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Silver Succinylsulfadiazine and Silver Sulfadiazine Imidazole: Two New Derivatives of the Antibacterial Silver Sulfadiazine

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Because of the low water solubility of silver sulfadiazine (0.34 mg/100 ml) the preparation of more soluble derivatives has been studied. One such derivative was prepared by the introduction of a succinyl group on the aromatic amino group of sulfadiazine. The silver compound had the composition Ag_2(succinylsulfadiazine). The water solubility of this compound with respect to silver sulfadiazine was enhanced by the factor 2 for [sulfanilamide] and 60 for [Ag]. A second derivative was prepared by the introduction of imidazole into the first coordination sphere of the silver ion. The composition of the compound was Ag(imidazole)$_2$ sulfadiazine. Its solubility was enhanced by the factor 10 as compared with that of silver sulfadiazine. The MIC values of the compounds are comparable with those of silver sulfadiazine.

Silber-Succinylsulfadiazin und Silber-Sulfadiazin-Imidazol: Zwei neue Derivate des bactericiden Silber-Sulfadiazins

Wegen der geringen Wasserlöslichkeit des Silber-Sulfadiazins (0,34 mg/100 ml) ist die Synthese wasserlöslicher Derivate bearbeitet worden. Ein Derivat wurde erhalten durch Einführung einer Succinylgruppe in die aromatische Aminogruppe des Sulfadiazins. Die Silberverbindung hat die Zusammensetzung Ag_2(Succinylsulfadiazin). Die Wasserlöslichkeit dieser Verbindung ist im Vergleich mit Silber-Sulfadiazin erhöht um den Faktor 2 bez. auf [Sulfanilamid] und 60 bez. auf [Ag]. Das zweite Derivat wurde erhalten durch Einführung von Imidazol in die erste Koordinationssphäre des Silber-Ions. Die entstandene Verbindung war Ag(Imidazol)$_2$Sulfadiazin. Die Löslichkeit ist auf das Zehnfache erhöht. Die MIC-Werte der Verbindungen sind vergleichbar mit denen von Silber-Sulfadiazin.

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Silver sulfadiazine (AgSD) as compared with a range of other sulfanilamide derivatives and related compounds offers definite advantages in the treatment of burn infections. Its unique property seems to be the moderate initial dissociation followed by a continued release of silver, over time. Most of the other silver compounds dissociate completely with rapid removal of all silver and binding of the silver to wound components or else dissociate only slightly without release of silver[1]. The mode of antibacterial action of the silver ion and the role of the sulfadiazine moiety are not completely understood. To obtain more insight into the role of the sulfanilamide moiety we are performing a structure-activity study on a series of silver sulfanilamides. One of the most striking physical parameters of silver sulfadiazine and most of the other silver sulfanilamides is their very low water solubility (AgSD: 0.34 mg/100 ml). This can be explained by the polymeric nature of the compounds[2,3,4]. To express the antibacterial activity at least a temporarily dissolution of the silver compound seems to be necessary (transport into the aqueous phase). For this reason we attempted the preparation of more water soluble derivatives of the most active agent silver sulfadiazine. An important prerequisite for the preparation of an active derivative is to maintain the physico-chemical properties of the 2-(sulfonamido)pyrimidine part of the sulfadiazine molecule as much as possible. The silver ion which is responsible for the biological activity is coordinated to this part of the molecule[2].

We have investigated the problem in two ways:

a) the introduction of a solubilysing substituent on the aromatic 4-NH_2 group of sulfadiazine

b) depolymerisation of AgSD by the introduction of suitable ligands at Ag(I).

a) Silver succinylsulfadiazine (Ag_2SSD)

The introduction of a succinyl group on the aromatic amino group of sulfadiazine results in succinylsulfadiazine (H_2SSD)[5]. Substitution of both acidic protons by silver gives Ag_2SSD with a proposed structure as given in Fig. 1A. The product is light sensitive to some extent (AgSD is not light sensitive), possibly the silver ion coordinated to the carboxyl group is responsible for this phenomenon.

From the IR spectrum it is clear that one Ag ion is coordinated in the same way to the sulfonamido group as in AgSD. The positions of $\nu(SO_2)$ are almost identical: 1 230 cm^{-1} and 1 130 cm^{-1} (AgSD: 1 232 cm^{-1} and 1 130 cm^{-1}). The $\nu(C=O)$ in Ag_2SSD is shifted to 1 670 cm^{-1} as compared with the parent compound H_2SSD: 1 700 cm^{-1}. The 3 000 – 3 500 cm^{-1} region is not interpretable. The exact mode of coordination of the silver ions is more complicated then indicated in the structural formula. The molar conductivity in DMSO amounts to Λ_m: 3.2 $\Omega^{-1} \cdot cm^2 \cdot mole^{-1}$, indicating an undissociated complex in that hydrophilic solvent. The water solubility of Ag_2SSD was enhanced to 0.55 mg/100 ml in sulfanilamide concentration as compared with AgSD 0.34 mg/100 ml respectively; the enhancement in silver concentration is very large i.e. [Ag]: 2.96 mg/100 ml and 0.05 mg/100 ml respectively. The pH of the saturated Ag_2SSD solution was 6.90. In Ag_2SSD there are of course two Ag(I) ions per molecule available and the Ag(I) ion coordinated to the carboxyl group is loosely bounded (0 donor atom).

We have tried to prepare the 1 : 1 compound Ag(HSSD) and obtained a product with Ag: 20.7 % (theor: 23.60 %). This product was very light sensitive and decomposed at 120 °C to a grey compound.

b) Silver sulfadiazine imidazole (Im.) Fig. 1 B shows a proposed structure for the resulting compound (Ag(Im.)$_2$SD)

Each Ag(I) ion in AgSD is 4-coordinated and is surrounded by three SD molecules and is therefore polymeric in nature[2]. Substitution of the second and third SD molecule by another ligand results in depolymerisation. This was realized by the use of imidazole (Ag(Im.)$_2$SD). The product is not light sensitive. The $\nu(SO_2)$ bands in the IR spectrum have slightly different positions as compared with AgSD e.g. 1 245 cm^{-1}/1 120 cm^{-1} and 1 232 cm^{-1}/1 130 cm^{-1} resp. However, we do not have positive support for the proposed mode of coordination of Im. with silver. The molar conductivity in DMSO was Λ_m: 1.6 $\Omega^{-1} \cdot cm^2 \cdot mole^{-1}$, and indicated an undissociated compound; at least the AgSD part of the compound is not dissociated. The water solubility was enhanced to 3.4 mg/100 ml as compared with AgSD: 0.34 mg/100 ml. Possibly the relatively high pH: 9.0 of the saturated solution of Ag(Im.)$_2$SD, caused by the basic properties of Im., is partly responsible for this enhancement.

The nature of the immediately formed product in the preparation is unknown; the IR spectrum differs from HSD, AgSD and Im.

From the results it can be concluded that our aim to prepare more soluble derivatives of AgSD has been realized in both described cases. These compounds can be considered as the first members of two new series of AgSD derivatives.

The minimum inhibitory concentration (MIC) of Ag_2SSD, Ag(Im.)$_2$SD and AgSD against Ps. Boston was found to be 0.003 γmole/ml, 0.025 γmole/ml and 0.0125 μmole/ml resp. The in vivo antibacterial activities of the compounds will be reported separately with others.

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Experimental

Reagents and chemicals

All chemicals used were of analytical or reagent grade. The preparation of AgSD used in this study has already been described[3]. Succinylsulfadiazine (2-(N-4-succinylsulfanilamido)pyrimidine) was prepared according to the literature[5]: m. p. 215 – 217 °C, analysis: Calcd: C 48.0 H 4.03 N 16.0 S 9.2 Found C 47.5 H 4.0 N 15.9 S 9.0.

Equipment and analyses

IR spectra: Perkin Elmer model 577 (KBr, Nujol); *conductivity measurements:* Radiometer conductivity meter, type CDM^{2d} with a conductivity cell type CDC 104; solvent: dimethyl sulphoxide RG dried, Riedel-De Haën AG, Seelze-Hannover, Germany.

The *silver* was analyzed by *Volhard* titration after decomposition of the compound with 65 % nitric acid. The *elemental analyses* were performed by the Analytical Department of the Chemical Laboratories, University of Groningen.

The *solubility determinations* were made by equilibrating the silver compounds in doubly distilled water at 25 ± 0.1 °C (one week) in a vial with a parafilm-sheet covered rubber closure and wrapped with aluminium foil. The vials were rotated during equilibration in the thermostated bath. The saturated solutions were filtered through 25 mm diameter and 1.2 μm average pore size filters (Selectron-filter, type ST 69; Schleicher & Schüll, Dassel, Germany). The *solution pH* was measured with a pH meter, type PHM 22 r, Radiometer, Copenhagen. The solutions were analyzed for sulfanilamide by *UV-spectrometry* (Perkin Elmer 124) and for silver by *AAS* (Perkin Elmer, type 303, acetylene-air flame, lamp: 3 UAX/Ag-Cathodeon Ltd.: 328.1 nm).

The in vitro assay of *microbial inhibition* of the compounds was made in parallel with AgSD in nutrient broth inoculated with Pseudomonas Boston. Growth was observed by turbidity measurements after 24 – 48 hours incubation at 37 °C. The experiments were performed by Prof. *Ch. L. Fox, Jr.* from the College of Physicians and Surgeons, Columbia University, New York, USA.

Synthesis of silver succinylsulfadiazine

0.02 mole of succinylsulfadiazine were dissolved in 40 ml of 0.1 N – NaOH and 200 ml of water. To this solution was added dropwise with stirring a solution of 0.04 mole silver nitrate in 100 ml of water. The white precipitate was separated after standing 24 hr. in the dark, washed with 20 ml of water and dried at 120 °C. Yield: 94 %, analysis Calcd.: C 29.8 H 2.32 N 9.9 S 5.7 Ag 38.3; Found C 29.0 H 2.1 N 9.7 S 5.5 Ag 37.0.

Synthesis of silver sulfadiazine imidazole

0.01 mole of AgSD were dissolved in the minimum amount of 25 % w/v NH_3 solution (about 80 ml). To this stirred solution was added a solution of 0.2 mole imidazole in 50 ml of water. The precipitate which was immediately formed was filtered off and discarded (about 1.8 g). The filtrate was placed in the dark for five days in the open air. A crystalline precipitate was formed which was washed with 20 ml of water and dried i. vac. over silicagel. Yield: 15 %, analysis Calcd.: C 38.9 H 3.47 N 22.7 S 6.5 Ag 21.9; Found C 39.1 H 3.5 N 23.2 S 6.5 Ag 21.7, sulfadiazine by amperometric titration: 50.3 (50.52)[6].

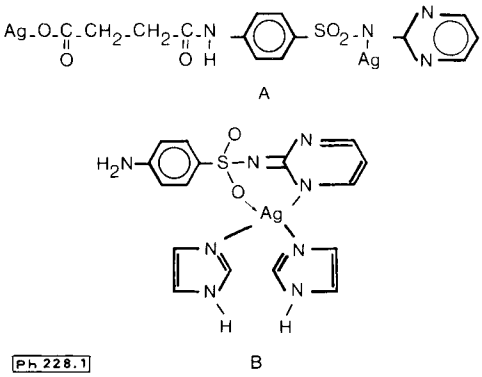

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Fig. 1: Proposed structure formulas of
A) silver succinylsulfadiazine
B) silver sulfadiazine imidazole

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Analyse des polymorphen Systems von Sulfametoxydiazin

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Es wird gezeigt, daß Sulfametoxydiazin insgesamt 8 polymorphe Modifikationen, mindestens 4 solvatisierte Kristallformen und eine glasartige Form bildet. Bei Raum- bzw. Körpertemperatur nimmt die Löslichkeit der untersuchten Formen in folgender Reihenfolge zu: Mod. III, I, VI, II, IV, V. Gegenüber den jeweils höher schmelzenden Modifikationen sind Mod. VI und III enantiotrop, Mod. V und II hingegen monotrop. Das thermodynamische Stabilitätsverhalten wird in einem Energie/Temperatur-Diagramm dargestellt. Die Ergebnisse stimmen mit der früher mitgeteilten Umwandlungs-, IR- und Dichteregel überein. Zur Identifikation der einzelnen festen Phasen eignen sich die IR-Spektren am besten.

Analysis of the Polymorphous System of Sulfametoxydiazine

It is shown, that sulfametoxydiazine exists in 8 polymorphous modifications, at least 4 solvated crystalline forms and a glasslike form. At ambient and body temperatures the solubility of the investigated forms increases in the order: III, I, VI, II, IV, V. Modifications VI and III are enantiotropic, and modifications V and II, on the contrary, are monotropic with those modifications, which have the higher melting points. The thermodynamic stability is presented in an energy/temperature diagram. The results agree with the previously published heat-of-transition rule, and with the infrared and density rules. For the identification of the solid phases the infrared spectra are most suited.

Um die thermodynamischen Beziehungen zwischen n polymorphen Modifikationen eines Stoffes festzulegen, ist es erforderlich, $(n\text{-}1) \cdot n/2$ mal über das Vorliegen von

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