OPTICALLY ACTIVE TRICYCLIC DILACTAMS WITH NON-PLANAR *cis*-AMIDE GROUPS: SYNTHESIS, X-RAY, NMR AND CD STUDIES

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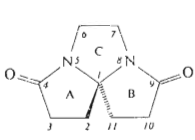
Three tricyclic dilactams were investigated as models for study of chiroptical properties of homoconjugated non-planar *cis*-amide groups. Racemic 5,8-diazatricyclo[6,3,0,$0^{1,5}$]undecane-4,9--dione (*I*) was partially resolved into enantiomers by chromatography on acetylcellulose. The 6-isobutyl (*II*) and 6-methyl (*III*) derivatives were prepared in optically pure forms by condensation of diethyl 4-oxoheptanedioate with (*S*)-1,2-diamino-4-methylpentane and (*S*)-1,2-diaminopropane, respectively. The respective diamines were synthesized starting from (*S*)-leucine and (*S*)-alanine: this determined the absolute configuration on the C(6) atom in both dilactams. As shown by ^{1}H and ^{13}C NMR spectra, the condensation reaction afforded only one of the two possible diastereoisomeric dilactams. The configurational relation between the chiral center at C(6) and the chirality of the tricyclic moiety was derived from coupling constants in the ^{1}H NMR spectra. The configuration of compound *II* was confirmed by X-ray diffraction. According to ^{1}H NMR spectra, the spatial arrangement of *II* in solution is similar to that in crystal, the only difference being in the local conformation of the isobutyl side chain at C(6). IR spectroscopy identified only minor differences in geometry of the two lactam groupings in *II* and *III*. All CD parameters of compounds *I*–*III*, measured in various solvents, are very similar. The CD curves show the same absolute configuration (1*S*, 6*S*) of compounds *II* and *III* and the opposite configuration of the studied enantiomer of *I* (1*R*). Parameters of the n-π^* dichroic band indicate a non--planar amide grouping whose geometry is known from the X-ray analysis. Its sign agrees with the relationship derived for the chiroptical properties of defined pyramidicity on nitrogen atom in non-planar amides. The π-π^* dichroic bands exhibit an exciton splitting into a couplet as a result of interaction between the amide groups.

Non-planar arrangement of amide (peptide) groups seems to be quite common in peptides, at least in the crystalline state[1]. It is, however, probable that also in solutions we can encounter non-planar amide groupings. The inherently chiral arrangement which is a consequence of such non-planarity may not affect very much the chemical or physical properties of compound under isotropic conditions, however, it can be

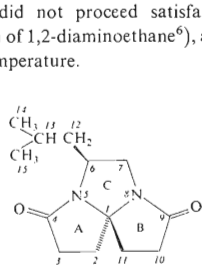
very important in situations when the amide interacts with another chiral factor, such as circularly polarized electromagnetic radiation or an enzyme. In our previous studies[2] we suggested for a rational investigation of non-planar amide bonds to use model compounds in which the non-planarity is forced (and fixed) by a rigid polycyclic structure. Up to now, our studies concerned only compounds containing one amide group (ref.[3,4]); in relation with peptides, however, structures with homoconjugated amide groups are important, in which interamide electronic interactions can operate.

In this communication we investigated dilactams *I*–*III*, containing fixed arrangement of two *cis*-amide groups, *i.e.* 5,8-diazatricyclo[6,3,0,$0^{1,5}$]undecane-4,9-dione (*I*) and its 6-isobutyl (*II*) and 6-methyl (*III*) derivatives.* The dilactam *I* has already been studied in its racemic form using IR spectroscopy[6] and X-ray diffraction[7]. The optically active compounds served now for study of the effect of non-planarity on the chiroptical properties.

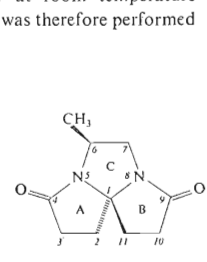
The dilactam *I* was prepared according to the procedure described previously[6] and its partial optical resolution was achieved by chromatography on acetylcellulose, affording both enantiomers in optically impure form. Absolute configuration of the optically purer enantiomer was determined by comparison of its CD curves with those of optically active dilactams *II* and *III*, prepared from optically active precursors of known absolute configuration.Compounds *II* and *III* were synthesized starting from (*S*)-1,2-diamino-4-methylpentane and (*S*)-1,2-diaminopropane which in turn were prepared by reduction of L-leucinamide (with diborane) and of L-alaninamide (with lithium aluminium hydride), respectively. Condensation of these diamines with diethyl 4-oxoheptanedioate did not proceed satisfactorily at room temperature (unlike the analogous reaction of 1,2-diaminoethane[6]), and it was therefore performed with good result at higher temperature.



I (1*R*)



II (1*S*, 6*S*)



III (1*S*, 6*S*)

The synthesized compounds *I*–*III* were investigated by X-ray diffraction, ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and circular dichroism with the aim to determine their conformation in detail.

* For a preliminary communication see ref.[5].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra were taken on Perkin Elmer spectrometers, models 621 and 580, calibrated by water vapour; concentration in tetrachloromethane 0·08 mol l^{-1}. CD spectra were measured on a Roussel Jouan Dichrograph CD 185/II instrument equipped with a cryostate, in cyclohexane, acetonitrile, methanol, water, 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol (0·05—0·5 cm cells, 24—26°C, concentrations $2 . 10^{-3}$ mol l^{-1}). Parameters of the individual Cotton effects were obtained by approximation of experimental curves by a sum of Gaussian bands, *cf.*[8]. The ^{1}H NMR spectra were taken in the FT-mode on a Bruker WH-360 instrument (at 360 MHz) in deuteriochloroform and hexadeuteriobenzene with tetramethylsilane as internal standard, ^{13}C NMR spectra were measured in the FT-mode on Bruker WP-200 and Varian XL-200 (at 50·29 MHz) spectrometers in deuteriochloroform (tetramethylsilane as internal standard) either as ^{1}H-noise decoupled or as off-resonance decoupled spectra.

(+)-(*S*)-1,2-Diaminopropane

(*S*)-(−)-Alaninamide (4·0 g) was added to a slurry of lithium aluminium hydride (4·5 g) in tetrahydrofuran (70 ml). The stirred mixture was refluxed for 8 h, diluted with tetrahydrofuran (100 ml), decomposed with water (30 ml) under cooling and filtered. The solid was washed with five portions of boiling methanol, the washings were combined with the filtrate, acidified with concentrated hydrochloric acid and taken to dryness *in vacuo*. The residue was mixed with a large excess of powdered sodium hydroxide and the mixture distilled *in vacuo* (1·3 kPa) into a receiver cooled with dry ice. The distillate was dried with small pieces of metallic sodium, the formed sodium hydroxide solution being removed. The product was distilled at atmospheric pressure, dried again with sodium and distilled, yielding 1·2 g (36%) of the diamine, b.p. 114—120°C. α_D^{20} +25·3° (neat); taking the reported[9] value $d_4^{20} = 0{\cdot}8588$, then $[\alpha]_D^{20}$ +29·5° (neat), (reported[9] $[\alpha]_D^{20}$ +29·7°).

(*S*)-1,2-Diamino-4-methylpentane

A 0·82M solution (35 ml) of diborane in tetrahydrofuran was added to a solution of L-leucinamide (1 g) in tetrahydrofuran (30 ml). The mixture was set aside at room temperature overnight under nitrogen, decomposed with methanol, taken down *in vacuo* (2 kPa; bath temperature 50°C), acidified with dilute hydrochloric acid to pH 4—5, made alkaline with ammonia and the base was

TABLE I

Crystallographic data for compound *II*

Molecular formula	$C_{13}H_{20}N_2O_2$
Molecular weight	236·31 g mol^{-1}
Space group	$P2_12_12_1$; $Z = 4$
(cell dimensions at −135°C)	$a = 12{\cdot}892(8)$ Å
	$b = 16{\cdot}704(6)$ Å
	$c = 5{\cdot}911(2)$ Å
Volume	1 272·92 A^2

taken up in chloroform. Distillation gave 0·45 g (50%) of the diamine, b.p. 95—100°C/2 kPa. Dipicrate m.p. 226—228°C (ethanol). For $C_{18}H_{22}N_8O_{14}$ (574·2) calculated: 37·63% C, 3·86% H, 19·51% N; found: 37·86% C, 3·83% H, 19·51% N.

(1*S*,6*S*)-6-Isobutyl-5,8-diazatricyclo[6,3,0,$0^{1,5}$]undecane-4,9-dione (*II*)

A mixture of diethyl 4-oxoheptanedioate (0·40 g) and (*S*)-1,2-diamino-4-methylpentane (0·20 g) was heated in a sealed tube to 180—200°C for 3 h. The crude product was chromatographed on a silica gel column (120 g) in ether–methanol (10 : 1). Further purification by sublimation at 13 Pa and crystallization from diethyl ether (at −5°C) gave 126·5 mg (31%) of the pure compound, m.p. 92—94°C. Mass spectrum, *m/e*: 236 (M^+), 221 (M − 15), 193 (M − 43), 180 (M − 56), 123 (M − 57 − 28 − 28). For $C_{13}H_{20}N_2O_2$ calculated: M^+ 236·1525, found: 236·1519; calculated: 66·08% C, 8·53% H, 11·85% N; found: 66·24% C, 8.48% H, 11·69% N.

(1*S*,6*S*)-6-Methyl-5,8-diazatricyclo[6,3,0,$0^{1,5}$] undecane-4,9-dione (*III*)

A mixture of diethyl 4-oxoheptanedioate (0·62 g) and (*S*)-1,2-diaminopropane (0·20 g) was heated in a sealed tube to 180—190°C for 5 h and then chromatographed on a column of alumina (activity II; 30 g) in benzene with 5—10% of chloroform, taking 50 ml fractions. Fractions 3—13, containing the product (thin-layer chromatography on silica gel; acetone–chloroform–ethanol–25% aqueous ammonia (50 : 50 : 0·3 : 0·1), detection with iodine), were combined and taken down. The residue was crystallized from diethyl ether, yielding 0·19 g (36%) of the product, melting at 110—112°C. For $C_{10}H_{14}N_2O_2$ (194·3) calculated: 61·88% C, 7·26% H, 14·42% N; found: 61·54% C, 7·21% H, 14·38% N.

Partial Resolution of 5,8-Diazatricyclo[6,3,0,$0^{1,5}$]undecane-4,9-dione (*I*)

The racemic dilactam *I* (100·1 mg) in water (0·5 ml) was applied on a column of cellulose triacetate (40 g; 120 mesh) and eluted with water, taking 1·5 ml fractions. The first four product-containing fractions exhibited a negative CD band at 220 nm with θ values decreasing from −800 for the first fraction to almost zero for the fifth fraction. The material in fractions 8 and 9 had θ +360 and +900. respectively. The resolution of the racemic compound was repeated three times, using same amounts of the racemic compound (total 400 mg). From each chromatography several fractions with θ greater than −200 were taken and combined, affording 89·2 mg of material which was again chromatographed. The first two fractions were combined and evaporated. Sublimation of the residue afforded 2·5 mg of the (1*R*)-enantiomer which was used for the CD measurements.

X-Ray Diffraction Measurements

Single crystals of the compound *II* were obtained from diethyl ether. Initial examination of the crystal chosen for data collection revealed the space group to be $P2_12_12_1$ with four molecules in the unit cell. The least squares cell dimensions were determined from the average $+2\theta$ and -2θ values of 64 reflections distributed throughout reciprocal space. Crystallographic data (Table I) and integrated intensity data were measured at −145(2)°C using a Nonius CAD-4 automatic diffractometer. Intensity data were collected using CuK$\bar{\alpha}$ radiation (λ = 1·54178 Å), while the unit cell constants were calculated with the CuK$\bar{\alpha}_1$ wavelength of 1·54051 Å. There were 1 548 reflections with a 2θ value between 2° and 150° whose intensities were recorded with the $\theta - 2\theta$ scanning technique. A variable scan width was calculated for each reflection using the formula: (1·0 + 0·10 tan θ)°. The receiving aperture, located 173 mm from the crystal, had a variable width

calculated as a function of θ: $(4{\cdot}0 + 0{\cdot}8\delta \tan\theta)$ mm. The height of the aperture was fixed at 4·0 mm. The maximum time spent on any measurement was 90 s with 2/3 of the time used for scanning the peak and the remaining 1/3 being equally divided between the left and right backgrounds. The total time for each measurement was split into two equal scans, and if the results of these scans differed by more than three standard deviations, a maximum of two additional scans were made. Only 66 intensities were considered indistinguishable from the background on the basis that $I < 2\sigma(I)$. For further data analysis, these reflections were assigned the value of $T^{1/2}$ where $T = [\text{peak} + 2(\text{right background} + \text{left background})]$. An intensity monitor was recorded every 1 800 seconds of crystal exposure to radiation. No significant variation occurred during data collection. The crystal orientation was checked after every 100 measurements with three additional reflections. If any of the angles varied by more than 0·1° from its initial value, a new orientation matrix was automatically determined. Lorentz and polarization corrections were made, and individual structure factor amplitudes were derived. Each amplitude was assigned an experimental weight, W_F, based on counting statistics using a weighting scheme described previously[7].

Structure Determination and Refinement

The positions of all non-hydrogen atoms were obtained by direct methods. Of the 20 E-map peaks produced by the program MULTAN (ref.[10]), the 17 largest were shown to correspond to the non-hydrogen atoms, and of these 17, the 6 largest peaks proved to be the two oxygen atoms, the two nitrogen atoms and the two carbonyl carbons.

Atomic scattering factors for the C, N and O atoms were taken from the International Tables for X-ray Crystallography[11], while those for hydrogen from Stewart, Davidson, and Simpson[12]. After 5 cycles of block-diagonal least-squares refinement[13], at an R-value ($R = (\sum||Fo| - |Fo||)/\sum|Fo|$) of 0·088 for all reflections, the non-hydrogen atoms were converted from isotropic to anisotropic refinement. After 3 additional cycles (with $R = 0{\cdot}077$), a difference Fourier was calculated. This yielded the positions of all 20 hydrogen atoms. Anisotropic refinement of non-hydrogen atoms and isotropic refinement of hydrogen atoms was continued until all shifts were less than 0·5 of their standard deviation. The R-value based on final parameters* (Tables II and III) was 0·030.

RESULTS AND DISCUSSION

X-Ray Structure Determination

The structure of the compound *II* was determined as the fifth in a series of tricyclic dilactams[7,14,15]. A stereo view of *II* is shown in Fig. 1. The atomic numbering scheme and bond lengths are shown in Fig. 2, while the lettering of the ring system and valence bond angles are reported in Fig. 3. The torsion angles in the three 5-membered rings of *II* are listed in Table IV along with the theoretical values for cyclopentane[16,17]. It can be seen from the pseudo-rotation parameter Δ (ref.[18]) that the three rings are in a twist or C_2 conformation, with rings A and C being slightly flattened.

* Anisotropic thermal parameters and structure factors are available (D.v.d.H.).

In Table V the geometric parameters χ_N, χ_C, and τ' (ref.[19]) have been tabulated for the multi-cyclic dilactam series. This shows that in all compounds the bonds around the carbonyl carbon atom are planar ($\chi_C \approx 0$). Most of the deformation of the amide bond is centered in the non-planarity of the bonds around the nitrogen

TABLE II

Positional parameters ($\times 10^5$) for C, N and O atoms in compound *II*

Atom	*x*	*y*	*z*
C(1)	100 311(9)	98 155(9)	32 824(23)
C(2)	103 709(10)	106 943(7)	29 921(26)
C(3)	113 524(11)	107 471(8)	44 350(27)
C(4)	118 101(10)	99 091(8)	42 311(23)
O(4)	127 137(7)	97 125(5)	44 500(19)
N(5)	110 106(8)	93 958(6)	37 444(19)
C(6)	111 424(9)	86 905(7)	22 696(24)
C(7)	104 504(10)	89 152(8)	2 287(24)
N(8)	96 451(8)	94 140(7)	12 501(19)
C(9)	86 214(10)	92 083(8)	13 808(24)
O(9)	81 665(7)	87 766(6)	461(19)
C(10)	81 897(10)	96 148(8)	34 815(27)
C(11)	91 478(10)	96 935(8)	49 991(25)
C(12)	108 229(10)	79 107(7)	34 208(25)
C(13)	114 679(10)	76 970(7)	55 076(25)
C(14)	109 923(11)	69 838(9)	67 478(30)
C(15)	126 004(11)	75 289(9)	48 842(32)

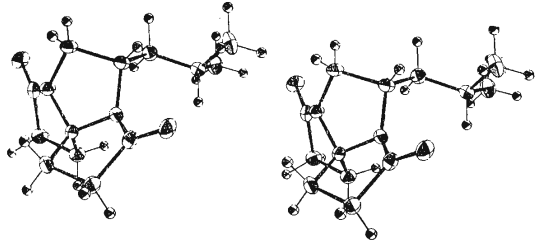


FIG. 1

Stereo view of dilactam *II* as determined by X-ray diffraction

TABLE III

Positional parameters ($\times 10^3$) and isotropic temperature factors for hydrogen atoms in compound *II*

Atom	X	Y	Z	B(Å^2)
H(C2)A	1 058(1)	1 075(1)	136(4)	2·9(4)
H(C2)B	981(1)	1 106	344(3)	1·8(3)
H(C3)A	1 187(1)	1 113(1)	385(3)	2·5(3)
H(C3)B	1 119(1)	1 082(1)	611(4)	3·8(4)
H(C6)	1 189(1)	866(1)	182(3)	1·4(3)
H(C7)A	1 088(1)	923(1)	−90(3)	1·8(3)
H(C7)B	1 012(1)	843(1)	−46(3)	3·0(4)
H(C10)A	789(1)	1 015(1)	305(4)	3·0(4)
H(C10)B	760(1)	931(1)	412(3)	2·9(4)
H(C11)A	909(1)	1 011(1)	608(4)	2·8(4)
H(C11)B	926(1)	921(1)	585(4)	3·2(4)
H(C12)A	1 089(1)	747(1)	219(3)	2·9(4)
H(C12)B	1 007(1)	796(1)	383(3)	2·2(3)
H(C13)	1 148(1)	817(1)	655(3)	2·1(3)
H(C14)A	1 140(1)	683(1)	800(4)	3·7(4)
H(C14)B	1 024(1)	711(1)	716(4)	3·7(4)
H(C14)C	1 100(1)	651(1)	581(3)	3·0(3)
H(C15)A	1 298(2)	736(1)	617(4)	4·1(5)
H(C15)B	1 294(1)	802(1)	418(4)	3·2(4)
H(C15)C	1 264(1)	709(1)	366(4)	3·4(4)

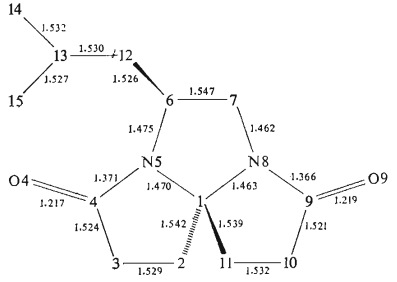


FIG. 2

Atomic numbering and bond lengths in dilactam *II*

atoms (χ_N) and a rotation around the C—N bond (τ'), while in general $|\chi_N| \approx 2\tau'$. Also, there is strong correlation between χ_N and a lengthening of the C—N bond

TABLE IV

Endocyclic conformational angles, pseudorotation parameters Δ and theoretical values for tricyclic dilactam *II* and for cyclopentane in C_2 and C_s conformations. Standard deviations are 0·1—0·2°

Ring A		Ring B	
C(4)—N(5)—C(1)—C(2)	+12·9	C(9)—N(8)—C(1)—C(11)	+11·1
N(5)—C(1)—C(2)—C(3)	−27·6	N(8)—C(1)—C(11)—C(10)	−27·1
C(1)—C(2)—C(3)—C(4)	+31·8	C(1)—C(11)—C(10)—C(9)	+32·8
C(2)—C(3)—C(4)—N(5)	−25·0	C(11)—C(10)—C(9)—N(8)	−27·2
C(3)—C(4)—N(5)—C(1)	+7·7	C(10)—C(9)—N(8)—C(1)	+10·2
$\|\Delta\|$	9·2	$\|\Delta\|$	0·8

Ring C		Cyclopentane	
		twist (C_2)	envelope (C_s)
N(5)—C(1)—N(8)—C(7)	−12·9	15·1	46·1
C(1)—N(8)—C(7)—C(6)	+27·5	−39·4	−28·6
N(8)—C(7)—C(6)—N(5)	−30·0	48·1	0·0
C(7)—C(6)—N(5)—C(1)	+24·2	−39·4	28·6
C(6)—N(5)—C(1)—N(8)	−8·2	15·1	−46·1
$\|\Delta\|$	9·4	0·0	36·0

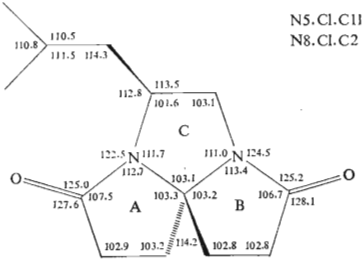


FIG. 3

Lettering of ring system and bond angles in dilactam *II*

from the 1·32 Å found in peptides and a weaker correlation with a simultaneous shortening of the C—O bond from the value of 1·24 Å reported for peptides[20]. The C—N bond lenghts in *II* are 20 standard deviations longer than 1·32 Å, while the C—O bonds are about 10 standard deviations shorter than 1·24 Å.

Analysis of intermolecular distances revealed only one short contact between C(4) and O(4) of 2·96 Å (transformed by $2\ 1/2 - x, 2 - y, 1/2 + z$).

The determination of the absolute configuration was undertaken using the Bijvoet method for the anomalous dispersion of the Cu radiation by all oxygen, nitrogen, and carbon atoms in the molecule. The general procedure for the selection of the proper Friedel pairs and subsequent measurements has been detailed by Ealick, van der Helm, and Weinheimer[21]. Briefly, this involved the repetitive measurement of the intensities for the *hkl*, $\bar{h}kl$, $h\bar{k}l$, and $\bar{h}\bar{k}l$ of each reflection shown to have a high sensitivity factor $[SF = \{F^{2\prime}(+) - F^2(-)\}/\delta(I)]$. The intensities of nine such reflections were measured 14 times at each position, then were averaged into 2 sets: (*hkl* ahd $\bar{h}\bar{k}l$) and ($\bar{h}kl$ and $h\bar{k}l$). The observed and calculated values for these parameters are summarized in Table VI. Seven of the nine reflections validate the absolute configuration reported in this publication, which is the one derived from L-leucine.

NMR *Spectroscopic Study of Spatial Arrangement in Dilactams* I–III

The ^1H as well as ^{13}C NMR spectra have shown unequivocally the diastereoisomeric purity of derivatives *II* and *III*. The presence of a second diastereoisomer has not

TABLE V

Geometrical parameters (ref.[19]) of amide groups in multi-cyclic dilactams. (*I* and *II*: values for the measured enantiomers are given; *IV*, *V* and *VI*: for arbitrary enantiomers)

Compound	χ_N (°)	χ_C (°)	τ' (°)	C—N, Å	C—O, Å
I[a]	−42·0	−0·3	21·3	1·362	1·223
II (ring A)[b]	42·1	0·0	−26·7	1·371	1·217
II (ring B)[b]	39·5	−0·3	−18·6	1·366	1·219
IV[c]	−43·7	−0·2	20·5	1·372	1·222
V[c]	−19·1	−0·6	7·3	1·351	1·220
VI (5'membered ring)[d]	−41·2	0·0	20·8	1·361	1·216
VI (6'membered ring)[d]	−16·7	0·9	17·8	1·339	1·239

[a] Ref.[7]. [b] This paper; for ring A ω_1 is the torsion angle C(3)—C(4)—N(5)—C(6), ω_2 O(4)—C(4)—N(5)—C(1), ω_3 O(4)—C(4)—N(5)—C(6); for ring B ω_1 C(10)—C(9)—N(8)—C(7), ω_2 O(9)—C(9)—N(8)—C(1), ω_3 O(9)—C(9)—N(8)—C(7). [c] Ref.[14]. [d] Ref.[15], values for 5-membered and 6-membered rings are given.

been detected even at extreme amplification and high signal-noise ratio. The relative configuration of dilactams *II* and *III* follows from the ^{1}H NMR spectral analysis of vicinal coupling constants in the three-proton fragment N—C(6)HR—C(7)H_2—N. Comparison of the $J_{6,7}$ values found for both *II* and *III* (about 6·0 Hz and 0·5 Hz), with the torsion angles, derived from Dreiding models for the tricyclic system (about 30° and 150° against about 30° and 90°) points unequivocally to the second alternative. In both cases diastereoisomer of the same type was formed (formulae *II* and *III*).

In the unsubstituted derivative *I*, the protons in the segment N—C(6)H_2—C(7). .H_2—N represent an AA'XX' system and give the corresponding spectrum. Its analysis afforded the pertinent parameters δ and J. The marked difference in the chemical shifts of the geminal N—CH_2-protons (δ = 4·05 and 2·88, respectively; in $CDCl_3$) is obviously due to the different orientation relative to the amide group. The N—CH protons in the vicinity of the amide group plane are less shielded than protons outside this plane. For compound *I* we can therefore expect the protons H-6A and H-7B to be in the downfield and protons H-6B and H-7A in the upfield part of the AA'XX' spectrum. Because of the C_2 symmetry of the molecule, the eight protons of the lactam rings form four pairs of symmetrically equivalent protons and form thus an AA'MM'PP'XX' system. Since the spin–spin decouplings between the protons of both rings are very small (^4J, ^5J, $^6J \ll 1$), they can be neglected and the spectrum may be analyzed as an AMPX system with double intensities. The multiplet in the lowest field (δ = 2·79 in $CDCl_3$) was ascribed to the H-3 and H-10 protons

TABLE VI

Comparison of observed and calculated Bijvoet differences

$$\mathrm{DEL} = \frac{2[F^2(+) - F^2(-)]}{F^2(+) + F^2(-)} \cdot 100$$

H	K	L	DEL		SF	
			Observed	Calculated	Observed	Calculated
5	1	2	−6·18	−14·05	−1·48	−0·66
1	17	2	3·42	7·92	1·51	0·52
2	12	2	6·08	8·56	1·75	0·50
4	11	2	5·35	−7·21	1·82	−0·49
10	12	3	−3·19	−6·92	−1·22	−0·46
4	8	2	0·44	−6·92	0·16	−0·49
4	4	3	5·90	4·82	2·48	0·48
7	1	2	3·89	4·37	3·49	0·47
4	11	1	−0·96	−4·26	−0·49	−0·41

vicinal to the carbonyl group on the basis of its chemical shift and the observed geminal interaction $^2J = 16$ Hz. The remaining protons at C(3), C(10), C(2) and C(11) were assigned to the corresponding signals by selective decoupling experiments. The configurational assignment of protons in four-proton fragments was done on the basis of the observed vicinal coupling constants so as they were in accord with the spatial arrangement determined by the tricyclic system, as found on models. The observed value $^3J = 0{\cdot}5$ Hz defines unequivocally the protons H-2B and H-3A. The spectral parameters of compound *I* in deuteriochloroform and in hexadeuteriobenzene are given in Tables VII and VIII.

The ^{1}H NMR spectra of compounds *II* and *III* have similar characteristic features. The presence of substituent destroys the symmetrical equivalence of the lactam rings as well as of the C-ring protons. Spectrum of the tricyclic system exhibits signals of eleven non-equivalent protons which can be completely assigned. The decoupling experiments proved essentially isolated spin systems of the three rings. The coupling constants in the three-proton fragment C(6)HR—C(7)H_2 are very similar to those for the unsubstituted derivative *I* showing that the three compounds have very similar spatial arrangement. The differences in the chemical shifts are due to the substitution. Signals of the two four-spin systems of the lactam rings A and B were assigned on the basis of the long-range interaction (1·0 Hz) between the proton H-7A and the proton, assigned the position H-10A. Thus, one is dealing with a ^5J coupling through the amide bond, analogous to a homoallylic ^5J coupling. Interactions of this type were observed between the C_α protons in a series of cyclic dipeptides[22-25]. Because the proton H-7A has no pseudosymmetrical counterpart at C(6) (the substituent being attached in the position 6B) no similar splitting is observed by the pseudo symmetrical counterpart of the proton H-10A, i.e. the H-3B proton. After assignment of H-10A and H-3B it was possible to assign the three remaining protons in both lactam rings on the basis of vicinal coupling constants.

The observed small but systematic differences in chemical shifts and coupling constants of protons in both lactam rings in the compounds *II* and *III* indicate a slightly different geometry of the rings. Also ^{13}C NMR spectra of *II* and *III* exhibit separated signals of carbon atoms in both lactam rings ($\Delta\delta < 0{\cdot}5$ ppm) whereas for the symmetrical derivative *I* the doublets disappear (Table IX). This is obviously caused by steric interaction between the substituent at C(6) and the proton H-11B or H-10B. This repulsive interaction would result in a slight planarization of the ring B (relative to A) or C (relative to C in *I*) with retention of bond angles and lengths, or (*ii*) deform the bond angles at C(11), C(10), C(10) or C(12) and lengths of the C(11)—H(11B) and C(10)—H(10B) bonds; a combination of both deformation types (*i*) and (*ii*) is also possible. For the analogous geminal and vicinal coupling constantss in the rings A and B, observed for the compounds *II* and *III* it was found that $^2J_{2A,2B} < {}^2J_{11A,11B}$, $^2J_{3A,3B} < {}^2J_{10A,10B}$, $^3J_{2A,3A} < {}^3J_{10B,11B}$, $^3J_{2A,3B} < {}^3J_{10A,11B}$, $^3J_{2B,3A} < {}^3J_{10B,11A}$, and $^3J_{2B,3B} < {}^3J_{10A,11A}$.

TABLE VII

Chemical shifts of protons in ^{1}H NMR spectra of compounds *I*, *II* and *III*

Compound	Solvent	H-2A	H-2B	H-3A	H-3B	H-6A	H-6B	H-7A	H-7B	H-10A	H-10B	H-11A	H-11B	H-12	H-13	H-14 H-15
I	$CDCl_3$	2·04	2·46	2·45	2·79	4·05	2·88	2·88	4·05	2·79	2·45	2·46	2·04	—	—	—
II	$CDCl_3$	2·02	2·38	2·41	2·75	4·29	—	3·04	3·81	2·82	2·52	2·48	2·03	1·16 1·23	1·63	0·91 1·01
III	$CDCl_3$	2·02	2·38	2·40	2·76	4·39	—	3·05	3·79	2·83	2·54	2·51	2·12	1·12	—	—
I	C_6D_6	1·17	1·39	1·88	2·01	3·60	2·09	2·09	3·60	2·01	1·88	1·39	1·17	—	—	—
II	C_6D_6	1·25	1·44	1·90	2·07	4·02	—	2·42	3·59	2·14	1·99	1·50	1·44	0·81 1·03	1·55	0·79 1·00
III	C_6D_6	1·21	1·38	1·87	2·03	4·05	—	2·35	3·49	2·11	1·98	1·49	1·39	0·69	—	—
								ASIS-values[a]								
I		−0·87	−1·07	−0·57	−0·78	−0·45	−0·79	−0·79	−0·45	−0·78	−0·57	−1·07	−0·87	—	—	—
II		−0·77	−0·94	−0·51	−0·68	−0·27	—	−0·64	−0·22	−0·68	−0·53	−0·98	−0·59	−0·35 −0·20	−0·08	−0·12 −0·01
III		−0·81	−1·00	−0·53	−0·73	−0·34	—	−0·70	−0·30	−0·72	−0·56	−1·02	−0·73	−0·43	—	—

[a] Defined as difference between chemical shifts in C_6D_6 and $CDCl_3$.

Whereas the found relations for $^3J_{H,H}$ can be interpreted by a mere change in the torsion angles, the differences in $^2J_{H,H}$ values indicate that the rings differ slightly also in bond angles and lengths. Comparison of geometric parameters, affecting the

TABLE VIII
Proton coupling constants for compounds *I*, *II* and *III*

Compound	Solvent	Geminal coupling $^2J_{H,H}$					
		2A,2B	3A,3B	6A,6B	7A,7B	10A,10B	11A,11B
I	$CDCl_3$	−11·9	−16·2	−11·6	−11·6	−16·2	−11·9
	C_6D_6	−11·8	−16·0	−11·6	−11·6	−16·0	−11·8
II	$CDCl_3$ [a]	−12·2	−16·2	—	−11·6	−16·4	−12·4
	C_6D_6 [b]	−12·1	−16·0	—	−11·6	−16·1	−12·2
III	$CDCl_3$	−12·2	−16·2	—	−11·6	−16·4	−12·5
	C_6D_6	−12·1	−15·9	—	−11·6	−16·2	−12·6

		Vicinal coupling $^3J_{H,H}$					
		2A,3A	2A,3B	2B,3A	2B,3B	6A,7A	6A,7B
I	$CDCl_3$	8·8	13·3	0·5	7·5	6·2	0·7
	C_6D_6	8·7	13·3	0·8	7·5	6·3	0·7
II	$CDCl_3$ [c]	8·3	13·6	≈0·0	7·5	6·1	0·5
	C_6D_6 [d]	8·3	13·6	1·2	7·2	6·2	0·6
III	$CDCl_3$ [e]	8·5	13·6	0·6	7·4	6·1	0·3
	C_6D_6 [f]	8·4	13·6	0·7	7·3	6·1	0·5

		6B,7A	6B,7B	10A,11A	10A,11B	10B,11A	10B,11B
I	$CDCl_3$	10·7	6·2	7·5	13·3	0·5	8·8
	C_6D_6	10·5	6·3	7·5	13·3	0·8	8·7
II	$CDCl_3$ [c]	—	—	7·9	13·0	≈0·5	8·8
	C_6D_6 [d]	—	—	7·5	12·8	≈0·3	8·2
III	$CDCl_3$ [e]	—	—	8·0	13·1	0·8	8·9
	C_6D_6 [f]	—	—	8·0	13·0	1·2	8·7

[a] $J_{12,12'} = -13·8$; [b] $J_{12,12'} = -13·7$; [c] $J_{6A,12} = 6·2$, $J_{6A,12'} = 9·9$, $J_{12,13} = 8·5$, $J_{12',33} = 5·3$, $J_{13,14} = 6·6$, $J_{13,15} = 6·5$; [d] $J_{6A,12} = 5·5$; $J_{6A,12'} = 10·6$; $J_{12,13} = 9·0$, $J_{12'13} = 4·8$, $J_{13,14} = 6·5$, $J_{13,15} = 6·5$; [e] $J_{6A,12} = 7·0$; [f] $J_{6A,12} = 7·0$.

magnitude of the mentioned constants $^2J_{H,H}$ and $^3J_{H,H}$ (determined by X-ray diffraction in the case of *II*) with the pertinent experimental values of J is given in Table X. The crystallographic data show only a minor difference between skeletal torsion angles C(1)—C(2)—C(3)—C(4) and C(1)—C(11)—C(10)—C(9) (31·8° *vs* 32·8°), more marked difference (about 10°) being found only for two H—C—C—H torsion angles; these were induced by different H—C—H bond angles in the segments C(2)—C(3) and C(10)—C(11). Having in mind the known[26,27] effects of the geometric parameters d, α, and Θ on the magnitude of J we can conclude that the observed small differences in ^2J and ^3J agree with those found in the geometric parameters in Table X. Also the values of $^3J_{H,H}$ in the fragment C(6)—C(7) (6·1 and 0·5 Hz) agree with the torsion angles found by X-ray diffraction (26·3° and 98·5°, respectively). Thus, the spatial arrangement of compound *II* in crystal and in solution is very similar and all the ^{1}H NMR parameters show a very close conformational similarity of compounds *I* and *III*. The only one interpretable difference between the conformation of compound *II* in the solid state and in solution concerns the behaviour of the isobutyl substituent. Whereas in crystal the compound exists in a staggered rotamer about the C(6)–C(12) bond with the isobutyl group pointing towards the O(4) oxygen in the A ring, the observed $^3J_{12,13}$ values (6·2 and 9·9 Hz) indicate a greater mobility of the substituent in solution. Assuming only staggered rotamers and using the values $^3J_{gauche}$ = 2·6 and $^3J_{anti}$ = 13·6 Hz (ref.[28]) we can calculate the population of rota-

TABLE IX
Chemical shifts of ^{13}C for compounds *I*, *II* and *III* in deuteriochloroform

Compound	C(1)	C(2)	C(3)	C(4)	C(6)	C(7)	
I	87·99	32·72	35·98	177·17	43·91	43·91	
II[a]	88·27	32·64	36·83	177·68	56·15	48·60	
III[b]	88·40	32·60	37·11	177·75	52·94	49·76	
	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(15)
I	177·17	35·98	32·72	—	—	—	—
II[a]	177·29	36·57	32·54	41·57	25·41	21·79	23·05
III[b]	177·41	36·65	32·60	19·39	—	—	—

[a] The assignment of C(2), C(11); C(3), C(10) and C(4), C(9) is tentative and may be interchanged in pairs; [b] the assignment of C(3), C(10) and C(4), C(9) is tentative and may be interchanged in pairs.

mers to be $a : b : c = 66 : 33 : 1$ (Fig. 4). Since the forms *a* and *b* are indistinguishable on the basis of $^3J_{H,H}$ values, the higher-populated rotamer was ascribed to the form *a* according to the crystallographic data.

For all the studied compounds, all the coupling constants found in hexadeuteriobenzene differed only negligibly from those found in deuteriochloroform, confirming thus the expected conformational identity in both solvents. In hexadeuteriobenzene all proton signals are shifted markedly upfield (Table VII, ASIS values) which indicates solvation of the amide bonds in *I*–*III* from both sides of the molecule. Introduction of substituent into the position 6 and its increasing steric bulk causes an expectable decrease of the benzene-induced shifts in the order *I*, *III* and *II*.

IR Spectroscopic Comparison of Compounds I–III

The introduction of alkyl groups into the ring C was accompanied by no significant change of the absorption bands due to amide vibrations. The fact that, unlike compound *I* (studied already earlier[6]), compounds *II* and *III* do not possess a C_2 symmetry, manifested itself only in a change of Fermi resonance effect on the carbonyl stretching vibrations in tetrachloromethane (Table XI).

TABLE X
Crystallographically determined geometrical parameters of dilactam *II*, affecting the $^2J_{H,H}$ and $^3J_{H,H}$ coupling constants and the experimentally found values of these constants

Ring	Fragment[a]	d_1	d_2	d_3	$\varkappa_1$	$\varkappa_2$	Θ	$J_{H,H}$
A	$H_{2A}—C_2—H_{2B}$	1·01	—	0·98	113	—	—	−12·2
B	$H_{11B}—C_{11}—H_{11A}$	0·96	—	0·95	106	—	—	−12·4
A	$H_{3A}—C_3—H_{3B}$	0·99	—	1·02	114	—	—	−16·2
B	$H_{10B}—C_{10}—H_{10A}$	0·99	—	1·01	105	—	—	−16·4
A	$H_{2A}—C_2—C_3—H_{3A}$	1·01	1·529	0·99	108	114	37	8·3
B	$H_{11B}—C_{11}—C_{10}—H_{10B}$	0·96	1·532	0·99	111	116	37	8·8
A	$H_{2A}—C_2—C_3—H_{3B}$	1·01	1·529	1·02	108	112	167	13·6
B	$H_{11B}—C_{11}—C_{10}—H_{10A}$	0·96	1·532	1·01	111	112	158	13·0
A	$H_{2B}—C_2—C_3—H_{3A}$	0·98	1·529	0·99	115	114	−91	0·0
B	$H_{11A}—C_{11}—C_{10}—H_{10B}$	0·95	1·532	0·99	113	116	−82	0·5
A	$H_{2B}—C_2—C_3—H_{3B}$	0·98	1·529	1·02	115	112	40	7·5
B	$H_{11A}—C_{11}—C_{10}—H_{10A}$	0·95	1·532	1·01	113	112	39	7·9

[a] Estimated standard deviations: C—H distances: 0·02 A°; H—C—H angles: 1·2°; H—C—C—H torsion angles: 1·5°.

Chiroptical Properties of Dilactams I–III

CD spectra of the three compounds (Fig. 5 and 6) exhibit three dichroic bands: the first (maximum in cyclohexane, shoulder in polar solvents) was ascribed to the $n-\pi^*$ transition because its position and intensity were sensitive toward the solvent polarity. The second band of the same sign at 203–205 nm is a long-wavelength branch of a $\pi-\pi^*$ couplet whose short-wavelength branch is represented by the dichroic absorption of oposite sign below 200 nm. The band parameters are very similar for all three compounds (even after band separation) and similar are also the solvent-induced changes (Table XII). The same band signs for compounds *II* and *III* prove the same absolute configuration and show also the same configurational relationship (relative configuration) between the chiral center at C(6) and the chiral

TABLE XI
Wavenumbers (cm^{-1}) of absorption bands in IR spectra of compounds *I–III*

Compound	Solvent[a]	ν(C=O)[b]	ν(C'—N)[b]
I	CCl_4	1 713·5 sh 1 723·7 max	1 339·5 max, 1 385·3 max
I	$CHCl_3$	1 701·5 max, 1 716·4 sh	1 355·0 max 1 397·9 max
II	CCl_4	1 715·8 max,—	1 343·5 max, 1 383·5 max
II	$CHCl_3$	1 698·0 max, 1 713·5 sh	1 358·5 max, 1 399·0 max
III	CCl_4	1 716·5 max, 1 722·5 sh	1 331·0 max, 1 379·4 max
III	$CHCl_3$	1 700·2 max, 1 724·2 sh	1 399·0 max, 1 393·5 max

[a] Concentration 0·08 mol l^{-1}; [b] calibrated values.

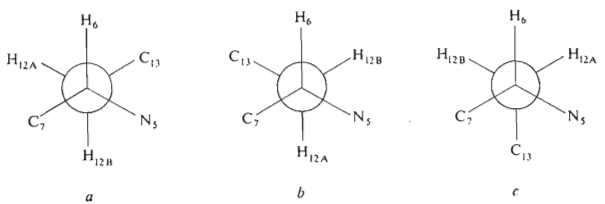


FIG. 4
Staggered rotamers around the C(6)—C(12) bond in compound *II*

TABLE XII

Apparent values of maxima in nm, values of $[\theta] \cdot 10^{-3}$ in parentheses

Solvent	*I*		*II*		*III*	
	n-π^*	π-π^*	n-π^*	π-π^*	n-π^*	π-π^*
Cyclohexane	—	—	229 (27·8)	205·5[a] (50·1)	229 (32·9)	207[b] (61·9)
Acetonitril	223 sh (−7·2)	204·5 (−11·5)	223 sh (27·4)	206[c] (44·6)	224 sh (23.7)	206[d] (43·8)
Methanol	—	—	222 sh (31·5)	204 (58·9)	222 sh (31·4)	206 (67·9)
Water	220 sh (−8·7)	202 (−16·9)	220 sh (35·3)	204 (58·9)	220 sh (33·8)	203 (66·2)
2,2,2-Trifluoroethanol	219 sh (−9·1)	202 (−16·8)	219 sh (31·8)	203 (60·2)	220 sh (26·3)	202 (60·9)
1,1,1,3,3,3-Hexafluoro-propanol	—	—	218 sh (34·3)	202 (61·9)	218 sh (35·9)	202 (70·0)

[a] Additional band at 195 nm (sh, $[\theta] = 25\,100$); [b] additional band at 191 nm (maximum, $[\theta] = 30\,100$); [c] additional band at 193 nm (sh, $[\theta] = 15\,900$); [d] additional band at 190 nm (sh, $[\theta] = 15\,400$).

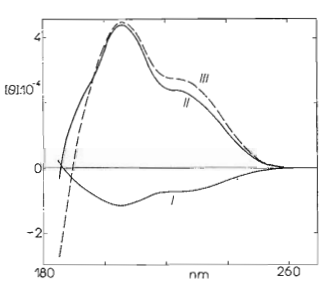


FIG. 5

CD Spectra of dilactams *I*—*III*, measured in acetonitrile

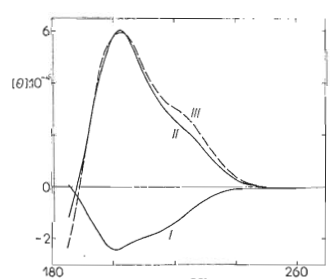


FIG. 6

CD Spectra of dilactams *I*—*III*, measured in 2,2,2-trifluoroethanol

arrangement of the tricyclic moiety (atom C(1)) which is obviously a decisive factor for the CD curve modelling. The chiral center at C(6) has only negligible effect on the curves. Compound *I* which was measured in its partly resolved form affords spectra of substantially lower intensity, nevertheless the position of the bands and their relative intensities are the same as those of compounds *II* and *III*. However, the CD spectrum of *I* is a mirror image of those of *II* and *III* and therefore the studied enantiomer of *I* has an opposite absolute configuration at C(1) (an opposite sense of the twist).

CD spectra of the lactams *II* and *III* are characteristic by the large elipticities of the dichroic bands, particularly those of the longest wavelength. This feature may be explained by a non-planar arrangement of the amide groups (Fig. 7). The sign of the $n-\pi^*$ transition in the spectra of *I*–*III* agrees with the relationship derived previously for the dichroic $n-\pi^*$ bands in monolactams with non-planar amide groups, *viz.* (−)-(3*S*)-4-azatricyclo[4,4,0,$0^{3,8}$]decan-5-one[29] (*VII*) and (−)-(1*R*)-3-azatricyclo-[5,4,0,$0^{4,9}$]undecan-5-one[30] (*VIII*), which also follows from quantum chemical computations of rotational strengths of non-planar formamide conformations[31]. On the other hand, the long wavelength branches of the $\pi-\pi^*$ bands in the spectra of compounds *I*–*III* are of opposite signs than the non-splitted $\pi-\pi^*$ bands found for compounds with single amide groups of the same absolute configuration[29–31]. The differences in the character and sign of the $\pi-\pi^*$ bands of both types of compounds are obviously due to an interaction between the two amide groups in the dilactams.

Stereochemical Conclusions

Since the dilactams *II* and *III* were prepared starting from L-leucine and L-alanine, respectively, their absolute configuration at the chiral center C(6), bearing the alkyl group, is known. In both cases we detected (by ^{1}H NMR and ^{13}C NMR spectroscopy) the formation of only one of the two possible diastereoisomeric dilactams differing in chirality of the tricyclic skeleton. The formation of the tricyclic system is thus highly stereoselective, controlled by the chiral center of the diamine compo-

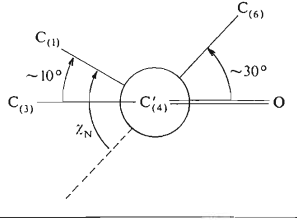
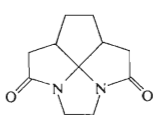
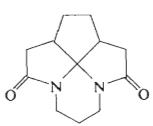


FIG. 7

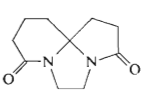
Perspective drawing of the non-planar amide chromophore with the absolute configuration corresponding to dilactams *II* and *III*



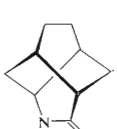
IV



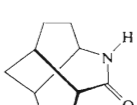
V



VI



VII



VIII

nent. The condensation reaction is obviously of a multistep character and its stereochemical interpretation is difficult. However, convincing stereochemical conclusions can be drawn on the basis of the physical studies. X-ray structure analysis has unequivocally shown the relative spatial arrangement of C(1) and C(6) in compound *II*. The ^{1}H and ^{13}C NMR spectra led to the same conclusion for both the compounds *II* and *III*. Thus, in both cases the condensation afforded the same diastereoisomeric type (1*S*, 6*S*). The fact that during the condensation no configurational change of the starting optically active component took place (which would be highly improbable) was confirmed by an anomalous X-ray diffraction, again of compound *II*.

Infrared and NMR spectroscopy further showed a practically identical geometry of compounds *I*–*III*. The effect of substituent at C(6) is only of local character causing some differences in conformation of both the lactam rings A and B. The torsion angles, found for the dilactam *II* in the crystalline state, are very close to those derived for *II* and *III* in solution by the ^{1}H NMR spectra. Due to rigidity of the skeleton, the conformations of the compounds are the same both in solution and crystals and therefore the found accurate crystallographic data can be used in further considerations and quantum chemical calculations. Only the isobutyl side chain in the dilactam *II* shows mobility, the assumed prevailing conformation being the rotamer a depicted in Fig. 4.

The almost complete accord of positions and solvent shifts of the dichroic CD bands of *I*–*III* proved that the rotational strengths are controlled by the pair of the neighbouring amide groups, held in a fixed arrangement by the tricyclic system of a given chirality. According to CD spectra the chirality of dilactams *II* and *III* is identical whereas the studied enantiomer of *I* (which was eluted first in the optical resolution and was optically more pure) has an opposite chirality. The non-planarity

of the amide groups in compounds *I* and *II* is known from the X-ray diffraction studies and according to the ^{1}H NMR spectra it cannot be significantly different in the dilactam *III*. It was therefore possible to use the known relationships between chirality of a non-planar amide group and its chiroptical properties. According to this comparison both the $n-\pi^*$ transitions behave independently and do not influence each other. On the contrary, the orientation of both the amide groups gives rise to a significant mutual interaction of the $\pi-\pi^*$ transitions and their exciton splitting.

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