Sept. 9, 1952 W. OROSHNIK 2,610,185

2-AMINO-4-DIALKYLAMINOPROPOXYPYRIMIDINES

Filed Nov. 7, 1950 2 SHEETS--SHEET 1

Fig. 1.

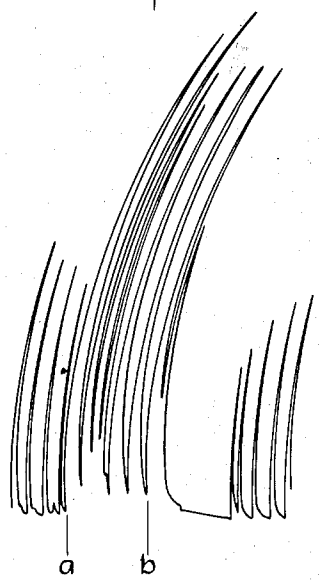


Fig. 2.

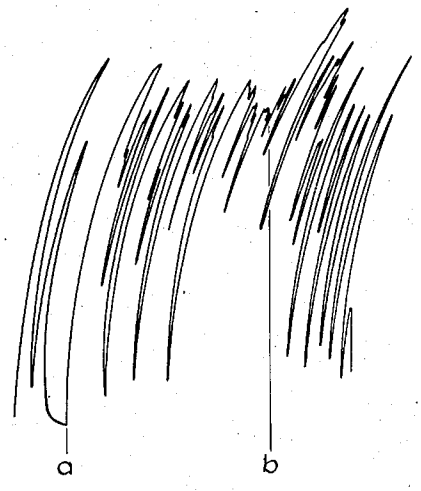
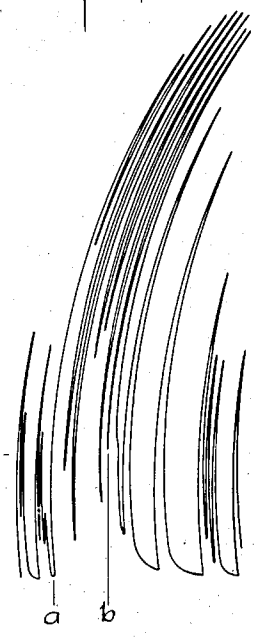


Fig. 3.



INVENTOR
WILLIAM OROSHNIK.
BY Leroy F. Halley
ATTORNEY

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Fig. 4.

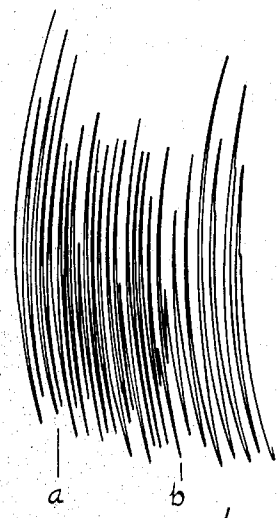


Fig. 5.

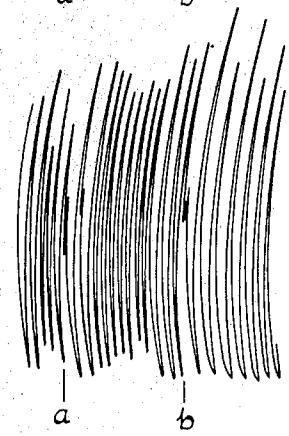
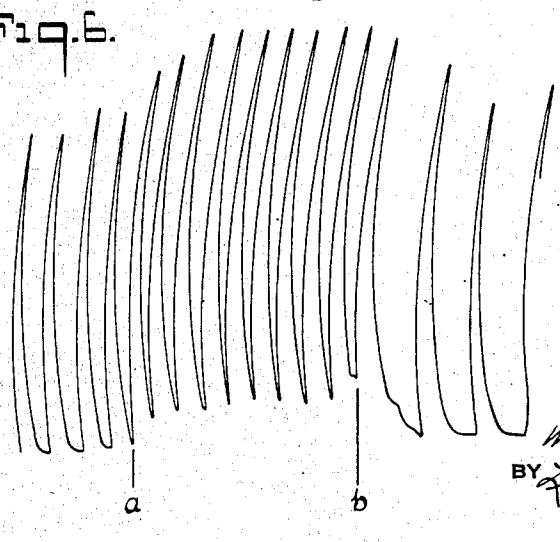


Fig. 6.



INVENTOR
WILLIAM OROSHNIK.
BY Leroy F. Halley
ATTORNEY

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2-AMINO-4-DIALKYLAMINOPROPOXY-PYRIMIDINES

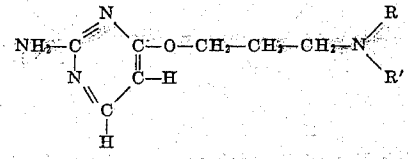
William Oroshnik, Plainfield, N. J., assignor to Ortho Pharmaceutical Corporation, a corporation of New Jersey

Application November 7, 1950, Serial No. 194,560

4 Claims. (Cl. 260—256.4)

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This invention relates to certain therapeutically effective organic compounds which are derivatives of isocytosine, 2-amino-4-hydroxypyrimidine; and to their use as therapeutic agents having the ability to stimulate contractions of the uterus. More specifically this invention relates to 2-amino-4-dialkylaminopropoxypyrimidines in which each alkyl group has at least three, and not more than five, carbon atoms. The said isocytosine derivitives having the ability to stimulate contractions of the uterus may be represented by the following formula:



in which R and R' are each an aliphatic radical having at least three, but not more than five carbon atoms.

A number of derivatives of isocytosine have been prepared and studied for various pharmaceutical and medical uses but it is believed that the particular derivatives of isocytosine which this invention is concerned with are new substances. It is also believed the ability of these substances to stimulate contractions of the uterus has not been known heretofore.

The derivatives of isocytosine which embody this invention may be used as such to stimulate contractions of the uterus. They may also be used as in the form of salts of the isocytosine derivatives with organic or inorganic acids and since the said derivatives are basic in character, they may be readily converted into salts having substantially more solubility in water than the free bases. Salts such as the succinate, maleate, tartrate, lactate, fumarate and the like are preferred, but salts of simple low-molecular weight aliphatic organic acids as well as salts of the free bases with inorganic acids, may be readily prepared from the free bases and are highly effective therapeutically.

The new and novel derivatives of isocytosine to which the present invention is directed have considerable value which renders their use as pharmaceutical products highly advantageous either alone or with known pharmacological products. The ability of these novel substances to stimulate contractions of the uterus has been shown by a number of experiments in which a salt of isocytosine derivative was added to a bath of nutrient solution having a strip of albino rat uterine tissue suspended therein. A continuous kymographic record was made of contractions of the uterine strip before and after addition to the bath of a salt of an isocytosine derivative. Additional derivatives of isocytosine which are homologues of 2-amino-4 dialkylaminopropoxypyrimidines specifically mentioned before as having therapeutic value were also tested in the same way to determine their effect on contractions of the uterus. Water-soluble hydrochloride salts or the sesquisuccinate salts of the following compounds were tested for their pharmacological property of stimulating contractions of the uterus:

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Compound I—2 - amino - 4 - di - n - propylaminopropoxypyrimidine

Compound II—2 - amino - 4 - di - n - amylaminopropoxypyrimidine

Compound III—2 - amino - 4 - di - n - butylaminopropoxypyrimidine

Compound IV—2 - amino - 4 - dimethylaminoethoxypyrimidine

Compound V—2 - amino - 4 - diethylaminoethoxypyrimidine

Compound VI—2 - amino - 4 diethylaminoethoxy - 6 - methylpyrimidine

The following procedure was employed in testing the effect of compounds I–VI on a rat uterus: A female albino rat weighing from 150–300 milligrams was killed by a blow on the head and the uterus was removed. A strip of the uterine tissue was suspended in a 100 cc. bath of an aerated Ringer-Locke solution. One end of the uterine strip was maintained in a stationary position and the other end was attached to a lever which made contact with a kymograph and continuously recorded contractions. After a short period of immersion in the bath, the strip of uterine tissue was contracting rhythmically and normally, and at this point an aqueous solution of a salt of an isocytosine derivative to be tested for its effect on contractions of uterine tissue was added to the bath. Figures 1–6 are kymographic records of contractions of the strip of uterine tissue before and after addition to the bath of the compounds to be tested. Normal contractions are recorded in the figures up to the point designated *a* and at this time a portion of the compound to be tested was added to the bath. The portion of the figures between letters *a* and *b* represents a record of contractions after addition to the bath of the compound being tested. The letter *b* in the figures designates the time at which the bath containing the compound be-

ing tested was removed and replaced by a nutrient bath containing no isocytosine derivative. That portion of Figures 1–6 after the letter *b* represents contractions as they return to normal and after the uterine strip is no longer in contact with a compound being tested for its effect on contractions of uterine tissue.

Figures 1, 2, and 3 show the effect of the addition to the bath of 5 milligrams of compounds I, II, and III, respectively, as the hydrochloride salts thereof. Figure 1 shows the addition to the bath of 5 milligrams of compound I in the form of its hydrochloride salt produced a marked increase in amplitude of contractions, some increase in tonus, and a small increase in frequency of contractions of the uterine muscular tissue. Figure 2 shows the addition to the bath of 5 milligrams of compound II in the form of its hydrochloride salt produced an increase in frequency of contractions, a very marked increase in tonus and some increase in amplitude of contractions of the uterine muscular tissue. Figure 3 shows the addition to the bath of 5 milligrams of compound III in the form of its hydrochloride salt produced a very marked increase in amplitude of contractions, a substantial increase in frequency of contractions, and a marked increase in tonus of the uterine muscular tissue.

Figures 4, 5, and 6 show only slight effects on the uterine muscular tissue result from the addition of sesquisuccinate salts of compounds IV, V, and VI to the bath. Figure 4 shows the addition of 10 milligrams of the sesquisuccinate salt of compound IV produced a slight decrease in amplitude of contractions and Figures 5 and 6 show the addition to the bath of 10 milligrams of the sesquisuccinate salts of compounds V and VI, respectively, produced a slight increase in amplitude of contractions and a slight increase in tonus of the uterine muscular tissue.

Tonus is a natural property of muscle and is a measure of degree of contraction independent of external influences. The degree of contraction produced by a stimulant depends upon the level of tonus, and, therefore, some investigators have defined tonus as the resistance offered to extension.

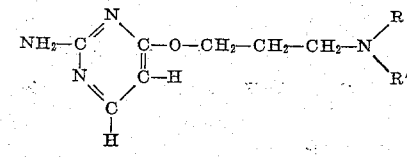
Amplitude may be defined as the height of a contraction wave measured from the base level to the peak of the wave; base level being the average lower level of the contractions.

Frequency is the number of contraction waves in a unit time period.

Derivatives of isocytosine such as 2-amino-4-dialkylaminopropoxypyrimidine may be prepared by reacting 2-amino-4-chloropyrimidine with the sodium salt of a dialkylaminopropanol. The following is an example of the preparation of 2-amino-4-di-n-propylaminopropoxypyrimidine, in which the parts are given by weight. Twenty-five parts of sodium metal were slowly added to 175 parts of di-n-propylaminopropanol, dissolved in 500 parts of xylene. Five hundred parts of benzene were then added to the resulting sodium salt of di-n-propylaminopropanol. One hundred twenty-nine parts of 2-amino-4-chloropyrimidine were added to the above solution and during the addition the solution was cooled sufficiently to maintain the temperature at 80° C. After the addition was complete, the reaction mixture was refluxed for one hour and cooled and then 100 parts of water containing 10 parts of dissolved sodium hydroxide were added with stirring. At this point two layers were formed; the organic layer was decanted, dried over anhydrous potassium carbonate, and the solvents, benzene and xylene, were removed by distillation. The residue in the distillation flask was distilled at a temperature of 120–125° C. and a pressure of 0.002 mm. of mercury. One hundred seventy-four parts of 2-amino-4-di-n-propylaminopropoxypyrimidine were obtained. The free pyrimidine base was only slightly soluble in water but reacted readily with hydrochloric acid in equimolar amounts to produce a water-soluble hydrochloride salt.

What is claimed is:

1. A compound having the structural formula



in which R and R′ each represent an alkyl group having at least three but not more than five carbon atoms.

2. A compound according to claim 1 in which R and R′ are each a normal propyl radical.

3. A compound according to claim 1 in which R and R′ are each a normal butyl radical.

4. A compound according to claim 1 in which R and R′ are each a normal amyl radical.

WILLIAM OROSHNIK.

REFERENCES CITED

The following references are of record in the file of this patent:

Sutherland et al.: J. Org. Chem. 14, 235–238 (1949).