The Very Beginning
—genesis of a chemical agent

By Eugene J. McDevitt

One of the goals of research in chemistry is to explain how molecules react with one another to form new substances. Modern chemists attempt to justify these reactions on an atomic scale by speaking in terms of the breaking and forming of electron bonds between atoms. It is then often possible to generalize a type of reaction for many particular chemicals of the same classes. For example: Carboxylic acids react with alcohols to form esters and water.

To prove a reaction's mechanism, chemists will select known chemicals and predict how they will react by carefully controlling the circumstances of their interaction. In organic chemistry, it is the custom of the profession to title specific chemical reactions after the author who first examined and reported them.

In the 1920's two American chemists synthesized a series of new compounds whose formation was predictable based on a generalized reaction that had been first described by a German chemist in 1896.[1,2] They did so, not so much to ape the known procedure, but to provide themselves with a new series of compounds whose chemical structure was of interest to them. They carefully reported their results to the chemistry community where they would lay dormant for over 20 years. Here is their story and the strange result of their work.

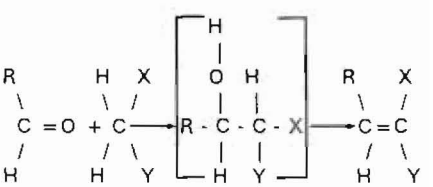
Ben B. Corson was born in Bridgeton, Maine, on August 12, 1896. After serving in the Army from 1917 to 1919, he received his academic training in chemistry at Harvard earning a BA in 1921, an MA in 1922, and a PhD in 1924. His doctoral work was under the supervision of Elmer P. Kohler. They co-authored an article in the August 1923 issue of the *Journal of the American Chemical Society* titled, "The Mechanism Underlying the Reaction Between Aldehydes or Ketones and Tautomeric Substances of the Keto-Enol Type."[3]

The article deals with a discussion of the several possible mechanisms for what is known as the Knoevenagel Reaction and offers chemical evidence justifying their explanation. The Knoevenagel Reaction is well known and is mentioned in just about every collegiate level organic chemistry text. Compendia such as *March* or *Organic Reactions* give detailed information as to the nature of the reaction and its numerous applications.

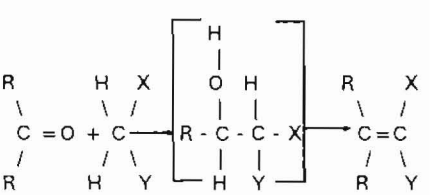
Heinrich Emil Albert Knoevenagel (1865-1921) was born in Hannover-Linden in Germany. He studied under Victor Meyer and received his PhD from the University of Goettingen. He then followed Victor Meyer to Heidelberg, working first as his assistant and finally succeeding him as professor of chemistry.

His reaction involves the condensation of an aldehyde or a ketone with a compound having an active methylene group, $-CH_2-$, whose activity is caused by the electron withdrawing nature of the other two groups attached to the methylene. This condensation can be shown by the following equations:

For aldehydes:



For ketones:



In these equations, the symbol R represents any carbon functionality such as methyl, ethyl, propyl, phenyl, and so forth, while X and Y are electron withdrawing groups such as CHO, COOR, CN, NO_2, and so forth.

Following his graduation, Corson began his teaching career at Middlebury College in Middlebury, Vermont, in 1924 as an instructor of

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chemistry. Middlebury was founded in 1800 and is a liberal arts college. In the 1920's Middlebury had a total of about 1,000 students. Its four-member chemistry department worked in their own chemistry building which had been erected in 1900.

Within one year, Corson was promoted to assistant professor. Early in 1928, he, along with Hazen and Thomas, continued the study of the mechanism of the Knoevenagel Reaction and offered their final experimental proof of a mechanism not requiring keto-enol tautomerism of the aldehyde or ketone.[5]

They explained that the first step of the reaction is the nucleophilic attack of the carbanion of the active hydrogen compound (the methylene grouping) on the carbon of the carbonyl group of the aldehyde or ketone. This reaction would create an unstable intermediate alcoholic compound. This, in turn, loses a molecule of water to form the final product. The nature of the chemical bonding in the electron withdrawing groups fosters the formation of what we refer to as a double bond between the carbon of the aldehyde/ketone and the methylene carbon.

Later in 1928 Corson co-authored a paper with Roger W. Stoughton titled, "Reactions of Alpha, Beta-Unsaturated Dinitriles."[6] Stoughton had received his BA from Middlebury in 1927 and worked with Corson in 1927 and 1928. Their paper moves on beyond the possible question of the mechanism of the Knoevenagel Reaction to the use of the reaction to form a series of compounds called substituted unsaturated malonodinitriles. Malononitrile's formula is $H_2C(CN)_2$ and one can see that it is a compound with an activated methylene group. By reacting malononitrile with various aldehydes, they would create substituted dinitriles. Molecules that include a double bond, C=C, are called unsaturated and show unique chemical properties. The Greek prefixes, alpha and beta, are indicators to chemists that the unsaturation exists between the first and second carbon of the malonodinitrile.

Corson and Stoughton describe their process for creating the different malonodinitriles starting with ten different aldehydes. Their procedure is quite clear and has been used by several chemists since they first reported it.

Dinitriles. *"Preparation.-Equivalent quantities of aldehyde and malononitrile were dissolved in a suitable solvent and a few drops of piperidine added with shaking. The solution warmed up somewhat and became more or less reddish. Within fifteen minutes the mixture was solid with crystalline condensation product. It is advisable to carry out the reaction in an open beaker in order to facilitate removal of the solid. These condensations can be run without solvent, but the products are apt to be dark colored. Solvent is desirable."*

They will, in the major portion of their paper, subject some of these new compounds to a series of reactions to examine their unsaturated nature. In tables IA and IB [of their paper]they describe the ten new dinitriles that they synthesized and characterized. They include in the tables usual information giving reaction solvent, crystallizing solvent, color, melting point, percent yield, some elemental analysis data, and, uniquely, a listing titled physiological action. For seven of the entries, the physiological action is listed as none, but for the other three, different entries are given:

I, benzalmalononitrile, sneeze and tear;

XVIII,m-nitrobenzalmalononitrile, sneeze;

XX, o-chlorobenzalmalononitrile, sneeze and skin irritant.

(In chemical literature, compounds are given Roman numerals in the order in which they occur in the article.)

In a special paragraph, they warn the reader of the unusual physiological properties of the three mentioned above.

"Physiological Properties.-Certain of these dinitriles have the effect of sneeze and tear gases. They are harmless when wet but to handle the dry powder is diastrous (sic). When crystallizing m-nitrobenzalmalononitrile, for instance, the alcohol solution should not be boiled very much since the alcohol vapor has a peppery sting. In sneezing caused by m-nitrobenzal- malononitrile (XVIII) the mucous discharge from the nose becomes bright yellow on exposure to air. In sneezing caused by o-chlorobenzalmalononitrile (XX) the face smarts, especially if damp. The smarting is intensified by washing. Most of the discomfort can be avoided if a gas mask is worn whenever dry solid is handled. However, the majority of the dinitriles reported in this paper have no irritant effect..."

The abstract of their article in *Chemical Abstracts* also clearly states the unusual physiological effects of the three new compounds.[7]

Roger Stoughton continued his education at the University of Illinois, receiving his doctorate working for Roger Adams, a giant in the field of

synthetic organic chemistry. Roger Adams had worked under Elmer P. Kohler at Harvard as had Ben B. Corson. Stoughton's work at Illinois had no connection with his earlier work at Middlebury. He served as a research associate in the Department of Pharmacy at Vanderbilt University and finally worked for the Mallinckrodt Corporation. All of his later work dealt with compounds of pharmacological interest. He published about 25 papers during his career in chemistry. He died a young man in St. Louis in 1957.

Ben B. Corson continued at Middlebury for several more years, being promoted to associate professor in 1929, but his reported research showed interests in different areas of chemistry. He was very active in the work of developing and checking procedures for the synthesis of organic compounds to be reported in *Organic Synthesis*. By the way, one on which he worked was the synthesis of malononitrile. In 1931 he moved to the Universal Oil Products Company, and then in 1939 to the Mellon Institute, where a majority of his work dealt with the chemistry of fuels. He authored or co-authored over 100 articles in chemistry. He died at Ventura, California, in 1987.

Corson's and Stoughton's article on dinitriles has been cited by many chemists seeking to synthesize similar compounds, but none seem too eager to repeat their work on compound XX, o-chlorobenzylidine malononitrile, or (2-chlorophenyl) methylene propanedinitrile as it is currently named. An article published in 1949[8] repeats and expands most of the work of Corson and Stoughton but misses, either accidently or purposefully, any mention of the formation of the irritant compound. The first article that specifically mentions o-chlorobenzylidine malononitrile is in *Cancer Research*.[9] This article deals with the measurement of possible activity of a large number of different malononitriles on tumors. o-Chlorobenzylidine malononitrile showed no unique activities.

The table below shows the number of times o-chlorobenzalmalononitrile has been mentioned in the chemical literature since Corson and Stoughton first reported it.

Years of Listing	Number of Entries
1927-1936	1*
1937-1946	0
1947-1956	2
1957-1966	9
1967-1976	80
1977-1986	88
1987-1993	48

* Corson and Stoughton's article

In our moments of idealism, most of us chemists imagine and hope that some day we will make a discovery that will aid humankind.

Corson's work in fuels was to seek to provide the world with a better source of energy for civilization. Stoughton's work in pharmacology was a direct effort to reduce the suffering in the world. Neither Corson nor Stoughton would have ever imagined that the minor, unimportant, nonuseful compound that causes sneezing and skin irritation that they had prepared early in their careers in chemistry would be produced by the thousands of tons for use in Vietnam, by police forces for riot control, and would be known worldwide by the combined first initials of their last names, CS.

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Notes

[1]Knoevenagel, Chem. Ber., 27, 2346 (1894).

[2]Knoevenagel, Chem. Ber., 29, 172 (1896).

[3]Corson and Kohler, Journal of the American Chemical Society, 45, 1974 (1923).

[4]Editor, Zeit. Angew. Chem., 35, 29 (1922)

[5]Corson, Hazen, and Kohler, Journal of the American Chemical Society, 50, 913 (1928).

[6]Corson and Stoughton, Journal of the American Chemical Society, 50, 2825 (1928).

[7]Chemical Abstracts 22:4514 (1928).

[8]Sturz and Noller, Journal of the American Chemical Society, 71, 2949 (1949)

[9]Can. Res. 12, 565-72 (1952).

Eugene J. McDevitt received his BS and MS from St. Bonaventure University. As an ROTC graduate he served for two years in Material Command at Edgewood Arsenal, Maryland. Following his military service, he was employed as an organic chemist in the Test Division of the Chemical Research and Development Labs. He has taught at Siena College since 1960. He has taken many courses and done research at Rensselaer Polytechnic Institute. His goal is to continue the story of the development of CS from its discovery to its current usage.