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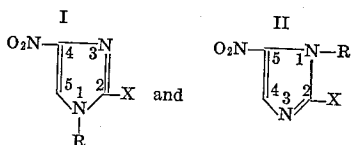
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NITROIMIDAZOLES AND THEIR PREPARATION
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This invention relates, in general, to a novel class of therapeutically active imidazole compounds and their preparation. More specifically, the invention relates to a new class of substituted nitroimidazoles and to methods for preparing them.

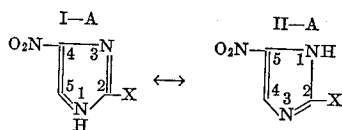
The structural formulae of the new compounds of this invention are illustrated below. Those compounds which have a substituent other than hydrogen in one of the nitrogen atoms of the imidazole nucleus exist in two isomeric forms depending upon which of the nitrogens has a substituent radical attached thereto. Since the numbering of the ring structure is such that the 1-position is always ascribed to the substituted nitrogen, the nitro group will appear in either the 4- or the 5-position depending upon which of the two nitrogens is substituted. In those compounds where neither of the nitrogen atoms in the imidazole nucleus has any substitution other than hydrogen, the 4-nitro and 5-nitro compounds are indistinguishable. In such cases, the general structures illustrated by Formulae I and II below are to be understood as representing only the two limiting forms of the structure of the actual compounds. All forms of these compounds are contemplated as coming within the scope of this invention. For convenience, these compounds are referred to elsewhere in this specification as 4(5)-nitroimidazoles. However, it will be readily appreciated by those skilled in the art that either the 4-nitro or the 5-nitro designation could as aptly be used. Thus, it will be understood that either structural Formula I or structural Formula II or any of the designations 4-nitro, 5-nitro and 4(5)-nitro could be used to denote the compounds of the general Formulae I and II which have no substitution other than hydrogen on the hetero nitrogen atoms.

In general, the compounds of this invention are considered as having one of the general structures



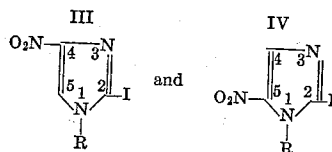
wherein R in each of the foregoing formulae is a member selected from the group consisting of hydrogen, lower alkyl and hydroxy lower alkyl; and X in each of the foregoing formulae is a member selected from the group consisting of iodine, hydroxy, lower alkoxy and aryloxy and their non-toxic alkali salts.

More specifically, those compounds which have no substitution other than hydrogen on the hetero nitrogen atoms are illustrated by the following structural formulae



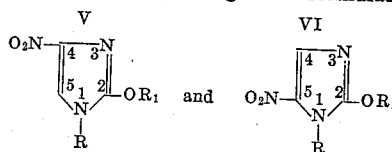
wherein X has the same significance as indicated above.

In one preferred embodiment, the invention comprises 2-iodonitroimidazoles encompassed within the class of compounds represented by general Formulae I and II and which have the general structure



wherein R in each of the foregoing formulae is a member selected from the group consisting of lower alkyl and hydroxy lower alkyl.

In another preferred embodiment, the invention comprises nitroimidazoles having an oxy group in the 2-position which are also encompassed within the class of compounds represented by the general Formulae I and II and which are represented by the general formulae



wherein R in each of the foregoing formulae is a member selected from the group consisting of lower alkyl and hydroxy lower alkyl; and wherein R₁ in each of the foregoing formulae is a member selected from the group consisting of hydrogen, lower alkyl, lower alkoxyalkyl and aryl.

As used in this disclosure, the term "lower alkyl" comprehends both straight and branched chain alkyl radicals preferably those containing from 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and the like. The term "lower alkoxy," as used in this disclosure, denotes any lower alkyl as defined above which is attached to a carbon of the imidazole ring through an oxygen atom and comprehends alkoxy groups in which the alkyl of the alkoxy group is further substituted by another lower alkoxy group such as a methoxy or ethoxy group. The preferred alkoxy radicals of this invention are those having an alkyl carbon chain of 1 to 7 carbon atoms. The preferred substituted alkoxy groups of this invention are the 2-ethoxyethoxy and the 2-methoxyethoxy radicals. The term "aryl," as used in this disclosure, denotes monocyclic benzenoid hydrocarbon radicals and the same which are substituted by halo, nitro or lower alkyl such as phenyl, p-chlorophenyl, o-chlorophenyl, p-nitrophenyl, o-nitrophenyl, p-tolyl and o-tolyl. The term "aryloxy," as used in this disclosure, denotes the group consisting of an aryl radical as defined above and an oxygen atom attaching it to a carbon of the imidazole ring. The preferred aryloxy groups of this invention are the phenoxy and the p-nitrophenoxy groups.

In naming the imidazole derivatives of this invention, the Chemical Abstracts rules on numbering of heterocyclic compounds and the numbering of the imidazole ring recommended by the Ring Index (American Chemical Society, Chemical Abstract Service, Washington, D.C., 1960) have been used. The numbering is that set forth in system No. 127 in the Ring Index.

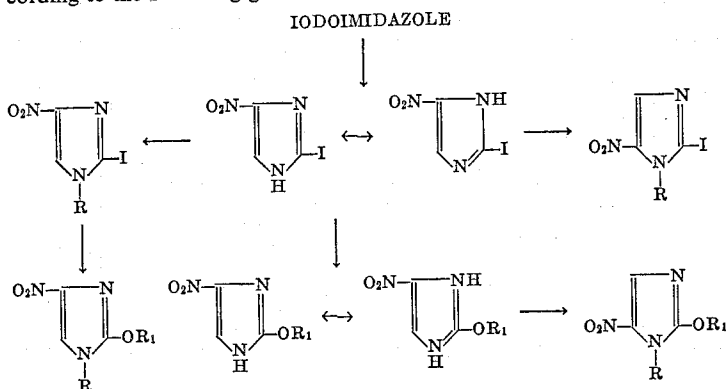
The new compounds of this invention and their pharmaceutically acceptable salts are useful as chemotherapeutic agents, particularly because of their anti-protozoal properties. More particularly, they are useful as trichomonacides, for example, the compounds are active against *Trichomonas vaginalis*.

The compounds of the invention can be administered systematically, for example, orally, with dosage adjusted to individual requirements. They can be administered in conventional pharmaceutical forms, for example, they can be administered in admixture with conventional organic or inorganic pharmaceutical carriers suitable for oral administration, such as starches, lactose, sucrose, gelatin,

magnesium stearate, talc, vegetable oils, gums and the like. The pharmaceutical preparations can be in conventional solid forms such as tablets, capsules, lozenges and the like, or in conventional liquid forms such as suspensions, emulsions and the like. They can be submitted to conventional pharmaceutical expedients, for example, sterilization, and they can contain pharmaceutical adjuvants such as preservatives, sterilization agents, wetting agents, emulsifying agents and the like. The pharmaceutical preparations can also contain other therapeutically valuable substances.

Additionally, the 2-iodo-4(5)-nitroimidazole is useful as an intermediate for the preparation of the 2-alkoxy-4(5)-nitroimidazole, the 2-aryloxy-4(5)-nitroimidazole and the compounds represented by Formulae III and IV. The 2-alkoxy-4(5)-nitroimidazole and the 2-aryloxy-4(5)-nitroimidazoles are in turn useful intermediates in the preparation of the compounds of Formulae V and VI.

The novel products of this invention are prepared according to the following general reaction scheme.



In one of the broad process aspects of the present invention, the novel 2-iodo-4(5)-nitroimidazoles are prepared by nitrating iodoimidazole as illustrated by the first step of the reaction scheme outlined above. In carrying out the nitration reaction it has been found that nitration of any of the iodoimidazoles, i.e., either the 2-iodo, the 2,4-diiodo or the 2,4,5-triiodoimidazole, gives the same nitration product, namely, the 2-iodo-4(5)-nitroimidazole. Consequently, the nitration reaction is not limited to the use of 2-iodoimidazole as a starting material but can be carried out with the diiodo or triiodo imidazoles or mixtures of the iodoimidazoles in any combination. Since the 2-iodoimidazole is prepared from 2,4-diiodoimidazole, the direct nitration of the diiodoimidazole constitutes a technical advantage. When diiodo and triiodoimidazoles are used in the nitration, elementary iodine is formed along with the 2-iodo-4(5)-nitroimidazole product. A suitable starting material for the nitration process of this invention is a crude diiodoimidazole containing small amounts of 2-iodo and 2,4,5-triiodoimidazole. The crude diiodoimidazole starting material is a known compound which can be prepared by known methods. One such suitable method comprises reacting an aqueous solution of imidazole with an aqueous solution of sodium iodide and iodine. This latter solution is slowly added to the imidazole solution together with an alkali such as powdered anhydrous sodium carbonate. The reaction is conveniently carried out at room temperature, though higher or lower temperatures may be used. After completion of the reaction, the mixture is acidified with a weak acid such as acetic acid, whereupon the product precipitates. The precipitate is recovered by techniques readily apparent to those skilled in the art such as by filtration, followed by washing and drying. The resulting product is a crude 2,4-diiodoimidazole containing minor amounts of the monoiodo and triiodoimidazoles. This crude diiodoimidazole product constitutes a suitable starting material for the process of this invention, though iodoimidazoles produced by any other method could also be used.

In contrast to the nitration of imidazoles and alkylene imidazoles which proceeds only under energetic conditions, it has been found that the nitration of the iodinated imidazoles proceeds at room temperature and below. A suitable process for nitrating the crude diiodoimidazole consists of first preparing a nitration mixture from concentrated sulfuric acid and nitric acid. The acid mixture is then chilled in a Dry-Ice acetone bath to a low temperature, preferably in the range of about -15°C . to -25°C ., through temperatures as low as about -80°C . could be used. Next, the crude diiodoimidazole starting material is slowly added with stirring to the chilled mixture. While the reaction is conveniently carried out at low temperatures, such are not essential and the entire reaction could be run at room temperatures or above. The preferred temperature range for carrying out the reaction is from about -80°C . to about 60°C . An especially preferred range is about -25°C . to 25°C . Upon completion of the reaction, the product is precipitated by pouring the reaction mixture into ice-water. The precipi-

tate which forms is then separated by filtration. While the foregoing procedure represents an advantageous method for nitrating the diiodoimidazole, the invention is not limited thereto. Thus, for example, the nitration could be carried out with any of the usual nitration mixtures such as a mixture of nitric acid and a strong acid, a mixture of nitric acid and acetic anhydride or any of the nitrating agents which are conventionally used to nitrate aromatic compounds such as sodium nitrate or copper nitrate together with a dehydrating agent such as concentrated sulfuric acid. It is not necessary that the nitration mixture be separately prepared and the nitration could be accomplished by adding the component parts of the nitration mixture to the iodoimidazole in any sequence.

In a next succeeding process step, the 2-iodo-4(5)-nitroimidazole, prepared by nitration of the diiodoimidazole starting material as outlined above, is optionally converted by alkylation to one or the other of two isomeric products which are represented by Formulae III and IV structures wherein R in both formulae stands for lower alkyl. The identity of the isomer, i.e., Formula III or Formula IV structure which is obtained upon alkylation of the 2-iodo-4(5)-nitroimidazole, is determined by the reaction conditions of the alkylation. The reaction conditions may be so chosen as to produce either the 5-nitro or the 4-nitro derivatives as desired. Carrying out the alkylation reaction at a pH in the neutral to acid range, i.e., pH 7 and below, produces predominantly the 5-nitro derivatives whereas alkylating at a pH ranging from alkaline to neutral, i.e., greater than 7 to pH 7 produces predominantly the 4-nitro derivatives. The following exemplary processes illustrate the methods for obtaining respectively the 5-nitro and 4-nitro derivatives of 2-iodo-4(5)-nitroimidazole which have an alkyl group in the 1-position.

In the one case, the 5-nitro derivatives (Formula IV compounds) are obtained by reacting the 2-iodo-4(5)-nitroimidazole with any of the conventional alkylating agents, such as dialkylsulfate or alkylhalide. In this, as

well as the succeeding alkylation steps of this invention, any of the conventional alkylating methods could be employed, though it has been found convenient to use dialkylsulfate at elevated temperatures. The appropriate dialkylsulfate, selected in accordance with the desired alkyl substitution, is added to the 2-iodo-4(5)-nitroimidazole and the resultant reaction mixture is heated at about 50–110° C. Since the dialkylsulfate is itself acidic, there is no need to acidify the reaction mixture. The reaction can be conveniently carried out by starting at neutral pH and allowing the mixture to become acid as the reaction proceeds. While the reaction temperature may be varied within wide limits, it is preferred to operate at an elevated temperature. The preferred temperature range is about 50° C. to about 100° C. An especially preferred temperature range is about 90–100° C. The reaction is conveniently carried out in the presence of an inert organic solvent, though it can, if desired, be carried out in the absence of any solvent. Suitable solvents for carrying out the alkylation in this aspect of the invention are those inert organic solvents which have a boiling point within the preferred temperature range of about 50–110° C. Representative examples of such solvents are dioxane, butanol and toluene.

In the other case, the 4-nitro derivatives (Formula III compounds) are obtained by carrying out the alkylation reaction with an alkalinized mixture of 2-iodo-4(5)-nitroimidazole and the appropriate dialkylsulfate. Any suitable base can be used to alkalinize the starting reaction mixture. Suitable bases are the alkali metal hydroxides and carbonates or aqueous alkaline buffer solutions. For example, one could use an aqueous solution of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium phosphate or potassium phosphate. The preferred alkaline solution is aqueous sodium hydroxide. The alkylation reaction, under these conditions, is slightly exothermic but does not require cooling. The product which forms as a precipitate is recovered by cooling and filtering. The 4-nitro derivatives obtained from this reaction can be further converted to the Formula V compounds as will be more fully discussed hereinafter.

In another process aspect of this invention, the 2-iodo-4(5)-nitroimidazole is converted to the novel imidazole compounds having the structure represented by Formulae I and II wherein R in both formulae stands for hydrogen and X in both formulae stands for hydroxy, alkoxy or aryloxy. This conversion is accomplished by substituting either an hydroxy, an alkoxy or an aryloxy group for the iodine of the 2-iodo-4(5)-nitroimidazole according to the following method.

The 2-hydroxy-4(5)-nitroimidazole, which is stable only in the form of salts, is produced by converting the 2-iodo-4(5)-nitroimidazole starting material to the alkali metal salt of 2-hydroxy-4(5)-nitroimidazole. The conversion is effected by reacting 2-iodo-4(5)-nitroimidazole with a suitable alkali metal alcoholate of a tertiary aliphatic alcohol, such as tertiary butanol or ethyldimethylcarbinol. The preferred alcoholates of this invention are the sodium and potassium tertiary butylates. While the reaction can be carried out in the absence of any solvent, it is conveniently carried out in an inert organic solvent. Hydrocarbon solvents such as xylene, benzene, toluene, etc. are preferred. In this reaction, at least three atoms of the alkali metal alcoholate must be used for each molecule of the 2-iodo-4(5)-nitroimidazole. The product obtained is the dialkali salt of 2-hydroxy-4(5)-nitroimidazole. Upon completion of the reaction, the product is extracted from the reaction mixture with warm water. The monoalkali salt of the 2-hydroxy-4(5)-nitroimidazole is then crystallized from the extraction solvent by neutralizing with a weak acid and chilling the mixture. Suitable weak acids for use in the practice of this invention are acetic, formic, propionic and oxalic acids. The mineral acids could also be used though care must be exercised to avoid addition of an excess. In order to precipitate the product as the

monoalkali salt, it is necessary to neutralize with at least one mole of acid per mole of the 2-hydroxy-4(5)-nitroimidazole product. The addition of lesser amounts of acid (to pH above 7) results in crystallization of the dialkali salt of the 2-hydroxy-4(5)-nitroimidazole product along with the monoalkali salt. While substantially all of the monosodium salt is crystallized by neutralizing with a weak acid and chilling, a more complete precipitation can be facilitated by the addition of alcohol such as ethanol or methanol following the neutralization and chilling steps. The product is recovered by filtering and washing with alcohol. Though the reaction can be carried out at temperatures varying within wide limits, it is preferred to use an elevated temperature. A suitable reaction temperature is the reflux temperature of the organic solvent employed.

The novel 2-alkoxy-4(5)-nitroimidazoles and 2-aryloxy-4(5)-nitroimidazoles of this invention are obtained by converting the 2-iodo-4(5)-nitroimidazole to the corresponding 2-alkoxy and 2-aryloxy compounds. This conversion is accomplished by reacting 2-iodo-4(5)-nitroimidazole with an alkali metal alcoholate of a primary or secondary alcohol selected in accordance with the desired alkoxy or aryloxy substitution. The alkali metal alcoholates suitably used in practicing this aspect of the invention are the alkali metal alcoholates of the lower aliphatic alcohols and the alkali metal phenolates. As suitable alcoholates one may use, for example, sodium methylate, potassium methylate, sodium ethylate, potassium ethylate, sodium butylate, potassium butylate, sodium phenolate or potassium phenolate. While the temperature is not critical to the success of the reaction, it is preferred to operate at an elevated temperature, preferably at a temperature within the range of about 60° C. and about 150° C. The reaction can be conveniently carried out in the presence of any of the conventional inert organic solvents. Suitable solvents for use in this aspect of the invention are the alcohols from which the respective alkali metal alcoholate reaction components are derived as well as any other inert solvents such as benzene or toluene. The preferred solvents are those which have boiling points within the preferred reaction temperature range of 60–150° C. In such case, the reaction can be conveniently carried out by refluxing the reaction mixture at the reflux temperature of the solvent employed. 2-aryloxy products of this reaction may be further converted to compounds having Formula VI structure as will be more fully discussed below.

In the case of the 2-phenoxy-4(5)-nitroimidazole product, further substitution in the phenyl ring is accomplished by known methods for nitrating, halogenating, alkylating, etc. In a preferred aspect, the 2-phenoxy-4(5)-nitroimidazole is reacted with nitric acid under cooling to produce 2-(p-nitrophenoxy)-4(5)-nitroimidazole.

In another of the process aspects of this invention, the compounds corresponding to Formulae V and VI structures, specifically those compounds having an alkoxy or an aryloxy group substituted in the 2-position and a lower alkyl group substituted in the 1-position, are prepared from the 2-iodo-4(5)-nitroimidazole as a starting material. These compounds are prepared by different procedures depending upon whether the 4-nitro or the 5-nitro derivatives are desired. Unlike the alkylation of the 2-iodo-4(5)-nitroimidazole which gives either the 4-nitro or the 5-nitro derivatives depending upon whether the reaction is carried out in an alkaline or acidic medium, it has been found that alkylation of the 2-alkoxy-4(5)-nitroimidazole or the 2-aryloxy-4(5)-nitroimidazole gives the 5-nitro derivatives exclusively. Moreover, only the 4-nitro alkylated derivatives of the 2-alkoxy and 2-aryloxy compounds can be obtained by reacting the corresponding alkylated derivatives of the 2-iodo compounds with an alkali metal alcoholate. The 1-alkyl-2-iodo-5-nitroimidazoles are too alkali-labile to sustain the reaction conditions necessary for conversion to the corre-

sponding 2-alkoxy or 2-aryloxy derivatives. A significant aspect of the invention is thus the finding that the 4-nitro and the 5-nitro derivatives of the 1-alkyl-2-alkoxy and the 1-alkyl-2-aryloxyimidazoles can be produced from the 2-iodo-4(5)-nitroimidazole as starting material via different intermediates. Broadly considered, the 4-nitro derivatives (Formula V compounds) are prepared by first alkylating the 2-iodo-4(5)-nitroimidazole in an alkaline medium so as to produce the 1-alkyl-2-iodo-4-nitroimidazole then substituting an alkoxy or an aryloxy group for the iodine in the 2-position. The 5-nitro derivatives (Formula VI compounds) are prepared by first substituting an alkoxy or an aryloxy group for the iodo radical of the 2-iodo-4(5)-nitroimidazole to form the corresponding 2-alkoxy or 2-aryloxy compound which is in turn alkylated to form the desired 1-alkyl-2-alkoxy-5-nitroimidazole or 1-alkyl-2-aryloxy-5-nitroimidazole.

In the first case, the 2-iodo-1-alkyl-4-nitroimidazole intermediate is prepared according to the procedure outlined above for the preparation of Formula III compounds. The corresponding 4-nitro derivatives of the 2-alkoxy and 2-aryloxy compounds are then prepared from the 2-iodo-1-alkyl-4-nitroimidazole by refluxing with an appropriate alkali metal alcoholate in a process analogous to the preparation of the 2-alkoxy-4(5)-nitroimidazole or the 2-aryloxy-4(5)-nitroimidazole.

The preparation of the 5-nitro derivatives of the 2-alkoxy and 2-aryloxy compounds differs from the method used in preparing the 4-nitro derivatives in that alkylation is not effected until after the conversion of the 2-iodo-4(5)-nitroimidazole starting material to its corresponding alkoxy or aryloxy-4(5)-nitroimidazole. The intermediate 2-alkoxy or 2-aryloxy compounds are prepared by refluxing the 2-iodo-4(5)-nitroimidazole with an appropriate alkali metal alcoholate according to the procedure outlined hereinabove for the preparation of these novel compounds. The intermediate 2-alkoxy or 2-aryloxy compounds is then reacted with an alkylating agent to obtain the desired alkyl substitution. This alkylation can be carried out under either neutral acidic or alkaline conditions since only the 5-nitro derivatives are formed in any case. The temperature for the alkylation may vary within wide limits. However, it is preferred to carry out the reaction at an elevated temperature. A preferred temperature range is from about 20° to about 100° C.

The novel imidazole compounds represented by the Formulae III, IV, V and VI structures wherein R, in each formula, is hydroxy lower alkyl, are prepared by reacting either the 2-iodo-4(5)-nitroimidazole, 2-alkoxy-4(5)-nitroimidazole or 2-aryloxy-4(5)-nitroimidazole respectively with an appropriate alkylene halohydrin such as ethylene chlorohydrin or propylene monochlorohydrin. The reaction is suitably carried out by first forming the alkali salt of the 2-iodo, 2-alkoxy or 2-aryloxy-4(5)-nitroimidazole which is then reacted with an alkylene halohydrin. In preparing the salts of these compounds, any suitable alkali can be used such as sodium hydroxide or potassium hydroxide. One convenient method of preparing the salts is by mixing the imidazole compound with a suitable alkali in a water-miscible alcohol such as ethanol or methanol and evaporating the mixture to dryness. The preferred alkali for preparing the salts is an aqueous solution of potassium hydroxide in methanol. When using the salts of the nitroimidazole compounds the reaction is preferably carried out by mixing the appropriate halohydrin with the nitroimidazole salt and heating the mixture with stirring. Alkali halide which precipitates out of the reaction mixture is separated by filtering. The product is recovered by conventional techniques such as by evaporating and washing. While the reaction temperature may vary within wide limits, it is preferred to maintain the reaction mixture under reflux conditions at the reflux temperature thereof. The preferred hydroxyalkyl substitution of this invention is the ethanol group which is conveniently obtained by reacting

the sodium salt of the 4(5)-nitroimidazole compounds with ethylene chlorohydrin. The reaction of the 2-iodo-4(5)-nitroimidazole with ethylene chlorohydrin produces a mixture of 4-nitro and 5-nitro derivatives which can be easily separated by dissolving the 5-nitro isomer in an organic solvent such as acetone and methyl ethyl ketone, the 4-nitro isomer remaining undissolved. Recovery of the products is then accomplished by conventional techniques readily apparent to those skilled in the art such as by filtering and drying.

The novel imidazole compounds of this invention can be purified by recrystallizing from suitable inert organic solvents such as water, ethanol, ether, acetone, benzene, ethyl acetate and dimethylformamide.

The novel nitroimidazole compounds which do not have any substitution other than hydrogen on the nitrogens in the imidazole ring, i.e., compounds having Formulae I and II structures wherein R, in each case, is hydrogen, can, if desired, be converted into salts by reacting pharmaceutically acceptable bases with the nitroimidazole compounds. Suitable bases are sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, ammonium hydroxide, methylamine, ethanolamine, diethanolamine and others.

Although an outline for the preparation of the novel compounds is shown above, the following examples disclose more fully specific methods of preparation of compounds falling within the invention. It will be understood, however, that these examples are merely illustrative of the compounds and processes of the invention. The examples are not to be taken as limitative of the invention either as to the compounds or the methods specifically disclosed. All temperatures are in degrees centigrade and all melting points are corrected.

Example 1

The diiodoimidazole starting material was prepared in the following way:

240 grams of sodium iodide were dissolved in 800 ml. of water and 226.8 grams of iodine were added. The mixture was stirred at 24–30° until the iodine had dissolved and then diluted with 800 ml. of water.

In the meantime, there was dissolved in a 5-liter, three-neck flask equipped with stirrer and dropping funnel, 31.0 grams of imidazole in 500 ml. of water. The iodine solution was slowly dropped into the mixture at such a rate that the reaction mixture stayed substantially colorless.

When disappearance of the brown color became slow (after 100–150 ml. of the iodine solution had been added), there was also added through the third neck of the flask, sodium carbonate powder in small portions. The addition of iodine solution was continued along with the sodium carbonate, the two being added at such a rate that the reaction mixture again stayed substantially colorless. 260 grams of anhydrous sodium carbonate was needed for the completion of the reaction. The whole operation required about 4–5 hours. After completion of the addition, it was stirred for an additional 30 minutes and then 90 ml. of acetic acid was carefully added to render the solution slightly acidic. The precipitated product was filtered by suction and washed twice using 100 ml. of water each time. It was dried at 60–70° to constant weight. The material consisted predominantly of diiodoimidazole with admixtures of mono- and triiodated material and melted unsharp at 180–190°.

The 2-iodo-4(5)-nitroimidazole was prepared from diiodoimidazole according to the following scheme:

125 grams of the crude diiodoimidazole, finely powdered, were added in small portions to a nitration mixture in a three-neck flask of 2-liters equipped with alcohol thermometer and stirrer. The nitration mixture was previously prepared from 300 ml. of nitric acid, $d=1.5$ (density) and 300 ml. of concentrated sulfuric acid and cooled to –15 to –25°, preferably in an acetone Dry

Ice bath. The addition of the crude diiodimidazole took about 30–45 minutes. After all the material had been added, the freezing mixture was removed and the reaction mixture allowed to assume room temperature. It was stirred for 2 hours at 20–25° and then poured under stirring into 1.5 liters of ice water. The product precipitated immediately crystalline together with iodine and a slight evolution of NO₂. The solid was filtered by suction and washed on the filter twice with 200 ml. of water.

To free it from iodine, it was suspended in 200 ml. of 10 percent sodium iodide solution, stirred for 30 minutes and filtered by suction. It was washed on the filter twice with 100 ml. of water each time and then dried at 60–70° to constant weight. It melts in this state at 275–278° and is sufficiently pure to be used as a starting material for the preparation of subsequent compounds. Recrystallized from dimethylformamide or dilute alcohol, the compound (2-iodo-4(5)-nitroimidazole) melted at 281°.

Example 2

75 grams of crude 2-iodo-4(5)-nitroimidazole was placed in a three-neck flask (2 liters) equipped with stirrer and dropping funnel, and dissolved in 125 ml. of 3 N NaOH. To this solution was added 250 ml. of hot water (50–60°). 33 ml. of dimethylsulfate was then dropped into the well-stirred solution within 3 to 5 minutes. The temperature rose to about 65–70° and a yellow precipitation developed rapidly. The reaction mixture was allowed to cool over 1 to 2 hours under stirring. The precipitate was filtered by suction, washed on the filter with water and dried at 60–70° to constant weight. The melting point of the material thus obtained was unsharp at 160–180° and it represented a mixture of about 75 percent 2-iodo-1-methyl-4-nitroimidazole and 25 percent 2-iodo-1-methyl-5-nitroimidazole.

To separate the compounds, the mixture was suspended in 200 ml. of acetone which dissolved the 2-iodo-1-methyl-5-nitroimidazole completely. The mixture was stirred for 15 minutes and filtered by suction. The undissolved material, M.P. 235–237°, was almost pure 2-iodo-1-methyl-4-nitroimidazole. Recrystallized from dimethylformamide or dilute alcohol, the product formed pale yellow prisms melting at 240°.

The 2-iodo-1-methyl-5-nitroimidazole was obtained from the acetone mother liquor by evaporation, washing the residue with water, and recrystallizing from dilute alcohol. The product so-obtained melted at 137–140°. It represents substantially pure 2-iodo-1-methyl-5-nitroimidazole. However, it does contain small amounts (up to 10 percent) of the 4-nitro isomer from which it can only be liberated with difficulty.

Example 3

The 2-iodo-1-methyl-5-nitroimidazole was prepared free from the 4-nitro compound by the following procedure:

23.9 grams of 2-iodo-4(5)-nitroimidazole, 40 ml. of dioxane and 11 ml. of dimethylsulfate were refluxed under stirring for 1 hour. After 10 minutes, most of the starting material had dissolved and after another 10 minutes the methyl sulfate of the product started to crystallize, soon filling the vessel as a thick mush. After allowing to cool, the mixture was diluted with 100 ml. of acetone and the solid filtered by suction: it was dissolved in 50 ml. of water and the solution neutralized with ammonia under chilling. The precipitated product was filtered by suction and recrystallized from dilute alcohol. The pale yellow plates showed a melting point of 150–151°, giving no depression when mixed with a sample of the impure product obtained as a by-product in the preparation of the 4-nitro isomer according to Example 2.

Example 4

The 1-ethyl-2-iodo-4-nitroimidazole was prepared by the following method:

5 grams of 2-iodo-4(5)-nitroimidazole were dissolved in 10 ml. of 3 N aqueous sodium hydroxide and 10 ml. of ethanol. 4 ml. of diethylsulfate were added and the mixture allowed to stand for 24 hours. The deposited crystals were filtered by suction and recrystallized from ethanol. The product so-obtained melted at 152°.

Upon evaporation of the mother liquor, the 5-nitro compound (1-ethyl-2-iodo-5-nitroimidazole) was obtained. It still contained, however, considerable amounts of the 4-nitro isomer. It melted at 98–100°.

Example 5

2-iodo-4-nitroimidazole-1-ethanol and 2-iodo-5-nitroimidazole-1-ethanol were prepared as follows:

24 grams (0.44 mole) KOH were dissolved in 500 ml. of methanol and 95.6 g. (0.4 mole) of 2-iodo-4(5)-nitroimidazole added. A clear solution was obtained by gently heating on a steam bath for some minutes. The solution was evaporated in a vacuum and the residue refluxed under stirring with 400 ml. of 2-chloroethanol for 60 to 90 minutes. Precipitated potassium chloride was filtered by suction and the filtrate evaporated in vacuo. The residue, slurried with 200 ml. of water, filtered by suction and dried at 70°, represented a mixture of 2-iodo-4-nitroimidazole-1-ethanol and 2-iodo-5-nitroimidazole-1-ethanol.

To separate the two compounds, the material was stirred with 200 ml. of acetone for 30 minutes, filtered by suction and washed with 50 ml. of acetone on the filter. It represented practically pure 2-iodo-4-nitroimidazole-1-ethanol, melting at 155–156° when recrystallized from water.

The acetone solution from Example 5 was evaporated to dryness and the residue slurried with 100 ml. of 3 N HCl. Undissolved material consisted of the 4-nitroimidazole derivative. The filtrate from it was neutralized with ammonia, the precipitate filtered and dried. It was again slurried with 100 ml. of 3 N aqueous hydrochloric acid, the solution filtered and the 5-nitro derivative precipitated with ammonia. Recrystallized from water in long pale yellow prisms, the product melted constant at 145°. The mixed M.P. with the isomeric 4-nitro compound showed depressions of more than 20°.

Example 6

In a three-neck flask of 2 liters equipped with stirrer and reflux condenser there was placed 200 ml. of methanol C.P. 10 grams of sodium (0.435 mole) was then dissolved in the methanol under refluxing and stirring. 47.8 grams (0.2 mole) of 2-iodo-4(5)-nitroimidazole were added after all the sodium had dissolved. An intense yellow, clear solution resulted. The reflux condenser was now exchanged for a descending condenser and 50 ml. of methanol were distilled off within 15–20 minutes. 200 ml. of toluene were now added and stirring and distilling were continued till again 50 ml. of methanol had distilled off (within 15 to 20 minutes). 100 ml. of toluene were added again and stirring and distilling continued until altogether 200 ml. of methanol had distilled and 600 ml. of toluene had been added. Towards the end, the content of the flask became increasingly a gelatinous yellow mass that at a certain point became crystalline and finally deposited a heavy yellow crystalline precipitate of the sodium salt of the reaction product together with NaI. The toluene layer was decanted and the precipitate at the bottom and on the walls of the flask dissolved in 60 ml. of hot water. The solution was acidified with 10 ml. of acetic acid and chilled. Crude 2-methoxy-4(5)-nitroimidazole crystallized rapidly. After 12 hours, it was filtered by suction, washed with 40 ml. of water, and then washed with 20 ml. of alcohol and dried at 80°. To purify the material, it was transformed into the well-crystallized potassium salt by the following technique.

52 grams of crude 2-methoxy-4(5)-nitroimidazole were dissolved in a solution of 20.3 g. of KOH in 60 ml. of water at 50–60°. Upon chilling, the potassium salt crys-

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tallized. Crystallization was completed by the addition of 200 ml. of ethanol. The product was filtered by suction, washed on the filter with ethanol and dried at 80°.

46 grams of potassium salt were dissolved in 100 ml. of hot water, the solution acidified with 20 ml. of acetic acid and chilled. The pure 2-methoxy-4(5)-nitroimidazole crystallized in pale yellow prisms. They were filtered by suction and washed on the filter with little water. The product melted at 219° with decomposition. A sample was recrystallized from methanol.

Example 7

14.3 grams (0.1 mole) of 2-methoxy-4(5)-nitroimidazole were dissolved in 50 ml. of 3 N sodium carbonate solution at 60–70° and the solution stirred with 11 ml. of dimethylsulfate at 60–70° for 20–30 minutes. The mixture was allowed to cool, the deposited crystals filtered and recrystallized from ethyl acetate. The product so-obtained was 2-methoxy-1-methyl-5-nitroimidazole melting at 138°.

Example 8

5 grams of sodium were dissolved in 70 ml. of methanol and methanol distilled off until sodium methylate began to crystallize. 25.3 grams of powdered 2-iodo-1-methyl-4-nitroimidazole (Example 2) were added at once to the sodium methylate and the mixture which boiled up due to an exothermic reaction was kept hot for 7 minutes. The solution was now poured into 200 ml. of ice cold saturated ammonium sulfate solution and extracted without delay twice with 200 ml. of ethyl acetate each time. The ethyl acetate was evaporated in a vacuum and the crystalline residue recrystallized from water or methanol. The product so-obtained was 2-methoxy-1-methyl-4-nitroimidazole, melting at 144–144.5°.

Example 9

18.5 grams of the potassium salt of 2-methoxy-4(5)-nitroimidazole (Example 7) were slurried with 16 ml. of diethylsulfate, first for 15 minutes at 90° and then for additional 15 minutes at 100–110°. The clear fusion mixture was dissolved in 200 ml. of water and the 1-ethyl-2-methoxy-5-nitroimidazole product precipitated by the addition of 50 g. of ammonium sulfate. It was filtered by suction and recrystallized from water.

Example 10

The 1-ethyl-2-methoxy-4-nitroimidazole compound was prepared from 26.7 g. of 1-ethyl-2-iodo-4-nitroimidazole (Example 4) by a process analogous to that of Example 9. Recrystallized from water, the compound melted at 87° and gave melting point depressions of 20° and more when mixed with the isomeric 5-nitro compound of Example 10.

Example 11

22 grams of potassium salt of 2-methoxy-4(5)-nitroimidazole (Example 7) were refluxed in 300 ml. of monochlorohydrin for 90 minutes. The resulting brown solution was filtered from potassium chloride by suction and evaporated in a vacuum. The residual syrup was crystallized by slurrying with 100 ml. of saturated ammonium sulfate solution. The crystals were filtered by suction and washed on the filter with 50 ml. of saturated ammonium sulfate solution containing 5 ml. of concentrated ammonia. It was extracted with 200 ml. of hot ethyl acetate and filtered from inorganic material. The ethyl acetate solution was evaporated in a vacuum to approximately 30–50 ml. when the material crystallized. Crystallization was completed by the addition of 150 ml. of heptane. The product so-obtained was 2-methoxy-5-nitroimidazole-1-ethanol melting at 136–137°.

Example 12

10 grams of sodium (0.435 mole) was dissolved in 1 liter of N butanol under stirring and refluxing. 47.8 grams of 2-iodo-4(5)-nitroimidazole was added and the

solution refluxed under stirring for 2.5 to 3 hours. After allowing to cool, 500 ml. of water and 500 ml. of benzene were added, the layers separated and the aqueous layer was acidified with 15 ml. of acetic acid. The organic layer was extracted twice with 50 ml. of 3 N sodium hydroxide and the aqueous extract was acidified with acetic acid. The ensuing precipitates of the 2-butoxy-4(5)-nitroimidazole product were filtered by suction, washed with water on the filter and recrystallized once from alcohol and once from ethyl acetate.

Example 13

The 1-methyl-2-butoxy-5-nitroimidazole compound was obtained in analogy to Example 8 from 18.5 g. of 2-butoxy-4(5)-nitroimidazole. Recrystallized from alcohol or a large amount of water, it formed pale yellow needles having a melting point of 59°.

Example 14

5 grams of sodium were dissolved in 200 g. of ethoxyethanol at 80–100°. 24 grams of 2-iodo-4(5)-nitroimidazole were added and after completion of the spontaneous reaction at 130°, the reaction mixture was kept at 130–135° for 20 minutes. After chilling, it was acidified with 10 ml. of acetic acid and evaporated in a vacuum until close to dryness. The residue was slurried with 150 ml. of saturated aqueous ammonium sulfate solution and extracted with 20 ml. of ethyl acetate. The ethyl acetate layer was evaporated in vacuo to approximately 30–50 ml. and the product precipitated in crystalline form by the gradual addition of petroleum ether. The product so-obtained was 2-(2-ethoxyethoxy)-4(5)-nitroimidazole melting at 119–120°. A sample was recrystallized from water.

Example 15

To a stirred suspension of sodium phenolate in toluene, prepared by refluxing 10 g. of sodium in 1 liter of toluene with 60 g. of phenol for 1 hour and subsequent chilling to 20–30°, there was added 48 g. of 2-iodo-4(5)-nitroimidazole. The mixture was first stirred for 15 minutes at room temperature and then refluxed under stirring for 8 hours. After allowing to cool, the solid material was filtered by suction, dissolved in 200 ml. of water and the solution acidified with 25 ml. of acetic acid. The resulting precipitate was filtered by suction and recrystallized from 400 ml. of 75 percent alcohol. It formed pale yellow crystals of 4(5)-nitro-2-phenoxyimidazole melting at 209–210°.

Example 16

20 grams of 4(5)-nitro-2-phenoxyimidazole were dissolved in 100 ml. of nitric acid, $d=1.5$ under cooling with ice water at 15–20°. The solution was allowed to stand for 24 hours at 25–28° and then diluted with 500 ml. of water. The 4(5)-nitro-2-(p-nitrophenoxy)imidazole product crystallized rapidly and was collected by filtration. Recrystallized from alcohol, it melted at 185–186°.

Example 17

To a suspension of sodium phenolate, prepared by refluxing under stirring a mixture of 5 g. of sodium, 1 liter of toluene and 30 g. of phenol for 1 hour, there was added 35 g. of 1-methyl-2-iodo-4-nitroimidazole (Example 2). The mixture was refluxed for 30 minutes. The crystalline product was filtered by suction and washed out with water to free it from NaI. Additional material was obtained by evaporating the toluene filtrate in vacuo. Recrystallized from alcohol or ethyl acetate, the product formed pale yellow plates of 1-methyl-4-nitro-2-phenoxyimidazole melting at 117°.

Example 18

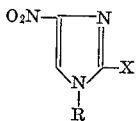
15 grams of sodium were suspended in 500 ml. of xylene under stirring and heating to melt the sodium. In the course of 8 hours, there was added to the sodium

suspension, while refluxing and stirring, 200 ml. of tertiary butanol. The mixture was allowed to reflux with stirring for an additional 12 hours. A thick, white suspension of sodium tertiary butylate resulted. After allowing to cool to room temperature (20–30°), 50 g. of 2-iodo-4(5)-nitroimidazole were added. The mixture was stirred for 30 minutes and then refluxed under stirring for 2 hours. After allowing to cool to 45–50°, 500 ml. of water of 45–50° was added, whereupon the layers separated. The aqueous layer was chilled and neutralized with 20 ml. of acetic acid. Crystallization of the monosodium salt of the 2-hydroxy-4(5)-nitroimidazole product was completed by the addition of 500 ml. of ethanol. The crystals were filtered by suction and washed with 300 ml. of alcohol on the filter. Dried at 70°, the product formed yellow crystals consisting of the monosodium salt of 2-hydroxy-4(5)-nitroimidazole which decomposed gradually above 150°.

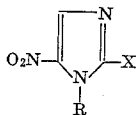
To purify the product, it was dissolved in 300 ml. of 1 N NaOH, the solution charcoaled and reprecipitated with 20 ml. of acetic acid and 300 ml. of alcohol.

What is claimed is:

1. A compound selected from the group consisting of a member having the formula



and a member having the formula

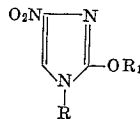


wherein R in each of the foregoing formulas is a member selected from the group consisting of hydrogen, lower alkyl and hydroxyl lower alkyl; and wherein X in each of the foregoing formulas is a member selected from the group consisting of iodo, hydroxy, lower alkoxy, phenoxy, nitrophenoxo, halophenoxy and lower alkylphenoxy and alkali salts of the compounds of Formulae I and II where R in each case is hydrogen.

2. 2-iodo-4(5)-nitroimidazole.
3. 2-(lower)alkoxy-4(5)-nitroimidazole.
4. 2-methoxyl-4(5)-nitroimidazole.
5. 2-aryloxy-4(5)-nitroimidazole wherein said aryloxy moiety is a member selected from the group consisting of phenoxy, halophenoxy, nitrophenoxo and lower alkylphenoxy.
6. 1-(lower)alkyl-2-iodo-4-nitroimidazole.
7. 1-(lower)alkyl-2-iodo-5-nitroimidazole.
8. A method of preparing 2-iodo-4(5)-nitroimidazole which comprises treating diiodoimidazole, with a nitrating agent.
9. A method of preparing 2-iodo-1-alkyl-4-nitroimidazole which comprises treating 2-iodo-4(5)-nitroimidazole with an alkylating agent at pH 7 and above.
10. A method of preparing 2-hydroxy-4(5)-nitroimidazole which comprises treating 2-iodo-4(5)-nitroimidazole with an alkali metal alcoholate of a tertiary lower alkanol.
11. A method of preparing a compound selected from the group consisting of 2-lower alkoxy-4(5)-nitroimidazole and 2-aryloxy-4(5)-nitroimidazole wherein said aryloxy moiety is a member selected from the group consisting of phenoxy, halophenoxy, nitrophenoxo and lower alkyl phenoxy which comprises treating 2-iodo-4(5)-nitroimidazole with the appropriate alkali metal alcoholate selected from the group consisting of alkali metal alcoholates of primary and secondary lower alkanols and alkali metal phenolates and alkali metal phenolates in

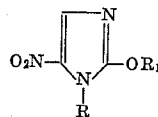
which the phenyl moiety is substituted by halogen, nitro or lower alkyl to form the corresponding 2-alkoxy-4(5)-nitroimidazole or 2-aryloxy-4(5)-nitroimidazole.

12. A method of preparing a compound of the formula



- 10 wherein R₁ is a member selected from the group consisting of lower alkyl, lower alkoxy alkyl, phenyl, halo-phenyl, nitrophenyl and lower alkyl phenyl and R is a member selected from the group consisting of lower alkyl and hydroxy lower alkyl which comprises treating alkylized 2-iodo-4(5)-nitroimidazole with an alkylating agent and thereafter treating the alkylation product with an alkali metal alcoholate selected from the group consisting of alkali metal alcoholates of primary and secondary lower alkanols, alkali metal phenolates and alkali metal phenolates in which the phenyl moiety is substituted by halogen, nitro or lower alkyl to form the corresponding 1-R-2-lower alkoxy-4-nitroimidazole or 1-R-2-aryloxy-4-nitroimidazole wherein R has the same meaning as above.

13. A method of preparing a compound of the formula



- 30 wherein R₁ is a member selected from the group consisting of lower alkyl, lower alkoxy alkyl, phenyl, halo-phenyl, nitrophenyl and lower alkyl phenyl and R is a member selected from the group consisting of lower alkyl and hydroxy lower alkyl which comprises treating 2-iodo-4(5)-nitroimidazole with an alkali metal alcoholate selected from the group consisting of alkali metal alcoholates of primary and secondary lower alkanols, alkali metal phenolates and alkali metal phenolates in which the phenyl moiety is substituted by halogen, nitro or lower alkyl to form the corresponding 1-R-2-lower alkoxy-5-nitroimidazole or 1-R-2-aryloxy-5-nitroimidazole wherein R has the same meaning as above and thereafter treating the so-formed product with an alkylating agent.

References Cited

UNITED STATES PATENTS

2,944,061	7/1960	Jacob et al.	260—309
3,029,236	4/1962	Staeuble	260—249.5
3,037,909	6/1962	Rogers et al.	260—309

FOREIGN PATENTS

1,084,729	12/1960	Germany.
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OTHER REFERENCES

- Balaban et al.: Jour. Chem. Soc. (London), vol. 121, pp. 947–958 (1922).
- Pyman et al.: Jour. Chem. Soc., vol. 123, pp. 494–503 (1923), (Chemical Abstracts, vol. 17, p. 1964 (1923)).
- Hazeldine et al.: Jour. Chem. Soc., vol. 125, pp. 1431–1441 (1924).
- Hofmann: Imidazole and Its Derivatives, pp. 3–5, 26–30, and 127–35, vol. 6 of the Chemistry of Heterocyclic Compounds (New York) Interscience, 1953.
- Schipper et al. In: Elderfield, Heterocyclic Compounds, vol. 5, p. 208, New York, Wiley, 1957.
- WALTER A. MODANCE, *Primary Examiner*.
- JOHN D. RANDOLPH, *Examiner*.
- N. TROUSOF, *Assistant Examiner*.