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REACTION OF 4-METHYL-3,4-EPOXYTETRAHYDROPYRAN WITH NUCLEOPHILES

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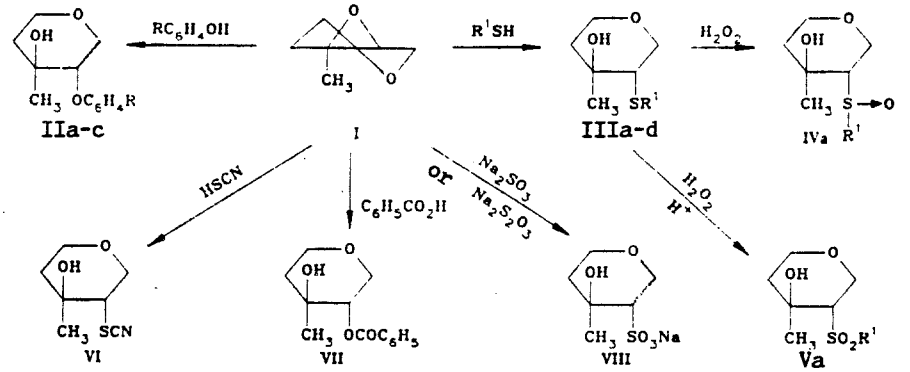
Reaction of 4-methyl-3,4-epoxytetrahydropyran with phenols, thiols, thiocyanic acid and benzoic acid, thiourea, and with sodium sulfite and thiosulfate occurs with opening of the epoxide ring. Using IR spectroscopy it was shown that the products occur via trans-diaxial opening of the oxide ring at the least-substituted carbon atom.

Reaction of nucleophilic agents with pyran epoxides is a convenient method for the stereoselective synthesis of functionally substituted derivatives of this class [1], being of interest as biologically active materials. In this connection, we have investigated the reaction of 4-methyl-3,4-epoxytetrahydropyran (I) with a series of available nucleophiles (phenols, thiols, thiocyanic and benzoic acids, sodium sulfite and thiosulfate, and thiourea.



II a R=C_6H_5, b R=4-$CH_3C_6H_4$, c R=4-BrC_6H_4; IIIa R^1=cyclohexyl, b $R^1=(CH_2)_2OH$, c R^1= piperidyl, d $R^1=CH_2CO_2H$; IVa, Va R^1= cyclohexyl

Treatment of epoxide I with phenols in aqueous NaOH solution (100°C, 4 h) gives 3-aryloxytetrahydropyrans IIa-c in 50-72% yields. Being more powerful nucleophiles, thiols react more rapidly in the same conditions (2 h) and give 3-alkylthiotetrahydropyrans IIIa-d in 65-82% yields. Treatment of sulfide IIIa with 30% hydrogen peroxide in methyl ethyl ketone gives the sulfoxide IVa and the sulfone Va in the presence of sulfuric acid. Epoxide I reacts with an ether solution of HSCN at 20°C over 48 h to give the 3-thiocyanotetrahydropyran VI in 52% yield. Heating I in $CHCl_3$ with benzoic acid in the presence of p-toluenesulfonic acid over 50 h yields the 3-tetrahydropyranyl benzoate VII (58%). Reaction of the epoxide with a

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TABLE 1. Physical Data for Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}*	PMR spectrum, δ, ppm (in CCl_4)**	Yield, %
IIa	$C_{12}H_{16}O_3$	84	1100 (CH_2OCH_2), 3375 (OH)	1,15 (3H, s, 4-CH_3); 1,75 (2H, t, CH_2); 3,52...3,76 (5H, m, CH_2OCH_2 and CHO); 3,85 (1H, s, OH); 6,72...7,34 (5H, m, C_6H_5)	60
IIb	$C_{13}H_{18}O_3$	77	1100 (CH_2OCH_2), 3370 (OH)	1,15 (3H, s, 4-CH_3); 2,15 (3H, s, $CH_3C_6H_4$); 2,25 (2H, t, CH_2); 3,52...3,75 (5H, m, CH_2OCH_2 and CHO); 3,85 (1H, s, OH); 6,74...7,32 (4H, m, $CH_3C_6H_4$)	72
IIc	$C_{12}H_{15}BrO_3$	90...91	1120 (CH_2OCH_2), 3370 (OH)	1,35 (3H, s, 4-CH_3); 1,55...1,95 (2H, m CH_2); 2,15 (1H, s, OH); 3,45...4,12 (5H, m, CH_2OCH_2 and CHO); 6,72...7,48 (4H, m, BrC_6H_4)	50
IIIa	$C_{12}H_{22}O_2S$	57...58	1120 (CH_2OCH_2), 3445 (OH)	1,15 (3H, s, 4-CH_3); 1,35 (6H, m, CH_2 cyclohexyl); 1,75 (4H, m, CH_2 cyclohexyl and 5-CH_2); 2,75 (1H, t, CHS); 2,85 (1H, s, OH); 3,56...4,12 (5H, m, 2-CH_2, 6-CH_2 and CH)	81
IIIb	$C_8H_{15}O_3S$	71...72	1110 (CH_2OCH_2), 3450 (OH)	1,36 (3H, s, 4-CH_3); 1,8 (4H, t, $(CH_2)_2$); 2,85 (1H, s, OH); 3,64...4,25 (5H, m, 2-CH_2, 6-CH_2 and CH)	60
IIIc	$C_{13}H_{25}NO_2S$	34	1100 (CH_2OCH_2), 3440 (OH)	1,52 (3H, s, 4-CH_3); 1,75 (2H, t, 5-CH_2); 2,68 (4H, t, $(CH_2)_2$); 2,94 (10H, t, $(CH_2)_5$piperidine); 3,65...4,26 (5H, m, 2-CH_2, 6-CH_2 and CH); 4,34 (1H, s, OH)	72
IIId	$C_8H_{14}O_4S$	94...95	1100 (CH_2OCH_2), 3430 (OH)	1,32 (3H, s, 4-CH_3); 1,85 (2H, t, 5-CH_2); 3,71...4,10 (5H, m, 2-CH_2, 6-CH_2 and CH); 4,15 (1H, s, OH)	76
IVa	$C_{12}H_{22}O_3S$	168	1015 (SO), 1100 (CH_2OCH_2), 3440 (OH)	1,45 (3H, s, 4-CH_3); 1,73 (12H, m, $(CH_2)_5$ cyclohexyl and CH_2); 2,75 (4H, m, CH_2OCH_2); 3,55 (1H, s, OH); 3,75 (1H, s, CHS); 3,95 (1H, t, CH cyclohexyl)	98
Va	$C_{12}H_{22}O_4S$	278	1100 (CH_2OCH_2), 1130, 1300 (SO_2)	1,65 (3H, s, 4-CH_3); 1,85...2,05 (12H, m, $(CH_2)_5$ cyclohexyl and CH_2); 3,08 (1H, s, OH); 3,64 (4H, m, CH_2OCH_2); 4,12 (1H, m, CH cyclohexyl); 4,15 (1H, t, CHS)	53
VI	$C_{17}H_{11}NO_2S$	—***	1120 (CH_2OCH_2), 2150 (SCN), 3350 (OH)	1,15 (3H, s, 4-CH_3); 1,74 (2H, t, CH_2); 3,35 (1H, d, CH—SCN); 3,78 (2H, t, CH_2O); 3,85 (2H, d, CH_2O); 5,65 (1H, s, OH)	52
VII	$C_{13}H_{16}O_4$	34	1100 (CH_2OCH_2), 1700 (C=O), 3450 (OH)	1,15 (3H, s, 4-CH_3); 1,75 (2H, t, CH_2); 4,32...3,76 (5H, m, CH_2OCH_2 and CHO); 6,25 (1H, s, OH); 7,45...7,95 (5H, m, C_6H_5)	58
VIII	$C_6H_{11}NaO_5S$	275	1120 (CH_2OCH_2), 3500 (OH)	1,64 (3H, s, 4-CH_3); 2,05...2,20 (2H, m, CH_2); 3,64...4,26 (5H, CH_2OCH_2 and CHO); 4,35 (1H, s, OH)	59
X	$C_{11}H_{21}NOS$	78	1120 (CH_2OCH_2), 3450 (SH···N)	1,26 (3H, s, 4-CH_3); 1,54 (2H, t, 5-CH_2); 3,50 (1H, s, CHN); 3,64...3,98 (4H, m, CH_2OCH_2); 4,15 (1H, s, SH); 2,14...2,96 (10H, m, $(CH_2)_5$ piperidine)	40
XI	$C_7H_{16}N_2O_6S_2$	164	675 (CS), 1675 ($C{=}\overset{+}{N}H_2$), 3300 (OH), 3420 (NH_2), 1100 (CH_2OCH_2)		70

*Spectra of IIa-c, IIIa-d, IV, and Va recorded as films; VI-VIII, X, XI in Vaseline oil.

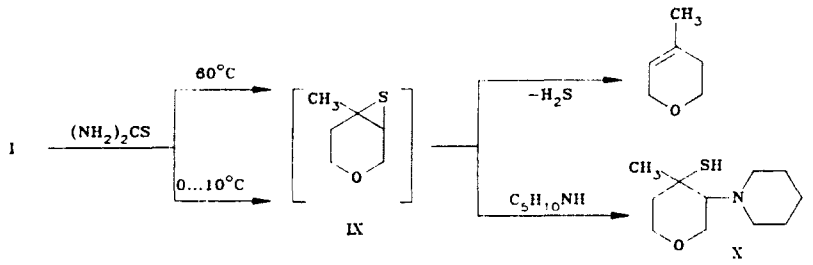
**Spectra of VIII and XI in CF_3COOD.

***bp 132°C (1 mm Hg).

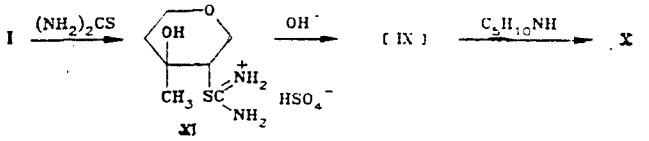
saturated aqueous-alcoholic solution of Na_2SO_3 or $Na_2S_2O_3$ gives sodium tetrahydropyran-3-yl sulfonate VIII (63 and 59% yields, respectively).

The IR spectra of dilute solutions of II-VII, as in the case of the aminolysis products [2], shows intense absorption at 3360-3440 cm^{-1}. These are characteristic of intramolecularly hydrogen bonded hydroxyl groups, which points to the occurrence of trans-diaxial opening of the epoxide ring at the least-substituted carbon atom in each of the examples discussed above.

Alkene oxides react unusually with thiourea to form episulfides [3]. A similar reaction has not been reported for pyran-type compounds. We attempted to exchange the oxygen atom of the oxirane ring for sulfur by heating epoxide I with thiourea in methanol. However, it was only possible to isolate from the reaction mixture 4-methyl-5,6-dihydro-2H-pyran which probably arises by elimination of H_2S from the episulfide IX. Formation of the latter as intermediate is confirmed by the isolation of the aminothiol X when the reaction is carried out in milder conditions with subsequent addition of piperidine.



In the presence of an equimolecular amount of H_2SO_4 (0-5°C, 6 h), the thiouronium sulfate XI is formed in 70% yield. Addition of an excess of aqueous base should also form the episulfide IX, but it could only be separated as the piperidine derivative X.



In general, the reaction of different nucleophiles with 4-methyl-3,4-epoxytetrahydropyran demands a longer reaction time than with aliphatic epoxides. This is evidently due to the effect of the pyran heteroatom which can form complexes with compounds containing labile hydrogen atoms.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument as a film or in Vaseline oil. The PMR spectra were taken on a Tesla BS-487 C (80 MHz) instrument using CCl_4 or CF_3COOD as solvent and HMDS internal standard.

Physical parameters for the prepared compounds are given in Table 1. Elemental analytical data for C, H, N, and S agreed with that calculated.

4-Methyl-3,4-epoxytetrahydropyran (I) was obtained by [1].

4-Hydroxy-4-methyl-3-phenoxytetrahydropyran (IIa). A mixture of I (5.5 g, 50 mmoles), phenol (13.6 g, 150 mmoles), NaOH (2 g, 50 mmoles), and water (7 ml) was heated with a reflux condenser for 4 h on a steam bath and the contents of the flask poured into iced water (100 ml) containing NaOH (8 g, 20 mmoles). The mixture was extracted with ether (3 × 30 ml), the ether layer dried with $CaCl_2$, and the solvent distilled off. The precipitate was filtered off and crystallized from ether to give IIa (6.2 g).

Compounds IIb, c were obtained similarly from epoxide I.

4-Hydroxy-4-methyl-3-cyclohexylthiotetrahydropyran (IIIa). A mixture of epoxide I (11.4 g, 100 mmoles), cyclohexanethiol (12.8 g, 110 mmoles), and a solution of NaOH (4 g, 100 mmoles) in water (14 ml) was heated with a condenser on a steam bath for 4 h. The precipitate was filtered off, washed with a solution of HCl (10%, 10 ml), a little water, and recrystallized from ethanol to give IIIa (18.6 g).

Compounds IIIb-d were obtained similarly.

4-Hydroxy-4-methyl-3-tetrahydropyranylcyclohexylsulfoxide (IVa). H_2O_2 (30%, 0.8 ml, 90 mmoles) was added to a solution of tetrahydropyran IIIa (2 g, 8 mmoles) in methyl ethyl ketone (30 ml). The mixture was refluxed with a condenser for 0.5 h, evaporated in vacuo, and the residue crystallized from butyl acetate to give IVa (2 g).

4-Hydroxy-4-methyl-3-tetrahydropyranylcyclohexylsulfone (Va). A mixture of tetrahydropyran IIIa (3 g, 10 mmoles), H_2O_2 (30%, 3.9 ml, 60 mmoles), and concentrated H_2SO_4 (0.02 ml) was refluxed with a condenser for 3 h. The product was evaporated in vacuo to 2 ml volume and the precipitate filtered off and recrystallized from water to give Va (1.8 g).

4-Hydroxy-4-methyl-3-thiocyanotetrahydropyran (VI). $HClO_4$ (33%, 21.6 ml) was added to a solution of potassium thiocyanate (7.8 g, 80 mmoles) in water (60 ml). The precipitate was filtered off, the filtrate extracted with ether (3 × 50 ml), the ether layer washed with saturated NaCl solution (50 ml), and dried over magnesium sulfate. Epoxide I (4.3 g, 40 mmoles) was added to the ether solution removed from the desiccant and the mixture was kept at 20°C for 48 h. The reaction mixture was washed with 5% Na_2CO_3 solution followed by saturated NaCl solution and the ether solution dried over magnesium sulfate. Removal of ether in vacuo gave VI (3.4 g).

4-Hydroxy-4-methyltetrahydropyran-3-yl Benzoate (VII). Epoxide I (1.2 g, 10 mmoles) and p-toluenesulfonic acid (0.2 g, 0.5 mmole) were added to benzoic acid (1.5 g, 10 mmoles) in $CHCl_3$ (10 ml). The mixture was stirred at 80°C for 50 h, neutralized with 5% Na_2CO_3 solution, washed with water, dried over $CaCl_2$, and the solvent distilled off. The residue was treated with hot water and the oily material removed. Upon standing it crystallized to give VII (1.4 g).

Sodium 4-Hydroxy-4-methyltetrahydropyran-3-yl Sulfonate (VIII). A mixture of sodium sulfite (2.5 g, 20 mmoles), water (20 ml), epoxide I (2.2 g, 20 mmoles), and ethanol (30 ml) was refluxed for 3.5 h, cooled, evaporated on a rotary evaporator, and the residue crystallized from ethanol to give VIII (2.6 g). Compound VIII (2.7 g, 63%) was also obtained similarly from sodium thiosulfate (3.5 g, 20 mmoles), epoxide I (2.2 g, 20 mmoles), water (6 ml), and ethanol (30 ml).

4-Methyl-4-mercapto-3-piperidinotetrahydropyran (X). Epoxide I (5 g, 50 mmoles) was added dropwise with stirring at room temperature to a solution of thiourea (5 g, 70 mmoles) in methanol (40 ml). The mixture was stirred for 5 days, the consumption of epoxide being monitored by GLC. Piperidine (9.2 g, 100 mmoles) and water (1 ml) were added and the stirring continued for a further 5 days. Piperidine was distilled off to give X (4.1 g) (from ethanol).

S-(4-Hydroxy-4-methyltetrahydropyran-3-yl)thiouronium Sulfate (XI). Epoxide I (11.4 g, 100 mmoles) was added dropwise to a solution of thiourea (8 g, 100 mmoles) in concentrated H_2SO_4 (3 ml) and water (35 ml). The mixture was stirred at 0-5°C for 5 h, gently evaporated, and the residue crystallized from ethanol to give XI (20 g).

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