

ALIEN PROPERTY CUSTODIAN

P - AMINO PHENYL - P' - AMINO PYRIDYL SULFONE AND A PROCESS OF MAKING THE SAME

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This invention relates to sulfones and more particularly to p-aminophenyl-p'-amino pyridyl sulfone and a method of making the same.

As is well known p,p'-diamino diphenyl sulfone has an extraordinary bactericide effect, but at the same time it is also rather toxic, so that it did not find use in human therapy.

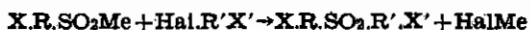
Now, it has been found that a sulfone of similar constitution, wherein one phenyl residue is substituted by a pyridyl residue, is of almost equal effectiveness as the p,p'-diamino diphenyl sulfone, but is distinguished therefrom by a considerably lower toxicity. This sulfone corresponds to the following structural formula:



Compounds of this kind are obtained according to methods already known for the manufacture of sulfones (see, for instance, Houben-Weyl "Die Methoden der organischen Chemie", 3rd edition, vol. 3, pp. 1278 ff.).

As especially suitable there has proved the method consisting in reacting a salt of a benzene sulfonic acid, suitably an alkaline salt, containing in p-position to the sulfonic acid group an amino group or a group convertible thereinto, for instance, an acyl amino, nitro, nitroso, azo, hydrazo and the like groups, with a halogenated pyridine, also containing an amino group or a group convertible thereinto, suitably in p-position to the halogen.

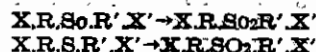
This reaction may be illustrated by the following formulas



wherein X and X' indicate an amino group or a group convertible thereinto, while R represents a benzene radical, R' a pyridyl radical, Me a metal, especially an alkaline metal and Hal halogen. Compare U. S. application Serial No. 237,926. As halogenated pyridine compounds there may be preferably employed compounds in which the halogen is rendered especially reactive by an activating substituent. Especially suitable for this purpose has proved the nitro group, which, after condensation, may be converted into the amino group. Thus, the p-amino phenyl-p'-amino pyridyl sulfone is obtained by reacting 2-chloro-5-nitro pyridine with the sodium salt of an acyl amino phenyl sulfonic acid with subsequent reduction and saponification. The transformation may be carried out while heating in a suitable solvent, for instance, in alcohol, or under pressure. The forming of the amino group is, if need be, brought about by the aid of hy-

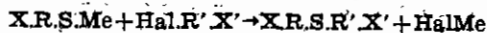
drolisis or reduction or the like measures. The reduction of a nitro group present in the pyridyl residue may also be carried out simultaneously with the saponification of an acylamino group present in the phenyl residue. Thus, for instance, on reduction by means of stannous chloride or sodium hydrosulfite in glacial acetic acid at 40-60° C the nitro group is converted into the amino group while an acyl amino group present remains unchanged thereby. When using in the place of the above mentioned reducing agents stannous chloride and concentrated hydrochloric acid at a temperature of 80-90° C the acyl group is split off at the same time. Hence the latter method of reduction is of special importance as it saves one step, namely saponification of the acylamino group.

In order to obtain the sulfones claimed one may also proceed in such a manner that sulfides or sulfoxides containing an amino phenyl group as well as an amino pyridyl group, are oxidized to the corresponding sulfones. This reaction may be illustrated by the following formulas



wherein X and X', R and R' have the same meaning as indicated above. For this reaction such compounds are preferably used as starting material in which the amino groups are transformed into groups which are re-convertible into amino groups. The oxidation of these sulfides or sulfoxides is carried out in a customary manner, using, for instance, nitric acid, potassium permanganate, chromic acid, hydrogen peroxide, while heating, and others.

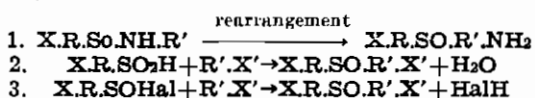
The sulfides used may be obtained by reacting the salts, especially the alkali salts of the corresponding mercapto compounds with the above mentioned halogenated pyridines. This reaction may be illustrated by the following formulas



wherein X and X', R and R', Me and Hal have the same meaning as indicated above.

The sulfoxides employed for oxidation to sulfones may be produced, for instance, by rearrangement of the corresponding sulfonic acid amides which is facilitated by the presence of halogen hydrides or of the halogen hydride salt of the amine forming the amide. One may further proceed in such a manner that the corresponding sulfonic acids or their halogenides are condensed with aminopyridines. Such ways of procedure are described, for instance, in U. S.

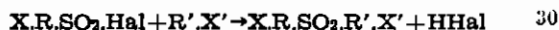
application Serial No. 314,512 and German application Sch. 119,772 IVc/12q. The reactions described above may be illustrated by the following formulas:



Of course, other methods for making the corresponding sulfides and sulfoxides may be used likewise.

Furthermore, other methods of manufacturing the sulfones claimed may be employed, though in general lesser yields are obtained thereby than with the above-mentioned methods, and though mixtures of asymmetric and symmetric products may be produced. Of course, there are not to be employed such methods in which the amino groups or the groups convertible thereinto are influenced or even split off during reaction. Amongst these methods there may be mentioned the following:

The corresponding benzene sulfonic acid halogenides are condensed with pyridines containing a group convertible into the amino group, whereby the reaction is accelerated and facilitated by the presence of an aluminum halogenide, such as aluminum chloride. The condensation takes place according to the following formulas:



after condensation the groups convertible into amino groups present in the sulfone, may be transformed into amino groups, for instance, by the aid of hydrolysis or reduction, so as to yield p,p'-diamino phenyl pyridyl sulfone.

Instead of the benzene sulfonic acid halogenides the sulfonic acid themselves may be employed whereby the reaction is carried out in the presence of dehydrating agents, such as, for instance, phosphorus pentoxide. The yield obtained by this method, however, is appreciably lower than by the above mentioned processes. Reactions starting with sulfonic acids or their halogenides are described, for instance, in U. S. application Serial No. 335,868.

The following examples serve to illustrate the invention, without, however, limiting the same to them.

Example 1

200 gs of the sodium salt of p-acetyl amino benzene sulfonic acid are boiled under reflux with 156 gs of 2-chloro-5-nitro pyridine in 4.5 liters of alcohol for 7 to 8 hours. After allowing the reaction mixture to stand for a longer period of time the crystallized mass is filtered off, thoroughly washed with water and recrystallized from alcohol. Melting Point 225-226° C.

5 gs of the thus obtained p-acetyl amino phenyl-p'-nitro pyridyl sulfone are dissolved in 40 ccs of glacial acetic acid and within about 10 minutes 10 gs of sodium hydrosulfite dissolved in 50 ccs of water, are added to the hot solution while stirring. After heating on the water bath for another hour, the solution is evaporated to dryness in a vacuum, the residue treated with dilute sodium hydroxide solution until it shows lasting alkaline reaction, and recrystallized from dilute alcohol. Melting Point 271-272° C.

For saponification 3 gs of the p-acetyl amino phenyl-p'-amino pyridyl sulfone are heated to boiling in 60 ccs of 20% hydrochloric acid for half an hour, the cooled solution is mixed with ice water and rendered alkaline with sodium hydroxide solution while cooling. The p,p'-diamino

phenyl-pyridyl-sulfone precipitated melts at 183° C (from dilute alcohol).

The reduction of the nitro compound with stannous chloride in glacial acetic acid is carried out in the following way:

Over 6.4 gs of the nitro compound there are poured portion by portion 32 ccs of a 45% solution of stannous chloride in glacial acetic acid within about 30 minutes, keeping the temperature thereby at 50-60° C. After allowing the reaction mixture to stand for a longer period of time the tin double salt precipitated is treated with dilute sodium hydroxide solution in order to convert it into the free base.

Example 2

65 gs of the p-acetyl amino phenyl-p'-nitro pyridyl sulfone obtained according to Example 1 are suspended in 350 ccs of concentrated hydrochloric acid and reduced in the usual manner with 150 gs of stannous chloride in 250 ccs of concentrated hydrochloric acid at 40-50° C and thereupon heated for one more hour on the water bath. The tin double salt precipitates on standing. It is converted into the free base in the usual manner. The p,p'-diamino phenyl pyridyl sulfone with a melting point of 183-184° C (from dilute alcohol) is obtained with a yield of 30 gs.

Example 3

5.0 gs of the sodium salt of p-acetyl amino benzene sulfonic acid and 3.2 gs of 2-chloro-5-amino pyridine in 15 ccs of methanol are heated in a sealed tube up to 160° C for 8 hours. After cooling the contents of the tube are filtered off by suction and the filtrate is precipitated with water, whereby the p-acetyl amino phenyl-p'-amino pyridyl sulfone precipitates at first in the form of an oil, which solidifies after long standing.

The acetyl compound is recrystallized from dilute alcohol and saponified to the p,p'-diamino phenyl pyridyl sulfone according to Example 1.

Example 4

3.8 gs of nitro phenyl sulfonic acid and 2.0 gs of anhydrous calcium acetate and 3.2 gs of 2-chloro-5-nitro pyridine in 120 ccs of ethanol are boiled under reflux for 7 to 8 hours. After cooling the precipitate obtained, representing p-nitro phenyl-p'-nitro pyridyl sulfone, is filtered off by suction, washed with water and recrystallized from glacial acetic acid. Melting Point 253-254° C. Yield 70% (of the theory).

3.6 gs of p-nitro phenyl-p'-nitro pyridyl sulfone are reduced in 200 ccs of methanol by means of hydrogen in the presence of a nickel catalyst. After having taken up the calculated amount of hydrogen the catalyst is filtered off and the filtrate is concentrated by evaporation. The thereby obtained raw product of p-amino-phenyl-p'-amino pyridyl sulfone melts at 183-184° C. Yield 70-80%.

Example 5

15.5 gs of p-nitro thiophenol and 15.8 gs. of 2-chloro-5-nitro pyridine are dissolved at 75° C in 370 ccs of ethanol. To this solution there are added 5.6 gs of potassium hydroxide in 200 ccs of ethanol. Subsequently the solution is heated to boiling for about half an hour on the steam bath. After cooling and filtering off by suction the crystalline precipitate, which, besides p-nitro-phenyl-p'-nitro pyridyl sulfide, contains p,p'-dinitro diphenyl sulfide, is recrystallized from methanol wherein the latter is insoluble. The p-

nitrophenyl-p'-nitro pyridyl sulfide melts at 125-126° C. Yield: 60-70%.

3,9 gs of p-nitro phenyl-p'-nitro pyridyl sulfide are dissolved while heating in 50 ccs of glacial acetic acid, and 3,0 gs of chromic acid anhydride are added to the solution at a temperature of about 90° C. Already during the introduction of the chromic acid a crystalline precipitate begins to form. After keeping the temperature for about 30 minutes at 90° C and cooling, the p-nitro 10

phenyl-p'-nitro pyridyl sulfone obtained is filtered off by suction, washed with water and recrystallized from glacial acetic acid. Melting Point 253-254° C. Yield 50%.

5 The reduction of the dinitro compound to the diamino compound is carried out according to Example 4.

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