974. *Synthesis of* (±)-cis-9-*Hydroxyoctadec*-12-*enoic Acid.*

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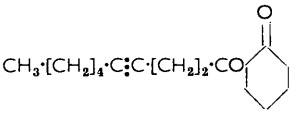
The structure assigned to a naturally-occurring isomer of ricinoleic acid has been confirmed by synthesis of the racemate.

The lævorotatory isomer of ricinoleic acid occurring in the seed oil of *Strophanthus sarmentosus*,[1] *S. hispidus, and S. courmontii* [2] has been shown by degradative studies [1] to be *cis*-9-hydroxyoctadec-12-enoic acid (I). Synthetic confirmation of this constitution has been obtained in the following manner.

$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot[CH_2]_2\cdot CH(OH)\cdot[CH_2]_7\cdot CO_2H$ (I)



(II)

$CH_3\cdot[CH_2]_4\cdot C{:}C\cdot[CH_2]_2\cdot CO\cdot[CH_2]_n\cdot CO_2H$ (III)

Oct-2-yn-1-ol was conveniently prepared by alkylation of tetrahydropyranyloxyprop-1-yne with n-pentyl bromide and subsequent acid hydrolysis. Malonation of the corresponding bromide followed by hydrolysis and decarboxylation gave crystalline dec-4-ynoic acid. The acid chloride of the latter was condensed with 1-morpholinocyclohex-1-ene to produce, after hydrolysis, 2-dec-4′-ynoylcyclohexan-1-one (II); basic hydrolysis of this β-diketone gave 7-oxohexadec-10-ynoic acid (III; $n = 5$), chain extension of which was carried out by the following sequence. Simultaneous acid-catalysed ketalisation and esterification were effected with an excess of ethylene glycol, and the product was reduced with lithium aluminium hydride to give, after acid hydrolysis, 7-oxohexadec-10-yn-1-ol. Malonation of the derived bromide, hydrolysis, and decarboxylation furnished 9-oxo-octadec-12-ynoic acid (III; $n = 7$). An attempt was made to obtain this acid more simply by treating 1-morpholinocyclo-oct-1-ene with dec-4-ynoyl chloride followed by basic fission of the resulting 2-dec-4′-ynoylcyclo-octan-1-one. Unfortunately, treatment of the latter β-diketone with a wide variety of basic reagents produced fission in the unwanted manner with regeneration of cyclo-octanone and dec-4-ynoic acid.

Reduction of 9-oxo-octadec-12-ynoic acid, first with sodium borohydride and then with hydrogen in the presence of Lindlar catalyst, gave the required *cis*-9-hydroxyoctadec-12-enoic acid. This synthetic racemate was identical in all physical properties, except optical rotation, with the naturally-occurring lævorotatory acid kindly provided by Dr. F. D. Gunstone. For a more direct comparison, the latter acid was converted into the racemate by oxidation to the crystalline *cis*-9-oxo-octadec-12-enoic acid and reduction of this keto-acid with sodium borohydride.

Experimental

Oct-2-yn-1-ol.—Tetrahydropyranyloxyprop-1-yne [3] (35 g.) in ether (50 ml.) was added during 1 hr. to a stirred suspension of sodamide in liquid ammonia, prepared from sodium (6·5 g.). After 2 hr., n-pentyl bromide (41·0 g.) in ether (50 ml.) was added dropwise over 1 hr. The mixture was stirred for a further 4 hr., and the ammonia was allowed to evaporate overnight. The product obtained after addition of water and isolation by ether extraction, was dissolved in methanol (125 ml.) containing 25% aqueous sulphuric acid (10 ml.) and left for 8 hr. at room temperature. The mixture was poured into water (250 ml.), the solution was extracted with ether, and the ether extracts were washed successively with aqueous sodium hydrogen carbonate and sodium chloride. Distillation gave oct-2-yn-1-ol (39·4 g., 63%), b. p. 102—106°/23 mm., n_D^{25} 1·4540 (lit.,[4] b. p. 76—82°/2 mm., n_D^{20} 1·4550).

Diethyl Oct-2-ynylmalonate.—A stirred solution of diethyl sodiomalonate, prepared from

[1] Gunstone, *J.*, 1952, 1274.
[2] Gunstone, *J. Sci. Food Agric.*, 1953, **4**, 129.
[3] Henbest, Jones, and Walls, *J.*, 1950, 3646.
[4] Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4263.

diethyl malonate (197 g.), sodium (22·7 g.), and ethanol (1100 ml.), was treated dropwise with 1-bromo-oct-2-yne [4] (143 g.), and the mixture was refluxed for 6 hr. After concentration of the ethanol solution, water (500 ml.) was added and the mixture extracted with ether. Distillation gave *diethyl oct-2-ynylmalonate* (145 g., 71%), b. p. 124—128°/0·3 mm., $n_D^{17.5}$ 1·4488 (Found: C, 67·1; H, 8·85. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%). There was also obtained a higher-boiling fraction consisting of *diethyl dioct-2-ynylmalonate* (25 g., 9%), b. p. 154—160°/0·3 mm., n_D^{25} 1·4620 (Found: C, 73·0; H, 9·5. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%).

Oct-2-ynylmalonic Acid.—Diethyl oct-2-ynylmalonate (145 g.) was hydrolysed by refluxing it for 3 hr. with potassium hydroxide (91 g.) in ethanol (700 ml.). The *malonic acid* crystallised from light petroleum (b. p. 60—80°) as plates (93 g., 80%), m. p. 110—111° (Found: C, 62·2; H, 7·5. $C_{11}H_{16}O_4$ requires C, 62·2; H, 7·6%).

Dec-4-ynoic Acid.—Oct-2-ynylmalonic acid (47·5 g.) was heated in an oil bath at 160° for 3 hr. The product, *dec-4-ynoic acid* crystallised from light petroleum (b. p. 40—60°) as plates (27 g., 72%), m. p. 36·5—37° (Found: C, 71·5; H, 9·3. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). The *anilide* crystallised from benzene–light petroleum as needles, m. p. 105—105·5° (Found: C, 79·1; H, 8·4; N, 5·7. $C_{16}H_{21}NO$ requires C, 79·0; H, 8·7; N, 5·8%).

Hydrogenation in ethanol over 10% palladium–charcoal and crystallisation from light petroleum (b. p. 40—60°) gave decanoic acid, m. p. 30—31° (lit., m. p. 31°) (Found: C, 69·6; H, 11·4. Calc. for $C_{10}H_{20}O_2$: C, 69·7; H, 11·7%) [anilide, m. p. 69°, from benzene–light petroleum (lit., m. p. 69·5°) (Found: C, 77·5; H, 10·1; N, 5·7. Calc. for $C_{16}H_{25}NO$: C, 77·7; H, 10·2; N, 5·7%)].

Dec-4-ynoyl Chloride.—A solution of dec-4-ynoic acid (58 g.) in benzene (120 ml.) was treated dropwise with oxalyl chloride (52 g.) and the mixture was left at room temperature overnight. Distillation gave the acid chloride as an oil (57 g., 90%), b. p. 76—78°/0·5 mm., n_D^{26} 1·4592, $\nu_{max.}$ (thin film) 1800 cm.$^{-1}$.

2-*Dec*-4′-*ynoylcyclohexanone.*—Dec-4-ynoyl chloride (23 g.) in dry chloroform (50 ml.) was added slowly to a solution of 1-morpholinocyclohex-1-ene [5] (23 g.) and triethylamine (15·2 g.) in dry chloroform (50 ml.) at 40°. After a further 1 hr. at 40°, the mixture was stirred overnight at room temperature; 20% sulphuric acid (95 ml.) was added and the mixture was refluxed for 6 hr. The chloroform layer was separated and washed with water until the washings were at pH 6. The combined aqueous layer and washings were brought to pH 6 with 2N-aqueous sodium hydroxide and extracted with chloroform. Distillation of the combined chloroform extracts gave 2-*dec*-4′-*ynoylcyclohexanone* (19 g., 62%), b. p. 130°/10^{-3} mm., n_D^{25} 1·5032 (Found: C, 77·3; H, 9·85. $C_{16}H_{24}O_2$ requires C, 77·3; H, 9·75%); $\nu_{max.}$ (thin film) 3200—2700, 1600 cm.$^{-1}$; $\lambda_{max.}$ (ethanol) 290 mμ (ε 8090).

7-*Oxohexadec*-10-*ynoic Acid.*—2-Dec-4′-ynoylcyclohexanone (18 g.) was refluxed with 10% aqueous potassium hydroxide (75 ml.) for 3 hr., and set aside overnight. Acidification with 3N-sulphuric acid and ether extraction gave the *acid*, which crystallised from aqueous ethanol as plates (15 g., 79%), m. p. 57·5—58° (Found: C, 72·35; H, 9·7. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·8%); $\nu_{max.}$ (Nujol mull) 1705, 1700 cm.$^{-1}$. The *anilide* crystallised from aqueous ethanol as needles, m. p. 107—108° (Found: C, 76·7; H, 9·2; N, 4·4. $C_{22}H_{31}NO_2$ requires C, 77·3; H, 9·15; N, 4·1%).

2-*Dec*-4′-*ynoylcyclo-octanone.* Cyclo-octanone (12·6 g.), morpholine (8·7 g.) and toluene-*p*-sulphonic acid (0·2 g.) were refluxed in benzene (40 ml.) until water no longer separated (*ca.* 4 hr.). The cooled mixture was washed with saturated aqueous sodium hydrogen carbonate and dried. Distillation gave 1-morpholinocyclo-oct-1-ene (19·5 g., 70%), b. p. 142—148°/12 mm., n_D^{21} 1·5148.

Acylation of the above enamine with dec-4-ynoyl chloride (3·73 g.) as in the above cognate preparation gave 2-*dec*-4′-*ynoylcyclo-octan*-1-*one* as an oil (2·1 g., 38%), b. p. 150—156°/0·1 mm., n_D^{21} 1·5050 (Found: C, 78·0; H, 10·3. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%); $\nu_{max.}$ (thin film) 3200—2700, 1600 cm.$^{-1}$; $\lambda_{max.}$ (ethanol) 290 mμ (ε 6700).

Treatment of this β-diketone with alkali under the conditions described above for the analogous cyclohexanone, gave, as the only products, dec-4-ynoic acid (76%), subliming at 60°/10^{-4} mm., m. p. and mixed m. p. 35°, together with cyclo-octanone (67%) [2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 174°]. Similar results were obtained when the diketone was refluxed for 30 hr. with aqueous barium hydroxide or kept for 12 hr. in dilute aqueous alcoholic potassium hydroxide.

[5] Hunig, Benzing, and Lucke, *Chem. Ber.*, 1957, **90**, 2833.

7-*Oxohexadec*-10-*yn*-1-*ol*.—7-Oxohexadec-10-ynoic acid (28 g.), ethylene glycol (12 g.), and toluene-*p*-sulphonic acid (0·3 g.) were refluxed in benzene (400 ml.), with constant separation of water, for 36 hr. The cooled mixture was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated to give the crude ketal-ester (33 g.), $\nu_{max.}$ (thin film) 3500, 1745, 1070 cm.$^{-1}$.

This ketal-ester in ether (60 ml.) was slowly added dropwise to a stirred slurry of lithium aluminium hydride (7·4 g.) in ether (100 ml.), and the mixture was refluxed for 12 hr. After destruction of the excess of hydride with ethyl acetate, water (100 ml.) was added and the mixture was extracted with ether. Evaporation gave the ketal, $\nu_{max.}$ (thin film) 3400, 1080 cm.$^{-1}$.

The crude ketal, in ether (75 ml.), was shaken with 6N-sulphuric acid (80 ml.) for 6 hr. The ether layer was washed with saturated aqueous sodium hydrogen carbonate and dried. Evaporation gave the *alcohol*, which crystallised from methanol as plates (17·3 g., 65%), m. p. 41—42° (Found: C, 76·0; H, 10·9. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%); $\nu_{max.}$ (Nujol mull) 3350, 1705 cm.$^{-1}$.

Diethyl 7-*Oxohexadec*-10-*ynylmalonate*.—Phosphorus tribromide (1·26 g.) was added dropwise to a cooled solution of 7-oxohexadec-10-yn-1-ol (3·51 g.) and pyridine (5 ml.) in ether (20 ml.). After a 4 hours' reflux, water (20 ml.) was added and the mixture was extracted with ether. The ether extracts were washed successively with 25% sulphuric acid, saturated aqueous sodium hydrogen carbonate, and brine. Evaporation gave crude 1-bromo-7-oxohexadec-10-yne (3·2 g.), $\nu_{max.}$ (thin film) 1705 cm.$^{-1}$.

The crude bromo-compound was added dropwise to a solution prepared from sodium (0·46 g.), ethanol (15 ml.), and diethyl malonate (2·4 g.). After 5 hours' reflux, the solution was concentrated to half its volume and water (15 ml.) was added. Ether extraction afforded *diethyl* 7-*oxohexadec*-10-*ynylmalonate* (1·86 g., 46%), b. p. 138—146°/10^{-3} mm. (Found: C, 69·6; H, 9·4. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%); $\nu_{max.}$ (thin film) 1748, 1720 cm.$^{-1}$.

7-*Oxohexadec*-10-*ynylmalonic Acid*.—The substituted malonic ester (8·0 g.) was refluxed for 2 hr. with potassium hydroxide (2·3 g.) in aqueous ethanol (60 ml.). After removal of solvent, water (30 ml.) was added and the mixture was extracted with ether to remove unchanged ester. The aqueous solution was acidified, and extracted with ether to give the *malonic acid* which crystallised from ethyl acetate–light petroleum as plates (4·5 g., 66%), m. p. 108—109° (Found: C, 67·0; H, 8·7. $C_{19}H_{30}O_5$ requires C, 67·4; H, 8·9%).

9-*Oxo-octadec*-12-*ynoic Acid*.—7-Oxohexadec-10-ynylmalonic acid (2·5 g.) was heated at 160° (oil bath) until evolution of carbon dioxide had ceased. The product, in ether, was filtered through a short silica column. The *acid* crystallised from light petroleum (b. p. 40—60°) as plates (1·1 g., 51%), m. p. 66—67° (Found: C, 73·5; H, 10·3. $C_{18}H_{30}O_3$ requires C, 73·4; H, 10·3%); $\nu_{max.}$ (Nujol mull) 1710, 1705 cm.$^{-1}$.

(±)-cis-9-*Hydroxyoctadec*-12-*enoic Acid*.—(*i*) 9-Oxo-octadec-12-ynoic acid (200 mg.) in ethanol (3 ml.) was treated with sodium borohydride (80 mg.) in water (2 ml.) and kept at 0° for 24 hr. 4% Aqueous sodium hydroxide (1 ml.) was added and the mixture was heated on the steam bath for 1 hr. Acidification and ether extraction gave 9-hydroxyoctadec-12-ynoic acid which, after several crystallisations from light petroleum (b. p. 40—60°) at −70°, formed waxy plates (100 mg., 50%), m. p. 38—42°.

The above hydroxy-acid (40 mg.) in ethanol (10 ml.) was hydrogenated over Lindlar catalyst (30 mg.) until 1 mol. of hydrogen was absorbed. After removal of the catalyst and evaporation, crystallisation of the residue from light petroleum (b. p. 40—60°) at −70° gave (±)-*cis*-9-hydroxyoctadec-12-enoic acid as waxy plates (35 mg., 87%), m. p. 28—32°. The infrared and mass spectra were identical with those of the naturally occurring (−)-enantiomorph, m. p. 30—34°.

(*ii*) 9-Oxo-octadec-12-enoic acid [see (*i*) below] (40 mg.) was reduced with sodium borohydride in aqueous ethanol as in the above experiment. (±)-9-Hydroxyoctadec-12-enoic acid was obtained as a solid (25 mg.), m. p. 24—28°. The infrared spectrum was identical with that of the (±)-acid obtained as above.

cis-9-*Oxo-octadec*-12-*enoic Acid*.—(*i*) Natural *cis*-9-hydroxyoctadec-12-enoic acid (0·5 g.) in acetone (5 ml.) was cooled to 0°, and a solution of chromium trioxide (0·12 g.) in concentrated sulphuric acid (0·4 g.) and water (1 ml.) was added dropwise. After 6 hr., water was added and the mixture was extracted with ether. Evaporation and crystallisation from light petroleum (b. p. 40—60°) at −70° gave the *keto-acid* as plates (0·35 g., 70%), m. p. 44—45° (Found: C, 72·5; H, 10·8. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%); $\nu_{max.}$ (Nujol mull) 1710, 1705 cm.$^{-1}$.

(*ii*) Oxidation of synthetic (±)-*cis*-9-hydroxyoctadec-12-enoic acid (20 mg.) under the same conditions gave, after crystallisation, plates (14 mg.), m. p. 40—42°. This was shown by mixed m. p. and by the identity of the respective infrared and mass spectra to be identical with a sample of the keto-acid prepared as in (*i*).

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