

Sept. 9, 1952

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2,610,187

2-AMINO-4-DIALKYLAMINOETHOXY-6-METHYLPYRIMIDINES

Filed Nov. 7, 1950

2 SHEETS—SHEET 1

Fig. 1.

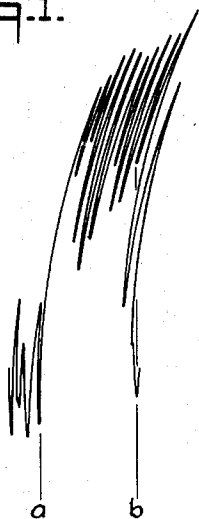


Fig. 2.

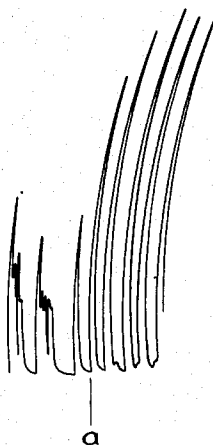


Fig. 3.



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2 SHEETS—SHEET 2

Fig. 4.

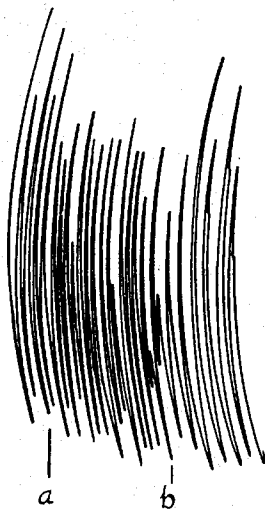


Fig. 5.

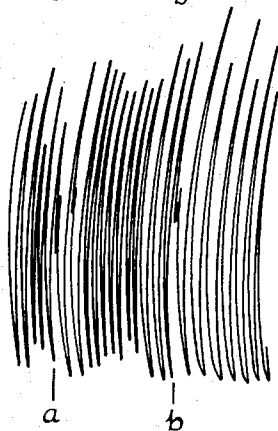
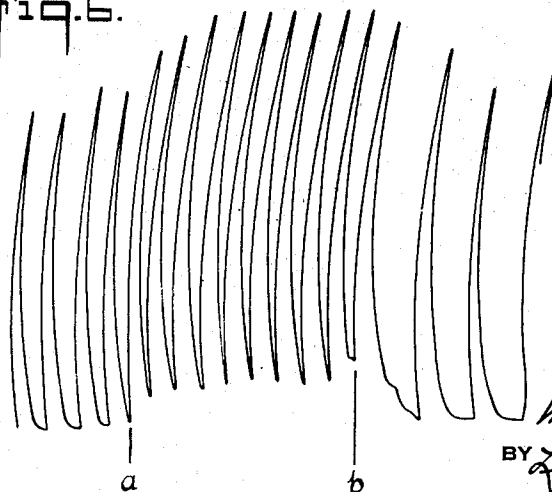


Fig. 6.



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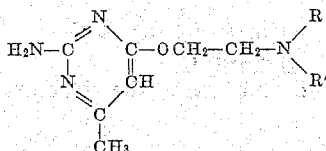
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5 Claims. (Cl. 260—256.4)

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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-dialkylaminoethoxy-6-methylpyrimidines in which each alkyl group is a normal propyl, isopropyl, secondary butyl, or normal butyl radical. The said isocytosine derivatives having the ability to stimulate contractions of the uterus may be represented by the following graphic formula:



in which R and R' are each an aliphatic radical which may be normal propyl, isopropyl, secondary butyl, or normal butyl.

A number of derivatives of isocytosine have been prepared and studied for various pharmaceutical and medicinal uses but it is believed that the particular derivatives of isocytosine with which this invention is concerned 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 the isocytosine derivative was added to a bath of nu-

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trient 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-dialkylaminoethoxy-6-methylpyrimidines specifically mentioned before as having therapeutic value were also tested in the same way to determine their effect on contractions of the uterus. The sesquisuccinates of the following compounds were tested for their pharmacological property of stimulating contractions of the uterus:

- 15 Compound I—2-amino-4-di-n-propylaminoethoxy-6-methylpyrimidine
- Compound II—2-amino-4-diisopropylaminoethoxy-6-methylpyrimidine
- 20 Compound III—2-amino-4-di-n-butylaminoethoxy-6-methylpyrimidine
- Compound IV—2-amino-4-dimethylaminoethoxypyrimidine
- Compound V—2-amino-4-diethylaminoethoxypyrimidine
- 25 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 a sesquisuccinate 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 being tested was removed and re-

placed 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 of 10, 10, and 5 milligrams of the sesquisuccinate salts of compounds I, II, and III, respectively, to the bath. Figures 4, 5, and 6 show the effect of the addition of 10 milligrams of compounds IV, V, and VI, respectively, to the bath.

Figure 1 shows the addition of 10 milligrams of the sesquisuccinate salt of compound I to the bath produced a marked increase in amplitude of contractions and a very marked increase in tonus of the uterine muscular tissue. Frequency of contractions was not increased to any substantial degree. Figure 2 shows the addition of 10 milligrams of the sesquisuccinate salt of compound II to the bath produced a very marked increase in amplitude of contractions but practically no increase in tonus of the uterine muscular tissue. A substantial increase in the frequency of contractions was also produced. Figure 3 shows the addition of 5 milligrams of the sesquisuccinate salt of compound III to the bath produced a very marked increase in amplitude of contractions and tonus of the uterine muscular tissue, as well as a slight increase in frequency of contraction. Figures 4, 5, and 6 show only slight effects on the uterine muscular tissue result from the addition of the 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 to the bath produced a slight decrease in amplitude of contractions, and Figures 5 and 6 show the addition of 10 milligrams of the sesquisuccinate salts of compounds V and VI, respectively, to the bath produced a slight increase in amplitude of contractions and a slight increase in tonus of the uterine muscular tissue.

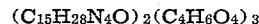
Tonus is a natural property of muscle and is a measure of degree of contraction independent of external influences. The degree of contraction produced by a stimulant depends upon the level of tonus, and, therefore, some investigators have defined tonus as the resistance offered to extension.

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.

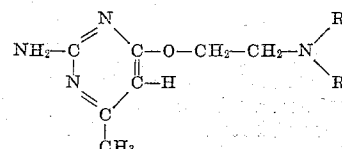
Derivatives of isocytosine such as 2-amino-4-dialkylaminoethoxy-6-methylpyrimidines may be prepared by reacting 2-amino-4-chloro-6-methylpyrimidine with the sodium salt of a dialkylaminoethanol. The following is an example of the preparation of 2-amino-4-di-n-butylaminoethoxy-6-methylpyrimidine, in which the parts are given by weight. Twenty-five parts of sodium metal were slowly added to 200 parts of di-n-butylaminoethanol, dissolved in 500 parts

of xylene. Twelve hundred parts of benzene were then added to the resulting sodium salt of di-n-butylaminoethanol. One hundred forty-three parts of 2-amino-4-chloro-6-methylpyrimidine 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 and 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 124-140° C. and a pressure of 0.001 mm. of mercury. One hundred and eighty parts of 2-amino-4-di-n-butylaminoethoxy-6-methylpyrimidine were obtained and subsequently recrystallized from ether. The crystalline product had a melting point of 51-52° C. The pure compound is soluble in most organic compounds and insoluble in water. A water-soluble sesquisuccinate of the free base was prepared as follows: 5 grams of the base and 3.15 grams of succinic acid were dissolved in 30 cc. of hot acetone. A white crystalline material precipitated on cooling this solution. The precipitate was removed by filtering and recrystallized from acetone. The recrystallized material had a melting point of 127-128° C. The crystalline salt had the following formula:



What is claimed is:

1. A compound having the structural formula



in which R and R' each represent an alkyl radical selected from the group consisting of normal propyl, isopropyl, secondary butyl, and normal butyl radicals.

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 propyl radical.

4. A compound according to claim 1 in which R and R' are each a secondary butyl radical.

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

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REFERENCES CITED

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

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Braker et al.: J. Am. Chem. Soc. 69, 3072-3078 (1947).