948,860

PATENT SPECIFICATION

NO DRAWINGS

948,860

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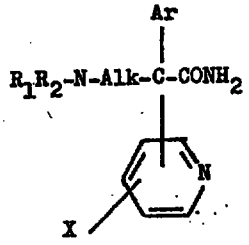
International Classification:—C 07 d.

COMPLETE SPECIFICATION

ω-Amino-2-Aryl-2-Pyridylalkanamide Derivatives

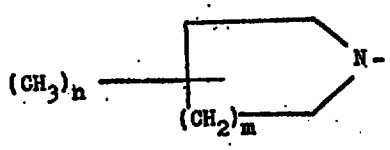
We, G. D. SEARLE & Co., a corporation organised and existing under the laws of the State of Delaware, United States of America, of P.O. Box 5110, Chicago 80, Illinois, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to ω-amino-2-aryl-2-pyridylalkanamide derivatives and provides novel compounds of the general formula



(I)

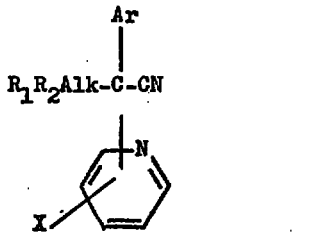
wherein X is a hydrogen or chlorine atom; Ar is a phenyl, tolyl, xylyl, naphthyl, halophenyl, anisyl, dimethoxyphenyl or pyridyl radical; Alk is an ethylene or trimethylene radical; R_1R_2N— is a tertiary amino radical of the general formula $(alkyl)_2N$— or a cyclic amino radical of the general formula



wherein the alkyl group contains 3 carbon atoms, *m* is 1 to 3, and *n* is 1 to 4, and acid addition and quaternary ammonium salts thereof.

The compounds of formula (I) above possess valuable pharmacological properties. In particular, they possess quinidine-like eurhythmic activity, e.g. they cause aconitine nitrate or electrically-induced arrhythmias to revert to a normal sinus rhythm. They do not cause some of the undesirable side-effects of quinidine. In addition, the dialkylamino derivatives have the ability to reduce hexobarbital sleep time, while the cyclic amino derivatives have the ability to reduce the intensity of tremorine effects. The cardio-regularity effects of the compounds of this invention commend their use in the treatment of various cardiac dysfunctions associated with rhythm changes of the heart caused by disturbances in the regular automacity or conductance pattern of its beat.

The ω - amino - 2 - aryl - 2 - pyridylalkanamide derivatives of Formula (I) are prepared by the hydration of an ω - amino - 2 - aryl - 2 - pyridylalkanonitrile of the general formula



(II)

[*Price 4s. 6d.*]

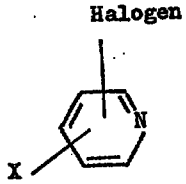
Suitable hydrating agents are concentrated acids (e.g. strong mineral acids and typically sulphuric, polyphosphoric, hydrochloric, or a mixture of sulphuric and acetic acids) and bases (e.g. alkali in a suitable solvent, typically, alcoholic potassium hydroxide).

The amides can be also formed by heating a nitrile with water and an ion-exchange basic resin.

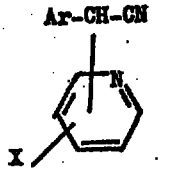
Equivalent to the ω - amino - 2 - aryl - 2 - pyridyl alkanamide derivatives for the purposes of this invention are the corresponding acid addition and quaternary ammonium salts. The acid addition salts are conveniently formed by the mixing of the base, and an acid such as sulphuric, phosphoric, hydrochloric, hydrobromic, hydriodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic, and ascorbic acids. The quaternary ammonium salts are conveniently formed by the mixing of the base and an organic ester such as methyl chloride or bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride or bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulphate, diethyl sulphate, methyl benzenesulphonate, ethyl toluenesulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide, crotyl bromide, and related sulphuric, hydrohalic, and aromatic sulphonic acids.

The nitrile starting materials of formula (II) above are prepared as follows:

First, the appropriate aryl acetonitrile of the general formula $Ar—CH_2CN$ is converted to the alkali metallo derivative (e.g. by treating with sodamide) then condensed with a halopyridine derivative of the general formula



in an inert solvent (e.g. toluene) to give an α-aryl-α-pyridylacetonitrile of the general formula



In this way, there is prepared:

α - Phenyl - 2 - pyridineacetonitrile melting at about 87—88°C.

α - (4 - Chlorophenyl) - 2 - pyridineacetonitrile melting at about 67.5—68°C.

α - Phenyl - 4 - pyridineacetonitrile, melting at about 76—76.5°C.

α - Phenyl - 3 - pyridineacetonitrile, boiling at about 145—150°C. at 0.5 mm. pressure.

α - Phenyl - 2 - (5 - chloropyridine)acetonitrile, boiling at about 150° C. at 0.8 mm. pressure.

α - (3,4 - Dimethoxyphenyl) - 2 - pyridineacetonitrile, boiling at about 175—178°C. at 0.5 mm. pressure. Secondly this α - aryl - α - pyridylalkanonitrile is again converted to the alkali metallo derivative (e.g. by heating with sodamide) and an ω-aminoalkyl halide derivative of the general formula R_1R_2N-Alk-halogen in an inert solvent (e.g. toluene) to afford the nitrile of the formula (II) above. Alternatively, this two-step procedure can be accomplished in a single step by carrying out the first step as before, but using enough sodamide for carrying out both steps, then adding the ω-aminoalkyl halide to the resultant mixture without isolating the intermediate α - aryl - α - pyridylalkanonitrile. In this way, there is obtained:

4 - Diisopropylamino - 2(3 - tolyl) - 2 - (2 - pyridyl) - butyronitrile, boiling at about 164—168°C. at 0.2 mm. pressure.

4 - Diisopropylamino - 2 - (α - naphthyl) - 2 - (2 - pyridyl - butyronitrile, boiling at about 196—202°C. at 2 mm. pressure.

4 - Dipropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 164—165°C. at 0.1 mm. pressure.

4 - Diisopropylamino - 2 - phenyl - 2 - (4 - pyridyl)butyronitrile, boiling at about 164—168°C. at 0.7 mm. pressure.

4 - Diisopropylamino - 2 - phenyl - 2 - (3 - pyridyl)butyronitrile, boiling at about 180—190°C. at 0.3 mm. pressure.

4 - Diisopropylamino - 2 - phenyl - 2 - [2 - (5 - chloropyridyl)]butyronitrile, boiling at about 165—172°C. at 0.25 mm. pressure.

4 - Diisopropylamino - 2 - (3,5 - dimethylphenyl) - 2 - (2 - pyridyl)butyronitrile, boiling at about 165—175°C. at 0.2 mm. pressure.

4 - Diisopropylamino - 2 - (4 - methoxyphenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 160—170°C. at 0.1 mm. pressure.

4 - Diisopropylamino - 2 - (3,4 - dimethoxyphenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 185—190°C. at 0.1 mm. pressure.

4 - Diisopropylamino - 2 - (4 - chlorophenyl) - 2 - (2 - pyridyl)butyronitrile, boiling at about 176—179°C. at 0.4 mm. pressure.

4 - Diisopropylamino - 2 - (4 - fluorophenyl) - 2 - (2 - pyridyl)butyronitrile, boiling at about 154°C. at 0.4 mm. pressure.

4 - Diisopropylamino - 2 - (2 - fluorophenyl) - 2 - (2 - pyridyl)butyronitrile, boiling at about 145—155°C. at 0.3 mm. pressure.

4 - Diisopropylamino - 2 - (4 - iodophenyl) - 2 - (2 - pyridyl) - butyronitrile.

4 - (4 - Methylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl) - butyronitrile, boiling at

about 172—175°C. at 0.15 mm. pressure.

4 - (3 - Methylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl) - butyronitrile, boiling at about 169—171°C. at 0.15 mm. pressure.

4 - (4 - Methylhexamethylenimino) - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 190—198°C. at 0.4 mm. pressure.

4 - (2,4 - Dimethyl - 1 - pyrrolidinyl) - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 165—175°C. at 0.15 mm. pressure.

4 - (2,6 - Dimethylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, melting at about 90—91°C.

4 - (2,4,6 - Trimethylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 180—182°C. at 0.2 mm. pressure.

4 - (2,2,4,6 - Tetramethylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile, boiling at about 185—190°C. at 0.3 mm. pressure.

The following examples illustrate the preparation of the compounds of the formula (I) above. Amounts of materials are given in parts by weight, unless otherwise specified, and temperatures in degrees centigrade (°C.).

Example 1

A solution of 27.3 parts of 4-diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyronitrile and 200 parts of concentrated sulphuric acid was heated on a steam bath for 4 hours and then poured on to ice. The resultant mixture was alkalised with ion sodium hydroxide, and the pH was adjusted to 6 by the addition of acetic acid. The solution was washed once with benzene before it was alkalised again with 10 N sodium hydroxide solution. The resultant mixture was extracted with benzene and the solvent was evaporated from the benzene extract. The resultant residue was dissolved in ethanol and the alcohol solution was then treated with charcoal and sulphur. Evaporation of the solvent left a residue which was recrystallised from hexane to give 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl) - butyramide, melting at about 94.5—95°C.

Substitution of the appropriate ω-dialkylamino - 2 - aryl - 2 - pyridylalkanonitrile in the procedure of the above paragraph afforded:

4 - Diisopropylamino - 2 - phenyl - 2 - (3 - pyridyl)butyramide, a high boiling oil.

4 - Diisopropylamino - 2 - phenyl - 2 - (4 - pyridyl)butyramide, melting at about 138.5—139°C.

4 - Diisopropylamino - 2 - phenyl - 2 - [2 - (5 - chloropyridyl)]butyramide, a resin.

4 - Dipropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide, melting at about 63—64° C.

4 - Diisopropylamino - 2 - (4 - chlorophenyl) - 2 - (2 - pyridyl)butyramide, a resin.

4 - Diisopropylamino - 2 - (4 - fluorophenyl) - 2 - (2 - pyridyl)butyramide, melting at about 77—78°C.

4 - Diisopropylamino - 2 - (2 - fluorophenyl) - 2 - (2 - pyridyl)butyramide, a yellow oil.

4 - Diisopropylamino - 2 - (4 - iodophenyl) - 2 - (2 - pyridyl)butyramide, an amber resin.

4 - Diisopropylamino - 2 - (α - naphthyl) - 2 - (2 - pyridyl)butyramide, melting at about 152—155°C.

Example 2

A mixture of 20 parts of 4 - (4 - methylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)-butyronitrile in 150 parts of concentrated sulphuric acid was heated on a steam bath for 1.5 hours. The resultant mixture was poured on to ice and alkalised with concentrated ammonium hydroxide solution with cooling. The mixture was extracted twice with ether and the ether extracts were combined and dried. Evaporation of the solvent from the ether solution gave an oil which solidified on standing. This oil was recrystallised from acetone to give 4 - (4 - methylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyramide, melting at about 144—145°C.

Substitution of a molecular equivalent quantity of the appropriate ω - (cyclic amino) - 2 - aryl - 2 - pyridylalkanonitrile in the procedure of the above paragraph afforded:

4 - (3 - Methylpiperidino) - 2 - phenyl - 2 - (2 pyridyl) - butyramide melting at about 100—101°C.

4 - (4 - Methylhexamethylenimino) - 2 - phenyl - 2 - (2 - pyridyl)butyramide, a high boiling orange-coloured oil.

4 - (2,4 - Dimethyl - 1 - pyrrolidinyl) - 2 - phenyl - (2 - pyridyl)butyramide, a high melting amber-coloured resin.

4 - (2,6 - Dimethylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyramide, melting at about 152—152°C.

4 - (2,4,6 - Trimethylpiperidino) - 2 - phenyl - 2 - -(2 - pyridyl)butyramide, melting at about 117—119°C.

4 - (2,2,4,6 - Tetramethylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyramide, melting at about 100—103°C.

Example 3

A mixture of 25 parts of 4 - diisopropylamino - 2 - (3 - tolyl) - 2 - (2 - pyridyl)-butyronitrile, 48 parts of potassium hydroxide, 100 parts of ethanol, and 4 parts of water was refluxed for 21 hours. The reaction mixture was poured into 600 parts of water, and the resultant mixture was extracted twice with ether. The combined ether extracts were dried and the solvent was evaporated. Pentane was added to the residue to make it crystallise. The resultant solid was recrystallised from a mixture of ether and hexane to give 4 - di-

isopropylamino - 2 - (3 - tolyl) - 2 - (2 - pyridyl)butyramide, melting at about 113—114°C.

Substitution of the appropriate ω-substituted amino - 2 - aryl - 2 - pyridylalkanonitrile in the above procedure afforded:

4 - Diisopropylamino - 2 - (3,4 - dimethoxyphenyl) - 2 - (2 - pyridyl)butyramide, melting at about 102—103°C.

4 - Diisopropylamino - 2 - (4 - methoxyphenyl) - 2 - (2 - pyridyl)butyramide, a clear orange resin.

4 - Diisopropylamino - 2 - (3,5 - dimethylphenyl) - 2 - (2 - pyridyl)butyramide, a yellowish resin.

EXAMPLE 4

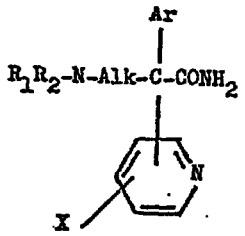
A solution of 33.8 parts of 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide in 200 parts of water was mixed with 6 parts of acetic acid. The resultant solution was then evaporated to afford 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)-butyramide acetate which melted at about 78—82°C.

Substitution of molecular equivalent amounts of the appropriate acid or organic ester for the acetic acid in the above procedure afforded the following salts of 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide.

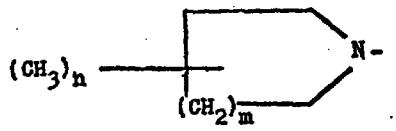
SALT	MELTING CHARACTERISTICS
Ethyl disulhponate	softens at 90°C., foams at 100—110°C.
Citrate	softens at 62.5°C., melts at about 65—70°C.
Sulphonate	melts at about 65—83°C.
p-toluenesulphonate	melts at about 65—83°C.
Sodium acid sulphate	melts at about 110—120°C.
Hydrobromide	melts at about 89°C.
Hydrochloride	melts at about 102—105°C.
Phosphate	melts at about 198—200°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula

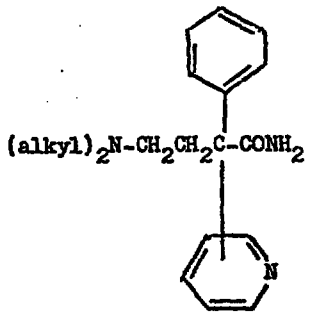


wherein X is a hydrogen or chlorine atom; Ar is a phenyl, tolyl, xylyl, naphthyl, halophenyl, anisyl, dimethoxyphenyl or pyridyl radical; Alk is an ethylene or trimethylene radical; and R_1R_2N— is a tertiary amino radical of the general formula $(alkyl)_2N$— or a cyclic amino of the general formula



wherein the alkyl group contains 3 carbon atoms, and acid addition and quaternary ammonium salts thereof and *m* is 1 to 3 and *n* is 1 to 4.

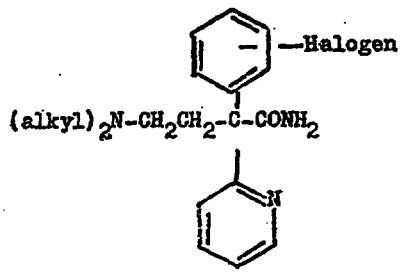
2. Compounds of the general formula



wherein the alkyl group contains 3 carbon atoms and acid addition and quaternary ammonium salts thereof.

3. 4 - Diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide and acid addition and quaternary ammonium salts thereof.

4. Compounds of the general formula



isopropylamino - 2 - (3 - tolyl) - 2 - (2 - pyridyl)butyramide, melting at about 113—114°C.

Substitution of the appropriate ω-substituted amino - 2 - aryl - 2 - pyridylalkanonitrile in the above procedure afforded:

4 - Diisopropylamino - 2 - (3,4 - dimethoxyphenyl) - 2 - (2 - pyridyl)butyramide, melting at about 102—103°C.

4 - Diisopropylamino - 2 - (4 - methoxyphenyl) - 2 - (2 - pyridyl)butyramide, a clear orange resin.

4 - Diisopropylamino - 2 - (3,5 - dimethylphenyl) - 2 - (2 - pyridyl)butyramide, a yellowish resin.

EXAMPLE 4

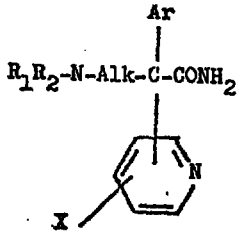
A solution of 33.8 parts of 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide in 200 parts of water was mixed with 6 parts of acetic acid. The resultant solution was then evaporated to afford 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)-butyramide acetate which melted at about 78—82°C.

Substitution of molecular equivalent amounts of the appropriate acid or organic ester for the acetic acid in the above procedure afforded the following salts of 4 - diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide.

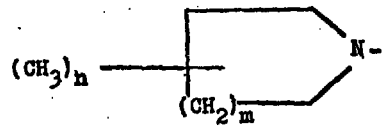
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Hydrobromide	melts at about 89°C.
Hydrochloride	melts at about 102—105°C.
Phosphate	melts at about 198—200°C.

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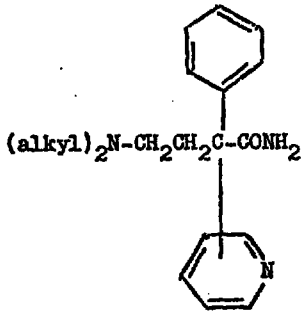


wherein X is a hydrogen or chlorine atom; Ar is a phenyl, tolyl, xylyl, naphthyl, halophenyl, anisyl, dimethoxyphenyl or pyridyl radical; Alk is an ethylene or trimethylene radical; and R_1R_2N— is a tertiary amino radical of the general formula $(alkyl)_2N$— or a cyclic amino of the general formula



wherein the alkyl group contains 3 carbon atoms, and acid addition and quaternary ammonium salts thereof and *m* is 1 to 3 and *n* is 1 to 4.

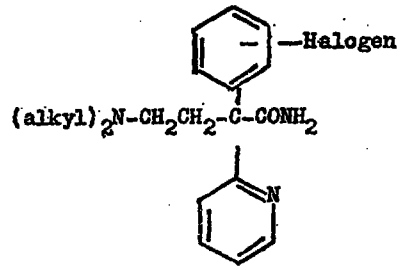
2. Compounds of the general formula



wherein the alkyl group contains 3 carbon atoms and acid addition and quaternary ammonium salts thereof.

3. 4 - Diisopropylamino - 2 - phenyl - 2 - (2 - pyridyl)butyramide and acid addition and quaternary ammonium salts thereof.

4. Compounds of the general formula



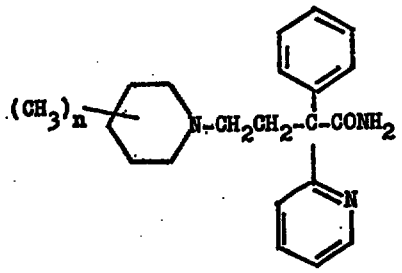
wherein the alkyl group contains 3 carbon atoms and acid addition and quaternary ammonium salts thereof.

5. 4 - Diisopropylamino - 2 - (3 - tolyl) - 2 - (2 - pyridyl)butyramide, and acid addition and quaternary ammonium salts thereof.

6. 4 - Diisopropylamino - 2 - (3,4 - dimethoxyphenyl) - 2 - (2 - pyridyl)butyramide and acid addition and quaternary ammonium salts thereof.

7. 4 - Diisopropylamino - 2 - (α - naphthyl) - 2 - (2 - pyridyl)butyramide and acid addition and quaternary ammonium salts thereof.

8. Compounds of the general formula



wherein n is 1 to 4 and acid addition and quaternary ammonium salts thereof.

9. 4 - (4 - Methylpiperidino) - 2 - phenyl - 2 - (2 - pyridyl)butyramide and acid addition and quaternary ammonium salts thereof.

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* C L M S *