TABLE I
STEREOCHEMICAL DISTRIBUTION AND CH_3 PMR DATA OF CARBINOL PRODUCTS FORMED BY REACTION OF THE CORRESPONDING METHYLCYCLOHEXANONE WITH PhMgBr OR PhLi

Compd	PhMgBr, %	PhLi, %	J, Hz	δ, ppm
1-Phenyl-*c*-2-methyl-*r*-cyclohexanol[a] (1)	87	88	6	0.60
1-Phenyl-*t*-2-methyl-*r*-cyclohexanol (2)	13	12	6	0.62
1-Phenyl-*c*-3-methyl-*r*-cyclohexanol (3)	59	56	6	0.95
1-Phenyl-*t*-3-methyl-*r*-cyclohexanol (4)	41	44	3	0.93
1-Phenyl-*c*-4-methyl-*r*-cyclohexanol (5)	54	47	0	0.99
1-Phenyl-*t*-4-methyl-*r*-cyclohexanol (6)	46	53	7	0.92

[a] Nomenclature usage is in conformity with IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E. Fundamental Stereochemistry. See *J. Org. Chem.*, **35**, 2849 (1970).

ketone.[5] In cyclohexanones with substituents at more remote positions, the usual result is that there is no such preference for one addition mode to the other.[6] The results reported herein appear consistent with these trends.

Experimental Section[7]

Preparation of 1-Phenylmethylcyclohexanols. A. From Phenylmagnesium Bromide.—The Grignard reagent was prepared from Mg (10 g, 417 mg-atoms) and bromobenzene (67.5 g, 430 mmol) in ether. The appropriate methylcyclohexanone (39.0 g, 350 mmol) was added drop by drop in ether solution. The product was hydrolyzed with 10% NH_4Cl and ice, the ether layer was separated, and the standard work-up involved ether extraction, washing with $NaHCO_3$, drying overnight (Drierite), removal of the ether, and vacuum distillation of the carbinol product. The yields of carbinol mixtures recovered from the distillation were 2-methyl-1-phenylcyclohexanols (58%), 3-methyl-1-phenylcyclohexanols (54%), and 4-methyl-1-phenylcyclohexanols (53%).

B. From Phenyllithium.—The typical preparation involved preparation of phenyllithium from bromobenzene (31.0 g, 198 mmol) and lithium (1.8 g, 260 mg-atoms) in ether solution. The appropriate methylcyclohexanone was added drop by drop, and the product was isolated as described in procedure A. The yields were for 2-methyl-1-phenylcyclohexanols, 75%; 3-methyl-1-phenylcyclohexanols, 68%; and 4-methyl-1-phenylcyclohexanols, 74%.

Separation of Stereoisomers.—The crude carbinol product (1.00 g) was chromatographed on a 2.5 × 30 cm silica gel column slurry packed in hexane. The column was eluted with hexane in 125-ml fractions and then by hexane solutions of gradually increasing ether concentration. The 4-methyl isomer **5** eluted at 2% ether–hexane and **6** at 15% ether–hexane. The 2-methyl isomer **1** eluted at 5% ether–hexane and **2** at 7.5% ether–hexane. The 3-methyl isomer **3** eluted at 7.5% ether–hexane and **4** at 10% ether–hexane.

These compounds and their properties are as follows.

1 gave $n^{22}D$ 1.5331; ir (neat) 3509 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.60 (d, J_{Me-H} = 6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 190 (0.041), 172 (0.592), 157 (0.265), 147 (0.163), 143 (0.265), 134 (0.122), 133 (1.00), 130 (0.816), 129 (0.796), 115 (0.490), 105 (0.510).

Carbinol **2** gave mp 56.5–57.5°; ir (KBr) 3413 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.62 (d, J_{Me-H} = 6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 172 (M^+ − 18) (0.619), 157 (0.323), 143 (0.355), 130 (0.897), 129 (1.00), 115 (0.581), 104 (0.155), 91 (0.665).

Carbinol **3** gave mp 61–63°; ir (KBr) 3356 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.95 (d, J_{Me-H} = 6 Hz); mass spectrum (70 ev) *m/e* (rel intensity) 172 (M^+ − 18) (0.773), 157 (0.665), 143 (0.324), 130 (0.481), 129 (1.00), 115 (0.481), 91 (0.702).

Carbinol **4** gave mp 118–119°; ir (KBr) 3340 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.93 (d, J_{Me-H} = 3 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 172 (M^+ − 18) (0.734), 157 (0.605), 143 (0.323), 130 (0.532), 129 (1.00), 115 (0.500), 104 (0.153), 91 (0.965).

Carbinol **5** gave mp 62–64° (lit.[1] 63.5°); ir (KBr) 3413 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.99 (m); mass spectrum (70 eV) *m/e* (rel intensity) 172 (M^+ − 18) (0.553), 157 (0.288), 143 (0.258), 130 (0.902), 129 (1.00), 115 (0.785), 104 (0.492), 91 (0.394).

Carbinol **6** gave mp 66–67° (lit.[1] 68–69.5°); ir (KBr) 3268 cm^{-1} (OH); methyl nmr ($CDCl_3$) δ 0.92 (d, J_{Me-H} = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 172 (0.507), 157 (0.239) 143 (0.224), 130 (0.791), 129 (0.776), 115 (0.522), 104 (0.433), 91 (0.313), 28 (1.00).

Anal. Calcd for $C_{13}H_{18}O$ (1–6): C, 82.06; H, 9.53. Found for **1**: C, 81.88; H, 9.62. Found for **2**: C, 82.10; H, 9.43. Found for **3**: C, 81.84; H, 9.38. Found for **4**: C, 82.13; H, 9.75. Found for **5**: C, 82.03; H, 9.73. Found for **6**: C, 81.84; H, 9.78.

Registry No.—**1**, 30689-79-3; **2**, 30689-80-6; **3**, 30689-81-7; **4**, 30689-82-8; **5**, 30689-83-9; **6**, 30689-84-0; phenylmagnesium bromide, 100-58-3; phenyllithium, 591-51-5.

(5) J. Ficini and A. Maujean, *C. R. Acad. Sci., Ser. C*, **266**, 227 (1968); G. D. Maio, M. T. Pellegrini, and P. A. Tardello, *Ric. Sci.*, 240 (1968).

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(7) Spectroscopic information was obtained using a JEOL-C6OH nmr spectrometer, Perkin–Elmer 237B infrared spectrometer, and Hitachi RMU-6B mass spectrometer. All melting points are corrected.

Group III Metal Complexes in the Preparation of Vitamin E

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Karrer, *et al.*,[2] in their numerous syntheses of vitamin E **3** and analogs have alkylated methyl-substituted hydroquinones with phytol or isophytol **2** in boiling formic acid. This method, as well as an alternative one employing phytyl bromide, $ZnBr_2$, and trimethylhydroquinone (TMHQ) **1** at 80–100°,[3] suggests a carbonium ion mechanism as outlined in Scheme I. Later modifications[4] of the same reaction employ strong Brønsted acids (HCl, *p*-toluenesulfonic acid) in combination with a Lewis acid catalyst such as those used in typical Friedel–Crafts reactions (BF_3, $ZnCl_2$, $FeCl_2$, etc.). In the cases described, the water formed in the reaction is removed azeotropically.

With the advent of more sophisticated methods of analysis, it became evident that *dl*-α-tocopherol pro-

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(2) P. Karrer and H. Fritzsche, *Helv. Chim. Acta*, **21**, 1234 (1938).

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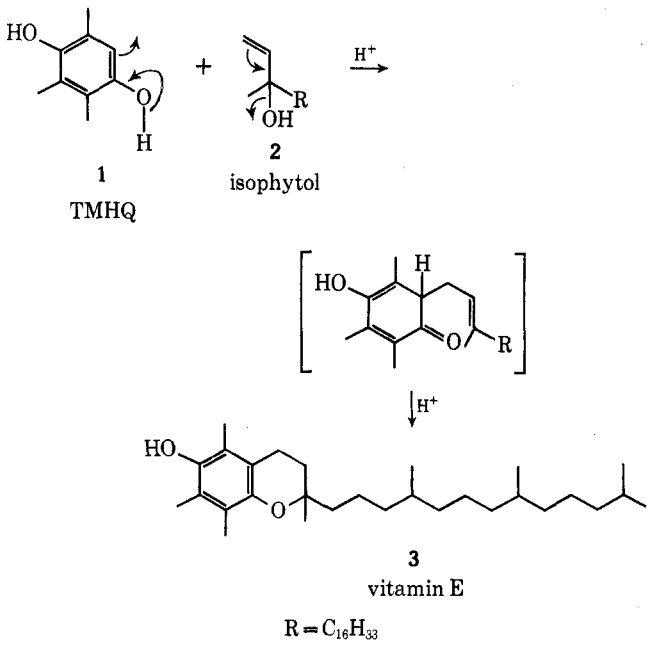
(4) See patent literature, compiled by W. F. Kujawski in "Annotated Bibliography of Vitamin E," Distillation Products Industries, Rochester, N. Y. 14603.

SCHEME I



duced *via* the classical methods described above contained a number of impurities. Some of these contaminants are detectable semiquantitatively by thin layer chromatography and quantitatively by gas chromatography.[5] Attempts to remove the impurities efficiently by distillation were only partially successful —a number of impurities codistilled with the main product. It therefore became necessary to reinvestigate the various procedures for the production and purification of vitamin E.

A step in this direction was undertaken in 1965 by Miller and Wood.[6] These investigators activated the isophytol moiety by transforming it to the diphenyl phosphate ester prior to heating at 100° with trimethylhydroquinone. However, this method gave pure *dl*-α-tocopherol only if the product was chromatographed over silica gel.

In contrast with this method which merely activated the phytol, we embarked on a program aimed at increasing the activity of both reaction partners, which would enable the reaction to proceed under much milder conditions. Our goal was reached when we found that trimethylhydroquinone forms relatively stable 1:1 complexes with either BF_3 or $AlCl_3$ and that both complexes react very smoothly and almost instantaneously with isophytol between −20 to −60° to give pure *dl*-α-tocopherol.

We attribute the greatly enhanced reactivities to the following factors. (a) Trimethylhydroquinone is transformed into a strong Brønsted acid by complexation with either BF_3 or $AlCl_3$. (b) Protonation of the isophytol with *this* Brønsted acid has two effects: (1) simultaneous activation of *both* the allylic alcohol (by protonation) and the trimethylhydroquinone (by deprotonation of the complex) and (2) ion-pair association of the reaction partners, which keeps the molecules in close contact. (c) Water is removed efficiently by complexation with either BF_3 or $AlCl_3$ (see Scheme II).

(5) F. P. Maln, V. Viswanathan, C. Plinton, A. Menyharth, and B. Z. Senkowski, *J. Pharm. Sci.*, **57**, 2149 (1968).

(6) J. A. Miller and H. C. S. Wood, *Chem. Commun.*, 40 (1965).

In the preparation of the trimethylhydroquinone–BF_3 complex (or the corresponding $AlCl_3$ complex), as well as for the alkylation and cyclization reaction with phytol or isophytol, the choice of solvent is critical. In general, chlorinated hydrocarbons, nitroparaffins, nitrotoluenes, nitrobenzene, or mixtures of these solvents are preferred. In fact, none of the desired complex formation is observed in solvents such as ether, tetrahydrofuran, ethyl acetate, acetone, or alcohols, due most likely to competitive or preferred complexation with these solvents. As a consequence, no (or only trace) formation of vitamin E is observed under our reaction conditions (−20 to −60°) in these latter solvents.

It is interesting to note that virtually no *dl*-α-tocopherol was obtained when BF_3 was replaced by BCl_3. $AlBr_3$, under standard conditions, produced vitamin E in markedly lower yield (*ca.* 30%). Further, some halogenides of other than group III metals were tested for their ability to bring about this alkylation–cyclization reaction. We found that $TiCl_4$, $SbCl_5$, and $SnBr_2$ yielded only trace amounts of *dl*-α-tocopherol as judged by tlc.

The BF_3– and $AlCl_3$–trimethylhydroquinone complexes are crystalline compounds which were difficult to handle and purify. Both of them, however, on microanalysis, gave values which closely approximated the 1:1 composition. The ir spectra were also compatible with the postulated structures (see Experimental Section).

Experimental Section[7]

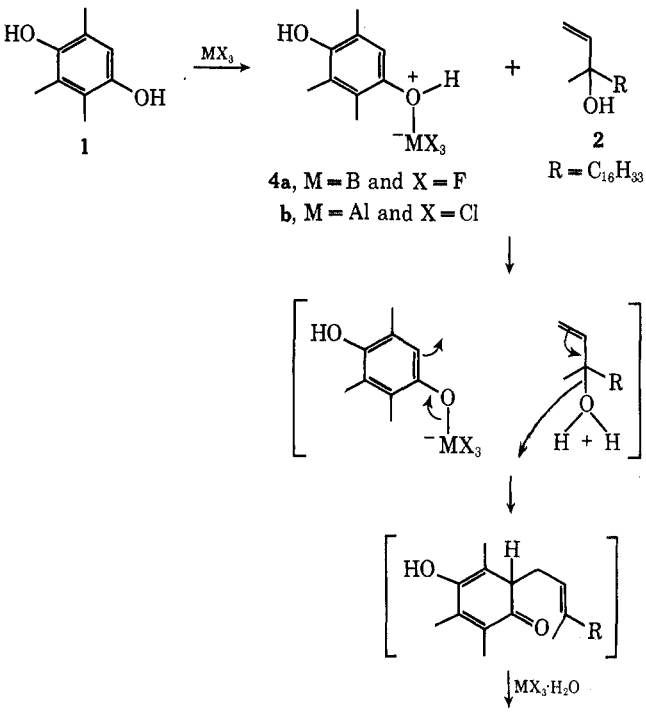
Trimethylhydroquinone–BF_3 Complex (4a).—To a suspension of 5.00 g (32.9 mmol) of trimethylhydroquinone, mp 172–174°, in 50 ml of dry CH_2Cl_2, 2.6 ml (2.95 g, 48.4 mmol) of nitromethane was added. With water cooling, a slow stream of BF_3 gas was passed into the solution. The suspension turned light green and after about 1 min a white precipitate started to crystallize. BF_3 addition was stopped as soon as the saturation point was reached (judged by the white funes emerging from the attached $CaCl_2$ drying tube). The precipitate was stirred for 15 min longer. After filtration under N_2, the crystals were washed with two 25-ml portions of CH_2Cl_2. The wet material was dried directly with a high vacuum pump to give 5.98 g (83%) of white crystals, mp 116–118°, which were analyzed as is: ir (Nujol) 3500 s, 1170 s (broad), 1080 s (broad), 860 s, 725 s, 604 s, 560 s, cm^{-1}. The ir spectrum (Nujol) of the free ligand TMHQ shows the following bands: 3300 m (broad), 1210 s, 1075 s, 1020 m, 840 m, 830 m, 720 w, 700 m cm^{-1}.

Anal. Calcd for $C_9H_{12}O_2 \cdot BF_3$: C, 49.13; H, 5.50; F, 25.91. Found: C, 50.93; H, 6.14; F, 22.28.

Trimethylhydroquinone–$AlCl_3$ Complex (4b).—$AlCl_3$ powder, Baker, AR quality (6.64 g, 50 mmol), was weighed into a dry 100-ml flask, and 20 ml of CH_2Cl_2 was added. With ice cooling and a slight flow of N_2, 4.54 g (40 ml, 74 mmol) of CH_3NO_2 was added dropwise with magnetic stirring. The resulting colorless solution contained a small amount of insoluble material which was removed by filtration under N_2 through a glass wool packed tube. To the completely clear filtrate was added 7.6 g (50 mmol) of

(7) Infrared spectra were recorded on a Perkin–Elmer Model 21 spectrophotometer. The symbols s, m, and w refer to strong, medium, and weak intensity bands. Gas chromatographic analyses were performed on a Perkin–Elmer 881 gas chromatograph with a differential flame ionization detector; dual glass spiral column, 6 ft × 2 mm i.d. packed by suction with 4% SE-30 on Gas-Chrom Q (100–120 mesh size); starting temperature 120° programmed at 6°/min to 250° and kept at upper limit for 20 min; injection port 255°; detector 245°; Barber–Coleman recorder series 8300-26000-000-0-18, 5 mV, chart speed 20 in./hr, equipped with Disc integrator; attenuation of 50 used for the first 30 min in order to pick up impurities, then switched to 500 to keep *dl*-α-tocopherol on scale. Thin layer chromatograms performed on silica gel Merck F_{254} plates using a cyclohexane–ether, 4:1 system. The spots were developed by spraying with 10% phosphomolybdic acid followed by heating at 110°.

SCHEME II



pure trimethylhydroquinone (recrystallized from monochlorobenzene, mp 172–174°, slightly ground material containing no lumps) and the mixture was swirled until all material was dissolved (under N_2, color change to green). After about 2 min, rapid crystallization of the complex was observed. The reaction mixture was allowed to stand without stirring for 3 hr at room temperature before the crystals were filtered under N_2. After two washings with CH_2Cl_2 (10 ml and 15 ml, always under N_2) the material was dried directly with a high vacuum pump. The resulting 12.5 g (87.7%) of grayish looking crystals were used for analysis: ir (Nujol)[8] 3500 m, 1630 w ($AlCl_3$ absorption), 1310 m, 1180 s, 1080 s, 830 m, 720 m, 535 s cm^{-1}.

Anal. Calcd for $C_9H_{12}O_2 \cdot AlCl_3$: C, 37.86; H, 4.24; Cl, 37.25. Found: C, 38.46; H, 4.42; Cl, 35.31.

***dl*-α-Tocopherol *via* TMHQ–BF_3 Complex.**—Trimethylhydroquinone (46.0 g, 0.303 mol), 250 ml of CH_2Cl_2, and 18 ml (20.4 g, 0.334 mol) of CH_3NO_2 were put into a 500-ml three-necked flask and blanketed with N_2. The flask was then immersed in a cooling bath at −20°. With continuous stirring, a strong flow of BF_3 gas (the cyclinder was mounted on a scale) was passed into the suspension of trimethylhydroquinone. At the beginning of the BF_3 addition the color turned green, the suspension became thinner, and after approximately 5 min crystallization of the boron trifluoride–trimethylhydroquinone complex started. The appearance of the reaction mixture changed to a beige color and the contents were a readily stirrable slurry. After *ca.* 20 min a total of 20.6 g (0.304 mol) of BF_3 had been introduced (the rate of the BF_3 flow was controlled by a gas washing bottle containing CH_2Cl_2). During this time, the temperature fell from initially 20° to −20°. At this point, slow subsurface addition of 100 g (0.338 mol) of isophytol was started by way of a peristaltic pump. The temperature was maintained at −20°. The color of the reaction mixture changed from beige *via* yellow to an amost clear dark brown at the end of the 2–3 hr addition period. The stirring was maintained for an additional 1 hr before the reaction mixture was transferred to a separatory funnel using a small amount of CH_2Cl_2 for rinsing the three-necked flask. This solution was washed under N_2 three times with a total of 400 ml of distilled H_2O (200, 100, 100 ml; *no heat generation* was observed with the first H_2O addition). The water layers in turn were washed with 50 ml of CH_2Cl_2. After combination of all yellow-orange layers and evaporation of the solvent at the rotavap, the residue was dissolved in 200 ml of hexane and washed with five 50-ml portions of 78% CH_3OH–H_2O mixture. Each H_2O phase was reextracted with 50-ml portions of hexane. After combination of all organic layers and evaporation of the hexane at the rotavap, there was obtained 143–146 g of orange-colored crude *dl*-tocopherol. This residue, on simple high-vacuum distillation through a 5-cm Vigreux adapter, yielded a light yellow-colored main fraction, 120 g (82% based on isophytol), bp 220–239° (0.07–0.1 mm).[9] This material assayed >98% by vpc.

***dl*-α-Tocopherol *via* TMHQ–$AlCl_3$ Complex.**—Into a stoppered three-necked flask (rinsed with dry N_2), 33.7 g (0.252 mol) of $AlCl_3$ powder (Baker, AR grade) was weighed, the flask was immersed in a cooling bath at 0°, and 250 ml of CH_2Cl_2 was added. To the stirred suspension, cooled to 0° while a slow flow of N_2 was maintained throughout the procedure, 33.7 ml (38.2 g, 0.626 mol) of CH_3NO_2 was added. All the $AlCl_3$ dissolved and the temperature rose to 12°. After the temperature had dropped to 0° again, the stirring was stopped[10] and 51.4 g (0.338 mol) of trimethylhydroquinone was added through a powder funnel. The stirrer was started again and the solid material almost dissolved with a color change to dark green (no rise in temperature was observed.). With continued stirring the contents were cooled to −20°. After *ca.* 3–5 min a very fine reaction intermediate started to crystallize and it was necessary to increase the rate of stirring. The heat of crystallization increased the temperature by about 2 or 3°. The color was now light yellow and the slurry was readily stirrable. As soon as the temperature reached −20°, 100 g (0.388 mol) of isophytol was introduced in the same manner as in the experiment described for the TMHQ–BF_3 complex. Analogous work-up and high vacuum distillation of the crude *dl*-α-tocopherol yielded a main fraction of 111.4 g (76.4%), bp 215–232° (0.07 mm). Vpc analysis indicated the vitamin E thus obtained to have a purity in excess of 98%.

Registry No.—**3**, 364-50-1; **4a**, 30783-58-5; **4b**, 26162-55-0.

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(8) Cell preparation was carried out in a drybox.

(9) Bp 200–220° (0.1 mm): The Merck Index, 8th ed, 1968, p 114.

(10) This must be done to prevent crystallization of the trimethylhydroquinone–aluminum chloride complex before all the trimethylhydroquinone has been added.

A Study of Syn/Anti Oxime Ratios from the Paramagnetic-Induced Shifts in the Proton Magnetic Resonance Spectra Using Tris(dipivalomethanato)europium(III)[1a]

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Tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$] has been recently used to effect paramagnetic-induced shifts in the proton magnetic resonance spectra of alcohols and amines.[2-4] We have found that this reagent has considerable value in the study of syn–anti isomerism in oximes. Nuclear magnetic resonance

(1) (a) Supported by Public Health Service, Cancer Institute, Grant CA-07202-09; (b) Research Associate, 1969–1972.

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