319. *Tocopherols. Part I. Synthesis of 7-Methyltocol (η-Tocopherol).*

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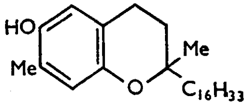
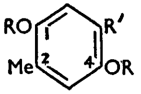
Racemic 7-methyltocol has been synthesised by an unambiguous route and found to have paper-chromatographic properties identical with those of natural η-tocopherol.

A comparison of the ultraviolet absorption spectra of tocol and all the *Bz*-methyltocols is included.

Recently Green and Marcinkiewicz [1] reported the isolation of 7-methyltocol (η-tocopherol) (I) from the lipid fraction of rice and thus showed that all the seven possible *Bz*-methylated tocols occurred in Nature. It was possible that the 7-methyltocol obtained from rice contained a small amount of 5-methyltocol (ε-tocopherol) which would be virtually undetectable in the presence of the 7-methyltocol, and thus it was apparent that a synthesis of 7-methyltocol free from other tocopherols would be of value to provide a sample for analytical and biological studies.

Karrer and Fritzsche [2] prepared 7-methyltocol in admixture with other monomethyltocols by direct condensation of toluquinol and phytol. Work in this laboratory [3] has shown that 5-, 7-, and 8-methyltocol are formed in this reaction. An attempt by Karrer and Dutta [4] to prepare 5- and 7-methyltocol by the condensation of methylthiotoluquinols with phytol and subsequent desulphurisation with Raney Nickel was inconclusive because the starting material condensed and cyclised in two directions. Using the paper-chromatographic technique of Green, Marcinkiewicz, and Watt [5] to identify the products, repetition of this work indicated that Karrer and Dutta incorrectly assumed the configuration of one of the methylthiotoluquinols: their 8-methyltocol was in fact 7-methyltocol, which almost certainly contained some 5-methyltocol (this work will be reported in full in a paper relating to the synthesis of 5-methyltocol).

(I)




(II)

Because of the difficulty in separating mixtures of methyltocols, an unambiguous preparation was required and for this purpose the method used by Smith and Miller [6] for α-tocopherol was adapted. The chroman was built by known reactions leading *via* intermediates of unambiguous structure to the final product (I).

Toluquinol (II; $R = R' = H$) was brominated to yield the known 5-bromotoluquinol [7] (II; $R = H$, $R' = Br$). The conversion of this compound into 5-bromotoluquinol dimethyl ether (II; $R = Me$, $R' = Br$) by the method of Smith, Wawzonek, and Miller [8] proceeded only in low yield, but the use of methyl iodide and potassium carbonate in acetone gave an almost quantitative yield. The bromo-ether was converted, by an entrainment technique with ethyl iodide, into a Grignard reagent (II; $R = Me$, $R' = MgBr$) which gave with ethylene oxide 5-2'-hydroxyethyltoluquinol dimethyl ether (II; $R = Me$, $R' = CH_2{\cdot}CH_2{\cdot}OH$). Treatment with phosphorus tribromide then yielded 5-2'-bromoethyltoluquinol dimethyl ether (II; $R = Me$, $R' = CH_2{\cdot}CH_2Br$) from which the Grignard

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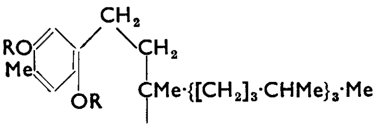
[1] Green and Marcinkiewicz, *Nature*, 1956, **176**, 86.
[2] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[3] Mamalis, McHale, Green, and Marcinkiewicz, unpublished work.
[4] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[5] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[6] Smith and Miller, *J. Amer. Chem. Soc.*, 1942, **64**, 440.
[7] Clark, *Amer. Chem. J.*, 1892, **14**, 569.
[8] Smith, Wawzonek, and Miller, *J. Org. Chem.*, 1941, **6**, 229.

derivative was prepared by the entrainment technique with ethyl iodide. This Grignard derivative on reaction with the ketone (III) yielded a mixture of 5-(3-hydroxy-3 : 7 : 11 : 15-tetramethylhexadecyl)toluquinol dimethyl ether (IV; R = Me) and probably 3 : 7 : 11 : 15-tetramethylhexadecan-3-ol (V), the latter resulting from the reaction of ethylmagnesium iodide and ketone (III). Demethylation and cyclisation were carried out on the mixture, vacuum-distillation of the product yielding an oil containing approximately 30% of 7-methyltocol. A 70% concentrate was obtained after adsorption on a zinc carbonate column and was suitable for the preparation of the derivatives, *e.g.*, the 3 : 5-dinitrophenylurethane and the 4-phenylazobenzoate were prepared. The latter derivative, on hydrolysis and molecular distillation, yielded pure 7-methyltocol, whose paper chromatographic behaviour was identical with that of natural η-tocopherol.

The ketone (III) was derived from phytol by ozonolysis in methylene chloride containing a small amount of pyridine. This solvent mixture gave a higher yield of a purer product than that obtained by using Smith and Miller's conditions.[6]



(IV)

$\mathrm{Me{\cdot}\{CHMe{\cdot}[CH_2]_3\}_3{\cdot}COMe}$ (III)

$\mathrm{Me{\cdot}\{CHMe{\cdot}[CH_2]_3\}_3{\cdot}CMeEt{\cdot}OH}$ (V)

It had originally been the intention to use the dibenzyl ether throughout the synthesis, but although 5-bromotoluquinol dibenzyl ether (II; R = $\mathrm{Ph{\cdot}CH_2}$, R′ = Br) was readily obtained, it was not possible to form a Grignard derivative from this compound. This was in agreement with the fact that Smith and Miller [6] could not form a Grignard derivative from bromotrimethylquinol dibenzyl ether.

Eggitt and Norris [9] previously compared the ultraviolet absorption spectra of five of the tocopherols. 7-Methyltocol, 5 : 7-dimethyltocol, and tocol [10] itself were not included and for this reason a completed list is given in the annexed Table. The 5 : 7-dimethyltocol was synthesised by the original method of Karrer and Fritzsche [11] but purification was through the 4-phenylazobenzoate and not by chromatography. Pure 5 : 7-dimethyltocol, which crystallised in prisms at —4°, is the first racemic tocopherol to be obtained crystalline.

Comparison of the ultraviolet absorption spectra of the tocopherols.

Tocopherol	Wavelength at minimum (mμ)	Wavelength at maximum (mμ)	$E^{1\%}_{1\,\mathrm{cm.}}$ at max.
Tocol	255	298·5	97
5-Methyltocol	257·5	295·5	87·5
7-Methyltocol	255	298	103
8-Methyltocol	257	298	87·3
5 : 7-Dimethyltocol	255	292	83·0
5 : 8-Dimethyltocol	257·5	296	89·4
7 : 8-Dimethyltocol	257	298	91·4
5 : 7 : 8-Trimethyltocol	256	292	75·8

EXPERIMENTAL

5-Bromotoluquinol (II; R = H, R′ = Br).—To a stirred and cooled solution of toluquinol (49·6 g.) in dry ether (100 ml.) was added, dropwise, bromine (64 g.) in dry chloroform (50 ml.).

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[9] Eggitt and Norris, *J. Sci. Food Agric.*, 1955, **6**, 689.
[10] Mamalis, McHale, Green, and Marcinkiewicz, unpublished work.
[11] Karrer and Fritzsche, *Helv. Chim. Acta*, 1938, **21**, 1234.

5-Bromotoluquinol separated almost immediately and crystallisation was completed by addition of chloroform (400 ml.). Recrystallisation from water, containing sufficient ethanol to bring about solution, gave the bromo-compound (55 g.), m. p. 182—184° (Found: C, 41·6; H, 3·5; Br, 39·2. Calc. for $C_7H_7O_2Br$: C, 41·4; H, 3·5; Br, 39·3%) (Clark [7] gave m. p. 179°).

5-*Bromotoluquinol Dimethyl Ether* (II; R = Me, R′ = Br).—Methyl iodide (37 g.) was added rapidly to a stirred mixture of 4-bromotoluquinol (25 g.), anhydrous potassium carbonate (34 g.), and acetone (150 ml.) and the whole refluxed for 3 hr. The product was isolated by steam-distillation, and recrystallisation from aqueous ethanol gave the *ether* (26 g.) as prisms, m. p. 91° (Found: C, 46·8; H, 4·8; Br, 34·5. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%).

5-*Bromotoluquinol Dibenzyl Ether* (II; R = Ph·CH$_2$, R′ = Br).—This was obtained from 5-bromotoluquinol (3·2 g.) by the method Smith and Miller [6] used for bromotrimethylquinol dibenzyl ether. Crystallised from light petroleum (b. p. 80—100°) the *ether* (3·8 g.) had m. p. 131° (Found: C, 65·5; H, 4·8; Br, 20·9. $C_{21}H_{19}O_2Br$ requires C, 65·8; H, 5·0; Br, 21·1%).

5-2′-*Hydroxyethyltoluquinol Dimethyl Ether* (II; R = Me, R′ = $CH_2{\cdot}CH_2{\cdot}OH$).—4-Bromotoluquinol dimethyl ether (23·1 g.) and ethyl iodide (15·6 g.) in dry ether (100 ml.) were added slowly, with stirring, to magnesium turnings (4·8 g.) activated with a crystal of iodine and gently heated on a steam-bath. After 2 hours' refluxing, the Grignard derivative had separated; the suspension was cooled to 0°, and ethylene oxide (15 g.) in dry ether (35 ml.) was added with stirring (inefficient stirring of the thick suspension leads to very low yields). The resulting mixture was allowed to come to room temperature, then refluxed for 2 hr. After cooling, it was hydrolysed by ice-cold 25% sulphuric acid (50 ml.). Butanol and other volatile impurities were removed by steam-distillation and the residual oil was extracted with ether. After removal of solvent, distillation gave the *hydroxyethyl compound* (13·5 g.), b. p. 123—124°/0·2 mm., m. p. 58—59° [from light petroleum (b. p. 40—60°)] (Found: C, 67·8; H, 7·7. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

5-2′-*Bromoethyltoluquinol Dimethyl Ether* (II; R = Me, R′ = $CH_2{\cdot}CH_2Br$).—Phosphorus tribromide (23 g.) in light petroleum (100 ml.; b. p. 80—100°) was added slowly to a stirred solution of the hydroxyethyl compound (20 g.) in light petroleum (250 ml.; b. p. 80—100°) at 50°. After 2 hr., the mixture was cooled and hydrolysed by water (100 ml.), and the organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, dried, and evaporated. Crystallization from aqueous methanol gave the *bromoethyl compound* (12·1 g.), m. p. 56—58° (Found: C, 51·0; H, 5·8; Br, 30·8. $C_{11}H_{15}O_2Br$ requires C, 51·0; H, 5·8; Br, 30·8%).

When kept, the original aqueous layer deposited needles which contained no bromine and on recrystallization from ethyl acetate had m. p. 93—94°. This compound was assumed to be the *dihydrogen phosphite* of the hydroxyethyl compound [II; R = Me, R′ = $CH_2{\cdot}CH_2{\cdot}O{\cdot}P(OH)_2$] (Found: C, 51·2; H, 6·4. $C_{11}H_{17}O_5P$ requires C, 50·9; H, 6·6%).

6 : 10 : 14-*Trimethylpentadecan*-2-*one* (III).—Phytol (12 g.) in methylene chloride (200 ml.) containing pyridine (12 ml.) was ozonised [ozone (0·6 g.) in oxygen (20 l./hr.)] at 0° until absorption was complete. After reductive cleavage by zinc dust (10·9 g.) in acetic acid (13 ml.), the hydroxylic impurities were removed by washing, and distillation yielded the ketone (7·3 g.), b. p. 120—130°/0·2 mm., n_D^{24} 1·4441 (Lukes and Zobacova [12] gave b. p. 132—134°/1 mm., n_D^{25} 1·4434).

7-*Methyltocol* (I).—The bromoethyl compound (2·6 g.) and ethyl iodide (1·6 g.) in dry ether were added slowly to magnesium turnings (0·48 g.) activated by a crystal of iodine, and the whole was refluxed for 4—5 hr., then cooled to 0°. The ketone (III) (5·4 g.) was added dropwise and the mixture refluxed for a further 2 hr., cooled, and hydrolysed by dilute hydrochloric acid. The ether layer yielded on evaporation a mixture (7·8 g.) of alcohols (IV) and (V) which was refluxed for 8 hr. with hydrobromic acid (10 g.) in acetic acid (100 ml.). The product was diluted with light petroleum (100 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 (6·6 g.) which contained 14% of the tocol. Distillation yielded two fractions: (*a*) a pale yellow mobile oil (2·9 g.), b. p. 140°/0·1 mm.; (*b*) a yellow viscous oil (2·0 g.), b. p. 220°/0·1 mm. The high-boiling fraction contained 42% of the tocol. Further purification was carried out by adsorption from light petroleum (b. p. 40—60°), on several columns (30 × 2·5 cm.) of zinc carbonate–Hyflo Supercel (1 : 1), previously treated with sodium fluorescein in methanol and activated at 150° for 1 hr. After development with light

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[12] Lukes and Zobacova, *Chem. Listy*, 1957, **51**, 330.

petroleum–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 yielded a pale brown, viscous oil (1·2 g.), which assayed as 70% 7-methyltocol.

This concentrate (0·2 g.) in dry ethylene chloride (5 ml.), containing pyridine (0·4 ml.), was treated with 4-phenylazobenzoyl chloride (0·2 g.) in dry ethylene chloride (5 ml.) and refluxed for 1 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 then with water. The organic layer was filtered from the insoluble 4-phenylazobenzoic acid and evaporated. The oil was redissolved in light petroleum, and the solution filtered; on evaporation it yielded a red oil (0·2 g.) which eventually solidified and, after recrystallisation from propan-2-ol, had m. p. 55—56°. It appeared that the 4-*phenylazobenzoate* crystallised with solvent of crystallisation which was rapidly lost on filtration, the solid changing from needles into a waxy solid (Found: C, 78·1; H, 8·8; N, 4·3. $C_{40}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

The azobenzoate (0·1 g.) was refluxed in ethanol–propan-2-ol (10 ml.; 1 : 1) and two pellets of potassium hydroxide were added down the condenser. After 20 minutes' refluxing, concentrated hydrochloric acid (2 ml.) was added to the refluxing solution. The inorganic salt was dissolved in water and the organic layer was taken up in light petroleum (b. p. 40—60°). The aqueous layer was separated, and the organic layer was washed several times with water, filtered from 4-phenylazobenzoic acid, and evaporated to a yellow oil (69 mg.). Short-path distillation [150° (bath)/10^{-4} mm.] gave 7-*methyltocol* (54 mg.) as a pale yellow oil (Found: C, 81·0; H, 11·8. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%), $\lambda_{max.}$ 298 mμ ($E^{1\%}_{1\,cm.}$ 104·1), $\lambda_{min.}$ 255 mμ in EtOH, $\nu_{max.}$ 3370 m, 2890 vs, 1620 w, 1500 s, 1455 vs, 1410 s, 1370 s, 1340 m, 1240 m, 1175 vs, 1100 m, 1005 m, 935 m, 909 m, 885 m, 870 s, 813 w cm.$^{-1}$ (liquid film). On assay by the method of Green *et al.*,[5] a spectrophotometric factor of 88·3 was obtained and the development of colour was complete after 2 min.

7-*Methyltocol* 3′ : 5′-*Dinitrophenylurethane*.—7-Methyltocol 70% concentrate (0·3 g.) and 3 : 5-dinitrobenzazide (0·4 g.) in dry toluene (5 ml.) were refluxed for 1 hr., during which nitrogen was evolved. The yellow solution was diluted with light petroleum (b. p. 40—60°), filtered from 3 : 5-dinitrophenylurea, and evaporated. The resulting oil solidified on treatment with ethanol–water and gave the 3′ : 5′-*dinitrophenylurethane* (0·15 g.), m. p. 115—117° (from ethanol–water) (Found: C, 67·2; H, 8·1; N, 7·0. $C_{34}H_{49}O_7N_3$ requires C, 66·8; H, 8·1; N, 6·9%).

5 : 7-*Dimethyltocol*.—2 : 6-Dimethylquinol (5 g.), treated with phytol by the method of Karrer and Fritzsche,[11] yielded a yellow oil (13 g.), which contained 61% of the tocol. Vacuum-distillation gave a main fraction, b. p. 200—220°/0·05 mm., containing 87·5% of the tocol. The 4-*phenylazobenzoate*, prepared as above, had m. p. 61° (from propan-2-ol) (Found: C, 79·2; H, 8·8; N, 4·2. $C_{41}H_{56}O_3N_2$ requires C, 78·8; H, 9·0; N, 4·5%). Hydrolysis and short-path distillation, as above, yielded 5 : 7-dimethyltocol as a pale yellow oil which tended to crystallise in prisms at −4°; $\lambda_{max.}$ 292 mμ ($E^{1\%}_{1\,cm.}$ 83·0), $\lambda_{min.}$ 255 mμ in EtOH; $\nu_{max.}$ 3450 m, 2920 vs, 1460 s, 1375 m, 1340 m, 1320 m, 1245 m, 1220 m, 1155 m, 1105 m, 1050 m, 1020 w, 971 w, 909 w, 885 w, 855 m cm.$^{-1}$ (liquid film). The spectrophotometric factor, determined as for 7-methyltocol, was 93·5.

5 : 7-*Dimethyltocol* 3′ : 5′-*dinitrophenylurethane* was prepared as was the 7-methyltocol derivative and crystallised in plates, m. p. 65°, from propan-2-ol–water (Found: C, 67·1; H, 8·2; N, 7·1. $C_{35}H_{51}O_7N_3$ requires C, 67·3; H, 8·2; N, 6·7%).

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