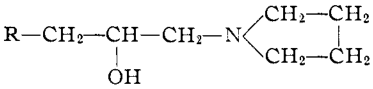
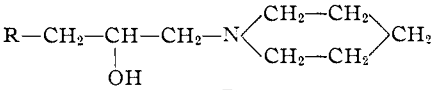
TABLE I

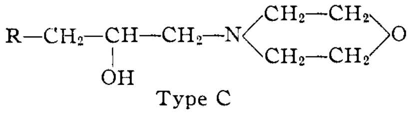
1-ARYLOXY-3-(N-HETEROCYCLICAMINO)-2-PROPANOLS



Type A



Type B

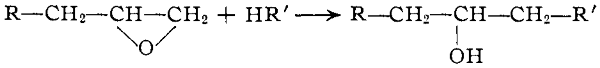


Type C

Type	R	Formula	B.p., °C.	Mm.	M.p., °C. cor.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found	Chlorine, % Calcd.	Chlorine, % Found	Bromine, % Calcd.	Bromine, % Found
A	Phenoxy	$C_{13}H_{19}NO_2$	130–166	1	....	83.2	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{13}H_{20}ClNO_2$	.....	..	118.2–119.2	..	5.43	5.31	...	...	13.76	13.70	...	...
	Hydrobromide	$C_{13}H_{20}BrNO_2$	.....	..	116.2–118.2	..	4.63	4.56	...	...	...	...	26.44	26.37
A	*p*-Chlorophenoxy	$C_{13}H_{18}ClNO_2$	.....	..	90–91	Quant.	5.48	5.46	255.7	256	...	...	...	...
A	*o*-Chlorophenoxy	$C_{13}H_{18}ClNO_2$	144–145	0.7	61–62	79	5.48	5.34	255.7	254	...	...	...	...
A	2,4-Dichlorophenoxy	$C_{13}H_{17}Cl_2NO_2$	162–165	1	79.1–79.6	93.3	4.83	5.02	...	...	...	...	...	...
A	*m*-Toloxy	$C_{14}H_{21}NO_2$	135–139	1	....	92.8	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_2$	.....	..	117.2–117.7	..	5.15	4.94	...	...	13.05	12.80	...	...
A	*o*-Toloxy	$C_{14}H_{21}NO_2$	124–128	1	48.7–50.2	87.8	5.95	5.69	235.3	238	...	...	...	...
A	α-Naphthoxy	$C_{17}H_{21}NO_2$	178–186	0.5	71.5–72.5	76.4	..	..	...	...	...	....	...	...
	Hydrochloride	$C_{17}H_{22}ClNO_2$	.....	..	161.5–163	..	4.55	4.24	...	...	11.52	11.34	...	...
B	Phenoxy[a]	$C_{14}H_{21}NO_2$	155–180	1	....	84.4	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_2$	.....	..	150.9–151.9	..	..	..	271.8	276	13.04	12.97	...	...
	Hydrobromide	$C_{14}H_{22}BrNO_2$	.....	..	134.1–135.1	..	..	..	...	...	...	...	25.27	25.03
B	*p*-Chlorophenoxy[a]	$C_{14}H_{20}ClNO_2$	.....	..	74.6–75.1	Quant.	..	..	269.8	266.	...	...	...	...
	Hydrochloride	$C_{14}H_{21}Cl_2NO_2$	.....	..	157–158	..	..	..	...	...	11.58[b]	11.51[b]	...	...
B	*o*-Chlorophenoxy[a]	$C_{14}H_{20}ClNO_2$	158–159	0.9	70.1–71.1	87	..	..	269.8	267	...	...	...	...
	Hydrochloride	$C_{14}H_{21}Cl_2NO_2$	.....	..	151.4–152.4	..	..	..	...	...	11.58[b]	11.39[b]	...	...
B	2,4-Dichlorophenoxy	$C_{14}H_{19}Cl_2NO_2$	168–170	1	88–89	87.6	..	..	304.2	300	...	...	...	...
	Hydrochloride	$C_{14}H_{20}Cl_3NO_2$	.....	..	149.9–150.9	..	..	..	...	...	10.40[b]	10.29[b]	...	...
B	*m*-Toloxy[a]	$C_{15}H_{23}NO_2$	132–136	1	....	91.8	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{15}H_{24}ClNO_2$	.....	..	128.6–129.6	..	..	..	...	...	12.41	12.32	...	...
B	*o*-Toloxy	$C_{15}H_{23}NO_2$	.....	..	59–60	80.3	..	..	249.3	248	...	...	...	...
	Hydrochloride	$C_{15}H_{24}ClNO_2$	.....	..	134.5–135.5	..	..	..	...	...	12.41	12.29	...	...
B	α-Naphthoxy[a,c]	$C_{18}H_{23}NO_2$	182–187	0.3	82.1–83.1	84.2	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{18}H_{24}ClNO_2$	.....	..	183.6–184.6	..	..	..	...	...	11.02	10.89	...	...
C	Phenoxy[d]	$C_{13}H_{19}NO_3$	150–184	1	67.5–68	94.1	5.90	5.97	...	...	...	...	...	...
C	*p*-Chlorophenoxy	$C_{13}H_{18}ClNO_3$	.....	..	65.5–66.6	Quant.	5.16	5.07	271.7	275.	...	...	...	...
C	*o*-Chlorophenoxy	$C_{13}H_{18}ClNO_3$	170–177	1	69–70	88.2	5.16	5.12	271.7	271.	...	...	...	...
C	2,4-Dichlorophenoxy	$C_{13}H_{17}Cl_2NO_3$	176–183	1	....	90.5	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{13}H_{18}Cl_3NO_3$	.....	..	147.5–149	..	4.09	4.34	...	...	10.35[b]	10.28[b]	...	...
C	*m*-Toloxy	$C_{14}H_{21}NO_8$	148–152	1	....	83.3	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_3$	.....	..	143.9–144.9	..	4.87	5.04	...	...	12.32	12.32	...	...
C	*o*-Toloxy	$C_{14}H_{21}NO_3$	139–141	1	66–67	90.4	5.57	5.47	251.3	252	...	...	...	...
C	α-Naphthoxy	$C_{17}H_{21}NO_3$	190–206	0.5	....	86.4	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{17}H_{22}ClNO_3$	.....	..	190.1–191.1	..	4.33	4.23	...	...	10.95	10.82	...	...

[a] Since this work was completed the hydrochlorides of these compounds have been reported by H. R. Ing and W. E. Omerod, *J. Pharm. Pharmacol.*, **4**, 21 (1952). [b] Ionic chlorine. [c] Reported by Fourneau, *et al.*, *Bull. soc. chim.*, **43**, 454 (1928). [d] Reported by Geigy, Swiss Patent 227,033 (August 2, 1943).

efforts were directed toward the synthesis of compounds which were both ethers and alcohols, as shown by the general equation



$$R{-}CH_2{-}\underset{\diagdown O \diagup}{CH{-}CH_2} + HR' \longrightarrow R{-}CH_2{-}\underset{OH}{\underset{|}{CH}}{-}CH_2{-}R'$$

R = an aryloxy group
R′ = 1-pyrrolidyl, 1-piperidyl or 4-morpholinyl

Twenty-one of these compounds were synthesized by slow addition of the intermediate epoxide to the amine at gentle reflux, using catalytic amounts of water, with subsequent distillation or recrystallization. Table I shows their structures and some pertinent physical and analytical data. The hydrochlorides and hydrobromides were made by passing the dry gas into solutions of the bases in ether.

Experimental[3]

Epoxides.—The epoxides required for this investigation were prepared[4] by heating a mixture of the phenol and dichlorohydrin[5] to 70° and then adding a 27% solution of sodium hydroxide over a period of about two hours. The temperature of the mixture was maintained below 80° throughout the addition period. The mixture was then heated for 15 to 60 minutes at 100°, cooled, extracted with ether, dried, and distilled at reduced pressure. The yields varied from 22.8 to 56%. The residues were shown to contain 1,3-diaryloxy-2-propanols in two cases, and it is suspected that analogous by-products were obtained in all similar reactions.

1-(Phenoxy)-3-pyrrolidine-2-propanol.—Thirty grams (0.20 mole) of 1,2-epoxy-3-phenoxypropane was added dropwise to 15.6 g. (0.22 mole) of boiling pyrrolidine containing catalytic amounts of water. After all of the epoxide had been added (45 minutes), the mixture was heated at temperatures below 150° for 135 minutes. The reaction mixture was distilled *in vacuo;* 36.7 g. of product was collected (83.2% crude yield). The hydrochloride was prepared by saturating an ice-cold solution of the compound with dry hydrogen chloride. The insoluble hydrochloride was collected by filtration and recrystallized from butanol-hexane. The same procedure was used in preparing the hydrobromide.

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Esterification of Hindered Carboxylic Acids

BY RUSSELL REED, JR.

RECEIVED JANUARY 11, 1955

Bourne[1] found that trifluoroacetic anhydride was

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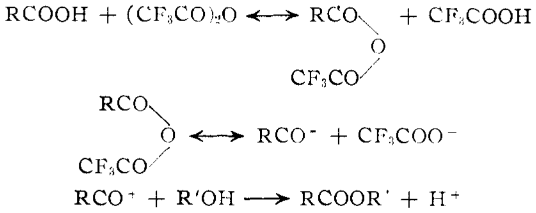
[3] All melting and boiling points are corrected.

[4] Arthur Fairbourne, George Philip Gibson and David William Stephens, *J. Chem. Soc.*, 1965 (1932).

[5] Dichlorohydrin used was approximately 70% 2,3-dichloro-1-propanol and 30% 1,3-dichloro-2-propanol.

[1] E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).

an effective and mild reagent for the esterification of carboxylic acids, and proposed a mechanism involving the formation of the reactive acylium ion,[2] RCO^+.



$$RCOOH + (CF_3CO)_2O \longleftrightarrow \begin{array}{l} RCO\diagdown \\ \quad\; O \\ CF_3CO\diagup \end{array} + CF_3COOH$$

$$\begin{array}{l} RCO\diagdown \\ \quad\; O \\ CF_3CO\diagup \end{array} \longleftrightarrow RCO^+ + CF_3COO^-$$

$$RCO^+ + R'OH \longrightarrow RCOOR' + H^+$$

Since Newman[3] has shown that the esterification of certain 2,4,6-trisubstituted benzoic acids (in 100% sulfuric acid) proceeds *via* the acylium ion, it was of interest to determine whether trifluoroacetic anhydride would esterify sterically hindered carboxylic acids. Trifluoroacetic anhydride was found to be a very effective and convenient reagent for the esterification of the hindered acids: trimethylacetic, 2,6-dimethylbenzoic, and *meso-cis*- and *trans*-2,6-dimethylcyclohexanecarboxylic acids. While trimethylacetic acid is slowly esterified by the usual acid-catalyzed esterification procedures, the latter acids are unreactive.

Although 2,6-dimethylbenzoic acid may be readily esterified in 100% sulfuric acid, the *meso-cis*- and *trans*-2,6-dimethylcyclohexanecarboxylic acids and trimethylacetic acid are more conveniently esterified using the trifluoroacetic anhydride procedure. Although the latter acids are also esterified in sulfuric acid, the reaction appears to proceed more cleanly and in higher yield in the anhydride. Only 2,4,6-trinitrobenzoic acid failed to give an ester, possibly because of the low solubility of the acid in the trifluoroacetic anhydride. However, a small amount of the latter acid was dehydrated to the anhydride. *meso-cis*-2,6-Dimethylcyclohexanecarboxylic acid gave a mixture of *cis* and *trans* esters; at high temperatures the *meso-cis* acid has been shown by Jacobs[4] to undergo acid-catalyzed inversion to the *trans* form. The inversion was apparently caused by trifluoroacetic acid, since a solution of the *meso-cis* acid in trifluoroacetic acid (at room temperature) gave a mixture of *cis* and *trans* acids. However, neither 100% sulfuric acid nor 12 N hydrochloric acid caused inversion of configuration of the acid or its esters at ambient temperatures.

With the exception of the *meso-cis* acid, trifluoroacetic acid did not affect the esterification or hydrolysis of the aforementioned acids (or their esters). *meso-cis*-2,6-Dimethylcyclohexanecarboxylic acid, methanol and trifluoroacetic acid gave approximately the same yield of methyl ester as with trifluoroacetic anhydride. The explanation may involve the fact that the *meso-cis* acid is the weakest studied ($K_{25}° = 2.3 \times 10^{-6}$) and hence probably the most easily protonated. Loss of water by the protonated form with relief of steric strain would then lead to the reactive acylium ion, from which the ester is obtained.

Experimental[5]

All of the methyl esters were prepared under the same conditions.

Methyl 2,6-Dimethylbenzoate.—To 105 g. (0.50 mole) of trifluoroacetic anhydride was added 15.0 g. (0.10 mole) of 2,6-dimethylbenzoic acid (m.p. 115–116°) and 4.0 g. (0.225 mole) of methanol. The clear, colorless solution was allowed to stand two hours at room temperature, and the trifluoroacetic anhydride and trifluoroacetic acid were removed under vacuum at room temperature. The viscous, oily residue was dissolved in 50 ml. of ether, and the solution shaken with 25 ml. of saturated potassium bicarbonate solution. Acidification of the bicarbonate solution gave 3.1 g. (21%) of unreacted 2,6-dimethylbenzoic acid, m.p. 114–116°. Evaporation of the ether solution yielded 14.3 g. of methyl 2,6-dimethylbenzoate; distillation gave 12.1 g. (74%), b.p. 106–107° (7 mm.), $n^{20}D$ 1.5090.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.02; H, 7.49.

Attempted Esterification of 2,4,6-Trinitrobenzoic Acid.—The above procedure failed to yield isolable amounts of either methyl or *p*-nitrobenzyl esters. 2,4,6-Trinitrobenzoic acid was nearly insoluble in trifluoroacetic anhydride. A mixture containing 3.00 g. (0.0117 mole) of 2,4,6-trinitrobenzoic acid, 2.23 g. (0.0145 mole) of *p*-nitrobenzyl alcohol and 50 ml. of trifluoroacetic anhydride was refluxed (38° (710 mm.)) for a week and the anhydride removed under reduced pressure, leaving 3.10 g. of yellow crystals which were extracted with 3 × 100 ml. of ether. Evaporation of the ether gave 0.060 g. (2.1%) of the anhydride of 2,4,6-trinitrobenzoic acid as slightly yellow crystals, m.p. > 270°.

Anal. Calcd. for $C_{14}H_4O_{15}N_6$: C, 33.88; H, 0.81; N, 16.94. Found: C, 34.0; H, 0.94; N, 16.7.

Methyl *meso-cis*- and *trans*-2,6-Dimethylcyclohexanecarboxylates.—The yield was 2.38 g. (28%), b.p. 104–105° (59 mm.), $n^{25}D$ 1.4398 (reported[4] $n^{25}D$ 1.4410 for the *meso-cis* ester and $n^{25}D$ 1.4393 for the *meso-trans*) from 7.80 g. (0.050 mole) of *meso-cis*-2,6-dimethylcyclohexanecarboxylic acid; 4.29 g. (55%) of *meso-trans* acid was recovered. The yield was 2.55 g. (30%), b.p. 104–105° (59 mm.), $n^{25}D$ 1.4394 from 7.80 g. of the *meso-trans* acid; 4.21 g. (54%) of *meso-trans* acid was recovered. The ester from the *meso-cis* acid was a mixture of *cis* and *trans* since hydrolysis with 98% sulfuric acid gave a mixture of *cis* and *trans* acids; the *trans* ester gave only *trans* acid.

All of the *p*-nitrobenzyl esters were prepared under the same conditions.

***p*-Nitrobenzyl 2,6-Dimethylbenzoate.**—A solution containing 1.50 g. (0.0100 mole) of 2,6-dimethylbenzoic acid and 0.40 g. (0.0125 mole) of methanol in 10.5 g. (0.050 mole) of trifluoroacetic anhydride was allowed to stand two hours at room temperature. After removal of the anhydride under vacuum, the mixture was dissolved in 30 ml. of ethyl acetate and shaken with an equal volume of a saturated solution of potassium bicarbonate. Acidification of the potassium bicarbonate solution gave 0.20 g. (14%) of 2,6-dimethylbenzoic acid, m.p. 114–116°. Evaporation of the ethyl acetate gave 3.39 g. of solid which was boiled with two 50-ml. portions of water to remove unreacted *p*-nitrobenzyl alcohol, and then recrystallized from cyclohexane giving 1.60 g. (56%) of *p*-nitrobenzyl 2,6-dimethylbenzoate, m.p. 59.5–60.5°.

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.73; H, 5.29; N, 5.04.

***p*-Nitrobenzyl Trimethylacetate.**—The yield was 10.0 g. (42%), m.p. 47–48° (after recrystallization from petroleum ether), from 10.2 g. (0.100 mole) of trimethylacetic acid; 4.08 g. (40%) of trimethylacetic acid was recovered.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.91. Found: C, 60.60; H, 6.54; N, 5.80.

***p*-Nitrobenzyl *meso-cis*- and *trans*-2,6-Dimethylcyclohexanecarboxylate.**—The esterification procedure gave 2.21 g. (76%) of crude ester, m.p. 30–60°, from 1.56 g. (0.0100 mole) of the *meso-cis*-carboxylic acid. There was recovered 0.41 g. (26%) of the *meso-trans* acid, m.p. 101.5–103°. Recrystallization of the crude ester from hexane (solution A) gave 0.87 g. (30%) of the *meso-trans* ester as yellow needles, m.p. 37.6–39°; two recrystallizations gave 0.54 g., m.p. 47.5–48.5°.

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(2) E. J. Bourne, E. B. Randles, J. C. Tatlow and J. M. Tedder, *Nature*, **168**, 942 (1951).

(3) M. S. Newman, THIS JOURNAL, **63**, 2431 (1941).

(4) T. L. Jacobs, R. Reed and E. Pacovska, *ibid.*, **73**, 4505 (1951).

(5) All melting points are uncorrected.

Anal. Calcd. for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.16; H, 7.12; N, 4.98.

The mother liquor of solution A (above) deposited 0.93 g. (32%), m.p. 63.5–65.5°, of the *meso-cis* ester as long needles; recrystallization from 80% methanol gave 0.81 g., m.p. 69.5–70.5°. A mixture of equal parts of the *cis* and *trans* esters melted at 37–60°.

Anal. Calcd. for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.17; H, 7.20; N, 4.91.

Hydrolysis of the *meso-cis* ester with 98% sulfuric acid gave 57% of the *meso-cis* acid, m.p. 84–86°; hydrolysis of the *trans* ester gave a 60% of the *meso-trans* acid, m.p. 101.5–102°. The *meso-trans* acid, 1.56 g., also yielded the *meso-trans* ester, 1.85 g. (64%), m.p. 37.7–39.0° (m.p. 47.5–48.5 after two recrystallizations; a mixed melting point with the *meso-trans* ester obtained from the *meso-cis* acid showed no depression). This ester gave *meso-trans* acid by hydrolysis with sulfuric acid.

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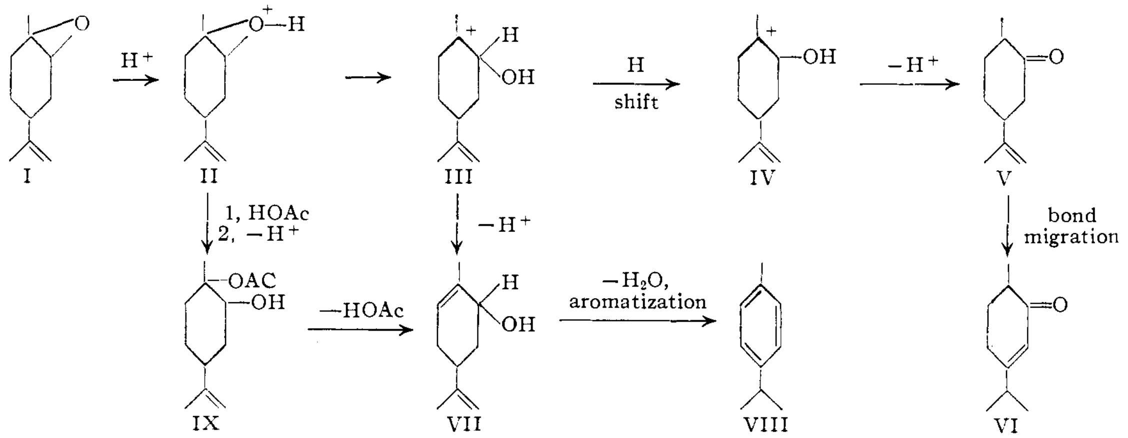
Oxygenated Derivatives of *d*-α-Pinene and *d*-Limonene. Preparation and Use of Monoperphthalic Acid[1]

BY E. EARL ROYALS AND L. L. HARRELL, JR.

RECEIVED OCTOBER 13, 1954

A simplified procedure[2] for the preparation of an ethereal solution of monoperphthalic acid in 65% yield has been developed, and the reagent so prepared has been used to effect the epoxidations of cyclohexene, *d*-limonene and *d*-α-pinene in yields of 64, 71 and 48%, respectively. The low yield of pinene epoxide is probably to be accounted for on the basis of isomerization of the oxide and, perhaps, cleavage of the oxirane ring by phthalic acid produced in the reaction mixture. Appreciable quantities of campholenaldehyde, a known product of isomerization of pinene oxide, were isolated from the epoxidation reaction mixture.



Treatment of limonene monoxide with glacial acetic acid at room temperature for a period of four hours led to the formation of a small amount of dihydrocarvone (V) probably containing some carvenone (VI); 24% of unreacted epoxide was recovered. The dihydrocarvone might conceivably have arisen from direct acid-catalyzed isomerization of limonene monoxide through the intermediates II–IV, or through an initial cleavage of the epoxide ring to the hydroxyacetate, IX, followed by pyrolysis of the acetate during distillation of the product with formation of carveol (VII). Isomerization of carveol in the presence of acetic acid through the intermediates III and IV would lead to dihydrocarvone. In another experiment, limonene monoxide was treated with glacial acetic acid containing 1% of sulfuric acid at 16° for a period of eight hours. The reaction mixture was neutralized and the reaction product distilled under reduced pressure to obviate the possibility of pyrolysis of an intermediately formed hydroxyacetate. Under these conditions, 90% of the reaction product distilled below 100° at 10 mm. indicating the presence of little or no hydroxyacetate. Fractional distillation of the reaction product led to the isolation of *p*-cymene, dihydrocarvone and carvenone in yields of 10, 16 and 35%, respectively. These results indicate that limonene monoxide reacts with acetic acid, particularly in the presence of sulfuric acid, according to the indicated isomerization scheme; *i.e.*, under acid conditions, isomerization of the epoxide is faster than ring cleavage.

In contrast to the above results in acid media, treatment of *d*-limonene monoxide with glacial acetic acid containing sodium acetate led to the formation of a monoacetate of 8-*p*-menthene-1,2-diol in 82% yield. This monoacetate was most probably the 2-acetoxy-1-hydroxy structure, since base-catalyzed cleavage of unsymmetrical epoxides is known[3] to preferentially involve nucleophilic attack at carbon in the order primary > secondary > tertiary. That the product contained at least some of this isomer was shown by boric acid dehydration to give carveyl acetate in 16% yield; *p*-cymene and dihydrocarvone were also isolated in 19 and 21% yields. Dehydration of the hydroxyacetate with *p*-toluenesulfonic acid in benzene led to the isolation of *p*-cymene and carvenone in 31 and 37% yields; no carveyl acetate was isolated.

Reaction of α-pinene oxide with glacial acetic

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[1] Abstracted from a thesis presented by L. L. Harrell, Jr., to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 5, 1954.

[2] Compare, H. Böhme, *Ber.*, **70**, 379 (1937); *Org. Syntheses*, **20**, 70 (1940); G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944).

[3] See S. Winstein and R. B. Henderson in R. C. Elderfield, Editor, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 32–39.