

PATENT SPECIFICATION

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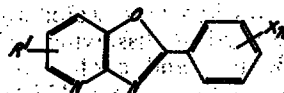


(54) OXAZOLO [4,5-b] PYRIDINES

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

This invention is concerned with oxazolo[4,5-b]pyridines.

The novel compounds of the present invention have the general formula:

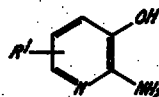


in which n is 1, 2 or 3, each X , which may be the same as or different from any other X , is a halogen atom or a C_{1-3} alkyl, C_{1-3} alkoxy or trifluoromethyl group; and R' is a hydrogen atom or a C_{1-3} alkyl group.

Among compounds in accordance with the present invention are:

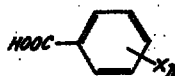
- 2-(3-*t*-butylphenyl)oxazolo[4,5-b]pyridine,
- 2-(3,5-di-*t*-butylphenyl)oxazolo[4,5-b]pyridine,
- 2-(2-methyl-3-chlorophenyl)oxazolo[4,5-b]pyridine,
- 2-(2-methyl-3-methoxyphenyl)oxazolo[4,5-b]pyridine,
- 2-(3-methyl-5-*t*-butylphenyl)oxazolo[4,5-b]pyridine,
- 2-(3,5-di-*t*-butylphenyl)-5-methyloxazolo[4,5-b]pyridine, and
- 2-(3-chloro-2-methylphenyl)-5-methyloxazolo[4,5-b]pyridine.

In accordance with the present invention, the novel compounds are prepared by heating a pyridine compound of formula:



I

and a carboxylic acid of formula:



II

in which R' , X and n are as defined above, with polyphosphoric acid at a temperature in the range 100 to 300°C for a period of from 5 minutes to 2 hours.

In a preferred method of carrying out this procedure, a mixture of the pyridine and a slight excess of the carboxylic acid, in the presence of

polyphosphoric acid, is heated for from 5 minutes to one hour at a temperature in the range 130°C. to 230°C. The polyphosphoric acid is decomposed with water, and the desired product is obtained by making the solution alkaline.

Oxazolopyridines of this invention are particularly useful as topical anti-inflammatories in the treatment of dermatological disorders such as sunburn, atopic dermatitis, contact dermatitis, eczema of the hands and feet, including dyshidrosis and pompholyx, nummular eczema, neurodermatitis, lichen simplex chronicus, eczematous dermatitis, lichen planus, infantile eczema, psoriasis, seborrheic dermatitis, otitis externa, stasis dermatitis, insect bites, exfoliative dermatitis, acute actinic dermatitis, cheilitis, eczematoid mycotic dermatitis, food eczema, neurotic excoriations, postanal surgery, pruritus with lichenification, anogenital pruritus, intertrigo, miliaria, and diaper rash. They are characterized in having a rather low order of activity in the usual carrageenin induced rat foot edema test following systemic administration, and an unusually high order of activity as inhibitors of prostaglandin synthetase. Their low systemic activity is the result of rapid metabolism which provides the distinct advantage of eliminating the danger of common anti-inflammatory side effects after absorption of these compounds following topical administration.

For topical use creams, ointments, gels, solutions or suspensions containing the active component are used. The compositions include from 0.01% to 0.25% of active ingredient, preferably about 0.1% by weight in admixture with a suitable topical vehicle.

The following Examples illustrate the invention.

Example 1

2-(2-Methyl-3-chlorophenyl)oxazolo[4,5-b]pyridine

A mixture of 3.4 g. of 2-methyl-3-chlorobenzoic acid and 1.0 g. of 2-amino-3-hydroxypyridine was ground in a mortar and intimately mixed with 17 g. of polyphosphoric acid. The gummy mixture, under nitrogen, was slowly heated over 75 minutes to 178°C. with stirring. The resulting solution was poured slowly into 300 ml. of ice-water with stirring. After 1 hour the precipitate was collected and added with stirring to dilute sodium hydroxide solution. After 15 minutes the precipitate was collected, washed with water and dried to give 2.1 g. of crude product. This was recrystallized by dissolving in 75 ml. of cyclohexane, filtering, concentrating to about 50 ml., and cooling to give 1.76 g. of 2-(2-methyl-3-chlorophenyl)oxazolo[4,5-b]-pyridine, m.p. 118.5–120°C.

Carrying out the procedure of Example 1 but substituting for the 2-methyl-3-chlorobenzoic acid and the 2-amino-3-hydroxypyridine used therein, equimolar amounts of the substituted benzoic acids and the aminohydroxypyridines, respectively, identified in Table I, there were produced the 2-(substituted phenyl)oxazolo[4,5-b]pyridines also identified in Table I, in accordance with the following equation:



TABLE I

R	R'	m.p. (°C.)
2-chloro-3-methylphenyl	H	75—77
3,5-dimethylphenyl	H	155—157
3-isopropoxyphenyl	H	68.5—70.5
3-t-butyl-5-methylphenyl	H	131—132
2-methyl-3-methoxyphenyl	H	138—141
2-methyl-3-chlorophenyl	6—CH ₃ —	139—143
3-iodophenyl	H	172—176
2-chloro-3-methoxyphenyl	H	165.5—167
3-fluoro-2-methylphenyl	H	98—100
3-chloro-5-methylphenyl	H	121—123
3-methyl-5-methoxyphenyl	H	
2-methyl-3-trifluoromethyl-phenyl	H	
2-chloro-3-ethylphenyl	H	
3-t-butylphenyl	H	124—126
3,5-di(t-butyl)phenyl	6—CH ₃ —	161—163

Example 2.

2-(3-Chloro-2,5-dimethylphenyl)oxazolo[4,5-b]pyridine

5 Step A: Preparation of 3-amino-2,5-dimethylbenzoic Acid
2,5-Dimethyl-3-nitrobenzoic acid (10.0 g.) was hydrogenated in 200 ml. of methanol in the presence of 0.5 g. of 5% palladium on carbon. The catalyst was removed on a filter and the filtrate was concentrated to dryness to give 8.3 g. of 3-amino-2,5-dimethylbenzoic acid, m.p. 145.5—146.5°C.

10 Step B: Preparation of 3-chloro-2,5-dimethylbenzoic acid
A slurry of 4.95 g. of amino compound from Step A in 25 ml. of 6 N hydrochloric acid was cooled in an ice-acetone bath (–3 to 0°C.) and a solution of 2.3 g. of sodium nitrite in 6 ml. of water was added in 0.5 ml. portions over about 20 minutes. After about 1 hour at 0 to 5°C. the mixture was poured into a solution of 4 g. of cuprous chloride in 25 ml. of concentrated hydrochloric acid at 1°C. After 0.5 hour at 1 to 2°C., 2 hours at room temperature, 1 hour at 60°C. and 15 hours at room temperature, the precipitate was collected, washed with water and dried to give 4.5 g. of 3-chloro-2,5-dimethylbenzoic acid, m.p. 167.5—170°C.

20 Step C: Preparation of 2-(3-chloro-2,5-dimethylphenyl)oxazolo[4,5-b]pyridine
Following the procedure substantially as described in Example 1, but substituting for the 2-methyl-3-chlorobenzoic acid used therein, a molar equivalent of 3-chloro-2,5-dimethylbenzoic acid, there was produced 2-(3-chloro-2,5-dimethylphenyl)oxazolo[4,5-b]pyridine, m.p. 99.5—101°C.

Example 3.

2-(2-Chloro-5-*t*-butylphenyl)oxazolo[4,5-*b*]pyridineStep A: Preparation of 5-*t*-butyl-2-nitrobenzoic acid

3-*t*-Butylbenzoic acid (7.0 g.) was added portionwise over 50 minutes to 50 ml. of fuming red nitric acid at -5°C . with stirring. After 15 minutes at 0°C ., the mixture was poured into ice-water and after stirring for 15 minutes the precipitate was collected and washed with water (m.p. $128-134^{\circ}\text{C}$.). This (12 g.) was dissolved in 65 ml. ethanol, filtered, heated to 70°C . and water added to about 400 ml. volume. After cooling the precipitate was collected, washed with water and dried (9.55 g.). This was extracted with 200 ml. of warm cyclohexane and the insoluble material was collected to give 6.4 g. of 5-*t*-butyl-2-nitrobenzoic acid, m.p. $137-139^{\circ}\text{C}$.

Step B: Preparation of 2-amino-5-*t*-butylbenzoic acid

The nitro compound from Step A (6.2 g.) was hydrogenated in 100 ml. of methanol over 0.5 g. of 5% palladium on carbon. The catalyst was removed on a filter and the filtrate was concentrated to dryness to give 5.0 g. of 2-amino-5-*t*-butylbenzoic acid, m.p. $142-145^{\circ}\text{C}$. resolidifying and remelting at 151°C .

Step C: Preparation of 2-chloro-5-*t*-butylbenzoic acid

The amino compound (3.86 g.) from Step B was stirred in 25 ml. of 6 *N* hydrochloric acid and at -2°C . a solution of 1.6 g. of sodium nitrite in 3 ml. of water was added over 0.5 hour. After an additional 0.5 hour at 0°C . the mixture was poured into 2.7 g. of cuprous chloride in 20 ml. of concentrated hydrochloric acid at 0°C . After 0.5 hour at 0°C . and 0.5 hour at room temperature, the precipitate was collected, washed with water and dried to give A (0.17 g., m.p. $88-94^{\circ}\text{C}$.). The filtrate plus a little copper powder was heated at 100°C . for 0.5 hour and cooled. The precipitate was collected, dissolved in sodium hydroxide and re-precipitated by adding hydrochloric acid. This material was collected, washed with water and dried to give B (3.15 g., m.p. $99-103^{\circ}\text{C}$.). A and B were combined and recrystallized from 20 ml. of *n*-hexane to give 1.6 g. of 2-chloro-5-*t*-butylbenzoic acid, m.p. $106-108.5^{\circ}\text{C}$.

Step D: Preparation of 2-(2-chloro-5-*t*-butylphenyl)oxazolo[4,5-*b*]pyridine

By the procedure substantially as described in Example 1, but substituting for the 2-methyl-3-chlorobenzoic acid used therein a molar equivalent of 2-chloro-5-*t*-butylbenzoic acid, there was obtained 2-(2-chloro-5-*t*-butylphenyl)oxazolo[4,5-*b*]pyridine, m.p. $111-112^{\circ}\text{C}$.

Example 4.

2-(3-*t*-Butyl-5-methoxyphenyl)oxazolo[4,5-*b*]pyridineStep A: Preparation of 3-*t*-butyl-5-methoxybenzoic acid

A mixture of 2.8 g. of potassium hydroxide in 9 ml. of water, 17.1 g. of pyridine and 5.0 g. of 3-*t*-butyl-5-methoxytoluene was heated in an oil bath at 95°C . With rapid stirring 11.1 g. of potassium permanganate was added over 2 hours and heating at 95°C . was continued for 1.5 hours more. After cooling to room temperature 5 ml. of alcohol was added. The mixture was filtered and the filtrate was shaken with 100 ml. ether to give 3 layers. The bottom layer (50 ml.) and middle layer (25 ml.) were collected separately, each was concentrated to about 1/2 volume, and acidified to pH 2 with 4*N* sulfuric acid. The precipitates were collected, washed with water, and air dried to give respectively 0.6 g. and 1.1 g. of crude product, m.p. $75-85^{\circ}\text{C}$. which, after combining and recrystallizing from 10 ml. of acetic acid and 5 ml. of water, gave 0.85 g. of 3-*t*-butyl-5-methoxybenzoic acid, m.p. $84-87^{\circ}\text{C}$.

Step B: Preparation of 2-(3-*t*-butyl-5-methoxyphenyl)oxazolo[4,5-*b*]pyridine

A mixture of 6.0 g. of polyphosphoric acid, 0.8 g. of 3-*t*-butyl-5-methoxybenzoic acid, and 0.46 g. of 2-amino-3-hydroxypyridine under nitrogen was placed in a pre-heated oil bath at 150°C . After about 12 minutes of stirring, the melt was poured into 100 ml. of an ice slurry. The precipitated gum was taken up in methylene chloride, washed with 1×20 ml. of 2.5 *N* sodium hydroxide and 1×25 ml. of water, dried over magnesium sulfate, filtered, and concentrated to oil which crystallized to give 0.8 g. of product, which after recrystallization from *n*-hexane gave 0.5 g. of 2-(3-*t*-butyl-5-methoxyphenyl)oxazolo[4,5-*b*]pyridine, m.p. $119-121^{\circ}\text{C}$.

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Example 5.
Gel Formulation

5 0.1 mg. disodium edetate
1.30 mg. of water
300 mg. isopropanol
26 mg. hydroxypropylcellulose
q.s.a.d. 1 gm. propylene glycol
1.09 mg. 2-(2-methyl-3-chlorophenyl)oxazolo[4,5-b]pyridine

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Example 6.
Ointment Formulation

10 50 mg. wool alcohols B.P.
150 mg. Amerchol C (*Amerchol* is a trade mark).
350 mg. wax white Be square 170/175°C.
q.s.a.d. 1 gm. isopropyl myristate
15 1.09 mg. 2-(2-chloro-3-methylphenyl)oxazolo[4,5-b]pyridine
0.4% citric acid anhydrous
0.58% sodium phosphate dibasic anhydrous

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Example 7.
Solution Formulation

20 84.9 gm. ethanol
12.0 gm. propylene glycol
3.0 gm. methyl salicylate
0.1 gm. 2-(3,5-di-*t*-butylphenyl)oxazolo[4,5-b]pyridine

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Example 8.

25 2-[3,5-di(*t*-butyl)phenyl]oxazolo[4,5-b]pyridine
A mixture of 30 g. of polyphosphoric acid, 5.0 g. of 3,5-di(*t*-butyl)benzoic acid
and 2.1 g. of 2-amino-3-hydroxypyridine, under nitrogen and with rapid stirring,
was heated at 180°C. for 40 minutes. The mixture was poured into 500 ml. of an
ice-water mixture. The mixture was adjusted to pH 8.0 with concentrated
30 ammonium hydroxide and stirred until the precipitate was finely divided. The
precipitate was collected on a filter, washed with 2 x 100 ml. of water, and dried.
The crude product was dissolved in 200 ml. of *n*-hexane, treated with decolorizing
carbon, filtered and concentrated to about 75 ml. On cooling, the product
crystallized to give 3.5 g. of 2-[3,5-di(*t*-butyl)phenyl]oxazolo[4,5-b]pyridine, m.p.
35 154—156°C.

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Example 9.

40 2-[3,5-Di(isobutyl)phenyl]oxazolo[4,5-b]pyridine
Step A: Preparation of 2-[3,5-di(bromomethyl)phenyl]oxazolo[4,5-b]pyridine
A mixture of 10 millimoles of 2-(3,5-dimethylphenyl)oxazolo[4,5-b]pyridine
and 21 millimoles of N-bromosuccinimide in 50 ml. of carbon tetrachloride was
stirred and irradiated with a sun lamp for 45 minutes. The insolubles were removed
by filtration and the filtrate was concentrated to dryness with a stream of nitrogen
and the residue is triturated with 25 ml. of methanol. The crude 2-[3,5-di(bromo-
methyl)phenyl]oxazolo[4,5-b]pyridine was collected.

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45 Step B: Preparation of 2-[3,5-di(2-methylallyl)phenyl]oxazolo[4,5-b]pyridine
A mixture of 5 millimoles of the product from Step A and 11.0 millimoles of
triphenylphosphine in 15 ml. of dimethylformamide was stirred and refluxed
under nitrogen for 3 hours. The mixture was cooled and the phosphonium salt is
collected on a filter. A mixture of 4 millimoles of the phosphonium salt, 100 ml. of
50 ethanol, 1 ml. of acetone and 40 ml. of 0.3 *N* ethanolic lithium ethoxide was stirred
at room temperature under nitrogen for 2 hours. Water (100 ml.) was added and
the mixture was cooled in an ice-bath. The precipitate was collected and purified
by chromatography on silica gel using 2% methanol in chloroform as the eluant to
give 2-[3,5-di(2-methylallyl)phenyl]oxazolo[4,5-b]pyridine.

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55 Step C: Preparation of 2-[3,5-di(isobutyl)phenyl]oxazolo[4,5-b]pyridine
The product from Step B (3 millimoles) was hydrogenated in 25 ml. of
methanol in the presence of 500 mg. of 5% palladium on carbon under 3
atmospheres of hydrogen. The catalyst is removed by filtration and the filtrate is
concentrated to dryness. The residue is recrystallized from *n*-hexane to give 2-[3,5-
60 di(isobutyl)phenyl]oxazolo[4,5-b]pyridine.

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Example 10.

2-(3-*t*-Butyl-2-methoxyphenyl)oxazolo[4,5-*b*]pyridineStep A: Preparation of 3-*t*-butyl-2-methoxytoluene

A mixture of 0.12 mole of 2-*t*-butyl-6-methylphenol and 12.0 ml. of 10.0 N sodium hydroxide solution was stirred and heated on the steam bath for 1 hour. The water is evaporated *in vacuo*. The residue was added portion-wise with stirring to 0.24 mole of dimethyl sulfate and the mixture was stirred at 95°C. for 6 hours and at room temperature for 15 hours. Sodium carbonate (0.25 mole) in 100 ml. of water was added and stirring continued for 5 hours. The mixture was extracted with 3 x 100 ml. of ether and the extract dried and concentrated to dryness to give 3-*t*-butyl-2-methoxytoluene.

Step B: Preparation of 3-*t*-butyl-2-methoxybenzoic acid

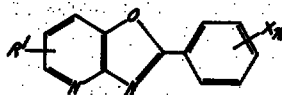
A mixture of 0.01 mole of 3-*t*-butyl-2-methoxytoluene, 0.01 mole of potassium permanganate, and 100 ml. of 1 N sodium hydroxide solution was heated to reflux and another 0.01 mole of potassium permanganate was added each hour until a total of 0.05 mole had been added (4 hours). After another 2 hours of reflux the unreacted starting material was steam distilled. Ethanol was added to the residue to decompose excess of permanganate and the mixture was filtered hot. Acidification with sulfuric acid of the filtrate caused precipitation of the product, which was collected, washed with water and dried to give 3-*t*-butyl-2-methoxybenzoic acid.

Step C: Preparation of 2-(3-*t*-butyl-2-methoxyphenyl)oxazolo[4,5-*b*]pyridine

By the procedure of Example 1 but substituting for the 2-methyl-3-chlorobenzoic acid used therein an equivalent amount of 3-*t*-butyl-2-methoxybenzoic acid, there was produced 2-(3-*t*-butyl-2-methoxyphenyl)oxazolo[4,5-*b*]pyridine.

WHAT WE CLAIM IS:—

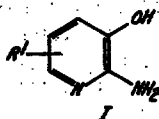
1. A compound of formula:



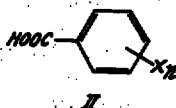
in which *n* is 1, 2 or 3, each X, which may be the same as or different from any other X, is a halogen atom or a C₁₋₃ alkyl, C₁₋₃ alkoxy or trifluoromethyl group; and R' is a hydrogen atom or a C₁₋₃ alkyl group.

2. 2-(3-*t*-Butylphenyl)oxazolo[4,5-*b*]pyridine.
3. 3-(3,5-Di-*t*-butylphenyl)oxazolo[4,5-*b*]pyridine.
4. 2-(2-Methyl-3-chlorophenyl)oxazolo[4,5-*b*]pyridine.
5. 2-(2-Methyl-3-methoxyphenyl)oxazolo[4,5-*b*]pyridine.
6. 2-(3,5-Di-*t*-butylphenyl)-5-methyloxazolo[4,5-*b*]pyridine.
7. 2-(3-Chloro-2-methylphenyl)-5-methyloxazolo[4,5-*b*]pyridine.
8. 2-(3-Methyl-5-*t*-butylphenyl)oxazolo[4,5-*b*]pyridine.
9. 2-(3-*t*-Butyl-5-methoxyphenyl)oxazolo[4,5-*b*]pyridine.

10. A method of preparing a compound as claimed in Claim 1, that comprises heating a pyridine compound of formula:



and a carboxylic acid of formula:



in which R', X and *n* are as defined in Claim 1, with polyphosphoric acid at a temperature in the range 100 to 300°C for a period of from 5 minutes to 2 hours.

Example 10.

2-(3-t-Butyl-2-methoxyphenyl)oxazolo[4,5-b]pyridine

Step A: Preparation of 3-t-butyl-2-methoxytoluene

A mixture of 0.12 mole of 2-t-butyl-6-methylphenol and 12.0 ml. of 10.0 N sodium hydroxide solution was stirred and heated on the steam bath for 1 hour. The water is evaporated *in vacuo*. The residue was added portion-wise with stirring to 0.24 mole of dimethyl sulfate and the mixture was stirred at 95°C. for 6 hours and at room temperature for 15 hours. Sodium carbonate (0.25 mole) in 100 ml. of water was added and stirring continued for 5 hours. The mixture was extracted with 3 x 100 ml. of ether and the extract dried and concentrated to dryness to give 3-t-butyl-2-methoxytoluene.

Step B: Preparation of 3-t-butyl-2-methoxybenzoic acid

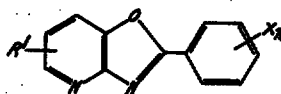
A mixture of 0.01 mole of 3-t-butyl-2-methoxytoluene, 0.01 mole of potassium permanganate, and 100 ml. of 1 N sodium hydroxide solution was heated to reflux and another 0.01 mole of potassium permanganate was added each hour until a total of 0.05 mole had been added (4 hours). After another 2 hours of reflux the unreacted starting material was steam distilled. Ethanol was added to the residue to decompose excess of permanganate and the mixture was filtered hot. Acidification with sulfuric acid of the filtrate caused precipitation of the product, which was collected, washed with water and dried to give 3-t-butyl-2-methoxybenzoic acid.

Step C: Preparation of 2-(3-t-butyl-2-methoxyphenyl)oxazolo[4,5-b]pyridine

By the procedure of Example 1 but substituting for the 2-methyl-3-chlorobenzoic acid used therein an equivalent amount of 3-t-butyl-2-methoxybenzoic acid, there was produced 2-(3-t-butyl-2-methoxyphenyl)oxazolo[4,5-b]pyridine.

WHAT WE CLAIM IS:—

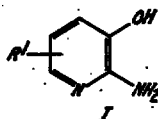
1. A compound of formula:



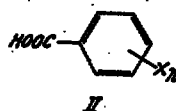
in which n is 1, 2 or 3, each X , which may be the same as or different from any other X , is a halogen atom or a C_{1-3} alkyl, C_{1-3} alkoxy or trifluoromethyl group; and R' is a hydrogen atom or a C_{1-3} alkyl group.

2. 2-(3-t-Butylphenyl)oxazolo[4,5-b]pyridine.
3. 3-(3,5-Di-t-butylphenyl)oxazolo[4,5-b]pyridine.
4. 2-(2-Methyl-3-chlorophenyl)oxazolo[4,5-b]pyridine.
5. 2-(2-Methyl-3-methoxyphenyl)oxazolo[4,5-b]pyridine.
6. 2-(3,5-Di-t-butylphenyl)-5-methyloxazolo[4,5-b]pyridine.
7. 2-(3-Chloro-2-methylphenyl)-5-methyloxazolo[4,5-b]pyridine.
8. 2-(3-Methyl-5-t-butylphenyl)oxazolo[4,5-b]pyridine.
9. 2-(3-t-Butyl-5-methoxyphenyl)oxazolo[4,5-b]pyridine.

10. A method of preparing a compound as claimed in Claim 1, that comprises heating a pyridine compound of formula:



and a carboxylic acid of formula:



in which R' , X and n are as defined in Claim 1, with polyphosphoric acid at a temperature in the range 100 to 300°C for a period of from 5 minutes to 2 hours.



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11. A method as claimed in Claim 10, in which the temperature is in the range 130 to 230°C, the time ranges from 5 minutes to 1 hour, and a slight excess of the compounds of formula II is used.
- 5 12. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound claimed in Claim 2. 5
13. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound claimed in Claim 3.
14. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound claimed in Claim 4.
- 10 15. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound as claimed in Claim 5. 10
16. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound as claimed in Claim 6.
- 15 17. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound as claimed in Claim 7. 15
18. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound as claimed in Claim 8.
19. A method as claimed in Claim 10 or 11, as applied to the preparation of the compound as claimed in Claim 9.
- 20 20. A method as claimed in Claim 10, substantially as hereinbefore described in any one of Examples 1 to 4, 8 and 10. 20
21. A compound as claimed in Claim 1 when prepared by a method as claimed in any one of Claims 10 to 20.
- 25 22. A pharmaceutical formulation for topical application comprising a carrier and a compound as claimed in any one of Claims 1 to 9 and 21. 25
23. A formulation as claimed in Claim 22 in the form of a cream, gel, ointment, solution or suspension.
24. A formulation as claimed in Claim 22 or 23, containing 0.01 to 0.25% by weight of the said compound.
- 30 25. A formulation as claimed in Claim 24, containing about 0.1% by weight of the said compound. 30
26. A formulation as claimed in Claim 22, substantially as hereinbefore described in any one of Examples 5 to 7.

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which copies may be obtained.



* C L M S *

ERRATUM

SPECIFICATION No. 1,475,426

Page 1, Heading, (54), for [4,5-6] read
[4,5-b]

THE PATENT OFFICE
14th November, 1977

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