819. *Acid-catalysed Rearrangements of Alkyl Aryl Ethers. Part II.*[1] *Rearrangements in the Presence of Sulphuric–Acetic Acid Mixtures.*

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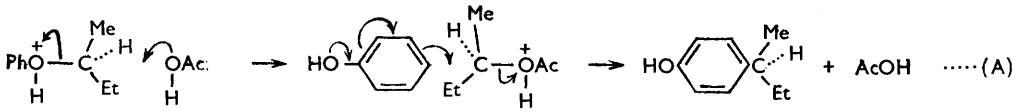
Rearrangement of phenyl s-butyl ether in the presence of sulphuric acid in acetic acid has been studied and the products have been compared with those of alkylation of phenol with s-butyl alcohol under similar conditions. Crossed products have been isolated after rearrangement of a mixture of isopropyl *p*-tolyl and *p*-ethylphenyl s-butyl ether. A number of isopropyl and s-butyl derivatives of phenol have been synthesised as reference compounds.

Previous workers have favoured an intramolecular mechanism for the rearrangements of secondary alkyl ethers of phenols catalysed by sulphuric acid in acetic acid. Niederl and Natelson [2] reported that isopropyl phenyl ether gave *o*-isopropylphenol in over 50% yield, and no other alkyl- or dialkyl-phenol. Sprung and Wallis [3] obtained *o*-s-butylphenol as the only identifiable rearrangement product of phenyl s-butyl ether, although in only 8% yield. Since alkylation of phenol gives *p*-alkylphenol as the main product, these results suggested that the rearrangements of the phenyl ethers must be intramolecular.

Sprung and Wallis [3] also found that the rearrangement of optically active phenyl s-butyl ether gave optically active *o*-s-butylphenol; Diassi [4] later showed that the migration of the s-butyl group took place with retention of configuration, as would be expected if the rearrangement were intramolecular. It is true that retention of configuration might be observed in a two-step intermolecular process, the s-butyl group being removed as s-butyl



(A)

acetate, and this then alkylating the phenol; each of these reactions would involve a nucleophilic replacement on the s-butyl group which could occur with complete (S_N2) or partial (S_N1) inversion (cf. reactions A).

[1] Part I, preceding paper.
[2] Niederl and Natelson, *J. Amer. Chem. Soc.*, 1931, **53**, 1928.
[3] Sprung and Wallis, *ibid.*, 1934, **56**, 1715.
[4] Diassi, personal communication.

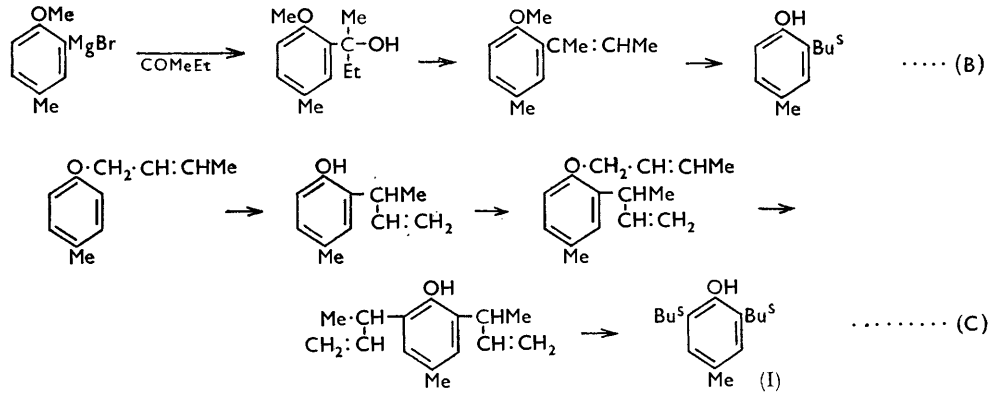
This possibility was excluded by Gilbert and Wallis [5] who showed that the intermolecular s-butylation of *p*-cresol by optically active mesityl s-butyl ether gave racemic 4-methyl-2-s-butylphenol, whereas rearrangement of optically active s-butyl *p*-tolyl ether gave optically active 4-methyl-2-s-butylphenol.

Gilbert and Wallis [5] also claimed that rearrangement of a mixture of isopropyl phenyl ether and s-butyl *p*-tolyl ether gave only isopropylphenol and s-butyl-*p*-cresol; if the rearrangement had been intermolecular, one would have expected some s-butylphenol and isopropyl-*p*-cresol to be formed.

These arguments are, however, by no means conclusive. The first and third rest on the failure to isolate certain compounds from complex products; the analytical methods available at the time were inadequate. Moreover the rates of rearrangement of an alkyl phenyl and an alkyl *p*-tolyl ether may differ greatly; in this case a mixture of the two could rearrange independently, even if each rearrangement were intermolecular. The argument based on retention of optical activity would be more convincing if retention were complete; the rotation reported by Sprung and Wallis [3] for *o*-s-butylphenol ($[\alpha]_D$ 4·77°) corresponds to an optical purity of 26·3%, based on the value ($[\alpha]_D$ 18·1°) quoted by Hawthorne and Cram [6] for the pure stereoisomer. Intramolecular rearrangements involving migration of optically active alkyl groups normally take place with complete retention of configuration.

We therefore re-examined the rearrangement of phenyl s-butyl ether, using modern analytical techniques, and also the rearrangement products from a mixture of isopropyl *p*-tolyl ether and *p*-ethylphenyl s-butyl ether. Crossed products would certainly be expected in the latter reaction if the rearrangements were intermolecular, since the electronic effects of methyl and ethyl substituents are similar.

The isopropyl and s-butyl derivatives of *p*-cresol and *p*-ethylphenol were prepared as were their analogues in Part I [1] (*e.g.*, by route B). 4-Methyl-2,6-di-s-butylphenol (I) was prepared by the method used [1] for the corresponding phenol derivative (C).



Results.—Rearrangements were carried out with molar amounts of concentrated sulphuric acid in a fourfold excess of glacial acetic acid for 2·5 hr. at 108—125°. The phenolic products were analysed by infrared spectroscopy of solutions in carbon tetrachloride (2% w/w) on a Grubb-Parsons G.S. 2A double-beam grating spectrometer over the range 900—1120 cm.$^{-1}$.

The main products from the rearrangement of phenyl s-butyl ether and the alkylation of phenol by s-butyl alcohol were butene, phenol, and sodium hydroxybenzenesulphonate, while the yields of s-butylphenols were quite small (8—12%). These results were in agreement with those obtained by Sprung and Wallis.[3] However, the phenolic fraction

[5] Gilbert and Wallis, *J. Org. Chem.*, 1940, **5**, 184.
[6] Hawthorne and Cram, *J. Amer. Chem. Soc.*, 1952, **74**, 5859.

was a mixture of *o*-, *m*-, and *p*-s-butylphenol together with 2,4-di-s-butylphenol; it resembled quite closely the corresponding products obtained [1] by using aluminium chloride as catalyst.

The presence of the *m*- and the 2,4-isomer was clearly indicated by the infrared spectrum; the *p*-isomer was characterised by its phenylurethane. The only other products identified were butyl and phenyl acetate and a mixture of hydroxyacetophenones.

Table 1 records the products formed by rearrangement of phenyl s-butyl ether; Table 2 records the products formed in comparable alkylations of phenol.

TABLE 1. *Rearrangements in sulphuric–acetic acid.*

			s-Butylphenol				
C_4H_8	PhOH	Na salt	*o*-	*m*-	*p*-	2,4-$Bu^s_2C_6H_3$·OH	*ortho*/*para* ratio
69·9	19·9	11·9	2·5	0·4	2·4	0·9	1·04
55·0	20·5	18·8	3·8	0·6	3·8	1·5	1·00

TABLE 2. *Alkylation of phenol with s-butyl alcohol in sulphuric–acetic acid.*

			s-Butylphenol				
C_4H_8	PhOH	Na salt				2,4-$Bu^s_2C_6H_3$·OH	*ortho*/*para* ratio
76·2	31·4	19·4	4·0	0·4	7·2	0·9	0·56
69·4	25·6	15·5	4·2	0·4	7·7	1·3	0·54

The competitive rearrangement of isopropyl *p*-tolyl ether and *p*-ethylphenyl s-butyl ether was shown to give crossed products; 4-ethyl-2-isopropylphenol and 4-methyl-2,6-di-s-butylphenol were identified by infrared spectroscopy.

Discussion.—Our results show that two of the lines of evidence quoted by Wallis and his collaborators must be rejected. The rearrangement of phenyl s-butyl ether does not give *o*-s-butylphenol as the sole product, and rearrangement of a mixture of two different ethers can give crossed products. There can therefore be little doubt that these rearrangements are at least partly intermolecular.

Comparison of Tables 1 and 2 shows, however, that the products obtained by rearranging phenyl s-butyl ether, and by s-butylating phenol were not identical. A much higher proportion of *ortho*-isomer was obtained in the rearrangement. The rearrangement cannot therefore be entirely intermolecular. A similar conclusion was reached, on similar reasoning, in our previous study of the heterogeneous rearrangements and alkylations catalysed by aluminium chloride; here the conclusion is much more definite since both reactions took place in homogeneous solution under carefully defined conditions. It seems clear that the rearrangement must take place by two distinct paths, one intermolecular, giving predominantly the *para*-isomer, the other giving mainly the *ortho*-isomer.

The work of Gilbert and Wallis [5] suggests very strongly that intermolecular transfer of an s-butyl group from an ether to a phenol takes place with complete loss of configuration. The second reaction must therefore take place with a high degree of retention [3] of configuration, since only part of the product is formed by it, and since the product was 26% resolved. This suggests that the second reaction is indeed an intramolecular rearrangement; it cannot be a bimolecular reaction of phenyl s-butyl ether with phenol or a phenyl ether, since such a reaction would involve partial or complete inversion.

EXPERIMENTAL

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

Alkyl aryl ethers prepared from the phenol, alkyl bromide, and potassium hydroxide by Niederl and Natelson's method.[2] Isopropyl *p*-tolyl ether had b. p. 197°, n_D^{17} 1·4984; *p*-ethylphenyl s-butyl ether had b. p. 91°/3 mm., n_D^{26} 1·4910; and *p*-ethylphenyl isopropyl ether had b. p. 202°, n_D^{14} 1·4974. See also Part I.

Aryloxyacetic acids were prepared as described earlier [1].

Phenylurethanes were prepared by the procedure of Steinkopf and Hopner [7] and recrystallised from light petroleum (b. p. 60—80°).

p-Ethylphenol, prepared by Clemmensen's method, had m. p. 46°; (aryloxyacetic acid, m. p. 95—96°; phenylurethane, m. p. 121°).

2-*Isopropyl*-4-*methylphenol*.—Bromination of *p*-cresol in carbon tetrachloride at room temperature gave 2-bromo-4-methylphenol, b. p. 77°/2 mm., n_D^{19} 1·5792, which with dimethyl sulphate gave 2-bromo-4-methylanisole, b. p. 84°/1 mm., n_D^{17} 1·5663 (Found: Br, 39·7. Calc. for C_8H_9Br: Br, 39·8%). Acetone (35 g.) in dry ether (100 ml.) was added to a Grignard reagent prepared from magnesium (13·4 g.) and 2-bromo-4-methylanisole (92 g.) in dry ether (200 ml.). After 24 hr. the complex was hydrolysed, the ether layer evaporated, and the residue boiled under reflux for 8 hr. with acetic anhydride (500 ml.), then poured into water. The organic layer was separated and distilled; 2-(2-methoxy-5-methylphenyl)propene (68%) was collected at 57°/0·5 mm. Hydrogenation over 10% palladised charcoal (in ethanol at room temperature and 2 atm.) gave 2-isopropyl-4-methylanisole, b. p. 46°/0·4 mm., n_D^{19} 1·5070 (Found: C, 80·5; H, 9·6. Calc. for $C_{11}H_{16}O$: C, 80·4; H, 9·8%). Demethylation with acetic acid and hydriodic acid gave 2-isopropyl-4-methylphenol,[8] m. p. 35° (Found: C, 80·2; H, 9·4. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 9·4%), (phenylurethane, m. p. 98°; aryloxyacetic acid, m. p. 135°).

4-*Ethyl*-2-*isopropylphenol*.—This was prepared in an analogous manner to the 4-methyl isomer, from 2-bromo-4-ethylanisole, and had b. p. 92°/1 mm., n_D^{20} 1·5562; 2-(5-ethyl-2-methoxyphenyl)propene had b. p. 75°/0·6 mm., n_D^{18} 1·5253; 4-ethyl-2-isopropylanisole had b. p. 218°, n_D^{20} 1·5033; 4-ethyl-2-isopropylphenol had b. p. 227·5°, n_D^{17} 1·5190 (Found: C, 80·4; H, 9·5. Calc. for $C_{11}H_{16}O$: C, 80·5; H, 9·8%) (phenylurethane, m. p. 126°; aryloxyacetic acid, m. p. 95—96°).

4-*Methyl*-2-*s*-*butylphenol*.—This was prepared by a similar method to the isopropylphenols from ethyl methyl ketone. Products were: 2-(2-methoxy-5-methylphenyl)but-2-ene (62%), b. p. 228·5°, n_D^{16} 1·5274 (Found: C, 81·7; H, 9·4. Calc. for $C_{12}H_{17}O$: C, 81·8; H, 9·2%); 4-methyl-2-s-butylanisole, b. p. 72°/0·6 mm., n_D^{19} 1·5049; 4-methyl-2-s-butylphenol, m. p. 43·5—44·5° (Found: C, 80·5; H, 10·0. Calc. for $C_{11}H_{16}O$: C, 80·4; H, 9·8%) (aryloxyacetic acid, m. p. 82°; phenylurethane, m. p. 94—95°).

4-*Ethyl*-2-*s*-*butylphenol*.—This was prepared analogously to the methyl isomer, from ethyl methyl ketone. Products were 2-(5-ethyl-2-methoxyphenyl)but-2-ene, b. p. 245°, n_D^{22} 1·5238; 4-ethyl-2-s-butylanisole, b. p. 72°/0·6 mm., n_D^{18} 1·5025; 4-ethyl-2-s-butylphenol, b. p. 244°, n_D^{19} 1·5152 (Found: C, 80·7; H, 10·2. Calc. for $C_{12}H_{18}O$: C, 80·9; H, 10·2%) (phenylurethane, m. p. 105°).

s-Butylphenols were prepared as described earlier.[1]

4-*Methyl*-2,6-*di*-*s*-*butylphenol*.—But-2-enyl *p*-tolyl ether was prepared and rearranged to 2-but-2′-enyl-4-methylphenol,[9] b. p. 82/0·8 mm., n_D^{19} 1·5259 (phenylurethane, m. p. 63—64°). The butenyl ether, b. p. 88°/0·3 mm., n_D^{17} 1·5220, from this product was boiled under reflux for 5 hr. in dimethylaniline, giving 4-methyl-2,6-bis-(1-methylpropenyl)phenol, b. p. 103°/0·6 mm., n_D^{16} 1·5325. Hydrogenation over palladised charcoal in ethanol gave 4-methyl-2,4-*di*-*s*-*butylphenol*, b. p. 95°/0·5 mm., n_D^{18} 1·5100 (Found: C, 81·5; H, 10·9. $C_{15}H_{24}O$ requires C, 81·8; H, 10·9%) (no solid urethane was obtained).

Rearrangement of Phenyl s-Butyl Ether.—(*a*) Phenyl s-butyl ether (95·5 g.) was heated in sulphuric acid–acetic acid (161 ml.) to 108°; rapid evolution of gas then occurred. The evolved butene was condensed in a cold trap and weighed. After 1·5 hr. the temperature was raised to 120—125° for a further ½ hr.; the mixture became homogeneous and dark red. When cold, the products were partially separated (cf. Wallis *et al.*[3,5]) by addition of 20% ice cold sodium hydroxide solution almost to neutrality and were extracted with ether. The aqueous residue, after several days at 0°, gave a precipitate of sodium hydroxybenzenesulphonate which was dried at 120° (17·5 g.). The hydrocarbon layer was extracted with 4% sodium hydroxide solution. The alkali-soluble material (16·2 g.) was distilled under reduced pressure. Fraction (i) (11·9 g.), b. p. 54—56°/2 mm., gave a phenylurethane, m. p. 128° undepressed on admixture with *ON*-diphenylurethane. Fraction (ii), b. p. 86—90°/2 mm., was shown by infrared spectroscopy to be a mixture of 2- and 4-hydroxyacetophenone. The alkali-insoluble material (6·8 g.) was also

[7] Steinkopf and Hopner, *J. prakt. Chem.*, 1926, **113**, 137.
[8] Carpenter and Easter, *J. Org. Chem.*, 1955, **20**, 401.
[9] Claisen and Tietze, *Ber.*, 1926, **59**, 2344.

distilled. Fraction (*a*), b. p. 72—78°/1 mm., was shown by infrared spectroscopy to be mainly *o*-s-butylphenol with a small amount of phenyl acetate. Fraction (*b*), b. p. 82—88°/1 mm., gave an aryloxyacetic acid, m. p. 112° alone or mixed with *o*-s-butylphenoxyacetic acid. Fraction (*c*), b. p. 92—96°/1 mm., 240°/760 mm., n_D^{20} 1·5110, was shown (infrared) to be a mixture of *o*- (40%), *m*- (9%), and *p*-s-butylphenol (39%). The last fraction, b. p. 100—106°/1 mm., which gave a phenylurethane, m. p. 102° undepressed by *p*-s-butylphenylphenylurethane, was shown (infrared) to contain also 2,4-di-s-butylphenol. s-Butyl acetate (0·2 g.) was recovered from the cold trap protecting the pump.

(*b*) The above rearrangement was repeated with phenyl s-butyl ether (74 g.) and sulphuric acid–acetic acid (125 ml.); the products, separated as above, gave sodium hydroxybenzenesulphonate (21·5 g.), phenol (9·5 g.), and a mixture of hydroxyacetophenones (2·7 g.). The alkali-insoluble fraction (8·3 g.) was analysed spectroscopically.

Alkylation of Phenol by s-Butyl Alcohol.—A sulphuric acid–acetic acid solution (125 ml.) of phenol (46 g., 0·5 mole) and s-butyl alcohol (37 g., 0·5 mole) was heated to 106°, rapid evolution of gas then occurring. The gas was condensed in a cold trap and weighed. The reaction mixture was kept at 106° for 1½ hr. and at 125° for a further ½ hr. The products were partially separated as described above, to give sodium hydroxybenzensulphonate (22 g.), phenol (14·5 g.), and mixed hydroxyacetophenones (4 g.). The material (9·5 g.) insoluble in 4% sodium hydroxide solution was fractionated as before and the various fractions were analysed spectroscopically.

Rearrangement of Mixture of Isopropyl p-*Tolyl Ether and* p-*Ethylphenyl s-Butyl Ether.*—A mixture of isopropyl *p*-tolyl ether (18·2 g., 0·12 mole) and *p*-ethylphenyl s-butyl ether (21·6 g., 0·12 mole) was treated with sulphuric acid–acetic acid (61 ml.) as before. The hydrocarbon layer was extracted with 10% potassium hydroxide solution and then with Claisen solution [potassium hydroxide (350 g.) in water (250 ml.), made up to 1 l. with methanol]. The material (7·5 g.) soluble in potassium hydroxide solution was distilled; fraction (i) (5·1 g.) was shown (infrared) to be a mixture of *p*-cresol and *p*-ethylphenol. The other fraction had an infrared spectrum showing a large carbonyl absorption, indicating that it consisted of acylated phenols. The material (13·3 g.) soluble in Claisen solution was fractionated on a spinning-band column. One fraction was shown (infrared) to be a mixture of 2-isopropyl-4-methylphenol and 4-ethyl-2-isopropyl phenol; another fraction was a mixture of 4-ethyl-2-s-butylphenol and 4-methyl-2,6-di-s-butylphenol. No conclusive results were obtained with the other fractions, which were very complex mixtures.

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[*Received, May 4th,* 1959.]