ASYMMETRIC SYNTHESIS OF CYCLOALKANO-2,3-PIPERID-4-OLS*

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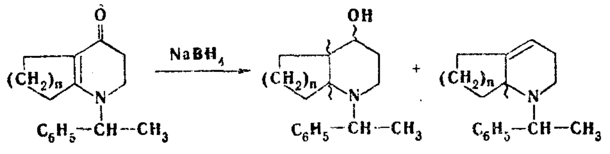
A new method for the asymmetric synthesis of cycloalkano-2,3-piperid-4-ols by the reaction of a number of chiral enamino ketones with sodium borohydride is proposed. It is shown that the reduction proceeds via 1,4-hydride addition and leads to the formation of primarily one diastereomeric pair of cycloalkano-2,3-piperidols and their dehydration products. The asymmetric synthesis was confirmed by the production of optically active nitrogen-unsubstituted cycloalkano-2,3-piperid-4-ols when the chiral substituent was removed.

To ascertain the possibility of the asymmetric synthesis and production of optically active cycloalkano-2,3-piperid-4-ols we investigated the reduction with sodium borohydride of a number of two-ring enamino ketones (I-III) with a chiral substituent attached to the nitrogen atom.

We carried out the reduction by refluxing the corresponding enamino ketone with a fourfold excess of sodium borohydride in a mixture of equal amounts of ethanol and pyridine for 10 h; the formation of three compounds, which were isolated in 80% overall yield by means of chromatography with a column filled with aluminum oxide, was observed for each of the enamino ketones by chromatography.



I-III IV-VI a,b VII-IX

I, IV a,b VII n=1; II, V a,b VIII n=2; III, VI a,b, IX n=3

It was established that the reaction of enamino ketones I-III with sodium borohydride gives primarily an isomeric pair of cycloalkano-2,3-piperidols (IV-VIa, b) and their dehydration products (VII-IX) (Table 1).

A mass-spectrometric study of the isolated cycloalkano-2,3-piperidols (IV-VI) confirmed their structure and demonstrated the identical specificity of the fragmentation, regardless of the size of the carbocycle.

The IR spectra of isomeric piperidols IV-VI contain a band at 3200-3400 cm^{-1}, which corresponds to the stretching vibrations of the OH group.

It must be noted that the reduction of the enamino ketones does not go to completion under the reaction conditions. Changing the solvent and the heating time and the use of a large excess of sodium borohydride did not change the trend of the reaction. The reaction does not occur at all in the case of reduction of the enamino ketones under ordinary conditions (in alcohol at room temperature or by heating the components) [2].

Thus in the reaction of enamino ketones I-III with sodium borohydride the enamino ketone group is reduced completely, and new asymmetric centers develop in the cycloalkano-2,3-piperid-4-ol molecules. As we have already noted, the formation of only two diastereomeric optically active amino alcohols IVa-VIa (larger R_f values) and IVb-XIb (smaller R_f values)

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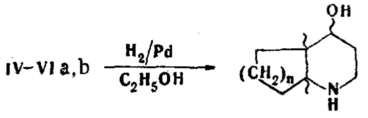
TABLE 1. Properties of N-(α-Phenylethyl)cycloalkano-2,3-piperid-4-ols (IV-VI) and Their Dehydration Products (VII-IX)

Compound	mp, °C[a]	R_f[b]	IR spectrum, OH, cm^{-1}		M+	PMR spectrum, ppm		$[\alpha]_D^{20}$, deg (nm)	Found, %			Empirical formula	Calc., %			Yield, %
			calculated	CH₂Cl₂		CH₃	CH		C	H	N		C	H	N	
IVa	99—100	0,5	3190 3270	3610 3400	245	—	—	+28,5 (300)	78,4	9,6	5,8	$C_{16}H_{23}NO$	78,3	9,5	5,7	29
IVb	117—118	0,2	3440	3610	245	—	—	+48,5	78,2	9,5	5,4					29
VIIc	93—94	1) 0,4[d] 2) 0,3						—	57,9	5,5	—	$C_{22}H_{24}N_4O_7$	57,6	5,3	—	13
Va	133—134	0,5	3240 3310	3610	259	—	—	−17,1	78,7	9,9	5,4	$C_{17}H_{25}NO$	78,7	9,7	5,4	36
Vb	85—86	0,3	3380 3420	3610	259	—	—	+31,6	78,8	9,8	5,5					19
VIIIc	116—118	1) 0,5[d] 2) 0,3			241	1,29 (d) 1,32 (d)	3,89 (q) 3,92 (q)		58,5	5,6	—	$C_{23}H_{26}N_4O_7$	58,7	5,6	—	24
VIa	94—95	0,4	3300 3360	3610	273	—	—	+87,2 (300)	78,8	10,1	4,8	$C_{18}H_{27}NO$	79,0	10,0	5,1	36
VIb	100—101	0,3	3300	3610	273	—	—	−83,5	79,0	9,8	5,3					36
IXc	106—108	1) 0,5[d] 2) 0,4			245	1,20 (d) 1,23 (d)	3,66 (q) 3,63 (q)	—	59,5	5,8	—	$C_{24}H_{28}N_4O_7$	59,5	5,8	—	8

[a] Crystallized from hexane. [b] Chromatography on activity II Al_2O_3 [elution with benzene—ethyl acetate (4:1)]. [c] The picrate was crystallized from a mixture of ether and pentane. [d] Chromatography on Silufol [elution with benzene—acetone (1:1)].

was observed by chromatography in each case. In the case of the reduction of five- and seven-membered enamino ketones I and III the corresponding alcohols were obtained in equal amounts, according to the results of chromatography on aluminum oxide, whereas they were obtained in a ratio of 2:1 in the case of six-membered enamino ketone II; this was also confirmed by gas—liquid chromatography (GLC).

To verify the occurrence of asymmetric synthesis in the reduction of enamino ketones I-III with sodium borohydride we removed the α-phenylethyl group from the nitrogen atom. The corresponding optically active cycloalkano-2,3-piperid-4-ols (X-XIIa, b) are formed in the hydrogenolysis of each of the isomeric N-α-phenylethyl derivatives of cycloalkano-2,3-piperidols (IV-VIa, b) in absolute ethanol in the presence of palladium black at room temperature.



X–XII a,b

The properties of X-XIIa, b, are presented in Table 2.

Compounds VII-IX, in the PMR spectra of which (Table 1) the singlet of a vinyl proton appears at 5.30-5.33 ppm, in accordance with which the double bond in these compounds is found in the 3 and 4 positions of the cycloalkanopiperidine system, are formed in small amounts in the reduction of enamino ketones I-III. We were unable to conduct a similar spectral investigation of five-membered system VII because of its instability. However, the results of elementary analysis and mass spectrometry of the picrate of VII made it possible to assign the N-(α-phenylethyl)-$\Delta^{4,9}$-hexahydropyridine structure to it.

Thus, the data obtained provide evidence that the reduction of enamino ketones I-III proceeds via asymmetric 1,4-hydride addition and leads to the production of previously unknown optically active 4-piperidols (a, b). The three-dimensional structures of all of the cycloalkano-2,3-piperid-4-ols and the stereochemistry of the reduction of enamino ketones I-III with sodium borohydride will be presented in our next communication.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of CCl_4 were recorded with an XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer equipped with a system for direct introduction of the samples into the ion source at a vaporization temperature of 70-100°C, an ionizing-electron energy of 50 eV, and an emission current of 1.5 mA. The rotation was measured with a JASCO-20 spectropolarimeter.

TABLE 2. Properties of Cycloalkano-2,3-piperid-4-ols (X-XIIa,b)

Compound	n	mp, °C (petroleum ether	IR spectrum, ν, cm^{-1} (in mineral oil)		M+	$[\alpha]_D^{20}$, deg (nm)	Found, %			Empirical formula	Calc., %		
			OH	NH			C	H	N		C	H	N
Xa	1	104—105	3100	3250	141	−45,0	68,1	10,8	10,0	$C_8H_{15}NO$	68,0	10,7	9,9
Xb		81—82	3055	3220 3300	141	+114,0	68,3	10,7	9,6				
XIa	2	124—125	3150	3270	155	−48,5	69,2	11,1	9,2	$C_9H_{17}NO$	69,2	11,2	9,1
XIb		136—137	3060	3230	155	+61,4	69,4	11,4	8,9				
XIIa	3	237—239[a]			169[b]	+48,0[a] (300)	58,1	9,9	6,5	$C_{10}H_{19}NO \cdot HCl$	58,4	9,8	6,8
XIIb		107—108	3010	3210	169	+153,0[a] (300)	70,7	11,2	8,5	$C_{10}H_{19}NO$	70,9	11,3	8,3

[a] In the hydrochloride form, which was crystallized from alcohol—ether. [b] Free base.

The synthesis of the starting enamino ketones I-III was described in [3, 4].

Reduction of N-(α-Phenylethyl)cycloalkeno-2,3-piperid-4-ones (I-III). A 0.04-mole sample of sodium borohydride was added to 0.01 mole of enamino ketones I-III in 100 ml of a mixture of absolute ethanol and pyridine in a ratio of 1:1, and the mixture was refluxed in a stream of argon for 10 h. It was then decomposed with water, and the aqueous mixture was extracted with chloroform. Removal of the solvents gave 80-90% of the reaction mixture in the form of yellow oil. Chromatography in a thin layer of Al_2O_3 in a benzene—ethyl acetate system (4:1) showed the presence of a mixture of four compounds, one of which corresponded to the starting enamino ketone. The reaction mixture was separated with a column (50 by 2.5 cm) filled with neutral Al_2O_3; the mixture was applied to the column by the dry method and eluted with a mixture of benzene and ethyl acetate (4:1). The chromatographically homogeneous fractions were combined, and chromatographically individual isomers of N-(α-phenylethyl)cycloalkano-2,3-piperid-4-ols (IV-VIa, b) and the corresponding cycloalkano compounds VII-IX were obtained. The properties are presented in Table 1.

Hydrogenolysis of N-(α-Phenylethyl)piperid-4-ols (IVa, b-VIa, b). A 1.5-mmole sample of amino alcohols IV-VIa, b was reduced in 50 ml of absolute ethanol in the presence of 0.05 g of freshly prepared palladium black at room temperature for 3 h (with chromatographic monitoring). The catalyst was removed by filtration, the solvent was removed in vacuo, and the residue was recrystallized from petroleum ether (70-100°C) to give 70-80% of the corresponding cycloalkano-2,3-piperid-4-ol (X-XIIa, b). The properties of the compounds obtained are presented in Table 2.

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