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3,702,849

4-(ISOQUINOLIN-1-YL) PIPERAZINE-1-CARBOXYLIC ACID ESTERS

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Int. Cl. C07d *51/70*

U.S. Cl. 260—268 C 4 Claims

ABSTRACT OF THE DISCLOSURE

4(isoquinolin - 1 - yl) - piperazine - 1 - carboxylic acid, esters and 1 - amino - 6,7 - dialkoxyisoquinolines and their pharmaceutically-acceptable acid addition salts. Compounds manifest bronchodilator activity and antihypertensive response with minimal adverse effects upon administration to afflicted subjects.

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a division of application Ser. No. 678,191, filed Oct. 26, 1967 (now U.S. Pat. No. 3,517,005), which, in turn, is a continuation-in-part of application Ser. No. 590,494, filed Oct. 31, 1966 and now abandoned.

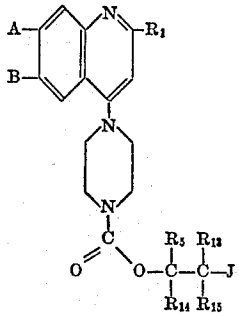
BACKGROUND OF THE INVENTION

This invention relates to certain novel organic nitrogen compounds, and more particularly, it is concerned with various new and useful organic heterocyclic nitrogen compounds which are valuable in alleviating bronchoconstriction in afflicted subjects and in reducing the blood pressure of hypertensive subjects.

Treatment of subjects suffering from bronchoconstriction or hypertension requires that the therapeutic agent effectively cause gronchodilation or lower the blood pressure of the treated subject at dosage levels which do not cause other undesirbale effects in the subject. The compounds of this invention manifest bronchodilatory and/or hypotensive activity at dosage levels at which no adverse effects are manifested in the treated individual.

SUMMARY OF THE INVENTION

Among the compounds of this invention are those of the formula:



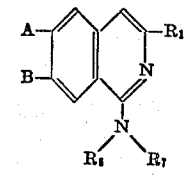
VI

and their pharmaceutically-acceptable acid addition salts.

In these compounds of Formula VI, A and B may each be alkoxy containing from 1 to 5 carbon atoms, hydrogen, hydroxy, or methyl. When A or B are hydrogen, the other is never hydrogen. A and B, taken together, may be benzo or alkylenedioxy having up to 4 carbon atoms. R_1 may be H or alkyl containing from 1 to 6 carbon atoms. R_5, R_{13}, R_{14} and R_{15} each may be H, alkyl containing from 1 to 4 carbon atoms or hydroxymethyl and R_5 and R_{13}, taken together, may be cycloalkyl having from 4 to 7 carbon atoms. J may be H, hydroxy, formyloxy, acyloxy containing from 2 to 5 carbon atoms, aroyloxy containing up to 11 carbon atoms, alkoxy containing from 1 to 4 carbon atoms, aryloxy containing up to 10 carbon atoms, chloro, bromo, formamido, alkylamido having up to 4 carbon atoms in the alkyl group, arylamido having up to 10 carbon atoms in the aryl group or amino, containing up to two substituents. Each amino substituent may be hydrogen, alkyl having up to 4 carbon atoms or aryl containing up to 10 carbon atoms. The two substituents, taken together, may be cycloalkyl containing from 4 to 7 carbon atoms.

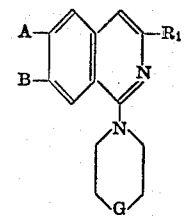
These compounds are useful as bronchodilators and as smooth muscle relaxants. Of particular interest as bronchodilators are the compound 4-(6,7-dimethoxyquinolin - 4 - yl) - piperazine - 1 - carboxylic acid, isobutyl ester, and the compound 4-(6,7-dimethoxyquinolin-4-yl)-piperazine - 1 - carboxylic acid, 2 - methyl - 2 - hydroxypropyl ester.

Other compounds of this invention are those of the formulae:



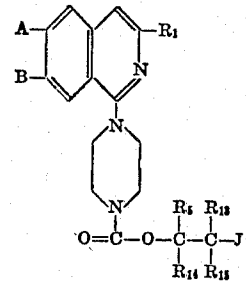
VII

and



VIII

and



IX

and their pharmaceutically-acceptable acid addition salts.

In the compounds of Formulae VII, VIII and IX, A and B may each be alkoxy containing from 1 to 5 carbon atoms, hydrogen, hydroxy, or methyl. When A or B are hydrogen, the other is never hydrogen. A and B, taken together may be benzo or alkylenedioxy having up to 4 carbon atoms. R_1 is H or alkyl containing from 1 to 6 carbon atoms. R_6 and R_7 may each be H, alkyl or alkenyl containing up to 6 carbon atoms, aryl hydrocarbon containing up to 10 carbon atoms, aralkyl hydrocarbon containing up to 3 carbon atoms in the alkyl moiety and 7 carbon atoms in the aryl moiety, or β-hydroxyethyl. When R_6 and R_7 are aryl or aralkyl, the aryl moiety may be substituted with up to 3 substituents which may be halogen or alkoxy containing up to 4 carbon atoms. R_6 and R_7, taken together, may be cycloalkyl containing from 3 to 7 carbon atoms.

G may be oxygen, sulfur, amino, alkylamino having up to 6 carbon atoms in the alkyl group, alkenylamino having from 3 to 6 carbon atoms in the alkenyl moiety, unsubstituted aryl hydrocarbon amino having up to 10 carbon atoms in the aryl moiety, acylamino having up to 6 carbon atoms in the acyl moiety, aroylamino having up to 11 carbon atoms in the aroyl moiety, carbalkoxyamino having up to 6 carbon atoms in the alkyl moiety, carbalkenyloxyamino having up to 6 carbon atoms in the alkenyl moiety or carbaryloxyamino having up to 10 carbon atoms in the aryl moiety. R_5, R_{13}, R_{14} and R_{15} may each be H, alkyl containing from 1 to 4 carbon atoms or hydroxymethyl. R_5 and R_{13}, taken together, may be cycloalkyl having from 4 to 7 carbon atoms.

J may be H, hydroxy, formyloxy, acyloxy containing from 2 to 5 carbon atoms, aroyloxy containing up to 11 carbon atoms, alkoxy containing from 1 to 4 carbon atoms, aryloxy containing up to 10 carbon atoms, chloro, bromo, formamido, alkylamino having up to 4 carbon atoms in the alkyl group, arylamido having up to 10 carbon atoms in the aryl group or amino, containing up to two substituents. Each amino substituent may be hydrogen, alkyl having up to 4 carbon atoms or aryl containing up to 10 carbon atoms. The two substituents, taken together, may be cycloalkyl containing from 4 to 7 carbon atoms.

These compounds of Formulae VII, VIII and IX are useful as bronchodilators and as smooth muscle relaxants. Particularly preferred as bronchodilators are the compound 4-(6,7 - dimethoxyisoquinolin - 1 - yl)-piperazine-1-carboxylic acid isobutyl ester, the compound 4-(6,7-dimethoxyisoquinolin - 1 - yl) - piperazine - 1 - carboxylic acid, ethyl ester, the compound 4 - (6,7 - dimethoxyisoquinolin - 1 - yl)-piperazine - 1 - carboxylic acid, 2-methyl-2 - hydroxypropyl ester, and the compound 4 - ethylamino - 6,7 - dimethoxyisoquinoline.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula VI are prepared from the corresponding 4-chloro-6,7-substituted quinolines. These latter compounds are prepared by the method given by B. Riegel et al., J. Am. Chem. Soc., 68, 1264 (1946). The nature of the 6- and 7-substituents is determined by the original 3,4 di-substituted aniline which is used to prepare the 6,7-substituted quinoline. The nature of the 2-substituent is determined by the malonic ester which is used to cyclize the 3,4-disubstituted aniline.

The compounds of Formula VI are prepared by reacting the 4 - chloro - 6,7 - substituted quinoline with an appropriate piperazine-1-carboxylic acid ester. This reaction may be carried out in an appropriate aqueous or organic solvent and, while ethanol is a preferred solvent, other polar solvents such as dimethylformamide, dioxane, tetrahydrofuran or methanol may be used. A molar excess of the piperazine acid ester may be employed. The reaction mixture is heated at a temperature from 100° C. to 170°. for a period ranging from one to sixteen hours. Preferred reaction times are from 1.5 to 2.5 hours and

preferred temperatures range from 120° C. to 140° C., where ethanol is the solvent.

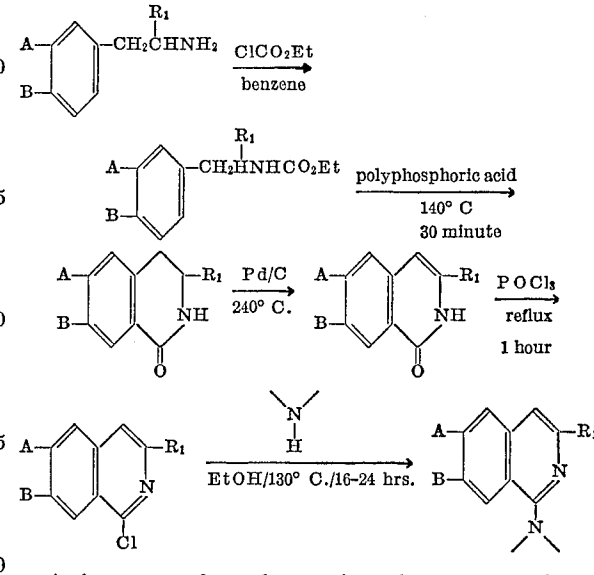
An alternative procedure may be used which involves the preparation of 4 - piperazinyl quinoline, as an intermediate. The compounds of Formula VI are prepared from the intermediate, as indicated below.

The appropriate 4-bromo quinolines, 4-alkoxy quinolines and 4-thioalkoxy quinolines may be used in place of the 4-chloro quinolines to prepare the compounds of Formula VI. When these compounds are used, the reaction duration and conditions may slightly differ from those used when the 4-chloro quinolines are the starting compounds. Those skilled in the art will easily be able to determine the appropriate reaction conditions for use where the 4-bromo, 4-alkoxy or 4-thioalkoxy quinolines are used as reactants. The preferred reactants are the 4-chloro quinolines.

Compounds VII, VIII and IX may be prepared from the appropriate 1 - chloro-6,7-substituted isoquinolines. These latter compounds may be prepared by a method derived from that given by E. L. Anderson et al., J. Am. Pharm. Assoc., Sci. Ed., 41, 643 (1952).

The preparation method involves the reaction of a substituted phenethylamine with ethyl chloroformate, in benzene, to form the substituted phenethyl carbamic acid, ethyl ester. This latter compound is cyclized by treatment with polyphosphoric acid at about 140° C. for 30 minutes to form the 3,4-dihydro-1(2H)-isoquinolinone which is converted to the 1(2H) - isoquinolinone by use of a palladium on carbon catalyst. This reaction is continued until hydrogen evolution ceases. The 1(2H)-isoquinolinone is converted to the 1-chloro-isoquinoline by reaction with phosphorus oxychloride. The 1-chloro-isoquinoline is reacted with the appropriate amine to form the compounds of Formulae VII, VIII, and IX.

A typical reaction scheme may be shown as:



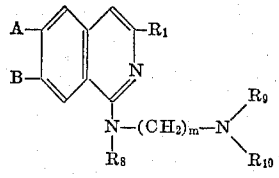
As is apparent from the reaction scheme set out above, the substituents at the 3-, 6- and 7-positions (R_1, A and B) are determined by the nature of the original substituted phenethylamine and the amino substituent at the 1-position is determined by the amine used in the final reaction step. In the compounds of Formula IX, where the substituents R_5, R_{13}, R_{14}, R_{15} and J are complex, it may be necessary or preferable to form the final compound in two or more steps, from the 1-chloro compound, as is outlined below.

The amination of the 1-chloro isoquinoline is generally carried out in an aqueous or organic solvent and, while ethanol is preferred as a solvent, other polar solvents such as dimethylformamide, dioxane, tetrahydrofuran or methanol may be used. A molar excess of amine or base

may be used advantageously. The amination reaction takes place at a temperature ranging from 100° C. to 200° C. and a reaction duration of 10 to 36 hours. Preferred reaction temperatures are 120° C. to 140° C. and preferred reaction times range from 16 to 24 hours when ethanol is used as a solvent.

The compounds of Formulae VII, VIII and IX may also be produced using the appropriate 1-bromo isoquinoline, the 1-alkoxy isoquinoline or the 1-thioalkoxy isoquinoline in place of the preferred 1-chloro compound. Where these compounds are used in place of the 1-chloro isoquinolines, the reaction conditions may differ from those given above for the 1-chloro compound. Those skilled in the art will easily be able to determine appropriate reaction temperatures and durations for producing the compounds of Formulae VII, VIII and IX from the 1-bromo, 1-alkoxy or 1-thioalkoxy isoquinolines.

The methods used to prepare the compounds of Formulae VII, VIII and IX may also be used to prepare compounds of the following Formula X:



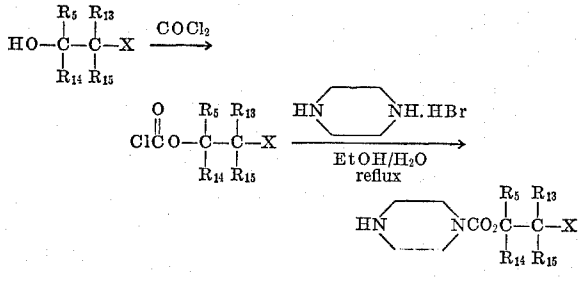
X

where A, B and R_1 are as defined for their compounds of Formulae VII, VIII and IX and R_8, R_9 and R_{10} are each H or alkyl having up to 6 carbon atoms. The number of methylene groups, *m*, is from 2 to 5. These compounds are useful as intermediates in preparing the compounds of Formulae VII, VIII and IX.

Where compounds of Formulae II, IV, V, VA, VI and IX are produced it is often preferable to prepare the final compound from the chloro derivative in two or more steps.

Nevertheless, the final compound may, in some cases, be more easily prepared in a single step by direct amination of the chloro derivative. Thus, the 4-(2-alkyl-6,7-dimethoxyquinazolin-4-yl)-piperazine - 1 - carboxylic acid, isobutyl esters are prepared, directly, by reacting the 2-alkyl-4-chloro-6,7-dimethoxyquinazolines with piperazine-1-carboxylic acid, isobutyl ester. Similarly, the 4-(6,7-dimethoxyquinolin-4-yl)-piperazine-1-carboxylic acid, isobutyl ester is prepared, directly, by reacting 4-chloro-6,7-dimethoxyquinoline with the appropriate ester.

Suitable amino compounds, useful for producing the compounds of this invention, in one or more steps, from the chloro, derivatives may be prepared by the following scheme:

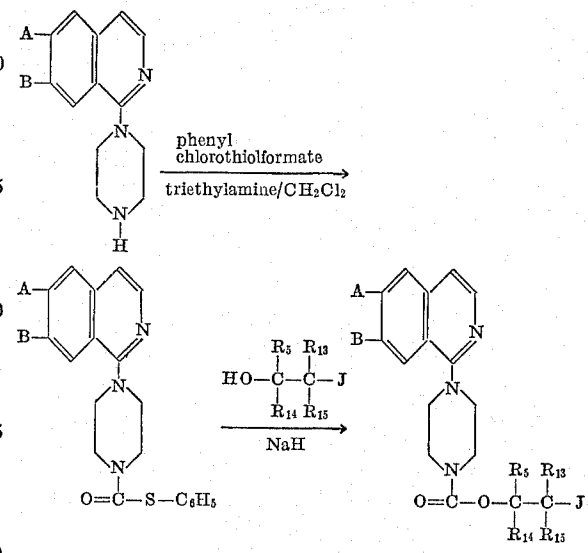


In these reactions X is chloro or bromo. The last compound is reacted directly with the 4-chloro quinazoline, the 4-chloro-quinoline or the 1-chloro-isoquinoline to form the compounds of this invention where J is chloro or bromo.

The compound where J is chloro or bromo may then be converted to the corresponding compound, where J is hydroxyl, by treatment with 0.1 N hydrochloric acid.

The compound where J is hydroxyl may then be converted to the compounds where J is acyloxy or aroyloxy by use of the appropriate acid chloride.

The compounds of Formulae II, IV, V, VA, VI, and IX may also be prepared in several stages, analogously to the scheme shown below:



Compounds where J alkylamido, arylamido or formamido may be produced from compounds where J is unsubstituted amino by treatment of the latter compounds with the appropriate acid chloride.

Variations of these procedures which also may be used to prepare the compounds of this invention from other similar compounds and by other methods will be obvious to those skilled in the art.

The well-known procedures for preparing salts of basic compounds are also applicable to the preparation of the compounds of this invention and are illustrated in the examples below. Such salts may be formed with both pharmaceutically-acceptable and pharmaceutically-unacceptable acids. By "pharmaceutically-acceptable" is meant those salt-forming acids which do not substantially increase the toxicity of the basic compound. The preferred salts, which are of particular value in therapy, are the acid addition salts. These include salts of mineral acids such as hydrochloric, hydriodic, hydrobromic, phosphoric, metaphosphoric, and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, maleic, methanesulfonic, ethansulfonic, benzenesulfonic, paratoluenesulfonic and gluconic as well as other suitable acids.

The pharmaceutically-unacceptable acid addition salts, while not useful for therapy, are vulable for use in the isolation and purification of these newly discovered compounds. Furthermore, they are useful for the preparation of the therapeutically valuable pharmaceutically-acceptable salts. Of this group, the more common salts include those formed with hydrofluoric and perchloric acids. Hydrofluoride salts are particularly useful for the preparation of the pharmaceutically-acceptable salts.

The compounds of this invention may be administered to hypertensive subjects or subjects suffering from bronchoconstriction in order to alleviate these conditions. The bronchoconstriction may be functional or may be caused by allergenic conditions or asthmatic conditions or may have come about as the result of a microbial infection. The compounds of this invention may be administered alone or in combinations with pharmaceutically-acceptable carriers. The proportion of the active ingredient to carrier is determined by the solubility and chemical nature of the therapeutic compounds, the

chosen route of administration and the needs of the standard pharmaceutical practice. For example, where these compounds are administered in tablet form, excipients such as lactose, sodium citrate, calcium carbonate and dicalcium phosphate may be used. Various disintegrants such as starch, alginic acids, and certain complex silicates, together with lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc, may also be used in producing tablets for the oral administration of these compounds. For oral administration in capsule form, lactose and high molecular weight polyethylene glycols are preferred materials for use as pharmaceutically-acceptable carriers. Where aqueous suspensions are to be used for oral administration, the compounds of this invention may be combined with emulsifying or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and their combinations may be employed as well as other materials. Solutions of the compounds of this invention in combination with other solutes such as glucose or saline may be used where the compounds are to be administered parenterally. Such aqueous solutions should be suitably buffered, if necessary, to render them isotonic.

The compounds of this invention may be administered to subjects suffering from bronchoconstriction by means of inhalators or other devices which permit the active compounds to come into direct contact with the constricted areas of the tissues of the subject.

The dosage required to reduce the blood pressure of hypertensive subjects and to relieve the bronchoconstriction in affected subjects will be determined by the nature and the extent of the hypertension or bronchconstriction. Generally, small dosages will be administered initially with gradual increase in dosage until the optimal dosage level is determined for the particular subject under treatment. It will generally be found that when the composition is administered orally, larger quantities of the active ingredient will be required in order to produce the same level of blood pressure reduction or bronchoconstriction relief as would be produced by the smaller quantity of active compound which is administered parenterally. In general, dosages will be in the range from about 0.02 to 200 milligrams of active ingredient per kilogram of body weight of subject, administered in single or multiple dosage units. Dosages at this level will effectively reduce blood pressure in hypertensive subjects and relieve bronchoconstriction in subjects suffering therefrom. Tablets containing 0.1 to 50 milligrams of active ingredient are found to be particularly useful.

The therapeutic effects of the compounds of this invention have been evaluated in guinea pigs and dogs. It was found that the compounds manifested therapeutic action over extended periods of time, were easily absorbed into the treated subjects upon administration and showed relatively small effects on the central nervous systems of the treated subjects. The effectiveness of the compounds of this invention as therapeutic agents was measured with respect to theophylline, a known bronchodilator and with respect to known hypotensive agents.

The compounds of this invention also have been observed to inhibit the activity of the enzyme phosphodiesterase, which catalyzes the conversion of adenosine-3′,5′-monophosphate (3′,5′–AMP) to adenosine-5′-monophosphate (5′–AMP). Thus, in systems containing phosphodiesterase in which it is desirable to maintain a high 3′,5′–AMP level, the instant compound might be used to great advantage. The ability of the novel compounds to inhibit the enzyme activity is of significance since it is well known that the mononucleotide 3′,5′–AMP is an important regulator of numerous cellular and tissue processes, e.g. smooth muscle relaxation, lipolysis and glycolysis. The instant compounds are tissue-specific inhibitors of the enzyme, i.e., they will inhibit the enzyme in certain tissues and not in others; therefore, when it is desirable to raise the 3′,5′–AMP level in only one of several types of tissues which are present, use of the instant compounds is particularly advantageous.

This phosphodiesterase inhibition is also significant for the relaxation of bronchial and peripheral vascular smooth muscle. Many of the novel compounds have been evaluated with respect to their ability to inhibit phosphodiesterase activity with a view to their potential activity as bronchodilators, smooth muscle relaxants or anti-hypertensives.

It will be understood that various changes in the details, materials and steps which have been herein described and illustrated in order to explain the nature of this invention may be made by those skilled in the art within the principle scope of the invention.

The following examples are given by way of illustration only and are not to be construed as limiting the scope of this invention in any way.

EXAMPLE I

Preparation of 4-(2-ethyl-6,7-dimethoxyquinazoline-4-yl)-piperazine-1-carboxylic acid, isobutyl ester

PART A.—PREPARATION OF N-CARBETHOXY-6-AMINOVERATRIC ACID

A quantity of ethyl chloroformate totaling 20.0 grams (0.185 mole) was added, dropwise, to a solution of 35.0 grams (0.177 mole) of 6-aminoveratric acid dissolved in 100 ml. of pyridine. The addition was accomplished over a 30 minute period and the temperature of the reacting mixture was always held below 60° C. The precipitation of the product began after about half of the dropwise addition had taken place. After completion of the addition, the mixture was cooled to room temperature and poured into 400 ml. of water. This mixture was filtered, washed with three 200 ml. portions of water, and dried over phosphorus pentoxide. The procedure yielded 46.0 grams of N-carbethoxy-6-aminoveratric acid as a white solid with a melting point of 211–213° C. The procedure produced a yield of 96.5 percent.

PART B.—PREPARATION OF 6-AMINOVERATRAMIDE

A slurry of 46.0 grams (0.171 mole) of N-carbethoxy-6-aminoveratric acid in 100 ml. of thionyl chloride was stirred until the exothermic reaction had subsided. The mixture was then heated for 15 minutes at reflux. The slurry was diluted with hexane and refluxed for 15 minutes after which the resultant mixture was filtered to yield 45.0 grams of crude 4,5-dimethoxy-N-carboxyanthranilic anhydride. The crude product of this step evidenced a melting point of 225–256° C. and was used, without purification, as follows.

A slurry of 35.0 grams of the crude 4,5-dimethoxy-N-carboxyanthranilic anhydride with 600 ml. of ethanol saturated with ammonia was stirred at reflux for 30 minutes while a stream of ammonia was passed through the mixture. A complete solution resulted after 15 minutes. The solution was cooled to room temperature and filtered and the filtrate was concentrated to separate 25.4 grams of crystalline 6-aminoveratramide. This sample evidenced a melting point of 133–136° C. Further crystallization of the product from benzene yielded an analytical sample which evidenced a melting point of 147–148° C.

Analysis.—Calc'd for $C_9H_{12}H_2O_3$ (percent): C, 55.09; H, 6.17; N, 14.28. Found (percent): C, 55.24; H, 5.83; N, 14.54.

PART C.—PREPARATION OF 6-PROPIONAMIDO-VERATRAMIDE

A dropwise addition of 10.1 grams (0.1 mole) of propionyl chloride was made to a solution of 19.6 grams (0.1 mole) of 6-amino-veratramide in 50 ml. of pyridine. The solution was held at a temperature below 10° C. during the addition. Precipitation was initiated about 5 minutes after the completion of the addition and the

resultant mixture was permitted to attain room temperature. The mixture was combined with 400 ml. of water, with constant stirring, and the crystalline product was removed by filtration. The filter cake was washed with water and then dried over phosphorus pentoxide. This procedure afforded 21.6 grams of 6-propionamido-veratramide which was separated as a white amorphous solid. The melting point of this solid was 196–197° C. and it represented a yield of 86.5 percent. Recrystallization of a 2.5 gram portion of the white solid from 60 ml. of methanol yielded 2.3 grams of white crystals which were used as the analytical sample. The recrystallized sample had a melting point of 196–197° C. and was found to be homogeneous by thin layer chromatography.

Analysis.—Calc'd for $C_{12}H_{16}N_2O_4$ (percent): C, 57.13; H, 6.39; N, 11.11. Found (percent): C, 57.09; H, 6.27; N, 11.04.

PART D.—PREPARATION OF 2-ETHYL-6,7-DIMETHOXY-4(3H)-QUINAZOLINONE

A mixture containing 17.1 grams (0.068 mole) of 6-propionamido-veratramide, 4.45 grams (0.079 mole) of potassium hydroxide and 100 ml. of absolute ethanol was stirred and refluxed under a nitrogen atmosphere for 90 minutes. The resultant clear yellow solution was evaporated to remove the bulk of the ethanol and the residue was added to 500 ml. of water and acidified with glacial acetic acid to pH of 6. The mixture was filtered and the filter cake was washed with ethanol and water. The solid was dried over phosphorus pentoxide and 16.0 grams of product were obtained as a white, microcrystalline solid. The white solid, which represented a yield of 100 percent, had a melting point of 252–253° C. and was homogeneous by thin layer chromatography.

PART E.—PREPARATION OF 2-ETHYL-4-CHLORO-6,7-DIMETHOXYQUINAZOLINE

A mixture of 16.0 grams (0.068 mole) of 2-ethyl-6,7-dimethoxy-4-(3H)-quinazolinone in 160 ml. of phosphorus oxychloride was stirred with reflux for 3.5 hours. The resulting solution, which was formed after 2.5 hours of stirring at reflux, was concentrated to an oily residue which was dissolved in 500 ml. of methylene chloride. This solution was added to 500 ml. of concentrated ammonium hydroxide solution with constant stirring. The methylene chloride layer was drawn off and the resultant aqueous phase was extracted with two 200 ml. portions of methylene chloride. The combined organic phases were washed with two 200 ml. portions of water and dried over sodium sulfate. Evaporation of the methylene chloride yielded 15.3 grams of 2 - ethyl-4-chloro-6,7-dimethoxyquinazoline as a homogeneous yellow amorphous solid. The solid evidenced a melting point of 150–154° C. and represented a yield of 89 percent. An analytical sample was obtained by recrystallization from a methylene chloride-hexane mixture. The product, which was separated as small colorless needles, evidenced a melting point of 155–156.5° C. and was homogeneous by thin layer chromatography.

PART F.—PREPARATION OF 4 - (2 - ETHYL-6,7-DIMETHOXYQUINAZOLIN - 4 - YL)-PIPERAZINE-1-CARBOXYLIC ACID, ISOBUTYL ESTER

A mixture of 5.0 grams (0.02 mole) of 2-ethyl-4-chloro-6,7-dimethoxyquinazoline and 7.43 grams (0.04 mole) of piperazine-1-carboxylic acid, isobutyl ester was dissolved in 50 ml. of absolute ethanol and was stirred at reflux for 1 hour. The resultant clear solution was concentrated to a crystalline residue and mixed with 150 ml. of boiling hexane. The resultant mixture was filtered and the filtrate was concentrated. On cooling, 6.4 grams of 4-(2-ethyl-6,7-dimethoxyquinazolin - 4-yl)-piperazine-1-carboxylic acid, isobutyl ester was deposited as a white microcrystalline solid which evidenced a melting point of 98–101° C. and was homogeneous by thin layer chromatography. This amount represented a yield of 79.5 percent. An analytical sample was obtained by a further recrystallization from hexane to yield a product comprised of white needles which evidenced a melting point of 96–97° C.

EXAMPLE II

Preparation of 4-dimethylamino-6,7-dimethoxyquinazoline

PART A.—PREPARATION OF 6,1-DIMETHOXY-4-(3H)-QUINAZOLINONE

The procedures of Part A and Part B of Example I were carried out to prepare 6-aminoveratramide.

A mixture of 25.4 grams (0.129 mole) of 6-aminoveratramide and 50 ml. of 97 percent formic acid was stirred at reflux for 2 hours to yield complete dissolution of the solid. Upon cooling to room temperature, crystallization occurred. The mixture was diluted with 200 ml. of ethanol and filtered. The filter cake was dried and 21.5 grams of white solid was obtained. The white solid, which evidenced a melting point of 293–294° C., was homogeneous by thin layer chromatography. The yield obtained by this procedure was 81 percent. An analytical sample was obtained by recrystallization from dimethylformamide and white needles, which melted at 296–298° C., were obtained.

Analysis.—Calc'd. for $C_{10}H_{10}N_2O_3$ (percent): C, 58.25; H, 4.89; N, 13.58. Found (percent): C, 58.10; H, 5.01; N, 13.49.

The hydrochloride was prepared by the method of Example II and evidenced a melting point of 260–261° C.

Analysis.—Calc'd. for $C_{10}H_{10}N_2O_3HCl$ (percent): C, 49.49; H, 4.57; N, 11.54; Cl, 14.61. Found (percent): C, 49.68; H, 4.76; N, 11.33; Cl, 14.85.

PART B.—PREPARATION OF 4-CHLORO-6,7-DIMETHOXLQUINAZOLINE

A mixture of 21.5 grams (0.104 mole) of 6,7-dimethoxy-4(3H)-quinazolinone and 215 ml. of phosphorus oxychloride was stirred at reflux for 4 hours. A complete solution resulted after one hour. The solution was concentrated to an oily residue which was added slowly to 400 ml. of concentrated ammonium hydroxide solution. The resultant solid was filtered, washed well with water and dried in air to yield 19.5 grams of solid material which evidenced a melting point of 181–185° C. Upon recrystallization from ethanol, 14.5 grams of a white crystalline product, which evidenced a melting point of 184–186° C., was produced in a yield of 62.5 percent.

PART C.—PREPARATION OF 4-DIMETHYLAMINO-6,7-DIMETHOXYQUINAZOLINE

A stainless steel pressure bottle was charged with 4.0 grams (0.0179 mole) of 4-chloro-6,7-dimethoxyquinazoline and 90 ml. of a 1:2 dimethylamine-ethanol solution. The bottle was heated at 130° C. for 4 hours. Upon cooling, 1.7 grams of white crystalline 4-dimethylamino-6,7-dimethoxyquinazoline was deposited. The product, which manifested a melting point of 157–159° C., was obtained in a yield of 41 percent. The filtrate was evaporated to dryness and the crude residue, which totalled 3.3 grams, was eluted from a Florisil column with benzene (7 x 150 ml. fractions) to separate a further yield of 1.2 grams of crystalline material which mainifested a melting point of 158–160° C. This was identical with the first product crop and both crops showed a single spot upon thin layer chromatography. The total yield for this procedure was 70 percent.

Analysis.—Calc'd. for $C_{12}H_{15}N_3O_2$ (percent): C, 61.78; H, 6.48; N, 18.02. Found (percent): C, 61.97; H, 6.37; N, 18.05.

EXAMPLE III

Preparation of 4-piperazinyl-6,7-dimethoxyquinazoline

The procedure of Parts A and B of Example II were used to prepare 4-chloro-6,7-dimethoxyquinazoline.

A solution of 20.5 grams (0.09 mole) of 4-chloro-6,7-dimethoxyquinazoline dissolved in 1 liter of chloroform

was added, dropwise, over a 24 hour period, to a stirred, refluxing solution of 77.4 grams (0.9 mole) of anhydrous piperazine dissolved in 1 liter of absolute ethanol. The resultant solution was evaporated to a crystalline residue which was dissolved in 600 ml. of water. The aqueous solution was extracted with four 200 ml. portions of methylene chloride and the combined extracts were dried over sodium sulfate. Evaporation of the solvent afforded 23.7 grams of a crystalline residue which melted at 143–147° C. The residue was recrystallized from 150 ml. of ethyl acetate to separate 18.2 grams of white rods, with a melting point of 147–148° C., which were homogenous by thin layer chromatography. Further recrystallization from ethyl acetate provided an analytical sample, as white rods, which melted at 150–151.5° C. The procedure afforded a yield of 74 percent.

Analysis.—Calc'd. for $C_{14}H_{18}N_4O_2$ (percent): C, 61.29; H, 6.61; N, 20.43. Found (percent)3: C, 61.24; H, 6.40; N, 20.26.

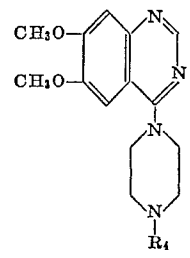
EXAMPLE IV

Bronchodilator activity

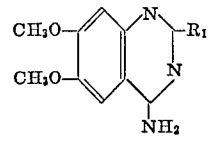
Conscious female guinea pigs, which had been fasted for 12 hours, recived oral or parenteral dosages of the compound which was to be tested for effectiveness. Control animals received doses of saline solution which did not contain the compound which was under test. Subsequent to this administration, each animal was challenged with histamine aerosol.

The challenge procedure consisted of spraying a 0.4 percent aqueous solution of histamine, at a pressure of 5 lb./in.^{2} into an 8 x 8 x 12 inch plastic container for one minute. Immediately after the container was subjected to the histamine spray the animal was placed within it. At the end of one minute of exposure, the respiratory status, which is a reflection of bronchoconstriction, was evaluated. Evaluation levels were designated and scored as normal breathing (0), slightly deepened breathing (1), labored breathing (2), severely labored breathing and ataxia (3) and unconsciousness (4). Each group of animals contained 8 to 10 individuals and a control group containing the same approximate number was used. The scores for the control group and the group which had been treated with the compound under test were compared and the difference was expressed as percent protection.

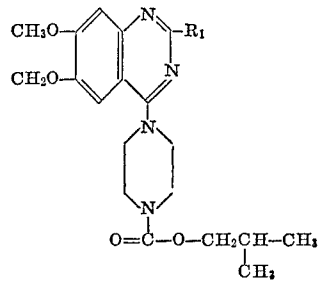
The doses, which were given orally, were 60 mg./kg. and the animals were challenged with histamine 60 minutes later. The standard compound used was theophylline which gave 25 percent protection after a dose of 60 mg./kg. was administered orally and the animal was challenged one hour later. When the compounds listed in Table VI below were administered according to this procedure and the animals were challenged accordingly, the following percent protection was observed.



R_4:	Percent protection
C_6H_5—	27
CH_3CH_2—OOC—	28
$CH_3CH_2CH_2OOC$—	40
$CH_3(CH_2)_3OOC$—	14
$(CH_3)_2CHCH_2OOC$—	50
$CH_3(CH_2)_4OOC$—	20
$CH_3(CH_2)_5OOC$—	13
CH_3OC—	16
$CH_3(CH_2)_5OC$—	23
$(Cl)_3COC$—	16



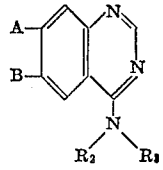
R_1:	Percent protection
H—	42.
CH_3CH_2—	32.
CH_3—	Short duration.



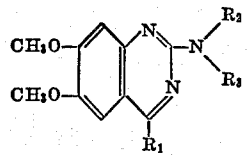
R_1:	Percent protection
H—	50
CH_3—	[1] 40
CH_3CH_2—	56
$CH_3CH_2CH_2$—	53
$(CH_3)_2CH$—	23
$(CH_3)_3C$—	19

[1] After 15 minutes.

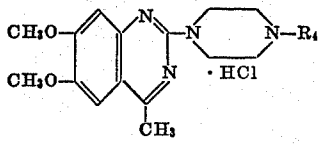
TABLE VI



A	B	R_2	R_3	Percent protection
$(CH_3)_2CH$—O—	$(CH_3)_2CH$—O—	H—	H—	19
CH_3O—	CH_3O—	H—	H—	42
CH_3O—	CH_3O—	H—	CH_3—	52
CH_3O—	CH_3O—	H—	CH_3CH_2—	22
CH_3O—	CH_3O—	H—	$CH_3(CH_2)_2$—	10
CH_3O—	CH_3O—	H—	$(CH_3)_2CH$—	41
CH_3O—	CH_3O—	H—	Cyclopropyl—	39
CH_3O—	CH_3O—	CH_3—	CH_3—	47
CH_3O—	CH_3O—	CH_3CH_2—	CH_3CH_2—	53



R_1	R_2	R_3	Percent protection
CH_3—	H—	H—	41
CH_3—	CH_3CH_2—	CH_3CH_2—	53
CH_3—	CH_3—	CH_3—	27



R_4	Percent protection
	22
CH_3CH_2OOC—	41
CH_2CHCH_2—	16

EXAMPLE V

Preparation of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-chloropropyl ester

To a cold (0° C.) solution of 2.74 g. (0.010 mole) of 4-piperazinyl-6,7-dimethoxyquinazoline, prepared by the method of Example III, and 1.10 g. (0.010 mole) of triethylamine in 40 ml. of methylene chloride was added a solution of 1.7 g. (0.010 mole); of 2-methyl-2-chloropropyl chloroformate in 20 ml. of methylene chloride, dropwise, over 10 minutes. After warming to room temperature, the cloudy mixture was diluted with 50 ml. of methylene chloride, washed with 50 ml. of water and dried over sodium sulfate. Evaporation of the solvent left 4.3 g. of white crystalline solid, M.P. 140–146° C. Recrystallization from acetone-water mixture produced 2.6 g. (63.5%) of the analytical sample as a white crystalline solid, M.P. 158–159° C.

Analysis.—Calc'd. for $C_{19}H_{25}O_4N_4Cl$ (percent): C, 55.80; H, 6.19; N, 13.70; Cl, 8.67. Found (percent): C, 55.50; H, 6.15; N, 13.77; Cl, 8.59.

EXAMPLE VI

Preparation of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-hydroxypropyl ester

A solution of 6.0 g. (0.0147 mole) of crude 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-chloropropyl ester in 225 ml. of 0.1 N hydrochloric acid was allowed to reflux for 1 hour. The cooled solution was extracted with three 100 ml. portions of methylene chloride, and the aqueous phase subsequently made basic with dilute sodium hydroxide solution and extracted with three 100 ml. portions of methylene chloride. These latter organic extracts were combined, dried over sodium sulfate and evaporated and the resulting residue recrystallized from a chloroform-ethyl acetate mixture to separate 2.1 g. (37%) of white prisms M.P. 199–220° C.

Analysis.—Calc'd. for $C_{19}H_{26}O_5N_4$ (percent): C, 58.45; H, 6.71; N, 14.35. Found (percent): C, 58.36; H, 6.63; N, 14.62.

EXAMPLE VII

Preparation of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-propenyl ester, hydrochloride

A mixture of 40.4 g. (0.18 mole) of 4-chloro-6,7-dimethoxyquinazoline, prepared by the method of Part B of Example II, and 33.0 g. (0.18 mole) of piperazine-1-carboxylic acid, 2-methyl-2-propenyl ester in 400 ml. of ethanol was refluxed for 4 hours, and then evaporated to dryness to leave 73 g. (100%) of crystalline solid. This was dissolved in 600 ml. of water and extracted with four 500 ml. portions of methylene chloride. The combined extracts were evaporated to a volume of 500 ml. and ethyl acetate added until crystallization began. Filtration separated 48.0 g. (65%) of the hydrochloride salt of the product as a pale yellow microcrystalline solid M.P. 212–213° C. (dec.).

A second crop (6.2 g., 8.4%) of product as a yellow microcrystalline solid, M.P. 210–213° C. (dec.) was obtained by concentration of the filtrate. This material was homogenous by thin layer chromatography.

EXAMPLE VIII

Preparation of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-hydroxypropyl ester

To 200 ml. of 50% sulfuric acid-water mixture was added 25 g. (0.0615 mole) of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-propenyl ester, hydrochloride. The resulting yellow solution was stirred at room temperature for 1 hour, poured into 200 g. of ice and made basic with 40% sodium hydroxide solution, keeping the temperature below 40° C. The resulting solution was extracted with four 200 ml. portions of methylene chloride, and the combined organic extracts were extracted with 0.5 N hydrochloric acid and finally with three 100 ml. portions of water. The combined aqueous extracts were made basic with 40% sodium hydroxide solution and extracted with three 200 ml. portions of methylene chloride. The latter methylene chloride extracts were combined, dried over sodium sulfate and evaporated to leave 18.0 g. (75%) of crystalline solid M.P. 192–195° C. This was recrystallized from chloroform-ethyl acetate mixture to separate 14.5 g. (80%) of analytically pure product M.P. 198–199.5° C.

EXAMPLE IX

Five parts, by weight, of the 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-hydroxypropyl ester is dissolved in pyridine at 0° C. and an excess of propionyl chloride is added, dropwise. At the completion of the addition, the resulting mixture is refluxed for 1 hour, cooled, diluted with water and extracted three times with methylene chloride. After washing, the combined methylene chloride layers with dilute acid, they are dried and evaporated to dryness to give 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-propionoxypropyl ester which is purified by recrystallization if necessary.

In a similar manner, the 2-methyl-2-butyryloxypropyl ester, the 2-methyl-2-naphthoyloxypropyl ester, the 2-methyl-2-benzoxypropyl ester and the 2-methyl-2-acetoxypropyl ester are prepared.

EXAMPLE X

Preparation of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-dimethylaminoethyl ester

PART A.—PREPARATION OF 4-(6,7-DIMETHOXYQUINAZOLIN-4-YL)-PIPERAZINE-1-THIOL CARBOXYLIC ACID, PHENYL ESTER

To a cold (0°) solution of 20.0 g. (0.073 mole) of 4-piperazinyl-6,7-dimethoxyquinazoline, prepared by the

methods of Example III, and 8.05 g. (0.084 mole) of triethylamine in 150 ml. of methylene chloride was added, dropwise, 12.9 g. (0.075 mole) of phenyl chlorothiolformate. The resulting mixture was allowed to stir at room temperature for 15 minutes and 100 ml. of methylene chloride was added. This solution was washed with two 50 ml. portions of water, dried over sodium sulfate and evaporated to separate 27.46 g. of crude product, M.P. 146–151° C. Recrystallization from 500 ml. of methanol separated 15.84 g. (53%) of product as o pale yellow microcrystalline solid, M.P. 170–173° C. An additional 5.59 g. (19%), M.P. 166–170° C., of product was obtained from further concentration of the mother liquor.

PART B.—PREPARATION OF 4-(6,7-DIMETHOXYQUINAZOLIN-4-YL)-PIPERAZINE-1-CARBOXYLIC ACID, 2-DIMETHYLAMINOETHYL ESTER

To a suspension of 1.60 g. (0.044 mole) of sodium hydride (60% mineral oil dispersion) in 50 ml. of tetrahydrofuran was added 3.92 g. (0.044 mole(of 2-dimethylaminoethanol and the solution refluxed until gas evolution ceased (45 minutes). The resulting solution was cooled to room temperature and a solution of 4.1 g. (0.01 mole) of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine - 1 - thiol carboxylic acid, phenyl ester in 15 ml. of tetrahydrofuran was added at once and the solution stirred at room temperature for 45 minutes. After dilution with 50 ml. of water, the solution was concentrated to remove the tetrahydrofuran, and extracted with four 50 ml. portions of methylene chloride. The combined extracts were dried over sodium sulfate and evaporated to separate 4.39 g. of crude product, M.P. 110–114° C. Recrystallization from ethylacetatehexane mixture gave 2.52 g. (65%) of product as an off-white microcrystalline solid M.P. 100–104° C.

The corresponding hydrochloride evidenced a melting point of 230–232° C.

In a similar manner, the compound 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine - 1 - carboxylic acid, 2-diethylaminoethyl ester was prepared, M.P. 90–93° C.; recrystallized from isopropyl ether; M.P. of hydrochloride 151° C.

EXAMPLE XI

When the procedure of Example X are employed, using the appropriate aminoalkanol or aminocarbinol in the procedure of Part B of Example X and the product of Part A of Example X, the 4-(6,7-dimethoxyquinazoline-4-yl(-1-carboxylic acid, 2-methyl-2-ethylmethylaminopropyl ester, the 2-methyl-2-aminopropyl ester, the 2-methyl-2-anilinopropyl ester, the 2-methyl-2-butylaminopropyl ester, the 2-methyl-2-m-tolylaminopropyl ester, the 2-methyl-2-naphthylaminopropyl ester, the 2-methyl-2-pyrrolinylpropyl ester, the 2-methyl-2-piperidinylpropyl ester and the 2-methyl-2-homopiperidinylpropyl ester are produced.

When the procedures of Example X are employed, using the appropriate 2-alkoxycarbinol, 2-alkoxyalkanol, 2-aryloxycarbinol or 2-aryloxyalkanol in place of the 2-dimethylaminoethanol of Part B of Example X together with the product of Part A of Example X, the 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-propoxypropyl ester, the 2-methyl-2-isobutoxypropyl ester, the 2-methyl-2-phenoxypropyl ester, the 2-methyl-2-naphthoxypropyl esters, the 2-methyl-2-xyloylpropyl ester and the 2-methyl-2-methoxypropyl ester may be formed.

EXAMPLE XII

Five parts, by weight of 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-aminopropyl ester, prepared by the method of Example X, is dissolved in pyridine. To the solution is added, dropwise, at 0° C., a slight excess of propionyl chloride. After the addition is complete, the resultant mixture is heated at reflux. The cooled mixture is diluted with water and the product 4-(6,7-dimethoxyquinazolin-4-yl)-piperazine - 1 - carboxylic acid, 2-methyl-2-ethamidopropyl ester is removed by filtration or extraction of the aqueous solution with methylene chloride.

In a similar manner, the 2-methyl-2-formamidopropyl ester and the 2-methyl-2-butyramidopropyl ester are formed.

EXAMPLE XIII

Preparation of 4-(6,7-dimethoxyquinolin-4-yl)-piperazine-1-carboxylic acid, isobutyl ester

A mixture of 3.4 g. (0.0152 mole) of 4-chloro-6,7-dimethoxyquinoline, prepared by the general methods given by B. Riegel et al., J. Am. Chem. Soc., 68, 1264 (1946), and 5.65 g. (0.031 mole) of piperazine-1-carboxylic acid, isobutyl ester in 80 ml. of ethanol was heated at 130° C. for 2 hours. The resulting solution was concentrated to dryness and the residue slurried in water and filtered to separate 6.1 g. of crude product. Recrystallization from 50 ml. of ethanol afforded 4.3 g. (76%) of an off-white crystalline product, M.P. 172–173° C.

Analysis.—Calc'd. for $C_{20}H_{27}O_4N_3$ (percent): C, 64.32; H, 7.29; N, 11.25. Found (percent): C, 64.13; H, 7.16; N, 11.36.

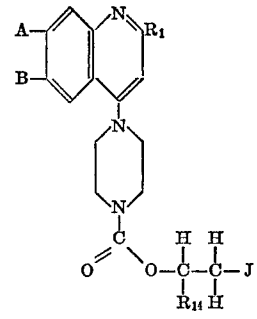
EXAMPLE XIV

Preparation of 4-(6,7-dimethoxyquinolin-4-yl)-piperazine-1-carboxylic acid, 2-methyl-2-hydroxypropyl ester

The methods used in Example VIII were used to prepare the 2-methyl-2-hydroxypropyl ester which evidenced a melting point of 172–173° C. and was recrystallized from ethyl acetate.

EXAMPLE XV

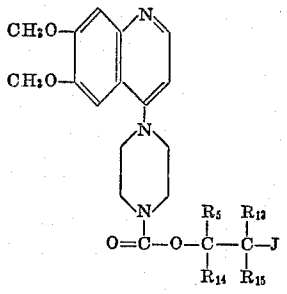
The methods of Examples V to XIV inclusive are used to prepare compounds of the following formulae:

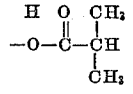
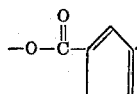
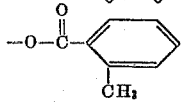
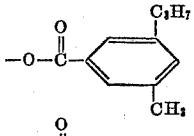
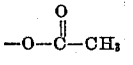
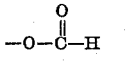
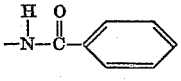
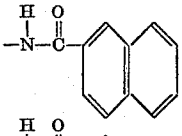
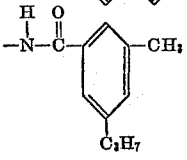
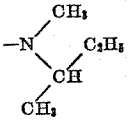
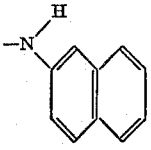


A	B	R_1	R_{14}	J
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CH_3O	CH_3CHCH_3 (O, CH_2)	C_3H_7	CH_3	OH
$C_6H_{13}O$	CH_3O	Isobutyl	C_2H_5	Cl
$CH_3-CH-CH_3$ ($(CH_2)_3$, O)	CH_3O	C_6H_{13}	CH_3	OH
OH	OH	CH_3	H	OH
	Benzo	CH_3	H	OH
CH_3	CH_3O-	H	H	H
CH_3	CH_3	CH_3	H	H
H	CH_3O	H	H	Cl
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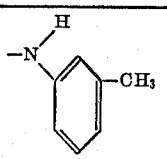
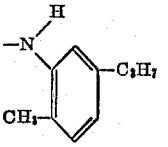
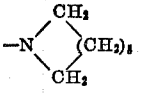
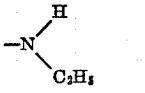
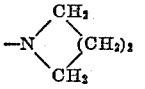
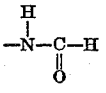
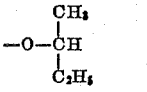
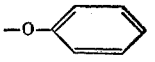
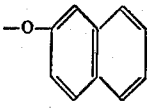
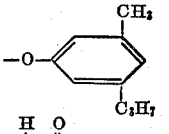
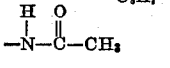
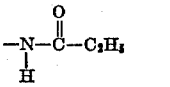
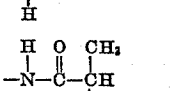
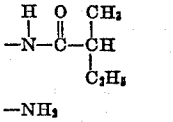
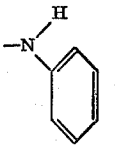
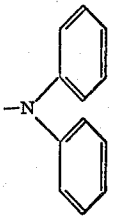
EXAMPLE XVI

The methods of Examples V to XIV inclusive are used to prepare compounds of the following formula:

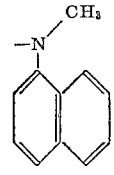
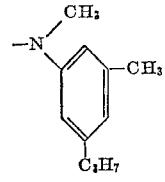


R_5	R_{13}	R_{14}	R_{15}	J
CH_3	H	CH_3	H	H
C_2H_5	H	H	C_2H_5	OH
Isobutyl	H	H	H	Br
CH_3	CH_3	C_2H_5	H	Cl
CH_3	H	Isobutyl	H	NH_2
CH_3OH	H	H	Isobutyl	H
CH_3	Isobutyl	H	CH_3OH	
CH_3	C_3H_7	H	H	
H	H	H	H	
H	CH_3	H	H	
H	H	H	H	
$-(CH_2)_6-$		H	CH_3	
$-(CH_2)_7-$		C_2H_5	H	
H	H	H	H	
H	H	CH_3	H	
CH_3	H	H	H	
H	CH_3	CH_3	H	
H	C_2H_5	H	H	
H	H	H	H	

TABLE—Continued

R_5	R_{13}	R_{14}	R_{15}	J
H	H	H	H	
CH_3	H	H	H	
	H	H	H	
	H	CH_3	H	
H	H	H	CH_3	
H	H	CH_3	H	
H	CH_3	CH_3	H	$-O-CH_3$
H	H	H	CH_3	$-O-C_2H_5$
H	CH_3	H	H	
CH_3	H	H	H	
H	CH_3	C_2H_5	H	
H	H	H	H	
H	H	H	H	
H	H	H	H	
H	H	H	H	
H	CH_3	H	H	
CH_3	H	H	H	$-NH_2$
CH_3	H	H	H	
H	H	H	H	

TABLE—Continued

R_5	R_{13}	R_{14}	R_{15}	J
H	H	H	H	
H	H	H	H	

EXAMPLE XVII

Preparation of 4-(6,7-dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid, isobutyl ester

PART A.—PREPARATION OF N-CARBETHOXYHOMOVERATRYLAMINE

To a solution of 362 g. (2.0 mole) of homoveratrylamine in 500 ml. dry benzene was added a solution of 109 g. (1.0 mole) of ethyl chloroformate in 200 ml. of benzene, dropwise, keeping the temperature at 50–55° C. The resulting slurry was stirred for 16 hours at room temperature and poured into 500 ml. of water. The benzene layer was separated, washed with 500 ml. of saturated sodium bicarbonate solution and dried over sodium sulfate. Evaporation of solvent and distillation of the residual oil afforded 186 g. (74%) of clear colorless liquid; B.P. 174–177° C. (0.2 mm.), which crystallized on standing to give the product as a white crystalline solid, M.P. 61–62° C.

PART B.—PREPARATION OF 6,7-DIMETHOXY-3,4-DIHYDRO-1(2H)-ISOQUINOLINONE

To one liter of stirred polyphosphoric acid was added 330 g. (1.3 moles) on N-carbethoxyhomoveratrylamine. The resulting mixture was stirred at 140° C. for 30 minutes and poured onto 2 liters of ice-water. The aqueous solution was made basic with ammonium hydroxide and extracted several times with chloroform. The combined extracts were dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from methylene chloride-ethyl acetate to afford 120 g. (44.5%) of white plates, M.P. 159–161° C.

PART C.—PREPARATION OF 6,7-DIMETHOXY-1(2H)-ISOQUINOLINONE

A mixture of 46.0 g. (0.222 mole) of 6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinone and 7.0 g. of 25% palladium on carbon was stirred at 240° C. for 30 minutes (when hydrogen evolution had ceased) under a nitrogen atmosphere. The mixture was cooled to room temperature and leached several times with hot chloroform. The combined chloroform extracts were concentrated to dryness to afford 39.0 g. (86%) of white crystalline product, M.P. 228–232° C.

PART D.—PREPARATION OF 1-CHLORO-6,7-DIMETHOXYISOQUINOLINE

A mixture containing 39 g. (0.191 mole) of 6,7-dimethoxy-1(2H)-isoquinolinone and 200 ml. of phosphorous oxychloride was stirred at reflux for 1 hour. The resulting amber solution was concentrated to dryness and the residue dissolved in methylene chloride and added slowly to 100 ml. of concentrated ammonium hydroxide solution. The methylene chloride layer was separated and the aqueous layer extracted with three 100 ml. portions of methylene chloride. The combined organic extracts were dried over sodium sulfate and evaporated to afford 35.0 g. (82%) of white crystalline product, M.P. 135–137° C.

Analysis.—Calcd. for $C_{11}H_{10}NO_2Cl$ (percent): C, 59.07; H, 4.51; N, 6.26; Cl, 15.85. Found (percent): C, 59.33; H, 4.60; N, 6.30; Cl, 16.06.

PART E.—PREPARATION OF 4-(6,7-DIMETHOXYISOQUINOLIN-1-YL) - PIPERAZINE-1-CARBOXYLIC ACID, ISOBUTYL ESTER

A mixture containing 4.0 g. (0.018 mole) of 1-chloro-6,7-dimethoxyisoquinoline and 6.7 g. (0.036 mole) of piperazine-1-carboxylic acid, isobutyl ester in 80 ml. of ethanol was heated at 130° C. for 16 hours in a closed vessel. The resulting amber solution was concentrated, slurried in water and filtered to give 4.3 g. of crude product. This was recrystallized from 30 ml. of methanol to afford 2.58 g. (38.5%) of product as slightly pink needles, M.P. 130–132° C.

Analysis.—Calcd. for $C_{20}H_{27}N_3O_4$ (percent): C, 64.32; H, 7.29; N, 11.25. Found (percent): C, 64.47; H, 7.16; N, 11.29.

EXAMPLE XVIII

Preparation of 4-(6,7-dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid esters

The 1-chloro-6,7-dimethoxyisoquinoline, produced by the methods of Part D of Example XVII was reacted with the appropriate piperazine-1-carboxylic acid ester, according to the methods of Part E of Example XVII to yield the following compounds:

4 - (6,7 - dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid, ethyl ester; M.P. 130–131° C.; recrystallized from isopropyl ether; M.P. of hydrochloride salt 107–108° C. (decomposition).

The methods of Example VIII were used to prepare the following compound:

4 - (6,7 - dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid, 2-methyl-2-hydroxypropyl ester; M.P. 133–134° C.; recrystallized from ethyl acetate-hexane; M.P. of hydrochloride salt 110° C. (decomposition).

EXAMPLE XIX

Preparation of 1-ethylamino-6,7-dimethoxyisoquinoline

The 1-chloro-6,7-dimethoxyisoquinoline, produced by the methods of Part D of Example XVII was reacted with ethylamine, according to the methods of Part E of Example XVII, to yield 1-ethylamino-6,7-dimethoxyisoquinoline, which evidenced a melting point of 194–195° C. and was recrystallized from methanol-water. The hydrochloride salt evidenced a melting point of 224–225° C. (decomposition).

EXAMPLE XX

Preparation of 1-piperazinyl-6,7-dimethoxyisoquinoline

A solution of 84.0 g. (0.243 mole) of 4-(6,7-dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid, ethyl ester, prepared by the methods of Example XVIII, in one liter of methanol and 250 ml. of 30% sodium hydroxide solution was refluxed for 18 hours. The resulting suspension was concentrated to remove the methanol, diluted with 500 ml. of water and extracted with three 250 ml. portions of methylene chloride. The combined extracts were dried over sodium sulfate and concentrated to 250 ml. To this was added 700 ml. of isopropyl ether and the solution concentrated to 300 ml., chilled in an ice bath and filtered to sepaarte 51 g. (77%) of white crystalline product M.P. 134–135.5° C. An additional 15 g. (22.6%) of material was obtained by further concentration of the mother liquor.

EXAMPLE XXII

Preparation of 4-(6,7-dimethoxyisoquinolin-1-yl)-piperazine-1-carboxylic acid, 2-dimethylaminoethyl ester

PART A.—PREPARATION OF 4-(6,7-DIMETHOXYISOQUINOLIN-1-YL)-PIPERAZINE-1-THIOL CARBOXYLIC ACID, PHENYL ESTER

To a cold (0° C.) solution of 19.0 g. (0.0695 mole) of 1-piperazinyl-6,7-dimethoxyisoquinoline, prepared by the

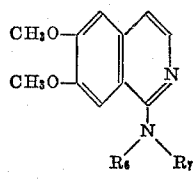
methods of Example XX, and 7.65 g. (0.076 mole) of triethylamine in 100 ml. of methylene chloride was added dropwise, 12.0 g. (0.0695 mole) of phenyl chlorothiolformate. The resulting suspension was allowed to stir at room temperature for 15 minutes and diluted with 100 ml. of methylene chloride. This solution was washed with two 50 ml. portions of water, dried over sodium sulfate and concentrated to a crystalline residue. The residue was recrystallized from 100 ml. of methanol to separate 18.7 g. (66%) of product as a pale yellow crystalline solid, M.P. 137–138° C.

PART B.—PREPARATION OF 4-(6,7-DIMETHOXYISOQUINOLIN-1-YL) - PIPERAZINE-1-CARBOXYLIC ACID, 2-DIMETHYLAMINOETHYL ESTER

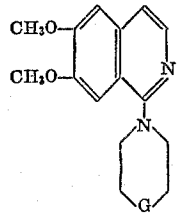
To a suspension of 1.6 g. (0.044 mole) of sodium hydride (60% mineral oil dispersion) in 100 ml. of tetrahydrofuran was added 3.92 g. (0.044 mole) of 2-dimethylaminoethanol and the solution refluxed until gas evolution ceased (45 minutes). After cooling to room temperature 4.1 g. (0.01 mole) of 4-(6,7-dimethoxyisoquinolin-1-yl)-piperazine-1-thiolcarboxylic acid, phenyl ester was added and the solution stirred at room temperature for 30 minutes. This was diluted with 70 ml. of water and concentrated to remove the tetrahydrofuran, and the resulting solution extracted with three 100 ml. portions of methylene chloride. The combined extracts were dried over sodium sulfate and evaporated to leave a viscous oil which was triturated with isopropyl ether to separate 3.1 g. (80%) of white crystalline product M.P. 114–115° C. Recrystallization from methylene chloride-isopropyl ether mixture gave 2.3 g. of white crystalline product, M.P. 115° C.

EXAMPLE XXII

The procedures of Examples V to XIV and XVII to XXI inclusive were used to produce the compounds of the following formulae:

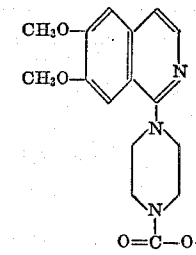


R_6	R_7	M.P. base, ° C.	M.P. hydrochloride, ° C.	Recrystallization solvent
H	$CH(CH_3)_2$	138–140	200–204	Methanol.
CH_3	CH_3	72–75	148–151	Purified by chromatography;
CH_2CH_3	CH_2CH_3	137–138.5	189–191	Acetone-water.



G	M.P. base, ° C.	M.P. hydrochloride, ° C.	Recrystallization solvent
$-N-CH_3$	163–166	220–225	Ethyl acetate.
$-N-C_6H_5$	138–141	222–228	Methanol.
$-N-\overset{O}{\overset{\|}{C}}-CH_3$	137–138	[1] 157–8	Methylene chloride-isopropyl ether.
$-N-\overset{O}{\overset{\|}{C}}-CH_2CH_3$	146–147	[1] 135–7	Do.

[1] Decomposition.

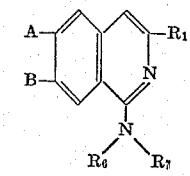


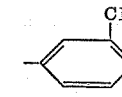
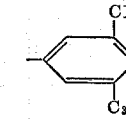
R	M.P. base, ° C.	M.P. hydrochloride, ° C.	Recrystallization solvent
$-CH_2CH_2Cl$	137.5–8	[1] 105–6	Methanol-water.
$-CH(CH_3)_2$	155–6	[1] 102–4	Methanol.
$-CH_2CH_2CH_3$	137–8	[1] 120–3	Do.
$-(CH_2)_2N(C_2H_5)_2$	103–4	78–91	Isopropyl ether.
$-(CH_2)_2N(CH_3)_2$	115	[1] 169–72	Methylene chloride-isopropyl ether.
$-(CH_2)_2NH_2$	134–7	[1] 173–5	Ethyl acetate-hexane.
$-(CH_2)_2OCH_3$	119–20	[1] 103–5	Do.

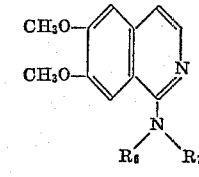
[1] Decomposition.

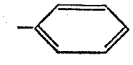
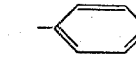
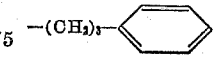
EXAMPLE XXIII

The procedures of Examples V to VIII and XVII to XXII inclusive are used to prepare compounds of the following formulae:



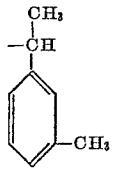
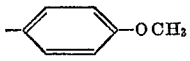
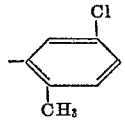
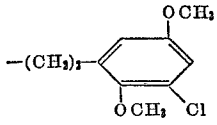
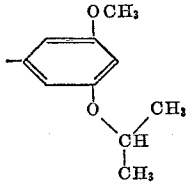
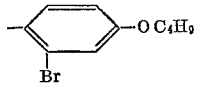
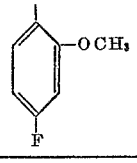
A	B	R_1	R_6	R_7
	Benzo	CH_3	H	CH_3
	$-O-CH_2-O$	C_2H_5	Isobutyl	H
	$-O-(CH_2)_2-O-$	Isobutyl	H	Phenyl.
	$-O-(CH_2)_4-O-$	C_6H_{13}	H	Naphthyl.
CH_3O-	C_2H_5O	H	C_6H_{13}	CH_3
CH_3	OH	CH_3		$-(CH_2)_2-$
OH	OH	H		$-(CH_2)_7-$
CH_3O-	CH_3O-	H	H	$-CH_2CH=CH_2$
OH	$-O-\underset{\|}{\overset{CH_3}{CH}}-C_2H_5$	H	H	
CH_3	CH_3	H	H	
CH_3O	CH_3O	H	CH_3	$-CH_2CH_2OH$
H	CH_3O	CH_3	H	CH_3
CH_3O	H	H	CH_3	CH_3
CH_3	CH_3O	H	H	H

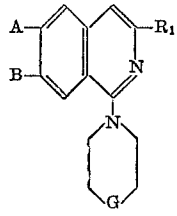


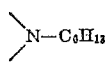
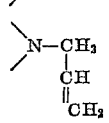
R_6	R_7
	
	H

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TABLE—Continued

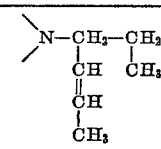
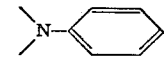
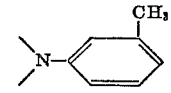
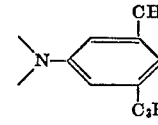
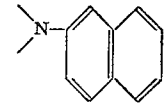
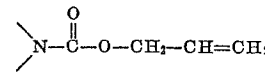
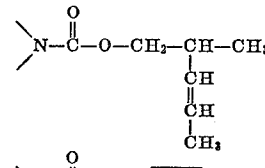
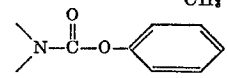
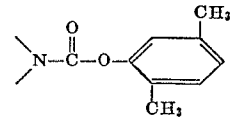
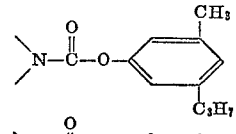
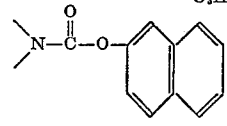
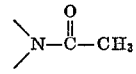
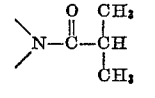
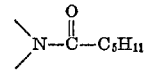
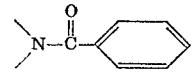
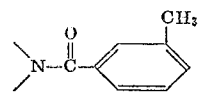
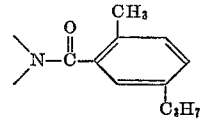
R_6	R_7
H	
$-CH_3$	$-CH_2C(=CH_2)CH_2CH_3$
	H
H	
	H
	H
H	
H	



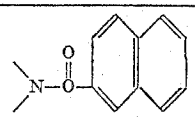
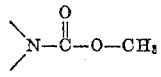
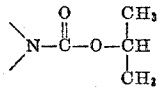
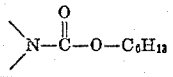
A	B	R_1	G
	Benzo	CH_3	—O—
$-O-(CH_2)_3-O-$		Isopropyl	—S—
$-O-(CH_2)_4-O-$		C_6H_{13}	
OCH_3	OH	CH_3	
OH	OC_2H_5	H	
OH	OH	CH_2	
CH_2	OCH_3	H	
H	OCH_3	H	

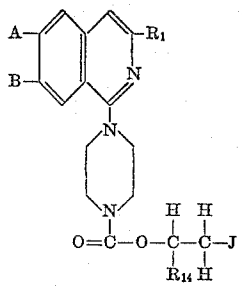
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TABLE—Continued

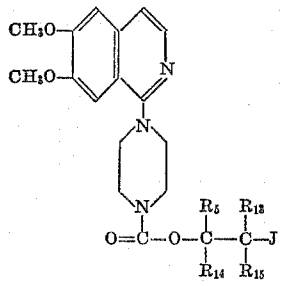
A	B	R_1	G
OCH_3	OCH_3	H	
CH_2	CH_2	H	
OC_2H_5	OH	H	
OCH_2	OH	CH_3	
OCH_2	OH	H	
OH	OCH_3	H	
	Benzo	H	
OH	OH	CH_3	
OC_2H_5	OH	CH_3	
OCH_3	OH	CH_3	
OCH_3	OH	CH_3	
OCH_2	OCH_3	H	
OCH_3	CH_2	CH_3	
OC_2H_5	OH	H	
	Benzo	H	
$-O-(CH_2)_3-O-$		H	
OCH_3	OH	CH_3	

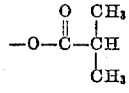
TABLE—Continued

A	B	R_1	G
H	OCH_3	H	
OCH_3	OCH_3	H	
OCH_3	OCH_3	H	
OH	OCH_3	CH_3	

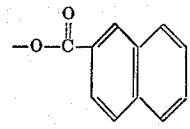
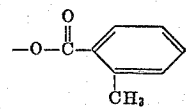
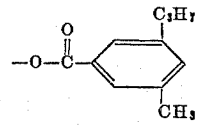
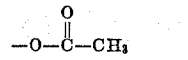
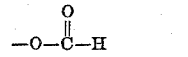
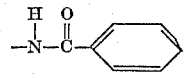
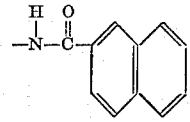
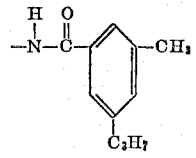
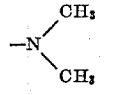
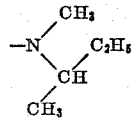
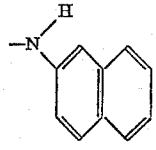
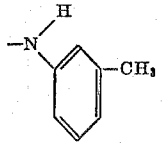
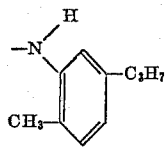
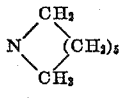
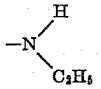


A	B	R_1	R_{14}	J
CH_3O	C_3H_7O	CH_3	CH_3OH	OH
CH_3O	CH_3CHCH_3 CH_2 O	C_4H_7	CH_3	OH
$C_6H_{13}O$	CH_3O	Isobutyl	C_2H_5	Cl
$CH_3-CH-CH_2$ $(CH_2)_3$ O	CH_3O	C_6H_{13}	CH_3	OH
OH	OH	CH_2	H	OH
	Benzo	CH_3	H	OH
CH_3	CH_3O-	H	H	H
CH_3	CH_3	CH_3	H	H
H	CH_3O	H	H	Cl
	$-O-CH_2-O-$	H	H	Br
	$-O-(CH_2)_4-O-$	H	H	CH_3
CH_2O	H	H	Isobutyl	OH

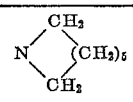
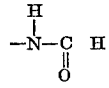
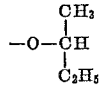
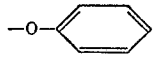
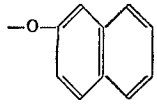
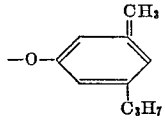
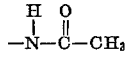
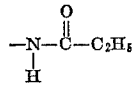
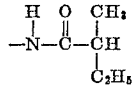
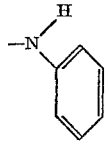
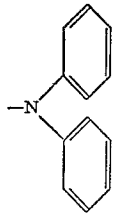
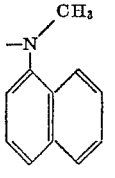
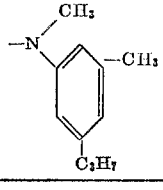


R_5	R_{13}	R_{14}	R_{15}	J
CH_3	H	CH_2	H	H
C_2H_5	H	H	C_2H_5	OH
Isobutyl	H	H	H	Br
CH_3	CH_3	C_2H_5	H	Cl
CH_2	H	Isobutyl	H	NH_2
CH_2OH	H	H	Isobutyl	H
CH_3	Isobutyl	H	CH_2OH	H
CH_3	C_3H_7	H	H	

TABLE—Continued

R_5	R_{13}	R_{14}	R_{15}	J
H	H	H	H	
H	CH_3	H	H	
H	H	H	H	
	$-(CH_2)_4-$	H	CH_3	
	$-(CH_2)_7-$	C_2H_5	H	
H	H	H	H	
H	H	CH_3	H	
CH_3	H	H	H	
H	CH_3	CH_3	H	
H	C_2H_5	H	H	
H	H	H	H	
H	H	H	H	
CH_3	H	H	H	
H	H	H	H	
H	H	CH_3	H	

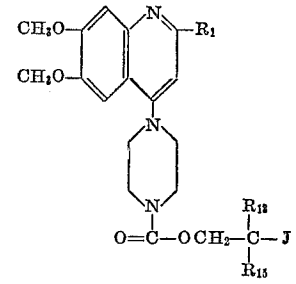
TABLE—Continued

R_5	R_{13}	R_{14}	R_{15}	J
H	H	H	CH_3	
H	H	CH_3	H	
H	CH_3	CH_3	H	$-O-CH_3$
H	H	H	CH_2	$-O-C_2H_5$
H	CH_3	H	H	
CH_3	H	H	H	
H	CH_3	C_2H_5	H	
H	H	H	H	
H	H	H	H	
H	H	H	H	
H	CH_3	H	H	
CH_3	H	H	H	$-NH_2$
CH_3	H	H	H	
H	H	H	H	
H	H	H	H	
H	H	H	H	

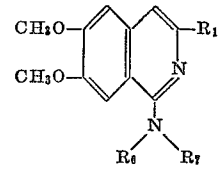
EXAMPLE XXIV

Bronchodilator activity

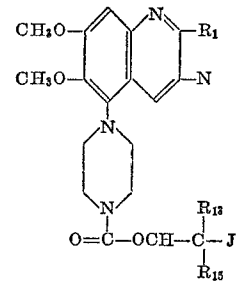
The procedures given in Example IV were used to evaluate the bronchodilator activities of the following compounds. The percent protection was avaluated in the manner given in Example IV. The same dosage levels were used.



R_1	R_{13}	R_{15}	J	Percent protection
H	CH_3	CH_3	H	24
H	CH_2	CH_3	OH	17



R_1, H; R_6, H; R_7, CH_2CH_3; Percent protection 14.



R_1	R_{13}	R_{15}	J	Percent protection
H	H	H	H	20
H	CH_2	CH_3	H	30
H	CH_3	CH_3	OH	*62

*This compound shows 80% protection after 8 hours.

EXAMPLE XXV

Spirally cut strips of guinea pig trachea were prepared as described by J. W. Constantine, J. Pharm. Pharmacol., 16, 384 (1965). Isometric relaxations were recorded using a force displacement transducer (Model FT-03, Grass Instrument Co., Quincy, Mass.) connected to a Grass Model 7 polygraph (Grass Instrument Co., of Quincy, Mass.).

The relative smooth muscle relaxing effects of each of the compounds tested were compared as follows:

(1) The muscle relaxant effect of a bathing medium of 0.03 μg./ml. of isoproterenol was determined for each strip and was shown to be supramaximal. This response was taken as the maximum relaxation of the strip.

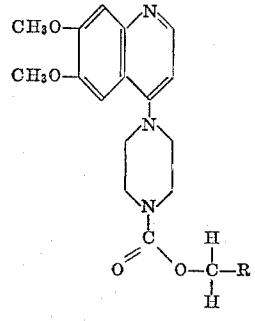
(2) Subsequent relaxations of a given strip, to logarithmically-spaced concentrations of the compounds under test, were determined and were converted to percent of isoproterenol-induced relaxation. Curves of dosage vs. percent of maximum relaxation were obtained for each compound.

(3) The figure reported below for each compound was that concentration (expressed in μg./mil.) of compound which was needed to obtain 50% of maximum relaxation (EC_{50}) of the tracheal strip. Consequently, the smaller the EC_{50} the more potent the compound was as a smooth muscle relaxant.

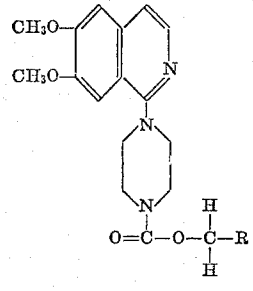
(4) Two standard compounds, theophylline (a known bronchodilator) and papaverine, were evaluated as well.

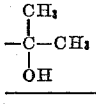
The following compounds were tested with corresponding values of EC_{50}:

	EC_{50}
Theophylline	6.4
Papaverine	0.3



R	EC_{50}
$-CH(CH_3)_2$	0.7
$-CH_3$	1.2
	0.8



R	EC_{50}
$-CH_3$	0.25
$-CH(CH_3)_2$	0.7
	0.25

EXAMPLE XXVI

The compounds of this invention were evaluated with respect to their power to inhibit the action of cyclic 3',5'-nucleoside phosphodiesterase which can act to destroy 3',5' adenosine monophosphate.

The cyclic 3',5'-nucleoside phosphodiesterase was isolated using the procedure of R. W. Butcher and E. W. Sutherland, J. Biol. Chem., 237, 1244 (1962) and their purification procedure was carried through the third step given, namely through the ammonium sulfate fractionation, dialysis and freezing steps, but not through the chomatographic fractionation step.

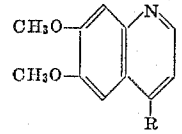
For each compound tested, two substrates, containing each of the two control inhibitory compounds, and one substrate containing no inhibitory compound were prepared. Each substrate had a total volume of 2 ml., was 4×10^{-4} molar in 3',5' adenosine monophosphate, contained 0.02 ml. of cyclic 3',5'-nucleoside phosphodiesterase and 4.0 μmoles of $MgSO_4$, 0.2 μmoles ethylene diamine tetraacetate and 80 μmoles of a suitable buffer which was to maintain the pH at 7.5. Where the substrate also contained a novel compound whose phosphodiesterase inhibitory power was to be tested or contained a control inhibitory compound, the compound was present at a concentration of 10^{-4} molar.

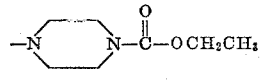
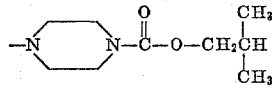
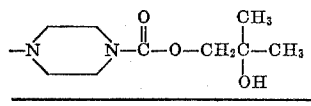
Two control compounds, papaverine and theophylline, a known bronchodilator, were run with each novel compound. Thus, at least four substrates, each containing 3',5' adenosine monophosphate, were run for each novel compound evaluated. One contained the novel compound another contained theophylline, another contained papaverine and the last contained no phosphodiesterase inhibitor at all.

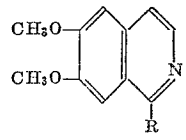
Each substrate was incubated for 30 minutes at 30° C. after which the reaction was stopped by boiling for 10 minutes. At this point one mg. of lyophilized *Crotolus atrox* venom dissolved in one ml. of pH 7.5 buffer was added and the new mixture was incubated for 30 minutes at 30° C. and this reaction was also stopped by boiling for 10 minutes. The venom reacts with 5'-adenosine monophosphate, a product of the reaction between phophodiesterase and 3',5'-adenosine monophosphate, to release inorganic phosphate. Thus, a low final concentration of inorganic phosphate indicates that a small amount of 5'-adenosine monophosphate was formed and, therefore, that the phosphodiesterase activity was inhibited. The inorganic phosphorus was determined colorimetrically by the methods of C. H. Fiske and Y. Subbarow, J. Biol. Chem., 66, 375 (1925).

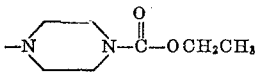
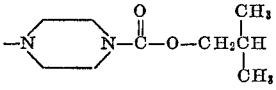
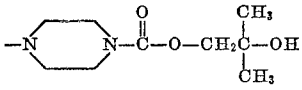
The percent inhibition was taken as the difference between the inorganic phosphate concentration in the substrate containing the inhibiting compound and the concentration in the substrate containing no inhibitor divided by the concentration in the substrate without inhibitor.

The following compounds were tested:



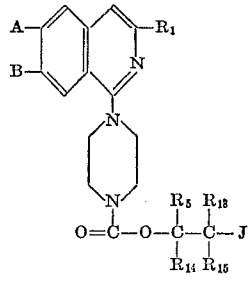
R	Percent inhibition	Theophylline, percent inhibition	Papaverine, percent inhibition
	39	4	70
	55	4	70
	33	4	77



R	Percent inhibition	Theophylline, percent inhibition	Papaverine, percent inhibition
	35	23	75
	55	23	75
	38	18	76

What is claimed is:

1. A compound selected from the group consisting of those of the formula



and the pharmaceutically-acceptable mono-acid addition salts thereof wherein A and B are each selected from the group consisting of methoxy, hydrogen, hydroxy and methyl with the proviso that when A or B is hydrogen, the other is never hydrogen; R_1, R_5, R_{13}, R_{14} and R_{15} are each selected from the group consisting of hydrogen and methyl and J is selected from the group consisting of hydrogen, hydroxy, alkoxy having from 1 to 4 carbon atoms, chloro, bromo, and amino having up to two substituents, each being selected from the group consisting of hydrogen and alkyl having up to 4 carbon atoms.

2. The compound of claim 1 wherein R_5, R_{13}, R_{14}, R_{15}, J and R_1 are hydrogen and A and B are methoxy.

3. The compound of claim 1 wherein R_5, R_{14}, R_1 and J are hydrogen, A and B are methoxy and R_{13} and R_{15} are methyl.

4. The compound of claim 1 wherein R_5, R_{14} and R_1 are hydrogen, A and B are methoxy, R_{13} and R_{15} are methyl and J is hydroxy.

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DONALD G. DAUS, Primary Examiner

U.S. Cl. X.R.

260—268 BQ, 283 R, 283.8, 288 R, 284 R; 424—250, 258