# United States Patent

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[31] **3,774/67**


[54] **2,4,6-TRISUBSTITUTED DERIVATIVES OF PYRIMIDINE**
**7 Claims, No Drawings**


[52] **U.S. Cl.** ..... **260/256.4 N,** 260/246, 260/247.5, 424/248, 424/251
[51] **Int. Cl.** ..... **C07d 51/42,** C07d 87/38
[50] **Field of Search** ..... 260/256.4 N



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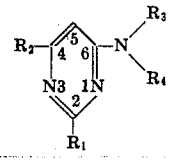
**ABSTRACT:** New 2,4,6-trisubstituted pyrimidine derivatives of the general formula

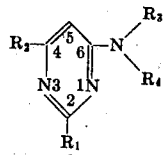



in which $R_1$ is hydrogen, lower alkyl, aralkyl,
$R_2$ is hydrogen, halogen, lower alkyl, hydroxyalkylamino, omega-aryl-omega-hydroxyalkylamino, morpholino,
$R_3$ is hydrogen, lower alkyl eventually hydroxyl-substituted, aralkyl,
$R_4$ is lower alkyl substituted by at least one hydroxyl group separated from N by at least two carbon atoms, or
$R_3$ and $R_4$ together with the extranuclear N are morpholino, as well as their salts with inorganic or organic acids.
These compounds are hypotensives, peripheral and coronary vasodilators, diuretics, bronchodilators, spasmolytics and circulatory and respiratory analeptics.

## 2,4,6-TRISUBSTITUTED DERIVATIVES OF PYRIMIDINE

The present invention is concerned with new 2,4,6-trisubstituted derivatives of pyrimidine and their addition salts with pharmaceutically acceptable acids, as well as with the preparation thereof and their therapeutic use.

The new 2,4,6-trisubstituted pyrimidine derivatives according to the present invention are compounds of the general formula:



in which

$R_1$ is a member selected from the group consisting of hydrogen, alkyl containing up to five carbon atoms and aralkyl,

$R_2$ is a member selected from the group consisting of hydrogen, halogen, alkyl containing up to five carbon atoms, hydroxyalkylamino, omega-aryl-omega-hydroxyalkylamino and morpholino,

$R_3$ taken separately, is a member selected from the group consisting of hydrogen, alkyl containing up to five carbon atoms which may be substituted by at least one hydroxyl group and aralkyl,

$R_4$ taken separately, is alkyl containing from to two to five carbon atoms, substituted by at least one hydroxyl group separated from the N atom by at least two carbon atoms, and

$R_3$ and $R_4$ taken together with the extranuclear nitrogen atom to which they are attached form a morpholino radical,

as well as their salts with inorganic and organic acids.

Pharmacological studies have shown that the new compounds according to the present invention possess interesting properties, some being hypotensives, peripheral and coronary vasodilators, diuretics, bronchodilators and spasmolytics and some being circulatory and respiratory analeptics.

The following list of compounds according to the invention has been chosen to illustrate the pharmacological activity. This is on the understanding that said list is not restrictive, as all the compounds of the invention have been submitted to the test mentioned below.

A. 2-propyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine

B. 2-methyl-4-propyl-6-morpholino-pyrimidine

C. 2-ethyl-4-chloro-6-morpholino-pyrimidine

D. 2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl((ethyl)amino] -pyrimidine

E. 2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl)(methyl)amino]-pyrimidine

F. 2-methyl-4-chloro-6-morpholino-pyrimidine

G. 2-benzyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine

H. 2-benzyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine

I. 2-propyl-4-(2-hydroxyethyl)amino-6-morpholino-pyrimidine

J. 2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-[bis(2-hydroxyethyl)amino]-pyrimidine

K. 2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-morpholino-pyrimidine

L. 2-methyl-4,6-dimorpholino-pyrimidine

M. 2-propyl-4-methyl-6-[N,N-(2-hydroxyethyl)(benzyl)amino]-pyrimidine

N. 2-propyl-4-methyl-6-[N,N-(2-hydroxyethyl)(ethyl)amino]-pyrimidine

O. 2-propyl-4-methyl-6-(5-hydroxypentyl)amino-pyrimidine



P. 2-isopropyl-4-methyl-6-(2-hydroxyethyl)amino-pyrimidine

a. Hemodynamic influence as detected by measuring the cardiac output (of dogs)

The tested products are intravenously injected. The following results are obtained on four pairs of dogs from the administration on one hand of theophylline and on the other hand of product A according to the invention.

| Doses mg./kg. | Theophylline I | Theophylline II | Product A I | Product A II |
|---|---|---|---|---|
| 2 | 7 | 20 | 14 | >140 |
| | 10 | 10 | 33 | >140 |
| 5 | 10 | 20 | 37.5 | 140 |
| | 10 | 20 | 27.5 | 30 |
| 10 | 12.5 | 20 | 14 | >90 |
| | 50 | 30 | 65 | 60 |
| 20 | 35 | 10 | 77.5 | >270 |
| | 25 | 20 | 25 | 150 |

I= cardiac output increase in % (maximal effect)

II= duration of increase in minutes.

Product A proves to be considerably superior to theophylline both as to the increase in cardiac output and as to the duration of that increase. This circulatory analeptic action manifests itself, among other features, by an increase in renal output which may result in an interesting diuretic power. A respiratory analeptic power has also been observed.

b. Peripheral vasodilator effect on dog's leg

The dog's leg is perfused with a constant blood output according to the technique described by D. WELLENS (Arch.int.Pharmacodyn.151, (1964),281–285). The products are injected in the perfusion circuit and their vasodilator effect is manifested by a decrease in perfusion pressure.

Vasodilator action in % of that of theophylline

Product B=370 Product D=530 Product H=150 Product M=900

Product C=300 Product E=300 Product L=100 Product P=310

The products according to the invention reduce the peripheral resistence and, in this way, they can relieve the cardial work, improve the peripheral circulation and cope with the arterial hypertension.

c. Coronarodilator effect

A variant of the known method of LANGENDORFF is applied. The details of the technique and apparatus combine certain features described by E. VANREMOORTERE, J. LECOMTE, H. MAZZELLA and F. NELEMANS (Arch.int.Pharmacodyn.95,(1953),466–487) with certain modifications used by R. CHARLIER (Monographs on pure and applied Biology, Vol.10, Pergamon Press, 1961).

| Product | Dose 2μg./ml. | 50μg./ml. | 100μg./ml. |
|---|---|---|---|
| Theophylline | 39 | 35 | |
| Product B | 46 | 80 | |
| Product C | 73 | 165 | |
| Product F | 34 | 71 | |
| Product G | | | 116 |
| Product H | 120 | | |
| Product I | 30 | | |
| Product J | 30 | | |
| Product L | | | 131 |
| Product N | 23 | | |
| Product O | 26 | | |

Above-given figures indicate the percentage increase in coronary output. The coronarodilator effect of the products according to the invention is often more significant than that of theophylline.

d. Dilatation of the isolated trachea of guinea-pigs

The dilator effect of the products is determined by means of a continuous recording of the endotracheal tonus of the guinea pig. The trachea is isolated and prepared according to the technique described by D. WELLENS (Med.Pharm.Exptl.14,(1966),427–434). The endotracheal tonus decrease is expressed in mm. H2O

| Product | Dose 2μg./ml. | Dose 20μg./ml. |
|---|---|---|
| Theophylline | 2.3 mm. $H_2O$ | 25 mm. $H_2O$ |
| Product A | 11 | |
| Product G | | 10 |
| Product I | | 9 |
| Product O | | 14 |

e. Protective effect against bronchospasm induced in guinea-pigs

The method of H. KONZETT and R. ROESSLER (Arch.exp.Path.Pharmakol.195, (1940),71–74) is applied on masculine and feminine albino guinea-pigs weighing between 300 and 500 g.

The following table gives the results of comparative tests between theophylline and certain products of the invention.

| Compound | Bronchospasm | Doses mg./kg. | Maximum effect (at 2 min.) | Effect after 12 min. |
|---|---|---|---|---|
| Theophylline | Acetylcholine | 2 | 18 | 3.7 |
| | | 4 | 41 | 15.2 |
| | | 8 | 76 | 38.1 |
| | | 16 | 92 | 60.6 |
| Histamine | | 2 | 30 | 4.6 |
| | | 4 | 50.4 | 17 |
| | | 8 | 81.6 | 52 |
| | | 16 | 93.7 | 92.7 |
| | 5-hydroxy-tryptamine | 2 | 20.5 | 2 |
| | | 4 | 48.4 | 20 |
| | | 8 | 79.6 | 48 |
| | | 16 | 86 | 79 |
| Product A | Acetylcholine | 0.4 | 17.2 | 0.4 |
| | | 0.8 | 37.2 | 9.6 |
| | | 1.6 | 63.2 | 33.2 |
| | | 3.2 | 84 | 57.2 |
| | Histamine | 0.4 | 18.3 | 1.5 |
| | | 0.8 | 39.5 | 14.3 |
| | | 1.6 | 53.3 | 38 |
| | | 3.2 | 71.5 | 40 |
| | 5-hydroxy-tryptamine | 0.4 | 6.6 | 3.6 |
| | | 0.8 | 26 | 11.7 |
| | | 1.6 | 53.6 | 19.7 |
| | | 3.2 | 66.7 | 45 |
| Product K | 5-hydroxy-tryptamine | 3 | 55 | 9 |
| | | 9 | | 10 98 |
| Product P | Acetylcholine | 1 | 2 | 1 |
| | | 3 | 22 | 5 |
| | | 9 | 36 | 15 |
| | 5-hydroxy-tryptamine | 1 | 16 | 10 |
| | | 3 | 48 | 22 |
| | | 9 | 79 | 43 |

With reference to the efficaceous dose, Product A appears to be four to five times more active than theophylline. The properties put forward are such that they preconise a therapeutical application in the treatment of spastic states of the bronchial unstriated muscles (asthma, bronchitis, emphysema).

f. Spasmolytic effect on isolated organs.

Isolated intestine preparations (of rat or guinea-pig) are placed in a survival bath according to the known method described by R. MAGNS (P flueger Arch. 102, (1904),123–151). The efficaceous dose DE 50 is determined (in micrograms/ml.) that antagonizes 50 percent of the convulsivant effect (induced by barium chloride or acetylcholine).

The found DE 50 value is given in the following table for both theophylline and the Product A according to the invention:

| | Theophylline | Product A |
|---|---|---|
| BaCl2 | 572 | 233 |
| Acetylcholine | 292 | 117 |

Product A proves to be more than twice as active as theophylline.

g. Spasmolytic effects "in situ"

The spasmolytic effect observed in vitro on an isolated organ (test *f*) is also observed "in situ" in the animal (anesthetized dog). The Product A e.g., at doses of 0.5 to 5 mg./kg., obviously inhibits spasms induced by the injection of morphine (0.25 mg./kg.).

The products of the invention show, in intravenous toxicity tests on rats, a mean toxicity which is less than that of theophylline, as can be seen from the following table (DL 50 expressed in mg./kg.).

| Product | DL 50 |
|---|---|
| Theophylline | 176 |
| Product A | 240 |
| Product B | 110 |
| Product C | 240 |
| Product D | 200 |
| Product E | 350 |
| Product F | 364 |

From the pharmacological tests (*a*) to (*g*) it appears that the products of the invention have analogous effects to those of theophylline, besides pronounced advantages over that substance.

Consequently, the products of the invention can be used in the therapeutical applications wherever theophylline is used.

The new compounds of the present invention may be prepared by the known methods of preparing substituted pyrimidines.

In particular, they may be prepared by the following methods:

a. when $R_2$ is a member selected from the group consisting of hydrogen and alkyl, reacting a member selected from the group consisting of 2-$R_1$-6-halo-pyrimidine and 2-$R_1$-4-alkyl-6-halo-pyrimidine with an organonitrogen compound selected from the group consisting of primary and secondary hydroxyalkylamines and morpholine;

b. when $R_2$ is a member selected from the group consisting of halogen, hydroxyalkylamino and morpholino, reacting a 2-$R_1$-4,6-dihalo-pyrimidine with an organonitrogen compound selected from the group consisting of primary and secondary hydroxyalkylamines and morpholine, in such quantities and under such working conditions that a member of the group consisting of 2-$R_1$-4-halo-6-hydroxyalkylamino-pyrimidine, 2-$R_1$-4-halo-6-morpholino-pyrimidine, 2-$R_1$-4,6-bis-hydroxyalkylamino-pyrimidine and 2-$R_1$-4,6-dimorpholino-pyrimidine is isolated.

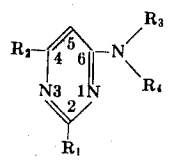
c. when $R_2$ is a member selected from the group consisting of hydroxyalkylamino and morpholino, reacting a member selected from the group consisting of 2-$R_1$-halo-6-hydroxyalkylamino-pyrimidine and 2-$R_1$-4-halo-6-morpholino-pyrimidine with an organonitrogen compound selected from the group consisting of primary and secondary hydroxyalkylamines and morpholine.

The 2,4,6-trisubstituted pyrimidine derivatives thus obtained may subsequently be converted into their salts with mineral and organic acids.

The following examples are given for the purpose of illustrating the present invention.

EXAMPLE 1

2-propyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine.



A mixture of 371 g. (2.17 mol) 2-propyl-4-methyl-6-chloro-pyrimidine, 457 g. (4.45 mol) diethanolamine and 1,500 cc. anhydrous dioxan is boiled under reflux for 30 hours. The reaction mixture is cooled and the upper layer is separated from the lower layer which consists of diethanolamine hydrochloride. By the addition of ether to the dioxan solution, 2-propyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine crystallizes out. It is recrystallized from dioxan, ethyl acetate or ethanol. Yield 430.5 g. (1.8 mol), which is 83 percent of theory. M.p. 102°–103° C.

There is given below a list of compounds which have been prepared by the same process, starting from the appropriate 6-chloropyrimidine and from the appropriate amine. Some of the compounds were isolated by concentration of the dioxan solution and distillation of the residue or by conversion into the hydrochloride:

2-propyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 183°–184° C., after recrystallization from isopropanol-ether.

2-isobutyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 218°–219° C. after recrystallization from ethanol-ether. (This product may also be prepared from 2-isobutyl-4-chloro-6-morpholino-pyrimidine described in example 2 by the known catalytic dehalogenation method using palladiated carbon.

6-morpholino-pyrimidine; m.p. of the hydrochloride 193°–194° C, after recrystallization from isopropanol-ether. (Also prepared from 4-chloro-6-morpholino-pyrimidine by catalytic dehalogenation suing palladiated carbon.

2,4-dimethyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 148°–149° C., after recrystallization from dioxan.

2,4-dimethyl-6-morpholino-pyrimidine; b.p. 101°–103° C./0.01 mm.Hg.

2-ethyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 93°–94° C., after recrystallization from propanol-ether.

2-ethyl-4-methyl-6-morpholino-pyrimidine; b.p. 109°–110° C./0.001 mm. Hg.

2-propyl-4-methyl-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 106°–107° C., after recrystallization from dioxan-ether.

2-propyl-4-methyl-6-(3-hydroxypropyl)amino-pyrimidine; m.p. of the hydrochloride 116°–117° C., after recrystallization from alcohol.

2-propyl-4-methyl-6-(2,3-dihydroxypropyl)amino-pyrimidine; m.p. 107°–108° C., after recrystallization from ethyl acetate-hexane.

2-propyl-4-methyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 181°–182° C., after recrystallization from alcohol-ether.

2-propyl-4-methyl-6-[bis(2-hydroxypropyl)amino]-pyrimidine; nondistillable and noncrystallizable oil which gives only a spot on electrophoresis; analysis: calculated molecular weight 267, found molecular weight 267; nitrogen calculated 15.73 percent, nitrogen found 15.58 percent.

2-propyl-4-methyl-6-[N,N-(2-hydroxyethyl)(ethyl)amino]-pyrimidine; b.p. 130°–132° C./0.001 mm. Hg.

2-propyl-4-methyl-6-[N,N-(2-hydroxyethyl)(methyl)amino ]-pyrimidine; b.p. 124°–126° C./0.001 mm. Hg.

2-propyl-4-methyl-6-(5-hydroxypentyl)amino-pyrimidine; m.p. 73°–74° C., after recrystallization from ethyl acetate.

2-propyl-4-methyl-6-[N,N-(2-hydroxyethyl)(benzyl)amino ]-pyrimidine; m.p. 73°–74° C., after recrystallization from ethanol-water.

2-isopropyl-4-methyl-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 156°–157° C., after recrystallization from ethyl acetate-hexane.

2-isopropyl-4-methyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 211°–212° C., after recrystallization from ether.

2-isopropyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 118°–119° C., after recrystallization from acetone.

4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 104°–105° C., after recrystallization from ethyl acetate-hexane.

2-butyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 53°–54° C., after recrystallization from ethyl acetate.

2-isobutyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 65° C., after recrystallization from ethyl acetate.

2-butyl-4-methyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 102°–103° C.

2-isobutyl-4-methyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 185°–186° C.

2-methyl-4-propyl-6-morpholino-pyrimidine; b.p. 121°–122 °C./0.001 mm. Hg.

2-methyl-4-propyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 100°–101° C., after recrystallization from ethyl acetate.

2-4-dipropyl-6-morpholino-pyrimidine; b.p. 124°–125° C./0.001 mm. Hg.

2-4-dipropyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 63°–64° C., after recrystallization from ethyl acetate.

2-pentyl-4-methyl-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 71° C., after recrystallization from ether.

2-pentyl-4-methyl-6-[bis-(2-hydroxyethyl)amino]-pyrimidine; m.p. of the hydrochloride 120°–121° C., after recrystallization from ether.

2-pentyl-4-methyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 171°–172° C., after recrystallization from ether.

2-benzyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 78°–79° C., after recrystallization from ethyl acetate-hexane.

2-benzyl-6-morpholino-pyrimidine; m.p. of the hydrochloride 170° C., after recrystallization from isopropanol-ether.

EXAMPLE 2

2-propyl-4-chloro-6-morpholino-pyrimidine

17.4 g. (0,2 mol) morpholine are added to 19.1 g. (0.1 mol) 2-propyl-4,6-dichloro-pyrimidine in 100 cc. dioxan. During the course of the addition, there is observed an increase of the temperature to about 70° C. At the end of the addition, the reaction mixture is heated to 80° C. for 10 hours. After cooling the reaction mixture, morpholine hydrochloride formed during the reaction is filtered off. The filtrate is then evaporated to dryness and the residue recrystallized from water. There are finally isolated 23.3 g. (0,096 mol) 2-propyl-4-chloro-6-morpholino-pyrimidine, the yield being 96 percent of theory; m.p. 59°–60° C.

The corresponding hydrochloride may be prepared in ether; m.p. 139°–140° C.

The following compounds are also prepared by this process. Some of them are purified by distillation. In the syntheses in which diethanolamine is used, the diethanolamine

hydrochloride formed in the course of the reaction is separated by decantation.

4-chloro-6-morpholino-pyrimidine; m.p. 151°–152° C., after recrystallization from ethyl acetate-hexane.

4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. of hydrochloride 122°–123° C., after recrystallization from isopropanol-ether.

4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 114°–115° C., after recrystallization from ethyl acetate-hexane.

2-propyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. of the hydrochloride 108° C., after recrystallization from alcohol-ether.

2-propyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 79°–80° C., after recrystallization from ethyl acetate.

2-methyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 96°–97° C., after recrystallization from toluene-hexane.

2-methyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 134°–135° C., after recrystallization from ethyl acetate.

2-methyl-4-chloro-6-morpholino-pyrimidine; m.p. 94°–95° C., after recrystallization from water.

2-ethyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 109° C., after recrystallization from ethyl acetate.

2-ethyl-4-chloro-6-morpholino-pyrimidine; m.p. 79°–80° C., after recrystallization from water.

2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl)(methyl)amino]-pyrimidine; b.p. 145°–147° C./0.001 mm.Hg.

2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl)(ethyl)amino]-pyrimidine; b.p. 141°–142° C./0.001 mm. Hg.

2-propyl-4-chloro-6-[N,N-(2-hydroxyethyl)(methyl)amino ]-pyrimidine; b.p. 145°–147° C./0.001 mm. Hg. m.p. of the hydrochloride 128°–129° C.

2-isopropyl-4-chloro-6-morpholino-pyrimidine; m.p. 74° C., after recrystallization from isopropanol-water.

2-isopropyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 76°–77° C., after recrystallization from ethyl acetate-hexane.

2-isopropyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 57°–58° C., after recrystallization from ethyl acetate-hexane.

2-isobutyl-4-chloro-6-morpholino-pyrimidine; b.p. 135°–137° C./0.005 mm. Hg; $n^{21.5}$=1.5498.

2-isobutyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 93°–94° C., after recrystallization from ethyl acetate-hexane.

2-isobutyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 123°–124° C., after recrystallization from isopropanol-ether.

2-benzyl-4-chloro-6-morpholino-pyrimidine; m.p. 141°–142° C., after recrystallization from ethyl acetate-hexane.

2-benzyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine; m.p. of the hydrochloride 126°–128° C., after recrystallization from isopropanol-ether.

2-benzyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. of the hydrochloride 129° C., after recrystallization from isopropanol-ether.

## EXAMPLE 3

2-propyl-4-(2-hydroxyethyl)amino-6-morpholino-pyrimidine.

24.15 g. (0.1 mol) 2-propyl-4-chloro-6-morpholino-pyrimidine and 100 g. (1.64 mol) monoethanolamine are heated to 140° C. for 20 hours. The excess ethanolamine is then distilled off in a vacuum and the residue taken up in dioxan. The ethanolamine hydrochloride formed during the reaction is separated by filtration through "Hyflocel" or norite. The filtrate is then evaporated to dryness. The residue (29 g.) is dissolved, with heating, in the minimum amount of ethyl acetate and hexane then added until the appearance of a slight cloudiness. After cooling, crystallization takes place. By filtration, there are then isolated 23.3 g. (0.088 mol) 2-propyl-4-(2-hydroxyethyl)amino-6-morpholino-pyrimidine; yield 88 percent of theory; m.p. 87°–88° C.

The following compounds have been prepared in a similar way:

2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-morpholino-pyrimidine; m.p. 136°–137° C., after recrystallization from ethyl acetate-hexane.

2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-[bis(2-hydroxyethyl)amino]-pyrimidine; m.p. 144°–145° C., after recrystallization from ethyl acetate-hexane.

2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-(2-hydroxyethyl)amino-pyrimidine; m.p. 131° C., after recrystallization from ethyl acetate-hexane.

## EXAMPLE 4

2-propyl-4,6-dimorpholino-pyrimidine

87 g. (1 mol) morpholine are carefully added to 19.1 g. (0.1 mol) 2-propyl-4,6-dichloropyrimidine. During the course of the addition, the temperature increases to 140° C. Subsequently, the temperature is maintained at 130°–140° C. for 25 hours. The reaction mixture is then cooled and water and ether added. The ethereal layer is separated, washed with water, dried and evaporated to dryness. The residue is recrystallized from hexane.

There are finally obtained 26 g. (0.089 mol) 2-propyl-4,6-dimorpholino-pyrimidine. Yield 89 percent of theory; m.p. 102° C.

The 2-methyl-4,6-dimorpholino-pyrimidine has also been prepared by this method; m.p. 170°–171° C., after recrystallization from ethyl acetate-hexane.

I claim:

1. 2-propyl-4-methyl-6-[bis(2-hydroxyethyl)amino]-pyrimidine.

2. 2-pentyl-4-methyl-6-(2-hydroxyethyl)amino-pyrimidine.

3. 2-propyl-4-chloro-6-(2-hydroxyethyl)amino-pyrimidine.

4. 2-propyl-4-chloro-6-[bis(2-hydroxyethyl)amino]-pyrimidine.

5. 2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl)(methyl)amino]-pyrimidine.

6. 2-ethyl-4-chloro-6-[N,N-(2-hydroxyethyl)(ethyl)amino]-pyrimidine.

7. 2-propyl-4-(2-phenyl-2-hydroxyethyl)amino-6-(2-hydroxyethyl)amino-pyrimidine.

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