UNITED STATES PATENT OFFICE.

ERNEST FOURNEAU, OF PARIS, FRANCE.

PREPARATION OF AMINO ALCOHOL.

No. 829,262. Specification of Letters Patent. Patented Aug. 21, 1906.

Application filed March 21, 1904. Serial No. 199,283.

To all whom it may concern:

Be it known that I, ERNEST FOURNEAU, a citizen of the Republic of France, residing in the city of Paris, in the Republic of France, have invented certain new and useful Improvements in the Preparation of Amino Alcohols, of which the following is a specification.

The present invention relates to a process for making alkamins (amino alcohols) which contain a tertiary alcohol group and a tertiary amino group.

The processes generally used for producing alkamins are limited to four: First, action of amins on the halogen hydrins, (Wurtz, *Liebig's Ann.* 121, 228;) second, action of amins on ethylenoxids, (Wurtz, *Suppl. Ann.* 6, 202;) third, reduction of the aminoacetones, (Heintz, *Liebig's Ann.* 182, 29; *Cloez's Ann.* 6, 9, 159;) fourth, fixing the ingredients of the water onto the double compound of a base which contains an ethylene group (Willstätter, *Liebig's Ann.* 326, p. 93; Einhorn, *Berichte* 23, p. 2889.) In reality the first process alone is available for the alkamins of the kind mentioned at the beginning, and it was a question still of discovering a process which permits the production in an easy way of the suitable halogen hydrins.

The researches of Grignard (*Comptes-Rendus de l'Academic des Sciences* 132, pp. 528, 836, 133, &c.) have enabled Tiffeneau to bring about the synthesis of these halogen-hydrins with ease. His process consists herein that the magnesium organic compounds are permitted to act on halogen acetones (*C. R. Ac. D. Sc.* 134, p. 774.) The yield, however, is usually too slight and too irregular. Besides, complicated secondary reactions may arise, which are to be ascribed to the intense chemical activity of the halogen in the molecule. Finally, the halogen hydrin once formed changes very easily. Now the process forming the object of the present application is founded on an entirely new application of Grignard's reaction, and consists herein that the magnesium organic compounds are brought to act on aminoacetones or on the ester of an amino acid with tertiary amino group.

Examples.

1. $CH_3IMg + CO(CH_2.N(CH_3)_2)(CH_3) =$

$CH_3CH_2N(CH_3)(CH_3)$ H_2O $COH(CH_3)(CH_3)-CH_2.N(CH_3)_2$

$COMgI$

HC_3

2. $2CH_2MgBr + CO(OC_2H_5)(CH_2N(CH_3)_2) =$

$C_2H_5C_2H_5$ $COMgBrCH_3$ $CH_2.N(CH_3)_2$

H_2O $COH(C_2H_5)(C_2H_5)-CH_2.N(CH_3)_2$

The advantages which the present method show as compared with the known processes are as follows:

First. This method makes the production of halogen hydrins unnecessary, and thus the reactions connected with this production do not appear. Consequently the yield almost corresponds to the theoretical one, and the product of reaction distils to the last drop without undergoing the slightest decomposition.

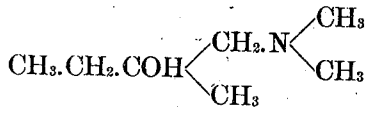
Second. It permits not only to produce the alkamins, which are derived from the halogen hydrins of Tiffeneau, but also all alkamins which are derived from any desired aminoacetone or amino-acid ester. Thus, for instance, the alkamins which are derived from tropinone or from triacetonamin.

Third. By means of the process the heating under pressure is avoided as, figuring from the halogenacetone (Störmer *Berichte* 28, 223) and the halogen-acid esters (Willstätter *Berichte* 35, p. 594) the corresponding amino derivates are formed in the cold, and in their turn also enter into reaction on the magnesium organic compounds in the

cold. The action of the amins on halogen hydrins, on the other hand, is usually only complete when heated under pressure. From the industrial standpoint the alkamins, with tertiary alcohol and amino groups, which have apparently not yet been described in the chemical works, are of a certain interest. Their benzoylized derivatives, as well as the salts of these benzoylized derivatives, are well adapted to produce local anesthesia and possess also a very slight toxicity, which is slighter than that of the eucaines and cocaines. These salts, moreover, are exceedingly easily soluble in water with the exception of those of the aromatic series, which are less easily soluble. Furthermore, the solutions under action of heat are completely sterilizable, as they undergo no changes even with a continuous heating to 110°.

Example.

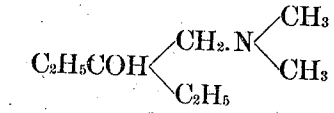
1. Ethyldimethylaminopropanol:



Twenty-four grams of magnesium are dissolved in one hundred and eighty grams of ethyl bromid as well as three hundred grams of ether free of water, according to Grignard's directions, (*loco citato.*) As soon as the ingredients are dissolved one hundred grams of dimethylaminacetone, which boils at 123°, (Stoermore, *loco citato,*) are slowly introduced into the cooled-off liquid. The reaction is a very lively one. A white powder is precipitated and the ether is brought to boil. The liquid remains but little colored, and the introduction of the dimethylacetone keeps on for about three hours. After the same is ended the mixture is left to itself for half a day. Then it is mixed with pounded ice and hydrochloric acid, which latter is added in just sufficient quantity to make the medium slightly acid. Now the existing acid layer is decanted and evaporated as much as possible with rarefication of air. It then suffices to treat the remaining salty mass at low temperature with a concentrated solution of soda in order to be able to take up the base in a solution of ether, whereafter the whole is distilled with rarefication of air after the solvent has been dried out and evaporated. The product boils at 37° and twenty-three millimeters mercurial column. It consists of a mobile, almost colorless, liquid of slight odor, which is very easily soluble in water and the other solvents. The corresponding salts are crystallizable with difficulty excepting the oxalate. The chlorplatin-acid salt is very soluble in water and alcohol. The aurate, on the other hand, is very difficult to dissolve, but liquefies when it is permitted to crystallize anew. The hydrochloric compound (chlorhydrate) of the benzoylized derivative, on the other hand, crystallizes completely from absolute alcohol. This compound is very easily dissolved in water and melts at 175°. The body, as well as all of its homologues, causes a lively analgetic effect when a small quantity of the same is placed on the tongue.

Example.

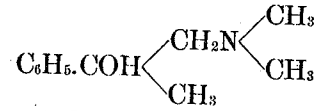
2. Ethyldimethylaminobutanol:



The process used herefor is exactly the same as that before described, with the single exception that the ethylmagnesium bromid is no longer allowed to be acted upon by dimethylaminoacetone, but ethyl or methyl dimethylaminoacetate, which has been obtained by the Willstätter process, (*Berichte* 35, p. 594.) The yield is much less satisfactory and there very probably arise alkamins which contain an oxid-ester group. At all events the reigning product, about sixty per cent., consists of ethyldimethylbutanol, which boils at 76° to 79° and twenty-four millimeters Hg. The product consists of an almost wholly colorless liquid which is less soluble in water than the body before described. The hydrochloric compound of the benzoylized derivative is slightly soluble in cold absolute alcohol and crystallizes from out of this solvent in beautifully shining little plates, which melt at 189°. Like all its homologues it is but slightly soluble in acetone.

Example.

3. Phenyldimethylaminopropanol:

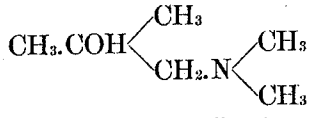


This body can be obtained by either allowing phenylmagnesiumbromid to act on dimethylaminoacetone, which represents the most practical process, or methylmagnesiumiodid may also be caused to act on dimethylaminoacetophenone for this purpose. Seventy grams magnesium, in strips or in form of powder, are dissolved in four hundred grams of iodidemethyl and two thousand grams of ether free from water. As soon as the solution is complete, (the mixture is) cooled off, and three hundred grams dimethylamidoacetophenone (previously dissolved in five hundred grams of ether free from water) are allowed to flow into the liquid drop by drop. The reaction is a lively one and is conducted exactly as in the previous cases. The whole is left to itself for twenty-four hours, and the

mass is then decomposed by means of ice and hydrochloric acid. The base is then freed from the acidiferous solution by means of soda and finally subjected to a fractionated distillation after the same has been lixiviated by means of ether. The body boils at 130° to 135° and twenty-four millimeters Hg. It is liquid, very slightly soluble in water, less soluble in warm than in cold water. The body in time, in cold, reduces permanganate of potassium in acid solution, and this reduction takes place very rapidly, heat being applied. The hydrochloric compound crystallizes out of acetone in very fine needles, in which it is very slightly soluble in cold and melts at 158° to 160°. Chlor-aurate in raw state melts at 110°. The benzoylized derivative is viscous and colorless. Its hydrochloric compound is very slightly soluble in absolute, even warm, alcohol and dissolves pretty badly in cold water. It crystallizes out of absolute alcohol in beautiful prisms, which melt at 205° to 206°.

Example.

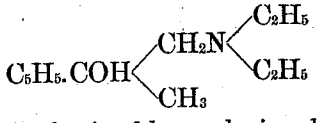
4. Methyldimethylaminopropanol:



This body is obtained by allowing dimethylaminoacetone to act upon methylamagnesiumiodid. The base boils at 160° and forty-eight millimeters Hg. Its properties are the same as those of the base before described. The hydrochloric compound of their benzoylized derivatives crystallizes out of the solution in boiling absolute alcohol in large cubes, which decompose in the air and melt at 202°.

Example.

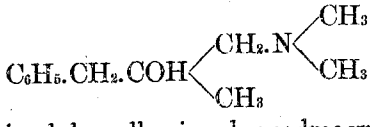
5. Phenyldiethylaminopropanol:



This body is obtained by replacing dimethylaminoacetone by diethylaminoacetone. This body is thick flowing and boils at 147° to 149° and twenty-four millimeters Hg. The salts are difficult to crystallize. Furthermore, the hydrochloric compound of the benzoylized derivative is syrupy.

Example.

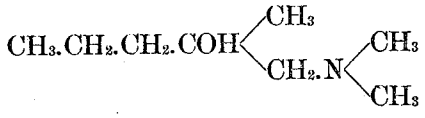
6. Benzyldimethylaminopropanol:



is obtained by allowing benzylmagnesiumchlorid to act upon dimethylaminoacetone. This product presents a thick liquid, which boils at 144° and twenty-four millimeters Hg. The chlorhydrate of its benzoylized derivative crystallizes from out of absolute alcohol and out of methyl alcohol in beautiful transparent prisms several millimeters in length, which melt at 195°.

Example.

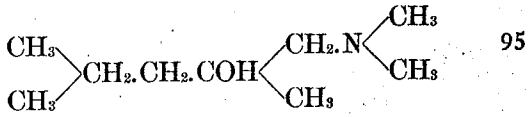
7. Propyldimethylaminopropanol:



is obtained by allowing propylmagnesiumbromid and dimethylaminoacetone to act upon each other. This base is very soluble in water and boils at 78° and thirty-five millimeters Hg. The salt compounds are uncrystallizable. The chlorhydrate of the benzoylized derivative melts at 140° and crystallizes out of an alcohol ether mixture in very fine needles. It is very soluble in absolute alcohol and hygroscopic besides.

Example.

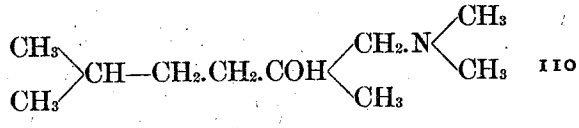
8. Isobutyldimethylaminopropanol:



This base boils at 83° and 34 millimeters Hg. The chlorhydrate of the benzoylized derivative melts at 134° and crystallizes out of an alcohol-ether mixture in long hygroscopic needles.

Example.

9. Isoamyldimethylaminopropanol:



is obtained by allowing isoamylmagnesiumbromid to act upon dimethylamidoacetone. This base spreads a strong odor, soon colors in the air, and is very slightly soluble in water. The product boils at 98° to 99° and twenty-four millimeters Hg. The chlorhydrate of the benzoylized derivative crystallizes out of an alcohol-ether mixture in long silk-like non-hygroscopic needles, which are almost insoluble in acetone; but, on the other hand, very soluble in alcohol, and melt at 138°.

I claim as my invention—

The process for producing alkamins containing tertiary alcohol group and tertiary amino group, which consists in causing magnesium organic compounds to act upon aminoacetones whereby bodies are obtained adapted to produce local anesthesia, &c.

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

ERNEST FOURNEAU.

Witnesses:

HANSON C. COXE,

ANTONIN MOUHEALHE—.