Benzoyl-*tert.*-amylamine.—The benzoyl derivative was prepared from the amine hydrochloride by the Schotten-Baumann method. After recrystallization from ligroin the melting point was 93–94° (uncorr.).

Anal. Subs., 0.1982, 0.1617: 10.4, 8.49 cc. of 0.1 *N* HCl. Calcd. for $C_{12}H_{17}ON$: N, 7.33. Found: 7.34, 7.35.

Summary

The yields of amines and ammonia in the reaction of monochloro-amine with Grignard reagents prepared from secondary and tertiary halogen compounds are much the same as with reagents prepared from primary halogen compounds.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 595]

FURTHER STUDIES OF SYRINGIC ACID AND ITS DERIVATIVES[1]

BY MARSTON TAYLOR BOGERT AND BERNARD B. COYNE[2]

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In previous articles[3] from these Laboratories, we have described various derivatives of syringic acid and incidental compounds, and the present paper continues and supplements these earlier investigations.

The flow sheet represents the various products prepared in the course of the work and the origin of each.

The nitration of polyhydroxylated benzoic acids is complicated by the tendency of such compounds either to undergo complete decomposition, or to have the carboxyl displaced by the nitro group.[3a,4] These tendencies have been overcome by protecting the carboxyl group by esterification and the hydroxyls by alkylation or esterification.[3a,5] Bogert and Plaut[3a] obtained the dinitropyrogallol dimethyl ether by direct nitration of syringic acid. We have found similarly that when nitrosyringic acid is boiled with tin and hydrochloric acid, the product is the monaminopyrogallol dimethyl ether, but that the aminosyringic acid can be obtained by carrying out the reduction at 40–45° under suitable conditions.

Schiffer[6] encountered similar difficulties when he sought to reduce nitrotriethylgallic acid. We have also ascertained, in line with the above, that acetylsyringic acid can be nitrated easily, in acetic anhydride solution, to give the nitro-acetylsyringic acid without loss of carbon dioxide.

[1] Presented in abstract before the Division of Organic Chemistry at the Swampscott Meeting of the American Chemical Society, September, 1928.

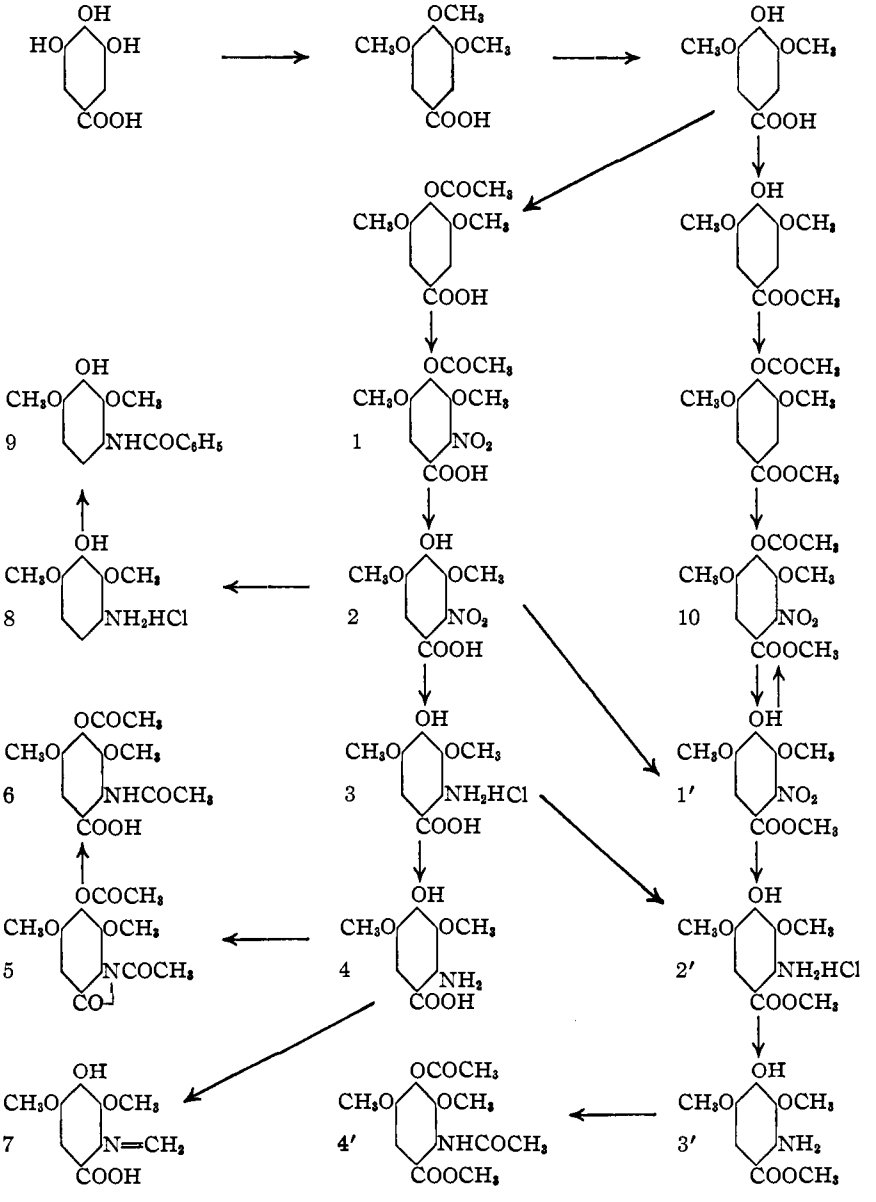
[2] DuPont Fellow at Columbia University, 1925–1927.

[3] (a) Bogert and Plaut, THIS JOURNAL, **37**, 2723 (1915); (b) Bogert and Ehrlich, *ibid.*, **41**, 798 (1919).

[4] (a) Harding, *J. Chem. Soc.*, **99**, 1585 (1911); (b) De Lange, *Rec. trav. chim.*, **45**, 19 (1926).

[5] (a) Hamburg, *Monatsh.*, **19**, 598 (1898); (b) Power and Shedden, *J. Chem. Soc.*, **81**, 73 (1902).

[6] Schiffer, *Ber.*, **25**, 727 (1892).



The methylene-aminosyringic acid refused to yield the corresponding indigo, under the experimental conditions employed. This recalls the recent unsuccessful efforts of Overmyer[7] to prepare a hexamethoxy indigo from aminotrimethylgallic acid.

[7] Overmyer, THIS JOURNAL, 49, 499 (1927).

Experimental Part

Trimethylgallic Acid.—The method adopted for the preparation of this acid was based upon that of Graebe and Martz[8] as modified by Mauthner,[9] but involved a sufficient number of variations to make it seem advisable to describe the procedure.

A 5-liter flask containing 200 g. of gallic acid suspended in 1 liter of water was fitted with a 3-holed rubber stopper carrying thermometer, stopcock funnel tube and guard tube filled with sodium hyposulfite (to exclude oxygen). The acid was dissolved by the addition of a solution of 320 g. of sodium hydroxide and a small amount of sodium bisulfite (to prevent oxidation) in 1 liter of water, and 356 g. of methyl sulfate was then run in gradually and the flask shaken for twenty to thirty minutes while the temperature of the mixture was maintained below 35°. When evolution of heat was no longer caused by the reaction, a further 356 g. of methyl sulfate was added and the temperature of the mixture allowed to rise to 45°, after which it was refluxed for two hours, 80 g. of sodium hydroxide added (to saponify excess of methyl sulfate), the refluxing continued for a further two hours, the solution cooled, acidified with dilute hydrochloric acid, the precipitate collected, washed with cold water and recrystallized from a large volume of boiling water in the presence of a decolorizing carbon. The colorless crystalline product melted at 168° (corr.), in agreement with the literature; yield of crude product, 220 g., or 87%; after one crystallization, 180 g., or 72%, without figuring in that still recoverable from the mother liquor. It did not pay, however, to work over the mother liquor from the precipitation of the original crude acid.

As Overmyer[7] has pointed out, the crude product may be crystallized also from glacial acetic acid.

The use of sodium hydrosulfite, in place of the bisulfite, to prevent oxidation during the methylation of the gallic acid, was not so satisfactory and often imparted a foul odor to the product, possibly due to the formation of traces of mercaptan or sulfide from the methyl sulfate.

Syringic Acid.—Most of this acid required for the experimental work was obtained from the trimethylgallic acid by the method of Bogert and Ehrlich.[3b]

Alimchandani and Meldrum,[10] as well as others, have suggested the use of concentrated sulfuric acid, in place of the fuming acid, for accomplishing this demethylation but, in our experience, unless the reaction was conducted as follows, the product contained some unchanged trimethylgallic acid.

To 300 g. of concentrated sulfuric acid, 60 g. of trimethylgallic acid was added all at once and the solution kept for six hours at 40° with occasional agitation. It was allowed to cool, left overnight at room temperature and then stirred into 300 cc. of water without external cooling. The syringic acid which separated was collected, washed with cold water and crystallized from boiling water in the presence of a decolorizing carbon. From the original mother liquor more syringic acid separated on standing and

[8] Graebe and Martz, *Ann.*, **340**, 219 (1905).

[9] Mauthner, "Organic Syntheses," John Wiley and Sons, Inc., New York, **6**, 96 (1926).

[10] Alimchandani and Meldrum, *J. Chem. Soc.*, **117**, 967 (1920).

on concentration. Additional amounts may be recovered from the wash waters and second mother liquor; total yield of crude acid, 45 g., or 80%; after one crystallization, 35 g., or 63%. The carefully purified acid was odorless. The melting point varies somewhat depending upon the rapidity of heating and is generally preceded by a sintering or softening. The product obtained as described sintered at 204° and melted at 206.5° (corr.). Koerner[11] and Gadamer[12] reported the m. p. as 202°, Graebe and Martz[8] and Bogert and Ehrlich[3b] as 204°, Alimchandani and Meldrum[10] as 206–207° and Anderson and Nabenhauer[13] as 209–210°.

The methyl ester was obtained easily and in good yield by the method of Bogert and Ehrlich[3b] and in the anhydrous form melted at 107° (corr.), as stated by them; yield, 75%.

Acetylsyringic acid was prepared first by Gadamer,[14] by the oxidation of acetylsinapinic acid, and more recently by Anderson and Nabenhauer,[13] by oxidation of the acetyl derivative of the anthocyanidin of Isabella grapes and by the direct acetylation of syringic acid. Our procedure differed somewhat from the latter. A suspension of 10 g. of syringic acid in 30 g. of acetic anhydride was warmed gently until a clear solution was obtained, 0.5 g. of fused sodium acetate was added and the solution left overnight at room temperature. The next morning the solution, including any crystals which had separated, was poured into 100 cc. of water and stirred thoroughly, to insure the hydrolysis of any excess anhydride. As the solution cooled, the crude acetylsyringic acid crystallized in amount essentially equal to that calculated. By a single recrystallization from water the pure acid was secured, m. p. 190.5° (corr.); yield, 78%, without including that recoverable by working over the mother liquors. Gadamer reported a m. p. of 181–183°; Anderson and Nabenhauer, 190–191°.

When this acid was dissolved in absolute methanol and the solution saturated with dry hydrogen chloride, the acetyl group was removed and the carboxyl simultaneously esterified, with production of methyl syringate.

The methyl ester was prepared similarly, by direct acetylation of methyl syringate, as carried out first by Bogert and Plaut,[3a] and later by Alimchandani and Meldrum;[10] yield of crude product, 97%. Recrystallized from alcohol, the pure ester melted at 131.5° (corr.). Bogert and Plaut found a m. p. of 129° (corr.) and Alimchandani and Meldrum reported 131°.

Nitrosyringic Acid.—A suspension of 9 g. of nitro-acetylsyringic acid (see beyond) in 150 cc. of 5% hydrochloric acid was refluxed until a clear solution was secured (about two hours). As the solution cooled, the nitrosyringic acid separated in long pale yellow needles, carrying one mole of water, some of which was lost even at room temperature; yield, 91%. Recrystallized from water, or from dilute (30%) alcohol, and dried at 110°, it formed colorless crystals which softened at 213° (corr.) and melted with decomposition at 218° (corr.); yield, 78%.

Anal. Calcd. for $C_9H_9O_7N$: C, 44.44; H, 3.70. Found: C, 44.46; H, 3.74.

The product was soluble more or less freely in alcohol, ether, acetone or boiling water, but slightly soluble in cold water or in strong hydrochloric acid and practically insoluble in petroleum ether, chloroform or benzene. It dissolved in sodium bicarbonate solution, coloring it red. In contradistinction to the well-known sweet taste of *o*-nitrobenzoic acid, the taste of this analog was sour and brackish.

The introduction of this nitro group interfered so seriously with the methylation of the hydroxyl group in the meta position that such methylating agents as methyl

[11] Koerner, *Gazz. chim. ital.*, **18**, 215 (1888).

[12] Gadamer, *Ber.*, **30**, 2330 (1897).

[13] Anderson and Nabenhauer, THIS JOURNAL, **48**, 2997 (1926).

[14] Gadamer, *Arch. Pharm.*, **235**, 570 (1897).

iodide and methyl sulfate were without effect upon it. This is in accord with the experience of Hemmelmayr,[15] who encountered similar difficulties in trying to methylate nitro-β-resorcylic acid.

Methyl Ester.—This was obtained by digesting methyl nitro-acetylsyringate with dilute hydrochloric acid, in practically the same way as just described for the free acid; yield of crude product, 95%. Recrystallized from alcohol, it formed colorless needles, m. p. 210° (corr.); yield, 83%.

Anal. Calcd. for $C_{10}H_{11}O_7N$: C, 46.69; H, 4.28. Found: C, 47.05; H, 4.50.

The same product was obtained by dissolving nitrosyringic acid or its acetyl derivative in absolute methanol and saturating the solution with dry hydrogen chloride.

This nitro ester was very stable toward both acids and alkalies and could not be hydrolyzed to the free acid without decomposition. The experience of Schiffer[16] with ethyl nitrotriethylgallate, or of Thoms and Siebeling[17] with methyl nitrotrimethylgallate, was much the same.

Bogert and Plaut[3a] nitrated methyl syringate, in acetic anhydride solution, at low temperature, and reported the formation of a methyl nitrosyringate, melting at 68.3° (corr.), and that the same product was obtained by the action of concentrated (48%) hydrobromic acid upon methyl nitrotrimethylgallate, but we have been unable to check this direct nitration of methyl syringate or obtain the product, m. p. 68.3°, reported by them.

We endeavored to repeat this direct nitration of methyl syringate, but found the crude product very difficult to purify (as did Bogert and Plaut also), and failed to isolate either the compound of m. p. 68.3°, or the one of m. p. 210°. Further work is necessary to explain this discrepancy in results since, as noted beyond, both products seem to yield the same aminosyringate on reduction.

Nitro-acetylsyringic Acid, $(CH_3O)_2(CH_3COO)C_6H(NO_2)COOH$.—A mixture of 10 g. of acetylsyringic acid and 30 g. of acetic anhydride was nitrated with 5 cc. of fuming nitric acid (sp. gr. 1.6) at −5°, adding the nitric acid very slowly with vigorous mechanical stirring. The acetylsyringic acid used must be pure and dry and the addition of the nitric acid be conducted very carefully, especially at first, or the reaction may proceed with explosive violence. After all of the nitric acid had been added, the stirring was continued for an hour longer, when a mass of minute crystals separated. After this mixture had stood for two hours at low temperature, it was poured into 200 cc. of ice water, the mixture well agitated to hydrolyze any excess of acetic anhydride and the insoluble nitro acid collected and crystallized from 50% alcohol. The product formed colorless, minute, diamond-shaped plates which melted with decomposition at 190° (corr.). It dissolved in sodium bicarbonate solution to a colorless solution, but in aqueous sodium hydroxide a red color developed rapidly; yield of crude product, 92%; of pure substance, 82%. It dissolved quite readily in acetone or hot alcohol, less easily in ether or chloroform and was difficultly soluble or insoluble in water, petroleum ether or benzene.

A 1:1 mixture of acetylsyringic and nitro-acetylsyringic acids melted at 158–165°.

Anal. Calcd. for $C_{11}H_{11}O_8N$: C, 46.34; H, 3.89. Found: C, 46.28; H, 3.99.

[15] Hemmelmayr, *Monatsh.*, **26**, 185 (1905).

[16] Schiffer, *Ber.*, **25**, 727 (1892).

[17] Thoms and Siebeling, *ibid.*, **44**, 2115 (1911).

The methyl ester was obtained by nitrating methyl acetylsyringate in the manner just described for the acid itself and also by the acetylation of methyl nitrosyringate with acetic anhydride and sodium acetate. The pure ester crystallized from 95% alcohol in long, colorless needles, m. p. 107.5° (corr.); yield of crude product, 98%, of pure substance 85%.

Anal. Calcd. for $C_{12}H_{13}O_8N$: C, 48.16; H, 4.35. Found: C, 48.09; H, 4.38.

Aminosyringic Acid.—To a solution of 5 g. of stannous chloride in 10 cc. of concentrated hydrochloric acid, containing a little metallic tin, there was added gradually 5 g. of finely powdered nitrosyringic acid. During the addition of the nitro acid the mixture was stirred mechanically, its temperature was maintained at 40–45°, and tin and hydrochloric acid were replenished from time to time until a total of 10 g. of the former and 250 cc. of the latter had been used. The nitro acid slowly dissolved and the colorless tin double salt of the amino acid separated. Too much nitro acid should not be added at a time, since the separated tin double salt tends to coat it over and protect it from reduction. When the reduction was complete, the double salt was collected, washed with concentrated hydrochloric acid, dissolved in water and de-tinned by hydrogen sulfide. The filtrate from the stannous sulfide was evaporated under diminished pressure, at room temperature first and then at 60°. Colorless, fine needles of the amino acid hydrochloride were obtained, melting with decomposition at 185° (corr.); yield, 59%. It was partly hydrolyzed by pure water, but could be crystallized from dilute hydrochloric acid.

It was dissolved in water, a slight excess of ammonium hydroxide solution and a little sodium sulfite (to retard oxidation) added, and then dilute acetic acid in slight excess. When the solution was cooled, the free amino acid separated in colorless needles which, after recrystallization from water, melted with decomposition at 169° (corr.); yield of crude acid, 97%; of pure product, 86%.

Anal. Calcd. for $C_9H_{11}O_5N$: C, 50.74; H, 5.16. Found: C, 50.98; H, 4.97.

The troublesome tin sulfide precipitation may be avoided and the amino acid obtained more quickly, although in somewhat lower yield, by dissolving the tin double salt in a small amount of water, adding sufficient ammonium hydroxide solution to precipitate all of the tin as hydroxide, neutralizing the filtrate with acetic acid and recovering the amino acid as already described.

The free acid is moderately soluble in acetone, hot water or hot alcohol, only slightly soluble in ether or chloroform and practically insoluble in petroleum ether or benzene. Its hydrochloride was treated with potassium cyanate, for the purpose of getting the corresponding ureido acid, but the results were negative.

Methyl Ester.—Prepared by reduction of the methyl nitrosyringate with tin and hydrochloric acid, essentially as described by Bogert and Plaut,[3a] the hydrochloride was obtained in colorless needles which darkened at 192° and melted with decomposition at 217° (corr.); yield, 65%. Bogert and Plaut gave the m. p. as 192°.

Anal. Calcd. for $C_{10}H_{14}O_5NCl$: Cl, 13.48. Found: Cl, 13.80.

A few crystals of sodium sulfite were added to an aqueous solution of this hydrochloride and the free ester was then precipitated by a slight excess of sodium bicarbonate and crystallized from dilute alcohol in the dark, as recommended by Bogert and Plaut. The colorless granular crystals obtained melted at 126.5° (corr.). Bogert and Plaut reported a m. p. of 110° (corr.).

The same product was secured by dissolving the aminosyringic acid in absolute methanol, saturating the cold solution with dry hydrogen chloride, dissolving the resultant hydrochloride in water and precipitating the solution by the addition of sodium bicarbonate.

Anal. Calcd. for $C_{10}H_{13}O_5N$: C, 52.86; H, 5.73. Found: C, 52.53; H, 5.59.

Attempts to hydrolyze this ester to the free acid all failed, acids or alkalies causing deeper-seated changes.

When this ester was diazotized and the diazo solution treated with cuprous oxide, a vigorous evolution of nitrogen occurred and the product isolated proved to be methyl syringate; yield, 69%. Power and Shedden[18] diazotized ethyl aminogallate and succeeded in isolating a diazo derivative, which lost nitrogen when heated with water at 220° and gave ethyl gallate.

Acetanthranil of Acetylsyringic Acid, $(CH_3O)_2(CH_3COO)C_6HN(COCH_3)CO$.—When a solution of aminosyringic acid (3 g.) in acetic anhydride (9 cc.), containing a trace of fused sodium acetate, was allowed to stand, crystals of this acetanthranil separated, which were recrystallized from acetic anhydride or from dry benzene. The compound then formed colorless needles, m. p. 169° (corr.); yield, 78%.

Anal. Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.66. Found: C, 55.82; H, 4.71.

The conversion of this acetanthranil into quinazolones, by the action of amines,[19,20] has not been accomplished as yet. Preliminary experiments with ammonia and aniline seem to indicate that it is less reactive in this respect than acetanthranil itself.

Acetamino-acetylsyringic acid, $(CH_3O)_2(CH_3COO)C_6H(NHCOCH_3)COOH$, was obtained very easily from the above acetanthranil by evaporating its aqueous solution, and was recrystallized from water; m. p. 193° (corr.); yield, 75%.

Anal. Calcd. for $C_{13}H_{15}O_7N$: C, 52.52; H, 5.05. Found: C, 52.23; H, 4.98.

Methyl Ester.—Prepared as described by Bogert and Plaut.[3a] The colorless crystals secured by us melted at 154° (corr.), whereas Bogert and Plaut found a m. p. of 139.9° (corr.).

Anal. Calcd. for $C_{14}H_{17}O_7N$: C, 54.02; H, 5.47. Found: C, 53.91; H, 5.44.

Structurally this acid is of methacetin type but no pharmacological tests have been conducted with it.

Hydrochloride of 3-Amino-2,6-dimethylpyrogallol, $(CH_3O)_2(HO)C_6H_2NH_2$.—A suspension of 10 g. of nitrosyringic acid in 100 cc. of concentrated hydrochloric acid was heated under a reflux condenser, while 20 g. of tin was added gradually. When solution was complete (about four to five hours), the mixture was cooled, the double tin salt collected, dissolved in water, the tin precipitated as sulfide, the filtrate evaporated to dryness under diminished pressure and the residue crystallized from water. Large, colorless orthorhombic crystals of the hydrochloride resulted, m. p. 198° (corr.) with decomposition; yield, 78%.

Anal. Calcd. for $C_8H_{12}O_3NCl$: Cl, 17.27. Found: Cl, 17.24.

When nitrosyringic acid was boiled with ferrous sulfate and ammonium hydroxide solution, the aminopyrogallol dimethyl ether was again the product.

Benzoyl Derivative.—This was prepared by the action of benzoyl chloride upon the amine, in the presence of a slight excess of sodium bicarbonate and a few crystals of sodium sulfite. It crystallized from alcohol in large colorless flakes, m. p. 158.3° (corr.); yield, almost that calculated.

Anal. Calcd. for $C_{15}H_{15}O_4N$: C, 65.93; H, 5.50. Found: C, 66.06; H, 5.56.

Its alcoholic solution was colored deep red by ferric chloride. It was insoluble in cold dilute hydrochloric acid, or in sodium bicarbonate solution.

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[18] Power and Shedden, *J. Chem. Soc.*, **81**, 73 (1902).

[19] Anschütz, Schmidt and Greiffenberg, *Ber.*, **35**, 3480 (1902).

[20] Bogert and Chambers, THIS JOURNAL, **27**, 649 (1905).

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-

[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).