258. *Studies on Vitamin E. Part V. Synthesis of Racemic α-Tocopherol and of a Lower Homologue.*

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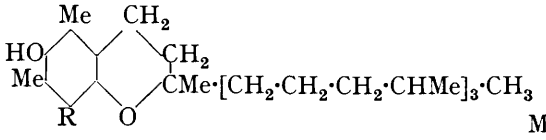
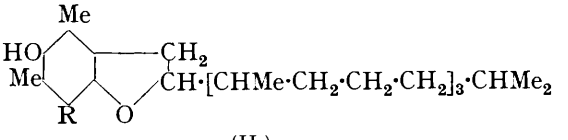
Racemic α-tocopherol may be synthesised by condensation of phytol with ψ-cumoquinol. When *m*-xyloquinol is used, a product is obtained which also has vitamin E activity and may be isomeric or identical with racemic β-tocopherol. The synthetic method does not, however, distinguish between a chroman or a coumaran type of structure for the tocopherols.

In the preceding paper we proposed for α-tocopherol the structure (I; R = Me) or (II; R = Me) (cf. also Fernholz, *J. Amer. Chem. Soc.*, 1938, **60**, 700; Karrer, Salomon, and Fritzsche, *Helv. Chim. Acta*, 1938, **21**, 309), β-tocopherol being regarded as differing from the α-compound by having only two methyl groups on the aromatic nucleus. Recently, Karrer, Fritzsche, Ringier, and Salomon (*ibid.*, p. 520) have reported the first synthesis of a substance having structure (I; R = Me) or (II; R = Me) by heating together phytyl bromide and ψ-cumoquinol in presence of zinc chloride, and they have now shown (*Nature*, 1938, **141**, 1057) that this material, giving an allophanate m. p. 172°, is indeed racemic α-tocopherol, since they have been able to resolve it by means of *d*-bromocamphorsulphonic acid and have obtained a product which they state is identical with the natural vitamin.



(I.)



(II.)

As announced in a preliminary note (Bergel, Jacob, Todd, and Work, *Nature*, 1938, **142**, 36), we have synthesised racemic α-tocopherol by a rather simpler method than that used above. Phytol can be directly condensed with ψ-cumoquinol by heating a mixture of the two substances, preferably in decalin solution, in presence of zinc chloride. The product has high vitamin E activity, but we have not yet resolved it into optical isomers. This synthesis, although fairly satisfactory as regards yield of product, is, like that of the Swiss workers, unsatisfactory in that it fails to distinguish between formulæ (I; R = Me) and (II; R = Me) for α-tocopherol. Karrer and his colleagues believe that their synthetic product has structure (II; R = Me) on the grounds that allyl bromide yields coumarans when condensed with phenols in presence of zinc chloride. Since phytyl bromide, however, is a γγ-dialkylallyl bromide, it seems to us that the argument is not necessarily valid, and it may well be that the synthetic product has a chroman structure. We are now engaged on the synthesis of the tocopherols by unequivocal methods in order to solve the problem finally. According to the view expressed in Part IV (preceding paper), β-tocopherol might have one of three isomeric structures derived severally from *o*-, *m*-, and *p*-xyloquinol and phytol. When phytol is condensed with *m*-xyloquinol, the product has properties similar to those of β-tocopherol. The condensation seems more difficult than in the case of ψ-cumoquinol. This product, which should have structure (I; R = H) or (II; R = H), has high vitamin E activity, and yields a crystalline *allophanate*, m. p. 148—149°, but whether or not it represents a racemic form of β-tocopherol can only be decided by resolution and by synthesis of the corresponding substances from *o*- and *p*-xyloquinol.

In preliminary experiments both of these synthetic " tocopherols " have shown a high degree of vitamin E activity, but it is not yet possible to state the minimum active dose. A series of biological experiments to this end is being made by one of us (A. M. C.), and the results will be reported elsewhere.

Experimental.

Condensation of Phytol with ψ-Cumoquinol.—(A). A mixture of phytol (1·0 g.), ψ-cumoquinol (0·7 g.), and anhydrous zinc chloride (0·3 g.) was heated rapidly to 180—190° and kept at this temperature during 15 minutes. The melt became brown, and a certain amount of ψ-cumoquinol sublimed out of the mixture. After cooling, the mixture was shaken with light petroleum (50 c.c.; b. p. 60—80°), decanted from zinc chloride, left overnight, filtered, and submitted to chromatographic analysis on activated aluminium oxide (Merck), being developed with light petroleum (b. p. 60—80°). The narrow brownish layer at the top of the column was discarded, as was the purplish lowest layer, and the broad middle portion, which was nearly colourless, was eluted with benzene–acetone–methyl alcohol (8 : 1 : 1). The yellowish oil obtained (200 mg.) reduced neutral silver nitrate on warming, and gave a bright yellow colour with a mixture of concentrated sulphuric and glacial acetic acids. On pyrolysis at about 360°, a crystalline product, m. p. *ca.* 215°, was obtained having the properties of duroquinol; oxidation with ferric chloride gave a quinone, m. p. 101—103°, a mixture of which with duroquinone (m. p. 106—108°) melted at 104—106°.

Treatment with cyanic acid in benzene solution gave an allophanate, m. p. 169—170°, identified by mixed m. p. (169—171°) with the allophanate (m. p. 170—171°) obtained by following the method of Karrer, Fritzsche, Ringier, and Salomon (*loc. cit.*) (Found: C, 71·9; H, 10·1; N, 5·3. Calc. for $C_{31}H_{52}O_4N_2$: C, 72·0; H, 10·2; N, 5·4%). The absorption spectrum of the allophanate (max. 2860 A.; min. 2520 A.) was almost identical with that of α-tocopheryl allophanate, and that of the oily alcohol obtained on hydrolysis (max. 2980 A.; min. 2600 A.) was almost identical with that of α-tocopherol itself.

(B). A mixture of phytol (1 g.), ψ-cumoquinol (0·52 g.), anhydrous zinc chloride (0·5 g.), and decalin (10 c.c.) was heated to 200° for 30 minutes, then for a further 4 hours at 160—180°; it was then cooled, diluted with light petroleum (b. p. 60—80°), filtered, and subjected to chromatographic analysis as above. The oil obtained (350 mg.) gave the same allophanate as that described above.

m-*Xyloquinol.*—*m*-Xylenol (7·8 g.) was dissolved in a solution of sodium hydroxide (12·5 g.) in water (375 c.c.), and powdered potassium persulphate (15 g.) added in small portions with shaking. The solution became slightly warm and developed a brown colour. After standing for 2 days at 37°, it was made slightly acid with hydrochloric acid, neutralised with sodium bicarbonate, and unchanged *m*-xylenol blown off with steam. The residue was made strongly acid, boiled for a few minutes, cooled, extracted thoroughly with ether, and the extracts dried

and evaporated. The solid residue, recrystallised from xylene, gave *m*-xyloquinol, m. p. 150—151° (lit., m. p. 149°).

Condensation of Phytol with m-*Xyloquinol.*—Phytol (1 g.), *m*-xyloquinol (0·46 g.), decalin (7·0 c.c.), and anhydrous zinc chloride (0·5 g.) were refluxed gently during 6 hours, a further amount (0·5 g.) of zinc chloride being added after 3 hours' heating, and worked up in the manner employed in the ψ-cumoquinol condensation. The product was a yellowish oil (450 mg.), which reduced neutral silver nitrate on warming and gave a bright yellow colour with a mixture of concentrated sulphuric and glacial acetic acids. On pyrolysis at about 360°, it gave a crystalline distillate, m. p. 168—170°, identified as ψ-cumoquinol by m. p. and mixed m. p. Treatment with cyanic acid in benzene solution gave an allophanate, m. p. 148—149°, having an absorption spectrum (max. 2860 A.; min. 2520 A.) closely similar to that of the tocopheryl allophanates and giving on hydrolysis an oily alcohol spectroscopically (max. 2980 A.; min. 2620 A.) very similar to the tocopherols. The same *allophanate*, m. p. and mixed m. p. 148—149°, was obtained by substituting *m*-xyloquinol for ψ-cumoquinol in the process used by the Swiss workers (*loc. cit.*) (Found: C, 71·8; H, 10·1; N, 5·4. $C_{30}H_{50}O_4N_2$ requires C, 71·7; H, 10·0; N, 5·6%).

We have to thank Messrs. Hoffmann-La Roche & Co. and Messrs. Glaxo Laboratories Ltd. for their assistance, and the Medical Research Council for a grant to one of us (A. M. C.).

THE LISTER INSTITUTE LONDON, S.W. 1. [*Received, July 1st,* 1938.]