The Biosynthesis of Phenols. Part XX.[1] Synthesis of Anthraquinones through Carbanions of *ortho*-Substituted Benzophenones.

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Treatment of 2-cyanomethyl-2′,4′-dimethoxybenzophenone with sodium methoxide in dimethyl sulphoxide gave 9-cyano-2-methoxyanthracen-10-ol in 95% yield. This was oxidised to 2-methoxyanthraquinone in almost quantitative yield, under mild conditions. The relevance of this synthesis of anthraquinones to possible pathways of biosynthesis has been discussed. The interaction of 2-cyanomethyl-2′,4′-dimethoxybenzophenone and sodium methoxide in methanol gave 3-methoxy-1-(2,4-dimethoxyphenyl)isoquinoline.

It has been suggested [2] that a benzophenone may arise *in vivo*, from oxidation of the related anthraquinone which is itself derived from a polyketide.[3] The co-occurrence of the anthraquinone (I) and the polyacetate–derived benzophenone sulochrin (II) in cultures of *Aspergillus terreus* [4] and *Penicillium frequentans* [5] has been regarded as evidence in support of this suggestion. Although attempts to achieve such an oxidation from an anthraquinone, *in vitro*, have not been successful,[6] and there is no evidence, as yet, to confirm that it occurs *in vivo*, the step has been included in several postulated pathways of biosynthesis.[7,8] Evidently, other explanations for the co-occurrence of benzophenones and related anthraquinones are possible. They could arise through separate ' polyacetate ' pathways. Alternatively, an anthraquinone could be derived from a related benzophenone. In this connection it seemed to us that a plausible *in vitro* model for the conversion of a benzophenone to an anthraquinone under mild conditions might involve the carbanion (III) of 2-substituted-2′-hydroxybenzophenones. With natural products an adjacent carbonyl group could facilitate carbanion formation. The carbanion, once formed, might be expected to participate, in intramolecular nucleophilic displacement of the 2′-hydroxy- (or substituted hydroxy-) group, with the formation of a hydroxyanthracene derivative. This could then be oxidised to an anthraquinone. The ring-closure step shows some similarity to that proposed for the biosynthesis of certain xanthones from 2,2′-dihydroxybenzophenones [9,10] and to the intermolecular process involving displacement of the *ortho*-methoxy-group when a Grignard reagent acts on a benzophenone such as (V) to give the product (VI).[11]

We have investigated the possibility of such a conversion of benzophenones to hydroxyanthracenes through the preparation of the nitrile (XVI), which could evidently be expected to form an appropriate carbanion readily. With the synthesis of such a nitrile in mind, an attempt was made to obtain the 2-bromomethyl-2′,4′-dimethoxybenzophenone, directly, by treatment of the corresponding 2-methyl derivative with *N*-bromo-succinimide. When this failed, the nitrile was prepared through the corresponding benzyl alcohol. Initially, it was envisaged that the alcohol (VII) could be obtained

[1] Part XIX, M. Afzal, J. S. Davies, and C. H. Hassall, *J. Chem. Soc.* (*C*), 1969, 1721.
[2] H. Raistrick, *Suomen Kem.*, 1950, **23**, 221.
[3] S. Gatenbeck, *Svensk Kem. Tidskr.*, 1960, **72**: **3**, 188.
[4] R. F. Curtis, P. C. Harries, C. H. Hassall, J. D. Levi, and D. M. Phillips, *J. Chem. Soc.* (*C*), 1966, 168; R. F. Curtis, P. C. Harries, and C. H. Hassall, unpublished results.
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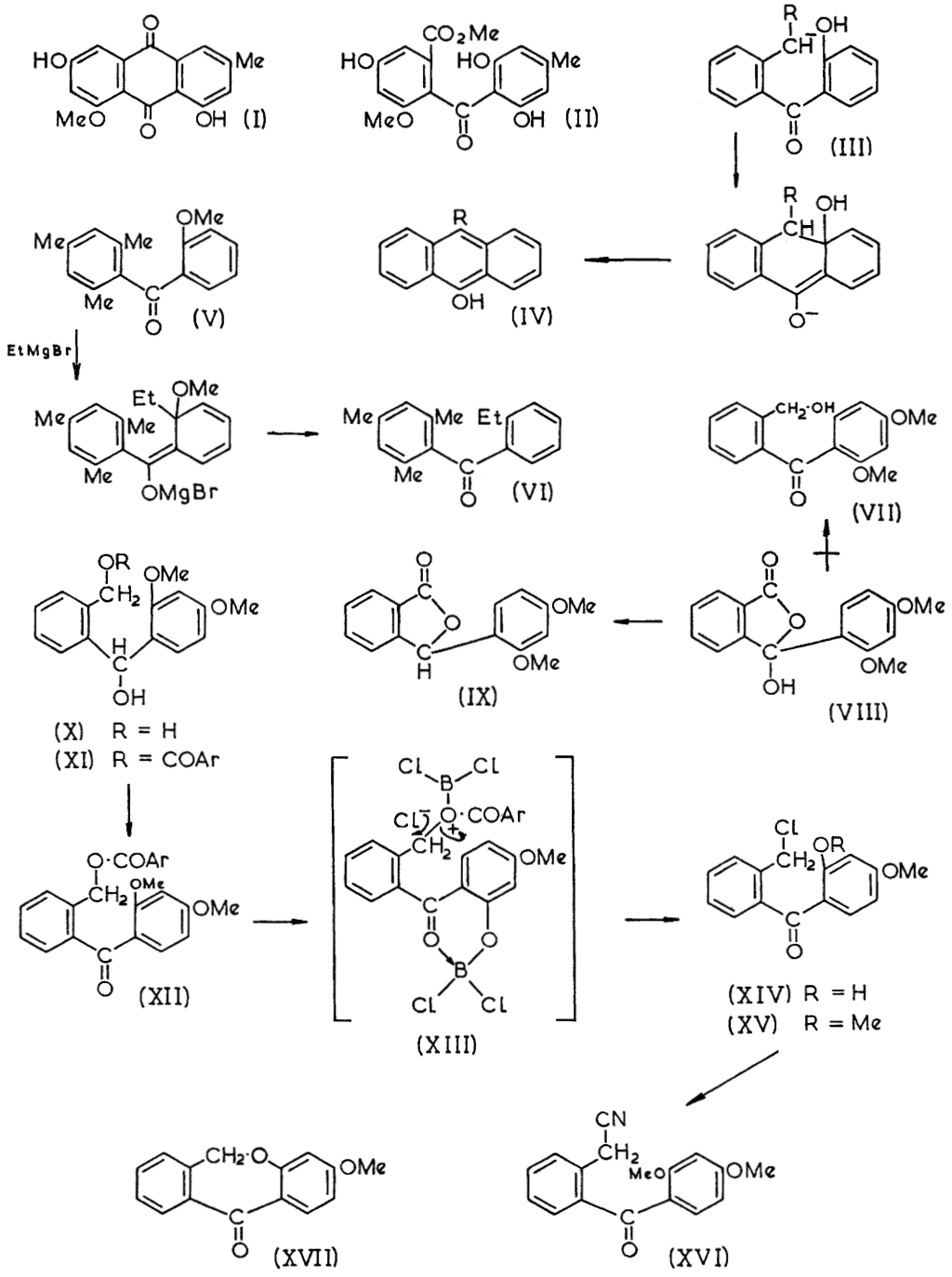
[6] B. Franck, V. Radtke, and U. Zeidler, *Angew. Chem. Internat. Edn.*, 1967, **6**, 952.
[7] D. Groger, D. Erge, B. Franck, U. Ohnsorge, H. Flasch, and F. Huper, *Chem. Ber.*, 1968, **101**, 1970.
[8] J. W. ApSimon, J. A. Corran, N. G. Creasy, K. Y. Sim, and W. B. Whalley, *Proc. Chem. Soc.*, 1963, 209.
[9] J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074.
[10] S. Neelakantan and T. R. Seshadri, *Current. Sci.*, 1961, **30**, 90.
[11] R. Gaertner, *Chem. Rev.*, 1949, **45**, 493.

readily from the corresponding acid (VIII) by selective reduction with diborane, as in the related case of *p*-benzoylbenzoic acid.[12] However, the substituted *o*-benzoylbenzoic acid was converted by diborane to the phthalide (IX), probably through preferential



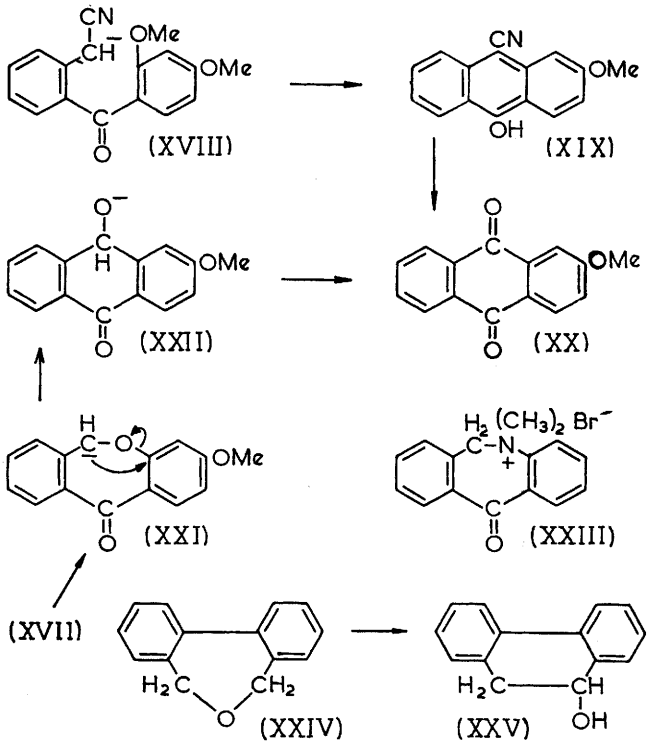
reduction of the pseudo-form (VIII). As a result, our synthesis utilised the corresponding diol. This diol (X), after partial protection by benzoylation to give (XI), was oxidised with manganese dioxide, and the product (XII) was selectively demethylated and converted to the substituted benzyl chloride (XIV), in a single step, by the action of boron trichloride. The selective demethylation reaction has been fully investigated by Dean and his co-workers [13] but the observation relating to the ester function, which presumably proceeds through the complex with boron trichloride (XIII), appears to be novel. Although the chloride (XIV) was relatively

[12] B. C. Subba Rao and G. P. Thakar, *Current Sci.*, 1963, **9**, 404.

[13] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

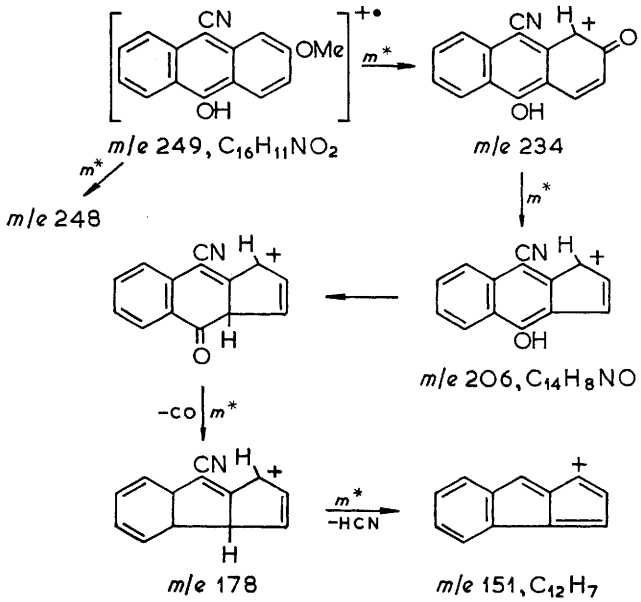
stable and was fully characterised, it could not be employed directly for conversion into the nitrile. Treatment with sodium cyanide in acetone or in dimethyl sulphoxide led to the formation of the corresponding oxepinone (XVII). However, the methylation product (XV), which, as anticipated from the loss of hydrogen bonding, was less stable than (XIV), was converted under these conditions into the crystalline nitrile (XVI), in 70% yield.

The reaction of 2-cyanomethyl-2′,4′-dimethoxybenzophenone with alkali under various conditions has been investigated. Red colours developed due to the formation of the carbanion (XVIII) with sodium hydroxide or sodium methoxide in solvents such as dimethyl sulphoxide or dimethylformamide but there was no colour in methanol or ethanol. Aerial oxidation of the carbanion occurred readily in the non-hydroxylic solvents to give 2-carboxy-2′,4′dimethoxybenzophenone. This may be compared with the formation of benzoic acid by aerial oxidation of the carbanion of 1-nitro-1-phenylmethane.[14] However, when a mixture of sodium methoxide and the nitrile (XVI) in dimethyl sulphoxide



was heated under nitrogen to 140° during 10 min., 9-cyano-2-methoxyanthracen-10-ol (XIX) was formed in 95% yield. The crystalline compound, $C_{16}H_{11}NO_2$, had a u.v. spectrum and a ^1H n.m.r. spectrum [τ 5·93, s, 3H (·OCH_3); 7H, ArH] in accord with the structure (XIX). The mass spectrum, which was investigated in detail, supported the formulation. Scheme 1 summarises the major metastable transitions and the postulated structures of the ions involved. The cyanoanthranol (XIX) was oxidised by hydrogen peroxide in dilute alkali to give 2-methoxyanthraquinone (XX) in almost quantitative yield.

It was interesting to observe that the oxepinone (XVII) obtained from the action of mild alkali on either the ester (XII) or on 2-chloromethyl-2′-hydroxy-4′-methoxybenzophenone (XIV), was converted in 90% yield into 2-methoxyanthraquinone by refluxing N-sodium hydroxide during 100 hr. This was probably the result of the Wittig rearrangement of the corresponding carbanion (XXI) followed by aerial oxidation of the product (XXII). The process resembles the conversion of the azapinone (XXIII) to anthraquinone [15] and of diphenan (XXIV) to 9,10-dihydro-9-hydroxyphenanthrene [16] (XXV).



SCHEME 1 Pattern of fragmentation resulting from electron bombardment

*m** signifies a measured metastable ion; in each case where a molecular formula is given it has been determined by accurate mass measurement; the structural formulae are tentative and are postulated on the basis of the measurements and of proposals for analogous fragmentations (H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden Day, 1967, p. 1160 and 237).

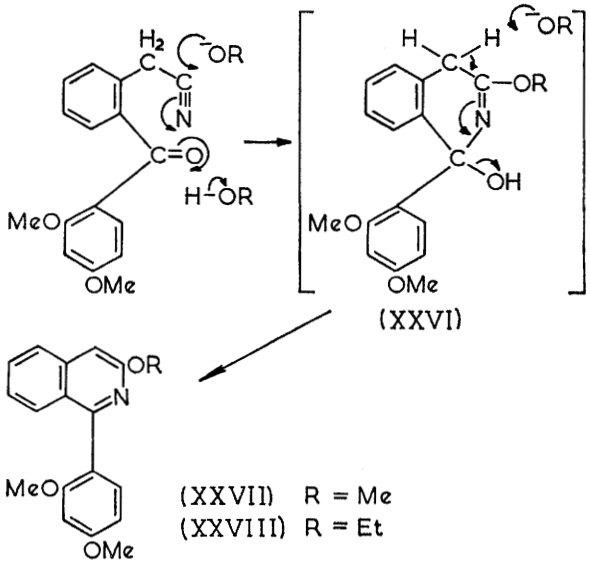
The action of sodium methoxide on the 2-cyanomethyl-2′,4′-dimethoxybenzophenone in methanol followed a very different course. The product $C_{15}H_8N(OMe)_3$, a base, m.p. 137°, was obtained in 86% yield. The product from a similar reaction in ethanol had the formula $C_{15}H_8N(OMe)_2(OEt)$. Structures have been assigned to these compounds largely by means of spectroscopic evidence. The ^1H n.m.r. spectra were particularly informative. The aromatic region, τ 2·2—3·6, included signals which integrated for eight protons, one of which (τ 3·05, singlet) must be associated with a new ring

[14] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Amer. Chem. Soc.*, 956, **78**, 1497.

[15] G. Wittig, G. Closs, and F. Mindermann, *Annalen*, 1955, **594**, 89.

[16] A. J. Weinheimer, S. W. Kantor, and C. R. Hauser, *J. Org. Chem.*, 1953, **18**, 801.

system; the original benzophenone included seven protons, all of which gave rise to multiplets in the ^{1}H n.m.r. spectrum. A comparison with published evidence of ^{1}H n.m.r.,[17] i.r.,[18] and u.v. spectra [19,20] indicated that the products were either 1,3-disubstituted isoquinolines or 2,4-disubstituted quinoline derivatives. In the latter case, however, a proton at position-8 would give a signal, a multiplet, at a lower field than any of the observed



SCHEME 2

resonances.[21] Reference to the structure of the starting material, indicated that the products of the reactions in methanol and ethanol were the 3-alkoxy-1-phenylisoquinolines (XXVII) and (XXVIII) respectively.

U.v. absorption spectra of isoquinolines

Compound	Solution	$\lambda_{max.}$	log $\varepsilon_{max.}$	Ref
Isoquinoline	Water, pH 9·2	216, 267, 319	4·81, 3·57, 3·47	19
Isoquinoline	Water, pH 2·0	227, 266, 332	4·66, 3·30, 3·63	19
3-Methoxyisoquinoline	Ethanol	224, 265, 337	4·91, 3·67, 3·68	20
3-Methoxy-1-methylisoquinoline	Ethanol	226, 274, 338	4·72, 3·62, 3·58	20
(XXVII)	Ethanol	221, 279, 343	4·53, 3·73, 3·84	
(XXVII)	Ethanol–HCl	229, 268, 383	3·84, 3·89	
(XXVIII)	Ethanol	226, 282, 348	4·60, 3·76, 3·85	
(XXVIII)	Ethanol–HCl	230, 268, 383	3·89, 3·97	

The u.v., ^{1}H n.m.r. and the mass spectra of the 3-methoxyisoquinoline and 1-methyl-3-ethoxyisoquinoline showed close similarities to the two products now formulated as (XXVII) and (XXVIII). In the case of the u.v. spectra (see Table) the differences were in accord with the rules formulated by Tombacz.[22]

We attribute the formation of these 3-alkoxyisoquinolines to a process (Scheme 2) in which the alkoxide ion reacts initially with the nitrile group to form the intermediate (XXVI), rather than with the methylene group of the benzylnitrile to give the carbanion (XVIII).

This investigation has indicated that it is possible to convert a 2-substituted-2′-alkoxy (or hydroxy)-benzophenone, through intramolecular nucleophilic displacement of the 2′-substituent by the 2-carbanion, to give a hydroxyanthracene derivative which could then be converted to the corresponding anthraquinone, by oxidation under mild conditions. However, there is no evidence, as yet, to establish that such a reaction pathway occurs *in vivo*.

EXPERIMENTAL

Physical data for compounds were obtained as described in Part XIX.[1] Accurate mass-measurements were obtained relative to fragment ions from heptacosafluoro-tri-*N*-butylamine at a resolving power of 15,000. In the mass-spectra, intensities of ions above 10% are shown. In addition, ions of lesser abundance are included if they are diagnostic. T.l.c. was carried out on Kieselgel (Merck). The solvent systems employed were: *A*, benzene–ether (5 : 1, v/v); *B*, chloroform–ethyl acetate (1 : 1, v/v); *C*, benzene–acetic acid–water (20 : 10 : 4, v/v) upper phase. Chromoplates were routinely examined under u.v. light and suspected phenolic compounds were sprayed with a freshly prepared solution of a stabilised diazonium salt of 4,4′-diamino-3,3-dimethoxybiphenyl (0·05 g.) in methanol–water (1 : 1, v/v; 40 ml.), followed by 50% methanolic ammonium hydroxide (*d* 0·88) to promote the coupling reactions. Alternatively the chromoplates were sprayed with iodine in chloroform solution. Silica gel (200—300 mesh) was used for column chromatography. Light petroleum refers to a fraction boiling point 60—80°. Organic solutions were dried over anhydrous magnesium sulphate and evaporated under reduced pressure.

Reduction of 2-Carboxy-2′,4′-dimethoxybenzophenone (VIII) *with Diborane*.[12]—Sodium borohydride (0·10 g., 2·5 mmole) in carefully dried diglyme [23] (12·5 ml.) was added dropwise during 90 min. to twice-distilled boron trifluoride–ether (0·6 ml., 4·5 mmole) in dry diglyme (3 ml.) contained in a gas generator constructed from a three-necked flask (25 ml.) fitted with a pressure-equalised dropping funnel. By using a slow stream of dry nitrogen the diborane gas produced was passed into a solution of the benzophenone [24] (VIII) (0·70 g., 2·5 mmole) in dry tetrahydrofuran [25] (10 ml.) which had been cooled to −5°. A slow stream of nitrogen was bubbled through the yellow-green solution for a further 2·5 hr. The precipitated boron complex was hydrolysed by addition of methanol–concentrated hydro-

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[18] Y. Ban, O. Yonemitsu, and M. Terashima, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 194.
[19] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 1956, 4191.
[20] D. A. Evans, G. F. Smith, and M. A. Wahid, *J. Chem. Soc.* (*B*), 1967, 590.
[21] M. H. Palmer, ' Heterocyclic Compounds,' Arnold, London, 1967, p. 106; C. W. Haigh, M. H. Palmer, and B. Semple, *J. Chem. Soc.*, 1965, 6004.
[22] E. Tombacz, *Magyar Kém. Folyóirat*, 1950, **56**, 175.
[23] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.
[24] W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1908, 489.
[25] *Org. Synth.*, 1966, **46**, 105.

chloric acid (5 : 1, v/v; 10 ml.) to yield a colourless solution. After evaporation of the solution, the residue in methylene chloride (50 ml.) was extracted with N-sodium hydroxide. The organic phase yielded a white solid (600 mg.) which crystallised from ether–light petroleum to give 3-(2,4-*dimethoxyphenyl*)*phthalide* (550 mg., 83%), m.p. 108° (Found: C, 70·7; H, 5·15. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), *M* (mass spectrometry) 270, $\lambda_{max.}$ (EtOH) 215, 233, 278, and 283 nm. (log ε 4·14, 4·23, 3·64, 3·64), $\nu_{max.}$ 2940, 2840 (OCH_3), 1770 (phthalide CO), 1615 and 1590 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 1·83—2·00 [1H, m, Ar*H* at C(7)], 2·20—2·40 (3H, m, 3Ar*H*), 2·94 [1H, d, *J* = 9Hz, Ar*H* at C(6′)], 3·11 [1H, s, phthalide *H* at C(3)], 3·30—3·60 [2H, m, 2Ar*H* at C(3′) and C(5′)], 6·08 (3H, s, $ArOCH_3$), and 6·13 (3H, s, $ArOCH_3$).

1-(2-*Hydroxymethylphenyl*)-1-(2,4-*dimethoxyphenyl*)*methanol* (X).—A solution of 2-carboxy-2′,4′-dimethoxybenzophenone [24] (34·5 g., 0·121 mole) in tetrahydrofuran (450 ml. from a freshly opened bottle) was added dropwise with stirring to a suspension of lithium aluminium hydride (14 g., 0·368 mole) in tetrahydrofuran (400 ml. as above), during 30 min. After a further 16 hr. at 20°, the stirred solution was carefully treated with water (75 ml.). The lithium aluminate formed, was coagulated to a brown mass by the addition of anhydrous magnesium sulphate. The mixture was filtered and the filtrate was evaporated to give a brown oil, which on work up with ether yielded a white solid (24 g.), m.p. 84—89°. A further 4·5 g. of the solid was obtained by ether extraction of the solid initially filtered off. The compound recrystallised from ether–light petroleum to give 1-(2-*hydroxymethylphenyl*)-1-(2,4-*dimethoxyphenyl*)*methanol*, white needles, m.p. 85—90° (Found: C, 69·9; H, 6·4. $C_{16}H_{18}O_4$ requires C, 70·05; H, 6·6%), $\lambda_{max.}$ (EtOH) 215, 234, 273, 279, and 284 nm. (log ε 4·15, 3·98, 3·38, 3·47, 3·42),[26] $\nu_{max.}$ 3440 (OH), 3350 (OH), 2960 (CH_3), 2840 (OCH_3), 1614 and 1590 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 2·65—3·05 (5H, m, Ar*H*), 3·45—3·70 (2H, m, 2Ar*H*), 3·80 (1H, s, $Ar_2CH{\cdot}OH$), 5·40 (2H, s, $ArCH_2{\cdot}OH$), 6·22 (3H, s, $ArOCH_3$), 6·26 (3H, s, $ArOCH_3$), 6·3—6·8 [2H, broad hump, 2RO*H* (exchanged with D_2O)]. In the isolation of the diol (X) it was found essential to avoid the use of dilute acid to dissolve the precipitated hydroxides. Under acid conditions partial dehydration occurred to give 1-(2,4-dimethoxyphenyl)phthalan.

1-(2,4-*Dimethoxyphenyl*)*phthalan*.—The diol (X) (1 g., 3·65 mmole) in ether (100 ml.) was treated with toluene-*p*-sulphonic acid (250 mg., 1·3 mmole). After 2·5 hr. at 20°, the ethereal solution was washed with 5% sodium hydrogen carbonate solution and, on work up, yielded the product (950 mg.). Recrystallisation from pentane gave 1-(2,4-*dimethoxyphenyl*)*phthalan* (800 mg., 86%) as white needles, m.p. 63—64° (Found: C, 75·1; H, 6·3. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), *M* (mass spectrometry) 256, $\lambda_{max.}$ (EtOH) 215, 233, 267, 273, 279, and 285 nm. (log ε 4·11, 4·01, 3·34, 3·47, 3·46, 3·39), $\nu_{max.}$ 2940 (CH_3), 2860 (OCH_3), 1615 and 1590 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 2·75—3·01 (5H, m, 5Ar*H*), 3·40—3·75 [3H, m, 2Ar*H* at C(3′) and C(5′), 1 phthalan *H* at C(1)], 4·79 [2H, s, 2 phthalan *H* at C(3)], 6·17 (3H, s, $ArOCH_3$), and 6·25 (3H, s, $ArOCH_3$).

1,(2-*Benzoyloxymethylphenyl*)1-(2,4-*dimethoxyphenyl*)*methanol* (XI).—Benzoyl chloride (32 ml., 0·27 mole) was added dropwise during 2 hr. to a stirred solution of the diol (X) (67 g., 0·245 mole) in anhydrous pyridine (400 ml., freshly distilled over barium oxide) at −5°. The resulting suspension, containing a white solid, was kept at 0° for 16 hr. After addition of water and extraction with ether, the product was isolated as a gum which solidified on trituration with ether–light petroleum. The bulk of this precipitated solid (82·5 g.) was used directly for the synthesis of the benzophenone ester (XII). Purification of a sample for analysis was carried out by dissolving the solid in methanol (any precipitated diester was filtered off). Evaporation of the solvent gave a solid which recrystallised from ether–light petroleum to give 1-(2-*benzoyloxymethylphenyl*)-1-(2,4-*dimethoxyphenyl*)*methanol* as white needles, m.p. 100—101° (Found: C, 72·7; H, 5·5. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·9%), $\lambda_{max.}$ (EtOH) 215, 231, and 279 nm. (log ε 4·26, 4·31, 3·53), $\nu_{max.}$ 3480 (OH), 2940 (CH_3), 2840 (OCH_3), 1695 (chelated ester CO), 1615 and 1595 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 1·99—2·18 (2H, m, 2Ar*H*), 2·20—2·80 (7H, m, 7Ar*H*), 3·04 [1H, d, *J* = 9Hz, Ar*H* at C(6′)], 3·47—3·80 [3H, m, 2Ar*H* at C(3′) and C(5′) and $1Ar_2CH{\cdot}OH$], 4·65 (2H, s, $ArCH_2{\cdot}O{\cdot}CO{\cdot}Ar'$), 6·25 (6H, s, $2ArOCH_3$), and 7·08 [1H, d, *J* = 4Hz, (exchanged with D_2O), $Ar_2CH{\cdot}OH$].

2-*Benzoyloxymethyl*-2′,4′-*dimethoxybenzophenone* (XII).—Manganese dioxide (2 kg., B.D.H. precipitated grade) was added to a stirred solution of the crude mono-ester (XI) (82·0 g.) in ether (5 l.). The suspension was stirred at at 20° for 12 hr., and then filtered. The filtrate and ether washings on evaporation gave a solid, which on recrystallisation from ether–light petroleum yielded 2-*benzoyloxymethyl*-2′,4′-*dimethoxybenzophenone* (55 g., 60%) as white prisms, m.p. 91° (Found: C, 73·1; H, 5·1. $C_{23}H_{20}O_5$ requires C, 73·4; H, 5·4%), *M* (mass spectrometry) 376, $\lambda_{max.}$ (EtOH) 215, 231, 278, and 312 nm. (log ε 4·29, 4·35, 4·00, 3·88), $\nu_{max.}$ 2960 (CH_3), 2840 (OCH_3), 1720 (ester CO), 1646 (benzophenone CO) and 1595 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 1·95—2·15 (2H, m, 2Ar*H*), 2·40—2·80 (8H m, 8Ar*H*), 3·45—3·70 [2H, m, 2Ar*H* at C(3′) and C(5′)], 4·45 (2H, s, $ArCH_2{\cdot}O{\cdot}CO{\cdot}Ar'$), 6·18 (3H, s, $ArOCH_3$), and 6·48 (3H, s, $ArOCH_3$).

The benzophenone (XII) (376 mg., 1·0 mmole) was hydrolysed by powdered sodium hydroxide (300 mg., 7·5 mmole) in refluxing absolute methanol (60 ml.) for 30 min. The reaction mixture was evaporated to dryness and 5% sodium hydrogen carbonate solution (50 ml.) was added to the residue to give a white suspension which was extracted with ether. Isolation of the product from the ether gave 2-*hydroxymethyl*-2′,4′-*dimethoxybenzophenone* (270 mg., 99%) as a gum (Found: C, 70·4; H, 6·2. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%), *M* (mass spectrometry) 272, $\lambda_{max.}$ (EtOH) 213, 235, 278, and 309 nm. (log ε 4·20, 4·04, 3·91, 3·83), $\nu_{max.}$ (thin film) 3450 (OH), 2940 (CH_3), 2840 (OCH_3), 1640 (benzophenone CO), 1600 and 1580 $cm.^{-1}$ (phenyl), τ ($CDCl_3$) 2·47—2·80 (5H, m, 5Ar*H*), 3·40—3·60 [2H, m, 2Ar*H* at C(3′) and C(5′)], 5·38 (2H, s, $ArCH_2OH$), 6·18 (3H, s, $ArOCH_3$), 6·39 (3H, s, $ArOCH_3$), and 6·70br [1H, s (exchanged with D_2O), $ArCH_2{\cdot}OH$]. The alcohol was found to be unstable in acid solutionn. On treatment with glacial acetic acid the alcohol gave 1-*hydroxy*-1-(2,4-*dimethoxyphenyl*)*phthalan* in good yield as a yellow amorphous solid, m.p. 270—280° (decomp.). A satisfactory analysis could not be obtained for the required formula $C_{16}H_{16}O_4$, but a low resolution mass spectrum gave *M* 272, with a base peak at *m/e* 254 (*M* − 18) as would be expected of a tertiary alcohol, $\nu_{max.}$ 3450 (OH), 2940 (CH_3), 2840 (OCH_3), 1615 and 1585 $cm.^{-1}$ (phenyl).

[26] W. A. Bonner, *J. Amer. Chem. Soc.*, 1963, **85**, 439.

The reaction of 2-hydroxymethyl-2′,4′-dimethoxybenzophenone with thionyl chloride in pyridine gave the chloromethylbenzophenone (XV) in low yield together with a mixture of other products, while reaction with phosphorus tribromide in pyridine gave a product whose spectral data closely resembled (XV), but was not completely characterised.

2-*Chloromethyl*-2′-*hydroxy*-4′-*methoxybenzophenone* (XIV).—Boron trichloride (25 g., 0·214 mole) in anhydrous methylene chloride (250 ml.) at 0°, was added to a solution of the ester-benzophenone (XII) (25 g., 0·066 mol.) in anhydrous methylene chloride (250 ml.) at 0°, during 2—3 min. The dark red complex obtained, was kept at 20° for 16 hr., when a few yellow crystals separated. The reaction mixture was carefully added in small portions to a vigorously agitated solution of sodium acetate (2 l.). Chloroform (1 l.) was added and the two layers were equilibrated in a separating funnel. The organic phase, on work up, yielded the product as a gum which was chromatographed on a silica gel column (100 × 5 cm.) involving elution with ether–light petroleum (20 : 80, v/v). Fractions from the column, on evaporation, gave a solid (15·5 g.) which on recrystallisation from pentane gave 2-*chloromethyl*-2′-*hydroxy*-4′-*methoxybenzophenone* as prisms, m.p. 54—56° (Found: C, 65·1; H, 4·5; Cl, 12·4. $C_{15}H_{13}ClO_3$ requires C, 65·1; H, 4·7; Cl, 12·8%), *M* (mass spectrometry) 276, $\lambda_{max.}$ (cyclohexane) 224, 240, 287, and 328 nm. (log ε 4·04, 3·95, 4·18, 3·93), $\nu_{max.}$ 2940 (CH_3), 2840 (OCH_3), 1638 (chelated benzophenone CO), 1610, 1600, and 1580 cm.$^{-1}$ (phenyl), τ ($CDCl_3$) −2·78 [1H, broad s, chelated ArO*H* (exchanged with D_2O)], 2·40—2·82 (5H, m, 5Ar*H*), 3·45—3·75 [2H, m, 2Ar*H* at C(3′) and C(5′)], 5·32 (2H, s, ArCH_2·Cl), 6·15 (3H, s, ArOCH_3).

3-*Methoxy*-6,11-*dihydrodibenzo*[*b*,*e*]*oxepin*-11-*one* (XVII).—The phenolic chloride (XIV) (550 mg., 2·0 mmole) in methanol (30 ml.) was treated with powdered sodium hydroxide (120 mg., 3·0 mmole). After 5 min., a white solid separated out of the bright yellow solution. The solid, m.p. 116° (190 mg.) was collected, and on evaporation of the methanol filtrate, followed by trituration of the residue with water, a further quantity (270 mg.) of the same product was obtained. The total product was recrystallised from ether–light petroleum to give 3-*methoxy*-6,11-*dihydrodibenzo*[*b*,*e*]*oxepin*-11-*one* (420 mg., 85%) as needles, m.p. 116° (Found: C, 74·95; H, 5·0. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%), *M* (mass spectrometry) 240, $\lambda_{max.}$ (EtOH) 213, 249, 292, and 321 nm. (log ε 4·24, 3·91, 4·07, 3·99), $\nu_{max.}$ 2950 (CH_3), 2840 (OCH_3), 1642 (conjugated CO), 1618 and 1585 cm.$^{-1}$ (phenyl), τ ($CDCl_3$) 1·76 [1H, d, J = 9Hz, Ar*H* at C(1)], 1·96—2·13 [1H, m, Ar*H* at C(10)], 2·40—2·75 (3H, m, 3Ar*H*), 3·31 [1H, q, Ar*H* at C(2)], 3·51 [1H, d, J = 2Hz, Ar*H* at C(4)], 4·83 (2H, s, ArCH_2·OAr′), and 6·19 (3H, s, ArOCH_3).

Treatment of the phenolic chloride (XIV) with either sodium cyanide and sodium iodide in refluxing acetone, or with sodium cyanide in dimethyl sulphoxide at room temperature, also gave the oxepinone (XVII) as the major product.

The oxepinone (XVII) was also obtained from 2-hydroxymethyl-2′,4′-dimethoxybenzophenone (prepared *in situ*) on treatment with sodium hydroxide. The ester–benzophenone (XII) (100 mg.) and powdered sodium hydroxide (400 mg.) in anhydrous methanol (15 ml.) were heated under reflux for 100 hr. Evaporation of the solvent, followed by addition of water (25 ml.), and extraction with ether gave a solid (55 mg.). Recrystallisation from methanol or ether–light petroleum gave 2-methoxyanthraquinone (XX) (3 mg., 5%), m.p. 197° undepressed on mixing with an authentic sample.* Evaporation of the mother liquors from the above crystallisations gave a solid (50 mg.) which on recrystallisation from ether–light petroleum gave the oxepinone (XVII), (40 mg., 63%), m.p. and mixed m.p. 115°.

2-*Chloromethyl*-2′,4′-*dimethoxybenzophenone* (XV).—The phenolic chloride (XIV) (50 mg.) and silver oxide (50 mg.) in methyl iodide (1 ml.) were kept at 0° for 12 days. Filtration of the reaction mixture, followed by evaporation of the filtrate yielded the product (48 mg.) as a yellow gum which rapidly darkened at room temperature go give a green-black gum. A freshly prepared sample of the product was chromatographed on a silica-gel column involving elution with ether–light petroleum (7 : 93, v/v). The major product, a colourless gum, appeared to be extremely pure (t.l.c. System A), and was found to be stable, only if kept as an ethereal solution over anhydrous potassium carbonate. The product was identified, using freshly prepared samples, as 2-*chloromethyl*-2′,4′-*dimethoxybenzophenone* (Found: *M* (mass spectrometry) molecular ion, 290·0698 ± 15. $C_{16}H_{15}O_3{}^{35}Cl$ requires 290·070965. Found *m*/*e* (base peak): 254·0942 ± 13. $C_{16}H_{14}O_3$ requires 254·094288), $\lambda_{max.}$ (EtOH) 219, 236sh, 280, and 312 nm., $\nu_{max.}$ (thin film) 2950 (CH_3), 2840 (OCH_3), 1650 (benzophenone CO), 1605 and 1580 cm.$^{-1}$ (phenyl), τ($CDCl_3$) 2·36—2·76 (5H, m, 5Ar*H*), 3·37—3·58 [2H, m, 2Ar*H* at C(3′) and C(5′)], 5·20 (2H, s, ArCH_2·Cl), 6·20 (3H, s, ArOCH_3), and 6·40 (3H, s, ArO*H*$_3$).

2-*Cyanomethyl*-2′,4′-*dimethoxybenzophenone* (XVI).—Freshly prepared benzophenone (XV) (3·4 g.) in dimethyl sulphoxide (250 ml.) was treated with sodium cyanide (680 mg.) under nitrogen. The resulting orange-red solution was kept at room temperature for 3 hr., and was then added to water (1·5 l.). Ether extraction of the white suspension, yielded on isolation, a white solid (3·1 g.) which was recrystallised from ether–light petroleum to give 2-*cyanomethyl*-2′,4′-*dimethoxybenzophenone* (2·2 g., 69%), as needles, m.p. 77—78° (Found: C, 72·6; H, 5·4; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%), *M* (mass spectrometry) 281, $\lambda_{max.}$ (EtOH) 215, 241, 281, and 314 nm. (log ε, 4·15, 4·11, 3·95, 3·89), $\nu_{max.}$ 3000, 2990, 2950 (CH_3), 2850 (OCH_3), 2255 (weak and broad, C≡N), 1640 (benzophenone CO), 1610 and 1575 cm.$^{-1}$ (phenyl), τ ($CDCl_3$), 2·34—2·70 (5H, m, 5 Ar*H*), 3·34—3·50 [2H, m, 2Ar*H* at C(3′) and C(5′)], 5·95 (2H, s, Ar·CH_2·CN), 6·12 (3H, s, ArOCH_3), and 6·35 (3H, s, ArOCH_3).

9-*Cyano*-2-*methoxyanthracen*-10-*ol* (XIX).—Dry nitrogen was bubbled through a solution of the cyanide (XVI) (250 mg., 0·89 mmole) in dimethyl sulphoxide (25 ml.). Anhydrous sodium methoxide (125 mg., 2·3 mmole) was added to the solution and a dark red colour was formed immediately. The reaction mixture was heated whilst a continuous stream of nitrogen was bubbled through the solution. On reaching 100° (5 min.) the reaction mixture became very dark, but became lighter on heating to 140° (9 min.) signifying that the reaction was complete. The fluorescent yellow-red solution was cooled and acidified with N-hydrochloric acid to give a bright yellow solution which on addition to water (200 ml.) afforded a bright yellow precipitate. The suspension was extracted with ether,

* Obtained from Imperial Chemical Industries Limited, Dyestuffs Division.

washed with 0·5N-sodium hydroxide, and on acidification, the alkali-soluble component gave the product as a yellow precipitate. Further purification of the product by extraction with ether and washing with water, gave on work-up 9-*cyano*-2-*methoxyanthracen*-10-*ol* (210 mg., 95%) as yellow needles, m.p. 219—223°. The product sublimed at a block temperature of 125° and a pressure of 0·1 mm. of Hg (Found: C, 76·65; H, 4·3; N, 5·4, *M* (mass spectrometry) 249·0790 ± 12. $C_{16}H_{11}NO_2$ requires C, 77·1; H, 4.45; N, 5·6%, *M*, 249·078973), $\lambda_{max.}$ (EtOH) 263, 274sh, 284sh, 329, 344, 363, 399, 418, and 441 nm. (log ε 4·65, 4·52, 4·34, 3·16, 3·45, 3·61, 3·75, 3·81, 3·62), $\nu_{max.}$ 3350 (OH), 2210 (C≡N), 1630 (anthracene C=C) and 1565 cm.$^{-1}$ (phenyl), τ [$(CD_3)_2CO$] 1·30—2·85 (7H, m, 7Ar*H*), and 5·93 (3H, s, $ArOCH_3$). Significant peaks observed in the mass spectrum were as follows: *m/e* (*I*) 249 (100), 248 (5), 234 (1), 207 (4), 206 (23), 190 (3), 178 (4), 177 (12), 152 (2), 151 (6), and 150 (3) with metastable peaks at *m/e* $m(_2^2/_{m_1})$: 219·9 ($234^2/249$), 170·4 ($206^2/249$), 153·8 ($178^2/206$), 128·8 ($151^2/177$), 128·1 ($151^2/178$).

When sodium methoxide (200 mg.) was added to a solution of the cyanide (XVI) (100 mg.) in dimethyl sulphoxide (25 ml.) in the absence of nitrogen, the red solution initially formed, faded on exposure to the atmosphere for 1 hr. After acidification with N-hydrochloric acid, followed by extraction with chloroform, the dried chloroform extracts gave a gum (70 mg.) on evaporation. Crystallisation from ether–light petroleum or chloroform gave 2-carboxy-2′,4′-dimethoxybenzophenone (VIII) (40 mg., 39%), m.p. and mixed m.p. 165°.[24]

Oxidation of 9-*Cyano*-2-*methoxyanthracen*-10-*ol* (XIX).—The anthranol (XIX) (210 mg., 0·84 mmole) in 0·1N-sodium hydroxide (100 ml.) was treated with hydrogen peroxide (100 vol., 4 ml.). The dark yellow solution was left for 36 hr. at 20°. The precipitated yellow solid was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide. The product on recrystallisation from ethanol was obtained as yellow needles (195 mg., 97%), m.p. 197°, undepressed on admixture with authentic 2-methoxyanthraquinone.

Conversion of the Oxepinone (XVII) *into* 2-*Methoxyanthraquinone*.—The oxepinone (XVII) (80 mg.) and powdered sodium hydroxide (1·5 g.) in absolute methanol (50 ml.) were heated under reflux for 100 hr. Evaporation of the solvent, followed by trituration of the residue with water (50 ml.) gave a yellow suspension, which was extracted with chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to yield a solid (80 mg.) which on recrystallisation from ethanol gave 2-methoxyanthraquinone (35 mg., 45%) as yellow needles, m.p. and mixed m.p. 196°. Evaporation of the mother liquors gave the oxepinone starting material (40 mg.) as the only other component from the reaction mixture.

A similar result was also obtained when sodium hydroxide was replaced by sodium ethoxide in the above reaction.

3-*Methoxy*-1-(2,4-*dimethoxyphenyl*)*isoquinoline* (XXVII).—The cyanide (XVI) (200 mg., 0·712 mmole) and anhydrous sodium methoxide (100 mg., 1·85 mmole) were dissolved in absolute methanol (20 ml.). The almost colourless reaction mixture was either heated under reflux for 2 hr. or, alternatively, left at 20° for 2—3 days. The reaction mixture was then evaporated to dryness and water (25 ml.) was added to the residue to give a white suspension. The solid was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide. The product (210 mg.), was recrystallised from methanol to give 3-*methoxy*-1-(2,4-*dimethoxyphenyl*)*isoquinoline* (180 mg., 86%) as white needles, m.p. 137°. The compound sublimed at a block temperature of 120° and at a pressure of 0·1 mm. Hg [Found: C, 73·3; H, 6·0; N, 4·65, *M* (mass spectrometry) 295·1209 ± 14. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8; N, 4·7%, *M* 295·120835], $\lambda_{max.}$ (see Table), $\nu_{max.}$ 2960 (CH_3), 2850 (OCH_3), 1630 (isoquinoline –C=N–), 1615, 1595 and 1585 cm.$^{-1}$ (phenyl), τ ($CDCl_3$) 2·20—2·82 (5H, m, 5Ar*H*), 3·03 [1H, s, Ar*H* at C(4)], 3·25—3·45 [2H, m, 2Ar*H* at C(3′) and C(5′)], 6·00 (3H,s, $ArOCH_3$), 6·15 (3H, s, $ArOCH_3$), and 6·34 (3H, s, $ArOCH_3$). Significant peaks observed in the mass spectrum were as follows: *m/e* (*I*) 295 (100), 294 (42), 280 (19), 279 (10), 278 (24), 264 (11), 250 (6), 249 (5), 238 (8), 237 (7), 236 (6), 235 (6), 234 (5), 160 (7), 147·5 (8), with metastable peaks at *m/e* (m_2^2/m_1): 293 ($294^2/295$), 265·8 ($280^2/295$), 262·9 ($278^2/294$), 248·8 ($263^2/278$), 236·3 ($264^2/295$).

3-*Ethoxy*-1-(2,4-*dimethoxyphenyl*)*isoquinoline* (XXVIII).—The cyanide (XVI) (250 mg., 0·89 mmole) was treated with sodium ethoxide (150 mg., 2·2 mmole) in absolute ethanol (25 ml.) under identical conditions to those described in the previous experiment. The product (280 mg.) on recrystallisation from methanol gave 3-*ethoxy*-1-(2,4-*dimethoxyphenyl*)*isoquinoline* (240 mg., 87%), white needles, m.p. 117—118°. The compound sublimed at a block temperature of 110° at a pressure of 0·05 mm. Hg (Found: C, 73·6; H, 5·7; N, 4·7; *M* (mass spectrometry) 309·1363 ± 15. $C_{19}H_{19}NO_3$ requires C, 73·8; H, 6·2; N, 4·5%. *M*, 309·136485), $\lambda_{max.}$ (see Table), $\nu_{max.}$ 2970, 2940, 2840 (OCH_3), 1630 (isoquinoline C=N), 1612, 1595 and 1585 cm.$^{-1}$ (phenyl), τ ($CDCl_3$) 2·25—2·85 (5H, m, 5Ar*H*), 3·07 [1H, s, Ar*H* at C(4)], 3·29—3·46 [2H, m, 2Ar*H* at C(3′) and C(5′)], 5·64 (2H, q, $ArOCH_2{\cdot}CH_3$), 6·15 (3H, s, $ArOCH_3$), 6·35 (3H, s, $ArOCH_3$), 8·56 (3H, t, $ArOCH_2{\cdot}CH_3$). Significant peaks observed in the mass spectrum were as follows: *m/e* (*I*) 309 (100), 308 (19), 295 (20), 294 (94), 292 (5), 281 (14), 280 (15), 278 (10), 266 (7), 265 (14), 264 (10), 263 (5), 252 (6), 250 (10), 238 (29), 237 (18), 236 (7), 235 (8), 195 (10), 178 (10), 126·5 (10), with metastable peaks at *m/e* (m_2^2/m_1): 307·0 ($308^2/309$), 279·7 ($294^2/309$), 276·8 ($292^2/308$), 264, 255·5 ($281^2/309$), 253·7 ($280^2/309$).

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