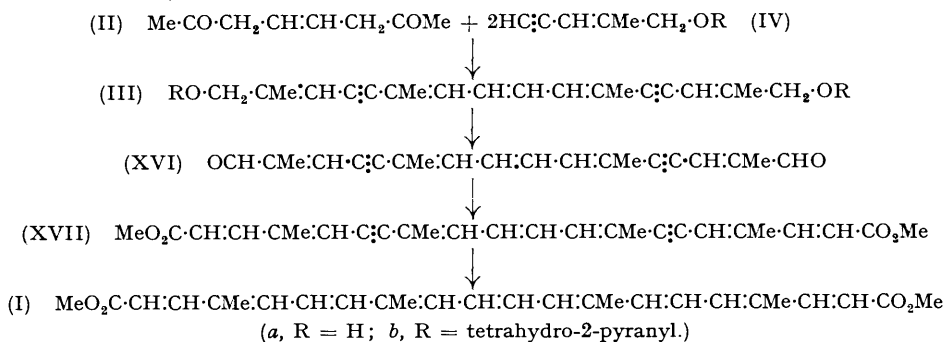**651.** *Carotenoids and Related Compounds. Part I. Total Synthesis of " all-*trans *"-Methylbixin and of a Diketone with the Capsorubin Chromophore.*
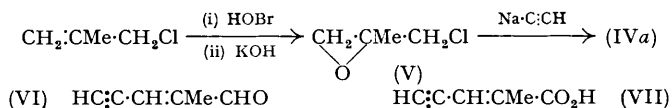
By RASHID AHMAD and B. C. L. WEEDON.

Direct total syntheses of the two compounds mentioned in the title are described.

WITHIN the last few years syntheses of β-carotene, lycopene, and some related hydrocarbons have been reported by the Karrer and the Inhoffen school (for summaries see *Ann. Reports*, 1950 and 1951; Inhoffen and Siemer, *Fortschritte der Chemie organischer Naturstoffe*, 1952, **9**, 1). The present series of papers will describe investigations undertaken primarily to develop routes to the many important natural carotenoids, and derived compounds, which in addition to a chain of conjugated double bonds possess two or more functional groups (cf., Karrer and Jucker, " Carotinoide," Birkhäuser et Cie. A-G., Basel, 1948; Goodwin, " The Comparative Biochemistry of the Carotenoids," Chapman and Hall Ltd., London, 1952). This communication deals mainly with a new and direct total synthesis of " all-*trans* "-methylbixin (I) * by the route indicated in the following reaction scheme : †

(II) $Me \cdot CO \cdot CH_2 \cdot CH \colon CH \cdot CH_2 \cdot COMe + 2HC \vdots C \cdot CH \colon CMe \cdot CH_2 \cdot OR$ (IV)

$\downarrow$

(III) $RO \cdot CH_2 \cdot CMe \colon CH \cdot C \vdots C \cdot CMe \colon CH \cdot CH \colon CH \cdot CH \colon CMe \cdot C \vdots C \cdot CH \colon CMe \cdot CH_2 \cdot OR$

$\downarrow$

(XVI) $OCH \cdot CMe \colon CH \cdot C \vdots C \cdot CMe \colon CH \cdot CH \colon CH \cdot CH \colon CMe \cdot C \vdots C \cdot CH \colon CMe \cdot CHO$

$\downarrow$

(XVII) $MeO_2C \cdot CH \colon CH \cdot CMe \colon CH \cdot C \vdots C \cdot CMe \colon CH \cdot CH \colon CH \cdot CH \colon CMe \cdot C \vdots C \cdot CH \colon CMe \cdot CH \colon CH \cdot CO_3Me$

$\downarrow$

(I) $MeO_2C \cdot CH \colon CH \cdot CMe \colon CH \cdot CH \colon CH \cdot CMe \colon CH \cdot CH \colon CH \cdot CH \colon CMe \cdot CH \colon CH \cdot CH \colon CMe \cdot CH \colon CH \cdot CO_2Me$

(*a*, R = H; *b*, R = tetrahydro-2-pyranyl.)

A formal synthesis of (I), by degradation of natural lycopene, was described earlier by Kuhn and Grundmann (*Ber.*, 1932, **65**, 1880).

Recently a convenient preparation of oct-4-ene-2 : 7-dione (II), which possesses a carbon skeleton identical with that of the central portion of most carotenoids, was reported (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089). To extend the chain of this diketone in both directions to give a C_{20} intermediate (IIIa), with a polyisoprenoid structure, a condensation with 2-methylpent-2-en-4-yn-1-ol (IVa) was envisaged. This hitherto unknown alcohol was prepared from β-methylepichlorohydrin (V) (Hurd and Winberg, *J. Amer. Chem. Soc.*, 1951, **73**, 917) by adapting the reaction discovered by

$$CH_2 \colon CMe \cdot CH_2Cl \xrightarrow[\text{(ii) KOH}]{\text{(i) HOBr}} \underset{O}{\underset{(V)}{CH_2 \cdot \underset{\diagdown \diagup}{C}Me \cdot CH_2Cl}} \xrightarrow{Na \cdot C \vdots CH} (IVa)$$

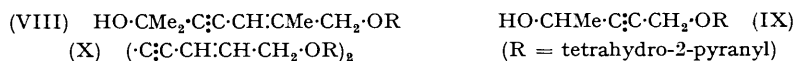(VI) $HC \vdots C \cdot CH \colon CMe \cdot CHO$ $HC \vdots C \cdot CH \colon CMe \cdot CO_2H$ (VII)

Haynes, Heilbron, Jones, and Sondheimer (*J.*, 1946, 1584) with epichlorohydrin. Treatment of (V) with sodium acetylide in liquid ammonia furnished (35%) the alcohol (IVa) directly. It exhibited the expected light-absorption properties, and on catalytic hydrogenation gave the known 2-methylpentan-1-ol. Oxidation of the alcohol (IVa), in acetone,

* Note on nomenclature (cf. Escue and Zechmeister, *J. Amer. Chem. Soc.*, 1944, **66**, 322) : Bixin, the natural carotenoid from the seeds of the Annato tree (*Bixa orellana* L.), is a methyl hydrogen ester of the nonaenedicarboxylic acid " norbixin "; the corresponding diester is termed " methylbixin." Irradiation (in the presence of iodine) of natural bixin and methylbixin, both of which contain one double bond in the *cis*-configuration, gives the " all-*trans* "-isomers.

† A preliminary account of this work was given in *Chem. and Ind.*, 1952, 882.
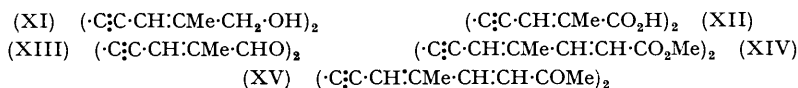
with manganese dioxide (cf. Bharucha and Weedon, *J.*, 1953, 1584) yielded the aldehyde (VI), whilst with chromic acid (cf. Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586) the crystalline acid (VII) was formed (55%).

Unpromising results were obtained in attempts to cause the Grignard reagent from methylpentenynol (IV*a*) to react with ketones. However, with acetone, the lithium derivative of its tetrahydro-2-pyranyl ether (IV*b*) (cf. Parham and Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 4187) gave the alcohol (VIII) in 80% yield. [Similarly (IX) was prepared (65%) from 3-tetrahydro-2′-pyranyloxyprop-1-yne (Henbest, Jones, and Walls, *J.*, 1950, 3646) and acetaldehyde.] This procedure seemed suitable for use with the C_8 diketone (II), but a method was now required for regenerating polyene glycols from their bistetrahydropyranyl ethers under mild conditions. Experiments with the bis-ether (X), prepared by oxidative coupling of the tetrahydropyranyl ether of pent-2-en-

(VIII) $HO \cdot CMe_2 \cdot C \vdots C \cdot CH \vdots CMe \cdot CH_2 \cdot OR$ $HO \cdot CHMe \cdot C \vdots C \cdot CH_2 \cdot OR$ (IX)

(X) $(\cdot C \vdots C \cdot CH \vdots CH \cdot CH_2 \cdot OR)_2$ (R = tetrahydro-2-pyranyl)

4-yn-1-ol in the presence of cuprous ammonium chloride, showed that this could be achieved almost quantitatively by treatment with alcohol containing catalytic amounts of toluene-*p*-sulphonic acid. While this work was in hand a very similar process was reported (Dauben and Bradlow, *J. Amer. Chem. Soc.*, 1952, **74**, 559) for the regeneration of cholesterol from its tetrahydropyranyl ether.

As a readily available model substance with which to develop methods for transformations which it was proposed to carry out with the C_{20} intermediate (III*a*), the C_{10} glycol (XI) was prepared (70%) by oxidative coupling of the methylpentenynol (IV*a*). Similar oxidation of the corresponding acid (VII) gave the dicarboxylic acid (XII) in 80% yield.
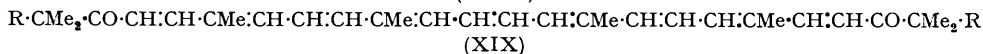
(XI) $(\cdot C \vdots C \cdot CH \vdots CMe \cdot CH_2 \cdot OH)_2$ $(\cdot C \vdots C \cdot CH \vdots CMe \cdot CO_2H)_2$ (XII)

(XIII) $(\cdot C \vdots C \cdot CH \vdots CMe \cdot CHO)_2$ $(\cdot C \vdots C \cdot CH \vdots CMe \cdot CH \vdots CH \cdot CO_2Me)_2$ (XIV)

(XV) $(\cdot C \vdots C \cdot CH \vdots CMe \cdot CH \vdots CH \cdot COMe)_2$

Oxidation of the C_{10} glycol (XI) in acetone with manganese dioxide (cf. Ahmad *et al.*, *loc. cit.*) gave (85%) the dialdehyde (XIII) which, by condensation with malonic acid followed by esterification, was converted into the diester (XIV) in 5% overall yield. It is noteworthy that in this Doebner reaction, and in those described below and in Part III (*J.*, 1953, 3299), the alkylidenemalonic acids formed initially, unlike those from polyene monoaldehydes containing four or more double bonds (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1318), were decarboxylated spontaneously under the conditions of the reaction. Condensation of the dialdehyde (XIII) with acetone in the presence of aluminium *tert.*-butoxide furnished the diketone (XV) in 40% yield.

Reaction of the lithium derivative of the tetrahydropyranyl ether (IV*b*) with the C_8 diketone (II), and dehydration of the initial product, gave the crystalline diether (III*b*) in 8% overall yield. This on treatment with alcoholic toluene-*p*-sulphonic acid afforded (90%) the C_{20} glycol (III*a*), possessing the same carbon skeleton as crocetin. When the glycol (III*a*) was shaken in acetone with manganese dioxide the dialdehyde (XVI) was produced in almost quantitative yield. Condensation of (XVI) with malonic acid, and esterification of the resulting diacid, furnished the diester (XVII) in 20% overall yield. Partial reduction of (XVII) over a lead-poisoned palladium catalyst (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) gave " all-*trans* "-methylbixin (I), identical in all respects with an authentic specimen prepared from methyl-(natural-)bixin (for which the authors are greatly indebted to Prof. L. Zechmeister). It is very probable that in this partial hydrogenation an unstable intermediate was formed initially, and subsequently rearranged to " all-*trans* "-methylbixin; after removal of the latter from the reaction product, irradiation of the residue in the presence of a trace of iodine gave a further small amount of " all-*trans* "-methylbixin (total yield 10%).

Condensation of the dialdehyde (XVI) with pinacolone yielded (45%) the diketone (XVIII*a*) which, by partial reduction, was converted (5%) into the polyene (XIX*a*). The latter possesses the same chromophore as capsorubin, a carotenoid from paprika to which

Zechmeister and Cholnoky (*Annalen*, 1934, **509**, 269; 1935, **516**, 30) assigned the provisional structure (XIX*b*), and β-carotenone (XIX*c*), an oxidation product of β-carotene (Kuhn and Brockmann, *Annalen*, 1935, **516**, 123).

$$R \cdot CMe_2 \cdot CO \cdot CH\!:\!CH \cdot CMe\!:\!CH \cdot C\!:\!C \cdot CMe\!:\!CH \cdot CH\!:\!CH \cdot CH\!:\!CMe \cdot C\!:\!C \cdot CH\!:\!CMe \cdot CH\!:\!CH \cdot CO \cdot CMe_2 \cdot R$$

(XVIII)

$$R \cdot CMe_2 \cdot CO \cdot CH\!:\!CH \cdot CMe\!:\!CH \cdot CH\!:\!CH \cdot CMe\!:\!CH \cdot CH\!:\!CH \cdot CH\!:\!CMe \cdot CH\!:\!CH \cdot CH\!:\!CMe \cdot CH\!:\!CH \cdot CO \cdot CMe_2 \cdot R$$

(XIX)

[*a*, R = Me; *b*, R = $CH_2 \cdot CH(OH) \cdot CH_2 \cdot CH_2Me$; *c*, R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot COMe$.]

All the fully conjugated polyenes reported above were isolated as crystalline solids. As expected, the ultra-violet light-absorption properties, given in Table 1, of the methylpentenynol (IV*a*), the C_{10} glycol (XI), and related substances, are very similar to those of

TABLE 1.

	Methylpentenynol series (R = Me)		Pentenynol series (R = H)	
	($\lambda_{max.}$ mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
$HC\!:\!C \cdot CH\!:\!CR \cdot CH_2 \cdot OH$	226	14,500	223 [1]	15,000
			229 *	10,000
$HC\!:\!C \cdot CH\!:\!CR \cdot CH_2 \cdot OTp$ §	227	15,000	218 }	16,500
			223 }	
$HC\!:\!C \cdot CH\!:\!CR \cdot CHO$	251 ‡	15,000	—	—
	256	18,000	—	—
	264	18,000	(261 [2]	12,500)
$HC\!:\!C \cdot CH\!:\!CR \cdot CO_2H$	247 }	18,000	242 [3]	12,500
	251 }			
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CH_2 \cdot OH)_2$	—	—	233 [3]	38,000
	242	33,500	237	39,000
	251	30,000	247	30,000
	267	10,000	262	12,000
	280	17,500	276	20,000
	298	22,000	293	30,000
	320	17,500	312	23,000
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CH_2 \cdot OTp)_2$	—	—	227	38,000
			237	31,000
			248	22,000
			278	15,000
			294	22,000
			313	18,000
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CHO)_2$	—	—	251 † [4]	12,500
	286	24,500	270	23,500
	289	24,500	280	27,000
	314	20,500	310	20,000
	332	28,500	330	25,500
	356	24,500	353	23,500
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CO_2Me)_2$	—	—	219 [3]	26,000
	258	25,000	258	27,500
	268	25,000	268	27,500
	280	24,000	—	—
	304	21,000	297	17,500
	325	27,000	316	28,500
	347	25,500	339	27,500
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CH\!:\!CH \cdot CO_2Me)_2$	346 †	37,500	—	—
	370	48,000		
	399	43,500		
$(\cdot C\!:\!C \cdot CH\!:\!CR \cdot CH\!:\!CH \cdot COMe)_2$	328 ‡	30,000	—	—
	348	35,000		
	369	39,500		
	402	35,000		

* Inflexion.   † In chloroform.   ‡ In hexane.   § Tp = tetrahydro-2-pyranyl
[1] Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583.   [2] 3-Methylpent-2-en-4-ynal, Jones and Weedon, *J.*, 1946, 939.   [3] Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586.   [4] Weedon, unpublished result.

the corresponding compounds from pent-2-en-4-yn-1-ol. The absorption data for the C_{20} glycol (III*a*), and derived compounds, are given in Table 2. The differences between the spectra of " all-*trans* "-methylbixin (I), the polyene diketone (XIX*a*), and those of

their diacetylenic analogues (XVII) and (XVIIIa), are striking; both $\lambda_{max.}$ and $\varepsilon_{max.}$ are markedly reduced in the latter pair (see also Figure). Previously it has been found that substitution of one double bond in a polyene hydrocarbon by a triple bond results in a

TABLE 2.

	$\lambda_{max.}$ (mμ)	ε	Solvent		$\lambda_{max.}$ (mμ)	ε	Solvent
Bisether (IIIb)	367	55,500	cyclo-	Dialdehyde (XVI)	400	45,000	EtOH
			Hexane	Diketone (XVIIIa)	296	37,000	CHCl₃
Glycol (IIIa)	353	42,500	EtOH		418	37,000	
	364	48,500			435	38,500	
Diester (XVII)	284	44,000	CHCl₃	Polyene diketone	485	105,000	C_6H_6
	420	44,000		(XIXa)	518	90,000	
" all-*trans* "-(I), syn-	475	125,000	C_6H_6	Capsorubin (XIXb) [1]	486	—	C_6H_6
thetic	507	118,000			520	—	
" all-*trans* "-(I), au-	475	128,000	C_6H_6	β-Carotenone (XIXc) [2]	486	—	C_6H_6
thentic	507	120,000			522	—	

[1] Zechmeister and Cholnoky, *Annalen*, 1934, **509**, 269. [2] Kuhn and Brockmann, *ibid.*, 1935, **516**, 123.

displacement of the main maximum by 10—20 mμ to shorter wave-lengths (Inhoffen, Pommer, and Meth, *Annalen*, 1949, **565**, 45; Inhoffen, Bohlmann, and Rummert, *ibid.*, 1950, **569**, 226; Inhoffen, Bohlmann, Bartram, Pommer, and Rummert, *ibid.*, 1950, **570**, 54), whilst with two adjacent triple bonds in a polyene chain shifts of up to 36 mμ have

——— " all-*trans* "-Methylbixin.
– – – – Diacetylenic analogue.
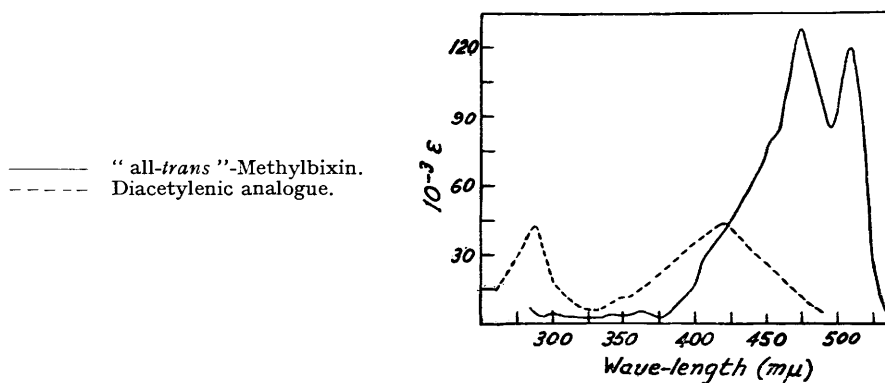
been observed (Bohlmann, *Chem. Ber.*, 1951, **84**, 545; Inhoffen, Bohlmann, Aldag, Bork, and Leibner, *Annalen*, 1951, **573**, 1). In the present examples, in which the two triple bonds are separated, the maximum in the visible region is shifted to an even greater extent (50—55 mμ), and a high-intensity partial chromophore band, reminiscent of a " *cis*-peak " (cf. Zechmeister, *Chem. Reviews*, 1944, **34**, 267), is produced in the ultra-violet region. Similar effects are apparent in the recently published spectrum of the hydrocarbon (XX) (Garbers, Eugster, and Karrer, *Helv. Chim. Acta*, 1952, **35**, 1850).

(XX) Ph·CH:CH·CMe:CH·C⋮C·CMe:CH·CH:CH·CH:CMe·C⋮C·CH:CMe·CH:CHPh
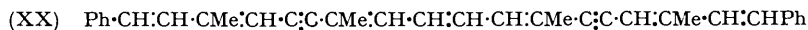
The extension of the routes described above to the synthesis of other carotenoids is now being examined.

EXPERIMENTAL

Whenever possible, operations were carried out in an atmosphere of pure nitrogen. Solutions of polyenes were evaporated under reduced pressure.

Light-absorption data were determined in alcohol unless stated otherwise.

Chromatography was on alumina, pretreated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 3120), and graded (Brockmann and Schodder, *Ber.*, 1941, **74**, 73).

2-*Methylpent-2-en-4-yn-1-ol* (IVa).—A solution of β-methylepichlorohydrin (95 g.) (Hurd

and Winberg, *J. Amer. Chem. Soc.*, 1951, **73**, 917) in ether (200 c.c.) was added during 1½ hr. to a stirred solution of sodium acetylide (from 48 g. of sodium; cf. Heilbron, Jones, and Weedon, *J.*, 1945, 83) in liquid ammonia (2 l.). After the mixture had been stirred for 15 hr., ammonium chloride (125 g.) was added to decompose the complex, and the ammonia was allowed to evaporate. Isolation of the product from the residue with ether gave the *alcohol* (33 g.), b. p. 85—87°/20 mm., n_D^{20} 1·4890 (Found : C, 74·5; H, 8·5. C_6H_8O requires C, 75·0; H, 8·4%). Light absorption : see Table 1. The α-*naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 104° (Found : C, 76·85; H, 5·85. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·65%).

2-Methylpentan-1-ol.—The preceding alcohol (1·0 g.) in methanol (5 c.c.) was shaken in hydrogen in the presence of a platinum catalyst (Adams; 50 mg.) until absorption was complete (754 c.c. at 20°/757 mm., equiv. to 2·9 double bonds). Removal of catalyst and solvent, and distillation of the residue, gave 2-methylpentan-1-ol (0·5 g.), b. p. 145—147°, n_D^{21} 1·4171. The α-naphthylurethane crystallised from light petroleum as needles, m. p. 75—77°, undepressed on admixture with an authentic specimen and with that described by Heilbron, Jones, McCombie, and Weedon (*J.*, 1945, 84).

2-Methylpent-2-en-4-yn-1-al (VI).—A solution of 2-methylpent-2-en-4-yn-1-ol (2·5 g.) in acetone (100 c.c.) was shaken with manganese dioxide (20 g.) for 24 hr. Removal of oxide and solvent, and distillation of the residue, gave the aldehyde as an unstable liquid (0·9 g.), b. p. 48—49°/24 mm. Light absorption : see Table 1. The *semicarbazone* crystallised from alcohol as plates which decomposed at *ca.* 125° without melting (Found : N, 27·65. $C_7H_9ON_3$ requires N, 27·8%). Light absorption : Max., 292 mμ; ε = 28,500. Inflexions, 284 and 298 mμ; ε = 25,500. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as prisms, m. p. 163° (decomp.; bath preheated to 155°) (Found : C, 52·5; H, 3·95. $C_{12}H_{10}O_4N_4$ requires C, 52·6; H, 3·7%). Light absorption in $CHCl_3$: Max. (main band only), 378 mμ; ε = 33,500.

2-Methylpent-2-en-4-ynoic Acid (VII).—An aqueous solution (25 c.c.) of chromium trioxide (4·8 g.) and concentrated sulphuric acid (8 g.) was added during 20 min. to a cooled (10°) solution of 2-methylpent-2-en-4-yn-1-ol (2·5 g.) in acetone (15 c.c.). The mixture was stirred at 20° for 2 hr. and then poured into water and extracted thoroughly with ether. The extract was concentrated (to *ca.* 100 c.c.) and washed repeatedly with saturated aqueous sodium hydrogen carbonate. The alkaline extract was acidified and the product isolated with ether, giving a solid (1·8 g.), m. p. 68—71°. Crystallisation from light petroleum (b. p. 40—60°) yielded the *acid* as needles, m. p. 72—73° (Found : C, 65·7; H, 5·75. $C_6H_6O_2$ requires C, 65·5; H, 5·45%). Light absorption : see Table 1.

2-Methyl-1-tetrahydro-2'-pyranyloxypent-2-en-4-yne (IV*b*) (cf. Henbest, Jones, and Walls, *J.*, 1950, 3646).—Phosphorus oxychloride (50 mg.) was added to a cooled (ice-bath) solution of 2-methylpent-2-en-4-yn-1-ol (6·0 g.) in dihydropyran (5·4 g.; freshly distilled). When the vigorous exothermic reaction had subsided, the mixture was kept at 20° for 3 hr. and then diluted with ether. The ethereal solution was washed with aqueous potassium hydroxide (10% w/v), then with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the *tetrahydropyranyl ether* (9·2 g.), b. p. 68—69°/0·1 mm., n_D^{22} 1·4880 (Found : C, 73·1; H, 9·25. $C_{11}H_{14}O_2$ requires C, 73·35; H, 8·9%). Light absorption : see Table 1.

2 : 6-Dimethyl-7-tetrahydro-2'-pyranyloxyhept-5-en-3-yn-2-ol (VIII).—A solution of phenyl-lithium (from 0·5 g. of lithium) in ether (50 c.c.) was added dropwise to a cooled (0°) solution of the preceding tetrahydropyranyl ether (6·1 g.) in ether (60 c.c.). After the mixture had been stirred at 0° for 7 hr., acetone (2·0 g.) in ether (25 c.c.) was added (15 min.) and the temperature of the mixture was allowed to rise to 20° over a period of 8 hr. The mixture was then boiled for 10 min. and again cooled. Decomposition of the complex with a saturated solution of ammonium chloride, and isolation of the product in the usual way, gave the *alcohol* (6·3 g.), b. p. 70—80° (bath-temp.)/10⁻⁴ mm., n_D^{23} 1·4991 [Found : C, 70·35; H, 9·25%; active H (Zerewitinoff), 1·1 atoms. $C_{14}H_{22}O_3$ requires C, 70·55; H, 9·25%]. Light absorption : Max., 227 mμ; ε = 14,500. Inflexion, 234 mμ; ε = 12,000.

When the preceding reaction was carried out with the Grignard complex of the tetrahydropyranyl ether in either ether or tetrahydrofuran solution the required alcohol was isolated in only 30 and 25% yield respectively (50 and 65% based on unrecovered starting material).

5-Tetrahydro-2'-pyranyloxypent-3-yn-2-ol (IX).—An ethereal solution of phenyl-lithium (from 1·2 g. of lithium) was added to 3-tetrahydro-2'-pyranyloxyprop-1-yne (12·2 g.) (*idem, loc. cit.*), in ether (100 c.c.), and the mixture was stirred at 0° for 8 hr. Acetaldehyde (5·0 g.; *ca.* 20% excess) in ether (25 c.c.) was added dropwise and the temperature of the mixture was then allowed to rise to 20° during 8 hr. Isolation of the product in the usual way gave the

alcohol (10·5 g.), b. p. 83—85°/10^{-3} mm., n_D^{22} 1·4761 (Found : C, 65·25; H, 8·8. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%).

5-Tetrahydro-2′-pyranyloxypent-3-en-2-ol.—The preceding tetrahydropyranyl ether (5·5 g.) in ethyl acetate (15 c.c.) was shaken with a lead-poisoned palladium on calcium carbonate catalyst (1·0 g.) (Lindlar, *Helv. Chim. Acta,* 1952, **35,** 446) until 1 mol. had been absorbed (800 c.c. at 19°/775 mm.). Removal of catalyst and solvent gave the *alcohol* (4·9 g.), b. p. 75—80° (bath-temp.)/10^{-4} mm., n_D^{22} 1·4710 (Found : C, 64·4; H, 9·75. $C_{10}H_{18}O_3$ requires C, 64·45; H, 9·75%).

1 : 10-Bistetrahydro-2′-pyranyloxydeca-2 : 8-diene-4 : 6-diyne (X).—Pent-2-en-4-yn-1-ol (5·5 g.) (Haynes, Heilbron, Jones, and Sondheimer, *J.,* 1947, 1583) was treated, in the manner described above for its 2-methyl derivative, with dihydropyran (6·0 g.) and gave 1-tetrahydro-2′-pyranyl-oxypent-2-en-4-yne (10·0 g.), b. p. 55—56°/0·3 mm., n_D^{23} 1·4860. Light absorption : see Table 1.

A solution of the tetrahydropyranyl ether (3·0 g.) in alcohol (6 c.c.) was added to one of cuprous ammonium chloride (from 3·0 g. of cuprous chloride and 8·0 g. of ammonium chloride) in water (20 c.c.). The mixture was shaken in oxygen until 100 c.c. had been absorbed. Isolation of the product with ether, and crystallisation from light petroleum (b. p. 40—60°), gave the *bistetrahydropyranyl ether* (2·1 g.) as needles, m. p. 42—43° (Found : C, 72·3; H, 8·05. $C_{18}H_{24}O_4$ requires C, 72·7; H, 7·95%). Light absorption : see Table 1.

Attempts to prepare this bisether from the corresponding glycol (Heilbron, Jones, and Sondheimer, *J.,* 1947, 1589) and dihydropyran were unsuccessful.

Deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol.—A solution of the preceding bistetrahydropyranyl ether (500 mg.) and toluene-*p*-sulphonic acid (25 mg.) in alcohol (10 c.c.) was boiled under reflux for 1 hr., and then cooled and concentrated to 5 c.c. under reduced pressure. Water was added and the solid (290 mg.), m. p. 145—148°, thus precipitated was collected. Crystallisation from benzene gave the glycol, m. p. 154—155°, undepressed on admixture with an authentic specimen (*idem, loc. cit.,* give m. p. 155°).

2 : 9-Dimethyldeca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (XI).—2-Methylpent-2-en-4-yn-1-ol (7·0 g.) in alcohol (15 c.c.) was added to a solution of cuprous ammonium chloride (from 7 g. of cuprous chloride and 20 g. of ammonium chloride) in 0·05N-hydrochloric acid (60 c.c.). The mixture was shaken in oxygen until 600 c.c. had been absorbed, the precipitated green salts were then dissolved by the addition of dilute hydrochloric acid, and the resulting solution was extracted thoroughly with ether. Evaporation of the extract and crystallisation of the residue (5·5 g.), m. p. 122—124°, from benzene gave the *glycol* as needles, m. p. 129—130° (Found : C, 75·6; H, 7·65. $C_{12}H_{14}O_2$ requires C, 75·65; H, 7·4%). Light absorption : see Table 1.

2 : 9-Dimethyldeca-2 : 8-diene-4 : 6-diynedial (XIII).—A solution of the preceding glycol (1·0 g.) in acetone (100 c.c.) was shaken with manganese dioxide (20 g.) for 24 hr. Removal of the oxide and solvent gave a solid (0·83 g.), m. p. 108—112°. Crystallisation from methanol yielded the *dialdehyde* as pale yellow plates, m. p. 116—117° (Found : C, 77·7; H, 5·7. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%). Light absorption : see Table 1.

The *dioxime,* purified by precipitation from dioxan solution by addition of water, had m. p. 240° (decomp.; bath preheated to 230°; evacuated capillary) (Found : C, 66·8; H, 5·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%).

2 : 9-Dimethyldeca-2 : 8-diene-4 : 6-diynedioic Acid (XII).—2-Methylpent-2-en-4-ynoic acid (1·0 g.) in alcohol (10 c.c.) was added to a solution of cuprous ammonium chloride (from 2·0 g. of cuprous chloride and 4·0 g. of ammonium chloride) in 0·02N-hydrochloric acid (15 c.c.). The mixture was shaken in oxygen until 70 c.c. had been absorbed. Dilute hydrochloric acid was then added and the acidic product was isolated in the usual way (NaHCO$_3$), giving a solid (0·82 g.). Purification by precipitation from alcohol with water gave the *acid,* m. p. 292° (decomp.) (Found : C, 66·0, 64·95; H, 5·5, 4·8. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%). Light absorption : Max., 251, 258, 266, 280, 304, 324, and 347 mμ; ε = 25,000, 27,000, 27,000, 25,000, 20,000, 29,500, and 27,500 respectively.

Ethereal diazomethane was added in small portions to a suspension of the acid (400 mg.) in ether (5 c.c.) until a clear solution was obtained. Evaporation, and crystallisation of the residue from methanol, gave the *methyl* ester (400 mg.) as plates, m. p. 88—89° (Found : C, 68·4; H, 6·0. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·75%). Light absorption : see Table 1.

Methyl 4 : 11-Dimethyltetradeca-2 : 4 : 10 : 12-tetraene-6 : 8-diynedioate (XIV).—Malonic acid (1·4 g.) was added to a solution of 2 : 9-dimethyldeca-2 : 8-diene-4 : 6-diyne-1 : 10-dial (0·7 g.) in pyridine (7 c.c.) containing 1 drop of piperidine. The mixture was heated on a steam-bath for 2 hr. The resulting dark red solution was cooled, acidified with mineral acid, and then thoroughly extracted with chloroform. The extract was washed with N-sodium hydroxide, and

the alkaline solution was acidified and extracted with ethyl acetate. Evaporation of the solvent and crystallisation of the residue from acetic acid gave the dioic acid (60 mg.) as prisms, m. p. > 325°.

Ethereal diazomethane was added in small portions to a suspension of the acid (45 mg.) in methyl acetate (15 c.c.) until all the acid had reacted and a clear solution was obtained. Evaporation of the solvent and crystallisation of the residue (47 mg.), m. p. 176—179°, from methyl acetate gave the *dimethyl* ester as needles, m. p. 181—182° (Found : C, 72·45; H, 6·25. $C_{18}H_{18}O_4$ requires C, 72·45; H, 6·1%). Light absorption : see Table 1.

5 : 12-*Dimethylhexadeca*-3 : 5 : 11 : 13-*tetraene*-7 : 9-*diyne*-2 : 15-*dione* (XV).—A mixture of 2 : 9-dimethyldeca-2 : 8-diene-4 : 6-diyne-1 : 10-dial (0·5 g.) in acetone (60 c.c.) with aluminium *tert.*-butoxide (1·4 g.) in benzene (80 c.c.) was boiled under reflux for 16 hr., then cooled and poured into dilute sulphuric acid. Isolation of the product with ether and chromatography on alumina (grade IV) from benzene gave a solid (250 mg.), m. p. 142—146°. Crystallisation from benzene–*cyclo*hexane yielded the *diketone* as yellow prisms, m. p. 149—151° (evacuated capillary) (Found : C, 81·6; H, 7·0. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%). Light absorption : see Table 1.

1 : 16-*Bistetrahydro*-2'-*pyranyloxy*-2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 8 : 14-*triene*-4 : 12-*diyne*-6 : 11-*diol*.—Oct-4-ene-2 : 7-dione (2·3 g.) (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089) in ether (150 c.c.) was added to a cooled (0°) ethereal solution (250 c.c.) of the lithium derivative of 2-methyl-1-tetrahydro-2'-pyranyloxypent-2-en-4-yne [prepared in the manner described above from 8·0 g. of the tetrahydropyranyl ether and phenyl-lithium (from 0·62 g. of lithium)]. The temperature of the mixture was allowed to rise to 20° during 8 hr. and the mixture was then boiled for 10 min. and again cooled to 0°. Saturated aqueous ammonium chloride was added, to decompose the lithium complex, and the ethereal layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. A suspension of the residue in light petroleum (b. p. 60—80°; 200 c.c.) was shaken with aqueous methanol (15 : 85 v/v; 4 × 100 c.c.). The methanolic solutions were combined, diluted with a large excess of water, and extracted thoroughly with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure, giving the glycol (7·0 g.) as a viscous yellow oil, n_D^{21} 1·5064. Light absorption : Max., 227 and 234 mμ; ε = 35,000 and 30,000 respectively.

1 : 16-*Bistetrahydro*-2'-*pyranyloxy*-2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diyne* (IIIb).—A hot solution of toluene-*p*-sulphonic acid (250 mg.; dried by being melted *in vacuo*) in toluene (100 c.c.) was added to a warm (*ca.* 50°) solution of the preceding glycol (7·0 g.) in toluene (150 c.c.). The mixture was heated rapidly and boiled for *ca.* 3 min., the water which separated being removed by azeotropic distillation. The mixture was cooled in an ice-bath and then washed with a saturated aqueous solution of sodium hydrogen carbonate. The dark red solution was diluted with light petroleum (b. p. 40—60°; 300 c.c.) and extracted with aqueous methanol (15 : 85 v/v; 4 × 100 c.c.). The petroleum solution was washed with water, dried, and evaporated under reduced pressure. The residue, in light petroleum (b. p. 40—60°), was poured on to alumina (grade II—III) and the chromatogram was developed with benzene–light petroleum (b. p. 40—60°) (1 : 1). Evaporation of the product from the main band gave a residue which solidified partly at 0°. Crystallisation from *cyclo*hexane gave the *bistetrahydropyranyl ether* (550 mg.) as yellow needles, m. p. 103° (bath preheated to 90°) (Found : C, 77·65; H, 8·3. $C_{30}H_{40}O_4$ requires C, 77·55; H, 8·6%). Light absorption : see Table 2.

2 : 6 : 11 : 15-*Tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diyne*-1 : 16-*diol* (IIIa).—A solution of the preceding ether (480 mg.) and toluene-*p*-sulphonic acid (30 mg.) in alcohol (10 c.c.) was boiled under reflux for 1 hr., then cooled and concentrated to *ca.* 4 c.c. under reduced pressure. Water was added and the solid (275 mg.), m. p. 96—98°, thus precipitated was collected. Crystallisation from benzene gave the *glycol*, m. p. 101—102° strongly depressed on admixture with the starting material (Found : C, 81·15; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·15%). Light absorption : see Table 2.

2 : 6 : 11 : 15-*Tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diynedial* (XVI).—A solution of the preceding glycol (260 mg.) in acetone (40 c.c.) was shaken with manganese dioxide (6·0 g.) for 24 hr. Removal of the oxide and solvent, and crystallisation of the residue from alcohol, gave the *dialdehyde* (245 mg.) as deep yellow needles, m. p. 137—138° (evacuated capillary) (Found : C, 82·4; H, 7·2. $C_{20}H_{20}O_2$ requires C, 82·15; H, 6·9%). Light absorption in alcohol : see Table 2; in $CHCl_3$, max. 409 mμ (ε = 45,000).

Oxidation of the dialdehyde with silver oxide or, in acetone, with chromic acid, did not yield the corresponding acid.

Methyl 4 : 8 : 13 : 17-*Tetramethyleicosa*-2 : 4 : 8 : 10 : 12 : 16 : 18-*heptaene*-6 : 14-*diynedioate* (XVII).—Malonic acid (700 mg.) was added to a solution of the preceding dialdehyde (280 mg.) and piperidine (1 drop) in pyridine (5 c.c.), and the mixture was heated on a steam-bath for 2 hr. The resulting dark red solution was evaporated under reduced pressure, and dilute acetic acid was added to the residue. The orange-red solid was collected and crystallised from acetic acid, giving the dioic acid (105 mg.), m. p. >325°. Light absorption in pyridine : Max., 420 mμ; ε = 43,000.

Esterification of the acid (90 mg.) in pyridine (5 c.c.) with ethereal diazomethane, evaporation of the solvents, and crystallisation of the residue gave the *methyl* ester (60 mg.), m. p. 182—183° (evacuated capillary), which formed orange prisms from chloroform–methanol or needles from ethyl acetate (Found : C, 76·75; H, 7·15. $C_{26}H_{28}O_4$ requires C, 77·1; H, 6·95%). Light absorption : see Table 2.

"*all*-trans "-*Methylbixin* (I).—To determine the optimum conditions for the catalytic reduction of the preceding diester to methylbixin, a series of experiments (on a 5-mg. scale) were carried out, in a micro-hydrogenation apparatus, with ethyl acetate as solvent and a lead-poisoned palladium catalyst (Lindlar, *loc. cit.*). After each hydrogenation the catalyst was removed, and the solution was exposed to diffused daylight for 2 hr. in the presence of a trace of iodine, and then diluted to a standard volume with benzene. The intensity of the light absorption maximum at 475 mμ was taken as a measure of the methylbixin content. As is shown in the following Table the highest yield was obtained after 3 mols. of hydrogen had been absorbed; these conditions were therefore followed in the preparative run described below.

Mols. of hydrogen	2·0	2·5	3·0	4·0	6·0
$E_{1\ cm.}^{1\%}$ (475 mμ)	180	220	350	250	140

A solution of the diacetylenic diester (65 mg.) and quinoline (1 drop) in ethyl acetate (30 c.c.) was shaken with Lindlar's catalyst (100 mg.) in hydrogen until 3 mols. had been absorbed (12 c.c. at 26°/750 mm.). The reaction was interrupted, the catalyst and solvent were removed, and the residue, in benzene–light petroleum (b. p. 40—60°) (1 : 1; 20 c.c.), was poured on to a column of alumina (grade IV). The chromatogram was developed with a mixture (1 : 2) of the same solvents, giving (i) a diffuse yellow band (least strongly adsorbed); (ii) a red band; and (iii) a small brown band. The column was divided mechanically and the red band was eluted with acetone. Evaporation of the solvent and crystallisation of the residue from chloroform–methanol gave "all-*trans*"-methylbixin (4—5 mg.), m. p. 200—202° (Kofler block), undepressed on admixture with an authentic specimen, m. p. 200—202° (Kofler block), prepared by isomerisation of methyl natural-bixin [cf. Escue and Zechmeister, *J. Amer. Chem. Soc.*, 1944, **66**, 322, who give m. p. 198° (corr.)]. Light absorption : see Table 2. A mixed chromatogram of the synthetic and the authentic specimen showed no separation.

The yellow band was eluted with acetone, and the solvent was evaporated. The residue and a trace of iodine, in ethyl acetate, were exposed to diffused daylight for 4 hr. The solution was washed with aqueous sodium thiosulphate, dried, and evaporated. Chromatography of the residue in the manner described above gave more crystalline methylbixin (1 mg.). No attempt was made before irradiation to isolate the unstable intermediate.

2 : 2 : 6 : 10 : 15 : 19 : 23 : 23-*Octamethyltetracosa*-4 : 6 : 10 : 12 : 14 : 18 : 20-*heptaene*-8 : 16-*diyne*-3 : 22-*dione* (XVIIIa).—A mixture of 2 : 6 : 11 : 15-tetramethylhexadeca-2 : 6 : 8 : 10 : 14-pentaene-4 : 12-diynedial (75 mg.) in pinacolone (15 c.c.), with aluminium *tert*.-butoxide (1·5 g.) in benzene (15 c.c.), was boiled under reflux for 15 hr. and then cooled to 0°. Addition of dilute sulphuric acid and isolation of the product in the usual way gave the *diketone* (45 mg.) which crystallised from benzene as yellow needles and from ethyl acetate as orange rods, m. p. 189° (Found : C, 84·45; H, 8·85. $C_{32}H_{40}O_2$ requires C, 84·15; H, 8·8%). Light absorption : see Table 2.

2 : 2 : 6 : 10 : 15 : 19 : 23 : 23-*Octamethyltetracosa*-4 : 6 : 8 : 10 : 12 : 14 : 16 : 18 : 20-*nonaene*-3 : 22-*dione* (XIXa).—The preceding diketone (34 mg.) in ethyl acetate (12 c.c.) was shaken with a lead-poisoned palladium catalyst (Lindlar, *loc. cit.*) (50 mg.) in an atmosphere of hydrogen until 3 mols. (5·3 c.c. at 23°/755 mm.) had been absorbed. The catalyst was removed, and iodine (1 mg.) added to the solution which was then kept in diffuse daylight for 6 hr. The solution was washed with aqueous sodium thiosulphate, dried, and evaporated. The residue in benzene (10 c.c.) was poured on a column of alumina (grade IV), and the chromatogram was developed with benzene–light petroleum (b. p. 40—60°) (1 : 1). The column was divided mechanically and the bright red band was eluted with acetone. Evapor-

ation, and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°), gave the diketone as dark red plates (2·5 mg.), m. p. 220—221° (Kofler block). Light absorption : see Table 2.

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