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BIOGENETIC-TYPE SYNTHESES OF o-ISOPENTENYLPHENOLS

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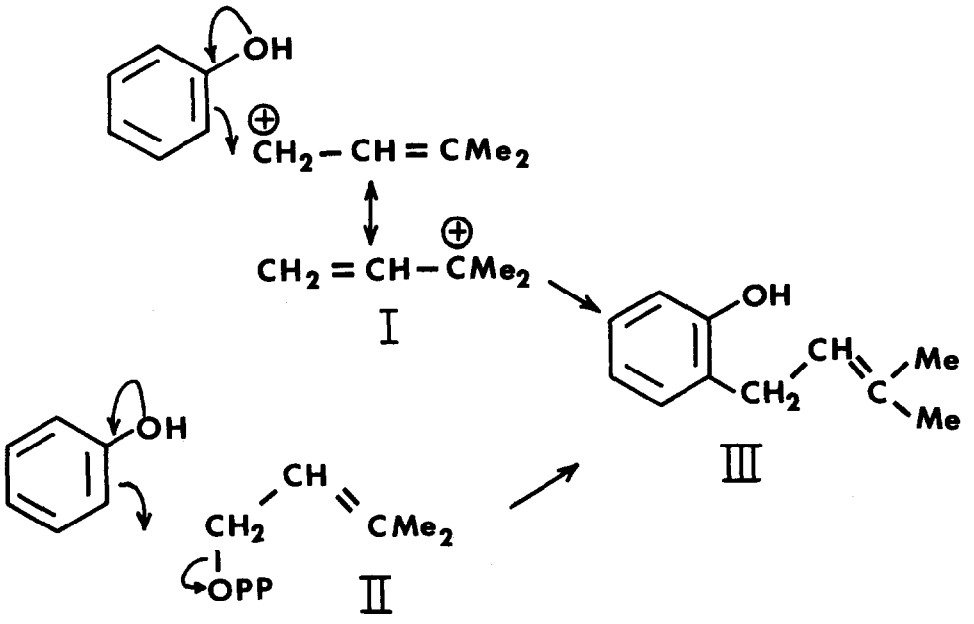
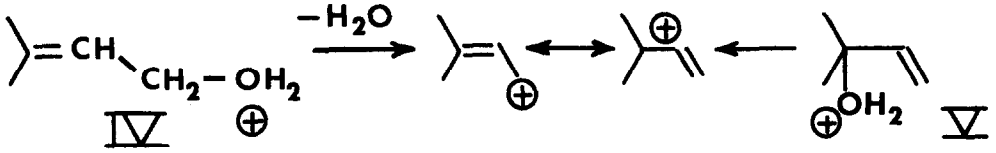
o-Isopentenylphenols occur frequently in plants and microorganisms (1), and are essential intermediates in the biosynthesis and in some syntheses of a variety of other natural products, e.g., 2,2-dimethylchromenes (2), which contain modified isoprenoid units. o-Isopentenylphenols are usually synthesized by direct alkylation of phenols with allylic halides in alkaline media (3), or by Lewis-acid, e.g., boron trifluoride (4, 5, 6), catalyzed condensation of allylic alcohols with phenols in an aprotic solvent. Birch and his associates recently noted (7) that the reported methods for the synthesis of o-isopentenylphenols by direct alkylation are inefficient in most cases, yields being poor and the products structurally equivocal. They proposed an alternate synthetic route requiring an initial synthesis of 2,2-dialkylchromenes followed by reduction with lithium in liquid ammonia.

It has been suggested that the biogenesis of o-isopentenylphenols involves C-isopentenylation of a preformed phenol or its poly-β-ketonic precursor by an activated allylic alcohol derivative such as isopentenyl pyrophosphate or γ,γ-dimethylallyl pyrophosphate (8). Condensation may then occur by nucleophilic attack of the phenol on the stabilized cation (**I**) described by Cornforth and Popják (9), or by an S_N2-type displacement of a pyrophosphate leaving group from (II), as proposed by Ollis and Sutherland (10):



The possible synthesis of o-isopentenylphenols in mildly acidic, aqueous solutions by reactions modeled on the biogenetic proposals is an attractive route to these compounds. The mesomeric cation (I) required to effect alkylation can be generated from protonated γ,γ-dimethylallyl alcohol (IV) or, more conveniently, of 2-methylbut-3-en-2-ol (V).

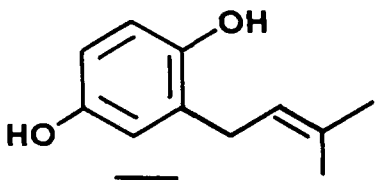


However, a recent attempt (11) to synthesize o-isopentenylphenols by condensation of phenols with (IV) and (V) in boiling aqueous citric acid solutions invariably gave cyclized products. Miller and Wood (12) similarly reported that S_N2-type condensations of phenols with γ,γ-dimethyl allyl diphenylphosphate and other allylic phosphate esters gave only cyclized products, viz., chromans and coumarans.

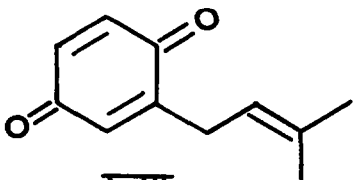
Reinvestigation of the aqueous acid catalyzed condensation of the allylic alcohols (IV) and (V) with the model phenol, p- cresol, has revealed that the nature of the product formed is determined largely by the temperature and time of reaction. In dilute aqueous formic or acetic acid solutions at room temperature the protonated alcohols react quite rapidly with the cresol to yield 2-isopentenyl-4-methylphenol. Protonation and subsequent cyclization of this compound to

yield the chroman is a relatively slow process and occurs to a significant extent only when the reaction is maintained at elevated temperatures for longer periods. As a result of these observations a number of phenols, including the nuclei most commonly found in natural products, have now been readily isopentenylated in aqueous solutions to yield pure o-isopentenylphenols.

An example of the general isopentenylation procedure is provided by the facile synthesis of 2-isopentenylhydroquinone (VI) and 2-isopentenylbenzoquinone (VII), both of which were recently isolated (4) from Phagnalon sexitale Cass.



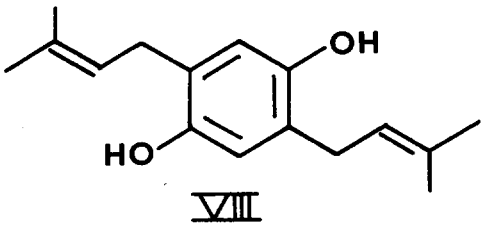
VI



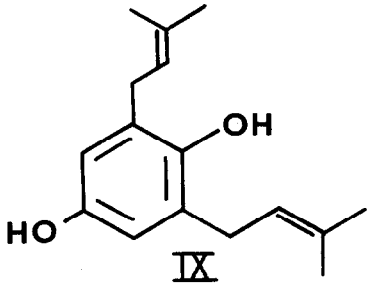
VII

2-Methylbut-3-en-2-ol (8.6 g; 1 mol. equiv.) was added dropwise to a stirred solution of hydroquinone (22 g; 2 mol. equiv.) in warm (80°) water (25.0 ml.) and formic acid (10.0 ml.), the temperature of the reaction solution being allowed to drop to room temperature during the addition. After stirring for an additional 30 minutes the product was precipitated with excess of water, dried and warmed with low boiling petroleum ether. The crystalline residue thereby obtained (7.2 g; m.p. 90-93°) consisted of a mixture of two substances. The minor constituent was easily separated by crystallization of the crude product from hot 50 percent aqueous methanol. The minor component crystallized from the warm solution and was recrystallized from benzene to yield colorless plates, m.p. 148° (0.70 g). The major reaction product crystallized from the aqueous methanol filtrate upon addition of excess water. Recrystallized from benzene it separated as colorless plates, m.p. 102° (5.7 g.) (Found: C, 74.2; H, 8.05. Calc. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.92.) The 100 MHz spectrum of this compound in $CDCl_3$ showed the presence of two allylic methyl groups (6 H, singlet at δ 1.75), a methylene group (2H, doublet at δ 3.27, J = 7.0 Hz), two hydroxyl protons (δ 4.70), a methine proton (1H, triplet at δ 5.27, J = 7.0 Hz) and three aromatic protons (3H, multiplet at δ 6.30-δ6.70). On the basis of this spectrum the product is clearly the non-cyclized monoprenylhydroquinone (VI), identical with the natural product (m.p. 102°). This structure assignment was confirmed by its formation of a crystalline dibenzoate (m.p. 102°) and its facile oxidation to a crystalline, yellow quinone, $C_{11}H_{12}O_2$, whose properties (m.p. 30°, and NMR spectrum) are identical with those described for the natural quinone (VII). The minor product (m.p. 148°) formed in this isopentenylation reaction has a molecular formula, $C_{16}H_{22}O_2$, and

its 100 MHz spectrum shows the presence of two γ,γ-dimethyllallyl groupings and two aromatic protons (singlet). This compound, therefore, is the diprenylhydroquinone (VIII) or (IX). Unequivocal evidence in favor of either one of these two possible structures has not been obtained.



VIII



IX

Isopentenylation of pyrogallol in dilute aqueous formic acid as described above has given the crystalline o-isopentenylpyrogallol (m.p. 97-98°; tribenzoate, m.p. 114°)which, heated with ethanolic HCl, cyclizes to the known chroman (m.p. 99°; dibenzoate, m.p. 152°). Isopentenylation of resorcinol under similar conditions yields an oily mixture (b.p. 140-145°/ 0.4 min.) containing about 20 percent and 80 percent of the isomeric o-isopentenyl-resorcinols and traces of cyclized products.

REFERENCES

1. R. Aneja, S. K. Mukerjee, and T. R. Seshadri, Tetrahedron 4, 256 (1958).
2. G. Cardillo, R. Cricchio, and L. Merlini, Tetrahedron 24, 4825 (1968).
3. A. C. Jain, P. Lal, and T. R. Seshadri, Indian J. Chem. 7, 1072 (1969).
4. F. Bohlmann and K. M. Kleine, Chem. Ber. 99, 885 (1966).
5. G. D. Daves, Jr., H. W. Moore, D. E. Schwab, R. K. Olsen, J. J. Wilczynski, and K. Folkers, J. Org. Chem. 32, 1414 (1967).
6. A. C. Jain, P. Lal, and T. R. Seshadri, Tetrahedron 26, 2631 (1970).
7. A. J. Birch, M. Maung, and A. Pelter, Aust. J. Chem. 22, 1923 (1969).
8. A. J. Birch, Fortschr, Chem. Org. Naturstoffe, 14, 186 (1957).
9. J. W. Cornforth and G. Popják, Tetrahedron Letters, No. 19, 29 (1959).
10. W. D. Ollis and I. O. Sutherland, "Isoprenoid units in natural phenolic compounds," in "Chemistry of Natural Phenolic Compounds" (Edited by W. D. Ollis) p. 47, Pergamon Press, Oxford (1961).
11. R. J. Molyneux and L. Jurd, Tetrahedron 26, 4743 (1970).
12. J. A. Miller and H. C. S. Wood, J. Chem. Soc. C, 1837 (1968).