STRUCTURE OF 6-β-[(HEXAHYDRO-1H-AZEPIN-1-YL)METHYLENEAMINO]-PENICILLANIC ACID SULFOXIDE

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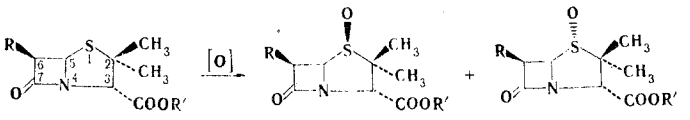
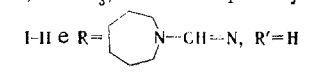
The oxidation of 6-β-[(hexahydro-1H-azepin-1-yl)methyleneamino]penicillanic acid with potassium periodate or m-chloroperbenzoic acid leads to the corresponding sulfoxide. Its structure was proved by alternative synthesis by splitting out the N-phenylacetyl group from the benzylpenicillin sulfoxide and condensation of the 6-aminopenicillanic acid sulfoxide with N-formylhexamethyleneimine dibutylacetal.

It is known that only one stereoisomer (IIa-c), which has an S configuration of the sulfoxide group, is formed in the oxidation of the sulfur atom in penicillins Ia-c with organic peracids, hydrogen peroxide, or sodium periodate. This configuration is due to a considerable extent to a hydrogen bond between the oxygen atom and the proton of the amido group in the 6 position of the heterocyclic ring of the antibiotic [1]. When an amide proton is absent, the steric factor plays the primary role in the orientation of the sulfide group, and the bulky phthalimido group in the side chain of penicillin Id promotes the formation of only one R epimer IIId [2].



I a-e II a-c III d

I-II a R = $C_6H_5OCH_2CONH$, R′ = H, CH_3; b R = $C_6H_5CH_2CONH$, R′ = H, CH_3;
c R = CH_3CONH, R′ = CH_3; I-III d R = phthalylamino, R′ = CH_3;

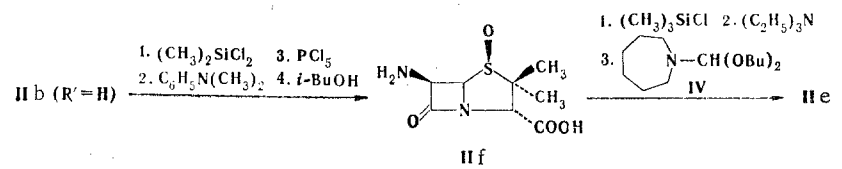


I-II e R = , R′ = H

In this connection, it seemed of interest to study the structure of the product of oxidation of 6-β-[(hexahydro-1H-azepin-1-yl)methyleneamino]penicillanic acid (Ie), the bulky side chain of which has an amide structure that is not capable of forming a hydrogen bond.

The oxidation of Ie was carried out with potassium periodate in water or with m-chloroperbenzoic acid in chloroform. In both cases we obtained sulfoxides that have identical physicochemical and spectroscopic characteristics, including the specific rotation.

To establish the percentages of stereoisomeric sulfoxides in the oxidation product we undertook the alternative synthesis of S epimer IIe by splitting out the N-benzylcarbonyl group from the benzylpenicillin sulfoxide (IIb, R′ = H) and condensation of the 6-aminopenicillanic acid sulfoxide (IIf) with N-formylhexamethyleneimine dibutylacetal (IV).



IIb (R′ = H) → (1. $(CH_3)_2SiCl_2$ 3. PCl_5; 2. $C_6H_5N(CH_3)_2$ 4. *i*-BuOH) → IIf → (1. $(CH_3)_3SiCl$ 2. $(C_2H_5)_3N$; 3. IV) → IIe

In both reactions the carboxy groups of penicillin derivatives IIb, f were protected by alkylsilyl groupings, which promote stabilization of the β-lactam ring in the process of modification of their side chain and are readily split out by lower alcohols.

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A comparison of the physicochemical and spectroscopic characteristics of stereoisomer IIe obtained in this way with the analogous data for the products of direct oxidation of 6-β-[(hexahydro-1H-azepin-1-yl)methyleneamino]penicillanic acid revealed that they are in complete agreement. Thus an amidino group in the side chain of penicillin, like an amido group, orients the sulfoxide group stereospecifically to give only one S epimer IIe.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra of solutions in D_2O were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with sodium 3-(trimethylsilyl)propanesulfonate as the internal standard; the chemical shifts are presented on the δ scale.

6-β-[(Hexahydro-1H-azepin-1-yl)methyleneamino]penicillanic Acid Sulfoxide (IIe). A) A 2.3-g (0.01 mole) sample of potassium periodate was added to a solution of 3.25 g (0.01 mole) of penicillanic acid Ie in 10 ml of water, and the suspension was stirred at 18-22°C for 4 h and allowed to stand in a refrigerator for 12 h. The precipitate was removed by filtration, and the mother liquor was diluted with 90 ml of acetone. The resulting precipitate was removed by filtration and recrystallized repeatedly from aqueous acetone to give 2.2 g (65%) of colorless crystals with mp 153-154°C and $[\alpha]_D^{20}$ = +213° (c 0.5, water). IR spectrum: 1780 (C=O, β-lactam), 1680 (C=O, carboxy), 1610 (C=N), and 1050 cm^{-1} (S=O). PMR spectrum: 1.31 (3H, s, 2α-CH_3), 1.72 (3H, s, 2β-CH_3), 1.20-1.40 [8H, m, $(CH_2)_4$], 3.40-3.90 (4H, m, N-CH_2), 4.48 (1H, s, 3-H), 5.42 (1H, d, J = 4.7 Hz, 5-H), 5.58 (1H, d, J = 4.7 Hz, 6-H), and 8.14 ppm (1H, s, CH=N). Found: C 50.88; H 6.46; N 11.88%. $C_{15}H_{23}N_3SO_4$. Calculated: C 51.12; H 6.79; N 12.32%.

B) A solution of 1.73 g (0.01 mole) of m-chloroperbenzoic acid in 5 ml of chloroform was added with stirring at 0°C in the course of 30 min to a suspension of 3.25 g (0.01 mole) of acid Ie in 10 ml of chloroform, and the mixture was stirred at this temperature for another hour. The resulting solution was washed with water, and the aqueous solution was evaporated to 3-4 ml. The concentrate was diluted with 20 ml of acetone to give 2.5 g (73%) of colorless crystals with mp 153-154°C and $[\alpha]_D^{20}$ = +213° (c 0.5, water). The IR and PMR spectra of the substance coincided with the spectra of the sulfoxide obtained by method A.

C) A 1.10-ml (0.08 mole) sample of triethylamine and 1.00 ml (0.08 mole) of trimethylchlorosilane were added with stirring at 0°C to a suspension of 0.93 g (0.04 mole) of sulfoxide IIf in 10 ml of methylene chloride, and the mixture was stirred at 0°C for 20 min. A solution of 1.20 ml (0.04 mole) of N-formylhexamethyleneimine dibutylacetal in 5 ml of methylene chloride was added to the resulting solution, and the mixture was stirred at 0°C for 1 h and filtered. The filtrate was washed with 20 ml of water, and the aqueous solution was evaporated to a volume of 3-4 ml. The concentrate was diluted with 30 ml of acetone, and the resulting precipitate was removed by filtration and recrystallized from aqueous acetone to give 0.50 g (37%) of colorless crystals with mp 152-153°C and $[\alpha]_D^{20}$ = +213°C (c 0.5, water).

The IR and PMR spectra of the substance obtained coincided completely with the spectra of the sulfoxide obtained by methods A and B.

6-Aminopenicillanic Acid Sulfoxide (IIf) [3]. An 8.1-ml (0.072 mole) sample of dimethylaniline and 1.8 ml (0.015 mole) of dimethylchlorosilane were added to a suspension of 6.4 g (0.018 mole) of benzylpenicillin sulfoxide in 50 ml of methylene chloride, and the mixture was stirred for 30 min. It was then cooled to −30°C and treated with 3.96 g (0.019 mole) of phosphorus pentachloride. The solution was stirred at −30°C for 2.5 h, cooled to −50°C, and diluted with 28 ml of isobutyl alcohol. The resulting solution was stirred at −40°C for another hour, after which 10 g (0.052 mole) of p-toluenesulfonic acid monohydrate in 18 ml of methanol and 6 ml of water was added. The mixture was warmed to 0°C to give 2.97 g (40%) of a crystalline precipitate of the p-toluenesulfonate of sulfoxide IIf with mp 170-171°C. The salt was stirred for 1 h in a mixture of 7.7 ml of 2-propanol, 1.3 ml of water, and 1.0 ml of triethylamine. The precipitate was removed by filtration and dried in a vacuum desiccator to give 1.58 g of sulfoxide IIf with mp 137°C.

LITERATURE CITED

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REACTIONS OF 4-AMINO-1,3,5-DITHIAZINE WITH AMMONIA AND AMINES

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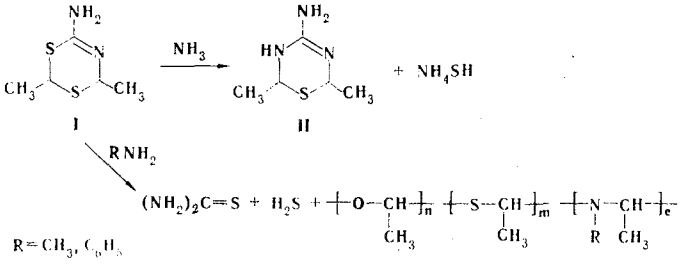
It is shown that selective replacement of the sulfur atom in the 3 position by a nitrogen atom, which leads to 2,6-dimethyl-4-amino-3H-2,6-dihydro-1,3,5-thiadiazine, occurs when 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine is treated with ammonium hydroxide. Under the same conditions, amines cause profound destruction of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine with the production of thiourea.

Many heterocycles that contain simultaneously nitrogen and sulfur atoms, particularly thiourea derivatives, are unstable with respect to the action of nucleophiles.

According to the data in [1], 2-amino-4-oxo-2-thiazoline undergoes cleavage in aqueous alkaline solutions to give thiourea and 2-hydroxycarboxylic acid. Ring opening, profound decomposition, dimerization, or oxidation may occur when 1,3,4-thiadiazolium salts are treated with bases, depending on the substituents and the conditions [2]. The reaction of 2,4,6-triaryl-4H-1,3,5-thiadiazines with catalytic amounts of aliphatic amines is accompanied by the liberation of elementary sulfur and the formation of 2,4,5-triarylimidazole [3].

The present communication is devoted to a study of the transformations of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine (I) [4] under the influence of ammonia and amines. As we have already reported [5], in 10-15% aqueous alcohol solutions of ammonia at 20-70°C dithiazine I or its salts (the nitrate and chloride) undergo selective replacement of the sulfur atom in the 3 position by a nitrogen atom to give a new heterocyclic system, viz., 2,6-dimethyl-4-amino-3H-2,6-dihydro-1,3,5-thiadiazine in 62-88% yields.



The PMR spectra of II [6] in various solvents and when the temperature is varied, as well as its IR spectrum [5, 7], provide evidence in favor of the amino form.

In analogy with the reaction presented above, in the reaction of dithiazine I with primary amines (methylamine and aniline) one might have expected the formation of 2,6-dimethyl-3-N-alkyl(aryl)-4-amino-2,6-dihydro-1,3,5-thiadiazine. However, we found that the reaction in this case proceeds with profound decomposition of the starting heteroring to give thiourea, H_2S, and products of condensation of acetaldehyde, thioacetaldehyde, and aldimines, which were not investigated in greater detail. Secondary and tertiary amines in an aqueous alcohol medium give rise to similar decomposition of dithiazine I.

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