

γ -(2-Benzimidazolyl)perfluorobutyramide (IIb). A) A 3.3-g (0.01 mole) sample of anilide Ib was heated to 182°, after which it was cooled and worked up to give 2.9 g (93.5%) of a product with mp 231-232°. According to the DTA data, this compound melts at 245° (dec.). Found: F 36.6; N 13.3%. $C_{11}H_7F_6N_3O$. Calculated: F 36.6; N 13.5%.

B) Amide IIb was obtained from 0.9 g (2.7 mmole) of acid chloride IVb by the method described for amide IIa. Workup gave 0.83 g (98.8%) of a product with mp 231-232°.

γ -(2-Benzimidazolyl)perfluorobutyryl Chloride (IVb). This compound was obtained from 3.12 g (0.01 mole) of acid IIIb and 2.085 g (0.01 mole) of phosphorus pentachloride as in the preparation of acid chloride IVa. Workup gave 2.7 g (81.8%) of a product with bp 121-122° (12 mm). The product crystallized when it was cooled and was readily hydrolyzed by air moisture.

2-(γ -Hydroperfluoropropyl)benzimidazole (Vb). A 0.78-g (2.5 mmole) sample of amide IIb was heated at 255° for 15 min, after which it was cooled and extracted with benzene. Workup of the benzene extract gave 0.07 g (10.4%) of a product with mp 193-194° (from benzene containing petroleum ether). Found: F 42.7%; M (mass spectroscopically) 268. $C_{10}H_6F_6N_2$. Calculated: F 42.5%; M 268.

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NEW PYRAZINO[1,2-a]BENZIMIDAZOLE DERIVATIVES

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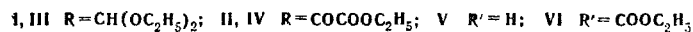
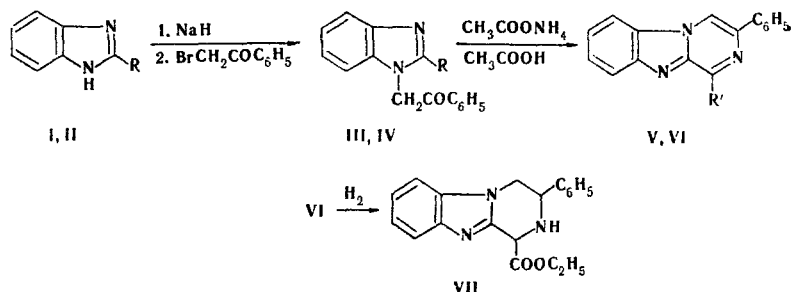
1-Ethoxycarbonyl-3-phenyl- and 3-phenylpyrazino[1,2-a]benzimidazoles were synthesized by reaction of 2-ethoxalyl- and 2-diethoxymethyl-N-phenacylbenzimidazoles, obtained from the corresponding sodium derivatives of benzimidazole and phenacyl bromide, with ammonium acetate.

In order to synthesize new derivatives of pyrazino[1,2-a]benzimidazole, which is the aza analog of the psychotropic preparation pirazidol [1, 2], we studied alkylation with phenacyl bromide of the sodium derivatives of 2-formylbenzimidazole diethylacetal (Ia) [3] and 2-ethoxalylbenzimidazole (II), which we obtained for the first time. The synthesized N-phenacyl-2-diethoxymethyl- and N-phenacyl-2-ethoxalylbenzimidazoles (III, IV) are smoothly converted to pyrazino[1,2-a]benzimidazole derivatives (V, VI) on heating in acetic acid solutions with ammonium acetate. Derivatives V and VI differ from the previously known [1] compounds of analogous structure with respect to the presence of an ethoxycarbonyl group and the position of the phenyl group. Heating 1-ethoxycarbonyl-3-phenylpyrazino[1,2-a]benzimidazole (VI) in 100% orthophosphoric acid causes elimination of the ethoxycarbonyl group and the formation of 3-phenylpyrazino[1,2-a]benzimidazole (V). Hydrogenation of VI over a Raney nickel catalyst leads to 1,2,3,4-tetrahydro-1-ethoxycarbonyl-3-phenylpyrazino[1,2-a]benzimidazole (VII). (See scheme on following page.)

The structures of the products were confirmed by their IR spectra and the results of elementary analysis.

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EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

2-Ethoxalylbenzimidazole (II). Finely ground selenium dioxide was added to a hot solution of 8.8 g (43 mmole) of ethyl 2-benzimidazolyacetate [4] in 440 ml of toluene, and the mixture was stirred and refluxed for 5 h. The hot solution was decanted from the precipitated selenium and cooled. The resulting precipitate was removed by filtrations and washed with acetone to give 6.5 g (69%) of a product with mp 161-162° (from CH₃COOH). IR spectrum, cm⁻¹: 2700-3100 (NH); 1765 (CO). Found: C 60.4; H 4.8; N 12.8%. C₁₁H₁₀N₂O₃. Calculated: C 60.5; H 4.6; N 12.8%.

1-Phenacyl-2-diethoxymethylbenzimidazole (III). A suspension of 0.33 g (14 mmole) of sodium hydride in 3 ml of dimethylformamide (DMF) was added with stirring and ice cooling to 2.2 g (10 mmole) of 2-diethoxymethylbenzimidazole (I) in 50 ml of dry DMF. After 15 min, 2.5 g (12.5 mmole) of phenacyl bromide was added to the resulting solution of the sodium derivative, and the mixture was stirred at room temperature for 30 min. It was then poured into 250 ml of water, and the resulting precipitate was removed by filtration to give 2.5 g (79%) of a product with mp 114-115° (from hexane). IR spectrum, cm⁻¹: 1680 (CO). Found: C 71.3; H 6.6; N 8.3%. C₂₀H₂₂N₂O₃. Calculated: C 71.0; H 6.6; N 8.3%.

1-Phenacyl-2-ethoxalylbenzimidazole (IV). This compound was obtained from 4.7 g (21.5 mmole) of ethoxalylbenzimidazole II by the method used to prepare III. Workup gave 6.5 g (89%) of a product with mp 157-159° (from ethyl acetate). IR spectrum, cm⁻¹: 1690, 1740 (CO). Found: C 67.8; H 4.8; N 8.4%. C₁₉H₁₆N₂O₄. Calculated: C 67.8; H 4.8; N 8.3%.

3-Phenylpyrazino[1,2-a]benzimidazole (V). A mixture of 1 g (3.14 mmole) of benzimidazole III, 1.6 g of ammonium acetate, and 15 ml of acetic acid was refluxed for 15 min, and the resulting solution was then poured into 75 ml of water. The precipitate was removed by filtration to give 0.68 g (61%) of a product with mp 164-165° (from alcohol). Found: C 78.3; H 4.3; N 17.0%. C₁₆H₁₁N₃. Calculated: C 78.3; H 4.5; N 17.1%.

1-Ethoxycarbonyl-3-phenylpyrazino[1,2-a]benzimidazole (VI). This compound was obtained from 2.75 g (8.2 mmole) of IV and 4.1 g of ammonium acetate in acetic acid solution under the conditions of the synthesis of pyrazinobenzimidazole V. Workup gave 2.36 g (91%) of a product with mp 170-172° (from alcohol). IR spectrum, cm⁻¹: 1720 (CO). Found: C 71.5; H 4.6; N 13.3%. C₁₉H₁₅N₃O₂. Calculated: C 71.9; H 4.7; N 13.2%. The hydrochloride of VI had mp 219-220° (from alcohol-acetone-ether). Found: Cl 9.8%. C₁₉H₁₆ClN₃O₂. Calculated: Cl 10.0%.

Hydrolysis of 1-Ethoxycarbonyl-3-phenylpyrazino[1,2-a]benzimidazole. A mixture of 1.0 g (3.15 mmole) of ester VI and 15 ml of 100% orthophosphoric acid was heated to 160° with stirring, after which it was stirred at this temperature for 1 h. It was then poured over ice, and the resulting precipitate was removed by filtration to give 0.75 g (96%) of 3-phenylpyrazino[1,2-a]benzimidazole (V). No melting-point depression was observed for a mixture of this product with an authentic sample.

1-Ethoxycarbonyl-3-phenyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (VII). A solution of 9.0 g (28.4 mmole) of ester VI in 250 ml of absolute alcohol was hydrogenated at 70° and an initial pressure of 100 atm in the presence of 4.0 g of a Raney nickel catalyst.

The reaction was complete after 10 h. The catalyst was removed by filtration and washed with hot alcohol. The filtrate was evaporated to give 5.0 g (55%) of a product with mp 194-196° (from ethyl acetate). IR spectrum, cm^{-1} : 1635 (CO), 3290 (NH). Found: C 71.0; H 5.24; N 13.4%. $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2$. Calculated: C 71.4; H 5.4; N 13.2%.

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CYCLIZATION OF N-(4-QUINAZOLYL)- α -AMINO CARBOXYLIC ACIDS

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2,3-Dihydroimidazo[1,2-c]quinazolin-2-one derivatives were obtained by cyclization of N-(4-quinazolyl)- α -amino carboxylic acids. A scheme including cleavage of the $\text{C}_{(2)}\text{-N}_{(3)}$ bond of the quinazoline ring and subsequent rearrangement is proposed for the mechanism of the cyclization. The structures of the synthesized compounds were established by means of chemical and physicochemical methods.

Continuing our research on the synthesis of imidazo[1,2-c]quinazoline derivatives [1], we attempted to cyclize N-(4-quinazolyl)- α -amino carboxylic acids [2], which were previously obtained from 4-chloroquinazoline and α -aminocarboxylic acids. Heating the N-(4-quinazolyl)- α -amino carboxylic acids in glacial acetic acid or in a mixture of glacial acetic acid and acetic anhydride gave 2,3-dihydroimidazo[1,2-c]quinazolinones (I-V), the hydrolytic cleavage of which in alkaline media did not regenerate the starting acids. Ammonia was evolved as a result of hydrolysis of imidazoquinazolinone I, and we obtained α -4-quinazolon-3-yl)propionic acid (X), which was identical to the acid synthesized from 4-quinazolinone and α -bromopropionic acid by the method in [3]. We suppose that the imidazolone ring is opened in the first step of the hydrolysis to give α -(4-imino-3-quinazolyl)propionic acid, which is readily converted to quinazolinone X. The above-indicated cyclization of N-(4-quinazolyl)- α -amino carboxylic acids consequently does not lead to the formation of the expected 2,3-dihydroimidazo[1,2-c]quinazolin-3-ones but rather to the isomeric 2,3-dihydroimidazo[1,2-c]quinazolin-2-ones (I-V). (See scheme on following page.)

The formation of I-V can be explained by assuming destruction of the $\text{C}_{(2)}\text{-N}_{(3)}$ bond of the pyrimidine ring of the quinoline two-ring system, as in the cyclization of N-(2-pyrimidin-4-yl)amino carboxylic acids [4]. (See scheme on following page.)

It is known that 4-aminopyrimidines [5] and their benzo analogs - quinazolines [6] - exist in the form of systems in dynamic equilibrium. In our case N-(4-quinazolyl)- α -amino carboxylic acids A exist in tautomeric equilibrium with structure B. Since acetic anhydride and glacial acetic acid are not only dehydrating agents but also acylating agents, there is no doubt regarding the possibility of acetylation of the $\text{N}_{(1)}$ atom (structure C). Protonation of the latter at the $\text{N}_{(3)}$ atom probably leads to systems D and E. Specific interaction

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