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PROCESS FOR PREPARING AMINOTHIAZOL-DERIVATIVES

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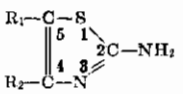
The present invention relates to new industrial products, to diarylsulfonyl-derivatives of 2-aminothiazols of the formula:

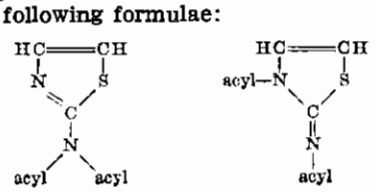


one of the arylsulfonyl groups being bound to the amino-group in position 2, the other being bound to the nuclear N-atom of the thiazol-nucleus. R_1 and R_2 means in the above-standing formula members of the group consisting of: H, alkyl, oxoalkyl, carboxyl, carbalkoxyl. Preferred representants of the new products are those in which R_1 means H-atom and R_2 means either H or an aliphatic radical, such as methyl, ethyl. Specially valuable diarylsulfonyl products are those in which the arylsulfonyl groups are benzolsulfonyl groups, the benzene-ring being substituted in the para-position by a member of the group consisting of H, acyl.NH,NO_2. In these compounds the position 4 of the thiazol-nucleus preferably contains a member of the group consisting of H, alkyl-radical. The present invention relates further to diaryl-sulfonyl-derivatives of 2-aminothiazoles in which one of the arylsulfonyl groups is bound to the amino-group in position 2, while the other is bound to the nuclear N-atom of the thiazole-nucleus, at least one of the arylsulfonyl groups being a p-acylamino-benzolsulfonyl group.

A further object of the present invention is to provide for processes to prepare the new diarylsulfonyl-derivatives. The process consists in subjecting 2-aminothiazols to the action of acylating agents, generally used to introduce arylsulfonyl groups and in isolating from the reaction mixture the acylation products containing two arylsulfonyl groups. One may use as acylating agents those ones which are generally used to introduce amino-arylsulfonyl groups. Such acylating agents are e. g. the p-acylamino-benzol-sulfonyl-halogenides.

The introduction of two arylsulfonyl groups can be also carried out in two separate steps, in each step only one arylsulfonyl group being introduced.

Amino-thiazole, such as the 2-amino-thiazol, are supposed to show two tautomeric forms. Therefore, two possibilities exist for the structure of diacyl-amino-thiazol derivatives as illustrated on the following formulae:



In these formulae the "acyl" means any arylsulfonyl group such as an acylamino-benzolsulfonyl group. Considerable difference exists between the fixation of the two arylsulfonyl groups, as one of these groups can be easily split off from the molecule by hydrolysis, resulting mono-arylsulfonyl derivative which contains the remaining arylsulfonyl group bound to the amino group in the position-2. Our further investigations proved that the diacyl products obtained according to the present invention correspond in their structure to the right-hand formula. This fact could be established by introducing two different acyl groups in two separate steps resulting thus two different diacyl derivatives depending on the sequence of the two acylations.

The acylation according to present invention can be effected in various manners. The acylating agent is preferably used in a proper excess, the more as the theory requests at least two moles of the acylating agent. The acylation is preferably carried out in the presence of a diluent such as acetone, using preferably an agent to bind the acid resulting in the acylation. One may use, as such an agent, an alkali bicarbonate, such as sodium bicarbonate. One may use for the same purpose other ingredients, as well, such as tertiary bases, for instance dimethylaniline. By using dimethylaniline the main products of the acylation is the di-(acetamino-aryl-sulfonyl)-derivative even in cases when only one mole of the acylating agent, such as of p-acetylamino-benzolsulfonyl-chloride, has been used.

One may further use as agent to bind acid aqueous alkalis, as well, such as 2-normal sodium hydroxide solution; in this case the acylation is preferably carried out in acetone as medium at temperatures not exceeding 50°.

After terminating the acylation, the reaction mixture can contain—although unconsiderable amounts—monoacyl derivatives, which can be eliminated from the diacyl derivative by means of extraction by aqueous alkalis. The monoacyl derivatives are, namely, soluble in alkalis.

As acylating agents sulfonyl-halogenides can be preferably used, such as p-acetamino-benzolsulfonyl chloride, p-nitro-benzolsulfonyl chloride, benzolsulfonyl chloride, etc.

The amino-thiazols, as the 2-amino-thiazol, can contain substituents in the heterocyclic ring, such as alkyl groups (2-amino-4-methyl-thiazol) or aryl groups (2-amino-4-phenyl-5-methyl-thiazol).

The di-(arylsulfonyl)-amino-thiazols separated from the reaction mixture can be subjected to a further treatment, namely to a hydrolysis, one of the arylsulfonyl groups being split off completely from the molecule, the acyl group being split likewise from the remaining arylsulfonyl group, if the latter contained an acylamino group.

The hydrolysis can be carried outdirectly with the reaction mixture, as well. The hydrolysis can be effected by diluted alkali solutions, such as sodium hydroxide of 8–10% or by diluted acids, such as by diluted hydrochloride acid.

The di-(arylsulfo)-amino-thiazols are sensible to alcohols. By boiling a di-arylsulfonyl derivative in an alcohol, preferably in absolute ethyl-alcohol, containing a haloid acid, preferably dry hydrochloric acid, the arylsulfonyl group bound to the tertiary nitrogen atom of the heterocyclic ring is split off completely and if the arylsulfonyl group contained an acetylamino group as substituent, the acetyl groups are likewise split off, in the form of acetic ether.

The diacyl products of the present process can also be obtained by effecting the acylation in two steps. In the first step one acetyl group is introduced into the amino group in position 2, this first acylation being preferably carried out by the method decribed already in our U. S. A. Application No. 267,168. The monoacyl derivative, thus obtained is now acylated in a further step. The acylation in this second step is preferably carried out by means of acylation methods as described above for the preparation of the diacyl derivatives in a single step. The introduction of the two acyl groups in two steps give possibility to introduce different acyl groups into the molecule which is not at all possible by effecting the acylation in a single step. Different acyl groups can preferably be the following: p-acylamino-benzolsulfonyl, p-nitro-benzolsulfonyl, p-acyl-aminobenzolsulfonyl, p-acylamino-o-alkoxy-benzolsulfonyl, p - acetamino - m-alkyl-benzol-sulfonyl, benzol-sulfonyl-, etc. groups.

Some of the products of the process are starting materials in the preparation of anticoccic products, others being themselves of anticoccic action, for instance of antipneumococcic or antigonococcic action.

Further details are to be found in the following examples:

Examples

1. 10 grams (0.1 g mol) of 2-amino-thiazol, 50 grams (0.215 g mols) of p-acetamino-benzol-sulfonyl-chloride, 20 grams of sodium bicarbonate and 100 ccs of dry acetone are stirred for about 2 hours in the water bath. The acetone is then evaporated and 200 ccs of water added. The di(p-acetamino-benzolsulfo)-2-amino-thiazol remains undissolved and isolated by suction, washed and dried in vacuo. Its amount is nearly the theoretical. The produce can be purified by extracting it (after pulverisation) with diluted sodium hydroxide solution and washing with water. In this experiment mono-acyl derivatives do not result however, in practical amount.

The raw product can be recrystallised for instance as follows:

10 grams are dissolved in 100 ccs of boiling acetone of 80%. On cooling the product crystallises in uniform needles containing solvent of crystallisation. The melting point is rather unsharp, the product becomes at about 200° brownish and decomposes at 260°. The melting point does not become sharp on further recrystallisation from acetone. The product repeatedly crystallised from acetone shows on analysis a relation of 1 atom of sulfur to 1.31 atoms of nitrogen, i. e. a relation of 1 atom of sulfur to 4 atoms of nitrogen. The product persistently retains the solvent of crystallisation which can be eliminated therefore only by drying at higher temperature, however incompletely.

On hydrolysis by alkali one of the acyl-amino-aryl-sulfo-groups is split off as shown in the following:

10 grams of the raw di-(p-acetyl-amino-benzolsulfo)-2-amino-thiazol are boiled in 100 ccs of sodium hydroxide of 10% for about an hour. The excess of the alkali is now neutralized by hydrochloric acid at the end by acetic acid using lithmus as indicator. The p-amino-benzolsulfo-2-amino-thiazol separates in nearly theoretical amount. It melts at about 203°. If further purification is wanted, it may be dissolved in the threefold amount of hot sodium hydroxide of 20%. On cooling the sodium salt separates. It is suctioned, washed by sodium hydroxide of 20%, then dissolved in hot water and—after treating with animal charcoal—the filtrate is acidified first with hydrochlorid acid, at the end by acetic acid. The product shows antipneumococcic action.

2. 10 grams (0.1 g mol) of 2-amino-thiazol, 25 grams (0.107 g mols) of p-acetamino-benzolsulfonyl chloride are dissolved in 100 ccs of acetone. While stirring, 57 ccs of 2-normal sodium-hydroxide are dropped at 36°. The reaction mixture becomes practically neutral to lithmus. After a short time the reaction mixture solidifies in crystals. On further standing the crystals are suctioned, washed by aqueous acetone and by water and dried in vacuo. One obtains about 15 grams of di-(p-acetylamino-benzolsulfo)-2-amino-thiazol. The product melts unsharply between 130–150°. By extracting with tenfold amount of cold normal sodium hydroxide small amounts of contaminations can be eliminated. A recrystallisation from acetone of 70% can be used for further purification. The product contains solvent of crystallisation. On analysis it shows 18,4% of sulfur and 10.7% of nitrogen. The atomic relation of sulfur and nitrogen is thus S:N=3:4. These crystals on recrystallisation from alcohol show the following behaviour: 1 g of the product dissolves in 10 ccs of boiling alcohol, followed rapidly by separation of great amounts of crystals which do not dissolve on addition of further amounts of boiling alcohol. After cooling the snowwhite crystal mass is suctioned. At the determination of the melting-point one may observe a sintering at about 215° and a decomposition at about 250°.

This product yields on hydrolysis by means of sodium hydroxide the mono-(amino-benzolsulfo)-amino-thiazol described already in example 1.

3. 10 grams (0.10 g mol) of 2-amino-thiazol, 25 grams (0.10 g mol) of p-acetyl-amino-benzol-sulfonyl chloride, 25 ccs of dry acetone and 12.1 grams (0.10 g mol) of dimethyl-aniline are kept 2 hours on the hot water bath, then the acetone evaporated. On addition of 150 ccs hydrochloric acid of 5% one obtains a blueish-greenish crystalline precipitate which is suctioned, washed by water then by an aqueous sodium bicarbonate solution, by water again and dried. One obtains about 18 grams of the diacyl derivative showing an unsharp melting point between 130 and 160°. It does not dissolve in diluted sodium hydroxide.

On hydrolysing by alkali such as by sodium hydroxide, one obtains the p-amino-benzolsulfo-2-amino-thiazol.

One may proceed as given above, starting from 2-amino-4-methyl-thiazol or from 2-amino-4-phenyl-5-methyl-thiazol, obtaining the corresponding acylated products.

On starting for instance from 2-amino-4-methyl-thiazol one obtains the di-(p-acetyl-amino - benzolsulfo) - 2 - amino-4-methyl-thiazol which yields on hydrolysis by means of sodium hydroxide of 10% the p-amino-benzolsulfo-2-amino-4-methyl-thiazol melting at about 243°.

On acylating p-acetamino-benzolsulfo-2-amino-4-methyl-thiazol by means of p-acetamino-benzolsulfonyl-chloride, one obtains the di-(p-acetamino-benzolsulfo) - 2 - amino-4-methyl-thiazol mentioned above or in a more correct nomenclature: the 2-(p-acet-amino-benzol-sulfimido) - 3 -(p-acetamino-benzolsulfo) - 4 - methyl-thiazoline. The melting point of this product varies depending on the solvent used for recrystallisation. Crystallised from alcohol it melts at about 250°.

The same product can be obtained in excellent yield by starting from 11.4 grams of 2-amino-4-methylthiazol by dissolving it in 100 ccs of dry acetone and adding 50 grams of p-acetamino-benzolsulfonyl chloride and 25 grams of finely pulverized sodium bicarbonate. One stirs for about half an hour at about 20° and then for about two and half hours in the water bath of 65°. Now the acetone is distilled off at common pressure and finally in vacuo one adds 200 ccs of water. The remainder is acidified with acetic acid. The precipitate is suctioned and washed by water. The raw product is extracted by an ice-cold 0.5 normal sodium hydroxide and suctioned and thoroughly washed with water. The product after having been boiled with alcohol melts at about 250°.

4. 10 grams of 2-amino-thiazol, 17.6 grams of benzol-sulfonyl chloride, 10 ccs of dry pyridine and 25 ccs of acetone are boiled for 2 hours. Then the acetone is evaporated. On addition of 100 ccs of water to the remainder, the benzol-sulfo-2-amino-thiazol crystallizes. It can be purified by converting it into the sodium salt and regenerating it from this salt. It melts at about 175°.

2.2 grams of the above described benzolsulfo-2-amino-thiazol and 7.5 grams of p-acetamino-benzolsulfonyl chloride and 32 ccs of 2-normal sodium hydroxide are added in portions to the reaction mixture kept at 15°. The materials dissolve at the beginning and after addition of the total amount of the alkali an oily precipitate occurs which soon crystallizes. One obtains 11 grams of 2 -(benzolsulfimido) - 3 (p-acetamino-benzolsulfo) -thiazoline, that is the diacyl derivative of the tautomeric form of 2-amino-thiazol. It melts at about 120°.

5. 3 grams of p-acetamino-benzolsulfo-2-amino-thiazol (obtained as described in our U. S. A. application No. 267,168), 1.8 grams of benzolsulfonyl chloride, 15 ccs of acetone and 10 ccs of 2-normal sodium hydroxide are worked up as given in the preceding example. The raw product thus obtained is extracted by diluted sodium hydroxide. One obtains the 2-(p-acetamino-benzolsulfimido) - sodium - hydroxide. One obtains the 2-(p-acetamino-benzolsulfimido) -3-(benzolsulfo) -thiazoline, that is as well a mixed diacyl derivative contains the arylsulfo groups in an exchanged position relating to the product described in the preceding example. The product of the present example melts at about 180°.

6. 3 grams of p-acetamino-benzolsulfo-2-amino-thiazol and 2.5 grams of p-acetamino-benzolsulfonyl chloride are mixed with 20 ccs of acetone and 10 ccs of normal sodium hydroxide are dropped at 25–30°, while shaking. The alkaline reaction disappears soon, the acyl product dissolves and on short standing crystallisation occurs. The crystals are collected, extracted by 50 ccs of normal sodium hydroxide, suctioned washed by water and dried in vacuo. The dry di-(p-acetamino - benzolsulfo) - 2 - amino-thiazol shows an unsharp melting point; it melts completely at about 180°.

One may proceed similarly on starting from corresponding derivatives of 2-amino-thiazols substituted in the heterocyclic ring, for instance starting from the corresponding derivative of 2-amino-4-methyl-thiazol.

7. The alcoholysis is shown in the following example: 10 grams of di-(p-acetamino-benzolsulfo) -2-amino-thiazol are refluxed for about half an hour with 50 ccs of abs. alcohol, containing at about 4% of dry hydrochloric acid. One may observe the formation of acetic ether. After cooling, the crystals are suctioned and washed by alcohol. One obtains the p-amino-benzolsulfo-2-amino-thiazol which is partly present in form of its chlorhydrate. This product is stirred with a watery solution of sodium acetate yielding p-amino-benzolsulfo-2-amino-thiazol now free from its salt formed by hydrochloric acid. One may proceed in similar manner starting from the diarylsulfo derivatives of 2-amino-4-methyl-thiazol.

8. 1.14 grams of 2-amino-4-methyl-thiazol are dissolved in 5 ccs of dry acetone, 2.5 grams of sodium bicarbonate and then 2.24 grams of p-nitro-benzolsulfonyl chloride added. After heating a further portion of 2.25 grams of p-nitro-benzolsulfonyl chloride is added. The reaction mixture is boiled for about ¾ hour and then the acetone evaporated off. On addition of water to the residue, one obtains a yellow solid precipitate which is suctioned, washed with water and dried in vacuum exsiccator. This product of about 4 grams is stirred for a few minutes by 25 ccs of 0.5-normal sodium hydroxide, then suctioned, washed by water and dried in exsiccator. It melts at about 196°. This product is the di-(p-nitro-benzolsulfo) -2-amino-4-methyl-thiazol. It can be recrystallised from the fortyfold amount of boiling anizol. The melting-point rises thus to 214°.

From the alkaline mother liquors one obtains on acidification by hydrochloric acid the mono-nitro-benzolsulfo-derivative which melts in this state at about 196°. On dissolving it in sevenfold boiling acetone and adding fifteenfold amount of water, this product crystallises in well developed uniform yellow plates and shows a melting point of about 200°. This product yields on catalytic hydrogenation (palladium as catalyst) in an alcoholic suspension the p-amino-benzolsulfo-2-amino-4-methyl-thiazol melting at about 240°.

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