257. *Studies on Vitamin E. Part IV. Synthetic Experiments in the Coumaran and Chroman Series. The Structure of the Tocopherols.*

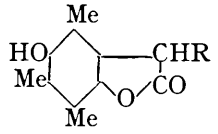
By F. Bergel, (Miss) A. Jacob, A. R. Todd, and T. S. Work.

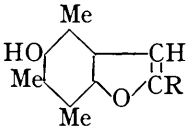
Confirmation of the view expressed in Part III of this series that the tocopherols are chroman or coumaran derivatives bearing a long side chain in the heterocyclic nucleus has been sought by model synthetic experiments. ψ-Cumoquinone, condensed with ethyl sodiostearoylacetate, gave as main product 5-*hydroxy*-3-*stearoyl*-4 : 6 : 7-*trimethyl*iso*coumaranone* from which was prepared 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumaran*. This compound is isomeric with β-tocopherol and resembles it closely in absorption spectrum and reducing properties, but it has no vitamin E activity in doses up to 100 mg. Condensation of ethyl sodiopalmitoylacetate and ψ-cumoquinone proceeded similarly. 5-*Hydroxy*-2 : 4 : 6 : 7-*tetramethylcoumaran*, synthesised by two methods, also resembles the tocopherols closely in properties. Similarly close resemblance is shown by 6-*hydroxy*-2 : 2 : 4-*trimethylchroman*, synthesised from 6-hydroxy-4-methylcoumarin. Structural formulæ for the tocopherols are proposed and discussed. The degradative and synthetic evidence available does not distinguish definitely between chroman and coumaran formulæ for the tocopherols.

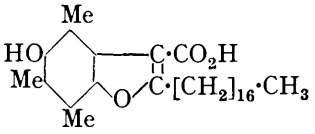
In Part III of this series (this vol., p. 253) it was suggested that α- and β-tocopherol were probably coumaran or chroman derivatives bearing a long side chain in the heterocyclic nucleus. With a view to test this hypothesis we undertook the synthesis of compounds of this type. Some of our results have already been reported (*Nature*, 1938, **141**, 646) and are now given in more detail.

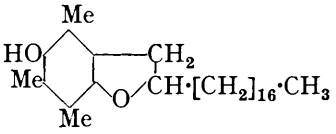
Smith and MacMullen (*J. Amer. Chem. Soc.*, 1936, **58**, 630) showed that condensation of ψ-cumoquinone with ethyl sodioacetoacetate, followed by acidification of the initially formed addition product, yielded a mixture of 5-hydroxy-4 : 6 : 7-trimethyl*iso*coumaranone

(I; R = H) and 5-hydroxy-2 : 4 : 6 : 7-tetramethylcoumarone (II; R = Me). Since coumarans can be prepared by partial hydrogenation of coumarones, this method applied to higher homologues of acetoacetic acid appeared to offer an unambiguous route for the synthesis of 5-hydroxy-coumarans bearing a long side chain in position 2. This proved to be the case, although the reaction took a somewhat unexpected course.

(I.) 

 (II.)

(III.) 

 (IV.)

Condensation of stearoyl chloride with ethyl sodioacetoacetate afforded *ethyl stearoylacetoacetate* which gave on gentle hydrolysis *ethyl stearoylacetate*. The latter substance when subjected to further hydrolysis yielded *methyl* n-*heptadecyl ketone*. When condensed with ψ-cumoquinone in a manner similar to that employed by Smith and MacMullen (*loc. cit.*), ethyl sodiostearoylacetate gave 5-*hydroxy*-3-*stearoyl*-4 : 6 : 7-*trimethyl*isocoumaranone (I; R = $CO{\cdot}C_{17}H_{35}$) in good yield, accompanied by small amounts of 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone* (II; R = $C_{17}H_{35}$) and 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone*-3-*carboxylic acid* (III). The occurrence of (I; R = $CO{\cdot}C_{17}H_{35}$) as main product of the reaction is presumably to be attributed to the increased stability of the higher β-ketonic acids as compared with acetoacetic acid. The reactions of the various products leave no doubt as to their constitution.

It seemed possible that the *iso*coumaranone (I; R = $CO{\cdot}C_{17}H_{35}$) might be converted into the desired coumarone (II; R = $C_{17}H_{35}$) by opening the lactone ring, decarboxylating the initially formed acid, and again closing the ring *via* the enolised keto-group. Warming with alkali proved unsatisfactory for this purpose; much decomposition occurred, and the only readily identifiable product was stearic acid. Better results were obtained by heating the *iso*coumaranone with alcoholic hydrochloric acid in presence of zinc. The reaction product consisted of a mixture of the coumarone (II; R = $C_{17}H_{35}$) and the *ethyl* ester of (III). To eliminate formation of this ester, the experiment was repeated, glacial acetic acid being substituted for the alcohol previously used; this proved entirely satisfactory, the coumarone (II; R = $C_{17}H_{35}$) being obtained in almost theoretical yield. The structure of the acid (III) was confirmed by decarboxylation to (II; R = $C_{17}H_{35}$).

The *iso*coumaranone derivative (I; R = $CO{\cdot}C_{17}H_{35}$) on pyrolysis gave a mixture of substances from which could be isolated 5-hydroxy-4 : 6 : 7-trimethyl*iso*coumaranone (I; R = H), identical with the condensation product from ψ-cumoquinone and ethyl acetoacetate. The condensation of ethyl sodiopalmitoylacetate with ψ-cumoquinone proceeded in a manner analogous to that of the stearoyl compound, the main product being 5-*hydroxy*-3-*palmitoyl*-4 : 6 : 7-*trimethyl*isocoumaranone (I; R = $CO{\cdot}C_{15}H_{31}$) from which could be prepared 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*pentadecylcoumarone* (II; R = $C_{15}H_{31}$) and *ethyl* 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*pentadecylcoumarone*-3-*carboxylate*.

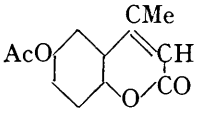
Partial hydrogenation of 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone* (II; R = $C_{17}H_{35}$) in glacial acetic acid with palladised charcoal as catalyst gave 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumaran* (IV). This compound is isomeric with β-tocopherol and shows a close resemblance to the tocopherols in most of its properties, although it appears to lack vitamin E activity when tested in dosages of 50 mg. and 100 mg. In reducing properties and absorption spectrum it is almost identical with the tocopherols, and on thermal decomposition it yields duroquinol. Conversion of (IV) into its *allophanate* causes a change in absorption spectrum similar to that observed on allophanating the tocopherols. The details of the spectra are summarised in Table I. Surface-film measurements of β-tocopherol and of 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone*

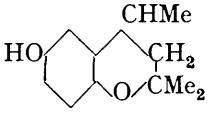
(II; R = $C_{17}H_{35}$) were made by Dr. J. F. Danielli, to whom we express our thanks. The results, which have been reported elsewhere (*Nature*, 1938, **141**, 646), indicate that the two compounds are analogous in structure. Accurate measurements could not be made with the coumaran (IV) itself since it formed solid films. As an example of a somewhat simpler coumaran derivative we also prepared *5-hydroxy-2 : 4 : 6 : 7-tetramethylcoumaran* by heating *ψ*-cumoquinol with allyl bromide in presence of zinc chloride, a reaction which proceeded with some difficulty. The same substance was also obtained by heating *ψ-cumoquinol monoallyl ether* to a high temperature, followed by cyclisation of the initially formed trimethylallylquinol by heating with pyridine hydrochloride. This compound also shows close similarity to the tocopherols in reducing properties and absorption spectrum.

TABLE I.

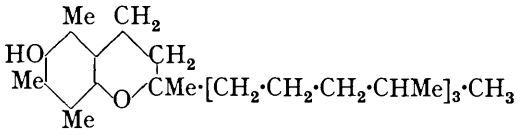
Substance.	Wave-length, A. Max.	Min.	$\epsilon_{mol.}$, max.
β-Tocopherol	2950	2600	3698
5-Hydroxy-2 : 4 : 6 : 7-tetramethylcoumaran	2960	2700	3840
Compound (IV)	2970	2580	3993
Compound (VI)	3010	2560	3803
β-Tocopheryl allophanate	2850	2550	2320
Allophanate of compound (IV)	2870	2540	2683
Allophanate of compound (VI)	2830	2560	1925

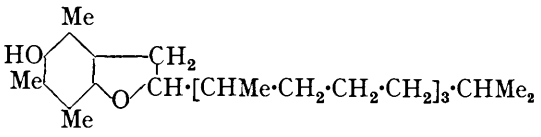
The experimental evidence is in accordance with the view that the tocopherols are coumaran derivatives, but the possibility of a chroman structure is not excluded. Spectroscopically, at least, one would not expect 5-hydroxycoumarans to differ materially from 6-hydroxychromans (cf. von Auwers, *Annalen*, 1918, **415**, 98). To test this point we synthesised *6-hydroxy-2 : 2 : 4-trimethylchroman* (VI) by a method leaving no doubt as to its structure. Treatment of 6-acetoxy-4-methylcoumarin (V) (Borsche, *Ber.*, 1907, **40**, 2732) with methylmagnesium iodide gave *6-hydroxy-2 : 2 : 4-trimethyl-Δ³-chromen*, readily hydrogenated to (VI). As anticipated, the compound (VI) also resembled the tocopherols closely in reducing properties and absorption spectrum, and the allophanates were also similar (cf. Table I). The standard methods of chroman synthesis have been developed largely with resorcinol derivatives. When applied to substituted quinols, they do not as a rule function satisfactorily. Formation of the heterocyclic ring is not so readily achieved, and the susceptibility to oxidation of the starting material and products is an added complication. We have been engaged for some time on a series of synthetic investigations on substituted 6-hydroxychromans, and our results will be communicated later.

(V.) 

 (VI.)

(VII.) $CH_3{\cdot}[CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2]_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}OH$

(VIII.) 

(IX.) 

The formula of β-tocopherol, $C_{28}H_{48}O_2$, differs from that of α-tocopherol, $C_{29}H_{50}O_2$, by CH_2, and the close similarity in properties between the two compounds makes it reasonable to assume that they are simple homologues. The formation of *ψ*-cumoquinol as pyrolytic product from the former (John, *Z. physiol. Chem.*, 1937, **250**, 11; Bergel, Todd, and

Work, *loc. cit.*) and of duroquinol from the latter (Fernholz, *J. Amer. Chem. Soc.*, 1937, **59**, 1154) indicates that α-tocopherol differs from β-tocopherol in having an additional methyl group on the aromatic nucleus. Since 5-hydroxy-4 : 6 : 7-trimethyl-2-*n*-heptadecylcoumaran gives duroquinol on pyrolysis, it may be concluded that α-tocopherol has three such methyl groups on the aromatic nucleus. As to the nature of the side chain, it has been established that the tocopherols contain several side methyl groups in addition to those on the aromatic ring. Since the tocopherols contain 20 carbon atoms in addition to those accounted for by the aromatic nucleus, it is attractive on biogenetic grounds to regard them as built up by condensation of quinols with phytol (VII). This substance occurs in all green plants as a constituent of chlorophyll, and it is noteworthy that it also accompanies the tocopherols in wheat-germ oil (Todd, Bergel, and Work, *Biochem. J.*, 1937, **31**, 2259). On this basis, α-tocopherol would have structure (VIII) or (IX) according to whether it is a chroman or coumaran derivative.

For β-tocopherol, if it differs from the α-compound only by having one less methyl group on the aromatic ring, three isomers (derived from *o*-, *m*-, and *p*-xyloquinol) are possible, both with coumaran and chroman structures, and it is likely that synthesis will prove the best means of distinguishing between them. In Part III (*loc. cit.*) we reported the presence of traces of an unidentified higher-melting quinol in addition to ψ-cumoquinol in the pyrolytic products of β-tocopherol. There is a possibility that this may have been *p*-xyloquinol (m. p. 215°) or *o*-xyloquinol (m. p. 221°) produced by fission of the heterocyclic ring at the point of attachment to the aromatic ring. It should, of course, be possible to obtain dimethylmaleic acid by oxidation of β-tocopherol if it is derived from *o*-xyloquinol but this would require considerably larger amounts of material than are at our disposal.

The conclusion that α-tocopherol might possess structure (VIII) was independently reached by Fernholz (*J. Amer. Chem. Soc.*, 1938, **60**, 700), and somewhat later the view that the tocopherols were coumarans or chromans with long side chains was also advanced by John (*Z. physiol. Chem.*, 1938, **252**, 222) and by Karrer, Salomon, and Fritzsche (*Helv. Chim. Acta*, 1938, **21**, 309). Fernholz favoured structure (VIII) rather than (IX) for α-tocopherol because he obtained on chromic acid oxidation a γ-lactone, $C_{21}H_{40}O_2$. He maintained that formation of a γ-lactone indicated a chroman structure for the vitamin, but, as Karrer, Fritzsche, Ringier, and Salomon (*ibid.*, p. 520) have pointed out, it is possible to derive the lactone $C_{21}H_{40}O_2$ from a coumaran structure also, so the evidence is not conclusive. Recently, John, Dietzel, Günther, and Emte (*Naturwiss.*, 1938, **26**, 366) have also brought forward evidence in support of a chroman structure for the vitamin, but it seems as though a final decision will be most readily attained by complete and unambiguous synthesis.

Before the appearance of Fernholz's publication (*loc. cit.*) we had carried out some further oxidations on β-tocopherol. Our quantities of material were too small to permit of the isolation of any identifiable products other than a fatty acid, apparently $C_{12}H_{24}O_2$; in view of Fernholz's results we have not continued the investigation. The results of catalytic hydrogenation of α-tocopherol are also recorded in the experimental section; it absorbs 4 mols. of hydrogen in the same way as β-tocopherol (Part III; *loc. cit.*).

Experimental.

Ethyl Stearoylacetoacetate.—To sodium dust (2·5 g.) covered with dry ether (400 c.c.), ethyl acetoacetate (28·2 g.; 2 mols.) diluted with dry ether (100 c.c.) was gradually added, and the mixture set aside overnight. Stearoyl chloride (32·7 g.) (Izar, *Biochem. Z.*, 1912, **40**, 403), dissolved in ether (100 c.c.), was added fairly rapidly at room temperature, and the whole subsequently refluxed for 1 hour in a nitrogen atmosphere, sodium chloride separating. After cooling, the mixture was diluted with water, and the ethereal layer tapped off and dried. After removal of ether and excess ethyl acetoacetate by distillation, the residue crystallised from alcohol. After two recrystallisations, the *ester* had m. p. 42° (Found: C, 72·7; H, 11·4. $C_{24}H_{44}O_4$ requires C, 72·7; H, 11·1%). Yield 29 g.

Ethyl Stearoylacetate.—The above ester (23 g.), suspended in water (300 c.c.) containing sodium hydroxide (2·3 g.), was heated on the water-bath during 45 minutes, and the milky liquid quickly cooled and extracted with ether. After being washed successively with sodium

carbonate solution and water, the ethereal solution was dried over sodium sulphate and evaporated. The oily residue set to a mass of colourless crystals. After six recrystallisations from alcohol, these had m. p. 46·5° (Found : C, 74·7; H, 11·8. $C_{22}H_{42}O_3$ requires C, 74·5; H, 11·8%). Yield 15 g. On addition of ammoniacal copper acetate to an alcoholic solution the copper salt separated as pale green crystals, m. p. 111—112°.

Methyl n-*Heptadecyl Ketone.*—To ethyl stearoylacetate (0·5 g.) dissolved in alcohol (10 c.c.), sodium hydroxide solution (20 c.c. of 2N) was added, and the mixture boiled under reflux for 12—14 hours. On diluting with water, extracting with ether and evaporating the ethereal solution, an oil was obtained which solidified on standing. Recrystallised from alcohol, the *ketone* formed colourless platelets, m. p. 57°. Despite repeated trials satisfactory analytical values could not be obtained (Found : C, 80·1; H, 12·9. $C_{19}H_{38}O$ requires C, 80·8; H, 13·5%). The *semicarbazone* crystallised from methyl alcohol as needles, m. p. 124—125° (Found : N, 12·2. $C_{20}H_{41}ON_3$ requires N, 12·4%), and from it the ketone, m. p. 57°, could be readily regenerated.

Condensation of ψ-Cumoquinone with Ethyl Sodiostearoylacetate.—To the ester (3·5 g.) in absolute alcohol (150 c.c.), a solution of sodium (0·23 g.) in absolute alcohol (25 c.c.) was added at room temperature. A solution of ψ-cumoquinone (1·5 g.) in absolute alcohol (25 c.c.) was dropped slowly into the mixture, which was frequently shaken during the addition. The ethyl sodiostearoylacetate slowly dissolved, and after standing overnight the purple-red solution was poured on a mixture of crushed ice (300 g.) and concentrated hydrochloric acid (9·4 c.c.). The brown precipitate, initially resinous, soon solidified, and was collected and dissolved in hot alcohol to which were added a few drops of alcoholic hydrogen chloride. On cooling, 5-*hydroxy*-3-*stearoyl*-4 : 6 : 7-*trimethyl*iso*coumaranone* (I; R = $CO{\cdot}C_{17}H_{35}$) separated in waxy crystals. Recrystallised from benzene–light petroleum, it had m. p. 104° (1·2 g.) (Found : C, 76·1; H, 9·9. $C_{29}H_{46}O_4$ requires C, 76·0; H, 10·0%). The substance reduced neutral silver nitrate fairly readily on heating, was soluble in aqueous sodium hydroxide, and gave a blue colour with ferric chloride in alcoholic solution.

The alcoholic mother-liquors from the first crystallisation of the above substance yielded on concentration small amounts of 5-hydroxy-4 : 6 : 7-trimethyl-2-*n*-heptadecylcoumarone (II; R = $C_{17}H_{35}$), m. p. 101—102° (see below), and 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone*-3-*carboxylic acid* (III). The latter, recrystallised from benzene–light petroleum, formed a colourless crystalline powder, m. p. 158—159° (Found : C, 76·1; H, 9·8. $C_{29}H_{46}O_4$ requires C, 76·0; H, 10·0%). It was soluble in dilute sodium carbonate solution, and on heating to 230—240°/14 mm. during 2 hours it lost carbon dioxide, yielding (II; R = $C_{17}H_{35}$), identified by m. p. and mixed m. p.

5-*Hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone* (II; R = $C_{17}H_{35}$).—(A) The *iso*coumaranone (I; R = $CO{\cdot}C_{17}H_{35}$) (0·5 g.) was dissolved in a mixture of absolute alcohol (10 c.c.) and concentrated hydrochloric acid (2·5 c.c.), and after addition of zinc dust (1·5 g.), the mixture was heated on the water-bath during 5 hours, cooled, diluted with water, and extracted with ether, the extract being washed with sodium carbonate solution and dried over sodium sulphate. The oily residue left on evaporation of the ether quickly solidified. On dissolution in hot alcohol and cooling, the *coumarone* separated as a colourless crystalline powder. After recrystallisation from methyl or ethyl alcohol it had m. p. 101—102° (Found : C, 80·8; H, 10·9. $C_{28}H_{46}O_2$ requires C, 81·2; H, 11·1%) (yield 0·2 g.). Insoluble in sodium hydroxide solution (2N), it gave with concentrated sulphuric acid a deep yellow, and with a mixture of concentrated sulphuric and glacial acetic acids a green colour. It reduced neutral silver nitrate on warming for 5 minutes on the water-bath; under the same conditions it reduced ammoniacal silver nitrate almost instantaneously. In alcoholic solution its absorption spectrum showed maxima at 2930 A. ($\epsilon_{mol.}$ = 4554) and 2550 A. ($\epsilon_{mol.}$ = 18216).

On keeping the alcoholic mother-liquors of the above substance for a few days, *ethyl* 5-*hydroxy*-4 : 6 : 7-*trimethyl*-2-n-*heptadecylcoumarone*-3-*carboxylate* separated as colourless needles. Recrystallised from methyl alcohol, it had m. p. 68—69° (Found : C, 76·5; H, 10·3. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·3%). On hydrolysis with alcoholic potassium hydroxide (20%), the ester yielded an acid, m. p. 158—159° undepressed on admixture with (III).

(B) The above *iso*coumaranone (I; R = $CO{\cdot}C_{17}H_{35}$) (1 g.) was refluxed for 5 hours with a mixture of glacial acetic acid (40 c.c.), concentrated hydrochloric acid (20 c.c. of 25%), and zinc dust (3 g.). After cooling, the mixture was diluted with water, washed thoroughly with sodium bicarbonate solution, dried, and evaporated. The colourless crystalline residue was recrystallised from alcohol and then had m. p. 101—102° (0·9 g.), undepressed on admixture with the coumarone (II; R = $C_{17}H_{35}$).

5-Hydroxy-4 : 6 : 7-trimethyl-2-n-heptadecylcoumaran (IV).—The above coumarone (0·6 g.), dissolved in glacial acetic acid (*ca.* 75 c.c.), was shaken at 46—47° with hydrogen in presence of palladised charcoal (*ca.* 0·4 g.) during 3 hours. Hydrogen absorption was then complete, the total amount absorbed corresponding approximately to 1 mol. After being filtered, the solution was diluted with water, extracted with ether, and the extracts, after being washed thoroughly with water and sodium bicarbonate, were dried and evaporated. The residue, which solidified on standing, crystallised from methyl alcohol in colourless waxy flakes, m. p. 95—95·5° (Found : C, 81·1; H, 11·6. $C_{28}H_{48}O_2$ requires C, 80·8; H, 11·5%). The coumaran, like α- and β-tocopherol, reduced neutral silver nitrate fairly readily on warming, and gave a bright yellow colour with a mixture of concentrated sulphuric and glacial acetic acids. On treatment with cyanic acid in benzene solution at 0°, it gave a colourless *allophanate*, which, recrystallised from acetone, had m. p. 192° (Found : C, 71·9; H, 9·8; N, 5·7. $C_{30}H_{50}O_4N_2$ requires C, 71·7; H, 10·0; N, 5·6%).

Pyrolysis of (IV).—The above coumaran (80 mg.) was heated in a nitrogen atmosphere at 360—365° during 6 hours. The semi-solid distillate was washed with light petroleum (b. p. 100—120°), and the sparingly soluble crystalline residue was purified by sublimation and by recrystallisation from this solvent. The product, of which only a few mg. were available, showed the properties of duroquinol and had m. p. 220—222°; a mixture with duroquinol (m. p. 228—230°) melted at 226—228°.

Pyrolysis of (I; R = $CO{\cdot}C_{17}H_{35}$).—When the *iso*coumaranone (I; R = $CO{\cdot}C_{17}H_{35}$) was heated to 350—400° in a nitrogen atmosphere, a semi-solid distillate was obtained, and crystallisation from alcohol afforded 5-hydroxy-4 : 6 : 7-trimethyl*iso*coumaranone (I; R = H), m. p. 195—196°; mixed with an authentic specimen (m. p. 197—198°) the m. p. was 196—197°.

Condensation of ψ-Cumoquinone with Ethyl Sodiopalmitoylacetate.—To a solution of ethyl palmitoylacetate (5·8 g.) (Levene and Haller, *J. Biol. Chem.*, 1925, **63**, 669) in absolute alcohol (10 c.c.), sodium (0·41 g.) dissolved in absolute alcohol (30 c.c.) was added. To the stiff soap formed, more alcohol was added (*ca.* 100 c.c.), and to the suspension ψ-cumoquinone (2·7 g. dissolved in 30 c.c. alcohol) was added at room temperature in small quantities with frequent shaking. The suspended matter passed into solution, and after standing overnight, the red-violet liquid was poured on a mixture of crushed ice (400 g.) and concentrated hydrochloric acid (15 c.c.). The brown precipitate was collected, dissolved in hot alcohol and cooled, whereupon *5-hydroxy-3-palmitoyl-4 : 6 : 7-trimethyl*isocoumaranone (I; R = $CO{\cdot}C_{15}H_{31}$) separated. Recrystallised from alcohol containing a trace of hydrogen chloride, it had m. p. 104° (Found : C, 75·4; H, 9·6. $C_{27}H_{42}O_4$ requires C, 75·6; H, 9·8%). The substance was soluble in dilute sodium hydroxide and gave a blue colour with ferric chloride in alcoholic solution. On pyrolysis at 350—400° it gave, together with unidentified products, 5-hydroxy-4 : 6 : 7-trimethyl*iso*coumaranone (I; R = H), identified by m. p. and mixed m. p.

The alcoholic mother-liquors of the above *iso*coumaranone were subjected to steam-distillation, which removed some unchanged quinone as well as alcohol. The residue was taken up in ether, and the ethereal solution dried and evaporated. The oil obtained was dissolved as far as possible in light petroleum (b. p. 40—60°) and subjected to chromatographic analysis on activated aluminium oxide (Merck), the column being developed with a mixture of light petroleum (b. p. 40—60°) and benzene (10 : 1). The chromatogram showed several indistinct bands in the upper part of the column, from which only resinous material could be obtained, but the lowest portion, which had a distinct blue fluorescence when viewed in ultra-violet light, yielded on elution with ether–methyl alcohol (1 : 4) a small amount of *5-hydroxy-4 : 6 : 7-trimethyl-2-n-pentadecylcoumarone* (II; R = $C_{15}H_{31}$). Recrystallised from methyl alcohol, it had m. p. 100—101° (Found : C, 80·6; H, 10·7. $C_{26}H_{42}O_2$ requires C, 80·8; H, 10·9%). The substance reduced neutral silver nitrate slowly on warming, and resembled the corresponding *n*-heptadecyl compound (II; R = $C_{17}H_{35}$) closely in its other properties. In alcoholic solution its absorption spectrum showed maxima at 2950 A. ($\epsilon_{mol.}$ = 3474) and 2550 A. ($\epsilon_{mol.}$ = 18914).

5-Hydroxy-4 : 6 : 7-trimethyl-2-n-pentadecylcoumarone (II; R = $C_{15}H_{31}$).—Treatment of the *iso*coumaranone (I; R = $CO{\cdot}C_{15}H_{31}$) (0·3 g.) with zinc and alcoholic hydrochloric acid in the manner already described for the corresponding heptadecyl compound yielded the coumarone (0·1 g.), m. p. 103—104° (Found : C, 80·5; H, 10·7%). Mixed with the above-described product, it had m. p. 102—104°. From the alcoholic mother-liquors of this substance, a second crystalline product (0·1 g.) was obtained, m. p. 63° to an opaque liquid which cleared at 71°. From analysis and mode of preparation it was considered to be *ethyl 5-hydroxy-4 : 6 : 7-trimethyl-2-n-pentadecylcoumarone-3-carboxylate* (Found : C, 75·9; H, 10·2. $C_{29}H_{46}O_2$ requires C, 76·0; H, 10·0%).

ψ-Cumoquinol Monoallyl Ether.—ψ-Cumoquinol (0·7 g.) was added to powdered potassium (0·2 g.) in toluene (20 c.c.), and the mixture refluxed in a hydrogen atmosphere for 30 mins. Ethyl alcohol (0·5 g.) was added, and the mixture refluxed until no more potassium remained. Allyl bromide (1·5 mol.) was added to the black gel, and the mixture refluxed for 2½ hours. Unchanged quinol was removed by pouring the product into aqueous sodium hyposulphite, extracting with ether, and separating the extract into fractions soluble and insoluble in light petroleum. The petroleum-soluble oil was distilled under 0·5 mm., the fraction of b. p. 110—120° being O-*monoallyl ψ-cumoquinol* (yield 40%) (Found : C, 75·1; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

5-*Hydroxy*-2 : 4 : 6 : 7-*tetramethylcoumaran.*—(A) The above allyl ether (0·4 g.) was heated at 230° for 1½ hours. The trimethylallylquinol so formed was not purified but mixed with pyridine hydrochloride (1 g.) and heated at 210° for a further hour. The product was extracted with ether, washed with sulphuric acid, and the extracted oil steam-distilled. The colourless crystalline *coumaran* distilling over was recrystallised from light petroleum (b. p. 60—80°); m. p. 128—129° (Found : C, 74·6; H, 8·1. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%) (yield 0·1 g.).

(B) ψ-Cumoquinol (0·25 g.) was refluxed for 3 days with allyl bromide (1 mol.) and zinc chloride (0·25 g.) in a mixture of equal parts of carbon disulphide and carbon tetrachloride (25 c.c.). Unchanged quinol was removed by pouring into petroleum (60—80°) and keeping the mixture overnight at 0°. The petroleum solution was filtered, evaporated, and the residual oil steam-distilled. The coumaran distilling over recrystallised from light petroleum (b. p. 60—80°), m. p. 128—129° (yield 30 mg.).

p-*Xyloquinol Monoallyl Ether.*—*p*-Xyloquinol (1·38 g.) was dissolved in ethyl alcohol (25 c.c.), and potassium (0·39 g.) added. The mixture was refluxed for ½ hour in hydrogen, and allyl bromide (1·21 g.) added. After refluxing for a further 2½ hours, the mixture was poured into water, extracted with ether, and the extracted oil distilled under 0·5 mm. The fraction, b. p. 115—120°, was p-*xyloquinol monoallyl ether* (Found : C, 73·8; H, 7·9. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·8%) (yield 0·73 g.).

6-*Hydroxy*-2 : 2 : 4-*trimethyl*-Δ^3-*chromen.*—6-Acetoxy-4-methylcoumarin (5·9 g.) (Borsche, *Ber.*, 1907, **40**, 2732), dissolved in dry benzene (250 c.c.), was gradually added to a solution of methylmagnesium iodide [prepared from magnesium (11·4 g.) and methyl iodide (67 g.) in ether–benzene], the whole being cooled in ice. After removal of ether by distillation, the mixture was refluxed for 2 hours, cooled, and treated with crushed ice and hydrochloric acid. The benzene layer was tapped off and evaporated, leaving a colourless oil which crystallised rapidly. Recrystallised from light petroleum (b. p. 60—80°), 6-*hydroxy*-2 : 2 : 4-*trimethyl*-Δ^3-*chromen* was obtained as faintly yellowish prisms, m. p. 104—105° (Found : C, 75·8; H, 7·3. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%). The acetyl group present in the initial material seems to be completely removed in working up, since the crude product, m. p. 102—104°, was unaffected by treatment with alkali. The substance gave a deep cherry-red colour with concentrated sulphuric acid alone or mixed with glacial acetic acid, and reduced neutral silver nitrate readily on warming. 6-Hydroxy-4-methylcoumarin gives practically no colour with sulphuric acid and does not reduce silver nitrate save in presence of ammonia. In alcoholic solution the absorption spectrum of the chromen had a maximum at 3340 A. ($\epsilon_{mol.} = 3724$).

6-*Hydroxy*-2 : 2 : 4-*trimethylchroman* (VI).—The above chromen (0·5 g.), dissolved in methyl alcohol (50 c.c.), was shaken with hydrogen at room temperature in presence of palladised charcoal (1 g.). After 30 minutes, hydrogen absorption had ceased, the volume absorbed being 65 c.c. (Calc. for 1 mol. : 66 c.c.). The mixture was filtered, the methyl-alcoholic solution evaporated, and the residue recrystallised from light petroleum (b. p. 60—80°), affording colourless needles, m. p. 107—108° (Found : C, 74·8; H, 8·2. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The *compound* gave a bright yellow colour with a mixture of concentrated sulphuric and glacial acetic acids, and reduced neutral silver nitrate readily on warming. Treatment with cyanic acid in benzene solution yielded an allophanate, m. p. 182°.

Oxidation of β-*Tocopherol.*—β-Tocopheryl allophanate (350 mg.) was hydrolysed by boiling for 1 hour with 5% methyl-alcoholic potassium hydroxide; the product was dissolved in methanol (25 c.c.), silver nitrate (1 g.) added, and the solution heated on the water-bath for 1 hour, diluted with water, and extracted with ether. The deep red ethereal solution of the quinone so obtained was completely decolorised with sodium hyposulphite solution. The colourless oil was allowed to stand with excess diazomethane in ether for 12 hours, and the methylated product treated with a mixture of potassium hydrogen sulphate (100 mg.) and chromic acid (225 mg.; 5 mols.) in glacial acetic acid (25 c.c.) and warmed on the water-bath until oxidation was complete. The crude mixture was steam-distilled, the distillate extracted with ether,

the ether freed from acetic acid by washing with water, and the extract separated into a neutral and an acid fraction. The oily acid fraction possessed a strong smell of a lower fatty acid, but an attempt to prepare a crystalline anilide was unsuccessful. The neutral volatile fraction gave, on crystallisation from acetone, a trace of a compound, m. p. 50—52°, and a micro-Zeisel determination indicated 10·5% OCH_3. There was insufficient material for complete purification and identification.

The non-steam-volatile oxidation products were also separated into neutral and acid fractions, and the former, which corresponded in weight to about 50% of the starting material, was further oxidised with chromic acid (225 mg.) and worked up as before. The combined non-volatile acid (90 mg.) was distilled in a high vacuum. There was considerable decomposition, but 31 mg. of a colourless acid were collected (Found, by titration with NaOH: *M*, 192. Calc. for $C_{12}H_{24}O_2$: *M*, 200). The acid gave a crystalline *p*-phenylphenacyl ester, m. p. 98—100° (Found: C, 79·2; H, 8·2. Calc. for $C_{26}H_{34}O_3$: C, 79·2; H, 8·6%).

Micro-hydrogenations.—These determinations were carried out by Mr. F. Boston, of Manchester University, using platinum oxide as catalyst. (I) α-Tocopherol (2·675 mg.) absorbed 0·5453 c.c. (3·9 mols.) of hydrogen at *N.T.P.*, the solvent being glacial acetic acid. No absorption occurred in the cold, but slow and regular absorption took place at 90°. (II) α-Tocopheryl allophanate (2·94 mg.) absorbed 0·5220 c.c. (4·09 mols.) of hydrogen at *N.T.P.*, the solvent being decalin–acetic acid; 1 mol. was absorbed in the cold, and the other 3 mols. on heating to 90° for 8 hours.

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