United States Patent Office 3,106,562 Patented Oct. 8, 1963

3,106,562

ESTERS OF NICOTINIC ACID

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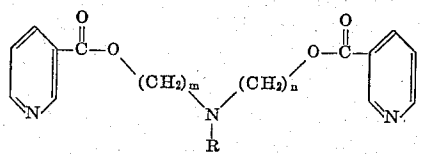
No Drawing. Filed July 27, 1961, Ser. No. 127,158
9 Claims. (Cl. 260—295.5)

This invention relates to esters of nicotinic acid. More particularly, it is directed to novel esters of nicotinic acid having the formula



(I)

wherein: *m* and *n* have a minimum value of 2 and a maximum value of 4 and R designates hydrogen or an alkyl group having a maximum of 4 carbon atoms.

It has been known for a long time that nicotinic acid and some of its esters have a hyperaemic effect on skin. This effect occurs after a certain latency time with different intensity and duration, depending upon the individual configuration of the esters and according to a physiological mechanism which has not yet been completely elucidated.

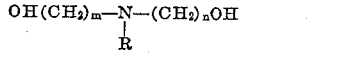
A number of esters of simple alcohols with both straight, branched and cyclic hydrocarbon chains have previously been produced. A number of amino alcohol esters are also known in literature.

Many of the last mentioned esters have a comparatively short time of onset and an intensive effect combined with the disadvantage that they give the same side effects as the nicotinic acid, prickling of the skin and sometimes itching. These esters moreover give too short a duration, as the intensive vasodilating effect also rapidly diminishes.

Tests have been made with nicotinic acid esters of high molecule polyols. These esters almost without exception show too slight an effect in the blood vessels of the skin, and for this reason, cannot be used.

Extensive scientific investigations leading to the present invention have resulted in the discovery that nicotinic acid esters of the above Formula I have extremely good therapeutic properties. The new compounds have an approximate time of onset of 5–10 minutes and a duration of 5–6 hours.

The new esters are manufactured according to usual and known esterification methods. Thus, dialcohols of the formula



(II)

wherein: *m*, *n*, and R have the same significance as in Formula I, can be made to react with nicotinic acid, nicotinic acid chloride or with a lower nicotinic acid ester. The esters obtained have the character of an oil and are suitable for the production of ointments with a hyperaemic effect.

If it is desired to inject the esters of this invention, the esters should be transformed into salts soluble in water, which a human being can stand. It is then appropriate to treat the esters with an inorganic acid such as phosphoric acid, sulfuric acid, hydrochloric acid or some other appropriate acid which forms a pharmaceutically acceptable acid addition salt with the ester.

The amino alcohol nitrogen facilitates the salt formation to the highest possible degree. These novel esters when injected produce vasodilation.

The present invention will be described in more detail in connection with the following examples.

Example 1

1275 g. of nicotinic chloride hydrochloride, divided up into small portions, is placed in a round flask with a reflux cooler, stirrer and thermometer. The flask is arranged in such a way that both cooling and heating can take place. The flask has previously been charged with 500 g. of propyl diethanol amine and 1000 g. of pyridine. While adding the nicotinic acid chloride hydrochloride the flask is cooled with water around it, so that the temperature does not exceed 80° C. Thereafter the reaction mixture is heated for 1 hour at 100° C. After the mixture has cooled somewhat, it is poured out into 5 litres of ice water, and a sufficient quantity of ice is used so that the temperature does not exceed 20° C. A yellowish brown solution is obtained from which the color is removed by treating it with active carbon after the pH has been raised to approximately 5 with 40% sodium hydroxide solution with simultaneous cooling. Under continued stirring the pH is raised after filtering to 11–12. The precipitated oil is separated and the water phase is extracted twice with 500 ml. of benzene. The benzene layer is mixed with the oil and the mixture is thereafter washed first twice with 5% sodium hydroxide and thereafter twice with water.

The mixture is finally digested twice with 100 g. of anhydrous sodium sulphate and once with active carbon. After the carbon has been filtered off, the benzene is distilled off, as well as the pyridine which has not been washed out. If there is an odor of pyridine from the residue in the distillation flask, 100 ml. of xylene is added, which is distilled off in vacuum. This operation is followed by the same operation with 100 ml. of benzene. The lightly opalescent residue, an oil, consisting of propyl-diethanol-amino dinicotinate is filtered through infusorial earth. A yield of approximately 950 g. is obtained, or approximately 90%. Nitrogen content according to Dumas 11.86% (theoretically 11.76%). Specific gravity: 1.1530 20/4.

Example 2

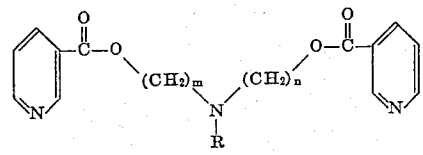
If the propyl-diethanol-amine according to Example 1 is replaced by ethyl-diethanol amine, after a reaction time of 4 hours at 110° C. ethyl-diethanol-amino dinicotinate is obtained as a final product. After the end of the reaction time the reaction substance is poured out into 8 liters of ice water and the temperature is then not allowed to exceed 20° C. At a pH of approximately 1, the solution is treated with 100–200 g. of active carbon and filtered. Thereafter 40% sodium hydroxide solution is added to the solution to pH 12 and the oil thereby obtained is separated and the residue is extracted several times with ether. The ether extract is mixed with the oil, and the mixture is washed twice with 1000 ml. of 5% sodium hydroxide and finally several times with water. The ether extract is dried with sodium sulphate and the ether is distilled off. The residue is mixed with 250 ml. of xylene, which is distilled off in vacuum. The same operation is repeated with benzene. The distillation residue is dissolved in 2500 ml. of ether and the solution is treated with active carbon and filtered. Ethyl-diethanol-amino-dinicotinate remains in the form of a brown oil with a low viscosity, when the ether has evaporated. Approximately 900 g. corresponding to a yield of approximately 80% is obtained. Nitrogen content according to Dumas 12.18% (theoretically 12.28%). Refractive index, N_D^{25}: 1.5394.

It will be understood that the foregoing description of the invention and the examples set forth are merely illustrative of the principles thereof. Accordingly, the

appended claims are to be construed as defining the invention within the spirit and scope thereof.

We claim:

1. A member of the group consisting of nicotinic acid esters and the pharmaceutically acceptable acid addition salts thereof, said esters having the formula



(I)

wherein: *m* and *n* each have a minimum value of 2 and a maximum value of 4 and R is a member of the group consisting of hydrogen and an alkyl group having a maximum of 4 carbon atoms.

2. Propyl-diethanol-amino dinicotinate.

3. Ethyl-diethanol-amino dinicotinate.

4. The phosphoric acid addition salts of the compound of claim 2.

5. The sulfuric acid addition salts of the compound of claim 2.

6. The hydrochloric acid addition salts of the compound of claim 2.

7. The phosphoric acid addition salts of the compound of claim 3.

8. The sulfuric acid addition salts of the compound of claim 3.

9. The hydrochloric acid addition salts of the compound of claim 3.

References Cited in the file of this patent

UNITED STATES PATENTS

2,766,252	Schlesinger	Oct. 9, 1956
2,863,873	Ekenstam et al.	Dec. 9, 1958

OTHER REFERENCES

"Chemical Abstracts," vol. 29, p. 8001[1] (1935), abstracting Russian Patent 35,836, Apr. 30, 1934.

"Chemical Abstracts," vol. 41, p. 2737C (1947), abstracting Mndzhoyan, "J. Gen. Chem. (USSR)," vol. 16, pp. 1029–40 (1946).

Noller: "Chemistry of Organic Compounds," 2nd edition, pages 165–171 (Saunders) (1957).