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INTERACTION OF BENZOTHIENO[2,3-c]PYRYLIUM SALTS WITH HYDRAZINE. DERIVATIVES OF 5H-[2,3]BENZOTHIENO[2,3-e]DIAZEPINES

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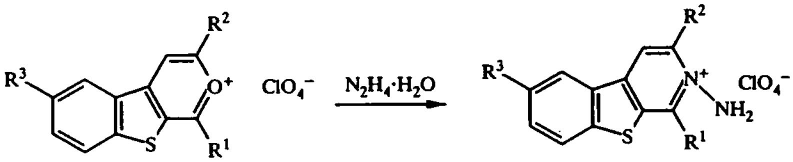
A study has been made of the reaction of 1,3-disubstituted benzothieno[2,3-c]pyrylium salts with hydrazine. It has been shown that 1,3-dialkyl-substituted benzothieno[2,3-c]pyrylium salts interact with hydrazine to give N-amino-1,3-dialkylbenzothieno[2,3-c]pyridines. The presence of a pyrylium ring on one of the positions of the phenyl group leads to a mixture of N-amino derivatives and 5H-[2,3]benzothieno[2,3-e]diazepines. In contrast, 1,3-diphenylbenzothieno[2,3-c]pyrylium perchlorate gives exclusively 5H-[2,3]benzothieno[2,3-e]diazepine.

The discovery of tranquilizing properties of compounds of the benzodiazepine series has stimulated intensive research on these compounds. In this area, the 1,4-benzodiazepines have been particularly well studied [1]. The 2,3-benzodiazepines also manifest this sort of activity. For example, the preparation Tofizopam, a popular daytime tranquilizer, is a compound of the benzo-2,3-diazepine series [2]. One of the paths of synthesis of 2,3-diazepines consists of the reaction of benzo[c]pyrylium salts with hydrazine [3]. However, hydrazine can react with benzo[c]pyrylium salts as a mononucleophile, in the same manner as primary amines, giving N-aminoisoquinolines, and also as a binucleophile, forming diazepines [4, 5]. With the aim of synthesizing previously unknown 5H-[2,3]benzothieno[2,3-e]diazepines, we have investigated the reaction of 1,3-disubstituted benzothieno[2,3-c]pyrylium salts with hydrazine. The reaction was carried out by refluxing an alcohol solution of the pyrylium salt with excess hydrazine hydrate. We found that the 1,3-dialkyl-substituted benzothieno[2,3-c]pyrylium salts I-III, in their reaction with hydrazine, form exclusively the perchlorates of N-amino-1,3-dialkylbenzothieno[2,3-c] pyridines IV-VI; the direction of the reaction of the salts I-III does not depend on the length of the aliphatic radical R^1, the reaction time, or the quantity of hydrazine hydrate that is used.



Ia-d, IIa,b, IIIa,b

IVa-d, Va,b, VIa,b

I, IV) R^3 – H, a R^1 – R^2 – Me, b R^1 – Pr, R^2 – Me, c R^1 – Bu, R^2 – Me, d R^1 – Me, R^2 – Et;
II, V) R^3 – Me, a R^1 – R^2 – Me, b R^1 – Pr, R^2 – Me; III,VI) R^3 – Cl, a R^1 – Me, b R^1 – Bu, a,b R^2 – Me

Identical results were obtained when the reaction mass was refluxed from 1 to 10 h with a twofold to tenfold excess of hydrazine hydrate. In the IR spectra of the perchlorates of the N-amino-1,3-dialkylbenzothieno[2,3-c]pyridines IV-VI, there are absorption bands from the pyridinium ring in the 1620-1610 cm^{-1} region, and from the NH_2 group in the 3250 and 3320

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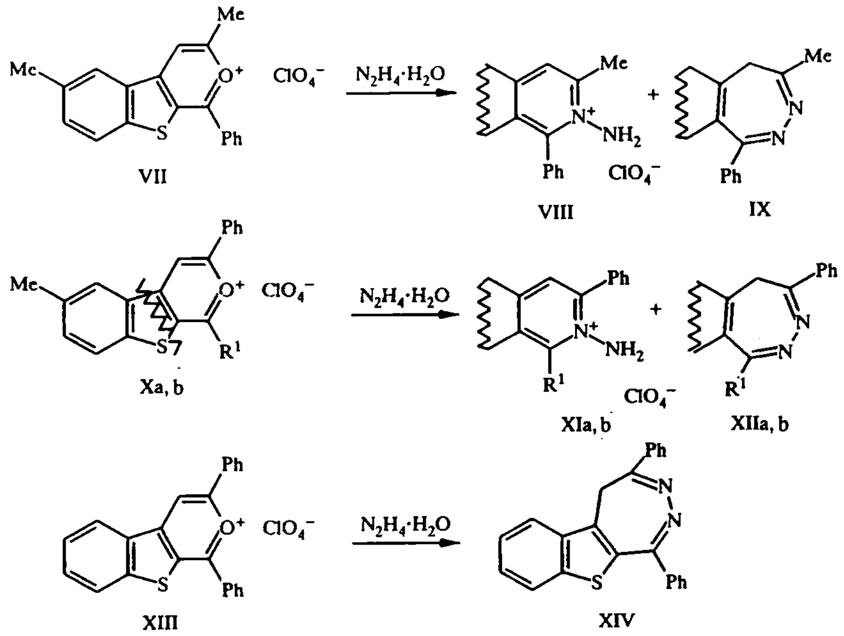
TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, %
		C	H	N	Cl	S		
IVa	$C_{13}H_{13}N_2ClO_4S$	47,8 47,5	4,2 4,0	8,7 8,5	10,9 10,8	9,9 9,7	260...261	87
IVb	$C_{15}H_{17}N_2ClO_4S$	50,4 50,1	4,6 4,8	7,7 7,9	10,1 10,0	9,2 9,0	240	90
IVc	$C_{16}H_{19}N_2ClO_4S$	51,5 51,8	5,2 5,1	7,8 7,6	9,8 9,6	8,5 8,6	263	88
IVd	$C_{14}H_{15}N_2ClO_4S$	49,4 49,1	4,5 4,4	8,4 8,2	10,6 10,4	9,1 9,3	255	91
Va	$C_{14}H_{15}N_2ClO_4S$	49,3 49,1	4,5 4,4	8,0 8,2	10,2 10,4	9,5 9,3	241...242	90
Vb	$C_{16}H_{19}N_2ClO_4S$	51,5 51,8	5,3 5,1	7,5 7,6	9,8 9,6	8,3 8,6	247	87
VIa	$C_{13}H_{12}N_2Cl_2O_4S$	44,7 44,4	3,5 3,4	8,3 8,0	20,5 20,2	9,2 9,1	289	91
VIb	$C_{16}H_{18}N_2Cl_2O_4S$	47,7 47,4	4,6 4,4	6,7 6,9	17,2 17,5	7,6 7,9	280...281	89
VIII	$C_{18}H_{15}N_2ClO_4S$	55,5 55,3	3,6 3,8	7,5 7,2	9,0 9,1	8,5 8,2	247	53
IX	$C_{19}H_{16}N_2S$	74,7 75,0	5,4 5,3	9,3 9,2	—	10,3 10,5	218	44,9
XIa	$C_{19}H_{17}N_2ClO_4S$	56,7 56,4	4,4 4,2	6,8 6,9	8,7 8,8	7,7 7,9	220	22,3
XIb	$C_{21}H_{21}N_2ClO_4S$	58,5 58,3	4,8 4,9	6,7 6,5	8,0 8,2	7,6 7,4	163	48,4
XIIa	$C_{21}H_{20}N_2S$	75,3 75,0	5,1 5,3	9,2 9,2	—	10,7 10,5	177...178	74
XIIb	$C_{21}H_{20}N_2S$	75,7 75,9	6,2 6,0	8,5 8,4	—	9,8 9,6	160...161	42
XIV	$C_{23}H_{16}N_2S$	78,6 78,4	4,4 4,6	8,2 8,0	—	9,2 9,1	190	89

TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	PMR spectrum, δ (ppm) and J (Hz)
IVa	2,88 (3H, s, 3-CH_3), 3,04 (3H, s, 1-CH_3), 7,27 (2H, s, 2-NH_2), 7,77 (1H, t, 7-H), 7,84 (1H, t, 6-H), 8,30 (1H, d, J = 8,0, 8-H), 8,56 (1H, d, J = 8,0, 5-H), 8,79 (1H, s, 4-H)
IVb	1,05 (3H, t, 1-CH_2—CH_2—$\underline{CH_3}$), 1,86 (2H, m, 1-CH_2—$\underline{CH_2}$—CH_3), 2,91 (3H, s, 3-CH_3), 3,41 (2H, t, 1-$\underline{CH_2}$—CH_2—CH_3), 7,21 (2H, s, 2-NH_2), 7,75 (1H, t, 7-H), 7,86 (1H, t, 6-H), 8,23 (1H, d, J = 8,0, 8-H), 8,60 (1H, d, J = 8,0, 5-H), 8,85 (1H, s, H)
IVd	1,43 (3H, t, 3-CH_2—$\underline{CH_3}$), 3,25 (2H, q, 3-$\underline{CH_2}$—CH_3), 7,23 (2H, s, 2-NH_2), 7,70 (1H, t, 7-H), 7,82 (1H, t, 6-H), 8,26 (1H, J = 8,0, 8-H), 8,63 (1H, d, J = 8,0, 5-H), 8,66 (1H, s, 4-H)
Va	2,55 (3H, s, 6-CH_3), 2,89 (3H, s, 3-CH_3), 3,05 (3H, s, 1-CH_3), 7,24 (2H, s, 2-NH_2), 7,70 (1H, d, J = 8,2, 7-H), 8,20 (1H, J = 8,2, 8-H), 8,40 (1H, s, 5-H), 8,75 (1H, s, 4-H)
Vb	1,06 (3H, t, 1-CH_2—CH_2—$\underline{CH_3}$), 1,86 (2H, m, 1-CH_2—$\underline{CH_2}$—CH_3), 2,55 (3H, s, 6-CH_3), 2,89 (3H, s, 3-CH_3), 3,05 (3H, s, 1-CH_3), 3,41 (2H, t, 1-$\underline{CH_2}$—CH_2—CH_3), 7,21 (2H, s, 2-NH_2), 7,70 (1H, d, J = 8,2, 7-H), 8,20 (1H, d, J = 8,2, 8-H), 8,40 (1H, s, 5-H), 8,75 (1H, s, 4-H)
IX	2,08 (3H, s, 4-CH_3), 2,49 (3H, s, 7-CH_3), 2,70 (1H, d, J = 13,1, 5-H), 4,30 (1H, d, J = 13,1, 5-H), 7,30...8,05 (8H, $H_{arom.}$)
XIIa	2,55 (3H, s, 7-CH_3), 3,17 (3H, s, 1-CH_3), 3,86 (1H, d, J = 13,0, 5-H), 4,98 (1H, d, J = 13,0, 5-H), 7,18...8,10 (8H, $H_{arom.}$)
XIV	2,91 (1H, d, J = 13,1, 5-H), 5,20 (1H, d, J = 13,1, 5-H), 7,37...8,46 (14H, $H_{arom.}$)

cm^{-1} region. In the PMR spectra, the signal of the protons of the NH_2 group is manifested at 7.2 ppm; the remainder of the spectrum is similar to those of benzothieno[2,3-c]pyridines and benzothieno[2,3-c]pyrylium salts [6] (Table 2). The benzothieno[2,3-c]pyrylium salts VII and Xa, b, which have a phenyl group in position 1 or 3, react with hydrazine to give mixtures of the corresponding N-amino derivatives VIII and XIa, b and the 5H-[2,3]benzothieno[2,3-e]diazepines IX and XIIa, b. The 1,3-diphenylbenzothieno[2,3-c]pyrylium perchlorate XIII gives exclusively 5H-[2,3]benzothieno[2,3-e]diazepine. In the PMR spectrum of 1,4-diphenyl-5H-[2,3]benzothieno[2,3-e]diazepine XIV, taken at 20°C, we observe signals from protons of the CH_2 group in the form of two broad doublets with chemical shifts of 5.20 and 2.91 ppm and a geminal constant > 13 Hz. The nonequivalence of the protons is due to the different spatial orientation of the C-H bonds relative to the aromatic ring, and also the relative rigidity of the seven-membered ring. An experiment to determine the influence of temperature supports this conclusion (the material from this experiment will be presented in a separate publication).



X, XI, XII a R^1 = Me, b R^2 = Pr

EXPERIMENTAL

The IR spectra were recorded in white mineral oil in a Perkin-Elmer 180 spectrometer, the PMR spectra in a Gemini-200 instrument in $DMSO\text{-}d_6$ with TMS internal standard.

General Procedure for Obtaining Perchlorates of N-Aminobenzothieno[2,3-c]pyridines IV-VI, VIII, and XI. To a suspension of 0.01 mole of compound I-III, VII, or X in 50 ml of alcohol, a twofold to tenfold excess of hydrazine hydrate was added, and the reaction mass was refluxed for 1 to 10 h. The original compounds dissolved completely in a matter of a few minutes, and the perchlorates of the N-aminobenzothieno[2,3-c]pyridines began to precipitate out. The mixture was cooled, and the precipitate was filtered out and washed with alcohol and ether. The product was crystallized from alcohol. The characteristics of the synthesized compounds are listed in Table 1.

General Procedure for Obtaining 5H-[2,3]benzothieno[2,3-e]diazepines. To a suspension of 0.01 mole of compound VII, X, or XIII in 50 ml of alcohol, a fivefold excess of hydrazine hydrate was added, and the reaction mass was refluxed 2 h. After cooling the reaction mixture, 30 ml of ether was added, up to complete precipitation of the corresponding N-amino derivative of the benzothieno[2,3-c]pyridine. The precipitate was filtered off and washed with 10 ml of ether, and the filtrate was evaporated down. The residue was crystallized from a benzene–hexane mixture (Table 1).

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