V with m.p. 312–316°, $[\alpha]^{25}\text{D}$ +12°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.59 μ (note similar shift in the infrared lactone band of IV) and broad band at 5.88–5.92 μ; no color with alcoholic ferric chloride. Chromatography of the mother liquors furnished 41 mg. of the keto alcohol II, which was identified as its acetate.

Anal. Calcd. for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07. $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 77.00; H, 9.21.

A portion (68 mg.) of the dione V was reduced in ethanol solution with 11 mg. of sodium borohydride in the above indicated manner. Acetylation of the crude reduction product gave 46 mg. of dumortierigenin diacetate with m.p. 315–318°; $[\alpha]^{23}\text{D}$ −11°; identity was confirmed by infrared analysis.

The dioxime was prepared in the standard manner (ethanol–pyridine, hours refluxing) and was recrystallized from methanol; m.p. 274–278°, no ketone carbonyl absorption in the infrared.

Anal. Calcd. for $C_{30}H_{44-46}N_2O_4$: N, 5.62, 5.64. Found: N, 5.19.

Dumortierigenin Monoacetate (III).—The partial hydrolysis[23] was performed by refluxing for 40 minutes 162 mg. of dumortierigenin diacetate with 300 mg. of potassium carbonate in 70 cc. of methanol, 6 cc. of dioxane and 6 cc. of water. The crude material was chromatographed on 10 g. of alumina deactivated with 2% of a 10% acetic acid solution, the bulk of the substance being eluted with 1:1 ether–chloroform. Recrystallization from methanol yielded 60 mg. of colorless needles with m.p. 307–310°, $[\alpha]^{23}\text{D}$ −9.0°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.78, 5.68, 5.81 and 8.0 μ (type A band[11] in contrast to type B band of starting material).

Anal. Calcd. for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44; acetyl, 8.37. $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.89; H, 9.60; acetyl, 7.36.

x-Acetoxy-y-ketodumortierigenin (IV).—In an attempt to oxidize 60 mg. of the monoacetate III with chromium trioxide–pyridine by the above described procedure, 39 mg. of the pure starting material was recovered. The oxidation of 55 mg. of the monoacetate III was, therefore, carried out by the use of chromium trioxide–sulfuric acid in essentially the same manner indicated above for the diketone except that the reaction time was extended to 30 minutes at 10°. The crude product was purified by chromatography on deactivated alumina and elution with benzene–ether (9:1); recrystallization from methanol–chloroform furnished 34 mg. of long platelets with m.p. 312–316°, $[\alpha]^{23}\text{D}$ −6.8°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.59 (similar shift in V), 5.80 (shoulder), 5.86 (note contrasting good resolution in this region in the isomer II) and 8.02 μ (type A band).

Anal. Calcd. for $C_{32}H_{46}O_5$: C, 75.26; H, 9.08. $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 74.79; H, 9.55.

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[23] In a model experiment, 290 mg. of methyl oleanolate acetate (VIIb) was refluxed for 40 minutes with 80 cc. of methanol, 12 cc. of dioxane, 8 cc. of water and 400 mg. of potassium carbonate. Chromatography of the product followed by recrystallization gave 157 mg. of recovered starting material with m.p. 215–217°, undepressed when mixed with an authentic specimen.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Condensations by Sodium. XXXV. The Metalation and Cleavage of Ethers, Principally of Alkyl Phenyl Ethers,[1] by Amylsodium and Sodium

BY AVERY A. MORTON AND ARMAND E. BRACHMAN

RECEIVED AUGUST 14, 1953

The addition of amyl chloride to sodium in heptane which contains anisole will produce *o*-sodioanisole, sodium phenoxide or *o*-amylanisole, according to the temperature. At 35° the yield of *o*-sodioanisole is 80%. Sodium phenoxide appears to result from pyrolysis (at 50–80°) of *o*-sodioanisole. Other alkyl phenyl ethers undergo metalation and cleavage in a similar manner and the ease of cleavage is dependent upon the availability and reactivity of hydrogens in the β-position of the alkyl group. Metalation in the cresyl methyl ethers also is limited to the vicinity of the oxygen atom. Cleavage of 2,4,6-triisopropylphenyl isopropyl ether and of dialkyl ethers by amylsodium shows that metalation is not always a prerequisite to cleavage. Di-*n*-butyl ether has enough resistance to amylsodium to be useful as a medium for some reactions with that reagent. Anisole is attacked by sodium alone to give *o*-sodioanisole and sodium phenoxide. All results are interpreted on the basis that amylsodium is a reactive salt with bifunctional character and with initiation of the reaction at the cation but with the ion-pair probably dissociating to radicals, as the active intermediates.

Introduction

The previous work in this Laboratory with amylsodium has been concerned primarily with the metalation of hydrocarbons, reactions of the Wurtz type and polymerization. The present paper on the reaction with ethers began with the intention of studying cleavage. With phenyl alkyl ethers, however, metalation seemed to be the precursor of cleavage and considerable attention has been paid to that phase of the process in the first section. The larger part of the work has been done on anisole. In the second part of this paper, the action on various dialkyl ethers is described and di-*n*-butyl ether is shown to be moderately resistant to amylsodium. In the third section, the action of sodium alone on anisole is reported because sodium may be formed by the decomposition of amylsodium during the reaction. A few side reactions in the metalation of anisole are then mentioned. An explanation, based on radicals instead of ions is favored for these processes.

Amylsodium and Alkyl Phenyl Ethers.—This study began with the supposition that the formation of amylsodium in the presence of anisole in heptane might cause immediate cleavage of that ether to sodium phenoxide, and in order to locate suitable conditions a series of experiments at different temperatures in the absence and in the presence of potassium isopropoxide was first carried out, whereupon three products instead of one were revealed. At 35°, metalation gave *o*-sodioanisole and the maximum yield of *o*-anisic acid by carbonation thereof was 80%, referred to amyl chloride as per equations 1 and 2. Potassium isopropoxide usually lowered this yield a little, but increased the amounts of disproportionations.

$$C_5H_{11}Cl + 2Na \longrightarrow NaCl + C_5H_{11}Na \quad (1)$$

$$C_5H_{11}Na + C_6H_5OCH_3 \longrightarrow o\text{-}NaC_6H_4OCH_3 + C_5H_{12} \quad (2)$$

Between 50 and 80° the sodium phenoxide origi-

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[1] This work was performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

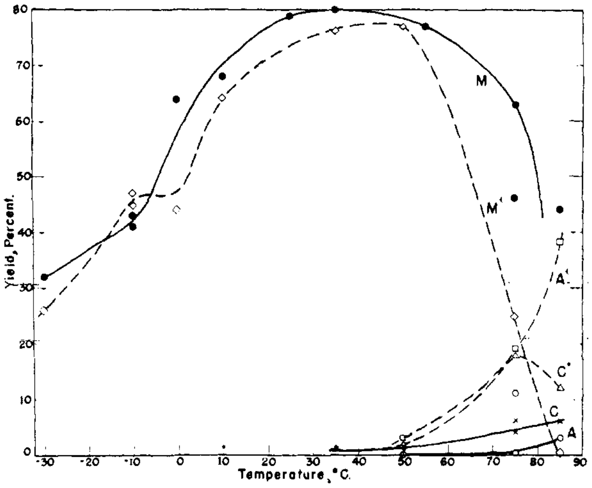

Fig. 1.—Yield *vs.* temperature for the reaction of amyl chloride with sodium in the presence of anisole. Continuous lines are for experiments in the absence of potassium isopropoxide. Dotted lines show the results when the alkoxide is present. M (dots) and M' (diamonds) are for metalation in the absence and in the presence, respectively, of alkoxide. C (crosses) and C' (triangles) are for the corresponding cleavages and A (circles) and A' (squares) are for the corresponding alkylations.

nally expected was formed, although in very small yield until potassium isopropoxide brought the reaction into better focus (see Fig. 1). A natural inference, however, is that a reaction at this temperature is preceded by the one at the lower level and may be the result of an intramolecular change, as in equation 3. This view was confirmed by preparing *o*-sodioanisole at 35° and then heating to 75°

$$o\text{-NaC}_6\text{H}_4\text{OCH}_3 \longrightarrow \text{C}_6\text{H}_5\text{ONa} + [\text{-CH}_2\text{- ?}] \quad (3)$$

for 14 hours to give 27% of phenol with only about half of the *o*-sodioanisole decomposed. Of the fraction of *o*-sodioanisole affected by heating, 69% changed to sodium phenoxide. Between 65 to 85°, alkylation gave *o*-amylanisole but this process will be discussed separately in a later paper.

The steps of metalation and intramolecular cleavage were next applied to some homologs of anisole. Amyl chloride was added to sodium at 35° and at 75° in the presence of an equal molal quantity of each other. In a third series, the mixture from a 35° reaction was heated to 75° for 45 minutes. In Table I, the compounds are listed in the order of increasing yield of phenol in all three series. Correspondingly the amounts of *o*-sodiophenyl alkyl ether decrease except for *o*-sodioanisole in the first and third series and *o*-sodiophenyl isopropyl ether in the second, but these differences, usually small, can be attributed largely to a lack of equal degrees of metalation of the ethers. The ease of cleavage by rearrangement of the *o*-alkoxyphenylsodium compounds seems affected by (a) the number of hydrogen atoms in the β-position and (b) their relative reactivity. It thus happens that isobutyl phenyl ether, with one such hydrogen, is metalated slightly less than anisole, with no hydrogen at that place, but the product is more stable than *o*-sodioanisole to cleavage with rearrangement.

TABLE I

METALATION BY AMYL CHLORIDE WITH SODIUM AND CLEAVAGE OF PHENYL ALKYL ETHERS

Alkyl component	Reacn. at 35° Yield of RNa.[b] %	Phenol, %	Reacn. at 75° Yield[a] of RNa.[b] %	Phenol. %	Rearr. at 75°/45 min. of 35° product RNa.[b] %	Phenol. %
Isobutyl	80	0.5			71	2
Methyl	84	0.8	64[c]	5	72[d]	4
n-Butyl	76	1.0			67	5
Ethyl	72[e]	5.0	12[f]	29	17	49
Isopropyl	50	14.0	39	34	5	64

[a] In the absence of any ether but with other conditions the same the yield of amylsodium prepared at 75° was only 57%, measured as caproic acid instead of the 85% yield at 35°. [b] R signifies the *o*-alkoxyphenyl anion. [c] This same reaction, when carried out in the presence of a half mole of sodium 2-pentoxide, sodium isopropoxide, potassium isopropoxide and potassium 2-pentoxide, caused, respectively, yields of 15, 17, 18 and 7% of phenol. [d] This same reaction was carried out under more severe conditions in order to confirm the tendency to rearrange. At 75° and 14 hours, the amount of *o*-sodioanisole remaining was only 41% and of phenol was 27%. At 115° and 45 min. the respective quantities were 20 and 29%. [e] At −10° and at 0° instead of 35°, metalation of phenetole gave 36 and 66% of *o*-ethoxybenzoic acid, respectively. Under the same conditions anisole yielded 42 and 64% of *o*-anisic acid. [f] This same reaction in the presence of potassium isopropoxide caused the disappearance of the organosodium compound without change in the phenol.

In a similar way, tests were made on two cresyl methyl ethers. Those with the *meta* isomer (see Table II) showed that metalation was limited to the vicinity of the methoxy group but only on the one side far from methyl. Heating of the reaction mixture to 75° did not cause this sodium to move from the ring to the *para* methyl group to give *m*-methoxybenzylsodium, a change which takes place readily when the methoxy-free compound, *p*-tolylsodium, is heated[2] to give benzylsodium. The sodium, therefore, is anchored rather firmly to the vicinity of oxygen and the only shift was to give a sodium cresoxide, which took place to about the same extent as with *o*-sodioanisole.

TABLE II

METALATION OF CRESYL METHYL ETHERS

Cresol isomer	Reaction Temp., °C.	Time, min.	Metalated products[a] Mono-, %	Di-, %	Unident., %
Meta	35	45	52		
	35–37		49[b]		
Ortho[c]	0	45	6	0.6	1.6[e]
Ortho[d]	−15	180	6	.2	2.5[e]

[a] The only carboxylic acid obtained from the *meta* isomer corresponded to 2-Na-5-$CH_3C_6H_3OCH_3$. The mono-product from the *ortho* isomer corresponded to 2-$CH_3OC_6H_4CH_2Na$, the diproduct was from 2-CH_3O-3-$NaC_6H_3CH_2Na$. [b] A trace of cresol was formed also. [c] Amyl chloride was added to sodium sand in the ether and heptane. [d] Amylsodium was prepared in pentane and the ether added afterwards. [e] From these combined fractions a small amount of 2-methoxy-3-methylbenzoic acid, corresponding to 2-Na-6-CH_3-$C_6H_3OCH_3$, was isolated.

The principal purpose of the experiments with *o*-cresyl methyl ether was to observe if any ring metalation, *ortho* to methoxy, took place, followed by an intramolecular shift of sodium over the oxygen and to the methyl group. The tests were accordingly

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(2) H. Gilman, H. A. Pacevitz and O. Baine, THIS JOURNAL, **62**, 1514 (1940).

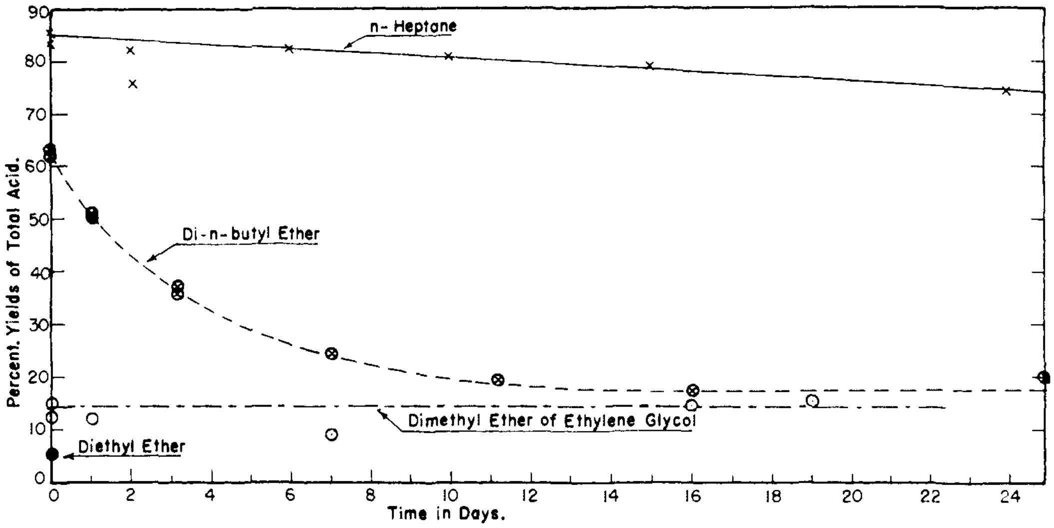

Fig. 2.—Stability of amylsodium in different solvents.

made at low temperature and for the early phase of reaction. But the product was almost entirely that from metalation of the side methyl group—Letsinger and Schnizer[3] also obtained this compound at 40°—although a very small amount of 2-methoxy-3-methylbenzoic acid, corresponding to the ring metalation sought, was eventually isolated from the combined residues. The quantity was too small to study for its role as a possible intermediate on the way toward side chain metalation.

Experiments with 2,4,6-triisopropylphenyl isopropyl ether showed that cleavage would take place even when the two *ortho* positions were blocked by a hydrocarbo group which itself is not metalated easily (isopropylbenzene is metalated[4,5] by amylsodium on the ring *para* to the isopropyl group). At 75° the amount of cleavage was 25% and no metalation of the ring or side alkyl groups was detected. In fact, substantially all of the small quantity of carboxylic acid obtained by carbonation was caproic, indicative of amylsodium, the cleaving agent.

Amylsodium and Dialkyl Ethers.—Tests were made also with aliphatic ethers in order to observe effects in the absence of any aromatic nucleus. Di-*n*-butyl ether, as might be expected from analogy with the phenyl alkyl ether, showed a reasonable degree of resistance to cleavage, quite out of the class of diisopropyl ether, which was cleaved so easily in the formation of an Alfin catalyst,[6] or of ethyl ether. The addition at 15° of a half mole of this ether to amylsodium (previously prepared at −10°) and carbonation showed only a small amount of a dicarboxylic acid and a trifle of unsaturated acid, both of which might be derived from either butene or pentene. Actually an 85% yield of acid was obtained and was mostly caproic acid which represents unaffected amylsodium. Even at 35°, under conditions the same as for Table I, only 3% of unsaturated acid and 3% of a diacid were obtained and the total yield was 72%, again mostly caproic, with 96% of the ether recovered unchanged.

This high stability of a small amount of di-*n*-butyl ether toward amylsodium led to a test of this ether as the medium for preparing amylsodium in the hope that it might serve as does ethyl ether for the Grignard reagent. Comparisons were also made with heptane, ethyl ether and the dimethyl ether of ethylene glycol. At the usual temperature, −10°, amylsodium remained in sufficient quantity (see Fig. 2) to permit the use of di-*n*-butyl ether as a medium for reactions, but after ten days the larger part of the reagent was lost. By contrast, ethyl ether destroyed virtually all of the amylsodium, and the dimethyl ether of ethylene glycol, which has proven so valuable for the addition[7] of sodium to naphthalene, was almost as unsuitable as ethyl ether. The reactivity of the glycol ether also was tested by reaction with sodium and amyl chloride at 75° in heptane by the technique used for Table I. The total quantity of acid obtained was 15% and only 11% of the ether was recovered unchanged.

The results with the alkyl phenyl ethers also suggest that diisobutyl ether would be better even than di-*n*-butyl ether, but this solvent is not available commercially. Its preparation and purification proved less easy than had been anticipated from the literature and there was no time to study the conditions needed.

Sodium and Anisole.—A previous paper[8] has indicated that the bifunctional character and high reactivity of amylsodium is exhibited through dissociation to amyl radical and sodium as well as, or perhaps more than, through separation to ions and considerable interest, accordingly, exists in how sodium alone, as a monofunctional reagent, will attack anisole. Fine sodium sand at 75°, under conditions otherwise comparable to those used with amylsodium, attacked anisole with formation

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[3] R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, **16**, 869 (1951).

[4] A. A. Morton, J. T. Massengale and M. L. Brown, THIS JOURNAL, **67**, 1620 (1945).

[5] A. A. Morton and E. L. Little, Jr., *ibid.*, **71**, 487 (1949).

[6] A. A. Morton, E. E. Magat and R. L. Letsinger, *ibid.*, **69**, 950 (1947).

[7] N. D. Scott, J. F. Walker and V. L. Hansley, *ibid.*, **58**, 2442 (1936).

[8] A. A. Morton and E. F. Cluff, *ibid.*, **74**, 4056 (1952).

of *o*-sodioanisole and sodium phenoxide. Table III shows that these two products, particularly in the absence of alkoxides, were formed in about equal amounts over a wide range of time; and such facts suggest that an initial cleavage, followed by metalation of another molecule of anisole by one of the products, methylsodium, may have taken place, as in equations 4 and 5. *o*-Sodioanisole here showed surprising thermal stability, tested for

$$2Na + C_6H_5OCH_3 \longrightarrow C_6H_5ONa + CH_3Na \quad (4)$$

$$CH_3Na + C_6H_5OCH_3 \longrightarrow o\text{-}NaC_6H_4OCH_3 + CH_4 \quad (5)$$

as long as 27 hours, whereas in the experiments described in Table I (see particularly footnote *d*), it underwent intramolecular cleavage to sodium phenoxide as per equation 3. The difference between the two cases may lie in the presence of sodium phenoxide from the start when sodium only was the agent, whereas in the other case (Table I), a quantity of sodium phenoxide necessary to stabilize *o*-sodioanisole was not reached until considerable cleavage by rearrangement had taken place. Such an effect would not be surprising because associated salts have a great influence on the behavior of these reagents.

TABLE III

REACTION OF METALLIC SODIUM ON ANISOLE AT 75°

Na equiv. mole	Time, hours	Added salts	Yields, % RNa	Yields, % Phenol
1	1.75	NaCl. KOC_3H_7-2	4	6
2	1.75	NaCl	4	3
2	1.75	NaCl. $NaOC_5H_{11}$-2	2	8
1	17.0	NaCl	38	38
1	27.5	NaCl	30	33

Side Reactions in the Metalation of Anisole.—A few other facts deserve mention because they show possible trends of reaction under special conditions. When half the usual amount of anisole was added at 75° to amylsodium, previously prepared at low temperature, the yield of dicarboxylic acid—2-methoxyisophthalic acid—rose to 27%, where in all other cases, the highest obtained had been 7% and usually was negligible. On the other hand, the use of twice the amount of anisole at 75° gave only 52% of *o*-sodioanisole instead of the 64% shown in Table I. Two preparations where amylsodium, previously prepared in pentane, was allowed to react with anisole in the presence of sodium isopropoxide and sodium 2-pentoxide at 15° in pentane gave mixtures of *o,o'*-dianisyl ketone and tris-(*o*-anisyl)-carbinol, in addition to the *o*-anisic acid (72 and 64%, respectively) usually obtained. From no other experiments (all others were with potassium alkoxides and in heptane) were those non-acidic products obtained, although the method of separation would have disclosed their presence. The alkoxide chosen for most of the experiments (Fig. 1 and other cases) was potassium isopropoxide, chiefly because of the favorable results shown in a previous study[9] on the alkylation of toluene and partly because an isopropoxide has had such pronounced effects in Alfin catalysis.[6] Greater effects might have been obtained in the present work, however, if the 2-pentoxide or *t*-pentoxide had been used.

Discussion

A reasonable interpretation of all of these reactions can be made along the lines suggested by the previous paper,[8] whereby the sodium reagent dissociates into two radicals of unequal activity, one inorganic, which is sodium metal *in situ*, and the other organic. The sodium radical participates directly in the formation of a new salt and the organic radical terminates the process by taking the hydrogen loosened at the beta or other position. The picture is that of a biradical, chemically active, state sandwiched between two ionic states, one of which is more stable thermally than the other. In the cleavage of the dialkyl ethers or of triisopropylphenyl isopropyl ether, the alkoxide or phenoxide is formed directly. In the cleavage of the alkyl phenyl ether, the process can be leveled off at an intermediate ionic state, the *o*-sodiophenyl alkyl ether, which is warmed to create again the instability necessary to go to the phenoxide.

The above explanation avoids some difficulties which arise from the idea that these sodium reagents must be regarded as strong bases, among the strongest of all bases when the series of acid strengths, as determined by Conant[10] and McEwen,[11] is considered. One of the common reactions of a base is the removal of a proton, and bases with unusual strength would be expected to have more than ordinary power in that way. It was, in fact, this view of an unusually powerful reagent which led Whitmore[12] to suggest a β-attack by a "hydrocarbo base," and caused Gould[13] and co-workers to postulate a coördination and polarization of the carbon–sodium bond which "thus permits attack by the carbanion on a β-proton." The general concept is, indeed, that the carbanion is the "driving force"[14] and that the "strongly nucleophilic carbanion . . . after all, must have some affinity for a proton, beta or otherwise."[14] Considerable interest exists, therefore, in the problem of β-attack and the location of the driving force in this cleavage reaction.

Powerful as this reagent is, no instance of indiscriminate attack[15] has been encountered in all of the work that has been done in this Laboratory. Nor has there been any attack at a position beta to an activating group. The α-hydrogen has been the only one attacked. Hence neither in the system a below, where ether is coördinated with the sodium cation and the activating group would be regarded as NaO, nor in the system b where the above activating group is augmented by a second

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[9] A. A. Morton and A. E. Brachman, THIS JOURNAL, **73**, 4363 (1951).

[10] J. B. Conant and G. W. Wheland, *ibid.*, **54**, 1212 (1932).

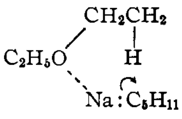
[11] W. K. McEwen, *ibid.*, **58**, 1124 (1936).

[12] F. C. Whitmore and H. D. Zook, *ibid.*, **64**, 1783 (1942).

[13] D. H. Gould, K. H. Schaef and W. L. Ruigh, *ibid.*, **73**, 1263 (1951).

[14] These quotations are taken from the comments of a referee of this paper who has kindly given a detailed picture of the manner of the reaction from a nucleophilic viewpoint.

[15] At one time a metalation of decalin (THIS JOURNAL, **64**, 2250 (1942)) seemed to have taken place in small yield. In a careful review of this work with Stanley M. Bloom, to be published later, the product has been traced to a small amount of impurity. Decalin itself is not attacked by amylsodium even though the reagent is pyrolyzed in that medium.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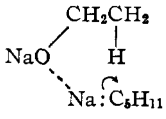
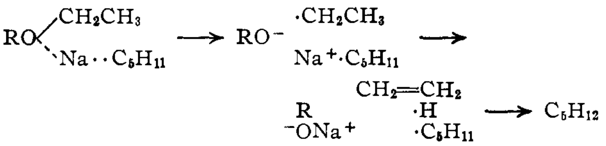

b

cation, has there been any evidence of β-metalation. Indeed, if any metalation did occur, it would be expected at the α- rather than at the β-position. The reasonable view therefore is that no attack whatever would be expected at the β-position unless some way was provided for activation of the hydrogen at that point.

Any concerted process should be considered from this viewpoint. As a driving force, the carbanion, if it were truly the major influence, could contribute at the β-position only the difference in energy between the formation and the breaking of a primary carbon–hydrogen bond which amounts to zero, and it is doubtful if the carbanion could be a factor in initiating an attack.

The better idea is to make use of the fact that dissociation of the reagent to radicals definitely occurs, and to assume that this dissociation is, as a rule, augmented by coördination about the cation. The reagent is then rated as powerful according to the number of radicals that are formed, and a process initiated in this manner proceeds clockwise in the scheme below to produce the activation at the β-position.



Radicals produced according to the above scheme are not really free because the biradical character of the system insures that reactions will terminate promptly with the formation of a new and more thermally stable salt. The situation pictured above is, of course, an extreme, intended to show the separate contributions which are a factor in changes that proceed with great rapidity.[8]

The difference between *n*-butyllithium and *t*-butyllithium also can be considered from this viewpoint. Both reagents are soluble in ether and lack the ionic character attributed to amylsodium. The former does not cleave ether while the latter does. The covalency of the lithium agents suggests that the ionic character in the sodium reagent is not the prime cause of activity in ether cleavage. The relative thermal stabilities are probably more in line with the relative reactivities.

Experiments

Apparatus and General Conditions.—The high-speed stirring apparatus and special creased flask, described[16] previously, were employed except that a $^5/_8$" propeller shaft and three oblique shaped propellers which provide more surface were used. These changes were introduced a few years ago and the improved apparatus is regularly used in most experiments. A "Glascol" heater was used for heating and a cellosolve bath with solid carbon dioxide for cooling.

Reagents.—The amyl chloride was made in this Laboratory from technical *n*-amyl alcohol with thionyl chloride and the crude product was washed thoroughly with a small amount of concentrated sulfuric acid, dried over potassium carbonate, distilled and filtered[9] through successive layers of calcium chloride, alumina and calcium sulfate (Drierite). The heptane was Phillips "Pure" grade. It was stirred vigorously with concentrated sulfuric acid, dried over sodium wire and distilled. The anisole was obtained from Eastman Kodak Co. It was distilled over sodium metal and the fraction boiling at 150° was used. The alkali metal alkoxides were prepared separately by adding slowly an equivalent amount of the desired alcohol to a suspension of sodium or potassium sand in heptane and stirring the mixture vigorously until reaction was complete. The slurry was then transferred to a storage bottle and subsequently to a reaction flask by means of nitrogen pressure which forced the suspension out through a tube (as in the common wash bottle), this system being regularly used for transferring or sampling organosodium reagents. The same precautions of dry nitrogen (prepurified grade) atmosphere were maintained at all times for the preparation and handling of alkoxides as were used for the sodium reagents.

Reactions.—The proportions of reagents, unless otherwise stated, were 1 g. atom of sodium, previously made into finely divided sand by stirring at 10,000 r.p.m. in decane in the manner commonly employed,[17] one-half mole of amyl chloride, one-half mole of anisole or other ether, 1200 ml., or thereabouts, of heptane, pentane or other medium. An alkoxide, if used, was in one-half mole quantity and was added before amyl chloride. The rate of addition of the organic chloride was approximately 1 ml. per minute (total time about one hour), and the stirring was continued for 45 minutes after the chloride had been added. The temperature, time, order of addition or other special condition is given in the tables or for the separate experiment. When amylsodium was prepared separately or in the absence of an ether, the temperature was −10°, as is the usual practice,[17] and the stirring time before addition of the ether was 30 minutes.

Analysis of the Products from Anisole.—At the conclusion of all reactions the mixture was forced out of the flask onto solid carbon dioxide. Subsequently water was added, carefully at first, to decompose small quantities of sodium metal and to dissolve the sodium carboxylates. The aqueous layer was acidified with 2:1 by volume sulfuric acid and the acids and phenols were extracted with ether. The ether layer in turn was extracted with 50-ml. portions of saturated sodium bicarbonate solution until no more carbonic acid was liberated. Usually 400 ml. of total carbonate solution was needed to remove the carboxylic acids. The amount of phenol was then determined by distilling the ether, dissolving the phenol in carbon tetrachloride and adding an excess of 0.1 *N* bromine solution to an aliquot part. Potassium iodide, sodium thiosulfate and a starch indicator were then used to determine the excess bromine in the standard way. The tribromo derivative melted at 94.5–95° and contained 72.5% bromine (theory 72.4%).

The aqueous solution of carboxylates was acidified by sulfuric acid and the acids dissolved in enough ether to make exactly 1,000 ml. A 10-ml. aliquot was then dissolved in 50 ml. of ethanol and titrated with 0.1 *N* base. If only *o*-anisic and caproic acid were present, a semi-distillation of a 20-ml. aliquot, according to the method of Virtanen and Pulkki,[18,19] served to determine the composition. Control experiments showed an accuracy of 2%. If the mixture were more complex, a partition chromatography method,. developed from directions furnished by Marvel.[20] was employed so that the amounts of salicylic, *o*-methoxybenzoic, 2-methoxyisophthalic and caproic acids could be determined. Forty grams of 100 mesh silicic acid was ground with 10 ml. of ethylene glycol and 13 ml. of water in a mortar and the powder was then added to a mixture of 120 ml. of carbon tetrachloride and 40 ml. of pentane. This smooth slurry was poured into a 25-mm. tube about 1 meter long, fitted with a stopcock at the bottom. Excess solvent was drained out and the mixture, always kept wet, was made as compact as possible by pressure at the top. About 30 mg. of acid was dissolved in 0.5–1 ml. of carbon tetrachlo-

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[16] A. A. Morton and L. S. Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[17] A. A. Morton and co-workers, THIS JOURNAL, **72**, 3785 (1950).

[18] A. I. Virtanen and Pulkki, *ibid.*, **50**, 3138 (1928).

[19] A. A. Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 127.

[20] C. S. Marvel, private communication.

ride with, if necessary, a few drops of *n*-butyl alcohol. The solution was added to the top of the column (still wet) and was washed through with 50-ml. portions of gradually more polar effluent, first with 40 ml. of carbon tetrachloride plus 10 ml. of pentane, then successively with 45 ml. of carbon tetrachloride plus 5 ml. of pentane, 50 ml. of carbon tetrachloride, 49 ml. of carbon tetrachloride plus 1 ml. of *n*-butyl alcohol, 48 ml. of carbon tetrachloride plus 2 ml. of butanol and finally with 47 ml. of carbon tetrachloride plus 3 ml. of butanol. Each 10-ml. portion of effluent was titrated with 0.200 *N* base with phenol red as an indicator. Caproic acid and salicylic acid were present in the first 90–120 ml. of effluent. Their quantities could be differentiated by steam distillation of a second sample of the original mixture to remove caproic acid, followed by a second chromatogram so that the first portion of effluent then contained only salicylic acid. *o*-Methoxybenzoic acid came through in the 190–230 ml. portion.

Caproic and *o*-methoxybenzoic acid could thus be determined within 2% and by combination with steam distillation, could be measured with 0.7% accuracy. A chromatogram with *o*-methoxybenzoic and 2-methoxyisophthalic acids was correct for the former and within 30% for the latter but the amount of the dicarboxylic acid was usually so small that the effect upon the yield calculated from amyl chloride would have been only about 1%. A correction was, however, applied. If four acids were present the errors were large (10–20%) but such cases were rare. In fact, caproic acid was not present in those products (Table I and Fig. 1) from the reactions at 35° and higher.

To ensure that no acids were overlooked and to characterize the acids, the products left from seventeen early experiments were combined. Crystallization from ether gave 300 g. of *o*-methoxybenzoic acid (m.p. 101–101.5° from ligroin) identical in properties with a sample from Eastman Kodak Co., similarly crystallized. Steam distillation of the remaining acids gave 5 g. of caproic in the distillate which was identified as the *p*-bromophenacyl ester, m.p. 70–71° (reported[21] 72°). The remaining acid in the distillate proved to be more *o*-methoxybenzoic. The residue from the steam distillation was subjected to a 10-flask counter-current extraction,[22] after the manner frequently used in this work.[23] By such means about 2 g. of 2-methoxyisophthalic acid was found in the last flask and was characterized by its melting point (245.4–246.4°, reported[24] 243–244°) and neutralization equivalent 99.4 (calcd. 98). A trace of solid acid (m.p. 230–240° and neut. equiv. 122) which gave a purple color with ferric chloride was also in the last flask and may have been 2-hydroxyisophthalic acid. Actually the three acids caproic, *o*-methoxybenzoic and 2-methoxyisophthalic were the only acids present in yields exceeding 0.5%.

The neutral products of the reactions were always fractionated in order to observe the amount of anisole not used and to recover all products as far as possible. The *o*-amylanisole thus found will be described in a forthcoming paper.

From the two experiments in pentane and in the presence of sodium isopropoxide and 2-pentoxide (Table I, footnote *c*) solids were obtained which were crystallized from ligroin and from ethanol–water. One of these solids melted at 100–101°, within the range (98° and 104°) recorded[25] for 2,2'-dimethoxybenzophenone, and showed no depression when mixed with another sample (m.p. 101.5–102.5°) prepared from *o*-sodioanisole and *o*-methoxybenzoyl chloride in pentane at −30°. Infrared curves of the two preparations were the same. Also the dinitrophenylhydrazone derivatives melted at 180–182° and 183–183.5°, respectively, when crystallized from ethanol–ethyl acetate and were identical.

Anal. Calcd. for $C_{21}H_{18}O_6N_4$: C, 59.71; H, 4.29; N, 13.27. Found: C, 59.55; H, 4.23; N, 13.00.

The other solid from these two experiments was tris-(*o*-methoxyphenyl)-carbinol which, after crystallization from ligroin and from acetone, melted at 179–180° (literature[26] 181°). It was identical (mixed melting point and infrared) with another sample made from the above ketone and *o*-sodioanisole in pentane at 5°, which melted at 181.5–182.5°.

Other Phenyl Alkyl Ethers and Their Products.—The experimental conditions and yields are listed in Table II. The analyses of the products were made in a manner similar to those from anisole.

From phenetole (Eastman Kodak Co. material, redistilled over sodium and boiling at 167–168°) was obtained *o*-ethoxybenzoic acid which melted at 20.7° (literature[27] value 19.5, 24.5–25.5°). Nitration gave the 2-ethoxy-5-nitrobenzoic acid which melted at 161–162° (literature[28] 163°). Neutralization equivalents and elemental analyses were correct for these compounds.

Isopropoxybenzene was prepared by a Williamson synthesis from 3 moles of sodium phenoxide and 3 moles of an equal mixture of isopropyl chloride and bromide in absolute alcohol and boiled at 182.2–182.6° with n^{25}D 1.4892. The product from metalation and carbonation was *o*-isopropoxybenzoic acid which boiled at 93–98° (13 mm.) and had the correct neutralization equivalent, 180. It was identical with an authentic sample (made by reaction of sodium methyl salicylate with a mixture of isopropyl chloride and bromide in boiling ethanol followed by saponification) in that it boiled within the same range and showed an identical behavior in partition chromatography in a mixture with salicylic acid.

From *n*-butoxybenzene, likewise prepared by a Williamson synthesis from sodium phenoxide and *n*-butyl chloride in 69% yield, was obtained *o*-*n*-butoxybenzoic acid which boiled at 153° (4.5 mm.) and had the correct neutralization equivalent. Treatment with concentrated hydriodic acid gave salicylic acid. The *p*-nitrobenzyl ester melted at 46–47° after crystallization from ethanol–ligroin. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 63.64; H, 5.81; N, 4.25. Found: C, 65.56; H, 5.78; N, 4.32.

From isobutoxybenzene (made in 40% yield from sodium phenoxide and isobutyl bromide by 17 hours refluxing in ethanol and distilling, b.p. 101° (29 mm.), n^{25}D 1.4906) was obtained *o*-isobutoxybenzoic acid which boiled at 135–136° (1 mm.), had n^{25}D 1.5222 and had the correct neutralization equivalent. The *p*-nitrobenzyl ester crystallized from ethanol–ligroin, and melted at 60–61°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 63.64; H, 5.81; N, 4.25. Found: C, 65.56; H, 5.78; N, 4.32.

When this acid was refluxed for one hour with concentrated hydriodic acid, a small amount of salicylic acid was obtained and, in addition, a small quantity of white solid which might have been 2-hydroxy-5-*t*-butylbenzoic acid because it gave a purple color with ferric chloride, melted at 151°, as described in the literature,[28] and had the correct empirical analysis. It would be derived as a secondary product in this cleavage reaction if the isobutyl iodide reacted in a Friedel–Crafts alkylation process with the salicylic acid.

Metalation of Methyl Ethers of *m*- and *o*-Cresol.—*m*-Cresol (40 g.) was purified by formation of the addition complex[29] with sodium acetate (80 g.) in 600 ml. of dry pentane. The crystals were recovered by filtration and were then treated with water to recover the phenol which boiled at 98° (18 mm.). It was converted to the methyl ether by reaction with a slight excess of 33% sodium hydroxide followed by dimethyl sulfate. The ether boiled at 99° (65 mm.) and had n^{25}D 1.5100. When this ether was metalated, as described in Table III, 2-methoxy-4-methylbenzoic acid was obtained. Any caproic acid (only 2% in the experiment at 25°) was removed by steam distillation. This methoxytoluic acid melted at 103–104° (literature[30] 103°) and had the correct neutralization equivalent. From the preparation where the metalated product was heated to 75°, this acid only was obtained as good crystals and amounted to 90% of all acids obtained. A trace of material which gave a purple color, indicative of a little cresol or hydroxy acid, was observed.

o-Cresol was purified by a process[29] similar to that used

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(21) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 223.

(22) T. G. Hunter and A. W. Nash, *Ind. Eng. Chem.*, **27**, 837 (1935). See also reference 19, p. 200.

(23) A. A. Morton and E. Grovenstein, Jr., THIS JOURNAL, **74**, 5437 (1952). See also reference 19.

(24) C. Grache and H. Kraft, *Ber.*, **39**, 800 (1906).

(25) R. Richter, *J. prakt. Chem.*, [2] **28**, 287 (1883); C. Graebe and A. Feer, *Ber.*, **19**, 2610 (1886).

(26) A. Baeyer and V. Villiger, THIS JOURNAL, **35**, 3025 (1902).

(27) J. L. E. Erickson and W. H. Ashton, *ibid.*, **63**, 1769 (1941).

(28) R. L. Shriner and R. C. Fuson, ref. 21, p. 259.

(29) G. Darzens, *Compt. rend.*, **192**, 1657 (1931).

(30) W. H. Perkin, Jr., and C. Weizmann, *J. Chem. Soc.*, **89**, 1658 (1906)

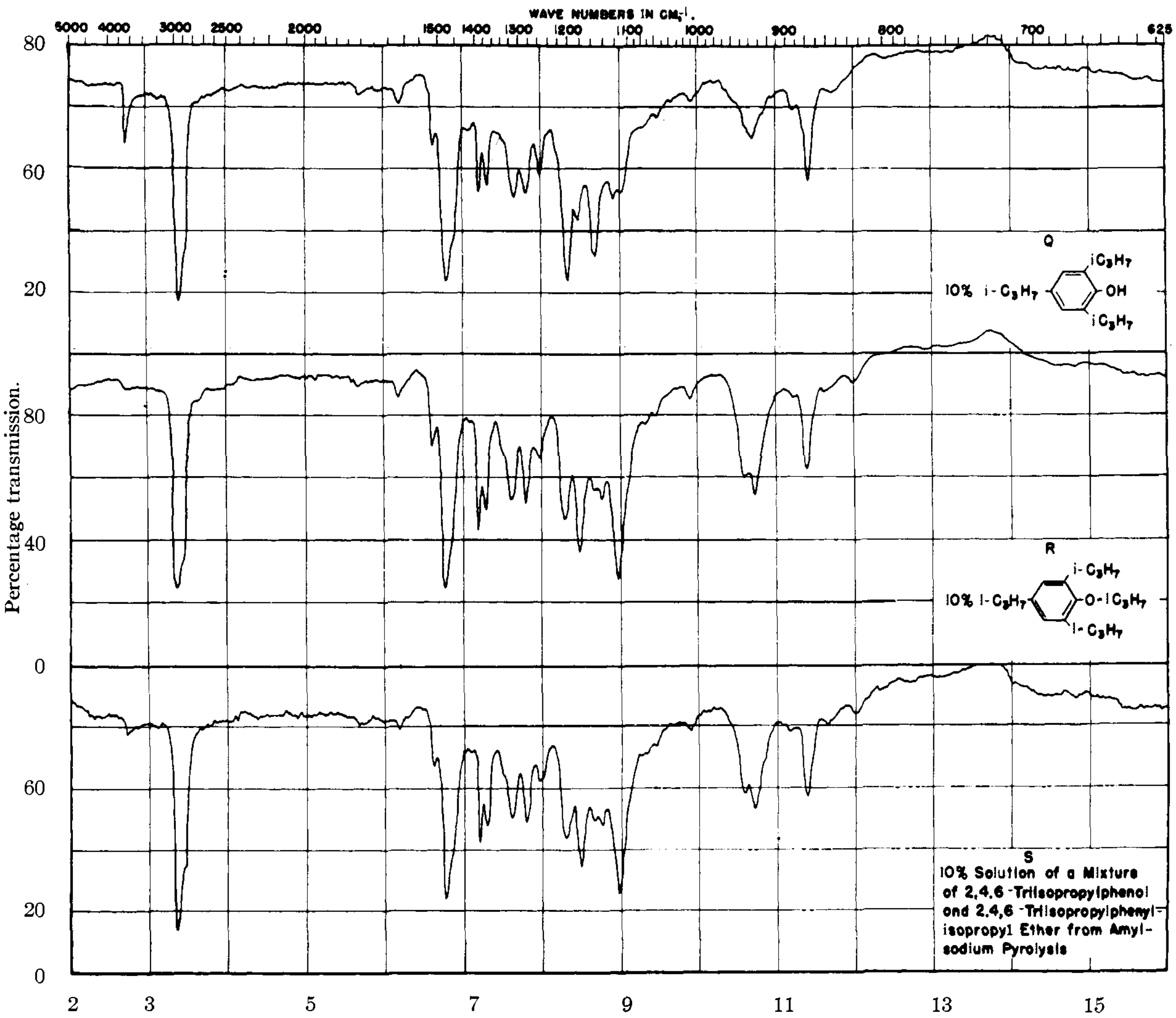

Fig. 3.—Infrared spectra of 2,4,6-triisopropylphenol and 2,4,6-triisopropylphenyl isopropyl ether.

for *m*-cresol. The cresol was dissolved in pentane and the *meta* isomer removed as the insoluble sodium acetate complex. Anhydrous sodium oxalate then removed the *para* isomer. The *o*-cresol precipitated as a light tan solid when the pentane solution was cooled in a bath with solid carbon dioxide. This solid cresol product was dissolved in 33% sodium hydroxide, treated with dimethyl sulfate and refluxed for 17 hours. Fractionation of the crude material thereby obtained gave a product which boiled at 172.5° and had $n^{25}D$ 1.5148.

This *o*-cresyl methyl ether yielded, after metalation and carbonation, a mixture of acids from which caproic acid was removed by distillation at reduced pressure. The solid residue, when recrystallized from ligroin, yielded *o*-methoxyphenylacetic acid (m.p. 119–123°) which corresponded to the value recorded.[3] Some material which melted at 162–163° proved to be 2-methoxyhomoisophthalic acid, hitherto unreported.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.24; H, 4.79; neut. equiv., 105. Found: C, 57.09; H, 4.84; neut. equiv., 106.

Oxidation with basic permanganate yielded 2-methoxyisophthalic acid (m.p. 216–217°) which was identical with the product from dimetalation of anisole.

The combined acid residues from two metalations of the *o*-cresyl ether (see Table II) were crystallized repeatedly from ligroin to remove all *o*-methoxyphenylacetic acid and were then passed through a column of silicic acid. The material from the first effluent, after being recrystallized from water, melted at 82–83° (recorded[3] value for 2-methoxy-3-methylbenzoic acid is 83°) and had a neutralization equivalent of 168 (calcd. 166).

Metalation of 2,4,6-Triisopropylphenyl Isopropyl Ether.—This ether, sometimes referred to as tetraisopropylphenol, was made from three moles (282 g.) of phenol, 0.155 mole (10.5 g.) of boron trifluoride and propylene gas after the manner described by Nieuwland[31] but for a much longer time. The crude product boiled at 144° (118 mm.) but had to be distilled four times from metallic sodium before no more gas was evolved and before an infrared absorption showed the absence of phenol. This purified product boiled at 151–151.5° (25 mm.) and had $n^{25}D$ 1.4872. The removal of the corresponding phenol from this ether was difficult because the phenol is sparingly soluble in 10% sodium hydroxide, a point overlooked by the original investigators. The phenol itself boiled at 114–114.2° (4.5 mm.) and had $n^{25}D$ 1.4984. Upon prolonged standing the colorless ether became yellow, acquired an increased refractive index and began to show an infrared absorption at 2.75 μ, all indicative of the formation of the phenol.

This ether was treated with amyl chloride and sodium in heptane at 75° in the usual way. The carbonated product was acidified with 2:1 (by volume) sulfuric acid and the aqueous portion was extracted twice with ethyl ether and added to an original ether extract. The ether portion was extracted with sodium bicarbonate until the caproic acid was removed, then dried, and distilled through a 1-foot Vigreux

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[31] F. J. Sowa, H. D. Hinton and J. A. Nieuwland, THIS JOURNAL, 54, 3694 (1932).

column. The fraction which boiled from 103–118° (4 mm.) was examined by infrared absorption for the differences at the 2.75 μ and 10.7 μ wave lengths for the ether and its corresponding phenol, respectively. Figure 4 shows the absorption curves for the two pure compounds and the mixture. By suitable calculations from Beer's law, the composition was estimated as 123 meq. of phenol and 340 meq. of the ether.

Experiments with Dialkyl Ethers.—Di-*n*-butyl ether was distilled over sodium wire and stored over sodium until used. One-half mole of the ether was added at 15° to a heptane suspension of amylsodium which had been prepared in the usual way from 1 g. atom of sodium and 0.5 mole of amyl chloride at −10°. The mixture was allowed to react for 45 minutes and then carbonated. In addition to 83% yield of caproic acid, 11 meq. of a dicarboxylic acid and 5 meq. (1%) of unsaturated acid were found. The recovered butyl ether amounted to 87%. The decane yield was 15%.

In the second experiment, 0.5 mole of amyl chloride was added at 35° to 1 g. atom of sodium sand in heptane which contained 0.5 mole of di-*n*-butyl ether.

For the comparison of preparations of amylsodium in three different ethers and in heptane, the experimental conditions, −10° etc., were the same as regularly employed in this Laboratory.

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Condensations by Sodium. XXXVI. The Alkylation of Anisole and of *o*-Cresol Methyl Ether and the Composition of a Reacting Aggregate[1,2]

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Alkylation on the aromatic ring by reaction of sodium with amyl chloride in the presence of anisole occurs readily if certain alkoxides are present, whereas earlier work in this Laboratory had been relatively unsuccessful. The necessary sodium intermediate, *o*-sodioanisole, is associated with sodium chloride in the more active portion of the ionic aggregate and reacts faster when additional sodium chloride is added. It also reacts faster with chlorobenzene than with amyl chloride. Phenylation is better than alkylation. The heterogeneous character of these reactions must be considered in interpreting these processes.

Introduction.—The alkylation of toluene[3-6] or of the xylenes[7] by reaction of an alkyl chloride with sodium metal in the presence of the hydrocarbon has been shown[3,4] to be a simple and direct procedure for preparing certain alkylbenzenes, and the sodium atom on a side methyl group has been especially recommended[3,8] for use in Wurtz type couplings. The same reaction applied to the alkylation of benzene has been reported[5] unsuccessful. The present work with anisole shows that alkylation on the aromatic nucleus can, after all, be relatively successful if done in the presence of certain alkoxides, but the alkylation of a cresyl ether at the side methyl group is still easier. Phenylation of anisole also can be carried out, probably with even greater ease than alkylation. Finally some observations on the composition and reactivity of a reacting aggregate are described wherein: (a) sodium chloride is found to accelerate the last step of a Wurtz coupling and (b) the reaction of *o*-sodioanisole with amyl chloride (alkylation) is shown to be slower than the corresponding reaction with chlorobenzene (phenylation), although the reverse order of reactivity would have been expected. The study is an outgrowth of the one immediately preceding on the metalation and cleavage of anisole.[9]

Alkylation of Anisole and its *o*-Methyl Homolog.—Alkylation proceeds in three steps: first, the formation of amylsodium as in equation 1, then the transition from amyl to anisyl (2) and, finally, the Wurtz coupling of *o*-sodioanisyl with amyl chloride as in (3). These steps follow each other in a rapid cascade when amyl chloride is added to

$$C_5H_{11}Cl + 2Na \longrightarrow C_5H_{11}Na + NaCl \quad (1)$$

$$C_5H_{11}Na + C_6H_5OCH_3 \longrightarrow NaC_6H_4OCH_3 + C_5H_{12} \quad (2)$$

$$o\text{-}NaC_6H_4OCH_3 + C_5H_{11}Cl \longrightarrow o\text{-}C_5H_{11}C_6H_4OCH_3 + NaCl \quad (3)$$

sodium and anisole in heptane. At 75° the addition of one-half mole of amyl chloride to one atom of sodium suspended in heptane that contained one-half mole of anisole gave around 4% of *o*-amylanisole, in line with the previous experience,[8] but in the presence of sodium 2-pentoxide, sodium isopropoxide, potassium isopropoxide and potassium *t*-pentoxide the yields were 4, 10, 19 and 23%, respectively. At 85° the yields were 3% and 38%, respectively, in the absence and presence of potassium isopropoxide, all yields being referred to the amyl chloride added. Clearly certain alkoxide salts improve the reaction, even as they have had pronounced effects in the alkylation of toluene,[6] in Alfin catalysis[10] in pyrolysis[11] of amylsodium and in metalations by sodium reagents.[12] These results are very good in view of the fact that anisole was not used as a solvent but was present only in equivalent amount, because in previous experiments[6] on

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[1] This work was performed as a part of the research project sponsored by The Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

[2] This paper was presented in part at the American Chemical Society Meeting, Chicago, Ill., 1953.

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