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A PHARMACEUTICAL STUDY OF ACETYLSALICYLIC ACID.

BY HARRIET V. SNIDOW AND H. A. LANGENHAN.

No. 1 Historical.

Gerhard[1] is given credit for having been the first to prepare acetylsalicylic acid, using acetyl chloride and sodium salicylate as the reacting ingredients. He applied the name *Wasserfreie Salicylsæure Essigsæure* (anhydrous salicylic acetic acid), being of the opinion that the compound was the anhydride of the two acids. In 1859 von Gilm[2] reported the discovery of a crystalline substance obtained from chloracetyl and salicylic acid, which he called *acetylierte Salicylsæure*(acetylized salicylic acid). Kraut[3] in 1869, determined the constitution of the chemical and named it *Acetylosalisæure* (Acetylsalicylic acid).

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[1] *Liebig's annal. d. chem.*, v. 87, p. 162 (1853); (*Annal. de. chim. et de physique*, v. 7 (series 3), p. 326 (1853); *Pract. Drug.*, v. 30 (Dec, 1912), p. 23.

[2] *Annal. d. chem.*, v. 112, p. 180 (1859).

[3] *Ibid.*, v. 150, p. 9 (1896).

In 1898 Newton[1] obtained an English patent for this preparation and the same year Hoffman obtained the following U. S. patent[2] No. 644,077.

"Acetylsalicylic acid. Felix Hoffman, Elberfeld, Germany, Assignor to the Farbenfabriken of Elberfeld Co. of N. Y., filed August 1, 1898. Serial No. 687, 385.

"In the *Annalen der Chemie und Pharmacie*, Vol. 150, pages 11 and 12, Kraut has described that he obtained by the action of acetyl chloride on salicylic acid a body which he thought to be acetylsalicylic acid. I have found that on heating salicylic acid with acetic anhydride a body is obtained the properties of which are perfectly different from those of the body described by Kraut. According to my researches the body obtained by means of my new process is undoubtedly the real acetylsalicylic acid.

$$C_6H_4\begin{cases}OCO.CH_3\\COOH\end{cases}$$

Therefore the compound described by Kraut cannot be the real acetylsalicylic acid, but is another compound. In the following, I point out specifically the principal differences between my new compound and the body described by Kraut.

"If a Kraut product is boiled even for a long while with water (according to Kraut's statement) acetic acid is not produced, while my new body when boiled with water is readily split up, acetic and salicylic acid being produced. The watery solution of the Kraut body shows the same behavior on the addition of a small body of ferric chloride as a watery solution of salicylic acid when mixed with a small quantity of ferric chloride, that is to say, it assumes a violet color. If a melted test of the Kraut body is allowed to cool, it begins to solidify (according to Kraut's statement), at from 118 degrees to 188.5 degrees centigrade, while a melted test portion of my product solidifies at about 70 degrees centigrade. The melting points of the two compounds cannot be compared, because Kraut does not give the melting point of his compound. It follows from details that the two compounds are absolutely different.

"In producing my compound I can proceed as follows (without limiting myself to the particulars given): A mixture prepared from 50 parts of salicylic acid and 75 parts of acetic anhydride is heated for about two hours at 150 degrees centigrade in a vessel provided with a reflux condenser. Thus a clear liquid is obtained, from which on cooling a crystalline mass is separated which is acetylsalicylic acid. It is freed from the acetic anhydride by pressing and then recrystallized from dry chloroform. The acid is thus obtained in the shape of glittering white needles melting at about 130 degrees centigrade, which are easily soluble in benzene, alcohol, glacial acetic acid, and chloroform, but difficultly soluble in cold water. It has the formula

$$C_6H_4\begin{cases}OCOCH_3\\COOH\end{cases}$$

and exhibits therapeutical properties.

"Having now described my invention and in what manner the same is to be performed, what I claim as new, and desire to secure by Letters Patent, is

$$C_6H_4\begin{cases}O.COCH_3\\COOH\end{cases}$$

being when crystallized from the dry chloroform in the shape of white glittering needles, easily soluble in benzine, alcohol and glacial acetic acid, difficultly soluble in cold water, being split by hot water into acetic acid and salicylic acid, melting at about 135 degrees centigrade subsequently as herein described."

"No. 32, 805. Antirheumatic—Farben fabriken of Elberfeld Co., New York, N. Y. Filed April 3, 1899."

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[1] *Pract. Drug.*, Vol. 30 (Dec., 1912). p. 23.

[2] "N. N. R." (1911), p. 38.

ASPIRIN.

"Essential feature, the word Aspirin used since February 1, 1899."

The substance under its trade name Aspirin was widely advertised and within a few years its use became so common that it might be classified with "household remedies." Its popular use in most civilized countries led to its introduction into the national Pharmacopœias. The following list represents a chronological arrangement of Pharmacopœial titles and synonyms obtained from texts available:

1907 *Pharmacopœa Helvetica.*
Acidum acetylosaliçylicum
Acetylsalicyl sæure
Acide acetylsalicylique
Acido acetilosalicilico

1907 *Pharmacopœa Danica*
Acidum Acetylo-salicylicum
Acetylsalicylsyre

1907 *Pharmacopœa Japonnica.*
Acidum Acetsalicylicum
Acetylsalicylic Acid

1908 *Pharmacopœa Française.*
Acetylalicylique (acide)[1]
Acidum Acetylsalicylicum
[1] Aspirine (Marque deposée)

1908 *Pharmacopœa Svecica.*
Acidum acetylo-salicylicum
Acetylsalicylsyra

1908 *Pharmacopœa Hungarica.*
Acidum acetylsalicum
(Through N. N. R.)

1910 *Pharmacopœa Germanica.*
Acidum acetylosalicylicum
Acetylsalicylsæure
Aspirin

1912 *Pharmacopœa Belgica.*
Acidum acetylsalicylicum
Acide acetylsalicylique
Aspirine

1913 *Pharmacopœa Norvegica.*
Acidum acetylo-salicylicum
Acetylsalicylsyre

1914 *Pharmacopœa Britannica.*
Acidum Acetylsalicylicum
Acetylsalicylic Acid

1920 *Pharmacopœa Italiana*
Acido acetilsalicilico
Acidum acæthylosalicylicum

Whereas the foreign Pharmacopœias have already introduced acetylsalicylic acid. The U. S. P. 1910 does not contain it. During the last decade comments have appeared in the literature relative to its introduction (see Baumgarten,[1] Bissell,[2] Raubenheimer;[3] Remington[4] and others), and in 1923[5] a portion of the proposed text for the U. S. P. X contained this compound under the Latin title *Acidum Acetylsalicylicum*—Syn. Aspirin.

The popular use of acetylsalicylic acid naturally led to its introduction on the market under many trade names a few of which are here appended.

Acetosal.—"Acetylsalicylic Acid," *Jour. Soc. Chem. Ind.*, 1914, p. 1028.
Acetosalic acid.—"Acetylsalicylic acid," "B. P. C." (1923).
Acetosalin.—"Acetylsalicylic acid," "B. P. C." (1923).
Acet-salicyl.—"Former name for acetylsalicylic acid," *Merck's Report* (1916).
Acetyline.—"Name given to tablets of A. S. A.," *Pharm. Weekblad.* (1914), p. 578 (through Y. B.).
Acidum Salaceticum.—"B. P. C." synonym for acetylsalicylic acid.
Acyline.—"Acetylsalicylic acid," *Pharm. Ztg.* (1920), p. 542.
Acylosal.—"Trade name, Gehe and Co.," *Arch. d. Pharm.*, p. 423 (1924),
Aletodin.—"Acetylsalicylic acid," *Pract. Drug.*, Dec. 30, p. 23 (1912).

[1] *West Drug.*, Vol. 32, p. 16 (1910).
[2] "Proc. N. Y. Ph. A.," p. 91 (1911).
[3] "Dig. of Com., U. S. P. and N. F." (1911).
[4] "Proc. W. Va. Ph. A.," p. 89 (1914).
[5] Jour. A. Ph. A., Vol. 12, p. 1102 (1923).

Anglopyrin.—"An acetylsalicylic acid," "Y. B." (1916).

Atonin.—"A trade name for acetylsalicylic acid," *Chem. & Drug.* (1915), p. 162 (Dig. of Com.).

Aspirin.—"Acetylsalicylic acid," *Merck's archives* (1900), p. 13.

Asposal.—"An acetylsalicylic acid," "Y. B." (1916).

Astrophyrin.—"Name for acetylsalicylic acid," *Pharm. Weekblad,* (1919), p. 153.

Coxpyrin.—"Trade name for acetylsalicylic acid," *Chem. & Drug.* (1915) (Dig. of Com.).

Empirin.—"Acetylosalicylic acid," B. W. & Co., trade list.

Entosal.—"Name for acetylsalicylic acid," *Chem. & Drug.* (1919), p. 627.

Genaspirin.—"A safe brand of aspirin," *Chem. & Drug.,* (1923), p. 8.

Helicon.—"Trade name for acetylsalicylic acid," *Chem. & Drug.* (1915), p. 162 (Dig. of Com.).

Isospirin.—"Trade name for acetylsalicylic acid," *Pharm. Zentr.* (1921), p. 487.

Nupirin.—"Trade name for acetylsalicylic acid," *Chem. & Drug.* (1915), p. 162 (Dig. of Com.).

Regepyrin.—"Trade name for acetylsalicylic acid," *Chem. & Drug.* (1915), p. 162 (Dig. of Com.).

Rhodine.—"Copyright name of acetylsalicylic acid," *Pharm. Weekblad.,* 191 p. 80.

Salacetin.—"Acetylsalicylic acid," "B. P. C." (1923).

Salacetol.—"Trade name for acetylsalicylic," *Chem. & Drug* (1915), p. 162 ("Dig. of Com.).

Salaspin.—"An acetylsalicylic acid," Y. B. (1917).

Saletin.—"Acetylsalicylic acid," *Pract. Drug.,* Dec. 30, 1912, p. 23.

Salicyl-acetic acid.—"Acetylsalicylic acid," *Pract. Drug.* (Dec. 30, 1912), p. 23.

Spirol.—"Trade name for acetylsalicylic acid," *Chem. & Drug.* (1915), p. 449 (Dig. of Com.).

Xaxa.—"An acetylsalicylic acid, "*J. Soc. Chem. Ind.* (1914), p. 1034.

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THE PARAMECIAL METHOD FOR THE BIOLOGIC ASSAY OF THE DIGITALIS SERIES.*

(PRELIMINARY REPORT.)

BY ALBERT SCHNEIDER.

Species of Paramecium have been extensively employed in a great variety of biologic experimentations. Elsewhere the writer has described the use of *Paramecium caudatum* in determining the phenol coefficient of disinfectants. The same organism has also proven valuable for the purpose of determining the comparative toxicity of chemicals and of therapeutic agents, giving results which compare well with other biologic methods, as the frog and gold fish methods. For several years the writer has made use of this protozoan in the pharmacologic laboratory to demonstrate the mode of the diuretic action of the caffeine series.

The best culture medium for *Paramecium caudatum* (commonly known as the "slipper animalcule") is a rather weak infusion of dry alfalfa to which a small amount of thyroid extract is added. Quart Mason jars about half full of the liquid and tightly sealed, kept at a temperature of 20° to 22° C., will maintain fairly pure cultures for periods of weeks and even months. Hay infusion and horse manure

* Scientific Section, A. Ph. A., Buffalo meeting, 1924.