678. *Tocopherols. Part III.* Reaction of Phytol with Some Toluquinol Derivatives.*

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The preparation of some toluquinol derivatives is described and their reaction with phytol investigated.

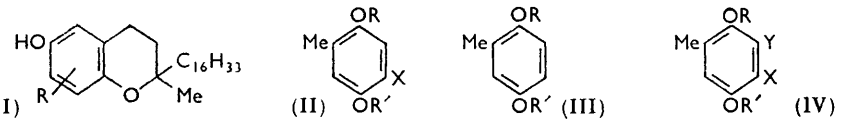
Whereas 2,3,5-trimethylquinol and the three dimethylquinols condense with phytol to give in each case only one tocol, toluquinol can theoretically give rise to three tocols, 5-, 7-, and 8-methyltocol (I; R = Me). Reaction of toluquinol with phytol was first carried out by Karrer and Fritzsche [1] who obtained a mixture of monomethyltocols of undetermined composition. Recently, Pendse and Karrer [2] identified 7-methyltocol and stated that smaller quantities of isomeric monomethyltocols may also have been present in the reaction product. Work in these laboratories [3] showed that under the conditions of the Swiss workers, all three tocols are formed, the ratios of 5- : 7- : 8-methyltocol being 1 : 2 : 1, respectively.

In connection with the synthesis of 5-methyltocol, we investigated the reaction of phytol with suitably substituted toluquinols (II; R′ = H) that might be expected to lead to isomer-free 5-methyltocol derivatives. Some toluquinol derivatives have therefore been

* Part II, *J.*, 1958, 1850.

[1] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[2] Pendse and Karrer, *ibid.*, 1958, **41**, 396.
[3] Marcinkiewicz, McHale, Mamalis, and Green, *J.*, 1959, 3377.

prepared and their reaction with phytol studied. Benzoylation of toluquinol in pyridine has been stated to yield a mixture of the dibenzoate and 4-benzoate (III; R = R′ = Bz, and R = H, R′ = Bz respectively).[4] A sample of toluquinol 4-benzoate prepared in this way gave, on treatment with benzyl bromide in acetone, a mixture of two substances, (A) m. p. 118—119°, and (B) m. p. 87—89°. Both products gave correct analyses for benzoyloxybenzyloxytoluene and appeared to be isomers; clearly our sample of toluquinol



4-benzoate, although having an m. p. in accordance with the literature, must have been contaminated with some of the 1-benzoate (III; R = Bz, R′ = H). Hydrogenation of substance (A) afforded a toluquinol benzoate, m. p. 120—122°, assumed to be pure 4-benzoate (Jacob, Sutcliffe, and Todd [4] gave m. p. 113° for this compound, its structure being assigned by analogy with the monoalkylation product of toluquinol), while hydrogenation of substance (B) yielded toluquinol 1-benzoate, m. p. 145—146°. It follows that substance (A) was 5-benzoyloxy-2-benzyloxytoluene (III; R = CH_2Ph, R′ = Bz), and substance (B) its isomer. Alkaline hydrolysis of (A) furnished toluquinol 1-benzyl ether (III; R = CH_2Ph, R′ = H); similarly (B) afforded the 4-benzyl ether. The tedious separation of the monobenzoates was later found unnecessary, benzylation of the crude product giving a readily separable mixture of (A) and (B). Benzylation of toluquinol afforded toluquinol dibenzyl ether and a mixture of toluquinol monobenzyl ethers: the latter on benzoylation yielded substance (B) as the sole crystalline product.

Bromination of toluquinol 1-benzyl ether in chloroform yielded 5-bromotoluquinol 1-benzyl ether (II; R = CH_2Ph, R′ = H, X = Br) together with some 5-bromotoluquinol.[5] Addition of calcium carbonate to the bromination mixture prevented the rather easy cleavage of the bromobenzyl ether, the structure of which was confirmed by its hydrogenation to 5-bromotoluquinol. When the ether was heated with phytol in benzene–formic acid, a dark oil was obtained. Paper-chromatographic examination [6] of the oily product obtained after debenzylation showed that, although reaction had taken place, no tocols were present, a result possibly connected with the unusual lability of the $C_{(5)}$ bromine atom.[7] 5-Bromotoluquinol likewise failed to give any identifiable products when treated with phytol under the same conditions, only a dark oil being formed.

Toluquinol 1-benzyl ether and diazotised sulphanilic acid gave a red azo-derivative which was reduced without isolation to the aminophenol and acetylated to give a low yield of 4-acetamido-5-acetoxy-2-benzyloxytoluene (II; R = CH_2Ph, R′ = Ac, X = NHAc), the structure of which was confirmed by an alternative synthesis. Cold alkaline hydrolysis of this product yielded 5-acetamidotoluquinol 1-benzyl ether (II; R = CH_2Ph, R′ = H, X = NHAc), which did not react with phytol under the usual conditions or when zinc chloride in boiling acetic acid was used.

Reaction of toluquinol 1-benzyl ether with phytol in decalin, zinc chloride being used as catalyst, gave, after hydrogenation, a poor yield of the expected mixture of 5- and 7-methyltocol. Reaction in benzene–formic acid yielded a cleaner product containing about 68% of an unseparable mixture of 5- and 7-methyltocol. Reaction of toluquinol 1-methyl ether with phytol in benzene–formic acid followed by demethylation gave a 45% yield of 5- and 7-methyltocol. As it was inseparable, this material was at first thought to be of no help in the preparation of 5-methyltocol. However, a concentrated

[4] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327; cf. Aparicio and Waters, *J.*, 1952, 4666, for the dibenzoate.
[5] Clark, *Amer. Chem. J.*, 1892, **14**, 569.
[6] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[7] Green, McHale, Mamalis, and Marcinkiewicz, *J.*, 1959, 3374.

mixture of 5- and 7-methyltocol benzyl ethers behaved as did tocol benzyl ether [8] on distillation and paper-chromatography of the distillate showed that two reducing bands were present, the slower band being in the position expected for 5- and/or 7-methyltocol, the faster band moving to a position expected for a *C*-benzylmethyltocol. Whereas the slower band coupled with diazotised *o*-dianisidine, the fast band did not, indicating that the $C_{(5)}$ position was blocked and that this product was probably 5(7)-benzyl-7(5)-methyltocol. Cleavage and rearrangement might therefore have occurred at the high temperature of the distillation. Cleavage and intermolecular rearrangement of benzyl [9] and phenyl [10] ethers in the absence of catalyst has been reported.

Four products could clearly be obtained from a mixture of 5- and 7-methyltocol benzyl ether: 5-methyltocol benzyl ether could give 7-benzyl-5-methyltocol and 5-methyltocol, while 7-methyltocol benzyl ether could give 5-benzyl-7-methyltocol and 7-methyltocol. There was reason to suppose that the ratio of cleavage to rearrangement of the two benzyl ethers would be different, since, because of the considerably greater reactivity of position $C_{(5)}$ than of position $C_{(7)}$ in tocols, 5-methyltocol benzyl ether was less likely to rearrange and hence give preferentially 5-methyltocol, while the 7-methyl benzyl ether might give more of the rearrangement product, 5-benzyl-7-methyltocol. This assumption was supported by evidence [11] that radical attack may take place preferentially at positions reactive from polar considerations.

When a 70% concentrate of the monomethyltocol benzyl ethers was heated without solvent at 250°, appreciable cleavage and rearrangement occurred to give a product containing 15% of monomethyltocols and a similar amount of benzylmethyltocols: a cleaner product containing 28% of monomethyltocols resulted from reaction in tetradecane. The product was chromatographically separated into two components, the faster of which failed to couple with diazotised *o*-dianisidine, could not be nitrosated, and contained 71% of mixed benzylmethyltocols. Distillation afforded slightly impure benzylmethyltocol. The slower band after further chromatography afforded a small quantity of almost non-coupling yellow oil (assay 94%) and a residual oil which coupled strongly. Distillation of the former gave apparently 5-methyltocol. In replicate experiments it was extremely difficult to isolate the non-coupling 5-methyltocol even when the product was rebenzylated and again heated at 250°. The reason became clear with the development of a method for the determination of 5- and 7-methyltocols in the presence of one another, based on the assay of their nitrosation products.[12] The product of condensation of phytol with toluquinol 1-benzyl ether was then shown to contain 5- and 7-methyltocol in the ratio 1 : 2, a result very close to that observed from the reaction of toluquinol itself with phytol.[3] The condensation product of toluquinol 1-methyl ether with phytol similarly contained 38% of 5-methyl- and 62% of 7-methyl-tocol. In one experiment the relative proportions of the two tocols were little altered by thermal reaction. Since the condensation gave rise to 7-methyltocol as main product, and since successful alternative methods for the synthesis of 5-methyltocol had been developed,[13] this approach was abandoned.

The Table records the yields of crude tocols, formed by condensation of various toluquinols with phytol, as assayed by paper chromatography after removal of the protecting group.

The feature of these results is the effect of a $C_{(5)}$-substituent; in general, condensations with $C_{(5)}$-substituted toluquinols or toluquinol monoether give much lower yields of tocols than do toluquinols not substituted in this position (cf. expts. 5—8 and 10 with 1—4). 5-Substituted derivatives furnish considerably poorer yields than do the 6-substituted

[8] Mamalis, McHale, Green, and Marcinkiewicz, *J.*, 1958, 1850.
[9] Behagel and Freiensehner, *Ber.*, 1934, **67**, 1368.
[10] *Idem*, *Ber.*, 1935, **68**, 341.
[11] Augood, Hey, and Williams, *J.*, 1952, 2094; 1953, 44; Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412; Cadogan, Hey, and Williams, *J.*, 1954, 794.
[12] Marcinkiewicz and Green, *Analyst*, 1959, **84**, 304.
[13] McHale, Green, Marcinkiewicz, and Mamalis, following paper.

Condensation of phytol with toluquinols: yields of tocols derived by assay of crude product.

Expt.	Toluquinol (IV)	Yields (%) 5-methyl-	7-methyl-	8-methyl-
1	R = R′ = X = Y = H [a]	18	32	21
2	R = Me, R′ = X = Y = H	17	28	0
3	R = CH_2Ph, R′ = X = Y = H	24	44	0
4	R = X = Y = H, R′ = Me	0	22	14
5	R = R′ = Y = H, X = Br	0	0	0
6	R = CH_2Ph, R′ = Y = H, X = Br	0	0	0
7	R = CH_2Ph, R′ = Y = H, X = NHAc	0	0	0
8	R = R′ = YH, X = SMe [b]	6	0	19
9	R = R′ = XH, Y = SMe [b]	25	31	0
10	R = Me, R′ = Y = H, X = $S{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ [b]	5	0	0
11	2,3-Dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one [c]	0	0	22

[a] Ref. 3. [b] Ref. 13. [c] Ref. 7.

compounds (expts. 8 and 9). The free $C_{(5)}$ position appears to be so reactive that toluquinol 4-methyl ether yields more 7- than 8-methyltocol on reaction with phytol (expt. 4), the initial attack by phytol taking place at $C_{(5)}$ adjacent to the methoxyl group, rather than at $C_{(6)}$ adjacent to the hydroxyl: no reaction appears to take place at $C_{(3)}$. 2,3-Dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one has been included since it is in effect a toluquinol 4-ether blocked at $C_{(5)}$.

Repetition of the reaction of pure toluquinol 4-benzoate with phytol as described by Jacob *et al.*[4] gave only one tocol, 8-methyltocol. This confirmed the structure of the 4-benzoate since if the product had been the 1-isomer or had been contaminated with it, both 5- and 7-methyltocol should have been found in the product. The report of Pendse and Karrer [2] that 7-methyltocol was obtained from this reaction must be attributed to the use of an impure sample of the 4-benzoate. In the same way, the structure of toluquinol 1-benzyl ether followed from the fact that only 5- and 7-methyltocol were obtained from its reaction with phytol. Conversion of 5-acetamidotoluquinol 1-benzyl ether into the known 5-bromotoluquinol dimethyl ether [14] by standard reactions confirmed the structure assigned earlier. Catalytic hydrogenation of 5-acetamidotoluquinol 1-benzyl ether afforded 5-acetamidotoluquinol (II; R = R′ = H, X = NHAc), which on methylation gave 5-acetamidotoluquinol dimethyl ether (II; R = R′ = Me, X = NHAc). Acid hydrolysis of the dimethyl ether gave the aminoquinol dimethyl ether (II; R = R′ = Me), X = NH_2), and the latter was converted by means of the Sandmeyer reaction into 5-bromotoluquinol dimethyl ether (II; R = R′ = Me, X = Br).

5-Acetamidotoluquinol dimethyl ether was also obtained by mild alkaline hydrolysis of 5-acetamido-5-acetoxy-2-methoxytoluene to 4-acetamido-5-hydroxy-2-methoxytoluene (II; R = Me, R′ = H, X = NHAc) followed by methylation.

It was also observed that nitration of toluquinol dimethyl ether gave an excellent yield of 5-nitrotoluquinol dimethyl ether (II; R = R′ = Me, X = NO_2), the structure of which was confirmed by reduction to the amine (II; R = R′ = Me, X = NH_2).

Experimental

All tocol assays and paper-chromatographic examinations were carried out as described by Green *et al.*[6]

Benzoylation of Toluquinol.—Toluquinol (50 g.) was benzoylated according to Jacob *et al.*[4], giving toluquinol dibenzoate (4·4 g.), m. p. 122°, toluquinol 4-benzoate (18·5 g.), m. p. 113—115°, and mixed monobenzoates (40 g.), m. p. 102—104°. Jacob *et al.* give m. p. 113—114° for the 4-benzoate and m. p. 122° for the dibenzoate, while Aparicio and Waters [4] give m. p. 124° for the latter.

5-Benzoyloxy-2-benzyloxy- and 2-Benzoyloxy-5-benzyloxy-toluene.—Toluquinol 4-benzoate (7·1 g.; m. p. 113—115°), benzyl bromide (5·2 ml.), potassium carbonate (9·1 g.), and acetone

[14] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.

(100 ml.) were heated under reflux for 4 hr. and then cooled. Water was added, and the oil extracted into ether and washed with N-sodium hydroxide and with water. Removal of the solvent and crystallisation from light petroleum (b. p. 60—80°) gave needles (6·6 g.), m. p. 117—119°.

5-Benzoyloxy-2-benzyloxytoluene (A) when recrystallised had m. p. 118—119° (Found: C, 79·3; H, 5·9. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·7%). Distillation of the crystallisation mother-liquors afforded a pale yellow oil (2·4 g.), b. p. 190—205°/0·05 mm., m. p. 75—79°. After two crystallisations from light petroleum (b. p. 60—80°), needles of *2-benzoyloxy-5-benzyloxytoluene* (B), m. p. 87—89°, were obtained (Found: C, 79·0; H, 5·7%).

Toluquinol 4-Benzoate.—5-Benzoyloxy-2-benzyloxytoluene (1·0 g.) in ethanol (20 ml.) was shaken with hydrogen and palladised charcoal (10%) till uptake ceased (85 ml.). The white product (0·61 g.), m. p. 120—122° on crystallisation from ethanol–light petroleum (b. p. 60—80°) formed prismatic needles, m. p. 120—122°. The *trityl ether* separated from alcohol as needles, m. p. 138—139° (Found: C, 83·8; H, 5·6. $C_{33}H_{26}O_3$ requires C, 84·0; H, 5·6%).

Toluquinol 1-Benzoate.—2-Benzoyloxy-5-benzyloxytoluene (1·0 g.), partially dissolved in ethanol (40 ml.), was reduced catalytically as above; it gave a white *product* (0·65 g.), which after crystallisation from ethanol–light petroleum (b. p. 60—80°) formed needles, m. p. 145—146° (Found: C, 73·3; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·6; H, 5·3%).

Toluquinol 1-Benzyl Ether.—A suspension of 5-benzoyloxy-2-benzyloxytoluene (25·1 g.) in ethanol (230 ml.) was stirred under nitrogen at 60° while N-sodium hydroxide (157 ml.) was added during 5 min. After a further 2 hr. at 60° the mixture was cooled and acidified with concentrated hydrochloric acid (10 ml.), and most of the ethanol removed under reduced pressure. An oil separated which was extracted into ether, and washed thoroughly with aqueous sodium hydrogen carbonate and water; acidification of the alkaline solution gave benzoic acid (8·3 g.), m. p. 122°, while evaporation of the ethereal layer gave a cream solid (14·4 g.), m. p. 67—69°. *Toluquinol 1-benzyl ether* separated from ether–light petroleum (b. p. 40—60°) as needles, m. p. 70—71° (Found: C, 78·0; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

Toluquinol 4-Benzyl Ether.—Similarly prepared from 2-benzoyloxy-5-benzyloxytoluene, the *4-benzyl ether* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in prisms, m. p. 85—86° (Found: C, 78·7; H, 6·6%).

Direct Preparation of 5-Benzoyloxy-2-benzyloxy- and 2-Benzoyloxy-5-benzyloxy-toluene from Toluquinol.—Benzoylation of toluquinol (78·6 g.) gave toluquinol dibenzoate (11·5 g.) and the mixed monobenzoates (87·4 g.). Benzylation of the latter afforded a product which on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) yielded the 5-benzoyloxy-derivative (54·9 g.) as needles, m. p. 115—116°. Distillation of the evaporated mother-liquors gave the 2-benzoyloxy-derivative (b. p. 190—210°/0·2 mm.), crystallising from light petroleum (b. p. 60—80°) as needles (30·3 g.), m. p. 86—89°.

Benzylation of Toluquinol.—Toluquinol (6·2 g.), benzyl bromide (8·6 g.), potassium carbonate (6·9 g.), and acetone (25 ml.) were heated under reflux for 4 hr. Water was added, the oil extracted into ether, and the extracts washed with water and dried. The solvent was removed and the residual oil distilled, two fractions being collected: (i) b. p. 50—148°/0·02 mm. (1·2 g.), consisting of toluquinol (0·23 g.), m. p. 122—124°, and benzyl bromide; and (ii) an oil, b. p. 148—152°/0·02 mm. (4·6 g.), which partially solidified. An ethereal solution of the solid (1·1 g.) from the higher-boiling fraction was washed with N-sodium hydroxide and evaporated. Crystallisation yielded long soft white needles of *toluquinol dibenzyl ether*, m. p. 49—51° (Found: C, 82·4; H, 6·6. $C_{21}H_{20}O_2$ requires C, 82·7; H, 6·6%), the structure of which was confirmed by hydrogenation to toluquinol. The dark oil (3·0 g.) remaining after removal of the solid was treated with pyridine (15 ml.) and benzoyl chloride (2·0 g.), then heated on the steam-bath for 1 hr. The tan-coloured solid (2·7 g.) separated from light petroleum (b. p. 60—80°) as needles of 2-benzoyloxy-5-benzyloxytoluene, m. p. 78—89° (Found: C, 78·8; H, 5·6. Calc. for $C_{21}H_{18}O_3$: C, 79·3; H, 5·7%).

5-Bromotoluquinol 1-Benzyl Ether.—(*a*) Toluquinol 1-benzyl ether (2·1 g.) in chloroform (10 ml.; dry) was stirred at 5° while bromine (1·6 g.) in chloroform (10 ml.) was added rapidly. The mixture was immediately evaporated, the residue stirred with cold chloroform (5 ml.), and the solid collected (0·52 g.). Crystallisation from water containing a little ethanol afforded 5-bromotoluquinol, m. p. 181—183° undepressed on admixture with an authentic specimen.[14] The original chloroform mother-liquors were evaporated to afford a sticky brown solid (1·85 g.). Three crystallisations from light petroleum (b. p. 60—80°) yielded prismatic needles, m. p.

66·5—68°, of *5-bromotoluquinol 1-benzyl ether* (Found: C, 57·3; H, 4·4; Br, 27·3. $C_{14}H_{13}O_2Br$ requires C, 57·3; H, 4·5; Br, 27·3%). Catalytic hydrogenation of a sample furnished 5-bromotoluquinol, m. p. 181—183°.

(*b*) Toluquinol 1-benzyl ether (6·4 g.), calcium carbonate (9·0 g.), and chloroform (90 ml.) were stirred at 5° while bromine (4·8 g.) in chloroform (30 ml.) was added during 15 min. After being left overnight, the mixture was filtered and the residue washed with chloroform; evaporation of the filtrate and crystallisation from light petroleum gave prismatic needles (7·8 g.), m. p. 65·5—67°.

4-Acetamido-5-acetoxy-2-benzyloxytoluene.—To a solution of sulphanilic acid (1·73 g.) and sodium carbonate (0·44 g.) in water (8 ml.) was added sodium nitrite (0·61 g.) in water (2·0 ml.). The mixture was poured on ice (10 g.) and concentrated hydrochloric acid (1·75 ml.) and left for 15 min. The diazonium solution was then added to an ice-cold solution of sodium hydroxide (1·25 g.) in water (5 ml.) containing toluquinol 1-benzyl ether (1·22 g.), set aside overnight, then stirred with sodium dithionite (2·1 g.) for 30 min. at room temperature. The oil which separated was extracted into ethyl acetate, the solvent removed, and the residue kept with acetic anhydride (5 ml.) and concentrated sulphuric acid (1 drop) for 3 hr. After the addition of water, the solid was collected and crystallised from aqueous ethanol, the *product* separating as long white needles, m. p. 180—183°. Recrystallisation gave needles, m. p. 181° (Found: C, 68·7; H, 6·3; N, 4·6. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%).

5-Acetamidotoluquinol 1-Benzyl Ether.—The diacetyl derivative (0·6 g.), ethanol (12 ml.), and N-sodium hydroxide (4·8 ml.) were kept at room temperature for 1 hr., the mixture was then acidified with concentrated hydrochloric acid, water was added, and the solid *product* collected (0·5 g.) and crystallised from aqueous ethanol, giving white needles, m. p. 168—169° (Found: 70·8; H, 6·2; N, 5·3. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%).

Attempted Reactions with Phytol.—(*a*) 5-Bromotoluquinol 1-benzyl ether (2·9 g.), phytol (3·0 g.), anhydrous formic acid (15 ml.), and benzene (15 ml.) were heated under reflux for 4 hr., the mixture becoming very dark. The benzene layer was separated, washed with N-sodium hydroxide and water, dried, and evaporated. The dark oil was shaken with hydrogen and palladised charcoal (10%) until uptake ceased. Paper-chromatographic examination failed to indicate any tocol products.

(*b*) 5-Bromotoluquinol (2·0 g.), phytol (3·0 g.), formic acid (15 ml.), and benzene (15 ml.) were heated under reflux for 3 hr. Separation and evaporation of the benzene layer left a dark oil that did not contain tocol products.

(*c*) 5-Acetamidotoluquinol 1-benzyl ether (150 mg.), phytol (170 mg.), benzene (1·5 ml.), and formic acid (1·5 ml.) were heated under reflux for 5 hr. The pale benzene layer was separated, washed with N-sodium hydroxide and water, and evaporated. The crude oil (170 mg.), after catalytic hydrogenation, was examined paper-chromatographically; no tocol products were identified. Acidification of the alkaline washings yielded unchanged material.

5- and 7-Methyltocol.—(*a*) Toluquinol 1-benzyl ether (5·0 g.), phytol (7·0 g.), anhydrous zinc chloride (3·3 g.), and decalin (90 ml.) were stirred at 140—150° for 3 hr. The hot supernatant solution was decanted off, and the residual gum, after being washed once with decalin (20 ml.), was rejected; the combined decalin solutions, when cooled, deposited white solid (0·45 g.). Crystallisation from benzene–light petroleum (b. p. 40—60°) gave toluquinol, m. p. and mixed m. p. 126—127°. The decalin solution was evaporated to give a dark oil (10·6 g.) which was taken up in ethanol (50 ml.) and ethyl acetate (20 ml.) and shaken with hydrogen and palladised charcoal (10%). When hydrogen uptake ceased (450 ml.), the mixture was worked up to give an oil (7·5 g.), which was assayed by paper chromatography. Three reducing bands were observed, one on the origin (12%), one in the position expected for 5- and 7-methyltocol (34%), and a fast running band (11%) which did not couple with diazotised *o*-dianisidine. This is probably due to a $C_{(5)}$-substituted tocol of higher molecular weight; the overall yield of 5- and 7-methyltocols was 27%.

(*b*) Toluquinol 1-benzyl ether (1·1 g.), phytol (1·5 g.), formic acid (12 ml.), and benzene (12 ml.) were heated under reflux for 3 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and evaporated to give an oil which was hydrogenated in ethyl acetate (25 ml.). Working up afforded a pale brown oil (2·45 g.), which was shown to contain 5- and 7-methyltocol (assay 57%, overall yield 68%); distillation of this gave a dark yellow oil, b. p. 210—220°/0·03 mm. (assay 73% of 5- and 7-methyltocol). Very little fast-running material was obtained by this method.

5-Benzoyloxy-2-methoxy- and 2-Benzoyloxy-5-methoxy-toluene.—Mixed toluquinol monobenzoates (11·4 g.), methyl iodide (28 g.), potassium carbonate (13·8 g.), and acetone (40 ml.) were stirred under reflux for 3 hr. Water was added and the oil extracted into ethyl acetate, washed with N-sodium hydroxide and water, and dried. After removal of the solvent the residue was crystallised from light petroleum (b. p. 60—80°) giving buff crystals (5·6 g.), m. p 71—79°, a second crop (3·5 g.), m. p. 50—56°, and a third crop (1·6 g.), m. p. 46—50°. Fractional crystallisation from light petroleum (b. p. 60—80°) finally gave two pure products: *5-benzoyloxy-2-methoxytoluene* separated as prisms (3·6 g.), m. p. 88—89° (Found: C, 74·6; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·5; H, 5·8%), while *2-benzoyloxy-5-methoxytoluene* formed needles (2·9 g.), m. p. 55—57° (Found: C, 74·4; H, 5·6%). The 5-benzoyloxy-derivative was also prepared by methylation of toluquinol 4-benzoate (11·2 g.), giving the methyl ether (9·9 g.), m. p. and mixed m. p. 88—89°.

Toluquinol 1-Methyl Ether.—Alkaline hydrolysis of 5-benzoyloxy-2-methoxytoluene, as described for the corresponding benzyl ether, and crystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 44—46° (Bamberger [15] gives m. p. 46—46·5°). Toluquinol 4-methyl ether, similarly prepared from the isomeric benzoate, formed needles, m. p. 70—71°, from light petroleum (b. p. 40—60°) (lit.,[15] m. p. 70·5—71·5°).

5- and 7-Methyltocol from Toluquinol 1-Methyl Ether.—The methyl ether (1·3 g.), phytol (3·7 ml.), benzene (15 ml.), and formic acid (15 ml.) were heated under reflux for 4 hr. The upper layer was separated, the lower layer extracted with benzene, and the combined benzene solutions washed with N-sodium hydroxide and with water. Evaporation of the solvent left a brown oil (4·15 g.), which was heated with hydrogen bromide in acetic acid (42 ml.; 22%) and concentrated hydrochloric acid (4 ml.) for 4 hr. Working up yielded a 48% concentrate (3·4 g.) containing both 5- and 7-methyltocol the overall yield being 45%).

5- and 7-Methyltocol Benzyl Ethers.—The mixed tocols (2·47 g., 73% concentrate), benzyl bromide (1·6 ml.), and acetone (50 ml.) were shaken with sodium hydroxide solution (3·6 ml.; 36% w/v) for 2 hr. Water was added and the oil isolated with ether, washed with water, and dried. After removal of solvent and excess of benzyl bromide, the oil, now non-reducing, was distilled in a short-path still as a yellow oil, b. p. 210° (bath)/0·02 mm. The distillate was now reducing. On catalytic reduction of a sample of the distilled benzyl ether, the concentration of 5- and 7-methyltocol was found to be 71%.

Thermal Reaction of 5- and 7-Methyltocol Benzyl Ethers.—The benzyl ether mixture (1·55 g.; 71%) in tetradecane (35 ml.) was heated under gentle reflux for 1 hr. The solvent was removed under vacuum, and the dark residual oil (1·1 g.) examined by paper chromatography. Two reducing bands were present, a slower band containing 5- and 7-methyltocol (amounting to 28% of the total material) and a faster band containing benzylmethyltocols (*ca.* 22% of total). The two reducing products were separated by chromatography on zinc carbonate–Hyflo Super-cel.

(*a*) The faster brown oil was free from 5- and 7-methyltocol, did not couple with diazotised *o*-dianisidine, and gave an assay of *ca.* 71%. The exact concentration was uncertain since the requisite spectrophotometric factor was assumed to be the same as for 5,7-dimethyltocol. Distillation gave the mixed benzylmethyltocols as an orange-yellow oil, b. p. 180° (bath)/10^{-2} mm. (Found: C, 82·1; H, 10·5. Calc. for $C_{34}H_{52}O_2$: C, 82·8; H, 10·6%), $\nu_{max.}$ 3509 w, 2907 vs, 1460 s, 1376 m, 1344 w, 1323 m, 1225 w, and 1157 m cm.$^{-1}$.

(*b*) The slower brown oil was rechromatographed to give a dark yellow oil (69 mg.) which was almost non-coupling with diazotised *o*-dianisidine; assay showed 92% of 5-methyltocol. Distillation afforded a pale yellow oil, b. p. 130° (bath)/5 × 10^{-4} mm. (Found: C, 81·6; H, 12·1. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%).

Proportions of 5- and 7-Methyltocol in Phytol Condensation Products.—The proportions were determined as described by Green and Marcinkiewicz,[12] involving the preparation and quantitative separation of the nitrosated tocols. Toluquinol 1-benzyl ether with phytol gave 5-methyltocol (35%) and 7-methyltocol (67%), while toluquinol 1-methyl ether gave 5-methyltocol (38%) and 7-methyltocol (62%). In one experiment, after thermal treatment of the mixed tocol benzyl ethers, the tocol band comprised 5-methyltocol (34%) and 7-methyltocol (66%).

5-Acetamidotoluquinol.—5-Acetamidotoluquinol 1-benzyl ether (1·0 g.) in alcohol (30 ml.) was shaken with hydrogen and palladised charcoal (10%) till uptake ceased. The catalyst and solvent were removed and the *product* was crystallised from ethyl acetate–light petroleum

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

(b. p. 60—80°), forming small white prisms (0·55 g.), m. p. 175—177° (Found: C, 59·6; H, 6·2; N, 8·0. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·8%). The *dibenzyl ether* separated from aqueous alcohol in fine white needles, m. p. 116—117° (Found: C, 76·3; H, 6·1; N, 4·2. $C_{23}H_{23}O_3N$ requires C, 76·5; H, 6·4; N, 3·9%).

5-Acetamidotoluquinol Dimethyl Ether.—5-Acetamidotoluquinol (0·9 g.), methyl iodide (2·5 g.), potassium carbonate (1·4 g.), and acetone (15 ml.) were heated under reflux for 5 hr. After removal of most of the solvent, addition of water caused separation of a solid which was taken up in ethyl acetate, washed with N-sodium hydroxide and water, and dried. Evaporation of solvent and crystallisation from aqueous alcohol gave flat white needles, m. p. 164—166° (Found: C, 63·2; H, 7·0; N, 6·7. $C_{11}H_{15}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%).

5-Aminotoluquinol Dimethyl Ether.—The acetamido-derivative (1·5 g.), concentrated hydrochloric acid (10 ml.), acetic acid (10 ml.), and water (10 ml.) were heated under reflux for 2 hr. The mixture was concentrated and the product crystallised from alcohol–ethyl acetate, the *amine hydrochloride* separating as white needles, m. p. 207—208° (decomp.) (Found: C, 53·5; H, 7·0; N, 7·0. $C_9H_{14}O_2NCl$ requires C, 53·1; H, 6·9; N, 6·9%). The *base* formed plates, m. p. 112—113°, from aqueous alcohol (Found: C, 64·2; H, 7·8; N, 8·1. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·9; N, 8·4%).

5-Bromotoluquinol Dimethyl Ether.—5-Aminotoluquinol dimethyl ether (1·95 g.), hydrobromic acid (3·5 ml.; 48%), and water (1·5 ml.) were stirred at 0° while sodium nitrite (0·82 g.) in water (1·5 ml.) was slowly added. The diazonium solution was added in portions to cuprous bromide (1·5 g.) in hydrobromic acid (1·0 ml.; 48%) heated on the steam-bath. After completion of the addition the product was isolated by steam-distillation, the distillate was extracted with ethyl acetate, and the extracts were dried and evaporated. The residue was crystallised from aqueous alcohol, 5-bromotoluquinol dimethyl ether separating as prisms (1·65 g.), m. p. 92—93°, not depressed on admixture with an authentic specimen [15] possessing an identical infrared spectrum (Found: C, 46·9; H, 4·5; Br, 35·0. Calc. for $C_9H_{11}O_2Br$: C, 46·7; H, 4·8; Br, 34·6%).

4-Acetamido-5-acetoxy-2-methoxytoluene.—This *amide* was prepared from toluquinol 1-methyl ether, as previously described for the 2-benzyloxytoluene derivative, and formed needles, m. p. 145—147°, from alcohol (Found: C, 61·0; H, 6·5; N, 5·7. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·4; N, 5·9%). Hydrolysis with cold aqueous alcoholic sodium hydroxide afforded *5-acetamidotoluquinol 1-methyl ether*, which crystallised from aqueous alcohol as white needles, m. p. 161° (Found: C, 61·4; H, 6·7; N, 7·2. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·8; N, 7·2%). Methylation of this product yielded 5-acetamidotoluquinol dimethyl ether, m. p. 164—166°, identical with the product described above.

5-Nitrotoluquinol Dimethyl Ether.—Toluquinol dimethyl ether (1·5 g.) in glacial acetic acid (10 ml.) was stirred at 20° and nitric acid (0·7 ml.; *d* 1·42) was added during 15 min. After a further hour, the mixture was poured into water, and the product crystallised from alcohol, the *nitro-compound* forming glistening yellow needles, m. p. 117—118° (Found: C, 54·6; H, 5·9; N, 7·4. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6; N, 7·1%). Catalytic reduction (palladised charcoal) gave 5-aminotoluquinol dimethyl ether, m. p. 112—113°, identical with the product already described.

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