SYNTHESIS OF THIOPYRANO[4,3-b]BENZOFURANS

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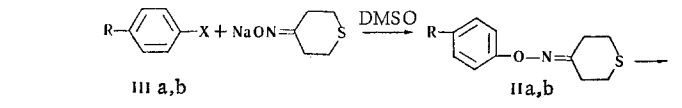
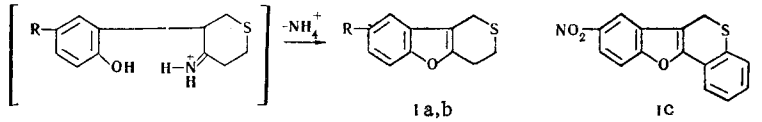
Representatives of a new heterocyclic system – thiopyrano[4,3-b]benzofuran – were synthesized by cyclization of the O-aryl ethers of tetrahydro-4-thiopyrone and 4-thiochromanone oximes in acid media.

We have previously [1] studied compounds of the 1,3,4,5-tetrahydrothiopyrano[4,3-b]indole series, and some of them manifested interesting pharmacological activity, particularly the hydrochloride of β-dimethylaminoethyl 1,3,4,5-tetrahydrothiopyrano[4,3-b]indole-8-carboxylate (tioindol) [2]. Compounds containing an an oxygen atom instead of a sulfur atom – 1,3,4,5-tetrahydropyrano[4,3-b]indoles – were obtained by the Fischer reaction [3]. Analogs which have an oxygen atom in place of the nitrogen atom – the corresponding benzofuran derivatives – were unknown up to now. Using the method of formation of a benzofuran ring from O-aryl ethers of ketoximes in acid media [4-6], we synthesized 1H-3,4-dihydrothipyrano[4,3-b]benzofurans (Ia,b) by cyclization of O-aryl ethers of tetrahydro-4-thiopyrone oxime (IIa,b). The use of this reaction for the 4-nitrophenyl ether of 4-thiochromanone oxime (IIc) made it possible to go to a dehydro system, viz., to 8-nitro-6H-benzo[5,6]thiopyrano[4,3-b]benzofuran (Ic).



III a,b IIa,b



Ia,b Ic

I–IIIa R=NO_2, b R=$COOC_2H_5$; IIIa X=Cl; IIIb X=F

The ethers of oximes IIa and IIb were obtained by the reaction of 4-nitrochlorobenzene or 4-ethoxycarbonylfluorobenzene with the oximes in dimethyl sulfoxide (DMSO) after conversion of the oximes to their sodium salts by the action of sodium hydride. The intramolecular condensation of ethers IIa and IIb was carried out by heating them in 25-28% alcoholic hydrogen chloride. The structures of I were confirmed in the case of Ia by UV and PMR spectra. The UV spectrum of Ia is similar to the spectrum of the model compound – 2-methyl-5-nitrobenzofuran [5]. The PMR spectrum of Ia (in pyridine) contains an unresolved signal at 2.8 ppm with an intensity of 4 proton units from the protons of the CH_2CH_2 grouping, in which the protons of the methylene groups are about equally deshielded by the effect of the divalent sulfur atom and by the 2-furyl radical, respectively. A broad signal from the protons of the isolated CH_2 group is located at weaker field at 3.6 ppm. In this case, the greater deshielding of the protons is caused by the joint effect of the sulfur atom and the 3-furyl radical directly bonded to the same CH_2 group.

The β-dimethylaminoethyl ester of 1H-3,4-dihydrothiopyrano[4,3-b]benzofuran-8-carboxylic acid (IV), the oxygen analog of tipindol, was synthesized by transesterification of Ib by the action of β-dimethylaminoethanol under basic catalysis conditions.

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The conditions for the sufficiently smooth reduction of nitro compound Ia to amine V could not be selected because of the low solubility of Ia in both polar and nonpolar solvents. Amine V was obtained in 26% yield by hydrogenation over $Pb/SrCO_3$ of a suspension of Ia in alcohol. According to preliminary data, ester IV does not have tipindol's activity.

EXPERIMENTAL

The UV spectra of $1 \cdot 10^{-5}$ to $1 \cdot 10^{-4}$ M alcohol solutions were recorded with an SF-4 spectrophotometer. The PMR spectra were obtained with an RS-60 spectrometer with an operating frequency of 60 MHz in the δ scale relative to hexamethyldisiloxane. The IR spectra were recorded with a UR-10 spectrometer. The purity of the substances was confirmed by thin-layer chromatography on activity IV Al_2O_3.

4-Nitrophenyl Ether of Tetrahydro-4-thiopyrone Oxime (IIa). A solution of 4.5 g (0.034 mole) of tetrahydro-4-thiopyrone oxime in 27 ml of DMSO was added to 1.07 g of 75% (with respect to active hydrogen) powdered sodium hydride in 25 ml of DMSO, and the mixture was stirred at 20° for 1 h. A solution of 5.3 g (0.034 mole) of 4-nitrochlorobenzene (IIIa) was then added dropwise, and the mixture was stirred for 1 h and poured into water. The resulting precipitate was filtered, washed with water, dried, and crystallized from heptane to give 1.8 g (21%) of IIa with mp 114.5-116°. Found %: N 11.1; S 13.1. $C_{11}H_{12}N_2O_3S$. Calculated %: N 11.1; S 12.7.

4-Ethoxycarbonylphenyl Ether of Tetrahydro-4-thiopyrone Oxime (IIb). The reaction of 1.2 g of 75% of sodium hydride with 5 g (0.034 mole) of tetrahydro-4-thiopyrone oxime in 40 ml of DMSO and 6 g (0.034 mole) of 4-ethoxycarbonylfluorobenzene (IIIb) in 20 ml of DMSO was carried out similarly to give 6.5 g (60.7%) of IIb with mp 79-80° (from heptane). Found %: C 60.0; H 6.1; N 5.3; S 11.5. $C_{14}H_{17}NO_3S$. Calculated %: C 60.4; H 6.1; N 5.0; S 11.5.

4-Nitrophenyl Ether of 4-Thiochromanone Oxime (IIc). A solution of 5 g (0.028 mole) of 4-thiochromanone oxime in 30 ml of DMF was added to 0.9 g of 75% sodium hydride in 20 ml of dimethylformamide (DMF), and the mixture was stirred at 20° for 8 h. A solution of 4.4 g (0.028 mole) of IIIa was then added, and the mixture was stirred at 20° for 1 h and at 90-95° for 4 h. The mixture was poured into water and extracted with chloroform. The extract was vacuum evaporated, and the residue was recrystallized from alcohol (with charcoal) to give 0.5 g (6%) of IIc with mp 139-140°. Found %: N 9.3; S 10.6. $C_{15}H_{12}N_2O_3S$. Calculated %: N 9.3; S 10.7. UV spectrum, λ_{max}, nm (log ε): 234 (4.18), 3.12 (4.18). PMR spectrum (in $CDCl_3$), ppm: 6.8-8.3 (two groups of C_6H_4 signals), 2.9 and 3.3 (CH_2CH_2).

8-Nitro-1H-3,4-dihydrothiopyranol[4,3-b]benzofuran (Ia). A mixture of 1.4 g (0.0055 mole) of ether IIa in 30 ml of 28% HCl in absolute alcohol was refluxed for 50 min and poured into water. The resulting precipitate was filtered to give 0.7 g (54%) of Ia with mp 205.5-206° (from alcohol). Found %: N 5.9; S 13.8. $C_{11}H_9NO_3S$. Calculated %: N 6.0; S 13.6. UV spectrum, λ_{max}, nm (log ε): 246 (4.52), 284-288 (3.81); for 2-methyl-5-nitrobenzofuran: 242 (4.42), 284-286 (3.92). IR spectrum (in mineral oil), cm^{-1}: 1630 and 1595 (weak), 1515 and 1337 (strong, NO_2). PMR spectrum (in pyridine), ppm: 2.8 (unresolved $-CH_2CH_2-$ signal), 3.6 (broad $-CH_2-$ signal).

Ethyl 1H-3,4-dihydrothiopyrano[4,3-b]benzofuran-8-carboxylate (Ib). A solution of 1.5 g (0.005 mole) of IIb in 15 ml of 25% HCl in absolute alcohol was refluxed for 1 h and poured into water. The resulting precipitate was filtered to give 1.1 g (79%) of Ib with mp 104-105° (from heptane). Found %: C 64.3; H 5.5; S 12.4. $C_{14}H_{14}O_3S$. Calculated %: C 64.1; H 5.4; S 12.2.

8-Nitro-6H-benzo[5,6]thiopyrano[4,3-b]benzofuran (Ic). This was obtained in the same way as Ia after refluxing 0.37 g (0.0012 mole) of IIc for 1 h in 10 ml of 27% HCl in absolute alcohol. The yield of Ic with mp 207-209° (from absolute alcohol) was 0.24 g (73%). Found %: N 5.2; S 11.0. $C_{15}H_9NO_3S$. Calculated %: N 4.9; S 11.3.

β-Dimethylaminoethyl 1H-3,4-Dihydrothiopyrano[4,3-b]benzofuran-8-carboxylate (IV). A mixture of 2 g (0.007 mole) of Ib in 90 ml of absolute toluene, 4.5 g of β-dimethylaminoethanol, and 2-3 mg of sodium was refluxed for 1 h with removal of 70% toluene by distillation. Another 90 ml of toluene and 3.5 g of amino alcohol were added, and the distillation was repeated. The residue was mixed with ether, and the ether layer was washed with water, dried, and evaporated. The residue began to crystallize on standing to give 2.2 g (95%) of IV with mp 125-126° (from heptane). Found %: C 63.0; H 3.1; N 4.5; S 10.7. $C_{16}H_{19}NO_3S$. Calculated %: C 62.9; H 6.1; N 4.6; S 10.5. The hydrochloride had mp 236-237° (from alcohol). Found %: Cl 10.3; N 4.2. $C_{16}H_{20}ClNO_3S$. Calculated %: Cl 10.4; N 4.1.

Hydrochloride of 8-Amino-1H-2,3-dihydrothiopyrano[4,3-b]benzofuran (V). A suspension of 2 g (0.0085 mole) of Ia in 200 ml of alcohol was hydrogenated over 2 g of 2.3% $Pd/SrCO_3$ for 20 h, and the catalyst (a total of 5 g) was added periodically. The catalyst was removed by filtration, the alcohol was evaporated, and the residue was dissolved in ether and alcoholic HCl to give 0.65 g (27%) of the hydrochloride of V with mp 261-263° (decomp., from alcohol with charcoal). Found %: Cl 14.8; N 5.7; S 13.4. $C_{11}H_{11}NOS \cdot HCl$. Calculated %: Cl 14.7; N 5.8; S 13.6.

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