ON THE TAUTOMERISM OF 5-AMINOTETRAZOLE

VI. Sulfanilamides of 1- and 2-Methyl-5-aminotetrazoles*

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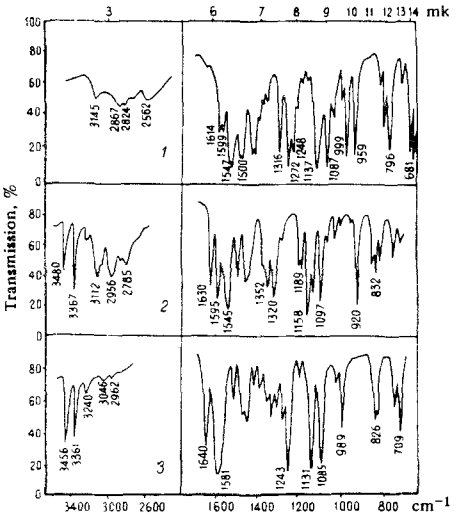
In order to study the connection between the structure of sulfanilamides and their antibacterial action, sulfanilamide derivatives of 1- and 2-methyl-5-aminotetrazoles and of 1,3-dimethyl-5-iminotetrazole have been synthesized. A study of their IR spectra has shown that 1-methyl-5-sulfanilimidotetrazole has the imide structure in the crystalline state and 2-methyl-5-sulfanilamidotetrazole the amide structure. The sulfanilamide derivatives of 1- and 2-methyl-5-aminotetrazoles possess a considerable antibacterial activity, while 1,3-dimethyl-5-sulfanilimidotetrazole is inactive.

The preparation of sulfanilamide derivatives of 1-methyl-5-aminotetrazole (1-methyl-5-AT) and 2-methyl-5-AT) and 2-methyl-5-AT** is of interest for the study of the connection between structure and antibacterial activity. There is a hypothesis, first put foward as early as 1940 by I. M. Polyakova and A. V. Kirsanov [4], that the activity of sulfanilamide derivatives of nitrogen-containing heterocycles depends to a considerable extent on the position of the amide-imide tautomerism, the presence of the imido form playing an essential role in activity. The results obtained by Shepherd et al. [5] may apparently be regarded from the same point of view; they showed that the product of the methylation of 2-sulfanilamidothiazole (norsulfazole) at the terminal nitrogen atom (imide structure) had an activity not inferior to that of norsulfazole itself, while the isomer having the methyl group attached to the cyclic nitrogen atom (amide structure) possessed no activity.

As shown previously, acyl derivatives of 1- and 2-methyl-5-ATs have different positions of the amide-imide tautomeric equilibrium [6–8]. With a sufficiently electronegative acyl residue, while the acyl derivatives of 1-methyl-5-AT readily pass into the imide form, acyl derivatives of 2-methyl-5-AT with any acyl residue exist only in the amide form, both in the crystalline state and in solution. On this basis, a comparison of the bacteriostatic activity of sulfanilamide derivatives of 1- and 2-methyl-5-ATs is of definite interest and could promote the development of ideas on the connection between the structure of the sulfanilamides and their antibacterial action.

Sulfanilamide derivatives of 1-methyl-5-AT could not be obtained by the usual method for the synthesis of sulfanilamides—the reaction of 1-methyl-5-AT with p-acetylaminobenzenesulfonyl chloride in pyridine—because to obtain arylsulfonyl derivatives of 1-methyl-5-AT the duration of a reaction of this type would have to be not less than 19–20 hr [7], and during this time considerable resinification and, apparently, hydrolysis of the acetyl group takes place. As a result of this,



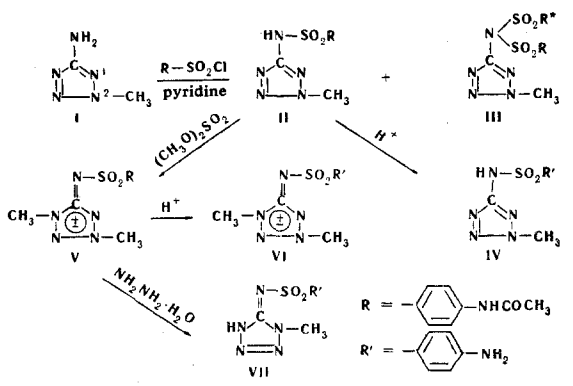
IR spectra: 1) 1-methyl-5-sulfanilimidotetrazole (VII); 2) 2-methyl-5-sulfanilamidotetrazole (IV); 3) 1,3-dimethyl-5-sulfanilimidotetrazole (VI) (all in the crystalline state).

it is impossible to isolate the product obtained from the reaction mixture. It was found that this sulfanilamide can be obtained in good yield by the elimination of the methyl group present on the N_3 atom in 1,3-dimethyl-5-arylsulfonylimidotetrazoles under the action of such a strong nucleophilic agent as hydrazine hydrate [9]. The 1,3-dimethyl derivative V necessary for this purpose was obtained by methylating 2-methyl-5-p-acetylaminobenzenesulfonamidotetrazole (II) [10] with dimethyl sulfate in an anhydrous medium*. When V was heated with hydrazine hydrate, not only did the splitting off of the methyl group but also the saponification of the acetyl group take place, and 1-methyl-5-sulfanilamidotetrazole (VII) was obtained.

*For communication V, see [1].

**The sulfanilamide of 5-aminotetrazole has been described in the literature [2, 3].

*The structure of V is not a matter of doubt, since by studying the reactivity of acyl derivatives of 2-methyl-5-AT in their reaction with dimethyl sulfate in an anhydrous medium it was found that methylation takes place under such conditions at the ring nitrogen atom in position 4 [7, 11].



The sulfanilamides IV and VI were obtained by the hydrolysis of compounds II and V, respectively, with hydrochloric acid.

The structure of the sulfanilamides synthesized, IV, VI, and VII, was confirmed by a study of their IR spectra** (see figure). As has been shown previously [7], the structure of the arylsulfonyl derivatives of 1- and 2-methyl-5-ATs can be established from the position of the absorption bands relating to the symmetrical (ν_s) and asymmetrical (ν_{as}) stretching vibrations of the SO_2 group: compounds with the amide structure have bands in the 1158–1190 cm^{-1} (ν_s) and 1325–1380 cm^{-1} (ν_{as}) regions, and those with the imide structure in the 1130–1150 cm^{-1} (ν_s) and 1260–1285 cm^{-1} (ν_{as}) regions.

From a consideration of the IR spectra of the sulfanilamides obtained, taking these data into account, it follows that, as was to be expected, the derivatives of 2-methyl-5-AT (IV) have the amide structure, while the derivatives of 1-methyl-5-AT have the imide structure in the crystalline state.

It is interesting that the bands relating to the stretching and deformation vibrations of the NH_2 group in the spectrum of 1-methyl-5-sulfanilamidotetrazole have a much lower frequency and are in the 3145 cm^{-1} (νNH_2) and 1599 cm^{-1} (δNH_2) region. The same displacement of the frequencies of the stretching and deformation vibrations of the NH_2 group has been found in the IR spectra of the sulfanilamides of thiazole and thiadizaole [12]. In all probability, these facts indicate that in the sulfanilamides (nonmethylated) having the imide structure in the crystalline state there is extremely considerable intermolecular interaction due to the formation of hydrogen bonds of the type >NH... ...NH_2—. At the same time, in the spectrum of the sulfanilamide of 2-methyl-5-AT, which has the amide structure, the positions of the bands of the stretching and deformation vibration, 3480 and 3367 cm^{-1} (νNH_2) and 1630 cm^{-1} (δNH_2), are the same as in the spectrum of its methylated derivative, 1,3-dimethyl-5-sulfanilimidotetrazole (VI), which has no acidic hydrogen atom. This shows that in the sulfanilamide of 2-methyl-5-AT (IV) the amino group of the sulfanilyl residue does not take part appreciably in the formation of hydrogen bonds of the >NH... NH_2— type.

Preliminary experiments on their antibacterial action in liquid nutritional media (Hottinger's bouillon) have shown that the sulfanilamide derivatives of 1- and 2-methyl-5-ATs (VII, IV) and also 5-AT itself possess approximately the same antibacterial activity. These sulfanilamides retard the growth of staphylococci and streptococci and dysentery and coli bacteria to a somewhat greater extent than 2-sulfanilamidothiazole (norsulfazole), while the derivatives of 1-methyl-5-AT and 5-AT possess bactericidal and the derivative of 2-methyl-5-AT only bacteriostatic properties. In a study of antibacterial action in solid nutritional media (agar) it was found that the derivative of 1-methyl-5-AT, which has the imide structure, possesses a greater activity than the derivative of 2-methyl-5-AT (amide structure). So far as concerns the sulfanilamide with a mesoionic structure VI this possesses no activity in either liquid or solid nutritional media.

EXPERIMENTAL

5-Sulfanilamidotetrazole was synthesized by a published method [3], mp 202–203° C (decomp.). The preparation of 2-methyl-5-p-acetylaminobenzenesulfonamidotetrazole (II) has been described previously [10].

2-Methyl-5-sulfanilamidotetrazole (IV). One gram (~4 mM) of II was boiled in 10 ml of 2 N hydrochloric acid for 15 min. The solution obtained was evaporated on the water bath, the residue was treated with concentrated ammonia solution, and the mixture was then acidified with 50% acetic acid. The precipitate which deposited was filtered off and washed with cold water. This gave 0.75 g (87%) of IV. After crystallization from water, mp 145–146° C (plates). The substance was readily soluble in ethanol and dioxane and insoluble in benzene. Found, %: C 38.16; H 4.17; N 33.34. Calculated for $C_8H_{10}N_6O_2S$, %: C 37.80; H 3.94; N 33.10.

1,3-Dimethyl-5-p-acetylaminobenzenesulfonimidotetrazole (V). A mixture of 4.5 g (0.015 mole) of II, 1.57 ml (0.017 mole) of dimethyl sulfate, and 2 ml of anhydrous dioxane was heated with stirring in the boiling water bath for 1 hr. The resulting red-brown mass was treated with 10 ml of methanol and 4 ml of concentrated ammonia solution. After 3–4 hours' standing in the cold (at −5 to −3° C), the precipitate was filtered off and washed with ethanol. In this way 2.8 g (60%) of V was obtained with mp 244–245° C (flat prisms, from water). The substance was readily soluble in ethanol and insoluble in alkalies and dilute hydrochloric acid. Found, %: N 27.20; S 9.92. Calculated for $C_{11}H_{14}N_6O_3S$, %: N 27.11; S 10.30.

1,3-Dimethyl-5-sulfanilimidotetrazole (VI). A mixture of 2 g of V and 7 ml of concentrated HCl was boiled for 10 min. Then the solution was cooled and made alkaline, and the precipitate that deposited was filtered off. The weight of the precipitate was 1.47 g (85%), mp 252–253° C (decomp., plates, from water). The compound was insoluble in ethanol and alkalies and readily soluble in concentrated and dilute HCl. Found, %: C 40.47; H 4.70; S 11.91. Calculated for $C_9H_{12}N_6O_2S$, %: C 40.31; H 4.48; S 11.92.

1-Methyl-5-sulfanilimidotetrazole (VII). A mixture of 2 g (~7 mM) of V and 10 ml of hydrazine hydrate was boiled for 4 hr. The solvent was distilled off in vacuum, the residue was treated with 5 ml of 2 N NaOH, and the mixture was evaporated to dryness on the water bath. It was acidified with concentrated HCl, which was then evapo-

*For the structure of the diarylsulfonyl derivatives of 2-methyl-5-AT, see [10].

**The IR spectra were recorded on an IKS-14 spectrometer. The substances were studied in the crystalline state in the form of mulls in paraffin oil (NaCl prism) and in perfluorohydrocarbons (LiF prism). We take this opportunity to express our thanks to I. I. Mudretsova for recording the spectra.

rated, and the residue was extracted with hot ethanol (2 × 10 ml). The ethanolic extracts were combined, the ethanol was distilled off, and the residue was washed with 2 ml of cold water. This gave 1.2 g (72%) of VII, mp 175–176° C (small needles, from water). Found, %: C 37.97; H 4.06; N 33.41; S 12.76. Calculated for $C_8H_{10}N_6O_2S$, %: C 37.80; H 3.94; N 33.10; S 12.59.

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