

UNITED STATES PATENT OFFICE.

CARL HARRIES, OF BERLIN, GERMANY, ASSIGNOR TO THE CHEMISCHE
FABRIK AUF ACTIEN, VORMALS E. SCHERING, OF SAME PLACE.

UNSTABLE ACETONALKAMINS AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 663,754, dated December 11, 1900.

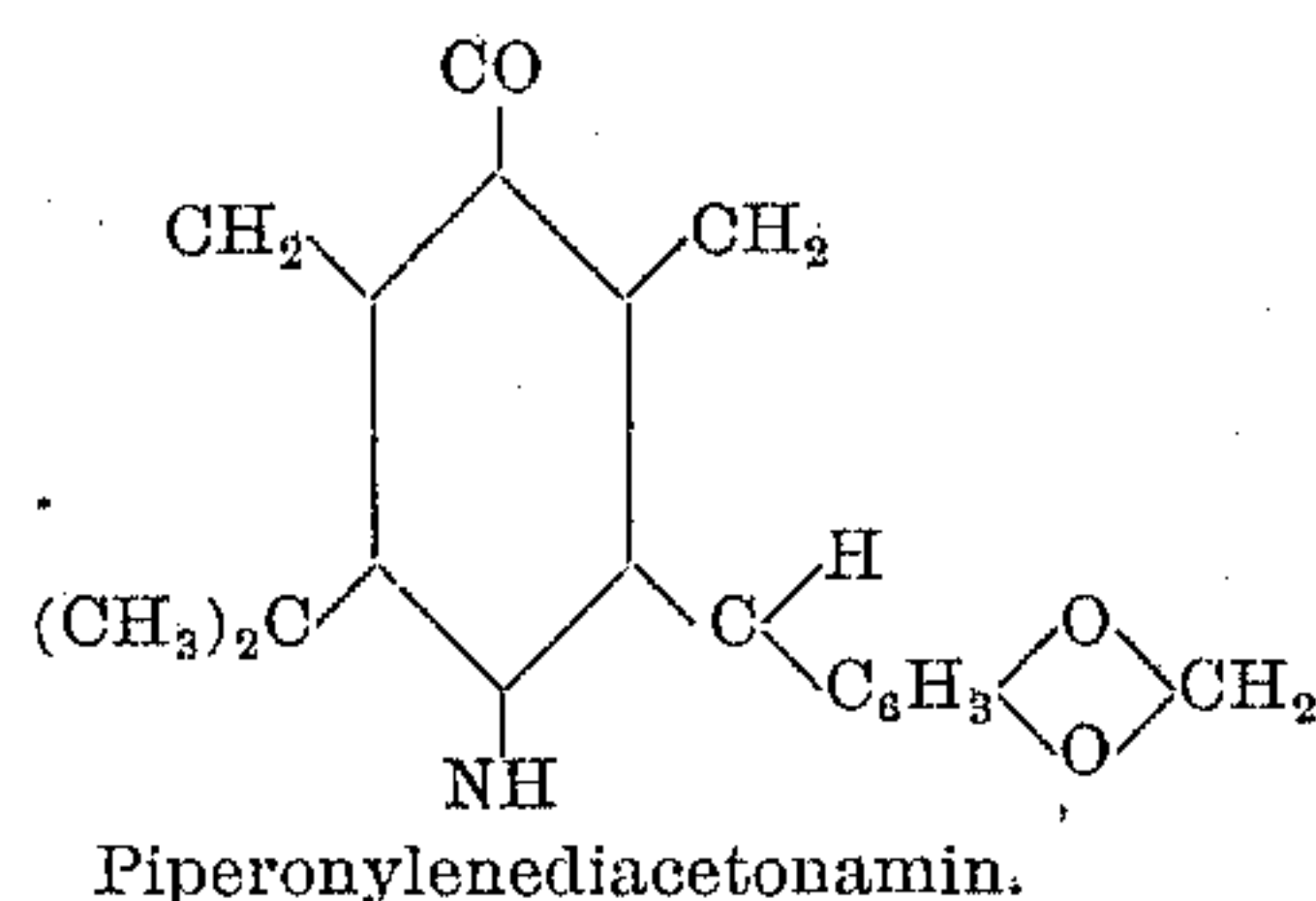
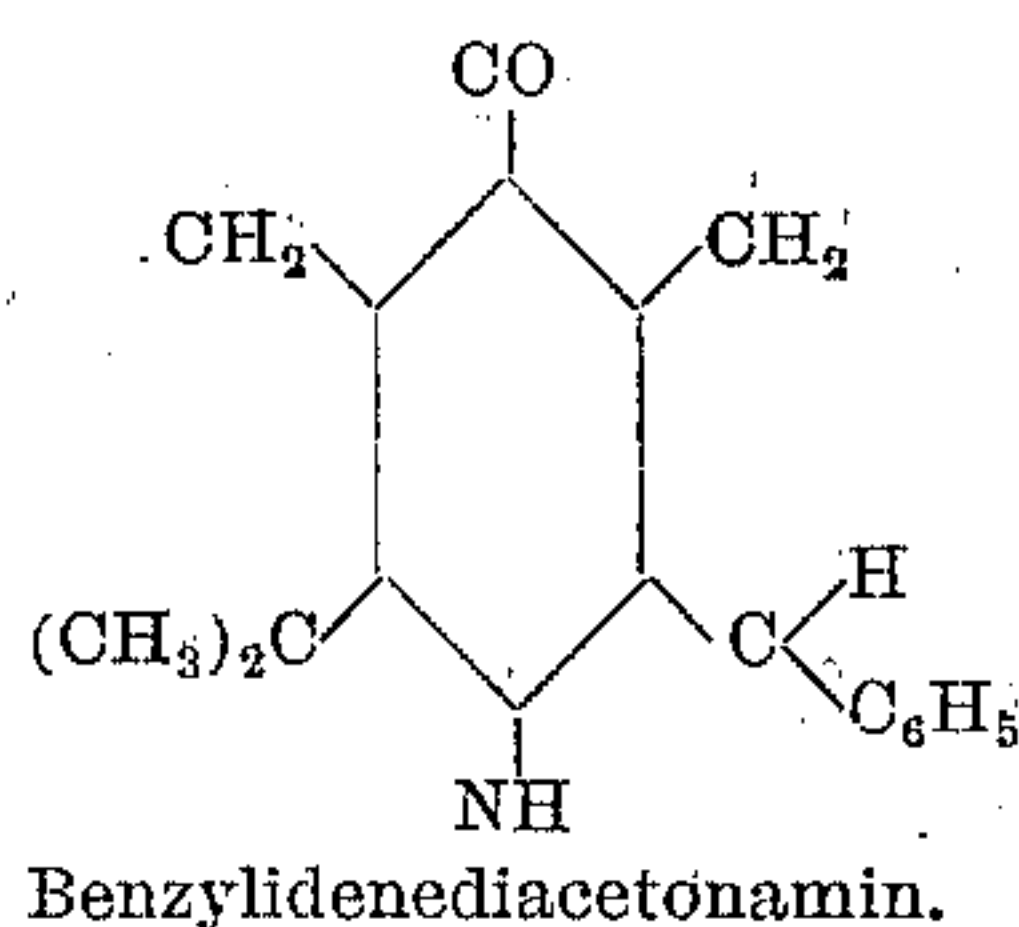
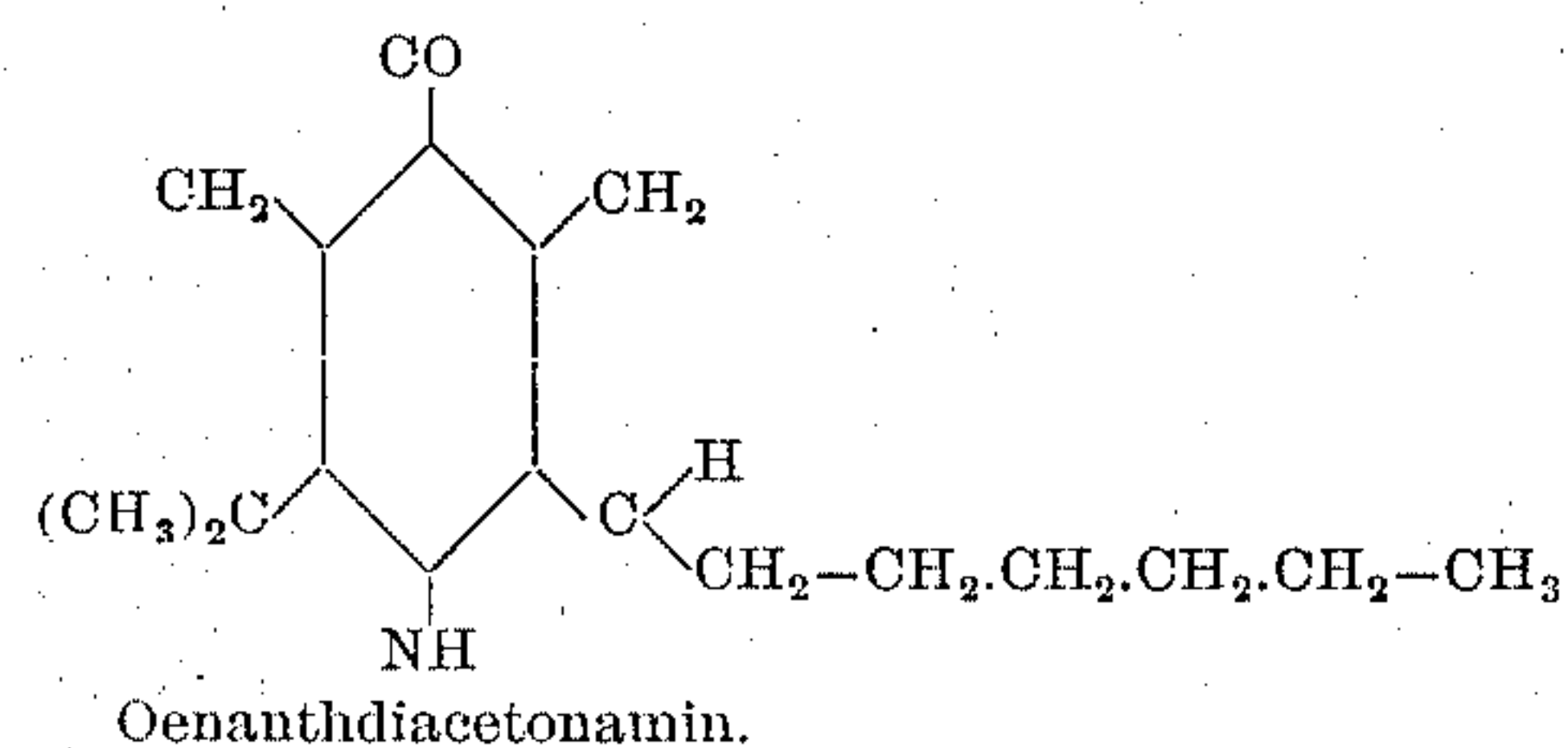
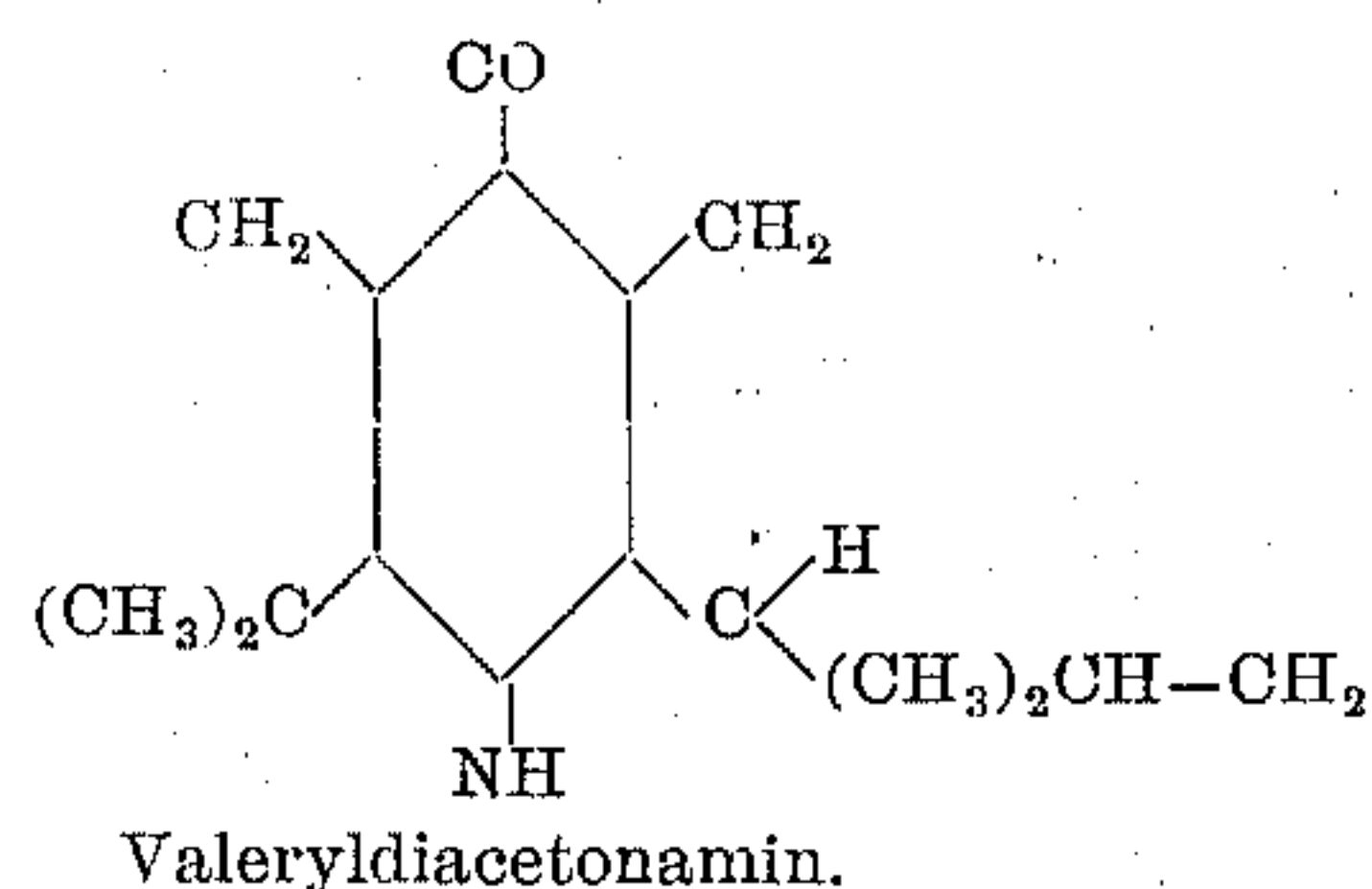
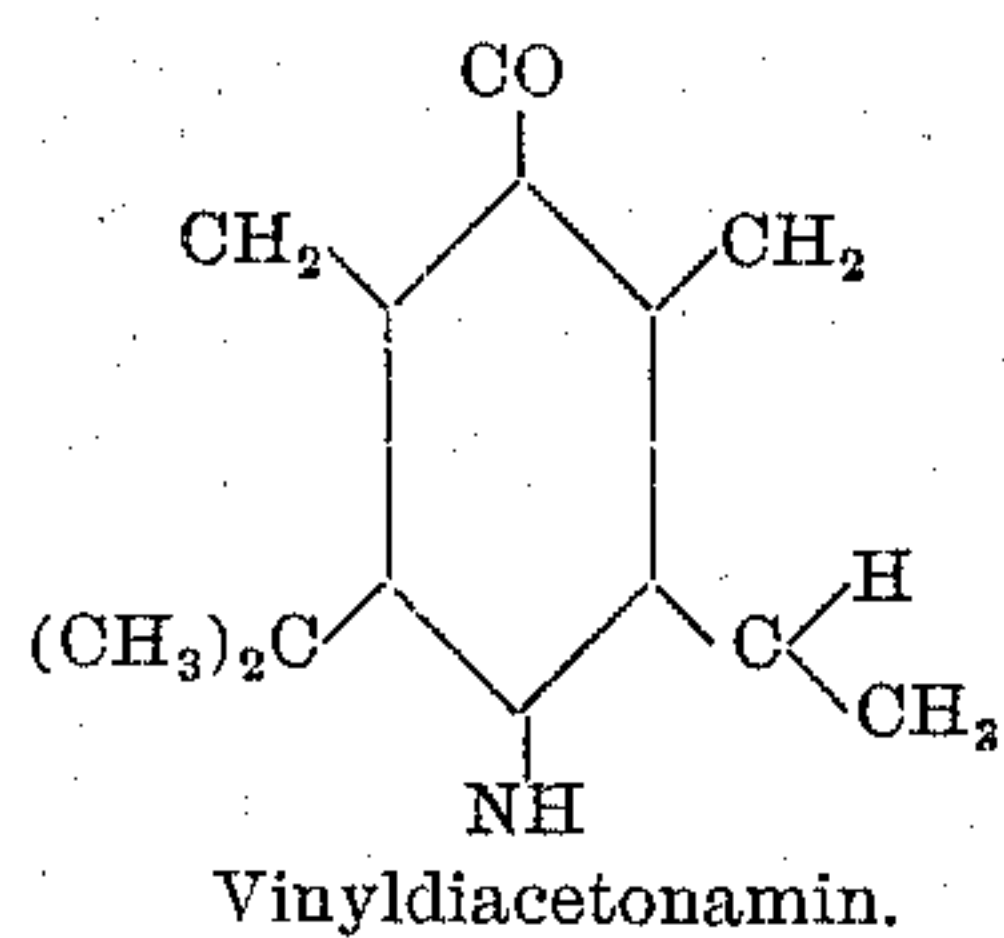
Application filed December 11, 1897. Serial No. 661,514. (No specimens.)

To all whom it may concern:

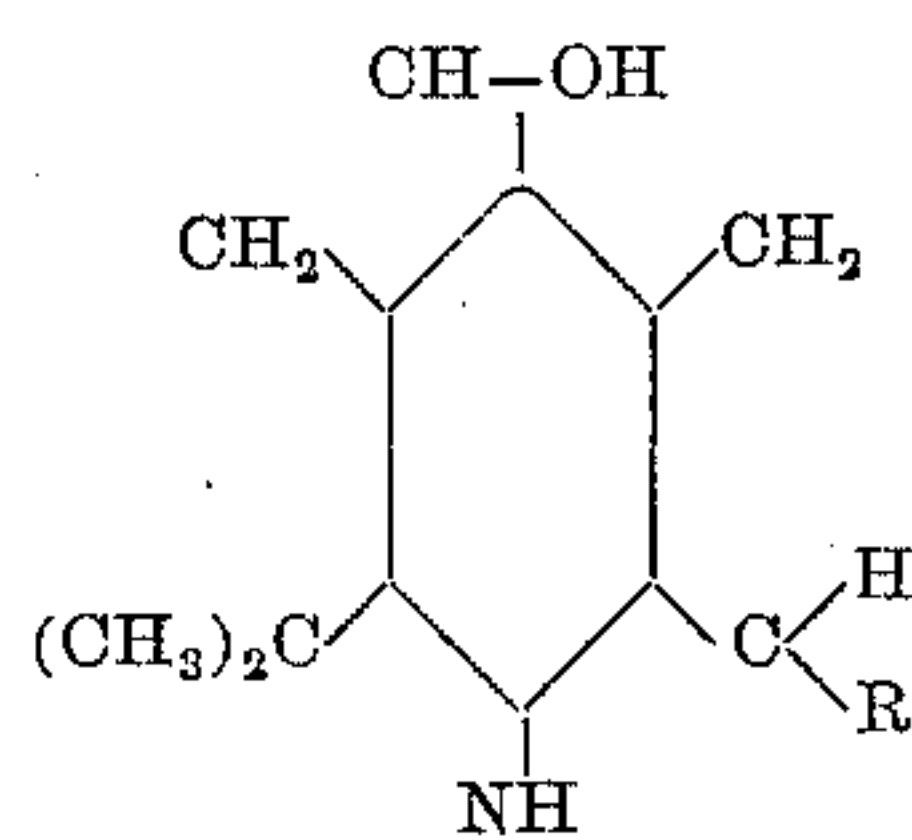
Be it known that I, CARL HARRIES, of Berlin, in the Empire of Germany, have invented certain new and useful Improvements in the Manufacture of Unstable Unsymmetrical Acetonalkamins and Acidyl Derivatives therefrom, (for which Letters Patent have been obtained in Germany, No. 95,620, dated May 10, 1896, and in Great Britain, No. 20,697 of 1896,) of which the following is a specification.

The present invention relates to the production of acidyl derivatives of the unstable modifications of the unsymmetrical acetonalkamins, in which for the present invention also their n-alkali derivatives—i. e., normal alkyl derivatives—are included.

I have discovered that by reducing the unsymmetrical bases of the triacetonamin series—as, for example, vinylldiacetonamin, valeryldiacetonamin, oenanthdiacetonamin, benzylidenediaceonamin, piperonylenediaceonamin—



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 best way of obtaining the unstable forms of the unsymmetrical cyclical acetonalkamins—as, for instance, of vinylldiacetonalkamin, valeryldiacetonalkamin, oenanthdiacetonalkamin, benzylidenediaceonalkamin, piperonylenediaceonalkamin—is the electrolytic reduction of the corresponding acetona-min bases. By this means only the unstable

modifications are produced, while the stable forms are not obtained. Of course the unstable forms may also be obtained in the manner described in my application, which is entitled "Improvements in the manufacture of isomeric unsymmetrical acetonalkamins," &c., Serial No. 661,513, filed December 11, 1897. The electrolytic reduction is best effected in weak alkaline solution. The electrolytic hydrogen reacts upon the greatest part of the acetonamins only in alkaline solution—for example, upon vinylldiacetonamin, valerylldiacetonamin. In these cases no reduction takes place in acid solution. The use of a diaphragm is preferred. The number of volts and amperes may be varied within a wide range. Six amperes and four volts were used in my experiments. The hydrogen pole had a surface of about four square inches and the oxygen pole a surface of about 0.4 square inches.

A. PRODUCTION OF THE UNSTABLE UNSYMMETRICAL ACETONALKAMINS.

1. *Production of the unstable vinylldiacetonalkamin.*—The cathodic cell of an electrolytic apparatus is filled with a solution of one kilogram of vinylldiacetonamin in a ten-per-cent. solution of sulfate of ammonia, while the anodic cell is filled with ten-per-cent. sulfuric acid. Then the electrolytic reduction is commenced. Now and then a small quantity of sulfate of ammonia or of sulfuric acid is added to the cathodic cell. Care must be taken that the reaction always remains alkaline. As soon as the reduction is finished an excess of soda-lye is added, whereby the alkamin base is precipitated. After sucking the liquid off the base is dissolved in boiling alcohol. On cooling the unstable vinylldiacetonalkamin crystallizes therefrom in glossy needles melting at 161° or 162° centigrade. The mother-lye is evaporated with hydrochloric acid to dryness. On treating the residue with cold absolute alcohol all is dissolved excepting a small quantity of common salt. It may be seen therefrom that the stable modification melting at 138° centigrade has not been formed. From the hydrochloric-acid salt of the mother-lye another quantity of the unstable alkamin base may be precipitated by means of alkali.

2. *Production of the unstable valerylldiacetonalkamin.*—The reduction of valerylldiacetonamin is brought about in the same manner. It is only necessary to add some alcohol on reducing valerylldiacetonamin on account of its being dissolved only with difficulty. As soon as the reduction is finished the product of the reaction is oversaturated with soda-lye and shaken with ether. After distilling the ether an oil remains behind which gradually passes into a solid state. On adding cold petroleum ether the unstable valerylldiacetonalkamin formed is separated as a white powder. It crystallizes from a mixture of

petroleum ether and benzene into glossy prisms melting at 93° or 94° centigrade.

The unstable forms of oenanthdiacetonalkamin, benzylidenediaceonalkamin, piperonylenediaceonalkamin are produced in a similar way to that described for vinylldiacetonalkamin and valerylldiacetonalkamin.

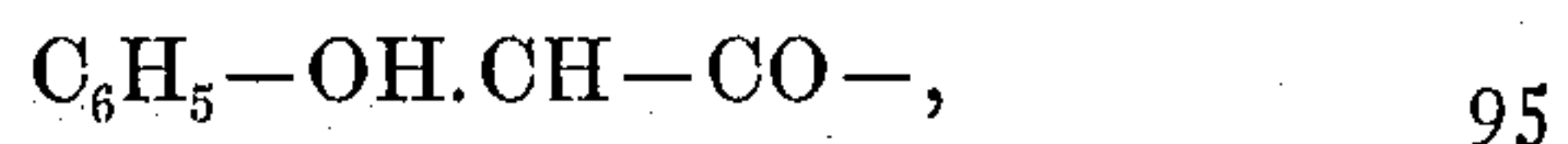
The unstable oenanthdiacetonalkamin crystallizes out of ligroin in glossy scales melting at 77° to 79° centigrade.

The unstable benzylidenediaceonalkamin crystallizes out of ligroin and has a melting-point of about 68° centigrade.

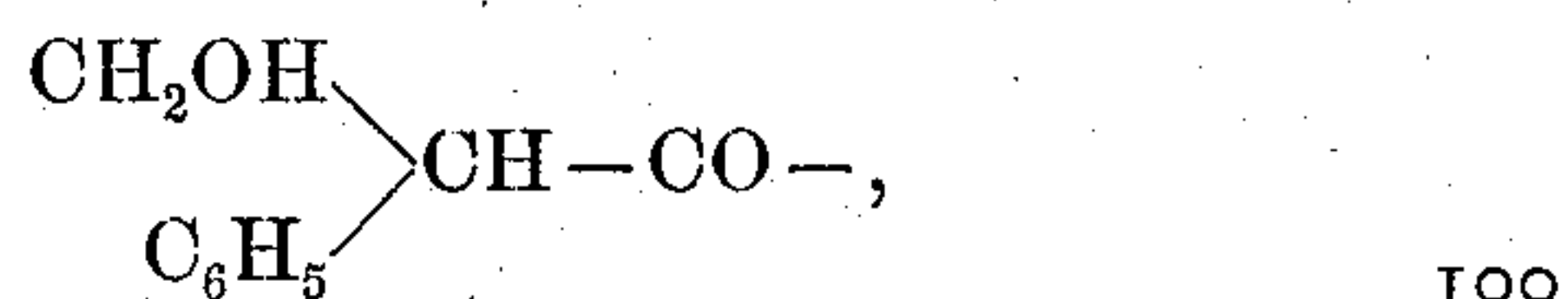
The unstable piperonylenediaceonalkamin crystallizes from benzene in needles melting at 108° to 109° centigrade.

B. PRODUCTION OF ACIDYL DERIVATIVES FROM THE UNSTABLE UNSYMMETRICAL ACETONALKAMINS.

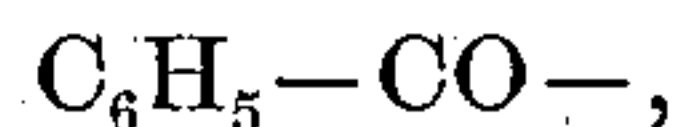
If the hydrogen atom of the hydroxyl in the unstable unsymmetrical acetonalkamins (in which for the purposes of the present invention their n-alkyl derivatives—that is, normal alkyl derivatives—are also included) be replaced by acid radicals, preferably with the phenylglycolyl or mandelic acid group



tropic-acid group



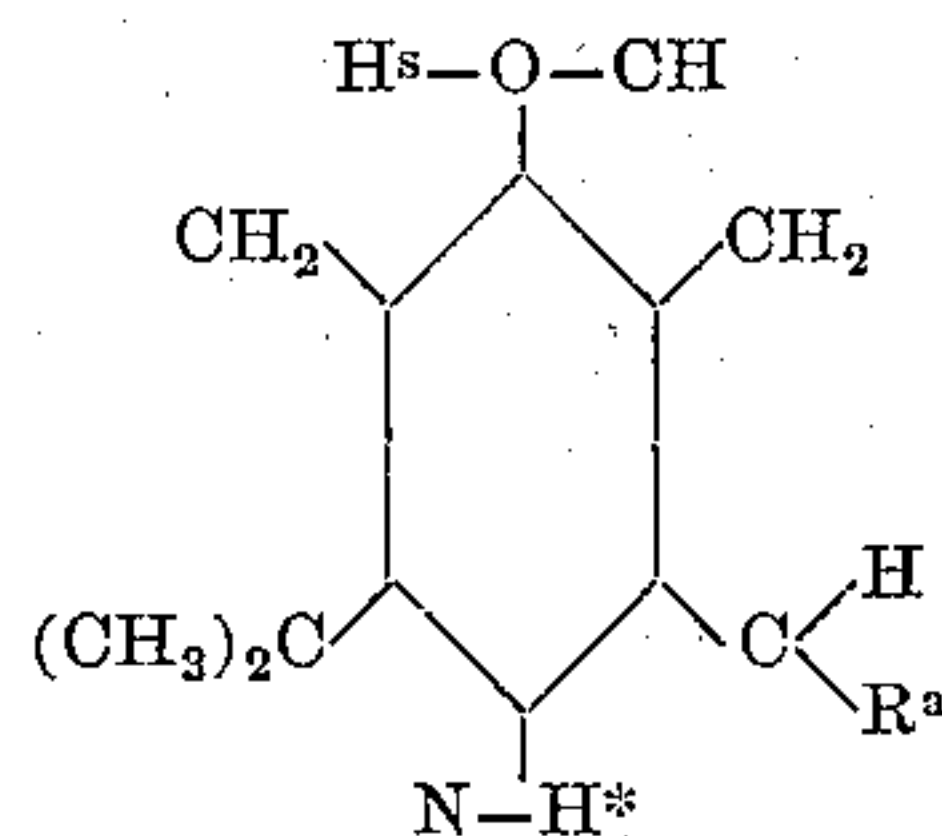
benzoyl group



phenylacetyl group



valuable alkaloids are obtained. The composition of the so-formed acidyl compounds answers the chemical formula



in which formula H^s signifies a hydrogen atom which can be replaced by 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 unstable 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 especially mydriatic properties.

In the following description the letter "n" before "methyl" or "methylated" indicates that in these compounds the hydrogen atom of the N. H. group can be replaced by the methyl group.

Examples.

1. *Phenylglycolyl-n-methyl-vinyldiacetonalkamin from the unstable vinyldiacetonalkamin melting at 161° or 162°.*—The n-methyl-vinyldiacetonalkamin necessary for the purpose is preferably produced in the following manner: Molecular quantities of vinyldiacetonalkamin and methyl iodid, dissolved in forty-per-cent. methyl alcohol, are allowed to stand at the temperature of the atmosphere for about forty-eight hours. After that time a mixture of the iodic-acid salt of n-methyl-vinyldiacetonalkamin, unaltered vinyldiacetonalkamin, and n-methyl-vinyldiacetonalkamin iodmethylate separate out. The mixture is evaporated to dryness, taken up with water, supersaturated with potash, and shaken out several times with ether, whereby the ammonium compound remains behind undissolved. After evaporation of the ethereal solution it is boiled several times with petroleum ether. The unaltered vinyldiacetonalkamin is thereby retained. The n-methyl-vinyldiacetonalkamin crystallizes out of petroleum ether on cooling in silk glossy needles melting at 84° or 85° centigrade. The methyl derivative from the vinyldiacetonalkamin, as well as from the other unsymmetrical acetonealkamins, may also be obtained by heating the alkamin with an excess of watery solution of formaldehyde on a water-bath for about ten hours. From the carbonate of alkamin thus formed the n-methylated alkamin base is set in freedom by soda-lye. This method of methylation yields the best results.

To produce the phenylglycolyl derivative, Ladenburg's method is the best to follow. A thin solution of the n-methylated base to which an excess of mandelic acid is added is several times evaporated with small quantities of hydrochloric acid. The residuum is taken up with water, mixed with a few drops of hydrochloric acid, and shaken several times with ether. The acid solution is then supersaturated in the cold with soda solution and shaken out with ether, whereupon the ether residuum is washed with water. The oil remaining behind after the evaporation of the ether gradually solidifies to a crystalline mass, which is washed with cold petroleum ether, in which the alkaloid is difficultly soluble. It crystallizes out of hot petroleum ether in small pieces composed of very fine needles, melting at 112° or 113° centigrade. The hydrochloric-acid salt is extraordinarily deliquescent, and it possesses a strong mydriatic action in a two-per-cent. solution. The mandelic-acid derivative may also, but little

advantageously, be obtained by treating the vinyldiacetonalkamin melting at 161° or 162° with mandelic acid according to Ladenburg's method, and methylating the phenylglycolyl-vinyldiacetonalkamin produced thereby in small quantities with methyl iodid. The phenylglycolyl derivatives may also be produced by the action of mandelic anhydrid in place of mandelic acid, or by passing hydrochloric acid through a melted mixture of the alkamin and mandelic acid—for example, at about 100° centigrade. In the same way the unstable vinyldiacetonalkamin contained in Fischer's base may be transformed into the phenylglycolyl derivative.

2. *Phenylglycolyl-n-ethyl-vinyldiacetonalkamin from the unstable vinyldiacetonalkamin.*—The n-ethyl-vinyldiacetonalkamin required therefor is produced in exactly the same way as the corresponding methyl product and forms an oil. The phenylglycolyl derivative obtained therefrom is a microcrystalline powder melting at 88° to 91° centigrade. The base is insoluble in water, as is the corresponding alkaloid from n-methyl-vinyldiacetonalkamin, but easily soluble in alcohol and ether. The salts are very easily soluble in water and possess strong mydriatic action.

3. *Phenylglycolyl-vinyldiacetonalkamin.*—The product of reaction obtained by Ladenburg's method is mixed with soda solution, repeatedly shaken with ether, the ethereal solution dried with potash, evaporated, and the product treated with cold water. The greater portion of the unstable vinyldiacetonalkamin not reacted upon is thereby dissolved, while the phenylglycolyl alkaloid remains behind undissolved. It has a melting-point of 150° to 177° centigrade. It has hitherto not been obtained in a pure state. It contains, however, mandelic acid in a great measure combined, which after saponification of the alkaloid is easily demonstrated. The salts of the base possess weak but recognizable mydriatic action.

4. *Tropyl-n-methyl-vinyldiacetonalkamin.*—Proceed exactly as before by repeatedly evaporating upon the water-bath the solution in water of the n-methylated vinyldiacetonalkamin mixed with tropic acid, hydrochloric acid being added from time to time. The further working is carried out as under Example 1. After washing the crude product with water tropyl-n-methyl-vinyldiacetonalkamin remains behind as a quickly-solidifying oil. The base is very difficultly soluble in water. It is easily saponified by a boiling soda solution. The hydrochloric-acid salt is very deliquescent. It possesses strong mydriatic action very similar to the hydrochloric-acid salt of the corresponding mandelic-acid derivative.

5. *Benzoyl derivative from the unstable vinyldiacetonalkamin.*—The ethereal solution of the base melting at 161° or 162° centi-

grade is first transformed into the hydrochloric-acid salt. This is heated for a long time with molecular quantities of benzoyl chlorid to about 140° centigrade. The product of the reaction is placed in water and shaken with ether to eliminate the excess of benzoyl chlorid. The solution in water is then supersaturated with soda and again shaken out with ether. After distillation of the ether benzoyl-vinyldiacetonalkamin remains behind as an uncrystallizable oil. The hydrochloric-acid salt is obtained in a microcrystalline state by mixing an ethereal solution of the base with ethereal hydrochloric acid. It possesses mydriatic and anesthetic properties.

6. *Benzoyl-n-methyl-vinyldiacetonalkamin.*—The benzoyl-n-methyl product is obtained either by the action of methyl iodid upon the unmethylated base obtained, as under Example 5, by heating molecular quantities in methylalcoholic solution with methyl iodid or by benzoylating n-methyl-vinyldiacetonalkamin. The resulting base is an oil. The hydrochloric-acid salt possesses mydriatic and anesthetic properties.

7. *Phenylacetyl-vinyldiacetonalkamin.*—Phenylacetyl-vinyldiacetonalkamin is obtained by the reaction of phenylacetic-acid chlorid upon the unstable alkamin and also forms an oil. It splits up by boiling with caustic-soda solution into phenylacetic acid and vinyldiacetonalkamin melting at 161° or 162° centigrade. The salts are very easily soluble in water and possess weak mydriatic and strong anesthetic properties. In the same way as the unstable vinyldiacetonalkamin the unstable modifications of analogously constituted unsymmetrical acetonealkamins—such as, for example, the valeryl, piperonylene, benzylidene, and oenanthdiacetonealkamins—may be transformed into acidyl derivatives.

8. *Phenylglycolyl-valeryldiacetonalkamin.*—It has a melting-point of 141° to 143° centigrade. Its mydriatic action is minimal.

9. *Phenylglycolyl-n-methyl-valeryldiacetonalkamin.*—The base is an oil, as is the product of the first step—namely, the n-methyl-valeryldiacetonalkamin, which is produced in an analogous manner to the n-methyl-vinyldiacetonalkamin. The alkaloid base is itself insoluble in water, but easily soluble in alcohol, ether, and warm petroleum ether. It possesses pronounced mydriatic action. By boiling the base with caustic-soda solution it is split up into mandelic acid and n-methyl-valeryldiacetonalkamin. The mandelic acid may be easily recognized by acidifying and shaking with ether. The salts are all easily soluble in water.

10. *Phenylglycolyl-n-methyl-benzylidenediacetonealkamin.*—The n-methyl derivative of the unstable benzylidenediacetonealkamin melts at 84° to 88° centigrade and crystallizes out of a mixture of benzene and petroleum

ether. The mandelic derivative of this base is an oil which has only weak mydriatic properties. The salts are easily soluble in water.

11. *Phenylglycolyl-n-methyl-oenanthdiacetonealkamin.*—The n-methyl derivative of the unstable oenanthdiacetonealkamin is an oil, as is also the mandelic derivative obtained therefrom, which possesses recognizable mydriatic action.

12. *Phenylglycolyl-n-methyl-piperonylenediacetonealkamin.*—The n-methyl-piperonylenediacetonealkamin of the unstable piperonylenediacetonealkamin crystallizes out of benzene in satin shining leaves having a melting-point of 152° or 153° centigrade. The mandelic derivative remains after distilling off the ether as a crystalline powder melting at about 150° centigrade. It possesses mydriatic properties.

By the term "acetonealkamins" in the following claims I intend to include also the derivatives of acetonealkamins.

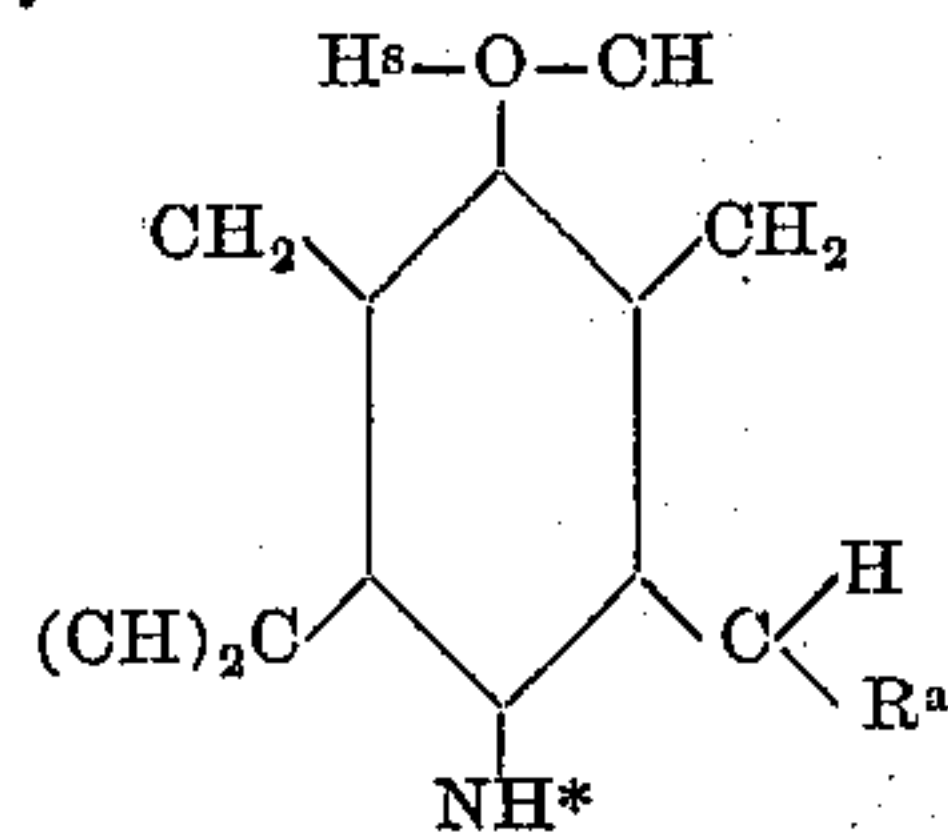
I wish it to be understood that I do not claim under this application the acidyl compounds of the stable vinyldiacetonalkamin melting at 138° centigrade and of its alkyl derivatives as new products or the method of production of such acidyl derivatives from the stable vinyldiacetonalkamin melting at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

I claim as my invention—

1. The herein-described process of obtaining acidyl compounds of the unstable modifications of the unsymmetrical cyclical acetonealkamins consisting in subjecting these alkamins to the action of an acidyl reagent and thus substituting the corresponding acidyl group for the hydrogen atom of the hydroxyl group of the said alkamin.

2. The herein-described process of obtaining acidyl compounds of the unstable unsymmetrical acetonealkamins consisting in first subjecting the corresponding amin bases to the action of the electric current to produce the unstable alkamins and then subjecting these alkamins to the action of an acidyl reagent, as and for the purpose set forth.

3. As new chemical products the herein-described unstable acetonealkamins, the composition of which products answers the general formula:



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

group, of which products the products containing the hydrogen atom H^s as such are more or less soluble in water, while the products—in which the hydrogen atom H^s has been
5 replaced by an acidyl group in the form of the free bases are insoluble in water and decompose upon boiling with watery or alcoholic alkalies into the respective alkamin base and a salt of that acid, the radical of
10 which was substituted for the hydrogen atom

of the hydroxyl—combined with inorganic and organic acids form the corresponding salts which have especially mydriatic properties.

In testimony whereof I have hereunto set my hand this 26th day of November, 1897. -5

CARL HARRIES.

Witnesses:

WOLDEMAR HAUPT,
HENRY HASPER.