

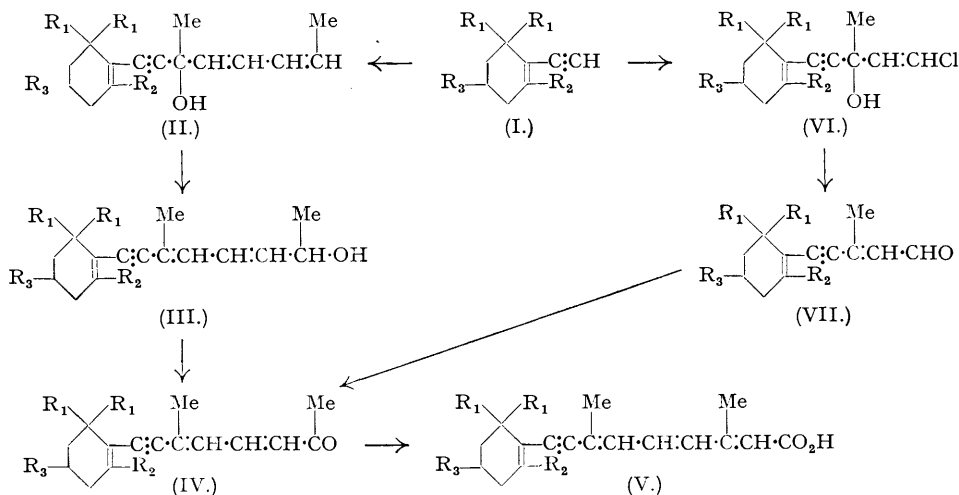
657. Studies in the Polyene Series. Part XXXV. A New Method for the Synthesis of Some Acetylenic Acids related to Vitamin A.

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A new method has been developed for the preparation of acetylenic acids of the type (V), some of which have been shown previously to produce slight but definite growth responses when administered as the sodium salt to rats deficient in vitamin A.

Condensation of the ethynylcyclohexenes (I; $R_1 = R_2 = R_3 = H$; $R_1 = Me$, $R_2 = R_3 = H$; and $R_1 = R_2 = H$, $R_3 = Me$) with methyl 2-chlorovinyl ketone gives the corresponding carbinols (VI). These, on treatment with dilute sulphuric acid, are converted into the aldehydes (VII) which on condensation with acetone yield the ketones (IV). Reaction of the ketone (IV; $R_1 = R_2 = H$, $R_3 = Me$) with ethyl bromoacetate and zinc leads to the isolation of the crystalline acid (V; $R_1 = R_2 = H$, $R_3 = Me$).

PREVIOUS papers in this Series (Heilbron, Jones, and Richardson, this vol., p. 287; Heilbron, Jones, Lewis, and Weedon, *ibid.*, p. 2023; cf. Heilbron, *J.*, 1948, 386) have described the synthesis of the acids (V; R_1 , $R_2 = H$ or Me , $R_3 = H$) which, with one exception (V; $R_1 = R_3 = H$, $R_2 = Me$), showed small but definite growth-promoting properties when administered as the sodium salt to rats deficient in vitamin A. The method of preparation may be summarised as follows. The appropriate ethynylcyclohexenes (I) were condensed with crotonylideneacetone and the resulting carbinols (II) isomerised, by treatment with dilute acids, to the fully conjugated carbinols (III), which were oxidised to the corresponding ketones (IV). Treatment of the latter with methyl bromoacetate under Reformatsky conditions led to the isolation of the crystalline acids (V). A new route for the preparation of the intermediate ketones (IV) has now been developed and employed for the synthesis of the crystalline acid (V; $R_1 = R_2 = H$, $R_3 = Me$).



The Grignard reagents from the ethynylcyclohexenes (I; $R_1 = R_2 = R_3 = H$; $R_1 = Me$, $R_2 = R_3 = H$; and $R_1 = R_2 = H$, $R_3 = Me$) were condensed with methyl 2-chlorovinyl ketone, by a method similar to that previously employed (Jones and Weedon, *J.*, 1946, 937) in analogous condensations with other acetylenes, and gave the carbinols (VI) in excellent yields.

As was expected, treatment of these carbinols with dilute mineral acids resulted in anionotropic re-arrangement, followed by elimination of hydrogen chloride, yielding the

aldehydes (VII; $R_1 = R_2 = R_3 = H$; $R_1 = Me, R_2 = R_3 = H$; and $R_1 = R_2 = H, R_3 = Me$) (cf. *idem, loc. cit.*) which were purified by regeneration from the *semicarbazones* (cf. Heilbron, Jones, and O'Sullivan, *J.*, 1948, 866). The most satisfactory method of effecting these conversions was found to be steam-distillation of mixtures of the chloro-carbinols and 1% sulphuric acid, the aldehydes thus obtained requiring no further purification before use in the next stage of the synthesis.

Condensation of the aldehydes (VII; $R_1 = R_2 = R_3 = H$; and $R_1 = Me, R_2 = R_3 = H$) with acetone occurred readily in the presence of aluminium *tert.*-butoxide yielding the ketones (IV; $R_1 = R_2 = R_3 = H$; and $R_1 = Me, R_2 = R_3 = H$), identical with those obtained previously by the alternative route described above. Similarly the aldehyde (VII; $R_1 = R_2 = H, R_3 = Me$) gave the *ketone* (IV; $R_1 = R_2 = H, R_3 = Me$); treatment of this with

	$\lambda_{\max.}, A.$	$\epsilon_{\max.}$
Carbinol (VI; $R_1 = R_2 = R_3 = H$)	2290	13,000
(VI; $R_1 = Me, R_2 = R_3 = H$)	2280	12,500
(VI; $R_1 = R_2 = H, R_3 = Me$)	2290	18,000
$CH_2:CH:C:CMe(OH):CH:CHCl^1$	2230	14,500
	2320	12,500
Aldehyde (VII; $R_1 = R_2 = R_3 = H$)	2230	14,000
	2810	10,500
	3140	14,000
(VII; $R_1 = Me, R_2 = R_3 = H$)	2290	16,000
	2820	12,500
	3080	17,000
	3150	17,500
(VII; $R_1 = R_2 = H, R_3 = Me$)	2220	12,500
	3100	12,000
$CH_2:CH:C:CMe:CH:CHO^1$	2200	9,000
	2820	12,000
	2920	12,000
	3000	11,500
Ketone (IV; $R_1 = R_2 = R_3 = H$) ²	2450	18,000
	3350	23,000
(IV; $R_1 = R_2 = H, R_3 = Me$)	2410	10,500
	3360	16,500
Acid (V; $R_1 = R_2 = R_3 = H$) ³	3380	33,000
	2580	14,000
(V; $R_1 = R_2 = H, R_3 = Me$)	3390	34,000

¹ Jones and Weedon, *loc. cit.* ² Heilbron, Jones, and Richardson, *loc. cit.* ³ Heilbron, Jones, Julia, and Weedon, this vol., p. 1823.

ethyl bromoacetate and zinc, and dehydration of the resulting hydroxy-ester and hydrolysis, led to the isolation of the crystalline *acid* (V; $R_1 = R_2 = H, R_3 = Me$), m. p. 205–206°, in 13% yield.

This acid produced no growth responses when administered orally, as an aqueous solution of the sodium salt buffered to pH 10, to young rats on a diet deficient in vitamin A (the tests were carried out at doses which would have revealed activity of the order of one thousandth of that of vitamin A itself).

All compounds described in this paper exhibited the expected light-absorption properties (see table).

EXPERIMENTAL.

Light-absorption data were determined in ethanol except where stated otherwise. 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-cyclohex-1'-enyl-3-methylpent-1-en-4-yn-3-ol (VI; $R_1 = R_2 = R_3 = H$).—Ethylnylcyclohexene (24 g.) in ether (50 c.c.) was added dropwise during 30 minutes to a solution of ethylmagnesium bromide (prepared from 6 g. of magnesium) in ether (150 c.c.), and the mixture refluxed for 2½ hours. After cooling, a solution of methyl 2-chlorovinyl ketone (12 g.; freshly prepared) in ether (50 c.c.) was added during 30 minutes and the mixture refluxed for 1 hour and then cooled. The Grignard complex was decomposed with ice and ammonium chloride (15 g.), and the product was isolated with ether, and heated at 90°/18 mm. to remove excess of ethynylcyclohexene (*ca.* 9 g.). Distillation of the residue from a short-path still gave the *carbinol* (21.1 g.) as a colourless viscous liquid, b. p. 65° (bath temp.)/10⁻⁴ mm.,

n_D^{25} 1.5354 (Found: C, 68.15; H, 7.15. $C_{12}H_{15}OCl$ requires C, 68.4; H, 7.15%). Light absorption: see table.

5-cycloHex-1'-enyl-3-methylpent-2-en-4-yn-1-al (VII; $R_1 = R_2 = R_3 = H$).—A mixture of the preceding chloro-carbinol (3.4 g.) and sulphuric acid (500 c.c.; 1% w/v) was steam-distilled, and the product was isolated from the distillate by ether extraction. After being dried, the ethereal extract was evaporated, and the residue distilled giving the crude aldehyde (1.8 g.), b. p. 55° (bath temp.)/10⁻⁵ mm. This material was treated with semicarbazide acetate in aqueous methanol, and gave the semicarbazone (1.72 g.) which crystallised from alcohol in colourless needles, m. p. 200° (decomp.) (Found: N, 17.95. $C_{13}H_{17}ON_3$ requires N, 18.15%). Light absorption: Maximum, 3130 Å.; $\epsilon = 29,000$.

A mixture of the semicarbazone (1.60 g.; m. p. 200°), sulphuric acid (50 c.c.; 10% w/v), and light petroleum (50 c.c.; b. p. 80—100°) was refluxed and stirred vigorously until all the solid had disappeared (4½ hours). After isolation, distillation gave the aldehyde (0.84 g.) as a yellow liquid, b. p. 45—50° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.5730 (Found: C, 82.0; H, 8.35. $C_{12}H_{15}O$ requires C, 82.75; H, 8.1%). Light absorption: see table. The 2:4-dinitrophenylhydrazone crystallised from alcohol in red prisms, m. p. 161° (Found: N, 16.1. $C_{18}H_{18}O_4N_4$ requires N, 15.85%). Light absorption in chloroform (main band only): Maximum, 3950 Å.; $\epsilon = 39,000$.

8-cycloHex-1'-enyl-6-methylocta-3:5-dien-7-yn-2-one (IV; $R_1 = R_2 = R_3 = H$).—A solution of the preceding aldehyde (2.61 g.) and aluminium *tert.*-butoxide (3.65 g.) in benzene (120 c.c.) and acetone (70 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into cold dilute sulphuric acid (200 c.c.; 2.5% w/v) and the organic layer was separated, washed with sodium hydrogen carbonate solution and water, and dried, and the solvent evaporated. Distillation of the residue gave the ketone (2.13 g.), b. p. 95—105° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.6070. Light absorption: Maxima, 2300 and 3340 Å.; $E_{1\text{cm}}^{1\%} = 460$ and 920, respectively, indicating a purity of ca. 85%. The 2:4-dinitrophenylhydrazone crystallised from alcohol in red needles, m. p. 204°, undepressed on admixture with a specimen prepared from the ketone made according to Heilbron, Jones, and Richardson (this vol., p. 287) (Found: N, 14.1. $C_{21}H_{22}O_4N_4$ requires N, 14.2%). Light absorption in chloroform (main band only): Maximum, 4100 Å.; $\epsilon = 38,500$. The semicarbazone crystallised from alcohol in colourless needles, m. p. 190° (decomp.), undepressed on admixture with an authentic specimen. Light absorption: Maximum, 3360 Å.; $\epsilon = 42,000$. Inflexion, 3520 Å.; $\epsilon = 26,000$ [*idem, loc. cit.*, give m. p. 194° (decomp.) (rapid heating). Light absorption: Maximum, 3360 Å.; $\epsilon = 46,500$. Inflexion, 3520 Å.; $\epsilon = 26,000$]. A specimen of the pure ketone, regenerated from the semicarbazone, had b. p. 80—85° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.6170. Light absorption: Maxima, 2420 and 3360 Å.; $\epsilon = 15,500$ and 23,000, respectively [*idem, loc. cit.*, give b. p. 80—85° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.6185. Light absorption: see table].

1-Chloro-5-(6:6-dimethylcyclohex-1-enyl)-3-methylpent-1-en-4-yn-3-ol (VI; $R_1 = Me, R_2 = R_3 = H$).—6:6-Dimethylethynylcyclohexene (15.8 g.) (Heilbron, Jones, Lewis, and Weedon, this vol., p. 2023) in ether (100 c.c.) was added dropwise during 30 minutes to a solution of ethylmagnesium bromide (from 2.85 g. of magnesium) in ether (150 c.c.), and the mixture was refluxed for 3½ hours. After cooling, a solution of methyl 2-chlorovinyl ketone (7.0 g.; freshly prepared) in ether (100 c.c.) was added during 1 hour, and the mixture was refluxed for 1 hour and then cooled. The Grignard complex was decomposed with ice and ammonium chloride, and the product was isolated with ether. After being heated at 90°/0.1 mm., to remove excess of 6:6-dimethyl-1-ethynylcyclohexene (5 g.), the crude carbinol (15.6 g.) was obtained as a dark yellow viscous oil. Light absorption: Maximum, 2290 Å.; $E_{1\text{cm}}^{1\%} = 540$. Distillation of a small portion of the product gave the carbinol as a colourless viscous liquid, b. p. 50—55° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.5228 (Found: C, 71.05; H, 8.4. $C_{14}H_{19}OCl$ requires C, 70.6; H, 8.2%). Light absorption: see table.

5-(6:6-Dimethylcyclohex-1-enyl)-3-methylpent-2-en-4-yn-1-al (VII; $R_1 = Me, R_2 = R_3 = H$).—The preceding chloro-carbinol (14.0 g.) was added to sulphuric acid (1350 c.c.; 1% w/v) and the mixture steam-distilled. The product was isolated with ether giving the crude aldehyde (10.5 g.) as a dark yellow liquid. Light absorption: Maxima, 2290 and 3040 Å.; $E_{1\text{cm}}^{1\%} = 580$ and 520, respectively, indicating a purity of ca. 60%. The crude aldehyde (8.0 g.) was treated with semicarbazide acetate in aqueous methanol and gave the semicarbazone (4.7 g.) which crystallised from aqueous alcohol in colourless needles, m. p. 210° (Found: N, 16.0. $C_{15}H_{21}ON_3$ requires N, 16.2%). Light absorption: Maximum, 3150 Å.; $\epsilon = 36,000$. Inflexion, 3250 Å.; $\epsilon = 29,500$.

Regeneration of the semicarbazone (4.3 g.) gave 5-(6:6-dimethylcyclohex-1-enyl)-3-methylpent-2-en-4-yn-1-al (2.3 g.) as a yellow liquid, b. p. 55° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.5588 (Found: C, 83.2; H, 9.25. $C_{14}H_{19}O$ requires C, 83.1; H, 9.0%). Light absorption: see table. The 2:4-dinitrophenylhydrazone crystallised from alcohol in orange prisms, m. p. 153—154° (Found: C, 62.65; H, 6.05. $C_{20}H_{22}O_4N_4$ requires C, 62.8; H, 5.8%). Light absorption in chloroform (main band only): Maximum, 3910 Å.; $\epsilon = 36,000$.

8-(6:6-Dimethylcyclohex-1-enyl)-6-methylocta-3:5-dien-7-yn-2-one (IV; $R_1 = Me, R_2 = R_3 = H$).—A solution of the above aldehyde (2.0 g.; crude) and aluminium *tert.*-butoxide (4.0 g.) in benzene (120 c.c.) and acetone (60 c.c.) was refluxed for 64 hours. Isolation of the product gave the ketone (1.52 g.) as a light yellow liquid, b. p. 85—90° (bath temp.)/10⁻⁵ mm., n_D^{25} 1.5775. Light absorption: Maxima, 2480 and 3220 Å.; $E_{1\text{cm}}^{1\%} = 370$ and 720, respectively, indicating a purity of ca. 85%. The 2:4-dinitrophenylhydrazone crystallised from alcohol in dark red plates, m. p. 186—187° undepressed on admixture with an authentic specimen (Heilbron, Jones, Lewis, and Weedon, this vol., p. 2023, give m. p. 187°). The semicarbazone crystallised from aqueous methanol in colourless needles, m. p. 189—190°, undepressed on admixture with an authentic specimen (*idem, loc. cit.*, give m. p. 187°).

1-Chloro-5-(4-methylcyclohex-1-enyl)-3-methylpent-1-en-4-yn-3-ol (VI; $R_1 = R_2 = H, R_3 = Me$).—A solution of 4-methyl-1-ethynylcyclohexene (25 g.; Heilbron, Jones, Toogood, and Weedon, this vol., p. 2028) in ether (100 c.c.) was added to ethylmagnesium bromide (prepared from 4.9 g. of magnesium) in ether (150 c.c.) and the mixture refluxed for 2½ hours. The mixture was cooled, and a solution of methyl

2-chlorovinyl ketone (13 g.) in ether (100 c.c.) was added during 30 minutes. After being stirred for a further 30 minutes at 20° and then 1 hour under reflux, the mixture was again cooled and the Grignard complex decomposed with ice and ammonium chloride (15 g.). The product was isolated with ether. After being heated at 60°/5 × 10⁻² mm. to remove excess of 4-methyl-1-ethynylcyclohexene (8.5 g.), the crude carbinol (28.2 g.) was obtained as a dark yellow viscous oil. Light absorption: Maximum, 2290 Å.; $E_{1\text{cm.}}^{1\%} = 720$. Distillation of a small portion of the product gave the *carbinol* as a colourless viscous liquid, b. p. 75–80°(bath temp.)/10⁻³ mm., $n_D^{25} 1.5232$ (Found: C, 69.95; H, 7.85. C₁₃H₁₇OCl requires C, 69.45; H, 7.75%). Light absorption: see table.

5-(4-Methylcyclohex-1-enyl)-3-methylpent-2-en-4-yn-1-al (VII; R₁ = R₂ = H, R₃ = Me).—The preceding chloro-carbinol (28.2 g.; crude) was divided into 3 approximately equal portions and each was added to sulphuric acid (1200 c.c.; 1% w/v) and the mixtures steam-distilled. The distillates were combined, and the product isolated with ether giving the crude aldehyde (17.7 g.) as a dark yellow liquid. Light absorption: Maxima, 2220 and 3090 Å.; $E_{1\text{cm.}}^{1\%} = 650$ and 425, respectively, indicating a purity of ca. 65–70%. The crude aldehyde (2.0 g.) was treated with semicarbazide acetate in aqueous methanol, and gave the *semicarbazone* (0.90 g.) which crystallised from aqueous alcohol in colourless needles, m. p. 205° (Found: C, 68.25; H, 7.45. C₁₄H₁₉ON₃ requires C, 68.5; H, 7.8%). Light absorption: Maxima, 3090 and 3280 Å.; $\epsilon = 26,500$ and 21,500, respectively.

Regeneration from the semicarbazone (0.70 g.; m. p. 205°) gave the *aldehyde* (0.40 g.) as a yellow liquid, b. p. 50–55° (bath temp.)/10⁻⁴ mm., $n_D^{25} 1.5600$ (Found: C, 82.4; H, 8.45. C₁₃H₁₆O requires C, 82.9; H, 8.55%). Light absorption: see table. The 2:4-dinitrophenylhydrazone crystallised from acetic acid in red prisms, m. p. 178° (Found: C, 61.9; H, 5.1. C₁₅H₂₀O₄N₄ requires C, 61.95; H, 5.55%). Light absorption in chloroform (main band only): Maximum, 3940 Å.; $\epsilon = 39,500$.

8-(4-Methylcyclohex-1-enyl)-6-methylocta-3:5-dien-7-yn-2-one (IV; R₁ = R₂ = H, R₃ = Me).—A solution of the preceding aldehyde (17.7 g.; crude) and aluminium *tert.*-butoxide in benzene (600 c.c.) and acetone (400 c.c.) was refluxed for 62 hours. The product was isolated and distilled, giving the ketone (13.4 g.) as a yellow viscous liquid, b. p. 95°(bath temp.)/10⁻³ mm. Light absorption: Maxima, 2310 and 3350 Å.; $E_{1\text{cm.}}^{1\%} = 500$ and 720, respectively, indicating the presence of only traces of impurities. A portion (2.4 g.) of this material was treated with an excess of semicarbazide acetate in aqueous methanol and gave the *semicarbazone* (1.2 g.) which crystallised from aqueous alcohol in pale yellow needles, m. p. 171° (Found: N, 14.75. C₁₇H₂₃ON₃ requires N, 14.75%).

A mixture of the semicarbazone (1.0 g.; m. p. 171°), dilute sulphuric acid (50 c.c.; 10% w/v), and light petroleum (50 c.c.; b. p. 80–100°) was refluxed and stirred vigorously until all the solid had disappeared (45 minutes). Isolation gave the *ketone* (0.55 g.) as a yellow viscous oil, b. p. 80–85° (bath temp.)/10⁻⁴ mm., $n_D^{25} 1.5850$ (Found: C, 84.2; H, 9.15. C₁₆H₂₀O requires C, 84.15; H, 8.85%). Light absorption: see table. The 2:4-dinitrophenylhydrazone crystallised from acetic acid in dark red plates, m. p. 197° (Found: C, 64.25; H, 5.75. C₂₂H₂₄O₄N₄ requires C, 64.65; H, 5.9%). Light absorption in chloroform (main band only): Maximum, 4100 Å.; $\epsilon = 38,000$.

8-(4-Methylcyclohex-1-enyl)-2:6-dimethylocta-1:3:5-trien-7-yn-1-carboxylic Acid (V; R₁ = R₂ = H, R₃ = Me).—A mixture of the above ketone (6.45 g.), ethyl bromoacetate (5.6 g.), activated zinc turnings (2.1 g.), mercuric chloride (0.1 g.), and dry benzene (125 c.c.) was heated under reflux for 1 hour, during which time most of the zinc dissolved. The dark red mixture was cooled, decanted from unreacted zinc, and shaken with acetic acid (200 c.c.; 5% w/v). The benzene layer was separated, washed free of acid, and dried and the solvent evaporated giving the crude hydroxy-ester (9.2 g.), $n_D^{25} 1.538$. Light absorption: Maxima, 2270, 2820, and 2910 Å.; $E_{1\text{cm.}}^{1\%} = 540, 500, \text{ and } 500$, respectively.

A mixture of the hydroxy-ester and anhydrous oxalic acid (25 g.) was heated at 90–100°/0.05 mm. for 3 hours. After being cooled, the residue was extracted with light petroleum (300 c.c.; b. p. 60–80°), and the extract was washed with water and dried, and the solvent evaporated, yielding the unsaturated ester (6.9 g.), $n_D^{25} 1.586$. Light absorption: Maxima, 2600, 2800, and 3430 Å.; $E_{1\text{cm.}}^{1\%} = 440, 360, \text{ and } 460$, respectively.

The ester was dissolved in a solution of potassium hydroxide in methanol (300 c.c.; 10% w/v) and kept at 20° for 48 hours. Water (1 l.) was then added, the non-saponifiable material was extracted with ether and the aqueous layer was acidified to pH 4–5 with phosphoric acid (ca. 100 c.c.; 50% w/v). The liberated acid was extracted with ether, and the extract was washed with water, dried, and evaporated. The residual brown gum was triturated with light petroleum (5 c.c., b. p. 40–60°). The solid (1.46 g.) thus obtained was recrystallised from methanol giving the *acid* (1.00 g.) as pale yellow needles, m. p. 205–206° (Found: C, 79.65; H, 8.45. C₁₈H₂₂O₂ requires C, 79.95; H, 8.2%). Light absorption: see table.

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