α-Tocopherol: A New Synthesis and its Biosynthetic Implications

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RECENT experiments[1] have shown that 2,2-dialkylchromans can be synthesised from phenols and 3,3-dialkylallyl diphenyl phosphate esters (I). We now report the synthesis of α-tocopherol (II; R = $C_{16}H_{33}$), and of simple analogues, in yields which compare favourably with previous syntheses.[2,3]

2,3,5-Trimethylquinol (III), when heated at 100° with 3,3-dimethylallyl diphenyl phosphate (I; R = Me) forms a viscous red oil which, after chromatography on alumina and crystallisation, gives 6-hydroxy-2,2,5,7,8-pentamethylchroman (II; R = Me) (77%), m.p. 94–95° (lit.,[3] 94–95°).

When heated with geranyl diphenyl phosphate (I; R = 4-methylpent-3-enyl), 2,3,5-trimethylquinol (III) gives, after chromatography, a clear viscous oil identified as 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-enyl)chroman (II; R = C_6H_{11}) (27%); $\lambda_{max.}$ 293 mμ (ε, 4000) in EtOH; $\nu_{max.}$ 3497 (OH) and 1256 cm.$^{-1}$ (Ar–O–C);

[1] J. A. Miller and H. C. S. Wood, preceding communication.
[2] P. Karrer, H. Fritzsche, B. M. Ringier, and H. Salomon, *Helv. Chim. Acta*, 1938, **21**, 520, 820; F. Bergel, A. M. Copping, A. Jacob, A. R. Todd, and T. S. Work, *J.*, 1938, 1382.
[3] L. I. Smith, H. E. Ungnade, and W. W. Prichard, *Science*, 1938, **88**, 37.

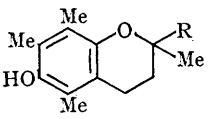
τ 4·9 ($Me_2C{=}CH{-}$) 5·6 (ArO*H*). The decrease in yield, compared with the above experiment, is due to a competitive reaction, in which geranyl diphenyl phosphate (I; R = 4-methylpent-3-enyl) decomposes spontaneously to give monoterpenoid hydrocarbons.[4]

When heated with the same quinol (III), phytyl diphenyl phosphate (I; R = $C_{16}H_{33}$) yields a red oil which, after chromatography on silica gel, gives a viscous, pale yellow oil, identified as racemic α-tocopherol (II; R = $C_{16}H_{33}$) (89%) by comparison of its spectroscopic properties (u.v., i.r., and n.m.r.) with published data.[5]

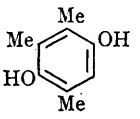
It has been suggested by Lynen[6] that, in the biosynthesis of the co-enzyme Q group, an isoprenoid allylic pyrophosphate ester reacts with a quinol precursor to give a dihydro-co-enzyme Q. If a similar mechanism were to operate in the biosynthesis of α-tocopherol then the experiments described above would provide a close laboratory analogy for the alkylation of a quinol precursor and subsequent cyclisation to a chroman derivative.

$(PhO)_2P(:O)O{\cdot}CH_2{\cdot}CH{=}CMeR$

(I)



(II)



(III)

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[4] J. A. Miller and H. C. S. Wood, *Angew. Chem.*, 1964, **76**, 301; *Internat. Edn.*, 1964, **3**, 310.
[5] M. Kofler, P. F. Sommer, H. R. Bolliger, B. Schmidli, and M. Vecchi, *Vitamins and Hormones*, 1962, **20**, 407.
[6] F. Lynen, *J. Cell. Comp. Physiol.*, 1959, **54**, *Suppl.* 1, 33.