STEREOCHEMISTRY OF THE ASYMMETRIC 1,4-HYDRIDE REDUCTION OF N-SUBSTITUTED DERIVATIVES OF $\Delta^{9,10}$ -OCTAHYDRO-4-QUINOLONE

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It is shown that the reaction of LiAlH₄ with $\Delta^{9,10}$ -ocathydro-4-quinolones that have chiral (S)-sec-butyl and (S)- α -benzylethyl substituents at the nitrogen atom proceeds as asymmetric 1,4-hydride reduction with the primary formation of trans isomers of (1S)-sec-butyl(9S,10S)- and (1S)- α -benzylethyl(9S,10S)decahydro-4-quinolones, the three-dimensional structures and absolute configurations of which were established by ¹³C NMR spectroscopy and circular dichroism measurements.

In order to ascertain the dependence of the stereochemistry of the asymmetric 1,4hydride reduction of two-ring enamino ketones on the nature of the substituent attached to the nitrogen atom we studied the stereospecificity of the reduction with LiAlH₄ of $\Delta^{9,10}$ octahydro-4-quinolones I and II, which have chiral sec-butyl and α -benzylethyl substituents attached to the nitrogen atom. The reduction of enamino ketones I and II was carried out by the method in [1], and 1-sec-butyl- (IV) and 1- α -benzylethyldecahydro-4-quinolone (V) were obtained in quantitative yields, which constitutes evidence that 1,4-hydride addition takes place in the enamino ketone fragment.



By chromatographic monitoring of the reduction we observed the formation of one 1-secbutyldecahydro-4-quinolone isomer (IVa) (larger R_f value) and a mixture of 1- α -benzylethyl-

decahydro-4-quinolone isomers (Va, b) with significant preponderance of the Va isomer. However, after chromatographic isolation of isomers IV and V with a column packed with SiO_2 , we observed the formation of a mixture of isomers IV and V with preponderance of the isomer with greater chromatographic mobility. We carried out the isolation of isomers IVa and Va, which predominate in the equilibrium mixture, through the picrates. From the mixture of isomers IVa, b we obtained a picrate with mp 172-173°C, from which after two recrystallizations from ethanol we isolated a picrate with mp 183-184°C, which is the picrate of pure isomer IVa with R_f 0.5 [Al₂O₃, petroleum ether-ether (1:1)]. The second chromatographically pure isomer IVb was isolated by passing a solution of the picrates of the mixture of isomers IVa, b in

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Fig. 1. Circular dichroism curves of trans-(1S)-sec-butyldecahydro-4-quino-lone (1), trans-(1S)- α -phenylethyl-decahydro-4-quinolone (2), and trans-(9S, 10S)-decahydro-4-quinolone (3) in heptane.

TABLE 1. ¹³C Chemical Shift of Decahydro-4-quinolones (relative to tetramethylsilane, ppm, in CCl₄)

Carbon atom No.	trans-1-α-Phenyl- ethyldecahydro-4- quinolone (VIa)	IVa	Va
2 3 5 6 7 8 9 10	45,0 42,0 24,9 23,9 31,2 63,7 55,5	43,8 41,8 25,0 28,1 24,0 30,7 63,7 55,0	44,4 42,1 23,9 24,6 24,9 30,3 63,8 54,5

chloroform through a short column filled with Al_2O_3 by elution with chloroform. When we carried out all of the operations rapidly by this method, we were able to obtain chromatographically individual isomers IVa, b. The formation of a mixture of isomers IVa, b was again observed (by chromatographic monitoring) in the case of slow elution. Isomers Va, b (the picrate of Va had mp 154-156°C) were isolated by a similar procedure.

A study of the ¹³C NMR data for trans-decahydro-4-quinolone and its N-methyl- and N- α -phenylethyl-substituted derivatives showed that the chemical shifts of some of the atoms of the quinolone system may serve as a criterion of their affiliation with the trans series [2]. In conformity with this we analyzed the data from the ¹³C NMR spectra for individual isomers IVa and Va (Table 1), which are formed in larger amounts.

It is apparent from Table 1 that very good conformity is observed between the chemical shifts of the characteristic $C_{(3)}$, $C_{(8)}$, $C_{(9)}$, and $C_{(10)}$ atoms of trans-1- α -phenylethyl-

decahydro-4-quinolone (VIa) and isomers IVa and Va, which, on the basis of this, also belong to the trans series. Isomers IVb and Vb, which are formed from trans isomers IVa and Va upon contact with sorbents, i.e., under thermodynamic conditions, are cis isomers that develop as a result of enolization of the carbonyl group. In order to estimate the relative thermodynamic stabilities and the ratios of the cis and trans isomers that are formed by enolization we obtained conformationally stable amino ketals VII-IX from the mixture of isomers IV and V and the previously investigated 1- α -phenylethyldecahydro-4quinolone (VI) [1] (Table 2). After separation of ketals VII-IX with a column packed with Al₂O₃, we obtained chromatographically individual isomers VII-IX, the purity of which was no less than 99.5% according to chromatographic mass-spectrometric data. Peaks of molecular ions corresponding to the calculated values are observed in the mass spectra of pairs of isomeric ketals VII-IX. The isomeric pairs of amino ketals have identical characteristic

TABLE 2. Properties of Amino Ketals VII-IX

Compound	a:b ratio	R_j^*	mp,°C	M.	IR spectrum, v, cm ⁻¹		Yield.
					C-O-C	C ₆ H ₅	%
VII a b	3:1	0,3 0,2	Oil Oil	253 253	1125 1125		47,5 16,0
VIII a b	6:1	0,3 0,2	Oil 112—113	315 315	1125 1130	1610 1610	32,4 5,6
IX b	1:7	0,8 0,7	66—67 80—82	301 301	1130 1130	1615 1615	61,5 9,3

*On Silufol in a petroleum ether-ether system (1:1).

ions corresponding to fragmentation of the amine type; however, the intensities of the ions differ. According to the ¹³C NMR data, amino ketals VII and VIII, which are formed in larger amounts, and amino ketal IXa [2] belong to the trans series. On the basis of this it may be assumed that the optically active decahydroquinolones IV and V are also formed in the same ratios under thermodynamic conditions.

Two new asymmetric centers develop in the reduction of enamino ketones I and II with LiAlH₄, and two diastereomeric pairs of quinolones IV and V may consequently be formed. We established the formation of only one diastereomeric pair of decahydro-4-quinolones (IV, V) with significant preponderance of the thermodynamically more stable isomers of the trans series, the diastereomeric purity of which reaches 98%. This stereochemical result constitutes evidence for virtually 100% efficiency of the asymmetric synthesis of 1-substituted decahydro-2-quinolones IV and Va, whereas the stereoselectivity within the conformationally labile diastereomeric pair of cis-trans isomers is 75-90%. One should note that it was not necessary to remove the asymmetrizing substituent from the nitrogen atom, since we followed the course of the asymmetric reaction from the diastereomeric purity of the compounds obtained by ¹³C NMR spectroscopy.

To determine the absolute configurations of the chiral trans-decahydro-4-quinolones obtained (IVa, Va) we compared the circular dichroism (CD) data for trans isomers IVa and Va and trans-(9S,10S)-decahydro-4-quinolone with a known absolute configuration [1]. A positive Cotton effect (CE) at 293 nm with $[\theta] + 2400^{\circ}$ is observed for trans isomer IVa; this is in good agreement with data from the UV spectrum in isooctane $[\lambda_{max} 295 \text{ nm} (\lambda 42)]$. A positive CE at 304 nm with $[\theta] + 2240^{\circ}$ is also displayed for amino ketone Va; in the UV spectrum in heptane the maximum of the corresponding band lies at 307 nm (ϵ 67) (Fig. 1). A comparison of the CD curves recorded in heptane for trans-1-substituted decahydroquino-lones IVa and Va with the data for trans-(9S,10S)-decahydro-4-quinolone, the absolute configuration of which is known [1], made it possible to assign a (9S,10S) configuration of the asymmetric centers to them also. The virtually identical molecular ellipticities of the n-m* bands of the carbonyl chromophore in the series of chiral 4-quinolones under consideration constitute evidence for their high optical purity (which also follows from the ¹³C NMR data).



The trans-decahydroquinolones are conformationally rigid compounds in which ring fusion between two cyclohexane rings in the chair form is realized by two diequatorial bonds. The use of the octant rule also indicates a 95,10S configuration of the asymmetric centers of amino ketones IVa and Va. It is apparent from the octant projections that a negative CE should have been observed for the trans-(9R,10R)-amino ketones.

Thus the octant rule can be used for trans-decahydro-4-quinolones IVa and Va.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer, the UV spectra were obtained with a Specord spectrophotometer, the ¹³C NMR spectra were recorded with a CFT-20 spectrometer, and the mass spectra were obtained with MKh-1303 mass spectrometer and a Hewlett-Packard 5992B chromatographic mass spectrometer. The circular dichroism (CD) curves were measured with a Roussel-Jouan III apparatus.

Chiral enamino ketones I-III were synthesized by the method in [3].

<u>Mixture of cis and trans Isomers of 1-sec-Butyldecahydro-4-quinolone (IV).</u> A solution of 2.07 g (10 mmole) of enamino ketone I in 50 ml of absolute ether was added dropwise at 0°C to a suspension of 0.76 g (20 mmole) of LiAlH₄ in 50 ml of absolute ether, and the mixture was stirred at room temperature for 30 min, decomposed with ethyl acetate and water, and filtered. The residue was extracted with benzene and dried with MgSO₄, and the solvent was removed to give 2.06 g (98%) of a light-yellow oil. The reaction product was applied to a column filled with aqueous silicic acid and eluted with petroleum ether, petroleum ether—ether (2:1 and 1:1), and ethyl acetate. The chromatographically homogeneous fractions were combined and evaporated to give 1.88 g (91%) of a mixture of the cis and trans isomers of IV with R_f 0.5 (trans ketone IVa) and R_f 0.3 (cis ketone IVb) [Al₂O₃, petroleum ether—

ether (1:1)]. The reaction gave almost pure trans ketone IVa, which underwent isomerization during separation with the column to give a mixture of cis and trans ketones IVa, b with significant preponderance of trans isomer IVa.

Isolation of trans-1-sec-Butyldecahydro-4-quinolone (IVa). A boiling solution of picric acid in ether was added to a solution of 1.0 g (4.8 mmole) of a mixture of cis and trans isomers IVa, b in 5 ml of ether, and the resulting precipitate was removed by filtration, washed with ether, and dried to give 1.85 g (88%) of the picrates of the mixtures of isomeric IVa, b with mp 172-173°C. Recrystallization from ethanol gave 1.43 g of the picrate of pure trans isomer IVa with mp 183-184°C. Found: C 52.2; H 6.0%. $C_{19}H_{26}N_4O_8$. Calculated: C 52.1; H 6.0%. A 0.8-g sample of picrate IVa was applied to a short column packed with Al₂O₃ and eluted with CHCl₃. The eluate was evaporated to give 0.36 g (94%) of trans isomer IVa in the form of an oil. IR spectrum (film): 1725 cm⁻¹ (CO). UV spectrum (in isooctane): 298 (ϵ 42), 211 (ϵ 1230), and 230 nm (shoulder, ϵ 180).

<u>Mixture of cis and trans Isomers of 1- α -Benzylethyldecahydro-4-quinolone (V).</u> A solution of 4.5 g (17 mmole) of enamino ketone II in a mixture of 90 ml of absolute benzene and 30 ml of absolute ether was added dropwise at 0°C to a suspension of 1.31 g (34 mmole) of LiAlH₄ in 75 ml of absolute ether, and the mixture was stirred at room temperature for 30 min, decomposed with ethyl acetate and water, and filtered. The residue was extracted with benzene, and the extract was dried with MgSO₄. The solvent was removed to give 4.50 g (99%) of a light-yellow oil. The product was applied to a column filled with aqueous silicic acid and eluted successively with petroleum ether, petroleum ether—ether (40:1, 20:1, 5:1, 3:1, and 1:1), and ethyl acetate. The chromatographically homogeneous fractions were combined and evaporated to give 3.81 g (85%) of a mixture of the cis and trans isomers of V with R_f 0.6 (trans ketone Va) and R_f 0.5 (cis ketone Vb) [Silufol, petroleum ether—ether—acetone (5:10:2)].

<u>Isolation of trans-1- α -Benzylethyldecahydro-4-quinolone (Va).</u> A saturated solution of picric acid in ether was added to a solution of 0.413 g (1.5 mmole) of a mixture of cis and trans isomers Va,b in 2 ml of ether until precipitation ceased. The precipitate was removed by filtration, washed with ether, and dried to give 0.664 g (87%) of the picrate of a mixture of isomeric Va,b with mp 137-140°C. Two recrystallizations from ethanol gave 0.22 g of the picrate of pure trans isomer Va with mp 154-156°C. Found: C 57.2; H 5.5%. C₂₄H₂₈N₄O₈. Calculated: C 57.6; H 5.6%. A 0.22-g sample of picrate Va was applied to a short column filled with Al₂O₃ and eluted with CHCl₃. The eluate was evaporated to give 0.11 g (92%)

of trans isomer Va in the form of an oil. IR spectrum (film): 1730 (CO) and 1615 cm⁻¹ (C₆H₅). UV spectrum (in heptane): λ_{max} 307 (ϵ 67) and 253 nm (shoulder, ϵ 470).

Decahydro-4-quinolone Ethylene Ketals (VII-IX). A mixture of 3 mmole of the mixture of isomers IV-VI, 3 mmole of p-toluenesulfonic acid, 6 mmole of ethylene glycol, and 30 ml of absolute benzene was refluxed with a Dean-Stark trap for 4 h (with chromatographic monitoring), after which the mixture was made alkaline with aqueous NaOH, and the benzene layer was washed with water until the wash liquid was neutral and dried with Na₂SO₄. The solvent was removed to give a mixture of cis- and trans-amino ketals VII-IX. The individual isomers were isolated by chromatography with a column filled with neutral Al_2O_3 by successive elution with petroleum ether and petroleum ether-ether (15:1, 10:1, 5:1, and 3:1). The chromatographically homogeneous fractions were combined and evaporated to give chromato-graphically individual isomers of ethylene ketals VIIa,b-IXa,b.

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6-SUBSTITUTED 1-HETARYLAMINO-3-ARYLOXINDOLES

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6-Substituted l-hetarylamino-3-aryl-2,3-dihydro-2-indolones were obtained by cyclization of diarylglycolic acid hetarylhydrazides in concentrated H_2SO_4 . The ability of the compounds obtained to undergo acylation was demonstrated. A cyclization mechanism is proposed. The IR, PMR, and mass spectra of the synthesized compounds were studied.

It is known that diarylglycolic acid 2-aryl-1,2-dialkylhydrazides are converted to cinnolones under the influence of concentrated sulfuric acid [1], whereas diarylglycolic acid 2-acyl-1-arylhydrazides are converted to 1-acyl-amino-3,3-diarylindolones [2]. We have studied the reaction with concentrated sulfuric acid of diarylglycolic acid 2-pyridyl-(IIa-c [3]), 2-quinolyl-(IId,e [4]), and 8-quinolylhydrazides (IIf-h, Table 1); the latter were synthesized by the method in [5] by the reaction of oxalic acid ethyl ester 8-quinolyl-hydrazide (I) with Grignard reagents:



Intensely colored halochromic salts are formed when hydrazides IIa-h are added to concentrated sulfuric acid [6]. The color of the solution vanishes on standing as a consequence of conversion of the carbonium ion to stable colorless substances, which are isolated from the reaction mixtures by dilution with water and neutralization. According to the

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