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# PATENT SPECIFICATION

953,876

NO DRAWINGS

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(Divided out of No. 953,875.)
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SEE ERRATA SLIP ATTACHED

Index at acceptance:—C2 C(2B3A4, 2B3B, 2B3G4, 2B3G5)

International Classification:—C 07 d

COMPLETE SPECIFICATION

## Preparation of 4-Amino-5-(Lower Alkoxy)-Methyl-2-Propyl-Pyrimidines

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company, of 124—194, Grenzacherstrasse, Basle, Switzerland, 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 relates to the preparation of 4 - amino - 5 - (lower alkoxy) - methyl - 2 - propyl - pyrimidines.

The present invention provides a process for preparing 4 - amino - 5 - (lower alkoxy) - methyl - 2 - propyl - pyrimidines by reacting butyramidine hydrochloride [obtained by the action of hydrogen chloride, a lower alkanol such as methanol or ethanol, and ammonia on butyronitrile] with an alkali metal salt (e.g. the sodium salt) of a lower alkyl $\alpha$ - (lower alkoxy) - methyl - $\beta$ - hydroxy - acrylate [obtained by interaction of a lower alkyl acrylate, a lower alkyl formate and an alkali metal lower alkoxide (e.g. sodium methoxide or ethoxide)], treating the resulting 4 - hydroxy - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine with phosphorus oxychloride and aminating the 4 - halogeno - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine thus obtained with concentrated ammonia under pressure to form a 4 - amino - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine. Examples of lower alkyl formates and lower alkyl acrylates which can be used are methyl and ethyl formates and methyl and ethyl acrylates respectively.

The term "lower" as used herein in relation to alkoxy and alkyl radicals means such radicals containing from 1 to 7 carbon atoms and in relation to alkanols, alkoxides and alkylating agents means such compounds containing from 1 to 7 carbon atoms in the molecule.

According to an embodiment of this process butyramidine hydrochloride [$CH_3CH_2CH_2$—C(NH)—$NH_2$,HCl] is first prepared from butyronitrile [i.e. propyl-cyanide, $CH_3CH_2CH_2CN$] by treatment with hydrogen chloride, a lower alkanol and ammonia in accordance with well known procedures. Methyl acrylate and methyl formate are then condensed with the aid of sodium methoxide to form the sodium salt of methyl $\alpha$ - methoxymethyl - $\beta$ - hydroxy acrylate [$CH_3$—$OCH_2$—C(CH—ONa)—CO—$OCH_3$]. This acrylate is then reacted with the butyramidine hydrochloride to form 4 - hydroxy - 5 - methoxymethyl - 2 - propyl - pyrimidine. This compound is converted to the corresponding 4 - chloro - 5 - methoxymethyl - 2 - propyl - pyrimidine by treatment with phosphorus oxychloride [$POCl_3$]. The 4 - chloro - 5 - methoxymethyl - 2 - propyl - pyrimidine is then treated with concentrated aqueous ammonia under an elevated pressure to form 4 - amino - 5 - methoxymethyl - 2 - propyl - pyrimidine.

The present invention also includes a process for preparing 4 - amino - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidines by reacting acrylonitrile with a lower alkyl formate (such as methyl or ethyl formate) in the presence of an alkali metal lower alkoxide (such as sodium methoxide or ethoxide) alkylating the resulting alkali metal salt of $\alpha$-(lower alkoxy) methyl-$\beta$-hydroxy-acrylonitrile with a lower alkylating agent and reacting the $\alpha$ - (lower alkoxymethyl - $\beta$ - (lower alkoxy) - acrylonitrile thus obtained with butyramidine. A convenient procedure consists in reacting acrylonitrile with

[*Price 4s. 6d.*]

SPECIFICATION AMENDED - SEE ATTACHED SLIP

a lower alkanol such as methanol or ethanol in the presence of a basic agent and condensing the resulting β-alkoxy-propionitrile with a lower alkyl formate. Because of the tendency of lower alkyl formates, especially methyl formate, to undergo decomposition to a lower alkanol and carbon monoxide, it is advantageous to carry out the reaction with the lower alkyl formate in the presence of carbon monoxide under pressure. The resulting alkali metal salt of an α - (lower alkoxy) - methyl - β - hydroxy - acrylonitrile is then alkylated with a lower alkylating agent such as a lower alkyl halide (e.g. methyl or ethyl iodide) or a lower dialkyl sulphate (e.g. dimethyl or diethyl sulphate). The α - (lower alkoxy) - methyl - β - (lower alkoxy) - acrylonitrile thus obtained is then condensed with butyramidine.

In accordance with a preferred embodiment of the invention acrylonitrile is condensed with methyl formate to form a α - methoxymethyl - β - hydroxy - acrylonitrile. This reaction is carried out using approximately molar amounts of the starting materials and employing sodium methoxide in an inert organic diluent as condensing agent. The sodium methoxide is preferably used in a slight excess over the molar quantity, for example in an amount of 1.1 mols. Inert organic diluents which can be used include aromatic and aliphatic hydrocarbons boiling below 70°C. at 5 mm. absolute pressure. Examples of such diluents are benzene, toluene, hexane and heptane. The reaction takes place readily at room temperature. Under these conditions, the product formed is the sodium salt of α - methoxymethyl - β - hydroxy - acrylonitrile [$CH_3O—CH_2—C(CH—ONa)—CN$]. For the reasons set forth hereinbefore it is advantageous to carry out the condensation between acrylonitrile and methyl formate in the presence of gaseous carbon monoxide under a pressure between about 10 and about 20 atmospheres, preferably about 14 atmospheres. This use of carbon monoxide under pressure leads to higher yields of the desired sodium salt of α - methoxymethyl - β - hydroxy - acrylonitrile. This sodium salt is then converted by methylation with dimethyl sulphate to α - methoxymethyl - β - methoxy - acrylonitrile. The dimethyl sulphate is conveniently used in an amount of about 1 mol (preferably in a slight excess, e.g. from 1.1 to 1.2 mols per mol of the sodium salt). The α - methoxymethyl - β - methoxy - acrylonitrile is then condensed with butyramidine hydrochloride in the presence of sodium methoxide to form 2 - propyl - 4 - amino - 5 - methoxymethyl - pyrimidine. This reaction requires essentially molar amounts of the three materials, although a slight excess of sodium methoxide may advantageously be used.

The invention is further illustrated by the following Examples without being limited thereto.

EXAMPLE 1

To 691 grams of dry butyronitrile, cooled by a brine bath to 5°C. in an all glass 5-litre apparatus, there are added 1000 grams of a solution of hydrogen chloride in absolute ethanol, saturated at room temperature. The addition is made with stirring in increments of 100 grams, maintaining the temperature at 5°C. and not permitting the temperature in the charge to rise above 10°C. When all the ethanolic hydrogen chloride has been added, dry hydrogen chloride is bubbled in from a cylinder at the rate of 100 grams per hour for 3 hours, holding the temperature at 50°C. The temperature is then allowed to rise to 15—25°C., after which the charge is allowed to stand for 16 hours. The excess hydrogen chloride is then removed by subjecting the system at 25°C. to vacuum of 10 mm. of mercury absolute pressure and keeping under this vacuum for at least 2 hours. The charge is then cooled to 0°C.

An alcoholic ammonia solution is prepared by passing ammonia from a cylinder into absolute ethanol at 5°C. until the pressure is finally 10 psig. The ammonia solution is cooled to 0°C. The alcoholic ammonia solution is added to the butyronitrile/5 (hydrogen chloride) reaction product which is the imino-ether hydrochloride [$CH_3CH_2CH_2—C(NH)—OCH_2CH_3,HCl$]. Alcoholic ammonia is added until the excess hydrogen chloride has been neutralised and the temperature is allowed to rise to about 60°C. After standing for an hour, the product is filtered through a warmed filter kept at 60°—65°C. and the clear solution is concentrated under vacuum, warming the solution to 60°C. and finally at 10 mm. of Hg. absolute pressure until the charge reaches 70°C. The residual charge is cooled to 50°C. 1800 grams of heptane added with stirring and the temperature allowed to drop to ambient (25°C.) while agitating. The product is filtered on the centrifuge and the solid is spun as dry as possible and dried in a vacuum drier at 60°C. It is butyramidine hydrochloride. The yield is 90% of theoretical.

One hundred grams of sodium are dispersed in 1000 grams of heated, predried white oil, under a nitrogen blanket, to form sodium sand at about 140°C. Then 1000 grams of methanol are added, still under nitrogen blanket, to form sodium methoxide,

cooled to 25°C. and then a mixture of 167 grams of methyl acrylate and 261 grams of methyl formate is run in gradually with cooling under a nitrogen blanket. To this mixture is added 405 grams of butyramidine hydrochloride with stirring. The mixture is agitated carefully and 1200 ml of water (ice-water at 0—5°C.) are added, with agitation, and finally a litre of concentrated ammonia is added, and the charge is held at 0°C. overnight. The layers are permitted to separate and the temperature allowed to rise to room temperature. The aqueous layer is carefully separated, the oil layer is washed with water, and the washings are added to the water layer. The aqueous solution is filtered to remove oil particles.

The solution is evaporated under vacuum to remove 25% of its volume and thus to remove volatile materials. The residue is diluted with an amount of water to bring it back to its original volume and the pH is adjusted to 5.5 with strong hydrochloric acid, and 200 ml. of strong hydrochloride acid is added in excess.

Evaporation under vacuum is carried out until the volume is reduced to 55% of the original volume, the concentrated solution is cooled to 25°C. and the solution is allowed to crystallise. The crystals are centrifuged, washed with a little cold water, and the product is dried at 70°C. in vacuo. The yield is 210 grams of 4 - hydroxy - 5 - methoxy - methyl - 2 - propyl - pyrimidine.

To 500 grams of 4 - hydroxy - 5 - methoxymethyl - 2 - propyl - pyrimidine in a flask there are added 1120 grams of phosphorus oxychloride, and the mixture is warmed slowly to 80°C. and held at that temperature for 1 hour. It is then cooled to 30°C. and evacuated under a vacuum of 50 mm. of mercury. After holding for 1 hour, it is warmed slowly while maintaining vacuum to remove excess phosphorus oxychloride. It is cooled to 30°C. and transferred to 1500 grams of crushed ice, pH adjusted to about 8.5 with ammonia water and it is extracted 4 times each with 600 ml. of chloroform. The united chloroform extracts are distilled under vacuum of about 200 mm. of mercury absolute pressure at a temperature not exceeding 70°C. The vacuum is then increased to an absolute pressure not exceeding 10 mm. of mercury. A forerun is collected to about 115°C., and the main product comes over above this and is collected until the temperature drops. The weight of product is 510 grams of 4-chloro-5-methoxymethyl-2-propyl-pyrimidine.

To a 5-litre stainless steel autoclave charge containing 625 ml. of concentrated ammonia water is added 90 grams of 4-chloro-5-methoxymethyl-2-propyl-pyrimidine and then 1800 ml. of aditional concentrated ammonia water. The autoclave is closed and heated to 90°C. The heat is cut off and the temperature rises to about 125°C., and the pressure rises to 150 psig. after about half an hour. The charge is cooled to 30°C., and the charge is transferred to a tank and the autoclave is washed with 500 ml. of water. The washings are added to the main charge. The aqueous ammoniacal charge is extracted 6 times each with a litre of chloroform, and the combined extracts are concentrated under a vacuum of about 200 mm. of mercury absolute pressure below 40°C. until the residue becomes stiff. The vacuum is then raised to 100 mm. of mercury absolute pressure and the temperature to 70°C. The residue after removal of volatile components is cooled to 30°C. and sufficient xylene is added to make a filterable slurry. The slurry is filtered, washed with a little xylene, and the solid finally dried at 50°C. in vacuum. The yield is 77 grams of 4-amino-5-methoxymethyl-2-propyl-pyrimidine.

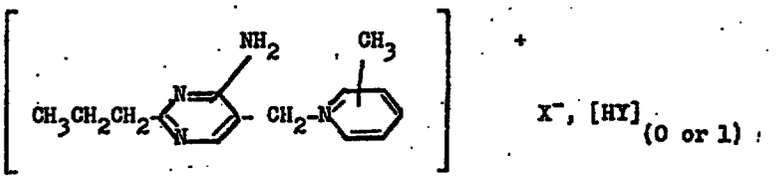
## EXAMPLE 2

In a 1.5 litre stainless steel autoclave equipped with agitator, reflux condenser and heating means, there is formed a suspension of 23 grams of sodium in 500 ml. of dry toluene with constant agitation and under reflux. After half an hour, the charge is cooled to room temperature and 32 grams of dry methanol are added slowly, with agitation, holding the temperature at about 70°C. with gentle refluxing. After the sodium is completely dissolved, the mixture is cooled to room temperature (ca. 25°C.) and a mixture of 48 grams of acrylonitrile and 67.5 grams of methyl formate is added, with agitation. The autoclave is then flushed out with carbon monoxide and finally pressurised with carbon monoxide to 14 atmospheres and is agitated overnight. A considerable drop in pressure occurs, to about 10 atmospheres, by morning. The pressure is released and 150 grams of dimethyl sulphate are added with agitation and the temperature is raised slowly to 50°C. with constant agitation in the course of 4 hours. The charge is then cooled to 25°C. and is carefully transferred to a 2 litre separating funnel. The autoclave is washed with 200 ml. of 0.5. sodium hydroxide solution and the washings are transferred to the separating funnel. The funnel is carefully swirled and allowed to settle. The aqueous layer is carefully drawn off and discarded. The charge is washed twice more with 200 ml. of 0.5% sodium hydroxide solution, and then three

times with 200 ml. of water to remove excess dimethyl sulphate and water-soluble components. The wet toluene layer is then carefully dried by distilling *in vacuo* at 40°C. or lower, whereby the water is first removed and then the toluene. The residual oil is then distilled at 5 mm. of mercury absolute pressure. The material distilling to 80°C. is rejected as forerun. The fraction coming over at 88°—102°C. at 5 mm. pressure is α-methoxymethyl-β-methoxy-acrylonitrile. There remains a small undistilled residue. The yield of desired product is 61 grams, about 52% on the acrylonitrile.

A solution is prepared from 11.5 grams of sodium and 265 ml. of methanol. When the sodium is completely dissolved there are added 61.3 grams of dry butyramidine hydrochloride and then 64.1 grams of α - methoxymethyl - β - methoxy - acrylonitrile. This mixture is heated to reflux (about 71°C.) for 3 hours, and then concentrated *in vacuo* to remove methanol completely. The oil is heated with 125 grams of 50% sodium hydroxide solution in a boiling water bath for 2 hours. The mixture is cooled to room temperature and extracted 4 times each with 150 ml. of chloroform. The combined chloroform extracts are concentrated on the water bath. To the residue 500 ml. of xylene are added and the mixture is concentrated to about 110 ml., and then is cooled overnight at room temperature. The slurry is filtered and dried in the oven at 60°C. under vacuum for 4 hours. The yield is 68 grams of 4 - amino - 5 - methoxymethyl - 2 - propyl - pyrimidine, about 75.1% of theory.

Our co-pending Application No. 16121/60 (Serial No. 953,875) claims compounds of the general formula:




wherein X and Y are identical or different halogen atoms and processes for the manufacture thereof.

WHAT WE CLAIM IS:—

1. A process for preparing 4 - amino - 5 - (lower alkoxy) - methyl - 2 - propyl - pyrimidines by reacting butyramidine hydrochloride [obtained by the action of hydrogen chloride, a lower alkanol and ammonia on butyronitrile] with an alkali metal salt of a lower alkyl α - (lower alkoxy) - methyl - β - hydroxy acrylate [obtained by interaction of a lower alkyl acrylate, a lower alkyl formate and an alkali metal lower alkoxide], treating the resulting 4 - hydroxy - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine with phosphorus oxychloride and aminating the 4 - halogen - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine thus obtained with concentrated ammonia under pressure.

2. A process as claimed in claim 1, wherein butyramidine hydrochloride is reacted with the sodium salt of methyl α - methoxy - methyl - β - hydroxy acrylate [obtained by the condensation of methyl acrylate with methyl formate in the presence of sodium methoxide], the resulting 4 - hydroxy - 5 - methoxymethyl - 2 - propyl - pyrimidine treated with phosphorus oxychloride and the resulting 4 - chloro - 5 - methoxymethyl - 2 - propyl - pyrimidine reacted with ammonia to form 4 - amino - 5 - methoxymethyl - 2 - propyl - pyrimidine.

3. A process for preparing 4 - amino - 5 - (lower alkoxy)methyl - 2 - propyl - pyrimidines by reacting acrylonitrile with a lower alkyl formate in the presence of an alkali metal lower alkoxide, alkylating the resulting alkali metal salt of an α - (lower alkoxy)methyl - β - hydroxy - acrylonitrile with a lower alkylating agent and reacting the α - (lower - alkoxymethyl - β - (lower alkoxy) - acrylonitrile thus obtained with butyramidine.

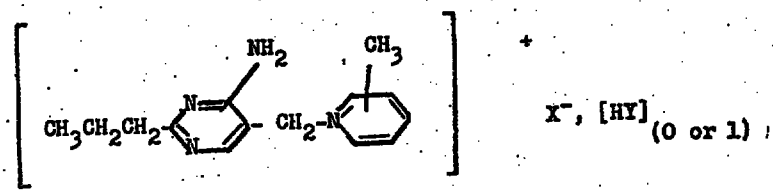
4. A process in accordance with claim 3, for preparing a 4 - amino - 5 - (lower alkoxy)methyl - 2 - propyl pyrimidine by reacting acrylonitrile reacted with a lower alkanol in the presence of a basic agent condensing the resulting β-(lower alkoxy)-propionitrile with a lower alkyl formate in the presence of an alkali metal lower alkoxide, alkylating the resulting alkali metal salt of α - (lower alkoxy)methyl - β - hydroxy - acrylonitrile with a lower alkylating agent and reacting the α - (lower alkoxy - methyl) - β - (lower alkoxy)acrylonitrile thus obtained with butyramidine.

5. A process as claimed in claim 3 or 4, wherein the sodium salt of α - methoxymethyl - β - hydroxy - acrylonitrile is produced by using acrylonitrile, methyl formate

times with 200 ml. of water to remove excess dimethyl sulphate and water-soluble components. The wet toluene layer is then carefully dried by distilling *in vacuo* at 40°C. or lower, whereby the water is first removed and then the toluene. The residual oil is then distilled at 5 mm. of mercury absolute pressure. The material distilling to 80°C. is rejected as forerun. The fraction coming over at 88°—102°C. at 5 mm. pressure is α-methoxymethyl-β-methoxy-acrylonitrile. There remains a small undistilled residue. The yield of desired product is 61 grams, about 52% on the acrylonitrile.

A solution is prepared from 11.5 grams of sodium and 265 ml. of methanol. When the sodium is completely dissolved there are added 61.3 grams of dry butyramidine hydrochloride and then 64.1 grams of α - methoxymethyl - β - methoxy - acrylonitrile. This mixture is heated to reflux (about 71°C.) for 3 hours, and then concentrated *in vacuo* to remove methanol completely. The oil is heated with 125 grams of 50% sodium hydroxide solution in a boiling water bath for 2 hours. The mixture is cooled to room temperature and extracted 4 times each with 150 ml. of chloroform. The combined chloroform extracts are concentrated on the water bath. To the residue 500 ml. of xylene are added and the mixture is concentrated to about 110 ml., and then is cooled overnight at room temperature. The slurry is filtered and dried in the oven at 60°C. under vacuum for 4 hours. The yield is 68 grams of 4 - amino - 5 - methoxymethyl - 2 - propyl - pyrimidine, about 75.1% of theory.

Our co-pending Application No. 16121/60 (Serial No. 953,875) claims compounds of the general formula:




wherein X and Y are identical or different halogen atoms and processes for the manufacture thereof.

WHAT WE CLAIM IS:—

1. A process for preparing 4 - amino - 5 - (lower alkoxy) - methyl - 2 - propyl - pyrimidines by reacting butyramidine hydrochloride [obtained by the action of hydrogen chloride, a lower alkanol and ammonia on butyronitrile] with an alkali metal salt of a lower alkyl α - (lower alkoxy) - methyl - β - hydroxy acrylate [obtained by interaction of a lower alkyl acrylate, a lower alkyl formate and an alkali metal lower alkoxide], treating the resulting 4 - hydroxy - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine with phosphorus oxychloride and aminating the 4 - halogen - 5 - [(lower alkoxy) - methyl] - 2 - propyl - pyrimidine thus obtained with concentrated ammonia under pressure.

2. A process as claimed in claim 1, wherein butyramidine hydrochloride is reacted with the sodium salt of methyl α - methoxy - methyl - β - hydroxy acrylate [obtained by the condensation of methyl acrylate with methyl formate in the presence of sodium methoxide], the resulting 4 - hydroxy - 5 - methoxymethyl - 2 - propyl - pyrimidine treated with phosphorus oxychloride and the resulting 4 - chloro - 5 - methoxymethyl - 2 - propyl - pyrimidine reacted with ammonia to form 4 - amino - 5 - methoxymethyl - 2 - propyl - pyrimidine.

3. A process for preparing 4 - amino - 5 - (lower alkoxy)methyl - 2 - propyl - pyrimidines by reacting acrylonitrile with a lower alkyl formate in the presence of an alkali metal lower alkoxide, alkylating the resulting alkali metal salt of an α - (lower alkoxy)methyl - β - hydroxy - acrylonitrile with a lower alkylating agent and reacting the α - (lower - alkoxymethyl - β - (lower alkoxy) - acrylonitrile thus obtained with butyramidine.

4. A process in accordance with claim 3, for preparing a 4 - amino - 5 - (lower alkoxy)methyl - 2 - propyl pyrimidine by reacting acrylonitrile reacted with a lower alkanol in the presence of a basic agent condensing the resulting β-(lower alkoxy)-propionitrile with a lower alkyl formate in the presence of an alkali metal lower alkoxide, alkylating the resulting alkali metal salt of α - (lower alkoxy)methyl - β - hydroxy - acrylonitrile with a lower alkylating agent and reacting the α - (lower alkoxy - methyl) - β - (lower alkoxy)acrylonitrile thus obtained with butyramidine.

5. A process as claimed in claim 3 or 4, wherein the sodium salt of α - methoxymethyl - β - hydroxy - acrylonitrile is produced by using acrylonitrile, methyl formate

* C L M S *

and sodium methoxide as the reactants, the resulting sodium salt is methylated and the α - methoxymethyl - β - methoxyacrylonitrile thus obtained reacted with butyramidine to form 4 - amino - 5 - methoxymethyl - 2 - propylpyrimidine.

6. A process as claimed in any one of claims 3 to 5 inclusive, wherein the condensation with a lower alkyl formate is carried out in a carbon monoxide atmosphere under pressure.

7. A process as claimed in claim 5 or 6, wherein the condensation of acrylonitrile with methyl formate is carried out in the presence of sodium methoxide in an inert organic diluent and in a carbon monoxide atmosphere under a pressure between about 10 and about 20 atmospheres to form the sodium derivative of α - methoxymethyl - β - hydroxy - acrylonitrile.

8. A process as claimed in claim 5, wherein the methylation of α - methoxymethyl - β - hydroxy - acrylonitrile is brought about by reacting the sodium salt thereof with dimethyl sulphate.

9. A process as claimed in claim 5, wherein the reaction between the α-methoxymethyl-β-methoxy-acrylonitrile and butyramidine is carried out in the presence of sodium methoxide.

10. A process for preparing 4-amino-5-(lower alkoxy)-methyl-2-propyl-pyrimidines substantially as described with reference to either of the Examples.

11. 4-Amino-5-(lower alkoxy)methyl-2-propyl-pyrimidines when prepared by the process claimed in any one of the preceding claims.

12. 4-Amino-5-methoxymethyl-2-propyl-pyrimidine when prepared by the process claimed in any one of the preceding claims 1 to 10 inclusive.

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## ERRATA

SPECIFICATION No. 953,876

Page 1, line 2, *for* "194" *read* "184"
Page 1, line 25, *for* "CM3" *read* "CH3"
Page 2, line 50, *delete* "5"
Page 3, line 13, *for* "hydrochloride" *read* "hydrochloric"
Page 3, line 34, *for* "aditional" *read* "additional"

THE PATENT OFFICE
*1st February 1965*

SPECIFICATION NO. 953,876

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of MERCK & CO. INC., of Rahway, New Jersey, United States of America, a corporation organised and existing under the laws of the State of New Jersey, United States of America.

THE PATENT OFFICE

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