897. *Lipids. Part VII.* Synthesis of 8-Hydroxyoctadec-*cis-11- *and* -trans-11*-en-9-ynoic Acid: the Status of Natural 8-Hydroxyximenynic Acid.*

By L. Crombie and B. P. Griffin.

Fatty acids containing conjugated oxo-acetylenic groups in the centre of a long chain can be synthesised by condensing silver acetylides with half-ester acid chlorides. Dec-*cis*-3- and *trans*-3-en-1-yne are formed, in the proportion 72 : 28, when 4-toluene-*p*-sulphonyloxydec-1-yne is treated with sodamide in liquid ammonia: the mixture of geometrical isomers can be resolved by gas–liquid chromatography or fractional distillation. Employment of these hydrocarbons in the coupling procedure, followed by borohydride reduction, gives a simple synthesis of the acids named in the title, and the *trans*-stereoisomer agrees in properties with Ligthelm's description of natural 8-hydroxyximenynic acid. *cis*(unnatural)-Ximenynic acid is also synthesised.

The kernel oil of *Ximenia caffra* Sond. contains large quantities of octadec-*trans*-11-en-9-ynoic (ximenynic) acid, syntheses of which were reported in Parts II and V (ref. 4). Ligthelm further states[1] that 3—4% of an unsaturated hydroxy-acid, which he tentatively formulates as 8-hydroxyoctadec-*trans*-11-en-9-ynoic (8-hydroxyximenynic) acid, can be isolated with some difficulty. Our interest in its synthesis was aroused because it seemed

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* Part VI, *J.*, 1957, 1632.

[1] Ligthelm, *Chem. and Ind.*, 1954, 249.

to be a suitable example on which to test a new approach to the construction of natural fatty acid molecules with centrally placed functional groups. This involves coupling a

$$\mathrm{Me{\cdot}[CH_2]_5{\cdot}CH{=}CH{\cdot}C{\equiv}CAg + Cl{\cdot}OC{\cdot}[CH_2]_6{\cdot}CO_2Me}$$

$$\downarrow$$

$$\text{(I)}\quad \mathrm{Me{\cdot}[CH_2]_5{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO_2Me}$$

$$\downarrow$$

$$\text{(II)}\quad \mathrm{Me{\cdot}[CH_2]_5{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}[CH_2]_6{\cdot}CO_2Me}$$

silver acetylide with a half-ester acid chloride. Nef [2] has recorded that silver phenylacetylide reacts violently with warm benzoyl chloride to yield 1 : 3-diphenylprop-2-yn-1-one, and Davis and Scheiber [3] have recently made a useful contribution to the control of the reaction. They showed that some silver acetylides are soluble in carbon tetrachloride, chloroform, or benzene and react with simple acyl halides in such solvents to form α-acetylenic ketones.

$$\mathrm{Me{\cdot}[CH_2]_3{\cdot}C{\equiv}C{\cdot}CO{\cdot}[CH_2]_4{\cdot}CO_2R}\quad \text{(III)}$$

$$\mathrm{Me{\cdot}[CH_2]_3{\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}[CH_2]_4{\cdot}CO_2R}\quad \text{(IV)}$$

For the synthesis of 8-hydroxyximenynic acid the annexed route was followed, but first the reaction was tested on a simpler example, the synthesis of 6-hydroxydodec-7-ynoic acid. A solution of hex-1-ynylsilver in carbon tetrachloride was heated under reflux with 5-ethoxycarbonylpentanoyl chloride, to give ethyl 6-oxododec-7-ynoate (III; R = Et) in 36% yield. The latter showed the expected infrared characteristics and had an ultraviolet maximum at 222 mμ (ε 9500). It could be hydrogenated and hydrolysed to the known 6-oxododecanoic acid. On reduction with potassium borohydride, followed by hydrolysis, 6-hydroxydodec-7-ynoic acid (IV; R = H) was obtained and purified as the methyl ester. The latter was obtained in 67% overall yield from the oxo-ester (III; R = Et).

Dec-3-en-1-yne, required for the hydroxyximenynic acid sequence, has been reported earlier [4, 5] as the product from treatment of 4-toluene-*p*-sulphonyloxydec-1-yne with sodamide. It has now been made in much larger quantity and this has enabled its stereochemistry to be thoroughly examined. Earlier,[4] it was pointed out that the elimination step is not necessarily stereospecific and though the hydrocarbon was successfully used for the synthesis of natural *trans*-ximenynic acid, purification procedures could have resulted in the removal of *cis*-material (for a synthesis of the latter, see below). It is now certain that this was the case, for dec-3-en-1-yne produced in the above reaction can be separated into *cis*- and *trans*-components by gas–liquid chromatography. Rigorous fractional distillation of the mixture produced pure dec-*cis*-3- and -*trans*-3-en-1-yne on a preparative scale. As a check on purity, the two stereoisomers were converted into their crystalline mercury derivatives, these were purified, and the hydrocarbons regenerated

TABLE 1. *Dec*-cis-3- *and* -trans-3-*en*-1-*yne*.

	B. p. at 51 mm.	n_D^{25}	$\lambda_{max.}$ (mμ) [a]	Infrared: ε at 742	Infrared: ε at 961 cm.$^{-1}$	Hg derivative M. p.	Hg derivative $\lambda_{max.}$ (mμ) [a]
cis	90—91°	1·4496	222·6 (13,590)	51	—	9·5—10·5°	247 (23,900)
trans	97·7—99·2	1·4532	221·6 (13,980)	—	119	76·5—77·5°	246·5 (29,200)

[a] ε in parentheses.

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[2] Nef, *Annalen*, 1899, **308**, 277.

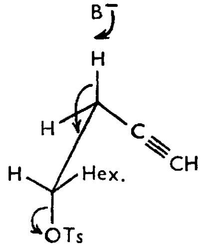
[3] Davis and Scheiber, *J. Amer. Chem. Soc.*, 1956, **78**, 1675.

[4] Crombie and Jacklin, *J.*, 1955, 1740; 1957, 1622.

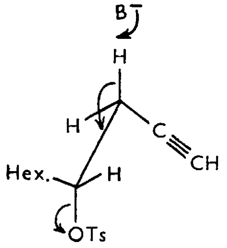
[5] Surber. Theus, Colombi, and Schinz, *Helv. Chim. Acta*, 1956, **39**, 1299.

with no significant alteration in their constants. Ultraviolet data for the hydrocarbons are similar, but the strong bands in the infrared spectrum at 961 cm.$^{-1}$ (·CH=CH· out-of-plane deformation) for the *trans*- and at 742 cm.$^{-1}$ for the *cis*-compound, each of which is absent from the spectrum of the other stereoisomer, clearly characterise the two liquids. Data are summarised in Table 1 and the Experimental section.

If *trans*-elimination and coplanar arrangement of the four centres involved are assumed, elimination from conformations (V) and (VI), leading to *cis*- and *trans*-hydrocarbon respectively, is possible. Of the two conformations, (VI) might be expected to be the more stable with the energy difference between the two perhaps lower than usual since the acetylene grouping is slim and its steric effect less than that of an alkyl group. It is, however, surprising that the elimination reaction actually yields more *cis*- than *trans*-hydrocarbon (72 : 28 by infrared analysis). The result is paralleled by Allen and Whiting's finding [6] that elimination from 4-toluene-*p*-sulphonyloxypent-1-yne gives *cis*- and *trans*-pentenyne in the proportions 60—65 : 35—40. They postulate electrostatic interaction between the alkyl and the acetylene group as a stabilising factor for the transition state which gives rise to the *cis*-isomer.



(V)



(VI)

With pure dec-*cis*- and -*trans*-3-en-1-yne in hand, coupling of their silver salts with 7-methoxycarbonylheptanoyl chloride was studied. Silver chloride was in each case precipitated almost quantitatively, but crude methyl 8-oxo-octadec-*cis*- and -*trans*-11-en-9-ynoate were difficult to purify. Distillation caused major losses of material but still did not effect complete purification, so the impure product was used directly in the next stage. The crude ester, however, showed the expected infrared characteristics for structure (I) and the en-yne-conjugated oxo-function was established by the ultraviolet max. at 268 mμ (ε 8000). Further, each stereoisomer gave 8-oxo-octadecanoic acid when hydrogenated.

In a trial run,* using a mixture of decenyne stereoisomers, an attempt was made to hydrolyse methyl 8-oxo-octadec-11-en-9-ynoate to the acid with aqueous-ethanolic potassium hydroxide before the borohydride reduction. The oily product, isolated after acidification, gave a strong red-violet ferric chloride reaction and its spectrum in neutral ethanol showed maxima at 278 and 282 mμ (ε 5700 for both), shifted by alkali to 298 and 300 mμ (ε 9000). This is characteristic of a 1 : 3-diketone and showed that under these conditions a net hydration of the acetylenic linkage had occurred. The infrared spectrum of the oil [bands at 1704 (CO_2H), 1653 (C=C), 1597 (enolised β-diketone), and 970 cm.$^{-1}$ (*trans*-CH=CH)] supports the assigned structure.

Reduction of crude methyl 8-oxo-octadec-*cis*-11- and -*trans*-11-en-9-ynoate with

* We thank Dr. A. G. Jacklin (Ph.D. Thesis, London, 1956) for this preliminary work which convinced us that synthesis of *cis*- and *trans*-8-hydroxyximenynic acid by the method reported here was feasible. These early results were communicated to Dr. B. C. L. Weedon who was independently contemplating a synthesis of 9 : 11-dioxononadecanoic acid, the ozonolysis product of sterculic acid, by a similar route. This has since been executed.[7]

[6] Allan and Whiting, *J.*, 1953, 3314.

[7] Narayanan and Weedon, *Chem. and Ind.*, 1957, 394.

potassium borohydride followed by acid, then alkaline, hydrolysis gave (±)-8-hydroxyoctadec-*cis*-11- and -*trans*-11-en-9-ynoic acid in 86 and 38% overall yield from 7-methoxycarbonylheptanoyl chloride. Attempted purification was incomplete, though chromatography on "neutral" alumina from benzene containing 0·5% of methanolic acetic acid gave fairly good results. The best technique proved to be distillation of the methyl esters. Both esters absorbed 3 mol. of hydrogen over a catalyst to give methyl (±)-8-hydroxyoctadecanoate and both gave *n*-heptanoic acid on ozonolysis. Crystalline *p*-phenylphenacyl esters were obtained from each geometrical isomer: data are summarised in Table 2.

TABLE 2. (±)-8-*Hydroxyoctadec*-cis-11- *and* -trans-11-*en*-9-*ynoic acid.*

	Methyl ester					
	B. p. at 10^{-3} mm.	n_D^{23}	Micro-hydrogn.	$\lambda_{max.}$ (mμ) [a]	$\nu_{max.}$ (cm.$^{-1}$) [a]	*p*-Phenylphenacyl ester, m. p.
cis-	152—156°	1·4806	3·00	228 (16,200)	735 (91·3)	55—55·5°
trans-	150—152	1·4842	2·95	229 (15,300)	955 (116)	67—68

[a] ε in parentheses.

At this stage it was hoped to compare the two synthetic (±)-8-hydroxyximenynic acids with natural (presumably optically active) acid by solution infrared techniques. Unfortunately we understand from Dr. Nunn that none of Dr. Ligthelm's unique specimen remains. Also no crystalline derivatives of the natural acid were reported, and we have been unable to obtain the original infrared trace. We can only say that the properties of our (±)-8-hydroxyoctadec-*trans*-11-en-9-ynoic acid agree with those of the natural acid in so far as the significant observations [1] from which Ligthelm deduced his structure can be duplicated on our synthetic *trans*-acid. Thus, apart from points already covered, alkaline isomerisation produces conjugated tetraene absorption in the ultraviolet, and boiling with lithium aluminium hydride in ether gives the diene-diol (VII) showing a strong conjugated *trans-trans* infrared absorption. The spectrum is readily distinguished from that of the *cis-trans*-diol similarly obtained from (±)-8-hydroxyoctadec-*cis*-11-en-9-ynoic acid. The (±)-*trans*-compound also forms a methyl ester acetate readily.

$$Me\cdot[CH_2]_5\cdot CH{=}CH\cdot CH{=}CH\cdot CH(OH)\cdot[CH_2]_7\cdot OH \quad (VII)$$

The availability of dec-*cis*-3-en-1-yne has enabled us to carry out a synthesis of *cis*-(unnatural)-ximenynic acid. The route follows that described in Part V (which led to the *trans*-acid), with certain modifications. Now that pimelic acid is easily made in high yield [8] from commercial pimelo-γ-dilactone,[9] we have reverted to Huber's route [10] to heptane-1 : 7-diol and hence 1-chloro-7-iodoheptane. Condensation of the latter with sodiodecenyne proceeded smoothly only if freshly distilled liquid ammonia (from sodium) was used. Conversion of 17-chloroheptadec-*cis*-7-en-9-yne into the nitrile and then the corresponding acid caused little stereomutation, and traces of *trans*-contaminant were removed by repeated urea-complex formation. The *cis*-acid was isolated crystalline and its properties are compared with those of the *trans*-acid in Table 3.

TABLE 3. cis- *and* trans-*Ximenynic acid.*

	M. p.	Micro-hydrogn.	$\lambda_{max.}$ (mμ) [a]	CH=CH δ (cm.$^{-1}$)	*p*-Phenylphenacyl ester, m. p.
cis-	25·5—26·5°	2·95 H_2	227 (14,250)	737·5	42—43°
trans- [b]	39—40	2·95 H_2	228 (16,800)	952	61·5—62 [c]

[a] ε in parentheses. [b] Crombie and Jacklin (synthetic acid). [c] Ligthelm and Schwartz (natural acid).

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[8] Gardner, Rand, and Haynes, *J. Amer. Chem. Soc.*, 1956, **78**, 3425.

[9] Cf. Hopff and Griesshaber, U.S.P. 2,302,321 (*Chem. Abs.*, 1943, **37**, 2020).

[10] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.

EXPERIMENTAL

Hex-1-*ynylsilver*.—Silver nitrate (102·4 g.) was dissolved in water (500 ml.) containing methanol (300 ml.), and ammonia solution (*d* 0·880) added until the precipitate just redissolved. Hex-1-yne (24·8 g.) was added with cooling, and the mixture was shaken for 2 hr. The lilac-coloured solid was filtered off, washed until neutral, dissolved in carbon tetrachloride (300 ml.), and dried over calcium chloride.

Ethyl 6-*Oxododec*-7-*ynoate*.—5-Ethoxycarbonylpentanoyl chloride (38·1 g., 10% excess; b. p. 104—106°/5 mm., n_D^{22} 1·4481) was heated under reflux for 18 hr. with hexynylsilver in carbon tetrachloride (178 ml., above) and the precipitated silver chloride (23·5 g., 92%) was filtered off. The filtrate was washed with ammonia solution, 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. After drying ($MgSO_4$), evaporation, and distillation, *ethyl* 6-*oxododec*-7-*ynoate* (17·6 g., 36%), b. p. 129°/0·03 mm., n_D^{19} 1·4630, was isolated (Found: C, 69·8; H, 9·25. $C_{14}H_{22}O_3$ requires C, 70·55; H, 9·3%), $\lambda_{max.}$ 222 mμ (ε 9500), $\nu_{max.}$ 2225 (C≡C), 1740 (CO_2Et), and 1681 cm.$^{-1}$ (conjugated C=O). On hydrogenation in ethyl acetate over palladised charcoal, 2·16 mol. of hydrogen were absorbed. Working up and hydrolysis gave 6-oxododecanoic acid, m. p. 61·5—62° (Found: C, 67·5; H, 10·5. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%). The semicarbazone had m. p. 132—132·5°. Keskin [11] gives m. p. 61·5° for 6-oxododecanoic acid and m. p. 132° for its semicarbazone.

When the oxo-acetylenic ester was treated with 10% ethanolic potassium hydroxide at room temperature for 24 hr., an acidic yellow oil was formed which gave a brown-red colour with ferric chloride and had infrared bands at 1712 (CO_2H) and 1585 cm.$^{-1}$ [C(OH)=CH·CO].

Methyl 6-*Hydroxydodec*-7-*ynoate*.—Potassium borohydride (4 g.) in water (45 ml.) was added to ethyl 6-oxododec-7-ynoate (6·8 g.) in methanol (360 ml.) and set aside at 0° for 20 hr. Potassium hydroxide (17·5 g.) was added and the mixture was refluxed for 5 hr. After evaporation of most of the methanol *in vacuo*, neutral material was removed with ether. The acid was then isolated, after acidification, as a yellow oil with infrared bands at 3311 (OH), 2244 (C≡C), and 1708 cm.$^{-1}$ (CO_2H). With diazomethane it gave *methyl* 6-*hydroxydodec*-7-*ynoate* (5·1 g., 67%), b. p. 112°/0·01 mm., n_D^{18} 1·4467 (Found: C, 68·55; H, 9·85. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·8%), $\nu_{max.}$ 3448 (OH), 2225 (C≡C), and 1739 cm.$^{-1}$ (CO_2Me).

Dec-cis-3- *and* -trans-3-*en*-1-*yne*.—Dec-1-yn-4-ol [4] (142·2 g.) was mixed with pyridine (74 ml.) and toluene-*p*-sulphonyl chloride (176 g.) and set aside for 48 hr. The product was poured into water and extracted with ether (4 × 100 ml.), and the united ethereal extracts were washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. Evaporation of the dried ethereal solution gave the crude oily toluene-*p*-sulphonate (252 g., 89%) which was re-dissolved in ether (250 ml.) and added during 2 hr. to a solution of sodamide [from sodium (40 g.)] in liquid ammonia (3 l.). The solution was stirred overnight and ammonium chloride (200 g.) was added. The ammonia was allowed to evaporate and water (500 ml.) was added. The product was extracted with pentane (4 × 100 ml.), and the combined extracts were washed as above and dried ($MgSO_4$). Evaporation and distillation gave dec-3-en-1-yne (74 g., 67%), b. p. 74—78°/15 mm., n_D^{25} 1·4514. The infrared spectrum showed a band (CS_2 solution) at 954 cm.$^{-1}$ (ε 33·5) due to the out-of-plane *trans*-CH=CH vibration. Examination by vapour-phase chromatography showed two components to be present in roughly comparable quantity. Crombie and Jacklin [4] give b. p. 65°/10 mm., n_D^{20} 1·4500.

The mixture of geometrical isomers (144 g.) was fractionated under nitrogen in the presence of quinol (50 mg.), through a Stedman gauze-packed column provided with a heated jacket and automatic pressure-control. The reflux ratio was 48 : 1 and the operation was carried out continuously during 20 hr. Omitting fore-runnings and tailings the following fractions were taken at 51 mm.: (1) b. p. 89·8—90·0°, $n_D^{21·5}$ 1·4490 (15·4 g.); (2) b. p. 90°, $n_D^{21·5}$ 1·4500 (20·0 g.); (3) b. p. 90—91°, $n_D^{21·5}$ 1·4505 (16·7 g.); (4) b. p. 91—97·7°, $n_D^{21·5}$ 1·4536 (8·9 g.); (5) b. p. 97·7—99·2°, $n_D^{21·5}$ 1·4549 (12·9 g.); (6) b. p. 99·2—113·7, $n_D^{21·5}$ 1·4529 (2·1 g.). Fractions (1)—(3) are *dec*-cis-3-*en*-1-*yne*, fraction (2) being the purest (Found: C, 88·25; H, 11·95. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%). There was no absorption near 955 cm.$^{-1}$. The hydrocarbon quickly became yellow at 20° and its refractive index changed: it was stored at low temperature in a sealed vessel under nitrogen. Fraction (5) is the *trans*-isomer (analysis below). It had an infrared band at 955 cm.$^{-1}$ (ε 115 in CS_2). This stereoisomer changed colour and refractive index only after several weeks.

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[11] Keskin, *Rev. Fac. Sci. Univ. Istanbul*, 1952, **17**, *A*, 344.

Mercury Derivative of Dec-cis-*3-en-1-yne.*—Hydrocarbon from fraction (3) (1·36 g.) was dissolved in methanol (10 ml.) and shaken with a solution of potassium mercuric iodide (5 ml.) [made by adding a solution of potassium iodide (163 g.) and mercuric chloride (66 g.) in water (163 ml.) to 10% sodium hydroxide solution (125 ml.)]. The colourless oil (1 g.) which separated was extracted with light petroleum (b. p. 40—60°), washed, dried, concentrated *in vacuo*, and allowed to crystallise at low temperature. Two further crystallisations at low temperature from this solvent gave the cis-*mercury derivative* (cf. Table 1) [at 20° the oil ($n_D^{23\cdot5}$ 1·5467) became yellow] (Found: C, 50·9; H, 6·35. $C_{20}H_{30}Hg$ requires C, 50·4; H, 6·35%), $\nu_{max.}$ 2149 ($C\equiv C$), 1616 (conjugated C=C), and 737 cm.$^{-1}$ (*cis*-C=C: in CS_2, ε 12·0). There was no band at 3302 cm.$^{-1}$ ($C\equiv CH$).

Infrared spectra (*cm.*$^{-1}$ *and* ε) *of dec*-cis- *and dec*-trans-3-*en*-1-*yne.**

cis		*cis*		*cis*		*trans*		*trans*	
3302	(64) [a]	1393 [c]		1006	(8) [b]	3291	(96) [a]	1263 [c]	
3022	(23) [b]	1380	(27) [b]	950	(7) [b]	3058	(218) [a]	1204	(18) [a]
2924	(195) [a]	1349 [c]		927 [c]		2915	(140) [a]	1114	(9) [b]
2907	(109) [a]	1318 [c]		905 [c]		2849	(21) [b]	1063	(9) [b]
2705 [c]		1298 [c]		888	(7) [b]	2116	(6) [b]	1029	(9) [b]
2110	(5) [b]	1271	(14) [b]	850 [c]		1629	(6) [b]	961	(119) [a]
1723	(13) [b]	1216	(29) [b]	817	(5) [b]	1461 [c]		882 [c]	
1695	(7) [b]	1115	(19) [b]	781 [c]		1440 [c]		865 [c]	
1618 [c]		1053	(8) [b]	742	(51) [a]	1378	(25) [b]	724	(9) [a]
1465 [c]		1043 inf. [c]		729 inf. [c]		1354	(2) [b]		
1444 inf. [c]						1303	(14) [b]		

* All frequencies measured on liquid film: ε in parentheses where measured.

[a] Apparent ε in 1% solution in CS_2. [b] Apparent ε in 3% solution in CS_2. [c] Band does not appear significantly in CS_2 solution.

The *cis*-mercury derivative was shaken with concentrated hydrochloric acid for 1 hr. at 20° and the liberated hydrocarbon was isolated with ether and distilled, to give pure dec-*cis*-3-en-1-yne (see Table 1; temp. coeff. of n −0·0004/°c) (Found: C, 88·0; H, 11·9%). The infrared spectrum (see below) was identical with that of fraction (2) above.

Mercury Derivative of Dec-trans-*3-en-1-yne.*—Hydrocarbon from fraction (5) (1·36 g.) gave, by the above procedure, a white solid (1·1 g.) which was crystallised three times from light petroleum (b. p. 40—60°), to give the trans-*mercury derivative* as leaflets (cf. Table 1) (Found: C, 50·8; H, 6·65%). The infrared spectrum was similar to that of the *cis*-derivative, but for a prominent band at 952 cm.$^{-1}$ (ε 31·0 in CS_2) and the absence of the prominent *cis*-band at 737 cm.$^{-1}$ (ε 12·0 for the *cis*-compound).

Regeneration of dec-*trans*-3-en-1-yne as above gave, after distillation, hydrocarbon (see Table 1; temp. coeff. of n −0·00038/°c) (Found: C, 88·0; H, 11·9%. Microhydrogenation 3·05H_2).

Silver Dec-cis-*3-en-1-yne.*—The hydrocarbon (6 g.) in methanol (30 ml.) was added dropwise to silver nitrate (15 g.) in water (50 ml.) to which sufficient ammonia solution (*d* 0·880) had been added just to redissolve the precipitate, and the whole was shaken for 15 min. at 10°. The oily precipitate of *silver dec*-cis-*3-en-1-yne* (solid below ~15°) was extracted with carbon tetrachloride (5 × 10 ml.), and the extract was washed with water until the washings were neutral. The extract was dried and filtered, and a portion (5 ml.) of the brown solution (58 ml.) gave silver chloride (0·426 g.) when treated with concentrated hydrochloric acid. This is equivalent to a yield of 77%.

7-*Methoxycarbonylheptanoyl Chloride.*—Dimethyl suberate (7·6 g., b. p. 78—82°/0·04 mm., n_D^{20} 1·4360), suberic acid (11·3 g.), di-*n*-butyl ether (4 ml.), and concentrated hydrochloric acid (1 ml.) were heated under reflux in an oil-bath at 170°. When homogeneous, the mixture was rapidly cooled and methanol (2·2 ml.) was added. The mixture was again heated in the oil-bath for 2 hr. After rapid cooling, methanol (0·7 ml.) was added and refluxing continued for a further 2 hr. On direct distillation methyl hydrogen suberate (7·7 g., 40%), b. p. 127—142°/0·06 mm., n_D^{17} 1·4460, was isolated. Bounds *et al.*[12] give b. p. 135—138°/0·12 mm., n_D^{17} 1·4461. The half-ester (9·3 g.) was heated under reflux for 5 hr. with thionyl chloride (6 ml.). Excess of reagent was removed at the pump and the product on distillation gave 7-methoxycarbonylheptanoyl chloride (8·5 g., 83%), b. p. 118—121°/3 mm., n_D^{20} 1·4495.

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[12] Bounds, Linstead, and Weedon, *J.*, 1954, 448.

*Methyl 8-Oxo-octadec-*cis*-11-en-9-ynoate.*—A solution of silver dec-*cis*-3-en-1-yne in carbon tetrachloride (53 ml.; see above: it represents a 39% excess) was heated under reflux in nitrogen for 24 hr. with 7-methoxycarbonylheptanoyl chloride (5·08 g.). The precipitated silver chloride (4·2 g., 99%) was filtered off through kieselguhr, and the filtrate was shaken with 0·1N-ammonia and 0·1N-hydrochloric acid and then washed with water until neutral. After drying, the solution was evaporated and distilled to give crude methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (2·2 g., 29%), b. p. 152°/10^{-3} mm., $n_{\mathrm{D}}^{21\cdot5}$ 1·4788. There was an ultraviolet maximum at 268 mμ (ε 8200), the curve being broad and rather flat between 266 and 272 mμ. In the infrared there were bands at 2193 (conjugated C≡C), 1739 (CO_2Me), 1674 (conjugated C=O), 1610 and 740 cm.$^{-1}$ (conjugated *cis*-CH=CH). There was no band at 950 cm.$^{-1}$. Other runs gave yields of 14—22%, the distilled product being brown and of somewhat variable refractive index. For preparative work undistilled ester, $n_{\mathrm{D}}^{22\cdot5}$ 1·4894, obtained in 79% yield, was used [$\lambda_{\mathrm{max.}}$ 266 mμ (ε 7200)]. Its infrared spectrum differed only from that of distilled material in bands at 1712 (saturated acid or ester impurity) and at 1567 cm.$^{-1}$ (slight, β-diketone)

An ethanolic solution (0·03%) of the ester, on treatment with aqueous alkali, exhibited a new maximum after 24 hr. at 293 mμ (ε 10,300): this was displaced to 259 mμ (ε 11,500) after acidification. Methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (50 mg.) was dissolved in 10% ethanolic alkali (2 ml.) and after 24 hr. the acidic product was isolated as a brown oil which showed a strong ferric chloride reaction and bands at 1706 (CO_2H) and 1586 cm.$^{-1}$ [CH(OH)=CH·CO]. Methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (0·182 g.) was hydrogenated in methanol (15 ml.) over palladised charcoal and absorbed 95·5% of the expected volume of hydrogen for saturation of the en-yne system. After filtration, the product was hydrolysed with sodium hydroxide to 8-oxostearic acid, m. p. 83·5—84° [from chloroform–light petroleum (b. p. 40—60°)] (Found: C, 72·15; H, 11·35. Calc. for $C_{18}H_{34}O_3$: C, 72·45; H, 11·5%). The m. p. was undepressed on admixture with a specimen of the authentic keto-acid (m. p. 83—83·5°).

*8-Hydroxyoctadec-*cis*-11-en-9-ynoic Acid.*—Undistilled methyl 8-oxo-octadec-*cis*-11-en-9-ynoate (4·42 g.) in methanol (300 ml.) was treated with potassium borohydride (2 g.) in water (20 ml.) at 5°. After 2 days the mixture was acidified with concentrated hydrochloric acid, the methanol was removed *in vacuo*, and the product was hydrolysed by refluxing it for 1 hr. with sodium hydroxide (1 g.). The solution was diluted with brine (100 ml.), neutral material was removed by extraction with ether, and, after acidification, the acidic product was collected with ether. The ethereal solution was washed, dried ($MgSO_4$), and evaporated to give an oil (3·67 g., 86%) having infrared bands at 3280 (OH), 2224 (C≡C), 1713 (CO_2H), 1597 (conjugated C=C) and 737·5 cm.$^{-1}$ (*cis*-CH=CH). Attempted urea-complex formation, low-temperature crystallisation, purification through the lead or benzylamine salts, and reversed-phase partition chromatography all failed to effect complete purification. Best results were obtained by chromatography on neutral alumina from benzene solution, and elution with 0·5% methanolic acetic acid. The product was then obtained as a pale-yellow oil, $n_{\mathrm{D}}^{20\cdot5}$ 1·4801, $\lambda_{\mathrm{max.}}$ 226·6 mμ (ε 13,520) (Found: C, 72·45; H, 10·35. Calc. for $C_{18}H_{30}O_3$: C, 73·45; H, 10·25%. Microhydrogenation 2·71 H_2). There was no infrared band near 955 cm.$^{-1}$: the *cis*-band at 735·3 cm.$^{-1}$ had ε 56·5 in CS_2. For further purification the acid (1 g.) was converted by diazomethane into the *methyl ester* which after two distillations had b. p. 152—156°/10^{-3} mm., n_{D}^{23} 1·4806 (0·625 g.) (Found: C, 73·75; H, 10·35. $C_{19}H_{32}O_3$ requires C, 73·95; H, 10·45%. Microhydrogenation 3·0 H_2), $\lambda_{\mathrm{max.}}$ 228 mμ (ε 16,200), $\nu_{\mathrm{max.}}$ (liquid film) 3390 (OH), 2259 (C≡C), 1743 (CO_2Me), 1608 (conjugated C=C) and 735 cm.$^{-1}$ (conjugated *cis*-CH=CH) (in CS_2 the last band had ε 91·3). Hydrogenation of the methyl ester gave methyl 8-hydroxyoctadecanoate, m. p. 54·5—55·5° (Found: C, 72·65; H, 12·7. $C_{19}H_{38}O_3$ requires C, 72·55; H, 12·2%). p-*Phenylphenacyl 8-hydroxyoctadec-*cis*-11-en-9-ynoate* was purified chromatographically and had m. p. 55—55·5° (Found: C, 78·8; H, 8·3. $C_{32}H_{40}O_4$ requires C, 78·65; H, 8·25%).

*Ozonolysis of Methyl 8-Hydroxyoctadec-*cis*-11-en-9-ynoate.*—The methyl ester (0·107 g.) in glacial acetic acid (4 ml.) and ethyl acetate (2 ml.) was ozonised at 0°. The solvent was removed at the pump, hydrogen peroxide (100-vol.; 1 ml.) and acetic acid (4 ml.) were added, and the mixture was set aside for three days. The solvents were removed *in vacuo* and the acidic residue was esterified with diazomethane. Methyl *n*-heptanoate was identified by a gas–liquid phase chromatogram and mixed chromatogram.

*Reduction of 8-Hydroxyoctadec-*cis*-11-en-9-ynoic Acid with Lithium Aluminium Hydride.*—The crude acid (0·758 g.) in ether (5 ml.) was added to a suspension of lithium aluminium hydride (0·61 g.) in ether (12 ml.) and heated under reflux for 1 hr. After cooling, ethyl acetate (10 ml.) was added and then 5% sulphuric acid (10 ml.). Extraction with ether, followed by distillation, gave octadeca-*trans*-9 : *cis*-11-diene-1 : 8-diol (0·423 g.), b. p. 166°/10^{-3} mm., $n_{\mathrm{D}}^{20\cdot5}$ 1·4892. Analysis indicates that it was not quite pure [Found: C, 75·7; H, 12·0. Calc. for $C_{18}H_{34}O_2$: C, 76·55; H, 12·15%. Microhydrogenation 2·4 H_2 (saturation of two double bonds and perhaps some allylic cleavage of the 8-hydroxyl)], $\lambda_{\text{max.}}$ 229·5 mμ (ε 19,780), $\nu_{\text{max.}}$ 3355 (OH), 1663 and 1622 (conjugated diene), 986 and 944 (conjugated *cis-trans*-diene), 736 cm.$^{-1}$ (*cis*-C=C). The impurity was revealed by traces of absorption at 2259 (C≡C) and 1744 (ester) cm.$^{-1}$.

Silver Dec-trans-*3-en-1-yne*.—This was prepared from hydrocarbon (6 g.) as described for the *cis*-compound, with shaking for 2 hr. during which the silver derivative was precipitated as a grey sticky solid. It was extracted with carbon tetrachloride; an aliquot part (2 ml.) of the solution (65·5 ml.) yielded 0·132 g. of silver chloride, equivalent to a yield of 68·5%. Another run gave 61·5% yield.

Methyl 8-Oxo-octadec-trans-*11-en-9-ynoate*.—A solution of the silver salt of dec-*trans*-3-en-1-yne in carbon tetrachloride (63·5 ml.; see above: it represents a 26% excess) was heated under reflux and in nitrogen for 24 hr. with 7-methoxycarbonylheptanoyl chloride (4·7 g.). Silver chloride (3·7 g., 94%) was precipitated and the solution was worked up as in the case of the *cis*-stereoisomer to give crude methyl 8-oxo-octadec-*trans*-11-en-9-ynoate (7·08 g.). The ultraviolet max. was at 264·5 mμ (ε 8000), raised after chromatography on " neutral " alumina (from benzene) to ε 10,300. Infrared spectral max. were at 2186 (C≡C), 1740 (CO_2Me), 1672 (conjugated C=O), 1625 (C=C), and 959 cm.$^{-1}$ (*trans*-CH=CH). An ethanolic solution of the ester (0·06%), on treatment with aqueous alkali showed, after 24 hr., an ultraviolet max. at 286—290 mμ (ε 7200), displaced on acidification to 263 mμ (ε 6750). Isolation of the product in a larger scale experiment gave a product having bands at 1712 (CO_2H), 1595 [C(OH)=CH·CO], and 953 cm.$^{-1}$ (*trans*-CH=CH). Hydrogenation of the crude ester was possible only after it had been shaken with Raney nickel for 12 hr. Using palladium–strontium carbonate and hydrolysing the product gave 8-oxo-octadecanoic acid, m. p. and mixed m. p. 83° (Found: C, 72·9; H, 11·55%). Crude, undistilled, oxo-ester was used below.

8-Hydroxyoctadec-trans-*11-en-9-ynoic Acid*.—The oxo-ester (3·55 g.) in methanol (200 ml.) was treated with potassium borohydride (4 g.) in water (15 ml.) at 5°. After being set aside for 3 days the solution was acidified and the solvents were removed *in vacuo*. The residue was hydrolysed (45 min.) with sodium hydroxide (0·6 g.) in methanol (20 ml.), and the crude 8-hydroxyoctadec-*trans*-11-en-9-ynoic acid (1·29 g.) was isolated as a brown semi-solid, m. p. 29—34°, $\lambda_{\text{max.}}$ 228·6 mμ (ε 13,500). The acid (0·726 g.) was esterified with diazomethane, to give the pure *methyl ester* (0·266 g.), b. p. 150—152°/10^{-3} mm., n_{D}^{21} 1·4850 (Found: C, 73·8; H, 10·4. $C_{19}H_{32}O_3$ requires C, 73·95; H, 10·45%. Microhydrogenation 2·95 H_2), $\lambda_{\text{max.}}$ 229 mμ (ε 15,320). In the infrared there were bands at $\nu_{\text{max.}}$ 3429 (OH), 2225 (C≡C), 1755 (CO_2Me), 1601 (C=C), and 955 cm.$^{-1}$ (*trans*-CH=CH) [the ε value (CS_2) for the last band was 116]. On hydrogenation over palladised charcoal, the ester yielded methyl 8-hydroxyoctadecanoate, m. p. 54·5—55·5° (Found: C, 72·95; H, 12·25. Calc. for $C_{19}H_{38}O_3$: C, 72·55; H, 12·2%). When heated with acetic anhydride (15 ml.) and anhydrous sodium acetate (1 g.) for 3 hr., followed by isolation and then treatment with diazomethane, methyl 8-hydroxyoctadec-*trans*-11-en-9-ynoate (100 mg.) gave *methyl 8-acetoxyoctadec*-trans-*11-en-9-ynoate* (80 mg.), b. p. 130°/10^{-4} mm., $n_{\mathrm{D}}^{23\cdot5}$ 1·4726 (Found: C, 72·4; H, 9·8. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·75%. Microhydrogenation 2·95 H_2), $\lambda_{\text{max.}}$ 228·5 mμ (ε 15,360), $\nu_{\text{max.}}$ 2235 (C≡C), 1743 (ester), 1652 (C=C), and 960 cm.$^{-1}$ (*trans*-CH=CH). p-*Phenylphenacyl 8-hydroxyoctadec*-trans-*11-en-9-ynoate* had m. p. 67—68° after purification by chromatography (Found: C, 78·45; H, 8·5%).

Reduction of Methyl 8-Hydroxyoctadec-trans-*11-en-9-ynoate with Lithium Aluminium Hydride*.—The ester (0·209 g.) in ether (5 ml.) was treated with a suspension of lithium aluminium hydride (0·5 g.) in ether (10 ml.), and the mixture was heated under reflux (2 hr.) and then worked up as described above. Octadeca-*trans*-9 : *trans*-11-diene-1 : 8-diol (0·115 g., undistilled) was isolated but did not crystallise; it had $\lambda_{\text{max.}}$ 231·2 mμ (ε 15,200), and $\nu_{\text{max.}}$ at 3367 (OH), 1661 (C=C), and 988 cm.$^{-1}$ (*trans-trans*-diene).

Ozonolysis of Methyl 8-Hydroxyoctadec-trans-*11-en-9-ynoate*.—This was effected on the ester (46 mg.) according to the procedure described for the *cis*-stereoisomer, and methyl-*n*-heptanoate identified by gas–liquid chromatography.

Alkaline Isomerisation of 8-Hydroxyoctadec-trans-*11-en-9-ynoic Acid*.—The acid (1·98 mg.)

in a 6% solution of potassium hydroxide in ethylene glycol (2 ml.) was heated to 180° for 35 min., cooled rapidly, and diluted with ethanol to 25 ml. Spectroscopic examination against a blank determination carried out at the same time showed reduction of the intensity of the band at 229·8 mμ (ε 13,000) and the appearance of new bands at 263 (ε 3440), 298 (1210), and 313 mμ (ε 970, inflexion).

Heptane-1 : 7-*diol*.—Pimelic acid was prepared from commerical[9] pimelo-γ-dilactone in 98·5% yield by Huang-Minlon reduction,[8] and converted into the diethyl ester (b. p. 114—120°/1 mm., n_{D}^{22} 1·4291) by refluxing it for 12 hr. with ethanol, benzene, and sulphuric acid (yield 85%). The ester was reduced by Huber's method,[10] but by paying greater attention to the extraction procedure (adding sodium carbonate and evaporating the liquors after as much diol as possible had been removed in ether, and then re-extracting), the yield of heptane-1 : 7-diol, m. p. 20°, b. p. 139—140°/~2 mm., $n_{\text{D}}^{24\cdot5}$ 1·4528, was increased to 71%.

1-*Chloro*-7-*iodoheptane*.—By the procedures described in Part V, heptane-1 : 7-diol gave 1 : 7-dichloroheptane (70%) which in turn gave 1-chloro-7-iodoheptane, b. p. 80—90°/0·3 mm., n_{D}^{20} 1·5206, in 41·5% yield.

1-*Chloroheptadec*-cis-10-*en*-8-*yne*.—Dec-*cis*-3-en-1-yne (9·08 g.) was added to a stirred solution of sodamide prepared from freshly distilled (from sodium) liquid ammonia (200 ml.), sodium (1·5 g.), and ferric nitrate (50 mg.) and contained in a strip-silvered vacuum-flask. After 3½ hr., a clear yellow solution was obtained and 1-chloro-7-iodoheptane (17·5 g.) was added during 30 min. The mixture was stirred for 18 hr., ammonium chloride (10 g.) added, and the ammonia allowed to evaporate. Water (50 ml.) was added and the product extracted with light petroleum (b. p. 40—60°) (5 × 10 ml.). The extracts were washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and distilled, to give 1-*chloroheptadec*-cis-10-*en*-8-*yne* (9·0 g., 50%), b. p. 128—132°/10^{-3} mm., n_{D}^{22} 1·4812 (Found: C, 75·25; H, 10·9. $C_{17}H_{29}Cl$ requires C, 75·95; H, 10·85%), $\lambda_{\text{max.}}$ 226·5 mμ (ε 14,820), and $\nu_{\text{max.}}$ 2207 (C≡C), 1611 (C=C), and 734 (*cis*-CH=CH) cm.$^{-1}$. The band at 954 cm.$^{-1}$ (*trans*-CH=CH conjugated with an acetylenic linkage) characteristic of the *trans*-isomer (Part V) was absent.

Another run gave a yield of 26·5% but two using undistilled liquid ammonia gave yields of only 8·5% and 5%.

Octadec-cis-11-*en*-9-*ynoic Acid*.—1-Chloroheptadec-*cis*-10-en-8-yne (4·1 g.) was heated under reflux for 16 hr. with sodium iodide (5 g.) in acetone. After evaporation of the acetone the residue was extracted with light petroleum (b. p. 40—60°), and the extracts were washed with sodium thiosulphate solution. Drying ($MgSO_4$) and evaporation gave crude iodo-compound showing no infrared band near 954 cm.$^{-1}$.

The crude iodide was heated under reflux with potassium cyanide (5 g.) in ethanol (40 ml.) and water (10 ml.) for 18 hr. Most of the ethanol was evaporated *in vacuo* and the residual solution was extracted with ether. After drying and evaporation these extracts gave crude nitrile (4·0 g.) showing infrared bands at 2200 (C≡C) and 2240 (·C≡N) cm.$^{-1}$ but none near 954 cm.$^{-1}$. The nitrile was heated under reflux for 48 hr. with potassium hydroxide (5 g.) in 80% aqueous ethanol (50 ml.): ammonia had by then ceased to be evolved. Isolation of the crude acid in the usual way yielded a yellow oil (2·72 g.) which was dissolved in hot methanol (20 ml.) saturated with urea. The mixture was cooled to 0° and the precipitate removed. The filtrate was re-saturated with urea, and the cooling and filtration were repeated. The process was repeated twice more. [Dissolution of these urea precipitates in water afforded 56 mg. of very crude *trans*-ximenynic acid (infrared spectrum).] The final filtrate was poured into water, and the purified acid isolated by ether-extraction as a yellow oil (1·84 g.). On dissolution in light petroleum (b. p. 40—60°) and storage at 0°, an impurity (63 mg.) of m. p. 98—106° was deposited; it was filtered off. The acid in the filtrate was recovered and crystallised five times at low temperature from a mixture of light petroleum (b. p. 40—60°) and methylene chloride. *Octadec*-cis-11-*en*-9-*ynoic acid* was obtained having m. p. 25·5—26·5°, $n_{\text{D}}^{21\cdot5}$ 1·4843 (supercooled) (Found: C, 77·4; H, 10·8. $C_{18}H_{30}O_2$ requires C, 77·65; H, 10·85%. Microhydrogenation 2·95 H_2), $\lambda_{\text{max.}}$ 226·9 mμ (ε 14,250), $\nu_{\text{max.}}$ 2225 (C≡C), 1709 and 937 (CO_2H), 1617 (C=C), and 737·5 (*cis*-CH=CH) cm.$^{-1}$. There was no band at 952 cm.$^{-1}$ as in the spectrum of *trans*-ximenynic acid. The p-*phenylphenacyl ester*, crystallised from light petroleum (b. p. 60—80°), had m. p. 42—43° (Found: C, 81·55; H, 8·45. $C_{32}H_{40}O_3$ requires C, 81·3; H, 8·53%). The *methyl ester* had b. p. 130—132°/6 × 10^{-4} mm., $n_{\text{D}}^{24\cdot5}$ 1·4690 (Found: C, 77·5; H, 11·2. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%), $\lambda_{\text{max.}}$ 226·8 mμ (ε 13,920), $\nu_{\text{max.}}$ 2225 (C≡C), 1740 (CO_2Me), 1620, and 737·5 (*cis*-CH=CH) cm.$^{-1}$, but no maximum near 952 cm^{-1}. On ozonolysis under the conditions described above, followed by conversion of the products into their methyl esters, *cis*-ximenynic acid (51 mg.) yielded methyl *n*-heptanoate and dimethyl azelaate, identified by gas–liquid chromatography.

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