UNITED STATES PATENT OFFICE.

CARL HARRIES, OF BERLIN, GERMANY, ASSIGNOR TO CHEMISCHE FABRIK AUF ACTIEN, VORM. E. SCHERING, OF BERLIN, GERMANY.

ACIDYL DERIVATIVE OF UNSYMMETRICAL ACETONALKAMINS AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 692,656, dated February 4, 1902.

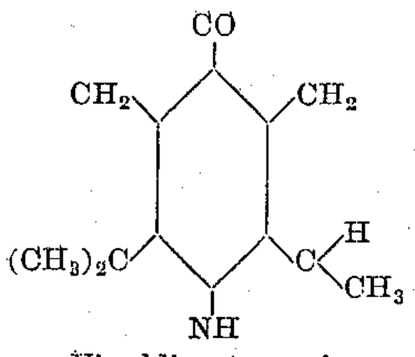
Application filed December 11, 1897. Serial No. 661,513. (No specimens.)

To all whom it may concern:

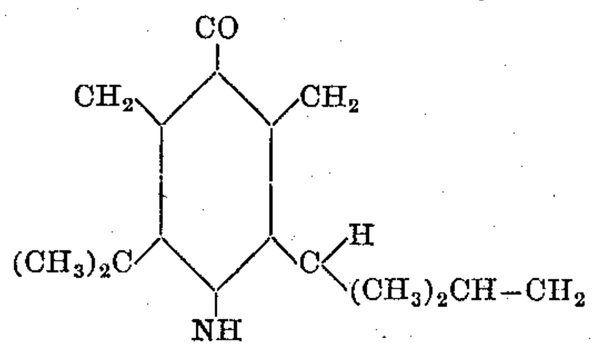
Be it known that I, CARL HARRIES, of Berlin, in the Empire of Germany, have invented certain new and useful Improvements in the Manufacture of Isomeric Unsymmetrical Cyclical Acetonalkamins and Acidyl Derivatives from the Stable Modifications of the Unsymmetrical Acetonalkamins, (for which patents have been obtained in Germany, Nos. 95,621 and 95,622, dated May 10, 1896, and in Great Britain, No. 20,697 of 1897,) of which the following is a specification.

The present invention relates to the production of acidyl derivatives from stable modifications of the unsymmetrical cyclical acetonalkamins, which acidyl derivatives possess anesthetic properties, so that the same may be advantageously used as anesthetics, similarly to cocain.

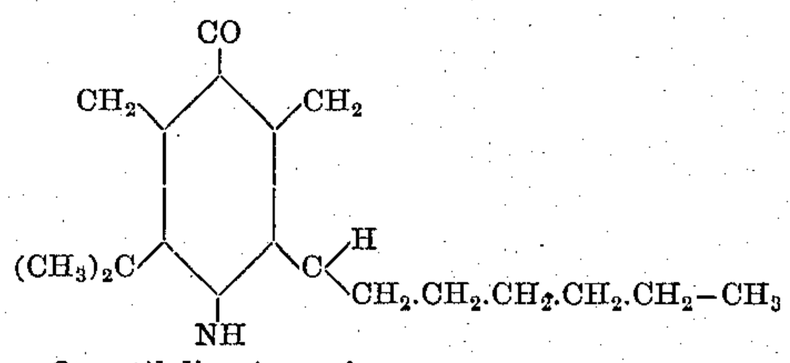
I have discovered that by reducing the unsymmetrical bases of the triacetonamin series—as, for example, vinyldiacetonamin, valeryldiacetonamin, oenanthdiacetonamin, benzylidenediacetonamin, piperonylenediacetonamin:



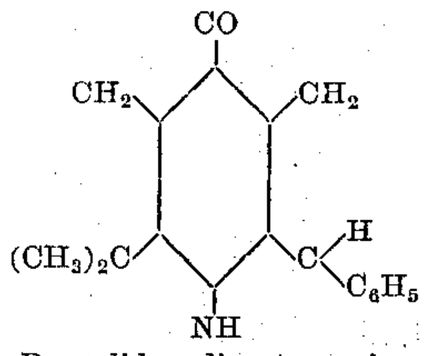
Vinyldiacetonamin.



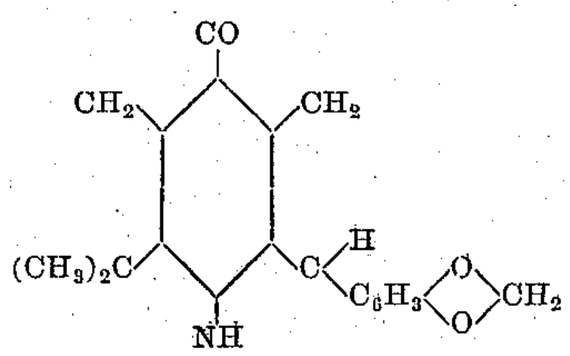
Valeryldiacetonamin.



Oenanthdiacetonamin.

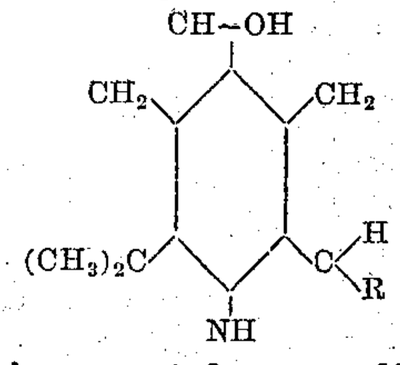


Benzylidenediacetonamin.



Piperonylenediacetonamin.

as well as generally the analogously-constituted unsymmetrical acetonamin bases, which contain other aliphatic or aromatic radicals joined to the alpha-asymmetrical carbon, a mixture of two isomeric alkamins is produced, one of which represents the stable, the other the unstable, modification. The constitution of the stable and unstable alkamins corresponds to the general chemical formula:



in which R is meant for an aliphatic or aromatic radical. The isomery of the said unsymmetrical alkamins is a stereo-isomery similar to that of tropin and pseudo-tropin, and therefore the true structure cannot be expressed by a written formula.

The isomeric unsymmetrical acetonalkamins can be separated from the mixture obtained by the reduction of the corresponding acetonamin bases by crystallizing this mixture or a salt therefrom—for instance, the hydrochloric-acid salt. Further, I have found that the unstable modifications may be transformed into the stable ones by treating the unstable forms with alkylates—for example, with sodium amylate. The stable modifications are likewise produced if the mixture of the acetonalkamin bases resulting from the reduction of the corresponding amin bases be

treated with sodium amylate. The following examples more clearly explain this:

(*A*) *Production and Separation of the Isomeric Unsymmetrical Acetonalkamin Bases.*

1. Isomeric vinyldiacetonalkamins—(*a*) *In acid solution.*—Fifty grams of vinyldiacetonamin are dissolved in five hundred grams of water and gradually mixed with one kilogram of sodium amalgam. The reduction liquor is kept slightly acid by addition of dilute sulfuric acid, and is kept also at a temperature of about 35° to 40° centigrade. When all has been added, it is made alkaline and the product of reduction extracted with about one kilogram of warm ether, if necessary, under pressure. The ether is afterward distilled off to one-half and the solution then left to crystallize. Needles then crystallize out, which, crystallized out of benzene, melt at 161° to 162° centigrade. This body, hitherto unknown, represents the unstable form of vinyldiacetonalkamin. In the ethereal filtrate there is found a body which after crystallizing out of benzene melts at about 121° to 122° centigrade. It is identical with the vinyldiacetonalkamin obtained by Fischer (see *Berichte der Deutschen Chemischen Gesellschaft*, XVII, page 1794) and appears to be a uniform combination of the unstable vinyldiacetonalkamin, melting at 161° to 162°, and the true stable vinyldiacetonalkamin, which melts at 138° and which is produced, according to the specification of Georg Merling and Albrecht Schmidt, Serial No. 607,110, filed September 26, 1896, by crystallizing the hydrochloric-acid salt of the said Fischer's base.

(*b*) *Reduction in neutral solution.*—Fifty grams of vinyldiacetonamin are dissolved in one kilogram of ether and reduced with two hundred and fifty grams of aluminium amalgam without cooling, a little water being gradually added. After completion of the reduction it is filtered and the bases are separated by crystallization, as stated before.

2. Isomeric valeryldiacetonalkamins.—Example: Fifty grams valeryldiacetonamin are dissolved in fifty grams of water and gradually mixed with about one kilogram of two and one-half per cent. sodium amalgam. The reduction liquor is constantly kept slightly acid by addition of dilute sulfuric acid and its temperature at about 35° to 40°. The product of the reduction is made alkaline, shaken with ether, and the ethereal solution dried with potash and evaporated. The separation of the bases is here preferably performed by crystallization out of petroleum ether. To the residuum is added twice its weight of petroleum ether and is kept cool. After some time the unstable valeryldiacetonalkamin crystallizes out, which after repeated recrystallizations melts at 93° to 94° centigrade. The stable modification of the alkamin is contained in the filtrate and has in a pure state a melting-point of 80° to 82° centigrade.

3. Isomeric benzylidenediacetonalkamins.—By reducing benzylidenediacetonamin in the manner above described two isomeric benzylidenediacetonalkamins are also obtained. On long standing, after reduction is complete, a salt separates out. If this be mixed with caustic-soda solution, a base is obtained which after recrystallization out of petroleum ether melts at about 68° and must be looked upon as the unstable modification. In the filtrate of the difficultly-soluble salt there is found the salt of an oily base which has hitherto not been obtained in a crystalline form.

4. Isomeric piperonylenediacetonalkamins.—If piperonylenediacetonamin be reduced in the manner above described, an alkamin is obtained by crystallization out of petroleum ether, which represents the unstable form and possesses a melting-point of 108° to 109° centigrade. The stable modification is found in the filtrate as an oily body.

5. Isomeric oenanthdiacetonalkamins.—In the same way the production and separation of the two isomeric oenanthdiacetonalkamins are brought about. The unstable modification melts at about 77° to 79° centigrade. The stable form is an oily body.

The isomeric unsymmetrical acetonalkamin bases can further be produced in the manner as stated in the specification of Georg Merling and Albrecht Schmidt, Serial No. 607,110, for the two vinyldiacetonalkamins—that is to say, by crystallizing a salt of the mixture of acetonalkamins obtained by the reduction of the corresponding acetonamin bases.

(*B*) *Transformation of the Unstable Acetonalkamins into the Stable Modifications by Means of Alkylates.*

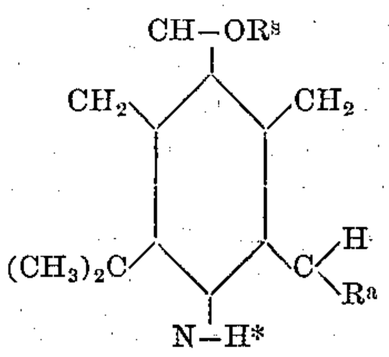
Example — Vinyldiacetonalkamin. — The transformation may be brought about with, for instance, sodium amylate in a similar way to that given by Willstätter for the transformation of tropin into pseudo-tropin. Two hundred grams of amyl alcohol and twenty grams of sodium are added to twenty grams of vinyldiacetonalkamin, melting at 161° to 162° centigrade, and boiled for about twenty hours. After mixing the product of reaction with dilute hydrochloric acid and shaking the hydrochloric-acid solution with ether an isomeric vinyldiacetonalkamin is precipitated out of the solution by means of potash. The isomeric vinyldiacetonalkamin melts after recrystallizing out of benzene at 138° centigrade. In the same way from the body melting at 121° to 122° centigrade (Fischer's base) a base melting at 138° centigrade is obtained by treating with sodium amylate. This base is identical with the base obtained from the vinyldiacetonalkamin melting at 161° to 162°.

The stable forms of the alkamins mentioned under 2, 3, 4, and 5 may also be produced in the manner described for the stable vinyldiacetonalkamin—viz., by treating the corresponding unstable modification or the mix-

ture of both alkamins obtained by the reduction of acetonamin bases with sodium amylate.

(*C*) *Production of Acidyl Derivatives from the Stable Modifications of the Unsymmetrical Acetonalkamins.*

Valuable alkaloids can be obtained if the hydrogen atom of the hydroxyl in the stable unsymmetrical acetonalkamins (in which for the present also their n-alkyl derivatives are included) is replaced by an acidyl group—as, for instance, the benzoyl group, (C_6H_5-CO,) the toluyl group, ($C_6H_4-CH_3-CO$,) the phenylacetyl group, ($C_6H_5-CH_2-CO$,) the cinnamyl group, ($C_6H_5-CH=CH-CO$.) The n-alkyl derivatives referred to may be produced in any suitable manner, preferably by treating the said alkamins with alkyl reagents, such as alkyl iodid, or in case n-metyl derivatives are desired by treating the said alkamin base with a watery solution of formaldehyde on a water-bath for about ten hours. The composition of the so-formed acidyl compounds answers the chemical formula:



in which formula R^s signifies an acidyl group, R^a an aliphatic or aromatic radical, and H* a hydrogen atom which can be replaced by an alkyl group.

The bases expressed by the before-mentioned formula are insoluble in water and decompose upon boiling with watery or alcoholic alkali into the respective stable alkamin base (non-alkylated or alkylated) and into a salt of that acid the radical of which has been substituted for the hydrogen atom of the hydroxyl. The bases combine with inorganic and organic acids, thus forming the corresponding salts, which possess anesthetic properties.

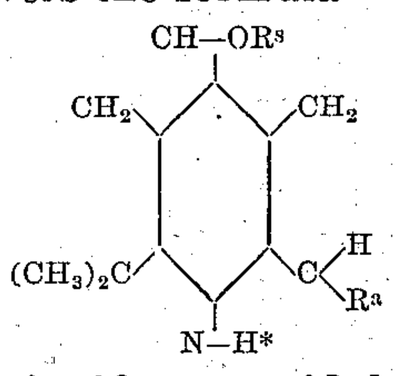
The acidyl derivatives from the stable vinyldiacetonalkamin, melting at 138° centigrade, are described in the specification of Georg Merling and Albrecht Schmidt, Serial No. 607,110, filed September 26, 1896. In a similar way to the acidyl derivatives from the vinyldiacetonalkamin, melting at 138°, the acidyl derivatives from the other analogously-constituted unsymmetrical acetonalkamins of the stable modifications are obtained.

Example—Benzoyl derivative from the stable valeryldiacetonalkamin.—The ethereal solution of the stable valeryldiacetonalkamin, which melts at 80° to 82° centigrade, is transformed into its hydrochloric-acid salt, and the salt, dried at 100° centigrade, is heated with benzoyl chlorid to about 130° centigrade. The melt is then dissolved in much water and shaken with ether to eliminate the unaltered benzoyl chlorid. The watery liquor is then made alkaline and shaken with ether. The oil remaining behind crystallizes out of petroleum ether in shining needles, which melt at 65° to 66° centigrade. The hydrochloric-acid salt is fairly difficultly soluble in water and crystallizes therefrom in compact crystals shining like glass. The benzoyl derivative from the stable oenanthdiacetonalkamin obtained in the same manner represents a yellow oil. The hydrochloric acid difficultly dissolves in water and crystallizes therefrom in glossy hygroscopic crystals. The benzoyl derivative from the stable benzylidenediacetonalkamin is likewise an oil. The benzoyl derivatives may, of course, also be produced by using benzoic anhydrid in place of benzoyl chlorid or by starting with the free bases instead of using the hydrochlorates. The toluyl, phenylacetyl, and cinnamyl derivatives are obtained in an analogous manner. The toluyl-benzylidenediacetonalkamin is an oil gradually solidifying. It melts at about 78° to 80° centigrade. The toluyl derivatives from the stable valeryl and oenanth diacetonalkamin represent oils. The hydrochlorates are hygroscopic. The cinnamyl-benzylidenediacetonalkamin melts at from 118° to 119° centigrade. The corresponding derivatives from the valeryldiaceton, oenanthdiaceton, and piperonylenediaceton alkamin are oily bodies. The phenylacetyl derivatives from the stable acetonalkamins are likewise oily bodies. The alkylated acidyl derivatives from the stable unsymmetrical acetonalkamins also represent oils.

I wish it to be understood that I do not claim under this application the acidyl compounds of the vinyldiacetonalkamin melting at 138° centigrade and of its alkyl derivatives as new products or the method of production of such acidyl derivatives from the vinyldiacetonalkamin melting at 138°, which form the object of the application of Georg Merling and Albrecht Schmidt, Serial No. 607,110, filed September 26, 1896, but that subject to the above disclaimer.

What I claim is—

1. As new chemical products, acidyl compounds of the stable unsymmetrical acetonalkamins the composition of which compounds answers the formula



in which R^s signifies an acidyl group, R^a an aliphatic or aromatic radical and H* a hydrogen atom which can be replaced by an alkyl group; such compounds in the form of free bases are oily bodies, insoluble in water, decompose upon boiling with watery or alcoholic alkali into the respective alkamin base and a salt of that acid, the radical of which

was substituted for the hydrogen atom of the hydroxyl acids and combines with inorganic and organic acids to form the corresponding salts which have anesthetic properties.

2. The process of obtaining local anesthetics from the stable modifications of the unsymmetrical cyclical acetonalkamins, which consists in treating the unsymmetrical bases of the triacetonamin series with a suitable reducing agent, then heating the product thus obtained with an alkylate, thus producing the stable modifications of the unsymmetrical bases of the triacetonalkamins, and then substituting in these bases an acidyl group for the hydrogen atom of the hydroxyl, by treating them with an acidyl reagent preferably after transforming them into a salt, substantially as described.

3. In the process of obtaining local anesthetics reacting on the stable modifications of the unsymmetrial cyclical acetonalkamins, preferably after transforming them into a salt, with an acidyl reagent whereby the acidyl group is substituted for the hydrogen atom of the hydroxyl, substantially as described.

4. In the process of obtaining local anesthetics from the stable modifications of the unsymmetrical cyclical acetonalkamins, the production of the alkyl derivatives from the said bases by reacting thereon with alkyl reagents.

In testimony whereof I have hereunto set my hand this 26th day of November, 1897.

CARL HARRIES.

Witnesses:
HENRY HASPER,
WOLDEMAR HAUPT.