106. *Researches on Polyenes. Part V.* The Synthesis of Cortisalin.*

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The synthesis of cortisalin (I) is described. The aldehyde (III; $n = 6$) is condensed with malonic acid, and after decarboxylation the product is esterified with diazomethane and demethylated with aluminium bromide to give a product essentially identical with the natural pigment.

THE pigment cortisalin (I) was isolated by Gripenberg [1] from the fungus *Corticium salicinum* Fries, which forms small red sporophores on dead branches in marshes in Sweden and Finland. It is an extremely insoluble compound with an indefinite melting point, for which satisfactory analytical data were difficult to obtain, and is best characterised as its dimethyl derivative (II; $n = 7$), m. p. 255—256°. This was therefore the obvious target for synthetical work; the route envisaged required the chain-extension of *p*-methoxybenzaldehyde to the hexaenal (III; $n = 6$), then the conversion of the latter *via* the malonic acid (IV) into the acid (V; $n = 6$). Methylation should then give (II; $n = 7$), and demethylation of (II; $n = 7$) or (V; $n = 6$) should give cortisalin.

(I) *p*-HO·C$_6$H$_4$·[CH=CH]$_7$·CO$_2$H *p*-MeO·C$_6$H$_4$·[CH=CH]$_n$·CO$_2$Me (II)

p-MeO·C$_6$H$_4$·CHO ⟶ *p*-MeO·C$_6$H$_4$·[CH=CH]$_n$·CHO (III) ⟶

p-MeO·C$_6$H$_4$·[CH=CH]$_n$·CH=C(CO$_2$H)$_2$ (IV) ⟶ *p*-MeO·C$_6$H$_4$·[CH=CH]$_n$·CH=CH·CO$_2$H (V)

The preparation of the requisite aldehydes (III; $n = 2$, 4, and 6) has already been described; [2] the lower homologues were employed in model experiments. The dienal (III; $n = 2$) condensed with malonic acid in pyridine, giving a malonic acid (IV; $n = 2$) which crystallised in dimorphous forms of extraordinarily different colours, the unstable form being light orange and the stable form deep violet. As it was possible to interconvert these at will, it seems unlikely that any more fundamental cause (*e.g.*, stereoisomerism) need be sought. Decarboxylation did not take place in quinoline at 125° or in boiling 20% aqueous potassium hydroxide, but was effected by heating the acid above the melting point (193°) or, better, in a boiling mixture of acetic acid and acetic anhydride.[3] The acid (V; $n = 2$) underwent normal esterification in methanolic sulphuric acid.

The tetraenal (III; $n = 4$) did not react when heated with malonic acid in pyridine, but did so when piperidine was added.[3] After decarboxylation in acetic acid–acetic

* Part IV, *J.*, 1956, 4082.

[1] Gripenberg, *Acta Chem. Scand.*, 1952, **6**, 580.
[2] Marshall and Whiting, *J.*, 1956, 4082.
[3] Kühn and Grundmann, *Ber.*, 1937, **70**, 1318.

anhydride, the acid (V; $n = 4$) was obtained, and was esterified in methanolic sulphuric acid suspension; both acid and ester were virtually insoluble, but infrared examination of the solid proved that a reaction had occurred. When the hexaenal (III; $n = 6$) was condensed with malonic acid in the same way, a good yield was obtained of an acid (V; $n = 6$), m. p. 269—270°, which agreed poorly with the melting point (280—282°) quoted for cortisalin methyl ether.[1] Esterification of the heptaene acid with methanolic sulphuric acid unexpectedly proved impossible; the acid remained insoluble and unchanged even after prolonged heating, with or without the addition of solvents, *e.g.*, *m*-cresol. However, the technique employed by Gripenberg for the dimethylation of cortisalin,[1] *i.e.*, prolonged stirring of the acid with an excess of diazomethane in ether (the use of tetrahydrofuran proved to be an improvement) was successful, giving an ester, m. p. 257—258°, undepressed on admixture with a specimen of dimethylcortisalin, m. p. 255—256°, kindly supplied by Dr. Gripenberg. Infrared spectra, perforce determined on Nujol suspensions, were fairly detailed and were indistinguishable. The ultraviolet absorption spectrum of the synthetic sample is compared, in Fig. 1, with that published by Gripenberg for the naturally derived dimethyl derivative,[1] as insufficient material was available for redetermination on the

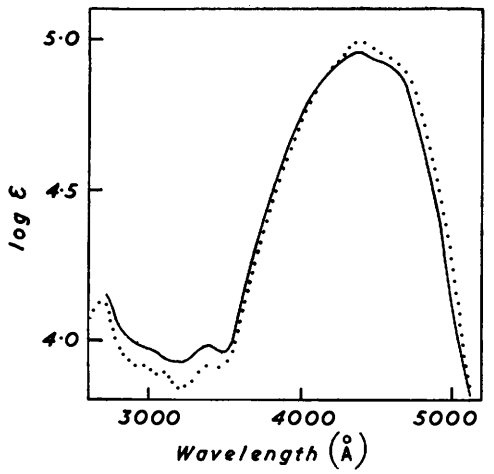


FIG. 1. *Dimethylcortisalin in chloroform.*

—— *Naturally derived ester.*

. . . *Synthetic ester.*

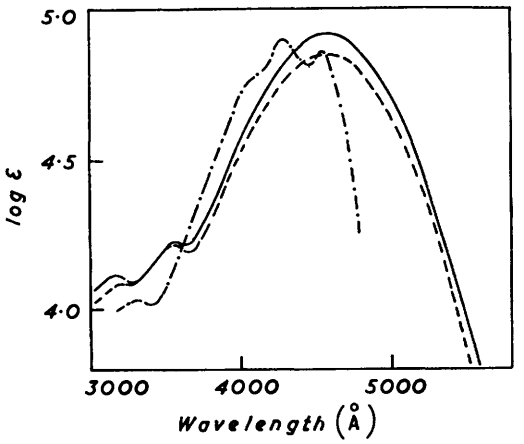
same instrument. They differ slightly, in such a way as to suggest that the natural ester was slightly less pure than the synthetic sample, but their essential identity is evident.

To complete the synthesis of cortisalin, demethylation was now necessary; and any such experiments would require the separation of the cortisalin produced from its methyl ether. The latter proved to be totally insoluble in aqueous sodium and potassium hydroxide solution, failing even to impart a yellow colour to them, although the suspended particles changed colour to a light yellow. In a 2% solution of potassium hydroxide in ethylene glycol (subsequently referred to as " glycol–alkali "), an estimated 2—3 parts per million dissolved, giving a solution of which the absorption spectrum showed polyene fine structure (Fig. 2). Cortisalin itself, however, though almost insoluble in aqueous alkalis, dissolved readily in " glycol–alkali," presumably giving a dipotassium derivative, with a spectrum easily differentiated from that of the methyl ether. Thus it appeared that this solvent would suffice for both separation and identification of the demethylated compound.

A wide range of demethylation techniques were employed on the tri- and penta-enoic acids and esters, without appreciable success; as the higher aldehydes became available, demethylation attempts were then concentrated on the heptaene-acid (V; $n = 6$). The principal difficulties were of course due to the insolubility and instability toward acidic reagents which are characteristic of compounds with long polyene chains. Heating with aluminium bromide in " 2 : 4 : 6-collidine " (probably containing other pyridine bases)

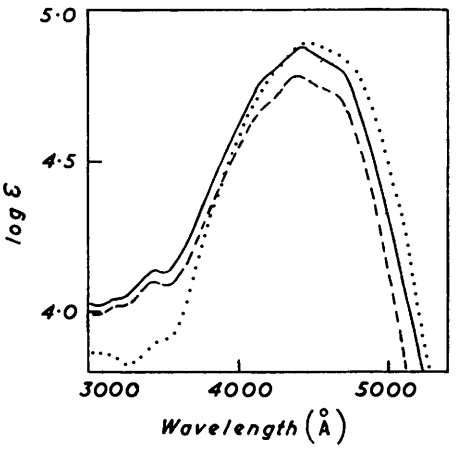
ultimately proved the least unsatisfactory method. It was found, however, that direct treatment of the product with " glycol–alkali " resulted in the dissolution of considerable quantities of the methoxy-acid. This may have been because of solubilisation of the salt of acid (V; $n = 6$) by the salts of the degraded and cyclised by-products present, or more probably because the ether was now present as an equilibrium mixture of stereoisomers, rather than as the all-*trans*-form. After crystallisation from pyridine, however, the fraction insoluble in the cold (mainly all-*trans*?) was treated with " glycol–alkali," the hydroxy-acid fraction alone dissolving. Reprecipitation and recrystallisation from pyridine gave in low yield a product which closely resembled cortisalin in physical properties and had an infrared spectrum (Nujol suspension) identical with that of the natural pigment, although neither specimen gave a very detailed curve. Ultraviolet and visible spectra on the two specimens are shown in Figs. 2 and 3, that (Fig. 2) observed in " glycol–alkali " being the more reliable. It is clear that the synthetic pigment contained a little non-absorbing

FIG. 2. *Cortisalin and acid* (VI; $n = 6$) *in " glycol–alkali."*



—— *Natural cortisalin.* – – – – – *Acid* (I; $n = 7$). —·—·— *Acid* (V; $n = 6$).

FIG. 3. *Cortisalin in pyridine.*



. . . . . *Natural cortisalin (reproduced from ref.* 1). —— *Natural cortisalin (present work).* – – – – – *Synthetic acid* (I).

material, or else a proportion of a less intensely absorbing stereoisomer; but the structural identity of the two compounds is not in doubt. The spectra in pyridine changed appreciably during their observation, the absorptive intensities increasing in the short-wavelength region at the expense of that above 4000 Å. This is probably due to stereoisomerisation, and presumably explains the difference between Gripenberg's published curve [1] and that now recorded for the natural pigment, the former being apparently the less affected. In the two spectra observed here an attempt was made to standardise the experimental techniques, as proof of the identity of the specimens was of more importance than the recording of the most accurate absorption curve. No analogous behaviour was found for the " glycol–alkali " solution, or for the chloroform solution of the ester (II; $n = 7$).

The *p*-methoxyphenylpolyene esters (II) show main absorption maxima at wavelengths appreciably shorter than those of the corresponding aldehydes,[2] although as solids they are more deeply coloured. Whereas the spectra of the aldehydes show rounded, smooth maxima, those of the higher polyene esters show discernible shoulders, indicating poorly resolved vibrational fine structure. In the anion derived from (V; $n = 7$) the typical polyene fine structure is sharply resolved, the absorption band as a whole being displaced to much shorter wavelengths; while, on the other hand, in the dianion of cortisalin, in which O^- is substituted for the tautomerically less effective MeO grouping, the absorption band moves out to about the same position as that of the methoxy-aldehyde, while all

trace of fine structure is lost. Thus there is a good correlation between band position and fine-structure resolution, and between both and the degree of electronic delocalisation :

$$X{\cdot}C_6H_4{\cdot}[CH{=}CH]_n{\cdot}CY{=}O \longleftrightarrow \overset{+}{X}{=}C_6H_4{=}CH{\cdot}[CH{=}CH]_{n-1}{\cdot}CH{=}CY{-}O^-$$

A similar generalisation can probably be applied to the simple polyenes, if one may judge by the contrast between the polyenes and the polyene aldehydes. Between a representative polyene, where such polarisation vanishes, and on the other hand either a highly polarised *mero*cyanine, where the two forms are nearly equivalent in importance, or a symmetrical cyanine cation or oxonol anion, where they are identical, a continuous range of examples can be found. As the degree of delocalisation increases, loss of vibrational fine structure is observed at an early stage, while a transition from the " convergent " ($\lambda = kn^{\frac{1}{2}}$) to the " non-convergent " ($\lambda = kn$) relation [4] between wavelength of the main absorption band and polyene chain length occurs much later.

The infrared spectra of the *p*-methoxyphenylpolyene acids, esters, and aldehydes may conveniently be discussed together; since most of these compounds were examined only as Nujol suspensions, only broad differences are significant. All compounds in the three series showed strong bands at *ca.* 1150 and 1260 cm.$^{-1}$, evidently characteristic of the *p*-methoxyphenyl group.[5] All absorbed intensely near 1000 cm.$^{-1}$ (conjugated C–H out-of-plane deformation modes); the single bands of the methoxy-esters have been listed,[6] and the methoxy-acids and cortisalin itself similarly showed one band only, at *ca.* 1015 cm.$^{-1}$. The aldehydes, however, showed double or ($n>3$) triple bands, the tetraene, for example, absorbing at 1002, 1018, and (less strongly) 1038 cm.$^{-1}$, the hexaene at 1008, 1018, and 1028 cm.$^{-1}$. The C=C stretching frequencies occurred at about 1600 cm.$^{-1}$ and were sometimes multiple. In the aldehydes, the carbonyl stretching frequency fell from 1688 cm.$^{-1}$ (CCl_4) for *p*-methoxycinnamaldehyde to *ca.* 1660 cm.$^{-1}$ (Nujol) for the penta-, hexa-, and hepta-enes, whereas the esters (II; $n = 2$, 4, and 6) all absorbed at 1710 cm.$^{-1}$ (Nujol). Cortisalin (both natural and synthetic) and cortisalin methyl ether showed broad and rather weak absorption at 1667—1680 cm.$^{-1}$; the aralkyl ether bands at 1150 and 1260 cm.$^{-1}$ were conspicuously absent from the spectra of both natural and synthetic cortisalin.

Ultraviolet absorption spectra.

$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$
Esters (II) in chloroform							
$n = 1$		$n = 3$		$n = 5$		$n = 7$	
3080	40	3580	67	4040	85	4590 *	94
						4390	99
						3390	9·2
2260	12·4	2540	7·8	3060 *	8·8	3100	8·9
2100	10·8					3000 *	9·2
						2680	13

Cortisalin (natural) in pyridine		Cortisalin (natural) in " glycol–alkali "		Cortisalin methyl ether	
4620 *	83 †	—	—	4540	0·9 ‡
4430	88 †	4600	91	4290	1·0
4200 *	79 †	—	—	4030 *	0·8
3450	14·1 †	3570	17·0	3330	0·1
3180 *	10·9 †	3190	13·0		

* Inflexion. † Approximate. ‡ Relative values.

Experimental

M. p.s denoted (cap.) were observed in an evacuated capillary tube and are uncorrected; those given as m. p. (K) were observed on the Kofler block and are corrected. Ultraviolet

[4] Lewis and Calvin, *Chem. Rev.*, 1939, **25**, 237.
[5] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 102.
[6] Allan, Meakins, and Whiting, *J.*, 1955, 1874.

absorption spectra were determined in $CHCl_3$ with a Beckman or Unicam S.P. 500 spectrophotometer, and infrared spectra with a Perkin-Elmer 21 spectrophotometer. "Glycol–alkali" refers to a 2% solution of potassium hydroxide in ethylene glycol, the latter being purified by redistillation from potassium hydroxide.

6-p-*Methoxyphenylhexa*-1 : 3 : 5-*triene*-1 : 1-*dicarboxylic Acid.*—5-*p*-Methoxyphenylpenta-2 : 4-dien-1-al (3·76 g.), malonic acid (4·0 g.), pyridine (30 c.c.), and piperidine (0·25 c.c.) were heated at 95° for 2 hr., then cooled and poured into an excess of 4N-sulphuric acid with ice-cooling. The precipitated acid was washed with water until free from mineral acid and dried *in vacuo* over phosphoric oxide. A small portion was crystallised slowly from hot methanol, giving the *acid* as purple prisms, m. p. (K) 192—193° (decomp.). Rapid crystallisation by cooling or addition of water to an alcoholic solution gave an orange form which became deep red at 145° and melted at 185—187° (decomp.); the forms were easily interconverted and had similar ultraviolet absorption spectra (Found: C, 65·6; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%). Light absorption in EtOH; max. 3870 and 2600 Å, relative intensities 7·5 : 1.

7-p-*Methoxyphenylhepta*-2 : 4 : 6-*trienoic Acid.*—The bulk of the crude dicarboxylic acid prepared as above was heated under reflux with acetic acid (30 c.c.) and acetic anhydride (30 c.c.) for 4 hr. The *acid* which separated on cooling was recrystallised from methanol (2·0 g., 44%), forming orange-red plates, m. p. (K) 220—221° (Found: C, 72·85; H, 5·8. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·15%). The *methyl ester* was prepared from the acid (1·0 g.), methanol (100 c.c.), and concentrated sulphuric acid (5 c.c.); after 35 minutes' heating under reflux it began to separate from the hot solution, and was collected after standing overnight at 20° in 90% yield. It formed yellow needles, m. p. (K) 167—168° (Found: C, 73·4; H, 6·75. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%).

11-p-*Methoxyphenylundeca*-2 : 4 : 6 : 8 : 10-*pentaenoic Acid.*—9-*p*-Methoxyphenylnona-2 : 4 : 6 : 8-tetraenal (2·6 g.), malonic acid (4·0 g.), pyridine (50 c.c.), and piperidine (0·45 c.c.) were heated to 95° for 2·5 hr. The crude malonic acid, isolated as above, was decarboxylated in acetic acid (50 c.c.) and acetic anhydride (50 c.c.); cooling and crystallisation of the separated solid [1·0 g., m. p. (cap.) 238°] from pyridine gave the orange-brown *acid*, m. p. (cap.) 244—245° (decomp.) (Found: C, 76·55; H, 6·55. $C_{18}H_{18}O_3$ requires C, 76·55; H, 6·45%). The *methyl ester* was obtained in 80% yield after the acid (0·4 g.), methanol (200 c.c.) and sulphuric acid (12 c.c.) had been heated under reflux for 18 hr.; it separated from the hot solution. After crystallisation from ethyl propionate it formed orange leaflets, m. p. 226—228° (Found: C, 77·1; H, 6·65. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

15-p-*Methoxyphenylpentadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenoic Acid.*—13-*p*-Methoxyphenyltrideca-2 : 4 : 6 : 8 : 10 : 12-hexaenal (2·0 g.), malonic acid (4·0 g.), pyridine (60 c.c.), and piperidine (0·5 c.c.) were heated to 95° for 2 hr., and the crude condensation product was heated for 4 hr. in acetic acid (50 c.c.) and acetic anhydride (50 c.c.). On cooling, the crude *acid* (1·6 g., 70%) separated as a red powder, m. p. (cap.) 263—265° (decomp.); after crystallisation from pyridine, then *m*-cresol, it formed flat needles, m. p. (cap.) 263—265° (decomp.), with a metallic bronze lustre (Found: C, 79·0; H, 6·6. $C_{22}H_{22}O_3$ requires C, 79·0; H, 6·65%). The *methyl ester* was obtained by adding a solution of diazomethane, prepared from *N*-nitrosomethylurea (2·0 g.) in ether (50 c.c.) and tetrahydrofuran (50 c.c.), to a suspension of the acid (0·4 g.) in tetrahydrofuran (100 c.c.) and stirring overnight at 20° with exclusion of light. The excess of diazomethane was destroyed by addition of acetic acid. The crystalline suspension of the acid was replaced by a lighter-red microcrystalline powder, which crystallised from *m*-cresol, giving the ester (0·4 g.) as bronze leaflets, m. p. (K) 257—258°, undepressed on admixture with a specimen, m. p. (K) 255—256°, derived from the natural pigment (Found: C, 78·2; H, 7·0. $C_{23}H_{24}O_3$ requires C, 79·3; H, 6·95%).

Hydrolysis of the synthetic methoxy-ester under the conditions described by Gripenberg [1] gave a specimen of the methoxy-acid containing some of its potassium salt, which melted diffusely above 265°. This may explain the higher m. p. (280—282°) recorded for the naturally derived methoxy-acid.

Demethylation Experiments.—In preliminary experiments, of which 7 were made in the triene, 7 in the pentaene, and 21 in the heptaene series, the reaction product was added to "glycol–alkali"; any phenolic acid should dissolved with the formation of a dianion with a bathochromically displaced absorption spectrum. Potassium hydroxide in ethylene glycol at 160° effected extensive degradation; magnesium iodide at 165° had no effect; fused pyridine hydrochloride or the fused complex, $2C_5H_5N,AlBr_3$, gave a carbonaceous mass; boron

tribromide in nitrobenzene at 20° apparently demethylated the triene-acid, but gave no phenolic acids in the penta- and hepta-ene series, and was equally unsuccessful in " 2 : 4 : 6-collidine." Collidine–collidine hydrochloride at 176° had no effect. Aluminium bromide was investigated in nitrobenzene, xylene, *m*-cresol, pyridine, and " 2 : 4 : 6-collidine " at various temperatures. The last at the b. p. alone gave definite indications of demethylation of the heptaene acid and ester, and was examined in detail, the following method being evolved :

15-p-*Hydroxyphenylpentadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenoic Acid* (*Cortisalin*).—The methoxy-ester (II; $n = 7$) (600 mg.), anhydrous aluminium bromide (3·0 g.), and " 2 : 4 : 6-collidine " (56 c.c.) were heated under reflux for 2 hr., cooled, and poured into an excess of 2N-sulphuric acid. The precipitate was washed with water until free from mineral acid, dried (P_2O_5), and extracted with boiling pyridine (12 c.c.), the dark residue being discarded. The red solid which separated was warmed with " glycol–alkali " (40 c.c.) and centrifuged, the yellow salt of the methoxy-acid (V; $n = 7$) being separated from a deep red clear solution. Acidification now gave a dark precipitate (20 mg.) which was crystallised from pyridine to give esentially pure cortisalin (6 mg.) as microscopic purple-red crystals, much darker than acid (V; $n = 7$), which decomposed without melting at 300° (cap.), $\lambda_{max.}$ 4600 Å (ε 66,000 in " glycol–alkali "). This material showed the infrared bands listed above; for a final purification the cycle of dissolution in " glycol–alkali," centrifugation, acidification, and recrystallisation from pyridine was repeated, giving a product with the absorption spectra illustrated (*i.e.*, $\lambda_{max.}$ 4590 and 4400 Å; ε 70,300 and 60,000, respectively, in " glycol–alkali " and pyridine).

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