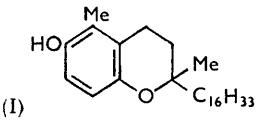
679. *Tocopherols. Part IV.*[1] *Synthesis of 5-Methyltocol.*

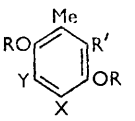
By D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green.

Racemic 5-methyltocol has been synthesised by an unambiguous route.

During paper-chromatographic analysis of the tocopherol fraction from wheat-germ oil, Brown [2] observed a spot that reduced Emmerie and Engel's reagent,[3] but failed to couple with diazotised *o*-dianisidine. Eggitt *et al.*, by reason of its chromatographic behaviour [4] and a number of other reactions,[5] suggested that the spot was due to 5-methyltocol (I) and used the name ε-tocopherol for the substance.



(I)



(II)

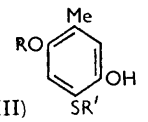
Karrer and Fritzsche [6] condensed toluquinol with phytol and obtained a mixture which was later shown by Marcinkiewicz, McHale, Mamalis, and Green [7] to contain 5-, 7-, and 8-methyltocol. Karrer and Dutta [8] tried to prevent the formation of these isomeric mixtures by condensing phytol with a methylthio-toluquinol, the methylthio-group being removed subsequently by Raney nickel. Two routes were used for the preparation of the methylthio-compounds but both led to a mixture of the same two isomers. One of these isomers was shown to be 5-methylthiotoluquinol (II; R = R′ = Y = H, X = SMe), which when condensed with phytol and desulphurised gave the expected mixture of 5- and 8-methyltocol. The other isomer when similarly treated gave a methyltocol whose *p*-phenylazobenzoate melted at 46—47°. A mixture with a specimen of the *p*-phenylazobenzoate that Stern, Robeson, Weisler, and Baxter [9] obtained from natural 8-methyltocol (δ-tocopherol) melted without depression, although their compound melted several degrees lower. This led Karrer and Dutta to assume that their synthetic compound was 8-methyltocol and that the methylthio-compound, from which it was derived, was 3-methylthiotoluquinol (II; R = X = Y = H, R′ = SMe). By using the paper-chromatographic technique [10] to identify the products, our repetition of this work showed that the " so-called " 8-methyltocol, synthesised by Karrer and Dutta, was in fact a mixture of 5- and 7-methyltocol and, therefore, that the methylthio-compound was 6-methylthiotoluquinol (II; R = R′ = X = H, Y = SMe) and not 3-methylthiotoluquinol as supposed.

Because of the difficulty in separating mixtures of monomethyltocols none of these earlier routes was suitable for the preparation of pure 5-methyltocol. An alternative approach was therefore considered, of using a type of blocked compound that, if the route were successful, would give only one isomer. Karrer and Dutta attempted to prevent formation of mixtures in the synthesis of the monomethyltocols by condensing phytol with a bismethylthiotoluquinol; although they obtained the bismethylthiomethyltocol they were unable to convert it into the monomethyltocol. It was shown in Part III [1] that when the 1-hydroxy-group of toluquinol was blocked by a benzyl group no condensation occurred at position 6, only 5- and 7-methyltocol being formed. Therefore, it was thought that

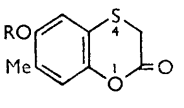
[1] Part III, preceding paper.
[2] Brown, *Biochem. J.*, 1952, **51**, 237; 1952, **52**, 523.
[3] Emmerie and Engel, *Rec. Trav. chim.*, 1938, **57**, 1351.
[4] Eggitt and Ward, *J. Sci. Food Agric.*, 1953, **4**, 569.
[5] Eggitt and Norris, *ibid.*, 1955, **6**, 689; 1956, **7**, 493.
[6] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[7] Marcinkiewicz, McHale, Mamalis, and Green, *J.*, 1959, 3377.
[8] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[9] Stern, Robeson, Weisler, and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 869.
[10] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **5**, 274.

condensation of phytol with a 5-alkylthiotoluquinol 1-alkyl ether (III) would lead to 5-methyltocol. If the deactivating influence of the ether group was insufficient to prevent condensation occurring *ortho* to it, the product, an alkoxyphenol, would be separable by chromatography from the other condensation product, a substituted methyltocol ether.

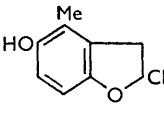
Methylation of 2,3-dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one (IV; R = H)[11] gave the 6-methoxy-compound (IV; R = Me), which was reduced by lithium aluminium hydride to 5-2′-hydroxyethylthiotoluquinol 1-methyl ether (III; R = H, R′ = CH_2·CH_2·OH). The condensation of this compound with phytol gave only a low yield, most of the methyl ether being recovered, and all attempts to improve the yield failed. The product, after desulphurisation with Raney nickel and demethylation with hydrobromic acid in acetic acid, gave an oil, which after chromatography and molecular distillation assayed as 100% of 5-methyltocol (the ε-tocopherol spectrophotometric factor of



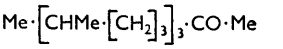
(III)



(IV)



(V)



(VI)

96 being used[5]). The paper-chromatographic properties were similar to those of natural ε-tocopherol but the compound appeared to be heterogeneous in that part of the band coupled with diazotised *o*-dianisidine.[12] As the simple 5-hydroxy-4-methylcoumarans, unsubstituted at position 6, couple with diazotised *o*-dianisidine [15] some cyclisation to the coumaran (V) might have occurred.

Alternative approaches were then considered and 5-methyltocol was eventually synthesised by a route similar to that which McHale *et al.*[13] used for 7-methyltocol. 2,3-Dimethylquinol (II; R = X = Y = H, R′ = Me) was prepared from 2,3-dimethylphenol by Smith and Austin's method [14] and methylated. The resulting dimethyl ether (II; X = Y = H, R = R′ = Me), on bromination with *N*-bromosuccinimide, gave 3-bromomethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2Br) together with some 2,3-bisbromomethylquinol dimethyl ether. The bromination had to be carried out under strictly anhydrous conditions and the dimethylquinol to be free from monoether, or nuclear bromination occurred. All attempts to obtain 3-2′-hydroxyethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CH_2·OH) from the bromomethyl compound by a Grignard reaction with formaldehyde failed, the main product being 3,3′,6,6′-tetramethoxy-2,2′-dimethylbibenzyl. The bromomethyl compound was converted into 3-cyanomethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CN), which on alkaline hydrolysis gave 3,6-dimethoxy-2-methylphenylacetic acid (II; X = Y = H, R = Me, R′ = CH_2·CO_2H). Although lithium aluminium hydride reduced this compound to 3-2′-hydroxyethyltoluquinol dimethyl ether, the yield was low, as an insoluble complex separated before reduction. Unchanged acid was obtained when the residue was acidified. The yield of hydroxyethyl compound on reduction of the methyl ester (II; X = Y = H, R = Me, R′ = CH_2·CO_2Me) was almost quantitative. With phosphorus tribromide the hydroxyethyl compound gave 3-2′-bromoethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CH_2Br); the Grignard derivative of this ether was treated with ketone (VI), derived from phytol by ozonolysis.[13] No attempt was made to separate the products, demethylation and cyclisation being carried out on the crude mixture. A crude concentrate containing 14% of 5-methyltocol was obtained, which after adsorption on alumina and molecular distillation afforded an oil that gave correct analyses for 5-methyltocol and from which the *p*-phenylazobenzoate was prepared.

[11] Green, McHale, Mamalis, and Marcinkiewicz, *J.*, 1959, 3374.
[12] Weisler, Robeson, and Baxter, *Analyt. Chem.*, 1947, **19**, 906.
[13] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.
[14] Smith and Austin, *J. Amer. Chem. Soc.*, 1942, **64**, 530.
[15] Green, McHale, Marcinkiewicz, and Mamalis, following paper.

Experimental

2,3-Dihydro-6-methoxy-7-methylbenz-1,4-oxathiin-2-one (IV; R = Me).—The 6-hydroxy-compound [11] (IV; R = H) (5·6 g.), methyl iodide (9·5 g.), anhydrous potassium carbonate (2 g.), and acetone (20 ml.) were refluxed for 6 hr. The product was obtained *via* ether extraction. Crystallisation from 95% ethanol gave the *methyl ether* (3·6 g.), m. p. 83—84° (Found: C, 57·1; H, 4·8; S, 14·9. $C_{10}H_{10}O_3S$ requires C, 57·2; H, 4·8; S, 15·3%).

5-2′-Hydroxyethylthiotoluquinol 1-Methyl Ether (III; R = Me, R′ = $CH_2 \cdot CH_2 \cdot OH$).—To a stirred suspension of lithium aluminium hydride (0·4 g.) in dry ether was added, dropwise, the 6-methoxybenzoxathiinone (1·5 g.) in dry ether. After decomposition of the excess of lithium aluminium hydride by ether saturated with water, the product was poured on a mixture of ice and concentrated hydrochloric acid and extracted with ether. The extract was washed with water, and dried and evaporated. Crystallisation from light petroleum (b. p. 80—100°) gave the *hydroxyethylthio-compound* (1·2 g.), m. p. 82—83° (Found: C, 56·0; H, 6·4; S, 14·8. $C_{10}H_{14}O_3S$ requires C, 56·0; H, 6·6; S, 15·0%).

Condensation of 5-2′-Hydroxyethylthiotoluquinol 1-Methyl Ether with Phytol.—The hydroxyethylthio-compound (0·54 g.), phytol (0·75 g.), anhydrous zinc chloride (0·1 g.), and acetic acid (20 ml.) were refluxed for 6 hr. The product was diluted with light petroleum (b. p. 40—60°), and washed successively with water, N-sodium hydroxide, and water. Acidification of the alkaline extract gave the hydroxyethylthio-compound (0·2 g.). The light-petroleum extract was evaporated, and an ethanolic solution (20 ml.) of the oil (0·55 g.) refluxed for 6 hr. with Raney nickel (1 g.). After filtration and evaporation the residue was refluxed for 3 hr. with hydrobromic acid (2·5 g.) in acetic acid (7·5 ml.). The product was diluted with light petroleum (b. p. 40—60°), and washed with water, followed by saturated aqueous sodium hydrogen carbonate, and evaporated to a brown oil (0·5 g.) which contained 4·5% of 5-methyltocol (by assay).[10] This concentrate was purified by adsorption from light petroleum (b. p. 40—60°) on alumina (Peter Spence type "O"; 3 g.). After development of the column with light petroleum–benzene the 5-methyltocol was eluted with ether. Evaporation and distillation [at 160° (bath)/10^{-3} mm.] gave a pale yellow oil (9 mg.) which gave an assay of 100% of 5-methyltocol. When the chromatogram was sprayed successively with 5% aqueous sodium carbonate and diazotised *o*-dianisidine [12] part of the tocol zone coupled to give a purple dye.

2 : 3-Dimethylquinol Dimethyl Ether (II; X = Y = H, R = R′ = Me).—2,3-Dimethylquinol [14] (20 g.), methyl iodide (40 g.), anhydrous potassium carbonate (40 g.), and acetone (150 ml.) were stirred under reflux for 16 hr. The product was isolated by steam-distillation and extracted into ether. After removal of the monomethyl ether by extraction with N-sodium hydroxide, evaporation and crystallisation from aqueous ethanol gave the *dimethyl ether* (12 g.), m. p. 78—79° (Found: C, 72·6; H, 6·7. $C_{10}H_{14}O_2$ requires C, 72·3; H, 6·7%). Acidification of the alkaline extract and crystallisation from light petroleum (b. p. 60—80°) gave the *monomethyl ether* (2·2 g.), m. p. 98—99° (Found: C, 71·2; H, 8·0. $C_9H_{12}O_2$ requires C, 71·0; H, 8·0%).

3-Bromomethyltoluquinol Dimethyl Ether (II; X = Y = H, R = Me, R′ = CH_2Br).—2,3-Dimethylquinol dimethyl ether (11 g.), *N*-bromosuccinimide (12 g.), benzoyl peroxide (0·1 g.), and dry carbon tetrachloride (200 ml.) were refluxed for 1 hr. A second portion of benzoyl peroxide (0·1 g.) was then added and refluxing continued until no *N*-bromosuccinimide remained. After cooling, the succinimide was filtered off and the filtrate evaporated to an oil which was taken up in light petroleum (b. p. 40—60°) and allowed to crystallise. The solid (A) was filtered off and the filtrate evaporated and distilled, giving the *bromomethyl compound* (9·9 g.), b. p. 102°/0·2 mm., m. p. 51—52° (Found: C, 48·4; H, 5·4; Br, 33·4. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·4; Br, 32·6%).

Recrystallisation of solid (A) from light petroleum (b. p. 60—80°) gave *2,3-bisbromomethylquinol dimethyl ether* (1·9 g.), m. p. 149° (Found: C, 37·6; H, 3·5; Br, 49·1. $C_{10}H_{12}O_2Br_2$ requires C, 37·1; H, 3·7; Br, 49·4%).

Reaction of 2,3-Dimethylquinol Dimethyl Ether with N-Bromosuccinimide in the Presence of 2,3-Dimethylquinol Monomethyl Ether.—2,3-Dimethylquinol dimethyl ether (containing traces of monomethyl ether) (11 g.), *N*-bromosuccinimide (12 g.), benzoyl peroxide (0·1 g.), and dry carbon tetrachloride (200 ml.) were refluxed for 30 min., by which time all the *N*-bromosuccinimide was converted into succinimide and hydrobromic acid was being evolved. Filtration, evaporation, and distillation gave an oil (9·5 g.), b. p. 88—90°/0·05 mm., m. p. 41—42° [from light petroleum (b. p. 40—60°) at −10°]. This compound was assumed to be *5-bromo-2,3-dimethylquinol dimethyl ether* (Found: C, 49·7; H, 5·4; Br, 32·5. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·4; Br, 32·3%).

3,3',6,6'-*Tetramethoxy*-2,2'-*dimethylbibenzyl*.—3-Bromomethyltoluquinol dimethyl ether (5 g.) in dry ether (25 ml.) was added slowly, with stirring, to magnesium turnings (0·6 g.) activated with a crystal of iodine and gently heated on a steam-bath. After 1·5 hr. the suspension was cooled to 0°, and formaldehyde [from paraformaldehyde (1·5 g.)] was introduced above the surface of the ether. The resulting mixture was hydrolysed by ice-cold 25% sulphuric acid (10 ml.). The solid was filtered off and crystallised from benzene to give the *bibenzyl compound* (3 g.), m. p. 181—183° (Found: C, 72·9; H. 7·9. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). Evaporation of the original ether solution gave a small amount of viscous oil.

3-*Cyanomethyltoluquinol Dimethyl Ether* (II; X = Y = H, R = Me, R' = CH_2·CN).—A solution of 3-bromomethyltoluquinol dimethyl ether (10 g.) in dioxan (100 ml.) was added to a stirred solution of sodium cyanide (5·0 g.) in water (5 ml.), heated on a steam-bath, during 1·5 hr. The mixture was heated for a further 3 hr., diluted with water, and extracted with ether. After being washed free from dioxan, the ether extract was dried and evaporated. The solid (5·2 g.), when crystallised from light petroleum (b. p. 60—80°) gave the *cyanomethyl compound* (4·2 g.), m. p. 63—64° (Found: C, 69·1; H, 7·1; N, 7·3. $C_{11}H_{13}O_2N$ requires C, 69·2; H, 6·9; N, 7·3%).

3,6-*Dimethoxy*-2-*methylphenylacetic Acid* (II; X = Y = H, R = Me, R' = CH_2·CO_2H).—The cyanomethyl compound (4·8 g.) in ethanol (40 ml.) was refluxed with potassium hydroxide (6 g.) in water (12 ml.) for *ca.* 36 hr. Evaporation of the ethanol gave a solid that was taken up in water and extracted with ether. Acidification of the aqueous layer gave the *acetic acid* (3·2 g.), m. p. 144—146° [from light petroleum (b. p. 80—100°)] (Found: C, 63·0; H, 7·1. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%).

The methyl ester (prepared by use of diazomethane in ether and crystallised from methanol–water) had m. p. 64° (Found: C, 63·7; H, 6·9. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

Reduction by Lithium Aluminium Hydride of the Acetic Acid.—To a stirred suspension of lithium aluminium hydride (1·2 g.) in ether (30 ml.) was added, dropwise, a suspension of the acetic acid (4 g.) in ether (30 ml.). The mixture was then refluxed for 30 min., cooled, and hydrolysed by ether saturated with water. The inorganic solid was filtered off and washed with ether; the filtrate and washings were combined and evaporated. Crystallisation from light petroleum (b. p. 80—100°) gave 3-2'-*hydroxyethyltoluquinol dimethyl ether* (II; X = Y = H, R = Me, R' = CH_2·CH_2·OH) (1·6 g.), m. p. 82—83° (Found: C, 67·4; H, 8·4. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

Acidification of the inorganic residue and extraction with ether gave the unchanged acetic acid (2 g.), m. p. 144—146°.

Reduction by Lithium Aluminium Hydride of Methyl 3,6-*Dimethoxy*-2-*methylphenylacetate*.—The ester was reduced by lithium aluminium hydride as already described for the acid. The hydroxyethyl compound (7·5 g. from 9·9 g.), m. p. 82—83°, was obtained.

3-2'-*Bromoethyltoluquinol Dimethyl Ether* (II; X = Y = H, R = Me, R' = CH_2·CH_2Br).—Phosphorus tribromide (3 g.) in light petroleum (10 ml.; b. p. 80—100°) was added slowly to a stirred solution of the hydroxyethyl compound (2·7 g.) in light petroleum (50 ml.; b. p. 80—100°) at 50°. After 2 hr. the mixture was cooled, hydrolysed by water (10 ml.), and decanted from the small amount of oil present. The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, and evaporated. Crystallisation from methanol gave the *bromoethyl compound* (1·2 g.), m. p. 65—66° (Found: C, 51·2; H, 6·0; Br, 30·0. $C_{11}H_{15}O_2Br$ requires C, 51·0; H, 5·8; Br, 30·8%).

5-*Methyltocol* (I).—The bromoethyl compound (1·3 g.) and ethyl iodide (0·8 g.) in dry ether were added slowly to magnesium turnings (0·24 g.) activated by a crystal of iodine, and the whole was refluxed for 4—5 hr., then cooled to 0°. The ketone (VI) [13] (2·7 g.) was added dropwise and the mixture refluxed for a further 2 hr., cooled, and hydrolysed by dilute hydrochloric acid. Evaporation of the ether layer yielded an oil which was refluxed for 8 hr. with hydrobromic acid (5 g.) in acetic acid (50 ml.). The product was diluted with light petroleum (50 ml.; b. p. 40—60°) and washed successively with water, saturated aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water. Evaporation yielded a pale brown oil (3·1 g.) which contained 14% of 5-methyltocol (the ε-tocopherol spectrophotometric factor of 96 being used [5]). This oil was adsorbed from light petroleum (b. p. 40—60°) on to alumina (Peter Spence type "O"; 50 g.), which contained a small quantity of alumina previously treated with sodium fluorescein in methanol and activated at 150° for 1 hr. After development with benzene the band due to the tocol was detected by its quenching of the fluorescence under ultraviolet light.

The column was cut and the tocol extracted with ether. Evaporation gave a brown viscous oil (0·4 g.) which contained 63% of 5-methyltocol. Molecular distillation [at 140° (bath)/10^{-3} mm.] gave 5-*methyltocol* as a pale yellow oil (Found: C, 80·0; H, 11·5. $C_{37}H_{46}O_2$ requires C, 80·5; H, 11·5%); $\lambda_{max.}$ 296 mμ ($E^{1\%}_{1cm.}$ 82·4), $\lambda_{min.}$ 258 mμ in ethanol; $\nu_{max.}$ 3440 m., 2915 vs, 1460 s, 1380 s, 1340 m, 1310 w, 1285 w, 1245 s, 1155 m, 1100 w, 1065 w, 1025 w, 911 w, 883 w, 862 w, and 807 m $cm.^{-1}$ (liquid film).

5-*Methyltocol* p-*Phenylazobenzoate*.—5-Methyltocol (0·1 g.), in dry ethylene chloride (5 ml.) containing pyridine (0·4 ml.), was heated under reflux with *p*-phenylazobenzoyl chloride (0·2 g.) in dry ethylene chloride (5 ml.) for 2 hr. Water (2 ml.) was added and after 1 hr. the product was taken up in light petroleum (b. p. 40—60°) and washed with dilute hydrochloric acid and water. The organic layer was filtered from the insoluble *p*-phenylazobenzoic acid and evaporated. The oil was redissolved in light petroleum, and the solution filtered; evaporation and crystallisation from propan-2-ol, gave needles, m. p. 69—70° (Found: C, 78·5; H, 9·0; N, 4·8. $C_{40}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

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