CONFORMATIONAL ANALYSIS AND STEREOCHEMISTRY OF THE REDUCTION OF 2-ALKOXYMETHYL-4-OXOPIPERIDINES

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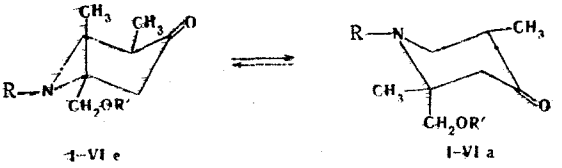
The isomer with an axially oriented alkoxymethyl group predominates in the equilibrium mixture of 1-aklyl-2,5-dimethyl-2-alkoxymethyl-4-piperidones investigated under both alkaline and acidic equilibrium conditions, and its percentage increases as the volume of the alkoxy group increases in the order Me, Et, iso-Pr. The reduction of 4-ketopiperidines that contain a polar function in the 2 position follows the same principles as those that obtain when it is absent, i.e., exclusively the equatorial alcohols are obtained in the case of reduction with lithium and ethanol in liquid ammonia, whereas primarily the axial alcohols are obtained in the case of reduction with sodium borohydride. The selectivity of the reduction increases on passing from the free bases to the hydrochlorides.

We recently reported the significant effect of both the substituent attached to the nitrogen atom and the acidity of the medium on the ratio of diasteromers of disubstituted 4-ketopiperidines [1, 2]. In the present communication we present data relative to similar sorts of equilibria of 2-alkoxymethyl-substituted ketones that we have previously synthesized [3].



I-VI e I-VI a

The signals of the methyl groups attached to C_2 in the spectrum of a mixture of the isomers are observed at 0.8 and 1.05 ppm. Only the signal at 1.05 ppm is present in the spectrum of individual isomer (a). On the basis of the well-known rule that the protons of the axial groups resonate at stronger field than the equatorial groups, we assumed that the methyl group in the isolated C_2 isomer is oriented equatorially and that, correspondingly, the alkoxymethyl group is oriented axially. This was also confirmed by the IR spectra (by the presence of an intramolecular hydrogen bond in the corresponding alcohols of the a,a series). Since the C_5 signal of the methyl group in the PMR spectra of both the mixture and individual isomer (a) is observed at the same δ value of 0.9 ppm ($J = 6$ Hz), it follows that its orientation remains unchanged.

Equilibrium mixtures were obtained by the methods in [1, 2].

Despite the reasonable expectation that for a certain N-series the relative amount of the e isomers in the equilibrium mixture will increase as the volume of the R' group increases, the opposite dependence actually occurs in the case of equilibrium in a basic medium, i.e., the axial isomer is more stable. Thus unusual behavior of the alkoxymethyl group is to some degree in agreement with the earlier data on the steric interaction between compounds with N- and C_2-alkyl substituents, in which the bulkier substituent attached to the nitrogen atom forces the vicinal alkyl group to occupy an axial position [1, 2]. In actuality, the stabilities of the a isomers for R' = Me increases [sic] in the order NH > NCH_3 > NEt > NPr-iso (IV, I, V, and VI in Table 1), where the apparent effective volume of CH_2OCH_3 decreases in the homologous series ($\Delta G^{\circ}_{CH_3} - \Delta G^{\circ}_{CH_2OCH_3}$ = —0.76 kcal/mole for NH, —0.11 for NCH_3, and approximately zero for NC_2H_5 and NPr-iso).

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TABLE 1. Equilibria of I-VII at 50°C

Compound	R	R′	Method A				Method B			
			a epimer, %	e epimer, %	K	ΔG^0 kcal/mole	a epimer, %	e epimer, %	K	ΔG^0, kcal/mole
I	Me	Me	45,8	54,2	1,18	−0,11	62,5	37,5	0,60	0,33
II	Me	Et	60,0	40,0	0,66	0,27	70,0	30,0	0,43	0,54
III	Me	*i*-Pr	64,6	35,4	0,55	0,24	70,5	29,5	0,42	0,56
IV	H	Me	23,3	76,7	3,29	−0,76	62,5	37,5	0,60	0,33
V	Et	Me	50,2	49,8	0,99	0,005	71,0	29,0	0,41	0,57
VI	*i*-Pr	Me	51,0	49,0	0,96	0,03	63,6	31,4	0,46	0,50
VII			73,0	27,0	0,33	0,71	67,3	32,7	0,48	0,50

TABLE 2. Results of Reduction of 2a-Alkoxymethylpiperidones I-IV and VII

Starting ketone	Reduction conditions[a]	Alcohol ratio, %[b]		bp, °C (mm)	n_D^{20}	d_4^{20}	ν_{OH}, cm^{-1}	Found, %			Empirical formula	Calc., %		
		a	e					C	H	N		C	H	N
I	A	—	100	95—96[c]	—	—	3628	64,2	11,3	7,5	$C_{10}H_{21}NO_2$	64,1	11,3	7,5
II	A	—	100	65—66[c]	—	—	3627	65,6	11,6	7,0	$C_{11}H_{23}NO_2$	65,6	11,5	7,0
III	A	—	100	73—75[c]	—	—	3628	67,0	11,7	6,6	$C_{12}H_{25}NO_2$	66,9	11,7	6,5
IV	A	—	100	111—113 (5)	1,4711	0,9116	3626	62,4	11,1	8,0	$C_9H_{19}NO_2$	62,4	11,0	8,1
VII	A	—	100	119—121[c]	—	—	3628	68,7	11,1	6,2	$C_{13}H_{25}NO_2$	68,7	11,1	6,2
I	B	54,6 (72,0)	45,4 (28,0)	115—118 (5)	1,4810	1,0263	3628 3434	64,1	11,3	7,5	$C_{10}H_{21}NO_2$	64,1	11,3	7,5
II	B	55,0 (67,0)	45,0 (33,0)	121—123 (5)	1,4800	1,0181	3627 3434	65,6	11,6	7,0	$C_{11}H_{23}NO_2$	65,6	11,5	7,0
III	B	53,7 (60,5)	46,9 (39,5)	128—130 (5)	1,4790	1,0073	3628 3434	67,0	11,7	6,5	$C_{12}H_{25}NO_2$	66,9	11,7	6,5
IV	B	56,7 (65,1)	43,3 (34,9)	111—113 (5)	1,4711	1,0116	3626 3434	62,4	11,1	8,1	$C_9H_{19}NO_2$	62,4	11,0	8,1
VII	B	80,8 (66,6)	19,2 (33,4)	115—117[c]	—	—	3628 3434	68,7	11,1	6,2	$C_{13}H_{25}NO_2$	68,7	11,1	6,2

a) Reduction methods: by means of lithium in liquid ammonia (method A), and by means of sodium borohydride (method B). b) The results of reduction of the hydrochlorides are presented in parentheses. c) These are the melting points.

A comparison of the results with respect to the acidic and alkaline equilibria shows that the transition to acid solutions leads to a change in the relative stabilities of the epimers (for example, for IV in Table 1 the overall difference in ΔG° is on the order of 1 kcal/mole) and an increase in the percentage of the a isomers in the equilibrium mixtures.

Also of interest is the observation that crystallization of the equilibrium mixture of the corresponding hydrochlorides from ethyl acetate gives the pure a isomer in high yield.

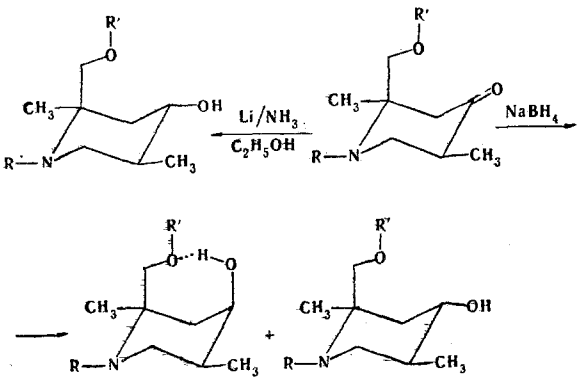
The last line in Table 1, in which data on the equilibrium of 1,2-dimethyl-2-methoxymethyldecahydro-4-quinolone (VII) are presented, is worthy of special comment because of the high percentage of the a isomer and the conditions of alkaline epimerization. This suggests the possibility of a decrease in the interaction of the alkylamine and alkoxymethyl groups in the one-ring series due to conformational distortion of the ring.

The stereochemistry of the reduction of substituted γ-piperidones has been previously examined (see [4] and the literature cited therein). In the present communication we describe the reduction of 2,5-dimethyl-2-alkoxymethyl-4-piperidones (Table 2). One might have expected that the presence of a polar function in the molecule might affect the direction of attack of the reagent in reduction reactions.

The configurations of the alcohols were derived on the basis of data from gas–liquid chromatography (GLC) and IR spectroscopy (from the presence of an intramolecular hydrogen bond in the a,a isomer).

It is known that the reduction of 1,2,2,5-tetramethyl-4-piperidone with sodium borohydride leads to the primary formation of alcohols with an axially oriented hydroxy group, whereas in the lithium–liquid ammonia–ethanol system the primary products are the equatorial

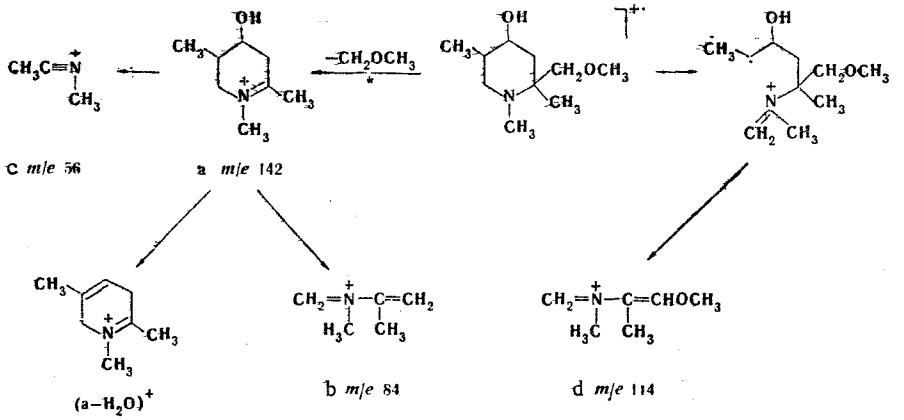
alcohols. We obtained similar results in the reduction of 2a-alkoxymethylpiperidones I-IV, VII.



The reduction of piperidones I-IV and VII in the lithium–liquid ammonia–ethanol system both in the form of the free bases and the hydrochlorides leads to absolutely identical results – one isomer of the alcohol with an equatorially oriented hydroxy group is formed in both cases. However, in the case of reduction with borohydride, alcohols with primarily an axially oriented hydroxy group are obtained, and the selectivity of the reduction increases on passing from the free bases to the hydrochlorides.

The frequency of the absorption of the resulting piperidols with an equatorial hydroxy group in the IR region under conditions that exclude an intermolecular hydrogen bond (0.005 mole/liter) is 3628 cm^{-1}, whereas an absorption band of a hydrogen-bonded hydroxy group at 3434 cm^{-1} was observed for alcohols with an axial hydroxy group.

No molecular-ion peaks are present in the mass spectra of any of the investigated compounds. The most intense peak in the spectra corresponds to the $[M-CH_2OR']^+$ ion (a), which subsequently undergoes fragmentation to give $[a-H_2O]^+$, b, c, and d ions.



The fundamental scheme of the fragmentation of the 4-piperidols (in the case of I) is presented on the basis of the principles of fragmentation of cyclic amines [5-8]. The mass spectra of stereoisomeric alcohols I-IV do not differ substantially. However, a rather intense (~5% of the maximum) peak of the $M-H_2O$ ion, which is absent in the spectrum of the isomer with an equatorial hydroxy group, is present in the case of the stereoisomers of VII with an axial orientation of the hydroxy group.

EXPERIMENTAL

Chromatographic analysis was carried out with a Khrom-4 chromatograph with a glass capillary column with a length of 60 m and an inner diameter of 0.2 mm with the use of XE-60 nitrosilicone (in the case of the piperidones) and PEG-20000 (in the case of the epimeric alcohols) as the stationary phase. The temperature of the thermostat was maintained at 150-160°C (ketones I-VI), 200°C (VII), 160-180°C (4-piperidols), and 220°C (decahydro-4-quinolol). The detector was a flame-ionization apparatus, and the carrier gas was nitrogen. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ionization region at an input temperature of 40-60°C and an ionizing-electron energy of

30 eV. The IR spectra (0.005 mole/liter solutions in CCl_4) were recorded with a UR-20 spectrometer.

Epimerization of 1-Alkyl-2,5-dimethyl-2-alkoxymethyl-4-piperidones and 1,2-Dimethyl-2-methoxymethyldecahydro-4-quinolone. A) A solution of 0.03 g of the piperidone in 0.5 ml of tert-butylamine and 0.25 ml of water was heated in a sealed ampul at 50°C for 5 h. The isomerization product was analyzed without additional purification by GLC (Table 1).

B) A stream of dry hydrogen chloride was passed into a solution of 0.1 g of piperidone in 2 ml of dry ethyl acetate until the precipitated hydrochloride dissolved, and the resulting solution was heated in a sealed ampul at 50°C for 5 h. The ethyl acetate was then removed by distillation, one drop of water was added, and the ether and piperidone were salted out with potassium carbonate. The ether extract was washed with water and passed through a column filled with aluminum oxide. The solvent was removed by distillation, and the isomerization products were analyzed by GLC (Table 1).

Reduction in the Lithium–Liquid Ammonia–Ethanol System. A 0.7-g (0.1 mole) sample of lithium was added gradually to a solution of 0.02 mole of piperidone (or its hydrochloride) and 5.8 ml of absolute ethanol in 200 ml of liquid ammonia, and the resulting blue solution was stirred for 30 min. Ammonium chloride (7 g) was added, the ammonia was evaporated, water was added to the residue, and the reaction product was extracted with ether after saturation with potassium carbonate. The extract was dried with magnesium sulfate, the solvent was removed by distillation, and the product crystallized on standing. The products (the e alcohols) were obtained in quantitative yields.

Reduction with Sodium Borohydride. A solution of 1.9 g (0.05 mole) of sodium borohydride in 30 ml of methanol was added gradually along with one drop of concentrated sodium hydroxide solution to a solution of 0.1 mole of piperidone or its hydrochloride in 30 ml of methanol while maintaining the temperature of the reaction medium betweeen 20 and 25°C, after which the mixture was stirred with gentle refluxing for 2 h. It was then cooled and acidified with concentrated sulfuric acid, diluted to 150 ml with water, made alkaline, and extracted with ether. The aqueous layer was salted out thoroughly with potassium carbonate. The combined ether extracts were dried with magnesium sulfate, the solvent was removed by distillation, and the residue was vacuum-distilled (except in the case of V). The yields of the products (the mixtures of a, e alcohols in the ratios indicated in Table 2) were quantitative.

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