ω -(2-BENZIMIDAZOLYL) PERFLUORINATED CARBOXYLIC ACIDS

AND THEIR DERIVATIVES

N. A. Malichenko, A. P. Krasnoshchek, T. P. Medvedeva, and L. M. Yagupol'skii

A convenient method is proposed for the preparation of ω -(2-benzimidazolyl) perfluorinated carboxylic acids and their amides by condensation of o-phenylenediamine with imides of perfluorinated dicarboxylic acids. The transformations of the o-aminoanilides of the amides of the perfluorinated dicarboxylic acids were studied by thermal analysis and mass spectroscopy.

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 ω -(2-Benzimidazolyl)perfluoroacetic and ω -(2-benzimidazolyl) perfluoropropionic acids have been obtained [1] by fusion of o-phenylenediamine with difluoromalonic and perfluorosuccinic acids, but difficulties were encountered in their isolation and purification. We have developed a new convenient method for the preparation of ω -(2-benzimidazolyl)perfluorinated carboxylic acids and have studied their properties.

o-Aminoanilides (Ia,b) of the amides of the corresponding acids are formed by the action of imides of perfluorinated dicarboxylic acids on o-phenylenediamine.



It was found that anilide I has an unusually high melting point that is not characteristic for noncyclic compounds. It might have been assumed that Ia undergoes cyclization during the determination of its melting point. In order to determine the temperature at which this transformation occurs, we made thermal studies.



1. IVa n=2; b n=3

The differential-thermal-analysis (DTA), thermogravimetry (TGA), and differentialthermal-gravimetry (DTG) curves are presented in Fig. 1. Exothermic and endothermic extrema, which can be associated with the occurrence of chemical or phase transformations, are

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Fig. 1. Thermal analysis of amides I: a) Ia; b) Ib.

present on the DTA curve. The endothermic minimum with a peak at 155°, which is associated with melting of the compound, is immediately converted to an exothermic maximum with a peak at 162°, which indicates a process accompanied by heat evolution. A decrease in the weight of the sample by 6.5% is observed on the TGA curve at 145-165°; this is equivalent to the loss of one molecule of water. A peak attesting to a chemical transformation that occurs at a maximum rate at 155° is present on the DTG curves over the same temperature range. This process was identified as one involving the splitting out of water and the formation of benzimidazole derivative IIa, the structure of which was confirmed by IR spectroscopic data and proved by alternative synthesis from acid chloride IVa. However, upon examination of the subsequent changes in aminoanilide Ia on heating (Fig. 1, curve a) it was found that the melting point determined for Ia in a capillary does not pertain to the melting point of amide IIa but rather characterizes the melting point of another compound formed during heating of the amide. The substance again loses 6.5% of its weight at 205-260°; this corresponds approximately to splitting out of an ammonia molecule. The theoretical weight loss in this case is 6.09%. The DTG curve over this same temperature range contains two peaks that characterize the maximum rate of two different processes that take place almost simultaneously. A diffuse endothermic minimum that attests to parallel processes accompanied by the absorption and evolution of heat and leads to the formation of two compounds is observed on the DTA curve.



An analysis of the mass spectrum of amide IIa also indicates the presence in the decomposition products of two substances with molecular weights of 218 and 244. When we heated IIa to 280°, we isolated benzimidazole Va. We could not isolate the second compound (VIa) in pure form either by crystallization or by thin-layer chromatography (TLC). The solubilities and polarities of IIa and VIa probably differ only slightly.

Compound VIa is formed by intramolecular splitting out of ammonia. The production of VA from amide IIa is accompanied by loss of a CONH grouping instead of NH_3 , and this is the reason for the difference between the theoretically calculated and experimentally found decrease in the weight of the sample.

Anilide Ib, the behavior of which on heating is similar to the behavior of I, is formed from o-phenylenediamine and perfluoroglutarimide. At 180-190° the DTA curve (Fig. 1, curve b) contains an endothermic minimum with a peak at 183° (the melting point of Ib), which is immediately converted to an exothermic maximum with a peak at 200°. The peak on the DTG curve corresponds to the same temperature, whereas a 5.55% weight loss is observed on the TGA curve. The theoretical weight loss in the case of splitting out of a water molecule is 5.47%. In fact, water is liberated when anilide Ib is heated at 180-185°, and amide IIb, which was also obtained from acid chloride IVb, is formed. An endothermic minimum for the peak at 245° is observed at 215-265° on the DTA curve (Fig. 1, curve b). There is a peak on the DTG curve at the same temperature. The sample again loses 5.75% of its original weight over the indicated temperature range. The reason for the discrepancy between this value and the theoretically calculated value in the case of splitting out of ammonia (5.46%) is similar to that described above for Ia, since the mass spectrum of anilide Ib recorded at 250° provides evidence that the products of the thermal transformations contain two substances — Vb and VIb — with molecular weights of 268 and 294, respectively. In this case also, we were able to isolate only preparation Vb in pure form when a weighed sample of Ib was heated at 250° . Compound VIb has not yet been isolated in pure form.

EXPERIMENTAL

Thermal analysis was carried out with a MOM derivatograph (Hungary) in platinum crucibles at a temperature-rise rate of 6 deg/min. The mass spectra were recorded with an MKh-1303 mass spectrometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer.

<u>Perfluorosuccinamide o-Aminoanilide (Ia)</u>. A mixture of 1.65 g (9.6 mmole) of perfluorosuccinimide and 1.04 g (9.6 mmole) of o-phenylenediamine in 30 ml of chloroform was shaken at 5° for 20 min and at 20° for 30 min, after which the precipitate was removed by filtration and dried to give 2.56 g (95%) of a product with mp 159-160° (from methanol containing benzene). IR spectrum, cm⁻¹: 1145, 1170 (CF), 1700 (C=0), 3380 (NH₂). Found: N 15.1%. $C_{10}H_9F_4N_3O_2$. Calculated: N 15.0%.

<u>Perfluoroglutaramide o-Aminoanilide (Ib)</u>. This compound was obtained as in the preparation of anilide Ia from 7 g (0.0316 mole) of perfluoroglutarimide and 3.42 g (0.0316 mole) of o-phenylenediamine in 50 ml of chloroform. Workup gave 9.5 g (91.5%) of a product with mp 182-183° (from methanol containing benzene). IR spectrum, cm⁻¹: 1145, 1170 (CF), 1720 (C=0), 3400 (NH₂). Found: F 34.6%. $C_{11}H_{9}F_{6}N_{3}O_{2}$. Calculated: F 34.6%.

 β -(2-Benzimidazolyl)perfluoropropionamide (IIa). A) A 2.5-g (8.9 mmole) sample of anilide Ia was heated at 170-190° for 20 min, after which the mixture was worked up to give 2.1 g (90.1%) of a product with mp 299° (dec., from aqueous alcohol). According to the DTA data, this compound melts at 155°. IR spectrum, cm⁻¹: 1140, 1160 (CF), 1700 (C=0), 3385 (NH₂). Found: F 29.1%. C₁₀H₇F₄N₃O. Calculated: F 29.1%.

B) A total of 2 ml of 25% ammonium hydroxide solution was added with stirring and cooling to a solution of 1.2 g (4.27 mmole) of acid chloride IVa in 10 ml of anhydrous benzene, and the mixture was allowed to stand at 20° for 30 min. The resulting precipitate was removed by filtration, washed with water, and dried to give 1.05 g (95%) of a product with mp 155° (according to the DTA data).

 β -(2-Benzimidazoly1)perfluoropropionic Acid (IIIa). A mixture of 2.13 g (7.6 mmole) of anilide Ia and 15 ml of 17% hydrochloric acid was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 1.34 (67%) of a product with mp 255-256° (from water). The product was identical to the compound obtained by the method in [1].

 β -(2-Benzomidazolyl)perfluoropropionyl Chloride (IVa). A mixture of 2.62 g (0.01 mole) of acid IIIa and 2.085 g (0.01 mole) of phosphorus pentafluoride was heated at 110° until hydrogen chloride evolution ceased. The phosphorus oxychloride was then removed by distillation, and the residue was vacuum fractionated to give 2.38 g (85%) of a product with bp 119-120° (12 mm). The product crystallized when it was cooled and was readily hydrolyzed by air moisture.

 $\frac{2-(\beta-\text{Hydroperfluoroethyl})\text{benzimidazole (Va)}. A 0.4-g (1.53 \text{ mmole}) \text{ sample of IIa was} \\ \text{heated at } 260-270^\circ \text{ for 15 min}, \text{ after which it was cooled and extracted with benzene. Workup} \\ \text{of the extract gave 0.05 g (16%) of a product with mp 185-186^\circ (from benzene containing petroleum ether)}. Found: F 34.8%; M (mass spectroscopically) 218. C_9H_6F_4N_2. Calculated: F 34.9%; M 218.$

 γ -(2-Benzimidazoly1)perfluorobutyric Acid (IIIb). A mixture of 5.3 g (0.0161 mole) of Ib and 40 ml of 17% hydrochloric acid was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 4.3 g (83%) of a product with mp 274-275° (dec., from aqueous alcohol). Found: C 42.3; H 1.9; F 36.6%. C₁₁H₆F₆N₂O₂. Calculated: C 42.3; H 1.9; F 36.5%.

<u> γ -(2-Benzimidazoly1)perfluorobutyramide (IIb)</u>. 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%. C₁₁H₇F₆N₃O. 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°.

 $\frac{\gamma-(2-\text{Benzimidazolyl})\text{perfluorobutyryl Chloride (IVb)}}{g (0.01 mole) of acid IIIb and 2.085 g (0.01 mole) of phosphorus pentachloride as in the preparation of acid chloride IVa. Workup gave 2.7 g (81.8%) of a product with bp 121-122° (12 mm). The product crystallized when it was cooled and was readily hydrolyzed by air moisture.$

 $\frac{2-(\gamma-\text{Hydroperfluoropropyl)benzimidazole (Vb)}{\text{Morkup of the benzene extract gave 0.07 g (10.4\%) of a product with mp 193-194° (from benzene containing petroleum ether). Found: F 42.7%; M (mass spectroscopically) 268. C₁₀H₆F₆N₂. Calculated: F 42.5%; M 268.$

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NEW PYRAZINO[1,2-a]BENZIMIDAZOLE DERIVATIVES

A. N. Grinev, A. A. Druzhinina, UDC 547.785.5'861.1.3:543.422.4 and I. K. Sorokina

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 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.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1266-1267, September, 1976. Original article submitted October 6, 1975.

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