ALKYLATION OF XANTHINE AND BENZIMIDAZOLE DERIVATIVES WITH EPITHIOCHLOROHYDRIN

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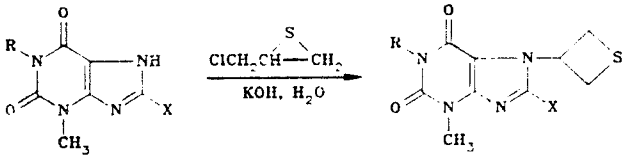
N-(3-Thietanyl)-substituted heterocycles are formed in the alkylation of xanthine and benzimidazole derivatives with epithiochlorohydrin (ETCH) in an aqueous medium as a consequence of a thiirane–thietane rearrangement.

We have previously shown that 8-haloxanthines in the form of potassium salts react with epithiochlorohydrin (ETCH) in DMF to give dihydrothiazolo[2,3-f]xanthine derivatives [1]. However, it is known that a thiirane–thietane rearrangement is possible in the case of alkylation with ETCH in protic solvents [2].

In the present research we studied the reaction of xanthine (Ia-e) and benzimidazole (IIIa-c) derivatives with ETCH in an aqueous medium in order to synthesize their N-(3-thietanyl)-substituted derivatives, which are of interest as potential biologically active compounds.

It was established that a thiirane–thietane rearrangement occurs in the alkylation of 8-substituted xanthines Ia-e with ETCH at 60°C in an aqueous medium in the presence of an equimolar amount of potassium hydroxide and that 8-substituted 7-(3-thietanyl)xanthines IIa-e are formed. The yields of the products range from 28% to 44%, and the unchanged starting xanthine is recovered quantitatively.



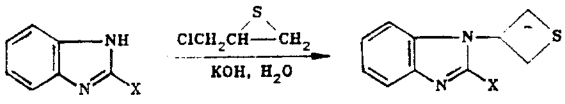
I a-e II a-e

I, II: a–d $R=CH_3$, e $R=H$; a,e $X=Cl$, b $X=Br$, c $X=NHCH_2C_6H_5$, d $X=NHC_6H_5$

The principal method of identification of IIa-e is PMR spectroscopy (Table 1). Singlets of N-methyl groups and signals of the protons of the substituents in the 8 position are present in the PMR spectra. The signals of the protons of the thietane ring show up in the form of three multiplets: the multiplet at 5.50-6.27 ppm with an intensity of 1H belongs to a methylidyne proton, while the two triplets at 3.62-4.48 ppm and 2.90-3.62 ppm with intensities of 2H each belong to methylene protons. The complexity of the spectra is evidently a consequence of the rigid nonplanar structure of the thietane ring [3], which is responsible for the magnetic nonequivalence of the methylene protons. This opinion is confirmed by a double-resonance experiment with respect to the methylidyne proton, as a result of which the apparent simplicity of the triplets of the methylene protons, which change to a typical AA'BB' spectrum [4], vanishes.

The structures of IIa,b,d were also confirmed by mass spectrometry (Table 2). Their molecular ions ($M^{+\cdot}$) are recorded in the form of two peaks with characteristic intensity ratios that attest to the presence of the corresponding halogen atom in the compositions of the molecules. The $[M - Hal]^+$ and $[C_3H_5S]^+$ peaks are the most intense peaks. The spectra of all three compounds contain $[M - C_3H_4S]^{+\cdot}$ peaks, the origin of which is confirmed by the recording of metastable ions.

The alkylation of 2-substituted benzimidazoles IIIa-c with ETCH in an aqueous medium also leads to N-(3-thietanyl)-substituted derivatives. In contrast to the xanthine derivatives, 2-substituted 1-(3-thietanyl)benzimidazoles IVa-c are formed in higher yields (39-73%) and are not accompanied by the isolation of the starting compounds.



III a-c IV a-c

III, IV a $X=Cl$, b $X=SO_2CH_3$, c $X=SO_2C_2H_5$

In addition to signals of protons of an aromatic ring and the substituents in the 2 position, the PMR spectra of IVa-c contain characteristic multiplets of protons of the thietane ring (see Table 1).

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TABLE 1. Characteristics of IIa-e and IVa-c

Compound	Empirical formula	mp, °C	PMR spectrum,* δ, ppm				Yield, %
			NCH (1H, m)	$S(CH_2)_2$ (2H, m)	$S(CH_2)_2$ (2H, m)	other protons	
IIa	$C_{10}H_{11}ClN_4O_2S$	229...230	5,86...6,27	4,27...4,48	3,22...3,42	3,47 (3H, s, NCH_3); 3,55 (3H, s, NCH_3)	31
IIb	$C_{10}H_{11}BrN_4O_2S$	220...221	5,78...6,14	4,24...4,46	3,14...3,36	3,40 (3H, s, NCH_3); 3,48 (3H, s, NCH_3)	44
IIc	$C_{17}H_{19}N_5O_2S$	199...200	5,76...6,20	3,70...3,96	3,44...3,62	3,34 (3H, s, NCH_3); 3,52 (3H, s, NCH_3); 4,66 (2H, s, NCH_2); 7,22 (5H, br.s, 5CH arom)	36
IId	$C_{16}H_{17}N_5O_2S$	249...250	5,50...5,94	3,62...3,88	3,10...3,34	3,10 (6H, s, $2NCH_3$); 6,86...7,18 (5H, m, 5CH arom)	33
IIe	$C_9H_9ClN_4O_2S$	241...243	5,56...5,96	3,86...4,10	2,90...3,14	3,25 (3H, s, NCH_3)	28
IVa	$C_{10}H_9ClN_2S$	113...115	5,60...6,00	4,00...4,24	3,26...3,50	7,04...7,88 (4H, m, 4CH arom)	73
IVb	$C_{11}H_{12}N_2O_2S_2$	129...131	6,22...6,64	3,80...4,08	3,30...3,60	3,24 (3H, s, SO_2CH_3); 7,32...8,44 (4H, m, 4CH arom.)	41
IVc	$C_{12}H_{14}N_2O_2S_2$	92...94	6,20...6,66	3,80...4,08	3,16...3,60**	1,10 (3H, t, J=7 Hz, CCH_3); 3,16...3,60 (m, SO_2CH_2)**; 7,30...8,50 (4H, m, 4CH arom)	39

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*The following solvents were used to record the spectra: $CDCl_3$ for IIa,b and IVa and CF_3COOH for IIc-e and IVb,c.

**The signals of the $S(CH_2)_2$ and SO_2CH_2 protons are overlapped, thereby forming a multiplet with an intensity of 4H.

TABLE 2. Mass Spectra of IIa, b, e

Compound*	m/z value (I_{rel}, %)**
II a	288 (7), 286 (15), 251 (13), 216 (9), 214 (21), 110 (5), 73 (100), 69 (8), 68 (5)
II b	332 (37), 330 (37), 260 (60), 258 (60), 251 (100), 175 (6), 173 (6), 122 (18), 94 (23), 93 (5), 79 (18), 75 (17), 74 (17), 73 (67), 72 (19), 71 (5), 45 (33)
II e	274 (18), 272 (50), 237 (40), 202 (15), 200 (45), 194 (24), 159 (5), 157 (14), 105 (17), 74 (25), 73 (100), 69 (15), 57 (20), 55 (20), 45 (50)

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*The ionization-chamber temperature for IIa was 65°C, as compared with 100°C for IIb,e.

**The ion peaks with intensities ≥ 5% are presented.

The IR spectra of IVb, c contain absorption bands at 1135 and 1315 cm^{-1}, which confirm retention of the alkylsulfonyl groups.

Thus thiirane—thietane rearrangement to give N-(3-thietanyl)-substituted heterocycles occurs in the alkylation of xanthine and benzimidazole derivatives with ETCH in an aqueous medium. The results obtained are in agreement with the conclusions of Fokin and Kolomiets [2] regarding the relative reactivities of the electrophilic centers of ETCH and the influence of solvolytic effects on the structures of the products of alkylation with ETCH.

EXPERIMENTAL

The IR spectra (of suspensions in mineral oil) were recorded with a Beckmann 620 MX spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ and CF_3COOH were obtained with a Tesla BS-567 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with an MKh-1320 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 70 eV.

The individuality of the compounds was monitored by TLC on Silufol UV-254 plates in an n-butanol—acetic acid—water (4:1:2) system with development by iodine vapors.

The characteristics of the synthesized compounds are presented in Tables 1 and 2. The results of elementary analysis for C, H, N, and S were in agreement with the calculated values.

General Method for the Alkylation of Xanthine and Benzimidazole Derivatives with ETCH. A 12-mmole sample of ETCH was added to a solution of 10 mmole of Ia-e or IIIa-c and 12 mmole of potassium hydroxide in 50-70 ml of water heated to 60°C, and the mixture was stirred at this temperature for 3 h. The reaction mixture was then cooled to room temperature and filtered, and the precipitate on the filter was treated as follows.

A. In the case of the xanthine derivatives the precipitate was dried, and 100 ml of chloroform was added. The undissolved starting xanthine was removed by filtration, and evaporation of the chloroform gave IIa-e. Compounds IIa-c were crystallized from ethanol, while IId,e were crystallized from isobutyl alcohol.

B. In the case of the benzimidazole derivatives the precipitate was dried and crystallized from ethanol. This procedure gave IVa-c.

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