681. *Tocopherols. Part VI.* A Novel Synthesis of 8-Methyltocol.*

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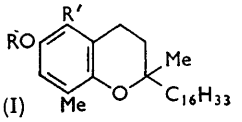
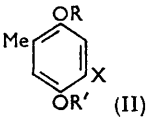
Racemic 8-methyltocol has been synthesised by two routes, one of which also gives 7-methyltocol.

8-Methyltocol (δ-tocopherol) (I; R = R′ = H), isolated from soybean oil by Stern, Robeson, Weisler, and Baxter,[1] had similar properties to a monomethyltocol previously prepared from phytol and toluquinol 4-benzoate (II; R = X = H, R′ = Bz) by Jacob, Sutcliffe, and Todd.[2] Mamalis, Green, Marcinkiewicz, and McHale [3] observed that the toluquinol 4-benzoate was contaminated with the 1-benzoate (II; R′ = X = H, R = Bz) and that this probably accounted for the report [4] that 7-methyltocol was a product of the condensation of phytol with the 4-benzoate. The presence of 7-methyltocol in the synthetic 8-methyltocol would also explain the variation [1] in the melting point of the 2,6-dimethylquinols derived by pyrolysis from synthetic 8-methyltocol and from natural 8-methyltocol. The 7-methyltocol would yield 2,5-dimethylquinol which would not have separated readily from 2,6-dimethylquinol. Although the use of pure toluquinol 4-benzoate gave 8-methyltocol free from isomers, the yield was poor and the purification difficult. An alternative synthesis was therefore sought.



(I)



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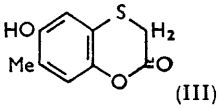

(III)

Because of the difficulty of separating isomeric mixtures of the monomethyltocols, neither the condensation [5] of toluquinol with phytol to give a mixture of 5-, 7-, and 8-methyltocol, nor the condensation [6] of 5-methylthiotoluquinol (II; R = R′ = H, X = SMe) with phytol, which gave a mixture of 5- and 8-methyltocol, afforded a satisfactory route to pure 8-methyltocol. Since the condensation of pure toluquinol 4-benzoate with phytol gave 8-methyltocol, free from isomers, it was thought that esterification of the 4-hydroxyl group of a 5-alkylthiotoluquinol (II; R = R′ = H, X = SAlk) might prevent formation of 5-methyltocol during the condensation with phytol. 5-Bromotoluquinol (II; R = R′ = H, X = Br) [7] was readily converted into 5-mercaptotoluquinol (II; R = R′ = H, X = SH) by refluxing alcoholic sodium sulphide. This method was superior to that used by Karrer and Dutta.[6] Treatment of the thio-compound with chloroacetic acid gave 5-carboxymethylthiotoluquinol (II; R = R′ = H, X = S·CH_2·CO_2H), which was cyclised to the benzo-1,4-oxathiinone (III) at 180°. Condensation of this compound with phytol, subsequent desulphurisation with Raney nickel, and hydrolysis gave a product containing 20% of 8-methyltocol. Chromatography followed by molecular distillation gave pure 8-methyltocol, with infrared spectrum identical with that of natural δ-tocopherol. Stern *et al.*[1] found that the *p*-phenylazobenzoate of natural δ-tocopherol was a low-melting solid; in view of its racemic nature it was not surprising, therefore, that the *p*-phenylazobenzoate of synthetic 8-methyltocol was an oil at ordinary temperatures.

Because it was thought that the low yields obtained in the preparation of 8-methyltocol from toluquinol 4-benzoate were due to the deactivating influence on the ring of the benzoyloxy-group, the condensation of toluquinol 4-methyl ether (II; R = X = H, R′ = Me) with phytol was examined, the necessary ether being obtained together with

* Part V, preceding paper.

[1] Stern, Robeson, Weisler, and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 869.
[2] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327.
[3] Mamalis, Green, Marcinkiewicz, and McHale, *J.*, 1959, 3350.
[4] Pendse and Karrer, *Helv. Chim. Acta*, 1958, **41**, 396.
[5] Marcinkiewicz, McHale, Mamalis, and Green, following paper.
[6] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[7] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.

toluquinol dimethyl ether (II; R = R′ = Me, X = H) by the partial methylation of toluquinol. Contrary to expectation, the demethylated product from the condensation of toluquinol 4-methyl ether and phytol consisted of two parts of 7- and one part of 8-methyltocol; and, because the 4-hydroxyl group was blocked by a methyl group, the 7-methyltocol must have been present, before demethylation, as the open-chain 4-methoxy-phenol (II; R = H, R′ = Me, X = CH_2·CH:CMe·$C_{16}H_{33}$), and the 8-methyltocol as a methyl ether (I; R = Me, R′ = H). These two compounds were separated by selective adsorption on alumina, and purified by distillation, and demethylated to 7- and 8-methyltocol.

The high-boiling residue from the distillation of 8-methyltocol methyl ether, on molecular distillation, gave a viscous oil that gave correct analytical results for a phytyl-substituted 8-methyltocol methyl ether, probably of structure (I; R = Me, R′ = CH_2·CH:CMe·$C_{16}H_{33}$).

Experimental

All tocopherol assays were carried out as described by Green, Marcinkiewicz, and Watt.[8]

5-Mercaptotoluquinol (II; R = R′ = H, X = SH).—5-Bromotoluquinol [7] (20 g.) and sodium sulphide (30 g.) in 95% ethanol were refluxed for 2 hr. and then acidified (concentrated hydrochloric acid) at the b. p. The mixture was cooled and diluted with ether, and the ethereal solution washed several times with water, dried, and evaporated. The solid obtained was dried *in vacuo* over calcium chloride. Crystallisation from water gave 5-thiotoluquinol (10·8 g.), m. p. 186—188° (Found: C, 53·6; H, 4·8; S, 20·4. Calc. for $C_7H_8O_2S$: C, 53·8; H, 5·2; S, 20·5%).

5-Carboxymethylthiotoluquinol (II; R = R′ = H, X = S·CH_2·CO_2H).—5-Mercaptotoluquinol (7·3 g.) and chloroacetic acid (4·7 g.) in ether were shaken for 2 hr. with a solution of sodium carbonate (5·2 g.) in water (50 ml.) containing sodium dithionite (1 crystal). The aqueous layer was separated, acidified with concentrated hydrochloric acid, and extracted with ether. The extract was dried and evaporated to give *5-carboxymethylthiotoluquinol* (8·2 g.), m. p. 168—170° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 50·4; H, 4·6; S, 15·1. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7; S, 15·0%).

2,3-Dihydro-6-hydroxy-7-methylbenzo-1,4-oxathiin-2-one (III).—5-Carboxymethylthiotoluquinol (0·8 g.) was heated at 180° for 1 hr. Crystallisation of the product from benzene gave the *benzoxathiinone* (0·6 g.), m. p. 163—164° (Found: C, 55·0; H, 3·9; S, 16·2. $C_9H_8O_3S$ requires C, 55·1; H, 4·1; S, 16·3%).

8-Methyltocol (I; R = R′ = H).—The benzoxathiinone (5·0 g.), phytol (7·5 g.), benzene (50 ml.), and anhydrous formic acid (50 ml.) were heated under reflux for 14 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and concentrated to an oil (7·3 g.) which was taken up in ethanol (200 ml.) and refluxed for 8 hr. with Raney nickel (7 g.). After the mixture had cooled, it was filtered through Hyflo Super-cel. The filtrate was heated to the boil and potassium hydroxide (2·5 g.) added through the condenser. After 20 min. concentrated hydrochloric acid (5 ml.) was added to the refluxing solution. The organic layer was diluted with light petroleum (b. p. 40—60°), washed with water and saturated aqueous sodium hydrogen carbonate, and concentrated to an oil (5·9 g.) which contained 22% of 8-methyltocol. This concentrate was adsorbed from light petroleum (b. p. 40—60°) on alumina (Peter Spence type " O "; 50 g.). After elution of the impurities with light petroleum, followed by benzene, the tocol was eluted with ether. Evaporation gave a pale brown oil (0·9 g.) which contained 91% of 8-methyltocol (by assay). Molecular distillation [150° (bath)/10^{-3} mm.] gave pure 8-methyltocol, $\nu_{max.}$ 3360 m, 2915 vs, 1605 w, 1460 vs, 1375 s, 1340 m, 1295 m, 1210 s, 1145 m, 1100 w, 1040 w, 990 m, 938 m, 855 m, 795 w, 717 m cm.$^{-1}$ (liquid film).

8-Methyltocol p-Phenylazobenzoate.—8-Methyltocol (91% concentrate; 0·15 g.) in dry ethylene dichloride (5 ml.) containing pyridine (1 ml.) was treated with *p*-phenylazobenzoyl chloride (0·15 g.) in dry ethylene dichloride (5 ml.) and refluxed for 1 hr. Water (5 ml.) was added, after 1 hr. the product was taken up in light petroleum (b. p. 40—60°), and the solution washed with dilute hydrochloric acid and then with water. The organic layer was filtered and concentrated, the oil was redissolved in light petroleum, and the solution filtered and concentrated. The red oil (0·2 g.) on distillation [250° (bath)/10^{-3} mm.] gave the *p-phenylazobenzoate* (Found: C, 78·3; H, 9·0; N, 4·8. $C_{40}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

[8] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.

Toluquinol 4-Methyl Ether (II; R = X = H, R′ = Me).—Methyl iodide (20 ml.) was added rapidly to a stirred mixture of toluquinol (12·4 g.), anhydrous potassium carbonate (13·8 g.), and acetone (30 ml.), and the whole refluxed for 4 hr. Steam-distillation gave an oil (6·7 g.) which was taken up in ether and extracted into N-sodium hydroxide. The alkaline extract was acidified and extracted with ether. Evaporation of the dried extract gave toluquinol 4-methyl ether (3·3 g.), m. p. 72°, from ether–light petroleum (b. p. 40—60°) (Bamberger [9] gave m. p. 70·5—71·5°). The dried alkali-insoluble extract on evaporation gave toluquinol dimethyl ether (2·3 g.), n_D^{19} 1·5210.

Condensation of Toluquinol 4-Methyl Ether with Phytol.—Toluquinol 4-methyl ether (7 g.), phytol (15 g.), dry benzene (75 ml.), and anhydrous formic acid (75 ml.) were heated under reflux for 6 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and concentrated to a straw-coloured oil (19·5 g.). A sample (1·0 g.) was refluxed for 3 hr. with hydrobromic acid (5 g.) in acetic acid (15 ml.), then diluted with light petroleum (b. p. 40—60°) and washed successively with water, saturated aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water. Evaporation gave a pale brown oil which contained 22% of 7-methyltocol and 13·6% of 8-methyltocol.

The remainder of the original oil was taken up in light petroleum (b. p. 40—60°; 50 ml.) and adsorbed on alumina (Peter Spence type " O "; 120 g.). Elution gave the following fractions: (1), 5·0 g., n_D^{19} 1·4887, (2) 5·8 g., n_D^{20} 1·4880, both eluted by light petroleum; (3), 4·2 g., n_D^{20} 1·5028, eluted by benzene; (4), 1·3 g., n_D^{18} 1·4865; and (5), 0·4 g., n_D^{24} 1·5150 both eluted by ether. Distillation of fraction (1) gave three fractions: (1a), 1·0 g., b. p. 120—130°/0·1 mm., n_D^{18} 1·4761; (1b), 0·7 g., b. p. 130—180°/0·1 mm., n_D^{20} 1·4869; and (1c), 2·5 g., b. p. 200—210°/0·1 mm. Fraction (1c) was refluxed for 3 hr. with hydrobromic acid (7·5 g.) in acetic acid (20 ml.), and the product, worked up as above, gave a pale brown oil (2·5 g.) which contained 32% of 8-methyltocol. Further purification was carried out by adsorption from light petroleum (b. p. 40—60°) on alumina (Peter Spence type " O "; 50 g.). After development with light petroleum followed by benzene, the tocol was eluted with ether. Evaporation gave a pale brown oil (0·8 g.), which after distillation [150° (bath)/10^{-3} mm.] gave pure 8-methyltocol as a pale yellow viscous oil.

Fraction (2) on distillation gave three fractions: (2a) a yellow mobile oil (1·0 g.), b. p. 150—180°/0·1 mm., n_D^{19} 1·4729; (2b) a viscous yellow oil (1·9 g.), b. p. 210°/0·1 mm., n_D^{19} 1·4955; (2c) a viscous yellow oil (1·4 g.), b. p. 220°/0·1 mm., n_D^{19} 1·5000. Fraction (2b) was refluxed for 3 hr. with hydrobromic acid (5 g.) in acetic acid (15 ml.), and the product worked up in the usual way to give a pale brown oil (1·7 g.), which contained 14·5% of 7-methyltocol and 25% of 8-methyltocol.

Fraction (2c) was dissolved in ethanol (20 ml.) and shaken with hydrogen and palladised charcoal till hydrogen uptake ceased. After filtration and evaporation the resulting oil was refluxed for 3 hr. with hydrobromic acid (5 g.) and acetic acid (15 ml.), and the product isolated in the usual way. Paper-chromatographic assay showed that the product contained 12·5% of 8-methyltocol and some reducing material which remained on the origin-line and was presumably the quinol derived from the reduced methoxy-phenol (II; R = H, R′ = Me, X = $[CH_2]_2{\cdot}CHMe{\cdot}C_{16}H_{33}$).

The residues from the distillation of fractions (1) and (2) were combined and distilled [220° (bath)/10^{-3} mm.], giving a pale yellow, viscous oil which was presumably *8-methyl-5-phytyltocol methyl ether* (I; R = Me, R′ = $CH_2{\cdot}CH{:}CMe{\cdot}C_{16}H_{33}$) (Found: C, 83·0; H, 12·5. $C_{48}H_{86}O_2$ requires C, 82·9; H, 12·4%).

Fraction 3 distilled as a yellow mobile oil (3·8 g.), b. p. 220°/0·1 mm. Distillation [190° (bath)/10^{-3} mm.] gave pure *5-phytyltoluquinol 4-methyl ether* (II; R = H, R′ = Me, X = $CH_2{\cdot}CH{:}CMe{\cdot}C_{16}H_{33}$), n_D^{19} 1·5030 (Found: C, 80·6; H, 11·2. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). This compound (3·6 g.) was refluxed for 8 hr. with hydrobromic acid (15 g.) in acetic acid (45 ml.) and, on isolation in the usual way, gave a red oil (3·5 g.) which contained 78% of 7-methyltocol and could not be further purified by molecular distillation.

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[9] Bamberger, *Annalen*, 1912, **390**, 174.