871. *Colouring Matters of the Aphididae. Part XXIII.*[1] *Synthesis of the Xanthoaphin Chromophore.*

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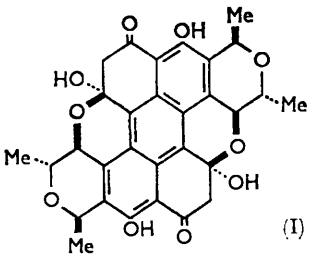
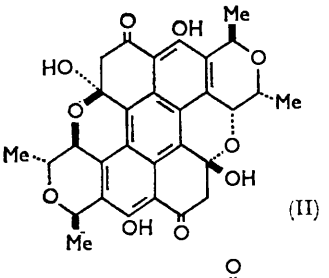
The synthesis of 1,5-diacyl-2,6-dihydroxyanthracenes has been studied. Initial attempts to obtain the cyclic dione (III) as an approach to an aphin synthesis were unsuccessful. However, 1,5-diacetyl-2,6-dihydroxyanthracene could readily be prepared. It contains the same hypothetical chromophore as the structures (I) and (II), previously assigned to xanthoaphin-*fb* and -*sl*, and was spectroscopically similar to them.

In an earlier Paper[2] of this series we deduced structures (I) and (II) for the isomeric xanthoaphins-*fb* and -*sl*, largely on the basis of an extensive study of the related protoaphins and erythroaphins. The xanthoaphins themselves were too unstable to be degraded directly and attempts to do so, or even to convert them into simple derivatives, generally resulted in dehydration to erythroaphins. However structures (I) and (II) were consistent with their properties and received indirect support from spectroscopic arguments,[2] which indicated that they were almost certainly derivatives of anthracene.



(I)



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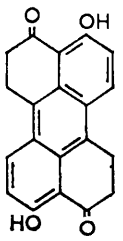

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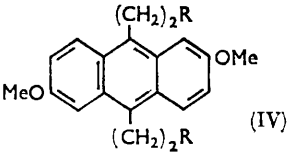

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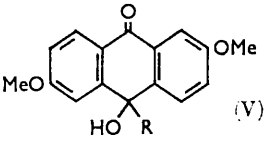

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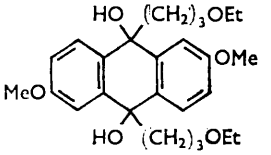

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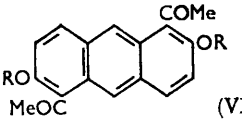


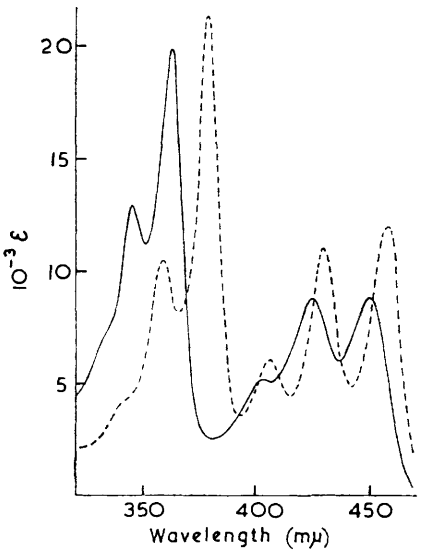
(VII)

In order to provide further confirmation we decided to synthesise a simple model compound containing the complete xanthoaphin chromophore, which, on the basis of structures (I) and (II), should be essentially a 1,5-diacyl-2,6-dihydroxyanthracene. The preparation of such a system might also be valuable as an approach to the problem of total synthesis in the aphin field.

In order to achieve both these ends our initial experiments were directed towards the dione (III) and in particular its logical precursor, the diacid (IV; R = CO_2H). The direct introduction of activated 9,10-dialkyl groups into anthracene itself can readily be effected, *e.g.*, by chloromethylation,[3] but such an approach cannot be applied to 2,6-dimethoxyanthracene which undergoes electrophilic attack at the 1,5-positions (see later).

[1] Part XXII, Cameron, Kingston, Sheppard, and Todd, *J.*, **1964**, 98.
[2] Calderbank, Cameron, Cromartie Hamied, Haslam, Kingston, Todd, and Watkins, *J.*, **1964**, 80.
[3] Postovskii and Bednyagina, *J. Gen. Chem.* (*U.S.S.R.*), **1937**, **7**, 2919 (*Chem. Abs.*, **1938**, **32**, 5396).

Similarly, the presence of 2,6-dimethoxy-groups profoundly influences nucleophilic addition to anthraquinones, *e.g.*, when treated with sodium acetylide in liquid ammonia, anthraquinone itself gives a di-adduct [4] whereas its 2,6-dimethoxy-derivative, similarly treated, gives only the mono-adduct (V; R = C:CH); the use of more vigorous conditions [5] gave no better result. Similar mono-adducts from other anthraquinones containing mesomeric electron-donating substituents have been obtained by Ried and Lukas.[6] The structure of the adduct was confirmed spectroscopically; its ultraviolet absorption was similar to that of 2,6-dimethoxy anthrone which was synthesised by reduction of the corresponding quinone and characterised as its anthranyl acetate. Di-addition to 2,6-dimethoxyanthraquinone was, however, achieved with a Grignard reagent. Clark [7] described the di-addition of 3-ethoxypropylmagnesium bromide to anthraquinone, and the 2,6-dimethoxy-derivative reacted similarly, to yield the diol (VI). (Attempts to prepare a Grignard reagent from the diethyl acetal of 3-bromopropanal were unsuccessful.) The



Absorption spectra of xanthoaphin (– – – –) and 1,5-diacetyl-2,6-dihydroxyanthracene (——).

diol (VI) smoothly underwent reduction to the tetraether (IV; R = CH_2OEt). This was demethylated with hydrogen bromide in acetic acid and then remethylated to yield the dibromo-compound (IV; R = CH_2Br), which on alkaline hydrolysis gave the diol (IV; R = CH_2OH). It was anticipated that this compound would be readily oxidised to the required diacid (IV; R = CO_2H) but all attempts to do so failed because of the remarkable ease with which the anthracene nucleus preferentially underwent oxidative attack. Even with limited amounts of oxidants under mild conditions no more than traces of acidic material were produced. The course of reaction could best be studied by oxidation of the tetraether (IV; R = CH_2OEt) which yielded a mixture of the anthrone (V; R = $[CH_2]_3$·OEt) and a trace of 2,6-dimethoxyanthraquinone. The former underwent further oxidation to the latter and its structure was confirmed by its ultraviolet spectrum which was virtually identical to that of 2,6-dimethoxyanthrone. A similar compound [8] has previously been obtained by oxidation of an anthracene derivative under more vigorous conditions.

Further work towards the dione (III) was abandoned at this stage in view of more

[4] Ried and Schmidt, *Chem. Ber.*, 1957, **90**, 2553.
[5] Ried, Donner, and Schlegelmilch, *Chem. Ber.*, 1961, **94**, 1051.
[6] Ried and Lukas, *Chem. Ber.*, 1960, **93**, 589.
[7] Clark, *J.*, 1956, 1511.
[8] Blicke and Weinkauff, *J. Amer. Chem. Soc.*, 1932, **54**, 1460.

promising results in the synthesis of the simpler compound (VII; R = H). This proved an adequate xanthoaphin model, though its preparation is not directly capable of extension into an aphin synthesis. 2,6-Dihydroxyanthracene is known to undergo bromination [9] and diazo-coupling [10] at the 1,5-positions and its dimethyl ether similarly would be expected to undergo 1,5-attack by other electrophiles. Indeed, when treated with acetyl chloride under Friedel–Crafts conditions, it gave the 1,5-diacetyl derivative (VII; R = Me) in 50% yield. Confirmation of the orientation of substituents in this compound was provided by its nuclear magnetic resonance (n.m.r.) spectrum. This included a singlet at 1·58 τ (intensity 2), corresponding to the 9,10-protons, together with the two unsymmetrical doublets of an AB system (J = 9 c./sec.) [11] centred at 1·90 and 2·55 τ (intensity 2), representing the 4,8- and 3,7-protons, respectively. Demethylation of this compound with aluminium chloride in boiling benzene gave the desired dihydroxy-compound (VII; R = H), as a yellow solid which, like xanthoaphin, had an intense green fluorescence in solution. (It is noteworthy that attempted demethylation with hydrogen bromide in acetic acid appeared to cause deacylation.) Its visible spectrum, apart from the expected small hypsochromic shift was virtually identical with that of the xanthoaphins (see Figure), as was its infrared carbonyl absorption [12] ($\nu_{max.}$ 1622 cm.$^{-1}$). Like xanthoaphin it gave a pink anion in aqueous sodium carbonate but, unlike xanthoaphin, this colour was stable, none of the changes due to dehydration being observed. An alternative method of preparation involved Fries rearrangement of 2,6-diacetoxyanthracene. Acetylation of the crude reaction mixture yielded the diacetate (VII; R = COMe) which readily underwent saponification to the phenol (VII; R = H). Finally, this compound was also prepared, though less satisfactorily, by direct acylation of 2,6-hydroxyanthracene. The general agreement between its properties and those of the xanthoaphins leaves no doubt that it represents an adequate model chromophore and therefore provides strong support for structures (I) and (II).

Experimental

Unless otherwise stated, infrared spectra were measured in Nujol mulls, and ultraviolet and visible spectra in ethanol. N.m.r. spectra were obtained at 40 Mc./s, using tetramethylsilane.

2,6-*Dimethoxyanthraquinone*.—Prepared by methylation of 2,6-dihydroxyanthraquinone,[13] this had m. p. 257°, $\lambda_{max.}$ 216, 272, 298, 344 mμ (log ε 4·45, 4·60, 4·36, 3·95), $\nu_{max.}$ 1670 (C:O), 1590 cm.$^{-1}$ (C:C).

2,6-*Dimethoxyanthracene*.—Reduction of 2,6-dihydroxyanthraquinone yielded 2,6-dihydroxyanthracene [14] (characterised as its diacetate, m. p. 261—262°), $\lambda_{max.}$ 220, 259, 301, 326, 343, 393, 414 mμ (log ε 4·10, 4·95, 3·81, 3·57, 3·58, 3·38, 3·36), $\lambda_{infl.}$ 229 mμ (log ε 4·06), $\nu_{max.}$ 3180 (OH), 1640 (C:C) cm.$^{-1}$. Methylation with dimethyl sulphate gave 2,6-dimethoxyanthracene,[14] m. p. 262° (from benzene), $\lambda_{max.}$ 260, 294, 307, 322, 338, 360, 379, 400 mμ (log ε 5·22, 3·23, 3·47, 3·63, 3·51, 3·23, 3·54, 3·58), $\nu_{max.}$ 1633 cm.$^{-1}$.

10-*Ethynyl*-10-*hydroxy*-2,6-*dimethoxyanthrone* (V; R = C:CH).—A solution of 2,6-dimethoxyanthraquinone (5 g.) in toluene (100 ml.) was added during 30 min. to sodium acetylide [from sodium (1·25 g.)] in liquid ammonia [4] (50 ml.). The mixture was kept at −50° for 24 hr., treated with ammonium chloride (10 g.), and evaporated to dryness. Water (200 ml.) was added and the resulting solid filtered off, dried, and extracted with ether–toluene (1 : 1). The extract was dried, evaporated, and recrystallised from benzene to yield the *anthrone* (2·7 g.) as a pale yellow-brown solid, m. p. 165—168° (Found: C, 73·4; H, 5·1. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%), $\lambda_{max.}$ 229, 246, 304 mμ (log ε 4·34, 4·31, 4·21), $\lambda_{infl.}$ 276, 332 mμ (log ε 3·85, 3·80), $\nu_{max.}$ 3340, 3250 (OH, CH), 2120 (C:C), 1650 (C:O), 1600, 1583, 1568 cm.$^{-1}$ (C:C).

2,6-*Dimethoxyanthrone*.—A solution of 2,6-dimethoxyanthraquinone (15 g.) in acetic acid

[9] Fries, Walter, and Schilling, *Annalen*, 1935, **516**, 248.
[10] Fieser and Lothrop, *J. Amer. Chem. Soc.*, 1936, **58**, 749.
[11] Jonathan, Gordon and Dailey *J. Chem. Phys.*, 1962, **36**, 2443.
[12] Hunsberger, *J. Amer. Chem. Soc.*, 1950, **72**, 5626.
[13] Briggs and Nicholls, *J.*, 1951, 1138.
[14] Hall and Perkin, *J.*, 1923, **123**, 2029.

(400 ml.) was treated with stannous chloride (120 g.) in concentrated hydrochloric acid (300 ml.). The mixture was warmed until a clear solution was obtained, filtered, and diluted with water to incipient crystallisation. Refrigeration then yielded 2,6-dimethoxyanthrone (10 g.), m. p. 156° (from acetone), $\lambda_{max.}$ 220, 306 mμ (log ε 4·42, 4·23), $\lambda_{infl.}$ 271, 330 mμ (log ε 3·95, 3·90), $\nu_{max.}$ 1647 (C:O), 1603 cm.$^{-1}$ (C:C). Correct analyses could not be obtained, perhaps because of contamination with a trace of the corresponding quinone and it was characterised as its acetate (below).

9-*Acetoxy*-2,6-*dimethoxyanthracene*.—2,6-Dimethoxyanthrone (2 g.) was warmed in acetic anhydride (20 ml.) and pyridine (0·5 ml.) on a water-bath. It first dissolved and, on continued warming, the solution deposited pale yellow needles of the *product*, m. p. 226° (from acetone) (Found: C, 73·0; H, 5·9. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%), $\lambda_{max.}$ 236, 254, 263, 295, 310, 325, 342, 384, 406 mμ (log ε 4·25, 4·94, 5·32, 3·28, 3·53, 3·69, 3·59, 3·63, 3·67), $\lambda_{infl.}$ 232, 367 mμ (log ε 4·24, 3·32), $\nu_{max.}$ 1766 (OAc), 1632 cm.$^{-1}$ (C:C).

9,10-*Di*-(3-*ethoxypropyl*)-9,10-*dihydro*-9,10-*dihydroxy*-2,6-*dimethoxyanthracene* (VI).—A solution of 3-ethoxypropylmagnesium bromide [7] [from 1-bromo-3-ethoxypropane (28 g.)] was cooled to 0°, diluted with benzene (100 ml.), stirred vigorously, and treated portionwise with 2,6-dimethoxyanthraquinone (10 g.). More benzene (150 ml.) was added, the solution stirred for 1 hr. and then refluxed for 15 hr. The complex was decomposed with concentrated aqueous ammonium chloride, unchanged starting material filtered off, and the filtrate washed with water and with alkaline sodium dithionite until the extracts were colourless. The organic phase was evaporated to dryness yielding a red oil which was triturated with light petroleum (b. p. 40—60°) to yield the *diol* (5 g.), m. p. 120° [from light petroleum (b. p. 40—60°)] (Found: C, 69·9; H, 8·2. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%), $\lambda_{max.}$ 275, 286, 343 mμ (log ε 3·65, 3·63, 2·71), $\nu_{max.}$ 3360 (OH), 1614, 1569 cm.$^{-1}$ (C:C).

9,10-*Di*-(3-*ethoxypropyl*)-2,6-*dimethoxyanthracene* (IV; R = CH_2OEt).—The crude red oil from the Grignard reaction above was refluxed in acetic acid (200 ml.), and zinc dust (20 g.) added over 1 hr. The mixture was filtered, the filtrate poured on ice, extracted with ether, and the extracts washed, dried, and evaporated. Recrystallisation of the crude product from aqueous acetone or light petroleum yielded the *tetra-ether*, needles, m. p. 115°. A sample was sublimed at 80°/10^{-4} mm. for analysis (Found: C, 75·8; H, 8·3. $C_{26}H_{34}O_4$ requires C, 76·1; H, 8·3%), $\lambda_{max.}$ 232, 260, 269, 302, 318, 333, 350, 373, 394, 417 mμ (log ε 4·08, 4·68, 5·05, 2·48, 3·23, 3·56, 3·52, 3·23, 3·56, 3·63), $\nu_{max.}$ 1634 cm.$^{-1}$ (C:C).

9,10-*Di*-(3-*bromopropyl*)-2,6-*dimethoxyanthracene* (IV; R = CH_2Br).—The tetra-ether (IV; R = CH_2OEt) (5 g.) was dissolved in acetic acid containing 50% hydrogen bromide (w/v) (100 ml.) and heated at 100° for 1 hr. under nitrogen. The mixture was then poured into ice–water and the green precipitate filtered off and shaken with dimethyl sulphate (10 ml.) and 5% sodium hydroxide (100 ml.) under nitrogen in the dark. Further quantities of dimethyl sulphate (10 ml.) and 10% sodium hydroxide (45 ml.) were added after 30 min. and the mixture shaken for an additional 20 min. Saturated aqueous ammonia (20 ml.) was added and the crude product (5 g.) filtered off, washed, dried, and chromatographed on alumina. Elution with benzene yielded the *bromo-compound* (2·2 g.), m. p. 202° (from acetone) (Found: C, 55·0; H, 5·4. $C_{22}H_{24}Br_2O_2$ requires C, 55·0; H, 5·0%), $\lambda_{max.}$ 233, 260, 269, 303, 318, 333, 350, 374, 394, 417 mμ (log ε 4·26, 4·86, 5·24, 3·14, 3·43, 3·69, 3·74, 3·43, 3·76, 3·83), $\nu_{max.}$ 1637 cm.$^{-1}$ (C:C).

9,10-*Di*-(3-*hydroxypropyl*)-2,6-*dimethoxyanthracene* (IV; R = CH_2OH).—A suspension of the bromo-compound (IV; R = CH_2Br) (95 mg.) in dioxan–0·5N-sodium hydroxide (20 ml.; 1 : 1) was refluxed for 2 hr. and the resulting solution poured into water, set aside overnight at 0°, filtered, and the precipitate (70 mg.) washed, dried, and recrystallised from acetone to give the yellow *diol*, m. p. 178° (Found: C, 74·6; H, 7·4. $C_{22}H_{26}O_2$ requires C, 74·6; H, 7·4%), $\lambda_{max.}$ 233, 260, 269, 302, 318, 333, 351, 373, 394, 418 mμ (log ε 4·27, 4·79, 5·19, 3·13, 3·40, 3·65, 3·68, 3·41, 3·72, 3·78), $\nu_{max.}$ 3330, 3250 (OH), 1637 cm.$^{-1}$ (C:C).

Oxidation of the Tetraether (IV; R = CH_2OEt).—A solution of tetra-ether (750 mg.) in acetone (10 ml.) was treated at 0° with 8N-chromic acid (10 ml.), set aside for 2 hr. at room temperature, poured into water and extracted with chloroform. The extract was washed with dilute sodium hydroxide solution, dried, and evaporated to give a crude neutral product (430 mg.). This, when chromatographed in benzene on alumina (Brockmann IV; 50 g.), yielded two fractions, (i) pale yellow crystals (10 mg.), m. p. 257° (from acetone), undepressed in admixture with 2,6-dimethoxyanthraquinone and having an identical infrared spectrum and (ii) a yellow oil (240 mg.) which (on crystallisation from carbon tetrachloride and light

petroleum) gave 10-(3-*ethoxypropyl*)10-*hydroxy*-2,6-*dimethoxyanthrone* (V; R = $[CH_2]_3$·OEt). On heating, it first melted at 50—60°, resolidified, and had final m. p. 102—103° (Found: C, 70·5; H, 7·0. $C_{21}H_{24}O_5$ requires C, 70·8; H, 6·8%), $\lambda_{max.}$ 224, 244, 304 mμ (log ε 4·33, 4·20, 4·22), $\lambda_{infl.}$ 218, 277, 337 mμ (log ε 4·36, 3·87, 3·77), $\nu_{max.}$ 3440 (OH), 1647 (C:O), 1599, 1583, 1570 cm.$^{-1}$ (C:C).

A sample of this anthrone (25 mg.) in acetone (10 ml.) was oxidised with 8N-chromic acid (10 ml.) for 12 hr. at room temperature. Extraction with chloroform gave 2,6-dimethoxyanthraquinone (10 mg.) m. p. and mixed m. p. 252° (from acetone). A sample of 2,6-dimethoxyanthracene (0·5 g.) was oxidised as for the tetra-ether above. Chromatography gave 2,6-dimethoxyanthraquinone (110 mg.) m. p. 255° confirmed by infrared spectrum. No other neutral product could be isolated.

1,5-*Diacetyl*-2,6-*dimethoxyanthracene* (VII; R = Me).—Acetyl chloride (50 ml.) in dry chloroform (50 ml.) was added in portions to a suspension of aluminium chloride (84 g.) in chloroform (200 ml.) and stirred at 30—35° until all the aluminium chloride had dissolved. The flask was then cooled in ice and a solution of 2,6-dimethoxyanthracene (2 g.) in chloroform (1 l.) added over 10 min. The solution, which immediately developed a deep red colour, was stirred at 0° for 6 hr. then poured on to a mixture of ice and hydrochloric acid. The resulting solution was washed with dilute sodium hydroxide solution and water, dried, and evaporated to yield 1,5-*diacetyl*-2,6-*dimethoxyanthracene* (1·9 g.), needles (1·3 g.), m. p. 240° (from benzene) (Found: C, 74·5; H, 5·6. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%), $\lambda_{max.}$ ($CHCl_3$) 269, 322, 338, 357, 408 mμ (log ε, 5·09, 3·43, 3·60, 3·68, 3·74), $\lambda_{infl.}$ 427 mμ (log ε 3·68), $\nu_{max.}$ 1683 (C:O), 1613, 1544 cm.$^{-1}$ (C:C); n.m.r. signals (in CH_2Cl_2) at 1·58, 1·90 (doublet, J = 9 c./sec.), 2·55 (doublet, J = 9 c./sec.), 5·93 (MeO), 7·28 τ (MeCO).

2,6-*Diacetoxyanthracene*.—Prepared from the dihydroxy-derivative by treatment with acetic anhydride and pyridine,[14] this had m. p. 261—262°, $\lambda_{max.}$ ($CHCl_3$) 257, 347, 359, 380 mμ (log ε 5·15, 3·62, 3·64, 3·63), $\lambda_{infl.}$ 320, 335 mμ (log ε 3·31, 3·54).

2,6-*Diacetoxy*-1,5-*diacetylanthracene* (VII; R = COMe).—An intimate mixture of 2,6-diacetoxyanthracene (1 g.) and aluminium chloride (1·8 g.) was heated at 140—150° for 1·5 hr. The cooled product was stirred with dilute hydrochloric acid and the insoluble material filtered off, washed, dried, and digested with acetic anhydride (50 ml.) and pyridine (5 drops). The material which separated was collected, washed with acetic acid and water, and dried to give 2,6-*diacetoxy*-1,5-*diacetylanthracene* (0·65 g.), needles, m. p. 259° (from acetone) (Found: C, 69·9; H, 5·0. $C_{22}H_{18}O_6$ requires C, 69·8; H, 4·8%), $\lambda_{max.}$ ($CHCl_3$) 261, 363, 383 mμ (log ε 5·06, 3·76, 3·68), $\lambda_{infl.}$ 350 mμ (log ε 3·68), $\nu_{max.}$ 1761 (OAc), 1697 (C:O), 1620, 1557 (C:C) cm.$^{-1}$.

1,5-*Diacetyl*-2,6-*dihydroxyanthracene* (VII; R = H).—(*a*) A solution of 1,5-diacetyl-2,6-dimethoxyanthracene (200 mg.) in dry benzene was refluxed with aluminium chloride for 10 min. then poured on to a mixture of ice and dilute hydrochloric acid. The product was extracted into chloroform, then into sodium carbonate solution, acidified, re-extracted into chloroform which was washed, dried, and evaporated to yield 1,5-*diacetyl*-2,6-*dihydroxyanthracene* (120 mg.), needles, m. p. 283° (from acetone) (Found: C, 73·6; H, 4·8. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%), $\lambda_{max.}$ ($CHCl_3$) 276, 345, 363, 403, 425, 451 mμ (log ε 4·67, 4·11, 4·29, 3·72, 3·95, 3·45), $\nu_{max.}$ 1622 (C:O), 1585, 1550 cm.$^{-1}$ (C:C).

(*b*) To a solution of 2,6-diacetoxy-1,5-diacetylanthracene (VII; R = COMe) (110 mg.) in methanol (10 ml.) was added dilute sodium hydroxide solution (10 ml.) and the mixture refluxed 30 min. under nitrogen. It was acidified, extracted with chloroform, and the extract washed, dried, and evaporated to yield 1,5-diacetyl-2,6-dihydroxyanthracene (70 mg.), m. p. and mixed m. p. 284° (from acetone). Its infrared spectrum was identical with that from (*a*) above.

(*c*) 2,6-Dihydroxyanthracene (200 mg.) was suspended in chloroform (100 ml.) and added to a stirred solution of acetyl chloride (5 ml.) and aluminium chloride (9 g.) in chloroform (100 ml.). The solution immediately turned deep red and was stirred at 0° for 2 hr., brought to room temperature, and set aside overnight. The complex was decomposed with dilute hydrochloric acid, the product extracted into chloroform, and then into aqueous sodium hydroxide. Acidification, re-extraction into chloroform, and evaporation gave 1,5-diacetyl-2,6-dihydroxyanthracene (37 mg.) confirmed by spectroscopic comparison with the product from (*a*) above.

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