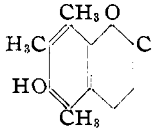
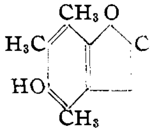
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XXX. Condensation of Butadiene and of Crotyl Systems with Trimethylhydroquinone[1]

BY LEE IRVIN SMITH AND JOHN A. KING[2]

Condensation of crotyl derivatives (chloride, bromide, and alcohol), as well as that of the related diene, butadiene, with trimethylhydroquinone would be expected to lead to 2,5,7,8-tetramethyl-6-hydroxychroman (I), or 2-ethyl-4,6,7-trimethyl-5-hydroxycoumaran (II), or to mixtures of the two. Karrer and collaborators[3] first prepared the chroman I, m. p. 143°, by condensation of crotyl *bromide* with the hydroquinone, and in subsequent papers[4] as well as in papers by John[5] and by v. Werder[6] the structure of this compound has been fully elucidated. Somewhat later, Karrer[7] stated that the reaction between crotyl *bromide* and the hydroquinone gave not only the chroman I, but also some of the isomeric coumaran II, m. p. 120° (m. p. of a mixture of I and II, also 120°). The structure of II was proved by its identity with a specimen prepared by addition of propionylacetic ester to trimethylquinone, according to the procedure of Smith and MacMullen.[8]


I

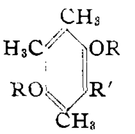

II

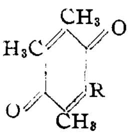
According to earlier work of Smith and collaborators[9] it was thought probable that condensation of butadiene with trimethylhydroquinone would also give the chroman I, or a mixture of this and the coumaran II. If so, this method would offer a relatively simple and attractive synthesis of these substances. Accordingly, butadiene and trimethylhydroquinone were dissolved in acetic acid containing a little zinc chloride and a drop of sulfuric acid, and the solution was allowed to stand in a sealed tube for a week at room temperature.[10] There resulted a good yield of a product (A), melting at 145°, which had the composition required by I (m. p. 143°). But this product failed to undergo the Furter–Meyer reaction with nitric acid, a characteristic property of I, and a mixture with known specimens of I melted at 115–130°. The same product A, m. p. and mixed m. p. 142–144°, resulted when crotyl *alcohol* was condensed with the hydroquinone according to the procedure of Karrer.[3]

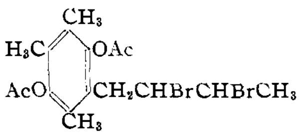
When crotyl *chloride* was condensed with trimethylhydroquinone, the product was the coumaran II, but when crotyl *bromide* was used, the product was a mixture of the chroman I and the coumaran II. No A was isolated from either of these condensations.

A, $C_{13}H_{18}O_2$, formed a diacetate $C_{17}H_{22}O_4$ (IV). This diacetate reacted with bromine to give a dibromide $C_{17}H_{22}O_4Br_2$ (V) with no evolution of hydrobromic acid. When A was oxidized with nitric acid, no red color developed, and the product was a yellow oil (VI) which could be reductively acetylated to the same diacetate IV, as was obtained from A. Methylation of A with methyl sulfate and alkali gave a yellow oil (VII) which, on ozonolysis, gave a white acid (VIII) identified as 2,5-dimethoxy-3,4,6-trimethylphenyl-

$$\begin{tikzcd}
& & \mathrm{VI} \arrow[dr] & & \\
\mathrm{II} & \mathrm{III} \arrow[l] \arrow[ur] \arrow[rr, dashed] \arrow[dr] & & \mathrm{IV} \arrow[r] & \mathrm{V} \\
& & \mathrm{VII} \arrow[r] & \mathrm{VIII} &
\end{tikzcd}$$




VI, R = crotyl


V

III, R = H; R′ = crotyl
IV, R = Ac; R′ = crotyl
VII, R = CH_3; R′ = crotyl
VIII, R = CH_3; R′ = $—CH_2COOH$

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(1) Paper XXIX, THIS JOURNAL, **63**, 1018 (1941).

(2) This work will be incorporated into the Ph.D. Thesis of John A. King. Published at the present time with the approval of a Committee of the Graduate Faculty of the University of Minnesota.

(3) Karrer, Escher, Fritzsche, Keller, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 939 (1938).

(4) (a) Karrer and Jensen, *ibid.*, **21**, 1622 (1938); (b) Karrer and Escher, *ibid.*, **22**, 264 (1939); (c) Karrer, Fritzsche and Escher, *ibid.*, **22**, 661 (1939).

(5) (a) John, Günther and Schmeil, *Ber.*, **71**, 2637 (1938); (b) John and Günther, *ibid.*, **72**, 1649 (1939); (c) John and Schmeil, *ibid.*, **72**, 1653 (1939); (d) John, Dietzel and Emde, *Z. physiol. Chem.*, **257**, 178 (1939).

(6) Von Werder and Jung, *Ber.*, **71**, 2650 (1938).

(7) Karrer, Escher and Rentschler, *Helv. Chim. Acta*, **22**, 1287 (1939).

(8) Smith and MacMullen, THIS JOURNAL, **58**, 631 (1936).

(9) (a) Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, **4**, 311 (1939); (b) Smith, Ungnade, Stevens and Christman, THIS JOURNAL, **61**, 2615 (1939).

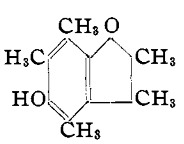
(10) These experiments were initiated by Dr. Cyrus O. Guss, who unfortunately was unable to continue the work.

acetic acid by comparison with an authentic specimen.[11] When A was dissolved in acetic acid and refluxed with hydrobromic acid, it was converted into the coumaran II.

In view of these facts, only one structure was possible for A, namely, 1-(2,5-dihydroxy-3,4,6-trimethylphenyl)-2-butene (III).

The fact that the crotyl derivative III resulted when butadiene and the hydroquinone reacted indicates that the aromatic nucleus added 1,4 to the diene. Moreover, the formation of this same crotyl derivative III when crotyl *alcohol* was used indicates that the aromatic nucleus reacts directly with the allylic alcohol, and not via phenyl crotyl ether, since it has been shown[12] that in the rearrangement of phenyl crotyl ethers, the crotyl group becomes inverted to an α-methylallyl group. It is not unreasonable to suppose that the crotyl halides react in a manner similar to the alcohol, and that the crotyl derivative III is likewise an intermediate in these cases. But when the halides are used, halogen acids are formed in the reaction and these cyclize III to the heterocyclic compound I or II. Nor is it difficult to explain why crotyl *chloride* should give only the coumaran II, while crotyl *bromide* gives a mixture of I and II, cyclization taking place in both directions. It has been shown by Hurd and Hoffman[13] that certain of these ring closures are subject to a peroxide effect when hydrobromic acid is used, whereas condensations with hydrochloric acid are not so affected, and very recently Tishler and Wendler[14] have shown that the addition of hydrobromic acid to the double bond in trimethylphytylhydroquinone produces two compounds, whereas addition of hydrochloric acid produces only one.

It has previously been reported[9b] that trimethylhydroquinone, when condensed with methylvinyl*carbinol*, gave the coumaran IX, whereas crotyl *bromide* gave the chroman I, although the chroman was difficult to purify and it was stated that the impurity was most likely II, or possibly IX, derived from the allylic isomer 3-bromobutene-1, present in the crotyl bromide. The close agreement between the melting points of II and the supposed IX, and of their acetates, led to a re-examination of the data. Condensation of methylvinylcarbinyl *chloride* with the hydroquinone led to a good yield of II; and finally, mixed melting point determinations showed that II and the original specimens labeled IX (prepared from methylvinylcarbinol) were identical. It is difficult to understand the formation of II from the secondary allylic compounds unless a rearrangement of the allylic system is involved at some stage. But in any event, it is clear that the tentative hypothesis as to the mechanism of the reaction between allylic compounds and hydroquinones, which was stated in an earlier paper[9b] will need some modification unless it can be shown definitely that a rearrangement of the secondary allylic derivatives occurs, and occurs not before but during the cyclization.



IX

Experimental Part[15]

Trimethylquinone was prepared by the method previously described[16] except that hydrated ferric sulfate was used as the oxidizing agent instead of ferric chloride. When ferric chloride was used, there was always an orange-red oil remaining after distillation of the quinone. This material consisted largely of trimethyl chloroquinone (m. p. 80–82°; hydroquinone, m. p. 194–195°; hydroquinone diacetate, m. p. 168–169°). Use of ferric sulfate gave a product quite free from halogen.

Crotyl alcohol was prepared from the aldehyde by the method of Young, Hartung and Crossley.[17] The product (45% yield) boiled at 120–125° under 740 mm.

Crotyl bromide, b. p. 105–110°, was prepared from the alcohol using phosphorus tribromide and pyridine.[18]

Crotyl Chloride.[19]—A commercial specimen was redistilled and the fraction boiling at 77–79° under 740 mm. was used.

Methylvinylcarbinyl Chloride.[19]—A commercial specimen was redistilled and the fraction boiling at 65–67° under 740 mm. was used.

Butadiene.—A commercial sample was used without purification.

2,5,7,8-Tetramethyl-6-hydroxychroman I.—This was prepared by the three unequivocal methods to be found in the literature.[5a,5b,5d,6] All specimens melted at 141–142°, alone or when mixed.

2-Ethyl-4,6,7-trimethyl-5-hydroxycoumaran (II).—This substance was prepared by addition of propionylacetic ester to trimethylquinone.[7,8] The coumaran, when very

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(11) Ref. 8, p. 634.

(12) (a) Lauer and Filbert, THIS JOURNAL, **58**, 1388 (1936); (b) Lauer and Ungnade, *ibid.*, **58**, 1392 (1936).

(13) Hurd and Hoffman, *J. Org. Chem.*, **5**, 212 (1940).

(14) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941).

(15) Microanalyses by E. E. Renfrew and C. H. Stratton.

(16) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 318 (1939).

(17) Young, Hartung and Crossley, THIS JOURNAL, **58**, 100 (1936).

(18) (a) Kirrmann, *Bull. soc. chim.*, [4] **39**, 698 (1926); (b) Prévost, *Ann. chim.*, [10] **10**, 153 (1928).

(19) We wish to thank Dr. E. C. Williams and the Shell Development Co. for generous gifts of these chlorides.

pure, melted at 123–124°, but usually specimens melted a degree or two below this point. It was planned also to prepare II by an independent synthesis starting with 2,5-dihydroxy-3,4,6-trimethylbenzaldehyde. Although the aldehyde was prepared readily, it could not be condensed with chloroacetone in the presence of sodium ethoxide[20]; instead, the aldehyde group was lost and the only product isolated was trimethylhydroquinone.

2,5-Dihydroxy-3,4,6-trimethylbenzaldehyde was prepared from trimethylhydroquinone (10.0 g.), zinc cyanide (15.5 g.), hydrogen chloride and aluminum chloride (14 g.) according to the method of Adams and Montgomery.[21] The product, after crystallization from water containing a little bisulfite, weighed 5.55 g. (47%) and formed yellow needles which melted at 146–147°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 67.04; H, 6.98.

Semicarbazone.—Prepared from the aldehyde in the usual way, and crystallized from 60% ethanol, the semicarbazone formed orange-yellow needles which melted at 234–235° with decomposition.

Anal. Calcd. for $C_{11}H_{15}O_3N_3$: C, 55.69; H, 6.32. Found: C, 56.85; H, 6.18.

1-(2,5-Dihydroxy-3,4,6-trimethylphenyl)-2-butene (III).—Trimethylhydroquinone (15.2 g.) was dissolved in pure dry benzene (100 cc.). Crotyl alcohol (14.4 g.) and zinc chloride (15 g., freshly fused) were added and the mixture was refluxed on the steam-bath for five hours. Water was added, and the product was removed and crystallized from petroleum ether (b. p., 60–68°). It formed a white solid (9.5 g., 41%) which melted at 143.5–144.5° and which acquired a reddish-brown color rather rapidly on standing in air.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.72; H, 8.73. Found: C, 75.37; H, 8.61.

When mixed with the chroman I (m. p. 140–141°), the butene melted at 110–130°. The Furter–Meyer test[22] was negative; a simultaneous determination carried out on the chroman I was positive.

Cyclization.—The butene III (1.0 g.) was dissolved in acetic acid (10 cc.). Hydrobromic acid (6.0 cc., 48%) was added and the mixture was refluxed for two hours. The solution was poured into water and the product was removed and crystallized from petroleum ether (b. p. 60–68°). It weighed 0.8 g., and melted at 117–118°, alone or when mixed with the coumaran II.

Diacetate IV.—The above butene III (0.75 g.) was acetylated by warming it with acetic anhydride (10 cc.) containing a drop of sulfuric acid. The product (0.9 g.), after crystallization twice from petroleum ether (b. p. 60–68°), melted at 83–84°.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.29; H, 7.62. Found: C, 70.72; H, 7.65.

1-(2,5-Diacetoxy-3,4,6-trimethylphenyl)-2,3-dibromobutane (V).—The diacetate IV (0.75 g.) was dissolved in carbon tetrachloride (10 cc.) and the solution was cooled (0°) and brominated by the slow addition of a cold solution of bromine (2.0 g.) in carbon tetrachloride (20 cc.) until a faint bromine color persisted. The pink solution was washed once with a little 10% potassium hydroxide, then dried and concentrated. The product was removed and crystallized from petroleum ether (b. p. 60–68°) when it weighed 1.1 g. and melted at 148–148.5°.

Anal. Calcd. for $C_{17}H_{22}O_4Br_2$: C, 45.33; H, 4.88. Found: C, 45.09; H, 4.81.

Trimethylcrotylquinone VI (By C. O. Guss).—The butene III (0.5 g.) was refluxed for one hour in dry ethanol (20 cc.) containing silver nitrate (5 g.). The yellow solution was poured into water and extracted with ether. The extract was dried (sodium sulfate) and the solvent was removed under reduced pressure. The product, (VI) an orange oil, could not be crystallized. It was refluxed in acetic anhydride (15 cc.) containing zinc dust (0.5 g.) and sodium acetate (0.5 g.). The product, after crystallization from petroleum ether (b. p. 60–68°), melted at 79–80.5° and was the diacetate IV as shown by mixed melting point.

1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-butene VII.—The butene III (3.0 g.) was dissolved in a mixture of methanol (30 cc.) and methyl sulfate (19.0 g.). The solution was gently refluxed, and then, with vigorous stirring, a hot solution of potassium hydroxide (28 g.) in methanol (100 cc.) was added as rapidly as possible without causing the material to be thrown out of the flask. The mixture was refluxed for twenty minutes and was then steam distilled. The distillate was diluted with ice and extracted with ether. Removal of the ether left an oil (about 2 cc.) which was distilled in an atmosphere of nitrogen. It boiled at 150° under 10 mm.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.49; H, 9.40. Found: C, 76.62; H, 9.35.

2,5-Dimethoxy-3,4,6-trimethylphenylacetic Acid VIII.—The dimethyl ether VII (500 mg.) was dissolved in ethyl bromide (60 cc.) and subjected for fifteen minutes to a rapid current of ozonized oxygen (5% O_3) at −15°. The solution was poured into water (40 cc.) containing hydrogen peroxide (10 cc., 3%),[23] and warmed on the steam-bath until the ethyl bromide was removed. The aqueous solution was cooled, made alkaline with 10% potassium hydroxide, extracted with ether and the extract was discarded. The aqueous layer was acidified with hydrochloric acid and again extracted with ether. Removal of the ether left an oil which solidified on standing overnight in the refrigerator. The white solid, after crystallization four times from dilute ethanol, melted at 152–154° and showed no depression in melting point (154–156°) when mixed with an authentic specimen (m. p. 154–157°).[11]

Condensation of Butadiene with Trimethylhydroquinone (by C. O. Guss).—The following directions represent the best procedure found in twelve experiments in which the conditions, reagents, etc., were varied. Liquid butadiene (8 cc.) was introduced into an ordinary Carius tube cooled in a liquid air-bath. To this was added, in order, the hydroquinone (5 g.), acetic acid (25 cc.), anhydrous zinc chloride (1 g., freshly fused and powdered) and sulfuric acid (2 drops). The tube was sealed, removed from the bath and allowed to stand, with occasional shaking, at

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[20] Stoermer, Chydenius and Schinn, *Ber.*, **57**, 75 (1924).

[21] Adams and Montgomery, THIS JOURNAL, **46**, 1518 (1924).

[22] *Helv. Chim. Acta*, **22**, 240 (1939).

[23] Riebsomer and Tallman, *Proc. Indiana Acad. Sci.*, **43**, 136 (1933).

room temperature for seven days. The tube was then opened and the contents poured over ice. The mixture was extracted with ether, the extract was dried (sodium sulfate) and the solvent was removed under reduced pressure. The residue after one crystallization from petroleum ether (b. p. 60–68°) weighed 3.3 g. and melted at 140–141°. After crystallization twice more from the same solvent, the substance melted at 143–145°. It was the butene III, identical with the product obtained above from crotyl alcohol. The diacetate (IV) m. p. 84° was likewise identical with a specimen prepared from crotyl alcohol.

No condensation occurred when gaseous butadiene was bubbled through a warm solution of the hydroquinone in acetic acid in the presence of zinc chloride; nor could any product other than unchanged hydroquinone be isolated if the sealed tube were heated; likewise no condensation occurred when dioxane and oxalic acid were substituted for the acetic acid and zinc chloride, respectively, whether the tube was heated or not.

Condensation of Methylvinylcarbinyl Chloride with Trimethylhydroquinone.[3,9b]—The chloride (3.6 g., freshly distilled) and the hydroquinone (4.0 g.) were added to dry petroleum ether (80 cc., b. p. 90–100°) containing zinc chloride (4.0 g., freshly fused), and the mixture was refluxed on the steam-bath for five hours while a continuous stream of dry nitrogen was bubbled through the liquid. The clear yellow solution was decanted from a red oily solid and the latter was extracted with four 80-cc. portions of hot petroleum ether. The petroleum ether solutions were combined, an equal volume of ether was added and the mixture was washed six times with water (100 cc. each time), twice with potassium hydroxide (2 *N*, 100 cc. each time) and filtered. After drying, the solution was concentrated to a small volume (20 cc.) and cooled. The white solid (1.5 g.) melted at 116–118°, alone or when mixed with the coumaran II. A second crop of 2.0 g., m. p. 116–117°, and a third crop of 0.8 g., m. p. 115–116°, were obtained.

Condensation of Crotyl Chloride with Trimethylhydroquinone.—This condensation was a duplicate of the above, using crotyl chloride (6.0 g., freshly distilled) and the same amounts of the other reagents. The product (3.5 g.) melted at 117–118°, alone or when mixed with the coumaran II.

Condensation of Crotyl Bromide with Trimethylhydroquinone.[3]—The hydroquinone (4.0 g.), crotyl bromide (4.3 g.) and zinc chloride (3.0 g., freshly fused) were mixed with petroleum ether (100 cc., b. p. 60–68°) and the mixture was refluxed until all of the hydroquinone dissolved (about forty minutes). The petroleum ether solution was decanted from the black residue and mixed with an equal volume of ether. The solution was washed twice with water (100 cc. each time), once with sodium carbonate (5%) and twice more with water. After drying, the solution was concentrated to about 50 cc., cooled and the product (4.2 g., m. p. 102–109°) was removed. By repeated crystallization from petroleum ether (b. p. 60–68°), each time allowing only about two-thirds of the solid to separate, there were obtained ultimately 10–15 mg. of the less soluble chroman I, m. p. 138–140°, and 3.0 g. of the more soluble coumaran II, m. p. 116–118°.

Summary

1. Pseudocumohydroquinone, when condensed with crotyl *alcohol* or with butadiene, forms trimethylcrotylhydroquinone.

2. Pseudocumohydroquinone, when condensed with crotyl *chloride* or methylvinylcarbinyl *chloride*, forms 2-ethyl-4,6,7-trimethyl-5-hydroxycoumaran.

3. Pseudocumohydroquinone, when condensed with crotyl *bromide*, forms a mixture which consists largely of the above coumaran, but which contains also some 2,5,7,8-tetramethyl-6-hydroxychroman.

4. The relation of these facts to the mechanism of the condensations is discussed.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

The Bromination of 2-Phenylphenyl Acetate

BY STEWART E. HAZLET AND HARRY A. KORNBERG

The studies on substitutions in esters containing diphenyl groups[1] have been continued, and the acetate of 2-phenylphenol[2] has now been brominated. The bromination of this ester gives rise chiefly to 4-bromo-2-phenylphenyl acetate when the ester is allowed to react with somewhat more than one molecular proportion of the halogen. By the interaction of slightly more than two molecular proportions of the halogen with one of 2-phenylphenyl acetate, 4,6-dibromo-2-phenylphenyl acetate is formed. Similar substitutions occur when 2-phenylphenol is brominated.[3]

4-Bromo-2-phenylphenol is a liquid; therefore, when it was encountered in this work, it was converted to the corresponding aryloxyacetic

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(1) For the last paper in this series see Hazlet and Kornberg, THIS JOURNAL, **61**, 3037 (1939).

(2) Vorozhtsov and Troshchenko, *J. Gen. Chem.* (U. S. S. R.), **8**, 424 (1938) (*Chem. Abst.*, **32**, 7907 (1938)).

(3) (a) Auwers and Wittig, *J. prakt. Chem.*, **108**, 99 (1924); (b) Harris and Christiansen, *J. Am. Pharm. Assoc.*, **22**, 723 (1933).