tically every group there will be crystals of variable size, some so small that they are scarcely visible under the high power. Among the perfect crystals are numerous broken fragments of large and small crystals, retaining, however, the characteristics of the larger crystals.

THE CHEMISTRY OF ASPIRIN OR ACETYLSALICYLIC ACID.[1]

OTTO RAUBENHEIMER, PH. G., BROOKLYN, N. Y.

The flowers of *Spiraea Ulmaria L.,* Meadow Sweet, or Queen of the Meadow, which were formerly official in the French Codex, 1884, and which as Flos Spiraeae are still official in the fourth edition of the Swiss Pharmacopoeia, contain methyl salicylate, and used to be the source of salicylic acid, which was isolated, from the flowers, by Löwig in 1839.

Acidum Spiricum is even today a synonym for salicylic acid, and *Spirin,* the active principle of *Spiraea,* denotes the same.

The prefix "A" in Aspirin stands for "Acetyl" and the meaning of the coined word "Aspirin" is consequently "*Acetylsalicylic Acid.*"

The author cannot help but admit that the short and euphonious word "Aspirin" is coined in a very clever and scientific way.

That this name is very valuable as a trademark can be appreciated. The word Aspirin has been registered as a trademark in Germany as Warenzeichen No. 36,433, in Austria, Wortmarke No. 1899/399, and in the United States as Trademark No. 32,805.

The owners of this trademark are the manufacturers Farbenfabriken vorm. (formerly) Friedr. Bayer & Co., Elberfeld, Germany, and in the United States, The Farbenfabriken of Elberfeld Co., New York City.

In 1853 *Gerhardt*[2] was the first to prepare this chemical from acetyl chloride and sodium salicylate, and named same "Anhydrous Salicylic-Acetic Acid (wasserfreie Salicylsäure—Essigsäure.) Although he did not give any further details of the constitution of the new substance, he was of the opinion that it was an anhydride of the two acids. In 1859 *von Gilm*[3] reported the discovery of a crystalline substance from chloracetyl and salicylic acid, and named the same "Acetilized Salicylic Acid" (acetylierte Salicylsäure).

In 1869 Kraut[4] determined the constitution of the chemical and named it "Acetylsalicylic Acid" (Acetylosalicylsaure).

On December 22, 1898, Newton took out an English patent on the preparation of acetylsalicylic acid. In 1900 Hoffman, of the Farbenfabriken Elberfeld obtained a patent "for a medicinal body whose trade name is aspirin, a product of coaltar, otherwise known as acetylsalicylic acid."

Hoffman discovered a waterless process by which a pure chemical was obtained. Although impure acetylsalicylic acid had been known long ago, Hoff-

[1] Reprinted from the Practical Druggist, Dec., 1912.

[2] Gerhardt: Untersuchungen über die wasserfrien Säuren. Ann-der Chemie 87, 162 (1853).

[3] von Gilm: Acetylderivate der Phloretin-und Salicylsäuren. Ibid 112, 180 (1859).

[4] Kraut: Uber Salicylverbindungen. Ibid 150, 9 (1869).

man was the first to prepare and patent the pure chemical and his patent which has been contested several times, has been upheld by the courts. Since then aspirin or acetylsalicylic acid has become a very valuable remedy in therapeutics and is used all over the world.

Acetylsalicylic acid is officially recognized in the following pharmacopœias and standard works under the title:

Acidum Acetylosalicylicum: Pharmacopœia Helvetica IV, 1908; Danica VII 1907; Svecica (Swedish) IX, 1908; Hungarica III, 1909; Deutsches Arzneibuch V, 1910.

Acidum Acetylsalicylicum: Codex Medicamentarius Gallicus (French) V, 1908.

Acidum Salaceticum: British Pharmaceutical Codex I, 1907.

Acidum Acetyl—Salicylicum: British Pharmaceutical Codex, II, 1911.

Besides the titles just mentioned, acetylsalicylic acid is also known under the following names: Aspirin, Acetosalicylic Acid, Acetosalin, Acetysal, Aletodin, Salacetin, Saletin, Salicyl-Acetic Acid, Xaxa, etc.

Acetylsaicylic Acid is the acetyl derivative, or monoaceticacid ester of salicylic acid.

$$C_6H_4.\ O(CH_3CO).\ COOH,\ 1:2=C_9H_8O_4$$

It is manufactured by heating 50 parts of salicylic acid with an excess or about 75 parts of acetic anhydride for about 2 hours at 150° C. (302° F.) under a reflux condenser, or on a large scale in an autoclave.

The following reaction takes place:

$$2\left\{C_6H_4<\begin{matrix}OH\\COOH\end{matrix}\right\}+\begin{matrix}CH_3CO\\CH_3CO\end{matrix}>O$$

$$=2\left\{C_6H_4<\begin{matrix}O.CO.CH_3\\COOH\end{matrix}\right\}+H_2O$$

In order to bind the formed water, anhydrous, fused sodium acetate is added. The excess of acetic acid is removed by distillation. Upon cooling the acetylsalicylic acid separates in crystals, which are purified by crystallization from chloroform. The author might state here that there are also other processes in use to manufacture acetylsalicylic acid, which, however, we cannot describe at this time, owing to the limited space.

The Farbenfabriken, vorm. Friedr. Bayer & Co., Elberfield, manufacture the chemical under the German Patent, D. R. P., No. 85,565, and the Farbenfabriken of Elberfeld Co., New York City under the U. S. Patent No. 644,077, of February 27, 1900, which expires in 1917. This is a so-called "product patent" in which the word "Aspirin," which is also trademarked, identifies the acetylsalicylic acid manufactured by this firm. Nobody else has the right to manufacture this chemical in the United States or to sell this chemical as "acetylsalicylic acid" or under any name whatsoever. And furthermore nobody has the right to use acetylsalicylic of anybody else's manufacture during the life of this product patent in the United States. In the opinion of the writer these points should be well borne in mind by druggists and pharmacists in order to save

serious trouble. For the benefit of those who have made objections to foreign chemicals, etc., because they were not manufactured in the United States by American workmen and American machinery, we might mention that Aspirin is manufactured at the Hudson River Aniline Color Works, Albany, N. Y., a fact which has only lately come to our attention.

It occurs in colorless small shining crystals or as a white crystalline powder. The author begs to point out that the shape of the crystals and also in the powdered condition under the microscope differs according to the process of manufacture. It should be odorless and should not be used when it has an acetic odor, which might be due to careless manufacture or to decomposition through the influence of heat or moisture. Its taste is sweet and acidulous. Melting point is about 135° C. (275° F.) The author wants to emphasize *"about,"* as much has been written on this very point.[5]

The Swiss Pharmacopœa of 1908 and the Swedish of 1908 do not give the melting point at all. The French of 1908 states 135° C. and the Danish of 1907 and the German of 1910 state *"about"* 135° C. According to the experience of the author the melting point is 135° C., after the acid has been thoroughly dried, viz., over sulphuric acid. It is also well to remember that by melting the chemical will be decomposed; so that the same sample will melt at about 125° C. at the second melting. A slight decomposition also takes place when heated to 100° C. In determining the melting point of acetylsalicylic acid or aspirin it is well to take the precaution to rapidly heat to about 125° C. and continue to gradually increase the temperature one degree per minute.

The melted acetylsalicylic acid solidifies again at about 70° C.

On ignition it should leave no residue. The German Pharmacopœia permits 0.1 percent, i. e., by igniting 1 gm., the residue should not be over 0.001 gm. practically no residue.

SOLUBILITY:	Water.	Alcohol.	Ether.	Chlorof.
Helv. IV.....	Sparingly	5	Freely	Freely
Fr. Cod, 1908.....	125	Very	Very	
N. N. R. 1915.....	100	Freely	Freely	
B. P. C. Cx. II.....	300	5	Soluble	Soluble
D. A.-B. V.....	300	Freely	20	

It is sparingly soluble in cold, but very soluble in hot benzol, and freely soluble with decomposition in solutions of alkalies and alkali carbonates. According to experiments of the author its solubility in chloroform is about 1 in 25 parts.

The aqueous and alcoholic solutions decompose on standing, forming salicylic and acetic acids. This decomposition takes place readily when heat is used and very rapidly in alkaline solutions.

REACTION: The aqueous solution is acid to litmus.

TESTS OF IDENTITY.

(a) The principal test of identity is based on the hydrolysis or decomposition into its constituents. Boil 0.5 gm. with 10 cc. solution of sodium hydroxide (15%) during 2 or 3 minutes, thus forming sodium salicylate and acetate. On cooling add an excess of diluted sulphuric acid which will precipitate crystals of

[5] H. Dichgans: Acidum Ocetylo-Salicylicum. Ph. Ztg., 1909, 47 Utz, Aspirin, Ph. Zhalle 43, 451 (1902). Madsen, Aspirin, Ph. Ztg. 1909, 210.

salicylic acid, which upon washing and drying should have a melting point of 157° C. An aqueous solution of these crystals assumes a violet color by the addition of ferric chloride T. S. The liquid portion which was separated from the salicylic acid crystals contains acetic acid, which is detected by its odor and also by the formation of acetic ether upon boiling with a little alcohol and concentrated sulphuric acid.

(b) Other tests of identity are as follows: A saturated cold aqueous solution is neutralized with sodium carbonate T. S. The liquid thus obtained, which, however, must not be alkaline, but can be slightly acid, by the addition of ferric chloride T. S. produces a light brown precipitate, and lead acetate T. S. produces a white precipitate. The liquid is not changed by barium nitrate T. S. or mercuric chloride T. S.

c) Upon warming about 0.25 gm. together with a little dry calcium oxide in a test tube the odor of phenol will be noticed.

TESTS OF PURITY.

(a) Absence of free salicylic acid: A cold solution of 0.1 gm. in 5 cc. alcohol and diluted with 20 cc. distilled water should not be colored violet by the addition of one drop of a diluted ferric chloride solution 1 :25. The precaution must be used to employ a fresh solution of acetylsalicylic acid, prepared cold.

(b) Absence of free acetic acid: This can readily be detected by its odor. As pointed out under "Properties," acetylsalicylic acid should be odorless.

(c) Absence of hydrochloric acid and chlorides.

(d) Absence of sulphuric acid and sulphates.

(e) Absence of heavy metals.

(f) Resinous impurities: Dissolve about 0.5 gm. in alcohol and allow to evaporate, well protected. The residue should be colorless, especially at the edges.

(g) Organic impurities: It should form clear and colorless solutions with water, alcohol, sulphuric acid and nitric acid.

(h) Absence of phenol: A solution of 0.5 gm. in 10 cc. sodium carbonate T. S. is shaken with about 5 cc. ether, and the ethereal layer is then separated. Upon evaporation only traces of residue should remain, which should be odorless.

ASSAY.

According to the Swiss Pharmacopœia: If 1 gm. is boiled for 3 minutes with 15 cc. normal sodium hydroxide volumetric solution and a few drops of phenolphthalein T. S. are added when cool, then 38.6 to 38.9 cc. of tenth-normal hydrochloric acid volumetric solution should be required for neutralization. A more correct method, in the opinion of the author, would be to make at the same time a blank titration between the alkali and the acid. The addition of salicylic acid and also the presence of not esterized molecular amounts of acetic and salicylic acid reduce the required volume of NaOH, while free acetic acid increases same.

EXPERIMENTS.

The author obtained different samples of acetylsalicylic acid in crystals and in powder, and also of aspirin, and subjected them to the above tests, and has reached the conclusion *that both are identical chemically,* although some difference

in the melting points of the examined samples of acetylsalicylic acid seem to indicate a greater or lesser degree of purity. The question has also arisen if Aspirin-Bayer contained a "tracer" in order to distinguish it from the acetylsalicylic acid of other manufacturers. Up to the present time the writer has been unable to detect such a "tracer."

INCOMPATIBILITY.

From the standpoint of a pharmacist the editor of The Practical Druggist takes this opportunity to mention the principal incompatibilities, namely, heat, moisture, alkalies and their carbonates and bicarbonates.

Acetylsalicylic acid or aspirin should be preserved in well-stoppered bottles in a dry place. The author must express his surprise that the manufacturers who in former years employed bottles have discarded the same and are now using cartons as containers.

When aspirin powders are ordered it is best to dispense these in parchment paper, so as to prevent decomposition through the influence of moisture.

PRESERVATION OF SPIRIT OF NITROUS ETHER.

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I know that this is an old subject and you may feel that it has been threshed to the limit, yet there are many druggists today who do not keep this preparation under the proper conditions, either because they do not know how to do it or because they do not care to take the little time necessary to do it. Hence this discussion.

With sample No. 1 we tried to duplicate the condition found in many drug stores. The solution was kept in a pint, colorless bottle in the laboratory and opened from time to time to remove some of the solution. You will note that this solution lost 31 percent from December to February. In the case of samples Nos. 2 and 3, kept in 1-oz. full bottles sealed with sealing wax and paraffin and stored in the basement, you will note that from December to May these solutions lost but 4.4 percent. Samples Nos. 4, 5 and 6 were kept under similar conditions to those of samples Nos. 2 and 3, except that the bottles were one-half full. You will note that these samples lost from 9 to 12 percent in a little over a month. In the case of the rest of the samples, we attempted to determine whether this solution would keep better if made with stronger alcohol. It has been claimed that the small amount of water in U. S. P. alcohol causes hydrolysis and therefore more rapid decomposition of this product. The results of our experiments do not seem to bear this out. However, we have not done sufficient work with this to feel sure that we are right.

In conclusion, I would say that this solution will keep very well if put up into 1-oz. or 2-oz. bottles, the bottles filled and sealed with sealing wax or paraffin and stored in a dark, cool place. Many druggists think that this is too much work. This is a very wrong idea. I think that, if you try it, you will find that,