200. *Acid-catalysed Rearrangements of Alkyl Aryl Ethers. Part IV.*[1] *Rearrangement of Alkyl Tolyl Ethers by Aluminium Chloride.*

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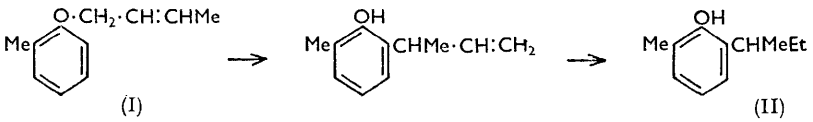
The rearrangements of isopropyl and s-butyl *o*- and *p*-tolyl ethers with aluminium chloride have been studied and the products compared with those formed by alkylation of the corresponding cresols under similar conditions. A number of alkylcresols have been synthesised as reference compounds.

In an earlier paper [2] we described the rearrangements of alkyl phenyl ethers in presence of aluminium chloride. This work has now been extended to some alkyl tolyl ethers.

The only previous report of such a rearrangement concerned isopropyl *p*-tolyl ether; Smith [3] obtained only 2-isopropyl-4-methylphenol by treating this ether with aluminium chloride. Sowa and his collaborators [4] rearranged the same ether with boron trifluoride as catalyst; they also obtained 2-isopropyl-4-methylphenol, together with *p*-cresol, 2,6-di-isopropyl-4-methylphenol, and two compounds which they described as the isopropyl ethers of 2-isopropyl- and 2,6-di-isopropyl-4-methylphenol. The last claim seems dubious, for no products of this nature have ever been obtained by acid-catalysed rearrangement of alkyl aryl ethers.

We have re-examined the reaction reported by Smith, and have also studied the analogous rearrangements of isopropyl *o*-tolyl ether and of s-butyl *o*- and *p*-tolyl ether; and we have compared the products from the rearrangements of the *p*-tolyl ethers with those obtained by reaction of the corresponding alkyl chloride and *p*-cresol under similar conditions.



(I) (II)

Preparation of Reference Compounds.—In order to analyse our reaction mixtures by infrared spectroscopy, we had first to synthesise pure samples of the possible rearrangement products.

Addition of 4-methoxy-3-methylphenylmagnesium bromide to ethyl methyl ketone, followed by dehydration and reduction, gave 4-s-butyl-2-methylphenol; and 2,6-di-isopropyl-4-methylphenol was prepared likewise from 3-isopropyl-4-methoxy-5-methylphenylmagnesium bromide and acetone. 2-s-Butyl-4-methyl-, 6-s-butyl- and 4,6-di-s-butyl-2-methyl-, and 2,6-di-s-butyl-4-methyl-phenol were prepared by Claisen rearrangement [5] of the appropriate but-2-enyl ethers, followed by hydrogenation, *e.g.*, (I) ⟶ (III). The infrared spectra of these compounds are included in D.M.S. publications.

Rearrangements and Alkylations.—These were carried out by adding an equimolecular amount of aluminium chloride in small portions to the ether, or to a mixture of the phenol

[1] Part III, *J.*, 1959, 4090.
[2] Part I, *J.*, 1959, 4080.
[3] Smith, *J. Amer. Chem. Soc.*, 1934, **56**, 717.
[4] Sowa, Hinton, and Nieuwland, *ibid.*, 1933, **55**, 3402.
[5] Claisen and Tietze, *Ber.*, 1926, **59**, 2344.

and alkyl chloride, during 30 min., with external cooling so that the temperature remained in the range 15—25°. No solvent was used. The products were separated by treatment with alkali into alkali-soluble and alkali-insoluble components; these were fractionally distilled under reduced pressure through a 20 cm. Dixon gauze column, and the fractions were analysed by infrared spectroscopy [in carbon tetrachloride solution (2% w/w) on a Grubb-Parsons G.S. 2A double-beam grating spectrometer over the range 820—1100 cm.$^{-1}$].

Results

The products in each case consisted of a mixture of cresol, monoalkylcresols, and dialkylcresols. The same compounds were obtained both from rearrangement of a given ether and from alkylation of the corresponding cresol.

p-*Tolyl Series.*—The monoalkylcresol fraction in each case contained two isomers. One was the 2-alkyl-4-methylphenol; the second isomer in the isopropyl series gave an aryloxyacetic acid and phenylurethane with melting points identical with those reported [6] for the derivatives of 3-isopropyl-4-methylphenol, and so the second isomer was assumed in each case to be the 3-alkyl-4-methylphenol. The dialkylcresol fraction contained at least two components, one of which was shown by infrared spectroscopy to be the 2,6-dialkyl-4-methylphenol. Two lines of argument suggest that the only other compound present in significant amount was the corresponding 2,5-dialkyl-4-methylphenol. First, we could reconstruct the infrared spectrum of the second component by subtracting the spectrum of the 2,6-dialkyl-4-methylphenol from that of the mixture; using this spectrum we could then analyse fractions containing variable proportions of the two isomers. The fact that these analyses were successful, and that the spectra of the mixtures could be reproduced in such terms, implies that the second component was indeed a single compound. Secondly, the following theoretical considerations suggest that the main products of reaction should have been the 2,6- and the 2,5-dialkyl-4-methylphenol. Dialkylcresols must arise by alkylation of monoalkylcresols; since in *p*-cresol *ortho*- are more reactive than *meta*-positions, it is unlikely that 3,5-dialkyl-4-methylphenol

TABLE 1. *Products (moles %, based on reactant) obtained by rearranging isopropyl and s-butyl* p-*tolyl ethers, and by alkylating* p-*cresol with isopropyl and s-butyl chloride, in presence of aluminium chloride* (1 *mole*) *at* 15—25°.

		Monoalkyl-*p*-cresol		Dialkyl-*p*-cresol		2,5-Dialkyl-
Reaction	*p*-Cresol	2-	3-	2,6-	2,5-	phenol
Rearrangement $PrOC_7H_7$	41·4	24·0	trace	7·8	trace	14·7
$PrCl + C_7H_7OH$	49·1	20·5	trace	4·6	trace	17·4
Rearrangement $BuOC_7H_7$	43·8	29·0	trace	7·2	trace	12·4
$BuCl + C_7H_7OH$	44·6	23·7	trace	6·0	trace	17·3

would be produced in significant amount. Moreover, formation of a 2,3-dialkyl-4-methylphenol should be severely hindered. Therefore 2,6- and 2,5-dialkyl-4-methylphenols should be the main constituents of the dialkylcresol fraction, and so it was assumed that the second component was the 2,5-dialkyl-4-methylphenol.

A fifth component was in each case obtained crystalline from fractions intermediate between the mono- and the dialkyl-cresols; its analyses indicated a dialkylphenol, the methyl group of the cresol apparently having been lost. These compounds were not 2,4- or 3,4-dialkylphenols and so could not have been formed by a direct replacement of methyl by alkyl; nor could they have arisen by demethylation followed by alkylation, since neither phenol nor a monoalkylphenol was formed in the reaction. Therefore these fractions must have arisen by demethylation of a dialkylcresol. Since the only dialkylcresols formed (see above) are probably the 2,6- and the 2,5-isomers, the fifth fractions must be 2,5- or 2,6-dialkylphenols. They were, however, different from the known 2,6-isomers; therefore they can be formulated with some certainty as 2,5-di-isopropylphenol and 2,5-di-s-butylphenol. Neither of these compounds has been characterised; the latter has been described in a patent,[7] but no physical properties were quoted.

The ready demethylation of 2,5-dialkyl-4-methylphenols, in contrast to the apparent

[6] Carpenter and Easte, *J. Org. Chem.*, 1955, **20**, 401.
[7] Moyle and Vand Duzee, U.S.P. 2,207,753.

stability of 2,6-dialkyl-4-methylphenols, is not surprising. Such reactions are essentially electrophilic replacements of methyl by H^+; in the former case the methyl will be activated both by the *p*-hydroxyl and an *o*-alkyl group. The reaction will be further facilitated by steric repulsions between the methyl and the adjacent alkyl group.

Table 1 summarises the products obtained.

o-*Tolyl Series*.—Three monoalkylcresols were obtained from each ether, or by alkylation of *o*-cresol. Two of these were the 4- and the 6-isomer. Spectroscopic comparison showed the third isomer in the isopropyl series to be 5-isopropyl-2-methylphenol. The dialkylcresol fraction consisted in each case of a 4,6-dialkyl-2-methylphenol, together with at least one other isomer. Since the spectra deduced for the latter by difference from fractions of varying composition agreed, it is likely that only one other isomer was present in significant amount. Since the position *para* to hydroxyl in *o*-cresol is much the most reactive, and since formation of a 3,4-dialkyl-2-methylphenol would be sterically hindered, it seems likely that the second component was in each case a 4,5-dialkyl-2-methylphenol. This structure was supported by the presence of infrared bands at 10·8, 11·6, and 12·0 μ.

Table 2 records the products from rearrangement of isopropyl and s-butyl *o*-tolyl ether.

TABLE 2. *Products (moles %, based on reactant) obtained by rearranging isopropyl and s-butyl* o-*tolyl ether in presence of aluminium chloride* (1 *mole*) *at* 15—25°.

		Monoalkyl-2-methylphenol			Dialkyl-2-methyl phenol	
	o-Cresol	4-	5-	6-	4,6-	4,5-
Rearrangement of $PrOC_7H_7$	29·2	42·1	Trace	7·2	(Not determined)	
Rearrangement of $BuOC_7H_7$	29·4	40·2	(Not determined)	7·1	14·3	

DISCUSSION

Tables 1 and 2 show that the products formed in these reactions are consistent with an intermolecular mechanism involving free carbonium ions as intermediates; moreover, the same products seem to be formed both by rearrangement of an ether and by alkylation of the corresponding cresol.

The formation of 2,5-dialkylphenols as major products of rearrangements of *p*-cresol ethers and by alkylation of *p*-cresol is interesting; the molar yields were almost double those of the corresponding 2,6-dialkyl-4-methylphenols. This must imply that more 2,5-dialkyl-4-methylphenol is formed in the reaction, and that, unlike the 2,6-isomer, it very readily undergoes demethylation. Both these factors can be understood theoretically. Thus further alkylation of a 3-alkyl-4-methylphenol should occur very readily in the 6-position (*ortho* to hydroxyl and *para* to alkyl), while further alkylation of a 2-alkyl-4-methylphenol could occur preferentially in the 5-position (*ortho* to methyl; *para* to alkyl) rather than in the 6-position (*ortho* to hydroxyl but *meta* to both alkyl and methyl). Thus dialkylation of *p*-cresol might well be expected to give more 2,5- than 2,6-dialkyl-4-methylphenol.

The demethylation under Friedel–Crafts conditions is an electrophilic replacement of methyl by H^+. Such a process should be facilitated by $-E$ or $-I$ groups in the *ortho*- or *para*-position, and so should occur much more readily with the 2,5-dialkyl isomer (*p*-hydroxyl and *o*-alkyl) than with the 2,6-dialkyl isomer (*p*-hydroxyl only). Moreover, steric repulsion between the methyl and the adjacent alkyl group must further facilitate displacement of methyl from 2,5-dialkyl-4-methylphenol.

EXPERIMENTAL

Microanalyses were carried out by Alfred Bernhardt, Max-Planck-Institut, Mülheim, Germany, and the Microanalytical Laboratory, Imperial College, South Kensington, London, S.W.7.

Alkyl aryl ethers, prepared according to Niederl and Natelson's method,[8] were as follows:

[8] Niederl and Natelson, *J. Amer. Chem. Soc.*, 1931, **53**, 1928.

isopropyl 2-methylphenyl ether, b. p. 68°/2 mm., n_D^{18} 1·4984; s-butyl 2-methylphenyl ether, b. p. 205°, n_D^{17} 1·4956; isopropyl 4-methylphenyl ether, b. p. 85°/6 mm., n_D^{17} 1·4939; s-butyl 4-methylphenyl ether, b. p. 214°, n_D^{18} 1·4939.

Aryloxyacetic acids were prepared as described earlier.[2]

Phenylurethanes were prepared according to the method of Steinkopf and Hopner [9] and recrystallised from light petroleum (b. p. 60—80°).

4-s-Butyl-2-methylphenol.—Methylation of 4-bromo-2-methylphenol,[10] m. p. 64° (Found: Br, 42·5. Calc. for C_7H_7OBr: Br, 42·7%), gave 4-bromo-2-methylanisole, m. p. 68°, the Grignard reagent from which (25 g.) in ether (150 ml.) was treated with ethyl methyl ketone (16·8 g.) in ether (50 ml.). After 24 hr. water was added, the ether layer evaporated, and the residue boiled under reflux for 10 hr. with acetic anhydride (150 ml.). Addition of water and ether-extraction gave 3-methyl-4-(1-methylpropenyl)anisole, b. p. 79°/0·6 mm., n_D^{19} 1·5460, which on hydrogenation over 10% palladised charcoal in ethanol at 3 atm. gave 4-s-butyl-2-methylanisole, b. p. 215°, n_D^{19} 1·5052. Demethylation with acetic anhydride–hydriodic acid gave 4-s-butyl-2-methylphenol, b. p. 238°, n_D^{18} 1·5214 (Found: C, 80·3; H, 9·7. Calc. for $C_{11}H_{16}O$: C, 80·4; H, 9·8%) (aryloxyacetic acid, m. p. 97—98°; phenylurethane, m. p. 123°).

6-s-Butyl-2-methylphenol.—A solution of but-2-enyl *o*-tolyl ether, b. p. 61°/0·3 mm., n_D^{19} 1·5172 (34 g.), in diethylaniline (200 ml.) was boiled under reflux for 5 hr. When cold, the solution was poured into hydrochloric acid and extracted with light petroleum (b. p. 40—60°). The hydrocarbon layer was extracted with Claisen solution (350 g. of potassium hydroxide in 250 ml. of water, made up to 1 l. with methanol); acidification of the extract, recovery of the phenol, and distillation gave 2-methyl-6-1′-methylallylphenol, b. p. 66°/0·4 mm., n_D^{13} 1·5366; hydrogenation as above gave 6-s-butyl-2-methylphenol, b. p. 229°, n_D^{18} 1·5206 (Found: C, 80·6; H, 9·9. Calc. for $C_{11}H_{16}O$: C, 80·4; H, 9·8%) (phenylurethane, m. p. 104—105°).

4,6-Di-s-butyl-2-methylphenol.—But-2-enyl bromide (6·4 g.) was added slowly to a solution of 4-s-butyl-2-methylphenol (7·8 g.) in acetone (50 ml.) containing anhydrous potassium carbonate (6·6 g.). The mixture was stirred at room temperature for 12 hr., then boiled under reflux for 3 hr. Water and light petroleum (b. p. 40—60°) were added, and the organic layer was separated and washed with Claisen solution. Working up as above gave but-2-enyl 4-s-butyl-2-methylphenyl ether, b. p. 108—110°/0·8 mm., n_D^{16} 1·5110. Rearrangement of this ether as above gave 4-s-butyl-2-methyl-6-1′-methylallylphenol, b. p. 94°/0·4 mm., n_D^{14} 1·5208, whence hydrogenation gave 4,6-di-s-butyl-2-methylphenol, b. p. 258°, n_D^{13} 1·5101 (Found: C, 81·6; H, 10·9. Calc. for $C_{15}H_{24}O$: C, 81·8; H, 11·0%) (phenylurethane, m. p. 98°).

2,6-Di-isopropyl-4-methylphenol.—2-Isopropyl-4-methylanisole was brominated in carbon tetrachloride, to yield *6-bromo-2-isopropyl-4-methylanisole*, b. p. 92°/0·8 mm., n_D^{19} 1·5410 (Found: Br, 32·8. $C_{11}H_{15}OBr$ requires Br, 32·9%). This was converted as above *via* 2,6-di-isopropyl-4-methylanisole, b. p. 225°, n_D^{20} 1·5005 (Found: C, 81·4; H, 10·7. Calc. for $C_{14}H_{22}O$: C, 81·5; H, 10·8%), into *2,6-di-isopropyl-4-methylphenol*, b. p. 246°, n_D^{21} 1·5165 (Found: C, 81·0; H, 10·6. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%) (phenylurethane, m. p. 174°).

2-s-Butyl-4-methylphenol.—This was prepared as described earlier.[11]

2,6-Di-s-butyl-4-methylphenol.—2-s-Butyl-4-methylphenol was converted by the above method into but-2-enyl 2-s-butyl-4-methylphenyl ether, b. p. 82°/0·2 mm., n_D^{20} 1·5140, which was rearranged as above to 2-s-butyl-4-methyl-6-1′-methylallylphenol, b. p. 86°/0·2 mm., n_D^{16} 1·5212; hydrogenation gave 2,6-di-s-butyl-4-methylphenol which was shown by its infrared spectrum to be identical with the sample synthesised earlier.

Rearrangement of Alkyl Aryl Ethers.—Powdered aluminium chloride (1 mol.) was added during 30 min. to the stirred ether cooled so that the temperature remained in the range 15—25°. The mixture was then stirred at room temperature until the dark red product became too viscous. After 24 hr. ice and hydrochloric acid were added and the organic layer separated with ether.

Alkylations of Cresols.—These were carried out similarly, the ether being replaced by an equimolecular mixture of cresol and alkyl chloride.

Analyses.—The crude reaction product was separated into three fractions by treatment, first, with dilute potassium hydroxide solution, in which phenols with a bulky *ortho*-substituent do not readily dissolve, and then with Claisen solution. The insoluble residue consisted of tars;

[9] Steinkopf and Hopner, *J. prakt. Chem.*, 1926, **113**, 137.
[10] Claus, *ibid.*, 1888, **38**, 324.
[11] Part II, *J.*, 1959, 4086.

no ethers derived from alkylcresols could be detected. Each fraction was then further subdivided by distillation under reduced pressure through a 20 cm. Dixon gauze column; the individual sub-fractions were analysed by infrared spectroscopy.

The analysis was complicated by the presence of products for which no authentic reference compounds were available. Of these the compounds presumed to be 3-isopropyl-4-methylphenol, 3,5-di-isopropylphenol, and 3,5-di-s-butylphenol were isolated and their spectra were measured. The spectra of 3-s-butyl-4-methylphenol, of the two 2,5-dialkyl-4-methylphenols, and of the two 4,5-dialkyl-2-methylphenols, were estimated by difference. Analogy with the isopropyl series indicated that the former constituent was a single compound; the evidence that the same was true for the dialkylcresols was outlined above.

Full experimental details will be found in a thesis by one of us.[12] The following properties are recorded here:

3-Isopropyl-4-methylphenol, b. p. 228°, gave an aryloxyacetic acid, m. p. 151—152° (lit.,[8] 151°) (Found: C, 69·3; H, 8·0. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·8%), and a phenylurethane, m. p. 127—128° (Found: C, 76·0; H, 7·2; N, 5·2. Calc. for $C_{17}H_{19}O_2N$: C, 75·8; H, 7·1; N, 5·2%).

2,5-*Di-isopropylphenol*, crystallised from aqueous ethanol, had m. p. 95·5° (Found: C, 80·7; H, 10·3; O, 8·7%; *M*, 172. $C_{12}H_{18}O$ requires C, 80·9; H, 10·2; O, 8·9%; *M*, 178).

2,5-Di-s-butylphenol crystallised from light petroleum (b. p. <40°) and had m. p. 69° (Found: C, 81·4; H, 11·0. Calc. for $C_{12}H_{22}O$: C, 81·5; H, 10·8%).

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[12] Puttnam, Ph.D. Thesis, London, 1958.