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SUBSTITUTED 3,5-DIOXO-ISOXAZOLIDINES AND A PROCESS FOR THE MANUFACTURE THEREOF

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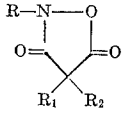
14 Claims. (Cl. 260—307)

The present invention relates to new isoxazolidine compounds and, in particular, to substituted 3,5-dioxo-isoxazolidines and salts thereof with bases. These substituted 3,5-dioxo-isoxazolidines and their salts have valuable therapeutic properties and are useful in the treatment of afflictions involving inflammatory phenomena such as rheumatic diseases. Furthermore, the invention relates to a process for the manufacture of said substituted 3,5-dioxo-isoxazolidines.

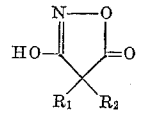
The substituted 3,5-dioxo-isoxazolidines provided by this invention can be represented—in one of their tautomeric forms—by the general formula

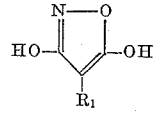


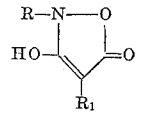
(I)

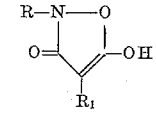
wherein each of the symbols R, R_1 and R_2 represents a member selected from the group consisting of hydrogen and hydrocarbon radicals having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds, with the proviso that at least one but not more than two of said symbols stand for hydrogen.

These compounds can also exist in other tautomeric forms to which the following formulae can be attributed:









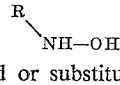
A preferred class of compounds corresponding to the above Formula I includes those 3,5-dioxo-isoxazolidines in which each of the symbols R, R_1 and R_2 is hydrogen or a hydrocarbon radical having not more than 10 carbon atoms and being free from aliphatic unsaturated bonds, with the proviso that at least one but not more than two of said symbols stand for hydrogen. More preferred compounds within this class are those 3,5-dioxo-isoxazolidines in which R, R_1 and R_2 taken together comprise not more than 20 carbon atoms. The most preferred 3,5-dioxo-isoxazolidines are those which carry in the 2-position a phenyl radical and in the 4-position one hydrocarbon radical having from 4 to 7 carbon atoms and being free from aliphatic unsaturated bonds. Specific

examples of such compounds are 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine, 2-phenyl - 4 - n - butyl-3,5-dioxo-isoxazolidine, 2 - phenyl-4-cyclopentyl-3,5-dioxo-isoxazolidine, 2,4-diphenyl-3,5-dioxo-isoxazolidine and 2-phenyl-4-cyclopentylmethyl-3,5-dioxo-isoxazolidine.

Further specific examples of substituted 3,5-dioxo-isoxazolidines having the activity described above are 2-phenyl-3,5-dioxo-isoxazolidine, 4 - benzyl-3,5-dioxo-isoxazolidine and 4,4-dibenzyl-3,5-dioxo-isoxazolidine.

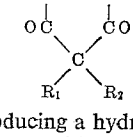
In the above Formula I R, R_1 and R_2 can represent a great variety of hydrocarbon radicals having no aliphatic unsaturated bonds, for instance straight or branched chain alkyl radicals, preferably those having up to 10 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl and isomers thereof, n-hexyl and isomers thereof, n-heptyl and isomers thereof, n-octyl and isomers thereof, n-nonyl and isomers thereof, n-decyl and isomers thereof; cycloalkyl radicals such as cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; substituted cycloalkyl radicals, preferably those having up to 10 carbon atoms, such as 3-methyl-cyclobutyl, 4-methyl- or 4-ethyl-cyclohexyl, 4-isopropyl-hexyl and 2,6-dimethyl-cyclohexyl; cycloalkyl-alkyl radicals, preferably those having up to 10 carbon atoms, such as cyclobutyl-methyl, cyclobutyl-ethyl, 1-methyl-2-cyclobutyl-ethyl and 5-cyclopentyl-n-pentyl; unsubstituted and substituted aryl radicals such as phenyl, α- and β-naphthyl, tolyl, xylyl, p-ethylphenyl, p-propyl-phenyl, p-butylphenyl and 2,6-dimethylphenyl; or aralkyl radicals, preferably those having up to 14 carbon atoms, such as benzyl, phenylethyl, phenylpropyl, phenylbutyl, 2-methyl-2-phenyl-propyl and benzhydryl; and the like.

According to the present invention the new substituted 3,5-dioxo-isoxazolidines are prepared by a process which comprises acylating with ring closure a compound having the general formula



(II)

with an unsubstituted or substituted malonylating agent yielding the divalent radical of the formula



(III)

and, if desired, introducing a hydrocarbon radical R_1 into the 4-position of the resulting acylation product if said position is unsubstituted, each of the symbols R, R_1 and R_2 in the above formulae representing hydrogen or a hydrocarbon radical having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds, with the proviso that at least one but not more than two of said symbols stand for hydrogen, and, if desired, reacting the resulting substituted 3,5-dioxo-isoxazolidine with a base to form a salt.

The starting compounds used for carrying out the process of this invention are generally known or can be obtained by known conventional methods. Suitable unsubstituted or substituted malonylating agents include functional derivatives of unsubstituted, mono-substituted and di-substituted malonic acids which are capable of acylating the hydroxylamine component under mild conditions, i.e. conditions which do not result in a decomposition of the isoxazolidines formed in the reaction. The acid halides, e.g. the chlorides and bromides, particularly the easily accessible chlorides of unsubstituted, mono-substituted and di-substituted malonic acids, as well as carbon suboxide have been found to be particularly convenient malonylating agents.

The process of this invention actually is an acylation in

which hydroxylamine or mono-substituted hydroxylamine is acylated at the nitrogen atom as well as at the oxygen atom with simultaneous ring closure.

Hydroxylamines acylated both at the nitrogen and oxygen atoms are known to be thermo-labile compounds (cf. L. Horner and H. Steppan, Ann. 606, 24–47 (1957)).

Therefore, it was by no means possible to anticipate whether the heterocyclic compounds described herein could exist at all or not. We have found, and this was very surprising and unexpected, that it was possible to prepare 3,5-dioxo-isoxazolidines by the acylating and cyclizing reaction of this invention. Actually, the new compounds obtained by this invention are also thermolabile as the N,O-di-acylated hydroxylamines are; however, if some simple precautions are taken, they are stable and storable without decomposition. The new compounds differ from the N,O-di-acylated hydroxylamines in that the former have pronounced acidic properties.

In one embodiment of the process according to this invention unsubstituted or N-mono-substituted hydroxylamine is acylated with an unsubstituted or substituted malonyl halide, e.g. a chloride or bromide, in an organic solvent or diluent in the presence of an acid-binding agent at low temperatures, conveniently between about −20 and +30° C., and advantageously in an oxygen-free atmosphere, e.g. in a nitrogen atmosphere. Organic solvents or diluents which can be used for this purpose include hydrocarbons, e.g. benzene and toluene; halogenated hydrocarbons, e.g. chloroform; ethers, e.g. diethyl ether; and other solvents which are known to be suitable for acylations. The acid-binding agent is preferably a non-acylatable organic amine such as pyridine or triethylamine. The acylation of unsubstituted or N-substituted hydroxylamine with the unsubstituted or substituted malonyl halide can also be carried out in an aqueous medium. In this latter case it is advisable to use an inorganic acid-binding agent such as sodium bicarbonate or calcium carbonate. In aqueous media the acylation can be effected at about room temperature.

In another embodiment of the process according to this invention carbon suboxide is used as the malonylating agent. The acylation is carried out by reacting carbon suboxide with an N-mono-substituted hydroxylamine, conveniently in an inert organic medium, e.g. in tetrahydrofuran or diethylene glycol dimethyl ether, at moderate temperatures, e.g. between about 10 and 60° C. The substituted 3,5-dioxo-isoxazolidines obtained in this embodiment are unsubstituted in the 4-position. These compounds are also valuable intermediates which are useful in the synthesis of other therapeutically active 3,5-dioxo-isoxazolidines.

If desired, a hydrocarbon radical R_1 as defined above can be introduced into the 4-position of the 3,5-dioxo-isoxazolidines which result from the acylation of N-mono-substituted hydroxylamine with unsubstituted malonyl halides or carbon suboxide and which are unsubstituted in the 4-position. This substitution can be effected by conventional methods, for instance by condensation with alkyl, cycloalkyl or aralkyl esters of strong acids, such as butyl bromide, benzyl chloride, dimethyl sulfate, 2-methyl-cyclobutylmethyl p-toluenesulfonate or isopropyl methanesulfonate, or by reductive condensation with carbonyl compounds, such as benzaldehyde or cyclohexanone.

The substituted 3,5-dioxo-isoxazolidines obtained according to the present invention have pronounced acidic properties and can, therefore, easily be converted into salts by reaction with equivalent amounts of inorganic or organic bases according to conventional methods. The salts obtained with alkalis, ammonia, or organic bases, such as methylamine, ethanolamine, diethanolamine, diethylaminoethanol, triethylamine and morpholine, are mostly colorless, highly water-soluble compounds which dissolve in water to give substantially neutral solutions. Salts with other cations can also be prepared easily. The alkaline earth metal salts, e.g. the calcium and magnesium salts of the compounds of this invention are as a rule difficulty soluble in water.

The substituted 3.5-dioxo-isoxazolidines obtained by this invention are characterized by their valuable biological activity. They have an antiphlogistic, analgesic or local anaesthetic activity and are, therefore, intended to be used as therapeutic agents in medicine, particularly in the treatment of affections involving inflammatory phenomena, e.g. rheumatic diseases. With regard to their biological activity the new compounds are comparable to such known pyrazole derivatives as antipyrine, 4-dimethylamino-antipyrine and phenylbutazone. A comparison of phenylbutazone and for instance 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine obtained by this invention has shown that with equal doses the average antiphlogistic and anti-rheumatic activity of the latter compound is at least as strong as that of phenylbutazone, and that this latter compound is considerably more toxic and causes much more undesirable secondary reactions than said substituted isoxazolidine. The 3,5-dioxo-isoxazolidines in which R is phenyl, R_1 is a hydrocarbon radical having from 4 to 7 carbon atoms and being free from aliphatic unsaturated bonds and R_2 is hydrogen having a particularly beneficial activity and low toxicity.

For therapeutic purposes the new substituted 3,5-dioxo-isoxazolidines can be administered orally in solid form as such or in the form of their salts with bases, for instance after having been formulated into tablets or sugar-coated pills, or in capsules. The water-soluble salts of the substituted 3,5-dioxo-isoxazolidines with bases can be administered parenterally. In those cases where these salts are not indefinitely stable in squeous solution the dry salts can be filled in ampuls and freshly dissolved in water immediately before injection. The salts can also be dissolved in non-toxic solvents in which they are stable, e.g. in propylene glycol or polyethylene glycol.

The invention is illustrated in the following examples without being limited thereto. In these examples all temperatures are given in centigrade degrees.

EXAMPLE 1

12.8 g. of benzyl-malonic acid are refluxed for 2 hours with 25 ml. of thionyl chloride with the exclusion of humidity. The excess thionyl chloride is then evaporated in a partial vacuum, and the yellow oily residue is taken up in 20 to 30 ml. of absolute chloroform. This solution is added dropwise within 20 to 30 minutes in a nitrogen atmosphere and with the exclusion of humidity, to a well stirred mixture, cooled to −10°, of 35 ml. of absolute pyridine and 200 ml. of absolute chloroform. 4.6 g. of hydroxylamine hydrochloride are added in one portion, and the mixture is stirred for 1 hour in a bath of 0° and then for 2 hours at 20 to 25°. The hydroxylamine hydrochloride dissolves after a short period. The reaction mixture is extracted twice with 100 ml. of 2 N hydrochloric acid and then with 100 ml. of water. The reaction product is removed from the chloroform solution by extracting three times with 200 ml. of 1 N sodium carbonate solution. The combined sodium carbonate solutions are washed with a small amount of ether, cooled to 0 to 5° and acidified to Congo by the addition of 6 N hydrochloric acid. The resulting precipitate which is partly in crystalline form is taken up in ether, the ethereal solution is washed neutral with water and dried over sodium sulfate. The ethereal solution which contains 5.1 g. of crude reaction product is filtered through a column of 15 g. of neutral alumina of activity I. The column is eluted with 300 ml. of ether, and the eluate is concentrated at not more than 40–50°, finally in vacuo at room temperature. The residue consists of 4-benzyl-3,5-dioxo-isoxazolidine which can be obtained in analytically pure colorless form of M.P. 98–99° by recrystallization from benzene-gasoline and ethyl acetate-petroleum ether.

EXAMPLE 2

By proceeding in the manner described in Example 1 and using 9.3 g. of cyclohexyl-malonic acid, 20 ml. of thionyl chloride and 3.5 g. of hydroxylamine hydrochloride as starting materials there is obtained 4-cyclohexyl-3,5-dioxo-isoxazolidine of M.P. 100 to 101°.

EXAMPLE 3

By proceeding in the manner described in Example 1 and using 6.7 g. of (ω-phenyl-propyl)-malonic acid, 15 ml. of thionyl chloride and 2.1 g. of hydroxylamine hydrochloride as starting materials there is obtained 4-(ω-phenyl-propyl)-, 3,5-dioxo-isoxazolidine of M.P. 114–115°.

EXAMPLE 4

By proceeding in the manner described in Example 1 and using 13.5 g. of benzhydryl-malonic acid, 30 ml. of thionyl chloride and 3.5 g. of hydroxylamine hydrochloride as starting materials there is obtained 4-benzhydryl-3,5-dioxo isoxazolidine of M.P. 132–133°.

EXAMPLE 5

A solution of 7.35 g. of α-phenyl-α-ethyl-malonyl chloride in 25 ml. of absolute chloroform is added dropwise within 20 to 30 minutes, in a nitrogen atmosphere and with the exclusion of humidity, to a stirred mixture, cooled to −10°, of 15 ml. of absolute pyridine and 100 ml. of absolute chloroform. 2.1 g. of hydroxylamine hydrochloride are added to the yellow-brown solution. The hydroxylamine hydrochloride dissolves after a short period. The solution is stirred for a further 4 hours at 20 to 30° and then extracted twice with 50 ml. of 2 N hydrochloric acid and once with water. The reaction product is then removed from the chloroform solution by extracting three times with 50 ml. of 2 N sodium carbonate solution. The combined sodium carbonate solutions are washed with ether, cooled to 0 to 5° and acidified to Congo by the addition of 6 N hydrochloric acid. The oil that separates is taken up in 200 ml. of ether, the ethereal solution is washed neutral with water and dried over sodium sulfate. The solution contains 4.5 g. of crude 4-ethyl-4-phenyl-3,5-dioxo-isoxazolidine. The ethereal solution is purified by filtration through a column of 22.5 g. of neutral alumina of activity I and elution with 300 ml. of ether. By concentrating the eluate at not more than 40–50°, finally in vacuo at room temperature, there is obtained a colorless crystalline residue which, upon recrystallization from gasoline-benzene, is converted into colorless crystals of M.P. 66–67°.

Hydroxylamine hydrochloride and α-ethyl-α-phenyl-malonyl chloride used in the above reaction can be replaced by equivalent amounts of free hydroxylamine or hydroxylamine sulfate and α-ethyl-α-phenyl-malonyl bromide, respectively.

EXAMPLE 6

By proceeding in the manner described in Example 5 and using 5.91 g. of diethyl-malonyl chloride and 2.1 g. of hydroxylamine hydrochloride as starting materials there is obtained 4,4 - diethyl - 3,5 - dioxo - isoxazolidine melting at about 20°.

EXAMPLE 7

By proceeding in the manner described in Example 5 and using 7.0 g. of α-phenyl-α-n-hexyl-malonyl chloride and 1.65 of hydroxylamine hydrochloride as starting materials there is obtained 4-n-hexyl-4-phenyl-3,5-dioxo-isoxazolidine having a refraction index $n_D^{20}=1.5180$.

EXAMPLE 8

By proceeding in the manner described in Example 5 and using 6.42 g. of dibenzyl-malonyl chloride and 1.5 g. of hydroxylamine hydrochloride there is obtained, 4,4-dibenzyl-3,5-dioxo-isoxazolidine of M.P. 220–225° (decomp.).

EXAMPLE 9

55.8 g. of cyclohexyl-malonic acid are refluxed for 6 hours with 150 ml. of thionyl chloride with the exclusion of humidity. The excess thionyl chloride is evaporated in vacuo. The liquid yellow residue consisting of cyclohexyl-malonyl chloride is diluted with 50 ml. of absolute chloroform. This solution is added dropwise within 20 to 30 minutes, in a nitrogen atmosphere and with the exclusion of humidity and oxygen to a stirred mixture, cooled to −10 to −15°, of 100 ml. of absolute pyridine and 1000 ml. of absolute chloroform. To the resulting yellow-brown solution there is added in one portion a slurry of 32.7 g. of N-phenyl-hydroxylamine in about 100 ml. of absolute chloroform whereupon the yellow-brown color immediately turns yellow. The reaction mixture is stirred for a further hour, while cooling with ice water, and for two hours at room temperature. The solution is then extracted twice with portions of 600 ml. of 2 N hydrochloric acid and once with 500 ml. of water and then three times with portions of 500 ml. of 2 N sodium carbonate solution. The combined yellow, slightly turbid sodium carbonate solutions are washed with 250 ml. of ether, cooled with ice water and acidified to Congo by the addition of 6 N hydrochloric acid. The resulting crystalline precipitate is dissolved by the addition of 1000 ml. of ether. The ethereal solution is washed with water, dried over sodium sulfate, and the ether is evaporated at a temperature not exceeding 40°, finally in vacuo at room temperature. The residue weighs 61.4 g. and consists of yellowish crystals. The latter can be purified by recrystallization from 60 ml. of methanol. There are thus obtained 58.0 g. of colorless 2-phenyl-4-cyclohexyl - 3,5 - dioxo-isoxazolidine of M.P. 65°. The new compound can also be recrystallized from cyclohexane whereby the melting point remains unchanged.

EXAMPLE 10

11.8 g. of n-butyl-malonyl chloride are added dropwise, while stirring, to a mixture of 11 ml. of absolute pyridine and 300 ml. of absolute ether cooled with an ice-salt mixture, in a nitrogen atmosphere and with the exclusion of humidity and oxygen, whereby a light yellow precipitate forms. Then 6.6 g. of N-phenyl-hydroxylamine in 50 ml. of absolute ether are rapidly added and the mixture is stirred for three hours with cooling in an ice water bath and for one hour at room temperature. The yellow colouration of the slurry disappears and a white precipitate forms. The reaction mixture is washed with 100 ml. and then twice with portions of 50 ml. of 2 N hydrochloric acid and with 50 ml. of water. The thus purified ethereal solution is then extracted three times with 50 ml. of 2 N sodium carbonate solution. The combined alkaline solutions are washed with chloroform and then acidified to Congo with 2 N hydrochloric acid, while cooling with ice water. The resulting oily precipitate is taken up in 100 ml. of ether and the acid aqueous solution is then extracted twice with 50 ml. of ether. The combined ethereal solutions are dried over sodium sulfate and concentrated in vacuo. The residue consists of 10.9 g. of a yellow oil having a refraction index of $n_D^{20}=1.5370$. The oil is dissolved in 150 ml. of petroleum ether, the solution is filtered on a column of 100 g. of alumina having the activity I, and the column is eluted with three portions of 150 ml. of petroleum ether. The eluate is concentrated in vacuo, and the residue is dried for six hours at room temperature in a high vacuum. The residue which weighs 4.2 g. has a refraction index of $n_D^{20}=1.5395$ and consists of analytically pure 2-phenyl-4-n-butyl - 3,5 - dioxo-isoxazolidine. The new compound crystallises on prolonged standing at 10 to 20°; these crystals melt at about 25°. This compound is not stable at elevated temperatures and can, therefore, not be distilled without decomposition, even in a high vacuum.

EXAMPLE 11

A mixture of 9.2 ml. of triethylamine and 10 ml. of absolute chloroform is added dropwise into a stirred solution, cooled to −10°, of 2.8 g. of malonyl chloride and 2.2 g. of N-phenylhydroxylamine in 100 ml. of absolute chloroform in a nitrogen atmosphere and in the absence of humidity and air oxygen. The mixture is then stirred for 1 hour at 0 to 5° and for 2 hours at 20–30°. The brown solution is extracted with 50 ml. and then twice with portions of 20 ml. of 2 N hydrochloric acid and finally once with 25 ml. of water. The reaction product is separated by extracting the solution three times with 25 ml. of sodium carbonate solution, washing the extract with a small amount of ether, cooling to 0° and acidifying to Congo by the addition of 2 N hydrochloric acid. The resulting crystalline precipitate is filtered off by suction, washed with water and dried in a vacuum desiccator over phosphorus pentoxide. 1.7 g. of brown crystals melting at 118–128° are obtained. They are purified by dissolution in chloroform, filtration of the solution through a column of the five-fold amount of neutral alumina having the activity I and elution with 100 ml. of chloroform. After removal of the chloroform the resulting residue is readily crystallizable from benzene-gasoline and from methanol. The analytically pure colorless 2-phenyl-3,5-dioxo-isoxazolidine melts at 132–133°.

EXAMPLE 12

5.16 g. of cyclopentyl-malonic acid are converted into the dichloride by boiling with 15 ml. of thionyl chloride. The dichloride is reacted with 3.3 g. of N-phenyl-hydroxylamine in the manner described in Example 9, and the reaction product is isolated in a similar manner. After recrystallization from methanol there are obtained 4.9 g. of colorless 2-phenyl-4-cyclopentyl-3,5-dioxo-isoxazolidine melting at 34–35°.

EXAMPLE 13

Phenyl-malonyl chloride (obtained from 10.8 g. of phenyl-malonic acid and 30 ml. of thionyl chloride) is reacted with 6.6 g. of N-phenyl-hydroxylamine in the manner described in Example 9. After working up the reaction mixture there is obtained 2,4-diphenyl-3,5-dioxo-isoxazolidine in a yield of 6.6 g. The new compound is a crystalline solid which is crystallizable from ethyl acetate or acetone. It melts at 108 to 109° with decomposition.

EXAMPLE 14

(Cyclopentylmethyl)-malonyl chloride [obtained from 5.58 g. of (cyclopenylmethyl)-malonic acid and 15 ml. of thionyl chloride] is reacted with 3.3 g. of N-phenyl-hydroxylamine in the manner described in Example 9. After working up the reaction mixture there are obtained 4.15 g. of 2-phenyl-4-cyclopentylmethyl-3,5-dioxo-isoxazolidine, recrystallized from methanol, in the form of colorless crystals of M.P. 64–65°.

EXAMPLE 15

7.5 g. of n-hexyl-malonic acid are converted into the chloride by boiling with 15 ml. of thionyl chloride. After removal of the excess thionyl chloride and the n-hexyl-malonyl chloride is cyclized with 4.4 g. of N-phenyl-hydroxylamine in the manner described in Example 9. When working up the reaction mixture 2-phenyl-4-n hexyl-3,5-dioxo-isoxazolidine crystallizes spontaneously from the acidified aqueous sodium carbonate solution. After recrystallization from methanol there are obtained 4.95 g. of the isoxazolidine compound in the form of colorless crystals of M.P. 45–46°.

EXAMPLE 16

By proceeding in the manner described in Example 9 and using 6.0 g. of (cyclohexylmethyl)-malonic acid, 15 ml. of thionyl chloride and 3.3 g. of N-phenyl-hydroxylamine as starting materials there are obtained 5.2 g. of analytically pure 2-phenyl-4-cyclohexylmethyl-3,5-dioxo-isoxazolidine in the form of yellowish crystals melting at 79–80°. The new compound is easily recrystallizable from methanol or cyclohexane.

EXAMPLE 17

2.2 g. of N-phenyl-hydroxylamine are vigorously stirred with 50 ml. of benzene and 120 ml. of aqueous saturated sodium hydrogen carbonate solution in a nitrogen atmosphere and with the exclusion of oxygen. A solution of 4.62 g. of benzyl-malonyl chloride in 5 ml. of absolute benzene is slowly added, and the mixture is well stirred overnight. The reaction is carried out at room temperature. No temperature change is observed during the reaction. The reaction mixture is mixed with 25 ml. of benzene, the aqueous layer is separated, and the benzene solution is extracted twice with portions of 25 ml. of 2 N sodium carbonate solution. The combined aqueous layers are washed with a small amount of ether and acidified to Congo by adding hydrochloric acid, while cooling with ice. The oily product which separates is taken up in 100 ml. of ether. After washing with water, drying and removing the ether there is obtained a residue of 5.15 g. This residue is partly crystalline and has a brown coloration. By recrystallization from a small amount of methanol there is obtained pure 2-phenyl-4-benzyl-3,5-dioxo-isoxazolidine in the form of slightly yellowish crystals of M.P. 81–83°.

EXAMPLE 18

By proceeding in the manner described in any one of Examples 9 to 17 and using 13.2 g. of isopropyl-malonyl chloride and 7.85 g. of N-phenyl-hydroxylamine as starting materials there is obtained 2-phenyl-4-isopropyl-3,5-dioxo-isoxazolidine of M.P. 60–61°.

EXAMPLE 19

By proceeding in the manner described in any one of Examples 9 to 17 and using 10.95 g. of (ω-phenyl-propyl)-malonic acid, 25 ml. of thionyl chloride and 5.45 g. of N-phenyl-hydroxylamine as starting materials there is obtained 2-phenyl-4-(ω-phenyl-propyl)-3,5-dioxo-isoxazolidine of M.P. 54–55°.

EXAMPLE 20

By proceeding in the manner described in any one of Examples 9 to 17 and using 4.62 g. of benzyl-malonyl chloride and 1.84 g. of N-methyl-hydroxylamine oxalate as starting materials there is obtained 2-methyl-4-benzyl-3,5-dioxo-isoxazolidine having a refraction index

$$n_D^{20}=1.5412$$

EXAMPLE 21

By proceeding in the manner described in any one of Examples 9 to 17 and using 10.8 g. of benzhydryl-malonic acid, 30 ml. of thionyl chloride and 3.68 g. of N-methyl-hydroxylamine oxalate as starting materials there is obtained 2-methyl-4-benzhydryl - 3,5 - dioxo - isoxazolidine melting at about 20°.

EXAMPLE 22

By proceeding in the manner described in any one of Examples 9 to 17 and using 4.75 g. of cyclohexyl-malonic acid, 15 ml. of thionyl chloride and 2.88 g. of N-cyclohexyl-hydroxylamine as starting material there is obtained 2,4-dicyclohexyl-3,5-dioxo-isoxazolidine of M.P. 75–76°.

EXAMPLE 23

By proceeding in the manner described in any one of Examples 9 to 17 and using 6.65 g. of benzyl-malonyl chloride and 3.32 g. of N-cyclohexyl-hydroxylamine as starting materials there is obtained 2-cyclohexyl-4-benzyl-3,5-dioxo-isoxazolidine of M.P. 75–76°.

EXAMPLE 24

By proceeding in the manner described in any one of of Examples 9 to 17 and using 10.8 g. of benzhydryl-malonic acid, 25 ml. of thionyl chloride and 4.36 g. of N-phenyl-hydroxylamine as starting materials there is obtained 2-phenyl-4-benzhydryl-3,5-dioxo-isoxazolidine of M.P. 105–106°.

EXAMPLE 25

By proceeding in the manner described in any one of Examples 9 to 17 and using 9.6 g. of n-butyl-malonic acid, 25 ml. of thionyl chloride and 7.4 g. of N-p-tolyl-hydroxylamine as starting materials there is obtained 2-p-tolyl-4-n-butyl-3,5-dioxo-isoxazolidine of M.P. 27–28°.

EXAMPLE 26

By proceeding in the manner described in any one of Examples 9 to 17 and using 7.4 g. of cyclohexyl-malonic acid, 15 ml. of thionyl chloride and 4.92 g. of N-p-tolyl-hydroxylamine as starting materials there is obtained 2-p-tolyl-4-cyclohexyl - 3,5 - dioxo - isoxazolidine of M.P. 102–103°.

EXAMPLE 27

By proceeding in the manner described in any one of Examples 9 to 17 and using 5.6 g. of cyclohexyl-malonic acid, 25 ml. of thionyl chloride and 4.1 g. of N-2,6-dimethylphenyl-hydroxylamine as starting materials there is obtained 2-(2',6'-dimethylphenyl)-4-cyclohexyl-3,5-dioxo-isoxazolidine of M.P. 87–88°.

EXAMPLE 28

6.4 g. of n-butyl-malonic acid are refluxed for a few hours with thionyl chloride with the exclusion of humidity. After removal of the excess thionyl chloride in vacuo the residue is taken up in 25 ml. of absolute chloroform and the solution is added dropwise, while stirring, at about −10° to 200 ml. of absolute chloroform and 15 ml. of absolute pyridine. Then 6.36 g. of α-naphthyl-hydroxylamine are added, and the mixture is stirred for a short time while cooling with ice and then for 3 hours at room temperature. After removal of pyridine and by-products from the chloroform solution with 2 N hydrochloric acid the reaction product is extracted by the addition of 1 N sodium carbonate solution in the manner described in Example 9. The precipitate resulting from the acidification of the sodium carbonate solution is taken up in 200 ml. of ether, the solution is washed with water and dried over sodium sulfate. The residue obtained after removal of the ether consists of 4.5 g. of a brownish crystalline mass of crude 2-α-naphthyl-4-butyl-3,5-dioxo-isoxazolidine. This product can be purified by taking it up ether and filtering the solution through a column of 20 g. of neutral alumina having the Activity I. After elution with ether there are obtained colorless, needle-like crystals of M.P. 208–209°. After recrystallization from ethyl acetate-petroleum ether or methanol and melting point is unchanged.

An aqueous solution of the sodium salt of 2-α-naphthyl-4-butyl-3,5-dioxo-isoxazolidine can be prepared by dissolving the latter in boiling methanol, cooling the solution to room temperature and adding 1 mole of aqueous sodium hydroxide solution to the resulting crystal slurry. The methanol is removed in vacuo at room temperature. The remaining aqueous solution is clear.

EXAMPLE 29

33.25 g. of diethyl n-nonyl-malonate are dissolved in 50 ml. of ethanol, then a solution of 18.5 g. of potassium hydroxide in 50 ml. of water is added and the mixture is refluxed for ¾ hour. The alcohol is distilled off at reduced pressure, the aqueous solution acidified to Congo while cooling with ice and then extracted twice with 100 ml. of ether. The ethereal solution is washed with a small amount of water, dried over sodium sulfate and concentrated. The resulting crystalline residue is recrystallized from benzene-gasoline. The thus obtained n-nonyl-malonic acid forms colorless crystals and melts at 99–102° with decomposition. In the electrometric titration the calculated value is obtained.

11.5 g. of n-nonyl-malonic acid are refluxed for 1½ hours with 25 ml. of thionyl chloride with the exclusion of humidity. The excess thionyl chloride is removed in vacuo. The residue is taken up in 25 ml. of absolute chloroform, and the solution is added dropwise, while stirring, a mixture, cooled to −10°, of 20 ml. of absolute pyridine and 150 ml. of absolute chloroform. Then 5.45 g. of N-phenyl-hydroxylamine, suspended in a small amount of chloroform, are added, and the mixture is stirred first at 0° and then at 20–30° for a few hours. The pyridine is removed from the chloroform solution by extracting it several times with 2 N hydrochloric acid. The chloroform solution is then extracted three times with 100 ml. of 1 N sodium carbonate solution. The sodium carbonate solution is washed with a small amount of ether and then acidified with 6 N hydrochloric acid. The crude product which precipitates in crystalline form is filtered off by suction and washed with water. It weighs 12.55 g. and can be obtained in the form of pure colorless crystals of M.P. 44° by recrystallization from methanol. The resulting 2-phenyl-4-n-nonyl-3,5-dioxo-isoxazolidine is readily soluble in benzene, petroleum ether and ethyl acetate.

EXAMPLE 30

Diethylaminoethanol salt of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine in aqueous solution

2.59 g. of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine prepared as described in Example 9 are stirred with 10.5 ml. of 1 N diethylaminoethanol solution and 9 ml. of water. A clear solution is obtained within a short time at room temperature. This solution is diluted to 25.9 ml. After filtering through a bacteriological filter, the diluted solution can be used for parenteral application in medicine. The solution is acidic to phenolphthalein and, when it is acidified with mineral acid, 2-phenyl-4-cyclohexyl-3,5-dioxo - isoxazolidine precipitates therefrom in crystalline form at 0 to 20°.

EXAMPLE 31

Sodium salt of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine in solid form

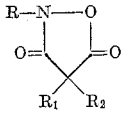
2.59 g. of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine are pasted with a small amount of absolute methanol, and then 2 ml. of 5 N sodium methoxide solution in methanol are slowly added while cooling with ice water and with the exclusion of humidity. The pH of the resulting clear solution should be 8 to 8.5. If necessary, the pH is adjusted to this value by the addition of sodium methoxide solution or of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine. The mixture is then concentrated to dryness in vacuo at a temperature not exceeding about 20°. A white powder is obtained as the residue. The residue consists of the sodium salt of 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine which is hygroscopic and must, therefore, be stored with exclusion of humidity.

In order to ascertain whether the organic compound has not been decomposed by the treatment with sodium methoxide and during storage, a sample which had been stored for one month was dissolved in distilled water. By acidification of this clear solution with mineral acid a white crystalline precipitate was obtained which, after a single recrystallisation from a small amount of methanol, yielded uniform crystals of M. P. 65°. The melting point of a mixture of this product with authentic 2-phenyl-4-cyclohexyl-3,5-dioxo-isoxazolidine showed no depression.

We claim:

1. A compound selected from the class consisting of a free acid and its therapeutically useful salt with a sub-

stantially therapeutically neutral base, said free acid having in one of its tautomeric forms the formula



wherein each of the symbols R, R_1 and R_2 represents a member selected from the group consisting of hydrogen and hydrocarbon radicals having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds, with the proviso that at least one but not more than two of the symbols R, R_1 and R_2 stand for hydrogen.

2. 3,5-dioxo-isoxazolidine substituted in the 4-position with a hydrocarbon radical having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds.

3. A therapeutically useful salt of the 3,5-dioxo-isoxazolidine of claim 2 with a substantially therapeutically neutral base.

4. 3,5-dioxo-isoxazolidine substituted in the 4-position with two hydrocarbon radicals, each of said radicals having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds.

5. A therapeutically useful salt of the 3,5-dioxo-isoxazolidine of claim 4 with a substantially therapeutically neutral base.

6. 3,5-dioxo-isoxazolidine substituted in both the 2- and the 4-positions with hydrocarbon radicals, each of said radicals having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds.

7. A therapeutically useful salt of the 3,5-dioxo-isoxazolidine of claim 6 with a substantially therapeutically neutral base.

8. 3,5-dioxo-isoxazolidine substituted in the 2-position with a hydrocarbon radical having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds.

9. 3,5-dioxo-isoxazolidine substituted in the 4-position with a hydrocarbon radical having not more than 10 carbon atoms and being free from aliphatic unsaturated bonds.

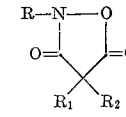
10. 3,5-dioxo-isozazolidine substituted in the 4-position with two hydrocarbon radicals, each of said radicals having not more than 10 carbon atoms and being free from aliphatic unsaturated bonds.

11. 3,5-dioxo-isoxazolidine substituted in both the 2- and the 4-positions with hydrocarbon radicals, each of said radicals having at most 10 carbon atoms and being free from aliphatic unsaturated bonds.

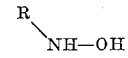
12. 3,5-dioxo-isoxazolidine substituted in the 2-position with a hydrocarbon radical having at most 10 carbon atoms and being free from aliphatic unsaturated bonds.

13. 2-phenyl-3,5-dioxo-isoxazolidine substituted in the 4-position by a hydrocarbon radical having from 4 to 7 carbon atoms and being free from aliphatic unsaturated bonds.

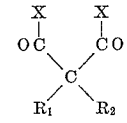
14. A process for the manufacture of a compound selected from the class consisting of a free acid and its therapeutically useful salt with a substantially therapeutically neutral base, said free acid having in one of its tautomeric forms the formula



wherein from one to two of the symbols R, R_1 and R_2 is hydrogen and the other of said symbols is a hydrocarbon radical having not more than 14 carbon atoms and being free from aliphatic unsaturated bonds, which comprises reacting a compound having the formula



with a compound of the formula



wherein X is a member of the group consisting of chlorine and bromine.

No references cited.