acetone, in which the higher derivatives were almost insoluble, while the corresponding alcohols were very soluble. Cooling with dry-ice was necessary to remove from solution the esters below tetradecyl.

The melting points were taken, with mechanical stirring, in a 200-cc. bulb, fitted with a side-arm for the thermometer and melting point tube. Standard Anschütz thermometers were used so the melting points may be regarded as corrected.

This problem was suggested by Dr. E. Emmet Reid, Research Adviser, University of South Carolina, and to him the authors wish to express their appreciation for his valuable help. The alcohols from decyl to octadecyl were furnished by Dr. Reid and were from those prepared by

Summary

The diesters of adipic acid from n-pentyl to n-eicosyl alcohols were prepared and the melting points determined. The melting points show slight alternation, the esters of the odd carbon alcohols being slightly higher than the even on the mean curve.

The Synthesis of 5-Methylchrysene and Related Compounds

BY MELVIN S. NEWMAN[1,2]

In a previous publication,[3] the author pointed out the desirability of synthesizing methyl derivatives of chrysene and described a new synthesis by which chrysene and 6-alkylchrysenes could be prepared readily. In order to explore the generality of this method for the preparation of various chrysene derivatives desired for biological testing in connection with the cancer problem, further work has been done. In this paper, the syntheses of 5-methylchrysene, 5-ethylchrysene and 5,6-dimethylchrysene are described, together with a new and more generally applicable procedure for the preparation of α,γ-diphenylbutyric acid, an important intermediate.

The α,γ-diphenylbutyric acid previously[3] used was prepared in five steps, of which the first was the condensation of benzaldehyde with acetophenone. The second step involved 1,4-addition of hydrogen cyanide to the chalcone thus produced. It was feared that in certain projected syntheses, the corresponding chalcones (bearing alkyl groups on the α-carbon) might prove difficult to prepare or purify and also that conditions for the addition of hydrogen cyanide might be difficult to find.[4] In the present work α,γ-diphenylbutyric acid was prepared by the alkyla-

tion of benzyl cyanide with phenethyl bromide using sodium amide.[5] The α,γ-diphenylbutyronitrile thus produced was hydrolyzed to the corresponding acid in excellent yield. Inasmuch as a variety of substituted phenethyl bromides and of substituted benzyl cyanides is easily prepared, the new approach is seen to be quite general.

The cyclization of the acid chloride of α,γ-diphenylbutyric acid by aluminum chloride was further improved (94% yield) by decreasing the time of reaction.[3] It was also determined that if the volatile phosphorus compounds formed when the acid was treated with phosphorus pentachloride were not removed prior to the treatment with aluminum chloride, the yield was decreased to 77%. The remaining steps in the synthesis are indicated in the chart.

The Reformatsky condensations of 1,2,3,4-tetrahydro-1-keto-2-phenylnaphthalene, I, with ethyl α-bromopropionate and ethyl α-bromobutyrate proceeded smoothly and the corresponding unsaturated acids, II (R = CH_3 and C_2H_5), were isolated in fair yields. The double bond is placed in the ring instead of the alternate position of conjugation with the carboxyl group as in the analogous case of 3,4-dihydro-2-phenyl-1-naphthaleneacetic acid.[3] It is interesting to note that from the neutral fraction of the reaction products (after dehydration and hydrolysis) con-
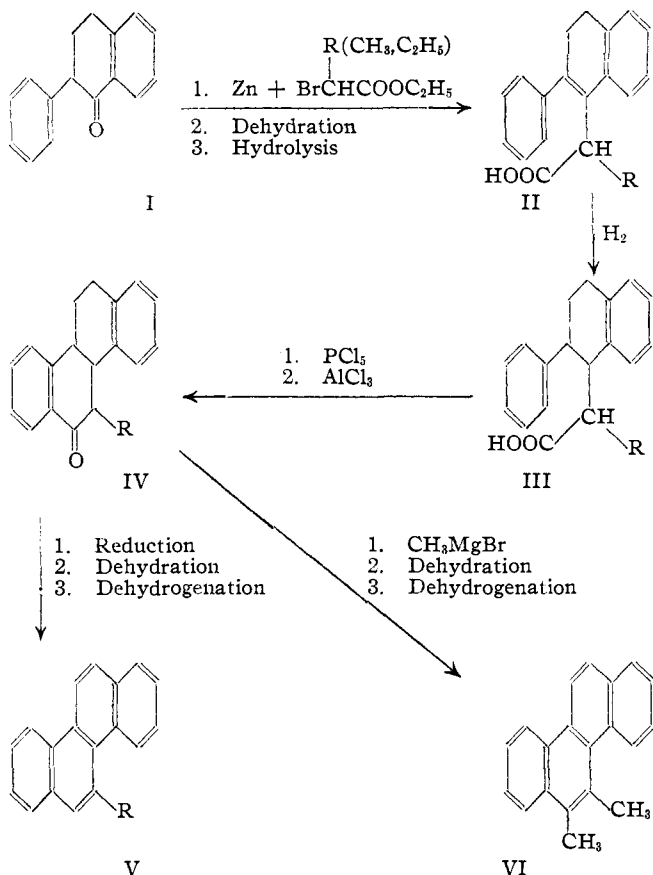
the use of iodine for initiation of the reaction. If strictly anhydrous conditions were carefully observed and sandpapered zinc foil[7] used, the reactions always started easily without the use of iodine. However, the yield of desired product was better if a small amount of iodine was used to initiate the reaction. Thus, in comparable runs using I and ethyl α-bromopropionate, the yield of unsaturated acid, II (R = CH₃), was 23.0% when no iodine was used and 37.6% when it was.

Difficulty was again encountered in the reduction of the unsaturated acids, II. Reduction was finally accomplished by high pressure hydrogenation over a copper-barium chromite catalyst[8] at 200°. A small amount of decarboxylation also took place but at lower temperatures reduction was incomplete. The reduction of the esters over a nickel catalyst supported on kieselguhr was also tried but at 200° saturation of the double bond was incomplete and it was feared that at higher temperatures the aromatic rings might have been hydrogenated.

No attempts were made to separate in a pure condition the stereoisomeric reduced acids, III, although in one case a separation into crystalline and non-crystalline fractions was made. Both fractions yielded the same end-products when put through the remaining steps of the synthesis. No crystalline ketone corresponding to IV was isolated. To form the 5-alkylchrysenes, the crude ketones were reduced to the alcohols using the aluminum isopropylate procedure.[9] The alcohols were dehydrated by heating with a trace of iodine and the tetrahydrochrysenes dehydrogenated by heating with sulfur. The hydrocarbons, 5-methylchrysene, m. p. 117.2–117.8°, and 5-ethylchrysene, m. p. 91.4–92.4°, were obtained in fair yields. In connection with the latter, it should be pointed out that the ethylchrysene, m. p. 236°, prepared from the acetylchrysene, m. p. 254°, is not the 5-derivative as tentatively advanced.[10]

After treating IV (R = CH₃) with methylmagnesium bromide, followed by dehydration and

siderable amounts of starting ketone, I, were recovered in spite of varying the amount of excess reagents used in the Reformatsky reactions. In an experiment using ethyl α-bromobutyrate and zinc with I, it has been shown that at least part of the recovered unchanged ketone results from the reaction of its enolic form with the postulated organozinc intermediate according to the equation

$$\overset{C_2H_5}{\underset{}{R-COCHR}} + BrZn\overset{C_2H_5}{\underset{}{CHCOOC_2H_5}} \longrightarrow$$
$$\underset{I}{}$$

$$R-\overset{OZnBr}{\underset{Ia}{C{=}CR}} + C_2H_5CH_2COOC_2H_5$$
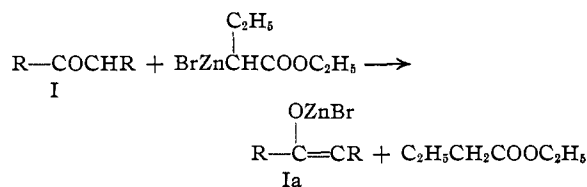
Upon hydrolysis, the bromozinc enolate, Ia, regenerates I. This explanation is supported by the isolation (in 15% yield) of ethyl butyrate from the reaction products. Such behavior of a ketone in the Reformatsky reaction has its analogy in similar reactions of ketones with Grignard reagents.[6]

Another interesting observation had to do with

(6) For example, the enolization of acetomesitylene, Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932).

(7) Natelson and Gottfried, *ibid.*, **61**, 970 (1939). The zinc foil was obtained from the J. T. Baker Chemical Company, Phillipsburg, N. J.

(8) Catalyst 37KAF, Connor, Folkers, and Adkins, *ibid.*, **54**, 1138 (1932).

(9) Lund, *Ber.*, **70**, 1520 (1937).

(10) Funke and Müller, *J. prakt. Chem.*, **144** 242 (1936).

dehydrogenation, a mixture of hydrocarbons was obtained. By fractional crystallization of the picrates formed from this mixture followed by adsorption of the picric acid on alumina, 5,6-dimethylchrysene, VI, was obtained. The nature of the impurity has not been determined positively but it is probably 5-methylchrysene, since the melting point of the mixture of hydrocarbons obtained was not depressed by the addition of 5-methylchrysene.

The new hydrocarbons are being tested for biological activity. Unpublished results would indicate a very slight carcinogenic activity for 6-methylchrysene[3] as it has produced one sarcoma in twenty mice during eighteen months.[11]

Experimental[12,13]

α,γ-Diphenylbutyric acid.—To 39 g. of powdered sodium amide[14] under 500 cc. of dry sulfur-free benzene in a three-necked flask fitted with mercury-sealed stirrer, reflux condenser, gas inlet tube, and dropping funnel was added 106 g. of benzyl cyanide[15] with stirring and cooling, the air in the system having been displaced with dry nitrogen. Ammonia was evolved copiously and the benzene took on a deep red color. The mixture was refluxed for one hour and on cooling a light colored complex separated from a deep red solution. Owing to the vigorous exothermic reaction two hours were required for the addition (with cooling) of 156 g. of phenethyl bromide. After three hours of stirring at room temperature, during which time the color became light brown and much white solid appeared, the mixture was refluxed for thirty minutes, cooled, and treated with an excess of dilute hydrochloric acid. The benzene layer was washed and the product distilled to give 114 g. (61%) of a clear yellow viscous oil, b. p. 147–151 at 0.5–1 mm. A fairly large higher boiling residue accounted for the low yield. In spite of several modifications of procedure, the yield varied from 56 to 63%. In a typical hydrolysis, 165 g. of nitrile was refluxed with 600 cc. of acetic acid and 100 cc. of 70% sulfuric acid for two days to yield 170 g. (95%) of acid, m. p. 70–72°. Alkaline hydrolysis of the nitrile was not as satisfactory.

1,2,3,4-Tetrahydro-1-keto-2-phenylnaphthalene. I.— The yield of this ketone was increased to 94% when the directions previously given[3] were modified to include in the following order: one-half hour for addition of aluminum chloride at room temperature; one-half hour each at 40 and at 60°; and a final cooling to room temperature during one-half hour before decomposition. In a compa-

(11) Private communication from Dr. M. J. Shear.

(12) All melting points corrected.

(13) The author acknowledges the valuable assistance of Mr. O. Woolfolk in the preparation of several intermediates and of Mr. J. H. Walker who performed the semi-micro analyses. Their assistance was made possible by The Ohio State W. P. A. Project No. 65-1-42-89.

(14) The sodium amide used was prepared by Dr. M. Orchin essentially according to the method of Dennis and Browne, THIS JOURNAL, **26**, 587 (1904), using ammonia from a tank.

(15) The benzyl cyanide was purified according to Johnson, "Organic Syntheses," Vol. 16, John Wiley and Sons, Inc., New York, p. 89.

rable experiment in which the acid chloride was treated directly with aluminum chloride without removing any of the volatile phosphorus compounds formed in the reaction of the acid with phosphorus pentachloride, the yield fell to 77%.

The Reformatsky Reactions.—Considerable experimentation upon the Reformatsky reaction was carried out, the best conditions found being illustrated by the following description: to a hot solution of 44.4 g. (0.2 mole) of I and 54 g. (0.3 mole) of ethyl *α*-bromopropionate in 250 cc. of dry sulfur-free benzene contained in a 1-liter flask fitted with a ground-in condenser was added 20 g. (0.3 mole) of zinc foil which had been freshly sandpapered[7] and about 0.2 g. of iodine. After the initial reaction moderated the benzene was kept gently refluxing for three hours. The solid complex which separated was decomposed with dilute hydrochloric acid. The organic reaction products were heated at 230° with a small crystal of iodine to effect dehydration and then distilled at 2 mm. The fraction boiling from 180 to 210° was refluxed for sixteen hours with alcoholic potassium hydroxide. From the neutral portion of the hydrolyzed products was isolated 12.3 g. of I (27.3%) and from the acid fraction, by crystallization from benzene-ligroin, 20.92 g. (37.6%, or 52.5% if allowance for recovered ketone is made) of 3,4-dihydro-*α*-methyl-2-phenyl-1-naphthaleneacetic acid, II (R = CH₃), m. p. 204–210°. A sample recrystallized for analysis separated as small colorless dense prisms, m. p. 210.2–210.6°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.15; H, 6.52.

In decomposing the insoluble complex formed in the Reformatsky reaction, there was always a certain amount which was not easily decomposed by shaking with dilute acid at room temperature. In a run using 0.1 mole of ketone, this insoluble complex was collected by filtration and decomposed by boiling with dilute hydrochloric acid and a little alcohol. On cooling 3.2 g. of organic matter crystallized. This crystalline material proved to be ethyl 1,2,3,4 - tetrahydro - 1 - hydroxy - *α* - methyl - 2 - phenyl-1-naphthaleneacetate, m. p. 90.4–91.4°, as shown by analysis and by dehydration and hydrolysis to II (R = CH₃).

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.49; H, 7.51.

In a comparable reaction using 44.4 g. of I, 58.5 g. of ethyl *α*-bromobutyrate, 20 g. of zinc, and 0.2 g. of iodine, there was isolated 21.4 g. (48%) of unchanged ketone and 16.0 g. (27.6% or 53.4% if allowance for recovered ketone is made) of a mixture of isomeric unsaturated acids, m. p. 151–168°, designated as 3,4-dihydro-*α*-ethyl-2-phenyl-1-naphthaleneacetic acid. No attempt was made to separate pure isomers and the portion for analysis, crystallized from benzene–ligroin, melted at 156–169°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.39; H, 6.88.

Isolation of Ethyl Butyrate.—In an exactly similar reaction using 0.1 mole of ketone, the organic reaction products were extracted with benzene and after washing, the benzene removed in an insulated column packed with glass helices. The remaining material was distilled with steam and after salting out the distillate with ammonium chloride, the non-aqueous layer was dried over sodium sulfate

and distilled. A forerun, b. p. 80–121°, was discarded and 1.7 g. of ethyl butyrate, b. p. 121.2–121.5°, was obtained. On hydrolysis, butyric acid was identified by odor and by its *p*-bromphenacyl ester,[16] m. p. and mixed m. p. 62.6–63.0°.

The Reduced Acids. III.—After several methods of reduction had been attempted unsuccessfully, the acids were reduced smoothly in dioxane over catalyst 37KAF[3] under an initial hydrogen pressure of 1900 lb. (127 atm.). A temperature of 200° was necessary, as at lower temperatures reduction was incomplete. The reduced acids, III, contain three asymmetric carbon atoms and no attempt was made to separate pure isomers. By the reduction of 10.0 g. of II (R = CH₃) there was obtained 5.91 g. of colorless needles, m. p. 143–148°, of 1,2,3,4-tetrahydro-α-methyl-2-phenyl-1-naphthaleneacetic acid, III (R = CH₃), by a single crystallization from benzene–ligroin. On evaporation of the mother liquors to dryness, 4.06 g. of a pale yellow viscous oil was obtained which consisted of a mixture of isomeric acids. A small amount of the crystals was recrystallized from benzene–ligroin to yield colorless rosets of needles, m. p. 147.6–148.8°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.42, 81.44; H, 6.94, 6.92.

In the case of the corresponding acid, III (R = C_2H_5), no crystalline fraction was obtained and the pale colored oil obtained in over 90% yield was used directly for the succeeding steps.

5-Methylchrysene, V(R = CH₃).—Either the crystalline or non-crystalline acid III (R = CH₃) could be used for the preparation of 5-methylchrysene. In a typical experiment, 2.00 g. of acid III (R = CH₃) in 10 cc. of benzene was treated with 1.5 g. of phosphorus pentachloride. After refluxing for several minutes, all volatile compounds were removed under reduced pressure at 80°. The pale yellow residue was dissolved in 15 cc. of dry sulfur-free benzene and 1.0 g. of aluminum chloride added in three portions with cooling. After swirling at room temperature until the evolution of hydrogen chloride slackened, the reaction mixture was warmed slowly to 50°. The bromine colored solution was cooled after thirty minutes and was decomposed by adding dilute hydrochloric acid. The benzene solution was washed with acid and alkali and the organic matter remaining after the evaporation of the solvent was pale brown in color. This crude ketone IV (R = CH₃) was suitable for the further steps described below. A solution of the above ketone in isopropanol containing aluminum isopropylate (from 0.5 g. of aluminum) was distilled slowly until no further test for acetone was given by the distillate.[9] The reaction mixture was treated with dilute hydrochloric acid and the organic product dehydrated by heating at 230° for ten minutes under reduced pressure after the addition of a crystal of iodine. The residue was dehydrogenated by heating at 240 to 250° for forty minutes with 0.23 g. of sulfur. After vacuum distillation from a small amount of zinc dust, the hydrocarbon was isolated by crystallization from benzene–alcohol as almost colorless needles, m. p. 115–117°, in 36% yield (0.621 g.). A sample purified for biological testing and analysis by recrystallization of the picrate followed by chromatographic adsorption on alumina formed

(16) Judefind and Reid, THIS JOURNAL, **42**, 1043 (1920).

colorless needles, m. p. 117.2–117.8°, with brilliant blue-violet fluorescence in ultraviolet light.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.04, 93.96; H, 5.96, 5.59.

The picrate crystallized from alcohol in orange-red needles, m. p. 142.6–143.0°.

Anal. Calcd. for $C_{25}H_{17}O_7N_3$: C, 63.69; H, 3.64; N, 8.91. Found: C, 63.93; H, 3.49; N, 8.70.

The *s*-trinitrobenzene derivative crystallized from benzene–alcohol in shining orange needles, m. p. 172.6–173.6°.

Anal. Calcd. for $C_{25}H_{17}O_6N_3$: C, 65.93; H, 3.76; N, 9.23. Found: C, 66.20; H, 3.74; N, 9.24.

5,6-Dimethylchrysene. VI.—A solution of the ketone, IV (R = CH₃), prepared as above from 4.26 g. of acid, III (R = CH₃), in 25 cc. of benzene was refluxed with an excess of ethereal methylmagnesium bromide for thirty minutes. The alcohol thus formed was dehydrated by heating at 220° under reduced pressure and then distilled at 10 mm. The pale yellow distillate (3.60 g.) was heated with 0.89 g. of sulfur at 230–240° for one hour, when the evolution of hydrogen sulfide had ceased. The product was distilled from a small amount of zinc dust and, since the solids obtained by crystallization had an unsharp melting point (118–125°), the entire product was treated with picric acid. After fractional crystallization of the picrates from benzene–alcohol followed by chromatographic adsorption on alumina, there was obtained 1.06 g. of colorless 5,6-dimethylchrysene, VI, m. p. 128.6–129.8°, having intense blue-violet fluorescence in ultraviolet light. If a benzene–alcohol solution of the hydrocarbon were cooled rapidly, thin plates, m. p. 128.0–129.0°, were obtained. On slow cooling needles of m. p. 128.6–129.8° separated. From other fractions of the picrates, 0.71 g. of a hydrocarbon mixture, m. p. 118–128°, was obtained and no depression of melting point was noticed on mixing in some 5-methylchrysene, m. p. 117°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.47, 93.61; H, 6.15, 6.20.

The picrate crystallized from benzene–alcohol in red needles, m. p. 134.4–135.4° with decomposition.

Anal. Calcd. for $C_{26}H_{19}O_7N_3$: C, 64.33; H, 3.95; N 8.66. Found: C, 64.52; H, 3.82; N, 8.34.

The *s*-trinitrobenzene derivative crystallized from benzene–alcohol in bright orange needles, m. p. 158.6–159.4°.

Anal. Calcd. for $C_{26}H_{19}O_6N_3$: C, 66.52; H, 4.08; N, 8.95. Found: C, 66.66; H, 3.88; N, 9.11.

5-Ethylchrysene, V(R = C_2H_5).—No crystalline acid corresponding to III (R = C_2H_5) was isolated. A solution of 4.16 g. of acid III (R = C_2H_5) in 20 cc. of benzene was treated with 3.0 g. of phosphorus pentachloride. The acid chloride was cyclized in benzene solution using 2.0 g. of aluminum chloride, the ketone reduced, the alcohol dehydrated, and the residue dehydrogenated as above to yield a total of 1.15 g. (32%) of 5-ethylchrysene, m. p. 88–90°. A sample purified for analysis by crystallization of the picrate and chromatographic adsorption on alumina formed colorless needles, m. p. 91.4–92.4°, having an intense blue-violet fluorescence in ultraviolet light.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.49, 93.39; H, 6.16, 6.10.

The picrate crystallized from benzene–alcohol in red needles, m. p. 99.2–100.6°.

Anal. Calcd. for $C_{26}H_{19}O_7N_3$: C, 64.33; H, 3.95; N, 8.66. Found: C, 64.33; H, 3.61; N, 8.46.

The *s*-trinitrobenzene derivative crystallized from benzene–alcohol in orange rectangular prisms, m. p. 125.2–125.8°.

Anal. Calcd. for $C_{26}H_{19}O_6N_3$: C, 66.52; H, 4.08; N, 8.95. Found: C, 66.45; H, 3.82; N, 8.76.

Summary

The synthesis of 5-methylchrysene, 5-ethylchrysene, and 5,6-dimethylchrysene is described, together with a new and more generally applicable synthesis for α,γ-diphenylbutyric acid.

The recovery of a considerable amount of 1,2,3,4-tetrahydro-1-keto-2-phenylnaphthalene from the Reformatsky reaction between this ketone and ethyl α-bromobutyrate despite a large excess of reagents is noted. An explanation is offered involving reaction of the enol form of the ketone with an organozinc intermediate to produce a bromozinc enolate and ethyl butyrate. This explanation is supported by the isolation of ethyl butyrate from the reaction mixture.
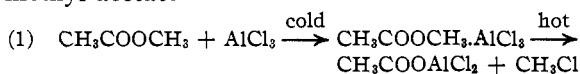

The Condensation of Esters with Aromatic Hydrocarbons by Means of Aluminum Chloride

BY JAMES F. NORRIS AND PAUL ARTHUR, JR.[1]

Preliminary results of the study of the condensation of ethyl acetate and of phenyl acetate with benzene were given in a recent paper[2] from this Laboratory. The work was continued because the reaction appeared to give a new and valuable method for the preparation of aromatic ketones. When the investigation was about completed, an abstract of a German patent,[3] bearing on the subject, was published. Our results are not in accord with certain statements in the patent; these will be considered in the experimental part of this paper.

In a communication by Bowden[4] on the alkylation of benzene by esters by the Friedel–Crafts reaction one phase of the condensation is described. In our work special attention was paid to acylation and the study of the conditions to be used to produce alkylation alone or simultaneous alkylation and acylation.

A study of possible mechanisms of the reactions involved was made in order to gain information to be used as a guide in directing the syntheses. The results led to the following steps in the case of methyl acetate

(1) $CH_3COOCH_3 + AlCl_3 \xrightarrow{\text{cold}} CH_3COOCH_3 \cdot AlCl_3 \xrightarrow{\text{hot}}$
$CH_3COOAlCl_2 + CH_3Cl$

(2) $CH_3Cl + C_6H_6 + AlCl_3 \longrightarrow$
$C_6H_5CH_3 + C_6H_4(CH_3)_2$ etc. $+ HCl$

(3) $CH_3COOAlCl_2 + C_6H_6(C_6H_5CH_3, \text{etc.}) + AlCl_3 \longrightarrow$
$C_6H_5COCH_3 + C_6H_4CH_3COCH_3$ (etc.) $+ AlOCl$

From work to be discussed later it is probable that a third step is involved in the alkylation, namely, the formation of an intermediate which contains three components, the hydrocarbon, the alkyl chloride and aluminum chloride.

One mole of aluminum chloride dissolves in one mole of methyl acetate and forms a compound which melts at about 60°. When this was heated it was stable at 132°, decomposed moderately rapidly at 143°, and rapidly at 170°. The yield of methyl chloride isolated was 0.7 mole. The solid residue ($CH_3COOAlCl_2$) obtained after the pyrolysis of the complex made from ethyl acetate and aluminum chloride, was condensed with benzene by aluminum chloride; the yield of acetophenone was 42% of the theoretical.

When methyl acetate, toluene, and aluminum chloride were heated, the products were dimethyl- and trimethylbenzene and a 60% yield of a mixture of methyl acetophenones. Since all of the dimethyl acetophenones have not been described, it was necessary to synthesize certain isomers by methods which gave evidence in regard to structure. The product obtained contained mostly 2,4-dimethylacetophenone; a smaller amount of 4-methylacetophenone was shown to be present.
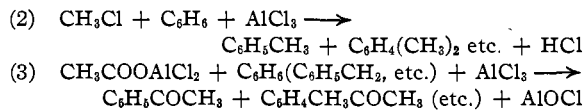
(1) From the thesis presented by Paul Arthur, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1938.

(2) Norris and Sturgis, THIS JOURNAL, **61**, 1413 (1939).

(3) *Chem. Abs.*, **31**, 703 (1937).

(4) Everett Bowden, THIS JOURNAL, **60**, 645 (1938).