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FORMATION OF 2H-BENZIMIDAZOLE-1,3-DIOXIDES BY REACTION OF BENZOFUROXANS WITH ALCOHOLS AND ALKYL HALIDES IN THE PRESENCE OF ACIDS

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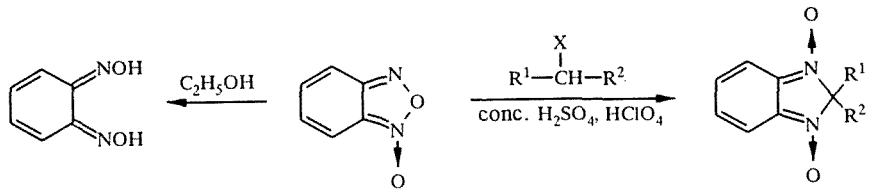
Reaction of benzofuroxan and 5-nitrobenzofuroxan with alcohols and alkyl halides in concentrated sulfuric or perchloric acid leads to the formation of 2H-benzimidazole-1,3-dioxides.

The furoxan ring of benzofuroxans is readily converted to other heterocycles by nucleophilic reagents but at the same time it is fairly stable towards electrophilic reagents; only very strong alkylating agents such as alkyl esters of trifluoromethanesulfonic acid open up the ring to form benzimidazole-1-oxide derivatives [1, 2]. Taking these facts into consideration, it was hard to expect that benzofuroxans would react with alcohols and alkyl halides. It transpired, however, that benzofuroxan Ia readily reacts with isopropanol, cyclopentanol, cyclohexanol, and benzhydrol in concentrated sulfuric or perchloric acids at 20-40°C to form the corresponding 2H-benzimidazole-1,3-dioxides IIa-c, e in high yield. The reaction of benzofuroxan with 1-phenylethanol in perchloric acid yields 2-phenyl-2-methyl-2H-benzimidazole-1,3-dioxide (IIf), whereas only o-benzoquinone dioxime (III) was isolated when this reaction was carried out in concentrated sulfuric acid. Only compound III was isolated again when the reaction with ethanol was carried out in both concentrated sulfuric and perchloric acid. Benzofuroxan reacts with the primary alcohols propanol and butanol to form 2H-benzimidazole-1,3-dioxide (IIa) and 2-methyl-2-ethyl-2H-benzimidazole-1,3-dioxide (IId), respectively. Alkyl halides also readily react with benzofuroxans in these acids to form the corresponding 2H-benzimidazole-1,3-dioxides, as demonstrated by us in the case of 2-propyl bromide, cyclohexyl chloride, and 1-butyl bromide.



III Ia IIa-f

X = OH, Cl, Br; IIa $R^1 = R^2 = CH_3$, b $R^1 + R^2 = -(CH_2)_4-$, c $R^1 = R^2 = -(CH_2)_5-$, d $R^1 = CH_3$; $R^2 = C_2H_5$, e $R^1 = R^2 = C_6H_5$, f $R^1 = CH_3$; $R^2 = C_6H_5$

5-Nitrobenzofuroxan Ib also readily reacts with alcohols and alkyl halides to form the corresponding 2H-benzimidazole-1,3-dioxides IVa, b. It should be noted that the general method for synthesizing 2H-benzimidazole-1,3-dioxides is based on the reactions of benzofuroxans with nitroalkanes; at the same time it was reported [3] that with nitro derivatives of benzofuroxan, including 5-nitrobenzofuroxan, 2H-benzimidazole derivatives are not formed and tar formation occurs.

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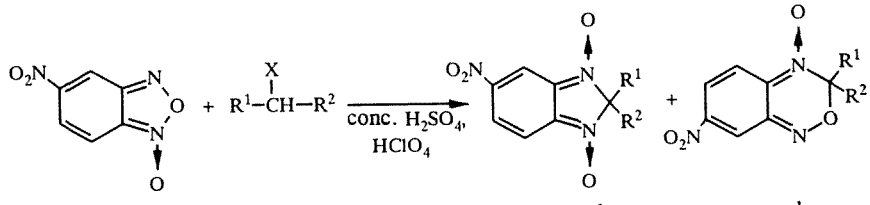
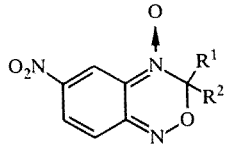
TABLE 1. Properties of Compounds Synthesized

Compound	Empirical formula	mp, °C	UV spectrum, λ_{max} (log ε)	Yield, %
IId	$C_{10}H_{12}N_2O_2$	128...129	210(3,93); 249(4,43); 530(3,90)	65
IIe*	$C_{19}H_{14}N_2O_2$	50...51	210(4,38); 250(4,13); 400(3,04); 540(3,50)	25
IVa	$C_9H_9N_3O_4$	154...156	228(4,13); 262(4,16); 333(3,96); 560(3,58)	79
IVb	$C_{12}H_{13}N_3O_4$	122...124	224(4,03); 268(4,02); 330(3,76); 560(3,46)	80
Va	$C_9H_9N_3O_4$	89...91	208(4,20); 245(4,11); 312(4,01); 465(3,60)	8
Vb	$C_{12}H_{13}N_3O_4$	171...173	210(4,04); 240(3,94); 280(3,83); 315(3,55); 410(3,78); 455(3,48)	8

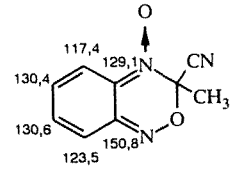
*Compound IIe was reported in [5], but none of its properties were given, so we considered it necessary to list our data on it.



Ib IV a,b V a,b



VIa,b



VII

X = OH, Br; IV—VI a $R^1 = R^2 = CH_3$, b $R^1 + R^2 = -(CH_2)_5-$

In addition to the main products — IVa, b — from the reaction between nitrobenzofuroxan Ib and alcohols and alkyl halides, we have isolated in low yield (~8%) in all cases from the reaction mixture compounds which on the basis of the spectroscopic data and elemental analysis have been assigned the structure of the corresponding 7-nitro-3,3-dialkyl-2,1,4-benzoxadiazine-4-oxides (Va, b). The choice between the possible isomeric structures VI and V was made by comparing the ^{13}C NMR spectra of the synthesized compounds Va, b with those of the known 3-methyl-3-cyano-2,1,4-benzoxadiazine-4-oxide (VII) [4], taking into account the fact that an electron-withdrawing group located next to a carbon atom will displace its signal to higher field. If the compound had structure VI, the chemical shift of the $C_{(5)}$ atom should be less than 117.4 ppm while in structure Va, b the nitro group will reduce the chemical shift of the $C_{(6)}$ and $C_{(8)}$ atoms. The latter occurs in the ^{13}C NMR spectra of compounds Va, b (see Table 3).

It may be assumed from the experimental data that the reaction of benzofuroxans with alcohols and alkyl halides occurs by a route similar to that reported in a previous monograph [1]. The carbocation formed from the alcohol or alkyl halide attacks the benzofuroxan molecule on the nitrogen atom at the 3-position. The resulting adduct A isomerizes with ring-opening to cation B, which by losing a proton is converted to the nitrosonitrone C. Ring-closure in the latter leads either to 2H-benzimidazole-1,3-dioxide, as in the case of nucleophilic attack by the nitrogen atom of the nitroso group, or to benzoxadiazine-N-oxide, when there is nucleophilic attack by the oxygen atom on the nitrone group. When only an unstable primary carbocation can be formed (such as $CH_3C^+H_2$ from ethanol), only reduction of the furoxan ring occurs. However, if it is possible for the primary cation

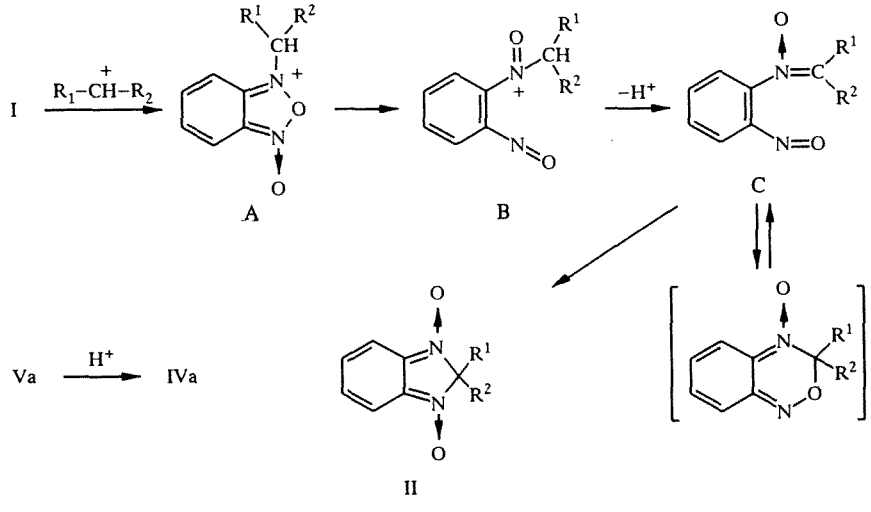
TABLE 2. PMR Spectra of Compounds Synthesized

Compound	δ, ppm in $CDCl_3$, spin-spin coupling constant (J), Hz
IId	0,48 (3H, t, CH_3); 1,48 (3H, s, CH_3); 1,97 (2H, q, CH_2); 6,68...6,78 (2H, m, =CH); 7,00...7,06 (2H, m, =CH)
IIe	6,41...6,96 (2H, m, =CH); 7,17...7,37 (2H, m, =CH); 7,43 (10H, s, 2Ph)
IVa	1,65 (6H, s, $2CH_3$); 7,32 (1H, d, =CH, J_{AB} = 8); 7,49 (1H, d, =CH, J_{AB} = 8); 8,09 (1H, s, =CH)
IVb	1,48...1,53 (2H, m, CH_2); 1,80...2,00 (8H, m, $4CH_2$); 7,26 (1H, d, =CH, J_{AB} = 8); 7,45 (1H, d, =CH, J_{AB} = 8); 8,04 (1H, s, =CH)
Va	1,67 (6H, s, $2CH_3$); 7,30 (2H, s, 2=CH); 7,91 (1H, s, =CH)
Vb	1,10...2,12 (10H, m, $5CH_2$); 7,32 (1H, d, =CH, J_{AB} = 8); 7,92 (1H, d, =CH, J_{AB} = 8)

TABLE 3. Chemical Shifts in the ^{13}C NMR Spectra of Compounds IVa, b and Va, b in $CDCl_3$

Compound	C—NO_2	C=N	CH	C	CH_2, CH_3
IVa	149,1	135,3, 135,7	113,5, 123,5, 117,3	99,5	23,6
IVb	149,7	135,2, 135,3	113,3, 122,9 116,9	99,9	33,5, 18,5, 23,6
Va	148,9	148,4, 128,9	120,9, 122,5, 123,3	96,6	20,5
Vb	149,5	148,5, 129,3	120,4, 121,2, 123,4	97,5	28,7, 21,8, 24,3

to undergo isomerization to a more stable secondary cation, as in the case of 1-butanol, the reaction pathway leading to the corresponding 2H-benzimidazole-1,3-dioxide can occur (depicted in the following scheme).



The predominance of 2H-benzimidazole-1,3-dioxide in the reaction mixture is due to its greater stability in an acid medium. Thus, when benzoxadiazine-N-oxide Va is dissolved in sulfuric acid and poured into water, 2H-benzimidazole-1,3-dioxide IVa is formed almost quantitatively.

Thus, in the present study we have found a new method for the synthesis of 2H-benzimidazole-1,3-dioxides, which can be used in the synthesis of heterocyclic compounds, as was demonstrated in a recent study [6].

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument in KBr (concentration 0.25%). The UV spectra were recorded on a Specord UV-vis instrument; the PMR spectra were recorded on a Varian A-56-60 instrument and the ^{13}C NMR spectra recorded on a WP-200 spectrometer. The melting points were determined on a Kofler hot-stage microscope. Elemental analysis of the compounds was carried out in the microanalysis laboratory of the Institute of Organic Synthesis, Siberian Branch, Russian Academy of Sciences. The properties of the compounds synthesized are listed in Tables 1-3.

The elemental analysis data for the compounds synthesized corresponded to the calculated values.

Reaction of Benzofuroxan Ia with Alcohols and Alkyl Halides

2,2-Dimethyl-2H-benzimidazole-1,3-dioxide (IIa). To a solution of 1.36 g (0.01 mole) of benzofuroxan Ia in 10 ml of concentrated sulfuric acid was added dropwise 1 ml (0.017 mole) of isopropanol, maintaining the temperature of the reaction mass at about 40°C. The reaction mixture was kept for 2 h at room temperature then poured into 100 ml of ice-water. The product was extracted with chloroform (4 × 50 ml), the extract was washed with water, dried over magnesium sulfate, and evaporated, the residue was ground with hexane, and the crystalline product was filtered off. Yield 1.34 g (75%) of compound IIa, whose spectroscopic properties and melting point are exactly the same as those given in the literature [3].

In a similar manner starting from 1-propanol, 1-butanol, cyclopentanol, cyclohexanol, or benzhydrol, products IIa (60%), IId (65%), IIb (72%), IIc (78%), and IIe (25%) were obtained, respectively.

After reaction with 1-phenylethanol and ethanol under the conditions described above, benzoquinone dioxime III was obtained in about 60% yield by extraction from the reaction mixture with ethyl acetate.

2-Propyl bromide, cyclohexyl chloride, and 1-butyl bromide, when the reaction mixture was maintained at 40°C for 2 h, gave dioxides IIa (60%), IIc (62%), and IId (60%), respectively.

2-Phenyl-2-methyl-2H-benzimidazole-1,3-dioxide (IIf). To a solution of 1.36 g (0.01 mole) of benzofuroxan in 10 ml of perchloric acid was added 1.3 ml (0.01 mole) of 1-phenylethanol, and the mixture was maintained at 40°C for 2 h. The mixture was poured into 100 ml of ice-water and extracted with chloroform (4 × 50 ml). The extract was washed with water, dried over magnesium sulfate, and evaporated, the residue was ground with hexane, and the crystals were filtered off. Yield 0.96 g (40%) of product IIf [3].

Compounds IIa (68%), IIb (70%), and IIc (75%) were synthesized in a similar manner from the respective alcohols.

Reaction of 5-Nitrobenzofuroxan Ib with Alcohols and Alkyl Halides

2,2-Dimethyl-5-nitro-2H-benzimidazole-1,3-dioxide (IVa) and 3,3-Dimethyl-7-nitro-2,1,4-benzoxadiazine-4-oxide (Va). To a solution of 1.81 g (0.01 mole) of 5-nitrobenzofuroxan Ib in 10 ml of concentrated sulfuric acid was added dropwise 1 ml (0.017 mole) of isopropanol, and the mixture was kept for 2 h at room temperature. It was then poured into 100 ml of ice-water and extracted with chloroform (4 × 50 ml). The extract was dried over magnesium sulfate and evaporated, and the residue was chromatographed on silica gel with chloroform as eluant. Compounds Va (0.18 g) and IVa (1.78 g) were isolated.

2,2-Spirocyclohexane-5-nitro-2H-benzimidazole-1,3-dioxide (IVb) and 3,3-spirocyclohexane-7-nitro-2,1,4-benzoxadiazine-4-oxide (Vb) were obtained under similar conditions from cyclohexanol, while compounds IVb (65%), Vb (6%) and IVa (70%), Va (4%) were obtained, respectively, from chlorocyclohexane and 2-bromopropane.

Isomerization of Oxide Va to Dioxide IVa. To 5 ml of concentrated sulfuric acid was added 0.5 g of benzoxadiazine Va and the mixture was kept at room temperature for 10 min, then poured into 50 ml of ice-water, and extracted with chloroform (4 × 20 ml). The extract was washed with water, dried over magnesium sulfate, evaporated, and the residue was ground with hexane to give 0.47 g (94%) of compound IVa.

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