(3*R*)-5-AZATRICYCLO[4.3.1.0^{3,8}]DECAN-4-ONE, A LACTAM WITH A NON-PLANAR *cis*-AMIDE GROUP: SYNTHESIS, GEOMETRY AND CHIROPTICAL PROPERTIES*

Miloš TICHÝ, Ahmed M. FARAG**, Petr MALOŇ, Petr KÁLAL and Karel BLÁHA

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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Stereospecific synthesis of the title lactam (+)-*I* starting from (1*R*,5*R*,6*R*)-3-oxobicyclo[3.2.1]-octane-6-carboxylic acid is described. X-Ray structure determination has shown a marked non-planarity of the amide group in *I*. In accord with theoretical calculations, CD spectrum of the studied (+)-(3*R*)-enantiomer exhibits a positive $n-\pi^*$ and negative $\pi-\pi^*$ band. The rotational strength of the $n-\pi^*$ transition is three times higher than that of the $\pi-\pi^*$ transition, contrary to the behaviour of lactams with virtually planar amide groups.

Polycyclic lactams have served as model compounds in investigations of non-planar amide (peptide) groups[1]. Moreover, their synthesis offers an approach to (and comparison with) the analogous lactones because the preparation of both types is usually closely connected. In addition to the mentioned non-planarity, the properties of amide (or ester) groups are influenced by the size and conformation of the ring in which the functional group is embedded; also constitution effects of the nearest surroundings are of importance. Therefore, it is necessary to investigate and compare a greater number of suitable model compounds in order to separate single structural effects. The series of previously described lactams[2-4] derived principally from the twistane skeleton has been now extended by the title compound *I*, containing a *cis*-amide group in a six-membered ring. The geometry and chiroptical properties of its lactone analogue – (3*R*)-5-oxatricyclo[4.3.1.0^{3,8}]decan-4-one – have been described already previously[5].

The aim of our present work was to prepare the optically active lactam *I* of known absolute configuration and spatial arrangement and to study its CD spectra.

The compound (+)-*I* was prepared starting from the described[6] keto acid (+)-*II* of known absolute configuration[5] by the reaction sequence shown in Scheme 1. Since this synthesis is stereochemically straightforward, the absolute

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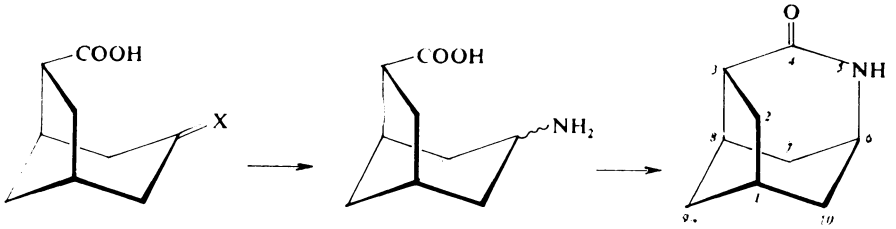
** Present address: Chemistry Department, Faculty of Sciences, Cairo University, Cairo, Egypt.

configuration of (+)-*I* is 3*R*, as depicted by the formula. The complete optical purity of the lactam (+)-*I* was proved by ^{1}H NMR spectroscopy using a chiral shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium).



(+)-*II*, X = O
(+)-*II*, X = NOH

(−)-*III*

(+)-*I*

SCHEME 1

Molecular geometry of crystalline lactam *I* was determined by X-ray structure analysis of a racemic sample the results of which will be published in detail in a separate paper[7]. Despite the obvious rigidity of *I*, two molecules of slightly different geometry (A and B) have been found in the asymmetric unit cell, the amide group being significantly non-planar in both these forms. Both molecules in the assymmetric part of the unit cell are of the same absolute configuration and the sense of deviation from planarity of the amide group is also the same. The geometric parameters characterizing the arrangement of the amide group and its immediate surroundings in both molecules are given in Table I. The non-planar amide group can be described by the following specific parameters: in the molecule B $\Delta\omega = +18{\cdot}2°$, $\chi_N = -10{\cdot}7°$, $\chi_C = +4{\cdot}8°$; in the molecule A $\Delta\omega = +14{\cdot}8°$, $\chi_N = -2{\cdot}0°$, $\chi_C = +3{\cdot}1°$. The differences between the conformations A and B concentrate mainly to bond angles within the amide group. This fact, together with small and varying values of the angle χ_N suggests that the observed differences in geometry are connected with differences in hydrogen bonding within the crystal lattice. In accord with the previous X-ray and quantum chemical study of (−)-4-azatricyclo[4.4.0.0^{3,8}]decan-5-one, it is only the spatial position of the amide hydrogen atom and, consequently, the angle χ_N which is influenced more seriously by the packing in the crystal. Other geometric parameters are approximately transferable from the crystalline state to molecules in solution.

The lactam *I* displays rather intense CD spectra, especially in the $n-\pi^*$ region (Fig. 1, Table II). In accord with the found sense of the amide group non-planarity ($\Delta\omega > 0°$), the (+)-(3*R*)-enantiomer exhibits a positive $n-\pi^*$ CD band together with negative $\pi-\pi^*$ band. Similarly to the lactams *V* and *VI* studied earlier[2,4], there is an additional weak band at about 210 nm which can be detected as a shoulder in solvents of lower polarity (cyclohexane, acetonitrile). However, with the lactam *I* the intensity

TABLE I

Selected geometric parameters found by X-ray diffraction for the two conformations A and B in the asymmetric unit cell of *I* (for numbering of atoms see formula *I*)

Bond length		Bond angle		Torsion angle	
$C_{(3)}—C_{(4)}$	A 0·1514 B 0·1491	$C_{(3)}—C_{(4)}—N_{(5)}$	A 115·1° B 113·0°	$C_{(3)}—C_{(4)}—N_{(5)}—C_{(6)}$	A +14·8° B +18·2°
$C_{(4)}—N_{(5)}$	A 0·1312 B 0·1299	$C_{(3)}—C_{(4)}—O$	A 122·4° B 125·5°	$O—C_{(4)}—N_{(5)}—H$	A +9·7° B +2·7°
$N_{(5)}—C_{(6)}$	A 0·1464 B 0·1514	$O—C_{(4)}—N_{(5)}$	A 122·4° B 121·5°	$O—C_{(4)}—N_{(5)}—C_{(6)}$	A −168·3° B −166·6°
$C_{(4)}—O$	A 0·1242 B 0·1219	$C_{(4)}—N_{(5)}—C_{(6)}$	A 119·2° B 117·7°	$C_{(3)}—C_{(4)}—N_{(5)}—H$	A −167·2° B −172·5°
$N_{(5)}—H$	A 0·0901 B 0·0856	$C_{(4)}—N_{(5)}—H$	A 121·2° B 118·4°	—	
—		$H—N_{(5)}—C_{(6)}$	A 118·8° B 122·9°	—	

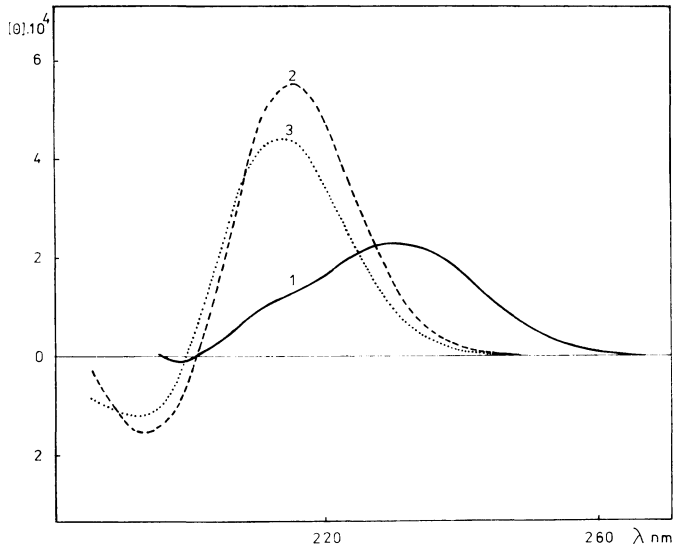
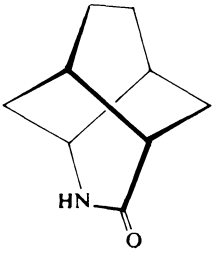


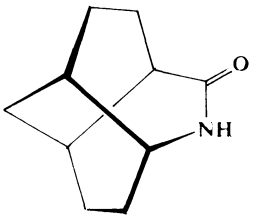
FIG. 1

CD Spectra of lactam (+)-*I* in cyclohexane (*1*), water (2) and 2,2,2-trifluoroethanol, (*3*) ([θ] $\times 10^{-4}$)

of this dichroic band decreases with decreasing concentration (in cyclohexane solution). Hence, it is possible that the band is related to self-association of *I* in contrast to compounds *V*, *VI* where it was ascribed[2,4] to a Rydberg type transition. The



V



VI

$n-\pi^*$ band exhibits a pronounced hypsochromic shift with increasing solvent polarity and a marked hyperchromic effect. The $\pi-\pi^*$ band shows no systematic dependence on solvent polarity and its intensity is rather low, particularly in cyclohexane solution. As expected for the rigid polycyclic skeleton of *I*, its CD spectra are not sensitive to temperature changes.

The lactam *I* represents a model which in the present series has the greatest non-planarity of the amide group. The signs of both the $n-\pi^*$ (positive) and $\pi-\pi^*$

TABLE II

Solvent and temperature dependence of CD spectra of lactam (+)-*I*

Solvent	λ_{max} ($[\theta]_{max}$)[a]	
	n-π^*transition	π-π^*transition
Cyclohexane	230 (+22·6)	198 (−0·4)
Acetonitrile	226 (+34·0)	197 (−15·6)
Methanol	218 (+42·8)	[b]
Water	215 (+54·8)	193 (−15·6)
TFE[c]	213 (+43·8)	192 (−12·0)
HFP[c]	209 (+58·7)	[b]
Methanol–ethanol +40°C	218 (+38·6)	[b]
Methanol–ethanol −80°C	215 (+43·3)	[b]

[a] λ_{max} wavelength of the maximum (nm), $[\theta]_{max}$ molar ellipticity of the maximum $\times 10^{-3}$ (deg cm^2 dmol^{-1}); [b] the band maximum is situated outside the region accessible to measurement; [c] TFE 2,2,2-trifluoroethanol, HFP 1,1,1,3,3,3-hexafluoro-2-propanol.

(negative) CD bands for the given chirality (R, $-ap$) of the amide chromophore (Fig. 2) follow the relation calculated for a non-planar formamide molecule[8,9]. The series of model lactams allows to find some general relations between the chiroptical properties and spatial arrangement of the isolated amide group. For the virtually planar conformation the $n-\pi^*$ band is usually weaker than the corresponding $\pi-\pi^*$ band. This relation is significantly changed when the chromophore becomes non-planar[1]. The rotatory strength of the $n-\pi^*$ transition markedly increases and in the extreme case of the lactam I the $n-\pi^*$ band is about three times stronger than the $\pi-\pi^*$ band.

EXPERIMENTAL

The CD spectra were measured on a Roussel-Jouan CD 185/II Dichrographe equipped with a cryostat. The measurements were performed at 25°C in about 6.10^{-3} mol l^{-1} solutions. For details of experimental curves processing see refs[2-4]. The X-ray structure analysis is described in ref.[7].

3-Oximino[3.2.1]octane-6-*endo*-carboxylic Acid (*III*)

A solution of hydroxylamine hydrochloride (0·4 g) and sodium acetate trihydrate (1·0 g) in water (6 ml) was added with stirring to the keto acid *II* (ref.[6]) (0·4 g) in water (4 ml). The keto acid dissolved and the product started to precipitate after a short time (3–4 min). The stirring was continued for one hour and the mixture was left to stand overnight. The product was filtered, washed with cold water (4 ml) and dried to give 430 mg of a product, m.p. 183–186°C, which was directly used for the next reaction. A small sample was crystallized from water, m.p. 185 to 186°C. For $C_9H_{13}NO_3$ (183·1) calculated: 59·00% C, 7·15% H, 7·65% N; found: 58·86% C, 7·12% H, 7·73% N.

5-Azatricyclo[4,3,1,$0^{3,8}$]decan-4-one (*I*)

The oximino acid (400 mg) was hydrogenated in 50% aqueous acetic acid (10 ml) over PtO_2 (100 mg). The mixture was filtered, taken down and the residue coevaporated several times with water, affording 368 mg of 3-aminobicyclo[3.2.1]octane-6-*endo*-carboxylic acid (*IV*). The crude amino acid (350 mg) was heated to 160–180°C at 15 Pa. The sublimed substance was collected and resublimed twice to afford 185 mg of solid product which was crystallized from ethyl acetate; m.p. 243–245°C. For $C_9H_{13}NO$ (151·1) calculated: 71·49% C, 8·66% H, 9·25% N; found: 71·39% C, 8·85% H, 9·21% N. IR spectrum (chloroform): 3 420, 3 210 cm^{-1} (ν(N—H)), 1 660 cm^{-1} (ν(C=O)). Mass spectrum: calculated: M^+ 151·0997; found: 151·0992, M–42, M–15, M–17, M–28.

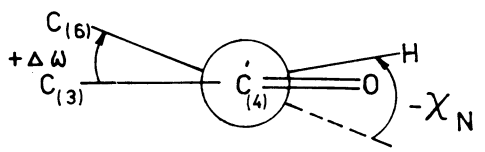


FIG. 2

Projection of non-planar amide group of (R, $-ap$) chirality in (+)-*I*

(1*R*,5*R*,6*R*)-3-Oximino[3.2.1]octane-6-carboxylic Acid ((+)-*III*)

The keto acid (+)-*II* (ref.[5]; 0·22 g, $[\alpha]_D^{22}$ +37·3° (*c* 0·3, dichloromethane)) was treated with hydroxylamine as described for the racemic material, giving 210 mg (88%) of the oximino acid (+)-*III*, m.p. 182–184°C (water), $[\alpha]_D^{22}$ +26·1° (*c* 0·5, methanol). For $C_9H_{13}NO_3$ (181·1) calculated: 59·00% C, 7·15% H, 7·65% N; found: 59·22% C, 7·16% H, 7·62% N.

(3*R*)-5-Azatricyclo[4.3.1.0^{3,8}]decan-4-one ((+)-*I*)

The oximino acid (+)-*III* (183 mg, 1 mmol) in 50% aqueous acetic acid (8 ml) was hydrogenated over PtO_2 (50 mg) at room temperature as described for the racemic compound, affording 166 mg (98%) of crude (−)-*IV*, $[\alpha]_D^{22}$ −11·6° (*c* 0·3, methanol), a part (120 mg) of which was heated in a sublimation apparatus to 200–220°C and 15 Pa. The sublimate was twice sublimed and purified by crystallization from ethyl acetate to give 56 mg (52%) of (+)-*I*, m.p. 255–256°C, $[\alpha]_D^{22}$ +137·2° (*c* 0·3, methanol). For $C_9H_{13}NO$ (151·1) calculated: 71·49% C, 8·66% H, 9·25% N; found: 71·35% C, 8·70% H, 9·18% N. IR spectrum in chloroform was identical with that of the racemic compound.

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