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Reactions of 4-Oxo-1,3-Benzoxazinium Perchlorates with Sodium Borohydride

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Abstract—Reduction of 4-oxo-1,3-benzoxazinium perchlorates with sodium borohydride depending on the structure of starting salt and the reaction conditions leads to different products. 2-Alkyl- and 2-phenylsubstituted salts react with sodium borohydride to give 2,3-dihydro-4-oxo-1,3-benzoxazines. 2-Arylvinyl- and 2-heterylvinyl-substituted perchlorates either form 4-oxo-1,3-benzoxazines or undergo hydrogenation to aryl- or heterylethyldihydrobenzoxazinones.

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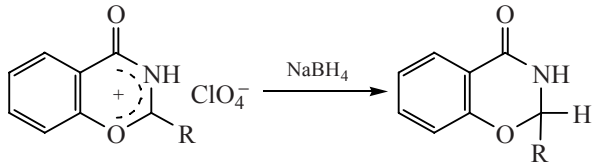
Substances of 4-oxo-1,3-benzoxazine series exhibit interesting biological activity. In detail, among the derivatives of 4-oxo-1,3-benzoxazines are found compounds posessing the antiichemic action [1].

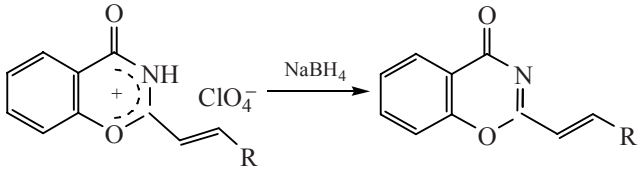
With the purpose of searching new potentially biologically active compounds we have involved 4-oxo-1,3-benzoxazinium perchlorates **Ia, b**, **IIIa–IIIf** [2] in the reaction with sodium borohydride. It occured that in the case of 2-alkyl- and 2-phenylsubstituted 4-oxo-1,3-benzoxazinium salts **Ia, Ib** C=O group does not react with sodium borohydride in acetonitrile, and the reduction proceeds at the electronodeficient position 2 of heteroring with formation of 2,3-dihydro-4-oxo-1,3-benzoxazines **IIa, IIb**.



I **II**

R = CH_3 (**a**), Ph (**b**).

2-Arylvinyl- and 2-heterylvinyl substituted 4-oxo-1,3-benzoxazinium perchlorates **III** prepared according to [3, 4] react with $NaBH_4$ ambiguously depending on their structure and the reaction conditions. When methoxyphenyl- and indolylvinyl substituted perchlorates **IIIa, IIIb** are involved in the reaction no formation of 2,3-dihydro-4-oxo-1,3-benzoxazines of the type **II** takes place at room temperature as well as on boil. The only process observed is deprotonation of salts leading to formation of 4-oxo-1,3-benzoxazines **IVa, IVb**.

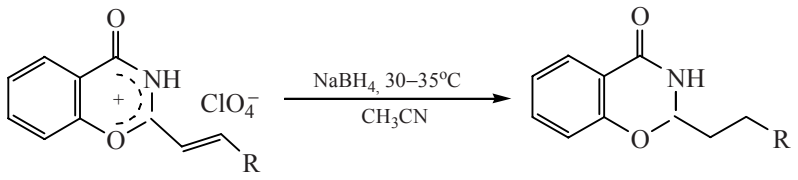


IIIa, IIIb **IVa, IVb**

R = 4-$CH_3OC_6H_4$ (**a**); indol-3-yl (**b**).

It is connected probably with low solubility of benzoxazines **IVa, IVb** in acetonitrile that prevents further hydrogenation.

When perchlorates **IIIc–IIIe** are reacted with $NaBH_4$ instead of the expected aryl- and heterylvinyl-dihydrobenzoxazinones analogous to **II** were isolated aryl- and heterylethylbenzoxazinones **Vc–Ve**. In this case hydrogenation proceeds at the position 2 of heteroring as well as at the double bond of substituent.



IIIc–IIIe **Vc–Ve**

R = thienyl (**c**), Ph (**d**), 4-F-C_6H_4 (**e**).

Such unusual reaction pathway may be explained probably by activation of C=C bond of the substituent with the adjacent electronodeficient carbon atom in the position 2 of heteroring of perchlorates **III** or corresponding benzoxazinones **IV**.

Reaction of perchlorate **IIIf** with $NaBH_4$ proceeding at 20–23°C yields arylvinyl benzoxazinone **IVf** while at 30–35°C arylethyl-substtituted dihydrobenzoxazinone **Ve** is formed.

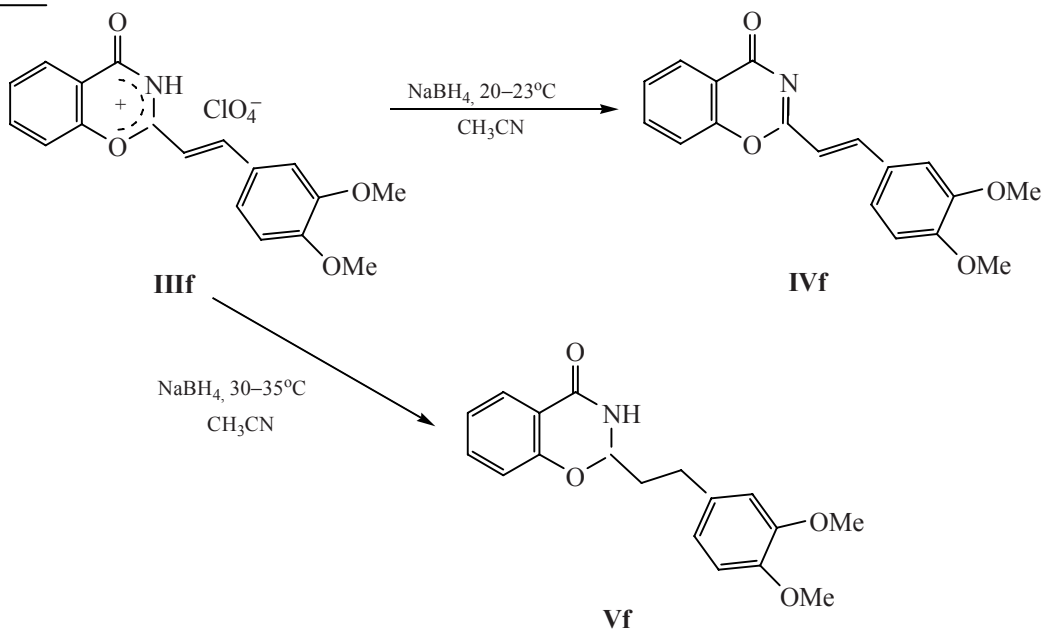
The composition and structure of the compounds obtained were confirmed by elemental analysis data and the IR and NMR spectroscopy. In the IR spectra of benzoxazinones **IV** the absorption band of high intensity at 1693–1680 cm^{-1} belonging to C=O group is observed. Two strong bands at 1660–1590 cm^{-1} relate to C=C and C=N bonds. In ^1H NMR spectra of these compounds AB-system of the CH=CH protons is observed at 6.7–8.4 ppm, and the multiplet of aromatic protons is located in the range 6.75–8.2 ppm.

Presence of two characteristic absorption bands in the IR spectra of dihydrobenzoxazinones **Vc–Vf** in the range 3200–3167 cm^{-1} and at 3086 cm^{-1} is caused by the symmetric and asymmetric bond vibrations of NH group. IR spectra contain also the band of high intensity at 1690–1687 cm^{-1} attributed to C=O group and two strong bands of aromatic absorption at 1620–1587 cm^{-1}. ^1H NMR spectra of these compounds are also characteristic. The triplet at 2.1–2.2 ppm and the multiplet at 2.6–3.1 ppm relate to β- and α-methylene protons of substituent. The triplet of methine proton at 5.2 ppm and the singlet of NH proton at 8.7 ppm together with the signals of aromatic protons tell in favor of formation of 2-arylethyl- and 2-heterylethyldihydrobenzoxazinones.

EXPERIMENTAL

^1H NMR spectra were taken on a Varian Unity 250 (250 MHz) spectrometer in DMSO-d_6. IR spectra were recorded on a Specord IR-75 spectrometer in vaseline oil. Elemental analysis was carried out on an automatic Perkin-Elmer 2400 CHN-analyzer.

Perchlorates **I, III** were prepared according to [2–4].



IIIf **IVf**

Vf

2-Methyl-2,3-dihydro-4-oxo-1,3-benzoxazine (IIa). To a suspension of 2.61 g of perchlorate **Ia** in 20 ml of acetonitrile 0.65 g of sodium borohydride was added slowly. The reaction mixture was handled at room temperature for 20 h. After that 150 ml of water were added, and the precipitate formed was filtered off. Yield 68%, colorless crystals, mp 145ºC (from aqueous methanol). IR spectrum, ν, cm^{-1}: 3175 and 3080 (NH), 1696 (C=O), 1613 and 1582 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.65 d (3H, CH_3, *J* 5.61 Hz), 5.41 q (1H, CH), 6.85–7.45 m (4H, ArH), 8.81 d (1H, NH). Found, %: C 66.45; H 5.31; N 8.67. $C_9H_9NO_2$. Calculated, %: C 66.26; H 5.52; N 8.59.

2-Phenyl-2,3-dihydro-4-oxo-1,3-benzoxazine (IIb). This compound was prepared analogously, yield 55%, colorless crystals, mp 168-169&ºC. IR spectrum, ν, cm^{-1}: 3180 and 3078 (NH), 1688 (C=O), 1611 and 1579 ($C=C_{arom}$). Found, %: C 74.45; H 4.91; N 6.37. $C_{14}H_{11}NO_2$. Calculated, %: C 74.67; H 4.89; N 6.22.

2-[2-(4-Methoxyphenyl)vinyl]-4-oxo-1,3-benzoxazine (IVa). To a suspension of 2.14 g of perchlorate **IIIa** in 12 ml of acetonitrile 0.38 g of finely pulverized $NaBH_4$ was added slowly (to avoi foaming) at room temperature or at 35ºC. The reaction mixture was left for 10 h and then treated with 50 ml of cold water. The crystals formed were filtered off and crystallized from butanol. Yellow crystals with mp 210ºC were obtained, yield 0.71 g (40%). IR spectrum, ν, cm^{-1}: 1680 (C=O), 1620 and 1590 (C=C and C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.85 s (3H, OCH_3), 6.78 d (1H, CH, *J* 15.1 Hz), 6.98 d (2H, ArH, *J* 9.2 Hz), 7.48–8.08 m (7H, ArH, CH). Found, %: C 71.95; H 4.81; N 5.20. $C_{16}H_{13}NO_3$. Calculated, %: C 71.90; H 4.90; N 5.24.

2-[2-(1*H*-Indol-3-yl)vinyl]-4-oxo-1,3-benzoxazine (IVb) was obtained analogously and crystallized from butanol. Yellow crystals, mp 305ºC, yield 42%. IR spectrum, ν, cm^{-1}: 3273 (NH), 1693 (C=O), 1880 and 1620 (C=C and C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.71 d (1H, CH, *J* 6.3 Hz), 7.11-8.22 m (9H, ArH), 8.41 d (1H, CH, *J* 6.3 Hz), 12.12 s (1H, NH). Found, %: C 74.90; H 4.31; N 9.90. $C_{18}H_{12}N_2O_2$. Calculated, %: C 74.99; H 4.20; N 9.97.

2-[2-(3,4-Dimethoxyphenyl)vinyl]-4-oxo-1,3-benzoxazine (IVf) was obtained analogously to compound **IVa** at 20–23ºC. Yellow crystals, mp 305ºC (from isobutanol), yield 48%. IR spectrum, ν, cm^{-1}: 1690 (C=O), 1660 and 1620 (C=C and C=N), ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.82 s (3H, OCH_3), 3.91 s (3H, OCH_3), 6.75-8.12 m (9H, ArH, CH=CH). Found, %: C 79.95; H 4.81; N 4.46. $C_{18}H_{15}NO_4$. Calculated, %: C 69.89; H 4.89; N 4.53.

2-[2-(2-Thienyl)ethyl]-2,3-dihydro-4-oxo-1,3-benzoxazine (Vc). To a suspension of 3.85 g of perchlorate **IIIc** in 22 ml of acetonitrile 0.72 g of sodium borohydride was added slowly to avoid foaming at 30–35ºC. The reaction mixture was handled at 30ºC for 15 h. After that 50 ml of cold water was added, and the precipitate formed was filtered off and crystallized from propanol-2. Brown crystalline powder was obtained, mp 140–142ºC, yield 1.59 g (50%). IR spectrum, ν, cm^{-1}: 3160 and 3086 (NH), 1687 (C=O), 1625, 1620 ($C=C_{arom}$). ^1H NMR spectrum δ, ppm: 2.21 t (2H, CH_2), 2.91–3.12 m (2H, CH_2), 5.25 t (1H, 2-CH), 6.91–7.91 m (7H, ArH), 8.72 s (1H, NH). Found, %: C 64.80, H 5.11, N 5.35, S 11.10. $C_{14}H_{13}NO_2S$. Calculated, %: C 64.84, H 5.05, N 5.40, S 11.02.

2-(2-Phenylethyl)-2,3-dihydro-4-oxo-1,3-benzoxazine (Vd) was obtained analogously. White crystals, mp 141–143ºC (from octane), yield 52%. IR spectrum, ν, cm^{-1}: 3167 and 3086 (NH), 1687 (C=O), 1607 and 1587 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 2.12 t (2H, CH_2), 2.71–3.12 m (2H, CH_2), 5.21 t (1H, 2-CH), 6.81–7.51 m (8H, ArH), 7.82 d (1H, ArH), 8.71 s (1H, NH). Found, %: C 75.75; H 5.88; N 5.26. $C_{16}H_{15}NO_2$. Calculated, %: C 75.87; H 5.97; N 5.53.

2-[2-(4-Fluorophenyl)ethyl]-2,3-dihydro-4-oxo-1,3-benzoxazine (Ve) was obtained analogously to compound **Vc.** Colorless crystals, mp 135–137ºC (from propanol-2), yield 47%. IR spectrum, ν, cm^{-1}: 3200 and 3086 (NH), 1690 (C=O), 1600 and 1590 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.11 t (2H, CH_2), 2.71–2.92 m (2H, CH_2), 5.21 t (1H, 2-CH), 6.81–7.42 m (7H, ArH), 7.81 d (1H, ArH, *J* 6.2 Hz), 8.71 s (1H, NH). Found, %: C 69.70; H 5.17; F 6.20; N 5.50. $C_{15}H_{13}FNO_2$. Calculated, %: C 69.76; H 5.07; F 6.20; N 5.42.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3-dihydro-4-oxo-1,3-benzoxazine (Vf) was prepared analogously to compound **Vc**. Colorless crystals, mp 140ºC (from butanol), yield 52%. IR spectrum, ν, cm^{-1}: 3160 and 3086 (NH), 1680 (C=O), 1620 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 2.11 t (2H, CH_2), 2.61–2.91 m (2H, CH_2), 3.71 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.21 t (1H, 2-CH), 6.71–7.12 m (5H, ArH), 7.41–7.92 m (2H, ArH), 8.17 s (1H, NH). Found, %: C 69.32; H 7.10; N 4.26. $C_{18}H_{19}NO_4$. Calculated, %: C 69.28; H 7.04; N 4.25.

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