PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 213/74 — A2

(11) International Publication Number: WO 94/22836

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/US94/02548

(22) International Filing Date: 15 March 1994 (15.03.94)

(30) Priority Data:
08/040,181 26 March 1993 (26.03.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/040,181 (CIP)
Filed on 26 March 1993 (26.03.93)

(71) Applicant *(for all designated States except US)*: THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

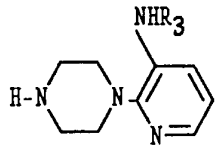
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PEARLMAN, Bruce, Allen [US/US]; 3411 Willow Lake Drive, #308, Kalamazoo, MI 49008 (US). KROOK, Mark, A. [US/US]; 7579 Hunters Ridge Drive, Kalamazoo, MI 49002 (US). PERRAULT, William, R. [US/US]; 5108 Pavilion Drive, Kalamazoo, MI 49001 (US). DOBROWOLSKI, Paul, J. [US/US]; 2002 W. Kilgore, Kalamazoo, MI 49008 (US).

(74) Agent: STEIN, Bruce; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, TJ, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PIPERAZINYLPYRIDINYL WATER CLATHRATES



(III)

(57) Abstract

The invention is a process to produce 3-alkylamino-2-piperazinylpyridines (III), where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_2$, a process to purify them and their water clathrates. The 3-alkylamino-2-piperazinylpyridines (III) are used in the production of known compounds useful for treating individuals who are HIV positive.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PIPERAZINYLPYRIDINYL WATER CLATHRATES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention is a process to produce 3-alkylamino-2-piperazinylpyridines (III), a process to purify them and their water clathrates. The 3-alkylamino-2-piperazinylpyridines (III) are used in the production of known compounds useful for treating individuals who are HIV positive.

2. Description of the Related Art

It is known that certain organic and inorganic molecules form "polyhydrates", also known as "water clathrates", which are crystalline solids that consist of a "host lattice" of water molecules surrounding a "guest molecule." In polyhydrates, molecules of water form a lattice with voids which the guest molecules occupy.

In *Prog. Inorg. Chem.*, 8, 43 (1967) in an article entitled the "The Clathrate Hydrates", the subject of polyhydrates was reviewed. This review contains a list of all the organic molecules that were known to form water clathrates at that time. Mostly small molecules such as diethylamine, ethylamine, t-butylamine, etc., are listed.

The hexahydrate of piperazine is known which melts at 44-45^{0}, see *Journal of Chemical Physics*, 48, 4134 (1968). However, no example of a monosubstituted piperazine water clathrate is listed.

The prior art contains no suggestion that water clathrate formation can be an extraordinarily effective means of purification of organic molecules.

It is highly advantageous to purify crude 3-ethylamino-2-(1-piperazinyl)pyridine via water clathrate formation.

It is known that it is difficult to displace the chlorine of 3-amino-2-chlorosubstituted pyridines by amines. The literature teaches that it is necessary to catalyze the displacement by including copper (II) salt. Even so, yields are low, in the range of 48-59%. For example, in the presence of a catalytic amount of copper(II) sulfate, 3-amino-2-chloro-pyridine condenses with excess ammonium hydroxide (130°, 20 hrs.) to produce 2,3-diaminopyridine in 58.9% yield and with excess aq. methylamine (150°, 17 hrs.) to produce 3-amino-2-methylamino-pyridine in 48.2% yield, see *Ber.* 69, 2593 (1936) and DE 667,219 (Nov. 7, 1938). Also, in the presence of a catalytic amount of copper (II) sulfate, 3-methylamino-2-chloro-pyridine condenses with excess ammonium hydroxide (130°, 30 hrs.) to produce 2-amino-3-methylamino-pyridine in 54% yield, see *J. Chem. Soc.* 442 (1957) and with excess aq. methylamine (160°, 20 hrs.) to produce 2,3-di-(methylamino)-pyridine in 55% yield, *J. Chem. Soc., Perkin I* 673 (1973). Copper (II) sulfate also catalyzes the reaction between 3-ethylamino-2-chloropyridine and piperazine (by a factor of 3-4).

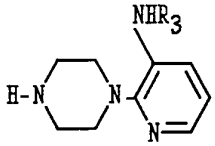
It is also known that strong proton acids such as hydrochloric acid catalyze the displacement of the chlorine of chloroheterocycles by aniline to form the corresponding anilino-substituted heterocycle. For example, hydrochloric acid catalyzes the reaction between aniline and 2-chloro-s-triazene, see *J. Am. Chem. Soc.*, 66, 1127 (1944); 4-chloroquinolines, see US 3,632,761, US 4,025,629 and US 4,167,567; and various 4-chloro-pyrimidines, see *J. Chem. Soc.*, 1014 (1949), *J. Am. Chem. Soc.*, 66, 1127 (1944) and *J. Chem. Soc.*, 370 (1946).

However, the ability of hydrochloric acid to act as a catalyst is believed to be restricted to cases in which the displacing amine is a relatively weak base such as aniline (pK_a = 4.6). If the pK_a of the amine is greater than 5.1, then it has been asserted that hydrochloric acid does not catalyze the displacement, see *J. Chem. Soc.*, 1014 (1949) but rather simply protonates the amine. For example, benzylamine (pK_a = 9.3) does not condense with 4-chloro-(6 or 7)-nitro-quinazoline in the presence of hydrochloric acid. Since piperazine (pK_a = 9.8) is an even stronger base than benzylamine, it would be expected that hydrochloric acid would not catalyze the reaction of 3-alkylamino-2-chloropyridine with piperazine, but would simply protonate the piperazine. The literature contains no indication that reaction between a chloroheterocycle and piperazine can be accelerated by a strong proton acid.

It is highly advantageous to conduct the displacement of 3-alkylamino-2-chloropyridines (I) by piperazine (II) in the presence of a strong proton acid.

SUMMARY OF INVENTION

Disclosed is the water clathrate of the 3-alkylamino-2-piperazinylpyridine of formula (III)



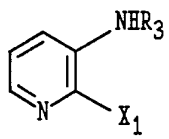
$\cdot$ 5 H_2O (IIIA)

where R_3 is $-CH_2-CH_3$.

Also disclosed is the water clathrate of the 3-alkylamino-2-piperazinylpyridine of formula (III) where R_3 is $-CH(CH_3)_2$.

Further disclosed is a process for the production of 3-alkylamino-2-piperazinylpyridines of formula (III) where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_2$, which comprises

(1) contacting a 3-aminopyridine of the formula (I)



(I)

where X_1 is -Cl or -Br and where R_3 is as defined above with piperazine (II) and

(2) heating the mixture of step (1) to greater than 110°.

Additionally disclosed is a process for purification by producing a water clathrate of a 3-alkylamino-2-piperazinylpyridine (III) of the formula where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_2$, which comprises:

(1) adding an impure 3-alkylamino-2-piperazinylpyridine (III), salt or hydrate thereof to an aqueous mixture,

(2) keeping the pH greater than 7 and

(3) crystallizing the water clathrate 3-alkylamino-2-piperazinylpyridine (III) from the mixture.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for producing the 3-alkylamino-2-piperazinyl-pyridines (III), a process for their purification and the water clathrates of the 3-alkylamino-2-piperazinylpyridines (III) where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_3$.

The 3-alkylamino-2-piperazinylpyridines (III) are produced from the corresponding 3-aminopyridine (I) and piperazine (II) as set forth in CHART A. It is preferred to obtain the 3-alkylamino-2-piperazinylpyridines (III) in water clathrate form. The 3-aminopyridines (I) and piperazine (II) are known.

For the 3-aminopyridines (I), R_3 is either ethyl $-CH_2-CH_3$, or isopropyl $-CH(CH_3)_2$. X_1 is -Cl or -Br; preferably -Cl. The 3-aminopyridine (I) is contacted with piperazine (II) and heated to greater than 110° in the absence of copper (II) ion. While the process is operable with only one equivalent of piperazine (II), it is preferable to use about 3-10, with about 5 equivalents being most preferred. It is preferred that the reaction mixture be heated to greater than 135°; more preferred that it be heated in the range of about 145 to about 170°. Since the preferred temperature range exceeds the boiling point of piperazine (II), it is preferred that the contacting and heating be conducted in a sealed system. An organic solvent can be added to the reaction mixture when the process is practiced in an open system. The solvent is added to prevent the piperazine (II) from crystallizing during reflux. When the process is practiced in a closed system, it is preferred not to have solvent present as it adds to the pressure. It is realized that a minimal amount of solvent may be present even in the closed system as a carry over from the previous reaction; in the closed system it is preferred to have none or the minimum amount of an organic solvent present. If added to the open system, it is preferred that the solvent be in the range of about 0 to about 20% by volume. Preferably the organic solvent will have a boiling point in the range of about 80 to about 150°. Suitable organic solvents include for example toluene, xylene, methanol, ethanol, isopropanol, n-propanol, n-butanol, sec-butanol and t-butanol. It is preferred that if an organic solvent is used, that it be toluene.

It is preferred to perform the process in the presence of an acid because the acid will

enhance the rate of the reaction. During the course of the reaction the halogen ($-X_1$) and a -H (from piperazine) generate one equivalent of hydrochloric acid. Since the reaction rate is increased by acid, it is advantageous to add additional acid. It is preferred that the exogenously added acid (preferably anhydrous) be selected from the group consisting of acids with a pK_a of 2.0 or less; it is preferred that the acid is hydrochloric or methanesulfonic. When the process is performed in the presence of an acid, it is preferred that the temperature be in the range of about 135 to about 170°. While addition of acid accelerates the rate of reaction, the desired 3-alkylamino-2-piperazinylpyridines (III) and piperazine (II) are protonated by the acid which then co-crystallize during workup and some of the desired 3-alkylamino-2-piperazinylpyridines (III) is lost. Alternatively, it is preferred to perform the process in the presence of a base (preferably anhydrous) because less product is lost during workup. Operable bases are those whose conjugate acid has a pK_a of about 5 or greater. It is preferred that the base be selected from the group consisting of bases whose conjugate acid has a pK_a of about 5 to about 14; it is more preferred that the base is carbonate. Non-aqueous acids/bases are preferred because water would depress the boiling point of the reaction mixture. When the reaction is complete, the reaction mixture is cooled, diluted with toluene and the excess piperazine, if any, crystallizes out leaving the desired 3-alkylamino-2-piperazinylpyridines (III) in the mother liquor. The desired 3-alkylamino-2-piperazinylpyridines (III) along with basic impurities such as 3-amino-2-piperazinylpyridine are extracted into aqueous acid. This extraction removes neutral impurities such as the bisadduct and unreacted 3-aminopyridine (I). The acidic extract is then basified by addition of aqueous base, seeded and the water clathrate of the 3-alkylamino-2-piperazinylpyridines (III) crystallizes out in analytically pure form, free of any of the above identified impurities. The desired 3-alkylamino-2-piperazinylpyridine (III) is isolated from the crystallization mixture by filtration, washed with water and dried to a workable solid. This solid may contain more or less water then the pure clathrate (about 3 to about 10 water molecules/3-alkylamino-2-piperazinylpyridine (III)), due to the presence of adsorbed water and/or adsorbed anhydrous 3-alkylamino-2-piperazinylpyridine (III).

3-Alkylamino-2-piperazinylpyridines (III) in impure form can be purified by crystallization from water or an aqueous mixture. The aqueous mixture can contain a water-miscible organic solvent or inorganic or organic salt. The salt is generated upon neutralization of the reaction mixture.

The polyhydrate forms of the 3-alkylamino-2-piperazinylpyridines (III) obtained by crystallization from an aqueous medium are true water clathrates and not simply mixtures of anhydrous crystals with water as evidenced by an X-ray crystallographic study of the water clathrates of 3-ethylamino-2-piperazinylpyridine and 3-isopropylamino-2-piperazinylpyridine.

The 3-alkylamino-2-piperazinylpyridines (III) are useful as intermediates in the

preparation of various pharmaceutical agents, see US Patents 4,996,318, 5,120,843 and 5,175,281. N-Ethyl-2-[4-(5-methoxy-1H-indol-2-ylcarbonyl)-1-piperazinyl]-3-pyridineamine (V) is known to be useful in treating individuals who are HIV positive, see International Publication No. WO91/09849, published July 11, 1991 based on International Patent Application No. PCT/US90/07390, EXAMPLE 16. N-Ethyl-2-[4-(5-methoxy-1H-indol-2-ylcarbonyl)-1-piperazinyl]-3-pyridineamine (V) is produced from the corresponding appropriately substituted indole (IV) by reaction with 3-ethylamino-2-(1-piperazinyl)pyridine (III), see CHART B.

2-[4-(5-Methanesulfonamido-1H-indol-2-ylcarbonyl)-1-piperazinyl]-N-(1-methylethyl)-3-pyridineamine (V) is known to be useful in treating individuals who are HIV positive, see International Publication No. WO91/09849, published July 11, 1991 based on International Patent Application No. PCT/US90/07390, EXAMPLE 105. 2-[4-(5-Methanesulfonamido-1H-indol-2-ylcarbonyl)-1-piperazinyl]-N-(1-methylethyl)-3-pyridineamine (V) is produced from the corresponding appropriately substituted indole (IV) by reaction with 3-isopropylamino-2-(1-piperazinyl)pyridine (III), see CHART B.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

HPLC refers to high-pressure liquid chromatography.

LOD refers to loss on drying.

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.

MS refers to mass spectrometry expressed as m/e or mass/charge unit. $[P + H]^+$ refers to the positive ion of a parent plus a hydrogen atom. CI refers to chemical ionization.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

The term 3-alkylamino-2-piperazinylpyridines (III) includes the 3-ethylamino-2-piperazinylpyridine (IIIA) and the 3-i-propylamino-2-piperazinylpyridine (IIIB).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed

examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 2-Chloro-3-ethylaminopyridine (I)

To a 500 ml flask is added in sequence 3-amino-2-chloropyridine (20.01 g, 0.1556 mol, 1.000 eq), anhydrous p-toluenesulfonic acid (0.080 g, 0.47 mmol, 0.0030 eq) and trimethylorthoacetate (23.36 g, 0.1945 mol, 1.25 eq). The slurry is agitated and an endotherm from about 22° to about 10° is observed. The mixture is warmed to about 30° with concomitant dissolution of starting material. The solution is maintained at 25-30° for 10 minutes, then vacuum is slowly applied to 70 mm mercury with simultaneous distillation of methanol cooling the mixture to 10°. The methanol is further distilled with heating to 30° at 70 mm mercury to give methyl-1-(2'-chloro-3'-pyridinyl)imino-ethyl ether, CMR ($CDCl_3$, ppm δ) 16.33, 53.44, 122.75, 130.03, 142.40, 142.99, 143.40, 163.64; NMR ($CDCl_3$, ppm δ) 1.82, 3.84, 7.16, 7.21, 8.08; MS (CI, CH_4) m/e = 185, 187 (100.%, P+1).

This material is diluted with toluene (150 ml) and the mixture cooled to -20°. Diisobutylaluminum hydride (50.282 g, 0.3536 mol, 2.272 eq.) is added dropwise with stirring maintaining -17 ±3°. The mixture is stirred 15 min. at -20°, at which point HPLC shows < 0.2% iminoether and a thin slurry has formed. Methanol (2.84 ml, 0.0701 mol, 0.451 eq) is then added slowly at -17 ±3° with concomitant distillation of hydrogen gas. To a 1 liter flask is added in sequence water (100 ml), and 20° baume hydrochloric acid (49.09 g, 0.431 mol, 2.770 eq). To this mixture is added the diisobutylaluminim hydride reaction mixture, via cannulation, with an exotherm to, and then maintenance of, 45-55° via ice bath cooling. This addition is done carefully to allow for distillation of isobutane from the quench mixture. The mixture is stirred at 45° for 15 min at which point a biphasal liquid mixture has formed. The cloudy lower aqueous phase is discarded. The organic layer is concentrated under 70 mm mercury vacuum at 70° to give the title compound, 2-chloro-3-ethylaminopyridine (containing 14 wt% toluene) by NMR and MS, CMR ($CDCl_3$, ppm δ) 14.46, 37.86, 117.21, 123.41, 136.11, 136.95, 140.87; NMR ($CDCl_3$, ppm δ) 1.32, 3.18, 4.3, 6.87, 7.09, 7.69; MS (CI, CH_4): m/e = 157, 159 (100.%, P+1).

PREPARATION 2 2-Chloro-3-isopropylaminopyridine methanesulfonate salt (I)

3-Amino-2-chloropyridine (26.9 kg), acetic acid (75.3 l) and acetone (258.2 l) are mixed and stirred at 20-25° under nitrogen. Sodium borohydride pellets (13.3 kg) are added portionwise, maintaining a temperature of between 25°-30°. At the completion of the addition, the mixture is stirred for 1 hour at 20-25°C. The reaction is quenched with water (403.5 l) and

the pH adjusted to 8.0 by the addition of sodium hydroxide (50%). The aqueous solution is extracted with ethyl acetate (3 x 133 l), the organic extracts are combined, washed with sodium bicarbonate (5%, 140 l), saline (140 l) and concentrated. Azeotroping with heptane removes any residual isopropanol.

The residue is redissolved in THF (236 kg) and stirred at 20-25° under nitrogen. To this mixture is added methanesulfonic acid (13.5 l). If necessary, the mixture may be seeded to effect crystallization. The resulting slurry is cooled to -20°, filtered, washing with 0° tetrahydrofuran, and dried at 20-25° to give the title compound, mp = 110.5-112°; NMR ($CDCl_3$, ppm δ) 10.2, 8.0, 7.4, 3.7, 2.81, 1.25; CMR ($CDCl_3$, ppm δ) 140.9, 132.2, 131.3, 125.1, 124.5, 45.4, 39.3, 21.6.

EXAMPLE 1 3-Ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III) With Sodium Carbonate As Base

Piperazine (II, 70.10 g), sodium carbonate (22.55 g) and 2-chloro-3-ethylaminopyridine (I, PREPARATION 1) are mixed, a condenser with 1 atmosphere steam on it is added and the solid mixture warmed to ≈100° without agitation. The mixture is further heated to reflux at 144°. During the warmup, a large amount of piperazine sublimes into the upper part of the flask, but on reaching reflux this is washed back down. The mixture is stirred at reflux until complete (<1% 2-chloro-3-ethylaminopyridine remains) by HPLC (16 hrs) during which time the reflux temperature slowly rises to 152°. The reaction mixture is then cooled to 147° and toluene (250 ml) is added adiabatically and dropwise. The addition is completed at 74°. The slurry is further cooled to -3°. The solids are collected by vacuum filtration and washed with 0° toluene (2 x 50 ml). The combined filtrate and washes mixed with a toluene rinse. Water (150 ml) is added with stirring. The pH is adjusted from 10.9 to 5.4 with 37 wt% hydrochloric acid (25.17 g) to give a biphasal mixture; the upper phase is discarded. The aqueous phase is adjusted to pH 8.9 with 50 wt% aqueous sodium hydroxide (10.22 g). The mixture is cooled to 20° and seeded with a prior lot of 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate. The pH is further adjusted to > 12.5 with 50 wt% aqueous sodium hydroxide (15.49 g) while maintaining < 30°. The resultant slurry is cooled to 16°. The product is collected by vacuum filtration and slurry washed with 15° water (50 ml), then displacement washed with 10° water (50 ml). The solids are dried under 5 psi nitrogen for 20 min to give the title compound, TLC eluant: 89/10/1 methylene chloride/methanol/29% aq. ammonia, R_f = .37; CMR ($CDCl_3$, ppm δ) 14.80, 38.13, 46.55, 50.56, 115.94, 119.87, 135.21, 137.57, 151.00; NMR ($CDCl_3$, ppm δ) 1.31, 1.79, 3.02, 3.12, 4.23, 6.81, 6.91, 7.71; MS (CI) m/e = 207 (100.%, P+1), LOD = 30.5%, yield = 80.1% (chemical) from (I).

EXAMPLE 2 3-Ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III) Without A Base

Following the general procedure of EXAMPLE 1 and making non-critical variations but not using any base, but only piperazine, and heating at reflux (152-158°) for 14 hours, the title compound is obtained, 44.60 g, LOD 46.9%, 73.8% overall yield.

EXAMPLE 3 3-Isopropylamine-2-(1-piperazinyl)pyridine (III)

A mixture of 2-chloro-3-isopropylaminopyridine methanesulfonate salt (I, PREPARATION 2, 51.57 kg), piperazine (II, 99.9 kg) and toluene (9.7 l) are heated to 150°. After refluxing for 20-24 hours, the reaction mixture is cooled to 110° and toluene (380 l) is added while maintaining the reaction temperature at more than 105°. The reaction is further cooled to 0° and the precipitated solids are removed by filtration, washing with toluene (3 x 50 l). The filtrates are combined and water (180 l) is added. The pH of the aqueous is adjusted to 4.3-4.5 by the addition of concentrated hydrochloric acid. The layers are separated, retaining the aqueous phase, and the pH is adjusted to 12.5-13.0 by the addition of sodium hydroxide (50%). The aqueous phase is extracted with toluene (3 x 100 l), the organic extracts are combined and washed with saturated sodium chloride (50% saturated, 150 l). Concentration under reduced pressure provides the title compound, NMR ($CDCl_3$, ppm δ) 7.1, 6.8, 4.2, 3.5, 3.0, 1.2; CMR ($CDCl_3$, ppm δ) 151.0, 136.5, 134.8, 119.8, 116.1, 50.6, 46.6, 43.8 and 22.9.

EXAMPLE 4 Preparation Of A Crystalline Hydrate Of 3-Isopropylamino-2-(1-piperazinyl)pyridine pentahydrate (III)

A small amount of the title compound as a slurry in water is prepared by starting with a small amount of an oily mixture of anhydrous 3-isopropylamino-2-(1-piperazinyl)pyridine [III, EXAMPLE 3, ~92% and toluene ~8%] is concentrated under reduced pressure to a viscous oil. A small amount of water is added and the biphasal liquid mixture is frozen at - 25°. On warming to 20-25° and melting, a slurry of the title compound is formed. Crystals from this slurry were used to seed larger lots, which were prepared using the following method.

A liquid mixture of anhydrous 3-isopropylamino-2-(1-piperazinyl)-pyridine [EXAMPLE 3, ~70% and toluene ~30%, 10.028 g] is concentrated under reduced pressure to a viscous oil (7.106 g). A portion (5.580 g) is mixed with water (30 ml) to give a liquid biphasal mixture. A seed crystal of the title compound is added and on cooling to 0° with stirring, a thick slurry is formed. The product is collected by vacuum filtration and washed with water at 0°. The mixture is dried in an ambient air stream to a workable solid to give the title compound, Karl Fischer = 49.6 wt% water, mp = 26-27°).

EXAMPLEs 5-7 demonstrate that crystallization of the pentahydrate derivative of 3-ethylamino-2-(1-piperazinyl)pyridine (EXAMPLE 5) upgrades the purity much more than does crystallization of either the anhydrous free base (EXAMPLE 6) or the dihydrochloride (EXAMPLE 7).

EXAMPLE 5 Purification Of 3-Ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III)

From Water When Contaminated With 3-amino-2-(1-piperazinyl)pyridine (III)

To pure 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III, 9.916 g, LOD = 46.4%, 25.765 mmoles) is added pure anhydrous 3-amino-2-(1-piperazinyl)pyridine (62 mg) equivalent to 1.15 wt% on an anhydrous, free base basis. Next, water (25 ml) is added and the mixture is warmed to 48° at which point it becomes an homogeneous solution. The mixture is cooled to 20° and the product collected by vacuum filtration and washed with water (40 ml). The mixture is dried in an air stream for 10 minutes to give 3-ethylamino-2-(1-piperazinyl)-pyridine pentahydrate (7.899 g; LOD = 41.6%; 22.381 mmoles, 86.9%). The product assays by HPLC at 0.1 wt% 3-amino-2-(1-piperazinyl)pyridine on an anhydrous free base basis, reflecting a significant improvement in purity in this crystallization.

EXAMPLE 6 Purification Of 3-Ethylamino-2-(1-piperazinyl)pyridine dihydrochloride (III) When Contaminated With 3-amino-2-(1-piperazinyl)pyridine dihydrochloride As 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate

3-Ethylamino-2-(1-piperazinyl)pyridine dihydrochloride (III, 7.587 g) containing 0.3% of 3-amino-2-(1-piperazinyl)pyridine dihydrochloride is added 3-amino-2-(1-piperazinyl)pyridine dihydrochloride (0.069 g) and water (28 ml). To the resultant solution at pH = 1.5 is added sodium hydroxide (50% aqueous, 4.1 g) to a pH of 9.5. The mixture is seeded with 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III) and then the pH is further adjusted to 12.7 with 3.8 g of 50% aqueous sodium hydroxide. The product is collected under reduced pressure at 20-25^0 and washed with water (20 ml). The product is dried in a slow air stream for 1 day to give the title compound which assays at 27.0 % water by LOD, mp = 46-48^0, and contains no detectable 3-amino-2-(1-piperazinyl)pyridine by TLC.

EXAMPLE 7 Attempted Purification Of 3-ethylamino-2-(1-piperazinyl)pyridine (III) As Anhydrous Free Base From Organic Solvents When Contaminated With 3-amino-2-(1-piperazinyl)pyridine (III)

To pure 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III, 10.268 g, LOD = 46.4%) is added methylene chloride (50 ml). The mixture is warmed to dissolve the solids and the phases separated. The aqueous phase is washed with methylene chloride (10 ml) and the organic phases are combined. To the organic phase is then added pure anhydrous 3-amino-2-(1-piperazinyl)pyridine (64 mg) equivalent to 1.15 wt% on an anhydrous, free base basis. Methyl t-butyl ether (21 ml) and hexane (15 ml) are added and the resultant mixture concentrated under reduced pressure to a total volume of 10 ml. Methyl t-butyl ether (10 ml) is then added and the product is allowed to crystallize at 20-25^0. Next, hexane (20 ml) is slowly added to the resultant slurry. The mixture is cooled to 0° and the product collected by vacuum filtration and washed with hexane (~10 ml). The product is dried in a 20-25^0 nitrogen stream to afford

anhydrous 3-ethylamino-2-(1-piperazinyl)pyridine (3.372 g). The product assays by HPLC at 1.5 wt% 3-amino-2-(1-piperazinyl)pyridine, reflecting a decrease in purity in this low yielding crystallization.

EXAMPLE 8 Attempted Purification Of 3-ethylamino-2-(1-piperazinyl)pyridine dihydrochloride (III) From Methanol/Ethyl Acetate When Contaminated With 3-amino-2-(1-piperazinyl)pyridine dihydrochloride (III)

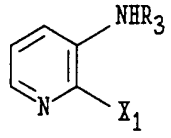
To pure 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III, 9.988 g, LOD = 46.4%, 25.954 mmoles) is added methylene chloride (50 ml). The mixture is warmed to dissolve the solids and the phases separated. The aqueous phase is washed with methylene chloride (10 ml then 5 ml) and the organic phases combined. To the organic phase is then added pure, anhydrous 3-amino-2-(1-piperazinyl)pyridine (61.0 mg) equivalent to 1.13 wt% on an anhydrous, free base basis. A solution of hydrogen chloride (4.13 g) in methanol (49 ml) is then added with stirring to give an homogeneous solution. Solvent is then distilled off in vacuo to a total volume of about 12 ml. Ethyl acetate (73 ml) is then added and solvent distilled off under reduced pressure to a total volume of about 12 ml. Ethyl acetate (73 ml) is then added and solvent distilled off under reduced pressure to a total volume of about 22 ml. The product is collected by vacuum filtration, washed with ethyl acetate (37 ml), and dried in a 50° vacuum oven for 3 days to give 3-ethylamino-2-(1-piperazinyl)pyridine dihydrochloride (7.215 g, 25.841 mmoles, 99.6% yield). The product assays by HPLC at 1.03 wt% 3-amino-2-(1-piperazinyl)-pyridine on an anhydrous, free base basis. However, only 2.16 mg of 3-amino-2-(1-piperazinyl)pyridine dihydrochloride and 1.39 mg of 3-ethylamino-2-(1-piperazinyl)pyridine dihydrochloride is detected in the filtrate by HPLC, clearly indicating that nearly all the 3-amino-2-(1-piperazinyl)pyridine and 3-ethylamino-2-(1-piperazinyl)pyridine are precipitated as the dihydrochloride salts resulting in insignificant upgrading.

EXAMPLE 9 3-Ethylamino-2-(1-piperazinyl)pyridine pentahydrate (III) With Added Hydrochloric Acid

Piperazine (68.20 g, 0.7917 moles), hydrochloric acid (5.16 g, 0.1415 moles) and 2-chloro-3-ethylaminopyridine (26.65 g, containing 7.23% toluene, 24.72 g, 0.1579 moles) are mixed. The solid mixture is warmed to about 110° without agitation. The mixture is further heated to reflux at 152°. The mixture is stirred at reflux until the reaction is complete (<1% 2-chloro-3-ethylaminopyridine) by HPLC (8 hrs). The reflux temperature slowly rises to 168° through the course of the reaction. The mixture is slowly cooled to 126° at which point the piperazine hydrochloride precipitates. Toluene (150 ml) is then added adiabatically and dropwise with good agitation. The addition is completed at 75°. The slurry is further cooled to 3°. The solids are collected by vacuum filtration, washed with 0° toluene (2 x 40 ml) and discarded. The combined filtrate and washes are transferred to a 500 ml flask with a toluene

rinse. Water (89 ml) is added with stirring. The pH is adjusted from 11.1 to 4.9 with 20° baume hydrochloric acid (28.41 g, 0.2494 mol. 1.58 eq) to give a liquid biphasal mixture. The upper phase is discarded. The lower phase is washed with toluene (100 ml). The aqueous phase is adjusted to pH 9.1 with aqueous sodium hydroxide (50%, 13.30 g, 0.1663 mol, 1.05 eq). The mixture is cooled to 25° and seeded with a prior lot of the title compound. The pH is further adjusted to > 12.5 with aqueous sodium hydroxide (50%, 11.52 g, 0.1440 mol, 0.91 eq), maintaining < 30°. The resultant slurry is cooled to 12°. The product is collected by vacuum filtration and the slurry washed with 10° water (89 ml), then displacement washed with 10° water (89 ml). The solids are dried under 5 psi nitrogen for 30 minutes to give 3-ethylamino-2-(1-piperazinyl)pyridine pentahydrate (44.60 g, LOD = 34.7%).

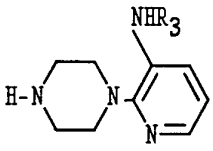
CHART A



(I)

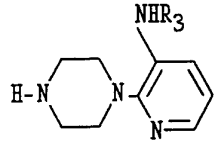
+

Piperazine (II)



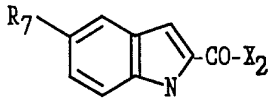
(III)

CHART B

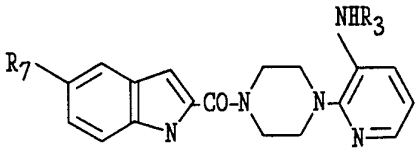


(IIIA or B)

+



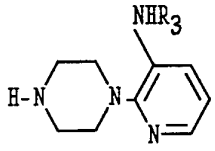
(IV)



(V)

CLAIMS

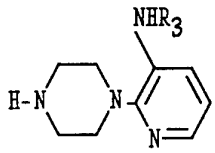
1. The water clathrate of the 3-alkylamino-2-piperazinylpyridine of formula (III)



$\cdot$ 5 H_2O (IIIA)

where R_3 is $-CH_2-CH_3$.

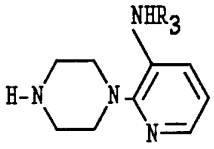
2. The water clathrate of the 3-alkylamino-2-piperazinylpyridine of formula (III)



$\cdot$ 5 H_2O (IIIB)

where R_3 is $-CH(CH_3)_2$.

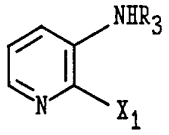
3. A process for the production of 3-alkylamino-2-piperazinylpyridines of formula (III)



(III)

where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_2$, which comprises

(1) contacting a 3-aminopyridine of the formula (I)



(I)

where X_1 is -Cl or -Br and where R_3 is as defined above with piperazine (II) and

(2) heating the mixture of step (1) to greater than 110°.

4. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the reaction is performed in the presence of an organic solvent selected from the group consisting of toluene, xylene, methanol, ethanol, isopropanol, n-propanol, n-butanol, sec-butanol and t-butanol.

5. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 4

where the organic solvent is toluene.

6. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the reaction is heated to greater than 135°.

7. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the reaction is heated in the range of about 145 to about 170°.

8. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the contacting and heating take place under sealed conditions.

9. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the reaction is performed in the presence of exogenously added acid selected from the group consisting of acids with a pK_a of 2.0 or less.

10. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 9 where the acid is hydrochloric or methanesulfonic.

11. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the reaction is performed in the presence of an exogenously added base selected from the group consisting of bases whose conjugate acid has a pK_a of about 5 or greater.

12. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 11 where the exogenously added base who conjugate acid has a pK_a of about 5 to about 14.

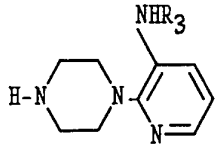
13. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 11 where base is carbonate.

14. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where X_1 is -Cl.

15. A process for the production of 3-alkylamino-2-piperazinylpyridine (III) according to claim 3 where the 3-alkylamino-2-piperazinylpyridine (III) is crystallized from a mixture containing water.

16. A process for purification by producing a water clathrate of a 3-alkylamino-2-

piperazinylpyridine (III) of the formula



(III)

where R_3 is $-CH_2-CH_3$ or $-CH(CH_3)_2$, which comprises:

(1) adding an impure 3-alkylamino-2-piperazinylpyridine (III), salt or hydrate thereof to an aqueous mixture,

(2) keeping the pH greater than 7 and

(3) crystallizing the water clathrate 3-alkylamino-2-piperazinylpyridine (III) from the mixture.

17. A process for purification of a 3-alkylamino-2-piperazinylpyridine (III) according to claim 16 where the crystallization takes place from a mixture containing a salt.

18. A process for purification of a 3-alkylamino-2-piperazinylpyridine (III) according to claim 17 where the salt is M (cation) Q (anion) where M is selected from the group consisting of sodium, potassium, lithium and magnesium; where Q is selected from the group consisting of chloride, sulfate, bromide, phosphate, hydroxide and carbonate.

19. A process for purification of a 3-alkylamino-2-piperazinylpyridine (III) according to claim 17 where the salt is sodium chloride or sodium sulfate.