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# STEREOCHEMISTRY OF THE ASYMMETRIC REDUCTION OF N-(α-PHENYLETHYL)-$\Delta^{8,9}$-HEXAHYDRO-4-PYRINDONE*

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The reduction of optically active N-(α-phenylethyl)-$\Delta^{8,9}$-hexahydro-4-pyrindone with lithium aluminum hydride proceeds as asymmetric stereospecific 1,4-hydride addition and leads to the formation of primarily the thermodynamically stable trans-(8S,9S)-N-(α-phenylethyl)octahydro-4-pyrindone and a small amount of the corresponding cis isomer. Only cis-(8S,9S)-octahydro-4-pyrindone was obtained from each isomer and the mixture of isomers after removal of the chiral substituent from the nitrogen atom. The absolute configurations of the compounds obtained were established on the basis of circular dichroism data and the octant rule.

Continuing our study of methods for the synthesis of chiral γ-piperidones and their conformational behavior we investigated the stereochemical specificity of the reduction of optically active N-(α-phenylethyl)-$\Delta^{8,9}$-hexahydro-4-pyrindone (I) with lithium aluminum hydride.

The reduction of chiral enamino ketone I with lithium aluminum hydride and the isolation of the reaction products were accomplished as in [2] with equimolar ratios of the reagents. Column chromatography of the reaction mixture on aluminum oxide and silica gel gave N-(α-phenylethyl)octahydro-4-pyrindone (II) and N-(α-phenylethyl)octahydro-4-pyrindole (III) in quantitative yield in a ratio of 3:1; the structures and compositions of the products were confirmed by the result of elementary analysis, mass spectrometry, and IR and PMR spectroscopy (see the scheme on the following page).

Chromatography of the analytically pure octahydro-4-pyrindone II after separation with a column in various systems of solvents on Silufol showed the presence of a mixture of two isomers, IIa and IIb, with considerable predominance of isomer IIa. Only traces of isomer IIb were detected by chromatographic monitoring of the reaction mixture during and after reduction. The amount of isomer IIb increased somewhat on contact with the sorbent. Chromatographically individual isomer IIa was isolated from the mixture of isomers by means of column chromatography on silica gel; we were able to obtain isomer IIb in small amounts after repeated column chromatography of isomer IIb-enriched fractions. On the basis of the results of chromatographic separation of the mixture of isomers IIa and IIb it was established that the isomer ratio is 8:1.

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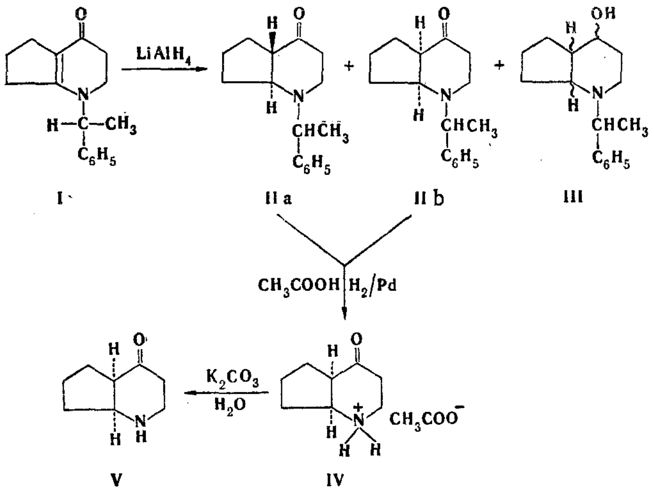


In the isolation of isomers IIa,b as the free bases from the corresponding picrates by alkalization or by filtration of a solution of the picrate in methylene chloride through aluminum oxide we obtained a mixture of isomers; i.e., we observed that they are interconvertible. Similar behavior of individual isomers IIa,b was observed during their thermal isomerization and when they were heated in benzene in the presence of aluminum oxide: A mixture of isomers with predominance of isomer IIa was detected chromatographically in both cases. It may be assumed that the interconvertibility of isomers IIa,b is associated with a change in the configuration of the 9-C atom of the perhydropyrindone system due to enolization of the carbonyl group; this also leads to the formation of trans and cis isomers IIa and IIb.

An absorption band at 1720 cm$^{-1}$, which corresponds to the C=O stretching vibrations, is present in the IR spectra of individual isomers IIa and IIb; the remaining portions of the spectra are not identical. The appearance in the PMR spectra of distinct signals of a methyl group in the form of a doublet (1.34 ppm for IIa and 1.4 ppm for IIb) and of a methylidyne group in the form of a quartet (3.82 ppm for IIa and 3.8 ppm for IIb) for each isomer confirms their diastereomeric purity. A mass spectrometric study of isomers IIa and IIb confirmed their structures and demonstrated virtually identical fragmentation with only a slight difference in the relative intensities of the peaks of the fragment ions.

To verify the occurrence of asymmetric synthesis in the reduction of enamino ketone I we removed the α-phenylethyl group from the nitrogen atom. The hydrogenolysis of isomer IIa in glacial acetic acid in the presence of palladium black at room temperature leads to the formation of the optically active acetate (IVa) and the free base (V) of octahydro-4-pyrindole, the structures of which were proved by the set of physicochemical data. In the case of hydrogenolysis of a mixture of isomers IIa and IIb under similar conditions we also isolated acetate IVb, which was identical to acetate IVa with respect to its melting point, chromatographic mobility, and chiral-optical properties.

On the basis of this, we feel that the reduction of enamino ketone I proceeds as asymmetric stereoselective 1,4-hydride addition and leads to the production of chiral octahydro-4-pyrindones (II, V), information regarding which is not available in the literature. In the reduction of enamino ketone I one may theoretically expect the formation of three diastereomeric pairs of octahydro-4-pyrindones; however, we observed the formation of only one pair with substantial predominance of the more stable isomer IIa. As we have already indicated above, the formation of only traces of IIb are observed during the reaction.

## Establishment of the Absolute Configuration of the Compounds

We made a comparison of the circular dichroism (CD) data for isomer IIa with the corresponding data for trans-(9S,10S)-N-(α-phenylethyl)decahydro-4-quinolone (VI), the absolute configuration of which was established in [2]. It is apparent from Fig. 1 that a positive band of the $n-\pi^*$ transition of the carbonyl group at 292 and 305 nm and a negative band [1] of the $L_B$ transition of the phenyl chromophore at 247 and 236 nm, respectively, are observed on the CD curves of heptane solutions of IIa and VI; the sign of the Cotton effect (CE) and the trends of the curves are identical. On the basis of this we feel that the predominant

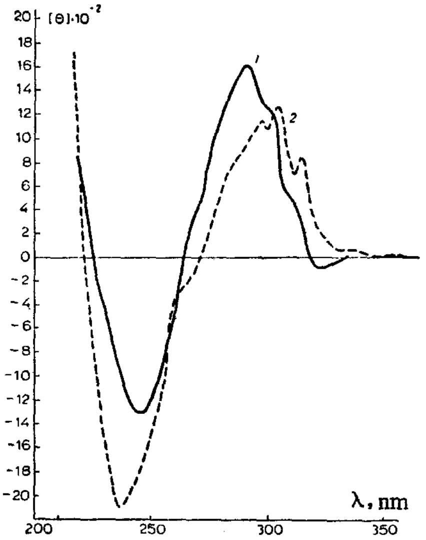


Fig. 1

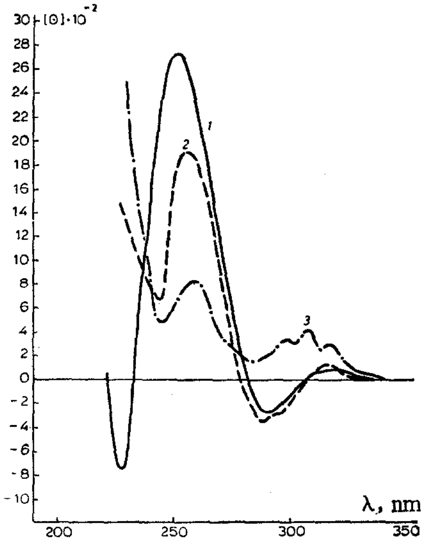


Fig. 2

Fig. 1. Circular dichroism in heptane of trans isomer IIa (1) and (9S,10S)-trans-N-(α-phenylethyl)decahydro-4-quinoline VI (2).

Fig. 2. Circular dichroism of cis isomer IIb in methanol (1), acetonitrile (2), and heptane (3).

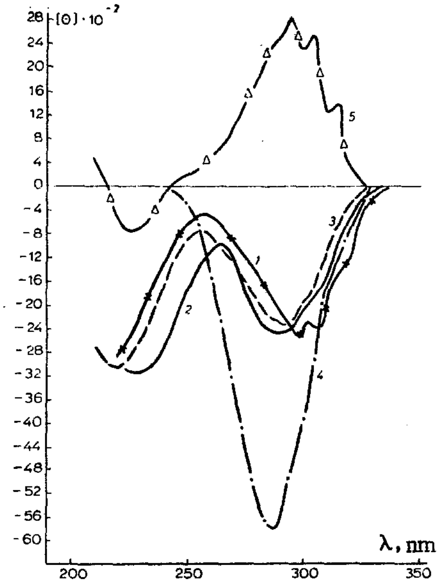
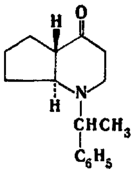


Fig. 3. Circular dichroism of cis-octahydro-4-pyrindone (V) in heptane (1), acetonitrile (2), methanol (3) and of the hydrochloride of V in water (4) and of trans-decahydro-4-quinoline in heptane (5).

isomer IIa is trans-(8S,9S)-octahydro-4-pyrindone, the absolute configuration of which is expressed by formula IIa:

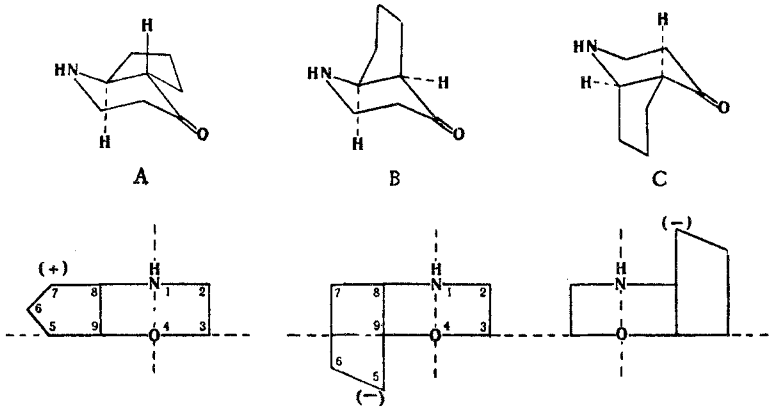


IIa

We assigned isomer IIb to the cis series; however, an examination of the CD data for isomer IIb in solvents with different polarities (Fig. 2) showed that the data are complex in character, probably because of the existence of a conformational or solvation equilibrium; this requires further study.

We also recorded the CD curves of the isolated optically active octahydro-4-pyrindone (IV) and its hydrochloride in various solvents (Fig. 3). A negative band of an $n-\pi^*$ transition at 298 nm with $\theta = +2560°$ and a negative branch of an $n-\sigma^*$ transition of a nitrogen atom are observed on the CD curve of octahydro-4-pyrindone in hexane, and the trend of the CD curves in acetonitrile and methanol does not change. Only a negative CE effect at 287 nm, which is associated with an $n-\pi^*$ transition of the carbonyl group, is observed on the CD curve of the hydrochloride of IV in water, and the identical trend of the CD curves of octahydro-4-pyrindone and its hydrochloride in different solvents provides evidence for retention of the geometry of the molecule during quaternization of the nitrogen atom.

It should be noted that the isolated trans-N-(α-phenylethyl)octahydro-4-pyrindone isomer and the octahydro-4-pyrindone (V) obtained from it have Cotton effects of the $n-\pi^*$ transition of the carbonyl groups with opposite signs (Figs. 1 and 3). It may be assumed that the thermodynamically more stable cis isomer of octahydro-4-pyrindone was formed during hydrogenolysis; this is in agreement with the literature data on the existence of octahydro-4-pyrindone only in the cis configuration [3]. Confirmation of the cis configuration of optically active octahydro-4-pyrindone follows from a comparison of its chiral-optical data with the data for trans-(9S,10S)-decahydro-4-quinolone [2] (Fig. 3). It follows from an examination of the CD curves of both compounds in heptane that the Cotton effects of the $n-\pi^*$ transition have opposite signs, whereas the Cotton effects of the $n-\sigma^*$ transition have identical signs; i.e., these compounds differ only with respect to the absolute configuration of the carbon atom adjacent to the carbonyl group. The establishment of the cis configuration of octahydro-4-pyrindone was also accomplished by means of the octant rule [4]. The octant diagrams of trans- and cis-octahydro-4-pyrindone (V) show that the trans isomer (A) should display a positive CE of the $n-\pi^*$ transition of the carbonyl chromophore and that the cis isomer should display a weak (conformation B) or strong (conformation C) negative CE. The octahydro-4-pyrindone and its hydrochloride that we isolated in the present research show negative CE of the $n-\pi^*$ transition of the carbonyl group in all of the investigated solvents, and its absolute configuration consequently is expressed by formula V.



## EXPERIMENTAL

The IR spectra of the compounds were recorded with IKS-22 and UR-20 spectrometers. The PMR spectra of $CCl_4$ solutions of the compounds were recorded with an XL-100 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer at room temperature at an ionizing voltage of 50 V and an emission current of 1.5 mA and with a Varian MAT-111 mass spectrometer at room temperature at an ionizing voltage of 70 V and an emission current of 0.3 mA. The CD curves were measured with a J-20 spectropolarimeter.

Reduction of N-($\alpha$-Phenylethyl)-$\Delta^{8,9}$-hexahydro-4-pyrindone (I). A solution of 4.82 g (0.02 mole) of enamino ketone I in 70 ml of a mixture of absolute ether and benzene (1:1) was added at 0°C to 0.76 g (0.02 mole) of lithium aluminum hydride in 100 ml of absolute ether, and the mixture was stirred at room temperature for 20 min. It was then cooled thoroughly and decomposed by the successive addition of ethyl acetate and water. The ether layer was separated and worked up to give 4.65 g (98%) of a light yellow oil. Chromatography in a thin layer of activity II aluminum oxide in a benzene—ethyl acetate system (9:1) showed the presence of compounds with $R_f$ 0.7 and 0.2. A 4.65-g sample of the reaction mixture was applied to a short column filled with aluminum oxide in petroleum ether, and the products were eluted successively with petroleum ether, petroleum ether—benzene (9:1, 4:1, and 1:1), benzene, benzene—ether (9:1, 4:1, and 1:1), and ether. This procedure gave 3.5-g (75%) of N-($\alpha$-phenylethyl)octahydro-4-pyrindone (II) with $R_f$ 0.7 [benzene—ethyl acetate (9:1), $Al_2O_3$]. IR spectrum (in film); 1705 $cm^{-1}$ (C=O). Found: C 78.6; H 8.8%. $C_{16}H_{21}NO$. Calculated: C 78.9; H 8.7%. Elution with benzene—ether gave 1.15 g (25%) of N-($\alpha$-phenylethyl)octahydro-4-pyrindole with $R_f$ 0.4 [benzene—acetone (4:1), $Al_2O_3$] with mp 96-98°C (from hexane). IR spectrum (in mineral oil): 3220 (OH) and 707 $cm^{-1}$ (monosubstituted phenyl ring). Found: C 78.7; H 9.0; N 5.8%. $C_{16}H_{23}NO$. Calculated: C 78.3; H 9.4; N 5.7%. Mass spectrum*: $M^+$ 245.

Isolation of the cis and trans Isomers of N-($\alpha$-Phenylethyl)octahydro-4-pyrindone. A 1-g sample of a mixture of II isomers in petroleum ether was applied to a column (1.5 by 50 cm) filled with silica gel (100-150 μ), and the products were eluted successively with petroleum ether, petroleum ether—ether (50:1, 20:1, 10:1, 5:1, and 1:1), and ether to give 0.6 g of trans isomer IIa with $R_f$ 0.7 [petroleum ether—ether (1:2), Silufol]. IR spectrum (film): 1720 (C=O), 3090, 3070, 3035, 2980, 2920, 2880, 2820, 1980, 1610, 1500, 1460, 1420, 1390, 1360, 1310, 1290, 1250, 1230, 1210, 1190, 1180, 1160, 1125, 1090, 1075, 1035, 1015, 1000, 980, 940, 920, 890, 870, 790, 770, 750, 710, 690 $cm^{-1}$. PMR spectrum ($CCl_4$), δ: 1.34 (d, $CH_3$), 3.82 (q, phenylethyl substituent CH), and 7.25 ppm (m, $C_6H_5$). Mass spectrum (%): $M^+$ 243 (35), 229 (10), 228 (35), 215 (9), 214 (33), 166 (8), 138 (7), 124 (5), 118 (13), 111 (6), 110 (35), 106 (14), 105 (100), 104 (11), 103 (10), 91 (9), 79 (13), 77 (9), 67 (6), 56 (7). The picrate had mp 181-183°C (from ethanol). Found: C 55.8; H 5.2%. $C_{22}H_{24}O_8N_4$. Calculated: C 55.9; H 5.1%. The remaining substances were isolated in the form of mixtures of the II isomers.

A 0.4-g sample of a mixture of isomers IIa and IIb enriched with isomer IIb was applied to a column (1.5 by 25 cm) filled with silica gel (100-160 μ) in petroleum ether, and the mixture was eluted successively with petroleum ether, petroleum ether—ether (50:1, 20:1, 10:1, 5:1, and 1:1), and ether to give 0.1 g of isomer IIa, 0.2 g of a mixture of II isomers, and 0.1 g of isomer IIb with $R_f$ 0.5 [petroleum ether—ether (1:2), Silufol]. IR spectrum (film): 1720 (C=O), 3090, 3070, 3035, 2970, 2940, 2880, 2820, 2050, 1610, 1500, 1460, 1420, 1360, 1320, 1290, 1230, 1210, 1190, 1170, 1150, 1120, 1090, 1040, 1030, 1010, 980, 920, 780, 750, 710 $cm^{-1}$. PMR spectrum ($CCl_4$), δ: 1.4 (d, $CH_3$), 3.8 (q, phenylethyl substituent CH), and 7.2 ppm (s, $C_6H_5$). Mass spectrum (%): $M^+$ 243 (36), 229 (7), 228 (32), 215 (8), 214 (36), 166 (8), 138 (9), 124 (5), 118 (12), 111 (7), 110 (31), 106 (18), 105 (100), 104 (14), 103 (10), 91 (10), 79 (14), 77 (10), 67 (8), 56 (9). The picrate had mp 173-175°C (ethanol—ether) and $R_f$ 0.5 [petroleum ether—ether (1:2), Silufol]. A mixture of the picrates of IIa and IIb melted at 142-149°C.

Thermal Isomerization of trans Isomer IIa. A 0.01-g sample of trans isomer IIa was refluxed in 10 ml of absolute benzene in an argon atmosphere for 30 h. Chromatography of the mixture on Silufol in a benzene—acetone system (7:2) showed the presence of a mixture of isomers with predominance of the trans isomer.

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*Here and subsequently, the m/e values are given for the ion peaks, and the intensities relative to the maximum peak in percent are given in parentheses.

Isomerization of cis Isomer IIb on Aluminum Oxide. A 0.01-g sample of cis isomer IIb was heated in 10 ml of absolute benzene in the presence of a small amount of activity II $Al_2O_3$ for 1 h. Chromatography of the mixture on Silufol showed the presence of a mixture of isomers.

cis-Octahydro-4-pyrindone Acetate (IV). A 0.02-g (0.001 mole) sample of trans isomer IIa was hydrogenated in 20 ml of glacial acetic acid in the presence of 0.05 g of freshly prepared palladium black at room temperature for 2 h, after which the catalyst was removed by filtration, and the solvent was removed in vacuo to give 0.15 g (92%) of octahydro-4-pyrindone acetate, which was purified by vacuum sublimation to give a product with mp 89-91°C and $R_f$ 0.5 ($CHCl_3$, saturated with $NH_3$, Silufol). IR spectrum (in mineral oil): 1720 $cm^{-1}$ (C=O). Mass spectrum: $M^+$ 139 (free base). When 0.5 g of a mixture of isomers IIa and IIb was hydrogenated in 50 ml of glacial acetic acid under similar conditions for 5 h, 0.3 g of octahydro-4-pyrindone acetate, with mp 89-91°C (purified by sublimation) and $R_f$ 0.5 ($CHCl_3$, $NH_3$, Silufol), was obtained. No melting-point depression was observed for a mixture of this product with a sample of acetate obtained by hydrogenolysis of trans isomer IIa. The trend of the CD curve of this product in methanol was also identical to the trend of the CD curve of the latter product.

cis-Octahydro-4-pyrindone (V). Hydrogenation of 0.5 g of trans isomer IIa in 25 ml of absolute ethanol in the presence of palladium black gave 0.25 g of cis-octahydro-4-pyrindone with $R_f$ 0.4 ($CHCl_3$, saturated with ammonia, Silufol). IR spectrum (film): 1720 (C=O) and 3340 $cm^{-1}$ (NH). Mass spectrum: $M^+$ 139 (17), 124 (7), 111 (10), 110 (100), 96 (6), 69 (8), 67 (12), and 56 (6). The hydrochloride had mp 138-142°C (ethanol–ether). Found: C 54.5; H 7.9; N 7.9%. $C_8H_{13}NO \cdot HCl$. Calculated: C 54.2; H 7.9; N 7.8%.

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