

AMINO ACIDS AND PEPTIDES. CX.*

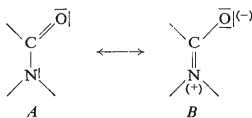
THE INFRARED SPECTRA OF POLYCYCLIC SPIRO-DILACTAMS WITH NON-PLANAR AMIDE BONDS

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Tri- and tetracyclic dilactams of the type 5,8-diazatricyclo[6,3,0,0^{1,5}]undecane-4,9-dione (*Ia*) and 1,4-diazatetracyclo[5,3,1,0^{4,13},0^{10,13}]tridecane-5,12-dione (*Ila*) with various combinations of 5- and 6-membered rings were synthesized by condensation of the esters of oxodicarboxylic acids with diamines. The infrared spectra were measured. For identification of the bands to which stretching vibrations of the C_(O)—N bond contribute, the solvent effect was used. Values of wave-numbers of $\nu(\text{C}=\text{O})$ and $\nu(\text{C}_{(\text{O})}-\text{N})$ are discussed in relation to geometric structural parameters, in particular to the torsion angles at the amide bonds.

The planar amide (peptide) group (both in *cis*- and *trans*-conformation) is formulated¹ by means of mesomeric structures *A* and *B* (Scheme 1). In some compounds steric factors may prevent the mesomerism from being evident²⁻⁴. There are then deviations from planarity which involve on the one hand the torsion angle about the C_(O)—N bond, and on the other a non-planar arrangement of the bonds arising from the N atom⁵ and the carbonyl C atom. The first two components would appear to be the most significant with the same high energy requirements⁶. As a result of these changes in geometry there is a decrease in the overlapping of π -orbitals in the carbonyl groups with the free electron pair of N. All of the bonds involved lose properties characteristic for amide groups and approximate the properties of analogous structural units in amino ketones. For detection of distorted amide groups one can use spectroscopic methods.



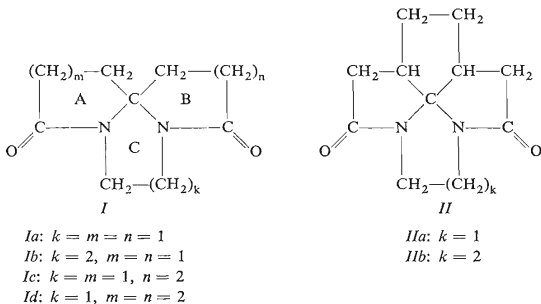
Scheme 1

The occurrence of non-planar amide groups can be expected primarily in cyclic compounds. Three-dimensional X-ray analysis has demonstrated non-planarity in *cis*-peptide bonds in cyclo-(L-alanyl-L-alanine)^{7,8}. According to calculations of conformational energies, in cyclo(tris-L-pro-

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lyl) one must consider marked distortion of the peptide bond⁹, and some physical properties of this substance are in agreement with this¹⁰. The non-planar *trans*-amide group was studied in 1-aza-2-cyclononane⁶. This may, of course, occur even in simple peptides¹¹ and cannot be excluded even in protein molecules.

Within the framework of a systematic study of the physical properties of peptides¹² we have attempted to find suitable model compounds for spectroscopic investigation of non-planar *cis*-amide groups. One useful model has been found to be tricyclic (*I*) or tetracyclic (*II*) dilactams with a quarternary carbon atom common to all rings in the molecule. Variation in the ring size allows changes in the conformation and thus in the degree of the resulting distortion which should be manifest in quantitative differences in the measured values. From the chemical point of view substances *I* and *II* represent a new type of polycyclic compounds; a surprisingly simple way for synthesis was found, however.* Synthesis of substances *I* and *II* and their spectroscopic properties are the subject matter of this communication.



EXPERIMENTAL

Melting points are not corrected.

Preparation of Dilactams *I* and *II*

Equimolar amounts of the diethyl ester of the corresponding oxodicarboxylic acid and diamine were mixed and heated to boiling for 1–2 h, following which crystals separated out which gave pure products on recrystallisation from ethanol. Analyses and constants are given in Table I.

* The synthetic part of this work was carried out at the instigation and under the direction of Academician R. Lukeš in the former Laboratory of Heterocyclic Compounds, Czechoslovak Academy of Sciences, Prague, in 1959–1960. Even if the original goal of the synthesis of these substances differed from the use put to them in this work, the present results fit in with the long term goals of Prof. Lukeš who gave much attention to amide groups in his research work¹³.

TABLE I

Products of Reaction of Diethyl Esters of Oxo Acids with Diamines

| Substance (Yield) | M.p., °C (solvent) | Formula (m.w.) | Calculated/Found | | |
|----------------------|-----------------------|---------------------------------|------------------|------|-------|
| | | | % C | % H | % N |
| <i>Ia</i> (65·5) | 190 (ethanol) | $C_9H_{12}N_2O_2$ (180·2) | 59·97 | 6·71 | 15·54 |
| | | | 59·91 | 6·96 | 15·75 |
| <i>Ib</i> (45) | 241 (ethanol) | $C_{10}H_{14}N_2O_2$ (194·2) | 61·83 | 7·26 | 14·42 |
| | | | 61·92 | 7·31 | 14·51 |
| <i>Ic</i> (38) | 111 (benzene) | $C_{10}H_{14}N_2O_2$ (194·2) | 61·83 | 7·26 | 14·42 |
| | | | 61·73 | 7·65 | 14·62 |
| <i>Id</i> (31) | 150 (benzene) | $C_{11}H_{16}N_2O_2$ (208·3) | 63·43 | 7·74 | 13·45 |
| | | | 63·58 | 7·69 | 13·67 |
| <i>IIa</i> (49) | 264 (ethanol) | $C_{11}H_{14}N_2O_2$ (206·2) | 64·05 | 6·84 | 13·58 |
| | | | 64·00 | 7·00 | 13·46 |
| <i>IIb</i> (40) | 215 (ethanol) | $C_{12}H_{16}N_2O_2$ (220·3) | 65·43 | 7·32 | 12·72 |
| | | | 65·48 | 7·39 | 12·43 |

1,4-Diazaundecane-5,11-dione (*III*)

To 750 ml benzene we added simultaneously by drops a solution of 6 g (0·06 mol) of the dichloride of pimelic acid and 3·4 g 1,2-diaminoethane (0·12 mol), both in 500 ml benzene, over 4·5 hours at room temperature. A precipitate formed during the reaction. After adding the full amounts of the solutions we mixed for 1 h, the crystals which separated out were collected and extracted in a Soxhlet apparatus for 6 h with benzene. Cooling of the benzene solution resulted in the separation of a substance which after crystallisation from ethanol gave a m.p. of 164–165°C; yield 1·5 g (27·5%). For $C_9H_{16}N_2O_2$ (184·2) calculated: 58·67% C, 8·76% H, 15·21% N; found: 58·37% C, 9·02% H, 15·20% N.

Diethyl 5-Oxononanedioate

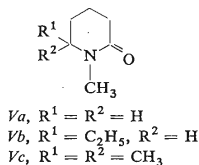
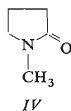
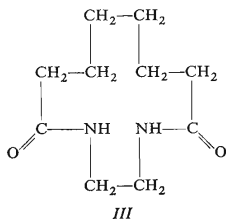
To dry sodium methoxide (prepared from 6·2 g Na) we added 34 g N-methylglutarimide and heated at 130°C for 1 h. After cooling the mixture was treated with 40 ml conc. HCl, NaCl was removed and the filtrate was boiled for 5 h, then concentrated *in vacuo*, and the water remnant was removed by distillation with benzene. The crude reaction mixture was subjected to azeotropic esterification with ethanol in the presence of sulphuric acid. Distillation gave a yield of 12 g of the ester (35%), b.p. 130–135°C/0·5 Torr. IR spectrum (tetrachloromethane): 1722 cm^{-1} , $\nu(C=O)$ ketone; 1736, 1179 cm^{-1} ($COOC_2H_5$). For $C_{13}H_{22}O_5$ (258·3) calculated: 60·44% C, 8·59% H; found: 60·05% C, 8·44% H.

RESULTS

In the synthesis of tri- and tetracyclic lactams *I* and *II* we started from the diesters of the oxodicarboxylic acids: 4-oxoheptanedioic acid¹⁴ for substances *Ia*, *Ib*, 4-oxo-

octanedioic acid^{14,15} for substance *Ic*, the 5-oxononanedioic acid, prepared by condensation of N-methylglutarimide by the action of sodium methoxide analogous to the condensation of N-methylsuccinimide¹⁶, for substance *Id*, and finally 2-cyclopentanone-1,3-diacetic acid¹⁷ for substances *Iia* and *Iib*. The reaction of their diethyl esters with 1,2-diaminoethane or 1,3-diaminopropane without the use of solvent gave us the required compounds with yields of 30 to 65%. Higher yields were shown by compounds with all rings 5-membered, as opposed to compounds with one or more rings 6-membered. This fact is somewhat surprising, since compounds with 6-membered rings show less strain (Dreiding models). However, the transition state in transannular cyclisation is spatially more favourable for five-membered ring C. In this case, the π -electron orbitals of both nitrogen atoms are properly oriented towards the keto group. The dependence of the result of the reaction on the length of the diamine chain was to be seen in the reaction of the ester of 4-oxoheptanedioic acid with 1,4-diaminobutane and 1,8-diaminooctane, which should result in compounds with a 7-membered or 11-membered ring. In these cases an individual product was not isolated. The reaction of the dilactone of 4-oxoheptanedioic acid with 1,2-diaminoethane¹⁸ was shown to be unsuitable for the synthesis of substance *Ia*. For comparison we prepared the monocyclic dilactam *III* corresponding to substance *Iia* without a spiro-atom.

Model compounds: In the spectra of model lactams *IV* and *V* we observed a strong band in the 1389–1405 cm^{-1} band (in tetrachloromethane) with molar extinction coefficient ϵ_{max}^a about 150, sensitive to solvent. In agreement with the literature¹⁹, we assigned this band to a symmetric deformation vibration of the N-methyl group, combined with the stretching vibration of the $\text{C}_{(0)}\text{—N}$ bond. The low wavenumber and high sensitivity to solvent of this band in the spectrum of substance *Vc* were apparently caused by greater or lesser overlapping with the band of symmetric deformation vibration of the geminal dimethyl group (in neighbouring position 6) which is also somewhat sensitive to solvent change. The nearest band with a higher wavenumber (1420–1426 cm^{-1} , ϵ_{max}^a about 100) is absolutely insensitive to solvent



change. This was attributed to scissoring vibration of the methylene group next to the carbonyl^{20,21}. A further band in the region 1432–1438 cm⁻¹ (ϵ_{\max}^a 60–100) showed the highest degree of sensitivity to solvent change. This is attributed to stretching vibration of the C_(O)—N bond with a contribution from the deformation of the C—H bond. An alternative explanation, *i.e.* the antisymmetric deformation vibration of the N-methyl group with a strong contribution from the ν (C_(O)—N) vibration, does not seem justifiable. Even if the molecule as a whole belongs to the lowest point group of symmetry C₁, one can consider local symmetry C_{3v} with respect to the characteristic vibration of this atomic group. Within the framework of this local symmetry it is clear that vibrational coupling between antisymmetric vibrations of methyl groups (type *E* with respect to group C_{3v}) and the (C_(O)—N) vibration cannot be significant. Bands in the region 1449–1473 cm⁻¹ (ϵ_{\max}^a 80–150) show only an insignificant solvent effect. We have attributed this to scissoring deformation vibrations of the ring methylene groups^{21,23} and to the antisymmetric deformation vibration of N-methyl group¹⁹. In substances *Vb* and *Vc* there was in addition a band at 1461 cm⁻¹, the position of which agrees with that of antisymmetric deformation vibration of the C-methyl group. On the other hand, with the methylene

TABLE II

Wavenumber of Maxima (cm⁻¹) and Approximate Assignment of Absorption Bands in the Spectra of Substances *IV* and *V* in the Region 1400–1500 cm⁻¹

The first value is in tetrachloromethane, the second in chloroform.

| Substance | $\delta(\text{CH}_3)\text{---N}$ <i>sym</i> | $\delta(\text{CH}_2)$ $\alpha\text{-CO}$ | $\nu(\text{CN})^a$ | $\delta(\text{CH}_2)$ sciss | $\delta(\text{CH}_3)\text{---N}$ <i>anti</i> | $\delta(\text{CH}_3)\text{---C}$ <i>anti</i> | $\delta(\text{CH}_2)$ sciss $\alpha\text{-N}$ |
|-----------|--|---|----------------------|--------------------------------|---|---|--|
| <i>IV</i> | 1 403.3 | 1 426.8 | 1 434.6 | 1 458.6 | 1 472.8 | — | 1 500.2 |
| | 1 405.6 | 1 427.3 | 1 440.5 | 1 459.5 | 1 474.0 | — | 1 503.0 |
| <i>Va</i> | 1 400.8 | 1 420.8 | 1 437.4 sh | 1 448.7 | 1 467.0 | — | 1 501.6 |
| | 1 402.6 | 1 420.2 | 1 449.0 ^b | 1 449.0 | 1 468.4 | — | 1 505.2 |
| <i>Vb</i> | 1 398.5 | 1 420.5 | 1 433.4 | 1 449.0 | 1 471.2 ^c | 1 461.5 | — |
| | 1 401.2 | 1 420.0 | 1 436.8 | 1 449.0 | 1 471.0 | 1 462.0 | — |
| <i>Vc</i> | 1 389.0 | 1 421.0 | 1 432.5 | 1 449.0 | 1 473.5 | 1 461.0 | — |
| | 1 394.5 | 1 419.5 | 1 436.0 | 1 451.0 | 1 473.2 | 1 460.3 | — |

^a Band with the largest $\nu(\text{C}=\text{N})$ contribution, admixture of $\delta(\text{CH}_2)$ sciss. of some methylene groups is here probable. ^b Overlapped by the neighbouring $\delta(\text{CH}_2)$ vibration, the position of which is not shifted by solvent effect. ^c Vibration of CH₂ group in ethyl at 1 481.7 cm⁻¹ (tetrachloromethane) and 1 485.6 cm⁻¹ (chloroform); this band does not occur in substances *III* and *IV*. Its higher wavenumber is in agreement with the localisation of the methylene group in the side chain²³.

group next to the nitrogen atom such substances have a band at 1500 cm^{-1} which shows marked solvent sensitivity. In our view it is caused mainly by a scissoring deformation vibration of the cited methylene group along with a stretching vibration of the $\text{C}_{(0)}\text{—N}$ bond. Wavenumbers of bands of the individual substances are shown in Table II.

The most probable position of the stretching vibrations *per se* of the $\text{C}_{(0)}\text{—N}$ bond would appear to be the region between the deformation vibrations of the ring methylene groups and the vibrations of CH_2 groups next to CO. The medium value lies at 1435 cm^{-1} . This value is in good agreement with that given for $\nu(\text{C}_{(0)}\text{—N})$ in nonadeuterio-N,N-dimethylacetamide²², even if the wavenumber of the nonadeuterio derivative band is decreased by the effect of mass. In this compound of course there can be no coupling with deformation vibrations of methylene and methyl groups, and the band at 1430 cm^{-1} must correspond to the characteristic $\nu(\text{C}_{(0)}\text{—N})$.

Stretching vibration of C=O of model lactams IV—V: All substances show one intense band along with several shoulders markedly sensitive to solvent change. Wavenumbers of the principal maxima (first data in tetrachloromethane, second in chloroform, cm^{-1}): *Va* 1 641, 1 629; *Vb* 1 645.5, 1 621.5; *Vc* 1 646, 1 615; for substance *IV* 1 697.0 in tetrachloromethane 1 696 in benzene, 1 692.0 in *trans*-1,2-dichloroethylene, 1 686.0 in acetonitrile, 1 676.0 in chloroform, 1 671.1 in bromoform.

Stereochemical analysis of spiro-lactams: The polycyclic character of dilactams *I—II* introduces marked strain and conformational rigidity into the molecules. The main characteristics of their spatial organisation arise from the spiro-arrangement of A and B rings, basically oriented orthogonally to one another. Bridging of the spiro-atom with involvement of the C ring of necessity involves a tendency to decrease the angle between both planes. This change would of course require a change in the bond angle at the sp^3 hybridised spiro-atom, which is difficult particularly in tetracyclic compounds *Ila* and *Ilb*. There would be therefore a greater or lesser deviation of the lactam groups from planarity. The most significant component of this deviation is the formation of a pyramidal arrangement at both bridgehead nitrogen atoms. To a lesser degree there would also occur direct torsion at the $\text{C}_{(0)}\text{—N}$ bond. Both components cannot be separated and the summation of these deviations can be labelled as angle ω , torsion angle of the C=O and N—C_α bonds (C_α in ring C).

Analysis of the spatial structure by means of Dreiding models is faced with the fact that a suitable construction unit is not available which would, by its mechanical properties, imitate the mesomeric character of the system $\text{O}=\text{C}=\text{N}$ changing with non-planarity. For an estimate of angle ω we used as the lactam bond either two sp^2 atoms rotationally joined or non-rotational peptide units. Average values obtained by measurement in both approaches can be used as an approximation to real values. The order of members of the series according to relative values of the torsion angle ω is given by an analysis of the models quite clearly: *Ib*, *Ilb*, *Id* 15° , *Ic* 20° , *Ia* 25° , *Ila* 30° .

In substances *Ib* and *Ilb*, where the C ring is closed by a 3-membered bridge (and assumes a twisted chair conformation), the deviation of the lactam groups

from planarity is least. Greater deviation from planarity is shown when we introduce a 5-membered C ring (which assumes a C_2 conformation with both bridgehead N-atoms and the spiro-atom in the same plane). Deviation is manifest primarily by a more marked pyramidal arrangement at both bridgehead atoms. It is highly probable that in tricyclic systems at least to some degree there is decreased strain by change of the bond angles at the spiro-atom. Introduction of a further D ring of course limits this strain decrease, and non-planarity of the amide groups further increases. The difference between a 5- and 6-membered A and B ring (lactam) is not great in terms of torsion. The differences are manifest mainly in changes in the bond angles. The bond angle in the 6-membered ring is much nearer the optimal angle at the spiro-atom; for this reason in 6-membered A, B rings there is no significant deformation of the bond angles in comparison with monocyclic 1-methyl-2-piperidone (*Va*). On the other hand in 5-membered A, B rings in comparison with 1-methyl-2-pyrrolidinone (*IV*) there is a great difference. Decrease in strain from deformation of the bond angle is particularly evident in the 5-membered ring of compound *Ic*.

TABLE III

Wavenumber Maxima (cm^{-1}) of Absorption Bands of the Stretching Vibrations of Carbonyl Groups in the Spectra of Substance *I* and *II*

Data in the first row in tetrachloromethane (0.001M), cell 2 mm, in the second row 0.03M in chloroform, cell 0.1 mm. The bands were separated by computer.

| Substance | $\nu(\text{C}=\text{O})$ | | Integrated intensity | | % Partition | |
|------------------------|--------------------------|----------------------|----------------------|--------------------|-------------|------|
| | 1st band | 2nd band | | | | |
| <i>Ia</i> | 1 712.8 | 1 724.6 | 11 158 | 46 015 | 24.2 | 100 |
| | 1 700.7 | 1 718.9 | 37 161 | 16 877 | 100 | 45.4 |
| <i>IIa</i> | 1 712.5 | 1 723.0 | 11 023 | 43 602 | 25.3 | 100 |
| | 1 699.2 | 1 716.8 | 50 569 | 13 495 | 100 | 26.7 |
| <i>Ib</i> | 1 704.2 | 1 714.2 | 38 072 | 17 628 | 100 | 46.3 |
| | 1 689.5 | 1 707.3 ^a | 47 102 | 7 721 ^a | 100 | 16.4 |
| <i>IIb</i> | 1 701.1 | 1 712.7 | 37 519 | 18 076 | 100 | 48.2 |
| | 1 683.5 | 1 700.1 | 48 361 | 16 877 | 100 | 34.4 |
| <i>Ic</i> ^c | 1 667.0 ^b | 1 723.5 | 36 929 | 30 285 | — | — |
| | 1 648.2 | 1 706.0 | — | — | — | — |
| <i>Id</i> ^c | 1 661.0 ^b | — | 60 337 | — | 100 | — |
| | 1 641.1 ^b | — | — | — | 100 | — |

^a With calculated separation a further band at 1677.2 cm^{-1} was discovered, with integrated intensity 7698; ^b $\nu(\text{C}=\text{O})$ in a 6-membered ring; ^c not separated by computer.

The NMR spectrum of substance *Ila* shows that one proton on the carbon atoms of the ethylene bridge of the C ring lies approximately in the plain of the carbonyl group (in trifluoroacetic acid 4.05–4.40 p.p.m., 2 H, AA' part of an AA'BB' system). The result is in agreement with the concept of a C_2 conformation of the 5-membered C ring.

Bands of stretching vibrations of carbonyl groups in spiro-lactams: In the spectra of substances *Ia*, *Ib*, *Ila* and *Ilb* there is a band of $\nu(C=O)$ vibrations composed of two sub-bands (Table III). The origin of the doublet can be a) dipole association in solution, b) complex formation with solvent, c) Fermi resonance, d) vibrational coupling of both carbonyl groups. The first possibility was excluded by measurement of the concentration dependence of the appropriate bands in substance *Ilb*. The ratio ϵ_{\max}^a did not change even with a 20-fold change in concentration ($6 \cdot 10^{-3}$ and $3 \cdot 10^{-4}$ M). Complex formation is more or less out of the question since all the substances have a $\nu(C=O)$ band in the form of a doublet even when measuring the spectra in nujol suspension. Not even mutual interaction of the vibrations of both C=O groups can cause doublet bands, since with a change in solvent from non-polar (tetrachloromethane) to polar (chloroform) there was a shift of band maxima to lower wavenumbers and a large change in the intensity of both bands. The bands were separated on a computer. The most logical explanation would appear to be Fermi resonance. With a shift of band to lower wavenumbers in substances *Ib* and *Ilb* there was an increase in intensity of the band with lower wavenumber. In this band the participation of $\nu(C=O)$ is larger when the band is more distant from the interacting band. In substances *Ia* and *Ila* there was even an altered order of band intensities. In order to compare the wavenumbers of vibrations of carbonyl groups in substances *Ia*, *Ib*, *Ila* and *Ilb*, which are split by Fermi resonance, with wavenumbers of carbonyl groups of substances *Ic* and *Id*, which do not have doublets, we calculated for substances *Ia*, *Ib*, *Ila* and *Ilb* values of wavenumbers of unperturbed vibrations by procedures presented in the literature²⁴.

| Substance | <i>Ilb</i> | <i>Ib</i> | <i>Ila</i> | <i>Ia</i> |
|------------------|------------|-----------|------------|-----------|
| Band $\nu(C=O)$ | 1 704.9 | 1 707.4 | 1 720.8 | 1 722.2 |
| Interacting band | 1 708.9 | 1 711.0 | 1 714.5 | 1 714.2 |

Unperturbed remain $\nu(C=O)$ vibrations of 6-membered lactams in substances *Ic*, *Id*, the wavenumbers of which are too different from the wavenumber of the interacting vibrations. Probably for this reason the $\nu(C=O)$ vibration in the 5-membered ring of substance *Ic* is not perturbed.

Bands of stretching vibrations of $C_{(O)}$ —N bonds of spiro-lactams: In the region 1300–1420 cm^{-1} of the spectra of substances *I* and *II* there is a strong band which on changing from a non-polar to a polar solvent shifts in a sense opposite to that of the $\nu(C=O)$ bands, i.e. to higher wavenumbers. At the same time in this region

there is a shift in the same direction of a further weak band. Both can be considered as bands of stretching vibrations of the $C_{(O)}-N$ bond (Table IV). Of possible explanations for doublet formation one can consider two: Fermi resonance and vibrational interaction of both $\nu(C_{(O)}-N)$ with the formation of one in-phase and one out-of-phase vibrations. The existence of two conformers does not come into consideration because of the rigidity of the molecule; the possibility of a dipolar interaction was excluded by measurement at various concentrations (*c.f.* $\nu(C=O)$ of these substances.) For differentiation of both possibilities we determined the ratio of intensities of both parts of the doublet in substance *IIa* (where the doublet is very clear and does not greatly overlap with other bands) with a transition from tetrachloromethane to chloroform. Whereas the wavenumber of the doublet (both branches) increased with this solvent change by 15 cm^{-1} , the intensity of the lesser band increased by 6% (the more intensive band is set at 100%). Fermi resonance thus appears to be excluded, since with such a great solvent shift the intensity change would have to be far greater.

The effect of solvent on the spectrum of substance *Ia* in the range $200-3600\text{ cm}^{-1}$: in the ranges $2000-1250$, $1200-820$, $650-200\text{ cm}^{-1}$ we used as a polar solvent chloroform, with the others bromoform; as a non-polar solvent we used tetrachloromethane, benzene and *trans*-1,2-dichloroethylene. Because of poor solubility we had to use saturated solutions. Comparison of the spectra in both types of solvent showed no deviations in wavenumbers greater than 3 cm^{-1} .

The UV spectra were measured in methanol and in cyclohexane (Table V). The measured maxima correspond to $\pi-\pi^*$ transitions of amide bonds. We could not measure separate maxima corresponding to $n-\pi^*$ bands, which should show a bathochrome shift in relation to the model substances due to bond torsion³. In no case was there a measurable shift between polar and non-polar solvents.

TABLE IV

Wavenumbers (cm^{-1}) of Absorption Bands of $\nu(C_{(O)}-N)$ in Substances *I* and *II*

Measured on a Perkin-Elmer model 621 instrument with a precision of $\pm 0.5\text{ cm}^{-1}$; saturated solution in tetrachloromethane, cell 0.5 mm , in $0.06M$ chloroform solution in a 0.1 mm cell.

| Substance | Tetrachloromethane | | | Chloroform | | |
|------------|--------------------|---------|------------|------------|---------|------------|
| | doublet | | mean value | doublet | | mean value |
| <i>Ib</i> | 1 393.2, | 1 415.8 | 1 404.5 | 1 404.8, | 1 422.4 | 1 413.6 |
| <i>IIb</i> | 1 391.5, | 1 408.9 | 1 400.2 | 1 403.2, | 1 415.2 | 1 409.2 |
| <i>Id</i> | 1 381.3, | 1 412.8 | 1 397.0 | 1 393.0, | 1 429.0 | 1 411.0 |
| <i>Ic</i> | 1 360.9, | 1 405.1 | 1 383.0 | 1 374.7, | 1 410.5 | 1 392.6 |
| <i>Ia</i> | 1 339.5, | 1 385.3 | 1 362.4 | 1 355.9, | 1 397.9 | 1 376.9 |
| <i>IIa</i> | 1 334.9, | 1 375.9 | 1 355.4 | 1 350.0, | 1 391.6 | 1 370.8 |

TABLE V
UV Spectra, λ_{\max} (log ϵ)

| Substance | Ia | Ic | Id | IIa | IIb | IV | Va | Vb |
|--------------------------|---------------|---------------|---------------|---------------|---------------|---------------|-----------------|---------------|
| Methanol ^a | 204 (4.11) | 201 (4.15) | 200 (4.27) | 205 (4.08) | 205 (4.11) | 198 (3.82) | 202.5 (3.82) | 202 (3.90) |
| Cyclohexane ^b | 205 | 201.5 | 200.5 | 205.5 | 204.5 | — | — | — |

^a Measured in suprasil cells, 1 mm at a concentration of $1 \cdot 10^{-4}$ M and 1 cm for $1 \cdot 10^{-3}$ M;


^b measured in saturated solution in 1 mm and 1 cm cells; spectrum did not change if for increased solubility (to $3 \cdot 10^{-3}$ M) we used cyclohexane with 2% ethanol or acetonitrile.

DISCUSSION

Stretching vibrations $\nu(\text{C}=\text{O})$ and $\nu(\text{C}_{(O)}-\text{N})$ appeared to be the most suitable approach for the study of stereochemical factors, *i.e.* the relation between geometric parameters of amide bonds and their spectral characteristics. Both of these vibrations lie in the available region of the spectra and are the most frequently studied vibrations of amides and peptides.

The wavenumber of the $\nu(\text{C}=\text{O})$ vibration would appear to be dependent upon the ring bond-angle. This in the first place differentiates the group of lactams with a 5-membered ring from lactams with a 6-membered ring, similarly as in monocyclic model substances. Changes in each of these types of molecule are superpositions of shifts of wavenumbers of $\nu(\text{C}=\text{O})$ to higher values as a result of torsion and, on the other hand, to lower values of wavenumber as a result of widening of the internal bond angle ϱ_1 (Table VI). The mutual quantitative relation of both factors cannot be discussed at this time.

TABLE VI
Comparison of Internal Valence Angles of 5- and 6-Membered Lactams

|  | Ring atoms | ϱ_1 | | ϱ_2 | |
|---|------------|--------------------|--------------------|--------------------|--------------------|
| | | calc. | exp. | calc. | exp. |
| | 5 | 108.4 ^a | 110 ^b | 114.3 ^a | 114 ^b |
| | 6 | 117.7 ^a | 114.8 ^c | 124.0 ^a | 129.2 ^c |

^a Ref.²⁸; ^b found by X-ray for 5-iodomethyl-2-pyrrolidinone²⁹; ^c found by X-ray for 3-chloro-2-piperidone³⁰.

We used the solvent effect to study stretching vibrations of the $C_{(o)}-N$ bond in the studied substances. This approach is based upon changes in the distribution of electrons in the amide bond in relation to varying weight of the limiting structures *A* and *B* (Scheme 1). Molecules of a polar solvent function as dipoles which orient their charged ends to the opposite charge in the dissolved molecule and thus exert a specific effect on the latter. In non-polar solvents the actual structure of the amide group should approximate limiting structure *A*, whereas in polar solvents the dipolar character of structure *B* should be emphasized. Formation of an H-bond between a lactam carbonyl group and chloroform as a polar solvent exhibits the same effect. The O-atom in structure *B* has more electrons than in structure *A* and therefore becomes a better electron donor. Formation of H-bonds shifts the mesomeric arrangement in the direction of *B* as a result of a fixation of electron pairs on the O-atom. Stretching vibrations of the $C_{(o)}-N$ bond should therefore in non-polar solvents lie at lower wavenumbers than in polar solvents, and $C=O$ stretching vibrations should be at higher wavenumbers in non-polar solvents than in polar. Differences between spectra in the two types of solvent should parallel differences between spectra in gaseous and condensed phases. We have shown this in a study of heptadeuteriodimethylformamide.* In the latter spectrum in the region $1300-1800\text{ cm}^{-1}$ there are only two types of $\nu(C_{(o)}-N)$ and $\nu(C=O)$ bands, unperturbed by other vibrations, since deformation vibrations of $C-D$ bonds occur below 1200 cm^{-1} . Increase in the wavenumber of $\nu(C_{(o)}-N)$ by about $+15\text{ cm}^{-1}$ and a decrease in the wavenumber of $\nu(C=O)$ by about -20 cm^{-1} on transition from tetrachloromethane to chloroform is qualitatively comparable to changes in wavenumber of both bands on transition from gaseous to liquid phases²². The solvent shift must be greater in the $\nu(C=O)$ vibration since in this case the effect is in the same direction as a change in mesomerism, along with the generally valid empirical relation that with increasing solvent polarity the wavenumber of stretching vibrations decreases. On the other hand in bands of stretching vibrations $\nu(C_{(o)}-N)$, both effects work in an opposite direction; a change in mesomerism leads to an increased bond order of $C_{(o)}-N$ in a polar medium, with an increased wavenumber. The overall shift must therefore be lower. Data from the above studied substances are in agreement with this concept.

Bands of $\nu(C=O)$ vibrations lie in a clear region and are easily identifiable. In the region of $\nu(C_{(o)}-N)$ bands the situation is far more complex. The wavenumber of the $\nu(C_{(o)}-N)$ vibration lies in the region of deformation vibrations of $C-H$ bonds; there is therefore strong interaction and in all cases there is not a single band of intensity significantly higher than the nearby bands of $\delta(C-H)$ vibrations. There can be contributions from the other bands in this region²⁵⁻²⁷. In the present material we have

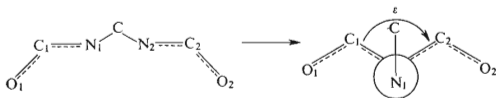
* Following bands were observed in the IR spectra of heptadeuteriodimethylformamide: in tetrachloromethane $\nu(C=O)$ $1653.0, 1665.4$ (main maximum), 1699 cm^{-1} , $\nu(C_{(o)}-N)$ 1382.3 (main maximum), 1388.8 cm^{-1} ; in deuteriochloroform $\nu(C=O)$ 1644.3 (main maximum), $1660.8, 1700.3\text{ cm}^{-1}$, $\nu(C_{(o)}-N)$ $1385.8, 1397.4$ (main maximum) cm^{-1} .

seen a distribution of the $C_{(0)}-N$ stretching vibration into several absorption bands in model compounds *IV* and *V*. Here we get interaction of $\nu(C_{(0)}-N)$, $\delta(CH_2)_{\text{sciss}}$ and $\delta(NCH_3)_s$ vibrations. On the other hand in dilactams *I* and *II* there is no interaction, the $\nu(C_{(0)}-N)$ vibration is characteristic and occurs as a single band very sensitive to solvent change. We assume that this approach can therefore be used to determine the degree of interaction. The band with the largest solvent shift in wavenumber is considered to be the band with the highest $\nu(C_{(0)}-N)$ contribution. Bands with these characteristics were then taken as bands identifying $\nu(C_{(0)}-N)$ vibrations for the given substance.

In model compounds *IV* and *V* wavenumbers of $C_{(0)}-N$ stretching vibrations determined in this manner have basically the same value for all substances without regard to ring size. These values are therefore independent of ring bond angles ϱ_1 and ϱ_2 , which are quite different for 5-membered and 6-membered rings (Table VI). On the other hand the $\nu(C=O)$ vibration is markedly dependent on angle ϱ_1 , as is known for analogous vibrations in cyclic ketones³¹ and lactones³². An analogous dependence on ring size occurs for $\nu(C=O)$ in non-methylated compounds³³ (2-pyrrolidinone 1717 cm^{-1} , 2-piperidone 1677 cm^{-1}). From the data in Table II for compounds *IV* and *V* it is further seen that the intensity of the $\nu(C_{(0)}-N)$ bands is not related to ring size. From X-ray data it is also known that *cis*-amide bonds in 5- and 6-membered lactams do not have a significant degree of non-planarity. We can therefore use the measured wavenumber values for $\nu(C_{(0)}-N)$ and $\nu(C=O)$ as basic ones for comparison with analogous vibrations in the studied dilactams.

Bands of stretching vibrations of $C_{(0)}-N$ bonds occur in dilactams *I* and *II* in the form of doublets as a result of the interaction of vibrations of both amide groups. Conditions are correct in substances *I* and *II* for this interaction. The orientation of both $C_{(0)}-N$ bonds resembles that of the $C=O$ bond in cyclic anhydrides, where there also occurs vibrational interaction³⁴. There are similar doublets in both cases: the band with the larger wavenumber has the lower intensity. In anhydrides this band is considered an in-phase vibration, the band with the lower wavenumber having the higher intensity as an out-of-phase vibration. It is suggested here that the same analysis can be carried over to dilactams *I* and *II*.

The distance of both branches of the doublet ($\Delta\nu_1$) in the separate substances is varied and can be correlated with geometric parameters by estimates from models; attention has to be given to the torsion angle ω , characterising the deviation of the



SCHEME 2

amide group from planarity, and to the relative position of both partially doubled $C_{(O)}-N$ bonds. In fragments including the spiro-atom and both amide bonds, the relative position can be characterised by angle ε (Scheme 2).

| Compound | <i>Ib</i> | <i>IIb</i> | <i>Id</i> | <i>Ic</i> | <i>Ia</i> | <i>IIa</i> |
|---------------|-----------|------------|-----------|-----------|-----------|------------|
| $\Delta\nu_1$ | 22.6 | 17.6 | 31.5 | 44.2 | 45.8 | 41.0 |
| ω | 15° | 15° | 15° | 20° | 25° | 30° |
| ε | 95° | 105° | 0° | 25° | 70° | 80° |

Both factors play an equal and independent role. With increasing torsion on the $C_{(O)}-N$ bond the negative charge on the N atom increases with separation of both branches of the doublet, which means that the interaction increases. This is shown by comparison of $\Delta\nu$ of substances *Ib*, *IIb* with values for *Ia*, *IIa*. In the first pair the 6-membered ring permits a far more planar arrangement of the amide group than in the other pair. The double value of angle ω in the *Ia*, *IIa* pair is paralleled by a practically double value of the difference $\Delta\nu_1$. On the other hand in substance *Id* the angle ω is relatively small, both bonds are located practically in the same plane with angle ε near to 0. This position permits a large degree of interaction, as witnessed by the high values of $\Delta\nu_1$. In substance *Ic* both factors reinforce one another. A further factor, however, cannot be excluded — a different non-planarity of the amide bonds in both rings. This should be manifest by somewhat different wavenumbers of the stretching vibrations of both $C_{(O)}-N$ bonds, which with vibrational interaction of both bonds²³ further increase $\Delta\nu_1$.

The studied dilactams can be considered as "negatives" of anhydrides. In the latter is a conjugated system in which electronic effects can be operative along the chain. In the present case it is a homoconjugated system where one must consider interaction of electrons on nitrogen atoms in space.



In a planar arrangement we can have interaction of π -electron systems of both amide bonds which have their N atoms oriented towards one another. In comparison with molecules of cyclic anhydrides we must take into account that in the latter there is a marked difference between $\nu(C=O)$ vibrations for 5- and 6-membered rings, which depends on the valence angle. In dilactams such a difference is negligible due to the independence of $\nu(C_{(O)}-N)$ on the internal valence angle (see above). If we compare the stretching vibrations of the $C_{(O)}-N$ bond in dilactams and in model lactams *IV* and *V* it is clear that in substances *I* and *II* $\nu(C_{(O)}-N)$ had the properties of a characteristic vibration. There is a considerable shift to higher wavenumbers with a change from a non-polar to a polar solvent (about $11-15\text{ cm}^{-1}$, in comparison

with a 15 cm^{-1} change in the same band in heptadeuteriodimethylformamide). Both branches of the doublet do not show the same degree of shift, just as in anhydride doublets³⁵. The reason for the limited interaction can be the fact that the $\nu(\text{C}_{(O)}-\text{N})$ doublet lies outside (because of the shift to lower wavenumbers) the region of scissoring vibration of methylene groups, and is also outside of the region of wagging vibration, *i.e.* $1300-1400 \text{ cm}^{-1}$. Of course geometric factors can also play an important role, on the one hand altered geometric relations of the amide groups in the vicinity, or (more probable) altered delocalisation of electrons as a result of torsion on the amide bond and thus altered possibilities of interaction of the π -system with neighbouring orbitals. Bands of $\nu(\text{C}_{(O)}-\text{N})$ in the dilactams have a high intensity in comparison with lactams *IV* and *V*. The lower branch of the doublet has $\epsilon_{\text{max}}^{\text{a}}$ 130–200, the higher 700–800 $\text{l mol}^{-1} \text{ cm}^{-1}$. For comparison we measured the intensity of this bond in heptadeuteriodimethylformamide, with an $\epsilon_{\text{max}}^{\text{a}}$ of 200 $\text{l mol}^{-1} \text{ cm}^{-1}$ in deuteriochloroform. The dilactams therefore have approximately twice the intensity at the one bond. This must also be considered with relation to torsion at the bond. Altered delocalisation of electrons into the $\text{N}-\text{C}=\text{O}$ system increases the negative charge on the N atom and the positive charge on the C atom³⁵, and in this way the bond polarity is increased and the intensity of $\nu(\text{C}_{(O)}-\text{N})$ as well. Increasing torsion is also manifest by an increase in the distance from mean points of the doublet vibration $\nu(\text{C}=\text{O})$ and $\nu(\text{C}_{(O)}-\text{N})$; $\Delta\nu_2$. Because of the sensitivity of $\nu(\text{C}=\text{O})$ to changes in valence angle it is necessary to compare separately for 5- and 6-membered rings:

| Substance | <i>Ib</i> | <i>IIb</i> | <i>Id</i> | <i>Ic</i> | <i>Ia</i> | <i>IIa</i> |
|--|-----------|------------|-----------|-----------|-----------|------------|
| $\Delta\nu_2, \text{ cm}^{-1}, 5 \text{ ring}$ | 302.9 | 304.7 | — | 340.0 | 359.8 | 365.5 |
| $\Delta\nu_2, \text{ cm}^{-1}, 6 \text{ ring}$ | — | — | 264 | 284.0 | — | — |

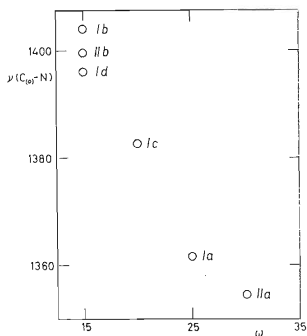


FIG. 1
Dependence of Unperturbed Vibration of $\nu(\text{C}_{(O)}-\text{N})$ on Angle ω

Wavenumbers of $\nu(C_{(0)}-N)$ in the spectra of substances *I* and *II* are correlated (Fig. 1) with values of angle ω , estimated from Dreiding models. For this correlation we used values of $\nu(C_{(0)}-N)$ taken as arithmetic means of wavenumbers of both parts of the doublet. The approximately linear relation indicates that a correlation exists between the wavenumber of the stretching vibration of $C_{(0)}-N$ bonds and the degree of deviation of the amide group from planarity, *i.e.* with the degree of torsion about the $C_{(0)}-N$ bond, or with the extent of the pyramidal arrangement about the nitrogen atom. Quantitative aspects of the relation cannot obviously be generalised here, until we have far more data. However, since the relation is present for this bond even in heptadeuteriodimethylformamide and bands with the largest contribution from $\nu(C_{(0)}-N)$ are also in model substances, we can assume that this situation applies to tertiary amides. The relation is common for compounds with 5- and 6-membered lactam rings. This indicates that the stretching vibration of the $C_{(0)}-N$ bond in compounds *I* and *II* is not influenced by the size of the bond angle; this conclusion was reached by comparison of wavenumbers of $\nu(C_{(0)}-N)$ in model substances *IV* and *V*. In general it can be stated that in agreement with previous conclusions²⁷ wavenumbers of $C_{(0)}-N$ stretching vibrations are primarily dependent upon the extent of non-planarity of the amide bond (values decrease with increasing non-planarity) not upon the valence angle, as opposed to the situation for the $C=O$ bond.

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