UNITED STATES PATENT OFFICE.

OTTO WOLFES, OF DARMSTADT, GERMANY, ASSIGNOR TO THE FIRM OF E. MERCK, OF DARMSTADT, GERMANY.

PROCESS OF MAKING BARBITURIC ACIDS.

No. 814,496. Specification of Letters Patent. **Patented March 6, 1906.**

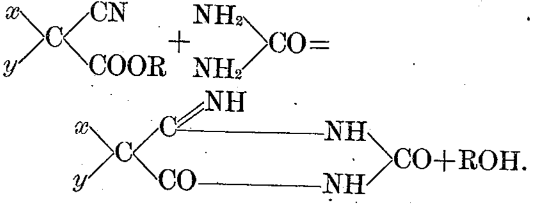
Application filed November 8, 1904. Serial No. 231,873.

To all whom it may concern:

Be it known that I, OTTO WOLFES, doctor of philosophy, a subject of the German Emperor, residing at the city of Darmstadt, in the Empire of Germany, have invented certain new and useful Improvements in the Process of Manufacturing Barbituric Acids, of which the following is a description.

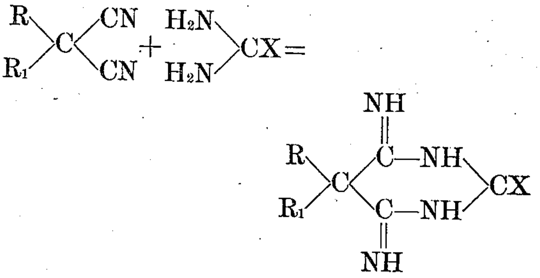
My invention relates to the manufacture of barbituric acids; and it consists of certain novel processes particularly pointed out in the concluding claims.

From experiments made by Traube, Conrad, and myself it is known that cyanacetic ester and its substitution products may be condensed with urea, guanidin, and similar bodies to derivates of pyrimidin, one amid of the urea, &c., combining with the cyanogen group of the ester, while the carboxethyl in separating alcohol participates with the second amid of the ring formation. The process is represented by the following equation:



It has been discovered by me that compounds with two cyanogen groups—as, for instance, the malonitrile—may be condensed with urea and with compounds constituted in an analogous way—as, for example, guanidin and the derivatives and homologues of urea and guanidin—if condensing means (viz., alkali metals, their amids, or alcoholates) are employed; but even without the employment of such condensing means the combination is successful if the bodies are permitted to act on each other for a prolonged time at a high temperature or under pressure.

My process as outlined above and embodied in various forms in the following examples may be expressed by the following formula:



In the above formula R and R_1 indicate hydrogen atoms or simple alkyl radicals, and X indicates a bivalent body, such as oxygen and imino, (NH radical.) The bodies obtained in this way may be easily converted into the corresponding barbituric acids by an agent separating ammonia. Such agent may be sulfuric acid, hydrochloric acid, or nitric acid or even alkalis. (the latter, however, being less suitable.)

I will now describe the manner in which I at present prefer to practice my invention, giving, by way of illustration, a number of examples thereof; but it will be understood that various modifications and changes, both as to materials and treatment, may be made without departing from the spirit of my invention and without exceeding the scope of my claims.

First example: A solution of 9.6 kilograms guanidinhydrochlorate (one molecule) in alcohol is mixed with a solution of 2.3 kilograms sodium (one molecule) in fifty liters of alcohol, the separated chlorid of sodium drawn off, and the solution of the free guanidin then heated with 12.2 kilograms (one molecule) diethylmalonitrile for five hours to 100° centigrade. After being cooled off the reactionary mass, fine colorless needles, is drawn off and carefully washed with alcohol. The new product contains alcohol of crystallization and melts at 240° centigrade while foaming up. It is dissolved easily in water and in diluted acids even in the cold. In cold alcohol it can be dissolved only with difficulty. This triiminodiethyl-barbituric acid (diiminodiethylmalonyl-guanidin) is converted smoothly into diethylbarbituric acid by being heated for three hours to 120° centigrade with diluted hydrochloric acid in a closed receptacle. When cooled off, the product congeals to a crystalline mass. Separate from the mother-liquor, wash with water, and again crystallize from hot water. The thus-purified substance melts at 191° centigrade and has all the properties of the known diethylbarbituric acid.

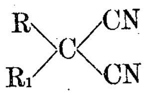
Second example: 12.2 kilograms diethylmalonicacidnitrile are heated with six kilograms urea and 2.3 kilograms sodium in fifty liters of absolute alcohol for four hours in an autoclave to 100° centigrade. After adding six liters of glacial acetic acid the alcohol is evaporated. The residue is heated for an hour with about one hundred liters of water and is then left standing over night. After being dissolved in two molecules of warm diluted hydrochloric acid and being precipitated with ammonia the base crystallizes in tufted aggregates of crystal. It is a 5-diethyl-2 oxy-4, 6-diiminopyrimidin. It melts, while developing basic vapors, at about 272°, (277° corr.) The chlorid is dissolved with more difficulty in water than the sulfate or nitrate. In alkalis the base is soluble, but not in ammonia. From hot water it may be crystallized over again. If boiled with five times the amount of thirty per cent. sulfuric acid, it is converted also into diethylbarbituric acid. The purifying and isolating is done as in the first example.

Third example: 9.4 kilograms monoethylmalonitrile are heated for five hours with an equivalent amount of guanidin in alcoholic solution in an autoclave to 100° centigrade. Lustrous small leaves are separated containing alcohol of crystallization. After being crystallized over again from alcohol and being dried at 100° centigrade they melt at 189°, (190° corr.) They can be easily dissolved in cold water and hot alcohol. If this compound is heated for several hours in a closed vessel with diluted hydrochloric acid (1:3) to 120°, it is converted into the monoethylbarbituric acid. This acid melts at 194° corr., (Conrad and Guthzeit giving 190° corr.) It reacts and tastes rather strongly acid just as the barbituric acid itself. It differs thereby distinctly from the diethylbarbituric acid, which tastes bitter and possesses a reaction which is acid only to a very small degree.

Fourth example: 6.6 kilograms malonitrile are heated to 100° centigrade for one hour in an autoclave with an equivalent amount of guanidin prepared from 9.6 kilograms hydrochlorate and 2.3 kilograms sodium in eighty liters of alcohol. When cooled off, colorless small needles are separated, the amount of which needles is about 6.5 kilograms when dried. The melting-point of this triiminobarbituric acid is 248°, (corr. 252°.) The base forms with diluted cold mineral acid salts, which are dissolved only with difficulty. With nitrate of sodium and glacial acetic acid a light violet nitroso body is formed at once. It has a remarkable resistance against warm strong sulfuric acid or boiling sodium hydroxid. By prolonged and highly heating it with acids barbituric acid is obtained therefrom.

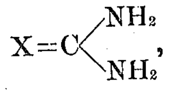
Having thus fully described my invention, what I claim, and desire to secure by Letters Patent, is—

1. The process of manufacturing a barbituric acid consisting in the condensation of a malonitrile of the general formula



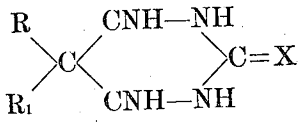
$$\begin{matrix}R\\R_1\end{matrix}>C<\begin{matrix}CN\\CN\end{matrix}$$

with a substance having the general formula



$$X=C<\begin{matrix}NH_2\\NH_2\end{matrix},$$

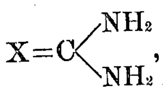
whereby a 4.6 diimino-pyrimidin of the general formula



$$\begin{matrix}R\\R_1\end{matrix}>C<\begin{matrix}CNH-NH\\CNH-NH\end{matrix}>C=X$$

is produced, the latter being subsequently converted by saponification into a 4-6-dioxypyrimidin.

2. The process of manufacturing a barbituric acid consisting in condensing a malonitrile with a substance of the general formula



$$X=C<\begin{matrix}NH_2\\NH_2\end{matrix},$$

and converting the iminobarbituric acid thus formed into barbituric acid by saponification.

3. The process consisting in condensing diethylmalonitrile with guanidin with the aid of sodium alcoholate, and subsequently saponifying to produce barbituric acid.

In testimony whereof I have signed my name to this specification in the presence of two subscribing witnesses.

OTTO WOLFES.

Witnesses:
MAX CONRAD,
WALTER HOUSING.