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PATENT SPECIFICATION

DRAWINGS ATTACHED

1,117,063

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Int. Cl.:—C 07 c 119/14

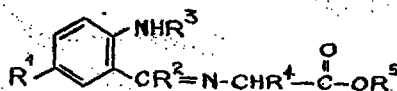
COMPLETE SPECIFICATION

N-Substituted Ortho-Aminoarylketimines

We, ETABLISSEMENTS CLIN-BYLA, a French Body Corporate, of 20 rue des Fosses Saint-Jacques, Paris, France, 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 N-substituted ortho-aminoaryl ketimines which are valuable intermediates in the production of pharmacologically valuable benzodiazepines and are also pharmacologically active materials *per se*.

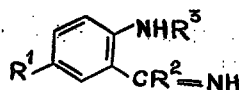
The N-substituted ortho-aminoaryl ketimines of the present invention have, in one tautomeric form, the general formula



in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl group having 1 to 7 carbon atoms, an alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom or by a trifluoromethyl group or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or is an alkyl group having 1 to 7 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R⁴ is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms or an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal and R⁵ is an alkyl group having 1 to 7 carbon atoms or, when R⁴ is a carbamoyl or —COOCat group, a cation Cat as already defined.

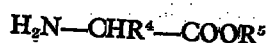
The alkyl and alkoxy groups present in such compounds have 1 to 7 carbon atoms in a straight or branched chain, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tertiary-butyl, amyl and hexyl groups.

In accordance with a feature of the invention a process for the production of an ortho-aminoaryl ketimine having the above general formula but excluding the case in which R⁴ is —COOCat and/or R⁵ is Cat comprises reacting an ortho-aminoaryl ketimine having the general formula



(II)

in which R^1 , R^2 and R^3 are as above defined, with an aliphatic α -aminocarboxylic acid ester having the general formula

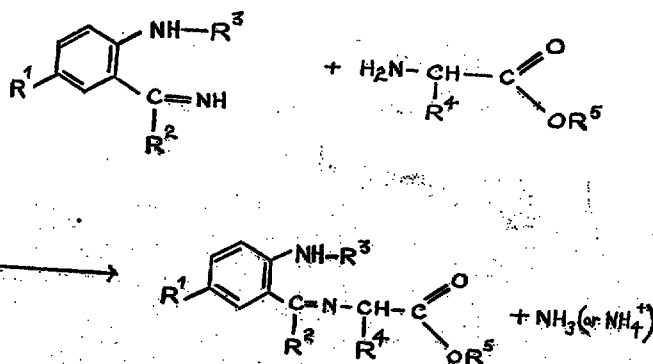


5 in which R^4 is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms, an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group or an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, and R^5 is an alkyl group having 1 to 7 carbon atoms, or a salt thereof.

The imines having the general formula (II), and their production, are described and claimed in our copending application No. 42698/67 Serial No. 1,117,062.

10 In the α -aminocarboxylic acid ester the group R^4 may be an alkyl group having 1 to 7 carbon atoms or an alkylthioalkyl group having 2 to 7 carbon atoms and may be derived by the use of an alkyl ester of a naturally occurring optically active or racemic α -amino acid such as alanine, leucine or methionine. In addition the α -aminocarboxylic acid ester may be a dialkyl ester of aminomalonic acid, for example dimethyl or diethyl aminomalonate or an alkyl aminoacetate, for example, ethyl aminoacetate.

15 These esters may be used in the form of bases but preferably in the form of salts which are easier to deal with than the base, especially the hydrochloride. The reaction is accompanied by liberation of ammonia, either free or combined in the form of a salt according to the equation given below:



25 The reaction may be carried out in an inert diluent, in particular an aliphatic alcohol having 1 to 7 carbon atoms or a hydrocarbon such as benzene or toluene, and at a temperature between room temperature and the reflux temperature of the diluent. The reaction time may vary between 1 and 12 hours; the higher the temperature employed, the shorter will be the reaction time. In certain cases, the reaction product separates spontaneously from the alcoholic solution at room temperature. Nevertheless, it is advantageous to evaporate off the solvent when the reaction is terminated, extract 30 the product with an inert solvent and isolate it by crystallisation from a suitable solvent.

35 The substituted imines which have an ester function are obtained in the form of pale yellow products, in most cases crystalline but sometimes in the form of oils. Their structure is determined by elementary analysis, study of their infra-red spectra and the results of acid hydrolysis.

As could be expected theoretically, the substituted imines can exist in two stereoisomeric forms one of which, generally obtained in larger quantity, is characterised by an intramolecular N—H hydrogen bond between a hydrogen on the amino group and

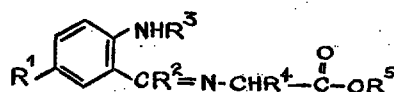
the nitrogen of the imino group (forming a chelate ring). In two of the appended examples (see Examples 1 and 2) these two forms were isolated by fractional crystallisation; in the other cases, the product isolated was generally a crystalline product corresponding to the chelate form.

The infra-red spectra, determined in methylene chloride, of the chelate forms have a vibration band of the N—H group in the region of 3480 cm^{-1} (a fine line would not be seen in the case of a secondary amine) and a wide band at $3150\text{--}3300\text{ cm}^{-1}$ due to the chelate bond N—H of the group NHR^3 ; in the region of $1730\text{--}1740\text{ cm}^{-1}$ a vibration band of $>\text{C}=\text{O}$ of the ester radical; in the region of $1610\text{--}1620\text{ cm}^{-1}$ a band of the aromatic $>\text{C}=\text{Q}<$ (and $>\text{C}=\text{N}-$); at $1200\text{--}1180\text{ cm}^{-1}$ a C—O—C band (ester) shifted to 1220 cm^{-1} in the case of malonic esters. The non-chelate forms differ from the above by the existence of doublet formed by two fine lines due to the N—H vibrations of the NHR^3 group (a single line at 3400 cm^{-1} in the case of secondary amines) and by the absence of absorption bands between 3150 and 3300 cm^{-1} .

Investigation of the reaction of the imines with a strong mineral acid, particularly hydrochloric acid, leads to different results according to the presence or absence of an internal hydrogen bond: if there is chelation, the action of hydrochloric acid leads to the formation of the corresponding ortho-amino ketone due to severing of the imine bond; if there is no chelation, the imino bond is not severed and the corresponding benzodiazepine is formed, the configuration of which is moreover favourable to cyclisation.

In Table I, a certain number of substituted imines are shown which correspond to the general formula above in which R^5 is an alkyl group; these imines are all new.

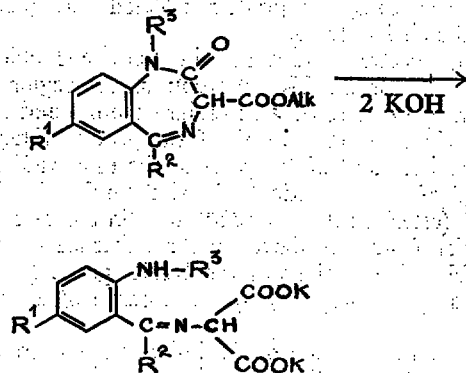
TABLE I



No.	R^1	R^2	R^3	R^4	R^5	Example
4292 CB(1)	Cl	C_6H_5	H	H	C_2H_5	1
4361 CB(1)	Cl	C_6H_5	CH_3	H	C_2H_5	2
4346 CB	Cl	C_6H_5	H	COOC_2H_5	C_2H_5	3
4362 CB	Cl	C_6H_5	CH_3	COOC_2H_5	C_2H_5	4
4363 CB	H	C_6H_5	H	H	C_2H_5	5
4351 CB	H	C_6H_5	H	COOC_2H_5	C_2H_5	6
4364 CB	CH_3	C_6H_5	H	H	C_2H_5	7
4365 CB	Cl	$n\text{--C}_4\text{H}_9$	H	H	C_2H_5	8

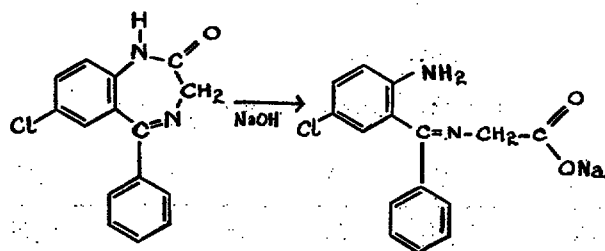
(1) isolated in two stereoisomeric crystalline forms.

With a view to obtaining products in a convenient water-soluble form for pharmacodynamic studies and clinical use, we have saponified 3-carbalkoxybenzodiazepines containing the substituents R^1 , R^2 and R^3 (see formula below), with an alkali metal hydroxide, preferably potassium hydroxide, in solution in an alkanol having 1 to 7 carbon atoms. The said 3-carbalkoxybenzodiazepines, and their preparation, are described and claimed in our copending application No. 25133/65 Serial No. 1,117,061. In every case, the di-metal salt of the dibasic acid is obtained in accordance with the equation given below:



Thus, saponification of the ester group is accompanied by opening of the benzodiazepine ring at the position of the lactam function.

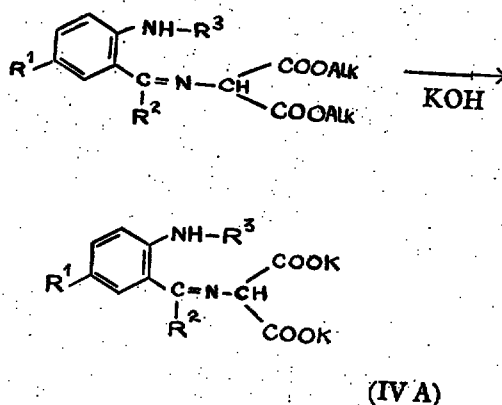
This reaction may be compared with the conversion of 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine into the corresponding monosodium salt by the action of a sodium hydroxide solution as described by Bell, Sulkowski, Gochman and Childress in Journal of Organic Chemistry, 1962, Volume 27, pages 562 to 566.



The infra red spectra of the di-metal salts, determined in a potassium bromide disc, agree with the structure, in particular the absence of the $>C=O$ bands (amide, acid or ester) between 1650 and 1750 cm^{-1} ; moreover, they show among other things a very wide and intense absorption band in the region of 3400 cm^{-1} (vibrational frequencies of $N-H$ of highly chelated NH_2) and a wide and complex absorption in the region of $1600-1550\text{ cm}^{-1}$ (aromatic $>C=C<$, $>C=N-$, $>C=O$ of carboxylate ions).

For ease of manipulation, it is best to work in 95% ethyl alcohol; the temperature should be between room temperature and the boiling point. The purest products are obtained by operating at room temperature. The reaction is accompanied by a transient yellow coloration. For rapid discoloration, it is advisable to use at least three equivalents of potassium hydroxide. The yield of the dipotassium salt is practically quantitative. These dimetal salts, a number of which are given in Table II below, are colourless powders (with the exception of the nitro and amino derivatives which are yellow), very soluble in water and strongly alkaline in reaction. On acidification, the aqueous solutions give rise to the corresponding benzodiazepines unsubstituted on the 3-carbon atom.

The same dimetal salts can be obtained by saponification of imines having the above general formula in which R^4 is a carbalkoxy group and R^5 is an alkyl group with an alkali metal hydroxide. Using potassium hydroxide the reaction proceeds as follows:

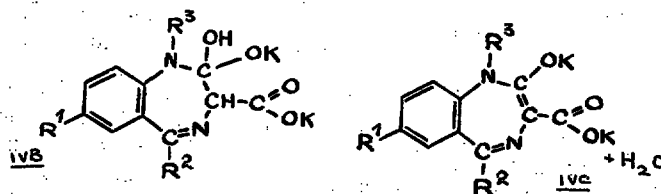


The infra-red spectra of the dipotassium salts thus prepared are practically identical with those of the corresponding salts prepared by opening of the benzodiazepine ring. Moreover, the aqueous solutions of the dipotassium salts (prepared by either one or the other method) when treated with dilute hydrochloric acid undergo decarboxylation and cyclisation to give the same benzodiazepine derivative.

The dialkali metal salts of the ortho-aminoaryl ketimines may be treated in aqueous solution with a water-soluble salt of an alkaline earth metal thus giving the corresponding alkaline earth metal salts of the ketimines.

In the case of compound 4306 CB, pharmacodynamic studies confirm the identity of the products obtained by the two methods.

As regards formula IV A, it should be remarked that the analytical results obtained, which will be discussed below, are more easily explained if one assumes a ring structure such as IVB or IV C instead of the structure IV A for the compounds considered.



Analytical studies have been carried out especially on compound 4306 CB (compound IVA in which R¹ = Cl, R² = C₆H₅, R³ = H).

Even after prolonged drying of this substance at 50°C under a high vacuum, the products obtained still contain approximately 10% of the solvent (10% aqueous ethyl alcohol) in which the preparation was carried out.

To determine the quantity of ethyl alcohol, the substance under investigation is dissolved in water and the solution obtained is distilled; the distillate is oxidised with nitrochrome reagent and the excess reagent is titrated with a solution of ferrocyanide in the presence of diphenylbenzidine.

To determine the quantity of water, the Karl Fischer method cannot be used owing to the strong basicity of the product, and therefore the product is suspended in xylene and water is driven off as an azeotropic mixture.

The determination of ethyl alcohol and water carried out as indicated above show that, in addition to the 10% of solvent retained, the product can liberate by azeotropic distillation one molecule of water, which is easily explained if one assumes the structure IV B or IV C in which water is present as water of crystallisation.

Elementary analysis of the product dried at 50°C, taking into account the quantity of solvent of crystallisation present, agrees with the values calculated for one of the three formulae IV A, IV B or IV C, which are identical in their empirical formulae.

Determination of the basic functions of the molecule yields interesting results especially if, for example, one compares the potentiometric diagrams obtained for 4306 CB, for the potassium salt of 7 - chloro - 5 - phenyl - 2 - oxo - 2,3 - dihydro-

1H-benzo[f]-1,4-diazepine-3-carboxylic acid (4311 CB) and for 7-chloro-5-phenyl-2-oxo-2,3-dihydro-*1H*-benzo[f]-1,4-diazepin (indicated by the reference A below).

In an anhydrous medium consisting of a mixture of chloroform (3 vols.) and acetic acid (1 vol.), titration with perchloric acid in acetic acid solution gives the results shown in the accompanying drawing which is a graph in which the abscissae represent the volume in ml. of titrating agent and the ordinates the potential in mV.

For compound 4306 CB (continuous line curve) a first jump in potential with an equivalent point located at -370 mV and a second jump in potential with an equivalent point located at -600 mV, the total volume of titrating agent added to reach the second equivalent point being 1.5 times the volume added in order to reach the first point.

For compound 4311 CB (discontinuous curve), a first jump in potential with an equivalent point located at -360 mV and a second potential jump with an equivalent point located at -590 mV, the volume added in order to reach the second equivalent point being twice the volume added to reach the first point;

For compound (A) (dotted line) a jump in potential with an equivalent point situated at -580 mV.

From these experimental data and the known formulae of compound 4311 CB and compound (A), it is obvious that the second jump in potential obtained in the titration of compound 4306 CB corresponds to neutralisation of the imine function and that the first corresponds to neutralisation of the two other functions, namely:

If one adopts the cyclic formula IV B or IV C, the alcohol (or enolic) and carboxylic functions; or

If one adopts formula IVA, one of the carboxylic acid functions and the amino group, assuming that the second carboxylic function has too low a pK value to be determined owing to its proximity to the first carboxylic acid function.

Protometric determination in an anhydrous medium would thus not appear to be suitable for distinguishing between the possible structures. In fact, the result in an aqueous medium rather tends to favour a ring structure; if this procedure is adopted, it is not possible to carry out the determination below pH 7 owing to the precipitation of compound 4311 CB and compound (A); only functions corresponding to high pK values can be determined in this way. Compound 4306 CB determined in an aqueous medium by means of hydrochloric acid has an equivalent point at pH 9.5, which could be attributed to an alcoholic (or enolic) function but less easily to one of the functions of the isomer IV A.

The possibility should not be excluded that under the operating conditions, the compound 4306 CB used in these tests will assume one of the isomeric forms in preference to another. Prolonged heating of this particular compound in the solid state at 100°C seems to favour the formation of the IV A isomer, as indicated by the protometric determination in an aqueous medium, in addition to some alteration of the product.

Lastly, it is to be noted that the infra-red spectra of compounds of type IV A, IV B or IV C and in particular of 4306 CB and 4335 CB are compatible with the three formulae proposed.

The invention is not in any way limited to a particular representative formula among the group of formulae IV A, IV B and IV C.

Table II gives by way of example some dipotassium salts prepared according to a process of the invention.

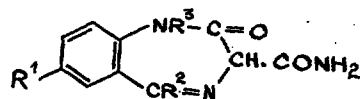
TABLE II
Formula IVA, IVB or IVC

No.	R ¹	R ²	R ³	Example
4306 CB(1)	Cl	C ₆ H ₅	H	9, 10 and 19
4350 CB	Cl	C ₆ H ₅	CH ₃	11 and 12
4337 CB	H	C ₆ H ₅	H	13
4339 CB	CH ₃	C ₆ H ₅	H	14
4335 CB	NO ₂	C ₆ H ₅	H	15 and 20
4371 CB	NH ₂	C ₆ H ₅	H	16

(1) The disodium salt and the calcium salt were also prepared, the latter (4372 CB; Example 18) by double decomposition from the dipotassium salt.

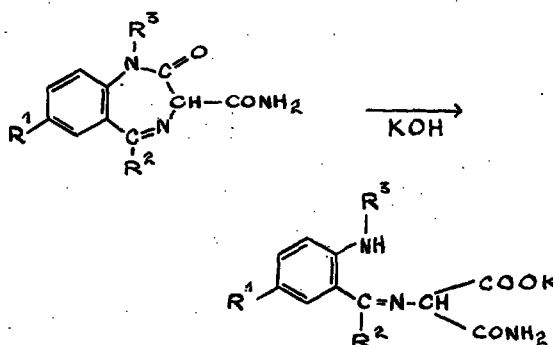
(1) The disodium salt and the calcium salt were also prepared, the later (4372 CB; Example 18) by double decomposition from the dipotassium salt.

Ortho-aminoaryl ketimines containing a carboxamide group are obtained by treating a benzodiazepine having the general formula



in which R¹, R² and R³ are as above defined, with an alkali metal hydroxide in solution in an alkanol having 1 to 7 carbon atoms. These benzodiazepines are claimed in application No. 25133/65 Serial No. 1,117,061.

Compound 4348 OB, which has an amide group in the 3-position, gives rise, on saponification with an alkali metal hydroxide, to the corresponding carboxylic derivatives in which the initial amide group is preserved.



(4349 CB; Example 17)

We have further found that the dimetal salts such as those given in Table II may, under carefully controlled conditions, be converted into benzodiazepine derivatives carrying on the 3-carbon atom a carboxylic acid function salified by the original cation.

The following examples illustrate the nature of the invention. The melting points are designated by M.pt., and are measured on a Kofler block. In these examples, compounds of type IV A have been named according to the formulae of the "open" types without thereby intending to emphasize these formulae in favour of the cyclic formulae IV B and IV C indicated earlier.

EXAMPLE 1

1-Phenyl-1-(2-amino-5-chloro-phenyl)-4-oxo-5-oxa-2-aza-1-heptene (4292 CB).

A mixture of 27.6 g (0.12 mol) of (2-amino-5-chloro-phenyl)-phenyl-methane-imine and 20.7 g (0.15 mol) of the hydrochloride of ethyl glycinate in 150 ml of methanol is stirred at room temperature for 2.5 hours. A suspension of a pale yellow solid is obtained which consists of the mixture of imine and ammonium chloride formed in the reaction. The solvent is evaporated under reduced pressure and the residue taken up in methylene chloride. It is washed with a 10% aqueous solution of sodium carbonate, then with water, dried over sodium sulphate and the solvent removed by evaporation. A yellow solid remains behind which is crystallised from acetone. 32.4 g of the crystalline product is obtained; M.pt._K: 130—135°C; yield: 85%.

This product is a mixture of the two stereoisomeric forms.

However, each of these forms can be obtained in the pure state by fractional crystallisation from acetone. They have the following melting points: Chelate form: M.pt._K 148—150°C, non-chelate form: M.pt._K 142—144°C. Mixing these two forms lowers the melting point.

EXAMPLE 2

1-Phenyl-1-(2-methylamino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene (4361 CB).

This compound is prepared by the method indicated in Example 1, the (2-amino-5-chloro-phenyl)-phenyl-methane-imine being replaced by the stoichiometric quantity of (2-methylamino-5-chloro-phenyl)-phenyl-methane-imine.

On crystallisation from hexane, a solid is obtained which consists of a mixture of the two stereoisomeric forms. M.pt._K: 70—75°C; yield: 82%.

Each of the two forms can be isolated in the pure state by fractional crystallisation from hexane.

The melting points of these two are as follows: Chelate form: M.pt._K 110°C, non-chelate form: M.pt._K 85°C.

The mixture of the two forms has a considerably lower melting point.

EXAMPLE 3

Diethyl [2-phenyl-2-(2-amino-5-chlorophenyl)-1-aza-vinyl]-malonate (4346 CB).

A solution of 9.2 g (0.04 mol) of (2-amino-5-chloro-phenyl)-phenyl-methane-imine in 16 ml of absolute alcohol is added dropwise to a boiling solution of 10.6 g (0.05 mol) of the hydrochloride of diethyl aminomalonate in 30 ml of absolute alcohol. When this is completed, the mixture is heated under reflux for 30 minutes and the solvent is then evaporated in vacuo.

The residue is taken up in water and in ether, the ethereal solution is decanted, washed with water, dried over sodium sulphate and the solvent evaporated. The product is recrystallised from diisopropyl ether. Yellow crystals are obtained (7.8 g; yield: 50%; M.pt._K: 106°C).

EXAMPLE 4

Diethyl [2-phenyl-2-(2-methylamino-5-chloro-phenyl)-1-aza-vinyl]-malonate (4362 CB).

This compound is prepared by the method indicated in Example 3, the (2-amino-5-chloro-phenyl)-phenyl-methane-imine being replaced by the stoichiometric quantity of (2-methylamino-5-chloro-phenyl)-phenyl-methane-imine. The product is a yellow solid, M.pt._K: 88°C (diisopropyl ether). Yield: 25%.

EXAMPLE 5

1-Phenyl-1-(2-amino-phenyl)-4-oxo-5-oxa-2-aza-1-heptene (4363 CB).

This compound is obtained by the technique described in Example 1, the (2-amino-5-chloro-phenyl)-phenyl-methane-imine being replaced by an equimolecular quantity of (2-amino-phenyl)-phenyl-methane-imine.

The product is obtained in the form of yellowish crystals; M.pt._K: 106°C (diisopropyl ether); yield: 58%.

EXAMPLE 6

Diethyl [2-phenyl-2-(2-amino-phenyl)-1-aza-vinyl]-malonate (4351 CB).

Using the same method as described in Example 3 but replacing the (2-amino-5-chloro-phenyl)-phenyl-methane-imine by the equimolecular quantity of (2-amino-phenyl)-phenyl-methane-imine, compound 4351 CB is obtained in a yield of 31%. Pale yellow crystals are obtained; M.pt._K: 100°C (diisopropyl ether).

It is to be noted that in this method of preparation, a small quantity of the cyclised product 3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1*H*-benzo[f]-1,4-diazepine (4352 CB) can be isolated from the mother liquor in addition to the main product.

EXAMPLE 7

1-Phenyl-1-(2-amino-5-methyl-phenyl)-4-oxo-5-oxa-2-aza-1-heptene (4364 CB).

This product is obtained by the method described in Example 1, the (2-amino-5-chloro-phenyl)-phenyl-methane-imine being replaced by the equimolecular quantity of (2-amino-5-methyl-phenyl)-phenyl-methane-imine.

Yellowish crystals; M.pt._x: 131°C (diisopropyl ether); yield: 35%.

EXAMPLE 8

1-*n*-butyl-1-(2-amino-5-chloro-phenyl)-4-oxo-5-oxa-2-aza-1-heptene (4365 CB).

This compound is prepared by the method indicated in Example 1, substituting for (2-amino-5-chloro-phenyl)-phenyl-methane-imine an equivalent quantity of butyl-(2-amino-5-chloro-phenyl)-methane-imine. Yellow crystals are obtained; M.pt._x: 96—97°C (diisopropyl ether); yield: 55%.

EXAMPLE 9

Dipotassium salt of [2-phenyl-2-(2-amino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4306 CB).

50 g of caustic potash are dissolved in 1350 ml of 96% ethyl alcohol, and 82 g (0.25 mol) of 7-chloro-3-methoxycarbonyl-5-phenyl-2-oxo-2,3-dihydro-1*H*-benzo[f]-1,4-diazepine are then added all at once at a temperature of about 70°C.

The solid dissolves rapidly to form a yellow solution which then loses colour whilst simultaneously an abundant colourless precipitate appears.

After cooling, the solid is filtered by suction and washed with 96% alcohol. The product is dried at ordinary temperature in a high vacuum. A colourless solid is obtained (quantitative yield), which is completely soluble in water. The aqueous solution is strongly alkaline in reaction.

The preparation may be carried out by replacing the methoxycarbonyl compound by the corresponding ethoxycarbonyl compound. A similar yield of the dipotassium salt is obtained.

The corresponding disodium salt can be obtained in the same manner by replacing potassium hydroxide by sodium hydroxide.

EXAMPLE 10

Dipotassium salt of [-phenyl-2-(2-amino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4306 CB).

2 g of the product of Example 3 are added to a solution of 0.84 g (0.015 mol) of potassium hydroxide in 1 ml of water and 25 ml of methanol and the mixture then heated to reflux. The solid dissolves, giving rise to a red solution which rapidly loses its colour, a precipitate appearing at the same time. After cooling, the solid is filtered by suction and washed with methanol. A colourless solid is obtained (1.25 g). This compound is found to be identical with that prepared in Example 9.

EXAMPLE 11

Dipotassium salt of [2-phenyl-2-(2-methylamino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4350 CB, first preparation).

This product is obtained by the method described in Example 9, the benzo-diazepine of that example being replaced by a stoichiometric quantity of 7-chloro-3-carbethoxy-1-methyl-5-phenyl-2-oxo-2,3-dihydro-1*H*-benzo[f]-1,4-diazepine. It is a colourless powder which is very soluble in water. Yield: 71%. The aqueous solution is strongly alkaline in reaction.

EXAMPLE 12

Dipotassium salt of [2-phenyl-2-(2-methylamino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4350 CB, second preparation).

This compound may be obtained as described in Example 10, the product of Example 3 being replaced by an equimolecular quantity of the product of Example 4. It is a colourless powder completely soluble in water and identical with the product of Example 11; yield: 50%.

EXAMPLE 13

Dipotassium salt of [2-phenyl-2-(2-amino-phenyl)-1-aza-vinyl]-malonic acid (4337 CB).

This substance is prepared by the method described in Example 9, the benzo-diazepine of that example being replaced by a stoichiometric quantity of 3-ethoxycarbonyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine.

Colourless leaflets are obtained which are completely soluble in water and strongly alkaline in reaction; substantially quantitative yield.

EXAMPLE 14

Dipotassium salt of [2-phenyl-2-(2-amino-5-methyl-phenyl)-1-aza-vinyl]-malonic acid (4339 CB).

This substance is prepared by the procedure given in Example 9, the benzo-diazepine of that example being replaced by an equimolecular quantity of 7-methyl-3-ethoxycarbonyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine. It is obtained in the form of a colourless solid completely soluble in water. The yield is practically quantitative.

EXAMPLE 15

Dipotassium salt of [2-phenyl-2-(2-amino-5-nitrophenyl)-1-aza-vinyl]-malonic acid (4335 CB).

This compound is obtained by the procedure described in Example 9, the benzo-diazepine of that example being replaced by an equimolecular quantity of 7-nitro-3-ethoxycarbonyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine. It is a yellow powder which dissolves completely in water and is strongly alkaline in reaction; the yield is substantially quantitative.

EXAMPLE 16

Dipotassium salt of [2-phenyl-2-(2,5-diamino-phenyl)-1-aza-vinyl]-malonic acid (4371 CB).

This compound is obtained by the method described in Example 9, the benzo-diazepine of that example being replaced by a stoichiometric quantity of 7-amino-3-ethoxycarbonyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine. It is a yellow solid completely soluble in water and having a strongly alkaline reaction. The yield is quantitative.

EXAMPLE 17

Potassium salt of 4-phenyl-4-(2-amino-5-chloro-phenyl)-2-carbamoyl-3-aza-3-butenic acid (4349 CB).

This product is obtained by the method described in Example 9, the benzo-diazepine of that example being replaced by an equivalent quantity of 7-chloro-3-carbamoyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine. Fine yellow crystals completely soluble in water are obtained in quantitative yield.

EXAMPLE 18

Calcium salt of [2-phenyl-2-(2-amino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4372 CB).

A solution of 0.55 g (0.00375 mol) of calcium chloride dihydrate in 5 ml of water is added to a solution of 1 g (0.0025 mol) of the dipotassium salt of [2-phenyl-2-(2-amino-5-chloro-phenyl)-1-aza-vinyl]-malonic acid (4306 CB) in 15 ml of water.

A solid separates out immediately. After it has been left to stand for 10 minutes, it is filtered by suction, then washed with a small quantity of water and finally dried at ordinary temperature in a high vacuum. A yellowish white solid is obtained which is sparingly soluble in water (0.75 g); yield: 80%.

EXAMPLE 19

Compound of Example 10.

341.5 g (1 mol) of 7-chloro-3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine are added as rapidly as possible, with stirring, at 18 to 20°C to a solution of 224 g (4 mols) of potassium hydroxide in 5130 ml of ethyl alcohol containing 10% by volume of water. A clear yellow solution forms after about 2 minutes. Stirring is stopped; crystallisation of compound 4306 CB begins after several minutes and is accompanied by progressive decolorisation. The product is filtered by suction after 4 hours, washed with absolute alcohol (500 ml) and then dried to constant weight at 50°C under an absolute pressure of 0.1 mm. 422 g of yellowish white leaflets are obtained.

EXAMPLE 20

Compound of Example 15.

The procedure employed is that described in Example 19 but the benzodiazepine used is replaced by an equimolecular quantity of 7-nitro-3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine. The reaction follows the same course.

Some of the compounds described in the present application have been studied with regard to their action on the central nervous system, as psycholeptics, myorelaxants and tranquillisers. In addition, the acute toxicity has been determined for a number of these compounds.

The study of certain compounds of known pharmacodynamic and clinical activity, such as diazepam and chlordiazepoxide, has been undertaken under the same experimental conditions, with the same tests and with animals of the same origin as for the new compounds. It has thereby been possible to make quantitative comparisons of the activity of the different compounds for the different tests employed.

In the series of tests briefly described hereinafter, each compound was tested with the use of five or six scaled doses on batches of 10 or 20 animals for each dose; it was thereby possible to determine with sufficient exactitude by the method of probits the 50% effective dose (ED_{50}), that is to say the dose for which half the animals are protected and react in a predetermined manner according to a particular action.

Tests employed.

The following tests were employed:

1) Traction test (mice).

This consists in observing when the treated animals are capable of retrieving a rod grasped by the front paws only. Inability to carry this out was interpreted as a sign of myorelaxant activity.

2) Balance test: rotating rod (mice).

This test consists in observing whether the treated animals are capable of maintaining their balance on a horizontal rod kept in rotation.

Numerous neuroleptic compounds or tranquillisers disturb the equilibration reflex.

3) Anti-convulsant activity (anti-pentetrazole) (mice).

Pentetrazole injected intraperitoneally in a dose of 125 mg/kg produces fatal convulsions in 100% of the animals.

Certain compounds exert a protective action preventing convulsions and permitting survival.

4) Anti-convulsant activity (electric shock) (mice).

The test consists in determining the intensity of the electric current required to produce a fatal shock in a batch of test animals.

Certain preventively administered compounds effectively protect a certain percentage of animals subjected to an electric current of an intensity which is fatal to untreated animals.

5) Exploration test (mice)

This extremely simple test consists in placing a mouse at the centre of a floor pierced with holes and in noting how many holes the mouse explores in 5 minutes. This test is carried out in a room in which complete silence is observed and which contains no person except the experimenter who is seated and still. It appeals to the curiosity of the animals. The doses of the compounds employed are, however, very small and considerably less than those required to impair movement. This simple test makes it possible to observe whether the compounds examined produce a more or less pronounced lack of interest in the environment and it gives information which is interesting from the clinical point of view with regard to the treatment of anxiety and restlessness.

6) Spontaneous motor activity in the rat and mouse and provoked motor activity.

The effect of drugs on voluntary movements of animals can be studied statistically by methods the details of which will not be discussed. The mouse, which is an extremely lively animal and moves about a great deal, is particularly suitable for this type of experiment.

Moreover, this spontaneous mobility can be increased by administration to the

animals of certain substances such as 1-phenyl-2-aminopropane mescaline and methyl α -phenyl- α (piperidyl-2) acetate.

The experimental results obtained by these methods give valuable information for clinical purposes with regard to the treatment of ambulatory psychomotor crises.

5 7) Anti-strychnine activity.

This test demonstrates the activity of drugs against a medullary excitant.

8) —Morphine excitation.

In the cat, morphine produces a specific state of excitation with hallucinations which can be attenuated or suppressed by certain psycholeptic drugs.

10 In the mouse, the action of morphine is different but also manifested by marked central excitation. 10

9) Aggressiveness (cat/mouse).

In general, 75 to 80% cats are aggressive when confronted with white mice. Psycholeptics and tranquillisers may make the cat indifferent and sometimes even amiable to the mouse. Similarly, in the case of cats that are furious and aggressive in relation to humans, diminution or suppression of the instinctive fear and establishment of a climate of confidence are observed. 15

10) Combativeness.

20 It is possible to make a male rat aggressive towards another male rat enclosed in the same cage by passing an electric current of more or less high voltage through the floor of the cage. 20

This test, like the preceding one, can obviously give information of clinical value for the treatment of aggression diseases.

11) Conditioning test.

25 The test used consists in educating rats to avoid an electric current passed through the floor of a cage of two compartments when they change compartments. The animal is first warned by a lamp which lights up in the compartment through which the current is passing while the other is in relative darkness. 25

30 This test, which requires more or less daily training at the rate of 50 times for each rat, makes it possible to follow the animals and note their progress. The performances realised at the end of a certain (3 weeks to one month of training) are fairly constant, the percentage of errors made by adequately gifted subjects being less than 10 and very often zero. 30

35 One would imagine that disturbances produced in these performances which call upon the memory of animals would be of great importance for the choice of a new medicament. A deconditioning drug of sufficient intensity could have the result of partly depriving the patient of the idea of danger and would consequently require special surveillance of the sick persons. 35

12) Potentiation of narcosis.

40 Most psycholeptics are hypnotics in large doses but many of them can in small doses, without themselves producing any hypnosis, either prolong the time of sleep obtained with a true hypnotic (for example a barbiturate) or appreciably lower the dose of barbiturate required to obtain sleep. 40

45 In the following Table are summarised all the results obtained in the different tests briefly recorded above with certain compounds described in the present application, compared with various reference substances of known clinical activity. In the Table diazepam is 7-chloro-1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine and nor-diazepam is 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo-[f]-1,4-diazepine. 45

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TABLE
 RECAPITULATING THE ACTIVITIES
 (The figures in the table indicate the 50% effective
 PO = per os; IP = intraperitoneal)

M = mouse
 R = rat
 C = cat

	Acute toxicity (M) LD ₅₀	Traction (M)	Equilibration (M)	Anti-pentetrazole (M)	Electric shock (M)	Exploration (M)	Spontaneous motor activity (R)	Spontaneous motor activity (M)	1-Phenyl-2-aminopropane provoked motor activity (R)
Diazepam (compound B)	720 PO; 220 IP; 800 SC	1.60 PO	4.4 PO	1.7 PO	5 PO	6 PO	25 PO	5 PO	100 PO
Nor-diazepam (compound A)		3.5 PO	8.6 PO	2.9 PO	9 PO	7.8 PO	50 PO	50 PO	100 PO
Chlordiazepoxide	200 PO; 80 IP	3 PO	13 PO	5 PO	17 PO	20 PO			>100 PO
4292 CB		20 PO	>20 PO	20 PO	100 PO	>100 PO			

III

doses in mg/kg and the route of administration:

doses in mg/kg and the route of administration:
SC = subcutaneous; IV = intravenous)

1-Phenyl-2-aminopropane provoked motor activity (M)	> 20 PO	> 20 PO	
Mescaline provoked motor activity (M)			
Methyl- α -phenyl α (piperidyl-2) acetate provoked motor activity (M)			
Anti-strychnine (M)	> 50 PO		
Morphine excitation (M)	25 PO		
Morphine crisis (C)	25 SC	100 SC	
Aggressiveness (C/M)	25 SC		
Combativeveness (R)	25 PO	100 PO	100 PO
Double box conditioning (R)	without effect	without effect	
Narcotic potentiation (M)	2.5 PO		

TABLE III

	Acute toxicity (M) LD ₅₀	Traction (M)	Equilibration (M)	Anti-pentrazole (M)	Electric shock (M)	Exploration (M)	Spontaneous motor activity (R)	Spontaneous motor activity (M)	1-Phenyl-2-aminopropane provoked motor activity (R)
4306 CB	700 PO 250 IP	1.10 PO	14 PO	1.7 PO	4.6 PO	4 PO	<25 PO	5 PO	>100 PO
Ca 2053 the same formula as 4306 CB but obtained by saponification of the non-cyclic inter- mediate (4346 CB)		1.25 PO	9.6 PO	1.7 PO	3 PO	6.25 PO	25 PO	10 PO	
4350 CB		5 PO	>10 PO	7.5 PO	20 PO	10 PO		>20 PO	
4335 CB	560 PO	1.25 PO	4.3 PO	0.44 PO	3.2 PO	1.8 PO	25 PO	5 PO	100 PO
4349 CB		10 PO	>10 PO	>10 PO	>10 PO	>10 PO		10 PO	
4337 CB		5 PO	>10 PO	>10 PO	>10 PO	>10 PO			
4339 CB		>10 PO	>10 PO	>10 PO	>10 PO			>10 PO	

(Continued)

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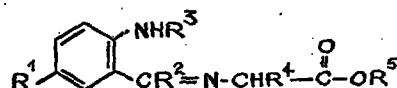
From an examination of the figures given in the Table it is found that

1) The nitro derivative of Example 15 is extremely active in different tests, especially as a myorelaxant and as an anticonvulsant in the test for curiosity; on the other hand, it appears to have less effect on the faculties of displacement. Lastly, it has a marked effect in diminishing aggressiveness (test for combativeness).

2) The compound of Examples 9, 10 and 19, which is very similar to that of Example 15, is also highly active and in most of the tests it is at least equal and frequently superior to diazepam.

WHAT WE CLAIM IS:—

1. An ortho-aminoaryl ketimine having, in one tautomeric form, the general formula



in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl group having 1 to 7 carbon atoms, an alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom, by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms or is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R⁴ is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms or an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkyl-carbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal and R⁵ is an alkyl group having 1 to 7 carbon atoms or, when R⁴ is a carbamoyl or —COOCat group, a cation Cat as already defined.

2. 1-Phenyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.

3. 1-Phenyl-1-(2-methylamino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.

4. Diethyl [2-phenyl-2-(2-amino-5-chlorophenyl)-1-aza-vinyl]-malonate.

5. Diethyl [2-phenyl-2-(2-methylamino-5-chlorophenyl)-1-aza-vinyl]-malonate.

6. 1-Phenyl-1-(2-aminophenyl)-4-oxo-5-oxa-2-aza-1-heptene.

7. Diethyl [2-phenyl-2-(2-aminophenyl)-1-aza-vinyl]-malonate.

8. 1-Phenyl-1-(2-amino-5-methylphenyl)-4-oxo-5-oxa-2-aza-1-heptene.

9. 1-n-Butyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.

10. A process according to claim 18 in which the α-amino-carboxylic acid 1-aza-vinyl]-malonic acid.

11. Dipotassium salt of [2-phenyl-2-(2-methylamino-5-chlorophenyl)-1-aza-vinyl]-malonic acid.

12. Dipotassium salt of [2-phenyl-2-(2-aminophenyl)-1-aza-vinyl]-malonic acid.

13. Dipotassium salt of [2-phenyl-2-(2-amino-5-methylphenyl)-1-aza-vinyl]-malonic acid.

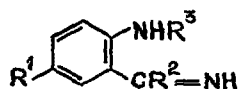
14. Dipotassium salt of [2-phenyl-2-(2-amino-5-nitrophenyl)-1-aza-vinyl]-malonic acid.

15. Dipotassium salt of [2-phenyl-2-(2,5-diaminophenyl)-1-aza-vinyl]-malonic acid.

16. Potassium salt of 4-phenyl-4-(2-amino-5-chlorophenyl)-2-carbamoyl-3-aza-3-butenic acid.

17. Calcium salt of [2-phenyl-2-(2-amino-5-chlorophenyl)-1-aza-vinyl]-malonic acid.

18. A process for the production of an ortho-aminoaryl ketimine having the general formula given in claim 1 but excluding the case in which R⁴ is —COOCat and/or R⁵ is Cat, which comprises reacting an ortho-aminoaryl ketimine having the general formula



in which R¹, R² and R³ are as defined in claim 1, with an aliphatic α-aminocarboxylic acid ester having the general formula



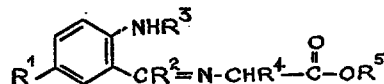
From an examination of the figures given in the Table it is found that

1) The nitro derivative of Example 15 is extremely active in different tests, especially as a myorelaxant and as an anticonvulsant in the test for curiosity; on the other hand, it appears to have less effect on the faculties of displacement. Lastly, it has a marked effect in diminishing aggressiveness (test for combativeness).

2) The compound of Examples 9, 10 and 19, which is very similar to that of Example 15, is also highly active and in most of the tests it is at least equal and frequently superior to diazepam.

WHAT WE CLAIM IS:—

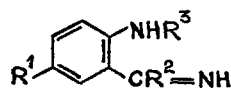
1. An ortho-aminoaryl ketimine having, in one tautomeric form, the general formula



in which R^1 is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl group having 1 to 7 carbon atoms, an alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R^2 is a phenyl group which may be substituted by a halogen atom, by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms or is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R^3 is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R^4 is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms or an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkyl-carbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or a group having the formula $-\text{COOCat}$ in which Cat is the cation of an alkali metal or semication of an alkaline earth metal and R^5 is an alkyl group having 1 to 7 carbon atoms or, when R^4 is a carbamoyl or $-\text{COOCat}$ group, a cation Cat as already defined.

2. 1-Phenyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.
3. 1-Phenyl-1-(2-methylamino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.
4. Diethyl [2-phenyl-2-(2-amino-5-chlorophenyl)-1-aza-vinyl]-malonate.
5. Diethyl [2-phenyl-2-(2-methylamino-5-chlorophenyl)-1-aza-vinyl]-malonate.
6. 1-Phenyl-1-(2-aminophenyl)-4-oxo-5-oxa-2-aza-1-heptene.
7. Diethyl [2-phenyl-2-(2-aminophenyl)-1-aza-vinyl]-malonate.
8. 1-Phenyl-1-(2-amino-5-methylphenyl)-4-oxo-5-oxa-2-aza-1-heptene.
9. 1-n-Butyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene.
10. A process according to claim 18 in which the α -amino-carboxylic acid 1-aza-vinyl]-malonic acid.
11. Dipotassium salt of [2-phenyl-2-(2-methylamino-5-chlorophenyl)-1-aza-vinyl]-malonic acid.
12. Dipotassium salt of [2-phenyl-2-(2-aminophenyl)-1-aza-vinyl]-malonic acid.
13. Dipotassium salt of [2-phenyl-2-(2-amino-5-methylphenyl)-1-aza-vinyl]-malonic acid.
14. Dipotassium salt of [2-phenyl-2-(2-amino-5-nitrophenyl)-1-aza-vinyl]-malonic acid.
15. Dipotassium salt of [2-phenyl-2-(2,5-diaminophenyl)-1-aza-vinyl]-malonic acid.
16. Potassium salt of 4-phenyl-4-(2-amino-5-chlorophenyl)-2-carbamoyl-3-aza-3-butenic acid.
17. Calcium salt of [2-phenyl-2-(2-amino-5-chlorophenyl)-1-aza-vinyl]-malonic acid.

18. A process for the production of an ortho-aminoaryl ketimine having the general formula given in claim 1 but excluding the case in which R^4 is $-\text{COOCat}$ and/or R^5 is Cat, which comprises reacting an ortho-aminoaryl ketimine having the general formula



in which R^1 , R^2 and R^4 are as defined in claim 1, with an aliphatic α -aminocarboxylic acid ester having the general formula

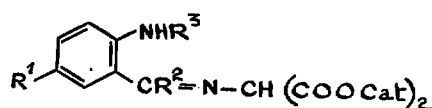


in which R^4 is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms, an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group or an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups and R^5 is an alkyl group having 1 to 7 carbon atoms, or a salt thereof.

19. A process according to claim 18 in which the α -amino-carboxylic acid ester is a dialkyl aminomalonate or an alkyl aminoacetate.

20. A process according to either of claims 18 or 19 which is carried out in an inert organic diluent.

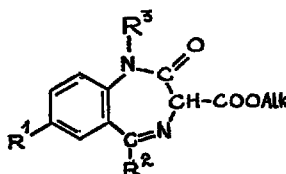
21. A process for the preparation of an alkali metal salt of an ortho-aminoaryl ketimine having the general formula



in which R^1 , R^2 and R^3 are as defined in claim 1 and each Cat is an alkali metal cation, which comprises saponifying with an alkali metal hydroxide an N-substituted ortho-aminoaryl ketimine produced by the process of any of claims 18—20 in which R^4 is a carbalkoxy group and R^5 is an alkyl group.

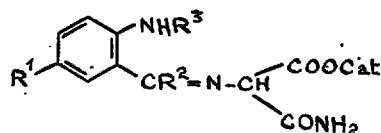
22. A process for producing an alkaline earth metal salt of an ortho-aminoaryl ketimine having the general formula given in claim 21 but in which Cat_2 is an alkaline earth metal cation which comprises producing an alkali metal salt of an ortho-aminoaryl ketimine by the process claimed in claim 21 and thereafter treating an aqueous solution thereof with a water-soluble salt of an alkaline earth metal.

23. A process for the preparation of an alkali metal salt of an ortho-aminoaryl ketimine having the general formula given in claim 21, which comprises treating a 3-carbalkoxy benzodiazepine having the general formula

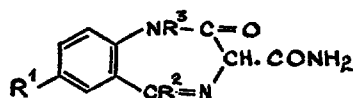


in which R^1 , R^2 and R^3 are as defined in claim 1 and Alk is an alkyl group having 1 to 7 carbon atoms, with an alkali metal hydroxide in solution in an alkanol having 1 to 7 carbon atoms.

24. A process for the production of an alkali metal salt of an ortho-aminoaryl ketimine having the general formula



in which R^1 , R^2 and R^3 are as defined in claim 1 and Cat is an alkali metal cation, which comprises treating a benzodiazepine having the general formula



in which R^1 , R^2 and R^3 are as defined in claim 1, with an alkali metal hydroxide in solution in an alkanol having 1 to 7 carbon atoms.



25. A process for the production of an N-substituted ortho-aminoaryl ketimine according to any of claims 18, 21, 22, 23 or 24 and substantially as hereinbefore described with reference to any appropriate example.

5 26. An N-substituted ortho-aminoaryl ketimine whenever produced by the process of any of claims 18—25.

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