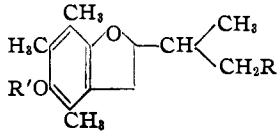
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

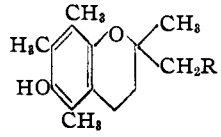
The Chemistry of Vitamin E. XL.[1] Synthesis and Properties of 2-Isopropyl-4,6,7-trimethyl-5-hydroxycoumaran

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

After the gross structure of α-tocopherol had become well established, considerable discussion centered about the question as to whether the hetero ring contained five or six atoms—*i. e.*, whether this substance was a coumaran (I) or a chroman (II). In the early work, the chroman



I, R = $C_{15}H_{31}$, R′ = H
III, R = R′ = H
XI, R = H, R′ = Ac

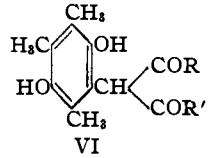


II, R = $C_{15}H_{31}$
IV, R = H

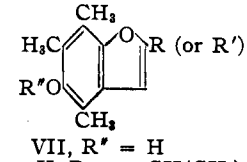
IV served as a model substance for many of the experiments; in fact, this compound has been synthesized in several laboratories by no less than nine independent methods[3] and its chemistry has been extensively investigated. On the other hand, simple analogs of I, such as III, are not well known and very few representatives of the class of 2-*s*-alkyl-5-hydroxycoumarans have been prepared and studied. With the exception of the 2-isopropyl-6-methoxycoumaran studied by Shriner and his students[4] practically all of the 2-alkyl-5-hydroxycoumarans noted in the literature have primary alkyl groups in the 2-position.[5]

It was of interest to synthesize the coumaran III, an isomer of the chroman IV, and to compare the chemistry of these two isomeric substances. Curiously enough, III was not an easy substance to prepare. Five series of reactions, apparently straightforward and leading to III, were investigated before a successful synthesis of III was achieved. In every one of these five unsuccessful synthesis, some reaction for which there were models in the literature, either did not produce the expected intermediate or else failed entirely.[6] The sixth and successful synthesis was based upon the work of Smith and Kaiser[7] who found that addition of the sodium enolates of β-diketones (V) to trimethylquinone produced trimethylhydroquinones with the β-diketone residue attached at the 6-position of the ring (VI). Action of hydrochloric acid upon the hydroquinones VI converted them into 2-alkyl coumarones (VII), one

$RCOCH_2COR'$
V



VI



VII, R″ = H
X, R = —$CH(CH_3)_2$
R″ = Ac

acyl group being lost during the cyclization. When an unsymmetrical β-diketone was used, the final product was a mixture of two coumarones; from trimethylquinone and acetylisobutyrylmethane (V, R = —$CH(CH_3)_2$, R′ = CH_3) a mixture of the corresponding coumarones VII was obtained, but these could not be separated. It appeared, therefore, that for successful preparation of any given coumarone by the method of Smith and Kaiser it was necessary that the β-diketone V should be a symmetrical one.

Diisobutyrylmethane was prepared by a Claisen condensation of ethyl isobutyrate and methyl isopropyl ketone[8]; the sodium enolate of this diketone, when added to trimethylquinone, produced the corresponding hydroquinone VI (R and R′ are isopropyl) in about 75% yield. When the hydroquinone VI was subjected to the action of acetic anhydride, there resulted the diacyl hydroquinone VIII, formed by migration of one of the C-isobutyryl groups to the ortho hydroxyl group and acetylation of the other hydroxyl group. Formation of the ester VIII was in accordance with the general behavior of such hydroquinones as VI. When the hydroquinone VI was refluxed

(1) XXXIX, THIS JOURNAL, **64**, 1084 (1942).

(2) Abstracted from a Thesis presented by J. A. King to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, August, 1942.

(3) (a) Smith, Ungnade and Prichard, *Science*, **88**, 37 (1938); (b) John, Günther and Schmeil, *Ber.*, **71**, 2637 (1938); (c) Smith, Hoehn and Ungnade, *J. Org. Chem.*, **4**, 351 (1939); (d) John and Schmeil, *Ber.*, **72**, 1653 (1939); (e) John and Günther, *ibid.*, **72**, 1649 (1939); (f) John and Rathmann, *ibid.*, **74**, 890 (1941); (g) Smith and Miller, THIS JOURNAL, **64**, 404 (1942).

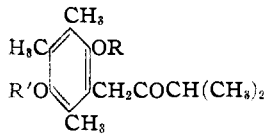
(4) (a) Shriner and Damschroder, THIS JOURNAL, **60**, 894 (1938); (b) Shriner and Anderson, **60**, 1415 (1938); (c) Shriner and Witte, **61**, 2328 (1939); (d) **63**, 1108 (1941).

(5) For some syntheses of these substances, see, in addition to ref. 4, v. Auwers and Pohl, *Ann.*, **405**, 243 (1918); *Ber.*, **48**, 85 (1915).

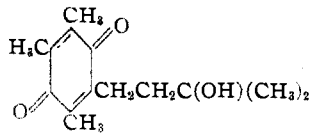
(6) For a detailed discussion of one of these, see Smith, King and Irwin, THIS JOURNAL, **65**, in press (1943).

(7) Smith and Kaiser, *ibid.*, **62**, 133 (1940).

(8) (a) Sprague, Beckham and Adkins, *ibid.*, **56**, 2665 (1934); (b) Morgan and Taylor, *J. Chem. Soc.*, **127**, 797 (1925).



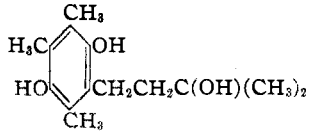
VIII, R = $(CH_3)_2CHCO$, R′ = Ac
IX, R = R′ = H



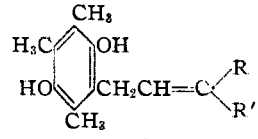
XII

with hydrochloric acid, it was smoothly converted into the coumarone VII (R = isopropyl), possibly via the hydroquinone IX. The coumarone formed an acetate (X), and it was readily and quantitatively reduced in the presence of Raney nickel catalyst to the coumaran III, which likewise formed an acetate (XI).

The coumaran III was then used in a study of the mechanism of ring closure of ortho hydroxyalkylhydroquinones. It is well known that mild oxidation of para hydroxy-chromans and -coumarans produces yellow para quinones in which one of the side chains is hydroxylated. Reduction of the yellow quinones gives the hydroquinones, which in every case so far studied have been isolated. The hydroquinones may then be cyclized to the original heterocyclic compounds by action of acids. For the pentamethylchroman IV, the sequence is IV, XII, XIII and IV. But it is not known whether intermediates such as XIV exist between XIII and IV, or whether the cyclization proceeds directly from XIII to IV. Substance XIV is unknown, but a lower homolog XV, has been studied[9] and it, on cyclization by

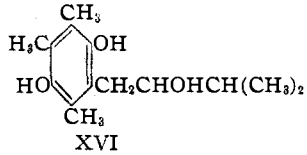


XIII

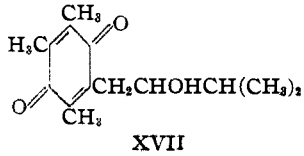


XIV, R = R′ = CH_3
XV, R = H, R′ = CH_3

action of hydrochloric acid, is converted into the corresponding 2-ethylcoumaran. But in XIV the structural relationships are such that only a chroman (IV) would be expected when cyclization occurred. Hence, if the isopropyl coumaran III were converted to hydroquinone XVI and the latter then cyclized, it could be decided from the nature of the product whether or not XIV was an intermediate, for any XIV produced in this sequence of reactions would appear as IV, particularly if care were taken to exclude peroxides during the cyclization.[10]



XVI



XVII

The coumaran III was oxidized to the yellow quinone XVII, an oil, by action of either ferric chloride or auric chloride. The quinone was then reduced under very mild conditions by two methods: action of sodium hydrosulfite and of zinc and dilute acetic acid. In both cases the product, obtained in quantitative yield, was the coumaran III, and no hydroquinone XVI could be isolated. This result indicated that the mechanism of the cyclodehydration of the hydroquinone XVI involved direct elimination of the elements of water between the two hydroxyl groups and did not involve the unsaturated intermediate XIV. But even more, the result indicated that this β-hydroxyalkylhydroquinone, with a secondary group in the γ-position, was so prone to undergo cyclization that it could not even be isolated when it was formed in the presence of neutral or mildly acidic reducing agents.

Experimental Part[11]

Diisobutyrylmethane (V, R = R′ = $(CH_3)_2CHCO$).[8]—Powdered sodium (105 g., 4.58 moles) was added, with stirring, to ethyl isobutyrate (985 g., 8.5 moles, b. p. 99–101° (740 mm.)). An exothermic reaction occurred, and the sodium was displaced by a slightly yellow solid. Methyl isopropyl ketone[12] (86 g., 1.0 mole, b. p., 92–94° (740 mm.)) was slowly (one hour) added to the well-stirred suspension, the mixture was stirred for three hours longer and was allowed to stand at room temperature overnight. The mixture was diluted with an equal volume of water and the layers were separated. The organic layer was extracted with three 400-cc. portions of water, and the extracts were combined with the main aqueous solution. The combined aqueous solutions were extracted with three 400-cc. portions of ether (ether extracts discarded) and then acidified with acetic acid (290 cc.). The upper organic layer was removed and added to a well-stirred solution of cupric acetate dihydrate (200 g.) in water (3 l.). The copper enolate was removed, suspended in ether, and decomposed by shaking the suspension with dilute sulfuric acid. Removal of the ether left an orange-red oil (43.5 g., 28%) which boiled at 62–63° (3 mm.).

2,6-Dimethyl-4-[2′,5′-dihydroxy-3′,4′,6′-trimethylphenyl]-heptane-3,5-dione (VI).—Diisobutyrylmethane

(9) Smith and King, THIS JOURNAL, **63**, 1887 (1941).

(10) (a) Hurd and Hoffman, *J. Org. Chem.*, **5**, 212 (1940); (b) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941).

(11) Microanalyses by E. E. Renfrew and S. T. Rolfson.

(12) Whitmore, Evers and Rothrock, *Org. Syn.*, **13**, 68 (1933).

(16.85 g., 0.108 mole) was slowly (fifteen minutes) added to a cooled (below 25°) and stirred solution of sodium ethoxide (7.34 g., 0.108 mole)[13] in dry alcohol (50 cc.). A solution of trimethylquinone (16.0 g., 0.107 mole) in dry alcohol (50 cc.) was slowly (one hour) added, with continued stirring and cooling below 25°. The reaction mixture was stirred at room temperature for forty-five minutes, after which it was cooled (0°), carefully acidified with hydrochloric acid (litmus), and poured into water (800 cc.). The suspension of red solid was extracted with ether until the aqueous layer was colorless, and the solvent was removed under reduced pressure from the combined ether extracts. The residual red solid was recrystallized first from petroleum ether (250 cc., b. p. 60–68°), and then from a benzene–petroleum ether mixture. The light tan solid weighed 25 g. (76%) and melted at 133–135°. A specimen was recrystallized from dilute methanol; it then melted at 135–135.5°.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.59; H, 8.49. Found: C, 70.54; H, 8.64.

3-Methyl-1-[2′-isobutyroxy-5′-acetoxy-3′,4′,6′-trimethylphenyl]-butanone-2 (VIII).—The diketone VI (20 mg.) was dissolved in acetic anhydride (5 cc.), and a drop of sulfuric acid was added. The solution was immediately poured over ice (25 cc.) and allowed to stand until the ice melted. The solid was removed and crystallized twice from petroleum ether (b. p. 60–68°); it then melted at 113°.

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.97; H, 8.04. Found: C, 69.20; H, 8.22.

2-Isopropyl-4,6,7-trimethyl-5-hydroxycoumarone [VII, R = $-CH(CH_3)_2$].—The diketone VI (11.4 g., m. p. 133–135°) was refluxed for three hours with hydrochloric acid (250 cc.) and alcohol (10 cc.). The mixture was diluted with water (500 cc.) and subjected to distillation with superheated steam (110°) until no more solid appeared in the condensate. The residue in the distillation flask deposited 4.9 g. of unchanged VI, m. p. 133–135°. The white solid in the distillate was removed and crystallized twice (Norite) from dilute alcohol. It then weighed 4 g. and melted at 118°. The same coumarone VII resulted when the diester VIII was subjected to this procedure.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 77.22; H, 8.68.

2-Isopropyl-4,6,7-trimethyl-5-acetoxycoumarone (X).—The coumarone VII (50 mg.) was acetylated as described above for acetylation of VI. The product, after crystallization from petroleum ether (b. p. 28–38°), melted at 69–70°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.85; H, 7.71. Found: C, 73.41; H, 7.56.

2-Isopropyl-4,6,7-trimethyl-5-hydroxycoumaran (III).—A solution of the coumarone VII (2.5 g.) in alcohol (50 cc.) was refluxed over Raney nickel (2 g.) for thirty minutes. The solution was then decanted into a small hydrogenation bomb, fresh catalyst (2 g.) was added, and the mixture was subjected for one hour at 125° to the action of hydrogen under 1300 lb. The cooled mixture was filtered and the filtrate was concentrated to a volume of 20 cc., diluted with water to incipient cloudiness, and cooled. The solid (2.4 g., m. p. 105–107°) was removed and crystallized twice from dilute alcohol and once from petroleum ether (b. p. 28–38°). It then melted at 112°; when mixed with the starting material (VII), it melted at 103–108°. When prepared by reduction of the quinone XVII (see below), the coumaran III melted at 115°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.83; H, 9.04.

2-Isopropyl-4,6,7-trimethyl-5-acetoxycoumaran (XI).—The coumaran III (40 mg.) was acetylated as described for VI. The product was removed by ether extraction and crystallized from petroleum ether (b. p., 28–38°). It then melted at 72–73°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.28; H, 8.39. Found: C, 73.09; H, 8.74.

2,3,5-Trimethyl-6-[2′-hydroxy-3′-methylbutyl]-1,4-benzoquinone (XVII). A. Gold Chloride Oxidation.—Auric chloride trihydrate (1.50 g., 20% excess) in water (15 cc.) was added to a solution of the coumaran III (1.0 g.) in alcohol (10 cc.). The reaction was immediate. After the mixture had stood for thirty minutes, the gold was removed by filtration (hardened paper), the filtrate was concentrated under reduced pressure to a volume of 10 cc., diluted with water (40 cc.), and extracted with two 25-cc. portions of ether. The combined extracts were washed with five 25-cc. portions of saturated carbonate and dried (sodium sulfate). Removal of the solvent left a residue (950 mg.) of an orange oil which could not be crystallized.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47. Found: C, 70.76; H, 8.15.

B. Ferric Chloride Oxidation.—A solution of ferric chloride hexahydrate (491 mg., no excess) in water (15 cc.) was added to a solution of the coumaran III (200 mg.) in alcohol (10 cc.). The mixture was warmed on the steam bath for one hour, then diluted with water (50 cc.) and processed as above in A. The product was a yellow oil, XVII (150 mg.).

Coumaran III from Quinone XVII. A. Reduction by Hydrosulfite.—The above quinone (100 mg.) was dissolved in methanol (20 cc.) and shaken for thirty minutes with a solution of sodium hydrosulfite (1 g.) in water (5 cc.). The solution was added to a mixture of water (30 cc.) and petroleum ether (20 cc., b. p. 60–68°) and the mixture was thoroughly shaken. The organic layer was removed, dried (sodium sulfate), and concentrated. The product weighed 94 mg. and melted at 115°; when mixed with III (m. p. 112°) prepared by reduction of the coumarone, it melted at 114–115°. The chroman IV melts at 94°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 75.87; H, 8.86.

B. Reduction by Zinc and Acetic Acid.—The quinone XVII (1.0 g.) was refluxed for two hours with acetic acid (15 cc.), water (10 cc.), and zinc (1.0 g., 20 mesh). The mixture was poured over ice (100 g.) and extracted with ether (50 cc.). The ether extract was washed with saturated carbonate solution until it was neutral, and the solvent was removed. The residue, after crystallization from petroleum ether (b. p. 28–38°), weighed 620 mg. and melted at 114–115°, alone or when mixed with III prepared from VII.

(13) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1935, p. 343.

Summary

1. Diisobutyrylmethane has been added to trimethylquinone, and the resulting product has been cyclized to 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumarone VII.

2. The coumarone has been reduced to the corresponding coumaran (III), which is the only representative known of its class—a *p*-hydroxy-2-alkylcoumaran having a secondary alkyl group in the 2-position.

3. This coumaran has been oxidized by two methods to the corresponding yellow *p*-benzoquinone XVII.

4. The yellow quinone XVII, when reduced either in a neutral or slightly acid medium, gives a quantitative yield of the coumaran III and no intermediate hydroquinone can be isolated. None of the isomeric chroman IV is obtained. These results show that the cyclodehydration of a hydroquinone ortho substituted by a side chain containing a secondary alkyl group and a hydroxyl group in the β-position involves direct elimination of water between the two hydroxyl groups and does not involve a preliminary dehydration of the side chain. Moreover, cyclization of this substituted hydroquinone occurs with such great ease that the hydroquinones cannot be isolated when the quinone is reduced.

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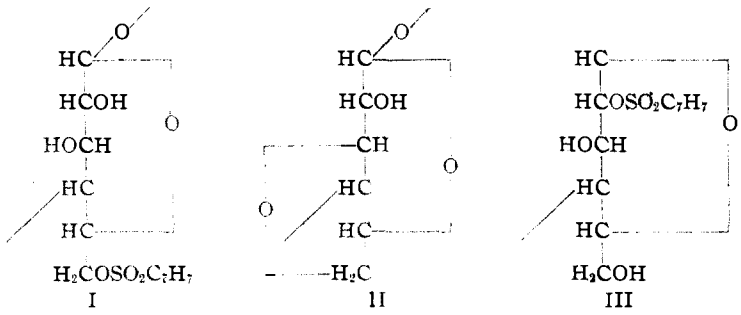
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 277]

The Formation of Anhydro Structures by the Alkaline De-acylation of a Partly Substituted Cellulose Acetate *p*-Toluenesulfonate

BY THOMAS S. GARDNER[1] AND C. B. PURVES

Earlier investigations[2,3] showed that a technical, acetone-soluble cellulose acetate, of average substitution 2.44, contained 0.362 mole of unesterified hydroxyl groups distributed in the second and third positions of the glucose residues. The remaining 0.198 mole was assigned to the primary alcohol or sixth position because the corresponding *p*-toluenesulfonyl ester (tosyl ester) was unstable to sodium iodide in hot acetonylacetone. Since the rates at which alcoholic groups in the second, third and sixth positions reacted with tosyl chloride in pyridine were in the approximate ratio of 22 : 1 : 230,[3] an interruption of the esterification at a suitable stage produced an acetate in which almost all of the unacetylated sixth, a few of the unacetylated second and practically none of the unacetylated third positions were tosylated. The tosylated glucose residues in such a mixed ester therefore occurred mainly, but not exclusively, as the structures I and III, from which the acetyl substituents were omitted for the sake of clarity.



Peat[4] and Isbell[5] carefully reviewed the behavior of partly tosylated hexose derivatives in the presence of various reagents and analogy with the work in that field suggested that structure I would produce the 3,6-anhydro unit II when deacylated with a methanol solution of sodium methylate. The removal of the tosyl group from III by the same reagent would bring about a Walden inversion on carbon atom two and the transitory formation of the 2,3-anhydromannose derivative IV. The immediate addition of sodium methylate to the ethylene oxide ring of IV would proceed with a Walden inversion, either at the second or at the third carbon atom, and the final result would be a mixture of 2-methylglucose V and 3-methyl-

(1) DuPont Post-Doctoral Research Fellow, 1941–1942; Present address: Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) Cramer and Purves, THIS JOURNAL, **61**, 3458 (1939).

(3) Gardner and Purves, *ibid.*, **64**, 1539 (1942).

(4) Peat, *Chem. Soc. Ann. Reports*, **36**, 258 (1939).

(5) Isbell, *Ann. Rev. Biochem.*, **9**, 65 (1940).