the ring form. In at least some instances this may be due to steric hindrance to ring opening by the alkyl groups, as discussed. Of course the rate of ring closure must also be considered in deciding the position of equilibrium.

The data concerning the effect of methyl substitution on the rates of ring opening reactions of sultones should also prove helpful in understanding the reverse (ring closing) reactions. However, it seems best not to speculate about ring closures until more information on ring openings becomes available.[26]

Acknowledgment.—It is a pleasure to acknowledge the help derived in several discussions of this problem with Professor Ralph G. Pearson and with Dr. J. C. Martin of the University of Illinois. We are grateful to the Research Corporation and the Nitrogen Division of the Allied Chemical and Dye Corporation for financial assistance.

EVANSTON, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Heterogeneity as a Factor in the Alkylation of Ambident Anions: Phenoxide Ions[1,2]

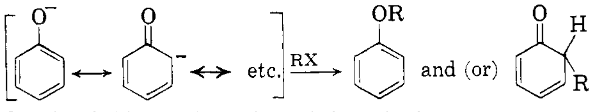
BY NATHAN KORNBLUM AND ARNOLD P. LURIE[3]

RECEIVED OCTOBER 29, 1958

Sodium and potassium salts of phenol and *p-t*-octylphenol have been alkylated with benzyl and allyl halides in a variety of solvents. Quantitative yields of the ether (oxygen alkylation) are obtained whenever the reaction is conducted in solution. In addition, it is demonstrated that the truly heterogeneous reaction gives exclusively carbon alkylation. Reactions carried out with the phenolic salt present as a solid phase ordinarily give both carbon and oxygen alkylation, but this result is clearly a consequence of incursion by the homogeneous process. The factors, other than heterogeneity, which may influence the course of phenoxide alkylations are briefly discussed. An explanation is offered for the fact that heterogeneity confers an essentially irresistible preference for carbon alkylation.

In a recent paper[4] the alkylation of ambident anions, *i.e.*, ions wherein covalent bond formation can take place at either of two alternative positions, was discussed; in particular, attention was directed toward the influence of electrical effects on the reaction course.

The present study is concerned with phenoxide ions, which, being ambident anions, are capable of undergoing alkylation either on carbon[5] or on oxygen

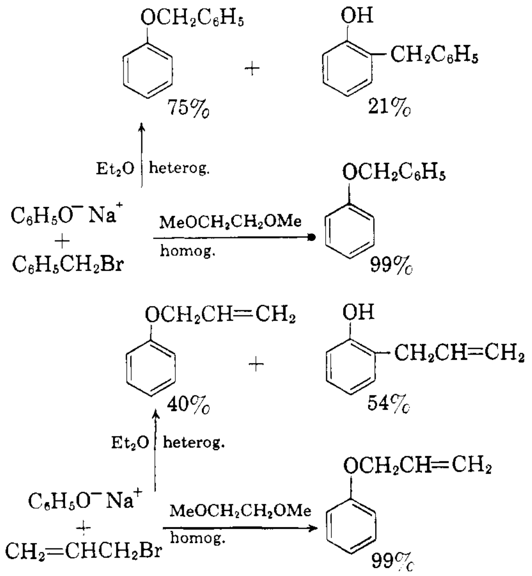


Our initial intention of studying the influence which electrical effects have on the course of phenoxide alkylations was temporarily set aside when it became clear that a new factor, heterogeneity *vs.* homogeneity, is of paramount importance; the present investigation is concerned with this new factor.

The demonstration that heterogeneity is a factor which must be reckoned with consists of two parts. The first rests upon divergences resulting from conducting reactions in anhydrous ether on the one hand and ethylene glycol dimethyl ether on the other. The second part of the demonstration is based on a study of the alkylation process in a single solvent—toluene.

The experiments summarized in Chart I were conducted at 35°; they derive their significance from the fact that sodium phenoxide has a low solubility in anhydrous ethyl ether but dissolves readily in the dimethyl ether of ethylene glycol; in the first solvent we deal with a heterogeneous system while in the second the reaction occurs in solution. It will be seen that alkylations in ethyl ether (heterogeneous) give substantial yields of carbon alkylated phenols[6] whereas the same alkylations, conducted homogeneously in ethylene glycol dimethyl ether, give no carbon alkylated products.[7]

CHART I



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[1] This research was supported by the United States Air Force under Contract No. AF49(638)-324 monitored by the A. F. Office of Scientific Research of the Air Research and Development Command and by the Purdue Research Foundation.

[2] Presented at the San Francisco Meeting of the American Chemical Society, April, 1958.

[3] From the doctoral dissertation of Arnold P. Lurie, Purdue University, June, 1958.

[4] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, THIS JOURNAL, **77**, 6269 (1955).

[5] The dienone produced by carbon alkylation is not usually isolated since, by proton removal, it is rapidly transformed into the salt of the *o*-alkylated phenol.

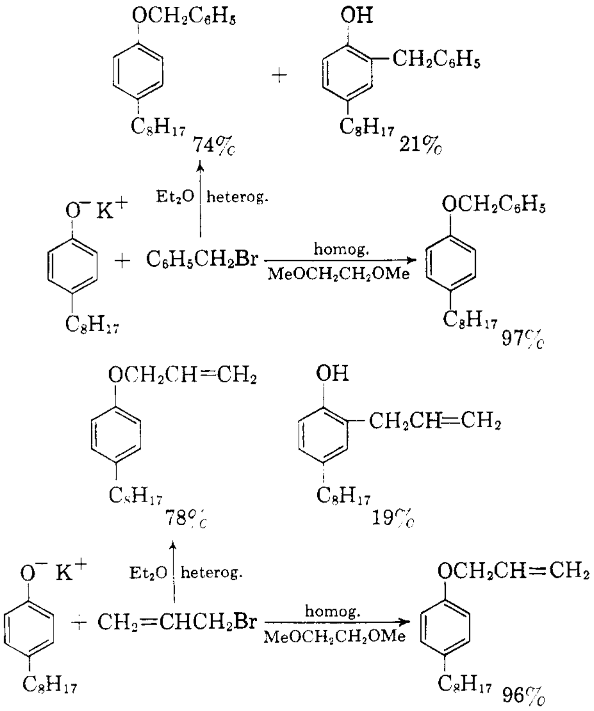
[6] Allyl phenyl ether does not isomerize to *o*-allylphenol under the conditions of this experiment (*cf.* Experimental).

[7] Here, and throughout, care was taken to conduct comparative reactions at the same temperature and concentration.

The possibility that this difference derives from specific solvation by one of the two solvents is ruled out by experiments which employ the sodium salt of *p-t*-octylphenol.[8] This particular salt dissolves readily in anhydrous ethyl ether and also in ethylene glycol dimethyl ether. When a solution of sodium *p-t*-octylphenoxide in either solvent is treated with benzyl bromide a 99% yield of the oxygen alkylated product, benzyl *p-tert*-octylphenyl ether is obtained; in the same way, allyl bromide gives 98–99% yields of allyl *p-t*-octylphenyl ether. Here, as with sodium phenoxide, alkylations conducted in solution give exclusively oxygen alkylation.

The third set of experiments is summarized in Chart II. Their significance hinges on the fact that the potassium salt of *p-t*-octylphenol, in contrast to the sodium salt, is but sparingly soluble in anhydrous ethyl ether although, like the sodium salt, it dissolves readily in ethylene glycol dimethyl ether. From the data of Chart II it is clear that the *p-t*-octyl group is not responsible for the differences noted between the first and second set of experiments. The correlation is, instead, simply one of heterogeneity *vs.* homogeneity. In all three sets of experiments, carbon alkylation is always associated with heterogeneity while quantitative oxygen alkylation is invariably the result of an experiment conducted homogeneously.

CHART II



That this is so becomes especially clear from experiments conducted in a single solvent—toluene. At 25°, the potassium salt of *p-t*-octylphenol has a solubility of *ca.* 0.8 g. in 100 ml. of toluene. A reaction employing 24 g. (0.1 mole) of this salt in 88 ml. of toluene is, then, heterogeneous; under these conditions the reaction of the potassium salt of *p-t*-octylphenol with benzyl chloride gives 79% O-alkylation and 13% C-alkylation.[9] In contrast, when a *solution* of 24 g. of potassium *p-t*-octylphenoxide in 3.5 liters of toluene is treated with benzyl chloride the product is benzyl *p-t*-octylphenyl ether (97–99% yield) and none of the C-benzylated phenol is detected.[10]

The difference between the heterogeneous and homogeneous reactions in toluene, in any case a significant one, takes on even greater importance when it is realized that the "heterogeneous" reaction is far from a truly heterogeneous process as shown by the fact that the reaction mixture becomes *completely homogeneous* after the reaction has gone 50–60% to completion.[11] This suggested that the 13% yield[9] of *o*-benzyl-*p-t*-octylphenol (C-alkylation) obtained from the "heterogeneous" reaction of benzyl chloride with potassium *p-t*-octylphenoxide actually derives from the early stages of the reaction when a minimal amount of the phenoxide salt is in solution.[11] Consequently, the "heterogeneous" reaction of benzyl chloride with potassium *p-t*-octylphenoxide in 88 ml. of toluene was repeated three more times, except that now the reaction was allowed to go only 46, 16 and 4% to completion. Fortunately, the O-benzylated product is readily isolated in a high state of purity and establishing the composition of the phenolic fraction by quantitative infrared analysis offers no difficulties. The results, which are recorded in Table I, not only confirm the conclusion that heterogeneity is a necessary condition

TABLE I

THE "HETEROGENEOUS" REACTION OF BENZYL CHLORIDE WITH POTASSIUM *p-t*-OCTYLPHENOXIDE IN TOLUENE AT 25°[a]

% to completion	Products		O-Benzylation,[b] %	C-Benzylation,[b] %
	Benzyl *p-t*-octylphenyl ether, mole	*o*-Benzyl-*p-t*-octylphenol, mole		
100	0.079	0.013	86	14
46	.025	.018	58	42
16	.0008	.015	5	95
4	.00	.003	0	100

[a] 0.1 mole of each reactant in 88 ml. of anhydrous toluene. [b] Calcd. by taking the total number of moles of *pure* C- + O-benzylated products isolated and determined as the % of this total. *E.g.*, in the reaction carried 46% to completion a total of 0.043 mole of benzylated products was obtained; of this (0.025/0.043) = 58% is the O-benzylated product and (0.018/0.043) = 42% is the yield of C-benzylated product. Alternatively, the yields could be calculated on the basis that titration for chloride ion showed the reaction to be 46% complete; or again, one could use the % recovered *p-t*-octylphenol as the basis for calculation. These alternate modes of expressing the % C- and % O-benzylation give values which differ insignificantly from those recorded in this table. No matter how one chooses to express it, the change in the fate of the benzyl group, as a function of the % the reaction has proceeded toward completion, is unambiguous.

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(8) The *t*-octyl group is $(CH_3)_3CCH_2C(CH_3)_2$-. We are indebted to the Rohm and Haas Co., and to Dr. Charles Levesque of the Rohm and Haas Co., for a very generous gift of this phenol.

(9) These are the yields of pure products. This experiment is recorded in Table I; footnote *b* should be consulted.

(10) The possibility that this difference derives from the different proportions of benzyl chloride and toluene employed was eliminated by a direct test (*cf.* Experimental).

(11) This is rather striking since it means that *ca.* 5 g. of potassium chloride and 10 g. of the potassium salt of *p-t*-octylphenol are in solution. Not only does the potassium chloride fail to precipitate as it forms but, in addition, the amount of potassium *p-t*-octylphenoxide which goes into solution is far in excess of its solubility in pure toluene (0.8 g./100 ml.).

for carbon alkylation but, in addition, constitute a demonstration that the truly heterogeneous reaction gives exclusively carbon alkylation. At the outset, when only a minor fraction of the potassium *p*-*t*-octylphenoxide is in solution, the amount of O-benzylation is undetectably small even though a method of isolating the ether easily capable of detecting a 0.5% yield is employed. Here we deal with the heterogeneous process and here we obtain only C-benzylation. But as the reaction progresses the potassium *p*-*t*-octylphenoxide goes into solution[11] with the consequence that the homogeneous process soon intrudes. Indeed, by the time the reaction has gone *ca.* 15% the homogeneous process has taken over completely and, from this point on, only benzyl *p*-*t*-octylphenyl ether is produced.[12]

Completely analogous results were obtained on allylating potassium *p*-*t*-octylphenoxide. The homogeneous reaction with allyl chloride, conducted in 3.5 liters of toluene, gave a 97% yield of pure allyl *p*-*t*-octylphenyl ether; no *o*-allyl-*p*-*t*-octylphenol was found even though an infrared procedure capable of detecting a 1% yield of this phenol was used.

Four "heterogeneous" experiments were carried out. In each instance 0.1 mole of potassium *p*-*t*-octylphenoxide was suspended in a solution of 0.1 mole of allyl chloride diluted to 100 ml. with toluene. In the first experiment the reaction was allowed to proceed to completion; the mixture became completely homogeneous when the reaction was 42% complete and a 79% yield of allyl *p*-*t*-octylphenyl ether, along with a 17% yield of *o*-allyl-*p*-*t*-octylphenol, was obtained.[13] The other three "heterogeneous" experiments, identical in every way with the first, were interrupted after the reactions had gone 34%, 22 and 10% so as to provide a closer and closer approach to the truly heterogeneous process. Just as when benzyl chloride was used as the alkylating agent, the closer the approximation to a truly heterogeneous process the greater the yield of C-alkylated phenol. As can be seen from the data of Table II, there is no ambiguity; the genuinely heterogeneous reaction gives only carbon allylation.[14]

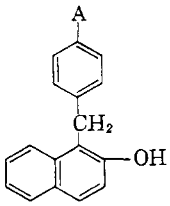
Heterogeneity is not the only device for producing carbon alkylation. A number of other factors may operate so as to produce carbon alkylation even under homogeneous conditions[15]:

(1) Variations in the Relative Nucleophilicity of Oxygen and Carbon.—The relative nucleophilicity of oxygen and carbon in different phenoxide ions is not constant and, as a consequence, the relative amounts of O- and C- alkylation will vary. Thus, while solutions of sodium phenoxide yield only ethers on treatment with allyl or benzyl bromide, a solution of sodium β-naphthoxide reacts with benzyl bromide to give the carbon alkylated product Ia in *ca.* 22% yield; similarly when *p*-nitrobenzyl bromide reacts with a solution of lithium β-naphthoxide Ib is formed in 14% yield.[16] This is fully consistent with the following facts:

TABLE II
THE "HETEROGENEOUS" REACTION OF ALLYL CHLORIDE WITH POTASSIUM *p*-*t*-OCTYLPHENOXIDE IN TOLUENE AT 25°[a]

% to completion	Products: Allyl *p*-*t*-octylphenyl ether, mole	Products: *o*-Allyl-*p*-*t*-octylphenol, mole	O-Allylation,[b] %	C-Allylation,[b] %
100	0.079	0.018	81	19
34	.014	.018	44	56
22	.002	.017	11	89
10	.0001	.0076	1	99

[a] 0.1 mole of potassium *p*-*t*-octylphenoxide treated with a solution consisting of 0.1 mole of allyl chloride made up to 100 ml. with anhydrous toluene. [b] % of the total number of moles of *pure* C- and O-allylated products (*cf.* footnote *b*, Table I).

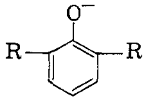


Ia, A = H
Ib, A = NO_2

(a) the α-carbon of the β-naphthoxide ion has greater nucleophilic reactivity than any carbon of the phenoxide ion[17]; (b) β-naphthol is a stronger acid than phenol[18] from which it is reasonable to conclude that the oxygen atom in the β-naphthoxide ion has a lower electron density than in the phenoxide ion.

β-Naphthol is not unique. For example, the homogeneous reaction of methyl iodide with sodium (or potassium) salts of various phloroglucinol derivatives leads to C-methylation.[19,20]

(2) Steric Hindrance.—It is to be anticipated that in phenoxide ions of the type II, as the series R = hydrogen, methyl, ethyl, isopropyl and



II

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[12] It will be recalled that when a *solution* of potassium *p*-*t*-octylphenoxide in toluene is treated with benzyl chloride only O-benzylation is observed (*vide supra*).

[13] As in the benzyl chloride studies it was shown that the differences observed in the homogeneous and "heterogeneous" allylations are not due to the different proportions of allyl chloride and toluene used (*cf.* Experimental).

[14] Several additional illustrations of the fact that heterogeneity is a potent force favoring carbon alkylation are described in the last section of the Experimental part of this paper.

[15] What follows is a minimal discussion necessary to establish proper perspective as regards heterogeneity. When experimental work now in progress is completed a comprehensive discussion of these and other factors will be presented.

[16] V. A. Zagorevsky, *J. Gen. Chem.* (*USSR*), **27**, 3055 (1957); **28**, 488 (1958). We are indebted to Professor D. Y. Curtin for kindly calling these papers to our attention.

[17] Naphthalene more readily undergoes electrophilic substitution (especially in the α-position) than benzene. Also coupling with diazonium salts occurs more readily with β-naphthoxide ion than with phenoxide ion, [K. H. Saunders, "The Aromatic Diazo-Compounds and their Technical Applications"; ed. 2, Arnold and Co., London, 1949, p. 199.]

[18] K. Lauer, *Ber.*, **70**, 1130 (1937); H. C. Brown, D. H. McDaniel and O. Häfliger in "Determination of Organic Structures by Physical Methods," Edited by E. A. Braude and F. C. Nachod, Academic Press, Inc., New York, N. Y., 1955, p. 598. Also relevant is the fact that the β-naphthylammonium ion is a stronger acid than the anilinium ion [N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932)].

[19] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **42A**, 279 (1955).

[20] Solutions of the sodium salts of resorcinol and phloroglucinol react with acrylonitrile to give 56% and 78% yields, respectively, of carbon alkylated products [G. S. Misra and R. S. Asthana, *Ann.*, **609**, 240 (1957)], but it is not clear whether this is a consequence of kinetic or thermodynamic control.

t-butyl is ascended, ether formation will become increasingly difficult and, while carbon alkylation will also be impeded, the hindrance offered to *o*-carbon alkylation will be less than that presented to ether formation—especially when the steric requirement of the alkylating agent is large. The few data which are presently available bear out these expectations.

Thus, on treating a solution of sodium 2,6-dimethylphenoxide with allyl bromide, although the main product is the allyl ether, small amounts of carbon allylated products are obtained.[21,22] And the homogeneous reaction of sodium 2,4,6-trimethylphenoxide with allyl bromide gives, in addition to an excellent yield of the ether, traces of carbon allylation products.[23,24] In these cases the electrical effect of the methyl groups probably serves to increase the electron density on the *o*-carbons proportionately more than on the oxygen[25] and this, coupled with the steric requirement of the 2,6-methyl groups, operates in favor of substitution at an *o*-carbon. Consequently, even with the relatively small methyl and allyl groups some carbon alkylation is found. Preliminary work[26] confirms the expectation that with bulkier groups the steric factor becomes of overriding importance. Thus, a solution of the potassium salt of 2,6-di-*t*-butylphenoxide on treatment with methyl iodide gives mostly the methyl ether whereas with ethyl iodide or isopropyl iodide carbon alkylation preponderates.

(3) **Attack by Carbonium Ions.**—When carbonium ions are generated in solutions containing the phenoxide ion, alkylation on carbon, as well as ether formation, is observed.[27] An important characteristic of these carbonium ion processes is the formation of *para*, as well as *ortho*, -alkylated products.[27] Since carbon alkylation of sodium phenoxide (and various other phenolic salts) using allylic and benzylic halides only occurs at an *o*-position,[22,28] it is likely that such reactions do not involve carbonium ions. The view that *p*-alkylation is diagnostic of the intermediacy of carbonium ions is strongly supported by the fact that those halides which give carbonium ions readily are the ones which on reacting with sodium phenoxide give *p*-substituted products, *e.g.*, benzhydryl chloride,[22] benzhydryl bromide[3,29] and trityl chloride.[16,30]

(4) **Variations in the Proportion of SN1 and SN2 Character of the Transition State.**—In 1954, Hart and Eleuterio[31] made the very reasonable suggestion that Claisen C-alkylation (*o*-alkylation) is a nucleophilic displacement of halogen from the alkyl halide by phenoxide ion. A year later it was proposed[4] that the greater the SN2 contribution to the transition state the greater will be the preference for *o*-carbon alkylation (and, conversely, the greater the SN1 contribution to the transition state of such graded nucleophilic displacements the greater will be the proportion of O-alkylation). Obviously, no valid test of this proposal is possible so long as the alkylation of a phenolic salt is conducted heterogeneously and, consequently, a study of homogeneous alkylations designed to test the importance of the SN1–SN2 factor has been undertaken.

Recognition of factors other than heterogeneity which are productive of carbon alkylation does not connote confusion. Actually, the available data indicate that the compounding of heterogeneity with these factors gives rise to increased carbon alkylation. Thus, the homogeneous reaction of sodium 2,6-dimethylphenoxide with allyl bromide gives principally the ether whereas the heterogeneous reaction results mainly in carbon allylation.[21,22] Similarly, although a solution of sodium 2,4,6-trimethylphenoxide is converted to the ether in excellent yield on treatment with allyl bromide,[23,24] the heterogeneous reaction provides a preparative method for the C-allylated product.[24] And although the reaction of benzhydryl bromide with sodium phenoxide in ethylene glycol dimethyl ether solution gives benzhydryl phenyl ether in 59% yield, C-alkylation occurring to the extent of but 17%, when a suspension of sodium phenoxide in ethyl ether is employed the yield of benzhydryl phenyl ether drops to 6% and that of C-alkylated phenols rises to 80%.[3]

Why heterogeneity confers an essentially irresistible preference for carbon alkylation remains to be discussed. Although detailed knowledge of the crystal structure of phenoxide and *p*-*t*-octylphenoxide salts is lacking a simple explanation which invokes only well established principles can be offered. The sodium (and potassium) salts of phenol and *p*-*t*-octylphenol have been shown to be crystalline[32]; it is an important feature of such an ionic crystal that two, or more, sodium (or potassium) ions are in close proximity to each phenoxide ion and, of course, each metal ion is surrounded by a corresponding number of phenoxide ions. Let

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[21] D. S. Tarbell and J. F. Kincaid, THIS JOURNAL, **62**, 728 (1940).

[22] D. Y. Curtin, R. J. Crawford and M. Wilhelm, *ibid.*, **80**, 1391 (1958).

[23] H. Conroy and R. A. Firestone, *ibid.*, **78**, 2297 (1956).

[24] K. Kalberer and H. Schmid, *Helv. Chim. Acta*, **40**, 780 (1957).

[25] For one thing the inductive effect falls off rapidly on going down a chain of atoms and, for another, the oxygen already carries a negative charge.

[26] By Mr. Raymond Seltzer.

[27] Unpublished work by Dr. R. B. Smyth, Purdue University. This type of reaction is to be distinguished from the graded SN1–SN2 processes (*vide infra*) in which a solution of sodium phenoxide reacting with a *molecule*, *e.g.*, allyl bromide, gives no C-alkylation. With carbonium ions non-discriminating attack on the phenoxide ion is a factor which must be taken into account. Thus, Smyth has found that on going from *t*-butyl to benzhydryl to trityl carbonium ions, the reaction with phenoxide gives more and more O-alkylation. Whereas *t*-butyl carbonium ion gives *ca.* 25% O-alkylation and *ca.* 75% C-alkylation, the reaction of trityl carbonium ion with phenoxide ion gives *ca.* 95% O-alkylation and *ca.* 5% C-alkylation. In other words, whatever C-alkylation is observed with a carbonium ion is a consequence of its very great reactivity which results in a lack of selectivity; the higher the energy of the carbonium ion the less discriminating it is. Presumably a carbonium ion such as $(p\text{-MeOC}_6\text{H}_4)_3\text{-C}^+$ would be highly selective and would simply collapse onto the oxygen of a phenoxide ion, *i.e.*, onto the point of maximum electron density.[15]

[28] L. Claisen, F. Kremers, F. Roth and E. Tietze, *Ann.*, **442**, 210 (1925); F. M. Elkobaisi and W. J. Hickinbottom, *J. Chem. Soc.*, 2431 (1958).

[29] As Curtin, Crawford and Wilhelm[22] have pointed out, *p*-alkylation resulting from thermal isomerization of an initially formed *o*-alkylate is distinct from direct *p*-substitution.

[30] M. Busch and R. Knoll, *Ber.*, **60**, 2249 (1927).

[31] H. Hart and H. S. Eleuterio, THIS JOURNAL, **76**, 518 (1954).

[32] We are greatly indebted to Professor James W. Richardson and Mr. Mario Gimenez-Huguet of this Department for taking the X-ray powder diffraction photographs of these salts, and for interpreting them.

us now consider the O- and C-alkylation processes under heterogeneous and under homogeneous conditions.

Heterogeneous Alkylations.—Ether formation by a phenoxide ion which is part of a crystal lattice would proceed through a linear transition state (Fig. 1) with the negative charge originally resident on oxygen progressively being transferred to halogen. Two factors operate to render such a transition state improbable. In the non-polar solvents used to maximize C-alkylation, *e.g.*, benzene or toluene, the departing halide ion would be very poorly solvated. Then, too, the removal of electron density from oxygen deprives the sodium ions of the negative charge which made it possible to bring them close together; loss of the charge on oxygen gives rise to strong electrostatic repulsions between sodium ions and, since the sodium ions *in the crystal lattice* cannot move away from one another, the energy of the system must increase sharply.

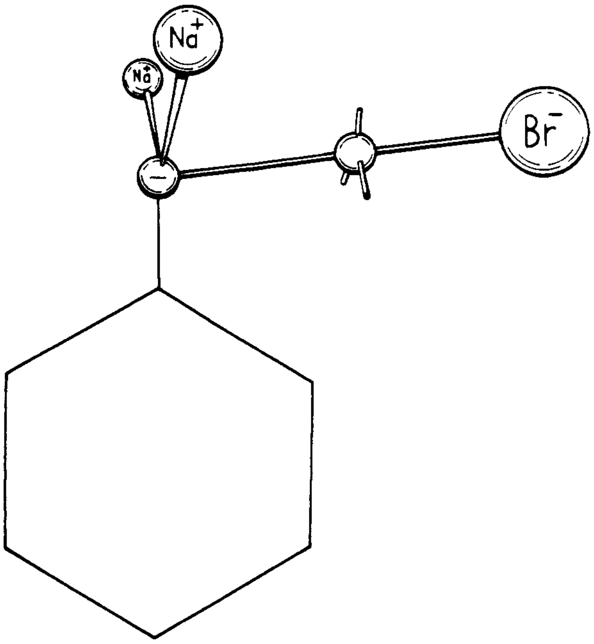

Fig. 1.

In contrast to ether formation, C-alkylation does not proceed through a transition state having the linear oxygen–carbon–halogen disposition of Fig. 1. Instead, the transition state for attack at the *o*-carbon has a non-linear arrangement in which the sodium ion nestles between the oxygen and halogen atoms[33] (Fig 2). This geometry confers two important advantages. The departing halide ion is "solvated" by ion-pair formation with a sodium ion; this, as noted above, is especially important inasmuch as non-polar solvents are employed.[34] Then, too, ion-pair formation as a feature of the transition state results in the removal of positive charge from the cluster of positive charges surrounding the oxygen even as the oxygen is losing its negative charge. This prevents the build-up of coulombic repulsions between sodium ions which, as noted above, is a major liability of ether formation. It is clear, then, why a phenoxide ion which is part of a crystal lattice exhibits such a marked preference for *o*-carbon alkylation.[35]

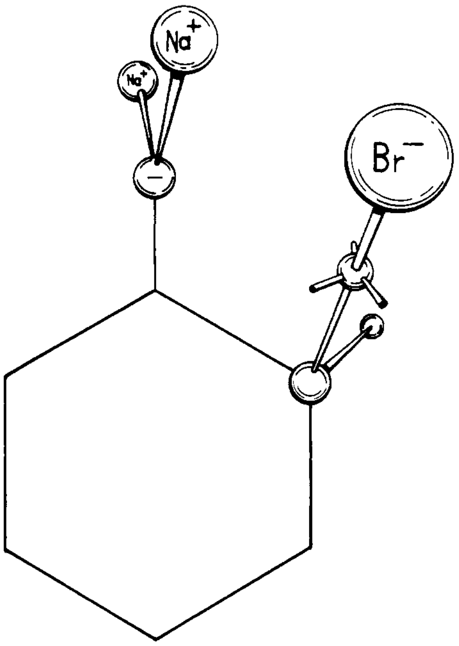

Fig. 2.

Homogeneous Alkylations.—Ether formation by a phenoxide ion in solution presents no problems. Even when the solution consists of ionic clusters having two or more sodium ions close to a phenoxide ion, which is undoubtedly the case in toluene, as the charge on oxygen is lost in the course of displacing halide ion from the alkylating agent, the sodium ions are not constrained to remain as they were; instead, they are free to increase their distance from one another (and from the oxygen) so that electrostatic repulsions do not become important. This is in accord with the idea that the solvation shell of a dissolved ion falls away as that ion loses its charge and forms a covalence. In an ion aggregate the sodium ions merely constitute part of the solvation shell of the phenoxide ion.

Finally, as discussed in an earlier section of this paper, when the nucleophilicity of carbon is sufficiently enhanced relative to that of oxygen,

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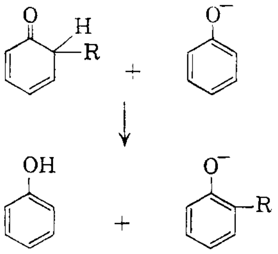
(33) Following a suggestion made by Ingold in 1926, Curtin has proposed that carbon alkylation derives from the reaction of ion pairs (in solution) *via* a transition state possessing this non-linear geometry and that, on the other hand, dissociated phenoxide ions give a preponderance of the oxygen alkylated product [Abstracts Fifteenth National Organic Chemistry Symposium, Rochester, N. Y., June 17–20, 1957, pp. 61–71]. The present demonstration of the crucial importance of heterogeneity does away with the basis of such differentiation. The proposal[22] that ion aggregates larger than ion pairs may be responsible for carbon alkylation also rests on experiments in which the factor of heterogeneity was not controlled and is, therefore, equally without foundation.

(34) Actually, one can argue that this advantage is of itself sufficient to render C-alkylation of a phenoxide ion on a crystal surface the preferred process. For it is in O-alkylation that the departing halide ion is most unambiguously being thrust away from the crystal surface which is, after all, the source of metal ions.

(35) By the same token it is clear why *p*-alkylation is not observed except in reactions which presumably involve carbonium ions (*vide supra*). It is also noteworthy that carbon alkylation cannot be a consequence of a preferred orientation of the hydrocarbon portion of the phenoxide ion into the hydrocarbon solvent for, if this were the important factor, *p*-alkylation would be observed.

carbon alkylation even occurs in solution. Relatively few authentic cases are known and, in particular, there does not appear to be any definitive information relating to the matter of *ortho vs. para* substitution in homogeneous, non-carbonium ion, alkylations.

It will be seen that this paper provides a rationale for the procedure which Claisen empirically set up to obtain C-alkylation. By his use of hydrocarbon solvents a high degree of heterogeneity is achieved and good yields of the *o*-carbon alkylated products are obtained. Full utilization in synthesis of the fact that the heterogeneous reaction results in carbon alkylation would provide quantitative yields of carbon alkylated products. But this requires that the reaction actually be maintained as a heterogeneous process through its full course and, in practice, this proves extremely difficult, if not impossible. For, the initially produced dienone is an acid which readily transfers a proton to a phenoxide ion on the crystal surface thereby causing it to go into solution. The products of reaction 1, now in solution, will be in mobile acid-base equilibrium with the net result that a device exists for rapidly bringing phenoxide ions from the crystal surface into solution. Then, too, the phenols of equations 1 and 2 will also protonate, and thereby solubilize, phenoxide ions on the crystal surface. Thus, even though the solubility of a phenoxide salt in a given solvent is low, carbon alkylation produces proton donors and these provide a means of achieving great mobility in maintaining (or approximating) the equilibrium concentration of phenoxide in solution.[36]



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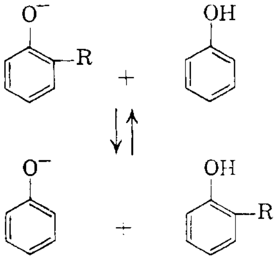

(2)

Finally, it would be surprising if heterogeneity did not prove to be an overriding factor in the reactions of at least some ambident anions other then phenoxide ions.

Experimental[37,38]

All reactions were conducted under dry nitrogen in 3-necked flasks fitted with a Trubore stirrer; if necessary a reflux condenser was provided. The rate of disappearance of the organic halide was followed using a centrifuged portion of the reaction mixture. An aliquot of the clear solution was extracted with a mixture of ethyl ether and distilled water; the organic layer was analyzed for unreacted organic halide according to Schwenk, Papa and Ginsberg[39] while the aqueous phase was titrated for inorganic halide. In addition, the amount of inorganic halide which had precipitated was determined by taking an aliquot of the reaction slurry, extracting it with a mixture of ethyl ether and distilled water and titrating the aqueous layer for ionic halide.

Reagent quality phenol was used. Rohm and Haas *p-t*-octylphenol was recrystallized from petroleum ether; m.p. 84–85°. Each batch of a salt prepared from these phenols was analyzed. Reagent grade toluene was dried, distilled and stored over calcium hydride. Cyclohexane and ethylene glycol dimethyl ether (Ansul Chemical Corp.) were purified by passage over silica gel (200 mesh) and distillation over sodium; the glycol ether so purified ($n^{20}\text{D}$ 1.4788) was peroxide free[40] and its infrared spectrum was devoid of an –OH band. Mallinckrodt anhydrous grade ethyl ether was employed. Benzyl and allyl halides were obtained from commercial sources and, when necessary, were redistilled. Claisen potash solution consists of 350 g. of potassium hydroxide in 250 ml. of water made up to 1000 ml. with methanol.

Sodium Phenoxide.—To 96 g. (1.02 moles) of phenol dissolved in the least amount of methanol (100 to 200 ml.) was added 40.0 g. (1.0 mole) of sodium hydroxide dissolved in the least amount (200 to 300 ml.) of 85% aq. methanol. The flask was flushed with nitrogen and placed on a Rinco evaporator and the solvents were removed at 50° *in vacuo*. The resulting white solid was ground in a mortar and the last trace of solvents, as well as the excess phenol, were removed by heating the powder at 60° and 1 mm. for 12 to 24 hours. The yield was 115 g. (99%).

Anal. Calcd. for C_6H_5ONa: Na, 19.82. Found: Na, 19.58.

Potassium phenoxide was prepared, as outlined for the sodium salt, from 200 g. (2.13 moles) of phenol and 130 g. (2.0 moles) of potassium hydroxide (85.8% assay) in aqueous methanol.

Anal. Calcd. for C_6H_5OK: K, 29.55. Found: K, 29.39.

Sodium *p-t*-Octylphenoxide.—To 208 g. (1.01 moles) of *p-t*-octylphenol dissolved in 150 ml. of methanol is added a solution of 40.0 g. (1.00 mole) of sodium hydroxide in 200–300 ml. of 80% aqueous methanol. The flask is flushed with nitrogen and the solvents are removed at 50° under the vacuum of a water aspirator; the solid so produced is ground in a mortar and dried overnight at 100° at 1 mm. pressure. The resulting powder is stirred with 200 ml. of petroleum ether (b.p. 65–67°), filtered, and finally dried at 100° and 1 mm. for *ca.* 4 hours.

Anal. Calcd. for $C_{14}H_{21}ONa$: Na, 10.09. Found: Na, 9.97.

Potassium *p-t*-octylphenoxide was prepared from 1.03 mole of *p-t*-octylphenol dissolved in 150 ml. of methanol and 65.0 g. (1.0 mole) of potassium hydroxide (85.8% assay) in (200 to 300 ml.) of 80% aq. methanol as described for the sodium salt of this phenol.

Anal. Calcd. for $C_{14}H_{21}OK$: K, 15.98. Found: K, 15.90.

Benzyl Bromide with Sodium Phenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—To 11.6 g. (0.10 mole) of sodium phenoxide dissolved in 80 ml. of ethylene glycol dimethyl ether at 35° there was added 17.1 g. (0.10 mole) of benzyl bromide ($n^{20}\text{D}$ 1.5760) in 20 ml. of ethylene glycol dimethyl ether. Within a few minutes a white solid started to form. After one day at 35° the reaction mixture was poured into 500 ml. of distilled water and extracted with

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(36) One obvious device for circumventing this difficulty would be to add a proton trap which is incapable of reacting with the halide, *e.g.*, 2,6-*di-t*-butylpyridine. This might, however, result in the formation of appreciable amounts of the ether of the *o*-alkylated phenol by enhancing the concentration of the anion of the *o*-alkylated phenol.

(37) Analyses are by Dr. C. S. Yeh, Mrs. S. L. Margerum and Mrs. B. Groten, Purdue University, and Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(38) The infrared absorption spectra were determined by Miss M. Haley and Mrs. B. Pollister on a Perkin–Elmer model 21 spectrophotometer. Unless otherwise stated, spectra were determined using pure liquids while solids were dissolved in carbon tetrachloride.

(39) E. Schwenk, D. Papa and H. Ginsberg, *Anal. Chem.*, **15**, 576 (1943).

(40) A. Ionesco-Matiu and C. Popescu, *Bull. Soc. Stiinte Farm. Romania*, **3**, 387–390 (1938); *C. A.*, **33**, 9193 (1939).

ethyl ether. The aqueous layer was made up to 1.0 l. with distilled water; titration of a 1.0-ml. aliquot with standard silver nitrate solution showed the reaction to be complete. The ethereal layer was washed several times with 10% aq. sodium hydroxide and dried over anhydrous magnesium sulfate (solution I). The alkaline washings were combined and slowly added to 18% aq. hydrochloric acid maintained between 0 and 10°. The acidified mixture was extracted with ethyl ether, and the combined ethereal extract (solution II) was dried over anhydrous magnesium sulfate. The solvents were removed from solution II; no residue (no phenols) remained. The solvents were removed from solution I to give 18.2 g. of product (m.p. 37–38.5°) which on recrystallization from hexane gave a total of 17.3 g. of benzyl phenyl ether, m.p. 38.2–38.5°; lit. m.p. for benzyl phenyl ether,[41] 39°.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.42; H, 6.42.

Allowing for the losses (5%) incurred in taking aliquots to follow the course of the reaction, a 99% yield of recrystallized benzyl phenyl ether was obtained. A duplicate experiment, conducted at 25°, gave only benzyl phenyl ether (99% yield) without any evidence of the carbon benzylated product.

Benzyl Bromide with Sodium Phenoxide in Ethyl Ether (Heterogeneous).—To 23.2 g. (0.20 mole) of sodium phenoxide suspended in 175 ml. of ethyl ether at 35° there was added 34.2 g. (0.20 mole) of benzyl bromide in 25 ml. of ethyl ether. The reaction was complete after 3 days at 35°. At no time during the reaction did the system become homogeneous. A large part of the solvent was removed under reduced pressure, the residue was treated with distilled water and the mixture extracted with toluene. The toluene solution was extracted exhaustively with 10% aqueous sodium hydroxide and then exhaustively with Claisen potash. The toluene solution was washed with saturated aqueous sodium chloride until it was neutral and then dried over anhyd. magnesium sulfate (solution I). Acidification of the aqueous sodium hydroxide solution by addition to 18% hydrochloric acid at 0 to 10° was followed by extraction with ethyl ether; the resulting ethyl ether solution was dried over anhyd. magnesium sulfate (solution II). In the same way acidification of the Claisen potash extracts gave solution III.

Distillation of solution I gave 26.4 g. (72% yield) of pure benzyl phenyl ether, b.p. 107–110° (1 mm.), m.p. 38.1–38.7°, mixed m.p. with an analytically pure sample of benzyl phenyl ether undepressed. In addition, 2.89 g. of higher boiling material was obtained which yielded, after chromatographing on Merck's alumina, 2.75 g. of 2-benzyloxydiphenylmethane; m.p. 37–38°; lit.[41] m.p. 38°.

Distillation of solution II gave an 0.82-g. forerun of phenol (b.p. 40–50° (1 mm.), m.p. 40°) and then 5.5 g. (15% yield) of pure *o*-benzylphenol, b.p. 121–123° (1 mm.), $n^{20}D$ 1.5994–1.5995, m.p. 20.2–20.9°, lit.[42] m.p. 21°. The infrared spectrum shows strong phenolic absorption at 2.95 μ.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.94; H, 6.59. On removing the diethyl ether from solution III there was 0.6 g. of residue.

The 2.75 g. of 2-benzyloxydiphenylmethane constitutes a 5% yield (based on sodium phenoxide). Dibenzylation could not have occurred subsequent to the formation of benzyl phenyl ether, so that this 5% yield can only be derived from a sequence whose first step is carbon benzylation of sodium phenoxide. Thus, a 20% yield of *o*-benzyl phenol, either as such or as the product of subsequent benzylation, was isolated. When allowance is made for the 4% loss in following the rate of reaction, it is seen that 75% O-benzylation and 21% C-benzylation occurred.

Allyl Bromide with Sodium Phenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—To 11.7 g. (0.10 mole) of sodium phenoxide dissolved in 80 ml. of ethylene glycol dimethyl ether at 35° there was added 12.1 g. (0.10 mole) of allyl bromide in 20 ml. of ethylene glycol dimethyl ether. After 14 hours at 35° the reaction was complete. The reaction mixture was worked up as usual except that the ethereal solution of reaction products was extracted with Claisen potash rather than 10% aq. sodium hydroxide. Despite the use of Claisen potash no phenolic material was found. In contrast, the Claisen potash-insoluble fraction on distillation gave 12.8 g. (96% yield) of pure allyl phenyl ether, b.p. 74–76° (1 mm.), $n^{20}D$ 1.5204–1.5205, lit.[43] $n^{20}D$ for allyl phenyl ether 1.5208. The infrared spectrum was devoid of a phenolic hydroxyl band, but strong absorption at 8.10 μ (ether) was noted. Allowing for 3% lost in aliquots taken to follow the rate of reaction, 99% O-allylation occurred.

Anal. Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.50; H, 7.45.

Allyl Bromide with Sodium Phenoxide in Ethyl Ether (Heterogeneous).—To 34.8 g. (0.30 mole) of sodium phenoxide suspended in 200 ml. of ethyl ether, at 35°, was added 36.9 g. (0.30 mole) of allyl bromide in 100 ml. of ethyl ether. The reaction required 8 days at 35° to go to completion. On working up in the usual way, 15.5 g. (39% yield) of pure allyl phenyl ether was isolated, b.p. 57–60° (1 mm.), $n^{20}D$ 1.5203–1.5205; it had the same infrared spectrum as the sample which had been analyzed (*vide supra*). In addition, 0.40 g. of a liquid boiling higher than allyl phenyl ether was obtained b.p. 72–74° (1 mm.), $n^{20}D$ 1.5259–1.5261. This small amount of material, which may well have been the allyl ether of *o*-allylphenol, was not further investigated.

From the alkali-soluble fraction of the reaction product 20.9 g. of pure *o*-allylphenol (52% yield) was isolated, b.p. 61–62° (1 mm.), $n^{20}D$ 1.5459–1.5461, lit.[43] $n^{20}D$ 1.5450, $n^{14}D$ 1.5485.[44] As would be expected, the *o*-allylphenol infrared spectrum has a strong –OH band at 3.0 μ.

Anal. Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.52; H, 7.46.

Since 3% of the reaction mixture was lost as aliquots in following the rate, the yields were 40% O-allylation and 54% C-allylation. The *o*-allylphenol does not arise from rearrangement of allyl phenyl ether (see below).

Attempt to Isomerize Allyl Phenyl Ether.—To 5.0 g. of sodium phenoxide suspended in 350 ml. of ethyl ether was added 15.5 g. of allyl phenyl ether. The mixture was allowed to reflux (35–36°) for 7 days. On cooling to room temperature the mixture was extracted with water, enough ethyl ether being added to maintain two discrete layers. After separation from thd aqueous phase (A) the ethereal layer was extracted with Claisen potash in the usual way. The aqueous phase (A) was acidified with dilute hydrochloric acid, extracted exhaustively with ethyl ether and the ethyl ether solution was dried. On removing the solvent 4.0 g. of phenol remained as a white solid, m.p. 40°. Hence 100% of the sodium phenoxide was recovered. On acidification of the Claisen potash extract nothing was obtained. Thus, no isomerization to *o*-allylphenol had taken place. This was confirmed by distillation of the ethyl ether solution which had been extracted with Claisen potash; 14.6 g. (94% recovery) of allyl phenyl ether was obtained which had the same refractive index and infrared spectrum as the original sample.

Benzyl Bromide with Sodium *p-t*-Octylphenoxide in Ethyl Ether (Homogeneous).—To 22.8 g. (0.10 mole) of sodium *p-t*-octylphenoxide *dissolved* in 100 ml. of ethyl ether at 35° was added 18.7 g. (0.11 mole) of benzyl bromide. The reaction was complete in two days at 35°. On working up in the usual way, no phenolic material was obtained from the Claisen potash extracts. The Claisen potash-insoluble fraction weighed 28.9 g. (m.p. 103–104°). Recrystallization from low boiling petroleum ether gave 28.6 g. of pure benzyl *p-t*-octylphenyl ether, m.p. 103.1–104°.

Anal. Calcd. for $C_{21}H_{\;8}O$: C, 85.09; H, 9.51. Found: C, 85.09; H, 9.48.

The infrared spectrum shows strong ether absorption at 8.07 μ and is devoid of the band at 3.07 μ which is characteristic of *p-t*-octylphenol. Allowing for a 2% loss incurred in following the rate, 99% O-benzylation occurred.

Benzyl Bromide with Sodium *p-t*-Octylphenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—To 22.8 g. (0.10 mole) of sodium *p-t*-octylphenoxide *dissolved* in 100 ml. of ethylene glycol dimethyl ether at 35° was added 17.2 g. (0.10 mole) of benzyl bromide; the reaction was complete

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(41) S. G. Powell and R. Adams, THIS JOURNAL, **42**, 646 (1920); W. Short and M. Stewart, *J. Chem. Soc.*, 553 (1929).

(42) L. Claisen, *Ann.*, **442**, 210 (1925).

(43) C. D. Hurd and L. Schmerling, THIS JOURNAL, **59**, 108 (1937); E. M. Filachione, J. H. Lengel and W. P. Ratchford, *ibid.*, **72**, 839 (1950).

(44) K. von Auwers, *Ann.*, **422**, 174 (1920).

in 8 hours at 35°. No C-alkylated material was found. A total of 28.8 g. of pure benzyl *p*-*t*-octylphenyl ether, m.p. 103.2–104°, was isolated. This had an infrared spectrum identical with that of the sample obtained in the preceding experiment. Allowing for 1.5% lost as aliquots, 99% O-benzylation occurred.

Allyl Bromide with Sodium *p*-*t*-Octylphenoxide in Ethyl Ether (Homogeneous).—To 22.8 g. (0.10 mole) of sodium *p*-*t*-octylphenoxide *dissolved* in 100 ml. of ethyl ether, at 35°, was added 14.5 g. (0.12 mole) of allyl bromide; the reaction required two days at 35° to go to completion. No phenolic material was detected. The Claisen potash-insoluble fraction gave, on distillation, 24.0 g. of a colorless liquid, b.p. 111–113° (1 mm.), n^{20}D 1.5073–1.5074. The infrared spectrum showed strong ether absorption at 8.05 μ and was devoid of phenolic bands. Allowing for a 2% loss in following the reaction rate, a 99% yield of allyl *p*-*t*-octylphenyl ether was isolated.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.93; H, 10.59. Found: C, 82.87; H, 10.55.

Allyl Bromide with Sodium *p*-*t*-Octylphenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—A duplicate of the preceding experiment except for the use of 100 ml. of ethylene glycol dimethyl ether instead of ethyl ether, the reaction was complete in 8 hours at 35°. No phenolic material was found. Allyl *p*-*t*-octylphenyl ether (23.8 g.) was isolated from the Claisen potash-insoluble fraction; b.p. 112–113° (1 mm.), n^{20}D 1.5073–1.5075. The infrared spectrum was identical with that of the allyl *p*-*t*-octylphenyl ether obtained in the preceding experiment. Allowing for 1.5% lost as aliquots, 98% O-allylation occurred.

Benzyl Bromide with Potassium *p*-*t*-Octylphenoxide in Ethyl Ether (Heterogeneous).—To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide was added 17.8 g. (0.104 mole) of benzyl bromide made up to a volume of 100 ml. with anhydrous ethyl ether; reaction was complete in 9 hours at 35–36°. The crude Claisen potash-insoluble fraction weighed 22.2 g., m.p. 102.4–103.4°. Recrystallization from low boiling petroleum ether gave 21.6 g. of benzyl *p*-*t*-octylphenyl ether, m.p. 103–104°. The infrared spectrum was identical with that of an analytically pure sample of this ether and a mixed m.p. was undepressed. The Claisen potash-soluble fraction (6.4 g., m.p. 52.5–53.6°) was recrystallized from low boiling petroleum ether to give a total of 6.2 g. of pure *o*-benzyl-*p*-*t*-octylphenol, m.p. 54–54.7°. The infrared spectrum shows strong hydroxyl absorption at 2.80 μ and a phenolic band at 8.00 μ. Allowing for the 1% loss in following the rate, 74% O- and 21% C-benzylated products were isolated.

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.09; H, 9.51. Found: C, 85.27; H, 9.78.

Benzyl Bromide with Potassium *p*-*t*-Octylphenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—A duplicate of the previous experiment using ethylene glycol dimethyl ether instead of ethyl ether, the reaction was complete in 35 minutes at 35°. No C-benzylated material was found. A 97% yield (28.9 g.) of pure benzyl *p*-*t*-octylphenyl ether was isolated, m.p. 103–104°. The infrared spectrum was identical with that of the analytically pure sample.

Allyl Bromide with Potassium *p*-*t*-Octylphenoxide in Ethyl Ether (Heterogeneous).—To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide was added 13.1 g. (0.108 mole) of allyl bromide made up to 100 ml. with anhydrous ethyl ether; the reaction was complete in 14 hours at 35°. From the Claisen potash-insoluble fraction 19.03 g. of allyl-*p*-*t*-octylphenyl ether, b.p. 108–110° (1 mm.), n^{20}D 1.5073–1.5075, was isolated; it had an infrared spectrum identical with that of analytically pure allyl-*p*-*t*-octylphenyl ether. The Claisen potash-soluble fraction gave 4.72 g. of pure *o*-allyl-*p*-*t*-octylphenol, b.p. 117–118° (1 mm.), n^{20}D 1.5168. The infrared spectrum showed strong hydroxyl absorption at 3.10 μ and a phenolic band at 8.10 μ. Adjusting for a 2% loss in following the rate, 78% O- and 19% C-allylation occurred.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.93; H, 10.57. Found: C, 83.01; H, 10.78.

Allyl Bromide with Potassium *p*-*t*-Octylphenoxide in Ethylene Glycol Dimethyl Ether (Homogeneous).—The same amounts of reactants as in the preceding experiment were used except that ethylene glycol dimethyl ether was employed instead of ethyl ether. At 35°, within 2 minutes after mixing, the initially homogeneous system began to deposit potassium bromide. The reaction was over in 45 minutes. No phenolic material was found, but from the Claisen potash-insoluble fraction 23.8 g. (96% yield) of pure allyl *p*-*t*-octylphenyl ether was isolated, b.p. 113–115° (1 mm.), n^{20}D 1.5073–1.5075. This had the same infrared spectrum as analytically pure allyl-*p*-*t*-octylphenyl ether.

Benzyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° (Homogeneous).—A mixture of 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide and 3500 ml. of dry toluene was maintained at 80° for one day whereupon a clear solution resulted. On cooling to room temperature no solid settled out and on seeding with the potassium salt no precipitation occurred. To this pale orange solution was added 1135 g. (9 moles) of benzyl chloride and the solution was stirred occasionally. After 4 weeks at room temperature the solution was extracted with distilled water rendered acidic to congo red with 10% aq. nitric acid. Titration of the aqueous layer with standard silver nitrate showed the reaction was 62% complete. The organic phase was washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure (1 mm.); the first 4000 ml. came over with the bath maintained between 25–32°; the last 300–500 ml. came over at a bath temp. of 40–50° and the residue was pumped (bath temp. 40–50°) to constant weight (26.8 g.). The total time in the 40–50° bath was *ca.* 12 hours. The residue was taken up in 1000 ml. of diethyl ether and treated with Claisen potash in the usual way. The crude Claisen potash-insoluble fraction weighed 18.5 g. and had m.p. 101.9–103.4°. Its infrared spectrum was devoid of phenolic bands and was superimposable on the spectrum of the pure O-benzylated product. Recrystallization from low boiling petroleum ether gave a total of 18.2 g., m.p. 103.1–104.1°; mixed m.p. with pure benzyl *p*-*t*-octylphenyl ether, 103.2–104.1°.

The Claisen soluble fraction, after acidification and extraction into ethyl ether, was washed with sodium bicarbonate solution to neutralize any residual hydrochloric acid and dried over anhydrous potassium carbonate. Removal of the solvent gave 7.64 g. of yellow crystals (m.p. 83–85°) having the same infrared spectrum as pure *p*-*t*-octylphenol. This, after decolorizing over charcoal in low boiling petroleum ether, gave 7.43 g. of white crystals (m.p. 83.9–84.9°); the mixed m.p. with analytically pure *p*-*t*-octylphenol of m.p. 84.0–85.1° was 84.0–85.1°. As a further check on the possibility that the 7.43 g. of recovered *p*-*t*-octylphenol might have contained some *o*-benzyl-*p*-*t*-octylphenol a quantitative infrared analysis was carried out; in carbon tetrachloride solution, *o*-benzyl-*p*-*t*-octylphenol has a band at 14.37 μ (absent in the spectrum of *p*-*t*-octylphenol), whereas *p*-*t*-octylphenol exhibits absorption at 14.90 μ (something which the *ortho* benzylated *p*-*t*-octylphenol does not do). Although 2% of *o*-benzyl-*p*-*t*-octylphenol could readily be detected in the presence of 98% of *p*-*t*-octylphenol (as shown by the use of a set of standard mixtures) none was detected in the 7.43 g. of phenolic material. (If 2% of 7.43 g. of phenolic material had been *o*-benzyl-*p*-*t*-octylphenol this would have corresponded to 0.15 g. (0.8% yield) of the C-benzylated product.) Based on the fact that the reaction was only 62% complete (bromide ion titration) the 18.2 g. of benzyl-*p*-*t*-octylphenol ether constitutes a 99% yield; if, instead, the yield is based on unrecovered *p*-*t*-octylphenol, the 18.2 g. corresponds to a 97% yield of the O-benzylated product.

100% Reaction of Benzyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous"). (a) Using a 12% Benzyl Chloride Solution.—To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide was added 12.7 g. (0.10 mole) of benzyl chloride diluted to 100 ml. with toluene. The initially heterogeneous reaction mixture became homogeneous within 24 hr. at 25° (at which time the reaction had gone 60% to completion) and remained homogeneous for the next 12 hours (at the end of which time 80% reaction had occurred). During this interval, all of the potassium chloride produced (4.4–5.8 g.) was found in the aqueous extract of the *clear* toluene solution. Also, at 60% completion *ca.* 10 g. of the phenolic salt was in solution; this contrasts with a solubility of less than 1 g. in 100 ml. of toluene. Thirty-six hours after the reaction began the solution became cloudy but even at the end of the reaction (48 hours total) more than half of the potassium chloride formed remained in solution. On working up in the usual way, the Claisen potash-soluble fraction gave 4.02 g. (m.p.

52–54°) which, recrystallized from low boiling petroleum ether, yielded 3.68 g. of pure *o*-benzyl-*p*-*t*-octylphenol, m.p. 54.1–54.8°, and having the characteristic infrared spectrum of this compound. The Claisen potash-insoluble fraction gave 22.2 g. (m.p. 102–104°) which, recrystallized from low boiling petroleum ether, yielded 21.7 g. of pure benzyl *p*-*t*-octylphenyl ether, m.p. 103.3–104.1°; infrared spectrum identical with that of the analytically pure ether. Since 7% was lost in the rate study, 79% O- and 13% C-benzylation occurred.

A duplicate of this experiment gave an 81% yield of pure benzyl *p*-*t*-octylphenyl ether and a 14% yield of pure *o*-benzyl-*p*-*t*-octylphenol.

(b) **Using a 50% Benzyl Chloride Solution.**—To 24.4 g. (0.1 mole) of potassium *p*-*t*-octylphenoxide was added 50.4 g. (0.4 mole) of benzyl chloride made up to a volume of 100 ml. with anhydrous toluene. Within 5 hours the initially heterogeneous system was a clear red solution (reaction 56% complete); homogeneity persisted for 75 minutes after which potassium chloride began to precipitate; the reaction required 11 hours to go to complete (90% of the potassium chloride produced was still dissolved in the toluene at this point). It was shown that under the conditions used to extract inorganic chloride from the toluene–benzyl chloride phase only a trifling amount of hydrolysis of the benzyl chloride occurred.

On working up, 3.66 g. of pure *o*-benzyl-*p*-*t*-octylphenol, m.p. 54.1–54.9°, having the typical infrared spectrum was obtained. The Claisen potash-insoluble fraction yielded 23.6 g. of pure benzyl *p*-*t*-octylphenyl ether, m.p. 103–104°; infrared spectrum identical with that of the analytically pure ether. Adjusting for a 3% loss in the rate study, 83% O- and 12% C-benzylation occurred.

Thus, varying the percentage benzyl chloride from 12 to 50% does not change the proportions of C- and O-benzylation. Clearly, since the homogeneous experiment (*vide supra*) used a 24% benzyl chloride solution, the fact that only benzyl *p*-*t*-octylphenyl ether was formed cannot be attributed to the concentration of benzyl chloride employed in that experiment.

46% Reaction of Benzyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous").—The run using a 12% benzyl chloride solution [(a) of preceding section] was repeated but allowed to proceed for only 16 hours. The mixture was then extracted with a mixture of ethyl ether and distilled water acidified with 10% aq. nitric acid; titration of the aqueous phase for chloride ion showed the reaction to be 46% complete. The ethereal layer was dried, the excess benzyl chloride and slovents were removed under reduced pressure (temp. 35–40°) and the residue was worked up as usual. The crude Claisen potash-insoluble fraction was a pale yellow solid, 7.8 g., m.p. 102.7–104°, which had an infrared spectrum identical with that of analytically pure benzyl *p*-*t*-octylphenyl ether. Recrystallization from petroleum ether (Norite) gave 7.4 g. (25% yield) of white crystals, m.p. and mixed m.p. with analytically pure benzyl *p*-*t*-octylphenyl ether 103–104°.

The Claisen potash-soluble material (17.2 g.) was an orange solid which melted from 40–60°. Recrystallization from petroleum ether (Norite) gave 16.8 g. of a pale yellow solid, m.p. 40–61°. An infrared analysis (*vide supra*) showed that this contained between 30 to 35% of the carbon benzylated phenol; and, indeed, its infrared spectrum proved to be superimposable on that of a synthetic mixture consisting of 67% *p*-*t*-octylphenol and 33% *o*-benzyl-*p*-*t*-octylphenol. Thus, 11.3 g. (55%) of *p*-*t*-octylphenol and 5.5 g. (18% yield) of *o*-benzyl-*p*-*t*-octylphenyl ether were obtained.

16% Reaction of Benzyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous").—The preceding experiment was repeated but allowed to proceed for only 7 hours (16% complete by chloride ion titration). The crude Claisen potash-insoluble fraction (0.24 g., 0.8% yield) melted 102–104° and had the same infrared spectrum as analytically pure benzyl *p*-*t*-octylphenyl ether. The crude phenolic fraction (20.9 g.) was recrystallized from petroleum ether (Norite) giving 20.6 g. (m.p. 42–68°); this had an infrared spectrum identical with that of a mixture consisting of 78% *p*-*t*-octylphenol and 22% *o*-benzyl-*p*-*t*-octylphenol. Thus, 0.78 × 20.6 g. = 16.1 g. (78% recovery) of *p*-*t*-octylphenol and 0.22 × 20.6 g = 4.52 g. (15% yield) of *o*-benzyl-*p*-*t*-octylphenol were obtained.

4% Reaction of Benzyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous").—The preceding experiment was repeated but allowed to run for only 4.5 hours (4% complete). On working up in the usual way, no Claisen potash insoluble material was found. The crude Claisen potash-soluble fraction (20.9 g.) was an orange solid (m.p. 60–80°) which, on recrystallization from petroleum ether (Norite), gave 20.7 g. of pale yellow crystals (m.p. 61–80°). This, by infrared analysis, was found to contain 4 to 5% of the *o*-benzylated phenol. Finally, the infrared spectrum of this phenolic mixture was shown to be virtually identical with that of a synthetic mixture consisting of 95.5% *p*-*t*-octylphenol and 4.5% *o*-benzyl-*p*-*t*-octylphenol. Thus, 0.955 × 20.7 g. = 19.8 g. (96%) *p*-*t*-octylphenol was recovered and 0.045 × 20.7 g. = 0.93 g. (3% yield) of *o*-benzyl-*p*-*t*-octylphenol was obtained.

Since no benzyl-*p*-*t*-octylphenyl ether had been detected it was of interest to ascertain how sensitive the isolation procedure is in regard to detecting this ether. A mixture of 0.15 g. of benzyl-*p*-*t*-octylphenyl ether and 20.6 g. of *p*-*t*-octylphenol was dissolved in 100 ml. of toluene and then subjected to the usual working up procedure. Without any difficulty, 0.09 g. of benzyl-*p*-*t*-octylphenyl ether, m.p. 102.3–103.8°, was isolated from the Claisen potash-insoluble fraction. Since 0.15 g. (0.0005 mole) of the ether represents a 0.5% yield it is clear that the isolation procedure is easily capable of detecting a 0.5% yield of the ether.

Allyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° (Homogeneous).—A mixture of 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide and 3500 ml. of toluene was heated at 80° for 12 hours to effect complete solution. The pale yellow solution was cooled to 25° and seeded with a few crystals of potassium *p*-*t*-octylphenoxide; no precipitation occurred. To the solution was then added 988 g. (13 moles) of allyl chloride. After 8 weeks at 25° (reaction 40% complete), the reaction mixture was worked up in the same way as the corresponding (homogeneous) reaction employing benzyl chloride except that most of the excess allyl chloride was removed at 25° (1 mm.). The temperature was then raised to 35° and the last bits of allyl chloride and most of the toluene were removed at 1 mm. (final volume *ca.* 600 ml.); the entire evaporative process took 8 hours.

The crude Claisen potash-insoluble material (9.63 g., $n^{20}\text{D}$ 1.5039) was distilled; the 9.49 g. (96% yield) so obtained had b.p. 133–134° (3 mm.), $n^{20}\text{D}$ 1.5073–1.5057; its infrared spectrum was identical with that of pure allyl *p*-*t*-octylphenyl ether. When account is taken of a 1% loss in taking aliquots to follow the rate of reaction, the yield of ether becomes 97%. The crude Claisen potash-soluble fraction (12.0 g.) was a pale yellow solid, m.p. 83.7–85.0°. In an effort to detect the presence of any C-allylated product an infrared analysis was performed. *p*-*t*-Octylphenol has an absorption band at 11.52 μ which is absent from the spectrum of *o*-allyl-*p*-octylphenol. The latter has a strong band at 11.10 μ which is not exhibited by *p*-*t*-octylphenol. Standard mixtures of these two phenols were prepared using a total of 4.0314 g. made up to a volume of 5.0 ml. with anhydrous ethyl ether. Although it was possible to detect the presence of 1% *o*-allyl-*p*-*t*-octylphenol by this procedure there was no evidence of the presence of *o*-allyl-*p*-*t*-octylphenol in the spectrum of the solid of m.p. 83.7–85.0°. Recrystallization from petroleum ether gave 11.6 g. of white crystals, m.p. 84.1–85.0; mixed m.p. with pure *p*-*t*-octylphenol, 84.0–85.0°.

100% Reaction of Allyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous"). (a) **Using an 8% Allyl Chloride Solution.**—To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide was added 7.7 g. (0.10 mole) of allyl chloride which had been diluted with toluene to a volume of 100 ml. The initially heterogeneous reaction mixture became completely homogeneous after 17 hours, when the reaction was 42% complete, and remained a clear wine-red solution for the next 24 hours (reaction 90% complete). At this point a slight cloudiness appeared but, even after an additional 23 hours, most of the potassium chloride remained in solution. To ensure completion of reaction 1.0 g. (0.01 mole) of allyl chloride was added and the reaction mixture was stirred an additional 5 hours.

On working up in the usual way, 19.0 g. of allyl *p*-*t*-octylphenyl ether, b.p. 115–117° (1 mm.), $n^{20}\text{D}$ 1.5074–1.5076, infrared spectrum identical with that of the pure ether, was obtained. The Claisen potash-soluble fraction yielded 4.33

g. of colorless liquid, b.p. 114–116° (1 mm.), $n^{20}\mathrm{D}$ 1.5167–1.5168; this had an infrared spectrum superimposable upon that of pure *o*-allyl-*p*-*t*-octylphenol. Adjusting for a 2% loss in the rate study, 18% C- and 79% O-allylation occurred.

(b) **Using a 32% Allyl Chloride Solution.**—To 48.8 g. (0.20 mole) of potassium *p*-*t*-octylphenoxide was added 61.2 g. (0.80 mole) of allyl chloride which had been diluted to 200 ml. with toluene. The initially heterogeneous mixture was only faintly cloudy after 12 hours; however, it was not under observation during this period and may have, actually, been homogeneous at some time between 0 and 12 hours. The reaction was complete in 24 hours at which time 80% of the potassium chloride produced still remained in solution.

On working up, the Claisen potash-soluble fraction yielded 10.52 g. (b.p. 118–120° (1 mm.), $n^{20}\mathrm{D}$ 1.5168–1.5169) of *o*-allyl-*p*-*t*-octylphenol; infrared spectrum identical with that of the analytically pure phenol. The insoluble fraction gave 34.9 g. of a colorless liquid, b.p. 116–117° (1 mm.), $n^{20}\mathrm{D}$ 1.5074–1.5076 whose infrared spectrum was superimposable upon that of pure allyl-*p*-*t*-octylphenyl ether. Adjusting for a 2% loss in the rate study 21% C- and 73% O- allylation occurred.

Thus the proportions of C- and O- allylation are not significantly affected by variations in the percentage allyl chloride over the range 8 to 32%. Clearly, since the homogeneous experiment (*vide supra*) employed a 22% allyl chloride solution, the fact that only allyl *p*-*t*-octylphenyl ether was produced in that experiment cannot be attributed to the concentration of the allyl chloride solution.

34% Reaction of Allyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25 ("Heterogeneous").—The experiment employing an 8% allyl chloride solution [(a) of preceding section] was repeated but allowed to go only 14 hours (34% reacted). Although still heterogeneous at this point, the reaction mixture had thinned considerably. Working up in the usual way gave 3.37 g. (14% yield) of allyl *p*-*t*-octylphenyl ether, b.p. 108–110° (1 mm.), $n^{20}\mathrm{D}$ 1.5074, infrared spectrum that of the analytically pure ether. The Claisen potash-soluble fraction yielded 18.4 g. (m.p. 39–57°); infrared analysis, as described for the homogeneous experiment (*vide supra*), showed it to consist of 76% *p*-*t*-octylphenol and 24% *o*-allyl-*p*-*t*-octylphenol. Thus, 14.0 g. (68%) of the *p*-*t*-octylphenol was recovered and 4.4 g. (18% yield) of *o*-allyl-*p*-*t*-octylphenol was produced.

22% Reaction of Allyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous").—The preceding experiment was repeated but only allowed to proceed 8 hours (22% reacted). The crude Claisen potash-insoluble fraction weighed 0.48 g. (2% yield); it had $n^{20}\mathrm{D}$ 1.5073 and the same infrared spectrum as pure allyl *p*-*t*-octylphenyl ether. The phenolic fraction (19.5 g.) melted 50–71°. Quantitative infrared analysis showed it to consist of 22% *o*-allyl-*p*-octylphenol and 78% *p*-*t*-octylphenol; hence 4.3 g. (17% yield) of *o*-allyl-*p*-*t*-octylphenol was formed.

10% Reaction of Allyl Chloride with Potassium *p*-*t*-Octylphenoxide in Toluene at 25° ("Heterogeneous").—The preceding experiment was repeated, but only allowed to run for 5 hours (10% reacted). The crude Claisen potash-insoluble fraction was a smear which weighed 0.03 g. If this is taken to be allyl *p*-*t*-octylphenyl ether it represents a 0.1% yield. The crude phenolic fraction (20.84 g., m.p. 69–80°) was dissolved in petroleum ether and decolorized with Norite; evaporation of the solvent gave 20.71 g. (m.p. 70–81°). This was melted and 4.0321 g. was made up to 5 ml. with anhydrous ethyl ether. Quantitative infrared analysis using a set of standards as described above showed that it contained 9% *o*-allyl-*p*-*t*-octylphenol and 91% *p*-*t*-octylphenol; thus, 1.86 g. (7.6% yield) of *o*-allyl-*p*-*t*-octylphenol was produced.

In order to ascertain how sensitive the isolation procedure is in regard to detecting allyl *p*-*t*-octylphenyl ether a mixture of 0.246 g. (0.001 mole) of this ether ($n^{20}\mathrm{D}$ 1.5073) and 20.6 g. of *p*-*t*-octylphenol was dissolved in 100 ml. of toluene and subjected to the usual working up procedure. The crude Claisen potash-insoluble fraction weighed 0.214 g. and had $n^{20}\mathrm{D}$ 1.5071. Since 0.1 mole of potassium *t*-octyl phenoxide was employed in the various experiments described above, and since 0.246 g. (0.001 mole) of the ether represents a 1% yield, it is clear that the isolation procedure is easily capable of detecting a 1% yield of ally *p*-*t*-octylphenyl ether.

Solubility of Potassium *p*-*t*-Octylphenoxide in Toluene.—A 3-g. sample of this salt was stirred in 250 ml. of toluene for 48 hours at 25°. The mixture was then filtered and the solid dried to constant weight; the filtrate was evaporated to dryness and the residue weighed. Under these conditions 2.0 g. of the salt dissolved in 250 ml. of toluene. In a duplicate experiment using 12 g. of the potassium salt, 2.2 g. dissolved in 250 ml. of toluene.[45]

Some Further Examples of the Importance of Heterogeneity. (1) Potassium *p*-*t*-Octylphenoxide and Allyl Bromide.—(a) To a solution of 12.2 g. (0.05 mole) of potassium *p*-*t*-octylphenoxide in 1500 ml. of *p*-*t*-butyltoluene 6.5 g. (0.05 mole) of allyl bromide was added. After two days at 25° (reaction 78% complete) the products were isolated in the usual way. The phenolic fraction consisted of 1.93 g. of the starting phenol, m.p. 84–85° (19% recovery). In addition, 9.27 g. (75% yield) of allyl *p*-*t*-octylphenyl ether (b.p. 112–133° (1 mm.), $n^{20}\mathrm{D}$ 1.5072–1.5074) was isolated. On taking into account a 2% loss as aliquots in following the rate and the recovery of starting phenol the yield of ether is 96%.

(b) To 24.4 g. (0.1 mole) of potassium *p*-*t*-octylphenoxide suspended in 50 ml. of *p*-*t*-butyltoluene 13.1 g. (0.1 mole) of allyl bromide was added. The initially thick slurry became very thin in one hour. After 24 hours at 25° (reaction 94% complete) the mixture was worked up in the usual way: 85% O and 11% C-allylation had occurred.

(c) To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide was added 12.1 g. (0.10 mole) of allyl bromide made up to 100 ml. with toluene. Within 45 minutes at 25° the initially heterogeneous reaction mixture became completely homogeneous and remained so for an additional 110 minutes. This period covered 60–84% reaction during which time all of the potassium bromide produced could be titrated in the aqueous extract of the toluene solution. The reaction required one day at 25° to go to completion at which time 30% of the potassium bromide produced was still in solution. The usual work-up gave an 84% yield of allyl *p*-*t*-octylphenyl ether and a 10% yield of *o*-allyl-*p*-*t*-octylphenol.

(2) **Sodium *p*-*t*-Octylphenoxide and Allyl Bromide at 25°.**—To 45.6 g. (0.20 mole) of sodium *p*-*t*-octylphenoxide was added 25.4 g. (0.21 mole) of allyl bromide made up to 200 ml. with toluene. The reaction mixture remained heterogeneous. However when the reaction was 75% complete (30 hours), more than half of the sodium bromide produced was found dissolved in the toluene; the amount decreased as the reaction proceeded to completion (3 days) at which time only a trace was in solution. On working up in the usual way it was found that 65% O- and 31% C-allylation had occurred.

(3) **Potassium Phenoxide and Allyl Bromide at 50° (Heterogeneous).**—To 13.2 g. (0.100 mole) of potassium phenoxide suspended in 80 ml. of toluene was added 13.8 g. (0.114 mole) of allyl bromide in 20 ml. of toluene at 50°. The reaction was over in 2 days at 50°; 58% O- and 35% C-allylation occurred.

(4) **Sodium Phenoxide and Allyl Bromide at 65° (Heterogeneous).**—To 11.6 g. (0.10 mole) of sodium phenoxide suspended in 75 ml. of toluene was added 13.1 g. (0.11 mole) of allyl bromide in 25 ml. of toluene at 65°. The reaction required two days to go to completion; 80% C- and 17% O-allylation occurred.

(5) **Sodium Phenoxide and Benzyl Bromide at 60° (Heterogeneous).**—To 23.2 g. (0.20 mole) of sodium phenoxide was added 34.4 g. (0.20 mole) of benzyl bromide made up to 200 ml. with toluene; the mixture was stirred at 60°. Reaction was complete after 17 hours; 63% C- and 30% O-benzylation occurred.

(6) **Potassium Phenoxide and Benzyl Bromide at 50° (Heterogenous).**—To 39.6 g. (0.3 mole) of potassium phenoxide was added 51.3 g. of benzyl bromide made up to 300 ml. with petroleum ether (b.p. 65–67°). The mixture was stirred for one week at 50° (reaction 96% complete); 33% C- and 56% O-benzylation occurred.

(7) **Sodium *p*-*t*-Octylphenoxide and Benzyl Bromide. (a) In Toluene at 70° (Homogeneous).**—A solution of 11.6 g. (0.05 mole) of sodium *p*-*t*-octylphenoxide in 3500 ml. of toluene at 70° was treated with 342 g. (2.0 moles) of benzyl bromide. The solution was stirred at 70°. Within 6 hours sodium bromide had begun to precipitate. The

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[45] We are indebted to Mr. Paul J. Berrigan for this experiment.

mixture was worked up after the reaction had gone 70% to completion (62 days). Infrared analysis (*vide supra*) of the phenolic material failed to reveal the presence of any *o*-benzyl-*p*-*t*-octylphenol, but a 94% yield of pure benzyl *p*-*t*-octylphenyl ether was isolated.

(b) **In Toluene at 25° (Heterogeneous).**—To 68.4 g. (0.30 mole) of sodium *p*-*t*-octylphenoxide was added 53.0 g. (0.31 mole) of benzyl bromide made up to 300 ml. with toluene at 25°. The initially heterogeneous mixture became much thinner and approached homogeneity after 7.5 hours when the reaction was *ca.* 60% complete. At this point all of the sodium bromide produced was found in the toluene solution. The reaction was complete in 2.5 days; 72% O- and 23% C-alkylation occurred.

(8) **Potassium *p*-*t*-Octylphenoxide and Benzyl Bromide at 25° (Heterogeneous).**—To 24.4 g. (0.10 mole) of potassium *p*-*t*-octylphenoxide suspended in 75 ml. of toluene was added 19.8 g. (0.11 mole) of benzyl bromide in 25 ml. of toluene at 25°. The initially heterogeneous reaction mixture became *completely* homogeneous in 50 minutes at which time the reaction was 60% complete. Incipient cloudiness appeared in 115 minutes by which time the reaction had gone 80% to completion. During these 65 minutes all of the potassium bromide produced could be titrated in the aqueous extract of the clear toluene solution. The reaction was complete in 12 hours; 84% O- and 15% C-benzylation occurred.

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[CONTRIBUTION FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis and Biological Activity of Some Cycloalkaneglyoxylic Acids

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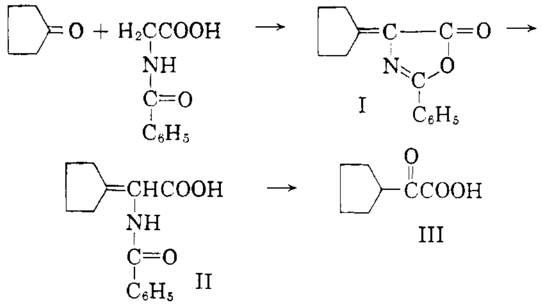
Cyclopentane- and cyclohexaneglyoxylic acids were prepared from the corresponding cyclic ketones by condensation with hippuric acid to form the oxazolone followed by an initial alkaline hydrolysis to form the α-benzamido-β-cycloalkylideneacetic acids, and then acid hydrolysis to form the cycloalkaneglyoxylic acids. Cyclopentaneglyoxylic acid inhibits in a competitive manner the utilization of α-keto-β-methylvaleric acid in *Lactobacillus arabinosus* 17–5; whereas, the corresponding cyclohexane derivative is inactive. These biological effects are comparable to the results obtained with the corresponding amino acid analogs.

In biological systems, the inhibitory effect of an analog of a natural amino acid may frequently be circumvented by the corresponding natural α-keto acid. In the investigation of such effects, it is desirable to study the inhibitory properties of the α-keto acid analog corresponding to the amino acid antagonist.[2] Cyclopentaneglycine is an inhibitory analog of isoleucine,[3a] while cyclohexaneglycine does not exert any appreciable inhibitory effects upon biological utilization of amino acids.[3b] In order to study the mode of action of the keto acid (α-keto-β-methylvaleric acid) corresponding to isoleucine in preventing the toxicity of cyclopentaneglycine, its corresponding keto acid analog (cyclopentaneglyoxylic acid) was prepared as a potential antagonist of the natural keto acid. Further, in an effort to demonstrate the specificity of the cyclopentyl group in replacing the *sec*-butyl group of natural metabolites with the resultant retention of enzyme binding ability of the corresponding carbon skeleton, cyclohexaneglyoxylic acid was also prepared to demonstrate its inactivity in antagonizing the natural keto acid.

Two different approaches to the synthesis of cyclopentaneglyoxylic acid were examined in this study. One involved the initial preparation of 2-oxocyclopentaneacetonitrile by the interaction of cuprous cyanide with the acid bromide of cyclopentanecarboxylic acid. The subsequent reaction of this ketonitrile with anhydrous hydrogen chloride and ethyl alcohol gave an extremely hydroscopic and quite unstable product, presumably the corresponding imino ester hydrochloride. Hydrolysis of this intermediate product gave a reaction mixture containing the presumed keto derivative which was difficult to purify; therefore, an alternative procedure for the preparation of the keto acid was selected. The latter method involved the interaction of cyclopentanone with hippuric acid[4] to form 2-phenyl-4-cyclopentylidene-5-oxazolone (I). Upon alkaline hydrolysis, this oxazolone was converted to α-benzamido-β-cyclopentylideneacetic acid (II) which in turn was further hydrolyzed to yield cyclopentaneglyoxylic (III) as indicated in the accompanying equations.



Although the initial condensation step did not give good yields, most of the unreacted cyclopentanone could be subsequently recovered. Cyclopentaneglyoxylic acid was ultimately isolated by sublimation, and is a hygroscopic substance which was normally converted to its potassium salt for storage and subsequent biological study. Reaction of either the acid or its potassium salt with 2,4-dinitrophenylhydrazine gave identical 2,4-dinitrophenylhydrazones. Hydrogenolysis of the 2,4-dinitrophenylhydrazine derivative[5] produced cy-

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