teen hours. After cooling the bomb, the gas was allowed to escape through a trap cooled by solid carbon dioxide, and the deposited furan was returned to the reaction mixture. The whole was distilled in three fractions: the first, of unreacted furan, 14–16 g.; the second, b. p. 40–118°, chiefly furan, 1.5 g., the third, a colorless liquid, b. p. 118–122°, 1.2–1.5 g. This last was 3,6-epoxycyclohexene, b. p. 118–119°, $n^{20}D$ 1.4629; yield, 5–8% on the furan consumed.

The triazoline derivative, formula II,[3] was prepared by mixing a few drops of phenyl azide with a similar quantity of epoxycyclohexene and allowing the resulting yellow solution to crystallize in the ice box overnight. Repeated crystallization from ethyl acetate gave fine white needles, m. p. 166–167° (cor.) (after drying over phosphorus pentoxide).

Anal.[4] Calcd. for $C_{12}H_{13}ON_3$: C, 67.0; H, 6.1; N, 19.5. Found: C, 67.1; H, 6.1; N, 19.5.

The epoxycyclohexene (4.5 g.) in 12 ml. of methanol was hydrogenated using 50 mg. of Adams catalyst. Distillation of the residue remaining after removal of the catalyst and methanol gave a fraction b. p. 110–120°. This material was refluxed, without further purification, with acetic anhydride and several crystals of zinc chloride for two hours. The excess acetic anhydride was distilled off and the remaining brown oil poured into hot water. Crystallization did not occur. The oil was extracted with ether, the solution dried and the ether evaporated. The residual oil on standing deposited crystals, m. p. 102–103.6°, from aqueous ethanol. A mixture with authentic ester,[5] m. p. 102–104°, also melted at 102–103.6°.

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[3] Alder and Stein, *Ann.*, **501**, 1 (1935).

[4] Analysis by Dr. T. S. Ma, University of Chicago.

[5] Baeyer, *Ann.*, **278**, 93 (1894). The *trans*-quinitol diacetate was kindly furnished by Mr. A. M. Gaddis, who prepared it from hydroquinone.

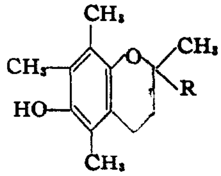
BUREAU OF ANIMAL INDUSTRY
AGRICULTURAL RESEARCH ADMINISTRATION
UNITED STATES DEPARTMENT OF AGRICULTURE
BELTSVILLE, MARYLAND

RECEIVED OCTOBER 2, 1943

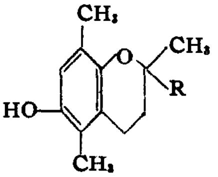
Coupling of Gamma Tocopherol and Failure of β-Tocopherol to Couple with Diazonium Salts

BY MARY LOUISE QUAIFE

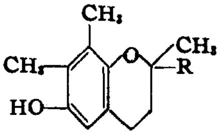
Inspection of the structural formulas of α-tocopherol (I), β-tocopherol (II), and γ-tocopherol (III) suggests that both II and III are capable of



I



II



III

R = $C_{16}H_{33}$

coupling with diazonium salts.[1] We have found that γ-tocopherol couples readily, but the beta isomer, surprisingly, does not. Consequently, III can be determined in the presence of I and II. This note describes the reaction upon which the procedure is based and also experiments showing the failure of β-tocopherol to couple.

γ-Tocopherol is determined by photometric estimation of the red dye produced by its reaction with diazotized *p*-nitroaniline in aqueous alcohol solution at *p*H of about 6. The dye, extracted with Skellysolve H, gives a stable color with absorption maxima at 530 mμ and 380 mμ. Over the range of quantity of γ-tocopherol employed in the analysis (0.2 to 0.5 mg.) absorption at either wave length is proportional to concentration. It is measured at 520 mμ for convenience. The method has been applied to estimation of γ-tocopherol content of tocopherol concentrates with results as shown in Table I. Total tocopherols were determined by the method of Emmerie and Engel.[2]

TABLE I

γ-TOCOPHEROL CONTENT OF VEGOL (CONCENTRATE OF NATURAL MIXED TOCOPHEROLS) FRACTIONS (DUPLICATE ANALYSES)

Sample	γ-Tocopherol, %	% total tocopherols	Ratio of γ- to total tocopherol; % γ-
Vegol (C)	2.8	4.3	65
	3.1	4.5	69
Vegol (I)	16.3	26.3	62
	17.8	26.7	67
Vegol (II)	21.4	42.0	51
	19.7	42.3	47
Vegol (III)	9.0	40.2	22
	9.5	40.2	24

When the procedure was applied to natural β-tocopherol, it required 12 mg. to give absorption at 520 mμ, equivalent to that given by only 0.05 mg. of γ-tocopherol. Since in this case the *p*H was about 6, the ability of β-tocopherol to couple with benzenediazonium chloride was tested over a *p*H range of 4.5 to 11. The test procedure was similar to that used in the analytical method except for increased amounts of β-tocopherol. Control series were run using equal amounts of γ-tocopherol as well as aqueous alcohol blanks. The resultant Skellysolve extracts of the reaction mixtures of the tocopherols (0.4 mg./cc.) and of the blank had colors as shown in Table II.

TABLE II

COLORS OF COUPLING PRODUCTS OF TOCOPHEROLS AND BENZENEDIAZONIUM CHLORIDE

*p*H	Blank	β-Tocopherol	γ-Tocopherol
4.5	Colorless	Colorless	Colorless
9.0	Light yellow	Light yellow	Deep orange
11.0	Light yellow	Light yellow	Deep orange

Absorption spectra over the range of 310 to 620 mμ of the reaction products at *p*H 9 show no difference in absorption between the Skellysolve extracts of the β-tocopherol reaction mixture and the blank. The γ-tocopherol azo dye formed at *p*H 9 had a density of 1.7 at 475 mμ, the peak of absorption.

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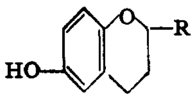
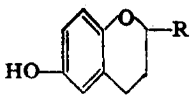
[1] Scudi and Buhs, *J. Biol. Chem.*, **146**, 6 (1942).

[2] Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

This difference in coupling ability of γ- and β-tocopherols suggests possible fixation of the bond structure in the benzenoid nucleus of the tocopherols according to IV instead of V. The substituted tetralins, which have a ring system similar to that of the tocopherols, are considered to have a double bond between the rings. The observed difference in the tocopherol isomers may also be related to the Mills–Nixon effect.[3,4]


IV


V

The advice of Dr. C. F. H. Allen is gratefully acknowledged.

(3) Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

(4) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, 2nd Ed., Vol. I, p. 136.

COMMUNICATION NO. 56
FROM THE LABORATORIES OF
DISTILLATION PRODUCTS, INC.
ROCHESTER, NEW YORK
RECEIVED DECEMBER 7, 1943

The Alkylation of Isopropylmalonic Ester Using Sodium Triphenylmethide[1]

BY J. C. SHIVERS, B. E. HUDSON, JR., AND CHARLES R. HAUSER

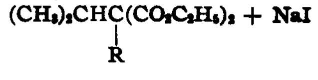
The difficulty of alkylation of secondary alkyl malonic esters, for example, isopropylmalonic ester, by the ordinary procedure using sodium ethoxide[2] in alcoholic solution has been ascribed to the incomplete formation of the sodio derivative.[3]

$$\mathrm{RCH(CO_2C_2H_5)_2 + NaOC_2H_5 \rightleftarrows [RC(CO_2C_2H_5)_2]Na + C_2H_5OH}$$

Wallingford and co-workers[3b] found that, by substituting an alkyl carbonate for alcohol as a reaction medium and distilling all alcohol produced from the reaction with sodium ethoxide, certain secondary alkyl malonic esters could be alkylated. We have found that alkylation of isopropylmalonic ester may be achieved by using the stronger base, sodium triphenylmethide, in an inert solvent. The yields of alkylation product with ethyl iodide and isopropyl iodide were 73 and 23%, respectively.

$$\mathrm{(CH_3)_2CHCH(CO_2C_2H_5)_2 + NaC(C_6H_5)_3 \longrightarrow Na[(CH_3)_2CHC(CO_2C_2H_5)_2] + HC(C_6H_5)_3}$$

$$\mathrm{RI + Na[(CH_3)_2CHC(CO_2C_2H_5)_2] \longrightarrow}$$



$$\mathrm{(CH_3)_2CH\underset{\displaystyle R}{\underset{|}{C}}(CO_2C_2H_5)_2 + NaI}$$

Crossley and Le Sueur[2b] found that ethylisopropylmalonic ester (R = ethyl, prepared by isopropylating ethylmalonic ester using sodium ethoxide) undergoes alkaline hydrolysis to form partly ethylisopropylmalonic acid and partly ethylisopropylmalonic acid ester, which on decarboxylation gives ethyl ethylisopropylacetate. We have found that di-isopropylmalonic ester (R = isopropyl) undergoes alkaline hydrolysis only with difficulty yielding di-isopropylmalonic acid ester, which undergoes decarboxylation with difficulty.

Experimental

Diethyl isopropylmalonate (b. p. 217–218°)[4] was prepared in 56% yield essentially according to the directions given in "Organic Syntheses"[5] for the preparation of diethyl *n*-butyl malonate.

Diethyl Ethylisopropylmalonate.—To sodio-isopropylmalonic ester, prepared from 42.0 g. (0.205 mole) of the ester and 0.205 mole of an ether solution of sodium triphenylmethide,[6] was added 32 g. (0.205 mole) of ethyl iodide. After standing for seven days, the ether solution (above the thin layer of sodium iodide crystals) was transferred by means of nitrogen pressure to a flask and the solvent distilled through a column up to 40°. More ethyl iodide (11.6 g.) in 100 cc. of dry benzene was added to the residue and the mixture was refluxed eighteen hours. On working up the mixture there was obtained 35 g. (73%) of diethyl ethylisopropylmalonate, b. p. 118–120° (15 mm.) (234–236° at atm. pres.).[2b]

Refluxing diethyl ethylisopropylmalonate ten hours with 95% alcoholic potassium hydroxide and decarboxylation of the resulting malonic acid gave a 48% yield of ethylisopropylacetic acid, b. p. 104–105° (15 mm.). Neutral equivalent, calculated for $C_7H_{14}O_2$: 130.18. Found: 131.28. With aniline the acid gave the anilide, melting at 118–119°. (*Anal.*[7] Calcd. for $C_{13}H_{19}ON$: N, 6.83. Found: N, 6.53). No attempt was made to isolate ethyl ethylisopropylacetate obtained by Crossley and Le Sueur.[2b]

Diethyl Di-isopropylmalonate.—Sodio-isopropylmalonic ester was prepared by the decolorization of 0.1 mole of sodium triphenylmethide solution with 20.2 g. (0.1 mole) of isopropyl malonic ester, and practically all of the ether was distilled from the mixture in an atmosphere of nitrogen. To the residue was added 10 cc. of dry benzene followed by 21.2 g. (0.125 mole) of isopropyl iodide in 40 cc. of benzene. After standing overnight, the mixture was refluxed twenty-four hours, additional (4.3 g.) isopropyl iodide was added, and the mixture refluxed for twenty-four hours longer. On working up the mixture there was obtained 5.6 g. (23%) of diethyl di-isopropylmalonate, b. p. 122–124° (15 mm.).

Anal.[7] Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.52; H, 9.79.

Long refluxing (eighteen to twenty-four hours) of diethyl di-isopropylmalonate with alcoholic potassium hydroxide yielded unchanged ester and ethyl hydrogen di-isopropylmalonate, m. p. 71–72°. Neutral equivalent, calculated for $C_{11}H_{20}O_4$: 216.3. Found: 213.6. The mono acid-ester on heating slowly decarboxylated to form a neutral material, b. p. 71–72° (15 mm.), which was apparently ethyl di-isopropylacetate (*Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 68.71; H, 11.31).[7]

DEPARTMENT OF CHEMISTRY
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RECEIVED NOVEMBER 8, 1943

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[1] Paper XXII on "Condensations."

[2] (a) Fischer and Dilthey, *Ann.*, 335, 337 (1904); (b) Crossley and Le Sueur, *J. Chem. Soc.*, 77, 83 (1900).

[3] (a) See Shonle, Keich and Swanson, THIS JOURNAL, 52, 2440 (1930); (b) Wallingford, Thorpe and Homeyer, *ibid.*, 64, 580 (1942).

[4] Conrad and Bischoff, *Ann.*, 204, 144 (1880), report a boiling point of 213–214°.

[5] Adams and Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 245.

[6] Renfrow and Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc', New York, N. Y., 1943, p. 607.

[7] Microanalyses by Dr. T. S. Ma, University of Chicago.