CONVENTION APPLICATION FOR A PATENT

(a) Insert full name(s) of applicants.  
F. Hoffmann-La Roche & Co. Aktiengesellschaft

(b) Insert address(es) of applicant(s).
124-154 Grenzacherstrasse, Basle, Switzerland

(c) Insert title of invention.
Novel nitroimidazoles and process for the preparation thereof

(d) Insert country in which first basic application was made.
Great Britain

(e) Insert date(s) of basic application(s).
August 19, 1977 in Great Britain
May 15, 1978 in Great Britain

(f) Insert number of basic application.
34308/77 in Great Britain
19234/78 in Great Britain

(g) Insert date form signed.
18th day of July, 1978

(h) Signature(s) of applicant(s). If a company to be executed in a manner binding on the company (according to its Articles of Association).
Kurt Nesselbosch
Hans Stucklin

(i) Seal, if any.

To: The Commissioner of Patents.

ARTHUR S. CAVE & CO.
Patent and Trade Mark Attorneys

Sydney, New South Wales, Australia 2000.
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER
PART XVI FOR A PATENT OR PATENT OF ADDITION

To be signed by the applicant(s) or in the case of a Company, to be signed by a person authorised by the Company.

In support of the Convention application made for a patent for an invention entitled

Novel nitroimidazoles and process for the preparation thereof.

1/We (b) Hans Stüeli

of (c) 33, Im Hirshalm, Riehen, Switzerland

do solemnly and sincerely declare as follows:

1. I am/we are authorised by F. Hoffmann-La Roche & Co. Aktiengesellschaft the applicant for the patent of addition to make this declaration on its behalf.

2. The basic application(s) referred to in Section 141 of the Act was/were made in the following country or countries on the following date(s) namely:

<table>
<thead>
<tr>
<th>Country</th>
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<tr>
<td>Great Britain</td>
<td>August 19, 1977</td>
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<td>Great Britain</td>
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<td>19534/78</td>
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<td>(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)</td>
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3. (b) Carey, Ernest Smithen

of (i) 17, The Valley Green, Welwyn Garden City, Herts., Great Britain

is/are the actual inventor(s) of the invention and the facts upon which the Company is entitled to make this application are as follows:

Roche Products Limited, Welwyn Garden City, Herts., Great Britain is the assignee of the said Carey Ernest Smithen and F. Hoffmann-La Roche & Co. Aktiengesellschaft, Basle, Switzerland is the assignee of the said Roche Products Limited.

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at Base, this 18th day of July, 1978.

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

(Signature of Declarant)
The compounds are useful for combatting protozoal infections and sensitizing of hypoxic tumour cells in conjunction with single or multiple dose radio-therapy.

Claim 3. Compounds of the general formula

![Chemical structure image]

\[ \text{I} \]

wherein \( R^1 \) represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group and \( R^2 \) represents a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group or a grouping of the formula
in which \(m\) stands for zero and \(n\) stands for 1 or \(m\) stands for 1 and \(n\) stands for zero and \(R^3\) represents a hydrogen atom or the methyl or hydroxy group or an oxyl free radical, or \(R^1\) and \(R^2\) together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated heter monocyclic ring which may carry a hydroxy group on a carbon atom other than a carbon atom attached directly to the nitrogen atom or which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, and acid addition salts thereof.
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PATENTS ACT 1952-1973
COMPLETE SPECIFICATION
(ORIGINAL) 38915
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Lodged:

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TO BE COMPLETED BY APPLICANT

Name of Applicant: F. HOFFMAN-LA ROCHE & CO. AKTIENGESellschaft

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Actual Inventor: CAREY ERNEST SMITHEH

Address for service: C/- ARTHUR S. CAVE & CO. 1 ALFRED ST, SYDNEY. N.S.W. 2000

Complete Specification for the invention entitled

NOVEL NITROIMIDAZOLES AND PROCESS FOR THE PREPARATION THEREOF.

The following statement is a full description of this invention, including the best method of performing it known to me:-
The present invention relates to novel nitroimidazoles, a process for the manufacture thereof and pharmaceutical preparations containing same.

The nitroimidazoles provided by the present invention are compounds of the general formula

\[
\begin{align*}
\text{N} & \quad \text{NO}_2 \\
\text{CH}_2 & \quad \text{CH} - \text{CH}_2 - \text{N} \\
& \quad \text{OH} \\
& \quad \text{I}
\end{align*}
\]

wherein \( R \) represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group and \( R^2 \) represents a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group or a grouping of the formula

\[
\begin{align*}
\text{H}_3 \text{C} & \quad \text{CH}_3 \\
\text{C} & \quad \text{N} - \text{R}^3 \\
\text{CH}_2 & \quad \text{C} \\
\text{H}_3 & \quad \text{C} \\
\text{CH}_3
\end{align*}
\]

in which \( m \) stands for zero and \( n \) stands for 1 or \( m \) stands for 1 and \( n \) stands for 1 or 2.

Mez/23.6.1978
zero and R\(^3\) represents a hydrogen atom or the methyl or hydroxy group or an oxyl free radical, or R\(^1\) and R\(^2\) together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated heteromonocyclic ring which may carry a hydroxy group on a carbon atom other than a carbon atom attached directly to the nitrogen atom or which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, and acid addition salts thereof.

As used in this specification, the term "lower alkyl" means a straight-chain or branched-chain alkyl group which preferably contains from 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, pentyl and hexyl). Examples of hydroxy-(lower alkyl) groups are the hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-hydroxybutyl and like groups. The term "lower cycloalkyl" means a cycloalkyl group which preferably contains up to 6 carbon atoms (e.g. cyclopropyl, cyclopentyl and cyclohexyl). The term "aryl" means the phenyl group or a phenyl group carrying one or more, preferably one or two, substituents, the substituents
being selected from halogen (i.e. fluorine, chlorine, bromine or iodine), trifluoromethyl, lower alkyl, lower alkoxy, nitro, amino and the like. Examples of such substituted-phenyl groups are the 4-chlorophenyl, 2,4-
5-dichlorophenyl, p-tolyl, 4-methoxyphenyl, 4-nitrophenyl, 4-aminophenyl and like groups. The term "lower aralkyl" means a lower alkyl group in which one of the hydrogen atoms has been replaced by an aryl group as hereinbefore defined. Examples of lower aralkyl groups are the benzyl, 4-chlorobenzyl, phenethyl, phenylpropyl and like groups. Examples of saturated heteromonocyclic rings which are formed by \( R_1 \) and \( R_2 \) and the nitrogen atom to which they are attached and which may carry a hydroxy group on a carbon atom other than a carbon atom attached directly to the nitrogen atom are the pyrrolidino, piperidino, 3-hydroxy-pyrrolidino, 4-hydroxy-piperidino, 3-hydroxy-hexahydro-1H-azepino and like groups. Examples of saturated heteromonocyclic rings which are formed by \( R_1 \) and \( R_2 \) and the nitrogen atom to which they are attached and which contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted as defined earlier are the piperazino, N-methylpiperazino, N-(2-hydroxyethyl)piperazino, morpholino, thiamorpholino and like groups. The term "lower alkoxy" means a straight-chain or branched-chain alkoxy group which preferably contains from 1 to 6 carbon atoms (e.g. methoxy, ethoxy).
An interesting class of nitroimidazole derivatives provided by the present invention comprises compounds of formula I in which \( R_1 \) represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group and \( R_2 \) represents a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group or \( R_1 \) and \( R_2 \) together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated heteromono-cyclic ring which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, and acid addition salts thereof.

An especially interesting class of nitroimidazole derivatives provided by the present invention comprises compounds of formula I in which \( R_1 \) and \( R_2 \) together with the nitrogen atom to which they are attached represent a 6-membered heteromonocyclic ring which may contain an oxygen atom or a further nitrogen atom which may be substituted by a lower alkyl group, and acid addition salts thereof.

Examples of compounds of formula I hereinbefore are:

2-Nitro-\( \alpha \)-(piperidino)methyl-1-imidazole-ethanol,
\( \alpha \)-(morpholino)methyl-2-nitro-1-imidazole-ethanol,
\( \alpha \)-(4-methylpiperazino)methyl-2-nitro-1-imidazole-ethanol,
2-nitro-α-(pyrrolidino)methyl-1-imidazole-ethanol,
α-(diethylamino)methyl-2-nitro-1-imidazole-ethanol,
α-[di(2-hydroxyethyl)amino]methyl-2-nitro-1-
-imidazole-ethanol,
α-(tert.-butylamino)methyl-2-nitro-1-imidazole-
-ethanol,
α-(benzylamino)methyl-2-nitro-1-imidazole-ethanol,
α-[(4-methoxyphenyl)amino]methyl-2-nitro-1-imidazole-
-ethanol,
α-(dimethylamino)methyl-2-nitro-1-imidazole-ethanol,
α-(hexahydro-lH-azepino)methyl-2-nitro-1-imidazole-
-ethanol,
4-[2-hydroxy-3-(2-nitro-1-imidazolyl)propylamino]-
-2,2,6,6-tetramethylpiperidin-N-oxyl,
α-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]methyl-2-
-nitro-1-imidazole-ethanol,
α-(cyclohexylamino)methyl-2-nitro-1-imidazole-
-ethanol,
α-(dicyclohexylamino)methyl-2-nitro-1-imidazole-
-ethanol and
1-[2-hydroxy-3-(2-nitro-1-imidazolyl)propyl]-3-
-pyrrolidinol.

According to the process provided by the present
invention, the nitroimidazole derivatives aforesaid (i.e.
the compounds of formula I and their acid addition salts)
are manufactured by

(a) reacting the epoxide of the formula
wherein $R_1$ and $R_2$ have the significance given earlier,
or
(b) for the manufacture of a compound of formula I in which $R^1$ represents other than a hydrogen atom, condensing the compound of the formula with an epoxide of the general formula

wherein $R^{10}$ and $R^{20}$ have any of the values accorded to $R^1$ and $R^2$ hereinbefore except that $R^{10}$ does not represent a hydrogen atom,
in the presence of a base,
or

(c) reacting a halohydrin of the general formula

\[
\begin{align*}
\text{VI} \\
\text{CH}_2\text{CH-CH}_2\text{-X} \\
\text{OH}
\end{align*}
\]

wherein X represents a chlorine or bromine atom,
with an amine of formula III hereinbefore,
and, if desired, converting a compound of formula I obtained into an acid addition salt. Preferments follow.

The reaction of the epoxide of formula II with an amine of formula III in accordance with embodiment (a) of the present process can be carried out in the presence or absence of an inert organic solvent. When an inert organic solvent is used, this may suitably be a lower alkanol (e.g. methanol, ethanol), dimethylformamide, dimethylacetamide or the like. Alternatively, an excess of an amine of formula III can be used and can thereby serve as the solvent. The temperature and pressure at which the reaction is carried out are not critical; the reaction may be carried out at room temperature and atmospheric pressure or at an elevated temperature and/or pressure. In a preferred procedure, the reaction is carried out at a temperature of from about 50°C up to the
reflux temperature of the reaction mixture and at atmospheric pressure.

The condensation of the compound of formula IV (azomycin) with an epoxide of formula V in accordance with embodiment (b) of the process is carried out in the presence of a base. The base is preferably used in catalytic amounts, although larger amounts of base can be used if desired. Preferred bases are alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), although other bases such as alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide) can also be used. The condensation is conveniently carried out in the presence of an inert organic solvent which may suitably be a lower alkanol (e.g. methanol, ethanol). Although the condensation can be carried out at room temperature and atmospheric pressure or at an elevated temperature and/or pressure, it is preferably carried out at an elevated temperature, especially at the reflux temperature of the condensation mixture, and at atmospheric pressure.

The reaction of a halohydrin of formula VI hereinbefore with an amine of formula III hereinbefore in accordance with embodiment (c) of the process is conveniently carried out using at least one mol of amine per mol of halohydrin. The reaction is conveniently carried out in the presence of an acid-binding agent such as an alkali metal carbonate (e.g. sodium carbonate,
potassium carbonate) or a tertiary organic amine (e.g. pyridine) or, preferably, an excess of the amine of formula III. Accordingly, it is especially preferred to carry out the reaction using at least two moles of amine of formula for each mol of halohydrin of formula VI. The reaction is conveniently carried out in the presence of an inert organic solvent which may suitably be a lower alkanol (e.g. methanol, ethanol). The temperature and pressure at which the reaction is carried out are not critical. It may be carried out at room temperature and atmospheric pressure or at an elevated temperature and/or pressure. In a preferred procedure, the reaction is carried out at an elevated temperature, especially at the reflux temperature of the reaction mixture, and at atmospheric pressure. The preferred halohydrin of formula VI hereinbefore is the chlorohydrin.

The compounds of formula I hereinbefore can be converted into acid addition salts by treatment with an inorganic acid such as a hydrohalic acid (e.g. hydrochloric acid or hydrobromic acid), sulphuric acid, nitric acid, phosphoric acid etc or with an organic acid such as acetic acid, citric acid, maleic acid, malic acid, fumaric acid, succinic acid, methanesulphonic acid, paratoluenesulphonic acid. The pharmaceutically acceptable acid addition salts, especially the hydrochlorides, are preferred. Non-pharmaceutically acceptable acid addition salts can be converted into pharmaceutically acceptable acid addition
salts by treatment with a base to form a compound of formula I and treatment of said compound with a pharmaceutically acceptable acid.

The starting materials used in the foregoing process, namely the epoxide of formula II, the amines of formula III, the compound of formula IV, the epoxides of formula V and the halohydrins of formula VI, are known compounds.

The compounds of formula I and their pharmaceutically acceptable acid addition salts are useful in sensitising hypoxic cells to the effects of radiation. They may accordingly be used as hypoxic-cell radiosensitisers in conjunction with the treatment of hypoxic tumour cells with radiation. The effectiveness of compounds of formula I and pharmaceutically acceptable acid addition salts thereof as hypoxic-cell radiosensitisers can be demonstrated in vitro using hypoxic Chinese hamster V79 cells (see Adams et al., Radiation Research, 1976, 67, 9-20). For example, 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol hydrochloride and α-(benzylamino)methyl-2-nitro-1-imidazole-ethanol hydrochloride, two novel nitroimidazole derivatives provided by this invention, provide an enhancement ratio of 1.6 (ER1.6) at concentrations of 30 micromoles and 40 micromoles, respectively. In order to achieve the same enhancement ratio with misonidazole and metronidazole, both of which are known nitroimidazoles, a concentration thereof of 300 micromoles and 4000 micromoles, respectively, is required.
The compounds of formula I and their pharmaceutically acceptable acid addition salts are also useful in combatting protozoal infections, especially infections caused by Trichomonas vaginalis. They may accordingly be used as antiprotozoal agents.

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material which is suitable for enteral (e.g. oral) or parenteral administration; for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gum arabic, polyalkylene glycols, petroleum jelly and the like. The pharmaceutical preparations may be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. The pharmaceutical preparations may contain other therapeutically valuable substances.

When used for the sensitisation of hypoxic tumour cells in conjunction with single or multiple dose radiotherapy regimens, the compounds of formula I and their
pharmaceutically acceptable acid addition salts can be administered orally in a daily dosage of from about ca. 20 mg/kg body weight to ca. 60 mg/kg body weight. In general, the total dosage should not exceed ca. 200 mg/kg body weight for any one course of multiple-dose treatment. When used as antiprotozoal agents, the compounds of formula I and their pharmaceutically acceptable acid addition salts can be administered orally in a daily dosage of from ca. 20 mg/kg body weight to ca. 60 mg/kg body weight. It will be appreciated that the aforementioned dosage ranges are given by way of example only and that they can be increased or decreased depending on individual requirements as directed by the attending physician.

The pharmaceutical preparations are manufactured in accordance with known procedures in that the active ingredient, i.e. a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, is mixed with non-toxic, inert, therapeutically compatible solid or liquid carriers, commonly used in such preparations and is brought into a suitable pharmaceutical dosage form.
The following Examples illustrate the process provided by the present invention:

Example 1

(a) A mixture of 5.1 g (30 mmol) of 1-(2,3-epoxypropyl)-2-nitroimidazole, 3.3 g (45 mmol) of diethylamine and 100 ml of methanol was heated under reflux for 12-18 hours. The solvent was removed under reduced pressure to give 8.1 g of a pale brown residue which was redissolved in ca. 25 ml of hot ethanol, treated with decolorising charcoal, filtered and allowed to crystallise to give 5.2 g (72% yield) of α-(diethylamino)methyl-2-nitro-1-imidazole-ethanol as a pale yellow crystalline solid of melting point 92°-93°C.

(b) 3.6 g of α-(diethylamino)methyl-2-nitro-1-imidazole-ethanol were dissolved in a minimum amount of warm ethanol and treated with a small excess of anhydrous ethereal hydrogen chloride. The mixture was then allowed to cool and crystallise for several hours. There were obtained 4.0 g of cream coloured hydrochloride salt. This was collected, redissolved in ca. 40 ml of hot ethanol, treated with decolorising charcoal, filtered and allowed to crystallise, after the addition of a few ml of anhydrous
diethyl ether if necessary, to yield 4.0 g of α-(diethyl-amino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 145°-146°C (decomposition).

Example 2

(a) In a manner analogous to that described in Example 1(a) there was obtained, after crystallisation from isopropanol, 2-nitro-α-(pyrrolidino)methyl-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 83°-85°C; yield 79%.

(b) In a manner analogous to that described in Example 1(b) there was obtained 2-nitro-α-(pyrrolidino)methyl-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 158°-159°C (decomposition); yield 87%.

Example 3

(a) In a manner analogous to that described in Example 1(a) there was obtained, after crystallisation from ethanol, 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 110°-112°C; yield 88%.
In a manner analogous to that described in Example 1(b) there was obtained 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 144°-145°C (decomposition); yield 90%.

**Example 4**

(a) In a manner analogous to that described in Example 1(a) there was obtained, after crystallisation from ethanol, α-(morpholino)methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 112°-113°C; yield 88%.

(b) In a manner analogous to that described in Example 1(b) there was obtained α-(morpholinomethyl)-2-nitro-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 196°-197°C (decomposition); yield 93%.

**Example 5**

(a) In a manner analogous to that described in Example 1(a) there was obtained, after crystallisation from ethanol, α-(4-methylpiperazino)methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 144°-145°C; yield 62%.
(b) In a manner analogous to that described in Example 1(b) there was obtained α-(4-methylpiperazino)methyl-2-nitro-1-imidazole-ethanol dihydrochloride in the form of an almost colourless microcrystalline solid of melting point 215°-216°C (decomposition); yield 77%.

Example 6

(a) In a manner analogous to that described in Example 1(a), but using equimolar amounts of reagents, there was obtained, after crystallisation from isopropanol, α-[di-(2-hydroxyethyl)amino]methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 92°-93°C; yield 79%.

(b) In a manner analogous to that described in Example 1(b) there was obtained α-[di-(2-hydroxyethyl)amino]methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 151°-152°C (decomposition); yield 75%.

Example 7

(a) In a manner analogous to that described in Example 1(a), but using two molar equivalents of tert.-butylamine, there was obtained, after crystallisation from ethanol α-(tert.-butylamino)methyl-2-nitro-1-imidazole-ethanol in
the form of a pale yellow crystalline solid of melting point 114°C-115°C; yield 36%.

(b) In a manner analogous to that described in Example 1(b) there was obtained α-(tert.-butylamino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured microcrystalline solid of melting point 198°C-199°C (decomposition); yield 87%.

Example 8

(a) In a manner analogous to that described in Example 1(a), but using equimolar amounts of reagents, there was obtained α-(benzylamino)methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow gum which was homogeneous according to thin-layer chromatography.

(b) 4.5 g of α-(benzylamino)methyl-2-nitro-1-imidazole-ethanol were dissolved in a minimum amount of warm ethanol and treated with an equivalent amount of ethanolic maleic acid (1.9 g). The mixture was allowed to cool and crystallise for several hours. There were obtained 5.2 g of cream coloured hydrogen maleate salt. This was collected, redissolved in ca. 50 ml of hot ethanol, treated with colorising charcoal, filtered and allowed to crystallise, after addition of a few ml of anhydrous diethyl ether if necessary, to yield 3.6 g of α-(benzyl-
amino)methyl-2-nitro-1-imidazole-ethanol hydrogen maleate in the form of a very pale cream coloured microcrystalline solid of melting point 153°-154°C (decomposition).

(c) In a manner analogous to that described in part (b) of this Example there was obtained, after crystallisation from ethanol, α-(benzylamino)methyl-2-nitro-1-imidazole-ethanol hydrogen oxalate in the form of a colourless microcrystalline solid of melting point 197°-198°C (decomposition).

Example 9

(a) In a manner analogous to that described in Example 1(a), but using equimolar amounts of reagents, there was obtained, after crystallisation from ethanol, α-[(4-methoxyphenyl)amino]methyl-2-nitro-1-imidazole-ethanol in the form of a brown crystalline solid (needles) of melting point 162°-163°C; yield 80%.

(b) In a manner analogous to that described in Example 1(b) there was obtained α-[(4-methoxyphenyl)amino]methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a very pale pink coloured microcrystalline solid of melting point 156°-157°C (decomposition); yield 97%.
Example 10

(a) In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from isopropanol, $\alpha$-(dimethylamino)methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 78°-79°C; yield 40%.

(b) In a manner analogous to that described in Example 1(b) there was obtained, after recrystallisation from methanol/diethyl ether, $\alpha$-(dimethylamino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a colourless microcrystalline solid of melting point 202°-203°C (decomposition).

Example 11

(a) In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from isopropanol, $\alpha$-(hexahydro-1H-azepino)methyl-2-nitro-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 102°-103°C.
(b) In a manner analogous to that described in Example 1(b) there was obtained, after recrystallisation from ethanol/diethyl ether, α-(hexahydro-1H-azepino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of an almost colourless crystalline solid of melting point 133°-134°C (decomposition).

Example 12

In a manner analogous to that described in Example 1(a) there was obtained in 62% yield, after chromatography on alumina (elution being carried out with dichloromethane, the eluates of the red-orange band being combined and concentrated and the concentrate being left to crystallise), 4-[2-hydroxy-3-(2-nitro-1-imidazolyl)propylamino]-2,2,6,6-tetramethylpiperidin-N-oxyl in the form of an orange coloured crystalline solid of melting point 150°-151°C.

Example 13

In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from isopropanol, α-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]methyl-2-nitro-1-imidazole-ethanol in the form of a cream coloured solid of melting point 151°-153°C; yield 60%.
Example 14

(a) In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from isopropanol, α-(cyclohexylamino)methyl-2-nitro-1-imidazole-ethanol in the form of a cream coloured crystalline solid of melting point 66°-68°C; yield 90%.

(b) In a manner analogous to that described in Example 1(b) there was obtained, after recrystallisation from ethanol/diethyl ether, α-(cyclohexylamino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of an almost colourless microcrystalline solid of melting point 192°-193°C (decomposition).

Example 15

(a) In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from ethanol, α-(dicyclohexylamino)methyl-2-nitro-1-imidazole-ethanol in the form of a yellow-orange crystalline solid of melting point 149°-150°C; yield 31%.
In a manner analogous to that described in Example 1(b) there was obtained, after recrystallisation from ethanol/diethyl ether, \( \alpha \)-(dicyclohexylamino)methyl-2-nitro-1-imidazole-ethanol hydrochloride in the form of a cream coloured microcrystalline solid of melting point 208°-209°C (decomposition).

Example 16

In a manner analogous to that described in Example 1(a) there was obtained, after recrystallisation from ethanol, 1-[2-hydroxy-3-(2-nitro-1-imidazolyl)propyl]-3-pyrrolidinol in the form of a cream coloured crystalline solid of melting point 126°-130°C.

Example 17

(a) A mixture of 5.65 g (50 mmol) of 2-nitroimidazole and 250 mg of anhydrous potassium carbonate in 150 ml of ethanol was heated under reflux for 15 minutes. 7.05 g (50 mmol) of freshly distilled 3-piperidino-propylene oxide in a minimum amount of ethanol were added to the mixture and heating under reflux was continued for 3 hours. The mixture was filtered and the filtrate was evaporated to dryness in vacuo to give ca.13 g of a yellow oil which was partitioned between 100 ml of ethyl acetate and 100 ml of water. The aqueous layer was separated and washed once
with 50 ml of ethyl acetate. The combined organic phases were extracted with four 50 ml portions of 2-N hydrochloric acid. The combined aqueous-acidic solutions were made basic by the addition of excess solid sodium carbonate and extracted with three 100 ml portions of dichloromethane. The combined organic phases were dried over anhydrous sodium carbonate and filtered. The filtrate was evaporated to dryness in vacuo to give 6.5 g of a pale yellow solid which was redissolved in 25 ml of hot ethanol, treated with decolorising charcoal, filtered and left to crystallise, there being obtained 1.4 g (11% yield) of 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 108°-109°C.

(b) 1.27 g of 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol were dissolved in 25 ml of warm ethanol and treated with a small excess of anhydrous ethereal hydrogen chloride. The mixture was then allowed to cool and crystallise for several hours. There were obtained 1.4 g of 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol hydrochloride in the form of a very pale cream coloured micro-crystalline solid identical with the product prepared as described in Example 3(b).
A mixture of 4.1 g (20 mmol) of 3-chloro-1-(2-nitro-1-imidazolyl)-2-propanol, 3.4 g (40 mmol) of piperidine and 75 ml of methanol was heated under reflux for 12-18 hours. The solvent was removed under reduced pressure to give 7.3 g of a cream coloured solid which was suspended in 75 ml of water and acidified with a small excess of 2-N hydrochloric acid. The homogeneous solution was washed with three 25 ml portions of dichloromethane and the dichloromethane washings were discarded. The aqueous solution was treated with a small excess of 2-N sodium hydroxide solution and extracted with three 75 ml portions of fresh dichloromethane. The dichloromethane extracts were combined, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness in vacuo to give 4.3 g of a cream coloured solid. This solid was dissolved in ca. 25 ml of hot ethanol, treated with decolorising charcoal, filtered and allowed to crystallise to give 3.3 g (65% yield) of 2-nitro-α-(piperidino)methyl-1-imidazole-ethanol in the form of a pale yellow crystalline solid of melting point 110°-112°C. This product was identical with the product prepared as described in Example 3(a) and was converted into the hydrochloride in a manner analogous to that described in Example 1(b).

The following Example illustrates a typical pharmaceutical preparation containing a compound of formula I or
a pharmaceutically acceptable acid addition salt thereof (hereinafter referred to as the "active ingredient"):

**Example A**

**Capsule formulation:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Per capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>500.00 mg</td>
</tr>
<tr>
<td>Cellulose</td>
<td>10.00 mg</td>
</tr>
<tr>
<td>Methylhydroxypropylcellulose</td>
<td>5.00 mg</td>
</tr>
<tr>
<td>Dioctyl sodium sulfosuccinate</td>
<td>1.00 mg</td>
</tr>
<tr>
<td>Maize starch</td>
<td>12.00 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.00 mg</td>
</tr>
<tr>
<td><strong>Total weight</strong></td>
<td>530.00 mg</td>
</tr>
</tbody>
</table>

The foregoing pharmaceutical preparation should be prepared and stored in the dark.
The claims defining the invention are as follows:

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:

1) A process for the manufacture of the nitroimidazole derivatives of the general formula

\[
\begin{align*}
\text{N} & \quad \text{NO}_2 \\
\text{CH}_2 & \quad \text{CH} \quad \text{CH}_2 \quad \text{N} \\
\text{OH} & \quad \text{R}^1 \\
\end{align*}
\]

wherein \( R^1 \) represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group and \( R^2 \) represents a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group or a grouping of the formula

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{(CH}_2\text{)}_n\text{C} & \quad \text{C} \\
\text{CH}_2 & \quad \text{N} \quad \text{R}^3 \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\end{align*}
\]

in which \( m \) stands for zero and \( n \) stands for 1 or \( m \) stands for 1 and \( n \) stands for zero and \( R^3 \) represents a hydrogen atom or
the methyl or hydroxy group or an oxyl free radical, or \( R^1 \) and \( R^2 \) together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated heteromonocyclic ring which may carry a hydroxy group on a carbon atom other than a carbon atom attached directly to the nitrogen atom or which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-\(-(\text{lower alkyl}), \text{aryl}\) or lower aralkyl group, and acid addition salts thereof, which process comprises

(a) reacting the epoxide of the formula

\[
\begin{align*}
\text{II} & \\
\text{CH}_2-\text{CH}-\text{CH}_2-\text{NO}_2 & \\
\end{align*}
\]

with an amine of the general formula

\[
\begin{align*}
\text{III} & \\
\text{HN} & \\
\text{R}^1 & \\
\text{R}^2 & \\
\end{align*}
\]

, wherein \( R^1 \) and \( R^2 \) have the significance given above,
or

(b) for the manufacture of a compound of formula I in which \( R^1 \) represents other than a hydrogen atom, condensing the compound of the formula

\[
\begin{array}{c}
\text{V} \\
\text{H}_2\text{C} - \text{CH} - \text{CH}_2 - \text{N} - \text{R}^{10} \text{R}^{20}
\end{array}
\]

with an epoxide of the general formula

\[
\begin{array}{c}
\text{V} \\
\text{H}_2\text{C} - \text{CH} - \text{CH}_2 - \text{N} - \text{R}^{10} \text{R}^{20}
\end{array}
\]

wherein \( R^{10} \) and \( R^{20} \) have any of the values accorded to \( R^1 \) and \( R^2 \) above except that \( R^{10} \) does not represent a hydrogen atom, in the presence of a base, or

(c) reacting a halohydrin of the general formula

\[
\begin{array}{c}
\text{VI} \\
\text{CH}_2 - \text{CH} - \text{CH}_2 - \text{X}
\end{array}
\]

wherein \( X \) represents a chlorine or bromine atom, with an amine of formula III given earlier in this claim,
and, if desired, converting a compound of formula I obtained into an acid addition salt.

2) A process according to claim 1, wherein a compound of formula I in which $R^1$ represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group and $R^2$ represents a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated hetero-monocyclic ring which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, or an acid addition salt thereof, is manufactured by reacting the epoxide of formula II with an amine of formula III in which $R^1$ and $R^2$ have the significance given in this claim and, if desired, the compound of formula I obtained is converted into an acid addition salt.

3) A process according to claim 2, wherein there is manufactured a compound of formula I in which $R^1$ and $R^2$ together with the nitrogen atom to which they are attached represent a 6-membered heteromonocyclic ring which may contain an oxygen atom or a further nitrogen atom which may be substituted by a lower alkyl group, or an acid addition salt thereof.
4) A process for the manufacture of the nitroimidazole derivatives of the general formula I as set forth in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 18.

5) A process for the manufacture of a pharmaceutical preparation containing a compound of the general formula I as set forth in claim 1 or a pharmaceutically acceptable acid addition salt thereof as active ingredient which process is characterized in that the active ingredient is mixed with non-toxic, inert, therapeutically compatible solid or liquid carriers, commonly used in such preparations and is brought into a suitable pharmaceutical dosage form.

6) A pharmaceutical preparation containing a compound of the general formula I as set forth in claim 1 or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier material.

7) A nitroimidazole derivative of the general formula I as set forth in claim 1, when manufactured by the process claimed in any one of claims 1 to 4 inclusive or by an obvious chemical equivalent thereof.
Compounds of the general formula

![Chemical structure](image)

where \( R^1 \) represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group and \( R^2 \) represents a lower alkyl, hydroxy-(lower alkyl), lower cycloalkyl, aryl or lower aralkyl group or a grouping of the formula

![Chemical structure](image)

in which \( m \) stands for zero and \( n \) stands for 1 or \( m \) stands for 1 and \( n \) stands for zero and \( R^3 \) represents a hydrogen atom or the methyl or hydroxy group or an oxyl free radical, or \( R^1 \) and \( R^2 \) together with the nitrogen atom to which they are
attached represent a 5-membered, 6-membered or 7-membered saturated heteromonocyclic ring which may carry a hydroxy group on a carbon atom other than a carbon atom attached directly to the nitrogen atom or which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, and acid addition salts thereof.

9) Compounds of formula I given in claim 8, wherein R represents a hydrogen atom or a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group and R' represents a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group or R and R' together with the nitrogen atom to which they are attached represent a 5-membered, 6-membered or 7-membered saturated heteromonocyclic ring which may contain an oxygen or sulphur atom or a further nitrogen atom which may be substituted by a lower alkyl, hydroxy-(lower alkyl), aryl or lower aralkyl group, and acid addition salts thereof.

10) Compounds of formula I given in claim 8, wherein R and R' together with the nitrogen atom to which they are attached represent a 6-membered heteromonocyclic ring which may contain an oxygen atom or a further nitrogen atom which may be substituted by a lower alkyl group, and acid addition salts thereof.
11) 2-Nitro-α-(piperidino)methyl-1-imidazole-ethanol.

12) α-(Morpholino)methyl-2-nitro-1-imidazole-ethanol.

13) α-(4-Methylpiperazino)methyl-2-nitro-1-imidazole-ethanol.

14) 2-Nitro-α-(pyrrolidino)methyl-1-imidazole-ethanol.

15) α-(Diethylamino)methyl-2-nitro-1-imidazole-ethanol.


17) α-(Tert.-butylamino)methyl-2-nitro-1-imidazole-ethanol.

18) α-(Benzylamino)methyl-2-nitro-1-imidazole-ethanol.

19) α-[(4-Methoxyphenyl)amino]methyl-2-nitro-1-imidazole-ethanol.

20) α-(Dimethylamino)methyl-2-nitro-1-imidazole-ethanol.

21) α-(Hexahydro-1H-azepino)methyl-2-nitro-1-imidazole-ethanol.

22) 4-[2-Hydroxy-3-(2-nitro-1-imidazolyl)propylamino]-2,2,6,6-tetramethylpiperidin-N-oxyl.
23) α-[(2,2,6,6-Tetramethyl-4-piperidinyl)amino]methyl-2-nitro-1-imidazole-ethanol.

24) α-(Cyclohexylamino)methyl-2-nitro-1-imidazole-ethanol.

25) α-(Dicyclohexylamino)methyl-2-nitro-1-imidazole-ethanol.

26) 1-[2-Hydroxy-3-(2-nitro-1-imidazolyl)propyl]-3-pyrrolidinol.

DATED this 14th day of August, 1978.

F. HOFFMANN–LA ROCHE & CO. AKTIENGESELLSCHAFT

BY THEIR PATENT ATTORNEYS

ARTHUR S. CAVE & CO.