red silky needles identical with the picrate isolated from the chloranil dehydrogenation.

The hydrocarbon regenerated from the pure picrate in ether–benzene–chloroform solution, by selective adsorption on activated alumina, crystallized from methanol in elongated colorless prisms, m. p. 96–97°. A mixture with 4-isopropyl-1,3,6,7-tetramethylnaphthalene (IX) (synthetic,[3] m. p. 96.5–97°) melted at 96–97°. A mixture with 4-isopropyl-1,2,6,7-tetramethylnaphthalene (X) (from cadinine,[3] m. p. 102–103°) melted at 71–74°.

Acknowledgment.—The authors wish to express their appreciation to the firms of Fritzsche Brothers, Inc., and the Dodge and Olcott Company, for their generous grants of the ginger oil used in this work.

Summary

By the action of the methyl Grignard reagent on isozingiberene dioxide, methyl groups were introduced marking the positions of the double bonds in isozingiberene. The dimethylcadalene obtained by subsequent dehydration and dehydrogenation was identical with synthetic 4-isopropyl-1,3,6,7-tetramethylnaphthalene, indicating that the double bonds are in the 3,4 and 6,7 positions in the isozingiberene molecule.

The recent revision of the formula for cadinene is supported by the evidence that one of the previous formulas for cadinene, and the formula previously assigned to cadinene dihydrochloride, represent the structures of isozingiberene and isozingiberene dihydrochloride.

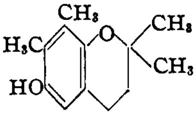
NORTHAMPTON, MASS. RECEIVED JULY 6, 1944

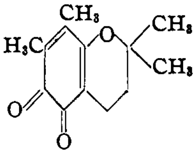
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

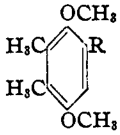
Vitamin E. XLIII.[1] Synthesis of 2,2,7,8-Tetramethyl-6-hydroxychroman and its Behavior upon Oxidation

BY LEE IRVIN SMITH AND ROY W. H. TESS[2]

In a previous paper,[3] it was reported that 2,2,7,8-tetramethyl-6-hydroxychroman (I), when oxidized by action of silver nitrate in ethanol, gave the red ortho-quinone II, m. p. 109.5–110.5°. However, the substance actually oxidized was an oil obtained by extracting, with Claisen alkali, the product of a condensation between *o*-xylohydroquinone and isoprene. The condensation product was itself an oil, and although from the method of preparation it was reasonable to assume that the alkali-soluble fraction of this oil would consist largely of I, the material was not analyzed, and it was characterized only by its conversion into II upon oxidation. Recently, some question arose concerning the generality of the statement previously made[3] with reference to the behavior upon oxidation of *p*-hydroxychromans, such as I, and in order to acquire more definite information, the chroman I has now been prepared in a pure state, and the behavior upon oxidation has been studied. The results confirm the previous work—oxidation of the pure chroman, m. p. 84.5–85.5°, by action of silver nitrate in ethanol, gave the red *o*-quinone II, m. p. 109.5–110.5°, in a yield of 26%.


I


II



III, R = H VI, R = $CH_2CH_2COCH_3$
IV, R = CH_2Cl VII, R = $CH_2CH_2C(OH)(CH_3)_2$
V, R = $CH_2CH(COCH_3)COOC_2H_5$

The chroman I cannot be prepared in a pure form by condensation of *o*-xylohydroquinone with isoprene, for the product of this reaction is an inseparable mixture of I, the double chroman, the hydroquinone and polymers of isoprene. Although this mixture can be separated into two fractions by extraction with Claisen alkali, these fractions are both oils and no pure I can be obtained from the alkali-soluble fraction. It was necessary, therefore, to synthesize I by a method which would lead only to the desired compounds and in which the intermediates could be readily purified. The synthetic route involved the sequence of compounds III, IV, V, VI, VII and I.

Experimental Part[4]

2,3-Dimethylphenol[5] was coupled with diazotized sulfanilic acid according to the procedure previously developed,[6] and the azo compound was reduced to 2,3-dimethyl-4-aminophenol by action of aqueous sodium hydrosulfite.[7] A small sample of the aminophenol, recrystallized several times from benzene, formed white needles which melted at 172–173°.[8]

Anal. Calcd. for $C_8H_{11}ON$: C, 70.04; H, 8.08. Found: C, 69.99; H, 8.33.

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[1] XLII, THIS JOURNAL, **65**, 745 (1943).

[2] Abstracted from a thesis by R. W. H. Tess, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, March, 1944.

[3] Smith, Irwin and Ungnade, THIS JOURNAL, **61**, 2424 (1939).

[4] Microanalyses by Stanley T. Rolfson.

[5] Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941).

[6] Smith, Opie, Wawzonek and Prichard, *ibid.*, **4**, 318 (1939).

[7] For an example of the procedure, see Smith, Hoehn and Whitney, THIS JOURNAL, **62**, 1863 (1940).

[8] Hinkel, Collins and Ayling, *J. Chem. Soc.*, 2968 (1923), give the m. p. as 175°.

The aminophenol obtained from 36.6 g. (0.3 mole) of 2,3-dimethylphenol was partially dissolved in dilute sulfuric acid (400 cc., *ca.* 10%), and the mixture was slowly (two hours) added to a solution of ferric sulfate (600 g., 1.5 moles) in water (1 liter) in an apparatus arranged for steam distillation under about 100 mm. As the aminophenol was added, *o*-xyloquinone was removed from the reaction mixture continuously by steam distillation; the distillation with steam was continued for one hour after all the aminophenol had been added. The distillate was cooled and the quinone (21.1 g., m. p. 57–58°) was collected. The filtrate was extracted with ether, the ether was evaporated, and the residue, sublimed under reduced pressure, yielded 3.6 g. of *o*-xyloquinone melting at 52–56°. The total yield of quinone, 24.7 g., was 61% based upon the phenol. Oxidation of the aminophenol by action of manganese dioxide according to the procedure of Arnold and Zaugg[9] and with continuous removal of the product by steam distillation under reduced pressure, gave the quinone in 54% yield, based upon the phenol. This procedure, however, was advantageous in that less foaming occurred during the steam distillation.

***o*-Xylohydroquinone.**—Water (62 cc.) and zinc (28.4 g., 0.43 gram atom, 20–30 mesh) were added to a solution of *o*-xyloquinone (28.4 g., 0.21 mole) in acetic acid (125 cc.). The mixture was boiled until it became colorless (thirty minutes); hot water (125 cc.) was then added and the solution was decanted from the zinc. The zinc was washed by decantation with several portions of hot water; from the combined aqueous solutions the hydroquinone (25.3 g., 88%) separated on cooling. It melted at 220° with partial decomposition.

2,3-Dimethyl-4-methoxyphenol.—Sulfuric acid (9.5 g.) was added, with cooling, to a solution of *o*-xylohydroquinone (7.62 g.) in methanol (80 cc.), and the solution was allowed to stand at room temperature for two days.[10] Water (250 cc.) was added, and the oily solid was removed and crystallized from methanol. The product (1.56 g., 19%) melted at 92–96°. The analytical sample, prepared by crystallizing the material several times from methanol, melted at 95–97°.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.30; H, 8.27.

***o*-Xylohydroquinone dimethyl ether** (III), m. p. 77.5–78.5°, was prepared from the hydroquinone by the method of Smith and Austin.[11]

2,5-Dimethoxy-3,4-dimethylbromobenzene.—A solution of bromine (3.2 g., 0.02 mole) in chloroform (30 cc.) was added to a solution of the dimethyl ether III (3.32 g., 0.02 mole) in chloroform (40 cc.). The solution was stirred for thirty-five minutes, and then was washed successively with water, aqueous sodium bicarbonate (5%), and water. The solvent was removed by distillation and the residue was distilled under reduced pressure. The product (4.16 g., 85%) boiled at 165–166° (31 mm.).

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.34. Found: C, 48.89; H, 5.07.

This bromo ether failed to react with magnesium under the ordinary conditions for formation of Grignard reagents; the method of entrainment was not, however, tried.

2,5-Dimethoxy-3,4-dimethylbenzyl Chloride (IV).—The procedure of Smith and Austin[11] was modified, and the yield of IV was increased from 52 to 73%. Dry hydrogen chloride was passed into a vigorously stirred mixture of the dimethyl ether III (28 g., 0.168 mole), formalin (20 cc., 40%), and hydrochloric acid (100 cc., 12 *N*). After one hour and forty-five minutes, the reaction flask was immersed in an oil-bath at 90°. The solid material melted; passage of the gas was continued (at 90°) for thirty minutes. The mixture was cooled, and the solid (36.6 g.) was removed and crystallized from petroleum ether (b. p. 60–68°). The product (22.5 g.) melted at 67–68°. Second and third crops of material were obtained by concentrating the filtrates; these were combined and recrystallized from petroleum ether (b. p. 60–68°), resulting in 3.74 g. of material also melting at 67–68°. The total material, 26.2 g., represented a yield of 73%.

2,5-Dimethoxy-3,4-dimethylbenzylacetone (VI).—Ethyl acetoacetate (23.4 g., 0.18 mole) was added to a solution of sodium (2.53 g., 0.11 gram atom) in dry ethanol (120 cc.). A solution of the benzyl chloride IV (19.64 g., 0.092 mole) in ethanol (250 cc.) was added, with stirring, to the sodioacetoacetic ester, and the mixture was allowed to stand overnight. It was then refluxed for two and one-half hours, diluted with water (1.2 liters) and extracted with ether. Removal of the ether left an oily residue (the benzylacetoacetic ester V) which was stirred with aqueous sodium hydroxide (500 cc., 5%) for four hours. A small amount of insoluble oil (*ca.* 1 cc.) was removed and the aqueous solution was acidified (Congo red) with sulfuric acid and heated on the steam-bath for thirty minutes to complete the decarboxylation. The mixture was cooled, and the white solid was removed and crystallized from dilute ethanol. The ketone (10.7 g.) melted at 55.5–56.5°, a second crop (4.16 g., m. p. 53–56°) was obtained by concentrating the filtrate. The total material, 14.86 g., represented a yield of 69%. A small sample, crystallized several times from dilute ethanol, melted at 56–57°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.11; H, 8.27.

When this alkylation was carried out in toluene instead of in ethanol, the yield of VI was only 28%.

1-(2,5-Dimethoxy-3,4-dimethylphenyl)-3-methylbutanol-3 (VII).—A solution of the ketone VI (4.28 g., 0.18 mole) in ether (50 cc.) was slowly added to a Grignard reagent prepared from methyl iodide (3.34 g., 0.0235 mole), ether (65 cc.), and magnesium (0.53 g., 0.22 gram atom). The mixture was refluxed for fifty minutes and then stirred with aqueous ammonium chloride (200 cc., 20%). The layers were separated; the aqueous layer was extracted several times with ether. The combined ethereal solutions were washed with water and dried (sodium sulfate). Removal of the ether left an oil which could not be crystallized, and which was used without further purification in the subsequent reactions. Cleavage of this carbinol by action of hydrobromic acid (40%) in acetic acid gave the methyl ether of I in 59% yield (based upon the ketone VI). This methoxychroman in turn was demethylated by action of 48% hydrobromic acid in acetic acid and isolated as the acetate of I (44% yield based upon the ketone VI). Hydrolysis of the acetate produced I in 70% yield. The chroman I was also produced directly from the carbinol by action of 48% hydrobromic acid in acetic acid.

2,2,7,8-Tetramethyl-6-methoxychroman.—A solution of the carbinol VII (derived from 0.01 mole of the ketone VI) in acetic acid (20 cc.) containing hydrobromic acid (20 cc., 40%) was boiled for two and one-half hours. The dark mixture was poured into water, the solid was removed, washed with water and crystallized from dilute ethanol (Norite). The white solid (0.63 g.) melted at 57–59°; a second crop (0.53 g.) was obtained by diluting the filtrate. The total yield (1.16 g.) was 59%. The analytical sample, prepared by several crystallizations from dilute ethanol, melted at 58.5–59.5°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15, Found: C, 76.61; H, 9.21.

2,2,7,8-Tetramethyl-6-acetoxychroman.—The above methoxychroman (200 mg.) in acetic acid (20 cc.) containing hydrobromic acid (6 cc., 48%), was boiled for three hours. The pink solution was poured into water, and the oil was removed by ether extraction. Removal of the ether left an oil which could not be crystallized. The oil was taken up in ether and extracted with Claisen alkali. The alkaline extract was acidified, and the resulting oil was dissolved in acetic anhydride, a drop of sulfuric acid was added, and the solution was warmed for three minutes. The solution was poured into water, the resulting oil was taken up in ether and washed with aqueous sodium bicarbonate (5%) and then with water. Removal of the ether left an oil which, when crystallized from petroleum ether,

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(9) Arnold and Zaugg, THIS JOURNAL, **63**, 1317 (1941).

(10) Procedure of John and Rathmann, *Ber.*, **73**, 995 (1940).

(11) Smith and Austin, THIS JOURNAL, **64**, 532 (1942).

gave the acetoxychroman (100 mg., 44%) which melted at 69–71.5°. The analytical sample, prepared by crystallizing the material three times from petroleum ether (b. p. 28–38°), melted at 70.5–71.5°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.64; H, 8.14.

2,2,7,8-Tetramethyl-6-hydroxychroman (I).—Hydrochloric acid (2 cc.) was added to a solution of the above acetate (190 mg.) in methanol (20 cc.). The mixture was allowed to stand for two days and then poured into water. The oil was removed by ether extraction, the ether solution was washed with aqueous sodium bicarbonate (5%) and then with water. Removal of the solvent left an oil which was crystallized from petroleum ether (b. p., 28–38°). The chroman I (110 mg. 70%) melted at 83–84.5°. A sample, recrystallized from petroleum ether (b. p. 28–38°) (Norite) several times, melted at 84.5–85.5°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.42; H, 8.81.

A mixture of the carbinol VII (from 0.21 mole of ketone VI), hydrobromic acid (20 cc., 48%), and acetic acid (60 cc.), was boiled for four hours. The solution was poured into water and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate (5%) and then with water. Removal of the ether left an oil which, when crystallized from dilute methanol (Norite) gave the chroman I (2.5 g., 50% based upon the ketone VI) melting at 84–85°.

2,2,7,8-Tetramethyl-5,6-chromanquinone (II).—A mixture of the chroman I (500 mg.), dry ethanol (35 cc.), and silver nitrate (5 g.) was boiled for one hour and twenty minutes. The red solution was poured into water (300 cc.) and the mixture was extracted five times with ether. The combined ether solutions were washed with water and dried (sodium sulfate). Removal of the ether under reduced pressure at room temperature left a red oil which, when crystallized from ether at the temperature of Dry Ice gave the red *o*-quinone II (140 mg., 26%) melting at 100–107°. Three more crystallizations from ether gave 80 mg. of red crystals which melted at 109.5–110.5°.[3]

The successful synthesis of the hydroxychroman I suggested a possible independent synthesis of the red *o*-quinone II *via* the 5-nitroso compound of I, a tautomer of the 5-oxime of II, but this nitroso compound could not be prepared. A mixture of butyl alcohol (1 cc.), water (2 cc.), sodium nitrite (104 mg.) and sulfuric acid (1 drop) was shaken for three minutes. The alcohol layer was separated, washed once with water (1 cc.) and poured into a solution of the chroman I (150 mg.) in acetic acid (5 cc.) containing a drop of sulfuric acid. The solution soon became red. It was allowed to stand overnight and then was poured into water and extracted with ether. The ether solution was dried (sodium sulfate) and the ether was removed, finally under reduced pressure. The resulting red oil could not be crystallized.

Summary

1. 2,2,7,8-Tetramethyl-6-hydroxychroman, I, has been prepared in a pure state by an unequivocal synthesis. This chroman is a white solid which melts at 84.5–85.5°, and which is converted to the red *o*-quinone II in 26% yield when it is oxidized by action of silver nitrate in ethanol.

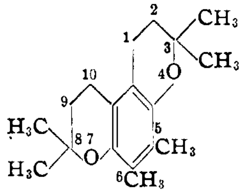
MINNEAPOLIS 14, MINNESOTA RECEIVED JUNE 2, 1944

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

Vitamin E. XLIV.[1] Synthesis of 3,3,5,6,8,8-Hexamethylbenzo[1,2-b,4,3-b']dipyran,[2] and its Behavior upon Oxidation

BY LEE IRVIN SMITH AND ROY W. H. TESS[3]

It was stated in a previous paper[4] that the double chroman I, when oxidized by action of silver nitrate in ethanol, gave the red *o*-quinone II.



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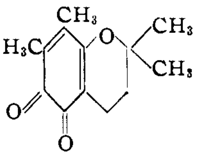

II

But the substance actually oxidized was the alkali-insoluble fraction of an oil obtained by condensation of *o*-xylohydroquinone with isoprene. As stated in the preceding paper,[1] some questions have arisen concerning the validity of certain statements made with reference to the formation of the red *o*-quinones from *p*-hydroxychromans, and it was therefore decided to prepare a pure specimen of I and to re-investigate its behavior toward alcoholic silver nitrate.

The double chroman I was prepared in yields of 63–84% by condensation of *o*-xylohydroquinone with isoprene according to methods previously published.[5] Practically no material insoluble in Claisen alkali resulted from this condensation, and the chroman I was isolated as a white solid melting at 102.5–103.5°. Contrary to the previous report,[4] the chroman I was recovered unchanged even when its solution in ethanol was boiled with silver nitrate for seven hours; no red color was produced, and no II whatever was formed. Oxidation of I by action of nitric acid in ethanol gave a red solution in a few minutes; however, no II could be isolated from the resulting red oil. When the red oil was adsorbed from carbon tetrachloride on Brockmann alumina, and the column then eluted with ethanol, the product was a red oil which formed a yellow solution in petroleum ether, and from which only a few crystals of a dull red solid could be isolated. This material was not the red *o*-quinone II.

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(1) Paper XLIII, THIS JOURNAL, **66**, 1523 (1944).

(2) This ring system is not represented in the Ring Index; the system most nearly resembling it is No. 1984.

(3) Abstracted from a thesis by R. W. H. Tess, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, March, 1944.

(4) Smith, Irwin and Ungnade, THIS JOURNAL, **61**, 2424 (1939).

(5) (a) Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, **4**, 311 (1939); (b) Smith and King, THIS JOURNAL, **65**, 441 (1943).