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Oxidation and Isomerism of Thietane-containing Heterocycles

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Abstract—Oxidation of 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione, 5(6)-nitro-1-(thiethan-3-yl)-benzimidazole, 2-methyl-4-nitro-1-(thiethan-3-yl)- and 5-bromo-2-methyl-4-nitro-1-(thiethan-3-yl)imidazoles was examined. Corresponding 1-oxothietan-3-yl- and 1,1-dioxothietan-3-yl derivatives were synthesized for the first time. Some factors affecting the quality of the final products and optimal conditions of the oxidation of thietanyl derivatives of pyrimidine-2,4(1*H*,3*H*)-dione, nitrobenzimidazole, and nitroimidazole were found. According to ^{1}H NMR spectroscopy data, the obtained sulfoxides are mixtures of *cis*/*trans* isomers, the diastereomers ratio determined by the substituent at position 3 of thietane ring.

Keywords: thiethane, pyrimidine, benzimidazole, imidazole, *cis*/*trans* isomerism

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Thietanylpyrimidines, thietanylbenzimidazoles, and thietanylimidazoles, the products of thiirane-thietane rearrangement, are representatives of a new series of hetaryl derivatives with four-membered sulfur-containing ring. In this work we studied stability of thietane ring in the oxidation reactions and the spectral features of new 1-oxothietanyl and 1,1-dioxothietanyl heterocycles.

To date, many methods of oxidation of organosulfur compounds including thiethanes has been known. In particular, thietanes readily give sulfoxides or sulfones upon oxidation with hydrogen peroxide, potassium permanganate, sodium periodate, and monoperoxyphthalic acid (solvents and the oxidizer concentration being variable) as well as in the course of photochemical oxidation [1–3]. In this work, we tested peracetic, *m*-chloroperbenzoic, and monoperphthalic acids, as well as hydrogen peroxide and potassium permanganate in acidic media as oxidants.

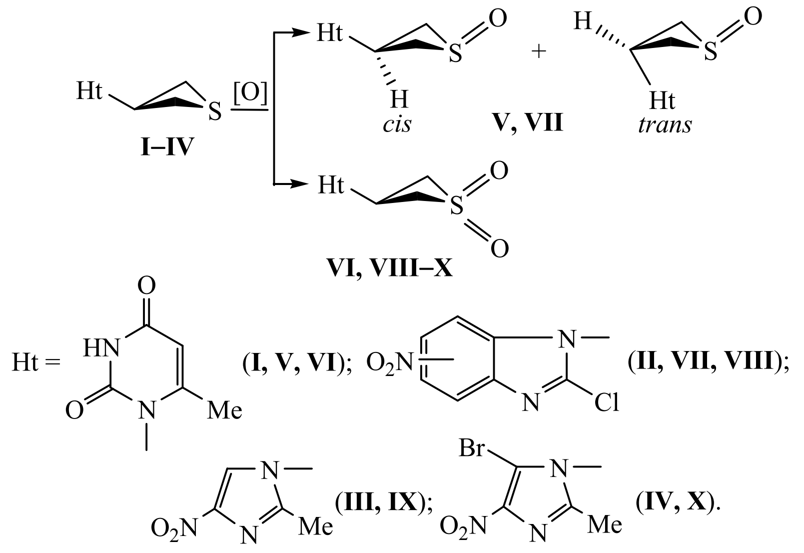
Oxidation of 6-methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **I** with 2 mol of hydrogen peroxide in acetic acid (room temperature, 1 hour) resulted in 6-methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **V**. Those reaction conditions were found to be optimal for preserving thietane ring intact. Increase in the amount of hydrogen peroxide up to 10 mol and maintaining the reaction mixture overnight at room temperature led to formation of sulfone **VI** with yield of 80%.

Selective oxidation of thietanylnitrobenzimidazole **II** into 5(6)-nitro-1-(1-oxothietan-3-yl)benzimidazole **VII** was performed upon heating (30°C, 12 h) in acetic acid using 0.8-fold molar amount of peracetic acid. Oxidation of compound **II** with potassium permanganate in acetic acid medium during 2 h resulted in 1-(1,1-dioxothietan-3-yl)-5(6)-nitro-2-chlorobenzimidazole **VIII** with yield of 78%.

Oxidation of thietanylnitroimidazoles **III** and **IV** with the above-listed oxidizing agents led to formation of mixture of unidentified products. Sulfones **IX** and **X** were obtained with highest yields via oxidation of compounds **III** and **IV** with 10-fold excess of hydrogen peroxide under reflux in acetic acid during 20 min (Scheme 1).

The substituted 1-oxothietanes can exist in the form of *cis*- and *trans*-isomers. The ^{1}H NMR spectroscopy data confirmed that compounds **V** and **VII** were formed as diastereomeric mixtures (see table). The ^{1}H NMR spectrum of **V** contained two sets of signals corresponding to *cis*- and *trans*-isomers. The protons of oxothietane ring are diastereotopic and appear as a pair of two pseudotriplets and one multiplet. The signals of one of the $S(CH)_2$ groups of *cis*- and *trans*-isomers were shifted downfield by 0.20 and 0.73 ppm, and the signals of another $S(CH)_2$ group were shifted upfield by 0.43 and 0.19 ppm compared to the signals of the corresponding groups of thietane ring. Reliable

Scheme 1.



criterion for the signals assignment was the signal of NCH group of oxothietane ring. The NCH proton in the *trans*-isomer was spatially close to the oxygen atom of S=O group. Consequently, the signal of that proton was shifted upfield by 1.02 ppm as compared with the multiplet of the *cis*-isomer, which was shifted by only 0.04 ppm relative to the corresponding proton signals of thietane ring.

^{1}H NMR spectrum of **VII** contained the signals of oxothietane ring. In the case of *trans*-isomer, the signal of NCH proton of oxothietane ring, *cis*-positioned with respect to the oxygen atom of SO group, resonated in the range of 4.98–5.06 ppm. In contrast, in the spectrum of *cis*-isomer, that proton signal was found at 6.02–6.07 ppm. Diastereotopic protons of $S(CH_2)_2$ groups of oxothietane ring were registered as a pair of multiplets. The proposed assignment of the proton signals of 1-oxothietane ring in the spectra of *cis*- and *trans*-isomers of **V** and **VII** coincided with the reported data [1, 2].

Characteristic parameters of ^{1}H NMR spectra (δ, ppm) of compounds **I**–**VIII**, **X**

Comp. no.	$S(CH_2)_2$	$S(CH_2)_2$	NCH	Other signals
I	3.11–3.14 m	4.35–4.38 m	6.14–6.18 m	2.14 s (3H, CH_3), 5.49 s (1H, H^5), 11.11 br.s (1H, NH)
II	3.64–3.72 m	4.14–4.21 m	5.91–6.12 m	5-nitro: 8.09 d (1H, H^7, ^3J 9.0 Hz), 8.33 d. d (1H, H^6, ^3J 9.0, ^4J 2.2 Hz), 8.60 d (1H, H^4, ^4J 1.9 Hz) 6-nitro: 7.79 d (1H, H^4, ^3J 8.8 Hz), 8.27 d. d (1H, H^5, ^3J 8.9, ^4J 2.1 Hz), 8.89 d (1H, H^7, ^4J 1.9 Hz)
III	3.49–3.56 m	3.67–3.75 m	5.38–5.51 m	2.40 s (3H, CH_3), 8.02 s (1H, H^5)
IV	3.38–3.48 m	4.11–4.20 m	5.68–5.81 m	2.58 s (3H, CH_3)
V	3.31–3.36 m (*cis*) 3.84–3.89 m (*trans*)	3.92–3.96 m (*cis*) 4.16–4.21 m (*trans*)	6.18–6.22 m (*cis*) 5.12–5.19 m	2.00 s (3H, CH_3, *trans*), 2.01 s (3H, CH_3, *cis*), 5.47 s (1H, H^5, *trans*), 5.49 s (1H, H^5, *cis*), 11.25 br.s (1H, NH)
VI	4.23–4.28 m	4.89–4.94 m	(*trans*)	
VII	3.51–3.59 m (*cis*) 3.65–3.78 m (*trans*)	4.00–4.10 m (*cis*) 4.13–4.21 m (*trans*)	5.55–5.62 m 6.02–6.07 m (*cis*)	2.02 s (3H, CH_3), 5.51 s (1H, H^5), 11.31 br.s (1H, NH) 7.07–8.03 m ($6H_{Ar}$)
VIII	4.55–5.35 m	4.55–5.35 m	4.98–5.06 m (*trans*)	
X	4.29–4.32 m	4.56–4.64 m	5.80–6.20 m 5.05–5.12 m	5-nitro- and 6-nitro: 7.80–9.05 m ($6H_{Ar}$) 2.14 s (3H, CH_3)

It have been shown [2, 4] that formation of diastereomers and their ratio depends on the nature of oxidizing agent and the solvent used, but is independent of the structure of the substituent at position 3 of thietane ring. However, we confirmed that the structure of heterocyclic moiety in position 3 affected the diastereomers ratio as well. According to ^{1}H NMR spectrum of **V**, the ratio of *cis*- and *trans*-isomers was of 10 : 1, whereas in the case of oxothietanylnitrobenzimidazole **VII** it was of 1 : 2.

In the ^{1}H NMR spectra of sulfones **VI** and **X**, characteristic shifting the proton signals of two $S(CH_2)_2$ groups of dioxothietane ring downfield by 0.45–0.54 and 0.91–1.12 ppm was observed, along with upfield shifting of the signal of NCH proton by 0.59–0.63 ppm with respect to the signals of non-oxidized thietanylazoles **I** and **IV**. ^{1}H NMR spectrum of compound **VIII** contained multiplets of NCH proton (5.80–6.20 ppm) and of the $S(CH_2)_2$ groups of dioxothietane ring protons (4.55–5.35 ppm). The ratio of intensities of the proton signals of 5- and 6-nitronitrosulfone **VIII** was 1 : 3.

In summary, 1-oxothietanyl- and 1,1-dioxothietanyl derivatives were synthesized via oxidation of thietanyl-substituted pyrimidine, nitrobenzimidazole, and nitroimidazole. Their structure and selected physicochemical properties were studied. Ratio of diastereomers in a series of sulfinyl derivatives of pyrimidine and nitrobenzimidazole was determined. The diastereomeric ratio depended on the structure of heterocyclic substituent in position 3. In the case of pyrimidine-2,4(1*H*,3*H*)-dione **V**, *cis*-isomer prevailed, while in case of nitrobenzimidazole **VII** – *trans*-isomer was the major one.

EXPERIMENTAL

^{1}H NMR spectra (solution in DMSO-d_6, TMS as internal reference) were recorded with the Bruker AMX-300 (300 MHz) and the Bruker Avance III 500 (500 MHz) spectrometers. Thin-layer chromatography was carried out on Silufix plates eluting with butanol–acetic acid–water (4 : 1 : 2) and detecting with UV or iodine vapor.

6-Methyl-1-(thiethan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **I** was obtained according to the procedure reported in [5]; 5(6)-nitro-1-(thiethan-3-yl)benzimidazole **II** was synthesized according to [6]; 2-methyl-4-nitro-1-(thiethan-3-yl)imidazole **III** and 5-bromo-2-methyl-4-nitro-1-(thiethan-3-yl)imidazole **IV** were prepared as described in [7].

6-Methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (V). 0.9 g (10 mmol) of 37.7% hydrogen peroxide solution was added to solution of 1.0 g (5 mmol) of **I** in 18 mL of acetic acid. After 1 h, the reaction mixture was neutralized with 25% aqueous ammonia to pH 7 upon ice-cooling. The precipitate was filtered off and dried. Yield 70%, mp 234–235°C (DMF). Found, %: C 44.97, 45.01; H 4.57, 4.59; N 13.11, 13.16. $C_8H_{10}N_2O_3S$. Calculated, %: C 44.85; H 4.71; N 13.08.

1-(1,1-Dioxothietan-3-yl)-6-methylpyrimidin-2,4(1*H*,3*H*)-dione (VI) was obtained similarly from 1.0 g (5 mmol) of **I**, 18 mL of acetic acid and 4.51 g (50 mmol) of 37.7% hydrogen peroxide solution. The reaction time was 24 h. Yield 80%, mp 247–248°C (H_2O). Found, %: C 40.98, 41.65; H 4.24, 4.27; N 12.29, 12.36. $C_8H_{10}N_2O_4S$. Calculated, %: C 41.73; H 4.38; N 12.17.

5(6)-Nitro-1-(1-oxothietan-3-yl)-2-chlorobenzimidazole (VII). Peracetic acid (0.61 g, 8 mmol) was added to solution of 2.85 g (10 mmol) of compound **II** in 300 mL of acetic acid. The reaction mixture was stirred at 30°C during 12 h. Then the solvent was partially distilled off, and the residue was diluted with distilled water. The precipitate was filtered off, washed with water, and dried. Yield 60%, mp 200–201°C (EtOH–H_2O, 1 : 1). Found, %: C 42.12, 42.19; H 2.87, 2.94; N 14.79, 14.87. $C_{10}H_8ClN_3O_3S$. Calculated, %: C 42.04; H 2.91; N 14.66.

1-(1,1-Dioxothietan-3-yl)-5(6)-nitro-2-chlorobenzimidazole (VIII). Aqueous solution (150 mL) of 9.5 g (60 mmol) of potassium permanganate was added in several portions to solution of 5.4 g (20 mmol) of **II** in 300 mL of acetic acid over 1 h. The mixture was stirred at 30°C during 2 h. After adding 500 g of ice, the mixture was further stirred during 1 h, and then decolorized with a saturated sodium thiosulfate solution. The resulting precipitate was filtered off, washed with water, and dried. Yield 78%, mp 211–212°C (BuOH). Found, %: C 39.92 , 39.97; H 2.58, 2.59; N 13.89, 14.09. $C_{10}H_8ClN_3O_4S$. Calculated, %: C 39.81; H 2.69; N 13.88.

1-(1,1-Dioxothietan-3-yl)-2-methyl-4-nitro-imidazole (IX). 4.7 mL (50 mmol) of 36% hydrogen peroxide was added to solution of 1.0 g (5 mmol) of compound **III** in 20 mL of acetic acid (100°C) upon heating. After boiling during 20 min, the mixture was cooled down. The precipitate was filtered off. Yield 68%, mp 207–209°C (AcOH–H_2O, 3 : 1). Found, %: C

36.22, 36.31; H 3.83, 3.85; N 18.54, 18.57. $C_7H_9N_3O_4S$. Calculated, %: C 36.41; H 3.91; N 18.29.

5-Bromo-1-(1,1-dioxothietan-3-yl)-2-methyl-4-nitroimidazole (X) was prepared similarly from compound **IV**. Yield 75%, mp 218–221°C (AcOH–H_2O, 3 : 1). Found, %: C 27.32, 27.38; H 2.44, 2.45; N 13.83, 13.89. $C_7H_8BrN_3O_4S$. Calculated, %: C 27.18; H 2.61; N 13.65.

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