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The Mechanism of the Alkaline Fusion of Benzenesulfonic Acid.[1,2]

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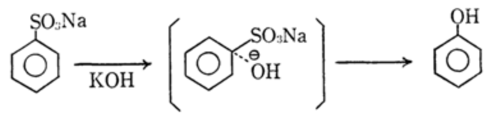
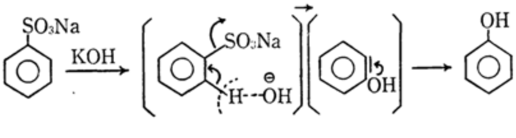
Benzenesulfonic acid-1-^{14}C was fused with potassium hydroxide at 320—350°C for five minutes. The phenol obtained was then degraded as usual, and the distribution of carbon-14 in the phenol was determined. Practically all the ^{14}C activity was found at the 1 position of the phenol, which means that there is no migration of the ^{14}C originally labeled at the position 1 or the benzenesulfonic acid. Benzenesulfonic acid was also treated with potassium hydroxide enriched with ^{18}O. The resulting phenol was found to be incorporated, with the same concentration of ^{18}O as that of the ^{18}O enriched water used. The results show that the mechanism of the reaction is of a simple S_N2 type and not of the elimination-addition type involving the benzyne intermediate, while there was no oxygen migration in the reaction.

The alkaline fusion of benzenesulfonic acid was first effected by Wurtz[3] or Kekulé[4] more than a hundred years ago. Since then, the method has been used as a conventional technique for the manufacture of phenol and related hydroxy compounds. Recently, however, the alkaline fusion process has been giving way to other, more simple methods for the production of phenol, and its use is quite limited nowadays. Yet the alkaline fusion is still considered to be one of the best methods to introduce the hydroxyl group into the aromatic ring. As for the reaction mechanism, the alkaline fusion of aromatic sulfonic acids has been classified only as a simple S_N2-type nucleophilic aromatic substitution,[5] without any concrete evidence. However, under strong alkaline conditions such as those employed in this reaction, one can postulate another mechanism involving the formation of a benzyne-type intermediate. It is interesting, in this respect, to compare the alkaline fusion of benzenesulfonic acid with that of halobenzene in a strong alkaline medium such as sodiumamide in liquid ammonia,[6] where the reaction is known to proceed via the initial abstraction of an ortho proton by the strong base, followed by the formation of an unstable intermediate benzyne which reacts very rapidly with a nucleophile to give the final product. In fact, a few previous works have not accepted the simple S_N2-type mechanism for the alkaline fusion reaction.[7] For instance, *p*-benzenedisulfonic acid or *p*-chlorobenzenesulfonic acid have been reported to produce resorsinol to some extent, and hence it has been suggested[8-10] that the alkaline fusion might not be a simple S_N2-type mechanism, but an elimination-addition type process which involves the participation of a benzyne-type intermediate to some extent. Meanwhile, another alternative pathway is also conceivable, the one involving the initial attack of the hydroxide anion on the sulfur atom, followed by the intramolecular migration of the oxygen atom to the benzene ring, thus giving phenol. This mechanism is not unlikely in view

I. Simple aromatic S_N-type mechanism



II. Elimination-addition mechanism



III. Oxygen migration mechanism

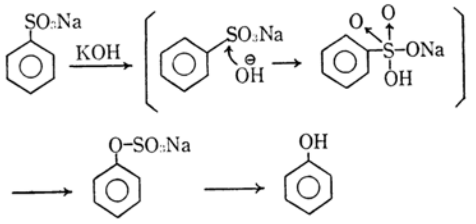


Fig. 1.

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[1] Phenols and Phenolic Esters. XI.

[2] This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this Fund.

[3] C. Wurtz, *Ann.*, **144**, 121 (1867).

[4] A. Kekulé, *Compt. rend.*, **64**, 753 (1866).

[5] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca (1953), p. 814.

[6] J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith and C. W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).

[7] H. E. Fierz-David and G. Stamm, *Helv. Chim. Acta*, **25**, 364 (1942).

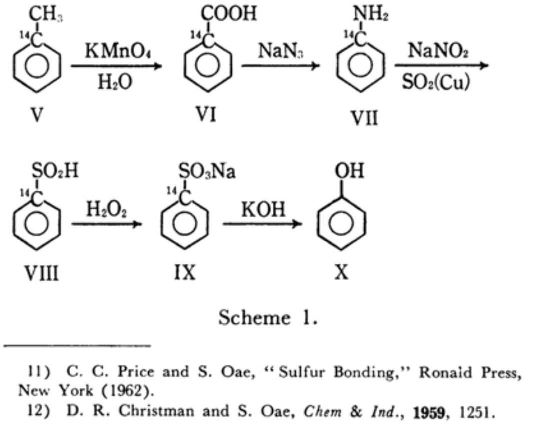
[8] R. Huisgen, *Angew. Chem.*, **72**, 91 (1960).

[9] D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill, New York (1964), p. 396.

[10] J. D. Roberts and M. Casserio, "Basic Principles in Organic Chemistry," W. A. Benjamin, New York (1964), p. 901.

of the fact that the sulfur atom is known to be attacked readily by a strong nucleophile because of its ability to expand the valence shell from an octet to a decet by using its d-orbitals.[11] In fact, in the alkaline fusion of diphenyl sulfone, the sulfur atom is the primary site of the nucleophilic attack by the hydroxide anion.[12] These three postulated mechanisms may be summarized as follows.

One of the most powerful ways to get a clear understanding of the mechanistic information of the alkaline fusion is the isotopic tracer technique. If one uses sodium benzenesulfonate specifically labeled with ^{14}C at its 1 position for the alkaline fusion and traces the ^{14}C radioactivity distribution in the resulting phenol, one can readily discriminate undesirable from desirable mechanistic schemes. If the reaction follows the mechanism I, all the ^{14}C activity originally labeled at benzenesulfonic acid-1-^{14}C will remain at the position 1 in the resulting phenol, whereas if the reaction proceeds through the benzyne-type intermediate, the distribution of the ^{14}C will be completely different from that to be expected from the mechanism I, and exactly a half of the ^{14}C will be found at the position 1 in the phenol, whereas the remaining half will be distributed equally at the 2 and 6 positions. In the meantime, the mechanism III can be tested by the use of $K^{18}OH$. If the reaction follows the path indicated by the mechanism III, the concentration of ^{18}O in the resulting phenol will be considerably lower than that of the potassium hydroxide employed, since the four oxygen atoms attached to the sulfur will be substantially equilibrated before collapsing to form the rearranged phenyl sodium sulfate. If the proton transfer among four oxygen atoms is very fast in the intermediate addition complex, the oxygen-18 content in the resulting phenol will become one-quarter that of the $K^{18}OH$ originally employed.

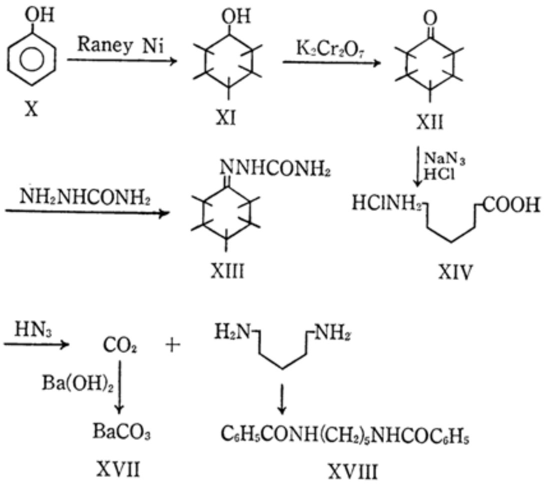


Scheme 1.

Results and Discussion

Benzensulfonic acid-1-^{14}C was synthesized as is shown in Scheme 1.

The degradative method is shown in Scheme 2.

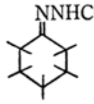
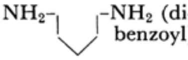


Scheme 2.

The results derived from the runs are shown in Table I. Cyclohexanonesemicarbazone was chosen as the standard sample for evaluating the activities of all the other products.

The degradation study indicates that practically all the ^{14}C activity of the phenol was found at position 1 where ^{14}C was originally labeled and the

TABLE I. THE ^{14}C COUNTING OBTAINED IN SCHEME 2

	 NNHCONH₂ (XIII)	CO_2 (XVII)	 NH_2–NH_2 (dibenzoyl) (XVIII)
c.p.m.	1726[a]	11714[a]	11[a]
	(2013)	(1952)	(42)
%	100	97.6	2.1
c.p.m.	912	6205	—
	(1064)	(1030)	
%	100	97.2	—

a) The activities are given after correction for background. The observed values are standardized to phenol, i. e., the corrected values are shown in brackets.

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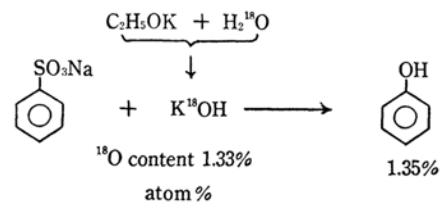
[11] C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York (1962).

[12] D. R. Christman and S. Oae, *Chem & Ind.*, **1959**, 1251.

TABLE II. THE ALKALINE FUSION WITH $K^{18}OH$

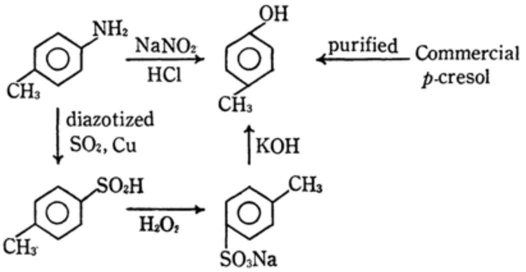


sulfonic acid group was originally attached. This observation clearly excludes the elimination-addition mechanism involving a benzyne-type intermediate, for it requires a half of the ^{14}C activity to be divided equally at the two ortho positions, and the remaining half to be at the position 1.

When the alkaline fusion of benzenesulfonic acid was carried out with ^{18}O-enriched potassium hydroxide (atom % of ^{18}O: 1.33), the resulting phenol was found to be incorporated with exactly the same concentration of ^{18}O (atom % of ^{18}O: 1.35). This observation does not favor the other alternative mechanism, which involves the initial nucleophilic attack of the hydroxide ion on the sulfur atom of the sulfonic acid, followed by the migration of the phenyl group from the sulfur atom to oxygen, since it is utterly inconceivable that he migration of the phenyl group takes place only at the entering oxygen atom. This fact is consistent with the findings of Makolkin.[13] According to this mechanism, the oxygen-18 concentration in the hydroxyl group of the resulting phenol should be between natural and a one-quarter excess of what was incorporated in the potassium hydroxide used, depending on the amount of proton-transfer during the reaction. The actual finding is not in accord with this prediction, but it is quite consistent with the mechanism of the simple aromatic S_N-reaction. In fact, this simple mechanism is only compatible with the data on the ^{14}C experiments. Therefore, both ^{14}C and ^{18}O tracer experiments unequivocally suggest that the alkaline fusion of benzenesulfonic acid proceeds through the path involving the direct nucleophilic attack of hydroxide on carbon 1, in a simple aromatic S_N-reaction as is shown by eq. I.

Another piece of evidence in support of the aromatic S_N-type mechanism for this reaction may be found in the fact that the alkaline fusion of *p*-toluenesulfonic acid did not give a mixture of *p*- and *m*-cresols, but only the isomer. Thus, the only product of the alkaline fusion of *p*-toluenesulfonic acid was, in all respects, identical to *p*-cresol. The cresol obtained from the alkaline fusion of *p*-toluidine via *p*-toluenesulfinic acid and *p*-toluenesulfonic acid (shown in Scheme 3) was also completely identical with that of an authentic sample prepared from the direct hydrolysis of the diazotized-*p*-toluidine.

In order to obtain further supporting evidence for the direct aromatic S_N mechanism, mesitylenesulfonic acid was subjected to alkaline fusion.[14] Since this compound has no ortho hydrogen available for the elimination of the hydrogen and sulfonic acid groups to form a benzyne-like intermediate, the formation of mesitylenol through the benzyne intermediate is not possible. Yet a substantial amount of mesitylenol was obtained in the ordinary alkaline fusion of mesitylenesulfonic acid. The rather low yield of the phenol, 30%, is probably due to the large steric compression of the transition complex of the reaction. All these observations clearly suggest that the alkaline fusion of these sulfonic acids proceeds through the path involving the nucleophilic replacement the SO_3H group by the hydroxide ion at position 1, much the same as in the usual aromatic S_N reaction of aromatic halides.



Scheme 3.

Characteristic infrared absorption band (cm^{-1}), *p*-cresol 815 (very strong) 1105 (strong) *m*-cresol 855, 875 (strong) 115 (strong) 1080 (doublets).

Experimental

The preparation of Benzenesulfonic Acid-1-^{14}C. —*Acetic Acid-1-^{14}C.*—Acetic acid-1-^{14}C was prepared following the usual method.[15] A typical example is as follows. A Grignard solution prepared from 1.89 g. of methyl iodide and 291 mg. of magnesium in 50 ml. of dry ether was carboxylated with dried $^{14}CO_2$ generated from 0.655 g. of barium carbonate, which has 1.0 mc. of ^{14}C activity in a vacuum system. Acetic acid-1-^{14}C was converted to sodium acetate. The yield was 0.200 g. (quantitative).

Ethyl Acetate-1-^{14}C.[16]—Sodium acetate-1-^{14}C (0.40 g.) was esterified with 1.5 ml. of freshly-prepared ethyl phosphate. The yield was 0.395 g. (90%).

1-Methyl Cyclohexanol-1-^{14}C.[16]—To the Grignard solution prepared from 32.5 g. of pentamethylenedibromide and 5.22 g. of magnesium, 2.96 g. of ethyl acetate-1-^{14}C in 150 ml. of absolute ether added. After the decomposition of the above Grignard solution with an ammonium chloride solution, 1-methyl cyclohexanol-1-^{14}C was obtained. The yield was 2.82 g., a 97% yield.

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13) I. A. Makolkin, *Acta Physicochim.*, **16**, 88 (1942).

14) R. Biedermann and A. R. Ledoux, *Ber.*, **8**, 250 (1875).

15) A. Murray and D. L. Williams, " Organic Synthesis with Isotopes," Part I, Interscience, New York (1958), p. 34.

16) A. Murray and D. L. Williams, ibid., p. 102.

*Toluene-1-^{14}C.*17)—The conversion of 1-methyl-cyclohexanol-1-^{14}C to toluene-1-^{14}C was carried out following the method employed by Sixma et al., using platinum chloride on alumina as the dehydration and dehydrogenation catalyst. From 5.00 g. of 1-methyl cyclohexanol-1-^{14}C, 2.60 g. of toluene-1-^{14}C was obtained (a 65% yield).

*Benzoic Acid-1-^{14}C.*16)—Toluene-1-^{14}C (1.53 g.) was oxidized with 7.0 g. of potassium permanganate in an aqueous solution. Benzoic acid (1.47 g.) was thus obtained (a 79% yield). Recrystallization from water gave colorless crystals with a m. p. of 122°C.

*Aniline-1-^{14}C.*18)—Benzoic acid-1-^{14}C (6.1 g.) was treated with 5.0 g. of sodium azide in a mixture of 40 ml. of chloroform and 20 ml. of concentrated sulfuric acid; aniline-1-^{14}C (3.9 g.) was thus obtained (a 84% yield). The b. p. was 181—182°C.

*Benzenesulfinic Acid-1-^{14}C.*19)—Aniline (3.9 g.) was diazotized with 3.2 g. of sodium nitrite and 5 ml. of concentrated sulfuric acid in 60 ml. of water. The diazonium solution was saturated with sulfur dioxide gas which had been generated from sodium bisulfite and sulfuric acid until the weight of the gas reached to 20 g. Then to this solution was added 25 g. of copper metal which had been freshly prepared from cupric salfate and zinc powder, with the temperature maintained below 5°C. After the gas evolution had ceased, the precipitated copper was filtered and washed with ether several times. The filtrate was then extracted three times with 50 ml. of ether. The combined ether solution was dried over anhydrous magnesium sulfate overnight. Then the ether was evaporated, and benzenesulfinic acid-1-^{14}C was obtained as slightly yellow-colored crystals. The yield was 4.7 g.; 78.3%; m. p. 84°C.

Benzenesulfonic Acid-1-^{14}C.—Benzenesulfinic acid-1-^{14}C (4.7 g.) was suspended in 90 ml. of a 2% hydrogen peroxide solution at room temperature. The mixture was then stirred with a magnetic stirrer at room temperature until the suspended sulfinic acid had been completely dissolved. The solution was kept standing overnight. Then the solution was titrated with a standard sodium hydroxide solution and dried over a water bath. Colorless hair-like crystals of sodium benzenesulfonate-1-^{14}C were thus obtained. The yield was 5.7 g. (100%).

The Alkaline Fusion of Sodium Benzenesulfonate-1-^{14}C.—A typical run was as follows. In a 50-ml. nickel muffle was fused 10 g. of potassium hydroxide. Into this molten potassium hydroxide 3.0 g. of sodium benzenesulfonate-1-^{14}C was stirred with a steel rod equipped with a thermometer. The reaction was carried out at temperatures between 300 and 340°C for 5 min. After that the vessel was rapidly cooled with water. The solidified reactants were dissolved with a concentrated hydrochloric acid solution until the solution had strongly acidified. The aqueous solution was then steam-distilled until the precipitate with bromine did not appear. The distillate was saturated with sodium chloride and then extracted three times with 60 ml. of ether. The ether solution was distilled. The yield of phenol-*x*-^{14}C was 1.1 g. (68%); b. p. 73°C/10 mmHg. Since no detectable change was observed when the experiment was performed under a nitrogen gas stream, the fusion was carried out in the open air.

The Degradation of Phenol-*x*-^{14}C.—The degradation method for phenol-*x*-^{14}C is shown in Scheme 2. A typical run was as follows:

*Cyclohexanol-x-^{14}C.*20)—Phenol-*x*-^{14}C was reduced as usual using Raney's nickel as a hydrogenation catalyst in a 100-ml. autoclave. The solvent used was methanol. From 5.0 g. of phenol-*x*-^{14}C, 4.2 g. of cyclohexanol-*x*-^{14}C was obtained (a 78% yield). B. p. 159—162°C.

*Cyclohexanone-x-^{14}C.*20)—Cyclohexanol-*x*-^{14}C was oxidized to cyclohexanone-x-^{14}C using with potassium bichromate as the oxidizing agent. From 4.2 g. of cyclohexanol-*x*-^{14}C, 3.5 g. of cyclohexanone-*x*-^{14}C was obtained (81.6%; b. p. 155—159°C). A part of the cyclohexanone was converted to its semicarbazone, which was then used as the standard sample for original ^{14}C activities. M. p. 167—167.5°C.

*6-Aminohexanoic Acid-x-^{14}C.*19)—Cyclohexanone-x-^{14}C was converted to 6-aminohexanoic acid according to the Schmidt reaction. Cyclohexanone (2.1 g.) in 30 ml. of water was treated with 7.4 g. of sodium azide; the ε-aminocaprolactum-x-^{14}C obtained was then hydrolyzed to afford 6-aminohexanoic acid-*x*-^{14}C hydrochloride. The hydrochloride was recrystallized from absolute-alcohol-anhydrous ether. The yield was 3.4 g. (90% yield).

The Decarboxylation of 6-Aminohexanoic Acid-x-^{14}C.20) — 6-Aminohexanoic acid-*x*-^{14}C hydrochloride (10.7 g.) was treated with 3.7 ml. of concentrated sulfuric acid, the resulting hydrochloride gas was removed by heating the solution up to 70°C under reduced pressure. The residue was placed in 100-ml. three-necked flask and connected to a Schmidt decarboxylation apparatus. To this mixture 20 ml. of 1.17 N hydrazoic acid was added drop wise over a 40-min. period at 40°C, and the ^{14}CO$_2$ generated was trapped with 0.25 N barium hydroxide. After the reaction had been completed (the time needed for this was 15 hr.), the apparatus was swept with CO$_2$-free nitrogen gas. The Ba^{14}CO$_3$ thus precipitated was collected in a dry box and washed with hot water and then with acetone. The yield of barium carbonate was 1.5 g. (84% yield). The residual 1,5-pentanediamine was changed to a dibenzoyl derivative, which was recrystallized four times from ethyl acetate-benzene. M. p. 133—133.5°C.

The Measurement of the Activities.—The activities of the samples were measured using a JRC Aloka-2π-gas flow G. M. counter using Q-gas. Known amounts of the samples were completely oxidized to carbon dioxide following the Van-Slyke wet-combustion method. The carbon dioxide generated was collected as barium carbonate; it was made into pellets and the activity were measured. The samples measured were cyclohexanone semicarbazone (XIII) as a standard total activity, barium carbonate (XV) generated by a Schmidt decarboxylation, and 1, 5-dibenzoyl pentanediamine (XVII). The amounts of pellets of barium carbonate obtained were 124 mg. (95%) from cyclohexanone semicarbazone, 173 mg. from barium carbonate and 151 mg. (97%) from 1, 5-dibenzoylaminopentane. The counting data are shown in Table I.

The Alkaline Fusion of Benzenesulfonic Acid

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17) H. Steinberg and F. L. J. Sixma., *Rec. Trav. Chim.*, **79**, 679 (1960).

18) E. F. Jenny and J. D. Roberts, *Helv. Chim. Acta*, **38**, 1248 (1955).

19) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

20) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

with $K^{18}OH$.—*The Preparation of Potassium Hydroxide-^{18}O.* —To a solution of 3 g. of potassium in 30 ml. of absolute ethanol, 1.5 ml. of water-^{18}O was added (^{18}O 1.645 atom %; Yeda Research and Development Co., Ltd., Israel). The ethanol and excess water were removed by distillation under reduced pressure, and the residue was dried over phosphorus pentoxide in vacuo. Thus, about 4.0 g. of potassium hydroxide-^{18}O (^{18}O 1.33 atom%) was obtained.

The Potassium Hydroxide-^{18}O Fusion of Sodium Benzenesulfonate.—A mixture of 1 g. of sodium benzenesulfonate and 2 g. of potassium hydroxide-^{18}O was heated at 320—330°C for 5 min. in a steel vessel, and cooled rapidly with tap water. The reaction mixture was then extracted with 50 ml. of hot water and acidified with concentrated hydrochloric acid. After the steam distillation of the mixture, a slight excess of bromine was added to the distillate, resulting in the formation of crude 2, 4, 6-tribromophenol; this was separated by filtration, washed, and dried. Repeated recrystallizations from aqueous ethanol and *n*-hexane afforded about 1.4 g. of colorless needles of a silky luster needles which melted at 92—94°C with sublimation. (Reported(21) m. p. 94—96°C). The atom percentage of ^{18}O was found to be 1.35%.

Attempts to Find Rearranged Products during the Alkaline Fusion of *p*-Toluene Sulfonic Acid.— Samples of *p*-cresols obtained by the following methods were checked by means of an Infrared Spectrum study to see if any rearrangement takes place during the alkaline fusion.

a) Commercially-available p-Cresol was purified by repeated distillation under reduced pressure; a fraction with a b. p. of 105°C/28 mmHg was collected.

b) p-Cresol from p-Toluidine.—*p*-Toludine was converted into its diazonium chloride, which was subsequently warmed on a water bath. Repeated distillation gave a fraction with a b. p. of 102°C/31 mmHg. The *p*-cresol thus obtained was used as a standard smaple for the infrared study.

c) p-Cresol from p-Toluenesulfonic Acid.—Potassium *p*-toluenesulfonate was fused with molten potassium hydroxide in a steel reaction vessel. Cresol was isolated and distilled under reduced pressure to give the main fraction (b. p. 104—105°C/28 mmHg).

d) p-Cresol from p-Toluenesulfonic Acid which had been Synthesized from p-Toluidine.—*p*-Toluidine was diazotized with sodium nitrite, and then converted into *p*-toluenesulfinic acid. *p*-Toluenesulfonic acid was prepared by oxidizing the above sulfinic acid with hydrogen peroxide. The method of alkaline fusion was the same as that described for the sodium benzene sulfonate. The infrared spectra of all these *p*-cresols, prepared by different methods, were consistent in all respects with that of the standard sample. In no case was there found any rearranged isomers or any other product than the starting material.

The Alkaline Fusion of Mesitylenesulfonic Acid. — Mesitylenesulfonic acid was synthesized from mesitylene and concentrated sulfuric acid following the usual procedure(14) (m. p. 76—78°C). To 30 g. of fused potassium hydroxide 12.5 g. of mesitylenesulfonic acid was added at 300—310°C for 5 min. After rapid cooling, the mixture was acidified with hydrochloric acid. Mesitylenol (3.5 g.) was obtained in a relatively low yield (29%); m. p. 70°C (sublimed).

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21) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Crowell, New York (1957), p. 517.