375. *Tocopherols. Part II.* Synthesis of Tocol*

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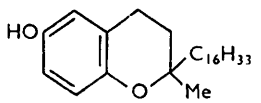
A simple synthesis of tocol is described and details of a colorimetric assay are given.

For syntheses of 5- and 7-methyltocol (ε- and η-tocopherol) (cf. 16th Internat. Congr. Pure Appl. Chem., Paris, July, 1957), a quantity of tocol (I) was required. Pendse and Karrer [1] recently described a preparation of tocol by one-stage reaction from quinol with phytol, and this prompts us to record our own work.

Attempts to repeat the synthesis by Jacob *et al.*[2] showed that it was unsatisfactory. We found, however, that quinol monomethyl or monobenzyl ether reacted smoothly with phytol in formic acid–benzene, to give the tocol ethers in moderate yield. These were purified by distillation and their structures were confirmed by light-absorption data. Acid cleavage afforded tocol concentrates as pale yellow oils which were assayed by the chromatographic method of Green, Marcinkiewicz, and Watt.[3] Later experiments showed that protection of one of the hydroxyl groups was unnecessary, and tocol was prepared by direct condensation of phytol with quinol in benzene–formic acid: double chromans and phytyl-substituted tocols of the type postulated by Smith and Ungnade [4] were not readily formed as by-products in these condensations, suggesting that tocol is less reactive than the methylated tocols.



(I)

As found in the preparation of other tocols by this route,[5] and contrary to the practice of Karrer and his co-workers,[6] it was unnecessary to treat the crude product with sodium methoxide in methanol before isolation. A 79% tocol concentrate, in 37% overall yield, was obtained by distillation of the crude product, from which the crystalline 3 : 5-dinitrophenylurethane and 4-phenylazobenzoate were readily prepared. Saponification of the latter derivative with potassium hydroxide in ethanol afforded pure tocol. The methyl and benzyl ethers were made from pure tocol and analytical and light-absorption data obtained.

Attempts to introduce a methyl or potential methyl group into the tocol molecule by (*a*) formaldehyde and hydrogen chloride in ether, (*b*) paraformaldehyde, hydrogen chloride, phosphoric and acetic acids, (*c*) formaldehyde and aqueous sodium hydroxide, and (*d*) dimethylformamide and phosphorus oxychloride, failed. Pendse and Karrer [1] also failed to convert tocol into formyltocol by the usual methods. These results confirm the lower reactivity of tocol than of the methylated homologues, which readily take part in reactions of this type.

The oxidation of tocol by ferric chloride in ethanol, in the presence of 2 : 2′-dipyridyl, was also different from the reaction of other tocopherols. The tocol samples were analysed colorimetrically by Eggitt and Ward's micro-procedure [7] as modified by Green *et al.*,[3] in which 20—100 μg. are oxidised by a large excess of ferric chloride in high concentration. This oxidation required about 80 minutes for completion, compared with 2 minutes (at most) for all the methylated tocols. This is no doubt related to the lack of nuclear reactivity,

* Part I, *J.*, 1958, 1600.

[1] Pendse and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1837.
[2] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327.
[3] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[4] Smith and Ungnade, *J. Org. Chem.*, 1939, **4**, 1298.
[5] Mamalis, Green, McHale, and Marcinkiewicz, unpublished work.
[6] Karrer and Fritzsche, *Helv. Chim. Acta*, 1938, **21**, 1234; 1939, **22**, 260; Karrer, Fritzsche, and Escher, *ibid.*, p. 661; Karrer, Koenig, Ringier, and Salomon, *ibid.*, p. 1139; Karrer and Leiser, *ibid.*, 1944, **27**, 678; Karrer and Kugler, *ibid.*, 1945, **28**, 436; Karrer and Dutta, 1948, **31**, 2080.
[7] Eggitt and Ward, *J. Sci. Food Agric.*, 1953, **4**, 176.

particularly at position 5, exemplified above. The diminished oxidation rate of the tocols, as nuclear methyl groups are removed, has already been noted by Stern and Baxter,[8] who found that 8-methyltocol (δ-tocopherol) only reacted completely, under their conditions, in 10 min., compared with 2·5 min. for 5 : 7 : 8-trimethyl-, 5 : 8-dimethyl- and 7 : 8-dimethyl-tocol (under our oxidation conditions, even 8-methyltocol reacts completely within 2 min.). The final stable spectrophotometric factor [7] of tocol is 75·2, identical with that found for 8-methyltocol in a 2 min. reaction; thus, in spite of the rate difference, both oxidations probably follow a similar course. The oxidation of 8-methyltocol has already been shown by Eggitt and Norris [9] to differ from that of more methylated tocols.

Experimental

All tocol assays were carried out by the method of Green *et al.*,[3] with reaction for 100 min.

Tocol Methyl Ether.—Quinol monomethyl ether (2·93 g.), phytol (7·0 g.), dry benzene (50 ml.), and anhydrous formic acid (50 ml.) were heated under reflux for 4 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, dried, and evaporated to give a straw-coloured oil (9·2 g.). Distillation afforded a pale yellow oil (5·1 g.), b. p. 195—205°/0·04 mm. This was redistilled in a micromolecular still, giving almost pure *tocol methyl ether*, b. p. 150° (bath)/5 × 10^{-4} mm. (Found: C, 80·0; H, 11·0. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%), $\lambda_{max.}$ 295 mμ ($E^{1\%}_{1cm.}$ 85·6), $\lambda_{min.}$ 255 mμ in EtOH.

Tocol-3 : 5-dinitrophenylurethane from Tocol Methyl Ether.—Tocol methyl ether (5·0 g.) was heated with hydrogen bromide in acetic acid (50 ml. of 43% w/v solution), acetic acid (50 ml.), and concentrated hydrochloric acid (10 ml.) for 6 hr. The cooled mixture was diluted with water and extracted with ether, the extracts were washed with saturated sodium hydrogen carbonate and water, then dried. Evaporation left a brown oil, which was distilled, giving a fraction (3·8 g.), b. p. 200—220°/0·1 mm (82% of tocol). This tocol concentrate (1·0 g.) in dry toluene (15 ml.) was heated with 3 : 5-dinitrobenzazide (0·83 g.) for 1 hr. After removal of solvent, the orange-red oil was diluted with light petroleum (10 ml.; b. p. 40—60°), and the insoluble dinitrophenylurea separated. The filtrate was again evaporated and the *dinitrophenylurethane* crystallised from aqueous ethanol as prismatic yellow needles (0·5 g.), m. p. 97° (Found: C, 66·3; H, 7·9; N, 6·9. $C_{33}H_{47}O_7N_3$ requires C, 66·3; H, 7·9; N, 7·0%).

Tocol from Quinol Monobenzyl Ether.—Quinol monobenzyl ether (1·0 g.), formic acid (10 ml.), and dry benzene (6 ml.) were heated under reflux while phytol (1·5 g.) in benzene (6 ml.) was added during 15 min., then the whole was heated further for 5½ hr. The benzene layer was separated, washed with N-sodium hydroxide followed by water, dried, and evaporated. Distillation of the resulting oil gave the benzyl ether concentrate as a yellow oil (2·0 g.), b. p. 190—200° (bath)/0·05 mm., which was shown by assay to contain a relatively large proportion of free tocol (27%) arising by fission of the ether. The distillate in ethanol (15 ml.) was shaken with hydrogen and 10% palladised charcoal till hydrogen uptake ceased (*ca.* 1 hr.), and the product isolated and distilled in a micromolecular still as a pale yellow oil (1·4 g.), b. p. 130—140° (bath)/10^{-3} mm. (57% of tocol). This material was suitable for conversion into solid derivatives.

Tocol from Quinol.—Quinol (4·4 g.), phytol (11·8 g.), formic acid (60 ml.), and dry benzene (60 ml.) were heated on the steam-bath under nitrogen for 4 hr. The benzene layer was separated, the acid layer was extracted with benzene, and the combined benzene solutions were worked up in the usual way. Removal of the solvent left a light brown oil (13·6 g.), which was distilled, giving tocol concentrate (7·4 g.), b. p. 200—220°/0·05 mm. (assay, 79%; overall yield 37%). Paper chromatography showed the product to be free from other reducing material. A mixture of the concentrate (7·4 g.) and dry pyridine (11 ml.) in dry chloroform (50 ml.) was treated with 4-phenylazobenzoyl chloride (5·6 g.) in portions and heated on the steam-bath for 2 hr. Water (5 ml.) was added to the cooled mixture and after 5 minutes' shaking the product was taken up in light petroleum (b. p. 40—60°), and excess of 4-phenylazobenzoic acid was removed by filtration. The organic layer was washed with 2N-hydrochloric acid, then

[8] Stern and Baxter, *Analyt. Chem.*, 1947, **19**, 902.
[9] Eggitt and Norris, *J. Sci. Food Agric.*, 1956, **7**, 493.

water, and evaporated to yield a non-reducing red oil (11·2 g.). *Tocol 4-phenylazobenzoate* crystallised from aqueous propan-2-ol as orange needles which reddened on storage (5·0 g.), m. p. 35—37°. A further crystallisation raised the m. p. to 37—38° (Found: C, 77·9; H, 8·7; N, 4·4. $C_{39}H_{52}O_3N_2$ requires C, 78·4; H, 8·7; N, 4·7%). The combined crystallisation mother-liquors were concentrated, to give a semi-solid product which after saponification (see below) contained about 95% of tocol.

Crystalline tocol phenylazobenzoate (1·22 g.) in boiling ethanol (25 ml.) was treated with potassium hydroxide (1·2 g., added rapidly down the condenser) and heated for 30 min. To the refluxing solution, concentrated hydrochloric acid (3·5 ml.) was added, and the mixture cooled, treated with water (20 ml.) and light petroleum (b. p. 40—60°; 30 ml.), and filtered. The insoluble 4-phenylazobenzoic acid was rejected, and the organic layer washed with water, dried and evaporated to furnish a yellow oil (0·79 g.). Micromolecular distillation gave tocol as an almost colourless oil (0·69 g.), b. p. 130° (bath)/5 × 10^{-4} mm. (Found: C, 80·5; H, 11·5. Calc. for $C_{26}H_{44}O_2$: C, 80·4; H, 11·4%), $\lambda_{max.}$ 298·5 mμ ($E^{1\%}_{1\,cm.}$ 97), $\lambda_{min.}$ 255 mμ in EtOH, $\nu_{max.}$ 3375 s, 2915 vs, 1615 w, 1490 vs, 1450 vs, 1375 s, 1348 m, 1319 m, 1285 m, 1217 vs, 1152 s, 1106 m, 971 m, 930 m, 909 m, 883 m, 861 m, 811 m, 790 m cm.$^{-1}$ (liquid film).

Tocol Ethers from Tocol.—(a) *Tocol methyl ether.* Tocol (0·75 g.; regenerated from the phenylazobenzoate) in acetone (10 ml.) was treated successively with dimethyl sulphate (0·5 g.) and 30% aqueous sodium hydroxide (0·66 ml.), then shaken for 2 hr. at room temperature. Aqueous ammonia (1·0 ml.; *d* 0·880) was added, followed by water and light petroleum (b. p. 40—60°), the mixture separated, and the organic layer washed with water, dried, and evaporated. The residual oil was taken up in a small volume of 20 : 1 light petroleum (b. p. 40—60°)–benzene, and poured on a column of alumina (Peter Spence type " O," 6 × 1 cm.), and the methyl ether eluted with the same solvent mixture (100 ml.). Evaporation of the solvent yielded a pale yellow non-reducing oil (0·51 g.) which was distilled in a micromolecular still [b. p. 130—140° (bath)/5 × 10^{-4} mm.] as an almost colourless oil (Found: C, 80·8; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%), $\lambda_{max.}$ 295 mμ ($E^{1\%}_{1\,cm.}$ 87·3), $\lambda_{min.}$ 259 mμ in EtOH, $\nu_{max.}$ 2890 vs, 1613 w, 1490 vs, 1460 s, 1430 m, 1375 m, 1319 m, 1299 m, 1269 n, 1218 m, 1099 s, 948 m, 896 m, 881 w, 858 w, 844 m, 813 m, 802 m cm.$^{-1}$ (liquid film).

(b) *Tocol benzyl ether.* Tocol (0·5 g.; regenerated from the phenylazobenzoate) in acetone (25 ml.) was shaken with benzyl bromide (0·90 ml.) and 4N-sodium hydroxide (1·8 ml.) at room temperature for 2 hr. The mixture was acidified with 2N-hydrochloric acid and extracted with light petroleum (b. p. 40—60°), and the extracts were washed with water. Distillation of the oil remaining after removal of solvent furnished *tocol benzyl ether* as a pale yellow viscous non-reducing oil, b. p. 150°(bath)/5 × 10^{-4} mm. (Found: C, 80·7, H, 11·0. $C_{33}H_{50}O_2$ requires C, 81·0; H, 10·5%), $\lambda_{max.}$ 296 mμ ($E^{1\%}_{1\,cm.}$ 88·5), $\lambda_{min.}$ 261 mμ in EtOH, $\nu_{max.}$ 3413 w, 2910 vs, 1720 w, 1610 w, 1500 vs, 1460 s, 1374 s, 1312 m, 1271 s, 1220, s, 1149 s, 1099 m, 1080 m, 1042 m, 1026 m, 948 w, 909 m, 885 w, 862 m, 842 m, 813 m, 779 w cm.$^{-1}$ (liquid film).

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