QUARTERLY REVIEWS

OXIDATIVE COUPLING OF PHENOLIC COMPOUNDS

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Introduction

It has long been recognised[1] that a considerable diversity of structural types can be derived from the oxidation of phenols with such reagents as ferric chloride and potassium ferricyanide. In more recent years mechanistic organic chemistry has lent such rigour to the interpretation of biosynthetic processes that the oxidative utilisation of phenolic substrates in biogenetic pathways, inferred earlier by inspection of the formulae of natural products[2–6] now seems to rest on a secure theoretical basis.[7,8] We shall term this interpretative mechanistic approach Biogenetic Analysis, and conveniently include in its operation those feeding experiments with labelled substrates which can be used to evaluate such an analysis.

At the same time, intensification of interest in molecular biochemistry has directed the organic chemist towards the synthesis of natural products by procedures which simulate certain steps of a proposed biosynthetic pathway. This approach has attracted attention for many years but has only recently met with sufficient success to be classified as Biogenetic-type Synthesis.[9] Recent progress in the application of phenol oxidation to synthetic chemistry has been due rather to this fresh analytical approach than to the discovery of new reagents and reactions.

In the sequel we shall review recent advances in both analytical and synthetic aspects of the chemistry of those natural products whose formation is believed to be mediated by the oxidative coupling of both like and unlike free radical species.

[1] (*a*) R. Pummerer and E. Frankfurter, *Ber.*, 1914, **47**, 1472; (*b*) R. Pummerer, *ibid.*, 1919, **52**, 1404.
[2] R. Pummerer, H. Puttfarcken, and P. Schopflocher, *Ber.*, 1925, **58**, 1811.
[3] H. Erdtman, *Biochem. Z.*, 1933, **258**, 177.
[4] C. Schopf and K. Thierfelder, *Annalen*, 1932, **497**, 22.
[5] J. M. Gulland and R. Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, **69**, 79; R. Robinson and S. Sugasawa, *J.*, 1931, 3163; 1932, 789; 1933, 280.
[6] R. Robinson, "The Structural Relationships of Natural Products", Clarendon Press, Oxford, 1955.
[7] D. H. R. Barton and T. Cohen, "Festschrift A. Stoll", Birkhauser, Basle, 1957, p. 117.
[8] H. Erdtman and C. A. Wachtmeister, ref. 7, p. 144.
[9] E. E. van Tamelen, *Fortschr. Chem. Org. Naturstoffe*, 1961, **19**, 242.

The Nature of Oxidative Coupling

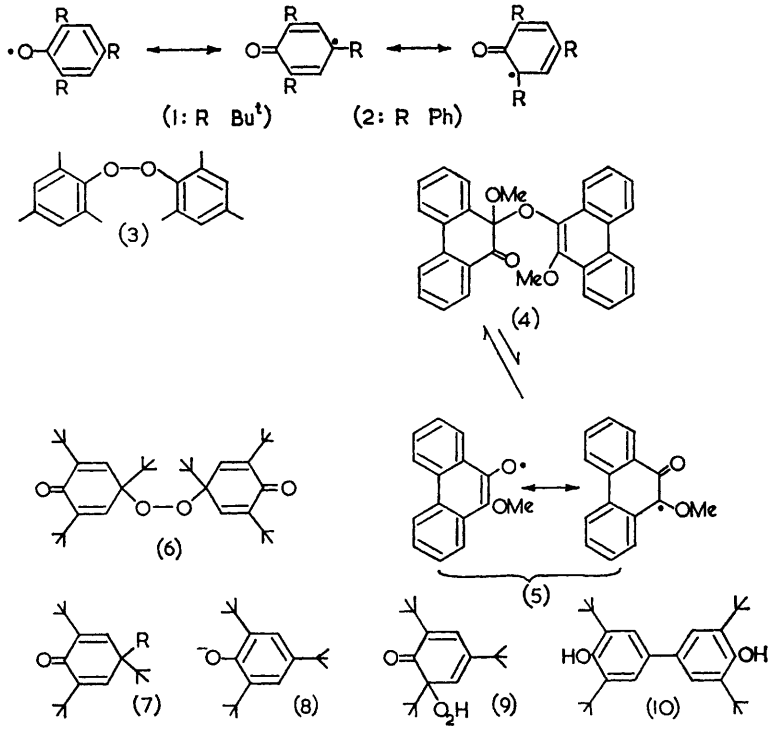
Mechanism.—*Monohydric phenols.* The production of stable phenol radicals (as 1) becomes possible where 2,4,6-trisubstitution prevents further reaction by coupling[10] and where the absence of α-C*H* in the substituents prohibits formation of a methylenequinone.[7,11,12] Many of these radicals are highly coloured both as solids and in solution (*e.g.*, 1).[13] Others (as 2) exist in the crystalline state as colourless dimers.[12,14] The latter were formerly thought[8] to be phenolic peroxides (3) corresponding to O–O coupling. They are now known to be dimeric quinol ethers. Thus "Goldschmidt's oxygen radical"[15] exists as the ether (4)[16] and has been found to dissociate in solution to the yellow-green radical (5) to the extent of only 0·1%. With the removal of this and other[17] alleged examples of O–O bond formation in radical coupling reactions it is now only necessary to consider the making of C–C and C–X bonds in these processes. The stable free radical (1) reacts with oxygen to form a peroxide (6) and with bromine and NO_2 to give (7, R = Br, NO_2).[7,10–13] When the phenoxide anion (8) is oxidized directly, however, the isomeric hydroperoxides (7; R = OOH) and (9) are formed.[18,19] These are in equilibrium under the reaction conditions and moreover can be reduced to the original phenol. Removal of one of the substituents in (1) allows *para–para* C–C coupling to occur,[18,19] yielding (10).

Stable free radicals have been detected by magnetic susceptibility and electron spin resonance measurements.[12,20,21,22] Detailed studies by E. Müller and his colleagues on the analysis of the hyperfine splitting of the E.S.R. spectra of these radicals have shown that the free-electron density is greater at the *para-* than at the *ortho*-position. The *meta*-position also shows a small but non-zero density.

The action of hydroxyl radicals on 2,4,6-trisubstituted phenols affords quinols (Bamberger oxidation)[23] (7, R = OH). Similarly, lead tetra-acetate

[10] C. D. Cook and N. D. Gilmour, *J. Org. Chem.*, 1960, **25**, 1429 and earlier papers.
[11] C. D. Cook and B. Norcross, *J. Amer. Chem. Soc.*, 1956, **78**, 3797; R. H. Bauer and G. M. Coppinger, *Tetrahedron*, 1963, **19**, 1201.
[12] E. Müller, R. Mayer, and K. Ley, *Angew. Chem.*, 1958, **70**, 73; E. Müller, A. Schnick, R. Mayer, and K. Scheffler, *Ber.*, 1960, **93**, 2649; K. Dimroth, *Angew. Chem.*, 1960, **72**, 714 and refs. cited therein.
[13] C. D. Cook and N. C. Woodworth, *J. Amer. Chem. Soc.*, 1953, **75**, 6242; E. Müller and K. Ley, *Ber.*, 1954, **87**, 922.
[14] E. Müller, K. Ley, and G. Schlechter, *Ber.*, 1957, **90**, 2660.
[15] S. Goldschmidt, *Ber.*, 1922, **55**, 3197.
[16] E. Müller, K. Schun, and K. Scheffler, *Annalen*, 1959, **627**, 132.
[17] G. W. Kirby, *J.*, 1962, 34 and refs. cited therein.
[18] M. S. Kharasch and B. S. Yoshi, *J. Org. Chem.*, 1957, **22**, 1439; K. Ley, E. Müller, N. Mayer, and K. Scheffler, *Ber.*, 1958, **91**, 2670.
[19] K. Ley, *Angew. Chem.*, 1958, **20**, 74; H. S. Blanchard, *J. Org. Chem.*, 1960, **25**, 264.
[20] E. Müller *et al.*, *Annalen*, 1961, **645**, 1—100.
[21] E. Müller *et al.*, *Ber.*, 1958, **91**, 2682; *Annalen*, 1961, **645**, 66.
[22] K. Schafer, *Z. Electrochem.*, 1961, **65**, 439.
[23] H. Musso, *Angew Chem. Internat. Edn.*, 1963, **2**, 723.

gives the quinol acetate (7, R = OAc) (Wessely oxidation).[24] In both of these reactions a radical coupling mechanism between the mesomeric phenolic radical and a second less bulky radical addend (*e.g.*, OAc·, OH·) offers the only entirely satisfactory explanation for the orientation of the observed products. In some cases, it has been found that C–O coupling can take place between one molecule of a radical (1) and a similar but distinct phenol (11),[25] to give the dienone (12). Rigorous evidence for participation of radical coupling in the oxidation of phenols of lighter substitution pattern than the 2,4,6-trisubstituted series has been more difficult to obtain.



Recently, observations[26] of e.s.r. signals from ceric sulphate oxidation of simple phenols using a flow system allowed an estimate of the lifetime of the short-lived radical species.

[24] G. Billek, J. Swoboda, and F. Wessely, *Tetrahedron*, 1962, **18**, 909, and previous publications. For a review see J. D. Loudon, "Progress in Organic Chemistry," Vol. 5, ed. J. W. Cook and W. Carruthers, Butterworths, London, 1961, p. 46.

[25] H. J. Cahnmann and T. Matsuura, *J. Amer. Chem. Soc.*, 1960, **82**, 2055 and earlier papers.

[26] T. J. Stone and W. A. Waters, *J.*, 1964, 213; F. R. Hewgill, T. J. Stone, and W. A. Waters, *ibid.*, p. 408.

These experiments are in full accord with the view that the first step in the oxidation of a monohydride phenol, ArOH, by a one-electron transfer oxidant[7,27] is the generation of the phenoxyl radical. The subsequent fate of the radical depends on the substitution pattern, but if oxidative dimerisation of the molecule is assumed, three mechanisms have to be considered,[28] *viz.*, (i) homolytic coupling, (ii) radical insertion, and (iii) heterolytic coupling. These possibilities are illustrated for alkaline ferricyanide oxidation:[28]

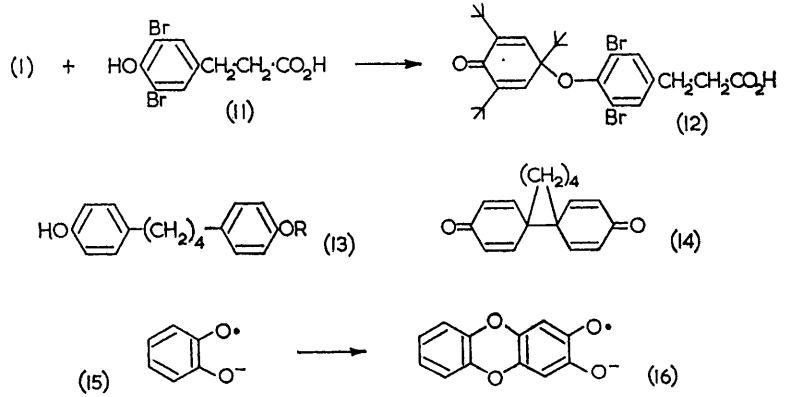
$$ArO^- + Fe(CN)_6^{3-} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ArO\cdot + Fe(CN)_6^{4-}$$

Homolytic coupling $2ArO\cdot \xrightarrow[k_3]{} (ArO)_2$ (i)

Radical insertion $ArO\cdot + ArO^- \xrightarrow[-e]{} (ArO)_2$ (ii)

Heterolytic coupling $ArO\cdot \xrightarrow{-e} (ArO)^+$

$$ArO^+ + ArO^- \rightarrow (ArO)_2 \quad \text{(iii)}$$



Although the second mechanism cannot be entirely disregarded, the intervention of radical insertion processes in such phenol oxidations seems unlikely. Thus, it has been found[29] that one-electron oxidation of *p*-cresol in the presence of a large excess of veratrole affords no evidence of cross-

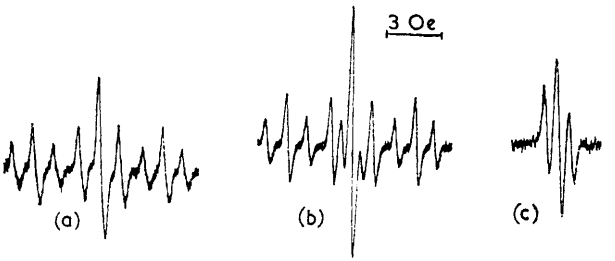
[27] W. A. Waters in "Progress in Organic Chemistry", vol. 5, ed. J. W. Cook and W. Carruthers, Butterworths, London, p. 35; *idem*. "The Chemistry of Free Radicals", Oxford University Press, 1946; B. C. Saunders, A. G. Holmes-Siedle, and B. P. Stark, "Peroxidase," Butterworths, London, 1964; O. Hayashi, "Oxygenases," Academic Press London, 1962.

[28] C. G. Haynes, A. H. Turner, and W. A. Waters, *J.*, 1956, 2823.

[29] D. H. R. Barton, "The Hugo Muller Lecture," *Proc. Chem. Soc.*, 1963, 293.

coupling. Also, whilst the phenol (13, R = H) can be oxidized to (14), the monomethyl ether (13, R = Me) only dimerises.[29]

Evidence for the intrusion of the cationic species ArO^+ in these oxidations is also lacking. We note that the inability of ArO^+ to capture any nucleophils other than phenol anions as required by the heterolytic mechanism (iii) offers some circumstantial evidence against this 2-electron oxidation mechanism. Recently, Waters and his co-workers[26] have elucidated the course of oxidation of catechol in alkaline solution. The e.s.r. spectrum of these solutions undergoes the changes shown in the Figure a→b→c. Thus, a triplet superimposed on the centre of the original spectrum



gradually replaces the triplet of triplets shown by *o*-benzosemiquinone (15). The coupling constant is identical with the triplet from semiquinone (16).

The predominance of experimentally observed *para*-coupling in competition with *ortho*-coupling is borne out by a recent determination of spin density for a number of short-lived phenoxy-radicals. These are summarised in Table 1.

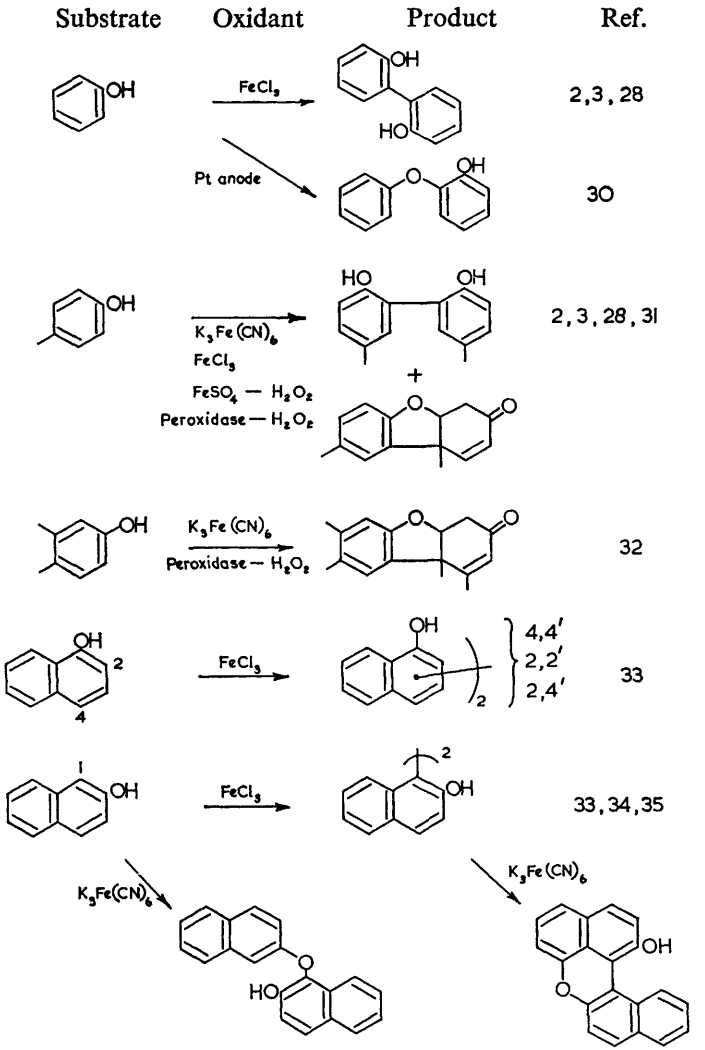
TABLE 1. *Spin densities for aryloxy-radicals.*

	Spin densities		
Radical form	ρ_o	ρ_m	ρ_p
Phenol	0·28	−0·075	0·42
p-Cresol	0·25	−0·06	0·44
2,6-Dimethylphenol	0·24	−0·07	0·40
2,4,6-Trimethylphenol	0·22	−0·06	0·44

Interpretation of coupling-constant data for variously substituted monohydric phenols is, at best, qualitative, and the conclusions which emerge are that (*a*) coupling constants of nuclear bound hydrogen atoms vary with electron spin densities at the corresponding carbon centres, (*b*) electron-repelling alkyl substituents lower the coupling constants in the *o*- and *p*-positions while electron attracting groups CO_2H, CHO, NO_2 enhance them, and (*c*) the major portion (75—80%) of the unpaired electron spin of the radicals of alkylated phenols resides in the carbon atoms of the ring not directly attached to the phenolic oxygen group.

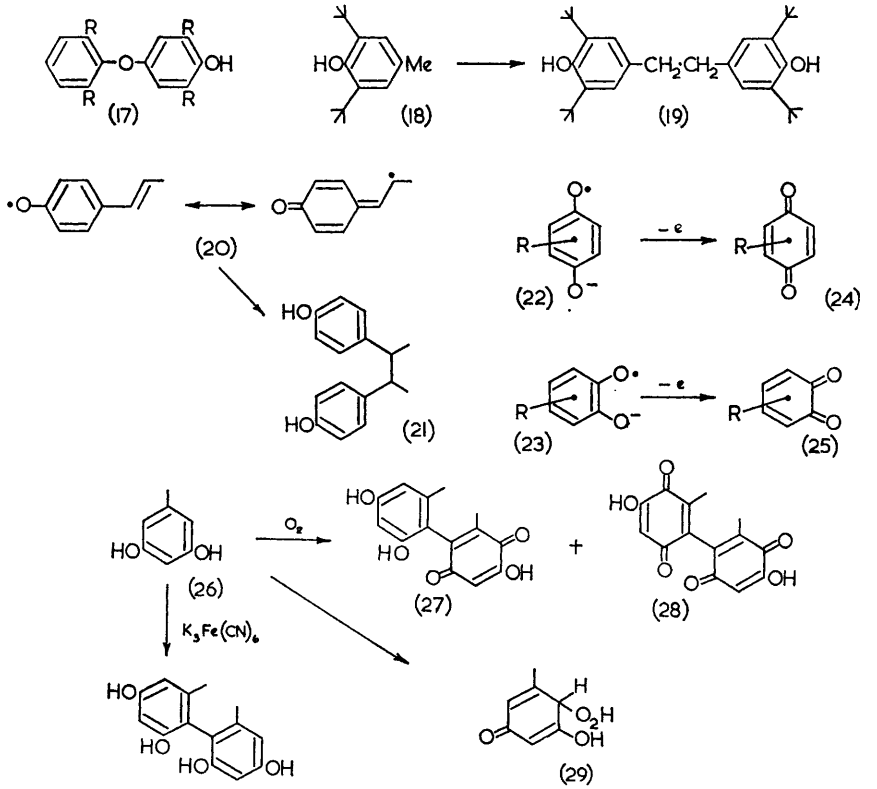
The influence of reaction conditions on the nature of the products of the oxidation of some monohydric phenols[30–35] is illustrated in Chart 1.

CHART 1.



[30] F. Fichter and F. Ackermann, *Helv. Chim. Acta*, 1919, **2**, 583 and later papers by Fichter and his colleagues.
[31] G. H. Nancollas, A. I. Scott, and D. W. Young, unpublished work.
[32] A. I. Scott, M. B. Meyers, A. J. Baker, and A. C. Day, unpublished work.
[33] J. D. Edwards and J. L. Cashaw, *J. Amer. Chem. Soc.*, 1954, **76**, 6141.
[34] R. Pummerer and E. Cherbuliez, *Ber.*, 1919, **52**, 1414; R. Pummerer and A. Rieche, *ibid.*, 1926, **59**, 2161.
[35] A. Rieche, B. Elschner, and M. Landbeck, *Angew. Chem.*, 1960, **72**, 385.

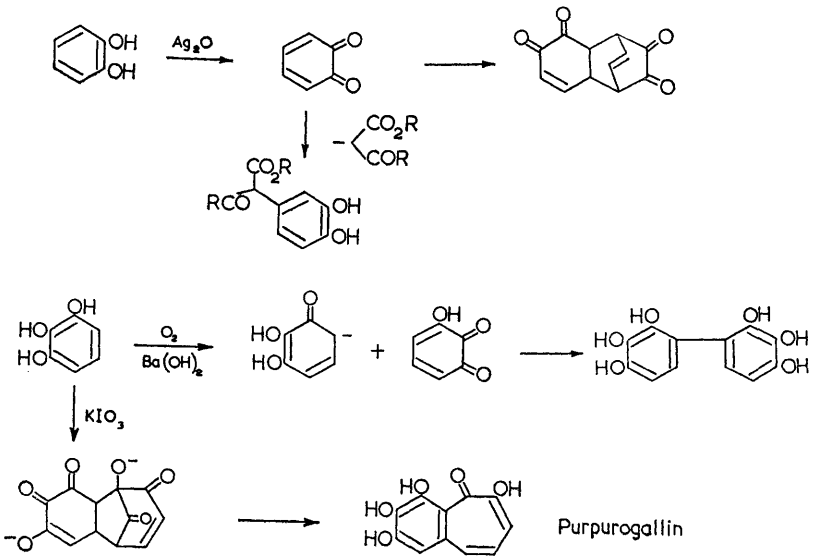
When alkyl groups are in the 2,6-positions *para–para* C–C (10) coupling is usually found with ferricyanide. With silver oxide C–O coupling predominates to give (17). Intramolecular ether formation is also favoured where a C–C bond is already present.[7,8,23,36] Coupling through benzyl-radicals in 2,4,6-trialkylphenols and dimerisation of quinonemethides are frequent when heavy substitution precludes facile C–C or C–O coupling[36–41] (18→19). Extension of the mesomeric radical over two further conjugated carbon atoms is exemplified by the *p*-hydroxystyrenes. The symmetrical coupling of form (20) is well known in the laboratory[42] and serves as a model for lignan biosynthesis (20→21).



[36] B. S. Thyagarajan, *Chem. Rev.*, 1958, **58**, 439.
[37] T. C. Bruice, *J. Org. Chem.*, 1958, **23**, 246.
[38] S. L. Cosgrove and W. A. Waters, *J.*, 1951, 388.
[39] C. D. Cook, N. Nahs, and H. R. Flanagan, *J. Amer. Chem. Soc.*, 1953, **75**, 6242; 1955, **77**, 1738.
[40] L. J. Fihar and S. Winstein, *Tetrahedron Letters*, 1960, **25**, 9.
[41] R. H. Bauer and G. M. Coppinger, *Tetrahedron*, 1963, **19**, 1201.
[42] H. Erdtman, *Biochem. Z.*, 1933, **258**, 172; B. Lindberg, *Svensk Papperstidn.*, 1953, **56**, 6.

Dihydric phenols. Removal of one electron from the anion of a catechol or quinol leads to the corresponding stable semiquinone radicals[43–47] (22) and (23). Removal of a second electron affords the quinones (24) and (25). Subsequent coupling of these molecules most probably[48] involves addition of a phenoxide anion (Chart 2).[48–51]

CHART 2. Anion addition to quinones (see also ref. 67 in main text).

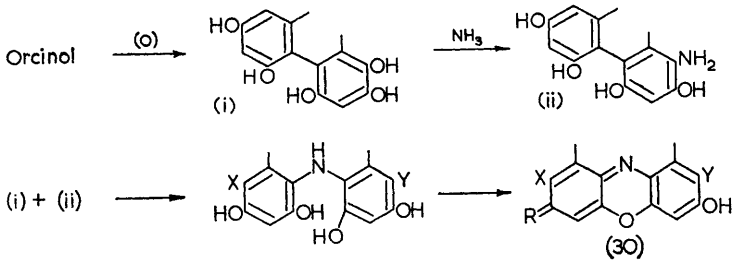


The oxidation of resorcinol derivatives is of importance in connection with the structures of orcein and litmus dyes.[52] Oxidation of orcinol (26) with oxygen gives a good yield of the quinones (27) and (28). It has been suggested[52] that the "extra" oxygen in (27) and (28) is introduced *via* hydroperoxide formation (29). The autoxidation of resorcinols in the presence of ammonia yields orcein and litmus exemplified by (30). Careful studies by Musso *et al.*[52] have led to an understanding of the processes

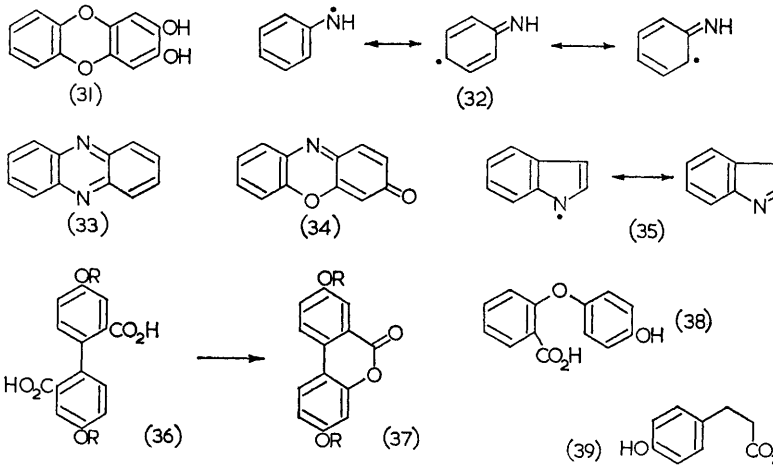
[43] L. Michaelis, M. P. Schubert, and S. Granick, *J. Amer. Chem. Soc.*, 1939, **61**, 1981.
[44] H. Diebler, M. Eigen, and P. Mathies, *Z. Electrochem.*, 1961, **65**, 634; M. Eigen and P. Mathies, *Ber.*, 1960, **94**, 3309.
[45] W. Flaig and J. C. Salfeld, *Naturwiss.*, 1960, **47**, 516.
[46] For a review of e.s.r. applications in this field see A. Carrington, *Quart. Rev.*, 1963, **17**, 67.
[47] K. Ley and E. Müller, *Angew. Chem.*, 1958, **70**, 469.
[48] L. Horner, K. H. Weber, and W. Durkheimer, *Ber.*, 1961, **94**, 2881 and other papers in this series.
[49] L. Horner and K. Sturn, *Annalen*, 1955, **597**, 1.
[50] B. Witkop, *J. Org. Chem.*, 1957, **22**, 1477.
[51] J. Harley-Mason and A. H. Laird, *J.*, 1958, 1218.
[52] Reviews: H. Beecken, U. Gizycki, E. M. Gottochaek, H. Kramer, D. Maassen, H. G. Mathies, H. Musso, C. Ralhjen, and U. I. Zahorsky, *Angew. Chem.*, 1961, **73**, 665; H. Musso, ref. 23.

summarised in Chart 3. The dyes consist of mixtures of types (30) (X = O, NH; Y = OH, NH_2).

CHART 3. Orcein and litmus.



Although the formation of (16) from catechol semiquinone was invoked[26] to explain formation of the ether (31), addition of the anion (15) to the *o*-quinone is an attractive alternative.

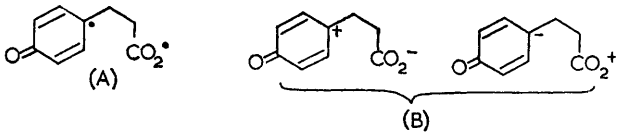


Amines. Aminophenols and amines couple *via* mesomeric radicals, *e.g.*, (32). Thus simple aromatic amines[53] and *o*-aminophenols[54–56] give rise to the dimeric phenazines (33) and phenoxazones (34) respectively.

Indoles may be oxidised *via* the β-radical (35) using ferric chloride.[57] The oxindoles which represent heterocyclic counterparts of phenols also undergo C–C coupling at the β-position.[58]

[53] L. R. Morgan and C. C. Aubert, *Proc. Chem. Soc.*, 1962, 73; L. Horner and J. Dehnert, *Ber.*, 1963, **96**, 786.
[54] H. Musso, *Ber.*, 1963, **96**, 1579.
[55] H. Nagasawa, *Biochim. Biophys. Acta*, 1958, **28**, 665.
[56] A. Butenandt, U. Schidet, E. Bickert, and R. J. T. Cromartie, *Annalen*, 1954, **590**, 75; A. Butenandt, "Festschrift A. Stoll", Birkhauser, Basle, 1957, p. 779.
[57] A. I. Scott, F. McCapra, and E. S. Hall, *J. Amer. Chem. Soc.*, 1964, **86**, 302.
[58] J. Harley-Mason and R. F. J. Ingleby, *J.*, 1958, 3639; J. B. Hendrickson, R. Goschke, and R. Rees, *Proc. Chem. Soc.*, 1962, 383; *Tetrahedron*, 1964, **20**, 565 and refs. cited therein.

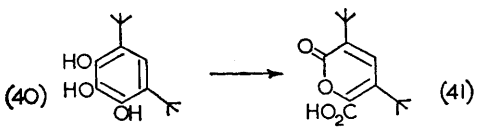
Carboxylic acids. Oxidative cyclisation of diphenic acids[59] (36)→(37), of diphenyl ether acids,[60,61] (as 38) and of phloretic acids[62] (39) can be interpreted as both radical coupling (*A*) or cationic (*B*) theories.



Quinol formation. The easy introduction of oxygen (as ·OR) has been developed[24,63] from the work of Bamberger, *e.g.*, (8)→(7) + (9). The intervention of hydroperoxides in biological systems is now being recognised[23,63] as a mechanistic possibility, although direct evidence is lacking.

Reagents.—Many successful coupling reactions illustrating all of the above modes of C–C, C–O, and C–N bond formation have been carried out in the laboratory. However, notwithstanding recent intensification of effort in this area, the selection of reagent and experimental conditions for a given substrate remains largely empirical. We may cite some of the broader generalisations which have emerged from recent work.

The most versatile reagents for oxidative coupling are alkaline potassium ferricyanide and ferric chloride.[7,8] The former is to be preferred where metal-complex formation with either starting material or product becomes a serious consideration. On the other hand, ring cleavage of sensitive polyphenols, *e.g.*, pyrogallols, under alkaline conditions can preclude successful use of the former reagent. Thus, 4,6-di-t-butylpyrogallol (40) is cleaved without loss of carbon to the pyrone acid[64] (41). This undesired reaction can be eliminated by using selective protecting groups[65] although



radical activity may be limited by such expedients. The ideal case is reached (see griseofulvin) where the (neutral) product is protected from further

[59] G. W. Kenner, M. A. Murray, and C. M. B. Tayler, *Tetrahedron*, 1957, **1**, 259; K. Chambers, G. W. Kenner, M. J. T. Robinson, and B. R. Webster, *Proc. Chem. Soc.*, 1960, 291.

[60] C. H. Hassall and J. R. Lewis, *J.*, 1961, 2312.

[61] J. R. Lewis, *Chem. and Ind.*, 1962, 159.

[62] (*a*) A. I. Scott, *Proc. Chem. Soc.*, 1962, 207; (*b*) A. I. Scott, F. McCapra, P. A. Dodson, and M. B. Meyers, *J. Amer. Chem. Soc.*, 1963, **85**, 3702; (*c*) J. S. Davies, C. H. Hassall, and J. A. Scholfield, *Chem. and Ind.*, 1963, 740.

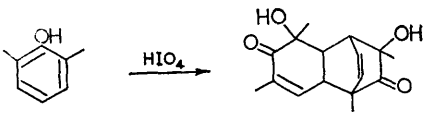
[63] B. Witkop, *J. Amer. Chem. Soc.*, 1957, **79**, 177.

[64] T. W. Campbell, *J. Amer. Chem. Soc.*, 1951, **73**, 4190.

[65] For a review see J. F. McCombie in "Advances in Organic Chemistry—Methods and Results," vol. III, ed. R. A. Raphael and B. Wynberg, Interscience, New York, 1962.

degradation by precipitation from alkaline ferricyanide solution. The use of ferric chloride solution has proved successful in the catechol and pyrogallol series.[66]

Oxidation of catechols, quinols and pyrogallols to the corresponding quinones is usually effected with silver oxide, ferricyanide, or tetrachloro-*o*-quinone.[7,8,23] Pyrogallol itself can be oxidised to the hexahydroxybiphenyl (Chart 2) by passage of air through its solution in barium hydroxide.[67] Substituted pyrogallols form purpurogallin derivatives[48,68,69] (Chart 2) with iodate or neutral ferricyanide. On the other hand, periodic acid frequently introduces hydroxyl groups, *i.e.*, Bamberger oxidation. The resultant quinol dimerise thus:[70]



Coupling of hydroxyl and phenol radical can be affected through the use of oxygen and copper(II) ion in the presence of morpholine.[71] The attack is *ortho* and takes place through a copper complex. A method of promise for enhancing such reactions has been described.[72]

Other oxidants which have been used in C–C, C–O, and C–N formation are maganese[73,74] and lead dioxides,[60,61,74] cerium(IV)[75,76] and vanadium(V)[75,76] salts, lead tetra-acetate,[7,8] and Fenton's reagent.[7,8] Examples of the use of these reagents are described later.

The stable free radicals (as 1) have also been used to abstract hydrogen atoms from phenols, thereby promoting radical coupling; however the reagent is frequently incorporated in the product.[77]

It appears that in spite of obvious advantages, electrolytic oxidation has not received detailed attention. The oxidation potential and conductance of the solvent system used are factors in the choice of experimental

[66] B. Franck, *Angew. Chem.*, 1963, **75**, 957; *Internat. Edn.*, 1964, **3**, 192.
[67] C. Harries, *Ber.*, 1902, **35**, 2054; H. Erdtman, *Proc. Roy. Soc.*, 1933, *A*, **143**, 196.
[68] J. C. Salfeld, *Angew. Chem.*, 1957, **69**, 723.
[69] L. Horner and W. Durkheimer, *Z. Naturforsch.*, 1959, **14b**, 744.
[70] E. Adler, I. Falkehrag, and B. Smith, *Acta Chem. Scand.*, 1962, **16**, 529 and refs. cited therein.
[71] W. Brackman and E. Havinga, *Rec. Trav. chim.*, 1955, **74**, 937.
[72] R. Resnik, T. Cohen, and Q. Fernando. *J. Amer. Chem. Soc.*, 1961, **83**, 3344.
[73] V. Juch, *Monatsh.*, 1905, **26**, 835.
[74] C. H. Hassall and A. I. Scott, in "Recent Developments in the Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon, Oxford, 1961, p. 119.
[75] J. S. Littler and W. A. Waters, *J.*, 1960, 2767 and earlier papers in this series.
[76] T. A. Davidson and A. I. Scott, unpublished work.
[77] T. Matsuura and H. J. Cahnmann, *J. Amer. Chem. Soc.*, 1960, **82**, 2050, 2055; T. Matsuura and A. Nishinaga, *J. Org. Chem.*, 1962, **27**, 3072; T. Matsuura, A. Nishinaga, and A. J. Cahnmann, *ibid.*, 1962, **27**, 3620.

conditions, but in spite of much early work by Fichter[78] and his colleagues, few recent examples of successful coupling reactions have been reported.[59,62b,78]

Rates of irreversible oxidation and relative oxidation potentials of several phenols toward one-electron oxidants have been studied.[79] The semi-qualitative method of Fieser[80] (critical potential method) gives a useful picture of the relative oxidisability of a given phenol. However, the organic chemist has until now simply used the many permutations of known reagents and conditions until a positive result has emerged.

Enzymic oxidative coupling. Several enzymes and cell-free extracts of higher plants have been found to catalyse the coupling of phenols and of amines. Most of these studies have been carried out with the system horseradish peroxidase–hydrogen peroxide, usually in phosphate buffer.[81] Table 2 summarises the results of some peroxidase oxidations[82–88] on various substrates. Of these, the most interesting from the standpoint of enzyme stereospecificity are perhaps 3, 4, 5, and 6 where centres of potential optical activity are generated.

By analogy with reductive experiments on "un-natural" substrates we should expect an optically active product in such cases. In none of these examples has any optical rotation been observed in the product. One explanation is that the coupling occurs outside the active site of the enzyme and that the specific catalytic activity of peroxidases and oxidases resides in their production of free radicals (*e.g.*,OH·) which in turn carry out the oxidative coupling. In this connection it is noteworthy that certain metabolites of lichens and moulds occur as (±)-compounds (*e.g.*, picrolichenic acid,[89] geodoxin[90]) suggesting non-stereospecific oxidative coupling in their biosynthesis. An experiment devised to examine possible racemisation during the enzymic formation of Pummerer's ketone in

(42) (43)

[78] F. Fichter and B. Muller, *Helv. Chim. Acta*, 1925, **8**, 290 and numerous earlier papers by Fichter in this series; see M. J. Allen, "Organic Electrode Processes," Chapman and Hall, London, 1958.

[79] See ref. 23, pp. 728—730.

[80] L. F. Fieser, *J. Amer. Chem. Soc.*, 1930, **52**, 4915, 5204.

[81] D. G. H. Daniels and B. C. Saunders, *J.*, 1951, 2112.

[82] E. Bourquelot and L. Marchadier, *Compt. rend.*, 1904, **138**, 1432.

[83] E. Willstatter and H. Heiss, *Annalen*, 1923, **433**, 17.

[84] W. W. Westerfield and C. Lowe, *J. Biol. Chem.*, 1942, **145**, 463.

[85] A. J. Baker, A. C. Day, M. B. Meyers, and A. I. Scott, unpublished result.

[86] B. R. Brown and S. M. Bocks, in "Enzyme Chemistry of Phenolic Compounds," ed. J. B. Pridham, Pergamon, Oxford, 1963.

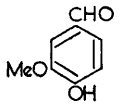
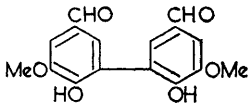
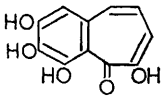
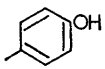
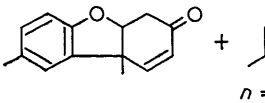
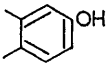
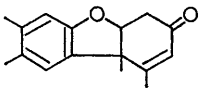
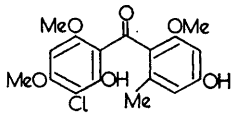
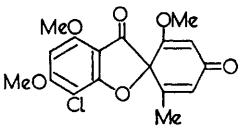
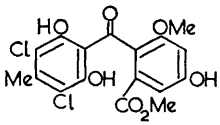
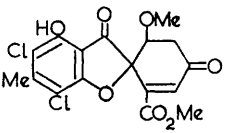
[87] T. A. Davidson, Ph.D. Thesis, Glasgow, 1961.

[88] H. Booth and B. C. Saunders, *J.*, 1940, 940.

[89] C. A. Wachtmeister and H. Erdtman, *Chem. and Ind.*, 1957, 1042; C. A. Wachtmeister, *Acta Chem. Scand.*, 1958, **12**, 147.

[90] C. H. Hassall and T. C. McMorris, *J.*, 1959, 2831.

TABLE 2. Peroxidase-catalysed oxidation of phenols with hydrogen peroxide.

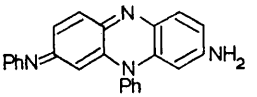
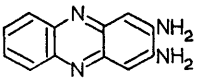
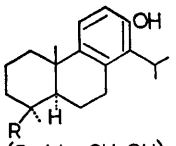
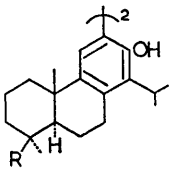
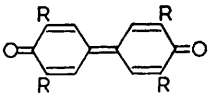
	Substrate	Product	Ref.
1.			82
2.			83
3.			3,84
4.			85
5.			85,86
6.			87
7.			88.

which 3,4-dimethylphenol was used as substrate, also resulted in an optically inactive homologue (42) of the neutral ketone, *via* a coupled intermediate (43) which, unlike that corresponding to Pummerer's ketone, still retained an asymmetric carbon atom.[84,85]

Recent studies on enzymes present in *Podocarpae* species reveal that many leaf extracts are capable of enzymic intermolecular coupling of monohydric phenols in the absence of hydrogen peroxide. Some of the substrates and extracts used are listed in Table 3.

The appearance of semiquinone and other free-radical species during enzymic oxidation with peroxidase has been examined by use of a flow

TABLE 3. Enzyme oxidation of amines and phenols.

Substrate	Product	Enzyme	Ref.
Aniline		Peroxidase	91
o-Phenylenediamine		Peroxidase	92
 (R=Me, CH_2OH)		*P. versicolor* *C. japonica*	93
		*P. versicolor* Mushroom oxidase	94

technique.[95] At the steady state obtained in this way the rule of the free-radical concentration [AH·] from a substrate [AH_2] is proportional to the square roots of the concentrations of both [AH_2] and the enzyme [E].

The semiquinone (22 and 23; R = H) from quinol and pyrogallol have been identified in this way.

Preliminary reports on the observation of free radicals in a natural environment have appeared.[95,96,97,98]

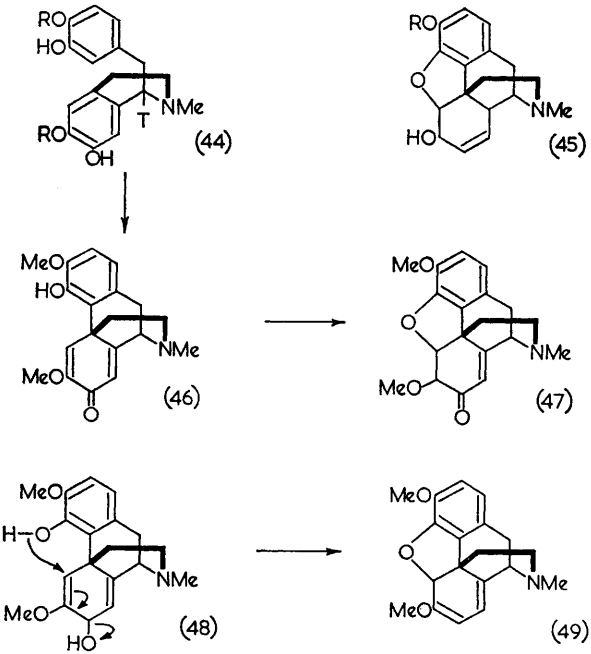
Biogenetic Analysis and Synthesis*

Under the heading of *analysis* we consider those compounds which are formally derived by oxidative coupling and whose biosyntheses have been studied using tracer or isolation techniques. The completion of the appropriate oxidation step either as part of a total or model *synthesis* in the

[91] P. J. G. Mann and B. C. Saunders, *Proc. Roy. Soc.*, 1935, *B*, **119**, 47.
[92] Chodat, Aberderhalden's "Handbuch", 1925, (4), **1**, 319.
[93] S. M. Bocks and R. C. Cambie, *Proc. Chem. Soc.*, 1963, 143; T. Takahashi, *Tetrahedron*, 1963, **19**, 1109.
[94] S. M. Bocks, B. R. Brown, and A. H. Todd, *Proc. Chem. Soc.*, 1962, 117.
[95] H. S. Mason and L. Piette in "Free Radicals in Biological Systems," ed. H. Blois, Academic Press, New York, 1962.
[96] F. Ehrenberg, *Acta Chem. Scand.*, 1960, **14**, 766 and other papers in this series.
[97] F. F. Nord and W. J. Schubert, in "Biogenesis of Natural Products," ed. P. Bernfeld, Macmillan, New York, 1963, p. 693.
[98] R. W. Rex, *Nature*, 1960, **188**, 1185.

laboratory has now become sufficiently frequent to regard oxidative coupling as a method of choice, for although yields are often very modest, the directness of the approach compensates for this in good measure.

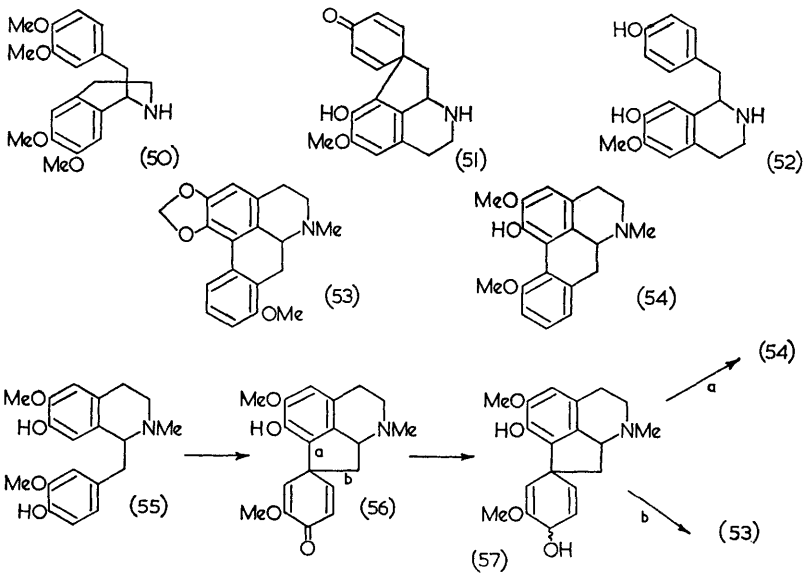
Alkaloids.—More than fifty years ago Gadamer[99,100] drew attention to the relationship between laudanosoline and glaucine. Similar ideas were promulgated by Pyman,[101] Robinson *et al.*,[5] and Schopf.[4,102] It was recognised by Barton and Cohen[7] that completely rigorous application of the principle of *ortho*- and *para*-C–C and C–O oxidative coupling accounts for the structural features found in many classes of alkaloid. Of almost 2000 known alkaloids more than 10% can be derived, in principle, by coupling of appropriate phenolic precursors.[66]



Morphine alkaloids (*a*). The relationship between the benzylisoquinolines (as 44) and morphine (45; R = H) was first suggested by Gulland and Robinson[5] and used to deduce the correct structure for the latter alkaloid and its relatives. Details of possible mechanisms for the coupling reaction were discussed by Barton and Cohen[7] and are illustrated by conversion of the diphenolic base (44; R = Me) into the dienone (46) followed by ether formation (47) and appropriate rearrangement of oxidation

[99] J. Gadamer, *Arch. Pharm.*, 1911, **249**, 680.
[100] J. Gadamer, *Arch. Pharm.*, 1911, **249**, 498.
[101] F. L. Pyman, *J.*, 1909, **95**, 1266.
[102] C. Schopf, *Naturwiss.*, 1952, **39**, 241.

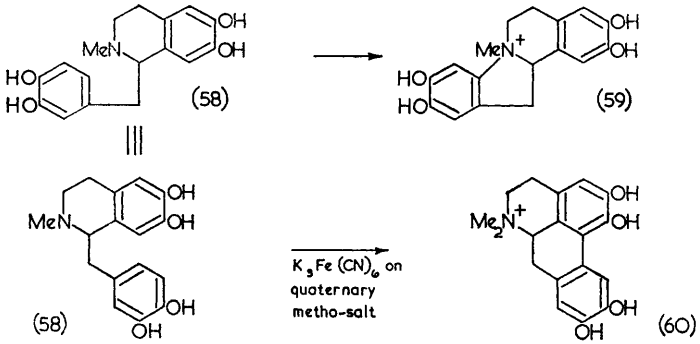
level *in vivo*. Modifications of the transformation of the dienone (46) into morphine involve reduction to the dienol (48) followed by dehydrative rearrangement.[103–106] In the realisation of the latter scheme *in vitro* the dienone (46) was found to exist in the "open" form and moreover could be converted under very mild laboratory conditions into thebaine (49) and thence to morphine.[104,107] Participation of oxidative coupling in the biosynthesis of these alkaloids has been demonstrated independently by Barton [104,107] and Battersby[103,108] and their co-workers. Thus the precursor (44; R = Me) labelled with ^{14}C and tritium is converted (0·14% incorporation) in *Papaver somniferum* into thebaine. The participation of oxidative coupling was inferred from experiments where norlaudanosoline (44; R = H) was incorporated more efficiently than tyrosine but *less* efficiently than the base (44; R = Me). However, labelled tetrahydropapaverine (50) was not incorporated. Later steps in the conversion of thebaine into morphine have been established. The recently revised



[103] A. R. Battersby, *Proc. Chem. Soc.*, 1963, 189 and refs. cited therein.
[104] D. H. R. Barton, *Proc. Chem. Soc.*, 1963, 293 and refs. cited therein.
[105] D. Ginsburg, "The Opium Alkaloids," Interscience Publishers, New York, 1962, p. 91.
[106] G. Stork, "The Alkaloids," ed. Manske and Holmes, Academic Press, New York, 1960, vol. VI, p. 233.
[107] D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 1963, 203.
[108] A. R. Battersby, R. Binks, D. M. Foulkes, R. J. Prancis, D. J. McCaldin, and H. Ramuz, *Proc. Chem. Soc.*, 1963, 203.

structures of crotonosine[109] (and that of pronuciferine)[110] constituted further (albeit indirect) evidence for coupling reactions in the biosynthesis of morphine alkaloids. This in crotonosine (51) the blocked dienone system indicates the oxidative coupling of precursor (52).*

Other variants of this theme which may arise by change in methylation pattern are stephanine[103,111] (53) and isothebaine[103,112] (54) to which oxidative coupling theory may be applied as in (55) and (56). Migration (*a*) of a bond in the dienol (57) leads directly to isothebaine whereas the alternative (*b*) migration affords a close relative of stephanine. The overriding influence of selective protection of phenolic function is nicely illustrated in this case as norlaudanosoline is formally convertible into both the isothebaine and morphine series. It seems probable that methylation precedes and controls the direction of oxidative coupling in the biosynthesis of these alkaloids.



(*b*). The labelled precursor (44; R = Me) of totally synthetic origin could be oxidized to the racemic dienone[107] (46) using manganese dioxide in 0·024% yield, as determined by radiochemical dilution. This constitutes a biogenetic-type synthesis of thebaine (49) and hence morphine (45). The importance of choosing not only the correct protection pattern for the phenolic groupings but also the proper state of the nitrogenous function is illustrated by the early synthesis of dehydrolaudanosoline[5,6] (59) by mild oxidation of laudanosoline (58). Quaternary laudanosoline can be oxidized to the aporphine series[66,113] (see p. 18).

When the methylation pattern is reversed as in (55), ferricyanide oxidation yields the dienone (56) (4%),[112] convertible into isothebaine (54) in

* In this and following sections (*a*) and (*b*) denote the analytical and synthetic descriptions respectively.

[109] L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *Proc. Chem. Soc.*, 1963, 280; L. J. Haynes and K. L. Stuart, *J.*, 1963, 1784, 1789.

[110] K. Bernauer, *Helv. Chim. Acta*, 1963, **46**, 1783.

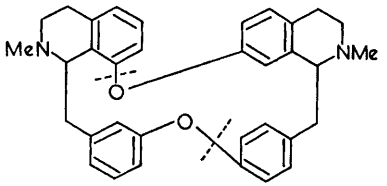
[111] M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *Chem. and Ind.*, 1964, 282.

[112] A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.

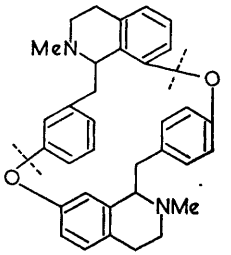
[113] B. Frank and G. Schlinghoff, *Annalen*, 1962, **659**, 123.

the first (and biogenetic) synthesis of this alkaloid. The stephanine series (53) may also be reached (in principle) by this method.

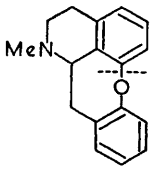
Aporphines and the dimeric disbenzylisoquinoline alkaloids (*a*). The relationship between laudanosoline (58) and glaucine (60) was noted at the



(61) Berbamine type



(62) Tubocurarine type



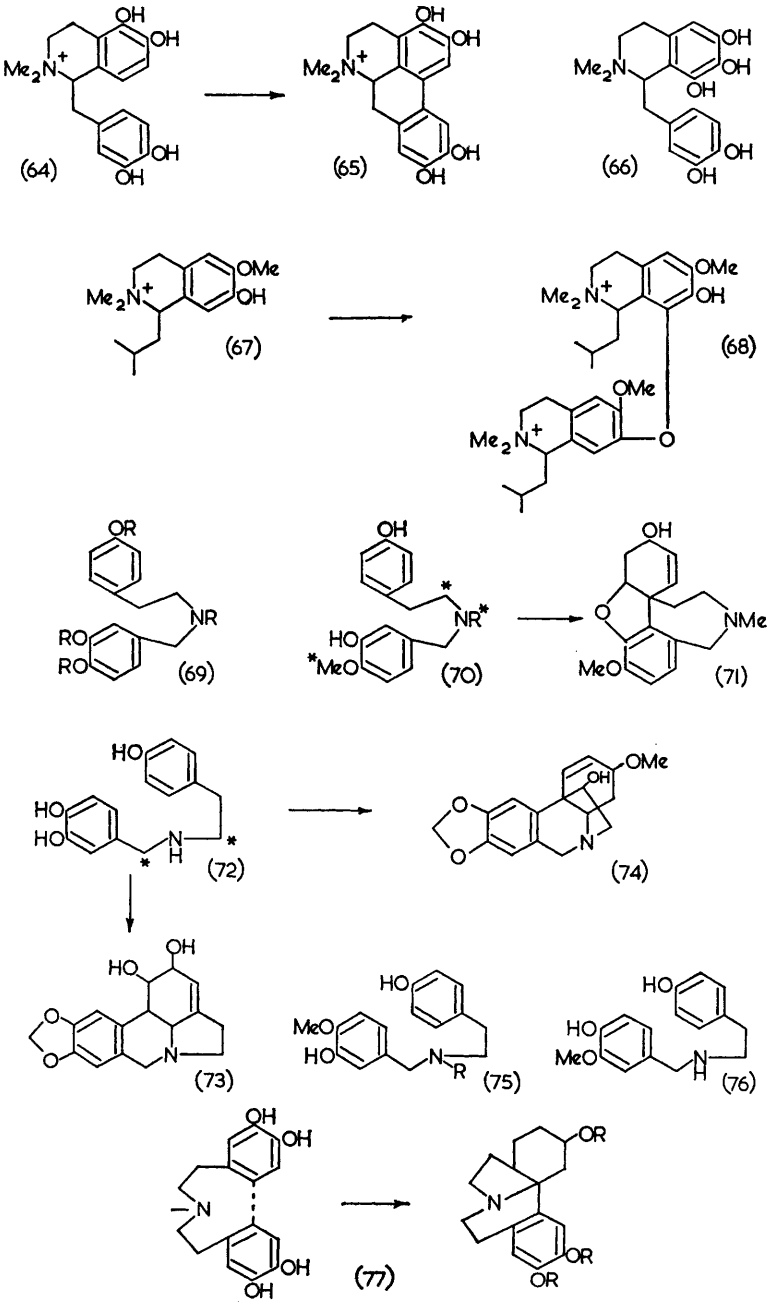
(63) Culanine type

turn of the century.[49,101] Although the results of feeding experiments are not yet available, it seems certain that the bonds marked (- - - -) in formulae (61)→(63) are formed by coupling *in vivo*. Again there is evidence that such couplings under laboratory conditions are indeed facile and several examples of synthesis of these alkaloidal classes are discussed below. In each of these types, C–C and C–O bond formation *via* coupling of laudanosoline (58) and its relatives provide a most satisfactory biosynthetic analysis.

(*b*). Oxidation of quaternary laudanosoline (58) with ferric chloride gives a 62% yield of the glaucine (60).[66] Similarly (64) affords the aporphine (65) in good yield.[66,113] Treatment of the pentahydric phenol (66) with ferric chloride gives instead of the expected cularine (63) or morphine type, the same aporphine (60) as obtained from the tetrahydric series. This appears to be a Lewis-acid catalysed condensation rather than an oxidation.[66]

The dimeric benzylisoquinolines, *e.g.*, isopilocereine (68) are reached by ferric chloride of ferricyanide oxidation of the monomer (67), either as the free base or as its quaternary derivative. By use of 1·3 equivalents of ferricyanide some of the trimer of (68), pilocereine, another cactus alkaloid, is produced.

Alkaloids of amaryllidaceae (*a*). Barton and Cohen[7] suggested that a phenolic precursor such as (69; R = H), now known[104] to be the alkaloid norbelladine, represented a single progenitor for the main three types of this alkaloid family. The validity of this scheme has been rigidly demonstrated by independent researches in three laboratories.[103,104]


(64)
(65)
(66)
(67)
(68)
(69)
(70)
(71)
(72)
(73)
(74)
(75)
(76)
(77)

Thus, on the basis of biogenetic analysis, not only was the correct formula (71) chosen for galanthamine but it was proved that the belladine (70) labelled as shown was incorporated without change of isotope ratio into galanthamine.[114] Similarly, doubly labelled norbelladine[115,116] (72) is incorporated into lycorine (73). Haemanthamine (74) is similarly derived from (72).[116,117] An important result which bears on the phenol coupling theory for these alkaloids is the detection by radiochemical dilution analysis of minute amounts of the phenolic precursors (75; R = H) and (75; R = Me) in two of the plants used in these studies. Also of interest are the first reports of a purified enzyme system isolated from *Nerine bowdenii* which in presence of a biochemical C_1-donor selectively methylates norbelladine (69; R = H) at the *para*-phenolic function to yield almost entirely the ether (75; R = H).[118] The subsequent coupling reaction is then directed by the free phenolic groups. Thus the isomeric *O*-methylnorbelladine (76) is not incorporated into these alkaloids.

The many examples representing each of these alkaloidal types has been fully reviewed recently.[119] Other alkaloidal families whose biosynthesis surely involves an oxidation coupling step are represented by the *Erythrina* type (77), and the bisbenzylisoquinolines (61)→(63).

(*b*). Of the three possible[103,104] structural types (71), (73), and (74) obtained by oxidation of norbelladine, only one has so far been obtained by biogenetic synthesis. The precursor (70) prepared for the study of the biosynthesis of galanthamine[120] and narwedine afforded a small (<1%) isolated yield of the latter when oxidized with manganese dioxide. Other oxidants [$K_3Fe(CN)_6$, PbO_2] were studied and yields determined by the radiochemical dilution method. In each case the yield was very small but significant.

Colchicum *alkaloids*. (*a*) Recent experiments[121,122] on the incorporation of aromatic amino-acids and their derivatives into colchicine in both *C. autumnale* and *C. byzantinum* are summarised in Chart 4. Phenylalanine is the source of ring A and the three-carbon bridge, whilst tyrosine, contrary to earlier evidence, supplies the seven carbon atoms of ring C. The sequence and mechanism of ring enlargement, restoration of nitrogen

[114] D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 1961, 254; 1962, 179; *J.*, 1963, 4545.

[115] A. R. Battersby, R. J. Binks, S. W. Brewer, H. M. Fales, and W. C. Wildman, *Proc. Chem. Soc.*, 1961, 243.

[116] W. C. Wildman, H. M. Fales, R. J. Highet, S. W. Brewer, and A. R. Battersby, *Proc. Chem. Soc.*, 1962, 180.

[117] D. H. R. Barton, G. W. Kirby, and J. B. Taylor, *Proc. Chem. Soc.*, 1962, 340.

[118] H. M. Fales, J. Mann, and S. H. Mudd, *J. Amer. Chem. Soc.*, 1963, **85**, 2025.

[119] K. Mothes and H. R. Schutte, *Angew Chem. Internat. Edn.*, 1963, **2**, 441.

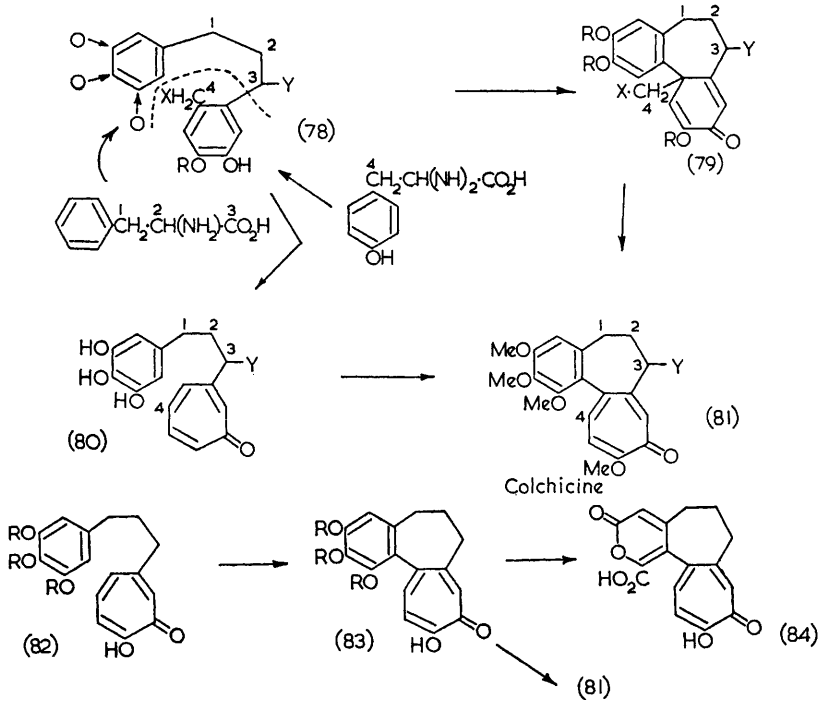
[120] A. I. Scott, *Nature*, 1960, **186**, 556.

[121] A. R. Battersby, R. Binks, and D. A. Yeowell, *Proc. Chem. Soc.*, 1964, 86 and refs. therein; A. R. Battersby, *Quart. Rev.*, 1961, **15**, 259; A. R. Battersby and R. B. Herbert, *Proc. Chem. Soc.*, 1964, 260.

[122] E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 3666.

to C* and closure of the third ring remain undetermined but two particular pathways, both involving oxidative coupling have been suggested.[120,121] The first of these[120] visualises ring enlargement followed by tropolone–phenol coupling. The second scheme[121] considers coupling at the C_6–C_3–C_6–C_1 stage, followed by ring enlargement by acceptable mechanistic pathways. Since the mould tropolones (*e.g.*, stipitatic acid) appear to be derived from aromatic precursors[123] the results of feeding experiments using types (79) and (80) substrates should cast light not only on colchicine biosynthesis but also on the general problem of the formation of tropolone rings in Nature. Laboratory analogy for the first hypothesis has been provided.[124]

CHART 4. Colchicine biosynthesis.



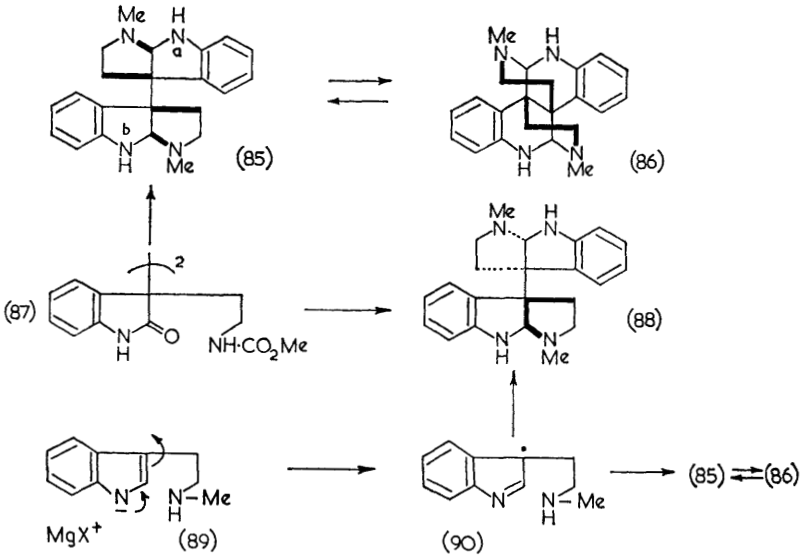
(*b*). The biogenetic-type synthesis of this alkaloid has now been completed.[124] Attempted oxidation of the bicyclic dimethyl ether (82; R = Me)

* The interesting possibility that several fully "aromatic" alkaloids may be artefacts resulting from vigorous acidic treatment during isolation and leading to dienone–phenol and dienol–benzene rearrangements must now be considered.

[123] R. Bentley, *Ann. Rev. Biochem.*, 1962, **31**, 589 and refs. therein.

[124] A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. J. Baker, T. A. Davidson, and A. C. Day, *J. Amer. Chem. Soc.*, 1963, **85**, 3040; A. I. Scott, F. McCapra, R. L. Buchanan, A. C. Day, I. G. Wright, and D. W. Young, *Proc. Symposium Chem. Natural Phenols*, Tokyo, 1964, p. 11; *Tetrahedron*, 1965, in the press.

failed to induce coupling of the phenolic and tropolonoid rings, but the free pyrogallol (82, R = H) afforded the ring A-cleaved product of coupling (84) with ferricyanide in bicarbonate solution, in 10% yield. The rupture of ring was avoided by using a two-phase (ferric chloride: sulphuric acid–chloroform) oxidising medium. The tricyclic product (83; R = H) (which can be converted into colchicine by established methods) is formed in 4% yield.[118] Although the coupling reaction proceeds with low efficiency, the alkaloid can be obtained in eight steps by this sequence.



Calycanthaceous alkaloids (*a*). An interesting set of six alkaloids[125] exemplified by (−)-chimonanthine (85) and calycanthine (86) are formally derived by $\beta\beta'$-oxidative coupling of *N*-methyltryptamine, itself an alkaloid. All six alkaloids have been isolated from *Calycanthus floridus* and while there is as yet no evidence that tryptamine is the biological precursor of these compounds, simulation of the biosynthesis of these compounds has been achieved in the laboratory.

(*b*). Five of the six members of this set have now been synthesised by oxidative coupling. From the outset the problem was one of reaction conditions since the postulate of $\beta\beta'$-coupling of tryptamine always seemed certain for the biosynthesis of this class of dimeric indole alkaloids.

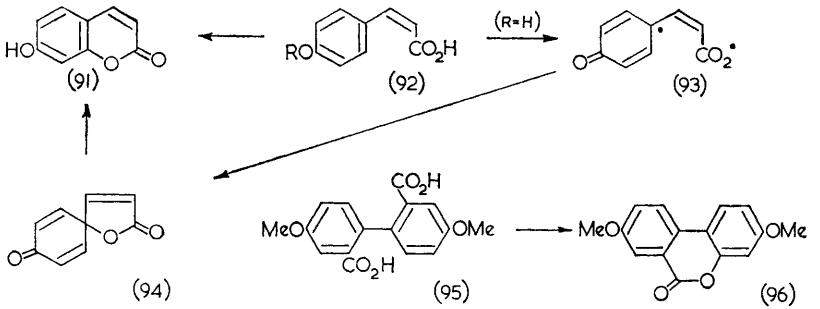
The first practical solution was found by Hendrickson *et al.*,[58] who used the oxindole coupling reaction (iodine, base) to prepare the protected bisoxindole (87). The *N*-CH_3 group and correct oxidation level (85) were then reached by hydride reduction and the *meso*- and (±)-isomer separ-

[125] See B. Robinson, *Chem. and Ind.*, 1963, 218 and refs. therein.

ated. In this way both (±)- and *meso*-chimonanthine (85) and (88) were isolated as well as (±)-calycanthine (86). The equilibrium of both natural and synthetic calycanthine and chimonanthine has also been revealed during these studies.[58] The previous work had correlated (85) with folicanthine (85; ^{a}NH = NMe) and calycanthidine (85; Both NH = NMe), thus constituting the first synthesis of four of the (then) known alkaloids, the fifth member being hodgkinsine.[125]

By use of the proposed biosynthetic pathway in more detail, and the establishment of carbanion activity at the β-position, the ionic magnesyl-*N*-methyltryptamine (89) was oxidised with anhydrous ferric chloride. Mild hydrolysis of the reaction mixture afforded presumably *via* (90), (±)-chimonanthine directly in 20% yield.[57] The *meso*-isomer [(2%) yield] was found to be identical with a new alkaloid from *C. floridus*.

Plant and Fungal Phenolic Compounds.—*Coumarins* (*a*). The precursor of 7-oxygenated coumarins, *e.g.*, umbelliferone (91) is *p*-hydroxycinnamic acid (92; R = H).[126,127] Two distinct mechanistic pathways

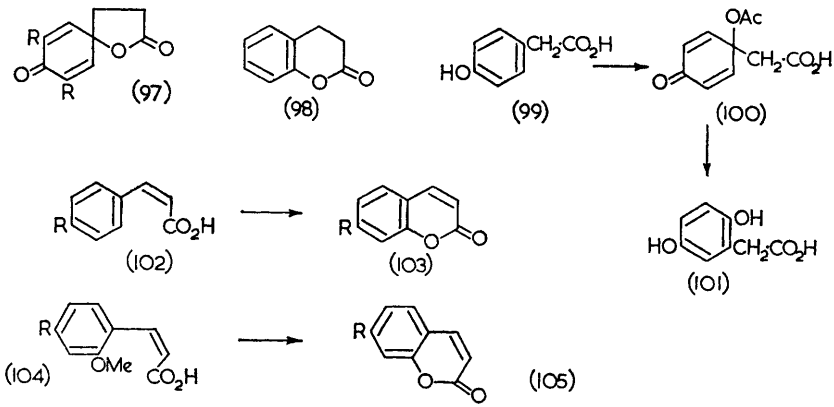


have been envisaged for the conversion of the C_6–C_3 acids into 7-hydroxycoumarins. The first[128] involves direct oxidation of the acid which cyclises *via* a radical or ionic mechanism to (91), regardless of the nature of R (in 92). This concept also embraces a direct *meta*-hydroxylation mechanism independent of the R group. The second mechanism takes cognisance of the usual orientation in phenol oxidation reactions, and in diverse forms[62b,129,130] implies oxidation *para* to an existing phenolic hydroxyl group (92)→(93). The resultant radical (93) can pair intramolecularly or add oxygen. Subsequent migration (C or O) leads to 6 and 7-hydroxycoumarins. Recent incorporation evidence[131] still leaves the full details of mechanism in question. Thus, *trans-p*-hydroxycinnamic acid is a more

[126] G. Gillick and H. Kindl, *Monatsh.*, 1962, **93**, 85.
[127] S. A. Brown, *Phytochem.*, 1963, **2**, 137.
[128] C. A. Bunton, G. W. Kenner, M. J. T. Robinson, and B. R. Webster, *Tetrahedron*, 1963, **19**, 1001.
[129] R. D. Haworth, *J.*, 1942, 448.
[130] H. Grisebach and W. D. Ollis, *Experientia*, 1961, **17**, 4.
[131] D. J. Austin and M. B. Meyers, *Tetrahedron Letters*, 1964, 765 and refs. therein.

efficient precursor of umbelliferone (91) than the *cis*-isomer.[131] A *meta*-oxidation mechanism involves oxygen insertion and does not accord with the ^{18}O-experiments in the novobiocin series.[128] In the latter studies, retention of both carboxyl oxygens implies direct (*meta*) cyclisation or intervention of a *spiro*-intermediate (94).

(*b*). Experiments designed to test the various proposals for coumarin biosynthesis by laboratory synthesis have recently been described. In the "direct" approach, *p*-hydroxy-*cis*-cinnamic acid (92) can be oxidised to umbelliferone directly[132] (0·1%) and the *Castoreum* pigment[128] (96) is prepared by direct *meta*-oxidation of the acid (95). The biochemical analogy for this reaction is the incorporations of *both* oxygens of the carboxyl group of tyrosine into novobiocin. These feeding experiments can however also be rationalised in terms of the indirect (or *para*) mechanism where oxidation is directed by the phenolic hydroxyl group. There is good experimental analogy for this in the oxidation of phloretic acid (90) with *N*-bromosuccinimide to give the *spiro*-lactone (97; R = Br) and in the preparation of homogentisic acid as in (99)→(101). Operation of radical

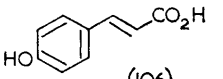


pairing (or ionic mechanism) involving the *para*-position of tyrosyl derivatives has been found in the oxidation of phloretic acid by lead dioxide[62c] or electrolysis[62a,b] to give the *spiro*-lactone (97; R = H). Electro-oxidation of *p*-hydroxy-*cis*-cinnamic acid affords the "Grisebach–Ollis intermediate"[130] (94) of coumarin biosynthesis.[62b] This unsaturated lactone can be converted into umbelliferone (91) in a biogenetic-type synthesis of this widely distributed 7-oxygenated coumarin.[62b] The rearrangement (97)→(98) also accords with retention of *both* oxygens of the original carboxyl group, although isotope studies have not confirmed this point *in vivo*. However, the laboratory rearrangement (97)→(98) is sensitive to reaction conditions and in some cases involves β-addition of base to the enone system.[62c]

[132] M. B. Meyers, *Proc. Chem. Soc.*, 1963, 243.

In contradiction to this *para*-mechanism, and to the incorporation of both oxygens of tyrosyl carboxyl, are the recent observations of Austin and Meyers[131] that *trans-p*-hydroxycinnamic acid (92) is a better precursor of umbelliferone in *Hydrangea macrophylla* than are the *cis*-acid or the *spiro*-lactone (94). It has been observed[133] that acids (as 102) are oxidised to the coumarins (103) by persulphate. Furthermore the methyl ethers (104) afforded the coumarins (105, R = H, R = Me) in 10—20% yields. The latter reaction, described[133] as unexpected, seems to be a further example of the well-known conversion of *O*-methoxycinnamic acids into coumarins by acid catalysis.[134]

Lignans (*a*). Earlier, extensive biogenetic analyses of lignin structures led to the postulation of coniferyl alcohol (106) as the building block.[97,135] Combination of the mesomeric radical forms (107) and (108) results in structures such as (109), (110), (111), and (118—121). This suggestive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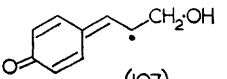
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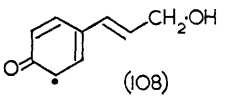
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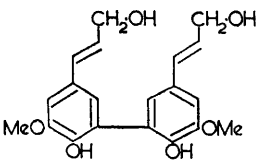
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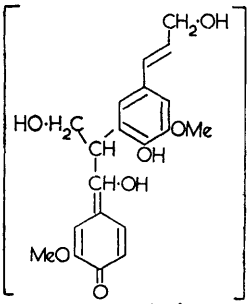
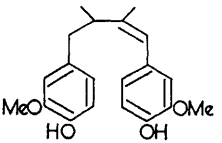

(110)

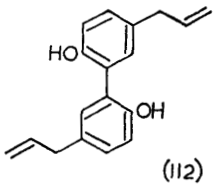

(111)

circumstantial evidence has now been reinforced by tracer experiments in which ^{14}C-coniferin was fed to spruce twigs. The resulting lignin is radioactive, but many problems of detail remain to be elucidated.

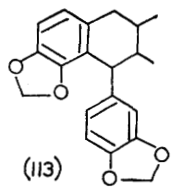
Other dimeric examples are magnolol[136] (112), otabin[137] (113), and schinzandoin[138] (114).

(*b*). Models for lignin biosynthesis involving oxidation of coniferyl

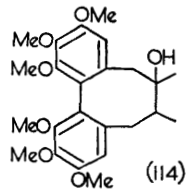
[133] G. Russell, R. H. Thompson, and A. Wylie, *Chem. and Ind.*, 1964, 34.
[134] Review: W. Baker and W. D. Ollis, in "Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon, Oxford, 1961.
[135] K. Freudenberg, *Fortschr. Chem. Org. Naturstoffe*, 1962, **20**, 41; K. Freudenberg and H. Geiger, *Ber.*, 1963, **96**, 1265 and refs. therein.
[136] J. Runeberg, *Acta Chem. Scand.*, 1958, **12**, 188.
[137] T. Gilchrist, R. Hodges, and A. L. Porte, *J.*, 1962, 1780; N. S. Bhacca and R. Stevenson, *J. Org. Chem.*, 1963, **28**, 1638.
[138] N. K. Kochetkov, A. Khorlin, O. S. Chizkor, and V. I. Sceichenko, *Tetrahedron Letters*, 1961, 730; 1962, 361.



(112)



(113)



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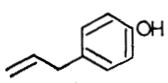

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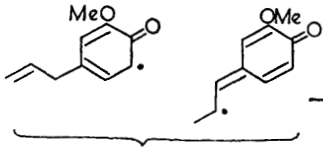

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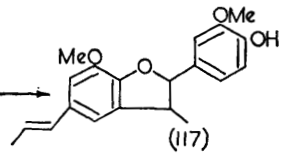
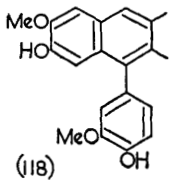


(117)

alcohol and its derivatives have been examined. Thus magnolol (112) is obtained by oxidation of chavicol (115). The oxidation of isoeugenol (Radical; 116) with ferric chloride illustrates both phenol and benzylic coupling in that (117) and (118) are formed with a mushroom phenol oxidase as reagent. Freudenberg showed that coniferyl alcohol was oxidised to a polymer similar to lignin and a soluble fraction containing dehydroconiferyl alcohol (119) (±)-pinoresinol (120), (121), and (122).



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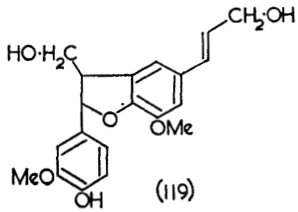

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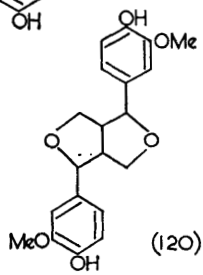

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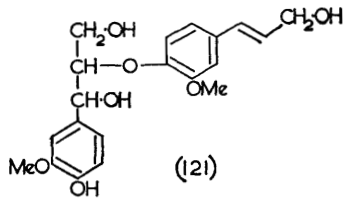
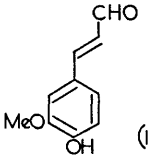


(121)

Freudenberg considers[135] that lignin biosynthesis is based on the building block of coniferyl alcohol but some criticism of this view has also been offered.[97]

Tannins (*a*). Structures such as those of ellagic acid (123), brevifolin (124), chebulagic acid (125), and corilagin (126) (all from *Terminalia*), valonic acid (*Quercus*) (127), and dehydrodigallic acid (128) (chestnut) are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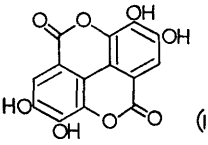
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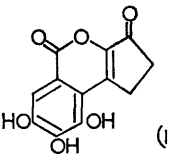
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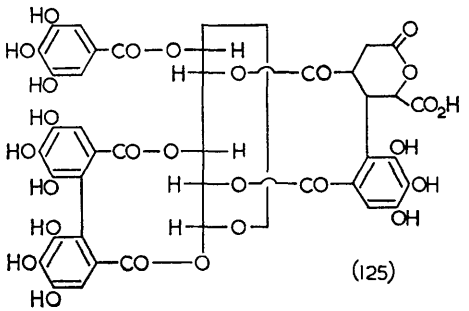
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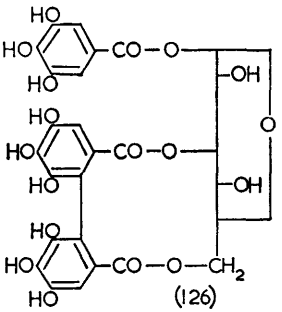
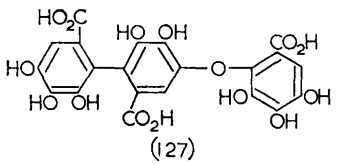

(126)

in full accord with oxidative coupling mechanism.[139] However an interesting alternative involving carbanion addition to a shikimic acid derivative (129) + (130)→(131) has been advanced by Wenkert.[140] Although the easy laboratory oxidation of, *e.g.*, gallic to ellagic acid and the well-known cleavage of pyrogallols to sorbic acid derivatives,[64] provide compelling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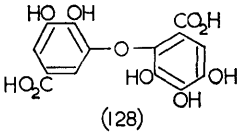
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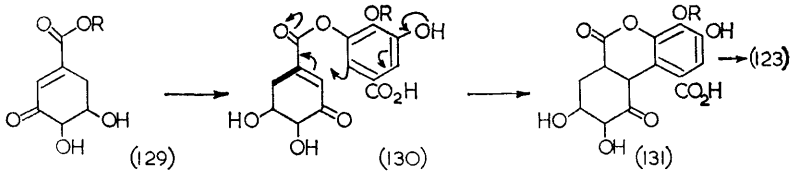

(129) (130) (131) →(123)

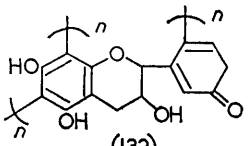
analogy for both the coupling reaction and degradations at the aromatic level, the biochemical test of these theories has not been made.*

* However, see T. Takini *et al.*, *J. Agr. Biol. Chem.*, 1963, **27**, 562, for a description of enzymic dehydrogenation (coupling) of ethyl gallate.

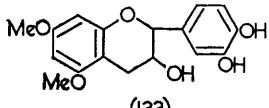
[139] Reviews: (*a*) O. T. Schmidt, ref. 130, p. 139; (*b*) S. G. Humphries in ref. 134, p. 617.

[140] E. Wenkert, *Chem. and Ind.*, 1959, 906.

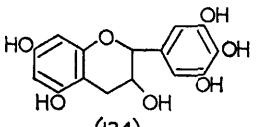
Interesting results on autoxidation[139b,140] and enzymic oxidation[139b,141] of catechins in connection with *post mortem* oxidation (browning) of plant polyphenols have been obtained. Hathaway concluded from spectroscopic evidence that *o*-quinone formation *via* a free-radical mechanism led through polymerisation to products of type (132). Similar autoxidation polymers were obtained from 5,7-di-*O*-methylcatechin (133) and by enzymic oxidation of catechin by polyphenoloxidases. An enzyme in the cambium of *Quercus* species readily acted on pyrogallols of type (134) to produce polymer (135). Of taxonomic interest is the observation that ginkgetin



(132)

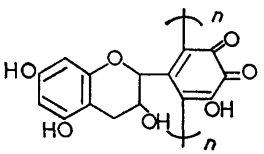


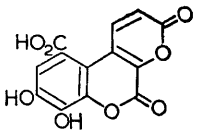
(133)



(134)

(135)

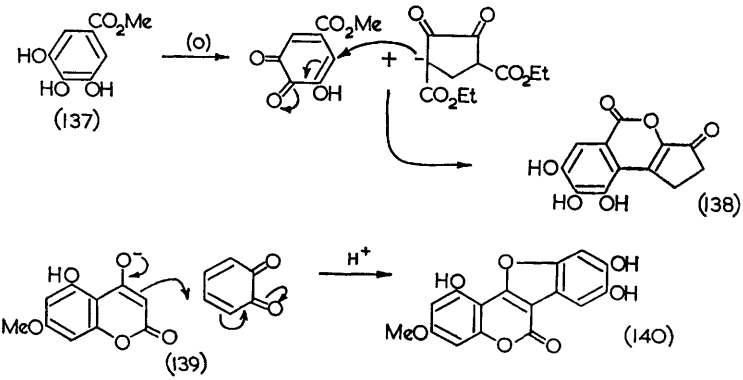




(136)

and other biflavonyls[134] co-occur with the polymeric leucoanthocyanidins.[139b] Further indirect support for oxidative coupling as a key step in the biosynthesis of tannins comes from the detection[98] of free-radical species in condensed tannin extracts.

(*b*). The successful enzymic coupling of gallic acid to its dehydro-dimer, and the easy oxidation of gallic acid and pyrogallols in the laboratory to furnish, for example, ellagic acid (12) or galloflavin (136) (where oxidative coupling is followed by lactonisation and ring cleavage respectively) serve as compelling analogies for the formation of such compounds in Nature.

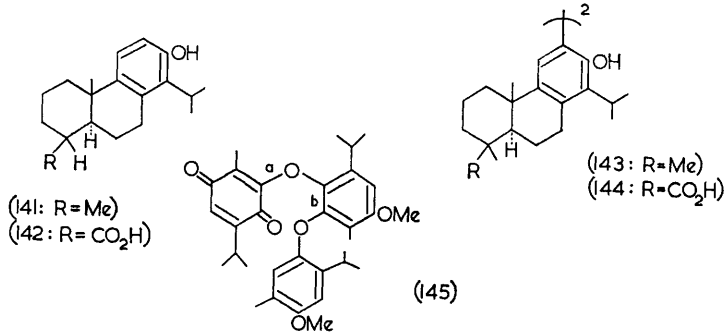


(137) (138) (139) (140)

[141] D. E. Hathway, *J.*, 1958, 520; *Biochem. J.*, 1959, **71**, 533.

The importance of addition mechanism to quinonoid forms of 1,2- and 1,4-oxygenated systems is reflected in ingenious syntheses of brevifolin[142] and wedelolactone[143] which are shown in (137)→(138) and (139)→(140) respectively.

Bisditerpenoids (*a*). The structural elucidation of podototarin (143) and macrophyllic acid (144)[144,145] reveals evidence of coupling of the monomers shown for each case. Some factual basis for this analysis was recently laid[93,144] by the successful enzymic oxidation of totarol (141) to podototarin (143).

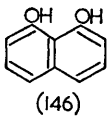


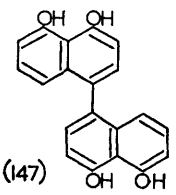
An interesting example of a monoterpene trimer is libocedroxythymoquinone[146] (145) in which bonds (a) and (b) are formed by C–O coupling. There is good analogy[23] however for bond (b) to be a result of phenoxide addition to a thymoquinone ring.

(*b*). The laboratory oxidations of totarol (141) to podototarin[93,144,145] (143), of the synthetic phenol ester (142) to (+)-macrophyllic acid[147] (144), and of ferruginol[145] have been described in addition to the earlier synthesis of gossypol.[146,148]

Pigments of Daldinia concentrica (*a*). The chromagen 4,5,4′,5′-tetrahydroxy-1,1′-binaphthyl (147) is present in the sporophores of this ascomycete and is oxidized *in situ* to 3,10-dihydroxyperylene-4,9-quinone (148) as well as black polymeric pigment. The fate of 1,8-dihydroxynaphthalene (146) in certain strains has been studied by Bu'Lock.[149] Thus in "wild" strains the sequence (146)→(147)→(148) is followed whereas in other selected strains the path (146)→(149) prevails. The presence of

[142] H. W. Wanzlick, *Ber.*, 1959, **92**, 3006.
[143] H. W. Wanzlick, R. Gritzky, and H. Heidepriem, *Ber.*, 1963, **96**, 305.
[144] S. M. Bocks and R. C. Cambie, *J.*, 1963, 2422.
[145] C. P. Falshaw, A. W. Johnson, and T. J. King, *Chem. and Ind.*, 1963, 451; *J.*, 1963, 2422.
[146] E. Zavarin, *J. Org. Chem.*, 1958, **23**, 1198.
[147] A. C. Day, *Chem. and Ind.*, 1963, 1760.
[148] J. D. Edwards and J. L. Cashaw, *J. Amer. Chem. Soc.*, 1957, **79**, 2283; J. D. Edwards, *bid.*, 1958, **80**, 3798.
[149] D. C. Allport and J. D. Bu'lock, *J.*, 1960, 654.


(146)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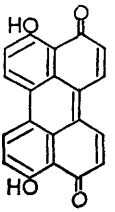
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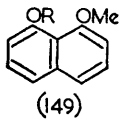
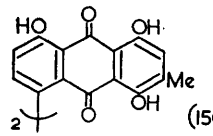
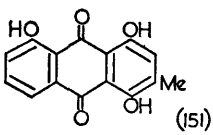

(149)


(150)

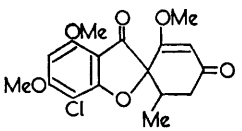

(151)

(147) in the spopophores is taken to indicate a plateau in oxidation potential of the oxidative enzyme, possibly induced by polymeric pigment.

(*b*). Oxidative experiments with (146) show that first the binaphthyl (147) and then the perylenequinone (148) are formed in simulation of the natural process.[149]

Iridoskyrin. Inspection of the formula (150) of this dimeric anthraquinone and its relations at once suggests C–C coupling. However, tracer experiments have shown that the monomer, islandicin (151), is not the precursor of iridoskyoin and that it is produced independently of its "dimer".[150]

Grisans. (*a*) The main representatives of this class of fungal metabolites are griseofulvin[151] (152), geodin[152] (153), erdin[152] (154) and osoic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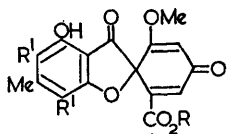
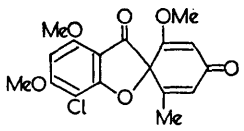
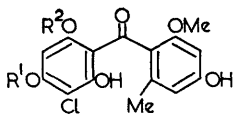
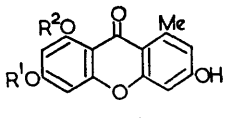
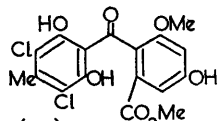

(153 : R=Me, R'=Cl)
(154 : R=H , R'=Cl)
(155 : R= R'=H)


(156)


(157)

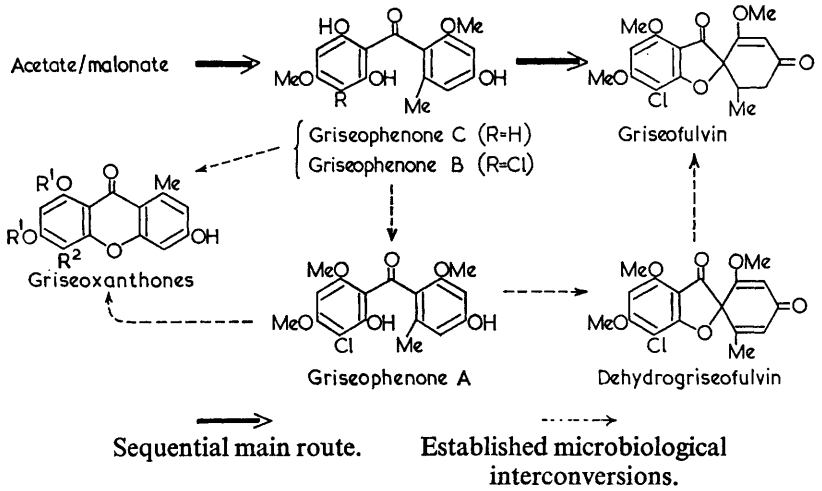

(158)


(159)

[150] S. Gatenbeck, *Svensk kem. Tidskr.*, 1960, **72**, 188 and refs. therein.
[151] J. F. Grove, *Quart. Rev.*, 1963, **17**, 1.
[152] D. H. R. Barton and A. I. Scott, *J.*, 1958, 1767.

acid E[153] (155). Isolation of dehydrogriseofulvin[154] (156), the griseophenones[155,156] (as 157) the griseoxanthones[154,155] (as 158) and dihydrogeodin[157] (159) provides good circumstantial evidence for the relationship between benzophenones and grisans.[7,151] Biochemical studies by Rhodes and his colleagues[155] have mapped the path of griseofulvin biosynthesis in *Penicillium patulum*. Following the primary cyclization of seven acetate (or malonate) units the polyhydroxybenzophenone (157; $R_1 = R_2 = H$; $OCH_3 = OH$; Cl = H) would represent the first aromatic product. Isolation experiments have demonstrated the validity of the sequence shown[156] in Chart 5. The analogy for the key oxidation step has been

CHART 5. Griseofulvin biosynthesis in *Penicillium patulum*.

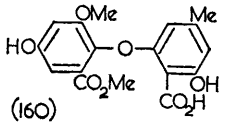


provided both from laboratory[158] and enzymic[156,157,159] experiments, *e.g.*, (157)→(156). Isolation of xanthones in these studies provides evidence for at least one pathway to these comparatively rare natural products.

Biochemical studies[157] with geodin (153) and its dihydro-derivative (159) in *P. paxillus* clearly demonstrates the intervention of radical coupling.

[153] R. F. Curtis, C. H. Hassall, S. Natori, and H. Nishikawa, *Chem. and Ind.*, 1961, 1360.
[154] W. J. McMaster, A. I. Scott, and S. Trippett, *J.*, 1960, 4628.
[155] A. Rhodes, "Progress in Industrial Microbiology," IV, Heywood, London, 1962, p. 167; A. Rhodes, G. A. Somerfield, and M. P. McGonagle, *Biochem. J.*, 1963, **88**, 349 and refs. therein.
[156] A. J. Baker, T. A. Davidson, A. C. Day, M. B. Meyers, and A. I. Scott, unpublished work.
[157] E. Kamatsu, *Nippon Nogie-Kagaku Kaishi*, 1957, **31**, 905; *Chem. Abs.*, 1958, **52**, 16473; A. Rhodes *et al.*, *Chem. and Ind.*, 1962, 611.
[158] A. C. Day, J. Nabney, and A. I. Scott, *Proc. Chem. Soc.*, 1960, 284; *J.*, 1961, 4067.
[159] B. R. Brown and S. M. Bocks, in "Enzyme Chemistry of Phenolic Compounds," ed. J. B. Pridham, MacMillan, New York, 1963, p. 129.

(*b*). Following the earlier successful laboratory conversion of griseophenone C (157; R = Me) into dehydrogriseofulvin (156)[158] the Merck group have recently examined the behaviour of a number of substituted 2,4′-dihydrobenzophenones towards one-electron oxidants.[160] The main generalisation derived is that 2′,6′-disubstitution appears to be necessary for success of the reaction. Under the usual[161] conditions, 2,4′-dihydroxybenzophenone is not coupled to the grisan nucleus.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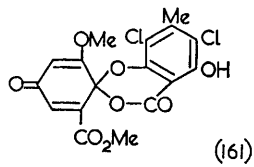
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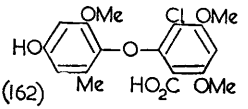
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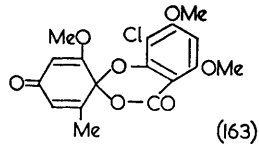
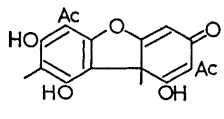

(163)

The benzophenones (as 159) corresponding to erdin, geodin, and its methyl ether are coupled to the appropriate antibiotics by ferricyanide[161,162] and peroxidase.[156] Similarly sulochrin (159; Cl = H) affords (±)-bisdechlorogeodin (155), the optically active (−) form of which has been identified as a metabolite of *Oospora sulphurea-ochracea*, which also produces sulochrin. The sequence (159; Cl = H)→asterric acid (160)→geodoxin (161) has been followed in the laboratory, the last reaction involving carboxyl–phenol coupling, utilising lead dioxide.[60,163] The latter reagent has also been used to oxidise the ether (162) to the geodoxin analogue (163) of griseofulvin.[164]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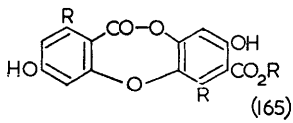
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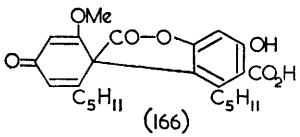
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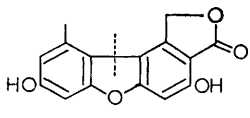
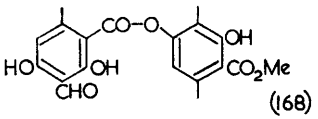

(167)

[160] D. Taub, S. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 3344.
[161] T. A. Davidson and A. I. Scott, unpublished work.
[162] C. H. Hassall and A. I. Scott, in ref. 74, p. 125.
[163] R. F. Curtis, C. H. Hassall, D. W. Jones, and T. H. Williams, *J.*, 1960, 4838; C. H. Hassall and T. C. McMorris, *J.*, 1959, 283.
[164] J. R. Lewis and J. A. Vickers, *Chem. and Ind.*, 1963, 779.

Lichen substances (*a*). The difficulty of laboratory culture has so far precluded tracer experiments. However many relationships involving coupling exist and we cite the examples of usnic acid[165] (164), the depsidones[7,8] (165), picrolichenic acid[73] (166) (a depsone), and stepsilin[7,8] (167) in which the bond formation is denoted by a broken line.

A new example of the depside–depsidone relationship is virensic acid[166] (169) which corresponds to the well-known depside atranorin (168).

(*b*). The first and sole examples of the synthesis of a depsidone, diploicin (171), employed radical coupling as the key step from the totally synthetic



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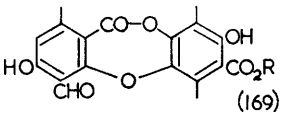

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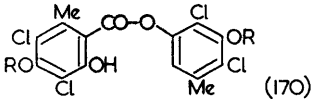

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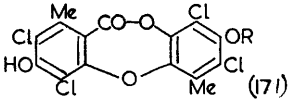

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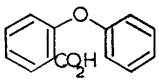

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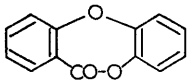

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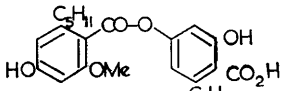


(174)

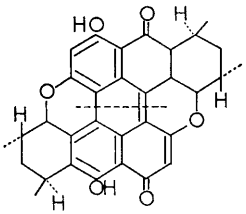
depside[167] (170). Manganese dioxide proved the only efficient oxidant for this reaction. The easy cleavage of the depside ester link restricts the use of many hydroxylic systems in these studies. The model system, salicyloylresorcinol, has so far failed to couple under these conditions, although carboxyl coupling of (172) yields (173) which represents the parent depsidone system,[61,164] without the key oxygenation pattern.

Indirect confirmation that C–O coupling is involved in the depside–depsidone relationship comes from the oxidation of the totally synthetic depside (174) to the *spiro*-lactone (±)-picrolichenic acid[168] (163) which occurs as the racemate in *Pertusaria* species.[89] In this synthesis also manganese dioxide was the only successful oxidant.

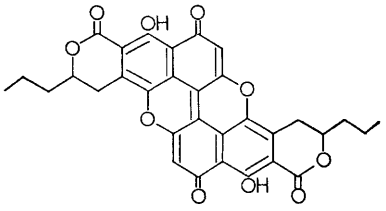
Other Natural Products.—Many compounds from plant and fungal sources have been studied since the last major reviews[7,8] of this subject. In Chart 6 are shown the structures of several of these, which may be formed by a coupling reaction involving the bonds marked in each case.

[165] D. H. R. Barton, A. M. DeFlorin, and O. E. Edwards, *Chem. and Ind.*, 1955, 1039; *J.*, 1956, 530.
[166] K. Aghoramurthy, K. G. Sarma, T. R. Seshadri, *Tetrahedron*, 1961, **12**, 173.
[167] C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.*, 1960, 393.
[168] T. A. Davidson and A. I. Scott, *J.*, 1961, 4075.

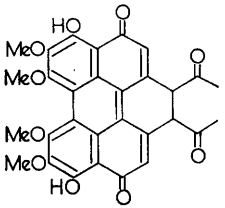
CHART 6. Natural phenols derived by coupling.



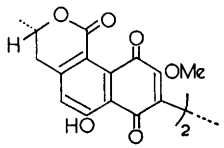
Erythroaphin



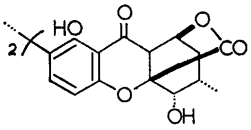
Xylindein



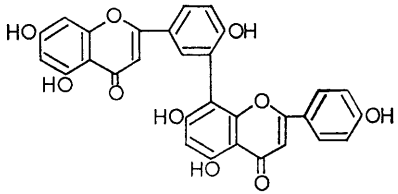
Elsinochrome A



Xanthomegnin



Ergoflavin



Armentoflavone

Erythroaphin (ref. 170); xylindein (ref. 171); Elsinochrome A (ref. 172); xanthomegnin (ref. 173); ergoflavin (ref. 174); armentoflavone (ref. 134).

Related Reactions

(i) **Tocopherol.**—Oxidation of tocopherol with potassium ferricyanide produces a dimer recently[169] shown to be (175).

[169] D. R. Nelan and C. D. Robeson, *J. Amer. Chem. Soc.*, 1962, **84**, 2963; P. Schudel, H. Mayer, J. Metzger, O. Ruegg, and O. Isler, *Helv. Chim. Acta*, 1963, **46**, 636. *cf.* A. S. Csallany and H. H. Draper, *J. Biol. Chem.*, 1963, **238**, 2912.

[170] Lord Todd, *Experientia*, 1962, **18**, 433.

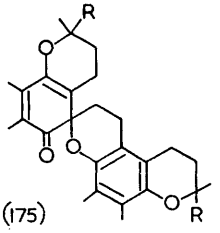
[171] G. M. Blackburn, A. H. Neilson, and Lord Todd, *Proc. Chem. Soc.*, 1962, 327.

[172] T. J. Batterham and U. Weiss, *Proc. Chem. Soc.*, 1963, 89.

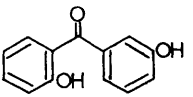
[173] G. Just, W. Day, and F. Blank, *Canad. J. Chem.*, 1963, **41**, 72.

[174] J. D. M. Asher, A. T. McPhail, J. M. Robertson, J. V. Silverton, and G. A. Sim, *Proc. Chem. Soc.*, 1963, 210; J. W. ApSimon, J. A. Corran, N. G. Creasey, K. Y. Sim, and W. B. Whalley, *ibid.*, p. 209.

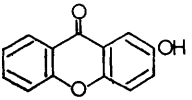
(ii) **Xanthones.**—A new xanthone synthesis involving C–O coupling (176)→(177) has been described.[175] The resultant oxygenation pattern in this reaction is different from that of the naturally-occurring xanthones.



(175)



(176)



(177)

[175] J. R. Lewis, *Proc. Chem. Soc.*, 1963, 373.