REACTION OF 2-METHYL-2-CINNAMOYLOXIRANES WITH BENZYLAMINE AND THIOACETIC ACID

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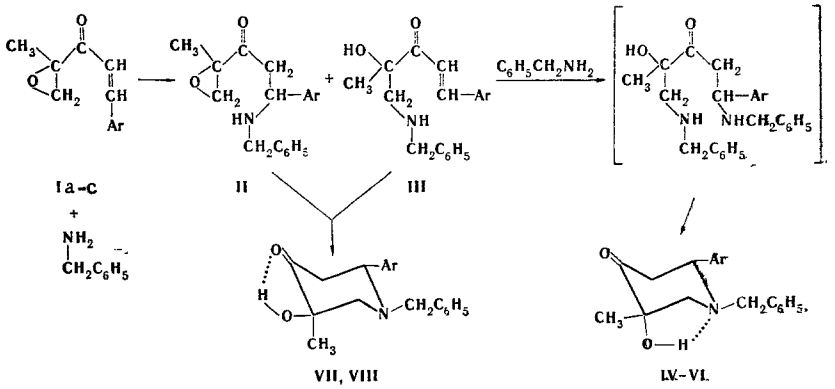
Reaction of 2-methyl-2-cinnamoyloxiranes with benzylamine gave stereoisomeric 3-hydroxy-3-methyl-1-benzyl-6-aryl-4-piperidones, which were converted to 3-hydroxy-1,3-dimethyl-6-aryl-4-piperidones by debenzylation and subsequent methylation. 3-Hydroxy-3-methyl-6-phenyltetrahydro-4-thiopyrone acetate was obtained by reaction of 2-methyl-2-cinnamoyloxirane with thioacetic acid. The three-dimensional configurations of the synthesized compounds were established by means of their IR and PMR spectra.

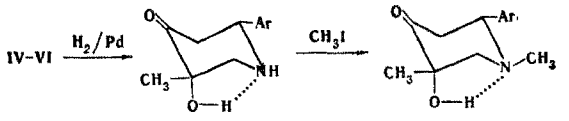
The reaction of 2-methyl-2-cinnamoyloxiranes with methylamine and hydrogen sulfide gives 3e-hydroxy-4-piperidones [1] and 3a-hydroxytetrahydro-4-thiopyrones [2, 3] – products of intramolecular cyclization of the intermediate unsaturated amino ketols and dimercapto ketols. In order to make a further investigation of the mechanism and stereochemical principles of the reactions of acyloxiranes, in the present research we studied the reaction of cinnamoyloxiranes Ia-c with benzylamine and thioacetic acid. It was found that the reaction of benzylamine, in contrast to the reaction of methylamine [1], with oxiranes Ia-c gives a mixture of stereoisomeric 3-hydroxy-4-piperidones (IV-VIII), the ratio between which is determined by the temperature conditions of the reaction. Thus primarily 3a-hydroxy-4-piperidones IV-VI are formed in refluxing isopropyl alcohol; when the reaction is carried out at 20-25°C, mainly 3e-hydroxy-4-piperidones VII and VIII are obtained.

In order to ascertain the pathways of formation of piperidones IV-VIII we isolated the primary product of addition of benzylamine to the double bond (II, Ar = C_6H_5) and to the oxide ring (III, Ar = C_6H_5). It was found that II is cyclized at 20-25° in isopropyl alcohol to piperidone VII and that III is cyclized to VII upon refluxing. Heating aminooxirane II in isopropyl alcohol is accompanied by conversion to piperidone VII and starting Ia, with predominance of the latter. Judging from the results of thin-layer chromatography (TLC), the cyclization of II occurs more rapidly and more readily than the cyclization of III. At the same time, amino alcohol III is converted to piperidone IV on heating in isopropyl alcohol in the presence of benzylamine. It must be noted that piperidones IV and VII are not epimerized in the presence of benzylamine.

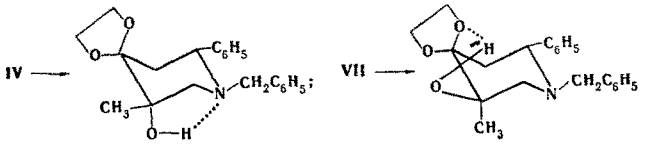


V. I. Lenin Belorussian State University, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 670-674, May, 1975. Original article submitted March 21, 1974.

The structure of benzylpiperidones IV-VI was confirmed by catalytic debenzylation to piperidones IX-XI and subsequent methylation with methyl iodide to 3a-hydroxy-4-piperidones XII-XIV, which are stereoisomers of the 3e-hydroxy-4-piperidones that we previously obtained by reaction of oxiranes Ia-c with methylamine [1].

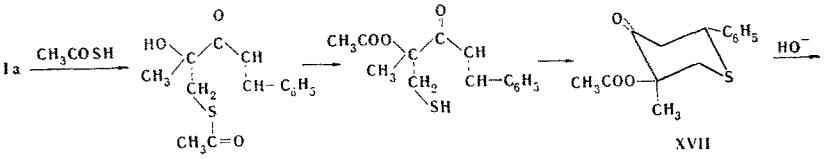


IX-XI XII-XIV

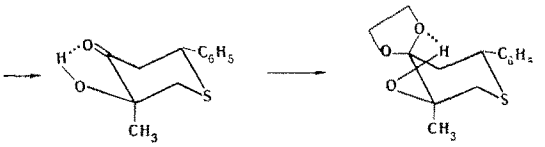


XV XVI

The primary product in the reaction of oxirane Ia with thioacetic acid is 3e-hydroxytetrahydro-4-thiopyrone acetate (XVII), the hydrolysis of which yielded hydroxythiopyranone XVIII, which is a stereoisomer of 3a-hydroxytetrahydro-4-thiopyrone, which we previously obtained by reaction of hydrogen sulfide with oxirane Ia [2, 3]. The formation of acetate XVII is evidently associated with migration of the acetyl group in the primary product of opening of the epoxide ring with thioacetic acid.



XVII



XVIII XIX

The positions of the OH absorption bands in the IR spectra of IV-XVI, XVIII, and XIX (Table 1) do not change on passing from the crystalline state to solutions up to a concentration of 10^{-3} M, and this constituted evidence for the presence of an intramolecular hydrogen bond between the equatorial hydroxyl group and the oxygen atom of the carbonyl group or between the axial hydroxyl group and the ring heteroatom. The configuration of the carbinol center was established by comparison of the IR spectra of IV, VII, and XVIII and the spectra of ethylene ketals XV, XVI, and XIX obtained from them. The OH absorption band in the spectrum of ketal XV is observed at the same frequency (3520 cm^{-1}) as in the spectrum of starting IV, and this is possible only when there is an intramolecular hydrogen bond between the axial hydroxyl group and the heteroring nitrogen atom. The band of an associated hydroxyl group in the IR spectra of ethylene ketals XVI and XIX is shifted to the high-frequency region (3580-3585 cm^{-1}); this is due to a change in the character of the intramolecular hydrogen bond and attests to equatorial orientation of the hydroxy groups in the ketols (VII and XVII) corresponding to them.

The 5- and 6-H protons in the PMR spectra of IV, VII, XII, and XVIII (Table 2) were isolated and analyzed with respect to a first-order AMX system. The observed constants are characteristic for vicinal protons in a six-membered ring in the chair conformation and correspond to interaction of the axially oriented 6-H protons with the equatorially and axially oriented 5-H protons; this corresponds to an equatorial orientation of the phenyl group. The shift in the signal of the equatorial 5-H proton to stronger field is probably due to the effect of the phenyl ring. A comparison of the J^{gem} constants and the difference in the chemical shifts of the 2-H protons with the analogous data for heterocyclic compounds with a known orientation of the unshared electron pair of the nitrogen atom [4] indicates an equatorial orientation of the methyl and benzyl groups attached to the nitrogen atom. The signals of the methylene protons of the benzyl group form a quartet in the PMR spectra of IV and VII with J = 13.5 Hz, owing to the presence of a chiral C_6 center, which creates a diastereotopic environment [5].

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Ar	mp, °C	Empirical formula	N (S), % found	N (S), % calc.	ν_{OH}, cm^{-1}	Yield, %
II	C_6H_5	72	$C_{19}H_{21}NO_2$	4,8	4,8	—	20
III	C_6H_5	43	$C_{19}H_{21}NO_2$	4,5	4,8	3450	46
IV	C_6H_5	117	$C_{19}H_{21}NO_2$	4,6	4,7	3520	52
V	4-$CH_3OC_6H_4$	146	$C_{20}H_{23}NO_3$	4,2	4,3	3520	60
VI	2-$CH_3OC_6H_4$	124	$C_{20}H_{23}NO_3$	4,5	4,3	3515	80
VII	C_6H_5	82	$C_{19}H_{21}NO_2$	4,6	4,8	3520	40
VIII	2-$CH_3OC_6H_4$	105	$C_{20}H_{23}NO_3$	4,2	4,3	3520	52
IX	C_6H_5	150	$C_{12}H_{15}NO_2$	6,6	6,7	3500	88
X	4-$CH_3OC_6H_4$	154	$C_{13}H_{17}NO_3$	6,0	6,0	3480	83
XI	2-$CH_3OC_6H_4$	145	$C_{13}H_{17}NO_3$	6,1	6,0	3490	88
XII	C_6H_5	85	$C_{13}H_{17}NO_2$	6,2	6,4	3500	72
XIII	4-$CH_3OC_6H_4$	107	$C_{14}H_{19}NO_3$	5,5	5,6	3500	93
XIV	2-$CH_3OC_6H_4$	74	$C_{14}H_{19}NO_3$	5,6	5,6	3510	85
XV	—	131	$C_{21}H_{25}NO_3$	4,1	4,2	3520	68
XVI	—	121	$C_{21}H_{25}NO_3$	4,2	4,2	3585	83
XVII	—	138	$C_{14}H_{16}O_3S$	(12,0)	(12,1)	—	68
XVIII	—	93	$C_{12}H_{14}O_2S$	(14,3)	(14,4)	3500	90
XIX	—	107	$C_{14}H_{18}O_3S$	(11,9)	(12,0)	3580	83

TABLE 2. Parameters of the PMR Spectra

Compound	δ, ppm								J, Hz			
	2-H_a	2-H_e	5-H_e	5-H_a	6-H_a	N—R	3-CH_3	OH	2-H_{ae}	5-H_{ae}	6-H_a, 5-H_a	6-H_a, 5-H_e
IV	2,33	3,74	2,60	3,14	3,74	3,06	1,23	3,96	13,5	14,5	9,5	4,8
VII	2,09	3,80	2,49	2,75	3,50	2,95	1,50	3,56	11,8	14,0	11,0	3,7
XII	2,31	2,89	2,28	2,95	3,19	2,06	1,18	3,92	12,0	12,0	10,5	3,0
XVIII	2,78	2,88	2,88	3,17	4,08	—	1,62	4,10	13,0	13,0	12,0	3,5

In conformity with the results obtained and the data in previously published papers [1, 3], the conversion of cinnamoyloxiranes in reactions with primary amines or hydrogen sulfide to the corresponding 3e-hydroxy-4-piperidones or 3e-hydroxytetrahydro-4-thiopyrones occurs via intramolecular cyclization of the primary products of addition of the amine or hydrogen sulfide to the oxide ring or the double bond, whereas intramolecular cyclization of the products of the secondary addition gives 3a-hydroxy-4-piperidones or 3a-hydroxytetrahydro-4-thiopyrones.

EXPERIMENTAL METHOD

The IR spectra of solutions of the compounds in carbon tetrachloride (10^{-1} and 10^{-3} M) and of KBr pellets were recored with a UR-20 spectrometer. The PMR spectra were recorded with Varian HA-100 D-15 and JNM-PS-100 spectrometers with hexamethyldisiloxane as the internal standard. The physical characteristics of compounds II-XIX are presented in Table 1.

5-Benzylamino-2-methyl-5-phenyl-1,2-epoxy-3-pentanone (II). A 0.1-mole sample of benzylamine and 1 g of methyltriethylammonium iodide were added to a solution of 0.1 mole of oxirane Ia in 180 ml of benzene, and the mixture was shaken at 20-25° for 48 h. The catalyst was then removed by filtration, the benzene was removed from the filtrate by distillation at reduced pressure, and the residue was crystallized from ether–petroleum ether (2 : 1) to give 5.9 g of amino ketone II. IR spectrum: 1720 (C=O) and 3370 cm^{-1} (NH).

1-Benzylamino-2-hydroxy-2-methyl-5-phenyl-4-penten-3-one (III). A solution of 0.05 mole of oxirane Ia, 0.04 mole of benzylamine hydrochloride, and 0.01 mole of benzylamine in 100 ml of methanol was held at 20-25° for 5 days. The methanol was then removed by distillation, and the residue was dissolved in 100 ml of water. The neutral reaction products were extracted with ether, after which the mixture was made alkaline with potassium carbonate. The liberated reaction product was extracted with ether, and the ether extracts were washed three times with water and dried with sodium sulfate. The ether was removed by distillation, and the residue was fractionally crystallized from ether–petroleum ether (1 : 1) to give 6.8 g of amino alcohol III. IR spectrum: 1620 (C=C), 1690 (C=O), 3370 (NH); 3450 cm^{-1} (OH).

3a-Hydroxy-3e-methyl-1e-benzyl-6e-aryl-4-piperidones (IV-VI). A) A 0.2-mole sample of benzylamine was added to a solution of 0.2 mole of oxirane Ia-c in 200 ml of isopropylalcohol, and the mixture was refluxed for 1 h. The solvent was removed by distillation, and the residue was acidified with 5% hydro-

chloric acid. The resulting solution was treated with ether, after which it was made alkaline with potassium carbonate. The liberated reaction product was removed by filtration, washed with water, dried in a desiccator over potassium hydroxide, and crystallized from heptane.

B) A few drops of benzylamine were added to a solution of 0.01 mole of amino alcohol III in 20 ml of isopropyl alohol, and the mixture was refluxed for 20 min. The solvent was then removed by distillation, and the residue was crystallized from heptane to give 2.4 g (80%) of piperidone IV.

3e-Hydroxy-3a-methyl-1e-benzyl-6e-aryl-4-piperidones (VII and VIII). A) A 0.05-mole sample of benzylamine was added to a solution of 0.05 mole of oxirane Ia, c in 100 ml of methanol, after which the mixture was held at 20-25° for 2 days and worked up as in the preceding experiment.

B) A 0.01-mole sample of amino ketone II was dissolved in 20 ml of methanol, and the solution was held at 20-25° for 30 min. The methanol was then removed by distillation, and the residue was crystallized from hexane to give 2.3 g (77%) of piperidone VII.

C) A solution of 0.01 mole of amino alcohol III in 20 ml of isopropyl alcohol was refluxed for 12 h, after which the solvent was removed by distillation, and the residue was crystallized from hexane to give 1.8 g (61%) of piperidone VII.

3a-Hydroxy-3e-methyl-6e-aryl-4-piperidones (IX-XI). A solution of 0.03 mole of piperidone IV-VI in 50 ml of glacial acetic acid was stirred vigorously in the presence of 1 g of 5% $Pd(OH)_2$ on carbon in a hydrogen atmosphere until 0.03 mole of hydrogen had been absorbed. The catalyst was then removed by filtration, the acetic acid was removed by distillation, and the residue was dissolved in 20 ml of water and made alkaline with potassium carbonate. The liberated reaction product was removed by filtration, washed with water, dried in a desiccator over potassium hydroxide, and crystallized from isopropyl alcohol–heptane (3 : 1).

3a-Hydroxy-1e,3e-dimethyl-6e-aryl-4-piperidones (XII-XIV). A 0.012-mole sample of methyl iodide and 2 g of potassium hydroxide were added to a solution of 0.01 mole of piperidones IX-XI in 50 ml of acetone, and the mixture was refluxed for 30 min. The resulting precipitate was removed by filtration, the acetone was removed by distillation, and the residue was crystallized from hexane.

3e-Hydroxy-3a-methyl-6e-phenyltetrahydro-4-thiopyrone (XVIII). A 0.5-g sample of sodium acetate and 0.05 mole of thioacetic acid were added to a solution of 0.05 mole of oxirane Ia in 300 ml of isopropyl alcohol, and the mixture was held at 20-25° for 12 h. The solvent was then removed by distillation, and the residue was crystallized from benzene–heptane (1 : 4) to give 9 g of 3e-acetoxy-3a-methyl-6e-phenyltetrahydro-4-thiopyrone (XVII). A solution of 0.01 mole of acetate XVII and 0.01 mole of potassium hydroxide in 50 ml of methanol was held at 20-25° for 2 h, after which the methanol was removed by distillation, the residue was treated with water, and the liberated reaction product was removed by filtration, air-dried, and crystallized from heptane to give 2 g of thiopyranone XVIII.

3a-Hydroxy-3e-methyl-1e-benzyl-6e-phenyl-4-piperidone Ethylene Ketal (XV). A 0.25-mole sample of ethylene glycol and 0.07 mole of p-toluenesulfonic acid were added to a solution of 0.05 mole of piperidone IV in 200 ml of benzene, after which the mixture was refluxed with a Dean–Stark trap for 40 min. The solvent was then removed by distillation, the residue was treated with 50 ml of 15% aqueous potassium hydroxide, and the liberated reaction product was removed by filtration, washed with water, air-dried, and crystallized from benzene–heptane (1 : 3).

Ethylene ketals XVI and XIX were similarly obtained.

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