_2SO_4). The *alcohol* distilled at 80—88°/3 × 10^{-3} mm. as a colourless oil (135·8 g., 83%), n_D^{20} 1·4835, m. p. 1·2—1·5°, $\lambda_{max.}$ 267·5 mμ ($E_{1\,cm.}^{1\%}$ 9·21), $\nu_{max.}$ 3400s, 2240—2300w cm.$^{-1}$ (Found: C, 80·4; H, 10·0. $C_{11}H_{16}O$ requires C, 80·45; H, 9·8%). The *α-naphthylurethane* [from light petroleum (b. p. 80—100°)] had m. p. 98—101·5° (Found: C, 79·0; H, 6·8; N, 4·2. $C_{22}H_{23}NO_2$ requires C, 79·25; H, 6·95; N, 4·2%).

(*b*) To ethylmagnesium bromide [from magnesium (8·28 g.) and ethyl bromide (33·7 g.)] in tetrahydrofuran (250 c.c.) was added tetrahydro-2-prop-2′-ynyloxypyran [13] (47·65 g.) at 20° during 0·5 hr. The mixture was heated under reflux for 3 hr. and then treated with 1-bromo-oct-2-yne (58·5 g.) and cuprous chloride (0·9 g.) as described above. The product, after decomposition of the ammonium chloride solution, was extracted with ether and hydrolysed by toluene-*p*-sulphonic acid (2·55 g.) in boiling ethanol (300 c.c.) for 3 hr. The resulting alcohol (17·5 g., 34%) had b. p. 75—80°/9 × 10^{-5} mm., n_D^{22} 1·4821. The infrared spectrum was identical with that of sample (*a*). Complete reduction of a sample (0·5 g.) with Adams catalyst (0·1 g.) in methanol, after an uptake of hydrogen (4 mol.) gave undecan-1-ol, characterised as phenylurethane, m. p. 58—59° (lit.,[17] m. p. 62°) (Found: C, 74·2; H, 10·05; N, 4·8. Calc. for $C_{18}H_{29}NO_2$: C, 74·2; H, 10·0; N, 4·8%).

The following alcohols were prepared essentially as described in (*a*):

Tetradeca-2,5,8-*triyn*-1-*ol* (VI). 1-Bromoundeca-2,5-diyne (1 mole) and the Grignard complex of propargyl alcohol (3 moles) gave the alcohol, b. p. 135—142°/0·08 mm., n_D^{20} 1·5024, that from light petroleum (b. p. 40—60°) at −10° gave buff-coloured crystals, m. p. 28—30° (69%). Owing to the rapid autoxidation several samples gave unsatisfactory analyses (Found: C, 81·8; H, 9·0. Calc. for $C_{14}H_{18}O$: C, 83·1; H, 9·0%). The product had $\lambda_{max.}$ 270 mμ ($E_{1\,cm.}^{1\%}$ 26·0), $\nu_{max.}$ (in CCl_4) 3660m, 3500m, 2220—2300 cm.$^{-1}$. Under nitrogen at 0° the crystalline material degenerates fairly rapidly to give a red-brown polymer; it should be used within 24 hr. Hydrogenation of the alcohol (0·59 g.) over Adams catalyst (0·05 g.) in methanol (10 c.c.) gave, after a rapid uptake of hydrogen (406 c.c.; theor. 390 c.c.), tetradecan-1-ol, m. p. 38—38·5° (lit.,[17] 38°) (74%) {α-naphthylurethane [from light petroleum (b. p. 80—100°)], plates, m. p. 82° (lit.,[18] 82°)}.

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[16] Herb and Riemenschneider, *J. Amer. Oil Chemists' Soc.*, 1952, **29**, 456.
[17] Ralston, " Fatty Acids and Their Derivatives," Wiley and Sons, New York, 1948.
[18] Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 267.

Heptadeca-2,5,8,11-*tetrayn*-1-*ol* (VII), prepared from 1-bromotetradeca-2,5,8-triyne (1 mole) and propargyl alcohol (6 moles) crystallised from light petroleum (b. p. 60—80°) in pale cream needles, m. p. 56—57° (74%) (Found: C, 84·45; H, 8·4. $C_{17}H_{20}O$ requires C, 84·95; H, 8·4%); it had no ultraviolet absorption and $\nu_{max.}$ (in CCl_4) 3680m, 3500m, 2220—2300w cm.$^{-1}$.

Eicosa-5,8,11,14-*tetrayn*-1-*ol*. (i) Condensation of 1-bromotetradeca-2,5,8-triyne (0·15 mole) and 5-hexyn-1-ol (0·27 mole) in tetrahydrofuran with cuprous chloride gave the tetrayne alcohol (m. p. 47·5—50°; 86%); the pure *alcohol* [from ether–light petroleum (b. p. 40—60°)] had m. p. 53·5—54·5° (Found: C, 84·9; H, 9·4. $C_{20}H_{26}O$ requires C, 85·1; H, 9·2%), $\nu_{max.}$ (in CCl_4) 3700m, 3550w, 2240—2280w, 1315s, 1050s cm.$^{-1}$.

(ii) Eicosa-5,8,11,14-tetraynoic acid (1·48 g.) in ether (100 c.c.) was added to lithium aluminium hydride (0·3 g.) in ether (100 c.c.), and the mixture boiled under reflux for 2 hr. After treatment with ethyl acetate (2 c.c.) and 2N-sulphuric acid (50 c.c.) the neutral material was obtained in the usual way and crystallised from ether–light petroleum (b. p. 40—60°) as cream-coloured plates (0·54 g.), m. p. and mixed m. p. 50·5—51·5°. A complete catalytic reduction of the tetrayne alcohol (0·7 g.) with palladised strontium carbonate in the usual way gave eicosan-1-ol, m. p. 65—65·5° (lit.,[17] 65·5°).

1-*Bromoundeca*-2,5-*diyne* (II).—To a solution of undeca-2,5-diyn-1-ol (28·97 g.) and pyridine (0·45 g.) in dry ether (125 c.c.), phosphorus tribromide (17·24 g.) was added dropwise during 0·5 hr. The solution was boiled under reflux for 3 hr., then poured on ice, and the product was extracted with ether and washed with sodium carbonate solution and water, and dried (Na_2SO_4). The bromide distilled at 86—94°/3 × 10^{-3} mm. (31 g., 77%). A portion, redistilled for analysis, had b. p. 64°/10^{-5} mm., n_D^{20} 1·5109 (Found: C, 57·6; H, 6·6; Br, 35·6. $C_{11}H_{15}Br$ requires C, 58·1; H, 6·65; Br, 35·2%), ultraviolet end absorption at 220 mμ, $\nu_{max.}$ 2280w, 2260w, trace of allene showing at 1950 cm.$^{-1}$.

1-*Bromotetradeca*-2,5,8-*triyne* (III).—Tetradeca-2,5,8-triyn-1-ol and phosphorus tribromide gave in a similar way the *bromide* (77%), b. p. 110—125°/2·5 × 10^{-3} mm., n_D^{20} 1·5245, m. p. 5·5—7·5° (Found: C, 63·0; H, 6·5; Br, 30·4. $C_{14}H_{17}Br$ requires C, 63·4; H, 6·5; Br, 30·1%).

1-*Bromoheptadeca*-2,5,8,11-*tetrayne* (IV).—In a similar way heptadeca-2,5,8,11-tetrayn-1-ol gave the corresponding bromide (36%). Before distillation the crude product was extracted with light petroleum (b. p. 40—60°) to eliminate thermally unstable polymer. The *bromide* had b. p. 160—162°/10^{-2} mm., n_D^{20} 1·5281, m. p. 26·5—28° (Found: C, 67·2; H, 6·7; Br, 26·1. $C_{17}H_{19}Br$ requires C, 67·3; H, 6·3; Br, 26·35%), $\nu_{max.}$ 2250w, 2270w cm.$^{-1}$ ($C\equiv C$).

6-*Triethoxyhex*-1-*yne* (XXIX).—To 5-cyanopent-1-yne (23·28 g., 0·25 mole) in absolute ethanol (12·66 g., 0·275 mole) at 0°, dry hydrogen chloride (10·02 g., 0·275 mole) was added. After 3 days at 5° the resulting imidoate hydrochloride (43·4 g.), m. p. 113° (decomp.), was ground with dry ether and filtered off. The hydrochloride (20·57 g.) was boiled in absolute ethanol (115 c.c.) and ether (200 c.c.) for 20 hr. Ammonium chloride (5·9 g.) was then removed, the solution concentrated, and the *orthoester* distilled; it had b. p. 104—106°/14 mm., n_D^{22} 1·4309, (15·43 g., 61%). (Found: C, 67·4; H, 10·5. $C_{12}H_{22}O_3$ requires C, 67·2; H, 10·35%), $\nu_{max.}$ 3330s ($HC\equiv C$), 2130w, 1150s cm.$^{-1}$.

7-*Triethoxyhept*-1-*yne* (XXX).—Similarly 6-cyanohex-1-yne gave the corresponding *ethyl non*-8-*ynimidoate hydrochloride*, m. p. 97—98° (decomp.) (80%) (Found: N, 7·3; Cl, 18·8. $C_9H_{16}ClNO$ requires N, 7·4; Cl, 18·7%). The ester hydrochloride, when kept in ethanol at 20° for 4 days, gave the *orthoester*, b. p. 103—118°/14 mm., n_D^{24} 1·4348 (50%) (Found: C, 68·85; H, 10·1. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%).

1-*Pent*-4′-*ynyl*-2,8,9-*trioxa-adamantane* (XXXI).—To a solution of 6-triethoxyhex-1-yne (11·78 g., 0·055 mole) and *cis*-cyclohexane-1,3,5-triol (6·6 g., 0·05 mole) in absolute ethanol (25 c.c.) was added boron trifluoride (45% solution, 1·5 c.c.). After 2 days at 20°, potassium carbonate (1 g.) was added and the ethanol removed. The *orthoester* crystallised from light petroleum (b. p. 40—60°) as colourless prisms (8·75 g., 84%), m. p. 53—54° (Found: C, 69·6; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%), $\nu_{max.}$ 3300s, 2120w, 1130s cm.$^{-1}$.

1-*Hex*-5′-*ynyl*-2,8,9-*trioxa-adamantane* (XXXII).—In a similar way 7-triethoxyhept-1-yne gave the corresponding *orthoester* (84%), m. p. 47—49° (Found: C, 70·4; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%).

Octadeca-9,12-*diynoic Acid* (XIV).—To magnesium (4·86 g., 0·2 g.-atom) under tetrahydrofuran (50 c.c.) was added ethyl bromide (23·98 g., 0·22 mole) in tetrahydrofuran (20 c.c.) during 1 hr. Reaction was initiated at 20°; the mixture was then cooled to −5° during the addition and later stirred at 20° for 3 hr. Dec-9-ynoic acid (16·8 g., 0·1 mole) in tetrahydrofuran (50 c.c.)

was added during $\frac{3}{4}$ hr. at 0° and the whole was stirred at 20° for 2 hr. Anhydrous cuprous cyanide (0·5 g.) was added, followed after 10 min. by 1-bromo-oct-2-yne [12] (9·45 g., 0·05 mole) in tetrahydrofuran (25 c.c.) during 15 min. at 20°. The mixture was boiled for 24 hr., poured on 2N-sulphuric acid and ice, and the product extracted with ether. The ether was extracted with 2N-ammonia, and the acidic fraction isolated in the usual way. Distillation gave fractions (i) b. p. 80—100°/0·04—0·01 mm. (6·33 g.), (ii) b. p. 100—140°/0·01 mm. (2·15 g.), and (iii) b. p. 143—154°/0·01—0·005 mm. (9·84 g.). The first two fractions were recovered decynoic acid. Fraction (iii) solidified (71%) and after crystallisation from light petroleum (b. p. 40—60°) gave the pure acid as plates (55%), m. p. 45—46° (lit.,[8] 41—43°, 42·6—44·7°) (Found: C, 77·9; H, 10·2. Calc. for $C_{18}H_{28}O_2$: C, 78·25; H, 10·2%), ultraviolet end-absorption at 220 mμ, $\nu_{max.}$ 1715s, 1755w (C=O), 2150w, 2275w cm.$^{-1}$ (C≡C), and no allene band. The *ethyl ester* prepared from the pure acid with methanolic hydrogen chloride at 20° had b. p. 182°/0·3 mm., n_D^{20} 1·4684 (Found: C, 78·45; H, 10·7. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%). The acid (0·25 g.) in methanol (20 c.c.) was hydrogenated over Adams catalyst (0·05 g.) to stearic acid, m. p. and mixed m. p. 69—70° (84%).

Nonadeca-10,13-*diynoic Acid* (XIII).—In a similar way 1-bromoct-2-yne and undec-10-ynoic acid gave the *diynoic acid*, b. p. 172—174°/10^{-3} mm., m. p. 39·5—41·5° (50%) (Found: C, 78·5; H, 10·35. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 1715s, 1755w (C=O), 2300w, and 2125w cm.$^{-1}$ (–C≡C–) (no allene band). The *ethyl ester* had b. p. 160°/2·8 × 10^{-3} mm., n_D^{20} 1·4682 (Found: C, 78·8; H, 10·75. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%), $\nu_{max.}$ 1730s cm.$^{-1}$. Catalytic reduction as above gave (without purification) pure nonadecanoic acid (95%), m. p. 68—69·5° (lit.,[17] 69·5°), as plates (Found: C, 76·2; H, 12·7. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·8%).

Octadeca-6,9,12-*triynoic Acid* (XV).—(i) Similarly 1-bromoundeca-2,5-diyne (0·04 mole) and hept-6-ynoic acid (0·09 mole) were condensed. This reaction was preferably carried out at 20° for 16 hr. It gave a 70—80% yield of the *triynoic acid.* The crude acid (very sensitive to air) was isolated by crystallisation from light petroleum (b. p. 40—60°) at −10° and formed almost colourless plates, m. p. 53·5—55° (Found: C, 79·1; H, 9·0. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·9%), $\lambda_{max.}$ 270 mμ ($E^{1\%}_{1\,cm.}$ 2·8), $\nu_{max.}$ 1700s, 2580m, 935m cm.$^{-1}$. The *methyl ester* had b. p. 140—143°/3 × 10^{-3} mm., n_D^{20} 1·4871 (Found: C, 79·2; H, 9·1. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%). Catalytic reduction ($6H_2$) gave pure stearic acid, m. p. and mixed m. p. 69—69·5° (85%).

(ii) To a solution of ethylmagnesium bromide (0·044 mole) in tetrahydrofuran (40 c.c.) was added 1-hex-5-ynyl-2,8,9-trioxa-adamantane (0·046 mole) in tetrahydrofuran (25 c.c.). After 1·5 hr. cuprous chloride (0·5 g.) and 1-bromoundeca-2,5-diyne (10·5 g.) were added and the mixture was boiled for 24 hr. The crude orthoester (3·9 g., 24%), b. p. 160°/5 × 10^{-3} mm., was hydrolysed in tetrahydrofuran (8 c.c.), ethanol (5 c.c.), and 2N-sulphuric acid (15 c.c.) at 80° for 1·5 hr. The acid crystallised from light petroleum (b. p. 40—60°) as prisms (0·5 g.), m. p. and mixed m. p. 52·5—53·5°.

Nona-5,8-*diynoic Acid* (XXVI).—Propargyl bromide (1 mole) and hex-5-ynoic acid (1 mole) condensed in tetrahydrofuran (cuprous cyanide as catalyst) at 20° (15 hr.). The product was extracted with light petroleum (b. p. 40—60°) before distillation. The pure *acid*, obtained in 45% yield (60% yield based on unrecovered hexynoic acid), had b. p. 116—117°/0·41 mm., n_D^{20} 1·4862, m. p. 18° (Found: C, 71·9; H, 6·9. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%), ultraviolet end-absorption at 220 mμ, $\nu_{max.}$ 3320 (HC≡C), 3040s, 2680 (OH), 2150 (C≡C), 1760w, 1715, 930s cm.$^{-1}$ (C=O). The acid was sensitive to air and coloured fairly rapidly. Catalytic reduction of the acid (0·43 g.) in methanol (10 c.c.) with Adams catalyst (0·05 g.) gave rapidly (absorption 267 c.c.; theor. 286 c.c.) nonanoic acid which was converted through the acid chloride into 1-nonamide (0·31 g.), m. p. 96—98° (from ether) (lit.,[17] 98·8°).

Eicosa-5,8,11,14-*tetraynoic Acid* (XVI).—(i) Similarly 1-bromotetradeca-2,5,8-triyne (0·025 mole) and hex-5-ynoic acid (0·08 mole) in tetrahydrofuran either at 20° or under reflux gave the tetraynoic acid in 75—86% yield. The *acid* crystallised from light petroleum (b. p. 40—60°), isopropyl ether, or methanol as buff-coloured prisms, m. p. 81—82° (Found: C, 80·7; H, 8·15. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%), $\nu_{max.}$ (in CCl_4) 1750w, 1710s, 925m cm.$^{-1}$. The tetraynoic acid in 5% methanolic hydrogen chloride at 20° gave the *methyl ester* (76%), b. p. 180—185°/3 × 10^{-3} mm., n_D^{20} 1·5100, m. p. 10—12°, that darkens rapidly in air (Found: C, 80·7; H, 8·45. $C_{21}H_{26}O_2$ requires C, 81·2; H, 8·4%). The *amide*, crystallised from methanol, had m. p. 104—106·5° (Found: C, 81·7; H, 8·7. $C_{20}H_{25}NO$ requires C, 81·3; H, 8·5%), $\nu_{max.}$ 3340s, 3180s, 1650s cm.$^{-1}$. Catalytic reduction of the acid (0·5 g.) in methanol (40 c.c.) with Adams catalyst (0·05 g.) gave arachidic acid, m. p. and mixed m. p. 75—75·5° (86%) (Found: C, 76·8; H, 12·6. Calc. for $C_{20}H_{40}O_2$: C, 76·8; H, 12·9%).

(ii) 1-Bromoundeca-2,5-diyne (1 mole) and nona-5,8-diynoic acid (2 moles) condensed in tetrahydrofuran at 20° or under reflux. The tetraynoic acid crystallised from isopropyl ether at $-5°$ (m. p. 73—78°) and recrystallisation from methanol gave the pure acid in 54% yield, with m. p. and mixed m. p. 81·5—82°. The infrared spectra of the two acids were identical. When the whole reaction sequence from hex-5-ynoic acid $\longrightarrow$ nona-5,8-diynoic acid $\longrightarrow$ eicosa-5,8,11,14-tetraynoic acid was carried out, without isolation of the intermediate C_9 acid, the overall yield based on 1-bromoundeca-2,5-diyne was 55%.

(iii) In a similar way to that described above, 1-pent-4′-ynyl-2,8,9-trioxa-adamantane and 1-bromotetradeca-2,5,8-triyne gave the orthoester which without isolation was hydrolysed as before to eicosa-5,8,11,14-tetraynoic acid (from methanol), m. p. and mixed m. p. 80—82·5° (*ca.* 5%).

Docosa-4,7,10,13,16-*pentaynoic Acid* (XVII).—1-Bromotetradeca-2,5,8,11-tetrayne (1 mole) and pent-4-ynoic acid (3 moles) condensed in the usual way in boiling tetrahydrofuran, to give the *pentaynoic acid* in 50% yield. This separated from methanol as cream-coloured needles, m. p. 100—101·5° (soften 99°) (ultraviolet absorption nil), $\nu_{max.}$ 2650m, 1750w, 1710s, 925m cm.$^{-1}$ (Found: C, 82·2; H, 7·5. $C_{22}H_{24}O_2$ requires C, 82·5; H, 7·55%). Catalytic reduction of the acid (0·8 g.) at Adams catalyst in methanol gave ($10H_2$) docosanoic acid (80%), m. p. 80—82° (lit.,[17] 80°).

Linoleic Acid (XIX).—(i) Octadeca-9,12-diynoic acid (2·87 g.) in pure light petroleum (b. p. 60—80°; 100 c.c.) containing a 5% solution (2 c.c.) of quinoline in light petroleum was partially reduced with Lindlar catalyst [15] (0·5 g.). After a hydrogen uptake of 523 c.c. (theor. 515 c.c.) reduction virtually stopped, the catalyst was removed and the crude linoleic acid, after removal of quinoline, had m. p. $-11°$ to $-9°$, n_D^{21} 1·4670, $\lambda_{max.}$ 230 ($E^{1\%}_{1\,cm.}$ 20), and showed in the infrared spectrum only a trace of *trans*-double bond at 965 cm.$^{-1}$. Purification was effected by preparation of the methyl ester (5% methanolic hydrogen chloride at 20°), b. p. 158—160°/0·4 mm., n_D^{20} 1·4604 (lit.,[17] 1·4594) (Found: C, 77·6; H, 11·6%; Iodine val., 169, 170. Calc. for $C_{19}H_{34}O_2$: C, 77·5; H, 11·6%; Iodine val., 176). The infrared spectrum indicated $<1\%$ of *trans*-isomer. The ultraviolet absorption was nil.

(ii) Ethyl octadeca-9,12-diynoate (3·72 g.) was reduced as described above. The resulting ethyl linoleate (3·02 g., 81%) had b. p. 156—158°/0·45 mm., n_D^{20} 1·4587, iodine val. 151 (theor. 164), $\lambda_{max.}$ 229 mμ ($E^{1\%}_{1\,cm.}$ 14·7), with only a trace of *trans*-isomer shown at 965 cm.$^{-1}$ in the infrared spectrum. Alkali-isomerisation [19] gave specific $\alpha = 89·6$ at 233 mμ (theor. 92·2; 97% pure). Hydrolysis with 4% aqueous-alcoholic potassium hydroxide at 20° for 15 hr. gave linoleic acid which crystallised from light petroleum (b. p. 40—60°) at $-60°$ and was then distilled; it had b. p. 148—152°/10^{-3} mm., n_D^{20} 1·4660, m. p. $-6°$ to $-5°$ (lit.,[20] n_D^{20} 1·4699, m. p. $-5·2°$ to $-5°$) (Found: C, 77·2; H, 11·6%; Iodine val., 171. Calc. for $C_{18}H_{32}O_2$: C, 77·1; H, 11·5%; Iodine val., 181), $\nu_{max.}$ 3020s, 2660m, 1705s, 715m cm.$^{-1}$. The tetrabromide number was determined by Brown and Frankel's method [21] on a 0·5 g. sample: this gave a value of 80·10 (theor. 87·5; purity *ca.* 91%). Alkali-isomerisation gave specific $\alpha = 79·75$ at 233 mμ (theor. 92·2; purity 86%). Gas-phase chromatography showed one main peak with a very small subsidiary contaminant, presumably the olefinic acid. The 9,10,12,13-tetrabromostearic acid produced by bromination in light petroleum (b. p. 30—40°) crystallised from ethylene chloride to give the pure acid, m. p. 114·5—116°. Comparison with an authentic specimen (m. p. 115—116°) by mixed m. p. and infrared spectra showed them to be identical. Synthetic tetrabromostearic acid (0·14 g.) in tetrahydrofuran was treated with ethereal diazomethane at 0° for 20 hr. The methyl ester, crystallised from light petroleum (b. p. 40—60°), had m. p. 57—58·5° (lit., [22] m. p. 56°, 63°).

Nonadeca-10,13-*dienoic Acid* [23] (XVIII).—Similarly, as in (ii) above, ethyl nonadeca-10,13-diynoate (3·45 g.) in light petroleum (b. p. 40—60°; 100 c.c.) and Lindlar catalyst (1·5 g.)

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[19] Stillman (Report of the Spectroscopy Committee), *J. Amer. Oil Chemists' Soc.*, 1949, **26**, 399.

[20] Matthews, Brode, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 1064.

[21] Brown and Frankel, *J. Amer. Chem. Soc.*, 1938, **60**, 54; White and Brown, *J. Amer. Oil Chemists' Soc.*, 1949, **26**, 385; 1952, **29**, 292.

[22] Haworth, *J.*, 1929, 1458; Smit, *Rev. Trav. chim.*, 1930, **49**, 543.

[23] Cf. Karrer and Koenig, *Helv. Chim. Acta*, 1943, **26**, 619; Whitcutt and Sutton, *Biochem. J.*, 1956, **63**, 469.

(hydrogen uptake = 518 c.c.; theor. 514) gave ethyl nonadeca-10,13-dienoate (2·83 g., 81%), b. p. 116°/3 × 10^{-3} mm., n_D^{20} 1·4580 (Found: C, 78·5; H, 12·0%; Iodine val., 148. Calc. for $C_{21}H_{38}O_2$: C, 78·2; H, 11·9%; Iodine val., 157·4).

γ-Linolenic Acid (XX).—Reduction of octadeca-6,9,12-triynoic acid (13·6 g.) in ethanol (200 c.c.) containing 5% quinoline–ethanol solution (10 c.c.), with Lindlar catalyst (5 g.), was rapid at 20° (water cooling) until 3630 c.c. of hydrogen had been absorbed and then stopped (theor. 3598 c.c.). After a further hour's shaking the solution was filtered and hydrogen chloride passed in until a 5% solution had been obtained. The ethyl ester (10·7 g.) had b. p. 156°/0·2 mm., n_D^{20} 1·4678 (Found: C, 78·2; H, 11·4%; Iodine val., 237. Calc. for $C_{20}H_{36}O_2$: C, 78·35; H, 11·2%; Iodine val., 248·5) (no ultraviolet absorption), $\nu_{max.}$ 3040s, 1735s, 1650m, 970sh, 710s $cm.^{-1}$. Alkali-isomerisation based on the ethyl ester gave specific α = 71·5, 71·5, 72·6 at 268 mμ (average 87% purity, based on values given for linolenic acid [16]); no tetraene absorption was found. The methyl ester had b. p. 162°/0·5 mm., n_D^{20} 1·4680 (Found: C, 78·25; H, 11·3%; Iodine val., 269. Calc. for $C_{19}H_{32}O_2$: C, 78·0; H, 11·0%; Iodine val., 260·4), $\nu_{max.}$ 3040s, 1735s, 700s $cm.^{-1}$. Gas-phase chromatography showed the ethyl ester to be *ca.* 95% pure; only one other (small) peak appeared just before the main peak. Addition of bromine to the crude γ-linolenic acid in ether gave 6,7,9,10,12,13-hexabromostearic acid, m. p. 199·5—200°; crystallisation from ethyl methyl ketone gave the pure acid, m. p. 201—202° (lit.,[4] m. p. 196°, 200—200·8°, 203°) (Found: C, 28·6; H, 3·9; Br, 63·9. Calc. for $C_{18}H_{30}Br_6O_2$: C, 28·55; H, 4·0; Br, 63·3%). Treatment of the hexabromo-acid in tetrahydrofuran with diazomethane [4] or addition of bromine to methyl γ-linolenate gave the same methyl 6,7,9,10,12,13-hexabromostearate, m. p. 174·5—176·5° (from acetone) (lit.,[4] 170·5—171·5°) (Found: C, 29·65; H, 4·1; Br, 61·9. Calc. for $C_{19}H_{32}Br_6O_2$: C, 29·6; H, 4·2; Br, 62·1%).

Arachidonic Acid (XXI).—Reduction of eicosa-5,8,11,14-tetraynoic acid (1·48 g.) in light petroleum (b. p. 65—67°; 110 c.c.) containing 5% quinoline–light petroleum (2 c.c.) with Lindlar catalyst (0·5 g.) was rapid until 515 c.c. of hydrogen had been absorbed (theor. 480 c.c.) and then stopped. After being further shaken for 15 min. the solution was filtered, concentrated, and esterified with 5% methanolic hydrogen chloride (50 c.c.) at 20° for 20 hr. The methyl ester (80—85% yield) had b. p. 172—174°/0·3 mm., n_D^{19} 1·4802 (lit., n_D^{20} 1·4798) (Found: C, 79·0; H, 11·1%; Iodine val., 318, 312. Calc. for $C_{21}H_{34}O_2$: C, 79·2; H, 10·8%; Iodine val., 318·6), $\lambda_{max.}$ 232 mμ ($E^{1\%}_{1\,cm.}$ 19). Infrared comparison with pure natural methyl arachidonate showed them to be identical ($\nu_{max.}$ 3030s, 1735s, 965 trace, 700s, $cm.^{-1}$). Alkali-isomerisation gave specific α = 57·5 at 315 mμ (theor. 60·6; purity 95%); there was no pentaene absorption at 346 mμ. Gas-phase chromatography showed a main peak (*ca.* 93%) and two small impurities on either side. The *ethyl ester* had b. p. 176°/0·3 mm., n_D^{21} 1·4769 (Found: C, 79·3; H, 10·95%; Iodine val., 295, 294, 291. $C_{22}H_{36}O_2$ requires C, 79·5; H, 10·9%; Iodine val., 305·4), $\lambda_{max.}$ 230 mμ ($E^{1\%}_{1\,cm.}$ 20·5), $\nu_{max.}$ 3050s, 1735s, 1650w, 965 trace $cm.^{-1}$. Alkali-isomerisation gave specific α = 55·8 at 315 mμ (purity 92%). Gas-phase chromatography showed the sample to be *ca.* 90% pure with two very small contaminant peaks. The infrared absorption disclosed virtually no *trans*-isomer. Addition of bromine to arachidonic acid in ether gave the insoluble 5,6,8,9,11,12,14,15-octabromoeicosanoic acid, m. p. 234—235° (decomp.) [lit.,[24] 234—235° (decomp.)]. Similarly, methyl arachidonate gave methyl 5,6,8,9,11,12,14,15-octabromoeicosanoate, m. p. 225·5—227·5° (lit.,[25] 228·5—229·5°) (Found: C, 26·0; H, 3·7. Calc. for $C_{21}H_{34}Br_8O_2$: C, 26·3; H, 3·6%).

Docosa-4,7,10,13,16-*pentaenoic Acid* (XXII).—Docosa-4,7,10,13,6-pentaynoic acid (2·2 g.) was suspended in pure benzene (150 c.c.) containing 5% quinoline–benzene (3 c.c.) and hydrogenated at 20° with Lindlar's catalyst (0·5 g.). After the absorption of hydrogen had stopped (900 c.c.; theor. 850 c.c.) the solution was filtered and the crude acid converted in the usual way into the *ethyl ester* (85% yield), b. p. 147—152°/0·01 mm., n_D^{20} 1·4841 (Found: C, 80·4; H, 10·9%; Iodine val., 326. $C_{24}H_{38}O_2$ requires C, 80·4; H, 10·7%; Iodine val., 354) (no ultraviolet absorption), $\nu_{max.}$ 3040s, 1732s, 1650w, 965w, 700s $cm.^{-1}$. The *methyl ester* had b. p. 138—146°/10^{-3} mm., n_D^{20} 1·4855 (Found: C, 80·3; H, 10·9%; Iodine val., 337, 330. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·5%; Iodine val., 368·4). Alkali-isomerisation gave specific α = 45·4, 46·5, 47·43 at 346 mμ [for a natural docosapentaenoic acid [16] (structure unknown) specific α = 50·4; this indicates a purity for our sample of 96%; for an eicosapentaenoic acid [16] specific α = 87·5 at 346 mμ (purity then = 60·5%)]. Gas-phase chromatography indicated a purity of

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[24] Hart and Heyl, *J. Biol. Chem.*, 1927, **72**, 399.

[25] Shinowara and Brown, *Oil and Soap*, 1938, **15**, 151.

85—90%, there being one main peak and two small peaks, slightly greater in proportion than were obtained from the arachidonic acid samples.

Arachidonyl Alcohol.—Eicosa-5,8,11,14-tetrayn-1-ol (14·12 g.) in ethanol (200 c.c.) and quinoline (2 c.c.) was partially reduced with Lindlar catalyst (5·0 g.), with water-cooling (20°). After a hydrogen uptake of 5250 c.c. (theor. 5032 c.c.) reduction stopped and, after a further hour's shaking, the catalyst and solvent were removed. The residue in light petroleum (b. p. 40—60°) was washed with 2N-hydrochloric acid and water and dried (Na_2SO_4). The *alcohol* (12·77 g.) had b. p. 122—126°/10^{-3} mm., n_D^{20} 1·4880 (Found: C, 82·8; H, 11·95%; Iodine val., 342·1. $C_{20}H_{34}O$ requires C, 82·8; H, 11·8%; Iodine val., 350) (no ultraviolet absorption between 220 and 400 mμ), $\nu_{max.}$ 3350s, 3040s, 700s cm.$^{-1}$. Alkali-isomerisation of two different samples gave specific α = 32·8, 30·1 at 315 mμ. No pentaene absorption was detected. A standard for this compound is not known; on the basis of arachidonic acid this represents *ca.* 50% purity. However, both the iodine value and gas-phase chromatography indicate that the sample is at least 90% pure: only a trace of *trans*-isomer was detected by infrared spectroscopy.

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