

## LITERATURE REFERENCES.

- (1) (a) Schaffer and Tilley, *J. Bact.*, 14 (1927), 259.  
(b) Johnson and Lane, *J. A. C. S.*, 43 (1921), 348.  
(c) Dohme, Cox and Miller, *Ibid.*, 48 (1926), 1688.  
(d) Coulthard, Marshal and Pyman, *J. Chem. Soc.* (1930), 280.  
(e) Klarmann, *J. A. C. S.*, 53 (1931), 3397.  
(f) Black, Stein and Walker, *J. Chem. Soc.* (1931), 277.
- (2) Auers and Wittig, *J. prakt. Chem.*, 108 (1924), 99.
- (3) "Organic Synthesis," Vol. V, page 7, Wiley and Sons, N. Y., 1925.

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## ISOMERIC NITRO-CRESOLS.\*

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In the preparation of a series of mercurials, it was necessary first to obtain the ten isomeric nitro-cresols. Most of the research on these compounds is found in the earlier literature, very little having been done in recent years. The methods vary and are in many cases indefinite and the results obtained by their use do not always lead to the conclusions described, either in yield or quality of the material.

We believe that a condensed comparison of the known methods coupled with a reference to the preparation of each isomer in the best obtainable yields and purity would be of service to the organic chemist. In those cases where we have improved the methods, a detailed description of the compound is given. We present, moreover, methods which involve the least expense in starting material and complication in process.

The nitro-cresols are prepared either by direct nitration of the cresol, resulting in single derivatives or mixtures, or by diazotization and subsequent replacement of the corresponding nitro-toluidine. The nitro-toluidines are prepared by direct nitration of the toluidines. In a few instances the nitro-cresols can also be prepared by simultaneous diazotization and nitration of the toluidines. The 5-nitro-2-hydroxy-toluene is also prepared by oxidation of the 5-nitroso derivative.

However, in the case of two isomers, the 6-nitro-2-hydroxy-toluene and 5-nitro-3-hydroxy-toluene, it is unavoidable to employ roundabout procedures inasmuch as the nitro group cannot be introduced, in the desired position, directly into the nucleus either of the cresol or the corresponding toluidine. In fact, we have as yet been unsuccessful in isolating any definite quantity of the former according to the described methods, but we are still working on what may prove a successful attempt.

## DISCUSSION AND EXPERIMENTAL PART—NITRO-ORTHO-CRESOLS.

*3-Nitro-2-Hydroxy-1-Methyl-Benzene.*—This was prepared by Wohl (1) using a mixture of meta-nitro-toluene and powdered alkali, keeping the temperature below 40° C. The material had to be mixed thoroughly for 24 hours and the unchanged nitro-toluene, of which there was a considerable quantity, separated from the sodium salt of the nitro-cresol.

Noelting and Wild (2) diazotized ortho-toluidine in dilute H<sub>2</sub>SO<sub>4</sub> and after adding dilute HNO<sub>3</sub> heated the mixture until no further evolution of nitrogen took place. The nitro-cresol was

\* Scientific Section, A. P. H. A., Madison meeting, 1933.

separated by steam distillation. Deninger (3) similarly used a large excess of sodium nitrite and omitted the nitric acid. The yields in either case were poor.

Nitration of *o*-cresol in presence of acetic acid was tried by Hofman and Miller (4), Rapp (5), Hirsch (6) and Gibson (7). In this way a better yield of the 3-nitro compound is obtained but it is contaminated with the 5-nitro and 3-5-dinitro compounds. They can be separated by steam distillation. The 5-nitro derivative is non-volatile with steam. We have observed that the 3-nitro-cresol distils over almost entirely, and after an interval is followed by the dinitro compound, which is also much lighter in color and a finer crystal than the mono-nitro derivative.

The method which gives the best yield of the 3-nitro-2-hydroxy methyl-benzene without much contamination of the di-nitro compound is that of Schultz (8), using benzene as a medium. Although he also claims a large yield of the 5-nitro-2-hydroxy methyl benzene, we were able to obtain only about 5% of this compound. However, by using a lower temperature (0° to 5°) we increased the yield of the 3-nitro isomer to 31%.

*4-Nitro-2-Hydroxy-1-Methyl-Benzene*.—This was first prepared by Noelting and Collin (9) by diazotization of the corresponding nitro-toluidine in dilute  $H_2SO_4$  and then allowing the mixture to stand, finally warming on a steam-bath to complete evolution of nitrogen. The above authors obtained a good yield of a material which melted at 106–108°. Later it was proven by Witt, Noelting and Grandmougin (10) that the above reaction does not take place entirely in the direction desired, but that a large amount of material shown to be 6-nitro-indazole is also formed. They and others (11) attempted to separate the nitro-indazole by fractional crystallization and also by use of its insolubility in  $Na_2CO_3$  solution. This of course reduced the yield of the nitro-cresol.

Ullman and Fitzenkam (12) devised a method which gave practically no nitro-indazole and a good yield of nitro-cresol. They added the diazo solutions slowly to boiling dilute sulphuric acid and separated the nitro-cresol on cooling. We have obtained yields as high as 85% with this method.

Ortho-toluidine is dissolved in 10 volumes of concentrated  $H_2SO_4$  and nitrated with an equivalent of concentrated  $HNO_3$  at 0° C. The mixture is poured into ice and water and the nitro-toluidine sulphate is filtered off. This is dissolved in water and  $Na_2CO_3$  added until neutral and the 4-nitro-2-amino-methyl benzene filtered off, washed and recrystallized from alcohol. M. p.—107°. Yield = 90%.

40 Gm. of this nitro-toluidine are dissolved in 600 cc. of 10%  $H_2SO_4$ , warming to dissolve. On cooling to 0° some crystals of sulphate separate. Add slowly, with good stirring, a solution of 18 Gm. of sodium nitrite in 50 cc.  $H_2O$ , keeping the temperature at 0°. Stir for 15 minutes after all is added. A clear solution is obtained. Add this cold solution, over a period of 15 minutes to a boiling solution of 400 cc. concentrated  $H_2SO_4$  in 800 cc.  $H_2O$ —a brisk evolution of nitrogen occurs. Boil further for 10 minutes and cool thoroughly. A brown oily material which forms on surface solidifies and crystals form in solution. Filter and wash with cold water. The crude material melts from 109° to 114° C. It can be purified by solution in alcohol, treatment with "nuchar" and precipitation with  $H_2O$ , or by solution in dilute  $NaOH$ , warming to 60° with small quantity of "nuchar," filtering and acidification with dilute hydrochloric acid. Cool and filter off crystals. Yield = 34 Gm. (85%). Pale yellow needles, m. p.—118°.

*5-Nitro-2-Hydroxy-1-Methyl-Benzene*.—As was previously shown (4), (5), (6), (7), this compound was formed simultaneously with the 3-nitro-2-hydroxy-toluene but in small quantities, and was extracted from the tarry residue of the steam distillation only by long and tedious boiling with successive portions of water. By diazotization of the corresponding nitro-toluidine and replacement of the diazo group by hydroxyl or by boiling the nitro-toluidine with strong aqueous alkali (13) better yields are obtained. However, the above toluidine is difficultly separated from the corresponding 3-nitro derivative.

Borsche and Birkhout (14) prepared a homogeneous product in good yields by the oxidation of 5-nitroso-2-hydroxy-toluene with potassium ferricyanide. We have devised a method, using nitric acid as the oxidant, which gives a pure nitro

compound without any contamination of dinitro or 3-nitro isomer, in yields of about 80–85%. This is a simpler and shorter method than the ferricyanide oxidation which involves several days' standing.

35 Gm. of solid sodium nitrite are added to a suspension of 27 Gm. of *o*-cresol in 2 liters of ice water with mechanical stirring. A solution of 9.5 cc. of concentrated sulphuric acid in 200 cc. of H<sub>2</sub>O is then added during the course of 1 hour, keeping temperature below 5° by further addition of ice. Allow to stand for 2 hours in cold. Filter off the nitroso compound, wash with ice water. This crude material can be used for the further oxidation. A small sample recrystallized from benzene melted at 136°.

27.5 Gm. of the crude nitroso compound are suspended in 200 cc. of a mixture of 1 part of concentrated nitric acid and 3 parts of water. This is agitated and cooled from time to time to prevent decomposition. After three hours the solid material is filtered and washed with water. It is purified by solution in 5% sodium hydroxide, treatment with charcoal and precipitation with dilute HCl (10%), which is added dropwise while cooling the alkaline solution. It separates as pale brownish yellow needles. M. p.—91°. The yield is 25 Gm. or about 82%.

*6-Nitro-2-Hydroxy-1-Methyl-Benzene*.—Since this isomer cannot be prepared by nitration of cresol, it must be obtained by the replacement of the diazo group from the corresponding toluidine. Green and Lawson (15) claimed that this nitro-toluidine was obtained simultaneously with the 4-nitro-2-amino-toluene by nitrating ortho-toluidine in sulphuric acid. They maintained that by fractional crystallization of the hydrochlorides they separated the more difficultly soluble 6-nitro-toluidine. We were unable to obtain any of this material even when the conditions of the toluidine nitration were varied. Cunerth (16), by nitration of toluene, obtained besides the 2-4-dinitro toluene, an oily substance (2-6-dinitro toluene) which he reduced with ammonium sulphide and claimed to obtain the 6-nitro-toluidine. His yields, however, are not given and the quantities of the oily dinitro toluene obtained are so small that we could not obtain a sufficient quantity for further reduction. Beilstein (17), Holleman (18) and Cohen (19) attempted to obtain the 2-6-dinitro toluene by reduction of the 2-4-6-trinitro-toluene to 2-6-dinitro-*p*-toluidine and subsequent elimination of the amino group by diazotizing and decomposing in absolute alcohol.

The trinitro-toluene is expensive, and when we attempted to reduce it by the above methods the yields were very poor, only a trace of the dinitro-toluidine being formed. Staedel (20) claims that in nitration of *o*-phthalyl-toluidide, two nitro derivatives are formed which on hydrolysis yield two corresponding nitro-toluidines one of which is the 6-nitro-2-amino-toluene. We are working on this method and may obtain some measure of success.

#### NITRO-META-CRESOLS.

*2-Nitro-3-Hydroxy-1-Methyl-Benzene*.—This material was originally considered an impurity which occurred with 4-nitro-3-hydroxy-toluene. However, Khotinsky and Jacobson-Jacobman (21) showed that in using *m*-toluidine in Deninger's (3) and Noelting's (2) methods, when the mixture was steam distilled, another volatile product was carried over which did not crystallize in the distillate. It remained oily and also was somewhat soluble in the aqueous portion of the distillate. The latter was extracted with ether after filtering off the crystalline 4-nitro derivative. More of the oily substance can be expressed from the crystals. On evaporation of the ether a dark oily substance remains which will not crystallize on cooling. It cannot be distilled without decomposition. It forms a dark red sodium salt. Khotinsky prepared a methoxy derivative which melted at 88°.

Gibson (22) could not isolate the 2-nitro-cresol from this methoxy derivative. He used the method of Kaufmann and de Pay (23) for the preparation of nitro-resorcinol, which involves first a di-sulphonation, then nitration with subsequent splitting off of the sulphonic acid groups by superheated steam. From meta-cresol he obtained a yield of yellow oil (80%) which would not crystallize, but which gave a methoxy derivative melting at 54° and an acetyl derivative, m. p.—59°.

By hydrolysis of this acetyl derivative and steam distillation of the product he obtained an oil which crystallized, m. p.—41°. Hodgson and Beard (24) modified Gibson's method by using a stronger fuming sulphuric acid and higher temperature in the initial sulphonation and obtained a product which solidified after the first steam distillation. We are using this method for the preparation of 2-nitro-3-hydroxy-toluene.

*4-Nitro-3-Hydroxy-1-Methyl-Benzene.*—This compound is obtained simultaneously with the 2-nitro and 6-nitro isomers as shown above (21). Khotinsky observed that using Staedel's (25) method and lowering the temperature in the reaction mixture to  $-8^{\circ}$  to  $-5^{\circ}$  the best yields of 4-nitro-3-hydroxy-toluene were obtained with correspondingly smaller amounts of the 6-nitro isomer and practically none of the 2-nitro derivative.

However, cooling and maintaining the reaction mixture at this temperature is rather difficult when using an ordinary ice-salt freezing mixture. Since ice could not be added directly to the reaction it was necessary to find some material which could, and at the same time have no effect in the reaction. We employed solid carbon dioxide (26) and found it rather easy to obtain temperatures as low as  $-15^{\circ}$  to  $-20^{\circ}$  C. with addition of only small amounts of solid  $\text{CO}_2$ . However, such low temperatures at the beginning of the nitration caused the acetic acid to crystallize and made it very difficult to stir to obtain a smooth reaction. We finally added only a small amount of  $\text{CO}_2$ , lowering the temperature to  $-5^{\circ}$ , and then after adding some of the cresol mixture, maintained the temperature at  $-10^{\circ}$  to  $-12^{\circ}$  by gradual addition of solid  $\text{CO}_2$ . The nitration can be done quickly and easily controlled within the desired temperature range, and at the same time better yields of the 4-nitro-cresol are obtained due to the low temperature.

100 Gm. of *m*-cresol are dissolved in 100 cc. of glacial acetic acid. This is added to a solution of 114 cc. of concentrated nitric acid in 290 cc. of glacial acetic acid which has been cooled to  $-5^{\circ}$  by the addition of a few pieces of dry ice (solid  $\text{CO}_2$ ) about the size of small nuts. As the cresol mixture is added, gradually increase the amount of dry ice until the temperature reaches  $-12^{\circ}$  C. and maintain thus until the end of the reaction. The mixture is then added to 2 liters of ice water. Filter off the precipitate and steam distil. In the distillate the 4-nitro-3-hydroxy-toluene separates. Yield 33 Gm. or 25%. It can be recrystallized by solution in alcohol and precipitation in water. It separates as yellow needles. M. p.—56°. The residue from the steam distillation contains about 60% of 6-nitro-3-hydroxy toluene which can be extracted by boiling water.

*5-Nitro-3-Hydroxy-1-Methyl-Benzene.*—By direct nitration of *m*-cresol or by simultaneous diazotization and nitration of *m*-toluidine, this compound cannot be obtained, due to the directing influence of the hydroxyl group. It is first necessary to prepare the corresponding 5-nitro-3-amino-toluene. This also cannot be prepared from the *m*-toluidine by direct nitration. Staedel (27) prepared it by a complicated procedure. He nitrated *p*-acetyl toluidine using an excess of fuming nitric acid forming 3-5-dinitro-*p*-acetyl toluidine. This is hydrolyzed by refluxing with alcoholic NaOH. The resulting 3-5-dinitro-*p*-toluidine is then diazotized in concentrated nitric acid, and the diazo-nitrate added gradually to boiling absolute alcohol. The mixture is cooled quickly and added to a double volume of water. The precipitate is 3-5-dinitrotoluol. M. p.—91°. This is then reduced by alcoholic ammonium sulphide to 5-nitro-3-amino-toluene. In some of these steps the yields were not given and we found them to be rather low. The nitro-cresol is obtained from the nitro-toluidine using the method as in the case of 4-nitro-2-hydroxy-toluene. The yield is low, only about 30%. Recrystallized from benzene it melts at  $89^{\circ}$  C.

*6-Nitro-3-Hydroxy-1-Methyl-Benzene.*—It is the chief product in all methods mentioned above in which either *m*-toluidine or *m*-cresol are the starting materials. By allowing the temperature to rise to  $5^{\circ}$ , in the nitration using acetic acid, the proportion of the 6-nitro-cresol can be increased.

In order to separate the 6-nitro-cresol from the other isomers it was previously necessary to steam distil the mixture, the 6-nitro-derivative being non-volatile with steam. We have found, however, that by extracting with boiling benzene practically all of the 2-nitro and 4-nitro isomers are removed and the difficultly soluble 6-nitro-3-hydroxy toluene remains, which after recrystallization from water is pure. M. p.—130° C.

The steam distillation can also be avoided by nitration of *m*-toluidine in sulphuric acid, obtaining 6-nitro-3-amino-toluene without contamination of any isomers. This can then be diazotized and converted into the corresponding cresol, according to the procedure employed in the preparation of 4-nitro-2-hydroxy-toluene and 5-nitro-3-hydroxy-toluene. The yield in the last step averaged 60%.

#### NITRO-PARA-CRESOLS.

*2-Nitro-4-Hydroxy-1-Methyl-Benzene*.—By direct nitration of *p*-cresol practically none of this isomer is formed. Simultaneous diazotization and nitration of *p*-toluidine according to method of Noelting (2), produces very little of the 2-nitro derivative. However, Noelting (28) found that in nitrating *p*-toluidine in sulphuric acid the 2-nitro-4-amino-toluene was obtained without any contamination of the 3-nitro-toluidine, especially when large amounts of H<sub>2</sub>SO<sub>4</sub> were used. Copisarow (29) using an adaptation of the method of Holleman and Holflake (30) prepared 2-nitro-*p*-hydroxy-toluene by nitrating *p*-cresyl carbonate. Lucas and Liu (31) studied this reaction and explained the introduction of the nitro group meta to the hydroxyl as due to the formation of the oxonium salt.

Knecht (32) and Neville and Winther (12) converted the nitro-toluidine into nitro-cresol by diazotization and replacement of amino group, using gentle heating with dilute sulphuric acid.

We found that these latter methods gave poor yields and in some cases no cresol at all, only tar resulting from the reaction. We applied the Ullman method, as used in the case of 4-nitro-2-hydroxy-toluene, and found it gave better results. Care must be taken that in the addition of the diazotized solution of the nitro-toluidine to the boiling sulphuric acid, heating should be continued until the red color which first forms changes to yellow. This may take over a half hour but it is necessary to obtain a good yield. A reflux condenser should not be used during the reaction, inasmuch as it seems to retard the color change. On cooling, the crude 2-nitrocresol separates. The yield after recrystallization from water is 50–55%. It separates as yellow prisms. M. p.—77–78°.

*3-Nitro-4-Hydroxy-1-Methyl-Benzene*.—Hofmann and Miller (4), Staedel (25), Frische (33) nitrated *p*-cresol in acetic acid and obtained fair yields of 3-nitro derivative. By use of the methods of Noelting (2) and Deninger (3), starting with *p*-toluidine, we obtained good yields. The nitro-cresol can be obtained from the corresponding nitro-toluidine (Neville (12)), which in turn is prepared by nitration of *p*-acetyl toluidine with fuming nitric acid (sp. gr. = 1.5) (34). Schultz (8) claimed yields of 85–90% by nitrating *p*-cresol in benzene. Using this method we were unable to duplicate the yields, averaging only about 40%. We finally adopted the method of Brasch and Freyss (35), by which we obtained consistent yields of 70–75%.

#### SUMMARY.

1. Nine of the ten possible isomeric nitro-cresols have been studied.
2. The methods of preparation described in the available literature have been discussed.
3. We have improved these methods and given in each case the procedure assuring the best results as to yield, purity and low cost of preparation.

## REFERENCES.

- (1) *D. R. P.* 116,790, see also *Zentralblatt*, 1 (1901), 149.
- (2) *Ber.*, 18 (1885), 1339.
- (3) *J. prakt. Chem.* (2), 40 (1889), 299.
- (4) *Ber.*, 14 (1881), 568.
- (5) *Ann.*, 224 (1884), 175.
- (6) *Ber.*, 18 (1885), 1512.
- (7) Gibson, *J. Chem. Soc.*, 127 (1925), 42.
- (8) *Ber.*, 40 (1907), 4319.
- (9) *Ibid.*, 17 (1884), 269.
- (10) *Ibid.*, 23 (1890) 3636.
- (11) Michel and Grandmougin, *Ibid.*, 26 (1893), 2349; Spiegel, Munblit and Kaufmann, *Ibid.*, 39 (1906), 3241.
- (12) *Ibid.*, 38 (1905), 3790.
- (13) Neville and Winther, *Ibid.*, 15 (1882), 2978.
- (14) *Ann.*, 330 (1904), 95.
- (15) *J. Chem. Soc.*, 59 (1891), 1013.
- (16) *Ann.*, 172 (1874), 221.
- (17) *Ber.*, 13 (1880), 242.
- (18) *Rec. trav. chim.*, 16 (1896), 426.
- (19) *J. Chem. Soc.*, 81 (1902), 26; 87 (1905), 1265.
- (20) *Ann.*, 225 (1884), 384.
- (21) *Ber.*, 42 (1909), 3098.
- (22) *J. Chem. Soc.*, 123 (1923), 1269.
- (23) *Ber.*, 37 (1904), 725.
- (24) *J. Chem. Soc.*, 127 (1925), 498.
- (25) *Ann.*, 217 (1883), 51.
- (26) The method of using solid carbon dioxide for internal cooling was the material for copending patent applications by G. W. Raiziss and H. Brahlin of the Dermatological Research Laboratories and I. T. Thornton of the National Aniline and Chemical Co. of Buffalo, N. Y.
- (27) *Ann.*, 217 (1883), 187-205.
- (28) Same as reference 9, page 261.
- (29) *J. Chem. Soc.*, 135 (1929), 251.
- (30) *Rec. trav. chim.*, 36 (1916), 271.
- (31) *J. Am. Chem. Soc.*, 55 (1933), 1271.
- (32) *Ann.*, 215 (1882), 87.
- (33) *Ibid.*, 224 (1884), 138.
- (34) Gattermann, *Ber.*, 18 (1885), 1483.
- (35) *Ibid.*, 24 (1891), 1960.

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ARSENOUS CHLORIDE AND 1,4-DIOXANE.\*

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It has been shown in previous reports that arsenous chloride reacts with amines to form substituted ammonium halides, in which one, two or three of the chlorines were replaced by amine groups, the halogens being ionized in the resulting complex (1,9). Thus for example piperidine and arsenous chloride form the compound  $(C_5H_{10}N.HCl)_3As$  which may be written structurally as:

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\* Scientific Section, A. Ph. A., Madison meeting, 1933.