EPOXIDATION OF 2-ARYL-4-METHYL-3,6-DIHYDROPYRANS AND REACTION OF THE PRODUCTS WITH PIPERIDINE

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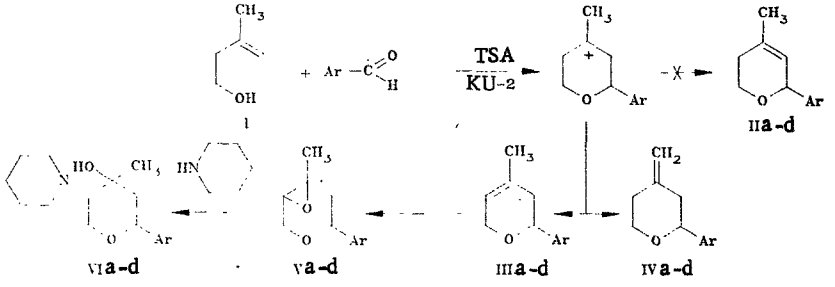
2-Aryl-4-methyl-4,5-epoxytetrahydropyrans, which react with piperidine regioselectively with trans-diaxial cleavage of the oxide ring at the least substituted carbon atom, were synthesized by the reaction of 2-aryl-4-methyl-3,6-dihydropyrans with peracids.

It is known that the condensation of 3-methyl-3-buten-1-ol (I) with aromatic aldehydes in the presence of p-toluenesulfonic acid (TSA) leads to 5,6- (II) and 3,6-dihydropyrans (III) with preponderance of the latter.* The third of the possible isomers (IV) with an exocyclic double bond has not been detected [1].

However, when we used KU-2 ion-exchange resin in the H^+ form, we obtained a mixture of isomers IIIa-d and, in smaller amounts, IVa-d.† According to the results of gas–liquid chromatography (GLC), isomers of the IIa-d type are virtually absent in the reaction mixture.



II—VI a Ar=C_6H_5; b Ar=*m*-BrC_6H_4; c Ar=*o*-OHC_6H_4; d Ar=*p*-$OCH_3C_6H_4$

The separation of isomers III and IV by the usual method is difficult, but, since pyrans with an exocyclic double bond are considerably less active in the Prilezhaev reaction [2], one might have hoped for the possibility of selective epoxidation of IIIa-d. As assumed, in all cases, we observed the formation of only one eopxide, viz., 2-aryl-4-methyl-4,5-epoxytetrahydropyrans (Va-d).

The IR spectra of epoxides Va-d contain an absorption band in the 800 cm^{-1} region, which corresponds to stretching vibrations of the $>C-C<$ (O) grouping. A doublet signal of a 5-H proton, which is affiliated with the epoxide group, is located at 2.8-3.0 ppm in the PMR spectra.

By means of thin-layer chromatography (TLC) on Al_2O_3 we ascertained that the reaction of V with piperidine has regioselective character and, as in the case in [3], leads to the formation of only one isomer (VIa-d).

Like other cyclic esters [4], tetrahydropyran VIa does not differ in stability under conditions of electron impact [intensity of molecular ion m/z 275 (2.94%)].

*In [1] structure II, which is designated as 3,6-dihydropyran, is actually the 5,6 isomer.
†Ratios of III to IV: a = 4:1, b = 17:3, c = 19:1, and d = 9:1.

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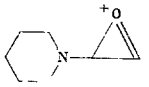
TABLE 1. 2-Aryl-4-methyl-4,5-epoxytetrahydropyrans and 2-Aryl-4-methyl-5-piperidinotetrahydropyran-4-ol

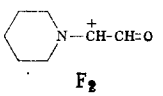
Compound	mp (bp), °C	n_D^{20}	PMR spectra, ppm				
			4-CH_3 (3H)	2-H (1H)	3-H (1H)	5-H (1H)	6-H (2H)
Va	(170)	1,5340	1,25, s	4,2	1,4, m	3,0, d	3,8, m
Vb	(335)	1,5392	1,30, s	4,16	1,8, m	2,85, d	3,7, m
Vc	89—90	—	0,9, s	4,1, s	1,7, m	3,4, d	3,5—3,7, dd
Vd	(186)	1,5380	1,1, s	4,1	1,4, m	2,9, d	3,7
VIa	125—129	—	1,25, s	4,0	1,5, m	3,0, t	4,0, t
VIb	59—60	—	1,35, s	4,16	1,8, m	3,2, t	3,7, dd
VIc	75—77	—	1,0, s	3,90, s.	1,7, m	3,5, t	3,6, m
VId	183—184	—	1,0, s	3,75	1,2, m	3,3, t	3,7, m

Compound	PMR spectra, ppm			Found, %			Empirical formula	Calc., %			Yield, %
	Aromatic	OH	Piperidine (10H)	C	H	N		C	H	N	
Va	7,1, s (5H)	—	—	75,8	7,4	—	$C_{12}H_{14}O_2$	75,8	7,4	—	46
Vb	7,2,m (4H)	—	—	53,5	4,8	—	$C_{12}H_{13}BrO_2$	53,5	4,8	—	46
Vc	7,2,m (4H)	4,15, s	—	69,9	6,8	—	$C_{12}H_{14}O_3$	69,9	6,8	—	42
Vd	7,2,m (4H)	—	—	70,9	7,3	—	$C_{13}H_{16}O_3$	70,9	7,3	—	50
VIa	7,2,s (5H)	4,6, d	2,2—2,5, m	74,2	9,1	4,90	$C_{17}H_{25}NO_2$	74,2	9,1	5,1	32
VIb	7,2,m (4H)	3,16, s	2,3—2,6, m	57,6	6,7	3,92	$C_{17}H_{24}BrNO_2$	57,6	6,8	3,9	25
VIc	7,2,m (4H)	4,45, s (2H)	2,2—2,45, m	70,1	8,6	4,79	$C_{17}H_{25}NO_3$	70,1	8,6	4,8	20
VId	7,2,m (4H)	4,37, s	2,3—2,5, m	70,8	8,9	4,53	$C_{18}H_{27}NO_3$	70,8	8,8	4,6	38

The fragment with m/z 126, the structure of which may be one of the following, has the maximum intensity:



F_1



F_2

Several virtually equally probable pathways that lead to F_1 and F_2, both in the case of cleavage of VIa and in the case of its regioisomer, are possible, and therefore this fragment cannot serve as a means of identification. On the other hand, the second most intense fragment with m/z 111 (51.4%), which is formed in the synchronous cleavage of the $O-C_{(6)}$ and $C_{(5)}-C_{(4)}$ bonds, is characteristic only for the VI structure. Of the remaining fragments, the most notable are those with m/z 127 (20.0), 110 (8.75), 98 (16.0), 96 (24.9), and 55 (3.5).

The results of TLC and PMR spectroscopy demonstrate the formation of primarily one stereoisomer of VIa-d, in contrast to the results obtained in [5]. This is due to the fact that, as a result of inversion of the initially formed products of trans-diaxial cleavage of the epoxide ring, an intramolecular bond between the hydroxy group and the nitrogen atom develops. An intense absorption band at 3450-3500 cm^{-1}, which corresponds to the stretching vibrations of the indicated bond, is present in the IR spectra of dilute solutions of VI.

EXPERIMENTAL

The IR spectra of thin films or suspensions in mineral oil and in CCl_4 solution were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with a Finnigan (Model 4021) chromatographic mass spectrometer at 68-70 eV.

The 2-aryl-4-methyl-3,6-dihydropyrans were obtained in mixtures with the corresponding 2-aryl-4-methylenetetrahydropyrans by the method in [1]. The catalysts used were TSK or KU-2 (in the H^+ form) ion-exchange resin.

2-Aryl-4-methyl-4,5-epoxytetrahydropyran (V). An ether solution of 0.22 mole of MNFK was added dropwise with stirring at 0°C to a mixture of 50 ml of dry ether and 0.2 mole of a mixture of pyrans III and IV, after which the reaction mixture was stirred at 20°C, and heated with stirring for 3 h in order to decompose the excess MNFK. The mixture was then

neutralized with 5% Na_2CO_3, the solvent was removed by distillation, and the residue was fractionated in vacuo. Oxidation with NBK was carried out in the same way as in $CHCL_3$.

2-Aryl-4-methyl-5-piperidinotetrahydropyran-4-ol (VI). A mixture of 0.02 mole of pyran V, 0.08-0.1 mole of piperidine, and 2 ml of water was maintained at 20°C for 7 days. After removal of the excess amine and water by distillation, the residue was recrystallized from a suitable solvent.

The yields, the results of elementary analysis, and the physicochemical characteristics of the products are presented in Table 1.

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SYNTHESIS OF MACROHETEROCYCLES ON THE BASIS OF 2,2-DIMETHYL-4-OXOTETRAHYDROPYRAN

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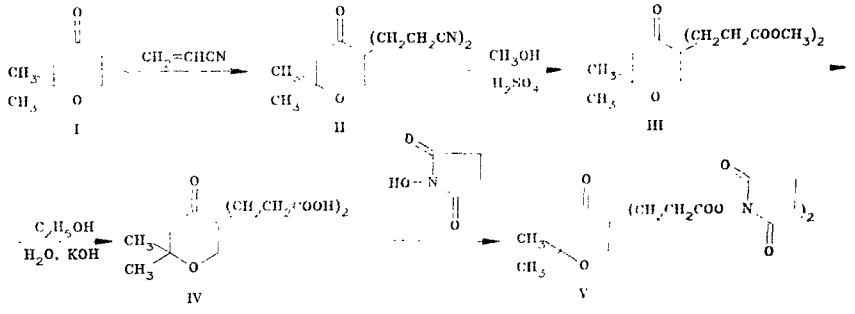
Macrocyclic compounds of a new type were synthesized by the reaction of 2,2-dimethyl-4-oxo-5,5-bis (γ-succiminidooxycarbonylethyl)tetrahydropyran with diamines under conditions that do not require high dilution of the reagents. It was established that 1,9-diazo-12,15-dioxa-2,8-dioxocycloheptadecane-5-spiro-3'-(6,6-dimethyl-4-oxo)tetrahydropyran forms a complex that includes water molecules.

Several natural macrocyclic antibiotics contain a saturated heterocyclic fragment. However, among the macroheterocyclic compounds obtained by synthetic means, representatives of this type are actually lacking [1]. In connection with this, it seemed expedient to synthesize macrocyclic compounds that contain a saturated heterocyclic ring built into the macroring or located in the side chain of the latter and to subsequently study their complexing, solvating, and pharmacological properties.

In the present communication we describe the synthesis of macrocyclic ester amides based on 2,2-dimethyl-4-oxotetrahydropyran.



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