RESEARCH ON BENZIMIDAZOLE. XXXVIII.* REACTION OF BENZIMIDAZOLE-

2-SULFONIC ACIDS WITH AMMONIA, AMINES, AND SOME AZOLES

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2-Amino derivatives of benzimidazole are formed in good yields by the action of amines with various structures on benzimidazole-2-sulfonic acid.

It is known that a sulfo group in the 2 position of benzimidazole can be readily replaced by alkoxy [2] and hydrazino [3] groups. We have found that the reaction of ammonia and amines with various structures with benzimidazole-2-sulfonic acid leads to substitution of the sulfo group by an amino group or alkyl-, aryl-, and heterylamino groups. The reaction proceeds in the case of both 1-substituted and 1-unsubstituted benzimidazole-2-sulfonic acids (Ia, b). The method makes it possible to obtain extremely pure 2-aminobenzimidazole in good yield and, with respect to its simplicity and the accessibility and nontoxicity of the starting materials, has definite advantages over the methods previously descrived in [4] (see [5]).

Highly basic amines of the aliphatic series react with Ia,b on refluxing in aqueous solutions, whereas the reaction with piperidine proceeds at its boiling point.

When high-boiling aliphatic amines (ethanolamine) and benzylamine are used the process can be carried out by heating a mixture of Ia, b and the amine to 160-180°. Ethylenediamine reacts with Ia to give the symmetrical N,N'-bis(2,2'-benzimidazolyl)ethylenediamine even when it is present in fivefold excess.



Ia R = H; b CH₃; II a R = R[•] = H; b R = H; R[•] = CH₂C₆H₅; c R = H; R[•] = C₂H₄OH; d R = H; R[•] = C₆H₅; e R = H; R[•] = 1-ethynyl-2-benzimidazolyl; f R = CH₃; R[•] = CH₃; R[•]

The reaction of Ia, b with aryl- and heterylamines[†] proceeds only when the mixture is heated to 170-180°. 1-Naphthylamine reacts with greater difficulty (prolonged heating is necessary). 2-Heterylbenzimidazoles (III) are formed in the reaction of Ia, b with heterocycles containing an unsubstituted NH group in the ring (imidazole and benzimidazole). The reaction begins at 180° and proceeds smoothly at 200°.

EXPERIMENTAL METHOD

Benzimidazole sulfonic acids Ia, b were synthesized by the method in [2].

*See [1] for communication XXXVII.

[†]The reaction proceeds at the NH_2 group, inasmuch as the products do not undergo hydrolysis on heating with acid and alkali solutions.

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TABLE 1. 2-Amino- (II) and 2-Heteryl-Substituted (III) Benzimidazoles

Compound	mp, °C	Reaction temp., °C	Reaction time, h	Yield, %
11b 11d 11g 11h 11i 11a 111b 111c	$\begin{array}{c} 160 - 162^7 \\ 192 - 194^{10} \\ 168 - 169^7 \\ 150^8 \\ 201 - 202^9 \\ 152 - 153^{11} \\ 170 - 171^{11} \\ 272 - 274^{12} \end{array}$	170 170 170 160 170 200 200 106	0,5 0,5 0,5 0,5 0,5 0,75 0,75 0,5 3	90 70 90 84 80 98 70 87

2-Aminobenzimidazole (IIa). A solution of 5.94 g (0.03 mole) of sulfonic acid Ia in 15 ml of 22% ammonium hydroxide in a sealed ampul was heated at 145-150° for 4 h, after which the ampul was cooled, and snow-white plates of IIa were removed by filtration and washed with 5 ml of 22% ammonium hydroxide and 10 ml of water to give 3 g (75%) of a product with mp 227° (from water) [5].

<u>1-Methyl-2-aminobenzimidazole (IIf)</u>. This compound was similarly obtained in 80% yield and had 202-203° (from water) [6].

<u>1-Methyl-2-(1-naphthylamino)benzimidazole (IIj)</u>. A mixture of 1.06 g (5 mmole) of sulfonic acid Ib with 1.43 g (0.01 mole) of 1-naphthylamine was heated at 160° for 2.5 h, after which the melt was cooled and triturated with 100 ml of ether. The resulting solid was removed by filtration to give 1 g (73%) of needles with mp 239-240° (from toluene). Found: C 78.4; H 5.4%. $C_{18}H_{15}N_3$. Calculated: C 79.1; H 5.5%.

 $\frac{2-(1-\text{Ethyl}-2-\text{benzimidazolyl}) \text{aminobenzimidazole} (IIe). A mixture of 0.99 g (5 mmole)}{of sulfonic acid Ia with 1.61 g (0.01 mole) of 1-ethyl-2-aminobenzimidazole was heated at 180° for 30 min, after which the melt was cooled and dissolved in chloroform. The solution was filtered through a layer of aluminum oxide to separate the reaction product from the starting 2-amino-1-ethylbenzimidazole. The chloroform was removed by distillation to give 1.2 g (90%) of needles with mp 237-238°. Found: C 69.0; H 5.7; N 25.3%. C₁₆H₁₅N₅. Calculated: C 69.3; H 5.5; N 25.2%.$

 $\frac{2-(1-\text{Ethyl-2-benzimidazolyl)amino-1-methylbenzimidazole (IIk)}{\text{prepare IIe was used to obtain this compound in 90% yield as needles with mp 131-132° (from alcohol). Found: C 69.7; H 5.5; N 23.9%. C₁₇H₁₇N₅. Calculated: C 70.1; H 5.9; N 24.0%.$

 $\frac{2-(4-\text{Phenyl-2-thiazolyl})\text{amino-1-methylbenzimidazole (II1)}}{\text{IIe was used to obtain this compound, with mp 184-185° (from benzene), from 2-amino-4-phenylthioazole. Found: N 18.5%. C₁₇H₁₄N₄S. Calculated: N 18.3%.$

 $\frac{2-(2-\text{Hydroxyethyl})\text{aminobenzimidazole (IIc).} A \text{ mixture of 0.99 g (5 mmole) of sulfonic acid Ia and 1.22 g (0.01 mole) of ethanolamine was heated at 160° for 30 min. The melt was cooled, 7 ml of water was added, and the resulting precipitate was removed by filtration to give 0.71 g (80%) of prisms with mp 181-182° (from aqueous alcohol). Found: C 60.7; H 6.6%. C_9H_1N_3O. Calculated: C 61.0; H 6.3%.$

The previously described compounds (IIb,d,g-i and IIIa-c) [7-12] were obtained by the methods presented above (Table 1).

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