ROLE OF POLAR AND STERIC FACTORS IN THE REDUCTION OF KETONES OF THE PIPERIDINE SERIES

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The polar factor plays a very important role during the hydride reduction and, especially, during a catalytic hydrogenation of derivatives of 4-ketopiperidine [1, 2]. In the present communication, we describe a number of new instances showing the relative role played by polar and steric factors in the reduction of the keto group of γ-piperidones. The results obtained are shown in Table 1. The configuration of the alcohols obtained was determined on the basis of the preparation method (see [1, 2]), chromatographic data (gas – liquid chromatography and thin layer chromatography*), IR spectroscopy data (free and bound hydroxyl groups), and the results of potentiometric titration [11]. On the basis of the previously published data [1, 2] (shown in Table 1) for epimeric vapors of 4-piperidols, it is possible to deduce their respective configurations from the composition of alcohol mixtures obtained by the hydride reduction of the corresponding ketones ($NaBH_4 - H_2O$ and $Li/NH_3 - C_2H_5OH$). In fact, if during the reduction of 4-ketopiperidines both reactants give a substantial predominance (80-90%) of the same alcohol epimer, such a result reliably indicates that the alcohol has an equatorial configuration. These data also indicate that the character of the alkyl substituent at the nitrogen atom does not essentially influence the stereochemistry of the reduction reaction. Thus, the reduction with $NaBH_4$ (or another reducing agent) of ketones (I) or (II) yields practically the same ratio of epimeric alcohols, as in the case of their N-methyl analogs [1]. The same rule applies to other homologs.

According to [1], during the reduction of unhindered ketones with $NaBH_4^-$, quaternary salts are reduced in a considerably more stereo-directed manner, giving predominantly the equatorial epimers. Such an increase in the stereospecificity of the quaternary forms is connected with the structure of the ion pair $N^+ \ldots BH_4^-$, because the axial orientation of the BH_4^- ion is assumed to be the most favorable for further transformations into the reduction products [1]. On examples of hindered ketones (IV), (X), (XI) and (XII),† it is possible to evaluate the role of the steric and polar factors. In fact, the axial orientation of the BH_4^- anion should be hindered by the axial bond C – C in these ketones. Table 1 indicates that in the case of the reduction of hindered ketones (X), (XI), and (XII) axial alcohols markedly predominate. In an analogous way proceeds the reaction of isopropylate or catalytic reduction. Thus, the steric effect of a meta-axial substituent apparently fully neutralizes the effect of the nitrogen function field and, during the ammoniation of the nitrogen function (Xb, c, g; XIb, g; XIIb, c, e, f), the composition of the reaction products changes only a little. For such ketones, the ratio of *a*- and e-epimers of alcohols is near to the epimer ratio resulting from the reduction with $NaBH_4$ of hindered carbocyclic ketones [14]. The stereospecificity of the $Li/NH_3 - C_2H_5OH$ reagent applies also to such hindered ketones which yield, like unhindered ketones, equatorial epimers of alcohols (IVa, Xd, and XIc). The relatively small stereospecificity of the reduction of ketone (XI) is apparently caused by the conformation lability of this ketone (of the type chair ⇌ boat). The relatively easy conversion of the cis-perhydropyrindine systems was already confirmed by chemical [8] and spectral [11, 15] data.

Catalytic hydrogenation of piperidine ketones is of special interest. In this case, the difference between the piperidine heterocycles and the carbocycles having a similar structure is more distinct than during the hydride reduction [2]. For instance, by the hydrogenation of trans-2,3-dimethylcyclohexanone over

* For N-alkyl derivatives (H, CH_3, C_2H_3 and iso-C_3H_7) of γ-piperidol the retained volumes of the axial alcohols during the gas – liquid chromatography [3] in PEG – Chromosorb columns were always smaller than the retained volumes of the equatorial alcohols. During the thin-layer chromatography, the R_f of the axial alcohols was always greater than the R_f of equatorial alcohols [10].

† On the basis of data from [8, 9, 11-13], it can be reckoned that the predominant conformation of these ketones is (Xa) and (XIIa); for ketone (IV), conformation with axial methyl at C_2 can be inferred from the results of the reduction with $NaBH_4^-$ and $Li/NH_3 - C_2H_5OH$ (see Table 1, IVa, b).

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TABLE 1

Ketone		Reaction conditions	Reaction products, %% (a- and e-epimers)	
			a	e
N-Ethyl-3-methylpiperidone-4 (I)	a Base	$NaBH_4-H_2O$ (0°)	5	95
	b The same	$Li/NH_3-C_2H_5OH$	0.5	99.5
2,3-Dimethylpiperidone-4 (trans-) (II)	a Hydrochloride [3]	$NaBH_4-H_2O$ (0°)	8	92
	b The same	$H_2/Pt-H_2O$	16	84
	c " "	$Al(O-i-C_3H_7)_8-i-C_3H_7OH$	70	30
1,2,3-Trimethylpiperidone-4 (trans-) (III)	a Base [3]	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$	60	40
	b The same	$NaBH_4-H_2O$ (0°)	15	85
	c Hydrochloride	The same	8	92
	d The same	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$	65	35
	e Base	The same *	60	40
	f Hydrochloride	$Li/NH_3-C_2H_5OH$	1	99
	g Iodomethylate	$NaBH_4-H_2O$ (0°)	2	98
N-Ethyl-2,3-dimethylpiperidone-4 (cis-) (IV)	a Hydrochloride	$NaBH_4-H_2O$ (0°)	92	8
	b The same	$Li/NH_3-C_2H_5OH$	30	70
N-Isopropyl-2,3-dimethylpiperidone-4 (trans-) (V)	a Base	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$ *	53	47
	b Hydrochloride	$NaBH_4-H_2O$ (0°)	2	98
	c The same	$NaBH_4-CH_3OH$ (0°)	4	96
	d " "	$Li/NH_3-C_2H_5OH$	1	99
2,5-Dimethylpiperidone-4 (trans-) (VI)	a Hydrochloride [4]	$NaBH_4-H_2O$ (0°)	6	94
1,2,5-Trimethylpiperidone-4 (trans-) (VII)	a Base [4]	$NaBH_4-H_2O$ (0°)	12	88
	b The same	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$ †	53	47
	c Hydrobromide	The same	66	34
	d The same	$NaBH_4-H_2O$ (0°)	3	97
	e " "	$Li/NH_3-C_2H_5OH$	0.5	99.5
	f Iodomethylate	$NaBH_4-H_2O$ (0°)	1	99
N-Isopropyl-2,5-dimethylpiperidone-4 (trans-) (VIII)	a Hydrochloride [5]	The same	4	96
	b The same	$Li/NH_3-C_2H_5OH$	1	99
1,3,3,5-Tetramethylpiperidone-4 (IX)	a Base [6]	$NaBH_4-H_2O$ (0°)	12 [6]	88 [6]
	b Hydrochloride	The same	10	90
	c Iodomethylate	" " †	1	99
	d Base	$Li/NH_3-C_2H_5OH$	1	99
	e The same	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$	88	12
	f " "	Pt/H_2-H_2O	5	95
	g Hydrochloride	The same	6.4	93.6
1,2,2,5-Tetramethylpiperidone-4 (X)	a Base [7]	$NaBH_4-H_2O$ (0°)	76.2 [6]	23.8 [6]
	b Hydrochloride	The same	81.5	18.5
	c Iodomethylate	" " †	79	21
	d Base	$Li/NH_3-C_2H_5OH$	2	98
	e The same	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$	92	8
	f " "	Pt/H_2-H_2O	96	4
	g Hydrochloride	The same	95.5	4.5
Perhydropyrindone-4 (cis-) (XI)	a Base [3]	$NaBH_4-H_2O$ (0°)	89 [8]	11 [8]
	b Hydrochloride	The same ‡	99	1
	c Base	$Li/NH_3-C_2H_5OH$	30	70
	d The same	$Al(O-i-C_3H_7)_3-i-C_3H_7OH$	78	22
	e " "	$Pt/H_2-CH_3OH/H_2O$ (1:1)	81	19
	f " "	Pt/H_2-ethyl acetate	80	20
	g " "	Pt/H_2-H_2O	90	10

(Table 1 continued overleaf)

TABLE 1 (Continued)

Ketone		Reaction conditions	Reaction products, % (a- and e-epimers)	
			a	e
1-Methylperhydropyrindone-4 (cis-) (XII)	a Base [3]	$NaBH_4-H_2O$ (0°)	82.5 [9]	17.5 [9]
	b Hydrochloride	The same	79	21
	c Iodomethylate	" "	79.5	20.5
	d Base	Pt/H_2-H_2O	82.3	17.7
	e Hydrochloride	The same	83.5	16.5
	f Quaternary nitrate	" "	75	25
Perhydroquinolone-4 (trans-) (XIII)	a Base	$Pt/H_2-CH_3OH/H_2O$ (1:1)	45 [1]	55 [1]
	b Hydrochloride	Pt/H_2-H_2O	15	85
1-Methylperhydroquinolone-4 trans-) (XIV)	a Base [3]	$Pt/H_2-CH_3OH/H_2O$ (1:1)	27 [6]	73 [6]
	b The same	Pt/H_2-dry dioxane	47.5	52.5
	c " "	$Pt/H_2-HN(C_2H_5)_2/H_2O$(5:1)	33	67
	d " "	Pt/H_2-0.5 N KOH/CH_3OH-H_2O (1:1)	42	58
	e " "	Pt/H_2-CH_3COOH	9	91
	f Hydrochloride	Pt/H_2-H_2O	11.2	88.8
	g Chloromethylate	The same	7.3	92.7

* A mixture of cis- and trans-isomers of the ketone was reduced.
† Analysis after dequaternization with Li/NH_3.
‡ Analysis after methylation with CH_2O-Pt/H_2.

platinum in an acid medium is obtained a mixture of alcohols consisting of 84% of the axial epimer, 7% of the equatorial epimer, and 9% of cis-alcohol [16]. On the other hand, the structural analog piperidone (IIb) gives under analogous conditions up to 84% of the e-epimer. Other unhindered 4-ketopiperidines, in the form of ammonium salts, have analogous stereospecificity, which was explained in [2] by a proposed scheme of heteropolar orientation of a ammoniated γ-piperidone molecule on the negatively charged surface of a platinum catalyst saturated with hydrogen (type A in Fig. 1). Another possible type of orientation (Fig. 1B) is less feasible from the energy standpoint and can occur only if the orientation scheme A is sterically hindered (ketones Xg, XIIe, f). However, the results of the reduction reaction shown in Table 1 also indicate that heteropolar orientation of the molecule of aminoketone cannot be the sole factor determining the stereochemistry of the hydrogenation of any derivatives of aminoketones in different solvents. Thus, during the hydrogenation of free bases of unhindered ketones (XIIIa, XIVa, b, c, d) in dry dioxane or ethyl acetate, and in alkaline aqueous solutions, the stereospecificity of the hydrogenation sharply decreases, but in not one case does there appear any distinct predominance of the axial epimers, such as in the case of carbocyclic ketones. On the basis of these considerations, the schemes mentioned above (see [2]) can be presented in a more general form. In particular, a characteristic feature of aminoketones is their two-center adsorption caused by the ketone and amine functions. However, depending on the nature of the medium, this two-center adsorption can be either of the heteropolar-covalent type (scheme A for unhindered ketones, and B for hindered ketones), or covalent only, because of the direct interaction of the free electron pair of the nitrogen atom and the electron system of the carbonyl group with the catalyst surface. In the latter case, a sufficiently near approach of both functions to the catalyst surface can be obtained only by a considerable deformation of the molecule (also in the case of the rigid conformations of the system of the (XIII) and (XIV) types); possibly with conversion into a "twist" conformer (Fig. 1C and D). In contrast to the heteropolar orientation, in the case of the "covalent" adsorption both orientation types (C and D) are nearly equivalent from the energy standpoint. This indicates that during the reduction of unhindered 4-ketopiperidines in aprotonic solvents (XIVa), the stereoselectiveness is nearly completely absent. Nevertheless, also in this case the direction of the orientation is sensitive to steric screening of either of the two functions (amine or carbonyl), as in the case of the heteropolar orientation. Thus, amine (IXf) having a hindered amine function [11] should be adsorbed according to scheme C, and amine (Xf) with hindered carbonyl function according to scheme D (Fig. 1).

EXPERIMENTAL

N-Ethyl-3-methylpiperidone-4. Methyl β-ethylamino-α-methylpropionate (bp 51–53°; 7 mm) was obtained from methyl acrylate and ethylamine according to [17]. This ester was then heated with acrylic ester for 4 h at 60°; subsequently the reaction mixture was distilled under vacuum. The diester so obtained (bp 125° (7 mm)) was cyclized with $NaNH_2$ in liquid NH_3, as described in [18]. After decarboxylation of the cyclization product by means of HCl, the base 1-ethyl-3-methylpiperidone-4 was liberated with K_2CO_3 and distilled, bp 70–71° (7.5 mm). Found: C 67.96; H 10.39; N 10.1%. $C_8H_{15}NO$. Calculated: C 68.08; H 10.63; N 9.92%.

To a solution of 8 g of 1,3-dimethylpiperidone-4 iodomethylate in 5 ml of water were added 5 ml of ethylamine and the solution was allowed to stand for 2 h. The excess of the reactant was driven off in a rotary evaporator at 50° under a pressure of 150 mm; the residue was saturated with K_2CO_3, extracted with ether, and distilled; 2.1 g (55% theor.) were obtained of N-ethyl-3-methylpiperidone-4 which, according to gas – liquid chromatography and thin-layer chromatography, was identical with the ketone produced by the process described above.

N-Methyl-trans-2,3-dimethylpiperidone-4. A 1:10 mixture of cis- and trans-isomers of 1,2,3-trimethylpiperidone-4 [3] with ethyl acetate was saturated with dry HCl until the initially precipitated hydrochloride was dissolved. The solvent and excess HCl were then driven off at 40° under vacuum (in a rotary evaporator), and the residue was crystallized from a methanol – ethyl acetate mixture. A second crystallization yielded pure trans-1,2,3-trimethylpiperidone-4 hydrochloride (mp = 132°). The free base of this ketone was obtained by treating the solution of the hydrochloride with K_2CO_3 in a minimum quantity of water, with cooling (0°) and simultaneous extraction with ether. The gas – liquid chromatographic analysis of this extract showed more than 99.5% of the trans-isomer and less than 0.5% of the cis-isomer. The iodomethylate was obtained by treating with CH_3I a solution of the trans-ketone in acetone, with cooling (mp = 165°).

N-Ethyl-2,3-dimethylpiperidone-4. Iodomethylate of 1,2,3-trimethylpiperidone-4 (a mixture of isomers) was reacted with an aqueous solution of ethylamine according to [18], and a 43:57 mixture of cis- and trans-isomers of 1-ethyl-2,3-dimethylpiperidone-4 was obtained. A mixture of a similar composition was also produced by alkylation of trans-2,3-dimethylpiperidone-4 (obtained from the hydrochloride according to [3]) by boiling in a C_2H_5I solution in the presence of moist K_2CO_3. The isomer mixture was treated with hydrochloric acid, and the product was crystallized from acetic anhydride and ethyl acetate; a small amount was obtained of cis-N-ethyl-2,5-dimethylpiperidone hydrochloride (mp = 149°), whose cis-structure was determined by comparative gas – liquid and thin-layer chromatography of the products of the reduction of this ketone with $NaBH_4$ and the products of ethylation-demethylation [6] of N-methyl-cis-2,3-dimethylpiperidol-4 (axial epimer).*

N-Isopropyl-2,3-dimethylpiperidone-4 (bp 88–89; 6 mm) was synthesized from 1-diethylamino-4-methylhexen-4-one-3 and an aqueous solution of isopropylamine according to the method described in [3], with a yield of 92%. Found: C 71.30; H 11.21; N 8.47%. $C_8H_{19}NO$. Calculated: C 71.0; H 11.24; N 8.28. The hydrochloride of this ketone was obtained by treatment with a 1:3 HCl solution, and crystallized from n-butanol (mp = 132.5°). This hydrochloride was purely trans-isomer (by gas – liquid chromatography). The configuration of the ketone was determined by comparing the basic isomer of the alcohol obtained by $NaBH_4$-reduction of the pure hydrochloride with the product of alkylation – dealkylation of e-isomer of trans-1,2,3-trimethylpiperidol-4 (see below).

1,2,3-Trimethylpiperidone-4 (Four epimers). An equiponderant mixture of cis- and trans-1,2,3-trimethylpiperidone-4 [3] was subjected to reduction by boiling with aluminum isopropoxide in absolute isopropanol, and the reaction mixture was chromatographed on Al_2O_3 (activity grade II) in the solvent system hexane – $CHCl_3$ – aqueous NH_3 (2:3:1, lower layer). There was obtained (in this order): α-epimer of trans-1,2,3-trimethylpiperidol-4 (R_f 0.6),† its hydrochloride had mp = 189° (found, in %: C 53.1; H 9.79; N 8.18; Cl 19.99); α-epimer‡ of cis-1,2,3-trimethylpiperidol-4 R_f 0.49,* its hydrochloride had mp = 143° (found,

* The basic product of the $NaBH_4$ reduction of hydrochloride (IV) proved to be identical (by thin layer chromatography) with the alcohol obtained from cis-1,2,3-trimethylpiperidol (α-epimer).

† In thin layer of Al_2O_3 (activity grade II); in the system $CHCl_3$ – NH_3 (saturated) – C_2H_5OH (100:1).

‡ The configuration of the hydroxyl was not strictly verified.

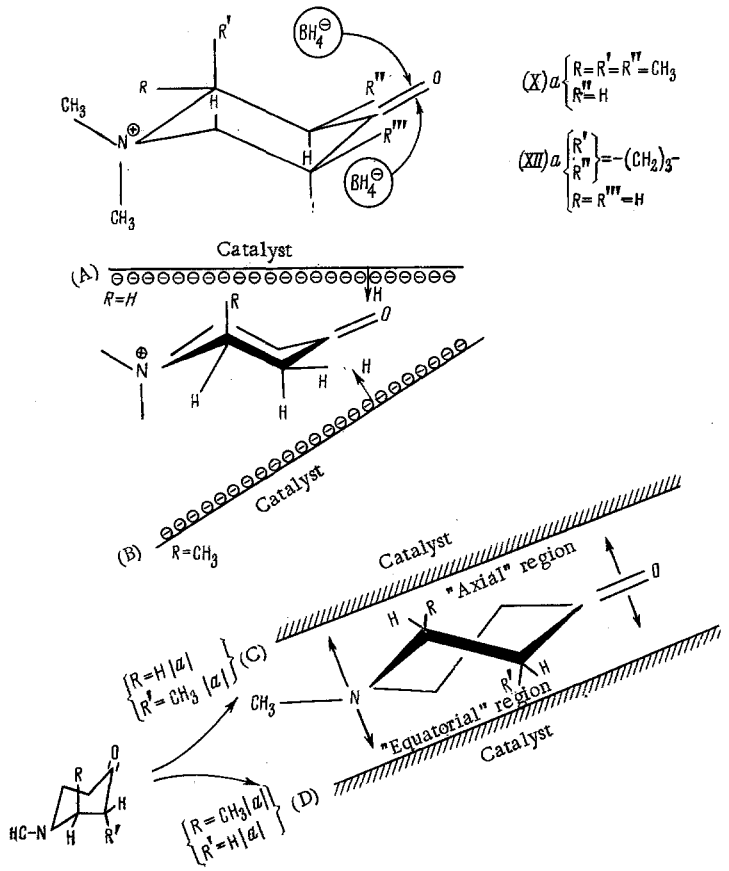

Fig. 1

in %: C 53.40, H 10.01, N 8.21, Cl 19.82%); e-epimer of cis-1,2,3-trimethylpiperidol-4 (R_f 0.42),* its hydrochloride had mp = 191° (found, in %: C 53.42, H 10.18, N 8.77, Cl 19.95); and e-epimer of trans-1,2,3-trimethylpiperidol-4 (R_f 0.34),* its hydrochloride had mp = 215° (found, in %: C 53.42, H 10.08, N 8.00, Cl 19.97; $C_8H_{18}NOCl$; calculated, in %: C 53.48, H 10.0, N 7.77, Cl 19.97). All the hydrochlorides were crystallized from methanol – ethyl acetate. The structure of the alcohols of the trans-series was confirmed by the reduction of the pure trans-1,2,3-trimethylpiperidone hydrochloride with Li – C_2H_5OH in liquid ammonia (e-epimer) and with aluminum isopropoxide (65% of *a*-epimer and 35% of e-epimer).

1,2,5-Trimethylpiperidols (Four epimers). An equiponderant mixture of both forms of 1,2,5-trimethylpiperidone-4 was reduced under the same conditions as in the above experiment. Chromatographic analysis on Al_2O_3 yielded: *a*-epimer of 1,2,5-trimethylpiperidol-4 (R_f 0.40),* mp = 72°, from hexane (found, in %: C 67.29, H 12.01, N 10.02; $C_8H_{17}NO$; calculated, in %: C 67.11, H 11.88, N 9.88); *a*-epimer of cis-1,2,5-trimethylpiperidol-4 (R_f 0.25),* its iodomethylate had mp = 310°, from acetone (found, in %: C 37.85, H 7.11, N 4.85, I 44.7; $C_9H_{20}NOI$; calculated, in %: C 37.98, H 7.00, N 4.89, I 44.50); e-epimer of cis-1,2,5-trimethylpiperidol-4 (R_f 0.15)* was not isolated in the pure form; e-epimer of trans-1,2,5-trimethylpiperidol-4 (R_f 0.10),* its hydrochloride had mp = 190.5° from methanol – ethyl acetate (found, in %: C 53.05, H 10.2, N 7.62, Cl 20.2; $C_8H_{18}NOCl$; calculated, in %: C 53.43, H 10.0, N 7.77, Cl 19.97). The identification of e- and *a*-alcohols of the trans-series was carried out in the same way as in the case of 1,2,3-isomers.

CONCLUSIONS

1. The role of polar and steric factors during reduction of γ-piperidones was investigated; the configuration of the alcohols obtained was determined.

2. Alkyl substituents at the nitrogen atoms do not essentially influence the stereochemistry of the reduction of γ-piperidones.

3. All the four possible isomers of 1,2,3-trimethylpiperidol-4 and 1,2,5-trimethylpiperidol-4 were isolated.

* In thin layer on Al_2O_3 (activity grade II); solvent $CHCl_3$ saturated with aqueous NH_3.

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