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Thienooxazolopyrimidinium Salts. Reaction of 1-Bromomethyl-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydro[1]benzothieno-[3,2-*e*][1,3]oxazolo[3,2-*a*]pyrimidin-11-ium Bromide with Oxygen-Centered Nucleophiles*

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Abstract—Reactions of [1]benzothieno[3,2-*e*][1,3]oxazolo[3,2-*a*]pyrimidin-11-ium bromide with oxygen-containing nucleophiles involve opening of the dihydrooxazole ring and lead to the formation of new functionally substituted thieno[2,3-*d*]pyrimidine derivatives.

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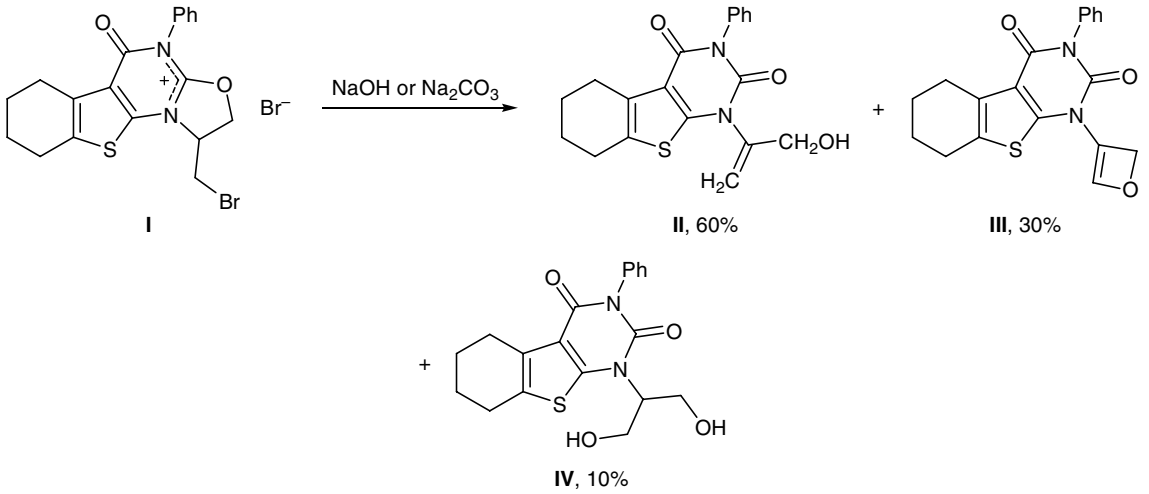
Derivatives of thieno[2,3-*d*]pyrimidine attract considerable interest as potential physiologically active substances. It is well known [2, 3] that thienopyrimidine fragment is a pharmacophore which endows compounds with strong analgetic and antiphlogistic properties. The chemical properties of fused thienopyrimidines were described in [4–6].

We previously reported on the synthesis of [1]benzothieno[3,2-*e*][1,3]oxazolo[3,2-*a*]pyrimidin-11-ium bromide **I** and showed that this salt is fairly stable to heating and to the action of such a weak nucleophile as sodium acetate [1]. In the present work we examined reactions of bromide **I** with stronger O-centered nucleophiles, sodium carbonate and sodium hydroxide with a view to obtain new functionalized derivatives of the thieno[2,3-*d*]pyrimidine system.

The reactions of salt **I** with nucleophiles were carried out in various solvents at various temperatures. No dihydrooxazole ring opening occurred under the action of sodium carbonate and sodium hydroxide in

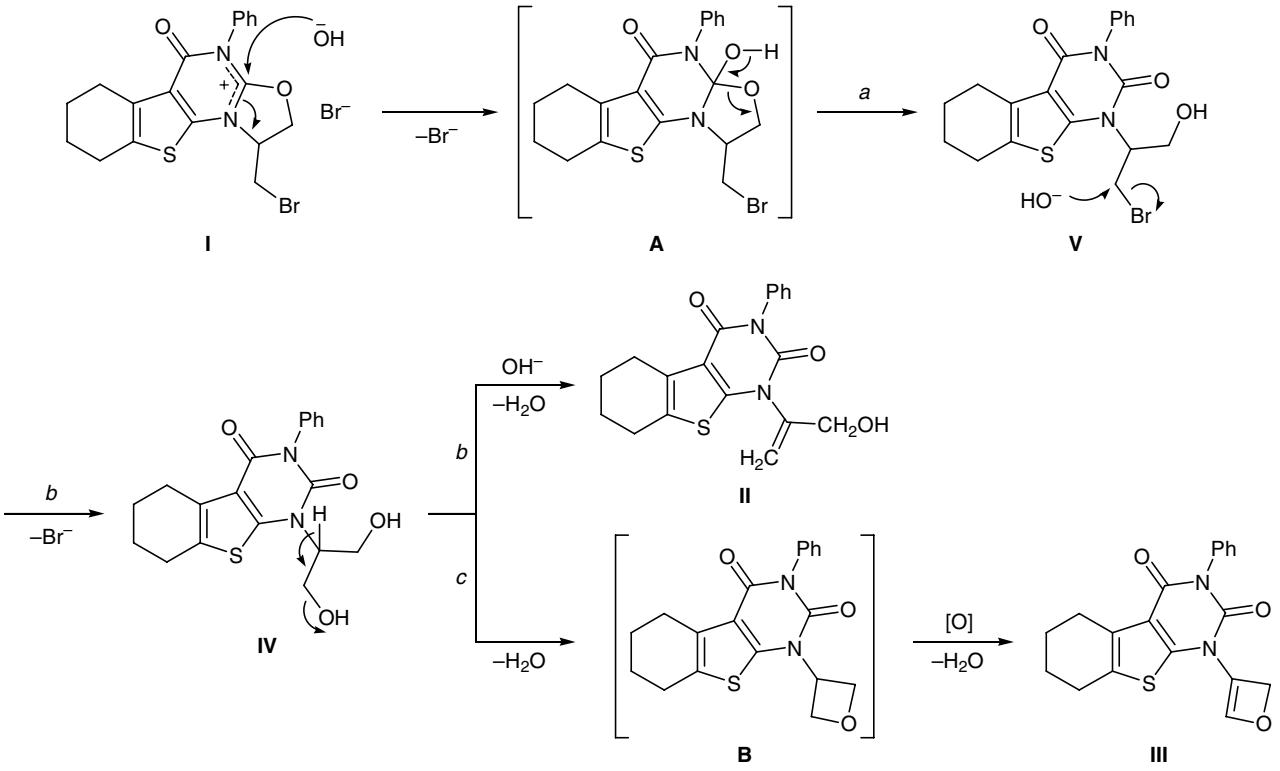
Scheme 1.



I **II**, 60% **III**, 30% **IV**, 10%

* For preliminary communication, see [1].
† Deceased.

Scheme 2.



aqueous medium and in ethanol both under usual conditions and on heating; in these cases, the initial bromide was recovered from the reaction mixtures. We succeeded in effecting nucleophilic cleavage of the dihydrooxazole ring in **I** by the action of aqueous sodium carbonate on a solution of salt **I** in DMSO on heating for 4 h, as well as by the action of aqueous sodium hydroxide on a solution of **I** in DMSO both on heating and at room temperature (Scheme 1).

According to the TLC and ^{1}H NMR data, the reactions of salt **I**, unlike its sulfur-containing analogs [5], with sodium carbonate and hydroxide were not selective; as a result, several alkaline hydrolysis products (thienopyrimidines **II**–**IV**) were formed; the yields of the hydrolysis products (Scheme 1) were calculated from the relative intensities of the methylene proton signals from compounds **II** and **III** and of the methine proton signal from **IV** in the ^{1}H NMR spectrum. Compound **IV** was identified by comparing the ^{1}H NMR spectrum of the product mixture with the spectrum recorded by us previously [6] for the alkaline hydrolysis product of salt **I**, obtained by the action of sodium acetate. The fraction of compound **IV** among the hydrolysis products increased with rise in the concentration of sodium carbonate and increase in the reaction time.

Individual compounds **II** and **III** were isolated by successive crystallization of the product mixture from ethanol, reprecipitation, and repeated crystallization from 50% aqueous ethanol or hexane–acetone (2:1). Their structure was determined on the basis of the ^{1}H NMR and IR spectra. The ^{1}H NMR spectra of **II** and **III** lacked *ABX* pattern typical of initial salt **I**, which indicated cleavage of the dihydrooxazole ring. The spectrum of the major hydrolysis product, compound **II**, contained signals from protons in the cyclohexene and benzene rings, a signal at δ 4.81 ppm from the methylene protons, and singlets from the methylidene group at δ 5.78 and 6.14 ppm. The hydroxy group in thienopyrimidine **II** gave rise to a broad IR absorption band in the region 3600–3400 cm^{-1} (OH proton signal was not observed in the ^{1}H NMR spectrum of **II** due to exchange with deuterium). Compound **III** showed in the ^{1}H NMR spectrum a singlet from the methylene protons at δ 5.89 ppm; the signal from the =CH–O proton was located in the aromatic region as a result of strong deshielding effect produced by the neighboring heteroatoms.

Taking into account that the maximal positive charge is located on the bridgehead carbon atom in the pyrimidine ring [6, 7], the formation of alkaline hydrolysis products **II**–**IV** may be rationalized according

to Scheme 2. In the first step, nucleophilic attack by hydroxide ion on the bridgehead carbon atom in the pyrimidine ring gives pseudobase **A**. Cleavage of the dihydrooxazole ring in **A** gives alcohol **V** which is capable of undergoing different transformations. Compound **V** is formed as the final product in reactions with such a weak nucleophile as sodium acetate (as well as with sodium carbonate under certain conditions [6]. Stronger nucleophiles (sodium carbonate or hydroxide) promote subsequent replacement of the bromine atom in **V** by hydroxy group to give diol **IV**, and elimination of water molecule from the latter could yield unsaturated alcohol **II**. Another mode of dehydration of diol **IV** leads to the formation of four-membered cyclic ether **B** which undergoes dehydrogenation to compound **III**; here, DMSO in alkaline medium acts as oxidant [8].

Thus we have found that alkaline hydrolysis of [1]benzothieno[3,2-*e*][1,3]oxazolo[3,2-*a*]pyrimidin-11-ium bromide **I** in the presence of sodium acetate gives thienopyrimidine **V** as the major product as a result of cleavage of the dihydrooxazole ring [6]; reactions with stronger oxygen-centered nucleophiles (sodium carbonate and sodium hydroxide) are accompanied by nucleophilic replacement of the halogen atom in the bromomethyl group and subsequent elimination of water with formation of compound **II** and partial dehydrogenation to compound **III**. The examined reaction may be regarded as a new method for functionalization of thieno[2,3-*d*]pyrimidine derivatives.

EXPERIMENTAL

Thin-layer chromatography was performed at 27°C on Sorbfil plates (silica gel; ethanol–diethyl ether–hexane, 1:3:1; development with iodine vapor). The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra were measured on a Varian VXR-300 spectrometer (300 MHz) from solutions in DMSO-d_6 relative to tetramethylsilane as internal reference.

1-Bromomethyl-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydro[1]benzothieno[3,2-*e*][1,3]oxazolo[3,2-*a*]-pyrimidin-11-ium bromide (**I**) was synthesized by the procedure described in [6].

1-(1-Hydroxymethylvinyl)-3-phenyl-1,2,3,4,5,6,-7,8-octahydro[1]benzothieno[2,3-*d*]pyrimidine-2,4-dione (II). *a*. Salt **I**, 0.50 g (0.001 mol), was dissolved in 20 ml of DMSO on heating, a solution of 0.53 g (0.005 mol) of sodium carbonate in 5 ml of water was added under continuous stirring, and the mixture was stirred for 4 h at 70–80°C. The mixture was diluted with 100 ml of cold water, and the precipitate was filtered off and washed with 50 ml of warm water containing 1 ml of acetic acid. The crude product was treated with boiling ethanol, the mixture was cooled, the precipitate was filtered off, water was added to the filtrate, and the precipitate was filtered off and recrystallized from 50% aqueous ethanol. Yield 0.24 g (69%), mp 148–149°C.

b. Salt **I**, 0.50 g (0.001 mol), was dissolved in 20 ml of DMSO on heating, the solution was cooled to room temperature, and a solution of 0.08 g (0.002 mol) of sodium hydroxide in 5 ml of water was added under continuous stirring. The mixture was stirred for 1 h at room temperature and diluted with 100 ml of cold water. The precipitate was filtered off, washed with 50 ml of warm water, and treated with boiling ethanol; after cooling, the precipitate was filtered off, the filtrate was evaporated, and the solid residue was recrystallized from acetone–hexane (2:1). Yield 0.11 g (32%), mp 141–143°C.

c. The procedure was the same as described above in *b* with the difference that the reaction mixture was heated for 1 h at 70–80°C. Yield 0.17 (49%), colorless crystals, mp 141–143°C, R_f 0.78. IR spectrum, ν, cm^{-1}: 3400–3600 br (O–H), 1680 s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.75 m (4H, CH_2), 2.69 m (2H, CH_2), 2.76 m (2H, CH_2), 4.81–4.83 m (2H, CH_2), 5.78 s (1H, =CH_2), 6.14 s (1H, =CH_2), 7.25–7.51 m (5H, C_6H_5). Found, %: C 64.11; H 5.11; N 7.97; S 9.09. $C_{19}H_{18}N_2O_3S$. Calculated, %: C 64.41; H 5.08; N 7.91; S 9.04.

1-(2*H*-Oxet-3-yl)-3-phenyl-1,2,3,4,5,6,7,8-octahydro[1]benzothieno[2,3-*d*]pyrimidine-2,4-dione (III). *a*. Salt **I**, 0.50 g (0.001 mol), was dissolved in 20 ml of DMSO on heating, a solution of 0.53 g (0.005 mol) of sodium carbonate in 5 ml of water was added under continuous stirring, and the mixture was stirred for 4 h at 70–80°C and diluted with 100 ml of cold water. The precipitate was filtered off, washed with 50 ml of warm water containing 1 ml of acetic acid, and treated with boiling ethanol. After cooling, the precipitate was filtered off and recrystallized from ethanol or dimethylformamide. Yield 0.10 g (29%), mp 219–220°C (from DMF), 215–216°C (from EtOH).

b. Salt **I**, 0.50 g (0.001 mol), was dissolved in 20 ml of DMSO on heating, the solution was cooled to room temperature, and a solution of 0.08 g (0.002 mol) of sodium hydroxide in 5 ml of water was added under continuous stirring. The mixture was stirred for 1 h at

room temperature, and the hydrolysis product was isolated as described above in *a*. Yield 0.09 g (26%), mp 219–220°C (from DMF).

c. The procedure was the same as described above in *b* with the difference that the reaction mixture was heated for 1 h. Yield 0.11 g (32%), colorless crystals, mp 219–220°C (from DMF), 215–216°C (from EtOH), R_f 0.85. IR spectrum: ν(C=O) 1680 cm^{-1}, s. ^1H NMR spectrum, δ, ppm: 1.76 m (4H, CH_2), 2.71 m (2H, CH_2), 2.76 m (2H, CH_2), 5.89 s (2H, CH_2, oxete), 7.23–7.52 m (5H, C_6H_5, and 1H, =CH, oxete). Found, %: C 64.51; H 4.51; N 8.02; S 9.00. $C_{19}H_{16}N_2O_2S$. Calculated, %: C 64.77; H 4.55; N 7.95; S 9.09.

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