658. *Macrocyclic Musk Compounds. Part V.* New Syntheses of Exaltone, Exaltolide, Dihydroambrettolide, and Δ^9-Isoambrettolide from Aleuritic Acid.*

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Pentadecanedioic acid has been prepared by a modified Barbier–Wieland degradation of ethyl 16-acetoxyhexadecanoate (obtained from aleuritic acid) and cyclised to the acyloin, the acetate of which on reduction with calcium in liquid ammonia furnished exaltone as the main product. The intermediate, 16,16-diphenylhexadec-15-en-1-ol, on oxidation with potassium permanganate under specific conditions afforded 15-hydroxypentadecanoic acid which was cyclised to exaltolide. Δ^9-Isoambrettolide and dihydroambrettolide were prepared by cyclisation of the respective ω-hydroxy acids obtained from ethyl 16-acetoxyhexadec-9-enoate and the corresponding saturated compound.

Exaltone (cyclopentadecanone) occurs, along with cyclopentadecanol, in the secretion of the North American musk rat.[1] The musk odour of angelica root oil is due to exaltolide (15-hydroxypentadecanoic acid lactone).[2] Various syntheses of exaltone[3] and exaltolide[4] have been reported. Exaltolide was recently prepared by high-dilution, intramolecular, oxidative coupling of terminal acetylenes followed by hydrogenation.[5]

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* Part IV, Nair, Mathur, and Bhattacharyya, *Tetrahedron*, 1963, in the press.

[1] Stevens and Erickson, *J. Amer. Chem. Soc.*, 1942, **64**, 144.

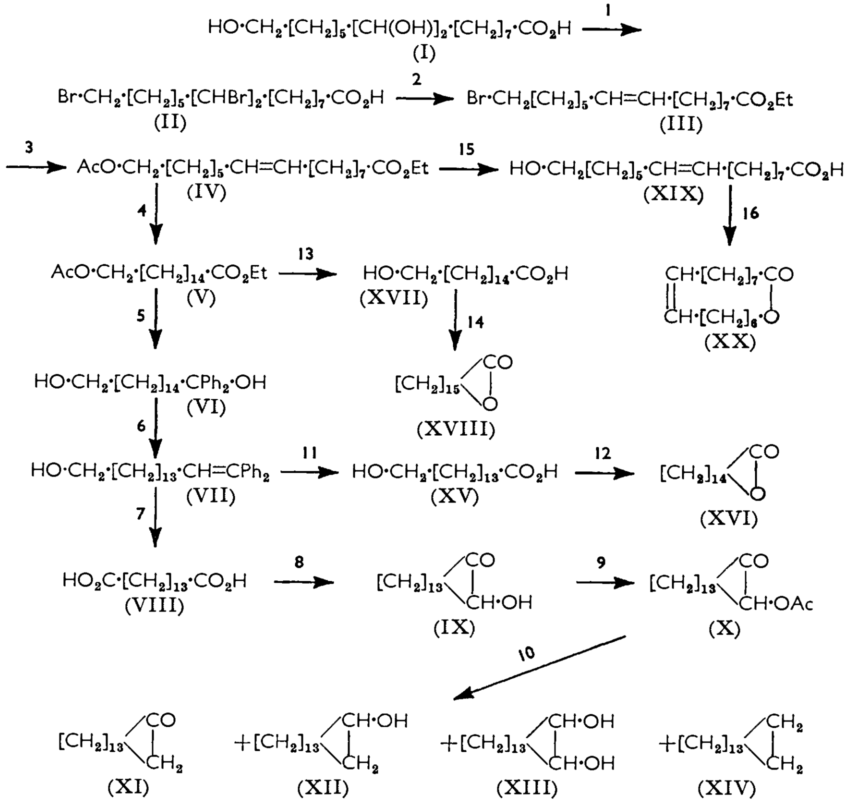
[2] Eglinton, Hamilton, Hodges, and Raphael, *Chem. and Ind.*, 1959, 955.

[3] Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1926, **9**, 249; Ziegler, Eberle, and Ohlinger, *Annalen*, 1933, **504**, 94; Stoll and Rouvé, *Helv. Chim. Acta*, 1947, **30**, 1822; Leonard and Schimelpfenig, *J. Org. Chem.*, 1958, **23**, 1708.

[4] Kerschbaum, *Ber.*, 1927, **60**, 902; Ruzicka and Stoll, *Helv. Chim. Acta*, 1928, **11**, 1159; Stoll and Rouvé, *ibid.*, 1934, **17**, 1283; 1935, **18**, 1087; Hunsdiecker and Erlbach, *Chem. Ber.*, 1947, **80**, 129; Lemieux, *Perfumery Essent. Oil Record*, 1953, **44**, 136; Beets and Essen, U.S.P. 2,936,310/1960.

[5] Carnduff, Eglinton, McCrae, and Raphael, *Chem. and Ind.*, 1960, 559; Bergelson, Molotkovsky, and Shemyakin, *ibid.*, 1960, 558.

Investigations in this laboratory[6] have led to the syntheses of pentadecanedioic acid suitable for cyclisation to exaltone, starting from kamlolenic acid, erucic acid, undec-10-enoic acid, and, as reported here, from aleuritic acid.



Reagents: 1, HBr–AcOH. 2, Esterifn.; Zn–EtOH. 3, NaOAc–AcOH. 4, H_2–Ni. 5, PhMgBr. 6, $-H_2O$. 7, CrO_3–AcOH. 8, Esterifn.; Na–xylene. 9, Ac_2O–pyridine. 10, Ca–NH_3. 11, Ac_2O–pyridine; Me_2CO–$KMnO_4$–AcOH. 12, 14, 16, Cyclisation. 13, 15, Hydrolysis.

Isomers of ambrettolide and dihydroambrettolide have not been found in Nature. However, Δ^9-isoambrettolide[7] and the Δ^5- and Δ^6-isomer[8] were synthesised earlier by high-dilution cyclisation of the corresponding ω-hydroxy-acids. Syntheses of dihydroambrettolide[9] have also been reported.

The reactions leading to the new syntheses of exaltone, exaltolide, dihydroambrettolide, and *trans*-Δ^9-isoambrettolide[10] from aleuritic acid, reported in this paper, are summarised in the chart.

Ethyl *trans*-16-bromohexadec-9-enoate (III) obtained from aleuritic acid (I) by hydrobromination and debromination of its ester,[11] was acetoxylated by treatment with fused sodium acetate and glacial acetic acid, and hydrogenated to furnish ethyl 16-acetoxyhexadecanoate (V). A modified Barbier–Wieland degradation[12] then yielded pentadecanedioic

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[6] Dhekne, Ghatge, Nayak, Chakravarti, and Bhattacharyya, *J.*, 1962, 2348; Ghatge, Nayak, Chakravarti, and Bhattacharyya, *Chem. and Ind.*, 1960, **1334**; Nair, Mathur, and Bhattacharyya, *Tetrahedron*, 1963, in the press.

[7] Mitter and Bhattacharyya, *J. Indian Chem. Soc.*, 1942, **19**, 69; Hunsdiecker, *Naturwiss.*, 1942, **30**, 587.

[8] Collaud, *Helv. Chim. Acta*, 1942, **25**, 965; 1943, **26**, 849.

[9] Crabalona, B.P. 655,428/1951; Tong, *Soap, Perfumery and Cosmetics*, 1954, **27**, 58.

[10] Mathur and Bhattacharyya, Indian Pat. 65,543/1958; *Chem. and Ind.*, 1960, 1441.

[11] Mathur and Bhattacharyya, *J.*, 1963, 114.

[12] Fierz-David and Kuster, *Helv. Chim. Acta*, 1939, **22**, 82.

acid (VIII), the diester of which on cyclisation furnished the acyloin (IX) which in the form of its acetate was treated with calcium in liquid ammonia.[13] The product was resolved by column chromatography into exaltone (XI), cyclopentadecanol (XII), the diol (XIII), and the hydrocarbon (XIV).

The hydrocarbon (XIV), purified by chromatography and distillation over sodium, did not crystallise, contrary to an earlier report.[14] It is being further examined. A liquid, saturated C_{15} ketone was also isolated in a small amount by elaborate chromatography and is being investigated.

For the preparation of exaltolide, the alcoholic group of 16,16-diphenylhexadec-15-en-1-ol (VII) was protected by acetylation, and the acetate was treated with permanganate in acetone containing a small amount of acetic acid (sufficient to prevent hydrolysis of the acetate group by the alkali formed). 15-Hydroxypentadecanoic acid (XV) so obtained was cyclised by vacuum-distillation of its polyester,[15] to yield exaltolide.

EXPERIMENTAL

Infrared spectra were recorded on a Grubb-Parsons double-beam spectrometer with sodium chloride optics, except for the lactones, the spectra of which were obtained on an Infracord instrument model 137b. The spectra of solids were recorded for Nujol mulls. Acid-washed alumina (grade II; pH 8·5) was employed for chromatography. Light petroleum had b. p. 40—60°.

Ethyl 16-*Acetoxyhexadecanoate* (V).—Ethyl *trans*-16-bromohexadec-9-enoate (III) (120 g.) (prepared from aleuritic acid [11]) was refluxed under stirring with glacial acetic acid (240 ml.) and fused sodium acetate (120 g.) for 12 hr. Acetic acid was distilled off under reduced pressure and the residue poured in cold water, extracted with light petroleum (b. p. 60—80°), and washed free from acid. The solution was dried (Na_2SO_4), solvent removed, and the residue distilled, affording ethyl *trans*-16-acetoxyhexadec-9-enoate (IV) (108 g.), b. p. 140°/0·016 mm., n_D^{27} 1·4570 (Found: C, 70·6; H, 10·8. Calc. for $C_{20}H_{36}O_4$: C, 70·5; H, 10·7%).

The acetoxy-ester (IV) (100 g.) was hydrogenated in alcohol (250 ml.) with Raney nickel (2 g.) for 4 hr. at 250 lb./sq. in. and 100°. The saturated *acetoxy-ester* (V) was distilled (95 g.) (b. p 148—150°/0·1 mm.); it then crystallised from light petroleum and had m. p. 41—41·5° (Found: C, 70·4; H, 11·25. $C_{20}H_{38}O_4$ requires C, 70·1; H, 11·2%).

16,16-*Diphenylhexadec*-15-*en*-1-*ol* (VII).—To phenylmagnesium bromide [from magnesium turnings (26·5 g.) and bromobenzene (172 g.)] in ether (170 ml.), ethyl 16-acetoxyhexadecanoate (83 g.) in ether (830 ml.) was added during 2 hr. with stirring and cooling. The mixture was then refluxed for 1 hr., cooled, and decomposed with sulphuric acid (112 g. in 200 ml. of water). The ether solution was washed and evaporated and the residue heated with a little iodine at 250° for 30 min. Diphenylethylene distilled (b. p. 72—73°/0·2 mm.); the residual 16,16-*diphenylhexadec*-15-*en*-1-*ol*, crystallised from light petroleum, had m. p. 47—48° (58·2 g.) (Found: C, 85·7; H, 10·3. $C_{28}H_{40}O$ requires C, 85·65; H, 10·3%).

Pentadecanedioic Acid [16] (VIII).—The alcohol (VII) (48 g.) in acetic acid (480 ml.) was treated at 70—75° (bath) with chromic anhydride (84 g.) in water (85 ml.), during 1 hr. with stirring. The solution was refluxed for 1 hr. and the acetic acid then removed under reduced pressure. The residue was digested with 10% sulphuric acid (500 ml.) on a water-bath for 1 hr. and allowed to cool. The organic layer which separated was removed, washed, dried, and refluxed with 10% alcoholic potassium hydroxide (300 ml.) for 1 hr., filtered hot to remove suspended inorganic matter, and evaporated. The residue was extracted repeatedly with light petroleum to remove benzophenone, freed from petroleum, dissolved in hot water, and acidified with dilute hydrochloric acid. The liberated acid was washed free from mineral acid and recrystallised from benzene and then from acetic acid, giving pure pentadecanedioic acid (27·9 g.), m. p. 114—114·5° (lit.,[16] 114·6—114·8°), $\nu_{max.}$ 2855 (associated OH [17]) and 1689 cm.$^{-1}$ (Found: C, 66·5; H, 10·6. Calc. for $C_{15}H_{28}O_4$: C, 66·4; H, 10·4%).

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[13] Chapman, Elks, Phillipps, and Wyman, *J.*, 1956, 4344.

[14] Ruzicka, Stoll, Huyser, and Boekenoogen, *Helv. Chim. Acta*, 1930, **13**, 1158; Hubert and Dale, *Chem. and Ind.*, 1961, 249.

[15] Spanagel and Carothers, *J. Amer. Chem. Soc.*, 1936, **58**, 654.

[16] Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.

[17] Corish and Davison, *J.*, 1955, 2431.

The dicarboxylic acid (27 g.) was esterified azeotropically and the diethyl ester distilled (30·1 g.; b. p. 144—145°/0·08 mm.). It had m. p. 31—32° (lit.,[16] 30°) (Found: C, 69·7; H, 10·9. Calc. for $C_{19}H_{36}O_4$: C, 69·5; 11·05%).

2-*Hydroxycyclopentadecanone* [18] (IX).—Diethyl pentadecanedioate (27·6 g.) in xylene (30 ml.) was added during 1 hr. to pulverised sodium (10 g.) in refluxing xylene (1 l.) under nitrogen, and the reaction continued for 30 min. The mixture was cooled, then decomposed with alcohol (145 ml.), and the xylene solution washed free from alkali and evaporated under reduced pressure. The residual crude acyloin (14·5 g.) was distilled; it had b. p. 138—141°/0·05 mm. and $\nu_{max.}$ 3445 and 1703 cm.$^{-1}$ (Found: C, 75·1; H, 11·8. Calc. for $C_{15}H_{28}O_2$: C, 74·95; H, 11·7%).

The acyloin (9·4 g.) was treated with acetic anhydride (15 ml.) and dry pyridine (30 ml.) at room temperature for 12 hr. and then at 90—100° for 6 hr. The *acetate* (X), when distilled (9·24 g.), had b. p. 123—127°/0·07 mm. and n_D^{27} 1·4740 (Found: C, 72·5; H, 10·4. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%). It showed no infrared hydroxyl absorption.

Reduction of the Acyloin Acetate (X) *with Calcium and Liquid Ammonia.*[13]—The acetate (X) (9·2 g.) in tetrahydrofuran (90 ml.) was added during 5 min. to a stirred solution of calcium (5·2 g.) in liquid ammonia (700 ml.). The reaction was continued for 5 min. and the excess of calcium then destroyed with bromobenzene (7 ml.). Water (4 ml.) was added and the ammonia allowed to evaporate. Tetrahydrofuran was recovered and the residue acidified, extracted with ether, and worked up to yield a solid product (7·6 g.). This was chromatographed on alumina (150 g.) (63 × 1·7 cm.) and resolved into seven major fractions as tabulated.

Fraction	Eluant (ml.)	Wt. (g.)		$\nu_{max.}$ (cm.$^{-1}$)
A	Hexane (75)	0·76	Viscous liquid	1714m
B	Hexane (650)	1·90	Solid	1710s
C	Hexane–benzene (1 : 1) (400)	0·52	Liquid	3460m, 1703s, 1666s
D	Benzene (300)	0·72	Solid	3240s, 1708w
E	Ether (275)	0·69	Liquid	3355s, 1700s
F	Chloroform (400)	1·24	Solid	3320s
G	Ethanol (200)	0·72	Solid	3280s

Fraction (B), crystallised from methanol, had m. p. 62·5—63° and gave a semicarbazone m. p. 188—189° (from methanol) (lit.,[19] 187—188°), $\nu_{max.}$ 3445, 3120, 2340, 1658, 1624, 1581, 1341, 1285, 1228, 1144, 1086, 771, and 736 cm.$^{-1}$ (Found: C, 68·7; H, 11·4; N, 14·9. Calc. for $C_{16}H_{31}N_3O$: C, 68·3; H, 11·1; N, 14·9%). From the semicarbazone, exaltone (XI) was regenerated by treatment with oxalic acid and sublimed; it had m. p. and mixed m. p. 63° (lit.,[19] 63°), $\nu_{max.}$ 1711 (C=O), 1404, 1281, 1208, 1154, 1125, 1073, 1052, and 735 cm.$^{-1}$ (Found: C, 80·4; H, 12·6. Calc. for $C_{15}H_{28}O$: C, 80·3; H, 12·6%). The carbonyl maximum in the spectrum of exaltone recorded in a potassium bromide disc (Perkin-Elmer spectrophotometer model 221) was at 1709 cm.$^{-1}$.

Fraction (D), after crystallisation from light petroleum, melted at 80·5—82°. It was treated with Girard's reagent P in the usual way and the non-ketonic fraction was sublimed at 115—120°/0·1 mm., to afford cyclopentadecanol, m. p. 81—82° (lit.,[20] 81°), $\nu_{max.}$ 3300, 2350, 1708vw, 1350, 1296, 1124, 1021, 1001, 936, and 711 cm.$^{-1}$ (Found: C, 79·4; H, 13·6. Calc. for $C_{15}H_{30}O$: C, 79·6; H, 13·4%).

Fraction (F), on repeated crystallisation from hexane, afforded *cyclopentadecane*-1,2-*diol* (XIII), m. p. 118·5—119°, $\nu_{max.}$ 3300, 2350, 1320, 1254, 1157, 1118, 1071, 1041, 1013, 993, 927, 902, and 861 cm.$^{-1}$ (Found: C, 74·4; H, 12·9. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%).

Fraction (G) was resolved by crystallisation from hexane into two epimers. One melting at 118—118·5° was identical with the above diol. The second epimer of *cyclopentadecane*-1,2-*diol* melted at 103·5—104·5° (Found: C, 74·2; H, 12·2%). The infrared spectra of the two epimers differed in the finger-print region.

Fraction (A) (0·6 g.) was chromatographed over alumina (60 g.) and separated into a hydrocarbon fraction (0·28 g.) and a ketone fraction (0·21 g.) by using hexane as the eluant. The hydrocarbon showed a trace of unsaturation ($\nu_{max.}$ 968 cm.$^{-1}$) and was shaken with 10% oleum (25 ml.) for 12 hr. This gave cyclopentadecane which, distilled over sodium (0·15 g.), had

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[18] Stoll and Rouvé, *Helv. Chim. Acta*, 1947, **30**, 1835.

[19] Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1926, **9**, 260.

[20] Kobelt, Barman, Prelog, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 263.

b. p. 150—152° (bath)/0·4 mm., n_D^{28} 1·4720, $\nu_{max.}$ 2850, 1600, 1461, 1449, 1373, 1304, and 730 cm.$^{-1}$ (Found: C, 85·4; H, 14·3. Calc. for $C_{15}H_{30}$: C, 85·6; H, 14·4%).

The ketone fraction had the characteristic musk odour, b. p. 148—149°/0·1 mm., n_D^{29} 1·4805, and $\nu_{max.}$ 1702, 1444, 1408, 1351, 1248, 1127, and 1068 cm.$^{-1}$ (Found: C, 79·8; H, 12·1. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). It did not form a semicarbazone by the acetate method.

15-*Hydroxypentadecanoic Acid* [21] (XV).—16,16-Diphenylhexadec-15-en-1-ol (VII) (10 g.) was refluxed with acetic anhydride (10 ml.) and pyridine (20 ml.) for 4 hr. and left overnight. The acetate (10·5 g.) had no infrared hydroxyl absorption. It was oxidised in acetone (150 ml.) containing acetic acid (15 ml.) by gradual addition of potassium permanganate (11·22 g.) during 1 hr. with stirring at 26°. Stirring was continued for another 2 hr., followed by refluxing for 3 hr. Acetone was distilled and into the residue in aqueous suspension sulphur dioxide was bubbled. The product thus liberated was extracted with ether, worked up, and saponified with alcoholic potassium hydroxide (10 g. in 100 ml.). Alcohol was distilled off and from the residue benzophenone was extracted with light petroleum. The product now left was dissolved in water and acidified with cold dilute hydrochloric acid, and the liberated hydroxy-acid filtered off, washed, and dried. The crude acid (3·75 g.), crystallised from benzene, had m. p. 84—84·5° (lit.,[21] 84·2—84·6°) and $\nu_{max.}$ 3055, 1694, and 1059 cm.$^{-1}$ (Found: C, 69·3; H. 11·7%; equiv., 260. Calc. for $C_{15}H_{30}O_3$: C, 69·7; H, 11·7%; equiv., 258).

Exaltolide (XVI).—The ω-hydroxy-acid (IX) (1·6 g.) was heated at 200—230° for 3 hr. and then at 240°/1 mm. for 1·5 hr., yielding a polyester which was depolymerised by addition of magnesium oxide (0·2 g.) and heating at 260—270° (bath)/0·15 mm. The distillate (0·6 g.) was taken into ether and washed with 5% sodium carbonate solution (25 ml.) and then chromatographed over alumina (10 g.). The column was eluted with hexane, and the middle fraction (0·4 g.), which was a solid, was sublimed, yielding pure exaltolide, m. p. 30·5—31° (lit.,[4] 31—32°), $\nu_{max.}$ (molten film), 2941, 2874, 1730 (macrocyclic lactone [22]), 1453, 1379, 1342, 1231, 1161 1104, 1066, 1011, and 715 cm.$^{-1}$ (Found: C, 74·8; H, 11·5. Calc. for $C_{15}H_{28}O_2$: C, 74·95; H, 11·7%).

16-*Hydroxyhexadecanoic Acid* (XVII).—Ethyl 16-acetoxyhexadecanoate (V) (28 g.) was refluxed with 10% alcoholic potassium hydroxide (150 ml.) and the hydroxy-acid liberated by acidification was processed. Crystallisation from ethanol and then from benzene gave 16-hydroxyhexadecanoic acid (juniperic acid) (19·8 g.), m. p. 94·5—95·5° (lit.,[21] 94°), $\nu_{max.}$ 3200, 1689, and 1058 cm.$^{-1}$ (Found: C, 70·4; H, 12·0. Calc. for $C_{16}H_{32}O_3$: C, 70·5; H, 11·8%).

Dihydroambrettolide (XVIII).—The acid (XVII) (15 g.) was converted into the polyester as described above. Magnesium chloride (0·3 g.) was added and the product depolymerised by distillation at 260—270° (bath)/0·2 mm. during 2 hr. Dihydroambrettolide, obtained as the distillate, was washed with sodium carbonate solution and redistilled (9·9 g.). The product, b. p. 133—134°/0·45 mm., was chromatographed and finally sublimed, then having m. p. 33·5—34° (lit.,[4] 33—34°), $\nu_{max.}$ 2941, 2874, 1730, 1450, 1376, 1339, 1235, 1159, 1104, 1060, and 719 cm.$^{-1}$ (Found: C, 75·75; H, 11·6. Calc. for $C_{16}H_{32}O_2$: C, 75·5; H, 11·9%).

trans-Δ^9-*Isoambrettolide* (XX).—16-Hydroxy-*trans*-hexadec-9-enoic acid (XIX) obtained by alkaline hydrolysis of ethyl 16-acetoxy-*trans*-hexadec-9-enoate (IV), on repeated crystallisation from benzene, melted at 70·5—71·5° (lit.,[7] 70°) and had $\nu_{max.}$ 3200, 1675, 1052, and 961 cm.$^{-1}$ (Found: C, 70·9; H, 11·0. Calc. for $C_{16}H_{30}O_3$: C, 71·1; H, 11·2%). The acid (XIX) (5 g.) was converted into the polyester by refluxing it in toluene (100 ml.) containing toluene-*p*-sulphonic acid (0·1 g.) for 8 hr. under an azeotropic head. The polyester was washed free from mineral acid, and depolymerised by means of magnesium chloride (0·1 g.). The distillate was purified as described above, affording Δ^9-isoambrettolide (2·4 g.), b. p. 115—116°/0·2 mm., n_D^{24} 1·4792, $\nu_{max.}$ 2941, 2874, 1730, 1451, 1433, 1376, 1333, 1235, 1171, 1143, 1111, 1078, 968 (*trans*-CH=CH), and 719 cm.$^{-1}$ (Found: C, 76·1; H, 11·2. Calc. for $C_{16}H_{28}O_2$: C, 76·1; H, 11·2%).

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[21] Chuit and Hausser, *Helv. Chim. Acta*, 1929, **12**, 463.

[22] Allen and Allan, *J. Org. Chem.*, 1949, **14**, 755; Jones, Angell, Ito, and Smith, *Canad. J. Chem.*, 1959, **37**, 2007.