656. *Studies in the Polyene Series. Part XXXIV. The Synthesis of a C_{17} Alcohol related to Vitamin A.*

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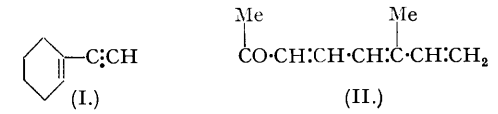
In continuation of the schemes previously outlined for the synthesis of vitamin A and its analogues, the crystalline C_{17} primary alcohol (IV), containing an acetylenic bond in the side chain and a *cyclo*hexene ring devoid of methyl groups, has now been prepared.

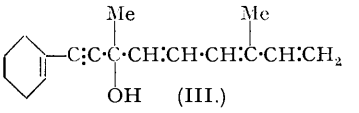
Condensation of ethynyl*cyclo*hexene (I) with 6-methylocta-3 : 5 : 7-trien-2-one (II) gives the tertiary carbinol (III) which on treatment with dilute acids is isomerised to the primary carbinol (IV).

Until recently, all successful syntheses in the vitamin-A field (for summary see Heilbron, *J.*, 1948, 386; see also Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, this vol., p. 1516; Isler *et al.*, *Helv. Chim. Acta*, 1949, **32**, 489; Schwarzkopf *et al.*, *ibid.*, p. 443; Milas *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1591, 1597) have commenced with β-ionone. However, this starting material leads to only a few of the structural variants of the vitamin-A molecule required for the complete elucidation of the relationship between biological activity and molecular structure. With a view to overcoming this limitation, and also to developing new approaches to vitamin A (V) itself, attention has recently been directed in this and other laboratories to the use of ethynyl*cyclo*hexene (I), and its methyl homologues, for the preparation of compounds related to vitamin A (Heilbron *et al.*, *J.*, 1948, 386; this vol., pp. 287, 742, 2023; Milas *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1292, 1829; Sobotka and Chanley, *ibid.*, p. 3914). This paper records the synthesis of (IV) in which the side chain differs from that of vitamin A only in the replacement of an ethylenic by an acetylenic linkage.

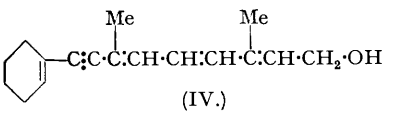


(I.)

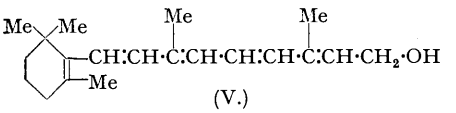
(II.)



(III.)



(IV.)



(V.)

When the Grignard reagent from ethynyl*cyclo*hexene (I) was condensed with 6-methylocta-3 : 5 : 7-trien-2-one (II) (Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, this vol., p. 2031), by a method similar to that previously used in the condensation with octa-2 : 4 : 6-trien-1-al (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742), the *tertiary carbinol* (III) was obtained. In order to avoid the losses involved in distillation, the crude condensation product, which was shown by light-absorption measurements to contain *ca.* 65% of (III), was employed in the preparation of the fully conjugated carbinol (IV).

The tertiary carbinol (III) underwent anionotropic re-arrangement on being shaken with 1% sulphuric acid to give the impure isomer (IV). In view of the instability of (IV) to prolonged treatment with acid, it was most satisfactorily prepared by effecting only partial re-arrangement of (III) and separating the resulting mixture of carbinols by chromatography.

Esterification of the crude carbinol (IV) with both *p*-phenylazobenzoyl chloride and anthraquinone-2-carboxyl chloride gave, after chromatographic purification, the corresponding crystalline *derivatives*, m. p. 106—109° and m. p. 153—155°, respectively. Hydrolysis of the anthraquinone-2-carboxylate yielded the crystalline primary carbinol, 9-cyclo*hex*-1′-*enyl*-3 : 7-*dimethylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (IV), m. p. 75—76°. Subsequently it was found possible to prepare the crystalline carbinol [in *ca.* 7% yield based on (III) consumed] simply by seeding the concentrates obtained by chromatography of the crude re-arrangement product.

Light-absorption data for the various compounds described in this paper are presented in Table I. The carbinol (III) exhibits absorption of high intensity consistent with the presence in the molecule of conjugated enyne and triene systems. The light-absorption properties of (IV) and its derivatives are similar to those of vitamin A and the corresponding derivatives.

When the carbinol (IV) was administered orally in arachis oil to rats deficient in vitamin A, growth responses were produced at doses which indicated that the carbinol possessed activity of the same order as that of the corresponding acid (*ca.* one thousandth that of vitamin A itself; Heilbron, Jones, and Richardson, *J.*, 1949, 287).

TABLE I.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Carbinol (III)	2280	18,500
	2600	27,500
	2700	38,000
	2800	31,500
 [1]	2690	60,000
	2780 *	52,000
Carbinol (IV)	3200	42,000
	3370 *	28,500
 [1]	2390	12,500
	3210	36,000
	3350	29,500
Vitamin A (V) [2]	3280	49,000
p-Phenylazobenzoate of (IV)	3250 †	56,500
p-Phenylazobenzoate of vitamin A [2]	3250—3280	81,500
Anthraquinone-2-carboxylate of (IV)	2580 †	72,500
	3280	48,500
Anthraquinone-2-carboxylate of vitamin A [2]	2550	53,500
	3250—3280	56,000

* Inflexion. † In chloroform.

[1] Heilbron, Jones, Lewis, Richardson, and Weedon, this vol., p. 742.
[2] Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1948, **30**, 1911.

EXPERIMENTAL.

Light-absorption data were determined in alcohol unless stated otherwise. All the operations were carried out in an atmosphere of nitrogen.

The alumina (Spence, type H, mesh 100—200) was washed with dilute hydrochloric acid (*ca.* 0·2N.), and then with water, until the filtrate no longer contained chloride ions, and finally with methanol. After being dried in air at 20°, the adsorbent was graded (III—IV; cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73) and stored in a tightly stoppered bottle.

9-cyclo*Hex*-1′-*enyl*-3 : 7-*dimethylnona*-1 : 3 : 5-*trien*-8-*yn*-7-*ol* (III).—Ethynyl*cyclo*hexene (20·0 g., 0·19 mol.) in ether (100 c.c.) was added dropwise to a solution of ethylmagnesium bromide (prepared from magnesium, 4·5 g., 0·18 mol.) in ether (300 c.c.) and the mixture was refluxed for 3 hours. After cooling to 20°, a solution of 6-methylocta-3 : 5 : 7-trien-2-one (18·5 g., 0·14 mol.; Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, this vol., p. 2031) in ether (100 c.c.) was added over a period of 45 minutes, and the mixture was stirred for 12 hours and then poured on ice and ammonium chloride (125 g.). The product was extracted with ether, and the ethereal solution was washed with water and dried ($MgSO_4$). After removal of the solvent and excess of ethynyl*cyclo*hexene under reduced pressure, a viscous dark red oil (32·0 g.), n_D^{18} 1·5420, was obtained. Light absorption : Maxima, 2280, 2700, and 2800 A.; $E_{1\,cm.}^{1\%}$ = 730, 1020, and 840 respectively, indicating a *ca.* 65% content of the carbinol.

Distillation of a portion (0·7 g.) of the crude material gave 9-cyclo*hex*-1′-*enyl*-3 : 7-*dimethylnona*-1 : 3 : 5-*trien*-8-*yn*-7-*ol* (0·3 g.) as a pale yellow oil, b. p. 100—110° (bath temp.)/10^{-4} mm., n_D^{18} 1·572 (Found : C, 83·65; H, 9·25. $C_{17}H_{22}O$ requires C, 84·25; H, 9·15%). Light absorption : see Table I.

9-cyclo*Hex*-1′-*enyl*-3 : 7-*dimethylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (IV).—A solution of the above carbinol (24·0 g.; *ca.* 65% pure) and a trace of quinol in peroxide-free ether (300 c.c.) was shaken at 20° for 18 hours with dilute sulphuric acid (1200 c.c.; 1% w/v). The ethereal layer was separated, washed with a saturated solution of sodium hydrogen carbonate and water, dried, and concentrated by evaporation under reduced pressure to a dark viscous oil (21·6 g.), n_D^{17} 1·569. Light absorption : Maxima, 2290, 2700, and 3080 A.; $E_{1\,cm.}^{1\%}$ = 600, 720, and 400, respectively.

A portion (10·9 g.) of the crude product was dissolved in light petroleum (60 c.c.; b. p. 40—60°) and the solution poured on to a column of alumina (700 g.). The chromatogram was developed with a range of solvents, and four bands were eluted (see Table II).

The oil (1·35 g.) obtained from zone (iii) was dissolved in light petroleum (10 c.c.) and the solution seeded with crystalline (IV) (for preparation see below). The solid (500 mg.) deposited was warmed with pentane (*ca.* 80 c.c.) and the insoluble polymeric material filtered off. The filtrate was cooled to 0°, and 9-cyclo*hex*-1′-*enyl*-3 : 7-*dimethylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (250 mg.) crystallised in colourless needles, m. p. 75—76°, which rapidly turned yellow on exposure to air (the m. p. was not raised by further recrystallisation) (Found : C, 83·9; H, 9·15. $C_{17}H_{22}O$ requires C, 84·25; H, 9·15% . Light absorption : Maxima, 3200 and 3370 A.; $E_{1\,cm.}^{1\%}$ = 1740 and 1170, respectively. Concentration of the pentane mother liquors gave a further crop (84 mg.) of crystalline product, m. p. 72—76°.

TABLE II.

Zone.	Eluant.	Wt. of material.	Appearance.	n_D.	Light absorption: $\lambda_{max.}$ A.	$E^{1\%}_{1\,cm.}$
(i)	Light petroleum, b. p. 40—60°	3·6 g.	pale yellow oil	n_D^{17} 1·558	2290	730
					2700	780
					2800	620
					3050	530
(ii)	Benzene	2·25 g.	pale yellow oil	n_D^{18} 1·575	2290	470
					2690	920
					2790	820
					3130	410
(iii) *	10% Ether in benzene	1·35 g.	pale yellow oil	n_D^{18} 1·617	—	—
(iv)	20% Ether in benzene	1·0 g.	dark yellow oil	n_D^{20} 1·558	2280	700
					2960	380

* Adsorbed on the column for *ca.* 6 hours.

After removal of the solvent from the combined mother liquors under reduced pressure, an oil (760 mg.), n_D^{22} 1·603, was obtained. Light absorption: Maxima, 2510 and 3210 A.; $E^{1\%}_{1\,cm.}$ = 660 and 1000, respectively: Inflexions, 3050 and 3340 A.; $E^{1\%}_{1\,cm.}$ = 830 and 700, respectively, indicating an appreciable content of the carbinol (possible a mixture of stereoisomers). A portion (300 mg.) of the oil was esterified with anthraquinone-2-carboxyl chloride in the manner described below. The crude product (530 mg.) was triturated with acetone and the solid then obtained was recrystallised from the same solvent giving the ester (80 mg.), m. p. 153—155°, undepressed on admixture with that described below.

p-*Phenylazobenzoate of* (IV) (cf. Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911). A solution of *p*-phenylazobenzoyl chloride (0·5 g.) in methylene chloride (5 c.c.) was added slowly to a solution of the crude carbinol (IV) [0·85 g.; $E^{1\%}_{1\,cm.}$ (3150 A.) = 470, indicating a purity of *ca.* 25%] in methylene chloride (6 c.c.) and dry pyridine (1 c.c.) causing the precipitation of a solid pyridine salt. The mixture was shaken at 20° for 24 hours. Water (1 c.c.) was added, and the mixture was warmed to 50° for 5 minutes to hydrolyse the excess of acid chloride. After the addition of hydrochloric acid (50 c.c.; 2N.), the aqueous layer was extracted with ether (3 × 25 c.c.), the ethereal solution was washed with hydrochloric acid (2N.), sodium hydroxide solution (0·5N.), and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a dark red oil (1·2 g.) which was dissolved in a mixture of benzene (2 c.c.) and light petroleum (4 c.c.; b. p. 40—60°), and the solution was filtered through a column of alumina (60 g.). The chromatogram was developed with the same mixture; the least strongly adsorbed band was eluted and, after removal of the solvent under reduced pressure, gave a red oil (360 mg.) which was dissolved in light petroleum (*ca.* 3 c.c.; b. p. 40—60°). When kept at 0°, the solution deposited an orange, crystalline solid (110 mg.), m. p. 96—106°, which was recrystallised from the same solvent giving the p-*phenylazobenzoate* in needles, m. p. 106—109° (Found: C, 79·9; H, 7·0; N, 6·55. $C_{30}H_{30}O_2N_2$ requires C, 79·95; H, 6·7; N, 6·2%). Light absorption: see Table I.

Anthraquinone-2-carboxylate of (IV) (cf. *idem, loc. cit.*). A solution of anthraquinone-2-carboxyl chloride (0·5 g.) in methylene chloride (8 c.c.) was slowly added to a solution of the crude carbinol (IV) [1·16 g.; $E^{1\%}_{1\,cm.}$ (3150 A.) = 385, indicating a purity of *ca.* 20%] in methylene chloride (3 c.c.) and dry pyridine (1 c.c.), causing the precipitation of a solid pyridine salt. The mixture was shaken at 20° for 24 hours. Water (1 c.c.) was then added, and the mixture kept at 50° for 5 minutes. After the addition of hydrochloric acid (50 c.c.; 2N.) the aqueous layer was extracted with ether (3 × 25 c.c.), and the ethereal solution was washed with hydrochloric acid (2N.), sodium hydroxide solution (0·5N.), and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a dark red oil (1·35 g.) which was dissolved in a mixture of benzene (3 c.c.) and light petroleum (6 c.c.; b. p 40—60°) and the solution was passed through a column of alumina (100 g.). The chromatogram was developed with the same mixture of solvents and the least strongly adsorbed, orange-coloured zone was eluted. Removal of the solvent from the orange yellow solution under reduced pressure yielded a partly solid residue (250 mg.). Crystallisation of the solid from acetone gave the *anthraquinone-2-carboxylate* (125 mg.) in crimson plates, m. p. 153—155°. Further crystallisation from the same solvent raised the m. p. to 154—156° (Found: C, 80·7; H, 6·2. $C_{32}H_{28}O_4$ requires C, 80·65; H, 5·9%). Light absorption: see Table I.

Regeneration of the carbinol (IV) *from the anthraquinone-2-carboxylate* (cf. *idem, loc. cit.*). The anthraquinone-2-carboxylate (84·6 mg.; m. p. 154—156°) was heated to 50° with alcoholic potassium hydroxide solution (2 c.c.; 2N.) until the crimson colour of the derivative had disappeared (*ca.* 10 minutes). The precipitated potassium anthraquinone-2-carboxylate was filtered off and washed well with alcohol. The combined alcoholic solutions were diluted with water, and the product isolated by extraction with light petroleum (b. p. 40—60°). The petroleum solution was washed with potassium hydroxide solution (0·5N.), dilute sulphuric acid (2N.), saturated sodium hydrogen carbonate solution and water, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil which rapidly solidified (m. p. 70—71°; 42·6 mg.). Recrystallisation from pentane gave (IV) in colourless needles, m. p. 74—75°.

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