PATENT SPECIFICATION (11) 1 573 569

1 573 569

(21) Application No. 5748/77 (22) Filed 11 Feb. 1977
(31) Convention Application No. 659291
(32) Filed 19 Feb. 1976
(31) Convention Application No. 679121
(32) Filed 21 April 1976 in
(33) United States of America (US)
(44) Complete Specification published 28 Aug. 1980
(51) INT CL³ C07D 471/22 A61K 31/505 (C07D 471/22 221/00 231/00 239/00 295/00)
(52) Index at acceptance
C2C 1341 1400 140X 1470 1532 1562 1582 1590 1626 214 215 220 226 22Y 246 247 250 251 252 253 255 256 25Y 28X 29X 29Y 305 30Y 311 313 31Y 321 322 323 326 327 32Y 337 338 351 352 355 35X 35Y 364 366 367 368 36Y 371 373 376 37X 37Y 386 387 388 38Y 401 40Y 43X 440 456 45Y 462 464 490 500 50Y 551 552 553 612 614 620 624 625 628 62Y 630 635 638 650 652 656 658 65X 660 662 665 670 672 675 678 682 694 699 69Y 761 762 771 775 776 778 77Y 802 80Y AA BC LF LK LL LS MC NF QL QS QU TR WC ZB ZF

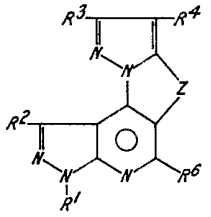
(72) Inventors THEODOR DENZEL and HANS HOEHN

(54) PYRIMIDINE DERIVATIVES

(71) We, E. R. SQUIBB & SONS INC., a corporation organised and existing under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

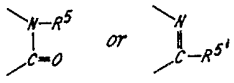
This invention provides new derivatives of pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido-[3,4-e]pyrimidine. These compounds may be used as antiinflammatory agents and central nervous system depressants.

More specifically the present invention provides compounds of the formula

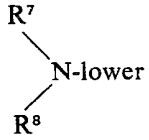


(I)

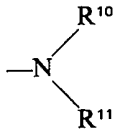
wherein Z is



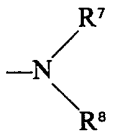
R^1 is hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, benzoyl or substituted phenyl or benzoyl wherein the phenyl or benzoyl substituent is one or two halogens, lower alkyl or trifluoromethyl groups; R^2 and R^3 each is hydrogen, lower alkyl or phenyl; R^4 is hydrogen, lower alkyl, phenyl, carboxy or lower alkoxycarbonyl; R^5 is hydrogen, lower alkyl, phenyl-lower alkylene, benzoyl, substituted benzoyl, lower alkanoyl, lower alkoxy-lower alkylene, lower alkylthio-lower alkylene, phenyl, substituted phenyl or



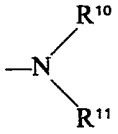
alkylene; R^5 is lower alkoxy, substituted lower alkoxy wherein the substituent is



phenyl-lower alkoxy, phenyloxy, substituted phenyloxy wherein the phenyl ring bears one or two halogen, lower alkyl or trifluoromethyl groups, halo,



or —S—R^9; R^6 is hydrogen or lower alkyl; R^7 is hydrogen, lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is



phenyl or substituted phenyl wherein the phenyl substituent is halogen, lower alkyl or trifluoromethyl, R^8 is hydrogen or lower alkyl, or R^7 and R^8 together with the nitrogen form one of the unsubstituted or substituted heterocyclics pyrrolidino; morpholino, thiamorpholino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl wherein the heterocycle substituent is lower alkyl or hydroxy-lower alkyl; R^9, R^{10} and R^{11} each is hydrogen or lower alkyl; and acid addition salts thereof.

The invention also extends to pharmaceutical compositions comprising such compounds or salts and a pharmaceutical carrier.

The various groups represented by the symbols are of the following types and have the same meanings throughout this specification:

The lower alkyl groups are straight or branched chain hydrocarbon groups having up to seven carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and pentyl. The lower alkylene groups are divalent radicals of the same kind. Examples of the phenyl-lower alkylene groups are benzyl, phenethyl and phenylisopropyl. The C_1—C_4 and especially the C_1—C_2 lower alkyl and lower alkylene groups are preferred. The lower alkoxy groups likewise have up to seven carbon atoms. The C_1—C_4 and C_1—C_2 groups are similarly preferred and especially preferred groups, respectively.

The substituted phenyl, substituted phenyloxy and substituted benzoyl groups are simply substituted groups bearing on the phenyl ring one or two halogen (preferably one), lower alkyl, lower alkoxy or trifluoromethyl groups, for example, p-chlorophenyl, o-chlorophenyl, p-bromophenyl, m-chlorophenyl, m-bromophenyl, p-tolyl, o-tolyl, o-ethylphenyl, p-methoxyphenyl, p-chlorophenyloxy, o-chlorophenyloxy, p-bromophenyloxy, m-chlorophenyloxy, m-bromophenyloxy, p-tolyloxy, o-tolyloxy, o-ethylphenyloxy, p-trifluoromethylphenyloxy, 3,4-dichlorophenyloxy, 3,5-dimethylphenyloxy, p-bromobenzoyl, m-bromobenzoyl, 3,5-dichlorobenzoyl, p-methylbenzoyl, o-ethylbenzoyl and p-trifluoromethylbenzoyl. Chlorine, bromine and methyl are the preferred substituents (only one) in both instances.

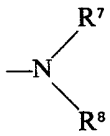
The halogens in each instance are the four common halogens but chlorine and bromine, especially chlorine, are preferred.

The lower alkanoyl groups are the acyl groups of the lower(C_2—C_7) fatty acids, e.g., acetyl, propionyl, butyryl and isobutyryl. Those with up to four carbons in the chain are preferred. especially acetyl.

The lower alkoxy-lower alkylene and lower alkylthio-lower alkylene groups represented by R^5 include such groups as methoxy-methylene, ethoxymethylene, methoxyethylene, methylthiomethylene, methylthioethylene, ethylthiomethylene and ethylthioethylene.

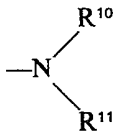
The amino-lower alkylene groups are e.g., aminomethyl, aminoethyl, etc. The di-lower alkylaminolower alkylene groups are groups wherein the nitrogen is substituted with two lower alkyl groups. In addition, the two lower alkyl groups may join in forming a heterocycle which may include an additional hetero atom. Preferably the lower alkyl and lower alkylene groups have up to 4 and especially 1 or 2 carbons. Thus, groups such as dimethylaminomethyl, diethylaminomethyl, dimethylaminoethyl, diethylaminoethyl, dimethylaminopropyl, piperidinomethyl, piperidinoethyl, morpholinomethyl, morpholinoethyl, thiamorpholinomethyl, thiamorpholinoethyl, piperazinomethyl, piperazinoethyl, piperazinopropyl are included.

The amino groups

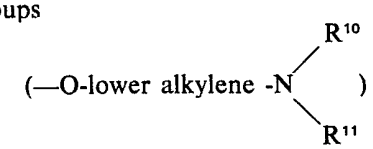


wherein R^7 and R^8 each represents hydrogen or lower alkyl include the amino group, lower alkylamino groups such as methylamino, ethylamino, propylamino, isopropylamino and butylamino and di-lower alkylamino groups such as dimethylamino, diethylamino, methylethylamino, dipropylamino and dibutylamino (preferably, but not necessarily, both lower alkyl groups are the same in a given compound). R^7 and R^8 can also join with the nitrogen to form one of the heterocyclic radicals pyrrolidino, morpholino, thiamorpholino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl. These heterocyclic radicals may be unsubstituted or substituted with a lower alkyl or hydroxy-lower alkyl group. The preferred heterocyclics are piperidino, morpholino and 4-methylpiperazino.

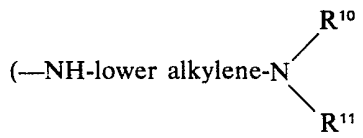
The substituted lower alkoxy groups represented by $R^{5'}$ and the substituted lower alkylamino groups represented by R^7 may bear an amino group



as described above resulting in $R^{5'}$ substituents which are amino-lower alkoxy groups

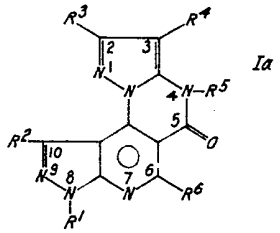


and amino-lower alkyleneamino groups



respectively, including, for example, aminomethoxy, aminoethoxy, aminopropoxy, methylaminoethoxy, ethylaminoethoxy, ethylaminopropoxy, dimethylaminomethoxy, dimethylaminoethoxy, dimethylaminopropoxy, diethylamino-ethoxy, dimethylaminobutoxy, diethylaminopropoxy, aminoethylamino, aminopropylamino, methylaminopropylamino, ethylaminoethylamino, dimethylaminomethylamino, diethylaminomethylamino, dimethylaminoethylamino, diethylaminoethylamino and dimethylaminopropylamino. Preferred are those groups wherein the lower alkyl and lower alkylene groups have up to 4 carbons, especially 1 to 2 carbons. Especially preferred group of this type are di-lower alkylamino-lower alkoxy, especially dimethylaminopropoxy and di-lower alkylamino-lower alkylene-amino, especially dimethylaminopropylamino.

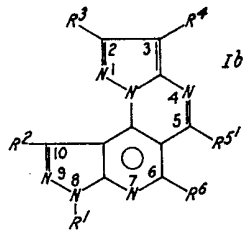
In compounds of the formula



Ia

the preferred groups are those wherein R^1 is lower alkyl, especially ethyl; R^2 is hydrogen or lower alkyl, especially hydrogen; R^3 is hydrogen or lower alkyl, especially methyl; R^4 is hydrogen or lower alkyl, especially hydrogen; R^5 is lower alkyl, especially methyl, ethyl and isopentyl, or di-lower alkylamino-lower alkylene, especially dimethylaminopropyl and dimethylaminoethyl; R^6 is lower alkyl or hydrogen, especially hydrogen.

In compounds of the formula



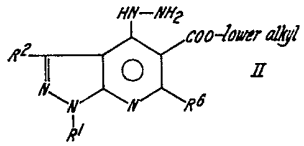
Ib

the preferred groups are those wherein R^1 is hydrogen or lower alkyl, especially the latter and most especially ethyl; R^2 is hydrogen or lower alkyl, especially hydrogen; R^3 is hydrogen or lower alkyl, especially methyl; R^4 is hydrogen or lower alkoxycarbonyl, especially ethoxycarbonyl; $R^{5'}$ is amino, mercapto, lower alkylmercapto, especially methylmercapto, lower alkylamino, especially C_1—C_4-lower alkylamino, lower alkoxy, especially C_1—C_5-lower alkoxy, di(lower alkyl)amino, especially C_1—C_4-di(lower alkyl)amino, di(lower alkyl)amino-lower alkylamino, especially wherein the lower alkyl groups are C_1—C_4 and most especially dimethylaminoethylamino and dimethylaminopropylamino, or di(lower alkyl)amino-lower alkoxy, especially wherein the lower alkyl and lower alkoxy groups are C_1—C_4 and most especially dimethylamino-propoxy. R^6 is hydrogen or lower alkyl, especially hydrogen.

The products of the examples are representative of the various compounds of this invention and constitute especially preferred embodiments.

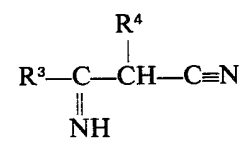
The new compounds of formula I may be formed by the following series of reactions. The symbols in the structural formulas have the same meaning as previously described.

A pyrazolo[3,4-b]pyridine of the formula



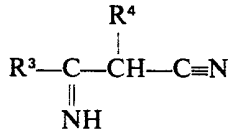
II

(produced according to the procedure given in U.S. Patent No. 3,761,487) is made to react with an iminonitrile of the formula



(III)

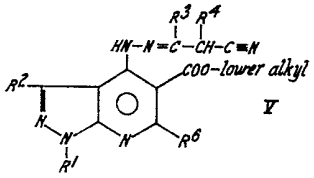
or a ketonitrile of formula



(IV)

in an organic solvent such as alcohol.

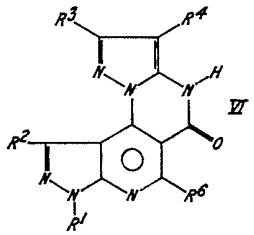
By this reaction a hydrazone of the formula



V

is formed.

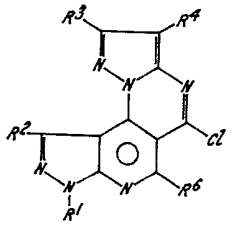
Treatment of the compound of formula V with a base, e.g., an alkali metal alkoxide such as sodium ethoxide or potassium ethoxide in alcoholic solution or with an organic acid and a Lewis acid such as zinc chloride or boron trifluoride (the organic acid may be a solvent such as acetic acid) yields a compound of the formula



VI

Compounds of formula Ia wherein R^5 is other than hydrogen, are obtained by treatment of a cyclized compound of formula VI wherein R^5 is hydrogen, obtained as just described, with the halide R^5-hal, wherein hal is a halogen, preferably chlorine or bromine, and R^5 has the meaning defined above, in the presence of a base, preferably a base of an alkali metal, such as sodium hydride, sodium or potassium alcoholate, sodium metal or sodium or potassium hydroxide, in a solvent, such as dimethylformamide or diethyleneglycol dimethyl ether.

Reaction of the compound of formula VI with a chlorinating agent such as phosphorus oxychloride or phosphorus pentachloride results in the formation of a compound of the formula.

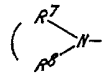


(VII)

Compounds of formula Ib wherein $R^{5'}$ is lower alkoxy, amino-lower alkoxy or phenyloxy are now produced by reaction of the compound of formula VII with an alcoholate of the formula

$$R^{12}—O—Me \qquad (VIII)$$

wherein Me is an alkali metal such as sodium or potassium and R^{12} is lower alkyl, aminolower alkyl

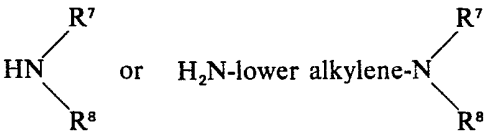


lower alkyl, phenyl, or substituted phenyl.

Compounds of formula I wherein $R^{5'}$ is lower alkylthio are obtained by reaction of a compound of formula VII with an alkali metalmercaptide of the formula

$$R^{12}—S—Me \qquad (IX)$$

wherein Me is again an alkali metal such as sodium or potassium and R^{12} is lower alkyl. Compounds of Formula I wherein R^5 is mercapto are obtained by reaction of a compound of formula VI with an alkali metal sulfide such as sodium sulfide. Compounds of formula I wherein $R^{5'}$ is an amino group or amino-lower alkylene group are produced by reaction of a compound of formula VII with an amine of the formula



(X)

at elevated temperatures.

When R^4 is lower alkoxycarbonyl, the free carboxylic acid is obtained by hydrolysis, e.g., with a base such as sodium hydroxide.

The compounds of formula I form salts which are also part of this invention. The salts include acid addition salts, particularly the physiologically acceptable members. These salts are formed by reaction with one or more equivalents of a variety of inorganic and organic acids providing acid addition salts including, for example, hydrohalides (especially hydrochloride and hydrobromide), sulfate, nitrate, borate, phosphate, oxalate, tartrate, maleate, citrate, acetate, ascorbate, succinate, aryl- and alkanesulfonates like benzenesulfonate, methane-sulfonate, cyclohexanesulfamate and toluenesulfonate, etc. The acid addition salts frequently provide a convenient means for isolating the

product, e.g., by forming and precipitating a salt (which is not necessarily non-toxic) in an appropriate medium in which the salt is insoluble, then after separation of the salt, neutralizing with a base such as barium hydroxide or sodium hydroxide, to obtain the free base of formula I. Other salts can then be formed from the free base by reaction with an equivalent or more of acid containing the desired anion.

Additional experimental details are found in the examples.

The compounds of this invention have central nervous system depressant activity and can be used as psychotropic agents, e.g., as ataratic agents for the relief of anxiety and tension states, for example, in mice, cats, rats, dogs and other mammalian species. For this purpose a compound or mixture of compounds of formula I, or physiologically acceptable acid addition salt thereof, is preferably administered orally, but parenteral routes such as subcutaneously, intramuscularly, intranenously or intraperitoneally in the described dosages, can also be employed. A single dose, or preferably 2 to 4 divided daily doses, provided on a basis of about 5 to 50 mg per kilogram per day, preferably about 10 to 25 mg per kilogram per day, is appropriate.

The compounds of this invention also have antiinflammatory properties and are useful as antiinflammatory agents, for example, to reduce local inflammatory conditions such as those of an edematous nature or resulting from proliferation of connective tissue in various mammalian species such as rats and dogs when given orally in dosages of about 1 to 50 mg/kg/day, preferably 2 to 15 mg/kg/day, in single or 2 to 4 divided doses, as indicated by the carrageenan edema or delayed hypersensitivity skin reaction tests in rats. They can also be used topically.

The compounds of the invention can be utilized by formulation in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspension for parenteral administration. about 10 to 300 mg. of a compound or mixture of compounds of formula I or physiologically acceptable acid addition salt is compounded with a physiologically acceptable vehicle, carrier, excipients, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate, a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor. Of course, any material used in preparing the dosage unit should be pharmaceutically pure and substantially non-toxic in the amounts employed.

For topical administration as an anti-inflammatory agent, a conventional lotion, ointment or cream containing about 0.1 to 3 percent by weight of a compound of formula I or its salt is formulated.

The following examples are illustrative of the invention. All temperatures are in degrees celcius.

Example 1

2,4 - Dimethyl - 8 - ethyl - 4H - pyrazolo-[1,5a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one

a) 4 - [2 - (2 - cyano - 1 - methyl-ethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-e]pyridine - 5 - carboxylic acid, ethyl ester

660 g of 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b] - pyridine - 5 - carboxylic acid, ethyl ester (3 mol.) and 246 g. of 3-iminobutyronitrile (3 mol.) are refluxed with stirring in 3 liters of butanol for 12 hours. The solvent is distilled off and the residual 4 - [2 - (2 - cyano - 1 - methylethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b] - pyridine - 5 - carboxylic acid, ethyl ester is recrystallized from alcohol, yield 756 g. (80%); m.p. 190—191°.

b) 8 - ethyl - 2 - methyl - 4H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one

750 g. of 4 - [2 - (2 - cyano - 1 - methylethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-e]pyridine - 5 - carboxylic acid, ethyl ester (2.8 mol.) are refluxed with stirring in 3 liters of acetic acid containing 50 g. of zinc chloride for 24 hours. The solution is cooled to room temperature and after the addition of about 3 liters of cold water, 8 - ethyl - 2 - methyl - 4H -

pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one crystallizes and is filtered off. The purification of the compound is accomplished by dissolving in the theoretical amount of aqueous sodium hydroxide and acidifying the mixture with acetic acid. Yield 562 g. (75%); m.p. 285—286°C.

c) 2,4 - dimethyl - 8 - ethyl - 4H pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one

2.7 g. of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo - [4',3':5,6]pyrido-[3,4-e]pyrimidin - 5(8H) - one (0.01 mol.) are added to a suspension of 0,03 g. of sodium hydride in 50 ml. of diethylene glycol dimethyl ether at reflux temperature. The temperature is maintained for one hour and then lowered to 120°. 2.8 g. of methyl iodide are added and heating is continued for 10 hours. the precipitated sodium iodide is filtered off, the solution evaporated to dryness and the residue recrystallized from ethyl-acetate, yield 1.9 g. (68%); m.p. 206—207°.

Example 2

4,8 - Diethyl - 2 - methyl - 4H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting ethyl iodide for the methyl iodide in the procedure of Example 1(c), 4,8 - dimethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one is obtained in 71% yield, m.p. 178—180° (ethyl acetate).

Example 3

8 - Ethyl - 2 - methyl - 4 - (3 - methylbutyl) - 4H - pyrazolo[1,5-a]-pyrazolo - [4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting 1 - bromo - 3 - methylbutane for the methyl iodide in the procedure of Example 1(c), 8 - ethyl - 2 - methyl - 4 - (3 - methylbutyl) - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [4,3-e]pyrimidin - 5(8H) - one is obtained, yield 59%, m.p. 126—128° (ethyl acetate).

Example 4

4 - [3 - (Dimethylamino)propyl] - 8 - ethyl - 2 - methyl - 4H - pyrazolo - [1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e] pyrimidin - 5(8H) - one

5.4 g. of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4e]pyrimidin - 5(8H) - one (0.02 mol.) are added to a solution of 1.5 g. of a sodium methoxide in 50 ml. of diethylene glycol-dimethyl-ether. The solution is refluxed with stirring for 30 minutes and then the temperature lowered to 100°. After the addition of 3 g. of dimethylaminopropyl chloride, the mixture is stirred for 24 hours. The inorganic precipitate is filtered off, the filtrate evaporated to dryness and the residue dissolved in 30 ml. of water. The aqueous solution is brought to pH 10 with sodium hydroxide and extracted three times with 50 ml. portions of diethylether. The ether layers are combined, dried with sodium sulfate and the solvent is distilled off. The residue is crystallized with ether to obtain 2.8 g. (40%) of 4 - [3 - (dimethylamino) - propyl] - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one, m.p. 65—68° (propanol). Treatment of the product with acetic acid yields the acetate salt.

Example 5

8 - Ethyl - 2 - methyl - 4 - (2 - morpholino)ethyl - 4H - pyrazolo[1,5-a] - pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

2.7 g. of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one (0.01 mol.) and 0.3 g. of sodium are refluxed for one hour in 30 ml. of diethylene glycoldimethyl-ether with stirring. The temperature is lowered to 90° and 2 g. of 1 - chloro - 2 - morpholinoethane are added and stirring is continued for 24 hours. The inorganic precipitate is filtered off, the solvent removed in vacuo and the crystalline product, 8 - ethyl - 2 - methyl - 4 - (2 - morpholino)ethyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one is recrystallized from ethyl acetate, yield 3.1 g. (81%); m.p. 140—141°.

Example 6

8 - Ethyl - 2 - methyl - 4 - (2 - piperidino)-ethyl - 4H - pyrazolo[1,5-a] - pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting for the dimethylamino-propyl chloride in Example 4 the equivalent amount of 1 - chloro - 2 - piperidino - ethane, 8 - ethyl - 2 - methyl - 4 - (2 - piperidino) - ethyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one is obtained, yield 62%; m.p. 134—137° (ethyl acetate).

Example 7

4 - [2 - (Diethylamino)ethyl] - 8 - ethyl - 2 - methyl - 4H - pyrazolo1,5-a]-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e] pyrimidin - 5(8H) - one

By substituting for the 1 - chloro - 2 - morpholinoethane in Example 5 the equivalent amount of 1 - chloro - 2 - dimethylaminoethane, 4 - [2 - (diethylamino)ethyl - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a] -

pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5(8H) - one is obtained, yield 63%; m.p. 90—92° (ethyl acetate).

Example 8

2,4 - Dimethyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting an equivalent amount of 4 - hydrazino - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a) and continuing as in parts (b) and (c), 2 - methyl - 4H - pyrazolo - [1,5-a]pyrazolo[4',3':5,6]pyrido]3,4 - e]pyrimidin-5(8H) - one and 2,4 - dimethyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido-[3,4-e]pyrimidin - 5(8H) - one are obtained.

Example 9

4 - Butyl - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3';5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting butyl iodide for the methyl iodide in the procedure of Example 1(c), 4 - butyl - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4 - e]pyrimidin - 5(8H) - one is obtained.

Example 10

2 - Methyl - 4 - Phenylmethyl - 4H - pyrazolo[1,5-a][4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting the 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one of Example 8 for the 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5(8H) - one and benzyl iodide for the methyl iodide in the procedure of Example 1 (c), 2 - methyl - 4 - phenylmethyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one is obtained.

Example 11

8 - Ethyl - 2 - methyl - 4 - phenylethyl - 4H - pyrazolo[1,5-a][4',3':5,6]pyrido-[3,4e]pyrimidin - 5(8H) - one

By substituting phenylethyl bromide for the methyl iodide in the procedure of Example 1(c), 8 - ethyl - 2 - methyl - 4 - phenylethyl - 4H - pyrazolo[1,5-a]-pyrazolo - [4',3':5,6]pyrido[3,4 - e]pyrimidin-5(8H) - one is obtained.

Example 12

2,4,8,10 - Tetramethyl - 4H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4e]-pyrimidin - 5(8H) - one

By substituting 1,3 - dimethyl - 4 - hydrazino - 1H - pyrazolo - [3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a) and proceeding as in parts (b) and (c), 2,8,10 - trimethyl - 4H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5(8H) - one and 2,4,8,10 - tetramethyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one are obtained.

Example 13

4 - Propionyl - 2,3,8 - triethyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 1 - isopropyl - 4 - hydrazino - 1H - pyrazolo - [3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester and 2 - ethyl - 3 - imino-pentanonitrile for the 3-iminobutyronitrile in the procedure of Example 1(a), proceeding as in part (b) and then substituting propionyl bromide for the methyl iodide in part (c), 2,3,8 - triethyl - 4H - pyrazolo - [1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4)e]pyrimidin - 5(8H) - one and 4 - propionyl - 2,3,8 - triethyl - 4H - pyrazolo[1,5-a]pyrazolo - [4',3':5,6]pyrido-[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 14

4 - (4 - Chlorobenzoyl) - 10 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting 4 - hydrazino - 3 - ethyl - 1H - pyrazolo - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid propyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a), proceeding as in part (b) and then substituting 4-chlorobenzoyl bromide for the methyl iodide in part (c), 10 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one and 4 - (4 - chlorobenzoyl) - 10 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 15

4 - Benzoyl - 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5-a] - pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 4 - hydrazino - 1 - phenyl - 1H - pyrazolo - [3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a),

proceeding as in part (b) and substituting benzoyl iodide for the methyl iodide in part (c), 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one and 4 - benzoyl - 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 16

8 - Ethyl - 2,4,6 - trimethyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4e]pyrimidin - 5(8H) - one

By substituting 1 - ethyl - 4 - hydrazino - 6 - methyl - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1, 2,6 - dimethyl - 8 - ethyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one and 8 - ethyl - 2,4,6 - trimethyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidine - 5(8H) - one, respectively, are obtained.

Example 17

8 - Benzyl - 2 - methyl - 4 - (3 - methylbutyl) - 4H - pyrazolo[1,5-a] - pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting 1 - benzyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a), proceeding as in part (b) and substituting 1 - bromo - 3 - methylbutane for the methyl iodide in part (c) (as in Example 3), 8 - benzyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5(8H) - one and 8 - benzyl - 2 - methyl - 4 - (3-methylbutyl) - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 18

4 - Methyl - 8 - phenylethyl - 3 - propyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 1 - phenylethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, methyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester and 2-iminomethylpentano-nitrile for the 3-iminobutyronitrile in the procedure of Example 1(a) and proceeding as in parts (b) and (c), 3 - propyl - 8 - phenethyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one and 4 - methyl - 8 - phenylethyl - 3 - propyl - 4H - pyrazolo - [1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 19

8 - Ethyl - 4 - methyl - 2 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido [3,4-e]pyrimidin - 5(8H) - one

By substituting 3 - imino - 3 - phenyl-propionitrile for the 3-iminobutyronitrile in the procedure of Example 1(a) and proceeding as in parts (b) and (c), 8 - ethyl - 2 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one and 8 - ethyl - 4 - methyl - 2 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 20

4 - Methyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e] - pyrimidin - 5(8H) - one

By substituting 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester and the 3-iminopropionitrile for the 3-iminobutyronitrile in the procedure of Example 1(a) and proceeding as in parts (b) and (c), 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one and 4 - methyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 21

8 - Benzoyl - 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - (8H) - one

a) 1 - Furfuryl - 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 4 - hydrazino - 1 - furfurylpyrazolo - [3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in Example 1(a) and proceeding as in parts (a) and (b), 8 - furfuryl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one is obtained. This compound is now processed as in Example 1, part (c), substituting bromobenzene for the methyl iodide. A small amount of copper catalyst is added to obtain 1 - furfuryl - 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one.

b) 2 - Methyl - 4 - phenyl - 4H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

0.01 mol. of 1 - furfuryl - 2 - methyl -

4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) is heated in 50 ml. of diethyleneglycol dimethyl ether containing 0.01 mol. of selenium dioxide at reflux temperature with stirring for two hours. The mixture is filtered hot and evaporated to dryness. Crystalline 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one remains.

c) 8 - Benzoyl - 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

0.01 mol. of 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one and 0.02 mol. of benzoyl chloride are stirred overnight in 50 ml. of dry pyridine at room temperature. On addition of 50 ml. of water, 8 - benzoyl - 2 - methyl - 4 - phenyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one is filtered off.

Example 22

2,4 - Dimethyl - 8 - (4 - methylbenzoyl) - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 1 - (4 - methylbenzoyl) - 4 - hydrazino - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 1(a) and proceeding as in parts (b) and (c), 2 - methyl - 8 - (4 - methylbenzoyl) - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one and 2,4 - dimethyl - 8 - (4 - methylbenzoyl) 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, respectively, are obtained.

Example 23

4 - (2 - Aminoethyl) - 2,6 - dimethyl - 8 - ethyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 5(8H) - one

By substituting the 2,6 - dimethyl - 8 - ethyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one obtained in Example 16 in the procedure of Example 4 and substituting 2-chloroethylamine for the dimethylamino-propyl chloride, 4 - (2 - aminoethyl) - 2,6 - dimethyl - 8 - ethyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one is obtained.

The hydrochloride salt is obtained by treating the above product with ethanolic HCl.

Example 24

4 - (3 - Ethoxypropyl) - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting 3-ethoxypropyl chloride for the dimethylaminopropyl chloride in the procedure of Example 4, 4 - (3 - ethoxypropyl) - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5(8H) - one is obtained.

Example 25

2 - Methyl - 4 - methylthiomethyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4 - e]pyrimidin - 5(8H) - one

By substituting methylthiomethyl chloride for the dimethylaminopropyl chloride in the procedure of Example 4 and substituting the 2 - methyl - 4H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5(8H) - one obtained in Example 8 for the 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one, 2 - methyl - 4 - methylthiomethyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]-pyrimidin - 5(8H) - one is obtained.

Example 26

8 - Benzoyl - 2 - methyl - 4 - (p - methylphenyl) - 4H - pyrazolo[1,5 - a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting p-methylphenyl bromide for the bromobenzene in the procedure of Example 21 a, and proceeding as in parts b and c, 8 - benzoyl - 2 - methyl - 4 - (p - methylphenyl) - 4H - pyrazolo[1,5-a]-pyrazolo - [4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one is obtained.

Example 27

4 - [2 - (Diethylamino)ethyl] - 2,8,10 - trimethyl - 4H - pyrazolo[1,5 - a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]-pyrimidin - 5(8H) - one

By substituting diethylaminoethyl chloride for the dimethyl - amino - propyl chloride and utilizing the 2,8,10 - trimethyl - 4H - pyrazolo[1,5 - a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one product of Example 12 instead of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5(8H) - one in the procedure of Example 4, 4 - [2 - (diethylamino)ethyl] - 2,8,10 - trimethyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one is obtained.

Example 28

4 - Dimethylaminomethyl - 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting dimethylaminomethyl

chloride for the dimethylaminopropyl chloride in the procedure of Example 4 and utilizing 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one product of Example 15 instead of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one, 4 - dimethylamino - methyl - 2 - methyl - 8 - phenyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5(8H) - one is obtained.

Example 29

8 - Ethyl - 2 - methyl - 4 - (2 - thiamorpholino)ethyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

By substituting 1 - chloro - 2 - thiamorpholinoethane for the 1 - chloro - 2 - morpholinoethane in the procedure of Example 5, 8 - ethyl - 2 - methyl - 4 - (2 - thiamorpholino)ethyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido]3,4 - e] - pyrimidin - 5(8H) - one is obtained.

Example 30

2 - Methyl - 4 - (3 - piperazino)propyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one

By substituting 3-piperazinopropyl chloride for the 1 - chloro - 2 - morpholinoethane in the procedure of Example 5 and utilizing the 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidin - 5(8H) - one product of Example 8, 2 - methyl - 4 - (3 - piperazino)propyl - 4H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5(8H) - one is obtained.

Example 31

The following ingredients are used to make 1,000 200 mg. tablets each containing 100 mg. of active ingredient:

2,4-dimethyl-3-ethyl-4H-pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido][3,4-e]-pyrimidine-5(8H)-one	100 gm.
Polyvinyl pyrrolidone	7.5 gm.
Lactose	20 gm.
Magnesium stearate	3.5 gm.
Corn starch	17.5 gm.
Avicel—Trade Mark (micro-crystalline cellulose	51.5 gm.

The medicament and lactose are thoroughly admixed. The polyvinyl pyrrolidone is dissolved in ethanol USP to make a 30% solution. This solution is used to granulate the mixture of medicament and lactose. The granulation is passed through a No. 16 screen and air dried. The dried granulation is then passed through a No. 20 screen. To the screened granulate are added the magnesium stearate, Avicel and the corn starch and the mixture is blended. The blend is then compressed into 200 mg. tablets on a standard concave punch. The tablets are then veneer coated with methyl cellulose in a spray pan.

Example 32

N - Butyl - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine

a) 4 - [2 - (2 - Cyano - 1 - methylethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester

249 g of 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b] - pyridine - 5 - carboxylic acid, ethyl ester (1 mol) and 82 g of 3-amino-crotono-nitrile (1 mol) are heated together in 1.5 liters of butyl alcohol with stirring for 24 hours. The solvent is removed in vacuo and the residual 4 - [2 - (2 - cyano - 1 - methyl ethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester is recrystallized from alcohol, yield 309 g (80%); m.p. 190—191°.

b) 8 - Ethyl - 2 - methyl - 4H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5(8H) - one

309 g of 4 - [2 - (2 - cyano - 1 - methyl-ethylidene)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-e]pyridine - 5 - carboxylic acid, ethyl ester (0.8 mol) are refluxed with stirring in 1 liter of acetic acid, containing 50 g of zinc chloride, for 24 hours. The solution is cooled to room temperature and after addition of about 1 liter of cold water, 8 ethyl - 2 - methyl - 4H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5(8H) - one crystallizes and is filtered off. Purification of the compound is accomplished by dissolving in the theoretical amount of aqueous sodium hydroxide and acidifying the solution with acetic acid, yield 161 g (75%), m.p. 285—286°.

c) 5 - Chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine

161 g of 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one (0.06 mol) are heated with stirring in 1 liter of phosphorus oxychloride at 80° for 48 hours. The mixture is decomposed by pouring onto crushed ice. The 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine is filtered off and recrystallized from butyl alcohol, yield 148 g (86%); m.p. 179—180°.

d) N - Butyl - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine

5.7 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine (0.02 mol) are dissolved in 50 ml of dry alcohol. After addition of 1.5 g of n-butylamine, the mixture is heated at reflux temperature with stirring for 12 hours. The solvent is removed and the crystalline residue is treated with water. The N - butyl - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[4,3-e]pyrimidin - 5 - amine is filtered off and recrystallized from ethyl acetate, yield 5 g (77%); m.p. 160—162°.

Example 33

8 - Ethyl - 2 - methyl - N - (1 - methylpropyl) - 8H - pyrazolo[1,5-a]-pyrazolo - [4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5 - amine, hydrate (1:1)

By substituting 1 - methylpropylamine for the n-butylamine in the procedure of Example 32 (d), 8 - ethyl - 2 - methyl - N - (1 - methyl - propyl) - 8H - pyrazolo [1,5 - a]pyrazolo[4',3':5,6]pyrido][3,4 - e] - pyrimidin - 5 - amine, hydrate (1:1) is obtained in 81% yield, m.p. 94—97° (alcohol).

Example 34

8 - Ethyl - 2 - methyl - N - (1 - methylethyl) - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine

By substituting 1 - methylethylamine, for the n-butylamine in the procedure of Example 32 (d), 8 - ethyl - 2 - methyl - N - (1 - methylethyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine is obtained, yield 78%; m.p. 98—100° (alcohol).

Example 35

N - [3 - (Dimethylamino)propyl] - 8 - ethyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

2.9 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazole[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine (0.01 mol) are dissolved in 30 ml of alcohol. 2.5 g of 3 - (dimethylamino) - propyl - 1 - amine are added and the mixture is refluxed for 5 hours. The solvent is distilled off in vacuo and the crystalline residue extracted twice with 50 ml portions of ethyl acetate. The solvent is removed until the volume is about 20 ml and then cooled. N - [3 - (dimethylamino)propyl] - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine crystallizes and is filtered off, yield 2.8 g (80%); m.p. 178—179° (ethyl acetate).

Example 36

N - [2 - (Dimethylamino)ethyl] - 8 - ethyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

By substituting 2 - (dimethylamino)-ethyl - 1 - amine for the 3 - (dimethylamino)propyl - 1 - amine in the procedure of Example 35, N - [2 - (dimethylamino)-ethyl] - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5 - amine is formed, yield 75%; m.p. 124—126° (ethyl acetate).

Example 37

8 - Ethyl - 2 - methyl - 5 - (4 - methyl - 1 - piperazinyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 4-methylpiperazine for the 3 - (dimethylamino)propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (4 - methyl - 1 - piperazinyl) - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine is formed in 69% yield; M.P. 167—169° (ethyl acetate).

Example 38

8 - Ethyl - 2 - methyl - 5 - (1 - piperidinyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting piperidine for the 3 - (dimethylamino)propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (1 - piperidinyl) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine is obtained, yield 71%; m.p. 176—177° (alcohol).

Example 39

8 - Ethyl - 2 - methyl - 5 - (4 - morpholinyl) - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine

By substituting morpholine for 3 - (dimethylamino)propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (4 - morpholinyl) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine is obtained, yield 76%; m.p. 179—180° (alcohol).

Example 40

8 - Ethyl - 2 - methyl - N - [3 - (trifluoromethyl)phenyl] - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

5.8 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidine (0.02 mol), 3 g of triethylamine and 3.3 g of 3-trifluoromethylaniline are refluxed in butyl alcohol for 24 hours with stirring. The solvent is removed in vacuo and the residue

treated with 20 ml of water and filtered off. Recrystallization from alcohol yields 6 g of 8 - ethyl - 2 - methyl - N - [3-trifluoromethyl) - phenyl] - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine; yield (73%) m.p. 205—206°.

Example 41

N,N,8 - Triethyl - 2 - methyl - 8H - pyrazolo[1,5 a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine

8.6 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine (0.03 mol) and 7.2 g of diethylamine are suspended in 50 ml of butyl alcohol and heated with stirring in an autoclave for 10 hours at 150° After this time, the solvent is removed, the residue is treated with water and filtered off. Recrystallization from alcohol yields 8 g (83%) of N,N,8 - triethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine; m.p. 106—108°.

Example 42

8 - Ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

By substituting aqueous ammonia (70%) for the diethylamine in the procedure of Example 41, 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4 - e]pyrimidin - 5 - amine is obtained, yield 69%; m.p. 248—250° (DMF).

Example 43

8 - Ethyl - N,2 - dimethyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4 - e]-pyrimidin - 5 - amine

By substituting methylamine for the diethylamine in the procedure of Example 41, 8 - ethyl - N,2 - dimethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]-pyrido - [3,4 - e]pyrimidin - 5 - amine is obtained, yield 76%; m.p. 254—255° (butyl alcohol).

Example 44

5 - (Butylamino) - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

a) 4 - [2 - (Cyano - 3 - ethoxy - 3 - oxo - 1 - propenyl)hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester

249 g of 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b] - pyridine - 5 - carboxylic acid, ethyl ester (1 mol) are suspended in 1.5 liters of n-butyl alcohol. The mixture is heated with stirring at reflux temperature. At this point, 169 g of ethoxymethylene-cyanoacetic acid, ethyl ester (1 mol), dissolved in 500 ml of warm butyl alcohol, are dropped in. After the addition is completed, heating is continued for 2 hours. The solution is cooled in an ice-bath and the precipitated 4 - [2 - (2 - cyano - 3 - ethoxy - 3 - oxo - 1 - propenyl) - hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester is filtered off, yield 351 g (94%); m.p. 170—172° (butyl alcohol).

b) 8 - Ethyl - 5,8 - dihydro - 5 - oxo - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

351 g of 4 - [2 - (2 - cyano - 3 - ethoxy - 3 - oxo - 1 - propenyl) - hydrazino] - 1 - ethyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester are heated in 2 liters of acetic acid containing 50 g of zinc chloride for 24 hours. After this time, the solution is cooled and 2 liters of cold water are added. The precipitated 8 - ethyl - 5,8 - dihydro - 5 - oxo - 4H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine - 3 - carboxylic acid, ethyl ester is filtered off and purified by dissolving in the theoretical amount of sodium hydroxide in water and precipitating the compound with acetic acid, yield 256 g (83%); m.p. 263—265°.

c) 5 - Chloro - 8 - ethyl - 8H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 e]-pyrimidine - 3 - carboxylic acid, ethyl ester

256 g of 8 - ethyl - 5,8 - dihydro - 5 - oxo - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester are refluxed in 1 liter of phosphorus oxychloride for 24 hours. The excess phosphorus oxychloride is decomposed by pouring the solution on ice and the crystallized 5 - chloro - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester is filtered off, yield 245 g (91%); m.p. 170—172° (butyl alcohol).

d) 5 - (Butylamino) - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

3.5 g of 5 - chloro - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4 - e]pyrimidine - 3 - carboxylic acid, ethyl ester (0.01 mol) and 7.3 g of n-butylamine are refluxed together with 30 ml of alcohol with stirring for 8 hours. The solution is evaporated to dryness and the residue treated with water and filtered off. Recrystallization from ethyl acetate yields 3.2 g (84%) of 5 - (n - butylamino) - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester; m.p. 275—277°.

Example 45

5 - [(1 - Methylpropyl)amino] - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting 1-methylpropylamine for the n - butyl - amine in the procedure of Example 44(d), 5 - [(1 - methylpropyl)-amino] - 8 - ethyl - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 -e] - pyrimidine - 3 - carboxylic acid, ethyl ester is obtained, yield 71%; m.p. 94—97°. Hydrolysis with aqueous sodium hydroxide solution yields the free carboxylic acid.

Example 46

8 - Ethyl - 5 - (methylamino) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

3.5 g of 5 - chloro - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester (0.01 mol) and 3.5 g of methylamine are heated in 50 ml of alcohol in an autoclave for 10 hours at 100°. The solvent is removed in vacuo and the residue treated with water, filtered off and recrystallized from butyl alcohol, yield 2.9 g (86%); m.p. 321—322°.

Example 47

5 - (Diethylamino) - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting diethylamine for the methylamine in the procedure of Example 46, 5 - (diethylamino) - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4 - e]pyrimidine - 3 - carboxylic acid, ethyl ester is formed, yield 73%; m.p. 170—172° (alcohol).

Example 48

5 - Amino - 8 - ethyl - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e]-pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting an equivalent amount of 30% aqueous ammonia for the methylamine in the procedure of Example 46, 5 - amino - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidine - 3 - carboxylic acid, ethyl ester is formed, yield 68%; m.p. 331—332° (DMF).

Example 49

8 - Ethyl - 5 - (4 - methyl - 1 - piperazinyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine - 3 - carboxylic acid, ethyl ester

3.5 g of 5 - chloro - 8 - ethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester (0.01 mol) are dissolved in 20 ml of butanol. 2 g of N-methylpiperazine are added and the solution is refluxed with stirring for 12 hours. After evaporation of the solvent, the residue is extracted three times with 50 ml portions of ethyl acetate. The ethyl acetate is distilled off until the volume is about 30 ml. The 8 - ethyl - 5 - (4 - methyl - 1 - piperazinyl) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester crystallizes, yield 3.1 g (76%); m.p. 111—113° (ethyl acetate).

Example 50

8 - Ethyl - 5 - (1 - piperidinyl) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting piperidine for the N-methylpiperazine in the procedure of Example 49, 8 - ethyl - 5 - (1 - piperidinyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrim - idine - 3 - carboxylic acid, ethyl ester is obtained, yield 2.6 g (67%) m.p. 183—184° (ethyl acetate).

Example 51

5 - [[3 - (Dimethylamino)propyl]amino]8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting 3 - (dimethylamino)-propylamine for the N-methylpiperazine in the procedure of Example 49, 5 - [[3 - (dimethylamino)propyl]-amino] - 8 - ethyl - 8H - pyrazolo[1,5-a] - pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester is obtained, yield 62%; m.p. 212—215° (ethyl acetate).

Example 52

5 - [3 - (Dimethylamino)propoxyl - 8 - ethyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

To a suspension of 3.6 g of sodium hydride in 100 ml of dry benzene 15.3 g of 3-(dimethylamino)propanol are added and the mixture is refluxed for 6 hours. After this time, 28.6 g of 5 - chloro 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine are added in small portions with stirring. The solution is refluxed for 10 hours, and then the solvent is distilled off. The residue is treated with water, filtered off and recrystallized from ethyl acetate, yield 25 g (71%); m.p. 62—64°.

Example 53

5 - Butoxy - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine

By substituting n-butyl alcohol for the 3 -

(dimethylamino)propanol in the procedure of Example 52, 5 - butoxy - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine is obtained, yield 71%; m.p. 103—104° (methanol).

Example 54

8 - Ethyl - 2 - methyl - 5 - (1 - methylethoxy) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 2-propanol for the 3 - (dimethylamino)propanol in the procedure of Example 52, 8 - ethyl - 2 - methyl - 5 - (1 - methylethoxy) - 8H - pyrazolo-[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidine is obtained, yield 68%; m.p. 129—130° (ethyl acetate).

Example 55

8 - Ethyl - 2 - methyl - 5 - (3 - methylbutoxy) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 3 - methylbutyl alcohol for the 3 - (dimethylamino)propanol in the procedure of Example 52, 8 - ethyl - 2 - methyl - 5 - (3 - methylbutoxy) - 8H - pyrazolo[1,5-a] - pyrazolo[4',3':5,6]pyrido-[3,4 - e]pyrimidine is obtained, yield 67%; m.p. 60—62° (ethyl acetate).

Example 56

5 - Ethoxy - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine

2.3 g of sodium are dissolved in 100 ml of dry alcohol with stirring. The solution is heated at reflux temperature and, at this point, 28.6 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine are added in small portions. Heating and stirring is continued for 6 hours. The precipitated sodium chloride is filtered off, the solvent is removed and the residual 5 - ethoxy - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidine is recrystallized from methanol, yield 82%; m.p. 142—144°.

Example 57

5 - [3 - (Dimethylamino)propoxy] - 8 - ethyl - 8H - pyrazolo[1,5-a] - pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrim - idine - 3 - carboxylic acid, ethyl ester

To a suspension of 3.6 g of sodium hydride in 100 ml of dry benzene 15.3 g of 3 - (dimethylamino)propanol are added dropwise at reflux temperature with stirring. Heating is continued for 10 hours. After this time, 34.4 g of 5 - chloro - 8 - ethyl - 8H - pyrazolo[1,5]pyrazolo[4',3':5,6]pyrido[3,4- e] pyrimidine - 3 - carboxylic acid, ethyl ester are added and the solution is refluxed for 5 additional hours. The solution is evaporated to dryness and the residue is treated with water, filtered off and recrystallized from ethyl acetate. 12 g of 5 - [3 - (dimethylamino)propoxy] - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4 - e]pyrimidine - 3 - carboxylic acid, ethyl ester are obtained (29.3%); m.p. 106—107°.

Example 58

8 - Ethyl - 5 - (3 - methylbutoxy) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting 3-methyl-butyl alcohol for the 3 - (dimethylamino)propanol in the procedure of Example 57, 8 - ethyl - 5 - (3 - methylbutoxy) - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine - 3 - carboxylic acid, ethyl ester is obtained, yield 61%; m.p. 117—118° (ethyl acetate). Hydrolysis with aqueous sodium hydroxide yields the free carboxylic acid.

Example 59

5 - Ethoxy - 8 - ethyl - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting for the 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine in the procedure of Example 56, 5 - chloro - 8 - ethyl-8H-pyrazolo-[1,5 - a]-pyrazolo - [4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester, 5 - ethoxy - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester is formed, yield 75%; m.p. 167—168° (alcohol).

Example 60

8 - Ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4e]-pyrimidine - 5 - thiol

5.6 g of 5 - chloro - 8 - ethyl - 2 - methyl - 4H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine (0.02 mol) are dissolved in 100 ml of dimethylformamide. 2 g of powdered sodium sulfide are added and the mixture is stirred for 1 hour. After this time, the solution is carefully acidified with acetic acid. 8 - Ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 5 - thiol precipitates and is filtered off, yield 5.1 g (91%; m.p. 320—322° (DMF).

Example 61

8 - Ethyl - 5 - mercapto - 8H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4-e] - pyrimidine - 3 - carboxylic acid, ethyl ester

By substituting for the 8 - ethyl - 2 -

methyl - 4H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5(8H) - one in the procedure of Example 50, 5 - chloro - 8 - ethyl - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine - 3 - carboxylic acid, ethyl ester, 8 - ethyl - 5 - mercapto - 8H - pyrazolo[2,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 3 - carboxylic acid, ethyl ester is formed, yield 86%; m.p. 238—240° (DMF).

Example 62

8 - Ethyl - 2 - methyl - 5 - (methylthio) - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine

5.6 g of 5 - chloro - 8 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine (0.02 mol) and 3 g of sodium methylmercaptide are refluxed together in 50 ml of dimethylformamide with stirring for 2 hours. The mixture is cooled to room temperature and diluted with 50 ml of water. 8 - Ethyl - 2 - methyl - 5 - (methylthio) - 8H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6pyrido[3,4 - e] - pyrimidine is filtered off and recrystallized from butyl alcohol, yield 3.5 g (59%); m.p. 168—169°.

Example 63

N - Butyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine - 5 - amine

By substituting an equivalent amount of 4 - hydrazino - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32 (a), and continuing as in parts (b), (c) and (d), 5 - chloro - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4 - e]pyrimidine and N - butyl - 2 - methyl - 8H - pyrazolo - [1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4 - e]pyrimidine - 5 - amine respectively, are obtained.

Example 64

N,2,8,10 - Tetramethyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

By substituting 1,3 - dimethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32 (a) and proceeding as in parts (b) and (c), and substituting methylamine for the butylamine in part (d), 5 - chloro - 2,8,10 - trimethyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidine and N,2,8,10 - tetramethyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido][3,4 - e]pyrimidin - 5 - amine are obtained.

Example 65

2,3 - Diethyl - 8 - isopropyl - 5 - phenoxy - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 1 - isopropyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester and 3 - amino - 2 - ethyl - 2 - pentenonitrile for the 3-aminocrotononitrile in the procedure of Example 32 (a), proceeding as in parts (b) and (c), then following the procedire of Example 52, but substituting phenol for the 3 - (dimethylamino)propanol, 5 - chloro - 2,3 - diethyl - 8 - isopropyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine and 2,3 - diethyl - 8 - isopropyl - 5 - phenoxy - 8H - pyrazolo[1,5 - a] - pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine, respectively, are obtained.

Example 66

5 - (4 - Chlorophenyloxy) - 10 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 4 - hydrazino - 3 - ethyl - 1H - pyrazolo - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid propyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32(a), proceeding as in parts (b) and (c), then following the procedure of Example 52 but substituting 4-chlorophenol for the 3 - (dimethylamino)-propanol, 5 - chloro - 10 - ethyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine and 5 - (4 - chorophenyloxy) - 10 - ethyl - 2 - methyl - 8H - pyrazolo[1,5 - a] - pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine, respectively, are obtained.

Example 67

5 - Benzyloxy - 2 - methyl - 8 - phenyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine

By substituting 4 - hydrazino - 1 - phenyl - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32(a), proceeding as in parts (b) and (c), then proceeding as in Example 52 but substituting phenylmethanol for the 3 - (dimethylamino)propanol, 5 - chloro - 2 - methyl - 8 - phenyl - 8H - pyrazolo[1,5-a]-

pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine and 5 - benzyloxy - 2 - methyl - 8 - phenyl - 8H - pyrazolo[1,5 - a] - pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine, respectively, are obtained.

Example 68

N - Butyl - 8 - ethyl - 2,6 - dimethyl - 8H - pyrazolo[1,5 - a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidine - 5 - amine

By substituting 1 - ethyl - 4 - hydrazino - 6 - methyl - 1H - pyrazolo-[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32, 5 - chloro - 2,6 - dimethyl - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine and N - butyl - 8 - ethyl - 2,6 - dimethyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4 - e]pyrimidine - 5 amine, respectively, are obtained.

Example 69

8 - Benzyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - thiol

By substituting 1 - benzyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32(a), proceeding as in part (b), then proceeding as in Example 50, 8 - benzyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4 - e]pyrimidine - 5 - thiol is obtained.

Example 70

N - Butyl - 8 - phenylethyl - 3 - propyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine

By substituting 1 - phenylethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, methyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester and 2-aminomethylenepentanonitrile for the 3-aminocrotononitrile in the procedure of Example 32(a) and proceeding as in parts (b), (c) and (d), 5 - chloro - 8 - phenylethyl - 3 - propyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine and N - butyl - 8 - phenylethyl - 3 - propyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine, respectively, are obtained.

Example 71

N - butyl - 8 - ethyl - 2 - phenyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine

By substituting 3 - amino - 3 - phenylcrotononitrile for the 3 - aminocrotononitrile in the procedure of Example 32 (a)- and proceeding as in parts (b), (c) and (d), 5 - chloro - 8 - ethyl - 2 - phenyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]pyrimidine and N - butyl - 8 - ethyl - 2 - phenyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine, respectively, are obtained.

Example 72

8 - Benzoyl - N - butyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6] - pyrido[3,4-e]pyrimidin - 5 - amine

a) N - Butyl - 8 - furfuryl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidin - 5 - amine

By substituting 4 - hydrazino - 1 - furfurylpyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in Example 32 a and proceeding as in parts a and b, 8 - furfuryl - 2 - methyl - 4H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5(8H) - one is obtained. This compound is now processed as in Example 32, parts c and d to obtain N - butyl - 8 - furfuryl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5 - amine.

b) N - Butyl - 2 - methyl - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

0.01 mol of N - butyl - 8 - furfuryl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine is heated in 50 ml of diethyleneglycol dimethyl ether containing 0.01 mol of selenium dioxide at reflux temperature with stirring for two hours. The mixture is filtered hot and evporated to dryness. N - butyl - 2 - methyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine remains.

c) 8 - Benzoyl - N - butyl - 2 - methyl - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine

0.01 mol of N - butyl - 2 - methyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidin - 5 - amine and 0.02 mol of

benzoyl chloride are stirred overnight in 50 ml of dry pyridine at room temperature. On addition of 50 ml of water, 8 - benzoyl - N - butyl - 2 - methyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine is filtered off.

Example 73

N - Butyl - 2 - methyl - 8 - (4 - methylbenzoyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidin - 5 - amine

By substituting 1 - (4 - methylbenzoyl) - 4 - hydrazino - 1H - pyrazolo[3,4-b]-pyridine - 5 - carboxylic acid, ethyl ester for the 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4-b]pyridine - 5 - carboxylic acid, ethyl ester in the procedure of Example 32(a) and proceeding as in parts (b), (c) and (d), 5 - chloro - 2 - methyl - 8 - (4 - methylbenzoyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine and N - butyl - 2 - methyl - 8 - (4 - methylbenzoyl) - 8H - pyrazolo[1,5-a]-pyrazolol[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 - amine, respectively, are obtained.

Example 74

5 - (2 - Aminoethoxy - 2,6 - dimethyl - 8 - ethyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine

By substituting the 5 - chloro - 2,6 - dimethyl - 8 - ethyl - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4 - e]pyrimidine obtained in Example 68 in the procedure of Example 52 and substituting ethanolamine for the 3-(dimethylamino)propanol, 5 - (2 - aminoethoxy) - 2,6 - dimethyl - 8 - ethyl - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine is obtained.

The hydrochloride salt is obtained by treating the above product with ethanolic HCl.

Example 75

8 - Ethyl - 2 - methyl - 5 - [(3 - propyl-amino)propoxy]8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting 3(propylamino)propanol for the 3(dimethylamino)propanol in the procedure of Example 52, 8 - ethyl - 2 - methyl - 5 - [(3 - propylamino)propoxy]-8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine is obtained.

Example 76

8 - Ethyl - 2 - methyl - 5 - (1 - piperazinyl) - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting piperazine for the 3-(dimethylamino) - propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (1 - piperazinyl) - 8H - pyrazolo[1,5-a]pyrazolo - [4',3':5,6]pyrido-[3,4-e]pyrimidine is obtained.

Example 77

N - Butyl - 8 - ethyl - 2,3 - diphenyl - 8H - pyrazolo[1,5 - a]pyrazolo-[4',3':5,6]pyrido[3,4 - e]pyrimidin - 5 amine

By substituting 3 - amino - 2,3 - diphenylcrotononitrile for the 3-amino-crotononitrile in the procedure of Example 32, 5 - chloro - 8 - ethyl - 2,3 - diphenyl - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]-pyrazolo[3,4-e]pyrimidine and N - butyl - 8 - ethyl - 2,3 - diphenyl - 8H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidin - 5 - amine, respectively, are obtained.

Example 78

8 - Ethyl - 2 - methyl - 5 - thiamorpholino - 8H - pyrazolo[1,5-a]-pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting thiamorpholine for the 3-(dimethylamino)propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - thiamorpholino - 8H - pyrazolo[1,5-a]pyrazolo[4',3':5,6]pyrido-[3,4-e]pyrimidine is obtained.

Example 79

8 - Ethyl - 2 - methyl - 5 - (1 - pyrazolyl) - 8H - pyrazolo[1,5-a]pyrazolo - [4',3':5,6]pyrido[3,4-e]pyrimidine

By substituting pyrazole for the 3 - (dimethylamino) - propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (1 - pyrazolyl) - 8H - pyrazolo[1,5 - a]pyrazolo[4',3':5,6]pyrido - [3,4-e]pyrimidine is obtained.

Example 80

8 - Ethyl - 2 - methyl - 5 - pyrrolidino - 8H - pyrazolo[1,5-a]pyrazolo-[4',3':5,6]pyrido[3,4-e]pyrimidine

By substituting pyrrolidine for the 3 - (dimethylamino) - propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - pyrrolidino - 8H - pyrazolo-[1,5 - a]pyrazolo[4',3':5,6]pyrido[3,4 - e] - pyrimidine is obtained.

Example 81

8 - Ethyl - 2 - methyl - 5 - (dihydropyridazin - 1 - yl) - 8H - pyrazolo-[1,5-a]pyrazolo[4',3':5,6]pyrido[3,4-e]-pyrimidine

By substituting dihydropyridazine for the 3 - (dimethylamino)propyl - 1 - amine in the procedure of Example 35, 8 - ethyl - 2 - methyl - 5 - (dihydropyridazin - 1 - yl) - 8H - pyrazolo - [1,5-a]pyrazolo[4',3':5,6]-pyrido[3,4-e]pyrimidine is obtained.

Example 82

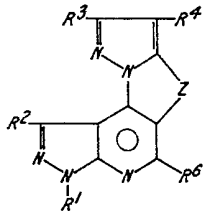
The following ingredients are used to make 1,000 200 mg tablets each containing 100 mg of active ingredient:

N-butyl-8-ethyl-2-methyl-8H-pyrazolo-[1,5-a]pyrazolo-[4',3':5,6]pyrido-[3,4-e]-pyrimidine-5-amine	100 gm.
Polyvinyl pyrrolidone	7.5 gm.
Lactose	20 gm.
Magnesium stearate	3.5 gm.
Corn starch	17.5 gm.
Avicel—Trade Mark (microcrystalline cellulose)	51.5 gm.

The medicament and lactose are thoroughly admixed. The polyvinyl pyrrolidone is dissolved in ethanol USP to make a 30% solution. This solution is used to granulate the mixture of medicament and lactose. The granulation is passed through a No. 16 screen and air dried. The dried granulation is then passed through a No. 20 screen. To the screened granulate are added the magnesium stearate, *Avicel* and the corn starch and the mixture is blended. The blend is then compressed into 200 mg. tablets on a standard concave punch. The tablets are then veneer coated with methyl cellulose in a spray pan.

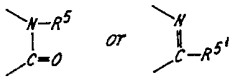
WHAT WE CLAIM IS:

1. A compound of the formula

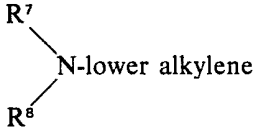


(I)

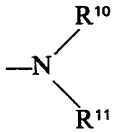
wherein Z is



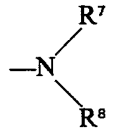
R^1 is hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, benzoyl or substituted phenyl or benzoyl wherein the phenyl or benzoyl substituent is one or two halogens, lower alkyl or trifluoromethyl groups; R^2 and R^3 each is hydrogen, lower alkyl or phenyl; R^4 is hydrogen, lower alkyl, phenyl, carboxy or lower alkoxycarbonyl; R^5 is hydrogen, lower alkyl, phenyl-lower alkylene, benzoyl, substituted benzoyl, lower alkanoyl, lower alkoxy-lower alkylene, lower alkylthio-lower alkylene, phenyl, substituted phenyl or



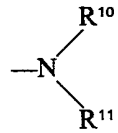
$R^{5'}$ is lower alkoxy, substituted lower alkoxy wherein the substituent is



phenyl-lower alkoxy, phenyloxy, substituted phenyloxy wherein the phenyl ring bears one or two halogen, lower alkyl or trifluoromethyl groups, halo,

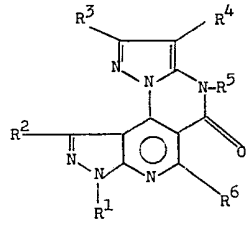


or —S—R^9; R^6 is hydrogen or lower alkyl; R^7 is hydrogen, lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is



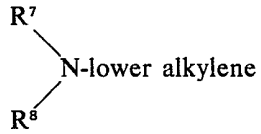
phenyl or substituted phenyl wherein the phenyl substituent is halogen, lower alkyl or trifluoromethyl, R^8 is hydrogen or lower alkyl, or R^7 and R^8 together with the nitrogen form one of the unsubstituted or substituted hetero-cyclics pyrrolidino, morpholino, thiamorpholino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl wherein the heterocycle substituent is lower alkyl or hydroxy-lower alkyl; R^9, R^{10} and R^{11} each is hydrogen or lower alkyl; or such a compound in acid addition salt form.

2. A compound as in Claim 1 having the formula



Ia

wherein R^1 is hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, benzoyl or substituted phenyl or benzoyl; R^2, R^4 and R^6 each is hydrogen or lower alkyl; R^3 is hydrogen, lower alkyl or phenyl; R^5 is hydrogen, lower alkyl, phenyl-lower alkylene, benzoyl, substituted benzoyl, lower alkanoyl, lower alkoxy-lower alkylene, lower alkylthio-lower alkylene, phenyl, substituted phenyl, amino-lower alkylene or



wherein R^7 and R^8 each is lower alkyl or together join to complete the heterocycle piperidine, morpholine, thiamorpholine or piperazine; or such a compound in acid addition salt form.

3. A compound as in Claim 2 wherein R^1 is lower alkyl; R^2, R^3, R^4 and R^6 each is hydrogen or lower alkyl; and R^5 is lower alkyl or di-lower alkylamino-lower alkylene.

4. A compound as in Claim 2 wherein R^1, R^2, R^3, R^4 and R^6 each is hydrogen or lower alkyl; and R^5 is hydrogen, lower alkyl, phenyl-lower alkylene, phenyl, amino-lower alkylene, di-lower alkylamino-lower alkylene, piperidino-lower alkylene, morpholino-lower alkylene or piperazino-lower alkylene.

5. A compound as in Claim 2 wherein the lower alkyl and lower alkylene groups have up to 4 carbon atoms.

6. A compound as in Claim 2 wherein R^5 is lower alkyl.

7. A compound as in Claim 2 wherein R^5 is di-lower alkylamino-lower alkylene.

8. A compound as in Claim 2 wherein R^5 is piperidino-lower alkylene.

9. A compound as in Claim 2 wherein R^5 is morpholino-lower alkylene.

10. A compound as in Claim 2 wherein R^1 is ethyl, R^3 is methyl and R^2, R^4 and R^6 each is hydrogen.

11. A compound as in Claim 10 wherein R^5 is methyl.

12. A compound as in Claim 10 wherein R^5 is ethyl.

13. A compound as in Claim 10 wherein R^5 is isopentyl.

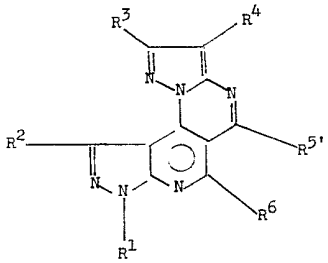
14. A compound as in Claim 10 wherein R^5 is 3-dimethylaminopropyl.

15. A compound as in Claim 10 wherein R^5 is 2-piperidinoethyl.

16. A compound as in Claim 10 wherein R^5 is 2-morpholinoethyl.

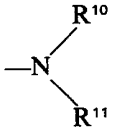
17. A compound as in Claim 10 wherein R^5 is 2-diethylaminoethyl.

18. A compound as in Claim 1 having the formula

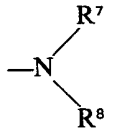


(Ib)

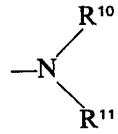
wherein R^1 is hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, benzoyl or substituted phenyl or benzoyl wherein the phenyl or benzoyl substituent is one or two halogens, lower alkyl or trifluoromethyl groups; R^2 and R^3 each is hydrogen, lower alkyl or phenyl; R^4 is hydrogen, lower alkyl, phenyl, carboxy or lower alkoxycarbonyl; $R^{5'}$ is lower alkoxy, substituted lower alkoxy wherein the substituent is



phenyl-lower alkoxy, phenyloxy, substituted phenyloxy wherein the phenyl ring bears one or two halogen, lower alkyl or trifluoromethyl groups, halo,



or —S—R^9; R^6 is hydrogen or lower alkyl; R^7 is hydrogen, lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is



phenyl or substituted phenyl wherein the phenyl substituent is halogen, lower alkyl or trifluoromethyl, R^8 is hydrogen or lower alkyl, or R^7 and R^8 together with the nitrogen form one of the unsubstituted or substituted heterocyclics pyrrolidino, morpholino, thiamorpholino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl wherein the heterocycle substituent is lower alkyl or hydroxy-lower alkyl; R^9, R^{10} and R^{11} each is hydrogen or lower alkyl; or such a compound in acid addition salt form.

19. A compound as in Claim 18 wherein R^1, R^2, R^3 and R^6 each is hydrogen or lower alkyl; R^4 is hydrogen or lower alkoxycarbonyl; $R^{5'}$ is amino, mercapto, lower alkylamino, di(lower alkyl)amino, di(lower alkyl)amino-lower alkylamino or di(lower alkyl)amino-lower alkoxy.

20. A compound as in Claim 18 wherein R^2 and R^6 each is hydrogen.

21. A compound as in Claim 18 wherein $R^{5'}$ is lower alkylamino.

22. A compound as in Claim 18 wherein $R^{5'}$ is lower alkoxy.

23. A compound as in Claim 18 wherein $R^{5'}$ is di(lower alkyl)amino-lower alkylamino.

24. A compound as in Claim 18 wherein $R^{5'}$ is di(lower alkyl)amino-lower alkoxy.

25. A compound as in Claim 18 wherein $R^{5'}$ is halogen.

26. A compound as in Claim 18 wherein $R^{5'}$ is lower alkylmercapto.

27. A compound as in Claim 20 wherein R^1 and R^3 each is lower alkyl, R^4 is hydrogen and $R^{5'}$ is lower alkylamino.

28. A compound as in Claim 20 wherein R^1 and R^3 each is lower alkyl, R^4 is hydrogen and $R^{5'}$ is lower alkoxy.

29. A compound as in Claim 18 wherein R^1 is lower alkyl, R^2 and R^6 are hydrogen, R^3 is hydrogen or lower alkyl, R^4 is hydrogen or alkoxycarbonyl and $R^{5'}$ is halogen.

30. A compound as in Claim 18 wherein R^1 is ethyl, R^2, R^4 and R^6 is hydrogen, R^3 is methyl and $R^{5'}$ is chloro.

31. A compound as in Claim 18 wherein R^1 is ethyl, R^2, R^3 and R^6 each is hydrogen, R^4 is ethoxycarbonyl and $R^{5'}$ is chloro.

32. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is butylamino.

33. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is ethoxy.

34. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is 3-(dimethylamino) propylamino.

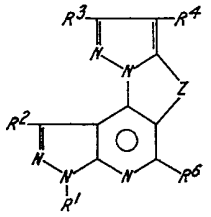
35. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is hydrogen, R^4 is ethoxycarbonyl and $R^{5'}$ is 3-(dimethylamino)-propylamino.

36. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is 3-methylbutoxy.

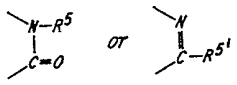
37. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is 1-methylethoxy.

38. A compound as in Claim 20 wherein R^1 is ethyl, R^3 is methyl, R^4 is hydrogen and $R^{5'}$ is 1-methylethylamino.

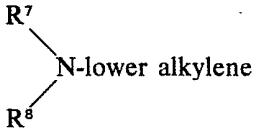
39. Process for preparing a compound of the formula



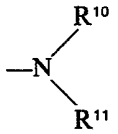
wherein Z is



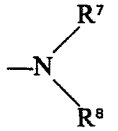
R^1 is hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, benzoyl or substituted phenyl or benzoyl wherein the phenyl or benzoyl substituent is one or two halogens, lower alkyl or trifluoromethyl groups; R^2 and R^3 each is hydrogen, lower alkyl or phenyl; R^4 is hydrogen, lower alkyl, phenyl, carboxy or lower alkoxycarbonyl; R^5 is hydrogen, lower alkyl, phenyl-lower alkylene, benzoyl, substituted benzoyl, lower alkanoyl, lower alkoxy-lower alkylene, lower alkylthio-lower alkylene, phenyl, substituted phenyl or



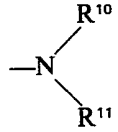
$R^{5'}$ is lower alkoxy, substituted lower alkoxy wherein the substituent is



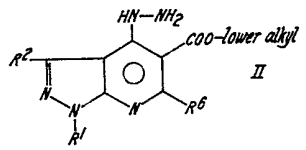
phenyl-lower alkoxy, phenyloxy, substituted phenyloxy wherein the phenyl ring bears one or two halogen, lower alkyl or trifluoromethyl groups, halo,



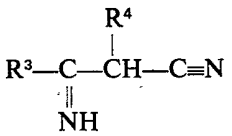
or —S—R^9; R^6 is hydrogen or lower alkyl; R^7 is hydrogen, lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is



phenyl or substituted phenyl wherein the phenyl substituent is halogen, lower alkyl or trifluoromethyl, R^8 is hydrogen or lower alkyl, or R^7 and R^8 together with the nitrogen form one of the unsubstituted or substituted heterocyclics pyrrolidino, morpholino, thiamorpholino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl wherein the heterocycle substituent is lower alkyl or hydroxy-lower alkyl; R^9, R^{10} and R^{11} each is hydrogen or lower alkyl; and acid addition salts thereof which comprises reacting a compound of the formula

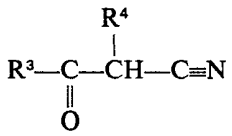


wherein R^1, R^2 and R^6 are defined as above with a compound of the formula



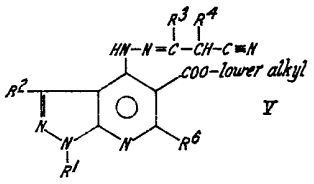
(III)

or



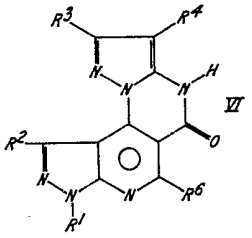
(IV)

wherein R^3 and R^4 are defined as above to form a compound of the formula



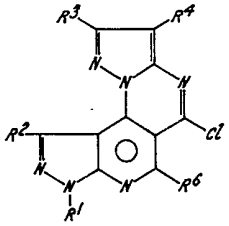
V

wherein R^1, R^2, R^3, R^4 and R^6 are defined as above, treating this compound with a base in alcoholic solution or with an organic acid and a Lewis acid catalyst to form a compound of the formula



VI

wherein R^1, R^2, R^3, R^4 and R^6 are defined as above and, if desired, reacting a compound of Formula VI with a halide of the formula R^5-hal wherein hal is halogen and R^5 is defined as above or, if desired, reacting a compound of Formula VI with a chlorinating agent to form a compound of the formula



VII

wherein R^1, R^2, R^3, R^4 and R^6 are defined as above and reacting the compound of Formula VII with a compound of the formula

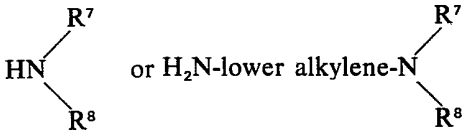
R^{12}—O—Me

wherein Me is an alkali metal and R^{12} is lower alkyl, amino-lower alkyl

lower alkyl), phenyl or substituted phenyl or with a compound of the formula

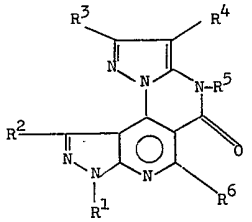
R^{12}—S—Me

wherein Me is an alkali metal and R^{12} is lower alkyl or with an alkali metal sulfide or with an amine of the formula

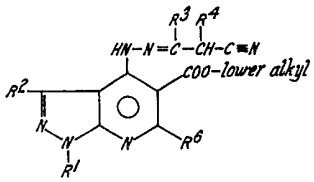


wherein R^7 and R^8 are defined as above.

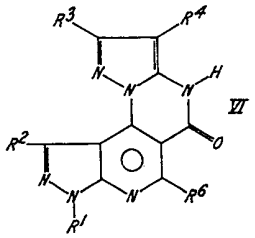
40. The process of Claim 39 for preparing a compound of the formula



wherein R^1, R^2, R^3, R^4, R^5 and R^6 are defined as in Claim 39 which comprises treating a compound of the formula



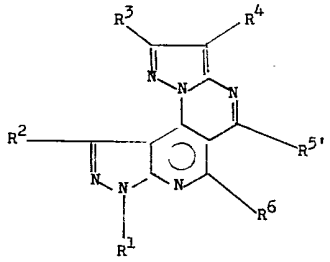
wherein R^1, R^2, R^3, R^4 and R^6 are defined as in Claim 39 with a base in alcoholic solution or with an organic acid and a Lewis acid catalyst to form a compound of the formula



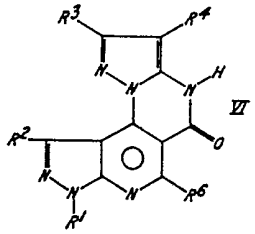
VI

wherein R^1, R^2, R^3, R^4 and R^6 are defined as in Claim 39 and, if desired, reacting a compound of Formula VI with a halide of the formula R^5-hal wherein hal is halogen and R^5 is defined as in Claim 39.

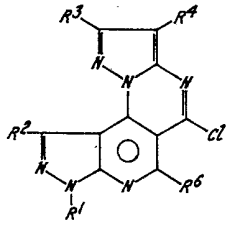
41. The process of Claim 39 for preparing a compound of the formula



wherein R^1, R^2, R^3, R^4, $R^{5'}$ and R^6 are defined as in Claim 39 which comprises reacting a compound of the formula



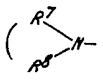
wherein R^1, R^2, R^3, R^4 and R^6 are defined as in Claim 39 with a chlorinating agent to form a compound of the formula



wherein R^1, R^2, R^3, R^4 and R^6 are defined as in Claim 39 and reacting the compound of Formula VII with a compound of the formula

R^{12}—O—Me

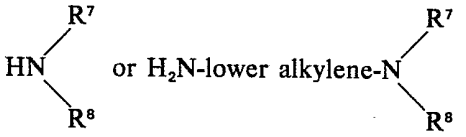
wherein Me is an alkali metal and R^{12} is lower alkyl, amino-lower alkyl



lower alkyl), phenyl or substituted phenyl or with a compound of the formula

R^{12}—S—Me

wherein Me is a alkali metal and R^{12} is lower alkyl or with an alkali metal sulfide or with an amine of the formula



wherein R^7 and R^8 are defined as in Claim 39.

42. A compound as in Claim 2 wherein prepared by a process as in Claim 40.

43. A compound as in Claim 18 when prepared by a process as in Claim 41.

44. A compound according to Claim 2 as named in any of Examples 1 to 30.

45. A compound according to Claim 18 as named in any of Examples 32 to 81.

46. A pharmaceutical composition comprising a compound according to any one of Claims 2 to 17, 42 or 44 and a pharmaceutical carrier.

47. A pharmaceutical composition comprising a compound according to any one of Claims 18 to 38, 43 or 45 and a pharmaceutical carrier.

48. A pharmaceutical composition according to Claim 46 in the form of a tablet, capsule, syrup, elixir, lotion, ointment or cream.

49. A pharmaceutical composition according to Claim 47 in the form of a tablet, capsule, syrup, elixir, lotion, ointment or cream.

50. A composition according to Claim 46 or 48 which includes a binder, an excipient, a disintegrating agent, a lubricant, a sweetening agent, a flavouring agent, a dye or a preservative.

51. A composition according to Claim 47 or 49 which includes a binder, an excipient, a disintegrating agent, a lubricant, a sweetening agent, a flavouring agent, a dye or a preservative.

For the Applicants:—
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London, WC1V 7RD.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.