We, Boehringer Ingelheim GmbH, a body corporate organized under the laws of the Federal Republic of Germany, of Ingelheim am Rhein, Federal Republic of Germany,

hereby apply for the grant of a Patent for an invention entitled "CHEMICAL PROCESS" which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered 78 11 735 for a patent or similar protection made in France, on 20th April, 1978.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 20th day of April, 1979.

Boehringer Ingelheim GmbH
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

To The Commissioner of Patents.
1. A process for the preparation of a compound of the formula:

\[
\begin{align*}
X & \quad \text{COOR}_1 \\
\text{CH}_2-\text{NH-CH-(CH}_2)_n-\text{S-R}_2 & \\
\text{NHR}_3 & \quad \text{Y}
\end{align*}
\]

[wherein X and Y, which may be the same or different, each represents a hydrogen or halogen atom;
R₁ represents a hydrogen atom or a lower, straight or branched alkyl group with 1 to 4 carbon atoms;
R₂ represents a hydrogen atom, a straight or branched alkyl group with 1 to 3 carbon atoms, a carboxyalkyl group (in which the alkyl moiety is a lower alkyl group) or an acyl group;]
R₃ represents a hydrogen atom or an acyl group; and
n is 1 or 2] or a salt thereof which comprises reducing
compound of the formula:

\[
\begin{array}{c}
\text{COOR}_1 \\
\text{X} \quad \text{CH=NH-(CH₂)ₙ-S-R₂} \\
\text{Y} \\
\text{NHR}_3
\end{array}
\]

(wherin X, Y, R₁, R₂, R₃ and n are as herein defined) or
a salt thereof whereby a compound of formula I as herein
defined is obtained.

12. A compound of formula I (as defined in claim 1) in
optically active form or a salt thereof.
Class:
Int. Cl:

Application Number:
Lodged:

Complete Specification—Lodged:
Accepted:
Published:

Priority:

Related Art:

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TO BE COMPLETED BY APPLICANT

Name of Applicant: Boehringer Ingelheim GmbH,
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Address of Applicant: Ingelheim am Rhein, Federal Republic of Germany.

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Complete Specification for the invention entitled: "CHEMICAL PROCESS"

The following statement is a full description of this invention, including the best method of performing it known to me—

Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 180 mm in width on tough white paper of good quality and it is to be inserted into this form.
Processes for the Preparation of Sulfur-Containing N-Benzyl Amino Acids

The present invention relates to processes for the preparation of sulfur-containing N-benzyl amino acids which possess interesting pharmacological properties. The present invention also relates to such compounds in optically active form. Processes for the production of sulfur containing N-benzyl amino acids have been described in French Patent No. 77 19825. On a laboratory scale, the processes described therein show satisfactory results, but when applied industrially there are a number of difficulties involved, especially, in the production of compounds of formula I in which X and/or Y represent halogen atoms.

Thus, for example, N-(2-amino-3,5-dibromobenzyl)-methionine of formula

\[
\text{Br} \quad \text{CH}_2 - \text{NH} - \text{CH} - \text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{Br} \quad \text{NH}_2 \\
\text{Br} \\
\text{COOH}
\]

is produced according to French Patent No. 7719825 by formation of the Schiff's base by reaction of o-nitrobenzaldehyde and methionine, followed by hydrogenation with sodium borohydride, subsequent reduction of the nitro group to the amino group and finally, by bromination.

If this process is applied on an industrial scale, a number of difficulties become apparent, in particular, the following:-
1) the relatively high price of \( p \)-nitrobenzaldehyde; 2) the need to effect reduction of the nitro group to the amino group using hydrogen under pressure and, 3) the necessity of separating out the desired product via columns since the bromination leads to the formation of secondary derivatives that must be eliminated.

The present invention is based on the discovery of a process for the preparation of sulfur-containing N-benzyl amino acids and the salts thereof which may readily be effected on an industrial scale using starting materials which are relatively easily obtainable and which may be obtained at a relatively low cost.

Thus according to one feature of the present invention there is provided a process for the preparation of a compound of the formula:

\[
\text{(1)}
\]

[wherein \( X \) and \( Y \), which may be the same or different, each represents a hydrogen or halogen atom; \( R_1 \) represents a hydrogen atom or a lower, straight or branched alkyl group with 1 to 4 carbon atoms; \( R_2 \) represents a hydrogen atom, a straight or branched alkyl group with 1 to 3 carbon atoms, a carboxyalkyl group in which the alkyl moiety is a lower alkyl group]
or an acyl group;
R₃ represents a hydrogen atom or an acyl group; an n is 1 or 2) or a salt thereof, which comprises reducing a compound of the formula

\[
\begin{align*}
X & \quad \text{COOR}_1 \\
\text{CH} = N - \text{CH} - (\text{CH}_2)_n \text{S} - R_2 \\
\text{NHR}_3 & \\
Y
\end{align*}
\]

wherein X,Y,R₁,R₂,R₃ and n are as herein defined) or a salt thereof, whereby a compound of formula I as herein defined is obtained.

A compound of formula II is preferably used in which R₂ represents a lower aliphatic acyl, e.g. a lower alkanoyl group and/or R₃ represents a lower aliphatic acyl, e.g. lower alkanoyl group.

The reduction is conveniently effected by the use of a metal hydride e.g. sodium borohydride, preferably in water and advantageously at a temperature of about 50°C.

The compound of formula II is preferably first prepared by reacting a compound of the formula:

\[
R_2 - \text{S} - (\text{CH}_2)_n - \text{CH} - \text{NH}_2
\]

(wherin R₁, R₂ and n are as hereinbefore defined) with a
compound of the formula:

\[
\begin{array}{c}
\text{X} \\
\text{CHO} \\
\text{Y} \\
\text{NHR}_3
\end{array}
\]

(wherin X, Y and R₃ are as hereinbefore defined whereby a compound of formula II (as hereinbefore defined) is obtained.

The reaction is preferably effected in the presence of a solvent such as for example ethanol, isopropanol or water, but especially methanol.

The compound of formula IV is preferably first prepared by reduction of a compound of the formula:

\[
\begin{array}{c}
\text{X} \\
\text{CONR}^1 \\
\text{NHR}_3 \\
\text{Y}
\end{array}
\]

(wherin X, Y and R₃ are as hereinbefore defined and CONR₁ represents a tertiary amide grouping) whereby a compound of formula IV (as hereinbefore defined) is obtained. The reduction is conveniently effected by the use of lithium aluminium hydride.

The compound of formula V is preferably first prepared by reacting a secondary amine with a compound of the formula:
(wherein $R_3$, $X$ and $Y$ as hereinbefore defined and $\text{Hal}$ represents a halogen atom) whereby a compound of formula $V$ is obtained. A compound of formula $VI$ is preferably used in which $\text{Hal}$ represents a chlorine atom. The reaction is preferably effected in the presence of a basic acid acceptor e.g. triethylamine.

The compound of formula $VI$ is preferably first prepared by halogenating a compound of the formula:

![Diagram](wherein $X$, $Y$ and $R_3$ are as hereinbefore defined) whereby a compound of formula $VI$ (as hereinbefore defined) is obtained. Where it is desired to prepare a compound of formula $VI$ in which $\text{Hal}$ represents a chlorine atom, the compound of formula $VII$ is preferably reacted with thionyl chloride. The acid chloride is conveniently prepared by effecting the reaction in the presence of a benzylated or chlorinated inert solvent such as benzene or chloroform.

In an alternative embodiment the compound of formula $IV$ is
preferably first prepared by oxidation of a compound of the formula:

\[
\begin{array}{c}
\text{X} \\
\text{O} \\
\text{Y} \\
\text{NHR}_3 \\
\text{CH}_2\text{OH}
\end{array}
\]

(wherein X, Y and R$_3$ are as hereinbefore defined) whereby a compound of formula VIII as hereinbefore defined is obtained. The oxidation is conveniently effected by the use of a metal oxidising agent e.g. a metal oxide preferably manganese dioxide. If R$_3$ represents a hydrogen atom, oxidation of the alcohol is, for example, effected, within the aldehyde, by the manganese dioxide, due to the presence of the NH$_2$-group conveniently in the presence of an apolar solvent such as chloroform, dichloroethane, dichloromethane; chloroform being preferred.

Where R$_3$ represents a hydrogen atom and it is desired that R$_3$ represents an acyl group acylation of the NH$_2$ group may be effected with the alcohol of formula VIII.

The compound of formula VIII is preferably first prepared by reduction of a compound of formula VII (as hereinbefore defined whereby a compound of formula VIII (as hereinbefore defined is obtained).

Reduction of the compound of formula VII to the corresponding alcohol may be performed according to different processes, which allow for transformation of an acid into the corresponding alcohol. Thus, for example, the reduction...
may be effected by catalytic hydrogenation e.g. by using hydrogen gas under pressure in the presence of a hydrogenation catalyst, such as a metal oxide; electrolysis of a sulfur solution with lead electrodes; reduction by metal hydrides, such as, for example, LiAlH₄ or diborane B₄H₆ e.g. prepared in situ. The reduction by means of diborane is to be preferred.

The compound of formula VII (wherein at least one of X and Y represents a halogen atom) is preferably first prepared by halogenating a compound of formula VII (where X and Y each represent a hydrogen atom) whereby a compound of formula VII (wherein at least one of X and Y represents a halogen atom) is obtained.

In a particularly preferred embodiment the process is effected as a stepwise synthesis starting from anthranilic acid. The stepwise synthesis may readily be effected on an industrial scale. Thus the synthesis is preferably effected as follows:-

A) the anthranilic acid is halogenated, if required;
B) the anthranilic acid, or halogenated derivative obtained according to (A) is transformed into the corresponding aldehyde;
C) the aldehyde obtained according to (B) is reacted with an amino compound of formula

\[
R_2S-(CH_2)_n-CH-NH_2
\]

(III)
(wherein \( R_1, R_2 \) and \( n \) are as hereinbefore defined) to form the corresponding Schiff's base; and
D) the Schiff's base obtained according to (C) is reduced to give the compound of formula I.

We have found that the process of the present invention is particularly of interest for the production of compounds of general formula I, wherein \( X \) and/or \( Y \) represent a chlorine, bromine or iodine atom and, in particular, for the production of the following compounds:

- \( \text{N-[(2-amino)-benzyl]methionine,} \)
- \( \text{N-[(2-amino-5-bromo)benzyl]methionine,} \)
- \( \text{N-[(2-amino-3,5-dibromo)benzyl]methionine,} \)
- \( \text{N-[(2-amino)benzyl]-S-methyl-cysteine,} \)
- \( \text{N-[(2-amino-5-bromo)benzyl]-S-methylcysteine,} \)
- \( \text{N-[(2-amino-3,5-dibromo)benzyl]-S-methylcysteine,} \)
- \( \text{N-[(2-amino)benzyl]-S-carboxymethylcysteine,} \)

The compounds of formula I exist in racemic and optically active (e.g. laevorotatory) form. The optically active compounds of formula I may, for example, be prepared from optically active compounds of formula II. The compounds of formula II are preferably prepared by reacting the compound of formula IV with an optically active compound of formula III. The optically active compounds of formula I may thus be obtained in high yield and purity.

In this connection we have found that optically active
e.g. the laevorotatory, compounds of formula I possess an enhanced mucolytic activity when compared with the racemic compound.

According to a further feature of the present invention there is provided a compound of formula I (as hereinbefore defined) in optically active form or a salt thereof. The optically active isomer is preferably the (-)-isomer. A particularly preferred compound of the present invention is L-N-(2-amino-3,5-dibromobenzyl) methionine or a salt thereof. The salt is preferably a salt with a basic amino acid. The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention as active ingredient together with a pharmaceutical carrier or excipient.

The following Examples illustrate the invention.
Example 1
Production of N-(2-amino-3,5-dibromo-benzyl)methionine via a tertiary amide

$\text{COOH}$

$\text{NH}_2$

(A)

$\text{COOH}$

$\text{NH}_2$

$\text{Br}$

$\text{Br}$

$\text{SOCl}_2$

$\text{Br}$

$\text{Br}$

(C)

anthranilic acid

$\text{C}_6\text{H}_5\text{NH}\left(\text{CH}_3\right)$

$\text{CON}\left(\text{CH}_3\right)\text{C}_6\text{H}_5$

$\text{NH}_2$

$\text{AlLiH}_4$

$\text{CHO}$

$\text{NH}_2$

(B)

(D)

(E)

methionine

$\text{NaBH}_4$

$\text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCOOH}$

$\text{Br}$

$\text{Br}$

(F)

$\text{Br}$

$\text{Br}$

N-(2-amino-3,5-dibromobenzyl)methionine
Bromination

Anthranilic acid (0.5 mol) in 350 g of methanol is heated to 40°C with stirring. Bromine (1 mol) is added slowly. It is cooled and filtered. The 3,5-dibromo-anthranilic acid is obtained in an 80% yield.

Preparation of the Aldehyde (E)

Preparation of anilide (D)

0.2 mol of 3,5-dibromo-anthranilic acid are heated in 200 ml of benzene with 0.4 mol of thionyl chloride for two hours. The solvent is partly distilled and a solution of N-methyl-aniline in benzene (0.2 mol) and triethylamine (0.1 mol) is added dropwise. After filtration, the triethylamine chlorohydrate is evaporated in order to precipitate the anilide (D). Yield of anilide: 95%.

Preparation of the aldehyde (E)

The 2-amino-3,5-dibromo-N-methylanilide (0.024 mol) is treated with lithium aluminium hydride (0.016 mol) at room temperature in tetrahydrofuran (70 ml). The product is hydrolyzed with dilute sulfuric acid. The tetrahydrofuran is then eliminated and the aldehyde (E) comprising 20% of the corresponding alcohol is precipitated in water. It is separated by filtering and dried. Yield: 60%.
Production of the Schiff's Base (E) and the reduction thereof:

0.12 mol of 2-amino-3,5-dibromo-benzaldehyde, 0.12 mol of soda and 0.12 mol of methionine are added to a 10% methanol solution and this is heated for 2 hours to 50°C. Then, 80 ml of water are added and the methanol is evaporated. Sodium borohydride is added in a very slight excess (5.3 g). It is stirred either overnight at room temperature or for 2 hours at 50°C.

Then, the aqueous phase is acidified to pH 3, whereby a precipitate is formed which is carefully washed with water of pH 3. 0.10 mol of the product are obtained. Yield: 95%, melting point: 198°C (with one mol of water). Yield based on anthranilic acid used is 35%.

Example 2
Production of N-(2-Amino-3,5-dibromobenzyl)methionine via 3,5-dibromo-anthranil alcohol

Bromination

This reaction step is carried out as described in Example 1.

Preparation of the aldehyde (E)

Preparation of alcohol

A solution of 0.04 mol of boron trifluoride etherate in 15 ml of tetrahydrofuran is added slowly to a solution of 0.03 mol of sodium borohydride and 0.01 mol of 3,5-dibromo-anthranilic acid in 25 ml of tetrahydrofuran cooled to 10°C. The mixture is refluxed for 2 hours; the alcohol is separated by hydrolysis and the tetrahydrofuran is evaporated. (Precipitation of the aqueous phase).

With reference to the acid, the yield amounts to almost 100%.
Preparation of the aldehyde (E)

28 g (0.1 mol) of 3,5-dibromo-anthranil alcohol with 200 ml of chloroform and 70 g of manganese oxide. The mixture is refluxed for 3 hours. It is filtered and the solvent is evaporated. The aldehyde is obtained without a trace of the alcohol. The yield is almost quantitative, if the loss during evaporation of the solvent is restricted to a minimum.

Preparation of the Schiff's Base and the reduction thereof

As described in Example 1.

Yield based on the anthranilic acid used as starting material is 68%.

Example 3

Production of N[(2-Aminobenzyl)methionine via anthranil alcohol

Anthranilic acid (0.1 mol) in a tetrahydrofuran solution is treated with diborane (0.3 mol). After hydrolysis and precipitation, the anthranil alcohol is obtained in a yield of 90%.

Anthranil aldehyde:

The obtained alcohol is treated in a chloroform solution with an excess of manganese dioxide. After refluxing for 3 hours, it is filtered and the aldehyde is obtained in a yield of 85%.

N[(2-Amino)-benzyl]methionine

0.1 mol of anthranil aldehyde and 0.1 mol of methionine are stirred for several hours in a soda solution (50 ml of water comprising 0.1 mol of sodium hydroxide solution).
When all solids are dissolved, 0.1 mol of sodium borohydride is added. The mixture is then stirred for 12 hours at room temperature. By acidifying to pH 3 the derivative precipitates and is then dried in a dryer. The yield amounts to 85%, the melting point is 198°C. The yield based on the anthranilic acid used is 68%.

Example 4
Production of (optically active) L-N-(2-amino-3,5-
dibromobenzyl)-methionine

0.12 mol of 2-amino-3,5-dibromobenzaldehyde, 0.12 mol of soda and 0.12 mol of L-methionine are added to 100 ml of methanol and heated to 50°C for 2 hours. 80 ml of water are added and the methanol is allowed to evaporate. Then a very slight excess (5.3 g) of sodium borohydride is introduced, and the mixture is stirred overnight at room temperature. The aqueous phase is acidified at pH 3, whereby a precipitate is formed which is washed carefully with water at pH 3. The yield amounts to 75% (0.9 mol). The optical rotation is -237.4° (C = 1% in 0.1 N NaOH). The melting point is 204°C.
The claims defining the invention are as follows:

1. A process for the preparation of a compound of the formula:

\[
\begin{align*}
X & \quad \text{COOR}_1 \\
\text{CH}_2 \text{-NH-CH-(CH}_2)_n \text{-S-R}_2 & \quad \text{NHR}_3
\end{align*}
\]

(\text{I})

[wherein \( X \) and \( Y \), which may be the same or different, each represents a hydrogen or halogen atom; \( R_1 \) represents a hydrogen atom or a lower, straight or branched alkyl group with 1 to 4 carbon atoms; \( R_2 \) represents a hydrogen atom, a straight or branched alkyl group with 1 to 3 carbon atoms, a carboxyalkyl group (in which the alkyl moiety is a lower alkyl group) or an acyl group; \( R_3 \) represents a hydrogen atom or an acyl group; and \( n \) is 1 or 2] or a salt thereof which comprises reducing compound of the formula:

\[
\begin{align*}
X & \quad \text{COOR}_1 \\
\text{CH=N-CH-(CH}_2)_n \text{-S-R}_2 & \quad \text{NHR}_3
\end{align*}
\]

(\text{II})

(wherein \( X, Y, R_1, R_2, R_3 \) and \( n \) are as herein defined) or a salt thereof whereby a compound of formula I as herein defined is obtained.
2. A process as claimed in claim 1 wherein the compound of formula II is first prepared by reacting a compound of the formula:

\[
\text{COOR}_1
\]
\[
R_2 - S - (\text{CH}_2)_n - \text{CH} - \text{NH}_2
\]  

(wherein \( R_1 \), \( R_2 \) and \( n \) are as defined in claim 1) with a compound of the formula:

\[
\begin{align*}
X & \quad \text{CHO} \\
Y & \quad \text{NHR}_3
\end{align*}
\]  

(wherein \( X \), \( Y \) and \( R_3 \) are as defined in claim 1) whereby a compound of formula II (as defined in claim 1) is obtained.

3. A process as claimed in claim 2 wherein the compound of formula IV is first prepared by reduction of a compound of the formula:

\[
\begin{align*}
X & \quad \text{CONR}_2 \\
Y & \quad \text{NHR}_3
\end{align*}
\]  

(wherein \( X \), \( Y \) and \( R_3 \) are as defined in claim 1 and \(-\text{CONR}_2\) represents a tertiary amide grouping) whereby a compound of formula IV (as defined in claim 2) is obtained.
4. A process as claimed in claim 3 wherein the compound of formula V is first prepared by reacting a secondary amine with a compound of the formula:

```
X  COHal  
    |      
    Y    
NHR₃
```

(wherein R₃, X and Y are as defined in claim 1 and Hal represents a halogen atom) whereby a compound of formula V is obtained.

5. A process as claimed in claim 4 wherein the compound of formula VI is first prepared by halogenating a compound of the formula:

```
X  COOH  
    |      
    Y    
NHR₃
```

(wherein X, Y and R₃ are as defined in claim 1) whereby a compound of formula VI (as defined in claim 4) is obtained.

6. A process as claimed in claim 3 wherein the compound of formula IV is first prepared by oxidation of a compound of the formula:

```
X  CH₂OH  
    |      
    Y    
NHR₃
```
(wherein X, Y and R₃ are as defined in claim 1) whereby a compound of formula IV (as defined in claim 2) is obtained.

7. A process as claimed in claim 6 for the preparation of compound of the formula VIII (wherein R₃ represents an acyl group) in which a compound of formula VIII (wherein R₃ represents a hydrogen atom) is acylated whereby a compound of formula VIII (wherein R₃ represents a acyl group) is obtained.

8. A process as claimed in claim 6 or claim 7 wherein the compound of formula VIII is first prepared by reduction of a compound of formula VII (as defined in claim 5) whereby a compound of formula VIII (as defined in claim 6) is obtained.

9. A process as claimed in claim 5 or claim 8 wherein the compound of formula VII (wherein at least one of X and Y represents a halogen atom) is first prepared by halogenating a compound of formula VII (wherein X and Y each represent a hydrogen atom) whereby a compound of formula VII (wherein at least one of X and Y represents a halogen atom) is obtained.

10. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 4.

11. A compound of formula I as defined in claim 1 when prepared by a process as claimed in any one of the preceding claims.

12. A compound of formula I (as defined in claim 1)
in optically active form or a salt thereof.

13. A compound as claimed in claim 12 in the form of the (−) isomer thereof.

14. L-\(N-(2\text{-amino}-3,5\text{-dibromobenzyl})\) methionine and the salts thereof.

15. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in optically active form or a physiologically compatible salt thereof as active ingredient together with pharmaceutical carrier or excipient and each and every novel process, compound, composition or feature herein disclosed either individually or collectively.

DATED this 20th day of April, 1979.

Boehringer Ingelheim GmbH
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

[Signature]