

1938

Some anomalous Friedel-Crafts reactions

Joseph Abraham Valentine Turck Jr.
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SOME ANOMALOUS FRIEDEL-CRAFTS REACTIONS

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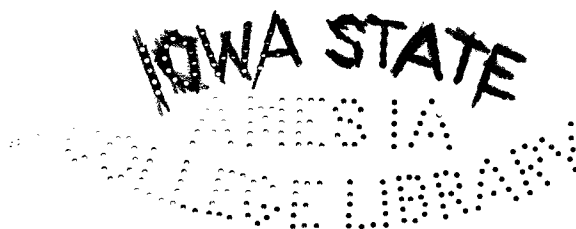
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Joseph A. V. Turck, Jr.

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry



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1938

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SOME ANOMALOUS FRIEDEL-CRAFTS REACTIONS

INTRODUCTION

Alkylation of aromatic nuclei by the Friedel-Crafts reaction holds an exceptionally prominent place in organic synthesis but its irregularity has gradually resulted in branding the reaction as unreliable. Since the first experiments conducted by Friedel and Crafts (1) the scope of this phase of the reaction bearing their names has spread till it includes a large variety of alkylating agents, catalysts, solvents and types of compounds to be alkylated. Kränzlein's book, Aluminiumchlorid in der organischen Chemie (2), and an article in Chemical Reviews by Calloway (3) give a good idea of the versatility of the Friedel-Crafts reaction. The second main division of this general reaction, acylation, is considerably more predictable. Also the mechanism of the latter is better understood. While more work has been done on acylation, a great deal of it has been just routine chemistry. That is, the comparative smoothness and dependability of acylation reactions have been conducive to their auxiliary use in the study of new compounds,

(1) Friedel and Crafts, Compt. rend., 84, 1392, 1450 (1877).

(2) Kränzlein, "Aluminiumchlorid in der organischen Chemie", 2d ed., Verlag Chemie, G. M. B. H., Berlin, 1932,

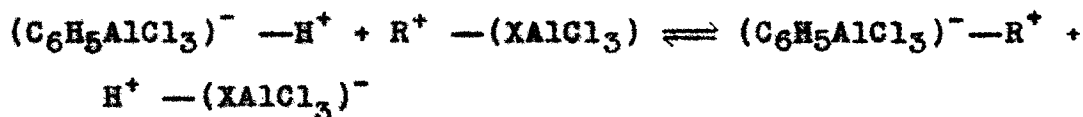
(3) Calloway, Chem. Rev., 17, 327 (1935).

e.g., preparation of derivatives, etc. On the other hand most of the work reported on alkylation is concerned basically with the reaction itself. This is to be expected when many unusual results are obtained, in addition to the variety of normal products. In alkylation, polysubstitution frequently occurs either by direct introduction of alkyl groups or secondarily through disproportionation. On the other hand polyacylation is a very rare case, and then it is apparently limited to activated aromatic nuclei and stops at disubstitution. Disproportionation is a process confined entirely to the alkylation subdivision of the Friedel-Crafts reaction. Rearrangement of the entering alkyl group is the rule in alkylation, but an analogous phenomenon is unknown in acylation. A third contrast which is not nearly as common as the two just mentioned, but certainly a distinct one, is the cleavage of carbon chains occasionally observed in alkylation, but unknown in acylation. The difference in the amount of catalyst usually required in these two reactions is common knowledge and it is only mentioned here as an additional point of distinction. The latter difference is linked with the difference that exists in the mechanisms. In spite of considerable study of the mechanisms the picture is not a clear one and an air of vagueness prevails, especially in the case of alkylation. However, there is a clearly recognizable difference in the mechanisms of

alkylation and acylation.

Mechanisms

Briefly the difference in mechanisms of alkylation and acylation is in the nature of the intermediate addition complexes formed in the two reactions. Egloff, et al. (3a) give considerable detail on mechanisms of alkylation and reactions incidental to alkylation. The octet theory of valence is used to give a closer and perhaps more exact viewpoint of these mechanisms. The works of Schroeter (4), Wohl and Wertyporoch (5), Ipatieff, Komarewsky and Grosse (6), Dougherty (7), and Kharasch (8) are outstanding on this subject. The mechanism for a truly catalytic Friedel-Crafts reaction is illustrated as follows by Dougherty (7):



(3a) Egloff, Wilson, Hulla and Van Arsdell, Chem. Rev., 20, 345 (1937).

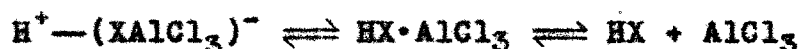
(4) Schroeter, Ber., 57, 1990 (1924).

(5) Wohl and Wertyporoch, ibid., 64, 1357 (1931).

(6) Ipatieff, Komarewsky and Grosse, J. Am. Chem. Soc., 57, 1722 (1935).

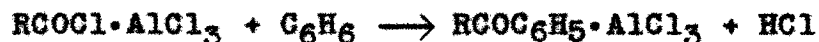
(7) Dougherty, ibid., 51, 576 (1929).

(8) Kharasch, J. Chem. Education, 5, 404 (1928); 8, 1703 (1931).



Olivier (9) would seem to refute this mechanism since he claims that benzene forms no addition product with aluminum chloride. Further evidence is offered, in the field of alkylation, in favor of Böeseken's (10) theory. The latter postulates that in the Friedel-Crafts reaction the formation of definite addition products has nothing to do with the catalytic action of the aluminum chloride. According to Böeseken this formation of addition compounds must be considered a poisoning of the catalyst rather than an explanation of the acceleration of the reaction as some would infer (7).

In acylation there is no question about the formation of complexes and the reaction is universally conceded to proceed as follows:



Here the aluminum chloride is tied up permanently instead of

(9) Olivier, *Rec. trav. chim.*, 45, 817 (1926).

(10) Böeseken, *ibid.*, 39, 623 (1920).

being released again as proposed in the alkylation mechanism. Böseken's (10) theory is borne out by the fact that even a slight excess of aluminum chloride over the necessary one equivalent causes a tremendous acceleration of the reaction (11). Wieland and Bettag (12) have shown that the addition of alkyl or acyl halides to aromatic nuclei in the Friedel-Crafts reaction is similar to their addition to olefin double bonds in the presence of aluminum chloride, followed by elimination of hydrogen chloride. The difference between olefins and benzene derivatives is only one of degree in this reaction. An aliphatic double bond adds more readily and the products are more stable, while the more sluggish aromatic double bond adds only under certain conditions and tends to eliminate hydrogen chloride.

Polysubstitution

While monoalkylation is generally the desired reaction and little difficulty, if any, is usually encountered in controlling it to this stage, the direct introduction of more than one group in the same ring is not uncommon. As a rule a mixture is obtained, the relative amounts of the various alkylated products depending on the concentration of the source of

(11) Olivier, Rec. trav. chim., 33, 91 (1914); 35, 109 (1915).
(12) Wieland and Bettag, Ber., 55, 2246 (1922).

alkyl groups and of the aluminum chloride. An increase in the amount of alkyl halide or olefin naturally increases the degree of polyalkylation, whereas the reverse effect is produced by increasing the amount of aluminum chloride after a certain point. *For instance, in a study of the mechanism of the Friedel-Crafts reaction, Wertyporoch and Firla (13) ran a series of experiments in which they varied the ratios of the various reagents (e.g., benzene, ethyl chloride and aluminum chloride). Keeping the amount of benzene and aluminum chloride constant, it was found that a high concentration of ethyl chloride was necessary to form hexaethylbenzene. With 10 cc. of ethyl chloride and 2 cc. of benzene, experiments were run using a) 1.33 g., b) 2.66 g., c) 3.99 g., and d) 5.32 g. of aluminum chloride. The following yields of hexaethylbenzene were obtained: a) 3.14 g., b) 4.56 g., c) 5.22 g., and d) 0.95 g. Triethylbenzene (1.65 g.) and tetraethylbenzene (2.44 g.) were also obtained in d).

Introduction of another alkyl group (same or different) into a nucleus already containing one or more alkyl groups can also be considered as polyalkylation. The presence of these groups appears to have no interfering action on the new alkylation. Steric influences undoubtedly come into play with

(13) Wertyporoch and Firla, Ann., 500, 287 (1933).

large groups but the formation of hexamethyl- and hexaethylbenzenes is effected with ease. In fact the presence of the smaller alkyl groups enhances the tendency for further substitution.

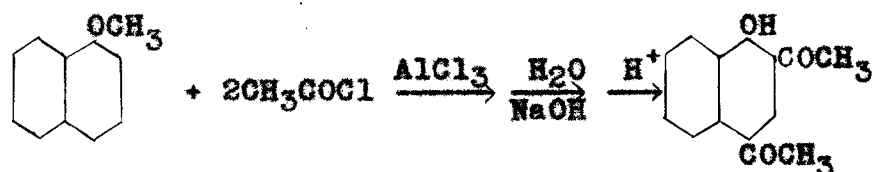
Substitution by an acyl group has the opposite effect, for its presence in an aromatic nucleus, unless the ring is an activated one, will not permit further introduction of acyl groups. Only a very few instances involving "superaromatic" (with respect to benzene) compounds have been reported and these are either polymethylated benzenes, phenol derivatives or polynuclear compounds. Even with these, only two acyl groups were introduced. Forced conditions were necessary to diacylate m-xylene with benzoyl chloride (14) forming the isomeric 1,3-dimethyl-4,6-dibenzoyl- and 1,3-dimethyl-2,4-dibenzoylbenzenes. Likewise mesitylene required a large excess of acetyl chloride (4 equivalents to 1) with refluxing (carbon disulfide solvent) to form 1,3,5-trimethyl-2,4-diacetylbenzene. Benzene and toluene did not give a similar reaction (15). Baum and Meyer (16) in an earlier investigation were not able to effect the above diacetylation of mesitylene possibly because of the shorter time of reaction used. However, the latter authors concluded from successful diacylation experiments

(14) Clar and John, Ber., 62, 3021 (1929).

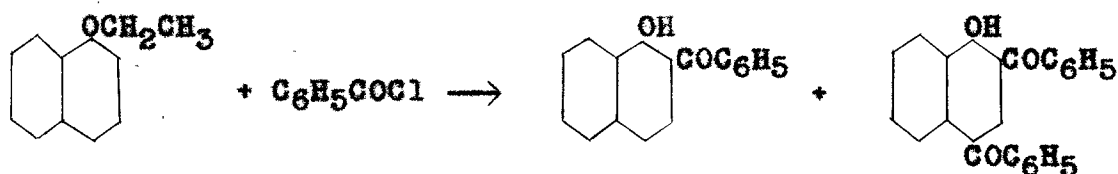
(15) Meyer, ibid., 29, 1413 (1896).

(16) Baum and Meyer, ibid., 28, 3212 (1895).

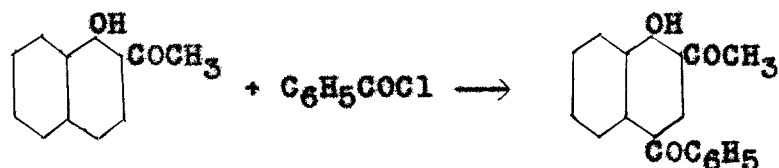
with 1,2,4,5- and 1,3,4,5-tetramethylbenzenes that long heating should be avoided in diacylation, for this causes one of the acyl groups to split out, forming the mono-derivative. Popov (17) obtained 1-hydroxy-2,4-diacetylnaphthalene exclusively in an acylation of the methyl ether of α -naphthol with acetyl chloride.



The ethyl ether and benzoyl chloride, however, gave a mixture of the mono- and diacyl derivatives:

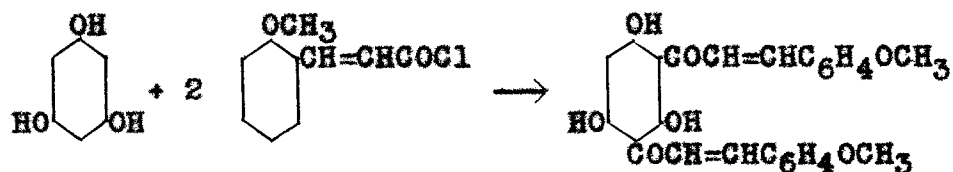


The ether splitting involved here is postulated to have been caused by the excess aluminum chloride used. A mixed diacylnaphthol was prepared by treating 1-hydroxy-2-acetylnaphthalene with benzoyl chloride:

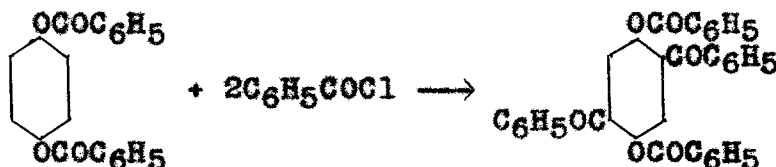


(17) Popov, *J. Gen. Chem. (U.S.S.R.)*, **5**, 986 (1935) *C.A.*, **30**, 1049 (1936).

Phloroglucinol diacylates with o-methoxycinnamoyl chloride to give a dichalcone (18):



The dibenzoate of hydroquinone when treated with benzoyl chloride and aluminum chloride forms the 2,5-dibenzoyl derivative (19):



Anthracene appears to be the only unsubstituted aromatic compound which has been diacylated. An excess of benzoic anhydride was used in this case to form 9,10-dibenzoylanthracene (20).

Baum and Meyer (16) announced an extension of their study of diacylation to thiophene but apparently had no success. In all the great amount of work done on thiophene, much of it including acylation studies, only one case of polyacylation has

- (18) Shinoda and Sato, J. Pharm. Soc. Japan, 51, 576 (1931)
G.A., 26, 1916 (1932).
 (19) Doebner and Wolff, Ber., 12, 661 (1879).
 (20) Cook, J. Chem. Soc., 1282 (1926).

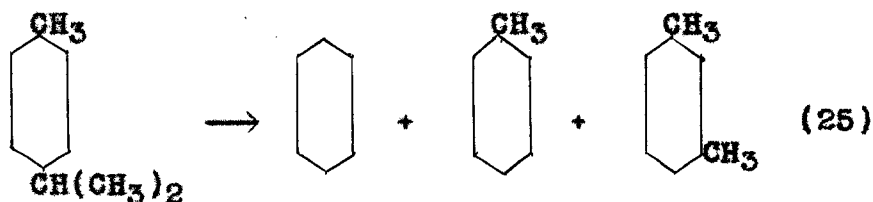
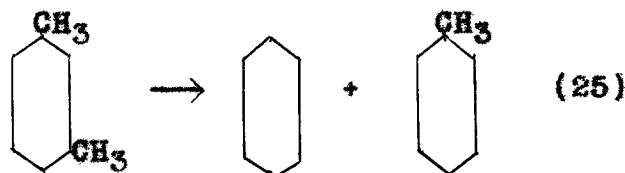
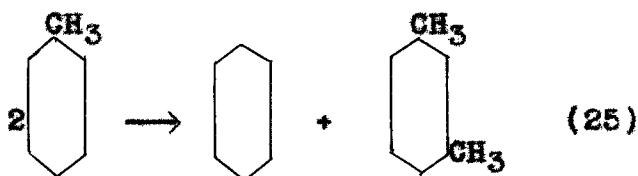
been reported. Goldfarb (21) acetylated a dibenzohydrilthiophene that he prepared from dibenzohydril ether and thiophene and obtained a diacetyl derivative. Since the exact structures of these compounds were not determined it is quite possible that the acetyl groups may have entered two of the four benzene rings present, and this would not be a case of diacylation as it is considered here. Indeed, polysubstitution by acyl groups in different rings of polynuclear compounds is quite common.

Disproportionation

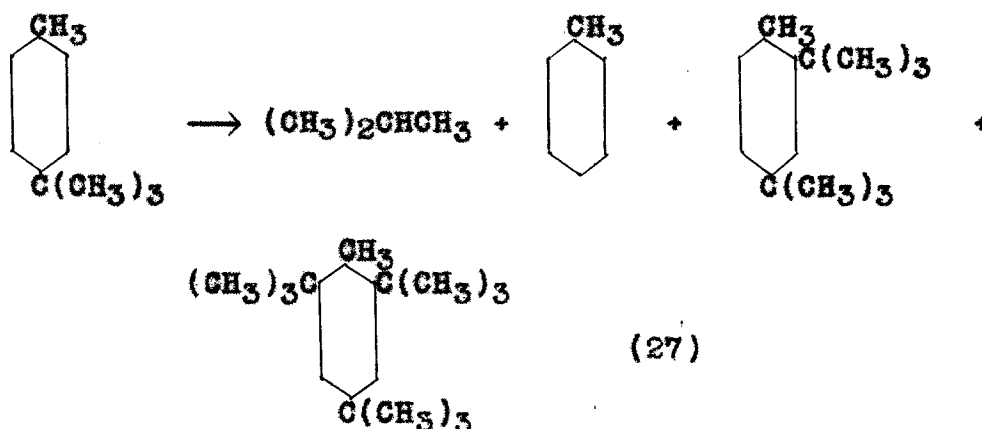
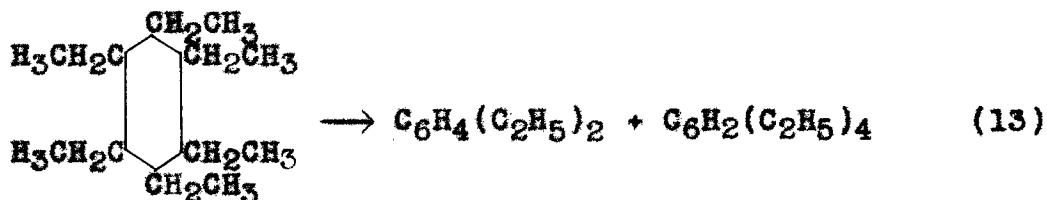
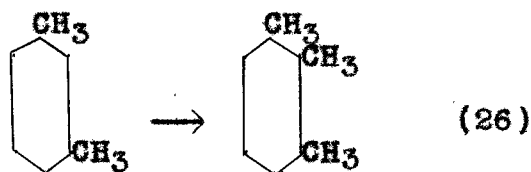
Many instances of disproportionation among alkylated aromatic compounds have been reported. (This term is used here to signify dealkylation with subsequent recombination of the dissociated alkyl radicals with new radicals or compounds.) Consideration of the possibilities of such a process, involving polysubstituted compounds with two to six groups (with benzene) either all the same or mixed, and different aromatic compounds, will give an idea of its complexity and number of products possible. Usually disproportionation occurs between a polyalkylated compound and an unsubstituted one. For instance, m-xylene in the presence of benzene and aluminum chloride will give toluene. p-Isopropyltoluene and benzene

(21) Goldfarb, J. Russ. Phys.-Chem. Soc., 62, 1073 (1930)
[C.A., 25, 2719 (1931)].

give toluene and isopropylbenzene (22). Di-t-butyl- and di-t-amylbenzenes in the presence of benzene and ferric chloride give the corresponding mono derivatives, but di-sec- and di-prim-alkylbenzenes are not dealkylated under these conditions (23). The same investigators found that benzene reacts with di-, tri- and tetracyclohexylbenzenes in the presence of aluminum chloride to give lower derivatives (24). Alkylbenzenes by themselves when heated with aluminum chloride give a variety of products as will be seen by the following reactions:

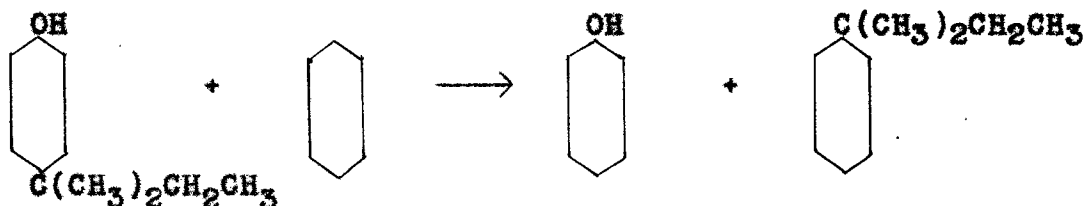
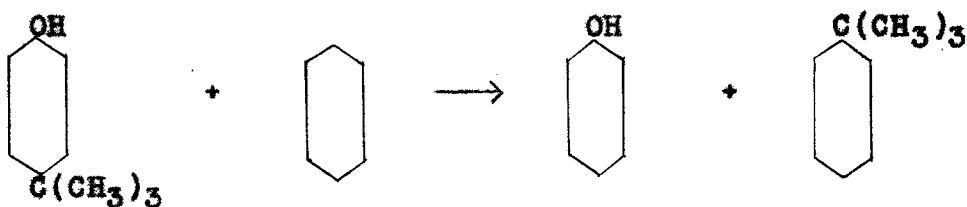


- (22) Boedtke and Halse, Bull. soc. chim., 19, 444 (1916).
(23) Ipatieff and Corson, J. Am. Chem. Soc., 59, 1417 (1937).
(24) Corson and Ipatieff, Ibid., 59, 645 (1937).
(25) Moore and Egloff, Met. Chem. Eng., 17, 61 (1917).



Migration of alkyls from one type of compound to another does not seem to be very common but in the case of p-t-butyl- and p-t-amylphenols with benzene, the reaction goes very smoothly to give good yields of the corresponding alkylbenzenes (28):

- (26) Smith and Cass, J. Am. Chem. Soc., **54**, 1603 (1932).
 (27) Lacourt, Bull. soc. chim. Belg., **38**, 1 (1929).
 (28) Smith, J. Am. Chem. Soc., **59**, 899 (1937).



With a p-octylphenol the migration is not smooth, in that cleavage of the alkyl group occurs. This will be discussed later.

Disproportionation in general may well be classified as a cleavage reaction. At least it involves cleavage.

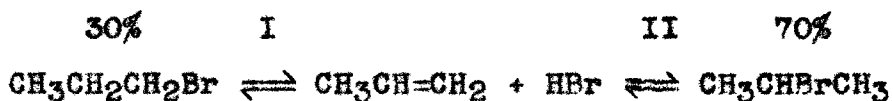
That disproportionation is unknown with acylated compounds might be expected from the infrequency of diacylated nuclei. The carbon-carbon bond joining the acyl group to the ring seems to be an unusually strong one. However, it is possible that a migration does occur during diacylation, for, as has already been stated, acyl groups split out from the diacyl compounds on long heating, forming more of the mono derivative (16). Since some monoacyl compound is practically always isolated, too, this process may occur to some extent in all diacylations.

Rearrangement

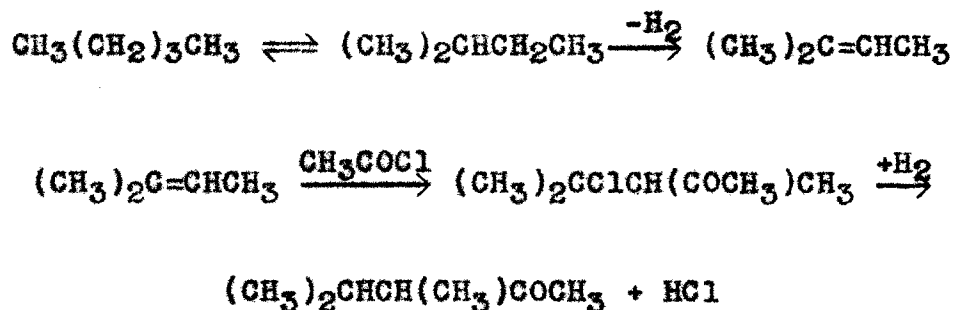
Rearrangement as discussed in this section will refer only to the atoms within the addenda, i.e., alkyl and acyl groups. The tendency for readjustment of carbon atoms, and necessarily the hydrogens, in an alkyl group during alkylation is so strong that it is practically impossible to keep it from occurring at least to some extent in every reaction. Frequently normal-alkyl radicals do not retain their original structure at all in the products. With very high alkyl halides there seems to be exception to this rule. This will be taken up later. Aluminum chloride produces rearrangements at low temperatures (about 20-100°) similar to those obtained at high temperatures (180-300°). In the great majority of reported rearrangements of this type the direction of reaction is toward the most highly branched chain. Even where a definite equilibrium has been demonstrated the more highly branched isomer predominates. The following examples are for equilibria reached by heating, but as stated above, they may be considered analogous to treatment with aluminum chloride at lower temperatures. Isobutyl bromide at 280° forms t-butyl bromide in about 90% yields, the other 10% remaining unchanged (29). Treatment of either n-propyl or isopropyl bromides at 250° resulted in an equilibrium mixture of

(29) Brunel, Ber., 44, 1000 (1911).

70% of the isopropyl bromide and 30% of the normal-isomer (30). The reversible isomerization of the two propyl bromides is represented by the following scheme:



Reaction II is faster than reaction I. This isomerization of a branched alkyl halide to a straight one is very unusual and apparently unknown in Friedel-Crafts reaction, except in the acylation of n-paraffin hydrocarbons to give branched chain ketones (31). For instance, the following reversible isomerization of n-pentane is postulated in the mechanism for acylation with acetyl chloride and aluminum chloride.



- (30) Brouwer and Wibaut, Rec. trav. chim., 53, 1001 (1934).
 (31) Nenitzescu and Chicos, Ber., 68, 1584 (1935). (This article contains leading references.)

Reilly and Hickinbottom (32) from their examination of the literature on the subject concluded that rearrangement of alkyl groups often occurs when they are introduced into a benzene ring, and that the rearrangement of n-butyl chloride and iso-butyl chloride in forming butylbenzenes by the Friedel-Crafts reaction is well established. Other workers (33) experimenting with n-hexane and n-octane found that the isomerization with the aid of aluminum chloride is greatly activated by hydrogen chloride or substances capable of splitting off hydrogen chloride, e.g., alkyl chlorides, etc. Reactions under these conditions proceed at an appreciable rate at room temperature, but without these activators (hydrogen chloride, etc.) the isomerization proceeds at a marked rate only at higher temperatures.

A careful search in the literature failed to disclose any such rearrangement of acyl groups as has been described above for alkyl groups and aliphatic hydrocarbons. Consideration must be taken of the fact that such rearrangements would be limited to the aliphatic acyls since they are unknown in aromatic nuclei, and that the acetyl group is used more commonly than all the other longer chained acyls combined. It is ob-

(32) Reilly and Hickinbottom, J. Chem. Soc., 103 (1920).

(33) Moldarskii, Kobuil'skays and Livshitz, J. Gen. Chem. (U.S.S.R.), 5, 1791 (1935) [C.A., 30, 3402 (1936)].

viously impossible for isomerization of the hydrocarbon part to occur in either an acetyl or propionyl group. A molecular transformation that might come under this type of rearrangement is the following reaction (34):



Cleavage

In a study of the reported cases of cleavage in the Friedel-Crafts reactions numerous instances were found, but little variation exists among the types. That is, catalytic scissions of carbon-carbon bonds in paraffin hydrocarbons, olefins and alkylated aromatic compounds constituted practically all the types that can be included under the Friedel-Crafts reaction. The most common alkylating agents are alkyl halides, but no citation of a cleavage involving this type of reagent has been made with the exception of one by Gilman and Burtner (35) which will be discussed later in this section. The breaking down of an octyl alcohol (36) during alkylation involves a compound similar to an alkyl halide but it is al-

(34) Favorsky and Tchilingaren, Compt. rend., 182, 221 (1926).

(35) Gilman and Burtner, J. Am. Chem. Soc., 57, 909 (1935).

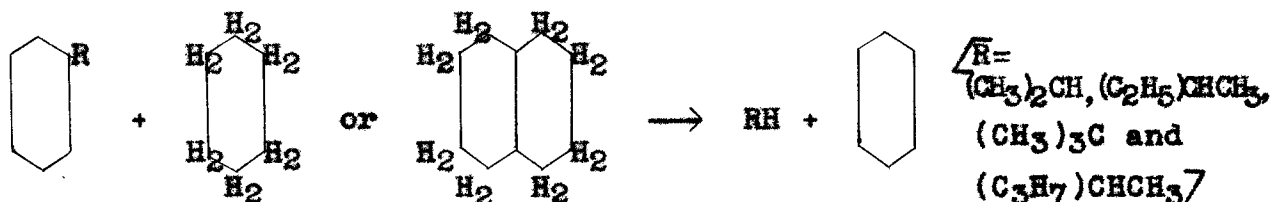
(36) McGreal and Niederl, ibid., 57, 2625 (1935).

together possible that these compounds eliminate water and hydrogen halide, respectively, to form olefins; or the hydrocarbons might very readily form alkyl chlorides, and basically no variation in types of compounds cleaved should be expected in any alkylation.

Egloff, et al. (3a), recently published a very comprehensive review of the action of aluminum chloride on pure hydrocarbons. A point that is emphasized from the very beginning and throughout the article is the key position of butanes, especially isobutane, in the products arising from the various reactions caused by the catalyst. As will be seen, this four carbon unit appears again and again through cleavage, as a t-butyl group.

That cleavage must occur during disproportionation has already received comment. The reason it is not included in this section is the inherent process of, essentially, immediate recombination of the aliphatic fragment with a new aromatic nucleus. Sometimes, however, these fragments combine with hydrogen to form the corresponding paraffin hydrocarbon. In fact it is likely that this occurs to some extent in all disproportionations of the discussed type, but the volatile hydrocarbon products are frequently overlooked. One case has already been cited where the investigator isolated such a fragment (27). Isobutane was obtained on treating p-t-butyltoluene with aluminum chloride at room temperature, in addition to

toluene and di- and tributyltoluenes. Similarly, propylbenzenes gave dipropylbenzenes, propane and benzene (37). At lower temperatures less propane was formed while the yield of diisopropylbenzene was increased. A decrease in the concentration of aluminum chloride tends also to lower the amount of hydrocarbon formed. Obviously some source of hydrogen is necessary for the production of hydrocarbons after dealkylation. Frequently this source is not shown, but the coupling of aryl radicals produces hydrogen, and this reaction frequently takes place, especially at high temperatures which is conducive to the formation of paraffins. In some experiments (38) saturated cyclic hydrocarbons were added expressly to furnish hydrogen. Thus, various alkylbenzenes, from isopropylbenzene up to s-amylbenzene, when heated to about 70-80° in the presence of cyclohexane or decahydronaphthalene and approximately one-third equivalent aluminum chloride gave good yields of the corresponding paraffins.

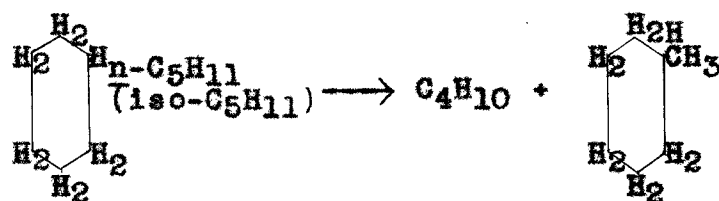


At temperatures between 120-180° alkylcyclohexanes were

(37) Heise and Töhl, Ann., 270, 155 (1892).

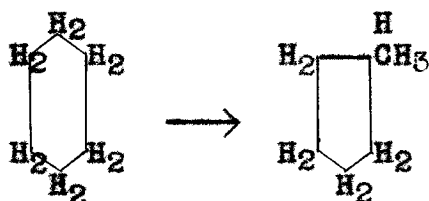
(38) Ipatieff and Pines, J. Am. Chem. Soc., 59, 56 (1937).

cleaved forming paraffin hydrocarbons. With n-amyl- and iso-amylcyclohexanes cleavage occurred to the extent of 70% and 42%, respectively, of the starting materials. Here an unusual thing happened in that butane was obtained in both cases resulting from a breakage of the side carbon between the first and second carbon. The other product was methylcyclohexane (39).



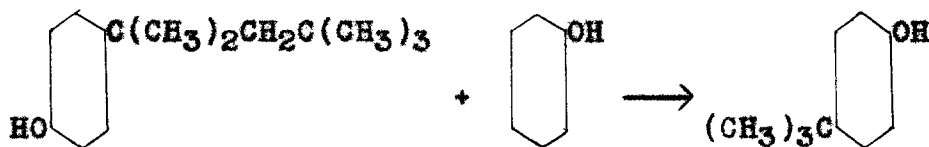
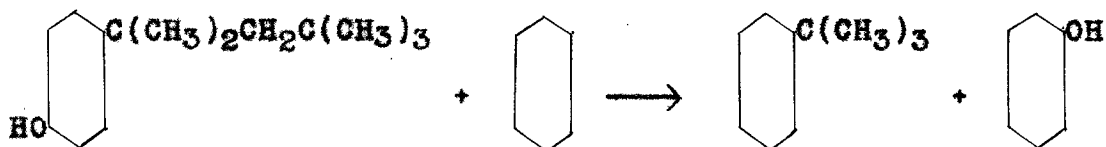
This result brings out an interesting contrast between alkylbenzenes and alkylcyclohexanes. In the former compounds the weakest carbon-carbon bonds are the ones joining the alkyl radicals to the benzene rings. This accounts for the fact that cleavage of an alkylbenzene always takes place at this bond. With a saturated ring this characteristic is much less pronounced, and bonds within the side chain not only break but the ring opens in cyclohexane itself in an isomerization to methylcyclopentane.

(39) Grignard and Stratford, Compt. rend., 178, 2149 (1924).



This latter reaction is one which has received much attention, the leading investigator being Nenitzescu who has published a series of articles on the subject (31).

A disproportionation reaction already mentioned, which would appear at first glance to be similar to the above cleavage of amylcyclohexane, is that between 4-(1,1,3,3)-tetramethobutylphenol and benzene to give butyl groups which alkylate the benzene (28). Phenol with this same octylphenol forms *p-t*-butylphenol in good yields (40).



While no mechanisms were offered, it is very probable that or-

(40) Smith and Rodden, J. Am. Chem. Soc., 59, 2353 (1937).

dinary dealkylation of the octyl group occurred as usual at the aryl-alkyl linkage to form diisobutylene and phenol. As will be seen below this olefinic dimer is dissociated readily either by depolymerization to isobutylene, or simply by cleavage to t-butyl radicals and isobutenyl radicals which combine at once with aryl nuclei or themselves. Depolymerization is more plausible.

Grosse and Ipatieff (41) have reported a remarkable series of reactions with paraffin hydrocarbons and benzene. Approximately molecular quantities of a saturated hydrocarbon (e.g., 2,2,4-trimethylpentane) and of benzene were mixed with about ten mole per cent of catalyst, e.g., aluminum chloride or zirconium chloride, for four hours at 25-50° and atmospheric pressure. With zirconium chloride a temperature range of 50-75° was used. The products with each chloride were good yields of isobutane, t-butylbenzene and di-p-t-butylbenzene. The presence of hydrogen chloride is essential. Two mechanisms are proposed. Either (I) the chain breaks down into t-butyl radicals, one of which unites with a phenyl group and the other with hydrogen to form isobutane; or (II) the cleavage may result in direct formation of isobutane together with isobutylene which alkylates benzene:

(41) Grosse and Ipatieff, J. Am. Chem. Soc., 57, 2415 (1935).

of aluminum chloride to give good yields of alkylated products. In contrast is the failure of primary alcohols to alkylate at all. Olefins and alkyl halides are formed with the tertiary and secondary alcohols. On the basis that the latter are the true alkylating agents it is easy to understand the reluctance of primary alcohols to react, for the ease with which aliphatic alcohols split out water is: tertiary > secondary > primary. The reactivity of these alcohols as alkylating agents is in the same order. Similar reasoning holds for the assumption that the hydroxyl group combines with a loosened hydrogen of the aromatic ring to form water, with coincident or subsequent alkylation.

Paraffins alone with aluminum chloride required substantially higher temperatures (150-200°) before appreciable reaction occurred (43). Splitting, isomerization and polymerization took place with butane, hexane, heptane and 2,2,4-trimethylpentane. Isomerization is accounted for by recombination (alkylation) at different carbons of the lower paraffin hydrocarbon and olefin, formed by primary splitting. Hydrogen chloride is also necessary here. Another study (39) was made similar to this using higher paraffins (octane, 2,5-dimethylhexane, decane, 2,7-dimethyloctane and heptadecane). Butane

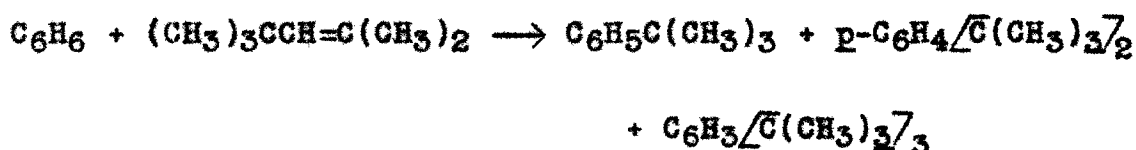
(43) Ipatieff and Grosse, Ind. Eng. Chem., 28, 461 (1936).

was produced in each case. Beginning with the decanes, butane was simultaneously split off from both ends, leaving an unsaturated residue which polymerized. Temperatures between 120-150° were used, with 20-30% aluminum chloride. Apparently no hydrogen chloride was added. It is probable, however, that enough moisture was present to generate hydrogen chloride for the reaction, for dry pentane and freshly sublimed aluminum chloride underwent essentially no reaction even at 133° (44). Addition of an activator, e.g., hydrogen chloride, hydrogen bromide, hydrated aluminum chloride or alkyl chlorides, caused isomerization and decomposition at once to isopentane, butane and isobutane. The latter was the chief product. Aluminum bromide, however, did not require any activator. Two of the highest paraffin hydrocarbons that apparently have been treated in the pure state with aluminum chloride are octadecane, $C_{18}H_{38}$, and hexatriacontane, $C_{36}H_{74}$ (45). Temperatures of about 110° and 150° were used, respectively. No unsaturated products were obtained but a great many saturated hydrocarbons were formed, for no clean cut fractions could be cut during distillation of the liquid portion, although the total range was 20-175°. None of the fractions, gaseous, liquid or solid, was identified.

(44) Glasebrook, Phillips and Lovell, J. Am. Chem. Soc., 58, 1944 (1936).

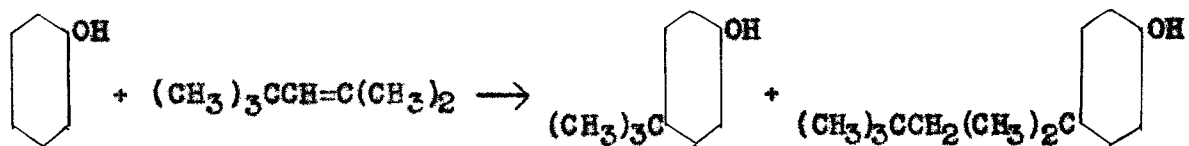
(45) Bauer and Toma, Ber., 67, 1135 (1934).

Cleavage with a more orthodox alkylating agent in the Friedel-Crafts reaction was found in an alkylation of benzene with diisobutylene (46). Mono-, di- and probably tri-t-butylbenzenes were obtained, apparently as the sole products.



The authors claim that the reaction proceeds through a process of depolymerization to isobutylene and subsequent alkylation, and propose the term "depolyalkylation" for this type of reaction. Similar reactions took place with sulfuric or phosphoric acid as a catalyst.

A very similar reaction was observed in experiments connected with the cleavage involved in the dealkylation of p-t-octylphenol (40). Diisobutylene reacted with phenol in the presence of aluminum chloride to form p-t-butylphenol in 67% yield while only 14% of the normal product, p-t-octylphenol, was obtained.

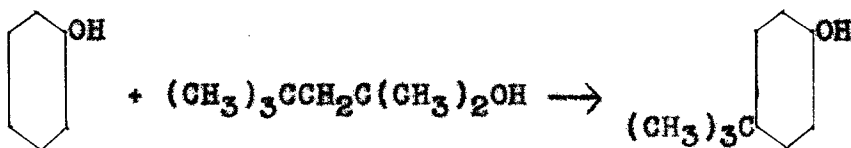


(46) Ipatieff and Pines, J. Am. Chem. Soc., **58**, 1056 (1936).

Peculiarly, no reference was made to the foregoing work (46) nor was any mechanism proposed. "Depolyalkylation" probably occurs here, too. Such a simple mechanism cannot be used, however, to explain the formation of amyl- and hexylbenzenes in addition to butylbenzene obtained from diamylene, benzene and aluminum chloride (47). Butylbenzene was the main product.

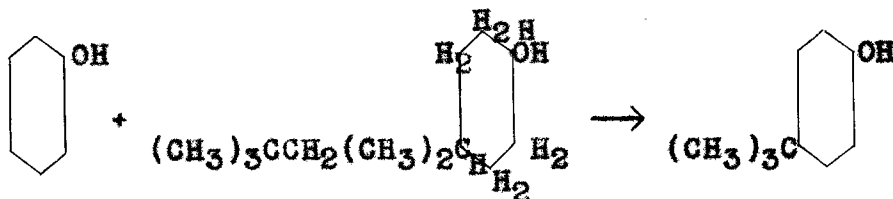


During a routine synthesis of various alkylphenols, an anomalous result was obtained in an attempt to prepare p-t-octylphenol by condensing 2,2,4-trimethylpentanol-4 with phenol at 150-180° using zinc chloride as catalyst (36). The expected product was not obtained but instead, p-t-butylphenol was the main reaction product.



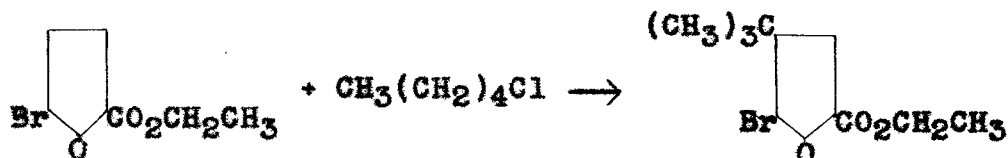
Likewise with 4-t-octylcyclohexanol-1 and phenol, p-t-butyl phenol was formed instead of the normal p-(4-t-octyl)-cyclohexylphenol.

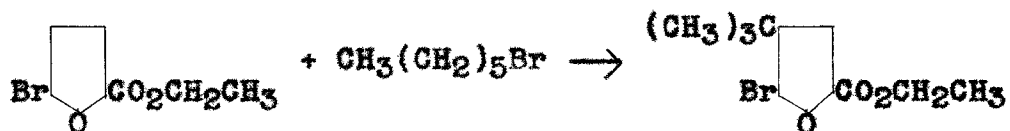
(47) Tilicheev and Kuruindin, Neftyanoe Khoz., 19, 586 (1930)
C.A., 25, 3469 (1931)✓.



The condensation of alcohols with phenols in the presence of zinc chloride to form the corresponding substituted phenols is termed the "Liebmann method" (36) but the reaction may also be classified as one of the many variations of the Friedel-Crafts reactions.

From the foregoing discussion of various cleavage phenomena by the action of metallic halides it is apparent that scission of carbon-carbon bonds by this type of reagent is common at elevated temperatures (100° and above) and occasional at lower ones. However, the type of compounds and conditions in all these cases bear many points in common with each other. The cleavage alkylation obtained by Gilman and Burtner (35) with ethyl 5-bromo-2-furoate and n-amyl chloride and n-hexyl bromide, successively, while similar to those above in some ways, is unique in most respects. They obtained ethyl 4-t-butyl-5-bromo-2-furoate with each of these higher alkyl halides.



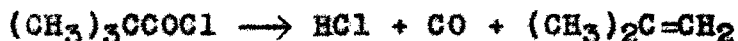


Here again the cleavage to a four carbon unit, a t-butyl group, is the most outstanding feature and is the main point of similarity to the cleavages just described. In fact the analogy tends to close with this fact. The uniqueness arises first from the use of carbon disulfide as a solvent, which appears to be the only one capable of producing this reaction besides a-tetrachloroethane, as will be developed later. Second, a low temperature (about 25°) was used. Third, the butyl derivative seems to be the only alkylated product. Fourth, a heterocycle is involved instead of a cyclic hydrocarbon. Fifth, the aromatic nucleus is substituted with two different negative groups. The fact that alkyl halides are primarily involved is not of much significance, for they are readily converted to olefins.

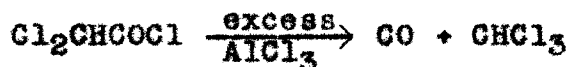
From the numerous cleavage phenomena in variations of alkylation by the Friedel-Crafts reaction, it would seem that cleavage is a characteristic rather than an anomaly. Scission of an alkylaryl linkage is characteristic but breaking up of alkyl groups at moderate temperatures must be considered anomalous.

Examination of the literature has failed to reveal any cleavage reactions during acylation, or of C-acylated products. However, certain acid chlorides have been found to dissociate

on treatment with aluminum chloride (48). For instance, trimethylacetyl chloride decomposes very energetically in the presence of aluminum chloride even at 0° to form hydrogen chloride, carbon monoxide and isobutylene.



Similarly, dichloroacetyl chloride with an excess of aluminum chloride yields carbon monoxide and chloroform.



Friedel-Crafts Reactions With Furans

Introduction of acyl and alkyl groups into α -positions in furan compounds goes smoothly and the reactions are quite reliable. With mono- α -substituted furans the entering group displaces the remaining α -hydrogen, with one very notable exception. 2-Furfural and isopropyl chloride form 4-isopropyl-2-furfural instead of the expected 5-isopropyl-2-furfural (49). Gilman and Calloway (50) discuss the Friedel-Crafts reaction with 2-furyl phenyl ketone, 2-furfural, furan, methyl 2-furoate,

(48) Böeseken, Rec. trav. chim., 29, 85 (1910).

(49) Gilman, Calloway and Burtner, J. Am. Chem. Soc., 57, 906 (1935).

(50) Gilman, and Calloway, ibid., 55, 4197 (1933).

2-furoic acid, ethyl 2-furoate and 2,5-dimethylfuran.

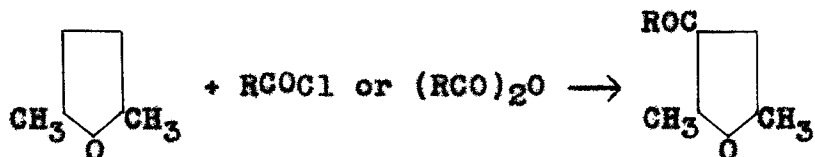
Acylation of methyl 2-furoate could not be effected using aluminum chloride with either an acid chloride or an acid anhydride. In the presence of ferric chloride or stannic chloride, however, the acylation proceeded with ease. While the latter catalysts are frequently observed to be superior to aluminum chloride in acylations (51), the difference is usually in degree rather than complete unreactivity of aluminum chloride as described above.

On the other hand substitutions in the β -positions of the furan ring are erratic. Very little work has been done with di- α -substituted furans in the Friedel-Crafts reaction and not a great deal is known about the reaction with these compounds. Only a few β -acylations have been reported. 2,5-Dimethylfuran with acetic anhydride and aluminum chloride gave 3-acetyl-2,5-dimethylfuran (52). A yield of 42% was obtained using ferric chloride (50). Benzoylation of 2,5-dimethylfuran was effected in 7% yield with benzoyl chloride and aluminum chloride in carbon disulfide. Benzoic anhydride and ferric chloride in carbon disulfide gave no better results, but benzoic anhydride and stannic chloride in benzene gave a 29% yield. The product

(51) Calloway, Iowa State Coll. J. Sci., 9, 141 (1934).

(52) Gilman and Burtner, Rec. trav. chim., 51, 667 (1932).

in each case was 2,5-dimethyl-3-furyl phenyl ketone.

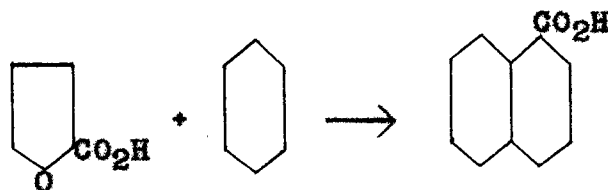


With methyl 5-methyl-2-furoate, acetic anhydride and stannic chloride the acetyl group entered the β -position adjacent to the methyl group to form methyl 4-acetyl-5-methyl-2-furoate (53). Ethyl 5-bromo-2-furoate did not acylate (3) to form a β -acyl derivative, but isopropyl chloride alkylated this same ester to form ethyl 4-isopropyl-5-bromo-2-furoate in 34% yield. In contrast, t-butyl chloride gave only a 3% yield of ethyl 4-t-butyl-5-bromo-2-furoate (35). With the next two higher homologous halides the amyl and hexyl groups were cleaved (35), as described in the previous section and ethyl 4-t-butyl-5-bromo-2-furoate was again the sole product isolated in each case.

Another anomalous Friedel-Crafts reaction was observed with 2-furoic acid and benzene (54). Here a condensation similar to the Diels-Alder reaction occurred, forming α -naphthoic acid in good yields.

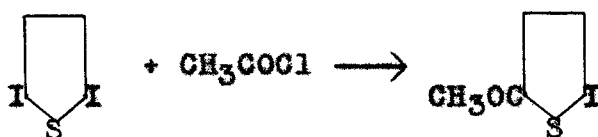
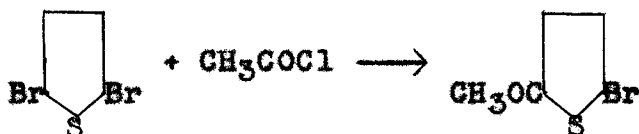
(53) Gilman, Calloway and Smith, J. Am. Chem. Soc., 56, 220 (1934).

(54) Gilman, McCorkle and Calloway, J. Am. Chem. Soc., 56, 745 (1934).



This type of reaction in the Friedel-Crafts synthesis appears to have no precedent.

An unusual and interesting replacement reaction was observed with two derivatives of the sulfur analog of furan, thiophene (55). 2,5-Dibromo- and 2,5-diiodothiophenes were treated with acetyl chloride and aluminum chloride. One of the halogens was replaced in each case by an acetyl group to form 2-bromo-5-acetyl- and 2-iodo-5-acetylthiophenes, respectively.

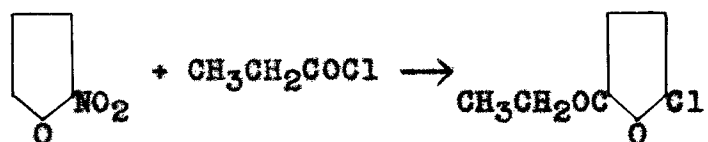


With 2-nitrofuran, propionyl chloride and titanium tetrachloride another replacement occurred (56). Here the acyl

(55) Gattermann and Römer, Ber., 19, 688 (1886).

(56) Gilman, Burtner, Calloway and Turck, J. Am. Chem. Soc., 57, 907 (1935).

group was assumed to enter the unsubstituted α -position and the nitro group to be replaced by chlorine, forming 2-chloro-5-furylethylketone.



Statement of Problem

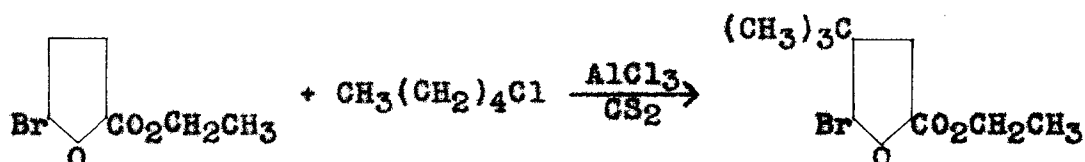
The purpose of this thesis was to study some of the differences between alkylation and acylation as outlined in previous sections, with emphasis on the unusual features of these reactions, particularly among furans. The greatest part of the work described in the following pages was devoted to an investigation of the cleavage phenomenon observed with ethyl 5-bromo-2-furoate (57). An attempt was made to establish the limits of this reaction and its mechanism.

(57) This Thesis, p.33.

THEORETICAL PART AND DISCUSSION OF RESULTS

Limits of Cleavage Reaction With Furans

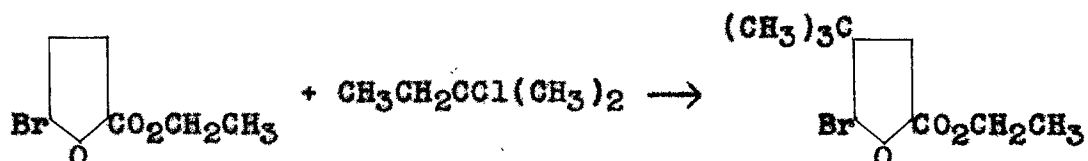
As a preliminary investigation in a study of the mechanism of the cleavage reaction with ethyl 5-bromo-2-furoate and *n*-amyl chloride or *n*-hexyl bromide (35), it seemed desirable to determine the limits of this reaction. To be systematic it was necessary to start with a single reaction using a definite procedure and then vary only one reagent or condition at a time. The following reaction was chosen and the conditions were essentially the same as those outlined by Gilman and Burtner (35).



Briefly these conditions are as follows: a solution of ethyl 5-bromo-2-furoate and the alkyl halide was added dropwise to a stirred suspension of the aluminum chloride in carbon disulfide at room temperature. Stirring was continued for twenty-four hours and the mixture worked up in the usual manner. Since the alkyl halide was the only thing that was different between this reaction and the one in which *t*-butyl chloride was used to give the same product, it was logical to vary this reagent first.

Alkyl Halides.

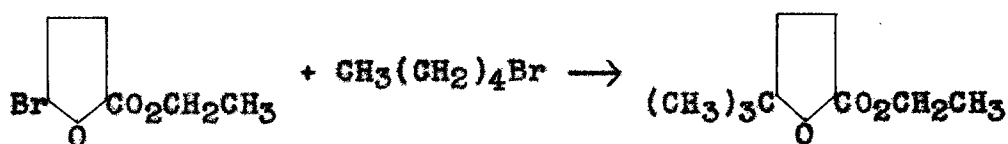
Variation is possible in two ways with each homolog: isomerization in the chain and difference in the halogen. Every combination, of course, was not attempted for reasons that the number of experiments necessary would be prohibitive and many alkyl halides are not available. Of the amyl chlorides, the n- and t-isomers were tried. Both of these were cleaved to form ethyl 4-t-butyl-5-bromo-2-furoate. The original yield reported for n-amyl chloride was 13 per cent, based on the theoretical amount of product (35), and in spite of many variations in experimental conditions an increase to 20 per cent was the maximum in any run. With t-amyl chloride the yield was substantially lower, 6 per cent.



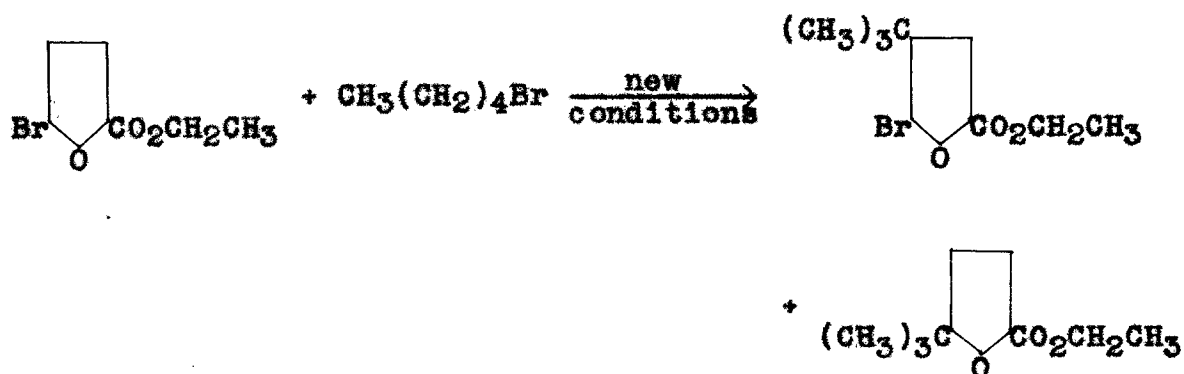
The fact that there was any cleavage in the t-amyl group is especially significant, for there is no reported instance where such a scission occurred under any conditions. Even assuming that hydrogen chloride split out to form an isocamylene, which was subsequently cleaved, there is still no precedent for the process.

Going to the next halogen, bromine, with a five carbon chain, n-amyl bromide gave a still more anomalous result. The

same cleavage and rearrangement of the n-amyl radical to a t-butyl group occurred, but instead of forming ethyl 4-t-butyl-5-bromo-2-furoate the α -bromine was replaced by the t-butyl group to give ethyl 5-t-butyl-2-furoate. The product was isolated in the form of the corresponding furoic acid in 31-40 per cent yields.



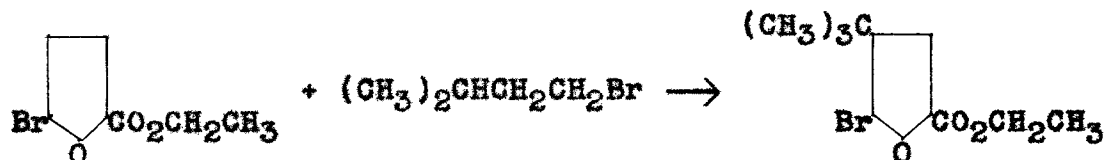
This reaction was entirely unexpected and is a novel one in the field of alkylation by the Friedel-Crafts synthesis. No ethyl 4-t-butyl-5-bromo-2-furoate was isolated in the first runs of this reaction in which the comparatively high (31-40 per cent) yields of 5-t-butyl-2-furoic acid were obtained. Later experiments, in which further variations were made, gave a mixture of these two compounds.



Still other variations gave only the "normal" ethyl 4-t-butyl-5-bromo-2-furoate. This reaction and the effect of divers var-

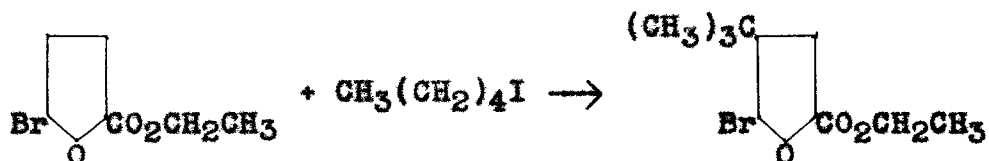
iations will be discussed more in detail in a later section of this thesis.

Another surprising result was obtained with isoamyl bromide, for only ethyl 4-t-butyl-5-bromo-2-furoate was obtained.



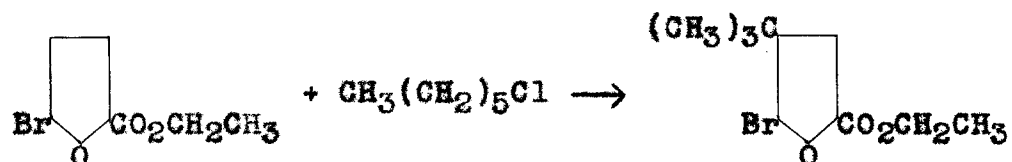
Here a mixture of the latter compound and 4-t-butyl-2-furoic acid was expected, or even the bromine replacement product alone. The yield (20 per cent) was comparable to that obtained with n-amyl chloride.

The only amyl iodide tried was the normal-isomer. Again the reaction was somewhat anomalous in that there was none of the product which was formed by n-amyl bromide (ethyl 5-t-butyl-2-furoate, or the corresponding acid). The yield of ethyl 4-t-butyl-5-bromo-2-furoate was 25 per cent, slightly better than with n-amyl chloride.



Going to the next higher alkyl group the six carbon chain was also found to undergo cleavage to a t-butyl group (35). The only other hexyl halides tried besides the n-hexyl bromide were n-hexyl chloride and cyclohexyl chloride.

n-Hexyl chloride gave no replacement of the α -bromine in ethyl 5-bromo-2-furoate, but the yield of ethyl 4-t-butyl-5-bromo-2-furoate (20 per cent) was decidedly increased over the 6 per cent with n-hexyl bromide.

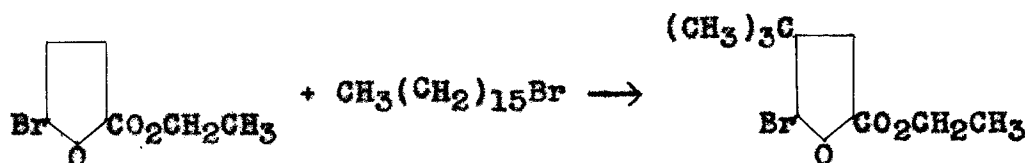
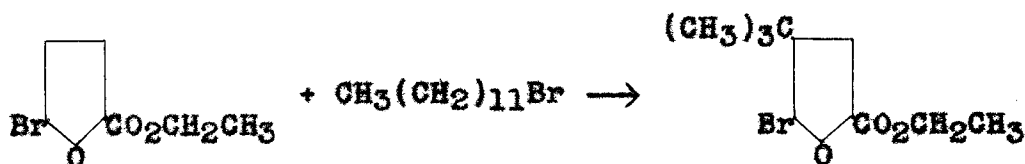


The use of cyclohexyl chloride in this reaction was a more stringent test than experiments with any other alkyl halide, for there is no instance reported of a cleavage of this alicyclic group to smaller groups under moderate Friedel-Crafts conditions. While there appeared to be considerable reaction on mixing the ingredients, no alkylated furan derivative could be isolated. There was more than the usual amount of tarry residue on distillation of the neutral products and no cyclohexyl chloride was recovered. Apparently the ring was cleaved but the fragments did not alkylate the ethyl 5-bromo-2-furoate as seems to be the case with open chain alkyl halides. No ethyl 4-t-butyl-5-bromo-2-furoate was obtained in spite of an exhaustive search for this compound.

Since the cleavage of open chain alkyl groups containing five and six carbon atoms appeared to be a consistent process in this reaction, it seemed that running a complete series of homologous halides was unnecessary. That is, it was assumed

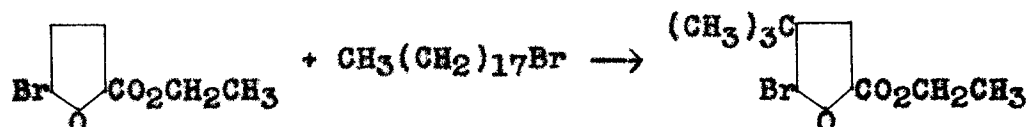
that if long chain alkyl halides were shown to be cleaved to t-butyl groups, the alkyl halides intermediate to hexyl- and the long-chain halides would undoubtedly be cleaved also. With this reasoning, experiments with heptyl, octyl, nonyl, etc., halides were passed by and a twelve carbon alkyl halide tried next. Lauryl (n-dodecyl) bromide behaved in a very similar manner to n-amyl chloride. The only alkylated product isolated was ethyl 4-t-butyl-5-bromo-2-furoate in a 13 per cent yield. Other dodecyl halides were not used because of the inaccessibility of branched isomers and the assumption that further investigation here was unnecessary.

In passing to the next alkyl halide in this investigation a jump of four carbons was made to cetyl (hexadecyl) bromide. Scission of the alkyl group occurred again giving the usual ethyl 4-t-butyl-5-bromo-2-furoate.



The yield was 20 per cent of the theoretical calculated from the amount of ethyl 5-bromo-2-furoate used.

n-Octadecyl bromide was the highest molecular weight alkylating agent used and surprisingly gave the highest yield, by a generous margin, of any of the reagents tried. The yield of ethyl 4-t-butyl-5-bromo-2-furoate here was 46 per cent in comparison with the next highest, 25 per cent, obtained with n-amyl iodide.



γ -Phenyl-n-propyl bromide should behave like any other n-alkyl bromide as far as the carbon-bromine bond is concerned, but this compound did not give any alkylated furan derivative, with cleavage or otherwise. The expected product was ethyl 4-isopropyl-5-bromo-2-furoate. The only product isolated was an ester which on saponification gave an acid with no melting point, partially decomposing at 289°. This latter compound was not identified, but it is not at all likely that it is a phenylpropyl derivative of 2-furoic or of 5-bromo-2-furoic acid, because of the fact that it fails to melt. γ -Phenyl-n-propyl bromide contains a total of nine carbon atoms, but the difference in the linkage between the six carbons in the phenyl group warrants special classification of the compound. That is, under no condition can it be considered a nonyl bromide.

Alcohols.

Other types of alkylating agents were tried in this reaction but not in such an extensive series as with the alkyl halides. An assumption was made on the basis of the consistent results obtained with the alkyl halides, that, if the particular compound actually used did or did not alkylate ethyl 5-bromo-2-furoate, then higher or lower homologs of this compound would behave similarly. For instance, t-amyl alcohol alkylated this furan derivative, with cleavage, to give ethyl 4-t-butyl-5-bromo-2-furoate in 10 per cent yield. From this result it was taken for granted that t-hexyl, t-heptyl, etc. and perhaps sec-amyl, sec-hexyl, sec-heptyl, etc. alcohols would also yield this same t-butylfuran derivative, and no other alcohol was tried. The foundation for this assumption is certainly not as strong as it might be, but neither is it based on the findings here with the alkyl halides alone. One of the primary principles of organic chemistry is the similarity in chemical properties in an homologous series. Further and closer to the point is the fact that other types of alkylating agents than alkyl halides do consistently split into four-carbon (butyl) groups on passing from one homolog to another. Thus, pentane (44), hexane (42), octanes, decanes and heptadecane (39) all give butanes in the presence of aluminum chloride. Similarly both diisobutylene (46) and di-

amylene (47) with benzene form butyl benzenes.

Olefins.

Olefin hydrocarbons serve as good alkylating agents in the Friedel-Crafts reaction and they have been found to undergo cleavage to give butyl derivatives under some conditions (46, 47). The only furan derivative that has been alkylated by an olefin, butylene, is methyl 2-furoate (58) but the yield (8 per cent) of methyl 5-t-butyl-2-furoate was poor in comparison to the yields obtained with butyl halides (about 50 per cent). It was expected that β -n-amylene would behave in a manner similar to amyl halides in the alkylation of ethyl 5-bromo-2-furoate. Surprisingly there was no alkylation at all and most of the ethyl 5-bromo-2-furoate was recovered unchanged except for hydrolysis of some of the ester to 5-bromo-2-furoic acid in check runs. There was considerable tarry residue in addition to high boiling resins, collected over a wide range and which would not saponify.

Cyclohexene also failed to give any alkylated product even at refluxing temperature (46°). The only compounds isolated from the reaction mixture were recovered ethyl 5-bromo-2-furoate and 5-bromo-2-furoic acid. There was a large tarry resi-

(58) Calloway, Doctoral Thesis, Iowa State College Library (1933).

due which would not distill. This negative result was not as surprising as that obtained with β -n-amylene, for in cyclohexene, as in cyclohexyl chloride, there are more stable connections between the carbon atoms, and cleavage was not expected.

The failure of β -n-amylene to give a cleavage alkylation, together with the fact that a lower yield was obtained with butylene compared with butyl halides in the alkylation of methyl 2-furoate, suggested the idea that olefins are not active enough alkylating agents to alkylate the less readily substituted ethyl 5-bromo-2-furoate. Accordingly butylene was used in an attempted alkylation of the latter furan derivative. In spite of repeated efforts using large excesses of butylene the combined recovery of ethyl 5-bromo-2-furoate as the original ester and the corresponding acid was almost quantitative in each run. Considerable quantities of resinous material were obtained which distilled over a wide range but would not saponify. These thick fluids were probably polymerization products from the butylene.

Diisobutylene has been observed to alkylate phenol to give p-t-butylphenol (40) and it was expected that a similar cleavage alkylation would take place with ethyl 5-bromo-2-furoate. Actually no alkylated product could be isolated and 96% of the ethyl 5-bromo-2-furoate was recovered in the forms of the original ester and the corresponding acid.

Nitriles.

Aliphatic nitriles have been used successfully as alkylating agents in the Friedel-Crafts reaction, and after the signal result obtained with n-octadecyl bromide it seemed logical that stearonitrile (n-heptadecyl cyanide) should also give a cleavage alkylation. Repeated experiments proved otherwise, however, for quantitative recovery of both the ethyl 5-bromo-2-furoate and stearonitrile was the only result. This is not very surprising on taking into consideration the inactivity of the furan nucleus in the negatively substituted derivative at hand. In other words aliphatic nitriles are not nearly as good alkylating agents as alkyl halides, in general, and no good in this case.

Alkylated Aromatic Compounds.

It has been shown (59) that polyalkylbenzenes become alkylating agents for benzene in the presence of aluminum chloride. Similarly, monoalkylated aromatic compounds under certain conditions act essentially as alkylating agents. Further, long chain alkyl groups have been observed to undergo cleavage in this type of alkylation (28, 40). p-t-Amylphenol alkylated benzene to give a 25 per cent yield of t-amylbenzene

(59) This thesis, p.15.

(28) but this alkylating agent failed to react with ethyl 5-bromo-2-furoate.

t-Amylbenzene apparently has not been used as an alkylating agent but it is very probable that it will alkylate another aromatic compound, e.g., phenol, in the presence of aluminum chloride. It was used in this work with ethyl 5-bromo-2-furoate in an attempt to effect a cleavage alkylation like that obtained with amyl halides. The effort was unsuccessful, for the only product was a high boiling ester which gave an acid void of bromine, melting at 187-187.5°. This is practically the melting point of 5-bromo-2-furoic acid (186-187°) but a 1:1 mixture of the two acids melted about thirty to forty degrees lower. This unusually great depression of the melting point of 5-bromo-2-furoic acid is significant in that impurities in general usually lower the melting point only a few degrees and mixed melting points with structurally similar compounds with melting points approximating 185° give depressions of only ten to twenty degrees. From this behavior it seems probable that the unknown acid is not a 2-furoic acid derivative. More direct evidence against the presence of a furan ring in combination with a carboxyl group is the low oxygen content calculated from carbon and hydrogen analyses. The neutral equivalent of the unknown acid was 185 and the average per cent of oxygen was about 18. A furoic acid would contain at least three oxygen atoms and with a molecular weight

of 185 the per cent oxygen would be 26. Two oxygens on the other hand constitute 17.3 per cent of a compound having this molecular weight. The empirical formula is approximately $C_{11}H_{16}O_2$. It is possible that a condensation between the benzene and furan ring occurred to form a naphthoic acid in a manner similar to the reaction between benzene and 2-furoic acid (54), but the high per cent of hydrogen belies this theory. The analysis corresponds more closely to a butyl- or amylbenzoic acid, but it is difficult to conceive a mechanism for the formation of such a compound. The small amount of the material at hand prevented further investigation of its chemical properties.

Furan Derivatives.

The other reactant besides the alkylating agent in the cleavage alkylation in question is ethyl 5-bromo-2-furoate. Variation of this factor should give more information on the limits and mechanism of the cleavage, for the alkylating agents which are cleaved with this particular furan derivative are not cleaved in the alkylation of benzene and some other furan derivatives such as methyl 2-furoate. That is, the cause of the cleavage seems to center in the nature of the compound to be alkylated.

In this study n-amyl chloride was used consistently un-

der the same conditions described for the alkylation of ethyl 5-bromo-2-furoate.

Methyl 5-bromo-2-furoate would be expected to give the same reactions that the corresponding ethyl ester does, and this was shown to be so in an alkylation with n-amyl chloride. A yield of 22% of the theoretical amount of methyl 4-t-butyl-5-bromo-2-furoate was obtained.

While ethyl 4-bromo-2-furoate is an isomer of ethyl 5-bromo-2-furoate and for this reason might be expected to behave as the latter does in alkylation, the distinct difference between an α - and a β - position in furan must be borne in mind. Methyl 2-furoate in which the 5-position is open, as it is in ethyl 4-bromo-2-furoate, does not give a cleavage alkylation with either n-amyl chloride or n-hexyl bromide. Therefore, whether or not there is cleavage during alkylation with ethyl 4-bromo-2-furoate would appear to hinge on the presence of the bromine atom. No ethyl 4-bromo-5-t-butyl-2-furoate was isolated from the reaction product obtained from ethyl 4-bromo-2-furoate, but a substantial yield (30%) of ethyl 5-t-butyl-2-furoate was isolated. The bromine atom must have split out after alkylation rather than before since ethyl 2-furoate alkylates without cleavage.

Ethyl 5-chloro-2-furoate resembles ethyl 5-bromo-2-furoate closely, and as far as ease of substitution is concerned it should give the same reactions that the bromo compound mani-

fects. The appreciable difference in the size of the two halogens may be a determining factor in regard to the size of the group which may enter the adjacent 4-position. In other words the smaller chlorine atom may permit an alkyl group larger than butyl to enter the ring. However, n-amyl chloride was again cleaved and ethyl 4-t-butyl-5-chloro-2-furoate was the only product isolated.

Ethyl 4,5-dibromo-2-furoate has the 4-position blocked as well as the 5-position and the remaining 3-position is very resistant to substitution as evidenced by its quantitative recovery in an attempted nitration (60). If any alkylation of this compound occurred at all, cleavage of higher alkyl halides would be expected. Unfortunately there was no alkylation, with cleavage or otherwise, using n-amyl chloride.

Since n-amyl bromide was observed to displace the 5-bromine atom in ethyl 5-bromo-2-furoate in some manner and introduce a t-butyl group in its place, it seemed possible that the same result might be obtained with ethyl 4,5-dibromo-2-furoate. However, there was no reaction, and the original furan derivative was recovered quantitatively. The same result was obtained in attempted alkylations with both t-butyl bromide and isopropyl chloride.

An attempt to acylate ethyl 4,5-dibromo-2-furoate with

(60) Wright, Doctoral Thesis, Iowa State College Library (1932).

acetic anhydride and stannic chloride was also without success.

Two attempts to alkylate 5-bromo-2-furfural with n-amyl chloride were unsuccessful. In the first run the reaction mixture was allowed to stir thirty-nine hours but no product could be isolated. When the reaction ran only five hours the recovery of 5-bromo-2-furfural was increased from 64% to 88%, but an intractable tar was again the sole product.

Catalysts.

Aluminum chloride was used as the catalyst in all the experiments described in this work, with one exception, in which anhydrous ferric chloride was substituted. However, there was considerable variation in the purity, particle size and amount of the aluminum chloride used in the cleavage alkylations discussed above.

a. Composition. Many different brands of anhydrous aluminum chloride are on the market and almost as many grades. Of five different brands used in this work the analyses were different for four of them and not known for the fifth. Except for resublimed material which was practically pure white, the color ranged from yellow to dark grey. Iron is a consistent impurity but varies considerably from 0.1 per cent to 0.002 per cent as maximum limits in these samples. The iron undoubtedly exists as ferric chloride.

Ferric chloride has an unpredictable influence on the activity of aluminum chloride in Friedel-Crafts reactions. Alone, ferric chloride is generally considered a poorer condensing agent in alkylation than aluminum chloride (51, 61, 62, 63), but in some cases it increases the activity of the latter, reaching a maximum at about 50 mole per cent (61). Other investigators (64) have found a similar phenomenon to exist in acylation, but in alkylation they observed that a maximum activity is reached in some reactions at a very much lower per cent of ferric chloride than fifty per cent. Percentages as low as 0.012 were found to greatly increase the velocity constant but more substantial amounts (about 3 per cent) decreased it again. In contrast to this is the observation that in some reactions there is an initial decrease in the yields as ferric chloride is added to aluminum chloride followed by an increase when large amounts are present (65). The latter effect was observed in benzene solution and a second type of reaction in this solvent was also found in experiments with mixtures of ferric chloride with aluminum chloride. The second type consisted of reactions in which the yields decreased consistently in proportion to the amount of ferric chloride added

- (61) Boswell and McLaughlin, Can. J. Res., 1, 400 (1929).
(62) Gallay and Whitby, ibid., 2, 31 (1930).
(63) Wertyporech, Kowalski and Roeske, Ber., 66, 1232 (1933).
(64) Martin, Pizzolato and McWaters, J. Am. Chem. Soc., 57, 2584 (1935).
(65) Riddell and Noller, ibid., 54, 290 (1932).

to the aluminum chloride. In carbon disulfide it appeared that all the reactions were of this second type (65). Most of this work was done with acid chlorides and acid anhydrides but some alkylation reactions were also used. A reaction reported earlier by the latter investigators falls into the above second type, since the yield is decreased in proportion to the amount of ferric chloride present (66). It is postulated that the detrimental action of ferric chloride is due to the acceleration or inauguration of an unknown side reaction.

From these accounts it is seen that the presence of ferric chloride has pronounced effects on the reaction but the cause for such effects is obscure. While the differences are quantitative it is conceivable from the above postulation regarding the acceleration or inauguration of side reactions that different grades of aluminum chloride might produce variations in the cleavage alkylation of ethyl 5-bromo-2-furoate. n-Amyl chloride gave the same alkylation regardless of the amount (0.002 to 0.1 per cent) of iron in the aluminum chloride, although there were slight differences in the yields, being greater with aluminum chloride relatively free of iron.

In check runs on the doubly anomalous alkylation of ethyl 5-bromo-2-furoate with n-amyl bromide in which there is a combination of cleavage and bromine replacement, it was found that

(66) Riddell and Noller, J. Am. Chem. Soc., 52, 4365 (1930).

Eastman's resublimed aluminum chloride would not give the bromine replacement product obtained with the material marketed by Baker and Adamson. The maximum limits of iron in the samples were 0.02 per cent and 0.08 per cent, respectively. Since the amount of iron present seemed to be the main difference between the two reactions it seemed plausible that the larger amount of iron was responsible for the side reaction (replacement of bromine). In an attempt to prove this theory an amount of ferric chloride calculated to give a mixture 0.12 per cent iron was added to a sample of Eastman aluminum chloride and the reaction repeated. There was bromine replacement with this combination but only to a slight extent in comparison with the yields obtained with the Baker and Adamson product.

Perhaps a better test of the influence of impurities in the aluminum chloride was an experiment in which the aluminum chloride used was a sample of Baker and Adamson product which had been sublimed and resublimed just before use. This purification gave white granules with only a tinge of yellow in the larger particles. With this catalyst there was no replacement of the bromine by a t-butyl group.

If traces of ferric chloride will promote the side reaction, (replacement of bromine by a t-butyl group), it seemed possible that ferric chloride alone would guide the reaction in this direction to a greater degree or perhaps even give 5-t-butyl-2-furoic acid entirely. Unfortunately this catalyst

was not active enough to cause any reaction at all.

A factor commonly believed to be the explanation for the variation in the yield of product sometimes obtained by using different lots of commercial grades of aluminum chloride, is the presence of moisture. It is possible that the less pure Baker and Adamson aluminum chloride contained more moisture than resublimed material but addition of a drop of water to a run with the latter catalyst did not appreciably change the reaction.

b. Particle size. Since one brand of aluminum chloride was available in three different particle sizes (coarse, medium and fine), it was thought desirable to investigate the effect of this difference, if any. The reaction between ethyl 5-bromo-2-furoate and n-amyl bromide was chosen since it seemed to be influenced profoundly by other minor differences in the catalyst. A series of three experiments under identical conditions using aluminum chloride marketed by the Hooker Electrochemical Company, in various degrees of fineness, gave essentially identical results. Both ethyl 4-t-butyl-5-bromo-2-furoate and 5-t-butyl-2-furoic acid were obtained in amounts that were practically the same for all three runs. This is not at all surprising since there are only two liquid phases shortly after the reactions are begun.

c. Amount. The amount (two equivalents) of aluminum chloride used in the experiments discussed to this point is noteworthy, for it constitutes an excess of one hundred mole per cent. Likewise in alkylations of other furan derivatives such as methyl 2-furoate, this same unusually large excess of catalyst was used.

As mentioned in the introduction of this thesis, one of the significant differences between alkylation and acylation reactions is that the former usually requires a small amount of metal halide and is truly catalytic, a good example of which is the alkylation of benzene with n-octadecyl bromide (67). On the other hand the latter type of reaction requires at least one equivalent of condensing agent to give the maximum yields. Most often a slight excess (1.1 equivalent) is used for acylations and in some reactions the use of a large excess tends to decrease the yield again (65). However, this is not common, since two equivalents of aluminum chloride are frequently used in acylations with acid chlorides.

It would seem at first consideration that the excess of catalyst used in the present work is superfluous. A series of experiments were made to determine whether this large excess or any excess is necessary, and if it is, what the causal factor is. The "vanishing point" of this cleavage alkylation

(67) Seidel and Engelfried, Ber., 69, 2567 (1936).

with respect to the amount of aluminum chloride was found to be one equivalent. That is, a trifle less than one equivalent (0.95) failed to produce any reaction while slightly more than one equivalent (1.1) was sufficient to induce cleavage alkylation, although to a lesser extent than with two equivalents. Similar phenomena were observed in alkylations of ethyl 5-bromo-2-furoate in which there was no cleavage, and also in an alkylation of methyl anisate, so the cleavage reaction is not the factor requiring the excess. It is quite obvious then that the ester group adds the first equivalent of aluminum chloride which is in accord with general observation.

Solvents.

Carbon disulfide is the best all-around solvent for most Friedel-Crafts reactions in so far as promotion of reaction and maximum yields are concerned. Also its low boiling point serves to act as a temperature control. On the other hand it is dangerous material to work with both from the standpoint of fire hazard and the poisonous nature of its fumes. More important is the handicap it produces by forming thio compounds which cannot be removed by distillation. Also, in some of this work, its high volatility was an obstacle in collecting gaseous products from cleavage alkylations. In fact these last two disadvantages of carbon disulfide were principal reasons

for the experiments with other solvents.

While the furan ring has been shown to have super-aromatic properties with regard to ease of alkylation by the Friedel-Crafts reaction (50) the deactivating effect of a carboalkoxy group and a bromine atom on the nucleus is strong enough to reduce the aromaticity of the furan ring in ethyl 5-bromo-2-furoate to below that of unsubstituted benzene. Obviously the latter cannot be used as a solvent for alkylations of ethyl 5-bromo-2-furoate.

Nitrobenzene has a high boiling point and gives no bothersome side reactions in Friedel-Crafts reactions, but this compound has what might be called a damping effect on the catalytic activity of aluminum chloride. Since the yields in the alkylation of ethyl 5-bromo-2-furoate are poor even in carbon disulfide which is considered to be a superior solvent in its ability to promote reactions, it seemed questionable that nitrobenzene would be satisfactory. Repeated attempts to alkylate ethyl 5-bromo-2-furoate with n-amyl chloride in this solvent were unsuccessful, so this surmise was apparently correct. There was, however, a small amount of neutral material isolated from the reaction mixture which contained nitrogen but no halogen. Recrystallization gave yellow needles melting at 86-87.5°. This was shown to be m-dinitrobenzene, an impurity commonly present in commercial nitrobenzene.

Chlorobenzene was found to be unsatisfactory as a solvent

since ethyl 5-bromo-2-furoate was recovered quantitatively when treated with aluminum chloride and n-amyl chloride in chlorobenzene, while a mixture of alkylated chlorobenzene derivatives was obtained.

Mixtures of paraffin hydrocarbons (petroleum ethers) are sometimes used as solvents in Friedel-Crafts reactions. Since even the regular higher boiling petroleum ethers contain traces of volatile hydrocarbons which would be objectionable when collecting gaseous reaction products a very high boiling sample was used. Kerosene has a high enough boiling point but contains unsaturated material. By redistillation and repeated shaking with concentrated sulfuric acid most of the impurities were removed and the sample was practically odorless. An attempted alkylation of ethyl 5-bromo-2-furoate with n-amyl chloride was without success in this solvent.

While the use of s-tetrachloroethane was contemplated early in this work unfortunately it was not until the last of this work that this solvent was actually tried. The results were very gratifying with this solvent, for ethyl 5-bromo-2-furoate is alkylated smoothly by n-amyl chloride giving water clear products on the first distillation. The yield of ethyl 5-t-butyl-2-furoate was 21 per cent.

In many Friedel-Crafts reactions with benzene, an excess of the hydrocarbon is used as the solvent. While ethyl 5-bromo-2-furoate is certainly not to be likened to unsubstituted

benzene too closely, it is conceivable that an excess of this furan derivative might serve as a suitable solvent in an alkylation of itself. Further, some Friedel-Crafts reactions can be run without any solvent. n-Amyl chloride with a hundred per cent excess of ethyl 5-bromo-2-furoate and one equivalent of aluminum chloride gave a strong evolution of hydrogen chloride but most of the ethyl 5-bromo-2-furoate was recovered unchanged and partly as 5-bromo-2-furoic acid. There was no alkylated product.

Equimolecular amounts of n-amyl chloride and ethyl 5-bromo-2-furoate in the presence of two equivalents of aluminum chloride gave a copious evolution of hydrogen chloride and the reaction soon became an immobile tar. Hydrolysis yielded a brown solid product which gave a small amount of 5-bromo-2-furoic on ether extraction. This solid was the aluminum salt of 5-bromo-2-furoic acid. There was no alkylated product and the recovery was almost quantitative.

Reaction Period.

It will be noted that the time of reaction in all but a few of the foregoing experiments was twenty-four hours or more. This is longer than the reaction period commonly used for Friedel-Crafts reactions and it appeared to be unnecessary. Experiments showed this to be so. Alkylation of ethyl 5-bromo-

2-furoate with n-amyl chloride gives the same results when the reaction is allowed to proceed five hours that it does for twenty-four hours. The cleavage alkylation obtained with n-amyl iodide which was allowed to run only six hours, on account of the liberation of free iodine, is further evidence that a shorter time than twenty-hours is sufficient. An attempt to introduce a group larger than butyl into ethyl 5-bromo-2-furoate by allowing the reaction to go only one hour was not successful in that the usual ethyl 4-t-butyl-5-bromo-2-furoate was still obtained, but the experiment proved that this very much shorter time would still permit reaction. The alkylating agent used here was n-octadecyl bromide. However, the yield was smaller which apparently was due to the short reaction period.

These observations were made after many of the other reactions had been run and to keep the conditions constant without a great deal of repetition, the use of a twenty-four hour period was continued.

Mechanisms of Cleavage Reactions

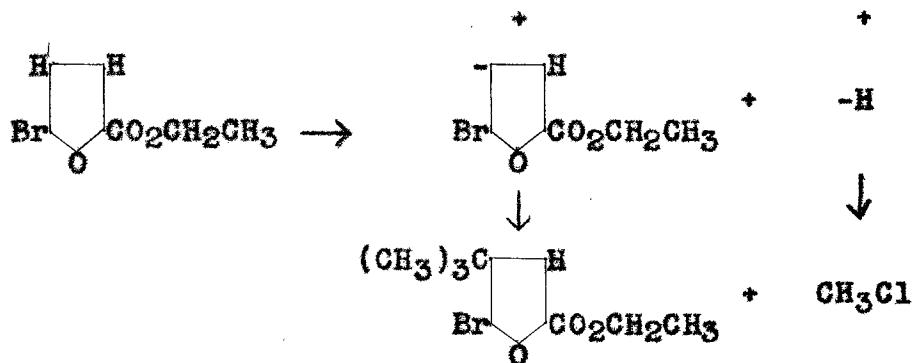
Possible Mechanisms.

Since the cleavage alkylation of ethyl 5-bromo-2-furoate has no close antecedent, there is little existing information

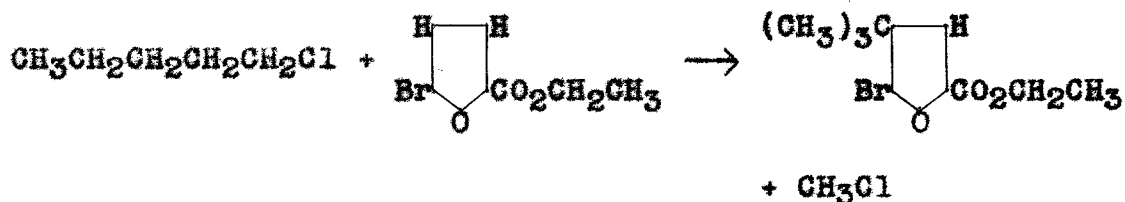
on which a mechanism for this reaction can be based. While at first contemplation the process of the cleavage may seem to be simply a scission at the fourth carbon from the functional group in the alkylating agent, there are inconsistencies which cannot be explained by such a scheme alone.

Obviously the cleavage must occur before, concurrent with or after the actual attachment of the alkyl group to the furan ring. These may be illustrated as follows with n-amyl chloride:

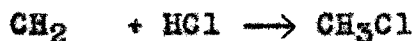
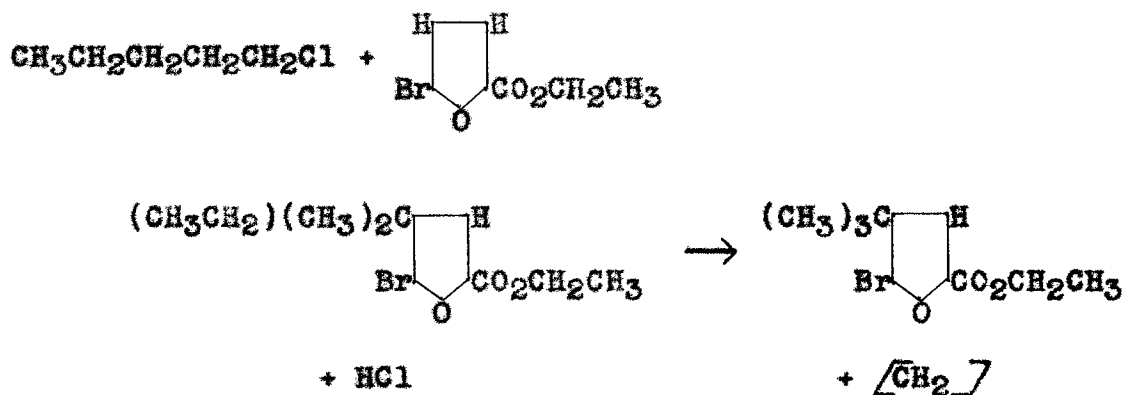
I. Cleavage Before Alkylation



II. Cleavage Concurrent With Alkylation



III. Cleavage After Alkylation



These mechanisms do not show the actual rearrangement of the straight chain to a branched one and this may be tied up with the cleavage. However, the phenomenon of isomerization of alkyl radicals to the most highly branched arrangement is common in alkylations by the Friedel-Crafts reaction in general and without exception with furan derivatives whether there is cleavage or not. It is probable that the rearrangement occurs simultaneously with the actual alkylation, although it may take place after the group has become attached to the ring.

The first two mechanisms, I and II, are the most probable

of the three but to determine which of these is correct is impossible since I probably approaches II as a limit. To simplify the discussion the last mechanism will be eliminated, for in no case has there been a rupture of an aliphatic carbon-carbon bond when there was an alkyl to aryl carbon-carbon linkage present. That is, the latter is so much weaker that scission would occur there completely before the other linkages would break at all. Of course there must be a momentary break in the bonds within the side chain, if rearrangement occurs after alkylation, and one of the carbons might be pared off, as it were, during this transition. Still the process of rearrangement here is undoubtedly like those in other alkylations where there is no cleavage, so the latter scheme is highly improbable.

The mechanisms under I will be seen to be very similar to those postulated by Grosse and Ipatieff (41) for "destructive alkylation" with paraffins. The fact that the experimental conditions for the latter reactions were mild (with regard to temperature) is supporting evidence for the analogy implied here. A feature that tends to discredit cleavage before alkylation is the absence of any cleavage with methyl 2-furoate and 2-furfural under similar experimental conditions. If mechanism I takes place, a similar process should occur with

methyl 2-furoate and at least some methyl 5-t-butyl-2-furoate should be formed, which is contrary to facts. Reasoning which serves to explain this inconsistency is as follows. There is very probably a factor of steric hindrance which is largely responsible for the cleavage during alkylation of ethyl 5-bromo-2-furoate. That is, the presence of the large substituent (bromine) in the α -position prevents an alkyl group larger than t-butyl from entering the adjacent β -position. This blocking effect prevents orthodox alkylation by an amyl group, so the cleavage reaction, which is less readily induced than ordinary alkylation, occurs first. The scission takes place at the particular linkage which will give a butyl group, rather than some other bond, for the same reason that practically every other cleavage in Friedel-Crafts reactions gives this same four-carbon group, whatever that reason may be. Alkylation occurs subsequent to the formation of a group small enough to enter the 4-position.

When cleavage is referred to as occurring before alkylation, in differentiation to cleavage at the same instant of joining the alkyl group to the ring, what is meant is that the splitting into fragments takes place just before alkylation, approaching a concurrent process as a limit. Thus there is very little difference between the two. The hydrogens on the furan ring are loosened by the action of the aluminum chloride, and when an activated fragment is formed by the cleavage, the

4-hydrogen is displaced by it.

In the above postulated mechanism the other product from the cleavage is assumed to be methyl chloride. It is questionable that this alkyl halide would retain its identity under the existing conditions; but if it remains unchanged long enough for it to be evolved, then its collection and identification should be good evidence for this type of cleavage.

A theory has been proposed that the t-butyl groups in ethyl 4-t-butyl-5-bromo-2-furoate, obtained in the Friedel-Crafts reaction between the higher alkyl halides (containing more than four carbon atoms) and ethyl 5-bromo-2-furoate, originated from the four carbons in the furan ring. This postulation has a certain amount of foundation in that furan compounds are sensitive to acids, and ring scission undoubtedly occurs in some cases with acidic reagents. Even the vastly more stable nuclei of benzenoid types have been observed to break down on treatment with aluminum chloride. Ipatieff and Komarewsky (68) obtained small yields (1.7%) of ethyl benzene when they heated benzene to 125° in the presence of aluminum chloride and hydrogen chloride. They explain the reaction as involving destructive hydrogenation of the benzene to form ethylene which subsequently alkylates unchanged benzene. A similar experiment with cyclohexane at 150° gave dimethyl-

(68) Ipatieff and Komarewsky, J. Am. Chem. Soc., 56, 1926 (1934).

cyclohexane which was formed by isomerization of the ethyl radical, subsequent to the synthesis of ethylcyclohexane by a process like that just described for benzene. Another ring scission of a saturated hydrocarbon ring is the formation of cyclohexane, methylcyclohexane and 1,3,5-trimethylcyclohexane from decalin by the action of aluminum chloride at 130° observed by Jones and Linstead (69) (an isomer, probably trans-1,4-dimethylbicyclo (0,3,3)-octane, was also isolated).

The singularity of the formation of ethyl 4-t-butyl-5-bromo-2-furoate here, and the consistency with which butyl derivatives are obtained as the only product add to the plausibility of the scheme involving scission of the furan ring to give a butyl radical. The fact that there is an excess of catalyst is also conducive to such reasoning.

Even considering all these favorable premises, there is good argument to discount this theory. In the first place the conditions of experiment with furan derivatives are certainly not comparable to those used in the ring cleavages just cited in spite of the high concentration of aluminum chloride. Furthermore, the furan derivatives that give this reaction are exceptionally stable ones in this series and no other instance has been reported of a Friedel-Crafts reaction with furan compounds, including less stable members, in which there is reason

(69) Jones and Linstead, J. Chem. Soc., 616 (1936).

to suspect ring scission, except where total decomposition resulted.

More convincing and absolute are the results of experiments intended to test directly for ring cleavage and subsequent alkylation by the open chain. A blank run under identical conditions, except for the omission of the alkyl halide, gave quantitative recovery of the ethyl 5-bromo-2-furoate. To make the conditions simulate more closely a Friedel-Crafts reaction, hydrogen and hydrogen bromide were bubbled successively into the mixture. Recovery was almost quantitative in the form of the acid. Perhaps still better tests, although inadvertent, were the number of negative results obtained with such potential sources of alkyl groups as butylene, amylene, stearonitrile, cyclohexyl chloride, cyclohexylene, and t-amylphenol. A series of experiments conducted under rather strenuous conditions were three attempts to alkylate ethyl 5-bromo-2-furoate using n-amyl chloride and an excess of the furoate as a solvent instead of carbon disulfide. In one run moderate heating (50-80°) was employed. The only reaction was formation of the acid (corresponding to the original ester) and its aluminum salt, in which forms the recovery was practically quantitative, in all three runs. Most conclusive is the fact that 91% of the furan ring is accounted for in the alkylation of ethyl 5-bromo-2-furoate with n-octadecyl bromide and the yield of alkylated product is in excess of the unreckoned 9%. The yield of

ethyl 4-t-butyl-5-bromo-2-furcate here was 46% with 45% recovery of the starting material. In other cases the sum of the yield and recovery approximate this total.

Collection of Fragments.

A large size run (0.45 mole) involving every care to collect all products showed the actual cleavage to be of a more complex nature than any of the mechanisms pictured above. If any methyl chloride were formed, it was subsequently decomposed, for no trace of this compound could be found among the several products. While the cleavage undoubtedly occurred at the 1,2-carbon-carbon bond, the fragment containing one carbon atom (methyl, chloromethyl or methylene radical) polymerized to form resinous compounds. Ethane, propane and butanes plus a small amount of pentane constituted the gaseous portion of the products. However, only small amounts of ethane and propane were obtained, while the main fraction consisted of n-butane and isobutane. This preponderance of butane is in keeping with the results of other investigators.

The cleavage products obtained do not elucidate the problem as much as was hoped. The absence of any alkyl chlorides (e.g. methyl or ethyl chloride) and the copious evolution of hydrogen chloride point to a preliminary splitting out of hydrogen chloride to give an olefin. Experimental results

which are conducive to this reasoning are those obtained with a mixture of ethyl 5-bromo-2-furoate, n-amyl chloride and aluminum chloride (no solvent). From this was evolved a large amount of hydrogen chloride, but the ethyl 5-bromo-2-furoate was recovered quantitatively, so the hydrogen chloride must have come from the n-amyl chloride. None of the latter reagent was recovered. Another experiment, in which n-amyl chloride alone was added to aluminum chloride, resulted in prompt evolution of hydrogen chloride, butanes and pentane. The non-volatile product was of a resinous nature and unsaturated, judging from its practically complete solubility in concentrated sulfuric acid. The absence of any gaseous products containing less than four carbons is noteworthy, in that small amounts of propane and either ethane or methane, or both, were obtained from a cleavage alkylation of ethyl 5-bromo-2-furoate with n-amyl chloride. This difference in cleavage products would indicate that there is a difference in the way n-amyl chloride is cleaved in these reactions. This might be expected since the conditions were substantially different.

If hydrogen chloride were initially split out from n-amyl chloride in the cleavage alkylation reaction, followed by the cleavage of a carbon-carbon bond, the alkylating agent would undoubtedly be butylene. However, butylene failed to alkylate ethyl 5-bromo-2-furoate in repeated efforts. This fact discredits the process just described, unless one makes the un-

warranted assumption that the butylene formed by such a cleavage is in an activated state.

With the hope of isolating larger fragments, principally tetradecanes, an alkylation of ethyl 5-bromo-2-furoate with n-octadecyl bromide was run using s-tetrachloroethane as the solvent, in which run all products were collected. This alkylation proved to be even more complex than with n-amyl chloride. While the gaseous fractions consisted only of butanes, pentanes and hexanes, the liquid products were impossible to separate cleanly by ordinary fractional distillation. Small amounts of what appeared to be paraffin hydrocarbons were obtained, boiling continuously from 25°/atmospheric pressure up to about 230°/2mm. Surprisingly the yield of ethyl 4-t-butyl-5-bromo-2-furoate was very small (10%) in comparison with the yield (46%) obtained with carbon disulfide as the solvent.

The absence of any fragments containing less than four carbons (ethane or propane) from n-octadecyl bromide is significant in that these products obtained from n-amyl chloride were probably formed by polymerization and hydrogenation from methylene radicals instead of direct cleavage. That is, the lowest hydrocarbon obtained by direct cleavage of alkyl halides appears to be butane.

Steric Hindrance in the Furan Ring.

As already mentioned in the previous section the cause for

the cleavage phenomenon observed with ethyl 5-bromo-2-furoate when alkylated by higher alkyl halides is primarily steric hindrance in the furan ring. If the bulky bromine atom in the 5-position prevents the introduction of a group larger than a t-butyl radical, it should exert a similar influence, if it were present in the 4-position. Thus ethyl 4-bromo-2-furoate alkylated with n-amyl chloride might be expected to give ethyl 4-bromo-5-t-butyl-2-furoate. An attempt to carry out this reaction was partly indeterminate, for an inseparable mixture of products was obtained which contained the main alkylated product. However, a comparatively good yield of ethyl 5-t-butyl-2-furoate was isolated. Formation of the latter compound is strong evidence in favor of the above steric hindrance postulation, for the actual alkylation must have occurred before the bromine atom was split out, since ethyl 2-furoate is alkylated by n-amyl chloride to give ethyl 5-t-amyl-2-furoate exclusively.

An alkylation of ethyl 5-chloro-2-furoate was run with the idea of throwing more light on the steric hindrance phase of this problem. The presence of the smaller chlorine atom should still exert a blocking influence in the furan ring but to a lesser degree than bromine. From this reasoning one might expect that n-amyl chloride would alkylate ethyl 5-chloro-2-furoate to give ethyl 4-t-amyl-5-chloro-2-furoate but that hexyl and higher alkyl halides would still give the amyl

derivative. However, n-amyl chloride was again cleaved and ethyl 4-t-butyl-5-chloro-2-furoate was the only product isolated. The difference between the sizes of a bromine atom and a chlorine atom is not very great, so this is not surprising. A better test of the effect of steric hindrance would be an alkylation of 5-fluoro-2-furoate with n-amyl chloride. The radius of a fluorine atom is considerably smaller than that of a chlorine atom, so it might permit alkylation by n-amyl chloride without cleavage.

Conclusions.

From the data collected in the present work the following conclusions can be drawn.

1. Ethyl 5-bromo-2-furoate is alkylated only by the more active alkylating agents, specifically alkyl halides and t-alcohols among those tried.

2. Alkylation of ethyl 5-bromo-2-furoate is invariably accompanied by cleavage and rearrangement of the alkyl group to a t-butyl group.

3. The presence of a large group such as a bromine atom in either the 4- or 5- position in ethyl 2-furoate causes cleavage of an amyl group to a butyl group in the process of alkylation.

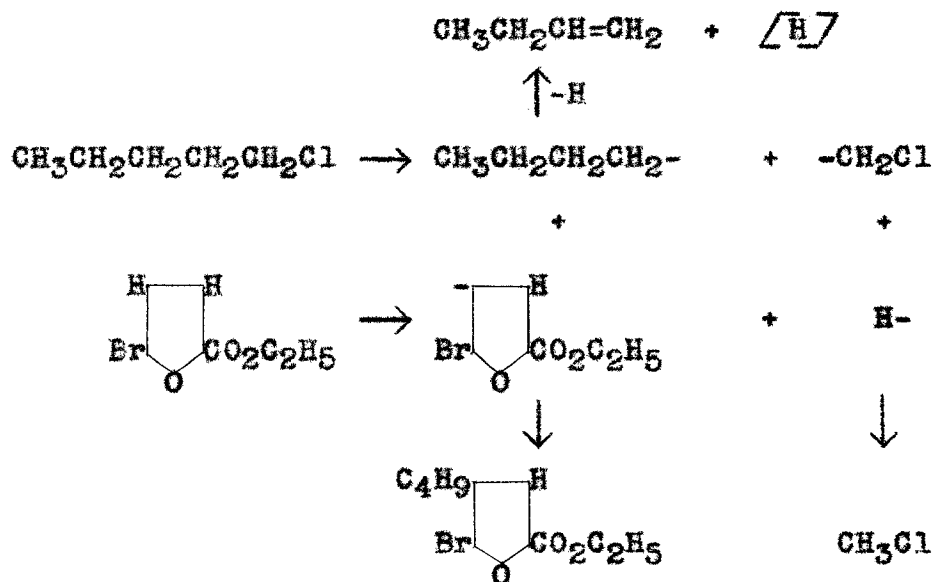
4. An active catalyst is required to alkylate ethyl 5-

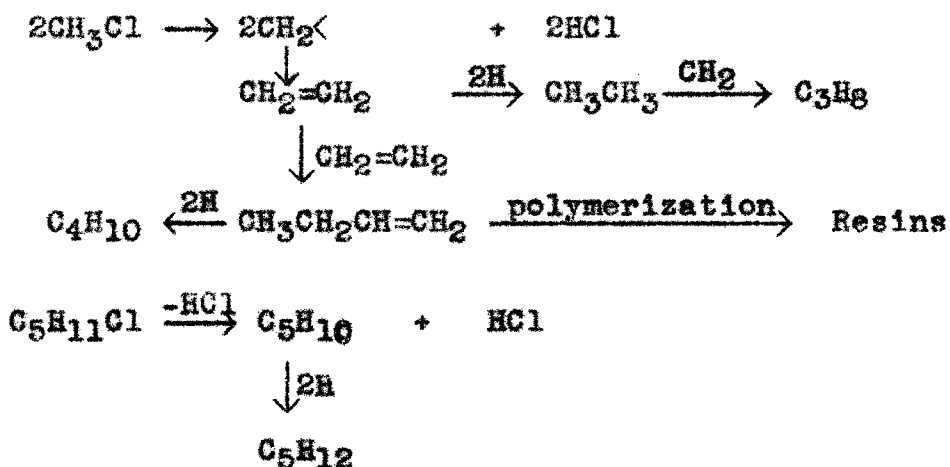
bromo-2-furoate, and an excess of one molar equivalent of catalyst must be used. The first equivalent combines with the carbethoxy group in such a way as to destroy its catalytic properties.

5. Cleavage alkylation of ethyl 5-bromo-2-furoate appears to be very rapid in that the evolution of the gaseous products was almost instantaneous, although the formation of cleavage by-products from n-octadecyl bromide is very gradual.

6. The cleavage reaction is not a simple process and is further complicated by polymerization of some of the fragments.

7. From the results and reasoning set down in the foregoing pages the following mechanism for cleavage alkylation of ethyl 5-bromo-2-furoate with n-amyl chloride is postulated to explain the formation of the products obtained:





Introduction of a Straight Chain by Alkylation

In a recent publication Seidel and Engelfried (67) described the alkylation of benzene with n-octadecyl bromide by the Friedel-Crafts synthesis in which they used a catalytic amount (15 mole per cent) of aluminum chloride. The product is simply called octadecylbenzene but there is the implication that their product was the same as the octadecylbenzene obtained by Krafft (70) by means of the Wurtz-Fittig reaction with n-octadecyl iodide and iodobenzene and the octadecylbenzene synthesized by Adam (71) through reduction of stearophenone. These last two methods of synthesizing alkylbenzenes are commonly accepted as being reliable means of introducing straight

(70) Krafft, Ber., 19, 298 (1886).

(71) Adam, Proc. Roy. Soc. (London), 103A, 684 (1923).

chains into an aromatic nucleus. While Seidel and Engelfried report a wide boiling range (25 degrees) for their product, which would suggest a mixture of isomers, they apparently obtained only one compound on sulfonation and subsequent formation of the sulfonamide. If their reference to the work of Krafft and of Adam signifies that the same product is obtained by all three methods of synthesis, then this Friedel-Crafts alkylation is anomalous, for there is a marked branching effect in this type of reaction which has already been emphasized.

Mention should be made at this point of work by Calloway (72) in which normal-alkylated products were obtained in high yield by allowing the alkylation to proceed for a short period of time. However, the reaction period employed by Seidel and Engelfried was much longer (total of forty-eight hours) even than ordinary alkylations where rearrangement to branched chains is predominant.

Since the exact nature of the side chain in the octadecylbenzene obtained by alkylation was unsettled, it was considered important to establish the inference of Seidel and Engelfried that it is straight. To accomplish this, three samples of octadecylbenzene were prepared by the three different methods mentioned. Since it was difficult to obtain sharp

(72) Private communication from Dr. N. O. Calloway to Dr. Henry Gilman.

melting points for the resulting hydrocarbon products, which melted slightly above room temperature, a standard derivative was prepared of each. Under identical treatment three samples of octadecylbenzenesulfonamide were obtained each melting at 99-100°. Mixed melting points with the three combinations possible showed no depressions. This is evidence that the alkylation product from n-octadecyl bromide and benzene in the presence of aluminum chloride is n-octadecylbenzene.

Comparison of the sulfonamide of a known branched-chain octadecylbenzene with these samples would give a more complete proof, if this new product were found to be different. Directions have recently been reported (73) for the preparation of several secondary octadecyl alcohols from substituted malonic esters. The corresponding octadecyl bromides from these alcohols would serve admirably in this proposed study, although use of tertiary isomers in addition would be still better.

Forced Acylation of Stearophenone with Stearoyl Chloride

Two attempts were made to prepare distearoylbenzene by acylating stearophenone under forced conditions with stearoyl chloride. Both were unsuccessful, for the only products ob-

(73) Brunner and Wiedman, Monatsh., 66, 4382 (1935).

tained besides recovered stearoyl chloride and stearophenone were stearone and o- and p-chloroaniline. In the first attempt equimolecular amounts of stearophenone, stearoyl chloride and aluminum chloride were heated in a sealed tube at 205° for about two hours. A liquid fraction was obtained on working up the product, but it was found to consist chiefly of stearophenone. An inseparable mixture of solid compounds which were probably stearophenone and stearone was the only other substance isolated besides a large amount of stearic acid from the recovered stearoyl chloride.

A second run was made at atmospheric pressure in nitrobenzene as solvent. Two equivalents of aluminum chloride was used to one equivalent each of stearophenone and stearoyl chloride. The solution was heated at 100° (bath) for twenty-four hours. The only products obtained were stearophenone, stearic acid, stearone, and minute amounts of o- and p-chloroaniline. Formation of the last two compounds was also noted in attempted forced alkylations of nitrobenzene with isobutyl and isopropyl bromides (56).

EXPERIMENTAL PART

Alkylation of Ethyl 5-Bromo-2-Furoate
with Alkyl Halides

n-Amyl Chloride.

The procedure used in this reaction is essentially that given by Gilman and Burtner (35). It is described here for review and to serve as a standard in other reactions. Considerable detail will be given of this and some other experiments, for slight variations sometimes appear to produce profound differences in the reaction.

In this series of experiments where the idea was to test the effect of varying the alkylating agent, it was of course necessary to keep the other factors constant. For this reason it will not be necessary to give the conditions in future experiments in this study, except for slight changes.

Tenth molar quantities of ethyl 5-bromo-2-furoate (21.9 grams) and of n-amyl chloride (10.6 grams) were used, together with a 100% excess (two-tenths mole in all) of catalyst, aluminum chloride (26.7 grams). With these amounts 200 cc. of carbon disulfide was used as a solvent.

For this size run it was found most convenient to use a 500 cc. three-necked flask. An efficient condenser fitted with a calcium chloride tube was fixed in one side-neck and a small dropping funnel in the other. An effective mercury sealed

stirrer in the center neck completed the set-up. The apparatus was placed in a ventilated hood to conduct away the hydrogen chloride evolved through the condenser.

The anhydrous aluminum chloride in powdered form was placed in the flask and about 150 cc. of carbon disulfide added. The brand and grade of aluminum chloride was Baker and Adamson's anhydrous, reagent quality, "Lot No.6", containing a maximum of 0.08% iron as the main impurity. The carbon disulfide was water-clear and dried over calcium chloride. Some lots required distillation, in case they were not perfectly clear and colorless.

The ethyl 5-bromo-2-furoate was prepared from purified 5-bromo-2-furoic acid. The latter compound was synthesized by refluxing 2-furoic acid with one and one-half moles of bromine in carbon tetrachloride for eight hours.

The n-amyl chloride was Eastman's reagent quality, dried over calcium chloride. This was used without further purification.

Experiments showed that the order of addition of the ethyl 5-bromo-2-furoate and n-amyl chloride to the aluminum chloride made no difference. Neither did the addition of a solution of the two reagents cause any modification of the reaction. However, in the series of experiments with alkyl halides the ethyl 5-bromo-2-furoate was added first followed by slower (about fifteen minutes) addition of the alkyl halide, unless

otherwise stated.

Stirring was continued for twenty-four hours, at the end of which time the contents of the flask were slowly poured into a 1:1 mixture of cracked ice and water (hood). Vigorous stirring is essential throughout this hydrolysis, especially toward the end when the thick, lower layer runs out. The mixture was shaken in a separatory funnel and the lower carbon disulfide layer tapped off. Considerable insoluble solid material was usually present which proved to be 5-bromo-2-furoic acid. This compound is unusually insoluble in carbon disulfide, and ether must be used to completely extract it. Three ether extractions were made and combined with the carbon disulfide solution. A saturated sodium bicarbonate solution was used to extract the acidic products. Three extractions with about 50 cc. each were found sufficient to completely remove the acids. The neutral solution was dried over sodium sulfate and the mixed solvents distilled off.

The residual liquid was transferred to a 50 cc. Claisen flask with indentations. After removing the last traces of solvent with a water pump, the red to black product was distilled at a pressure of 5 mm. The following fractions were collected: (1) 85.5-93.5°, 12.6 grams; (2) about 130-150°, 3.7 grams. A second and more careful fractionation gave: (1') 86-91°, 10.0 grams; (2') 91-130°, 3.1 grams; (3) 130-142°, 215 grams. Higher boiling products (up to about 180°) were also collected,

but they could not be separated into definite boiling fractions and would not saponify. On standing they rapidly turned to a semi-solid, black tar. After considerable unsuccessful effort to isolate definite compounds from these intractable resins it was concluded that they were polymerization products and were discarded, if they would not saponify. In addition to this distilled material there was always a considerable amount (2 to 7 grams) of tarry residue which solidified on cooling. These were likewise considered to be polymerized material and not further investigated after a few attempts to saponify some of them.

All the distillates contained traces of thio compounds which imparted a dark red color to them, especially the higher boiling products. These impurities could not be removed by any amount of distilling and were a constant impediment in purifying and identifying the products. The disagreeable odor of all the products was due also to these sulfur compounds. Their only virtue in this work was their service as a preliminary criterion of successful alkylation in carbon disulfide solvent. That is, where there was no alkylation there were no sulfur compounds formed and consequently no red coloration, and vice versa.

Fraction (1) was practically pure ethyl 5-bromo-2-furoate. Fraction (2) was a mixture of ethyl 5-bromo-2-furoate and ethyl 4-t-butyl-5-bromo-2-furoate, with the latter predominant.

ing. The third fraction, (3), was ethyl 4-t-butyl-5-bromo-2-furoate (total yield, about 15% of the theoretical). Here, as in other experiments, the wide boiling range of the alkylated product was due to small amounts of resinous material and traces of the ever-present sulfur compounds. Further distillation did not give much purer products, so two fractionations generally constituted the extent of the purification of the esters.

The products were identified by saponifying with 20 per cent alcoholic potassium hydroxide. Refluxing for about ten minutes was generally sufficient to saponify the esters. On cooling, the alcoholic solution was added to several times its volume of distilled water. The red color disappeared on this treatment. If any oily or flocculent material separated out on cooling in an ice bath, it was filtered through a cone filter, which retained the insoluble matter. A few chips of ice were dropped in the flask and concentrated hydrochloric acid added cautiously with swirling till the solution changed Congo red paper to blue. The higher boiling portions either gradually gave a crystalline deposit on standing or a brown oil separated out at once, which crystallized slowly on standing in the cold, depending on whether the product was pure or contaminated with resinous material.

While the crude acid from the first fraction melted only three to four degrees lower than pure 5-bromo-2-furoic acid

(186-187°), the crude acid from the alkylated product melted twenty to thirty degrees below that (163-164°) of pure 4-t-butyl-5-bromo-2-furoic acid. Pure 5-bromo-2-furoic acid is to be contrasted with 4-t-butyl-5-bromo-2-furoic acid in regard to the great depression in melting point produced by a small amount of foreign organic material in the alkylated acid. This alkylated compound has the further disadvantage of being the more soluble of the two in water and organic solvents. Fractional sublimation was found valuable in the purification of these acids, and a combination of this method with recrystallization was used to isolate a pure sample. Identification was effected by the method of mixed melting point.

The yield was calculated from the amount of alkylated ester obtained from the second distillation compared with the theoretical amount. The intermediate fraction was considered to be approximately half recovered ethyl 5-bromo-2-furoate and half ethyl 4-t-butyl-5-bromo-2-furoate. Careful separation and identification of the first runs showed this to be a reasonable assumption. From the above discussion it is evident that the alkylated product after two distillations contains appreciable impurities and the yield based on its amount is not an absolute value. The yields in this and other experiments become more relative than exact, but the duplication of conditions furnishes some justification for such a procedure. Unless otherwise stated the per cent yields are based on the

theoretical amount of product possible.

Acidification of the above sodium bicarbonate extract gave varying amounts (2 to 7 grams) of acid which was practically all 5-bromo-2-furoic acid, although small amounts of 4-t-butyl-5-bromo-2-furoic acid were separated in some runs.

t-Amyl Chloride.

After two unsuccessful attempts to alkylate ethyl 5-bromo-2-furoate with t-amyl chloride a third run gave a small amount of ester which yielded ethyl 4-t-butyl-5-bromo-2-furoic acid on saponification. The following fractions were collected on distillation: (1) 84-92°/5mm., 12.8 grams; (2) 123-130°/5mm., 1.0 gram; (3) 140-150°/5mm., 1.0 gram. Fraction (1) was recovered ethyl 5-bromo-2-furoate. Fractions (2) and (3) were mainly ethyl 4-t-butyl-5-bromo-2-furoate (yield, 6% of the theoretical amount).

n-Amyl Bromide.

In addition to the usual set-up, a cooling bath (10-15°) was applied to the flask in these experiments during addition of reactants. In the first runs of this reaction, as with some of the other alkylating agents, the whole crude product was distilled without removing the acid products with sodium bicarbonate beforehand. Thus the principal alkylated product

here came over as the corresponding acid on distillation: (1) 94-99°/5-6mm., 5.0 grams; (2) 99-125°/5-6mm., 4.5 grams; (3) 125-245°/5-6mm. (partly solidified), 5.4 grams. After standing several hours the liquid portion of (3) was separated from the main solid material. The latter weighed 5.2 grams and melted at 104-105°. The compound was acidic and gave a negative test for halogen. The neutralization equivalent was 168. This value and the melting point exactly check those of 5-t-butyl-2-furoic acid. A mixed melting point determination showed no depression (yield, 31%).

A second distillation of the liquid fractions gave: (1') 88-91°/5mm., 4.3 grams; (2') 91-94°/5mm., 3.1 grams; (3') 103-125°/5mm., 0.9 gram. Fractions (1') and (2') were recovered ethyl 5-bromo-2-furoate. On saponification of (3'), only 5-bromo-2-furoic acid was isolated, although there was probably some undetected ethyl 5-t-butyl-5-bromo-2-furoate in this fraction.

Another run gave 10.0 grams of recovered ethyl 5-bromo-2-furoate and 6.8 grams of 5-t-butyl-2-furoic acid (yield, 40%).

The fact that this product was always isolated as the acid may be explained by its apparent extreme ease of hydrolysis. That is, the acid solution resulting from the decomposition of the aluminum chloride complex with water seemed to be sufficient to hydrolyze completely the primarily formed ethyl 5-t-butyl-2-furoate.

To make sure of the identity and purity of the starting materials physical constants were taken. Values obtained for the saponification equivalent of the ethyl 5-bromo-2-furoate used were 211 and 214. The theoretical value is 219. The boiling point of the *n*-amyl bromide was 128° which checks the value (127.9°) given in a recent edition of a Handbook of Chemistry and Physics.

As another means of checking this reaction, a fresh lot of ethyl 5-bromo-2-furoate was prepared from especially purified 5-bromo-2-furoic acid, collecting the middle fraction on distillation at 94.5-97.5/5mm. Saponification equivalents of this material were 209 and 207. These values as well as those above are slightly low, but this determination tends to give low results and the presence of a small amount of already hydrolyzed ester, 5-bromo-2-furoic acid, would give a low experimental value.

Several new samples of *n*-amyl bromide were combined and distilled over calcium chloride through a long fractionating column. The first and last parts of the distillate were kept separate, although the whole boiling range was only $127-129^{\circ}$. The middle fraction (boiling at 128°) had a specific gravity of $1.215^{20^{\circ}}$. The value currently accepted is $1.223^{20^{\circ}}$. The observed value is slightly low but this could not be caused by the presence of any butyl bromide, for the specific gravities of the four possible isomers are equal to or greater than that

of n-amyl bromide. Elementary analysis gave a positive test for bromine and negative tests for chlorine and iodine. To further establish the presence of a n-amyl group the alkyl halide was converted to a Grignard reagent. Treatment of the latter with α -naphthyl isocyanate gave n-capro- α -naphthalide melting at 93-95° after purification. This was shown to be identical with samples of capro- α -naphthalide prepared from n-amyl chloride and α -naphthyl isocyanate and from n-caproyl chloride and α -naphthyl amine.

A run with these identified reagents gave results similar to those in the first two runs. A check on this reaction by Dr. J. M. Straley, using entirely separate materials, likewise gave similar results.

Isoamyl Bromide.

The additions were made with cooling as in the experiments with n-amyl bromide and stirring was continued for forty hours here. Distillation gave: (1) 89-96°/5mm., 8.5 grams; (2) 96-119°/5mm., 2.8 grams; (3) 119-135°/5mm., 4.8 grams. No solid material appeared in any of these fractions. A second fractionation gave: (1') 88-93°/5mm., 8.5 grams; (2') 105-118°/5mm., 1.8 grams; (3') 119-127°/5mm., 3.8 grams. Fraction (1') was recovered starting material, and (2') and (3') were principally ethyl 4-t-butyl-5-bromo-2-furoate (20% yield). In a second

run, an aqueous sodium bicarbonate extraction was used, but the only acid from this was 5-bromo-2-furoic acid.

n-Amyl Iodide.

A cooling bath was applied during the additions, and the reaction was allowed to continue only six hours because free iodine was liberated in the reaction flask. More iodine sublimed out during the first part of the distillation. The following fractions were collected: (1) 84-94°/5mm., 12.0 grams; (2) 94-110°/5mm., 4.5 grams; (3) 113-130°/5mm. (partly solidified), 7.2 grams. The solid material in (3) was 5-bromo-2-furoic acid. Redistillation of the liquids gave: (1') 86-94°/5mm., 11.0 grams; (2') 110-115°/5mm., 3.1 grams; (3') 115-122°/5mm., 3.8 grams; (4) 131-145°/5mm., 0.6 gram. Small amounts of 5-bromo-2-furoic acid separated out in all these fractions on standing, except (4) which solidified completely. Fraction (1') was recovered ethyl 5-bromo-2-furcate. Fractions (2') and (3') gave 4-t-butyl-5-bromo-2-furoic acid on saponification (yield of ester, 25%).

n-Hexyl Bromide.

A check run with n-hexyl bromide gave results similar to those originally obtained by Gilman and Burtner (35). Tenth molar quantities gave 1.7 grams of crude ethyl 4-t-butyl-5-

bromo-2-furoate (6% yield).

n-Hexyl Chloride.

Using the usual procedure, n-hexyl chloride and ethyl 5-bromo-2-furoate gave the following fractions on distillation at 5mm.: (1) 93-95°, 9.5 grams; (2) 98-120°, 4.3 grams; (3) 126-163°, 5.2 grams. Redistillation gave: (1') 88-93°, 7.8 grams; (2') 93-95°, 2.5 grams; (3') 118-131.5°, 5.6 grams; (4) 150-165°, 2.0 grams. Fractions (1') and (2') were recovered starting material. Fraction (3') was ethyl 4-t-butyl-5-bromo-2-furoate and the yield was 20% of the theoretical. Part of (4) crystallized on standing. These crystals were 5-bromo-2-furoic acid. The sodium bicarbonate extract gave 6.0 grams of crude acid, melting at 182-184° on pressing on clay plate. A mixed melting point with 5-bromo-2-furoic acid gave no depression.

Cyclohexyl Chloride.

Merck aluminum chloride was used in this experiment. Distillation of the neutral product gave: (1) 85-90°/3-4mm., 7.7 grams; (2) 90-92.5°/3-4mm., 1.1 grams; (3) 142-170°/3-4mm., 4.0 grams. Portion (3) was fractionated to yield: (3') 125-148°/2mm., 3.3 grams; (4) 148-180°/2mm., 1.7 grams. Fraction (3') was in turn distilled again giving: (3'') 120-135°/2mm.,

1.0 gram; (3^a) 135-152°/2mm., 2.5 grams. Portions (1) and (2) gave 5-bromo-2-furoic acid on saponification. Fractions (3ⁿ) and (3^a) gave brown oils on attempted saponification which would not crystallize or solidify even after weeks of standing in the cold. Fraction (4) gave an oil on treatment with alcoholic potassium hydroxide and subsequent acidification which gave a few crystals after standing in the cold for a week. At the end of two weeks in the cold the brown sticky mass was dried on clay plate. An attempt to sublime this material gave a small amount of resin which crystallized slowly. After pressing on a clay plate the material melted at 118-141°. The oily product from (3^a) solidified after about one month in the cold. Recrystallization from carbon disulfide gave crystals melting at 144-151°. Sublimation of this material raised the melting point to 151.5-153°.

Separate ether extractions after three carbon disulfide extractions of the original hydrolyzed mixture yielded 4.6 grams of 5-bromo-2-furoic acid. The acid portion in the carbon disulfide extract weighed 4.5 grams, crude. Sublimation and washing with carbon disulfide gave pure 5-bromo-2-furoic acid.

Lauryl Bromide.

Distillation at 1 mm. gave: (1) 70-80°, 2 grams; (2)

80-90°, 9.5 grams; (3) 113-140°, 4.5 grams. Redistillation gave: (1') 70-80°/2mm., (2') 80-90°/2mm.; (3') 90-112°/1mm., 3.6 grams. Distillates (1') and (2') yielded 5-bromo-2-furoic acid on saponification. The first fraction may have contained some recovered lauryl bromide although it was not isolated. Fraction (3') was ethyl 4-t-butyl-5-bromo-2-furoate (yield, 13%).

Cetyl Bromide.

In this reaction 0.12 mole of ethyl 5-bromo-2-furoate and 0.12 mole of cetyl bromide were used with 0.24 mole of aluminum chloride. On the third fractionation of the products, the following distillates were obtained: (1) 92-98°/5mm., 3.7 grams; (2) 100-116°/5mm., 1.4 grams; (3) 125-130°/5mm., 5.3 grams. Saponification of these fractions gave: (1) 5-bromo-2-furoic acid, (2) and (3) 4-t-butyl-5-bromo-2-furoic acid (yield of ester, 20%).

n-Octadecyl Bromide.

After three fractionations two products were obtained boiling at: (1) 96-107°/4mm., 11.5 grams; (2) 120-128°/4mm., 14.8 grams. The corresponding acid of (1) was 5-bromo-2-furoic acid, and of (2), 4-t-butyl-5-bromo-2-furoic acid. The yield of ethyl 4-t-butyl-5-bromo-2-furoate was 46% of the the-

oretical amount.

γ-Phenyl-n-Propyl Bromide.

This alkyl halide gave the usual initial indications of alkylation in that considerable hydrogen halide was evolved and a deep reddish coloration occurred. Stirring was continued for twenty-eight hours. Careful distillation of the volatile solvent, after hydrolysis and extraction with carbon disulfide, gave no fraction corresponding to benzene, although the Glinsky column used permitted the partial separation of a synthetic mixture of one part of benzene in five of carbon disulfide. Distillation of the residue at reduced pressure gave: (1) 100-105°/12mm., 16.3 grams; (2) 105°/12mm. - 170°/2mm., 4.6 grams. Saponification of (1) gave 5-bromo-2-furoic acid. On standing a small amount of 5-bromo-2-furoic acid separated out from (2). Saponification of the liquid portion of (2) gave a sticky precipitate which was pressed on a clay plate. This material would not melt or sublime at 200° and 1mm. pressure. It was insoluble in water and ether but dissolved readily in ethyl alcohol and in dilute sodium bicarbonate solution. Acidification of the latter solution of the compound reprecipitated it. This new precipitate decomposed at 289° without melting but left no residue when ignited on platinum. A Beilstein copper wire test for halogen was negative.

Alkylation of Ethyl 5-Bromo-2-Furoate with t-Amyl Alcohol.

Two attempts were made to alkylate ethyl 5-bromo-2-furoate with t-amyl alcohol using an excess of the former reactant as a solvent. Two-tenths mole of ethyl 5-bromo-2-furoate (43.8 grams) was added rapidly to 0.05 mole of aluminum chloride (6.7 grams) with cooling. One-tenth mole of t-amyl alcohol (8.5 grams) was then added dropwise and stirring continued for twenty-four hours. After working up in the usual manner only one fraction boiling at 92-94° was obtained on distillation at 5mm. This weighed 43.3 grams and proved to be recovered starting material. A similar run using 0.15 mole of aluminum chloride with the same amounts of other reagents gave 41.7 grams of recovered ethyl 5-bromo-2-furoate as the only product.

A third run was conducted in the conventional manner with carbon disulfide. The reaction was marked by a slight fuming inside the reaction flask which may have been produced by the formation of water from the alcohol. Distillation gave the following fractions: (1) 92-98°/5mm., 20.0 grams; (2) 115-125°/5mm., 4.0 grams. Redistillation of (2) gave: (2') 95-100°/5mm., 0.5 gram; (3) 123-131°/4mm., 2.8 grams. Fractions (1) and (2') were ethyl 5-bromo-2-furoate, and (3) gave 4-t-butyl-5-bromo-2-furoic acid on saponification (yield of ester, 10%).

Alkylation of Ethyl 5-Bromo-2-Furoate with Olefins.

β-n-Amylene. Three attempts were made to alkylate ethyl 5-bromo-2-furoate with *β-n*-amylenes but the only products isolated from the reaction were recovered ethyl 5-bromo-2-furoate, 5-bromo-2-furoic acid and resinous material boiling over a wide range which would not saponify. In the last run the following was obtained on the second distillation at 5mm.: (1) 89-93°, 13.1 grams; (2) 110-120°, 0.7 gram; (3) 120-about 170°, 1.8 grams. Fraction (1) was recovered starting material. Fractions (2) and (3) were apparently polymerization products for treatment with alcoholic potassium hydroxide gave oils which would not crystallize or solidify even after months of standing in the cold. The sodium bicarbonate extract gave 5.0 grams of 5-bromo-2-furoic acid on acidification.

Cyclohexene. Cyclohexene gave no evidence of reaction on adding it (0.1 mole) to ethyl 5-bromo-2-furoate and aluminum chloride, so the mixture was refluxed for five hours. This treatment caused considerable hydrogen halide to be evolved. Distillation of the hydrolyzed product gave only one fraction boiling at 84-90° and 3mm. (3.7 grams). The residue could not be distilled further because of foaming and clogging of the condenser with a high melting solid. Sublimation of a representative portion of the total undistilled product at 160° and 3mm. gave only 5-bromo-2-furoic acid. The above distillate was recovered ethyl 5-bromo-2-furoate.

Butylene. Butylene behaved similarly to n-amylene, for a series of resins were obtained in each of three runs, but no alkylated product. In the first reaction, dry butylene was passed into a stirred mixture of ethyl 5-bromo-2-furoate and aluminum chloride in carbon disulfide with cooling in an ice bath. To measure the flow the butylene was bubbled through mineral oil. At the rate of about two bubbles a second the reaction flask gained 6.9 grams in about one and a half hours. This constitutes a slight excess over one equivalent. Only traces of hydrogen halide could be detected throughout the twenty-four hour reaction period. Distillation gave: (1) 90-93°/5mm., 10.4 grams; (2) 125-about 160°/5mm., 3.0 grams. A second fractionation of (2) gave: (2') 100-126°/5mm.,; (3) 135-165°/5mm.,; (4) 165-185°/5mm. Part (1) was recovered ethyl 5-bromo-2-furoate, which, with 10.0 grams of 5-bromo-2-furoic acid from the sodium bicarbonate extract, constitutes a 100% recovery. Attempts to saponify (2'), (3) and (4) were unsuccessful.

In the second run, an excess (2.6 equivalents) of butylene was used. This gave no better results, for recovery was almost quantitative and the high boiling products could not be saponified.

In the third run, using almost 3 equivalents of butylene, the reaction was allowed to proceed only three hours. The distillation of neutral products gave 19.3 grams of recovered

ethyl 5-bromo-2-furoate and high boiling syrupy material which failed to saponify. Absence of any acidic products marked this reaction.

Diisobutylene. In a 0.1 mole run, using the usual proportions, a mixture of diisobutylene and ethyl 5-bromo-2-furoate was added dropwise to the aluminum chloride suspended in carbon disulfide. A trace of hydrogen chloride was evolved at the start but ceased promptly. There was marked warming and slow coloration. After working up in the usual manner the following fractions were cut on distillation at 5mm.: (1) 85-93°, 16.6 grams; (2) 93-100°, 0.5 gram; (3) 116-135°, 1.6 grams; (4) 142-170°, 0.5 gram; (5) 170-195°, 0.8 gram. Fractions (1) and (2) were recovered ethyl 5-bromo-2-furoate while (3), (4) and (5) consisted chiefly of resinous material together with minute amounts of 5-bromo-2-furoic acid. The sodium bicarbonate solution extract yielded 3.0 grams of 5-bromo-2-furoic acid. The latter along with (1) and (2) constitutes a 95% recovery.

Alkylation of Ethyl 5-Bromo-2-Furoate with Stearonitrile.

Stearonitrile (26.5 grams) was dissolved in carbon disulfide (100 cc.) and added dropwise to the ethyl 5-bromo-2-furoate and aluminum chloride in the rest (100 cc.) of the carbon disulfide. Distillation gave the following fractions at 5mm.:

(1) 94-99°, 16.7 grams; (2) 100-184°, 8.3 grams; (3) 184-190°, 20.5 grams (melted at 41-42.5°). The first fraction was ethyl 5-bromo-2-furoate and (2) was a mixture of this and stearonitrile, while (3) was pure stearonitrile.

A second run was refluxed for twenty-four hours and allowed to stir another thirty hours at room temperature. Distillation gave: (1) 88-95°/5mm., 17.8 grams; (2) 97-169°/5mm., 6.0 grams; (3) 169-176°/5mm., 23.6 grams. Portions (1) and (3) were pure recovered ethyl 5-bromo-2-furoate and stearonitrile, respectively, while (2) was a 2:1 mixture of the two, respectively.

Alkylation of Ethyl 5-Bromo-2-Furoate with Alkylated Aromatic Compounds.

p-t-Amylphenol. Two attempts under different conditions were made to alkylate ethyl 5-bromo-2-furoate with p-t-amylphenol. In the first one an excess of the furan derivative was used as a solvent. In this case the aluminum chloride [8.7 grams (0.066 mole)] was added to a solution of 8.2 grams (0.05 mole) of p-t-amylphenol in 29.0 grams (0.132 mole) of ethyl 5-bromo-2-furoate. There was marked evolution of hydrogen halide. The mixture was heated at 75-85° (bath) for sixteen hours, which treatment caused it to become almost solid and dark red in color. Hydrolysis with warm water gave a light brown solid. Ether extraction yielded a residue, after

removal of the solvent, which on distillation gave 10.0 grams of ethyl 5-bromo-2-furoate and 3.3 grams of impure p-t-amylphenol. An aqueous extract of the solid gave 0.5 grams of 5-bromo-2-furoic acid. The extracted solid was shaken with dilute hydrochloric acid and ether to decompose the aluminum salt. This ether solution was separated and extracted with a saturated sodium bicarbonate solution. The latter extract gave 9.1 grams of 5-bromo-2-furoic acid. The remaining ether solution on drying and removal of the ether gave a semi-solid residue which was distilled. Two fractions were cut: (1) 95-100°/4mm., 1.5 grams; (2) about 113-125°/4mm., 1.2 grams. The first was a mixture of ethyl 5-bromo-2-furoate, 5-bromo-2-furoic acid and a small amount of p-t-amylphenol. Fraction (2) was almost pure p-t-amylphenol. No alkylated product or phenol was isolated.

In the second run a small amount (15 cc.) of carbon disulfide was used as the solvent with 0.05 mole each of ethyl 5-bromo-2-furoate and p-t-amylphenol in the presence of 0.066 mole of aluminum chloride. There was marked warming and evolution of hydrogen chloride at first but this soon stopped, and the mixture was refluxed twelve hours. The mixture was then allowed to stand seven days before hydrolyzing. There were no acidic products obtained from a sodium bicarbonate solution extract, and no other compounds were isolated except recovered p-t-amylphenol (6.4 grams) and ethyl 5-bromo-2-furoate (9.4

grams).

t-Amylbenzene. t-Amylbenzene (0.05 mole) with 0.05 mole of ethyl 5-bromo-2-furoate in the presence of 0.1 mole of aluminum chloride gave no evolution of hydrogen chloride although the usual dark coloration occurred. Distillation of the neutral products gave the following fractions: (1) 85-88°/5mm., 5.0 grams; (2) 89-150°/5mm., 1.0 gram; (3) 150-170°/5mm., 1.5 grams. The first fraction was recovered ethyl 5-bromo-2-furoate and the second distillate gave an acid with a wide melting range. Part (3) on saponification gave an acid melting at 174-179° in a crude state. Sublimation raised the melting point to 181-184.5°. A mixture of this compound and 5-bromo-2-furoic acid melted at 140-165°. Further sublimation and recrystallization from methyl alcohol-water gave crystals melting at 187-187.5°. This material likewise depressed the melting point (186-187°) of 5-bromo-2-furoic acid to 152-171°. An elementary analysis gave a negative test for halogen. Values found for the neutralization equivalent were 185.2 and 184.5.

Anal. Found: C, 73.31, 73.00, 73.45; H, 9.04, 8.17, 7.87. The average molecular formula calculated from the above data is $C_{11}H_{16}O_2$. This compound was not identified.

Alkylation of Other Furan Derivatives with Alkyl Halides.

Methyl 5-Bromo-2-Furoate. In a 0.1 mole run of methyl 5-bromo-2-furoate (20.5 grams) with n-amyl chloride (10.5 grams), the following products were obtained on distillation: (1) 82-90°/5mm., 15.2 grams; (2) 112-121°/5mm., 5.8 grams. Redistillation gave: (1') 82-90°/5mm., 15.1 grams; (2') 111-125°/5mm., 3.3 grams. Saponification of (1') gave 5-bromo-2-furoic acid and (2') gave 4-t-butyl-5-bromo-2-furoic acid. The yield of (2') was 22%.

Ethyl 4-Bromo-2-Furoate. Ethyl 4-bromo-2-furoate was prepared by reducing 4,5-dibromo-2-furoic acid with zinc dust and ammonium hydroxide to 4-bromo-2-furoic acid, which was subsequently esterified with ethyl alcohol. Details of this synthesis are given by Hill and Sanger (73).

The same conditions were used for the alkylation of ethyl 4-bromo-2-furoate with n-amyl chloride as those described for ethyl 5-bromo-2-furoate. In a 0.06 mole run the following fractions were obtained on the second distillation of the neutral part of the product: (1) 81-85°/4mm., 3.4 grams; (2) 95-105°/4mm., 3.6 grams; (3) 108-130°/4mm., 2.7 grams. Saponification of these distillates gave oils which crystallized slowly on standing in the cold. The first fraction gave long

(73) Hill and Sanger, Proc. Am. Acad. Arts Sci., 21, 135 (1885).

needles which melted at 97-100° after pressing on a clay plate. Recrystallization from dilute methyl alcohol, and then from high boiling petroleum ether (75-115°), raised the melting point to 102-104°. A mixed melting point with an authentic specimen of 5-t-butyl-2-furoic acid was not depressed. This product gave a negative test for halogen. Distillates (2) and (3) gave crude acids melting at 112.5-130° and 110-130°, respectively. These were combined and repeatedly sublimed and recrystallized from dilute methyl alcohol and then from petroleum ether (75-115°), but no pure fraction was obtained.

Ethyl 5-Chloro-2-Furoate. A solution of 24.7 grams (0.142 mole) of ethyl 5-chloro-2-furoate and 14.8 grams (0.142 mole) of n-amyl chloride was added dropwise with stirring to 37.7 grams (0.284 mole) of aluminum chloride in 200 cc. of carbon disulfide. After allowing to stir for twenty-four hours and working up in the usual fashion the following fractions were obtained on the second distillation at 19mm.: (1) 88-90°, 10.6 grams; (2) 95-106°, 1.4 grams; (3) 112-121°, 1.8 grams; (4) 121-136°, 1.5 grams; (5) 145-170°, 1.5 grams. Fraction (1) and (2) were recovered ethyl 5-chloro-2-furoate. Fractions (3) and (4) gave acids melting at 168-172-5°, after pressing on clay plate and sublimation. Recrystallization from petroleum ether (75-115°) gave needles melting at 172-173°. A mixed melting point with 4-t-butyl-5-chloro-2-furoic acid

(melting at 169.5-172°) obtained by alkylating ethyl 5-chloro-2-furoate with t-butyl bromide was not depressed. The purified acid gave a positive test for chlorine.

Anal. Calc'd. for $C_9H_{11}O_3Cl$: Cl, 17.50. Found: Cl, 17.58, 17.76. Values found for the neutral equivalent were: 201.4 and 202.5. The theoretical value is 202.6.

Ethyl 4,5-Dibromo-2-Furoate.

a. With n-amyl chloride. Using the general procedure, 0.2 mole (59.6 grams) of ethyl 4,5-dibromo-2-furoate with 0.2 mole (21.0 grams) n-amyl chloride gave the following on fractional distillation of the crude neutral products: (1) 79-92°/10mm., 2.3 grams; (2) 100-116°/8mm., 41.0 grams. The second fraction proved to be recovered ethyl 4,5-dibromo-2-furoate but (1) would not saponify. The amount of 4,5-dibromo-2-furoic acid (15.0 grams) obtained from the sodium bicarbonate solution extract, together with the recovered ester, corresponds to an almost quantitative recovery of the starting furan compound.

b. With n-amyl bromide. One-tenth mole (29.8 grams) of ethyl 4,5-dibromo-2-furoate with an equivalent amount of n-amyl bromide in the presence of aluminum chloride gave outward appearances of reacting, but after hydrolyzing and working up in the usual fashion, 15.0 grams of recovered ethyl 4,5-di-

bromo-2-furoate was obtained as the principal fraction on distillation (boiled at 110-120°/5mm.). A small amount of forerun to this fraction, boiling at 82-102°/5mm. (1.3 grams), would not saponify. The acidic product weighed 12.0 grams and was identified as 4,5-dibromo-2-furoic acid.

c. With t-butyl bromide. In a 0.1 mole run, ethyl 4,5-dibromo-2-furoate (29.8 grams) and t-butyl bromide (13.7 grams) gave the following products: (1) 80-92°/5mm., 1.0 gram; (2) 104-113°/5mm., 19.3 grams. The first fraction would not saponify. Fraction (2) was recovered ethyl 4,5-dibromo-2-furoate. About 8 grams of 4,5-dibromo-2-furoic acid was isolated from a sodium bicarbonate solution extract.

d. With isopropyl chloride. Isopropyl chloride (3.9 grams) gave no indication of reaction with ethyl 4,5-dibromo-2-furoate (15.0 grams) at room temperature, so the mixture was refluxed (46°) for six hours and then stirred at room temperature for another 18 hours. In spite of this treatment the original dibromo ester was recovered quantitatively.

5-Bromo-2-Furfural. To 53.2 grams (0.4 mole) of aluminum chloride were added 350 cc. of carbon disulfide and 35.0 grams (0.2 mole) of 5-bromo-2-furfural, and then 21.2 grams (0.2 mole) of n-amyl chloride was added dropwise. Hydrogen halide was evolved profusely and there was marked heating. After

stirring for thirty-nine hours the dark solution was hydrolyzed in ice-water and extracted with carbon disulfide. The organic layer was washed with water and then with a saturated solution of sodium acetate. Steam distillation in the presence of sodium acetate solution gave only 5-bromo-2-furfural (22.5 grams). A sticky black residue remained in the distilling flask.

A second run using 0.1 mole each of 5-bromo-2-furfural and n-amyl chloride with 0.12 mole of aluminum chloride was stirred only five hours. The catalyst was added last over a period of fifteen minutes with cooling in an ice-bath. The reaction became vigorous when the cooling bath was removed, so it was retained for the first three hours. On working up as above, a total of 15.4 grams of 5-bromo-2-furfural was recovered. No other compound could be isolated. These recoveries amount to 64% and 88%, respectively, of the amounts started with.

Variation of the Catalyst in Alkylation of Furan and Benzene Derivatives.

Composition. Using the same procedure as previously described for the alkylation of ethyl 5-bromo-2-furoate with n-amyl bromide (74), a purer grade (Eastman's resublimed) of aluminum chloride was substituted for the material marketed by Baker and Adamson used formerly. The maximum limits of iron

(74) This thesis, p.89.

in these two brands are 0.02% and 0.08%, respectively. From a 0.1 mole run the following fractions were obtained on distillation of the neutral portion of the crude product: (1) 90-94°/5mm., 11.1 grams; (2) 97-115°/5mm., 2.0 grams; (3) 124-140°/5mm., 3.4 grams. A second distillation gave: (1') 97-100°/5mm., 10.9 grams; (2') 124-131°/5mm., 2.8 grams; (3') about 140-150°/5mm., 1.0 gram. Fraction (1') gave 5-bromo-2-furoic acid, and (2') gave 4-t-butyl-5-bromo-2-furoic acid. The last fraction would not saponify. The sodium bicarbonate extract yielded about 3 grams of acid which was recrystallized from water. Neither the crystals obtained by this process nor the aqueous filtrate contained any 5-t-butyl-2-furoic acid. 5-Bromo-2-furoic acid was the only acid isolated. A check run using the same conditions gave similar results.

In a third run using Eastman's aluminum chloride, a small amount (0.1 gram) of anhydrous ferric chloride was added to the aluminum chloride. This gave a catalyst containing about 0.12% iron. The third fractionation at 5mm. of the neutral products gave the following: (1) 92-96°, 8.0 grams; (2) 96-128°, 0.8 gram; (3) 128-135°, 4.0 grams; (4) 139-165°, 1.0 gram. The first two fractions gave 5-bromo-2-furoic acid on saponification and the last two gave 4-t-butyl-5-bromo-2-furoic acid. The crude acid obtained from the sodium bicarbonate extract came down as an oil but solidified on standing. Fine needles growing out of the plastic solid melted at 88-120° after prese-

ing on clay plate. Recrystallization of the total crude acid from water gave crystals melting at 147-160°. The aqueous filtrate on ether extraction yielded 3.7 grams acid melting at 160-172° plus a small amount of needle like crystals which proved to be 5-t-butyl-2-furoic acid (mixed melting point) on isolation from the rest of the crystals. Recrystallization of the 160-172° melting material gave two different kinds of crystals in about equal amounts which could be separated mechanically. They were identified as 5-bromo-2-furoic acid and 5-t-butyl-2-furoic acid.

In another experiment using the same conditions and reactants, the catalyst employed was a sample of Baker and Adamson aluminum chloride which had been sublimed twice just before use. The second distillation of the neutral products gave: (1) 90-100°/5mm., 8.3 grams; (2) 108-126°/5mm., 1.3 grams; (3) 126-133°/5mm., 4.0 grams. The first fraction was recovered ethyl 5-bromo-2-furoate, (3) was ethyl 4-t-butyl-5-bromo-2-furoate, and (2) was a mixture of the two. The crude acid on recrystallization from water gave 3.0 grams of crystals melting at 180-183°. Ether extraction of the aqueous filtrate gave material melting at 150-167°, but no 5-t-butyl-2-furoic acid could be isolated as above.

When anhydrous ferric chloride (32.4 grams) was substituted for aluminum chloride with ethyl 5-bromo-2-furoate (21.9 grams) and n-amyl bromide (15.1 grams), there was no evidence of re-

action on mixing the reagents. Distillation at atmospheric pressure of the neutral products gave: (1) 126-132°, 4.0 grams; (2) 132-195°, 3.0 grams; (3) 195-227°, 20.3 grams. The first and third distillates were n-amyl bromide and ethyl 5-bromo-2-furoate, respectively, while the middle fraction was a mixture of the two. There was no acidic product.

Particle Size. In a series of three experiments with 0.1 mole n-amyl bromide and 0.1 mole ethyl 5-bromo-2-furoate, three samples of aluminum chloride of different particle size, produced by the Hooker Electrochemical Company were used. The "coarse" sample consisted of lumps about 0.5 to 1 cm. in diameter. The "medium" sample had the appearance of small gravel and the "fine" material was a powder. The reactions were the same in all respects, yielding a mixture of ethyl 4-t-butyl-5-bromo-2-furoate and 5-t-butyl-2-furoic acid. The following details are representative of the three runs. The second distillation gave: (1) 83-88°/5mm., 8.0 grams; (2) 98-112°/5mm., 2.0 grams; (3) 115-160°/5mm., 4.1 grams. The first two fractions gave 5-bromo-2-furoic acid and the third gave 4-t-butyl-5-bromo-2-furoic acid (yield of ester, 15%). From the sodium bicarbonate extract there was obtained 5.3 grams of acid melting at 126-148°. Purification of this by recrystallization from water gave principally 5-t-butyl-2-furoic acid plus a smaller amount of 5-bromo-2-furoic acid.

Concentration. In the following experiments the original procedure was changed, in that the aluminum chloride was added slowly to the carbon disulfide solution of the alkyl halide and the compound to be alkylated. A funnel for Gooch crucibles with a glass rod which just fitted into the stem, passing through a rubber stopper in the funnel mouth, served admirably as a hopper for the gradual introduction of the aluminum chloride. The addition took twenty minutes.

Using this new procedure, 0.095 mole of aluminum chloride with 0.1 mole each of ethyl 5-bromo-2-furoate and n-amyl chloride gave only the slightest outward indication of reaction, and 20.7 grams (94%) of the original ethyl 5-bromo-2-furoate was recovered. There was no alkylated product or acidic material.

With 0.11 mole aluminum chloride there was marked outward evidence of reaction and a small amount (0.6 gram) of ethyl 4-t-butyl-5-bromo-2-furoate was isolated (2% yield), together with 20.2 grams (91%) of recovered ethyl 5-bromo-2-furoate.

A 0.01 mole increase (0.12 mole in all) in the amount of aluminum chloride raised the yield to 2.8 grams of ethyl 4-t-butyl-5-bromo-2-furoate (10% yield).

For some reason the yield of ethyl 4-t-butyl-5-bromo-2-furoate was only 2.7 grams (10% yield) when 0.2 mole of aluminum chloride was used, adding the catalyst last.

t-Butyl bromide (0.1 mole) failed to alkylate ethyl 5-

bromo-2-furoate (0.1 mole) when 0.095 mole aluminum chloride was added to the solution gradually. The recovery of ethyl 5-bromo-2-furoate was almost quantitative (21.4 grams).

In a 0.1 mole run, 0.095 mole aluminum chloride was added to a solution of ethyl 5-bromo-2-furoate and isopropyl chloride. There were practically no signs of reaction and 21.0 grams (95%) of the starting furan compound was recovered. A check run gave identical results.

With 0.11 mole of catalyst, 0.1 mole each of ethyl 5-bromo-2-furoate and isopropyl chloride gave 11.0 grams or 42% of the theoretical amount of ethyl 4-isopropyl-5-bromo-2-furoate (distilled at 105-110°/3-4mm.).

An attempt to alkylate 0.084 mole methyl anisate with 0.084 mole isopropyl chloride in the presence of 0.075 mole aluminum chloride was unsuccessful, for, in addition to the absence of any evolution of hydrogen chloride, the only compound isolated from the reaction mixture was 94% of recovered methyl anisate (13.1 grams).

On the other hand, 0.11 mole of catalyst with 0.1 mole each of isopropyl chloride and methyl anisate gave 5.7 grams of an ester distilling at 145-152°/25mm. This product was saponified, yielding an acid which melted at 161.5-163° after recrystallizing from alcohol and water. Gilman and Calloway (50) assumed this acid to be 3-isopropyl-4-methoxybenzoic acid (yield of ester was 27%). The recovered methyl anisate weighed

11.3 grams (68%).

Alkylation of Ethyl 5-Bromo-2-Furoate with *n*-Amyl Chloride Using Different Solvents.

Nitrobenzene. Following the general directions, 21.9 grams (0.1 mole) of ethyl 5-bromo-2-furoate was added to 26.7 grams (0.2 mole) aluminum chloride in 200 cc. of dry nitrobenzene. Then 10.5 grams (0.1 mole) *n*-amyl chloride was added dropwise and stirring continued for nine hours. No hydrogen halide was evolved at any time. The hydrolyzed product was extracted with nitrobenzene. Distillation of the neutral portion of the product gave the following fractions: (1) 68.5-80°/5mm., about 400 cc.; (2) 84-85°/5mm., 15.1 grams; (3) 85-110°/5mm., 3.2 grams. The first distillate was mostly nitrobenzene, although some ethyl 5-bromo-2-furoate undoubtedly came over in this fraction, too. The second fraction and most of (3) was ethyl 5-bromo-2-furoate. The last part of (3) solidified and melted at 81-86°. No ethyl 4-*t*-butyl-5-brom-2-furoate could be isolated. There was no acidic product.

In a second run, 100 cc. of nitrobenzene was used with the above quantities of the other reagents. Stirring was maintained for twenty-four hours. After extracting the hydrolyzed mixture twice with nitrobenzene, two more extractions were made with ether. The combined extracts were dried over magnesium sulfate after washing with sodium bicarbonate solution.

After removing the ether the nitrobenzene was distilled at 57-65°/5mm. At 82-85°/5mm., 16.2 grams of recovered ethyl 5-bromo-2-furoate distilled. A third distillate came over at 103-130°/10mm. (2.5 grams), the last part of which solidified. The liquid part of the latter fraction was ethyl 5-bromo-2-furoate. The solid material melted at 86-87.5°. Elementary analysis gave a positive test for nitrogen and a negative test for halogen. A mixed melting point with m-dinitrobenzene (melting at 88-89°) was not depressed. The original aqueous solution after the ether extraction was made strongly basic with sodium hydroxide, but no basic product could be isolated by ether extraction of this solution.

Chlorobenzene. Using the same procedure described for the alkylation of ethyl 5-bromo-2-furoate with n-amyl chloride in carbon disulfide, a 0.1 mole run was made substituting 200 cc. of chlorobenzene for the carbon disulfide. Hydrogen chloride was evolved promptly and the homogeneous solution gradually became dark red. After working up in the usual manner at the end of twenty-four hours, the following fractions were obtained on distillation of the neutral products at atmospheric pressure: (1) 128-137°, about 200 cc.; (2) 137-150°, 7.0 grams; (3) 150-213°, 6.7 grams; (4) 65-82°/5mm., 0.8 gram; (5) 84-90°/6mm., 14.5 grams; (6) 103-190°/6mm., 3.0 grams. Fraction (1) was recovered chlorobenzene, and (2) contained some chlorobenzene

together with what was probably an amyl chlorobenzene. Fraction (3) appeared to be a mixture of alkylated chlorobenzenes. Distillate (4) consisted mostly of ethyl 5-bromo-2-furoate, while (5) was practically pure starting material. Fraction (6) contained a small amount of 5-bromo-2-furoic acid, the liquid portion being unsaponifiable resinous material. The acidic product isolated from the sodium bicarbonate extract was practically pure 5-bromo-2-furoic acid and weighed 6.3 grams. This acid together with fraction (5) above constitutes a 99% recovery of ethyl 5-bromo-2-furoate.

Kerosene. Ordinary kerosene was purified by shaking with small portions of concentrated sulfuric acid until fresh sulfuric acid was only slightly colored by the kerosene. This required about ten extractions. This treatment was followed by distillation through a fractionating column, collecting the portion boiling at 190-250°. Substituting this purified sample for carbon disulfide, a 0.1 mole run was made according to the usual procedure. While part of the kerosene boiled at the same temperature as ethyl 4-t-butyl-5-bromo-2-furoate, none of the distillates from the reaction product contained any of this compound. A check run of 0.05 mole, using kerosene recovered from the previous run and distilled at 188-210°, confirmed this negative result. One gram of material boiling at 100-160°/6mm. was obtained but could not be saponified.

s-Tetrachloroethane. The s-tetrachloroethane used in this experiment was the "technical" grade produced by the Eastman Kodak Co. Before use the solvent was distilled through a Glinsky column, and the fraction boiling at 140.5-143° collected. In a 0.1 mole run with ethyl 5-bromo-2-furoate and n-amyl chloride the following fractions were collected on distillation, after removing the solvent: (1) 80-95°/2mm., 16.3 grams; (2) 110-140°/2mm., 7.0 grams. A second distillation gave: (1') 81-84°/2-3mm., 13.8 grams; (2') 99-110°/2mm., 3.4 grams; (3') 110-115°/2mm., 3.8 grams; (4) 130-140°/1mm., 1.0 gram. Refractionation of (2') gave 1.4 grams boiling at 86-94°/5mm. and 1.9 grams boiling 110-118°/5mm. Fraction (1') and the first part of (2') were recovered ethyl 5-bromo-2-furoate. The last part of (2') and (3') were ethyl 4-t-butyl-5-bromo-2-furoate (yield, 21%). Distillate (4) was mainly ethyl 4-t-butyl-5-bromo-2-furoate. The sodium bicarbonate extract gave 1.6 grams acid, m.p. 140-172°, crude. On washing with carbon disulfide 1.0 gram of insoluble acid melting at 185-186.5° was left. The carbon disulfide solution yielded 4-t-butyl-5-bromo-2-furoic acid on evaporation and subsequent sublimation of the residue.

Ethyl 5-Bromo-2-Furoate. In this experiment no carbon disulfide was used but in its stead an excess of ethyl 5-bromo-2-furoate was employed as the solvent. n-Amyl chloride (0.1

mole) was mixed with 0.2 mole ethyl 5-bromo-2-furoate and the resulting solution added rapidly to 0.2 mole aluminum chloride with cooling and stirring. The addition was marked by strong evolution of hydrogen chloride and internal heating. The cooling bath was removed and stirring continued for four hours. Distillation of the crude neutral product after working up in the usual manner gave 39.0 grams recovered ethyl 5-bromo-2-furoate plus 1 gram of resinous material which would not saponify. The crude acid from the sodium bicarbonate solution melted at 178-183° (5-bromo-2-furoic acid).

A check run with stirring for twenty-four hours resulted in recovery of 42 grams (96%) of the original furan compound. No alkylated product could be isolated.

Variation of the Reaction Period in the Cleavage Alkylation of Ethyl 5-Bromo-2-Furoate.

In two experiments in which Eastman aluminum chloride was used, the reaction was allowed to proceed twenty-four hours in one experiment and five hours in the other. A 0.1 mole run with ethyl 5-bromo-2-furoate and n-amyl chloride under the usual conditions with twenty-four hours of stirring gave the following fractions on distillation: (1) 85-91°/5mm., 9.8 grams; (2) 97-110°/5mm., 1.6 grams; (3) 110-122°/5mm., 2.4 grams. The first fraction was recovered starting material, while (2) and (3) were mainly ethyl 4-t-butyl-5-bromo-2-

furoate (14% yield).

With five hours stirring the following products were obtained on the third fractionation: (1) 83-89°/5mm., 8.5 grams; (2) 100-127°/5mm., 4.6 grams; (3) 130-144°/5mm., 1.0 gram. The first fraction was recovered material and the second fraction was ethyl 4-t-butyl-5-bromo-2-furoate (16% yield). Distillate (3) contained a small amount of the latter compound plus resinous material.

In a 0.05 mole run using n-octadecyl bromide the reaction mixture was allowed to stir exactly one hour, at the end of which it was hydrolyzed and worked up in the usual manner. Four and one-half grams or 30% of the theoretical amount of ethyl 4-t-butyl-5-bromo-2-furoate was obtained from this reaction.

Collection of Fragments in the Alkylation of Ethyl 5-Bromo-2-Furoate with Alkyl Halides.

n-Amyl Chloride. An alkylation of ethyl 5-bromo-2-furoate with n-amyl chloride was carried out using purified s-tetrachloroethane as the solvent by the usual procedure, with collection of all gaseous products. The collection of gases was effected by connecting the calcium chloride tube in the spiral condenser cooled by tap-water to a spiral condenser designed to remove easily condensable gases. The outlet of this condenser was in turn connected to a gas reservoir filled with 20-30% aqueous potassium hydroxide. Carbon dioxide was used

to sweep out the system. This sweeping gas as well as the hydrogen halide evolved was absorbed by the basic solution in the reservoir leaving only neutral gases. The jacket around the second spiral condenser was open at the top and permitted cooling with various refrigerants, e.g. cracked ice (0°), ice-salt mixture (-20°) or "dry-ice"-acetone (about -70°). After the first run it was found profitable to collect the gases as they are evolved with cracked ice in the spiral condenser, for the reaction period is too long to maintain lower temperatures without a great deal of attention and large amounts of ice or "dry-ice". At the end of the collection the total unabsorbed gases were fractionated by passing them slowly back and forth through the spiral condenser cooled by various refrigerants.

In the first run, about 350 cc. of gas was collected over a seven-hour reaction period. Only a small amount of the total gas was condensed on passing through the second condenser cooled to -11° to -20° as it was evolved. Evaporation of this condensate gave an additional 100 cc. of gas. None of the gaseous products was identified in this run. An attempt to prepare a Grignard reagent with part of the gas was unsuccessful.

A second run was made using 0.5 mole each of ethyl 5-bromo-2-furoate and n-amyl chloride with 1.0 mole of aluminum chloride in 600 cc. of s-tetrachloroethane. The latter reagent

was material recovered from a previous run. The tetrachloroethane was added to the aluminum chloride upon which considerable hydrogen chloride was evolved, together with 50 cc. of gas which analyzed for butane. When gas evolution from this mixture had ceased (after seven hours) the ethyl 5-bromo-2-furoate was added. A large amount of hydrogen chloride was again evolved and another 40 cc. of butane was collected over a period of four and one-half hours, at the end of which time there was no more gas evolution. At this point 60 cc. of the brown solution in the reaction flask was withdrawn and worked up separately in the usual manner. No trace of alkylated ethyl 5-bromo-2-furoate could be found in this "blank". After removal of the above aliquot the n-amyl chloride was added dropwise. At the end of one and one-half hours 1500 cc. of gas had been collected. After sweeping out the system while the reaction flask was heated to 60° (bath) at the end of the reaction period (twenty-four hours), a total of 2100 cc. of gas was obtained. Of this, 1200 cc. was condensed at -20° and proved to be a mixture of isobutane, n-butane and pentane. These and other gaseous hydrocarbons were identified by their boiling points, chemical inertness and carbon-hydrogen analyses. The portion of the gas (920 cc.) uncondensed at -20° was cooled to -62° with "dry-ice" and acetone. Two pounds of "dry-ice" was used to cool the apparatus and two liters of acetone to this temperature. About half (520 cc.) of this fraction con-

densed on this treatment and slow distillation yielded 85 cc. of gas distilling at -51° to -20° which analyzed for 24% propane, containing a small amount of isobutane. The remaining 76% consisted of nitrogen, oxygen and carbon dioxide. The rest of the -62° condensate consisted of butanes and a trace of pentane. The 400 cc. of the original gas uncondensed at -62° was found to contain 16.5% oxygen and 27% of saturated hydrocarbons having an average carbon atom content of 2.35. This was very probably a mixture of ethane and propane. Absence of methane was assumed since large amounts of propane (b.p. -44°) would have to be present to give the found analysis, and the low temperature used would not permit this. At least the amount of methane present was very small.

n-Octadecyl Bromide. Collection of volatile products from a 0.1 mole run with n-octadecyl bromide and ethyl 5-bromo-2-furcate was effected in the same manner described for n-amyl chloride. A solution of n-octadecyl bromide in s-tetrachloroethane was added last, after cessation of gas evolution from the mixture of the other reagents. The second spiral condenser was cooled with cracked ice throughout the twenty-four hour reaction period, but only 0.3 cc. of tetrachloroethane was condensed in it. The system was swept very slowly with dry carbon dioxide during the entire period. The total volume of gas collected, after heating the reaction

flask to 60° (bath) at the finish, was twenty-five hundred cubic centimeters. All but 125 cc. of this gas was condensed to a water-clear liquid at -20°. This uncondensed residue was found to contain 60% isobutane, 6% unsaturated hydrocarbons, 7% oxygen and 27% nitrogen. The condensate was evaporated very slowly (six hours) through the spiral which was allowed to warm up gradually to 27°. The following fractions were cut: (1) -11° to -9°, 650 cc. collected (the first part was allowed to escape in order to sweep out the residual gas); (2) -7° to -4.5°, 95 cc.; (3) -4.5° to 0°, 100 cc.; (4) 0° to 25°, 115 cc.; (5) 25° to 27°, 65 cc.; (6) 48° to 49° (micro-boiling point), 0.3 cc. liquid. Fractions (1) and (2) analyzed for butane contaminated with 3.5 to 4.5% unsaturated material and 1 to 3% oxygen, respectively. Fractions (3) and (4) consisted principally of a mixture of butanes and pentane, containing average carbon atom contents of 4.2 and 4.6, respectively. These products analyzed for 3.2% and 3.5% unsaturated hydrocarbons, but the absorption reagent used (fuming sulfuric acid) will take up butane slowly, so the found "unsaturations" is very probably just part of the saturated hydrocarbon which makes up the major portion of these gases. Fraction (5) had an average carbon atom content of 5.6 and was undoubtedly a mixture of pentane and hexane.

The liquid portion of the product was worked up in the usual manner exercising care to collect all products. The

second distillation of the neutral products gave the following fractions at atmospheric pressure: (7) 50-60°, 1.2 grams; (8) 60-90°, 1.1 grams; (9) 90-141°, 2.8 grams; (10) 141-146°, about 400 cc.; (11) 150-185°, 2.0 grams; (12) 185-220°, 1.5 grams; (13) 83-91°/6mm., 17.0 grams; (14) 91-110°/6mm., 0.5 gram; (15) 120-130°/6mm., 2.5 grams; (16) 130-155°/6mm., 1.0 gram; (17) 145-175°/2mm., 1.3 grams; (18) 175-about 230°/2mm., 2.5 grams. The residue from the first distillation weighed 3.8 grams. Fractions (7), (8) and (9) were assumed to be paraffin hydrocarbon mixtures from their chemical inertness and odor. Distillate (10) was the recovered solvent, s-tetrachloroethane. Fractions (11) and (12) appeared to be mixtures of tetrachloroethane and recovered ethyl 5-bromo-2-furoate. Fractions (13) and (15) were practically pure ethyl 5-bromo-2-furoate and ethyl 4-t-butyl-5-bromo-2-furoate, respectively, while (14) was probably a mixture of the two. Distillates (16), (17) and (18) consisted mostly of unsaturated resinous material together with small amounts of water-clear inert liquids, insoluble in concentrated sulfuric acid. In fact all of the higher boiling fractions contained varying amounts of such saturated compounds.

Preparation of n-Octadecylbenzene.

By Alkylation of Benzene with n-Octadecyl Bromide. Using

the customary set-up for a Friedel-Crafts reaction, 16.6 grams (0.05 mole) of n-octadecyl bromide was added to 38 cc. of dry benzene, and then 1.0 gram (0.0075 mole) of aluminum chloride added in one portion. The mixture was stirred for thirty-four hours and then heated at 50° (bath) for four hours. After the mixture was hydrolyzed with cracked ice and water and allowed to warm up to room temperature the layers were separated and the aqueous layer extracted with benzene. After drying and removing the benzene, the crude product was distilled at reduced pressures. The second fractionation gave: (1) 149-154°/15mm., 2.5 grams; (2) 187-218°/15mm.; (3) 218-228°/15mm.; (4) 182-187°/1mm.; (5) 210-about 220°/1mm. (0.85 gram). Redistillation of (2), (3) and (4) gave two fractions: (2') 165-179°/1-2mm., 1.0 gram; (3') 187-197°/1-2mm., 8.3 grams. Fraction (3') was octadecylbenzene (50% yield), 5.0 grams of which was dropped gradually into 12.5 grams of fuming sulfuric acid (15-20 per cent sulfur trioxide) cooled in an ice-bath. The addition took thirty minutes, after which the flask was allowed to warm slowly to room temperature. After standing forty-five minutes at this temperature the flask was heated cautiously at 45-55° (bath) for thirty minutes. On cooling the black material was poured into ice-water, taken up in ether and this solution shaken with a saturated solution of sodium chloride. The resulting precipitate was filtered, washed with ether and re-crystallized from 50 per cent alcohol. The purified sodium

salt weighed 2.1 grams. This compound was mixed thoroughly with warming under anhydrous conditions with an equal weight of phosphorus pentachloride until the mixture became a liquid. After standing an hour, dry ammonia was led into the flask with heating and stirring for three hours. The solid product was washed with water. Recrystallization from absolute alcohol gave a white solid melting at 92.5-96.5°. Two recrystallizations from petroleum ether (60-68°) and subsequent sublimation raised the melting point to 99-100°. Further sublimation did not raise the melting point. This compound was identified as n-octadecylbenzenesulfonamide by mixed melting point. This procedure is essentially that described by Seidel and Engel-fried (67).

By the Wurtz-Fitting Reaction. The n-octadecyl iodide for this synthesis of n-octadecylbenzene was prepared by the action of gaseous hydrogen iodide on molten n-octadecanol at 100°.

Thirteen and eight-tenths grams (0.036 mole) of n-octadecyl iodide was dissolved in 35 cc. of dry benzene and 8.2 grams (0.04 mole) of iodobenzene added. To this solution 4.6 grams (0.2 gram atom) of metallic sodium, cut into thin strips, was added. Vigorous stirring is essential. After gentle warming for two and one-half hours the benzene was distilled off and alcohol added to destroy the excess sodium.

After dilution with 250 cc. of water the mixture was ether extracted, dried over magnesium sulfate and distilled after removing the ether. The second distillation gave a middle fraction boiling at 178-200°/1-2mm. (4.2 grams). These directions are essentially those of Krafft (69). The sulfonamide derivative of this product was prepared by the method described in the previous section. After recrystallizing from alcohol and petroleum ether (60-68°), crystals were obtained melting at 99-100°. A mixed melting point with the sample obtained through the Friedel-Crafts alkylation was not depressed.

By the Clemmensen Reduction of Stearophenone. The stearophenone used in this synthesis was prepared by acylation of benzene with stearoyl chloride in the presence of aluminum chloride.

Modifications by Martin (75) were employed in a Clemmensen reduction of 9.5 grams of stearophenone. Fifty grams of mossy zinc was amalgamated by shaking for five minutes with a solution of 5 grams of mercuric chloride in 2.5 cc. of hydrochloric acid diluted with 75 cc. of water. After decanting and rinsing the zinc amalgam with water, 37 cc. of water, 85 cc. of concentrated hydrochloric acid, 50 cc. of toluene and the stearophenone were added in the order given. Finally 2 cc. of

(75) Martin, J. Am. Chem. Soc., 58, 1438 (1936).

glacial acetic acid was added and the mixture refluxed briskly for twenty-eight hours. The aqueous layer was removed, a fresh charge of amalgamated zinc and dilute hydrochloric acid were added and refluxing resumed for forty-eight hours. During both these refluxing periods, 25 cc. portions of concentrated hydrochloric acid were added at about six to ten hour intervals. On cooling the organic layer was taken up in ether, dried and distilled at 2mm. after removal of the ether and toluene. The first fraction boiled at 185-200° and weighed 2.1 grams. After recrystallizing from methyl alcohol, the sulfonamide of this product was prepared by the procedure outlined on page 126. The n-octadecylbenzenesulfonamide obtained here melted at 99-100° after several recrystallizations from petroleum ether (60-80°). Mixed melting points with samples obtained through the alkylation of benzene and through the Wurtz-Fittig reaction showed no depressions.

For a contemplated alkylation of benzene, a sample of n-octadecyl chloride was prepared by means of the Darzan reaction. To 27.0 grams (0.1 mole) of n-octadecanol in 30 cc. of benzene, 0.1 cc. of pyridine was added and then 18.1 grams (0.152 mole) of thionyl chloride, dropwise with cooling. At the end of an hour the evolution of gas (sulfur dioxide, etc.) was very slight, so a cooling bath was again applied and 50 cc. of 10 per cent sodium chloride solution added with stirring. More benzene was added to keep the organic layer entirely

fluid. The benzene solution was separated and washed successively with 10 per cent sodium carbonate solution and 10 per cent sodium chloride. After drying over magnesium sulfate, the benzene was distilled off. The resulting solid was taken up in hot alcohol and then cooled to room temperature, upon which, recovered *n*-octadecanol precipitated. The filtrate yielded a semi solid which was distilled at 4-5mm. giving two fractions: (1) 176-182°, 3.6 grams; (2) about 200°, 1 gram. Fraction (1) was a clear liquid which gave a positive test for chlorine.

The yield in this preparation was greatly increased by M. R. McCorkle (76) by lengthening the reaction period.

Forced Acylation of Stearophenone with Stearoyl Chloride.

Using a long stem glass funnel 2.0 grams (0.0145 mole) of aluminum chloride was introduced into the bottom of a Carius tube. To this were added 5.0 grams (0.0145 mole) of stearophenone and 4.4 grams (0.0145 mole) of stearoyl chloride. There was a slow evolution of hydrogen chloride on mixing the reagents, so the lower end was cooled and the tube swept out with dry nitrogen. Such a procedure is necessary to prevent hydrogen chloride from coming in contact with the hot glass during the sealing, since this causes crystallization of the glass. The sealed tube was heated at 205° in an electric

(76) M. R. McCorkle, unpublished results.

Carius furnace for two hours. There was considerable pressure released when the seal on the cold tube was opened. The black product was taken up in ether, shaken with dilute hydrochloric acid and then with dilute sodium hydroxide solution, upon which a large amount of sodium stearate precipitated. After drying and removing the ether, the neutral product was distilled at 3mm. to give: (1) 213-240°, 1.2 grams; (2) about 320-330°/3mm., 1.2 grams. Fraction (1) was a liquid. An attempt to oxidize this product to a carboxylic acid with acidic sodium dichromate gave only a neutral solid which melted at 55-62° after sublimation. After further purification this material melted at 60-63° and was identified as stearophenone. The second distillate, (2), solidified and melted at 57-63° after recrystallization from ethyl acetate and from alcohol. Sublimation did not change this melting point, nor did another recrystallization from alcohol. This was probably a mixture of stearophenone and stearone.

In another experiment nitrobenzene (25 cc.) was used as a solvent using the usual set up for a Friedel-Crafts reaction. To the aluminum chloride (0.029 mole) in a 250 cc. three-necked flask were added the nitrobenzene, 0.0145 mole of stearophenone and 0.0145 mole stearoyl chloride in the order given. There was no hydrogen chloride evolved until the solution was heated in an oil-bath to 100° (bath). Heating was continued for twenty-two hours, and the solution was then hydrolyzed by pouring

into ice-water, followed by strong acidification with hydrochloric acid. After standing overnight this mixture was extracted with ether. This extract was shaken with sodium hydroxide solution. After drying, the ethereal solution yielded a black slush on removal of the solvent. Filtration of this residue and subsequent sublimation of the solid portion at 160-170°/4mm. gave almost pure stearophenone and a small amount of greasy material. Recrystallization of the latter gave a white powder melting at 75-83°. The above filtrate on distillation gave 11.0 grams of nitrobenzene and a fraction boiling at 200-205°/2mm. (solidified). Fractional sublimation of the latter gave mostly stearophenone plus a small amount of material melting at 80-83.5°. The latter was combined with the above product melting at 80-83°, and recrystallized twice from petroleum ether (60-68°) which raised the melting point to 85.5-86.5°. This was identified as stearone by a mixed melting point. From the original aqueous layer, left after ether extraction, were isolated very small amounts (about 0.1 gram) of p-chloroaniline (mixed melting point) and an oil which was probably o-chloroaniline. These products were obtained by making the solution strongly alkaline, subsequent ether extraction and fractional sublimation of the residue obtained from the ether extract (56). A very small amount of stearophenone was also recovered from this process.

SUMMARY

A study has been made of the limitations and mechanisms of some cleavage alkylations of alkyl 5-halogeno-2-furoate by the Friedel-Crafts reaction. With ethyl 5-bromo-2-furoate and various alkyl halides, cleavage begins with amyl halides to give ethyl 4-t-butyl-5-bromo-2-furoate and continues on through n-octadecyl bromide, giving the same product in every case. n-Amyl bromide exhibits a singular behavior in that it gives ethyl 5-t-butyl-2-furoate in addition to ethyl 4-t-butyl-5-bromo-2-furoate.

The octadecylbenzene prepared by alkylation of benzene with n-octadecyl bromide by the Friedel-Crafts reaction has been identified as the normal isomer, which is novel in view of the fact that alkylation with a n-alkyl halide is almost invariably accompanied by rearrangement to a branched chain.

An unsuccessful attempt was made to diacylate benzene with stearoyl chloride under forced conditions. Negative results were also obtained in attempts to bring about rearrangement of the n-alkyl group in stearophenone to a branched chain.