STEREOISOMERIC CHIRAL 2,9-DIAZABICYCLO[4.4.0.]DECANE--3,10-DIONES AS MODELS OF DIPEPTIDE GROUPING: SYNTHESIS, X-RAY, IR, NMR AND CD STUDIES*

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Synthesis of the title optically active bicyclic dilactams *I* and *II* with *cis*- and *trans*-annelation of rings is described. The stereospecific synthesis started from (2*R*)-2-benzamido-2-(4-oxocyclohexyl)acetic acid ((—)-*VI*) whose absolute configuration was determined by chemical correlation with the known (2*R*)-2-amino-(4-hydroxyphenyl)acetic acid ((—)-*IIIb*). Relative configuration at the bridgehead atoms in *I* and *II* was assigned by ^{1}H and ^{13}C NMR spectroscopy and confirmed by X-ray diffraction analysis which showed the detailed conformation in crystal. According to the ^{1}H NMR spectra in solution the *trans*-isomer *II* has the same conformation as in crystal whereas the *cis*-isomer *I* exists in two forms one of which is identical with that in crystal. This conformational analysis agrees also with the IR spectra, detecting an intramolecularly hydrogen-bonded conformation for *II* but no hydrogen bond for *I*. The CD spectra of both lactams were successfully interpreted using the exciton theory in the $\pi-\pi^*$ region where it reflects the differences in the angles ϕ and ψ (for *I* $\phi = 110°$, $\psi = -143°$; for *II* $\phi = -145°$, $\psi = 162°$). In the $n-\pi^*$ transition region the interpretation was based on the quadrant rule and also inherent non-planarity of one of the amide groups in *II*.

Chiroptical properties of the peptide backbone are influenced by interactions between the conjugated amide groups, as well as by potential non-planarity of these groups. The first factor reflects the spatial arrangement of the peptide chain characterized by the torsion angles ϕ and ψ. Besides by theoretical computations[1,2], the CD spectra of peptide chains have been analyzed also using experimental results obtained with macromolecular polyamino acids[3] and low-molecular acyclic dipeptide models, most often N-acetylamino acid N'-methylamides[4,5]. Both these classes of compounds represent conformationally flexible structures which form in solutions equilibrium mixtures of several conformers, differing in the spatial arrangement of the

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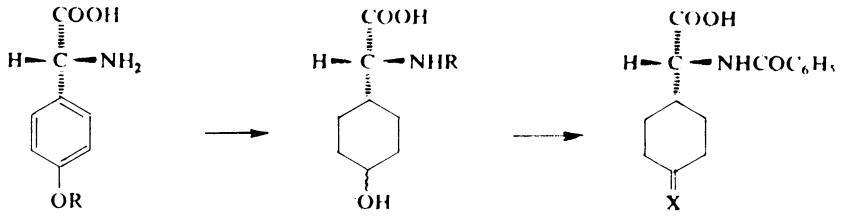
peptide chain. However, for comparison of the calculated and experimental data it would be extremely useful to investigate rigid models in which steric relations of the homoconjugated amide groups are defined with sufficient accuracy. While it is very difficult to satisfy such requirements for *trans*-amides we can find suitable models for *cis*-amide groupings. In this respect, cyclodipeptides have been already studied[6,7]. The amide groups in these models have a *cis*-conformation instead of the common *trans*-arrangement; in the first approximation, this is not necessarily a drawback since according to calculations both situations exhibit qualitatively comparable chiroptical properties.

This communication concerns a pair of bicyclic dilactams *I* and *II* for which we can assume a sufficient conformational rigidity of the backbone because they are structural analogues of *cis*- and *trans*-decalin. We have synthesized the dilactams *I* and *II* in the optically active forms, determined their relative and absolute configuration, studied their probable conformation in solution by the NMR and IR spectroscopy and compared the results with those obtained by X-ray diffraction analysis and CD spectra.

Synthesis

Since optically active compounds of defined chirality were required, we prepared the desired dilactams in a stereospecific way from a precursor whose absolute configuration was known. The key compound was the keto acid (−)-*VI*.* Its absolute configuration (2*R*) was determined in the following way: Hydrogenation of (2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid ((−)-*IIIb*) over Raney nickel in water afforded a mixture of stereoisomeric derivatives (2*R*)-*IV* which on Schotten–Baumann benzoylation and oxidation gave the acid (−)-*VI* (Scheme 1). This route to (−)-*VI*, though very smooth, was inconvenient for the optically active material because



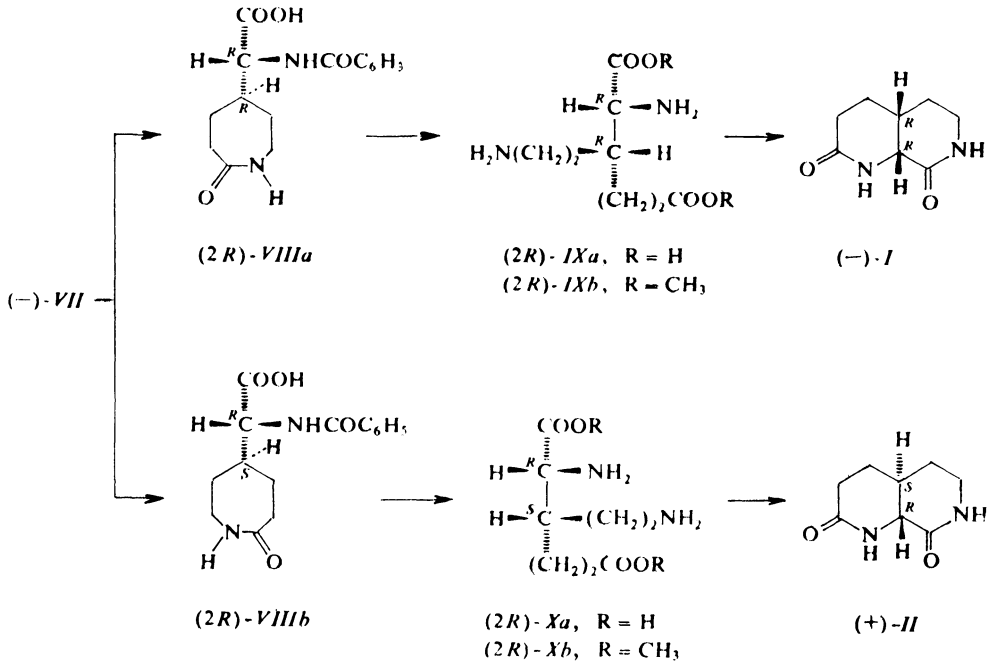
(−)-*IIIa*, R = CH_3 (2*R*)-*IV*, R = H (−)-*VI*, X = O
(−)-*IIIb*, R = H (2*R*)-*V*, R = COC_6H_5 (−)-*VII*, X = NOH

SCHEME 1

* Optically active compounds are described by their sign of rotation or the *R* or *S* symbol in front of their number; for the racemates the (±)-sign is omitted.

the starting acid (−)-*IIIb* was not easily accessible in larger quantities. Although its preparation by several methods has been described[8−10] in our hands the yields of optically pure acid were very low. We therefore used this reaction sequence only for correlation of (−)-*IIIb* with (−)-*VI*. The latter was readily obtained by resolution of the racemate *via* its quinine salt. Complete optical purity of the resolved acid (−)-*VI* was proved by its ^{1}H NMR spectra in the presence of a chiral shift reagent.

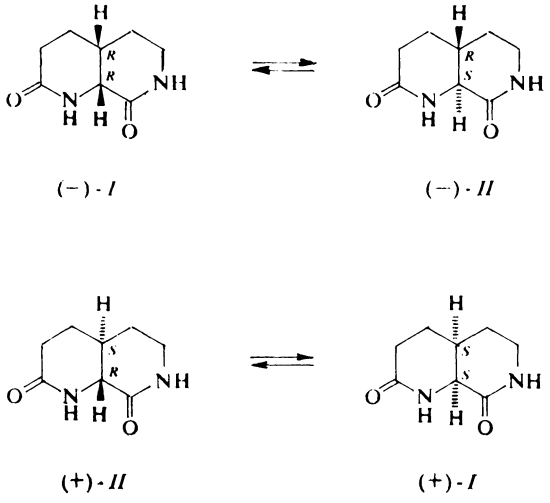
The keto acid (−)-*VI* was further converted into oxime (−)-*VII* which was subjected to Beckmann rearrangement. Since the rearrangement in polyphosphoric acid at 110°C, originally used for the racemic material, was evidently accompanied by racemization we performed the reaction *via* the benzenesulfonyl ester in an almost neutral medium. Acid hydrolysis of the resulting mixture of rearrangement products (2*R*)-*VIIIa* and (2*R*)-*VIIIb* gave the diamino diacids (2*R*)-*IXa* and (2*R*)-*Xa* as a 1 : 1 mixture (determined by HPLC) (Scheme 2). Cyclization by pyrolysis of the free



SCHEME 2

acids (convenient for the racemic compound) was evidently unsuitable for the optically active material because of epimerization at $C_{(2)}$ which, with a 1 : 1 system of diastereoisomeric acids, should lead to racemic products, one enantiomer of one diastereoisomer giving the other enantiomer of the other diastereoisomer and *vice*

versa (Scheme 3). Therefore, we used a milder cyclization[11] *via* the diesters made *in situ* from the acids which, as evidenced by recyclization experiments (*vide infra*), was not accompanied by epimerization. The stereoisomeric dilactams (−)-*I* and (+)-*II* were separated by HPLC (when working with the racemic compounds the isomers were separated by crystallization). The relative configuration of the dilactams was determined by ^{1}H NMR spectra of the racemic substances and confirmed by X-ray analysis.



SCHEME 3

To detect a possible epimerization during the cyclization reaction, the pure dilactams *I* and *II* were separately hydrolyzed with hydrochloric acid to give the pure starting diamino diacids *IXa* and *Xa*, respectively. These were cyclized *via* the esters *IXb* and *Xb* to the dilactams *I* and *II*. HPLC analysis revealed that – under the conditions employed – both the acid hydrolysis and the cyclization gave pure dilactams showing that in the optically active series the cyclization procedure did not affect the optical purity of the material.

The only stereochemically uncertain step might be the Beckmann rearrangement of (−)-*VII* for which there is no direct proof of complete retention of configuration at $C_{(2)}$. However, since all the transformations in going from (−)-*VI* to (−)-*VIIIa,b* take place at the site relatively far away from the chiral center at $C_{(2)}$ it is very probable that the optical rotation of the compounds (−)-*VI*, (−)-*VII* and (−)-*VIIIa,b* will not change substantially if their optical purity is preserved along the pathway. This is just what we observed, the optical rotations $[\alpha]_D$ of the respective substances being −68·9° (optically pure), −44·5° and −52°. No enrichment by one of the diastereo-

isomers (2*R*)-*VIIIa* or (2*R*)-*VIIIb* during the processing took evidently place since after hydrolysis the ratio of (2*R*)-*IXa* and (2*R*)-*Xa* was still 1 : 1 as expected for the outcome of a rearrangement, far from the chiral center.

We conclude that there is no substantial deterioration of the optical purity during the whole synthesis. Unfortunately, ^{1}H NMR experiments trying to check directly the optical purity of the desired dilactams by use of chiral shift reagents were unsuccessful.

NMR *Studies*

Assignment of configuration: ^{13}C NMR Spectra of both compounds exhibit the corresponding number of the CO, CH and CH_2 carbon signals which were assigned using the "attached proton test" method[12] as well as the expected effect of the C=O and NH groups on the neighbouring carbon atoms[13] (for data see Table I). The CH_2 and CH carbon signals of one of the isomers (m.p. 187°C) are shifted downfield ($\Delta\delta$ = 0·4 – 3·5 ppm). Similar systematic shifts were found[14] with *cis*- and *trans*-decalins, the *trans*-isomer having invariably higher δ-values for all corresponding carbon atoms. Analogously, we assigned the *trans*-configuration *II* to the isomer melting at 187°C and *cis*-configuration *I* to the isomer of m.p. 229°C, in agreement with the independent assignment based on the ^{1}H NMR spectra.

^{1}H NMR Spectra were measured at 200 MHz in deuteriochloroform, hexadeuteriodimethyl sulfoxide and deuterium oxide. In neither solvent it was possible to obtain the δ and J values for all the protons present. The CH_2 protons in positions 5 and 7 appeared as a complex multiplet at δ 1·5 – 2·1; moreover in the spectrum of the *trans*-compound *II* also the $H_{(6)}$ proton signal was situated in this region. The ^{1}H NMR data are given in Table II.

TABLE I

^{13}C NMR Data of *cis*-dilactam *I* and *trans*-dilactam *II*

Compound	Solvent	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(10)}$	$C_{(1)}$
I	^2H_2O	175·1[a]	29·8	22·6	29·9	25·1	38·6	172·5[a]	54·0
II	^2H_2O	175·3[a]	30·2	25·8	33·4	26·3	40·8	171·4[a]	56·4
	C^2HCl_3	170·5[a]	30·7	26·8	34·5	27·6	41·1	169·1[a]	56·8

[a] Signal assignment may be interchanged.

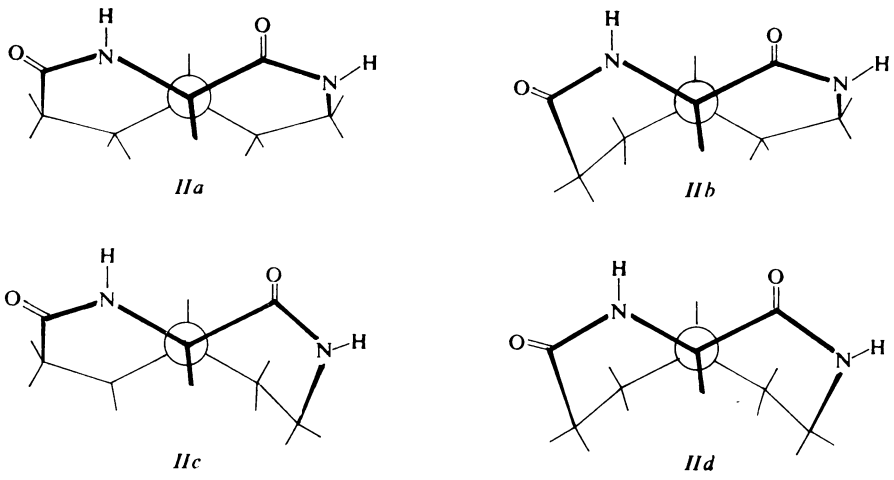
TABLE II

^{1}H NMR Data of dilactams *I* and *II*

Proton	*I*			*II*		
	C^2HCl_3	$C^2H_3SOC^2H_3$	^2H_2O	C^2HCl_2	$C^2H_3SOC^2H_3$	^2H_2O
$NH_{(2)}$	6·42	7·65	[a]	6·85	7·64	[a]
$H_{(41)}$	2·44	2·16	2·41	2·54	2·21–2·28	2·44
	$J_{41,42}$ = 17·6			$J_{41,42}$ = 18·2		
	$J_{41,51}$ = 5·8			$J_{41,51}$ = 2·0		
	$J_{41,52}$ = 5·8			$J_{41,52}$ = 7·3		
$H_{(41)}$	2·37	2·16	2·41	2·41	2·21–2·28	2·44
	$J_{42,41}$ = 17·6			$J_{42,41}$ = 18·2		
	$J_{42,51}$ = 8·5			$J_{42,51}$ = 6·6		
	$J_{42,52}$ = 6·4			$J_{42,52}$ = 11·1		
$H_{(51)}$	1·63–2·11	1·39–1·73	1·58–1·93	1·50–2·07	1·45–1·92	1·51–2·10
$H_{(52)}$	1·63–2·11	1·39–1·73	1·58–1·93	1·50–2·07	1·45–1·92	1·51–2·10
$H_{(6)}$	2·29–2·56	2·30	2·48	1·50–2·07	1·45–1·92	1·51–2·10
$H_{(71)}$	1·63–2·11	1·96	2·08	1·50–2·07	1·45–1·92	1·51–2·10
		$J_{71,72}$ = 13·8	$J_{71,72}$ = 14·2			
		$J_{71,81}$ = 8·8	$J_{71,81}$ = 8·9			
		$J_{71,82}$ = 6·0	$J_{71,82}$ = 6·0			
		$J_{71,6}$ = 5·0	$J_{71,6}$ = 4·6			
$H_{(72)}$	1·63–2·11	1·39–1·73	1·58–1·93	1·50–2·07	1·45–1·92	1·51–2·10
$H_{(81)}$	3·54	3·21	3·40	3·39–3·46	3·17–3·25	3·38
	$J_{81,82}$ = 12·3	$J_{81,82}$ = 12·7	$J_{81,82}$ = 13·1			
	$J_{81,71}$ = 8·4	$J_{81,71}$ = 8·8	$J_{81,71}$ = 8·9			
	$J_{81,72}$ = 5·3	$J_{81,72}$ = 5·2	$J_{81,72}$ = 5·0			
	$J_{81,9}$ = 2·4	$J_{81,9}$ = 2·8				
$H_{(82)}$	3·33	3·11	3·29	3·39–3·46	3·17–3·25	3·38
	$J_{82,81}$ = 12·3	$J_{82,81}$ = 12·7	$J_{82,81}$ = 13·1			
	$J_{82,71}$ = 5·4	$J_{82,71}$ = 6·0	$J_{82,71}$ = 7·0			
	$J_{82,71}$ = 5·4	$J_{82,72}$ = 5·1	$J_{82,72}$ = 5·1			
	$J_{82,9}$ = 2·6	$J_{82,9}$ = 2·8				
$NH_{(9)}$	6·14	7·38	[a]	6·15	6·57	[a]
$H_{(1)}$	3·95	3·76	4·09	3·56	3·52	3·75
	$J_{1,2}$ = 2·3	$J_{1,2}$ = 3·6		$J_{1,2}$ = 0	$J_{1,2}$ = 0·4	
	$J_{1,6}$ = 6·2	$J_{1,6}$ = 6·0	$J_{1,6}$ = 6·0	$J_{1,6}$ = 10·5	$J_{1,6}$ = 10·2	$J_{1,6}$ = 10·7

[a] Not detected, exchange for deuterium.

As follows from inspection of models with approximately planar amide groups (Scheme 4), the *trans*-dilactam *II* can in principle exist in four forms (*IIa–IId*) differing in the conformation of the six-membered rings. In all these forms the torsion



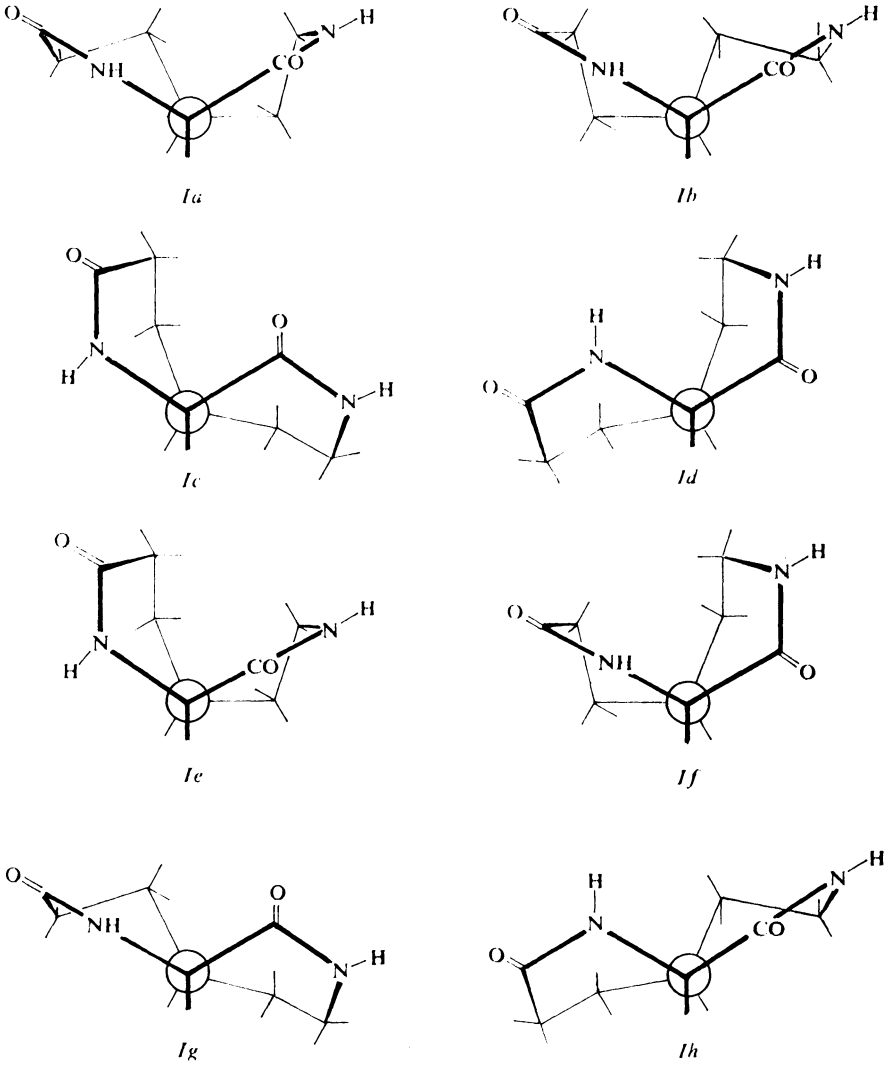
SCHEME 4

angle between the C—$H_{(6)}$ and C—$H_{(1)}$ bonds amounts to about 170° (Table III). The same analysis for the *cis*-dilactam *I* leads to 8 possible conformations (*Ia–Ih*) (Scheme 5) in which the absolute value of the torsion angle $H_{(6)}$—$C_{(6)}$—$C_{(1)}$—$H_{(1)}$ is about 40° (Table IV), the sign depending on the given conformation (and being of course, immaterial from the NMR point). We can thus expect a large coupling constant $J_{1,6}$ for the *trans*-dilactam *II* whereas that for the *cis*-isomer *I* should be significantly lower. The observed values of $J_{1,6}$ are 10·5 Hz for the dilactam melting at 187°C and 6 Hz for the isomer of m.p. 229°C. This corresponds to the respective torsion angles 170° and 40° and leads to the *trans*-configuration for the former and *cis*-configuration for the latter isomer, confirming thus the ^{13}C NMR spectral assignment.

Conformational behaviour of I *and* II *in solution*: The conformational behaviour of the dilactams *I* and *II* in solution is reflected particularly by the vicinal proton coupling constants. In principle, the $^3J_{H,H}$ values can furnish information on conformational situation about seven of the total eleven ring bonds (Table V) whereas the remaining four bonds involve the carbonyl carbon atoms.

As already mentioned with the *trans*-dilactam *II*, the value $J_{1,6}$ = 10·5 Hz may correspond to all of the four conformations *IIa–IId* in which the torsion angle $H_{(6)}$—$C_{(6)}$—$C_{(1)}$—$H_{(1)}$ is about 170° which is very close to the value (175°) found

in crystal. The very small value of $J_{1,2}$ (0–0·5 Hz) between the NH and the vicinal CH protons corresponds better to the conformations *IIa* and *IIc* (torsion angles



SCHEME 5

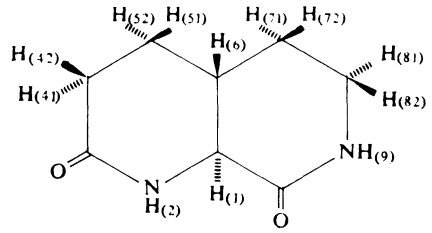
$\Theta_{1,2} \approx 80°$) rather than *IIb* and *IId* ($\Theta_{1,2} \approx 110°$). According to the X-ray data (for a conformation close to *IIa*), $\Theta_{1,2}$ amounts to 77°. The similar chemical shifts of both CH_2 protons in the 4- and 8-positions witness for their approximately symmetrical arrangement relative to the magnetically anisotropic amide groups. The

carbonyl oxygen at $C_{(3)}$ should thus have about the same torsion angle with both $C_{(4)}$ protons, similarly to the angle of $N_{(9)}$—H with both the $C_{(8)}$—H bonds which appears in the form *IIa* only and is again in good agreement with the X-ray data (the found torsion angles $N_{(2)}$—$C_{(3)}$—$C_{(4)}$—$C_{(5)}$, $H_{(9)}$—$N_{(9)}$—$C_{(8)}$—$H_{(81)}$ and $H_{(9)}$—$N_{(9)}$—$C_{(8)}$—$H_{(82)}$ are 10·9°, −63° and 57°, respectively). Although some further *J* values for comparison are lacking, we can conclude that in solution the *trans*-dilactam *II* exists in conformation *IIa*, practically identical with that found in crystal.

The ^{1}H NMR spectra of the *cis*-dilactam *I* give a more complete set of NMR parameters (Table II). However, their conformational interpretation can be complicated by the generally higher flexibility of the *cis*-annelated system reflected

TABLE III

Approximate values of interproton dihedral angles in possible conformations *IIa*—*IId* of *trans*-dilactam *II* (from Dreiding models)



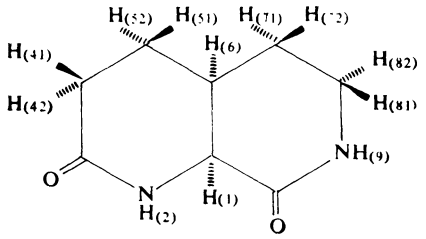
Hydrogens	*IIa*	*IIb*	*IIc*	*IId*
$H_{(1)}$,$H_{(2)}$	80	110	80	110
$H_{(41)}$,$H_{(51)}$	70	170	70	170
$H_{(41)}$,$H_{(52)}$	− 50	50	− 50	50
$H_{(42)}$,$H_{(51)}$	− 50	50	− 50	50
$H_{(42)}$,$H_{(52)}$	−170	− 70	−170	− 70
$H_{(6)}$,$H_{(51)}$	70	0	70	0
$H_{(6)}$,$H_{(52)}$	−170	120	−170	120
$H_{(6)}$,$H_{(71)}$	170	170	−150	−150
$H_{(6)}$,$H_{(72)}$	− 70	− 70	− 30	− 30
$H_{(6)}$,$H_{(1)}$	−170	−170	−170	−170
$H_{(71)}$,$H_{(81)}$	50	50	− 30	− 30
$H_{(71)}$,$H_{(82)}$	170	170	90	90
$H_{(72)}$,$H_{(81)}$	− 70	− 70	−150	−150
$H_{(72)}$,$H_{(82)}$	50	50	− 30	− 30
$H_{(81)}$,$H_{(9)}$	60	60	110	110
$H_{(82)}$,$H_{(9)}$	− 60	− 60	− 10	− 10

already in the double amount of the possible conformational types (*Ia*–*Ih*). The already mentioned interaction $J_{1,6}$ = 6 Hz is in accord with all the conformations considered, as well as with the corresponding torsion angle found in crystal (47°).

As regards the coupling constants of the NH protons, the observed value of $J_{1,2}$ (2·3 and 3·6 in C^2HCl_3 and $C^2H_3SOC^2H_3$, respectively) agrees in principle with six of the eight possible forms (in forms *Id* and *Ie* it should be markedly higher since $\theta_{1,2} \approx 10°$). The similar values observed for $J_{9,82}$ (2·4–2·8 Hz) cannot be inter-

TABLE IV

Approximate values of interproton dihedral angles in possible conformations *Ia*—*Ih* of *cis*-dilactam *I* (from Dreiding models)



Hydrogens	*Ia*	*Ib*	*Ic*	*Id*	*Ie*	*If*	*Ig*	*Ih*
$H_{(1)},H_{(2)}$	60	60	10	120	10	60	60	120
$H_{(41)},H_{(51)}$	60	−60	− 60	60	− 60	− 60	60	60
$H_{(41)},H_{(52)}$	−60	180	180	− 60	180	180	− 60	− 60
$H_{(42)},H_{(51)}$	180	60	60	180	60	60	180	180
$H_{(42)},H_{(52)}$	60	−60	− 60	60	− 60	− 60	60	60
$H_{(6)},H_{(51)}$	180	−60	10	−140	−110	− 60	180	−140
$H_{(6)},H_{(52)}$	−60	60	−110	− 20	10	60	− 60	− 20
$H_{(6)},H_{(71)}$	−60	60	20	− 10	− 60	− 10	20	180
$H_{(6)},H_{(72)}$	60	180	140	110	60	110	140	60
$H_{(6)},H_{(1)}$	40	−40	40	− 40	40	− 40	40	− 40
$\sum J_{6,X}$[a]	24·5	24·5	28	28	19·5	19·5	33	33
$H_{(71)},H_{(81)}$	180	60	60	180	180	180	60	60
$H_{(71)},H_{(82)}$	60	−60	− 60	60	60	60	− 60	− 60
$H_{(72)},H_{(81)}$	60	−60	− 60	60	60	60	− 60	− 60
$H_{(72)},H_{(82)}$	−60	180	180	− 60	− 60	− 60	180	180
$H_{(81)},H_{(9)}$	−90	−30	− 10	−110	− 90	−110	− 10	− 30
$H_{(82)},H_{(9)}$	30	90	110	10	30	10	110	90

[a] X = $H_{(51)},H_{(52)},H_{(71)},H_{(72)}$; following approximate values of $J_{6,x}$ were used for determination of $\sum J_{6,x}$: $J(10°)$ = 10·0; $J(20°)$ = 9·0; $J(30°)$ = 8·0; $J(60°)$ = 4·0; $J(110°)$ = 1·5; $J(140°)$ = = 7·5; $J(150°)$ = 9·5 and $J(180°)$ = 12·5 Hz.

TABLE V

Comparison of X-ray analysis and ^{1}H NMR data for *cis*-dilactam *I* and *trans*-dilactam *II*

Conformation about bond	X-Ray data: endocyclic end atoms	X-Ray data: dihedral angle *I*	X-Ray data: dihedral angle *II*	X-Ray data: hydrogen end atoms	X-Ray data: dihedral angle *I*	X-Ray data: dihedral angle *II*	^{1}H NMR data in C^2HCl_3[a]: $J_{H,H}$	^{1}H NMR data in C^2HCl_3[a]: *I*	^{1}H NMR data in C^2HCl_3[a]: *II*
$C_{(1)}$—$N_{(2)}$	$C_{(6)}$,$C_{(3)}$	−17·3	20·0	$H_{(1)}$,$H_{(2)}$	47	77	$J_{1,2}$	2·3(3·6)	0
$N_{(2)}$—$C_{(3)}$	$C_{(1)}$,$C_{(4)}$	1·4	1·7	—	—	—	—	—	—
$C_{(3)}$—$C_{(4)}$	$N_{(2)}$,$C_{(5)}$	−17·3	10·9	—	—	—	—	—	—
$C_{(4)}$—$C_{(5)}$	$C_{(3)}$,$C_{(6)}$	48·0	−43·9	$H_{(41)}$,$H_{(51)}$	47	69	$J_{41,51}$	5·8	2·0
				$H_{(41)}$,$H_{(52)}$	−68	− 54	$J_{41,52}$	5·8	7·3
				$H_{(42)}$,$H_{(51)}$	169	− 46	$J_{42,51}$	8·5(8·8)	6·6
				$H_{(42)}$,$H_{(52)}$	54	−169	$J_{42,52}$	6·4	11·1
$C_{(5)}$—$C_{(6)}$	$C_{(4)}$,$C_{(1)}$	−63·1	63·4	$H_{(51)}$,$H_{(6)}$	176	67	$J_{51,6}$	[b]	[b]
				$H_{(52)}$,$H_{(6)}$	−67	−174	$J_{52,6}$	[b]	[b]
$C_{(6)}$—$C_{(1)}$	$C_{(5)}$,$N_{(2)}$	47·5	−51·9	$H_{(6)}$,$H_{(1)}$	50	−175	$J_{6,1}$	6·2(6·0)	10·5
	$C_{(7)}$,$C_{(10)}$	47·8	59·5	—	—	—	—	—	—
$C_{(10)}$—$C_{(1)}$	$N_{(9)}$,$C_{(6)}$	−17·2	−36·4	—	—	—	—	—	—
$N_{(9)}$—$C_{(10)}$	$C_{(8)}$,$C_{(1)}$	− 1·0	16·6	—	—	—	—	—	—
$C_{(8)}$—$N_{(9)}$	$C_{(7)}$,$C_{(10)}$	−13·2	−20·0	$H_{(81)}$,$H_{(9)}$	−72	− 63	$J_{81,9}$	2·4(2·8)	[b]
				$H_{(82)}$,$H_{(9)}$	46	57	$J_{82,9}$	2·6(2·8)	[b]
$C_{(7)}$—$C_{(8)}$	$C_{(6)}$,$N_{(9)}$	45·3	43·1	$H_{(71)}$,$H_{(81)}$	166	48	$J_{71,81}$	8·4(8·8)	[b]
				$H_{(71)}$,$H_{(82)}$	46	167	$J_{72,82}$	5·4(6·0)	[b]
				$H_{(72)}$,$H_{(81)}$	44	− 75	$J_{72,81}$	5·3(5·2)	[b]
				$H_{(72)}$,$H_{(82)}$	−76	44	$J_{72,82}$	5·4(5·1)	[b]
$C_{(6)}$—$C_{(7)}$	$C_{(1)}$,$C_{(8)}$	−62·8	−63·2	$H_{(6)}$,$H_{(71)}$	−61	− 67	$J_{6,71}$	[b](5·0)	[b]
				$H_{(6)}$,$H_{(72)}$	57	172	$J_{6,72}$	[b]	[b]

[a] Data for hexadeuteriodimethyl sulfoxide solutions are given in parentheses; [b] the values could not be determined.

preted in terms of an exclusive existence of only one of the forms *Ia–Ih*, since all require a significant difference between the two constants. The same conclusion is obtained from analysis of conformations about the $C_{(4)}$—$C_{(5)}$ and $C_{(8)}$—$C_{(7)}$ bonds. In all the conformations *Ia–Ih* there are only two types of staggered arrangements, differing from each other by rotation of about 120° and all having interactions of the type $J_{ax,ax}$, $J_{ax,eq}$, $J_{eq,ax}$ and $J_{eq,eq}$. According to the X-ray data, in crystal the compound exists in the form *Ia* with the staggered arrangement about the $C_{(4)}$—$C_{(5)}$ and $C_{(8)}$—$C_{(7)}$ bonds. The observed values – one 8·5–8·8 Hz and the other three 5–6·4 Hz – do not fit any single conformation and indicate that the values are apparently averaged by the presence of both types of rotamers. Further information about the rotamer population can be obtained from the coupling of the $H_{(6)}$ with the CH_2 protons in positions 5 and 7. According to models, these constants should sensitively reflect the conformational differences between the types *Ia–Ih*. Because of character of the multiplet of protons in positions 5 and 7, the observed splitting 4·5 Hz, 5·0 Hz, 5·0 Hz and 10·5 Hz needs not necessarily correspond to the coupling constants and therefore we consider rather the sum of these interactions ($J_{6,51} + J_{6,52} + J_{6,71} + J_{6,72} = 25$ Hz). Comparison of this sum and the single constants with the values calculated for the conformations *Ia–Ih* shows a very good agreement only for the conformations *Ia* and *Ib* (Table IV). The existence of these two forms can explain also the partial averaging of vicinal coupling constants for protons in positions 4,5 and 5,6, the averaged constants $J_{9,81}$ and $J_{9,82}$ and particularly the proton chemical shifts of CH_2 groups adjacent to the amide bonds, *i.e.* in positions 4 and 8. In each of the forms *Ia* and *Ib* these protons are markedly asymmetric relative to the amide bond plane but on interconversion from *Ia* into *Ib* they interchange their positions. We can thus conclude that, contrary to the crystalline state in which the only conformation is the form *Ia*, a solution of the *cis*-dilactam *I* contains comparable amount of the form *Ib*.

X-*Ray Analysis*

A stereoview of a single molecule of *I* is shown in Fig. 1* and that of *II* is shown in Fig. 2*. In *II* the dilactam ring system has the normal *trans*-decalin type conformation, while in the *cis*-compound it assumes a folded conformation. The conformation of *I* is consistent with the observation that all *cis*-substituted fused ring systems show a twist about the bridging bond such that the bridgehead substituents are partially staggered[15]. The degree of twist about the bridgehead bond, $C_{(6)}$—$C_{(1)}$ is given by the torsion angles, $C_{(5)}$—$C_{(6)}$—$C_{(1)}$—$C_{(10)} = -76·4°(1)$ and $H_{(6)}$—$C_{(6)}$—$C_{(1)}$—$H_{(1)} = 49·7°(13)$.

The bond distances for the two compounds are given in Fig. 3 and bond angles are listed in Table VI. Equivalent distances and angles in the *cis*- and *trans*-com-

* See insert on the p. 742.

pounds do not differ from each other significantly. The only noticeable differences are in the bonds, $N_{(2)}$—$C_{(1)}$ (1·465(1) Å in *I* and 1·449(3) Å in *II*), $C_{(10)}$—$C_{(1)}$ (1·537(1) Å in *I* and 1·519(3) Å in *II*), and the angles $C_{(6)}$—$C_{(1)}$—$C_{(10)}$ (113·8(1)° in *I* and 111·9(2)° in *II*) and $C_{(1)}$—$C_{(10)}$—$N_{(9)}$ (118·3(1)° in *I* and 116·4(2)° in *II*). The endocyclic torsion angles for the two compounds are given in Fig. 4. Calculation of pseudorotation parameters according to the method of Cremer and Pople[16] shows that the conformations of the two rings (A, B) in *I* are quite similar, ring A ($Q = 0·51$ Å, $\phi_2 = 29·9°$, $\theta = 48·9°$) and ring B ($Q = 0·51$ Å, $\phi_2 = 33·7°$, $\theta = 50·6°$) both having an intermediate conformation between a half-chair and a twisted-boat. Conformations of the two rings in *II* are different from each other. The pseudorotation parameters in ring A ($Q = 0·53$ Å, $\phi_2 = 338·9°$, $\theta = 51·8°$) and ring B ($Q = 0·52$ Å, $\phi_2 = 51·5°$, $\theta = 39·3°$) indicate that while ring A has nearly the same conformation as the two rings in the *cis* compound, ring B has an intermediate conformation between a half-chair and a boat.

The out-of-plane deformation of the amide groups is described in terms of the twisting (τ) and bending (χ_C, χ_N) parameters as defined by Winkler and Dunitz[17]. These conformational parameters are listed in Table VII. All the amide groups appear to be essentially planar except the one in ring B of the *trans*-compound.

TABLE VI
Bond angles

Angle	*I*	*II*
$C_{(3)}$—$N_{(2)}$—$C_{(1)}$	126·2(1)	126·0(2)
$N_{(2)}$—$C_{(3)}$—$C_{(4)}$	118·8(1)	117·8(2)
$N_{(2)}$—$C_{(3)}$—$O_{(3)}$	120·8(1)	120·9(2)
$O_{(3)}$—$C_{(3)}$—$C_{(4)}$	120·4(1)	121·3(2)
$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	114·0(1)	115·4(2)
$C_{(4)}$—$C_{(5)}$—$C_{(6)}$	108·9(1)	109·0(2)
$C_{(5)}$—$C_{(6)}$—$C_{(7)}$	113·8(1)	116·4(2)
$C_{(5)}$—$C_{(6)}$—$C_{(1)}$	108·8(1)	107·1(2)
$C_{(7)}$—$C_{(6)}$—$C_{(1)}$	108·1(1)	106·5(2)
$C_{(6)}$—$C_{(7)}$—$C_{(8)}$	111·3(1)	110·4(2)
$C_{(7)}$—$C_{(8)}$—$N_{(9)}$	111·6(1)	112·3(2)
$C_{(8)}$—$N_{(9)}$—$C_{(10)}$	126·9(1)	126·3(2)
$N_{(9)}$—$C_{(10)}$—$C_{(1)}$	118·3(1)	116·3(2)
$N_{(9)}$—$C_{(10)}$—$O_{(10)}$	121·8(1)	123·4(2)
$O_{(10)}$—$C_{(10)}$—$C_{(1)}$	119·8(1)	120·2(2)
$C_{(10)}$—$C_{(1)}$—$C_{(6)}$	113·8(1)	111·9(2)
$C_{(10)}$—$C_{(1)}$—$B_{(2)}$	108·6(1)	109·2(2)
$N_{(2)}$—$C_{(1)}$—$C_{(6)}$	112·2(1)	112·6(2)

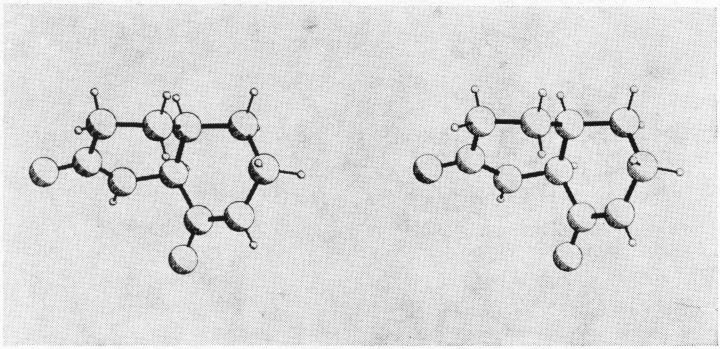


FIG. 1
Stereoview of a single molecule of *I*

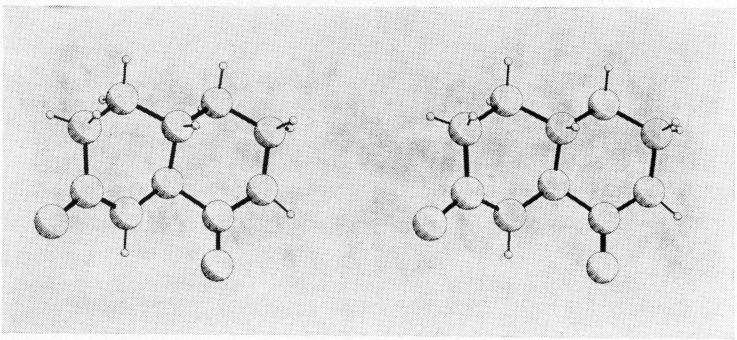


FIG. 2
Stereoview of a single molecule of *II*

For this amide group the χ_N value of 19° indicates substantial non-planarity. The value is sufficiently small, however, so that no lengthening of the C—N bond (1·339 Å) is observed. Correlation between the non-planar amide group and lengthening of C—N bond (and accompanying shortening of C=O bond) have been observed in a number of polycyclic spirolactams[18-20] but only occurs for larger values of χ_N. In both the structures, the molecules are linked by $N_{(9)}$—$H_{(9)}$...$O_{(3)}$ intermolecular hydrogen bonds ($N_{(9)}$...$O_{(3)}$ = 2·863 Å, $N_{(9)}$—$H_{(9)}$ = 0·87 Å, $H_{(9)}$...$O_{(3)}$ = 2·01 Å, angle $N_{(9)}$—H...$O_{(3)}$ = 167° in *II*, and $N_{(9)}$...$O_{(3)}$ = 2·897 Å, $N_{(9)}$—$H_{(9)}$ = 0·88 Å, $H_{(9)}$...$O_{(3)}$ = 2·06 Å, angle $N_{(9)}$—$H_{(9)}$...$O_{(3)}$ = 160° in *I*) to form unending chains. In *I* the chains are interlinked through a pair of $N_{(2)}$—$H_{(2)}$...$O_{(10)}$ hydrogen bonds ($N_{(2)}$...$O_{(10)}$ = 2·993 Å, $N_{(2)}$—$H_{(2)}$ = 0·88 Å, $H_{(2)}$...$O_{(10)}$ = 2·15 Å, angle $N_{(2)}$—$H_{(2)}$...$O_{(10)}$ = 161°) formed across a crystallographic center of symmetry. In the *trans*-structure, $N_{(2)}$ and $O_{(10)}$ do not form a hydrogen bond.

IR *Spectral Measurements*

The *trans*-isomer *II*, measured in tetrachloromethane in concentrations excluding self-association, exhibits one N—H band at 3 412 cm^{-1} and another one, stronger and broader, at 3 394·5 cm^{-1}. Transfer to chloroform changes the intensity ratio of these bands and also the extent of their overlap (because of different solvent shift). With increasing temperature (from 25°C to 95°C in tetrachloroethylene) the intensity of both bands decreases and they are shifted towards higher wavenumbers.

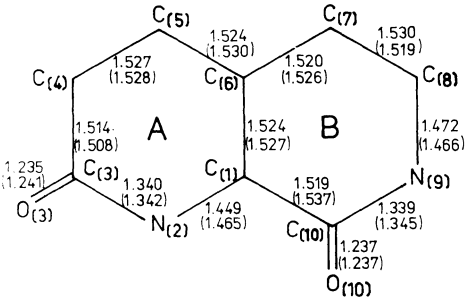


FIG. 3

Bond distances and numbering. Upper values belong to compound *II* and lower values to compound *I*. Estimated standard deviations: 0·003—0·004 Å for *II*, and 0·002 Å for *I*

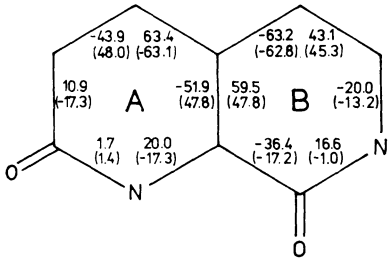


FIG. 4

Endocyclic torsion angles. Upper values belong to *II* and lower values to *I*. Estimated standard deviations: 0·2—0·3° for *II*, and 0·1—0·2° for *I*

In bromoform only one broad band, asymmetric at the low-wavenumber side, was observed which had a shape typical for two overlapping bands situated close to each other. With increasing temperature this band decreased in intensity and shifted to higher wavenumbers. A deuterated sample of *II* exhibited four overlapping bands of which the doublet at lower wavenumbers was stronger. The lower-wavenumber band can be ascribed to an intramolecularly bonded N—H group. In tetrachloromethane practically all molecules exist in a hydrogen bonded form whereas in chloroform some non-bonded species are already present. The deuteration experiment proves that the observed pair of bands is not exclusively due to Fermi resonance. The larger separation of the free and bonded N—^{2}H bands and the higher relative intensity of the bonded N—^{2}H band than that of the bonded N—^{1}H band indicates a stronger intramolecular hydrogen bond in the former case [21,22].

In the spectrum of the *cis*-isomer *I* the free N—H band is situated at wavenumbers lower than the corresponding band of the *trans*-isomer *II* and is much stronger than the bonded N—H band (the spectrum indicates the presence of about 25% of the bonded form). The bonded N—H band disappears completely in chloroform in which only free N—H band, asymmetric at the lower wavenumber side, is observed. Similarly to the *trans*-isomer, with increasing temperature the only N—H band in the spectrum in bromoform (chosen for solubility reason) was shifted towards

TABLE VII

Conformational parameters for the amide groups in *cis*-isomer *I* and *trans*-isomer *II*

Angle, deg	*I*		*II*	
	ring A	ring B	ring A	ring B
ω_1 $C_{(4)}—C_{(3)}—N_{(2)}—H_{(2)}$ or $C_{(1)}—C_{(10)}—N_{(9)}—H_{(9)}$	179(1)	178(1)	−175(3)	177(4)
ω_2 $O_{(3)}—C_{(3)}—N_{(2)}—C_{(1)}$ or $O_{(10)}—C_{(10)}—N_{(9)}—C_{(8)}$	−179·8(1)	178·2(1)	−177·3(3)	−166·9(3)
ω_3 $O_{(3)}—C_{(3)}—N_{(2)}—H_{(2)}$ or $O_{(10)}—C_{(10)}—N_{(9)}—H_{(9)}$	−2(1)	−3(1)	6(3)	−6(4)
ω_4 $C_{(4)}—C_{(3)}—N_{(2)}—C_{(1)}$ or $C_{(1)}—C_{(10)}—N_{(9)}—C_{(8)}$	1·4(2)	−1·0(2)	1·7(4)	16·6(4)
$\tau = \omega_1 + \omega_2$, $\lvert\omega_1 - \omega_2\rvert < \pi$ (mod 2π)	−1(1)	−4(1)	8(2)	10(2)
$\chi_C = \omega_1 - \omega_3 + \pi$ (mod 2π)	1(1)	1(1)	−1(3)	3(3)
$\chi_N = \omega_2 - \omega_3 + \pi$ (mod 2π)	2(1)	1(1)	−3(2)	19(2)

higher wavenumbers. Also in this case, the deuteration gave rise to four closely overlapping bands.

The IR spectra thus clearly show the predominance of intramolecularly hydrogen bonded species in *II* whereas in *I* the bonded conformers represent only a minor part of the conformational mixture. For the *trans*-isomer the four possible conformations possess approximately the same mutual orientation of the $N_{(2)}$—H and $C_{(10)}$=O bonds, engaged in the hydrogen bridge (torsion angle 0–30°) but with different torsion angles between the free $N_{(9)}$—H bond and the neighbouring C—H bonds, manifesting itself by different wavenumber of the free N—H band (ref.[23,24]). Of the eight possible conformations of *I*, two half-chair/boat (unchelated) and one half-chair/half-chair (possibly chelated) appear as the most advantageous.

Chiroptical Properties of (+)-I *and* (+)-II*

CD spectra of the dilactams (+)-*I* and (+)-*II* (Tables VIII and IX, Fig. 5 and 6) exhibit two dichroic bands which are clearly discernible under all experimental conditions. The band of lower intensity appearing in the range 210–250 nm corresponds to the amide $n-\pi^*$ transition while the stronger band at 190–210 nm can be ascribed to the long wavelength branch of a couplet arising from the interaction of the two $\pi-\pi^*$ electronic configurations. The short wavelength branch is detectable as a tail in the spectra of *I* only. The two main ($n-\pi^*$ and $\pi-\pi^*$) CD bands exhibit mutually opposite signs in all the experimental spectra and the bands of identical origin are oppositely signed for (+)-(1*S*,6*S*)-*I* and (+)-(1*R*,6*S*)-*II*. The spectra show only minor dependence on solvent polarity (Table VIII, Figs 5, 6) and temperature of the solution (Table IX). The apparent maximum of the $n-\pi^*$ band exhibits a hypsochromic shift with increasing solvent polarity. Its magnitude is comparable for both diastereoisomeric dilactams (about 8–10 nm when solutions in acetonitrile and hexafluoropropanol are taken as references). However, the intensity dependence of this band on solvent polarity is different for both isomers. With increasing polarity the band exhibits hypochromic effect for the *cis*-isomer *I*, whereas the hyperchromic effect is characteristic for the *trans*-isomer *II*. The long wavelength branch of the $\pi-\pi^*$ couplet is red shifted by about 8 nm in *I* when compared with *II*, the intensity being higher for the *trans*-isomer *II*. The dichroic absorption in the region of the $n-\pi^*$ band increases for both compounds with decreasing temperature. The increase is more pronounced in the case of the *trans*-isomer *II*. In addition to the above-mentioned bands a small positive band is detected at about 250 nm in the spectrum of (+)-*II* measured in acetonitrile. Its magnitude decreases with decreasing temperature.

* All the CD measurements and discussions refer to (+)-(1*S*,6*S*)-*I* and (+)-(1*R*,6*S*)-*II*. Since the X-ray data given for *II* correspond to the (−)-(1*S*,6*R*)-enantiomer, the sign of dihedral angles ϕ, ψ, ω and χ_N had to be reversed for the CD discussions.

TABLE VIII

CD Spectra of the dilactams (+)-*I* and (+)-*II* in various solvents

Solvent	$\lambda_{max}([\theta_{max}])^a$		$\lambda([\theta])$ end value
	$n-\pi^*$ band	$\pi-\pi^*_1$ band	
	cis-Isomer (+)-*I*		
Acetonitrile	224(+13·8)	203(−25·7)	185(+4·1)
Ethanol	221(+12·3)	202(−21·8)	191(+5·0)
Water	217(+12·4)	201(−23·1)	187(+6·5)
TFE[b]	217(+9·0)	199(−18·5)	187(+10·2)
HFP[c]	216(+10·3)	197(−23·9)	186(+10·5)
	trans-Isomer (+)-*II*		
Acetonitrile	250(+0·9) 224(−8·3)	196(+38·5)	187(+13·3)
Ethanol	221(−10·0)	192(+45·4)	192(+45·4)
Water	219(−11·0)	193(+41·6)	185(+24·5)
TFE[b]	216(−11·5)	191(+40·5)	185(+30·0)
HFP[c]	214(−15·1)	190(+50·5)	190(+50·5)

[a] Wavelength in nm, $[\theta]$ molar ellipticity . 10^{-3}, deg cm^2 dmol^{-1}; [b] TFE 2,2,2-trifluoroethanol; [c] HFP 1,1,3,3,3-hexafluoro-2-propanol.

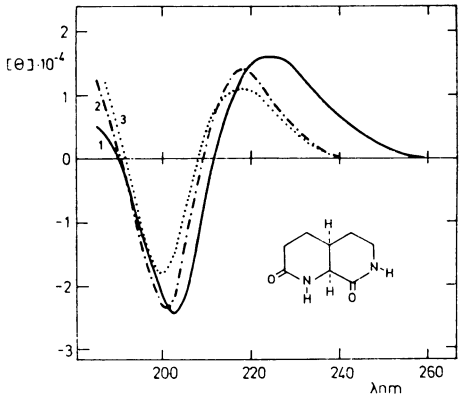


FIG. 5

CD Spectra of (+)-*I* in various solvents, *1* acetonitrile, *2* water, *3* trifluoroethanol

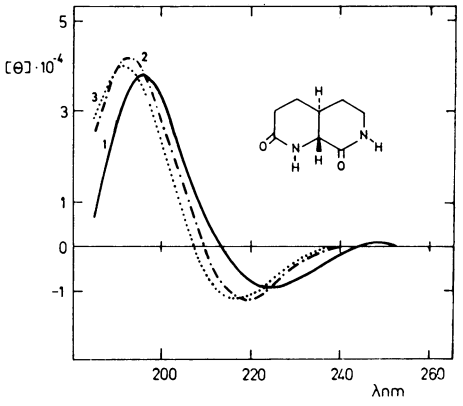


FIG. 6

CD Spectra of (+)-*II* in various solvents, *1* acetonitrile, *2* water, *3* trifluoroethanol

The two principal bands are ascribed to $n-\pi^*$ and $\pi-\pi^*$ transitions on the basis of their position within the wavelength scale together with the solvent-induced shift characteristic for $n-\pi^*$ transitions. The short wavelength branch of the $\pi-\pi^*$ couplet can be also assigned without difficulties. On the other hand, the assignment of the small positive band at the long wavelength side of the $n-\pi^*$ band in the spectrum of the *trans*-isomer (+)-*II* in acetonitrile is not so straightforward and additional information on the geometry of the molecule is needed. According to X-ray analysis, the geometry of both the amide groups in *II* is not equivalent since the group incorporated in the B ring is significantly non-planar. Moreover, the amide groups of *II* take part in the intramolecular hydrogen bond as demonstrated by IR spectral measurements in non-polar solvents and confirmed by the X-ray results in the crystalline state. It is therefore probable that the non-equivalence of the amide groups manifests itself by the indicated splitting of the $n-\pi^*$ band into two oppositely signed components. In accord with this interpretation, the *cis*-isomer *I*, exhibiting no splitting of the $n-\pi^*$ band, possesses essentially planar amide groups and the intramolecular hydrogen bond is of minor importance, if any.

TABLE IX

Temperature dependence of CD spectra of the dilactams (+)-*I* and (+)-*II* in acetonitrile and methanol–ethanol (1 : 1) mixture

Solvent	Temperature °C	$\lambda_{max}([\theta_{max}])^a$ $n-\pi^*$ band	$\lambda([\theta])^a$ end value
		cis-Isomer (+)-*I*	
Acetonitrile	40	225(+11·6)	200(−17·9)
	−40	220(+12·4)	200(−16·6)
Methanol-	+40	220(+7·6)	210(−1·0)
-ethanol	−80	220(+9·2)	210(+3·1)
		trans-Isomer (+)-*II*	
Acetonitrile	+40	250(+0·6)	210(−1·7)
		224(−9·6)	
	−40	250(+0·4)	210(−2·7)
		224(−10·9)	
Methanol-	+40	221(−9·8)	210(+4·6)
-ethanol	−80	220(−12·8)	210(+9·2)

[a] For the units see notes in Table VIII.

The sign of the $\pi-\pi^*$ CD band of dilactams *I* and *II* can be related to skeletal conformation of the molecule using the electric dipole coupling mechanism (ref.[25]). The qualitative MO theory elaborated by Snatzke[25] is applicable to the sign estimation. According to the exciton theory, a couple of oppositely signed bands with equal intensities is expected. In the molecule of the *cis*-isomer (+)-*I* the in-phase combination of individual electric transition moments corresponds to left-handed helical motion of the excited electron (Fig. 7*a*). Since this combination exhibits the attractive interaction between the two transition moments it corresponds to the long wavelength branch of the $\pi-\pi^*$ couplet. Consequently a negative sign is predicted, in accord with the experimental finding. Similarly, the in-phase combination of transition moments in the molecule of the *trans*-isomer (+)-*II* corresponds to a right-handed helicity of the excitation path (Fig. 7*b*) suggesting thus the positive sign for the long wavelength branch, again in accord with the experiment. The identical sign pattern is predicted when the ϕ and ψ dihedral angles are derived from the X-ray data of both dilactams ($\phi = 110°$, $\psi = -143°$ for (+)-*I* and $\phi = -145°$, $\psi = 162°$ for (+)-*II*) and these values are compared with calculations of $\pi-\pi^*$ optical rotatory strength of the dipeptide unit represented by a combination of two tertiary *cis*-amide groups (Fig. 8, ref.[26]). Although this model does not correspond precisely to the dilactams under study which contain two secondary *cis*-amide groups, the geometrical

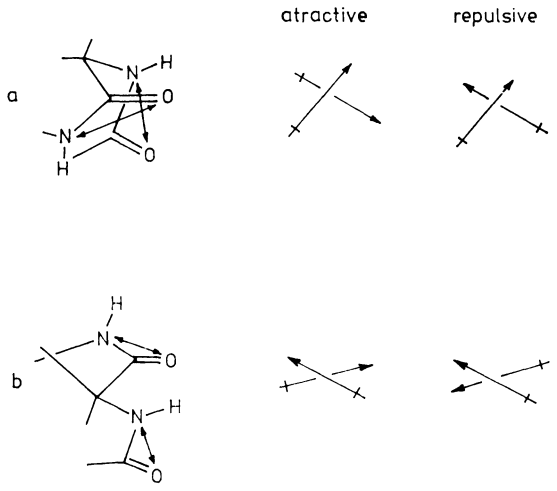


FIG. 7

Exciton coupling of the amide chromophores ($\pi-\pi^*$ transition); *a cis*-isomer (+)-*I*, *b trans*-isomer (+)-*II*. Predicted sign pattern of the $\pi-\pi^*$ couplet: for *a*) first CD band negative, the second positive; for *b*) first CD band positive, the second negative

arrangement is not violated. It is therefore probable that, in accord with previous results obtained with model dipeptides[27] and 2,5-piperazinediones[28], the sign pattern of the $\pi-\pi^*$ couplet is controlled mainly by the interaction of two amide chromophores *via* the electric dipole coupling mechanism.

On the other hand, the $n-\pi^*$ transition possesses only a very small electric transition moment and the sign of the corresponding CD band is controlled by other mechanisms. According to general observations, the optical activity associated with this transition is merely of local origin. The positive sign exhibited by the *cis*-isomer (+)-*I* can be rationalized on the basis of one-electron mechanism as expressed by the known amide quadrant rule (ref.[29]). Although the individual contributions lead to different signs of $n-\pi^*$ rotatory strengths for the two amide groups (Fig. 9), the positive contributions imposed by the atoms $N_{(2)}$, $C_{(3)}$ and $O(C_{(3)})$ on the amide group in the B-ring (Fig. 9*b*) are probably the decisive ones. These atoms act as sources of perturbation which are localized rather closely to the chromophore carbonyl group in the B ring. According to this analysis, the sign of the $n-\pi^*$ band in (+)-*I* is predicted to be positive with the decisive contribution coming from the amide group in the B ring and the minor negative contribution from that in the A ring. Analogously, in the case of the *trans*-isomer (+)-*II* a negative overall sign can be predicted as a consequence of a greater contribution of the amide group in the B ring (Fig. 10). However, the most important contribution determining the $n-\pi^*$ band sign arises probably from the inherent chirality of the non-planar amide group in the B ring. The sign of this contribution can be inferred from the previous experimental and computational studies of lactams possessing non-planar amide chromophores and from the calculations of rotatory strengths as well[30-33]. The specified (*S*, +*ap*) chirality of the amide group in (+)-*II* (Fig. 11, see also ref.[30]) corresponds to a nega-

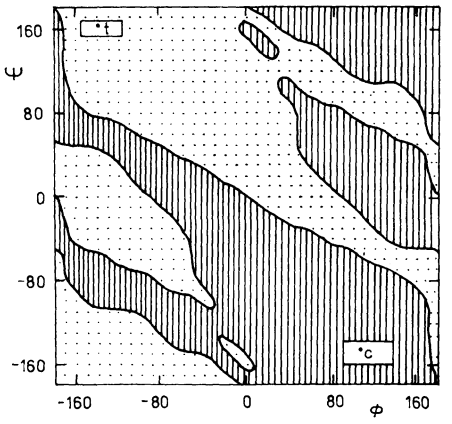


FIG. 8

Map of $\pi-\pi^*$ rotational strength (*cis*,*cis*-peptides, tertiary-tertiary combination). Dotted area (−), hatched area (+), *c cis*-(+)-*I*, *t trans*-(+)-*II*

tive $n-\pi^*$ CD band. Thus, there are at least two contributions to the negative band which is the major feature observed in this spectral region for (+)-*II*. The small positive band detected in acetonitrile solution at about 250 nm might then be assigned to the $n-\pi^*$ transition associated with the planar amide group in the A ring for which the positive sign can be suggested on the basis of the quadrant rule (Fig. 10*a*). The unusual blue shift of the band associated with the non-planar amide group is probably caused by the intramolecular hydrogen bond $N_{(2)}$—H...O=$C_{(10)}$. Since the non-planar amide group participates in this interaction by its carbonyl oxygen atom a considerable blue shift is expected. Thus, the splitting of the $n-\pi^*$ CD band into two components, as well as the observed sign pattern, are in agreement with the concept of two non-equal amide chromophores in the *trans*-isomer *II*.

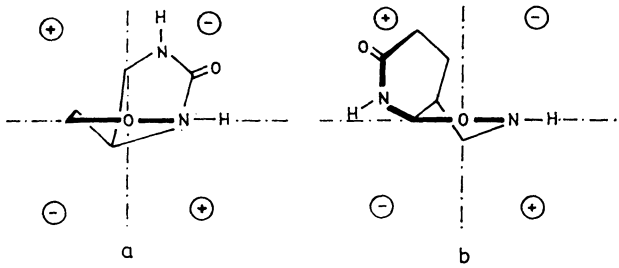


FIG. 9

Application of the amide quadrant rule to the $n-\pi^*$ transition of the *cis*-dilactam (+)-*I*; *a* amide group in the A ring, *b* amide group in the B ring

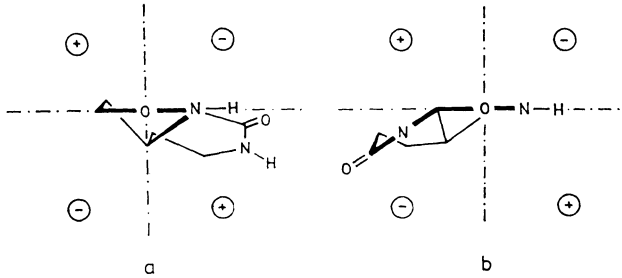
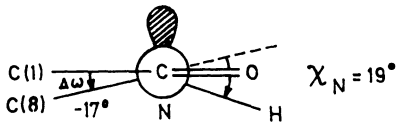


FIG. 10

Application of the amide quadrant rule to the $n-\pi^*$ transition of the *trans*-dilactam (+)-*II*; *a* amide group in the A ring, *b* amide group in the B ring

FIG. 11
Newman projection of the non-planar amide group in the **B** ring of the *trans*-isomer (+)-(1*R*,6*S*)-*II*



The above analysis of the CD spectra conforms well to the conformers found for both dilactams in the crystalline state. In solutions of the *cis*-dilactam *I* two conformers were detected by NMR spectroscopy; however, these two conformers cannot be distinguished on the basis of chiroptical properties since, according to Dreiding models studies, the sign pattern of the CD bands should be identical for both of them.

In general terms, the CD spectra of the model dilactams *I* and *II* are successfully interpreted using the exciton theory for the $\pi-\pi^*$ bands and the combination of the quadrant rule with the inherent chirality of the amide group in *II* for the $n-\pi^*$ band. This finding provides a further proof that in chiral molecules containing homoconjugated amide groups the sign of the $\pi-\pi^*$ transition is controlled by coupling of amide groups while the optical activity of the $n-\pi^*$ band is derived from effects which are merely local in origin, *i.e.* they originate either in the chromophore itself or in its close proximity.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The IR spectra were taken on a Perkin–Elmer 621 instrument, CD spectra on a Jouan CD 185/II Dichrographe. ^{1}H NMR Spectral measurements were carried out on a Varian XL-200 (200 MHz) spectrometer in solutions of about 2 mg of the compound in 0·4 ml of the solvent (deuteriochloroform, hexadeuteriodimethyl sulfoxide, deuterium oxide) with tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standards. The ^{13}C NMR spectra were taken at 30°C on the same instrument (at 50·31 MHz), using solutions of about 10 mg of the compound in 0·4 ml of deuterium oxide (the *cis*-isomer *I* was only sparingly soluble in deuteriochloroform) with hexadeuterioacetone as internal standard ($\delta(C^2H_3COC^2H_3) = 29{\cdot}8$). Both broad band proton decoupled and "attached proton test" spectra were taken. High performance liquid chromatography was carried out on an SP-8700 instrument, equipped with an SP-8400 continuously variable wavelength UV detector and SP-4100 integrator (all from Spectra Physics, Santa Clara, U.S.A.). Analytical chromatography was performed on a 25 × 0·4 cm Separon SI-C-18 column (Laboratorní přístroje, Prague) in methanol–water (20 : 80) containing 0·04% of trifluoroacetic acid as a buffer. Preparative chromatography was run on a 50 × 0·9 cm Partisil-ODS-2 column (Whatman, New Jersey, U.S.A.) in methanol–water (5 : 95).

X-Ray Measurements

Compound I: The crystals are prismatic in habit. Diffraction studies showed the crystals to be monoclinic, space group $P2_1/n$ (absences $h0l$, $h + l = 2n + 1$; $0k0$, $k = 2n + 1$).

Compound II: A prismatic blocky crystal was used for cell parameters determination and subsequent data collection. Preliminary investigation showed the crystal to be tetragonal. The space group was uniquely determined as $P\bar{4}2_1c$ from systematic absences, $00l$, $l = 2n + 1$; hhl, $l = 2n + 1$. Unit cell dimensions for both the compounds were determined from least-squares fit of $+2\Theta$ and -2Θ values of a number of reflections (40 for *I* and 24 for *II*) measured both at room temperature and at 138 K.

For each compound, the intensities of all unique reflections with $2\Theta \leqq 150°$ were measured at 138(2) K using Ni-filtered CuK_α radiation with an Enraf-Nonius CAD-4 automatic diffractometer equipped with a cold-stream low-temperature device. The $\Theta/2\Theta$ scan technique with variable scan width and variable scan speed was employed. The crystal data and specific parameters for data collection are given in Table X. During the data collection, intensities of three standard reflections were monitored after specific periods (3 600 s for *I*, 5 000 s for *II*) and three orientation control reflections were checked every 200 measurements to detect any change in crystal orientation. Neither crystal showed any sign of deterioration. Intensities were corrected for Lorentz and polarizations factors but no absorption correction was made ($\mu =$ $= 7{\cdot}5\ cm^{-1}$ for *trans*- and $7{\cdot}7\ cm^{-1}$ for *cis*-compound).

TABLE X

Crystallographic data and intensity data collection parameters for compounds *I* and *II*

Parameter	*I*		*II*	
Crystal data				
Formula	$C_8H_{12}N_2O_2$		$C_8H_{12}N_2O_2$	
F.W.	168·2		168·2	
Crystal system, space group	monoclinic, $P2_1/n$		tetragonal, $P\bar{4}2_1c$	
Cell parameters	at 138K	at 293K	at 138K	at 293K
a (Å)	6·969(2)	7·023(1)	14·772(8)	14·847(1)
b (Å)	8·788(2)	8·884(1)		
c (Å)	12·748(2)	12·779(1)	7·289(5)	7·423(1)
β(deg)	98·40(2)	98·75(1)		
V (Å^3)	772·4	788·0	1 590·5	1 636·3
Dx (g/cm^3)		1·417		1·365
Z		4		8
Intensity data				
Radiation	CuKα (Ni-filtered)		CuKα (Ni-filtered)	
2θ mas (deg)	150		150	
Scan mode	$\theta - 2\theta$		$\theta - 2\theta$	
Scan width (deg)	(0·80 + 0·20tan)		(1·0 + 0·20 tan)	
Aperture (mm)	(3·00 + 0·86tan)		(4·00 + 0·86tan)	
Max. scane time (s)	90		75	
Crystal size (mm)	0·41 × 0·19 × 0·12		0·50 × 0·48 × 0·15	
Total no. of unique reflections measured	1 578		946	

X-Ray Structure Determination

The structures of both the racemic compounds were solved by the direct methods as incorporated in the program system, SHELX (ref.[34]). Both the structures were refined by full-matrix least-squares routines. All the hydrogen atoms were located from difference Fourier maps. The final stages of the refinements were carried out by using anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. The refinement converged to an *R* factor 0·048 for *I* (all 1 578 reflections) and 0·046 for *II* (all 946 reflections). The final parameters of *I* are listed in Table XI and those of *II* in Table XII.*

2-Amino-2-(4-hydroxyphenyl)acetic Acid (*IIIb*)

Was prepared by hydrolysis of the methoxy acid *IIIa* (ref.[35]) with 48% hydrobromic acid according to a procedure, described[8,9] for the optically active compound.

Mixture of *cis*- and *trans*-2-Benzamido-2-(4-hydroxycyclohexyl)acetic Acid (*V*)

Freshly prepared Raney nickel (10 g) was added to a solution of the amino acid *IIIb* (10 g; 59·7 mmol) in 10% sodium hydroxide (75 ml). The mixture was hydrogenated in a 200 ml rocking autoclave at 100°C and 16—18 MPa. After 3 h the hydrogen uptake ceased. The catalyst was filtered off and the filtrate was cooled in an ice bath. Benzoyl chloride (10·9 g; 78 mmol) was

TABLE XI
Positional parameters of non-hydrogen atoms in *I*

Atom	$x \cdot 10^5$	$y \cdot 10^5$	$z \cdot 10^5$
$O_{(3)}$	−12 468(15)	27 357(13)	−8 922(8)
$O_{(10)}$	−52 953(14)	8 207(13)	12 819(8)
$N_{(2)}$	−20 601(18)	10 348(14)	2 820(9)
$N_{(9)}$	−34 529(18)	9 646(14)	28 893 (10)
$C_{(3)}$	− 9 789(19)	21 979(16)	179(10)
$C_{(4)}$	5 985(21)	28 237(17)	8 406(11)
$C_{(5)}$	3 985(20)	23 737(16)	19 770(10)
$C_{(6)}$	279(20)	6 595(16)	20 149(11)
$C_{(7)}$	− 662(21)	517(16)	31 279(11)
$C_{(8)}$	−16 423(23)	8 434(18)	36 306(11)
$C_{(10)}$	−36 878(20)	7 253(15)	18 361(11)
$C_{(1)}$	−18 974(20)	3 020(16)	13 233(16)

* Supplementary materials containing anisotropic thermal parameters, hydrogen atom parameters, distances, and structure factor tables for the two compounds can be obtained on request from the Oklahoma Laboratory.

added dropwise at 0–5°C with vigorous shaking during 1 h. The mixture was then stirred for 2 h at room temperature and acidified to pH 2 with dilute hydrochloric acid. The precipitated solids were filtered, washed with water (100 ml), ether (100 ml) and dried to give 15·3 g of crude product. Crystallization from 50% aqueous ethanol afforded 13·6 g (82%) of the *cis-trans* mixture *V*. For $C_{15}H_{19}NO_4.H_2O$ (295·3) calculated: 61·06% C, 7·17% H, 4·74% N; found: 61·43% C, 7·12% H, 4·86% N. Mass spectrum: M^+ found: 277·1309, calculated: 277·1314.

2-Amino-2-cyclohexylacetic Acid

The title compound was obtained by hydrogenation of the amino acid *IIIb* (0·5 g) in a mixture of acetic acid (25 ml) and dilute hydrochloric acid (5 ml) over Adams catalyst (400 mg) at room temperature; m.p. 289–290°C (reported[36] m.p. 289–290°C).

Benzoyl derivative: m.p. 202–203°C. For $C_{15}H_{19}NO_3$ (261·3) calculated: 68·94% C, 7·33% H, 5·36% N; found: 69·49% C, 7·42% H, 5·33% N.

Benzamido-2-(4-oxocyclohexyl)acetic Acid (*VI*)

A) *With ruthenium tetroxide*[37]: The hydroxy acid *V* (1·4 g; 5 mmol) was dissolved in a solution of sodium hydrogen carbonate (0·49 g in 5 ml of water). The neutral solution was stirred at room temperature and ruthenium dioxide (10 mg) was added. A solution of sodium periodate (1·5 g; 6 mmol) in water (15 ml) was added dropwise during 1 h. After addition, the mixture was stirred for 10 min and the excess ruthenium tetroxide was destroyed with 2-propanol (0·3 ml). Ruthenium dioxide was filtered off and the filtrate was acidified with dilute hydrochloric acid. The precipitated product was filtered, washed with cold water (20 ml) and dried to give 1·1 g (80%)

TABLE XII

Positional parameters of non-hydrogen atoms in *II*

Atom	$x \cdot 10^5$	$y \cdot 10^5$	$z \cdot 10^4$
$O_{(3)}$	30 408(14)	93 585(13)	752(3)
$O_{(10)}$	28 433(13)	65 122(12)	3 272(3)
$N_{(2)}$	25 315(15)	82 645(15)	2 615(4)
$N_{(9)}$	13 753(15)	61 999(14)	3 931(3)
$C_{(3)}$	24 052(18)	90 073(17)	1 592(4)
$C_{(4)}$	14 558(19)	93 897(17)	1 474(4)
$C_{(5)}$	7 737(18)	89 876(17)	2 822(4)
$C_{(6)}$	8 888(17)	79 629(16)	2 866(4)
$C_{(7)}$	2 355(18)	74 417(18)	4 082(4)
$C_{(8)}$	4 043(20)	64 231(20)	3 918(5)
$C_{(10)}$	20 580(16)	67 670(16)	3 555(4)
$C_{(1)}$	18 358(17)	77 709(17)	3 597(4)

of the keto acid *VI*, m.p. 201–202°C (aqueous ethanol). For $C_{15}H_{17}NO_4$ (275·3) calculated: 65·44% C, 6·22% H, 5·09% N; found: 65·29% C, 6·20% H, 5·12% N. Mass spectrum, *m/z*: 275 (M^+), 230, 179 ($C_9H_9NO_3$), 161 ($C_9H_7NO_2$), 122, 105, 77. IR spectrum (KBr), cm^{-1}: 1 528, 1 633 (C=O), 1 730 (COOH), 3 290 (CONH).

B) *With chromic acid*: Jones reagent[38] (10 ml; 26 mmol) was added dropwise to a stirred solution of the hydroxy acid *V* (6·93 g; 25 mmol) in acetone (200 ml) at 15–20°C. The mixture was stirred for 5 min more and decomposed with 2-propanol. The acetone solution was filtered from the green sludge which was washed with acetone. The solvent was evaporated *in vacuo* and the residue crystallized from aqueous ethanol to afford 5·9 g (86%) of the keto acid *VI*, m.p. 200 to 201°C, identical in all respects with the product obtained by the method *A*).

2-Benzamido-2-(4-oximinocyclohexyl)acetic Acid (*VII*)

The racemic keto acid *VI* (6·0 g; 21·8 mmol) was dissolved in a solution of sodium hydrogen carbonate (2·15 g; 25 mmol) in water (25 ml). A solution of hydroxylamine hydrochloride (2·1 g; 30 mmol) and sodium acetate trihydrate (4·3 g; 31·6 mmol) in water (15 ml) was added and the mixture was stirred for 10 min and left overnight at room temperature. The precipitated product was collected on filter, washed with cold water and dried to give 4·2 g (66%) of *VII*, m.p. 204–207°C (decomposition). Acidification of the mother liquors gave further product (1·9 g), m.p. 202–205°C, the total yield being 6·1 g (96%). The crude product was used directly in the next step. A sample was crystallized from aqueous methanol, m.p. 213–214°C (decomposition). For $C_{15}H_{18}N_2O_4$ (290·3) calculated: 62·05% C, 6·25% H, 9·65% N; found: 62·06% C, 6·20% H, 9·55% N. IR spectrum (KBr), cm^{-1}: 1 531, 1 641, 3 340 (CONH); 1 703, 1 730 (sh), 3 000 (diffuse) (COOH); 732, 3 350 broad (=NOH). Mass spectrum, *m/z*: 290 (M^+), 288 ($M^+ - H_2$), 179, 161, 152, 105, 77.

Stereoisomeric 2-Benzamido-2-(5-aza-4-oxocycloheptyl)acetic Acids (*VIIIa*, *VIIIb*)

A) *With polyphosphoric acid*: The powdered oxime *VII* (2·9 g; 10 mmol) was added under stirring at 115°C to polyphosphoric acid (30 g). The stirred solution was kept at 120–125°C for 2 min, cooled rapidly and decomposed with crushed ice (40 g). The precipitate was filtered, washed with water and dried to give 2·62 g (90%) of material, melting at 255–268°C (decomposition). An analytical sample was crystallized from aqueous ethanol; m.p. 268–272°C (decomposition). For $C_{15}H_{18}N_2O_4$ (290·3) calculated: 62·05% C, 6·25% H, 9·65% N; found: 62·11% C, 6·26% H, 9·48% N. IR spectrum (KBr), cm^{-1}: 1 529, 1 633 (amide), 1 668 (lactam), 1 715 (COOH).

B) *With benzenesulfonyl chloride*: The oxime *VII* (2·9 g; 10 mmol) was dissolved in 15 ml of sodium hydrogen carbonate solution (2·6 g; 30 mmol). Benzenesulfonyl chloride (2·1 g; 12 mmol) was added dropwise at 0–5°C with stirring during 0·5 h. After stirring for 4 h at room temperature, the precipitated solid was filtered, washed successively with water (15 ml), ethanol (3 ml) and ether (10 ml) and dried, affording 2·67 g (92%) of product, m.p. 259–267°C (decomposition), identical with the compound obtained by rearrangement with polyphosphoric acid.

Stereoisomeric 2-Amino-3-(2-aminoethyl)hexane-1,6-dioic Acids (*IXa* and *Xa*)

The crude rearrangement product *VIII* (4 g; 13·8 mmol) was refluxed with concentrated hydrochloric acid (40 ml) for 3 h. The mixture was cooled, extracted with ether (3 × 10 ml) and the aqueous layer was taken down *in vacuo*. The amorphous and hygroscopic residue (3·8 g; 99·5%)

was dissolved in water (5 ml) and applied on a column of Dowex 50 (H^+-form; 100 ml). After removal of hydrochloric acid by washing with water, the product was eluted with 3% aqueous ammonia. The eluate (150 ml) was coevaporated three times with water under reduced pressure, affording 2·7 g (96%) of hygroscopic material, m.p. 153–157°C. For $C_8H_{16}N_2O_4.H_2O$ (222·2) calculated: 43·24% C, 8·16% H, 12·60% N; found: 43·54% C, 8·14% H, 12·40% N.

cis- and *trans*-2,9-Diazabicyclo[4.4.0]decane-3,10-diones (*I* and *II*)

A) *By pyrolysis*: A mixture of the stereoisomeric acids *IXa* nad *Xa*, obtained in the preceding experiment (2·23 g; 10 mmol), was heated to 180–220°C at 15 Pa. The sublimed material was resublimed at 220–240°C/15 Pa, affording 1·1 g (68·7%) of a mixture of the dilactams *I* and *II*. Fractional crystallization from ethanol afforded 390 mg of pure *cis*-dilactam *I*, m.p. 228–229°C. For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·13% C, 7·19% H, 16·66% N; found: 56·90% C, 7·28% H, 16·72% N. IR spectrum (KBr), cm^{-1}: 1 640, 1 657 (C=O), 3 240, 3 295 (NH). Mass spectrum: M^+ calculated: 168·0899; found: 168·0899.

The *trans*-isomer *II* (210 mg), m.p. 186–188°C, was obtained from the mother liquors. For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·13% C, 7·19% H, 16·66% N; found: 57·91% C, 7·17% H, 16·87% N. IR spectrum (KBr), cm^{-1}: 1 634, 1 666 (C=O), 3 080, 3 205, 3 378 (NH). Mass spectrum, *m/z*: 168 (M^+), 139, 123, 110.

B) Via *the ester*: Thionyl chloride (1·1 g) was added dropwise to cold (−10°C) methanol (10 ml) and the mixture was stirred at −10°C for 15 min. A solution of the crude dihydrochlorides of *IXa* and *Xa* (0·5 g; 1·8 mmol) obtained by hydrolysis of the Beckmann rearrangement product (*vide supra*) in methanol (10 ml) was added. After stirring for 1 h at −5°C and for 4 h at 60°C, the mixture was taken down *in vacuo* and the residue was coevaporated three times with methanol *in vacuo*. The residue (mixture of dihydrochlorides of the esters *IXb* and *Xb*) (0·54 g; 98%) was dissolved in methanol (10 ml), the solution was adjusted with triethylamine to pH 8–9 and refluxed for 30 min. After evaporation, the residue was dissolved in water (5 ml) and applied on a column of Dowex 50 (H^+-form; 100 ml) and eluted with water. The first (acidic) fractions of the eluate were discarded and the neutral fraction was collected. Evaporation *in vacuo* yielded 165 mg (54%) of a mixture of *I* and *II* in the ratio of about 1 : 1. Crystallization from ethanol gave 35 mg of pure *I*, m.p. 227–229°C, and 18 mg of *II*, m.p. 185–187°C; the products were identical with the compounds obtained by the procedure *A*).

Isomerization of Dilactams *I* and *II*

A solution of the pure dilactam *I* or *II* (2 mg) in 0·5M sodium methoxide (1 ml) was kept at room temperature and the *I* : *II* ratio was followed by HPLC. Both isomers afforded the same mixture, containing *I* and *II* in the ratio 36·6 : 63·4. The equilibrium was achieved after 15 min and 30 min when starting from *I* and *II*, respectively. An attempted equilibration of *I* or *II* by reflux with an excess of triethylamine in methanol proceeded only slowly, affording less than 10% of *II*, from *I* after 1 h.

(2*RS*,3*RS*)-2-Amino-3-(2-aminoethyl)hexane-1,6-dioic Acid (*IXa*)

A mixture of pure dilactam *I* (200 mg) and concentrated hydrochloric acid (10 ml) was refluxed for 2 h, taken down *in vacuo* and the residue was coevaporated three times with water to give 329 mg (100%) of dihydrochloride of *IXa*. For $C_8H_{18}N_2O_4Cl_2$ (277·2) calculated: 34·66% C, 6·54% H, 10·10% N, 25·63% Cl; found: 34·47% C, 6·57% H, 10·19% N, 25·72% Cl. The free acid *IXa* (50 mg; 97%), m.p. 205–207°C, was obtained by applying a solution of the dihydro-

chloride (64 mg) in water (2 ml) on a column of Dowex 50 (H^+-form) and elution with water and then 3% aqueous ammonia as described for the mixture of *IXa* and *Xa*. For $C_8H_{16}N_2O_4.H_2O$ (222·2) calculated: 43·24% C, 8·16% H, 12·60% N; found: 43·02% C, 8·13% H, 12·45% N.

The diacid *IXa* was cyclized as described for the mixture of *IXa* and *Xa* (procedure *B*) affording the *cis*-dilactam *I*, free of *II*.

(2*RS*,3*SR*)-2-Amino-3-(2-aminoethyl)hexane-1,6-dioic Acid (*Xa*)

Pure *trans*-dilactam *II* (200 mg; 1·19 mmol) was hydrolyzed with conc. hydrochloric acid (10 ml) in the same way as described for *I*, yielding 329 mg (100%) of the dihydrochloride of *Xa*, m.p. 195–197°C. The free acid *Xa* was liberated in 97% yield on a column of Dowex 50 (H^+-form); m.p. 155–157°C (decomposition). For $C_8H_{16}N_2O_4.H_2O$ (222·2) calculated: 43·24% C, 8·16% H, 12·60% N; found: 43·11% C, 8·16% H, 12·69% N.

Cyclization of the acid *Xa* gave the *trans*-dilactam *II* which did not contain any *I*.

(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetic Acid ((−)-*IIIb*)

The acid was prepared by a known procedure[9]; m.p. 223–225°C (dec., water); $[\alpha]_D^{22}$ −158° (*c* 1, 1M-HCl); reported[8,10,39] m.p. 225°C (dec.), $[\alpha]_D^{22}$ −159° (*c* 1, 1M-HCl).

Mixture of *cis*- and *trans*-(2*R*)-2-Amino-2-(4-hydroxycyclohexyl)acetic Acids ((2*R*)-*IV*)

The acid (−)-*IIIb* (3 g; 18 mmol) was hydrogenated in water (150 ml) over Raney nickel (8 g) at 85°C and 15 MPa in a rocking autoclave. After 4 h the hydrogen uptake ceased, the catalyst was filtered off and the filtrate was taken down *in vacuo* affording 3 g (96%) of (2*R*)-*IV*, m.p. 254–257°C (dec.); $[\alpha]_D^{22}$ −37° (*c* 1, 1*M*-HCl). For $C_8H_{15}NO_3$ (173·2) calculated: 55·47% C, 8·73% H, 8·08% N; found: 55·45% C, 8·64% H, 7·98% N.

Mixture of *cis*- and *trans*-(2*R*)-2-Benzamido-2-(4-hydroxycyclohexyl)acetic Acids ((2*R*)-*V*)

The acid (−)-*IV* (2·2 g; 12·7 mmol) was benzoylated in 3M-NaOH (12·7 ml) as described for the racemic compound, affording 2·41 g (86%) of the product, m.p. 185–194°C, $[\alpha]_D^{22}$ −32° (*c* 0·2, ethanol). For $C_{15}H_{19}NO_4$ (277·3) calculated: 64·91% C, 6·91% H, 5·05% N; found: 64·30% C, 6·85% H, 5·00% N.

(2*R*)-2-Benzamido-2-(4-oxocyclohexyl)acetic Acid ((−)-*VI*)

a) *By oxidation of* (2R)-V: The mixture of optically active hydroxy acids (2*R*)-*V* obtained in the preceding experiment (1·5 g; 5·4 mmol) was oxidized as described for the racemic material. The keto acid (−)-*VI* was taken up in dichloromethane and crystallized from ethyl acetate; m.p. 166–167°C, $[\alpha]_D^{22}$ −66·5° (*c* 0·2, chloroform). Yield 1·1 g (74%). The product was optically pure according to the ^1H NMR spectrum in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium. For $C_{15}H_{17}NO_4$ (275·3) calculated: 65·43% C, 6·22% H, 5·09% N; found: 64·92% C, 6·12% H, 4·78% N. Mass spectrum, *m/z*: 275 (M^+), 230, 179 (HOOC—CH—$NHCOC_6H_5$), 161 (179–18), 105, 77. The IR spectrum was identical with that of the racemic compound.

b) *By resolution of racemic acid* VI: A warm solution of the racemic acid *VI* (11·0 g; 40 mmol) and quinine (13·6 g; 40 mmol) in 2-propanol (60 ml) was set aside overnight. The precipitated salt was filtered, washed with 2-propanol (10 ml) and ether (15 ml) and dried. The crude salt

(11·2 g) was crystallized twice from 2-propanol, affording 9·7 g of material of $[\alpha]_D^{22}$ −122° (*c* 0·5; ethanol). This salt (9·5 g) was decomposed with dilute hydrochloric acid and the liberated acid was taken up in dichloromethane (3 × 15 ml). After drying over sodium sulfate and evaporation of solvent, the residue (3·3 g) was crystallized from ethyl acetate to give 2·9 g (53%) of (−)-*VI*, m.p. 166–167·5°C; $[\alpha]_D^{22}$ −68·7° (*c* 0·5; chloroform).

(2*R*)-2-Benzamido-2-(4-oximinocyclohexyl)acetic Acid ((−)-*VII*)

A solution of hydroxylamine hydrochloride (0·51 g) and sodium hydrogen carbonate (0·61 g) in water (4 ml) was added to the keto acid (−)-*VI* (2 g; 7·27 mmol) which had been dissolved in a sodium hydrogen carbonate solution (0·61 g in 10 ml of water). After standing for 5 min, further hydroxylamine hydrochloride solution (0·51 g in 3 ml of water) was added slowly. After standing overnight in a refrigerator, the product was filtered, washed with cold water (5 ml) and dried, affording 1·88 g (89%) of (−)-*VII*, m.p. 185–188°C (dec., water); $[\alpha]_D^{22}$ −44·5° (*c* 0·2; ethanol). For $C_{15}H_{18}N_2O_4$ (290·3) calculated: 62·05% C, 6·25% H, 9·65% N; found: 62·37% C, 6·15% H, 9·69% N. Mass spectrum: M^+ calculated: 290·1266; found: 290·1267.

Stereoisomeric (2*R*)-2-Benzamido-2-(5-aza-4-oxocycloheptyl)acetic Acids ((2*R*)-*VIIIa* and (2*R*)-*VIIIb*)

Benzenesulfonyl chloride (1·24 g; 7·0 mmol) was added during 1 h at 0°C to a stirred solution of the oximino acid (2*R*)-*VII* (1·45 g; 5·0 mmol) in aqueous sodium hydroxide (0·6 g in 15 ml of water). Stirring was continued for 2 h at 5–10°C. The acidic (pH 2) reaction mixture was decanted from the sticky material and set aside in a refrigerator overnight. The precipitated product was filtered, washed with cold water (5 ml) and dried, affording 0·82 g (56%) of a mixture of (2*R*)-*VIIIa* and (2*R*)-*VIIIb*, m.p. 234–240°C (dec.), $[\alpha]_D^{22}$ −52° (*c* 0·1; ethanol). For $C_{15}H_{18}$·N_2O_4 (290·3) calculated: 62·05% C, 6·24% H, 9·65% N; found: 62·73% C, 6·15% H, 9·51% N. IR spectrum (KBr), cm^{-1}: 1 529, 1 633 (CONH in amide); 1 668 (CONH in lactam); 1 715 (COOH).

cis-(1*R*,6*R*)- and *trans*-(1*R*,6*S*)-2,9-Diazabicyclo[4.4.0]decane-3,10-dione ((−)-*I* and (+)-*II*)

A mixture of dihydrochlorides of (2*R*)-*IXa* and (2*R*)-*Xa* (500 mg), obtained by hydrolysis of the Beckmann rearrangement product, ((2*R*)-*VIIIa* and (2*R*)-*VIIIb*; 530 mg) was cyclized *via* the esters in the same manner as described for the racemic material (procedure *B*), yielding 200 mg (67%) of a mixture of (−)-*I* and (+)-*II*. The products were separated by HPLC in water–methanol (4 : 1) to give 22 mg of (−)-*I*, m.p. 217–219°C, $[\alpha]_D^{22}$ −8·12° (*c* 0·5; ethanol). For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·13% C, 7·19% H, 16·66% N; found: 57·17% C, 6·93% H, 16·16% N. Its IR spectrum in chloroform was identical with that of the racemic material. (+)-*II* (30 mg), m.p. 212–213°C, $[\alpha]_D^{22}$ +38·4° (*c* 0·7; ethanol). For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·13% C, 7·19% H, 16·66% N; found: 56·48% C, 7·00% H, 16·46% N.

cis-(1*S*,6*S*)-2,9-Diazabicyclo[4.4.0]decane-3,10-dione ((+)-*I*)

A solution of (+)-*II* (35 mg) in 0·5M sodium methoxide solution (10 ml) was kept at room temperature for 1 h. After neutralization with gaseous carbon dioxide, the precipitated salt was filtered and the solution was taken down under reduced pressure. The solid mixture of stereoisomeric dilactams was separated by preparative HPLC in methanol–water (4 : 1), affording 9 mg of (+)-*I*, m.p. 216–219°C, whose CD curve was a mirror image of that of the (−)-enantiomer.

trans-(1*S*,6*R*)-2,9-Diazabicyclo[4.4.0]decane-3,10-dione ((−)-*II*)

The title compound, m.p. 211—213°C, was obtained (8 mg) by epimerization of (−)-*I* (20 mg) according to the procedure described for (+)-. The CD spectrum of the resulting (−)-*II* was a mirror image of that of its (+)-enantiomer.

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