[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. VII. THE REARRANGEMENT OF OPTICALLY ACTIVE ALKYL PHENYL ETHERS[1]

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The early work carried out in this laboratory and published in Parts I, II, and III (1) of this series has demonstrated that in molecular rearrangements of the Curtius, Lossen, and Hofmann types involving optically active radicals, the optically active group maintains an asymmetric configuration during rearrangement. It has also been shown that no appreciable racemization occurs during such transformations.

The mechanism by which the radical originally attached to the carbon atom migrates to the nitrogen atom has been the subject of much discussion.[2] Its electronic nature has also been variously interpreted. In Part IV (2) of this series, however, experiments were described which clearly show that the migration of the optically active group *does not take place in any free form, either as a positive carbonium ion, a negative carbanium ion or a neutral free radical.*

At first thought, this might suggest that the electronic nature of the tercovalent group plays no vital part in the production of optical stability or instability during rearrangement. For, if the migrating group is never completely free either as a negative ion, positive ion, or neutral free radical, but by some means is always within the sphere of influence of the rest of the molecule during the rearrangement process, then, regardless of whether or not the asymmetric carbon atom is without its complete octet of electrons, it might happen that the rearrangement would take place in a manner that insured an asymmetric configuration in all stages of the reaction. A study of the literature, however, strongly suggests that this is not the case. Experimental facts have been recorded which demonstrate quite conclusively that the optical stability of a tercovalent group (3) is dependent on its electronic nature.

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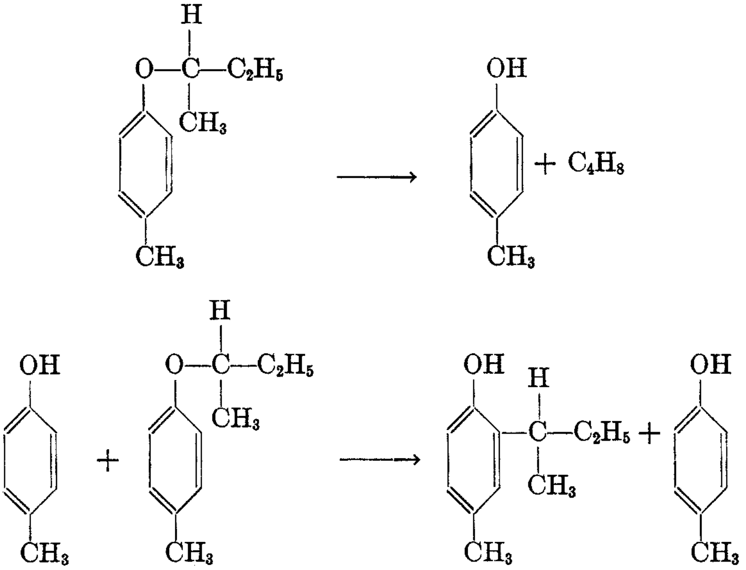
[1] The experimental results herein described were placed before the Society in a paper read before the Division of Organic Chemistry at the Society's meeting in Boston, September 11-15, 1939. Present address of W. I. Gilbert, Western Maryland College, Westminster, Md.

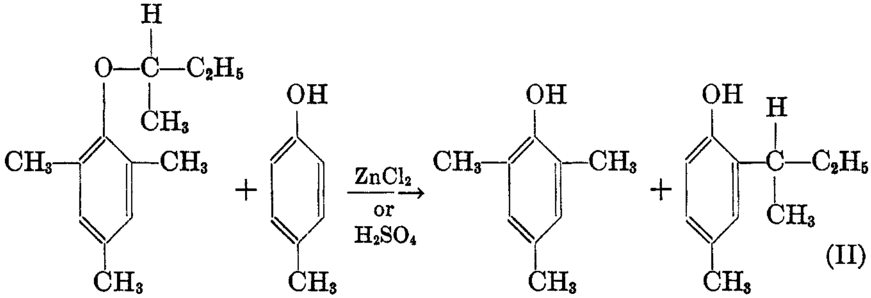
[2] For references see earlier papers in this series.

In Part V (4) of this series Sprung and Wallis studied from this point of view the nature of the products formed in the Claisen rearrangement of *d*- and *l*-*s*-butyl *m*-cresyl, and *d*, and *l*-*s*-butyl *p*-cresyl ethers. Although they found that the substituted phenols so obtained always were optically active, they did observe that the rearrangement is accompanied by partial racemization. Their results, together with those of other investigators in allied fields, indicated to them that a particular electronic arrangement of the migrating group was of fundamental importance in maintaining optical stability, and that consequently the stability was not wholly determined by some other phenomenon such as solvation or the like. In their discussion these authors did point out, however, that another explanation involving a bimolecular process had to be considered, especially in the light of certain experiments described by Short and Stewart (5) and by Sowa, Hinton and Nieuwland (6). They formulated such a possible mechanism as depicted in formulation I.



(I)

In this paper we wish to describe the results of certain experiments which were devised to test this mechanism, and to determine whether an alkyl radical containing an asymmetric carbon atom is actually able to enter a foreign nucleus without resultant loss of optical activity. For this purpose *d*-, and *l*-*s*-butyl mesityl ethers were prepared and the nature of their rearrangement products was determined. If the above metathetical mechanism is responsible for the optically active products obtained by Sprung and Wallis, then the reaction of *d*-, or *l*-*s*-butyl mesityl ether with *p*-cresol in the presence of either zinc chloride or sulfuric acid should lead to the formation of an optically active 4-methyl-2-*s*-butylphenol, as shown in formulation II.



(II)

Preliminary experiments with racemic *s*-butyl mesityl ether showed that when a mixture of it with *p*-cresol was allowed to react in acetic acid solution in the presence of zinc chloride at 115°, only small yields of 4-methyl-2-*s*-butylphenol were obtained. The main products were butylene, mesitol, the unchanged mesityl ether, *p*-cresol, and *s*-butyl acetate. When sulfuric acid was substituted for zinc chloride, better yields of the 4-methyl-2-*s*-butylphenol were produced.

Similar treatment of *d*-*s*-butyl mesityl ether ($[\alpha]_D^{22}$ + 6.97°) gave in all cases *d*,*l*-4-methyl-2-*s*-butylphenol. The crystalline acetic acid derivative was also inactive. The same results were of course obtained with the incompletely resolved *l*-ether ($[\alpha]_D^{19}$ − 3.94°). Therefore it can be definitely concluded that an intermolecular mechanism of the above type can not be used to explain the retention of optical activity in the experiments reported by Sprung and Wallis, and their alternative mechanism is much the more probable.

Recently Hurd and Pollack (7) have suggested an oxonium type of mechanism to explain the rearrangement of alkyl phenyl ethers by the use of acidic catalysts. The first phase of the reaction is the combination of the ether with a proton to give an oxonium salt. This salt then rearranges and finally gives off a proton to form the rearranged product. To us, however, the most interesting step of the process is the one in which the actual rearrangement occurs, for it is to be noted that in the formulation of their mechanism, the alkyl group, because of resonance phenomena at the double bond in the benzene nucleus, must migrate with its full quota of electrons. It is also to be concluded from their formulation that the group *is at all times within the sphere of influence of the molecule as a whole*, this latter conclusion again illustrating a principle so often stressed by us in this laboratory.

With the above reasoning in mind, the formation of inactive products which we have observed in the present investigation is easily explained. A scission of the *s*-butyl mesityl ether occurs to give butylene and mesitol. This is then followed by the reaction of the butylene with *p*-cresol to give *d, l*-*s*-butyl *p*-cresyl ether. The last compound then rearranges to give *d,l*-4-methyl-2-*s*-butyl phenol.

In order to make certain that the experimental facts are not to be explained on the basis of some other type of bimolecular reaction, we prepared isopropyl phenyl ether and inactive *s*-butyl *p*-cresyl ether and rearranged them in the presence of each other by means of sulfuric and acetic acids. If a bimolecular reaction occurs, one would expect to find products resulting from the exchange of isopropyl and *s*-butyl radicals between the phenol and *p*-cresol residues respectively. However, if an intramolecular reaction occurs, then one would expect only the normal products, namely, isopropylphenol and 4-methyl-2-*s*-butylphenol. We were able to isolate and identify as products of the reaction only *o*-isopropylphenol and 4-methyl-2-*s*-butylphenol. No other products could be isolated and identified. The rearrangement was carried out in the same manner as the previous reactions and the products worked up in the usual way. The phenols were identified by means of their acetic acid derivatives.

We are of the opinion, therefore, that the true course of the alkyl phenyl ether rearrangement is by way of an intramolecular path, and it appears that at present an oxonium electronic mechanism best explains the existing facts.

EXPERIMENTAL PART

Preparation of mesitol. Mesitylene was converted to mesitylene sulfonic acid by treatment with sulfuric acid at room temperature (8). The sulfonic acid so prepared was fused with powdered potassium hydroxide and converted into the phenol. The fused mass was leached with water. The solution was then acidified and steam distilled. Recrystallization of the product from petroleum ether gave crystals which melted at 69°.

It was found that larger quantities of mesitol could be more easily obtained from the "Remington Phenols" which were procured from the E. I. du Pont de Nemours Co. When this crude mixture was chilled, a large portion of the mesitol present crystallized. The crude product was filtered and recrystallized several times from petroleum ether. When pure it melted sharply at 69°.

Preparation of d, l-s-*butyl mesityl ether.* Fifteen-hundredths mole of *s*-butyl bromide and 0.15 mole of mesitol were dissolved in 900 cc. of absolute alcohol. To this solution was added an equivalent amount of sodium ethoxide dissolved in 100 cc. of alcohol. The mixture was refluxed on the steam-bath for eight hours, after which it was concentrated at reduced pressure to about 100 cc. The reaction-product was then added to 75 cc. of a 10% solution of potassium hydroxide and the mixture was extracted with ether. The ether solution was worked up in the usual manner and the product purified by distillation at reduced pressure.

d, l-s-Butyl mesityl ether is a liquid which can not be distilled at atmospheric pressure without decomposition. It boils at 72–73° at 1 mm.: d_{20} 0.9268, n_{D}^{20} 1.49886; M.R. (calc'd) 60.64; M.R. (obs.) 60.90.

Anal. Calc'd for $C_{13}H_{20}O$: C, 81.19; H, 10.48.

Found: C, 81.1; H, 10.37.

Preparation of the optically active s-*butyl mesityl ethers. s*-Butyl alcohol was resolved through its phthalic acid ester according to the method of Pickard and Kenyon (9) using the time-saving steps suggested by Sprung and Wallis. The *d-s*-butyl alcohol so obtained had a rotation $[x]_{\mathrm{D}}^{24}$ +11.67° (pure liquid 1 dm.) as compared with $[\alpha]_{\mathrm{D}}^{20}$ +12.0° reported by Sprung and Wallis. The mother liquors gave an *l-s*-butyl alcohol $[\alpha]_{\mathrm{D}}^{20}$ −10.84° (pure liquid 1 dm.).

The active alcohols were converted to the corresponding bromides by saturation at 0° with dry hydrogen bromide gas according to the method of Levene and Marker (10). The dextrorotatory alcohol gave a bromide of rotation $[\alpha]_{\mathrm{D}}^{22}$ −23.13° (pure liquid 1 dm. tube) as compared with $[\alpha]_{\mathrm{D}}^{25}$ −13.79° reported by Levene and Marker and $[\alpha]_{\mathrm{D}}^{22}$ −19.77° reported by Sprung and Wallis.

The levorotatory alcohol gave a bromide of $[\alpha]_{\mathrm{D}}^{20}$ +12.71° (pure liquid 1 dm. tube).

The corresponding *d*-, and *l-s*-butyl mesityl ethers were prepared according to the procedure described above for the racemic modification. The mesityl ether from the bromide ($[\alpha]_{\mathrm{D}}^{22}$ − 23.13°) had a rotation $[\alpha]_{\mathrm{D}}^{22}$ +6.97° (pure liquid). The ether which was prepared from the bromide ($[\alpha]_{\mathrm{D}}^{20}$ +12.71°) had a value $[\alpha]_{\mathrm{D}}^{20}$ −3.94° (pure liquid).

Experiments with d, l-s-*butyl mesityl ether.* (a) Rearrangement in the presence of *p*-cresol with zinc chloride and acetic acid.

1. In a typical experiment 48 g. (0.25 mole) of ether and 27 g. (0.25 mole) of pure *p*-cresol were placed in a 500 cc. round bottom flask and shaken with gentle warming until the mixture was homogeneous. To this solution was added 250 g. of a zinc chloride solution prepared by dissolving 75 g. of anhydrous zinc chloride in 200 cc. glacial acetic acid. A reflux condenser and a gas measuring burette with reservoir were connected to the flask and the mixture heated gradually in an oil-bath. At 105° gas was evolved rapidly. The temperature was raised to 115° and kept there until no more butylene was evolved. At this temperature considerable gas absorption occurred. The heating was discontinued when a decrease in volume began to take place.

2. Treatment of reaction product. The procedure used in working up the products of the reaction was essentially that described by Sprung and Wallis. The reaction-mixture was treated with ice-cold alkali until only very slightly acid. Then it was extracted with ether. The ether extract was washed repeatedly with 100-cc. portions of 4% sodium hydroxide solution until the alkaline layer was no longer colored. After the ether solution was washed with a 5% solution of sodium carbonate, and finally with water, it was dried with sodium sulfate and the ether distilled. The residue (56.5 g.) was distilled at reduced pressure in an atmosphere of nitrogen. The fractions collected are described in Table I.

3. Identification of products. None of the above fractions could be induced to crystallize, but crystalline acetic acid derivatives were prepared according to the directions of Niederl and Natelson (11). Fractions I, II, and III gave a product that melted at 144–145° and gave no depression of the melting point when mixed with an authentic sample of mesitoxyacetic acid (m.p. 145°). Fraction IV gave a product that melted at 74–75° and was found to be identical with an authentic specimen of 4-methyl-2-*s*-butylphenoxyacetic acid (m.p. 75–76°). From the material in the trap it was possible to isolate 11.2 g. of pure *s*-butyl acetate.

4. Material soluble in 4% alkali. The alkaline extract obtained above was acidified and extracted with ether. On working up the ether solution, 37.2 g. of residue was obtained. Distillation of this material at 2 mm. gave 23.4 g. of pure *p*-cresol and 2.8 g. of pure mesitol.

(b) Rearrangement of *d, l*-*s*-butyl mesityl ether in the presence of *p*-cresol by means of sulfuric and acetic acids. A procedure was used similar to that described above. Twenty grams of the inactive ether and 11.2 g. of *p*-cresol were treated with 28.5 cc. of Niederl's reagent (12.5 cc. of conc'd sulfuric acid was dissolved in an amount of glacial acetic acid sufficient to make the total volume 62.5 cc.) for one hour at 120–125°. The mixture was then refluxed for an additional half hour. Gas evolution took place, and 375 cc. of butylene was collected. The reaction-product was worked up in the usual manner and gave (1) 12.6 g. of material soluble in 4% alkali of which 5.5 g. was *p*-cresol and 7.1 g. was mesitol; (2) 18.0 g. of product insoluble in 4% alkali. This latter fraction on distillation yielded the fractions described in Table II. Fractions I and II were found to be mesitol as shown by their acetic acid derivatives (m.p. 143° and 142° respectively). Fraction III was a mixture of mesitol and 4-methyl-2-*s*-butylphenol. The mixture of their crystalline acetic acid derivatives, on fractional crystallization, gave two products. The less soluble melted at 143° and gave no depression when mixed with a sample of mesitoxyacetic acid. The more soluble fraction melted at 73° and was identical with the acetic acid derivative of 4-methyl-2-butylphenol. Fraction IV was practically pure 4-methyl-2-butylphenol. *s*-Butyl acetate was the principal constituent in the trap. From the original aqueous solution it was possible to isolate some sodium-*p*-cresol sulfonate.

TABLE I

FRACTION	BOILING RANGE AT 1 MM., °C.	WT., G.
I	65–75	8.9
II	75–80	16.6
III	80–85	6.0
IV	85–95	1.2
Residue		2.3
Trap		16.3

TABLE II

FRACTION	BOILING POINT RANGE 2 MM. PRESSURE, °C.	WT., G.
I	73–80	2.6
II	80–85	3.0
III	85–90	2.6
IV	90–110	4.4
Residue		1.5
Trap		2.5

Rearrangement of d-s-*butyl mesityl ether in the presence of* p-*cresol with sulfuric and acetic acids.* A mixture of 4.5 g. of the dextrorotatory ether $[\alpha]_D^{22}$ +6.97°, and 2.53 g. of *p*-cresol was treated in the usual manner with 7.2 cc. of Niederl's reagent.

The following products were obtained: (a) 49.2 cc. of butylene; (b) 3.4 g. of material insoluble in 4% alkali; (c) 2.7 g. of material soluble in 4% alkali (d) 1.4 g. of sodium *p*-cresol sulfonate; (e) a very small amount of *s*-butyl acetate. All products were optically inactive. As in the previous experiments, the material insoluble in 4% alkali was found to be a mixture of mesitol and *d, l*-4-methyl-2-*s*-butylphenol. Completely inactive products were also obtained when the *l*-ether $[\alpha]_D^{20}$ −3.94° was used.

Rearrangement of isopropyl phenyl ether and s-*butyl* p-*cresyl ether in the presence of each other.* The isopropyl phenyl ether was prepared from isopropyl bromide and phenol by the method of Smith. The *s*-butyl *p*-cresyl ether was prepared by the action of *s*-butyl bromide on sodium cresolate by the method of Sprung and Wallis (4).

Forty-five grams (.275 mole) of *s*-butyl *p*-cresyl ether and 37.4 g. of isopropyl phenyl ether were treated with 153 cc. of Niederl's reagent. The reaction-mixture was heated slowly to 115°, where gas was very vigorously evolved. The temperature was held at 115–120° for one hour, after which the solution was gently refluxed for an additional hour. The following products were obtained: (a) 3004 cc. gas (a mixture of propylene and butylene); (b) 21.0 g. of material soluble in 4% alkali; (c) 40 g. of material insoluble in 4% alkali; and (d) 2.3 g. of sulfonates.

TABLE III

FRACTION	BOILING RANGE AT 4 MM., °C.	WT., G.
I	105–109	6.1
II	109–120	9.6
III	120–124	6.4
Residue		8.0
Trap		4.7

The material insoluble in 4% alkali was distilled and gave the fractions described in Table III.

Fractions I and II formed crystalline acetic acid derivatives which melted at 130° and 128–130° respectively. Smith gives 130° as the melting point of the acetic acid derivative of 2-hydroxy-1-isopropylbenzene.

Fraction III was combined with the residue and fractionally distilled at atmospheric pressure. The fraction so obtained gave acetic acid derivatives which melted at 73–75°, the melting point observed for the acetic acid derivative of 2-*s*-butyl-*p*-cresol.

A careful examination of the mother liquors from the derivative preparations, and from the recrystallizations, yielded no crystalline products corresponding in melting point to the compounds one would expect to be formed if an exchange of alkyl groups between the two molecules in question takes place.

We wish to take this opportunity to express our thanks to Merck and Company for the analyses published in this article.

SUMMARY

Optically active *s*-butyl mesityl ether has been prepared and rearranged in the presence of *p*-cresol by treatment with a mixture of sulfuric and acetic acids.

In all the cases studied, optically inactive 4-methyl-2-*s*-butylphenol was produced.

Isopropyl phenyl ether and *s*-butyl *p*-cresyl ether have been prepared and rearranged in the presence of each other. There was no evidence of an intermolecular exchange of alkyl groups.

A discussion of these facts is given in the light of certain mechanisms for the reaction.

PRINCETON, N. J.

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