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SULPHONAMIDE DERIVATIVES

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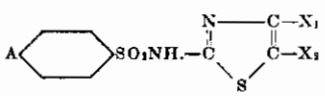
The present invention relates to new 2-amino-thiazole-derivatives of anticoccic action, as well as new 2-amino-thiazole-derivatives, which are suitable starting materials to prepare new 2-amino-thiazole derivatives of anticoccic action. These derivatives have the following general formula:



in which A represents a member of the group consisting of amino-, alkylamino-, acylamino, acylated alkylamino groups and X_1 and X_2 represents a member of the group consisting of H-, alkyl-, oxoalkyl, at least one of the groups X_1, X_2 being an oxoalkyl group.

Valuable starting materials are the acylamino-arylsulpho-thioureas, as well as the thioureides of heterocyclic aminosulphonic acids, such as the acylamino-pyridine-sulphonyl-thiourea.

Arylsulphonyl derivatives of the thiourea have been unknown till yet, especially such arylsulphonyl-thioureas or thioureids of heterocyclic sulphonic acids, in which the aryl group or the heterocyclic nucleus contains amino or substituted or acylated amino groups, or other groups which are convertible into the groups enumerated before. The thiourea can not be, namely acylated by acylating agents generally used for introduction of arylsulphonyl groups, because reactions of other course take place. Processes must have been created, thus, in order to obtain the starting materials of the present invention. These new starting materials can be obtained by splitting off α-alkoxy-alkyl group from the S-/α-alkoxy-alkyl/ethers of the iso-thiourea acylated by an aromatic or heterocyclic sulphonic acid group. The starting materials for the latter process were as well unknown till yet. These starting materials can be obtained by subjecting iso-thiourea-ethers to the action of acylating agents suitable to introduce arylsulphonic groups or heterocyclic sulphonic acid groups. Such acylating agents are e. g. the arylsulpho halogenides, especially those, in which the aryl group is substituted by amino, alkylamino, acylamino groups or groups (such as nitro, azo, etc. groups) convertible into the groups mentioned before.

Such acylating agents are e. g. the acylamino-benzol-sulpho-halogenides, such as the p-acetyl-amino-benzolsulphonyl chloride. Pyridine-sulphonyl halogenides can be used as well, e. g. the 2-acetamino-pyridine-5-sulphonyl bromide. One may use, preferably, as iso-thiourea-ethers the α-alkoxy-alkyl-ethers, such as the α-ethoxy-ethylether or, in the first place, the alkoxy-methyl-ethers, such as the methoxy-methyl or ethoxy-methyl ethers. These iso-thiourea-alkoxy-methyl ethers are preferably used in the form of their salts, as the free bases themselves are unstable. When using the salts, it is preferable to use acid binding agents, such as pyridine, sodium acetate, sodium alcoholate, etc.

Further details of the process for the obtention of arylsulpho-iso-thiourea-ethers are to be found in the examples.

The removal of the alkoxy-alkyl group from the aryl-sulpho-iso-thiourea ethers can be, preferably, effected by alcoholysis. For this splitting off specially those arylsulpho-iso-thiourea-alkyl ethers are suitable in which the alkyl group is an alkoxy-methyl or phenoxy-methyl group, preferably an ethoxy-methyl or methoxy-methyl group. The alcoholysis is effected, preferably, in the presence of acid catalysts, such as dry hydrochloric acid. The alcoholysis is effected in an absolute alcohol, containing 0.1–0.3 percent of dry hydrochloric acid. As alcohol, the methyl- or ethyl-alcohol can be advantageously used. The alkoxy-methyl groups are split off by this alcoholysis in form of acetales of the formaldehyde. As starting materials for this hydrolysis acylamino-arylsulpho- or nitro-aryl-sulpho-iso-thiourea-alkoxy-methyl ethers can be preferably used.

Further details of the alcoholysis are to be found in the examples.

As other components for the process of the present invention are α-halogene derivatives of di-ketones or poly-ketones, such as the chloro- or bromo-acetyl-acetone symmetric, the bromo-diacetyl-monoxime.

The reaction between the arylsulpho-thiourea and the α-halogenated oxo-compound is preferably carried out in the presence of an acid binding agent, such as of pyridine or other tertiary heterocyclic bases.

Further details concerning the preparation of the starting materials and of the end-products are to be found in the examples.

(1.) Thiourea and chloro-methylether are brought into interaction in acetone at room-temperature. The hydrochloride of the iso-thiourea-methoxy-methyl-ether separates. It melts at about 102°.

300 ccs of absolute methylalcohol are cooled to −10° and 62.4 grams of chlorhydrate of iso-thiourea-methoxy-methylether are added. While stirring the hydro-chloride dissolves. Now a sodium-methylate solution is added in portion at

—10°. The sodium-methylate solution has been prepared from 8.5 grams of sodium and 300 ccs of absolute methylalcohol. After the sodium-methylate solution has been added, 42 grams of finely powdered p-acetamino-bezol-sulpho-chloride are added in portions at —10°, while stirring. The stirring is continued at —10°, then for about one hour at about 0°. The p-acetamino - benzolsulpho - iso - thiourea - methoxy - methylether separates as a crystal mass. It is now filtered, the precipitate washed with water in order to eliminate the sodium chloride, then dried. One obtains about 40 grams of a white crystalline product, which melts at about 167°. It can be recrystallisated from alcohol.

One may prepare similarly the corresponding products, starting from benzolsulpho-chloride or from p-nitro-benzolsulpho-chloride or from 2-acetamino-pyridine-5-sulphonyl bromide.

(2.) 37.6 grams of finely powdered p-acetylamino - benzol - sulpho - iso - thiourea-methoxy-methylether are boiled for a minute in 222 ccs of 99% methyl-alcohol and 1.1 ccs of absolute ethyl-alcohol, containing 33% hydrochloric acid gas. The starting material passes into solution and crystallisation occurs soon. The mixture is boiled for further 2 minutes, then allowed to cool, then cooled by ice-water. The crystals are filtered. One obtains 25–28 grams of p-acetylamino-benzolsulpho-thiourea, as a white crystalline powder, which melts at about 200.5°. It dissolves in diluted alcohol and can be reprecipitated without alteration by acidification with acetic acid.

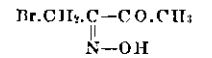
The splitting off of the methoxy-methyl group can be effected also in ethylalcoholic medium. Instead of the methoxy-methyl-ether of the p-acetamino-benzolsulpho-iso-thiourea, one may use the ethoxymethylether or the α-ethoxy-ethyl-ether as well. Instead of the p-acetamino-benzolsulpho-iso-thiourea ethers one may use the corresponding p-nitro-benzolsulpho-iso-thiourea ethers. One obtains, in this case, the p-nitro-benzolsulpho-thiourea. From 2-acetamino-pyridine - 5 - sulpho-iso-thiourea-methoxy-methyl-ether one obtains the 2-acetamino-pyridine-5-sulpho-thiourea.

(3.) 2.7 grams of mono-chloro-acetylacetone symmetric, 5.5 grams of p-acetylamino-benzol-sulpho-thiourea and 6 ccs of dry pyridine are mixed. A violent reaction takes place. The pale yellow melted mixture solidifies in crystals, on standing. After addition of 40 ccs of water it is ground and suctioned and washed by water. One obtains, in theoretical amount, the 2-(p-acetamino-benzol-sulphamido)-4-methyl-5-aceto-thiazole, which does not melt till 280°.

2.5 grams of this product are boiled in 20 ccs of sodium hydroxide of 10 volume % and in 5 ccs of water. The pale yellow solution is acidified by 2.5 ccs of glacial acetic acid. The precipitate is filtered, washed by water and dried. The product is boiled with 9 ccs of absolute alcohol, then cooled and filtered. One obtains the 2-(p-amino-benzolsulphamido)-4-methyl-5-aceto-thiazole, which melts at 213–14°.

The same product can be obtained by condensing mono-chloro-acetylacetone with p-amino-benzolsulpho-thiourea.

(4.) 3.6 grams of the mono-bromo-diacetyl-monoxime according to the formula:



and 5.5 grams of p-acetamino-benzolsulpho-thiourea and 6 ccs of dry pyridine are mixed. Under elevation of temperature a yellowish melt is formed, which is kept some minutes on the water-bath, then cooled and additioned by 20 ccs of water. On cooling and standing white crystals separate, which are suctioned and washed by water. One obtains the 2-(p-acetylamino-benzolsulphamido)-4-aceto-thiazole-oxime, which melts at about 204°. It dissolves readily in ½-normal sodium hydroxide.

On splitting off the acetyl group as well as the hydroxylamine by hydrolysis, one obtains the corresponding 4-aceto-derivative.

The experimental conditions given in the examples can be varied in many other respects as well.

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