

A C^{14} TRACER STUDY OF THE FRIEDEL-CRAFTS ALKYLATION

by

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ABSTRACT

Anisole was alkylated with 2-phenylethanol-1- C^{14} and 2-phenylethyl-1- C^{14} chloride respectively, using aluminum chloride as catalyst, to give p-methoxydibenzyl. Radioactivity assay of the p-methoxydibenzyl and of the anisic acid obtained by oxidative degradation with alkaline permanganate showed that a 50% rearrangement of C^{14} from the C-1 to C-2 positions occurred with both alkylating agents.

The reaction may proceed by means of electrophilic attack of a free carbonium ion, or by a nucleophilic attack of anisole on a polarized complex between the alkylating agent and catalyst, if it may be assumed that the observed rearrangement has taken place during the formation of the polarized complex. The possibility exists that the rearrangement may arise from a process separate from the alkylation reaction itself.

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TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS	i
ABSTRACT	ii
HISTORICAL INTRODUCTION	1
THE PROPOSED WORK	19
RESULTS AND DISCUSSION	21
EXPERIMENTAL	29
BIBLIOGRAPHY	35

HISTORICAL INTRODUCTION

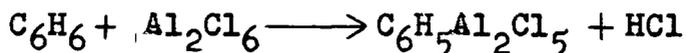
The new interest injected into organic chemistry by Frankland's discovery of organozinc compounds stimulated a series of studies on the action of various metals on alkyl halides, one of which resulted in the discovery of the Friedel-Crafts reaction (20). Prior to the observations of these investigators, several cases of alkylation by means of metals and metallic compounds had been reported.

In 1869, Zincke (90) reported the synthesis of diphenylmethane from benzyl chloride and zinc in benzene solution. In subsequent publications, (91,92,93) Zincke reported similar syntheses. Doebner and Stackmann (16) found that zinc oxide would introduce chloroform or phenyltrichloromethane into phenol to yield salicylaldehyde or o-benzoyl phenol. It was pointed out that zinc chloride was formed during the reaction. As Friedel and Crafts later showed, (19) zinc chloride was the active condensing agent in all of these syntheses. In benzene, the reaction was observed to yield well-defined substances with alkyl halides. Short or long-chained alkylbenzenes were obtained using aluminum chloride together with various alkyl halides. In every case, hydrogen halide was eliminated. In these early papers, it was pointed out that halogenbenzenes would not react in the manner of alkyl halides(21), and that alkyl iodides were too unstable to be generally useful in the reaction (20).

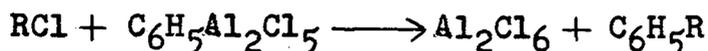
Aluminum chloride and zinc chloride were not the only efficient

condensing agents. Ferrous chloride, ferric chloride, and sodium aluminum chloride were found to be of value. It was further pointed out that only the anhydrous salts were suitable as condensing agents (20).

The mechanism of reactions effected in the presence of aluminum chloride was assumed by Friedel and Crafts to take place through a primary exchange of hydrogen in the hydrocarbon for an Al_2Cl_5 residue:



The postulated hydrocarbon-aluminum chloride complex combined with an aliphatic chloride, thus:



They were unable to isolate the compound $\text{C}_6\text{H}_5\text{Al}_2\text{Cl}_5$, although, at about the same time, Gustavson (26) reported the formation of compounds of the type $\text{Al}_2\text{Br}_6 \cdot 6\text{C}_6\text{H}_6$ and $\text{Al}_2\text{Br}_6 \cdot 6\text{C}_7\text{H}_8$ in Friedel-Crafts reactions of benzene or toluene in the presence of aluminum bromide.

Walker (85) noted the variation in conductivity on the addition of small portions of aluminum chloride to mixtures of ethyl bromide and benzene or naphthalene. Breaks in the curves indicated the formation of compounds $3\text{X} \cdot \text{AlCl}_3$, $2\text{X} \cdot \text{AlCl}_3$, and $\text{X} \cdot \text{AlCl}_3$ where X stands for a molecule of hydrocarbon. Since readings were taken before evolution of hydrogen bromide was noted, the breaks were not due to alkylation of the hydrocarbon. Varying the proportion of hydrocarbon used gave a corresponding variation in conductivity curves.

Working on intermediate complexes in the reaction, Norris

and Wood (55) prepared a ternary complex, $\text{Al}_2\text{Br}_6 \cdot 2\text{C}_6\text{H}_3(\text{CH}_3)_3 \cdot \text{C}_2\text{H}_5\text{Br}$ by shaking together a mixture of mesitylene, ethyl bromide, and aluminum bromide at 0° . Attempts to prepare complexes of definite composition, containing only hydrocarbon and aluminum halide were unsuccessful, and it was concluded that the presence of a third component seems to be necessary for the formation of an isolable complex.

Evidence for existence of a complex between aluminum chloride and alkyl halide is based on conductance studies. Walker (85) noted considerable conductivity with methyl-, ethyl-, and n-propyl iodides as well as with ethyl bromide and chloroform solutions of aluminum chloride and assumed the formation of a compound between the catalyst and alkyl halide.

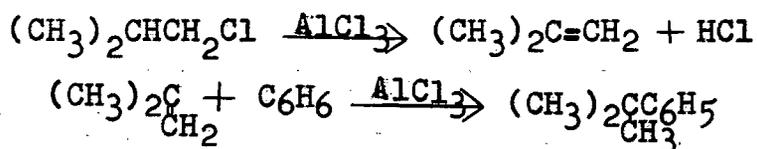
Shortly after the discovery of the Friedel-Crafts reaction, Gustavson (25) found that either isopropyl bromide or n-propyl bromide with benzene and aluminum chloride gave isopropylbenzene. Silva (73) confirmed this, using the two propyl chlorides. Heise (32) was the first to offer a derivative as proof of the structure of the propylbenzene obtained. He observed that at -2° , n-propyl bromide with benzene and aluminum chloride gave n-propylbenzene, identified as its sulfonamide. Genvresse (22) obtained both n-propylbenzene and isopropylbenzene by conducting the reaction at reflux temperature. Konovalof (42) found that below 0° n-propyl chloride gave n-propylbenzene, while from 0° to reflux temperatures it gave mixtures of n-propylbenzene and isopropylbenzene, the degree of isomerization depending on the temperature. A recent study of isomerization (36) has shown it to be dependent on the water content of the catalyst. For propyl

chloride, the effect of aluminum chloride is strongest at -50° to 0° when the water content is minimum.

Higher alkyl halides react similarly to the simple halides. Thus, butyl (27) and amyl (20,23) halides were observed to yield largely branched alkyl substances. The resulting alkyl groups above ethyl are rarely primary except from cycloparaffins (24,38,75) and primary alcohols (38) and under mild conditions from primary esters or halides (5,38). They are usually secondary from a straight chain olefin and other reagents, and tertiary from reactants having a branch adjacent to the functional group. The generalization has been made that alkylation with a primary alkyl halide will yield a secondary alkylbenzene if the alkyl halide contains only primary and secondary carbon atoms, and a tertiary alkylbenzene if it contains a tertiary carbon atom. The extrapolation was even so made (15) as to give the erroneous conclusion that alkylation of benzene with n-butyl chloride yields t-alkylbenzenes. Actually a mixture of n- and sec-butylbenzene is produced. The carbon skeleton is rarely isomerized in alkylation of aromatic hydrocarbons except with neopentyl derivatives. Even with this alkylating agent the product is primarily 2-methyl-3-phenylbutane rather than 2-methyl-2-phenylbutane (59). Isobutyl halides and t-butyl halides seem to be the only alkyl halides which yield t-alkylbenzenes as the major reaction product when aluminum chloride is used as catalyst. However, under vigorous conditions a sec-butyl group has been rearranged to a tertiary structure (52).

Balsohn's (2) discovery of the facile alkylation of benzene

with olefins and Schramm's (70) observation of the formation of olefins during the course of alkylation with alkyl halides led the latter author to propose that alkylation with alkyl halides proceeds through the intermediate formation of an olefin. Thus, the production of t-butylbenzene from isobutyl halide, benzene, and aluminum chloride was assumed to be due to dehydrohalogenation, followed by addition of benzene to the double bond of the resulting olefin. Isobutyl chloride was found to split into butylene and hydrogen chloride by the action of aluminum chloride. Addition of benzene would then result in formation of t-butylbenzene, the phenyl group, in accordance with the Markownikoff rule, attaching itself to the carbon atom which possesses the least number of hydrogen atoms:



The production of sec-butylbenzene from n-butyl chloride was explained in analogous fashion.

Wertyporoch and Firla (86) explained the differences in conductivities of several alkyl halide solutions by assuming a dehydrohalogenation of such alkyl halides as propyl and isopropyl chloride or chlorocyclohexane to the corresponding olefin, and subsequent formation of highly ionized olefin-aluminum chloride complexes. However, previous to these conductivity studies the alkylation by means of olefins, catalyzed by aluminum chloride, has been observed not to take place unless HCl was present and, accordingly Milligan and Reid (49) suggested that this would indicate that in olefin alkylation the reaction proceeds

through the prior formation of an alkyl halide.

If olefins are involved in the mechanism of the rearrangement of alkyl halides, the olefins should act in much the same way as the halides, themselves, but when benzene was alkylated with propylene catalyzed by aluminum chloride (3), boron trifluoride (76,89), hydrofluoric acid (74) and ferric chloride (60), only isopropylbenzene(s) was formed.

Alcohols will alkylate aromatic compounds in the presence of active metal halides or other Lewis acids. Isopropyl alcohol gave isopropylbenzene and secondary butyl alcohol gave secondary butylbenzene. Pentanol-2 was reported to give 2-phenylpentane, while 2-methylbutanol-3 gave 2-methyl-3-phenylbutane. No evidence other than boiling point was given for any of these structures (35). A number of tertiary heptyl alcohols have been shown to react with phenol and aluminum chloride to give t-heptylphenols (34).

Isomerization is common in the reactions of aliphatic alcohols with aromatic hydrocarbons. Thus, while isopropyl alcohol and secondary butyl alcohol reacted with benzene and toluene to give the unisomerized products (83), isoamyl alcohol with 1,2,3,4-tetrahydronaphthalene catalyzed by aluminum chloride, zinc chloride and phosphoric acid respectively, was shown in all cases to yield the tertiary isomer (78). Meyer and Bernhauer (48) alkylated benzene, toluene, phenol, and other aromatic compounds with alcohols in 80% sulfuric acid at 65°. Both isopropyl alcohol and normal propyl alcohol with benzene were reported to give isopropylbenzene. Isobutyl alcohol and tertiary butyl alcohol both yielded tertiary butylbenzene,

identified as its bromo derivative. Both secondary butyl alcohol and normal butyl alcohol gave secondary butylbenzene (38). Nightingale and Smith (52) obtained 1,3-dimethyl-4-s-butylbenzene from xylene and secondary butyl or normal butyl alcohols with sulfuric acid. Neopentyl alcohol with benzene and sulfuric acid produced tertiary amylbenzene, identified as its diacetamino derivative (59). Isoamyl alcohol gave tertiary amylbenzene (38). Normal amyl alcohol yielded a monoamylbenzene fraction of which 60-65% was 2-phenylpentane and 35-40% was 3-phenylpentane, when treated with benzene and 80% sulfuric acid at 70° for six hours. Apparently, 1-phenylpentane was absent. With boron trifluoride, both propyl alcohols gave isopropylbenzene; normal butyl alcohol and secondary butyl alcohol yielded secondary butylbenzene. Isobutyl alcohol and tertiary butyl alcohol gave tertiary butylbenzene (46).

Sowa (46,47,57) proposed that the mechanism for alkylation reactions using boron trifluoride as catalyst, with esters and ethers as well as with alcohols, consists primarily in the formation of an olefinic hydrocarbon to which the aromatic compound then adds under the influence of the catalyst. This was refuted by the work of Price and Ciskowski (62) who found that cyclohexanol, which reacts readily with naphthalene could be recovered quantitatively after treatment with boron trifluoride under conditions considerably more drastic than those required for alkylation. Not even traces of the olefin were detected. Furthermore, it was pointed out that formation of an olefin is impossible in the case of the benzyl group, which may be introduced as readily as any secondary or tertiary alkyl

group. Alkylations of benzene with cycloheptanol and cycloheptene respectively, catalyzed by sulfuric acid, exhibited markedly different behavior. For the monoalkylated fraction, cycloheptanol gave a 40% yield of cycloheptylbenzene while the corresponding yield from cycloheptene was 95%.

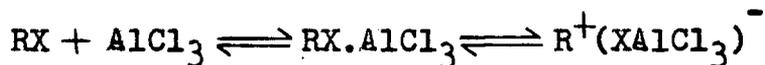
The sole basis for the supposition of intermediate olefin formation is that the products obtained in alkylations can be explained by addition of the aromatic nucleus to the supposed olefin, in accordance with Markownikoff's rule. Numerous authors have endorsed this mechanism. The alkylation of aromatic hydrocarbons with various alcohols catalyzed by aluminum chloride (82), sulfuric acid (46), phosphorus pentoxide (81), phosphoric acid (50,67), zinc chloride (43), and zinc chloride on aluminum oxide (72) have in all cases shown the expected product on the basis of intermediate olefin formation.

The alkylation of benzene with methyl and ethyl alcohols was investigated by Norris and Ingraham (53). They suggested that alcohols react with aluminum chloride to form compounds having the formula $ROAlCl_2$ which decompose when heated to produce RCl plus $AlOCl$, with subsequent reaction of the alkyl halide. This work was extended by Norris and Sturgis (54) who showed the formation of methyl chloride and ethyl chloride from contact of the corresponding alcohol with aluminum chloride. However, when secondary butyl alcohol was placed in contact with aluminum chloride at room temperature for fifteen hours, only traces of alcohol, and no alkyl halide was obtained (63). Tzukervanik (82) suggested that an alkoxy aluminum chloride

forms, followed by decomposition to yield an olefin and hydroxy-aluminum chloride.

It is of significance that diphenylmethyl bromide and phenol, or benzyl chloride with diphenyl, benzene, toluene, o-xylene or mesitylene will yield, at elevated temperatures, without a catalyst, normal condensation products (12,51). This emphasizes the fact that the alkylation by metal halides is essentially an activation reaction occurring when suitable activation of the nuclear hydrogen and aliphatic halogen are realized.

Walker (85) and Dougherty (17) found that certain meta-theoretical reactions occur between certain types of aliphatic halogen compounds in the presence of aluminum chloride. On this basis, the latter investigator suggested that ionization of an alkyl halide is induced by aluminum chloride:

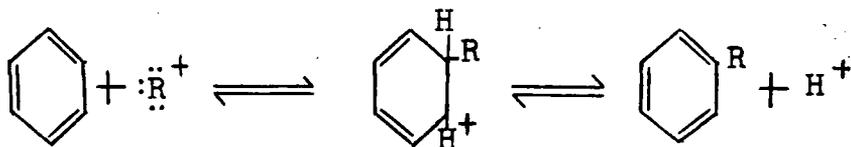


Such an ionization agreed with Prins' theory (64) who assumed that aluminum chloride ionizes benzene in such a way that it produces a phenyl ion and a hydrogen ion. The Friedel-Crafts reaction was then regarded as a reaction of the negative phenyl ion with the positive alkyl ion. Wertyporoch and Firla (86) did not believe that any further activation of the aromatic nucleus was necessary. Substantiation for this belief was obtained from the kinetic study of alkylation by Ulich and Heyne (84) who found definite evidence for the formation of the complex between alkyl halide and metal halide, and in fact were able to determine the equilibrium constant for its formation. The rate of alkylation was directly proportional

to the concentration of this complex and of the hydrocarbon, indicating that any further function of the catalyst in activating the latter is negligible.

Fairbrother (18) proposed that an initial and necessary step in the reaction is the transition of the mainly covalent carbon-halogen bond of the alkyl halide into an ionic bond through complex formation with the metal halide catalyst. Evidence for his proposal was the observed radio-isotopic exchange of halogen atoms between the organic and inorganic halides, an exchange which has recently been demonstrated to also occur between naphthyl halides $C_{10}H_7X$ and stannic halides SnY_4 (31), and by the observed large increment in dielectric polarizability when aluminum bromide and ethyl bromide were dissolved together in cyclohexane. In contrast, a mixture of bromobenzene and aluminum bromide showed no increment, the polarizability of the mixture being very nearly the sum of the partial polarizabilities of its components.

Price (61) concluded that substitution proceeds through an electron-deficient intermediate which acquires an electron pair from a double bond of the aromatic nucleus:



Rearrangement of alkyl halides by aluminum chloride was explained by Whitmore's theory of rearrangements (87), i.e., the electron deficiency in the alkyl ion migrates from a primary to a secondary to a tertiary carbon atom, to give a

carbonium ion of minimum energy.

Justification of the ionic theory of reaction has been advanced by stereochemical evidence. An alkylation of benzene with optically active secondary butyl alcohol, catalyzed by aluminum chloride and boron trifluoride respectively, gave a product which was completely racemized in the first case and over 99% racemized in the second (63). This work was substantiated and extended by Burwell and Archer (14) to hydrofluoric acid and phosphoric acid catalyzed reactions. They showed that the alcohol could not have been racemized before it reacted since with phosphoric acid and alcohol alone the recovered alcohol had the same rotation as the original. However, with hydrofluoric acid and alcohol alone, the recovered alcohol was 23% racemized (13). The extensive racemization was attributed to the result of a planar carbonium ion intermediate. Racemization of optically active α -phenylethyl chloride has been observed by the action of various metal salts which act as catalysts for the Friedel-Crafts reaction (4).

While the ionic mechanism of alkylation was at one time widely accepted, several points arose which could not be satisfactorily explained by such a scheme. Pearlson and Simons (58) were able to calculate the rate of reaction between toluene and tertiary butyl chloride as catalyzed by hydrogen fluoride and showed that the maximum rate so calculated on the basis of formation of an intermediate carbonium ion, was slower than the experimental rate to such an enormous extent, a factor of 10^{11} , that the assumption of intermediate carbonium ion formation was untenable. These authors also demonstrated the very

similar effects on promotion of the reaction by the very dissimilar compounds, water, methanol, diethyl ether, and hexamethylacetone and pointed out that on the basis of a mechanism which requires two or more consecutive reactions and active intermediates, it is difficult to explain the similarity of the observed effects. The proposal of a one-step condensed phase, catalyzed, and promoted reaction as the essential factor in the mechanism was shown to be satisfactory from kinetic considerations and reasonable from energy considerations.

A recent investigation of the alkylation of phenols with optically active α -phenylethyl chloride in acetone-potassium carbonate medium showed an observed inversion of configuration and high (at least 64%) retention of optical purity. It was suggested that the major reaction path is a nucleophilic displacement of halogen by phenoxide ions (28). It was further demonstrated that racemization occurred independently of alkylation at a rate comparable with it (30).

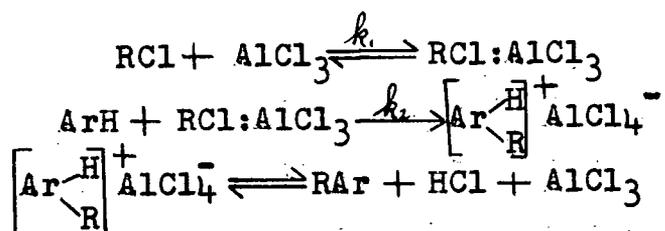
The independence of rearrangement and alkylation has been demonstrated. Contact of propyl chloride with aluminum chloride has been observed to cause nearly complete isomerization to isopropyl chloride in five minutes, considerably less time than is required for an alkylation with this reagent in which at least some normal propyl benzene is usually formed. When propyl chloride was stirred with $\text{AlCl}_2\text{HSO}_4$, no isomerization occurred. Yet, when benzene was alkylated with propyl chloride with this catalyst, the yield of propylbenzenes consisted of 22% normal propylbenzene and 78% isopropylbenzene (79).

In a reaction between tertiary butyl chloride and phenol,

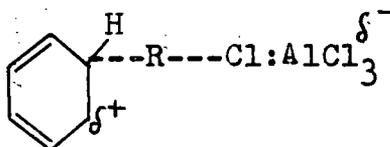
the activation energy was determined to be 13-17 kcal./mole. For a carbonium ion mechanism it was calculated that the energy required would be 28 kcal./mole. In addition, a very high order rate dependency upon concentration of phenol was observed (29).

Topchiev (80) studied the relationship between catalyst activity and electrical conductivity of various Friedel-Crafts catalysts. The absence of any correlation led to the conclusion that complex formation with the catalyst rather than carbonium ion formation was the source of catalytic action.

Brown and Grayson (7) concluded that in view of the supposed very high reactivity of carbonium ions and the observed progression of various alkylation reactions at moderate, measurable rates, that the first step of the reaction, the ionization of the alkyl halide must represent the rate-determining stage and therefore rate of reaction should be independent of the concentration or nucleophilic characteristics of the aromatic constituent undergoing alkylation. These authors were able to demonstrate that for alkylations with benzyl chloride, the rate was dependent both on the structure and concentration of the aromatic reactant and interpreted their results as being more consistent with a mechanism involving a rate-determining nucleophilic attack by the aromatic component on a polar benzyl halide-aluminum chloride compound.



The transition state in the displacement step was represented as a σ complex containing a partially formed carbon-carbon bond and a partially broken carbon-chlorine bond.



This theory was tested by extension of the study to the alkylation of benzene and toluene with various methyl halides with aluminum bromide catalyst. It was found that neither the isomer distribution nor relative reactivities were independent of the halide used(8).

With increased branching of the alkyl halide there should be observed an increased tendency for the formation and reaction of ionic intermediates. In order to obtain evidence on this point, Brown and Jungk (9) undertook an examination of the alkylation of aromatic compounds with ethyl, isopropyl, and tertiary butyl bromides. The results indicated that the rates of alkylation, isomerization, and disproportionation all increase sharply with increased branching of the alkyl group. In view of the fact that stability of carbonium ions also increases with increased branching, the results indicate carbonium ion formation. However, if carbonium ions are involved in the alkylation reaction, the toluene/benzene reactivity ratio should be expected to increase with increasing stability of the carbonium ion (10). The reactivity ratio as determined by Brown and Jungk showed the opposite trend. In contrast, it was pointed out that if the reaction were primarily a nucleophilic displacement by the aromatic component, the rate

of alkylation would be expected to decrease in the order: methylation > ethylation > isopropylation > t-butylation. The results showed the opposite trend.

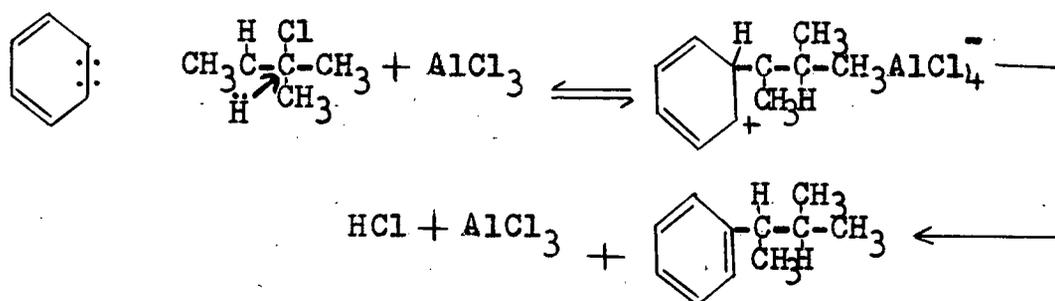
These authors maintain that the transition state is best described in terms of a nucleophilic attack by the aromatic on a strongly polarized alkyl bromide-aluminum bromide addition compound and in accordance with the interpretation of Winstein (88) suggested that as the alkyl group is changed to ethyl, isopropyl, and finally to tertiary butyl, the carbon-halogen bond must become more and more ionic in the transition state with a correspondingly decreasing covalent contribution from the aromatic, and expected at some point in the series to approach the "limiting" condition with the reaction proceeding through an essentially free carbonium ion.

Several anomalous results with regard to the structure of products has also cast doubt on the theory of intermediate carbonium ion formation. The ionic mechanism does not account for the high yields of normal propylbenzene obtained in the alkylation of benzene with normal propyl chloride (38) and the sole formation of the normal propyl isomer in the alkylation of benzene with normal propyl alcohol and aluminum chloride. Moreover, it was found that neopentylbenzene is formed in the alkylation of benzene with neopentyl alcohol and aluminum chloride (59).

If the carbonium ion theory is valid, then it is to be expected that alkylation with tertiary halides should yield exclusively tertiary alkyl benzenes. However, not more than about 20% of the pentylbenzene obtained with tertiary pentyl

chloride at 25-30° was tertiary pentylbenzene, the remainder being a mixture of isomeric compounds believed to consist chiefly of 1-phenyl-2-methylbutane and 2-methyl-3-phenylbutane (37). On the other hand, when either aluminum chloride dissolved in nitromethane or ferric chloride was used as catalyst, the product consisted of very pure tertiary pentylbenzene. The non-formation of tertiary alkylbenzenes as the principal product in the presence of aluminum chloride has been shown to be the general rule rather than the exception. Alkylation of benzene with a tertiary hexyl chloride, 2-chloro-2,3-dimethylbutane, in the presence of aluminum chloride at 1° resulted in a 62% yield of hexylbenzene which consisted of the secondary hexylbenzene, 2,2-dimethyl-3-phenylbutane, mixed with about 10% of the tertiary isomer, 2,3-dimethyl-2-phenylbutane. This rearrangement also occurred with zirconium chloride. Again, when the reaction was carried out at room temperature in the presence of ferric chloride or of a nitromethane solution of aluminum chloride, the product was the practically pure tertiary isomer (69).

The formation of the secondary isomer can be explained without using carbonium ions by assuming that the reaction occurs by way of a concerted bimolecular nucleophilic displacement reaction. It is suggested that substitution takes place at the secondary carbon atom rather than the tertiary atom because backside attack by the approaching phenyl group is more difficult at a tertiary carbon atom.



The displacement was expected to proceed through a bimolecular reaction involving the reaction of the alkyl chloride with a complex of benzene and aluminum chloride (68) or of benzene with a complex of the alkyl chloride and catalyst (6).

The proponents of this theory (69), however, themselves objected to it on the basis that such a displacement mechanism involves two simultaneous SN displacements, i.e., two Walden inversions on adjacent carbon atoms. The benzene displaces a hydride ion from one carbon atom and the hydride ion displaces the chloride ion from the adjacent carbon atom. Since the bulky entering and leaving groups are adjacent, reaction by this mechanism was stated to be unlikely. The authors suggested that in view of the ease with which tertiary alkyl ions are believed to be formed in the presence of catalysts of the Friedel-Crafts type, that a more likely mechanism was the intermediate formation of the tertiary alkylbenzene by reaction with the tertiary alkyl ion, followed by isomerization of this intermediate.

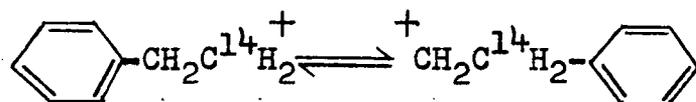
A recent investigation of the alkylation of benzene with ethyl- β -C¹⁴ chloride showed that there was no isomerization of the ethyl group (66). Ethylbenzene was prepared by the interaction of ethyl- β -C¹⁴ chloride, benzene, and aluminum chloride. Oxidation of the purified ethylbenzene gave non-radioactive benzoic acid, indicating that no isomerization of

the ethyl group had occurred during condensation. On the other hand, when ethyl- β -C¹⁴ chloride was placed in contact with aluminum chloride for one hour at room temperature, distilled and then used to alkylate benzene by the same procedure, almost complete isomerization was indicated by an almost equal distribution of C¹⁴ between the two positions. It was pointed out that while the nucleophilic displacement mechanism was the most probable, the alternative mechanism of formation of an intermediate carbonium ion could not be excluded since the possibility exists that the ethylcarbonium ion is produced but no hydrogen shift occurs before the ethyl group reacts with the aromatic nucleus. The formation of an intermediate olefin is definitely excluded.

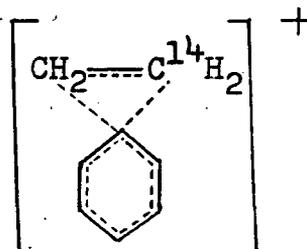
THE PROPOSED WORK

In view of the multiplicity of theories and interpretations set forth on the Friedel-Crafts alkylation, no proposed reaction mechanism can yet claim general and unequivocal acceptance. In the hope of shedding further light on the mechanism of this reaction, a study of the alkylation of anisole with 2-phenylethyl- C^{14} chloride and 2-phenylethanol- C^{14} in the presence of aluminum chloride was undertaken.

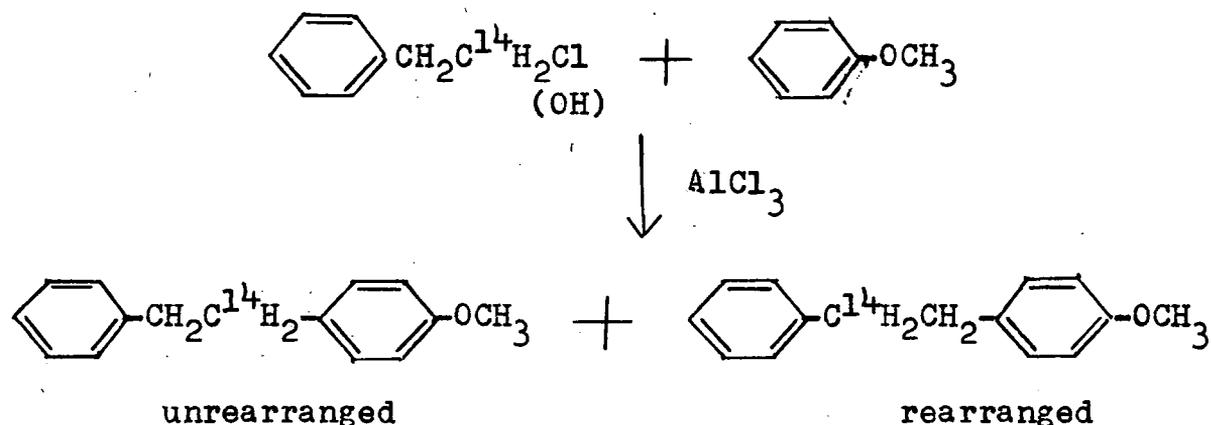
In reactions where carbonium ions are likely involved as intermediates, rearrangements of C^{14} -labeled atoms from C-1 to C-2 positions in the phenylethyl cation have been observed, either through the 1,2-phenyl shift:



or its equivalent, a "non-classical" phenonium ion (44,45,65).



Should the alkylation reaction under study involve the carbonium ion, analogous rearrangements should be observable:



Permanganate oxidation of the alkylation product, *p*-methoxydibenzyl, should afford anisic and benzoic acids. From the C^{14} content of these degradation products, the degree of rearrangement, if any, may be calculated.

In the present study, pure benzoic acid could not be isolated after the oxidative degradation. The degree of rearrangement was determined from the radioactivity assays of *p*-methoxydibenzyl and anisic acid, the activity theoretically present in the benzoic acid being calculated by difference.

RESULTS AND DISCUSSION

2-phenylethanol-1- C^{14} was prepared by the lithium aluminum hydride reduction of phenylacetic acid-1- C^{14} (56).

Conversion of the alcohol to the chloride was effected with thionyl chloride in pyridine (45). That all the C^{14} activity was located at the C-1 position was shown by the permanganate oxidation of both the alcohol and the chloride to give non-radioactive benzoic acid.

The alkylation of anisole with either 2-phenylethyl-1- C^{14} chloride or 2-phenylethanol-1- C^{14} was effected using an excess of anisole as solvent and slightly over one and a half molar equivalents of anhydrous aluminum chloride at 100° for several hours. The *p*-methoxydibenzyl obtained was assayed for radioactivity and then oxidized with potassium permanganate to yield anisic acid.

As a check on the total activity, the 2-phenylethyl-1- C^{14} chloride was converted to hydrocinnamic acid whose radioactivity was found to be essentially identical with that of the corresponding *p*-methoxydibenzyl. In the alcohol runs, the radioactivity of the phenylurethan of 2-phenylethanol-1- C^{14} was also shown to be the same as the corresponding *p*-methoxydibenzyl products.

If there were no rearrangement in the reactions studied, 100% of the total radioactivity in the *p*-methoxydibenzyl should be recovered in the anisic acid. The results from duplicate chloride and alcohol runs are tabulated in Table I, the % rearrangement being the difference between 100% and the % of total activity actually recovered in the anisic acid.

TABLE I

REARRANGEMENTS IN THE ALKYLATION OF ANISOLE

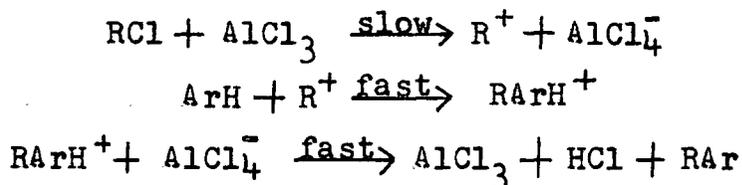
Alkylating Agent	Compound Counted ^a	Observed Activity ^b (cts/min/sample)		Corrected Activity ^c (cts/min/mole)		% Activity in Anisic Acid		% rear-rangement	
		Run I	Run II	Run I	Run II	Run I	Run II	Run I	Run II
		$C_6H_5CH_2C^{14}H_2OH$	$C_6H_5NHCOOCH_2CH_2C_6H_5$	590	590	8850	8850		
	<i>p</i> - $CH_3OC_6H_4CH_2CH_2C_6H_5$	594	592	8910	8880				
	<i>p</i> - $CH_3OC_6H_4COOH$	567	565	4536	4520	50.9	50.8	49.1	49.2
$C_6H_5CH_2C^{14}H_2Cl$	$C_6H_5CH_2CH_2COOH$	1929	1010	17360	9090				
	<i>p</i> - $CH_3OC_6H_4CH_2CH_2C_6H_5$	1152	595	17280	8925				
	<i>p</i> - $CH_3OC_6H_4COOH$	1073	537	8580	4296	49.7	48.2	50.3	51.8

- (a) All compounds were converted to barium carbonate and counted as infinitely thick samples of constant geometry in a windowless gas flow counter.
- (b) All samples were counted for a sufficient length of time to insure statistical deviation of not more than 1-2 %.
- (c) Corrected for the dilution by non-labeled C atoms. Equals the observed activity multiplied by the number of C atoms in the compound counted.

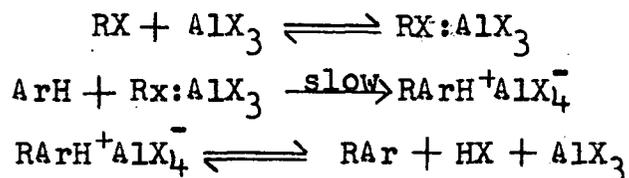
These results clearly indicate that essentially 50% rearrangement has taken place in the alkylation of anisole, in the presence of aluminum chloride, by both 2-phenylethyl-1-C¹⁴ chloride and 2-phenylethanol-1-C¹⁴. Such a complete equilibration of the labeled atoms in the C-1 and C-2 positions of the original chloride and alcohol may best be accounted for by the assumption that the phenylethyl cation is involved at some stage of the reaction process or processes, the rearrangement being the result of a 1,2-phenyl shift or the formation of a phenonium ion as previously indicated. It is very tempting, therefore, to simply conclude that the Friedel-Crafts alkylation of anisole with 2-phenylethyl chloride or 2-phenylethanol proceeds by way of a carbonium ion mechanism, i.e., the alkylating agent first gives rise to the alkyl cation which then effects an electrophilic attack on the aromatic hydrocarbon to give the final product. However, the observed results merely demonstrate that under the experimental conditions used, there is a rearrangement of the C¹⁴-labeled atoms which most probably results from the formation of the phenylethyl cation. These findings do not indicate what exact role such a cation would play in the Friedel-Crafts alkylation.

It is a fact that, in many cases, rearranged products have been obtained from Friedel-Crafts alkylation reactions (20,22,23,25,27,32,36,38,42,48,52,59,78). These rearrangements are generally explained by assuming the formation of a carbonium ion from the alkylating agent (61) followed by subsequent rearrangement to a more stable carbonium ion (87). By analogy with generally accepted cationic organic reaction processes (1),

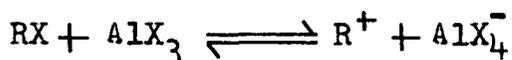
one may assume that in a carbonium ion mechanism for the Friedel-Crafts alkylation, the rate determining step may be formation of the ion, the subsequent reaction of the cation with the aromatic hydrocarbon being fast:

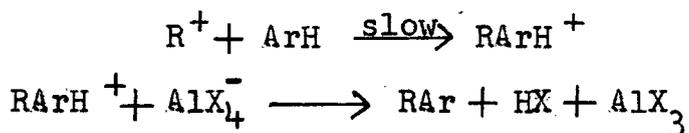


For such a mechanism, one would expect that the overall rate of reaction would be independent of the concentration of the aromatic hydrocarbon. Brown and co-workers recently found that in the Friedel-Crafts alkylation with several benzyl, methyl and ethyl halides, the reaction rate showed first order dependency on the alkyl halide, aluminum halide, and aromatic hydrocarbon (7,41). Consequently, these workers suggested that the Friedel-Crafts reaction of aromatic nuclei with primary halides may proceed by a displacement mechanism, with the aromatic contributing to the breaking of the carbon-halogen bond in the transition state:



On the other hand, Hine (33) has pointed out that the observed kinetic data of Brown et al. may also be accounted for by assuming a rate controlling attack of the carbonium ion or ion pair on the aromatic ring:





In their most recent papers, Jungk and Brown (40,41) pointed out that the rates of alkylation of benzene increase sharply with increased branching of the alkyl groups in the series where R represents methyl, ethyl, isopropyl and tertiary butyl groups. They therefore proposed that methylation proceeds essentially by a displacement mechanism involving nucleophilic attack by the aromatic nucleus on the polarized alkyl halide-aluminum halide addition compound. As the alkyl group becomes better able to accommodate a positive charge, i.e., methyl < ethyl < isopropyl < tertiary butyl, there will be an increase in the amount of ionic character in the carbon-halogen bond in the transition state, accompanied by a decrease in the nucleophilic contribution by the aromatic. They speculated that isopropylation may represent the limiting case where the aromatic will no longer contribute significantly to the breaking of the carbon-halogen bond. In such an event, the mechanism will become essentially one of the free carbonium ion type and the reaction rate will therefore be independent of the aromatic hydrocarbon. However, Brown and co-workers were unable to verify such conjectures, for they were not able to make detailed kinetic measurements of the very fast isopropylation and tertiary butylation reactions.

To interpret the presently observed rearrangement of the C^{14} -labeled atoms in the phenylethylation of anisole, firstly, one may subscribe to the ionic mechanism as suggested by Hine.

On the other hand, if one were to choose a nucleophilic displacement mechanism as suggested by Brown, one may rationalize the observed rearrangement by assuming that the rearrangement may have taken place during the formation of the polarized complex between the alkylating agent and the catalyst.

There is a third possibility which may also account for the present results. One may postulate that rearrangements in the Friedel-Crafts alkylation arise from a process separate from the alkylation reaction itself. The fact that the alkylation of benzene with ethyl- β - C^{14} chloride results in no rearrangement, whereas simple contact of this chloride with aluminum chloride results in the complete equilibration of the labeled atoms (66) appears to be quite dramatic evidence that alkylation and rearrangement can be independent of each other. Rearrangement of normal propyl to isopropyl chloride by contact with aluminum chloride has also been demonstrated (79). Moreover, the work of Hart and others (28,30) has shown that in the alkylation of phenol with optically active α -phenylethyl chloride, racemization occurred independently of alkylation, an appreciable part of the observed loss of optical purity being due to racemization prior to alkylation.

On the basis that separate processes account for rearrangement and alkylation in the Friedel-Crafts alkylation reactions, the 50% rearrangement observed in the present studies may be visualized as resulting from the action of aluminum chloride on the 2-phenylethyl-1- C^{14} chloride or 2-phenylethanol-1- C^{14} . The aluminum chloride, being a strong Lewis acid, promotes the formation of the labeled phenylethyl cation,

affording an opportunity for the 1,2-phenyl shift. The rate of this catalyst promoted rearrangement must be faster or at least comparable to the rate of alkylation; thus, the phenylethyl system would have the opportunity of attaining complete equilibration before yielding the final alkylation product. As a further test of such a postulate, possible rearrangement of 2-phenylethyl-1-C¹⁴ chloride and 2-phenylethanol-1-C¹⁴ on simple contact with aluminum chloride is currently being investigated.

In interpreting their results obtained from ethyl- β -C¹⁴ chloride, Roberts et al. (66) suggested that the non-rearrangement in the ethylation of benzene may mean either a displacement mechanism without the formation of the ethyl cation, or that a carbonium ion mechanism is operative but that no hydride shift takes place in the ethyl cation during the ethylation of benzene. However, since these same workers showed that contact of ethyl- β -C¹⁴ chloride with aluminum chloride alone resulted in the complete equilibration of the C¹⁴ activity in both α and β carbons, one may visualize, on the basis of separate processes governing the rearrangement and alkylation reactions, that in this case, the alkylation reaction is faster than the aluminum chloride promoted rearrangement. Non-rearranged ethylbenzene is therefore formed before the catalyst can effect a rearrangement of the labeled ethyl system. Brown and Jungk (8) have found that the rate of alkylation of benzene with methyl iodide is much slower than that with methyl chloride. Should the same difference exist between ethyl chloride and iodide, it may be possible that, if rearrangement and alkylation do take place by separate processes,

ethylation of benzene with ethyl- β -C¹⁴ iodide may lead to some rearranged product, because the expected slower rate of ethylation with the iodide would allow the catalyst promoted rearrangement to take place, at least to some extent, before the final formation of the end alkylation product. The work with C¹⁴-labeled ethyl iodide is therefore also under current investigation (39).

EXPERIMENTAL2-Phenylethanol-1-C¹⁴

A solution of 5.7 gm (0.15 moles) of lithium aluminum hydride in 200 ml of sodium-dried ether was placed in a one litre three-necked flask equipped with condenser, dropping funnel, and mercury-sealed stirrer. Through the dropping funnel, a solution of 13.9 gm (0.10 moles) of phenylacetic acid-1-C¹⁴ was added at such a rate as to maintain gentle reflux. One half hour after complete addition, the reaction vessel was immersed in an ice-bath and water added dropwise to the contents of the flask in order to decompose excess anhydride. With continued stirring, 200 ml of dilute sulfuric acid was added, when a clear solution resulted. The organic layer was then separated, the aqueous layer extracted with three 25 ml portions of ether and the combined ethereal solutions washed with sodium bicarbonate solution and water. After drying over anhydrous magnesium sulfate, the ether was removed by simple distillation and the residue distilled under reduced pressure. Average yield for the various trial and radioactive runs was 10.9 gm (88%), b.p.₂₁ 114.5-115.5°. * Lit. (56) yield 92%, b.p.₁₈ 112°. To recover traces of radioactive product, 10 gm of phenylethanol was added to the pot, distilled, and combined with the product.

Oxidation of 2-Phenylethanol-1-C¹⁴

Phenylethanol-1-C¹⁴ (1 gm), together with 8 gm potassium permanganate, 5 gm sodium hydroxide and 50 ml of distilled water was placed in a 125 ml erlenmeyer flask and heated on

* All boiling points are uncorrected

All melting points are corrected for stem exposure

a boiling water bath for three hours, with frequent stirring. The flask and contents were then cooled, filtered by suction, and the precipitate of manganese dioxide washed thoroughly with distilled water. The combined filtrate and washings were acidified with dilute sulfuric acid and treated with solid sodium bisulfite until the color of the permanganate was discharged. The resulting mixture was extracted repeatedly with ether, the extracts dried, the ether removed by evaporation and the residue recrystallized from water. The yield of benzoic acid was 0.70 gm (70%), m.p. 120-121°. Lit. (44) yield (70-80%), m.p. 121°.

Phenylurethan of 2-phenylethanol-1-C¹⁴

A mixture of 1 gm 2-phenylethanol-1-C¹⁴, 1 gm phenylisocyanate and 2 drops of pyridine were placed in a 5 ml beaker and heated on a low temperature hot plate for twenty minutes. The mixture was then cooled by refrigeration and the resulting solid transferred to a funnel and washed ten times with light petroleum ether. Recrystallization from chloroform-petroleum ether yielded 1.7 gm (82%) of product, m.p. 78.5-80°. Lit. (44) 79-80°.

2-Phenylethyl-1-C¹⁴ chloride

A solution of 17.5 gm of 2-phenylethanol-1-C¹⁴ in 80 ml of pyridine was placed in a 500 ml flask and cooled in an ice-bath. Thionyl chloride (35 ml) was added dropwise over a period of one-half hour. The reaction mixture was then heated on a boiling water bath for 10 minutes. The resulting black solution was allowed to stand at room temperature for one-half

hour and then poured slowly, with rapid stirring, into an ice-water mixture. The product was extracted with four 100 ml portions of ether and the combined extracts washed successively with distilled water, dilute hydrochloric acid, saturated sodium bicarbonate solution, and distilled water. After drying over anhydrous magnesium sulfate, the ether was removed by distillation and the residue distilled under reduced pressure. Average yield for the various runs was 13.1 gm (65%), b.p.₁₃ 82-83°. Lit. (45) yield 66%, b.p.₁₇ 85-87°. To recover traces of radioactive product, 10 gm of phenylethyl chloride was added to the pot, distilled, and combined with the product.

Oxidation of 2-Phenylethyl-1-C¹⁴ chloride

2-phenylethyl-1-C¹⁴ chloride (3 gm) was placed in a 500 ml flask attached to a reflux condenser. The chloride was heated with a free flame to the boiling point and then a saturated solution of potassium permanganate was added slowly. After a total of 10 gm of permanganate as a saturated solution had been added, the mixture was refluxed for 30 minutes, cooled, filtered by suction, and the precipitate of manganese dioxide washed thoroughly with distilled water. The combined filtrate and washings were acidified and treated with solid sodium bisulfite until clear. The resulting solution was extracted repeatedly with ether, the combined extracts dried over anhydrous magnesium sulfate and evaporated to dryness. The solid residue was taken up in dilute sodium hydroxide and washed twice with ether. The alkaline solution was then acidified with dilute hydrochloric acid, the resulting mixture extracted with ether

and the combined extracts dried over anhydrous magnesium sulfate. Removal of the ether and recrystallization of the residue from water yielded 1.6 gm (61%) of benzoic acid, m.p. 121-122°.

Hydrocinnamic acid-2-C¹⁴

A mixture of .68 gm (.028 moles) magnesium turnings, 1.5 gm (.011 moles) 2-phenylethyl-1-C¹⁴ chloride and 3 ml of ether was placed in a 200 ml three-necked flask equipped with condenser, mercury-sealed stirrer and dropping funnel. The mixture was stirred and heated gently to initiate reaction. A solution of 2.5 gm (.017 moles) of 2-phenylethyl-1-C¹⁴ chloride dissolved in 15 ml of ether was added dropwise at just the rate to maintain gentle reflux (20 minutes for addition). The mixture was then gently refluxed for one hour and the resulting Grignard reagent poured slowly onto 10 gm of "dry ice". Stirring was continued until all of the "dry ice" had evaporated and a stiff mass resulted. A mixture of 10 gm of crushed ice and 8 ml of dilute hydrochloric acid was then added and the mixture stirred until the solid had decomposed. The resulting mixture was extracted with three 10 ml portions of ether. The combined extracts were washed with water and then extracted with three 10 ml portions of 5% sodium hydroxide. The combined alkaline extracts were then reacidified with dilute hydrochloric acid. This solution was then extracted with ether, the extracts dried, the ether removed and the residue recrystallized from light petroleum ether. The yields of hydrocinnamic acid for the various runs averaged 2.0 gm (47%), m.p. 48-49°. Lit. (45) yield 70-80%, m.p. 48-49°.

Alkylation of Anisole with 2-Phenylethanol-1-C¹⁴

Anisole (130 gm, 1.20 moles) was placed in a three-necked 250 ml flask equipped with stirrer, dropping funnel and condenser. Aluminum chloride (30 gm, 0.23 moles) was added and the mixture stirred until solution was effected. Phenylethanol-1-C¹⁴ (17 gm, 0.14 moles) was added and the resulting solution, with vigorous stirring, heated on a boiling water bath for eight hours. The wine-coloured solution was then poured into an ice-hydrochloric acid mixture, the organic layer separated and the aqueous layer extracted with two 100 ml portions of ether. The combined organic solutions were then extracted with five 100 ml portions of 5% sodium hydroxide (until acidification of the alkaline layer after extraction no longer produced an appreciable precipitate). The organic solution was then reacidified with dilute hydrochloric acid and washed successively with dilute sodium bicarbonate solution and water. After drying overnight over anhydrous magnesium sulfate, the solvents were removed and the residue fractionated in vacuo. The product was collected over the range 157-163° at a pressure of 6 mm. Lit. (77) b.p.g 166-167°. On storing for several days in a refrigerator, the liquid product partially solidified. It was then recrystallized three times from 95% methanol. Yields of p-methoxydibenzyl for the various runs ranged between 2.82 and 2.96 gm (9.7-10.2%), m.p. 59.5°-60.5°. Lit. (77) 60-61°, (11) 61-62°.

Alkylation of Anisole with 2-Phenylethyl-1-C¹⁴ chloride

Anisole (130 gm, 1.2 moles) was placed in a three-necked

250 ml flask equipped with mercury-sealed stirrer, dropping funnel and condenser. Aluminum chloride (30 gm, 0.23 moles) was added and the mixture stirred until solution was effected. 2-phenylethyl-1-C¹⁴ chloride (19.3 gm, 0.14 moles) was then added and, with continued vigorous stirring, the resulting mixture heated on a boiling water bath for six hours. The reaction mixture was hydrolyzed and worked up as described in the alcohol run. Yields of p-methoxydibenzyl for the various runs ranged between 2.63 and 2.86 gm (9.0-9.8%), m.p. 59.5-60.5°.

Oxidation of p-Methoxydibenzyl

In a two-necked 1000 ml flask equipped with condenser and stirrer were placed 500 ml of 3.2% potassium permanganate solution, 3.5 gm potassium hydroxide, and 2.0 gm of p-methoxydibenzyl. The mixture was refluxed, with stirring, for 120 hours, after which the flask and contents were cooled and the manganese dioxide filtered off by suction. The water white filtrate was slowly evaporated to a volume of about 200 ml before acidifying with dilute sulfuric acid. The resulting mixture was extracted repeatedly with ether and the combined extracts dried and evaporated to dryness. The residue was dissolved in dilute sodium hydroxide, washed with ether, and reacidified. Repeated extraction with ether, followed by drying and removal of the ether and two recrystallizations of the resulting residue yielded pure anisic acid, m.p. 182.5-183.5°. Lit. (71) 184°. Yields for the various runs averaged 0.15 gm (10%).

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