CONFORMATION OF 6-AMINO-6-DEOXYHEXONOLACTAMS

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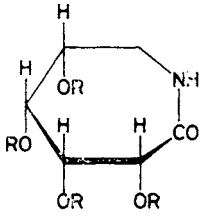
Dedicated to Prof. Jaroslav Staněk on the occasion of his 70th birthday.

Eight configurational isomers of 6-amino-6-deoxyhexonolactam *Ia*–*VIIIa* and their tetra-O-acetyl derivatives *Ib*–*VIIIb* were studied using NMR and CD spectroscopy. For all the compounds most values of chemical shifts of the ^1H and ^{13}C nuclei as well as of vicinal coupling constants were obtained. Comparison of the observed values with $^3J(H, H)$ values, calculated for various conformations of the studied compounds by a modified Karplus relationship, led to assignment of predominant conformation $^{1,N}C_4(D)$ or $^4C_{1,N}(D)$ to the lactams *Ia*–*VIIIa* and *Ib*–*VIIIb* in solution. For the measured set of compounds, the decisive conformation-determining requirement seems to be the equatorial position of substituent on the carbon next to the carbonyl group. The CD spectra of the lactams *Ia*–*VIIIa* in water, interpreted according to the currently used rules, in six cases agreed and in two cases disagreed, with the NMR results. The reasons of this discrepancy are discussed.

The seven-membered lactams attract considerable attention of chemists particularly thanks to the great importance of the parent compound – ε-caprolactam. As has been found[1] by X-ray diffraction, the geometry of this compound almost corresponds to the theoretically assumed planar "amide" segment C_2—C_1—N—C_6, which, together with the remaining atoms C_3–C_4–C_5 forms a chair conformation as the energetically most advantageous form. A similar result was obtained by other authors[2–6] in studies of various substituted seven-membered lactams, either monocyclic or with the ring attached to another cycle. Similarly to the six-membered ring, also the seven-membered ring can exist in another basic conformation – in the boat form. As estimated by American authors[2], the energy barrier of the chair-boat inversion for γ,γ-difluoro-ε-caprolactam amounts to 43·5 kJ mol^{-1} which is comparable with the values of 37·7–46 kJ mol^{-1} found for the same conformational process in cyclohexane[7,8]. However, no proof of a seven-membered lactam in a boat

conformation exists so far, the only exception being a study of Japanese authors[9] who, on the basis of ESR spectra, assigned boat conformation to the ε-caprolactam radical. It thus seems that the chair conformation, either of the $^4C_{1,N}$ or $^{1,N}C_4$ type (Fig. 1), represents in general the most favourable spatial arrangement of a seven--membered lactam. On the other hand, Klyne and co-workers[6] have shown that conformational situation in a seven-membered lactam may be considerably changed when it is attached to another cycle: in such cases the conformation of the ε-caprolactam ring deviates more or less from the nearly ideal chair geometry. A similar effect could be brought about by mutually interacting substituents on the carbon chain which affect not only the $^4C_{1,N} \rightleftharpoons {}^{1,N}C_4$ conformational equilibrium in the lactam molecule but also the magnitude of the ring torsion angles and the height of



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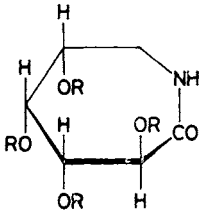

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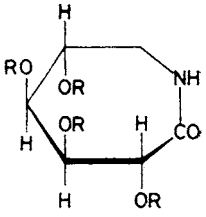

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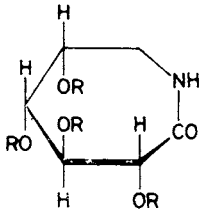

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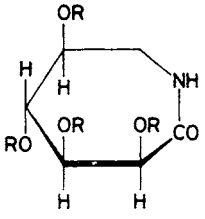

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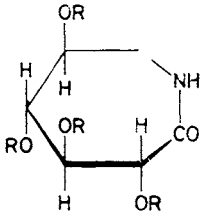

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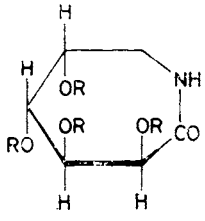

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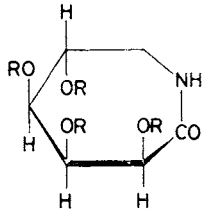

VIII

In formulae *I*–*VIII*: *a*, R = H *b*, R = $COCH_3$

the chair-boat energy barrier. No study has been made so far on a complete set of seven-membered lactams, with the aim to evaluate the effect of ring substituents in various configurational arrangements on the conformation of the lactam molecule. Our communication presents the results of a ^1H and ^{13}C NMR study of the eight possible configurational isomers of 6-amino-6-deoxyhexonolactam and their tetra--O-acetyl derivatives, together with the CD spectra of the former.

EXPERIMENTAL

The studied compounds, 6-amino-6-deoxy-D-allonolactam (*Ia*), 6-amino-6-deoxy-D-altronolactam (*IIa*), 6-amino-6-deoxy-D-galactonolactam (*IIIa*), 6-amino-6-deoxy-D-gluconolactam (*IVa*), 6-amino-6-deoxy-L-gulonolactam (*Va*), 6-amino-6-deoxy-L-idonolactam (*VIa*), 6-amino-6--deoxy-D-mannonolactam (*VIIa*), 6-amino-6-deoxy-D-talonolactam (*VIIIa*) and the corresponding 2,3,4,5-tetra-O-acetyl-6-amino-6-deoxyhexonolactams *Ib*—*VIIIb*, were prepared by the described procedures[10–14] and were characterized[14] by the usual physical constants. Their purity was checked by elemental and chromatographic analysis. In order to consider a consistent set of compounds, instead of the four compounds of the L-configuration (i.e. *Va*, *Vb*, *VIa* and *VIb*) we discuss (and tabulate) their D-enantiomers. Naturally, this purely formal transaction has no influence on the conclusions drawn from the measured data save that the discussed and tabulated conformations relate to enantiomers of the actually measured compounds *Va*, *Vb*, *VIa* and *VIb*. Accordingly, also the sign of the actually measured CD bands of compounds *Va* and *VIa* is reversed.

The NMR spectra were measured on a Bruker AM 400 instrument (^1H at 400·13 MHz, ^{13}C at 100·62 MHz), the free lactams *Ia*—*VIIIa* in deuterium oxide with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as standard ($\delta_C(CH_3) = -1{\cdot}61$ ppm), the tetra-O-acetyl derivatives *Ib*—*VIIIb* in deuteriochloroform with tetramethylsilane as internal standard. Unless stated otherwise, the measurements were performed at 24°C. The digital resolution for ^1H measurement was 0·18 Hz, for ^{13}C 0·8 Hz; matched exponential filter; resolution enhancement for J(H, H) determination. Spin–spin coupling constants were obtained by first order analysis. Proton signals were assigned using decoupling experiments or 2 D homonuclear correlated spectra (COSY, COSY with double quantum filter); assignment of the ^{13}C signals was verified by the ATP (attached proton test) and 2 D heterocorrelated experiments.

The CD spectra were obtained on a Jobin–Yvon Dichrographe Mark V instrument equipped with a data processor. The measurements were carried out at room temperature in a 0·05 cm cell

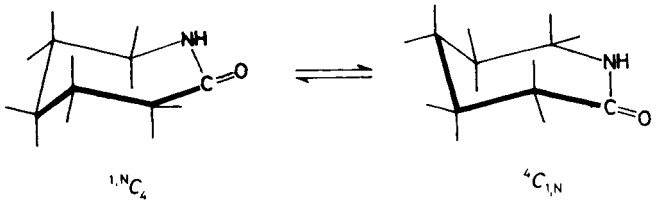

FIG. 1
ε-Caprolactam in the chair form

in the range 190—260 nm. Lactam concentration was about $2 . 10^{-3}$ mol l^{-1}, distilled water was used as solvent. The data are given as the difference of molar absorption coefficients for the left and right circularly polarized light $\Delta\varepsilon = \varepsilon_L - \varepsilon_R$ (cm^2 $mmol^{-1}$).

RESULTS AND DISCUSSION

NMR *Measurements of Lactams* Ia—VIIIa *and* Ib—VIIIb

The chemical shifts of the ^1H and ^{13}C lactam ring atoms, together with the $^3J(H, H)$ coupling constants, found in the spectra of compounds *Ia—VIIIa* and *Ib—VIIIb*, are summarized in Tables I and III. Most of the data in Table I were obtained by analysis of first order spectra. In the case of the complex ^1H NMR spectrum of 6-amino-6-deoxy-D-talonolactam (*VIIIa*), some chemical shifts and coupling constants were obtained by iterative correction of estimated values, leading to an optimal simulated spectrum, practically identical with the experimental one.

On the whole, the position of the proton signal corresponds to the general experience, e.g., signals of the axial protons H-3, H-4 and H-5 are located more upfield than those of equatorial protons. The only exception is the C-6 methylene group in both the free lactams and their tetraacetyl derivatives: here, the position of the signals is reversed, i.e. the H-6a signal appears downfield relative to the H-6e one. This somewhat unexpected relation of chemical shifts resembles analogous results found by Anteunis[15] for a series of substituted 1,3-dioxanes. The proton signals in the spectra of tetraacetyl derivatives are generally shifted downfield relative to those of the free lactams. This downfield shift for an acetylated lactam depends on the conformational character of the given proton (axial or equatorial) and also on the position of the neighbouring acetoxy groups. Thus, for example, the signal of H-2a proton with neighbouring equatorial 3-acetoxy group is located at 1·02—1·09 ppm higher δ for the tetraacetyl derivative than for the free lactam, the signal of the same proton with adjacent axial 3-acetoxy group has δ higher by 0·91—1·01 ppm. Still greater effects are observed for signals of the H-3 and H-4 protons (see, e.g., $\Delta\delta$ + 1·92 ppm for H-3a in lactam *VIb* vs *VIa*, or $\Delta\delta$ + 1·23 ppm for H-4e in lactam *Vb* vs *Va*). The downfield shift of δ was also observed with the H-6a and H-6e proton signals (approximately for 0·1—0·2 ppm for the tetraacetyl derivatives).

During our ^1H NMR spectral measurements of the free lactams in deuterium oxide we observed in some cases hydrolysis of the amide bond, leading to 6-amino-6-deoxyhexonic acid which could be followed by increase in intensity of the corresponding signals at appropriate time intervals. It seems that the hydrolysis rate depends on the lactam geometry: some isomers did not change at all, the *allo*- and *gulo*-isomers gave traces of the acid already during the first minutes after dissolution whereas in the case of the *manno*-isomer the acid was detected only after several hours. At room temperature, the hydrolyses proceeded by different rates: whereas the mannonolactam gave not more than 5% of the acid even after several

TABLE I

Proton NMR spectra of 6-amino-6-deoxyhexonolactams *Ia*—*VIIIa* and their 2,3,4,5-tetra-O-

Compound	Chemical shifts δ, ppm						
	H-2	H-3	H-4	H-5	H-6a	H-6e	NH
Ia	4·57	4·12	3·84	4·00	3·44—3·34		—
Ib	5·49	5·64	5·17—3·55		3·65—3·55		6·19
IIa	4·65	3·68	4·20	3·75	3·66	2·97	—
IIb	5·73	5·37	5·62	4·94	3·84	3·12	6·93
IIIa	4·58	3·87—3·82	4·00	3·87—3·82	3·63	3·28	—
IIIb	5·60	5·49	5·34	4·94	3·75	3·49	6·45
IVa	4·27	3·55	3·67	4·07	3·46	3·36	—
IVb	5·36	5·47	5·18—5·25	5·18—5·25	3·66—3·52		6·87
Va	4·72	3·97	4·04	3·78	3·61	3·34	—
Vb	5·73	5·23	5·27	4·80	3·77	3·54	5·84
VIa	4·40	3·40	3·51	3·48	3·34	3·20	—
VIb	5·47	5·32	5·41	4·88	3·51	3·39	6·93
VIIa	4·81	4·06—4·03		3·87	3·64	2·96	—
VIIb	5·76	5·33	5·42	5·04	3·85	3·11	6·79
VIIIa	4·62	4·09	3·66	3·63	3·23	3·17	—
VIIIb	5·53	5·71	5·21	5·05	3·45	3·35	6·42

[a] Proton signals of the CH_3CO–groups, affording mostly four well-separated singlets of δ 2·02 to 0·2 Hz.

days, for allonolactam the extent of conversion was 42% after 14 days and 65% after 6 weeks. The fastest hydrolysis was observed with gulonolactam which after six days afforded 60% and after 36 days more than 95% of the acid. In the spectra the arising acids were well detectable, being characterized particularly by two signals at δ 3·2 and 3·1 due to the H-6 and H-6′ protons, and by an H-2 proton doublet at δ 4·1—4·2. The chemical shifts and coupling constants for 6-amino-6-deoxy-D--allonic acid (*IX*) and 6-amino-6-deoxy-L-gulonic acid (*X*) are given in Table II. The spectrum of the former acid was obtained by measuring its mixture with the lactam and was correlated with the spectrum of pure acid, prepared by a described procedure[12].

Carbon-13 NMR spectra of the free lactams and their tetraacetyl derivatives are given in Table III. Although they reflect the configurational differences, we did not find more general correlations between the spectral parameters and configuration.

TABLE I

-acetyl derivatives[a] *Ib*—*VIIIb*

Coupling constants, Hz							
J(2, 3)	*J*(3, 4)	*J*(4, 5)	*J*(5, 6a)	*J*(5, 6e)	*J*(NH, 6a)	*J*(NH, 6e)	*J*(6a, 6e)
0·8	4·3	1·3	—[b]	—[b]	—	—	—[b]
0·5	2·7	2·9	0·3	2·0	5·3	6·9	15
10·3	—[c]	—[c]	10·3	—[c]	—	—	13
10·9	2·4	2·1	10·2	—[c]	5·2	8·5	15·4
9·1	—[c]	5·6	—[c]	5·6	—	—	14
8·4	2·5	6·4	—[c]	5·6	7·0	7·0	16
10·0	9·4	3·3	—[c]	5·4	—	—	15·7
10·6	9·1	3·3	—[c]	7·2	5·8	7·2	—[b]
—[c]	4·5	4·6	—[c]	4·9	—	—	14
0·3	4·6	3·5	—[c]	5·0	5·3	7·3	16·5
10·1	9·9	10·0	10·1	2·1	—	—	14·4
10·1	9·0	8·7	10·2	3·2	6·0	7·5	15·9
—[c]	6·3	—[c]	10·2	—[c]	—	—	14·6
0·5	5·4	2·6	9·5	—[c]	8·5	—[b]	15
1·1	3·9	9·4	9·5	3·7	—	—	15·4
0·3	3·0	10·1	10·4	3·2	5·3	8·4	15·4

2·20, are not given; [b] not accessible from first order analysis; [c] not resolved or smaller than

At 24°C the spectrum of 2,3,4,5-tetra-O-acetyl-6-amino-6-deoxy-D-galactonolactam (*IIIb*) exhibited an overlap of the C-2 and C-3 signals and, moreover, all the signals were unusually broad. On the other hand, at −60°C we observed sharply separated signals of two conformers in the ratio 1 : 2·2 (coalescence temperature for C-6 of about −25°C, $\Delta\delta$ C-6_{max} = 4). As indicated by the shape of signals, a similar conformational lability exists also in the tetraacetyl derivative of the *manno*-configuration; it was however not verified by temperature dependence measurements. This conclusion is also supported by the spin coupling constants ^3J(H, H).

Conformational considerations concerning the lactams *Ia*—*VIIIa* and *Ib*—*VIIIb* should be based on the above-mentioned fact that overwhelming majority of the hitherto described compounds of this type exists in the chair conformation of the seven-membered lactam ring. For the beginning we may assume that the actual geometry of the equilibrium conformations is similar to that of the forms in Fig. 1. In

polysubstituted seven-membered lactams the conformational equilibrium is probably influenced by steric interactions between the substituents, as is the case with cyclohexane derivatives in the chair conformation. Conformational positions of the hydroxy or acetoxy groups, attached to the ring in the eight stereoisomeric 6-amino-6-deoxy-D-hexonolactams in conformations $^{1,N}C_4$ and $^4C_{1,N}$, are given in Table IV. As seen from these data, we may expect predominant $^{1,N}C_4$(D) conformation in the *ido-*, *altro-*, *gulo-* and *talo*-isomers and $^4C_{1,N}$(D) conformation in the *gluco*-isomer. Lactams of the *allo-*, *galacto-* and *manno*-configuration have the same number of axial and equatorial substituents in both conformations and therefore, unless other factors are considered, it is difficult to predict the predominant conformation.

From the corresponding coupling constants in the ^{1}H NMR spectra of the lactams it is possible to calculate approximate magnitude of the torsion angles between the C—H bonds using the Karplus relationship, and thus to obtain information on steric arrangement of the given part of the molecule. From the practical viewpoint often more advantageous may be the reversed procedure consisting in comparison of the measured coupling constants with those calculated for a given conformation of the compound by the Karplus equation from parameters obtained by measurement of an accurate molecular model. For this procedure we chose a Karplus relationship, modified according to Netherlandish authors[16], in which the dependence of the magnitude of ^3J(H, H) on the cosine of dihedral angle between the studied C—H bonds is made more accurate by further parameters which evaluate the effect of electronegativity of other geminal and vicinal substituents according to their steric position (see Eqs (*1*) and (*2*)).

TABLE II

Proton NMR spectra of 6-amino-6-deoxy-D-allonic acid (*IX*) and 6-amino-6-deoxy-L-gulonic acid (*X*) in deuterium oxide

Compound	Chemical shifts δ, ppm/coupling constants ^3J(H, H), Hz					
	H-2	H-3	H-4	H-5	H-6	H-6′
IX	4·19	3·99	3·89	4·11	3·29	3·13
	J(2,3) = 3·2	J(3,2) = 3·2	J(4,3) = 7·1		J(6,5) = 3·5	J(6′,5) = 8·5
		J(3,4) = 7·1	J(4,5) = 4·7		J(6,6′) = 13·1	J(6′,6) = 13·1
X	4·13	3·90	3·79	4·03	3·21	3·12
	J(2,3) = 4·9	J(3,2) = 4·9	J(4,3) = 3·8	J(5,4) = 4·0	J(6,5) = 3·4	J(6′,5) = 9·1
		J(3,4) = 3·8	J(4,5) = 4·0	J(5,6) = 3·4	J(6,6′) = 13·1	J(6′,6) = 13·1
				J(5,6′) = 9·1		

$$^3J(\mathrm{H,H}) = P_1 \cos^2\phi + P_2 \cos\phi + P_3 + \\ + \sum\Delta\chi_i[P_4 + P_5 \cos^2(\xi_i\phi + P_6|\Delta\chi_i|)], \quad (1)$$

$$\Delta\chi^{\text{group}} = \Delta\chi^{\alpha\text{-substituent}} - P_7 \sum\Delta\chi_i^{\beta\text{-substituent}}, \quad (2)$$

where ϕ is torsion angle H—C—C—H, χ electronegativity of the substituents and $P_1 - P_7$ and ξ are parameters defined in the cited reference[16].

The thus-calculated values of vicinal coupling constants for atoms H-2, H-3, H-4, H-5, H-6e and H-6a in both the chair forms of lactams *Ia*—*VIIIa* and *Ib*—*VIIIb* are given in Table V. Comparison with the actually observed coupling constants in Table I shows a good agreement for $^3J(\mathrm{H,H})$ constants, corresponding to the $^{1,4}C_4$(D) conformation of lactams of the *ido*-, *altro*-, *manno*- and *talo*-configuration,

TABLE III

Carbon-13 NMR spectra of 6-amino-6-deoxy-D-hexonolactams *Ia*—*VIIIa* and their 2,3,4,5-tetra-O-acetyl derivatives[a] *Ib*—*VIIIb*

Compound	Chemical shifts δ, ppm					
	C-1	C-2	C-3	C-4	C-5	C-6
Ia	175·88	71·40	76·89	72·62	70·44	42·65
Ib	167·14	70·12	69·28	67·99	71·30	40·28
IIa	177·06	74·14	70·92	70·92	70·60	40·43
IIb	168·53	67·04	67·40	69·94	69·87	38·77
IIIa	177·00	73·97	69·76	69·76	69·76	41·31
IIIb	168·18	67·33	67·33	70·36	69·28	39·86
IVa	176·14	77·14	70·43	70·43	69·53	41·90
IVb	167·94	70·24	66·61	73·65	68·40	39·75
Va	176·89		72·2 — 75·25		70·52	41·32
Vb	167·82	69·62	69·62	67·80	68·60	38·96
VIa	176·06	79·82	72·40	73·09	69·48	42·99
VIb	167·44	69·32	68·72	73·66	71·33	40·38
VIIa	176·27	77·32	71·48	74·83	69·99	42·26
VIIb	168·15	69·39	69·85	67·70	68·75	38·85
VIIIa	175·04	70·61	76·00	69·27	76·87	43·49
VIIIb	166·66	69·79	69·76	73·36	69·23	41·22

[a] Carbon-13 signals of the acetyl group (δ(C=O) 168·18—170·04 and δ(CH_3) 20·31—20·79) are not given.

and to the $^4C_{1,N}$(D) conformation of the *gluco*- and *gulo*-lactams. Judging from the fit of the observed and calculated values of $J(3, 4)$, $J(5, 6a)$ and $J(5, 6e)$, also the galacto-lactam exists predominantly in the latter conformation. The prevailing $^4C_{1,N}$(D) conformation of the allonolactam is indicated only by the low value of $J(5, 6a)$ whereas the other measured coupling constants are of little use because the

TABLE IV

Position of hydroxy or acetoxy groups in 6-amino-6-deoxy-D-hexonolactams in the $^4C_{1,N}$(D) and $^{1,N}C_4$(D) conformations

Configuration	Conformation $^4C_{1,N}$(D)				Conformation $^{1,N}C_4$(D)			
	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5
allo	e	a	e	a	a	e	a	e
altro	a	a	e	a	e	e	a	e
galacto	e	e	a	a	a	a	e	e
gluco	e	e	e	a	a	a	a	e
gulo	e	a	a	a	a	e	e	e
ido	a	a	a	a	e	e	e	e
manno	a	e	e	a	e	a	a	e
talo	a	e	a	a	e	a	e	e

TABLE V

Calculated values of vicinal coupling constants ^3J(H, H) for the $^{1,N}C_4$(D) and $^4C_{1,N}$(D) conformations of 6-amino-6-deoxy-D-hexonolactams[a]

Lactam configuration	$J(2,3)$		$J(3,4)$		$J(4,5)$		$J(5,6a)$		$J(5,6e)$	
	$^{1,N}C_4$	$^4C_{1,N}$	$^{1,N}C_4$	$^4C_{1,N}$	$^{1,N}C_4$	$^4C_{1,N}$	$^{1,N}C_4$	$^4C_{1,N}$	$^{1,N}C_4$	$^4C_{1,N}$
allo	0·2	1·1	1·4	2·3	1·7	2·1	10·5	0·2	2·5	5·5
altro	10·0	0·5	1·6	1·6	1·7	2·0	10·6	0·3	0·5	5·6
galacto	7·3	10·1	1·7	2·0	8·6	4·4	10·5	0·2	2·5	5·5
gluco	7·3	9·8	5·0	9·1	1·7	1·9	10·5	0·2	2·5	5·5
gulo	0·5	0·6	9·6	4·9	8·6	4·6	10·5	0·3	2·7	5·5
ido	10·0	7·3	9·7	5·0	8·6	0·5	10·6	0·3	2·8	5·6
manno	0·6	0·5	4·9	9·6	1·8	2·0	10·6	0·3	0·5	5·6
talo	0·6	0·5	1·7	1·7	8·6	4·4	10·6	0·3	2·7	5·6

[a] The coupling constants were calculated using a modified[16] Karplus relationship and geometric parameters obtained by measurement of Dreiding models.

corresponding theoretical values for the forms with protons in positions *ax–eq–ax–eq* and *eq–ax–eq–ax* are very near each other. On the other hand, analogous comparison of the observed ^3J(H, H) values with those calculated for the conformations $_4B_{1,N}$ and $^4B^{1,N}$ did not show any agreement, indicating that the measured lactams exist predominantly in a boat conformation. The coupling constants $J(2, 3)$ and $J(4, 5)$ in the spectra of galactonolactam and $J(3, 4)$ in the spectrum of mannonolactam, whose values lay approximately between the theoretical values for the two chair conformations, indicate that these compounds exist either as an approximately 1 : 1 equilibrium mixture of these forms (in both cases, however, the $J(5, 6a)$ value is at variance with this conclusion) or as a slightly twisted chair.

Thus, of all the evaluated compounds only the *gulo*-lactams exist in predominant conformation other than predicted from the conformational position of substituents (Table IV). In the found predominating $^4C_{1,N}$(D) conformation of gulonolactams all substituents, except that on C-2, assume the axial position. This finding is not surprising if we realize that in the chair conformation of the seven-membered lactam ring the mutual position of the C-5, C-6, N, C-1, C-2 and C-3 atoms is very near to that of the six carbon atoms in a boat form of cyclohexane and that in the seemingly more advantageous $^{1,N}C_4$(D) conformation of gulonolactam (Fig. 2) the bulky axial substituent on C-2 would occupy the very unfavourable "flagpole" position. The categoric requirement of equatorial substituent on C-2, forced by this situation, naturally also holds for the other seven configurational isomers; however, only gulonolactam has to pay for it by the otherwise unfavourable axial position of substituents on C-3, C-4 and C-5 in the "forced" $^4C_{1,N}$(D) conformation. It is rather probable that the resulting steric strain (1,3-interaction between substituents on C-3 and C-5) may destabilize the lactam bond and thus cause the above-described relatively facile spontaneous hydrolysis of gulonolactam in aqueous solution.

The results of the ^{1}H NMR conformational study on lactams *Ia–VIIIa* and *Ib–VIIIb* can be summarized in the following main conclusions:

1. The predominant conformations of pairs of the free lactams *Ia–VIIIa* and the corresponding 2,3,4,5-tetra-O-acetyl derivatives *Ib–VIIIb* do not differ significantly.

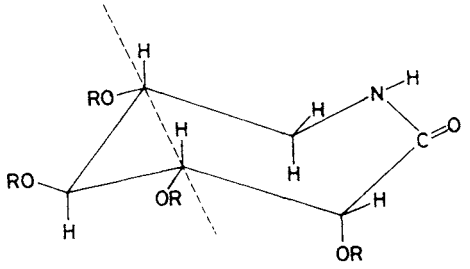

FIG. 2

6-Amino-6-deoxy-D-gulonolactam in the $^{1,N}C_4$ conformation

2. In the series of eight stereoisomeric 6-amino-6-deoxy-D-hexonolactams and their tetraacetyl derivatives the equatorial position of substituent on C-2 represents probably the main condition determining in which of the two chair conformations the lactam exists predominantly. Consequently, lactams of the D-*ido*-, D-*altro*-, D-*manno*- and D-*talo*-configuration assume predominantly the $^{1,N}C_4$(D) conformation whereas lactams of the D-*allo*-, D-*galacto*-, D-*gluco*- and D-*gulo*-configuration predominantly the $^4C_{1,N}$(D) form.

CD *Measurements of Lactams* Ia–VIIIa

The CD measurements were performed only with the free lactams *Ia–VIIIa* because in CD spectra of the acetyl derivatives the amide and ester transition bands overlapped. The CD measurements were limited by low solubility of the compounds which were well soluble only in water. The low solubility precluded measurements in solvents of various polarity and at low temperatures, desirable for conformational studies. Because of similar conditions of the NMR and CD measurements, the data obtained for the free lactams by both methods are comparable.

The CD bands observed in spectra of the studied lactams in the region 200–400 nm are due to the n–π^* transition of the amide chromophore. The π–π^* transition bands of the same chromophore, which are located below 200 nm, were not measured with a sufficient accuracy and are therefore not discussed. As follows from Table VI, wavelengths of the apparent maxima of the n–π^* bands are considerably scattered due to superposition; however, we may distinguish two groups of bands differing

TABLE VI

CD bands of the n–π^* amide transition of 6-amino-6-deoxy-D-hexonolactams

Lactam configuration	λ, nm ($\Delta\varepsilon$, cm^2 mmol^{-1})	
	1st band	2nd band
D-*gulo*[a]	—	212 (+8·17)
D-*allo*	234 (−0·17)	212·5 (+1·29)
D-*galacto*	229 (−0·32)	214 (−0·62)
D-*gluco*	220 (−3·51)	208 (−1·97)[b]
D-*manno*		207 (−6·61)
D-*talo*		209·5 (−5·57)
D-*altro*	226 (+0·73)	201 (−2·95)
D-*ido*[a]	220 (+2·57)	

[a] The actually measured compound was of the L-configuration and its $\Delta\varepsilon$ values had the opposite sign than given in the Table; [b] negative minimum corresponding to positive band.

on the average by 20 nm. In four cases both bands appear simultaneously whereas four compounds exhibit only one band, three of them the short-wavelength and one (idonolactam) the long-wavelength band. The band signs depend invariably on the configuration at the C-2 carbon atom. In the *R* series the long-wavelength band is negative and the short-wavelength one positive whereas in the *S* series the situation is reversed. In this sense the CD spectra thus reflect, in accord with the NMR spectra, the decisive effect of the configuration at C-2 on the overall conformation of the seven-membered lactams.

For interpretation of the CD spectra one may use rules relating CD parameters to spatial arrangement of the studied compound[17]. The so-called lactam rule, considering the chirality of the lactam ring as a whole, has been formulated by a group of Japanese authors[3,18,19]. According to this rule, four- to seven-membered lactams whose conformation is depicted in Fig. 3*a* (i.e. the nitrogen atom on the right side of the carbonyl and the remaining ring atoms behind them and above the *x*-axis) exhibit a negative CD band whereas the enantiomeric conformation gives rise to a positive band. Another rule that may be used is the so-called amide quadrant rule[20-22], depicted in Fig. 3*b*. Similarly to other sector rules, this approach evaluates the contribution of individual atoms on the lactam ring (including the substituent atoms, not shown in the drawing), projected into the quadrants, to the resulting Cotton effect of the studied compound. However, as seen from Fig. 3*a*,*b* these two rules lead to opposite signs of the CD bands for lactams with chiral C-2, C-3 and C-4 carbon atoms. For our set of lactams *Ia – VIIIa* we have to take into consideration also studies of other authors[23,24] on five- and six-membered lactams, substituted in position α to the carbonyl with a group containing an atom with free electron pair (–OR, $-NR_2$, –SR). A relationship has been found between absolute configuration of the mentioned hetero atom and sign of the CD band. Compounds of *R*-configuration at C-2 gave a negative band, compounds of *S*-configuration a positive

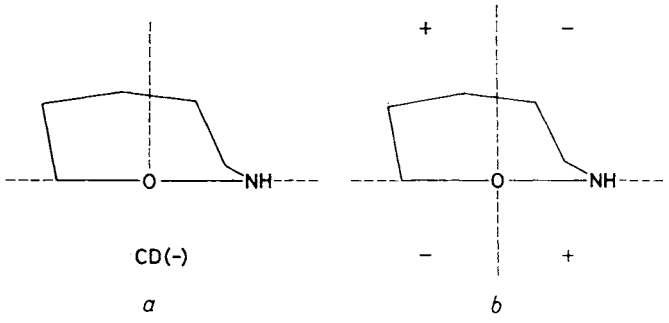

FIG. 3

Interpretation of the CD spectrum of 6-amino-6-deoxyhexonolactam in $^{1,N}C_4$ conformation according to: *a* lactam rule[3,18,19], *b* amide (quadrant) rule[20-22]

band. The authors[23,24] explained this behaviour by interaction between the amide carbonyl and the free electron pair of the hetero atom which gives rise to an inherently chiral chromophore.

The existence of the two CD bands could be explained by the presence of both possible chair conformers in the equilibrium mixture which cannot be detected by NMR spectroscopy because of other time scale.

Table VII compares the signs of the experimentally observed CD bands with those which follow from application of the above-mentioned rules to the conformations of *Ia* – *VIIIa*, determined by ^{1}H NMR spectroscopy. It is obvious that for the short-wavelength (usually stronger) band the lactam rule predicts the same conformation as found by NMR spectroscopy. However, for D-idonolactam (which has no short-wavelength band at all) and D-gluconolactam (for which this band is only very weak) the form with equatorial substituent on C-2 should be only little populated, which is at variance with the NMR results. On the other hand, the amide and Meguro's rules lead to the correct sign of the long-wavelength band but also to an obvious discrepancy between the CD and NMR results for D-mannono-, D-talono- and D-gulonolactam.

This failure of the interpretation rules consists probably in the fact that the CD spectra of the studied lactams reflect not only the overall conformation of the lactam ring but also the local conformation of the inherently chiral chromophore. An in-

TABLE VII

Correlation of the ^{1}H NMR results with results obtained from the observed CD data by application of various chiroptical rules for 6-amino-6-deoxy-D-hexonolactams

Lactam configuration	Configuration at C-2	Predominant conformation by ^{1}H NMR	Sign of CD extremum			
			observed[a]		theoretical according to	
			1st band	2nd band	lactam rule[b]	amide rule[c,d]
D-*allo*	*R*	$^4C_{1,N}$	–	+	+	–
D-*galacto*	*R*	$^4C_{1,N}$	–	+	+	–
D-*gluco*	*R*	$^4C_{1,N}$	–	+	+	–
D-*gulo*	*R*	$^4C_{1,N}$		+	+	–
D-*altro*	*S*	$^{1,N}C_4$	+	–	–	+
D-*ido*	*S*	$^{1,N}C_4$	+		–	+
D-*manno*	*S*	$^{1,N}C_4$		–	–	+
D-*talo*	*S*	$^{1,N}C_4$		–	–	–

[a] See Table VI; [b] refs[3,18,19]; [c] refs[20–22]; [d] the same results were obtained by Meguro's procedure[23,24].

herently chiral chromophore could arise by interaction of the hydroxyl on C-2 with the amide carbonyl, as suggested by Meguro[23,24] for smaller-ring lactams, or by twisting the amide group (a non-zero torsion angle C_6—N—C_1—C_2 ($\Delta\omega$)) as anticipated by Klyne[6] and Suginame[25] for seven-membered lactams with unexpected CD parameters. The mechanism of formation of rotational strength in an inherently chiral chromophore is very effective and its contribution might be decisive for the character of the CD spectrum. It seems that our case concerns rather the nonplanar amide group because for the preferred conformation (as found by NMR) the spatial relation of the substituent on C-2 to the carbonyl group, is the same for all the studied lactams. The sense of the nonplanar deformation of the amide group, which in addition to the torsion about the N—C bond also involves the formation of a pyramidal arrangement on the nitrogen atom (cf. e.g. refs[26,27]), is determined by chirality of the rest of the molecule which in our lactams depends on the absolute configuration at the C-2 atom, as follows unequivocally from the CD as well as the NMR data.

Another structural dependence of the CD spectra of the studied lactams may be seen from Table VI. In both series the strongest short-wavelength band is shown by the lactam with axial (according to NMR) hydroxy groups on C-3 and C-4 (Table IV), i.e. D-mannono- and D-gulonolactam. The relative intensity of this band decreases, whereas that of the long-wavelength band increases, with the decreasing number of axial substituents on C-3 and C-4 and with their increasing distance from the carbonyl group (i.e. in the order *aa*, *ae*, *ea* and *ee*). It follows from this observation that the local conformation in the chromophore neighbourhood (the extent of its deformation) depends on the conformation of the more distant hydroxy groups.

Our considerations do not allow an unequivocal assignment of the observed CD bands. Tentatively, we might ascribe the long-wavelength band to a strongly deformed amide group and the short-wavelength one to a planar, or a less and in another sense deformed, amide group. The final assignment of these CD bands might be significantly aided by X-ray diffraction or theoretical calculations of conformational energy and optical activity of these compounds. For the time being, we may only state that our results increase the number of exceptions found in the interpretation of CD spectra of lactams, using the amide[3,19] as well as the lactam[6,25] rule. No generally reliable interpretation of CD spectra of lactams in the terms of the overall conformation has been found so far and therefore one has to be very careful even in case of such structurally close compounds as lactams *Ia*–*VIIIa*.

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