SYNTHESIS AND ROTATORY DISPERSION OF CISOID BICYCLIC ENAMINO KETONES*

V. M. Potapov, G. V. Kiryushkina,
G. N. Koval', and G. P. Tokmakov

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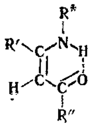
Optically active cisoid, bicyclic, enamino ketones – N-(α-phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline and N-(α-phenylethyl)-4-keto-$\Delta^{8,9}$-hexahydropyridine – were synthesized by the condensation of ethyl β-[N-(α-phenylethyl)amino]propionate with cyclohexanone and cyclopentanone, while ethyl β-(N-benzylamino)propionate and cyclohexanone gave N-benzyl-4-keto-$\Delta^{9,10}$-octahydroquinoline. A study of the rotatory dispersion of the compounds obtained demonstrated that a strong positive Cotton effect at 330-350 nm, which is associated with the presence of a cis-enamino ketone chromophore, is characteristic for them.

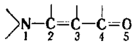
In a series of papers from our laboratory, we described optically active compounds of the enamino ketone type [2,3] and the similar enamino esters [4,5] – products of the condensation of (–)-phenylethylamine with benzoylacetaldehydes and with acetoacetic ester. The existence of isomeric forms that differ markedly with respect to the character of the optical rotatory dispersion curves (ORD curves) was noted for these compounds. This was explained by the existence of these compounds in cis-trans isomeric forms, while the strong positive Cotton effect (CE) of the cis form (Ia,b) was explained by the presence of a chelate, pseudoaromatic ring in the vicinity of the asymmetrical center.



I a $R'=H$, $R''=C_6H_4X$;
I b $R'=CH_3$, $R''=OC_2H_5$

For further investigation of the relationship between the structure and configuration of such compounds and the character of their CE, we turned to cyclic enamino ketones with a fixed cisoid structure.

Cyclic enamino ketones have become of interest in recent years because of the diverse possibilities for their synthetic utilization [6-8]. Owing to the conjugation of the free pair of p electrons of the nitrogen atom with the π electrons of the double bond and the carbonyl group, the creation of a strong chromophore in enamino ketones leads to the development of three electrophilic (1, 3, and 5) and two nucleophilic (2 and 4) centers, which also ensures great diversity in the chemical properties of enamino ketones.



$$>\underset{1}{N}-\underset{2}{\overset{|}{C}}=\underset{3}{\overset{|}{C}}-\underset{4}{\overset{|}{C}}=\underset{5}{O}$$

There is no information in the literature regarding optically active bicyclic enamino ketones.

We selected optically active N-(α-phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline (IIa) and N-(α-phenylethyl)-4-keto-$\Delta^{8,9}$-hexahydropyridine (IIb) for our investigations. To obtain them, we attempted to use the condensation reaction recently described in [9]. In [9], it was demonstrated that when a mixture of cyclic ketones and various β-aminopropionitriles is refluxed in toluene in the presence of an equivalent of

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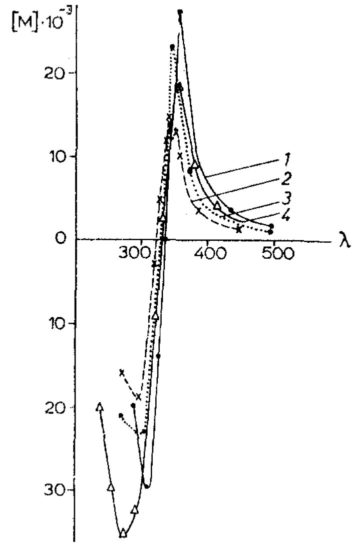


Fig. 1. RD of N-(α-phenylethyl)-$\Delta^{9,10}$-4-ketooctahydroquinoline (IIa): 1) in methanol (c 0.07); 2) in isooctane (c 0.05); 3) in acetonitrile (c 0.05); 4) in trifluoroacetic acid (c 0.07).

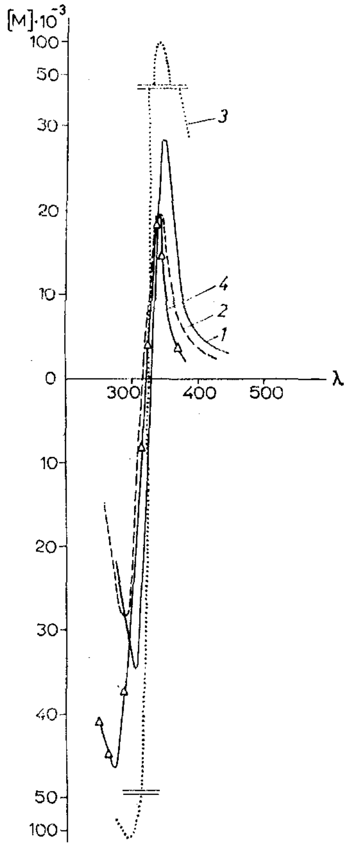
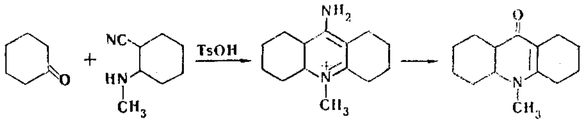
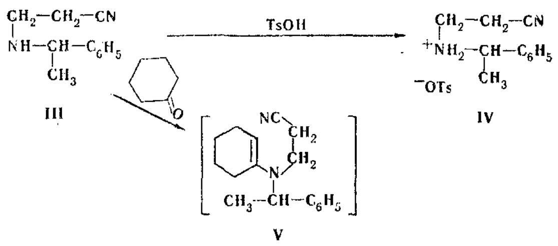


Fig. 2. RD of N-(α-phenylethyl)-$\Delta^{8,9}$-ketohexahydropyrindine (IIb): 1) in methanol (c 0.07); 2) in isooctane (c 0.03); 3) in acetonitrile (c 0.025); 4) in trifluoroacetic acid (c 0.076).

p-toluenesulfonic acid, the corresponding salts are formed in good yields; alkaline hydrolysis of the salts gives the cyclic enamino ketones:



Under similar conditions, we condensed cyclohexanone with β-[N-(α-phenylethyl)amino]propionitrile (III), obtained by the addition of optically active (–)-α-phenylethylamine to acrylonitrile. Heating (for 15 min) gave an almost quantitative yield of a crystalline substance, the IR spectrum of which did not contain the bands at 1640 and 1580 cm^{-1} that are characteristic for enamino ketones but did contain a band at 2240 cm^{-1}, which corresponds to the stretching vibrations of the $C \equiv N$ bond. Variation of the reaction conditions (the reaction time was increased to 20 h, and various solvents were used) did not alter the spectral characteristics of the compound obtained. The mass-spectral determination of the molecular weight of the compound unambiguously indicated that the substance is the salt of the starting amino nitrile (IV). It is possible that this reaction trend should be explained by steric hindrance to the formation of intermediate enamine V.



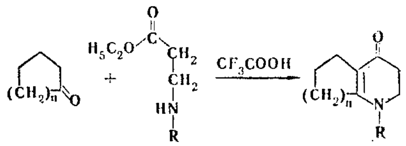
We also attempted to synthesize enamino ketones IIa and IIb by condensation of the optically active ethyl β-[N-(α-phenylethyl)amino]propionate (VIa) with cyclic ketones [10]. The starting amino ester (VIa) was obtained in almost quantitative yield by the addition of optically active (–)-α-phenylethylamine to ethyl acrylate. However, the condensation of the amino ester with cyclohexane under conditions similar to those described in the literature [11, 12] (refluxing initially in toluene in the presence of p-toluenesulfonic acid and then in ethylene glycol) gave only chromatographically detectable amounts of IIa.

The optimum reaction conditions were ascertained in the case of the condensation of cyclohexanone with ethyl β-(N-benzylamino)propionate (VIb). The effect of solvents and acid catalysts (p-toluenesulfonic acid, Dowex-50 resin, and polyphosphoric and trifluoroacetic acids) was studied. The maximum yield of N-benzyl-4-keto-$\Delta^{9,10}$-octahydroquinoline (52%) could be obtained by refluxing amino ester VIb with cyclohexanone in o-xylene in the presence of trifluoroacetic acid. Enamino ketones IIa and IIb were obtained under similar conditions, but the latter proved to be unstable and was isolated chromatographically.

TABLE 1. Rotatory Dispersion of N-(α-Phenylethyl)-$\Delta^{9,10}$-4-ketooctahydroquinoline (IIa) and N-(α-Phenylethyl)-$\Delta^{8,9}$-4-ketohexahydropyrindine (IIb)

Comp.	Solvent	λ, nm		Molecular amplitude
		peak	valley	
IIa	Methanol	358	313	+560
	Acetonitrile	348	315	+460
	Isooctane	339	300	+296
	Trifluoroacetic acid	355	275	+537
IIb	Methanol	350	310	+630
	Acetonitrile	344	300	+2060
	Isooctane	340	295	+480,8
	Trifluoroacetic acid	345	276	+483,6

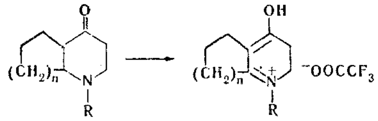
The structures of the enamino ketones obtained were confirmed by their IR spectra (the presence of bands at 1620-1630 and 1530-1560 cm^{-1}, which correspond to the stretching vibrations of a conjugated carbonyl group and a conjugated double bond), by the UV spectra (an absorption maximum is observed at about 340 nm, which, in conformity with the literature data [13-15], confirms the presence of an enamino ketone grouping), and also by the PMR spectra. The mass-spectrometric determination of the molecular weights of enamino ketones IIa-c confirmed their structures.



VI a $R=C_6H_5-\overset{|}{C}H-CH_3$, b $R=CH_2C_6H_5$;

IIa $n=2$, $R=C_6H_5-\overset{|}{C}H-CH_3$; b $n=1$, $R=C_6H_5-\overset{|}{C}H-CH_3$; c $n=2$, $R=CH_2C_6H_5$

The ORD curves in various solvents were recorded for enamino ketones IIa and IIb (Figs. 1 and 2). A strong positive CE at 340-350 nm (Table 1) is displayed for both enamino ketones in polar solvents (methanol and acetonitrile). The considerable increase in the molecular amplitude in acetonitrile (a = +2060) as compared with the amplitude in methanol (a = +630) should be noted for N-(α-phenylethyl)-$\Delta^{8,9}$-4-ketohexahydropyrindine. In isooctane, the position of the extrema is shifted to the short-wave region (339-340 nm).



It is interesting to examine the RD curves of enamino ketones IIa and IIb in trifluoroacetic acid. It is well-known that enamino ketones are readily protonated at oxygen [16, 17]. However, the trend of the RD curves of enamino ketones IIa and IIb in trifluoroacetic acid does not change appreciably, despite protonation and, consequently, a change in the nature of the chromophore (Figs. 1 and 2). This indicates that the optically active bands of both chromophores lie approximately in the same region. In this respect, the investigated compounds differ sharply from the previously studied β-[N-(α-phenylethyl)amino]vinyl ketones [2-5], which are capable of existing as cis-trans isomers.

The data obtained relative to the RD of enamino ketones IIa and IIb, which have a cisoid enamino ketone grouping, make the earlier considerations relative to the nature of the strong positive rotations of compounds of the Ia type more precise. This sort of character of the RD is associated with the presence of a cis-enamino ketone grouping, while the formation in this case of a pseudoaromatic ring, despite earlier assumptions [2-5], does not play a substantial role.

EXPERIMENTAL

The IR spectra were recorded with UR-20 and IKS-22 spectrometers, the UV spectra were recorded with a Cary-15 spectrometer, the PMR spectra were obtained with a Varian T-60 spectrometer, and the mass spectra were recorded with a Hitachi MU-6D spectrometer. The RD curves were measured with a JASCO ORD/UV-5 spectropolarimeter.

β-[N-(α-Phenylethyl)amino]propionitrile (III). A 10.1-g (0.19 mole) sample of acrylonitrile was added dropwise with stirring to 34.9 g (0.29 mole) of (-)-α-phenylethylamine. The reaction mixture was stirred at room temperature for 5 h, allowed to stand overnight, and vacuum-distilled to give 30 g (91%) of nitrile III with bp 110-111° (1 mm), n_D^{20} 1.5235, d_4^{20} 1.0031, and $[\alpha]_D^{20}$ − 64.9° (neat). Found: C 75.7, 75.8; H 8.1, 8.0%; MR_D 53.11. $C_{11}H_{14}N_2$. Calculated: C 75.8; H 8.1%; MR_D 52.82.

Tosylate of β-[N-(α-Phenylethyl)amino]propionic Acid (IV). A mixture of 5.22 g (0.03 mole) of aminonitrile III, 5.88 g (0.06 mole) of cyclohexanone, 5.16 g (0.03 mole) of p-toluenesulfonic acid, and 20 ml of absolute xylene was refluxed for 30 h in a flask equipped with a Dean–Stark adapter. The precipitate that separated out on cooling was removed by filtration to give 8.1 g (95%) of salt IV with mp 103-105°. Mass spectrum: molecular-ion peak with mass number 346. IR spectrum: 2240 cm^{-1} ($C \equiv N$).

Ethyl β-[N-(α-Phenylethyl)amino]propionate (VIa). A 9.4-g (0.094 mole) sample of ethyl acrylate was added dropwise with stirring to 12 g (0.1 mole) of (-)-α-phenylethylamine in 80 ml of absolute ethanol, and the reaction mixture was stirred at room temperature for 3 h and allowed to stand overnight. The alcohol was removed, and the residue was vacuum-distilled to give 20.5 g (92%) of amino ester VIa with bp 121-123° (2 mm), n_D^{20} 1.4997, d_4^{20} 1.008, and $[\alpha]_D^{20}$ −35.7° (neat). IR spectrum: 3300 cm^{-1} (NH), 1730 cm^{-1} (C=O). Found: C 70.9, 70.7; H 8.7, 8.8%; MR_D 64.58. $C_{13}H_{13}NO_2$. Calculated: C 70.6; H 8.6%; MR_D 63.78.

N-Benzyl-4-keto-$\Delta^{9,10}$-octahydroquinoline (IIc). A mixture of 3.1 g (0.015 mole) of amino ester VIb, 29 g (0.03 mole) of cyclohexanone, 5 drops of trifluoroacetic acid, and 30 ml of absolute o-xylene was refluxed for 30 h until the theoretical amount of water separated. The solvent was vacuum-evaporated, petroleum ether was added to the residue, and the precipitate was removed by filtration to give 1.8 g (52%) of enamino ketone IIc with mp 98-99° (from heptane) and R_f 0.4 [Al_2O_3, benzene–acetone (17:3)]. IR spectrum (in ethanol): λ_{max} 336 nm, log ε 4.16. PMR spectrum (CCl_4): δ 7.2 (singlet, C_6H_5), 4.5 (singlet, methylene group of the benzyl substituent), 3.46 ppm (triplet, CH_2–N group of the quinoline ring). Found: C 79.5, 80.0; H 7.9, 8.0%; M 241.[*] $C_{16}H_{19}NO$. Calculated: C 79.6; H 7.9%; M 241.

N-(α-Phenylethyl)-4-keto-$\Delta^{9,10}$-octahydroquinoline (IIa). This compound was obtained in 44% yield by the method used to prepare IIc and had mp 114-115° (from heptane) and R_f 0.36 [Al_2O_3, benzene–acetone (17:3)], 0.42 [Al_2O_3, benzene–ethyl acetate (1:1)], and 0.72 [silica gel, ethyl acetate–chloroform (1:1)]. IR spectrum: 1630, 1560 cm^{-1}. UV spectrum (in ethanol): λ_{max} 308 nm, log ε 4.27. PMR spectrum (CCl_4):[†] δ 7.21 (s, C_6H_5), 5.0 (q, methylidyne group of the phenylethyl substituent), 1.45 ppm (d, CH_3). Found: C 79.6, 79.8; H 7.8; 8.0; N 5.6, 5.1%; M 255. $C_{17}H_{21}NO$. Calculated: C 80.0; H 8.3; N 5.5%; M 255.

N-(α-Phenylethyl)-4-keto-$\Delta^{8,9}$-hexahydropyrindine (IIb). A mixture of 3.5 g (0.015 mole) of amino ester VIa, 2.52 g (0.03 mole) of cyclopentanone, 5 drops of trifluoroacetic acid, and 20 ml of absolute o-xylene was refluxed for 16 h until the theoretical amount of water had been liberated. The solvent was removed in vacuo, and the residue was vacuum-distilled to give a product with bp 145-152° (1 mm). Chromatography in a thin layer of Al_2O_3 demonstrated that the material partially decomposed during distillation. The yellow oil was passed through a column filled with neutral Al_2O_3 with elution by benzene. The solvent was removed, and the residual viscous substance was triturated with very cold petroleum ether, during which a yellowish, crystalline precipitate [1.29 g (36%) of enamino ketone IIb with mp 56-57° (from heptane) and R_f 0.52 [Al_2O_3, benzene–acetone (10:7)] formed. IR spectrum: 1630, 1540 cm^{-1}. UV spectrum (in ethanol): λ_{max} 334 nm, log ε 4.19. PMR spectrum (CCl_4): δ 1.6 (d, CH_3), 3.1 (t, CH_2–N), 4.9 (q, methylidyne group of the phenylethyl substituent), 7.2 ppm (s, C_6H_5). Found: C 78.6, 78.8; H 8.1, 8.1; N 5.6, 5.6%; M 241. $C_{16}H_{19}NO$. Calculated: C 79.2; H 7.8; N 5.8%; M 241.

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[*] The molecular weight was determined by mass spectrometry.

[†] The following abbreviations are used here and elsewhere: s is singlet, d is doublet, t is triplet, and q is quartet.

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