SYNTHESIS OF SOME 7-SUBSTITUTED THIAZOLINO[3,2-a] BENZIMIDAZOLES

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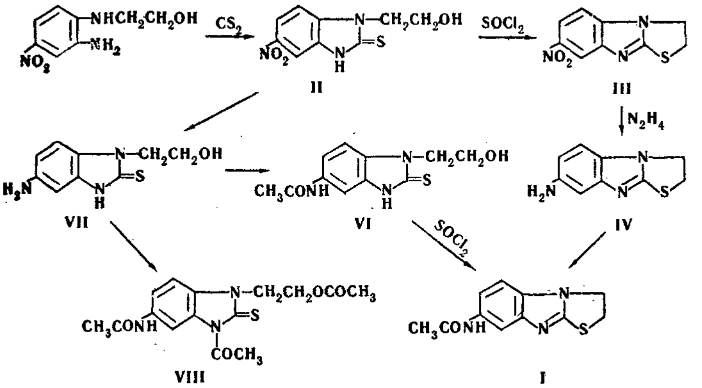
The 7-amino (IV) and 7-acetamido (I) derivatives of thiazolino[3,2-a]benzimidazole were synthesized. The IR spectra of I, its deutero derivative, and a number of intermediates were studied.

Thiazolino[3,2-a]benzimidazole derivatives are compounds to which little study has been devoted, whereas they may be of definite interest, since substances with considerable antispasmodic activity [1] were recently detected among them.

The syntheses of 7-amino- and 7-acetamidothiazolino[3,2-a]benzimidazoles and several of their derivatives are described in this paper, and the IR spectra of the synthesized compounds are also studied. The synthesis of 7-acetamidothiazolino[3,2-a]benzimidazole (I) was accomplished starting from N-(β-hydroxyethyl)-2-amino-4-nitroaniline [3] via the following scheme:



The condensation of N-(β-hydroxyethyl)-2-amino-4-nitroaniline with carbon disulfide or potassium ethylxanthate converted it to 1-(β-hydroxyethyl)-5-nitrobenzimidazole-2-thione (II), from which III was obtained by treatment with excess thionyl chloride. The reduction of III with hydrazine hydrate in the presence of a Raney nickel catalyst gave amine IV, the acetylation of which produced the 7-acetamido derivative (I).

The structures of the substances were confirmed by spectral data. When it was difficult to identify them, the assignment of the bands in the IR spectra of the compounds was made by means of a study of the deuterated derivatives.

The IR spectrum of III contains two bands that pertain to the asymmetrical and symmetrical vibrations of the NO_2 group. There are bands at 3245 and 3198 cm^{-1} in the spectrum of I that are affiliated with the stretching vibrations of the NH group participating in a hydrogen bond. After deuteration, the band of

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the ND group appeared at 2300 cm^{-1}, while the bands of the CH bonds, which are hidden in the spectrum of undeuterated I, are displayed distinctly at 2970 and 2895 cm^{-1}. There are a number of bands corresponding to the vibrations of a secondary amide group in the multiple bond absorption region: 1698 cm^{-1} (ν_{CO} of amide I) and 1563 cm^{-1} (amide II); the band at 1258 cm^{-1} is probably amide band III. After deuteration, ν_{CO} (amide I) was shifted to 1685 cm^{-1}, amide band II vanished, and a new band appeared at 1407 cm^{-1}, which may serve as a confirmation of the fact that δ_{NH} makes a large contribution to the vibration at 1563 cm^{-1}.

A number of bands at 1595-1635 and 1438-1480 cm^{-1} are observed in the spectra of I, III, and thiazolino[3,2-a]benzimidazole (V) [2] and are apparently characteristic for this sort of three-ring system.

7-Acetamidothiazolino[3,2-a]benzimidazole (I) was also obtained by another method – by ring closure of 1-(β-hydroxyethyl)-5-acetamidobenzimidazole-2-thione (VI) on treatment with thionyl chloride. The reduction of II by iron in the presence of catalytic amounts of hydrochloric acid gives 1-(β-hydroxyethyl)-5-aminobenzimidazole-2-thione (VII).

The selective acylation of only one amino group to give VI was carried out in aqueous acetic acid in the presence of sodium acetate. The hydrochloride of I was obtained smoothly by treatment of VI in dimethylformamide with thionyl chloride. Base I and its hydrochloride, obtained by the two routes, had identical melting points and IR spectra. A substance, to which the structure of the triacetyl derivative (VIII) was assigned on the basis of the results of elementary analysis and the IR spectra, was isolated from the reaction of VII with acetic anhydride.

The IR spectrum of VIII contains a band at 3344 cm^{-1} (ν_{NH}), which was shifted to 2300 cm^{-1} (ν_{ND}) after deuteration. The band at 1727 cm^{-1} may be simultaneously related to ν_{CO} of an ester group and ν_{CO} of a tertiary amide group attached to N_1. This assignment of ν_{CO} of a tertiary amide group was made on the basis of the fact that a similar band was observed at 1715 cm^{-1} in the spectrum of 1-acetyl-2-(β-chloroethylmercapto)benzimidazole. The high absorption of the amide group CO in the latter compound is evidence that this group is more likely a ketone CO than an amide CO, since the electron pair of nitrogen that enters into the formation of the aromatic benzimidazole system interacts weakly with the carbonyl group. The ν_{CO} band of a secondary amide group (amide band I) appears at 1684 cm^{-1}, while amide band II is found at 1558 cm^{-1}. On deuteration, the ν_{CO} bands of the ester and tertiary amide groups are split (1743 and 1733 cm^{-1}); the ν_{CO} band of the secondary amide group (amide II) was shifted to 1668 cm^{-1}, while the band at 1558 cm^{-1} vanished, and a new band appeared at 1478 cm^{-1}. As in the previously examined compound (I), δ_{NH} makes a large contribution to the vibration at this frequency.

In the spectrum of VI, the vibrations of the NH and OH groups that participate in hydrogen bonds appear as a broad, intense absorption at 3100-3300 cm^{-1} and are shifted after deuteration to 2450 and 2310 cm^{-1} (ν_{OD} and ν_{ND}). As compared with the amide band in the spectra of VIII and I, the amide band of the secondary amide group was shifted to 1665 cm^{-1} (ν_{CO}, amide I), while the amide II band was raised to 1568 cm^{-1}. After deuteration, the bands at 1665 and 1626 cm^{-1} merged into one band at 1651 cm^{-1}, the δ_{NH} absorption band (amide II) vanished, and two new bands appeared at 1508 and 1405 cm^{-1}. The bands at 1626, 1525, and 1478 cm^{-1} in the spectrum of VI and at 1635 and 1506 cm^{-1} in the spectrum of VIII apparently characterize the vibrations of the benzimidazolethione system as a whole.

EXPERIMENTAL

N-(β-Hydroxyethyl)-2,4-dinitroaniline [3], N-(β-hydroxyethyl)-2-amino-4-nitroaniline [3], and thiazolino[3,2-a]benzimidazole [2] were obtained by literature methods. 1-Acetyl-2-(β-chloroethylmercapto)-benzimidazole was obtained from 2-(β-chloroethylmercapto)benzimidazole and acetic anhydride in pyridine and had mp 106-107°C (from aqueous alcohol). Found: S 13.0; N 11.0; Cl 13.9%. $C_{11}H_{11}ClN_2OS$. Calculated: S 12.6; N 11.0; Cl 13.9%.

1-(β-Hydroxyethyl)-5-nitrobenzimidazole-2-thione (II). A 1 g (0.005 mole) sample of N-(β-hydroxyethyl)-4-nitro-o-phenylenediamine dissolved in a solution of 0.28 g of potassium hydroxide in 20 ml of alcohol was stirred with 1.15 g (0.015 mole) of carbon disulfide, and the mixture was refluxed for 10 h. The precipitated potassium salt of the mercaptan was removed by filtration and dissolved in water. The aqueous solution was acidified with dilute hydrochloric acid to give 1.1 g (92%) of a product with mp 230-231° (from alcohol). Refluxing a mixture of 1.67 g of the diamine and 2 g of potassium ethylxanthate in 40 ml of aqueous alcohol (1 : 3) also gave II in 73% yield. Found: N 17.8; S 13.2%. $C_9H_9N_3O_3S$. Calculated: N 17.6; S 13.4%.

7-Nitrothiazolino[3,2-a]benzimidazole (III). A 1 g (0.004 mole) sample of II was added in small portions to 4 ml of thionyl chloride, and the mixture was refluxed for 10 min. The excess thionyl chloride was removed by vacuum distillation, and the residue was treated with 10% sodium bicarbonate solution. The precipitate was removed by filtration and washed with water to give 0.9 g (90%) of a product with mp 229-230° (from dimethylformamide). Found: N 18.7; S 14.5%. $C_9H_7N_3O_2S$. Calculated: N 19.0; S 14.5%.

7-Aminothiazolino[3,2-a]benzimidazole (IV). A total of 25 ml of 80% hydrazine hydrate was added dropwise at 50-60° to a suspension of 8.8 g (0.04 mole) of 7-nitrothiazolino[3,2-a]benzimidazole (III) in 200 ml of alcohol and 20 g of Raney nickel catalyst. After 15 ml of hydrazine hydrate had been added to the reaction mixture, another 10 g of catalyst was added. The remaining hydrazine hydrate was added dropwise, and the mixture was refluxed for 30 min and filtered. The solid was washed with alcohol and hot water. The filtrate and wash waters were concentrated to a small volume, and the precipitate was removed by filtration to give 4.3 g (57%) of a product with mp 229-230° (from water). Found: C 56.4; H 4.6; N 22.0; S 16.7%. $C_9H_9N_3S$. Calculated: C 56.5; H 4.7; N 29.0; S 16.8%.

1-(β-Hydroxyethyl)-5-aminobenzimidazole-2-thione (VII). A total of 5.6 g of reduced iron and 4 ml of 3% hydrochloric acid were added simultaneously in small portions to a refluxing suspension of 4.5 g (0.018 mole) of 1-(β-hydroxyethyl)-5-nitrobenzimidazole-2-thione (II) in 80 ml of 50% alcohol. The mixture was refluxed for 2-3 h and filtered, and the filtrate was evaporated to give 3.7 g (95%) of the amine with mp 164-165° (recrystallized twice from isopropyl alcohol). Found: N 20.3; S 15.4%. $C_9H_{11}N_3OS$. Calculated: N 20.1; S 15.3%. The hydrochloride had mp 219-220° (from alcohol). Found: Cl 14.7%. $C_9H_{11}N_3OS \cdot HCl$. Calculated: Cl 14.5%.

1-(β-Hydroxyethyl)-5-acetamidobenzimidazole-2-thione (VI). A 7 ml sample of acetic anhydride and a solution of 7.7 g of sodium acetate in 30 ml of water were added dropwise simultaneously to a solution of 7 g of 1-(β-hydroxyethyl)-5-aminobenzimidazole-2-thione hydrochloride (VII) (0.03 mole) in 56 ml of glacial acetic acid and 100 ml of water. The mixture was stirred for 2 h, and the resulting precipitate was removed by filtration, washed with water, and dried to give 5 g (70%) of a product with mp 278-279° (dec., from dimethylformamide). Found: N 16.7; S 12.8%. $C_{11}H_{13}N_3O_2S$. Calculated: N 16.8; S 12.8%.

1-(β-Acetoxyethyl)-3-acetyl-5-acetamidobenzimidazole-2-thione (VIII). A 0.2 g sample of VII in 5 ml of acetic anhydride was refluxed for 30 min. The precipitate that formed on cooling was removed by filtration and washed with water to give 0.1 g (83%) of VIII with mp 179-180° (from absolute alcohol). Found: N 12.7; S 9.3%. $C_{15}H_{17}N_3O_4S$. Calculated: N 12.6; S 9.6%.

7-Acetamidothiazolino[3,2-a]benzimidazole (I). A) A 1.2 g (0.011 mole) sample of thionyl chloride was added dropwise to a cooled (to 10-15°) solution of 2.5 g (0.01 mole) of 1-(β-hydroxyethyl)-5-acetamidobenzimidazole-2-thione (VI) in 45 ml of DMF. The resulting precipitate was removed by filtration and washed with ether to give 2.2 g (81.5%) of the hydrochloride of I with mp >300° (from aqueous alcohol). Found: N 14.4; S 11.4; Cl 12.5%. $C_{11}H_{11}N_3OS \cdot HCl \cdot H_2O$. Calculated: N 14.4; S 11.1; Cl 12.4%.

Treatment of an aqueous solution of the hydrochloride with solid sodium bicarbonate gave base I with mp 243-245° (from water, dried at 100° for 3-5 h). Found: N 18.4; S 13.7%. $C_{11}H_{11}N_3OS$. Calculated: N 18.0; S 13.7%.

B) A 3 g sample of 7-aminothiazolino[3,2-a]benzimidazole (IV) in 25 ml of acetic anhydride was refluxed for 1.5 h, and the mixture was poured into water. The aqueous mixture was made alkaline with concentrated ammonium hydroxide, and the resulting precipitate was removed by filtration and dried to give 3.5 g (~100%) of I with mp 243-245° (from water). A sample of this product did not depress the melting point of the sample obtained by method A.

The IR spectra of mineral oil suspensions or KBr pellets of the compounds were recorded with a UR-10 spectrometer. Deuterated samples were obtained by refluxing a solution or suspension of the compounds in D_2O for 30 min and filtering off the precipitate that formed on cooling.

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