Cl 260

Published Apr. 20, 1943

Serial No. 387,979

ALIEN PROPERTY CUSTODIAN

SULPHONAMIDE DERIVATIVES

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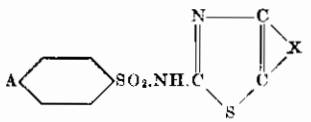
No Drawing. Application filed April 10, 1941

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 represents a bivalent aliphatic hydrocarbon chain, containing at least three carbon atoms. The bivalent group X can preferably be a tetramethylene chain which can wear a hydrocarbon side chain.

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 heterocyolic 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 the the p-acetyl-amino-benzol-sulphonyl chioride. 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 aryl-sulpho-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 acyl-amino-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 the α-halogen derivatives of cyclic ketones, such as the α-chloro-cyclohexanone or 2-chloro-methyl-cyclo-hexanones.

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-thiuorea-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-benzolsulphochloride 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-acetilamino - 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.

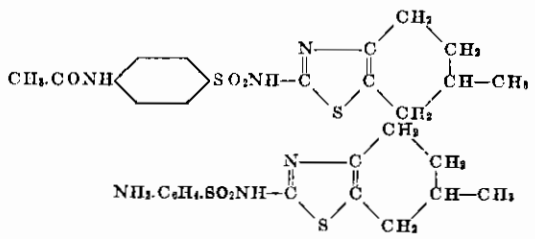
The splitting off of the methoxy-methyl group can be effected also in ethylalcoholic medium. Instead of the methoxy-methyl-ether of the p-acetamino-benzol-sulpho-iso-thiourea, one may use the ethoxymethylether or the α-ethoxy-ethylether as well. Instead of the p-acetamino-benzolsulpho-iso-thiourea ethers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

(3.) 132 grams of α-chloro-cyclohexanon, 273 grams of p-acetamino-benzolsulpho-thiourea and 300 ccs of dry pyridine are stirred and warmed on the water-bath. The reaction components go into solution. Then the mixture is cooled and the thick syrup is mixed with 2 litres of water. An oil separates, which crystallises soon. After standing the crystals are filtered, washed and dried. For further purification they can be crystallised from large amounts of hot alcohol of 90%. One obtains the 4.5-tetramethylene-2-(p-acetyl-amino-benzolsulphamido)-thiazole, which melts at about 265–280°.

This product, boiled with the eightfold amount of sodium hydroxyde of 10 volume % for half an hour and then acidified by hydrochloric acid, yields the 4,5-tetramethyle-2-(p-amino-benzolsulphamido)-thiazole, melting at about 244°. The product has anticoccic action.

When using, instead of p-acetylamino-benzolsulpho-thiourea, the p-amino-benzolsulpho-thiourea. One obtains directly the product described above.

One may obtain similarly from 2-chloro-methyl-cyclo-hexanone the compounds of the formula:



Starting from the cyclic α-halogeno-ketones mentioned in this example and condensing them with p-nitro-benzolsulpho-thiourea or with benzolsulpho-thiourea, one obtains the corresponding nitrobenzol-sulphonyl- or benzolsulphonyl-amino-thiazole derivatives.

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

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