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RESEARCHES ON ALLO- AND ISOALLOXAZINE

XIV. Synthesis of 6-Chloro-7-sulfoamidoalloxazine and its N-Oxide

V. M. Berezovskii, G. D. Glebova, N. V. Fedorova, and Zh. I. Aksel'rod

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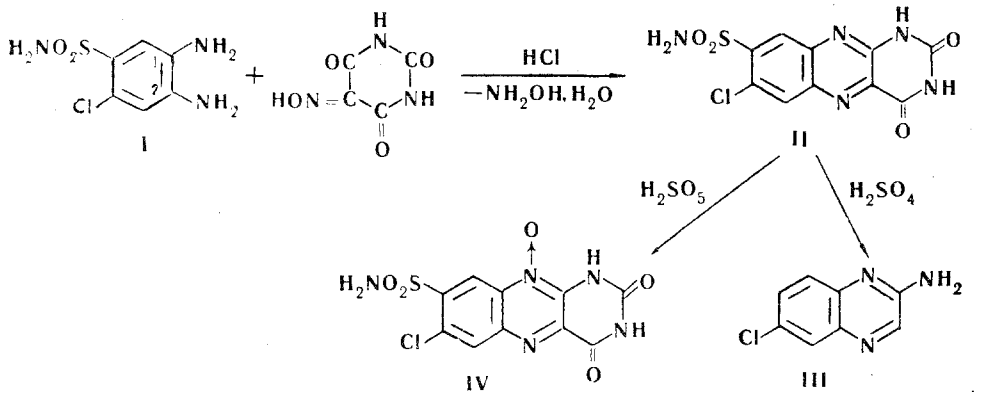
For a study of the diuretic properties of alloxazine, 6-chloro-7-sulfamidoalloxazine (II) has been synthesized for the first time, by condensing 4-chloro-5-sulfamido-o-phenylenediamine with violuric acid, and 6-chloro-7-sulfamidoalloxazine N-oxide (IV) is prepared by oxidizing II with permonosulfuric acid at the instant of formation. The structure of II is shown by splitting it with sulfuric acid to 2-amino-6-chloroquinoxaline.

It was of interest to enhance the diuretic properties of 7-chloroalloxazine [1] by introducing the sulfamide group into its molecule, it being known [2] that this group enhances the specific therapeutic activity. In an attempt to prepare 7-chloro-6-sulfamidoalloxazine use was made of a method which we developed, of condensing o-diamines with violuric acid [3]. However, that reaction can proceed in the direction of formation of alloxazine with a chlorine atom at position 6. Actually, we found that 4-chloro-5-sulfamido-o-phenylenediamine (I) [4] and violuric acid in the presence of hydrochloric acid gave 6-chloro-7-sulfamidoalloxazine (II) in 60% yield. The structure of compound II is, again, shown by splitting with 85% sulfuric acid at 205-210° C, into 2-amino-6-chloroquinoxaline (III), isolated as the sole reaction product.



I II IV III

It follows from the structure of compound I that because of the orientating effect of the electron-accepting substituents, the sulfamide group and the chlorine atom, the nucleophilic center of the molecule must be concentrated at the amino group in position 1. In this case condensation with violuric acid would lead to formation of the corresponding derivative of 7-chloroalloxazine. However, under the reaction conditions, in mineral acid, protonation of the nitrogen of this more basic amino group and transfer of the reaction center of the molecule to the nitrogen of the amino group at position 2 are possible. Thus nucleophilic addition of the nitrogen of the amino group at that position to the double bond of an electrophilic carbon atom at position 5' in the violuric acid, leads to formation of 6-chloro-7-sulfamidoalloxazine (II).

It is known that the N-oxide group in the molecule of 7-chloroalloxazine increases its directive action [5], so 6-chloro-7-sulfamidoalloxazine N-oxide (IV) was synthesized. Because of the great inertness of II with regard to oxidation, the N-oxide was obtained only by using a highly-active oxidizing agent, permonosulfuric acid at the instant when it was formed from ammonium persulfate and sulfuric acid.

Compound IV can be assigned an alloxazine N_9-oxide structure, since oxidation of the nitrogen atoms at positions 1 and 3 at position 10 in the pyrazine ring of the molecule, is hindered at carbonyl groups at positions 2 and 4. Thus 2-hydroxy-4, 6-dimethylpyrimidine does not give an N-oxide, while 4, 6-dimethylpyrimidine is readily oxidized by hydrogen peroxide to give monoxides [6]; a carboxyl group ortho to the nitrogen atom in the quinoxaline series, also hinders oxidation [7]. It is characteristic of isoalloxazines that compounds with a substituent at N_9 do not give N-oxides, e.g., riboflavin and lumiflavin are not oxidized by hydrogen peroxide in acid [8]. Further it was not possible to oxidize lumiflavin with permonosulfuric acid at the moment of formation of the latter.

The structures of compounds II and IV are confirmed by visible UV (Fig. 1), and IR (Fig. 2) absorption spectra. The visible and UV absorption spectra of these compounds are characteristic of alloxazines, but the absorption maxima are somewhat shifted towards the longwave region, and in the 340–380 mμ range there are unsharp peaks. Strong carbonyl absorption bands at 1715 and 1740–1725 cm^{-1} are found in the IR spectra of 6-chloro-7-sulfamidoalloxazine and

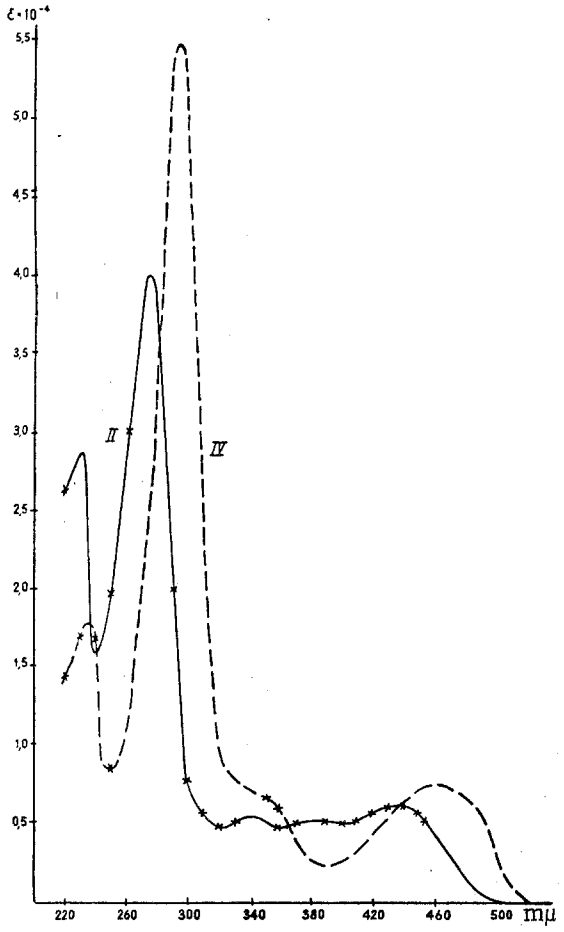


Fig. 1. UV spectra (in 0.1 N NaOH solution). II) 6-Chloro-7-sulfamidoalloxazine; IV) 6-chloro-7-sulfamidoalloxazine N-oxide (SF-4-spectrophotometer).

its N-oxide, the 1715 cm^{-1} band of highest absorption intensity is to be assigned to valence vibrations of the C=O group at position 4, conjugated with a C=N bond. There are also absorption band peaks in the 3240, 1170 and 1350–1330 cm^{-1} regions, corresponding to vibrations of the groups NH_2 and S=O. The IR spectrum of 6-chloro-7-sulfamidoalloxazine N-oxide also has a 1275 cm^{-1} absorption band, corresponding to N → O* group valence vibrations.

Experimental

6-Chloro-7-sulfamidoalloxazine (II). A mixture of 1.57 g (0.01 mole) violuric acid, 2.5 g (0.01 mole) 4-chloro-5-sulfamido-o-phenylenediamine (I), and 40 ml 2 N HCl, was refluxed for 4 hr, and the resultant precipitate of II, 2.0 g (60%), was filtered off, and washed, first with hot water, then with EtOH. The substance was recrystallized from formic acid. II formed greenish-yellow crystals, not melting up to 360° C, insoluble in pyridine, sulfuric acid, and alkalies; R_f 0.73 in the system isobutanol-pyridine-water-AcOH (33:33:33:1). Absorption spectrum (in 0.1 N NaOH): λ_{max} mμ (ε · 10^{-4}): 225 (3.15), 271 (4.15), 340 (0.54), 4.35 (0.63). Found: C 36.59, 36.44; H 1.95, 2.25; Cl 10.63, 10.78; S 9.33, 9.62%. Calculated for $C_{10}H_6ClN_5O_4$: C 36.59; H 1.84; Cl 10.82; S 9.78%.

2-Amino-6-chloroquinoxaline (III). 1.0 g (0.003 mole) II and 7 ml 85% H_2SO_4 were heated together for 1 hr at 205–210° C, and after cooling the reaction products were poured on to crushed ice. The brownish-green precipitate

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(0.5 g), consisting mainly of unreacted 6-chloro-7-sulfamidoalloxazine, was separated off, and the filtrate adjusted to pH 7-8 with 20% NaOH, after which III (0.1 g, 18%), was extracted with ether, then purified by distillation under reduced pressure, bp 150-160° C (10 mm). Lemon-yellow crystals, mp 216-217° C, the literature [9] gives mp 215-217° C. Mixed mp with authentic 2-amino-7-chloroquinoxaline (mp 196-197° C), 189-191° C. Found: C 53.47; H 3.75; Cl 19.77%. Calculated for $C_8H_6ClN_3$: C 53.50; H 3.37; Cl 19.74%.

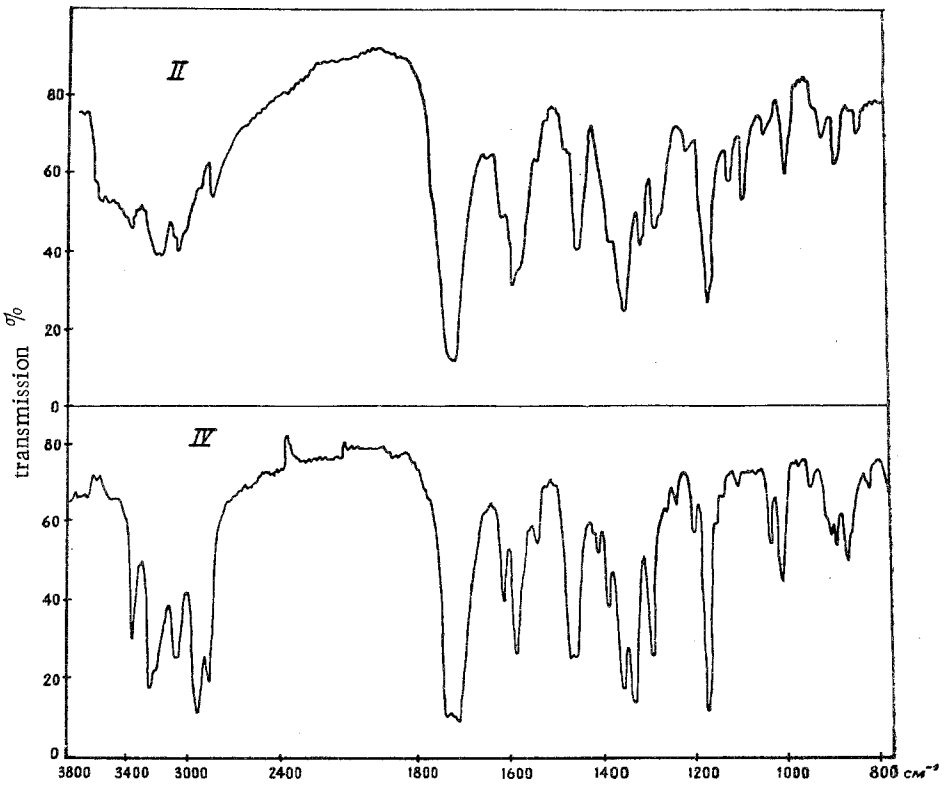

Fig. 2. IR spectra (in vaseline): II) 6-Chloro-7-sulfamidoalloxazine; IV) 6-chloro-7-sulfamidoalloxazine N-oxide (UR-10 spectrometer with LiF and NaCl prisms).

6-Chloro-7-sulfamidoalloxazine N-oxide (IV). A solution of 0.66 g (0.002 mole) II in 8 ml H_2SO_4 (d 1.84) was added dropwise to an aqueous solution of 4.6 g ammonium persulfate in 8 ml water, then left for 4 hr at 45-50° C. In the course of the reaction a yellow precipitate separated, (0.21 g) containing about 75% IV, and unreacted II as impurity, (determined by the decrease in molecular extinction coefficient in the UV region at λ_{max} 291 mμ). The precipitate was filtered off, the acid filtrate poured into 4 times its volume of water. The orange crystals of IV (0.31 g) which separated on standing were filtered off, carefully washed with water until neutral, then with EtOH and Me_2CO. Total yield 68%, compound did not melt up to 360° C; R_f 0.55 (yellowish-green fluorescence) in the system iso-BuOH-pyridine-water-AcOH (33:33:33:1). Absorption spectrum (in 0.1 N NaOH): λ_{max} mμ ($\varepsilon \cdot 10^{-4}$): 291 (5.5), 460 (0.77). Found: C 34.88, 34.83; H 1.91, 2.10; N 20.19, 20.10%. Calculated for $C_{10}H_6ClN_5O_5S$: C 34.94; H 1.75; N 20.37%.

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All-Union Vitamin Scientific Research Institute, Moscow