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Some Reactions of α-Metalated Ethers[1]

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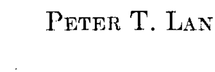
It seems advisable to regard the so-called "Wittig rearrangement" of ethers as proceeding by several competing mechanisms, the major path being dissociation to a carbonyl-organolithium complex followed by recombination in the usual manner to carbinol. The possibility of an SNi-type rearrangement mechanism for ethers in which a tertiary alkyl group "migrates" has been investigated and evidence for such an hypothesis obtained.

During the past twenty years, the base-catalyzed rearrangement of certain benzyl and benzhydryl ethers to alcohols has been investigated by Wittig and his co-workers,[2] and also by Hauser,[3] Curtin,[4] and Letsinger.[5] The earlier workers in general supported an intramolecular displacement mechanism, proceeding through a carbanion[6] intermediate (equation 1), since there seemed to be an analogy with the Stevens rearrangement,[7] rather than an alternative cleavage-recombination mechanism (equation 2). The latter reaction path was rejected by Hauser[3] on the grounds that the metalating base (R'Li) did not show any tendency to compete with R:⁻ for the aldehyde moiety resulting from cleavage. However, if the cleavage were to proceed in a solvent cage and the fragments kept from separating by coordination with the same lithium ion,[8] one could rationalize the absence of Ar—CHOH—R' in the product mixture. Indeed, the second mechanism seems attractive if one compares the Wittig rearrangement with the cleavage of similar ethers in protonic solvents such as liquid ammonia,[3] alcohols,[9a,b] and amines[9c] with metalating bases (amide, alkoxide, hydroxide) whose cations have weaker coordinating properties than lithium, *e.g.*, potassium. The products in these cases are generally[3,9a,c] the aldehyde and the conjugate acid of R:⁻ (equation 2), rather than the recombination product expected in the absence of a proton donor. Evidence that the organolithium-catalyzed ether rearrangement is mechanistically similar to the above cleavages was gained from the recent investigations of Schollkopf,[10] involving optically active benzyl *s*-butyl ether. Since this ether rearranges with predominant racemization of the migrating group, it was concluded that the reaction involves a series of steps similar to equation 2,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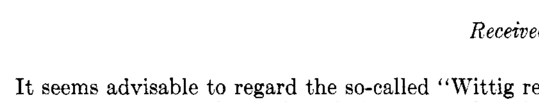
(2)

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[1] Supported by a grant from the U. S. Army Research Office (Durham).

[2] (a) G. Wittig and L. Lohman, *Ann.*, **550**, 260 (1942); (b) G. Wittig and R. Clausnizer, *ibid.*, **588**, 145 (1954); (c) G. Wittig and E. Stahnecker, *ibid.*, **605**, 69 (1957), and other papers in this series.

[3] C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

[4] D. Y. Curtin and M. J. Fletcher, *J. Org. Chem.*, **19**, 352 (1954).

[5] R. L. Letsinger and D. F. Pollart, *J. Am. Chem. Soc.*, **78**, 6079 (1956).

[6] The term "carbanion" for organolithium compounds is used here merely for brevity. It is acknowledged that such species have highly covalent carbon-lithium bonds and are at best fairly tight ion pairs, rather than dissociated ions.

[7] (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959, p. 640, and references cited therein; (b) D. J. Cram, in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 279–283.

[8] The effect of metal cation on rate has been noted by Wittig, ref. 2b and 2c.

[9] (a) D. Y. Curtin and S. Leskowitz, *J. Am. Chem. Soc.*, **73**, 2630 (1951); (b) J. Cast, T. S. Stevens, and J. Holmes, *J. Chem. Soc.*, 3521 (1960); (c) D. J. Cram, C. A. Kingsbury, and A. Langemann, *J. Am. Chem. Soc.*, **81**, 5785 (1959).

[10] (a) U. Schollkopf, *Angew. Chem.*, **72**, 570 (1960); (b) U. Schollkopf and W. Fabian, *Ann.*, **642**, 1 (1961).

rather than a concerted intramolecular displacement, since the latter transformation should proceed with essentially complete retention.[10] However, it should be noted that SNi reactions of alkyl chlorosulfites do not always proceed with complete retention of configuration[11] and hence Schollkopf's conclusions are not necessarily valid without other supporting evidence (*vide infra*). Cram and coworkers[9c] have also suggested that dissociation may be the first stage of the Wittig rearrangement, based on the similarity in stereochemical results of the cleavage of ethers and alkoxides, where optically active 2-phenylbutane is the common product. Thus, it appears that in the cases studied to date the main reaction path involves some form or modification of path 2, rather than 1. It should be pointed out, however, that Wittig rearrangements of ethers are usually accompanied by competing side reactions which sometimes become predominating, such as beta-elimination,[2,3,5] formation of isomeric carbonyl compounds,[10b] 1,4-elimination,[5] and even alpha-elimination to form carbenes.[12] Thus, quantitative data pertaining to mechanism is difficult to obtain.

We have studied the rearrangement of several benzyl and benzhydryl ethers in some detail. Careful product studies, utilizing gas-liquid partition chromatography, have demonstrated that carbinols bearing the carbanion portion of the metalating base are indeed formed, thus negating Hauser's argument[3] against the cleavage mechanism and supporting Schollkopf's assertions.[10] It should be noted, however, that our investigations involved more polar solvents than pure ether (see below) and this can lead to appreciable differences in product distribution from those which would arise in ether medium. Indeed this expectation has been confirmed. In addition we have demonstrated the first rearrangements of *t*-alkyl benzyl ethers and provide some justification for considering these latter isomerizations as SNi reactions. These findings are taken up in more detail below.

Benzyl Ether (I).—The action of organolithium reagents on I, using various ratios of ether to base, several solvents of varying polarity,[13] and different reaction times has been noted. In most cases, methyllithium was used as the metalating base, and it was prepared by the reaction of dimethylmercury with lithium metal in order to have it halogen-free. The results of a typical series are tabulated in Table I; duplicate runs gave similar data. Product analyses were performed using gas-liquid partition chromatography with several columns, using correction factors determined from the analysis of synthetic mixtures of authentic compounds. Although not quantitatively accurate, the data are internally consistent and definite trends are indicated. Large scale runs were also carried out, from which all products of interest were isolated and characterized by comparison of physical properties and infrared spectra with those of authentic specimens.

TABLE I

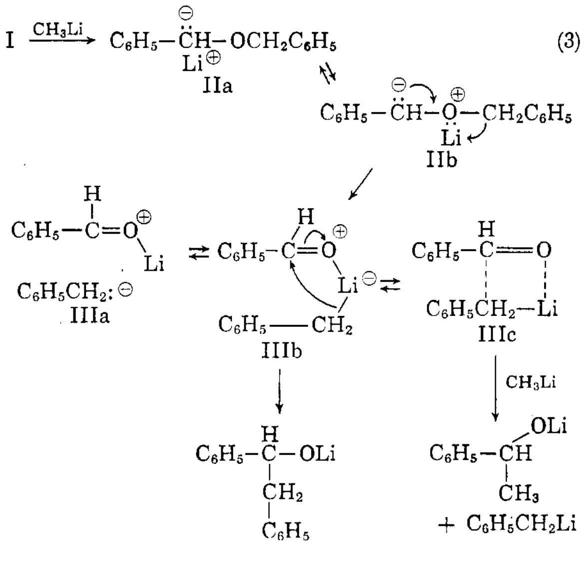
ISOMERIZATION OF BENZYL ETHER[a]

I/ CH_3Li	Solvent (v:v)	C_6H_5CH-$OHCH_2$-C_6H_5 (A)	C_6H_5CH-$OHCH_3$ (B)	A/B
5	Ether–THF(1:1)	97	3	32
5	THF–triethylamine (1:1)	91	9	10.1
5	THF	82	18	4.5
5	THF–dimethoxyethane (1:1)	75	25	3

[a] Reactions were run for forty-eight hours prior to hydrolysis, in nitrogen-flushed flasks. The amount of ether (I) used was 0.5 mmole. Several peaks of unknown identity have been omitted. Usually, I was completely consumed or present in <5% amount.

The above results demonstrate that benzaldehyde, resulting from cleavage of the metalated ether, can be scavenged by methyllithium, the extent depending quite markedly on the cation-solvating ability of the solvent, as well as dielectric constant.

The data can be discussed in terms of a mechanism which incorporates certain features previously pointed out by Wittig[2c] and Schollkopf.[10b] Solvation has not been pictured, although previous data[2c,10b] and our results (Table I) show that consideration of cation solvation and cage effects must be made. Wittig correctly concluded that species such as IIb are involved in the isomerization of benzhydryl phenyl ether[2c] since the effect of vary-



(3)

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[11] C. E. Boozer and E. S. Lewis, *J. Am. Chem. Soc.*, **75**, 3182 (1953).

[12] U. Schollkopf and M. Esitert, *Angew. Chem.*, **72**, 349 (1960).

[13] An attempt to evaluate dimethyl sulfoxide as solvent was complicated by the fact that methyllithium reacted with it, presumably by alpha-metalation, since a vigorous evolution of gas was observed when the two were brought into contact; subsequent addition of benzaldehyde to this mixture gave no α-phenylethanol. The metalated sulfoxide, in turn, induced the isomerization of dibenzyl ether to benzylphenylcarbinol but, since no methyllithium was left at this stage (see above), the significance of "cross-over" product formation could not be assessed.

ing the cation on rate ($Li^+ > Na^+ > K^+$) was in the order expected for complexing with oxygen, thereby rendering it highly electrophilic for more facile rearrangement. Lithium ion has also been shown to be most effective, among the alkali hydroxides, in promoting the benzilic acid rearrangement,[14] presumably due to its ability to coordinate with carbonyl oxygen of the migration terminus, thus facilitating migration. If species such as IIa were of primary importance in the Wittig rearrangement, the opposite reactivity sequence would be expected.[15] Species IIb, which is somewhat similar to a nitrogen ylid, may then rearrange to complex III, for which several contributing forms, which emphasize ion-pair character, are possible. Such species would account for the optical lability of the migrating group, since organolithium reagents are easily racemized in ether solvents, even at low temperatures.[16] Formulation IIIb has been postulated as the first (reversible) step in the addition of organolithium reagents to the carbonyl group.[17] Collapse of such a complex leads to "normal" product, whereas separation of the components, followed by reaction of benzaldehyde with methyllithium, explains the isolation of appreciable amounts of methylphenylcarbinol, the yield increasing in the more polar solvents. Earlier mechanistic interpretations had no provision for such "cross-over" products. It is understandable that these products were not detected previously[3] since they are minor products under the conditions used,[3] even though the metalating base is present in great excess. Other primary and secondary alkyl benzyl ethers, *e.g.*, *n*-butyl benzyl ether, give only traces of methylphenylcarbinol, presumably because less important contributions of IIIa to the migration transition state[18] result in a tighter coordination of the alkyl group as it moves to carbon from oxygen. In summary, our finding of minor amounts of methylphenylcarbinol in the reactions of I with bases such as methyllithium suggests that the isomerization occurs in a fairly tight solvent cage, thus reaffirming Schollkopf's mechanism,[10b] which was based mainly on stereochemical findings.

Benzhydryl Ether (IV).—Although, in other instances[3,9a] benzhydryl ether reportedly did not cleave or rearrange when treated with phenyllithium under Wittig conditions, diphenylmethide and benzophenone were formed when potassium amide[3] and potassium *t*-butoxide[9a] were used, in their corresponding conjugate acid solvents. Curtin and Fletcher[4] later found that some dimetalation of IV by excess phenyllithium occurred, as shown by isolation of the corresponding unrearranged dicarboxylic acids.

Our own examination of the reaction of IV with methyllithium, in the same series of solvents as used with I, revealed a variety of products, two of which remain unidentified. Definitely formed and isolated from large-scale runs by chromatography and fractional crystallization, are benzhydrol (up to 32%), 1,1,2,2-tetraphenylethane, tetraphenylethylene, diphenylmethane, and methyldiphenylcarbinol (up to 17%). The expected isomerization product, 1,1,2,2-tetraphenylethanol, was found to be unstable under the reaction conditions, reverting initially to diphenylmethide and benzophenone, which subsequently were converted to diphenylmethane and methyldiphenylcarbinol (*ca.* 35% each), respectively, after hydrolysis. Both 1,1,2,2-tetraphenylethane (V) and tetraphenylethylene (VI) are formed from IV in substantial yields (5 to 7%), even when special efforts were made to exclude air. Although V, which is itself stable in the presence of methyllithium in tetrahydrofuran, may be formed by air oxidation of diphenylmethide ion,[9a] one cannot readily ascribe the formation of VI to such a side reaction. Furthermore, only *ca.* 1% of VI is formed from 1,1,2,2-tetraphenylethanol under the reaction conditions (see above), thus ruling out dehydration of the alcohol as a major source for VI.

It is possible that metalated IV can decompose by an alpha-elimination mechanism, as well as by beta-elimination. Schollkopf[12] has shown that benzyl phenyl ether decomposes to phenylcarbene and phenoxide ion, when treated with phenyllithium. Moreover, Cope and co-workers[19] have confirmed the occurrence of alpha-elimination in the base-catalyzed isomerization of cyclooctene oxide, where an unstabilized alkoxide (as compared with phenoxide) is the leaving group. Alpha-elimination of metalated IV would lead to the anion of benzhydrol and diphenylcarbene. Dimerization of the latter would give VI, although one might expect reaction of the electrophilic diradical[20] with methyllithium to give 1,1-diphenylethane, which was not observed. Clearly, not enough data are at hand to allow one to explain, in mechanistic terms, the complex reactions which IV undergoes under Wittig conditions.

Benzyl *t*-Alkyl Ethers.—To our knowledge, no rearrangements of ethers in which a tertiary alkyl group is the migrating group are known. Since tertiary carbanions are extremely reactive,[21] it is not likely that they can be readily generated by a cleavage of the type formulated for I if other

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(14) W. H. Puterbaugh and W. S. Gaugh, *J. Org. Chem.*, **26**, 3513 (1961).

(15) H. D. Zook, J. March, and D. F. Smith, *J. Am. Chem. Soc.*, **81**, 1617 (1957).

(16) R. L. Letsinger, *ibid.*, **72**, 4842 (1950).

(17) C. G. Swain and L. Kent, *ibid.*, **72**, 518 (1950).

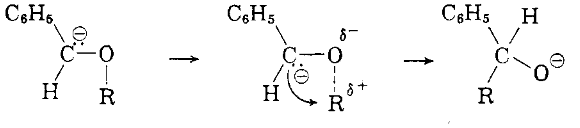
(18) E. A. Braude in J. W. Cook, "Progress in Organic Chemistry," Vol. 3, Butterworths Scientific Publications, 1955, p. 172.

(19) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Am. Chem. Soc.*, **82**, 6370 (1960).

(20) R. M. Etter, H. S. Skovronek, and P. S. Skell, *ibid.*, **81**, 1008 (1959).

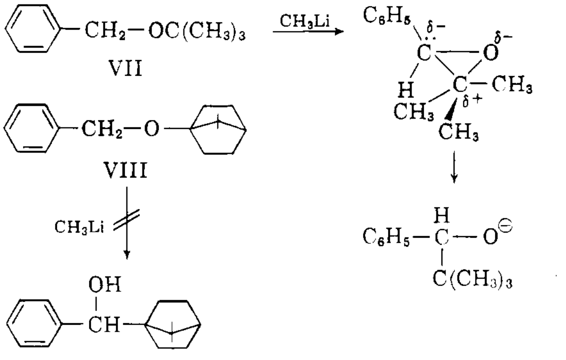
(21) P. D. Bartlett, S. Friedman, and M. Stiles, *ibid.*, **75**, 1771 (1953).

lower energy paths for reaction are available. For this reason, it seemed worthwhile to study the reaction of organolithium reagents with several selected benzyl *t*-alkyl ethers, in order to determine the possible role of an SNi transition state in their rearrangement. Such a mechanism would result in the development of considerable positive character in the migrating group[22] and would depend heavily on the ability of R (below) to stabilize a positive charge.



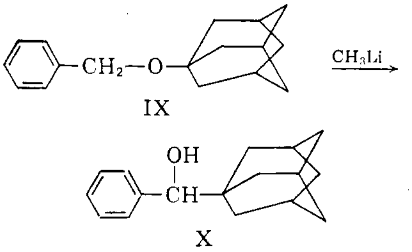
A suitable test would involve a study of benzyl *t*-butyl ether (VII) and benzyl apocamphyl ether (VIII). It is reported[22,23] that 1-apocamphanol does not react with thionyl chloride to give 1-chloroapocamphane, and moreover that the latter tertiary chloride shows complete inertness toward SN1 substitution reactions. Conceivably, VIII would not rearrange to the isomeric carbinol if a carbonium ion-like transition state were required.

Ethers VII and VIII were readily prepared by the reaction of benzyl chloride with the appropriate *t*-alkoxides. Treatment of these compounds with excess (*ca.* 5 moles) methyllithium in tetrahydrofuran for two days resulted in almost complete consumption of VII and the isolation of over 50% of phenyl-*t*-butylcarbinol. On the other hand, VIII was recovered essentially unchanged, there being only a trace of product whose vapor phase chromatographic behavior coincided with that of pure phenylapocamphylcarbinol. This behavior seems consistent with the view that tertiary ethers rearrange by an SNi mechanism, if possible, and not by the cleavage-recombination mechanism (equation 2), in which case one would expect that both or neither VII and VIII might rearrange in view of the expected similar stabilities of the *t*-butyl and 1-apocamphyl carbanions.[24]



Recent work by Schleyer[25] and others[25] has shown that bridgehead compounds of adamantane are unexpectedly reactive in carbonium ion reactions. In spite of the impossibility of rearside solvation, which apparently plays a minor role, 1-adamantyl compounds solvolyze quite rapidly, indicating that near-planar transition states may arise without too much angle strain. It was therefore of interest to examine the behavior of benzyl adamantyl ether (IX) under Wittig conditions in order to see if it rearranged as expected if the SNi mechanism were operative.

Ether IX was prepared from 1-bromoadamantane[25b] by solvolysis in benzyl alcohol containing several equivalents of sodium benzylate. Reaction of IX with methylithium under the usual conditions gave more than 50% of phenyladamantylcarbinol (X) and no recovered ether.



The structure of the rearranged carbinol was confirmed by its independent synthesis from 1-adamantanecarboxylic acid,[26] *via* the phenyl ketone which was subsequently reduced by lithium aluminum hydride.

The methyllithium-catalyzed isomerizations observed with ethers VII and IX, as compared with the inertness of benzyl apocamphyl ether (VIII), seem best explained by the postulate that, when possible, tertiary ethers will rearrange by an intramolecular displacement mechanism, in which the migrating group supports considerable positive charge.[22] When this is not possible, *e.g.* VIII, no rearrangement occurs, since the alternative cleavage-recombination would not be favorable if a tertiary carbanion were to be generated.

Conclusions

There seems to be no single mechanistic scheme which is applicable to all organolithium-catalyzed rearrangements of benzyl and benzhydryl ethers. It appears that the path followed depends on the nature of the "migrating" group, specifically its ability to tolerate positive or negative charge.

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(22) E. Eliel in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 79–83, and references cited therein.

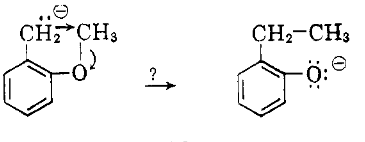
(23) P. D. Bartlett and L. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).

(24) D. E. Applequist and J. D. Roberts, *Chem. Rev.*, **54**, 1081 (1954). Bridgehead organometallic compounds are preparable from the halides without undue difficulty in a number of cases cited in the above review. A more recent review of carbanion reactions at the bridgehead of bicyclic systems is that of Schollkopf [*Angew. Chem.*, **72**, 147 (1960)].

(25(a) P. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83**, 2700 (1961); (b) S. Landa, S. Kriebel, and E. Knoblock, *Chem. Listy*, **48**, 61 (1954).

(26) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).

Our results, as well as those of others,[11] suggest that cleavage-recombination paths, similar to those involved in ether cleavages under different conditions[9] are important in the vast majority of previously observed cases. Indeed, if a simple intramolecular displacement mechanism were valid for the case of methyl benzyl ether,[2a] one should be able to isolate o-ethylphenol from rearrangement of alpha-metalated o-methylanisole. This intramolecular reaction would be facilitated by the readily achievable coplanar five-membered cyclic transition state, as well as by the fact that the displaced group, a phenoxide ion, is a better leaving group than the more basic alkoxides encountered in the earlier mechanistic proposals.[2,3] The absence of any o-ethylphenol from the products of metalation of o-methylanisole[27] seems to concur with the proposals set forth above. However, since the extent of side chain metalation of o-methylanisole was not reported,[27] we wished to prepare this species unambiguously in order to examine its behavior. Accordingly, n-butyl o-methoxybenzyl ether was prepared and cleaved with lithium in ether. After two hours, cleavage of the ether was nearly complete and after forty-eight hours, hydrolysis and work-up of the reaction mixture gave 86% o-methylanisole and no o-ethylphenol (by vapor phase chromatography). Thus, it can be confidently asserted that o-methoxybenzyllithium does not rearrange and and that an S_Ni mechanism for methyl benzyl ether[2a] is extremely unlikely.



Experimental[28]

Preparation of Compounds.—Benzyl ether, 1,2-diphenylethanol, 1-phenylethanol, and diphenylmethane were obtained from commercial sources. Solvents were reagent grade chemicals that were freshly distilled from lithium aluminum hydride or calcium hydride (for dimethyl sulfoxide).

Benzhydryl ether was prepared by refluxing benzhydryl chloride for 8 hr. in water. The crystals, which separated on cooling, were recrystallized twice from water, m.p. 108–110° (reported,[3] m.p. 110°), yield, 74%.

1,1-Diphenylethane was prepared from benzene and 1-phenylethanol in the presence of aluminum chloride, similar to the method of Spilker and Schade,[29] b.p. 145–148°/15 mm. (reported,[29] b.p. 148°/15 mm.), yield, 41%.

Tetraphenylethane was prepared by the addition of sodium to tetraphenylethylene in ether under nitrogen. Recrystallization of the crude product from carbon tetrachloride gave a 70% yield of product, m.p. 207–209° (reported,[30] m.p. 209°).

1,1,2,2-Tetraphenylethanol was obtained from the reaction of phenyl benzhydryl ketone with excess phenyllithium in ether–benzene solution. Recrystallization from benzene gave 26% of the carbinol, m.p. 235–237° (reported,[31] m.p. 243–244°).

Benzyl Adamantyl Ether (IX).—To a solution of benzyl alcohol (0.28 mole) containing 0.03 mole of sodium benzylate was added 2.1 g. (0.01 mole) of 1-bromoadamantane[25b] and the resulting mixture heated for 4 hr., during which a copious precipitate (NaBr) formed. After cooling, the reaction mixture was poured into water and the aqueous phase extracted with ether and the latter dried over sodium sulfate, then evaporated. Most of the benzyl alcohol was removed by distillation, leaving *ca.* 4 ml. of oil which was chromatographed over alumina. Elution with petroleum ether afforded 1.6 g. (67%) of product IX, b.p. 123–126°/0.25 mm. The infrared spectrum showed no O–H bands and was in accord with the expected structure.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.45; H, 8.84.

Phenyl 1-Adamantyl Ketone.—The reaction of 38 g. of adamantane-1-carboxylic acid[26] with excess thionyl chloride in ether at room temperature for 2 hr. followed by distillation of solvent and unused thionyl chloride then product, afforded 16.9 g. of the acid chloride (41%), b.p. 105–106°/1.3 mm., which solidified on standing. To a solution of this material in *ca.* 30 ml. ether was slowly added an equimolar quantity (0.086 mole) of freshly prepared phenylmagnesium bromide in ether. After standing for 14 hr., the reaction mixture was worked up in the usual manner, the crude product being distilled at reduced pressure. The resultant viscous oil was allowed to solidify, then recrystallized from petroleum ether (b.p. 30–60°), yielding colorless crystals, m.p. 52.5–54°, yield, 36%. The infrared spectrum showed strong carbonyl absorption at 1672 cm.$^{-1}$ (Nujol mull).

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.93; H, 8.28.

Phenyladamantylcarbinol (X).—Four and five-tenths grams (0.019 mole) of phenyl 1-adamantyl ketone was reduced by reaction with an equimolar amount of lithium aluminum hydride in ether. After a 1-hr. reflux period, the reaction mixture was hydrolyzed with 5% hydrochloric acid and worked up in the usual manner. Distillation of the crude product gave 3.3 g. (71%) of a viscous oil, b.p. 168–170°/0.8 mm., which crystallized on standing. Recrystallization from petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 66–67.5°. Infrared examination showed complete disappearance of carbonyl absorption.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.19; H, 8.90.

Apocamphyl Benzyl Ether (VIII).—Apocamphanol was prepared according to the scheme of Hawthorne, *et al.*,[32] starting from 1-apocamphanecarboxylic acid[23] and proceeding *via* 1-apocamphyl ketone and 1-apocamphyl benzoate.

Equimolar quantities (0.05 mole) of potassium metal and apocamphanol were allowed to react in 200 ml. of dimethoxyethane, first at room temperature then at reflux, until the metal had been consumed. The solvent was then removed under reduced pressure and replaced by 200 ml. of dimethylformamide. To this solution was added 9.5 g. (0.075 mole) of benzyl chloride, whereupon a white precipitate began to form. After 30 hr. at room temperature with stirring, the reaction mixture was poured into 500 ml. of 5% hydrochloric acid and the aqueous phase extracted with ether. The ether solution was worked up in the usual manner and the crude product chromatographed over alumina. The fraction eluted with petroleum ether was distilled through a short Vigreux column; b.p. 114–116°/1 mm., yield, 3.3 g. (29%).

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

(28) Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrometer. Melting points were determined in soft glass capillaries by means of a "Mel-temp" apparatus and are uncorrected. Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim, Germany.

(29) A. Spilker and W. Schade, *Ber.*, **65**, 1686 (1932).

(30) W. H. Zartman and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1668 (1932).

(31) P. J. Hamrick and C. R. Hauser, *ibid.*, **81**, 2096 (1959).

(32) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *ibid.*, **80**, 6393 (1958).

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.51; H, 9.40.

Apocamphylphenylcarbinol (X).—The reduction of apocamphyl phenyl ketone[32] (3.0 g.) by lithium aluminum hydride was performed exactly as that using phenyl adamantyl ketone. From the ether solution of product, there was obtained 2.9 g. (97%) of crystalline alcohol, whose infrared spectrum showed no carbonyl absorption. Recrystallization from petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 84.00; H, 9.45.

***t*-Butylphenylcarbinol.**—This alcohol was prepared in poor yield (14%) from *t*-butylmagnesium chloride and benzaldehyde. Distillation of the crude product, b.p. 98–100°/4.5 mm., followed by recrystallization, gave fairly pure material, m.p. 39–41.5° (reported[33] m.p. 42–44.5°), whose infrared spectrum was free of carbonyl absorption.

***t*-Butyl Benzyl Ether.**—The best method found was that employed for apocamphyl benzyl ether (VIII), namely the reaction of potassium *t*-butoxide with benzyl chloride in dimethylformamide. Yields ranged around 30–40%. The product had b.p. 203–205°/atm., 90–92°/10 mm. (reported,[34] b.p. 205.6–208°)

Methyllithium.—This reagent was prepared in small batches as needed from dimethylmercury[35] and lithium metal in tetrahydrofuran. Clear solutions of methyllithium were obtained by centrifugation and filtration through glass wool, under nitrogen. The solutions were titrated with standard acid and then used immediately.

General Procedure for Small-Scale Reactions.—The apparatus consisted of a 50-ml. one-neck flask with side arm. The side arm was fitted with a rubber septum to allow for addition of solutions by a hypodermic syringe. The neck of the flask was connected to a Nujol-filled U-tube by a short length of Tygon tubing. A 50–100-mg. quantity of ether, dissolved in the desired solvent was introduced into the flask. After thorough flushing with nitrogen through the hypodermic needle, the appropriate volume of standardized methyllithium in tetrahydrofuran was injected through the septum and the reaction mixture allowed to stand for 48 hr., during which a positive pressure of methane developed in the system. Aqueous ammonium chloride solution was then injected to effect hydrolysis, after which the contents of the flask were worked up as usual, the dried ether solution of products being evaporated to about one ml. before gas chromatography.

Analyses of reaction mixtures from such runs were performed on an F&M Model 300 programmed temperature gas chromatography apparatus. A 2-ft. silicone rubber (20%) on Chromosorb P column and a 3-ft. (15%) "Tide" on Chromosorb P column were used at temperatures of 150° up to 200–300°, the latter being needed for benzhydryl ether isomerization mixtures. The temperature was programmed linearly at 18°/min. using a helium flow rate of 50–60 cc./min. Correction factors were obtained from analyzing synthetic mixtures of the expected products and percentages of various components determined by calculating peak areas from the product of height × width at half height.

A large number of reactions of all the ethers discussed in this paper were carried out by the above technique and reproducible results obtained.

Large-Scale Benzyl Ether Rearrangement.—To 150 ml. of 0.98 *M* methyllithium in tetrahydrofuran (0.147 mole) in a 500-ml. three-neck flask, equipped with a U-tube bubbler and a rubber septum for flushing and addition of reagents, was added 5.8 g. (0.029 mole) of benzyl ether in a little tetrahydrofuran. The dark red solution was kept in the inert atmosphere for 48 hr. at room temperature, then hydrolyzed with ammonium chloride solution and worked up in the usual manner. Flash distillation of the dried ether extract afforded a large quantity of solvent which was carefully taken down to reduced volume by slow distillation. The concentrated solvent residue was shown to contain toluene by ultraviolet spectroscopy. The original pot residue, after removal of solvent, was crudely fractionated through a short Vigreux column, giving three fractions: the first, b.p. 90–105°/15 mm., weighed 0.150 g. and was essentially pure methylphenylcarbinol as judged by infrared and gas chromatography; the second, b.p. 105–150°/15 mm., consisted of equal amounts of methylphenylcarbinol and 1,2-diphenylethanol and weighed 0.143 g.; the third had m.p. 150–180°/15 mm. and weighed 3.73 g., its infrared spectrum and gas chromatographic behavior corresponding to 1,2-diphenylethanol.

Large-Scale Rearrangement of Benzhydryl Ether.—In an apparatus similar to that used above, 10.0 g. (0.029 mole) of benzhydryl ether in 100 ml. of tetrahydrofuran was treated with 144 ml. of 1.02 *M* methyllithium solution in tetrahydrofuran (0.147 mole). After standing for 2 days at room temperature, the reddish brown solution was hydrolyzed and worked up as above. Evaporation of the dried ether solution yielded a pale yellow residue which was triturated with warm petroleum ether (b.p. 30–60°) and filtered. The insoluble material was shown by infrared and vapor phase chromatography to be predominantly tetraphenylethane by comparison with authentic material. Evaporation of the above petroleum ether solution left approximately 4 g. of solid which was chromatographed over 80 g. of alumina. Elution with petroleum ether gave 0.36 g. of diphenylmethane, identified by infrared and vapor phase chromatography, followed by 0.90 g. of tetraphenylethylene, m.p. 223–226° (from ethanol), which was identified in similar fashion. Further elution with 4:1 petroleum ether–diethyl ether afforded 1.30 g. of recovered benzhydryl ether, m.p. 105–108°, which was identical to starting material. Increasing the ether content of the eluent (to 1:1) led to the recovery of 0.68 g. of crude diphenylmethylcarbinol, m.p. 78–80° (petroleum ether), which again was checked against authentic material.

Benzhydrol proved to be rather difficult to separate in pure form but was isolated from another large-scale run similar to the one just described. The crude product was, in this case, stirred with 95% ethanol and the solution separated from undissolved solid, evaporated down, and chromatographed, yielding benzhydrol, m.p. 61–62° and no depression with an authentic sample; the infrared spectrum was also superimposable with the standard.

Large-Scale Rearrangement of *t*-Butyl Benzyl Ether.—A solution of 3.8 g. (0.023 mole) of *t*-butyl benzyl ether in 120 ml. of tetrahydrofuran was placed in an apparatus of the type already mentioned, containing a rubber septum for flushing and addition of reagents, and 120 ml. of 0.95 *M* methyllithium in tetrahydrofuran added. The reaction mixture, which slowly turned red and ultimately became nearly colorless again, was kept at room temperature for 48 hr. and then worked up in the usual manner.

Chromatography of the crude product mixture over alumina afforded 1.92 g. (51%) of carbinol (eluted with ethyl ether) whose vapor phase chromatographic behavior corresponded to phenyl-*t*-butylcarbinol. Shortpath distillation of this oil gave pure product (infrared spectrum identical with that of authentic specimen), b.p. 110–120°/15 mm.

Reaction of 1,1,2,2-Tetraphenylethanol with Methyllithium.—A solution of 100 mg. of the alcohol in tetrahydrofuran, containing 5 equivalents of methyllithium, was kept for 2 days at room temperature in a nitrogen-flushed system. Hydrolysis and work-up, followed by vapor phase chromatographic analysis, indicated that diphenylmethane (34%) and methyldiphenylcarbinol (43%) were the main products. Tetraphenylethane (4%) and tetraphenylethylene (1%) were also present in low yield, in addition to several unknown compounds.

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Large-Scale Rearrangement of 1-Adamantyl Benzyl Ether.—A solution of 2.40 g. (0.01 mole) of the ether in 20 ml. of tetrahydrofuran was treated with 18 ml. of 1.1 *M* methyllithium (0.02 mole) in tetrahydrofuran. The reaction mixture was hydrolyzed and worked up after 48 hr. Chromatography of the crude product over alumina, with petroleum ether–ether (3:1) as eluent, led to the isolation of 1.29 g. (54%) of pure phenyl-1-adamantylcarbinol (X), identical by infrared with an authentic sample.

Preparation of *n*-Butyl *o*-Methoxybenzyl Ether.—The reaction of equimolar quantities (0.30 mole) of *o*-methylanisole and *N*-bromosuccinimide in refluxing carbon tetrachloride, in the presence of a trace of benzoyl peroxide, afforded *o*-methoxybenzyl bromide in 66% yield, b.p. 113–115°/10 mm. (reported,[36] b.p. 115°/10 mm.).

Twenty grams (0.10 mole) of the above bromide was slowly added to 400 g. of *n*-butyl alcohol containing 0.25 mole of sodium *n*-butoxide. A white precipitate began to form almost immediately. After 3 hr. of reflux, the reaction mixture was cooled and then poured into water. The product was taken up in ether, washed with salt solution, dried over sodium sulfate, and distilled through an 8-in. Vigreux column, yielding 10.7 g. (55%) of product, b.p. 129–130°/5 mm.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.32.

Cleavage and Attempted Rearrangement of *n*-Butyl *o*-Methoxybenzyl Ether.—The procedure of Gilman, *et al.*,[37] was used. Into a nitrogen-flushed, three-neck flask equipped with Herschberg stirrer, reflux condenser, and addition funnel, was placed 2.5 g. (0.35 g.-atom) of lithium ribbon, cut into small pieces, and 60 ml. of ether. To the cooled (−10°), stirred mixture was slowly added 5.0 g. (0.025 mole) of *n*-butyl *o*-methoxybenzyl ether, dissolved in 50 ml. of ether. The mixture was allowed to warm to room temperature and after 2 hr. a 10-ml. aliquot of the reddish brown solution was removed, hydrolyzed with dilute hydrochloric acid, washed with salt solution, and dried. Evaporation of the ether solution, followed by vapor phase chromatographic analysis revealed *ca.* 90% *o*-methylanisole and 10% starting material. After 48 hr., the entire reaction mixture was worked up in the usual manner, together with the previously isolated product, giving 2.60 g. (86%) of *o*-methylanisole, whose infrared spectrum was superimposable on that of an authentic sample. No *o*-ethylphenol was present, according to vapor phase chromatographic analysis.

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The Metalation of Methoxynaphthalenes[1]

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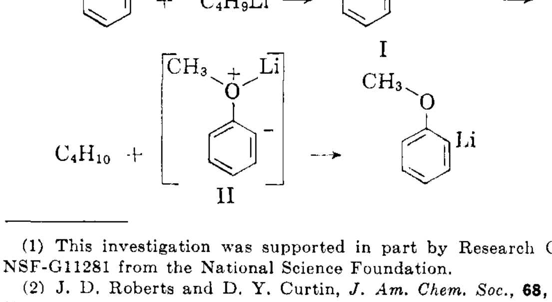
The molecular orbital procedure has been used for calculating the distribution of the π-electrons in the mono- and dimethoxynaphthalenes. These data together with an estimation of the inductive effect has been used in an attempt to predict the relative reactivities of these substances toward metalation with a reagent such as butyllithium. The predictions agree with the experimental data which is available. However, contrary to a previous report 1-methoxynaphthalene has been found to metalate most rapidly at the 8-position with the initial product undergoing rearrangement of the lithium atom to the 2-position.

The metalation reaction is rather unique among aromatic substitution reactions in that the π-electron system of the molecule is essentially undisturbed in the process. Thus, the metalation of anisole is represented by equation 1.



(1)

It has been suggested[2] that the inductive effect is most important in determining the course of the reaction. However, previous results with 1,7-dimethoxynaphthalene[3] indicate that, at least for this molecule, resonance effects are of prime importance.

In the present work it has been assumed that the metalation is a rate-controlled process and that the slow step is the removal of the hydrogen atom by the butyl carbanion (conversion of I to II). If this idea is correct the most acidic hydrogen should be removed most rapidly. The relative acidities of the hydrogen atoms at the various positions can, in turn, be estimated from the charge density on the carbon atom to which each hydrogen is bonded. The problem is thus resolved into one of calculating the charge at positions which may be available for metalation.

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