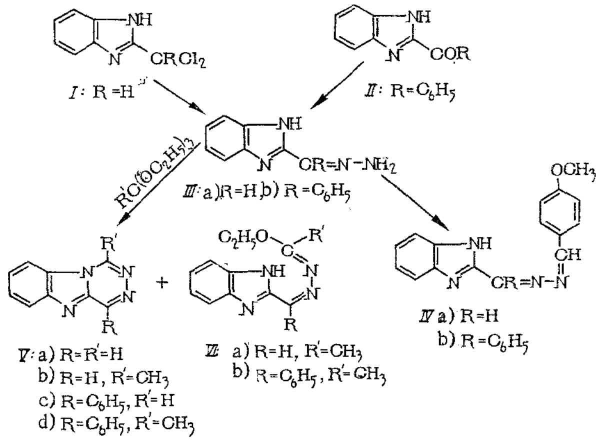
# SYNTHESIS AND PROPERTIES OF 1,2,4-TRIAZINO-[4,5-a]BENZIMIDAZOLE AND ITS ALKYL AND ARYL DERIVATIVES

Z. A. Pankina and M. N. Shchukina

UDC 615.31:547.785.5].012.1

Unsubstituted 1,2,4-triazino[4,5-a]benzimidazole and its 1-methyl-, 4-phenyl-, and 1-methyl-4-phenyl derivatives (Va-d) were prepared in this work, which is a continuation of our research [1-3] in the quest for biologically active substances. The synthesis of these compounds is of interest since they can be considered as compounds which have a hydrazine group in their structure. As is known, many physiologically active substances, for example hypotension preparations, monoaminoxidase inhibitors (prazid [4], nialamide [5], etc.), exist among hydrazine derivatives.

In order to obtain Va-d, a method was used based on the cyclization of 2- acyl(aroyl)benzimidazole hydrazones by reacting the ethyl esters of ortho acids with them. The path of the synthesis is shown in the following scheme.



The hydrazone of benzimidazole-2-aldehyde (IIIa) was obtained by boiling dichloromethylbenzimidazole (I) hydrochloride with hydrazine hydrate in ethanol. The hydrazone of II (IIIb) was synthesized under similar conditions from 2-benzoylbenzimidazole (II) and hydrazine hydrate. Both hydrazones (IIIa, b) yield the corresponding p-methoxybenzylidene derivatives (IVa, b) with anisaldehyde. There are absorption bands characteristic for the NH and $NH_2$ groups and also for the $C=N$ group in the IR spectra of compounds IIIa and IIIb. A singlet from the proton in the $CH=N$ group ($\delta = 7.73$ ppm) and a multiplet from the protons in the benzene ring ($\delta = 7.19$-$7.43$ ppm) occur in the PMR spectrum of IIIa run in d-alcohol.

Hydrazones IIIa, b were cyclized by heating them in excess ethyl orthoformate or orthoacetate. The reaction was accompanied by the splitting off of ethanol, and Va-d were obtained. When the reaction was carried out with the ester of ortho acetic acid, the ethoxyethylidene derivatives of the respective hydrazones (VIa and VIb) were successfully isolated from the reaction mixture. The structure of the compounds obtained was confirmed by data from elemental analysis, the IR and UV spectra, and also from the PMR* spectra

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*The IR, UV, and PMR spectra were run in the physicochemical research laboratory of the S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute.

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S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 10, pp. 8-12, October, 1972. Original article submitted November 30, 1970.

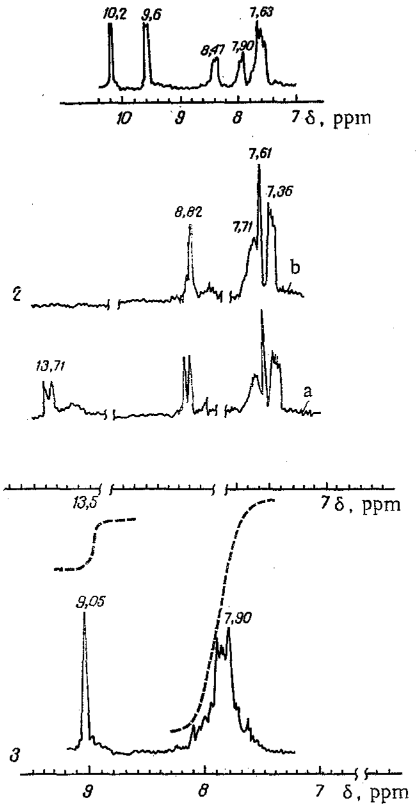


Fig. 1

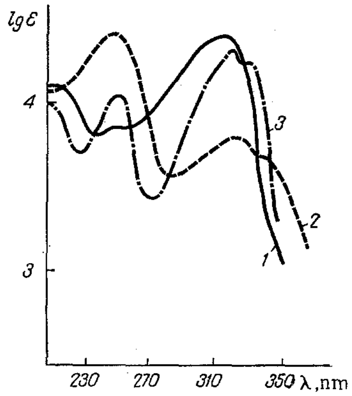
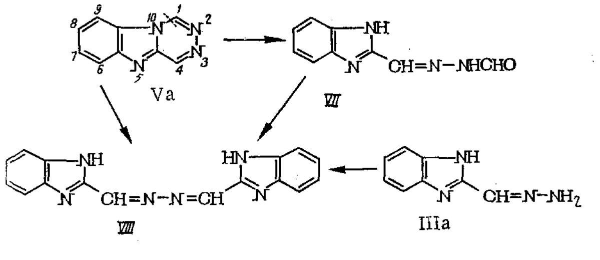


Fig. 2

Fig. 1. PMR spectra. 1) 1,2,4-Triazino[4,5-a]benzimidazole (Va in dimethylsulfoxide with hexamethyldisiloxane); 2) N-formylhydrazone of benzimidazole-2-aldehyde (VII) in $d_6$-dimethylsulfoxide (with hexamethyldisiloxane (a) and in $d_6$-dimethylsulfoxide to which deuteriomethanol was added (b); 3) azine of benzimidazole-2-aldehyde (VIII) in trifluoroacetic acid (with tetramethylsilane).

Fig. 2. UV spectra. 1) Hydrazone of benzimidazole-2-aldehyde (IIIa); 2) 1,2,4-triazino-[4,5-a]benzimidazole (Va); 3) N-formylhydrazone of benzimidazole-2-aldehyde (VII). The solvent is ethanol.

(Figs. 1 and 2). There are no absorption bands characteristic of the NH and $NH_2$ groups, which were observed in the IR spectra of the starting hydrazones IIIa, b, in the IR spectra of compounds Va-d. Signals from the protons in the benzene ring (multiplet, $\delta = 7.61$-$8.47$ ppm) are noted in the PMR spectrum of Va, as are also two signals in the form of doublets with $\delta = 10.2$ and 9.6 ppm which correspond to the protons at $C_1$ and $C_4$ with a spin–spin coupling constant $J = 2Hz$. The doublet nature of the signals is connected with the interaction of these protons among themselves, which was confirmed by the magnetic double resonance method. There is no signal from a proton at $C_4$ ($\delta = 9.6$ ppm) in the PMR spectrum of Vc, but there are signals from the proton at $C_1$ ($\delta = 10.2$ ppm) and also a complex multiplet which is attributed to the protons of the benzene ring and phenyl group. The signal from the proton with $\delta = 10.2$ ppm disappears in compound Vd and a signal from the protons of the methyl group appears at $\delta = 3.15$ ppm.



It was established from a study of the chemical properties of Va that this compound is not stable: when it was treated with a 10% aqueous sodium hydroxide solution at room temperature, the triazine ring was opened at the $C_1 = N_{10}$ bond which leads to the formation of the N-formylhydrazone of benzimidazole-2-aldehyde (VII).

Absorption bands characteristic for the NH and CO groups appear in the IR spectrum of VII at 3235 and 1685 $cm^{-1}$ respectively. The UV spectrum of VII differs from the UV spectrum of Va. Doublets at $\delta =$ 8.88 ppm (1H) and 13.71 ppm (1H) with a spin–spin coupling constant $J = 9.8$-10 Hz are observed in the PMR spectrum ($d_6$-dimethylsulfoxide) of compound VII. When deuteriomethanol is added to the solution investigated, the signal at $\delta = 8.88$ ppm is converted into a singlet and the signal at $\delta = 13.71$ ppm disappears. These data indicate that the NH–CHO group is present in compound VII and that its protons interact with each other.

The azine of benzimidazole-2-aldehyde (VIII) was obtained by reacting compound Va with 10% hydrochloric acid followed by treatment with an aqueous sodium bicarbonate solution. The structure of the synthesized compound was substantiated by elemental analysis and its PMR spectrum. Compound VIII was also obtained by reacting compounds IIIa or VII with 10% hydrochloric acid.

A study of the effect of 4-oxo- and 4-phenyl-1,2,4-triazino[4,5-a]benzimidazole (Vc) [3] on the behavior and condition of animal life, on sensitivity to pain, antispasmodic action, and their interaction with soporific agents showed that these preparation had little pharmacological activity.

## EXPERIMENTAL

The IR spectra of the substances were run on a UR-10 spectrophotometer. The samples were prepared as mineral oil mulls. The UV spectra were run on an EPS-3 spectrophotometer. The solvent was ethyl alcohol. The PMR spectra were run on a JNM-4H-100 spectrophotometer at an operating frequency of 100 MHz. The chemical shifts were measured on the $\delta$ scale relative to the signal of the protons in tetramethylsilane or hexamethyldisiloxane.

2-Dichloromethylbenzimidazole Hydrochloride (I). This compound was obtained by the method in [6], mp 165-168°C. According to the literature [6], the mp is 169-171°C.

2-Benzoylbenzimidazole (II). This compound was obtained by oxidizing 2-benzylbenzimidazole with chromium trioxide in acetic acid [7], mp 214-216°C. According to the literature [7], the mp is 210-212°C.

Hydrazone of Benzimidazole-2-aldehyde (IIIa). To a mixture of 25 ml of hydrazine hydrate and 50 ml of ethanol was added in portions 22 g of I, the mixture was boiled for 5 h, it was concentrated in vacuo to half its volume, and the remainder was treated with water. A total of 12 g (80%) of IIIa was obtained, mp 146-147°C (decomp., from dichloroethane), $R_f$ 0.5 (aluminum oxide, chloroform–hexane–methanol 10 : 5 : 2; detected with iodine vapors).

The PMR spectrum (in ethanol), $\delta$, ppm: 7.73 (CN=N, singlet), 7.19-7.43 (protons in the benzene ring, multiplet). IR spectrum: $\nu_{NH, NH_2}$ 3208, 3308, 3384 $cm^{-1}$; $\nu_{C=N}$ 1630 $cm^{-1}$. UV spectrum: $\lambda_{max}$ 256, 311 nm, log $\varepsilon$ 3.83, 4.39. Found, %: C 60.56; H 5.3; N 34.76. $C_8H_8N_4$. Calculated %: C 59.98; H 5.03; N 34.98.

Hydrazone of 2-Benzoylbenzimidazole (IIIb). Compound IIIb was similarly obtained from 2.22 g of II and 9 ml of hydrazine hydrate in 10 ml of ethanol. The yield was 2.24 g (95%), lemon-colored crystalline substance, mp 144°C (decomp., from water).

IR spectrum: $\nu_{NH, NH_2}$ 3312, 3432, 3452 $cm^{-1}$. UV spectrum: $\lambda_{max}$ 275, 315 nm, log $\varepsilon$ 4.09, 4.23. Found, %: C 71.42; H 5.21; N 24.02. $C_{14}H_{12}N_4$. Calculated, %: C 71.16; H 5.12; N 23.71.

N-(Benzimidazolylmethine)-N'-(p-methoxybenzylidene)hydrazine (IVa). To a solution of 0.1 g of IIIa in 3 ml of anhydrous ethanol was added 0.1 g of anisaldehyde. The precipitate (within 15 min) was filtered, washed with ethanol, and dried. A total of 0.13 g (76%) of IVa was obtained, pale yellow crystals, mp 217-218°C (from a mixture of ethanol–water, 1 : 1). Found, %: C 68.99; H 5.13; N 19.96. $C_{16}H_{14}N_4O$. Calculated, %: C 69.04; H 5.07; N 20.13.

N-(Benzimidazolylphenylmethine)-N'-(p-methoxybenzylidene)hydrazine (IVb). To a solution of 0.1 g of IIIb in 3 ml of anhydrous ethanol was added 0.1 g of anisaldehyde and 4-5 drops of glacial acetic acid. The solution was allowed to stand for 24 h at 20°C, the precipitate was filtered off, washed with ether, and dried. A total of 0.12 g (80%) of IVb was obtained, mp 160-161°C (from 50% aqueous ethanol), crystalline pale yellow substance, insoluble in water. Found, %: C 74.13; H 5.28; N 15.94. $C_{22}H_{18}N_4O$. Calculated %: C 74.55; H 5.11; N 15.85.

N-Formylhydrazone of Benzimidazole-2-aldehyde (VII). An alkaline solution of Va prepared from 0.5 g of Va and 2 ml of 10% sodium hydroxide was acidified with acetic acid. The precipitate obtained was filtered off, washed with water, and dried over phosphorus pentoxide. A total of 0.55 g of VII was obtained (quantitative yield), colorless substance, mp 228-230°C (decomp., from ethanol), insoluble in water, difficultly soluble in ethanol and other organic solvents, highly soluble in dilute hydrochloric acid and a solution of sodium hydroxide. IR spectrum: $\nu_{NH}$ 3235 $cm^{-1}$, $\nu_{CO}$ 1685 $cm^{-1}$. UV spectrum: $\lambda_{max}$ 253, 316, 328 nm; log ε 4.09, 4.37, 4.29. PMR spectrum (in $d_6$-dimethylsulfoxide), δ, ppm: 13.71 (NH, doublet), 8.88 (CHO, doublet), 7.67 (CH=N, singlet), 7.43-7.80 (aromatic protons in the benzene ring, multiplet). Found, %: C 57.15; H 4.24; N 29.40. $C_9H_8N_4O$. Calculated, %: C 57.43; H 4.28; N 29.77.

Azine of Benzimidazole-2-aldehyde (VIII). One gram of IIIa was dissolved in 5 ml of 10% hydrochloric acid at 20°C. The oil that precipitated out (within 30 min) was recovered and triturated with a saturated sodium bicarbonate solution. A total of 0.65 g (76%) of VIII was obtained, the substance had a bright yellow color and was in the form of long fine needles, mp 277-278°C (decomp., from ethanol), highly soluble in 10% sodium hydroxide, insoluble in the majority of organic solvents and in water, $R_f$ 0.7 (silica gel, chloroform isopropyl alcohol, 10:1, detection by absorption in UV light). PMR spectrum (in trifluoroacetic acid), δ, ppm: 9.05 (CH=N, singlet, 2H), 7.90 (protons in the benzene rings, multiplet, 8H). Found, %: C 66.44; H 4.43; N 29.22. $C_{16}H_{12}N_6$. Calculated, %: C 66.65; H 4.20; N 29.15.

1,2,4-Triazino[4,5-a]benzimidazole (Va). A suspension of 5.59 g of IIIa in 45 ml of freshly distilled ethyl orthoformate was heated for 2 h at 160-210°C; at the same time, the ethanol was gradually distilled off. The precipitate was filtered off and washed with ether. A total of 3.9 g (65%) of Va was obtained, pale yellow plates, mp 235-236°C (decomp., from ethanol), $R_f$ 0.63 (silica gel, chloroform–isopropyl alcohol 10:1, detection in UV light). UV spectrum: $\lambda_{max}$ 246, 316 nm, log ε 4.4, 3.78. PMR spectrum (in a mixture of dimethylsulfoxide and carbon tetrachloride), δ, ppm: 10.2 ($H_1$, doublet, $J_{1,4}=2$ Hz), 9.6 ($H_4$, doublet, J=2 Hz). Found, %: C 63.54; H 3.54; N 32.97. $C_9H_6N_4$. Calculated, %: C 63.51; H 3.55; N 32.92.

1-Methyl-1,2,4-triazino[4,5-a]benzimidazole (Vb). A mixture of 3 g of IIIa and 14 ml of ethyl orthoacetate [8] was heated for 2-3 h at 150-210°C while distilling off the ethanol formed. After cooling the reaction mixture, it was treated with ether, the precipitate was filtered off and washed with ether. A total of 2.43 g (70.4%) of the α-ethoxyethylidenehydrazone of benzimidazole-2-aldehyde (VIa) was obtained, mp 182-185°C (decomp., from benzene). IR spectrum: $\nu_{C-H}$, $\nu_{C=C}$, $\nu_{C=N}$ 3068, 1638, 1580 $cm^{-1}$. UV spectrum: $\lambda_{max}$ 255, 320 nm; log ε 3.95, 4.3. Found, %: C 62.58; H 6.31; N 24.15. $C_{12}H_{14}N_4O$. Calculated, %: C 62.58; H 6.12; N 24.33.

Substance VIa was heated without a solvent for 1 h at 200-210°C and Vb was obtained, mp 162°C (decomp., from ethanol). UV spectrum: $\lambda_{max}$ 226, 245, 320, 335 nm; log ε 4.18, 4.4, 3.98, 3.9. Found, %: C 64.96; H 4.64; N 30.42. $C_{10}H_8N_4$. Calculated, %: C 65.20; H 4.38; N 30.42.

4-Phenyl-1,2,4-triazino[4,5-a]benzimidazole (Vc). This compound was obtained analogously to Va from 2.2 g of IIIb and 12 ml of the orthoformate ester. The yield was 1.82 g (79.6%), mp 205-206°C (from benzene). IR spectrum: $\nu_{C-N}$, $\nu_{C=C}$, $\nu_{C-N}$ 3080, 1610, 1585 $cm^{-1}$. UV spectrum: $\lambda_{max}$ 255, 268, 315 nm; log ε 4.36, 4.34, 4.07. PMR spectrum (in dimethylsulfoxide), δ, ppm: 10.2 ($H_1$, singlet, 1H), 8.69-8.03 (protons of the benzene ring in benzimidazole, multiplet, 4H), 7.58 (protons of the phenyl ring, multiplet, 5H). Found, %: C 73.25; H 4.15; N 22.72. $C_{15}H_{10}N_4$. Calculated, %: C 73.17; H 4.06; N 22.77.

4-Phenyl-1,2,4-triazino[4,5-a]benzimidazole Hydrochloride (Vc•HCl). To a solution of 0.12 g of Vc in anhydrous dioxane was added an ethereal solution of hydrogen chloride, and the precipitate was filtered off. A total of 0.1 g (76%) of Vc hydrochloride was obtained; mp 203-203.5°C (from absolute ethanol), insoluble in water. Found, %: C 63.97; H 4.00; Cl 12.31; N 19.92. $C_{15}H_{10}N_4 \cdot HCl$. Calculated, %: C 63.72; H 3.92; Cl 12.54; N 19.92.

1-Methyl-4-phenyl-1,2,4-triazino[4,5-a]benzimidazole (Vd). The reaction was carried out with 1.4 g of IIIb and 5 ml of ethyl orthoacetate under conditions analogous to those used to obtain Va. From the reaction mixture was isolated a mixture of Vd and VIb which were separated by recrystallization from ethanol. A total of 0.65 g (42%) of Vd was obtained, mp 170-172°C (decomp.). UV spectrum: $\lambda_{max}$ 251, 268, 315 nm; log ε 4.43, 4.40, 4.02. PMR spectrum (in dimethylsulfoxide), δ, ppm: 3.15 ($CH_3$ group, singlet), 8.62, 8.82, 8.07, 7.58 (aromatic protons, multiplets). Found, %: C 73.52; H 4.81; N 21.42. $C_{16}H_{12}N_4$. Calculated, %: C 73.84; H 4.65; N 21.55.

From the ethanolic mother liquor was isolated 0.56 g (31%) of the $\alpha$-ethoxyethylidenehydrazone of 2-benzoylbenzimidazole (VIb), mp 209-210°C (decomp., from benzene). UV spectrum: $\lambda_{max}$ 275, 320 nm; log $\varepsilon$ 4.13, 4.40. PMR spectrum (in deuterioethanol), $\delta$, ppm: 3.55 ($CH_2$, quadruplet), 1.12 ($CH_3$ in the ethoxy group, triplet), 2.21 ($CH_3$, singlet). Found, %: C 70.21; H 5.71; N 18.56. $C_{18}H_{18}N_4O$. Calculated, %: C 70.56; H 5.93; N 18.35.

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