PATENT SPECIFICATION

NO DRAWINGS

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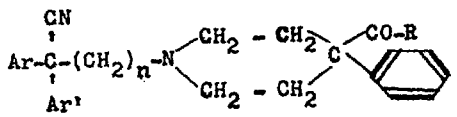
COMPLETE SPECIFICATION

Improvements in or relating to 2,2-Diaryl-ω-(4¹-Phenyl-1¹-Piperidino)Alkanonitriles

I, PAUL ADRIAAN JAN JANSSEN, a Citizen of Belgium, of Antwerpse Steenweg 16¹, Vosselaar, near Turnhout, Belgium, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to derivatives of 2,2 - diaryl - ω - (4¹ - phenyl - 1¹ - piperidino) butyronitriles and valeronitriles.

The novel compounds of the present invention are compounds of the general structural formula



and the salts thereof, wherein Ar and Ar¹ are aryl hydrocarbon radicals, containing less than nine carbon atoms, *n* is two or three and R is a lower alkyl group, O - alkyl group containing less than 8 carbon atoms, -O-(lower alkenyl), -O-cyclopentyl, O-cyclohexyl or -O-(lower alkylene) - phenyl group.

The term "lower" as used herein refers to groups containing less than 9 carbon atoms.

In the foregoing structural formula the radicals Ar and Ar¹ can represent phenyl, tolyl or xylyl groups. The radical R can be a lower alkyl group such as methyl, ethyl, straight-chained or branched propyl, butyl, amyl, or hexyl. The radical R can also represent a lower alkyloxy radical of less than eight carbon atoms wherein the alkyl group is of the same type as R or is heptyl. Highly active substances are also obtained where the group R is a corresponding alkenyloxy group such as allyloxy, butenyloxy, methallyloxy and pentenyloxy. The radical R can furthermore represent cyclopentoxy or cyclohexoxy. Highly potent compounds are also obtained where the radical R represents such aralkyloxy groups as phenethoxy, phenylpropoxy and benzyloxy.

The organic bases of this invention form non-toxic, acid-addition salts with a variety of organic and inorganic acids. Such salts are formed with such acids as sulphuric, phosphoric, hydrochloric, hydrobromic, hydriodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic, ascorbic and related acids. They also form quaternary ammonium salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethylsulphate, diethylsulphate, methyl benzenesulphonate, ethyl toluenesulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

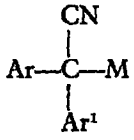
The esters of this invention are conveniently prepared by the condensation of a 2,2 - diaryl - 4 - halobutyronitrile or 2,2 - diaryl - 5 - halovaleronitrile with an equivalent of the appropriate ester of 4 - phenylisonipecotic acid. Since in this condensation an equivalent of hydrogen halide is liberated, it is necessary to use either an excess of the isonipecotic acid derivative or to use one equivalent of another base to combine with the acid. The condensation can be carried out in inert solvents such as the aromatic hydrocarbons containing six to nine carbon atoms, the lower alkanols and alkanones. An obvious equivalent method is to use the free 4 - phenylisonipecotic acid in lieu of the ester, typically in an alcoholic solvent in the presence of a base such as sodium carbonate, and to esterify the 2,2 - diaryl - ω - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)alkanonitrile thus produced.

For the preparation of the ketones, wherein the radical R represents a lower alkyl group, the appropriate 4 - phenyl - 4 - alkanoyl-

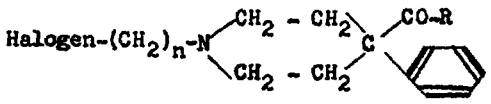
[*Price 3s. 6d.*]

piperidines are substituted for the isonipecotic acid derivatives.

An alternative procedure employs as a starting material a diarylacetonitrile which is reacted with an organometallic reagent to form the α - metallo derivative



where M is a metal, which is then condensed with a corresponding 1 - haloalkyl - piperidine derivative of the formula



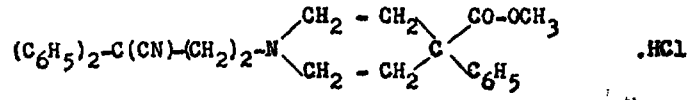
with elimination of the metal halide, M - Halogen.

The compounds of this invention are highly active inhibitors of gastro - intestinal propulsion and defecation and are therefore useful in the treatment of diarrhoea. They are preferable in use over morphine derivatives in that they do not produce analgesic effects in therapeutic dosage. Also, unlike some other drugs used in the treatment of diarrhoea, these compounds are devoid of parasympathicolytic activity in therapeutic dosage.

The following examples in which the parts are by weight illustrate the invention.

EXAMPLE 1.

In a sealed pressure reactor a mixture of 23 parts of the methyl ester of 4 - phenylisonipecotic acid and 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 90 parts xylene was heated at 120° C. for 24 hours. The mixture was then cooled and filtered. The filtrate was extracted with dilute hydrochloric acid, rendered alkaline with aqueous sodium hydroxide and then extracted with ether. Through the ether solution gaseous hydrogen chloride was led to cause precipitation of the hydrochloride of the methyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which melted at about 180—181° C. The compound had the structural formula



EXAMPLE 2.

A mixture of 23 parts of the ethyl ester of 4 - phenylisonipecotic acid and 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 19 parts of xylene was heated for 24 hours at 100—120° C. and then cooled and filtered to remove the precipitate of the hydrobromide of the ethyl ester of 4 - phenylisonipecotic acid. The filtrate was then extracted with dilute hydrochloric acid and the extract was rendered alkaline by the addition of concentrated aqueous potassium hydroxide and extracted with ether. This ether extract was treated with gaseous hydrogen chloride. The resulting precipitate was collected on a filter. The hydrochloride of the ethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino) butyronitrile thus obtained melted at about 220.5—222° C.

EXAMPLE 3.

In a sealed reactor a mixture of 46 parts of the ethyl ester of 4 - phenylisonipecotic acid and 31 parts of 2,2 - diphenyl - 5 - bromovaleronitrile was heated at about 110° C. for 24 hours. After cooling and filtration the filtrate was extracted with dilute hydrochloric acid and the extract was rendered alkaline and extracted with ether. Treatment of the ether solution with slightly more than one molecular equivalent of a 25% solution of hydrogen chloride in 2 - propanol and cooling yielded the hydrochloride of the ethyl ester of 2,2 - diphenyl - 5 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino) valeronitrile melting at about 201—203° C.

EXAMPLE 4.

In a pressure reactor a mixture of 49 parts of the normal propyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of butanone was heated for 24 hours and then cooled and filtered. The filtrate was extracted with dilute hydrochloric acid and the acidic solution was rendered alkaline and extracted with ether. Treatment of the ether solution with gaseous hydrogen chloride yielded the hydrochloride of the propyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 224—225° C.

EXAMPLE 5.

A mixture of 49 parts of the normal propyl ester of 4 - phenylisonipecotic acid and 31 parts of 2,2 - diphenyl - 5 - bromovaleronitrile in 200 parts of xylene was heated in a bomb at 100° C. The contents of the bomb were then cooled and filtered and the filtrate was extracted with dilute acid. The extract was rendered alkaline and extracted with ether. Treatment of the ether solution with gaseous hydrogen chloride yielded the hydrochloride of the propyl ester of 2,2 - diphenyl - 5 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino) valeronitrile melting at about 197—198° C.

EXAMPLE 6.

Substitution of the isopropyl ester of 4 -

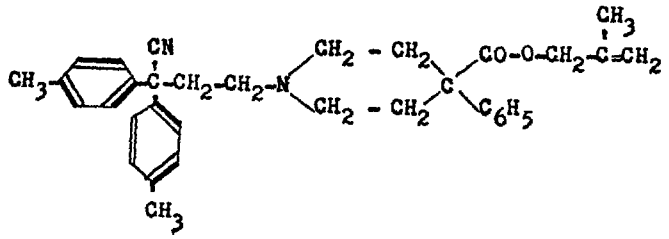
phenyl - isonipecotic acid for the normal propyl ester used in Example 4 yielded the isopropyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile as a hydrochloride melting at about 230.5—232.5° C.

EXAMPLE 7.

A mixture of 49 parts of the allyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of xylene was heated at 110° C. for 24 hours, cooled and filtered. The filtrate was extracted with acid and the acid extract was rendered alkaline and extracted with ether. The ether solution was treated with gaseous hydrogen chloride, and on cooling there precipitated the hydrochloride of the allyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 204.5—206° C.

EXAMPLE 8.

A mixture of 51 parts of the methallyl ester of 4 - phenylisonipecotic acid with 33 parts of 2,2 - di - (*p* - tolyl) - 4 - bromobutyronitrile in 230 parts of xylene was heated in a sealed reactor at 120° C. for 20 hours. After cooling the reaction mixture was filtered and the filtrate was extracted with dilute hydrochloric acid. The acid solution was rendered alkaline and extracted with ether. The ether solution was dried over anhydrous calcium sulphate, filtered and evaporated to yield the methallyl ester of 2,2 - di - (*p* - tolyl) - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile which has the structural formula



EXAMPLE 9.

A mixture of 51 parts of the butyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile was heated in a bomb at about 100—120° C., cooled and filtered. The filtrate was extracted with dilute hydrochloric acid and the acid extract was rendered alkaline and extracted with ether. Treatment of the ether solution with hydrogen chloride caused precipitation of the hydrochloride of the butyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which melted at about 208—208.5° C.

EXAMPLE 10.

A mixture of 54 parts of the pentyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of xylene was heated in a closed vessel for 24 hours, cooled and filtered. The filtrate was extracted with acid. The acid extract was rendered alkaline and extracted with ether. Treatment of the ether extract with gaseous hydrogen chloride caused formation of the hydrochloride of the pentyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino) butyronitrile melting at about 197.5—198.5° C.

EXAMPLE 11.

Reaction of 28 parts of the normal hexyl ester of 4 - phenylisonipecotic acid with 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 100 parts of xylene and working up by the procedure of Example 10 yielded the hydrochloride of the hexyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 189—190° C.

EXAMPLE 12.

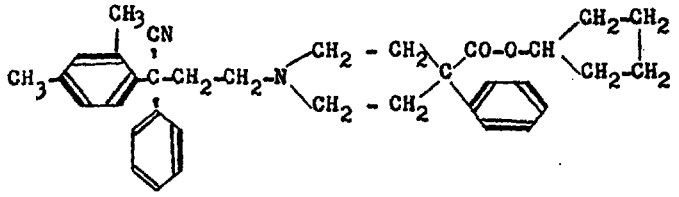
Reaction of a mixture of 78.5 parts of the heptyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 250 parts of xylene and working up as in Example 10 yielded the hydrochloride of the heptyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 189—191.5° C.

EXAMPLE 13.

Reaction of 28 parts of the cyclohexyl ester of 4 - phenylisonipecotic acid and 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile and working up as in Example 10 yielded the hydrochloride of the cyclohexyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 217—220° C.

EXAMPLE 14.

A mixture of 26.7 parts of the cyclopentyl ester of 4 - phenylisonipecotic acid and 16.4 parts of 2 - (2,4 - xylyl) - 2 - phenyl - 4 - bromobutyronitrile in 100 parts of xylene was heated at 110° C. for 15 hours, cooled and filtered. The filtrate was extracted with dilute hydrochloric acid and the extract washed with ether, rendered alkaline and extracted with ether. The ether extract was dried over anhydrous calcium sulphate, filtered and evaporated to yield the cyclopentyl ester of 2 - (2,4 - xylyl) - 2 - phenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which had the structural formula:



EXAMPLE 15.

A mixture of 40 parts of the β - phenethyl ester of 4 - phenylisonipecotic acid and 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of xylene was heated at 100—120° C. for 24 hours, cooled and filtered. The filtrate was extracted with acid, and the acid extract was rendered alkaline and extracted with ether. Treatment of the ether solution with gaseous hydrogen chloride yielded the hydrochloride of the phenethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 184—187° C.

EXAMPLE 16.

A mixture of 77 parts of the benzyl ester of 4 - phenylisonipecotic acid and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of xylene was heated for 24 hours, cooled and filtered. The filtrate was extracted with dilute hydrochloric acid. This extract was washed with ether, rendered alkaline, and extracted with ether. The ether extract was dried over anhydrous calcium sulphate, filtered and evaporated to yield the benzyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile.

EXAMPLE 17.

Reaction of 82.5 parts of the γ - phenylpropyl ester of 4 - phenylisonipecotic acid with 25.6 parts of 2,2 - diphenyl - 4 - chlorobutyronitrile in 200 parts of xylene for 36 hours at 120° C. and working up as in Example 16 yielded the γ - phenylpropyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile.

EXAMPLE 18.

A mixture of 43 parts of 4 - propanoyl - 4 - phenylpiperidine and 30 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 200 parts of xylene was heated at 100—120° C. for 24 hours, cooled and filtered. The filtrate was extracted with dilute hydrochloric acid. The acidic extract was rendered alkaline and extracted with ether. The ether extract was treated with gaseous hydrogen chloride to yield the hydrochloride of 2,2 - diphenyl - 4 - (4^1 - propanoyl - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile melting at about 229.5—231° C.

EXAMPLE 19.

Reaction of 90 parts of 4 - propanoyl - 4 - phenylpiperidine and 65 parts of 2,2 - diphenyl - 5 - bromovaleronitrile in 500 parts of toluene at 100° C. for 24 hours followed by working up as in Example 18 yielded the hydrochloride of 2,2 - diphenyl - 5 - (4^1 - propanoyl - 4^1 - phenyl - 1^1 - piperidino)-valeronitrile melting at about 210—212° C.

EXAMPLE 20.

A mixture of 23 parts of 4 - butanoyl - 4 - phenyl - piperidine and 15 parts of 2,2 - diphenyl - 4 - bromobutyronitrile in 100 parts of xylene at 100—120° C. and working up as in Example 18 yielded the hydrochloride of 2,2 - diphenyl - 4(4^1 - butanoyl - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 227—228.5° C.

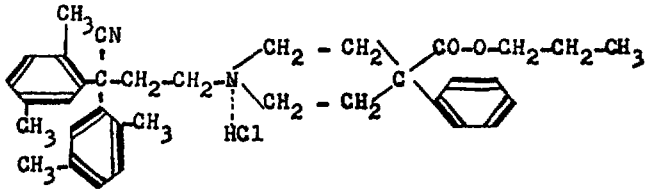
EXAMPLE 21.

Reaction of 96 parts of 4 - butanoyl - 4 - phenylpiperidine and 65 parts of 2,2 - diphenyl - 5 - bromovaleronitrile in 500 parts of benzene in a sealed pressure reactor at 100—120° C. for 24 hours and working up as in Example 18 yielded the hydrochloride of 2,2 - diphenyl - 4(4^1 - butanoyl - 4^1 - phenyl - 1^1 - piperidino)valeronitrile melting at about 236—238° C.

EXAMPLE 22.

To a stirred suspension of 7 parts of sodamide in 90 parts of benzene maintained at 30—35° C. there was added a solution of 33 parts of diphenylacetonitrile in 70 parts of benzene. This mixture was then refluxed for an hour, cooled and treated, by portionwise addition, with one equivalent of the propyl ester of 1 - (2 - chloroethyl) - 4 - phenylisonipecotic acid in 45 parts of xylene at 30—40° C. The resulting mixture was refluxed for 2 hours, cooled, filtered and extracted with dilute hydrochloric acid. The acidic extract was rendered alkaline and extracted with ether. The ether extract was treated with gaseous hydrogen chloride to yield the hydrochloride of the propyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 224—225° C.

Substitution of an equivalent amount of the di - (2,5 - xylyl)acetonitrile in the above procedure yielded the 2,2 - di - (2,5 - xylyl) - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile propyl ester hydrochloride of the structural formula

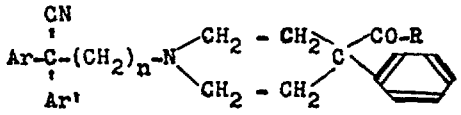


EXAMPLE 23.

To a stirred suspension of 7 parts of sodamide in 90 parts of benzene maintained at 30—35° C. there was added a solution of 33 parts of diphenylacetonitrile in 70 parts of benzene. This mixture was then refluxed for an hour, cooled and treated, by portionwise addition, with one equivalent of the ethyl ester of 1 - (2 - chloroethyl) - 4 - phenylisonipecotic acid in 45 parts of xylene at 30—40° C. The resulting mixture was refluxed for 2 hours, cooled, filtered and extracted with dilute hydrochloric acid. The acidic extract was rendered alkaline and extracted with ether. The ether extract was treated with gaseous hydrogen chloride to yield the hydrochloride of the ethyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile melting at about 220.5—222° C.

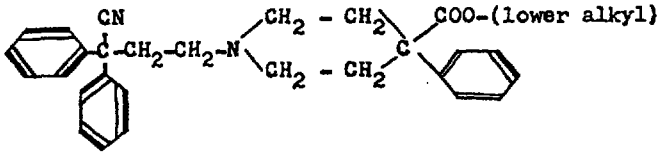
WHAT I CLAIM IS:—

1. Compounds of the general structural formula:



where Ar and Ar¹ are aryl hydrocarbon radicals containing less that 9 carbon atoms, *n* is 2 or 3 and R is a lower alkyl group, O-alkyl group containing less than 8 carbon atoms, -O-(lower alkenyl), -O-cyclopentyl, -O-cyclohexyl, or -O-(lower alkylene)-phenyl groups, and salts thereof.

2. Compounds of the general structural formula:



and salts thereof.

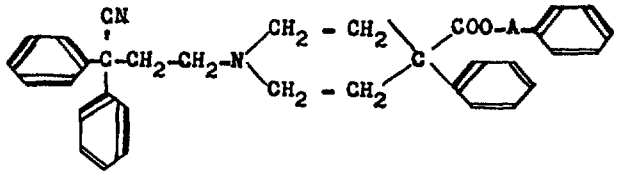
3. The ethyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)-butyronitrile, and salts thereof.

4. The butyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)-butyronitrile, and salts thereof.

5. Lower alkenyl esters of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile, and salts thereof.

6. The allyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)-butyronitrile, and salts thereof.

7. Compounds of the general structural formula



wherein A is a lower alkylene radical and salts thereof.

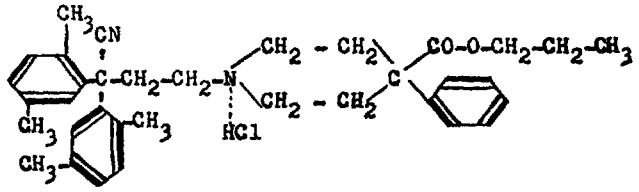
8. The phenethyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile and salts thereof.

9. A process for the preparation of the compounds claimed in claim 1 which comprises condensing a 2,2 - diaryl - 4 - haloalkanonitrile with at least one equivalent of an ester of 4 - phenylisonipecotic acid in an inert solvent.

10. A process for the preparation of the ethyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least one equivalent of the ethyl ester of 4 - phenylisonipecotic acid in an inert solvent.

11. A process for the preparation of the butyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least one equivalent of the butyl ester of 4 - phenylisonipecotic acid in an inert solvent.

12. A process for the preparation of the allyl ester of 2,2 - diphenyl - 4 - (4¹ - carboxy - 4¹ - phenyl - 1¹ - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least

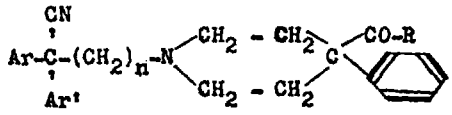


EXAMPLE 23.

To a stirred suspension of 7 parts of sodamide in 90 parts of benzene maintained at 30—35° C. there was added a solution of 33 parts of diphenylacetonitrile in 70 parts of benzene. This mixture was then refluxed for an hour, cooled and treated, by portionwise addition, with one equivalent of the ethyl ester of 1 - (2 - chloroethyl) - 4 - phenylisonipecotic acid in 45 parts of xylene at 30—40° C. The resulting mixture was refluxed for 2 hours, cooled, filtered and extracted with dilute hydrochloric acid. The acidic extract was rendered alkaline and extracted with ether. The ether extract was treated with gaseous hydrogen chloride to yield the hydrochloride of the ethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile melting at about 220.5—222° C.

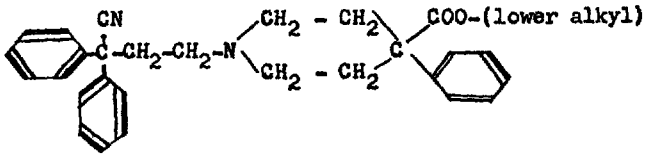
WHAT I CLAIM IS:—

1. Compounds of the general structural formula:



where Ar and Ar^1 are aryl hydrocarbon radicals containing less that 9 carbon atoms, n is 2 or 3 and R is a lower alkyl group, O-alkyl group containing less than 8 carbon atoms, -O-(lower alkenyl), -O-cyclopentyl, -O-cyclohexyl, or -O-(lower alkylene)-phenyl groups, and salts thereof.

2. Compounds of the general structural formula:



and salts thereof.

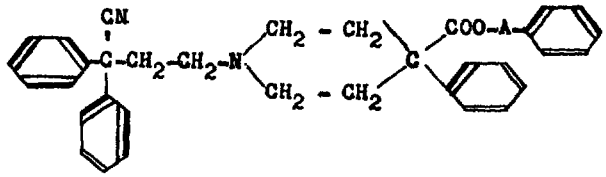
3. The ethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile, and salts thereof.

4. The butyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile, and salts thereof.

5. Lower alkenyl esters of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile, and salts thereof.

6. The allyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)-butyronitrile, and salts thereof.

7. Compounds of the general structural formula



wherein A is a lower alkylene radical and salts thereof.

8. The phenethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile and salts thereof.

9. A process for the preparation of the compounds claimed in claim 1 which comprises condensing a 2,2 - diaryl - 4 - haloalkanonitrile with at least one equivalent of an ester of 4 - phenylisonipecotic acid in an inert solvent.

10. A process for the preparation of the ethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least one equivalent of the ethyl ester of 4 - phenylisonipecotic acid in an inert solvent.

11. A process for the preparation of the butyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least one equivalent of the butyl ester of 4 - phenylisonipecotic acid in an inert solvent.

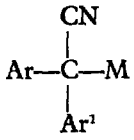
12. A process for the preparation of the allyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least

one equivalent of the allyl ester of 4 - phenylisonipecotic acid in an inert solvent.

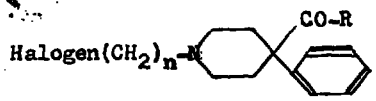
13. A process for the preparation of the phenethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which comprises condensing 2,2 - diphenyl - 4 - bromobutyronitrile with at least one equivalent of the β - phenethyl ester of 4 - phenylisonipecotic acid in an inert solvent.

14. A process as claimed in any of claims 10 to 13 wherein the inert solvent is an aromatic hydrocarbon containing six to nine carbon atoms.

15. A process for the preparation of the compounds claimed in claim 1 which comprises condensing a compound of the general structural formula



wherein Ar and Ar^1 are as defined in claim 1 and M is a metal, with a compound of the general structural formula



wherein n and R are as defined in claim 1, in an inert solvent.

16. A process for the preparation of the ethyl ester of 2,2 - diphenyl - 4 - (4^1 - carboxy - 4^1 - phenyl - 1^1 - piperidino)butyronitrile which comprises condensing

$$(C_6H_5)_2C(CN)Na$$

with at least one equivalent of the ethyl ester of 1 - (2 - chloroethyl) - 4 - phenylisonipecotic acid in an inert solvent.

17. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any one of the Examples.

ELKINGTON & FIFE,
Consulting Chemists and Chartered Patent Agents,
Bank Chambers, 329, High Holborn, London, W.C.1,
Agents for the Applicant.

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