[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Molecular Rearrangements Involving Optically Active Radicals. V. The Rearrangement of Optically Active Alkyl Phenyl Ethers[1]

BY MURRAY M. SPRUNG AND EVERETT S. WALLIS

Introduction

Previous investigations in this Laboratory[2] have shown that in certain molecular rearrangements involving optically active radicals, notably of the Curtius, Lossen and Hofmann types, the optically active group maintains an asymmetric configuration during the rearrangement. It has been shown that no appreciable racemization occurs during such transformations.

The mechanism by means of which the radical, originally attached to the carbon atom, migrates to the nitrogen atom has been the subject of much discussion, and the electronic nature of the migrating group has been variously interpreted.[3] It is generally accepted, however, that during such rearrangements there is a shift of an electron pair from the carbon atom to the nitrogen atom. Differences of opinion have arisen as to whether or not the electron pair and the group held by it migrate together. We are inclined to believe that they do,[4] for the relatively great optical stability of such radicals during rearrangement would indicate that at no time is the asymmetric carbon atom without its complete octet of electrons.

In an experimental investigation of a certain phase of this problem Wallis and Moyer[5] studied the rearrangement of *d*-3,5-dinitro-6-α-naphthylbenzamide. In this molecule optical activity is due to molecular asymmetry conditioned by the restriction of free rotation about the diphenyl linkage. On rearranging it, an optically active amine was obtained with no change in sign in the rotatory power, and no appreciable racemization. It was pointed out that these facts were in agreement with an earlier interpretation of the mechanism of such rearrangements by Jones and Wallis,[2] namely, that the migrating group is never completely free, either as a negative, positive or neutral fragment; for if it were free at any time rotation about the diphenyl linkage would be possible, and an inactive, or at least a partially racemized, product would be obtained.

However, there are facts recorded in the literature[6] which would indicate that the optical stability of a tricovalent group is dependent on its electronic nature. It seemed necessary, therefore, to continue further our studies in this series in order to determine more definitely whether the electronic nature of the migrating group is of importance in maintaining asymmetry during rearrangement.

A suitable reaction for this purpose is the rearrangement of the alkyl phenyl ethers to nuclear alkylated phenols. It seems certain that in the rearrangement of an aryl ether in which the alkyl group migrates from oxygen to the benzene ring, the oxygen will retain an octet of electrons, thus leaving the carbon atom with only six electrons. The nature of the products obtained would then give some indication regarding the optical stability of such positive groups during rearrangement.

The rearrangement of the racemic alkyl and alkenyl phenyl ethers has received much attention, and many theories as to the mechanism of the change have been proposed.[7] However, until the present no study has been made of these compounds when the group, R, contains an asymmetric carbon atom directly attached to the oxygen atom.

Nature of the Present Investigation

In order to investigate this problem *s*-butyl phenyl ether, *s*-butyl *m*-cresyl ether, and *s*-butyl *p*-cresyl ethers were prepared, and the rearrangements of the racemic, and the optically active

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[1] The experimental results herein described were placed before the Society in a paper read at the Fifth Organic Chemistry Symposium at Ithaca, New York, December 28–30, 1933.

[2] Jones and Wallis, THIS JOURNAL, **48**, 169 (1926); Wallis and Nagel, *ibid.*, **53**, 2787 (1931); Wallis and Dripps, *ibid.*, **55, 1701** (1933).

[3] Stieglitz, *Am. Chem. J.*, **29**, 57 (1903); THIS JOURNAL, **36**, 288 (1914); Hesse, see Stieglitz, *Am. Chem. J.*, **29**, 56 (1903); Jones, *ibid.*, **50**, 441 (1913); Jones and Wallis, Ref. 2; Whitmore, THIS JOURNAL, **54**, 3274 (1932).

[4] Private communication to F. C. Whitmore, THIS JOURNAL, **54** 3426 (1932).

[5] Wallis and Moyer, *ibid.*, **55**, 2598 (1933).

[6] McKenzie, Roger and Wills, *J. Chem. Soc.*, 779 (1926); McKenzie and Dennler, *Ber.*, **60**, 220 (1927); Roger and McKenzie, *ibid.*, **62**, 272 (1929); Kenyon and Phillips, *J. Chem. Soc.*, 1677 (1930); Wallis and Adams, THIS JOURNAL, **55**, 3833 (1933).

[7] Claisen and co-workers, *Ber.*, **45**, 3157 (1912); **58**, 275 (1925); **59**, 2344 (1926); *Ann.*, **401**, 21 (1913); **418**, 69 (1919); **442**, 210 (1925); **449**, 81 (1926); Hurd and Cohen, THIS JOURNAL, **53**, 1917 (1931); Van Alphen, *Rec. trav. chim.*, **46**, 287, 799 (1927); Short, *J. Chem. Soc.*, 528 (1928); Short and Stewart, *ibid.*, 553 (1929); Niederl and co-workers, THIS JOURNAL, **53**, 276, 1928 (1931); **54**, 1063 (1932); **55**, 284, 2571, 3025, 4151 (1933); Smith, *ibid.*, **55**, 849, 3718 (1933); Lapworth, *J. Chem. Soc.*, **73**, 1445 (1898).

modifications were studied under different conditions. Difficulties were encountered when *s*-butyl phenyl ether was rearranged, using the procedure of Niederl and Natelson.[8] The reaction did not proceed smoothly. Butylene and other side products and only very small amounts of alkylated phenol were produced.[9] Yields of the rearranged phenol were better, however, when *s*-butyl *m*-cresyl ether, and *s*-butyl *p*-cresyl ether were used. In some instances 35% of the theoretical quantity of alkylated phenol was produced when a mixture of sulfuric and glacial acetic acids was used as the rearranging agent. The principal side reaction was a scission into butylene and the simple phenol, a reaction which we would expect if the group, R, is momentarily without its electron pair, because such a group can stabilize itself not only by rearrangement but by the loss of a proton. The phenol so produced was attacked by the reagent, and although part of it was isolated as such, some of it always appeared as sulfonated and acetylated phenol. *s*-Butyl acetate was also formed. A crystalline alkylated phenol was produced only in the rearrangement of *s*-butyl *p*-cresyl ether. Here only one monosubstituted cresol is to be expected. In the other cases oils were obtained which in all probability were mixtures of the possible nuclear isomers. However, crystalline derivatives of these substances were prepared. There were indications that small amounts of higher alkylated phenols also were formed, but we were not able to isolate any of these in a pure state.

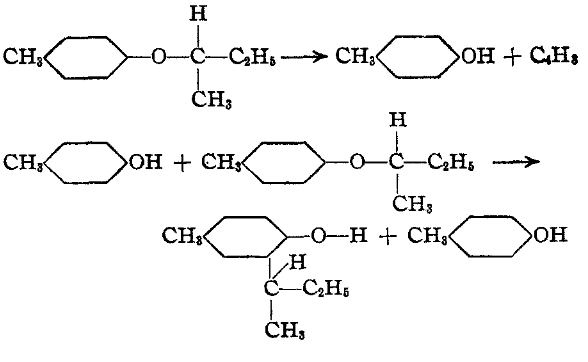
A mixture of anhydrous zinc chloride and glacial acetic acid was found to give superior yields of alkylated phenols and to possess certain other advantages over sulfuric and acetic acids. The by-products were identical with those previously mentioned except that sulfonation could not occur.

Results and Discussion

The alkylated phenols and their crystalline derivatives obtained under the above conditions from the optically active ethers were all optically active, and in each case the rotation of the rearranged product was of the same sign as that of the starting material. It is also to be noted that partial racemization accompanies this type of rearrangement, a fact which is significant in view of the results obtained in this Laboratory on the Hofmann, Curtius and Lossen rearrangements where no appreciable racemization occurred.

There is of course more than one possible interpretation of these facts. An explanation is suggested by the results of Wallis and Moyer.[5] If, during rearrangement, the migrating group is never completely free from the rest of the molecule, it is possible for it to maintain an asymmetric configuration during the period required for the complete readjustment of the valence forces. At least partially active products should then not be unexpected. However, we should not anticipate that such a group with a sextet of electrons would have as great optical stability as one in which the asymmetric carbon atom has at all times its complete octet of electrons, and such a difference might be expected to be disclosed by the appearance of partial racemization in the former case. It is no contradiction of this conception that at least part and perhaps all of the observed racemization may be explained by the assumption that a certain amount of the alkylated ether is formed through recombination of butylene with the free phenol, since the formation of butylene is likewise evidence of the inherent instability of such positive groups. The absence of racemization during the Curtius, Lossen and Hofmann types of rearrangement strongly suggests that in these cases the migrating group is always associated with its pair of binding electrons.

A second explanation of the activity of the products lies in the possibility that the alkyl phenols are not produced by a true rearrangement but result from a metathetical reaction involving two molecules of the ether. We must accordingly consider the possibility of a mechanism such as the following



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[8] Niederl and Natelson, THIS JOURNAL, 54, 1063 (1932), and earlier references.

[9] In our first experiments with optically active *s*-butyl phenyl ether we failed to isolate the very small quantities of alkylated phenol which are thus produced (8–15% of the theoretical). We were led, therefore, to state at the Washington meeting of the American Chemical Society that no rearranged phenol was obtained from *s*-butyl phenyl ether by the method of Niederl and Natelson, an impression we now wish to correct.

Evidence that a bimolecular process must be considered in reactions of the present type has already been furnished by Short and Stewart[7] and by Sowa, Hinton and Nieuwland.[10] The introduction of more than one alkyl group into the benzene nucleus can be explained on the basis of a metathetical reaction of the above type[11] in which an ether molecule reacts with the substituted phenol which has just been formed.

It is to be pointed out that as far as the present discussion is concerned it makes little difference whether the isomerization of the alkyl phenyl ethers to alkylated phenols is a true rearrangement, or a methathesis involving two or more molecules. The positive group which is involved is able to maintain an asymmetric configuration, at least to a considerable extent, during the course of the transformation. However, the conception of a bimolecular process such as has been formulated above can be tested experimentally by the use of optically active compounds. We have devised certain experiments designed 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. The results of these experiments will be reported at a later date.

Experimental Part

Preparation of the Sodium Phenolates.—One molecular weight of the phenol or cresol was dissolved in 200 cc. of pure benzene. To this was added rapidly and with vigorous shaking a solution of one mole of sodium hydroxide in the minimum amount of water (30 cc.). The crystals which resulted were filtered rapidly and dried in a vacuum desiccator over potassium hydroxide until constant weight was attained. The hydrated salts obtained in this manner were superior to the anhydrous phenolates in reactivity toward alkyl bromides.

Preparation of *dl-s*-Butyl Phenyl and Cresyl Ethers.—One mole of *s*-butyl bromide and 1.05 to 1.10 moles of the sodium phenolate or cresolate were heated at 110–120° for eighteen to twenty-four hours. The cold reaction mixture was then treated with water and extracted twice with ether. The ether extracts were washed repeatedly with a 10% solution of potassium hydroxide to remove unchanged phenol or cresol, then washed with water, and dried over calcium chloride. After removal of the ether the residue was fractionated under reduced pressure. *s*-Butyl phenyl ether: yield, 54–59%; b. p. 70–72° (5 mm.); 84–85° (14 mm.); 194.5° (corr.) (760 mm.); n_D^{25} 1.4926; d_4^{24} 0.9333.[12] *s*-Butyl *m*-cresyl ether (yield 61–66%) had the properties described by Niederl and Natelson.[8] *s*-Butyl *p*-cresyl ether: yield, 65–70%; b. p. 97–99° (14 mm.); 215–218° (761 mm.); n_D^{25} 1.4927; d_4^{24} 0.9226.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.41; H, 9.82. Found: C, 80.10; H, 9.82.

Preparation of the Optically Active *s*-Butyl Phenyl Ethers.—*s*-Butyl alcohol was resolved in the form of its phthalic acid ester according to the method of Pickard and Kenyon.[13] Much time was saved, however, and an equally satisfactory product was obtained by heating the pure brucine salt of the *s*-butyl phthalate directly with aqueous sodium hydroxide rather than following the original method. The optically active alcohol, as it was formed, was distilled over. The aqueous distillate was saturated with potassium carbonate. The alcohol was separated, dried over potassium carbonate, and distilled; $[\alpha]_D^{20}$ +12.0 (pure liquid).

The active *s*-butyl alcohol was saturated at 0° with dry hydrogen bromide gas, and the product worked up according to the method of Levene and Marker.[14] A certain amount of racemization occurs during this conversion for the relative rotations of the bromide and the alcohol were not always the same. The highest rotation observed for the bromide was $[\alpha]_D^{22}$ −19.77[15] (pure liquid).

The optically active ethers were prepared in the same way as the racemic ethers. The rotations recorded refer to the pure liquids in a 1-dm. tube.

Ether	B. p., °C.	α_{6563}	α_{5893}	α_{5461}	α_{4861}	$[\alpha]_{5893}$	Temp., °C.
d-s-Butyl phenyl	86–90 (16 mm.)	+22.98	+27.98	+33.52	+46.6	+30.02	25
d-s-Butyl *m*-cresyl	103–108 (17 mm.)	+19.76	+25.35	+30.39	+40.7	+27.35	27
d-s-Butyl *p*-cresyl[a]	97–100 (14 mm.)	+16.67	+21.40	+25.63	+34.5	+23.14	25

[a] n_D^{26} 1.4930.

Experiments with *dl-s*-Butyl Phenyl Ether

s-Butyl phenyl ether showed no appreciable decomposition when heated at the boiling point, or when boiled for several hours with half its weight of fused zinc chloride in the absence of acetic acid. Concentrated sodium hydroxide caused a slow decomposition into phenol. Anhydrous titanium tetrachloride in dry chloroform readily attacked the ether at room temperature, giving phenol and butylene. Anhydrous aluminum chloride caused partial decomposition to phenol, and partial rearrangement to *s*-butylphenol and higher boiling products which may be more highly butylated phenols.[7]

Action of a Mixture of Sulfuric and Acetic Acids (Niederl's Reagent) on *s*-Butyl Phenyl Ether.—A typical experiment with this ether is described in detail to illustrate the general procedure used throughout this work. To 37 g. (0.25 mole) of *s*-butyl phenyl ether there was added

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[10] Sowa, Hinton and Nieuwland, THIS JOURNAL, **54**, 2019, 3694 (1932); **55**, 3402 (1933). See also Smith, *ibid.*, **56**, 717 (1934).

[11] See also Lauer and Spielman, *ibid.*, **55**, 4923 (1933).

[12] Smith (*loc. cit.*) gives d_4^{21} 0.973, n_D^{24} 1.4943. Tronov [*Ber.*, **62**, 2845 (1929)] gives d_4^{20} 0.9415.

[13] Pickard and Kenyon, *J. Chem. Soc.*, **99**, 64 (1911); **103**, 1939 (1913); **105**, 850 (1914).

[14] Levene and Marker, *J. Biol. Chem.*, **91**, 445 (1931).

[15] Levene and Marker obtained a bromide having $[\alpha]_D^{25}$ −13.79 (pure liquid).

62.5 cc. of Niederl's reagent (12.5 cc. of concd. sulfuric acid made up to 62.5 cc. with glacial acetic acid). The flask was shaken, set in the bath, and a condenser and eudiometer were attached. The temperature was raised to 107°,[16] at which point butylene was evolved rapidly. The temperature was maintained at 105–108° until no more gas was evolved.[17] The total time required was two and one-half hours, and 1925 cc. of butylene was collected.

Separation of the Rearranged Phenols and *s*-Butyl Acetate.—The mixture was cooled and treated with 45 g. of sodium hydroxide dissolved in 200 cc. of ice water. (The solution should be slightly acid at this point; if alkaline a little acetic acid should be added to bring it to the desired acidity.) A yellow oil separated consisting of the rearranged phenols, phenol, acetylated phenols and *s*-butyl acetate. The sulfonated phenol is in the aqueous layer. Its separation is described later. It is very difficult to fractionate small amounts of such mixtures. However, a very good separation may be achieved by taking advantage of the differences in acid strength of the constituents: the simple and acetylated phenols are readily soluble in 4% aqueous alkali; the *s*-butylphenols are practically insoluble. Accordingly, the slightly acid mixture was extracted several times with ether and the ether extracts shaken with 4% sodium hydroxide (4 extractions totaling 300 cc.), washed twice with dilute sodium carbonate, twice with water and dried over sodium sulfate. The ether was evaporated, and the residue was fractionated at atmospheric pressure. It gave 3.2 g., b. p. 110–112° (*s*-butyl acetate); 1.0 g., b. p. 215–235°; 2.1 g., b. p. 235–250°. Assuming the last two fractions to be rearranged phenols,[18] the yield is 8.5%. The mixture of *s*-butylphenols obtained was insoluble in dilute alkali, but soluble in 40% potash or Claisen's solution. The last fraction gave an acetic acid derivative (prepared according to Niederl and Natelson) which melted sharply at 112°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.1; H, 7.76. Found: C, 68.7; H, 7.70.

Separation of Phenol and the Hydroxyacetophenones.—The 4% sodium hydroxide extract of these substances was acidified with 10 cc. of concentrated sulfuric acid. The oil so liberated was extracted with ether. The ether solution was washed and dried, the ether distilled at atmospheric pressure, and the residue fractionated under vacuum. This gave 5.5 g. of phenol (identified by b. p., m. p. and by conversion to tribromophenol, and to phenyl benzoate), and two higher boiling fractions, A, 110–120° (15 mm.); B, 180–190° (15 mm.). Fraction A, when redistilled at atmospheric pressure, boiled at 214–215°, the boiling point of *o*-hydroxyacetophenone. Its identity was confirmed by analysis for carbon and hydrogen. Fraction B usually solidified in the condenser. After several crystallizations from benzene and petroleum ether (30–60°) it melted at 107.5°. The formation of a phenylhydrazone which melted at 139–141° showed that fraction B was mainly *p*-hydroxyacetophenone. This was further checked by carbon and hydrogen analyses.

Separation of the Sodium Phenol Sulfonate.—The original aqueous solution, after the extraction with ether, gave a heavy colorless precipitate of sodium phenol sulfonate on standing twenty-four hours, or by salting out. The dry salt weighed 14.8 g. When crystallized from 50% acetic acid and air dried it retained two molecules of water of crystallization. When dried at 140° the anhydrous form was obtained.

Analysis for $C_6H_5O_4SNa \cdot 2H_2O$. Calcd.: Na, 9.91. Found: (air dried salt) 9.95. *Analysis* for $C_6H_5O_4SNa$. Calcd.: Na, 11.73. Found: (salt dried at 140°) Na, 11.73. Loss on drying, calcd. for $C_6H_5O_4SNa \cdot 2H_2O$: $2H_2O$, 15.63. Found: (at 140°) H_2O, 15.5.

The Action of Zinc Chloride in Glacial Acetic Acid.—This reagent has the advantage of bringing everything immediately into solution. Optimum yields of rearrangement products were obtained by using two moles of zinc chloride to one of the ether. In one experiment, 4.4 g. of *s*-butyl phenyl ether was added to 7.5 g. of anhydrous zinc chloride dissolved in 20 cc. of glacial acetic acid, and the solution heated at 112–114° for three hours. Upon working up the solution in the usual manner, the following products were obtained: 108 cc. of butylene (0.25 g.); 0.3 g. of *s*-butyl acetate; 0.8 g. of *s*-butylphenol, b. p. 233–238°; 1.6 g. of phenol; 0.5 g. of *p*-hydroxyacetophenone, m. p. 107°.

Experiments with *dl*-*s*-Butyl *m*-Cresyl Ether

Action of a Mixture of Sulfuric and Acetic Acids.—When 23.5 g. of the ether was heated for two and a half hours with one molecular equivalent of the reagent, the following products were obtained: 1530 cc. of butylene (3.8 g.); 10.3 g. of sodium *m*-cresol sulfonate (anhydrous as shown by analysis after crystallization from glacial acetic acid. *Anal.* Calcd. for $C_7H_7O_4SNa$: Na, 10.95. Found: Na, 10.87). 4.1 g. of *m*-cresol, b. p. 92–95° (14 mm.) (identified as tribromo-*m*-cresol, m. p. 79–80°, and as *m*-cresyl carbanilide, m. p. 120°); 0.6 g. of a phenolic oil, b. p. 110–112° (14 mm.) which from its b. p. is most likely 6-aceto-3-methylphenol (b. p. 105–106° (9 mm.)). The material insoluble in 4% sodium hydroxide on distillation gave 6.5 g., b. p. 130–140° (17 mm.), 244–260° (760 mm.); and 1.2 g., b. p. 260–275° (760 mm.). The lower boiling fraction gave an acetic acid derivative which melted at 150–152° and agreed in other properties with the product obtained by Niederl and Natelson, to which they assigned the structure 3-methyl-6-*s*-butylphenol. The composition of the higher boiling fraction was not definitely ascertained. It is phenolic in character and may contain the two other possible isomers or some dibutylated cresols.

Experiments with *dl*-*s*-Butyl *p*-Cresyl Ether

A mixture of 65.6 g. (0.4 mole) of the ether and 106 cc. of Niederl's reagent was heated at 117–120° for two hours, and then boiled for one-half hour. The following products were obtained: 10.0 g. of butylene; a trace of *s*-

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[16] The optimum temperature varies with the ether; in general it is somewhat below the boiling point of the reagent.

[17] It is best at this point to raise the reaction mixture to the boiling point for a few minutes in order to remove any butylene which may be dissolved in the mixture. The yield of *s*-butyl acetate was always increased when this was not done.

[18] Smith (*loc. cit.*) gives the b. p. of the product obtained from *s*-butyl phenyl ether and aluminum chloride as 236°. See also, in this connection, Estreicher, *Ber.*, **33**, 442 (1900); Meyer and Bernhauer, *Monatsh.*, **53–54**, 721 (1929); Hickinbottom, *J. Chem. Soc.*, **117**, 121 (1920).

butyl acetate; 30.0 g. of sodium 4-methyl-phenolsulfonate-2; 11.0 g. of *p*-cresol, b. p. 200–210°; 2.6 g. of 2-acetyl-4-methylphenol; 20 g. of material insoluble in 4% sodium hydroxide. The sodium sulfonate after crystallization from 50% acetic acid and drying at 90° for two hours retained one-half a molecule of water.[19]

Anal. Calcd. for $C_7H_7O_4SNa \cdot 0.5H_2O$: Na, 10.50. Found: Na, 10.24.

The *p*-cresol was identified as dibromo-*p*-cresol, m. p. and mixed m. p. 46–47°. The 2-acetyl-4-methylphenol melted at 48°. Its phenylhydrazone was prepared in good yield and melted at 153–154°.[20]

Two distillations of the material insoluble in 4% sodium hydroxide gave (a) 1.4 g., b. p. to 245°; (b) 5.6 g., b. p. 245–252°; (c) 4.3 g., b. p. 255–260°; (d) 3.0 g., b. p. 260–270°; (e) 2.5 g., b. p. 270–280°. Fractions a, b and c solidified to long colorless needles on standing for several days. They melted at 44–44.5° after crystallization from low boiling petroleum ether. Pure *s*-butyl-4-methylphenol is a colorless solid of strong thymol-like odor. It is insoluble in 4% alkali but soluble in 20% potassium hydroxide and readily soluble in Claisen solution. The acetic acid derivative melted at 80–81°.

Analysis of the phenol. Calcd. for $C_{11}H_{16}O$: C, 80.41; H, 9.82. Found: C, 80.43; H, 10.2.

Analysis of the acetic acid derivative. Calcd. for $C_{13}H_{18}O_3$: C, 70.20; H, 8.18. Found: C, 70.00; H, 8.40.

Fractions d and e could not be induced to crystallize. Since only one mono-*s*-butylcresol should be obtained from *s*-butyl *p*-cresyl ether it seems probable that these higher boiling fractions contain some di-butylated cresols.

Experiments with the Optically Active Ethers[21]

A. *d*-*s*-Butyl Phenyl Ether

Action of a Mixture of Sulfuric and Acetic Acids.—The ether (6.25 g.) having $\alpha = +27.98$ when treated with Niederl's reagent in the usual manner, gave 0.51 g. of butylene; 1.4 g. of sodium phenol sulfonate; 0.7 g. of phenol; and a portion insoluble in 4% sodium hydroxide. This last material was distilled at atmospheric pressure, and gave: (a) 0.3 g. of *s*-butyl acetate; (b) 0.3 g., b. p. 220–230°, $\alpha = +4.20$; (c) 0.2 g., 230–240°, $[\alpha]$ +4.77 in absolute alcohol ($c = 0.147$ g. in 5 cc.). The clear alkaline solution of fraction b (30% potassium hydroxide used) was also optically active.

Action of Zinc Chloride in Glacial Acetic Acid.—From 4.4 g. of the *d*-ether ($\alpha = +27.98$) there was obtained: 0.25 g. of butylene; 0.3 g. of *s*-butyl acetate; 1.4 g. of phenol; 1.2 g. of material which on redistillation boiled at 233–238°, and had the properties of a *s*-butylphenol, $\alpha = +5.80$.

B. *d*-*s*-Butyl *m*-Cresyl Ether

Action of a Mixture of Sulfuric and Acetic Acids.—In one experiment 8.6 g. of the ether ($\alpha^{27} = +25.35$) gave 0.44 g. of butylene; 1.9 g. of sodium *m*-cresol sulfonate; 1.7 g. of *m*-cresol; and a portion insoluble in 4% alkali. This material on distillation gave (a) 1.1 g., b. p. 100–120° (*s*-butyl acetate); (b) 0.8 g., b. p. 240–250°, $\alpha = +5.20$; (c) 1.0 g., b. p. 250–260°, $\alpha = +5.70$; (d) 0.3 g., b. p. 270–275°, $[\alpha]$ +6.48, in absolute alcohol ($c = 0.292$ g. in 10 cc.). An alkaline solution (20% KOH) of fraction c was also optically active. On treating the solution with bromoacetic acid, 0.5 g. of the acetic acid derivative was obtained; 0.4185 g. of this in 10 cc. of absolute alcohol gave $\alpha_{5463} = +0.40$ (2-dm. semi-micro tube); $[\alpha]_{5463}$ +4.76. On recrystallization from dilute alcohol it melted at 148–151°. 0.1354 g. in 5 cc. of absolute alcohol solution gave $\alpha_{5463} = +0.26$ (2-dm. semimicro tube); $[\alpha]_{5463}$ +4.82. After another crystallization it melted at 152.5–153.5°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2. Found: C, 70.0; H, 8.0.

C. *d*-*s*-Butyl *p*-Cresyl Ether

Action of a Mixture of Sulfuric and Acetic Acids.—From 10.5 g. of the ether, $\alpha = 21.40°$ the following products were obtained: 1.68 g. of butylene; 4.0 g. of sodium-4-methylphenolsulfonate-2; 1.7 g. of *p*-cresol; 0.2 g. of 4-methyl-2-acetylphenol (phenylhydrazone, m. p. 152–153°; 3.1 g. of material insoluble in 4% alkali. This last portion was distilled at atmospheric pressure, and gave the following fractions: (a) 0.2 g. of *s*-butyl acetate; (b) 0.7 g., b. p. 235–248°, $\alpha_{5463} = +2.59$; (c) 1.2 g., b. p. 248–255°, $\alpha_{5463} = +2.75$; (d) 0.7 g., b. p. 255–265°, $\alpha_{5463} = +2.88$. Fractions b and c partially solidified to long colorless needles on standing for two weeks at 0°. After crystallization from petroleum ether they melted at 43.5–44°; 0.0733 g. in 5 cc. of absolute alcohol gave $\alpha_{5463} = +0.09$, 2-dm. semi-micro tube, $[\alpha]_{5463}$ +3.0. The acetic acid derivative melted at 72–73°; 0.1038 g. dissolved in 5 cc. of absolute alcohol gave $\alpha_{5463} = +0.08$ (2-dm. semi-micro tube), $[\alpha]_{5463}$ +1.93.

Action of Zinc Chloride and Glacial Acetic Acid.—Five and three-tenths grams of the ether ($\alpha = +17.89$) gave 0.89 g. of butylene; 1.2 g. of *p*-cresol; 0.2 g. of 2-acetyl-4-methylphenol; 2.6 g. of material insoluble in 4% alkali. This last portion was fractionated, giving a trace of *s*-butyl acetate; 1.8 g., b. p. 225–240°, $\alpha_{5893} = +6.98$; $\alpha_{5463} = +8.37$; 0.7 g. b. p. 240–255°, $\alpha_{5893} = +9.29$; $\alpha_{5463} = +11.19$. One and one-half grams of the lower boiling fraction was converted to the acetic acid derivative. The crude product was recrystallized from petroleum ether, 0.0880 g. in 5 cc. of absolute alcohol solution gave $\alpha_{5893} = +0.22$, $\alpha_{5463} = +0.28$; $[\alpha]_{5893}$ +6.24, $[\alpha]_{5463}$ +7.93 (2-dm. semi-micro tube). The high rotation of these products compared to those obtained with sulfuric acid and acetic acid again indicates that partial racemization takes place during these reactions.

Summary

d-*s*-Butyl phenyl, *m*-cresyl and *p*-cresyl ethers have been prepared and converted to alkylated phenols by treatment with a mixture of sulfuric and acetic acids, or with anhydrous zinc chloride and acetic acid.

In all the cases studied optically active compounds were obtained, and in each case the rotation of the final product was of the same sign as

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[19] Anschütz and Hodenius, *Ann.*, **415**, 74 (1918).

[20] Von Auwers, *ibid.*, **365**, 343 (1909), gives 152.5°.

[21] Unless otherwise indicated all values of the rotatory power are for 25°, 1-dm. microtube, D line and without solvent.

that of the optically active ethers from which it was prepared.

Partial racemization always accompanied this change. This fact is significant in view of the absence of racemization observed in this Laboratory in rearrangements of the Curtius, Hofmann and Lossen types.

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

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Thiomorpholine Derivatives[1]

BY LAWTON A. BURROWS[2] AND E. EMMET REID

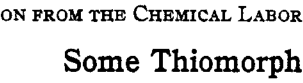
Introduction

In view of the local anesthetic activity and low toxicity of the esters of β-4-morpholine-ethanol and γ-4-morpholine-propanol,[3] it was thought that a study of the preparation and properties of analogous compounds in which the oxygen of the morpholine ring is replaced by sulfur should be of interest. Several investigators[4] have prepared derivatives of thiomorpholine but little attention has been paid to their pharmacological properties. Derivatives from amino alcohols have not been described.

Preparation

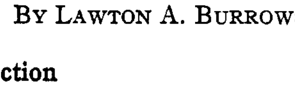
Thiomorpholine-4-ethanol, I; its oxide, II and its dioxide, III; Thiomorpholine γ-4-propanol, IV.

I



II

III



IV

I.—A solution of one mole of β,β'-dibromodiethyl sulfide in 1500 cc. of benzene was placed in a three-necked flask fitted with a reflux condenser and mechanical stirrer. Three moles of monoethanolamine[5] was added slowly. The reaction mixture was warmed on the steam-bath for six hours with constant stirring. After cooling, it was filtered through dry cotton and the residue was extracted three times with 200-cc. portions of benzene. The combined extracts were added to the original filtrate and dry hydrogen chloride was bubbled through the solution until precipitation was complete. The hydrochloride was recrystallized from 95% alcohol; yield 43.5% of theoretical.

II.—The procedure was exactly the same as in the preparation of I except that the solution of β,β'-dibromodiethyl sulfoxide was cooled to 20° during the addition of the amino alcohol and then warmed on the steam-bath for three hours; yield 45% of theoretical.

III.—The general procedure was the same as for I but chloroform was used as a solvent due to the insolubility of III in benzene. The solution of β,β'-dibromodiethyl sulfone was cooled in ice water during the entire addition of the monoethanolamine. The reaction was then allowed to run for one hour at room temperature and two hours on the steam-bath; yield 58% of theoretical.

IV.—A mixture of 32.5 g. of γ-propanolamine in 150 cc. of chloroform and 35.8 g. of β,β'-dibromodiethyl sulfide was heated on the steam-bath four hours. The hydrobromide of the amino alcohol which was formed in the reaction was filtered off and 15.5 g. of γ-propanolamine was recovered from it. The hydrochloride of IV was precipitated from the filtrate by dry hydrogen chloride and recrystallized from 95% alcohol: yield 42% of theoretical.

In the preparation of I, II, III and IV, it was found that much better yields were obtained and the products were more easily isolated when three moles of the amine were used to one of the dibromo compound instead of using only one mole of amine and sodium acetate or sodium carbonate to take up the hydrogen bromide liberated in the reaction. It was also found essential to use a non-polar solvent and isolate the products as their hydrochlorides instead of as the free bases. The use of alcohol as a solvent led to very poor yields. The above condensations were also tried using β,β'-dichlorodiethyl sulfide, sulfoxide and sulfone, but the corresponding β,β'-dibromo compounds gave much better yields.

Aliphatic Esters of I, II and III

I.—The aliphatic esters of I from the acetate to the heptoate inclusive were prepared by warming 10 g. of the hydrochloride of I with an excess of the proper acid chloride or anhydride until solution took place. The reaction mixture was then heated to 125° for ten minutes and poured with stirring into cold ether. The crystals were filtered, washed several times with ether and recrystallized from 95% alcohol. Yields in all cases were 90 to 95% of the theoretical.

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(1) Abstract of dissertation submitted by Lawton A. Burrows in partial fulfilment of requirements for the degree of Doctor of Philosophy in Chemistry at The Johns Hopkins University, Baltimore, Maryland. Read in preliminary form at the Chicago meeting of the American Chemical Society, September, 1933.

(2) William R. Warner & Co., Inc., Fellow 1931–34.

(3) J. H. Gardner and E. O. Haenni, THIS JOURNAL, **53**, 2767 (1931); J. H. Gardner, D. V. Clarke and Joseph Semb, *ibid.*, **55**, 2999–30 (1933).

(4) Clarke, *J. Chem. Soc.*, **101**, 1538 (1912); Davies, *ibid.*, **117**, 297 (1920); Helfrich and Reid, THIS JOURNAL, **42**, 1208 (1920); Cashmore and McCombie, *J. Chem. Soc.*, **123**, 2884 (1923); Lawson and Reid, THIS JOURNAL, **47**, 2821–2836 (1925); Alexander and McCombie, *J. Chem. Soc.*, 1913–1918 (1931).

(5) The monoethanolamine used in this investigation was generously furnished by the Carbide and Carbon Chemicals Corp.