653. *Carotenoids and Related Compounds. Part III.* The Synthesis of a Bisnorcrocetin, a Pentaene Degradation Product of Azafrin, and Other Polyenes.*

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Condensations of the Doebner and the Claisen type with 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (I) and 2 : 7-dimethylocta-2 : 4 : 6-trienedial (II) have been studied, and used to synthesise a bisnorcrocetin, the azafrin degradation product methyl 4 : 9-dimethyldodecapentaenedioate (IV), an isomer of azafrinal-II methyl ester (III), and other polyenes.

IN the preceding paper the two C_{10} dialdehydes (I) and (II) were described. Progress made in developing synthetical routes, based on these intermediates, to carotenoids and related compounds is now reported.

Condensations of the Doebner type have been used extensively to prepare polyene acids from αβ-unsaturated aldehydes (cf. Jones, *Ann. Reports*, 1941, **38**, 178). Such reactions with dialdehydes have received little study (Part I) but, applied to (I) and (II), offered routes to two of Kuhn and Brockmann's (*Annalen*, 1935, **516**, 95) azafrin degradation products, *viz.*, " azafrinal-II methyl ester " (III) and methyl 4 : 9-dimethyldodecapentaenedioate (IV). Condensation of the acetylenic dialdehyde (I) with malonic acid, and esterification of the initial product, gave (10% overall yield) the aldehydo-ester (V) which was characterised as its oxime. Partial reduction of (V) over Lindlar's catalyst (*Helv. Chim. Acta*, 1952, **35**, 446) led to the corresponding polyene (III). This exhibits light-absorption maxima at wave-lengths very similar to those of " azafrinal-II methyl ester," but its melting point, and that of its oxime, differ appreciably from the values reported by Kuhn and Brockmann (see Experimental section). The two specimens are, presumably, either polymorphs or geometrical isomers.

(I) $\mathrm{OCH\cdot CMe{:}CH\cdot C{\vdots}C\cdot CH{:}CMe\cdot CHO}$ $\mathrm{OCH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CHO}$ (II)

(V) $\mathrm{OCH\cdot CMe{:}CH\cdot C{\vdots}C\cdot CH{:}CMe\cdot CH{:}CH\cdot CO_2Me}$

(III) $\mathrm{OCH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}CH\cdot CO_2Me}$

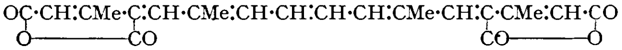
(IV) $\mathrm{MeO_2C\cdot CH{:}CH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}CH\cdot CO_2Me}$

(VI) $\mathrm{MeO_2C\cdot CR{:}CH\cdot CH{:}CH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}CH\cdot CH{:}CR\cdot CO_2Me}$

(VII)

$\mathrm{RO_2C\cdot CH{:}CMe\cdot \underset{CO_2R}{C}{:}CH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}\underset{CO_2R}{C}\cdot CMe{:}CH\cdot CO_2R}$

(VIII)



$$\begin{array}{l}\mathrm{OC\cdot CH{:}CMe\cdot C{:}CH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}C\cdot CMe{:}CH\cdot CO} \\ \mathrm{O\text{————}CO} \qquad\qquad\qquad\qquad\qquad\qquad \mathrm{CO\text{————}O}\end{array}$$

(IX) $\mathrm{Me_3C\cdot CO\cdot CH{:}CH\cdot CMe{:}CH\cdot C{\vdots}C\cdot CH{:}CMe\cdot CH{:}CH\cdot CO\cdot CMe_3}$

(X) $\mathrm{Me_3C\cdot CO\cdot CH{:}CH\cdot CMe{:}CH\cdot CH{:}CH\cdot CH{:}CMe\cdot CH{:}CH\cdot CO\cdot CMe_3}$

With the triene dialdehyde (II), in the presence of piperidine, condensation with malonic acid occurred at both ends of the molecule. After esterification of the initial product, the pentaene diester (IV) was obtained (10%). Its melting point and wave-length of maximal absorption are in excellent agreement with those reported for the degradation product of azafrin (*idem, loc. cit.*).

Ethyl ethylidenemalonate, $\mathrm{CHMe{:}C(CO_2Et)_2}$ has previously been used in reactions of the Doebner type with aromatic aldehydes (Gardner, Horton, Thompson, and Twelves, *J. Amer. Chem. Soc.*, 1952, **74**, 5527). Condensation of this ester with the triene dialdehyde (II), followed by partial hydrolysis of the initial product and re-esterification with diazomethane, gave the heptaene tetra-ester (VI; $R = CO_2Et$). Total hydrolysis of the initial product, and decarboxylation of the resulting tetra-acid, yielded a " bisnorcrocetin " which was isolated as its methyl ester (VI; $R = H$). As expected, the latter exhibits light-absorption maxima at wave-lengths exactly half-way between those of the esters of natural

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* Part II, preceding paper.

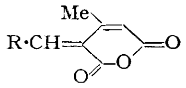
crocetin (VI; R = Me) and of Kuhn and Grundmann's (*Ber.*, 1937, **70**, 1318) synthetic " descrocetin," *i.e.*, crocetin without the four side-chain methyl groups (see Table). Preliminary attempts to condense the triene dialdehyde (II) with methyl tiglate, CHMe:CMe·CO_2Me, have given very erratic results, but, in one run in pyridine–ether with potassium ethoxide as condensing agent, a crude product was obtained which showed the two characteristic light-absorption maxima of crocetin.

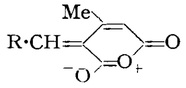
An alternative route to heptaenes of the crocetin type is illustrated by the preparation of the tetra-acid (VII; R = H), in 17% yield, by condensation of the triene dialdehyde (II) with methyl β-methylglutaconate (cf. Petrow and Stephenson, *J.*, 1950, **1310**; Baxter, *Fortschritte der Chemie organischer Naturstoffe*, 1952, **9**, 65). The tetra-acid and its ester (VII; R = Me) exhibit maximal light absorption of lower intensity, and at much shorter wave-lengths, than either crocetin ester (VI; R = H) or the tetra-ester (VI; R = CO_2Et) (see Table). Similar hypsochromic and hypochromic shifts have been noted in the spectra of other alkylideneglutaconic acids, and ascribed to steric interference of resonance as the result of the $C_{(4)}$-carboxyl substituent (Petrow and Stephenson, *loc. cit.*). Treatment of the tetra-acid (VII; R = H) with acetic anhydride furnished the dianhydride (VIII) which, as expected, shows maximal absorption at much longer wave-lengths than (VII; R = H). To account for the pronounced spectral differences between alkylideneglutaconic acids and their anhydrides, Petrow and Stephenson (*loc. cit.*) have suggested that resonance in the latter involves canonical forms such as (*a*) and (*b*).

	$\lambda_{\text{max.}}$ (mμ)	ε	Solvent
Acetylenic aldehydo-ester (V)	338	46,000	EtOH
	352	41,000	
Polyene aldehydo-ester (III)	330	38,000	*n*-Hexane
	348	57,000	
	367	55,000	
Azafrinal-II methyl ester [1]	331	—	*n*-Hexane
	351	—	
	365	—	
Pentaene diester (IV,) synthetic	389	45,000	CS_2
	412	43,000	
,, (IV), from azafrin [1]	413	—	CS_2
Methyl ester of crocetin (VI; R = Me) [2]	434	—	$CHCl_3$
	463	—	
Methyl ester of bisnorcrocetin (VI; R = H)	427	110,000	$CHCl_3$
	453	102,000	
Methyl ester of " descrocetin " [3]	418	—	$CHCl_3$
	444	—	
Tetra-ester (VI; R = CO_2Et)	452	75,000	$CHCl_3$
	473	70,500	
Tetra-acid (VII; R = H)	385	40,000	EtOH
,, ,,	390	62,000	2% KOH
	400 *	50,000	
Tetra-ester (VII; R = Me)	395	45,000	$CHCl_3$
	412	41,500	
Dianhydride (VIII)	476	47,500	$CHCl_3$
Vitamin A acid [4]	353	45,500	EtOH
4-Carboxyvitamin A acid [5]	320	30,500	Pr^{i}OH
4-Carboxyvitamin A acid anhydride [5]	435	34,000	*cyclo*Hexane
Acetylenic diketone (IX)	376	40,500	$CHCl_3$
	393	37,500	
Pentaene diketone (X)	398	58,000	$CHCl_3$
	420	53,000	

* Inflexion. [1] Kuhn and Brockmann, *Annalen*, 1935, **516**, 95. [2] Kuhn and Winterstein, *Ber.*, 1933, **66**, 209. [3] Kuhn and Grundmann, *Ber.*, 1938, **71**, 2274. [4] Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719. [5] Petrow and Stephenson, *J.*, 1950, 1310.

(*a*)





(*b*)

Both the dialdehydes (I) and (II) condense normally with methyl ketones. Thus with pinacolone the diketones (VIII) and (IX) were obtained in 30 and 35% yield respectively.

EXPERIMENTAL

See notes preceding Experimental section of Part I.

Methyl 9-*Formyl*-4 : 9-*dimethylnona*-2 : 4 : 8-*trien*-6-*ynoate* (V) (with PAUL MILDNER).—Malonic acid (1·0 g.) was added to a solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (1·0 g.) in pyridine (10 c.c.), and the mixture was heated on a steam-bath for 1 hr. and then cooled. Excess of 2N-sulphuric acid was added and the product was extracted with ether. Evaporation of the extract gave a crude acid (400 mg.) which was treated with ethereal diazomethane. Evaporation of the solution and crystallisation of the residue from methanol gave the *aldehydo-ester* (150 mg.) as pale yellow plates, m. p. 88—89° (Found : C, 71·45; H, 6·8. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·45%). Light absorption : see Table. The *oxime* crystallised from methanol as yellow prisms, m. p. 156° (Found : N, 6·2. $C_{13}H_{15}O_3N$ requires N, 6·0%).

Methyl 9-*Formyl*-4 : 9-*dimethylnona*-2 : 4 : 6 : 8-*tetraenoate* (III).—The preceding aldehydo-ester (45 mg.) in methyl acetate (5 c.c.) was shaken with Lindlar's catalyst (50 mg.) (without quinoline) in hydrogen until absorption ceased (5 c.c. at 22°/750 mm., equiv. to 1·0 double bond). The catalyst was filtered off, and the filtrate was irradiated with ultra-violet light for 2 hr. after the addition of a trace of iodine. Evaporation of the solvent, and crystallisation of the residue from methanol, gave the ester (21 mg.) as prisms, m. p. 129°. Light absorption : see Table. [Kuhn and Brockmann (*Annalen*, 1935, **516**, 95) give m. p. 106° for azafrinal-II methyl ester.] The *oxime* crystallised from methanol as yellow prisms, m. p. 177—178° (Found : N, 16·25. $C_{13}H_{17}O_3N$ requires N, 15·95%) (*idem, loc. cit.*, give m. p. 194° for the oxime of azafrinal-II methyl ester).

Methyl 4 : 9-*Dimethyldodeca*-2 : 4 : 6 : 8 : 10-*pentaenedioate* (IV).—Malonic acid (500 mg.) was added to a solution of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (200 mg.) and piperidine (1 drop) in pyridine (4 c.c.). The mixture was heated on a steam-bath for 2 hr. and then cooled. Excess of 2N-sulphuric acid was added, and the product was extracted with ethyl acetate. The extract was washed thoroughly with saturated aqueous hydrogen carbonate, and the combined washings were then acidified. The crude acid thereby precipitated was collected, washed with ether, and treated with excess of ethereal diazomethane. Evaporation of the resulting solution, and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°), gave the diester (30 mg.) as yellow plates, m. p. 177° (Found : C, 69·7; H, 7·3. Calc. for $C_{16}H_{20}O_4$: C, 69·5; H, 7·65%). Light absorption : see Table (*idem, loc. cit.*, give m. p. 176°).

Methyl 2 : 15-*Bisethoxycarbonyl*-6 : 11-*dimethylhexadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenedioate* (VI; R = CO_2Et).—Aqueous benzyltrimethylammonium hydroxide (1·0 c.c.; 40%) was added to 2 : 7-dimethylocta-2 : 4 : 6-trienedial (100 mg.) and ethyl ethylidenemalonate (1·0 c.c.) in alcohol (10 c.c.), and the solution was kept at 20° for 24 hr. More quaternary ammonium hydroxide solution (1·5 c.c.) was added, and the mixture was boiled under reflux for 15 min. and then cooled and poured into excess of 2N-hydrochloric acid. Extraction of the product with ethyl acetate, and isolation of the acidic fraction in the usual way ($NaHCO_3$), gave a product which was treated with ethereal diazomethane. Evaporation of the solvents, chromatography of the residue, in benzene–light petroleum (b. p. 40—60°) (1 : 2), on alumina (grade IV), and isolation of the single red band gave the *tetra-ester* which crystallised from methyl acetate as bright red plates (9 mg.), m. p. 158—160° (Kofler block) (Found : C, 65·9; H, 7·1. $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·8%). Light absorption : see Table.

Methyl 6 : 11-*Dimethylhexadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenedioate* (VI; R = H).—Aqueous benzyltrimethylammonium hydroxide (3 c.c.; 40%) was added to 2 : 7-dimethylocta-2 : 4 : 6-trienedial (250 mg.) and ethyl ethylidenemalonate (3 c.c.) in alcohol (25 c.c.), and the solution was kept at 20° for 24 hr. More quaternary base solution (10 c.c.) was added, and the mixture was boiled under reflux for 20 min. and then cooled and poured into excess of 2N-hydrochloric acid. Extraction of the product with ethyl acetate, and isolation of the acidic fraction ($NaHCO_3$), gave a solid tetra-acid which was dissolved in acetic acid (10 c.c.) and acetic anhydride (10 c.c.). The solution was boiled under reflux for 2 hr., cooled, and evaporated under reduced pressure. The residue was washed with ether, suspended in chloroform, and treated with excess of ethereal diazomethane. Evaporation of the resulting solution, chromatography of the residue on alumina (grade IV) from benzene–light petroleum (b. p. 40—60°) (1 : 2), and isolation of the single red band gave the diester which crystallised from chloroform–methanol as red plates (1 mg.), m. p. 218—220° (Kofler block). Light absorption : see Table.

4 : 13-*Dicarboxy*-3 : 14-*dimethylhexadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenedioic Acid* (VII; R = H).—A solution of potassium hydroxide (2·3 g.) in methanol (10 c.c.) was added to one of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (500 mg.) and methyl β-methylglutaconate (1·1 g.) in

methanol (15 c.c.). The mixture was kept at 55—60° for $1\frac{1}{2}$ hr. and then for 12 hr. at 0°. The potassium salts which had separated were collected, washed with ethyl acetate, and treated with excess of 2N-sulphuric acid. The mixture was extracted with ethyl acetate, and the extract was washed with warm dilute mineral acid (to remove β-methylglutaconic acid), dried (Na_2SO_4), and evaporated, giving a solid (250 mg.), m. p. 205—210°. Light absorption: Max., 385 mμ; $E_{1\,\text{cm.}}^{1\%} = 900$. Crystallisation from aqueous methanol gave the tetra-acid, m. p. 238°. Light absorption: Max., 385 mμ; $E_{1\,\text{cm.}}^{1\%} = 950$ (see Table). Treatment of the tetra-acid with ethereal diazomethane, and purification of the product by chromatography on alumina (grade IV) from benzene–light petroleum (b. p. 40—60°), and crystallisation from the same solvent, gave the *tetra-ester* (VII; R = Me) as prisms, m. p. 157—160° (Found: C, 65·45; H, 7·1. $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·85%). Light absorption: see Table.

A suspension of the tetra-acid (50 mg.) in acetic anhydride (2 c.c.) and ethyl acetate (10 c.c.) was kept at 60—65° until a homogeneous red solution was obtained ($1\frac{1}{2}$ hr.). Alcohol (2 c.c.) was added, the mixture was concentrated (to 3 c.c.) under reduced pressure, and the residual solution was kept at 0°. The solid which separated was collected and crystallised from ethyl acetate, giving the *dianhydride* as violet needles (10 mg.), m. p. 193° (Kofler block) (Found: C, 69·45; H, 5·55. $C_{22}H_{20}O_6$ requires C, 69·4; H, 5·3%). Light absorption: see Table.

2 : 2 : 6 : 11 : 15 : 15-*Hexamethylhexadeca*-4 : 6 : 10 : 12-*tetraene*-8-*yne*-3 : 14-*dione* (IX).—A solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (100 mg.) in pinacolone (10 c.c.), and one of aluminium *tert.*-butoxide (2·0 g.) in benzene (20 c.c.), were heated together under reflux for 16 hr., then cooled and poured into 2N-sulphuric acid. Isolation of the product with ether, and crystallisation from benzene, gave the *diketone* (45 mg.) as yellow needles, m. p. 196°, containing benzene of crystallisation (Found: C, 82·95; H, 9·25. $C_{22}H_{30}O_2,C_6H_6$ requires C, 83·2; H, 8·95%). Recrystallisation from chloroform–light petroleum (b. p. 40—60°) gave a solvent-free product, m. p. 196° (Found: C, 80·65; H, 9·55. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·25%). Light absorption: see Table.

2 : 2 : 6 : 11 : 15 : 15-*Hexamethylhexadeca*-4 : 6 : 8 : 10 : 12-*pentaene*-3 : 14-*dione* (X).—A solution of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (75 g.) in pinacolone (10 c.c.), and one of aluminium *tert.*-butoxide (1·5 g.) in benzene (15 c.c.), were heated together under reflux for 12 hr. Isolation of the product as in the preceding experiment, and crystallisation from benzene, gave the *diketone* (50 mg.) as yellow plates, m. p. 209° (Found: C, 80·7; H, 9·75. $C_{22}H_{32}O_2$ requires C, 80·45; H, 9·75%). Light absorption: see Table.

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