

UNITED STATES PATENT OFFICE.

ERNEST FOURNEAU, OF PARIS, FRANCE.

PREPARATION OF ESTERS OF OXYAMINO ACIDS.

952,006.

Specification of Letters Patent. Patented Mar. 15, 1910.

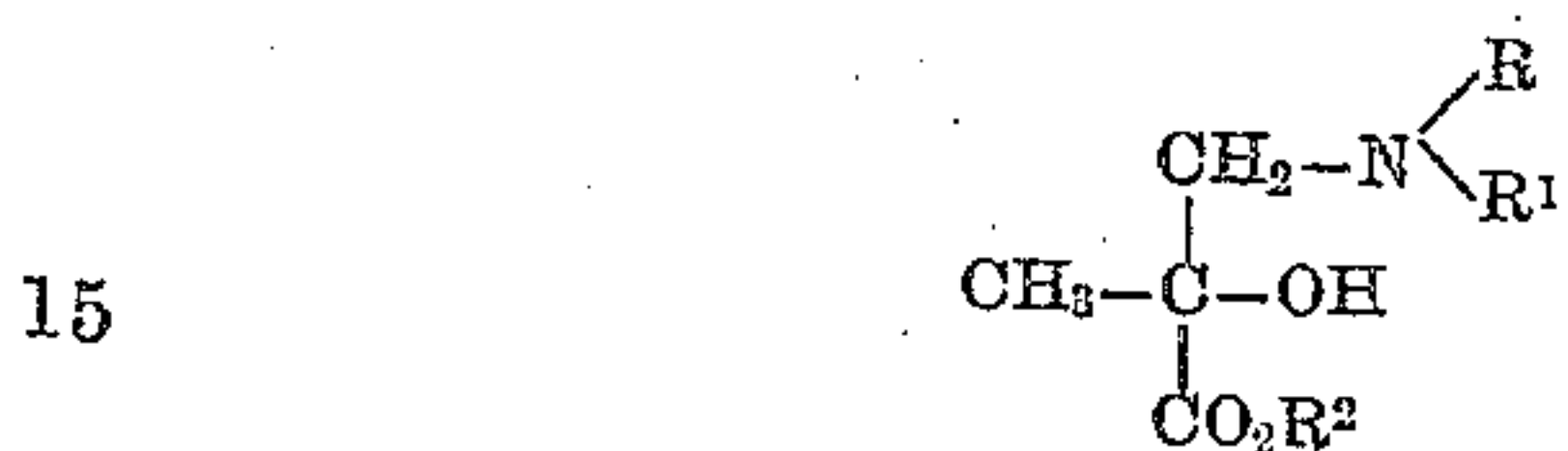
No Drawing.

Application filed January 28, 1907. Serial No. 354,464.

To all whom it may concern:

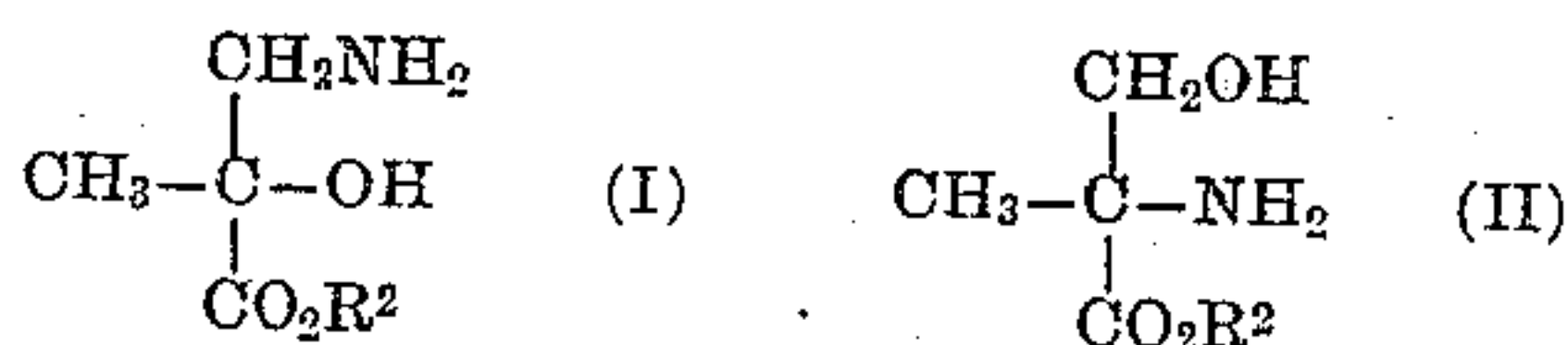
Be it known that I, ERNEST FOURNEAU, a citizen of the Republic of France, residing in Paris, France, have invented certain new and useful Improvements in Obtaining the Esters of a Group of Oxyamino Acids, for which application has been made in France February 1, 1906, and in Germany July 6, 1906.

Preparation of the esters of oxy-amino acids of the general formula



in which R and R¹ represent either hydrogen or an alkyl group and R² represents an alkyl group.

By the action of ammonia on methyl-glyceric acid an oxy-amino acid is obtained, in which the position of the amino group, though probably represented by formula 1 (see below) is not definitely established.



See Melikoff, *Liebig's Annalen* 234, 207, and 217. *Berichte* 12, 2227.—13, 958.—15, 2585. Beilstein I, 1209.

The acid is slightly soluble in water, stable and has no sweet taste. Melikoff does not describe its esters. Other publications on the oxy-amino acids are those of—

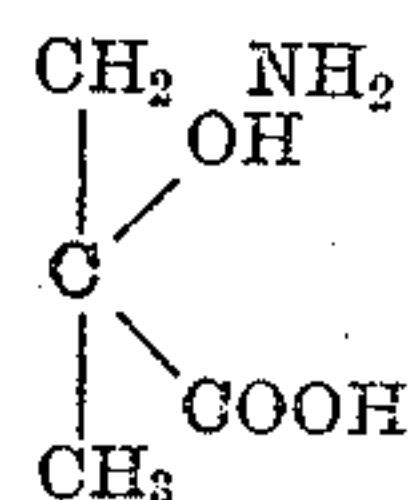
(1) Zelinsky. *Journal of the Russian Chemical Society* Vol. 16, page 687 in which the methyl-amino-oxy-butyric acid is described. The position of the —NH(CH₃) group is not determined.

(2) Heintz, *Liebig's Annalen* 192, 329, and Weill, *Liebig's Annalen* 232, 209 in which amino-tri-methyl-oxy-butyric acid is described.

(3) Erlenmeyer and E. Fischer (*Berichte* 1902, 3787) describe the oxy-amino acids obtained by the decomposition of the albuminoids.

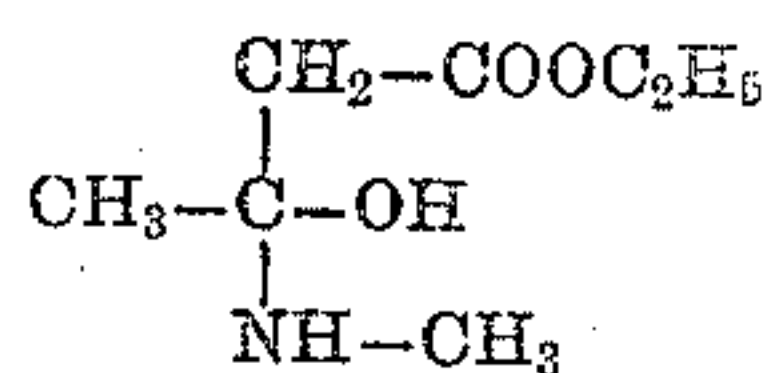
(4) Egoroff (*Centralblatt* 1903. II, 555)

describes the preparation of amino dimethyl-oxy-acetic acid



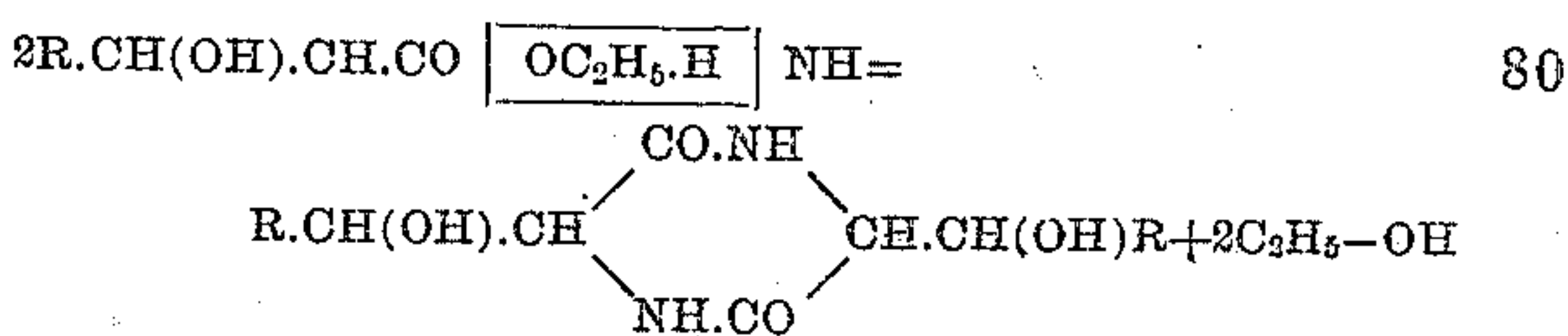
by the reduction of the corresponding nitro body obtained by the action of nitrogen peroxid (N₂O₄) on methyl acrylic acid.

No esters of the oxy-amino acids are known except those in which the amino group and hydroxyl group are attached to the same carbon atom. See Kuchert, *Berichte* 18, 618.



These bodies are very unstable losing water even at ordinary temperatures.

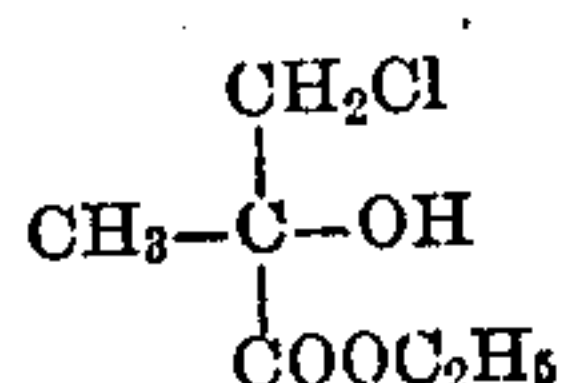
E. Fischer (*Berichte* 1902, 3787,) and Sorensen, (*Centralblatt* 1905. II, 400) have investigated the esters of the oxy-amino acids but they have not been able to isolate them owing to the ease with which such esters lose alcohol, two molecules condensing together as shown, giving derivatives of acipiperazin.



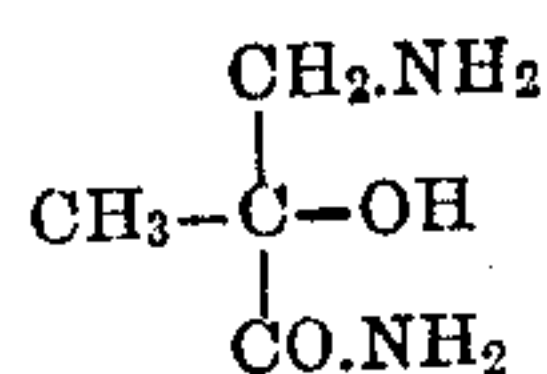
E. Fischer and Dilthey (*Berichte* 35, 844 and 856) after having studied the action of ammonia on the di-alkylmalonic esters and upon the acid esters in which a tertiary carbon atom is attached to the —COO R² group in general, show that in these cases the above described acipiperazin formation is very difficult. Thus by the action of ammonia on the di-ethyl-malonic acid there is no such direct amid formation. It was therefore to be expected that the esters of the oxy-amino acids derived from di-methyl-oxy-acetic acid and its homologues would be distillable without decomposition. They belong in fact to a group of esters giving amids with difficulty and consequently have but little tendency to

lose alcohol and give the di-aci-oxypiperazines. This was found to be the case, all the esters of the amino derivatives of di-methyl-oxy-acetic acid being stable and distillable without alteration, even at ordinary pressure. The properties of these bodies resemble closely those of the amino derivatives of tertiary alcohols described in the U. S. Patents Nos. 828846 and 829262. In these esters of amino-di-methyl-oxyacetic acids the hydrogen of the hydroxyl group is replaceable by acid radicals with formation of esters differing from one another according to the substituting acid used.

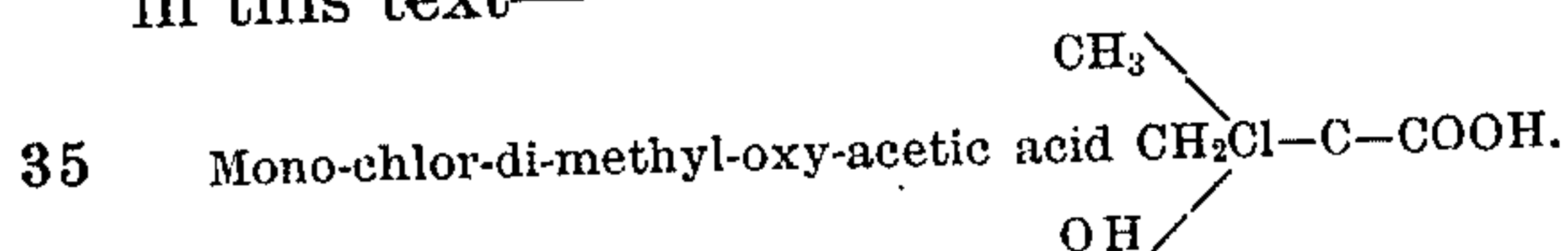
The esters of the oxy-amino acetic acids are obtained 1st by the esterification of the oxy-amino acids, 2nd by the action of the secondary amines on the halogen derivatives of the acid esters such as



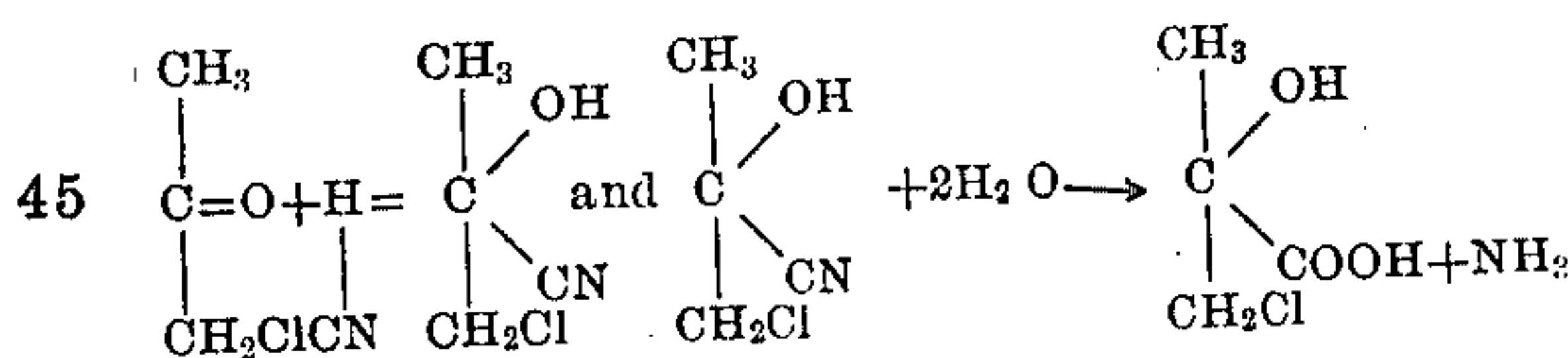
If ammonia and a primary amine be allowed to react in place of the secondary amine an acid amide is also formed, thus with ammonia



The first method only will be described in this text—

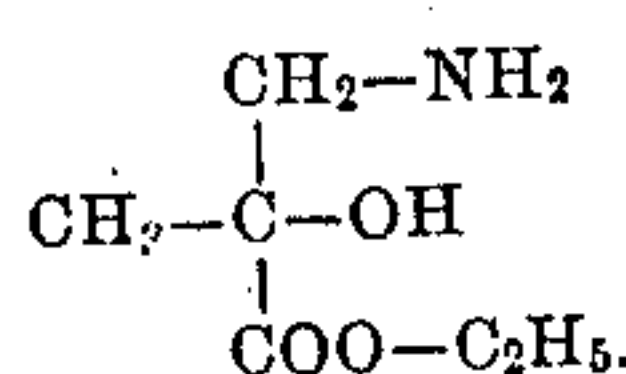


forms the primary material for the preparation of these ethers. It is obtained by the action of hydrocyanic acid on mono-chlor-aceton and subsequent saponification of the nitrite so obtained



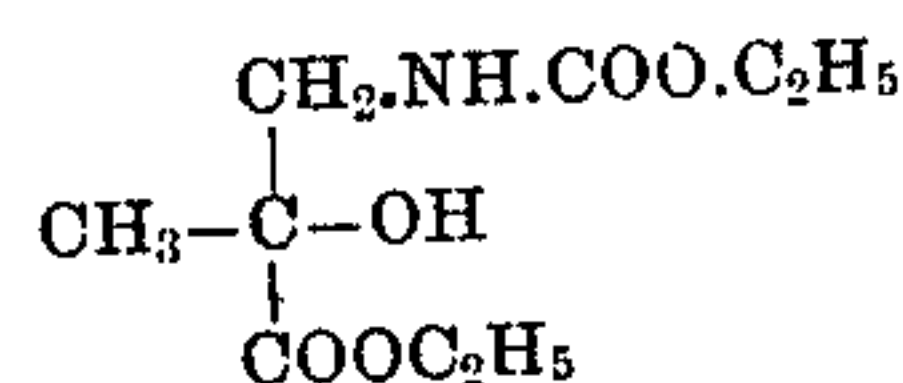
On heating the chlor-di-methyl-oxy-acetic acid so obtained under pressure for half an hour in a sealed tube with ammonia or amines the chlorine is replaced by an amino group (or a substituted amino group) oxy-amino-acids being thus obtained whose constitution is clearly established. On treating with alcohols in presence of mineral acids the carboxyl group is converted to $-\text{COOR}_1$ i. e. it is esterified in the well known manner.

Example 1: Ethylester of amino-di-methyl-oxy-acetic acid.



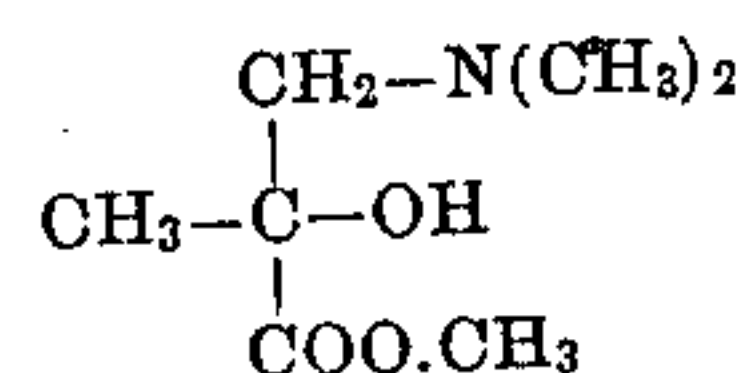
50 grs. amino-di-methyl-oxy-acetic acid are treated with 200 grs. of ethyl alcohol, previously saturated with hydrochloric acid gas, for 2 hours in a flask provided with a reflux condenser: at the end of this time the excess of alcohol and hydrochloric acid is distilled off and the hydrochlorid of the ethyl ester of amino-di-methyl-oxy-acetic acid allowed to crystallize out. The free base or ethyl ester of the above acid is liberated by treating with the requisite quantity of a 10% solution of caustic soda, excess of sodium carbonate is then added until the mass becomes pasty when it is extracted with either chloroform or ether. The ether or chloroform extract is then dried over anhydrous sodium sulfate and the solvent evaporated. The residue is fractionated *in vacuo*. The ethyl ester distils over at 107 to 109° C. under 15 mm. pressure without the least decomposition solidifying to colorless crystals, soluble in alcohol, ether and water.

Treated in ether solution with hydrochloric acid, the hydrochlorid is formed, which after recrystallization from alcohol forms fine needles, very soluble in water, sparingly so in alcohol and insoluble in chloroform and ether, M. P. 105° C. The corresponding urethane—



is obtained by the action of mono-chloroformic ester on the ethyl ester described in Example 1. It boils at 164–165° C. under 16 mm. pressure. It is soluble in water.

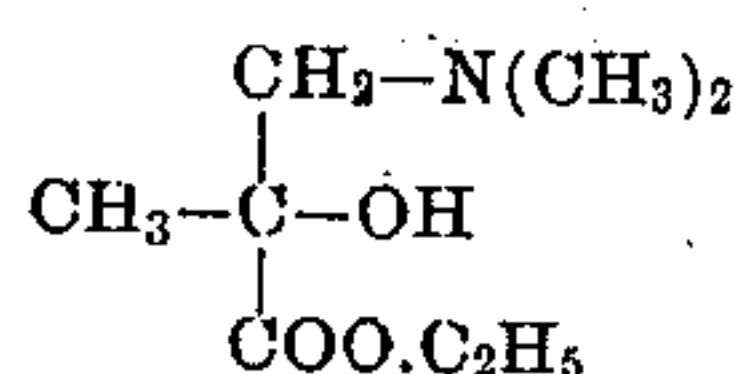
Example 2: Methyl ester of di-methyl-amino-di-methyl-oxy-acetic acid.



The free acid is obtained by the action of di-methylamin on chloro-di-methyl-oxy-acetic acid. It forms large hygroscopic crystals neutral toward litmus and of a sweet taste. M. P. 174° C. Its methyl ester is obtained by heating with 4 parts of methyl alcohol saturated with hydrochloric acid gas, as in the case of Example 1. The base boils at 107° C. under 35 mm. pressure. It is a liquid, soluble in organic solvents and in cold water, but almost insoluble in hot water.

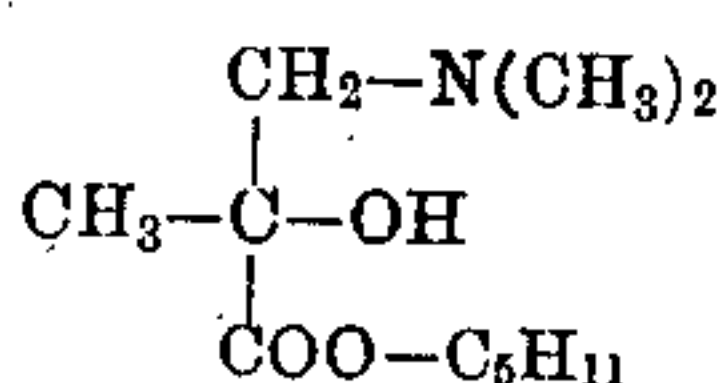
Gold chlorid precipitates an oil from its solution in hydrochloric acid. Platinum chlorid however does not do so. The hydrochlorid of its benzoyl derivative crystallizes from a mixture of alcohol and ether in beautiful needles. M. P. 149–150° C.

Example 3: Ethyl ester of di-methyl-amino dimethyl-oxy-acetic acid.



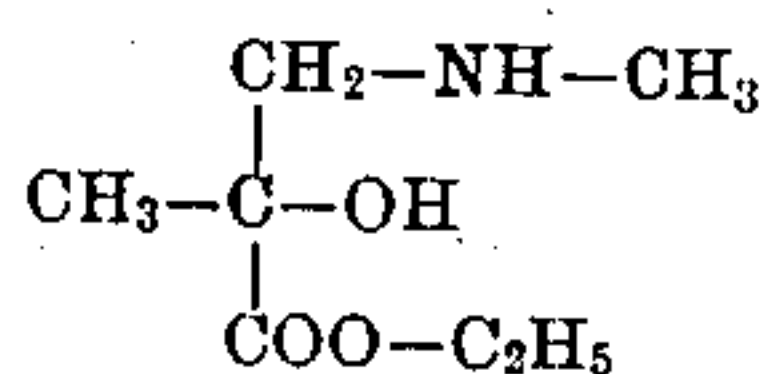
This is obtained like the corresponding methyl ester (Example 2), using an ethyl alcoholic solution of hydrochloric acid and di-methyl-amino-di-methyl-oxy-acetic acid. This ester boils at 88 to 91° C. under 16 mm. pressure. It forms a mobile liquid of feeble odor. Like the methyl ester it is more soluble in cold water than hot. The hydrochlorid forms a syrup but the hydrochlorid of the benzoyl derivative crystallizes in fine needles. M. P. 137° C. The hydrochlorid of the Valeryl derivative melts at 134-135° C.

Example 4: Iso-amyl ester of di-methyl-amino di-methyl-oxy-acetic acid.



45 grs. amino-di-methyl-oxy-acetic acid are heated with 200 grs. iso-amyl alcohol and 60 grs. gaseous hydrochloric acid for 3 hours on an oil bath in a flask fitted with a reflux condenser. The excess of amyl alcohol is now distilled off under reduced pressure, the residue is dissolved in water and the aqueous solution is extracted with ether to remove the last traces of amyl alcohol. The aqueous solution is then concentrated *in vacuo* and the free base or iso-amyl ester is liberated by sodium carbonate and extracted by ether. The iso-amyl ester boils at 121° C. under 12 mm. pressure. The yield is about 40 grs. It is almost insoluble in water. The hydrochlorid of its benzoyl derivative is fairly soluble in benzene. M. P. 134° C.

Example 5: Ethyl-ester of mono-methyl-amino-di-methyl-oxy-acetic acid.



The corresponding acid, which has never been described is prepared like its homologue, using mono methyl-amin in place of di-methyl-amin. It is a crystalline body whose solubility and other physical properties are intermediate between those of the ethyl esters of amino-di-methyl-oxy-acetic acid and di-methyl-amino-di-methyl-oxy-acetic acid. It is neutral to litmus, very soluble in water, of a sweet taste sparingly

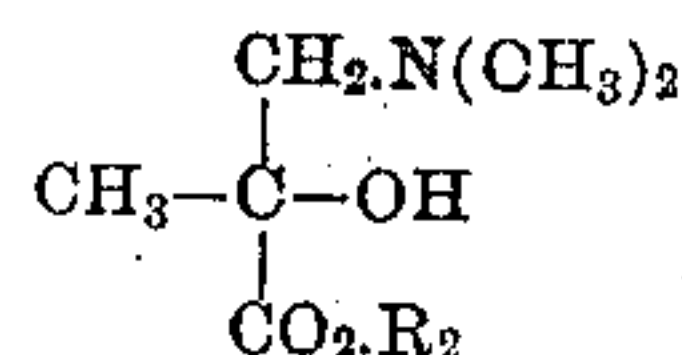
soluble in absolute alcohol and insoluble in acetone. It can be crystallized from a mixture of acetone and water. M. P. 222-231° C., with decomposition.

The ethyl ester is obtained by treating the free acid with 4 times its weight of ethyl alcohol saturated with hydrochloric acid. It is isolated as in the previous examples. B. P. 112° C. under 38 mm. pressure.

The esters of the oxy-amino acids, produced according to this invention, serve principally for preparing acidyl derivatives which are used as local anesthetics, and for other like purposes in medicine. The esters themselves also possess different properties according to the radical used, some of them having hypnotic properties, and they are of particular value in many cases on account of the fact that they are but slightly poisonous.

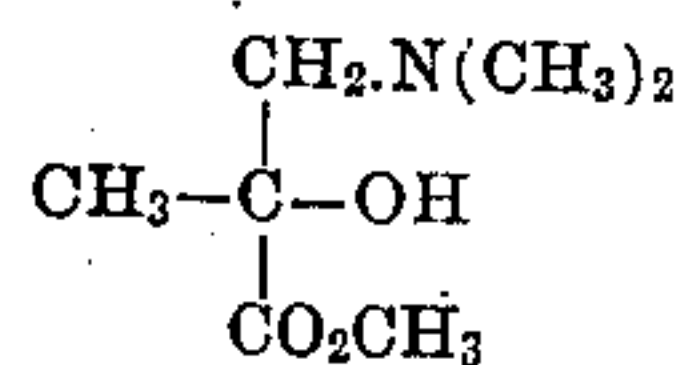
I declare that what I claim is:—

1. The hereinbefore described process for obtaining esters of oxy-amino acids, of the general formula—



in which R₂=an alkyl group, consisting in treating oxy-amino acids with ethyl alcohol previously saturated with gaseous hydrochloric acid in the cold, heating the mixture, distilling off the excess of alcohol and hydrochloric acid, crystallizing out the hydrochlorid, setting free the desired ester by the addition of a caustic soda solution, rendering pasty with sodium carbonate and extracting with ether.

2. As a new article of manufacture, di-methyl-amino-di-methyl-oxy-acetate of methyl



is obtained by warming methyl alcohol saturated with hydrochloric acid gas with the free di-methyl-amino-di-methyl-oxy-acetic acid, the resultant product boiling at 107° C. under 35 millimeters pressure, soluble in cold water, almost insoluble in hot water, yielding a benzoyl derivative, the hydrochlorid of which melts at 150° C.

In witness whereof, I have hereunto signed my name this 14th day of January 1907, in the presence of two subscribing witnesses.

ERNEST FOURNEAU.

Witnesses:

ANTONIO MONTEILHET,
HANSON C. COXE.