Preparation of *cis*- and *trans*-2,3-Dimethyl-2,3-dihydrobenzofurans and Related Compounds. Cyclizations Involving Oxonium Ions[1]

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Crotyl 2,4-dichloro-5-methylphenyl ether (A) gave a mixture of the expected product, 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol (B-2), and 2,4-dichloro-3-methyl-6-(α-methylallyl)phenol (C-2) when refluxed in dimethylaniline. Compound B-2 was converted to 2-methyl-6-oxo-1-cyclohexene(2-propionic acid) (H) by methylation, oxidation with permanganate–periodate, reduction with lithium–liquid ammonia, and acid hydrolysis. The phenol B-2 and its methyl ether were cyclized by concentrated sulfuric acid to *cis*- and *trans*-2,3-dihydro-2,3,4-trimethyl-5,7-dichlorobenzofurans (J and I); these were separated, configurations were assigned, and the equilibration of the *cis* and *trans* forms studied. Treatment of B-2 and its methyl ether with ICl gave the *cis*- and *trans*-iodomethyl compounds, M and L, whose configurations have been related to those of the dimethyl compounds J and I. J_{2H-3H} for the *cis*- and *trans*-2,3-dihydrobenzofurans have been measured and compared with calculated values.

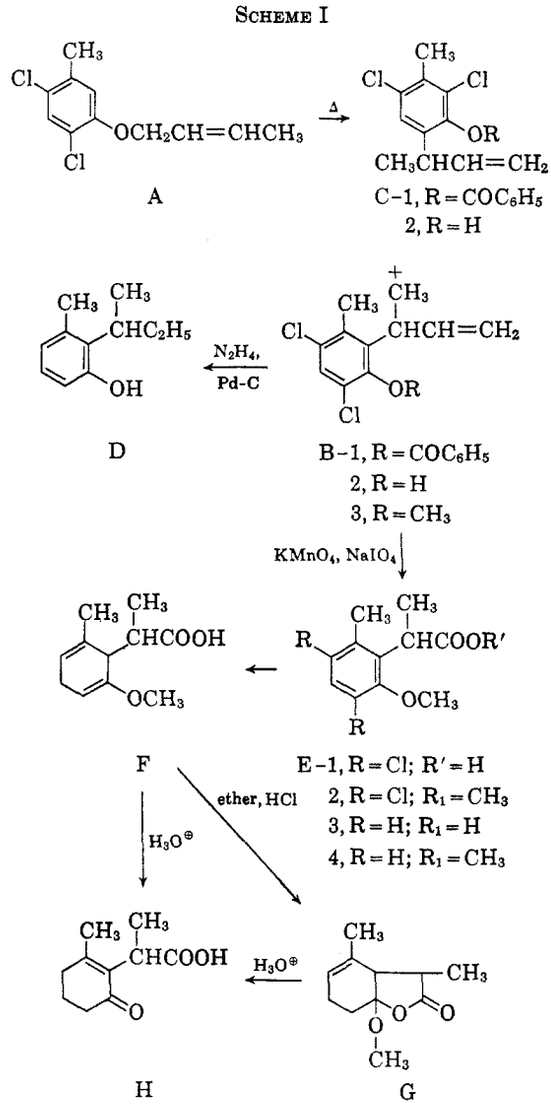
Previous papers[2,3] have documented sufficiently the interest in this laboratory in syntheses in the fumagillin series.[4,5]

The present paper describes the synthesis of 6-methyl-2-oxo-1-cyclohexene-(2-propionic acid) (H), the cyclization of 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol (B-2) and its methyl ether (B-3) to the corresponding *cis*- and *trans*-2,3-dimethyl-2,3-dihydrobenzofurans (J and I), along with some studies on the mechanism of the cyclization, and the acid-catalyzed equilibration of the *cis* and *trans* isomers. The *cis*- and *trans*-2-iodomethyl-3-methyl-2,3-dihydrobenzofurans J and I have been prepared, and their configurations established. Spectroscopic data, particularly nmr spectra of the isomeric 2,3-dimethyl-2,3-dihydrobenzofurans, and the infrared hydroxyl absorption of a series of *o*-chlorophenols are presented.

Synthesis of 2-Methyl-6-oxo-1-cyclohexene-(2-propionic acid) (H).—Crotyl 2,4-dichloro-5-methylphenyl ether (A) (Scheme I), mp 36.5–37°, was rearranged in refluxing dimethylaniline to give a mixture of two isomeric phenols, in a 4:1 ratio. Isomer B, the major product, was separated by preparing the benzoates of the mixture; the benzoate B-1 was obtained from the mixture in 73% yield. The evidence for structure B, assigned to the major product of the Claisen rearrangement, is as follows.

Hydrolysis of the crystalline benzoate gave the free phenol B-2, whose infrared absorption showed that the hydroxyl was adjacent to chlorine (see below). The nmr spectrum showed, among others, one aromatic proton at δ 7.20 (singlet), one vinyl proton as a multiplet centered at δ 6.14, two vinyl protons centered at δ 5.00, and a three-proton singlet (aromatic methyl) at δ 2.33. Treatment of the phenol B-2 with hydrazine and palladium–carbon[4,6,7] gave 2-(2-butyl)-3-methylphenol (D); this phenol showed infrared bands, which are considered characteristic of a 1,2,3-trisubstituted benzene.[8] The nmr spectrum of the phenol

SCHEME I



D showed three aromatic protons with a splitting pattern consistent with, although not conclusive for, their vicinal arrangement. A conclusive chemical proof for the structure of B was obtained by its conversion to an iodomethyl-2,3-dihydrobenzofuran (L), from which was obtained by base 2,3,4-trimethyl-5,7-

(1) Aided by Grant AI-01138 from the National Institutes of Health.

(2) S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, **28**, 928 (1963).

(3) D. P. Brust and D. S. Tarbell, *ibid.*, **31**, 1251 (1966).

(4) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961).

(5) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962).

(6) W. L. Mosby, *Chem. Ind.* (London), 1348 (1959).

(7) D. S. Tarbell and S. S. Stradling, *J. Org. Chem.*, **27**, 2724 (1962). In more recent work, difficulty has been experienced in repeating this type of dechlorination; presumably this is due to variation in the catalyst.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co. Ltd., London, 1960, p 78.

dichlorobenzofuran (K); the latter was synthesized by an unambiguous method (see below).

The infrared evidence for structure C for the minor product of the Claisen rearrangement is given below.

The methyl ether B-3 of the phenol was oxidized with permanganate–periodate[9] to the acid E-1, whose structure was apparent from its analysis and nmr spectrum. Dechlorination of the acid was finally achieved by adding Raney alloy to the acid in sodium hydroxide solution,[10] which gave the chlorine-free acid E-3 in 93% yield.

Attempts to prepare the phenolic acid corresponding to E-1 directly by carbon alkylation of sodium 2,4-dichloro-5-methylphenoxide with ethyl α-bromopropionate[11] were unsuccessful; only oxygen-alkylated product was obtained.

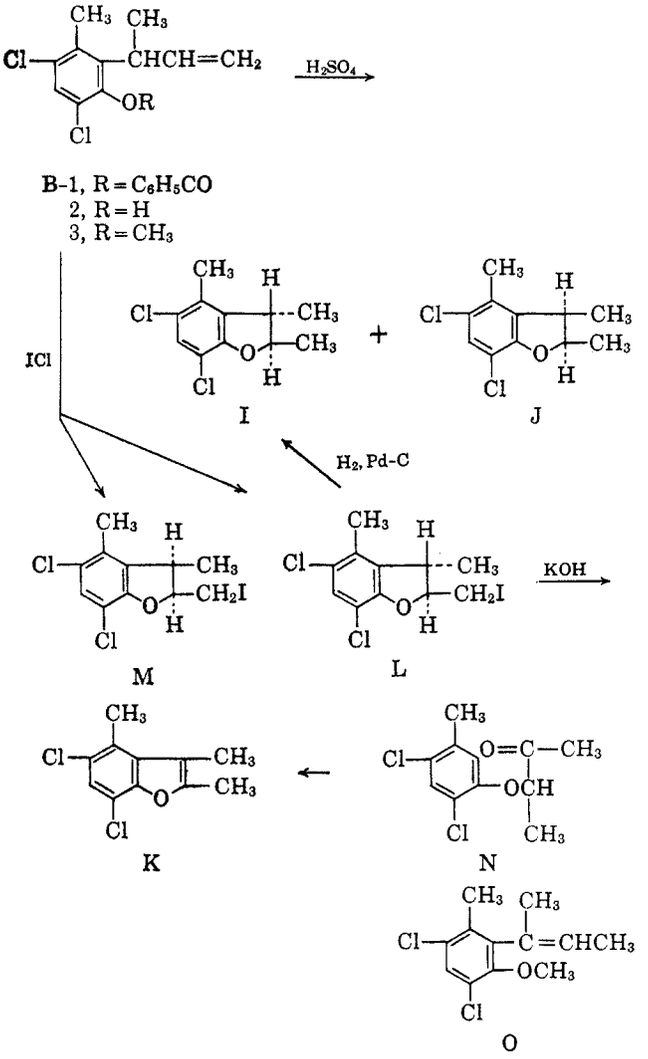
Reduction of the ether acid E-3 with lithium, liquid ammonia, *t*-butyl alcohol, and ether,[3,12] followed by hydrolysis in 10% aqueous hydrochloric acid, gave the acid H; its structure was apparent from its analysis, infrared spectrum, and its ultraviolet absorption, which agreed with the calculated[13] λ_{max} for structure H. The nmr spectrum also supported structure H; the over-all yield of H from the aromatic compound E-3 was *ca.* 50%.

Hydrolysis of the crude reduction product at room temperature in ether containing a small amount of aqueous hydrochloric acid gave a 29% yield (based on E-3) of the tetrahydrobenzofuranone G; the structure was based on analysis, on the infrared spectrum, with a strong band at 1783 cm^{-1} (γ-lactone[14]), and on the nmr spectrum. Hydrolysis of G in 10% hydrochloric acid gave a 74% yield of the unsaturated keto acid H, thus confirming the structure assigned on the basis of spectral evidence. The formation of G apparently proceeded by protonation of the enol ether double bond of the dihydrobenzene F to give a carbonium ion, which was in turn attacked by the carboxyl group.[14]

cis- and *trans*-2,3-Dimethyl-2,3-dihydrobenzofurans by Cyclization. Equilibration and Proof of Configuration.[15]—As part of the structure proof for 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol (B-2), its cyclization in sulfuric acid was investigated. *o*-Allylphenols have long been known to be cyclized by acids to dihydrobenzofurans or chromans.[16,17] Cyclization of B-2 occurred readily in 98% sulfuric acid at room temperature to give a good yield of the diastereoisomeric dihydrobenzofurans, *trans*- and *cis*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I and J) (Scheme II).

The products I and J were isolated by preparative vpc, the *trans* isomer being eluted first. Their infrared

SCHEME II



spectra showed the absence of the bands due to hydroxyl and RCH=CH_2 shown by the starting material. The nmr spectra of these compounds[15] clearly established their structures; a chroman structure was eliminated by the fact that both I and J showed two methyl doublets. Further structure proof was obtained from a relationship established between I and 5,7-dichloro-2,3,4-trimethylbenzofuran (see below).

Time–composition studies (Table I) indicated that the *cis* and *trans* compounds were equilibrated by concentrated sulfuric acid, the equilibrium mixture containing at room temperature one form preponderating by *ca.* 4:1. The predominant isomer was assigned the *trans* configuration, on the grounds that the *trans*, with less interaction between the 2-methyl and the 3-methyl, should be the thermodynamically more stable. This assignment was supported by the determination of the coupling constants $J_{2H\text{-}3H}$ for the two stereoisomers. The observed values[15] were 4.2 cps for the isomer predominating at equilibrium, and 7.4 for the other. The coupling constants were calculated from the Karplus equation,[18] using the dihedral angle φ found to be optimum from an examination of models. The calculated $J_{2H\text{-}3H}$ for the *trans* isomer ($\phi = 120 \pm 5°$) was 2.3 ± 0.7 cps and for the *cis* ($\phi = 25 \pm 5°$), 6.7 ± 0.6 cps. The configurations assigned from the

(9) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).
(10) E. Schwenk, D. Papa, B. Whitman and H. Ginsberg, *J. Org. Chem.*, **9**, 1 (1944).
(11) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959); D. Y. Curtin and D. H. Dybvig, *ibid.*, **84**, 225 (1962).
(12) H. L. Dryden, Jr., *et al.*, *J. Org. Chem.*, **26**, 3237 (1961); *cf.* A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).
(13) R. B. Woodward, *ibid.*, **63**, 1123 (1941); the calculated value for the isomeric Δ^4 acid is 226 mμ.
(14) T. H. Fife [*ibid.*, **87**, 271 (1965)] reported that γ-ethoxy-γ-butyrolactone shows an intense band at 1790 cm^{-1}.
(15) Preliminary publication: D. P. Brust, D. S. Tarbell, and S. M. Hecht, *Proc. Natl. Acad. Sci. U. S.*, **53**, 233 (1965).
(16) R. C. Elderfield and V. B. Meyer, "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., John Wiley and Sons, Inc., 1951, p 1 ff.
(17) S. Wawzonek, ref 16, p 393 ff.
(18) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

TABLE I

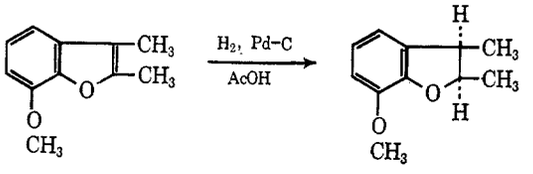
THE RATIO OF THE *trans-cis*-2,3-DIMETHYL-2,3-DIHYDROBENZOFURANS (I/J) BY CYCLIZATION OF THE PHENOL (B-2) AND ITS METHYL ETHER IN CONCENTRATED SULFURIC ACID AT ROOM TEMPERATURE[a]

	—*trans/cis* ratio[b]—		—Yield (J + I), %—	
Time, min	B-2	B-3	B-2	B-3
1	0.33	6.4	84[c,d]	49[c,e]
7	1.2	4.1	78[c]	42[c]
15	3.0	4.1	55[c]	68[c]
40	3.6	3.9	51[c]	61[c,f]

[a] The reactions were carried out on 2.00×10^{-3} mole of substrate in 8.7 ml of 98% sulfuric acid. [b] *trans/cis* ratio, *i.e.*, I/J, was determined by vpc analysis on the product mixture before distillation. [c] Based on weight of isolated product and vpc analysis. [d] The usual work-up involved extraction with Claisen's alkali. Omission of this gave a product mixture shown by infrared and vpc analysis to contain no phenolic material. [e] The remainder of the isolated product mixture consisted of 2% starting material and 29% of two conjugated isomers of the starting material. [f] The conjugated isomers of the starting material were no longer present in product mixture.

coupling constants thus agree with those made from the composition of the equilibrium mixture.[19]

Further support for the configuration assignment to I and J was obtained from the coupling constant, $J_{2H\text{-}3H}$ = 8.3 cps, shown by *cis*-2,3-dimethyl-2,3-dihydro-7-methoxybenzofuran; this compound was assigned the *cis* configuration because it was obtained by reduction with hydrogen and palladium–carbon in acetic acid of the aromatic heterocycle.



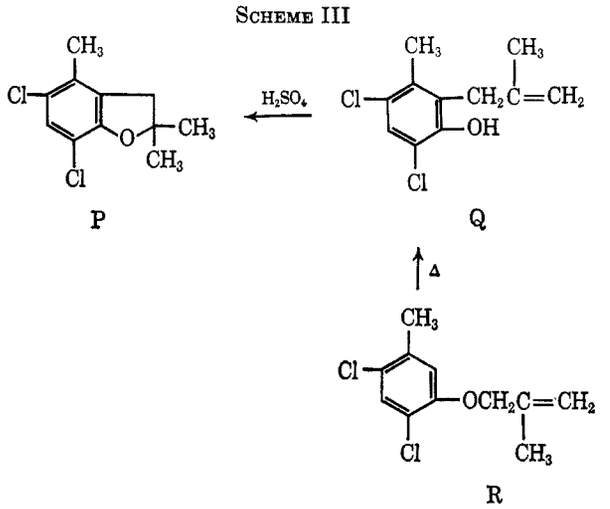
As shown in Table I, cyclization of the methyl ether B-3 by 98% sulfuric acid also yielded a mixture of the *cis*- and *trans*-dihydrobenzofurans J and I. At short reaction times, the product ratio was much different from the equilibrium ratio, and hence the cyclization of the phenol methyl ether, like that of the phenol, was under kinetic rather than equilibrium control at short reaction times. The products from the methyl ether cyclization were shown to be the same as those from the phenol by preparative vpc and comparison of the infrared and nmr spectra, as well as the vpc retention times, with known samples. That the *cis* and *trans* forms J and I were actually equilibrating was shown by exposing the pure *cis* and *trans* forms to concentrated sulfuric acid; the same equilibrium mixture was obtained in these cases, and the pure *cis* and *trans* forms were isolated and identified from the reaction mixture.

The product mixture from the cyclization of the methyl ether B-3 in sulfuric acid at 1-min reaction time showed the presence of about 29% of the conjugated isomers of B-3, *i.e.*, 2,4-dichloro-5-methyl-6-(2-buten-2-yl)phenyl methyl ethers (O). After a 40-min reaction time, these compounds had virtually disappeared from the product mixture. No such conjugated products were found on cyclization of phenol B-2 at 1-min reaction time when the usual extraction with Claisen's alkali was omitted from the work-up. The infrared spectrum of the product mixture showed no hydroxyl band nor did a vpc analysis show any new peaks, not even one for starting material, which had a retention time between that of J and I. An increase in the yield of the dihydrobenzofurans from the methyl ether as the reaction time increased, in conjunction with the disappearance of the conjugated methyl ethers O, suggested that the dihydrobenzofurans J and I were also formed from the conjugated methyl ethers O.

At reaction times longer than those given in Table I, there was evidently some destruction of material by the sulfuric acid, probably by sulfonation.

In the product mixture from the cyclization of both the phenol B-2 and its methyl ether B-3 in sulfuric acid, a minor product was detected which increased with reaction time. This product had a retention time 2 min less than the *trans*-dihydrobenzofuran I on vpc. In the 40-min runs, its vpc peak area amounted to *ca.* 3% of the total peak areas in the case of the phenol and *ca.* 10% in the case of the methyl ether. In the equilibrium studies of J and I in sulfuric acid, a small comparable peak was also detected on vpc analysis. This product was isolated as a crystalline material, mp 51–52°; its analysis and nmr spectrum indicated that it had structure P (Scheme III), and this was confirmed by the synthesis shown below. It is

SCHEME III



noteworthy that, in the rearrangement of the β-methylallyl ether R, the product Q was homogeneous and was isolated in high yield, in contrast to the behavior of the crotyl ether A. The difference in the behavior of the two is to be attributed to the fact that in the rearrangement of R, the carbon approaching the free position of the aromatic ring in the transition state[21] is primary, whereas it is secondary in A; in the latter case, the normal rearrangement is slowed up enough so that the competing isomerization reaction can occur.

Treatment of the ether B-3 with iodine monochloride gave the crystalline *trans*-iodomethyl compound L in

(19) In saturated six-membered rings, the *trans* diaxial protons have much greater coupling constants than the *cis* [R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957) and later papers]; in the present case, the relationships are altered by the constraint of the fused aromatic ring and of the five-membered ring.[20]

(20) F. A. L. Anet and J. M. Muchowski [*Chem. Ind.* (London), 81 (1963)] have reported that certain N-substituted 2,3-dimethylindolines show a larger $J_{2H\text{-}3H}$ for the *cis* isomer than for the *trans*, while the parent indoline shows the same $J_{2H\text{-}3H}$ for both isomers.

(21) *Cf.* J. F. Kincaid and D. S. Tarbell, *J. Am. Chem. Soc.*, **61**, 3085 (1939).

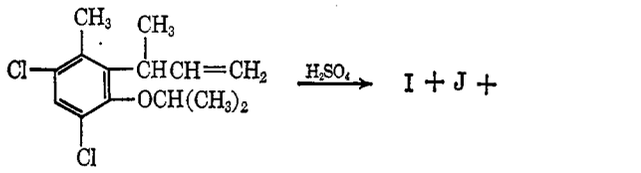
72% yield; its configuration was established by removal of the iodine with hydrogen and palladium–charcoal. This yielded the pure *trans*-2,3-dimethyl compound I; conversion of the crude iodomethyl compound L to I, followed by vpc analysis of the product, gave a *trans/cis* (I/J) ratio of *ca.* 56, showing that the original cyclization to give the *trans*-iodomethyl compound was highly stereospecific. The *trans* configuration of L was supported by a determination of the coupling constant $J_{2H\text{-}3H}$, which was 3.2 cps, in agreement with that for I.

Treatment of the iodomethyl compound L with alcoholic alkali gave elimination and isomerization to 2,3,4-trimethyl-5,7-dichlorobenzofuran (K), whose structure was confirmed by synthesis from 2,4-dichloro-5-methylphenol and 3-chloro-2-butanone to give N, followed by cyclization.[4] This not only proved the structure of L and I, but also the structure of the phenol B-2 from the Claisen rearrangement.

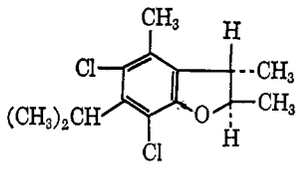
The *cis*-iodomethyl compound, corresponding to L, was obtained by the action of iodine monochloride on the free phenol E-2.

The *trans*-iodomethyl compound L offers several possibilities which are being investigated for the synthesis of the perhydrobenzofurans[4] derived from fumagillin; the latter, based on reasonable mechanisms for their formation, probably have the alkyl groups on the hetero ring in the *trans* arrangement.

The isopropyl ether S of the phenol B-2 was prepared and treated with sulfuric acid, because it was thought that this compound might give a larger proportion of the *trans* isomer I. The product was shown by vpc analysis to consist of the *cis*- and *trans*-dimethyldihydrobenzofurans J and I, with two additional prod-



S



T

ucts, which were collected by vpc. An elemental analysis of these two compounds showed them to be isomeric with each other as well as the starting material. Their infrared spectra showed that neither was starting material, but suggested that the compounds were structurally similar. The nmr of the predominant isomer showed it to be *trans*-5,7-dichloro-2,3-dihydro-6-isopropyl-2,3,4-trimethylbenzofuran (T). The compound was shown to be devoid of aromatic protons by the nmr spectrum, and the appearance of a six-proton doublet at δ 1.40 indicated the presence of an isopropyl group.

These facts and comparison with the nmr spectrum of the dihydrobenzofuran I clearly established the structure (Table II). The compound T also showed $J_{2H\text{-}3H}$ = 4.1 cps in agreement with that shown by I, $J_{2H\text{-}3H}$ = 4.2 cps. The product isomeric with T was

TABLE II

COMPARISON OF THE NMR SPECTRA OF I AND T SHOWING CHEMICAL SHIFT (δ), MULTIPLICITY, AND RELATIVE AREAS

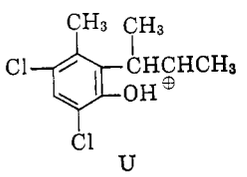
I	T	Assignment
1.28 (d) (3)	1.28 (d) (3)	3-CH_3
1.33 (d) (3)	1.35 (d) (3)	2-CH_3
2.33 (s) (3)	2.24 (s) (3)	4-CH_3
3.05 (m) (1)	3.04 (m) (1)	3-H
4.47 (m) (1)	4.45 (m) (1)	2-H
7.12 (s) (1)	...	6-H
	1.40 (d) (6)	6-$CH(CH_3)_2$
	3.90 (m) (1)	6-$CH(CH_3)_2$

not examined further, but was probably the corresponding *cis*-dihydrobenzofuran.

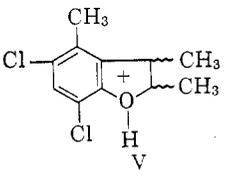
The methinyl proton of the isopropyl group in T showed a shift of 1.0 ppm from that of cumene (δ 2.90).[22] Using Catalin molecular models, it was found that this methinyl proton in compound T was locked in the plane of the benzene ring, because the adjacent chlorine atoms of the ring prevented rotation of the isopropyl group. Restriction of this proton to the plane of the benzene ring would explain the large downfield shift observed. Subsequent to this observation, the same type of shift was described[23] for the methinyl proton of the isopropyl groups in the nmr spectrum of hexaisopropylbenzene.

The results obtained on cyclization of the isopropyl ether S were suggestive of the incursion of an acid catalyzed ether cleavage to generate the phenol, which then cyclized. The fact that the ratio of I/J observed at 7 and 15 min resembles the *trans/cis* ratios obtained from the phenol B-2 at the same times rather than those of the methyl ether B-3 would indicate that cleavage to the phenol occurred before cyclization. The formation of I can also be considered evidence for the occurrence of an acid-catalyzed rearrangement typical of alkyl aryl ethers having a secondary or tertiary alkyl group.[24,25]

Mechanism of the Cyclization Reactions of the Phenol B-2 and the Phenol Methyl Ether B-3 and of the Equilibration of the Dimethyldihydrobenzofurans I and J.—The cyclization of the phenol E-2 in concentrated sulfuric acid presumably involves protonation of the allyl group to the carbonium ion U, which can then cyclize to V, and by loss of a proton, can give the final products I and J. Further equilibria involving other carbonium ions occur, a fact which is demonstrated by the occurrence of the rearranged product P, which must have as a precursor a carbonium ion formed by methyl migration and hydride shift from U.



U



V

(22) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Inc., Palo Alto, Calif., 1962, Spectrum 240.

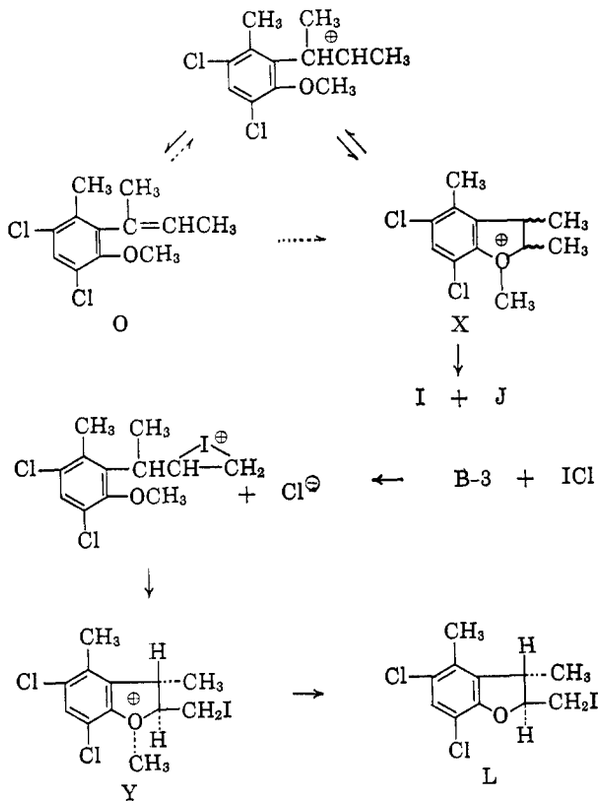
(23) E. M. Arnett and J. M. Bollinger, *J. Am. Chem. Soc.*, **86**, 4729 (1964).

(24) M. J. S. Dewar, "Molecular Rearrangements," Part I, P. de Mayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 313; D. S. Tarbell and J. C. Petropoulos, *ibid.*, **74**, 244, 1249 (1952).

(25) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 618.

The cyclization of the phenol ether probably involves the oxonium ion X (Scheme IV); it is not possible to say at present whether the conjugated isomer O is involved in the cyclization process as an obligatory intermediate, or whether it merely represents a dead-end equilibrium.

SCHEME IV



The *trans/cis* ratio for cyclization from the free phenol is very small for the kinetically controlled process, but the ratio increases as the equilibration proceeds (Table I). The *trans/cis* ratio starting with the phenol ether is large during the kinetically controlled process and drops to the equilibrium value of *ca.* 4, as the reaction time increases. The larger proportion of *trans* at small reaction times when the phenol ether is the starting material may mean that the methoxonium ion X is formed in a rate-determining step, and that this oxonium ion is of lower energy when the methyl groups on the hetero ring are staggered, leading to a predominance of the *trans* form I.[26] This tendency for *trans* product is accentuated in the case of the iodomethyl derivative, of which very little *cis* product is obtained from the phenol methyl ether, *via* the methoxonium ion Y. The free phenol, as would be expected, forms both *cis*- and *trans*-iodomethyl compounds, because, in the oxonium intermediate corresponding to V, there is not the same steric factor favoring the *trans* compound.

Methoxonium ion intermediates similar to X and Y apparently are involved in solvolyses[26-28] of methoxy compounds; pathways analogous to that postulated above for the action of ICl on the phenol B-2 or the phenol ether B-3 are undoubtedly involved in the bromination of 2-allylanisole to 2-bromomethyl-2,3-dihydrobenzofuran.[29]

The equilibration of I and J by sulfuric acid must involve protonation of the ether oxygen, followed by cleavage of the carbon-oxygen bond to a carbonium ion, or at least enough stretching to allow inversion at C-2. It seems most unlikely that the configuration at C-3 is affected.[30] Further studies are underway on the mechanism of equilibration of I and J.

Infrared Spectra of *o*-Chlorophenols.—*o*-Chlorophenols in dilute solution in CCl_4 are known[31,32] to show in the infrared a weak band near 3600 cm^{-1}, assigned to free hydroxyl stretching, and a strong band near 3540 cm^{-1}, attributed to internal hydrogen bonding between the hydroxyl and the chlorine. The infrared spectra of several of the phenols described in this paper, along with some model compounds, have been determined, as a check on the assigned structures, and are given in Table III.

TABLE III

HYDROXYL STRETCHING BAND OF SOME *o*-CHLOROPHENOLS AND RELATED COMPOUNDS[a]

Compound	Hydroxyl band position (cm^{-1}) in CCl_4, molality	Hydroxyl band position (cm^{-1}) thin film
2,4-Dichloro-5-methyl-6-(α-methylallyl)phenol (B-2)	3540 (4.33×10^{-2}) 3540 (0.218)	3530 (sharp)
2,4-Dichloro-5-methylphenol	3555 (6.64×10^{-2})	
2,4-Dichloro-5-methyl-6-(2-butyl)phenol	3545 (0.142)	3535 (sharp)
2,4-Dichloro-3-methyl-6-(α-methylallyl)phenol (C-2)	3535	
2-(2-Butyl)-3-methylphenol (D)	3620 (0.138)	
o-Allylphenol[b]	3620 (0.140)	3480 (broad)
o-Propylphenol[c]	3615 (0.136)	3430 (broad)

[a] The spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer utilizing matched 0.1-mm sodium chloride cavity cells for measurements in carbon tetrachloride solution. [b] Obtained from Aldrich Chemical Co. (99+% pure by vpc). [c] Obtained by hydrogenation of *o*-allylphenol over 5% Pd-C in a Parr apparatus, bp 108–109.5° (19 mm) ($n^{23}D$ 1.5234); the reported value of bp 65° (1 mm) ($n^{25}D$ 1.5280) is given by G. G. S. Dutton, *et al.*, *Can. J. Chem.*, **31**, 837 (1953).

The results are in agreement with the earlier measurements[31,32] and confirm the structures assigned. The structure of C, while not conclusively proved, is in agreement with the infrared data and with earlier observations on halogen rearrangement during Claisen rearrangement.[33]

(26) Similar ideas have been proposed by S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(27) R. Heck, J. Corse, E. Grunwald, and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3278 (1957).

(28) S. E. Cantor and D. S. Tarbell, *ibid.*, **86**, 2902 (1964).

(29) R. Adams and R. E. Rindfusz, *ibid.*, **41**, 648 (1919). R. T. Arnold, M. M. Campos, and K. L. Lindsay [*ibid.*, **75**, 1044 (1953)] reported analogous reactions.

(30) Only one of the two possible enantiomers of I and J is indicated.

(31) (a) O. R. Wulf, U. Liddel, and S. B. Hendricks, *J. Am. Chem. Soc.*, **58**, 2287 (1936); (b) A. W. Baker, *ibid.*, **80**, 3598 (1958).

(32) H. Bourassa-Bataille, P. Sauvageau, and C. Sandorfy, *Can. J. Chem.*, **41**, 2240 (1963).

(33) E. Piers and R. K. Brown, *ibid.*, **41**, 329, 2917 (1963); *cf.* R. B. Carlin and E. E. Fisher, *J. Am. Chem. Soc.*, **70**, 3421 (1948).

Experimental Section[34]

Crotyl 2,4-Dichloro-5-methylphenyl Ether (A).—2,4-Dichloro-5-methylphenol (Aldrich, mp 70.5–71°, 119.3 g), 61.1 g of *trans*-2-chloro-1-butene,[35] 98 g of anhydrous potassium carbonate, and 100 mg of potassium iodide were refluxed for 20 hr. The product was worked up by conventional procedures and was crystallized from petroleum ether (bp 30–60°) solution at Dry Ice temperatures to yield a total of 111 g (71%) of white crystals, mp 36.5–37°.

Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23. Found: C, 56.97; H, 5.21.

The Rearrangement of Crotyl 2,4-Dichloro-5-methylphenyl Ether (A) to a Mixture of 2,4-Dichloro-5-methyl-6-(α-methylallyl)phenol (B-2) and 2,4-Dichloro-3-methyl-6-(α-methylallyl)-phenol (C-1).—A solution of 110.6 g of crotyl 2,4-dichloro-5-methyl phenyl ether in 250 ml of dimethylaniline was refluxed under nitrogen for 8.2 hr. Dilution with 600 ml of petroleum ether (bp 30–60°) was followed by extraction, once with 150 ml of Claisen's alkali,[36] then twice with 100-ml portions. The alkaline extracts were combined, extracted twice with petroleum ether, and were then acidified with 4.5 *M* sulfuric acid. During acidification, 1500 ml of water was added to dissolve precipitated salts. The precipitated oil was then extracted from the water with four 200-ml portions of ether, and the combined extracts were washed with water and brine. After drying, the ether was removed *in vacuo* to leave 102 g of an oil. Distillation through a 22-cm Vigreux column gave a main fraction (86.9 g), distilling at 96.8–99° (0.8 mm). Analysis by vpc on a 15-ft × 0.25 in. 20% QF-1 silicone on Chromosorb P column (column temperature = 172°, flow rate = 73 cc of He/min) showed two main peaks at 22.3 min (C-2) and 25.2 min (B-2) in a ratio of *ca.* 1:4, respectively.

Benzoylation of the Mixture of Phenols B-2 and C-2. Separation of the Benzoate of Phenol B-2.—A solution of 86.9 g of the mixture of the phenols from the rearrangement of the crotyl ether A and 55.5 g of benzoyl chloride in anhydrous pyridine was refluxed for 45 min. The product mixture was poured into 1 l. of 5% sodium bicarbonate, and, after cooling in ice for 2 hr, a solid was separated by filtration and washed on the filter with 500 ml of water in portions. The crude product (123.8 g, 98%, mp 61–80°) was dissolved in 450 ml of hot 95% ethanol, and, after standing overnight in a refrigerator, the solution deposited 95.8 g of crystals, mp 80–86°. Recrystallization from 250 ml of 95% ethanol gave 92.1 g (73%) of white crystals, mp 87–88.5°. Analytically pure product, mp 88–89°, was obtained by one further recrystallization. The infrared spectrum showed a band at 1760 cm^{-1} (phenol benzoate).

Anal. Calcd for $C_{18}H_{16}Cl_2O_2$: C, 64.49; H, 4.81. Found: C, 64.39; H, 4.85.

Evaporation of the ethanol mother liquors from the initial crystallization left 28 g of a viscous oil which contained the benzoate of phenol C-2.

2,4-Dichloro-5-methyl-6-(α-methylallyl)phenol (B-2).—The above benzoate (91.0 g) was saponified by refluxing for 2.3 hr in 75% aqueous ethanol containing 44 g of potassium hydroxide. The product was worked up in the usual way, and was obtained by distillation as an oil (59.9 g, 88%): bp 124° (2.5 mm), $n^{25}D$ 1.5591. Vpc showed only one peak.

Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23. Found: C, 57.50; H, 5.14.

The **p-nitrobenzoate**, prepared with *p*-nitrobenzoyl chloride in pyridine, melted at 92–93°.

Anal. Calcd for $C_{18}H_{15}Cl_2NO_4$: C, 56.86; H, 3.98. Found: C, 56.95; H, 4.15.

2,4-Dichloro-3-methyl-6-(α-methylallylphenol) (C-2).—The mixture of the isomeric phenols C-2 and B-2, obtained by saponification of the oily benzoate mixture C-1 and B-1, was converted into the *p*-nitrobenzoates. Repeated recrystallization from methanol–water yielded the ***p*-nitrobenzoate**, mp 123–123.5°.

Anal. Calcd: as above. Found: C, 57.12; H, 3.97.

Hydrolysis of the *p*-nitrobenzoate yielded the free **phenol C-2**, purified by chromatography on alumina, followed by distillation.

Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.24. Found: C, 57.16; H, 5.25.

The nmr spectra of B-2, C-2, and of their *p*-nitrobenzoates were in agreement with the assigned structures.

2-(2-Butyl)-3-methylphenol (D).—To a solution of 0.203 g of 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol in 6.3 ml of commercial absolute ethanol was added 0.5 ml of 99% hydrazine hydrate and 0.089 g of 15% palladium on carbon. After refluxing for 1 hr, the reaction mixture was allowed to cool for 20 min, the catalyst was removed by filtration, and most of the ethanol was removed at reduced pressure. To the residue, 10 ml of water was added, and the mixture was extracted four times with ether. Removal of the ether and recrystallization from petroleum ether at Dry Ice temperatures gave a total of 0.291 g (51%), mp 72.7–73.7° (sealed capillary). Vapor phase chromatography on a 10-ft 25% Ucon Polar column at 198° showed only one peak. The infrared spectrum (CCl_4) showed a band at 3620 cm^{-1} (OH) and the absence of bands due to R—CH=CH_2 shown by the starting material. Infrared bands at 780 and 742 cm^{-1} (KBr disk) were consistent with 1,2,3-substitution of the benzene ring. The nmr showed no olefinic protons but did show three aromatic protons centered at δ 6.75. Also present were a singlet at δ 2.22 (Ph–CH_3), a doublet at δ 1.26 (Ph–CH–CH_3), a triplet at δ 0.88 (terminal methyl of side chain), and multiplets at δ 1.68 (CH_2) and 2.89 (Ph–CH).

The analytical sample was obtained by sublimation at 10 mm (bath temperature, 60°), mp 72.5–73.5° (sealed capillary).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.85. Found: C, 80.45; H, 9.85.

2,4-Dichloro-5-methyl-6-(2-butyl)phenol.—A solution of 0.699 g of 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol (B-2) in 35 ml of ethanol was hydrogenated over 5% palladium–carbon for 20 min at 1 atm and 21°, when 1 equiv of hydrogen had been absorbed. The catalyst was removed by filtration through Celite and the filtrate was evaporated at reduced pressure to leave 0.564 g of a mobile oil. Evaporative distillation at 0.2 mm (bath temperature, 75°) gave 0.461 g (66% yield) of product. Vapor phase chromatography on a 15-ft 25% Ucon Polar column at 192° showed the product to be of 99+% purity. The infrared spectrum showed no bands due to R—CH=CH_2, but did show bands at 3535 cm^{-1} (OH) and 853 cm^{-1} (m) (pentasubstituted ring).

The analytical sample was obtained by vpc.

Anal. Calcd for $C_{11}H_{14}Cl_2O$: C, 56.67; H, 6.05. Found: C, 56.80; H, 6.08.

The **α-naphthylurethan** melted at 125.5–126° after three recrystallizations from petroleum ether (bp 100–110°).

Anal. Calcd for $C_{22}H_{21}NCl_2O_2$: C, 65.68; H, 5.26. Found: C, 65.69; H, 5.36.

2,4-Dichloro-5-methyl-6-(α-methylallyl)phenyl Methyl Ether (B-3).—The phenol B-2 (51 g) was methylated by adding 27.9 g of dimethyl sulfate to a solution of 51 g of the phenol B-2 in 9.6 g of sodium hydroxide in 211 ml of water. The reaction mixture was then stirred and heated on the steam bath for 3.3 hr. Sodium hydroxide (3.8 g) and 11.1 g of dimethyl sulfate were added, and the mixture was stirred and heated for an additional 2.8 hr. The reaction mixture, after conventional work-up, gave 43.4 g of an oil. Distillation gave 39.4 g (73%) of product, bp 117–118° (0.9 mm), $n^{25}D$ 1.5446. One run using only a single treatment with dimethyl sulfate gave only 57% yield after distillation.

Vapor phase chromatography on a 15-ft 20% QF-1 silicone column showed only one peak.

Anal. Calcd for $C_{12}H_{14}Cl_2O$: C, 58.79; H, 5.76. Found: C, 58.85; H, 5.80.

2-(3,5-Dichloro-2-methoxy-6-methylphenyl)propionic Acid (E-1).—To 220 ml of water in a 4-l. wide-mouth bottle were added 68.8 g of sodium metaperiodate and 12.8 g of anhydrous sodium carbonate. After complete solution, 400 ml of purified dioxane was added followed by 9.84 g of the methyl ether B-3 and 0.850 g of potassium permanganate. The bottle was then capped and sealed with adhesive tape; after shaking for 47 hr, an additional 0.425 g of potassium permanganate was added, and shaking was continued for 12 hr. The solution was allowed to stand for 12 hr, filtered, and extracted three times with petroleum

(34) Microanalyses were done by V. Landeryou and A. Revilla of these laboratories and by Micro-Tech Laboratories, Skokie, Ill. All melting points and boiling points are uncorrected. The infrared spectra of liquids were taken on thin films and those of solids on potassium bromide disks (unless otherwise specified) with a Perkin-Elmer Model 421 spectrophotometer. A Cary recording spectrophotometer Model 11-MS was used to obtain ultraviolet spectra. The nmr spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride (unless specified otherwise) using tetramethylsilane as an internal standard. Vapor phase chromatography was done on Aerograph A-90-P and A-90-P-2 instruments.

(35) L. F. Hatch and S. S. Nesbitt, *J. Am. Chem. Soc.*, **72**, 727 (1950).

(36) Claisen's alkali was made by diluting a solution of 350 g of potassium hydroxide in 250 ml of water to 1000 ml with methanol.

ether. The aqueous solution was acidified with 6 *M* hydrochloric acid and extracted with four 200-ml portions of ether. The ether extracts were combined and evaporated to 200 ml, then washed with three portions of 10% sodium carbonate. Acidification with 6 *M* hydrochloric acid, after boiling out the residual ether, precipitated an oil which crystallized on standing to give 7.60 g of a white solid. Recrystallization from 50 ml of petroleum ether (bp 100–110°) gave 7.18 g (68% yield) of white crystals, mp 133.8–135° (sealed capillary). The infrared spectrum showed a band at 1713 cm^{-1} (CCl_4) and the absence of R—CH=CH_2. The nmr spectrum ($CDCl_3$) showed singlets at δ 2.32 (Ar–CH_3), 3.86 (O–CH_3), 7.34 (Ar-H), and 9.63 (COOH); a doublet at δ 1.43 (Ar–CH–CH_3); and a quartet at δ 4.17 (Ar–CH).

An analytical sample was prepared by one further recrystallization and sublimation at 0.2 mm (bath temperature, 122°).

Anal. Calcd for $C_{11}H_{12}Cl_2O_3$: C, 50.21; H, 4.60. Found: C, 50.39; H, 4.71.

The **methyl ester E-2**, prepared by the method of Clinton and Laskowski,[37] was purified by evaporative distillation at 0.2 mm (bath temperature, 140°) and gave 0.262 g. Analysis by vpc on a 5-ft 25% Ucon Polar column at 190° showed only one peak; the infrared spectrum showed a strong band at 1740 cm^{-1} (ester C=O).

Anal. Calcd for $C_{12}H_{14}Cl_2O_3$: C, 52.00; H, 5.09. Found: C, 52.33; H, 5.18.

2-(2-Methoxy-6-methylphenyl)propionic Acid (E-3).—To 150 ml of 10% sodium hydroxide at 90° was added 5.02 g of 2-(3,5-dichloro-2-methoxy-6-methylphenyl)propionic acid (E-1). While stirring, 15.0 g of Raney nickel alloy was added in small portions over a period of 1.75 hr while maintaining the internal temperature at 90–94°. On completion of the addition of the alloy, stirring was continued for 1.25 hr while keeping the temperature at *ca.* 90°. After cooling, the reaction mixture was poured slowly into 180 ml of ice-cold 37% hydrochloric acid; an oil precipitated which crystallized on standing in an ice bath. The white solid was collected and washed on the filter with water to give 3.45 g (93% yield), mp 132.5–135.5°. Recrystallization from 90 ml of petroleum ether gave 3.25 g, mp 134–136°, whose infrared spectrum showed bands at 783 cm^{-1} (s) and 740 cm^{-1} (m) (1,2,3-substituted benzene). The nmr spectrum ($CDCl_3$) showed singlets at δ 3.75 (O–CH_3), 2.32 (Ar–CH_3), and 10.59 (COOH); a doublet at δ 1.39 (Ar–CH–CH_3) (J_{CH_3-H} = 7.1 cps); a quartet at δ 3.97 (Ar–CH); and a complex signal centered at δ 6.97 (three aromatic protons). The signals appeared in the ratio of 3:3:1:3:1:3, respectively.

An analytical sample was prepared by an additional recrystallization and sublimation at 0.08 mm (bath temperature, 90°), mp 136–137° (sealed capillary).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.78; H, 7.19.

The **methyl ester E-4** was made from the acid E-3 with diazomethane. After two crystallizations from petroleum ether, the white product E-4 melted at 65–66°.

An analytical sample was prepared by sublimation at 0.15 mm (bath temperature, 43°).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.75.

Reduction of 2-(2-Methoxy-6-methylphenyl)propionic Acid (E-3) by Lithium and *t*-Butyl Alcohol in Liquid Ammonia.—A solution of 1.94 g (0.01 mole) of 2-(2-methoxy-6-methylphenyl)-propionic acid E-3 in a mixture of 23 ml of *t*-butyl alcohol and 25 ml of anhydrous ether was added slowly with stirring to 48 ml of liquid ammonia. To the resultant solution, 1.13 g (0.16 g-atom) of lithium ribbon, cut into small pieces, was added during 20 min while stirring. The mixture was stirred for 3 hr at reflux, and 15 ml of absolute methanol was then added slowly from a dropping funnel. The blue color was discharged and a white precipitate was formed. The ammonia was allowed to evaporate through a mercury bubbler trap; after 3.5 hr, 100 ml of ice–water was added, and the solids were allowed to dissolve. The aqueous, alkaline solution was extracted four times with 50-ml portions of ether, then cooled to 0–3° in a salt–ice bath. While stirring vigorously, ice-cold 2 *N* hydrochloric acid was added slowly from a dropping funnel until the solution was just acid to congo red paper. The mixture, which contained an oily precipitate, was immediately extracted with four 40-ml portions of ether and the combined extracts were washed with three 50-ml portions of brine. After drying, the ether was removed at room temperature on a rotary evaporator, leaving 1.56 g of a viscous oil. This crude product, as such, was subjected to hydrolysis within a short time as described in the following section.

Hydrolysis of the Reduction Product of E-3 in Ether Containing Hydrochloric Acid. Formation of 3a,6,7,7a-Tetrahydro-7a-methoxy-3,4-dimethyl-2-(3H)benzofuranone (G).—The oily reduction product (1.56 g) was stirred at room temperature in 100 ml of ether containing 1 ml of 37% hydrochloric acid for 2.25 hr. The mixture was then extracted four times with 5% sodium bicarbonate solution. The ether solution, washed with water and brine, then dried, gave 0.56 g (29% from E-3) of a colorless oil on evaporation. Thin layer chromatography on silica gel-G with ether as a developer showed one spot. Chromatography of 0.250 g on 9.7 g of 200 mesh silica gel gave 0.235 g of a liquid on elution with 1:1 benzene–petroleum ether (bp 30–60°). Evaporative distillation at 0.3 mm (bath temperature, 90°) gave 0.194 g of G. The infrared spectrum showed a band at 1783 cm^{-1} (γ-lactone) and bands at 3040 (w), 1680 (w), 835 (m), and 809 cm^{-1} (m) (R—C=C—H in a six-membered ring). Strong bands also appeared at 1382, 1222, 1175, 1118, 1032, and 1008 cm^{-1}. The nmr showed a doublet at δ 1.43 (3-CH_3) (J = 6.6 cps); a singlet at δ 3.38 (7a-OCH_3); a multiplet at δ 5.50 (H—C=C—); and a multiplet at δ 1.71 (H—C=C—CH_3). These signals appeared in a ratio of 3:3:1:3, respectively. The remainder of the protons appeared as a complex band at δ 1.84–2.47.

An analytical sample was prepared by passing an ether solution of the product through a few grams of neutral, activity I alumina. After removal of the ether *in vacuo*, the oil was evaporatively distilled at 0.5 mm (bath temperature, 90°).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.80; H, 8.04.

The bicarbonate extract from above was extracted once with 25 ml of ether, acidified with 18% hydrochloric acid and re-extracted three times with 50 ml of ether. After washing the ether extract with brine and drying, the ether was removed at reduced pressure to leave 0.62 g of a viscous oil. Thin layer chromatography on silica gel-G with ether as the developer showed the presence of at least two compounds. This oil (0.259 g) was chromatographed on 200 mesh silica gel. Elution with 150 ml of benzene gave no product; elution with 9:1 benzene–ether gave 34 mg of an oil in the first 75 ml and 141 mg of oil in the next 225 ml of eluent; 3:1 benzene–ether eluted 7 mg of an oil in the first 50 ml and 36 mg of crystalline material in the next 125 ml. Solvents of increased polarity eluted nothing up to methanol which gave 15 mg of a brown oil. The crystalline product eluted by 3:1 benzene–ether was sublimed at 0.7 mm (bath temperature, 130°) to give 28 mg (4% from E-3) of a white solid, mp 166–167.5°. This product was shown to be identical (mixture melting point and superimposable infrared spectra) with the acid H which was obtained by hydrolysis of the reduction product of E-3 in 10% hydrochloric acid.

Hydrolysis of 3a,6,7,7a-Tetrahydro-7a-methoxy-3,4-dimethyl-2-(3H)benzofuranone (G).—The tetrahydrobenzofuranone (33 mg) was heated in 1.0 ml of 10% hydrochloric acid on the steam bath for 20 min. The white crystals obtained by cooling in ice and seeding (10 mg, mp 165–167°) were shown by mixture melting point and comparison of infrared spectra to be 2-methyl-6-oxo-1-cyclohexene(2-propionic acid) (H).

The mother liquor was evaporated to dryness to leave 19.5 mg of residue. The residue was extracted with 5 ml of boiling ether to leave 6.8 mg of a resinous material. Evaporation of the ether gave 12.7 mg of white solid, mp 159–164°. Sublimation at 1 mm (bath temperature, 120°) raised the melting point to 163–165.5°. The infrared spectrum of this material was identical with that of the first crop. The total yield of H was therefore 74%.

Hydrolysis of the Reduction Product of E-3 by 10% Hydrochloric Acid. 2-Methyl-6-oxo-1-cyclohexene(2-propionic acid) (H).—The reduction as previously described was repeated on 5.00 g of E-3 to give 4.96 g of the crude reduction product; 1.02 g of the product was hydrolyzed by heating on the steam bath in 10% hydrochloric acid with periodic agitation. During heating, the heavy oil dissolved, and heating was stopped when it disappeared. The solution was allowed to stand for 26 min, then placed in an ice bath. On scratching the flask with a glass rod and seeding, crystals formed. After standing for 16 hr in the refrigerator, 0.444 g of white crystals, mp 163–166°, were collected. Recrystallization from 9 ml of benzene and sublimation

(37) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

at 0.08 mm (bath temperature, 140°) gave 0.308 g of product (H), mp 165.5–167°.

The infrared spectrum showed bands at 1705 cm^{-1} (s) (COOH), 1660 cm^{-1} (s), and 1630 cm^{-1} (m) (C=C—C=O). The ultraviolet spectrum in 95% ethanol showed λ_{max} at 242 mμ (ϵ_{max} 1.30 × 10^4). The nmr spectrum ($CDCl_3$, 60°) showed singlets at δ 1.94 (CH_3—C=C) and 10.87 (COOH); a doublet at δ 1.25, (J = 7.1 cps) (CH_3—CH—COO); and a quartet at δ 3.80 (–CH—COO).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.15; H, 7.60.

Extraction of the aqueous mother liquor from above with three 10-ml portions of ether gave, after the ether had been washed with brine and dried, 0.299 g of a mixture of oil and crystals. The mixture was triturated twice with 5-ml portions of petroleum ether (bp 30–60°), and the remaining solid was recrystallized from 9 ml of benzene to give 72 mg of crystals, mp 157–163°. A second recrystallization from 2 ml of benzene gave an additional 46 mg of H for a total yield of 51% (based on E-3). The petroleum ether-soluble material showed three spots on thin layer chromatography on silica gel G with ether as the developer. Its infrared spectrum showed strong bands at 1770 and 1712 cm^{-1}.

***cis*- and *trans*-5,7-Dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (J and I). Cyclization in Sulfuric Acid of 2,4-Dichloro-5-methyl-6-(α-methylallyl)phenol (B-2).**—A solution of 0.460 g (2.00 × 10^{-3} mole) of 2,4-dichloro-5-methyl-6-(α-methylallyl)-phenol (B-2) in 8.7 ml of 98% sulfuric acid was let stand at room temperature for 15 min. During this time a slightly exothermic reaction occurred, accompanied by a color change from orange to dark red. The solution was then poured into 70 ml of ice–water to precipitate an oil. The mixture was extracted four times with petroleum ether and the combined extracts were washed three times with Claisen's alkali. The extract was washed with water and saturated sodium chloride solution, was dried, the solvent was removed by evaporation at reduced pressure, and the residual oil was subjected to evaporative distillation at 0.05 mm (bath temperature, 95°) to yield 0.258 g of an oil. Vapor phase chromatography of the product before distillation showed three peaks at 17.0, 19.0, and 26.2 min in a ratio of 0.1:3.0:1.0. Collection of the peaks at 19.0 and 26.2 min by preparative vpc of the distilled product gave *trans*- and *cis*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I and J), $n^{25}D$ 1.5517 and 1.5555, respectively. The combined yield of the *cis* and *trans* isomers was 55% (calculated from vpc analysis and the weight of the distilled product).

The analytical samples were prepared by evaporative distillation of the vpc cuts.

Anal. of *cis* isomer J. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23. Found: C, 57.09; H, 5.25.

Anal. of *trans* isomer I. Found: C, 57.17; H, 5.16.

The cyclization of the phenol B-2 was also carried out in 98% sulfuric acid for reaction times of 1, 7, and 40 min utilizing the same amount of reactants, the same work-up, and the same vpc conditions as for the 15-min run. In all cases the same peaks on vpc were observed as in the 15-min run; the identity of the *trans* and *cis* isomers (I and J) was established by collecting them by vpc, and comparing their infrared spectra and vpc retention times with knowns. As before, the vpc analysis was carried out on the product before distillation. The results are summarized in Table IV.

TABLE IV

VPC ANALYSIS

Time, min	Product ratios: *trans*/*cis*	Product ratios: Minor product P[b]/*cis*	Wt of distillate, g	% yield[a] (I and J)
1	0.33	0.01	0.388	84
7	1.2	0.01	0.364	78
40	3.6	0.15	0.234	49

[a] Calculated from the vpc analysis and the weight of distilled product. [b] Corresponds to minor product (retention time = 17 min) of the 15-min cyclization.

The cyclization with a 1-min reaction time was repeated without extraction by Claisen's alkali in the workup. Vapor phase chromatography showed *trans*/*cis* to be 0.32, and no new peaks appeared, not even starting material (retention time intermediate to that of the *cis* and *trans* isomers). An infrared spectrum of the product also showed the absence of hydroxyl absorption.

Cyclization of 2,4-Dichloro-5-methyl-6-(α-methylallyl)phenyl Methyl Ether (B-3) in Sulfuric Acid. Reaction Time of 15 Min.—A solution of 0.488 g (2.00 × 10^{-3} mole) of the methyl ether of 2,4-dichloro-5-methyl-6-(α-methylallyl)phenol B-3 in 8.7 ml of 98% sulfuric acid was let stand at room temperature for 15 min. An exothermic reaction occurred which was accompanied by color changes terminating at dark red. The solution was then poured into 70 ml of ice–water to precipitate an oil. The mixture was extracted three times with ether and the combined extracts were washed with water and brine; the ether was dried, evaporated at reduced pressure, and the residual oil was evaporatively distilled at 0.06 mm (bath temperature, 95°) to give 0.336 g of a liquid. Vapor phase chromatography of the product before distillation showed peaks at 11.5, 14.1, 16.6, 18.6, and 25.7 min. The peaks at 16.6, 18.6, and 25.7 min appeared in a ratio of 0.41:4.1:1.0, respectively, while those at 11.5 and 14.1 min were both <0.05 relative to the peak at 25.7 min. Collection of the peaks at 18.6 and 25.7 min gave *trans*- and *cis*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran, respectively, as shown by identity of their infrared spectra, vpc retention times, and nmr spectra with knowns. The combined yield of *cis* and *trans* isomers was 68% based on starting material (calculated from vpc analysis and the weight of the distilled product).

The material in the peak at 16.6 min is shown below to be 2,2,4-trimethyl-5,7-dichloro-2,3-dihydrobenzofuran (P).

Equilibration of *trans*-5,7-Dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I) in Sulfuric Acid.—A solution of 0.400 g of *trans*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I) in 7.6 ml of 98% sulfuric acid was allowed to stand at room temperature for 15 min. The dark red solution was then poured into 70 ml of ice–water, and the mixture was extracted three times with ether. The combined ether extracts were washed three times with water and twice with brine, were dried, and were evaporated at reduced pressure to leave 0.316 g of an oil. Analysis by vpc showed two peaks at 15.1 and 20.8 min in a ratio of 4.5:1.0, respectively. These peaks were collected by vpc and shown to be the starting *trans* isomer (I) (15.1 min) and the corresponding *cis* isomer (J) (20.8 min) by the identity of their infrared spectra and vpc retention times with knowns.

Equilibration of *cis*-5,7-Dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (J) in Sulfuric Acid.—A solution of 0.190 g of *cis*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (J) in 3.6 ml of 98% sulfuric acid was allowed to stand at room temperature for 15 min and was worked up as above. Vapor phase chromatography, as above, showed two main peaks at 15.0 and 20.6 min in a ratio of 1.4:1.0, respectively. A very small peak at 13.4 min was also noted. The peaks at 15.0 and 20.6 min were collected by vpc and shown to be the starting *cis* isomer (J) (20.6 min) and the *trans* isomer (I) (15.0 min) by the identity of their infrared spectra and vpc retention times with knowns.

Details of the Vapor Phase Chromatography of the Products from the Cyclizations.—The product mixtures were analyzed on a 5-ft × 0.25 in. 20% Ucon Polar HB-5100 on Chromosorb P (30–60 mesh) stainless steel column using an Aerograph A-90-P-2 instrument fitted with a Wheelco recorder. Representative conditions were column temperature = 179°, flow rate = 82 cc of He/min, injector = 232°, and detector = 269°. The sample sizes used were in the range of 0.1–0.4 μl. depending on the sample. The peak areas were obtained either by use of a disk integrator coupled with the recorder or by a planimeter.

Each sample was analyzed three times and the peak ratios given were arrived at by averaging the corresponding peak ratios from each run. The peak ratios were calculated from the areas to three significant figures and then rounded to two. In obtaining the *trans*/*cis* (I/J) ratios in Table I, the average deviation from the mean ranged from 0.3 to 3.3%; the average for all the cases was 1.6%.

The ratio I/J (*trans*/*cis*) was calculated directly from the peak areas, since these diastereoisomers would be expected to show little difference in thermal conductivity. One check of this assumption was made by analyzing a synthetic mixture with I/J = 1.24. Analysis under the usual conditions gave I/J = 1.20.

In order to calculate a combined percent yield of the *trans* (I) and *cis* (J) isomers from the cyclization reactions, the per cent of these isomers in the product was obtained by internal normali-

zation of the peak areas of all the components of the product mixture.

Pure samples of I and J did not isomerize on vpc under the conditions employed for analysis.

2,4-Dichloro-5-methyl-6-(α-methylallyl)phenyl Isopropyl Ether (S).—2,4-Dichloro-5-methyl-6-(α-methylallyl)phenol (B-2, 5.0 g) was converted to the isopropyl ether S with 6.0 g of 2-iodopropane in refluxing acetone with potassium carbonate. Distillation gave 4.8 g (81% yield) of a liquid, bp 97–99° (0.08 mm) ($n^{24}D$ 1.5359). The infrared spectrum showed bands at 3090, 1643, 1000, and 915 cm^{-1} (R—CH=CH_2); 1188, 1146 cm^{-1} [–$CH(CH_3)_2$]; and 868 cm^{-1} (pentasubstituted benzene). The nmr spectrum showed singlets at δ 2.27 (Ar–CH_3) and 7.28 (Ar–H); and doublets at δ 1.38 (Ar–CH–CH_3) (J = 7.2 cps), 1.26 and 1.32 [$CH(CH_3)_2$] (J = 6.2 cps). The vinyl protons appeared as multiplets near δ 5.0 and 6.0, and the methinyl protons of the isopropyl group and of the group Ar–CH–CH_3 appeared as a complex absorption centered at δ 4.4.

Anal. Calcd for $C_{14}H_{18}Cl_2O$: C, 61.55; H, 6.64. Found: C, 61.70; H, 6.80.

Cyclization in Sulfuric Acid of 2,4-Dichloro-5-methyl-6-(α-methylallyl)phenyl Isopropyl Ether (S).—A solution of 1.092 g of the isopropyl ether S in 17.4 ml of 98% sulfuric acid was allowed to stand at room temperature for 15 min, and the reaction mixture was worked up as in earlier cases. The residual oil was evaporatively distilled at 0.08 mm (bath temperature, 120°) to give 0.323 g of liquid. Analysis by vpc of the product before distillation showed peaks at 16.6, 18.6, 25.7, 32.2, 35.9, and 49.7 min. The peaks at 16.6 and 32.2 min were small, being no >0.1 relative to the peak at 25.7 min. The major peaks at 18.6, 25.7, 35.9, and 49.7 min appeared in a ratio of 3.4:1.0:9.2:2.4, respectively. The peaks at 18.6 and 25.7 min were collected and identified as *trans*- and *cis*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I and J), respectively, by the identity of their infrared spectra and vpc retention times with knowns.

The peaks at 35.9 and 49.7 min were also collected from the vpc. The compound of retention time 35.9 min was identified as *trans*-5,7-dichloro-2,3-dihydro-6-isopropyl-2,3,4-trimethylbenzofuran (T). The infrared spectrum showed bands at 1378, 1363, 1167, and 1142 cm^{-1} (isopropyl group). Strong bands were also present at 1410, 1238, 1095, 1050, 1030, 885, 788, 758, and 740 cm^{-1}. In addition to the nmr data shown for T in Table III, J_{2H-3H} was found to be 4.2 cps.

The analytical sample of T was prepared by evaporative distillation of the vpc cut at 0.08 mm (bath temperature, 100°).

Anal. Calcd for $C_{14}H_{18}Cl_2O$: C, 61.55; H, 6.64. Found: C, 61.63; H, 6.69.

The compound eluted at 49.7 min was probably the diastereoisomer of T (*i.e.*, *cis*). Its infrared spectrum was similar to that for the *trans* isomer T, showing bands at 1378, 1365, 1180, and 1169 cm^{-1} (isopropyl group) and strong bands at 1411, 1232, 1058, 1042, 870, 778, and 741 cm^{-1}. The analytical sample was prepared by evaporative distillation of the vpc cut at 0.08 mm (bath temperature, 100°).

Anal. Calcd for $C_{14}H_{18}Cl_2O$: C, 61.55; H, 6.64. Found: C, 61.24; H, 6.50.

The cyclization of the isopropyl ether S was also carried out at a reaction time of 7 min in the same manner and on the same scale as for the 15-min run. Evaporative distillation at 0.08 mm (bath temperature, 100°) gave 0.313 g of liquid. Vapor phase chromatography before distillation showed the same major products as in the 15-min run in a ratio of 1.2:1.0:1.2:0.73.

3-(2-Methoxyphenoxy)-2-butanone was prepared from 2-methoxyphenol and 3-chloro-2-butanone in acetone with potassium carbonate–potassium iodide in 50% yield: bp 92–93° (0.2 mm), $n^{22}D$ 1.5128.

The hydantoin[38] was recrystallized from ethanol and sublimed under vacuum: mp 236.5–237°.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.13. Found: C, 59.09; H, 6.14.

2,3-Dimethyl-7-methoxybenzofuran was prepared in 65% yield by cyclization of the above ketone with polyphosphoric acid: mp 46.5–47°.[39]

(38) Prepared by the general procedure of H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942).

(39) After the present work was completed, the preparation of this compound and of the above methoxyphenoxybutanone by nearly the same procedures was described by R. Boyer, *et al.*, *Bull. Soc. Chim. France*, 1003 (1963); they reported the benzofuran as melting at 38.5°.

***cis*-2,3-Dihydro-2,3-dimethyl-7-methoxybenzofuran.**—2,3-Dimethyl-7-methoxybenzofuran (3.53 g) was hydrogenated in 25 ml of glacial acetic acid with 1.05 g of 5% palladium–carbon. After 20.5 hr, the catalyst was removed by filtration and the reaction mixture was worked up in the usual way. The product was distilled through a short Vigreux column and collected in two fractions: 97–99° (1 mm) (2.07 g) and 102–103° (1 mm) (0.70 g). Vapor phase chromatography of the first fraction showed peaks at 3.9, 4.3, 6.4, 10.0, and 15.1 min. The peaks at 6.4, 10.0, and 15.1 min were in a ratio of 1.0:22.8:0.73, while the peaks at 3.9 and 4.3 min had areas amounting to about 1% of the total. The second fraction showed peaks at 10.0 and 15.1 min only, in a ratio of 5.9:1.0.

Samples of the peaks at 6.4, 10.0, and 15.1 min were collected by vpc. The material eluting at 15.1 min was identified as starting material, while the peak at 6.4 min was assumed to be a perhydrobenzofuran, since its infrared spectrum was devoid of bands attributable to unsaturation, but showed a very strong band at 1100 cm^{-1} and strong bands at 1075 and 1130 cm^{-1}. Collection of the peak at 10.0 min gave the *cis*-dihydro product, $n^{25}D$ 1.5311.

The nmr spectrum showed singlets at δ 3.78 (O–CH_3) and 6.62 (three aromatic protons); doublets at δ 1.14 (3-CH_3) (J = 7.2 cps), and 1.33 (2-CH_3) (J = 6.6 cps); an octet at δ 4.80 (O–CH–); and a quintet at δ 3.30 (Ar–C–H). The coupling constant J_{2H-3H} was 8.3 cps.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 8.03.

***trans*-5,7-Dichloro-2,3-dihydro-2-iodomethyl-3,4-dimethylbenzofuran (L).**—To a solution of 1.461 g of the methyl ether B-3 in 30 ml of carbon tetrachloride was added 0.97 g of iodine monochloride (Eastman Kodak Co.) in 3.0 ml of carbon tetrachloride. The addition was made over 40 min with stirring and cooling in ice water. After the addition was complete, the reaction mixture was allowed to stand at room temperature for 14 hr. The violet solution was decolorized by washing twice with 10% sodium thiosulfate solution. After further washing with water, the solution was dried, and the solvent was removed by evaporation at reduced pressure to leave 1.97 g of a crude solid, mp 87.5–102°. The crude product (1.035 g) was recrystallized from petroleum ether; 0.801 g (72% yield) of white crystals, mp 105–105.5°, was obtained. Further recrystallization did not change the melting point. From the mother liquors, an additional 0.021 g of impure L (mp 102–104.6°) was obtained as well as 0.132 g of a viscous oil.

The infrared spectrum showed strong bands at 1447, 1412, 1240, 1177, 1170, and 935 cm^{-1}, and medium bands at 1468, 1431, 1040, 847, and 743 cm^{-1}. The nmr spectrum showed singlets at δ 2.27 (Ar–CH_3) and 7.15 (Ar–H); a doublet at δ 1.39 (3-CH_3) (J = 7.0 cps); a multiplet centered at δ 4.52 (–O–C–H); and a complex band centered at δ 3.25 due to the proton on C-3 and the protons of the CH_2-I group. The coupling constant J_{2H-3H} was 3.2 cps.

Anal. Calcd for $C_{11}H_{11}Cl_2IO$: C, 37.01; H, 3.20. Found: C, 37.17; H, 3.01.

Dehydrohalogenation of 5,7-Dichloro-2,3-dihydro-2-iodomethyl-3,4-dimethylbenzofuran (L).—A solution of 0.209 g of compound L in 8 ml of 10% potassium hydroxide in 95% ethanol was refluxed for 48 min. The reaction mixture was then poured into 30 ml of water to precipitate a solid, which was collected and washed on the funnel with water, then allowed to dry in the air to yield 0.117 g of product: mp 92–93° (87% yield). On recrystallization from 95% ethanol, the melting point was raised to 95–95.5°. The infrared spectrum of this product was identical with that of 5,7-dichloro-2,3,4-trimethylbenzofuran (K), and no melting point depression was observed on mixing with the known K, prepared below.

Hydrogenation of *trans*-5,7-Dichloro-2,3-dihydro-2-iodomethyl-3,4-dimethylbenzofuran (L).—A solution of 0.203 g of compound L in 20 ml of methanol containing 0.062 g of anhydrous potassium acetate was hydrogenated at atmospheric pressure and room temperature over 0.108 g of 5% palladium on charcoal. After 38 min, the catalyst was filtered off through a Celite pad and the solvent was removed from the filtrate by evaporation at reduced pressure. To the liquid residue was added 10 ml of ether, and the potassium iodide was filtered off. Evaporation of the ether at reduced pressure gave 0.102 g of an oil. The infrared spectrum of this material was identical with that of I except for a weak, sharp band at 3520 cm^{-1}, apparently due to a small amount of phenolic product. The product was dissolved in 3 ml of petro-

leum ether, extracted twice with 1-ml portions of Claisen's alkali, washed with water, and dried. After removal of the solvent at reduced pressure, the residue was evaporatively distilled at 0.1 mm (bath temperature, 90–95°) to yield 0.56 g (42%) of a liquid. The infrared and nmr spectra of this material were identical with those of *trans*-5,7-dichloro-2,3-dihydro-2,3,4-trimethylbenzofuran (I). Vapor phase chromatography showed this product to be 99% pure, and its retention time was the same as that of known I.

Hydrogenation of the Crude Product Mixture from the Preparation of (L).—A solution of 0.200 g of the crude product, mp 87.5–102°, in 20 ml of methanol containing 0.106 g of anhydrous potassium acetate was hydrogenated at atmospheric pressure and room temperature over 0.103 g of 5% palladium on charcoal. After 1 hr, the catalyst was removed by filtration through Celite and the filtrate was evaporated at reduced pressure. The product was worked up as before. Vapor phase chromatography showed three main peaks at 11.3, 18.0, and 23.2 min in a ratio of 3.3:56:1.0. The peak at 18.0 min was assigned to the *trans* isomer I and that at 23.2 min to the *cis* isomer J on the basis of retention times observed for known samples under these conditions.

The compound eluted at 11.3 min was not identified; however, since the product did not arise during hydrogenation of pure L, it could not have arisen from L during hydrogenation of the crude product mixture. It, therefore, seems probable that it also did not arise from the corresponding *cis* isomer. Three very small peaks at 29.2, 44.7, and 60.8 min were also detected by vpc but were not investigated.

3-(2,4-Dichloro-5-methylphenoxy)-2-butanone (N) was prepared from 25.0 g of 2,4-dichloro-5-methylphenol, 15.0 g of 3-chloro-2-butanone,[40] 21.5 g of potassium carbonate, 0.24 g of potassium iodide, and 200 ml of acetone. After the usual work-up, recrystallization from petroleum ether at Dry Ice temperature gave 16.8 g (48% yield), mp 41.3–42.1°. The infrared spectrum (CCl_4) showed bands at 1727, 1249, and 1085 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.90. Found: C, 53.35; H, 4.98.

5,7-Dichloro-2,3,4-trimethylbenzofuran (K).—To 3 ml of ice-cold concentrated sulfuric acid was added 1.0 g of 3-(2,4-dichloro-5-methylphenoxy)-2-butanone (N). The reaction mixture was stirred for 4 min and was then poured onto 50 g of ice. The precipitate was extracted from the mixture with ether and the extract was dried. Evaporation of the ether and recrystallization from 95% ethanol gave 0.65 g (70% yield) of white crystals, mp 96–96.6°. The infrared spectrum showed strong bands at 1209, 1092, 920, 848, 792, and 765 cm^{-1}. The nmr spectrum showed singlets at 2.30 (3-CH_3), 2.40 (2-CH_3), 2.58 (4-CH_3), and 7.17 (Ar–H).

The analytical sample was prepared by recrystallization followed by sublimation *in vacuo*.

Anal. Calcd for $C_{11}H_{10}Cl_2O$: C, 57.67; H, 4.40. Found: C, 57.46; H, 4.61.

***cis*-5,7-Dichloro-2,3-dihydro-2-iodomethyl-3,4-dimethylbenzofuran (M).**—The phenol B-2 (1.02 g) was treated with 0.787 g of iodine monochloride in carbon tetrachloride, as in the preparation above. The oil was dissolved in 10 ml of boiling petroleum ether and the volume was reduced to 5 ml. On cooling to room temperature, 0.239 g of white crystals was obtained, mp 85–92°. The volume of the filtrate was reduced to 3 ml, cooled to room temperature, and then let stand in the refrigerator overnight. An additional 0.307 g of a mixture of white crystals was obtained, mp 59–61°, 86–90°. The first crop of crystals (mp 85–92°) was purified by recrystallization and shown to be identical to the *trans*-iodomethyl compound L by mixture melting point and infrared spectrum. The *cis*-iodomethyl compound was obtained from the second crop of crystals (0.307 g). These crystals were washed with 10 ml of boiling petroleum ether. The solution was separated by decantation from the crystals that did not readily dissolve, and the volume was reduced to 3 ml. The solution was allowed to stand in the refrigerator overnight. The resulting crystals were collected and treated once more in the same manner to give 0.174 g of white crystals, mp 64.5–65.5°. Further recrystallization did not change the melting point.

The nmr spectrum showed singlets at δ 2.25 (Ar–CH_3) and δ 7.10 (Ar–H); a doublet at δ 1.17 (3-CH_3) (J = 7.0 cps); a multiplet centered at δ 4.82 (–O–C–H); and a complex band centered at δ 3.42 due to the proton on C-3 and the protons of the CH_2–I group.

Anal. Calcd for $C_{11}H_{11}Cl_2IO$: C, 37.01; H, 3.20; I, 35.55. Found: C, 37.22; H, 3.23; I, 35.74.

Isolation of 2,2,4-Trimethyl-5,7-dichloro-2,3-dihydrobenzofuran (P).—2,4-Dichloro-5-methyl-6-(α-methylallyl)phenyl methyl ether (B-3, 9.76 g) was allowed to stand in concentrated sulfuric acid for 13.5 hr and was worked up in the usual way, giving a crude yield of 2.4 g; this was distilled in a short-path still at 120° (0.09 mm) and a total of 87 mg of crystalline material was obtained from the cold finger. This was crystallized twice from petroleum ether in a Dry Ice–acetone bath, giving 35.7 mg, mp 51.5–53.5°; the infrared spectrum was the same as that of a sample isolated by vpc.

Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.15; H, 5.23. Found: C, 57.09; H, 5.25.

The nmr spectrum showed six protons at δ 1.48, three at δ 2.15, two at δ 2.94, and one at δ 7.08, all unsplit.

2,4-Dichloro-5-methylphenyl-β-methylallyl ether (R) was prepared in 85% yield from 9.77 g of the phenol, 5 g of β-methylallyl chloride, 8 g of potassium carbonate, and 100 mg of potassium iodide in 25 ml of acetone; it boiled at 95° (0.09 mm) and showed the expected infrared and nmr spectral properties.

Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.15; H, 5.23. Found: C, 57.14; H, 5.15.

2,4-Dichloro-5-methyl-6-(β-methylallyl)phenol (Q) was prepared from the above ether in 88% yield by refluxing in dimethylaniline and working up in the usual way; it boiled at 108° (0.1 mm) and could be obtained crystalline, mp 38.5–40°.

Anal. Calcd: as above. Found: C, 57.39; H, 5.22.

The phenol Q was cyclized to P in 75% yield by allowing 1.464 g of Q to stand in 26 ml of concentrated sulfuric acid for 30 min, and working up in the usual way. The sample of P prepared in this way showed the same melting point and spectral properties (infrared and nmr) as the sample isolated from the cyclization of the ether B-3.

(40) P. J. C. Fierens, *Bull. Soc. Chim. Belges*, **64**, 772 (1955).