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Benzofurans from 2-Ethylphenols

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Substituted 2-ethylphenols when heated at or above 550°C produce substituted benzofurans along with other products. 4-Methyl-, 4-ethyl-, 4,5-dimethyl, 4-fluoro-, 6-fluoro-, 4-chloro-, 6-chloro-, 4,6-dichloro-, and 4-bromo-2-ethylphenols gave the appropriately substituted benzofurans. Substitutent loss was observed in several cases but was most pronounced with the bromo-substituent. Substituent rearrangement with these reactants was absent. Side-chain substitution as in 2-propylphenol gave 2-methylbenzofuran along with some 3-methylbenzofuran. Rearrangements of furan ring substituents were common. 2-Ethylanisole also undergoes the same reaction. 2-Ethylanisole-4-*d* cyclized to benzofuran-5-*d* without scrambling. Various catalysts and carrier gases were examined, of which carbonyl sulfide was most selective for benzofuran formation.

INTRODUCTION

Dehydrocyclization of 2-ethylphenol at or above 550°C is a known method for producing benzofurans (*1–7*). Only three 2-alkylphenols, *viz.*, 2-ethyl-, 2-allyl-, and 2-isopropylphenol, have been successfully

converted by this reaction to benzofurans in good yield and with good selectivity. Catalysts for this reaction have been chosen most often on the assumption that this reaction goes by a dehydrocyclization mechanism (*8*). These catalysts have almost always been types that are effective for cyclization and aromatization of paraffins. Recently, however, Boswell and co-workers (*1*) reported that dehydrogenation catalysts (Pt/Al_2O_3, Rh/Al_2O_3) severely poisoned with hydrogen sulfide effectively produce benzofuran from 2-ethylphenol under almost identical conditions. Further, the fact that hydrogen sulfide over magnesium oxide was also very effective led us to question the generally held view that catalytic dehydrogenation is a mechanistic requirement of this reaction.

The scope of this reaction is unknown. The generally poor selectivities for benzofurans that have been found (*2, 3, 5, 6*) are most likely related to the instability of reactants and products under the very severe reaction conditions. Since little information concerning thermal stabilities of various 2-alkylphenols and substituted benzofurans is available, the synthetic utility of this reaction up to now has been questionable, as witnessed by the fact that only one benzofuran with a substituent on the benzene ring has ever been prepared by this method (*3*), and even that gave very poor yields.

We reexamined the cyclization of 2-alkylphenols and report new data that significantly expands the synthetic scope and chemical understanding of this type of cyclization. The conversion patterns and product selectivities for a large number of previously unreported reactants are given. The influence of thermal stability of reactants and products on the selectivity is discussed. The role of catalysts and carrier gases in this reaction are considered. We

also reexamined some product analyses that were reported earlier.

Experimental Methods

Materials

Catalysts. The chromia-alumina was Harshaw Cr 0205; its surface area (SA) was 60 m^2/g. Magnesia was Harshaw 0601 (SA = 21 m^2/g). The alumina was prepared by the method of Pines (*9*), surface area 200 m^2/g. All catalysts were pelleted and sized to 8/14 mesh before activation in air for 1 hr at the temperature of the reaction.

2-Ethylphenols. These were prepared by a sequence of steps, beginning with substituted phenyl acetates, which were rearranged in the Fries reaction to the 2-hydroxyacetophenones. Clemmensen reduction of these hydroxyacetophenones gave the starting materials. Details of the preparation will be described elsewhere. Givens, E. N., Venuto, P. B. and Alexakos, L. G., *J. Chem. Eng. Data,* in press.

2-Ethylanisoles. 2-Ethylanisole was prepared by reacting equimolar amounts of 2-ethylphenol and dimethyl sulfate (*10*) (bp 185°, n_D^{20} 1.51490, 82% yield).

The 4-bromo-2-ethylanisole was prepared by reacting the phenol with dimethyl sulfate (*10*). The product was distilled (bp 80–81° (0.2 mm) lit. (*11*) bp 123 (17 mm), center cut, 63% yield). The mass spectrum showed parent ions at *m/e* 214 and 216 with fragment ions at *m/e* 201 and 199.

The 2-ethylanisole-4-*d* was prepared starting with 4-bromo-2-ethylphenol. The Grignard was prepared by refluxing 12.7 g (59 mmoles) of 4-bromo-2-ethylanisole in 150 ml of tetrahydrofuran with 2.4 g (0.065 g-atoms) of magnesium turnings for 2 hrs. After cooling 5 ml of D_2O was added slowly while stirring. The solvent was separated from the white precipitate, wasted with water, dried over magnesium sulfate and evaporated leaving an oil (6.2 g, 78% yield). A center cut was separated on distillation. The mass spectrum showed a parent ion at *m/e* 137 and fragment ions at *m/e* 122 ($M-CH_3$) and *m/e* 92 ($M-CH_3-CH_2O$). The infrared spectrum showed bands at 2970(s), 2940(s), 2880(w), 2840 (m), 1600(doublet, s), 1500(s), 1480(s), 1240(s), 1170(s), 1135(s), 1040(s), 905(m), 820(s), 750(m), 730(m), and 650(s) cm^{-1}.

2,6-Dimethylbenzofuran. Allyl 3-methylphenyl ether was prepared from *m*-cresol and 3-bromo-1-propene with potassium carbonate in acetone (*12*) (bp 57° at 1 mm, n_D^{20} 1.5175, 92% yield; lit. (*13*) bp 81–84° at 3 mm, n_D^{20} 1.5180). The ether was subjected to the Claisen rearrangement and the phenolic product separated by dissolving in 20% sodium hydoxide solution. After acidifying the product was treated directly with concentrated hydrobromic acid in acetic acid under reflux. The reaction mixture was poured into water and extracted with hexane. The product after distillation was found to be a 3:1 mixture of 2,3-dihydro-2,6-dimethylbenzofuran and 2,3-dihydro-2,4-dimethylbenzofuran.* The mixture was dehydrogenated to the corresponding benzofurans and separated by preparative GLC.

Apparatus, Procedure, and Analyses

All reactions were effected in Vycor glass tubular reactor systems that have been described in detail elsewhere (*15*). The reactants were flashed into the carrier gas and swept through the catalyst bed. The reactor effluent was condensed by passing through a water condenser and analyzed by GLC. The reaction conditions for the individual substituted 2-ethylphenols are shown in Table 1. Several of the 2-ethylphenols were diluted with an equal volume of benzene before passing into the reactor. The effluent was dissolved in hexane and extracted with 10% sodium hydroxide solution or chromatographed on alumina with hexane to remove the phenolic products. The benzofuran product mixture was separated by preparative gas chromatography. Elemental analysis (Table 2), infrared (Table 3), NMR† and mass spectrometry (*17*) of the benzofurans agreed with the expected structures. Conversions and product distributions are based on recovered

* Previously this sequence of steps was reported to give only the 2,6-dimethyl isomer (*13, 14*).

† The NMR will be discussed at length elsewhere.

TABLE 1
PRODUCTS FROM THE REACTION OF 2-ETHYLPHENOL AT 600–700°

Catalyst	Gas[a]	Temp.	Mole ratio gas/2-ethylphenol	LHSV[b]	Conv.[c]	Products (wt %)[d] Phenol	Benzofuran	*o*-Cresol	Other[e]
Quartz chips	N_2	685	2	0.25	94	19	38	26	16
	COS	700	2	0.25	84	9	54	31	4
	H_2S	680	2	0.25	89	9	57	29	5
	SO_2	690	2	0.25	85	17	41	31	11
	SO_2	650	2	0.25	34	20	42	30	7
	H_2S	645	2	0.25	44	13	52	31	4
	COS	625	2	0.25	32	17	45	32	5
Chromia–alumina[f]	N_2	600	7	2	28	8	84	6	2
	H_2S	600	7	2	40	4	89	4	3

[a] Flow rate, 70 ml/min.
[b] Volume (ml) liquid charge per hour for each volume of catalyst.
[c] Conversions are based on condensed effluent.
[d] Liquid products only; deposited material on catalyst is not included.
[e] Includes benzene, toluene, ethylbenzene, and styrene as main constituents.
[f] Harshaw catalyst Cr0205.

condensate. Recoveries were good in all cases. The infrared data heretofore unreported demonstrate the internal consistency in the structural assignments of the 5- and 7-substituted compounds. The high resolution NMR data are definitive in the final structural assignments.

RESULTS AND DISCUSSION

2-Ethylphenol. 2-Ethylphenol reacts very much the same over quartz chips at 700°C when either nitrogen, carbonyl sulfide, hydrogen sulfide, or sulfur dioxide is used as carrier gas (Table 1). Based on these results the previous supposition that a catalytic dehydrogenation function is necessary (*8*) seems unfounded. The fact that benzofuran forms quite well in nitrogen demonstrates a definite thermal reaction pathway. The similar product selectivities observed over chromia–alumina at 600°C in nitrogen and hydrogen sulfide indicate no special retarding effect by the hydrogen sulfide. If the dehydrogenation were catalyzed by the chromia–alumina, the enormous amounts of hydrogen sulfide used here would be ex-

TABLE 2
ELEMENTAL ANALYSIS

Benzofuran	Calc C	Calc H	Found C	Found H	M[a]
5-Methyl-[b]	81.79	6.10	81.80	6.23	132
5-Ethyl-[b]	82.16	6.90	82.16	6.87	146
5,6-Dimethyl-[b]	82.16	6.90	81.97	6.82	146
5-Chloro-[b]	62.97	3.30	62.57	3.19	152
7-Chloro-[b]	62.97	3.30	63.48	3.39	152
5,7-Dichloro-[c]	51.38	2.16	52.05	2.38	186
5-Fluoro-	70.58	3.70	70.40	3.88	136
7-Fluoro-	70.58	3.70	70.70	3.87	136

[a] Parent ion (M^+) m/e value.
[b] Stoermer [*Ann.* **312,** 237 (1900)] prepared these compounds by other methods.
[c] Kurdukan and Rao [*Proc. Indian Acad. Sci.*, Sect. A. **58,** 336 (1963); Chem. Abstr. **60,** 11972g (1964)] reported preparation of this compound by another method.

TABLE 3
INFRARED SPECTRA OF BENZOFURANS (cm^{-1})

Benzofuran[a]																			
5-Ethyl-	1260		1200		1130	1110		1030		882			815		770		740			
5-Methyl-	1265		1200		1130	1110		1032		885			805		765		735		603	
5-Fluoro-	1250		1185		1125	1105		1040	950	860			808		765	755	732		615	
5-Chloro-	1260		1172		1135	1110	1070	1035		875			808		765		735	695		
5-Bromo-	1260		1170		1133	1110	1050	1032		870			805		760		730	670	600	580
5-Methoxy-	1275		1200		1135	1120		1020		875		830	800	780	750		723			
7-Fluoro-	1270	1240	1190		1115		1045	1035		870		835	780				720			
7-Chloro-	1260	1228	1175	1148	1130			1030	955	870		835	790				730			
5,7-Dichloro-			1168		1125			1025		868		840			765		730			590
5,6-Dimethyl-	1290		1165		1125			1030	1000	870	850	835	790				730			

[a] Liquids run neat, solids as a suspension in a potassium bromide pellet.

pected to have some negative effect on this reaction. The thermal effect appears unquestionable. The effect of these catalysts and sulfur-containing gases on this reaction is unclear.

Substituted 2-ethylphenols. A number of substituted 2-ethylphenols were subjected to this reaction. The halogen and alkyl substituted 2-ethylphenols all gave the expected halo- or alkylbenzofurans, although in widely varying yields (Table 4). The 4-methyl- and 4,5-dimethyl-2-ethylphenols gave their respective substituted benzofuran products with little side reaction. For example, the 4-methyl substrate had less than 2% impurity present in the benzofuran products. The 2,4-diethylphenol was not as selective as the methyl reactants. It produced considerable amounts of 5-methylbenzofuran along with the expected 5-ethylbenzofuran. Also, trace amounts of 2- and 4-ethylphenols were also produced. These by-products are logically the result of cracking and dealkylation reactions occurring during the reaction. Since so much 5-methylbenzofuran and so little phenol product is formed, cracking probably occurs primarily to the ethylbenzofuran, otherwise substantial 4-ethyl-2-methylphenol would be present. Random cracking of the two ethyl groups would be expected thereby forming this phenol which could not convert to benzofuran product. From 4,5-dimethyl-2-ethylphenol the minor amounts of phenols produced were not identified because of their small quantity. These were mostly products of dealkylation and cracking reactions.

The halogen substituted 2-ethylphenols cyclized selectivity in the order F > Cl > Br. The 4-bromo-2-ethylphenol gave a product mixture which contained a considerable amount of 2-ethylphenol, even though the reaction was only run at 500°C. Some 5-bromobenzofuran was formed, but the main reaction path was one of dehalogenation of the reactant. The chloro-2-ethylphenols were much more selective (60%). Dehalogenation was evident from the formation of both 2-ethylphenol and benzofuran. The 4,6-dichloro-2-ethylphenol was less selective in forming 5,7-dichlorobenzofuran. The dehalogenated products, 5- and 7-chlorobenzofuran (5 isomer in excess) and benzofuran, were also formed along with several phenols. The fluoro-2-ethylphenols were very selective. Only minor amounts of defluorinated product were formed.

In all of these reactions we found no evidence for any positional rearrangements on the benzene ring even though considerable cracking, dehalogenation, and dealkylation were observed. This is surprising if the severe conditions of these reactions are considered.

Other 2-alkylphenols. We also examined 2-isopropyl-5-methylphenol (thymol **I**) and 2-(*n*)-propylphenol. Thymol (**I**), reported previously (*3*), reacted completely at 630°C. *m*-Cresol was the only phenol isolated, which agrees with the data of Hansch and co-workers (*3*). In contrast, in the benzofuran fraction, three products were found: 3,6-dimethyl- (**II**), 6-methyl- (**III**), and 2,6-dimethylbenzofuran (**IV**). Only the expected 3,6-isomer (**II**) has been reported (*3*). **III** was the major product in this reaction. The absence of benzofuran illustrates the tenacity with which the methyl group holds to the benzene ring, whereas a methyl group on the furan ring, as in **II** or **IV**, is apparently lost quite readily. Unequivocal identification of **IV** was made by comparing its infrared, mass spectrum and GLC retention times with an authenic sample prepared separately.

2-Propylphenol at 600° was 72% converted with COS. Phenolic products were formed along with benzofuran and a mixture of 2- and 3-methylbenzofuran. These two compounds could not be separated, but the NMR showed the presence of both isomers, the 2-isomer being the main component. The presence of two unresolved peaks by GLC on a diethylene glycol adipate column also gave firm evidence of the presence of two isomers. The presence of a sizable amount of benzofuran again illustrates how easily alkyl substituents on the furan ring are lost.

The origin of **III** and **IV** from **I** was considered. **II**, which had been isolated from the thymol run, when treated under the

TABLE 4

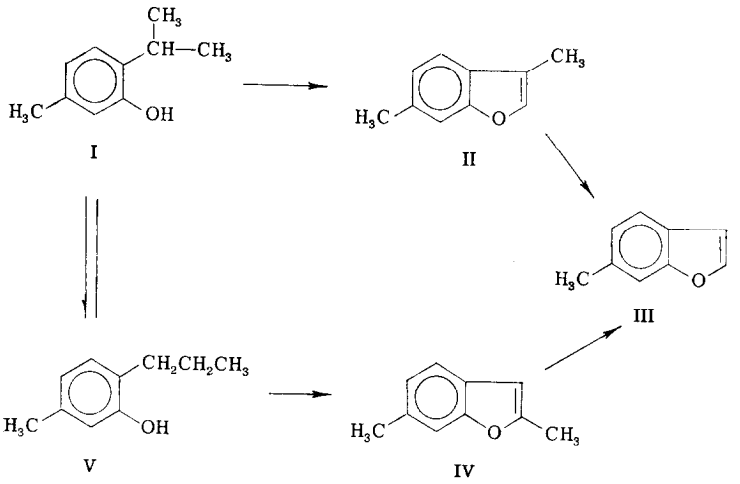
CYCLIZATION OF SUBSTITUTED 2-ETHYLPHENOLS AND THEIR PRODUCTS (wt %)[a]

Carrier gas	4-X-6-Y-2-Ethylphenol[b] X	Y	Catalyst	Temperature	Conversion (%)	Product distribution: 5-X-7-Y-Benzofuran X	Y	(%)	Others			(%)
COS	CH_3	H	MgO	600	60	CH_3	H	90				
	C_2H_5	H	MgO	600	70	C_2H_5	H	62	5-Methylbenzofuran			25
	Cl	Cl	MgO	550	54	Cl	Cl	42	5- and 7-chlorobenzofuran			24
									Benzofuran			12
									Phenol and 2-ethylphenol			19
	CH_3 (5-CH_3)	H	MgO	600	50	CH_3 (5-CH_3)	H	90	5- and 6-methylbenzofurans			0.5
									Other phenols			12
	F[c]	H	MgO	600	90	F	H	90	Phenol			6
									Benzofuran			3
	H	F	MgO	630	70	H	F	94	Benzofuran			3
										500°C	450°C	
	Br	H	MgO	500	98	Br	H	18	Benzofuran	8	1	
				450	70	Br	H	3	Phenol	17	18	
									2-Ethylphenol	43	73	
									Other	12	4	

H_2S	Cl	H	Chromia on alumina[d]	600	95	Cl	H	60	Benzofuran	25
									2-Ethylphenol	5
									Other peaks	10
	H	Cl	Chromia on alumina[d]	600	93	H	Cl	60	Benzofuran	25
									2-Ethylphenol	5
									Other peaks	10
COS	Thymol		MgO	630	100				*m*-Cresol	18
									6-Methylbenzofuran	54
									2,6-Dimethylbenzofuran	7
									3,6-Dimethylbenzofuran	21
	2-Propylphenol		Quartz chips	600	72				Benzofuran	18
									2- and 3-Methylbenzofuran	49
									Phenol	Negligible
									Other phenols	33

[a] Liquid products only; the deposited material on catalyst is not included.
[b] 50% (wt) in benzene.
[c] Charge contained 50% 4-fluorophenol, conversion applies only to 4-fluoro-2-ethylphenol.
[d] Harshaw catalyst Cr 0205.

same reaction conditions, produced **III** but no **IV** as shown in the scheme. This suggests that dealkylation of **II** (and **IV**) will give **III**. An alternate explanation that **III** forms from 2-ethyl-5-methylphenol seems unlikely since it would require its formation from **I** via a very selective cracking reaction. **II** and **IV** could form by cyclization of **I** and 2-*n*-propyl-5-methyl-phenol (**V**), respectively, assuming an equilibrium between **I** and **V**, which is not unexpected (*16*).



o-Ethylanisoles. *o*-Ethylanisole when heated at 600°C also formed benzofuran (Table 5). Regardless of whether nonacidic alumina (*9*) or chromia–alumina was used as reactor packing, in the presence of any of the gases we tested, *viz.*, H_2, CH_4, CO_2, COS, and H_2S, benzofuran was always formed, although in greatly varying amounts. Other catalysts would also be expected to give benzofuran under these conditions. The product depends on how the methoxyl groups fragment. If the O–CH_3

TABLE 5
CONVERSION (%) OF *o*-ETHYLANISOLE AT 600°C

Catalyst:	Chromia–alumina[b]		Alumina[c]			
Gas:[a]	COS	H_2S	H_2	CH_4	CO_2	COS
Conversion:	100	90	88	89	95	94
Ethylbenzene	7	53[d]	12	4	4	7
Styrene	14		3	4	4	8
Anisole			3			
Phenol	2	—	13	3	4	2
Benzofuran	57	21	11	14	14	19
o-Cresol	2	—	4	5	6	2
o-Ethylphenol	18	15	43	54	52	55
Unknown[e]			8	10	9	6

[a] LHSV = 2; gas/*o*-ethylanisole = 7 (mole ratio); quartz preheater with catalyst diluted to 5 ml with quartz.

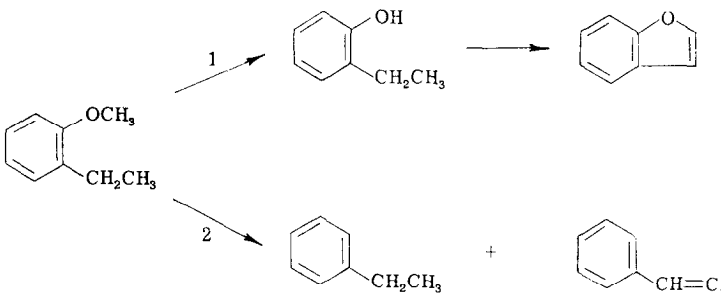
[b] Harshaw Cr 0205.

[c] B. H. Davis prepared: Catalyst 3 of H. Pines, Method B, Ref. (*9*).

[d] Also includes styrene.

[e] Benzene, toluene, anisole (except for H_2/alumina), *o*-anisaldehyde, and phenetole were absent or less than 1%.

bond is broken (Path 1) and 2-ethylphenol or a related phenoxy radical is formed, cyclization would ultimately result in benzofuran formation. Obviously, this is an important reaction pathway because of the large amount of 2-ethylphenol that is formed. Loss of the methoxyl from the



ring (Path 2) which involves a cleavage of the aryl–oxygen bond, leads to ethylbenzene and styrene. In the runs we have made, carbonyl sulfide gave the best selectivity for benzofuran over chromia–alumina, which suggests an important role for the catalyst. However, the thermal reaction is emphatically shown with methane and carbon dioxide over alumina where a catalytic dehydrogenation function is absent.

At 600° in the presence of carbonyl sulfide, 2-ethylanisole-4-*d* over MgO gave benzofuran-5-*d* without any evidence of deuterium scrambling. Presumably, 2-ethylphenol with COS under these conditions would also fail to give scrambled products since a common intermediate in benzofuran formation from the anisole and phenol substrates is likely. This is dramatic evidence that not only do alkyl and halogen substituents on the aromatic rings in both the starting phenol and the resulting benzofuran not rearrange but the hydrogen atoms also do not rearrange or exchange. Therefore, hydrogen exchange reactions commonly found on dehydrogenation catalysts are not found here.

Conclusions

1. 2-Ethylphenol and 2-ethylanisole cyclize well under thermal conditions. Good selectivity occurs in the presence of either carbonyl sulfide or hydrogen sulfide over selected catalysts.

2. 2-Ethylphenols bearing halogen substituents were converted to the corresponding benzofurans. Selectivities, which decreased in the order F > Cl > Br, reflect the degree of dehalogenation that occurs.

3. Alkyl substituent loss from the furan ring was a major factor when starting with 2-*n*-propyl- or 2-isopropylphenols. Alkyl substituent loss from the benzene ring was minor.

4. Alkylbenzofurans under these conditions are subject to thermal cracking, i.e., ethyl → methyl.

5. No evidence for rearranged benzene substituents in the benzofurans was found. However, a considerable amount of rearrangement of methyl groups on the furan ring in these benzofurans was found. These are evidently free radical aryl rearrangements occurring on the alkyl substituents.

6. 2-Ethylanisole-4-*d* cyclizes to give benzofuran-5-*d* without any evidence for deuterium scrambling or loss.

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