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THE MANUFACTURE OF ACETPHENETIDIN.

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(Continued from p. 290, April issue.)

PREPARATION OF INTERMEDIATES.

I. PREPARATION OF *p*-NITROPHENOL.

Para-nitrophenol is the initial intermediate in the processes of making acetphenetidin described by Hinsberg, Platt, Täuber and Paul. In the practical application of these processes the *p*-nitrophenol seems to have been always obtained from phenol by direct nitration, as no reference to any other source or method of preparation is to be found in the literature in connection with descriptions of these processes. Para-nitrophenol has, however, been made from phenol in several indirect ways, *viz.*, by the nitration and subsequent saponification of the esters of phenol with phosphoric acid,<sup>1</sup> benzene-sulphonic acid, toluene-sulphonic acid, etc.;<sup>2</sup> it has also been prepared from nitromalonaldehyde,<sup>3</sup> aniline, *p*-nitroacetanilid, and *p*-chlornitrobenzene. The indirect methods from phenol, and also the preparation from nitromalonaldehyde, need not be considered further, as they are obviously not economical for the technical preparation of large quantities of *p*-nitrophenol. Of the other methods, starting with phenol, aniline, *p*-nitroacetanilid, and *p*-chlornitrobenzene, a comparative study has been made as follows:

*Preparation of p-Nitrophenol from Aniline.*

HISTORICAL.

Deninger<sup>4</sup> was very successful in converting aniline into nitrophenol by the following method: 10 Gm. of aniline, 200 Cc. of concentrated sulphuric acid, and 800 Cc. of water were mixed and cooled below 15°. To this solution 300 Gm. of sodium nitrite, dissolved in 100 Cc. of water, were added, the first third slowly, with cooling, the remaining two-thirds rapidly, without cooling. The mixture was immediately heated on a boiling water-bath, and diluted sulphuric acid (50 Cc. of sulphuric acid and 50 Cc. of water) added as rapidly as the violent reaction permitted. When the reaction was complete the *o*-nitrophenol was distilled off with steam, and the *p*-nitrophenol obtained from the residue by crystallization from water or hydrochloric acid. The yield was reported as 4.7 Gm. of *o*-nitrophenol and 3.7 Gm. of *p*-nitrophenol, corresponding to 56 percent of the theoretical. The method is not suitable for technical use.

Nolting and Wild<sup>5</sup> converted aniline into nitrophenol according to the following method: 93 Gm. of aniline, 150-200 Gm. of concentrated sulphuric acid, and 2 l. of water were mixed and cooled to 0°. To this solution 69 Gm. of sodium nitrite were added, and somewhat later 119 Gm. of nitric acid of s. g. 1.335 (= 63 Gm. of HNO<sub>3</sub>) were run in. The mixture was then heated under reflux until the evolution of nitrogen ceased. The *o*-nitrophenol was then distilled off with steam, and the *p*-nitrophenol crystallized from the residue. The yields were not given. It was stated that the two isomers were obtained in approximately equal amounts.

EXPERIMENTAL.

The work of Nolting and Wild was repeated in three experiments. The chief product of the reaction was found to be phenol. Only about 5 Gm. of *o*-nitrophenol

<sup>1</sup> *Ann.*, 224, 156, 1884.

<sup>2</sup> *Gazz. chim. ital.*, 11, 76, 1881; *Société des Usines der Rhône, D. R. P. No. 91,314; Frdl. IV, 39; Brit. Pat. No. 24,193, 1895; J. Soc. Chem. Ind.*, 1897, 40.

<sup>3</sup> *Ber.*, 28, 2598, 1895.

<sup>4</sup> *J. prakt. Chem.*, [2] 40, 298.

<sup>5</sup> *Ibid.*, [2] 17, 189.

and 4.5 Gm. of *p*-nitrophenol were obtained from 93 Gm. of aniline. Considerable tar was formed in each case. It is probable that phenol is first formed from the diazo compound, and this is then nitrated. As the solution contains but one mol of nitric acid in a strength of 2-3 percent it is evident that effective nitration can not take place.

*Preparation of p-Nitrophenol from p-Nitroacetanilid.*

HISTORICAL.

In 1874 Paul Wagner<sup>6</sup> studied the effect of concentrated solutions of sodium hydroxide on *p*-nitroacetanilid in order to determine whether *p*-nitrophenol is formed. Wagner found his conjecture confirmed, and stated that "the change of the nitroacetanilid into nitrophenol is a complete one, provided the heating is continued sufficiently long." With regard to his method, Wagner says, "I heat the nitroacetanilid with a concentrated solution of caustic soda, when an abundant evolution of ammonia immediately results. I continue to heat until the evolution of ammonia ceases. On cooling, needle-like crystals separate, which it is not difficult to recognize as the sodium salt of nitrophenol. These are dried, and decomposed by means of boiling hydrochloric acid; from the strongly acid liquid, light yellow needles crystallize on cooling, which by repeated crystallization from very dilute alcohol are obtained pure. The melting point of the crystals lies at 114° C." Since *p*-nitroacetanilid can be obtained in yields of 95 percent<sup>7</sup> by the nitration of acetanilid, this method seemed promising, and the work of Wagner was repeated, but the results were less satisfactory than he reported.

EXPERIMENTAL.

10 Gm. of *p*-nitroacetanilid were heated with varying amounts of sodium or potassium hydroxide and water, in a vessel provided with a reflux-condenser and surrounded by a paraffin-bath heated to 150°. The heating was continued until moist litmus-paper held at the upper end of the condenser-tube no longer turned blue; this required 20-24 hours. Water was then added, and the mixture made acid with hydrochloric. After boiling for 10 minutes with a small amount of animal charcoal, the mixture was filtered and the filtrate allowed to crystallize. Additional portions of crystals were obtained by evaporating the mother-liquor until the inorganic salt began to appear. Ten experiments were made as follows:

<i>p</i> -Nitroacetanilid. Gm.	Sodium hydroxide. Gm.	Water. Gm.	<i>p</i> -Nitrophenol. Gm.	Yield. Percent.
10	10	10	3.8	50
10	15	15	4.5	59
10	20	20	3.8	50
10	20	35	3.6	47
10	15	200	( <i>p</i> -nitraniline)	0
<i>p</i> -Nitroacetanilid. Gm.	Potassium hydroxide. Gm.	Water. Gm.	<i>p</i> -Nitrophenol. Gm.	Yield. Percent.
10	10	10	3.5	45
10	10	25	4.6	60
10	15	15	4.5	58
10	20	20	3.4	44
10	20	35	4.0	54

The average yield is 52 percent.

An experiment was also carried out in which 10 Gm. of *p*-nitroacetanilid were heated under the same conditions with 20 Gm. of exsiccated sodium carbonate

<sup>6</sup> *Ber.*, 7, 77, 1874.

<sup>7</sup> *Ibid.*, 17, 262, 1884.

and 25 Gm. of water. The *p*-nitroacetanilid was recovered unchanged. Calcium hydroxide likewise had no effect.

Two experiments were run in which the alkali was replaced by strong mineral acid, thinking that this might effect a similar hydrolysis of the *p*-nitroacetanilid. In the one experiment 10 Gm. of *p*-nitroacetanilid were heated under pressure for 12 hours with 50 Cc. of 50 percent sulphuric acid, and in the other experiment 50 Cc. of concentrated hydrochloric acid were used. In both cases the product was the corresponding salt of *p*-nitraniline.

#### *Preparation of p-Nitrophenol from Phenol.*

#### HISTORICAL.

The nitration of phenol appears to have been first studied by Hoffmann,<sup>8</sup> in 1857. He reported two methods for the preparation of the mono-nitrophenols; first, by mixing small portions of phenol and concentrated nitric acid, both cooled in a freezing-mixture, and then pouring the mixture into water and distilling with steam; and second, by dissolving the phenol in a large amount of water, adding concentrated nitric acid and distilling with steam. The first method did not always prove successful on account of the violent reaction which occurs when the two substances are mixed in concentrated form. Hoffmann states, however, that it gave better yields when it was successfully carried out. The actual yields were not given.

Fritzsche,<sup>9</sup> in 1859, described very fully the preparation and separation of the mono-nitrophenols, but, like Hoffmann, he failed to report the yields which he obtained. His method was to dissolve 25 Gm. of phenol in 1250 Gm. of water, heat the solution to boiling, and add slowly, with stirring, 37.5 Gm. of nitric acid. The *o*-nitrophenol was distilled off with steam, and the *p*-nitrophenol crystallized from the residue.

The yields obtained by the nitration of phenol were first mentioned by Cook and Schmitt.<sup>10</sup> These investigators stated that by adding one part of crystallized phenol to two parts of nitric acid of s. g. 1.34 and four parts of water, 30 percent of the phenol is obtained as *o*-nitrophenol and 32 percent as *p*-nitrophenol. This is the method described by Platt (see page 288) in connection with the manufacture of acetphenetidin, and is also the method given in many textbooks on industrial chemistry.<sup>11</sup>

In 1875 Weselsky<sup>12</sup> reported that when nitrogen trioxide, obtained from nitric acid and starch, is passed into an ethereal solution of phenol (200 Gm. in 1 l.) phenol-diazo-nitrate is precipitated, and the mother-liquor contains much ortho- and para-nitrophenol. However, he did not state in what quantities he obtained these mono-nitrophenols.

In 1880 Natanson<sup>13</sup> treated phenol with ethyl nitrate and sulphuric acid and obtained an oil which was purified by converting it into the sodium compound and then decomposing it with hydrochloric acid. He states that 22 percent of ortho- and 0.5 percent of para-nitrophenol were obtained.

Schall,<sup>14</sup> in 1883, suspended sodium phenolate in carbon disulphide and added, with cooling, liquid nitrogen tetroxide. After standing for some time the mixture was filtered, the carbon disulphide distilled off, and the residue treated with steam. The *o*-nitrophenol passed over with the steam, and the *p*-nitrophenol was extracted from the residue with ether. The yields were not stated. The author claimed that the *p*-nitrophenol was obtained in greater purity than by the usual methods of nitration.

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<sup>8</sup> *Ann.*, 103, 347, 1857.

<sup>9</sup> *Ibid.*, 110, 150, 1859.

<sup>10</sup> *Lehrb.* (Kekulé), III, 40.

<sup>11</sup> "Dyestuffs and Coal-Tar Products," Beacall, Challenger, Martin and Sand, Appleton and Co., 1915.

<sup>12</sup> *Ber.*, 8, 98, 1875.

<sup>13</sup> *Ibid.*, 13, 416, 1880.

<sup>14</sup> *Ibid.*, 16, 1901, 1883.

In 1885 Neumann<sup>15</sup> found that adding the diluted nitric acid to the phenol increases the proportion of *o*-nitrophenol. His method was to add gradually to one part of phenol a mixture of one part of nitric acid of s. g. 1.38 and six parts of water cooled to 0°. The brown oil which formed was subjected to steam distillation in a copper still. The wash-water was also distilled with steam after neutralization with sodium bicarbonate. The proportion of ortho- to para-nitrophenol was not stated.

Goldstein<sup>16</sup> observed that the higher the temperature reached by the mixture of nitric acid and phenol the greater is the proportion of ortho-nitrophenol formed, low temperatures seeming to favor the formation of the para-compound.

In 1905 Martinsen<sup>17</sup> made a very thorough study of the reaction-kinetics of the nitration of phenol in aqueous solution. The work was divided into eight parts: preparation of the mononitrophenols, measurement of the reaction velocity, influence of the concentration of the nitric acid and the phenol, influence of the degree of dissociation of the nitric acid, influence of nitrous acid, determination of the mode of action of nitrous acid, relation between the nitration velocity and the formation of nitrous acid, and the influence of nitrosophenol. The work was carried out with solutions of phenol 0.05–0.2 *N* and of nitric acid 0.6–0.8 *N*. The results were expressed in terms of 0.1 *N* sodium hydroxide. Lacmoid was used as the indicator, but the color change was not distinct as the nitrophenols themselves give color changes. Martinsen's conclusions were as follows: The nitration of phenol in aqueous solution is a very complicated autocatalyzed reaction, the velocity increasing with increasing concentration of the acid and decreasing with increasing concentration of the phenol. The velocity is increased by substances which have an ion in common with the nitric acid, potassium nitrate and sulphuric acid acting in harmony and a little stronger than sodium nitrate and strontium nitrate, which also act in harmony. Nitrous acid is a strong positive catalyst. During the nitration nitrous acid is formed, which explains the autocatalysis. The velocity of nitration and the speed with which the nitrous acid is formed run parallel. If the formation of nitrous acid is hindered (with urea) the nitration is hindered, but least with low concentrations of the nitric acid. Nitrosophenol increases the velocity of nitration, but the influence is not dependent on the concentration.

In 1906 Francis<sup>18</sup> nitrated phenol in carbon tetrachloride with benzoyl nitrate, and found that a mixture of ortho- and para-nitrophenols is formed, the ortho-compound predominating.

In 1907 Pictet<sup>19</sup> nitrated phenol with acetyl nitrate, prepared from acetic acid and nitrogen pentoxide, and obtained a mixture of ortho- and para-nitrophenol in the proportion of 52 percent ortho and 48 percent para. The exact yields were not given.

In 1910 Hart<sup>20</sup> reported that the production of tar is completely avoided and a yield of 18 percent of *p*-nitrophenol (13 Gm. from 50 Gm. of phenol) is uniformly obtainable if the nitric acid is vigorously stirred during the time that the phenol is being added and for about one-half hour afterward. About 30 Gm. of ortho-nitrophenol were said to be obtained at the same time. The temperature was found to have little influence on the yields of either isomer; the best yield, however, was obtained at 25°; below 4° nitration could not be effected.

In 1911 Pictet<sup>21</sup> reported his experiments on the nitration of phenol at low temperatures. In two experiments, carried out respectively at 0° and at –20–30° about 6 Gm. of *p*-nitrophenol were obtained from 80 Gm. of phenol. At –50–60° no reaction occurred until an electric current was passed through the mixture when the reaction proceeded without increase of temperature and a yield of 15 Gm. of *p*-nitrophenol from 40 Gm. of phenol was obtained, practically five times as much as at normal temperatures.

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<sup>15</sup> *Ber.*, 18, 3320, 1885.

<sup>16</sup> *J. russ. phys. chem. Ges.*, 10, 353; Beilstein, II, 681.

<sup>17</sup> *Z. physik. Chem.*, 50, 385, 1905.

<sup>18</sup> *Ber.*, 39, 3801, 1906.

<sup>19</sup> *Ibid.*, 40, 1165, 1907.

<sup>20</sup> *J. Am. Chem. Soc.*, 32, 1105, 1910.

<sup>21</sup> *J. Roy. Soc. Arts*, 56, 678–702, 1911; *J. Soc. Chem. Ind.*, 1911, 683.

## EXPERIMENTAL.

*Preparation of ortho- and para-nitrophenol by the method of Cook and Schmitt.*—50 Gm. of crystallized phenol were added slowly, with vigorous stirring, to a mixture of 100 Gm. of nitric acid (s. g. 1.34) and 200 Gm. of water, the temperature being kept at about 20°. The mixture was stirred for one-half hour after the addition of the phenol was completed, and then allowed to stand one and one-half hours longer. Five hundred Cc. of water were then added, and the heavy oil separated, washed with water, and subjected to steam distillation. By this operation the *o*-nitrophenol distilled over. The residue was boiled with 20 Gm. of animal charcoal, filtered hot, and allowed to crystallize in the cold. The *p*-nitrophenol crystallized in long needles, mixed with some tar. The mother-liquor was evaporated until no more crystals were obtained. The *p*-nitrophenol was purified by recrystallization from water with the aid of a little hydrochloric acid and animal charcoal. The average yield of several experiments was 20 Gm. of *o*-nitrophenol and 12.5 Gm. of *p*-nitrophenol, corresponding to about 44 percent of the theoretical yield.

*Preparation of ortho- and para-nitrophenol by the method of Hart.*—50 Gm. of crystallized phenol, liquefied by the addition of 5 Gm. of alcohol, were added slowly, with vigorous stirring, to a solution of 80 Gm. of sodium nitrate and 100 Gm. of concentrated sulphuric acid in 200 Cc. of water, the temperature being kept at about 20°. The stirring was continued for one-half hour after the addition of the phenol was completed, the mixture was allowed to stand for an hour and one-half longer, and then treated with 500 Cc. of water. The separation of the products was effected as in the experiments above-described. The yield did not differ materially from those obtained by the method of Cook and Schmitt. The author was unable to obtain 30 Gm. of *o*-nitrophenol as reported by Hart. The formation of tar is not avoided by this method, and the *p*-nitrophenol could not be obtained pure without recrystallization as Hart claimed.

*Treatment of the Spent-Acid and Wash Water.*—The spent-acid and wash-water from the experiments above-described were treated with a concentrated solution of sodium carbonate until Congo Red paper was no longer turned blue, showing the absence of mineral acid. The solutions were then subjected to steam distillation and the residues evaporated to crystallization. 3–4 Gm. of *o*-nitrophenol and 4–5 Gm. of *p*-nitrophenol were obtained from the spent-liquors of each experiment. It is evident that a considerable loss of the nitrophenols is sustained by discarding these liquors as directed in the original methods. By neutralization in this way the yields may be increased to 56 percent.

*Effect of the Mass and Concentration of the Nitric Acid.*—In the experiments tabulated the following procedure was adopted:

50 Gm. of crystallized phenol, liquefied by warming with 5 Cc. of water, were added slowly, with vigorous stirring, to the acid solution, the temperature being kept at about 20°. The mixture was stirred for one-half hour after the addition of the phenol was completed, allowed to stand for four hours longer, and then treated with 500 Cc. of water. Sodium carbonate was then added until Congo Red paper was no longer turned blue. The *o*-nitrophenol was separated by steam distillation, and the residue boiled for thirty minutes with 20 Gm. of animal charcoal, filtered hot, and allowed to crystallize. Additional portions of *p*-nitrophenol were obtained by evaporating the mother-liquor until the inorganic salt began to appear. The *p*-nitrophenol was recrystallized from water with the aid of hydrochloric acid and animal charcoal.

Phenol. Gm.	Absolute nitric acid. Gm.	Molecular Ratio.	Water. Gm.	Strength of acid. Percent.	o-Nitro- phenol. Gm.	p-Nitro- phenol. Gm.
50	33.5	1:1	250	11.81	5.8	0.6
50	67.0	1:2	250	21.13	23.2	16.9
50	100.5	1:3	250	28.67	26.2	18.9
50	134.0	1:4	250	34.89	26.8	19.1
50	167.5	1:5	250	40.11	25.3	13.4
50	67.0	1:2	125	34.89	26.7	19.7
50	50.0	1:1.5	125	28.67	26.8	18.1
50	67.0	1:2	500	11.81	17.3	7.4
50	50.0	1:1.5	95	34.89	23.9	20.8
50	50.0	1:1.5	40	55.00	25.5	15.3
50	40.0	1:1.2	80	34.89	23.1	17.0

From these experiments it appears that the best results are obtained when nitric acid of about 35 per cent is used, although there is no great difference in yield between 28 and 35 percent. The acid used by Cook and Schmitt and by Hart is about 20 percent. Nitric acid of about 30 percent has a maximum specific conductivity, and it is possible that some relation exists between this property and the nitrating power of the acid. In Martinsen's experiments the non-dissociated part of the acid seemed to be the more active in effecting nitration.

For the preparation of the mono-nitrophenols the proportions given in the sixth experiment are the most suitable, these being practically one part of phenol to four parts of nitric acid (s. g. 1.21, 25° Bé.). About 65 Gm. of crystallized sodium carbonate are required for the neutralization of the acid liquid. By using these proportions and the process outlined above, yields of about 63 percent of the theoretical can be obtained.

*Effect of Nitrous Acid.*—Martinsen found nitrous acid to be a strong positive catalyst. In the following experiments sodium nitrate was added to the acid solution, a sufficient excess of nitric acid being used to decompose the sodium nitrite and liberate the nitrous acid.

Phenol Gm.	Absolute nitric acid. Gm.	Molecular ratio.	Water. Gm.	Strength of acid. Per cent.	Sodium nitrite. Gm.	o-Nitro- phenol. Gm.	p-Nitro- phenol. Gm.
50	51	1:1.5	94	34.89	2	25.8	19.3
50	53	1:1.5	94	34.89	7	21.2	21.1
50	68	1:2	250	21.13	2	26.0	19.0

The yield of the nitrophenols does not seem to be greatly affected by the addition of sodium nitrite. In these experiments it was observed that the nitrophenols did not separate in the form of an oil as usual, but as a mass of yellowish white needles, until about two-thirds of the phenol had been added. An experiment was run identical with the first above-described except that the addition of phenol was stopped when two-thirds, or 33 Gm., had been added. The yields, calculated to 50 Gm. of phenol, were 25.4 Gm. of ortho and 21 Gm. of para. Evidently the formation of the oil is not detrimental.

*Effect of Urea.*—Martinsen found that when the formation of nitrous acid is prevented the nitration of phenol is hindered. A solution containing 67 Gm. of absolute nitric acid in 245 Cc. of water was boiled for one hour under a reflux with 5 Gm. of urea in order to destroy the nitrous acid. Fifty Gm. of phenol, liquefied with 5 Cc. of water, were then added as before. About 18 Gm. of

ortho- and 7 Gm. of para-nitrophenol were obtained. Considerable tar was formed.

*Effect of Copper.*—When copper reacts with nitric acid, nitrous acid is produced. As nitrous acid was said to be catalytic it was thought that the addition of copper might improve the yields. Acid of 55 percent was usually used as this nitric acid gives the largest amount of nitrous acid with copper. The copper was obtained by adding zinc dust to a solution of copper sulphate.

Phenol Gm.	Absolute nitric acid. Gm.	Molecular ratio.	Water Gm.	Strength of acid. Percent.	Copper Gm.	o-nitrophenol. Gm.	p-nitrophenol. Gm.
50	51.5	1:1.5	95	34.89	1	25.0	15.0
50	51.5	1:1.5	65	55.00	1	27.5	20.2
50	53.0	1:1.5	65	55.00	2	26.9	19.8

*Effect of Sulphuric Acid.*—A number of experiments were run in which sulphuric acid was added to the solution of nitric acid. Some dinitrophenol was invariably formed with a corresponding decrease in the yield of mono-nitrophenols.

*Determination of the Velocity of Reaction.*—In order to determine how long it was necessary to allow the nitration mixture to stand before separating the nitrophenols, experiments were run in which 5 Cc. of the acid solution were removed every hour and titrated with a solution of sodium hydroxide. Congo Red was found to be the best indicator for this purpose, and if the acid portion is diluted with 50 Cc. of water the color-change is fairly distinct. The following is typical of the results obtained, and shows that the reaction is complete in about four hours after the addition of the phenol.

Time in hours.	Cc. of alkali required.	Note.
0	28.8	Before phenol was added
1	15.1	All phenol just added
2	13.6	
3	13.1	
4	12.9	
5	12.8	
6	12.8	

*Purification of p-Nitrophenol.*—The p-nitrophenol obtained by the nitration of phenol is invariably accompanied by considerable tar which it is quite difficult to separate. For purifying the p-nitrophenol boiling with hydrochloric acid and precipitation of this with concentrated sodium hydroxide solution, conversion into the calcium and then into the sodium salt, and crystallization from naphtha, acetone and chloroform-ligroin have been recommended. The author obtained the best results by crystallizing from water with the aid of hydrochloric acid and animal charcoal. Solutions of p-nitrophenol in water are yellow but the addition of a slight amount of acid decolorizes them. Very large crystals may be obtained by crystallizing from benzene. The solubility of p-nitrophenol in benzene at 25° and at the boiling-point of the benzene was determined, and found to be as follows: at 25° one gramme of benzene dissolves about 0.02 Gm. of p-nitrophenol and at the boiling-point of benzene about 0.6 Gm. of p-nitrophenol. Para-nitrophenol is therefore about 30 times as soluble at the boiling-point as at 25°.

*Preparation of p-Nitrophenol from p-Chloronitrobenzene.*

## HISTORICAL.

In 1862 Riche<sup>22</sup> reported that mono-chlorbenzene is easily converted into chloronitrobenzene by means of concentrated nitric acid.

In 1866 Sokoloff<sup>23</sup> made a study of the chloronitrobenzenes. He stated that by the action of nitric acid on chlorbenzene two nitro-compounds are produced, the one a solid, the other a liquid, at ordinary temperatures. To obtain the mono-chloronitrobenzenes he heated chlorbenzene with nitric acid (s. g. 1.49), and poured the resulting mixture into cold water. Sokoloff states that by this treatment chlorbenzene made from benzene gave a crystalline mass, but chlorbenzene made from phenol gave a fluid product. Both products, however, were mixtures of two isomers, which he separated by crystallization and fractionation. In the case of chlorbenzene made from benzene the relative proportion of the liquid isomer to the solid isomer was 5:1; in the case of chlorbenzene made from phenol the proportion was 2:1. When nitric acid of a lower specific gravity than 1.49 was used the proportion of the solid to the liquid isomer was increased; in all cases, however, two isomers were formed. Sokoloff reports that he tried the action of alcoholic potassium hydroxide on the chloronitrobenzenes. In one part of his paper he states that a strongly alcoholic solution of potassium hydroxide acts very weakly on the chloronitrobenzenes; by long heating the solution is colored brown, but on cooling the greater part of the chloronitrobenzenes separates unchanged. In another part of his paper he states that alcoholic potash solution works energetically on these nitro-compounds, probably producing the corresponding azo-compounds.

In 1870 Engelhardt and Latschinow<sup>24</sup> reported that by heating the chloronitrobenzenes with a solution of sodium hydroxide three days at 130° the chlorine atom is replaced by the hydroxyl group, the solid chloronitrobenzene giving *p*-nitrophenol, the liquid chloronitrobenzene giving the volatile, or ortho-nitrophenol.

In 1900 Holleman and de Bruyn<sup>25</sup> made a study of the relative proportion in which the two chloronitrobenzenes are formed; they used the freezing-point method. At first they added 25 Gm. of chlorbenzene to 50 Cc. of nitric acid (s. g. 1.52) at 0°. The product was partially fluid at -5°, while the eutectic of the system ortho- + para-chloronitrobenzene is 14.7°. A study of the specific gravity and boiling-point of the mixture led them to believe that the mixture contained chlordinitrobenzene. In subsequent experiments a more dilute acid was used. 25 Gm. of chlorbenzene were added to a mixture of 50 Cc. of nitric acid (s. g. 1.48) and 10 Cc. of nitric acid (s. g. 1.52) at 0°. This product gave only a trace of oil at 15°. The freezing-point of the mixture was 58.9°, corresponding to 30.1 percent of ortho- and 69.9 percent of para-chloronitrobenzene. An experiment carried out at -30°, with a mixture of 40 Cc. of nitric acid (s. g. 1.48) and 10 Cc. of nitric acid (s. g. 1.52) gave a product with a freezing-point of 61.75°, corresponding to 26.9 percent of ortho- and 73.1 percent of para-chloronitrobenzene. They concluded that the temperature has only a slight effect on the relative proportion of the two isomers.

In 1917 Ellis, Rabinovitz and Wells<sup>26</sup> stated that "mono-nitrochlorbenzol is readily obtained by the action of a mixture of commercial sulphuric acid (66° Bé.) and nitric acid (39° Bé.) on mono-chlorbenzol." They described their method as follows:

"One part (by weight) of chlorbenzol was gradually added to three parts (by weight) of a mixture of equal parts (by volume) of sulphuric acid (s. g. 1.8) and nitric acid (s. g. 1.43). In order to check the violence of the reaction it was necessary to cool the reaction vessel by immersing it in cold water during the introduction of the chlorbenzol into the acid mixture. The oil was then separated from the spent acid, washed and dried. A yield of about 95 percent of the theoretical was obtained. By several crystallizations from alcohol it was found that the mixture was made up of about 48 percent of the para-compound, melting at 81° (melting point given in the literature is 83° C.) and 52 percent of the ortho-derivative, which melted at 28° C."

<sup>22</sup> *Ann.*, 121, 357, 1862.

<sup>23</sup> *Bull. acad. St. Pétersb.*, 380; *Z. Chem.*, 1866, 621; *Chem. Zentr.*, 1866, 1089.

<sup>24</sup> *Z. Chem.*, VI, 2, 225.

<sup>25</sup> *Rec. trav. chim.*, 1900, 139.

<sup>26</sup> *Chem. Eng.*, 1917, XXV, 1, 22.



For the conversion of the chlornitrobenzenes into the corresponding nitrophenols these authors give the following directions:

"One part of the mixed nitrochlorbenzols was heated in an autoclave for 4 hours at 60 pounds' pressure, with one part of sodium hydroxide and 20 parts of water. The conversion of the nitrochlorbenzols into the sodium salts of the nitrophenols was practically quantitative. The amount of tar formed was slight, and the sodium salts crystallized out as well defined needles. The use of more concentrated solutions of sodium hydroxide in the hydrolysis is not advantageous, as they tend to form considerable amounts of tarry bodies.

"Milk of lime was used in several experiments in place of sodium hydroxide solution, but without success, the nitrochlorbenzols being recovered practically unchanged.

"Mono-nitrochlorbenzol was boiled at atmospheric pressure with a concentrated solution of sodium hydroxide. With the exception of a slight amount of resin formation, the action of the alkali was negligible."

"The liquid from the autoclave was filtered, acidified cautiously with dilute acid, cooled and treated with sodium chloride to saturation to separate the nitrophenols."

#### EXPERIMENTAL.

The following procedure was found most convenient for the laboratory separation of the nitrophenols from chlorbenzene, and was used in the experiments reported below:

A mixture of 132 Gm. of nitric acid, s. g. 1.42, and 168 Gm. of sulphuric acid, s. g. 1.84, is energetically stirred by means of a mechanical stirrer, and kept at about 20° by a stream of cold water surrounding the vessel. To this 100 Gm. of chlorbenzene are added, drop by drop, from a separatory funnel. The stirring is continued for several hours after the addition of the chlorbenzene is completed. The mixture is then poured upon 375 Gm. of crushed ice, and the nitrating-vessel washed out with 125 Cc. of ice-water, which are added to the ice-mixture. The temperature will fall to about -5°. When most of the ice has melted, the crystalline mass is broken up with a glass rod, filtered quickly at the pump, and washed with four portions of 50 Cc. each of ice-water. The chlornitrobenzenes, still wet, are then transferred to an autoclave containing 140 Gm. of sodium hydroxide dissolved in 2800 Cc. of water. The mixture is heated for four hours at 60 pounds' pressure. While still hot the solution of the sodium salts of the nitrophenols is transferred to an apparatus equipped for steam distillation, the mixture made acid to Congo Red test-paper with concentrated hydrochloric or sulphuric acid, and the *o*-nitrophenol then separated by passing a current of steam through the mixture. The residue is then filtered hot and allowed to crystallize in the cold. By evaporating the mother-liquor additional portions of crystals are obtained until the inorganic salt begins to appear.

The following results were obtained in three experiments:

<i>o</i> -Nitrophenol. Gm.	<i>p</i> -Nitrophenol. Gm.	Yield. Percent.
25.3	78.7	84.2
26.8	77.0	84.0
27.0	77.0	85.0

In order to determine whether the temperature has any effect on the relative proportion or yields of the isomers, two experiments were run, the first with the temperature of nitration at 50°, the second with the temperature at 5°, with the following results:

Temperature.	<i>o</i> -Nitrophenol. Gm.	<i>p</i> -Nitrophenol. Gm.	Yield. Per cent.
50	25.6	78.0	83.8
5	27.0	72.4	80.4

In the experiment carried out at the higher temperature about 0.3 Gm. of dinitrophenol was obtained. In the experiment at the lower temperature, it seems that the nitration was incomplete.

The quantity of alkali used in the preceding experiments is approximately that used by Ellis, Rabinovitz and Wells, and is about twice the quantity required by theory. The following experiments were run in which the amount of sodium hydroxide was reduced to about 1.15-1.25 times that required by theory.

Sodium hydroxide. Gm.	Water. Gm.	Pressure. Lb.	Hours.	<i>o</i> -Nitrophenol. Gm.	<i>p</i> -Nitrophenol. Gm.	Yield Per cent.
80	1600	60	4	22.8	63.0	69.4
80	1600	60	8	28.0	73.4	82.1
80	1600	80	8	30.8	81.2	90.7
80	1600	80	8	31.5	81.0	91.1
90	1800	80	8	31.2	84.0	93.2

From these experiments it appears that better results are obtained with 80-90 Gm. of sodium hydroxide at 80 lb. pressure for eight hours than with 140 Gm. of sodium hydroxide at a lower pressure and a shorter heating. The nitrophenols obtained in this way were very pure, and no tar whatever was formed during the reaction.

In the last experiment above-described 73 percent of the total yield is *p*-nitrophenol and 27 percent *o*-nitrophenol. These figures must also represent approximately the relative proportions of the two chlornitrobenzenes in the mixture from which the nitrophenols were made. The figures are practically identical with those obtained by Holleman and de Bruyn for the chlornitrobenzenes by means of the freezing-point method, *i. e.*, 73.1 percent and 26.9 percent. Ellis, Rabinovitz and Wells, who determined the relative proportion of the two isomers by means of fractional crystallization from alcohol, found the mixture to consist of 48 percent of the para- compound and 52 percent of the ortho-derivative. These investigators are undoubtedly in error.

#### CONCLUSION.

Para-nitrophenol is apparently most economically prepared by heating *p*-chlornitrobenzene under increased pressure with an aqueous solution of sodium hydroxide.

#### 2. PREPARATION OF *p*-NITROPHENETOL.

The next intermediate to *p*-nitrophenol in the processes of making acetphenetidin described by Hinsberg, Platt and Paul is *p*-nitrophenetol,  $C_2H_5.C_6H_4.NO_2$ .

#### HISTORICAL.

Para-nitrophenetol was probably first made by Cahours<sup>27</sup> in 1849 by the action of fuming nitric acid on phenetol. He obtained a solid and a liquid; the former he called dinitrophenetol and the latter mono-nitrophenetol.

The discovery of *p*-nitrophenetol is, however, usually credited to Fritzsche,<sup>28</sup> who prepared it in 1859 by the action of ethyl iodide on the silver salt of *p*-nitrophenol. The *p*-nitrophenetol was extracted and purified by treating the mixture with ether, evaporating the solvent, and distilling the remaining reddish yellow liquid. The product thus obtained was a colorless crystalline solid melting at 57-58°.

<sup>27</sup> *Ann. chim. phys.*, [3] 27, 465, 1849.

<sup>28</sup> *Bull. classe phys.-math.*, 17, 145, 1859; *J. prakt. Chem.*, 175, 257; *Ann.*, 110, 155; *Jsb. Chem.*, 11, 407.

In 1879 Hallock<sup>29</sup> repeated the experiments of Cahours with somewhat different results. The dark red, viscous liquid which Hallock obtained by the action of fuming nitric acid on pure phenetol, or on a solution of phenetol in acetic acid, was distilled in a current of steam. The product consisted of a solid and a liquid in varying proportions according to the conditions of nitration. The solid when purified by repeated crystallization both from acid and from alcohol, was proved by an ultimate analysis to be a mono-nitrophenetol. Its melting point and other physical properties corresponded to those of *p*-nitrophenetol prepared by Fritzsche as above-described. Hallock also obtained the same body by the action of potassium ethyl sulphate and potassium hydroxide on *p*-nitrophenol in closed tubes at high temperatures. In this operation, however, a considerable quantity of the nitrophenol remained unchanged. Ethyl iodide and potassium hydroxide heated in a sealed tube with *p*-nitrophenol also yielded the same body, but quite impure. The method of direct nitration, Hallock states, yields the purest product but is quite tedious. When the nitration was performed with nitric acid from which the red fumes had been removed by previous boiling, or by means of hot concentrated acid, the product was mostly liquid and refused to crystallize, even at low temperatures. This liquid Hallock regarded as a mixture of *o*-nitrophenetol and unchanged phenetol, holding some *p*-nitrophenetol in solution. Hallock<sup>30</sup> found that these different methods gave very poor yields of the ether.

In 1881 Willgerodt<sup>31</sup> found that when *p*-chloronitrobenzene is heated with an alcoholic solution of potassium hydroxide in a closed vessel at 100–130° *p*-nitrophenetol is one of the products; the yield, however, was very small, and the method unsuitable for the preparation of large quantities. In 1882 Willgerodt<sup>32</sup> reported that a larger yield of the ether could be obtained if the alcohol were properly mixed with water, and the mixture refluxed for a long time (36 hours). The product, however, was a mixture of unchanged *p*-chloronitrobenzene, dichlororazybenzene, *p*-nitrophenol, and *p*-nitrophenetol, the separation of which was rather tedious.

In 1883 Kolbe and Kauder<sup>33</sup> attempted to prepare *p*-nitrophenetol by the action of potassium ethyl sulphate on the sodium salt of *p*-nitrophenol. A concentrated aqueous solution of equimolecular quantities of the two compounds was refluxed in an oil-bath at 160–170° and then distilled. Very little *p*-nitrophenetol was obtained. The addition of an excess of sodium hydroxide did not improve the yield. Attempts to carry out the experiments under increased pressure were unsuccessful as the sealed tubes exploded before the temperature of 150° was reached.

In 1886 Willgerodt and Ferko,<sup>34</sup> believing that Kolbe and Kauder's poor results were due to the presence of water, substituted alcohol as the solvent. They heated the sodium salt of *p*-nitrophenol with an excess of alkali ethyl sulphate and alcohol in a closed tube for three hours. At 150° only traces of *p*-nitrophenetol were formed, but at 200° they state that the sodium salt of *p*-nitrophenol was completely converted into the ether. Higher temperatures, they found, produced charring.

In 1886 Hinsberg discovered the medicinal action of acetphenetidii, and the method which he adopted in his process of manufacture for the preparation of the *p*-nitrophenetol was as follows:<sup>35</sup> 50 Kg. of the potassium salt of *p*-nitrophenol were mixed with 300 Kg. of alcohol and 40 Kg. of ethyl bromide. The mixture was heated in an autoclave at a pressure of 3–4 atmospheres for about 8 hours. In order to separate the *p*-nitrophenol which had not taken any part in the reaction from the ether formed, the solution was treated with steam. This caused the ether to distill over, leaving behind the unchanged *p*-nitrophenol.

In 1896 Paul,<sup>36</sup> describing the manufacture of acetphenetidii, stated that the *p*-nitrophenetol was made as follows: 480 Gm. of the pure sodium salt of *p*-nitrophenol, 3120 Gm. of denatured alcohol, 300 Gm. of ethyl bromide (crude) and 100 Gm. of sodium carbonate, were

<sup>29</sup> *Am. Chem. J.*, 1, 271, 1879.

<sup>30</sup> *Ber.*, 14, 37, 1881.

<sup>31</sup> *Ibid.*, 14, 2636, 1881.

<sup>32</sup> *Ibid.*, 15, 1002, 1882.

<sup>33</sup> *J. prakt. Chem.*, 28, 62, 1883; *Chem. Zentr.*, 1883, 521.

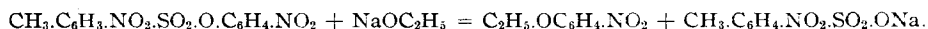
<sup>34</sup> *Ibid.*, 33, 152; *Chem. Zentr.*, 1886, 323.

<sup>35</sup> U. S. Pat. No. 400,086, Mar. 26, 1889.

<sup>36</sup> *Z. angew. Chem.*, 1896, 587.

heated under a reflux condenser for about ten hours. The contents of the vessel were then cooled, the solid *p*-nitrophenetol filtered off, and, in order to separate any unchanged *p*-nitrophenol it was washed with water until the washings were only faintly colored yellow. For complete purification the crude *p*-nitrophenetol was recrystallized from about three parts of alcohol.

In 1898<sup>37</sup> there was described a method of making *p*-nitrophenetol by treating the ester of *p*-nitrophenol and nitro-*p*-toluene-sulphonic acid with an alcoholic solution of sodium ethylate or with an alcoholic solution of sodium hydroxide when the following reaction was said to take place:



#### EXPERIMENTAL.

##### PREPARATION OF *p*-NITROPHENETOL FROM *p*-NITROACETANILID.

Para-nitroacetanilid when heated with concentrated aqueous solutions of sodium or potassium hydroxide is partially converted into *p*-nitrophenol, as has been stated. It was interesting to determine whether *p*-nitrophenetol would be produced if an alcoholic solution of the alkali were substituted for the aqueous solution. The reaction would then proceed thus:  $\text{NO}_2.\text{C}_6\text{H}_4.\text{NH}.\text{OC}.\text{CH}_3 + \text{C}_2\text{H}_5\text{OH} + \text{NaOH} = \text{NO}_2.\text{C}_6\text{H}_4.\text{OC}_2\text{H}_5 + \text{NH}_3 + \text{CH}_3.\text{COONa}$ . An experiment carried out by heating under a reflux for 24 hours a mixture of 18 Gm. of *p*-nitroacetanilid, 7 Gm. of potassium hydroxide, and 50 Gm. of absolute alcohol (commercial), gave *p*-nitraniline only. No ammonia was evolved. Sodium hydroxide gave the same results, and so did 90 percent alcohol.

##### PREPARATION OF *p*-NITROPHENETOL FROM *p*-NITROPHENOL.

*Ethylation according to the method of Claisen and Eisleb.*—Claisen and Eisleb<sup>38</sup> stated that alkylation could be easily and conveniently effected by heating together the substance to be alkylated, the proper alkyl halide, and potassium carbonate in acetone as the solvent. They worked with the allyl ethers only, but stated that other phenol-alkyl ethers could undoubtedly be made by the same method. In the case of the allyl ether of *p*-nitrophenol, these writers claim to have obtained a theoretical yield. The method was tried for the preparation of the ethyl ether of *p*-nitrophenol with the following results. 42 Gm. of *p*-nitrophenol and 45 Gm. of potassium carbonate, both dry and finely powdered, were refluxed with 36 Gm. of ethyl bromide and 100 Gm. of acetone for 8 hours. The acetone was then distilled off and the residue treated with steam. The *p*-nitrophenetol obtained from the steam-distillate amounted to 23.1 Gm. in one case and 23.4 Gm. in another, equivalent to 45.5 and 46.1 percent of the theoretical.

Since copper sometimes acts as a positive catalyst in the formation of ethers,<sup>39</sup> two experiments were run, identical with those above-described except that 0.5 Gm. of copper in one case, and 3 Gm. of copper in another, were added to the mixture. The copper was obtained by adding zinc dust to a solution of copper sulphate. The yield of ether was respectively 20.4 Gm. and 19.8 Gm., equivalent to 40.2 percent and 39 percent of the theoretical. From this it appears that copper has a detrimental effect.

<sup>37</sup> "Société chimique des Usines der Rhône anct Gilliard," P. Monnet and Cartier; *D. R. P.* No. 95,965; Lassar-Cohn, "Arbeitsmethoden," 4 Aufl., *Spez. Teil*, p. 289.

<sup>38</sup> *Ann.*, 401, 21, 1913.

<sup>39</sup> *Ber.*, 38, 2211 1905.

An experiment was also made in which the potassium salt of *p*-nitrophenol was first made by evaporating to dryness an aqueous solution of *p*-nitrophenol and potassium hydroxide in molecular proportions, drying the salt at 120°, and then refluxing with ethyl bromide in acetone solution as before. 42 Gm. of *p*-nitrophenol gave 19.8 Gm. of the ether, or 39 percent of the theoretical.

An experiment with 42 Gm. of *p*-nitrophenol, 45 Gm. of potassium carbonate, 36 Gm. of ethyl bromide, and 100 Gm. of acetone, heated under pressure at 100°, gave 42 Gm. of the ether, equivalent to 83.1 percent of the theoretical. An increase in pressure appears to be very favorable to the formation of the ether.

*Ethylation with Ethyl Bromide under increased pressure, (Method of Hinsberg).*—100 Gm. of the dry sodium salt of *p*-nitrophenol, 80 Gm. of ethyl bromide, and 500 Cc. of absolute ethyl alcohol (commercial), were heated in an autoclave at 50 pounds pressure for 8 hours. The alcohol was then distilled off, and the residue treated with steam to separate the ether. The yield was 84 Gm. equivalent to 81 percent of the theoretical.

*Ethylation with potassium ethyl sulphate under increased pressure.*—100 Gm. of the dry sodium salt of *p*-nitrophenol, 150 Gm. of potassium ethyl sulphate, and 500 Gm. of absolute alcohol (commercial), were heated in an autoclave at 150 pounds' pressure for 8 hours. After distilling off the alcohol, the residue was treated with steam in order to separate the ether. The yield of *p*-nitrophenetol was 80.5 Gm. equivalent to 77.5 percent of the theoretical.

*Ethylation with sodium ethyl sulphate under increased pressure.*—100 Gm. of the dry sodium salt of *p*-nitrophenol, 150 Gm. of sodium ethyl sulphate, and 500 Gm. of absolute alcohol (commercial), were treated as in the experiment with potassium ethyl sulphate. The yield of *p*-nitrophenetol was 56.5 Gm., equivalent to 54.5 percent of the theoretical. By increasing the quantity of sodium ethyl sulphate to 200 Gm., a yield of 72.2 percent of the theoretical was obtained. Pressures above 150 pounds produced large quantities of tar.

*Ethylation with Ethyl Chloride under increased pressure.*—100 Gm. of the sodium salt of *p*-nitrophenol, dried at 120°, 100 Gm. of ethyl chloride, and 500 Cc. of absolute alcohol (commercial) were heated in an autoclave at 100 pounds' pressure for six hours. The alcohol was then distilled off, and the residue steam-distilled. The yield of *p*-nitrophenetol was 79 Gm., equivalent to 76.1 percent of the theoretical. Two experiments carried out at 150 pounds pressure gave respectively 84.2 Gm. and 83.7 Gm. of *p*-nitrophenetol, equivalent to 81.2 and 80.7 percent of the theoretical.

#### CONCLUSION.

Para-nitrophenetol is apparently most economically prepared by heating sodium *p*-nitrophenolate under increased pressure with an alcoholic solution of ethyl chloride.

#### 3. PREPARATION OF *p*-AMINOPHENETOL.

##### HISTORICAL.

Para-aminophenetol appears to have been first described in detail by E. J. Hallock<sup>40</sup> in 1879. Having obtained a considerable quantity of *p*-nitrophenetol, Hallock attempted to reduce it by means of tin and hydrochloric acid. The resulting salt, after the separation of the tin

<sup>40</sup> *Am. Chem. J.*, 1, 271, 1879.



disulphostilbene-diazo-diphenol.<sup>47</sup> Brilliant Yellow is prepared by coupling phenol with diazotized disulpho-diamino-stilbene. It will be seen that this method of preparing *p*-aminophenetol is perfectly analogous to that of Riedel (see above). The advantages, if any, which it possesses over that method are not stated.

According to Paul,<sup>48</sup> who described a technical process of manufacturing acetphenetid in 1896, *p*-aminophenetol is made by reducing *p*-nitrophenetol with tin and hydrochloric acid, and precipitating the *p*-aminophenetol hydrochloride by means of concentrated hydrochloric acid, in which it is not very soluble. The details of this method are given on page 288.

In 1915 Hurst and Thorpe<sup>49</sup> reported that when *p*-nitrophenetol is reduced according to the method recommended by Hinsberg, in which tin and concentrated hydrochloric acid are used as the reducing agents, approximately equal quantities of *p*-aminophenetol and 3-chlor-4-aminophenetol are formed. It was found that pure *p*-aminophenetol could be obtained by using dilute acid, and that under proper conditions the chlorinated *p*-aminophenetol was the sole product with concentrated acid.

#### EXPERIMENTAL.

##### PREPARATION OF *p*-AMINOPHENETOL FROM *p*-AMINOPHENETOL (METHOD OF RIEDEL, MODIFIED BY THE PRESENT WRITER).

*Ethyl-p-dihydroxy-azobenzene*, ( $C_2H_5O.C_6H_4.N = N.C_6H_4.OH$ ).—150 Gm. of *p*-aminophenetol were dissolved in a mixture of 380 Cc. of 20 percent hydrochloric acid and 2200 Cc. of water. Ice was added until the temperature fell to 5°. A solution of 76 Gm. (according to Riedel, 70 Gm.) of sodium nitrite in 550 Cc. of water was then added slowly with stirring. A slightly blue coloration was obtained with starch-iodide paper when all the sodium nitrite had been added. The solution of the diazo-compound was then slowly run into a solution of 104 Gm. of phenol and 220 Gm. of crystallized sodium carbonate in 400 Cc. of water. This solution was stirred by a mechanical stirrer, and the stirring continued for one hour after the addition of the diazo solution was completed. The precipitated ethyl-*p*-dihydroxy-azobenzene, which is only slightly soluble in water, and practically insoluble in the presence of alkali carbonates, was filtered off at the pump and dried. It forms a brownish yellow powder, melting at 124.5° (according to Riedel 104.5°, probably a typographical error). Four experiments were made, and the yield in each case was practically quantitative, 264–266 Gm. The theoretical yield is 265 Gm. but the weight of the powder obtained is sometimes slightly more than this on account of the presence of a little inorganic salt.

*Diethyl-dihydroxy-azobenzene*, ( $C_2H_5O.C_6H_4.N = N.C_6H_4.OC_2H_5$ ).—100 Gm. of dry ethyl-*p*-dihydroxy-azobenzene and 17 Gm. of sodium hydroxide were dissolved in 500 Cc. of alcohol. To this solution 46 Gm. of ethyl bromide were added, and the whole heated in an autoclave ten hours at 150°. The alcohol was then distilled off, the residue washed with water to separate the sodium bromide, and then with a dilute solution of sodium hydroxide to separate any unchanged dihydroxy-azobenzene. The diethyl-*p*-dihydroxy-azobenzene is obtained in the form of brown plates, melting at 156°. The yield is about 100 Gm., or 90 percent of the theoretical.

*Para-aminophenetol*.—One hundred Gm. of diethyl-*p*-dihydroxy-azobenzene, 60 Gm. of granulated tin, and 500 Gm. of 20 percent hydrochloric acid, were heated

<sup>47</sup> Knecht, Rawson and Loewenthal, "A Manual of Dyeing," 2, 405–6, 1910.

<sup>48</sup> *Z. angew. Chem.*, 1896, 587.

<sup>49</sup> *J. Chem. Soc.*, 107, [2] 934, 1915.

on a water-bath till the azo-compound was completely dissolved; the heating was continued one hour longer. 1000 Cc. of water and 67 Gm. of zinc were then added to the cooled solution. After one hour the precipitated tin was filtered off, washed with water, 180 Gm. of sodium hydroxide, dissolved in water, added to the filtrate, and the mixture steam-distilled. The distillate was collected in 100 Gm. of concentrated hydrochloric acid (33.5 percent), diluted with a little water. The yield was 119 Gm. equivalent to 92.2 percent of the theoretical.

For this reduction Riedel directs the use of 170 Gm. of stannous chloride and 300 Cc. of concentrated hydrochloric acid. The use of tin, and its recovery by means of zinc, reduces the cost of this step considerably.

Theoretically one mol of *p*-aminophenetol yields two mols on treatment by the Riedel method. The foregoing experiments show, however, that only about one and two-thirds mols can be obtained in practice.

#### PREPARATION OF *p*-AMINOPHENETOL FROM *p*-NITROPHENETOL.

*Reduction with stannous chloride and hydrochloric acid.*—170 Gm. of crystallized stannous chloride were dissolved in 250 Cc. of 20 percent hydrochloric acid. To this solution 42.4 Gm. of *p*-nitrophenetol were added, and the mixture heated on a water-bath for two hours. To the cooled solution 300 Gm. of sodium hydroxide dissolved in water were added, and the mixture then distilled with steam. The distillate was collected in 30 Gm. of concentrated hydrochloric acid, diluted with a little water. On evaporating the distillate, 36.1 Gm. of *p*-aminophenetol hydrochloride were obtained, equivalent to 82.2 percent of the theoretical.

*Reduction with Tin and Hydrochloric Acid.*—33.4 Gm. of *p*-nitrophenetol, 47.6 Gm. of granulated tin, and 328.5 Gm. of 20 percent hydrochloric acid were heated on a water-bath for two hours. The solution was then diluted with water and 52.4 Gm. of zinc added. After one hour the tin was filtered off, washed, and the filtrates made alkaline with 144 Gm. of sodium hydroxide dissolved in water. The mixture was then distilled with steam, and the distillate collected in 25 Gm. of concentrated hydrochloric acid diluted with water. On evaporating the distillate, 29.8 Gm. of *p*-aminophenetol hydrochloride were obtained, equivalent to 86 percent of the theoretical.

*Reduction with Iron and Hydrochloric Acid.*—167 Gm. of *p*-nitrophenetol, 35 Gm. of concentrated hydrochloric acid, and 250 Cc. of water were placed in a flask provided with a condenser and mechanical agitator, and heated on the water-bath at a temperature from 70° to 80°. To this mixture 140 Gm. of iron powder were gradually added. The heating was continued for about two hours after the addition of the iron was completed. The mixture was then made alkaline with 25 Gm. of chalk and subjected to steam distillation. The distillate was collected in dilute hydrochloric acid. On evaporating the acid solution, 155 Gm. of *p*-aminophenetol hydrochloride were obtained, equivalent to 89.3 percent of the theoretical.

For this reduction Hinsberg directs the use of 250 Gm. of hydrochloric acid, 250 Gm. of water and 104 Gm. of iron. If concentrated hydrochloric acid is intended, this quantity is far in excess of that required, one-tenth of this quantity being sufficient. The amount of iron used is insufficient; theory (two reactions are possible) requires 112–168 Gm. In practice the mean is usually taken, which is 140 Gm.



The *p*-aminophenetol can also be absorbed in sulphuric acid, but the sulphate is more difficult to dry than the hydrochloride.

*Reduction with Sodium Sulphide and Sulphur.*—In the experiments tabulated below the following procedure was used: The crystallized sodium sulphide (33 percent), sulphur and water were boiled together under a reflux condenser for one hour. The *p*-nitrophenetol was added gradually to this solution, and the mixture boiled, with turbinig, for several hours. The cooled mixture was then extracted with ether, and the ethereal solution shaken with diluted hydrochloric acid. On evaporating the acid solution *p*-aminophenetol hydrochloride is obtained, and on evaporating the ethereal solution the unchanged *p*-nitrophenetol is recovered.

Para-nitrophenetol. Gm.	Sodium sulphide. Gm.	Sulphur. Gm.	Water. Gm.	Para-aminophenetol. Gm.	Yield. Percent.
33.4	48	6.4	40.0	19.1	55.2
33.4	81	10.8	67.5	22.0	63.5
33.4	81	10.8	140.0	26.4	76.0
33.4	81	10.8	300.0	28.6	82.6
33.4	60	8.0	300.0	25.8	74.5
33.4	60	8.0	500.0	24.2	70.0

The proportions given in the first experiment are those required by theory. It is of interest to note that the yield is increased, up to a certain point, by an increase in the quantity of water.

The method above-described is very convenient for the preparation of small quantities of *p*-aminophenetol hydrochloride. On a large scale the reduction mixture is allowed to stand until two layers separate. The upper layer, consisting of *p*-aminophenetol and unchanged *p*-nitrophenetol, is then separated from the lower aqueous layer, and the *p*-aminophenetol and *p*-nitrophenetol separated by fractional distillation, preferably in vacuo.

#### CONCLUSION.

Para-aminophenetol is apparently most economically prepared by heating *p*-nitrophenetol with iron and dilute hydrochloric acid.

#### 4. PREPARATION OF ACETYL-*p*-AMINOPHENOL.

##### HISTORICAL.

In 1878 Morse<sup>50</sup> reported that when *p*-nitrophenol is reduced with tin and glacial acetic acid acetyl-*p*-aminophenol is produced, reduction and acetylation occurring in one operation.

In 1907 Tingle and Williams<sup>51</sup> published an article, from which it appears that many of the chemists who tried the method recommended by Morse failed to obtain the compound. In reply to a letter from these writers Morse stated that the best results would be obtained by the use of absolutely anhydrous acetic acid. These writers therefore used in their experiments glacial acetic acid to which acetic anhydride had been added in quantity exactly sufficient to raise the acid content to 100 percent. By means of this mixture and by carefully excluding moisture from the apparatus they were able to obtain a yield of 47 percent of the theoretical. Their method is described as follows:

"Para-nitrophenol (12 grammes, 1 mol.) was mixed in a capacious, round-bottomed flask with glacial acetic acid, 50 grammes = 10.5 mol., to which sufficient recently distilled acetic anhydride had been added to bring the acid content to 100 percent. The flask was attached to a long reversed condenser, suitably protected from the moisture of the atmosphere, and the

<sup>50</sup> *Ber.*, 11, 232, 1878.

<sup>51</sup> *Am. Chem. J.*, 37, 51, 1907.

contents of the flask were heated until the nitrophenol had dissolved. To this solution granulated tin, 15 grammes, was added. The reduction commenced immediately and the reaction quickly became very vigorous. It is desirable to allow the reaction to proceed as rapidly as is possible without loss of substance. As soon as the reaction moderates, a second portion of tin, 15 grammes, is added, and, if necessary, external heat applied to bring practically all the metal into solution. The liquid is now poured into 2 liters of water, the mixture warmed and a current of hydrogen sulphide passed into it until no further precipitate of stannous sulphide takes place. Sometimes it is convenient to filter the liquid through cheese cloth before all the tin has been thrown down and then, later, to make a final filtration through paper. The clear filtrate is concentrated until crystals appear; after being cooled the crystals are drained and recrystallized twice from 95 percent alcohol."

These authors also obtained the compound by the action of tin amalgam on the nitrophenol, in the presence of acetic acid of 100 percent concentration. The experiments were carried out in an apparatus of special construction, in which the tin amalgam was produced continuously by means of an electric current. The yield by this method was about 40 percent of the theoretical.

In 1903 Dahl and Company,<sup>52</sup> who were interested in the preparation of acetyl-*p*-aminophenol for use in the manufacture of dyestuffs, stated that the compound was best prepared by heating *p*-aminophenol with glacial acetic acid.

In 1905 Lumiere and Barbier<sup>53</sup> in the course of their work on acetylation in aqueous solution prepared it by shaking a solution of 10.9 Gm. of *p*-aminophenol in 100 Cc. of water and 7 Gm. of acetic acid with 12.3 Gm. of acetic anhydride.

#### CONCLUSION.

Acetyl-*p*-aminophenol is apparently a comparatively expensive intermediate, the use of which in the manufacture of acetphenetidin is not economical.

### PREPARATION OF ACETPHENETIDIN.

#### HISTORICAL.

Hallock,<sup>54</sup> who first made acetphenetidin, prepared it by the action of acetyl chloride on *p*-aminophenetol, but apparently did not attempt the purification of the resulting crystalline solid.

In the technical process patented by Hinsberg,<sup>55</sup> the hydrochloride of *p*-aminophenetol is melted with fused sodium acetate and glacial acetic acid, the melted mass repeatedly boiled with water, and the acetphenetidin obtained from the filtrates after cooling. This product is crude and requires purification, but no method for this purification is described in the patent-specification.

The method described by Paul<sup>56</sup> is essentially the same as the preceding, but more details are given. The *p*-aminophenetol hydrochloride, sodium acetate, and glacial acetic acid are heated under a reflux condenser for three hours, the solution then dissolved in 10 parts of boiling water, and freed from resinous impurities by filtering. After cooling the acetphenetidin crystallizes out with a faint red color. By recrystallization from water with the aid of animal charcoal pure acetphenetidin is obtained.

For use in the laboratory Hinsberg<sup>57</sup> recommended acetylation by vigorously shaking *p*-aminophenetol in a separatory funnel with ice-water and an excess of acetic anhydride (about 1.5 molecular weights to 1 molecular weight of *p*-aminophenetol), filtering off the acetphenetidin after the disappearance of the anhydride, and crystallizing from dilute alcohol with the aid of animal charcoal.

<sup>52</sup> *Chem. Zentr.*, 2, 1227, 1903.

<sup>53</sup> *Ibid.*, 2, 465, 1905.

<sup>54</sup> *Am. Chem. J.*, 1, 271, 1879.

<sup>55</sup> U. S. Pat. No. 400,086, 1889.

<sup>56</sup> *Z. angew. Chem.*, 1896, 587.

<sup>57</sup> *Ann.*, 305, 276, 1899.

In this same article Hinsberg states that *p*-aminophenetol may also be acetylated by boiling with glacial acetic acid. Platt<sup>58</sup> states that acetphenetidin is made commercially by treating *p*-aminophenetol with anhydrous acetic acid. In Klimmek's process<sup>59</sup> equimolecular quantities of *p*-aminophenetol and glacial acetic acid are heated together in a flask having a return condenser and maintained at a temperature of 100° in a water-bath for from 4 to 5 hours. This solution is then thrown into 80 parts of boiling water, a sufficient quantity of animal charcoal having been added to secure, on filtration, a perfectly clear liquid. The solution is filtered while hot and allowed to crystallize rapidly. It is stated that the large amount of water above-mentioned thoroughly dissolves the solids, so that all the impurities and coloring matter are absorbed by the charcoal. After separating the water and drying the solid, pure acetphenetidin is obtained.

To go from acetyl-*p*-aminophenol to acetphenetidin, Täuber<sup>60</sup> directs that acetyl-*p*-aminophenol, potassium ethyl sulphate, and sodium hydroxide, dissolved in 60 percent alcohol, be heated at 150° for several hours. On diluting the resulting solution with water, acetphenetidin separates out in fairly pure crystals. Hinsberg<sup>61</sup> directs that acetyl-*p*-aminophenol and an equivalent part of sodium hydroxide and ethyl bromide or ethyl iodide, dissolved in sufficient alcohol to form a clear solution, be warmed on a water-bath for two or three hours under a reflux, and then diluted with water. In case pure acetyl-*p*-aminophenol is used, the purity of the acetphenetidin which separates out is said to be such that usually no further purification is required.

#### EXPERIMENTAL.

*Acetylation of p-Aminophenetol.*—68.5 Gm. of *p*-aminophenetol and 36 Gm. of glacial acetic acid were mixed in a flask fitted with an air-condenser, and boiled on a sand-bath for eight hours. The tube forming the air-condenser was of such a length that the water-vapor could escape, while the acetic acid and *p*-aminophenetol were condensed. The liquid was then poured into 300 Cc. of hot water containing 10 Cc. of hydrochloric acid, well stirred, and after cooling filtered at the pump and washed with a little cold water. The crude acetphenetidin obtained in this way has a lavender color. It was purified by dissolving in 80 parts of boiling water, adding 20 Gm. of animal charcoal, and boiling until the liquid was colorless. This operation is most satisfactorily carried out in the kind of apparatus used for steam distillation; the acetphenetidin dissolves more readily, the mixture is kept stirred by the steam, and the volume of water can be kept practically unchanged. When the liquid was decolorized the mixture was filtered at the pump, and the filtrate cooled rapidly with stirring. The pure acetphenetidin was then filtered off and dried. A yield of 69.6 Gm., equivalent to 77.8 percent of the theoretical, was obtained.

By using 50 Gm. of glacial acetic acid, a yield of 76 Gm. was obtained, equivalent to 85.8 percent of the theoretical.

*Acetylation of p-Aminophenetol Hydrochloride.*—83.5 Gm. of *p*-aminophenetol hydrochloride, 43.5 Gm. of fused sodium acetate, and 41.5 Gm. of glacial acetic acid, were treated exactly as described in the foregoing experiments. The yield was 72.8 Gm. equivalent to 84.3 percent of the theoretical.

With 36 Gm. of glacial acetic acid the yield was 68 Gm. equivalent to 76 percent of the theoretical.

*Acetylation of p-Aminophenetol Sulphate.*—93 Gm. of *p*-aminophenetol sulphate, 42.5 Gm. of fused sodium acetate, and 42.5 Gm. of glacial acetic acid, were

<sup>58</sup> *J. Anal. Appl. Chem.*, 7, 79, 1893.

<sup>59</sup> U. S. Pat. No. 006,288, 1898.

<sup>60</sup> *D. R. P.* No. 85,988, 1894.

<sup>61</sup> *Ann.*, 305, 276, 1899.

treated exactly as above-described. The yield was 75.3 Gm. equivalent to 84.1 percent of the theoretical.

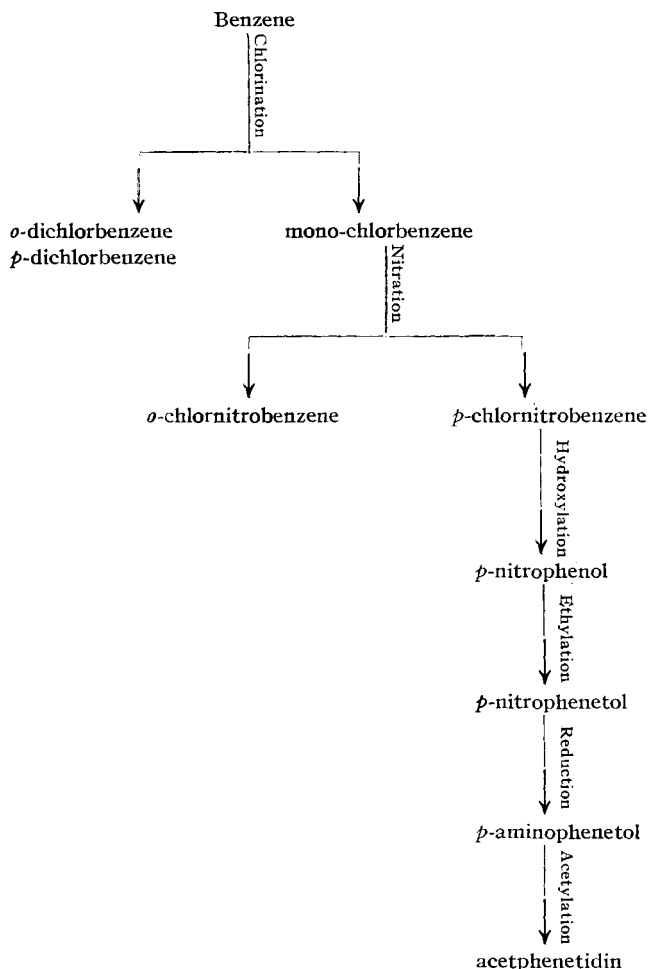
#### CONCLUSION.

Since *p*-aminophenetol hydrochloride is more readily obtained than the sulphate or the free base, acetphenetidín is apparently most economically prepared by heating the hydrochloride with fused sodium acetate and glacial acetic acid.

#### PROCESS RECOMMENDED FOR THE MANUFACTURE OF ACET-PHENETIDIN.

##### I. PLAN.

The studies of the preceding chapters have eliminated the methods of Riedel and Taüber, on account of their high cost of production, and have shown that the method of Hinsberg admits of substantial improvements. The process recommended, which includes these improvements, is based on the plan given below.



For completeness, the hydrocarbon benzene is here made the starting-point; it seems preferable, however, to regard the synthesis of acetphenetidin as beginning with *p*-chloronitrobenzene, since from this intermediate it follows a direct course, no by-products forming.

## 2. CRUDES AND APPARATUS.

The crudes which are required in carrying out the complete process as outlined above are benzene, chlorine, sodium hydroxide, nitric acid, sulphuric acid, hydrochloric acid, acetic acid, sodium acetate, ethyl chloride, and iron. Those manufacturers who chlorinate benzene obtain both chlorine and sodium hydroxide by the electrolysis of sodium chloride, and obtain hydrochloric acid as a by-product of the chlorination. By efficient operation, the sulphuric acid and acetic acid can be largely recovered, the latter as sodium acetate. Ethyl chloride is very easily and cheaply made from ethyl alcohol and hydrochloric acid by well-known methods.

No unusual apparatus is required in carrying out the operations of this process.

## 3. OPERATIONS.

### PREPARATION OF CHLORBENZENE.<sup>62</sup>

300 parts of benzene are mixed in a suitable vessel with 1 part of anhydrous ferric chloride and 1 part of powdered iron, and 150 parts of dry chlorine are led into the mixture. The hydrogen chloride which is evolved is absorbed in water. After all the chlorine has passed in, the mixture is fractionally distilled *in vacuo*. The first fraction consists chiefly of unchanged benzene, which is returned to the apparatus for further chlorination (requiring about 80 parts of chlorine). The second fraction consists chiefly of mono-chlorbenzene, and the third fraction of dichlorbenzene. On cooling the third fraction, pure *p*-dichlorbenzene crystallizes out, and is separated from the oily mother-liquor. The mother-liquor consists of approximately 75 percent of ortho- and 25 percent of para-dichlorbenzene. Yield, 335 parts of mono-chlorbenzene, 24 parts of *p*-dichlorbenzene, 13 parts of mixed ortho- and para-dichlorbenzene, and 115 parts of hydrochloric acid.

### NOTES.

The catalysts, ferric chloride and iron, can be used indefinitely. The chlorination is interrupted before all the benzene is acted on, in order that the conditions may not favor the formation of *p*-dichlorbenzene.

### PREPARATION OF CHLORNITROBENZENE.

A mixture of 100 parts of nitric acid (sp. gr. 1.42) and 150 parts of sulphuric acid (sp. gr. 1.84) is introduced into a suitable apparatus fitted with an agitator and a condenser. 100 parts of mono-chlorbenzene are slowly run in, while the agitator is kept in rapid movement and the temperature maintained around 25°. When the greater part of the chlorbenzene has been added, the temperature is raised by external heat to 70–80°. After all the chlorbenzene has been added, the stirring and heating are continued until there is no further reaction. The mixture

<sup>62</sup> *D. R. P.* No. 219,242; *J. Soc. Chem. Ind.*, 1910, 617; *Chem. Zentr.*, 81, 1074, 1910; cf. *Chem. Eng.*, [1] 25, 22, 1917.

is allowed to stand until the chlornitrobenzene separates as an oil on the surface of the acid. The acid is drawn off at the bottom, and the chlornitrobenzene washed with warm water.

*Separation.*<sup>63</sup>—The mixture of ortho- and para-chlornitrobenzene is cooled to about 16°, when the greater part of the para-isomer crystallizes out, and is separated from the oily mother-liquor. The oil is fractionated *in vacuo*; the para-isomer concentrates in the first fraction, and the ortho derivative in the second fraction. On cooling these fractions a portion of the pure isomer crystallizes out and is separated. The process of fractionation and crystallization is repeated until the separation is complete. Yield, 95–100 parts of *p*-chlornitrobenzene, and 35–37 parts of *o*-chlornitrobenzene.

#### NOTES.

The spent-acid may be “regenerated” by evaporating in the usual way, and used again for nitrating.

#### PREPARATION OF SODIUM *p*-NITROPHENOLATE.

Sixty-five parts of sodium hydroxide are dissolved in 1300 parts of water, and the solution introduced into an autoclave. One hundred parts of *p*-chlornitrobenzene are added, and the mixture heated for about eight hours at a pressure of 80 pounds. While still hot the solution is filtered, and evaporated to a small volume. After cooling the sodium *p*-nitrophenolate is separated from the mother-liquor and dried at 120°. Yield, 95–100 parts.

#### PREPARATION OF *p*-NITROPHENETOL.

One hundred parts of dry sodium *p*-nitrophenolate, 100 parts of ethyl chloride, and 500 parts of alcohol are mixed in an autoclave, and heated at a pressure of 150 pounds for about six hours. While still warm the solution is removed, the alcohol distilled off, and the residue washed with cold water. Yield, 95–100 parts of crude *p*-nitrophenetol, containing 85–90 percent of pure ether. For purification the crude ether is steam-distilled. Yield, about 85 parts.

#### NOTES.

The unchanged *p*-nitrophenol can be recovered from the wash-waters by acidifying and evaporating to crystallization.

For conversion into *p*-aminophenetol it is unnecessary to purify the *p*-nitrophenetol.

#### PREPARATION OF *p*-AMINOPHENETOL HYDROCHLORIDE.

One hundred parts of *p*-nitrophenetol (120 parts if crude), 150 parts of water, and 10 parts of hydrochloric acid, are mixed in a suitable vessel fitted with a condenser, an agitator and a direct-steam coil, and heated to 70°. Eighty-five parts of finely ground cast iron are added at such a rate that the temperature is maintained at about 70°, the mixture being stirred continuously. When all the iron has been added the heating is continued by steam until the reduction is complete. The contents are distilled with superheated steam, and the distillate collected in 65 parts of hydrochloric acid (s. g. 1.17). The distillate is evaporated to dryness. Yield, 90–95 parts.

<sup>63</sup> D. R. P. No. 97,013; *Frdl.* V, 48; *Chem. Zentr.*, 2, 238, 1898.

## NOTES.

The reduction is complete when a portion of the distillate, acidified with hydrochloric acid, leaves no undissolved oil or solid.

The steam-distillation is complete when a portion of the distillate, treated with a solution of ferric chloride, gives no purple or violet coloration.

## PREPARATION OF ACETPHENETIDIN.

One hundred parts of *p*-aminophenetol hydrochloride, 48 parts of fused sodium acetate, and 48 parts of glacial acetic acid, are mixed in a suitable vessel fitted with a condenser, and boiled for about eight hours. The excess of acetic acid is distilled off, and the residue washed with 500 parts of cold water containing 10 parts of hydrochloric acid. The crude acetphenetidin is dissolved in 8000 parts of boiling water, 25 parts of animal charcoal added, and the mixture boiled until the liquid is colorless. The mixture is filtered, and the filtrate cooled quickly with vigorous stirring. The pure acetphenetidin is filtered off and dried. Yield, 85–90 parts.

## NOTES.

The distillate of acetic acid can be used to make sodium acetate for another acetylation by neutralizing with sodium carbonate, evaporating and fusing.

The wash-water, containing unchanged *p*-aminophenetol hydrochloride, and coloring-matter, can be treated with chalk, and the *p*-aminophenetol distilled over with steam.

The filtrate from the pure acetphenetidin contains about 6 parts of acetphenetidin in solution, which can be obtained by evaporating the liquid.

The animal charcoal can be revived by gentle ignition in closed tubes.

## 4. CONCLUSION.

The process above-described is capable of producing acetphenetidin at a very low cost compared with the older methods. The materials required are cheap and easily accessible; the operations involved are simple; and the yields at each step are good. Only subordinate quantities of by-products are formed, and these occur in the earlier and less important phases of the synthesis.

## ABBREVIATIONS.

The following abbreviations have been used in the bibliographical references:

*Am. Chem. J.*—*American Chemical Journal*.

*Ann.*—*Justus Liebig's Annalen der Chemie*.

*Ann. chim. phys.*—*Annales de chimie et de physique*.

*Arch. exp. Path. Pharm.*—*Archiv für experimentelle Pathologie und Pharmakologie*.

*Ber.*—*Berichte der Deutschen chemischen Gesellschaft*.

*Berl. klin. Wochschr.*—*Berliner klinische Wochenschrift*.

*Brit. Pat.*—*British Patent*.

*Bull. acad. St. Pétersb.*—*Bulletin de l'Académie Impériale des Sciences de St. Pétersbourg*.

*Bull. classe phys.-math.*—*Bulletin de la classe physico-mathématique*.

*Chem. Eng.*—*Chemical Engineer*.

*Chem. Zentr.*—*Chemisches Zentralblatt*.

*D. R. P.*—*Patentschrift des Deutschen Reiches*.

*Frdl.*—*Friedlander's Fortschritte der Teerfarbenfabrikation*.

*Gazz. chim. ital.*—*Gazetta chimica italiana*.

*J. Am. Chem. Soc.*—*Journal of the American Chemical Society*.

*J. Anal. Appl. Chem.*—*Journal of Analytical and Applied Chemistry*.

*J. Chem. Soc.*—*Journal of the Chemical Society*.

*J. prakt. Chem.*—*Journal für praktische Chemie.*

*J. Roy. Soc. Arts.*—*Journal of the Royal Society of Arts.*

*J. russ. phys. chem. Ges.*—*Journal der russischen physikalisch-chemischen Gesellschaft.*

*J. Soc. Chem. Ind.*—*Journal of the Society of Chemical Industry.*

*Jsb. Chem.*—*Jahresbericht der Chemie.*

*Lehrb. (Kekulé).*—*Lehrbuch der Organischen Chemie, by Aug. Kekulé.*

*Rec. trav. chim.*—*Recueil des travaux chimiques des Pays-Bas.*

*U. S. Pat.*—United States Patent.

*Z. angew. Chem.*—*Zeitschrift für angewandte Chemie.*

*Z. Chem.*—*Zeitschrift für Chemie.*

*Z. klin. Med.*—*Zentralblatt für klinische Medizin.*

*Z. med. Wiss.*—*Zentralblatt für medizinischen Wissenschaften.*

*Z. physik. Chem.*—*Zeitschrift für physikalische Chemie.*

With a few exceptions, the above abbreviations are those recommended and used in *Chemical Abstracts* (see *Chemical Abstracts*, 1908, Vol. 2).

### CONIUM MACULATUM L., AND AETHUSA CYNAPIUM L., AN ADULTERANT.\*

BY CLARE OLIN EWING, ERNEST E. STANFORD, AND JOSEPH F. CLEVINGER.

*Conium maculatum* L., the Greater or Poison Hemlock, was known in ages past as a poisonous plant. It is asserted to have been the state poison of the ancient Greeks, and its use in early medicine is reported by Dioscorides. The plant was introduced to more recent practice by Störck<sup>11</sup>, who employed it in a wide variety of conditions. According to Henry<sup>7</sup>, *Conium* contains a series of six alkaloids, to whose action its medicinal properties have been commonly attributed. Coniine, the principal member of the series, was isolated by Giesecke in 1827. Other alkaloids occur only in minute amounts, and the mixture is usually known by the name of its most important representative—coniine. While hemlock enjoyed a considerable vogue for a time, the uncertainty of its preparations soon put it into disfavor. Harley,<sup>5</sup> investigating its physiological effects upon himself and others, considered the dried plant and its preparations therapeutically worthless. He extolled, however, the virtues of the juice expressed from the fresh plant. Farr and Wright<sup>3</sup> investigated the alkaloidal content of different parts of the plant, and of plants of different ages. With respect to the herb, they found alkaloids to be chiefly produced during the flowering and fruiting period. Wide variations were apparent in the alkaloidal yield of different specimens of the same growth stage. They found the alkaloidal yield of the fruit to be much above that of the herb, to culminate just before maturity, and thereafter to diminish. Harley<sup>5</sup> and others have reported little or no coniine at all in the dried herb. Both the seed and the herb, moreover, especially the latter, are said to deteriorate rapidly during storage, owing no doubt to the volatility of the alkaloids. Because of their uncertainty of composition *Conium* leaves have largely disappeared from prescriptive practice, and from the official standards. *Conium* seed is retained in the National Formulary IV but is not a drug of great importance.

*Aethusa cynapium* L., the so-called Lesser Hemlock or Fool's Parsley, has been

\* Contribution from Pharmacognosy Laboratory, Bureau of Chemistry, Department of Agriculture, Washington, D. C.