Summary.

In this article are described:

1. A modified method of brominating phenols.

2. A modified method of methylating phenols to prevent oxidation.

3. The preparation of dibromo-guaiacol sulfonic acid, diiodo-guaiacol sulfonic acid, mono-bromo-creosole, pyrogallol dimethyl ether sulfonic acid, pyrogallol trimethyl-ether sulfonic acid, dibromo-pyrogallol dimethyl ether and dibromo-pyrogallol trimethyl ether.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

THE FERROUS SULFATE AND AMMONIA METHOD FOR THE REDUCTION OF NITRO TO AMINO COMPOUNDS.

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The reduction of aromatic nitro compounds to their corresponding amino derivatives has been the subject of such exhaustive treatment in the past and so many excellent methods for accomplishing this end have been devised and so thoroughly discussed in the numerous laboratory manuals that it may seem scarcely necessary to reopen the question. But to those who, like ourselves, may be engaged in investigations which require the convenient and rapid preparation of substances on a scale sufficient for further synthetic work, we feel that our experience may be of service.

In the majority of instances in which nitro compounds have been reduced tin or tin salts have perhaps been the most popular reagent. Except in the case of alkali-insoluble substances, or where the hydrochloride of the base does not form a tin double salt, the metal must be removed with hydrogen sulfide, a very time-consuming operation. And when the substances are sensitive to acids this method is to be avoided.

Of the other methods available, that of reduction by means of ferrous sulfate and ammonia has been of service in the past in the preparation of such substances as the aminocinnamic acids, aminopropiolic acid and the otherwise inaccessible *o*-aminobenzaldehyde. It has occasionally been employed with success in other isolated cases, but appears on the whole to have been comparatively neglected. Our experience with the method in reducing a great many substances of varying type would seem to warrant its more frequent employment where the properties of the substances permit. It is the object of this paper to call attention to the ease of manipulation, rapidity, and cheapness of the method, and to the good yields which accompany its proper use.

Our attention was first turned to the method in seeking for a con-

venient means of reducing substituted nitro amides and nitro ureides. Because of the sensitiveness of these substances to acids and fixed alkali the iron sulfate and ammonia method recommended itself as a milder process, the reaction of the boiling solution being but faintly alkaline. The results obtained were gratifying, for in every instance where other methods were unsatisfactory or had failed this method yielded the desired result.

Another reducing reagent which seemed applicable to our problem was ammonium sulfide. This has, of course, frequently been employed in the past, for example, in the preparation of the aminobenzamides and of *m*-aminobenzoylurea. Our experience has shown that both *p*-nitrobenzamide and *p*-nitrobenzoylurea can be conveniently and rapidly reduced by this reagent. In the case of the isomers, however, it was not only necessary in each case to vary the amount of reagent and the time of the reaction, but the yields obtained were also uncertain. On the other hand the iron sulfate and ammonia method proved to be a uniform, rapid, and reliable procedure.

In the preparation of a considerable number of amino acids from the corresponding nitro compounds this procedure was also found to give very satisfactory results.

In the experimental part below, we have selected a number of examples which emphasize the usefulness of the ferrous sulfate and ammonia method, showing it to be, in most cases, a decided improvement over the methods given in the literature for the preparation of these compounds. Numerous additional instances of the successful use of the method will appear in the communications to follow.

Experimental.

As far as the manipulation is concerned, we have nothing to add to the method, the following procedure being essentially that adopted by previous workers: In the case of nitro acids the substance was first dissolved in sufficient dilute ammonia, using heat to aid solution, if necessary, while in the case of insoluble substances a thin paste was prepared with hot water. The solution or suspension was then poured in a thin stream, with vigorous shaking, into a boiling solution of 7 mol. equivalents (1 in excess) of ferrous sulfate ($FeSO_4.7H_2O$) in 2–2.5 parts of water. The solution was then immediately treated with small portions of concentrated aqueous ammonia, each addition being followed by vigorous shaking. The addition of ammonia was continued until the boiling solution became definitely alkaline to litmus. The mixture was then boiled 5 minutes and filtered hot with the aid of suction after adding more ammonia if the reaction did not remain alkaline. In many cases the amino compounds separated on cooling; in the case of acids or soluble substances the solution was concentrated to small bulk *in vacuo* or, in the case of amines showing

little tendency to oxidize, on the water bath. Amino acids were then liberated from the concentrated solutions of the ammonium salts by the addition of acetic acid. Deviations from the above procedure are mentioned below as they occur.

1. Reduction of Nitro Acids.

***m*-Aminophenylacetic Acid,** *m*-$H_2NC_6H_4CH_2CO_2H$. — The reduced ammoniacal solution from 39 g. *m*-nitrophenylacetic acid was concentrated on the water bath, filtered, and acidified with acetic acid. 25 g. of the acid separated, melting at 151°. Gabriel and Borgmann,[1] who reduced the nitro acid with tin and hydrochloric acid, give 148–9° as the melting point.

***p*-Aminophenylacetic Acid.**—This acid was prepared exactly as in the case of its isomer. 130 g. of the nitro acid yielded 83 g. of the amino acid, corresponding in properties to those recorded in the literature.

***p*-Aminophenoxyacetic Acid,** *p*-$H_2NC_6H_4OCH_2CO_2H$.—The *p*-nitrophenoxyacetic acid used as starting material was prepared as follows: 139 g. *p*-nitrophenol, 160 g. 50% sodium hydroxide solution (2 mols.), 95 g. chloroacetic acid (1 mol.), and 800 cc. water were boiled in an open flask until neutral to litmus, about 2 hours being required. Half the above quantities of alkali and chloroacetic acid and 200 cc. water were then added and the solution boiled again until neutral. After acidifying strongly with hydrochloric acid the solution was cooled, precipitating the nitro acid. This was recrystallized from alcohol or purified by dissolving in dilute alkali and reprecipitating with hydrochloric acid. The yield was 100–120 g., melting at 183° as recorded in the literature.

The solution obtained by reducing 20 g. of the nitro acid with ferrous sulfate and ammonia was concentrated *in vacuo* until the ammonium salt of the amino acid was salted out by the action of the ammonium sulfate present. The mixture was then heated until solution took place and acetic acid added in excess, the *p*-aminophenoxyacetic acid precipitating out almost immediately. The yield was 15.7 g. According to statements in the literature[2] the acid does not melt below 300°, but all of our samples, whether air-dry or anhydrous, or prepared as above or by hydrolysis of *p*-acetaminophenoxyacetic acid, melted with gas evolution and resolidification at about 220°, the residue not melting below 285°.

Kjeldahl: 0.2204 g. subst.; 17.9 cc. *N*/14 HCl.
Calcd. for $C_8H_9O_3N$: N, 8.38%. Found: N, 8.12%.

2. Reduction of Nitro Amides.

***o*-Aminobenzamide,** *o*-$H_2NC_6H_4CONH_2$.—55 g. *o*-nitrobenzamide were suspended in 650 cc. hot water and a solution of 650 g. ferrous sulfate in

[1] Gabriel and Borgmann, *Ber.*, **16**, 2065 (1883).

[2] Howard, *Ber.*, **30**, 547 (1897); Kym, *J. prakt. Chem.*, [2] **55**, 118 (1897).

1200 cc. hot water added. The mixture was made ammoniacal, with vigorous shaking, boiled 5 minutes, filtered, and evaporated to small bulk on the water bath. The *o*-aminobenzamide was filtered off after cooling, washed with cold water, and dried. Yield, 33 g. leaflets, melting at 109–11.5° with preliminary softening. Previously recorded melting points range from 108° to 113°.

***m*-Aminobenzamide.**—80 g. of powdered *m*-nitrobenzamide were added to a boiling solution of 950 g. ferrous sulfate in 3 liters of water. When all was dissolved, the solution was made ammoniacal, with vigorous shaking, and the boiling continued 5 minutes. The filtrate was then concentrated *in vacuo* until crystallization occurred. The whole was then diluted with a little hot water until clear and allowed to cool in the ice box, the amino amide separating in long, thin, serrated plates melting at 79–80°. The yield was 63 g. As we have been unable to find a description of the anhydrous amide in the literature it is given here. The water-free substance is readily obtained from the hydrate by solution in boiling benzene. It separates from the solvent in silky needles which melt at 113–4° (corr.) and are soluble in ether and difficultly soluble in cold chloroform or benzene.

Kjeldahl: 0.1437 g. subst.; 30 cc. *N*/14 HCl.
Calcd. for $C_7H_8ON_2$: N, 20.59%. Found: N, 20.87%.

3. Reduction of Nitro Ureas.

***o*-Aminobenzoylurea,** o-$H_2NC_6H_4CONHCONH_2$.—*o*-Nitrobenzoylurea was made by boiling nitrobenzoyl chloride and urea in benzene solution for 8 hours. The product obtained showed the same properties as those recorded by Diels and Wagner,[1] who used no solvent in the preparation. 41 g. of the nitro urea were reduced in 1.3 liters of boiling water with 375 g. ferrous sulfate and an excess of ammonia. An equal volume of 95% alcohol was added to the hot mixture, which was then digested on the water bath for 40 minutes and filtered. The aminobenzoylurea separated on cooling in a yield of 26 g. Recrystallized from 50% alcohol, it forms faintly yellowish leaflets which become pasty and evolve gas at about 200° and immediately resolidify to a product which does not melt below 280°. Diels and Wagner,[2] who reduced the nitro urea with the aid of zinc dust, describe *o*-aminobenzoylurea as forming brown needles. Contrary to these authors, it may be recrystallized unchanged from boiling acetic acid, as was shown by analysis of the product so obtained, conversion to benzoyleneurea taking place comparatively slowly. In other respects our specimen showed the properties recorded by Diels and Wagner.

0.0995 g. subst.; 19.8 cc. N, 778 mm., 21.0°.
Calcd. for $C_8H_9O_2N_3$: N, 23.46%. Found: N, 23.66%.

[1] Diels and Wagner, *Ber.*, **45**, 880 (1912).
[2] *Loc. cit.*, p. 881.

***m*-Aminobenzoylurea.**—The necessary *m*-nitrobenzoylurea was prepared by boiling the acid chloride and urea in benzene for 12 hours instead of following Griess' method[1] of fusing the components at 150°. The amino urea was obtained in the same way as the *o*-isomer, except that it was necessary to evaporate the alcohol before the substance separated completely on cooling. The yield was 6 g. from 10 g. of the nitro compound. As Griess' description of *m*-aminobenzoylurea is not complete, the following is appended: When rapidly heated it melts with gas evolution at about 210°, resolidifying and then remelting at about 275–80°. It is readily diazotized, in contradistinction to the *o*-isomer, yielding a scarlet color with R-salt, and dissolves readily in boiling water or 95% alcohol.

Kjeldahl: 0.0997 g. subst.; 16.50 cc. 0.1 *N* HCl.
Calcd. for $C_8H_9O_2N_3$: N, 23.46%. Found: N, 23.18%.

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METHODS FOR THE ACYLATION OF AROMATIC AMINO COMPOUNDS AND UREAS, WITH ESPECIAL REFERENCE TO CHLOROACETYLATION.

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The importance of the halogenacetyl compounds has been demonstrated by their frequent use in organic synthesis. The great reactivity of the halogen atom has permitted their use in practically all the reactions in which alkyl halides have been employed. In the work of the authors on the quaternary salts of hexamethylenetetramine[2] one phase of their usefulness in synthetic work in chemotherapy was demonstrated. In continuing our work along similar lines we have had occasion to prepare the chloroacetyl derivatives of a large number of aromatic amino compounds of such widely differing constitution and solubility relationships that the older acylation methods frequently proved inapplicable.

The well-known Schotten-Baumann method has been quite successfully applied in the past to chloroacetylation. In the case of amino compounds soluble in water or alkali the conditions are simple, although, owing to the great reactivity of chloroacetyl chloride with aqueous alkali, a considerable excess of the chloride is usually required to furnish a satisfactory yield. In the case of bases insoluble in water, the use of neutral organic solvents usually proves of service, either in connection with

[1] Griess, *Ber.*, 8, 222 (1875).

[2] *J. Biol. Chem.*, 20, 685; 21, 103, 145, 403, 455, 465 (1915); *J. Exp. Med.*, 23, 563, 577 (1916).