Methylene-aminosyringic Acid, $(CH_3O)_2(OH)C_6H(N{=}CH_2)COOH$.—A solution of aminosyringic acid (1 g.) in dilute hydrochloric acid (2 cc. of acid: 10 cc. of water) was cooled to 0° and a 40% formaldehyde solution (3 cc.) added slowly. The colorless crystals which separated were removed, dried and recrystallized from a mixture of chloroform and carbon tetrachloride, when they softened at 191° (corr.), and melted with decomposition at 195° (corr.); yield, 75%. When it was warmed with dilute sulfuric acid, formaldehyde was evolved.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.88. Found: C, 53.40; H, 4.79.

The crystals of methylene-anthranilic acid are luminescent in the dark when rubbed,[21] but these crystals were not.

Experiments conducted for the purpose of converting this methylene derivative into the corresponding glycine nitrile and indigo have proved unsuccessful so far.

Summary

1. The preparation and properties of the following new compounds are described: nitrosyringic acid, nitro-acetylsyringic acid and its methyl ester, aminosyringic acid, its hydrochloride, acetanthranil, diacetyl and methylene derivatives, 3-aminopyrogallol-2,6-dimethyl ether, its hydrochloride and benzoyl derivative.

2. In the case of methyl nitrosyringate, methyl aminosyringate, the hydrochloride and diacetyl derivative of the latter, the melting points found differ from those already in the literature.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF PRINCETON UNIVERSITY]

SOME OBSERVATIONS ON THE CATALYTIC ACTIVITY OF ALUMINUM CHLORIDE

BY GREGG DOUGHERTY

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Aluminum chloride forms addition compounds with many different types of organic molecules, and in almost every attempt to explain the mechanism of the Friedel-Crafts reaction, the catalytic activity of the aluminum chloride has been connected with the formation of these complexes. Little is known concerning the nature of the addition compounds and no adequate reasons for their catalytic activity have been suggested.

The additive power of aluminum chloride is usually explained electronically on the ground that the aluminum atom in aluminum chloride possesses an outer shell of six electrons, and in order to achieve the more stable arrangement of eight, it will share a pair previously belonging totally to some other atom or molecule. Unless a rearrangement of some sort occurs, this new molecule, according to the ideas of Lowry[1] and Sidg-

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[21] Badische Anilin- und Soda Fabrik, German Patent 158,090; *Friedländer*, **8**, 397 (1905).

[1] Lowry, *J. Chem. Soc.*, **123**, 822 (1923); *Phil. Mag.*, **45**, 964, 1013 (1923).

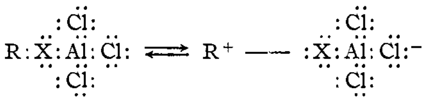
wick,[2] should have a polar character. It would seem likely that the active agents in the Friedel-Crafts synthesis are these polarized or even ionized addition compounds which exist, possibly in very small amount only, in equilibrium with the undissociated or unpolarized molecules. It is a fact that solutions of aluminum halides in alkyl halides, and organic aluminum halide solutions in general, often show considerable conductivity.

An explanation of the mechanism of the Friedel-Crafts synthesis involving in part this idea was advanced by the present author and published as an insert in an article on synthetic anthraquinone by K. H. Klipstein.[3]

Lately H. J. Prins[4] has suggested that under the influence of aluminum chloride benzene polarizes or ionizes in such a way as to give effectively a hydrogen ion and a phenyl ion. In this paper the ideas mentioned above concerning the nature of the Friedel-Crafts reactions are extended and the results of some experimental work bearing on the problem are offered.

Theoretical Part

If one adopts the current ideas of the electronic theory of valence, it is possible to show that if aluminum chloride adds to benzene and there is a subsequent polarization or dissociation, the probable result would be a polarized molecule of the type $(C_6H_5AlCl_3)^-—H^+$ or the ions $(C_6H_5AlCl)^-$ and H^+. Similarly, with an alkyl halide, RX, we would obtain



$$R:\ddot{\underset{\cdot\cdot}{X}}:\underset{:\underset{\cdot\cdot}{Cl}:}{\overset{:\ddot{Cl}:}{Al}}:\ddot{\underset{\cdot\cdot}{Cl}}: \rightleftharpoons R^+ — :\ddot{\underset{\cdot\cdot}{X}}:\underset{:\underset{\cdot\cdot}{Cl}:}{\overset{:\ddot{Cl}:}{Al}}:\ddot{\underset{\cdot\cdot}{Cl}}:^-$$

or R^+ and $(X\ Al\ Cl_3)^-$. The simplest example of the Friedel-Crafts reaction in which the action is truly catalytic, that is, the aluminum chloride is not taken from the system as the process proceeds in the form of a very inert addition compound with one of the resultants, as in a ketone synthesis, would be represented by the following

$$C_6H_6 + AlCl_3 \rightleftharpoons C_6H_6AlCl_3 \rightleftharpoons (C_6H_5AlCl_3)^-—H^+ \tag{1}$$

$$RX + AlCl_3 \rightleftharpoons RXAlCl_3 \rightleftharpoons R^+—(XAlCl_3)^- \tag{2}$$

$$(C_6H_5AlCl_3)^-—H^+ + R^+—(XAlCl_3)^- \rightleftharpoons (C_6H_5AlCl_3)^-—R^+ + H^+—(XAlCl_3)^- \tag{3}$$

$$(C_6H_5AlCl_3)^-—R^+ \rightleftharpoons C_6H_5R\cdot AlCl_3 \rightleftharpoons C_6H_5R + AlCl_3 \tag{4}$$

$$H^+—(XAlCl_3)^- \rightleftharpoons HX\cdot AlCl_3 \rightleftharpoons HX + AlCl_3 \tag{5}$$

These reactions indicate a situation somewhat similar to that which we have presumably when inorganic ionogens react. There would be displacement in one direction or another if any pair of ions formed an insoluble compound or a very volatile one. In the above a nearly complete reaction results due to the volatility of the hydrogen chloride. As the

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[2] Sidgwick, "The Electronic Theory of Valency," Oxford, **1927**, Chapter IV.

[3] Klipstein, *Ind. Eng. Chem.*, **18**, 1327 (1926).

[4] Prins, *Chem. Weekblad*, **24**, 615 (1927).

reactions indicate, the reaction should be reversible and it is a fact that we can de-alkylate alkyl benzenes by means of aluminum chloride and a stream of hydrogen chloride. In actual practice the situation is not so simple as the equations would lead one to believe. This is due to the fact that the C_6H_5R can add to aluminum chloride and become part of a polarized or ionized molecule just as benzene does. The result is a reaction mixture containing various polyalkylated benzenes in addition to the mono-alkyl compound. The former are formed in a proportion depending on the relative tendency to add to aluminum chloride and the extent to which each of the resulting addition compounds is dissociated.

The Action of Aluminum Chloride on Halogen Compounds.—The reactions given above for the formation of alkylbenzenes suggest that if benzene were replaced by another alkyl halide, or a halogen compound of like properties, different from RX, metathetical reactions should occur essentially similar in type to those of Friedel and Crafts. Such reactions would be represented by the following

$$RX + AlCl_3 \rightleftharpoons RX \cdot AlCl_3 \rightleftharpoons R^+—(XAlCl_3)^- \tag{6}$$

$$R_1X_1 + AlCl_3 \rightleftharpoons R_1X_1 \cdot AlCl_3 \rightleftharpoons R_1^+—(X_1AlCl_3)^- \tag{7}$$

$$R^+—(XAlCl_3)^- + R_1^+—(X_1AlCl_3)^- \rightleftharpoons R^+—(X_1AlCl_3)^- + R_1^+—(XAlCl_3)^- \tag{8}$$

$$R^+—(X_1AlCl_3)^- \rightleftharpoons RX_1 + AlCl_3, \text{ and } R_1^+—(XAlCl_3)^- \rightleftharpoons R_1X + AlCl_3 \tag{9}$$

If either of the new alkyl halides, R_1X or RX_1, happened to be volatile in comparison with RX and R_1X_1, the reaction $RX + R_1X_1 \longrightarrow R_1X + RX_1$ should occur. On the other hand, if all of the alkyl halides were of the same order of volatility, the reaction should proceed to an equilibrium point.

There are many cases noted in the literature in which there is an exchange of halogen between metallic halides and aliphatic halogen compounds,[5] but the only example found in which there was actual transfer from one hydrocarbon radical to another under the influence of aluminum chloride was one in which an alkyl iodide was involved. Walker[6] observed that when a small amount of aluminum chloride was added to a mixture of ethyl iodide and chloroform, a vigorous reaction resulted; the products were ethyl chloride and iodoform. Similarly, methyl iodide and carbon tetrachloride yielded methyl chloride and carbon tetra-iodide. He seemed doubtful whether these transformations were general and would take place in the case of mixtures of chlorides and bromides.

In order to make sure that Walker's reactions involving iodides were general and not specific to mixtures containing chloroform or carbon tetrachloride, some experiments have been carried out in which the chlorides were replaced by bromides. Methyl iodide and ethyl bromide were mixed and a small piece of aluminum chloride was added. After gentle warming for a minute, a vigorous reaction commenced; methyl bromide

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[5] Meyer, *J. prakt. Chem.*, [2] **34**, 104 (1886); Pouret, *Compt. rend.*, **130**, 1191 (1900); *Ber.*, [3] **25**, 191, 293 (1901).

[6] Walker, *J. Chem. Soc.*, **85**, 1082 (1904).

was evolved and ethyl iodide was isolated. Twenty g. of ethylene bromide and 30 g. of ethyl iodide were mixed and 1 g. of aluminum chloride was added. Here again there was a vigorous reaction; ethyl bromide was evolved and obtained in about a 70% yield. Undoubtedly the principal reactions which occurred were as follows

$$CH_3I + C_2H_5Br \longrightarrow CH_3Br\uparrow + C_2H_5I$$
$$C_2H_4Br_2 + C_2H_5I \longrightarrow C_2H_5Br\uparrow + C_2H_4I_2$$

The reaction mixtures became highly colored as soon as the aluminum chloride was added, some free iodine was liberated, tars were formed and the reactions were not clean cut.

Since alkyl iodides cannot be used successfully in the Friedel-Crafts syntheses, a reaction between chlorides and bromides in the presence of aluminum chloride would have much more bearing on the point under discussion. Walker observed that if chlorides and bromides react at all, they do so very slowly. It has been found that they do react and, under the proper conditions, without appreciable formation of complex by-products and tars. A solution was made of one mole of ethyl bromide and one of chloroform and a small amount of aluminum chloride added. There was distinct warming and the appearance of a bright red color. When warmed to 45–50°, there was bubbling and a slow evolution of ethyl chloride but no such activity as in the case of the iodides. Some hydrogen halide was formed and raising the temperature increased the amount, so it seemed best not to attempt to distil out all of the ethyl chloride formed in this way but to allow the reaction mixture to stand at room temperature. After thirty-six hours, water and dilute hydrochloric acid were added, the liquid was washed with dilute sodium hydroxide solution and dried over calcium chloride. On fractionating, in addition to a very low boiling portion which represented the remainder of the ethyl chloride formed, an ethyl bromide and a chloroform fraction, there was a small amount of liquid (b. p. 120–122°) and a rather larger fraction (b. p. 88–93°). The latter on redistillation boiled constantly at 91–92° and had a specific gravity of 1.975 at 15°. These are the properties of dichloromonobromomethane. *Anal.* Calcd. for $CHBrCl_2$: Cl and Br, 92.06. Found: 91.80. In this and other experiments the yield of the mixed halogen compound was about 35% of the theoretical based on the equation: $CHCl_3 + C_2H_5Br \longrightarrow CHCl_2Br + C_2H_5Cl$. The small fraction (b. p. 120–132°) ran high in halogen, above 93%, and was probably a mixture of dibromomonochloromethane and bromoform. Difficulties in the fractional distillation made it impossible to identify these two compounds with certainty or to make anything like a quantitative separation of all the constituents in the reaction mixture. Both tar formation and the evolution of hydrogen halide seemed to increase with rise of temperature and were kept at a minimum by running the reaction at 20–25°.

In order to make a semi-quantitative study of this type of reaction and to test its reversibility, reactants were chosen which should produce only one new compound and that one not very volatile. Ethylene bromide and ethylene chloride should give ethylene chlorobromide: $C_2H_4Cl_2 + C_2H_4Br_2 \longrightarrow 2C_2H_4ClBr$. The reactants were mixed in equimolar proportions and about 0.04 of a mole of aluminum chloride added. It was found that the reaction was complete after standing for 35 hours at 25°. The reaction mixture was treated as in the case of the chloroform–ethyl bromide experiment and submitted to careful and repeated fractional distillation using an efficient fractionating column. Only three distinct fractions were found: the first and third had the properties of the reactants, while the middle one (b. p. 106–109°) had a specific gravity of 1.73 at 19°, agreeing with that of ethylene chlorobromide. A halogen determination gave 80.7%; calculated for C_2H_4ClBr, 80.45%. Careful weighing of the fractions and taking account of losses of manipulation and material left in the fractionating apparatus indicated that the above reaction was complete when the three compounds were present in the ratio of 2 moles of ethylene chlorobromide to one each of ethylene chloride and ethylene bromide. This is what might be expected on the law of chances if it is assumed that the system contains highly polarized or ionized molecules and the energy content of the three compounds is approximately the same.

An attempt was made to test the reversibility of the reaction and to arrive at the equilibrium point from the other direction. Ethylene chlorobromide and aluminum chloride were mixed and allowed to stand under the same conditions as in the previous experiment. On fractionating the same three fractions were obtained and the weights were approximately in the same ratio, which indicates that the reaction is easily reversible and should be represented by the equation: $2C_2H_4ClBr \rightleftharpoons C_2H_4Cl_2 + C_2H_4Br_2$. The reaction mixtures darken in color as the reaction progresses and a small amount of hydrogen halide is evolved. Very little tar is formed, however, and this by-reaction is evidently very superficial in nature when the experiment is conducted at room temperature. To make sure that no exchange of halogen occurred between aluminum chloride and ethylene bromide, an experiment was tried in which ethylene chloride was omitted. The ethylene bromide was unchanged. Plans are being made to study these reactions more accurately; both equilibrium and velocity measurements will be attempted.

I wish to take this opportunity to thank Professor Frank O. Rice of Johns Hopkins University for his helpful advice in carrying out this work, and the Department of Chemistry at Johns Hopkins University for so kindly allowing me the privileges of the laboratory during the spring term of 1927–1928.

Summary

A mechanism for the Friedel-Crafts reaction has been suggested.

The hypothesis predicts that metathetical reactions will occur between certain types of aliphatic halogen compounds in the presence of aluminum chloride. Experimental evidence is given that such reactions do occur, and some of them have been studied.

Princeton, New Jersey

[Contribution from the Department of Chemistry, Yale University]

SYNTHESIS OF EPHEDRINE AND STRUCTURALLY SIMILAR COMPOUNDS. I. A NEW SYNTHESIS OF EPHEDRINE

By Richard H. F. Manske[1] and Treat B. Johnson

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Although the constitution of ephedrine (III) is no longer in doubt, interest in this base has been renewed by the pharmacological work of K. K. Chen.[2] Since it seemed not improbable that other bases analogously constituted might possess more desirable or at least interesting physiological properties,[3] the authors entered this field with a view to the improvement of known methods of synthesis or to the discovery of new ones.

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[1] Holder of the Eli Lilly Company Research Fellowship in Organic Chemistry, 1927–1928.

[2] Chen and Kao, *J. Am. Pharm. Assocn.*, **8**, 625a (1926). Bibliography is given in this paper.

[3] Hyde, Browning and Adams, This Journal, **50**, 2297 (1928).