2
COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952-1969

CONVENTION APPLICATION FOR A PATENT

We, SCHERING CORPORATION

of 2000 Galloping Hill Road,
Kenilworth, New Jersey 07033,
U.S.A.

hereby apply for the grant of a Patent for an invention entitled: "2-SUBSTITUTED-3-HETEROCYCLYL-INDOLES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application(s) numbered: 947,979

for a patent or similar protection made in U.S.A.

on 2nd October, 1978.

Our address for service is care of GRIFFITH, HASSEL & FRAZER, Patent Attorneys, of 323 Castlereagh Street, Sydney 2000, in the State of New South Wales, Commonwealth of Australia.

Dated this 28th day of September, 1979

SCHERING CORPORATION
By their Patent Attorneys:
DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

In support of the Application made by SCHERING CORPORATION
2000 Galloping Hill Road
Kenilworth, New Jersey 07033, U.S.A.

for a patent for an invention entitled: "2-SUBSTITUTED-3-HETEROCYCLYL-INDOLES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM."

I, Bruce M. Eisen
of the Applicant's

1. I am authorized by the applicant for the patent to make this Declaration on its behalf.

2. Steinman Martin, citizen of the United States of America, residing at 46 Glendale Avenue, Livingston, New Jersey 07039, U.S.A. and Tahbaz Pirouz, citizen of Iran, residing at 96 Oak Drive, Cedar Grove, New Jersey 07009, U.S.A.

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

The applicant is the assignee of the above mentioned inventors

3. The basic application(s) as defined in Section 141 of the Act, was/were made in

United States of America on the October 2, 1978

by Steinman Martin and Tahbaz Pirouz

4. The basic application(s) referred to in paragraph 3 of this Declaration was/ were-first application(s) made in a Convention country in respect of the invention, the subject of the application.

Declared at Kenilworth (Union County) this day of Sept. 13, 1979

SCHERING CORPORATION

(Signature)

Bruce M. Eisen
Director, Patents-U.S.

NOTE: Initial all Deletions and Alterations.
No witnessing or legalization required.
For a Non-Convention application delete paragraphs 3 and 4 and initial the deletion.
For Multiple Priorities incorporate details of all basic applications in paragraph 3.
For application for a Patent of Addition add "of Addition" after the word "patent" wherever the word occurs, and initial each such insertion.
Compounds are useful as immunodepressants.

Claim
1. 2-Substituted-3-heterocyclyl-indoles of the formula

\[
\text{wherein } X \text{ is a hydrogen or halogen atom,} \\
\text{n is 1, 2 or 3 (when } X \text{ is a halogen atom),} \\
\text{Q is an oxygen atom or the group } (\text{H,OH}),
\]
Z is a hydrogen atom or, provided that Q is an oxygen atom, Z can also be the group OR, wherein R is a hydrogen atom or a lower alkyl or loweralkoxy-loweralkyl group, "lower" indicating groups with 1 to 6 carbon atoms,
m is 1 or 2 when Z is a hydrogen atom and m is 0 when Z is the group OR,
and HAT is a heterocyclic radical selected from pyridyl, lower-alkyl-substituted pyridyl, pyrimidinyl, pyrida-
dinyl, pyrazinyl, pyrazolidinyl, imidazoyl, thiazolyl, oxazolyl, triazolyl, thiophenyl, furanyl, pyrrolid, oxazolyl, thienyl and hetero-
aryl.
Complete Specification for the invention entitled: "2-SUBSTITUTED-3-HETEROCYCYL-INDOLES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, with the best method of performing it known to me/us:
This invention relates to novel 2-substituted-3-heterocyclylindoles, to their preparation, to their use as immuno-suppressants, and to pharmaceutical compositions containing them.

According to the invention we provide novel 2-substituted-3-heterocyclylindoles of the formula

wherein X is a hydrogen or halogen atom,
\( n \) is 1, 2 or 3 (when X is a halogen atom),
\( Q \) is an oxygen atom or the group \((H,OH)\),
\( Z \) is a hydrogen atom or, provided that \( Q \) is an oxygen atom, \( Z \) can also be the group \( OR \), wherein \( R \) is a hydrogen atom or a lower alkyl or loweralkoxy-loweralkyl group, "lower" indicating groups with 1 to 6 carbon atoms,
m is 1 or 2 when Z is a hydrogen atom and m is 0 when Z is the group OR, and
Het is a heterocyclic radical selected from pyridyl, lower-alkyl-substituted-pyridyl, pyrimidinyl,
pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thiynyl, furanyl, pyrrolyl, oxazolyl and isoxazolyl.

The "Het" groups can be joint to the 3-position of the indole nucleus by any available ring atom, but are preferably joined through a carbon atom. Thus, for example, the pyridyl groups can be 2-, 3- or 4-pyridyl. A lower alkyl group substituting a pyridyl group is preferably methyl.

The term "halogen" comprises fluorine, chlorine, bromine and iodine. Halogen substituents in the fused benzene ring may be in any of the 4-, 5-, 6- and 7-positions; however, monosubstitution is preferably at the 5- or 6-position whereas polysubstitution is most preferably at the 5,6-positions but can also conveniently be at the 4,5- or 4,5,6-positions. $X_n$ thus preferably represents one or two halogen atoms, especially chlorine and/or bromine.
In particular, $X_n$ can represent a 5-chlorine atom, a 5-chlorine atom together with a 4-bromine atom, or especially a 5-chlorine atom and a 6-bromine atom.

The 2-substituent of the indole nucleus is preferably a methylsulfonylacetyl or especially a methylsulfinylacetyl group; i.e. $Q$ is an oxygen atom, $Z$ is a hydrogen atom and $m$ is 2 or especially 1. The 2-substituent can for example also be a methylthio-hydroxyacetyl, methylthio-loweralkoxyacetyl (especially methylthio-methoxyacetyl), 2-methylsulfanyl-1-hydroxyethyl or 2-methylsulfonyl-1-hydroxyethyl group.

Preferred compounds according to the invention include

6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(4-pyrimidinyl)indole (m.p. 206°C. (dec.)),

6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl) indole,

5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl) indole (m.p. 168-170°C.),

6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-pyridyl) indole (m.p. 204.5°C.), and

4-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl) indole (m.p. 177-178°C.).
Other preferred compounds according to the invention include:

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(4-pyridyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(oxazolyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(isoxazolyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(pyrimidinyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(pyridazinyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(pyrazinyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(pyrazolyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(imidazolyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(thiazolyl) indole,

6-bromo-5-chloro-2-[[methylsulfinyl]acetyl]-3-(thienyl) indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-(furanyl) indole, and
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-(pyrrolyl) indole.

A particularly preferred compound according to the invention is 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole (m.p. 198-199°C. (dec.)),

The invention further provides a process for the preparation of a compound of the formula I defined above, which comprises reacting an appropriate reactive derivative of an acid of the formula

\[
\begin{align*}
\text{Het} & \quad \text{II} \\
\text{X}_n & \quad \text{CO}_2\text{H}
\end{align*}
\]

wherein Het, X and n are as defined above with an anion of the formula

\[
\begin{align*}
\text{CH}_2\cdot\text{SO}_m\cdot\text{CH}_3 & \quad \text{III}
\end{align*}
\]

wherein m is 1 or 2,
in the presence of an anhydrous organic solvent and under an inert atmosphere, to yield a product of the formula

![Chemical Structure]

wherein Het, X, m and n are as defined above,

whereafter, for the preparation of a compound of the formula I or IA wherein m is 2 when m in the product of the formula IA is 1, this product is oxidised,

and/or for the preparation of a compound of the formula I wherein Q is the group (H,OH), the product of the formula IA is reduced at the carbonyl group,

or, for the preparation of a compound of the formula I wherein Q is O and Z is the group OR wherein R is as defined above, a product of the formula IA wherein m is 1 is subjected to the action of acid in the presence of a solvent comprising the compound ROH.
It will thus be understood that the products of the formula IA can either serve as final products of the formula I or be subjected to further steps to yield further products of the formula I.

The reactive derivative of the acid of the formula II is preferably an ester, especially a lower alkyl ester (the lower alkyl group having 1 to 6, preferably 1 to 4, carbon atoms), more especially the methyl or ethyl ester. The reactive derivative may also be the symmetrical anhydride of the acid or an N,N-disubstituted amide of the acid, e.g., an N,N-diloweralkylamide (wherein each lower alkyl group has 1 to 6, preferably 1 to 4, carbon atoms) or an N,N-pentamethylene amide.

The anion of the formula III can be prepared from dimethylsulfoxide or dimethylsulfone and a strong base, for example an alkali metal hydride, especially sodium hydride, an alkyl lithium, especially n-butyl-lithium, or potassium t-butoxide, by heating at a moderately elevated temperature, e.g., 60° to 75°C. for about two hours. If desired, an inert organic diluent or solvent, such as an aromatic hydrocarbon, especially benzene, may be present. Preparation of the anion of the formula III and its reaction
with the derivative of the acid of the formula II should take place in an anhydrous reaction medium and under an inert atmosphere e.g. nitrogen.

The reaction between the anion of the formula III and the derivative of the acid of the formula II is preferably carried out by stirring the reactants at about room temperature until reaction is complete (generally about 1 to 2 hours). The anion is preferably present in excess, e.g. about 3 equivalents in excess relative to the derivative of the acid of the formula II. After the reaction is complete, the reaction mixture is quenched with water and then acidified and the desired product is isolated for example by filtration and recrystallisation.

A so-obtained product of the formula IA wherein \( m \) is 1 can be oxidized to a corresponding product of the formula IA wherein \( m \) is 2. The oxidation is preferably effected by means of a peroxidic compound in an inert solvent, preferably hydrogen peroxide in acetic acid or an organic peracid in a halogenated organic solvent, e.g., a perbenzoic acid, especially \( m \)-chloroperbenzoic acid, in chloroform.
A product from these processes of the formula IA (wherein m is 1 or 2) can be preferentially reduced at the carbonyl group to yield a product of the formula I wherein Q is the group (H, OH), without reduction at the sulfinyl or sulfonyl group. This reduction is preferably effected by means of a borohydride, especially sodium borohydride, in a water-miscible inert organic solvent which may contain water, e.g. water-miscible ethers such as aqueous tetrahydrofuran or dioxan or lower alkanols, especially methanol or ethanol.

A product of the formula IA wherein m is 1 may be subjected to a Pummerer-type rearrangement in the presence of acid, preferably mineral acid, and a compound ROH (wherein R is as defined above) to yield a compound of the formula I wherein m is 0 and Z is OR (wherein R is as defined above). The mineral acid is conveniently hydrochloric acid. When this reaction is carried out in the presence of water, the product is a 2-[(methylthio)(hydroxy)acetyl]-3-heterocyclyl-indole (which may be called a 3-heterocyclyl-indole-2-glyoxal methyl hemimercap-tal); when this reaction is carried out in the presence of a lower alkanol (or loweralkoxy-loweralkanol), the product is a 2-[(methylthio)loweralkoxy- (or loweralkoxy-loweralkoxy)- acetyl]-3-heterocyclyl-indole.
The derivatives, e.g. the lower alkyl esters, of the 3-"Het"-indole-2-carboxylic acids of the formula II (wherein "Het" is a heterocyclyl group as defined for formula I) either are known compounds or can be prepared by known methods. Thus an appropriately \( X_n \)-substituted or unsubstituted phenylhydrazine hydrogen halide can be reacted with an appropriate lower alkyl \( \beta-"Het" \)-pyruvate, which is cyclized under conditions usual in the Fischer indole synthesis, i.e., using an acid catalyst e.g. a mineral acid such as sulfuric acid in acetic acid. This reaction often yields isomeric products, which can be separated by chromatography. For example, the cyclization of a 3,4-dihalophenylhydrazone of an alkyl \( \beta-(2\text{-pyridyl})\)-pyruvate by heating with concentrated sulfuric acid in glacial acetic acid will produce a mixture of an alkyl 5,6-dihalo-3-(2-pyridyl)indole-2-carboxylate and an alkyl 4,5-dihalo-3-(2-pyridyl)indole-2-carboxylate. The isomeric products are easily separated from this mixture by standard methods, e.g. by chromatography on silica gel in chloroform.

The required intermediates may be prepared by techniques well known to those of ordinary skill in the art. For example, ethyl 2-pyridylpyruvate-1-oxide is prepared...
according to Adams et al. (J. Amer. Chem. Soc. 76, 3168 (1954)), the succeeding ethyl 2-pyridylpyruvate according to S. Inaba et al. (Chem. Pharm. Bull., 20, 1628 (1972)), the pherylhydrazines according to Bullock et al. (J. Amer. Chem. Soc., 78, 5854 (1956)), and their aniline precursors according to Suthers et al. (J. Org. Chem., 27, 447 (1962)).

The following preparations show how the starting materials for the process according to the invention can be obtained:
PREPARATION 1

3-Bromo-4-chlorophenylhydrazine hydrochloride

Treat 3-bromo-4-chloroaniline (41.3 g., 0.2 mole) in 90 ml. of 6N hydrochloric acid at -10°C. with 14 g. of sodium nitrite in 30 ml. of water. Add this solution with stirring to a cold (-10°C.) solution of 55 g. of sodium bisulfite and 20 g. of sodium hydroxide in 200 ml. of water. After a red precipitate appears, allow the mixture to warm to room temperature. Add 200 ml. of concentrated hydrochloric acid and heat at 90-100°C. for 4 hours. Allow the mixture to cool overnight, collect the solid, wash it with 50 ml. of cold 3N hydrochloric acid and dry it. Recrystallization from ether-methanol yields the desired material, m.p. 208-210°C.

PREPARATION 2

3-Bromo-4-chlorophenylhydrazone of ethyl 2-pyridylpyruvate hydrochloride

Pass dry hydrogen chloride into 500 ml. of dry ethanol containing 54.4 g. of 3-bromo-4-chlorophenylhydrazine hydrochloride and 41.5 g. of ethyl 2-pyridylpyruvate until 50 g. of the dry acid is absorbed. With constant stirring reflux the resulting mixture for 2 hours; allow the mixture to cool overnight, collect the precipitate and wash it with cold ethanol, and dry it in vacuo to obtain the title compound, m.p. 207-208°C.
PREPARATION 3

Ethyl 6-bromo-5-chloro-3-(2-pyridyl)indole-2-carboxylate and Ethyl 4-bromo-5-chloro-3-(2-pyridyl)indole-2-carboxylate

Add the 3-bromo-4-chlorophenylhydrazone of ethyl 2-pyridylpyruvate hydrochloride (86 g.) to 330 ml. of glacial acetic acid with stirring and warm to 70°C. Add 80 ml. of concentrated sulfuric acid dropwise over an hour, maintaining a temperature of 80-95°C. After a further 15 minutes, cool the mixture to 25°C. and pour it onto ice.

Adjust the pH to 8-9 with ammonia. Collect the precipitate, wash it with water and dry it.

Treat the precipitate with 200 ml. of methylene chloride and stir for an hour. Filter off the insoluble material which is mainly the 6-bromo-5-chloro isomer, wash it with methylene chloride and dry it. The filtrate contains both indoles.

Recrystallize the precipitate from benzene to yield the 6-bromo-5-chloro isomer, m.p. 173-175°C. Further recrystallization from benzene (using charcoal) yields pure material (a single spot by thin layer chromatography); m.p. 179-180°C., analytical sample m.p. 181-182°C.

The methylene chloride filtrate is concentrated and cooled
to yield light yellow crystals, m.p. 208-210°C, of the 4-bromo-
5-chloro isomer; analytical sample m.p. 209-210°C.

The following starting materials for the process according to
the invention can be prepared analogously (or by other known
methods):

ethyl 5-chloro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 4,5,6-trichloro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 5,6-dichloro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 4,5-dichloro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 6-chloro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 4,6-dibromo-3-(2-pyridyl)indole-2-carboxylate,
ethyl 5-bromo-6-fluoro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 5,6-difluoro-3-(2-pyridyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(3-pyridyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(4-pyridyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-oxazolyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(3-isoxazolyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-pyrimidinyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(3-pyridazinyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-pyrazinyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(3-pyrazolyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-imidazolyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(3-isothiazolyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-thienyl)indole-2-carboxylate,
ethyl 6-bromo-5-chloro-3-(2-furanyl)indole-2-carboxylate, 
ethyl 6-bromo-5-chloro-3-(2-pyrrolyl)indole-2-carboxylate, and 
ethyl 6-bromo-5-chloro-3-(4-pyrimidinyl)indole-2-carboxylate.

The following Examples illustrate the preparation of com-

5 pounds of the formula I: 

EXAMPLE I

5-Bromo-5-chloro-2-[(methylsulfanyl)acetyl]-3-(2-pyridyl)in-
dole

Add 6.2 g. of sodium hydride in mineral oil (50%) to 50 ml. 
of dry dimethylsulfoxide at 15-25°C. and then heat at 60-70°C. 
for two hours under nitrogen. Cool the mixture to 20°C. and 
add a suspension of 15.2 g. of ethyl 6-bromo-5-chloro-3-(2-
-pyridyl)indole-2-carboxylate in 50 ml. of dimethylsulfoxide 
at 15-25°C. Stir the mixture at ambient temperature for a 

15 further hour, cool it to 15°C., add 10 ml. of water cautiously, 
and then add 190 ml. more. Filter, and add 10 ml. of 
acetic acid to the filtrate keeping the temperature below 
20°C. Decant to obtain the gray solid product; stir this 
with ether, filter it off, wash it with ether and dry it to 

20 obtain the title compound, m.p. 198-199°C. (dec.).

The following compounds can be produced similarly from the 
4-bromo-5-chloro isomer of Preparation 3 and from the list 
of compounds following Preparation 3:
4-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
4,5,6-trichloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
5,6-dichloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
4,5-dichloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
6-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
4,6-dibromo-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
5-bromo-6-fluoro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
5,6-difluoro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(4-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-oxazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-isoxazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyrimidinyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-pyridazinyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyrazinyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-pyrazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-imidazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-isothiazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-thiazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-thienyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-furanyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyrrolyl)indole,
6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(4-pyrimidinyl)indole.

EXAMPLE 2

6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole

Stir a mixture of 6.0 g. of 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole and 6.0 g. of m-chloroperbenzoic acid in 150 ml. of chloroform at room temperature for 2 hours. Concentrate the mixture to about 60 ml. in vacuo, filter off the product and wash it with 20 ml. of cold chloroform to obtain 6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole.
By replacing the 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole with the compounds obtained by the method of Example 1 and by substantially following the method of this Example, the following compounds are produced:

5 4-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole,
5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole, 4,5,6-trichloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole,
5,6-dichloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole, 4,5-dichloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole,
6-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole, 4,6-dibromo-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole,
5-bromo-6-fluoro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole, 5,6-difluoro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-pyridyl)indole, 6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(4-pyridyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-oxazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-isoxazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyrimidinyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-pyridazinyl) indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyrazinyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-pyrazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-imidazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-thiazolyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(3-isothiazolyl) indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-thienyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-furanyl)indole,
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyrrolyl)indole, and
6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(4-pyrimidinyl) indole.

**EXAMPLE 3**

6-Bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl) indole

To 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl) indole (2.5 g.) in 50 ml. of ethanol add 0.3 g. of sodium borohydride and, after a solution is obtained (about 10 mi-
nutes), stir the mixture for another 30 minutes. Slowly add 1 ml. of acetic acid and then add 100 ml. of water. Decant the liquid from the insoluble material, dissolve it in ethanol and add ether-hexane to obtain 6-bromo-5-chloro-2-[(1-

Replacing the 6-bromo-5-chloro-2-[(methylsulfanyl)acetyl]-3-(2-pyridyl)indole with the compounds obtained by the method of Example 1 and substantially following the method of this Example provides the following compounds:

10 4-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
4,5,6-trichloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole.
15 5,6-dichloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
4,5-dichloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
20 6-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
4,6-dibromo-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
5-bromo-6-fluoro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
5,6-difluoro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyridyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(3-pyridyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(4-pyridyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-oxazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(3-isoxazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyrimidinyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(3-pyridazinyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyrazinyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(3-pyrazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-imidazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(2-thiazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfinyl)ethyl]-3-(3-isothiazolyl)indole,
6-bromo-5-chloro-2-[(l-hydroxy-2-methylsulfinyl)ethyl]-3-(2-furanyl)indole,
6-bromo-5-chloro-2-[(l-hydroxy-2-methylsulfinyl)ethyl]-3-(2-pyrrolyl)indole, and
6-bromo-5-chloro-2-[(l-hydroxy-2-methylsulfinyl)ethyl]-3-(4-pyrimidinyl)indole.

**EXAMPLE 4**

6-Bromo-5-chloro-2-[(l-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole

To 6-bromo-5-chloro-2-[(methylsulfonyl)acetyl]-3-(2-pyridyl)indole (2.2 g.) in 75 ml. of ethanol add 0.175 g. of sodium borohydride. After a solution is obtained (about 10 minutes) stir the mixture for another 30 minutes, then slowly add 2 ml. of acetic acid. Treat with charcoal, filter, and add 100 ml. of water to the filtrate to obtain 6-bromo-5-chloro-2-[(l-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole.

Similarly, replacing the 6-bromo-5-chloro-2-[(2-methylsulfonyl)acetyl]-3-(2-pyridyl)indole with the compounds obtained by the method of Example 2 and substantially following the method of this Example provides the following compounds:

4-bromo-5-chloro-2-[(l-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole,
5-chloro-2-[(l-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole,
4,5,6-trichloro-2-[(l-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole,
5,6-dichloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
4,5-dichloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
6-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
4,6-dibromo-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
5-bromo-6-fluoro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
5,6-difluoro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyridyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(3-pyridyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(4-pyridyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-oxazolyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(3-oxazolyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyrimidinyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(3-pyridazinyl)indole, 
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyrazinyl)indole, 
25 6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyrazinyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(3-pyrazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-imidazolyl)indole,
5 6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-thiazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(3-isothiazolyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-thienyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-furanyl)indole,
6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(2-pyrrolyl)indole, and
15 6-bromo-5-chloro-2-[(1-hydroxy-2-methylsulfonyl)ethyl]-3-(4-pyrimidinyl)indole.

**EXAMPLE 5**

6-Bromo-5-chloro-3-(2-pyridyl)indole-2-glyoxal methyl hemimercaptal

20 Slowly add 15 ml. of 6N hydrochloric acid to 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole (2 g.) in dimethylsulfoxide (75 ml.), stir the resulting mixture for 3 hours, quench with ice water, and collect and dry the solid to yield 6-bromo-5-chloro-3-(2-pyridyl)indole-2-glyoxal methyl hemimercaptal.
Replacing the 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-\(\underline{\text{-}}\)-(2-pyridyl)indole with the compounds obtained by the method of Example 1 and substantially following the method of this Example provides the following compounds:

5-bromo-5-chloro-3-(2-pyridyl)indole-2-glyoxal methyl hemimercaptal,
5-chloro-3-(2-pyridyl)indole-2-glyoxal methyl hemimercaptal,
4,5,6-trichloro-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
5,6-dichloro-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
6-chloro-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
4,6-dibromo-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
5-bromo-6-fluoro-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
5,6-difluoro-3-(2-pyridyl)indole-2-glyoxal methyl mercaptal,
6-bromo-5-chloro-3-(3-pyridyl)indole-2-glyoxal methyl mercaptal,
6-bromo-5-chloro-3-(4-pyridyl)indole-2-glyoxal methyl mercaptal,
6-bromo-5-chloro-3-(2-oxazolyl)indole-2-glyoxal methyl mercaptal,
6-bromo-5-chloro-3-(3-isoxazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-pyrimidinyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(3-pyridazinyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-pyrazinyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-thiazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(3-pyrazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-imidazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-thiazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(3-isothiazolyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-thienyl)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-furany1)indole-2-glyoxal methyl hemimercaptal,
6-bromo-5-chloro-3-(2-pyrroly1)indole-2-glyoxal methyl hemimercaptal, and
6-bromo-5-chloro-3-(4-pyrimidinyl)indole-2-glyoxal methyl hemimercaptal.
EXAMPLE 6

6-Bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole

Add 2 ml. of concentrated hydrochloric acid to 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole (5.0 g.) in 50 ml. of methanol and 50 ml. of tetrahydrofuran and maintain the mixture at 60°C. for 2 hours. Cool, add water and collect and dry the resulting solid to obtain 6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole.

Replacing the 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole with the compounds obtained by the method of Example 1 and substantially following the method of this Example provides the following compounds:

4-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole,
5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole, 4,5,6-trichloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole, 5,6-dichloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole, 4,5-dichloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole, 6-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole, 4,6-dibromo-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole,
5-bromo-6-fluoro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole,
5,6-difluoro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyridyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(3-pyridyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(4-pyridyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-oxazolyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(3-isoxazolyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyrimidinyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(3-pyridazinyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyrazinyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(3-pyrazolyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-imidazolyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-thiazolyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(3-isothiazolyl)indole,
nylindole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-furanyl)indole,
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(2-pyrrolyl)indole, and
6-bromo-5-chloro-2-[(methylthio)(methoxy)acetyl]-3-(4-pyrimidinyl)indole.

Similarly, replacing the methanol of this Example with equivalent quantities of straight and branched-chain lower alcohols having up to six carbon atoms provides the corresponding 2-[(methylthio) (lower alkoxy)acetyl]-3-(2-pyridyl)indoles and other 3-heterocyclylindoles.

Also included within the scope of the foregoing examples, particularly Example 2, are the 4-oxazolyl, 5-oxazolyl, 4-isoxazolyl, 5-isoxazolyl, 4-pyrimidinyl, 5-pyrimidinyl, 4-pyridazinyl, 4-pyrazolyl, 4-imidazolyl, 4-thiazolyl, 5-thiazolyl, 4-isothiazolyl, 5-isothiazolyl, 3-thienyl, 3-furanyl and 3-pyrrolyl isomeric forms thereof.

Since about 1960, immunosuppressive agents have found widespread clinical application for treating diseases in which there is direct or indirect evidence for an immune etiology. Although treatment with corticosteroids has been successful in the clinical management of autoimmune diseases
and in suppressing rejection phenomena associated with organ transplantation, patients are rendered highly susceptible to infection by this treatment. Indeed, there is a higher incidence of mortality from infections among these patients than from the diseases themselves.

The use of corticosteroids in such treatment can be reduced or even obviated by the use of azathioprine or cyclophosphamide, but it has none the less been very difficult to develop therapeutic regimens that yield clinical improvement in the absence of undesired side effects, notably bone marrow depression. Moreover, both these drugs have a slow onset of action so that therapeutically beneficial effects appear only after about three weeks' treatment.

We have now discovered that the novel 3-heterocyclyl-indoles of this invention have advantageous properties that indicate their usefulness in the treatment of autoimmune diseases and in suppressing rejection phenomena associated with organ transplantation.

Thus the compounds of formula I inhibit antibody immune reactions and cell-mediated immune reactions. The antibody immune reactions include the immune response to sheep erythrocytes and the immune responses to trinitrophenylated liposaccharide in mice as assessed by the spleen assay of

From these tests and comparisons with known immunosuppressants, it may be determined that the compounds are effective in suppressing immune responses at about 0.5 to 50 mg./kg. mammalian body weight. Disease states against which the immunosuppressant activity of the compounds of this invention are useful include rheumatoid arthritis, ulcerative colitis, allergies, systemic lupus erythematosus, hemolytic anemia and Crohn's disease. In their use as immunosuppressants the compounds have low toxicity and in particular are substantially non-cytotoxic at therapeutic doses.

For oral administration, the compounds of this invention may be combined with inert pharmaceutical carriers or excipients such as lactose, mannitol and starch. For parenteral in-
jection, the compounds may be formulated with an inert, parenterally acceptable vehicle, such as water, saline or sesame oil. The formulations may be compounded according to methods well known to those skilled in the pharmaceutical art. Preferably the compounds are administered in 3-4 daily doses although the specific regimen will be dependent upon the severity and nature of the particular disease state.

The invention therefore provides pharmaceutical compositions comprising, as active ingredient, at least one compound of the formula I defined above in association with a suitable pharmaceutical carrier or excipient.

The compounds of the formula I can be administered in the form of dosage units, e.g., injectable dosage units in ampoules but in particular shaped dosage units such as tablets, capsules and suppositories. Dosage units conveniently contain from about 2 to about 300 mg., preferably 10 to 50 mg., of active compound of the formula I.
Example of a Pharmaceutical Preparation: Tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>For 10,000 tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient of formula I</td>
<td>250.0 g.</td>
</tr>
<tr>
<td>Lactose</td>
<td>1000.0 g.</td>
</tr>
<tr>
<td>Corn starch</td>
<td>680.0 g.</td>
</tr>
<tr>
<td>Corn starch as 10% paste</td>
<td>50.0 g.</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>20.0 g.</td>
</tr>
</tbody>
</table>

Mix the active ingredient, lactose and 600 g. of the corn starch, and pass through a pulverizing mill if necessary. Granulate the so-obtained mixture with the starch paste, adding additional water if necessary to make a damp granulation. Pass the granulation through an impact mill to produce 8-12 mesh granules. Spread the granulation on trays and dry in a draft-oven at 35-40°C. Reduce the dried granulation to 16-24 mesh size and blend it with the remaining 80.0 g. of corn starch and with the magnesium stearate until a uniform mixture is obtained. Compress to 200 mg. tablets containing 25 mg. of active ingredient.

In this Example, the active ingredient is preferably 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole, but may be any other compound of the formula I defined above, especially a compound named herein.
The claims defining the invention are as follows:

1. 2-Substituted-3-heterocyclyl-indoles of the formula

$$\text{Het}$$

$$\text{X}_n$$

$$\text{N}$$

$$\text{CQ.CHZ.SO}_m\text{CH}_3$$

wherein X is a hydrogen or halogen atom,

n is 1, 2 or 3 (when X is a halogen atom),

Q is an oxygen atom or the group (H,OH),

Z is a hydrogen atom or, provided that Q is an oxygen atom, Z can also be the group OR, wherein R is a hydrogen atom or a lower alkyl or loweralkoxy-loweralkyl group, "lower" indicating groups with 1 to 6 carbon atoms,

m is 1 or 2 when Z is a hydrogen atom and m is 0 when Z is the group OR,

and Het is a heterocyclic radical selected from pyridyl, lower-alkyl-substituted pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thienyl, furanyl, pyrrolyl, oxazolyl and iso-xazolyl.
2. Compounds as claimed in claim 1 wherein Het is a 3- or 4-pyridyl group or especially a 2-pyridyl group, or a 2-, 4- or 5-pyrimidinyl group, Q is an oxygen atom, Z is a hydrogen atom and m is 1, and $X_n$ represents two halogen atoms, preferably one chlorine and one bromine atom, especially a 5-chlorine and a 6-bromine atom.

3. 6-Bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole.

4. 5-Chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,

4-Bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole,

6-Bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(3-pyridyl)indole, and

6-Bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(4-pyrimidinyl) indole.

5. A process for the preparation of a compound claimed in claim 1, which comprises reacting a reactive derivative of an acid of the formula
wherein Het, X and \( n \) are as defined in claim 1

with an anion of the formula

\[
\text{III} \quad \ominus \text{CH}_2\cdot \text{SO}_m\cdot \text{CH}_3
\]

wherein \( m \) is 1 or 2,

in the presence of an anhydrous organic solvent and
under an inert atmosphere,

to yield a product of the formula

[Diagram of molecule II]

wherein Het, \( X, m \) and \( n \) are as defined in claim 1.

Whereafter, for the preparation of a compound of the formula I or IA wherein \( m \) is 2 when \( m \) in the product of the formula IA is 1, this product is oxidised.
and/or for the preparation of a compound of the formula I wherein Q is the group (H,OH), the product of the formula IA is reduced at the carbonyl group,
or, for the preparation of a compound of the formula I wherein Q is 0 and Z is the group OR wherein R is as defined in claim 1, a product of the formula IA wherein m is 1 is subjected to the action of acid in the presence of a solvent comprising the compound ROH.

6. A process as claimed in claim 5, wherein the reactive derivative is a lower alkyl ester, preferably an ethyl ester, and/or wherein the anion is present in excess, preferably in about 3 equivalents excess.

7. Pharmaceutical compositions containing as active ingredient at least one compound as claimed in any of claims 1 to 4 together with a pharmaceutical carrier or excipient.

8. Compositions as claimed in claim 7 in the form of dosage units, such as tablets, capsules or suppositories, especially dosage units containing from 2 to 300 mg. of active ingredient, preferably from 10 to 50 mg. of active ingredient.
9. Compositions as claimed in claim 7 in the form of injectable compositions.

10. Compositions as claimed in any of claims 7 to 9 wherein the active ingredient is 6-bromo-5-chloro-2-[(methylsulfinyl)acetyl]-3-(2-pyridyl)indole.

Dated this 28th day of September, 1979

SCHERING CORPORATION
By their Patent Attorneys
GRIFFITH, HASSEL & FRAZER.