# *Researches on Polyenes. Part I. The Synthesis of Corticrocin.*

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The constitution (I*a*; *n* = 6), proposed for the fungus pigment corticrocin, has been confirmed by synthesis.

A PIGMENT, " corticrocin," was recently isolated from the mycorrhizal fungus *Corticium croceum* Bres. by Erdtman (*Acta Chem. Scand.*, 1948, **2**, 209), and shown to be the unbranched polyenedicarboxylic acid (I*a*; *n* = 6). The immediate homologues (I*a*; *n* = 5 and 7) of this acid had been prepared by Kuhn and Grundmann (*Ber.*, 1936, **69**, 1979; 1937, **70**, 1318) from octa-2 : 4 : 6-trienal and dodeca-2 : 4 : 6 : 8 : 10-pentaenal, respectively, by long routes and in low overall yields. Deca-2 : 4 : 6 : 8-tetraenal is much less accessible than these aldehydes (Kuhn and Hoffer, *Ber.*, 1930, **63**, 2164; Blout and Fields, *J. Amer. Chem. Soc.*, 1948, **70**, 189); thus the analogous synthesis of (I*a*; *n* = 6) would in practice be tedious and difficult.

In contrast, rearrangements of the type described in the preceding papers offered a convenient route to (I*a*; *n* = 6), provided that a straight-chain $C_{14}$ αω-dicarboxylic acid with six units of unsaturation, and without αβ- or βγ-acetylenic linkages, could be obtained. Symmetrical acids are relatively accessible *via* the excellent oxidative coupling reaction of ω-acetylenic compounds, and two such acids, (II) and (III), were considered. The former was expected to give a higher yield of the polyene acid (I*a*) than would (III), with which the first step requires attack on a hydrogen atom which is only weakly activated, and the synthesis of (II) was therefore attempted first.

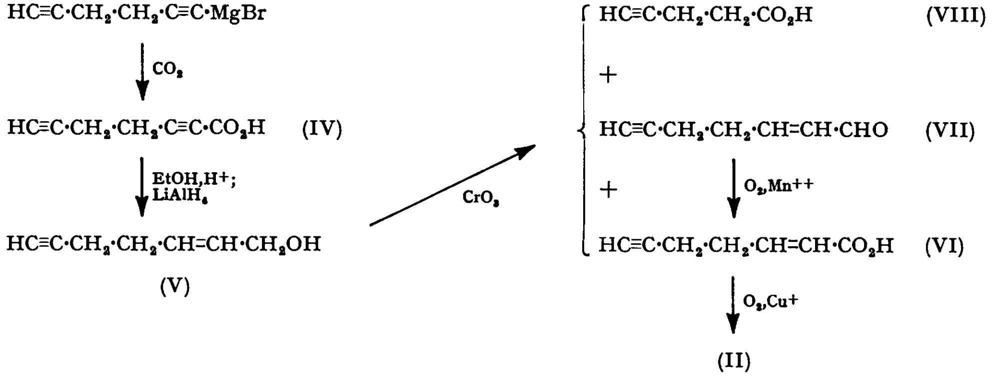
$RO_2C\cdot[CH{=}CH]_n\cdot CO_2R$ (I; *a*, R = H; *b*, R = Me)

$(C{\equiv}C\cdot CH_2\cdot CH_2\cdot CH{=}CH\cdot CO_2H)_2$ (II)

$(C{\equiv}C\cdot CH{=}CH\cdot CH_2\cdot CH_2\cdot CO_2H)_2$ (III)

The obvious route to (II) involves condensation of pent-4-ynal with malonic acid, followed by decarboxylation and coupling. Unfortunately the direct oxidation of pent-4-yn-1-ol with chromic acid did not give an appreciable quantity of the acetylenic aldehyde under the conditions tried. The corresponding nitrile was readily obtained from but-3-ynyl toluene-*p*-sulphonate, but reduction with stannous chloride proved unsuccessful.

During earlier work (preceding paper) the carboxylation of hexa-1 : 5-diynylenedimagnesium bromide (Lespieau, *Ann. Chim.*, 1912, **27**, 137) was repeated, and a small quantity of a by-product, hepta-2 : 6-diynoic acid (IV), was isolated. The monobromomagnesium derivative of the hydrocarbon gave 18% of this acid, together with much of the symmetrical product; no doubt this yield could be improved. Preferential reduction of the αβ-acetylenic linkage took place when its ester was treated with lithium aluminium hydride (see Bates, Jones, and Whiting, *J.*, 1954, 1854, and references cited there), giving hept-2-en-6-yn-1-ol (V) in excellent yield. Subsequent oxidation with chromic acid gave consistently poor (~10%) yields of the desired hept-2-en-6-ynoic acid (VI), but provided much more of the corresponding aldehyde (VII) under milder conditions. When (VII) was shaken with oxygen in the presence of manganese acetate (cf. Owen, *J.*, 1943, 463) a fair yield of the desired acid was obtained.



Oxidative coupling of the acid (VI) (cf. Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998) gave an almost quantitative yield of (II). This was heated with potassium hydroxide solution, and light-absorption maxima corresponding to those reported by Erdtman (*loc. cit.*) for corticrocin in alkaline solution were soon detected. After selection of optimal conditions (boiling 20% potassium hydroxide; the spectroscopic yield was subsequently estimated as 15%) the reaction was effected on a preparative scale. The crystalline potassium salt then separated even from the boiling solution, and was decomposed giving (I*a*; $n = 6$) in 11% yield. This high-melting and almost insoluble acid was characterised by conversion *via* the acid chloride into the dimethyl ester, m. p. 227—228·5° undepressed on admixture with the ester of natural corticrocin which was kindly supplied by Professor Erdtman.

The ultra-violet absorption spectrum of the product closely resembled that published by Erdtman (*loc. cit.*), but the extinction coefficients at the highest maxima were higher by up to 10%. A redetermination of the spectrum of the natural product gave results identical, within experimental error, with those obtained for the synthetic ester; Professor Erdtman has informed us that the optical densities actually recorded for the natural substance were in the range 1—1·5, where the Beckman instrument would be less accurate than usual.

As a final proof of identity infra-red spectra of the natural and synthetic esters were determined in Nujol. The results were strikingly different, showing respectively one band at 1710 cm.$^{-1}$ and a doublet at 1710 and 1720 cm.$^{-1}$, with other less obvious discrepancies. The explanation proved to be the dimorphism of this ester, which Erdtman had already observed (*loc. cit.*). When the two esters were recrystallised from acetic acid under similar conditions, spectra showing both bands, and otherwise identical, were obtained.

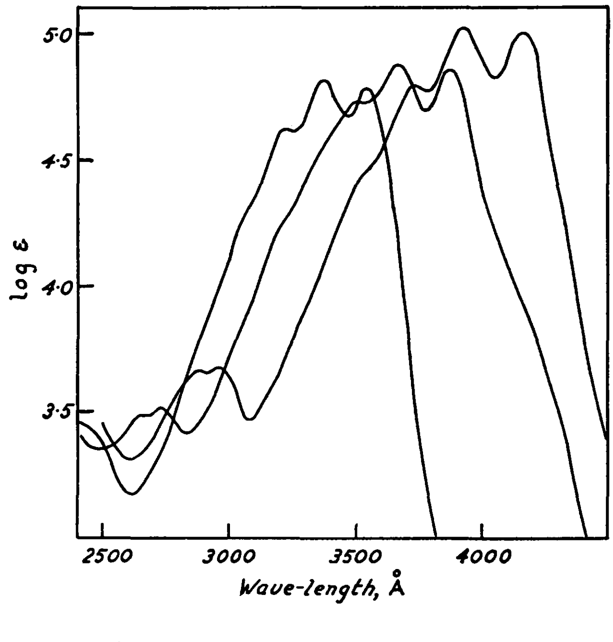
Erdtman concluded tentatively (*loc. cit.*) that corticrocin was an all-*trans*-compound (in contrast to the isoprenoid polyenedicarboxylic ester, bixin), basing his conclusion on the increase in the intensity of light absorption at short wave-lengths when the ester was equilibrated with its stereoisomerides by illumination in the presence of iodine. The synthetic ester reproduced this behaviour. The method of synthesis would clearly be expected to give, at least predominantly, the most stable or all-*trans*-isomer; indeed, the advantage in energy of the all-*trans*-isomer in alkaline solution must be a little greater than usual among polyenes, since in it the two $-CO_2^-$ groups are farthest apart. The infra-red spectrum of the methyl ester provides additional confirmation, since strong absorption at 1023 cm.$^{-1}$ (conjugated *trans*-CH=CH–) was unaccompanied by appreciable absorption in the 700—850 cm.$^{-1}$ region where conjugated *cis*-1 : 2-disubstituted ethylenes usually absorb.

In an early experiment a specimen of hept-2-en-6-ynoic acid (VI), prepared by oxidation of the corresponding alcohol, was coupled after only perfunctory purification. After alkaline isomerisation the insoluble potassium salt was acidified, and the polyene-acid converted *via* the acid chloride into the methyl ester. This was heterogeneous and on chromatographic separation gave, in addition to (I*b*; $n = 6$), an ester which showed an ultra-violet absorption spectrum similar to those of the esters (I*b*; $n = 4$ and 6), and exactly intermediate between them (see Figure). Clearly it must have been (I*b*; $n = 5$), which could have been formed by oxidative fission of hept-2-en-6-yn-1-ol at the ethylenic linkage (much more susceptible to electrophilic attack than the acetylenic bond), followed by cross-coupling of the resultant pent-4-ynoic acid (VIII) with (VI) to give the acid (IX):

*Absorption Spectra of Esters* (I*b*) *in Chloroform.*

| $n = 4$ | | $n = 5$ † | | $n = 6$ | |
|---|---|---|---|---|---|
| $\lambda_{max.}$, Å | $10^{-3}\varepsilon$ | $\lambda_{max.}$, Å | $10^{-3}\varepsilon$ | $\lambda_{max.}$, Å | $10^{-3}\varepsilon$ |
| 3540 | 60·5 | 3880 | 72 | 4165 | 103 |
| 3370 | 64·6 | 3670 | 74 | 3935 | 107 |
| 3225 | 42·2 | 3500 | 53 | 3735 | 67 |
| | | 2730 | 3·3 | 3560 * | 32 |
| | | 2660 * | 3·1 | 2955 | 4·8 |
| | | | | 2870 | 4·6 |

* Inflexion. † Containing *ca.* 7% of (I*b*, $n = 6$), on spectroscopic data.



$$(VI) + (VIII) \xrightarrow{O_2,Cu^+} HO_2C\cdot CH{=}CH\cdot CH_2\cdot CH_2\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH_2\cdot CH_2\cdot CO_2H \text{ (IX)} \xrightarrow{HO^-} (Ia;\ n = 5)$$

Since the publication of our preliminary communication (*Chem. and Ind.*, 1953, 409), Weedon has effected a very similar synthesis of corticrocin, involving alkaline hydrolysis and rearrangement of an ester closely related to (III) (*ibid.*, p. 1388).

## EXPERIMENTAL

Ultra-violet and infra-red spectra were obtained, in 95% ethanol and carbon tetrachloride unless otherwise stated, with a Unicam SP 500 and a Perkin-Elmer Model 21 spectrophotometer, respectively. "Light petroleum" implies the fraction, b. p. 40—60°; melting points were determined on the Kofler block.

4-*Cyanobut*-1-*yne*.—But-3-yn-1-yl toluene-*p*-sulphonate (Eglinton and Whiting, *J.*, 1950, 3650; 12 g.) was added to a solution of potassium cyanide (32·5 g.) in water (20 c.c.) and methanol (200 c.c.). The mixture was heated under reflux for 22 hr., cooled, and filtered; the precipitate was washed with methanol. Removal of most of the methanol by distillation through a short Dufton column, dilution, and extraction with ether, gave a persistent emulsion, easily broken by acidification; distillation of the neutral fraction then gave the *nitrile* (19·7 g., 50%), b. p. 79°/35 mm., $n_D^{22}$ 1·4367 (Found: N, 17·2. $C_5H_5N$ requires N, 17·7%). The expected infra-red maxima at 3275 and 2252 cm.$^{-1}$ (C≡N) were observed, the 1600—1750 cm.$^{-1}$ region being almost free from absorption bands.

*Hepta*-2 : 6-*diynoic Acid* (IV).—Hexa-1 : 5-diyne (7·8 g.) was added to a solution of ethylmagnesium bromide, prepared in ether from magnesium (2·7 g.), and the mixture heated under reflux for 2 hr. The suspension was transferred to a steel autoclave containing solid carbon dioxide (*ca.* 100 g.); after 24 hr. the complex was decomposed with dilute sulphuric acid, and the aqueous phase thoroughly extracted with ether. Evaporation of the ethereal solutions gave a semi-solid residue which was triturated with cold benzene, giving an insoluble residue of octa-2 : 6-diynedioic acid (3·7 g., 22%), m. p. 189—190° (decomp.) after recrystallisation [Lespieau, *loc. cit.*, gives m. p. 190° (decomp.)]. The filtrate was extracted with sodium carbonate solution, and the extract acidified and re-extracted with ether; evaporation gave a liquid residue which was distilled at 125—140° (bath temp.)/0·02 mm. Crystallisation of the distillate from light petroleum gave the diacetylenic *acid* (2·15 g.; 18%) as needles, m. p. 52·5—53·5° (Found: C, 68·7; H, 4·9. $C_7H_6O_2$ requires C, 68·8; H, 4·95%). Light absorption: maximum, 2060 Å; $\varepsilon = 6200$. The infra-red absorption spectrum included intense bands at 3290 and 2248 cm.$^{-1}$ (H–C≡C– and conjugated –C≡C–, respectively). Hydrogenation (uptake 3·9 equiv.) gave heptanoic acid, characterised as heptanoamide, m. p. and mixed m. p. 93—95°. The *ethyl* ester, obtained in 90% yield by use of 10% ethanolic sulphuric acid at 20° for 6 days, had b. p. 90° (bath temp.)/1·5 mm., $n_D^{17·5}$ 1·4718 (Found: C, 71·95; H, 6·7. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). The ester had $\lambda_{max.}$ 2080 Å, $\varepsilon = 6950$, and showed the expected intense bands at 3295 cm.$^{-1}$ and 2242 cm.$^{-1}$.

When the bis-bromomagnesium derivative was carboxylated under similar conditions the yields of di- and mono-carboxylic acids were 44% and 7%, respectively. The use of tetrahydrofuran in place of ether as solvent would probably afford a considerably increased yield.

*Hept*-2-*en*-6-*yn*-1-*ol* (V).—To a stirred suspension of lithium aluminium hydride (5·0 g.; 70% purity) in ether (240 c.c.), ethyl heptadiynoate (3·9 g.) in ether (10 c.c.) was added, and the mixture was stirred and heated under reflux for 4·5 hr. Addition of ice and sulphuric acid gave the alcohol (2·65 g., 94%), b. p. 106° (bath temp.)/14 mm., $n_D^{20}$ 1·4739. Analytical data were inconsistent and unsatisfactory, but intense bands at 3290 and 2224 cm.$^{-1}$, and weaker bands at 3605 and 1678 cm.$^{-1}$ (stretching frequencies of H–C≡, C≡C, H–O, and *trans*-CH=CH– groupings, respectively) adequately confirm the constitution of the product, which was free from carbonyl compounds. An α-*naphthylurethane* was readily obtained as matted needles, m. p. 101—102° (Found: C, 77·65; H, 6·2. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·15%).

*Hept*-2-*en*-6-*ynoic Acid* (VI).—(*a*) The above alcohol (4·35 g.) in acetone (26·5 c.c.) was treated with a solution of chromic acid (6N) in 12N-sulphuric acid (26·5 c.c.) at 20° with stirring, which was continued for a further 2 hr. After 18 hr. water was added and the acidic and neutral fractions were separated. The former gave the *acid* (550 mg., 11%) as plates, m. p. 82—83°, on crystallisation from water (Found: C, 67·55; H, 6·55. $C_7H_8O_2$ requires C, 67·75; H, 6·5%). Light absorption: maximum, 2080 Å; $\varepsilon = 12,000$; and strong bands at 3297 (H–C≡) and 1654 cm.$^{-1}$ (CH=CH, conjugated), and in regions typical of carboxylic acids. The neutral fraction was distilled giving *hept*-2-*en*-6-*ynal* (2·93 g., 69%), b. p. 90°(bath temp.)/10 mm., $n_D^{20}$ 1·4838. Light absorption: maximum, 2200 Å; $\varepsilon = 16,000$; and prominent infra-red bands at 3290, 1697, and 1632 cm.$^{-1}$. The aldehyde absorbed oxygen rapidly, and was therefore analysed as the *semicarbazone* (plates; m. p. 185—186°; from ethanol) (Found: C, 58·15; H, 6·85. $C_8H_{11}ON_3$ requires C, 58·15; H, 6·7%). Light absorption: maximum, 2470 Å; $\varepsilon = 24,000$.

(*b*) The above aldehyde (2·9 g.) was dissolved in light petroleum (b. p. 60—80°; 40 c.c.) and shaken in oxygen in the presence of manganese acetate (5 mg.). After 6 days the uptake was 275 c.c. and absorption had ceased. Isolation of the acidic fraction and crystallisation from water gave the acid (970 mg.; 30%), m. p. 82—83°.

*Tetradeca*-2 : 12-*diene*-6 : 8-*diynedioic Acid* (II).—The above acid (650 mg.), cuprous chloride (2 g.), ammonium chloride (3·5 g.), water (20 c.c.), and acetone (20 c.c.) were shaken in oxygen until uptake (*ca.* 250 c.c.) was complete. Acetone was removed under reduced pressure, and water (40 c.c.) and syrupy phosphoric acid (10 c.c.) were added; copper salts then dissolved and the dicarboxylic acid was precipitated. Filtration, extraction of the residue with sodium hydroxide, and acidification of the filtered extract gave the pure *acid* (582 mg., 90%), which formed needles from acetic acid, decomp. above 150° (Found: C, 68·2; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). Light absorption: maxima, 2070 and 2530 Å; $\varepsilon = 25,000$ and 800, respectively; inflexion, 2400 Å; $\varepsilon = 1550$; and a strong infra-red band at 1648 cm.$^{-1}$. The *dimethyl* ester, obtained in 60% yield, formed plates, m. p. 85—86°, from light petroleum (b. p. 80—100°) (Found: C, 69·95; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·05; H, 6·6%), and had $\lambda_{max.}$ 2070 and 2530 Å, $\varepsilon = 25,000$ and 820, respectively.

*Tetradeca*-2 : 4 : 6 : 8 : 10 : 12-*hexaenedioic Acid* (*Corticrocin*) (I*a*; $n = 6$).—The diacetylenic acid (586 mg.) and aqueous potassium hydroxide solution (20%; 30 c.c.) were heated under reflux for 1·5 hr. Golden plates began to separate after 5 min.; these were collected when the solution was still warm, washed with 20% potassium hydroxide solution, and dissolved in hot water containing a little sodium hydroxide. The filtered solution was acidified and centrifuged, giving the acid (66 mg.) as an orange-brown powder which decomposed near 300° without melting and proved to be insoluble in all solvents tried. The acid (20 mg.) was heated under reflux with thionyl chloride (2 c.c.) until it dissolved completely (1·5 hr.), and excess of the chloride was removed under reduced pressure, giving the crude acid chloride as a scarlet solid. Dry methanol was then added, and after 1 hr. the surplus was removed; sublimation of the residue at 160°/$10^{-4}$ mm. gave the dimethyl ester (15 mg.), m. p. 209—218°, raised to 227·5—228·5° by crystallisation from glacial acetic acid (yield 9 mg.). The corrected melting-point in an open capillary was 229—230°; no depression was observed on admixture with a specimen of corticrocin dimethyl ester kindly provided by Professor Erdtman (Found: C, 69·9; H, 6·75. Calc. for $C_{16}H_{18}O_4$: C, 70·05; H, 6·6%).

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