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XIII.* STERIC AND CONFORMATIONAL ASPECTS OF ALKYL ARYL ETHER METALATION**

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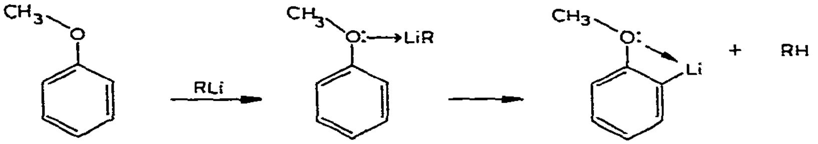
INTRODUCTION

Although metalation (hydrogen–metal exchange) reactions of lithium alkyls have provoked a considerable amount of mechanistic interpretation over the years, it is today axiomatic that reactions of organolithium compounds are greatly facilitated by coordination of the metal atom with a suitable donor †. In the reaction of anisole with butyllithium[2,3], for example, it was early proposed that an intermediate complex was formed[4,5] by interaction of a non-bonding electron pair on oxygen with the lithium atom. Such a complex is represented by (I), which on further reaction (eqn. 1) affords the exchange product, *o*-lithioanisole (II), represented as an internally coordinated species ††.



(1)

(I) (II)

The empirical basis for the postulation of intermediates such as (I) consisted in numerous observations that substrates lacking a donor atom were metalated by butyllithium very slowly, if at all. Furthermore, in nearly all cases where reaction does occur, the metal atom assumes a position on the benzene ring predominately *ortho*

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* For Part XII see ref. 1.

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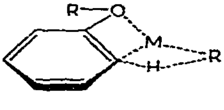
*** Petroleum Research Fund Fellow, September, 1962-December, 1963. This article is based on a thesis presented by J. W. Altschuld to the Department of Chemistry, Ohio State University, March, 1964, in partial fulfillment of the requirements for the Master of Science degree.

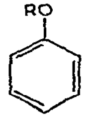
† This seems also to be the case with the heavier alkali metal compounds, although direct evidence is less extensive.

†† It is likely that (II), in common with other organolithium compounds, exists as an aggregate, and that the four-membered chelate ring is an over-simplification. For interesting speculation related to this point, see ref. 6.

to the heteroatom substituent[7-10]. This "directive effect" is also operative in the metalation of heterocyclic compounds, in many halogen-metal exchange reactions[11,12], and in corresponding reactions of sodium and potassium compounds[13]. The most direct evidence bearing on the metalation mechanism consists of measurements of hydrogen isotope effects on the metalation of anisole[14], benzene[15], toluene[15], and thiophene[16,17] which demonstrate clearly that hydrogen transfer is kinetically significant[*]. The intimate details of the process are far from clear, however, and the reaction has been described variously as involving a polar, "push-pull" type mechanism[5,15,18,19], a radical pair mechanism[20], or a radical-anion mechanism[14][**]. While reserving for the future a detailed discussion of these alternatives, we have adopted, for the present, a view of the transition state for this reaction schematically illustrated by (III)[***]. Coordination[†] of the metal atom with the donor oxygen increases the electron-withdrawing inductive effect of that substituent, the *ortho*-directing effect is the result of proximity to the site of coordination[27], and, although some bonding of the metal to its new partner is implied, proton transfer should be subject to a kinetic isotope effect[††].



(III)



(IV)

(IVa) $R = CH_3$
(IVb) $R = CH_2CH_3$
(IVc) $R = CH(CH_3)_2$
(IVd) $R = C(CH_3)_3$
(IVe) $R = CH(CH_2CH_3)_2$

Since both inductive and resonance[28] effects have been shown to be operative during aryl alkyl ether metalation, we sought to supplement this knowledge of the reaction by a systematic investigation of steric and conformational factors. Our approach was simply to examine the extent to which a series of ethers (IV) reacted with butyllithium under a standard set of conditions. For this series of ethers we made the reasonable assumption that any differences in the inductive effects of the R groups would be effectively swamped by that of the oxygen atom, so that the effects on the aromatic ring would be virtually identical. We further assumed that the resonance interaction between the ring and the substituent would be quite similar in each case and that any differences in reactivity would, therefore, represent a steric effect reflecting the differing sizes of the R groups[†††]. Another group of ethers proposed for study

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[*] We assume that these hydrocarbon metalations by sodium and potassium alkyls have certain general features in common with ether metalations.

[**] Radical intervention has also been implicated in other reactions of organoalkali metal compounds[20-24].

[***] One must bear in mind that the true molecularity and the aggregate nature of the reagents will require modification of structure (III) in matters of detail, but not in principle. Also, charge distribution in (III) is omitted for purposes of simplicity.

[†] The necessity of the coordination step has been questioned[13,25]. Although the large body of evidence favoring complexation is mainly circumstantial, NMR evidence for complex formation between butyllithium and 1-methoxynaphthalene has recently appeared[26].

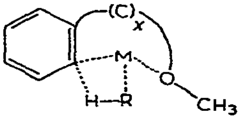
[††] The metalation of substrates lacking a hetero-atom donor is admittedly a more complex problem. The directive effect of alkyl substituents has not been satisfactorily explained, complications arising from the *apparent* heterogeneity of some of these systems are difficult to assess, and the possible role of π-complexation has not been discussed in detail. It is planned to present an extended discussion of these problems in a future publication.

[†††] This assumption is probably valid for all cases except the tert-butyl analog (IVd) for which the coplanar conformation of the alkoxyl group, preferred for maximum resonance interaction with the ring[29-31], appears to be unfavorable[32].

is represented by formula (V) in which the oxygen atom is moved progressively away from the aromatic nucleus. If complexation of the metal with the ether oxygen is a prelude to *ortho*-hydrogen removal, one might expect to find a value of *x* which

$C_6H_5CR^1R^2(CH_2)_nOCH_3$

(Va)	n	R^1	R^2
(Vb)	0	H	CH_3
(Vc)	0	CH_3	CH_3
(Vd)	1	H	H
(Ve)	2	H	H
(Vf)	3	H	H



(VI)

permits close approach of the metal alkyl to an *ortho*-position*, as for example in structure (VI), thereby facilitating *ortho*-metalation.

RESULTS AND DISCUSSION

Since the method employed in this study involved a determination of relative conversions, it was necessary to establish a standard set of reaction conditions so that, within experimental error, the only variable would be the structure of the substrate ether. A number of metalations carried out using anisole (IVa) as the substrate confirmed the previous experience of many workers that ethers, and in particular tetrahydrofuran, are far superior to hydrocarbon solvents for these reactions. We adopted finally a solvent mixture, approximately 3–4/1 tetrahydrofuran/hexane, which gave results comparable to those obtained by the use of the pure ether and which allowed us to take advantage of the commercial availability of hexane solutions of butyllithium. The metalations were carried out using equivalent quantities of butyllithium and substrate ether (*ca.* 0.35 *M*) at room temperature for times of 22–24 hours. Duplicate experiments were conducted in each case. At the end of the reaction time the mixtures were poured onto a large excess of powdered Dry Ice and products isolated and identified in normal fashion. Table 1 lists, with one exception, the results obtained with the first series of ethers, (IV). These data are most simply accommodated by the view that an increase in the steric bulk of the R group results in a decrease in the overall rate of metalation. It is considered likely that a steric effect would be most pronounced in the immediate vicinity of the oxygen atom, since in the preferred

TABLE 1

METALATION OF PHENYL ALKYL ETHERS, C_6H_5OR

Compound	*R*	*Conversion to ortho-acid* (%)[a]	*Conversion to total ortho-metalation* (%)	*Recovered ether* (%)
IVa	CH_3	50	54[b]	21
IVb	CH_2CH_3	42	43[c]	36
IVc	$CH(CH_3)_2$	25	25	51
IVe	$CH(CH_2CH_3)_2$	17	17	51

[a] Average of duplicate experiments. [b] Includes the formation of 2,2'-dimethoxybenzophenone and tris-(*o*-methoxyphenyl)carbinol. [c] Includes the formation of 2,2'-diethoxybenzophenone.

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* Metalation at the benzylic position might also be expected to result from such activation, depending on the value of *x*.

coplanar conformation of the ethers, one of the *o*-hydrogens should be equally unhindered in each case. We therefore suggest that the results in Table 1 indicate steric interference with the complexation* step which presumably involves the displacement of a specifically associated solvent molecule from the butyllithium aggregate[33] by the substrate ether**. We realize that the gross observations are the result of competition between metalation of the substrate ether and the destruction of butyllithium by reaction with the solvent, tetrahydrofuran. The reactivity of lithium alkyls toward tetrahydrofuran is well known[33-35]; in the present study this reactivity was verified by noting the complete disappearance of butyllithium in blank runs made in the absence of added substrate ether.

The results obtained with phenyl tert-butyl ether (IVd) do not fall directly into the pattern displayed in Table 1. The only product observed was salicylic acid which was formed in an average conversion of 27% (based on starting butyllithium) under the standardized reaction conditions. Cleavage of the substrate ether to lithium phenoxide followed by *ortho*-metalation[36] would account for the formation of this acid. The mechanism for aryl alkyl ether cleavage has been shown, at least for the case of aryl ethyl ethers and propylsodium[37], to involve β-hydrogen abstraction. Furthermore, it was suggested by Letsinger and Pollart[37], but not rigorously demonstrated, that the *ortho*-metalation product was not the intermediate which underwent elimination as might have been expected on the basis of some earlier results of Morton and Brachman[38]***. The facile cleavage of phenyl tert-butyl ether observed in the present work may be rationalized either on the basis of a simple *E*2-type β-elimination (increased number of primary β-hydrogens), or as the result of radical-anion formation (loss of a tertiary radical from the intermediate formed by electron transfer to the phenyl ring of the ether). Alternatively, the cleavage may involve an internal elimination† from the *ortho*-metalation product††. Repetition of the experiment at lower temperature (0.5–1°) in an attempt to detect an *ortho*-metalation product shed no further lights on the matter, since salicylic acid was again the only product obtained. In this case, however, the (crude) acid was isolated in quantitative yield. This increase in yield most likely stems from the slower rate of the (destructive) reaction of butyllithium with the solvent†††.

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* It is possible that the formation of a new complex is synchronous with the exchange step.

** The possibility that the steric effect is exerted during the carbonation step is considered untenably remote.

*** The cleavage of anisole by amylsodium apparently involves prior *ortho*-metalation. When *o*-sodioanisole, formed in at least 80% yield at 35° (as judged by carbonation and isolation of anisic acid) was heated at 50–80°, sodium phenoxide was produced[38]. The reaction was formulated[38] as an intramolecular α-elimination and the stoichiometric requirement that methylene be a product was clearly indicated. Although the ultimate fate of this product was neither discussed nor experimentally sought, the proposal itself seems not to have evoked the attention it deserves, especially in view of the widespread current interest in α-elimination processes. This experiment is definitely worthy of reinvestigation making use of modern techniques for the detection of carbenoid intermediates.

† Cram and Day[39] have recently proposed an exactly analogous intramolecular elimination of isobutylene from an intermediate formed by the addition of tert-butoxide ion to an aryne.

†† Steric inhibition of metalation or electron transfer processes may perhaps be offset by the increased electron withdrawing effect of the substituent which results if electron donation through resonance is repressed for conformational reasons.

††† It has been suggested[14] that cleavage of the tert-butyl ether may also occur during the hydrolytic work-up of the carbonation product. It is clear that this apparently unique member of the series requires additional detailed study.

The results obtained with the series of ethers (V) are listed in Table 2 where it may be seen that our efforts to demonstrate a conformational factor such as illustrated by (VI) were unsuccessful. The reactions were conducted in the same manner as described above for the series (IV); however, in each case carbonation of the reaction mixtures produced only traces of acidic materials which could not be characterized. In the case of the benzyl and 1-phenylethyl ethers (Va,b), not surprisingly, the carbinols resulting from Wittig rearrangement[24,40] were obtained. The lesser yield from (Vb) is the expected result of steric, inductive, and conformational factors as discussed in detail by Lansbury and his co-workers[24]. Metalation of (Vc), (Ve)* and (Vf) led to the recovery of starting ethers in high yield, whereas (Vd), in which the methoxyl group is exceptionally well disposed for β-elimination[41], styrene was formed and polymerized during the reaction.

TABLE 2

METALATION OF ω-PHENYLALKYL ETHERS, $C_6H_5CR^1R^2(CH_2)_nOCH_3$

Compound	*n*	*R*^{1}	*R*^{2}	*Conversion to products* (%)[a]	*Yield* (%)[b]
(Va)	0	H	H	26, Wittig rearrangement	62
(Vb)	0	H	CH_3	16, Wittig rearrangement	24
(Vc)	0	CH_3	CH_3	None identified	79[c]
(Vd)	1	H	H	51, polystyrene	71
(Ve)	2	H	H	None identified	75[c]
(Vf)	3	H	H	None identified	86[c]

[a] Average of duplicate experiments. [b] Based on unrecovered starting ether. [c] Recovered starting ether.

Some time after the completion of this work, there was reported from Hauser's laboratory[42] the results of experiments which were conceived and designed on the basis of considerations apparently similar to those which motivated our own studies with the ethers (V). In the reactions of the series of dimethylamines (VII) with butyllithium, Hauser and his colleagues[42] obtained positive evidence in support of the idea that metalation could be influenced by a donor atom located several atoms removed from the site of metalation. The (2-phenylethyl)amine (VIIa) underwent β-elimination with the production of styrene and ultimately, polymer, in a reaction sequence exactly parallel to that exhibited by the corresponding ether (Vd)**. Also, the unreactivity of the (4-phenylbutyl)amine (VIId) coincides with our results obtained with 4-phenylbutyl methyl ether (Vf). However, in the reaction of amine (VIIb), in which elimination of dimethylamine is blocked, a product resulting from *ortho*-

(VII) $C_6H_5{-}X{-}N(CH_3)_2$ (VIIa), $X = {-}CH_2CH_2{-}$

(VIIb), $X = {-}C(CH_3)_2CH_2{-}$ (VIIc), $X = {-}CH_2CH_2CH_2{-}$

(VIId), $X = {-}CH_2CH_2CH_2CH_2{-}$

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* Observations suggesting that, indeed, some reactions did occur between butyllithium and (Ve) are recorded in the EXPERIMENTAL PART.

** Just recently, however, the detection of *ortho*-metalation products derived from (VIIa) has been reported[43] but without mention of yields or reaction conditions.

metalation was indeed formed (17% conversion, 63% yield). Finally, from the (3-phenylpropyl)amine (VIIc), there was obtained a product resulting from metalation at the benzylic position (57% conversion, recovery of starting material not reported). The formation of six- and five-membered cyclic complexes was postulated to account for these results and it is likely that the failure of the ethers, especially (Ve), to undergo metalation derives in part from the lesser donating ability of the oxygen atom (relative to nitrogen), thus allowing the reaction of butyllithium with the solvent to be inefficiently contested.

EXPERIMENTAL PART

Infrared spectra were recorded with Perkin–Elmer model 137 or 237 spectrophotometers. Nuclear magnetic resonance spectra were determined with the Varian A60 instrument, using carbon tetrachloride solutions containing tetramethylsilane as internal standard. Melting points (Fisher–Johns block) and boiling points are uncorrected. Gas chromatography was carried out using a Wilkens Aerograph instrument, with helium as carrier gas at a flow rate of 50 cc/min, and equipped with a 5 ft. × 1/4 in. column packed with 20% SF-96 silicone on firebrick. Microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. Additional details are given by J. W. Altschuld, M. S. Thesis, Ohio State University 1964.

The starting ethers

Anisole (IVa), phenetole (IVb), benzyl methyl ether (Va), and 2-phenylethyl methyl ether (Vd) were all commercially available materials which were purified before use by fractional distillation through a Vigreux column. Phenyl isopropyl ether (IVc) was prepared by reaction of sodium phenoxide with isopropyl bromide in glyme. The crude ether was washed several times with 20% aqueous potassium hydroxide solution before being dried and distilled through a Vigreux column, b.p. 172–173° (Lit.[44] b.p. 178°). Phenyl tert-butyl ether (IVd) was prepared by treatment of tert-butyl perbenzoate with phenylmagnesium bromide following the directions of Lawesson and Yang[45]. The ether was purified by distillation through a Vigreux column, b.p. 46–51° at 5–6 mm. (Lit.[45] b.p. 70–71° at 11 mm). 3-Phenylpropyl methyl ether (Ve), 4-phenylbutyl methyl ether (Vf), and 1-phenylethyl methyl ether (Vb) were all prepared as follows. The appropriate alcohols (commercially available except for 4-phenylbutanol which was prepared by reduction of the available 4-phenylbutanoic acid) were transformed into their potassium salts by reaction in toluene solution with the metal. The suspended salts were then treated with an excess of dimethyl sulfate. The products were separated and purified by fractional distillation: (Ve), b.p. 58° at 4 mm. (Lit.[46] b.p. 100–102° at 20 mm); (Vf), b.p. 97° at 12 mm. (Lit.[47] b.p. 108° at 11 mm); (Vb), b.p. 25–30° at 3–6 mm (Lit.[48] b.p. 88° at 47 mm). 2-Phenyl-2-propyl methyl ether (Vc) was prepared from α-methylstyrene and methanol using the method described by Shaw[49]. The pure ether was obtained in 60% yield after distillation, b.p. 77–84° at 20 mm (Lit.[50] b.p. 78° at 13 mm).

Phenyl 3-pentyl ether (IVe) has not, to our knowledge, been previously described. It was prepared from sodium phenoxide and 3-pentyl bromide employing the same procedure which was used for the preparation of phenyl isopropyl ether. The purified product had b.p. 51–52° (2 mm) and its nuclear magnetic resonance spectrum showed an aromatic multiplet (5 hydrogens) centered at τ 3.28 ppm whose shape was very similar to the corresponding multiplet in the spectrum of anisole[51], a quintet (J 6 cps) centered at τ 6.12 as anticipated for the methine proton, a multiplet (4 hydrogens) at τ 8.55 assigned to the methylene hydrogens, and finally, a triplet (J 7 cps) (6 hydrogens) at τ 9.13 ppm arising from the presence of the two methyl groups. (Found: C, 80.55; H, 9.76. $C_{11}H_{16}O$ calcd.: C, 80.44; H, 9.76%.)

n-Butyllithium

Solutions of n-butyllithium in ether or tetrahydrofuran were prepared by treatment of the metal with butyl bromide using established procedures[52]. The preparation of decane solutions has been described[1] and hexane solutions were purchased from the Foote Mineral Company. The butyllithium content of the various solutions was determined by use of the double titration method[53].

General metalation procedure

A three-necked 250-ml round-bottomed flask was fitted with a stopper, an adapter for a serum cap, and a condenser to which a gas inlet tube was attached. The apparatus was thoroughly dried with a Bunsen burner while being flushed with dry nitrogen; a positive pressure of nitrogen was maintained in the flask throughout the reaction period. The ether to be metalated was placed in the flask along with a specified quantity of solvent (freshly distilled from lithium aluminum hydride). A solution of butyllithium was then added through the serum cap by means of a syringe. The contents of the flask usually warmed up somewhat during the addition of the metal alkyl. On some occasions this heat effect was quite pronounced and the flask was cooled in an ice bath for the remainder of the addition. After the addition was complete, the reaction mixture was allowed to stand at room temperature for 22–24 h. The concentration of reactants was 0.3–0.4 M. At the end of the reaction time the contents of the flask were quickly transferred to a 2-l erlenmeyer flask containing a large excess of powdered Dry Ice. When the excess Dry Ice had sublimed (several hours), the remaining salts were dissolved in 400–500 ml distilled water, the mixture filtered, then extracted with ether (4 × 40 ml). The combined extracts were dried and evaporated to provide a residue (mainly starting material) whose weight and infrared spectrum were recorded. The aqueous layer was acidified to pH 2 or less with concentrated hydrochloric or sulfuric acid and extracted again with ether (5 × 40 ml). After being dried, these extracts were evaporated to obtain the product acid. The methods of purification (when necessary) and identification of the products are described below for each experiment. All the infrared spectra were consistent with the assigned structures. Unless otherwise noted, all reactions were carried out in duplicate.

Metalation of Anisole (*4a*)

In each of two experiments, 5.5 ml (0.051 mole) of anisole in 85 ml tetrahydrofuran were allowed to react with 28 ml (0.041 mole) of 1.48 N butyllithium in hexane. There was obtained 3.15 g and 3.32 g of crude acid products which were washed with cold Skelly Solve B to provide 3.06 g (49%) and 3.14 g (51%), respectively, of *ortho*-anisic acid, m.p. 98.5–101.5° (Lit.[38] m.p. 101–101.5°). From the neutral extracts were obtained 1.63 g and 1.16 g of liquid residue from which solids deposited after they had stood for a long time. After removal of the solid products, the remaining liquid was shown to be recovered anisole by infrared comparisons. The solid (combined weight, 0.44 g) showed both carbonyl and hydroxyl absorption in the infrared and was estimated from subsequent chromatographic separation to be about a 3:1 mixture of 2,2'-dimethoxybenzophenone, ν_{max}^{KBr} 1635 cm^{-1}, m.p. 103–104.5° (Lit.[38] m.p. 101–102.5°), and tris(*ortho*-methoxyphenyl) carbinol, ν_{max}^{KBr} 3700 cm^{-1}, m.p. 187–187.5° (Lit.[38] m.p. 181.5–182.5°). The ketone was further characterized by preparation of a 2,4-dinitrophenylhydrazone, m.p. 188–188.5° (Lit.[38] m.p. 180–182°).

Metalation of phenetole (IVb)

Phenetole (0.038 mole) in 84 ml tetrahydrofuran was treated with 25.5 ml (0.037 mole) 1.46 *N* butyllithium in hexane. In each experiment, 2.97 g acid product was obtained. These were combined and distilled through a small Vigreux column to provide 5.15 g pure *o*-ethoxybenzoic acid, b.p. 95–97.5° at 0.3–0.4 mm (Lit.[54] b.p. 216–229° at 90 mm). The acid was converted into an amide by treatment with thionyl chloride and ammonium hydroxide, m.p. 124–126° (Lit.[55] m.p. 130°). The infrared spectra of the neutral products (1.57 g and 1.79 g) were nearly identical to that of the starting ether. A weak carbonyl band [$\nu_{max}^{(film)}$ 1610 cm^{-1}] was present, however, and after these samples had stood for some time a total of 80 mg of a solid precipitate was obtained. After several recrystallizations from chloroform/hexane mixtures, this carbonyl containing product had m.p. 110–110.5°. 2,2'-Diethoxybenzophenone is reported[56] to melt at 109°.

Phenyl isopropyl ether (IVc)

In these experiments, 0.036 mole phenyl isopropyl ether in 84 ml tetrahydrofuran was used along with 20.5 ml (0.03 mole) 1.46 *N* butyllithium in hexane. The crude acid products (1.95 g and 1.82 g) were combined and purified by distillation through a small Vigreux column to give 2.7 g liquid, b.p. 91–101° at 0.15–0.075 mm (Lit.[54] b.p. 216–227° at 93 mm for *o*-isopropoxybenzoic acid). The purified acid was further characterized as the amide, m.p. 59–60.5° (Lit.[55] m.p. 67–68°). The residues from the neutral extracts (2.19 and 2.83 g) had infrared spectra essentially identical to that of the starting ether.

Phenyl tert-butyl ether (IVd)

Phenyl tert-butyl ether (0.034 mole) in 84 ml tetrahydrofuran was treated with 22 ml (0.032 mole) 1.46 *N* butyllithium in hexane in two experiments. The crude acid products (1.36 g and 2.02 g) solidified on standing overnight. They were combined and washed with cold Skelly Solve B to give 1.17 g (27% based on two equivalents of butyllithium) salicylic acid. Sublimation (80–90° at 12–17 mm) gave material with m.p. 152–156°, alone or admixed with an authentic sample. The infrared spectrum of the purified product as well as that of the crude solid was identical with that of authentic salicylic acid. The infrared spectra of the neutral products (2.12 g and 2.13 g) were practically identical with that of the starting ether.

A single experiment was carried out as above (0.035 mole ether, 0.034 mole butyllithium) except that the reaction mixture was maintained at 0.5–1.0° by means of an ice bath. The neutral extract provided 2.74 g recovered starting ether. From the acid extract was obtained 2.52 g crude acid which solidified on standing. After being washed with cold Skelly Solve B, the solid product showed an infrared spectrum identical with that of salicylic acid.

Phenyl 3-pentyl ether (IVe)

In parallel experiments phenyl 3-pentyl ether (0.032 mole) in 84 ml tetrahydrofuran was treated with 20.5 ml of a hexane solution 1.5 *N* in butyllithium (0.031 mole). The residues (3.18 g and 3.36 g) from the neutral extracts were combined and distilled through a small Vigreux column to provide 5.29 g recovered ether (b.p. 82–88.5° at 13–13.5 mm), identified by its infrared spectrum. The acid extracts (1.56 g and 1.47 g) were combined and distilled to give 2.21 g pure *o*-(3-pentyloxy)benzoic acid, b.p. 118–123° at 0.44–0.45 mm. (Found: C, 69.04; H, 7.76; eq. wt., 217. $C_{12}H_{16}O_3$ calcd.: C, 69.21; H, 7.76%; eq. wt., 208.) The NMR spectrum of the acid substantiated its formulation as *o*-(3-pentyloxy)benzoic acid. The signals arising from the pentyl group were the same as in the starting ether except that they were shifted to lower field: *i.e.*, methyl hydrogens at τ 9.04, methylene hydrogens at 8.29, and methine hydrogen at 5.52 ppm. The carboxyl hydrogen gave rise to a signal at τ -1.05 ppm. The four aromatic hydrogens displayed a pattern of signals very similar to that shown by *o*-anisic acid[57]. Assignment of the low field doublet (*J* 8 cps) of doublets (*J* 1.5 cps) at τ 2.01 to the hydrogen *ortho* to the carboxyl and a multiplet at 2.66 ppm to the hydrogen *para* to the carboxyl follows the literature[57] assignment. Similarly, the multiplet (2 hydrogens) centered at τ 3.02 ppm is assigned to the hydrogens *ortho* and *para* to the alkoxy group. The acid was converted into an amide which was purified by recrystallization from an isohexane/chloroform mixture, m.p. 96.5–98°. (Found: C, 68.84; H, 8.21; N, 6.76. $C_{12}H_{17}O_2N$ cald.: C, 69.54; H, 8.27; N, 7.06%.)

Benzyl methyl ether (Va)

Benzyl methyl ether (0.04 mole) in 84 ml tetrahydrofuran was allowed to react with 0.034 mole butyllithium (22.5 ml 1.5 *N* hexane solution) in duplicate experiments. Addition of the metal alkyl caused rapid heating of the mixtures so that cooling was necessary. The solutions quickly assumed a dark purple color and at the end of the reaction time, they remained a deep amber color. The acidic extracts provided oily products (0.23 g and 0.30 g) which resisted all attempts at purification. Since the neutral products (4.37 g and 4.22 g), which showed strong hydroxyl absorption in the infrared, were not effectively rectified in an initial distillation attempt, the distillate and pot residue were analyzed by gas chromatography. Calculations based on these analyses indicated the recovery of 64% of the starting ether. The conversion (based on butyllithium) to rearrangement product (Table 2) was calculated to include an amount of styrene which was also detected and assumed to arise by dehydration of the carbinol product either during work-up, attempted distillation, or during gas chromatography.

1-Phenylethyl methyl ether (Vb)

As in the experiments described directly above, cooling was required during the addition of butyllithium (0.023 mole) (15.5 ml hexane solution, 1.5 *N*) to the tetrahydrofuran (62 ml) solutions of (Vb) (0.025 mole). A marked color change was also observed, although less rapidly than in the case of (Va), to a bright orange which faded finally to a dull yellow. Oily acidic products [0.19 g and 0.24 g, $\nu_{\max}^{(\text{film})}$ 1709 cm^{-1}] were obtained but as with those obtained from (Va), could not be characterized. The neutral products (2.92 g and 2.65 g, strong hydroxyl absorption), after an abortive attempt at fractional distillation, were analyzed by gas chromatography to provide the data listed in Table 2. Some unidentified materials were observed but the matter was not pursued.

2-Phenyl-2-propyl methyl ether (Vc)

In two experiments, 0.03 mole of (Vc) in 84 ml tetrahydrofuran was treated with 0.03 mole of butyllithium solution in hexane (20 ml, 1.5 *N*). Gummy acidic products were obtained [total 0.53 g, $\nu_{\max}^{(\text{film})}$ 1703 cm^{-1}] but could not be purified. Infrared and gas chromatographic analysis of the neutral products (3.58 g and 3.55 g) showed them to be primarily recovered starting material.

2-Phenylethyl methyl ether (Vd)

The starting ether (0.036 mole) in 84 ml tetrahydrofuran was treated with an equivalent quantity of butyllithium in hexane solution (24 ml). The reaction mixtures were cooled during addition of the bulk of the metal alkyl solution since the initial quantity rapidly caused a marked heat effect as well as a color change to deep red. The reactions were then allowed to proceed (at room temperature) for 43 h during which time the red color faded to a milky white. Resinous acidic products (0.10 g and 0.14 g) were obtained which could not be purified. Treatment of the liquid neutral products (3.15 g and 3.52 g) with ethanol resulted in the precipitation of a white solid, which after being washed repeatedly with ethanol and dried *in vacuo* (2.52 g and 1.25 g) gave an infrared spectrum nearly identical with that of an authentic polystyrene film. Evaporation of the ethanol solutions led to the recovery of starting ether (0.63 g and 2.27 g) identified by infrared spectral comparisons.

3-Phenylpropyl methyl ether (Ve)

In two experiments, 0.033 mole of the starting ether in 84 ml tetrahydrofuran was treated with 23.5 ml of butyllithium solution, 1.5 *N* in hexane (0.035 mole). During the addition, a slight warming of the reaction mixture was noted as was the production of a golden yellow color. At the end of the total reaction time, the color had deepened into an orange-gold. In spite of these evidences that some reaction had occurred, only small quantities (0.20 g and 0.07 g) of gummy acidic products were obtained. Persistent attempts to purify this material were unsuccessful. The starting material (3.58 g and 3.90 g) was recovered from the neutral extract and identified by its infrared spectrum.

4-Phenylbutyl methyl ether (Vf)

No evidence of reaction was observed when 0.033 mole (Vf) in 84 ml tetrahydrofuran was treated with 19 ml (0.029 mole) of a hexane solution of butyllithium. Acidic products (0.08 g and 0.15 g) (uncharacterized) and unreacted starting material (4.81 g and 4.46 g) were obtained.

Blank reaction of butyllithium with tetrahydrofuran

In a single experiment, 22.5 ml of butyllithium solution (1.5 *N* in hexane) was added to 84 ml tetrahydrofuran and the mixture allowed to stand for 22.5 h at room temperature. The reaction provided, after the usual work-up procedure, 0.05 g neutral product (volatile products were not sought) and 0.1 g of an acidic product which did not contain valeric acid as judged by its odor. Further examination of this reaction was not made.

SUMMARY

Treatment for 22–24 hours at room temperature of the methyl, ethyl, isopropyl, and 3-pentyl ethers of phenol with n-butyllithium in hexane/tetrahydrofuran, followed by carbonation and acidification, provided the corresponding *o*-alkoxybenzoic acids in conversions of 50, 42, 25, and 17%, respectively. Under these conditions, phenyl tert-butyl ether gave only salicylic acid (27% conversion) although at lower temperature, a quantitative conversion to this acid was noted. 2-Phenylethyl methyl ether produced mainly polystyrene (51% conversion). 3-Phenylpropyl and 4-phenylbutyl methyl ethers provided negligible amounts of acidic products even though visual evidence of reaction of the former ether with butyllithium was observed. Benzyl, α-methylbenzyl and α,α-dimethylbenzyl methyl ethers gave only small amounts of acidic products which were uncharacterized and the former two ethers afforded the Wittig rearrangement products in conversions of 26 and 16%, respectively.

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