THE MANUFACTURE OF ACETPHENETIDIN.*

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HISTORICAL REVIEW.

1. WORK OF HALLOCK.

Acetphenetidin was probably first made by the American chemist, E. J. Hallock,[2] in 1879, while investigating the properties of the mono-nitrophenetols ($NO_2.C_6H_4.OC_2H_5$) and some of their derivatives. Hallock treated *p*-aminophenetol ($NH_2.C_6H_4.OC_2H_5$) with acetyl chloride and observed that "this oil combines, like aniline, directly with acetyl chloride to form a crystalline solid." This crystalline solid must have been crude acetphenetidin; unfortunately, however, Hallock did not isolate it in the pure state and determine its physical properties and chemical constitution. He contributed practically nothing to our knowledge of the compound, and therefore he is not commonly regarded as the discoverer of acetphenetidin. His preparation of the crystalline solid is usually considered as merely the result of a test which he applied to confirm the presence of an amino group in *p*-aminophenetol, and not as a positive discovery of a new substance.

The method by which Hallock arrived at his crystalline solid has no value for the commercial synthesis of acetphenetidin; it is, however, of historical interest and deserves description. Pure phenetol ($C_6H_5.OC_2H_5$), or a solution of phenetol in acetic acid, was treated with fuming nitric acid, and the resulting dark red, viscous liquid 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, which was found to be *p*-nitrophenetol, was purified by repeated crystallization both from acid and from alcohol. Hallock also prepared *p*-nitrophenetol by the action of potassium ethyl sulphate and potassium hydroxide on *p*-nitrophenol in sealed tubes at high temperatures, and by heating ethyl iodide and potassium hydroxide with *p*-nitrophenol under the same conditions. The *p*-nitrophenetol obtained by these methods he reduced to *p*-aminophenetol by means of tin and hydrochloric acid. The resulting salt, after the removal of the tin with hydrogen sulphide, crystallized in rhombic plates of a pearly lustre. These crystals were treated with potassium hydroxide, when the free base was obtained as an oily liquid resembling aniline. Hallock's conversion of this base into acetphenetidin by means of acetyl chloride has been described. In his original paper, and also in a paper published two years later, Hallock[3] stated that the yields of *p*-nitrophenetol and *p*-aminophenetol which he obtained by these methods were very poor.

2. WORK OF HINSBERG.

The credit for the discovery of acetphenetidin is usually given to the German chemist, Oscar Hinsberg, who was the first to determine its chemical constitution, physical properties, and medicinal action. Hinsberg was led to his discovery by a consideration of the work of Fischer and Skraup and of Cahn and Hepp.[4]

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[2] *Am. Chem. J.*, 1, 271, 1879.

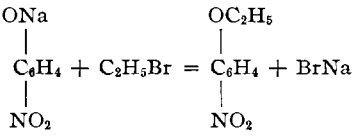
[3] *Ber.*, 14, 37, 1881.

[4] *Z. angew. Chem.*, 26, 158, 1913.

Fischer and Skraup had found that phenolic hydroxyl groups and their ethers produce antipyretic and analgesic effects, while the experiments of Cahn and Hepp[5] had proved that acetanilid is an antipyretic and analgesic of great power. Scmiedeberg[6] had also shown that aniline and its simple derivatives are partially converted by the organism into *p*-aminophenol. Knowing these facts and wishing to overcome the toxic action of acetanilid, Hinsberg conceived the idea of introducing into the molecule of acetanilid an alkoxyl group. One of the results of this idea was the discovery of acetphenetidin in 1886. Associated with Hinsberg were Kast, who determined the physiological action of acetphenetidin,[7] and Duisberg, director of the Farbenfabriken of Elberfeld, who made possible its production on a large scale.[8]

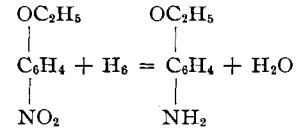
In the descriptive portion, or specification, of the United States patent[9] granted to Oscar Hinsberg and assigned to the Farbenfabriken of Elberfeld, we find the following description of the method which was first used in the commercial preparation of acetphenetidin:

"Fifty kilos of the potassium salt of paranitrophenole are mixed with three hundred kilos of alcohol, adding forty kilos of bromoethyl. The mixture is heated in an autoclave at a pressure of three to four atmospheres during about eight hours. At this time the reaction is finished, whereby paranitrophenetole is obtained according to the following equations:



"In order to separate the mononitrophenole, which has not taken any part in the process, from the ether recently formed, the solution is treated with steam. By this operation the ether distills, leaving behind the paramononitrophenole.

"For the reduction of the paranitrophenetole forty kilos of this ether are mixed with sixty kilos of muriatic acid and sixty kilos of water. To this mixture are gradually added, at a temperature of 70° C., twenty-five kilos of iron filings, the whole being stirred continually. As soon as the ether is entirely reduced, paramidophenetole is obtained, as explained by the following equation:



"The solution obtained in this manner is saturated with chalk diluted with water, and for the purification of the amido compound treated with steam the distillate is absorbed in water acidulated by muriatic acid. The muriatic salt of the paramidophenetole crystallizes in white leaves. Fifty kilos of this product are melted with one molecule of melted acetate of sodium and twenty-four kilos of glacial acetic acid. The melted mass is repeatedly boiled with water and the new monoacetylparamidophenetole obtained from the filtrates after cooling. It has the following formula:

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[5] *Z. klin. Med.*, 1886, 33; *Berl. klin. Wochschr.*, 1887, 1 and 2.

[6] *Arch. exp. Path. Pharm.*, 8, 1 (1878).

[7] *Z. Med. Wiss.*, 1887–9.

[8] *Z. angew. Chem.*, 26, 49, 158, 240, 352 (1913).

[9] U. S. Pat. No. 400,086, March 20, 1889.

$$\text{Para } C_6H_4(NH(C_2H_3O))(OC_2H_5) = C_{10}O_2H_{13}N$$

and is obtained according to the following equations:

$$\text{Para } C_6H_4(NH_2)(OC_2H_5) + CH_3COOH = C_6H_4(NHC_2H_3O)(OC_2H_5) + H_2O$$

"The monoacetylparamidophenetole crystallizes in white leaves, melting at 133° to 136° C. It is tasteless, little soluble in cold water, more so in hot water, but easily in alcohol, chloroform, benzole, etc."

The patentee claimed originality for the product but not for the process of manufacture. In fact, all the intermediates and methods described had been known to chemists for years prior to the time of application for the patent, so there was really nothing new in the process. The only useful improvement was its application on a commercial scale.[10]

Although the starting point in this synthesis is *p*-nitrophenol, no method for its production was described by the patentee. It is of interest to know that before the medicinal value of acetphenetidin was discovered, *p*-nitrophenol was a useless by-product in the manufacture of dianisidin from *o*-nitrophenol.[11] In order to complete the description of the method which was actually used in the manufacture of acetphenetidin it is necessary to add the nitration of phenol, which, according to Duisberg,[12] was carried out by the direct nitration of phenol in aqueous solution, the ortho and para nitrophenols thus formed being separated by distillation with steam, when the ortho compound passes over and the para isomer remains in the residue. The *o*-nitrophenol was used in the manufacture of dianisidin and the *p*-nitrophenol in the manufacture of acetphenetidin.

In 1889 Hinsberg[13] described two methods for the preparation of acetphenetidin which are suitable for use in the laboratory. These methods are as follows:

"The ethyl ether of *p*-nitrophenol is reduced in the usual manner by adding it to a warm mixture of tin and concentrated hydrochloric acid on the water-bath. The colorless solution is then freed from the greater part of the tin by adding sheet zinc, saturated with sodium hydroxide, and shaken out twice with ether. The ethereal solution is dried with potassium hydroxide and then distilled. The portion going over between 242–245° (unc.) is vigorously shaken in a separatory funnel with ice-water and an excess of acetic anhydride (about 1.5 molecular weights to 1 molecular weight of phenetidin). After the disappearance of the anhydride the acetphenetidin is filtered off and crystallized from diluted alcohol with the aid of animal charcoal. The phenetidin, like aniline, may also be acylated with boiling glacial acetic acid."

"To go from *p*-aminophenol, acetylaminophenol and an equivalent part of sodium hydroxide and ethyl bromide or ethyl iodide are dissolved in sufficient alcohol to form a clear solution and warmed on a water-bath for two or three hours under a reflux. On diluting the alcohol the product, in case pure acetaminophenol was used, is clean and white and usually requires no further purification."

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[10] Kebler, "Phenacetin: Methods of Analysis and Commercial Status," p. 34.

[11] *Z. angew. Chem.*, 26, 49, 1913.

[12] *Ibid.*, 26, 240, 1913.

[13] *Ann.*, 305, 276, 1899.

3. WORK OF RIEDEL.

In 1888 J. D. Riedel obtained a German patent[14] on a process for making *p*-aminophenetol, which he stated was serviceable in the manufacture of acetphenetidin. In this process one molecule of *p*-nitrophenol is ingeniously made to furnish a large number of molecules of acetphenetidin. The process seems to have been used on a commercial scale because *p*-nitrophenol was rather difficult to obtain in pure condition by the nitration of phenol, and because the cost of production of acetphenetidin was dependent on the utilization of the *o*-nitrophenol as dianisidin or in some other way.[15] The details of the method as described in the patent-specification are as follows:

"A solution of 150 grammes of para-amidophenetol and 380 cc. of 20 percent hydrochloric acid in 2200 cc. of cold water, is diazotized by adding, with cooling, a solution of 70 grammes of sodium nitrite in 550 cc. of water. The solution of the diazo compound thus formed is poured into a solution of 104 grammes of phenol and 220 grammes of sodium carbonate in 400 cc. of water. After one hour the ethyl-dihydroxy-azobenzene separates out quantitatively. After filtering from the liquid portion it may be recrystallized from dilute alcohol.

"100 grammes of dry ethyl-dihydroxy-azobenzene and 17 grammes of sodium hydroxide are dissolved in 500 cc. of alcohol, 46 grammes of ethyl bromide are then added and the solution heated in an iron autoclave for ten hours at 150° C. After distilling off the alcohol the sodium bromide is extracted from the residue with water and any unchanged ethyl-dihydroxy-azobenzene with dilute sodium hydroxide solution. The residue, diethyl-dihydroxy-azobenzene, is crystallized from alcohol.

"70 grammes of stannous chloride are dissolved in 300 cc. of concentrated hydrochloric acid, to this solution 100 grammes of diethyl-dihydroxy-azobenzene are added, and the mixture warmed gradually on the water-bath. As soon as the diethyl-dihydroxy-azobenzene is dissolved the mixture is rendered alkaline with 180 grammes of sodium hydroxide, and the para-amidophenetol distilled off with superheated steam."

The *p*-aminophenetol obtained in this way can be converted into acetphenetidin by acetylation or can be made to yield a double quantity of *p*-aminophenetol by repeating the above-described process of diazotizing and coupling with phenol.

The following equations illustrate the successive steps involved in the manufacture of acetphenetidin by this process:

1. $C_2H_5O.C_6H_4.NH_2 + -2HCl + NaNO_2 = C_2H_5O.C_6H_4.N_2Cl + NaCl + 2H_2O.$
   p-aminophenetol — phenetol-diazo-chloride

2. $C_2H_5O.C_6H_4.N_2Cl + Na_2CO_3 + C_6H_5OH = C_2H_5O.C_6H_4.N_2.C_6H_4.OH + NaHCO_3 + NaCl + H_2O.$
   phenetol-diazo-chloride — phenol — ethyl-dihydroxy-azobenzene

3. $C_2H_5O.C_6H_4.N_2.C_6H_4.OH + NaOH + C_2H_5Br = C_2H_5O.C_6H_4N_2.C_6H_4.OC_2H_5 + NaBr + H_2O.$
   ethyl-dihydroxy-azobenzene — ethyl bromide — diethyl-dihydroxy-azobenzene

4. $C_2H_5O.C_6H_4N_2.C_6H_4.OC_2H_5 + 2SnCl_2 + 4HCl = 2C_2H_5O.C_6H_4.NH_2 + 2SnCl_4.$
   diethyl-dihydroxy-azobenzene — *p*-aminophenetol

5. $C_2H_5O.C_6H_4.NH_2 + CH_3.COOH = C_2H_5O.C_6H_4.NH_2.OC.CH_3 + H_2O.$
   p-aminophenetol — acetic acid — acetophenetidin

4. WORK OF PLATT.

In 1893 Charles Platt[16] described the method of manufacturing acetphenetidin as follows:

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[14] *D. R. P.* No. 48,543, Dec. 28, 1888; *Frdl.* II, 526.

[15] May, "The Chemistry of Synthetic Drugs," p. 71.

[16] *J. Anal. Appl. Chem.*, 7, 77, 1893.

"There are four steps involved in the preparation of phenacetin from phenol, which is the starting-point in its manufacture, and these, though simple, require care and attention, that the resulting drug may be of the requisite purity. First, the phenol is converted to nitrophenol by gradually adding it (one part) to two of nitric acid in four of water. An oil separates which is washed and distilled with steam, when the volatile ortho-nitrophenol distills over, leaving the non-volatile para-nitrophenol as a residue.

$$C_6H_5OH + HNO_3 = C_6H_4(NO_2)OH + H_2O.$$

"In the second step the ethyl radical, C_2H_5, is substituted in the hydroxyl group of the nitrophenol by treatment with ethyl iodide forming ethyl nitrophenol.

$$C_6H_4(NO_2)OH + C_2H_5I = C_6H_4(NO_2)OC_2H_5 + HI.$$

"The third step consists in treatment with sodium-amalgam, whereby the nitro radical of the ethyl nitrophenol is reduced to amidogen with the formation of phenetidin.

$$C_6H_4(NO_2)OC_2H_5 + 3H_2 = C_6H_4(NH_2)OC_2H_5 + H_2O.$$

"The final step is the treatment of phenetidin with anhydrous acetic acid, then substituting the radical C_2H_3O for one atom of hydrogen in the amidogen group.

$$C_6H_4(NH_2)OC_2H_5 + C_2H_3OOH = C_6H_4(OC_2H_5)NHC_2H_3O + H_2O."$$

It will be observed that this description is quite general; it is typical of the descriptions which are given to this day in most text-books and reference-books concerning the method by which acetphenetidin is made commercially. The most valuable part of Platt's paper is that which treats of the qualitative examination of acetphenetidin, many tests being given for its identification and the determination of its purity.

5. WORK OF TÄUBER.

In 1878 H. N. Morse[17] reported that when *p*-nitrophenol is reduced with tin and glacial acetic acid, instead of obtaining the acetic acid salt of *p*-aminophenol, one obtains the acetyl derivative, $HO.C_6H_4.NH.OC.CH_3$. In 1894 E. Täuber was granted a German patent[18] on a process that converts this chemical into acetphenetidin. The process is described as follows:

"Mix 150 grammes of *p*-acetamidophenol, 165 grammes of potassium ethyl sulphate, and 40 grammes of sodium hydroxide (dissolved in 500 cc. of 60 percent alcohol) in an autoclave and heat the mixture for four hours at 150° C. On diluting the resulting solution with three parts of water the phenacetin separates out in fairly pure crystals."

It should be noted that this process is practically identical with one described by Hinsberg in 1889 (see Section 2).

6. WORK OF PAUL.

In 1896 Ludwig Paul[19] published an article on the technical applications of ortho and para nitrophenol, in which he described in some detail the different steps in the manufacture of acetphenetidin. The following paragraphs are quoted from his article:

"By the nitration of phenol there are formed, as is well known, two isomeric mononitrocompounds, *o*-nitrophenol, long, sulphur-yellow needles of a disagreeable odor, and *p*-nitrophenol, prismatic crystals of a faintly yellow to brown color according to their purity, possessing only a very faint odor.

"Their essential and, for the technical separation, valuable distinction, however, lies in their different behavior toward water-vapor.

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[17] *Ber.*, 11, 232, 1878.

[18] *D. R. P.* No. 85,988, June 19, 1894.

[19] *Z. angew. Chem.*, 1896, 587.

"Only the *o*-nitrophenol distills over with this, and in such purity, indeed, that it is suitable without further treatment for conversion into *o*-nitroanisol or dianisidin.

"On the other hand the *p*-nitrophenol remains behind as a crystalline mass mixed with tarry substances, from which it can be freed by repeated recrystallization from a small amount of naphtha."

"1. Purification of *p*-nitrophenol: 800 grammes of crude *p*-nitrophenol are dissolved in 8 to 10 liters of water with the addition of 250 grammes of chalk, and heated by passing in steam. The mixture is then filtered and 200 grammes of sodium carbonate and 5 kilos of salt added to the filtrate. After again filtering there crystallizes 950 grammes of the pure sodium salt of *p*-nitrophenol.

"2. Para-nitrophenetol: 480 grammes of the pure sodium salt of *p*-nitrophenol, 3120 grammes of denatured alcohol, 300 grammes of ethyl bromide (crude) and 100 grammes of sodium carbonate are heated under a reflux condenser for about 10 hours. The contents of the vessel are then cooled, the solid *p*-nitrophenetol filtered off, and, in order to separate any unchanged *p*-nitrophenol, washed with water until the washings are only faintly colored yellow. For complete purification the crude *p*-nitrophenetol is recrystallized from about 3 parts of alcohol, from which it is obtained in large, faintly yellow colored prisms, which melt at 56–57°.

"The yield amounts to 340 grammes, corresponding to 68 percent of the theory, according to which 499 grammes should be obtained. 22 percent of the *p*-nitrophenol remains unaltered, the greater part of which can be recovered from the mother liquor by evaporating and acidifying.

"3. Para-amidophenetol: 212 grammes of *p*-nitrophenetol are gradually added to a solution of 848 grammes of stannous chloride in 1060 grammes of hydrochloric acid, warmed to 50–60°. The reaction which ensues is a rather vigorous one, and is rendered complete by heating.

"When the reaction is ended, 250 grammes more of hydrochloric acid are added. After standing 12 hours the crystals of *p*-amidophenetol are filtered off, and, in order to free them completely of adhering tin, dissolved in 0.75 liter of hot water with the addition of 100 grammes of hydrochloric acid. Into this solution sheet-zinc is introduced until all the adhering tin is precipitated. After filtering the colorless solution and extracting the tin residue, a further addition of 100 grammes of hydrochloric acid is made. One obtains 140 grammes of the hydrochloride of *p*-aminophenetol, colorless prismatic crystals, 1 cc. long, corresponding to 64 percent of the theory.

"4. Phenacetin: Since the following-described experiment with 15 grammes of *p*-aminophenetol hydrochloride gave a yield of 75–90 percent of phenacetin, and by considering the amidophenetol recovered even the theoretical yield, further experiments would have been useless.

"16.7 grammes of the hydrochloride of *p*-aminophenetol, 8.7 grammes of dry sodium acetate, and 8.3 grammes of glacial acetic acid were heated under a reflux condenser for about 3 hours. The acetic acid solution was then dissolved in 10 parts of boiling water, and freed from resinous by-products by filtering. After cooling the phenacetin crystallizes out with a faint reddish color. By recrystallization from water with the aid of animal charcoal one obtains 15 grammes of phenacetin in the form of small, perlaceous, glistening flakes. The yield corresponds to 90 percent of the theory."

This method, it will be seen, is practically the same as that described by Hinsberg (see Section 2).

7. WORK OF KLIMMEK.

In 1898 United States letters-patent[20] were granted to Otto Klimmek of Chicago, Illinois, on the product oxyethylacetanilid, which is identical with acetphenetidin, and on a process of making the same from *p*-aminophenetol. This patent was subsequently found to be invalid. In the patent-specification we find the following description of the product and the method, both of which the patentee claimed were his inventions;

[20] U. S. Pat. No. 606,288, June 28, 1898.

"In carrying out the process of manufacture I add to the paramidophenetol one molecule of glacial acetic acid. The mass is placed in a flask having a return-condenser and maintained at a temperature of 100° C. in a water-bath for from four to five hours. This solution is then thrown into eighty parts of boiling water and maintained at the boiling-point for a few minutes, a sufficient quantity of animal charcoal having been added to secure on filtration a perfectly clear liquid. The solution is now filtered while hot and allowed to crystallize rapidly. The large volume of water above mentioned thoroughly dissolves the solids, so that all of the impurities and coloring-matter are absorbed by the charcoal. The resulting product, oxyethylacetanilid, having the formula $C_{10}H_{13}NO_2$ (1:4), after being separated from the water is a solid composed of very small, lustrous crystals taking the form of scales. It is white, very light and 'fluffy,' soft or velvety to the touch, and is tasteless. It is almost insoluble in cold water. In boiling water when agitated it dissolves readily."

8. DISCUSSION.

From a review of the work which has been published on the manufacture of acetphenetidin one can obtain a general idea of the processes which have been found technically useful; however, these processes lack the quantitative data which would enable one to determine their relative value.

The process most often referred to, and no doubt the one most largely used in practice, at least in the beginning, is that of Hinsberg, based on the scheme: phenol ⟶ *p*-nitrophenol ⟶ *p*-nitrophenetol ⟶ *p*-aminophenetol ⟶ acetphenetidin. The chief disadvantage of this synthesis is the fact that it is quite difficult to obtain a good yield of *p*-nitrophenol in pure condition by the direct nitration of phenol, for *o*-nitrophenol is the chief product, and the *p*-nitrophenol is invariably mixed with tarry substances which are troublesome to remove. The process is not altogether satisfactory because the cost of production depends to a great extent on the ease with which the *o*-nitrophenol can be disposed of and its value; thus acetphenetidin becomes the by-product instead of the main product as is desired.

This disadvantage is not overcome by the Täuber method, as its starting-point is likewise *p*-nitrophenol. The only advantage of the Täuber method seems to be that both the reduction and the acetylation are performed in one operation. It is probable, however, that this advantage is overcome by the cost of the materials required to effect the double change.

The only process which does not start with *p*-nitrophenol, and which therefore obviates the chief disadvantage of these other processes, is that of Riedel, and it might seem that this process would be chosen for the manufacture of acetphenetidin. It is conceivable, however, that the process might, in spite of its freedom from side reactions, fail in one particular, that of the cost of production, since many materials are used which are quite expensive from the technical point of view.

It is evident that our knowledge of the details of the different processes, and their possibilities of improvement, is very limited. In order to obtain a more thorough knowledge of these things this research was undertaken and the phases of the individual syntheses systematically investigated.

(To be concluded in next number.)