SOME PROPERTIES OF 2-NITROBENZIMIDAZOLES

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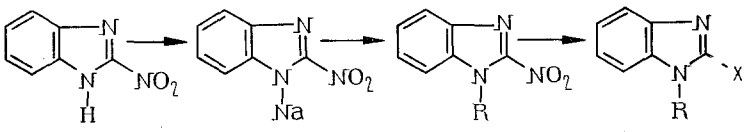
The chemistry of nitroimidazoles is attracting considerable attention in view of the biological activity of many compounds of this series. 2-Nitroimidazoles – analogs of the natural antibiotic azomycin – are especially interesting. This work presents information on certain properties of 2-nitrobenzimidazoles, which recently have become comparatively readily available [1, 2].

2-Nitrobenzimidazole (I) possesses acid properties, pKA 6.62 (determined potentiometrically in aqueous solution at 25°). I forms a stable sodium salt (II) and is readily methylated by diazomethane in ether. N-substituted 2-nitrobenzimidazoles (III) can also be produced by the action of methyl iodide, ethyl iodide, and dimethylphenylbenzylammonium chloride on the salt II in alcohol or aqueous solution or in an inert solvent:



I II III a) R = CH_3; b) R = C_2H_5; c) R = $C_6H_5CH_2$; IV a) R = CH_3, X = C_2H_5O; b) R = CH_3, X = $C_6H_5CH_2NH$

The nitro-group in III is in an electron-deficient position and therefore is distinguished by high mobility in nucleophilic substitution reactions. Thus, when IIIa is heated with sodium ethylate in alcohol or with benzylamine in xylene, there is an exchange of the nitro-group for an ethoxy or benzylamino group, forming compounds IV. 2-Nitrobenzimidazoles, especially with a free NH group, are relatively unstable compounds. After prolonged storage of a pure sample of I, traces of decomposition products appear on its chromatogram.

We investigated the bacteriostatic and fungistatic action of four of the substances obtained – I, II, IIIa, and IIIb (see Table 1). They possess weak or moderate germistatic activity with respect to all the microorganisms tested, with the exception of Bacillus pyocyaneus.

In a study of the antituberculosis activity of these substances it was established that substance IIIa in vitro retards the growth of tuberculosis mycobacteria (strain H-37-Rv) in a dilution of 1 : 500,000, while substance IIIb retards growth of this microorganism in a dilution 1 : 2,000,000. The addition of 10% horse serum to the nutrient medium only slightly lowers the activity of the substances. The treatment of white mice infected with tuberculosis with substance IIIa, administered internally in doses from 0.08 to 2.5 mg (maximum tolerable dose) per mouse weighing 16-17 g, gave no therapeutic effect. Thus, despite the high tuberculostatic activity in vitro, the substances studied do not possess chemotherapeutic antituberculosis activity in vivo.

The analogy of the substances described to azomycin served as a basis for studying their antiprotozoal activity. It was established that these substances practically do not suppress the growth of the dysentery ameba in vitro, but are rather effective with respect to the vaginal trichomonad, retarding its growth in vitro in the following concentrations: I – 4 μg/ml, II – 0.5 μg/ml; IIIa and IIIb – 16 μg/ml. A study of the preparations in vivo in the case of trichomonad abscess of white mice indicated that substance IIIb

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TABLE 1. Results of Microbiological Tests of 2-Nitrobenzimidazoles

Microorganism	Compound			
	I	II	IIIa	IIIb
Staphylococcus aureus	1 : 16,000	1 : 4,000	1 : 16,000	1 : 8,000
Streptococcus hemolyticus	1 : 8,000	1 : 4,000	1 : 16,000	1 : 8,000
Escherichia coli	1 : 4,000	1 : 4,000	1 : 8,000	1 : 8,000
Salmonella typhosa	1 : 8,000	1 : 4,000	1 : 16,000	1 : 8,000
Flexner's dysentery bacillus	1 : 8,000	1 : 4,000	1 : 8,000	1 : 8,000
Dysentery bacillus of strain PW_3	1 : 16,000	1 : 8,000	1 : 16,000	1 : 8,000
Bacillus pyocyaneus	0	0	0	0
Proteus vulgaris	1 : 8,000	1 : 2,000	1 : 4,000	1 : 8,000
Anthrax spores	1 : 8,000	1 : 4,000	1 : 8,000	1 : 8,000
Bacillus of avian tuberculosis	1 : 8,000	1 : 2,000	1 : 60,000	1 : 125,000
Acid-resistant saprophyte B_5	1 : 8,000	1 : 2,000	1 : 16,000	1 : 30,000
Myxosporon	1 : 4,000	1 : 4,000	1 : 16,000	1 : 4,000
Trichophyton	1 : 2,000	1 : 4,000	1 : 8,000	1 : 2,000
Achorion	1 : 4,000	1 : 4,000	1 : 8,000	1 : 4,000
Actinomycetes	1 : 4,000	1 : 8,000	1 : 8,000	1 : 4,000
Yeast-like fungus (candida alb.)	1 : 1,000	1 : 1,000	1 : 4,000	1 : 4,000

is not active, while substance IIIa possesses weak activity, giving no basis for recommending the preparation for practical use.

EXPERIMENTAL

2-Nitrobenzimidazole (I). Produced according to [2]; mp 258° (decomp.).

Sodium Salt of 2-Nitrobenzimidazole (II). Into a solution of sodium ethylate (from 0.031 g of sodium and 5 ml of alcohol) we introduced 0.19 g of I. The salt II thereupon formed precipitated when ether was added to the alcohol solution. The salt II is readily soluble in water, and does not melt when heated to 350°. Found, %: C 45.24; H 2.27; Na 12.63. $C_7H_4N_3NaO_2$. Calculated, %: C 45.42; H 2.18; Na 12.42.

1-Methyl-2-nitrobenzimidazole (IIIa). A. To a solution of 0.163 g I in 4 ml of alcoholic alkali, containing 0.08 g potassium hydroxide, we added 0.35 ml of methyl iodide. The mixture was boiled for 1 h, cooled, and the crystals of IIIa filtered off and washed with water. Yield 0.15 g (85%), mp 170° (from alcohol). λ_{max} (in methanol): 335 nm, log ε 3.40; λ_{max} (in 8.25 M solution of sulfuric acid): 340 nm, log ε 4.06, ν 1326, 1546 cm^{-1} (NO_2 group). Found, %: C 53.91; H 4.15. $C_8H_7N_3O_2$. Calculated, %: C 54.23; H 3.98.

B. A solution of 0.156 g diazomethane in 40 ml of ether was added to 0.26 g I. Thereupon vigorous evolution of nitrogen was observed. On the following day the ether was distilled off. Yield of IIIa 0.27 g (96%), mp 170°.

1-Ethyl-2-nitrobenzimidazole (IIIb). Produced by alkylation of I in alcoholic alkali with ethyl iodide analogously to IIIa. Yield 79.3%, mp 105° (from methanol). Found, %: C 56.51; H 4.87. $C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.75.

1-Benzyl-2-nitrobenzimidazole (IIIc). A saturated aqueous solution of 0.25 g dimethylphenylbenzylammonium chloride was added to a solution of 0.163 g I and 0.1 g potassium hydroxide in 3 ml of water. The mixture was heated for 30 min on a water bath, and then the dimethylaniline that separated out was distilled off. The viscous red oil isolated after cooling was extracted with chloroform. The extract was passed through a column with aluminum oxide (eluent – chloroform). IIIc travels with the solvent front and is readily separated from impurities. Yield 0.13 g (52%), mp 107° (from methanol). Found, %: C 66.32; H 4.30. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.39; H 4.38.

Interaction of 1-Methyl-2-nitrobenzimidazole (IIIa) with Sodium Ethylate. A mixture of 0.15 g IIIa and sodium ethylate (from 0.08 g of sodium) in 7 ml of absolute alcohol was boiled for 15 h. The solution was filtered, the alcohol distilled off, and the residue washed with water. The yield of technical 1-methyl-2-ethoxybenzimidazole (IVa) was 0.12 g (80.5%). Picrate: mp 163-164° (from alcohol), according to the literature data [3], mp 152-153°. Found, %: C 47.40; H 3.86. $C_{10}H_{12}N_2O$. $C_6H_3N_3O_7$. Calculated, %: C 47.41; H 3.37.

Interaction of 1-Methyl-2-nitrobenzimidazole (IIIa) with Benzylamine. A mixture of 0.25 g IIIa, 0.32 g benzylamine, and 5 ml of xylene was heated for 2 h at 90-100° and for 2 h at 120-130°. After cooling, crystals of 1-methyl-2-benzylaminobenzimidazole (IVb) precipitated from the solution. Yield 0.25 g (75%), mp 167° (from methanol). A mixed sample with known IVb showed no depression of the melting point.

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