vacuo; yield 30 mg.; m. p. 155° (dec.). The product may be recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: C, 71.6; H, 6.7.

2,3-Estracatechol Semicarbazone.—Forty mg. of 2,3-estracatechol, 200 mg. of semicarbazide hydrochloride, 200 mg. of anhydrous sodium acetate and 2 cc. of 95% ethanol are refluxed with stirring for five minutes. After cooling, 3 cc. of water is added dropwise. The resulting precipitate is filtered, washed with water and dried *in vacuo;* yield 25 mg.; m. p. above 250° (dec.). The product may be recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{25}O_3N_3$: N, 12.2. Found: N, 11.9.

2,3-Estracatechol 3-Methyl Ether.—A solution of estrone methyl ether-2-diazonium chloride is prepared as described from 200 mg. of 2-nitroestrone methyl ether. Twenty-five cc. of water is added and the mixture is extracted with five 40-cc. portions of ethyl acetate. The aqueous phase is separated and mixed with a solution of 1 g. of cupric sulfate pentahydrate in 4 cc. of hot water. The reaction mixture is heated in a boiling water-bath for fifteen minutes, cooled and kept at 5° for twenty-four hours. The crude product, after filtering, washing with water and drying, weighs 50 mg. and is treated with zinc and acid as described under 2,3-estracatechol; yield 25 mg.; m. p. 105° (dec.).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.0. Found: C, 75.9; H, 7.9.

2,3-Estracatechol 3-Methyl Ether Semicarbazone.—Thirty mg. of 2,3-estracatechol 3-methyl ether is treated as described under 2,3-estracatechol semicarbazone; yield 26 mg.; m. p. 249°.

Anal. Calcd. for $C_{20}H_{27}O_3N_3$: N, 11.8. Found: N, 11.6.

Physiological Tests.—The results of estrogenic assays are summarized in Table I.

TABLE I

ESTROGENIC ACTIVITY IN RATS

Compound	No. of rats	Dose,[a] gammas	Response, %
Estrone, U. S. P. (control)	10	0.65	50
2-Nitroestrone	6	2	33
2,3-Estracatechol	10	20	0
2,3-Estracatechol 3-methyl ether	10	13	0

[a] Injected subcutaneously in sesame oil.

Summary

1. The semi-micro synthesis of crystalline 2,3-estracatechol (2-hydroxyestrone) *via* the corresponding nitro, amino and diazonium compounds has been reported. The final product and its intermediates have been characterized by the preparation of derivatives.

2. The results of estrogenic assays have been presented. The lack of estrogenic activity of 2,3-estracatechol and its 3-methyl ether is in harmony with the view that hydroxylation may be involved in the *in vivo* degradation of estrone.

RECEIVED SEPTEMBER 22, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Synthesis of Terpinyl Ethers from *d*-Limonene

BY E. EARL ROYALS

The reaction of methanol with trimethylethylene in the presence of sulfuric acid to form methyl *t*-amyl ether was observed by Reychler[1] in 1907. Evans and Edlund more recently[2] made an extensive study of the reaction of olefins with alcohols in the presence of acid catalysts. These workers found that trisubstituted and unsymmetrically disubstituted olefins react readily with primary alcohols to yield tertiary alkyl ethers. Other types of olefins and secondary alcohols are less suitable reactants. The equilibrium nature of the reaction was demonstrated. Several applications of this etherification reaction have been made in the terpene field. Semmler produced[3] ethyl ethers from camphene, nopinene and sabinene, but was unable to obtain an ether from limonene. Other early workers reported only resinification on treatment of limonene with alcoholic sulfuric acid.[4] More recently, Treibs[5] studied the sulfuric acid catalyzed reaction of methyl alcohol with several cyclohexene derivatives. His conclusions regarding the influence of olefin structure on the etherification reaction were similar to those of Evans and Edlund.[2] He was not, however, able to obtain an ether from limonene (carven); this diolefin, according to Treibs, gave a diether in small yield, the principal reaction being dimerization. Despite these negative reports as to the ability of limonene to react additively with alcohols, several recent patents[6] describe the formation of terpene ethers by reaction of various terpenes, including dipentene, with alcohols in the presence of acid catalysts. Most of the examples in these patents, however, describe the use of α-pinene as terpene reactant.

We have found that *d*-limonene reacts readily with anhydrous primary alcohols to yield terpene ethers. It is believed on the basis of evidence presented below that these ethers are principally α-terpinyl alkyl ethers, although isomeric terpene ethers may be present. In Table I are presented data on the synthesis and properties of various terpinyl alkyl ethers derived from *d*-limonene by a standard procedure, namely,

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(1) Reychler, *Bull. soc. chim. Belg.*, **21**, 71 (1907).

(2) Evans and Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936).

(3) Semmler, *Ber.*, **33**, 3420 (1900).

(4) Clover, *Chem. Zentr.*, **78**, I, 1793 (1907); Wall, *Ann.*, **239**, 15 (1887).

(5) Treibs, *Ber.*, **70**, 593 (1937).

(6) See, for example: U. S. Patents 900,136, 2,220,462, 2,309,017, 2,321,978, 2,347,337, 2,388,765; British Patents 494,504, 556,579; French Patent 818,787; German Patents 711,915, 711,916.

TABLE I

TERPINYL ALKYL ETHERS[a] FROM REACTION OF *d*-LIMONENE WITH PRIMARY ALCOHOLS

Alkyl	Yield, %	B. p. °C.	B. p. Mm.	d^{25}_{4}	n^{25}_{D}	M^{25}_{D} Calcd.	M^{25}_{D} Obs.	α^{25}_{D}
Methyl	40.0	106–107.5	20	0.8978	1.4642	51.97	51.74	+53.22
Ethyl	30.8	112–114	20	.8854	1.4608	56.59	56.48	+44.70
n-Propyl	29.5	126–129	20	.8788	1.4590	61.21	61.07	+27.80
n-Butyl	28.9	140–143	20	.8743	1.4598	65.82	75.87	+17.64
iso-Butyl	32.8	133–136	20	.8700	1.4570	65.82	65.85	+ 9.32
n-Amyl	31.5	139–143	10	.8718	1.4600	70.44	70.49	+ 7.50
iso-Amyl	34.4	132–135	10	.8692	1.4585	70.44	70.50	+ 5.64
Allyl	11.2	125–130	20	.8949	1.4710	60.74	60.79	+ 0.66

[a] The ethers here reported are new to the scientific literature, although several are claimed in patents. Customary elemental analyses have been omitted, since the molecular refractions are in good agreement with calculated values and such analyses would add nothing to the more important question of isomeric identity of the ethers.

by treatment of the terpene with 4 moles of primary alcohol containing 10% by weight of concentrated sulfuric acid at 55–60° for five hours. Methanol is the most reactive of the primary alcohols, giving a 40% yield of terpinyl methyl ether under conditions which lead to approximately 30% yields with higher homologs. The greater reactivity of methanol was further demonstrated by the isolation in 7% yield of 1,8-dimethoxy-*p*-menthane. The yield of this diether was increased somewhat by largely increasing the ratio of methanol to limonene. From none of the other etherification reactions under the standard conditions described above was a dialkoxy-*p*-menthane isolated. 1,8-Diethoxy-*p*-menthane was formed in small yield by treatment of limonene with a large excess of ethanol. The secondary alcohols, isopropyl and cyclohexyl, failed completely to react with limonene under our standard conditions. Allyl alcohol gave a low yield (11%) of terpinyl allyl ether. That this low yield of ether was due to lack of reactivity of allyl alcohol rather than to some side reaction other than isomerization was indicated by the high hydrocarbon recovery in this experiment. The reaction with benzyl alcohol led to a 30% yield of benzyl terpinyl ether, which we suspect on the basis of its physical properties to be somewhat less pure than the other ethers prepared; this reaction was complicated by acid-catalyzed polymerization of the benzyl alcohol.

Successful etherification of *d*-limonene requires the use of an essentially anhydrous alcohol. We have found, for example, that whereas anhydrous (98–99%) *n*-propyl alcohol under our standard conditions leads to a 29.5% yield of terpinyl *n*-propyl ether, the presence of 4 moles of water reduces the yield of ether to 5.1% with simultaneous formation of 20% terpene alcohols.

Reaction time for our standard conditions was chosen on the basis of exploratory experiments with methyl and *n*-propyl alcohols. In both cases, shortening the reaction time from five hours to one or two hours led to greatly reduced yields. It is significant, however, that the ethers obtained from the short runs showed considerably higher optical rotations than those reported in Table I. Doubling the standard reaction time of five hours in the case of methanol gave a small increase in yield of diether at the expense of monoether; similarly, the yield of terpinyl *n*-propyl ether was slightly diminished in a longer run. The ethers resulting from these longer runs showed optical rotations considerably lower than those reported in Table I. Unreacted terpene hydrocarbons were recovered (20–40%) from all etherification experiments; this fact coupled with failure to increase the yield of ether by longer reaction periods indicated the equilibrium nature of the reaction. Further evidence on this point was obtained by carrying out certain ether exchanges; for example, the displacement of the propoxyl group by methoxyl. Ether exchanges in which a larger alkoxyl group displaced methoxyl were less successful, but it was possible to demonstrate that some exchange did occur. Although the etherification reaction involves an equilibrium, this is not the sole factor limiting the yield of terpinyl ether. Perhaps equally important is the fact that there is concurrent isomerization of *d*-limonene to products less active toward alcohol addition. Hydrocarbons accumulated from various etherification reactions were shown to give only half the yield of terpinyl methyl ether obtainable from pure *d*-limonene under our standard conditions; similarly, a terpene hydrocarbon mixture containing 70% α-terpinene failed to react with *n*-propyl alcohol. Evidently, the isomerization products are less reactive than *d*-limonene toward etherification, and the true equilibrium in etherification of *d*-limonene is more favorable than would be indicated by the actual yields reported in Table I.

It is probable that the ethers here reported are isomeric mixtures; that the principal isomer is 8-alkoxy-Δ^1*p*-methene is indicated by the following considerations: (1) Since the tendency is toward formation of monoether to the complete or nearly complete exclusion of diether, one double bond of limonene possesses greater reactivity toward etherification than the other. The ionic nature of the reaction suggests that the 8,9-unsaturation is involved. (2) Alcohols react preferentially with *d*-limonene since the isomerization products show reduced reactivity toward etherification. (3) The rather high optical activity of the lower ethers suggests that addition occurred at the 8,9-double bond. (4) The terpinyl methyl ethers prepared from *d*-limonene and from α-pinene are apparently identical. Treibs has previously reported[5] the preparation of a methyl ether from α-pinene to which the α-terpinyl structure was assigned. The reported boiling point (89–92° (20 mm.)) differs considerably from that found by us for terpinyl methyl ether (106–107.5° (20 mm.)). In view of this discrepancy, we prepared a methyl ether from α-pinene by a modification of our standard procedure and found the following comparison of properties.

	B. p. (20 mm.)	n^{25}_{D}	d^{25}_4
Methyl ether from *d*-limonene	106–107.5°	1.4642	0.8978
Methyl ether from α-pinene	106–107.5°	1.4647	.9007

Experimental

Apparatus and Materials.—The *d*-limonene was obtained from the Kuder Pulp Sales Company, Lake Alfred, Florida, and was stated by the manufacturer to be of 95% or better purity. This material showed n^{25}_{D} 1.4698, α^{25}_{D} +99.80°, b. p. 177° (738 mm.) and was used without further purification. The alcohols, with the exception of ethyl and *n*-amyl, were commercial anhydrous materials, and were used without further purification. Anhydrous ethyl alcohol was prepared by calcium oxide dehydration of 95% alcohol. The *n*-amyl alcohol available was a technical grade, which was fractionally distilled, a middle cut boiling 136–137° being taken for use.

All fractional distillations were carried out using the fractionation assembly manufactured by Todd Scientific Company.[7] The particular columns used were either a 90 cm./12 mm. column packed with single-turn glass helices or a 90 cm./5 mm. column with a monel spiral packing.[7] These columns will be referred to as the helix-packed and spiral-packed columns, respectively.

Synthesis of Terpinyl Alkyl Ethers.—The method is illustrated by preparation of terpinyl *n*-propyl ether: Concentrated sulfuric acid, 40 g., was dissolved in 360 g. (6.0 moles) of *n*-propyl alcohol contained in a 1-liter, 3-necked flask fitted with a reflux condenser, a modified Hershberg stirrer,[8] and a thermometer reaching into the reaction mixture. Limonene, 200 g. (1.47 moles) was added, and the mixture was stirred for five hours, the temperature being maintained at 55–60° by means of a Glas-Col heating mantle. The reaction mixture was homogeneous at all times, and gradually developed a deep red-brown color. The reaction mixture was cooled to room temperature and diluted with an equal volume of water. The red oily layer which separated was washed with water, with saturated sodium bicarbonate solution, again with water, and dried over anhydrous sodium sulfate. The material was than fractionally distilled through the helix-packed column to give 83 g. of recovered terpene hydrocarbons, a small terpene alcohol fraction, and 112 g. of crude terpinyl *n*-propyl ether, b. p. 125–130° (20 mm.), n^{25}_{D} 1.4580–1.4570. The crude ether was redistilled through the spiral-packed column to give 85 g. (29.5%) of terpinyl *n*-propyl ether with the properties reported in Table I.

All of the ethers reported in Table I were prepared by a similar procedure. In the case of the methyl ether, there was simultaneous formation of a small yield (7.1% after purification) of 1,8-dimethoxy-*p*-menthane. This substance showed the properties: b. p. 124–129° (20 mm.), n^{25}_{D} 1.4533, d^{25}_4 0.9289, M^{25}_{D} 58.32 (calcd. 58.70). By using a ratio of methanol to limonene of 11.5 rather than the standard 4, it was possible to increase the yield of this diether to 22%, largely at the expense of monoether. 1,8-Diethoxy-*p*-menthane was prepared in 10.3% yield by treatment of limonene with 10 moles of dry ethanol. This diether showed the properties: b. p. 134–138° (20 mm.), n^{25}_{D} 1.4479, d^{25}_4 0.9007, M^{25}_{D} 67.86 (calcd. 66.84). Whereas the monoethers reacted readily with bromine in alcohol–ether to give liquid bromides, the two diethers were completely inert toward bromine.

The effect of reaction time on optical rotation of the terpinyl ethers is illustrated by the following data: reaction times of two, four and eight hours gave methyl ethers showing α^{25}_{D} +78.50°, +53.22° and +5.14°, respectively. Similarly with reaction times of one, five and ten hours *n*-propyl ethers of α^{25}_{D} +45.12°, +27.80° and +6.00° were obtained.

The following experiment illustrates the influence of water on the etherification reaction: A mixture of 300 g. of *d*-limonene and 90 g. of concd. sulfuric acid in 810 g. of 95% ethanol was heated to reflux for two hours. The reaction mixture was worked up as described above. The crude product was fractionally distilled through the helix-packed column to give, in addition to recovered hydrocarbons, 119 g. of material, b. p. 100–113° (20 mm.), n^{25}_{D} 1.4622–1.4690. This material smelled strongly of terpineol, but failed to yield an isolable *p*-nitrobenzoate. On cooling the substance to −80° it became exceedingly viscous, but failed to crystallize. One hundred grams of the substance was heated to reflux for five hours with a solution of 100 g. of oxalic acid dihydrate in 250 g. of water, a procedure which was demonstrated to completely dehydrate α-terpineol. Fractional distillation of the product gave: (I) 32 g. of terpene hydrocarbons, b. p. 72–85° (20 mm.), (II) 5 g. of intermediate, (III) 51 g. of terpinyl ethyl ether, b. p. 105–115° (20 mm.), n^{25}_{D} 1.4614. Assuming that the terpene hydrocarbons arose exclusively from dehydration of alcohols, these results indicate that the product obtained by the action of 95% ethanol on *d*-limonene consists of a mixture of about 36% terpene alcohols and 51% terpinyl ethyl ether (13% of material unaccounted for in this calculation).

More conclusive results were obtained by treating *d*-limonene under our standard reaction conditions with a mixture of 4 moles each of *n*-propyl alcohol and water. In this case it was possible to separate the alcohols from terpinyl *n*-propyl ether by fractional distillation. Distillation of the product of such a reaction using 150 g. of *d*-limonene gave, in addition to 87 g. (58%) of terpene hydrocarbons, 34 g. (20%) of terpene alcohols, b. p. 112–117° (20 mm.), and 11 g. (5.1%) of terpinyl *n*-propyl ether, b. p. 125–130° (20 mm.), n^{25}_{D} 1.4609.

Ether Exchange Reactions.—Terpinyl *n*-propyl ether, 87 g. (0.444 mole), was stirred at 55–60° for five hours with a solution of 15.8 g. of concd. sulfuric acid in 142 g. (4.44 moles) of methanol. The reaction mixture, heterogeneous at first, became homogeneous and developed a red-brown color within thirty minutes. The reaction mixture was worked up by the procedure described above. Fractional distillation of the reaction product through the spiral-packed column gave: (I) 9 g. (15%) of terpene hydrocarbons, b. p. 73–85° (20 mm.), (II) 5 g., intermediate, b. p. 85–105° (20 mm.), (III) 20 g. (26.8%) terpinyl methyl ether, b. p. 105–110° (20 mm.), n^{25}_{D} 1.4648, (IV) 7 g., intermediate, b. p. 110–125° (20 mm.), (V) 22 g., b. p. 125–129° (20 mm.), n^{25}_{D} 1.4560, d^{25}_4 0.9165. The physical constants of cut V indicate that it is a mixture of recovered terpinyl *n*-propyl ether and 1,8-dimethoxy-*p*-menthane.

In a similar experiment, terpinyl isoamyl ether was treated with methanol. Materials isolated from this exchange reaction were: isoamyl alcohol (42%), methyl terpinyl ether (19.5%), 1,8-dimethoxy-*p*-menthane (8.5%), and recovered terpinyl isoamyl ether (29.4%). Attempts to displace the methoxy group by *n*-propoxy and isoamyloxy were less successful; very complex products were obtained from which it was not possible to isolate

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(7) *Ind. Eng. Chem.*, **17**, 175 (1945).

(8) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

pure components. The results indicated that at least some exchange occurred.

Terpinyl Methyl Ether from α-Pinene.—α-Pinene, 150 g. (1.1 moles), was added to a stirred solution of 15.7 g. of concd. sulfuric acid in 141 g. (4.4 moles) of methanol at 35°. No external heat was applied. Within one hour the temperature of the reaction mixture rose to about 50°, then began to fall. Stirring at room temperature was continued overnight. The reaction mixture, heterogeneous at room temperature, was diluted with its own volume of water. The organic layer was separated and washed with 10% sodium hydroxide solution, then several times with water. In two experiments the crude reaction product was washed with sodium bicarbonate solution instead of sodium hydroxide; attempted distillation in these cases led to decomposition and isolation of no terpene ether. The product was dried over sodium sulfate and fractionally distilled through the helix-packed column to give: (I) g., b. p. 55–70° (20 mm.), (II) 54 g., b. p. 70–95° (20 mm.), and (III) 70 g., b. p. 95–107° (20 mm.). Most of cut I boiled 55–60° (20 mm.) and represents recovered α-pinene; cut II boiled mostly at 70–85° (20 mm.) and represents monocyclic terpene hydrocarbons. Redistillation of cut III through the helix-packed column gave 56 g. (30.1%) of terpinyl methyl ether, b. p. 106–107.5° (20 mm.), n^{25}_D 1.4647, d^{25}_4 0.9007. No attempt was made to improve the yield in this reaction.

Acknowledgment.—The author is indebted to the Emory University Research Committee and to the Research Committee, University Center in Georgia, for grants-in-aid toward the purchase of equipment and to Mr. A. E. Robinson, Jr., for determination of the densities reported in this paper.

Summary

d-Limonene reacts readily with primary alcohols in the presence of sulfuric acid to give terpene ethers. Evidence is presented that these ethers are principally of the α-terpinyl structure, although isomers may be present. The preparation and properties of the ethers derived from eight primary alcohols are described. Secondary alcohols do not react with *d*-limonene under the conditions used in this work. The nature of the reaction, an equilibrium complicated by concurrent isomerization of *d*-limonene, is discussed.

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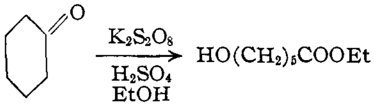
RECEIVED DECEMBER 2, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Reactions of Per Acids. II. The Reaction of Perbenzoic Acid with Simple Cyclic Ketones. Kinetic Studies

BY S. L. FRIESS

In an extension of the previously reported work[1] on the reaction of perbenzoic acid with simple alicyclic and aromatic methyl and ethyl ketones, the present study deals with the action of this peracid on the ketopolymethylenes cyclopentanone, cyclohexanone and cycloheptanone in chloroform solution. Previous investigators, notably Baeyer and Villiger[2] and Robinson and Smith,[3] have touched upon the over-all reaction of these ketones with inorganic peracids in aqueous medium. Baeyer and Villiger found that treatment of cyclohexanone or suberone with Caro's acid in aqueous sulfuric acid solution resulted in monomeric lactones of the ω-hydroxy acids, and pointed out a rather formal analogy between this reaction and the Beckmann rearrangement of oximes. They found further that the presence of alcohol in the reaction mixture led directly to the ω-hydroxy esters in yields as high as 40%, by the reaction



Robinson and Smith modified this procedure somewhat by first forming the lactone from the cyclic ketone and persulfuric acid in aqueous solution at about 15°, followed by refluxing of the crude lactonic product in ethanolic aqueous sulfuric acid to yield the ω-hydroxy ethyl esters in comparable yields. The latter workers also included cyclopentanone in their series of reactants, and were able to isolate ethyl δ-hydroxyvalerate in approximately 45% yield, but they were unable to obtain a lactone from 4-methylcyclohexanone.

In the present work, the reactions of three representative ketopolymethylenes with perbenzoic acid in moist chloroform have been carried out. The lactonic products of the reactions were characterized by conversion to the known, crystalline ω-hydroxy acid hydrazides, and the kinetics of the reactions briefly investigated to obtain some insight into the relative rates of reaction for the different members of the series, as well as the mechanism of the ring expansion involved in lactone formation.

Experimental[4]

Stock solutions of perbenzoic acid in moist chloroform were prepared according to the procedure of Braun.[5]

In the first part of the work, where products were isolated and investigated, a typical reaction with one of the cyclic ketones involved thorough mixing of 0.10 mole of the ketone with 0.12 mole of perbenzoic acid in 250-300 ml. of moist chloroform. The reaction mixture was kept in the dark at room temperature (22–25°), and occasionally swirled. Each reaction proved to be slightly exothermic. Aliquots of the reaction mixtures were removed at intervals and titrated iodimetrically in the nor-

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[1] For paper I of this series, see Friess, THIS JOURNAL, **71**, 14 (1949).

[2] Baeyer and Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900).

[3] Robinson and Smith, *J. Chem. Soc.*, 371 (1937).

[4] All melting and boiling points are corrected.

[5] Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 431.