CERTAIN DERIVATIVES OF 4-OXO-1,2,4-TRIAZINO(4,5-a)BENZIMIDAZOLE

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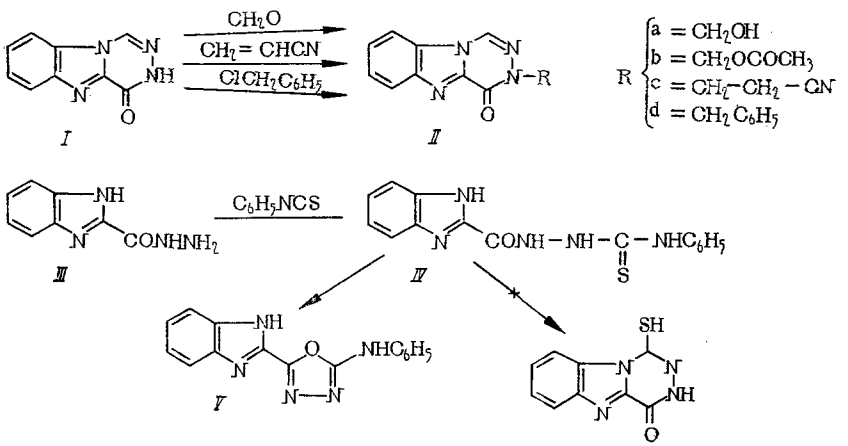
It is known that some 1,2-disubstituted derivatives of benzimidazole have an appreciable pharmacological activity [1, 2].

We synthesized the first representative of a new heterocyclic system, 4-oxo-1,2,4-triazino(4,5-a)-benzimidazole (I) [3]. This compound is a 1,2-disubstituted benzimidazole with a hydrazide grouping. It is well known that this grouping favors biological activity [4]. This paper describes hydroxymethylation, cyanomethylation, and benzylation of compound (I)

It was found that these reactions take place at the carbon atom in the 3-position. When compound (I) was heated in an alcoholic solution with formalin, the hydroxymethyl derivative (IIa) was obtained, and this was converted into the acetoxymethyl derivative (IIb) by boiling with acetic anhydride. The corresponding 3-cyanoethyl derivative (IIc) was obtained by boiling (I) with acrylonitrile in the presence of Triton W.



The benzylation reaction was carried out by heating (I) with benzyl chloride in dimethylsulfoxide at 65-75° in the presence of a catalytic amount of potassium iodide. The yield of the benzyl derivative (IId) formed was 57%.

The structure of the above compounds was confirmed by elementary analysis and from UV and IR spectra, and PMR spectra.* The absorption bands characteristic of the valence vibrations of the NH group present in the spectrum of the starting compound (I) were missing in the IR spectra of compounds (IIa-IId). The signals of H_1 proton (singlet at 9.3 ppm) and of the benzene ring protons (multiplet at 8.43-8.16 ppm) present in the PMR spectrum of the starting compound (I) and also the signals of protons of functional groups introduced into these compounds, were well marked in the PMR spectra of compounds (IIa-IIc). The signals of the hydroxymethyl group protons in compound (IIa) appear as a singlet at 3.82 ppm (the spectrum was obtained in a trifluoroacetic acid solution), and the signals of the cyanoethyl group protons, as two triplets: at 3.23 and 4.75 ppm (Fig. 1).

As expected, the UV spectrum of compound (IIa) coincides almost completely with the expectrum of the starting compound (I) (Fig. 2).

*The spectral analyses were carried out in the physical chemistry laboratory under the direction of Yu. N. Sheinker.

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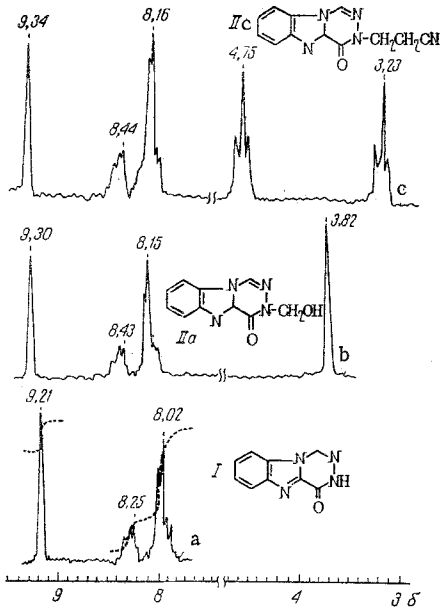

Fig. 1. PMR spectra. a) 4-Oxo-1,2,4-triazino(4,5-a)benzimidazole (I); b) 3-hydroxymethyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IIa); c) 3-cyanoethyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IIc).

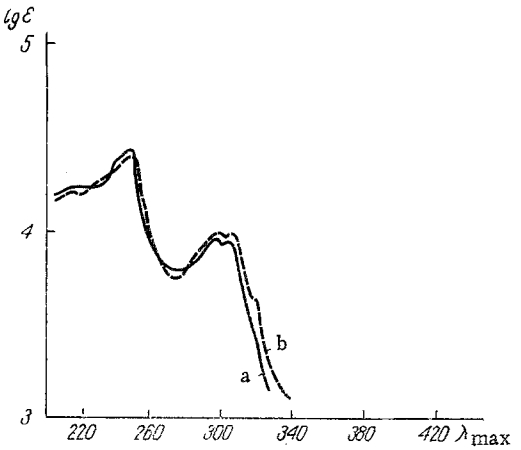

Fig. 2. UV spectra. a) 4-Oxo-1,2,4-triazino(4,5-a)benzimidazole (I); b) 3-hydroxymethyl-4-oxo-1,2,4-triazino-(4,5-a)benzimidazole (IIa).

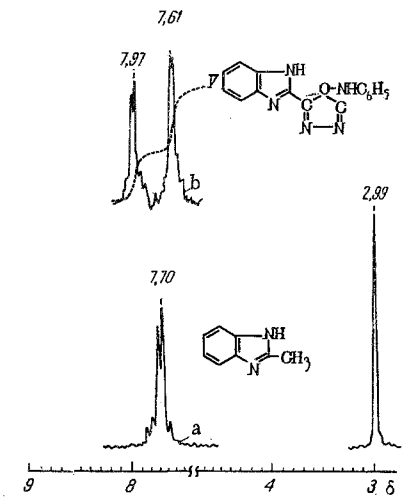

Fig. 3. PMR spectra. a) 2-Methylbenzimidazole; b) 2-(benzimidazolyl-2)-5-phenylamino-1,3,4-oxadiazole (V).

It is known that arylthiosemicarbazides undergo cyclizato form 1-mercapto derivatives of heterocyclic systems, and aniline separates [5, 6], or 2,5-disubstituted 1,3,4-oxadiazoles are formed and hydrogen sulfide is evolved [6]. It was interesting to carry out the cyclization of 1-(benzimidazolyl-2)-4-phenyl-thiosemicarbazide (IV). This compound was obtained by condensing benzimidazole-2-carboxylic acid hydrazide (III) with phenylisothiocyanate.

Hydrogen sulfide was evolved and 2-(benzimidazolyl-2)-5-phenylamino-1,3,4-oxadiazole (V) was formed when (IV) was heated in tetralin. The structure of compound (V) was confirmed by elementary analysis and from its IR and PMR spectra.

The absorption band at 1680 cm^{-1} characteristic of CO group valence vibrations is missing in the IR spectrum. In the PMR spectrum there are multiplets with peaks at 7.61 and 7.98 ppm, and a relative intensity of 5 : 4 due to the simultaneous presence of protons of the phenyl group bound through the nitrogen atom to the oxadiazole ring, and those of the phenyl group of the benzimidazole part of the molecule. The symmetrical nature of the multiplet of benzene ring protons is characteristic of benzimidazoles unsubstituted at the nitrogen atom (Fig. 3).

EXPERIMENTAL

The IR spectra of the compounds were obtained with a UR-10 spectrophotometer. The samples were prepared as a paste on a mineral oil base. The UV absorption spectra were obtained on a EPS-3 spectrophotometer, with 96% ethanol as solvent. For PMR spectra a JNM-4H-100 spectrometer was used, with a trifluoroacetic acid solution. The chemical displacements were measured with reference to the signal of protons in tetramethylsilane.

3-Hydroxymethyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IIa). A 4.3-ml portion of formalin was added to a solution of 0.372 g (0.002 mole) of compound (I) in 16 ml of alcohol. The mixture was boiled for 1 h, treated with 4.3 ml of formalin, and boiled for another 2.5 h. The solution was concentrated by evaporation, and the precipitate was filtered and washed with alcohol. The yield of (IIa) was 0.38 g (87%), mp 351-352° (decomp., from a mixture of DMF–C_6H_6, 1 : 1). IR spectrum: $\nu_{C=O}$ 1680 cm^{-1}; UV spectrum (in alcohol): λ_{max} 247, 295, 395 mμ, log ε 4.43, 3.99, 3.99, Found, %: C 55.8; H 3.79; N 26.01. $C_{10}H_8N_4O_2$. Calculated, %: C 55.59; H 3.73; N 25.9.

3-Acetoxymethyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IIb). A mixture of 0.19 g (0.00087 mole) of (IIa) in 3 ml of acetic anhydride was boiled for 3 h. It was then cooled, and the precipitate was filtered and washed with water, alcohol, and ether. The yield of (IIb) was 0.19 g (84%), mp 244-246° (decomp., from alcohol). Found,%: C 56.03; H 3.74; N 22.12. $C_{12}H_{10}N_4O_3$. Calculated, %: C 55.81; H 3.90; N 21.69.

3-Cyanoethyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IIc). A solution of 0.28 g (0.0015 mole) of (I) in 12.5 ml (0.19 mole) of acrylonitrile was treated with 0.05 ml of a 35% methanolic solution of Triton W, and then boiled for 3 h. The precipitate was filtered, and washed with alcohol. The yield of (IIc) was 0.25 g (70%), mp 277-278° (decomp., from DMF). IR spectrum: $\nu_{C=O}$ 1680 cm^{-1}. Found, %: C 60.65; H 4.08; N 29.5. $C_{12}H_9N_5O$. Calculated, %: C 60.24; H 3.79; N 29.27.

3-Benzyl-4-oxo-1,2,4-triazino(4,5-a)benzimidazole (IId). A 0.05-g portion of potassium iodide, 0.378 g (0.003 mole) of benzyl chloride, and an alcoholic solution of sodium ethoxide (0.07 g of Na in 2 ml of absolute alcohol) were added to a solution of 0.28 g (0.0015 mole) of (I) in 10 ml of dimethylsulfoxide. The mixture was then boiled at 67-75° for 7 h. The precipitate was filtered and washed with water. The yield of (IId) was 0.24 g (57%), mp 289-290° (decomp., from DMF). Found, %: C 69.14; H 4.47; N 20.44. $C_{16}H_{12}N_4O$. Calculated, %: C 69.55; H 4.38; N 20.28.

1-(Benzimidazolyl-2)-4-phenyl-thiosemicarbazide (IV). A mixture of 1 g (0.0056 mole) of compound (III), 1.6 g (0.012 mole) of phenylisothiocyanate, and 5 ml of dry benzene was boiled for 7 h. The precipitate was filtered, and washed with dry benzene. The yield of (IV) was 1.5 g, mp 195-196° (decomp., from alcohol). The compound is sparingly soluble in alcohols, acetone, chloroform, and ether. Found, %: C 57.78; H 4.11; N 22.26. $C_{15}H_{13}N_5OS$. Calculated, %: C 57.85; H 4.21; N 22.49.

2-(Benzimidazolyl-2)-5-phenylamino-1,3,4-oxadiazole (V). A solution of 1 g (0.0032 mole) of (IV) in 6 ml of tetralin was heated at 150-160° until hydrogen sulfide was no longer evolved (5-6 h). The precipitate was filtered, and washed with ether. The yield of (V) was 0.3 g (33%), mp 309-310° (decomp., from alcohol). Found, %: C 64.82; H 4.20; N 25.40. $C_{15}H_{11}N_5O$. Calculated, %: C 64.97; H 3.99; N 25.25.

The compounds (IIa-IId) were obtained as crystalline solids, sparingly soluble in the usual organic solvents.

CONCLUSIONS

1. 3-Substituted 4-oxo-1,2,4-triazino(4,5-a)benzimidazoles (IIa-IId) were obtained by hydroxymethylation, cyanoethylation, and benzylation reactions.

2. 2-(Benzimidazolyl-2)-4-phenyl-1-thiosemicarbazide (IV) was obtained by the reaction of benzimidazole-2-carboxylic acid hydrazide with phenylisothiocyanate. When (IV) is heated in tetralin, hydrogen sulfide is evolved, and 2-(benzimidazolyl-2)-5-phenylamino-1,3,4-oxadiazole (V) is formed.

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