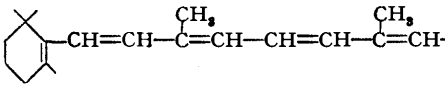
68. *Studies in the Polyene Series. Part XXV. Molecular Structure and Vitamin-A Activity. The Synthesis of a Biologically Active* C_{17} *Acid.*

By Sir Ian Heilbron, E. R. H. Jones, and R. W. Richardson.

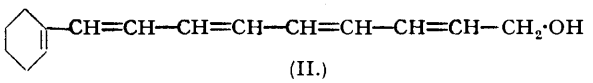
The relationship between molecular structure and vitamin-A activity is briefly discussed, and schemes for the synthesis of analogues of vitamin A with simplified structures are outlined. A novel synthesis of a C_{17} acid (IX), isolated in two geometrically isomeric forms, containing an acetylenic bond in the side chain and an otherwise unsubstituted *cyclo*hexene ring is described. One of these isomers, administered orally to young rats as the sodium salt, exhibits activity approximately one-thousandth of that of vitamin A itself.

Because of the difficult character of synthetic work on polyenes of the vitamin-A type, most of the information which is available at present concerning the relationship between molecular structure and vitamin-A activity has been accumulated from growth promotion tests with the naturally occurring carotenoid pigments and their degradation products and, to a lesser extent, with transformation products of the vitamin itself (cf. Jones, *Ann. Reports*, 1940, **37**,

290). The structural variations possible with the natural materials and derived substances are rather limited; few alterations involving the carbon skeleton have been possible, the main changes having been concerned with cyclic or open-chain structures (*e.g.*, β-carotene and lycopene), the presence or otherwise of oxygen-containing groups in the cyclic portion of the molecule (*e.g.*, xanthophylls), the length of the conjugated system (carotenes, *apo*carotenals, and vitamin A), geometrical isomerism, etc. The results available, however, from the tests on carotenoids and their degradation products, do not necessarily afford a true picture of the



(I.)



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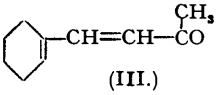


(III.)

effect of variations in molecular structure on vitamin-A activity, since structural factors may determine the mode of fission of carotenoid molecules in the animal body. The failure of a carotenoid to promote growth may be attributable to its inability to undergo fission in the required manner rather than to the inherent inactivity of its breakdown products. In this connexion there is some evidence to indicate that certain carotenoids may function directly (*i.e.*, without breakdown) as vitamins for some animals (Pirie and Wood, *Biochem. J.*, 1946, **40**, 557; With, *Nature*, 1946, **157**, 627).

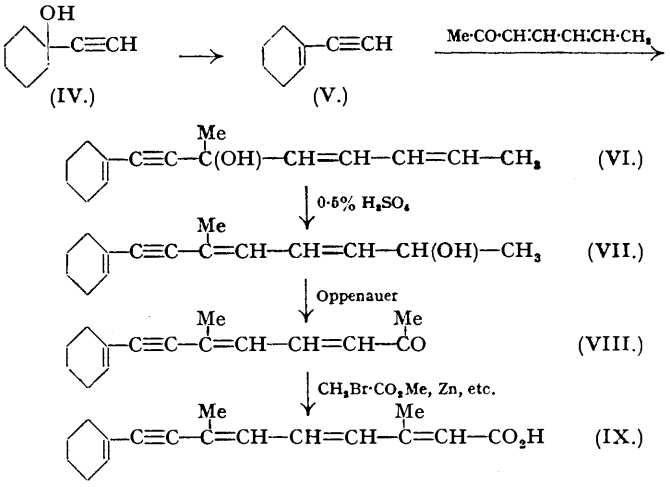
Until recently, the number of synthetic substances of indubitable structure which have been available for animal tests has been almost insignificant, due to the seemingly insuperable difficulties which have faced investigators in this field (cf. Jones, *Ann. Reports*, 1941, **38**, 170). In the last few years, however, following the discovery and development of new synthetic methods applicable in the polyene field, several routes leading to the synthesis of vitamin A and closely related compounds have been described (for summary see Heilbron, Pedler Lecture, *J.*, 1948, 386), and it is now possible to envisage the synthesis of a considerable number of polyenes of the vitamin-A type in a state of absolute purity. From biological tests on such substances much information concerning the relationship between molecular structure and biological activity will be forthcoming; it seems not unlikely that Nature will be found to have been over-elaborate in designing the vitamin-A molecule, and that substances with similar but simpler structures may exhibit considerable biological activity.

In this and subsequent papers in this series, we shall describe researches which have as their objective the synthesis of a variety of analogues of vitamin A (I) with simplified structures. An extreme example is the C_{15} alcohol (II), containing the same conjugated system as the natural vitamin, but none of the side-chain and ring-methyl groups. In other examples some of these methyl groups will be reintroduced, variations will be made in the ring system and in the terminal functional group, and the substitution of ethylenic by acetylenic bonds in the side chain and the effect of geometrical isomerism will be studied. Since all the successful syntheses recently reported have utilised β-ionone as starting material, in order to achieve our objectives we had either to synthesise the analogous ketone (III), devoid of methyl groups, or to devise a new synthesis of an entirely novel type. Both of these approaches have been successful, and the synthesis of the ketone (III), in which we have been interested for some years in connexion with light absorption studies, will be described in a later paper. Attention is now mainly directed to a new synthetic approach to compounds of the vitamin-A type by a route which, because of its simplicity and adaptability, appears to be eminently suited to our present purpose of preparing a variety of structural variants of the vitamin-A molecule.

Two crystalline geometrically isomeric C_{17} acids (IX) have been synthesised by the following route, the yields obtained at the various stages have been reasonably satisfactory, and the starting materials are all readily available. The dehydration of the ethynyl*cyclo*hexanol (IV) to ethynyl*cyclo*hexene (V)* proved to be the critical stage in the synthesis because of the ease with which three alternative reactions can take place. These are dehydration and isomerisation to ethylbenzene (particularly at high temperatures), isomerisation to acetyl*cyclo*hexene (under acidic conditions), and fission to *cyclo*hexanone and acetylene (especially over basic

* *Added in Proof.*—Since this paper was written, Milas *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1292, 1829) and Sobotka and Chanley (*ibid.*, p. 3914) have described the preparation of (V) and its use in the synthesis of compounds related to vitamin A.

catalysts). Previous claims (Merling, D.R.P. 280,226; Carothers and Coffman, *J. Amer. Chem. Soc.*, 1932, **54**, 4071) for the satisfactory preparation of the hydrocarbon (V) could not be substantiated, but we have now found that by passing the vapours of the carbinol (IV) over aluminium phosphate at 300—310°, preferably under reduced pressure, almost pure



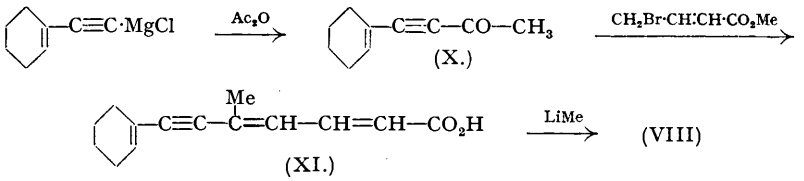
ethynyl*cyclo*hexene (V) can be obtained in conversions up to 55%, the greater part of the residue being unchanged carbinol. That our product is truly the acetylenic hydrocarbon has been amply confirmed by silver salt determination, quantitative hydrogenation, light-absorption measurements, ozonolysis, and partial hydrogenation to the known vinyl*cyclo*hexene.

The Grignard reagent from the hydrocarbon (V) was condensed with crotonylideneacetone by a method similar to that previously employed (Cymerman, Heilbron, and Jones, *J.*, 1944, 144) for the condensation of αβ-unsaturated ketones with hex-1-yne, and gave the *carbinol* (VI) in 55% yield. [Crotonylideneacetone prepared from crotonaldehyde and acetone by the method of Meerwein (*Annalen*, 1908, **358**, 85; see also Rapson and Shuttleworth, *J.*, 1940, 636) was found to be non-homogeneous, distillation effecting but little purification. By washing the crude product with water or by omitting Meerwein's salting out procedure, the pure ketone was readily obtained.] As was expected the carbinol (VI) underwent anionotropic rearrangement on being shaken with 0·5% sulphuric acid (cf. Heilbron, Jones, *et al.*, *J.*, 1943—1946), the fully conjugated *carbinol* (VII) (3 : 5-*dinitrobenzoate*), obtained in 75% yield, exhibiting light-absorption properties consistent with the quadruple conjugation. The *ketone* (VIII) was prepared from the rearranged carbinol by Oppenauer oxidation, using aluminium *tert.*-butoxide and acetone, being regenerated from the *semicarbazone* by the procedure used by Heilbron, Jones, and O'Sullivan (*J.*, 1946, 866).

The same ketone has also been synthesised, although rather less conveniently, by an alternative route similar to that employed by Arens and van Dorp (*Rec. Trav. chim.*, 1946, **65**, 338; cf. also Heilbron, Jones, and O'Sullivan, *loc. cit.*) for the synthesis of the structurally analogous C_{18} ketone of the vitamin-A series. *cyclo*Hexenylethynylmagnesium chloride was condensed with acetic anhydride at low temperatures (−60° to −0°) to give the *ketone* (X), characterised by a number of derivatives. The ketone exhibited the expected light-absorption properties, and hydrogenation gave cyclo*hexylbutan*-2-*one* which on oxidation with hypobromite yielded the known β-*cyclo*hexylpropionic acid. The Reformatsky reaction between the acetylenic ketone (X) and methyl ω-bromocrotonate proceeded rather unsatisfactorily, much decomposition occurring even in dilute solutions, and after dehydration of the crude hydroxy-ester with anhydrous oxalic acid, followed by hydrolysis, the crystalline *acid* (XI) was isolated in only 5% yield. Treatment of this acid with methyl-lithium in ethereal solution (cf. Arens and van Dorp, *loc. cit.*) gave the ketone (VIII) (85% yield), identical with that obtained by the alternative route described above.

Condensation of (VIII) with methyl bromoacetate and zinc, and dehydration and hydrolysis of the crude hydroxy-ester, gave the C_{17} *acid* (IX) which was readily isolated in two forms, m. p. 179° (20% yield) and m. p. 152° (10% yield), by fractional crystallisation. Since they are both derived from the same C_{15} ketone, these acids are probably geometrical isomerides

about the terminal double bond, as in the case of vitamin A and *neo*vitamin A (Robeson and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 136). Their light-absorption properties are practically



identical, secondary maxima due to the acetylenic system effectively preventing the detection of any *cis*-peak (Zechmeister, *Chem. Reviews*, 1944, **34**, 267).

When the sodium salt of the acid (IX), m. p. 179°, in aqueous solution buffered at pH 10, was administered orally to young rats on a vitamin-A deficient diet, growth responses were produced at doses which indicated that the acid exhibited activity of the order of one-thousandth of that of vitamin A itself.

Light-absorption data for the various compounds described in this paper are collected together in the Table. Ethynyl*cyclo*hexene (V) shows the characteristic maximum and inflexion

	$\lambda_{max.}$, A.	$\epsilon_{max.}$		$\lambda_{max.}$, A.	$\epsilon_{max.}$
Ethynyl*cyclo*hexene (V)	2230	12,500	Ketone (VIII)	3350	23,000
	2280 *	9,500		2450	18,000
Dimethylvinylacetylene [1]	2195	9,000	C_{18} ketone [4]	3350	38,000
	2260 *	7,000	Acid (XI)	3130	22,000
Carbinol (VI)	2270	39,000		2370	16,500
	2370	30,000		2420 *	14,500
Carbinol (VII)	2910	21,500	C_{17} acid [4]	3250	32,500
	3060	15,000	Acid A (IX)	3390	27,500
Decatetraenol [2]	2985	64,000		2600	12,000
	3110	64,000		2570	11,000
HC:C·[CH:CH]$_3$·CH(OH)·CH$_3$ [3]	2920	60,000	Acid B (IX)	3420	31,000
	3050	54,000		2600	9,500
	2790	40,000	Vitamin A acid [5]	3400	37,500

* Inflexion.

[1] Jones and McCombie, *J.*, 1943, 261. [2] Reichstein and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 1074. [3] Heilbron, Jones, and McCombie, *J.*, 1944, 134. [4] Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866. [5] Arens and van Dorp, *Rec. Trav. chim.*, 1946, **65**, 338.

observed with conjugated vinylacetylenes, and the carbinol (VI) exhibits high-intensity absorption in the 2300 A. region consistent with the presence of conjugated diene and enyne systems in the molecule. The light-absorption properties of the rearranged carbinol (VII) are similar to those of other compounds containing four unsaturated linkages in conjugation, and those of the ketone (VIII) and the two acids (XI) and (IX) approximate closely to those of the corresponding compounds synthesised from β-ionone (Arens and van Dorp, *loc. cit.*; Heilbron, Jones, and O'Sullivan, *loc. cit.*).

The number of variations which are possible on the synthetic schemes outlined in this paper are considerable. Ring methyl groups can readily be introduced by preparing the ethynylcarbinols from mono-, di-, and tri-methyl*cyclo*hexanones followed by dehydration to give homologues of ethynyl*cyclo*hexene (V). The side-chain methyl group in the carbinol (VI) and the subsequent products can be eliminated by employing sorbaldehyde in place of crotonylideneacetone with the Grignard reagents from ethyl*cyclo*hexenes. Since the anionotropic rearrangement involved in the conversion of (VI) into (VII) is of such a general nature (cf. Jones, *Ann. Reports*, 1944, **41**, 148), the extent of the conjugated system in the final product can be varied at will by utilising aldehydes and ketones such as, *e.g.*, ethylideneacetone and octatrienal for building up the major portion of the side chain.

The partial hydrogenation of the acetylenic linkage, using a palladium catalyst with diminished activity, could probably be effected in the final products [*e.g.*, the acid (IX)], but it would almost certainly be more effective if carried out on the intermediate carbinol (VI) before rearrangement. As has already been indicated the Reformatsky reaction involved in the final stage of the synthesis of the acid (IX) leads to the production of *cis–trans* isomers, presumably about the terminal ethylenic linkage. It is possible that the development of improved methods for the partial reduction of the acetylenic linkage may also permit of the controlled production of geometrical isomerides.

Much variation in the nature of the terminal functional group can be achieved by employing the new methods which are now available. Thus the carboxyl group in (IX) could be reduced to a primary alcohol group by using lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548), while the corresponding aldehyde and the same primary alcohol could be prepared by taking advantage of the procedure devised by Arens and van Dorp (*Nature*, 1947, **160**, 189) involving the condensation of the ketone (VIII) with ethoxyacetylene.

The ready availability of the ketone (III), a lower homologue of β-ionone, permits of additional alternative syntheses based on the now established routes to polyenes of the vitamin-A type. In this case also, the possibility of progressive introduction of ring methyl groups can be envisaged.

The considerable progress that has already been made in work along several of the lines outlined above will be reported in later papers in this series.*

Experimental.

Light-absorption measurements were carried out in ethanol except where stated otherwise. All the operations were carried out in an atmosphere of nitrogen.

Ethynylcyclohexene (V).—Ethynyl*cyclo*hexanol (100 g.; prepared by a method similar to that used by Heilbron, Jones, and Weedon, *J.*, 1945, 83) was distilled slowly (*ca.* 25 g./hr.) in nitrogen at 120—130° (bath temp.)/40 mm. through a " Pyrex " tube (70 × 2 cm.) containing a supported aluminium phosphate catalyst kept at 300—310°. The catalyst was prepared by immersing pieces of porous tile (250 g.; *ca.* 5 mm. diam.) in the minimum volume of water, and stirring in finely powdered aluminium phosphate (15 g.). The catalyst sludge was then introduced into the pyrolysis tube and dried *in situ* by heating it at 300°/10 mm. for 2 hours. A fresh charge of catalyst is necessary after about 150 g. of carbinol have been passed through the tube.

The emergent gases were condensed in air and water condensers, and the product was collected in a flask cooled in ice–salt. After separation of the water produced, the crude product was distilled, and the fraction, b. p. <65°/30 mm., was dried ($CaCl_2$) and fractionated to give ethynyl*cyclo*hexene (35 g.), a mobile liquid with an odour reminiscent of garlic, b. p. 60°/30 mm., $n_D^{19°}$ 1·494 ± 0·002 (Found: C, 90·2; H, 9·6. Calc. for C_8H_{10}: C, 90·5; H, 9·5%) (Merling, D.R.P. 280,226, gives b. p. 148—151°, $n_D^{20°}$ 1·4922; Carothers and Coffman, *J. Amer. Chem. Soc.*, 1932, **54**, 4071, give b. p. 40—43°/12 mm.; Mousseron and Julien, *Bull. Soc. chim.*, 1946, 241, give b. p. 145—146°, $n_D^{25°}$ 1·4669). Light absorption: see Table. On analysis by the method of Hill and Tyson (*J. Amer. Chem. Soc.*, 1928, **50**, 172) the hydrocarbon (0·412 and 0·409 g.) liberated nitric acid equivalent to 35·0 and 34·6 c.c. of 0·0968N-alkali, corresponding to 0·87 atom of acetylenic hydrogen. (That this method gives low values has been confirmed in other determinations; thus pure ethynyl*cyclo*hexanol gave a value of only 0·90 acetylenic hydrogen.) Active hydrogen (Zerewitinoff): The hydrocarbon (83 mg.) evolved 15·6 c.c. of methane at 18°/771 mm., equivalent to 0·87 atom of active hydrogen per molecule. Quantitative hydrogenation: The hydrocarbon (619 and 552 mg.) in methanol (10 c.c.) was shaken in hydrogen in the presence of platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 17°/747 mm., 381 and 345 c.c., equivalent to an average value of 2·65 ⊏.

Vinylcyclohexene.—Ethynyl*cyclo*hexene (5·0 g.) in ethyl acetate (20 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (0·5 g.; 0·3% Pd) until 950 c.c. of gas had been absorbed at 17°/763 mm. After removal of the catalyst by filtration through alumina, distillation gave vinyl*cyclo*hexene (2·2 g.), b. p. 145°, $n_D^{14°}$ 1·4911 (Cook and Lawrence, *J.*, 1938, 58, give b. p. 145°). The *p*-benzoquinone adduct crystallised from light petroleum (b. p. 40—60°) in pale yellow plates, m. p. 84—85° (Cook and Lawrence, *loc. cit.*, give m. p. 84—85·5°).

Ozonolysis of Ethynylcyclohexene.—Ozonised oxygen was slowly bubbled through a solution of the acetylene (1·0 g.) in glacial acetic acid (25 c.c.) at 0° for 10 hours. The ozonide was decomposed *in situ* by addition of hydrogen peroxide (20 c.c.; 50 vol.), and the solution evaporated under reduced pressure. Crystallisation of the residue from water gave adipic acid (0·3 g.), m. p. 146—147°, undepressed on admixture with an authentic specimen.

Crotonylideneacetone.—Crotonaldehyde (300 g.) was added dropwise during 4 hours to a well-stirred solution of acetone (600 g.) in aqueous sodium hydroxide (0·4%; 2000 c.c.) cooled to between 0° and 5°. After the addition of the aldehyde the mixture was stirred for a further 30 minutes, saturated with salt, acidified with 2N-sulphuric acid, and extracted with ether. After it had been washed to remove acid and dried, the ether was removed and the product distilled in steam. The distillate was extracted twice with ether, and the ethereal solution washed twice with a small volume of water, and dried. Distillation then gave crotonylideneacetone (42 g.), b. p. 63°/10 mm., $n_D^{15°}$ 1·5223—1·5227. Light absorption: Maximum, 2700 A.; ϵ = 28,500.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-2 : 4-*dien*-7-*yn*-6-*ol* (VI).—Ethynyl*cyclo*hexene (62 g.) in dry ether (100 c.c.) was added dropwise to a solution of ethylmagnesium bromide (from 12·5 g. of magnesium) in ether (1000 c.c.), and after the addition was complete the mixture was heated under reflux for 3 hours. Crotonylideneacetone (55 g.; distilled in nitrogen immediately before use) in ether (600 c.c.) was then gradually added to the stirred Grignard reagent at 0—5° during 3 hours. After being stirred overnight

* *Added in Proof.*—By the methods envisaged above, the C_{16} lower homologue of (IX) has been prepared from (V) by employing sorbaldehyde in place of crotonylideneacetone (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, in the press), and, also, mono- and di-methyl homologues of (IX) have been synthesised from 2-methyl- and 6:6-dimethyl-ethynyl*cyclo*hexene respectively (forthcoming publication).

at room temperature, the complex was decomposed with ice and ammonium chloride (250 g.), and the product was isolated *via* ether. Distillation in a short-path still gave 8-cyclo*hex*-1′-*enyl*-6-*methyl*-*octa*-2 : 4-*dien*-7-*yn*-6-*ol* (60 g.) as a pale yellow viscous liquid, b. p. 80—85° (bath temp.)/10^{-5} mm., $n_D^{16°}$ 1·5464 (Found : C, 83·25; H, 9·35. $C_{15}H_{20}O$ requires C, 83·25; H, 9·35%). Light absorption : see Table. Active hydrogen (Zerewitinoff) : The carbinol (116 mg.) evolved 13·5 c.c. of methane at 19°/766 mm., equivalent to 1·05 atoms of active hydrogen per mol.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VII).—The foregoing tertiary carbinol (55 g.) in ether (50 c.c.) was shaken for 15 hours with sulphuric acid (2500 c.c.; 0·5% w/v) and a trace of quinol. Isolation of the product gave the *carbinol* (40 g.) as an extremely viscous, pale yellow liquid, b. p. 100—110° (bath temp.)/10^{-5} mm., $n_D^{20°}$ 1·5790 (Found : C, 82·5; H, 9·65. $C_{15}H_{20}O$ requires C, 83·25; H, 9·35%). Light absorption : see Table. Active hydrogen (Zerewitinoff) : The carbinol (105 mg.) evolved 12·8 c.c. of methane at 19°/766 mm., equivalent to 1·1 atoms of active hydrogen per mol. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in small rosettes of bright yellow needles, m. p. 113° (Found : N, 6·8. $C_{22}H_{22}O_6N_2$ requires N, 6·85%).

8-cyclo*Hexyl*-6-*methyloctan*-2-*one*.—A solution of the above carbinol (VII; 2·83 g.) in methanol (50 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption was complete (1505 c.c. at 17°/755 mm., equivalent to 4·8 ⩭). The catalyst was filtered off, and, after removal of the methanol, the saturated carbinol was oxidised with a solution of chromium trioxide in acetic acid. Isolation of the product and distillation gave 8-cyclo*hexyl*-6-*methyloctan*-2-*one* (2·45 g.), b. p. 85°/0·1 mm., $n_D^{19°}$ 1·4668 (Found : C, 79·9; H, 12·1. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). The *semicarbazone* crystallised from aqueous methanol in glistening plates, m. p. 98° (Found : N, 14·85. $C_{16}H_{31}ON_3$ requires N, 14·95%).

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (VIII).—A solution of the rearranged carbinol (VII; 28·5 g.) and aluminium *tert.*-butoxide (50 g.) in dry acetone (1000 c.c.) and dry benzene (1500 c.c.) was refluxed for 50 hours. The cooled solution was poured into 2N-sulphuric acid (2000 c.c.), the mixture was quickly shaken to decompose the aluminium complex, and the organic layer was separated, washed with sodium hydrogen carbonate solution and water, and dried. Evaporation of the solvent and short-path high-vacuum distillation gave the crude ketone (25·5 g.), b. p. 80—100° (bath temp.)/10^{-5} mm., $n_D^{19°}$ 1·5994. Light absorption : Maxima, 2950 and 2360 A.; $E_{1\,cm.}^{1\%}$ 770 and 650 respectively. Inflexion, 3070 A.; $E_{1\,cm.}^{1\%}$ 650. This crude material was treated with semicarbazide acetate in aqueous methanol, and gave a product (17 g.), m. p. 187—188° after two crystallisations from methanol. Further recrystallisation from aqueous methanol gave the pure *semicarbazone* as needles, m. p. 194° (decomp.; rapid heating) (Found : N, 15·6. $C_{16}H_{21}ON_3$ requires N, 15·5%). Light absorption : Maximum, 3360 A.; ϵ = 46,500. Inflexion, 3520 A.; ϵ = 26,000.

The semicarbazone (17·5 g.; m.p. 187°) was refluxed with vigorous stirring with 2N-sulphuric acid (200 c.c.) and light petroleum (400 c.c.; b. p. 80—100°) until all the solid had disappeared. After isolation, high-vacuum distillation gave the *ketone* (12·7 g.) as a pale yellow viscous liquid, b. p. 80—85° (bath temp.)/10^{-5} mm., $n_D^{16°}$ 1·6185 (Found : C, 83·8; H, 8·4. $C_{15}H_{18}O$ requires C, 84·05; H, 8·5%). Light absorption : see Table.

Hydrogenation of the ketone in methanol, employing a platinic oxide catalyst, and treatment of the product with semicarbazide acetate gave the semicarbazone of 8-*cyclo*hexyl-6-methyloctan-2-one, m. p. 97—98°, undepressed on admixture with the specimen described above.

4-cyclo*Hex*-1′-*enylbut*-3-*yn*-2-*one* (X).—Ethynyl*cyclo*hexene (62 g.) in dry ether (100 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 12·25 g. of Mg), and the mixture was refluxed for 3 hours. After cooling, the cold ethereal suspension of the Grignard reagent was added slowly with stirring to a solution of acetic anhydride (102 g.) in dry ether (250 c.c.) at −60°. Stirring was continued while the temperature of the mixture was allowed to reach −5° during 4 hours; ice was then added, and the ethereal layer was washed free from acid and dried. Distillation gave 4-cyclo*hex*-1′-*enylbut*-3-*yn*-2-*one* (36 g.) as a pleasant smelling, mildly vesicant liquid, b. p. 70°/0·1 mm., $n_D^{17°}$ 1·5307 (Found : C, 80·7; H, 8·3. $C_{10}H_{12}O$ requires C, 81·0; H, 8·2%). Light absorption : Maxima, 2720 and 2200 A.; ϵ = 11,000 and 6000 respectively. The *semicarbazone* crystallised from aqueous methanol in needles, m. p. 126° (Found : C, 64·65; H, 7·5. $C_{11}H_{15}ON_3$ requires C, 64·4; H, 7·4%). Light absorption : Maximum 2820 A.; inflexion 2280 A.; ϵ = 16,500 and 15,500 respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in silky orange or yellow needles, m. p. 146°, the yellow form reverting to the orange at *ca.* 130° (Found : C, 58·4; H, 4·75. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9%). Light absorption (main band only) : Orange form, maximum 3700 A.; ϵ = 30,500. Yellow form, maximum, 3700 A.; ϵ = 27,000. The 2 : 4-*dinitrophenylsemicarbazone* crystallised from benzene in pale yellow needles, m. p. 157° (Found : C, 54·9; H, 4·8. $C_{17}H_{17}O_5N_5$ requires C, 54·95; H, 4·65%). Light absorption (in chloroform) : Maxima 2690, 3080, and 3160 A.; ϵ = 14,000, 14,000, and 14,000 respectively.

4-cyclo*Hexylbutan*-2-*one*.—A solution of the above ketone (2·0 g.) in ethyl acetate (15 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption ceased (985 c.c. at 20°/755 mm., equivalent to 3·3 ⩭). After removal of the catalyst, distillation gave 4-cyclo*hexylbutan*-2-*one* (1·5 g.) as a pleasant smelling liquid, b. p. 108°/15 mm., $n_D^{20°}$ 1·4584 (Found : C, 77·9; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·75%). The *semicarbazone* crystallised from aqueous methanol in needles, m. p. 163° (Found : C, 62·4; H, 9·8. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·05%). The 2 : 4-*dinitrophenylhydrazone* formed small orange plates, m. p. 106°, from methanol (Found : C, 57·8; H, 6·9. $C_{16}H_{22}O_4N_4$ requires C, 57·45; H, 6·65%). Oxidation of the ketone with hypobromite gave a crude acid, the amide of which when crystallised from aqueous methanol had m. p. 118° (Zelinsky, *Ber.*, 1908, **41**, 2677, gives m. p. 120° for β-*cyclo*hexylpropionamide).

6-cyclo*Hex*-1′-*enyl*-4-*methylhexa*-1 : 3-*dien*-5-*yne*-1-*carboxylic Acid* (XI).—The above acetylenic ketone (50 g.), methyl ω-bromocrotonate (60 g.), activated zinc turnings (23 g.), and dry benzene (500 c.c.) were heated under reflux. After 10—15 minutes the solution darkened and a vigorous reaction set in (a crystal of iodine was usually effective in initiating the reaction when it proved reluctant to start);

external cooling was then immediately applied. Refluxing was continued for a further 30 minutes after the spontaneous reaction had subsided. The deep greenish-black solution was decanted from unreacted zinc, and treated with ice-cold acetic acid (600 c.c.; 10%). The benzene layer was washed free from acid, dried, and evaporated, and distillation of the residue in a short-path still in high vacuum gave the crude hydroxy-ester (30·5 g.), b. p. 100—150° (bath temp.)/10^{-5} mm., $n_D^{17°}$ 1·525. Light absorption: Maximum, 2290 A.; $E_{1\,cm.}^{1\%}$ 700.

The crude ester was heated with anhydrous oxalic acid (75 g.) at 90—95°/10 mm. for 6 hours, and, after cooling, the product was extracted with light petroleum (b. p. 40—60°). The material (15·5 g.) obtained after distillation, b. p. 75—125° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·556, contained an appreciable amount of dehydrated ester. Light absorption: Maxima, 3120, 2800, and 2290 A.; $E_{1\,cm.}^{1\%}$ 360, 360, and 500 respectively.

The crude esters (15·3 g.) were dissolved in a solution of potassium hydroxide in methanol (115 c.c.; 10%), and the mixture was kept at 20° for 20 hours and then poured on crushed ice (500 g.). After extraction of the non-saponifiable portion with ether, the acid was liberated from the aqueous solution by acidification to pH 3 with phosphoric acid, and isolated by means of ether. The resulting orange-red gum (6·4 g.), which solidified partially, was triturated with 70% aqueous methanol to give a crude solid acid (4·1 g.). Crystallisation from light petroleum (b. p. 60—80°) yielded 6-cyclo*hex*-1′-*enyl*-4-*methylhexa*-1 : 3-*dien*-5-*yne*-1-*carboxylic acid* (3·2 g.) as pale yellow needles, m. p. 137°, decomposing rapidly in contact with air (Found: C, 77·55; H, 7·45. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·45%). Light absorption: see Table. Active hydrogen (Zerewitinoff): The acid (75 mg.) evolved 8·2 c.c. of methane at 27°/765 mm., equivalent to 0·95 atom of active hydrogen per mol. Quantitative hydrogenation: The acid (148 mg.) in ethyl acetate (20 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 23°/765 mm., 81 c.c., equivalent to 4·9 ⊢.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (VIII).—To a solution of the above acid (6·0 g.; 1 mol.) in dry ether was added slowly with shaking a solution of methyl-lithium (2·5 mols.) in ether (50 c.c.). The solution was then heated under reflux for 5 minutes, cooled, and treated with ice–water (100 c.c.). The crude ketone, after isolation, was dissolved in an aqueous methanolic solution of semicarbazide acetate, and yielded 5·8 g. of the semicarbazone of the ketone (VIII), m. p. 192° (decomp.) (undepressed on admixture with the specimen prepared by the alternative route), exhibiting light absorption properties identical with those previously recorded.

8-cyclo*Hex*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acids*. *The Isomeric* C_{17} *Acids* (IX).—A mixture of the regenerated ketone (VIII; 8·5 g.), freshly distilled methyl bromoacetate (6·1 g.), activated zinc turnings (2·6 g.), and dry thiophen-free benzene (500 c.c.), together with a crystal of iodine, was heated under reflux for 1 hour. The deep red mixture was then cooled, decanted from unreacted zinc, and shaken with N-acetic acid (200 c.c.). The benzene layer was washed free from acid, dried, and evaporated, giving a mixture of hydroxy- and unsaturated esters, mainly the former, $n_D^{14°}$ 1·585. Light absorption: Maxima, 3390, 3070, and 2190 A.; $E_{1\,cm.}^{1\%}$ 225, 640, and 770 respectively.

The ester mixture was dissolved in dry ether, the solution was poured on anhydrous oxalic acid (45 g.), and the ether was removed under diminished pressure. The residue was then heated at 95—100°/0·1 mm. for 3 hours, cooled, and extracted with light petroleum (b. p. 60—80°). The extract was washed and dried, and removal of the solvent under reduced pressure gave the unsaturated ester (10·6 g.), $n_D^{12°}$ 1·631. Light absorption: Maxima, 3420 and 2510 A.; $E_{1\,cm.}^{1\%}$ 1000 and 430 respectively.

The ester was dissolved in a solution of potassium hydroxide in methanol (250 c.c.; 10% w/v), and kept at 20° for 100 hours. Water (750 c.c.) was then added, the non-saponifiable material was extracted with ether, and the aqueous layer was acidified to pH 4 with phosphoric acid. The liberated acid was taken up into ether, and the solution was washed and dried. On concentration of the ethereal solution, *acid A* separated; it crystallised from ether as pale yellow iridescent needles (1·3 g.), m. p. 179° (Found: C, 79·5; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·65; H, 7·9%). Light absorption: see Table.

The solid obtained by evaporating the mother liquors, when crystallised from methanol, yielded a further amount (0·6 g.) of acid A, m. p. 175—176°. By diluting these mother liquors with water and keeping them at −5°, *acid B* was obtained, after crystallisation from methanol, as pale yellow needles (0·8 g.), m. p. 153° (Found: C, 79·25; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·65; H, 7·9%). Light absorption: see Table.

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