SYNTHESIS AND CHIROPTICAL PROPERTIES OF (—)-(1*R*)-3-AZATRICYCLO[5,4,0,$0^{4,9}$]UNDECAN-2-ONE — A LACTAM WITH NON-PLANAR *cis*-AMIDE GROUP

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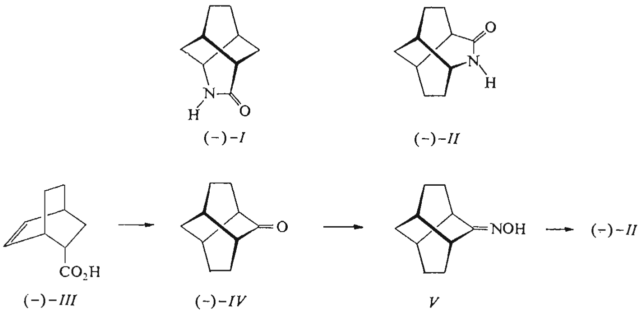
The title compound (—)-*II* was prepared starting from (—)-(2*S*)-*endo*-bicyclo[2,2,2]oct-5-ene-2-carboxylic acid ((—)-*III*). Parameters of the dichroic bands obtained in solvents of various polarity indicate the presence of a non-planar amide group in (—)-*II*. This amide group is of an opposite chirality and deviates less from planarity than the amide group in (—)-(3*S*)-4-azatricyclo-[4,4,0,$0^{3,8}$]decan-5-one (*I*). Comparison of the calculated ORD curves with the experimental ones shows that molecular chirality of the σ-skeleton does not participate directly in the dichroic absorption of the amide group.

In our previous communications, we investigated the properties of (−)-(3*S*)-4-azatricyclo[4,4,0,$0^{3,8}$]decan-5-one ((−)-*I*), rigid tricyclic lactam with a non-planar *cis*-amide group incorporated into a six-membered ring[1−4]. Comparison of the CD data of this model compound with those of lactams possessing virtually planar amide groups enabled us to find some features, characteristic for the chiroptical manifestation of a non-planar amide chromophore (increase in the rotatory strength of the $n-\pi^*$ transition relative to that of the $\pi-\pi^*$ transition, bathochromic shift of the $n-\pi^*$ dichroic band) and to ascribe the signs of the Cotton effects to the defined chirality of the amide group. Since the compound (−)-*I* represents the only one hitherto described monolactam with spatially fixed non-planar amide group, it seems desirable to investigate further model lactams in which the non-planar amide group would be part of a ring other than six-membered one and which would also satisfy the conditions of rigidity and known absolute configuration. These requirements are met in the case of (−)-(1*R*)-3-azatricyclo[5,4,0,$0^{4,9}$]undecan-2-one ((−)-*II*) in which the amide group is incorporated into a seven-membered ring. The study of chiroptical properties of this compound represents the subject of the present communication.

The lactam (−)-*II* was synthesized starting from the optically active (−)-(2*S*)-*endo*-bicyclo[2,2,2]oct-5-ene-2-carboxylic acid ((−)-*III*) by the reaction sequence shown in Scheme 1. As evident, both the lactam (−)-*I*, described previously, and the compound (−)-*II* have the same sense of skeletal twist.



SCHEME 1

EXPERIMENTAL

The CD measurements were carried out in 0·05—0·1 cm quartz cells on a Roussell-Jouan CD 185/II instrument equipped with a cryostate. Unless stated otherwise, the spectra were taken at 25°C, the concentration being about 0·25 mg/ml. The experimental CD curves were digitized and simulated by a sum of Gaussian bands. Parameters of these bands were estimated and then in a further step optimized using the algorithm described by Fletcher and Powell[5]. The experimental rotatory strengths relate to the thus-obtained parameters of the Gaussian bands. The ORD curves were measured on a Jasco UV/ORD-5 spectropolarimeter. The CD spectra, represented by the sums of Gaussian bands, were compared with the ORD curves, using the Kronig–Kramers transform. The transformations of the experimental data were carried out on a Hewlett–Packard 9830A calculator equipped with an HP-9862A digital $x - y$ plotter and an HP-9864A digitizer. The details of the procedure have been given in our previous communications[3,6,7].

(—)-(1*R*)-3-Azatricyclo[5,4,0,0^{4,9}]undecan-2-one ((—)-*II*)

(—)-(2*S*)-*endo*-Bicyclo[2,2,2]oct-5-ene-2-carboxylic acid ((—)-*III*), $[\alpha]_D^{25}$ —49·8° (*c* 0·6, methanol), was transformed into (—)-(1*R*)-tricyclo[4,4,0,0^{3,8}]decan-2-one ((—)-*IV*), $[\alpha]_D^{25}$ —472·7° (*c* 0·6, ethanol), using the procedure, described for the racemic compound by Whitlock and Siefken[8] (see also refs[9,10]). (The highest hitherto reported[10] specific rotation of the ketone *IV* is 412°). This ketone (240 mg) in methanol (2 ml) was added to a mixture of hydroxylamine hydrochloride (150 mg) and sodium acetate trihydrate (300 mg) in water (0·7 ml). After standing for 40 h the mixture was diluted with water, the product taken up in ether (three portions), the organic layer washed with sodium hydrogen carbonate solution and water, dried and taken down leaving 253 mg (96%) of the oxime *V*, m.p. 173—176°C, free of the starting ketone (thin-layer chromatography). A sample, crystallized from methylcyclohexane, melted at 177—177·5°C. Mass spectrum: for $C_{10}H_{15}NO$ M^+ calculated: 165·1154; found: 165·1155.

Benzenesulfonyl chloride (366 mg; 2·08 mmol) was added dropwise with stirring to a cooled suspension of the oxime (250 mg; 1·51 mmol) in 0·5M sodium hydroxide solution (4·0 ml; 2·00 mmol). After stirring overnight the mixture was neutralized with 0·5M sodium hydroxide and extracted with ten portions of dichloromethane. The organic solution was dried over sodium sulfate, taken down, the residue dissolved in ether and chromatographed on a silica gel column (50 g). The impurities were removed by elution with ether. The product ((—)-*II*) was eluted with methanol, sublimed *in vacuo*, crystallized from methylcyclohexane and again sublimed *in vacuo*; m.p. 267—269°C (sealed capillary); $[\alpha]_D^{25}$ —173·1° (*c* 0·12, methanol); yield 71·5 mg (28·6%). For $C_{10}H_{15}NO$ (165·2) calculated: 72·69% C, 9·15% H, 8·48% N; found: 72·02% C, 8·95% H, 8·44% N. Mass spectrum: M^+ calculated: 165·1154; found: 165·1162. IR spectrum (CCl_4, cm^{-1}): 1668 (amide I), 3420 (N—H).

The same procedure, applied to the racemic ketone (±)-*IV* afforded the racemic lactam (±)-*II*, m.p. 265—267°C (methylcyclohexane, sealed capillary) in essentially the same yield.

RESULTS

Similarly as observed for the lactam (−)-*I* (ref.[3]), the CD spectrum of the lactam (−)-*II* (Table I, Fig. 1) exhibits two intense dichroic bands, however, the signs of the corresponding bands in these two compounds are opposite. The positive Cotton effect, observed in the spectrum of the lactam (−)-*II* in the region of about 210 to 260 nm, can be ascribed to the amide $n-\pi^*$ transition on the basis of its position

TABLE I

CD Spectra of the Lactam (—)-*II* Measured in Various Solvents

Solvent	Direct readings		Separated Gaussian bands			
	λ_{max}, nm	$[\Theta]_{max}{}^a \cdot 10^{-3}$	λ_{max}, nm	$[\Theta]_{max}{}^a \cdot 10^{-3}$	Δ^b	$R^c \cdot 10^{39}$
			$n—\pi^*$ Transition			
Cyclohexane	230	16·8	230·5	16·7	16·2	1·45
Acetonitrile	226	20·8	225·8	21·2	15·8	1·83
Ethanol	222	22·3	217·9	28·4	14·7	2·37
Water	219	25·9	216·5	30·5	12·3	2·14
TFE[d]	217	25·2	214·5	31·0	12·2	2·18
HFP[e]	214	28·7	211·3	37·6	12·1	2·64
			$\pi—\pi^*$ Transition			
Cyclohexane	200	—51·3	199·8	—52·2	11·0	—3·53
Acetonitrile	199	—49·0	199·8	—50·5	11·5	—3·58
Ethanol	199	—40·4	199·8	—45·7	14·2	—4·01
Water	198	—32·2	199·7	—36·8	12·4	—2·80
TFE[d]	196	—35·5	196·9	—38·9	13·3	—3·23
HFP[e]	194	—33·5	196·2	—39·0	13·7	—3·36

[a] $[\Theta]_{max}$ maximum molar ellipticity (deg cm^2 $dmol^{1-}$); [b] Δ band halfwidth (nm); [c] *R* rotatory strength (esu^2 cm^2); [d] TFE 2,2,2-trifluoroethanol; [e] HFP 1,1,1,3,3,3-hexafluoro-2-propanol.

and of the bathochromic shift in less polar solvents. As compared with the lactam (−)-*I*, the apparent maximum is hypsochromically shifted by 1·5 nm (cyclohexane) and also the solvent shift is smaller. For the extreme solvents of the used series, 1,1,1,3,3,3-hexafluoro-2-propanol and cyclohexane, this shift is 16 nm for the lactam (−)-*II* whereas for the lactam (−)-*I* it amounts to 25 nm. If we use the separated Gaussian bands which afford data not so seriously influenced by the superposition of the $n-\pi^*$ and $\pi-\pi^*$ transitions (particularly in polar solvents), the solvent shifts are 19·2 nm for the former and 22·6 nm for the latter lactam. The dichroic $n-\pi^*$ absorption in the lactam (−)-*II* increases with increasing solvent polarity. This increase, however, is partly compensated by gradual decrease in the halfwidth of this CD band so that the rotatory strength of the $n-\pi^*$ transition increases only moderately with increasing solvent polarity. A similar increase in the absolute value of rotatory strength was observed also for the lactam (−)-*I*. However, the $n-\pi^*$ transition rotatory strength invariably amounts to only about two thirds of the values found for the lactam (−)-*I*. The $\pi-\pi^*$ amide transition in the compound (−)-*II* manifests itself by a negative Cotton effect at 198 nm. With the exception of solutions in fluorinated alcohols (where this band is hypsochromically shifted) the position of this band does not depend significantly on solvent polarity. The absolute values of the ellipticities and of the rotatory strengths for the lactam (−)-*II* are approximately 1·5−2 times larger than for (−)-*I*. However, the dependence on the solvent polarity for the former compound is different, the $[\Theta]_{\max}$ and R values slightly decreasing with increasing solvent polarity. The ratios of absolute values of the rotatory strengths of the $n-\pi^*$ and $\pi-\pi^*$ transitions ($|R_{n-\pi^*}|/|R_{\pi-\pi^*}|$) is thus different for both these compounds (about 1 : 1·5 to 1 : 2 for (−)-*II* and 1 : 1 to 1·5 : 1 for (−)-*I*).

In non-polar solvents, the spectra of the lactam (−)-*I* exhibited a weak but distinct CD band at 215 nm which we assigned to a Rydberg type transition[1,3]. Spectra of lactams with bornane skeleton were found to display bands in the same spectral

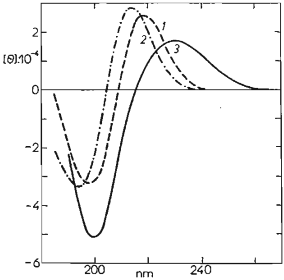


FIG. 1

CD Spectra of the Lactam (—)-*II*, Measured in Cyclohexane 3, Water 1 and 1,1,1,3,3,3-Hexafluoro-2-propanol 2 region which were ascribed to associated molecules[11]. The CD spectra of the lactam (−)-*II* exhibited no such bands. Moreover, its CD spectra in cyclohexane did not reveal any concentration dependence in the range $10^{-3}-10^{-4}$ mol l^{-1} which would indicate the presence of associates. In cyclohexane, acetonitrile and water we found another positive band at short wavelengths, outside the region accessible to measurement, whose long-wavelength part modifies the shape of bands in the region 185 to 190 nm. We were not able to determine satisfactory parameters of this band. Temperature dependence of the CD spectrum of the lactam (−)-*II* (Fig. 2), measured in methanol–ethanol (1 : 1) mixture, resembles that observed for the compound (−)-*I*. The Cotton effect of the $n-\pi^*$ transition is shifted hypsochromically with decreasing temperature, this shift being accompanied with an about 30% increase in dichroic absorption intensity. The position of the band due to the $\pi-\pi^*$ transition remains constant, only a moderate hypochromic effect was observed.

The ORD curves measured in acetonitrile (Fig. 3) and 2,2,2-trifluoroethanol (λ_{max} 268 nm, $[\Phi]_{max}$ $-1860°$; λ_{max} 230 nm, $[\Phi]_{max}$ $+5600°$; λ_{max} 208 nm, $[\Phi]_{max}$ $-48900°$; λ_{max} <190 nm, $[\Phi]_{max} > +15000°$) show the presence of a multiple Cotton effect in the region 190−250 nm. This observed ORD anomaly is superimposed on the negative background curve. The ORD curves, calculated from the CD spectra using the Kronig–Kramers transform, agree satisfactorily with the experimental ORD spectra in the region of anomalous dispersion; however, throughout

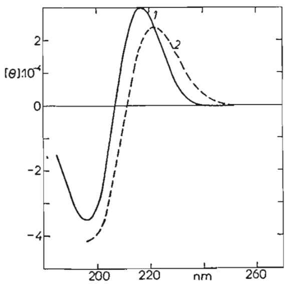


FIG. 2

Temperature Dependence of CD Spectra of the Lactam (—)-*II*, Measured in Methanol –Ethanol (1 : 1)

1 —160°C; *2* +40°C.

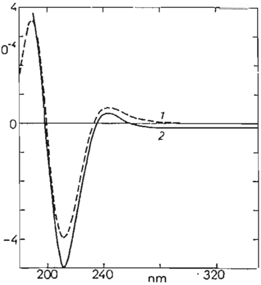


FIG. 3

ORD Spectra of the Lactam (—)-*II*; *2* Experimental Curve (acetonitrile); *1* Curve Computed from the CD Spectrum Using the Kronig–Kramers Relationship the whole spectral region the calculated rotation values are more positive than those found experimentally. This is obvious particularly at longer wavelengths in the normal dispersion region. The negative background curve is thus derived from Cotton effects in the far-ultraviolet region rather than from the $n-\pi^*$ and $\pi-\pi^*$ transitions of the amide chromophore. A similar negative background curve with superimposed Cotton effect of an opposite sign was found in ORD spectra of the lactam (−)-*I* (ref.[7]).

DISCUSSION

Inspection of Dreiding models shows that the *cis*-amide group in the lactam (−)-*II* is distinctly non-planar and that its deviation from planarity differs qualitatively from that in the lactam (−)-*I*. This difference consists in the opposite sense of torsion around the C′—N bond, expressed by the parameter $\Delta\omega$ ($\Delta\omega < 0°$ for (−)-*I*, $\Delta\omega > 0°$ for (−)-*II*). If we assume, in accord with the previous quantum chemical calculations[4,12-14,15], that the hydrogen atom bonded to the amide nitrogen is oriented so as to form an approximately regular pyramidal arrangement of the bonds at the nitrogen atom ($\chi_N = -2\,\Delta\omega$, ref.[12]), we can expect an approximately enantiomeric relation between the local arrangements of the inherently chiral non-planar amide chromophores in the lactams (−)-*I* and (−)-*II*. This conclusion agrees both with the opposite signs of the corresponding CD bands in these lactams and with the results of quantum chemical calculations of optical rotatory strengths of electronic transitions in an amide group, deviating from planarity in the above-mentioned manner[4]. Dreiding models show that, although the molecular skeleton of the lactams (−)-*I* and (−)-*II* is not completely identical, the spatial arrangement of their tricyclic systems can be related to the same absolute configuration of the parent twistane hydrocarbon (*i.e.* the sense of skeletal twist is the same for both compounds). Thus, the molecular chirality, which manifests itself by CD bands in the vacuum UV region, should be very similar for both these compounds. In accord with this assumption, we observe in both cases the same negative course of the background ORD curve which, in the case of the lactam (−)-*II*, does not coincide with the curve calculated from the CD spectrum (measured only in the region of the absorption bands of the amide chromophore). There is a kind of diastereoisomeric relation between the lactams (−)-*I* and (−)-*II*, and the chiroptical manifestation of the non-planar amide chromophore (enantiomeric) and of the tricyclic skeleton (identical) can be observed in the CD and ORD spectra separately. We can thus infer that *a*) no significant electronic interaction seems to exist between the non-planar amide chromophores and the tricyclic σ-skeletons of both lactams; *b*) the signs of the CD bands due to $n-\pi^*$ and $\pi-\pi^*$ transitions are determined decisively by the inherent chirality of the non-planar amide group. This can be regarded as a proof of superiority of inherent chromophore chirality over the chiral induction, assumed already previously. We see also the marked difference in the nature of information obtained from the spectra: the CD spectra indicate local chiral deformation of the chromophore whereas the ORD spectra reflect also the chirality of the molecule as a whole.

Both the position and intensity of the CD bands of the lactam $(-)$-*II* are in accord with the anticipated effect of non-planarity of an amide group on its chiroptical properties. An approximate information about the magnitude of the deviation from planarity can be obtained from comparison of CD spectra of the lactams $(-)$-*I* and $(-)$-*II* with those of lactams containing virtually planar amide groups. The ratio $|R_{n-\pi^*}|/|R_{\pi-\pi^*}|$ for the lactams with virtually planar amide group (4-azatricyclo$[4,3,1,0^{3,7}]$decan-5-one[5], 4-tert-butyl-1-aza-2-cyclohexanone[6], 5-tert-butyl-1--aza-2-cyclohexanone[6]) is about 1 : 3. The value, obtained with the lactam $(-)$-*II* thus indicates that the deviation of the amide group from planarity, though distinct, is smaller than in the case of the lactam $(-)$-*I*. This conclusion is supported also by the fact that in a non-polar medium the $n-\pi^*$ transition in the lactam $(-)$-*II* is hypsochromically shifted as compared with the analogous band of the lactam $(-)$-*I* and exhibits a smaller solvent shift.

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