SYNTHESIS AND CHIROPTICAL PROPERTIES OF SIX-MEMBERED LACTAMS SUBSTITUTED WITH TERT-BUTYL GROUP

M.TICHÝ, P.MALOŇ, I.FRIČ and K.BLÁHA

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

(4S)-4-Tert-butyl-1-aza-2-cyclohexanone ((−)-*I*) and its (5S)-5-tert-butyl isomer (−)-*II* were prepared by Beckmann rearrangement of optically active 3-tert-butylcyclopentanone oxime whose absolute configuration was determined by chemical correlation. CD spectra of (−)-*I* and (−)-*II* in solvents of different solvation ability were measured and their dependence on temperature was determined. The results indicate that both compounds exist predominantly in the half-chair conformation with an only slightly non-planar amide group. A conformational change was observed for (−)-*II* in very polar solvents.

Investigations of CD spectra of lactams containing non-planar amide groups have shown[1−3] that the inherent chirality of this group can have a significant effect on the chiroptical behaviour of lactams and amides. The existing empirical rules relating the structure to optical activity in amides assume exclusively a planar arrangement of the amide group, *i.e.* they are based on the concept of induced chirality of the amide chromophore. However, Ramachandran and coworkers[4] in their critical survey of X-ray data have shown that practically all the amide (peptide) groups in the hitherto analysed compounds are (at least in the crystalline state) more or less non-planar. It cannot be excluded that this deviation of the amide group from planarity may be caused by interactions present in the crystal lattice and that the same compounds in solution have indeed planar amide groups. However, in solutions, a great majority of the hitherto studied compounds can exhibit a substantial degree of conformational mobility. Such mobility affects the whole molecular skeleton and makes an interpretation of results difficult. We tried therefore to design such structures in which the spatial arrangement would be, at least to some extent, fixed[1−3]. Now, we used the principle of conformational fixation, first employed by Winstein[5], based on the introduction of tert-butyl group into an originally mobile cyclic system.

This work presents the synthesis and absolute configuration determination of two lactams generated according to the above mentioned lines: (4S)-4-tert-butyl-1-aza-2-cyclohexanone ((−)-*I*) and its constitutional isomer (5S)-5-tert-butyl-1-aza-

-2-cyclohexanone $((-)$-II). These compounds were subjected to detailed study by circular dichroism measurement. They were also analysed by X-ray diffraction[6] and IR spectroscopy[7]. This facilitated the interpretation since it was possible to compare the compounds in the crystalline state and in solutions.

Synthesis of the Compounds and Assignment of Absolute Configuration

The lactams $(\pm)$-I and $(\pm)$-II were synthesized by Beckmann rearrangement of 3-tert--butylcyclopentanone oxime (V), as shown in Scheme 1. The arising mixture $(I : II =$ $= 3 : 2)$ was separated by crystallisation, combined with chromatography. The structural asignment to the compounds was based on the fact that the more abundant lactam, m.p. $137-138°C$, on reduction with lithium aluminium hydride afforded 4-tert-butylpiperidine (IX) (Scheme 2) and thus has the structure I. 3-Tert-butyl-hexanedioic acid[8] (III) was resolved *via* the brucine salt and the thus-obtained $(+)$--enantiomer, $(+)$-III, was transformed into $(-)$-IV and further to $(-)I$- and$(-)$-II.
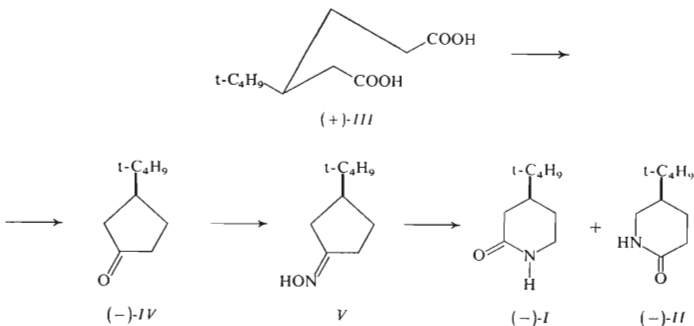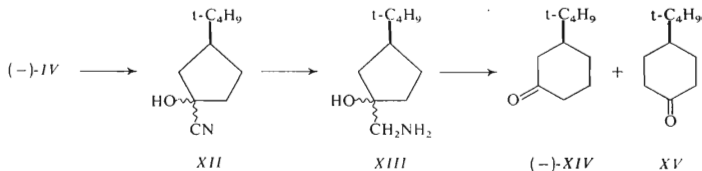

SCHEME 1
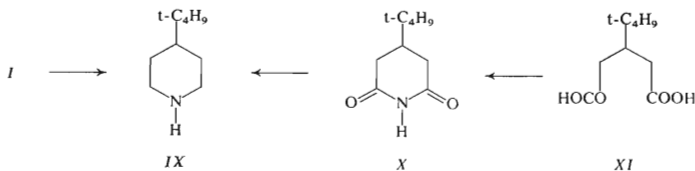
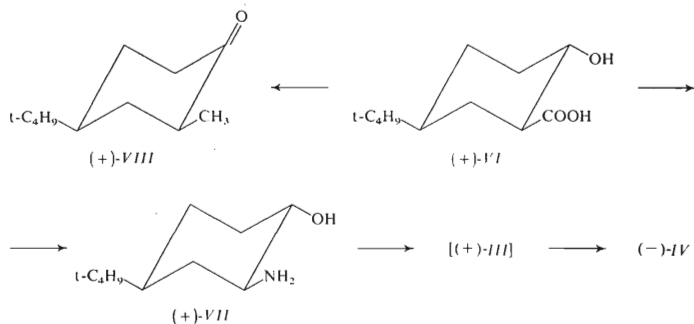SCHEME 2

The absolute configuration of $(-)$-3-tert-butylcyclopentanone $((-)$-IV) was determined by two sequences of reactions. In the first correlation, $(-)$-IV was transformed into the cyanohydrin XII which was reduced catalytically to the amino alcohol XIII (Scheme 3). This on treatment with nitrous acid according to Tchoubar[9] gave a 1 : 1 mixture of 4-tert-butylcyclohexanone (XV) (optically inactive) and $(-)$-3-tert-butylcyclohexanone $((-)$-XIV) which is known[10] to have the $(3S)$ configuration. The second reaction sequence (Scheme 4) consisted in the transformation of $(+)$-cis-5-tert-butyl-trans-2-hydroxycyclohexanecarboxylic acid, $((+)$-VI), which had been previously correlated[11] with $(2S)$-cis-4-tert-butyl-2-methylcyclohexanone $((+)$-VIII) into $(-)$-IV via the amino alcohol $(+)$-VII. Both the correlations show that $(-)$-IV has the $(3S)$ configuration and therefore the configuration of the lactams $(-)$-I and $(-)$-II is $(4S)$ and $(5S)$, respectively, as depicted in Scheme 1.

SCHEME 3

SCHEME 4

EXPERIMENTAL

The spectra were recorded on a Roussel Jouan Dichrograph CD 185/II equipped with a cryostat. Following spectral grade solvents were used: isopentane, cyclohexane, acetonitrile, methanol, 2,2,2-trifluoroethanol, and 1,1,1,3,3,3-hexafluoro-2-propanol. The solutions were measured in $0.05-0.5$ cm cells at $24-26°C$ at concentrations $2 . 10^{-3}$ mol l^{-1}, unless otherwise stated. The UV spectra were taken on a Cary 14 spectrophotometer in about $4 . 10^{-4}$ mol l^{-1} solutions in cyclohexane. Parameters of the individual Cotton effects were obtained on approximation of the experimental CD curves by a sum of Gaussian bands. The employed method[12] consists of three consecutive steps: a) Transcription of the spectrum into digital form using a Hewlett-Packard 9862A plotter as a digitizer under simultaneous conversion of the chart-read values into the plot of molecular ellipticity $[\theta]$ (deg cm^2 mol^{-1}) against wavelength λ (nm). b) Simulation of the experimental CD curve by the sum of suitably estimated Gaussian bands. c) Optimisation of the estimated band parameters by a curve-fitting procedure which minimizes the residual sum of squares using the algorithm described by Fletcher and Powell[13]. This procedure affords information about the minimum required number of bands, the integrated area below the CD curve and the approximate values of parameters of the individual Gaussian bands. As compared with the standard least-squares method used previously[3], the present procedure has an advantage of greater numerical stability gained on the expenses of a slower convergence. All the calculations were executed on a Hewlett-Packard 9830A calculator.

4-Tert-butyl-1-aza-2-cyclohexanone $((+)$-I$)$ and 5-Tert-butyl-1-aza-2-cyclohexanone $((\pm)$-II$)$

A solution of 3-tert-butylcyclopentanone (13·6 g; prepared according to ref.[8]) in methanol (150 ml) was added to a solution of hydroxylamine hydrochloride (15·0 g) and potassium acetate (23·0 g) in water (100 ml). After standing for 1 h the mixture was extracted with ether, the ethereal layer washed with a sodium carbonate solution and with water, dried and taken down yielding 14·7 g (97%) of the oxime, m.p. $51-63°C$. This was pulverised, mixed with a solution of sodium hydroxide (4·5 g) in water (120 ml), and benzenesulfonyl chloride (21·1 g) was added dropwise at 0°C under stirring during 1 h. The mixture was stirred at room temperature for 2 h, then another portion of sodium hydroxide (3·2 g) in water (30 ml) was added and the stirring was continued overnight. The solution was extracted several times with dichloromethane, the organic layer washed with water, dried and taken down, leaving 13·2 g of a mixture which, according to gas-liquid chromatography, consisted of $(\pm)$-I and $(\pm)$-II in the ratio 3 : 2. One crystallisation from ligroin (b.p. 100°C) and four from ethyl acetate afforded pure $(\pm)$-I (1·0 g), m.p. 137 to 138°C (ref.[14,15] reports m.p. 134—136°C). For C$_9$H$_{17}$NO (155·2) calculated: 69·63% C, 11·04% H, 9·02% N; found: 69·67% C, 10·91% H, 8·92% N. Any attempts to get further material from the mother liquors by crystallisation resulted in obtaining 1 : 1 mixture of $(\pm)$-I and $(\pm)$-II. The mother liquors were taken down and a part (0·8 g) of the residue was chromatographed on a silica gel column (300 g; ether-methanol 10 : 1). The lactam $(\pm)$-II was eluted first and was purified by crystallisation from water, m.p. 139—140°C; yield 102·1 mg. For C$_9$H$_{17}$NO (155·2) calculated: 69·63% C, 11·04% H, 9·02% N; found: 70·03% C, 11·01% H, 9·02% N. When mixed together, the lactams $(\pm)$-I and $(\pm)$-II melted at 90—105°C.

$(3S)$-3-Tert-butylhexanedioic Acid $((+)$-III$)$

Racemic 3-tert-butylhexanedioic acid (35·6 g; 0·176 mol) and brucine (162 g; 0·348 mol) were dissolved in boiling water (5·6 l), filtered while hot and allowed to cool. The salt was filtered and crystallised from water, yield 52·3 g. According to elemental analysis, the salt is a tetra-

hydrate. For $C_{56}H_{78}N_4O_{16}$ (1 063·2) calculated: 63·26% C, 7·39% H, 5·27% N; found: 63·26% C, 7·11% H, 5·45% N. The salt was decomposed with dilute hydrochloric acid and the product extracted continuously with ether. The extract was taken down, the crude residue dissolved in aqueous sodium hydroxide, extracted with ether, and the aqueous layer was acidified and continuously extracted with ether. This procedure afforded 9·9 g of (+)-*III* as a glass which could not be brought to crystallisation, $[\alpha]_D^{20}$ +17·2° (c 1, acetone). For $C_{10}H_{18}O_4$ (202·3) calculated: 59·39% C, 8·97% H; found: 59·67% C, 8·95% H.

(3S)-3-Tert-butylcyclopentanone ((−)-*IV*)

A. A mixture of (+)-*III* (9·8 g) and barium hydroxide (1·0 g) was heated in a Claisen flask with a free flame till the distillation of the product ceased. The distillate was diluted with ether, washed with sodium hydrogen carbonate solution, dried, taken down and distilled at 87°C/14 Torr, yield 4·1 g (60%), $[\alpha]_D^{25}$ −161·9° (c 0·86, methanol). ORD curve (methanol): $[M]_{272}$ +6200, $[M]_{294}$ 0, $[M]_{309}$ −6200, $[M]_{400}$ −750. These ORD data agree well with those published previously[16,17].

B. (5S)-*cis*-5-Tcrt-butyl-*trans*-2-hydroxycyclohexanecarboxylic acid[11] ((+)-*VI*), $[\alpha]^{20}$ +22·7° (c 6·0, ethanol), was transformed *via* the hydrazide, m.p. 194—194·5°C (ethanol), into (4S)-*trans*--4-tert-butyl-*trans*-2-aminocyclohexanol ((+)-*VII*), m.p. 104—105°C (ligroin), $[\alpha]_D^{20}$ +17·6° (c 1·0, ethanol), as described for the racemic compound[18]. The amino alcohol (+)-*VII* (0·5 g) was added to a stirred solution of sodium periodate (3·0 g) in 70% acetone (50 ml). Precipitation of sodium iodate commenced immediately. After 2 min ruthenium trichloride solution (2 mg in 0·1 ml) was added, the mixture was stirred for 4 h and left overnight. The salts were filtered off, washed with acetone and the filtrate was evaporated. The residue was extracted with ether, and the ethereal solution was extracted with sodium hydroxide solution. The aqueous layer was acidified with hydrochloric acid, the separated product was taken up in ether, the extract dried and taken down. The remaining thick oil (0·3 g) was heated in a Hickmann flask with barium hydroxide (50 mg) until distillation ceased. The distillate was dissolved in ether, washed with sodium hydrogen carbonate solution, dried and taken down. The product was distilled at 100°C (bath)/10 Torr, yield 84 mg. It was pure according to gas-liquid chromatography and its ORD curve and IR spectrum were identical with those of (−)-*IV* prepared by the method *A*.

(4S)-4-Tert-butyl-1-aza-2-cyclohexanone ((−)-*I*) and (5S)-5-tert-butyl-1-aza-2-cyclohexanone ((−)-*II*)

The ketone (−)-*IV* (3·7 g) was converted into its oxime, m.p. 60—63°C (3·9 g) and this (3·5 g) was transformed into a 3 : 2 mixture of (−)-*I* and (−)-*II* (3·4 g; 91%). Both steps were carried out as described for the racemic material. Three crystallisations from ethyl acetate afforded only 45·2 mg of (−)-*I*, m.p. 142°C, $[\alpha]_D^{25}$ −81·6°C (c 0·17, methanol). For $C_9H_{17}NO$ (155·2) calculated: 69·63% C, 11·04% H, 9·02% N; found: 69·74% C, 11·02% H, 9·15% N. The mother liquors were taken down and a portion (0·8 g) was chromatographed (300 g of silica gel, ether--methanol 10 : 1). First fractions afforded (−)-*II* (53·8 mg) m.p. 138·5—139°C (water), $[\alpha]_D^{25}$ −63·5° (c 0·17, methanol). For $C_9H_{17}NO$ (155·2) calculated: 69·63% C, 11·04% H, 9·02% N; found: 69·87% C, 10·99% H, 9·27% N.

Correlation of (−)-*IV* with (3S)-3-Tert-butylcyclohexanone ((−)-*XIV*)

The ketone (−)-*IV* (2·1 g) was added to a cold mixture of liquid hydrogen cyanide (3 ml), ethanol (3 ml) and 2 drops of concentrated aqueous potassium hydroxide. After 5 hours' standing the

mixture was acidified with saturated aqueous solution of oxalic acid and the excess hydrogen cyanide was distilled off under diminished pressure. The residue was diluted with water and the product was taken up in ether. The ethereal layer was washed with water, dried and taken down, leaving crude *XII* (2·5 g; 100%). IR spectrum (CHCl$_3$), cm^{-1}: 2240 (CN), 3435, 3585 (OH). The cyanohydrin *XII* (2·5 g) was hydrogenated over Adams catalyst (0·4 g) in acetic acid (50 ml) containing dilute hydrochloric acid (1 : 5, 1 ml); hydrogen consumption 950 ml. The catalyst was filtered off and the filtrate was diluted with water. The solution was taken to dryness *in vacuo* and the residue diluted with water. Non-basic material was removed by extraction with ether and the product was liberated from the aqueous layer by addition of sodium hydroxide solution, taken up into ether and distilled. After a small fraction boiling at 50°C/0·1 Torr (0·5 g, presumably a product of hydrogenolysis), the fraction boiling at 80—81°C/0·1 Torr was collected. Re-distillation gave 1·2 g (47%) of the stereoisomeric mixture *XIII* which partly crystallised. IR spectrum (CHCl$_3$), cm^{-1}: 1592, 3420 (NH$_2$), 3600 (OH). The amino alcohols *XIII* (0·9 g) were dissolved in 30% acetic acid (10 ml) and sodium nitrite (1·0 g) in water (10 ml) was added rapidly at 0°C under stirring. The mixture was stirred for 5 min, neutralised with solid sodium hydrogen carbonate and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and water and shaken with a solution of sodium bisulphite (6·0 g) in water (10 ml) for 4 h. The precipitated bisulphite compounds were filtered and washed with a large amount of ether. The ketones were recovered from these compounds by shaking with sodium carbonate solution, extraction with pentane and distillation at 90°C (bath)/10 Torr. The product (0·4 g; 50%) consisted of (−)-*XIV* and *XV* in the ratio 52 : 48 (gas-liquid chromatography); its IR spectrum did not show the presence of any other compounds than the two ketones mentioned. ORD (c 0·134, methanol): $[\phi]_{400}$ −90°, $[\phi]_{305}$ −1110°, $[\phi]_{266}$ −1560. For our sample the molecular rotations of both the extrema (corrected for 52% of (−)-*XIV* in the sample) are higher by a factor of about 1·4 than the values given by Djerassi and coworkers[10] (−2130° and +3000° as compared with −1550° and +2160°).

4-Tert-butyl-1-aza-cyclohexane-2,6-dione (*X*)

3-Tert-butylpentanedioic acid (*XI*) (17·2 g), prepared according to ref.[19], was dissolved in conc. aqueous ammonia (25 ml) and the solution was taken to dryness. The residue was heated to 250 to 260°C for 2 h with simultaneous introduction of dry ammonia into the melt. The mixture was distilled at 180—185°C/14 Torr, yielding 13·9 g (90%) of *X*, m.p. 178—179°C (ethyl acetate). For C$_9$H$_{15}$NO$_2$ (169·2) calculated: 63·88% C, 8·94% H, 8·28% N; found: 63·67% C, 8·82% H, 8·34% N.

4-Tert-butylpiperidine (*IX*)

A. The compound *X* (801 mg) was added portionwise to a solution of lithium aluminium hydride in ether (15 ml; 32 mg/ml) and the mixture was refluxed under stirring for 6 h. The work-up procedure afforded 491 mg (73%) of *IX*, b.p. 91°C/40 Torr. ^{1}H-NMR spectrum (deuteriochloroform), δ, ppm: 0·87 s, 9 H (tert-butyl), 2·54 m, 4 H (axial), 3·14 m, 4 H (equatorial). The product rapidly turned to a carbonate, m.p. 76—86°C, when exposed to the air (ref.[20] reports b.p. 70 to 75°C/17 Torr, m.p. of the carbonate 97—100°C). Picrate (precipitated in ether) m.p. 206·5 to 208°C (water). For C$_{15}$H$_{22}$N$_4$O$_7$ (370·4) calculated: 48·64% C, 5·99% H, 15·13% N; found: 48·67% C, 6·01% H, 15·00% N.

B. Reduction of *I* (400·3 mg) with ethereal lithium aluminium hydride (5 ml; 32 mg/ml) afforded 175·6 mg (48%) of *IX*. Its ^{1}H-NMR spectrum was identical with that of the compound

prepared by the procedure *A* and its picrate, m.p. 206·5—208°C, gave no melting point depression on admixture with the authentic sample.

RESULTS

The UV absorption spectra of the lactams $(-)$-*I* and $(-)$-*II* are almost identical. They exhibit only one maximum (λ_{max} 194 nm, ε_{max} 5500 (cyclohexane) or 7700 (water), $1 \text{ mol}^{-1} \text{ cm}^{-1}$) in the region of the $\pi-\pi^*$ transition of the amide group. The $n-\pi^*$ transition is not detectable. The CD curves of both lactams are complex and show large number of bands (Fig. 1—4). The intensity of the long-wavelength Cotton effects is relatively low (in the region above 200 nm, $[\theta]$ 5 . 10^3). Since in the corresponding regions the CD spectra of the lactams $(-)$-*I* and $(-)$-*II* exhibit bands mostly of different intensity but of the same sign we shall analyse the chiroptical properties of both lactams together. The observed CD bands can be classified in three classes (A, B and C) according to their manifestation in certain solvents and according to their sensitivity to concentration and temperature changes.

The class A involves such CD bands which are strongest in less polar solvents or which occur exclusively in these solvents (Fig. 1). These dichroic bands depend significantly neither on concentration nor on temperature (Fig. 2). First of all, this class involves the negative Cotton effect in the $n-\pi^*$ transition region, with the apparent maximum (in cyclohexane) at 230 and 235 nm for the lactam $(-)$-*I* and
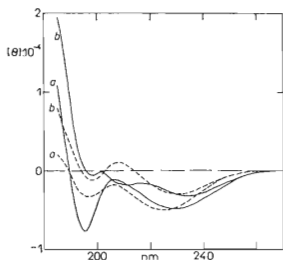

Fig. 1

CD Spectra of Lactams $(-)$-*I* (*a*) and $(-)$-*II* (*b*) Measured in Cyclohexane (———) and in Acetonitrile (— — —)
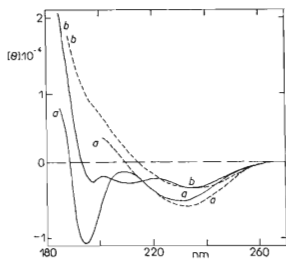

Fig. 2

CD Spectra of Lactams $(-)$-*I* (*a*) and $(-)$-*II* (*b*) in Cyclohexane at Various Concentrations and Temperatures
——— $t = 14°C$, $c = 1·7$. 10^{-3} mol 1^{-1};
— — — $t = 70°C$, $c = 1·7$. 10^{-4} mol 1^{-1}.

(−)-*II*, respectively. This Cotton effect exhibits in polar solvents the known hypso-chromic shift accompanied by a marked intensity decrease (Figs 3 and 4). In cyclo-hexane, (−)-*I* exhibits a somewhat stronger band than (−)-*II*. In this solvent and within the range of concentrations and temperatures employed this band for both (−)-*I* and (−)-*II* has almost constant parameters. Only at low temperature (∼ −100°C) in isopentane a decrease in intensity was observed. The second band is due to a positive Cotton effect of the $\pi−\pi^*$ transition in the short-wavelength region, the maximum of which lies outside the range accessible to measurement. This band can be observed only in cyclohexane and probably, as a weaker band, also in acetonitrile (Fig. 1) and its intensity does not seem to depend significantly on con-centration and temperature (Fig. 2).

The class B involves dichroic bands which occur in polar solvents (Figs 3 and 4). The positive Cotton effect in the region of $n−\pi^*$ transition belongs to this class; for the lactam (−)-*II* the position of its apparent maximum varies between 208 to 215 nm. In the CD spectra of the lactam (−)-*I* this band is not directly observable. Its presence is indicated only by a negative minimum in acetonitrile and methanol; in more polar solvents it manifests itself as a shoulder at about 210 nm (Fig. 3). To this class belongs also the negative Cotton effect with maximum at about 191 to 195 nm which obviously corresponds to the $\pi−\pi^*$ transition. The intensity of this band increases regularly with the increasing polarity of the solvent, except the case of aqueous solution of the lactam (−)-*I*. According to measurements performed in tenfold diluted solutions, the bands of the class B are not concentration dependent.

Fig. 3

CD Spectra of Lactam (−)-*I* Measured in 1,1,1,3,3,3-Hexafluoro-2-propanol (———), 2,2,2-Trifluoroethanol (− − −), Water (−·−·−) and Methanol (··········)

Fig. 4
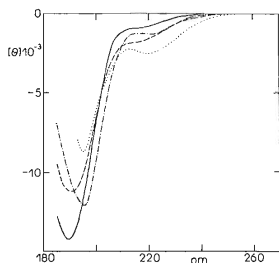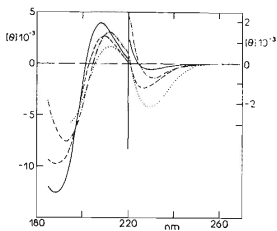
CD Spectra of Lactam (−)-*II* Measured in 1,1,1,3,3,3-Hexafluoro-2-propanol (———), 2,2,2-Trifluoroethanol (− − −), Water (−·−·−) and Methanol (··········)

The CD bands belonging to the class C depend significantly on concentration and temperature. They are found in the middle region of the spectra of both lactams in cyclohexane. In this region $(-)$-I exhibits two extrema (Figs 1 and 2); positive at 205 nm and strong negative at 195 nm (concentration $1 \cdot 7 \cdot 10^{-3}$ mol l^{-1} at room

TABLE I

Parameters of the Gaussian Bands in the CD Spectra of Lactam $(-)$-I

λ Wavelength of the band maximum (nm), $[\Theta]$ molecular ellipticity (deg cm^2 mol^{-1}), Δ band half-width (nm), R rotatory strength (c g s).

Solvent	λ	$[\Theta] \cdot 10^{-3}$	Δ	$R \cdot 10^{40}$	Classification[a]
		1st band			
Cyclohexane	228·2	$-$ 5·07	19·7	$-$ 5·4	A
Acetonitrile	225·3	$-$ 5·00	17·9	$-$ 4·9	A
Methanol	218·2	$-$ 2·81	16·8	$-$ 2·7	A
Water	219·4	$-$ 1·75	11·6	$-$ 1·1	A
TFE[b]	215·8	$-$ 1·94	15·1	$-$ 1·7	A
HFP[b]	215·3	$-$ 1·52	10·6	$-$ 0·9	A
		2nd band			
Cyclohexane	211·5	0·67	14·3	0·6	C
Acetonitrile	203·7	0·88	6·5	0·4	B
Methanol	215·2	0·40	9·2	0·2	B
Water	206·3	1·36	14·4	1·2	B
TFE[b]	202·7	1·15	14·1	1·0	B
HFP[b]	210·3	1·05	10·9	0·7	B
		3rd band			
Cyclohexane	194·1	$-$ 8·88	6·9	$-$ 3·9	C
Acetonitrile	196·7	$-$ 3·46	8·2	$-$ 1·8	B
Methanol	193·8	$-$ 8·17	9·9	$-$ 5·1	B
Water	194·5	$-$12·70	11·9	$-$ 9·6	B
TFE[b]	190·7	$-$11·73	12·8	$-$ 9·7	B
HFP[b]	189·4	$-$14·27	12·4	$-$11·5	B
		4th band			
Cyclohexane	177·8	19·94	10·4	14·4	A
Acetonitrile	177·6	4·46	10·5	3·3	A

[a] For classification of the bands see text; [b] TFE 2,2,2-trifluoroethanol, HFP 1,1,1,3,3,3-hexa-fluoro-2-propanol.

or slightly lower temperature). The CD curve of the lactam $(-)$-II in this region is complicated and, moreover, its recording suffered from an unfavourable signal to noise ratio. Four extrema can be found: positive at 220 and 203 nm and negative at 210 and 198 nm (Fig. 1). On tenfold dilution or heating the samples of both the lactams to 70°C, the bands of the class C disappear and manifest themselves only as a shoulder at about 200 nm (Fig. 2). Similar effects were observed also in the case of (S)-5-methyl-1-aza-2-cyclopentanone[21].

In addition to the experimental CD curves we report also parameters of the individual dichroic bands obtained upon fitting the sum of Gaussian bands to the experimental curves. The results thus obtained give experimental values of optical rotatory strength and are summarised in Tables I and II. Using these values we can gain some complemental information. The hypsochromic shift of the negative Cotton effect due to the $n-\pi^*$ transition (belonging to the class A) increases regularly with increasing polarity of the medium. The only exception is the spectrum of an aqueous solution of $(-)$-I, for which this band displays a smaller hypsochromic shift than in methanol (Table I). An analogous hypsochromic shift, accompanied by an increase of the rotatory strength in polar solvents, is exhibited also by the negative dichroic band of the $\pi-\pi^*$ transition belonging to the class B. However, a comparison of the positive Cotton effects due to the $n-\pi^*$ transition (class B) for both the studied lactams shows that whereas in the case of the lactam $(-)$-II the intensity and rotatory strength of this band exhibit a relatively regular increase with increasing polarity of the solvent, the band of the lactam $(-)$-I shows smaller and non-systematic changes. The parameters of this band in the spectra of $(-)$-I are not very accurate. Nevertheless, if this band is neglected, the agreement between the theoretical curve and the experimental spectrum becomes worse. Concerning the bands of the class C, it is interesting that the complex course of this part of the CD spectrum of the lactam $(-)$-II can be approximated by two Gaussian bands, similarly as in the case of $(-)$-I. Resolution of the CD curves into Gaussian bands is a difficult problem because the overlapping bands, often with opposite signs, exhibit a strong internal correlation of parameters[22]. This behaviour results in multiplicity of results which must be almost always taken only as possible alternatives.

Complications occur in the case of the lactam $(-)$-II measured in 1,1,1,3,3,3-hexafluoro-2-propanol for which we were not able to obtain satisfactory parameters of the long-wavelength negative band although it can be clearly discerned on the experimental CD curve, cf. Fig. 4. Similar complications arise also in the interpretation of the middle part of the CD spectra of $(-)$-I in polar solvents. However, the resulting set of data shown in Tables I and II is relatively consistent and since our interpretation requires no high accuracy we can consider the calculated data as satisfactory.

TABLE II

Parameters of the Gaussian Bands in the CD Spectra of Lactam (−)-*II*

Solvent[a]	λ	$[\Theta] \cdot 10^{-3}$	Δ	$R \cdot 10^{40}$	Classification
		1st band			
Cyclohexane	234·4	− 3·13	16·4	− 2·7	A
Acetonitrile	227·2	− 3·39	17·8	− 3·3	A
Methanol	226·7	− 0·94	13·5	− 0·7	A
Water	221·0	− 1·28	9·2	− 0·7	A
TFE	214·3	− 2·79	14·1	− 1·5	A
HFP	b	b	b	b	A
		2nd band			
Cyclohexane	210·1	− 1·39	7·2	− 0·6	C
Acetonitrile	210·2	2·07	13·5	1·6	B
Methanol	211·6	2·09	9·2	1·1	B
Water	212·5	3·71	10·7	2·3	B
TFE	207·1	6·15	11·5	4·2	B
HFP	204·7	8·78	10·0	5·3	B
		3rd band			
Cyclohexane	194·7	− 1·47	4·2	− 0·4	C
Acetonitrile	198·2	− 2·04	5·6	− 0·7	B
Methanol	193·6	− 5·98	10·2	− 3·9	B
Water	193·4	− 7·77	10·3	− 5·1	B
TFE	190·4	−10·65	13·9	− 9·6	B
HFP	190·7	−13·72	15·4	−13·6	B
		4th band			
Cyclohexane	183·2	20·43	7·3	10·0	A
Acetonitrile	180·9	10·02	8·3	5·7	A

[a] For description of symbols see notes in Table I; [b] we did not succeed in obtaining parameters of this band.

DISCUSSION

We may state that each of the classes A and B involves a pair of CD bands the parameters of which respond similarly to variations in the experimental conditions. In both pairs one of the bands can be assigned to the $n-\pi^*$ transition and the other to the $\pi-\pi^*$ transition. We can thus assume that the dichroic bands of particular

classes represent chiroptical manifestation of molecular species differing in conformation, solvation or molecular aggregation. The bands of the class A manifest themselves expressively in non-polar solvents and under conditions suppressing intermolecular aggregation (low concentration, high temperature). On the basis of this fact we assume that the negative Cotton effect at the longest wavelength and the strong positive Cotton effect in the short-wavelength part of the CD spectra of both the lactams approximate the chiroptical properties of isolated molecules in energetically most stable conformation. According to molecular models and analysis of the IR spectra[7] it seems that in both cases this conformation is a half-chair form with an equatorial tert-butyl group which has been also detected by X-ray structure analysis[6] of (−)-I in the crystalline state. Application of the "ring chirality rule"[23,24] or the sector rules derived for an amide chromophore[25,26] to this conformation leads to prediction of a negative Cotton effect of the $n−\pi^*$ transition for both the lactams. This is in accord with the experiment. We cannot exclude even a possible non-planarity of the amide group because, particularly for the lactam (−)-II, the $n−\pi^*$ transition exhibits a distinct bathochromic shift as compared with the situation usually found for amides and small peptides (Table I, cf. ref.[1]). The pair of bands of the class B represents chiroptical properties of the lactams (−)-I and (−)-II under conditions of solvation with a polar solvent. It would be difficult to interpret the observed bands assuming that the interaction with a solvent molecule can change the sign of the CD band without changing significantly the molecular geometry. This possibility seems unlikely also in view of the fact that the negative Cotton effect of the $n−\pi^*$ transition, ascribed to the half-chair conformation, exists also in polar solvents, even though it exhibits a hypsochromic shift and lower intensity (Figs 3 and 4; Tables I and II). A more probable alternative is that interactions with solvent molecules shift the conformational equilibrium towards the boat forms. Application of sector rules[25,26] to boat conformations with pseudoequatorial tert-butyl group predicts a negative CD band due to $n−\pi^*$ transition in the lactam (−)-I and an analogous positive band in the case of (−)-II. This prediction agrees with the experimental data only for the lactam (−)-II. Decomposition of the spectrum of (−)-I into Gaussian bands (Table I) reveals in this region a positive band of considerably uncertain parameters with extremely large half-width which does not seem to be real. Here, obviously, several CD bands compensate each other and we cannot exclude even a boat form with a pseudoaxial tert-butyl group which, according to the sector rule[25,26], should exhibit a positive Cotton effect. Since the bands belonging to class C are observed in non-polar solvents and their parameters are sensitive to concentration and temperature we can ascribe them to non-solvated self-associated lactam molecules of the type of cyclic dimers. The existence of this kind of aggregates in tetrachloromethane and tetrachloroethylene was proved by IR spectroscopy[7]. Detailed interpretation in terms of structure is hitherto not possible.

Hence, we can conclude that isolated molecules of the lactams (−)-*I* and (−)-*II* exist in energetically advantageous half-chair conformations with the tert-butyl substituent in the equatorial position. This form is characterised by a negative Cotton effect of the $n-\pi^*$ transition and a positive effect of the $\pi-\pi^*$ transition (bands of the class A). Both the compounds form associates with polar solvents which give rise to a hypsochromic shift of the $n-\pi^*$ band. It seems that the solvation, particularly with molecules of hydroxylic solvents, can to various extent be accompanied by the transition of the half-chair conformer into a boat conformer, characterised by a positive and negative Cotton effect of the $n-\pi^*$ and $\pi-\pi^*$ transition, respectively. The extent of this conformational change would be substantially greater for the compound (−)-*II* than for the compound (−) *I*.

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