REACTIONS OF EPOXIDES OF THE PYRAN SERIES INVOLVING RING EXPANSION. REACTION OF 4-METHYL-3,4-EPOXYTETRAHYDROPYRAN WITH POTASSIUM THIOCYANATE

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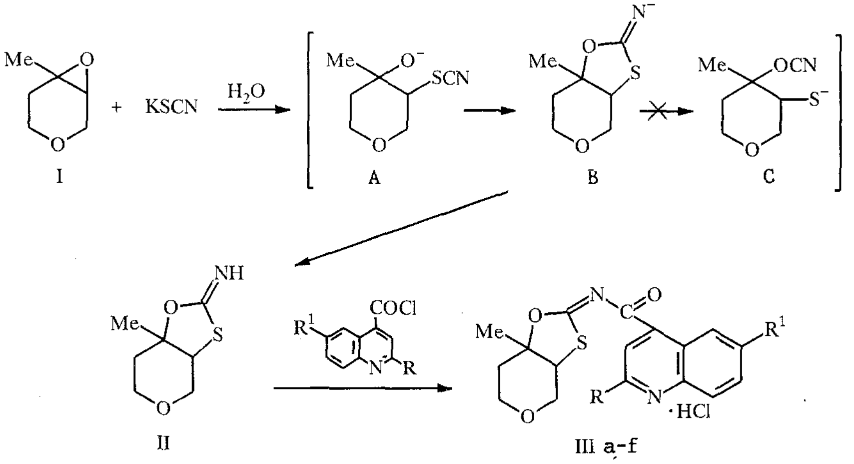
The reaction of 4-methyl-3,4-epoxytetrahydropyran with potassium thiocyanate occurs with expansion of the oxirane ring and leads to 6-methyl-8-amino-3,7-dioxa-9-thiabicyclo[4,3,0]nonane, the formation of which has been proven by the fact that products of its acylation by acid chlorides of 2-R-cinchonic acids are obtained, and also by the formation of Mannich bases when it is treated with formaldehyde and secondary amines.

Continuing the study of the reaction of nucleophiles with epoxides of the pyran series [1, 2], we have investigated the reaction of 4-methyl-3,4-epoxytetrahydropyran I with potassium thiocyanate. We know that oxides of alkenes react in an unusual fashion with thiourea and salts of thiocyanic acid, forming episulfides [3, 4]. Such reactions have not been described for epoxides of the pyran series. We have established that opening of epoxide I by potassium thiocyanate in water at 20°C for 1-2 h occurs with expansion of the oxirane ring and leads (through anions A and B) to 6-methyl-8-imino-3,7-dioxa-9-thiabicyclo[4,3,0]nonane II, the formation of which has been confirmed by the results of subsequent acylation by acid chlorides of 2-R-cinchonic acids.



IIIa: R = thienyl, R^1 = H; b: R = Ph, R^1 = H; c: R = p-ClC_6H_4, R^1 = Br; d: R = p-HOC_6H_4, R^1 = Br; e: R = p-$H_2NC_6H_4$, R^1 = H; f: R = p-$MeOC_6H_4$, R^1 = Br

Compounds II and IIIa-f are identified on the basis of elemental analysis results and spectral data. We should note that, in contrast to oxides of alkanes, upon reaction of epoxide I with KSCN conversion of the intermediate anion B to anion C does not occur, since the episulfide analogous to epoxide I was not observed in the reaction products.

The Mannich bases obtained from the heterocycles have been studied as drugs with a broad range of physiological action [5]. With the goal of expanding the synthetic possibilities of the Mannich reaction, we studied the behavior of dioxathiabicyclononane II in this reaction. We found that the latter reacts under mild conditions with formaldehyde, forming the hydroxymethyl derivative IV, which smoothly reacts with secondary amines of the aliphatic and heterocyclic series, being converted to the corresponding Mannich bases Va-c and VIa-d. The reactions are easily accomplished in one step (See scheme on page 870).

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TABLE 1. Characteristics of Synthesized Compounds IIIa-f, Va-c, VIa-d

Compound	Empirical formula	T_{mp} °C	PMR spectrum, δ, ppm				Yield, %
			CH_3 (3H, s)	5-H (2H, t)	1-H, 2-H, 4-H (5H, m), CH_2N (2H, m)*, $2(CH_2)_3CH_3$** (19H, m)	other protons	
IIIa	$C_{21}H_{19}N_2O_3S_2Cl$	331-332	1,15	1,75	3,36-3,70	7,40-7,80 (4H, m, $CH_{arom.}$)	75
IIIb	$C_{23}H_{21}N_2O_3SCl$	325-326	1,25	1,65	3,40-3,85	7,50-8,10 (10H, m, $CH_{arom.}$)	72
IIIc	$C_{23}H_{19}N_2O_3SCl_2Br$	344-345	1,30	1,55	3,45-3,75	7,40-8,15 (8H, m, $CH_{arom.}$)	68
IIId	$C_{23}H_{20}N_2O_4SClBr$	336-337	1,25	1,70	3,30-3,85	7,30-8,25 (8H, m, $CH_{arom.}$)	81
IIIe	$C_{23}H_{22}N_3O_3SCl$	325-316	1,15	1,65	3,35-3,85	7,40-8,15 (8H, m, $CH_{arom.}$)	78
IIIf	$C_{24}H_{22}N_2O_4SClBr$	339-340	1,20	1,75	3,45-3,85	7,30-8,10 (8H, m, $CH_{arom.}$)	83
Va	$C_{12}H_{20}N_2O_3$	315-316	1,15	1,70	3,35-3,80	2,35-2,80 (8H, m, CH morpholine)	83
Vb	$C_{12}H_{21}N_3O_2$	320-321	1,25	1,65	3,40-3,85	2,50-2,75 (8H, m, CH piperazine)	72
Vc	$C_{13}H_{22}N_2O_2$	331-332	1,30	1,85	3,35-3,80	2,15-2,95 (10H, m, CH piperidine	93
VIa	$C_{10}H_{18}N_2O_2$	309-310	1,25	2,05	3,20-3,80	2,38 (6H, s, $(CH_3)_2N$)	82
VIb	$C_{12}H_{22}N_2O_2$	312-313	1,30	1,80	3,30-3,80	1,10 (6H, t, $CH_2C\underline{H}_3$); 2,60 (4H, m, $\underline{CH_2}CH_3$)	95
VIc	$C_{14}H_{26}N_2O_2$	325-326	1,50	2,05	3,30-4,10	1,22 (6H, d, $CH(C\underline{H}_3)_2$); 2,87 (2H, m, $C\underline{H}(CH_3)_2$)	80
VId	$C_{16}H_{30}N_2O_2$	330-331	1,25	1,85	3,35-3,95	0,92 (6H, t, $(CH_2)_3C\underline{H}_3$)	81

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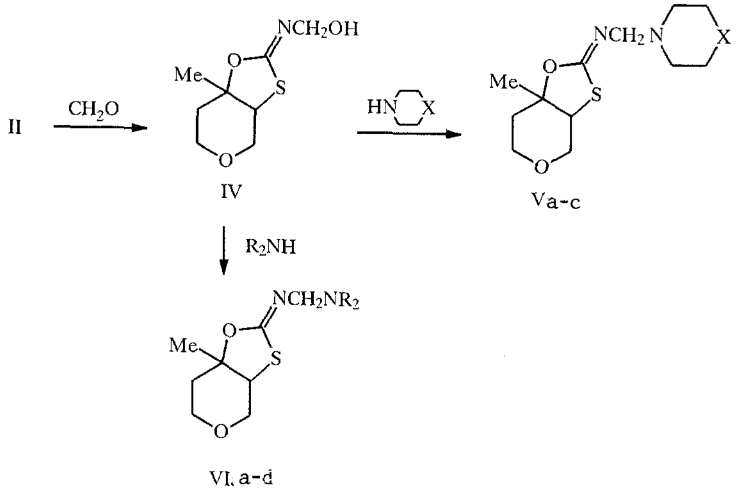
*For compounds Va-c and VIa-c.

**In the case of VId.



Va: X = O, b: X = NH, c: X = CH_2; VIa: R = Me, b: R = Et, c: R = C_3H_7, d: R = C_4H_9

EXPERIMENTAL

The IR spectra were recorded on the UR-20 instrument in a film; the PMR spectra were recorded on the Tesla BS-487 C instrument (80 MHz) in DMSO, internal standard HMDS. Tetrahydropyran I was obtained by the familiar technique in [1], while 2-R, 6-R^1-cinchonic acids and their acid chlorides were obtained as described in [6]. The characteristics of the synthesized compounds IIIa-f, Va-c, and VIa-d are presented in Table 1.

The elemental analysis results for C, H, N, and S correspond to the calculated values.

6-Methyl-8-imino-3,7-dioxa-9-thiabicyclo[4,3,0]nonane (II, $C_7H_{11}NO_2S$). A solution of 11.4 g (0.1 mole) epoxide I and 9.7 g (0.1 mole) KSCN in 10 ml water was stirred at 20°C for 1-2 days. The organic layer formed was separated. After 4-6 h compound II precipitated which was crystallized from ethanol. Mp 255-256°C. IR spectrum (cm^{-1}): 1120 (CH_2OCH_2); 1640 (C=N); 3350 (NH). PMR spectrum: 1.15 (3H, s, CH_3); 1.75 (2H, t, 5-H); 3.45-3.75 (5H, m, 1-H, 2-H, 4-H); 6.75 ppm (1H, s, NH). Yield 12.1 g (70%).

Hydrochloride of 6-methyl-8-[2-(2-thienyl)-4-(quinolinoylimino)]-3,7-dioxa-9-thia-bicyclo[4,3,0]nonane (IIIa). 4.7 g (0.017 moles) of the acid chloride of 2-(2-thienyl)-4-quinoline carboxylic acid was added with stirring to 3 g (0.017 mole) of compound II in absolute ether. After 15-30 min a precipitate formed which was washed with absolute ether. 5.7 g (75%) of product IIIa was obtained, calculated on the basis of the acid chloride. Compounds IIIb-f were synthesized analogously.

6-Methyl-8-hydroxymethylimino-3,7-dioxa-9-thiabicyclo[4,3,0]nonane (IV, $C_8H_{13}NO_3S$). At 20°C, 1 ml (0.03 mole) of 36% aqueous solution of formaldehyde was added to 3 g (0.01 mole) compound II and the reaction mixture was allowed to stand for 12 h. The precipitate of product IV was filtered, washed with water, and dried. Mp 271-272°C. IR spectrum (cm^{-1}): 1110 (CH_2OCH_2); 1630 (C=N); 3370 (OH); 1470 (CH_2N). PMR spectrum: 1.15 (3H, s, CH_3); 1.75 (2H, t, 5-H); 3.35-3.75 (7H, m, 1-H, 2-H, 4-H, CH_2N); 4.15 ppm (1H, t, OH). Yield 3.2 g (85%).

0.2 g (0.003 mole) morpholine was added to 0.4 g (0.002 mole) compound IV in 20 ml ethanol at 20°C and the mixture was allowed to stand for 12 h. The precipitate of product Va was filtered off and crystallized from ethanol. A sample of the latter mixed with a sample of Va synthesized directly from II did not cause depression of the melting point. Yield 0.38 g (80%).

6-Methyl-8-morpholinomethylimino-3,7-dioxa-9-thiabicyclo[4,3,0]nonane (Va). At 20°C, 1 ml (0.03 mole) of 36% aqueous solution of formaldehyde and 2.2 g (0.025 mole) of morpholine were added to 3 g (0.017 mole) compound II. The solution was stirred for 6-8 h and treated with acetone. The precipitate of product Va was crystallized from ethanol. Compounds Vb, c and VIa-d were obtained analogously.

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