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

I. 4-Oxo-, N-, and O-Alkyl Derivatives of 1, 2, 4-Triazino[4, 5-a]Benzimidazole

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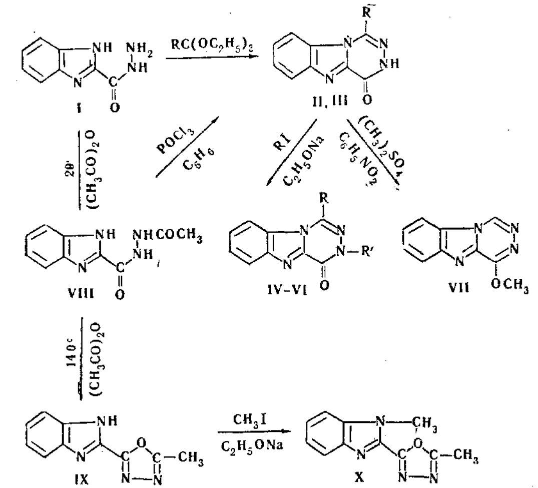
By cyclization of the hydrazide of benzimidazole-2-carboxylic acid (I) with orthoformic and orthoacetic esters, there were obtained, respectively, 4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (II) and its 1-methyl analog (III). Compound III was also prepared by the action of phosphorus oxychloride on the acetylhydrazide of benzimidazole-2-carboxylic acid (VIII). By alkylation of II and III with alkyl halides and with dimethyl sulfate the N_3- and O-alkyl derivatives were obtained. The reaction of II with acids and alkalis was studied. On heating VIII with an excess of boiling acetic anhydride 2-(benzimidazolyl-2')-1, 3, 4-oxadiazole (IX) was isolated.

Among benzimidazole derivates have been found many substances which possess diverse biological effects. It was of interest, therefore, to synthesize a tricyclic system with a common nitrogen atom based on benzimidazole which has not been previously described in the literature, to study its chemical properties, and examine the possibility of preparing derivatives which were of interest in the search for physiologically active substances. We brought about cyclization of the hydrazide of benzimidazole-2-carboxylic acid (I) by heating it at 140–185° C with excess orthoformic ester. Liberation of 3 moles of alcohol with formation of 4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (II) occurred. By heating I with excess orthoacetic ester, 1-methyl-4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (III) was obtained. Earlier we reported [1] that compound III is formed by the action of acetic anhydride on I. However, on further study, we established that the compound isolated from this reaction was not III. On the basis of the IR spectral data (absence of a C=O group absorption band) and the literature data for the synthesis of 1, 3, 4-oxadiazoles from the corresponding diacyl hydrazines [2] we now consider that the compound obtained by the action of acetic anhydride on I is a derivative of 1, 3, 4-oxadiazole, i. e., 2-(benzimidazolyl-2)-1, 3, 4-oxadiazole (IX). On alkylation of II and III with alkyl halides in an alcoholic solution of sodum ethylate, or with dimethyl sulfate in sodium hydroxide solution, the corresponding N_3-alkyl derivatives were obtained. By the action of dimethyl sulfate in nitrobenzene on II, the corresponding O-alkyl derivative, i. e., 4-methoxy-1, 2, 4-triazino[4, 5-a]benzimidazole (VII), was obtained. The phthalazones are known to be alkylated analogously [3].

The structures of II–X were established by IR and PMR spectra. In the IR spectra of II and III there are absorption bands at 1680 and 3200 cm^{-1}, due to the stretching vibrations of the C=O and NH groups, respectively. In the N_3 and O-alkyl derivatives (IV, VII) these absorption bands are absent. The 1680 cm^{-1} band is also absent in IX. In the PMR spectrum of II there is a singlet for C_1 (9.21 ppm) which is absent in III, and the proton signal due to the methyl group at C_1 appears in the spectrum of III at 3.27 ppm. Compound III was stable toward the action of dilute acids and alkalis for short periods of heating; on boiling for some hours the triazine ring was opened. From the acid hydrolysis products, benzimidazole-2-carboxylic acid and benzimidazole were isolated and identified, and from the alkali hydrolysis, benzimidazole-2-carboxylic acid. In alkali solution, II formed a sodium salt which yielded II again on acidification.



II R=H; III R=CH_3; IV R=H, R′=CH_3; V R=H, R′=C_2H_5; VI R=R′=CH_3

EXPERIMENTAL

IR spectra of the compounds were taken on the UR-10 recording spectrophotometer. Samples were prepared as pastes in paraffin oil. UV absorption spectra were taken on the EPS-3 recording spectrophotometer; the solvent was 96% ethanol. The PMR spectra were taken on the JNM-4-H-100 spectrometer operating at a frequency of 100 MHz. The solvent was a mixture of dimethyl sulfoxide and carbon tetrachloride (1 : 1), or trifluoro acetic acid. The internal standard was TMS (tetramethylsilane).

4-Oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (II). A solution of 2 g (0.0113 mole) of the hydrozide of benzimidazole-2-carboxylic acid [4] in 10 ml of orthoformic ester was heated 75 min at 140–185° C with simultaneous distillation of the alcohol formed (~2 ml). The precipitate which separated out was filtered off, washed with ether and yielded 1.71 g (80%) of colorless crystals of II, mp 336° C (DMF–water 1 : 1). Compound II is very difficult to dissolve in the usual organic solvents, both polar and nonpolar. It can be recrystallized from a large quantity of alcohol. In dilute alkalis and acids it dissolves only on heating. IR spectrum: $\nu_{C=O}$ 1680, ν_{NH} 3200 cm^{-1}. UV spectrum (dioxane), λ_{max}, nm (lg ε): 250 (4.49); 295 (3.94); 305 (3.92). Found, %: C 58.0; H 3.4; N 30.3. Calculated for $C_9H_6N_4O$, %: C 58.0; H 3.2; N 30.1.

1-Methyl-4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (III). A) The compound is obtained in a similar way to the preceding experiment from 1.5 g (0.0085 mole) I and 7 ml of orthoacetic ester. The yield was 0.8 g (47%), mp 345° C (dec.) (DMF–water 1 : 1). IR spectrum: $\nu_{C=O}$ 1680, ν_{NH} 3200 cm^{-1}, UV spectrum (alcohol): λ_{max}, nm (lg ε): 245 (4.44); 297 (3.97). Found, %: C 59.9; H 4.0; N 27.8. Calculated for $C_{10}H_8N_4O$, %: C 60.0; H 4.0; N 28.0.

B) To 2 g (0.0113 mole) I was added 10 ml of acetic anhydride, the precipitate which separated was filtered off and washed with ether to give the acetylhydrazide of benzimidazole-2-carboxylic acid (VIII), mp 278° C (from alcohol), yield quantitative. Found, %: C 55.6; H 4.4; N 25.6. Calculated for $C_{10}H_{10}N_4O_2$, %: C 55.4; H 4.6; N 25.7. 1 g (0.0046 mole) VIII was heated with 3.3 ml $POCl_3$ in 14 ml of anhydrous benzene at boiling unitl cessation of HCl evolution (~12 hr). The solution was decanted twice, and the precipitate with cooling was triturated with saturated $NaHCO_3$ solution, filtered off, washed with water and alcohol to give 0.65 g (70%) of a compound identical to that obtained by method A.

3-Methyl-4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (IV). A) To an alcohol solution of sodium ethylate (from 0.021 g Na and 10 ml ethanol) was added 0.17 g (0.0009 mole) II, 0.45 g (0.0032 mole) methyl iodide, and then heated 4.5 hr at boiling. After cooling the precipitate was filtered off, washed with alcohol to give 0.15 g (83%) of a white crystalline substance, mp 308–210° C (from DMF). IR spectrum: $\nu_{C=O}$ 1680. UV spectrum (alcohol), λ_{max}, nm (lg ε): 251 (4.46); 295 (3.97); 305 (3.96). Found, %: C 59.9; H 3.9; N 27.8. Calculated for $C_{10}H_8N_4O$, %: C 60.0; H 4.0; N 28.0.

B) A mixture of 1 g (0.0053 mole) I, 1.26 g (0.01 mole) dimethyl sulfate, 15 ml methanol and 4 ml 4 N NaOH was heated at boiling 75 min. The precipitate which formed was filtered off, washed with water, to give 0.95 g (89%) of a substance, which on admixture with IV did not depress the melting point.

3-Ethyl-4-oxo-1, 2, 4-triazino[4, 5-a]benzimidazole (V). Compound V was prepared in a similar way to IV (method A) from 0.23 g (0.0012 mole) II and 0.965 g (0.0062 mole) ethyl iodide in an alcoholic solution of sodium ethylate (0.027 g Na and 10 ml ethanol) by boiling for 8 hr. Yield 0.11 g (42%) of colorless crystals m 232° C (from alcohol). Found, %: C 62.0; H 5.0; N 26.1. Calculated for $C_{11}H_{10}N_4O$, %:C 61.7; H 4.7; N 26.2.

1, 3-Dimethyl-4-oxo-1, 2, 4-triazino[4,5-a]benzimidazole (VI). To an alcoholic solution of sodium ethylate (0.023 g Na in 10 ml ethanol) was added 0.2 g (0.001 mole) III, 0.456 g (0.0032 mole) methyl iodide and the mixture heated at boiling 4.5 hr. After cooling, the precipitate was filtered off, washed with alcohol to yield 0.18 g (84%) of a white crystalline substance mp 241–243° C (from alcohol). Found, %: C 62.0; H 4.9; N 26.5%. Calculated for $C_{11}H_{10}N_4O$, %: C 61.7; H 4.7; N 26.2.

4-Methoxy-1, 2, 4-triazino[4, 5-a]benzimidazole (VII). To a solution of 3.4 g (0.018 mole) II in 28 ml of freshly distilled nitrobenzene was added 3.06 g (0.024 mole) dimethyl sulfate. The mixture was heated 45 min at 130–140° C, the precipitate filtered off, washed with ether, to give the methyl sulfate of compound VII, mp 210° C (dec.) (from alcohol). Found, %: C 42.8; H 3.9; N 17.8; S 10.7. Calculated for $C_{10}H_8N_4O \cdot HSO_4CH_3$, %: C 42.3; H 3.9; N 18.0; S 10.3. The prepared salt was triturated with a saturated solution of sodium bicarbonate, the precipitate filtered off and washed with water to give 2.32 g (64%) of a white crystalline substance mp 207° C (from alcohol). UV spectrum (alcohol) λ_{max}, nm (lgε): 223 (4.27); 258 (4.28); 334 (3.84). Found, %: C 60.1; H 4.2; N 27.6. Calculated for $C_{10}H_8N_4O$, %: C 60.0; H 4.0; N 28.0.

2-(Benzimidazolyl-2')-1, 3, 4-oxadiazole (IX). A solution of 2 g (0.0113 mole) I in 10 ml of acetic anhydride was heated at boiling for 6 hr. After cooling the precipitate was filtered off, washed with water to give 0.4 g (18%) IX as colorless crystals, mp 276° C (from 50% alcohol). IR spectrum: ν_{NH} 3180 cm^{-1}. UV spectrum (alcohol) λ_{max}, nm (lgε): 238 (4.17); 243 (4.14); 300 (4.30). Found, %: C 60.2; H 4.2; N 28.0. Calculated for $C_{10}H_8N_4O$, %: C 60.0; H 4.0; N 28.0.

2-(N-Methylbenzimidazolyl-2')-5-methyl-1, 3, 4-oxadiazole (X). To an alcoholic solution of sodium ethylate (from 0.02 g Na and 6 ml of ethanol) was added 0.17 g (0.0008 mole) IX, 0.57 g (0.04 mole) methyl iodide, and the mixture boiled for 5 hr. After cooling the precipitate was filtered off, washed with alcohol to give 0.1 g (55%) X as a white crystalline substance, mp 173–175° C (from alcohol). Found, %: C 61.9; H 4.9; N 25.5. Calculated for $C_{11}H_{10}N_4O$, %: C 61.7; H 4.7; N 26.2.

Reaction of II with dilute acids and alkalis. A) 0.5 g (0.0026 mole) II was heated at boiling for 6 hr in 15 ml of 10% HCl. After cooling and concentration in vacuum to one-half the original volume, the precipitate which separated was filtered off, dissolved in sodium bicarbonate solution and acidified with HCl; 0.19 g (44%) was obtained of a substance mp 170° (dec.) which was not depressed in admixture with benzimidazole-2-carboxylic acid [5]. From the mother liquors, after rendering alkaline, was isolated 0.09 g (28%) of a substance mp 174–175° C, which in admixture with benzimidazole did not depress the melting point.

B) A solution of 0.5 g (0.0026 mole) II in 5 ml 40% NaOH was heated at boiling 5 hr. After cooling it was acidified, the precipitate filtered off, to give 0.21 g (49%) of benzimidizole-2-carboxylic acid.

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