Chemistry of Heterocyclic Compounds, Vol. 32, No. 7, 1996

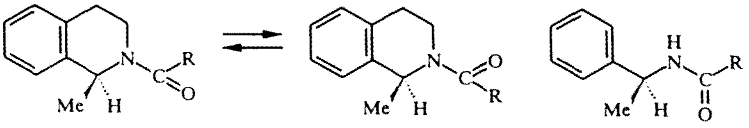
INFLUENCE OF Z,E-ISOMERISM ON THE CHIRAL-OPTICAL PROPERTIES OF AMIDES

V. M. Dem'yanovich and I. N. Shishkina

The study of the chiral-optical properties of N-acyl-(−)-1-methyl-1,2,3,4-tetrahydroisoquinolines and their acyclic analogs, the n-acyl-(−)-1-phenylethylamines, with the known ratio of Z- and E-isomers showed that the Z-isomers are characterized by the negative Cotton effect in the region of the absorption band of the amide chromophore. The observed Cotton effects of amides of phenylethylamine, which are higher by comparison with those of amides of tetrahydroisoquinoline, are explained by the interaction of the amide and aromatic chromophores, which are in proximity in certain conformations, possible for acyclic conformationally free phenylethylamides.

We previously [1] studied the conformational equilibrium of the amide group in N-acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines. Owing to the presence of the chiral center, these compounds can be obtained in the optically active form and can serve as models to evaluate the influence of Z,E-isomerism on the optical activity of amides.

Starting from (S)(−)-1-methyl-1,2,3,4-tetrahydroisoquinoline (I), obtained from (S)(−)-1-phenylethylamine (II) [2], we synthesized the corresponding acyl derivatives (IIIa-h) by analogy with the previously described racemates [1]. The acyclic analogs — N-acyl-(S)(−)-1-phenylethylamines (IVa-h) — and the benzoyl derivatives of both amines (IIIi) and (IVi) were also obtained for comparison.



Z E

IIIa-i

Z

IVa-i

III, IV a R = H, b R = Me, c R = Et, d R = *n*-Pr, e R = *i*-Pr, f R = *n*-Bu,
g R = *i*-Bu, h R = *t*-Bu, i R = Ph

Measurements of the UV spectra and the CD spectra of the amides (IIIa-i) and (IVa-i) in the region of 300-200 nm in alcohol show that, besides (IIIi), they all exhibit a complex positive Cotton effect (CE) in the region of 280-250 nm, which is determined by the ^1L_b of the absorption band of the aromatic chromone (Figs. 1 and 2).

Two CEs are shown in the short-wave spectral region for the amides (IIIa-h) — the strong negative CE at ∼220 nm and the positive CE at below 200 nm. The sign of this CE is indicated by the shape of the CD curves of the compounds (IIIa-h) and the positive CE of the N-pivaloyl derivative (IIIh) (Fig. 1).

At the same time, the negative CE of the amides (IVa-h) appears not very clearly in the form of a small anomaly on the CD curve in the region of 210 nm, since it is masked by the more intense negative CE in the region of 200 nm, which was successfully measured for the N-formyl and N-acetyl derivatives (IVa,b) (Fig. 2).

Therefore, the N-acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines (IIIa-h) and N-acyl-1-phenylethylamines (IVa-h) only differ essentially in the sign of the CE in the region below 200 nm.

Chemical Faculty, M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 944-949, July, 1996. Original article submitted May 23, 1996.

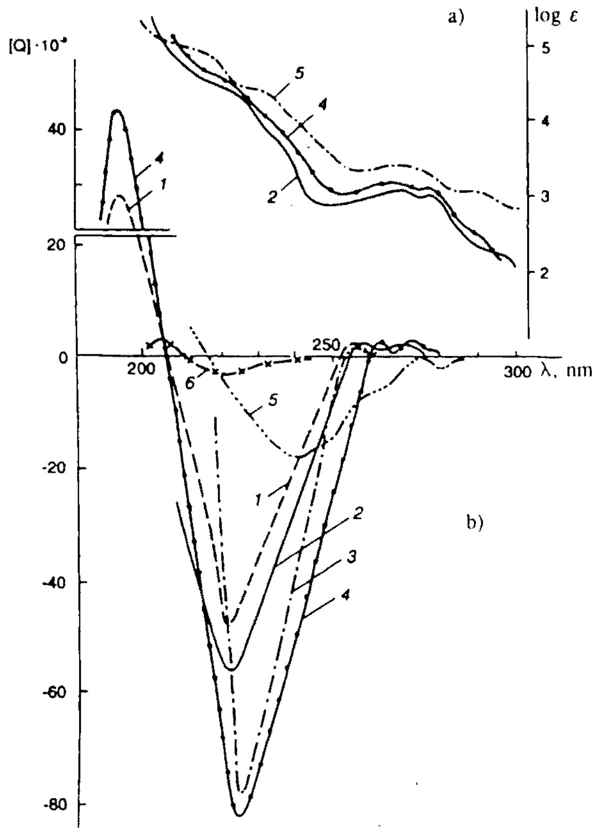


Fig. 1. UV spectra (a) and the CD spectra (b) of N-acyl-(S)(−)-1-methyl-1,2,3,4-tetrahydroisoquinolines (in ethanol). 1) IIIa; 2) IIIb-d,f; 3) IIIe; 4) IIIh; 5) IIIi; 6) (−)-1-methyl-1,2,3,4-tetrahydroisoquinoline.

It should be noted that a strong increase in the values of the CDs is observed in the transition from the amines (I) and (II), the spectra of which are analogous [2] to their N-acyl derivatives (III) and (IV), i.e., with the introduction of the amide chromophore into the molecule, whereby it is significantly greater for derivatives of 1-phenylethylamine than for derivatives of tetrahydroisoquinoline.

When two chromophores are present in the molecules of the studied amides (III) and (IV) — the amide and the aromatic — the deciding factor is probably not the fixing of the nitrogen and the aromatic chromophore in the cyclic structure of tetrahydroisoquinoline, but the possibility of interaction between the amide and aromatic chromophores. Such interaction is virtually impossible for the N-acyltetrahydroisoquinolines (IIIa-h), in which these chromophores are separated from each other. At the same time, owing to the free rotation around the C−N bond, the N-acyl-1-phenylethylamines (IVa-h) have conformations in which the amide and aromatic chromophores are drawn together, and there is the possibility of their mutual interaction analogous to the interaction of the aromatic and carboxyl chromophores in substituted phenylacetic acids [3].

It can be seen from the data of the CD spectra of the N-acyltetrahydroisoquinolines (IIIa-h) in the region of 220 nm that the radical R in the acyl part of the amide has practically no influence on the CE in the case of the amides (IIIa-d,f,g); this is in agreement with their identical conformational composition (~60% of the Z-conformer). When the portion of the Z-conformer increases for the amides (IIIe,h) by comparison with the amide (IIIa), an increase in the negative CE $\{[\theta]_{220}$ $-49{,}960°$ for (IIIa), $[\theta]_{220}$ $-80{,}000°$ for (IIIe), and $[\theta]_{220}$ $-85{,}000°$ for (IIIh)$\}$ is observed. Consequently, it can be proposed that the Z-conformers of the amides (IIIa-h) are characterized by the negative CE in the region of the absorption band of the amide chromophore; this is confirmed by measurements of the CD in the temperature range of 25 to −70°C. For the N-formyl and N-pivaloyl derivatives, (IIIa) and (IIIh) respectively, an increase in the negative CE was observed at 220 nm with a decrease in temperature: $[\theta]_{218}{}^{-70}$ $-73{,}650°$ for the amide (IIIa), and $[\theta]_{222}{}^{-70}$ $-98{,}000°$ for the compound (IIIh). Since it follows from the data of the PMR spectra [1] of the amide (IVh) that a decrease in the temperature is accompanied by a shift

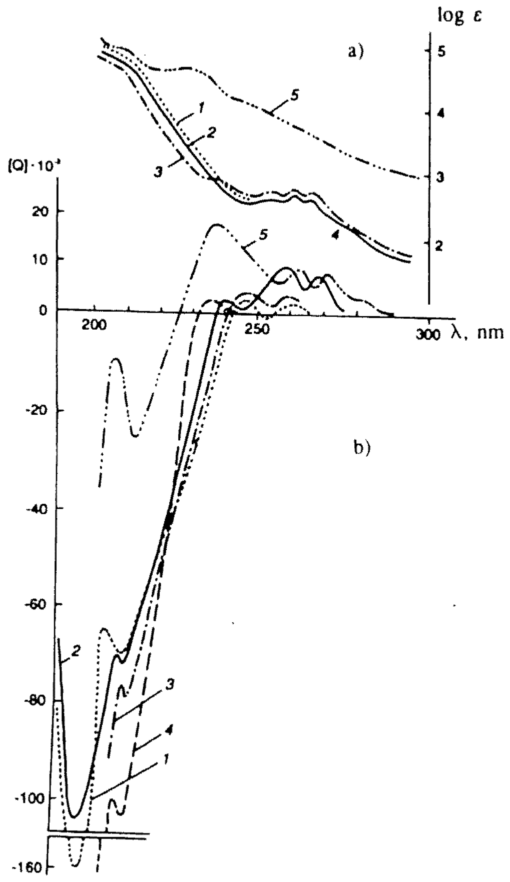


Fig. 2. UV spectra (a) and CD spectra (b) of N-acyl-(S)(−)-1-phenylethylamines (in ethanol). 1) IVa; 2) IVb-d,f; 3) IVe; 4) IVg; 5) IVi.

of the equilibrium in favor of the energetically more advantageous Z-conformer (78% of the Z-conformer at −40°C [1]), it can be assumed that it gives a negative contribution to the observed CE.

Such a conclusion is also indicated by the data of the CDs obtained for the 1-phenylethylamides (IVa-h). According to the data of the PMR spectra, the amide (IVa) exists preferentially in the form of the Z-conformer (~80%), which is in agreement with published data (87% [4]). For the other amides (IVb-h), separations of the signals in the PMR spectra could not be found. On the basis of the published data that the trans-form (the Z-conformation) is preferred for monosubstituted amides [4], it can be proposed that the other 1-phenylethylamides (IVb-h) also mainly occur in the Z-conformation. Significant CEs in the region of 210-220 nm, the magnitude of which was greater than that for the amides (IIIa-h), were observed for all the amides (IVa-h).

The N-benzoyl derivatives of both amines behave completely otherwise. Notwithstanding the identical configuration of the asymmetric center, N-benzoyl-(−)-1-methyl-1,2,3,4-tetrahydroisoquinoline (IIIi) and N-benzoyl-(−)-1-phenylethylamine (IVi) give antipodal CD spectra (Figs. 1 and 2). A complex CE which is negative for compound (IIIi) and positive for (IVi), caused by the ^1L_b of the absorption band of the aromatic chromophore, is observed in the region of 260-280 nm. In the region of ~240 nm, both compounds give a second CE of the same sign as the first, the cause of which is an electronic transition in the benzamide chromophore. Further, there is a negative CE in the region of 215 nm for N-benzoyl-(−)-1-phenylethylamine (IVi), which is probably associated with the ^1L_a of the absorption band of the aromatic chromophore. This CE is not measured for N-benzoyl-(−)-1-methyl-1,2,3,4-tetrahydroisoquinoline, but it can be seen that it should be positive according to the shape of the CD curve.

Such a difference is possibly determined by the differing conformational mobility of the amides (IIIi) and (IVi). Consideration of molecular models showed that it is possible for the E-form of the conformationally mobile compound (IVi) to have the conformation (V), in which both phenyl rings are in proximity and, consequently, between which interaction leading

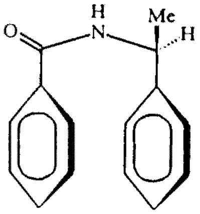
TABLE 1. CDs of N-Formyl- and N-Pivaloyl-(−)-1-methyl-1,2,3,4-tetrahydroisoquinolines, (IIIa) and (IIIh) Respectively, in Ethanol (c 0.02) at Different Temperatures*

λ (nm)	Temperature, °C			
	25	0	-40	-70
		IIIa		
271	1080	1110	1030	1030
268	870	840	840	840
264	1110	1110	1220	1200
218	-49960	-60092	-64242	-73650
193	31872	39508	41500	71500
		IIIh		
271	1360	1320	1360	2010
268	970	950	950	1000
264	1360	1340	1480	1640
222	-85000	-92000	-94000	-98000
192	42800	43600	46800	47800

---

*Measured on the Jobin Ivon dichrograph.

to the characteristically dissymmetric chromophore is possible. This is indicated by the stronger absorption of the amide (IVi) in the UV spectrum (Fig. 2a) by comparison with the amide (IIIi) (Fig. 1a) and the exciton splitting in the CD spectrum (Fig. 2b): the CD couplet of the positive band at ~240 nm and the negative band at 213 nm, of approximately equal magnitude, is observed.

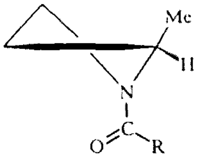


V

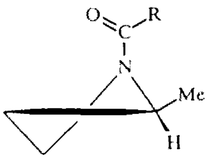
The optical activity of the characteristically dissymmetric chromophores is usually much higher than the optical activity caused by the contribution of the asymmetric center. Therefore, it is just that which determines the sign of the observed CE, notwithstanding the small population of the E-conformer (<20%). In the case of the N-benzoyl derivative of (−)-1-phenylethylamine, the contribution of such a conformation is probably positive since the positive band is observed in the long-wave region of the CD couplet.

In the benzoyl derivative of (−)-1-methyl-1,2,3,4-tetrahydroisoquinoline (IIIi), the benzamide chromophore cannot interact with the phenyl ring of the tetrahydroisoquinoline fragment on steric considerations, and the CD spectrum of the amide (IIIi) is analogous to the CD spectra of other acyl derivatives of (−)-1-methyl-1,2,3,4-tetrahydroisoquinoline with the difference that the CE is shifted bathochromically, and its intensity is much less.

For derivatives of tetrahydroisoquinoline, two conformations are possible for the piperidine ring — the P and the M. Investigations of 1-methyl-1,2,3,4-tetrahydroisoquinoline (I) [5] showed that the P-form is preferred for it.



VI, P-conformation



VII, M-conformation

A weak positive CE is observed for (−)-1-methyl-1,2,3,4-tetrahydroisoquinoline in the region of the ^1L_b of the transition of the aromatic chromophore as well as a negative CE of medium intensity at 220 nm [2]. The signs of these two CEs are maintained in the transition to the N-acyl derivatives, i.e., it can be assumed that the P-form of the piperidine ring of (VI) is maintained. Such an explanation is also favored by the fact that the conformational composition of N-acyl-1-methyl-1,2,3,4-tetrahydroisoquinolines has little dependence on the magnitude of R in the acyl residue. Consideration of Dreiding molecular models showed that the methyl group at the $C_{(1)}$ atom in the M-form of (VII) is sterically in the proximity of the alkyl group of the acyl residue, and such a conformation cannot be realized even only when R = Et. Therefore, the E-conformation of the amide group is scarcely probable. At the same time, the occurrence of two conformers, the Z and the E, is possible in the P-form; this was also shown by the PMR spectral data [1].

EXPERIMENTAL

The CD spectra were measured on the JASCO J-20 spectropolarimeter and the Jobin Ivon dichrograph in cuvettes of 0.1 cm and 0.05 cm thickness. The UV spectra were measured on the Specord spectrophotometer.

(S)(−)-1-Phenylethylamine (II). This compound was obtained by resolution with D-tartaric acid. It has the $[\alpha]^{20}_D$ −40.4° (without solvent); the published data [5] are $[\alpha]^{20}_D$ −40.8°.

(S)(−)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (I). This compound was synthesized from (S)(−)-(II) by the method described in [2]. The $[\alpha]^{20}_D$ −76.7° (c 0.1, ethanol). The published data [6] are $[\alpha]^{20}_D$ −71.5° (ethanol).

N-Acyl-(S)(−)-1-methyl-1,2,3,4-tetrahydroisoquinolines (IIIa-h). These compounds were obtained by the acylation of the (S)(−)-amine (I) by the action of the corresponding acids or their acid chlorides by analogy with the method previously described for the racemic compounds [1], and their identity was confirmed by the method of TLC on Silufol using the 3:1 system of benzene—acetone.

N-Benzoyl-(S)(−)-1-methyl-1,2,3,4-tetrahydroisoquinoline (IIIi). The mixture of 0.035 mole of the amine (−)-(I), 1.8 g of sodium carbonate, and 0.035 mole of benzoyl chloride in 50 ml of benzene is heated to boiling. The reaction mixture is washed with water, and the benzene is distilled off. The amide (IIIi) is obtained with the yield of 84%; it has the mp 126-127°C (from the mixture of benzene—isooctane). Found, %: C 84.15 and H 6.70. $C_{17}H_{17}NO$. Calculated, %: C 84.27 and H 6.77.

The IR spectrum is as follows: 3300 cm^{-1} (NH), 1630 cm^{-1} (amide I), and 1510 cm^{-1} (amide II).

(S)(−)-1-Phenylethylamides (IVa-i). These compounds were obtained according to the method described in [7].

The authors express their thanks to the Russian Fund of Fundamental Investigations for financial support of the work (Project 95-03-08852).

REFERENCES

1. V. M. Potapov, V. M. Dem'yanovich, L. B. Krivdin, T. V. Skvortsova, and Z. I. Bakhtti, Khim. Geterotsikl. Soedin., No. 5, 662 (1981).
2. V. M. Potapov, V. M. Dem'yanovich, and T. V. Skvortsova, Khim. Geterotsikl. Soedin., No. 9, 1238 (1987).
3. J. C. Craid, S.-J. C. Lee, R. P. K. Chan, and J. Y. F. Wang, J. Am. Chem. Soc., **99**, 7996 (1977).
4. W. E. Stewart and T. H. Siddall, Chem. Rev., **70**, 517 (1970).
5. V. V. Dunina, E. G. Rukhadze, and V. M. Potapov, Isolation and Investigation of Optically Active Substances, Moscow State University (MGU), Moscow (1979), p. 956.
6. W. Leithe, Monatch., **53**, 956 (1929).
7. V. T. Bezruchko, R. A. Gracheva, V. M. Potapov, V. M. Dem'yanovich, and A. P. Terent'ev, Zh. Obshch. Khim., **37**, 1467 (1967).