

Carotenoids and Related Compounds. Part V. Synthesis of Corticrocin.*

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Syntheses of the pentaene and hexaene members of the polyenedi-carboxylic acid series are described. The hexaene is identical with natural corticrocin.

UNTIL a few years ago all known natural polyene pigments were of the carotenoid type possessing an isoprenoid carbon skeleton. However the occurrence of a class of pigments with polyene chains devoid of the usual methyl substituents is now recognised (Erdtman, *Acta Chem. Scand.*, 1948, **2**, 209; Gripenberg, *ibid.*, 1952, **6**, 580; Schenck, Hargie, Tarbell, and Hoffman, *J. Amer. Chem. Soc.*, 1953, **75**, 2274). The first representative of this group was corticrocin, the bright yellow pigment in the mycorrhiza found on the roots of the Norway spruce, Scots pine, and whortleberry, growing on poor acid soil. The studies now reported were undertaken to confirm the structure (XIIa) assigned by Erdtman (*loc. cit.*) to corticrocin, and to develop synthetical methods of possible application in the carotenoid field.

Over ten years before the discovery of corticrocin, Kuhn and Grundmann (*Ber.*, 1936, **69**, 1757, 1979; 1937, **70**, 1318, 1894) developed a general procedure for the synthesis of polyenedicarboxylic acids from polyenemonoacids, but did not prepare the hexaene later found in Nature. Recently both the Döbner (Parts I and III, *J.*, 1953, 3286, 3299) and the Reformatsky reaction (Inhoffen, Isler, Bey, Raspé, Zeller, and Ahrens, *Annalen*, 1953,

* Part IV, *J.*, 1953, 3815.

TABLE 1. Light absorption of decadienediynes, X·CH₂·CH:CH·C≡C:C·CH:CH·CH₂·X.

X	Max. in mμ; ε in parentheses.	
	λ	ε
H ^a	230 (38,000)	261 (9,700)
OH ^b	227 (38,000)	262 (12,000)
Ip ^c	237 (39,000)	247 (30,000)
Cl ^d	237 (31,000)	248 (22,000)
CN	236 (31,500)	—
CO ₂ Me	228(33,000)	263 (7,000)
CO ₂ H	—	262 (6,000)
NEt ₃ ^d	229 (26,000)	264 (9,500)
Br ^e	228 (21,000)	247 (25,000)

^a Bruun, Christensen, Haug, Stene, and Sørensen, *Acta Chem. Scand.*, 1951, 5, 1244. Isomer, m. p. 97·5°, in light petroleum. ^b Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586. ^c Ahmad and Weedon, *J.*, 1953, 3286. Ip = tetrahydro-2-pyridyl. ^d Rose and Weedon, *J.*, 1949, 782. ^e Also 251 (25,000) and 256 (25,000).

TABLE 2. Effect on light absorption of allylic substituents.

X	Max. in mμ; ε in parentheses.	
	Ph·CH:CH·CH ₂ ·X	HC≡C·CH:CH·CH ₂ ·X
H	246 (12,000) ^a	224 (14,000) ^d
OH	248 (19,000) ^b	223 (15,000) ^e
Br	251 (19,500)	229 * (10,000)
	259 (16,500) ^c	235 (17,000) ^f
	264 (16,000)	—

^a Ramart-Lucas and Amagat, *Bull. Soc. chim.*, 1932, 51, 108. ^b Braude, Jones, and Stern, *J.*, 1946, 396. ^c Braude and Waight, *J.*, 1952, 1116. Hexane solution. ^d Allan and Whiting, *J.*, 1953, 3314. ^e Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583. ^f Henbest, Jones, and Walls, *J.*, 1950, 3646. ^g Booker, Evans, and Gillam, *J.*, 1940, 1453. ^h Bates, Jones, and Whiting, *J.*, 1954, 1854. ⁱ Bateman, Cunneen, Fabian, and Koch, *J.*, 1950, 986. ^j Mildner and Weedon, *J.*, 1953, 3294.

TABLE 3. Light absorption of fully conjugated diesters (in CHCl₃).

Diester	Max. in mμ; ε in parentheses.	
	λ	ε
Tetraenylne	272 (9,500)	280 * (8,000)
Pentaene	—	353 (45,500)
Hexaene	294 (4,500)	375 (57,500)
Hexaene from corticocin	294	375
Hexaene from corticocin ^b	—	374 (63,000)

* Inflection. ^b Kuhn and Brockmann; quoted by Erdtman, *Acta Chem. Scand.*, 1948, 2, 209. ^c Erdtman, *loc. cit.*

^a Kuhn and Brockmann; quoted by Erdtman, *Acta Chem. Scand.*, 1948, 2, 209. ^b Erdtman, *loc. cit.*

ation, followed by hydrolysis, it was converted into dodecanedioic acid. Its light absorption (Table 3) was that expected for a dodecatetraenyndioate, and, of the three possibilities, the symmetrical structure (VIb) is tentatively suggested.

The isomerisation of (Va) to a fully conjugated isomer is clearly related to the alkali-induced prototropic rearrangements recently observed with other acetylenic systems (Gensler and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 4601; Oroshnik, Mebane, and Karmas, *ibid.*, 1952, **74**, 295; 1953, **75**, 1050; Celmer and Solomons, *ibid.*, 1952, **74**, 3838; Whiting, *Chem. and Ind.*, 1953, 239; Shaw and Whiting, *loc. cit.*, p. 409), and opens up a new approach to polyenes. This is exemplified by the partial reduction of the dodecatetraenyndioate over a lead-palladium catalyst to give, after irradiation of the initial product with diffuse sunlight, the known methyl dodecapentaenedioate (VII) (Kuhn and Grundmann, *Ber.*, 1936, **69**, 1979) in 49% yield.

To prepare the next higher member of the polyene diacid series two routes were examined. Oxidation of the glycol (II) with manganese dioxide gave the dialdehyde (VIIIa), but attempts to condense this with malonic acid yielded none of the diacid (IXa) from which it was hoped to prepare corticocin by partial reduction. Under conditions used successfully to prepare the dimethyl derivative (IXb) (Part I; *J.*, 1953, 3286) only polymeric products were obtained. Attention was therefore directed to the following alternative method to synthesise corticocin.

Condensation of the dibromide (III) with ethyl sodiomalonate occurred readily, but hydrolysis of the resulting crude tetra-ester with alkali gave a mixture. As this was attributed to instability of the dienediyne chromophore under the alkaline conditions, the condensation was repeated with *tert.*-butyl potassiummalonate. When the resulting tetra-ester (X) was heated in glacial acetic acid with a trace of toluene-*p*-sulphonic acid (cf. Fonken and Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 831), a vigorous evolution of *isobutylene* and carbon dioxide occurred, and the required diacid (XI) was isolated in 6% overall yield. Heating this acid with 20% potassium hydroxide caused prototropic rearrangement, and the potassium salt of corticocin separated from the boiling solution. Liberation of the free acid, and esterification with diazomethane, gave the methyl ester (XIIb) in 13% overall yield from (XI). Its light absorption agreed well with that reported for the ester of natural corticocin (see Table 3), and it was identified with the latter by direct comparison with an authentic specimen kindly supplied by Professor H. Erdtman. Although acetylenic intermediates are used in this synthesis, no reduction of a triple bond is involved.

While this work was in progress, Shaw and Whiting (*Chem. and Ind.*, 1953, 409) outlined a synthesis of corticocin from dipropargyl. The final stage, the isomerisation of the diacid (XIII) to corticocin, is very similar to that employed in the above route, which was briefly reported elsewhere (*Chem. and Ind.*, 1953, 1388).

EXPERIMENTAL

Whenever possible, operations were carried out in an inert atmosphere.

Light absorption data were determined in alcohol unless otherwise stated.

M. p.s marked (K) were determined on a Kofler block and are corrected.

1 : 10-Dibromodeca-2 : 8-diene-4 : 6-diyne (III).—A rapid stream of air was aspirated through a vigorously stirred mixture of pent-2-en-4-yn-1-ol (17 g.) (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583), ammonium chloride (120 g.), and cuprous chloride (75 g.) in water (300 c.c.) at 50° for 2 hr. (cf. *idem*, *loc. cit.*, p. 1586). The mixture was cooled, 2*N*-hydrochloric acid was added to dissolve the copper salts which had been deposited, and the mixture was extracted thoroughly with ethyl acetate. The extract was washed with water, saturated aqueous sodium hydrogen carbonate, again with water, and then dried (Na₂SO₄) and evaporated under reduced pressure. The residual crude deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (17 g.), m. p. 150–156°, was suspended in benzene (175 c.c.; dried over sodium), and phosphorus tribromide (12 c.c.) was added to the well-stirred suspension during 5 min. After 1 hr. a homogeneous solution was obtained, but stirring was continued for a total of 5–7 hr. The mixture was then poured on ice, and the benzene layer was washed with saturated sodium hydrogen carbonate, dried (Na₂SO₄), and evaporated. Crystallisation of the solid residue from light petroleum (b. p. 60–

80°) gave the *dibromide* as plates (18 g.), m. p. 74—75° (Found: C, 41.85; H, 3.0. $C_{10}H_8Br_2$ requires C, 41.7; H, 2.8%). Light absorption: see Table 1.

Similar bromination of the pure glycol, m. p. 155°, gave the *dibromide* in 65% yield.

Bromination of Oct-3-en-5-yne-2:7-diol.—Phosphorus tribromide (18 c.c.) was added during 45 min. to a stirred and cooled (0°) suspension of oct-3-en-5-yne-2:7-diol (23 g.) (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089) in benzene (150 c.c.). Stirring was continued for a further 30 min. at 0° and then for 2 hr. at 20°. The mixture was poured on ice, and the product was isolated with benzene; this *dibromide* (29.6 g.) had b. p. 67°/3 × 10⁻³ mm., n_D^{25} 1.5658 (Found: C, 36.7; H, 3.7. $C_8H_{10}Br_2$ requires C, 36.1; H, 3.8%). Light absorption: max. 251 and 256 m μ ; ϵ = 15,000 and 15,000.

1:10-*Dicyanodeca-2:8-diene-4:6-diyne* (IV).—A mixture of the *dibromodecadienediyne* (III) (12.6 g.) and cuprous cyanide (10.7 g.) in acetonitrile (55 c.c.) was boiled under reflux for 1 hr. (a dark homogeneous solution was obtained after the mixture had been heated for a few minutes). The mixture was cooled slightly and then poured into ether. The copper salts thus precipitated were filtered off, and the filtrate was evaporated. Crystallisation of the residue from benzene gave the *dinitrile* (3.6 g.) as leaflets, m. p. 130° (Found: C, 80.05; H, 4.75; N, 15.25. $C_{12}H_8N_2$ requires C, 80.0; H, 4.5; N, 15.55%). Light absorption: see Table 1.

Methyl Dodeca-3:9-diene-5:7-diynedioate (Vb).—The preceding dinitrile (730 mg.) was added at 0° to saturated methanolic hydrogen chloride (10 c.c.). The mixture was shaken occasionally until homogeneous and then set aside overnight. The solution was evaporated under reduced pressure, the residue was triturated with water, and the solid was collected. Crystallisation from aqueous methanol gave the *diester* (540 mg.) as pale yellow leaflets, m. p. 56° (Found: C, 68.2; H, 5.75. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.75%). Hydrogen number: 44.4, equiv. to 5.5 double bonds. Light absorption: see Table 1.

Dodeca-3:9-diene-5:7-diynedioic Acid (Va).—A solution of the preceding diester (1.76 g.) in dioxan (36 c.c.) and *n*-hydrochloric acid (18 c.c.) was boiled under reflux for 1 hr. and then evaporated under reduced pressure. Trituration of the residue with water, and filtration, gave the *diacid* (1.5 g.) which crystallised from a large volume of boiling water in needles, m. p. ca. 194° (decomp.) (Found: C, 66.2; H, 4.8. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.6%). Hydrogen number: 37.0, equiv. to 5.9 double bonds. Light absorption: see Table 1.

A solution of the diacid (26 mg.) in dioxan (10 c.c.) was shaken with Adams catalyst in an atmosphere of hydrogen until absorption was complete (18 c.c. at 20°/760 mm.). Removal of catalyst and solvent, and crystallisation of the residue from water, gave dodecanedioic acid (17 mg.) as plates, m. p. 129—131° (K), undepressed on admixture with the specimen described by Baker, Kierstead, Linstead, and Weedon (*J.*, 1954, 1804).

Methyl Dodeca-2:4:8:10-tetraen-6-yneedioate (VIb).—A solution of dodeca-3:9-diene-5:7-diynedioic acid (1.4 g.) in 5% potassium hydroxide solution (50 c.c.) was kept at room temperature for 64 hr. The solution was cooled, acidified to pH 4 with dilute (1:1) phosphoric acid, and the solid diacid (282 mg.) thus precipitated was filtered off and dried in a vacuum-desiccator. The crude product exhibited light absorption maxima at 352 and 365 m μ ; $E_{1\%}^{1\text{cm}}$ = 1100 and 1020 respectively.

A suspension of the crude diacid (270 mg.) in ether was treated at 0° with an excess of ethereal diazomethane for 15 min. The mixture was evaporated under reduced pressure and the residue was extracted repeatedly with boiling light petroleum (initially with the fraction of b. p. 80—100°, and finally with that of b. p. 100—120°). Evaporation of the extracts and crystallisation of the residue from methanol yielded the *diester* (80 mg.) as yellow needles, m. p. 151—152° (K), which sublimed in rectangular plates at > ca. 130° (Found: C, 68.0; H, 6.0. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.75%). Light absorption: see Table 3.

This diester (4.145 mg.) in glacial acetic acid (5 c.c.) was shaken with Adams catalyst in an atmosphere of hydrogen until absorption was complete (2.145 c.c. at N.T.P., equiv. to 5.7 double bonds). The catalyst was filtered off, and the solvent was evaporated under reduced pressure. The residue was boiled with 2*N*-hydrochloric acid (2 c.c.) for $\frac{1}{2}$ hr. The mixture was cooled and the solid which separated was crystallised from water giving dodecanedioic acid, m. p. and mixed m. p. 130—131° (K).

Methyl Dodeca-2:4:6:8:10-pentaenedioate (VII).—A solution of the methyl dodecatetraenyneedioate (46.6 mg.) in ethyl acetate (6 c.c.), containing 1 drop of quinoline, was shaken with a lead-poisoned palladium catalyst (100 mg.) (Lindlar, *Helv. Chim. Acta*, 1952, 35, 446) in an atmosphere of hydrogen. After 1.1 mol. of hydrogen had been absorbed (4.59 c.c. at N.T.P.) the reaction was interrupted and the catalyst was filtered off. On being kept in daylight for some hours, the filtrate deposited the diester which was collected and had m. p. 224—225° (K). The

mother-liquors were evaporated and the residue was extracted with boiling methanol. The residual solid, and that slowly deposited by the methanol extracts on exposure to daylight, were crystallised from chloroform-methanol, giving the diester as deep yellow prisms, m. p. 224.5—225.5° (K), which sublimed in prisms at temperatures above *ca.* 150° (Kuhn and Grundmann, *Ber.*, 1936, 69, 1979, give m. p. 223°). The total yield of diester was 23 mg. (Found: C, 68.0; H, 7.0. Calc. for C₁₄H₁₆O₄: C, 67.75; H, 6.5%). Light absorption: see Table 3.

Deca-2:8-diene-4:6-diyne-1:10-diol (2.0 g.) (Heilbron, Jones, and Sondheimer, *loc. cit.*) in acetone (200 c.c.; "AnalaR") was shaken with manganese dioxide (40 g.) at 20° for 2 hr. (cf. Ahmad, Sondheimer, Weedon, and Woods, *loc. cit.*). Removal of oxide and solvent and crystallisation of the residue (1.4 g.) from aqueous methanol gave the *dialdehyde* (0.9 g.) as yellow plates, m. p. 144° (decomp.) (Found: C, 75.95; H, 4.1. C₁₀H₆O₂ requires C, 75.95; H, 3.8%). Light absorption in chloroform: max. 251, 270, 280, 310, 330, and 353 mμ; ε = 12,500, 23,500, 27,000, 20,000, 25,500, and 23,500 respectively. In EtOH: max., 227, 238, 248, 264, 280, 295, 315, and 326 (inflection) mμ; ε = 22,000, 22,000, 22,000, 20,500, 16,000, 16,500, 19,000, and 15,000 respectively. The *dioxime* crystallised from aqueous methanol in plates which decomposed without melting at *ca.* 220—225° (Found: C, 64.0; H, 4.8; N, 15.2. C₁₀H₆O₂N₂ requires C, 63.8; H, 4.3; N, 14.9%). Light absorption: max. 268, 280, 291, 312, 336, and 362 mμ; ε = 23,000, 25,000, 26,000, 23,000, 34,500, and 31,000 respectively.

When the glycol was oxidised in 1.0-g. batches, the yield of dialdehyde was raised to 60%, but longer reaction times resulted in extensive decomposition of the product.

Attempts to condense the dialdehyde with malonic acid, under the conditions used successfully with its dimethyl homologue (VIIIb) (Ahmad and Weedon, *J.*, 1953, 3286), gave only polymeric products. Condensation of the dialdehyde with acetone, in the presence of aluminium *isopropoxide* in benzene, gave a product which exhibited absorption maxima in chloroform at 365 and 387 mμ; $E_{1\text{cm.}}^{1\%} = 1080$ and 920 respectively, indicating an appreciable content of hexadeca-3:5:11:13-tetraene-7:9-diyne-2:15-dione. This crude product polymerised rapidly.

Methyl Tetradeca-2:4:6:8:10:12-hexaenedioate (XIIb).—A warm solution of 1:10-dibromodeca-2:8-diene-4:6-diyne (3.0 g.) in *tert.*-butanol (30 c.c.) was added rapidly to a well-stirred suspension of *tert.*-butyl potassiummalonate (from 1.65 g. of potassium and 13.5 g. of *tert.*-butyl malonate) in *tert.*-butanol (35 c.c.). After the exothermic reaction had subsided, the mixture was stirred rapidly for 20 hr. and then poured into 2*N*-sulphuric acid. The mixture was extracted thoroughly with ether, and the extract was washed with water, dried (Na₂SO₄; trace of K₂CO₃), and evaporated. The residue was extracted with light petroleum (b. p. 40—60°), and the extract was washed thoroughly with saturated sodium hydrogen carbonate, dried (Na₂SO₄), and evaporated under reduced pressure. After removal of the excess of *tert.*-butyl malonate at 100°/1 mm., a viscous yellow liquid (5.9 g.) was obtained which exhibited light absorption maxima at 251, 266, 280, 296, and 315 mμ; $E_{1\text{cm.}}^{1\%} = 250, 100, 165, 250, \text{ and } 200$ respectively.

A solution of the crude product and toluene-*p*-sulphonic acid (0.5 g.) in acetic acid (25 c.c.) and acetic anhydride (0.5 c.c.) was heated under reflux for 45 min.; a vigorous evolution of gas occurred during the first 5 min. The resulting dark solution was cooled and poured into water (200 c.c.), giving a colourless solid precipitate. The mixture was concentrated under reduced pressure to remove the acetic acid, and the product was extracted with ethyl acetate. The acidic fraction was isolated in the usual way by extraction with saturated sodium hydrogen carbonate, acidification of the alkaline extract, extraction with ethyl acetate, etc. Trituration with acetone yielded crude tetradeca-4:10-diene-6:8-diyne-2:15-dione as a colourless solid (158 mg.), which decomposed at *ca.* 230—260° and exhibited light absorption maxima at 228, 237, 248, 266, 278, 294, and 313 mμ; $E_{1\text{cm.}}^{1\%} = 1200, 1050, 870, 230, 550, 800, \text{ and } 330$ respectively.

A solution of the crude diacid (60 mg.) in 20% aqueous potassium hydroxide (2.5 c.c.) was boiled under reflux for 1 hr.; golden-yellow crystals of the potassium salt of corticrocin began to separate soon after heating had been commenced. The mixture was cooled in ice, and the yellow solid was then collected. Acidification with dilute (1:1) phosphoric acid gave corticrocin (14 mg.) which was filtered off and dried *in vacuo*.

The diacid was treated with excess of ethereal diazomethane (cf. Erdtman, *loc. cit.*), and the resulting mixture was evaporated under reduced pressure. Sublimation of the residue at 180°/10⁻³ mm. gave the diester as a yellow solid (7 mg.), m. p. 224° (K), which crystallised from glacial acetic acid in golden-yellow plates, m. p. 229—230° (K), undepressed on admixture with

a specimen, m. p. 229—230° (K), derived from natural corticrocin (*idem, loc. cit.*, gives m. p. 230—232°). Light absorption : see Table 3. A further quantity (2 mg.) of the diester was obtained by acidification of the mother-liquors of the potassium salt, esterification of the crude diacid, and purification as described above.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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