122. *Studies in the Polyene Series. Part XXXVI. Further Syntheses of Acetylenic Acids related to Vitamin A.*

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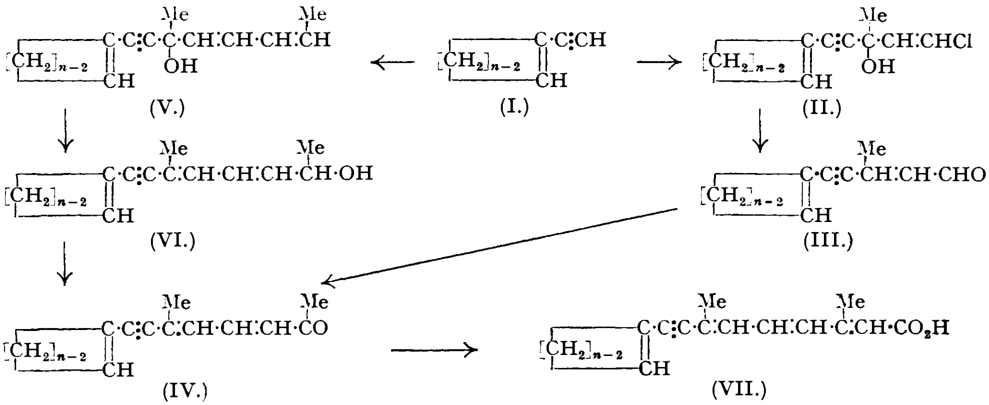
Methods previously developed for the preparation of the *cyclo*hexenyl acid (VII; $n = 6$), which possessed slight growth-promoting properties of the vitamin-A type, have now been applied to the synthesis of the *cyclo*pentenyl and *cyclo*heptenyl analogues (VII; $n = 5$ and 7), both of which were found to be biologically inactive.

As part of a general scheme for the synthesis of compounds with modified vitamin-A structures, the *cyclo*pentenyl and *cyclo*heptenyl acids (VII; $n = 5$ and 7) have now been prepared by the methods previously developed (Heilbron, Jones, and Richardson, *J.*, 1949, 287; Toogood and Weedon, *J.*, 1949, 3123) for the synthesis of the acid (VII; $n = 6$). The last was shown to possess slight but definite growth-promoting properties of the vitamin-A type, and it appeared of interest to examine the effect of varying the size of the ring system on biological activity.

The Grignard reagents from ethynyl*cyclo*pentene (I; $n = 5$) and ethynyl*cyclo*heptene (I; $n = 7$) (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827) were condensed with methyl 2-chlorovinyl ketone and gave the *carbinols* (II; $n = 5$ and 7) in 70 and 90% yields, respectively. The latter on treatment with dilute sulphuric acid underwent anionotropic rearrangement and simultaneous loss of hydrogen chloride, yielding the *aldehydes* (III; $n = 5$ and 7) which were converted into the *ketones* (IV; $n = 5$ and 7) by condensation with acetone in the presence of aluminium *tert.*-butoxide.

The same ketones were also synthesised by the following route. The *carbinols* (V; $n = 5$

and 7), prepared in 65 and 60% yields, respectively, by reaction of the Grignard reagents from (I; $n = 5$ and 7) with crotonylideneacetone, were isomerised by being shaken with dilute sulphuric acid to the fully conjugated *carbinols* (VI; $n = 5$ and 7). Oppenauer oxidation of the latter furnished the ketones (IV; $n = 5$ and 7), identical with those obtained by the alternative route described above.



Condensation of the ketones (IV; $n = 5$ and 7) with methyl bromoacetate and zinc gave, after dehydration of the crude hydroxy-esters and hydrolysis, the crystalline *acids* (VII; $n = 5$ and 7), in 11 and 7% yields, respectively. Neither of these acids showed any growth-promoting properties when fed orally, as aqueous solutions of the sodium salts buffered to pH 10, to young rats deficient in vitamin A [the doses administered would have revealed activity of the same order as that of (VII; $n = 6$), *viz.*, one-thousandth of that of vitamin A itself].

The various compounds described in this paper all exhibited light-absorption properties similar to those of the corresponding *cyclo*hexenyl analogues (see table).

		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Carbinol	(II; $n = 5$)	2290	12,000
	(II; $n = 6$)[1]	2290	13,000
	(II; $n = 7$)	2320	17,000
		2380 *	15,500
Aldehyde	(III; $n = 5$)	2270	15,500
		3110	14,500
	(III; $n = 6$)[1]	2230	14,000
		2810	10,500
		3140	14,000
	(III; $n = 7$)	2260	13,000
		3160	14,500
Ketone	(IV; $n = 5$)	2440	14,500
		3380	28,000
	(IV; $n = 6$)[2]	2450	18,000
		3350	23,000
	(IV; $n = 7$)	2450	13,500
		3350	20,000
Carbinol	(V; $n = 5$)	2280	34,500
		2390 *	27,000
	(V; $n = 6$)[2]	2270	39,000
		2370	30,000
	(V; $n = 7$)	2290	33,000
		2400 *	26,500
Carbinol	(VI; $n = 5$)	2260	16,500
		2830 *	21,500
		2930	23,500
		3000 *	21,500
		3080	19,000
	(VI; $n = 6$)[2]	2910	21,500
		3060	15,000
	(VI; $n = 7$)	2980	27,000
		3070 *	22,000
Acid	(VII; $n = 5$)	2600	18,000
		3400	36,000
	(VII; $n = 6$)[3]	2580	14,000
		3380	33,000
	(VII; $n = 7$)	2580	13,500
		2640	15,500
		3410	34,000

* Inflexion.

[1] Toogood and Weedon, *loc. cit.* [2] Heilbron, Jones, and Richardson, *loc. cit.* [3] Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823.

EXPERIMENTAL.

Light-absorption data were determined in alcohol unless stated otherwise : those not referred to below are to be found in the table. All the operations were carried out in an atmosphere of nitrogen. The 2 : 4-dinitrophenylhydrazones were purified by chromatographic adsorption on alumina from benzene solution.

1-*Chloro*-5-cyclo*pent*-1′-*enyl*-3-*methylpent*-1-*en*-4-*yn*-3-*ol* (II; $n = 5$).—Ethynyl*cyclo*pentene (21 g.) (Heilbron, Jones, Toogood, and Weedon, *loc. cit.*) in ether (50 c.c.) was added dropwise to a solution of ethylmagnesium bromide (from 5·6 g. of magnesium) in ether (100 c.c.), and the mixture was refluxed for 4 hours. After cooling, a solution of methyl 2-chlorovinyl ketone (Catch, Elliott, Hey, and Jones, *J.*, 1948, 278) (15·9 g.; freshly prepared) in ether (50 c.c.) was added during ½ hour and the mixture was refluxed for 1 hour and then cooled. The Grignard complex was decomposed with ice and ammonium chloride (20 g.) and the product was isolated with ether. Distillation gave the *carbinol* (20·9 g.) as a pale yellow viscous liquid, b. p. 65—70° (bath temp.)/10^{-4} mm., n_D^{15} 1·5398 (Found: C, 67·45; H, 6·85. $C_{11}H_{13}OCl$ requires C, 67·15; H, 6·65%).

5-cyclo*Pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (III; $n = 5$).—The above chloro-carbinol (26 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1·5 l.; 1% w/v), and the mixtures steam-distilled. The distillates were combined and the product was isolated by ether extraction. Evaporation of the ethereal solution gave the crude aldehyde (14·7 g.) as a yellow oil, n_D^{14} 1·5791. Light absorption: maxima, 3080 and 3170 A.; $E^{1\%}_{1\,\text{cm.}}$, 780 and 750, respectively, indicating a purity of *ca.* 80%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–methanol in dark red needles, m. p. 164—165° (Found: N, 16·7. $C_{17}H_{16}O_4N_4$ requires N, 16·45%). Light absorption in chloroform (main band only): maximum, 3940 A.; ε, 36,000.

The crude aldehyde (5 g.) was treated with an excess of semicarbazide acetate in aqueous methanol (80%) and gave the *semicarbazone* (2·5 g.), which crystallised from alcohol in plates, m. p. 206—207° (decomp.) (Found: N, 19·3. $C_{12}H_{15}ON_3$ requires N, 19·35%). Light absorption: maxima, 2450 and 3160 A.; ε, 11,500 and 30,500, respectively. Inflexion, 3300 A.; ε, 21,000. A mixture of the semicarbazone (1·6 g.), dilute sulphuric acid (50 c.c.; 10% w/v), and light petroleum (50 c.c.; b. p. 80—100°) was refluxed with vigorous stirring for 4 hours. After removal of unreacted semicarbazone (0·8 g.), the petroleum layer was separated, washed with water, dried, and evaporated. Distillation of the residue gave 5-cyclo*pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (0·3 g.) as a yellow viscous liquid, b. p. 60° (bath temp.)/10^{-4} mm., n_D^{20} 1·5830, which crystallised when kept at 0° (Found: C, 83·0; H, 7·85. $C_{11}H_{12}O$ requires C, 82·45; H, 7·55%).

1-cyclo*Pent*-1′-*enyl*-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (V; $n = 5$).—Crotonylideneacetone (14·4 g.) in ether (20 c.c.) was added during 1 hour to a cooled suspension of *cyclo*pentenylethynylmagnesium bromide (prepared as described above from 3·2 g. of magnesium and 12·1 g. of ethynyl*cyclo*pentene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed by addition of ice and ammonium chloride (20 g.). Isolation gave the *carbinol* (17·3 g.) as a pale yellow liquid, b. p. 75—80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5465 (Found: C, 83·1; H, 9·0. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VI; $n = 5$).—A mixture of the carbinol (V; $n = 5$) (4·8 g.), dilute sulphuric acid (250 c.c.; 1% w/v), ether (50 c.c.), and a trace of quinol was shaken at 20° for 18 hours. The ethereal layer was separated, washed well with water, dried, and evaporated. Distillation of the residue gave the rearranged *carbinol* (2·3 g.) as a yellow oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{18} 1·5882 (Found: C, 82·85; H, 9·1. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (IV; $n = 5$).—(*a*) A solution of the aldehyde (III; $n = 5$) (14·7 g.; crude) and aluminium *tert.*-butoxide (20·6 g.) in a mixture of acetone (400 c.c.) and benzene (675 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (1200 c.c.; 2·5% w/v), and the organic layer separated. The aqueous solution was extracted with ether and the combined ethereal extracts and benzene layer was washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvents and distillation of the residue (9·3 g.) gave the crude ketone (5·5 g.), b. p. 85—90° (bath temp.) 10^{-4} mm., n_D^{15} 1·6064. Light absorption: maxima, 2400 and 3300 A.; $E^{1\%}_{1\,\text{cm.}}$, 470 and 800, respectively. Inflexion, 3480 A.; $E^{1\%}_{1\,\text{cm.}}$, 680, indicating a purity of *ca.* 45—50%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°. The former were converted into the latter on keeping in contact with solvent and on heating (Found: N, 14·85. $C_{20}H_{20}O_4N_4$ requires N, 14·75%). Light absorption in chloroform (main band only): maximum, 4050 A.; ε, 47,500.

The crude ketone (0·6 g.) was treated with an excess of semicarbazide acetate in aqueous methanol and gave the *semicarbazone* (0·26 g.), which crystallised from methanol in needles, m. p. 169—170° (decomp.) (Found: N, 16·15. $C_{15}H_{19}ON_3$ requires N, 16·35%). Light absorption: maxima, 2640 and 3330 A.; ε, 16,500 and 47,000, respectively. A mixture of the semicarbazone (0·4 g.), dilute sulphuric acid (20 c.c.; 10% w/v), and light petroleum (20 c.c.; b. p. 80—100°) was refluxed with vigorous stirring until all the solid had disappeared (15 minutes). Isolation gave 8-cyclo*pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (0·17 g.) as a yellow viscous oil, b. p. 70° (bath temp.)/10^{-4} mm., n_D^{19} 1·6179, which crystallised when kept at 0° (Found: C, 84·05; H, 8·4. $C_{14}H_{16}O$ requires C, 83·95; H, 8·05%).

(*b*) A solution of the carbinol (VI; $n = 5$) (1·4 g.) and aluminium *tert.*-butoxide (4 g.) in a mixture of benzene (10 c.c.) and acetone (60 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (460 c.c.; 2·5% w/v), and the product isolated. Distillation gave the crude ketone (1·1 g.), n_D^{22} 1·5920. Light absorption: maxima, 2280, 2420, 3330, and 3380 A.; $E^{1\%}_{1\,\text{cm.}}$, 550, 550, 710, and 680, respectively. Inflexion, 3200 A.; $E^{1\%}_{1\,\text{cm.}}$, 680. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°, undepressed on admixture with a specimen from (*a*). The semicarbazone crystallised from methanol in needles, m. p. 169—170° (decomp.), undepressed on admixture with a specimen from (*a*).

8-cyclo*Pent*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; $n = 5$).—A mixture of the ketone (IV, $n = 5$) [4 g.; crude, from (*a*)], methyl bromoacetate (3·5 g.), activated zinc turnings (1·3 g.), a trace of mercuric chloride, and benzene (70 c.c.) was refluxed for ½ hour, all the zinc having then dissolved. The deep-red mixture was cooled and shaken with dilute acetic acid (125 c.c.; 5%). The benzene layer was washed free from acid, dried, and evaporated, giving a mixture (4·5 g.) of hydroxy- and unsaturated esters. Light absorption: maxima, 2820 and 2920 A.; $E^{1\%}_{1\,\text{cm.}}$, 620 and 620. Inflexion, 3000 A.; $E^{1\%}_{1\,\text{cm.}}$, 530. Anhydrous oxalic acid (15 g.) was added and the mixture was heated at 95—100° (bath temp.)/10·1 mm. for 2 hours. After cooling, the crude unsaturated ester was isolated by extraction with light petroleum (b. p. 40—60°). Light absorption: maxima, 2600 and 3450 A.; $E^{1\%}_{1\,\text{cm.}}$, 370 and 800, respectively.

The ester was dissolved in methanolic potassium hydroxide (150 c.c.; 10% w/v), and the solution kept at 20° for 64 hours. The solution was poured into water (500 c.c.), the non-hydrolysable material extracted with ether, and the aqueous layer acidified with phosphoric acid (50 c.c.; 50% w/v). The liberated acid was extracted with ether and the ethereal solution was washed with water, dried, and evaporated. Recrystallisation of the residue from methanol gave the *acid* (270 mg.), m. p. 185—186° (Found: C, 79·5; H, 8·0. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

1-*Chloro*-5-cyclo*hept*-1′-*enyl*-3-*methylpent*-1-*en*-4-*yn*-3-*ol* (II; $n = 7$).—Ethynyl*cyclo*heptene (24 g.) (*loc. cit.*) was condensed with methyl 2-chlorovinyl ketone (11·5 g.) by the procedure described above for the *cyclo*pentenyl analogue. Distillation of the product gave: (i) recovered ethynyl*cyclo*heptene (8·5 g.); (ii) the *carbinol* (21 g.) as a pale yellow viscous oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{18} 1·5372 (Found: C, 69·05; H, 7·7. $C_{13}H_{17}OCl$ requires C, 69·5; H, 7·6%).

5-cyclo*Hept*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (III; $n = 7$).—The chloro-carbinol (II; $n = 7$) (20 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1 l.; 1% w/v) and the mixtures steam distilled. The distillates were combined and the product was isolated with ether and distilled, giving the crude aldehyde (10 g.), b. p. 80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5716. Light absorption: maxima, 2270 and 3150 A.; $E^{1\%}_{1\,\text{cm.}}$, 580 and 560, respectively, indicating a purity of *ca.* 70%. The *semicarbazone* crystallised from methanol in plates, m. p. 205° (Found: N, 17·0. $C_{14}H_{19}ON_3$ requires N, 17·1%). Light absorption: maxima, 2410 and 3170 A.; ε, 12,500 and 29,500, respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from light petroleum (b. p. 60—80°) in dark-red plates, m. p. 156° (Found: N, 15·4. $C_{19}H_{20}O_4N_4$ requires N, 15·2%). Light absorption in chloroform (main band only): maximum, 3980 A.; ε, 39,000.

A mixture of the semicarbazone (1 g.), dilute sulphuric acid (30 c.c.; 10% w/v), and light petroleum (30 c.c.; b. p. 80—100°) was stirred vigorously under reflux until all the solid had disappeared (5 hours). Isolation of the product gave the *aldehyde* (0·5 g.) as a pale yellow oil, b. p. 80° (bath temp.)/10^{-4} mm., n_D^{20} 1·5700 (Found: C, 82·7; H, 9·15. $C_{13}H_{16}O$ requires C, 82·9; H, 8·55%).

1-cyclo*Hept*-1′-*enyl*-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (V; $n = 7$).—Crotonylideneacetone (14·5 g.) in ether (25 c.c.) was added during ½ hour to a cooled suspension of *cyclo*heptenylethynylmagnesium bromide (prepared from 3·0 g. of magnesium and 15·0 g. of ethynyl*cyclo*heptene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed and the product was isolated and distilled, giving the *carbinol* (18·0 g.), b. p. 85—95° (bath temp.)/10^{-4} mm., n_D^{21} 1·5430 (Found: C, 83·45; H, 10·0. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VI; $n = 7$).—A solution of the preceding carbinol (15·0 g.), and a trace of quinol, in ether (50 c.c.) was shaken for 15 hours with dilute sulphuric acid (900 c.c.; 0·5% w/v). Isolation of the product gave the crude carbinol. Distillation, which was accompanied by extensive polymerisation, yielded the *carbinol* (8·0 g.) as a viscous pale yellow oil, b. p. 90—100° (bath temp.)/10^{-5} mm., n_D^{18} 1·5800 (Found: C, 83·4; H, 9·9. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (IV; $n = 7$).—(*a*) A solution of the aldehyde (III; $n = 7$) (18 g.; crude) and aluminium *tert.*-butoxide (25 g.) in a mixture of benzene (800 c.c.) and acetone (400 c.c.) was refluxed for 48 hours. Isolation of the product and distillation gave the ketone (14 g.) as an oil, b. p. 100—110° (bath temp.)/10^{-4} mm., n_D^{24} 1·5920. Light absorption: maxima, 2280, 2370, 2800, and 3300 A.; $E^{1\%}_{1\,\text{cm.}}$, 510, 620, 420, and 770, respectively, indicating a purity of *ca.* 85—90%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark-red plates, m. p. 200° (Found: N, 13·8. $C_{22}H_{24}O_4N_4$ requires N, 13·7%). Light absorption in chloroform (main band only): maximum, 4080 A.; ε, 36,000. The *semicarbazone*, which formed slowly and in poor yield, crystallised from ethanol in pale yellow needles, m. p. 181° (Found: C, 71·55; H, 8·1. $C_{17}H_{23}ON_3$ requires C, 71·55; H, 8·1%). Light absorption: maximum, 3360 A.; ε, 42,500. Inflexion, 3480 A.; ε, 31,500.

A portion (0·8 g.) of the crude ketone was dissolved in light petroleum (b. p. 40—60°) and the solution was poured on a column of partially deactivated alumina (100 g.; Grade IV, cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with the same solvent and the yellow band formed was eluted and collected in two fractions. Removal of the solvent under reduced pressure and distillation of the residues gave: (i) (least strongly adsorbed) an oil (0·35 g.), b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{22} 1·5920, and (ii) the *ketone* (0·4 g.) as a pale yellow oil, b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{19} 1·6132 (Found: C, 84·2; H, 9·2. $C_{16}H_{22}O$ requires C, 84·15; H, 8·85%).

(*b*) A solution of the carbinol (VI; $n = 7$) (9·0 g.) and aluminium *tert.*-butoxide (12·5 g.) in a mixture of acetone (250 c.c.) and benzene (420 c.c.) was refluxed for 48 hours. Isolation gave the crude ketone (7·0 g.) as a pale yellow oil, b. p. 100—110° (bath temp.)/10^{-4} mm.; n_D^{21} 1·5840. Light absorption: maxima, 2450, 3160, and 3370 A.; $E^{1\%}_{1\,\text{cm.}}$, 560, 720, and 720, respectively, indicating an appreciable content of the required ketone.

A solution of the crude ketone (7·0 g.) and Girard reagent-T (7·0 g.) in acetic acid (7·5 c.c.) and alcohol (70 c.c.) was refluxed for 1 hour. Distillation of the crude ketonic material isolated in the usual manner gave the ketone (4 g.), b. p. 90—100° (bath temp.)/10^{-4} mm., n_D^{17} 1·6059. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red plates, m. p. 199°, undepressed on admixture with a specimen from (*a*). The semicarbazone, which formed slowly and in poor yield, crystallised from methanol in needles, m. p. 179°, undepressed on admixture with a specimen from (*a*).

8-cyclo*Hept*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; $n = 7$).—The ketone (IV; $n = 7$) [6·0 g. crude, prepared by route (*a*) above] in benzene (120 c.c.) was condensed with ethyl bromoacetate (5·3 g.) and zinc (1·9 g.). The resulting crude hydroxy-ester was dehydrated, giving the crude unsaturated ester (8·5 g.), n_D^{23} 1·572. Light absorption: maxima, 2490, 2800, and 3420 A.; $E^{1\%}_{1\,\text{cm.}}$, 540, 370, and 680, respectively.

The unsaturated ester was dissolved in a solution of potassium hydroxide in methanol (250 c.c.;

10% w/v), and the solution kept at 20° for 96 hours. Isolation of the acid fraction yielded a viscous yellow gum which partly solidified on trituration with ether. Recrystallisation of the solid from methanol gave the *acid* (0·5 g.) as needles, m. p. 181° (Found: C, 79·8; H, 8·55. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%).

A sample of the ketone (IV; *n* = 7), prepared by route (*b*) above, was also converted into the acid, which crystallised from methanol in needles, m. p. 181°, undepressed on admixture with the specimen described above.

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