ABSOLUTE CONFIGURATIONS OF OPTICALLY ACTIVE trans-4-KETOPERHYDROQUINOLINE AND ITS cis- AND trans-N-PHENYLETHYL DERIVATIVES*

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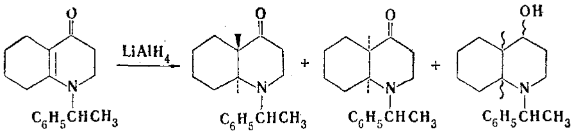
The reduction of optically active N-(α-phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline with lithium aluminum hydride gives a mixture of cis and trans isomers of N-(α-phenylethyl)-4-ketoperhydroquinoline. Only one optically active acetate and the free trans-4-ketoperhydroquinoline base were isolated in the hydrogenolysis of each of the isomers. The absolute configurations and conformations of the two-ring γ-piperidones obtained were established by optical rotatory dispersion, circular dichroism, and an examination of three-dimensional models.

A study of the chemical behavior of optically active two-ring enamine ketones [2] has made it possible to progress to the class of optically active two-ring γ-piperidones, for which there is no information in the literature.



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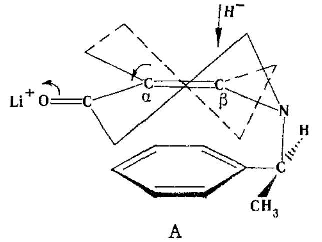
The reduction of N-(α-phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline (I) with lithium aluminum hydride in absolute ether at room temperature gave a reaction product from which three substances were isolated by chromatography on aluminum oxide. One of them, which was isolated in very low yield, was not identified. Another compound isolated is N-(β-phenylethyl)-4-ketoperhydroquinoline (II), as confirmed by the presence in the IR spectrum of a band at 1710-1720 cm^{-1}, which corresponds to the stretching vibrations of the carbonyl group, and by the results of elementary analysis. The IR spectrum of the third compound contains an absorption band at 3240 cm^{-1}, which corresponds to the stretching vibrations of the hydroxyl group. The smooth negative trend of the optical rotatory dispersion (ORD) curve (Fig. 1) and the results of elementary analysis make it possible to assign the N-(α-phenylethyl)-4-hydroxyperhydroquinoline (I) structure to this compound.



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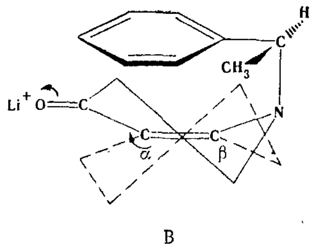

B

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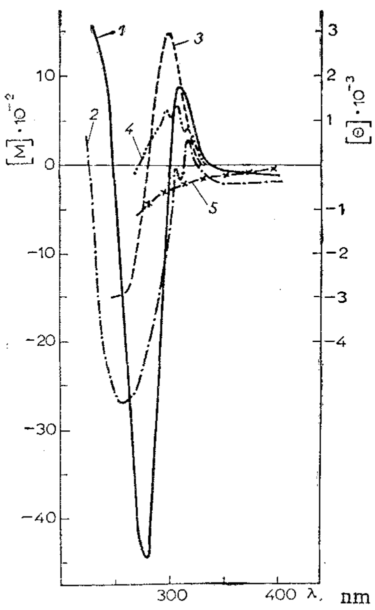


Fig. 1. Optical rotatory dispersion (ORD) curves and circular dichromism (CD) of trans-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIa) and N-(α-phenylethyl)-4-hydroxyperhydroquinoline (III): ORD of IIa in methanol (1), in hexane (2); CD of IIa in methanol (3) and in hexane (4); ORD of IIIc in methanol (5).

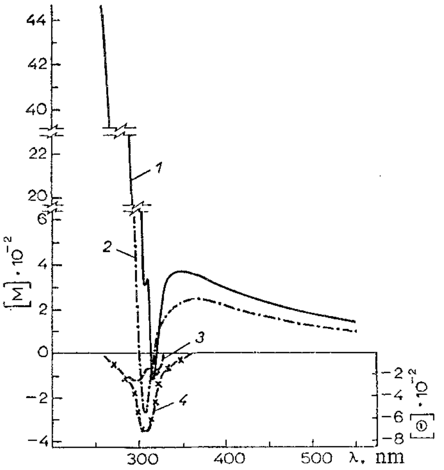
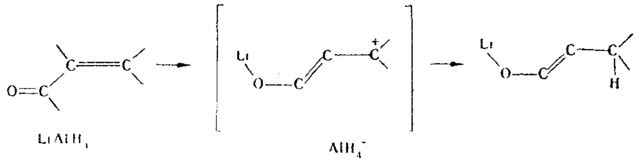


Fig. 2. RD and CD curves of cis-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIb): 1) RD in hexane; 2) RD in methanol; 3) CD in hexane; 4) CD in methanol.

Chromatography of analytically pure II in a thin layer of aluminum oxide in various systems did not lead to separation of the isomers, but two spots corresponding to the presence of cis and trans isomers were detected by chromatography on Silufol. The formation of different types of ring fusion in the reduction of enamine ketone I can be explained in analogy with the reduction of α,β-unsaturated ketones [3,4]. An examination of three-dimensional models of enamine ketone I indicates the possibility of the existence of two preferred conformations (A and B), which are probably fixed by intramolecular interaction of the carbonyl group and the phenyl ring. Conformation B (the antipodal configuration of the asymmetrical center is depicted) is less favorable because of steric hindrance caused by the methyl group attached to the asymmetrical carbon atom.

By virtue of this, one should assume that the reactive conformation is conformation A and that attack on the enamine ketone system by hydride ion can lead to the formation of only the S configuration of the β-carbon atom. Reduction, of course, proceeds through a step involving enolization. This is due to the fact that the Li^+ cation, which is associated with the enolate anion, reinforces the polarization of the enone system, and the hydride ion supplies a pair of electrons to fill the free orbital of the β-carbon atom:



The configuration of the α-carbon atom in the resulting piperidone (II) is determined primarily by the ketonization process, and this is also responsible for the formation of cis- and trans-fused rings. We separated the isomers through the corresponding picrates. A mixture of picrates with mp 194-197°C was obtained from the mixture of isomers of piperidone II. Two picrates with mp 185-186° and 210-211° were isolated after four recrystallizations of the mixture from methanol.

Crystalline isomer IIb was isolated from the high-melting picrate by alkylization. It was found that isomer IIb can also be isolated directly from the mixture of isomers by pronounced cooling of a hexane solution of this mixture. We were unable to isolate the second isomer (IIa) by freezing out the hexane solution of the mixture of isomers. The second isomer of piperidone II was therefore isolated as a light-yellow oil by alkalization of the low-melting picrate. The IR spectra of both isomers contain an intense absorption band at 1710-1720 cm^{-1}, which corresponds to the $C=O$ stretching vibrations, but the spectra differ in all other respects. The PMR spectra of the two isomers were also found to be different. However, in view of the complexity of the spectra, one cannot obtain reliable information regarding the type of ring fusion from the PMR data.

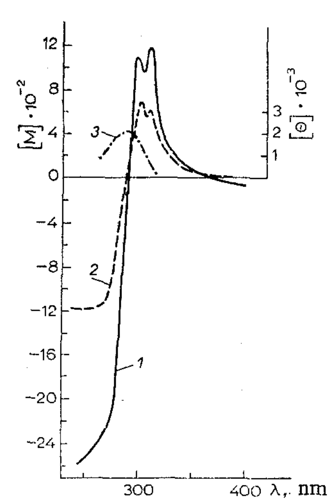


Fig. 3. RD and CD curves of trans-4-ketoperhydroquinoline acetate (IV): 1) RD in dioxane; 2) RD in methanol; 3) CD in dioxane.

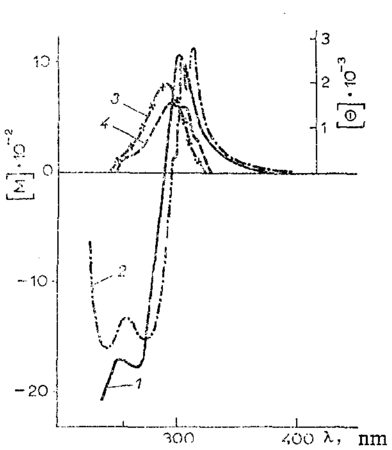


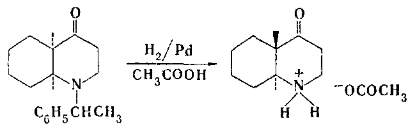
Fig. 4. RD and CD curves of trans-4-ketoperhydroquinoline (V): 1) RD in methanol; 2) RD in hexane; 3) CD in methanol; 4) CD in hexane.

In our opinion, liquid isomer IIa has trans ring fusion, while crystalline isomer IIb has cis ring fusion. The correctness of this assignment will be confirmed below by data from a study of the rotatory dispersion (RD) and circular dichroism (CD) of 4-ketoperhydroquinoline (IV), which was obtained by removal of the phenylethyl protecting group from each of the isomers of N-(α-phenylethyl)-4-ketoperhydroquinoline.

The RD and CD curves in solvents of different polarities were recorded for the trans-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIa). An RD curve with a positive Cotton effect (CE) corresponding to an n → π* transition of the carbonyl group with a peak at 311 nm and a valley at 279 nm is observed in methanol. The average CE point (λ_0 301 nm) on the RD curve coincides with the positive maximum on the CD curve (λ_{max} 300 nm) recorded in methanol at room temperature. It should be noted that the start of a negative dichroic absorption band, which corresponds to a π → π* transition of the aromatic chromophore (phenylethyl substituents) (Fig. 1), appears at shorter wavelengths on the CD curve. A positive CE with a clearly expressed vibrational structure with a peak at 318 nm (bathochromic shift) and a valley at 258 nm (Fig. 1) is also observed in hexane. A positive circular dichroism band with a distinct fine structure also appears on the CD curve in hexane.

The RD and CD curves of cis isomer IIb in solvents of different polarities were similarly investigated. A negative CE caused by an n → π* transition of the carbonyl chromophore (Fig. 2) is observed in all solvents. In methanol the RD curve contains a peak at 308 nm, which is shifted to the long-wave region in hexane (316 nm). A negative dichroic absorption band appears at 305 nm on the CD curve in hexane; this is in good agreement with the data from the UV spectrum and RD.

The phenylethyl group was removed from each of isomers IIa and IIb in order to obtain more rigorous proof of the type of ring fusion in the proposed cis (IIb) and trans (IIa) piperidones and also to verify the possibility of the realization of asymmetrical synthesis under the influence of the asymmetrical center of the phenylethyl substituent (to see whether predominant formation of one of the configurations occurs during the reduction of enamine ketone I with lithium aluminum hydride). The hydrogenolysis of cis isomer IIb in glacial acetic acid in the presence of palladium black at room temperature proceeds very readily:



II b IV

Hydrogenolysis gave an optically active 4-ketoperhydroquinoline acetate (IV), the IR spectrum of which contains an intense band at 1730 cm^{-1}, corresponding to the C=O stretching vibrations. A mass-spectral investigation of acetate IV demonstrated that this compound dissociates very readily to give a molecular ion with m/e 153, corresponding to the 4-ketoperhydroquinoline; the mass spectrum contains an intense peak with m/e 60, which corresponds to the acetic acid molecular ion.

TABLE 1. RD of (-)trans-1-Decalone and 4-Ketoperhydroquinoline in Methanol

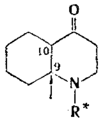
Compound	Peak		Valley		(A)
	λ, nm	[M]	λ, nm	[M]	
(-)trans-1-Decalone	309	+1086	267,5	−1740	+28,3
4-Ketoperhydroquinoline	303	+1062	266	−1746	+28,1

The RD and CD curves in methanol and dioxane were recorded for acetate IV. In this case, a positive CE with the appearance of a fine structure is observed on the RD curves. The average Cotton effect point in dioxane (λ_0 291 nm) coincides with the maximum of the positive dichroic absorption band on the CD curve at 290 nm (Fig. 3).

A chromatographically individual free 4-ketoperhydroquinoline (V) base was isolated from acetate IV; the IR spectrum of V contains an absorption band at 3200 cm^{-1}, corresponding to N−H stretching vibrations, and an absorption band at 1715 cm^{-1}, corresponding to C=O stretching vibrations. The RD and CD curves in methanol and hexane were recorded for 4-ketoperhydroquinoline (V). An RD curve with a positive CE with a peak at 303 nm and a valley at 266 nm is observed in methanol. The average CE point (λ_0 289 nm) coincides with the positive maximum of the dichroic absorption band on the CD curve at 289 nm (Fig. 4). An RD curve with a positive CE with a distinctly expressed fine structure is observed in hexane. A positive dichroic absorption band with a maximum at 297 nm, which corresponds to the average CE point at 294 nm (Fig. 4), is observed on the CD curve recorded in hexane at room temperature.

The hydrogenolysis of trans isomer IIa gave 4-ketoperhydroquinoline acetate, which was identical to acetate IV obtained from cis isomer IIb, according to the melting point and spectral and optical properties.

Induction of optical activity on the developing asymmetrical 9 carbon atom consequently occurs during the reduction of enamine ketone I with lithium aluminum hydride:



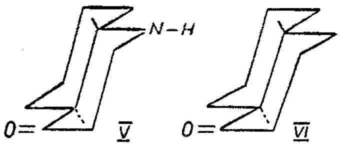
$R^* = C_6H_5-\overset{|}{C}H-CH_3$

The similar trend of the RD curves (CE with identical signs) of 4-ketoperhydroquinoline (V) and its acetate makes it possible to assume that quaternization of the nitrogen atom does not substantially change the molecular geometry. This will subsequently enable us to draw a stereochemical analogy between 4-ketoperhydroquinoline and its carbocyclic analog − 1-decalone.

Establishment of the Absolute Configurations and Conformations

The same compound − 4-ketoperhydroquinoline − was obtained in the hydrogenolysis of the cis and trans isomers of N-(α-phenylethyl)-4-ketoperhydroquinoline. In agreement with the conclusion in [5,6], this indicates the formation of a more stable form with trans ring fusion during hydrogenolysis. A proof of the correctness of the trans configuration of 4-ketoperhydroquinoline is a comparison of its RD curves with the RD curve of trans-1-decalone, the absolute configuration of which has been established [7]. It is known that the application of the octant rule to the RD curves of many compounds is widely used to establish the absolute configurations of optically active molecules.

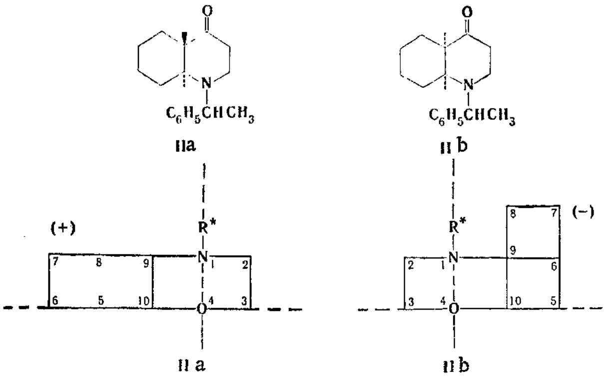
We found that the RD curve of 4-ketoperhydroquinoline in methanol practically coincides with the RD curve of (-)trans-1-decalone, the absolute configuration of which is represented by formula VI:



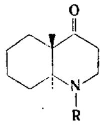
V VI

On the basis of this, we feel that 4-ketoperhydroquinoline has trans ring fusion, and the absolute configuration of (-)trans-(9S,10S)-4-ketoperhydroquinoline can be represented by formula V. This conclusion enables us to make a rigorous assignment of the cis and trans configuration of N-phenylethyl derivatives of 4-ketoperhydroquinoline. The sign of the CE depends particularly on the type of ring fusion. A negative CE appeared for the proposed cis isomer IIb in all solvents, while a positive CE appeared for the proposed trans isomer IIa. In conformity with the octant rule [8], a substituent in the 4 position relative to the C=O group (the N-phenylethyl substituent in our case) does not affect the sign of CE.

Isomer IIa, which retains the sign of its CE when the phenylethyl protecting group is removed, consequently has, like 4-ketoperhydroquinoline, trans ring fusion, while isomer IIb, which changes the sign of its CE, has cis ring fusion, and we assign the following absolute configurations to them: (-)trans-(9S,10S)-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIa) and (+)cis-(9S,10R)-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIb).



The N-(α-phenylethyl)-4-ketoperhydroquinoline isomers actually are affiliated with different types of ring fusion. If the IIa and IIb obtained by us were diastereomeric trans (1 and 2) or cis (3 and 4) pairs, one of the antipodes of 4-ketoperhydroquinoline would have been obtained on removal of the N-phenylethyl protecting group from IIa, and the other antipode would have been obtained from IIb. However, we did not observe this.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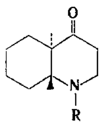
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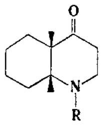
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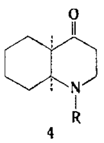
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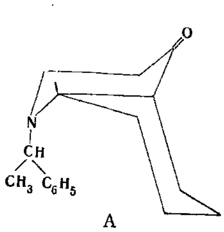
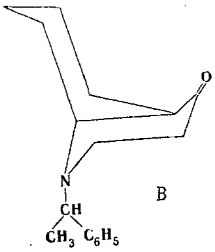
(+)cis-(9S,10R)-N-(α-Phenylethyl)-4-ketoperhydroquinoline can exist in two conformations (A and B):


A


B

Application of the octant rule demonstrates that a weak negative CE should be observed for conformation A, while a strong negative CE should be observed for conformation B. We were unable to estimate the magnitude of the amplitude of the CE of cis-piperidone IIb, since we were unable to measure the CE peak. However, an examination of three-dimensional models for cis isomer IIb enables us to assume the preferred existence of conformation B.

EXPERIMENTAL

The IR spectra were recorded with IKS-22 and UR-20 spectrometers, the UV spectra were recorded with a Cary-15 spectrometer, the PMR spectra were recorded with a Varian T-60 spectrometer, and the mass spectra were recorded with a Hitachi MU-6D mass spectrometer. The RD curves were measured with a Jasco ORD/UV-5 spectropolymeter, and the circular dichroism curves were recorded with a Roussel-Jouan dichrograph.

Reduction of N-α-Phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline (I). A solution of 11 g (0.043 mole) of enamine ketone I in 150 ml of absolute ether–absolute benzene (1 : 1) was added dropwise with ice cooling to 9.8 g (0.26 mole) of $LiAlH_4$ in 200 ml of absolute ether, and the mixture was stirred at room temperature for 30 min. It was then decomposed with pronounced cooling by the successive addition of ethyl acetate and water. The ether layer was separated and dried with magnesium sulfate, and the ether was removed to give 11 g (99%) of a light yellow oil. Chromatography in a thin layer of neutral Al_2O_3 with petroleum ether–ether (3 : 2) demonstrated the presence of compounds with R_f 0.12, 0.53, and 0.75. A 5.5-g sample of the reaction mixture in petroleum ether was applied to a column filled with neutral Al_2O_3. Elution was carried out successively with petroleum ether, petroleum ether–ether mixtures (9 : 1, 8 : 2, and 1 : 1), and ethyl acetate. The chromatographically homogeneous fractions were combined and evaporated to give 3.77 g (69%) of N-(α-phenylethyl)-4-ketoperhydroquinoline (II) with R_f 0.53 [petroleum ether–ether (3 : 2), Al_2O_3]. Found,%: C 79.3; H 9.0. $C_{17}H_{23}NO$. Calculated,%: C 79.3; H 9.0. Chromatography on Silufol of an analytically pure sample demonstrated the presence of trans (IIa) and cis (IIb) isomers with R_f 0.53 and 0.66 [benzene–acetone (6 : 1)] and 0.52 and 0.65 (ethyl acetate), respectively. Elution with ethyl acetate yielded 0.2 g (36%) of N-(α-phenylethyl)-4-hydroxyperhydroquinoline with R_f 0.12 [petroleum ether–ether (3 : 2), Al_2O_3] and 0.65 [benzene–acetone (4 : 1), Al_2O_3] with mp 123-124° (from hexane); $[\alpha]_D^{20}$ −17.2° (methanol, c 1.98). IR spectrum: 3240 (OH), 700 cm^{-1} (C_6H_5). Found,%: C 77.9; H 9.5. $C_{17}H_{25}NO$. Calculated,%: C 78.7; H 9.7. The compound with R_f 0.75 [petroleum ether–ether (3 : 2), Al_2O_3] was not identified, since it was isolated from the column as a mixture with N-(α-phenylethyl)-4-ketoperhydroquinoline [1.5 g (27%)].

Isolation of the cis and trans Isomers of N-(α-Phenylethyl)-4-ketoperhydroquinoline. An equivalent amount of picric acid in ether was added to an ether solution of 1.35 g of a mixture of isomers II, and the resulting precipitate was removed by filtration to give 2.45 g (96%) of a mixture of picrates. Recrystallization from methanol gave two picrates with different solubilities: 1.05 g of a slightly soluble picrate of the cis isomer IIb [mp 210-211° (from methanol); R_f 0.53, benzene–acetone (4 : 1), Silufol. Found,%: C 56.7; H 5.6. $C_{17}H_{23}NO \cdot C_6H_3N_3O_7$. Calculated,%: C 56.8; H 5.4] and 0.58 g of the picrate of trans isomer IIa [mp 185-186° (from methanol); R_f 0.41, benzene–acetone (4 : 1), Silufol]. A melting point depression was observed for a mixture of the picrates (174-175°).

Alkalization of 1.05 g of the picrate of perhydroquinoline IIb with subsequent extraction with methylene chloride and filtration through aluminum oxide gave 0.45 g (81%) of cis-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIb) with mp 75-77° (from hexane). The cis isomer (IIb) was also isolated directly from a mixture of isomers of N-(α-phenylethyl)-4-ketoperhydroquinoline by cooling a solution of the mixture in hexane to −60°. A 3.77-g sample of the mixture gave 1.23 g (33%) of isomer IIb with mp 75-77° (from hexane) and R_f 0.66 [benzene–acetone (6 : 1), Silufol] and 0.53 [petroleum ether–ether (3 : 2), Al_2O_3]. IR spectrum: 1718 (C=O), 1342, 1271, 1307, 1232, 1215, 1205, 1180, 1141, 1110, 1070, 898, 862, 783, 746, and 702 cm^{-1}. UV spectrum in methanol, λ_{max}, nm (log ε): 253 (2.68), 258 (2.67), 264 (2.56), shoulder 268 (2.42), shoulder 315 (1.24); in hexane, λ_{max}, nm (log ε): 252 (2.52), 258 (2.48), 265 (2.33), 268 (2.12), 294 (1.38), 303 (1.34). PMR spectrum (CCl_4):* δ 1.21 (d, CH_3), 4.4 (q, phenylethyl substituent CH), 7.2 ppm (s, C_6H_5). Found,%: C 79.6; H 8.9. $C_{17}H_{23}NO$. Calculated,%: C 79.3; H 9.0.

After isolation of the major amount of cis isomer IIb, the solution contained both isomers, which could not be separated by freezing out. The pure trans isomer was therefore isolated from the picrate. A 1.4-g sample of the picrate was decomposed by the addition of 40% NaOH, and the mixture was extracted with methylene chloride. The extract was dried with magnesium sulfate, filtered through aluminum oxide, and evaporated to give 0.7 g (95%) of trans-N-(α-phenylethyl)-4-ketoperhydroquinoline (IIa) as a light yellow oil with R_f 0.53 [benzene–acetone (6 : 1), Silufol] and 0.53 [petroleum ether–ether (3 : 2), Al_2O_3]. IR spectrum: 1714 (C=O), 1309, 1287, 1250, 1222, 1190, 1175, 1141, 1084, 1007, 881, 840, 767, 702 cm^{-1}. UV spectrum in hexane, λ_{max}, nm (log ε): 252 (2.79), 258 (2.72), 264 (2.57), shoulder 284 (1.88), shoulder 289 (1.86). PMR spectrum (CCl_4): δ 1.3 (d, CH_3), 3.75 (q, phenylethyl substituent CH), 7.2 ppm (s, C_6H_5). Found,%: C 79.3; H 9.2. $C_{17}H_{23}NO$. Calculated,%: C 79.3; H 9.0.

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*The following abbreviations were used here and elsewhere: s is singlet, d is doublet, and q is quartet.

trans-4-Ketoperhydroquinoline Acetate (IV). A 0.5-g (1.95 mmole) sample of cis-N-(α-phenylethyl)-4-ketoperhydroquinoline in 20 ml of glacial acetic acid was hydrogenated in the presence of 0.1 g of freshly prepared palladium black at room temperature for 15 min. The catalyst was removed by filtration, and the solvent was vacuum evaporated to give 0.4 g (97%) of acetate IV, which was purified by vacuum sublimation to give a product with mp 143-144° (in a sealed capillary). IR spectrum: 1730, 1660, 1340, 1315, 1290, 1270, 1230, 1160, 1140, 1090, 1037, 1020, 925, 850, 732 cm^{-1}. UV spectrum in methanol, λ_{max}, nm (log ε): 220 (2.78), shoulder 290 (1.60). Found,%: C 61.9; H 9.0. $C_9H_{15}NO \cdot C_2H_4O_2$. Calculated,%: C 61.9; H 9.0.

Acetate IV was also obtained in 97% yield by hydrogenation of trans isomer IIa and had mp 144-145° (in a sealed capillary). No melting-point depression was observed for a mixture of the acetates obtained from the cis and trans isomers. The spectral characteristics of the two samples of acetate IV were identical.

trans-4-Ketoperhydroquinoline (V). A 0.2-g sample of acetate IV was decomposed with 40% NaOH solution, and the mixture was extracted with CH_2Cl_2. The extract was dried with magnesium sulfate, and the solvent was removed by vacuum distillation to give 0.14 g (98%) of 4-ketoperhydroquinoline with mp 59-60° and R_f 0.52 [benzene–acetone (1:1), Al_2O_3]. IR spectrum: 3200 (N–H), 1714 cm^{-1} (C=O). UV spectrum in hexane, λ_{max}, nm (log ε): 223 (2.96), shoulder 280 (1.85). The molecular weight was 153 according to mass spectrometry.

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