Syntheses of Medium-Ring Benzoic Acid Lactones

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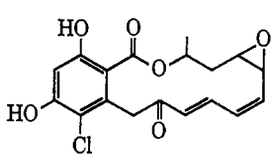
A study of synthetic reactions leading to medium-ring lactones of substituted benzoic acids is described. Ketones **4a–f** were converted *via* carbethoxylation and alkylation into the correspondingly substituted butanols **6a–f**. The alcohols were cyclized to yield enol ethers **7a–g**, which were used as substrates to study the per acid oxidation reaction. Enol ethers **7a, c, d, e,** and **g** on treatment with an excess of *m*-chloroperbenzoic acid generated the corresponding benzoic acid lactones **9a–f**. Similar treatment of **7b** and **7f** resulted in the formation of carbonates **8** and **16**, respectively. The influence of the conformation of the transitional intermediates and the extent of stabilization of the onium ions involved govern the course of the per acid reaction. A mechanism for the pathway leading to the carbonates is suggested. Carbonate **8** and lactone **9e** were transformed in alkaline medium *via* a transannular reaction into the cyclic ethers **11** and **18**, respectively. A rational pathway for the genesis of **11** and **18** is suggested.

Macrolides constitute a large group of naturally occurring compounds, having a broad spectrum of pharmacodynamic properties. To this class belongs a group of acetogenins, of relatively rare natural occurrence, biogenetically arising from the cyclization of a polyketo chain to a β-resorcylic acid nucleus, to yield what may be generally termed "β-resorcylic acid lactones." Radicicol[1] **1**, zearalenone[2] **2**, and two parent members lacking in the large ring found in isocoumarins[3] **3a** and **b** are the only examples known to date.



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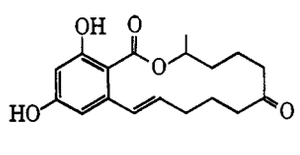

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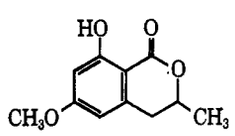
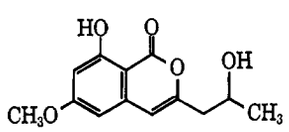


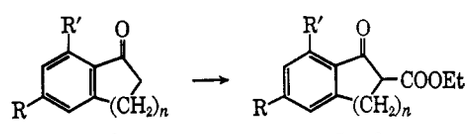
3a



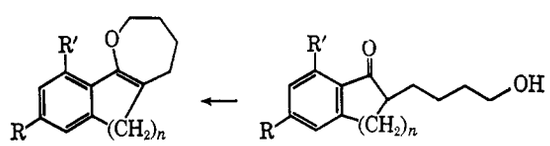
3b

In view of the antifungal properties[4] of radicicol and the anabolic and uterotrophic[5] action of zearalenone, it was of interest to explore synthetic methods potentially applicable to the synthesis of compounds of this group.

This article describes some of our work along these lines. Tetralone **4a** was carbethoxylated to yield the suitably substituted product **5a**. Condensation of **5a** with 4-bromobutyl 1-acetate[6] in dry *t*-butyl alcohol containing potassium *t*-butoxide yielded the alkylated acetoxy compound. Alkaline hydrolysis led through concomitant decarboxylation to the alcohol **6a**. Treatment of **6a** in dry benzene containing a catalytic amount of *p*-toluenesulfonic acid generated the enol ether **7a**.



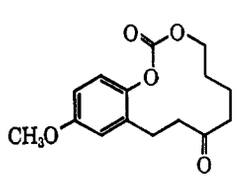
4a–f **5a–f**



7a–g **6a–g**

a, R = H; R′ = H; n = 2
b, R = OMe; R′ = H; n = 2
c, R = OMe; R′ = H; n = 3
d, R = OMe; R′ = H; n = 1
e, R = H; R′ = OMe; n = 1
f, R = OMe; R′ = OMe; n = 1
g, R = $OCOCH_3$; R′ = H; n = 2

Reaction[7] of **7a** in methylene chloride with an excess (3 mol) of *m*-chloroperbenzoic acid led to the formation of a compound whose spectral properties were in complete consonance with the structure **9a**.



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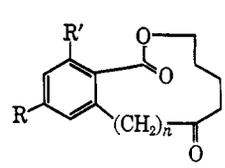


9a–f

a, R = H; R′ = H; n = 2
b, R = $OCOCH_3$; R′ = H; n = 2
c, R = OH; R′ = H; n = 2
d, R = OCH_3; R′ = H; n = 3
e, R = OCH_3; R′ = H; n = 1
f, R = H; R′ = OCH_3; n = 1

In a similar sequence of reactions, starting with methoxytetralone **4b**, the enol ether **7b** was prepared. The per acid oxidation of this compound generated a product, which showed in its infrared spectrum a carbonyl absorption at 1755 and 1700 cm^{-1}. The elemental analysis was consistent with the formula $C_{15}H_{18}O_5$ indicating one more oxygen than that required for the desired lactone. The ultraviolet spectrum was characteristic for that of an isolated aromatic ring (276 mμ,

(1) (a) R. N. Mirrington, E. Ritchie, C. W. Shoppee, and W. C. Taylor, *Tetrahedron Lett.*, 365 (1964); (b) F. McCapra, A. I. Scott, P. Delmotte, and J. Delmottee-Plaquee, *ibid.*, 869 (1964); (c) R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell, and W. C. Taylor, *Aust. J. Chem.*, **19**, 1265 (1966).

(2) (a) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966); (b) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Chem. Commun.*, 225 (1967); (c) N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967).

(3) (a) F. Sondheimer, *J. Amer. Chem. Soc.*, **79**, 5036 (1957); (b) E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, **49**, 1283 (1966).

(4) N. H. White, G. A. Chilvers, and O. Evans, *Nature*, **195**, 406 (1962).

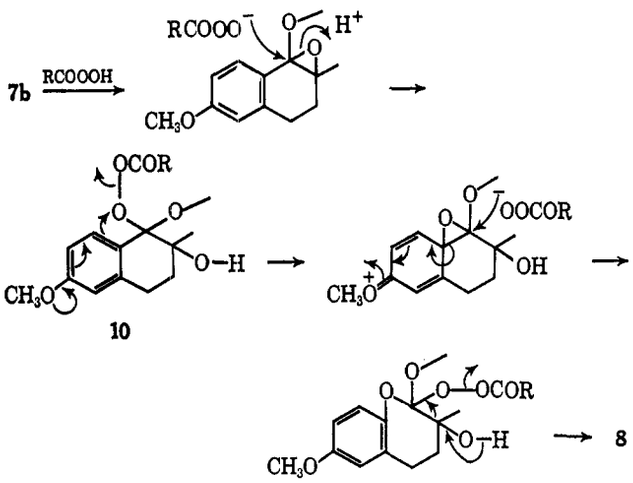
(5) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *ibid.*, **196**, 1318 (1962).

(6) J. B. Cloke and F. J. Pilgrim, *J. Amer. Chem. Soc.*, **61**, 2667 (1939).

(7) (a) I. J. Borowitz and G. J. Williams, *Tetrahedron Lett.*, 3813 (1965); (b) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

ϵ 2580). The structure **8** was assigned to this product and was corroborated by its nmr spectrum. A mechanism of formation of carbonate **8** is shown in Scheme I.

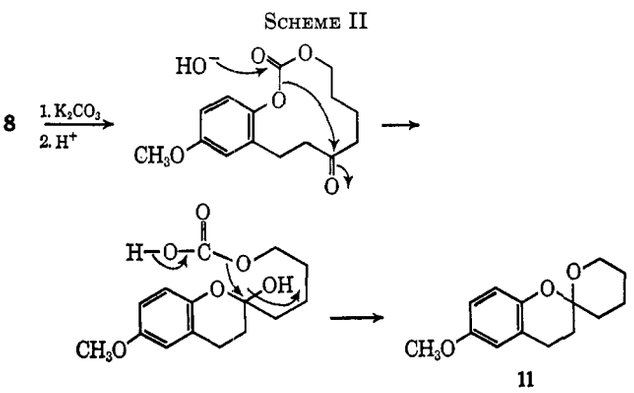
SCHEME I



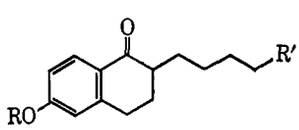
The positive character on the oxygen atom of the per ester **10**—an intermediate in the cleavage[7b] reaction —may be stabilized by participation of the methoxyl on the aromatic ring to divert the normal pathway as depicted above. That this indeed is the case is substantiated by the fact that the reaction yields almost exclusively a lactone, when the lone pair of electrons on the aromatic methoxyl group are made unavailable for such participation (see below).

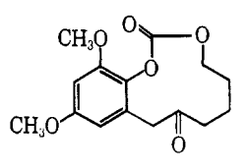
Treatment of the carbonate **8** with methanolic potassium carbonate and subsequent acidification led quantitatively to a transformation product, the mass spectrum of which exhibited a molecular ion peak at *m/e* 234. The infrared showed weak aromatic absorption at 1605 cm^{-1}, and the hydroxylic and ketonic bands were absent. The ultraviolet spectrum confirmed the presence of an isolated aromatic ring (288 mμ, ϵ 2850). The nmr spectrum of the compound revealed signals at δ 7.0–6.58 (3 H, aromatic, multiplet), 4.15–3.35 (5 H, methoxyl singlet at δ 3.76, and two protons, carbinolic multiplet), 3.3–2.35 (2 H, benzylic, poorly resolved triplet), and 2.3–1.15 (8 H, methylenic multiplet). The above analytical data concur with the empirical formula $C_{14}H_{18}O_3$, and permit the assignment of structure **11** to this product. Its formation from progenitor **8** may be rationalized as in Scheme II.

SCHEME II



A synthetic study leading to compounds of the type **1** and **2** must be adaptable to yield free phenols in view of their ubiquity in nature. An obvious detour was sought in the synthesis of the acetate **15** obtainable from methyl ether **6b**. Demethylation of methyl ether **6b** with 48% hydrobromic acid resulted in concomitant displacement of the terminal hydroxyl group by bromine to yield bromophenol **12**. Treatment of **12** with silver acetate in acetic acid followed by hydrolysis of acetate **13** generated diol **14**, in an over-all yield of 15% from ether **6b**. The yield of the diol **14** was highly ameliorated in the one-step reaction described below. The methyl ether **6b** when treated with potassium thiophenolate anion[8] in the presence of dry dimethyl sulfoxide at 120° (bath temperature) yielded the expected diol in excellent yield (85%). The diol was selectively





12, R = H; R′ = Br
13, R = H; R′ = $OCOCH_3$
14, R = H; R′ = OH
15, R = $COCH_3$; R′ = OH
20, R = $COCH_3$; R′ = $OCOCH_3$

16

acetylated[9] using 1.5 mol of acetic anhydride in a pyridine–acetic anhydride (50:1) mixture to yield the monoacetate **15**. Acid-catalyzed dehydration of acetate **15** led to the cyclic enol ether **7g**. The optimum yield of this reaction was 28%.

The diacetate **20** and diol **14** were detected in the crude reaction product. A possible explanation for the generation of diol **14** lies in the sensitivity of the phenolic acetate to the water produced in the reaction. The acetic acid thus generated may be instrumental in the production of diacetate by acetylating the starting alcohol.

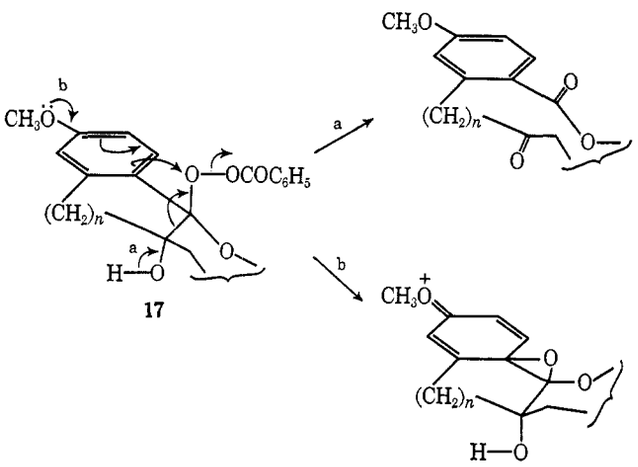
Reaction of enol ether **7g** with *m*-chloroperbenzoic acid yielded almost exclusively the lactone **9b**. This reaction coupled with the obtention of lactone as a sole product from the precursor **7a** clearly demonstrates that the presence of unshared electrons on methoxyl oxygen is essential for the stabilization (in formula **10**) *via* participation of the aromatic ring, to divert the reaction pathway from generating a lactone.

Employing the above sequence to benzocycloheptanone **4c** led to the synthesis of enol ether **7c**. The per acid oxidation of this enol ether, in contrast to that of **7b**, yielded lactone **9d**. Finally the enol ethers **7d** and **7e** were synthesized from ketones **4d** and **4e**. It was noted that these enol ethers were relatively unstable and slowly reverted to their progenitor under normal handling conditions. The reason for this unstability lies most likely in the strain exerted by the cyclopentadiene system generated in the enol ethers. The per acid oxidation of **7d** and **7e** proceeded in the normal manner to generate lactones **9e** and **9f**. Enol ether **7f** was obtained from ketone **6f** by treatment of the latter with *p*-toluenesulfonic acid in refluxing toluene–dimethylformamide (2:1). The per acid reaction with **7f** rather unexpectedly gave almost exclusively the carbonate **16**.

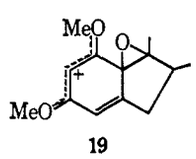
(8) G. Illuminati and H. Gilman, *J. Amer. Chem. Soc.*, **71**, 3349 (1949).
(9) O. V. Dominguez, J. R. Selly, and J. Gorki, *Anal. Chem.*, **35** (9), 1243 (1963).

It is noted that the products of oxidation of **7b**, **7c**, and **7d** varied from predominantly carbonate in the case of **7b** to mainly lactone with **7c**, and an intermediate mixture of lactone and carbonate with **7d**. These results strikingly indicate the critical spacial requirement of the per ester group in the transitional intermediate **17**,[10] for the preferential expulsion of benzoate *via* pathway b to generate the carbonate (*vide infra*) (Scheme III). Such stereochemistry is ideally offered by the tetrahydronaphthalene system produced from **7b**, in contrast to its higher (from **7c**) and lower (from **7d**) homologs.

SCHEME III



A second factor responsible for controlling the reaction course must involve the degree of stabilization resulting from the alkoxy substituents present in the *ortho* and/or *para* positions. Whereas **7d** reacts apparently by both pathways a and b to yield a mixture, in the case of **7f**, the conformational destabilization is balanced by the increased stabilization of the positive charge as shown in **19** by two methoxyl functions.



19

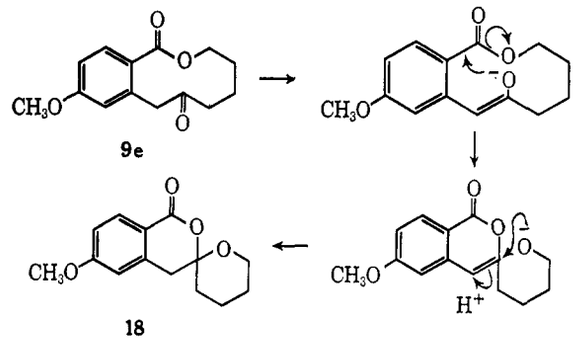
This is apparently sufficient to divert the reaction course *via* pathway b to produce carbonate **16**.

Treatment of lactone **9e** with sodium hydride in dry benzene led to a transannular reaction. The product **18** showed a molecular ion at *m/e* 248, which concurred with its elemental analysis to evolve the formula $C_{14}H_{16}O_4$. The ultraviolet spectrum (259 mμ, ε 15,600) was characteristic of a *p*-methoxybenzoic acid ester. The infrared and nmr spectra were in complete consonance with the structure assigned which follows from the mechanistic arguments outlined in Scheme IV.

This type of transannular reaction has been observed by Shoppee[1c] on alkaline treatment of radicicol derivatives.

(10) This postulate is further supported by the fact that no detectable amount of carbonate was formed from **7e**. In this case, the steric repulsion exerted by methoxyl in the *ortho* position clearly overbalances the electronic effect. However, the increased electronic stabilization as in **19** restores the generation of carbonate. Such competition between steric and electronic effect has also been observed by R. Huisgen [*Ber.*, **90**, 1946 (1957)] in the intensity variation of the ultraviolet spectra of 1,2-benzocycl-3-en-1-one.

SCHEME IV



18

Ultraviolet Spectra.—It is interesting to note that benzoic acid lactones when lactone is a part of a medium-size ring appear to follow the usual increment rule useful for simpler benzoic acid lactones.[11] Using 230 mμ as parent chromophore representing the electron-transfer (ET) band, the calculated and observed values of the ET bands are listed in Table I. An abnormality is noted in the unusually low intensity value of lactone **9f**. This marked[12] depression in intensity may be attributed to the increased loss of coplanarity.[13]

TABLE I

Compd	ET band		Benzenoid
	Calcd mμ	Obsd mμ (ε)	mμ (ε)
9a	233	233 (7,454)	279 (1,140)
9b	233	238 (9,280)	
9c	258	260 (14,250)	
9d	258	258 (17,400)	295 (3,247)
9e	258	260 (14,800)	
9f	240	239 (3,770)	292 (3,180)

Experimental Section[14a]

Ketones.—3,4-Dihydro-2H-naphthalen-1-one[14b] (**4a**) and **3,4-dihydro-6-methoxy-2H-naphthalen-1-one** (**4b**) used were those available commercially. **2,3,4,5-Tetrahydro-7-methoxy-1H-benzocyclohepten-1-one** (**4c**) was prepared as described,[15] mp 54.5–55.5. **5-Methoxyindan-1-one** (**4d**), mp 97–98° (lit.[16a] mp 102–103°), and **7-methoxyindan-1-one** (**4e**), mp 107–108° (lit.[16a] mp 109–110°), were prepared by ring closure of corresponding propionic acids as described for phenols.[16b] **5,7-Dimethoxyindan-1-one** (**4f**), mp 98–99° (lit.[16c] mp 98.5–99.5°), was prepared by hydrogen fluoride ring closure of the corresponding propionic acid.

Carbethoxylation of Ketones.—In a typical procedure, to a suspension of sodium hydride (10 g) washed free of oil in dry tetra-

(11) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press Ltd., Oxford, 1964, p 115.

(12) The value of the intensity of the *ortho*-substituted acids is usually about half that of their *para*-substituted counterparts [C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951)].

(13) E. A. Braude and E. S. Waight, *Progr. Stereochem.*, **1**, 144 (1954).

(14) (a) All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer with sodium chloride optics. Ultraviolet spectra were taken in ethanol with a Unicam Model SP 800. Nmr spectra were recorded on a Varian A-60A spectrometer. The mass spectra were recorded on Hitachi RMU-6D. Alumina (Woelm) and silica gel (Davison Grade 923, 100–200 mesh) were used for column chromatography. Silica gel G (according to Stahl, E. Merck Co., Germany) was used for thin layer chromatography. Petroleum ether refers to that fraction with bp 30–60°. Organic extracts were dried over magnesium sulfate and solvents were removed under vacuum. *t*-Butyl alcohol was dried by distilling over sodium, tetrahydrofuran was distilled over lithium aluminium hydride, and methylene chloride used for oxidation was distilled over potassium carbonate. (b) Nomenclature for all compounds was derived based on that described in "The Ring Index," American Chemical Society, Washington, D. C., 1960.

(15) W. J. Horton and L. L. Pitchforth, *J. Org. Chem.*, **25**, 131 (1960).

(16) (a) L. D. Louden and R. K. Razdan, *J. Chem. Soc.*, 4299 (1954); (b) W. S. Johnson, J. M. Anderson, and W. E. Shelborg, *J. Amer. Chem. Soc.*, **66**, 218 (1944); (c) R. Huisgen, G. Siedl, and I. Wimmer, *Ann. Chim.*, **677**, 21 (1964).

hydrofuran (100 ml) was added diethyl carbonate (26.8 g). The mixture was stirred and heated to reflux under an atmosphere of nitrogen. A solution of 6-methoxy-1-tetralone **4b** (20 g) in dry tetrahydrofuran (220 ml) was added dropwise. The refluxing was continued for 2 days. To the cooled reaction mixture glacial acetic acid (18 ml) was slowly added, and the reaction mixture taken in ether and washed several times with saturated sodium chloride solution. The solution was dried, the solvent removed, and the residue distilled (yield 79%): **3,4-dihydro-6-methoxy-2-carbethoxy-2H-naphthalen-1-one** (**5b**), bp 150–104° (0.3 mm) [*Anal.* Calcd for $C_{14}H_{16}O_4$ (248): C, 67.63; H, 6.50. Found: C, 67.85; H, 6.42]; **3,4-dihydro-2-carbethoxy-2H-naphthalen-1-one** (**5a**), bp 109° (0.2 mm), 85% [*Anal.* Calcd for $C_{13}H_{14}O_3$ (218): C, 73.02; H, 6.13. Found: C, 73.14; H, 6.40]; **2,3,4,5-tetrahydro-7-methoxy-2-carbethoxy-1H-benzocyclohepten-1-one** (**5c**), bp 154° (0.5 mm), 69% [*Anal.* Calcd for $C_{15}H_{18}O_4$ (262): C, 68.68; H, 6.92. Found: C, 69.23; H, 6.74]; **5-methoxy-2-carbethoxyindan-1-one** (**5d**), bp 153–156° (0.5 mm), 49% [*Anal.* Calcd for $C_{13}H_{14}O_4$ (222): C, 66.65; H, 6.02. Found: C, 66.71; H, 5.74]; **7-methoxy-2-carbethoxyindan-1-one** (**5e**), bp 156–158° (0.5 mm) (lit.[17] bp 165° (0.2 mm), 55%, on keeping the compound crystallized, mp 54–57°; **5,7-dimethoxy-2-carbethoxyindan-1-one** (**5f**), crystallized from acetone–hexane, mp 91–92°, 55% [*Anal.* Calcd for $C_{14}H_{16}O_5$ (264): C, 63.62; H, 6.10. Found: C, 63.36; H, 6.27].

Preparation of 4-Hydroxybutyl Ketones.—A characteristic procedure was as follows. Potassium (3.2 g) was dissolved in dry *t*-butyl alcohol (200 ml). Tetralone **5a** (8.16 g) dissolved in the same solvent (100 ml) was slowly added. The solution was refluxed in nitrogen atmosphere for 30 min, and cooled to room temperature. With stirring 4-bromobutyl 1-acetate[6] was added, and the mixture refluxed overnight. After cooling, glacial acetic acid (24 ml) was added, and most of the solvent was removed. The residue was taken in chloroform and washed several times with saturated salt solution and dried; the solvent was removed. The excess bromobutyl acetate was removed by distillation (at 0.3 mm). The residue was used directly for saponification. The product was dissolved in ethanol (30 ml), a solution of potassium hydroxide (6.8 g) in water (10 ml) was added, and the mixture was refluxed under nitrogen overnight. The mixture was cooled, diluted with ether, washed neutral with saturated sodium chloride solution, and dried, and the solvent removed to yield crude product (7.06 g). The material was filtered through neutral alumina (activity II) to yield **3,4-dihydro-2-(4-hydroxybutyl)-2H-naphthalen-1-one** (**6a**), homogenous by tlc: ν_{max} (neat) 3410 (broad, OH) 1675 (ketone), 1600 cm^{-1} (aromatic); nmr showed signals at δ 7.99 (1 H, *ortho*[18] aromatic proton, quartet), 7.65–6.92 (3 H, aromatic multiplet), 3.61 (2 H, carbionolic triplet poorly resolved), 3.14–2.8 (2 H, benzylic triplet).

3,4-Dihydro-2-(4-hydroxybutyl)-6-methoxy-2H-naphthalen-1-one (**6b**) was similarly prepared from **5b** in 96% yield and crystallized from ether–petroleum ether: mp 57–59°; ν_{max} (Nujol) 3475 (OH), 1656 (ketone), 1598 cm^{-1} (aromatic); nmr exhibited signals at δ 7.98 (1 H, J = 8 Hz, doublet *ortho*[18] aromatic proton), 7.05–6.54 (2 H, aromatic protons), 3.9–3.5 (5 H, two carbinolic and three methoxyl at 3.83), 3.1–2.75 (2 H, benzylic, triplet).

Anal. Calcd for $C_{15}H_{20}O_5$ (248): C, 72.53; H, 8.12. Found: C, 72.30; H, 7.85.

2,3,4,5-Tetrahydro-2-(4-hydroxybutyl)-7-methoxy-1H-benzocyclohepten-1-one (**6c**) was obtained in 43% yield from **5c**. Mass spectrum showed *m/e* 262 (M), *m/e* 244 (M − 18); ν_{max} (neat) 3430 (hydroxyl), 1670 (carbonyl), 1600 cm^{-1} (aromatic); nmr showed signals at δ 7.65 (1 H, *ortho*[18] aromatic), 3.61 (2 H, carbinolic).

5-Methoxy-2-(4-hydroxybutyl)indan-1-one (**6d**) was prepared from the corresponding precursor and crystallized from ether–petroleum ether: mp 51–52° (58%); ν_{max} (Nujol), 3400 (hydroxyl), 1705 (ketone), 1612, 1600 cm^{-1} (aromatic); nmr showed peaks at δ 7.6 (1 H, J = 9 Hz, *ortho*[18] aromatic proton), 6.95–6.66 (2 H, aromatic protons), 3.81 (3 H, methoxyl singlet), 3.61 (2 H, carbinolic).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 71.96; H, 7.67.

7-Methoxy-2-(4-hydroxybutyl)indan-1-one (**6e**) was crystallized from ether–petroleum ether: mp 71–72° (30%); ν_{max} (Nujol) 3500 (hydroxyl), 1700 (ketone), 1600 cm^{-1} (aromatic); nmr, δ 7.7–6.5 (3 H, aromatic, multiplet), 3.86 (methoxyl, singlet), 3.6 (2 H, carbinolic).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 71.81; H, 7.45.

5,7-Dimethoxy-2-(4-hydroxybutyl)indan-1-one (**6f**) was obtained from **5f** in 50% yield. Crystallization from acetone–hexane gave a solid: mp 86–87°; ν_{max} (Nujol) 3490 (hydroxyl), 1675 (ketone), 1600 cm^{-1} (aromatic); nmr showed signals at δ 6.52–6.20 (2 H, aromatic), 3.88 and 3.86 (6 H, two methoxyl, singlets), 3.77–3.47 (2 H, carbinolic multiplet).

Anal. Calcd for $C_{15}H_{20}O_4$ (264): C, 68.15; H, 7.63. Found: C, 68.10; H, 7.48.

Preparation of Enol Ethers.—Enol ethers were generally prepared by refluxing for 20 hr a solution of corresponding 4-hydroxybutyl ketones in dry benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, and continuous removal of water with a Dean–Stark water separator. The work-up was effected by passing the reaction mixture through a 20-fold amount of alumina (neutral, activity II) and eluting the product with benzene–petroleum ether (1:1). In case of **6f** the solvent had to be changed to toluene–dimethylformamide (2:1). In most cases enol ethers were purified by distillation and/or purity checked by thin layer plates, and the structure was confirmed by disappearance of hydroxyl and ketonic absorption and the presence of an enolic double bond in the infrared. These were immediately utilized for the oxidation. Their physical constants are recorded in Table II.

TABLE II

Compd	Criteria of purity, bp (mm) or mp, °C	Enolic band, cm^{-1}	Yield, %
7a	98 (0.2)	1650	72
7b	134 (0.3)	1650	71
7c	141–143 (0.3)	1640	74
7d	52°	1580, 1575	31
7e	Homogenous by tlc	1625, 1600	41
7f	Homogenous by tlc	1625, 1605	21

Per Acid Oxidation.—A typical oxidation procedure for the above enol ethers was as follows. The *m*-chloroperbenzoic acid (8.1 g) was suspended in methylene chloride (freshly distilled over potassium carbonate, 25 ml). A solution of enol ether (**7a**, 2.69 g) in methylene chloride (12 ml) was added dropwise with stirring. An exothermic reaction ensued. The mixture was kept at boiling point during addition. It was then stirred at room temperature overnight and filtered, and the residue washed with methylene chloride. The organic layer was washed with 7% potassium carbonate, followed by saturated salt solution, and dried, and solvent was removed. The residue was passed through a 20-fold amount of alumina (neutral, activity II) in benzene–petroleum ether (1:1). The eluate was homogenous by the tlc and yielded **3,4,5,6,8,9-hexahydro-2-benzoxacycloundecane-1,7-dione** (**9a**): bp 138–144° (0.2 mm); ν_{max} (neat) 1710 (broad carbonyl), 1600 cm^{-1} (aromatic); nmr, δ 8.03 (1 H, *ortho*[18] aromatic proton), 7.56–7.1 (3 H, aromatic proton), 4.38 (2 H, carbinolic, multiplet), 3.5–3.16 (2 H, benzylic, multiplet), 2.83–2.5 (4 H, α-ketomethylenes).

Anal. Calcd for $C_{14}H_{16}O_3$ (232): C, 72.39; H, 6.94. Found: C, 72.14; H, 6.82.

4,5,6,7,9,10-Hexahydro-12-methoxy-1,3-benzodioxacyclododecane-2,8-dione (**8**) was crystallized from methylene chloride–ether–petroleum ether to yield crystals: mp 90–91° (50%); ν_{max} (Nujol) 1755 (carbonate), 1700 (ketone), 1605 cm^{-1} (aromatic); nmr, δ 7.2–6.6 (3 H, aromatic), 4.3 (2 H, carbinolic, multiplet), 3.85 (methoxyl singlet), 3.2–2.2 (6 H, 2 benzylic, 4 α-ketomethylenic).

Anal. Calcd for $C_{15}H_{18}O_5$ (278): C, 64.73; H, 6.52. Found: C, 64.36; H, 6.35.

3,4,5,6,9,10-Hexahydro-12-methoxy-8H-2-benzoxacyclododecane-1,7-dione (**9d**) was crystallized from acetone–hexane: mp 92–93° (40%); ν_{max} (Nujol) 1700, 1675 (carbonyl), 1600 cm^{-1} (aromatic); nmr, δ 7.88 (1 H, *ortho*[18] aromatic proton), 6.87–6.62 (2 H, aromatic, multiplet), 4.4–4.17 (2 H, carbinolic, multiplet), 3.81 (3 H, methoxyl, singlet), 2.85 (2 H, benzylic, triplet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.54; H, 7.30. Found: C, 69.80; H, 7.35.

3,4,5,6-Tetrahydro-10-methoxy-8H-2-benzoxecin-1,7-dione (**9e**) was crystallized from acetone–hexane: mp 97–98° (58%);

(17) Z. Horii and T. Tanaka, *Chem. Ind.* (London), 1576 (1959).

(18) "*ortho* proton" refers to the proton *ortho* to the carbonyl substituent.

ν_{max} (Nujol) 1710, 1700 (carbonyls), 1605 cm^{-1} (aromatic); nmr, δ 8.06 (1 H, doublet, J = 7 Hz, *ortho*[18] aromatic proton), 6.95–6.57 (2 H, aromatic multiplet), 4.19 (2 H, carbinolic, multiplet), 3.93 (2 H, benzylic, singlet), 3.83 (3 H, methoxyl, singlet), 2.56 (2 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.94; H, 6.46.

3,4,5,6-Tetrahydro-12-methoxy-8H-2-benzoxecin-1,7-dione (**9f**) was crystallized from acetone–hexane: mp 123–124° (61%); ν_{max} (Nujol), 1725, 1700 (carbonyls), 1600, 1575 cm^{-1} (aromatic); nmr, δ 7.44–6.35 (3 H, aromatic), 4.4–4.1 (2 H, carbinolic poorly resolved triplets), 3.75 (3 H, methoxyl, singlet), 3.65 (2 H, benzylic, singlet), 2.6–2.25 (2 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.92; H, 6.49.

4,5,6,7-Tetrahydro-11,13-dimethoxy-9H-1,3-benzodioxacycloundecane-2,8-dione (**16**) was crystallized from acetone–hexane: mp 148–149° (54%); ν_{max} (Nujol) 1765 (carbonate), 1700 (ketone), 1610, 1600 cm^{-1} (aromatic); nmr, δ 6.48 (2 H, aromatic, multiplet), 4.3 (2 H, carbinolic, triplet), 3.85 (6 H, methoxyls), 3.60 (2 H, benzylic, singlet), 2.45 (2 H, α-ketomethylenic multiplet).

Anal. Calcd for $C_{15}H_{18}O_6$ (294): C, 61.21; H, 6.17. Found: C, 61.31; H, 6.36.

3,4-Dihydro-2-(4-bromobutyl)-6-methoxy-2H-naphthalen-1-one (**12**).—Methoxy ketone **6b** (15 g) was dissolved in 48% hydrobromic acid (300 ml) and the mixture was refluxed for 5 hr. The reaction mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with water and dried, and the solvent was removed. Residue crystallized from chloroform–hexane to give 11 g of **12**, mp 102–106°. An analytical sample from the same solvent mixture had mp 111–112°; $\nu_{max}^{CHCl_3}$ 3600, 3270 (hydroxyl), 1670 (ketone), 1600 cm^{-1} (aromatic); ultraviolet, 275 mμ (ϵ 15,300) neutral, 328 (29,000) alkaline; nmr δ 7.88 (1 H, *ortho*[15] aromatic proton, doublet, J = 7 Hz), 6.78 (2 H, aromatic), 3.39 (2 H, protons of C–Br carbon, triplet), 2.92 (2 H, benzylic, triplet).

Anal. Calcd for $C_{14}H_{17}O_2Br$ (297): C, 56.60; H, 5.72. Found: C, 56.83; H, 5.89.

3,4-Dihydro-2-(4-acetoxybutyl)-6-hydroxy-2H-naphthalen-1-one (**13**).—Bromo compound **12** (6 g) was dissolved in dry benzene, silver acetate (4.5 g) was added, and the mixture was refluxed with stirring for 6 hr. Another 4.5 g of silver acetate was added and refluxing continued for 16 hr. The mixture was cooled and filtered. The residue was washed with benzene and the solvent was removed. Residue was put on column of silica gel (180 g) in benzene. Elution with 10–20% ether–benzene yielded 1.7 g of solid, homogenous on tlc. An analytical sample from chloroform–hexane had mp 97–98°; $\nu_{max}^{CHCl_3}$ 3525, 3240 (nonbonded and bonded OH), 1720, 1660 (acetate and ketone), 1600 cm^{-1} (aromatic); ultraviolet, 275 mμ (ϵ 14,122); nmr, δ 7.88 (1 H, *ortho*[18] aromatic proton), 6.72 (2 H, aromatic protons), 4.03 (2 H, carbinolic, triplet), 2.88 (2 H, benzylic, triplet), 2.01 (acetate methyl singlet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.70; H, 7.25. Found: C, 70.01; H, 7.03.

3,4-Dihydro-2-(4-hydroxybutyl)-6-hydroxy-2H-naphthalen-1-one (**14**). **A. Hydrolysis of Acetate 13.**—To a solution of acetate **13** (2 g) in methanol (50 ml) was added a solution of potassium hydroxide (1.34 g) in water (20 ml). The solution was stirred at room temperature for 30 min. The mixture was concentrated to remove most of the methanol. The residue was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The usual work-up gave 1.6 g of solid. One crystallization from methanol–ether gave crystals: mp 171–172°; ν_{max} (Nujol) 3440 (hydroxyl), 1652 (ketone), 1605, 1575 cm^{-1} (aromatic); ultraviolet spectrum had maxima at 275 mμ (ϵ 15,000).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 72.14; H, 7.56.

B. Demethylation of Ketone 6b.—To a solution of thiophenol (21.15 g) in dry dimethyl sulfoxide under nitrogen was added potassium *t*-butoxide (24.6 g). The mixture was stirred until the solution was complete. To this solution was added a solution of methyl ether **6b** (7.2 g) in dimethyl sulfoxide (35 ml). The reaction mixture was heated to 120° and kept at that temperature for 7.5 hr. It was then cooled and poured into water (400 ml) containing acetic acid (4.4 ml). The liberated semisolid was extracted with ethyl acetate, washed with water, and dried; the solvent was removed. The residue when suspended in ice cold ether and filtered gave diol **14**: yield 4.56 g; mp 171–174°. The filtrate was separated into acid and the neutral fractions. The former gave 1.2 g more of diol **14** of the same purity as above. This was identical in all respects with the product obtained from hydrolysis of acetate described earlier.

3,4-Dihydro-2-(4-hydroxybutyl)-6-acetoxy-2H-naphthalen-1-one (**15**).—To a solution of diol **14** (4.5 g) in dry pyridine (73.5 ml) was added a mixture of pyridine–acetic anhydride (25:1, 73.5 ml) and the solution stirred for 40 min. The reaction was quenched by adding water (20 ml) and most of the solvent was removed. The residue was stirred with 10 ml of 10% hydrochloric acid for 5 min. The organic material was extracted with ether, washed with water, and dried, and the solvent evaporated. The residue was chromatographed on silica gel (125 g) in benzene. Eluate with 10–20% ether–benzene was pooled to yield monoacetate **15** (3.5 g) homogenous by tlc. An analytical sample crystallized from ether–hexane had mp 56–58°; $\nu_{max}^{CHCl_3}$ 3610, 3470 (hydroxyl nonbonded and bonded), 1755 (phenolic acetate), 1670 (ketone), 1600 cm^{-1} (aromatic); ultraviolet maxima at 252 mμ (ϵ 13,900); nmr, δ 7.98 (1 H *ortho*[18] aromatic proton), 6.88 (2 H, aromatic, protons), 3.62 (2 H, carbinolic, triplet), 2.95 (2 H, benzylic, triplet), 2.27 (3 H, acetate methyl, singlet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.70; H, 7.25. Found: C, 70.00; H, 7.14.

2,3,4,5,6,7-Hexahydro-9-acetoxynaphth[1,2-*b*]oxepin[14b] (**7g**).—A solution of monoacetate **15** (3 g) in dry benzene was refluxed to distill off some benzene. To this solution *p*-toluenesulfonic acid (0.15 g) was added. The solution was refluxed for 2 hr with a continuous water separator. The solution was cooled and diluted with petroleum ether and filtered through alumina (neutral, activity II, 50 g). The first 650 ml yielded in the eluate 1.3 g of enol ether **7g**: homogenous by tlc; $\nu_{max}^{CHCl_3}$ 1760 (phenolic acetate), 1655 cm^{-1} (enolic double bond); nmr, δ 7.2 (1 H, doublet, *ortho* proton), 6.65 (3 H, aromatic), 3.87 (2 H, carbinolic, triplet), 2.1 (3 H, acetyl methyl, singlet).

3,4,5,6,8,9-Hexahydro-11-acetoxy-2-benzoxacycoundecane-1,7-dione (**9b**).—To a suspension of *m*-chloroperbenzoic acid (2.7 g) in methylene chloride[13] (4 ml) was added dropwise a solution of enol ether **7g** (1.1 g) in methylene chloride (3.5 ml). An exothermic reaction ensued, and the mixture was kept at boiling point. The mixture was stirred for 2 hr at room temperature. The methylene chloride was removed and the residue was suspended in dry benzene and filtered. The precipitate was washed with benzene and the filtrate passed through a column of alumina (neutral, activity II, 40 g) in benzene. The first 200 ml of eluate yielded 1 g of crystalline solid. Crystallization from chloroform–hexane gave 0.6 g, mp 96–108°. An analytical sample had mp 109–110°; $\nu_{max}^{CHCl_3}$ 1760 (phenolic acetate), 1710 (ketone and lactone), 1605 cm^{-1} (aromatic); ultraviolet showed maxima at 238.5 mμ (ϵ 9280); nmr, δ 8.1 (1 H, *ortho*[18] proton, doublet, J = 7 Hz), 7.07 (2 H, aromatic), 4.33 (2 H, carbinolic, multiplet), 3.28 (2 H, benzylic, multiplet), 2.62 (4 H, α-ketomethylenic), 2.28 (3 H, acetyl methyl).

Anal. Calcd for $C_{16}H_{18}O_5$ (290): C, 66.20; H, 6.25. Found: C, 66.09; H, 6.21.

3,4,5,6,8,9-Hexahydro-11-hydroxy-2-benzoxacycloundecane-1,7-dione (**9c**).—To a solution of acetate **9b** (0.87 g) in methanol (6 ml) was added a solution of sodium carbonate (0.318 g) in water (3 ml). The mixture was stirred at room temperature for 10 min, then diluted with ether and washed with water. The aqueous layer was acidified with 3% hydrochloric acid (5 ml). The resulting mixture was extracted with ether, washed with water, and dried; the solvent was removed. Residue (0.65 g) crystallized from chloroform–hexane to yield 0.34 g solid, mp 145–150°. An analytical sample had mp 154–155°; $\nu_{max}^{CHCl_3}$ 3570, 3200 (nonbonded and bonded hydroxyl), 1692 cm^{-1} (carbonyl); ultraviolet, 260 mμ (ϵ 14,250) neutral, 300 (25,200) alkaline; nmr, δ 7.91 and 6.59 (3 H, aromatic), 4.33 (2 H, carbinolic), 3.2 (2 H, benzylic), 2.63 (4 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.79; H, 6.55.

3,4,3′,4′,5′,6′-Hexahydro-6-methoxyspiro[2H-1-benzopyran-2,2′(2H)-pyran] (**11**).—Carbonate **8** (0.3 g) was dissolved in methanol (10 ml), saturated with potassium carbonate, and left for 2 days at room temperature. The mixture was then diluted with ether and extracted with 2 *N* potassium carbonate (10 ml). The aqueous extract was cooled in ice and acidified with 10% sulfuric acid. The mixture was extracted with ether, washed with water, and dried; the solvent was evaporated. The residue (0.24 g) was put through alumina (neutral, activity II, 7.2 g) and

eluted with petroleum ether–benzene 4:1 (75%). The residue was distilled at 0.2-mm pressure. The distillate showed a single spot on tlc and a single peak in glpc (15% S.E. 30, 80–100 mesh, 248°, R_T 6.45 min). Mass spectrum showed a *m/e* 234 (M); ν (neat) 1605 cm^{-1} (aromatic); ultraviolet maxima at 288 mμ (ϵ 2850); nmr, δ 6.68 (3 H, aromatic, multiplet), 3.75 (5 H, methoxy and carbinolic), 3.3–2.58 (2 H, benzylic, multiplet).

1,4,3′,4′,5′,6′-Hexahydro-6-methoxyspiro[3H-2-benzopyran-3,2′(2H)-pyran]-1-one (18).—Sodium hydride (0.4-g oil suspension) was washed with hexane and suspended in tetrahydrofuran (15 ml). A solution of lactone **9e** (0.2 g) in dry tetrahydrofuran (5 ml) was added to the boiling suspension of sodium hydride. The mixture was refluxed overnight and cooled, acetic acid (1 ml) was added, and the mixture was diluted with ether, washed with water, and dried. Residue (0.5 g) was passed through alumina (neutral activity II, 4.5 g). Elution with petroleum ether–benzene gave crystals (0.118 g). Acetone–hexane gave crystals: mp 150–151°; ν_{max} (Nujol) 1700 (carbonyl), 1600, 1575 cm^{-1} (aromatic); ultraviolet, 259 mμ (ϵ 15,600); nmr, δ 7.99 (1 H, aromatic *ortho* to carbonyl, doublet, J = 8 Hz), 6.80 (2 H, aromatic), 3.81 (5 H, methoxyl, singlet and carbinolic), 3.05 (2 H, benzylic, doublet).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.5. Found: C, 67.79; H, 6.33.

Registry No.—**5a,** 6742-26-3; **5b,** 16425-80-2; **5c,** 16425-81-3; **5d,** 16425-82-4; **5e,** 16452-35-0; **5f,** 16425-83-5; **6a,** 16425-84-6; **6b,** 16425-85-7; **6c,** 16425-86-8; **6d,** 16425-87-9; **6e,** 16425-88-0; **6f,** 16425-89-1; **6g,** 16425-62-0; **7a,** 16425-91-5; **7b,** 16425-92-6; **7c,** 16425-93-7; **7d,** 16425-94-8; **7e,** 16425-95-9; **7f,** 16425-96-0; **7g,** 16425-65-3; **8,** 16425-53-9; **9a,** 16425-54-0; **9b,** 16425-55-1; **9c,** 16425-56-2; **9d,** 16425-66-4; **9e,** 16425-57-3; **9f,** 16452-36-1; **11,** 16425-58-4; **12,** 16425-59-5; **13,** 16425-60-8; **14,** 16425-61-9; **15,** 16425-62-0; **16,** 16425-63-1; **18,** 16425-64-2.

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Terpene–Formaldehyde Reactions. III. Camphene[1]

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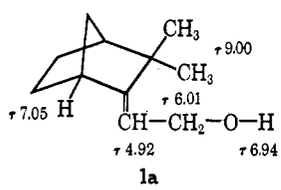
Boron trifluoride dihydrate catalysis of the camphene–formaldehyde reaction in solvent methylene chloride–acetic anhydride affords 8-hydroxymethyltricyclene acetate as the principal product (*ca.* 55%). The corresponding tricyclo alcohol is the main product when the reaction is carried out in solvent methylene chloride with stannic chloride as catalyst. In contrast to the foregoing, reaction of camphene with formaldehyde in solvent acetic acid, either in the absence of added catalyst or with added phosphoric acid, gives unrearranged 8-hydroxymethylcamphene acetate as the principal product together with smaller amounts of the parent alcohol and its formate. Depending upon conditions, the latter reactions afford yields of product that vary from *ca.* 47 to 94%.

As part of a general program concerned with the obtainment of primary alcohols from certain of the more readily available terpenes, it was of interest to make a thorough study of the camphene–formaldehyde reaction. Appropriate derivatives of primary alcohols derived from camphene, such as acrylic and methacrylic esters, could afford interesting and useful homo- and copolymers.

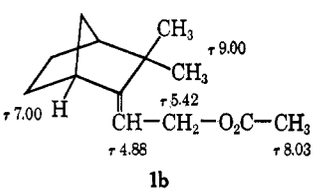
Earlier studies of the camphene–formaldehyde reaction have been limited to those carried out under simple thermal "noncatalyzed" conditions and those catalyzed by mineral acids;[3–8] there are no early reports on reactions effected in the presence of Lewis acid catalysts, conditions that afforded rather interesting results in the limonene–formaldehyde condensation.[1b]

This report supplements the preliminary account of observations made on the Lewis acid catalyzed camphene–formaldehyde reaction[1a] and also presents briefly pertinent results obtained in reexamination of the title reaction effected under thermal and mineral acid catalyzed conditions. The isolation, purification, analysis, and characterization of products formed in all reactions studied involved extensive use of the technique of glpc together with the methods of ir and nmr spectroscopy.

The thermal camphene–formaldehyde reaction is best done under atmospheric pressure in glacial acetic acid at reflux temperature (*ca.* 120°) as described by Langlois.[4] Under these conditions reaction for 2 days of a 2:1 mol ratio of camphene to formaldehyde gives a 94% yield of a 1:1 reaction product that comprises *ca.* 80% 8-hydroxymethylcamphene acetate (**1b**); the remainder consists mainly of 8-hydroxymethylcamphene (**1a**) and its formate. The pure alcohol **1a** is



1a



1b

readily obtained, *via* preparative glpc, from the acetate **1b** by (a) lithium aluminum hydride reduction, (b) methanolysis, or (c) alkaline hydrolysis. Nmr and ir spectral data together with chemical properties support the structural assignments (see Experimental Section). Use of camphene that contains 20–25% tricyclene[8] affords an 84% yield of the 1:1 reaction product whose principal component (*ca.* 85%) is the acetate **1b**. A reduced yield of the 1:1 reaction product (*ca.* 47 *vs.*

(1) For two closely related reports from this laboratory on terpene–formaldehyde reactions, see (a) A. T. Blomquist and R. J. Himics, *Tetrahedron Lett.*, 3947 (1967); (b) A. T. Blomquist and R. J. Himics, *J. Org. Chem.*, **33**, 1156 (1968).

(2) Abstracted from portions of the dissertations presented by R. J. Himics and J. D. Meador to the Graduate School of Cornell University for the Ph.D. degree, Feb 1967.

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