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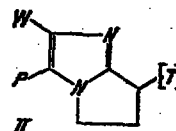
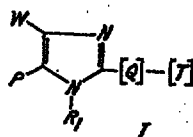
COMPLETE SPECIFICATION

Imidazole Derivatives, their preparation and Compositions containing them

We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with certain novel imidazole derivatives with chemical syntheses of such substances, and with compositions containing the imidazole derivatives of this invention as active ingredients. Compounds in accordance with the present invention are useful against parasitic diseases, for example, trichomoniasis, enterohepatitis and against helminths, ascarids and schistosomes. Certain of them are also effective against amoebiasis and trypanosomiasis as well as chronic respiratory diseases in fowl caused by PPLO organisms. Certain of the compounds of the present invention also show antibacterial activity.

The novel imidazole derivatives of this invention are represented by the following structural formulae:

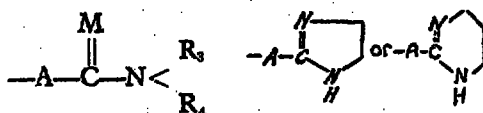


wherein R_1 is alkyl, suitably methyl, ethyl, propyl, butyl or pentyl, or substituted alkyl in which the substituent(s) on the alkyl group is or are aryl, such as phenyl; fluorophenyl; nitrophenyl; oxo; alkenyl; hydroxy; halo; alkanoyloxy, for example, acetoxy, propionyloxy, butyryloxy, or valeryloxy; aralkanoyloxy, suitably phenylalkanoyloxy, such as phenylacetoxy; benzoyloxy; alkoxy, such as methoxy, propoxy or butoxy; aralkoxy, such as phenylalkoxy, suitably benzylloxy; carboxy; carboalkoxy, preferably carbomethoxy, carboethoxy and carbopropoxy; carboaralkoxy, such as carbobenzylloxy; carbamoyl and N-substituted carbamoyl, where the N-substituents are alkyl, aralkyl and aryl, such as methyl, propyl, butyl and pentyl, phenylalkyl such as benzyl, and phenyl; cyano; substituted thio, substituted sulfinyl and substituted sulfonyl, in which the substituent groups are alkyl, aralkyl, or aryl, such as ethyl, propyl and butyl, phenylalkyl, such as benzyl, or phenyl; carbamoyloxy, or dialkylamino;

W represents nitro, cyano, phenyl or hydrogen and P represents hydrogen or nitro, provided that one and only one of W and P is nitro,

Q is C_{1-3} alkylene, suitably methylene, propylene, butylene and ethylene; C_{2-3} alkylidene, suitably ethylidene, propylidene and butylidene; C_{2-3} alkenylene, suitably propenylene; or aralkylidene, suitably phenyl (C_{1-3} alkylidene), for example phenyl-methylene;

T has the substructure



M is oxygen, sulfur, imino or alkylimino,

A is oxygen or sulfur, and each of R_3 and R_4 is hydrogen; alkyl, such as methyl, ethyl, propyl or butyl, or substituted alkyl, where the substituents of the alkyl group are

hydroxy; halo; (when halo and hydroxy, e.g. polyhalo and hydroxy occur together, preferred values are trichloro and hydroxy, trifluoro and hydroxy and tribromo and hydroxy; alkoxy, such as methoxy, propoxy or butoxy; oxo; aryl and oxo, such as phenyl and oxo; carboxy; carboalkoxy, such as carbomethoxy, carboethoxy and carbopropoxy; carboaralkoxy, such as carbophenylalkoxy, suitably carbobenzoyloxy; carbamoyloxy; alkanoyloxy such as acetoxy, propionyloxy or butyryloxy; aralkanoyloxy, for example, phenylalkanoyloxy, such as benzoyloxy; carbamoyl or sulfamoyl and the N-substituted derivatives thereof where the N-substituents are:

N-alkyl, such as N-methyl, N-propyl or N-pentyl, N-aryl, such as N-phenyl, or N-aralkyl such as N-phenylalkyl, such as N-benzyl;

mercapto and substituted mercapto where the substituents may be:

alkyl, for example, methyl, ethyl and propyl, and aralkyl, suitably phenylalkyl, such as benzyl;

thioncarbamoyl; substituted thioncarbamoylthio, where the substituents may be: N,N-dialkyl, such as N,N-dimethyl, N,N-diethyl, N,N-dipropyl, N,N-diaralkyl, such as N,N-di(phenylalkyl), suitably N,N-dibenzyl; amino; or substituted amino, wherein the substituents may be:

alkyl, such as dimethyl, dibutyl or dipentyl, or diaralkyl, such as di(phenylalkyl), suitably dibenzyl;

heterocycloalkyl, wherein the ring contains at least one nitrogen atom, bonded to the alkyl group, suitably a 4- or 5-membered saturated heterocycloalkyl group, for example, morpholino, thiamorpholino, piperidino, piperazino, 4-methylpiperazino, imidazolidino, and pyrrolidino;

phenyl, nitrophenyl, chlorophenyl or fluorophenyl; substituted methylene or alkylidene, in which the substituent(s) is or are:

alkoxy, such as methoxy, butoxy and pentoxy; aralkoxy, suitably phenylalkoxy, such as benzoxy, and aryloxy, for example, phenoxy, substituted amino, where the substituents may be dialkyl, such as dimethyl, dipropyl or dipentyl; or diaralkyl, for example di(phenylalkyl), suitably dibenzyl; alkanoyl, such as formyl, acetyl, propionyl, butyryl or valeryl; aralkanoyl, suitably phenyl alkanoyl, such as phenylacetyl; cyanoalkanoyl, such as cyanoacetyl or cyanopropionyl;

C₃₋₅ alkenoyl, such as acryloyl or crotonyl; and

aroyl, such as benzoyl;

hydroxy and substituted hydroxy, in which the substituents are alkanoyl, such as formyl, acetyl, propionyl, butyryl, or valeryl,

aralkanoyl, suitably phenylalkanoyl, such as phenylacetyl;

cyanoalkanoyl, such as cyanoacetyl or cyanopropionyl;

C₃₋₅ alkenoyl, such as acryloyl or crotonyl; and

aroyl, such as benzoyl;

alkyl, for example, methyl, ethyl, butyl or pentyl; aralkyl, such as phenylalkyl, suitably benzyl, and aryl, for example, phenyl;

carbamoyl, thiocarbamoyl and N-substituted carbamoyl and thiocarbamoyl in which the substituents are

alkyl, for example, methyl, ethyl, butyl and pentyl; aralkyl, such as phenylalkyl, suitably benzyl, and aryl, for example, phenyl;

heterocycloalkylcarbonyl, in which the heterocycloalkyl ring contains at least one nitrogen atom bonded to the carbonyl group, suitably a 6- or 5-membered saturated heterocycloalkyl, for example, morpholino, thiamorpholino, piperidino, piperazino, 4-methylpiperazino and pyrrolidino; nitro;

amino and substituted amino, in which the substituents are

carbamoyl and thiocarbamoyl; C₂₋₅ alkylidene, e.g. isopropylidene, 2-butyldiene, 3-pentylidene, and ethylidene; aralkylidene, for example, phenylalkylidene, such as benzylidene;

alkanoyl, such as formyl, acetyl, propionyl, butyryl, or valeryl;

aralkanoyl, suitably phenylalkanoyl, such as phenylbutyryl;

cyanoalkanoyl, such as cyanoacetyl or cyanopropionyl;

C₃₋₅ alkenoyl, such as acryloyl or crotonyl; and

aroyl, such as benzoyl;

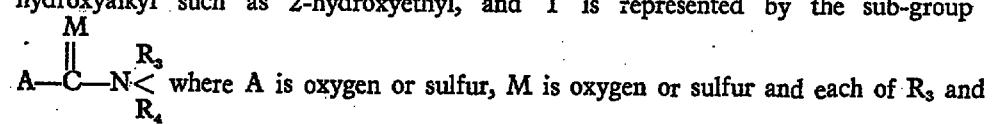
alkanoylalkanoyloxy, such as acetylacetoxy, propionylpropionoxy, valerylvaleroxy; aralkanoylaralkanoyloxy; such as phenylalkanoyl-phenylalkanoyloxy, such as phenylacetylphenylacetoxy, phenylpropionylphenylpropionoxy; sulfamoyl, diamino-phosphoryl, alkylsulfamoyl, dialkylsulfamoyl, bis(alkylamino)phosphonyl, bis(dialkylamino)-phosphonyl, aralkylsulfamoyl, bis(phenylamino)phosphoryl, or bis(diphenylamino)-phosphonyl; or R_s and R_t are joined to form the group $-(CH_2)_2R_s-(CH_2)_2-$, where R_s is oxygen, sulfur, $-CH_2-$, $>N-R_s$, where R_s is hydrogen or alkyl, or a carbon-carbon single bond; for example, taken together with the N-atom to which they are attached, R_s and R_t represent morpholino, thiamorpholino, piperidino, 4-methylpiperazino or pyrrolidino; the terms "alkyl", "alkanoyl" and "alkoxy" used above meaning such groups containing from one to five carbon atoms.

In various preferred groups of compounds in accordance with the present invention, W is hydrogen, P is nitro and T is carbamoyloxy, thioncarbamoyloxy, carbamoylthio, thiocarbamoylthio, pseudoureido or pseudothioureido, with compounds in which

Q is alkylene, alkylidene or phenylmethylene being particularly preferred. R₁ can be substituted or unsubstituted alkyl, and R₃ and R₄ can both be hydrogen or can have any of the values mentioned above. In a particularly preferred group falling within the above definitions, R₁ is C₁₋₅ alkyl, Q is C₁₋₅ alkylene, each of A and M is oxygen or sulfur, each of R₃ and R₄ is hydrogen, C₁₋₅ alkyl, C₁₋₅ alkanoyl, amino, hydroxy, C₁₋₅ alkoxy, phenyl-(C₁₋₅ alkoxy), di(C₁₋₅ alkyl)amino-(C₁₋₅ alkyl), phenyl, tosyl, C₁₋₅ hydroxyalkyl, carbamoyl, C₁₋₅ alkylidenylamino or carbo-(C₁₋₅ alkoxy)-(C₂₋₅ alkylenyl) provided that only one of the groups R₃ and R₄ is hydrogen, or NR₅. R₅ represents morpholino, 4-methylpiperazino or piperidino. In another particularly preferred such group, R₁ is alkanoyloxyalkyl, and each of R₃ and R₄ is hydrogen or hydroxy, only one of them being hydrogen.

Also within the purview of the invention are acid-addition salts of these imidazole derivatives. The salt may be of an inorganic acid such as the hydrochloride, hydrobromide, phosphate, nitrate or sulfate, or of an organic acid, examples of which are the citrate, tartrate, adipate, methanesulfonate and *p*-toluenesulfonate. Non-toxic acid-addition salts, i.e. those tolerated by the host at the dose levels used, are used when the compounds are to be used in their salt form as antiparasitic agents.

The preferred compounds of this invention are the 1-substituted-5-nitro-imidazole-2-ylalkyl carbamates and thiocarbamates and substituted carbamates and thiocarbamates. More specifically, the preferred compounds are those of Formula I above in which W is hydrogen, P is nitro, Q is C₁₋₅ alkylene or C₂₋₅ alkylidene, R₁ is alkyl, or hydroxyalkyl such as 2-hydroxyethyl, and T is represented by the sub-group



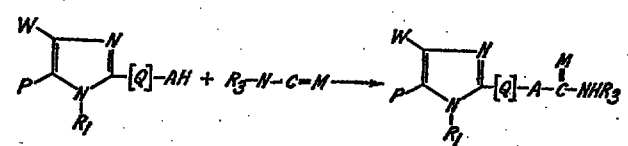
These preferred embodiments will be discussed at more length than others in the description of the invention. The following explanations of processes apply to most substances embraced by the generic Formulae I and II. However, it should be understood that these processes do not constitute the preferred processes for certain N-substituted carbamates and thiocarbamates. The preferred processes for this latter class of N-substituted carbamates and thiocarbamates will be discussed below following the discussion of the principal processes.

In accordance with the present invention, there are provided the following chemical syntheses of the novel imidazole derivatives. Throughout the syntheses, the terms "alkyl", "alkoxy" and "alkanoyl" mean such groups containing from 1 to 5 carbon atoms.

THE GENERAL PROCESSES

i. The Isocyanate and Isothiocyanate Procedure

One method for making the imidazole derivatives is by the reaction of an appropriate isocyanate or isothiocyanate with a 1-substituted-2-hydroxyalkyl-5-nitroimidazole or 1-substituted-2-mercaptoalkyl-5-nitroimidazole:



in which R₁ is alkyl or substituted alkyl, in which the substituent is hydroxy, oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, carbamoyl, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl, dialkylamino or carbamoyloxy; but R₁ is not hydroxyalkyl in the starting material; R₃ is hydrogen, alkyl, substituted alkyl in which the substituent is halo, alkoxy, oxo, phenyloxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, alkylthio, phenylalkylthio, dialkylidithiocarbamoyl, diphenylalkylidithiocarbamoyl, diphenyldithiocarbamoyl, dialkylamino, diphenylalkylamino, heterocycloalkyl, alkylsulfonyl or phenylsulfonyl; phenyl, alkanoyl, phenylalkanoyl, aroyl, cyanoacetyl, alkenoyl, chlorosulfonyl or dichlorophosphoryl and W, P, Q, A and M are as defined above.

In the preferred modification of this process, the significance of the symbols is as follows:

W is hydrogen;

P is nitro;

Q is C₁₋₅ alkylene, suitably methylene or ethylene; or C₂₋₅ alkylidene, suitably ethylidene; and R₁ is alkyl, suitably methyl, ethyl or propyl, or acyloxyalkyl, suitably alkanoyloxyalkyl, such as acetoxypropyl or valeroxyethyl, or aroyloxyalkyl such as benzoyloxyethyl or benzoyloxypropyl, which can be used to give a product in which R₁ is hydroxyalkyl.

When it is desired to prepare the 1-hydroxyalkylimidazole derivatives according to this and the other processes described herein, it is necessary to "block" this 1-substituent during the reaction involving the 2-hydroxyalkyl or 2-mercaptoalkyl radical of the imidazole, or else the free hydroxy group will react with the isocyanate or isothiocyanate. This "blocking" is conveniently accomplished by esterifying, e.g., by using a 1-acyloxyalkyl-imidazole as starting material. An ester of an alkanic acid or benzoic acid, for example, an ester of acetic acid, propionic acid or benzoic acid, is convenient; for example, the starting material may be 1-(2-acetoxyethyl)-2-hydroxymethyl-5-nitroimidazole, 1-(2-propionoxypropyl)-2-mercaptomethyl-5-nitroimidazole or 1-(2-benzoyloxyethyl)-2-(1-hydroxyethyl)-5-nitroimidazole.

This esterified radical normally survives the isocyanate reaction unchanged under the preferred process conditions, and the resulting 1-acyloxyalkylimidazole derivative may then be hydrolysed with an alkali to the corresponding 1-hydroxyalkyl derivative.

Where R₂ is halosulfonyl or dihalophosphoryl, the carbamate produced in accordance with this process may be readily converted to the corresponding N-sulfamoyl or N-diaminophosphoryl derivative by reaction with ammonia, suitably liquid ammonia. If desired, the corresponding N-(N'-substituted sulfamoyl) derivatives or N-(N'-substituted diaminophosphoryl) derivatives may be obtained by utilizing a suitably substituted amine in place of ammonia.

The isocyanate reaction of the above reaction scheme is conveniently brought about by contacting the imidazole and substituted isocyanate or isothiocyanate reactants, preferably in equimolar amounts or with a slight molar excess of isocyanate or isothiocyanate, in an inert solvent medium at a temperature from 20—120° C. Aromatic hydrocarbons such as benzene and toluene, or halogenated aliphatic hydrocarbons, e.g., dichloro- or tetrachloroethane are examples of suitable solvents. It is desirable to have present a minor amount of a base such as a tertiary amine, e.g., pyridine or triethylamine, or an even stronger base such as an alkali metal alkoxide, such as sodium methoxide or potassium ethoxide, since the reaction is base-catalysed.

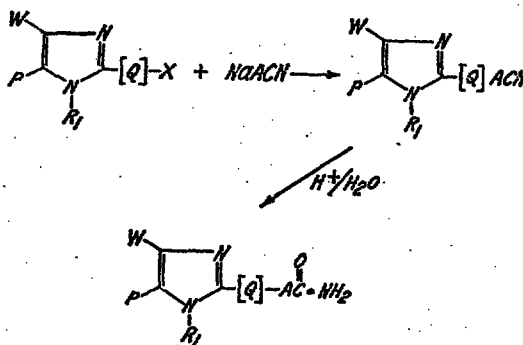
Examples of imidazole derivatives that may be obtained in this manner from the appropriate nitroimidazole are 1-methyl-5-nitroimidazol-2-ylmethyl benzoylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl acetylcarbamate, 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl ethylcarbamate, 1-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl methylcarbamate, 1-propyl-5-nitroimidazol-2-ylmethyl 4-morpholinecarboxylate, 1-methyl-5-nitroimidazol-2-ylmethyl methylthiolcarbamate and 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl phenylthioncarbamate.

The method may also be used for making carbamates where R₃ is hydrogen and M is oxygen, in which case the cyanic acid reactant is preferably generated *in situ* from an alkali metal cyanate, as by addition of acetic or trifluoroacetic acid to the reaction mixture. It might be mentioned, however, that other methods described herein are generally more satisfactory for making the unsubstituted carbamates, and further that this particular process is not suitable for preparing the unsubstituted thioncarbamates where R₃ in the formula is hydrogen and M is sulfur.

ii. Alkali Metal Cyanate or Thiocyanate/Acid Procedure

Certain of the 1-substituted imidazol-2-ylalkyl carbamates and thiocarbamates of this invention may be obtained by another process which comprises the reaction of the corresponding 1-substituted-2-halomethyl (or 2-alkyl or 2-aryl-sulfonyloxymethyl) imidazole with an alkali metal cyanate or thiocyanate to produce a 1-substituted-2-(cyanatomethyl or thiocyanatomethyl-imidazole and treatment of said compound with a mineral acid, preferably sulfuric acid. It is preferred, however, to use this method for the preparation of thiocarbamates rather than carbamates due to the possibility of rearrangement of the cyanato intermediate to an isocyanato derivative. This problem is not of practical importance where the thiocyanato intermediate is concerned. The thiocyanato intermediates are claimed in the specification of our

copending application No. 32952/68. The reaction may be schematically represented as follows:



where W, P and Q are as defined above; X is halo, alkylsulfonyloxy or phenylsulfonyloxy, and R₁ is alkyl or substituted alkyl, where the substituent is oxo, alkenyl, hydroxy, phenylalkoxy, alkoxy, carboxy, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, except that R₁ is not hydroxyalkyl in the starting material.

In the preferred modification of this process, the significance of the symbols is as follows:

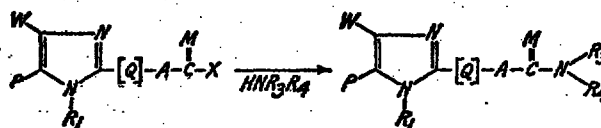
W is hydrogen; P is nitro; Q is alkylene, suitably methylene or ethylene, or alkylidene, suitably ethylidene; R₁ is alkyl, suitably methyl, ethyl or propyl or acyloxyalkyl, suitably alkanoyloxyalkyl, such as acetoxypropyl or valeroxyethyl, or aroyloxyalkyl such as benzoyloxyethyl or benzoyloxypropyl, and in the final product may be hydroxylalkyl corresponding to an acyloxyalkyl in the starting material; each of A and M represents oxygen or sulfur; and X is chloro, bromo, methanesulfonyloxy or *p*-toluenesulfonyloxy.

It is preferred to affect the reaction with the thiocyanate in a solvent medium such as a C₁₋₃ alkanol, for example methanol or ethanol, dimethylformamide or a C₂₋₃ alkanoylnitrile, such as acetonitrile, at a temperature of between 15° C. and 100° C. The immediate product is a 1-substituted-2-thiocyanato-5-nitroimidazole, for example a 1-alkyl or 1-acyloxyalkyl-2-thiocyanato-5-nitroimidazole, such as a 1-methyl, 1-ethyl or 1-acetoxyethyl-2-thiocyanato-5-nitroimidazole. A similar product is obtained when the starting material is a 2-alkylsulfonyloxymethyl or 2-arylsulfonyloxymethyl imidazole, such as 2-(methylsulfonyloxymethyl- or *p*-toluenesulfonyloxymethyl)-5-nitroimidazole, instead of the 2-halomethyl-imidazole, such as the corresponding 2-(chloro or bromo)methyl-5-nitroimidazole.

Conversion of the 1-substituted 2-thiocyanatoalkyl or 2-cyanatoalkyl-5-nitroimidazole to the imidazole derivative of the invention is conveniently accomplished by contacting it with an excess of strong acid, preferably concentrated sulfuric acid in the cold, for example at between 0° C. and 15° C. The reaction is quenched in water to precipitate the carbamate or thiolcarbamate. In those cases where the 1-substituent is acyloxyalkyl, it is hydrolysed to the corresponding 1-hydroxyalkyl radical during the sulfuric acid reaction. Examples of compounds prepared in accordance with this procedure include: 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl thiolcarbamate and 1-methyl-5-nitroimidazol-2-ylethyl thiolcarbamate.

iii. The Imidazole Halocarbonate Process

Still another process for making the compounds of this invention consists in reaction of the halocarbonate or halothioncarbonate ester of a 1-substituted-2-(hydroxyalkyl or mercaptoalkyl)-5-nitroimidazole with a primary or secondary amine of the formula R₃R₄NH. The reaction may be schematically represented as follows:



in which W, P, Q, A and M are as defined above, X is halo, R₁ is alkyl or substituted alkyl, where the substituent is hydroxy, carboxy, oxo, alkenyl, alkanoyloxy, phenyl-alkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl, or dialkylamino and each of R₂ and R₃ is hydrogen, alkyl, substituted alkyl, in which the substituents are halo, alkoxy, oxo, phenyloxy, carboxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, carbamoyl, alkylcarbamoyl, phenylcarbamoyl, phenylalkylcarbamoyl, alkylcarbamoyloxy, phenylcarbamoyloxy, phenylalkylcarbamoyloxy, sulfamoyl, alkylsulfamoyl, phenylsulfamoyl, phenylalkylsulfamoyl, mercapto, alkylthio, phenylalkylthio, thiocarbamoyl, dialkyldithiocarbamoyl, diphenylalkyldithiocarbamoyl, diphenyldithiocarbamoyl, amino, alkylamino, dialkylamino or diphenylalkylamino; phenyl, hydroxy, substituted hydroxy in which the substituent is alkyl, phenalkyl or phenyl; amino, substituted amino, in which the substituent is carbamoyl, alkylidene, phenylalkylidene, alkanoyl, phenylalkanoyl or benzoyl; or sulfamoyl.

In the preferred modification of this process, the significance of the substituents W, P, Q, R₁, A, M and X is as defined for the Cyanate or Thiocyanate procedure ii above; each of R₂ and R₃ represents hydrogen; alkyl, such as methyl, ethyl or propyl; aryl, such as phenyl; aralkyl, such as benzyl; hydroxyalkyl, such as hydroxypropyl or hydroxyethyl; alkoxyalkyl, such as ethoxyethyl or ethoxypropyl; hydroxy or amino; or R₂ and R₃ together represent the group $-(CH_2)_2R_4-(CH_2)_2-$, where R₄ is oxygen, sulfur, $-CH_2-$, $>N-R_5$ or a carbon-carbon single bond and R₅ is hydrogen or C₁₋₃ alkyl; for example, together with the N atom to which R₂ and R₃ are attached, they represent morpholino, thiamorpholino, piperidino, piperazino, 4-methylpiperazino or pyrrolidino.

The two reactants are contacted in a suitable inert solvent medium such as dioxane, tetrahydrofuran or an aromatic hydrocarbon, such as benzene, at a temperature in the range of about 0—75° C. An excess of amine reactant is generally employed and good results are obtained with from about 2.0—5.0 moles of amine per mole of halocarbonate ester, such as chlorocarbonate ester, at reaction temperatures of from about 10—40° C. for most amines.

A molar excess of amine is desired since it is convenient and customary to use 1 mole of the amine (in addition to the mole needed for the reaction itself) as an acid binding agent to neutralize the acid formed in the reaction. The haloformate ester starting material may be charged to the reaction mixture in the form of an acid addition salt, and it is then necessary to have another mole of amine to neutralize this salt. As previously indicated, the amine present in the reaction medium may hydrolyze a 1-acyloxyalkyl imidazole substituent to the corresponding 1-hydroxyalkyl substituent.

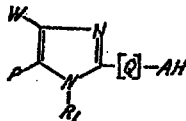
Amines which are suitable for use in this reaction include ammonia, methylamine, dimethylamine, aniline, benzylamine, ethanolamine, propanolamine, ethoxyethylamine, ethoxypropylamine, hydroxylamine, hydrazine and morpholine, thiamorpholine, piperidine, piperazine, 4-methylpiperazine and pyrrolidine.

When ammonia is used as the amine reactant to form carbamates where R₂ and R₃ are both hydrogen, a very large excess is generally used, and frequently liquid ammonia is employed as reaction solvent. When the process is carried out with ammonia, the reaction temperature may be from about -35° C. (refluxing liquid ammonia) to about room temperature. At the higher temperatures, it is, of course, necessary to use a pressure vessel, or to dissolve the ammonia in an organic solvent such as chloroform or a C₁₋₃ alkanol such as ethanol or methanol.

Examples of carbamates and thiocarbamates which may be prepared in this way from the corresponding chloroformate or chlorothionformate esters are 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl carbamate, 1-methyl-5-nitroimidazol-2-methyl *p*-fluorophenylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *p*-chlorophenylcarbamate, 1-propyl-5-nitroimidazol-2-ylmethyl *p*-nitrophenylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl methylcarbamate, 1-(2-hydroxyethyl)-5-nitroimidazol-2-ylmethyl ethylcarbamate, 1-(2-hydroxyethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl methylethylcarbamate, 1-(1-ethyl-5-nitroimidazol-2-yl)-ethyl ethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl 2-methoxyethylcarbamate and 1-(1-methyl-5-nitroimidazol-2-yl)ethyl methylthioncarbamate.

iv. Preparation of Imidazole Halocarbonate

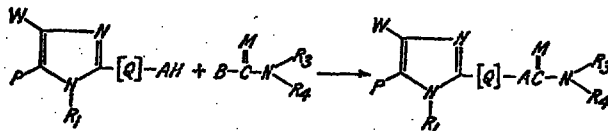
The imidazole chlorocarbonate or chlorothioncarbonate ester used in the above process can be obtained by the process described and claimed in the specification of our copending application No. 38884/68, which comprises reacting phosgene or thiophosgene at a temperature of between about -10°C . and room temperature with an imidazole of the structure



where W, P, Q, A and R_1 are as defined above. Generally the lower temperatures are used with phosgene and the higher temperatures with thiophosgene. The process is preferably conducted in an inert organic solvent medium. Satisfactory solvents are dioxan, tetrahydrofuran and toluene, or mixtures thereof, as well as ketones and esters such as ethyl acetate. It is desirable to use a medium in which the imidazole reactant is essentially completely soluble. For best results, the process is conducted in the presence of an acid binding agent, normally a tertiary amine such as trialkylamine or dimethylaniline, although solvents such as tetrahydrofuran and dioxan may themselves be used as said binding agents in this reaction. The chloroformate or chlorothionformate ester may then be isolated, if desired, but this is unnecessary and it is preferred to prepare the ester in solution and to react it without isolation with the amine.

v. The Carbamoyl or Thiocarbamoyl Halide C_{1-5} alkyl Carbamate or Thiocarbamate Process

An additional method for preparing the imidazolylalkyl carbamates of this invention comprises reacting a 1-substituted-2(hydroxyalkyl or mercaptoalkyl)-5-nitroimidazole with the appropriate carbamoyl halide or C_{1-5} alkyl carbamate, or a thio derivative thereof. This process may be schematically represented as follows:



in which W, P, Q, A and M are as defined above, B is halo or alkoxy, R_1 is alkyl or substituted alkyl, in which the substituent is hydroxy, carboxy, oxo, halo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, carbamoyloxy, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, carbamoyl, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl and each of R_3 and R_4 is hydrogen, alkyl, phenyl or substituted alkyl where the alkyl substituents are halo, alkoxy, oxo, phenyloxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, alkylthio, phenylalkylthio, dialkylamino, diphenylalkylamino or heterocycloalkyl; or R_3 and R_4 together represent the group $-(CH_2)_2R_5-(CH_2)_2-$ where R_5 is oxygen, sulfur, methylene, alkylimino, or a carbon-carbon single bond.

In the preferred modification of this process, the significance of W, P, Q and R_1 is as set forth for the Cyanato/Thiocyanato/Acid procedure ii above; R_3 and R_4 are as set forth for the imidazole Halocarbonate procedure iii above, and B is chloro or methoxy or ethoxy.

It will be understood that when B is chloro and M is oxygen, a carbamoyl chloride is reacted with the 2-substituted imidazole, and when B is C_{1-5} alkoxy, the reactant is an alkyl carbamate.

In order to prepare the imidazolylalkyl thioncarbamates, i.e. where M in the above structural formula is sulfur, a thiocarbamoyl chloride is used.

In the carbamoyl chloride method, the two reactants are brought together in a suitably inert solvent medium, such as benzene, toluene, tetrahydrofuran or dioxane. It is preferred to use a slight molar excess (e.g. 1—15%) of carbamoyl halide, and to have an acid binding agent present in the medium since acid is produced during the reaction. When this process is employed to make unsubstituted carbamates or thioncarbamates (where R_3 and R_4 are both hydrogen), the carbamoyl chloride

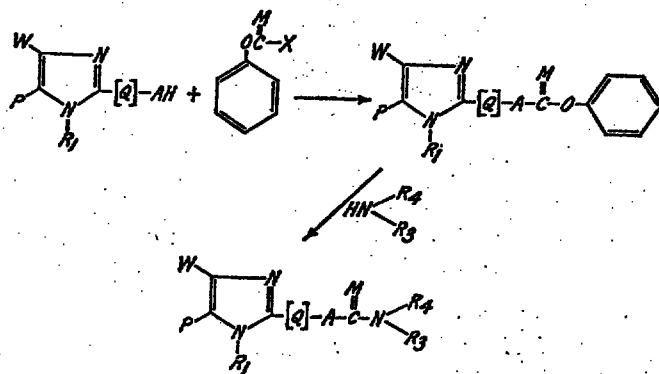
reactant is generated into the reaction medium since it is a highly unstable compound. The disubstituted carbamoyl chlorides are stable and are added directly to the reaction mixture.

When the imidazole is treated with a C_{1-5} alkyl carbamate, e.g., ethyl or methyl carbamate, the two reactants are brought together in essentially equimolar amounts in the presence of a strong base, preferably an alkali metal alkoxide such as sodium ethoxide, sodium methoxide or potassium isopropoxide in an inert solvent such as 1,2-dimethoxyethane. Because of the base present, an acyloxy C_{1-5} alkyl radical at the 1-position of the imidazole ring will be saponified to the corresponding C_{1-5} hydroxyalkyl substituent. Care should be taken not to prolong the reaction time unduly since the imidazole compound is sensitive to strong base.

Among the products which may be prepared by this process are 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl carbamate and 1-(2'-ethoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate.

vi. The Phenyl Halocarbonate Method

Still another process which is very useful for preparing the novel compounds described herein comprises the conversion of a 1-substituted-2-(hydroxyalkyl or mercaptoalkyl)-imidazole to a phenyl carbonate or phenyl thioncarbonate derivative and subsequent treatment of said carbonate or thioncarbonate with an amine, as illustrated below:



III

wherein W, P, Q, R₁, R₃, R₄, A and M are as defined above and X is halo.

This process is highly satisfactory for obtaining compounds of the above Formula III.

In the preferred modification of this process, the significance of W, P, Q, R, A and M is as set forth for the Cyanato/Thiocyanato/Acid procedure ii above; and R₃ and R₄ are as set forth for the Imidazole Halocarbonate procedure iii above.

In carrying out this last-mentioned process, a 1-(C_{1-5} alkyl)-2-(hydroxyalkyl or mercaptoalkyl)-5-nitroimidazole or a 1-acyloxyalkyl-2-(hydroxyalkyl or mercaptoalkyl)-5-nitroimidazole is first reacted, for example, with phenoxy carbonyl chloride (phenyl chloroformate) or phenoxythiocarbonyl chloride (phenyl thionchloroformate). This reaction is conveniently brought about in an organic solvent, such as pyridine, one of the picolines, or lutidine. These bases, in addition to serving as the liquid solvent medium, also serve to bind the acid formed during the reaction. Alternatively, a non-basic solvent for the reactants such as dioxane or chloroform may be used, and sufficient tertiary amine or alkali metal hydroxide added to bind the liberated hydrogen chloride. It is preferred to employ a slight molar excess of phenyl chloroformate reactant and to carry out the process at temperatures of from about -5° C. to about 45° C. Preferably, the reactants are mixed at about 0° C. and the reaction then continued at about room temperature for the desired time. When a phenyl carbonate of a 2-hydroxymethyl or 2-mercaptomethyl compound is being prepared, reaction times of from about 1-5 hours are satisfactory for good results. However, longer times of up to about 30 hours may be necessary for complete reaction in the case of 2-(α -hydroxyethyl) and 2-(α -mercaptoethyl)imidazoles. The resulting imidazole phenyl carbonate, such as 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate or 1-methyl-5-nitroimidazol-2-ylmethyl phenyl thioncarbonate is conveniently recovered by quenching the reaction mixture in ice-water, thus precipitating the desired product.

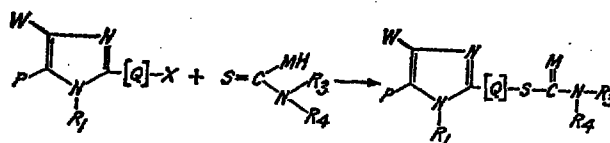
These substances may be used without further purification in the next step of the process, and this is preferred in the case of the phenyl thioncarbonates, which are less stable than the phenyl carbonates.

The imidazolylalkyl carbamate or thiocarbamate is then obtained by intimately contacting the imidazole phenyl carbonate or phenyl thioncarbonate with an amine in an inert organic solvent medium. For this purpose, chloroform or ethers such as dioxane, tetrahydrofuran or ethylene glycol dimethyl ether are satisfactory. It will, of course, be understood that the particular compound produced will depend upon the amine reactant used. The reaction is a rapid one and is normally substantially complete in about 1—5 hours. The imidazole phenyl carbonate and the amine may be reacted in essentially equimolar amounts although it is preferred to employ an excess of the amine. Good results are obtained by using from 1 to 4 moles of amine per mole of phenyl carbonate. When the unsubstituted carbamate itself is being prepared, it is convenient and preferred to use a very large excess of liquid ammonia since the excess serves as reaction solvent and the resulting carbamate moiety is stable and not destroyed under such conditions. In preparing the unsubstituted thioncarbamate, however, it is preferable to employ about 2 moles of ammonia per mole of thioncarbonate and to carry out the reaction at about room temperature in a solvent such as chloroform or an ether. Where R_1 in Formula III is hydroxyalkyl, it is preferred to carry out the reaction on a 1-acyloxyalkylimidazole, for example, a 1-acetoxyalkylimidazole or a 1-benzoyloxyalkylimidazole, such as 1-(2'-acetoxyethyl)-2-hydroxymethyl-5-nitroimidazole, followed by removal of the acyl group by alkaline hydrolysis after completion of the reaction. It should be noted, however, that in the second stage of the process, that is to say, the reaction with the amine, the basicity of the amine is often sufficient to bring about this hydrolysis.

Representative examples of imidazolylalkyl carbamates and thiocarbamates which may be prepared by this method are: 1-methyl-5-nitroimidazol-2-ylmethyl carbamate; 1-ethyl-5-nitroimidazol-2-ylmethyl *p*-fluorophenylcarbamate; 1-(2-hydroxyethyl)-5-nitroimidazol-2-ylmethyl *N*-(2-methoxyethyl)-carbamate; 1-(1-methyl-5-nitroimidazol-2-yl)ethylcarbamate; 1-methyl-5-nitroimidazol-2-ylmethyl thioncarbamate; 1-propyl-2-ylmethyl thiolcarbamate; 1-methyl-5-nitroimidazol-2-ylmethyl hydroxycarbamate and 1-(2-hydroxypropyl)-5-nitroimidazol-2-ylmethyl methylcarbamate.

vii. Preparation of Pseudo-thioureido Imidazoles

The compounds of Formula I above, where M is imino or alkylimino are obtained by reacting a 1-substituted-2-(halomethyl or sulfonyloxymethyl)-imidazole with a thiourea or substituted thiourea as shown by the following reaction scheme:



wherein W, P, R_1 , Q, S, R, and R_4 are as above and M is imino or alkyl imino, and X is halo or alkylsulfonyloxy or phenylsulfonyloxy.

In the preferred modification of this process, the significance of W, P, Q, R_1 , R, and R_4 are as for the procedures ii and iii above;

M is imino; or alkylimino, such as (methyl, propyl or pentyl)-imino; and

X is chloro, methylsulfonyl or *p*-toluenesulfonyl.

The reaction is carried out in an organic solvent medium, preferably a C_{1-5} alkanol, suitably ethanol or methanol. It is preferred to use essentially equimolar quantities of the two reactants, or a slight molar excess of the 2-(haloalkyl or sulfonyloxyalkyl)-imidazole reactant. Acid is formed in the reaction, and the products are normally recovered as the hydrochloride or sulfonate acid addition salts. Included among the compounds prepared in accordance with this process are: S-(1-methyl-5-nitroimidazol-2-ylmethyl)-pseudo-thiourea; S-1-(1-methyl-5-nitroimidazol-2-yl)ethyl-pseudo-thiourea; S-(1-acetoxyethyl-5-nitroimidazol-2-ylmethyl)-pseudo-thiourea; and S-(1-methyl-5-nitroimidazol-2-ylmethyl)-pseudo-N,N-dimethylthiourea.

II. THE SPECIFIC PROCESSES

The following processes are directed to the preparation of carbamates having particular substituents attached to the nitrogen atom of the carbamate group. Although these processes are directed to the formation of the compounds having these particular substituents, it should be understood that they are not specifically limited thereto.

i. 5-Nitroimidazol-2-ylalkyl allophanates and thioallophanates

5-Nitroimidazol-2-ylalkyl allophanates may be produced by reaction of a 5-nitroimidazol-2-yl alkanol or thioalkanol with excess cyanic acid. In the preferred procedure, the 5-nitroimidazole, suitably a 1- R_1 -5-nitroimidazol-2-yl methanol, wherein R_1 has the value shown at the beginning of the specification after Formulae I and II but having a significance other than hydroxyalkyl, suitably 1-methyl-5-nitroimidazol-2-yl methanol, is dissolved in an oxygenated organic solvent, suitably an ether, for example 1,2-dimethoxy ethane, cooled to dry ice temperature, that is to between -75°C . and -50°C ., and 2 moles of cyanic acid is added. It is a critical feature of this process that there be at least 2 moles of cyanic acid per mole of the nitroimidazole derivative. The reaction vessel is tightly sealed, allowed to warm to from about -5°C . to about 0°C . and allowed to stand from about 36 to about 60 hours. The product is then isolated. In the preferred procedure, the reaction mixture is filtered and the solid residue extracted with water, suitably hot water, having a temperature of from about 85°C . to 100°C . The hot extract is immediately filtered and the desired product obtained as a crystalline precipitate from the aqueous filtrate.

Included among the compounds which may be produced in accordance with this procedure are 1-methyl-5-nitroimidazol-2-ylmethyl allophanate, 1-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl allophanate, 1-[1'-(2-acetoxyethyl)-5'-nitroimidazol-2'-yl]ethyl allophanate and 1-(2-acetoxyethyl)-5-nitroimidazol-2-ylmethyl thioallophanate.

Where it is desired to produce the 1-(hydroxyalkyl)-5-nitroimidazol-2-ylalkyl allophanates, the corresponding 1-acyloxy-allophanate is produced in accordance with the above procedure and subsequently subjected to alkaline hydrolysis in the usual manner.

ii. 5 - Nitroimidazol - 2 - ylalkyl N - (2',2',2' - trihalo - 1' - hydroxyethoxy)-carbamates

5-Nitroimidazol-2-ylalkyl N-(2',2',2'-trihalo-1'-hydroxyethoxy)carbamates may be obtained by reacting the corresponding 5-nitroimidazol-2-ylalkyl N-hydroxycarbamate with a trihalo-substituted acetaldehyde. In the preferred procedure, the 5-nitroimidazole, suitably a 1- R_1 -5-nitroimidazol-2-ylmethyl N-hydroxycarbamate, where R_1 is as defined after Formulae I and II, but having a significance other than hydroxyalkyl, for example, 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate is mixed with the haloacetaldehyde, for example, chloral hydrate or bromal hydrate, in approximately equimolar proportions and heated under reflux in the presence of a drying agent, for example, anhydrous magnesium sulfate, for from about 6 to about 12 hours. In the preferred method of isolation, the reaction mixture is filtered and the product recovered from the filtrate. Among the compounds which may be produced in accordance with this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trichloro-1'-hydroxyethoxy)carbamate; 1-ethyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trichloro-1'-hydroxyethoxy)carbamate; 1-acetoxyethyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trichloro-1'-hydroxyethoxy)carbamate; and 1-methyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trifluoro-1'-hydroxyethoxy)carbamate.

Where it is desired to obtain a compound of this class having a 1-hydroxyalkyl substituent, the reaction is carried out using the corresponding 1-acyloxy-N-hydroxycarbamate and subjecting the thus produced N-(2',2',2'-trihalo-1'-hydroxyethoxy)carbamate to alkaline hydrolysis.

iii. 5-Nitroimidazol-2-ylalkyl N-hydroxymethylcarbamates

5-Nitroimidazol-2-ylalkyl N-hydroxymethylcarbamates may be obtained by reacting the corresponding 5-nitroimidazol-2-ylalkyl carbamate with formaldehyde. In the preferred modification of the process, the 5-nitroimidazole carbamate, suitably a 1- R_1 -5-nitroimidazol-2-ylmethyl carbamate, wherein R_1 is as in Step ii above but not hydroxyalkyl or carboxyalkyl, is dissolved in an inert solvent, dimethyl sulfoxide being particularly suitable, and heated in a sealed vessel with an excess of paraformaldehyde, 2 moles excess being preferred, at from $70-150^\circ\text{C}$. for from 18 to 30 hours. In one method of isolation, the solvent is evaporated from the reaction mixture, the residue dissolved in a suitable water-miscible solvent, such as dimethylformamide,

and water added. The product separates as a crystalline precipitate and may be isolated by filtration.

Included among the compounds which may be produced in accordance with this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethyl carbamate; 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-hydroxymethylcarbamate; 2-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-hydroxymethylcarbamate; and 1-ethyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate.

iv. 5-Nitroimidazol-2-ylalkyl N-alkoxyalkylcarbamates

5-Nitroimidazol-2-ylalkyl N-alkoxyalkylcarbamates may be produced by reacting the corresponding 5-nitroimidazol-2-ylalkyl N-hydroxyalkylcarbamate with an alkanol in the presence of an acid. In the preferred procedure, the N-hydroxymethylcarbamate, suitably a 1-R₁-5-nitroimidazol-2-ylmethyl-N-hydroxycarbamate, where R₁ is in Step ii above, but having a significance other than hydroxyalkyl or carboxyalkyl, for example, 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate, is mixed with the alkanol, for example, ethanol or methanol, in the presence of a catalytic amount of strong acid, hydrochloric acid or *p*-toluene sulfonic acid being preferred, and stirred for 12 to 24 hours, at between 15° C. and 30° C. The product may be isolated by extraction of the reaction mixture with a suitable solvent such as chloroform and working up in the usual manner.

Included among the products which may be obtained by means of this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-ethoxymethylcarbamate; 1-methyl-5-nitroimidazol-2-ylmethyl N-propoxymethylcarbamate; 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-methoxymethylcarbamate; and 1-ethyl-5-nitroimidazol-2-ylmethyl N-ethoxymethylcarbamate.

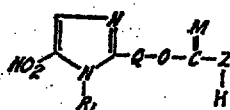
v. 5-Nitroimidazol-2-ylalkyl N-alkoxycarbamates

5-Nitroimidazol-2-ylalkyl N-alkoxycarbamates may be prepared by reacting the corresponding 5-nitroimidazol-2-ylalkyl N-hydroxycarbamate with a diazohydrocarbon. In the preferred procedure, the 5-nitroimidazole N-hydroxycarbamate, suitably a 1-R₁-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate, wherein R₁ is as shown in step ii above but having a significance other than hydroxyalkyl or carboxyalkyl, for example 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate, is dissolved in an alkanol, for example methanol or ethanol, and treated with an excess of a diazo-hydrocarbon, suitably in solution, for example an ethereal solution of diazomethane, diazoethane or diazophenylmethane. The product may be isolated in the form of an acid salt. In one suitable method of isolation, the reaction mixture is filtered, the residue chromatographed on silica gel and the residue, after evaporation of the eluate, treated with one equivalent of an acid solution, suitably *p*-toluenesulfonic acid in methylethylketone.

Included among the products which may be obtained by this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-methoxycarbamate; 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-methoxycarbamate; 1-ethyl-5-nitroimidazol-2-ylmethyl N-ethoxycarbamate; and 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl N-phenylmethoxycarbamate.

vi. Acylation of 5-nitroimidazol-2-ylalkyl carbamates, N-hydroxycarbamates and N,N-alkylhydroxycarbamates

5-Nitroimidazol-2-ylalkyl carbamates, N-hydroxycarbamates and N,N-alkylhydroxycarbamates may be acylated in the usual manner. In the preferred procedure, the compound to be acylated, for example a 1-R₁-5-nitroimidazol-2-ylmethylcarbamate of the formula



where Z is —NR*—, —NR*CH₂O— or —NR*O—, R* being alkyl, phenalkyl or phenyl and Q is C₁₋₃ alkylene, C₁₋₃ alkenylene, phenyl-(C₁₋₃ alkylene) or C₁₋₃ alkylidene, and R₁ is as shown in step ii above, provided however that R₁ has a value other than hydroxyalkyl or carbamoylalkyl, is reacted with an acylating agent such as an alcanoic acid anhydride, suitably a C₂₋₃ alcanoic acid anhydride, such as acetic anhydride, propionic anhydride or valeric anhydride; an alkanoyl halide, such as acetyl chloride or propionyl chloride; an aroyl halide, such as a benzoyl halide; an

alkenoyl halide, suitably a C_3 -alkenoyl halide, such as acryloyl chloride or crotonyl chloride; or a cyanoalkanoic acid in the presence of a dehydrating agent, for example, cyanoacetic acid in the presence of acetic anhydride.

The product of the acylation reaction may be isolated by any of the usual procedures.

vii. 5-Nitroimidazol-2-ylalkyl-4'-substituted allophanates

5-Nitroimidazol-2-ylalkyl-4'-substituted allophanates may be prepared by reacting a 5-nitroimidazole carbamate with a carbamoyl chloride derivative. In the preferred procedure, a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate, where R_1 is as shown in Step ii above but has a value other than hydroxy or carbamoyl, suitably 1-methyl-5-nitroimidazol-2-ylmethyl carbamate; a 1- R_1 -5-nitroimidazol-2-ylalkyl N-alkylcarbamates, such as 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-methyl carbamate; 1-(1'-acetoxyethyl-5'-nitroimidazol-2'-yl)ethyl N-methylcarbamate; or 2-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl N-propylcarbamate is dissolved in a base, suitably an organic base such as pyridine, lutidine or collidine, and the mixture cooled to a range of between -5°C . and $+5^\circ\text{C}$. and the carbamoyl chloride derivative introduced. This introduction may be achieved by passing the carbamoyl chloride into the reaction mixture in gaseous form, for example where carbamoyl chloride itself is used; or by dropwise addition of a substituted carbamoyl chloride, for example dimethyl carbamoyl chloride in the liquid form. The reaction proceeds at a temperature of between 5°C . and 30°C . in from 2 to 24 hours. The product may then be isolated; suitably, the isolation is carried out by concentration with the reaction mixture under reduced pressure, followed by extraction with a suitable solvent, for example, a water-immiscible solvent such as ethyl acetate, and working up in the usual manner.

Included among the products which may be obtained by this method are: 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl 4'-methylallophanate, 1-(1'-acetoxyethyl-5'-nitroimidazol-2'-yl)ethyl 4'-methylallophanate and 1-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl 4'-propylallophanate. Where the carbamoyl chloride derivative is a substituted carbamoyl chloride, for example dimethyl carbamoyl chloride, there are obtained compounds such as 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl-1',4',4'-trimethylallophanate, and 1-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl 1'-methyl-4',4'-dimethylallophanate.

Where the desired compound has a hydroxyalkyl substituent at the 1-position, the reaction is carried out with the corresponding 1-acyloxyalkyl compound, which is subsequently subjected to alkaline hydrolysis in the usual manner.

viii. 5-Nitroimidazol-2-ylalkyl 3'-thionallophanates and 4',4'-substituted 3'-thionallophanates

5-Nitroimidazol-2-ylalkyl 3'-thionallophanates and 4',4'-substituted 3'-thionallophanates are produced by reaction of a 5-nitroimidazol-2-ylalkyl haloformate with an anhydrous alkali metal thiocyanate followed by treatment with an amine. In a preferred modification of the process, a 5-nitroimidazol-2-ylalkyl chloroformate, for example a 1- R_1 -5-nitroimidazol-2-ylmethyl chloroformate, wherein R_1 is as shown in Step ii above, provided that R_1 has a value other than hydroxyalkyl, suitably 1-methyl-5-nitroimidazol-2-ylmethylchloroformate, and the alkali metal thiocyanate is taken up in a reaction-inert organic solvent such as benzene and stirred at moderately elevated temperatures, preferably from about 20°C . to about 55°C ., for a period of about 3 to about 6 days. This mixture is then treated with an excess of the desired amino compound, for example, anhydrous gaseous ammonia, to yield the unsubstituted 3'-thionallophanate, a monosubstituted amine, such as an alkylamine, e.g. ethylamine, to yield the corresponding 4'-alkyl-3'-thionallophanate or a disubstituted amine, for example, dibenzylamine, to yield the corresponding 4',4'-disubstituted-3'-thionallophanate, such as 1-methyl-5-nitroimidazol-2-yl-methyl 4',4'-dibenzyl-3'-thionallophanate.

Included among the compounds which may be produced by this method are: 1-methyl-5-nitroimidazol-2-ylmethyl 3'-thionallophanate, and 1-ethyl-5-nitroimidazol-2-ylmethyl 4'-butyl-3'-thionallophanate.

Where it is desired to obtain a compound of this group having a 1-hydroxyalkyl substituent, the reaction is suitably carried out on the corresponding 1-acyloxyalkyl chloroformate, which is then subjected to alkaline hydrolysis in the usual manner to yield the desired 1-hydroxyalkyl compound: It should be borne in mind, however, that the basicity of the ammonia or the amine added in the course of the present reaction may be sufficient to effect this hydrolysis.

ix. 5-Nitroimidazol-1-ylalkyl N-(N'-substituted thiocarbamoylthiomethyl) carbamates

5-Nitroimidazol-1-ylalkyl N-(N'-substituted thiocarbamoylthiomethyl)carbamates may be produced by the reaction of a 5-nitroimidazol-2-ylalkyl carbamate with a substituted amine, formaldehyde and carbon disulfide. In the preferred modification of the procedure, an amine, for example dimethylamine and formaldehyde, both in aqueous solution, suitably in solutions containing between 30 and 50 molar % of each of the reagents, are added to a solution of the 5-nitroimidazol-2-ylalkyl carbamate, such as a 1-R₁-5-nitroimidazol-2-ylmethyl carbamate where R₁ is as shown in Step ii above, provided that R₁ has a value other than hydroxyalkyl, carbamoyloxyalkyl, carbamoylalkyl or oxoalkyl, suitably 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, in a water-miscible organic solvent, suitably dimethylformamide. To this mixture is added an excess of carbon disulfide and the reaction mixture agitated, suitably for from 18 to 30 hours at a temperature of between about 10 and 30° C. The product is then isolated, suitably by the addition of an excess of water and separation of the product as a precipitate. Among the products which may be obtained by this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-(dimethylthiocarbamoylthiomethyl)carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-(diethylthiocarbamoylthiomethyl)carbamate and 1-(1'-acetoxyethyl-5'-nitroimidazol-2'-yl)ethyl N-(dibenzylthiocarbamoylthiomethyl)carbamate.

x. 5-Nitroimidazol-2-ylalkyl N-(disubstituted aminomethyl)carbamates

5-Nitroimidazol-2-ylalkyl N-(disubstituted aminomethyl)carbamates may be produced by the reaction of a 5-nitroimidazol-2-ylalkyl carbamate with a disubstituted amine together with formaldehyde. In the preferred modification of the procedure, the 1-R₁-5-nitroimidazol-2-ylalkyl carbamate, for example, 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, together with a paraformaldehyde and a disubstituted amine for example, a dialkylamine, such as dimethylamine, dipropylamine or dipentylamine, or an alkylarylamine, for example, N-methylaniline, a diarylamine such as diphenylamine, a diaralkylamine, such as dibenzylamine, or a secondary heterocyclic amine, for example, morpholine, thiamorpholine, pyrrolidine, or N-methylpiperazine, suitably in equimolar amounts, in a water-miscible inert organic solvent, suitably dimethylformamide and heated in a sealed vessel at a temperature of from about 80° to about 150° C. for a period of from about 12 to about 30 hours. In a suitable method of isolation, the reaction solvent is removed, preferably under reduced pressure, and the residue dissolved in a polar solvent, suitably a ketonic solvent, such as methyl ethyl ketone, and an acid suitably p-toluene sulfonic acid, in the same solvent is added and the product isolated as the acid-addition salt.

Included among the compounds which may be prepared in accordance with this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-(N',N'-dimethylaminomethyl)carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-(N',N'-dipropylamino methyl)carbamate, 1-acetoxyethyl-5-nitroimidazol-2-ylmethyl N-(N'-methyl-N'-phenylaminomethyl)carbamate, 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-(N',N'-diphenylaminomethyl)carbamate, 2-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl N-(morpholin 4-ylmethyl)carbamate, 1-propyl-5-nitroimidazol-2-ylmethyl N-(4-methylpiperazin-1-ylmethyl)carbamate, and 1-(1'-hydroxyethyl-5'-nitroimidazol-2'-yl)ethyl N-pyrrolidin-1-ylmethyl)carbamate.

xi. 5-Nitroimidazol-2-ylalkyl N-(carboalkoxyalkylidene)carbamates

5-Nitroimidazol-2-ylalkyl N-(carboalkoxyalkylidene)carbamates may be prepared by reacting a 5-nitroimidazol-2-ylalkyl carbamate with a β-keto ester in the presence of an acid. In the preferred procedure, a 5-nitroimidazol-2-ylalkyl carbamate, for example a 1-R₁-5-nitroimidazol-2-ylalkyl carbamate, wherein R₁ is as shown in Step ii above provided that R₁ is other than carbamoylalkyl, such as 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, is heated with a β-keto ester, such as ethylacetate or ethyl 3-oxopentanoate in the presence of a catalytic amount of an anhydrous acid, suitably an organic acid, such as p-toluene sulfonic acid, at a temperature of from about 60° C. to about 100° C. for a period of from about 3 hours to about 24 hours. The product may be isolated by any suitable method; for example, the solvent may be removed by evaporation under reduced pressure, the residue washed thoroughly with ether, filtered and the ether removed under reduced pressure to yield a residue which may then be recrystallized, suitably from ether, to yield the desired product. Included among the compounds which may be produced in accordance with this procedure are 1-methyl-5-nitroimidazol-2-ylmethyl N-[1'-carboethoxy-(prop-2'-

ylidene)] carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-[1'-carboethoxy-(pent-2'-ylidene)] carbamate, and 1-(1'-ethyl-5'-nitroimidazol-2'-yl)ethyl N-[1''-carboethoxy-(pent-2''-ylidene)] carbamate.

xii. 5-Nitroimidazol-2-ylalkyl N-(alkoxy or benzyloxy) methylene carbamates

5-Nitroimidazol-2-ylalkyl N-alkoxymethylene carbamates may be produced by reacting a 5-nitroimidazol-2-ylalkyl carbamate with a trisubstituted orthoformate in the presence of a Lewis acid. In the preferred procedure, a 5-nitroimidazol-2-ylalkyl carbamate, such as a 1- R_1 -5-nitroimidazol-2-ylmethyl-N-hydroxycarbamate, where R_1 is as shown in Step ii above, but having a significance other than hydroxyalkyl or carboxyalkyl, suitably 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, a Lewis acid, preferably boron trifluoride etherate, and tribenzyl ortho or a trialkyl orthoformate, such as triethyl orthoformate, are heated together at a temperature of from about 60° to about 100° C. for from about 12 to about 18 hours. The product is then isolated. In a suitable method of isolation, the excess trisubstituted orthoformate is removed under reduced pressure, the residue taken up in a suitable water-miscible organic solvent, for example chloroform, and washed with a mild base, suitably aqueous sodium bicarbonate; the product is then isolated from the chloroform solution. Included among the compounds which may be produced in accordance with the above procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-ethoxymethylene carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-propoxymethylene carbamate, and 1-[1'-(2''-hydroxyethyl)-5'-nitroimidazol-2'-ylethyl] N-benzyloxymethylene carbamate.

xiii. 5-Nitroimidazol-2-ylalkyl N-(amino and substituted amino)methylene carbamates

5-Nitroimidazol-2-ylalkyl N-(amino and substituted amino)methylene carbamates may be produced by reacting a 5-nitroimidazol-2-ylalkyl alkoxymethylene carbamate with an amine. In the preferred procedure, a 5-nitroimidazol-2-ylalkyl N-(alkoxy or benzyloxy) methylene-carbamate, such as is produced in accordance with the previous subsection, is heated together with an amine of formula NHR^oR^{oo} , where R^o is alkyl, benzyl or hydrogen and R^{oo} is alkyl or benzyl, e.g., ethylamine, diethylamine or dibenzylamine, in a moderately high boiling reaction-inert organic solvent, suitably an ether such as 1,2-dimethoxy-ethane, at a temperature of between 50° and 150° C. for from about 1 hour to about 3 hours. In a suitable method of isolation, the product is isolated as the acid-addition salt by the addition of a suitable anhydrous acid, for example, p-toluene sulfonic acid, to the cooled reaction mixture.

Included among the compounds which may be produced in accordance with this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-(dimethylaminomethylene)carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-(dibutylaminomethylene)carbamate, and 1-(1'-propyl-5'-nitroimidazol-2'-yl)ethyl N-(dibenzylaminomethylene)carbamate.

xiv. N'-(5-Nitroimidazol-2-ylalkoxycarbonyl) N^2, N^2 -dialkylformamidinium hydrohalides

N'-(5-Nitroimidazol-2-ylalkoxycarbonyl) N^2, N^2 -dialkylformamidinium hydrohalides may be prepared by reacting a 5-nitroimidazol-2-ylalkyl carbamate with a dialkylformamide in the presence of a thionyl halide. In the preferred procedure, a 5-nitroimidazol-2-ylalkyl carbamate, suitably a 1- R_1 -5-nitroimidazol-2-ylmethyl carbamate, where R_1 is as shown in Step ii above provided that R_1 is other than hydroxyalkyl, carboxyalkyl, or carbamoylalkyl, is dissolved in an excess of dialkylformamide, suitably dimethylformamide, and a small excess of a thionyl halide, such as thionyl chloride, is added thereto. The mixture is allowed to stand at a temperature of from about 15° C. to about 30° C. for from about 12 to about 24 hours. In the preferred method of isolation, the product is obtained as a crystalline precipitate and is separated from the reaction mixture for filtration.

Among the compounds which may be produced in accordance with this procedure are N'-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl) N^2, N^2 -dimethylformamidinium chloride hydrochloride, N'-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl) N^2, N^2 -dimethylformamidinium bromide hydrobromide, N'-(1-ethyl-5-nitroimidazol-2-ylmethoxycarbonyl) N^2, N^2 -dimethylformamidinium chloride hydrochloride, and N'-(1-acetoxyethyl-5-nitroimidazol-2-ylmethoxycarbonyl) N^2, N^2 -dimethylformamidinium chloride hydrochloride.

xv. 5-Nitroimidazol-2-ylalkyl N-formylcarbamates

5-Nitroimidazol-2-ylalkyl N-formylcarbamates may be produced by reacting an N'-5-nitroimidazol-2-ylalkoxycarbonyl) N²,N²-dialkylformamidine halide hydrohalide with a mild alkaline hydrolysing agent. In the preferred modification of the procedure, an N'-(1-R₁-5-nitroimidazol-2-ylmethoxycarbonyl) N²,N²-dialkylformamidine halide hydrohalide, as produced in accordance with the aforementioned procedure, is dissolved in a mild aqueous base, a solution of sodium bicarbonate in water being preferred, and the solution allowed to stand at a temperature of 15° to 30° C. for from about 12 to about 24 hours. The product may be isolated as the residue by filtration.

It should be noted that 1-hydroxyalkyl or 1-carboxyalkyl compounds of this class cannot be prepared by this method, although the corresponding acyloxy derivatives, that is to say, 1-acyloxyalkyl derivatives and 1-carboxyacyl analogs may be obtained. It should be noted that an attempted hydrolysis of the acyl groups would simultaneously remove the formyl substituent on the carbamoyl group.

xvi. 5-Nitroimidazol-2-ylalkyl N-nitrocarbamates

5-Nitroimidazol-2-ylalkyl N-nitrocarbamates may be produced by reaction of a 5-nitroimidazol-2-ylalkyl carbamate with nitric acid. In the preferred modification of the procedure, the 5-nitroimidazol-2-ylalkyl carbamate, suitably a 1-R₁-5-nitroimidazol-2-ylmethyl carbamate, where R₁ is as shown in Step ii above, suitably 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, is dissolved in an alkanolic acid anhydride, such as acetic anhydride, and treated with an equimolar amount of 95% nitric acid. After standing at a temperature of from about 15° to about 30° C. for a period of from about 15 minutes to 2 hours, the reaction is quenched, suitably by pouring the reaction mixture into an aqueous solution. The product may then be isolated, suitably by extraction of the aqueous mixture with a suitable water-immiscible organic solvent, and worked up in the usual manner.

A suitable form in which the product may be obtained is as the ammonium salt. This may be obtained by saturating the previously dried extract of the reaction mixture in the aforementioned organic solvent with ammonia gas and separating the precipitate thus produced as a residue by filtration.

Among the compounds which may be obtained by this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-nitrocarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-nitrocarbamate, and 1-ethyl-5-nitroimidazol-2-ylmethyl N-nitrocarbamate.

xvii. 5-Nitroimidazol-2-ylalkyl N²-alkylidene- and aralkylidene-carbazates

5-Nitroimidazol-2-ylalkyl N²-alkylidene- and aralkylidene-carbazates may be produced by reacting a 5-nitroimidazol-2-ylalkyl carbazate with a carbonyl compound. In the preferred modification of the procedure, a 1-R₁-5-nitroimidazol-2-ylmethyl carbazate where R₁ is as shown in Step ii above, such as 1-methyl-5-nitroimidazol-2-ylmethyl carbazate, is allowed to react (with or without a solvent) with an excess of a carbonyl compound, suitably an aldehyde or ketone, for example benzaldehyde, acetone, methylethylketone or acetophenone, and heated under reflux, for example, at a temperature of between 40° C. and 120° C. for a period of from 5 to 30 minutes. The product is then isolated, suitably the solvent is removed under reduced pressure and the product recrystallized from the residue. It should be noted that compounds wherein R₁ is oxoalkyl cannot be produced by this method.

Included among the compounds which may be produced in accordance with this procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N²-butylidenecarbazate, 1-ethyl-5-nitroimidazol-2-ylmethyl N²-benzylidenecarbazate, and 1-(1'-(2''-hydroxyethyl)-5'-nitroimidazol-2'-yl)ethyl N²-isopropylidenecarbazate.

xviii. 5-Nitroimidazol-2-ylalkyl N-acyl-N-acyloxycarbamates

5-Nitroimidazol-2-ylalkyl N-acyl-N-acyloxycarbamates may be produced by reacting a 5-nitroimidazol-2-ylalkyl N-hydroxycarbamate with an excess of an acid anhydride in the presence of a basic catalyst. In a preferred modification of the process, a 1-R₁-5-nitroimidazol-2-ylalkyl N-hydroxycarbamate, where R₁ is as shown in Step ii above, but having a value other than hydroxyalkyl or carboxyalkyl, such as 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate is heated together with a weak base, suitably potassium acetate or sodium carbonate, and an alkanolic acid anhydride or aralkanoic acid anhydride, for example, acetic anhydride, propionic anhydride or benzoic anhydride, at a temperature of from about 70° C. to about 100° C. for a period of from about 1 to about 5 hours. The product may then be isolated.

Suitably, the isolation is carried out by removing the volatile components from the reaction mixture at reduced pressure and extracting the residue with a mixture of water and a water-immiscible organic solvent, suitably chloroform. The product is then isolated and the chloroform extracted in the usual manner.

Included among the compounds which may be produced by the above procedure are: 1-methyl-5-nitroimidazol-2-ylmethyl N-acetyl-N-acetoxycarbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl N-butyryl-N-butyroxycarbamate, 1-(1'-ethyl-5'-nitroimidazol-2-yl)ethyl N-benzoyl-N-benzoyloxycarbamate, and 2-(1'-ethyl-5'-nitroimidazol-2'-yl)-ethyl N-phenylacetyl-N-phenylacetoxycarbamate.

xix. 1-Methyl-5-nitroimidazol-2-ylmethyl N-diaminophosphoryl and N-aminosulfonyl carbamates and thiocarbamates

1-Methyl-5-nitroimidazol-2-ylmethyl N-diaminophosphoryl and N-aminosulfonyl carbamates and thiocarbamates may be prepared by reacting a 2-(hydroxymethyl or mercaptomethyl)-5-nitroimidazole with a dihalophosphoryl or halosulfonyl isocyanate, followed by reaction with a suitable amine. In the preferred procedure, a 1-R₁-2-hydroxymethyl-5-nitroimidazole where R₁ is as shown in Step ii above, provided that R₁ is other than hydroxyalkyl, for example 1-methyl-2-hydroxymethyl-5-nitroimidazole, is taken up in a reaction-inert solvent, for example a hydrocarbon solvent such as benzene or an ether such as tetrahydrofuran or 1,2-dimethoxyethane, suitably, but not critically, in the presence of a trace of an organic base, such as pyridine, and heated with dichlorophosphoryl isocyanate or chlorosulfonyl isocyanate under reflux for from about 30 minutes to about 2 hours. The solvent is then removed under reduced pressure and the product taken up in a suitable solvent, for example tetrahydrofuran, and treated with ammonia or the desired amine, for example gaseous ammonia, an alkylamine such as methylamine or butylamine, an arylamine such as aniline, an aralkylamine such as benzylamine or a secondary amine such as morpholine. The mixture is allowed to stand for from 1 to 4 hours at from 10° C. to 30° C., filtered, and the solvent removed from the filtrate under reduced pressure. The product is then isolated. In a suitable procedure, the residue from the filtration is dissolved in water and any insoluble material is combined with the residue from the evaporation of the solvent and the combined fractions recrystallised, suitably from an alkaneol such as ethanol, to yield the desired 1-methyl-5-nitroimidazol-2-ylmethyl N-diaminophosphoryl or N-aminophosphoryl carbamate or thiocarbamate.

xx. 3-Nitro-5,6-dihydroimidazo-[1,2- α]pyrrol-7-yl carbamates

3-Nitro-5,6-dihydroimidazo-[1,2- α]pyrrol-7-yl carbamates may be prepared in the following manner:

3-Nitro-7-oxo-5,6-dihydroimidazo-[1,2- α]pyrrole is reduced to the corresponding 7-hydroxy compound and then converted into the corresponding 7-yl carbamate by means of any of the general procedures for the formation of carbamates disclosed in the present application, preferably method vi, wherein the hydroxy compound is reacted with a phenyl haloformate and subsequently treated with an amine. In the preferred modification of this procedure, 3-nitro-7-oxo-5,6-dihydroimidazo-[1,2- α]pyrrole is taken up in a lower alkaneol, such as ethanol, and treated with a reducing agent, suitably a metallic reducing agent, sodium borohydride being especially suitable, and the reaction mixture is allowed to stand at a temperature of from about 10° C. to about 25° C. for a period of from about 4 to about 8 hours. The product is then isolated. In the preferred method, a small amount of a volatile acid, suitably an organic acid, such as a lower alkanolic acid, suitably acetic acid, is added to decompose the excess borohydride. The reaction mixture is concentrated to a small volume under reduced pressure and an excess of water added slowly. The 3-nitro-7-oxo-5,6-dihydroimidazo-[1,2- α]pyrrole separates as a precipitate and is isolated by filtration.

The dried 3-nitro-7-hydroxy-5,6-dihydroimidazo-[1,2- α]pyrrole is taken up in an organic base, suitably pyridine, lutidine or collidine, and treated with a phenyl haloformate, suitably phenyl chloroformate, and the reaction allowed to proceed and the product isolated as set forth in method vi above. The product, 3-nitro-5,6-dihydroimidazo-[1,2- α]pyrrol-7-yl phenyl carbonate is then taken up in a suitable inert organic solvent, a haloalkane such as chloroform being especially suitable. Where it is desired to produce the corresponding carbamate, the solution is added to an approximately equal volume of liquid ammonia, and maintained at a temperature of from about -35° C. to about -75° C. The reaction mixture is then worked up in the usual manner and the product isolated.

Where it is desired to obtain an N-substituted carbamate, the solution of the 3-nitro-5,6-dihydroimidazo-[1,2- α]pyrrol-7-ylphenyl carbonate in chloroform is reacted with a substituted amine as set forth in the various procedures for the preparation of these compounds hereinabove.

Among the products which may be produced in accordance with this procedure are 3-nitro-5,6-dihydroimidazo-[1,2- α]pyrrol-7-yl carbamate and N-substituted derivatives thereof.

Compounds of Formulae I and II above have antiprotozoal activity, and are particularly active against the causative organisms of the protozoal parasitic diseases, trichomoniasis and enterohepatitis. Certain of them are also effective against amoebiasis and trypanosomiasis, as well as against the PPLO organisms and schistosomes. It will, of course, be understood that the compounds differ in their degree of efficacy against the various organisms.

Trichomoniasis is a protozoan disease caused by parasites of the genus *Trichomonas*. Compounds of the invention are effective against the particularly troublesome form of trichomoniasis known as *T. vaginalis vaginitis*, caused by infestation of the vagina with *T. vaginalis*. In treating this disease, the active ingredients may be administered either orally or topically, and normally in conjunction with a pharmaceutical diluent, carrier or coating. For oral administration, unit dosage forms such as tablets or capsules are normally used that may contain from about 50 to about 500 mg. of active ingredient. These are prepared by techniques known in the art, and contain the usual diluents, granulating agents, extenders and/or lubricating agents known to be satisfactory for the compounding of tablets and capsules. It is preferred to administer the compounds of the invention orally at a dose level of from about 25—1,000 mg./day, in either single or divided doses with divided doses being used more frequently than a single daily dose. An example of a suitable compressed tablet composition is the following:

Component	Mg. per Tablet
1-Methyl-5-nitroimidazol-2-ylmethyl carbamate	250
Dicalcium phosphate	100
Lactose	75
Starch	50
Guar gum	12
Magnesium stearate	2—3

If desired, tablets may be sugar-coated or enteric-coated by standard techniques. Alternatively, the antitrichomonal agent may be formulated in capsule form using fillers such as lactose, starch or kaolin. A typical capsule would contain 250 mg. of, for instance, 1-methyl-5-nitroimidazol-2-ylmethyl methylcarbamate, 2—3 g. of magnesium stearate and about 75 mg. of lactose in a No. 0 size capsule. Tablets and capsules containing smaller quantities of active ingredient may be made by reducing proportionately the amounts of excipients and diluents illustrated above. Alternatively, the active ingredients may be administered orally in liquid pharmaceutical vehicles such as solutions, emulsions, syrups or suspensions containing the diluents, flavoring agents and preservatives customarily used in the pharmaceutical art.

For topical application, vaginal creams or suppositories containing the active ingredient may be used. To illustrate, a cream is prepared by mixing sufficient quantities of hydrophilic ointment and water, containing from about 5 to 10% by weight of active ingredient, in sufficient quantities to produce a cream having the desired consistency.

Representative examples of imidazole derivatives of this invention that are highly active and thus particularly useful for treating trichomoniasis are: 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl methylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl 4-morpholinecarboxylate, 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl methylthioncarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl thioncarbamate, 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl carbamate, 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl hydroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl hydroxycarbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl carbamate and 1-ethyl-5-nitroimidazol-2-ylmethyl hydroxycarbamate. These represent preferred anti-trichomonal agents of the invention, although the other imidazole derivatives of the invention are of value against this disease.

Enterohepatitis is a disease occurring primarily in turkeys and is caused by the protozoan parasite *Histomonas meleagridis*. It is also known as turkey blackhead disease. Compounds of this invention are useful in the prevention and treatment of this disease and for this purpose are administered to turkeys mixed with an element of poultry sustenance, i.e. in the feed or drinking water of the turkeys. Although the optimum dose level will depend on the particular compound and the severity of the infection, good control of enterohepatitis is obtained by orally administering to the turkeys a feed containing from 0.003% to 0.1% by weight of active ingredient. When the material is administered via the drinking water, somewhat higher levels may be used, especially therapeutically. For instance, the drinking water may contain up to 0.2% by weight of the active ingredient with good results. Those substances previously mentioned as preferred anti-trichomonal agents are also among those preferred in combating turkey blackhead disease.

As previously stated, imidazole derivatives described herein may also be used against trypanosomiasis and amoebiasis. In addition, certain of them, and particularly 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl hydroxycarbamate and 1-ethyl-5-nitroimidazol-2-ylmethyl carbamate, possess activity against the pleuro-pneumonia-like organisms which have come to be known as PPLO organisms.

The following examples are given for the purpose of illustration of the invention. Other compounds that can be made by analogous methods are:

S-(1'-methyl-5'-nitroimidazol-2'-ylmethyl)pseudo-thiourea,
1-methyl-5-nitroimidazol-2-ylmethyl N-methylthioncarbamate,
1-(1'-methyl-5-nitroimidazol-2'-yl)ethyl N-hydroxycarbamate,
1-(2'-carbamoyloxyethyl)-5-nitroimidazol-2-ylmethyl carbamate,
1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate.

EXAMPLE 1

1-Methyl-5-nitroimidazol-2-yl-methyl chloroformate

3.12 g. 1-methyl-2-hydroxymethyl-5-nitroimidazole is dissolved in a mixture of 4.3 ml. of dimethylaniline and 20 ml. of dioxane. This solution is then added dropwise to 30 ml. of phosgene. The resulting suspension is stirred for two hours at 0-5° C. and then for two hours at room temperature. The solvent is then removed by blowing dry nitrogen through the suspension for two hours. The oil remaining at the end of this time consists predominantly of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate.

In accordance with the above procedure, but starting with 1-methyl-2-mercapto-methyl-5-nitroimidazole, in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained 1-methyl-5-nitroimidazol-2-yl-methyl chlorothiolformate.

In accordance with the above procedure and starting with either of the aforementioned nitroimidazoles but using thiophosgene in place of phosgene, there are obtained 1-methyl-5-nitroimidazol-2-yl-methyl chlorothionformate and 1-methyl-5-nitroimidazol-2-yl-methyl chlorodithioformate.

EXAMPLE 2

1-Methyl-5-nitroimidazol-2-ylmethyl carbamate

0.05 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with ethanol and recrystallized from methanol to yield 1-methyl-5-nitroimidazol-2-ylmethyl carbamate; m.p. 166-170° C.

In accordance with the above procedure, but starting with 1-(1-methyl-5-nitroimidazol-2-yl)-ethyl phenyl carbonate, 2-(1-methyl-5-nitroimidazol-2-yl)-ethyl phenyl carbonate and 3-(1-methyl-5-nitroimidazol-2-yl)-prop-2-en-1-yl phenyl carbonate in place of 1-methyl-5-nitroimidazol-2-yl-methyl phenyl carbonate there is obtained the corresponding 1-(1-methyl-5-nitroimidazol-2-yl)ethyl carbamate, 2-(1-methyl-5-nitroimidazol-2-yl)ethyl carbamate, and 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-enyl carbamate.

EXAMPLE 3

1-Methyl-5-nitroimidazol-2-ylmethyl carbamate

3.12 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole is dissolved in 100 ml. of methylene dichloride and cooled to 0° C. 2.64 g. of sodium cyanate and 4.5 g. of trifluoroacetic acid are added. The flask is stoppered tightly and the mixture stirred for 24 hours at 0° C. 200 ml. of methylene chloride is then added and the mixture washed with saturated aqueous potassium bicarbonate solution. The methylene chloride

solution is concentrated to dryness *in vacuo* to give a residue of 1-methyl-5-nitro-2-imidazolylmethyl carbamate. This solid is recrystallized from a minimum volume of ethyl acetate to give substantially pure 1-methyl-5-nitroimidazol-2-ylmethyl carbamate; m.p. 166—170° C.

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EXAMPLE 4

1-Methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate

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1.35 g. of 1-methyl-2-chloromethyl-5-nitroimidazole is dissolved in 25 ml. of dry ethanol at room temperature, and 1.11 g. of potassium thiocyanate is added to this solution. The resulting mixture is refluxed for two hours and then allowed to stand at room temperature for about 12 hours. It is warmed to about 75° C. on a steam bath and the solid material removed by filtration. The filtrate is diluted with an equal volume of water and the resulting solution chilled and scratched to induce crystallization. The solid which forms is removed by filtration, washed with ice-water and dried. It is 1-methyl-2-thiocyanatomethyl-5-nitroimidazole; m.p. 87—88° C. This product is crystallized from a minimum volume of benzene containing a trace of hexane to give yellow crystals of 1-methyl-2-thiocyanatomethyl-5-nitroimidazole; m.p. 87.5—88° C.

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5 g. of 1-methyl-2-thiocyanatomethyl-5-nitroimidazole is added portionwise over a period of 15 minutes to 25 ml. of cold concentrated sulfuric acid. The resulting solution is held at 0° C. for about 14 hours and then poured on to an excess of crushed ice. The solution is adjusted to pH 6 with saturated potassium bicarbonate solution. The solid material is removed by filtration and washed with ice-water. The solid is extracted with about 10 m. of ethyl acetate and the ethyl acetate solution dried over sodium sulfate and then concentrated essentially to dryness. A small volume of hexane is added to the residue and the solid 1-methyl-5-nitro-2-imidazolylmethyl thiolcarbamate removed by filtration. There are obtained in this way 4.34 g. of 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate; m.p. 138—140° C.

EXAMPLE 5

1-Methyl-5-nitroimidazol-2-ylmethyl carbamate

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1-Methyl-5-nitroimidazol-2-ylmethyl chloroformate, as obtained in accordance with Example 1, is cooled to 0° C. and 25 ml. of liquid ammonia added thereto. The resulting mixture is stirred for 10 minutes in the cold and then an additional 25 ml. of liquid ammonia is added. The mixture is then allowed to warm to room temperature and stirred until the excess ammonia evaporates. The residue thus obtained is dissolved in 100 ml. of water and the aqueous solution extracted with three 100 ml. portions of ethyl acetate. The ethyl acetate extracts are combined, backwashed with 25 ml. of water and then dried over sodium sulfate. The ethyl acetate is then concentrated to dryness *in vacuo* to give a residue consisting of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate. The product is recrystallized from ethyl acetate and then from water to give substantially pure material; m.p. 172—173° C.

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In accordance with the above procedure but starting with 1-methyl-5-nitroimidazol-2-ylmethyl chlorothiolformate, 1-methyl-5-nitroimidazol-2-ylmethyl chlorothionformate, 1-methyl-5-nitroimidazol-2-ylmethyl chlorodithioformate in place of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl thioncarbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl dithiocarbamate.

EXAMPLE 6

1-Methyl-5-nitroimidazol-2-ylmethyl carbamate

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3.1 g. (0.02 mole) of (1-methyl-2-hydroxymethyl)-5-nitroimidazole is dissolved in 100 ml. of benzene and 25 ml. of pyridine. 1.9 g., (0.022 mole) of gaseous carbamoyl chloride is introduced into the stirred solution. The solution is allowed to stand at 15° C. for 8 hours and then concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with ice-water, and the ethyl acetate extract dried over sodium sulfate. On evaporation of the solvent under reduced pressure, the residue is recrystallized from acetone or ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl carbamate; m.p. 166—170° C.

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In accordance with the above procedure but using dimethylcarbamoyl chloride or diethylcarbamoyl chloride and adding these reagents in liquid rather than gaseous form to the reaction mixture in place of carbamoyl chloride, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl N,N-dimethylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diethylcarbamate.

In accordance with the above procedure but using thiocarbamoyl chloride, dimethylthiocarbamoyl chloride, and diethylthiocarbamoyl chloride, in place of carbamoyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-yl-methyl thioncarbamate, 1-methyl-5-nitroimidazol-2-yl-methyl N,N-dimethylthioncarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diethylthioncarbamate.

EXAMPLE 7

1-Methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate

3.5 g., (.02 mole) of 1-methyl-2-mercaptopomethyl-5-nitroimidazole is dissolved in 100 ml. of benzene and 25 ml. of pyridine under nitrogen. 1.9 g., (0.022 mole) of gaseous carbamoyl chloride is introduced into the stirred solution. The solution is allowed to stand at 15° C. for 8 hours and then concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with ice-water and the ethyl acetate extract dried over sodium sulfate. On evaporation of the solvent under reduced pressure, the residue is recrystallized from acetone or ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate; m.p. 138—140° C.

In accordance with the above procedure but using dimethylcarbamoyl chloride or diethylcarbamoyl chloride and adding these reagents in liquid rather than gaseous form to the reaction mixture in place of carbamoyl chloride, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl N,N-dimethylthiolcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diethylthiolcarbamate.

In accordance with the above procedure but using thiocarbamoyl chloride and dimethylthiocarbamoyl chloride and diethylcarbamoyl chloride, in place of carbamoyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl dithiocarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N,N-dimethyldithiocarbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diethyldithiocarbamate.

EXAMPLE 8

1-Methyl-5-nitroimidazol-2-ylmethyl carbamate

1.57 g., (0.01 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole, 0.1 g. sodium ethoxide, 10 g. of ethyl carbamate, and 20 ml. of benzene are heated under reflux for 2 hours. The solvent is removed under reduced pressure and the residue stirred with 10 ml. of water. The mixture is extracted with ethyl acetate. The ethyl acetate fraction is dried over sodium sulfate and evaporated to give crude 1-methyl-5-nitroimidazol-2-ylmethyl carbamate.

In accordance with the above procedure but starting with 1-methyl-2-mercaptopomethyl-5-nitroimidazole, in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate.

EXAMPLE 9

1-Methyl-5-nitroimidazol-2-ylmethyl methylcarbamate

6 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole and 3.5 ml. of methyl isocyanate are added to 200 ml. of benzene containing 0.5 ml. of pyridine. The resulting mixture is refluxed until complete solution is obtained. The solvent is then removed by evaporation under reduced pressure. The partially crystalline material thus obtained is recrystallized from 12 ml. of water to give 1.14 g. of 1-methyl-5-nitroimidazol-2-ylmethyl methylcarbamate; m.p. 99—101° C.

In accordance with the above procedure, but starting with 1-methyl-2-mercaptopomethyl-5-nitroimidazole, in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl methyl thiolcarbamate.

EXAMPLE 10

1-Methyl-5-nitroimidazol-2-ylmethyl methylthioncarbamate

0.5 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole and 0.28 g. of methyl isothiocyanate are added to 20 ml. of benzene containing 0.54 ml. of triethylamine. The resulting mixture is refluxed for 23 hours. It is then concentrated almost to dryness *in vacuo* and the solid material removed by filtration. This product is 1-methyl-5-nitroimidazol-2-ylmethyl methylthioncarbamate; m.p. 133.5—135° C. It is recrystallized from water to give substantially pure material; m.p. 135.5—136° C.

In accordance with the above procedure, but starting with 1-methyl-2-mercaptopomethyl-5-nitroimidazole, in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl methyl dithiocarbamate.

EXAMPLE 11

2-(1-Methyl-5-nitroimidazol-2-ylmethyl) pseudourea hydrofluoroborate

A mixture of 3.14 g., (0.02 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole, 2.6 ml. of boron trifluoride diethylether, 50 ml. of 1,2-dimethoxyethane, and 1.0 g. of cyanamide is allowed to stand at 0° C. for 3 days. Anhydrous hydrogen fluoride (0.02 mole) in about 10 ml. of benzene is added. After the addition of another 40 ml. of benzene, the product, 2-(1-methyl-5-nitroimidazol-2-ylmethyl) pseudourea hydrofluoroborate, is obtained by filtration.

EXAMPLE 12

2-(1-Methyl-5-nitroimidazol-2-ylmethyl)-1,3-diethylpseudourea hydrochloride

A mixture of 3.14 g., (0.02 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole, 2.0 g., (0.02 mole) of diethylcarbodiimide and 100 ml. of 1,2-dimethoxyethane is allowed to stand at room temperature for 2 days. The addition of gaseous hydrogen chloride (0.7 g.), followed by 50 ml. of hexane, results in the crystallization of product. After filtration, and washing with diethyl ether, 2-(1-methyl-5-nitroimidazol-2-ylmethyl)-1,3-diethylpseudourea hydrochloride is obtained.

EXAMPLE 13

S-(1-Methyl-5-nitroimidazol-2-ylmethyl) pseudothiourea hydrochloride

0.25 g., (0.0016 mole) of 1-methyl-2-chloromethyl-5-nitroimidazole and 0.106 g., (0.0014 mole) of thiourea are added to 2 ml. of dry ethanol and the resulting mixture refluxed for 17 hours. At the end of this time, the mixture is cooled to about 15° C. and the solid material removed by filtration. The solid product is washed with a few ml. of alcohol and ether, and air-dried. Recrystallization is accomplished from a mixture of 4—5 ml. of ethanol and 2—3 ml. of methanol. The solution is filtered hot, then concentrated to a volume of about 6 ml. and chilled. The S-(1-methyl-5-nitroimidazol-2-ylmethyl) isothiuronium chloride is filtered, washed with alcohol and then ether, and dried to give substantially pure material; m.p. 200° C.

In accordance with the above procedure, but starting with 1-methyl-2-(1'-chloroethyl)-5-nitroimidazole, and 1-acetoxyethyl-2-chloromethyl-5-nitroimidazole, in place of 1-methyl-2-chloromethyl-5-nitroimidazole, there are obtained the corresponding S-1-[1'-methyl-5'-nitroimidazol-2'-yl]ethylpseudo-thiourea, and S-(1-acetoxyethyl-5-nitroimidazol-2-ylmethyl)-pseudo-thiourea.

Similarly, but using dimethylthiourea in place of thiourea, there is obtained the corresponding S-(1-methyl-5-nitroimidazol-2-ylmethyl)-pseudo-dimethylthiourea.

EXAMPLE 14

2-(1-Methyl-5-nitroimidazol-2-ylmethyl-thio)-2-imidazoline

0.175 g. (0.001 mole) of 1-methyl-2-chloromethyl-5-nitroimidazole and 0.102 g. (0.001 mole) of imidazolidine-2-thione are dissolved in 5 ml. of ethanol and heated under reflux for 30 minutes, after which time a crystalline precipitate is produced. The mixture is heated under reflux for a further 2 hours, cooled and filtered to yield 2-(1-methyl-5-nitroimidazol-2-ylmethyl-thio)-2-imidazoline; m.p. 220—226° C. (dec.).

EXAMPLE 15

1-n-Butyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 16.9 g. (0.1 mole) of 1-n-butyl-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-n-butyl-2-hydroxymethyl-5-nitroimidazole.

A solution of 2.0 g. (0.01 mole) of 1-n-butyl-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-n-butyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of 640 mg. (0.002 mole) of 1-n-butyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. The mixture is allowed to stand for 1 day at 5° C. 1-n-Butyl-5-nitroimidazol-2-ylmethyl carbamate is obtained after evaporating the solvent and washing the residue with water.

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In accordance with the above procedure, but starting with 1-methyl-5-nitroimidazole, 1-ethyl-5-nitroimidazole and 1-propyl-5-nitroimidazole, in place of 1-*n*-butyl-5-nitroimidazole, there are obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1-ethyl-5-nitroimidazol-2-ylmethyl carbamate, and 1-propyl-5-nitroimidazol-2-ylmethyl carbamate.

EXAMPLE 16

1-Benzyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 20.3 g. (0.1 mole) of 1-benzyl-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110–150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-benzyl-2-hydroxymethyl-5-nitroimidazole.

A solution of 2.3 g. (0.01 mole) of 1-benzyl-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3–4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-benzyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of 706 mg. (0.002 mole) of 1-benzyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. The mixture is allowed to stand for 1 day at 5° C. 1-Benzyl-5-nitroimidazol-2-ylmethyl carbamate is obtained in crystalline form after evaporating the solvent and washing the residue with water.

EXAMPLE 17

1-Allyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 15.3 g. (0.1 mole) of 1-allyl-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110–150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-allyl-2-hydroxymethyl-5-nitroimidazole.

A solution of 1.83 g. (0.01 mole) of 1-allyl-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3–4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-allyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of 606 mg. (0.002 mole) of 1-allyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. The mixture is allowed to stand for 1 day at 5° C. 1-Allyl-5-nitroimidazol-2-ylmethyl carbamate is obtained in crystalline form after evaporating the solvent and washing the residue with water.

EXAMPLE 18

1-Phenyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 18.9 g. (0.1 mole) of 1-phenyl-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110–150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-phenyl-2-hydroxymethyl-5-nitroimidazole.

A solution of 2.19 g. (0.01 mole) of 1-phenyl-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3–4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-phenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of .678 mg. (0.002 mole) of 1-phenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. The mixture is allowed to stand for 1 day at 5° C. 1-Phenyl-5-nitroimidazol-2-ylmethyl carbamate is obtained in crystalline form after evaporating the solvent and washing the residue with water.

EXAMPLE 19

1-*p*-Nitro-phenyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 23.4 g. (0.1 mole) of 1-*p*-nitro-phenyl-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-*p*-nitrophenyl-2-hydroxymethyl-5-nitroimidazole.

A solution of 2.64 g. (0.01 mole) of 1-*p*-nitrophenyl-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-*p*-nitrophenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of 768 mg. (0.002 mole) of 1-*p*-nitrophenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. The mixture is allowed to stand for 1 day at 5° C. 1-*p*-Nitrophenyl-5-nitroimidazol-2-ylmethyl carbamate is obtained in crystalline form after evaporating the solvent and washing the residue with water.

EXAMPLE 20

1-(2'-Acetoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate and 1-(2'-Hydroxyethyl)-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 24.25 g. of 1-(2'-acetoxyethyl)-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-acetoxyethyl)-2-hydroxymethyl-5-nitroimidazole; m.p. 138—145° C.

A solution of 1.4 g. of 1-(2'-acetoxyethyl)-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate, m.p. 93—95° C., is separated by filtration.

1.5 g. of 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with ethanol and recrystallized to yield 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate; m.p. 160—162° C.

6 g. of 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate is dissolved in 100 ml. of ethanol and the solution saturated with ammonia. The mixture is allowed to stand for 12 hours at 15° C. and the solvent removed by evaporation under reduced pressure. The residue is washed with methanol to yield 1-(2'-hydroxyethyl)-5-nitroimidazol-2-ylmethyl carbamate; m.p. 150—152° C.

EXAMPLE 21

1-(2'-Hydroxypropyl)-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 21.3 g. (0.1 mole) of 1-(2'-acetoxypropyl)-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yield 1-(2'-acetoxypropyl)-2-hydroxymethyl-5-nitroimidazole; m.p. 150—155° C.

A solution of 2.43 g. (0.01 mole) of 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

A solution of 726 mg. (0.002 mole) of 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform, cooled in an ice-bath, is saturated with dry ammonia. It is allowed to stand for 5 days at 5° C. 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl carbamate is obtained in crystalline form, m.p. 106—108° C., after evaporating the solvent and washing the residue with water.

The 1-(2'-acetoxypropyl)-5-nitroimidazol-2-ylmethyl carbamate produced as above is redissolved in methanol and the solution saturated with anhydrous ammonia. The mixture is allowed to stand for 2 days at 15° C. and concentrated under reduced pressure. The residue is recrystallized from ethyl acetate, ethyl alcohol or a mixture of the two, to yield 1-(2'-hydroxypropyl)-5-nitroimidazol-2-ylmethyl carbamate.

In accordance with the above procedure, but starting with 1-(2'-acetoxybutyl)-5-nitroimidazole, 1-(2'-acetoxypropyl)-5-nitroimidazole, 1-(3'-acetoxybutyl)-5-nitroimidazole, 1-(3'-acetoxypropyl)-5-nitroimidazole and 1-(3'-acetoxypropyl)-5-nitroimidazole, in place of 1-(2'-acetoxypropyl)-5-nitroimidazole, there is obtained the corresponding 1-(2'-hydroxybutyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-hydroxypropyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(3'-hydroxybutyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(3'-hydroxypropyl)-5-nitroimidazol-2-ylmethyl carbamate and the corresponding 1-(acetoxyalkyl)-5-nitroimidazol-2-ylmethyl carbamate analogs thereof.

In accordance with the above procedure, but using the propionyloxy, butyryloxy or valeryloxy analogs of any of the aforementioned 1-hydroxyalkyl-5-nitroimidazoles as starting materials in place of the 1-acetoxyalkyl-5-nitroimidazoles utilized above, there are obtained the corresponding 1-alkanoyloxyalkyl-5-nitroimidazol-2-ylmethyl carbamates and 1-hydroxyalkyl-5-nitroimidazol-2-ylmethyl carbamates.

EXAMPLE 22

1-(2'-Oxopropyl)-5-nitroimidazol-2-ylmethyl carbamate

20.5 g., (0.1 mole) of 1-(2-oxopropyl)-5-nitroimidazole hydrochloride is dissolved in 100 ml. 1,2-ethylenedithiol and dry gaseous hydrogen chloride passed through the solution for 30 minutes. The excess dithioglycol is removed by evaporation under high vacuum. The residue is treated with aqueous sodium bicarbonate, taken up in ethyl acetate, dried over sodium sulfate and the solvent removed by evaporation under reduced pressure to yield 1-(2'-methyl-1',3'-dithiolan-2'-ylmethyl)-5-nitroimidazole. The dithiolane is dissolved in 125 ml. of dimethyl sulfoxide and treated with 0.5 mole of paraformaldehyde in a sealed tube at 120° C. for 24 hours. Excess paraformaldehyde is removed by centrifugation and the dimethyl sulfoxide is removed by high vacuum concentration. The residue is dissolved in acetone and centrifuged to remove insoluble paraformaldehyde. After concentration, the residue is dissolved in ethyl acetate, thoroughly washed with water, dried and treated with dry hydrogen chloride to give a precipitate of 1-(2'-methyl-1',3'-dithiolan-2'-ylmethyl)-5-nitroimidazol-2-ylmethanol hydrochloride which is separated by filtration. The thus produced 5-nitroimidazol-2-ylmethanol derivative is dissolved in 100 ml. of dry pyridine and treated with 12.5 g., (0.08 mole) of phenyl chloroformate at ice-bath temperature. After 4 hours at room temperature, the mixture is concentrated to dryness, taken up in water, neutralized with sodium bicarbonate and extracted into ethyl acetate. After thorough washing with water, the solution is dried and concentrated. The product is triturated with ether and filtered to yield 1-(2'-methyl-1',3'-dithiolan-2'-ylmethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate. The product (5.0 g.) is treated with dry liquid ammonia (25 ml.) at -33° C. for 2 hours. After removal of the liquid ammonia, the residue is warmed on a steam-bath for one hour with 100 ml. 1 n aqueous hydrochloric acid to hydrolyze the dithiolane. The mixture is concentrated to dryness to yield the hydrochloride of 1-(2'-oxopropyl)-5-nitroimidazol-2-ylmethyl carbamate. The product may be further purified by recrystallization from acetone.

Treatment with aqueous sodium bicarbonate followed by extraction with ethyl acetate and removal of the solvent yields the free base.

In accordance with the above procedure, but starting with 1-(2'-oxobutyl)-5-nitroimidazole, 1-(2'-oxopentyl)-5-nitroimidazole, 1-(3'-oxobutyl)-5-nitroimidazole, and

1-(3'-oxopentyl)-5-nitroimidazole, in place of 1-(2'-oxopropyl)-5-nitroimidazole, there is obtained the corresponding 1-(2'-oxobutyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-oxopentyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(3'-oxobutyl)-5-nitroimidazol-2-ylmethyl carbamate, and 1-(3'-oxopentyl)-5-nitroimidazol-2-ylmethyl carbamate.

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EXAMPLE 23

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1-(2'-Ethoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 9.2 g. (0.05 mole) of 1-(2'-ethoxyethyl)-5-nitroimidazole, 15 g (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-ethoxyethyl)-2-hydroxymethyl-5-nitroimidazole.

A solution of 1.99 g. (0.01 mole) of 1-(2'-ethoxyethyl)-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(2'-ethoxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

3.19 g. of 1-(2'-ethoxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate. The residue is washed with ethanol and recrystallized from methanol to yield 1-(2'-ethoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate.

In accordance with the above procedure, but starting with 1-(2'-methoxyethyl)-5-nitroimidazole, 1-(2'-propoxyethyl)-5-nitroimidazole, 1-(2'-butoxyethyl)-5-nitroimidazole, 1-(2'-benzyloxyethyl)-5-nitroimidazole, 1-(2'-ethoxypropyl)-5-nitroimidazole, 1-(2'-ethoxybutyl)-5-nitroimidazole, and 1-(2'-ethoxypentyl)-5-nitroimidazole, in place of 1-(2'-ethoxyethyl)-5-nitroimidazole, there is obtained the corresponding 1-(2'-methoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-propoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-butoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-benzyloxyethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-ethoxypropyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-ethoxybutyl)-5-nitroimidazol-2-ylmethyl carbamate, and 1-(2'-ethoxypentyl)-5-nitroimidazol-2-ylmethyl carbamate.

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EXAMPLE 24

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Ethyl 2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetate

A mixture of 0.1 mole of ethyl 5-nitroimidazole-1-ylacetate, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields ethyl 2-hydroxymethyl-5-nitroimidazol-1-ylacetate.

A solution of 0.01 mole of ethyl 2-hydroxymethyl-5-nitroimidazol-1-ylacetate in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of ethyl 2-phenoxy-carbonyloxymethyl-5-nitroimidazol-1-ylacetate, m.p. 106—108° C., is separated by filtration.

2.0 g. of ethyl 2-phenoxy-carbonyloxymethyl-5-nitroimidazol-1-ylacetate is dissolved slowly in 20 ml of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with ethanol and recrystallized from methanol to yield ethyl 2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetate.

In accordance with the above procedure but starting with methyl 5-nitroimidazol-1-yl acetate, propyl 5-nitroimidazol-1-yl acetate, butyl 5-nitroimidazol-1-yl acetate, ethyl 5-nitroimidazol-1-yl propionate, methyl 5-nitroimidazol-1-yl propionate, propyl 5-nitroimidazol-1-yl propionate, or butyl 5-nitroimidazol-1-yl propionate, in place of ethyl 5-nitroimidazol-1-yl acetate, there is obtained the corresponding methyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl acetate, propyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl acetate, butyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl acetate, ethyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl propionate, methyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl propionate, propyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl propionate, or butyl 2-carbamoyloxymethyl-5-nitroimidazol-1-yl propionate.

EXAMPLE 25

2-Carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide

Ethyl 2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetate, as obtained from the procedure set forth in Example 24, is dissolved in 10 ml. of methanol saturated with gaseous ammonia at 0° C., sealed in a tube and heated at 60° C. for 2 hours. The reaction mixture is concentrated under reduced pressure and the residue recrystallized from ethyl acetate to yield 2-carbamoyloxymethyl-5-nitroimidazol-ylacetamide; m.p. 221—223° C.

In accordance with the above procedure, but starting with any of the alkyl 2-carbamoyloxymethyl-5-nitroimidazol-1-ylalkanoates produced in accordance with the previous example, there are obtained 2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide or 2-carbamoyloxymethyl-5-nitroimidazol-1-ylpropionamide.

EXAMPLE 26

1-(2'-Carbamoyloxyethyl)-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 0.1 mole of 1-(2'-hydroxyethyl)-5-nitroimidazole, 5 g. (0.015 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole.

A solution of 1.3 g. of 1-(2'-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 2.2 g. of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is extracted with ethyl acetate, the extract dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The residue, 1-(2'-carbamoyloxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate, is dissolved in 10 ml. of chloroform and the solution added to 50 ml. of dry liquid ammonia. The ammonia is allowed to evaporate and the residue recrystallized from ethyl acetate to yield 1-(2'-carbamoyloxyethyl)-5-nitroimidazol-2-ylmethyl carbamate; m.p. 174—175° C.

EXAMPLE 27

N,N-Diethyl-2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide

A mixture of 22.6 g. (0.1 mole) of N,N-diethyl-5-nitroimidazol-1-ylacetamide, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields N,N-diethyl-2-hydroxymethyl-5-nitroimidazol-1-ylacetamide.

A solution of 2.56 g. (0.01 mole) of N,N-diethyl-2-hydroxymethyl-5-nitroimidazol-1-ylacetamide in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(N',N'-diethylcarbamoylmethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is filtered.

2.0 g. of 1-(N',N'-diethylcarbamoylmethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with ethanol and recrystallized from methanol to yield N,N-diethyl-2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide.

In accordance with the above procedure, but starting with N,N-dibenzyl-5-nitroimidazol-1-ylacetamide, N,N-dimethyl-5-nitroimidazol-1-ylacetamide or N,N-dipropyl-5-nitroimidazol-1-ylacetamide, there is obtained N,N-dibenzyl-2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide, N,N-dimethyl-2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide, or N,N-dipropyl-2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetamide.

EXAMPLE 28

2-Carbamoyloxymethyl-5-nitroimidazol-1-ylacetonitrile

A mixture of 15.2 g. (0.1 mole) of 5-nitroimidazol-1-ylacetonitrile, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 2-hydroxymethyl-5-nitroimidazol-1-ylacetonitrile.

A solution of 1.82 g. (0.01 mole) of 2-hydroxymethyl-5-nitroimidazol-1-ylacetonitrile in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-cyanomethyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

To 3.0 g. of 1-cyanomethyl-5-nitroimidazol-2-ylmethyl phenyl carbonate dissolved in 50 ml. of chloroform is added 50 cc. of chloroform containing 0.4 g. of anhydrous ammonia. The solution is allowed to stand overnight at room temperature and then evaporated to dryness. The residue is washed with water and recrystallized from methanol to yield 2-carbamoyloxymethyl-5-nitroimidazol-1-ylacetonitrile.

In accordance with the above procedure, but starting with 3-(5'-nitroimidazol-1'-yl)propionitrile in place of 5-nitroimidazol-1-ylacetonitrile, there is obtained 3-(2'-carbamoyloxymethyl-5'-nitroimidazol-1'-yl)propionitrile.

EXAMPLE 29

1-(2'-N-Morpholinoethyl)-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 21.4 g. (0.1 mole) of 1-(2'-N-morpholinoethyl)-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-N-morpholinoethyl)-5-nitroimidazol-2-ylmethanol.

A solution of 2.44 g. (0.01 mole) of 1-(2'-N-morpholinoethyl)-5-nitroimidazol-2-ylmethanol in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(2'-N-morpholinoethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

0.05 moles of 1-(2'-N-morpholinoethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with ethanol and recrystallized from methanol to yield 1-(2'-N-morpholinoethyl)-5-nitroimidazol-2-ylmethyl carbamate.

In accordance with the above procedure, but starting with 1-(2'-N-pyrrolidinoethyl)-5-nitroimidazole, 1-(2'-N-piperidinoethyl)-5-nitroimidazole, 1-(2'-N,N-dimethylaminoethyl)-5-nitroimidazole or 1-(2'-N,N-diethylaminoethyl)-5-nitroimidazole, in place of 1-(2'-N-morpholinoethyl)-5-nitroimidazole, there is obtained 1-(2'-N-pyrrolidinoethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-N-piperidinoethyl)-5-nitroimidazol-2-ylmethyl carbamate, 1-(2'-N,N-dimethylaminoethyl)-5-nitroimidazol-2-ylmethyl carbamate or 1-(2'-N,N-diethylaminoethyl)-5-nitroimidazol-2-ylmethyl carbamate.

EXAMPLE 30

1-(2'-Ethylthioethyl)-5-nitroimidazol-2-ylmethyl N-methyl-carbamate

A mixture of 1.08 g. (0.005 mole) of 1-(2'-ethylthioethyl)-5-nitroimidazole, 0.5 g. (0.015 mole) of paraformaldehyde and 5 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 120° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is slurried in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-ethylthioethyl)-2-hydroxymethyl-5-nitroimidazole.

A mixture of 246 mg. (0.001 mole) of 1-(2'-ethylthioethyl)-2-hydroxymethyl-5-nitroimidazole, 68 mg. (0.0012 mole) of methyl isocyanate, and 120 mg. (0.0012 mole) of triethylamine in 20 ml. of 1,2-dimethoxyethane is refluxed overnight. The solvent is concentrated to a small volume, a little hexane added, and the solid that separates is removed by filtration. The 1-(2'-ethylthioethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate is recrystallized from a mixture of alcohol and water.

In accordance with the above procedure, but starting with 1-(3'-ethylthiopropyl)-5-nitroimidazole, 1-(4'-ethylthiobutyl)-5-nitroimidazole, 1-(2'-methylthioethyl)-5-nitroimidazole, 1-(2'-propylthioethyl)-5-nitroimidazole, 1-(2'-phenylthioethyl)-5-nitroimidazole and 1-(2'-benzylthioethyl)-5-nitroimidazole, in place of 1-(2'-ethylthioethyl)-5-nitroimidazole, there are obtained 1-(3'-ethylthiopropyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(4'-ethylthiobutyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-methylthioethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-propylthioethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-phenylthioethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate and 1-(2'-benzylthioethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate.

EXAMPLE 31

1-(2'-Ethylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate

A mixture of 1.08 g. (0.005 mole) of 1-(2'-ethylsulfinylethyl)-5-nitroimidazole, 0.5 g. (0.015 mole) of paraformaldehyde and 5 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 120° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-ethylsulfinylethyl)-5-nitroimidazol-2-ylmethanol.

A mixture of 246 mg. (0.001 mole) of 1-(2'-ethylsulfinylethyl)-5-nitroimidazol-2-ylmethanol, 68 mg. (0.0012 mole) of methyl isocyanate and 120 mg. (0.0012 mole) of triethylamine in 20 ml. of 1,2-dimethoxyethane is refluxed overnight. The solvent is concentrated to a small volume, a little hexane is added, and the material that separates is removed by filtration. The 1-(2'-ethylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate is recrystallized from a mixture of alcohol and water.

In accordance with the above procedure, but starting with 1-(3'-ethylsulfinylpropyl)-5-nitroimidazole, 1-(4'-ethylsulfinylbutyl)-5-nitroimidazole, 1-(2'-methylsulfinylethyl)-5-nitroimidazole, 1-(2'-propylsulfinylethyl)-5-nitroimidazole, 1-(2'-phenylsulfinylethyl)-5-nitroimidazole, and 1-(2'-benzylsulfinylethyl)-5-nitroimidazole, in place of 1-(2'-ethylsulfinylethyl)-5-nitroimidazole, there are obtained 1-(3'-ethylsulfinylpropyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(4'-ethylsulfinylbutyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-methylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-propylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-phenylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate and 1-(2'-benzylsulfinylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate.

EXAMPLE 32

1-(2'-Ethylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate

A mixture of 1.08 g. (0.005 mole) of 1-(2'-ethylsulfonylethyl)-5-nitroimidazole, 0.5 g. (0.015 mole) of paraformaldehyde and 5 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 120° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-(2'-ethylsulfonylethyl)-5-nitroimidazol-2-ylmethanol.

A mixture of 246 mg. (0.001 mole) of 1-(2'-ethylsulfonylethyl)-5-nitroimidazol-2-ylmethanol, 68 mg. (0.0012 mole) of methyl isocyanate, and 120 mg. (0.0012 mole) of triethylamine in 20 ml. of 1,2-dimethoxyethane is refluxed overnight. The solvent is concentrated to a small volume, a little hexane added, and the material that separates is removed by filtration. The 1-(2'-ethylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate is recrystallized from a mixture of alcohol and water.

In accordance with the above procedure, but starting with 1-(3'-ethylsulfonylpropyl)-5-nitroimidazole, 1-(4'-ethylsulfonylbutyl)-5-nitroimidazole, 1-(2'-methylsulfonylethyl)-5-nitroimidazole, 1-(2'-propylsulfonylethyl)-5-nitroimidazole, 1-(2'-phenylsulfonylethyl)-5-nitroimidazole and 1-(2'-benzylsulfonylethyl)-5-nitroimidazole,

in place of 1-(2'-ethylsulfonylethyl)-5-nitroimidazole, there are obtained 1-(3'-ethylsulfonylpropyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(4'-ethylsulfonylbutyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-methylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-propylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate, 1-(2'-phenylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate and 1-(2'-benzylsulfonylethyl)-5-nitroimidazol-2-ylmethyl N-methylcarbamate.

EXAMPLE 33

1-(1'-Methyl-5'-nitroimidazol-2'-yl)ethyl carbamate

A solution of 0.01 mole of 1-methyl-2-(1'-hydroxyethyl)-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-(1'-methyl-5'-nitroimidazol-2'-yl) ethyl phenyl carbonate is separated by filtration.

A solution of 0.005 mole of 1-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl phenyl carbonate in 10 ml. of chloroform is cooled in an ice-bath, and is saturated with dry ammonia. It is allowed to stand for 5 days at 5° C. 1-(1'-Methyl-5'-nitroimidazol-2'-yl) ethyl carbamate, m.p. 156.5—160° C., is obtained as a crystalline precipitate.

EXAMPLE 34

2-(1'-Methyl-5'-nitroimidazol-2'-yl)ethyl carbamate

A solution of 0.01 mole of 1-methyl-2'-hydroxyethyl)-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 2-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl phenyl carbonate is separated by filtration.

A solution of 0.005 mole of 2-(1'-methyl-5'-nitroimidazol-2'-yl)ethyl phenyl carbonate in 10 ml. of chloroform is cooled in an ice-bath, and is saturated with dry ammonia. It is allowed to stand for 5 days at 5° C. 2-(1'-Methyl-5'-nitroimidazol-2'-yl)ethyl carbamate is obtained as a crystalline precipitate; m.p. 165—166° C.

EXAMPLE 35

3-(1'-Methyl-5'-nitroimidazol-2'-yl)prop-2-en-1-yl carbamate

A solution of 0.01 mole of 1-methyl-2-(3'-hydroxyprop-2'-enyl)-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 3-(1'-methyl-5'-nitroimidazol-2'-yl)prop-2-en-1-yl phenyl carbonate is separated by filtration.

A solution of 0.005 mole of 3-(1'-methyl-5'-nitroimidazol-2'-yl)prop-2-en-1-yl phenyl carbonate in 10 ml. of chloroform is cooled in an ice-bath, and is saturated with dry ammonia. It is allowed to stand for 5 days at 5° C. 3-(1'-Methyl-5'-nitroimidazol-2'-yl)prop-2-en-1-yl carbamate is obtained as a crystalline precipitate; m.p. 173—175° C.

EXAMPLE 36

1-Methyl-5-nitroimidazol-2-ylmethyl N-methylcarbamate

2.77 g., (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 20 ml. of chloroform and 0.93 g. (0.03 mole) of methylamine in 20 ml. of chloroform is added at room temperature under a dry ice-cold finger. The mixture is stirred for 7 hours. The solvent is evaporated and the residue slurried with 15 ml. of water. The solid product is removed by filtration. Recrystallization from water yields 1-methyl-5-nitroimidazol-2-ylmethyl N-methylcarbamate; m.p. 99—101° C.

In accordance with the above procedure, but using ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and *n*-hexylamine in place of methylamine, and using the liquid amines directly rather than the solid amines in chloroform solution, there are obtained 1-methyl-5-nitroimidazol-2-yl-methyl N-ethylcarbamate, 1-methyl-5-nitroimidazol-2-yl-methyl N-*n*-propylcarbamate, 1-methyl-5-nitroimidazol-2-yl-methyl N-*n*-butylcarbamate, 1-methyl-5-nitroimidazol-2-yl-methyl N-*n*-pentylcarbamate and 1-methyl-5-nitroimidazol-2-yl-methyl N-*n*-hexylcarbamate.

EXAMPLE 37

1-Methyl-5-nitroimidazol-2-ylmethyl N,N-dimethylcarbamate

7.8 g. of dimethylamine is added to a solution of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate (prepared from 11.0 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole as described in Example 1). The temperature of the reaction mixture rises to about 24° C. The mixture is stirred with cooling for one hour and then evaporated to dryness under reduced pressure. 100 ml. of water and 800 ml. of ethyl acetate are added to the residue. The ethyl acetate layer is separated and the aqueous layer extracted with two 200 ml. portions of ethyl acetate. The ethyl acetate extracts are combined and evaporated to dryness. On addition of 10 ml. of ethyl acetate to the residue, 1-methyl-5-nitroimidazol-2-ylmethyl N,N-dimethylcarbamate crystallizes and is recovered by filtration to give 5.3 g.; m.p. 91—94° C. Recrystallization from a benzene-hexane mixture yields substantially pure material; m.p. 92—94° C.

In accordance with the above procedure, but using diethylamine, di-*n*-propylamine and diphenylamine, in place of dimethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N,N-di-*n*-propylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N,N-diphenylcarbamate.

EXAMPLE 38

1-Methyl-5-nitroimidazol-2-ylmethyl 4-morpholinecarboxylate

A cold solution of the chloroformate ester of 1-methyl-2-hydroxymethyl-5-nitroimidazole is prepared as in Example 1 (using 11.0 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole). To this solution there is added rapidly with stirring 15.6 g. of morpholine. The temperature rises from 0° C. to 15° C. The reaction mixture is cooled in an ice-bath and stirred for one hour. The tetrahydrofuran is evaporated under reduced pressure and the gummy residue extracted with a mixture of 100 ml. of water and 1 liter of ethyl acetate. The ethyl acetate layer is separated, back-washed with 100 ml. of water and then evaporated to dryness. The resulting residue is dissolved in a minimum volume of benzene. The benzene solution is concentrated to a volume of about 20 ml. An equal volume of diethyl ether is added to the benzene. 1-Methyl-5-nitroimidazol-2-ylmethyl 4-morpholinecarboxylate precipitates. There is obtained 7.3 g. of crude product which is recrystallized three times from benzene to give substantially pure material; m.p. 108—110° C.

In accordance with the above procedure, but starting with pyrrolidine, piperidine, N-methyl-piperazine, and thiamorpholine, in place of morpholine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl 1-pyrrolidinecarboxylate, 1-methyl-5-nitroimidazol-2-ylmethyl 1-piperidinecarboxylate, 1-methyl-5-nitroimidazol-2-ylmethyl N1-methyl-N4-piperazinecarboxylate and 1-methyl-5-nitroimidazol-2-ylmethyl 4-thiamorpholinecarboxylate.

EXAMPLE 39

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-chloroethylcarbamate

A cold solution of the chloroformate ester of 1-methyl-2-hydroxymethyl-5-nitroimidazole is prepared as in Example 1 using 11.0 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole. To this solution is added 14.4 g. of 2-chloroethylamine. The mixture is stirred with cooling for one hour and then evaporated to dryness under reduced pressure. 100 ml. water and 800 ml. of ethyl acetate are added to the residue. The ethyl-acetate layer is separated and the aqueous layer extracted with two 200 ml. portions of ethyl acetate. The ethyl acetate extracts are combined and evaporated to dryness. On addition of ethyl acetate to the residue, 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-chloroethylcarbamate crystallizes.

In accordance with the above procedure, but starting with 2-bromoethylamine, 2,2,2-trifluoroethylamine, 2-fluoroethylamine, 3-chloropropylamine and 3-bromopropylamine, in place of 2-chloroethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-bromoethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-2',2',2'-trifluoroethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-fluoroethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-chloropropylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-bromopropylcarbamate.

EXAMPLE 40

1-Methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate

A mixture of 2.0 g. (0.01 mole) 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 0.6 g. (0.02 mole) of paraformaldehyde and 6 ml. of dimethyl sulfoxide is heated at 100° C. in a sealed tube for 24 hours. Evaporation of the solvent leaves a viscous residue which is dissolved in 3 ml. of dimethylformamide. After the addition of 5

ml. of water and standing for 24 hours, a crystalline precipitate is obtained which is separated by filtration, air dried, and recrystallized from ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate.

EXAMPLE 41

- 5 1-Methyl-5-nitroimidazol-2-ylmethyl N-2',2',2'-Trichloro-1'-hydroxyethylcarbamate 5
1.7 g., (0.011 mole) of 2',2',2'-trichloro-1'-hydroxyethylisocyanate is dissolved in 50 ml. of dioxane and a solution of 1.57 g. (0.01 moles) of 1-methyl-2-hydroxy-
10 methyl-5-nitroimidazole in 200 ml. of dioxane is added. The mixture is left to stand for 48 hours at 15° C. The solution is concentrated to 25 ml. and the crystalline
10 residue removed by filtration. The residue is recrystallized from ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-2',2',2'-trichloro-1'-hydroxyethylcarbamate.

EXAMPLE 42

- 1-Methyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trichloro-1'-hydroxyethoxy)-
carbamate
15 A mixture of 2.16 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl N-
hydroxycarbamate, 1.81 g. (0.011 mole) chloral hydrate and 2.00 g. of anhydrous
magnesium sulfate are heated at reflux for 8 hours. The reaction mixture, after
cooling, is filtered and the filtrate evaporated to dryness to yield 1-methyl-5-nitro-
20 imidazol-2-ylmethyl N-(2',2',2'-trichloro-1'-hydroxyethoxy)carbamate.
20 In accordance with the above procedure, but starting with bromal hydrate or
trifluoroacetaldehyde hydrate, in place of chloral hydrate, there is obtained 1-methyl-
5-nitroimidazol-2-ylmethyl N-(2',2',2'-tribromo-1'-hydroxyethoxy)carbamate or 1-
methyl-5-nitroimidazol-2-ylmethyl N-(2',2',2'-trifluoro-1'-hydroxyethoxy)carbamate.

EXAMPLE 43

- 1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-hydroxy ethylcarbamate 25
1.22 g. of ethanolamine is added at 15° C. to a solution of 2.93 g. of 1-
methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform. The
mixture is stirred for 7 hours and at the end of this time, the solid product is
removed by filtration. Recrystallization from ethyl acetate gives 1-methyl-5-nitro-
30 imidazol-2-ylmethyl N-2'-hydroxyethyl-carbamate; m.p. 132—135° C.
30 In accordance with the above procedure, but starting with 3-propanolamine and
4-butanolamine, in place of ethanolamine, there are obtained 1-methyl-5-nitroimidazol-
2-ylmethyl N-3'-hydroxypropylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-
4'-hydroxybutylcarbamate.

EXAMPLE 44

- 1-Methyl-5-nitroimidazol-2-ylmethyl N-ethoxymethylcarbamate 35
A mixture of 1.15 g. (0.005 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl N-
hydroxymethylcarbamate, 0.05 g. of *p*-toluenesulfonic acid and 20 ml. of ethanol is
stirred overnight at room temperature. After evaporation, the residue is dissolved in
40 50 ml. of chloroform and the chloroform solution washed with dilute sodium
bicarbonate solution. The chloroform solution, after drying over sodium sulfate, is
evaporated to dryness. The residue is recrystallized from ethyl acetate to yield 1-methyl-
5-nitroimidazol-2-ylmethyl N-ethoxymethylcarbamate.
45 In accordance with the above procedure, but using *n*-propanol, *n*-butanol and
n-pentanol in place of ethanol, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl
N-propoxymethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-butoxymethylcar-
bamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-pentoxymethylcarbamate.

EXAMPLE 45

- 1-Methyl-5-Nitroimidazol-2-ylmethyl N-2'-ethoxyethylcarbamate 50
1.78 g., (0.02 mole) of 2-ethoxyethylamine is added at 15° C. to a solution of
2.93 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloro-
form. The mixture is stirred for 7 hours and, at the end of this time, the solution
is evaporated to dryness. The residue is slurried with water and the solid product,
after filtration, is recrystallized from ethanol-water to give 1-methyl-5-nitroimidazol-2-
55 ylmethyl N-2'-ethoxyethylcarbamate.
55 In accordance with the above procedure, but starting with 3-ethoxypropylamine,
4-ethoxybutylamine, 5-ethoxypentylamine and 6-ethoxyhexylamine, in place of 2-ethoxy-
ethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-ethoxy-
propylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-ethoxybutylcarbamate, 1-

methyl-5-nitroimidazol-2-ylmethyl N-5'-ethoxypentylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-6'-ethoxyhexylcarbamate.

EXAMPLE 46

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-oxopropylcarbamate

To a solution of 0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate in 50 ml. of tetrahydrofuran (anhydrous) at 0° C. is added 0.15 mole of triethylamine. To this solution is added dropwise, 0.05 mole of aminoacetone hydrochloride in 100 ml. of dry tetrahydrofuran. After stirring for 4 hours at 15° C., the triethylamine hydrochloride is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is recrystallized from ethyl acetate-benzene to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-oxopropylcarbamate.

In accordance with the above procedure, but starting with 1-amino-2-oxobutane hydrochloride, 1-amino-2-oxopentane hydrochloride and 1-amino-2-oxo-2-phenylethane in place of aminoacetone, there is obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-oxobutyl)-carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-oxopentyl)carbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-oxo-2'-phenylethyl)-carbamate.

EXAMPLE 47

N-(1-Methyl-5-nitroimidazol-2-ylmethoxycarbonyl) glycine

To a cold tetrahydrofuran solution (100 ml.) of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate (prepared as described in Example 1 from 3.12 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole) is added 1.50 g. (0.02 mole) of glycine. Triethylamine (1.0 g., 0.01 mole) is added and the mixture stirred for 24 hours with cooling in an ice-bath. It is then evaporated under reduced pressure to a gummy residue. This residue is washed with 20 ml. of water, the water is removed and about 100 ml. of ethyl acetate added to the remaining residue. The ethyl acetate addition causes crystallization of N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl) glycine, which is separated by filtration, dried, and recrystallized from ethyl acetate.

In accordance with the above procedure, but starting with α -alanine, β -alanine, serine and γ -amino-butyric acid in place of glycine, there are obtained N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl)- α -alanine, N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl)- β -alanine, N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl)-serine and N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl)- γ -aminobutyric acid.

EXAMPLE 48

1-Methyl-5-nitroimidazol-2-ylmethyl N-carbethoxymethylcarbamate

13.8 g., (0.05 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 100 ml. ethanol containing .05 mole of glycine ethyl ester. To this solution is added 10 g. (0.05 mole) of triethylamine. After standing for 24 hours, at 15° C. the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate and the solution washed with water, dried and the solvent removed under reduced pressure. The residue is recrystallized from ethyl acetate/ether to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-carbethoxymethylcarbamate.

In accordance with the above procedure, but starting with glycine propyl ester, glycine butyl ester, α -alanine methyl ester, α -alanine pentyl ester and β -alanine ethyl ester, in place of glycine ethyl ester, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-carbopropoxymethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-carbobutoxymethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-1-carbomethoxyethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-1-carbopentoxyethylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-2-carbethoxyethylcarbamate.

EXAMPLE 49

1-Methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethylcarbamate

13.8 g., (0.05 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenylcarbonate is dissolved in 100 ml. ethanol containing .05 mole of glycine amide. To this solution is added 10 g. (0.05 mole) of triethylamine. After standing for 24 hours, at 15° C. the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water, dried and the solvent removed under reduced pressure. The residue is recrystallized from ethyl acetate/ether to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethylcarbamate.

In accordance with the above procedure, but starting with α -alanine amide and β -alanine amide, in place of glycine amide, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-1-carbamoylethylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-2-carbamoylethylcarbamate.

EXAMPLE 50

1-Methyl-5-Nitroimidazol-2-ylmethyl N-carbamoylmethyl N-ethylcarbamate
13.8 g., (0.05 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenylcarbonate is dissolved in 100 ml. ethanol containing 0.05 mole of (N-ethylglycine) amide. To this solution is added 10 g. (0.05 mole) of triethylamine. After standing for 24 hours at 15° C., the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water, dried and the solvent removed under reduced pressure. The residue is recrystallized from ethyl acetate/ether to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethyl-N-ethylcarbamate.

In accordance with the above procedure, but starting with (N-propyl glycine) amide, (N-n-butyl glycine) amide (N-phenyl glycine) amide, or (N-benzyl glycine), in place of (N-ethylglycine) amide, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethyl-N-propylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethyl-N-n-butylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethyl-N-phenylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoylmethyl-N-benzylcarbamate.

EXAMPLE 51

1-Methyl-5-nitroimidazol-2-ylmethyl N-formyloxymethylcarbamate

A mixture of 2.3 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate and 90% formic acid (10 ml.) is heated on a steam-bath for 2 hours. After evaporation to dryness the residue is slurried with saturated aqueous sodium bicarbonate solution and filtered. The product is 1-methyl-5-nitroimidazol-2-ylmethyl N-formyloxymethylcarbamate.

EXAMPLE 52

1-Methyl-5-nitroimidazol-2-ylmethyl N-acetoxymethylcarbamate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate is dissolved in 25 ml. of pyridine and 0.055 moles of acetyl chloride introduced dropwise into the stirred solution. After 30 minutes' stirring, the solution is allowed to stand at 15° C. for 4 hours. The solvent is removed under reduced pressure. The residue is extracted with ethyl acetate, washed with water, dried, and the solvent removed under reduced pressure. The residue is recrystallized from acetone or ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-acetoxymethylcarbamate.

In accordance with the above procedure, but starting with propionyl chloride, butyryl chloride, valeryl chloride, or benzoyl chloride, in place of acetyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-propionoxymethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-butyroxymethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-valeroxymethylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-benzoyloxymethylcarbamate.

EXAMPLE 53

1-Methyl-5-nitroimidazol-2-ylmethyl N-carbamoyloxymethylcarbamate

0.05 moles of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate is dissolved in 25 ml. of pyridine and the mixture is cooled in an ice-salt bath while 0.055 mole of gaseous carbamoyl chloride is introduced into the stirred solution. The solution is allowed to stand at 15° C. for 24 hours. It is then concentrated and the product extracted with ethyl acetate. The ethyl acetate solution is washed with ice-water, dried, and concentrated. Recrystallization from ethyl acetate or acetone yields 1-methyl-5-nitroimidazol-2-ylmethyl N-carbamoyloxymethylcarbamate.

In accordance with the above procedure, but starting with 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-hydroxyethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-hydroxy-n-propylcarbamate, or 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-hydroxybutylcarbamate, in place of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-carbamoyloxyethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-carbamoyloxy-n-propylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-carbamoyloxy-n-butylcarbamate.

EXAMPLE 54

1-Methyl-5-nitroimidazol-2-ylmethyl N-(dimethylcarbamoyloxymethyl)carbamate

0.05 moles of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate is dissolved in 25 ml. of pyridine and the mixture is cooled in an ice-salt bath while 0.055 mole of dimethylcarbamoyl chloride is introduced into the stirred solution. The solution is allowed to stand at 15° C. for 24 hours. It is then concentrated and the product extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried and concentrated. Recrystallization from ethyl acetate or acetone yields 1-methyl-5-nitroimidazol-2-ylmethyl N-(dimethylcarbamoyloxymethyl)carbamate.

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In accordance with the above procedure, but starting with 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-hydroxyethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-hydroxy-*n*-propylcarbamate, or 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-hydroxy-*n*-butylcarbamate, in place of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxymethylcarbamate, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-dimethylcarbamoyloxyethyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(3'-dimethylcarbamoyloxy-*n*-propyl)carbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-(4'-dimethylcarbamoyloxy-*n*-butyl)carbamate.

EXAMPLE 55

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-sulfonamidoethylcarbamate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in ethanol containing 0.05 mole of 2-aminoethylsulfonamide and 0.05 mole triethylamine. After 24 hours at 15° C., the solution is evaporated. Trituration with water causes the crystallization of 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-sulfonamidoethylcarbamate.

In accordance with the above procedure, but using 3-amino-*n*-propylsulfonamide, 4-amino-*n*-butylsulfonamide and 5-amino-*n*-pentylsulfonamide, in place of 2-aminoethylsulfonamide, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-sulfonamido-*n*-propylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-sulfonamido-*n*-butylcarbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl N-5'-sulfonamido-pentylcarbamate.

EXAMPLE 56

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-(N',N'-diethylsulfonamido)ethylcarbamate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in ethanol containing 0.05 mole of 2-aminoethylsulfonic acid diethylamide, and 0.05 mole triethylamine. After 24 hours at 15° C., the solution is evaporated. Trituration with water causes the crystallization of 1-methyl-5-nitroimidazol-2-ylmethyl 2'-(N',N'-diethylsulfonamido)ethylcarbamate.

In accordance with the above procedure, but starting with 2-aminoethylsulfonic acid dipropylamide, 2-aminoethylsulfonic acid diphenylamide, or 2-aminoethylsulfonic acid dibenzylamide, in place of 2-aminoethylsulfonic acid diethylamide, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-(N',N'-dipropylsulfonamido)-ethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-(N',N'-diphenylsulfonamido)-ethylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-(N',N'-dibenzylsulfonamido)ethylcarbamate.

EXAMPLE 57

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-mercaptoethylcarbamate

1.54 g., (0.02 mole) of 2-mercaptoethylamine is added at 15° C. to a solution of 2.77 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform. The mixture is stirred for 7 hours and, at the end of this time, the solid product is removed by filtration. Recrystallization from ethanol gives 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-mercaptoethylcarbamate.

In accordance with the above procedure, but starting with 3-mercapto-*n*-propylamine and 4-mercapto-*n*-butylamine, in place of 2-mercaptoethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-3'-mercapto-*n*-propylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-4'-mercapto-*n*-butylcarbamate.

EXAMPLE 58

1-Methyl-5-nitroimidazol-2-ylmethyl N-2'-ethylthioethylcarbamate

2.12 g., (0.02 mole) of 2-ethylthioethylamine is added at 15 °C. to a solution of 2.77 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 10 ml. of chloroform. The mixture is stirred for 7 hours and then evaporated to dryness. The residue is triturated with ether and the solid product is removed by filtration. Recrystallization from ethanol gives 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-ethylthioethylcarbamate.

In accordance with the above procedure, but starting with 2-methylthioethylamine, 2-*n*-propylthioethylamine, 2-*n*-butylthioethylamine, or 2-benzylthioethylamine, in place of 2-ethylthioethylamine, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-methylthioethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-*n*-propylthioethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-*n*-butylthioethylcarbamate, or 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-benzylthioethylcarbamate.

EXAMPLE 59

1-Methyl-5-nitroimidazol-2-ylmethyl N-thioncarbamoylmethylcarbamate

13.8 g., (0.05 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 100 ml. ethanol containing glycineithioamide (4.5 g., 0.05 mole) and 5.1 g. (0.05 mole) of triethylamine. After standing for 24 hours, at 15° C. the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water and dried. The solvent is removed under reduced pressure and the residue is recrystallized from ethyl acetate/ether to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-thioncarbamoylmethylcarbamate.

In accordance with the above procedure but starting with α -alanineithioamide or β -alanineithioamide, in place of glycineithioamide, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-1'-thioncarbamoylethylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-2'-thioncarbamoylethylcarbamate.

EXAMPLE 60

1-Methyl-5-nitroimidazol-2-ylmethyl N-(N'-ethylthiocarbamoylmethyl)carbamate

13.8 g., (0.05 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 100 ml. ethanol containing .05 mole of N-ethyl-glycineithioamide. To this solution is added 5.1 g. (0.05 mole) of triethylamine. After standing for 24 hours at 15° C. the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water and dried. The solvent is removed under reduced pressure. The residue is slurried with water and ethyl acetate. The ethyl acetate extract is evaporated and the residue recrystallized from ethyl acetate/ether to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-ethylthiocarbamoylmethyl)carbamate.

In accordance with the above procedure, but starting with N-n-propyl-glycineithioamide, N-n-butyl-glycineithioamide, N-phenyl-glycineithioamide, or N-benzyl-glycineithioamide, in place of N-ethyl-glycineithioamide, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-n-propylthiocarbamoylmethyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-n-butylthiocarbamoylmethyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-phenylthiocarbamoylmethyl)carbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-benzylthiocarbamoylmethyl)carbamate.

EXAMPLE 61

1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-dimethyl(thiocarbamoylthio)methyl]carbamate

1.1 ml. of 40% aqueous dimethylamine and 37% aqueous formaldehyde (1.0 ml.) is added to a solution of 2.0 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate in 5 ml. of dimethylformamide. To the mixture is added carbon disulfide (1.0 g.). The reaction mixture is stirred for 24 hours at 15° C. Water (10 ml.) is added and the mixture stirred an additional 2 hours. The precipitate is removed by filtration and washed with water to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-dimethyl(thiocarbamoylthio)methyl]carbamate.

In accordance with the above procedure, but start- with diethylamine, di-n-propylamine, di-n-butylamine, diphenylamine, and dibenzylamine, in place of dimethylamine, there are obtained, 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-diethyl(thiocarbamoylthio)methyl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-di-n-propyl(thiocarbamoylthio)methyl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-di-n-butyl(thiocarbamoylthio)methyl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-diphenyl(thiocarbamoylthio)methyl]carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-[N'-dibenzyl(thiocarbamoylthio)methyl]carbamate.

EXAMPLE 62

1-Methyl-5-nitroimidazol-2-ylmethyl N-(2'-aminoethyl)carbamate

15.5 g., (0.02 mole) of 1-methyl-5-nitroimidazol-2-methyl phenyl carbonate is dissolved in 70 ml. of chloroform and 0.06 moles of ethylene diamine is added. The mixture is heated under reflux for 5 hours, cooled and allowed to stand for 18 hours. 170 ml. of chloroform is added and the mixture extracted with saturated aqueous potassium bicarbonate solution. The chloroform extract is washed with water and the solvent removed under reduced pressure. 0.1 g. of the residual brown oil is dissolved in methyl ethyl ketone. A solution of 8.53 g. of p-toluenesulfonic acid in 80 ml. of methyl ethyl ketone is prepared. An excess of the p-toluenesulfonic acid solution (i.e. more than 2 moles per mole of carbonate derivative) is added and the mixture allowed to cool. The solution is evaporated to dryness and 5 ml. of methyl ethyl ketone is added. After standing at 0° C. the di-p-toluenesulfonic acid-addition salt of 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-aminoethyl)carbamate is obtained.

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EXAMPLE 63

1-Methyl-5-nitroimidazol-2-ylmethyl N-(2'-N',N'-Diethylaminoethyl)carbamate

15.5 g. (0.02 mole) of 1-methyl-5-nitroimidazol-2-methyl phenyl carbonate is dissolved in 70 ml. of chloroform and 2.68 g. (0.023 moles) of 2-diethylaminoethylamine is added. The mixture is heated under reflux for 5 hours, cooled and allowed to stand for 18 hours. Chloroform (170 ml.) is added and the mixture extracted with saturated aqueous potassium bicarbonate solution. The chloroform extract is washed with water and the solvent removed under reduced pressure. 0.1 g. of the residual brown oil is dissolved in methyl ethyl ketone. A solution of 8.53 g. of *p*-toluenesulfonic acid in 80 ml. of methyl ethyl ketone is prepared. An excess of the *p*-toluenesulfonic acid solution (i.e. more than 2 moles per mole of carbonate derivative) is added and the mixture allowed to cool. The solution is evaporated to dryness and 5 ml. of methyl ethyl ketone is added. After standing at 0° C. the di-*p*-toluenesulfonic acid-addition salt of 1-methyl-5-nitroimidazol-2-ylmethyl N-(2'-N',N'-diethylaminoethyl)carbamate, m.p. 101—103° C., is obtained.

In accordance with the above procedure, but starting with 3-dimethylamino-*n*-propylamine and 2-dibenzylaminoethylamine, in place of 2-diethylaminoethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-(3'-N',N'-dimethylamino-*n*-propyl)carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-(N',N'-dibenzylaminoethyl)carbamate.

EXAMPLE 64

1-Methyl-5-nitroimidazol-2-ylmethyl N-(morpholin-4'-ylmethyl)carbamate

12.0 g., (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 0.3 g. (0.01 mole) of paraformaldehyde, and 0.86 g. (0.01 mole) of morpholine in 6 ml. of dimethylformamide as heated at 100° C. in a sealed tube for 24 hours. After evaporation of the solvent under reduced pressure, the residue is dissolved in 20 ml. of methyl ethyl ketone. A solution of 3.4 g. of *p*-toluenesulfonic acid in 20 ml. of methyl ethyl ketone is added to yield a precipitate of the di-*p*-toluenesulfonic acid-addition salt of 1-methyl-5-nitroimidazol-2-ylmethyl N-(morpholin-4'-ylmethyl)carbamate.

In accordance with the above procedure, but starting with N-methylpiperazine, pyrrolidine and thiamorpholine, in place of morpholine, there are obtained the di-*p*-toluenesulfonic acid salts of 1-methyl-5-nitroimidazol-2-ylmethyl N-(4-methylpiperazin-1-ylmethyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(pyrrolidin-1-ylmethyl)carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-(thiamorpholin-4'-ylmethyl)carbamate.

EXAMPLE 65

1-Methyl-5-nitroimidazol-2-ylmethyl N-phenylcarbamate

To a solution of 1-methyl-2-hydroxymethyl-5-nitroimidazole chloroformate prepared as in Example 1 (from 11.1 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole there is added 16.3 g. (0.175 mole) of aniline. The temperature of the mixture rises from 0° C. to about 16° C. The mixture is stirred for 90 minutes with cooling in an ice-bath. It is then evaporated under reduced pressure to a gummy residue. This residue is washed with 100 ml. of water; the water is removed and about 100 ml. of ethyl acetate is added to the remaining residue. The ethyl acetate addition causes crystallization of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbamate. The crystalline product is removed by filtration and dried to give 12.3 g.; m.p. 136—142° C. Recrystallization from methylene chloride and then from ethyl acetate affords substantially pure 1-methyl-5-nitroimidazol-2-ylmethyl N-phenyl carbamate; m.p. 145.5—148° C.

In accordance with the above procedure, but starting with *p*-fluoroaniline, *p*-chloroaniline and *p*-nitroaniline, in place of aniline, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-*p*-fluorophenylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*p*-chlorophenylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-*p*-nitrophenylcarbamate.

EXAMPLE 66

1-Methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-phenylcarbamate

A solution of the chloroformate ester of 1-methyl-2-hydroxymethyl-5-nitroimidazole is prepared as in Example 1 (from 11.1 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole) 18.7 g. of N-methylaniline is added to this solution, and the resulting mixture is stirred, with ice cooling, for one hour. The mixture is evaporated to dryness *in vacuo* to a gum which is extracted with 200 ml. of water and 600 ml. of ethyl acetate. The ethyl acetate extracts are separated and evaporated to dryness. The residue is crystallized from a benzene-hexane mixture to give 3.7 g. of 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-phenylcarbamate; m.p. 93—95° C. Recrystallization

from 50 ml. of a 1:1 benzene-hexane mixture affords substantially pure material; m.p. 94.5—98° C.

In accordance with the above procedure, but starting with *n*-prop-2-en-1-ylamine, *n*-but-2-en-1-ylamine, *n*-but-3-en-1-ylamine, *n*-pent-2-en-1-ylamine and *n*-pent-3-en-1-ylamine, in place of *N*-methylaniline, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(2-*n*-propenyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(2-*n*-butenyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(3-*n*-butenyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(2-*n*-pentenyl)carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(3-*n*-pentenyl)carbamate.

EXAMPLE 67

1-Methyl-5-nitroimidazol-2-ylmethyl *N*-ethoxymethylenecarbamate

2.0 g., (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 1.33 ml. (0.01 mole) of boron fluoride etherate and 25 ml. of triethyl orthoformate is heated on a steam bath overnight. The excess triethyl orthoformate is removed under vacuum. To the oily residue are added 100 ml. of chloroform and 10 ml. saturated sodium bicarbonate solution. The chloroform solution is separated, washed with 2 × 10 ml. of water, and dried over anhydrous sodium sulfate. Evaporation of the chloroform solution gives 1-methyl-5-nitroimidazol-2-ylmethyl *N*-ethoxymethylenecarbamate.

In accordance with the above procedure, but starting with trimethyl orthoformate, tri-*n*-propyl orthoformate, tribenzylorthoformate and triphenylorthoformate, in place of triethylorthoformate, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl *N*-methoxymethylenecarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-*n*-propoxymethylenecarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-benzyloxymethylenecarbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-phenyloxymethylenecarbamate.

EXAMPLE 68

1-Methyl-5-nitroimidazol-2-ylmethyl *N*-(diethylaminomethylene)carbamate

A mixture of 2.56 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl *N*-ethoxymethylenecarbamate and 0.73 g. (0.01 mole) of diethylamine in 25 ml. of 1,2-dimethoxyethane is refluxed for 2 hours. After cooling, the addition of 3.44 g. (0.02 mole) of *p*-toluenesulfonic acid results in the separation of the di-*p*-toluenesulfonate salt of 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(diethylaminomethylene)carbamate.

In accordance with the above procedure, but starting with dimethylamine, di-*n*-butylamine, di-*n*-propylamine, dibenzylamine, and diphenylamine, in place of diethylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl *N*-dimethylaminomethylenecarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-di-*n*-butylaminomethylenecarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-di-*n*-propylaminomethylenecarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-dibenzylaminomethylenecarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-diphenylaminomethylenecarbamate.

EXAMPLE 69

1-Methyl-5-nitroimidazol-2-ylmethyl *N*-(1'-carbethoxyprop-2-ylidene)carbamate

4.0 g., (0.02 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate, 150 ml. of ethyl acetoacetate and 0.02 g. of *p*-toluenesulfonic acid (anhydrous) are heated on a steam bath for 4 days. The solvent is removed by evaporation under reduced pressure. The residue is slurried with 1,000 ml. of ether and the mixture filtered. The ether extract is evaporated to dryness under reduced pressure. The residue, in 300 ml. of ether is refluxed with activated charcoal for 30 minutes. The mixture is filtered and the filtrate concentrated to about 100 ml. The ether solution is cooled to -40° C. and a crystalline precipitate of 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(1'-carbethoxyprop-2-ylidene)carbamate, m.p. 117—120° C., is obtained.

In accordance with the above procedure, but starting with methyl acetoacetate and benzyl acetoacetate, in place of ethyl acetoacetate, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(1'-carbomethoxy-prop-2-ylidene)carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(1'-benzyloxycarbonylprop-2-ylidene)carbamate.

EXAMPLE 70

N-(1-Methyl-5-nitroimidazol-2-ylmethyloxycarbonyl)-*N'*,*N'*-dimethylformamidinium chloride hydrochloride

0.02 g. (0.001 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate is dissolved in 2 ml. of dimethylformamide and 0.1 ml. of thionyl chloride added. The mixture is allowed to stand for 18 hours. Removal of the crystalline precipitate by filtration, followed by washing with ether yields *N*-(1-methyl-5-nitroimidazol-2-ylmethyloxy-

carbonyl N',N'-dimethylformamidinium chloride hydrochloride; m.p. 147—151° C. (dec.).

EXAMPLE 71

1-Methyl-5-nitroimidazol-2-ylmethyl formylcarbamate

3.28 g. (0.01 mole) of N-(1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl) N',N'-dimethylformamidinium chloride hydrochloride is dissolved in 20 ml. of water containing 0.84 g. of sodium bicarbonate. The solution is allowed to stand overnight. The product is 1-methyl-5-nitroimidazol-2-ylmethyl formylcarbamate. The same compound is obtained on heating on a steam bath 1-methyl-5-nitroimidazol-2-ylmethyl carbamate in an excess of 90% formic acid overnight.

EXAMPLE 72

1-Methyl-5-nitroimidazol-2-ylmethyl N-acetylcarbamate

2 g. of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate is added to a mixture of 40 ml. of acetic anhydride and 4 drops of concentrated sulfuric acid. The solution is heated for 18 hours on a steam bath. The solvent is removed under reduced pressure and the residue triturated with petroleum ether and the mixture filtered. The residue is taken up in hot benzene, the mixture filtered and the filtrate concentrated under reduced pressure to a small volume. After standing at 5° C. for 12 hours, 1-methyl-5-nitroimidazol-2-ylmethyl N-acetylcarbamate, m.p. 140—142° C., is obtained on filtration.

In accordance with the above procedure, but using propionic anhydride, butyric anhydride, or chloroacetic anhydride, in place of acetic anhydride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-propionylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-butyrylcarbamate or 1-methyl-5-nitroimidazol-2-yl methyl N-chloroacetylcarbamate.

EXAMPLE 73

1-Methyl-5-nitroimidazol-2-ylmethyl N-acetylcarbamate

5.9 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole and about 0.5 ml. of pyridine are added to a solution of acetyl isocyanate prepared by refluxing a solution of 15.9 g. oxalyl chloride and 5.9 g. of acetamide in 300 ml. of 1,2-dichloroethane for 16 hours, and the mixture is refluxed for 80 minutes. The solvent is then removed by concentration *in vacuo* to give an oil which crystallizes on standing. The crystals are slurried with 50 ml. of benzene and then recovered by filtration. Washing with a mixture of 50 ml. of benzene and 85 ml. of ether leaves crude 1-methyl-5-nitroimidazol-2-ylmethyl N-acetylcarbamate; m.p. 108—132° C. On recrystallization from benzene-hexane, substantially pure material is obtained; m.p. 132—135° C.

In accordance with the above procedure, but using benzylisocyanates or phenylacetyl isocyanate, in place of acetyl isocyanate, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-benzoylcarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-phenylacetylcarbamate.

Similarly, in accordance with the above procedure, but using 1-methyl-2-mercaptomethyl-5-nitroimidazole and 1-ethyl-2-hydroxymethyl-5-nitroimidazole in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole and using benzylisocyanate, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-benzoylthiolcarbamate and 1-ethyl-5-nitroimidazol-2-ylmethyl N-benzoylcarbamate.

EXAMPLE 74

1-Methyl-5-nitroimidazol-2-ylmethyl N-cyanoacetylcarbamate

2 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-yl carbamate, 0.93 g. (0.011 mole) of cyanoacetic acid and 10 ml. of acetic anhydride are heated on a steam bath for 3 hours. On cooling, a crystalline product is obtained. Recrystallization from ethanol gives 1-methyl-5-nitroimidazol-2-ylmethyl N-cyanoacetylcarbamate.

EXAMPLE 75

1-Methyl-5-nitroimidazol-2-ylmethyl N-acryloylcarbamate

To a solution of 2.0 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate in 5 ml. of dimethylformamide at 0° C. is added slowly 1.13 g. of acryloyl chloride. The mixture is allowed to warm to room temperature and stand for 8 hours. 10 ml. of water is added slowly and the product, 1-methyl-5-nitroimidazol-2-ylmethyl N-acryloylcarbamate, is removed by filtration.

In accordance with the above procedure, but using crotonoyl chloride in place of acryloyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-crotonoylcarbamate.

EXAMPLE 76

1-Methyl-5-nitroimidazol-2-ylmethyl allophanate

3 g. of a solution of 1-methyl-5-nitroimidazol-2-yl methanol in 75 ml. of 1,2-dimethoxyethane is added to 4 ml. of cyanic acid at dry ice temperature. The cyanic acid is obtained by heat depolymerization of cyanuric acid. The reaction mixture is tightly stoppered and allowed to stand at about 0° C. for 48 hours. The solids which are formed are filtered. Extraction of the solids with 300 ml. of boiling water followed by filtration gives, within a few minutes, in the filtrate a first crop of solids which is filtered. The filtrate then deposits 1.0 g. of the desired allophanate which on recrystallization from boiling water gives analytically pure 1-methyl-5-nitroimidazol-2-ylmethyl allophanate; m.p. 210—211° C. (dec.).

EXAMPLE 77

1-Methyl-5-nitroimidazol-2-ylmethyl 4',4'-dimethylallophanate

0.05 mole of 1-methyl-5-nitroimidazole-2-ylmethyl carbamate is dissolved in 25 ml. of pyridine and cooled in an ice-water bath. To this stirred solution is added .055 mole of dimethylcarbamoyl chloride. After the initial reaction, the mixture is allowed to stand for 24 hours and is then concentrated under reduced pressure. The residue is extracted with ethyl acetate. The ethyl acetate extract is washed with ice-water, and the dried solution is reconcentrated. The residue is recrystallized from ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-dimethylallophanate.

In accordance with the above procedure, but starting with diethylcarbamoyl chloride, di-*n*-propylcarbamoyl chloride, di-*n*-butylcarbamoyl chloride, dibenzylcarbamoyl chloride, or diphenylcarbamoyl chloride, in place of dimethylcarbamoyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-diethylallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-di-*n*-propylallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-di-*n*-butylallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-dibenzylallophanate or 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-diphenylallophanate.

EXAMPLE 78

1-Methyl-5-nitroimidazol-2-ylmethyl 2'-methylallophanate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl *N*-methylcarbamate is dissolved in 25 ml. of pyridine and the mixture is cooled in an ice-salt bath while 0.055 mole of gaseous carbamoyl chloride is introduced into the stirred solution. After 30 minutes, the solution is allowed to stand at 15° C. for 24 hours. It is then concentrated and the product extracted with ethyl acetate and washed with ice-water. The solution is dried and concentrated. Recrystallization from ethyl acetate or acetone yields 1-methyl-5-nitroimidazol-2-ylmethyl 2'-methylallophanate.

In accordance with the above procedure, but starting with 1-methyl-5-nitroimidazol-2-ylmethyl *N*-ethylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-*n*-propylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-*n*-butylcarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl *N*-phenylcarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-benzylcarbamate, in place of 1-methyl-5-nitroimidazol-2-ylmethyl *N*-methylcarbamate, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl 2'-ethylallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 2'-*n*-propylallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 2'-*n*-butylallophanate 1-methyl-5-nitroimidazol-2-ylmethyl 2'-phenylallophanate and 1-methyl-5-nitroimidazol-2-ylmethyl 2'-benzylallophanate.

EXAMPLE 79

1-Methyl-5-nitroimidazol-2-ylmethyl *N*-(piperidinocarbonyl)-carbamate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl carbamate is dissolved in 25 ml. of pyridine and cooled in an ice-water bath. To this stirred solution is added 0.55 mole of piperidinocarbonyl chloride. After the initial reaction, the mixture is allowed to stand for 24 hours and is then concentrated under reduced pressure. The residue is extracted with ethyl acetate. The ethyl acetate is washed with ice-water and the dried solution is reconcentrated. The residue is recrystallized from ethyl acetate or acetone to yield 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(piperidinocarbonyl)carbamate; m.p. 78.5—80.5° C.

In accordance with the above procedure, but starting with 4-methyl-piperazinocarbonyl chloride, morpholinocarbonyl chloride and thiamorpholinocarbonyl chloride, in place of piperidinocarbonyl chloride, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(4'-methyl-piperazinocarbonyl)carbamate, m.p. 101—104° C., 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(morpholinocarbonyl)carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl *N*-(thiamorpholinocarbonyl)carbamate.

EXAMPLE 80

1-Methyl-5-nitroimidazol-2-ylmethyl 3'-thionallophanate

0.1 mole of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate is dissolved in 200 ml. of benzene and stirred with 10.6 g. of anhydrous potassium thiocyanate for four days at 20–40° C. This mixture is treated with an excess of anhydrous gaseous ammonia. On cooling, the 1-methyl-5-nitroimidazol-2-ylmethyl 3'-thionallophanate separates in crystalline form.

In accordance with the above procedure, and utilizing a benzene solution of 1-methyl-5-nitroimidazol-2-ylmethoxycarbonyl isothiocyanate as produced above but using methylamine, ethylamine, *n*-butylamine, benzylamine, aniline, dimethylamine, diethylamine, di-*n*-butylamine, dibenzylamine and diphenylamine, in place of gaseous ammonia, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl 4'-methyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4'-ethyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4'-*n*-butyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4'-benzyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4'-phenyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-dimethyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-diethyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-di-*n*-butyl-3'-thionallophanate, 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-dibenzyl-3'-thionallophanate, and 1-methyl-5-nitroimidazol-2-ylmethyl 4',4'-diphenyl-3'-thionallophanate.

EXAMPLE 81

1-Methyl-5-nitroimidazol-2-ylmethyl N-nitrocarbamate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethylcarbamate is dissolved in 0.066 mole of acetic anhydride and treated with 0.05 mole of 95% nitric acid over a period of 2 minutes. After 11 minutes, it is poured into an equal volume of saturated sodium chloride solution. After completion of the decomposition of the acetic anhydride, the solution is extracted with ethyl acetate and the ethyl acetate extract washed with water. The dried ethyl acetate solution is saturated with ammonia gas to give the ammonium salt of 1-methyl-5-nitroimidazol-2-ylmethyl N-nitrocarbamate.

EXAMPLE 82

1-Methyl-5-nitroimidazol-2-ylmethyl carbazate

A mixture of 5 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate, 0.5 ml. of 95% hydrazine and 25 ml. of chloroform is stirred at room temperature for one hour. At the end of this time the solid is removed by filtration to give 3.8 g. of material; m.p. 101–105° C. This product is dried *in vacuo* at 68° C. to remove phenol and then recrystallized from water to give substantially pure 1-methyl-5-nitroimidazol-2-ylmethyl carbazate; m.p. 135–140° C.

EXAMPLE 83

1-Methyl-5-nitroimidazol-2-ylmethyl carbazate

To a solution of 1-methyl-2-hydroxymethyl-5-nitroimidazole chloroformate in dioxane as prepared in Example 1, there is added dropwise 0.06 mole of anhydrous hydrazine. The mixture is stirred for 90 minutes with cooling in an ice bath. The mixture is evaporated under reduced pressure, and the residue washed with water and dissolved in ethyl acetate. The ethyl acetate solution, after drying over sodium sulfate, is concentrated to yield 1-methyl-5-nitroimidazol-2-ylmethyl carbazate.

EXAMPLE 84

1-Methyl-5-nitroimidazol-2-ylmethyl N¹-methylcarbazate

0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate is dissolved in 50 ml. of anhydrous tetrahydrofuran and added to a solution containing 0.15 mole of methylhydrazine in 50 ml. of tetrahydrofuran at 15° C. After 2 hours, the methylhydrazine hydrochloride is removed by filtration. The tetrahydrofuran is removed under reduced pressure and the residue is recrystallized from ethyl acetate to yield 1-methyl-5-nitroimidazol-2-ylmethyl N¹-methylcarbazate.

In accordance with the above procedure, but starting with ethylhydrazine, *n*-propylhydrazine, or benzylhydrazine, in place of methylhydrazine, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N¹-ethylcarbazate, 1-methyl-5-nitroimidazol-2-ylmethyl N¹-*n*-propylcarbazate or 1-methyl-5-nitroimidazol-2-ylmethyl N¹-benzylcarbazate.

EXAMPLE 85

1-Methyl-5-nitroimidazol-2-ylmethyl N²-isopropylidenylcarbazate

200 mg. of 1-methyl-5-nitroimidazol-2-ylmethyl carbazate is dissolved in 3 ml. of acetone and heated under reflux for 10 minutes. The solvent is removed under reduced pressure and the residue recrystallized from a 1:1 mixture of benzene and hexane to yield 1-methyl-5-nitroimidazol-2-ylmethyl N²-isopropylidenylcarbazate; m.p. 160—162° C.

In accordance with the above procedure, but using methyl ethyl ketone, benzaldehyde or acetaldehyde, in place of acetone, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N²-2-butylidenylcarbazate, 1-methyl-5-nitroimidazol-2-ylmethyl N²-benzylidenylcarbazate or 1-methyl-5-nitroimidazol-2-ylmethyl N²-ethylidenylcarbazate.

EXAMPLE 86

1-Methyl-5-nitroimidazol-2-ylmethyl N²-benzoylcarbazate

0.1 mole of 1-methyl-5-nitroimidazol-2-ylmethyl carbazate is dissolved in 50 ml. of dry pyridine and cooled in ice. 0.1 mole of benzoyl chloride is added dropwise. After standing for 1 hour at 15° C., the solution is quenched with ice and water. The precipitated 1-methyl-5-nitroimidazol-2-ylmethyl N²-benzoylcarbazate is filtered, washed well with water and recrystallized from ethanol.

In accordance with the above procedure, but using acetic anhydride in place of benzoyl chloride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N²-acetylcarbazate.

Similarly, but using propionic anhydride, valeric anhydride, butyric anhydride or phenylacetic anhydride, in place of acetic anhydride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N²-propionylcarbazate, 1-methyl-5-nitroimidazol-2-ylmethyl N²-valerylcarbazate, 1-methyl-5-nitroimidazol-2-ylmethyl N²-butyrylcarbazate or 1-methyl-5-nitroimidazol-2-ylmethyl N²-phenylacetylcarbazate.

EXAMPLE 87

N⁴-(1'-Methyl-5'-nitroimidazol-2'-ylmethoxycarbonyl) semicarbazide

To 0.05 mole of 1-methyl-5-nitroimidazol-2-ylmethyl chloroformate in 50 ml. of dry purified tetrahydrofuran is added 0.05 mole of semicarbazide hydrochloride. To this mixture is added 0.3 mole of triethylamine. The mixture is stirred vigorously for 2 hours. The solid precipitate is filtered. The tetrahydrofuran filtrate is removed under reduced pressure and the residue is well washed with water. The combined water-insoluble materials are recrystallized from ethanol to yield N⁴-(1'-methyl-5'-nitroimidazol-2'-ylmethoxy carbonyl)semicarbazide.

In accordance with the above procedure, but using thiosemicarbazide hydrochloride in place of semicarbazide hydrochloride, there is obtained N⁴-(1'-methyl-5'-nitroimidazol-2'-ylmethoxycarbonyl)thiosemicarbazide.

EXAMPLE 88

1-Methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate

0.386 g. of sodium is dissolved in 40 ml. of methanol and the solution cooled in an ice bath. 1.17 g. of hydroxylamine hydrochloride is added to the cold methanol solution. To the resulting mixture there is added over a period of 45 minutes 2.33 g. of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate in 60 ml. of methanol. The resulting mixture is held for 15 hours at refrigerator temperature and, at the end of this time, the solid material present is removed by filtration. The solid is washed with alcohol and then with hexane, and dried to give 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate; m.p. 189—190° C.

In accordance with the above procedure, but starting with N-methylhydroxylamine hydrochloride, N-n-propylhydroxylamine hydrochloride, N-phenylhydroxylamine hydrochloride and N-benzylhydroxylamine hydrochloride, in place of hydroxylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-hydroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-n-propyl-N-hydroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-phenyl-N-hydroxycarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-benzyl-N-hydroxycarbamate.

EXAMPLE 89

1-(2'-Acetoxyethyl)-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate

3.66 g. of 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved in 20 ml. of methanol and treated with hydroxylamine, freshly prepared from 0.72 g. of hydroxylamine hydrochloride and 0.6 g. of sodium methoxide in 20 ml.

of methanol. The residue is recrystallized from ethanol to yield 1-(2'-acetoxyethyl)-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate; m.p. 153—155° C.

EXAMPLE 90

1-Methyl-5-nitroimidazol-2-ylmethyl N-hydroxythioncarbamate

0.56 g. (0.005 mole) of potassium *t*-butoxide is dissolved in 20 ml. of ethanol and 0.35 g. (0.005 mole) of hydroxylamine hydrochloride is added and the mixture stirred for 5 minutes. 0.732 g. (0.0025 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl phenyl thioncarbonate is added and the mixture allowed to stand for 1 hour. The solvent is removed under reduced pressure, and water is added to the residue to yield 1-methyl-5-nitroimidazol-2-ylmethyl-N-hydroxythioncarbamate; m.p. 94—95° C. (dec.).

In accordance with the above procedure, but starting with N-methylhydroxylamine, N-*n*-propylhydroxylamine, N-phenylhydroxylamine and N-benzylhydroxylamine, in place of hydroxylamine, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-hydroxythioncarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*n*-propyl-N-hydroxythioncarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-phenyl-N-hydroxythioncarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-benzyl-N-hydroxythioncarbamate.

EXAMPLE 91

1-Methyl-5-nitroimidazol-2-ylmethyl N-methoxycarbamate

2 g. of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate is dissolved in 100 ml. hot methanol. After cooling the solution is treated with an excess of an ethereal solution of diazomethane. At first, decolorization of the diazomethane is rapid, but later it is very slow. After several hours, the colorless solution is filtered from the starting material. The residue from the solution is chromatographed over a column of silica gel in ethyl acetate solution. The O-methyl derivative comes directly through the column and is non-crystalline. This material is treated with one equivalent of *p*-toluenesulfonic acid in methyl ethyl ketone to give the *p*-toluenesulfonic acid-addition salt of 1-methyl-5-nitroimidazol-2-ylmethyl N-methoxy-carbamate in 17% overall yield; m.p. 113—115° C.

In accordance with the above procedure, but starting with 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-hydroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*n*-propyl-N-hydroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-phenyl-N-hydroxycarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-benzyl-N-hydroxycarbamate, in place of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-methyl-N-methoxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*n*-propyl-N-methoxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-phenyl-N-methoxycarbamate or 1-methyl-5-nitroimidazol-2-ylmethyl N-benzyl-N-methoxycarbamate.

In accordance with the above procedure, but using diazoethane, diazopropane, diazobutane and phenyldiazomethane, in place of diazomethane, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-ethoxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*n*-propoxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-*n*-butoxycarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-benzylloxycarbamate.

EXAMPLE 92

1-Methyl-5-nitroimidazol-2-ylmethyl N-acetoxycarbamate

To a solution of 2.22 g. (0.01 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate in 10 ml. of pyridine, cooled in an ice bath, is added slowly 1.12 g. acetic anhydride. The mixture is allowed to warm to room temperature. The solvent is evaporated at reduced pressure leaving a residue which is slurried in ether and filtered giving 1-methyl-5-nitroimidazol-2-ylmethyl N-acetoxycarbamate.

In accordance with the above procedure, but starting with propionic anhydride, butyric anhydride, valeric anhydride and phenylacetic anhydride, in place of acetic anhydride, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-propionoxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-butyroxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-valeroxycarbamate, or 1-methyl-5-nitroimidazol-2-ylmethyl N-phenylacetoxycarbamate.

In accordance with the above procedure, but starting with trifluoroacetic anhydride, in place of acetic anhydride, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-trifluoroacetoxycarbamate.

EXAMPLE 93

1-Methyl-5-nitroimidazol-2-ylmethyl N-benzoyloxycarbamate

1 g. of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate in 15 ml. of 1N sodium hydroxide is stirred for 2 hours with 0.65 g. of benzoyl chloride. Benzoylation is repeated with 0.5 ml. of benzoyl chloride and additional sodium hydroxide. 25 ml. of benzene is added and the benzene layer is separated, washed with water and dried over sodium sulfate. Evaporation yields 1-methyl-5-nitroimidazol-2-ylmethyl N-benzoyloxycarbamate; m.p. 147—151° C.

EXAMPLE 94

1-Methyl-5-nitroimidazol-2-ylmethyl N-acetyl-N-acetoxycarbamate

0.22 g. (0.001 mole) of 1-methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate, 0.1 g. of potassium acetate and 5 ml. of acetic anhydride are heated on a steam bath for 3 hours. The reaction mixture is evaporated to dryness at reduced pressure and 5 ml. of water and 50 ml. of chloroform are added to the residue. The chloroform extract on evaporation gives a crystalline product which is slurried in ether and filtered to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-acetyl-N-acetoxycarbamate.

In accordance with the above procedure, but using propionic anhydride and potassium propionate, butyric anhydride and potassium butyrate, valeric anhydride and potassium valerate, phenylacetic anhydride and potassium phenyl acetate, in place of acetic anhydride and potassium acetate, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-propionyl-N-propionyloxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-butyryl-N-butyryloxycarbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-valeryl-N-valeryloxycarbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-phenylacetyl-N-phenylacetoxycarbamate.

EXAMPLE 95

1-Methyl-5-nitroimidazol-2-ylmethyl sulfamoylcarbamate

0.1 mole of 1-methyl-2-hydroxymethyl-5-nitroimidazole in 100 ml. of methylene chloride is treated with 0.1 mole of chlorosulfonylisocyanate with heating at 50° C. until all of the starting material is dissolved. On cooling the intermediate, 1-methyl-5-nitroimidazol-2-ylmethyl carbamate-N-sulfonyl chloride crystallizes. This product in methylene chloride is treated with methylene chloride containing an excess of ammonia while cooling to -20° C. After 2 hours the excess ammonia and solvent are removed by evaporation. The product is washed with water. The 1-methyl-5-nitroimidazol-2-ylmethyl sulfamoylcarbamate is recrystallized from methanol or ethanol.

In accordance with the above procedure, but using methylamine, dimethylamine, ethylamine, *n*-propylamine, aniline or benzylamine, in place of ammonia, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-methylsulfamoyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N',N'-dimethylsulfamoyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-ethylsulfamoyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-*n*-propylsulfamoyl)carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-phenylsulfamoyl)carbamate, and 1-methyl-5-nitroimidazol-2-ylmethyl N-(N'-benzylsulfamoyl)carbamate.

EXAMPLE 96

1-Methyl-5-nitroimidazol-2-ylmethyl N-(*p*-toluenesulfonyl)carbamate

0.1 mole of 1-methyl-5-nitroimidazol-2-ylcarbamate and 0.1 mole of *p*-toluenesulfonyl isocyanate are added to 200 ml. of benzene containing 0.5 ml. of pyridine. The resulting mixture is heated under reflux until complete solution is obtained. The solvent is then removed by evaporation under reduced pressure. The partially crystalline material thus obtained is recrystallized from ethyl acetate or acetone to yield 1-methyl-5-nitroimidazol-2-ylmethyl N-(*p*-toluenesulfonyl)carbamate; m.p. 159—172° C. (dec.).

In accordance with the above procedure, but starting with methanesulfonyl isocyanate in place of *p*-toluenesulfonyl isocyanate, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-methanesulfonylcarbamate.

In accordance with the above procedure, but starting with the corresponding isothiocyanates there are obtained the corresponding 1-methyl-5-nitroimidazol-2-ylmethyl N-sulfonylthiocarbamates.

EXAMPLE 97

1-Methyl-5-nitroimidazol-2-ylmethyl N-diaminophosphorylcarbamate

0.1 mole of dichlorophosphoryl isocyanate is added to an ice-cold solution of 0.1 mole of 1-methyl-2-hydroxymethyl-5-nitroimidazole dissolved in anhydrous tetrahydrofuran. After standing for 18 hours at 0° C., this solution is added to an excess of ammonia gas dissolved in tetrahydrofuran. After two hours at 15° C., the mixture

is filtered from ammonium chloride and the tetrahydrofuran is removed under reduced pressure. The ammonium chloride is dissolved in water and any insoluble material is combined with the residue from tetrahydrofuran. After washing with water, the 1-methyl-5-nitroimidazol-2-ylmethyl N-diaminophosphorylcarbamate is recrystallized from ethanol.

In accordance with the above procedure, but using methylamine, dimethylamine, ethylamine, n-propylamine, aniline and benzylamine, in place of gaseous ammonia, there are obtained 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(methylamino)phosphoryl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(dimethylamino)phosphoryl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(ethylamino)phosphoryl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(n-propylamino)phosphoryl]carbamate, 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(anilino)phosphoryl]carbamate and 1-methyl-5-nitroimidazol-2-ylmethyl N-[bis(benzylamino)phosphoryl]carbamate.

EXAMPLE 98

4-Phenyl-5-nitroimidazole

1.56 g. of 4-p-acetylamino-phenyl-5-nitroimidazole is suspended in 50 ml. of ethanol and 13 ml. of concentrated sulfuric acid added dropwise with cooling and stirring, temperature being maintained below 10° C. An aqueous solution containing 1.03 g. of sodium nitrite is cooled to below 10° C. and added slowly to the ethanolic solution. The reaction mixture is maintained at a temperature of less than 10° C. and stirred for 1 hour. A further aqueous solution of sodium nitrite containing 1.03 g. of sodium nitrite is added and the reaction mixture stirred for a further hour. 252 mg. of finely divided copper bronze alloy is added and the mixture warmed on a steam bath for 15 minutes until effervescence ceases. The reaction mixture is filtered and the filtrate added to a mixture of ethyl acetate and water which is again filtered. The ethyl acetate layer is separated and the aqueous layer further extracted with ethyl acetate. The combined ethyl acetate extract is dried and the solvent removed by evaporation under reduced pressure. The residue is combined with the residues from the previous two filtrations. The mixture is sublimed *in vacuo* at an oil bath temperature of circa 200° C. The sublimate is taken up in acetone, filtered, concentrated and cooled to yield 4-phenyl-5-nitroimidazole; m.p. 284—288° C. (dec.).

EXAMPLE 99

1-Methyl-4-phenyl-5-nitroimidazole

100 mg. of 4-phenyl-5-nitroimidazole and 0.06 g. of dimethyl sulfate are warmed to 145° C. over 45 minutes. The homogenous mixture is cooled in an ice bath, aqueous sodium hydroxide solution added and the mixture poured into excess water.

The mixture is filtered and the residue, after air drying, is recrystallized from ether/petroleum-ether to yield 1-methyl-4-phenyl-5-nitroimidazole; m.p. 74.5—75.5° C.

In accordance with the above procedure, but starting with 4-chlorophenyl-5-nitroimidazole and 4-nitrophenyl-5-nitroimidazole, in place of 4-phenyl-5-nitroimidazole, there are obtained 1-methyl-4-chlorophenyl-5-nitroimidazole and 1-methyl-4-nitrophenyl-5-nitroimidazole.

EXAMPLE 100

1-Methyl-4-phenyl-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 2 g. of 1-methyl-4-phenyl-5-nitroimidazole, 15 g. (0.05 mole) of paraformaldehyde and 15 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 110—150° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-methyl-2-hydroxymethyl-4-phenyl-5-nitroimidazole.

A solution of 2.33 g. (0.01 mole) of 1-methyl-2-hydroxymethyl-4-phenyl-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-methyl-4-phenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

0.005 mole of 1-methyl-4-phenyl-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate. The residue is washed with water and recrystallized from methanol to yield 1-methyl-4-phenyl-5-nitroimidazol-2-ylmethyl carbamate.

In accordance with the above procedure, but starting with 1-methyl-4-chlorophenyl-5-nitroimidazole or 1-methyl-4-nitrophenyl-5-nitroimidazole, there is obtained 1-methyl-4-chlorophenyl-5-nitroimidazol-2-ylmethyl carbamate or 1-methyl-4-nitrophenyl-5-nitroimidazol-2-ylmethyl carbamate.

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EXAMPLE 101

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1-Methyl-4-cyano-5-nitroimidazol-2-ylmethyl carbamate

A mixture of 15.2 g. (0.1 mole) of 1-methyl-4-cyano-5-nitroimidazole, 15 g. (0.5 mole) of paraformaldehyde and 150 ml. of dimethylsulfoxide is heated in a sealed tube overnight at 120° C. The dimethylsulfoxide is removed completely at reduced pressure, and the residue is dissolved in water and extracted with chloroform. The chloroform extract is dried and concentrated. The residue is dissolved in ethyl acetate, and the solution is charged on a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 1-methyl-2-hydroxymethyl-4-cyano-5-nitroimidazole.

A solution of 1.82 g. (0.01 mole) of 1-methyl-2-hydroxymethyl-4-cyano-5-nitroimidazole in 25 ml. of dry pyridine is stirred at 0° C. and 1.85 g. (0.012 mole) of phenyl chloroformate is slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 200 ml. of water. The mixture is cooled overnight and the precipitate of 1-methyl-4-cyano-5-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration.

0.005 g. of 1-methyl-4-cyano-5-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 50 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with water and recrystallized from methanol to yield 1-methyl-4-cyano-5-nitroimidazol-2-ylmethyl carbamate.

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EXAMPLE 102

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3-Nitro-5,6-dihydroimidazo-[1,2- α]-pyrrol-7-yl carbamate

A mixture of 1.67 g. (0.1 mole) of 3-nitro-7-oxo-5,6-dihydroimidazo-[1,2- α]-pyrrole, 0.39 g. (0.01 mole) of sodium borohydride and 100 ml. of ethanol is allowed to stand at 15° C. for 6 hours. After addition of a few drops of acetic acid to decompose the excess borohydride, the solution is evaporated to a small volume and 50 ml. of water is added slowly with stirring. The product, 3-nitro-7-hydroxy-5,6-dihydroimidazo-[1,2- α]-pyrrole, is filtered and dried.

To a solution of 1.69 g. (0.01 mole) of the above product in 10 ml. of pyridine, cooled in an ice bath, is added 1.57 g. of phenyl chloroformate dropwise over a period of 20 minutes. The mixture is allowed to warm to room temperature and held at this temperature for 48 hours. The reaction mixture is quenched in 60 ml. of ice-water and the resulting solid is recovered by filtration. After drying, the 3-nitro-5,6-dihydroimidazo-[1,2- α]-pyrrol-7-yl phenyl carbonate is dissolved in 50 ml. of chloroform and the resulting solution added dropwise to 20 ml. of liquid ammonia, cooled in a dry ice bath. After stirring for 30 minutes, the mixture is allowed to warm gradually to room temperature. The chloroform is removed by evaporation and the residue slurried with water. 3-Nitro-5,6-dihydroimidazo-[1,2- α]-pyrrol-7-yl carbamate is obtained on filtration.

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EXAMPLE 103

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1-Methyl-2-hydroxymethyl-4-nitroimidazole

To a mixture of 1.43 g. of 2-hydroxymethyl-4-nitroimidazole in 50 ml. of dry 1,2-dimethoxyethane at 0° C. is added 0.24 g. of sodium hydride. 1.26 g. of dimethyl sulfate is added and the mixture is refluxed for 2 hours. After cooling, the solvent is evaporated under reduced pressure. 10 ml. 0.4N ammonium hydroxide solution is added and the mixture is extracted with 2 x 75 ml. of ethyl acetate. The ethyl acetate extract is evaporated to dryness to give 1-methyl-2-hydroxymethyl-4-nitroimidazole; m.p. 166—168 °C.

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EXAMPLE 104

1-Methyl-4-nitroimidazol-2-ylmethyl carbamate

3 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole are heated under reflux with 10 ml. of methyl iodide in 20 ml. of benzene for 4 days. The solvent is removed to yield the methiodide which is not further purified. The 1-methyl-2-hydroxymethyl-5-nitroimidazole methiodide thus obtained is heated to *circa* 250° C. under .01 mm. Hg pressure to yield 1-methyl-2-hydroxymethyl-4-nitroimidazole as a crystalline sublimate which is recrystallized from acetone and ether to give a product having a melting point 168—172° C.

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A solution of 1.43 g. (.0091 mole) of 1-methyl-2-hydroxymethyl-4-nitroimidazole in 10 ml. of dry pyridine is stirred at 0° C. and 2.7 ml. of phenyl chloroformate is

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slowly added. The reaction mixture is stirred for 3—4 hours at room temperature and is poured into about 100 ml. of water. The mixture is cooled overnight and the precipitate of 1-methyl-4-nitroimidazol-2-ylmethyl phenyl carbonate is separated by filtration (2.1 g., m.p. 105—106° C.).

2 g. of 1-methyl-4-nitroimidazol-2-ylmethyl phenyl carbonate is dissolved slowly in 20 ml. of liquid ammonia. After solution is complete, the ammonia is permitted to evaporate and the residue washed with water and recrystallized from ethanol to yield 1-methyl-4-nitroimidazol-2-ylmethyl carbamate (1.2 g., m.p. 187—189° C.).

The starting materials used in the aforementioned examples may be prepared in the following manner. "Supercel" and "Celite" are trade marks.

Preparation 1

1-n-Butyl-5-nitroimidazole

24.2 g., (0.214 moles) of 4(5)-nitroimidazole is heated with 25.0 g. (0.11 mole) of n-butyl tosylate for one hour at 180—190° C. and cooled to give a hard solid. The mixture is shaken with 175 ml. of 2.5 N aqueous sodium hydroxide until it is dissolved and diluted with 175 ml. of water to give an oily precipitate. The mixture is extracted with ether and the ether extract is washed with 2.5 N aqueous hydrochloric acid and water. The aqueous acid wash is treated with excess aqueous sodium hydroxide and extracted with ether. This latter ether extract is evaporated to dryness and recrystallized from petroleum ether to yield 1-n-butyl-5-nitroimidazole, m.p. 51—54° C.

In accordance with the above procedure but starting with methyl tosylate, ethyl tosylate and propyl tosylate in place of n-butyl tosylate, there are obtained the corresponding 1-methyl-5-nitroimidazole, 1-ethyl-5-nitroimidazole, and 1-propyl-5-nitroimidazole.

Preparation 2

1-Allyl-5-nitroimidazole p-toluene sulphonate

14.0 g., (0.124 moles) of 4(5)-nitroimidazole is heated with 26.3 g. (0.124 moles) of allyl tosylate at 140—150° C. for 15 minutes and cooled. The resultant mixture is dissolved in 150 ml. of 2.5 N sodium hydroxide and diluted with 150 ml. of water. The mixture is extracted with ether and the ether extracts are extracted with 2.5 normal aqueous hydrochloric acid. The acid extracts are made basic by the addition of excess aqueous sodium hydroxide and extracted with ether. This latter ether extract is evaporated to dryness to give 1-allyl-5-nitroimidazole as an oil. The 1-allyl-5-nitroimidazole is dissolved in 50 ml. of dry ether and added to a solution of 4.01 g. of p-toluenesulfonic acid hydrate and 200 ml. of ether, the mixture is cooled in an ice bath and the precipitate removed by filtration. The precipitate is recrystallized from ethyl acetate to yield 1-allyl-5-nitroimidazolium p-toluene sulfonate, m.p. 145—149° C.

Preparation 3

1-Phenyl-5-nitroimidazole

10 g., (0.069 mole) of 1-phenylimidazole is dissolved in 30 ml. of chloroform and the solution is stirred in an ice bath while 5 g. (0.037 mole) of nitronium fluoborate is added in small portions over half an hour. After stirring for half an hour at room temperature, the two dark phases are diluted with 200 ml. of chloroform and the mixture is extracted with an excess of 1 N hydrochloric acid. The chloroform extract is evaporated and the residue dissolved in acetone-ether (1:1) and chromatographed on 12 g. of a charcoal/Supercel mixture to yield 1-phenyl-5-nitroimidazole, m.p. 150—165° C. Sublimation at less than 1 mm. of mercury pressure and 120° C. raises the melting point to 160—170° C.

U.V. λ MeOH
max 291.0 m μ ϵ 5,000

Preparation 4

1-p-Nitrophenyl-5-Nitroimidazole

1.98 g., (0.0137 mole) of 1-phenylimidazole is dissolved in 6 ml. of concentrated sulfuric acid and 3.0 ml. (0.07 mole) of fuming nitric acid is added slowly. The mixture is heated in an oil bath at 120° C. for 1 hour, cooled and poured into ice-water. The mixture is extracted with chloroform to give a partly crystalline mixture. The aqueous acid phase is made basic and extracted with chloroform to give crystalline 1-p-nitrophenylimidazole. The acid-insoluble fraction is repeatedly washed with small portions of chloroform and evaporation of the solvent is followed by filtration of an acetone solution of the residue through Celite/charcoal. Evaporation, followed by re-

crystallization from methanol gives 1-p-nitrophenyl-5-nitroimidazole; m.p. 156.8—158° C.

U.V. λ MeOH ϵ 275.0 m μ 13,100
max

Preparation 5

- 5 1-(2'-Hydroxyethyl)-5-Nitroimidazole 5
78 g. (0.615 mole) of 5-nitroimidazole is dissolved in 1500 ml. of acetic acid upon the addition of 72 ml. (0.57 mole) of boron trifluoride etherate. 175 ml., (3.5 moles) of ethylene oxide in 175 ml. of hexane, in a dropping funnel topped with a cold finger, is added slowly over 1 hour to the above solution maintained at 32—35° C.
10 with a water cooling bath. The mixture is concentrated under high vacuum to 100—150 ml. volume. The residue is diluted with 500 ml. of water, neutralized to pH 7 with aqueous sodium hydroxide, and extracted with 1.5 liters of ethyl acetate. The extract is dried and evaporated to yield 1-(2'-hydroxyethyl)-5-nitroimidazole. It is convenient to isolate the compound as the hydrochloride. Hydrogen chloride is passed through the ethyl acetate extract and 1-(2'-hydroxyethyl)-5-nitroimidazolium hydrochloride is isolated; m.p. 172—175° C. 15

- In accordance with the above procedure, but starting with 1,2-epoxypropane, 1,2-epoxybutane, 1,2-epoxypentane, 1,3-epoxypropane, 1,3-epoxybutane and 1,3-epoxypentane in place of ethylene oxide, there are obtained 1-(2'-hydroxypropyl)-5-nitroimidazole, 1-(2'-hydroxybutyl)-5-nitroimidazole, 1-(2'-hydroxypentyl)-5-nitroimidazole, 1-(3'-hydroxypropyl)-5-nitroimidazole, 1-(3'-hydroxybutyl)-5-nitroimidazole and 1-(3'-hydroxypentyl)-5-nitroimidazole. 20

Preparation 6

- 25 1-(2'-Oxopropyl)-5-Nitroimidazole 25
17.1 g., (0.1 mole) of 1-(2'-hydroxypropyl)-5-nitroimidazole is dissolved in 500 ml. of dimethylsulfoxide and heated with 8 ml. of dry pyridine, 4 ml. of trifluoroacetic acid and 61.8 g. (0.3 mole) of dicyclohexylcarbodiimide for 8 hours at 15—20° C. The mixture is treated with an excess of oxalic acid and filtered, and the filtrate is evaporated to dryness under low pressure, less than 1 mm. of mercury. The mixture is taken up in water, neutralized with aqueous sodium hydroxide to pH 8—9
30 and extracted thoroughly with ethyl acetate. The extract is dried over sodium sulfate and treated with dry gaseous hydrogen chloride and 1-(2'-oxopropyl)-5-nitroimidazolium hydrochloride (m.p. 198—200° C.) is precipitated and removed by filtration. This compound is converted to the free base (m.p. 100° C.) by stirring with a saturated solution of sodium bicarbonate. 35

- In accordance with the above procedure, but starting with 1-(2'-hydroxybutyl)-5-nitroimidazole, 1-(2'-hydroxypentyl)-5-nitroimidazole, 1-(3'-hydroxybutyl)-5-nitroimidazole and 1-(3'-hydroxypentyl)-5-nitroimidazole, in place of 1-(2'-hydroxypropyl)-5-nitroimidazole, there are obtained 1-(2'-oxobutyl)-5-nitroimidazole, 1-(2'-oxopentyl)-5-nitroimidazole, 1-(3'-oxobutyl)-5-nitroimidazole and 1-(3'-oxopentyl)-5-nitroimidazole. 40

Preparation 7

- 1-(2'-Acetoxypropyl)-5-nitroimidazolium hydrochloride
45 11.2 g., (.054 mole) of 1-(2'-hydroxypropyl)-5-nitroimidazolium hydrochloride is heated under reflux in 100 ml. of acetic anhydride for one hour. The mixture is then concentrated and the residue dissolved in ether. The ether solution is treated with anhydrous hydrogen chloride to yield 1-(2'-acetoxypropyl)-5-nitroimidazolium hydrochloride; m.p. 165—175° C. 45

Preparation 8

- 50 1-(2'-Acetoxyethyl)-5-nitroimidazole 50
55 g., (0.35 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole is dissolved in 200 ml. of pyridine and treated with 50 ml. of acetic anhydride. The solution is heated under reflux for one hour and then concentrated under reduced pressure to yield 1-(2'-acetoxyethyl)-5-nitroimidazole; m.p. 61—62° C.

- In accordance with the above procedure, but starting with 1-(2'-hydroxybutyl)-5-nitroimidazole, 1-(2'-hydroxypentyl)-5-nitroimidazole, 1-(3'-hydroxybutyl)-5-nitroimidazole, 1-(3'-hydroxypentyl)-5-nitroimidazole and 1-(3'-hydroxypropyl)-5-nitroimidazole, in place of 1-(2'-hydroxyethyl)-5-nitroimidazole, there are obtained 1-(2'-acetoxybutyl)-5-nitroimidazole, 1-(2'-acetoxy-pentyl)-5-nitroimidazole, 1-(3'-acetoxybutyl)-5-nitroimidazole, 1-(3'-acetoxy-pentyl)-5-nitroimidazole and 1-(3'-acetoxypropyl)-5-nitroimidazole. 60

In accordance with the above procedure but using propionic anhydride, butyric anhydride and valeric anhydride in place of acetic anhydride together with any of the aforementioned 1-(2'-hydroxyalkyl)-5-nitroimidazoles, there is obtained the corresponding 1-alkanoyloxyalkyl-5-nitroimidazole.

Preparation 9

1-(2'-Benzoyloxyethyl)-5-nitroimidazole

55 g., (0.35 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole is dissolved in 150 ml. of water and added to a mixture of 100 ml. of benzoyl chloride and 300 ml. of 2.5 N aqueous sodium hydroxide and agitated vigorously for 3 hours. The mixture is then concentrated under reduced pressure, extracted with ether and the ether extract is washed with sodium hydroxide, dried over sodium sulfate and evaporated to yield 1-(2'-benzoyloxyethyl)-5-nitroimidazole.

In accordance with the above procedure but starting with phenylacetyl chloride, propionyl chloride and valeryl chloride in place of benzoyl chloride, there are obtained 1-(2'-phenylacetoxyethyl)-5-nitroimidazole, 1-(2'-propionyloxyethyl)-5-nitroimidazole and 1-(2'-valeryloxyethyl)-5-nitroimidazole.

In accordance with the above procedure, but starting with any of the 1-(2'-hydroxyalkyl)-5-nitroimidazoles produced in accordance with Preparation 5, there is obtained the corresponding 1-(2'-acyloxyalkyl)-5-nitroimidazole.

Preparation 10

1-(2-Ethoxyethyl)-5-nitroimidazole

11.3 g., (0.1 mole) of 5-nitroimidazole is mixed thoroughly with 24.4 g. (0.1 mole) of β -ethoxyethyl tosylate and heated to 185–195° C. for 30 minutes. The mixture is cooled and shaken with a mixture of chloroform and 2.5 N aqueous sodium hydroxide. The chloroform layer is set aside while the aqueous layer is extracted with chloroform. The combined chloroform extracts are washed with water, dried over sodium sulfate and the solvent removed under reduced pressure. The residue is dissolved in ether and washed through a column of alumina using ether as the eluant. Evaporation of the eluate yields 1-(2-ethoxyethyl)-5-nitroimidazole, $\lambda_{\text{max}}^{\text{MeOH}}$ 310.0 m μ .

In accordance with the above procedure, but starting with 2-methoxyethyl tosylate, 2-propoxyethyl tosylate, 2-butoxyethyl tosylate and 2-benzyloxyethyl tosylate in place of ethoxyethyl tosylate, there are obtained 1-(2-methoxyethyl)-5-nitroimidazole, 1-(2-propoxyethyl)-5-nitroimidazole, 1-(2-butoxyethyl)-5-nitroimidazole and 1-(2-benzyloxyethyl)-5-nitroimidazole.

Preparation 11

1-(2-Ethoxypropyl)-5-nitroimidazole

11.3 g., (0.1 mole) of 5-nitroimidazole is mixed thoroughly with 25.8 g. (0.1 mole) of β -ethoxypropyl tosylate and heated to 185–195° C. for 30 minutes. The mixture is cooled and dissolved in a mixture of chloroform and 2.5 N aqueous sodium hydroxide. The chloroform layer is set aside, and the aqueous layer extracted with chloroform. The combined chloroform extracts are washed with water, dried over sodium sulfate and the solvent removed under reduced pressure. The residue is dissolved in ether and washed through a column of alumina using ether as the eluant. Evaporation of the eluate yields 1-(2-ethoxypropyl)-5-nitroimidazole.

In accordance with the above procedure but starting with 2-ethoxybutyl tosylate or 2-ethoxypentyl tosylate in place of ethoxypropyl tosylate, there are obtained 1-(2-ethoxybutyl)-5-nitroimidazole and 1-(2-ethoxypentyl)-5-nitroimidazole.

Preparation 12

5-Nitroimidazol-1-ylacetic acid

1.5 g., (0.01 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole is taken up in 15 ml. of water and treated with 5.2 ml. of a chromic acid/sulfuric acid mixture (composition: 27 g. of chromium trioxide and 2.35 ml. of concentrated sulfuric acid, made up to 100 ml. with water). The reaction mixture is heated to 70° C. for one hour and allowed to stand for 18 hours. The mixture is diluted with 200 ml. of water and extracted with chloroform. The solvent is removed under reduced pressure and the residue is taken up in sodium hydroxide and extracted with ether. The ether layer is discarded. The sodium hydroxide extract is acidified with acetic acid, extracted with chloroform and the chloroform extract evaporated under reduced pressure to yield 5-nitroimidazol-1-ylacetic acid; m.p. 225–230° C.

*Preparation 13***5-Nitroimidazole-1-ylacetic acid**

15.7 g., (0.1 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole is dissolved in 500 ml. of dimethylsulfoxide and heated with 8 ml. of dry pyridine, 4 ml. of trifluoroacetic acid and 61.8 g. (0.3 moles) of dicyclohexylcarbodiimide for 8 hours at 15—20° C. The mixture is treated with excess oxalic acid, filtered and the filtrate evaporated to dryness at a temperature of 80—90° C. under a vacuum of less than 1 mm. of mercury pressure. The mixture is taken up in water, neutralized with aqueous sodium hydroxide to pH 8—9 and extracted thoroughly with ethyl acetate. After drying over sodium sulfate, the ethyl acetate extract is treated with dry gaseous hydrogen chloride and 5-nitroimidazol-1-ylacetaldehyde hydrochloride is removed by filtration. 1.55 g., (0.01 mole) of the aldehyde hydrochloride is dissolved in 30 ml. of water and 4 ml. of 2.5 N aqueous sodium hydroxide added. 0.011 mole of sodium hydrochloride is added and the mixture allowed to stand at room temperature for 18 hours. The reaction mixture is then made acidic with acetic acid and extracted with chloroform. The chloroform extract, after drying over sodium sulfate, is evaporated under reduced pressure to yield 5-nitroimidazol-1-ylacetic acid; m.p. 225—230° C.

In accordance with the above procedure but starting with 1-(3'-hydroxypropyl)-5-nitroimidazole in place of 1-(2'-hydroxyethyl)-5-nitroimidazole, there is obtained 5-nitroimidazol-1-ylpropionic acid.

*Preparation 14***Ethyl 5-nitroimidazol-1-ylacetate**

22.6 g., (0.2 mole) of 4(5)-nitroimidazole is dissolved in 250 ml. of nitromethane and 26 ml. (0.2 mole) of boron trifluoride etherate is added. The mixture is cooled to 0° C. and a solution of 25 ml. of diazoacetic ester in 25 ml. of nitromethane is added. An additional 12 ml. of diazoacetic ester is then added and the solution concentrated under reduced pressure. The residue is taken up in ethyl acetate and the ethyl acetate solution washed with ice-cold aqueous dilute ammonia. A precipitate of 4(5)-nitroimidazole is formed and is separated by filtration. The filtrate is thoroughly washed with water. After the ethyl acetate phase has been dried over sodium sulfate, dry hydrogen chloride gas is passed through the solution. Ethyl 5-nitroimidazol-1-ylacetate hydrochloride; m.p. 165—175° C., is obtained as a crystalline precipitate.

The ester hydrochloride is dissolved in water, from which ethyl 5-nitroimidazol-1-ylacetate m.p. 76—77° C., crystallizes.

In accordance with the above procedure, but starting with methyl diazoacetate, propyl diazoacetate or benzyl diazoacetate in place of diazoacetic ester there are obtained methyl, propyl and benzyl 5-nitroimidazol-1-ylacetates.

*Preparation 15***Ethyl 5-nitroimidazol-1-ylpropionate**

22.6 g., (0.2 mole) of 4(5)-nitroimidazole is dissolved in 250 ml. of nitromethane and 26 ml. (0.2 mole) of boron trifluoride etherate is added. The mixture is cooled to 0° C. and a solution of 25 ml. of diazopropionic ester in 25 ml. of nitromethane is added. An additional 12 ml. of diazopropionic acid is then added and the solution concentrated under reduced pressure. The residue is taken up in ethyl acetate and the ethyl acetate solution washed with ice-cold aqueous dilute ammonia. A precipitate of 4(5)-nitroimidazole is formed and is separated by filtration. The filtrate is thoroughly washed with water. After the ethyl acetate phase has been dried over sodium sulfate, dry hydrogen chloride gas is passed through the solution. Ethyl 5-nitroimidazol-1-ylpropionate hydrochloride is obtained as a crystalline precipitate.

The ester hydrochloride is dissolved in water from which ethyl 5-nitroimidazol-1-ylpropionate crystallizes.

In accordance with the above procedure, but starting with methyl diazopropionate, propyl diazopropionate or benzyl diazopropionate in place of diazopropionic ester, there are obtained methyl 5-nitroimidazol-1-ylpropionate, propyl 5-nitroimidazol-1-ylpropionate and benzyl 5-nitroimidazol-1-ylpropionate.

*Preparation 16***5-Nitroimidazol-1-ylacetic acid**

10 g., (0.05 mole) of ethyl 5-nitroimidazol-1-ylacetate, dissolved in 50 ml. of methanol, is treated with 50 ml. of 1 N potassium hydroxide (0.05 mole) in 50 ml. of methanol. After ten minutes the solution is diluted with ether (50 ml.), which causes the potassium salt to crystallize. It is filtered, washed with 50% methanol-ether and dried.

This potassium salt is dissolved in 40 ml. of water and acidified slowly with concentrated hydrochloric acid to pH 2 or lower. The desired crystalline acid is filtered off, washed with water and dried; m.p. 226—228° C.

U.V. λ CH_3OH 297.5 $m\mu$, 226.0 $m\mu$; E $\frac{1\%}{1\text{ml}}$ 458, 199

λ $\text{CH}_3\text{OH}/\text{HCl}$ 266.0 $m\mu$; E $\frac{1\%}{1\text{ml}}$ 335.

Preparation 17

Ethyl 5-nitroimidazol-1-ylacetate

17.1 g., (0.1 mole) of 5-nitroimidazol-1-ylacetic acid is taken up in 200 ml. of ethanol and heated under reflux for 5 hours, during which time a slow stream of dry hydrogen chloride is passed through the reaction mixture. The ethanol is then removed by evaporation under reduced pressure and the residue recrystallized from acetone to yield ethyl 5-nitroimidazol-1-ylacetate hydrochloride; m.p. 165—175° C.

The ester hydrochloride is dissolved in water. On standing for 10 minutes, ethyl 5-nitroimidazol-1-ylacetate; m.p. 76—77° C., is precipitated in crystalline form and is isolated by filtration.

In accordance with the above procedure, but using methanol, *n*-propanol or *n*-butanol in place of ethanol, there is obtained the corresponding methyl, *n*-propyl or *n*-butyl ester.

In accordance with the above procedure, but starting with 5-nitroimidazol-1-ylpropionic acid in place of 5-nitroimidazol-1-ylacetic acid, there is obtained the corresponding ethyl, methyl, *n*-propyl or *n*-butyl 5-nitroimidazol-1-ylpropionate.

Preparation 18

5-Nitroimidazol-1-ylacetonitrile

3.4 g., (0.02 mole) of 5-nitroimidazol-1-ylacetamide in 50 ml. of dry benzene and 10 ml. of thionyl chloride are heated under reflux for 6 hours. The solvent and excess thionyl chloride are removed by evaporation under reduced pressure and the residue dissolved in chloroform. The chloroform is washed with dilute sodium carbonate solution and dried over sodium sulfate. Dry hydrogen chloride gas is introduced into the chloroform solution and 5-nitroimidazol-1-ylacetonitrile hydrochloride is isolated as a crystalline precipitate.

The 5-nitroimidazol-1-ylacetonitrile hydrochloride is treated with sodium bicarbonate solution. The mixture is extracted with ethyl acetate and the ethyl acetate removed under reduced pressure to yield 5-nitroimidazol-1-ylacetonitrile.

In accordance with the above procedure, but starting with 5-nitroimidazol-1-ylpropionamide in place of 5-nitroimidazol-1-ylacetamide, there is obtained 5-nitroimidazol-1-ylpropionitrile.

Preparation 19

1-(2'-Ethylthioethyl)-5-nitroimidazole

A mixture of 3.11 g. (0.01 mole) of 5-nitroimidazol-1-ylethyl *p*-toluenesulfonate and 1.03 g. (0.012 mole) of the potassium salt of ethanethiol in 20 ml. of dry dimethylformamide is heated at about 100° C. overnight. The reaction mixture is cooled and is poured into 500 ml. of ice-water containing a slight excess of ammonia. The mixture is extracted with ethyl acetate. The extract is dried and concentrated leaving a residue of 1-(2'-ethylthioethyl)-5-nitroimidazole.

In accordance with the above procedure but starting with 5-nitroimidazol-1-yl-*n*-propyl tosylate and 5-nitroimidazol-1-yl-*n*-butyl tosylate in place of ethyl tosylate derivative, there are obtained 1-(3'-ethylthio-*n*-propyl)-5-nitroimidazole and 1-(4'-ethylthio-*n*-butyl)-5-nitroimidazole.

In accordance with the above procedure, but using the potassium salt of methanethiol, *n*-propanethiol, thiophenol and benzylmercaptan in place of ethanethiol, there are obtained 1-(2'-methylthioethyl)-5-nitroimidazole, 1-(2'-*n*-propylthioethyl)-5-nitroimidazole, 1-(2'-phenylthioethyl)-5-nitroimidazole and 1-(2'-benzylthioethyl)-5-nitroimidazole.

Preparation 20

1-(2'-Ethylsulfinylethyl)-5-nitroimidazole

A solution of 1.0 g. (0.005 mole) of 1-(2'-ethylthioethyl)-5-nitroimidazole is cooled to about -20 to -30° C. and a cold solution of 55 ml. (0.0055 mole) of 0.1 *N* monoperphthalic acid in 1,2-dimethoxyethane is added. The mixture is kept overnight

at room temperature. The mixture is concentrated to dryness at reduced pressure leaving a residue which, after neutralization with dilute ammonia, is extracted several times with chloroform. Evaporation of the chloroform extract leaves a residue of 1-(2'-ethylsulfinylethyl)-5-nitroimidazole.

- 5 In accordance with the above procedure, but starting with 1-(2'-ethylthio-*n*-propyl)-5-nitroimidazole, 1-(2'-ethylthio-*n*-butyl)-5-nitroimidazole, 1-(2'-methylthio-ethyl)-5-nitroimidazole, 1-(2'-*n*-propylthioethyl)-5-nitroimidazole, 1-(2'-phenylthioethyl)-5-nitroimidazole or 1-(2'-benzylthioethyl)-5-nitroimidazole, in place of 1-(2'-ethylthioethyl)-5-nitroimidazole, there is obtained 1-(2'-ethylsulfinyl-*n*-propyl)-5-nitroimidazole, 1-(2'-ethylsulfinyl-*n*-butyl)-5-nitroimidazole, 1-(2'-methylsulfinylethyl)-5-nitroimidazole, 1-(2'-*n*-propylsulfinylethyl)-5-nitroimidazole, 1-(2'-phenylsulfinylethyl)-ethyl)-5-nitroimidazole, or 1-(2'-benzylsulfinylethyl)-5-nitroimidazole.
- 10

Preparation 21

- 15 5-Nitroimidazol-1-ylethyl ethylsulfone
A mixture of 438 mg. (0.02 moles) of 1-(2'-ethylsulfinylethyl)-5-nitroimidazole, 2 ml. of glacial acetic acid and 2 ml. of 30% hydrogen peroxide is heated for 8 hours at 100° C. The solution is concentrated under reduced pressure (but not to dryness), water is added to the residue. 5-Nitroimidazol-1-ylethyl ethylsulfone which precipitates is separated by filtration, washed with water and air-dried.
- 20 In accordance with the above procedure but starting with 1-(2'-methylsulfinylethyl)-5-nitroimidazole, 1-(2'-*n*-propylsulfinylethyl)-5-nitroimidazole, 1-(2'-*n*-butylsulfinylethyl)-5-nitroimidazole, 1-(2'-methylsulfinylethyl)-5-nitroimidazole, 1-(2'-ethylsulfinyl-*n*-propyl)-5-nitroimidazole, 1-(2'-phenylsulfinylethyl)-5-nitroimidazole and 1-(2'-benzylsulfinylethyl)-5-nitroimidazole, in place of 1-(2'-ethylsulfinylethyl)-5-nitroimidazole, there are obtained 5-nitroimidazol-1-ylmethyl ethylsulfone, 5-nitroimidazol-1-yl-*n*-propyl ethylsulfone, 5-nitroimidazol-1-yl-*n*-butyl ethylsulfone, 5-nitroimidazol-1-ylethyl methylsulfone, 5-nitroimidazol-1-ylethyl *n*-propylsulfone, 5-nitroimidazol-1-ylethyl phenylsulfone, and 5-nitroimidazol-1-ylethyl benzylsulfone.
- 25

Preparation 22

- 30 1-(2'-*p*-Toluenesulfonyloxyethyl)-5-nitroimidazole
20 (0.127 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole in 50 ml. of dry pyridine is reacted with 75 g. of *p*-toluenesulfonyl chloride at 15° C. for 4 hours. The reaction mixture is poured into ice and water and the crystalline precipitate is separated by filtration, washed with water and air-dried to yield 1-(2'-*p*-toluenesulfonyloxyethyl)-5-nitroimidazole; m.p. 126—127° C.
- 35 In accordance with the above procedure, but starting with 1-(2'-hydroxypropyl)-5-nitroimidazole, 1-(2'-hydroxybutyl)-5-nitroimidazole, 1-(2'-hydroxypentyl)-5-nitroimidazole, 1-(3'-hydroxypropyl)-5-nitroimidazole, 1-(3'-hydroxybutyl)-5-nitroimidazole and 1-(3'-hydroxypentyl)-5-nitroimidazole, in place of 1-(2'-hydroxyethyl)-5-nitroimidazole, there are obtained 1-(2'-*p*-toluenesulfonyloxypropyl)-5-nitroimidazole, 1-(2'-*p*-toluenesulfonyloxybutyl)-5-nitroimidazole, 1-(2'-*p*-toluenesulfonyloxypropyl)-5-nitroimidazole, 1-(3'-*p*-toluenesulfonyloxybutyl)-5-nitroimidazole and 1-(3'-*p*-toluenesulfonyloxypropyl)-5-nitroimidazole.
- 40

Preparation 23

- 45 1-(2'-*N*-morpholinylethyl)-5-nitroimidazole
16 g. (.057 mole) of 1-(2'-*p*-toluenesulfonyloxyethyl)-5-nitroimidazole and 9.3 ml. of morpholine are heated at 95° C. for 4 hours. The reaction mixture is taken up in water and extracted with ether. Evaporation of the ether extract yields 1-(2'-*N*-morpholinylethyl)-5-nitroimidazole; m.p. 109—110° C.
- 50 In accordance with the above procedure, but starting with pyrrolidine, piperidine, dimethylamine, and diethylamine, in place of morpholine, there are obtained 1-(2'-*N*-pyrrolidinylethyl)-5-nitroimidazole, 1-(2'-*N*-piperidinylethyl)-5-nitroimidazole, 1-(2'-*N,N*-dimethylaminoethyl)-5-nitroimidazole, and 1-(2'-*N,N*-diethylaminoethyl)-5-nitroimidazole.
- 55

Preparation 24

- 1-Methyl-2-hydroxymethyl-5-nitroimidazole
27.9 g. of 1-methyl-5-nitroimidazole and 30.1 g. of paraformaldehyde are added to 154 ml. of dimethylsulfoxide and the resulting solution is sealed into a glass-lined tube. The solution is heated at 110° C. for 24 hours, with shaking. The dimethylsulfoxide is removed by distillation at 53—56° C./2mm. The residue is extracted with
- 60

3 × 150 ml. of hot benzene. The benzene extracts are combined and cooled to room temperature. 1-Methyl-2-hydroxymethyl-5-nitroimidazole crystallizes, and is recovered by filtration. The yield of product is 23 g.; m.p. 112—114.5° C.

Preparation 25

1-[2'-(Tetrahydropyran-2''-yloxy)ethyl]-2-hydroxymethyl-5-nitroimidazole
15.7 g., (0.1 mole) of 1-(2'-hydroxyethyl)-5-nitroimidazole is heated under reflux in 200 ml. of dihydropyran in the presence of 1 g. of *p*-toluenesulfonic acid for 12 hours. The solvent is removed by evaporation under reduced pressure. The residue is taken up in a mixture of chloroform and aqueous sodium bicarbonate. The chloroform phase, after drying over sodium sulfate, is evaporated. The residue is dissolved in 75 ml. of dimethylsulfoxide containing 15 g. of paraformaldehyde, and the resulting solution is sealed into a glass-lined tube. The solution is heated at 110° C. for 24 hours, with shaking. The mass is then removed from the reaction vessel and the dimethylsulfoxide removed by distillation at 53—56° C./2mm. The residue is extracted with 3 × 150 ml. of hot benzene. The benzene extracts are combined and concentrated to a small volume. 1-[2'-(Tetrahydropyran-2''-yloxy)ethyl]-2-hydroxymethyl-5-nitroimidazole crystallizes and is recovered by filtration.

Preparation 26

1-Methyl-2-formyl-5-nitroimidazole
100 g. (0.64 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole is dissolved in 3500 ml. of benzene at 70° C. There is added over a 20 minute period 460 gm. of lead tetraacetate (previously washed with glacial acetic acid and air-dried in the dark). The reaction mixture is stirred at 78° C. for 8 hours during which time white, crystalline lead diacetate precipitates from the solution. The mixture is allowed to stand overnight at room temperature, and the lead diacetate then removed by filtration and washed with 2 × 100 ml. of benzene. The combined benzene filtrate and washes are extracted with two 1 litre portions of saturated aqueous potassium bicarbonate, and then with 1500 ml. of water. The aqueous extracts are combined and extracted with 3 × 2500 ml. portions of chloroform. The chloroform extracts are backwashed individually with 500 ml. of water and then combined with the benzene solution and evaporated *in vacuo* to dryness. The residue is dissolved in 500 ml. of 10% sulfuric acid and warmed on a steam cone at 75—90° C. for 35 minutes.

The acidic solution is then cooled to room temperature and neutralized with sodium bicarbonate. This aqueous solution is then extracted with 4 × 2500 ml. portions of chloroform and each extract is backwashed in turn with 500 ml. of water. The organic extracts are combined and evaporated to dryness, *in vacuo*. The crystalline residue thus obtained is dissolved in a minimum volume of chloroform and filtered over about 250 gm. of silica gel. The silica gel is eluted with 7500 ml. of methylene dichloride. The eluate is evaporated *in vacuo* to give a residue of substantially pure 1-methyl-2-formyl-5-nitroimidazole. Recrystallization of the product from 500 ml. of boiling hexane affords 79 gm. of 1-methyl-2-formyl-5-nitroimidazole; m.p. 90—94° C.

Preparation 27

1-Methyl-2-(1'-hydroxyethyl)-5-nitroimidazole.

A solution of methyl magnesium iodide is prepared from 4.5 g. of magnesium, 26.3 g. of methyl iodide and 90 ml. of diethyl ether. 2.8 mg. of this solution is diluted with 15 ml. of ether, and added to a solution of 0.5 g. of 1-methyl-2-formyl-5-nitroimidazole in 20 ml. of diethyl ether. The mixture is refluxed for 20 minutes. An additional 15 ml. of diethyl ether is then added, followed by 6.7 ml. of 0.5 *N* hydrochloric acid. The organic phase is separated, dried over sodium sulfate and evaporated to dryness *in vacuo* to give 0.27 g. of 1-methyl-2-(1'-hydroxyethyl)-5-nitroimidazole. This material is dissolved in ether, an equal volume of petroleum ether is added, and the resulting solution evaporated to give crystalline 1-methyl-2-(1'-hydroxyethyl)-5-nitroimidazole.

The acidic aqueous layer is extracted with an equal volume of methylene chloride. The methylene chloride solution is evaporated to a residue which is dissolved in a minimum volume of methylene chloride. One-half volume of petroleum ether is added and the solution evaporated to give a residue of 1-methyl-2-(1'-hydroxyethyl)-5-nitroimidazole.

The solid products obtained are combined and dissolved in ethyl acetate. The solution is filtered through acid-washed alumina, and the filtrate evaporated to a small volume. 1-Methyl-2-(1'-hydroxyethyl)-5-nitroimidazole crystallizes; m.p. 144—

145° C. It is recrystallized from ethyl acetate to give pure 1-methyl-2-(1'-hydroxyethyl)-5-nitroimidazole; m.p. 145—147° C.

Preparation 28

1-Methyl-2-(1'-hydroxyethyl)-5-nitroimidazole

5 To a solution of 1.5 g. (0.01 mole) of 1-methyl-5-nitroimidazole-2-carboxaldehyde in 15 ml. of 1,2-dimethoxymethane at 0° C., containing 1.33 ml. of boron trifluoride etherate, is added 0.9 g. of diazomethane in 50 ml. of diethyl ether solution dropwise over about 20 minutes. Nitrogen gas is evolved. After being stirred for one hour at 0° C., the solution is allowed to warm gradually to room temperature. The solvent is evaporated. Chloroform (100 ml.) and 20 ml. of water containing 5 ml. of 4 N ammonium hydroxide are added to the residue. The chloroform layer is separated, washed with 10 ml. of water, dried over anhydrous sodium sulfate and evaporated. The residue is chromatographed on silica gel to give 1-methyl-2-acetyl-5-nitroimidazole; m.p. 98° C.

15 To 1.83 g. (0.01 mole) of 1-methyl-2-acetyl-5-nitroimidazole, dissolved in 50 ml. of ethanol, is added 0.38 g. of sodium borohydride. The solution is allowed to stand overnight at room temperature. Following the addition of a few drops of glacial acetic acid to destroy unreacted sodium borohydride, 20 ml. of water is added and the solution evaporated to about 20 ml. 1-Methyl-2-(1'-hydroxyethyl)-5-nitroimidazole is separated by filtration, washed with water and air-dried.

20 In accordance with the above procedure, but using diazoethane, diazopropane or phenyldiazomethane in place of diazomethane, there is obtained 1-methyl-2-(1'-hydroxypropyl)-5-nitroimidazole, 1-methyl-2-(1'-hydroxybutyl)-5-nitroimidazole, or 1-methyl-2-(1'-hydroxyphenethyl)-5-nitroimidazole.

Preparation 29

α -(1-Methyl-5-nitroimidazol-2-yl)benzyl alcohol

25 6 g. of 2-benzylimidazole is added to 17 ml. of concentrated nitric acid in 75 ml. of acetic anhydride and cooled in an ice bath. The reaction mixture is warmed on a steam bath for 30 minutes, and then poured on to crushed ice. The crude product is extracted with 3 $\times$ 100 ml. of chloroform. The combined chloroform extract is washed with 3 $\times$ 15 ml. water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue is dissolved in 50 ml. of acetone. The addition of diethyl ether to the cloud-point results in the crystallization of 2-benzyl-4(5)-nitroimidazole.

35 2.03 g. of 2-benzyl-4(5)-nitroimidazole and 1.3 g. of dimethyl sulfate are heated for 30 minutes at 120° C. After cooling, 100 ml. of chloroform and 10 ml. of 4 N sodium hydroxide solution are added. The chloroform extract, after washing with 3 $\times$ 10 ml. of water, is dried over anhydrous sodium sulfate and evaporated. The crude 1-methyl-2-benzyl-5-nitroimidazole is purified by recrystallization from ethanol.

40 3.22 g. of 1-methyl-2-benzyl-5-nitroimidazole is dissolved in a mixture of 45 ml. of water and 15 ml. of sulfuric acid. 5.25 g. of sodium dichromate dihydrate in 30 ml. of water is added. 75 ml. of sulfuric acid is added so as to maintain the temperature between 75 and 90° C. Heating is continued for one hour at about 70° C. The reaction mixture is poured on to crushed ice and concentrated sodium hydroxide is added to neutrality. The product, 1-methyl-2-benzoyl-5-nitroimidazole, is filtered off.

45 To 2.15 g. of 1-methyl-2-benzoyl-5-nitroimidazole in 100 ml. of ethanol is added 0.28 g. of sodium borohydride. The mixture is allowed to stand overnight. After the addition of a few drops of glacial acetic acid, 25 ml. of water is added and the ethanol evaporated. The product, α -(1-methyl-5-nitroimidazol-2-yl)benzyl alcohol, is removed by filtration.

Preparation 30

2-(1-Methyl-5-nitroimidazol-2-yl)-ethanol

55 A mixture of 70 g. (0.5 mole) of 1,2-dimethyl-5-nitroimidazole, 75 g. (2.5 mole) of paraformaldehyde, and 1 liter of dry dimethylsulfoxide is heated in a glass-lined, rocking autoclave at 120—150° C. overnight. The bulk of the dimethylsulfoxide is removed at reduced pressure. The residue is dissolved in 400 ml. of 2.5 N hydrochloric acid, and the solution is exhaustively extracted with chloroform to remove the rest of the dimethylsulfoxide. The aqueous phase is adjusted to pH 7.5 by the addition of 50% sodium hydroxide solution, and is again extracted exhaustively with chloroform. The extract is dried and concentrated leaving an oily residue which soon crystallizes. The solid is dissolved in a little ethyl acetate, and the solution is

charged to a column of alumina. Elution with ethyl acetate and evaporation of the solvent yields 2-(1-methyl-5-nitroimidazol-2-yl)ethanol; m.p. 149—151° C.;

$\lambda_{\text{max}}^{\text{MeOH}}$ 310 m μ , (ϵ , 8800); together with 2-(1-methyl-5-nitroimidazol-2-yl)-propan-1,3-diol; m.p. 123—125° C.;

5 $\lambda_{\text{max}}^{\text{MeOH}}$ 310 m μ , (ϵ , 9000) and 2-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-ol; m.p. 140—142° C.;

$\lambda_{\text{max}}^{\text{MeOH}}$ 221 m μ , (ϵ , 9900), 315 m μ , (ϵ , 9700).

Preparation 31

10 3-(1-Methyl-5-nitroimidazol-2-yl)prop-2-en-1-al

A mixture of 0.155 g. (0.001 mole) of 1-methyl-2-formyl-5-nitroimidazole and 0.304 g. (0.001 mole) of formylmethyltriphenylphosphorane in 6 ml. of benzene is heated under reflux for 18 hours. The solvent is removed under pressure to give a crystalline residue which is dissolved in 75 ml. of ether. The solution is washed with 1 N aqueous hydrochloric acid. The hydrochloric acid fraction is made alkaline by the addition of an excess of potassium bicarbonate and the resulting aqueous solution is extracted with ether. The ethereal extract is dried and the solvent removed. The residue is taken up in warm benzene and chromatographed on silica gel. Elution with ether followed by recrystallization from ethanol yields 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-al; m.p. 147—149° C.

Preparation 32

20 3-(1-Methyl-5-nitroimidazol-2-yl)prop-2-en-1-ol

8.29 g., (0.046 mole) of 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-al is taken up in 2.2 liters of ethanol and 0.97 g. (0.026 mole) of sodium borohydride in 20 ml. of water is added and the mixture is allowed to stand for 5 hours. The reaction mixture is then made neutral to litmus paper by the addition of 7 ml. of glacial acetic acid, and concentrated under reduced pressure to 35 ml. The solids are separated by filtration. The product is recrystallized from butanol to yield 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-ol; m.p. 132—134° C.

Preparation 33

30 3-(1-Methyl-5-nitroimidazol-2-yl)propanol

A mixture of 200 mg. (0.001 mole) of 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-ol and 430 mg. (0.0022 mole) of potassium azodicarboxylate in 15 ml. of methanol is stirred under nitrogen at 15° C. Glacial acetic acid (0.264 ml., 0.0044 mole) is added and the resulting solution is stirred overnight. The solvent is removed at reduced pressure. The residue is dissolved in 5 ml. of water and the solution is extracted continuously with chloroform for 1—2 hours. The extract is dried and concentrated leaving a residue. The residue crystallizes on addition of water to yield 3-(1-methyl-5-nitroimidazol-2-yl)propanol; m.p. 170—175° C.

Preparation 34

40 1-Methyl-2-chloromethyl-5-nitroimidazole

1.0 g. (0.0064 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole is dissolved in 100 ml. of refluxing benzene. To this hot solution is added 20 ml. of thionyl chloride. The solution is warmed on a steam cone for 20 minutes and then evaporated to dryness *in vacuo*. The residue of 1-methyl-2-chloromethyl-5-nitroimidazole hydrochloride thus obtained is flushed several times with benzene to remove traces of thionyl chloride. (The 1-methyl-2-chloromethyl-5-nitroimidazole hydrochloride prepared in this manner is suitable for synthetic purposes without further purification). It is further purified as follows: It is dissolved in 25 ml. of water and the solution made slightly alkaline (pH 8—9) with dilute sodium hydroxide and extracted with 3 $\times$ 100 ml. of chloroform. The chloroform extracts are combined, backwashed with water and evaporated *in vacuo* to dryness to give substantially pure 1-methyl-2-chloromethyl-5-nitroimidazole.

The 1-methyl-2-chloromethyl-5-nitroimidazole may be characterized as the *p*-toluenesulfonic acid salt: To a 20% (W/W) solution of the imidazole in chloroform

there is added a solution of excess *p*-toluenesulfonic acid in ether. The 1-methyl-2-chloromethyl-5-nitroimidazole *p*-toluenesulfonic acid salt precipitates and is recovered by filtration and dried to substantially pure material; m.p. 153—155 °C.

In accordance with the above procedure, but using thionyl bromide in place of thionyl chloride, there is obtained 1-methyl-2-bromomethyl-5-nitroimidazole.

Preparation 35

1-Methyl-2-*p*-toluenesulfonyloxymethyl-5-nitroimidazole

To a solution of 1.57 g. (0.01 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole in 10 ml. of dry pyridine, cooled to -20° C., is added .190 g. (0.01 mole) of *p*-toluenesulfonyl chloride. The mixture is kept at -20° C. overnight. After the addition of 20 ml. of ice-water, the solid product is removed by filtration.

In accordance with the above procedure, but starting with methanesulfonyl chloride in place of *p*-toluenesulfonyl chloride, there is obtained 1-methyl-2-methanesulfonyloxymethyl-5-nitroimidazole.

Preparation 36

1-Methyl-2-mercaptomethyl-5-nitroimidazole

250 mg. of 1-methyl-2-chloromethyl-5-nitroimidazole and 106 mg. of thiourea are added to 2 ml. of dry ethanol, and the resulting mixture is refluxed for 17 hours. At the end of this time the mixture is cooled to about 15° C. and the solid material removed by filtration.

1.26 g. of the resulting 1-methyl-5-nitroimidazol-2-yl-methyl isothiuronium chloride is added to 20 ml. of water and 2 ml. of 2.5 N sodium hydroxide in a nitrogen atmosphere. The mixture is heated at 55° C. for 15 minutes. At the end of this time the mixture is cooled to room temperature and extracted with three 10 ml. portions of chloroform. The chloroform extracts are combined and concentrated to dryness to give 1-methyl-2-mercaptomethyl-5-nitroimidazole.

Preparation 37

1-Methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate

15.9 ml. dry pyridine and 4.87 g. (0.031 mole) of 1-methyl-2-hydroxymethyl-5-nitroimidazole are added to a flask fitted with a stirrer, thermometer and addition funnel. The mixture is stirred at room temperature until the solid dissolves and is then cooled to 0° C. 0.05 g. (0.0322 mole) of phenylchloroformate is added to the stirred solution over an 80 minute period, while maintaining the temperature at 5—10° C. with external cooling. On completion of the addition, the reaction mixture is stirred at about 25° C. for 2-1/2 hours. It is then poured into 60 ml. of ice-water with good agitation. The resulting slurry is stirred for 40 minutes and the resulting solid 1-methyl-5-nitroimidazol-2-ylmethyl phenyl carbonate collected by filtration. The solid is washed thoroughly with water and dried *in vacuo* at 50° C. A yield of 8.24 g. is obtained; m.p. 92—95° C. Recrystallization from 1:3 methanol-hexane gives pure product; m.p. 100—100.5° C.

In accordance with the above procedure, but starting with 1-methyl-2-mercaptomethyl-5-nitroimidazole, in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained 1-methyl-5-nitroimidazol-2-yl-methyl phenyl thiocarbonate.

In accordance with the above procedure, but starting with 1-methyl-2-(1-hydroxyethyl)-5-nitroimidazole, 1-methyl-2-(2-hydroxyethyl)-5-nitroimidazole and 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-ol in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there are obtained 1-(1-methyl-5-nitroimidazol-2-yl)-ethylphenyl carbonate, 2-(1-methyl-5-nitroimidazol-2-yl)-ethylphenyl carbonate and 3-(1-methyl-5-nitroimidazol-2-yl)prop-2-en-1-yl phenyl carbonate.

Preparation 38

1-Methyl-5-nitroimidazol-2-ylmethyl phenyl thionocarbonate

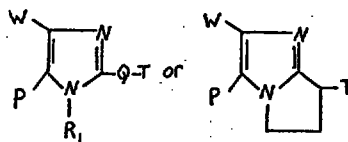
5.17 g. phenoxythiocarbonyl chloride is added dropwise to a cold solution of 4.71 g. of 1-methyl-2-hydroxymethyl-5-nitroimidazole in 15 ml. of pyridine. During addition the pyridine solution is cooled in an ice bath. After about one-third of the carbonyl chloride is added, 10 ml. of pyridine is added to the reaction mixture. On completion of the addition, the mixture is allowed to warm to room temperature and stirred for three and one-half hours. It is then poured into about an equal volume of an ice-water mixture. A gummy precipitate forms. The water is decanted from this precipitate and the solid triturated with 70 ml. of methanol. Water (70 ml.) is added and the solid product removed by filtration. It is recrystallized from benzene-

hexane to give 1-methyl-5-nitroimidazol-2-ylmethyl phenyl thionocarbonate; m.p. 92—98° C. On further recrystallization from benzene-hexane the product melts at 103—105.5° C.

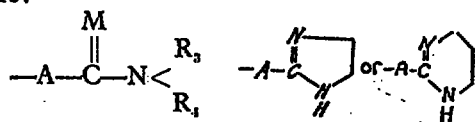
In accordance with the above procedure, but starting with 1-methyl-2-mercapto-methyl-5-nitroimidazole in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl phenyl dithiocarbonate.

WHAT WE CLAIM IS:—

1. A compound having the formula:



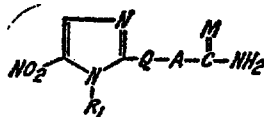
in which R₁ is alkyl or substituted alkyl where the substituent is aryl, fluorophenyl, nitrophenyl, oxo, alkenyl, hydroxy, halo, alkanoyloxy, aralkanoyloxy, benzoyloxy, alkoxy, aralkoxy, carboxy, carboalkoxy, carboaralkoxy, alkylcarbamoyl, aralkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, carbamoyloxy, carbamoyl, cyano, alkylthio, aralkylthio, arylthio, alkylsulfinyl, aralkylsulfinyl, arylsulfinyl, alkylsulfonyl, aralkylsulfonyl, arylsulfonyl or dialkylamino; Q is C₁₋₅ alkylene, C₃₋₅ alkenylene, aralkylidene or C₂₋₅ alkylidene; W is nitro, cyano, phenyl or hydrogen; and P is hydrogen or nitro, provided that one and only one of W and P is nitro; and T has the substructure:



where A is oxygen or sulfur; M is oxygen, sulfur, imino or alkylimino; each of R₂ and R₃ is hydrogen, alkyl, or substituted alkyl in which the substituent(s) is or are halo, hydroxy, alkoxy, oxo, aryl and oxo, carboxy, carboalkoxy, carboaralkoxy, carbamoyloxy, alkanoyloxy, aralkanoyloxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, dialkylcarbamoyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, aralkylsulfamoyl, dialkylsulfamoyl, mercapto, alkylthio, aralkylthio, thioncarbamoyl, dialkylthiocarbamoylthio, diaralkylthiocarbamoylthio, amino, alkylamino, dialkylamino, diaralkylamino or heterocyclicalkyl in which the ring contains at least one nitrogen atom, which is bonded to the alkyl group; phenyl; nitrophenyl; chlorophenyl; fluorophenyl; substituted methylene or alkylidene in which the substituent(s) is or are alkoxy, aralkoxy, aryloxy, dialkylamino or diaralkylamino; alkanoyl, aralkanoyl, aroyl, cyanoalkanoyl, or C₂₋₅ alkenoyl; hydroxy, substituted hydroxy, wherein said substituent is alkanoyl, aralkanoyl, aroyl, alkyl, aralkyl, aryl, cyanoalkanoyl or C₂₋₅ alkenoyl; carbamoyl and thiocarbamoyl and N-substituted carbamoyl and thiocarbamoyl wherein said substituent is alkyl, aralkyl or aryl; heterocycloalkylcarbonyl in which the heterocycloalkyl ring contains at least one nitrogen atom, which is bonded to the carbonyl group; nitro; amino and substituted amino, in which substituent(s) is or are carbamoyl, thiocarbamoyl, C₂₋₅ alkylidene, aralkylidene, alkanoyl, aralkanoyl, aroyl, cyanoalkanoyl or C₂₋₅ alkenoyl; alkanoylalkanoxyloxy, aralkanoyl aralkanoyloxy, sulfamoyl, alkylsulfamoyl, dialkylsulfamoyl, aralkylsulfamoyl, diaminophosphoryl, bis(alkylamino)phosphoryl, bis(dialkylamino)phosphoryl, bis(phenylamino)phosphoryl and bis(diphenylamino)phosphoryl; or R₂ and R₃ together represent the group —(CH₂)₂R₄—(CH₂)₂— where R₄ is oxygen, sulfur, methylene, imino, alkylimino, or a carbon-to-carbon single bond; the terms "alkyl," "alkanoyl," and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

2. A compound as claimed in Claim 1 in which W is hydrogen, P is nitro, R₁ is C₁₋₅ alkyl, and T is carbamoyloxy, carbamoylthio, thioncarbamoyloxy, thiocarbamoylthio, pseudo-ureido or pseudo-thioureido.

3. A compound as claimed in Claim 1 having the formula:

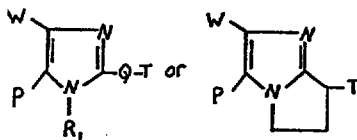


hexane to give 1-methyl-5-nitroimidazol-2-ylmethyl phenyl thionocarbonate; m.p. 92—98° C. On further recrystallization from benzene-hexane the product melts at 103—105.5° C.

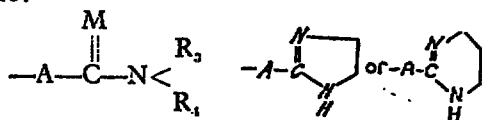
In accordance with the above procedure, but starting with 1-methyl-2-mercapto-methyl-5-nitroimidazole in place of 1-methyl-2-hydroxymethyl-5-nitroimidazole, there is obtained 1-methyl-5-nitroimidazol-2-ylmethyl phenyl dithiocarbonate.

WHAT WE CLAIM IS:—

1. A compound having the formula:



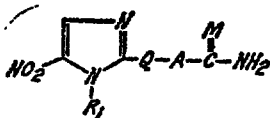
in which R_1 is alkyl or substituted alkyl where the substituent is aryl, fluorophenyl, nitrophenyl, oxo, alkenyl, hydroxy, halo, alkanoyloxy, aralkanoyloxy, benzoyloxy, alkoxy, aralkoxy, carboxy, carboalkoxy, carboaralkoxy, alkylcarbamoyl, aralkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, carbamoyloxy, carbamoyl, cyano, alkylthio, aralkylthio, arylthio, alkylsulfanyl, aralkylsulfanyl, arylsulfanyl, alkylsulfonyl, aralkylsulfonyl, arylsulfonyl or dialkylamino; Q is C_{1-5} alkylene, C_{2-3} alkenylene, aralkylidene or C_{2-3} alkylidene; W is nitro, cyano, phenyl or hydrogen; and P is hydrogen or nitro, provided that one and only one of W and P is nitro; and T has the substructure:



where A is oxygen or sulfur; M is oxygen, sulfur, imino or alkylimino; each of R_2 and R_3 is hydrogen, alkyl, or substituted alkyl in which the substituent(s) is or are halo, hydroxy, alkoxy, oxo, aryl and oxo, carboxy, carboalkoxy, carboaralkoxy, carbamoyloxy, alkanoyloxy, aralkanoyloxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, dialkylcarbamoyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, aralkylsulfamoyl, dialkylsulfamoyl, mercapto, alkylthio, aralkylthio, thioncarbamoyl, dialkylthiocarbamoylthio, diaralkylthiocarbamoylthio, amino, alkylamino, dialkylamino, diaralkylamino or heterocycloalkyl in which the ring contains at least one nitrogen atom, which is bonded to the alkyl group; phenyl; nitrophenyl; chlorophenyl; fluorophenyl; substituted methylene or alkylidene in which the substituent(s) is or are alkoxy, aralkoxy, aryloxy, dialkylamino or diaralkylamino; alkanoyl, aralkanoyl, aroyl, cyanoalkanoyl, or C_{2-3} alkenoyl; hydroxy, substituted hydroxy, wherein said substituent is alkanoyl, aralkanoyl, aroyl, alkyl, aralkyl, aryl, cyanoalkanoyl or C_{2-3} alkenoyl; carbamoyl and thiocarbamoyl and N-substituted carbamoyl and thiocarbamoyl wherein said substituent is alkyl, aralkyl or aryl; heterocycloalkylcarbonyl in which the heterocycloalkyl ring contains at least one nitrogen atom, which is bonded to the carbonyl group; nitro; amino and substituted amino, in which substituent(s) is or are carbamoyl, thiocarbamoyl, C_{2-3} alkylidene, aralkylidene, alkanoyl, aralkanoyl, aroyl, cyanoalkanoyl or C_{2-3} alkenoyl; alkanoylalkanoyloxy, aralkanoyl aralkanoyloxy, sulfamoyl, alkylsulfamoyl, dialkylsulfamoyl, aralkylsulfamoyl, diaminophosphoryl, bis(alkylamino)phosphoryl, bis(dialkylamino)phosphoryl, bis(phenylamino)phosphoryl and bis(diphenylamino)phosphoryl; or R_2 and R_3 together represent the group $-(CH_2)_2R_4-(CH_2)_2-$ where R_4 is oxygen, sulfur, methylene, imino, alkylimino, or a carbon-to-carbon single bond; the terms "alkyl," "alkanoyl," and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

2. A compound as claimed in Claim 1 in which W is hydrogen, P is nitro, R_1 is C_{1-3} alkyl, and T is carbamoyloxy, carbamoylthio, thioncarbamoyloxy, thiocarbamoylthio, pseudo-ureido or pseudo-thioureido.

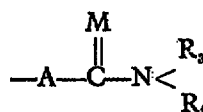
3. A compound as claimed in Claim 1 having the formula:



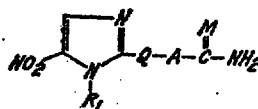


in which R_1 is C_{1-5} alkyl; Q is C_{1-5} alkylene, C_{2-5} alkylidene, or phenylmethylene; A is oxygen or sulfur; and M is oxygen, sulfur or imino.

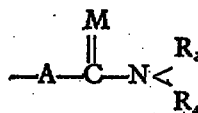
4. 1-Methyl-5-nitroimidazol-2-ylmethyl carbamate.
5. 1-Methyl-5-nitroimidazol-2-ylmethyl thiolcarbamate.
- 5 6. 1-Methyl-5-nitroimidazol-2-ylmethyl thioncarbamate.
7. 1-(1'-Methyl-5'-nitroimidazol-2'-yl)ethyl carbamate.
8. 1-Ethyl-5-nitroimidazol-2-ylmethyl carbamate.
9. 2-(1'-Methyl-5'-nitroimidazol-2'-yl)ethyl carbamate.
10. S-(1'-Methyl-5'-nitroimidazol-2'-ylmethyl)pseudo-thiourea.
- 10 11. A compound as claimed in Claim 1 in which W is hydrogen, P is nitro, R_1 is C_{1-5} alkyl, and T is



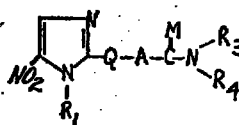
12. A compound as claimed in Claim 1 in which R_1 is C_{1-5} alkyl, Q is C_{1-5} alkylene, each of A and M is oxygen or sulfur, each of R_3 and R_4 is hydrogen, C_{1-5} alkyl, C_{1-5} alkanoyl, amino, hydroxy, C_{1-5} alkoxy, phenyl-(C_{1-5} alkoxy), di-
15 (C_{1-5} alkyl)amino-(C_{1-5} alkyl), phenyl, tosyl, C_{1-5} hydroxyalkyl, carbamoyl, C_{1-5} alkylidenylamino or carbo(C_{1-5} alkoxy)-(C₂₋₅ alkylenyl) provided that only one of the groups R_3 and R_4 is hydrogen, or NR_3 . R_4 represents morpholino, 4-methyl-
20 piperazino or piperidino.
13. 1-Methyl-5-nitroimidazol-2-ylmethyl N-methylcarbamate.
14. 1-Methyl-5-nitroimidazol-2-ylmethyl N-methylthioncarbamate.
15. 1-(1-Methyl-5-nitroimidazol-2-yl) ethyl N-hydroxycarbamate.
16. 1-Methyl-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate.
- 25 17. A compound as claimed in Claim 1 in which W is hydrogen, P is nitro, R_1 is substituted C_{1-5} alkyl, and T is carbamoyloxy, carbamoylthio, thioncarbamoyloxy, thio-
25 carbamoylthio, pseudo-ureido, or pseudo-thioureido.
18. A compound as claimed in Claim 1 having the formula:



- in which R_1 is substituted C_{1-5} alkyl, Q is C_{1-5} alkylene, C_{2-5} alkylidene or phenyl-
30 methylene, A is oxygen or sulfur, and M is oxygen, sulfur or imino.
19. 1-(2'-Acetoxyethyl)-5-nitroimidazol-2-ylmethyl carbamate.
20. 1-(2'-Hydroxyethyl)-5-nitroimidazol-2-ylmethyl carbamate.
21. 1-(2'-(carbamoyloxyethyl)-5-nitroimidazol-2-ylmethyl)carbamate.
- 35 22. A compound as claimed in Claim 1 in which W is hydrogen, P is nitro, R_1 is substituted C_{1-5} alkyl and T is

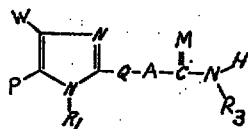


23. A compound as claimed in Claim 1 having the formula



- in which R_1 is alkanoyloxy or alkyl, and each of R_3 and R_4 is hydrogen or hydroxy,
40 provided that only one of R_3 and R_4 is hydrogen.
24. 1-(2'-Acetoxyethyl)-5-nitroimidazol-2-ylmethyl N-hydroxycarbamate.

25. A process for the preparation of a compound having the formula:

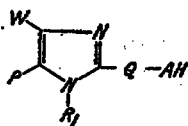


I

in which each of A and M is oxygen and sulfur, R_1 is alkyl or substituted alkyl in which the substituent is hydroxy, oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, carbamoyl, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl, dialkylamino or carbamoyloxy;

R_1 is hydrogen, alkyl, substituted alkyl in which the substituent is halo, alkoxy, oxo, phenyloxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, alkylthio, phenylalkylthio, dialkyldithiocarbamoyl, diphenylalkyldithiocarbamoyl, diphenyldithiocarbamoyl, dialkylamino, diphenylalkylamino heterocycloalkyl; alkylsulfonyl or phenylsulfonyl; phenyl, alkanoyl, phenylalkanoyl, aroyl, cyanoacetyl, alkenoyl, chlorosulfonyl or dichlorophosphoryl; and

P, Q and W are as defined in Claim 1; that comprises reacting a compound having the formula:

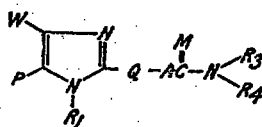


with a compound having the formula:



where A, M, W, P, Q, R_1 and R_3 are as defined above, except that R_1 is not hydroxy-alkyl, to produce the desired product and, where R_1 is alkanoyloxyalkyl, optionally hydrolysing with a base to obtain the corresponding compound in which R_1 is hydroxyalkyl, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

26. A process for the preparation of a compound having the formula:



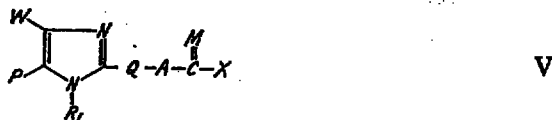
in which

R_1 is alkyl or substituted alkyl where the substituent is hydroxy, carboxy, oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or dialkylamino; each of A and M is oxygen and sulfur; and each of R_3 and R_4 is hydrogen, alkyl, substituted alkyl, in which the substituents are halo, alkoxy, oxo, phenyloxy, carboxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, carbamoyl, alkylcarbamoyl, phenylcarbamoyl, phenylalkylcarbamoyl, alkylcarbamoyloxy, phenylcarbamoyloxy, phenylalkylcarbamoyloxy, sulfamoyl, alkylsulfamoyl, phenylsulfamoyl, phenylalkylsulfamoyl, mercapto, alkylthio, phenylalkylthio, thiocarbamoyl, dialkyldithiocarbamoyl, diphenylalkyldithiocarbamoyl, diphenyldithiocarbamoyl, amino, alkylamino, dialkylamino or diphenylalkylamino; phenyl, hydroxy, substituted hydroxy in which the substituent is alkyl, phenylalkyl or phenyl; amino, substituted amino in which the substituent is carbamoyl, alkylidene, phenylalkylidene, alkonyl, phenylalkanoyl or benzoyl; or sulfamoyl; or

R_3 and R_4 together represent the group $-(CH_2)_2R_5-(CH_2)_2-$ where R_5 is oxygen, sulfur, methylene, imino, alkylimino, or a carbon-carbon single bond; and

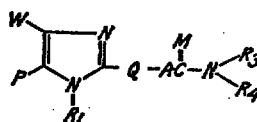


P, Q and W are as defined in Claim 1 that comprises reacting a compound having the formula:



5 with a compound of the formula R_1R_3NH in which R_1 , R_3 , R_4 , W, P, Q, A and M are as defined above and X is halogen, except that R_1 is not hydroxy alkyl or carboxy-alkyl, to produce the desired product, and optionally, where R_1 is alkanoyloxyalkyl or carboalkoxyalkyl, hydrolysing with a base to obtain the corresponding compound in which R_1 is hydroxyalkyl or carboxyalkyl; the terms "alkyl," "alkanoyl," and "alkoxy" hereinafter meaning such groups containing from 1 to 5 carbon atoms.

10 27. A process for the preparation of a compound having the formula:



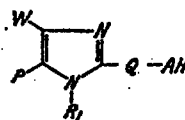
in which each of A and M is oxygen or sulfur,

15 R_1 is alkyl or substituted alkyl in which the substituent is hydroxy, carboxy, oxo, halo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, carbamoyloxy, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, carbamoyl, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl;

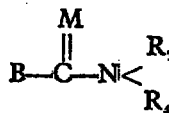
P, Q and W are as defined in Claim 1 and each of

20 R_3 and R_4 is hydrogen, alkyl, phenyl or substituted alkyl where the alkyl substituents are halo, alkoxy, oxo, phenyloxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, alkylthio, phenylalkylthio, dialkylamino, diphenylalkylamino or heterocycloalkyl; or

25 R_3 and R_4 together represent the group $-(CH_2)_2R_5-(CH_2)_2-$ where R_5 is oxygen, sulfur, methylene, alkylimino, or a carbon-to-carbon single bond; that comprises reacting a compound having the formula:

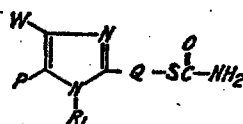


with a compound having the formula:



30 where A, M, W, P, R_1 , R_3 and R_4 are as defined above except that R_1 is not hydroxy-alkyl or carboxyalkyl, and B is halo or alkoxy, provided that where B is halo, R_3 and R_4 are both hydrogen or both other than hydrogen, to produce the desired product, and, when R_1 is alkanoyloxyalkyl or carboalkoxyalkyl, optionally hydrolysing with a base to obtain the corresponding compound in which R_1 is hydroxyalkyl or carboxyalkyl, the terms "alkyl," "alkanoyl" and "alkoxy" hereinafter meaning such groups containing from 1 to 5 carbon atoms.

35 28. A process for the preparation of a compound having the formula:

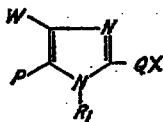


in which



R_1 is alkyl or substituted alkyl where the substituent is oxo, alkenyl, hydroxy, phenylalkoxy, alkoxy, carboxy, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl; and

P, Q and W are as defined in Claim 1, that comprises reacting a compound having the formula:

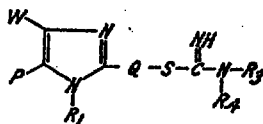


where

W, P, Q and R_1 are as defined above and

X is halo, alkylsulfonyloxy or phenylsulfonyloxy, with an alkali metal thiocyanate followed by a mineral acid to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

29. A process for the preparation of a compound having the formula:

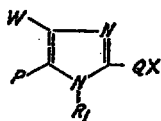


in which

P, Q and W are as defined in Claim 1;

R_1 is alkyl or substituted alkyl, in which the substituent is oxo, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl; each of

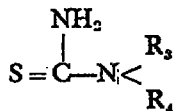
R_3 and R_4 is hydrogen, alkyl, or substituted alkyl, where the substituent is halo, alkoxy, oxo, phenyloxy, carboalkoxy, carbophenylalkoxy, carbamoyloxy, alkanoyloxy, phenylalkanoyloxy, carbamoyl, alkylcarbamoyl, phenylcarbamoyl, phenylalkylcarbamoyl, alkylthio, phenylalkylthio, dialkylidithiocarbamoyl, diphenylalkylidithiocarbamoyl or diphenylidithiocarbamoyl; alkanoyl, phenylalkanoyl, benzoyl, phenyl, alkoxy, phenalkoxy, phenoxy; carbamoyl; N-(alkyl, phenylalkyl or phenyl)-carbamoyl; heterocycloalkylcarbonyl; or nitro, or R_3 and R_4 together represent $-(CH_2)_2R_5(CH_2)_2-$ where R_5 is oxygen, sulfur, methylene, imino, alkylimino or a carbon-to-carbon single bond; that comprises reacting a compound having the formula:



wherein

W, P, Q, and R_1 are as defined above and

X is halo, alkylsulfonyloxy or phenylsulfonyloxy the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms; with a compound having the formula:



where R_3 and R_4 are as defined above, to produce the desired product.

30. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-(2',2',2'-trihalo-1'-hydroxyethoxy)carbamate where R_1 is alkyl or substituted alkyl, in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, halo, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl; that comprises reacting a 1- R_1 -5-nitroimidazol-2-yl-alkyl-





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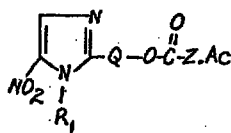
N-hydroxycarbamate wherein R_1 is as defined above, with a trihalo acetaldehyde to produce the desired product; the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

31. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl-N-hydroxymethylcarbamate wherein R_1 is alkyl or substituted alkyl, in which the substituent(s) is or are oxo, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or alkenyl; that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate wherein R_1 is as defined above with formaldehyde to produce the desired product; the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

32. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-alkoxy-methylcarbamate where R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl; that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-hydroxymethylcarbamate, where R_1 is as defined above, with an alkanol in the presence of an acid to produce the desired product; the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

33. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-alkoxy-carbamate wherein R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, carbamoyl, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, sulfonyl or phenylsulfonyl; that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-hydroxycarbamate where R_1 is as defined above with a diazoalkane to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

34. A process for the preparation of a compound having the structure:

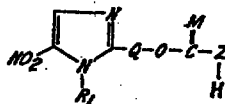


where

Z is $-\text{NR}^*$, $-\text{NR}^*\text{CH}_2\text{O}-$ or $-\text{NR}^*\text{O}-$, R^* being alkyl, phenylalkyl or phenyl and Ac is alkanoyl, cyanoacetyl, C_{1-5} , alkenoyl or benzoyl, and

Q is C_{1-5} alkylene, C_{1-5} alkenylene, phenyl- $(\text{C}_{1-5}$ alkylene) or C_{1-5} alkylidene, and

R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl or phenylalkylsulfonyl; that comprises reacting a compound having the structure:



in which Z, R_1 and Q are as defined above, with an acylating agent selected from the group derived from an alkanoyl or C_{1-5} alkenoyl acid, cyanoacetic acid or benzoic acid in the presence of a dehydrating agent to produce the desired product; the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

35. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N^2 - R_6 -allophanate or an N^4 -alkyl, phenalkyl or phenyl derivative thereof, in which R_1 is alkyl or substituted alkyl, wherein said substituent is hydroxy, oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, and R_6 is hydrogen or alkyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N^2 - R_6 -carbamate, where R_6 and R_1 are as above, except that R_1 is not hydroxyalkyl, with a carbamoyl chloride or

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substituted carbamoyl chloride in which the substituent is alkyl, phenalkyl or phenyl to produce the desired product, and, where R_1 is alkanoyloxyalkyl, optionally hydrolyzing with a base to obtain the corresponding compound in which R_1 is hydroxyalkyl, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

36. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl 4'-substituted-3'-thioallophanate, where R_1 is alkyl or substituted alkyl, in which the substituent is hydroxy, oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl and the substituent at 4' is hydrogen, alkyl, dialkyl, benzyl, dibenzyl or phenyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl chloroformate, where R_1 is as above, except that it is not hydroxyalkyl, with an alkali metal thiocyanate followed by ammonia, an alkylamine, a dialkylamine, benzylamine, dibenzylamine or aniline, to produce the desired product and, where R_1 is alkanoyloxyalkyl, optionally hydrolyzing with a base to obtain the corresponding compound in which R_1 is hydroxyalkyl, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

37. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-(N'-substituted thiocarbamoylthiomethyl)carbamate, where R_1 is alkyl or substituted alkyl in which the substituent(s) is or are alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate, wherein R_1 is as above, with an amine in the presence of formaldehyde and carbon disulfide to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

38. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-(N',N'-disubstituted aminomethyl)carbamate where R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, hydroxy, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate wherein R_1 is as above with formaldehyde in the presence of a secondary amine (including a secondary heterocyclic amine) to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

39. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-(R_6 -oxymethylene)carbamate where R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkoxy, phenylalkoxy, cyano alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, and R_6 is alkyl or benzyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate with a tri- R_6 -orthoformate in the presence of a Lewis acid to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

40. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-($-\text{CH}_2\text{NR}^\circ\text{R}^\circ$)carbamate, wherein R_1 is alkyl or substituted alkyl, in which the substituent(s) is or are oxo, alkenyl, alkoxy, phenylalkoxy, cyano alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, R° is alkyl, benzyl or hydrogen and $R^{\circ\circ}$ is alkyl or benzyl which comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-[(alkoxy or benzoxy)methylene]carbamate with an amine of formula $\text{NHR}^\circ\text{R}^\circ$ to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing 1 to 5 carbon atoms.

41. A process for the preparation of an N-(1- R_1 -5-nitroimidazol-2-yl-alkoxy-carbonyl) N,N-dimethylformamidinium halide, in which R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfanyl, phenylalkylsulfanyl, phenylsulfanyl, alkylsulfonyl, phenylalkylsulfonyl or arylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate in which R_1 is as above with dimethylformamide in the presence of a thionyl halide to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

42. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-formyl-



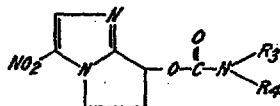
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- 5 carbamate in which R_1 is alkyl or substituted alkyl, in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting an N-(1- R_1 -5-nitroimidazol-2-ylalkoxy carbonyl) N,N-dimethylformamidinium halide with a weak aqueous base to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 5
- 10 43. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-nitro-carbamate in which R_1 is alkyl or substituted alkyl, in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carbo-alkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenyl-alkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbamate where R_1 is as above 10 with nitric acid to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 15
- 20 44. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N²-(alkylidene or aralkylidene) carbazate, in which R_1 is alkyl or substituted alkyl in which the said substituent(s) is or are hydroxy, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, alkylcarbamoyl, phenylalkyl-20 carbamoyl, phenylcarbamoyl, carbamoyl, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl carbazate, where R_1 is as above, with an aliphatic ketone, aldehyde or aromatic aldehyde to 25 produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 25
- 30 45. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-acyl-N-acyloxy-carbamate, in which R_1 is alkyl or substituted alkyl in which the substituent is oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboalkoxy, carbophenylalkoxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl or phenylsulfonyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-hydroxycarbamate, where R_1 is as above, with an acyl anhydride 35 to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 35
- 40 46. A process for the preparation of a 1- R_1 -5-nitroimidazol-2-ylalkyl N-(R_6 -sulfonyl)carbamate where R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carboalkoxy, carbophenylalkoxy, carbamoyl, alkylcarbamoyl, phenylalkylcarbamoyl, phenylcarbamoyl, carbamoyloxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or dialkylamino, and R_6 is amino or substituted amino where the sub-40 stituent(s) is or are alkyl, phenylalkyl or phenyl, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-halosulfonyl-carbamate where R_1 is as defined above with ammonia or a monosubstituted or disubstituted amine in which the substituent(s) is or are alkyl, phenylalkyl or phenyl to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 45
- 50 47. A process for the preparation of a 1- R_1 -2-ylalkyl N-(N',N'-di- R_6 -phosphoryl)-carbamate in which R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, alkoxy, phenylalkoxy, carboxy, carbo-alkoxy, carbophenylalkoxy, carbamoyl, alkylcarbamoyl, phenylalkylcarbamoyl, phenyl-50 carbamoyl, carbamoyloxy, cyano, halo, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or dialkylamino, and R_6 is as defined in Claim 46, that comprises reacting a 1- R_1 -5-nitroimidazol-2-ylalkyl N-dichlorophosphoryl-carbamate where R_1 is 55 as above with ammonia or a monosubstituted or disubstituted amine in which the substituent(s) is or are alkyl, phenylalkyl or phenyl to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms. 60



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48. A process for the preparation of a compound having the formula:

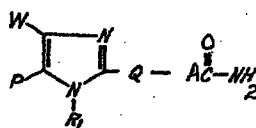


that comprises sequentially reacting of a 3-nitro-7-oxo-5,6-dihydroimidazo-[1,2-a]-pyrrole with a reducing agent, a phenylhaloformate and an amine having the formula:

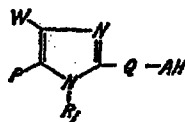


where each of R_3 and R_4 is hydrogen, amino, hydroxy, alkyl or substituted alkyl, in which the substituent(s) is or are halo, hydroxy, alkoxy, carboalkoxy, carbophenylalkoxy, alkanoyloxy, phenylalkanoyloxy, carbamoyl, alkylcarbamoyl, phenylcarbamoyl, phenylalkylcarbamoyl, sulfamoyl, alkylsulfamoyl, phenylsulfamoyl, phenylalkylsulfamoyl, alkylthio, phenylalkylthio, thioncarbamoyl, amino, dialkylamino, diphenylalkylamino or heterocycloalkyl; or R_3 and R_4 together represent the group $-(\text{CH}_2)_2\text{R}_5-(\text{CH}_2)_2-$ where R_5 is oxygen, sulfur, methylene, imino, alkylimino, or a carbon-carbon single bond to produce the desired product; the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

49. A process for the preparation of a compound having the formula:

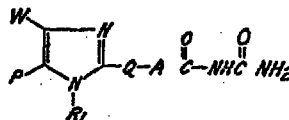


in which R_1 is alkyl or substituted alkyl where the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, phenylalkoxy, alkoxy, carbophenylalkoxy, carboalkoxy, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkyl sulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or halo, A is oxygen or sulfur, and Q, W and P are as defined in Claim 1, that comprises reacting a compound having the formula:

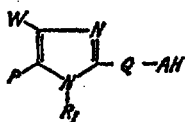


where W, P, Q, A and R_1 are as above, with one mole of cyanic acid per mole of imidazole to produce the desired product, the terms "alkyl," "alkanoyl," and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

50. A process for the preparation of a compound having the formula:



in which R_1 is alkyl or substituted alkyl in which the substituent(s) is or are oxo, alkenyl, alkanoyloxy, phenylalkanoyloxy, phenylalkoxy, alkoxy, carbophenylalkoxy, carboalkoxy, cyano, alkylthio, phenylalkylthio, alkylsulfinyl, phenylalkylsulfinyl, phenylsulfinyl, alkylsulfonyl, phenylalkylsulfonyl, phenylsulfonyl or halo, A is oxygen or sulfur, and P, Q and W are as defined in Claim 1, that comprises reacting a compound having the formula:



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where W, P, Q, A and R₁ are as above, with at least two moles of cyanic acid per mole of imidazole to produce the desired product, the terms "alkyl," "alkanoyl" and "alkoxy" hereinabove meaning such groups containing from 1 to 5 carbon atoms.

51. A process for preparing a compound as claimed in claim 1, substantially as hereinbefore described in any one of the foregoing Examples.

52. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 25—51 or its obvious chemical equivalent.

53. Each and every compound as claimed in claim 1, hereinbefore individually specified, with the exception of those claimed in claims 4—10, 13—16, 19, 20, 21 and 24.

54. A pharmaceutical composition comprising a compound as claimed in any one of claims 1—24, 52 and 53, and a pharmaceutical diluent, carrier or coating.

55. A composition as claimed in claim 54, in the form of a suppository.

56. A composition as claimed in claim 54, in the form of a cream.

57. A composition as claimed in claim 54, in orally administrable form.

58. A composition as claimed in claim 57, in the form of a pill, tablet, capsule, elixir or syrup.

59. A composition comprising an element of poultry sustenance in which is distributed a minor amount of a compound as claimed in any one of claims 1—24, 52 and 53.

60. A turkey feedstuff in which is distributed a minor amount of a compound as claimed in any one of claims 1—24, 52 and 53.

61. A water-dispensible powder that is orally administrable to poultry and that contains a compound as claimed in any one of claims 1—24, 52 and 53.

62. A method of controlling or preventing enterohepatitis in commercially reared poultry, that comprises administering to the poultry a compound as claimed in any one of claims 1—24, 52 and 53.

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ERRATUM

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