layer was washed with bicarbonate solution, then with water, and dried. Removal of the solvent left an oil which, on distillation, gave 4.1 g. (51%) of the coumaran boiling at 150–154° under 14–15 mm. The distillate solidified on cooling. The solid, recrystallized three times from a mixture of benzene and petroleum ether (b. p. 60–68°), was white and melted at 66–67°. When mixed with the hydroquinone (m. p. 91–92°) the substance melted at 48–58°.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.96; H, 6.72. Found: C, 71.96; H, 6.96.

Cyclization was not successful when the hydroquinone (3.0 g.) was heated at 135° for five hours with pyridinium chloride (12 g.). The hydroquinone (1.95 g., m. p. 86–88°, b. p. 161° under 10 mm.) was the only product isolated. Likewise unsuccessful was an attempt to cyclize the hydroquinone (1 g.) by saturating its solution in carbon tetrachloride (90 cc.) and ether (10 cc.) with dry hydrogen chloride. The only product isolated was unchanged hydroquinone. Cyclization could be brought about by refluxing the hydroquinone (13 g.) for three hours in acetic acid (40 cc.) and hydrobromic acid (20 cc., 40%) containing a little zinc dust. The mixture was poured into water and the coumaran (5.5 g., 42%) was isolated by ether extraction.

The **benzoate** and **acetate** of the coumaran were both liquids.

Summary

1. This paper contains the details of the synthesis of 2,4,6,7-tetramethyl-5-hydroxycoumaran and 2-methyl-5-hydroxycoumaran from the corresponding *o*-allylphenols. The steps in these syntheses involve diazo coupling, cleavage of the azo compound to the aminophenol, oxidation to the allylic quinone, reduction to the hydroquinone and cyclization. It is shown that the order of the different steps mentioned may be varied considerably without affecting the final yields of coumarans.

2. Both the tetramethylhydroxycoumaran and the tetramethylaminocoumaran have been oxidized to the same yellow *p*-quinone; the latter has been reduced to the hydroxyhydroquinone and cyclized, as well as oxidized to the red 2,6,7-trimethylcoumaran-4,5-quinone.

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The Chemistry of Vitamin E. XXIV.[1] The Structure of γ-Tocopherol

BY OLIVER H. EMERSON[2] AND LEE IRVIN SMITH

The isolation from cottonseed oil, palm oil and corn oil of a substance characterized by an allophanate melting at 137–140° for which the name γ-tocopherol was proposed, has been previously described.[3,4] The complete difference in the crystalline form of this allophanate from that of the slightly higher melting derivative of β-tocopherol, and the fact that the two allophanates when mixed show a distinct depression in melting point clearly indicate their non-identity. Furthermore, as the present communication reports, the *p*-nitrophenyl urethan of γ-tocopherol melts at 119–121°, while Karrer and Fritzsche[5] have reported that the corresponding derivative of β-tocopherol melts at 90°.

Oxidation of β- and γ-tocopherols[6] yielded the same lactone which Fernholz[7] had obtained from α-tocopherol, indicating that the aliphatic portions of all three tocopherols are alike. On pyrolysis γ- as well as β-tocopherol yielded trimethylhydroquinone[8,9] instead of tetramethylhydroquinone which had been obtained from α-tocopherol.[10] This indicated that β- and γ-tocopherols differ from each other only in the position of the methyl groups attached to the benzene ring.

Three "xylo-tocopherols' or "dimethyltocols"[11] —those derived from *o*-, *m*- and *p*-xylohydroquinones are possible. That β-tocopherol is 5,8-di-

(1) XXIII, Smith, Hoehn and Whitney, THIS JOURNAL, **62**, 1863 (1940).

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(3) Emerson, Emerson, Mohammad and Evans, *J. Biol. Chem.*, **122**, 99 (1937).

(4) Emerson, Emerson and Evans, *Science*, **89**, 183 (1939).

(5) Karrer and Fritzsche, *Helv. Chim. Acta*, **22**, 260 (1939).

(6) Emerson, THIS JOURNAL, **60**, 1741 (1938).

(7) Fernholz, *ibid.*, **60**, 700 (1938).

(8) John, *Z. physiol. Chem.*, **250**, 11 (1937).

(9) Bergel, Todd and Work, *J. Chem. Soc.*, 253 (1938).

(10) Fernholz, THIS JOURNAL, **59**, 1154 (1937).

(11) Karrer and Fritzsche (*Helv. Chim. Acta*, **21**, 1234 (1938)), have proposed the name "tocol" for the tocopherol nucleus, including the methyl group, the C_{16} side chain in the 2-position of the heterocyclic ring and the hydroxyl group in the 6-position, but not including the methyl groups attached to the benzene ring. The "xylotocopherols," *o*-, *m*- and *p*-, when named in this way, become 7,8-, 5,7- and 5,8-dimethyltocols, respectively.

methyltocol was shown by the production of *p*-xylenol when the substance was cleaved by hydriodic acid,[12] as well as by the synthesis of the three dimethyl tocols whose allophanates and *p*-nitrophenyl urethans were compared by mixed-melting with the corresponding derivatives of β-tocopherol.[5,13] Of the two remaining dimethyltocols, one must be identical with natural γ-tocopherol, and the work reported in this paper establishes the structure of this tocopherol as 7,8-dimethyltocol or *o*-xylotocopherol.

When heated with allyl bromide, γ-tocopherol gave a substance $C_{31}H_{52}O_2$ which showed no reactions for the hydroxyl group, indicating that ring closure had occurred. Since only those tocopherols which possess an unsubstituted position adjacent to the hydroxyl group in the benzene ring, *i. e.*, 5,8- and 7,8-dimethyltocols, could give allyl derivatives able to undergo ring closure, it follows that γ-tocopherol is 7,8-dimethyltocol. A tocopherol of this structure, when oxidized, should give dimethylmaleic anhydride as one of the products. Dimethylmaleic anhydride was not isolated in the earlier experiments on the oxidation of γ-tocopherol[6] but the amount of material oxidized was so small that the anhydride could easily have escaped detection. Accordingly, a larger amount of γ-tocopherol (1.87 g., 0.0045 mole) was oxidized with chromic acid, and it was possible to isolate from the reaction products 70 mg. (12.4% yield) of dimethylmaleic anhydride. While this yield of dimethylmaleic anhydride was considerably smaller than the 26% yield reported by Fernholz from the oxidation of 0.01 mole of α-tocopherol, the smaller amount of γ-tocopherol used in this experiment would increase the difficulty of isolating the anhydride in good yield. Under the same conditions, the oxidation of 1 g. (0.0045 mole) of 2,2,5,7,8-pentamethyl-6-hydroxychroman yielded 80 mg. of dimethylmaleic anhydride (14%) while the oxidation of 1.96 g. of α-tocopherol (0.0046 mole) yielded 99 mg. of the anhydride (17%). Thus the yield of dimethylmaleic anhydride from γ-tocopherol was 73% of that from α-tocopherol when the oxidations were carried out under the same conditions.

That the specimen of γ-tocopherol used in this investigation was not absolutely pure was shown by chromatographing the allophanate on a column of calcium carbonate. From the least strongly adsorbed fraction, a very small amount of α-tocopheryl allophanate, melting at 148–152°, was isolated. While this did not give quantitative measure of the amount of γ-tocopheryl allophanate present, it did indicate that it was small. An attempt to estimate the purity of the γ-tocopheryl allophanate by the ratio of the apparent solubility to the amount of solid phase added, a method used by Kunitz and Northrop[14] in their studies of enzymes, had no significance because it was found that the γ- and α-tocopheryl allophanates tended to form mixed crystals. The curve obtained would deceptively indicate that our γ-allophanate was 98% pure.

An attempt was made to confirm our structure of γ-tocopherol by synthesis. Since it had been previously observed that the allophanates of γ-tocopherol and synthetic 5,8-dimethyltocol gave no mixed melting point depression,[13] it was hoped that more suitable derivatives could be found.[15] A solid and more or less crystalline *p*-nitrophenyl urethan, and the benzyl thiuronium salt of the mono tocopheryl ester of succinic acid were obtained from γ-tocopherol, and while these derivatives gave no mixed melting point depression with the corresponding derivatives of synthetic 7,8-dimethyltocol, they also failed to give significant depressions with the corresponding derivatives of synthetic 5,8-dimethyltocol.

Experimental[16]

The γ-tocopherol was prepared from corn oil as previously described.[4] Thirty-two liters of corn oil yielded 11.5 g. of the allophanate melting at 137–139°.

Solubility Determinations.—A measured amount of the allophanate was placed with a measured amount of methanol in a glass vessel with a ground glass stopper, and rocked in a thermostat at 26.2°.[17]

Equilibrium was established within twelve hours, but the shaking was usually continued considerably longer. A portion of the solution was then filtered by very gentle

(12) John, Dietzel and Günther, *Z. physiol. Chem.*, **252**, 208 (1938).

(13) Karrer, Fritzsche and Escher, *Helv. Chim. Acta*, **22**, 661 (1939).

(14) Kunitz and Northrop, *Cold Spring Harbor Symposia Quant. Biol.*, **6**, 325 (1938), The Darwin Press, New Bedford, Mass.

(15) γ-Tocopheryl allophanate was also compared by mixed melting with the allophanates of synthetic 5,7- and 7,8-dimethyltocols. The former depressed the melting point of the γ-allophanate from 137–139° to 134°, while the latter depressed it to 135–136°. This led Karrer to suggest that γ-tocopherol might be a slightly impure form of β-tocopherol. However, we feel that too much importance should not be ascribed to slight depressions in mixed melting points of substances as difficult to purify as are the allophanates of natural γ-tocopherol and the synthetic dimethyltocols.

(16) The analyses reported in this paper were carried out by E. E. Renfrew of the Chemistry Department, University of Minnesota, to whom we wish to express our thanks.

(17) We wish to thank Professor C. L. A. Schmidt of the Biochemistry Department, University of California, for the use of the apparatus.

suction (by mouth) into a weighed flask, and the weight of solution and residue determined.

TABLE I

SOLUBILITY OF γ-TOCOPHERYL ALLOPHANATE AT 26.2° IN METHANOL

Mg. γ-allophanate added/g.	9.50	10.9	12.9	20.1	39.2	79.0
Soly., mg./g.	9.50	10.32	10.35	10.44	10.64	11.40

TABLE II

SOLUBILITY OF α-TOCOPHERYL ALLOPHANATE AT 26.2° IN METHANOL

Mg. α-allophanate added/g.	13.0	24.0
Soly., mg./g.	9.47	9.90

TABLE III

SOLUBILITY OF MIXTURES OF γ- AND α-TOCOPHERYL ALLOPHANATES AT 26.2° IN METHANOL

Mg. α-allophanate added per g.	11.2	13.0	3.8	2.3
Mg. γ-allophanate added per g.	11.5	11.0	11.8	12.0
Wt. of dissolved material per g.	14.0	13.3	10.8	10.5

Chromatograph of γ-Tocopheryl Allophanate.—The allophanate (113 mg. in 50 cc. benzene) was chromatographed on calcium carbonate (150 g.) using benzene (1000 cc.) to develop the chromatogram. The first 425 cc. of filtrate contained a very small amount of oil. When the residue from the next 300 cc. (28 mg.) was recrystallized from 0.5 cc. of methanol, there resulted a solid (17 mg.) which melted at 134–141°. This solid separated in fine granules resembling the mixtures of α- and γ-allophanates which are obtained from cotton seed oil. On further recrystallization a few milligrams of impure α-tocopheryl allophanate, melting at 148–152°, was obtained. The other fractions from the chromatograph were evaporated, and the solid residues, when crystallized from methanol and acetone, formed relatively large clusters of very fine hair-like needles, but several recrystallizations of these solids did not give a product melting above 137–140°.

Owing to the large amount of calcium carbonate needed, this procedure would not be practicable except for small amounts of material, and even as mild an adsorbent as calcium carbonate produced considerable decomposition.

Oxidation Experiment.—The oxidation of α- and γ-tocopherols and 2,2,5,7,8-pentamethyl-6-hydroxychroman were carried out as described by Fernholz[7] except that the dimethylmaleic anhydride was purified by steam distillation instead of vacuum sublimation. The dimethylmaleic anhydride obtained from γ-tocopherol was recrystallized from petroleum ether. It then melted at 93–94° alone or when mixed with an authentic sample.

γ-Tocopheryl-*p*-nitrophenyl Urethan.—The allophanate was hydrolyzed and the tocopherol converted to the *p*-nitrophenyl urethan as previously described for α-tocopherol.[18]

After crystallization from methanol, this compound melted at 119–121°. *Anal.* Calculated for $C_{35}H_{52}N_2O_5$: C, 72.36; H, 9.03. Found: C, 72.12; H, 8.78.

Benzylthiuronium Salt of γ-Tocopheryl Hydrogen Succinate.—γ-Tocopherol (200 mg.) and succinic anhydride (300 mg.) in pyridine (2 cc.) were heated an hour on the steam-bath. The mixture was diluted with water, acidified with hydrochloric acid, and extracted with ether. The ether was washed with water and extracted with dilute sodium carbonate, which was then acidified and re-extracted with ether. The mono γ-tocopheryl ester of succinic acid was an oil. It was converted to the benzyl thiuronium salt according to Donleavy.[19]

After crystallization from acetone, the salt melted at 104–105°. *Anal.* Calculated for $C_{40}H_{62}N_2SO_5$: C, 70.33; H, 9.16. Found: C, 70.02, 70.22; H, 9.16, 8.84.

Synthesis of 7,8-Dimethyltocol.—*o*-Xylohydroquinone monobenzoate (3.24 g.), phytyl bromide (4.8 g.), and zinc chloride (2 g.) were refluxed three hours in benzene in an atmosphere of nitrogen, according to the procedure of Jacob and her collaborators[20] and the tocopherol was converted to the *p*-nitrophenyl urethan and the benzyl thiuronium salt of its succinic acid mono ester as described above. The *p*-nitrophenyl urethan melted at 102°, slightly higher than the value previously reported (100°).[20] The benzyl thiuronium salt melted at 104–106°.

Synthesis of 5,8-Dimethyltocol.—This tocol was synthesized from *p*-xylohydroquinone monobenzoate (4.8 g.) and phytol (6 g.) in acetic acid (12 cc.) with zinc chloride (1.5 g.) as catalyst as previously described for α-tocopherol.[21] A large part of the xylohydroquinone monobenzoate was recovered unchanged. The tocopherol was converted to the *p*-nitrophenyl urethan, which melted at 111–112°, and to the benzyl thiuronium salt of its succinic acid mono ester, which melted at 104–106°.

Allylation of γ-Tocopherol (By H. E. Ungnade).—The tocopherol (from 600 mg. of the allophanate) was heated (150°, three hours) with allyl bromide (2 cc.) and zinc chloride (0.2 g.) in a sealed tube. The material was taken up in petroleum ether and chromatographed on alumina (Brockmann). A small amount of tarry impurity appeared as a narrow, dark band on the top of the column, but the bulk of the material was less strongly adsorbed and formed a wide brown band which could be rapidly moved to the bottom of the column by development with the same solvent. A small amount of odoriferous yellow oil was washed through the column during the development. The main product was eluted with ether and the ether was evaporated. The dark residue when distilled in a small molecular still (about 10^{-5} mm. pressure) gave a yellow oil which boiled at 160–180°. *Anal.* Calcd. for $C_{31}H_{52}O_2$: C, 81.28; H, 11.50. Found: C, 81.29; H, 10.48.

The distillate gave a very slight positive phenol test (Folin), but a negative Furter and Meyer test.[22] The Beilstein test for halogen was positive, but the substance did not absorb bromine in carbon tetrachloride. The oil was soluble in ether and petroleum ether, but only slightly soluble in methanol, ethanol, or sulfuric acid when these solvents were cold. Hot ethanol dissolved the substance, as did warm sulfuric acid. In the latter case a brownish-red color developed, which rapidly darkened in the upper part of the solution. These properties indicate that the oil consisted primarily of the tricyclic compound. No reaction

(18) Evans, Emerson and Emerson, *J. Biol. Chem.*, **113**, 330 (1936).

(19) Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(20) Jacob, Steiger, Todd and Work, *J. Chem. Soc.*, 542 (1939).

(21) Smith, Ungnade, Stevens and Christman, THIS JOURNAL, **61**, 2618 (1939).

(22) Furter and Meyer, *Helv. Chim. Acta*, **22**, 240 (1939).

occurred between allyl bromide and γ-tocopherol in the absence of the zinc chloride catalyst.

Summary

The formation of a coumaran derivative on treatment with allyl bromide and the formation of dimethylmaleic anhydride on oxidation indicate that γ-tocopherol is 7,8-dimethyltocol.

BERKELEY, CALIFORNIA
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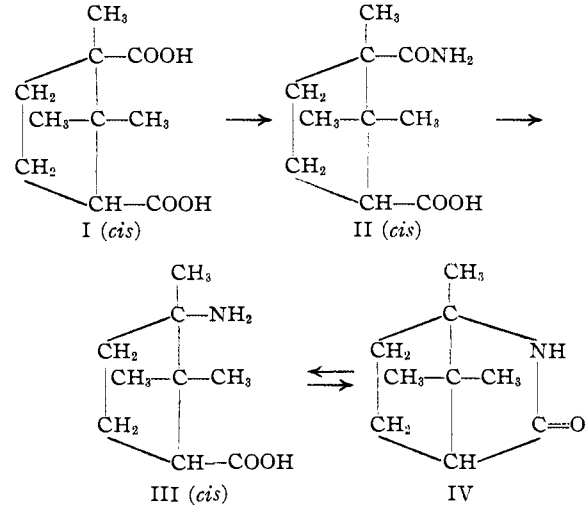
NOTES

The Walden Inversion and the Hofmann Rearrangement

BY S. ARCHER

For many years it has been merely assumed that the carbon atom that migrates to the nitrogen atom in the Hofmann rearrangement retains its configuration during the change.[1] Recently Bartlett and Knox[2] demonstrated that this reaction could proceed without inversion. However, the type of compounds used did not permit any unqualified statement concerning the stereochemistry of the migration. These authors state that ". . . no inversion or series of inversions, need be involved in the Hofmann rearrangement." It therefore seems proper to point out that there has long existed in the literature experimental evidence to prove that no inversion of configuration occurs in the Hofmann reaction. This evidence is in the papers of W. A. Noyes and his coworkers.[3]

Camphoric acid (I) was converted to β-camphoramidic acid (II) (*cis*). Treatment with hypobromite gave aminodihydrocampholytic acid (III), which, when heated for ten minutes with a solution of sodium acetate in acetic anhydride, gave the lactam (IV). The latter upon hydrolysis gave the amino acid (III) in optically pure form, showing that no inversion took place during lactamization. The amino and carboxyl groups in (III) must therefore be *cis* to each other. Since the starting acid (I) was of the *cis* series and since the only reaction wherein inversion might have occurred was the Hofmann rearrangement, it must be concluded that no inversion took place



when the amide (II) was converted to the amine (III). If, on the other hand, inversion had occurred during the conversion of II to III, the latter would have been of the *trans* series, which is contrary to fact.

The same set of reactions was carried out on the three isomers of β-camphoramidic acid. Substantially the same result was obtained in each case, namely, that no inversion took place during the Hofmann rearrangement.

DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNA. RECEIVED MAY 7, 1940

(1) (a) Braun and Friehmelt, *Ber.*, **66**, 684 (1933); (b) Arcus and Kenyon, *J. Chem. Soc.*, 916 (1939); (c) Bernstein and Whitmore, THIS JOURNAL, **61**, 1324 (1939).

(2) Bartlett and Knox, *ibid.*, **61**, 3184 (1939).

(3) (a) Noyes, *Am. Chem. J.*, **16**, 500 (1894); (b) Noyes and Potter, THIS JOURNAL, **37**, 189 (1915); (c) *ibid.*, **34**, 1067 (1912); (d) Noyes and Nickell, *ibid.*, **36**, 118 (1914). These papers give an account of the conversion of a half-amide of camphoric acid or isocamphoric acid to an amino acid by the Hofmann reaction. There was no optical inversion in any of the reactions. In the paper by Potter and myself, *ibid.*, **34**, 1068 (1912), however, a Walden inversion and structural rearrangement caused by nitrous acid is described. The Hofmann reaction was not involved in this.—W. A. Noyes.