1,167,735

PATENT SPECIFICATION

NO DRAWINGS

1,167,735

Date of Application (No. 48520/66) and filing Complete Specification: 28 Oct., 1966.

Application made in United States of America (No. 505,993) on 1 Nov., 1965.

Complete Specification Published: 22 Oct., 1969.

Index at acceptance:—C2 C(1J3B, 1J3C3, 1Q5, 1Q6C, 1Q8A, 1Q9C, 1Q9F2, 1Q9L, 1Q11J, 2D3, 2D19, 200, 202, 215, 22Y, 220, 221, 222, 225, 226, 246, 247, 25Y, 250, 251, 252, 253, 255, 28X, 29Y, 29X, 30Y, 31Y, 313, 314, 32Y, 321, 322, 323, 328, 332, 333, 334, 337, 338, 34Y, 342, 343, 36Y, 36X, 364, 366, 368, 470, 595, 597, 598, 601, 603, 604, 62X, 63X, 652, 658, 661, 67X, 670, 671, 672, 79Y, 790, 17X—186—272, 170—189—276, 171—191—280, 171—27X—289, 172—194—284, 172—195—285, 173—197—288, 175—193—286, 177—27X—277, 181—198—280, 182—19X—272, 183—190—274, 184—190—275, 278—281—283, KN, KR, KT, KV, KY, LW, LY, LZ); A5 B(38Y, 381, 382, 383, 39Y, 390, 396, 44Y, 446, 48Y, 480, 482, 484, 50Y, 500, 504, 51Y, 511, 512, 513, 52Y, 522, 54Y, 541, 542, 544, 56Y, 564, 565, 566, 567, 58Y, 586, 59Y, 595, 596, 597, 60Y, 606, 65Y, 65X, 650, 651, 652, 653, 67Y, 670)

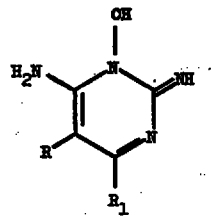
International Classification:—C 07 d 51/28, 57/00, 99/02

COMPLETE SPECIFICATION

Improvements in or relating to Substituted Pyrimidines and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, 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 relates to novel compounds and to methods for producing them. In particular, this invention relates to novel 1,2 - dihydro - 1 - hydroxypyrimidines of the formula:—



I

wherein R_1 is a group of the formula $-N<^{R_3}_{R_4}$ wherein R_3 and R_4 are hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower aralkyl of C_7—C_{14}, cycloalkyl of C_3—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, with the proviso that both R_3 and R_4 are not hydrogen, or an aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethyleneimino, octamethyleneimino, morpholino, or 4 - lower - alkyl (C_1—C_8) piperazinyl group, each of said heterocyclic groups having optionally attached as substituents on carbon atoms thereof one to 3 lower alkyls of C_1—C_8 inclusive, a nitrogen atom of each of said heterocyclic groups being the point of attachment of R_1 to the ring in said formula. When R_1 is $-N<^{R_3}_{R_4}$, R_3 and R_4 can be alike or different. When R_1 is

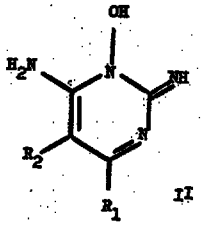
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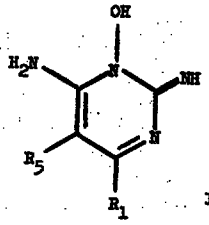
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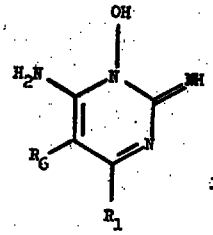
a heterocyclic group, the alkyls which can be attached thereto can all be different or any two or all of them can be alike.

R in formula I is a monovalent atom or a group as defined by R_1, and may be the same as or different from R_1 within the scope of the definition of R_1, hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower alkoxyalkyl of C_3—C_{10}, cycloalkyl of C_3—C_{10}, or lower-alkylcycloalkyl of C_3—C_{10}, a phenyl or naphthyl radical, lower aralkyl of C_7—C_{14}, lower alkaryl of C_7—C_{14}, lower alkaralkyl of C_8—C_{15}, lower alkoxyaralkyl of C_8—C_{15}, lower haloaralkyl of C_7—C_{14}, chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower alkyl(C_1—C_8)phenylthio or halophenylthio.

For convenience the novel compounds of the present invention may be represented by the following three general formulae:—

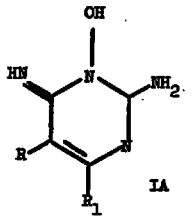

II

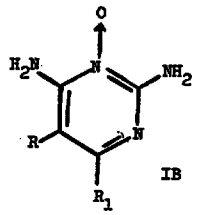

III


IV

wherein, in each instance, R_1 is as defined above, R_2 in formula II is hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower alkoxyalkyl of C_3—C_{10}, cycloalkyl of C_3—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, or a phenyl or naphthyl radical, lower aralkyl of C_7—C_{14}, lower alkaryl of C_7—C_{14} lower alkaralkyl of C_8—C_{15}, lower alkoxyaralkyl of C_8—C_{15} or lower haloaralkyl of C_7—C_{14}; R_5 in formula III is chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower alkyl (C_1—C_8) phenylthio or halophenylthio and R_6 in formula IV has the same meaning as R_1.

The novel 1,2 - dihydro - 1 - hydroxypyrimidines of this invention can be represented by formulae other than the formulae I, II, III and IV. For example, with regard to formula I, among such other formulae are:


IA


IB

Compounds of formulas IA and IB are tautomeric with compounds of formula I. For convenience, reference will be made hereinafter only to formulas I, II, III, and IV. It is to be understood, however, that the novel compounds of this invention are likely to be mixtures of tautomeric forms, the compositions of which are dependent on such factors as the nature of R_1, R_2, R_5, and R_6, and the environment. In some instances, one form or another may predominate.

Lower alkyl of C_1—C_8 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof. Examples of lower alkenyl of C_2—C_8 are allyl, 1-methylallyl, 2 - methylallyl (methallyl), 2 - butenyl (crotyl), 3 - butenyl, 1,2 - dimethylallyl, 1,1-dimethylallyl, 2 - ethylallyl, 1 - methyl - 2 - butenyl, 2 - methyl - 2 - butenyl, 3-methyl - 2 - butenyl, 3 - pentenyl, 2,3 - dimethyl - 2 - butenyl, 1,1,2 - trimethylallyl, 1,3 - dimethyl - 2 - butenyl, 1 - ethyl - 2 - butenyl, 4 - methyl - 2 - pentenyl, 2-ethyl-2 - pentenyl, 4,4 - dimethyl - 2 - pentenyl, 2 - heptenyl, 2 - octenyl, 5 - octenyl, and 1,4 - dimethyl - 4 - hexenyl. Examples of lower alkoxyalkyl of C_3—C_{10} are 2-methoxyethyl, 2 - ethoxyethyl, 2 - butoxyethyl, 2 - hexyloxyethyl, 2 - octyloxyethyl, 2 - meth-

oxypropyl, 3 - methoxypropyl, 3 - propoxypropyl, 2 - methoxybutyl, 3 - ethoxybutyl, 4 - butoxybutyl, 2 - ethoxyhexyl, 3 - methoxy - 3 - methylpentyl, and 4 - methoxyoctyl. Examples of cycloalkyl of C_3—C_{10} and lower alkylcycloalkyl of C_3—C_{10} are cyclopropyl, 2 - methylcyclopropyl, 2,2 - dimethylcyclopropyl, 2,3 - diethylcyclopropyl, 2 - butylcyclopropyl, cyclobutyl, 2 - methlcyclobutyl, 3 - propylcyclobutyl, 2,3,4 - triethylcyclobutyl, cyclopentyl, 2,2 - dimethylcyclopentyl, 3 - pentylcyclopentyl, 3 - tert-butylcyclopentyl, cyclohexyl, 4 - tert - butylcyclohexyl, 3 - isopropylcyclohexyl, 2,2-dimethylcyclohexyl, cycloheptyl, and cyclooctyl. Examples of lower alkaryl are *o*-tolyl, *m*-tolyl, *p*-tolyl, *m*-ethylphenyl, *p*-tert-butylphenyl, the isomeric forms of xylyl, the isomeric forms of trimethylphenyl, 4 - methyl - 1 - naphthyl, 6 - propyl - 2 - naphthyl, and 2,4,5,7 - tetramethyl - 1 - naphthyl. Examples of lower aralkyl of C_7—C_{14} are benzyl, phenethyl, 1 - phenylethyl, 2 - phenylpropyl, 4 - phenylbutyl, 6 - phenylhexyl, 5-phenyl-2-methylpentyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl, and 2-(2-naphthyl)-ethyl. Examples of lower alkaralkyl of C_8—C_{15} are *o*-tolylmethyl, *m*-tolylmethyl, *p*-tolylmethyl, 4 - tert - butylphenylmethyl, 2 - (*p* - tolyl)ethyl, 1 - (*m* - tolyl)ethyl, 3-(*o*-ethylphenyl)propyl, 4 - methyl - 1 - naphthylmethyl, and 6 - tert - butyl - 2 - naphthylmethyl. Examples of lower alkoxyaralkyl of C_8—C_{15} are *o*-methoxybenzyl, *m*-methoxybenzyl, *p*-methoxybenzyl, 2-(*m*-methoxyphenyl)ethyl, 3-(*p*-ethoxyphenyl)propyl, 4-(*p*-tert - butoxyphenyl)butyl, and 4 - methoxy - 1 - naphthylmethyl. Examples of lower haloaralkyl of C_7—C_{14} are *o* - chlorobenzyl, *m* - fluorobenzyl, *p* - bromobenzyl, 2-(*m* - iodophenyl)ethyl, 2,4 - dichlorobenzyl, 6 - bromo - 1 - naphthylmethyl, and 4 - *p* - chlorophenyl)butyl. Examples of lower alkyl(C_1—C_8)phenyl thio are *o*-tolylthio, *m*-tolylthio, *p*-tolylthio, the isomeric forms of xylylthio, *p* - ethylphenylthio, and *m* - butylphenylthio. Examples of halophenylthio are *p* - chlorophenylthio, *m*-bromophenylthio, *o*-fluorophenylthio, and 3,4 - dichlorophenylthio.

Examples of heterocyclic groups within the scope of R_1, in addition to those already mentioned above, are 2 - methylaziridinyl, 2 - ethylaziridinyl, 2 - butylaziridinyl, 2,3 - dimethylaziridinyl, 2,2 - dimethylaziridinyl, 2 - methylazetidinyl, 3-methylazetidinyl, 2 - octylazetidinyl, 2,2 - dimethylazetidinyl, 3,3 - diethylazetidinyl, 2,4,4 - trimethylazetidinyl, 2,3,4 - trimethylazetidinyl, 2 - methylpyrrolidinyl, 3-butylpyrrolidinyl, 2 - isohexylpyrrolidinyl, 2,3 - dimethylpyrrolidinyl, 2,2 - dimethylpyrrolidinyl, 2,5 - diethylpyrrolidinyl, 3 - tert - butylpyrrolidinyl, 2,3,5 - trimethylpyrrolidinyl, 3,4 - dioctylpyrrolidinyl, 2 - methylpiperidino, 3 - methylpiperidino, 4-methylpiperidino, 3 - isopropylpiperidino, 4 - tert - butylpiperidino, 2 - methyl - 5-ethylpiperidino, 3,5 - dipentylpiperidino, 2,4,6 - trimethylpiperidino, 2,6 - dimethyl-4 - octylpiperidino, 2,3,5 - triethylpiperidino, 2 - ethylhexahydroazepinyl, 4 - tert-butylhexahydroazepinyl, 3 - heptylhexahydroazepinyl, 2,4 - dimethylhexahydroazepinyl, 3,3 - dimethylhexahydroazepinyl, 2,4,6 - tripropylhexahydroazepinyl, 2-methylheptamethylenimino, 5 - butylheptamethylenimino, 2,4 - diisopropylheptamethylenimino, 3,3 - diethylheptamethylenimino, 2,5,8 - trimethylheptamethylenimino, 3-methyloctamethylenimino, 2,9 - diethyloctamethylenimino, 4 - isooctyloctamethylenimino, 2 - ethylmorpholino, 2 - methyl - 5 - ethylmorpholino, 3,3 - dimethylmorpholino, 2,6 - di - tert - butylmorpholino, 4 - methylpiperazinyl, and 4 - isopropylpiperazinyl. In each of the above examples of heterocyclic groups, the free valence, and hence the point of attachment to a carbon atom of the pyrimidine ring, is at the heterocyclic nitrogen atom.

The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formulae I, II, III, and IV are amines, and exist in the non-protonated or free base form, or in the protonated or acid addition salt form, depending on the pH of the environment. They form stable protonates, i.e., mono- or di-acid addition salts, on neutralization with suitable acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, acetic, benzoic, salicylic, glycolic, succinic, nicotinic, tartaric, maleic, malic, pamoic, methanesulphonic, cyclohexanesulphamic, picric, and lactic acids. These acid addition salts are useful for upgrading or purifying the free bases. The free bases are useful as acid acceptors in neutralizing undesirable acidity or in absorbing an acid as it is formed in a chemical reaction, for example a dehydrohalogenation reaction in which hydrogen and chlorine, bromine, or iodine are removed from vicinal carbon atoms.

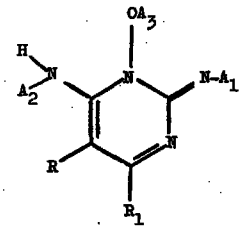
The novel formula I, II, III, and IV compounds form salts with fluosilicic acid which are useful as mothproofing agents according to U.S. Patents 1,915,334 and 2,075,359. They also form salts with thiocyanic acid which condense with formaldehyde to form resinous materials useful as pickling inhibitors according to U.S. Patents 2,425,320 and 2,606,155.

The formula I, II, III, and IV 1,2 - dihydro - 1 - hydroxypyrimidines of this invention also form salts with penicillins. These salts have solubility characteristics

which cause them to be useful in the isolation and purification of penicillins, particularly benzyl penicillin. Said salts can be formed either by neutralization of the free base form of a compound of formula I, II, III, or IV with the free acid form of a penicillin, or by a metathetical exchange of the anion of an acid addition salt of a formula I, II, III, or IV compound, for example the chloride ion of a hydrochloride, with the metal salt of a penicillin.

The novel formula I, II, III, and IV 1,2 - dihydro - 1 - hydroxypyrimidines also form carboxylicacylates on treatment with carboxylicacylating agents, for example, carboxylic acid anhydrides and carboxylic acid chlorides. These carboxylicacylates can be single compounds or mixtures of compounds depending on such factors as the nature of the 1,2 - dihydro - 1 - hydroxypyrimidine reactant, the carboxylicacylating agent, and the reaction conditions.

Carboxylicacylates obtained from formula I 1,2 - dihydro - 1 - hydroxypyrimidines can be represented by the formula:



V

wherein R and R_1 are as defined above. A_1, A_2, and A_3 are each hydrogen or carboxylicacyl, with the proviso that at least one of A_1 and A_2 is carboxylicacyl.

The carboxylicacylates of formula V can be used for upgrading a formula I, II, III, or IV 1,2 - dihydro - 1 - hydroxypyrimidine free base. The latter can be transformed to a carboxylicacylate, the carboxylicacylate purified by conventional techniques, e.g., recrystallization or chromatography, and the purified carboxylicacylate deacylated, advantageously by alcoholysis.

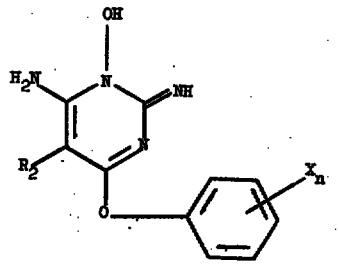
The dihydropyrimidine carboxylicacylates of formula V can be represented by other formulae. As for formula I compounds, these formula V carboxylicacylates are likely to be mixtures of tautomeric forms, the compositions of which are dependent on such factors as the nature of the substituents and the carboxylicacyl groups, and the environment. In some instances, one form or another may predominate. Formula V is used for convenience, and the other tautomeric forms are not excluded.

Carboxylicacylates of formula V are amines and exist in either the nonprotonated (free base) form or the protonated (acid addition salt) form depending upon the pH of the environment. They form stable protonates on neutralization with suitable strong acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, and perchloric acid. These acid addition salts are useful for upgrading or purifying the carboxylicacylate free bases.

The novel compounds of this invention, including the free bases of formulas I, II, III, and IV, the acid addition salts thereof, the carboxylicacylates of formula V, and the acid addition salts thereof possess pharmacological activity. For example, they are orally and parenterally active in birds and mammals, including man, as antihypertensive agents having vasodilatory activity, and are useful for lowering blood pressure and for the treatment of shock. They are also useful as antifertility agents, as antiviral agents, as anti-inflammatory agents, and as central nervous system stimulants. These compounds also cause electrolyte and water retention in laboratory animals such as rats and dogs, and hence are useful to produce laboratory animals with larger than normal amounts of sodium ions, potassium ions, chloride ions, and water. Such animals are useful in pharmacological research, for example in screening compounds for possible diuretic activity and in studying the action of known diuretics.

The compounds of formula II, for example, wherein R_2 is hydrogen or lower alkyl as hereinbefore defined and R_1 is dimethylamino, pyrrolidinyl, or piperidino are especially potent as antihypertensive agents in mammals, including man.

The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula II are produced by mixing a compound of the formula:

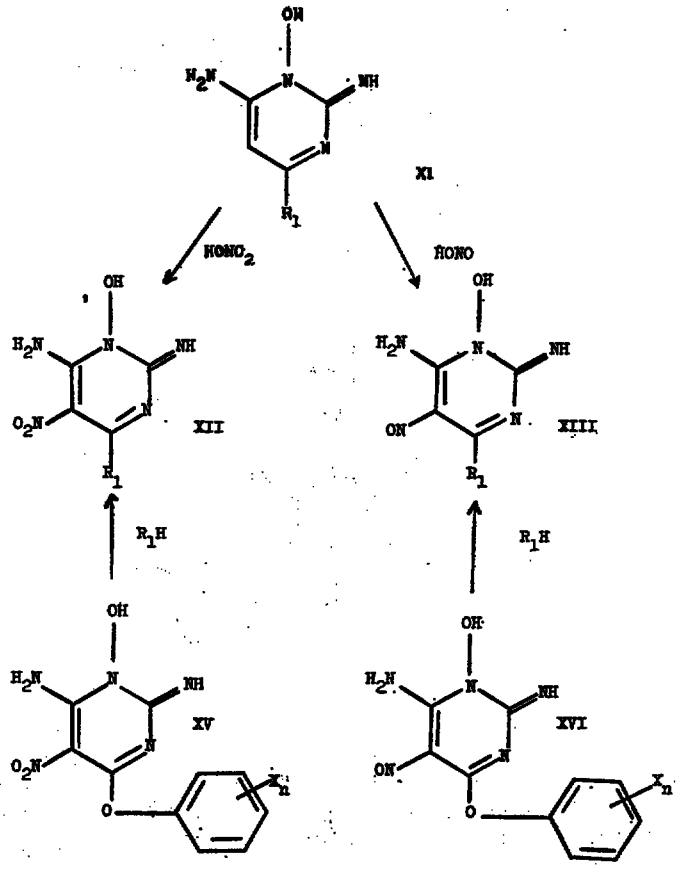


VI

wherein X is fluorine, chlorine, or bromine, and n is zero to 3, inclusive, and wherein R_2 is as defined above, with an amine of the formula R_1H, wherein R_1 is as defined above. The phenoxy group of the formula VI reactant is displaced by the R_1 group of the amine.

The compounds of formula VI and the preparation thereof are described and claimed in our copending application No. 4942/69 (Serial No. 1,167,736).

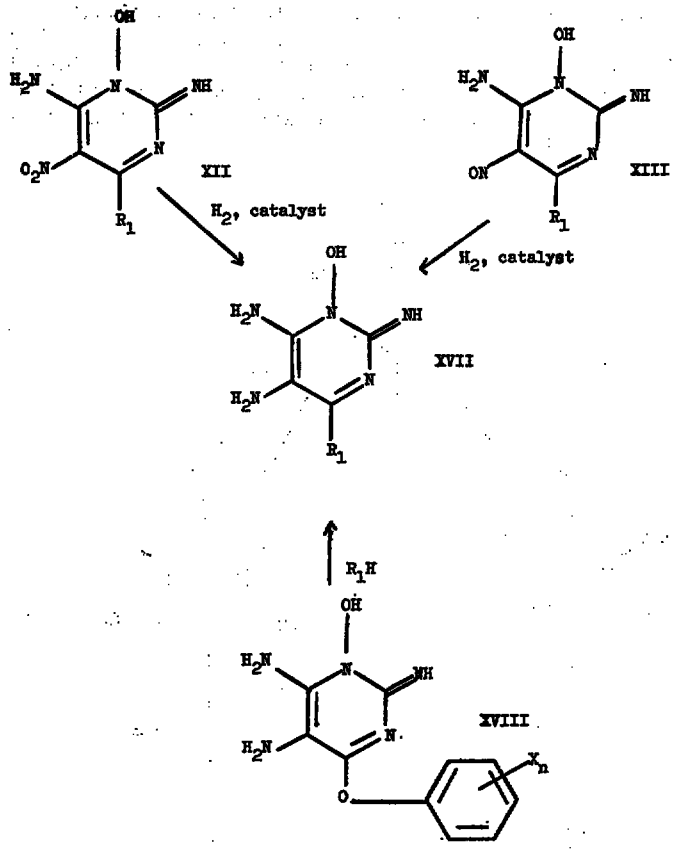
The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula III wherein R_5 is nitroso or nitro can be produced by either of two different reaction sequences. A formula II 1,2 - dihydro - 1 - hydroxypyrimidine wherein R_2 is hydrogen is nitrosated or nitrated. Alternatively, the phenoxy group of a 1,2 - dihydro - 1 - hydroxy-5 - nitro or 5 - nitroso - 4 - phenoxypyrimidine formula XV and XVI respectively is displaced with an amine of the formula RH, wherein R_1 is as defined above. These reaction sequences are as follows:



In the preparation of formula XV compounds by the nitration of the corresponding 1,2 - dihydro - 1 - hydroxy - 4 - phenoxypyrimidines, there is a tendency for the phenoxy group to be nitrated. A nitro substituent in the phenoxy group sometimes interferes with a subsequent displacement of the entire phenoxy group with a mono- or disubstituted amino group as in the production of formula XII by pyrimidines. For that reason, it is usually preferred to produce formula XII compounds by nitration of formula XI compounds rather than by the alternative route.

Compounds of formula XV and XVI and the preparation thereof are described and claimed in our copending application No. 4942/69 (Serial No. 1,167,736).

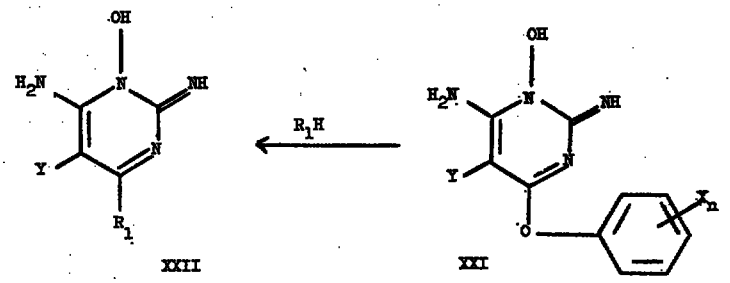
The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula III wherein R_5 is amino can be produced by any of several different reaction sequences. A formula XII 1,2 - dihydro - 1 - hydroxy - 5 - nitropyrimidine or a formula XIII 1,2 - dihydro-1 - hydroxy - 5 - nitrosopyrimidine is mixed with hydrogen in the presence of a hydrogenation catalyst. Alternatively, the phenoxy group of a formula XVIII 5-amine - 4 - phenoxypyrimidine is displaced with an amine of the formula R_1H, wherein R_1 is as defined above. Compounds of formula XVIII and the preparation thereof are also described and claimed in our copending application No. 4942/69 (Serial No. 1,167,736). These reaction sequences are as follows:



Quite unexpectedly, the carbon-carbon and carbon-nitrogen unsaturation in the 1,2-dihydropyrimidine ring is not hydrogenated with the same ease as the nitroso or nitro group. Therefore, the hydrogenation conditions can easily be selected to hydrogenate only the nitroso or nitro group. It should be noted, however, that 5 - aminopyrimidines of formula XVII wherein R_1 contains an alkenyl group cannot be prepared by catalytic hydrogenation of formula XII 5 - nitropyrimidines or formula XIII 5 - nitrosopyrimidines because any alkenyl groups will be transformed by hydrogenation to alkyl groups. Formula XVII 5 - aminopyrimidines with carbon-carbon unsaturation in the R_1 group can, however, be prepared by the alternative route, i.e., phenoxy group of the formula XVIII 5 - amino - 4 - phenoxypyrimidine with an amine, R_1H, which can

contain carbon-carbon unsaturation. Alternatively, the nitroso group in the XIII compounds or the nitro group in the XII compounds can be reduced by a chemical reducing agent which does not alter carbon-carbon unsaturation, for example, sodium dithionite or sodium hydrosulphite. See, for example, J. Chem. Soc. (London) 985 (1956); J. Am. Chem. Soc. 79, 1518 (1957); Ber. Deut. Chem. 88, 1306 (1955); ibid. 89, 2799 (1956); ibid. 90, 2272 (1957).

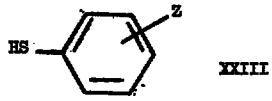
The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula III wherein R_5 is chlorine, bromine, or iodine are also produced by the following reaction, wherein R_1, X, and n are as defined above, and Y is chlorine, bromine, or iodine:



XXII XXI

Compounds having the general formula XXI and the preparation thereof are described and claimed in our copending Application No. 4942/69 (Serial No. 1,167,736).

The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula III wherein R_5 is phenylthio, lower-alkylphenylthio, and halophenylthio are produced by mixing a 1,2-dihydro - 1 - hydroxy - 5 - halopyrimidine of formula XXII with a thiophenol of the formula:

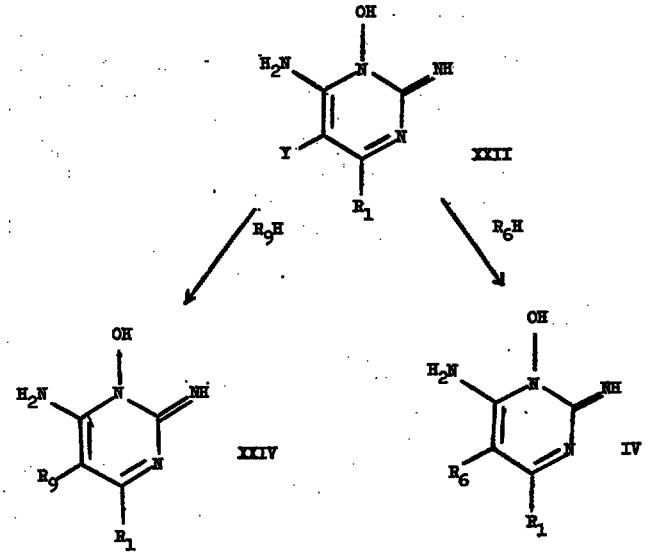


XXIII

wherein Z is hydrogen, lower alkyl of C_1—C_8, or halogen, i.e., fluorine, chlorine, bromine, or iodine.

The novel 1,2 - dihydro - 1 - hydroxypyrimidines of formula IV are produced by mixing a 1,2 - dihydro - 1 - hydroxy - 5 - halopyrimidine of formula XXII with an amine of the formula R_6H, wherein R_6 is as defined above.

These last two reactions can be formulated as follows:



XXII XXIV IV

wherein R_1, R_6, and Y are as defined above, and R_9 is phenylthio, lower-alkyl(C_1—C_8) phenylthio or halophenylthio. R_9 represents the same compounds as formula XXIII. R_6 in the amine R_6H can be the same as or different from R_1.

The reaction between a formula VI 1,2 - dihydro - 1 - hydroxy - 4 - phenoxy-

pyrimidine and an amine of formula R_1H, wherein R_1 is as defined above, to produce a formula II 1,2 - dihydro - 1 - hydroxypyrimidine is carried out by mixing those two reactants and preferably heating the mixture in the range from about 100° to about 200° C., and advantageously in the range from about 125° to about 175° C. Preferably at least one molecular equivalent of the amine should be mixed with each molecular equivalent of the pyrimidine reactant. It is usually advantageous to use an excess of the amine, for example about 2 to about 20 molecular equivalents or even more of amine per molecular equivalent of the pyrimidine, the excess amine then acting as a diluent. An inert organic diluent can also be present in the reaction mixture. Especially suitable for that purpose are dialkylformamides, particularly those where the dialkyl substituents are the same as those on the displacing amine, and alkanols.

When the reactant amine has a relatively low boiling point and is likely to escape from the reaction vessel during heating, it is advantageous to use a closed reaction vessel, for example a heavy-wall, sealed, glass tube or a closed metal autoclave, for the heating step.

A reaction time of about one to about 20 hours is usually required. The desired displacement reaction usually takes place more rapidly at higher temperatures than at lower. Moreover, when the phenoxy group has 2 or 3 halogen substituents, i.e., when n in formula VI is 2 or 3, the displacement usually takes place more rapidly and at a lower temperature than when fewer or no halogen substituents are present. In the latter instances, especially when no halogen is present in the phenoxy group, the displacement reaction is often accelerated by adding sodium or potassium metal to the reaction mixture. Preferably, about one atomic equivalent of the alkali metal is added per molecular equivalent of the pyrimidine reactant. Addition of a catalytic amount of a Lewis acid such as ferric chloride with the alkali metal will also often accelerate the displacement reaction or make feasible a lower reaction temperature. About 0.01 to 0.001 molecular equivalents of ferric chloride per atomic equivalent of alkali metal is usually a suitable catalytic amount.

Examples of suitable primary amine reactants for this displacement reaction are methylamine, ethylamine, propylamine, isopropylamine, butylamine, sec-butylamine, pentylamine, isopentylamine, hexylamine, heptylamine, octylamine, allylamine, 2-methylallylamine, 2 - butenylamine, 3 - butenylamine, 3 - pentenylamine, 4 - hexenylamine, 4,4 - dimethyl - 2 - pentenylamine, cyclobutylamine, cyclohexylamine, 4-tert - butylcyclohexylamine, benzylamine, and phenethylamine. Examples of suitable secondary amines for this purpose are dimethylamine, diethylamine, N - methylethylamine, dipropylamine, N - ethylisopropylamine, di - sec - butylamine, N - methylbutylamine, dipentylamine, N - ethyl - 2,4 - dimethylpentylamine, N - methyloctylamine, diheptylamine, diallylamine, N - methylallylamine, di - (1 - methylallyl)amine, di - (2 - methylallyl)amine, N - ethyl - 1 - methylallylamine, N - propyl - 2 - ethylallylamine, di - (2 - pentenyl)amine, di - (3 - butenyl)amine, di - (4 - hexenyl)amine, N - butyl - 2 - butenylamine, N - methylcyclohexylamine, dicyclohexylamine, N - ethylbenzylamine, dibenzylamine, di - (4 - methyl - 3 - hexenyl)amine, aziridine, 2-methylaziridine, 2,2 - dimethylaziridine, azetidine, 2 - ethylazetidine, 3 - octylazetidine, 3,3 - dimethylazetidine, 2,2,4 - trimethylazetidine, pyrrolidine, 2 - propylpyrrolidine, 3 - butylpyrrolidine, 2 - isohexylpyrrolidine, 2,3 - dimethylpyrrolidine, 2,2,4-trimethylpyrrolidine, 2,5 - diethylpyrrolidine, 3,4 - dioctylpyrrolidine, piperidine, 2-methylpiperidine, 3 - ethylpiperidine, 4 - butylpiperidine, 2,4,6 - trimethylpiperidine, 2 - methyl - 5 - ethylpiperidine, 3,5 - dipentylpiperidine, hexahydroazepine, 2 - ethylhexahydroazepine, 4 - tert - butylhexahydroazepine, 3,3 - dimethylhexahydroazepine, 2,4,6 - tripropylhexahydroazepine, heptamethylenimine, 2 - methylheptamethylenimine, 2,4 - diisopropyl - heptamethylenimine, octamethylenimine, 4 - isooctyloctamethylenimine, morpholine, 2 - ethylmorpholine, 2 - methyl - 5 - ethylmorpholine, 2,6 - dimethylmorpholine, and N - methylpiperazine.

The desired formula II 1,2 - dihydro - 1 - hydroxypyrimidine can usually be isolated from the reaction mixture in free base form by cooling the reaction mixture to about 0° to about 25°C. The free base form usually precipitates and can be isolated by conventional techniques, for example by filtration or centrifugation. Alternatively, excess amine and other diluent, if one is used, can be removed by distillation or evaporation, and the desired 1,2 - dihydro - 1 - hydroxypyrimidine isolated by conventional techniques, for example fractional recrystallization or extraction. The isolated pyrimidine can then be purified, if desired, by conventional techniques, for example, recrystallization from a suitable solvent or mixture of solvents, or by chromatography. Alternatively, an acid addition salt, e.g., the hydrochloride or acid phosphate,

of the pyrimidine product can be prepared, purified by recrystallization, and then, if desired, reconverted to the free base in the usual manner.

Nitrosation of the formula XI 1,2 - dihydro - 1 - hydroxypyrimidines is advantageously carried out by mixing the pyrimidine reactant with a strong acid, and then adding a nitrite salt, preferably sodium nitrite, to the mixture with cooling. Concentrated sulphuric acid is the preferred strong acid. About one molecular equivalent of the nitrite salt should be used for each molecular equivalent of the pyrimidine reactant. A reaction temperature in the range from about 0° to about 25° C. is preferred. It is advantageous to add an aqueous solution of the nitrite salt to the acid solution of the pyrimidine.

The desired nitrosation usually takes place within about 15 minutes to about 4 hours in the preferred temperature range. After the nitrosation is complete, the desired nitroso compound can be isolated by diluting the reaction mixture with water and neutralizing the acid with a base, preferably keeping the mixture below about 25° C. by addition of ice. Any base can be used but sodium hydroxide, sodium carbonate, or sodium bicarbonate are preferred. The nitroso product is usually a solid and can be isolated by conventional methods, for example by filtration or centrifugation, and can be purified, if desired, by recrystallization from a suitable solvent or mixture of solvents.

Nitration of the formula XI 1,2 - dihydro - 1 - hydroxypyrimidines is advantageously carried out by mixing the pyrimidine reactant with concentrated sulphuric acid (95%), cooling the resulting solution, and then slowly adding a mixture of concentrated sulphuric acid (95%) and concentrated nitric acid (70%) with continued cooling in the range from about 0° to about 25° C., preferably from about 10° to 15° C. A total reaction time of about one to about 5 hours is usually sufficient. One molecular equivalent of nitric acid is required for each molecular equivalent of pyrimidine reactant.

In some instances, a less concentrated sulphuric acid or less concentrated nitric acid can be used if the pyrimidine reactant is especially easily nitrated. It will be apparent to those skilled in the art that the optimum nitration conditions for each particular pyrimidine reactant, including nitric acid and sulphuric acid concentrations and amounts, reaction time, and reaction temperature, must be determined by preliminary small scale experiments.

The nitrated 1,2 - dihydro - 1 - hydroxypyrimidine of formula XII can be isolated from the reaction mixture by pouring the mixture onto crushed ice, making the resulting mixture basic, and then isolating the desired nitration product by conventional methods, for example filtration, centrifugation or extraction. The nitration products are usually solids and can be purified by recrystallization from a suitable solvent or mixture of solvents or by chromatography.

Reduction of the formula XII 1,2 - dihydro - 1 - hydroxy - 5 - nitropyrimidines and reduction of the formula XIII 1,2 - dihydro - 1 - hydroxy - 5 - nitrosopyrimidines is advantageously carried out by catalytic hydrogenation in the presence of a hydrogenation catalyst, for example a noble metal, e.g., platinum, palladium, rhodium, or a base metal, e.g., Raney nickel, Raney cobalt, and in the presence of an inert diluent, for example, methanol, ethanol, dioxane, or ethyl acetate. Palladium catalysts are preferred. Hydrogenation pressures ranging from about atmospheric to about 100 p.s.i., and hydrogenation temperatures ranging from about 10° to about 100° C. are preferred.

It is also preferred to add sufficient strong acid, for example a mineral acid such as hydrochloric acid, sulphuric acid, or phosphoric acid, to the pyrimidine reactant before hydrogenation so that the protonated form of the reactant is hydrogenated and the protonated or acid addition salt form of the 5 - aminopyrimidine product is produced. In some instances, the acid addition salt form of the product is substantially more stable and more easily isolated than the free base form.

The formula XVII 5 - aminopyrimidine reduction products are isolated from the hydrogenation reaction mixtures by conventional techniques, for example by removal of the catalyst by filtration or centrifugation, and then removal of the diluent by distillation or evaporation. If the 5 - nitropyrimidine or 5 - nitrosopyrimidine reactant is pure, it is usually unnecessary to purify the 5 - aminopyrimidine product. When purification is necessary, however, it is preferred to purify a suitable acid addition salt by recrystallization from a suitable solvent or mixture of solvents.

The displacement of phenoxy groups in formula XV 1,2 - dihydro - 1 - hydroxy - 5 - nitro - 4 - phenoxypyrimidines, formula XVI 1,2 - dihydro - 1 - hydroxy - 5 - nitroso - 4 - phenoxypyrimidines, formula XVIII 1,2 - dihydro - 1 - hydroxy - 5 - amino - 4 - phenoxypyrimidines, and formula XXI 1,2 - dihydro - 1 - hydroxy - 5 -

halo - 4 - phenoxypyrimidines with primary and secondary amines of the formula R_1H, wherein R_1 is is defined above, is carried out as described above for the displacement of phenoxy groups from formula VI 1,2 - dihydro - 1 - hydroxy - 4 - phenoxypyrimidines with primary and secondary amines of the same formula R_1H, and the resulting products are isolated and purified in the manner also described above. The displacement of phenoxy in formula XXI compounds is especially rapid and can be carried out in the range from about 0° to 100° C., preferably from about 20° to about 50° C.

The reaction between a formula XXII 1,2 - dihydro - 1 - hydroxy - 5 - halopyrimidine and thiophenol of formula XXIII to produce a formula XXIV 1,2 - dihydro - 1 - hydroxy - 5 - arylthiopyrimidine is advantageously carried out by heating a mixture of those two reactants in the presence of a strong base, preferably an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, in the range from about 50° to about 200° C., preferably in the range about 75° to about 125° C., until the desired displacement of halogen takes place. For this displacement, it is preferred that the displaced halogen be bromine, i.e., that Y in formula XXII be bromine. It is also preferred that an excess of the formula XXIII thiophenol be used, preferably about 2 to about 10 or even more molecular equivalents of thiophenol per molecular equivalent of the pyrimidine reactant. It is also preferred that about one molecular equivalent of the strong base be used per molecular equivalent of the pyrimidine reactant. A reaction time of about 1 to about 10 hours is usually required in the preferred temperature range. It is usually advantageous to add a small amount of water, preferably about 5 to about 25 percent by weight of the base used, to aid in forming a homogeneous reaction mixture. An inert diluent of appropriate boiling point can also be added for that purpose.

The desired formula XXIV 1,2 - dihydro - 1 - hydroxy - 5 - arylthiopyrimidine can be isolated from the reaction mixture by diluting said mixture with water containing enough alkali metal hydroxide to dissolve the excess thiophenol. The remaining desired product is usually a solid which can be separated by conventional methods, for example by filtration, centrifugation, or extraction, and can usually be purified, if desired, by recrystallization from a suitable solvent or mixture of solvents.

The reaction between a formula XXII 1,2 - dihydro - 1 - hydroxy - 5 - halopyrimidine and a primary or secondary amine of the formula R_6H to produce a formula IV 1,2 - dihydro - 1 - hydroxy - 5 - substituted - aminopyrimidine is advantageously carried out by heating a mixture of those two reactants in the range from about 90° to about 150° C., preferably in the range from about 105° to about 115° C. The reaction conditions and manipulations are otherwise similar to the above-described displacement of the phenoxy group of a formula VI 1,2 - dihydro - 1 - hydroxy - 4-phenoxypyrimidine with an amine of the formula R_1H. At least one molecular equivalent of the displacing amine should be used. Preferably about 2 to about 10 molecular equivalents are used so that the excess amine acts as a diluent which results in a homogeneous reaction mixture. Although any of the halogens within the scope of formula XXII can be displaced with an amine, it is preferred that the displaced halogen be bromine.

Examples of suitable amines for this halogen displacement are those listed above as suitable for the phenoxy displacement. A closed reaction vessel is preferred when using those amines whose boiling point at atmospheric pressure is lower than the desired reaction temperature.

The desired formula IV 1,2 - dihydro - 1 - hydroxy - 5 - substituted - aminopyrimidine can be isolated from the reaction mixture by evaporating excess amine and diluent, if one is used, followed by treatment with dilute aqueous base to transform any amine salts to the free base form. The crude amine product is then purified by distillation at reduced pressure, recrystallization from a suitable solvent or mixture of solvents, or chromatography, or by a combination of those methods.

The 1,2 - dihydro - 1 - hydroxypyrimidines of formulae I, II, II, and IV are transformed to monoacid and diacid addition salts by neutralization with appropriate amounts of the corresponding inorganic or organic acid, examples of which are given above. These transformations can be carried out by a variety of procedures known to the art to be generally useful for the preparation of amine acid additiona salts. The choice of the most suitable procedure will depend on a variety of factors including convenience of operation, economic considerations, and particularly the solubility characteristics of the formula I, II, III, or IV amine, the acid, and the acid addition salt. If the acid is soluble in water, the basic compound of formula I, II, III, or IV can be dissolved in water containing either one or two equivalent amounts of the acid,

and thereafter, the water can be removed by evaporation. If the acid is soluble in a relatively non-polar solvent, for example diethyl ether or diisopropyl ether, separate solutions of the acid and the basic formula I, II, III, or IV compound in such a solvent can be mixed in equivalent amounts, whereupon the acid addition salt will usually precipitate because of its relatively low solubility in the non-polar solvent. Alternatively, the basic formula I, II, III, or IV compound can be mixed with the acid in the presence of a solvent of moderate polarity, for example a lower alkanol of C_1—C_8, a lower alkanone of C_1—C_8, or a lower alkyl(C_1—C_8) ester of a lower alkanoic acid of C_1—C_8. Examples of these solvents are ethanol, acetone, and ethyl acetate, respectively. Subsequent admixture of the resulting solution of acid addition salt with a solvent of relatively low polarity, for example diethyl ether or hexane, will usually cause precipitation of the acid addition salt. Either monoacid or diacid salts can be formed by using one or two equivalents, respectively, of the acid.

Acid addition salts of the formula I, II, III, or IV pyrimidines can be transformed to other acid addition salts by a metathetical exchange of the original acid addition salt anion, e.g., the chloride ion, with another anion, for example as described above with regard to the formation of penicillin salts.

The carboxylicacylates of formula V are produced by mixing a formula I, II, III, or IV 1,2 - dihydro - 1 - hydroxypyrimidine with the appropriate amount of a carboxylicacylating agent, preferably in the presence of a diluent.

Although substantially any carboxylicacylating agent can be used to produce these carboxylicacylates, especially suitable are the anhydrides, mixed anhydrides, and acid chlorides of alkanoic, cycloalkanoic, alkenoic, cycloalkenoic, aralkanoic, aromatic, and heterocyclic carboxylic acids. These anhydrides and acid chlorides can also be substituted on any carbon but the carbonyl carbon with any of a wide variety of atomic or molecular substituents unreactive with the dihydropyrimidine reactants. Examples of such substituents are alkyl, e.g., methyl, butyl, decyl; alkoxy, e.g., methoxy, ethoxy, pentyloxy; alkylthio, e.g., methylthio, propylthio, heptylthio; dialkylamino, e.g., dimethylamino, diethylamino, dihexylamino; alkoxycarbonyl, e.g., methoxycarbonyl, propoxycarbonyl, nonoxycarbonyl; carboxylicacyl, e.g. acetyl, butyryl; acylamido, e.g., benzamido, acetamido; nitro; fluoro; and cyano. Chlorine, bromine, and iodine can also be substituents on aromatic portions of the carboxylicacylating agents.

Examples of suitable anhydrides are acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, acrylic anhydride, crotonic anhydride, cyclohexanecarboxylic anhydride, benzoic anhydride, naphthoic anhydride, and furoic anhydried, as well as the corresponding anhydrides substituted with one or more of the above-mentioned substituents. Examples of suitable acid chlorides are acetyl chloride, propionyl chloride, butyryl chloride, isobutyryl chloride, decanoyl chloride, acryloyl chloride, crotonoyl chloride, cyclohexanecarbonyl chloride, 3 - cyclohexenecarbonyl chloride, phenylacetyl chloride, succinyl chloride, benzoyl chloride, naphthoyl chloride; furoyl chloride, 3 - pyridinecarbonyl chloride, and phthaloyl chloride, as well as the corresponding acid chlorides substituted with one or more of the above-mentioned substituents.

At least one molecular equivalent of carboxylicacylating agent should be used for the introduction of each carboxylicacyl group. However, when reactive carboxylicacylating agents such as acetic anhydride are used, a diacyl compound is usually obtained even with only one molecular equivalent of carboxylicacylating agent. In such cases, part of the dihydropyrimidine reactant does not form a carboxylicacylate.

The carboxylicacylation usually takes place rapidly in the range from about $-20°$ to about $+50°$ C. Suitable diluents are ethers, e.g., diethyl ether and tetrahydrofuran; ketones, e.g., acetone and methyl ethyl ketone; esters, e.g., methyl acetate and ethyl acetate; acetonitrile; and pyridine. The desired carboxylicacylate often separates from the reaction mixture in crystalline form, and can be separated in the usual manner, for example by filtration or centrifugation. Alternatively, the diluent can be evaporated, preferably at reduced pressure. The carboxylicacylates can be purified by conventional techniques, for example by recrystallization from a suitable solvent or mixture of solvents.

The nature of each carboxylicacylate depends on such factors as the nature of the dihydropyrimidine reactant, the nature and amount of carboxylicacylating agent, the reaction time, and the reaction temperature. Usually a monoacylate or a diacylate, or a mixture of those, is obtained, although the formation of a triacylate is observed

in some instances. The monoacylates are usually N-acyl compounds. The diacylates are either N,N′ - diacyl or O,N - diacyl compounds. Use of the more reactive acylating agents, e.g. acetic anhydride, often results in N,N′ - diacylates. The less reactive agents, e.g., benzoic anhydride, usually give N - acylates and/or O,N-diacylates.

Carboxylicacylates produced at relatively low temperatures, i.e., about −20° to about 0° C., and with relatively short reaction times, i.e., a few seconds to about 10 minutes, usually contain larger amounts of N - monoacylate and O,N - diacylate, and less N,N - diacylate, than those produced at higher temperatures, i.e., about 10° C. to about 50° C., and with longer reaction times, i.e., about 30 minutes to 100 hours.

Dihydropyrimidine carboxylicacylates prepared as described above are easily transformed back to the formula I, II, III, or IV dihydropyrimidine free base, preferably by warming with a lower alkanol, e.g., methanol or ethanol. Simultaneous treatment with a base, for example gaseous ammonia, or an acid, for example, hydrochloric acid, usually accelerates the alcoholysis.

As mentioned above, the novel compounds of formulae I, II, III, IV and V, including the free bases and acid addition salts thereof, are useful as antihypertensive agents, antifertility agents, antiviral agents, anti-inflammatory agents, and as central nervous system stimulants in the treatment of birds and mammals, including man. For those purposes, especially as antihypertensive agents, said novel compounds can be used in the non-protonated (free base) form or in the protonated (acid addition salt) form in association with a pharmaceutical carrier in solid or liquid dosage forms, such as tablets, capsules, powders, pills, granules, syrups, elixirs, suppositories, or sterile aqueous or vegetable oil dispersions for parenteral use, alone or in combination with other drugs, for example in combination with diuretics, sympathetic blocking agents, ganglion-blocking agents, peripheral vasodilators, reserpinoids, tranquilizers, sedatives, muscle relaxants, antihistamines and other antihypertensives.

Powders are prepared by comminuting the active ingredient to a suitable fine size and mixing with a similarly comminuted diluent. The diluent can be an edible carbohydrate material such as starch. Advantageously, a sweetening agent is present as well as a flavoring agent.

Capsules are produced by preparing a powder mixture as hereinbefore described and filling into formed gelatin sheets. Advantageously, as an adjuvant to the filling operation, a lubricant such as talc, magnesium stearate and calcium stearate is added to the powder mixture before the filling operation.

Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and pressing into tablets. The powder mixture is prepared by mixing the active ingredient suitably comminuted, with a diluent or base such as starch, lactose, kaolin, dicalcium phosphate, or calcium sulphate. The powder mixture can be granulated by wetting with a binder such as syrup, gelatin solution, methylcellulose solution or acacia mucilage and forcing through a screen. As an alternative to wet granulating, the powder mixture can be slugged, i.e. run through a tablet machine, and the resulting large tablets broken down into granules. The granules are further lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets.

Advantageously, the tablet can be provided with a protective coating consisting of a sealing coat of shellac, a coating of sugar and methylcellulose, and a polish coating of carnauba wax.

Oral fluids are prepared in unit dosage forms such as syrups and elixirs wherein each teaspoonful of composition contains a predetermined amount of active ingredient for administration.

A syrup is prepared by dispersing the active ingredient in a suitably flavored aqueous sucrose solution. Similarly an elixir is prepared utilizing an aqueous-alcoholic vehicle. Elixirs are advantageous vehicles for use when a therapeutic agent, which is not sufficiently water-soluble, is in the composition.

For parenteral administration aqueous fluid unit dosage forms can be prepared. In preparing the parenteral form, a measured amount of active ingredient is placed in a vial, and the vial and its contents are sterilized and sealed. An accompanying vial of sterile water for injection is provided as a vehicle to form a dispersion prior to administration. Advantageously, the sterile water can have dissolved therein a local anesthetic and buffering agent. Parenteral aqueous solutions can also be made by utilizing a pharmacologically acceptable salt of the active ingredient, such as those mentioned above.

Alternatively, a parenteral suspension can be prepared by suspending the active ingredient in a parenterally acceptable vegetable oil with or without additional adjuvants, and sterilizing after filling into vials.

For veterinary oral use the active ingredient is conveniently prepared in the form of a food premix. The food premix can comprise the active ingredient in admixture with an edible pharmaceutical diluent such as starch, oatmeal, flour, calcium carbonate, talc, or dried fish meal. The prepared premix is then conveniently added to the regular feed, thereby providing medication to the animal in the course of feeding.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such active material for therapeutic use in humans and animals, as disclosed in detail in the specification, these being features of the present invention. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, suppositories, segregated multiples of any of the foregoing, and other forms as herein described.

The amount of active ingredient that is to be administered depends on the age, weight of the patient, the particular condition to be treated, the frequency of administration, and the route of administration. The dose range is from about 0.1 to about 30 mg. per kg. of body weight, preferably about 0.3 to about 10 mg. per kg. of body weight. The human dose ranges from 5 to 500 mg. daily given as a single dose or in 3 or 4 divided doses; preferably, the adult dose is from 25 to about 200 mg. Veterinary dosages will correspond to human dosages with amounts administered being in proportion to the weight of the animal as compared to adult humans.

The active ingredient is compounded with a suitable pharmaceutical diluent in unit dosage form, either alone or in combination with other active ingredients. The amount of such other active ingredients is to be determined with reference to the usual dosage of each such ingredient. Thus the novel compounds of the invention can be combined with other hypotensive agents such as α-methyldopa 100—250 mg.; with diuretics such as aminophylline 100—200 mg., bendroflumethiazide 2.5—5 mg., hydrochlorothiazide 10—50 mg., trichlormethiazide 2—4 mg., triamterene 25—100 mg., ethoxyzolamide 50—250 mg., amisometradine 200—400 mg., spironolacetone 25—100 mg.; sympathetic blocking agents such as guanethidine sulphate 10—50 mg., bethanidine sulphate 5—20 mg.; ganglion-blocking agents such as pentolinium bitartrate 20—200 mg., mecamylamine hydrochloride 2.5—5 mg., hexamethonium chloride 125—250 mg., chlorisondamine chloride 25—100 mg.; peripheral vasodilators such as hydralazine 10—100 mg., beta-pyridyl carbinol 50—150 mg., mebutamate 100—300 mg., reserpine type drugs such as reserpine 0.1—1 mg., alseroxylon 2—4 mg., syrosingopine 0.5—2 mg., deserpidine 0.1—1 mg.; tranquilizers such as meprobamate 200—400 mg., ectylurea 100—300 mg., chlorodiazepoxide hydrochloride 5—20 mg.; promazine hydrochloride 25—150 mg., diazepan 2—10 mg., sedatives such as phenobarbital 8—60 mg., methylprylon 50—100 mg., amobarbital 20—40 mg., ethchlorvynol 100—200 mg., muscle relaxants such as papaverine hydrochloride 20—100 mg., carisoprodol 200—400 mg., phenaglycodol 200—400 mg.

The invention can be more fully understood by the following Examples.

EXAMPLE 1

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine

A mixture of 6 -amino-4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy-2 - iminopyrimidine (3.5 g.) and piperidine (20 ml.) was heated in a sealed, heavy-wall, glass tube in an oil bath at 150° C. for 2.5 hours. The tube and contents were then cooled slowly to 255° C. The tube was opened and the reaction mixture filtered. The solid was washed first with piperidine and then with diethyl ether, and was dried to give 1.2 g. of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; m.p. 262—264° C. with decomposition.

Analysis:
Calcd. for $C_9H_{15}N_5O$:
C, 51.66; H, 7.22; N, 33.47; O, 7.65.
Found: C, 52.27; H, 7.00; N, 33.34; O, 7.56.

U.V. (ethanol) 230 mμ (ε=35,210); 261 mμ (ε=11,210); 285 mμ (ε=11,790). (0.01N H_2SO_4) 232 mμ (ε=26,350); 280 mμ (ε=23,850). (0.01N KOH) 231 mμ (ε=36,100); 261.5 mμ (ε=11,400); 285 mμ (ε=12,040).

I.R. (principal bands; mineral oil mull) 3450, 3420, 3400, 3370, 3260, 1655, 1250, 1230, 1210, 1165, 1020 $cm.^{-1}$.

Addition of absolute ethanol containing one equivalent of hydrogen chloride to an absolute ethanol solution of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine, followed by addition of about 4 volumes of diethyl ether, gives the corresponding monohydrochloride. Similar use of 2 equivalents of hydrogen chloride gives the corresponding dihydrochloride. Similar separate use of benzoic acid, lactic acid, succinic acid, maleic acid, sulphuric acid, and phosphoric acid gives the corresponding 1,2 - dihydro - 1 - hydroxypyrimidine acid addition salts.

EXAMPLE 2

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine

A mixture of 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine (22.0 g.) and piperidine (200 ml.) was heated in a sealed, heavy-wall, glass tube in an oil bath up to the range 175—180° C. during 1 hour, and was held within that range for 4 hours. The tube and contents were then cooled slowly to 25° C. during about 9 hours. The tube was opened and the reaction mixture was filtered. The solid was washed first with about 15 ml. of piperidine and then with a diethyl ether to give 12.1 g. of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine; m.p. 262—266° with decomposition starting at 262° C.

Following the procedure of Example 2 but using, in place of the piperidine, dimethylamine; diethylamine; dibutylamine; N - methylbutylamine; N - ethylhexylamine; butylamine; octylamine; diallylamine; dicrotylamine; di - (2 - hexenyl)-amine; N - methylallylamine; allylamine; 2 - octenylamine; dibenzylamine; diphenethylamine; N - methylbenzylamine; N - ethyl - (1 - naphthylmethyl)amine; benzylamine; 3 - phenylpropylamine; cyclohexylamine; dicyclohexylamine; cyclobutylamine; N - methyl - (4 - tert - butylcyclohexyl)amine; azetidine; pyrrolidine; 2 - methylpyrrolidine; 3 - ethylpyrrolidine; 2,5 - dimethylpyrrolidine; 2 - methyl - 5 - ethylpiperidine; 3 - isopropylpiperidine; 2,4,6 - trimethylpiperidine; hexahydroazepine; 4-tert-butylhexahydroazepine; heptamethylenimine; octamethylenimine; morpholine; 2-ethylmorpholine; and N - methylpiperazine, there are obtained 6 - amino - 1,2 - dihydro - 4 - dimethylamino - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - diethylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - dibutylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2-dihydro - 1 - hydroxy -2 - imino - 4 - (N - methylbutylamino)pyrimidine; 6 - amino-1,2 - dihydro - 4 - (N - ethylhexylamino) - 1 - hydroxy - 2 - iminopyrimidine; 6-amino - 4 - butylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6-amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - octylaminopyrimidine; 6 - amino - 4-diallylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4-dicrotylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4-[di - (2 - hexenyl)amino] - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (N - methylallylamino)pyrimidine; 4 - allylamino - 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (2 - octenylamino)pyrimidine; 6 - amino - 4 - dibenzylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2 - dihydro - 4 - diphenethylamino - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (N - methylbenzylamino) - pyrimidine; 6 - amino - 1,2 - dihydro - 4 - [N - ethyl - (1 - naphthylmethyl) - amino] - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - benzylamino-1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - imino - 4 - (3 - phenylpropylamino)pyrimidine; 6 - amino - 4 - cyclohexylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4-dicyclohexylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino-

4 - cyclobutylamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - [N - methyl - (4 - tert - butylcyclohexyl)amino]pyrimidine; 6 - amino - 4 - (1 - azetidinyl) - 1,2 - dihydro - 1-hydroxy-2 - iminopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1-pyrrolidinyl)pyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4-[1 - (2 - methylpyrrolidinyl)]pyrimidine; 6 - amino - 1,2 - dihydro - 4 - [1 - (3-ethylpyrrolidinyl)] - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2 - dihydro-4 - [1 - (2,5 - dimethylpyrrolidinyl)] - 1 - hydroxy - 2 - iminopyrimidine; 6-amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (2 - methyl - 5 - ethylpiperidino) - pyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (3 - isopropylpiperidino)pyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (2,4,6-trimethylpiperidino)pyrimidine; 6 - amino - 1,2 - dihydro - 4 - (1 - hexahydroazepinyl) - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - [1 - (4 - tert - butylhexahydroazepinyl)] - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 1,2-dihydro - 4 - (1 - heptamethylenimino) - 1 - hydroxy - 2 - iminopyrimidine; 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - octamethylenimino)pyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - morpholinopyrimidine; 6 - amino - 1,2 - dihydro - 4 - (2 - ethylmorpholino) - 1 - hydroxy - 2-iminopyrimidine; and 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (4-methyl - 1 - piperazinyl)pyrimidine, respectively.

Following the procedure of Example 1, each of the above-mentioned specific 1,2 - dihydro - 1 - hydroxypyrimidines is transformed to the corresponding hydrochloric acid, benzoic acid, lactic acid, maleic acid, phosphoric acid, sulphuric acid, and succinic acid addition salts.

Also following the procedure of Example 2 but using, in place of the piperidine, each of the primary and secondary amines corresponding to each of the specific examples of $-N<^{R_3}_{R_4}$ and heterocyclic radicals within the scope of R_1 as defined and given above, there are obtained the corresponding 6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - iminopyrimidines, substituted at the 4-position with a mono-substituted or disubstituted, including heterocyclic, amino group.

Also following the procedure of Example 2 but using in place of the 6 - amino-4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine, 6-amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5-methylpyrimidine; 6 - amino - 5 - butyl - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro-1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - isooctylpyrimidine; 5 - allyl - 6 - amino - 4-(2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6-amino - 5 - crotyl - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2-iminopyrimidine; 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 5 - (2-hexenyl) - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (2 - methoxyethyl)pyrimidine; 6 - amino - 5 - cyclopentyl - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy-2 - iminopyrimidine; 6 - amino - 5 - (4 - tert - butylcyclohexyl) - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino-4-(2,4-dichlorophenoxy)-1,2-dihydro-1-hydroxy-2-imino-5-phenylpyrimidine; 6-amino-4-(2,4 - dichlorophenoxy)-1,2-dihydro-1-hydroxy-2 - imino,5-(*p*-tolyl)pyrimidine; 6-amino-5-(*p*-tert-butylphenyl)-4-(2,4-dichlorophenoxy)-1,2-dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 5 - benzyl - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine; 6 - amino - 4 - (2,4 - dichlorophenoxy)-1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (4 - phenylbutyl)pyrimidine; 6 - amino-4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (*o*-methylbenzyl)pyrimidine; 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1-hydroxy - 2 - imino - 5 - (4 - methyl - 1 - naphthylmethyl)pyrimidine; 6 - amino-4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (*m* - methoxybenzyl)pyrimidine; and 6 - amino - 5 - (*p* - bromobenzyl) - 4 - (2,4-dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine, there are obtained 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - methyl - 4 - piperidinopyrimidine; 6 - amino - 5 - butyl - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - isooctyl - 4-piperidinopyrimidine; 5 - allyl - 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino-4 - piperidinopyrimidine; 6 - amino - 5 - crotyl - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 5 - (2 - hexenyl) - 1-

hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (2 - methoxyethyl) - 4 - piperidinopyrimidine; 6 - amino - 5 - cyclopentyl - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 5 - (4 - tert - butylcyclohexyl) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - phenyl - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidino - 5 - (*p* - tolyl)pyrimidine; 6 - amino - 5 - (*p* - tert - butylphenyl) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 5 - benzyl - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (4 - phenylbutyl) - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (*o*-methylbenzyl) - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (4 - methyl - 1 - naphthylmethyl) - 4 - piperidinopyrimidine; 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (*m* - methoxybenzyl) - 4 - piperidinopyrimidine; and 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - (*p* - bromobenzyl) - 4 - piperidinopyrimidine, respectively.

Following the procedure of Example 1, each of the above-mentioned specific 1,2 - dihydro - 1 - hydroxypyrimidines is transformed to the corresponding hydrochloric acid, benzoic acid, lactic acid, maleic acid, phosphoric acid, sulphuric acid, and succinic acid addition salts.

Also following the procedure of Example 2 but using, in place of the combination of the 6 - amino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine and the piperidine, each of the above-mentioned 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - phenoxypyrimidines or 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - halophenoxypyrimidines, unsubstituted or substituted at the 5-position as above-described, and each of the above-mentioned primary and secondary amines listed after Example 2, there are obtained the corresponding 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines wherein the 4-phenoxy or 4 - halophenoxy substituent has been replaced with a mono-substituted or disubstituted, including heterocyclic, amino group.

EXAMPLE 3

6 - imino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine.

6 - Amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine (4.5 g.) was mixed with 25 ml. of 95% sulphuric acid, keeping the temperature of the mixture below 40° C. The resulting solution was cooled to 15° C., and a solution of sodium nitrite (1.4 g.) in 2 ml. of water was added dropwise with stirring, keeping the mixture below 20° C. The resulting mixture was stirred for 45 minutes at 15° C., and was then poured into a mixture of sodium hydroxide (37 g.), crushed ice (100 g.), and water (200 ml.). That mixture was stirred and neutralized with solid sodium carbonate. The solid which formed was filtered, washed with water, and recrystallized from 75 ml. of ethanol to give 2.1 g. of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine; m.p. 190—191.5° C.

Analysis:

Calcd. for $C_9H_{14}N_6O_2$:
C, 45.37; H, 5.92.
Found: C, 45.51; H, 5.73.

U.V. (ethanol) 219 mμ (ε = 17,300); sh 240 mμ (ε = 12,800); 264 mμ (ε = 16,150); 325 mμ (ε = 12,350).
(0.01N H_2SO_4) 242 mμ (ε = 22,700); 322 mμ (ε = 12,550).
(0.01N KOH) 238 mμ (ε = 16,350); sh 270 mμ (ε = 6900); 347 mμ (ε = 12,050).

I.R. (principal bands; mineral oil mull) 3390, 3200, 3190, 1655, 1615, 1560, 1525, 1485, 1340, 1180, 1140, 1125, 1020, 855, 755, 725 cm^{-1}.

Addition of absolute ethanol containing one equivalent of hydrogen chloride to an absolute ethanol solution of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine, followed by addition of about 4 volumes of diethyl ether, gives the corresponding hydrochloride.

Following the procedure of Example 3 but using, in place of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine, each of the above mentioned

specific 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4- position with a mono-substituted or disubstituted including heterocyclic amino group, and unsubstituted at the 5-position, there are obtained the corresponding 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitrosopyrimidines, substituted at the 4-position as in the reactant.

EXAMPLE 4

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine.

Following the procedure of Example 2, 6 - amino - 4 - (2,4 - dichlorophenoxy)-1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitrosopyrimidine was mixed with piperidine and heated in a sealed glass tube to give 6 - amino - 1,2 - dihydro - 1-hydroxy-2 - imino - 5 - nitroso- 4 - piperidinopyrimidine with essentially the same physical properties described in Example 3.

Following the procedure of Example 4 but using, in place of piperidine, each of the above-mentioned primary and secondary including heterocyclic amines listed after Example 2, there are obtained the corresponding 6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - imino - 5 - nitrosopyrimidines substituted at the 4-position with a mono-substituted or disubstituted amino group, and with essentially the same physical properties as the compounds prepared by the alternative route as exemplified in Example 3.

EXAMPLE 5

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitro - 4 - piperidinopyrimidine.

A solution of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine (3.0 g.) in 10 ml. of 95% sulphuric acid was cooled to 10° C. A mixture of 70% nitric acid (1 ml.) and 95% sulphuric acid (4 ml.) was added dropwise with stirring during 1.5 hours. The resulting solution was stirred an additional 30 minutes, and was then poured onto 250 g. of crushed ice. The mixture was mixed first with potassium hydroxide (25.5 g. of 85%) and then with potassium bicarbonate (12.0 g.), keeping the temperature of the mixture below 20° C. The mixture was then filtered, and the filter cake was washed with water and slurried with 300 ml. of water. The slurry was filtered and the solid was recrystallized from a mixture of water (175 ml.) and ethanol (75 ml.) to give 2.4 g. of 6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 5 - nitro - 4 - piperidinopyrimidine; m.p. 248—250° C.

Analysis:

Calcd. for $C_9H_{14}N_6O_3$:
C, 42.51; H, 5.55; O, 18.88.
Found: C, 42.37; H, 5.44; O, 18.75.

U.V. (ethanol) 222 mμ (ε=21,000); 270 mμ (ε=20,900); sl sh 340 mμ (ε=5300); 378 mμ (ε=5800).
(0.01N H_2SO_4) sh 236 mμ (ε=1740); 260 mμ (ε=26,050); 293 mμ (ε=6750); 343 mμ (ε=7250).
(0.01N KOH) 220 mμ (ε=20,700); sh 248 mμ (ε=15,450); 268 mμ (ε=14,550); 378 mμ (ε=9350).

I.R. (principal bands; mineral oil mull) 3140, 3390, 3150, 1655, 1640, 1610, 1565, 1525, 1480, 1265, 1175, 1120, 1020 cm^{-1}.

Addition of absolute ethanol containing one equivalent of hydrogen chloride to an absolute ethanol solution of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino-5 - nitro - 4 - piperidinopyrimidine, followed by addition of about 4 volumes of diethylether gives the corresponding hydrochloride.

Following the procedure of Example 5 but using, in place of the 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine, each of the above mentioned specific 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with a mono-substituted or disubstituted including heterocyclic amino group, and unsubstituted at the 5-position, there are obtained the corresponding 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitropyrimidines, substituted at the 4-position as in the reactant.

EXAMPLE 6

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitro - 4 - piperidinopyrimidine.

Following the procedure of Example 2, 6 - amino - 4 - (2,4 - dichloro - 6 - nitrophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitropyrimidine was mixed with piperidine and heated in a sealed glass tube to give 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitro - 4 - piperidinopyrimidine with essentially the same physical properties recited in Example 5.

EXAMPLE 7

5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine.

A mixture of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitro - 4 - piperidinopyrimidine (5.5 g.), methanol (50 ml.), concentrated hydrochloric acid (2.0 ml.), and 10% palladium on charcoal (1.0 g.) was shaken with hydrogen at 50 p.s.i. initial pressure at about 25° C. The theoretical amount of hydrogen was absorbed in about 30 minutes. The mixture was then filtered, and solvent was removed under reduced pressure to give 5.3 g. of 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine hydrochloride in the form of a hygroscopic amorphous solid.

U.V. (ethanol) sh 223 mμ (ε=14,670); 240 mμ (ε=17,790); 315 mμ (ε=8640).
(0.01 KOH) sh 223 mμ (ε=15,750); 238 mμ (ε=18,540); sh 263 mμ (ε=7130); 317 mμ (ε=7540).
I.R. (principal bands; mineral oil mull) 3300, 3160, 2600, 1650, 1620, 1545, 1525, 1235, 1205, 1160, 1125, 1020 cm^{-1}.

Addition of an equivalent amount of aqueous sodium hydroxide solution to an aqueous solution of 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine hydrochloride gives the corresponding free base. That free base is isolated by passing a methanol solution of the hydrochloride over a basic ion exchange resin such as Amberlite IR—400 (Registered Trade Mark) followed by evaporation of the ether solution under reduced pressure and in the absence of moisture and oxygen.

Following the procedure of Example 7 but using, in place of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitro - 4 - piperidinopyrimidine, each of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitropyrimidines substituted at the 4-position with a mono-substituted or disubstituted including heterocyclic amino group mentioned at the end of Example 5, there are obtained the corresponding 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine hydrochlorides, substituted at the 4-position as in the reactant. Each of those 5,6 - diamino compounds is than transformed to the free base as described in Example 7.

EXAMPLE 8

5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine.

Following the procedure of Example 7, 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine is shaken with hydrogen in the presence of palladium on charcoal to give the hydrochloride of 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine with essentially the same physical properties recited in Example 7.

Following the procedure of Example 8 but using, in place of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitroso - 4 - piperidinopyrimidine, each of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 5 - nitrosopyrimidines substituted at the 4-position with a mono-substituted or disubstituted including heterocyclic amino group and mentioned at the end of Example 3, there are obtained the corresponding 5,6 - diamino - 1,2 - dihydro - 2 - iminopyrimidine hydrochlorides substituted at the 4-position as in the reactant. Each of those 5,6 - diamino compounds is then transformed to the free base as described in Example 7. Each hydrochloride and free base has essentially the same physical properties as the 5,6 - diamino compound prepared from the corresponding 5 - nitro compound as described above.

EXAMPLE 9

5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine.

Following the procedure of Example 2, 5,6 - diamino - 4 - (2,4 - dichlorophenoxy) - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidine was mixed with piperidine

and heated in a sealed glass tube to give 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 4 - piperidinopyrimidine hydrochloride with essentially the same physical properties recited in Example 7. The free base corresponding to this hydrochloride was obtained as described in Example 7.

Following the procedure of Example 9 but using, in place of the piperidine, each of the primary and secondary including heterocyclic amines mentioned above and as listed after Example 2, there are obtained first the hydrochlorides and then the free bases of the corresponding 5,6 - diamino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with a mono-substituted or disubstituted amino group and with essentially the same physical properties as the compounds prepared by the alternative route as exemplified in Examples 7 and 8.

EXAMPLE 10

6 - amino - 5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - pyrrolidinyl)pyrimidine.

A mixture of 6 - amino - 5 - bromo - 4 - (2,4 - dichlorophenoxy) - 1,2-dihydro-1 - hydroxy - 2 - iminopyrimidine (3.5 g.) and pyrrolidine (25 ml.) was heated at 70° C. for 2 hours. The reaction mixture was cooled, and the solid was filtered, washed successively with pyrrolidine and diethyl ether, and dried to give 6 - amino - 5-bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - pyrrolidinyl)pyrimidine.

Following the procedure of Example 10 but using, in place of the pyrrolidine, each of the above-mentioned primary and secondary including heterocyclic amines as listed after Example 2, there are obtained the corresponding 6 - amino - 5 - bromo-1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with mono-substituted and disubstituted groups, respectively.

EXAMPLE 11

6 - amino - 5 - [(*p* - chlorophenyl)thio] - 1,2 - dihydro - 1 - hydroxy - 2 - imino-4 - (1 - pyrrolidinyl)pyrimidine.

A mixture of *p* - chlorothiophenol (2.3 g.) dimethylformamide (15 ml.) and sodium hydroxide (0.2 g.) was stirred under nitrogen until solution was complete, after which 6 - amino - 5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1-pyrrolidinyl)pyrimidine (1.5 g.) was added. The resulting mixture was heated at 95° C. for 3 hours, and was then filtered. The filtrate was cooled to 25° C. and mixed with a solution of sodium hydroxide (0.6 g.) in 100 ml. of water. That mixture was filtered, and the filtrate was allowed to stand several hours. Refiltration gave a filter cake which was recrystallized from acetonitrile to give 6 - amino - 5 - [(*p* - chlorophenyl)thio] - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - pyrrolidinyl)pyrimidine.

Following the procedure of Example 25 but substituting for the *p* - chlorothiophenol, thiophenol; *p* - methylthiophenol; *o* - ethylthiophenol; *m* - bromothiophenol; and *o* - fluorothiophenol, there are obtained 6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 5 - phenylthio - 4 - (1 - pyrrolidinyl)pyrimidine; 6 - amino - 1,2-dihydro-1 - hydroxy - 2 - imino - 5 - [(*p* - methylphenyl)thio] - 4 - (1 - pyrrolidinyl)pyrimidine; 6 - amino - 1,2 - dihydro - 5 - [(*o* - ethylphenyl)thio] - 1 - hydroxy - 2-imino - 4 - (1 - pyrrolidinyl)pyrimidine; 6 - amino - 5 - [(*m* - bromophenyl)thio]-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - pyrrolidinyl)pyrimidine; and 6-amino - 1,2 - dihydro - 5 - [(*o* - fluorophenyl)thio] - 1 - hydroxy - 2 - imino - 4-(1 - pyrrolidinyl)pyrimidine, respectively.

Also following the procedure of Example 11 but substituting for the 6 - amino-5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1 - pyrrolidinyl)pyrimidine, each of the above-mentioned 6 - amino - 5 - halo - 1,2 - dihydro - 1 - hydroxy - 2-iminopyrimidines substituted at the 4-position with mono-substituted and disubstituted including heterocyclic amino groups as mentioned in Example 10, there are obtained the corresponding 6 - amino - 5 - [(*p* - chlorophenyl)thio] - 1,2 - dihydro - 1-hydroxy - 2 - iminopyrimidines, substituted at the 4-position as in the reactant.

Also following the procedure of Example 11 but substituting for the combination of the 6 - amino - 5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4-(1-pyrrolidinyl)pyrimidine and *p*-chlorothiophenol, each of the above-mentioned 6-amino-5 - halo - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with mono-substituted and disubstituted including heterocyclic amino groups as mentioned in Example 10 and each of the other above-mentioned thiophenols within the scope of formula XXIII, above, there are obtained the corresponding 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines, substituted at the 4-position as in

the pyrimidine reactant and substituted at the 5-position with an arylthio group corresponding to the particular thiophenol used.

EXAMPLE 12

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4,5 - di - (1 - pyrrolidinyl)-pyrimidine.

A mixture of 6 - amino - 5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino-4-(1 - pyrrolidinyl)pyrimidine (2.7 g.) and pyrrolidine (25 ml.) was heated in a sealed, heavy-wall, glass tube in a 120° C. oil bath for 2.5 hours. The tube was then cooled and opened, and the reaction mixture was evaporated to a dry residue under reduced pressure. That residue was extracted 4 times with 100-ml. portions of chloroform. The combined chloroform extracts were dried with anhydrous sodium sulphate and evaporated to give a solid residue. The latten residue was recrystallized from acetonitrile to give 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4,5 - di - (1-pyrrolidinyl)pyrimidine.

Addition of absolute ethanol containing one equivalent of hydrogen chloride to an absolute ethanol solution of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino-4,5 - di - (1 - pyrrolidinyl)pyrimidine, followed by addition of about 4 volumes of diethyl ether, gives the corresponding monohydrochloride. Similan use of ethanol containing 2 equivalents of hydrogen chloride gives the corresponding dihydrochloride. Similar use of benzoic acid, maleic acid, lactic acid, phosphoric acid, sulphuric acid, and succinic acid gives the corresponding mono- and di-acid addition salts.

Following the procedure of Example 12 but substituting for the pyrrolidine, each of the above-mentioned primary and secondary including heterocyclic amines listed after Example 2, there are obtained the corresponding free bases and acid addition salts of 6-amino-1,2-dihydro-1-hydroxy-2-imino - 4 - (1 - pyrrolidinyl) pyrimidines substituted at the 5-position with mono-substituted and disubstituted including heterocyclic amino groups.

Also following the procedure of Example 12 but substituting for the combination of the 6 - amino - 5 - bromo - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - (1-pyrrolidinyl)pyrimidine and the pyrrolidine, each of the 6 - amino - 5 - bromo - 1,2-dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4 - position with mono-substituted or disubstituted including heterocyclic amino groups mentioned in Example 10 and each of the above-mentioned primary and secondary including heterocyclic amines listed after Example 2, there are obtained the corresponding free bases and acid addition salts of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position and at the 5-position with the same or different mono-substituted and disubstituted including heterocyclic amino groups.

EXAMPLE 13

6 - acetamido - 2 - acetylimino - 1,2 - dihydro - 1 - hydroxy - 4 - piperidino-pyrimidine.

A mixture of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine (4.1 g.), acetic anhydride (4.0 ml.), and diethyl ether (200 ml.) was stirred at 25° C. for 60 hours. The solid which formed was filtered and washed with ether to give 5.5 g. of a solid, 3.0 g. of which was recrystallized from 400 ml. of dimethylformamide to give 1.5 g. of 6 - acetamido - 2 - acetylimino - 1,2 - dihydro-1 - hydroxy - 4 - piperidinopyrimidine; m.p. 204—205° C.

Analysis:

Calcd. for $C_{13}H_{19}N_5O_3$:
C, 53.23; H, 6.53; N, 23.88.
Found: C, 52.81; H, 6.23; N, 24.06.

U.V. (ethanol) 241 mμ (ε=35,100); 291.5 mμ (ε=21,000); 328 mμ (ε=6000).
(0.01N H_2SO_4) 241 mμ (ε=30,850); 291 mμ (ε=19,050); sl sh 335 mμ (ε=4050).
(0.01N KOH) 233 mμ (ε=32,650); 261 mμ (ε=13,950); 286 mμ (ε=12,500).
(chloroform) 296 mμ (ε=20,050); 341 mμ (ε=5600).

I.R. (principal bands; mineral oil mull) 3160, 3060, 1710, 1680, 1630, 1565, 1535, 1480, 1255, 1225, 1205, 1180,, 1130 cm^{-1}.

Following the procedure of Example 13 but using acetyl chloride in place of the acetic anhydride, the same product is obtained. Also following the procedure of

Example 12 but using, in place of the acetic anhydride, propionic anhydride; crotonic anhydride; cyclohexanecarboxylic anhydride; isobutyryl chloride, decanoyl chloride; phenylacetyl chloride; 3 - methoxybutyric anhydride; *p* - tert - butylcyclohexanecarbonyl chloride; and *p* - nitrophenylacetyl chloride, there are obtained 1,2 - dihydro-1 - hydroxy - 4 - piperidino - 6 - propionamido - 2 - propionyliminopyrimidine; 6-crotonamido - 2 - crotonoylimino - 1,2 - dihydro - 1 - hydroxy - 4 - piperidinopyrimidine; 6 - cyclohexanecarboxyamido - 2 - cyclohexanecarbonylimino - 1,2 - dihydro - 1 - hydroxy - 4 - piperidinopyrimidine; 1,2 - dihydro - 1 - hydroxy - 6 - isobutyramido - 2 - isobutyrylimino - 4 - piperidinopyrimidine; 6 - decanamido - 2-decanoylimino - 1,2 - dihydro - 1 - hydroxy - 4 - piperidinopyrimidine; 1,2-dihydro-1 - hydroxy - 4 - piperidino - 6 - phenylacetamido - 2 - phenylacetyliminopyrimidine; 1,2 - dihydro - 1 - hydroxy - 6 - (3 - methoxybutyramido) - 2 - (3 - methoxybutyrylimino) - 4 - piperidinopyrimidine; 6 - (*p* - tert - butylcyclohexanecarboxamido)-2 - (*p* - tert - butylcyclohexanecarbonylimino) - 1,2 - dihydro - 1 - hydroxy - 4 - piperidinopyrimidine, and 1,2 - dihydro - 1 - hydroxy - 6 - (*p* - nitrophenylacetamido) - 2 - (*p* - nitrophenylacetylimino) - 4 - piperidinopyrimidine, respectively.

Also following the procedure of Example 13 but using, in place of the 6-amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine, each of the above-mentioned 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with a mono-substituted or disubstituted including heterocyclic amino group mentioned in the previous Examples, and unsubstituted at the 5-position or substituted at the 5-position with lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower aralkyl of C_7—C_{14}, cycloalkyl of C_8—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower-alkyl(C_1—C_8)phenylthio, halophenylthio, or a mono-substituted or disubstituted including heterocyclic amino group, there are obtained the corresponding 6 - acetamido - 2 - acetylimino - 1,2-dihydro - 1 - hydroxypyrimidines substituted at the 4-position and at the 5-position as in the reactant.

Also following the procedure of Example 13 but using in place of the combination of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine and the acetic anhydride, each of the above mentioned 6 - amino - 1,2 - dihydro-1 - hydroxy - 2 - iminopyrimidines, variously substituted at the 4-position as above-described and unsubstituted or variously substituted at the 5-position as above-described, as set out in previous Examples and each of the above-mentioned carboxylic acid anhydrides and each of the above-mentioned carboxylic acid chlorides, there are obtained the corresponding 6 - carboxyamido - 2 - carboxacylimino - 1,2 - dihydro-1-hydroxypyrimidines substituted at the 4-position and at the 5-position as in the reactant.

Also following the procedure of Example 13 but contacting each of the above-mentioned 6 - amino - 1,2 - dihydro - 1 - hydroxypyrimidines with less of the carboxyacylating agent, preferably no more than one molecular equivalent thereof, and in the range from about −10° to 10° C., carboxylicacylates are obtained which contain substantial amounts of the corresponding O,N - diacylate and/or the corresponding N-monoacylate. For example, following the procedure of Example 13 but using 2.0 ml. of acetic anhydride and maintaining the reaction mixture in the range 0° to 5° C. for 24 hours, 2 - acetylimino - 6 - amino - 1,2 - dihydro - 1 - hydroxy - 4 - piperidinopyrimidine and 1 - acetoxy - 2 - acetylimino - 6 - amino - 1,2 - dihydro - 4-piperidinopyrimidine are present in the acylation reaction mixture along with the N,N-diacylate, 6 - acetamido - 2 - acetylimino - 1,2 - dihydro - 1 - hydroxy - 4-piperidinopyrimidine. These three acylates are separated by fractional crystallization or chromatography.

EXAMPLE 14

6 - acetamido - 1 - acetoxy - 2 - acetylimino - 1,2 - dihydro - 4 - piperidinopyrimidine.

A mixture of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine (4.1 g.) and acetic anhydride (25 ml.) was warmed in the range 70° to 80° C. for 60 hours. The excess acetic anhydride was then removed by distillation under reduced pressure and the residue was recrystallized from dimethylformamide to give the triacylate, 6 - acetamido - 1 - acetoxy - 2 - acetylimino - 1,2 - dihydro - 4-piperidinopyrimidine.

EXAMPLE 15

6 - amino - 2 - benzoylimino - 1 - benzoyloxy - 1,2 - dihydro - 4 - piperidinopyrimidine.

Benzoic anhydride (4.5 g.) was added with swirling to a mixture of 6 - amino-

1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine (4.1 g.) in 200 ml. of diethyl ether. The mixture was stirred at about 25° C. for 24 hours. The solid which formed was filtered, washed with diethyl ether, and dried to give 6 - amino-2 - benzoylimino - 1 - benzoyloxy - 1,2 - dihydro - 4 - piperidinopyrimidine.

Following the procedure of Example 15 but reducing the amount of benzoic anhydride to 2.25 g. (1 molecular equivalent), 6 - amino - 2 - benzoylimino - 1,2-dihydro - 1 - hydroxy - 4 - piperidinopyrimidine is obtained.

Also following the procedure of Example 15 but refluxing the reaction mixture for 24 hours, 6 - benzamido - 2 - benzoylimino - 1,2 - dihydro - 1 - hydroxy - 4-piperidinopyrimidine is obtained.

Also following the procedure of Example 15 and the two above-described variations thereof, but using, in place of the benzoic anhydride, *p* - toluic anhydride; *m*-chlorobenzoic anhydride; *p* - methoxybenzoic anhydride; *p* - (methylthio)benzoyl chloride; *o* - nitrobenzoyl chloride; naphthoyl chloride; furoyl chloride; and 3 - pyridinecarbonyl chloride, there are obtained the corresponding N-monoacylates, O,N-diacylates, and N,N-diacylates of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino-4 - piperidinopyrimidine.

Also following the procedure of Example 15 but using, in place of the combination of the 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine and the benzoic anhydride, each of the above-mentioned 6 - amino - 1,2-dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position with a mono-substituted or disubstituted including heterocyclic amino group, and unsubstituted at the 5-position or substituted at the 5-position with lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower aralkyl of C_7—C_{14}, lower cycloalkyl of C_8—C_{10}, chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower-alkyl(C_1—C_8)-phenylthio, halophenylthio, or a mono-substituted or disubstituted including heterocyclic group, and each of the above-mentioned aromatic including heterocyclic carboxylic acid anhydrides and carboxylic acid chlorides, there are obtained the corresponding N-monoacylates, O,N - diacylates, and N,N - diacylates of the 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - iminopyrimidines substituted at the 4-position and at the 5-position as in the reactant.

The following examples relate to the use of the novel compounds of this invention as antihypertensive agents. Each example relates to that use of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine. The other formula I, II, III, IV, and V novel compounds of this invention and their acid addition salts can be used in a similar manner, and these examples should not be construed as limiting.

EXAMPLE 16

Tablets

20,000 scored tablets for oral use, each containing 200 mg. of 6 - amino - 1,2-dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - imino - 4 - piperidinopyrimidine, micronized	4000 Gm.
Starch, U.S.P.	350 Gm.
Talc, U.S.P.	250 Gm.
Calcium Stearate	35 Gm.

The micronized 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base is granulated with a 4 percent w/v aqueous solution of methylcellulose U.S.P. (1500 cps.). To the dried granules is added a mixture of the remainder of the ingredients and the final mixture is compressed into tablets of proper weight. Satisfactory clinical response is obtained in adults showing hypertension with 1 tablet which can be repeated in 4 hours, if necessary. For moderate conditions, a half tablet is used.

EXAMPLE 17

Capsules.

20,000 two-piece hard gelatin capsules for oral use, each containing 100 mg. of

6 - amino - 1,2 - dihydro - 1 - hydroxy 2 - imino - 4 - piperidinopyrimidine free base are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1-hydroxy 2 - imino - 4 - piperidinopyrimidine	2000 Gm.
Lactose, U.S.P.	1000 Gm.
Starch, U.S.P.	300 Gm.
Talc, U.S.P.	65 Gm.
Calcium Stearate	25 Gm.

The micronized 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base is mixed with the starch-lactose mixture followed by the talc and calcium stearate. The final mixture is then encapsulated in the usual manner. One capsule is used every 3 hours to control hypertension.

Capsules containing 10, 25, 50 and 350 mg. of 6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - imino - 4 - piperidinopyrimidine free base are also prepared by substituting 200, 500, 1000 and 7000 gm. for 2000 gm. in the above formulation.

EXAMPLE 18

Soft Elastic Capsules.

One-piece soft elastic capsules for oral use, each containing 5 mg. of 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base are prepared in the usual manner by first dispersing the powdered active material in sufficient corn oil to render the material capsulatable.

EXAMPLE 19

Aqueous Preparation.

An aqueous preparation for oral use containing, in each 5 ml., 50 mg. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine hydrochloride, is prepared from the following ingredients:

6 - amino - 1,2 - dihydro-1 - hydroxy - 2 - imino - 4-piperidinopyrimidine hydrochloride	100 Gm.
Methylparaben, U.S.P.	7.5 Gm.
Propylparaben, U.S.P.	2.5 Gm.
Saccharin Sodium	12.5 Gm.
Cyclamate Sodium	2.5 Gm.
Glycerin	3000 Ml.
Tragacanth Powder	10 Gm.
Orange Oil Flavor	10 Gm.
F.D. and C. Orange Dye	7.5 Gm.
Deionized Water, q.s. to	10,000 Ml.

EXAMPLE 20

Parenteral Suspension.

A sterile aqueous suspension suitable for intramuscular injection and containing, in each milliliter, 25 mg. of 6 - amino - 1,2 - dihydro - 1 hydroxy - 2 - imino - 4-piperidinopyrimidine free base is prepared from the following ingredients:

Polyethylene Glycol 4000, U.S.P.	3 Gm.
Sodium Chloride	0.9 Gm.
Polysorbate 80, U.S.P.	0.4 Gm.
Sodium Metabisulphite	0.1 Gm.
Methylparaben, U.S.P.	0.18 Gm.
Propylparaben, U.S.P.	0.02 Gm.
6 - amino - 1,2 - dihydro - 1-hydroxy - 2 - imino - 4 - piperidinopyrimidine free base (micronized)	2.5 Gm.
Water for injection, q.s. to	100 Ml.

EXAMPLE 21

Aqueous Solution.

An aqueous solution for oral use and containing, in each 5 ml., 25 mg. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base is prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy-2-imino-4-piperidinopyrimidine free base	5 Gm.
Deionized Water, q.s. to	1000 Ml.

EXAMPLE 22

Parenteral Solution.

A sterile aqueous solution for intravenous or intramuscular injection and containing 20 mg. of 6 - amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine maleate in each 2 ml. is prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 4 - piperidinopyrimidine maleate	10 Gm.
Chlorobutanol	3 Gm.
Water for injection, q.s. to	1000 Ml.

EXAMPLE 23

Capsules.

One thousand hard gelatin capsules for oral use, each containing 25 mg. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 25 mg. of hydrochlorothiazide are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 4 - piperidinopyrimidine free base micronized	25 Gm.
Hydrochlorothiazide	25 Gm.
Starch	125 Gm.
Talc	25 Gm.
Magnesium Stearate	15 Gm.

One capsule 2 to 4 times a day is advantageous in the relief of moderate to severe hypertension in adult humans.

EXAMPLE 24

Capsules:

One thousand hard gelatin capsules for oral use, each containing 50 m.g. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base, 25 mg. of hydrochlorothiazide, 0.1 mg. of reserpine, and 400 mg. of potassium chloride are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 4 - piperidinopyrimidine free base micronized	50 Gm.
Hydrochlorothiazide	25 Gm.
Reserpine	0.1 Gm.
Potassium Chloride	400 Gm.
Talc	75 Gm.
Magnesium Stearate	20 Gm.

One or two capsules daily is advantageously used for reducing hypertension.

EXAMPLE 25

Tablets.

Ten thousand tablets for oral use, each containing 50 mg. of 6 - amino - 1,2-dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 25 mg. of chlorisondamine chloride, are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy-2 - imino - 4 - piperidinopyrimidine free base	500 Gm.
Chloroisondamine Chloride	250 Gm.
Lactose	1200 Gm.
Corn Starch	500 Gm.
Talc	500 Gm.
Calcium Stearate	25 Gm.

The powdered ingredients are thoroughly mixed and slugged. The slugs are broken down into granules which are then compressed into tablets. For relief of hypertension in adult humans, 1 tablet is administered 1 to 4 times daily after meals.

EXAMPLE 26

Tablets.

Ten thousand scored tablets for oral used, each containing 25 mg. of 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 0.1 mg. of reserpine, are prepared from the following ingredients and using the procedure of Example 16.

6 - amino - 1,2 - dihydro - 1 - hydroxy -2-imino-4-piperidinopyrimidine free base	250 Gm.
Reserpine	1 Gm.
Lactose	1500 Gm.
Corn Starch	500 Gm.
Talc	500 Gm.
Calcium Stearate	25 Gm.

This combination of active materials is effective in adult humans for the reduction of hypertension. The dose is one-half to two tablets 3 times a day depending on the severity of the condition.

EXAMPLE 27

Capsules.

Ten thousand hard gelatin capsules for oral use, each containing 25 mg. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 200 mg. of meprobamate, are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine free base	250 Gm.
Meprobamate	2000 Gm.
Starch	350 Gm.
Talc	250 Gm.
Calcium Stearate	150 Gm.

One capsule 4 times a day is useful in the treatment of hypertension.

EXAMPLE 28

Tablets.

Ten thousand tablets for oral use, each containing 25 mg. of 6 - amino - 1,2-dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 40 mg. of ethoxyzolamide, are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine free base	250 Gm.
Ethoxyzolamide	400 Gm.
Lactose	1200 Gm.
Corn Starch	500 Gm.
Talc	500 Gm.
Calcium Stearate	25 Gm.

The powdered ingredients are thorough mixed and slugged. The slugs are broken into granules which are then compressed into tablets. For relief of hypertension in adult humans, 1 tablet is administered 2 to 4 times daily.

WHAT WE CLAIM IS:—

1. The free base form or acid addition salt of a compound of the formula:—

The powdered ingredients are thoroughly mixed and slugged. The slugs are broken down into granules which are then compressed into tablets. For relief of hypertension in adult humans, 1 tablet is administered 1 to 4 times daily after meals.

EXAMPLE 26

Tablets.

Ten thousand scored tablets for oral used, each containing 25 mg. of 6 - amino-1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 0.1 mg. of reserpine, are prepared from the following ingredients and using the procedure of Example 16.

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino-4-piperidinopyrimidine free base	250 Gm.
Reserpine	1 Gm.
Lactose	1500 Gm.
Corn Starch	500 Gm.
Talc	500 Gm.
Calcium Stearate	25 Gm.

This combination of active materials is effective in adult humans for the reduction of hypertension. The dose is one-half to two tablets 3 times a day depending on the severity of the condition.

EXAMPLE 27

Capsules.

Ten thousand hard gelatin capsules for oral use, each containing 25 mg. of 6-amino - 1,2 - dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 200 mg. of meprobamate, are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine free base	250 Gm.
Meprobamate	2000 Gm.
Starch	350 Gm.
Talc	250 Gm.
Calcium Stearate	150 Gm.

One capsule 4 times a day is useful in the treatment of hypertension.

EXAMPLE 28

Tablets.

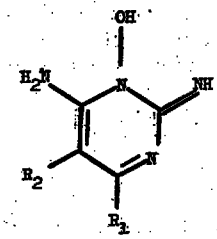
Ten thousand tablets for oral use, each containing 25 mg. of 6 - amino - 1,2-dihydro - 1 - hydroxy - 2 - imino - 4 - piperidinopyrimidine free base and 40 mg. of ethoxyzolamide, are prepared from the following ingredients:

6 - amino - 1,2 - dihydro - 1 - hydroxy - 2-imino - 4 - piperidinopyrimidine free base	250 Gm.
Ethoxyzolamide	400 Gm.
Lactose	1200 Gm.
Corn Starch	500 Gm.
Talc	500 Gm.
Calcium Stearate	25 Gm.

The powdered ingredients are thorough mixed and slugged. The slugs are broken into granules which are then compressed into tablets. For relief of hypertension in adult humans, 1 tablet is administered 2 to 4 times daily.

WHAT WE CLAIM IS:—

1. The free base form or acid addition salt of a compound of the formula:—



wherein R_1 is a group of the formula $-N<^{R_3}_{R_4}$ wherein R_3 and R_4 are hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower aralkyl of C_7—C_{14}, cycloalkyl of C_3—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, with the proviso that both R_3 and R_4 are not hydrogen, or an aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino or 4-lower-alkylpiperazinyl group, each of said heterocyclic groups having optionally attached as substituents on carbon atoms thereof one to 3 lower alkyls of C_1—C_8 inclusive, a nitrogen atom of each of said heterocyclic groups being the point of attachment of R_1 to the ring in said formula, and wherein R_2 is hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower alkoxyalkyl of C_3—C_{10}, cycloalkyl of C_3—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, a phenyl or naphthyl radical, lower aralkyl of C_7—C_{14}, lower alkaryl of C_7—C_{14}, lower alkaralkyl of C_8—C_{15}, lower alkoxyaralkyl of C_8—C_{15} or lower haloaralkyl of C_7—C_{14}.

2. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 1 in association with a pharmaceutical carrier.

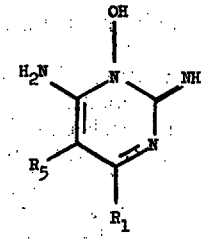
3. A composition according to claim 2 and containing also a diuretic.

4. A compound according to claim 1 wherein R_1 is piperidino and R_2 is hydrogen.

5. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 4 in association with a pharmaceutical carrier.

6. A composition according to claim 5 and containing also a diuretic.

7. The free base form or acid addition salt of a compound of the formula:



wherein R_1 is as defined in claim 1, and wherein R_5 is chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower-alkyl(C_1—C_8)phenylthio, or halophenylthio.

8. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 7 in association with a pharmaceutical carrier.

9. A composition according to claim 8 and containing also a diuretic.

10. A compound according to claim 7 wherein R_1 is piperidine and R_5 is nitroso.

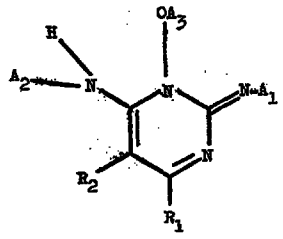
11. A compound according to claim 7 wherein R_1 is piperidino and R_5 is nitro.

12. A compound according to claim 7 wherein R_1 is piperidino and R_5 is amino.

13. The hydrochloride of a compound according to claim 12.

14. A compound of the formula:

* C L M S *



wherein R_1 and R_2 are as defined in claim 1 and wherein A_1, A_2, and A_3 are each hydrogen or carboxylicacyl, with the proviso that at least one of A_1 and A_2 is carboxylicacyl.

15. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 14 in association with a pharmaceutical carrier.

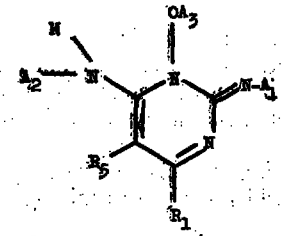
16. A composition according to claim 15 and containing also a diuretic.

17. A compound according to claim 14 wherein R_1 is piperidino, R_2 is hydrogen, A_1 and A_2 are acetyl, and A_3 is hydrogen.

18. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 17 in association with a pharmaceutical carrier.

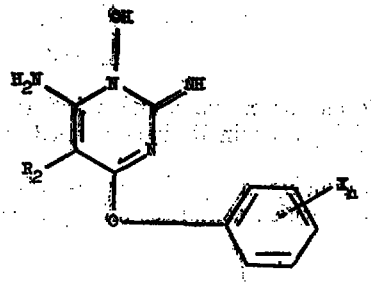
19. A composition according to claim 18 and containing also a diuretic.

20. A compound of the formula:



wherein R_1 is as defined in claim 1, R_5 is chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower-alkyl(C_1—C_8)phenylthio, or halophenylthio, and wherein A_1, A_2 and A_3 are each hydrogen or carboxylicacyl, with the proviso that at least one of A_1 and A_2 are carboxylicacyl.

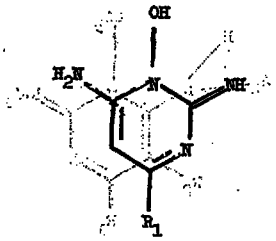
21. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 1 which comprises mixing a compound of the formula



wherein X is fluorine, chlorine or bromine, and n is zero or 1 to 3, inclusive, and wherein R_2 is as defined in claim 1, with an amine of the formula R_1H, wherein R_1 is as defined in claim 1, to form said 1,2-dihydro-1-hydroxypyrimidine.

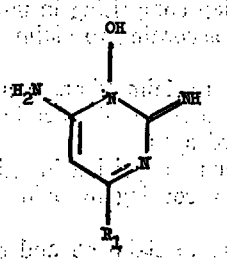
22. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is nitroso, which comprises mixing a compound of the formula:

* C L M S *



wherein R_1 is as defined in claim 7, with nitrous acid, to form said 1,2-dihydro-1-hydroxypyrimidine.

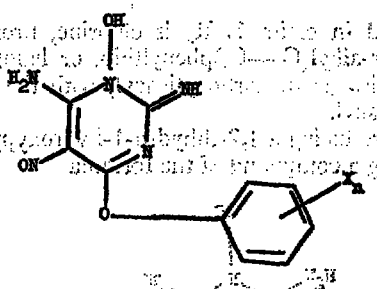
23. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is nitro which comprises mixing a compound of the formula:



wherein R_1 is as defined in claim 7, with nitric acid, to form said 1,2-dihydro-1-hydroxypyrimidine.

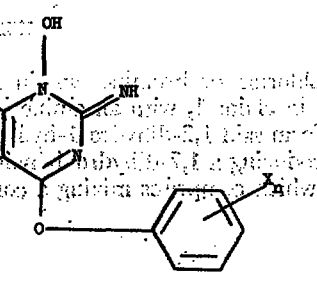
24. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is amino and wherein R_1 does not contain alkenyl, which comprises mixing a compound according to claim 7 wherein R_5 is nitroso or nitro, with hydrogen in the presence of a hydrogenation catalyst, to form said 1,2-dihydro-1-hydroxypyrimidine.

25. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is nitroso, which comprises mixing a compound of the formula:



wherein X is fluorine, chlorine, or bromine, and n is zero or one to 3, inclusive, with an amine of the formula R_1H, wherein R_1 is as defined in claim 7, to form said 1,2-dihydro-1-hydroxypyrimidine.

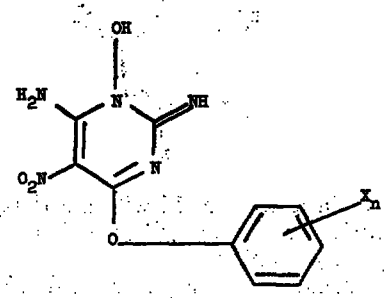
26. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is amino, which comprises mixing a compound of the formula:



wherein X is fluorine, chlorine or bromine, and n is zero or 1 to 3, inclusive, with an amine of the formula R_1H, wherein R_1 is as defined in claim 7, to form said 1,2-dihydro-1-hydroxypyrimidine.

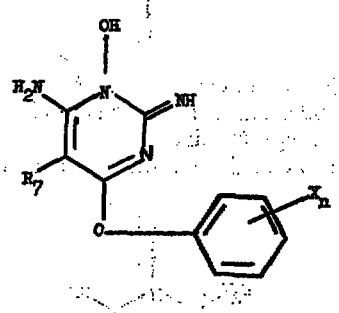
27. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to

claim 7 wherein R_5 is nitro which comprises mixing a compound of the general formula:—



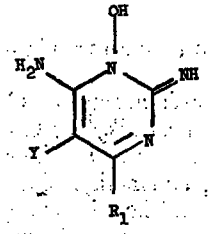
wherein X is fluorine, chlorine or bromine and n is zero or an integer from 1 to 3 inclusive with an amine of the formula R_1H wherein R_1 is as defined in claim 7 to form said 1,2-dihydro-1-hydroxypyrimidine.

28. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is chlorine, bromine or iodine, which comprises mixing a compound of the formula:—

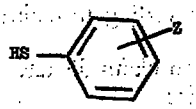


wherein X is fluorine, chlorine or bromine, R_7 is chlorine, bromine, or iodine, and n is zero or 1 to 3, inclusive, with an amine of the formula R_1H, wherein R_1 is as defined in claim 7, to form said 1,2-dihydro-1-hydroxypyrimidine.

29. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 7 wherein R_5 is phenylthio, lower-alkyl-(C_1—C_8)-phenylthio, or halophenylthio, which comprises mixing a compound of the formula:



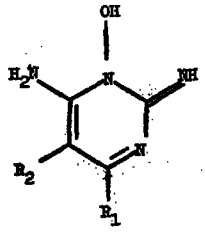
wherein Y is chlorine, bromine, or iodine, and wherein R_1 is as defined in claim 7 with a thiophenol of the formula:



wherein Z is hydrogen, lower alkyl of C_1—C_8, or halogen, to form said 1,2-dihydro-1-hydroxypyrimidine.

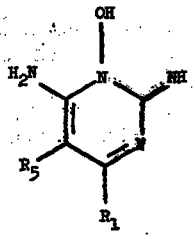
30. A process for producing a carboxylicacylated 1,2-dihydro-1-hydroxypyrimidine according to claim 14 which comprises mixing a compound of the formula:





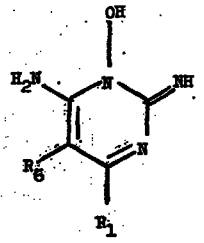
wherein R_1 and R_2 are as defined in claim 14 with a carboxylicacylating agent selected from carboxylic acid anhydrides and carboxylic acid chlorides, to form said carboxylic-acylated 1,2-dihydro-1-hydroxypyrimidine.

31. A process for producing a carboxylicacylated 1,2-dihydro-1-hydroxypyrimidine according to claim 20 which comprises mixing a compound of the formula:



wherein R_1 and R_5 are as defined in claim 20, with a carboxylicacylating agent selected from carboxylic acid anhydrides and carboxylic acid chlorides, to form said carboxylic-acylated 1,2-dihydro-1-hydroxypyrimidine.

32. The free base form or acid addition salt of a compound of the formula:—



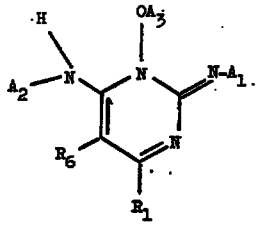
wherein R_1 and R_6 are each a group of the formula $-N<^{R_3}_{R_4}$ wherein R_3 and R_4 are hydrogen, lower alkyl of C_1—C_8, lower alkenyl of C_2—C_8, lower aralkyl of C_7—C_{14}, cycloalkyl of C_3—C_{10} or lower alkylcycloalkyl of C_3—C_{10}, with the proviso that both R_3 and R_4 are not hydrogen or an aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, or 4-lower-alkyl (C_1—C_8)piperazinyl group, each of said heterocyclic groups having optionally attached as substituents on carbon atoms thereof one to 3 lower alkyls of C_1—C_8, inclusive, a nitrogen atom of each of said heterocyclic groups being the point of attachment of R_1 and R_6 to the ring in said formula.

33. A therapeutic composition comprising in unit dosage form from 5 to 500 mg. per dosage unit of a compound according to claim 32 in association with a pharmaceutical carrier.

34. A composition according to claim 33 and containing also a diuretic.

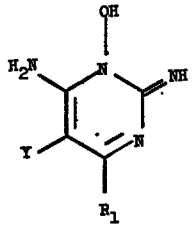
35. A compound of the formula:

* C L M S *



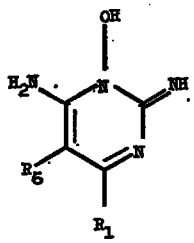
wherein R_1 and R_6 are as defined in claim 32, and wherein A_1, A_2, and A_3 are each hydrogen and carboxylicacyl, with the proviso that at least one of A_1 and A_2 is carboxylicacyl.

36. A process for producing a 1,2-dihydro-1-hydroxypyrimidine according to claim 32 which comprises mixing a compound of the formula:



wherein Y is chlorine, bromine, or iodine and R_1 is as defined in claim 35, with an amine of the formula R_6H, wherein R_6 is as defined in claim 35, to form said 1,2-dihydro-1-hydroxypyrimidine.

37. A process for producing a carboxylicacylated 1,2-dihydro-1-hydroxypyrimidine according to claim 35 which comprises mixing a compound of the formula:



wherein R_1 and R_6 are as defined in claim 38, with a carboxylicacylating agent selected from carboxylic acid anhydrides and carboxylic acid chlorides, to form said carboxylic-acylated 1,2-dihydro-1-hydroxypyrimidine.

38. A process for the preparation of a compound as claimed in any of claims 1, 4, 7, 10 to 14, 17, 20, 32 or 35 substantially as herein described with reference to Examples 1 to 15.

39. A compound as claimed in any of claims 1, 4, 7, 10 to 14, 17, 20, 32 or 35, when prepared by a process as claimed in claims 21 to 31 or 36 to 38.

40. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1, 4, 7, 10 to 14, 17, 20, 32, 35 or 39 together with a pharmaceutically acceptable carrier.

41. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1, 4, 7, 10 to 14, 17, 20, 32, 35 or 39 substantially as herein described with reference to Examples 16 to 28.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

