AMINO ACIDS AND PEPTIDES. CIX.*

SYNTHESIS AND INFRARED SPECTROSCOPY OF 2,5-PIPERAZINEDIONES DERIVED FROM PROLINE AND PIPECOLIC ACID

J.VIČAR, J.SMOLÍKOVÁ and K.BLÁHA

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

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The following cyclodipeptides containing proline (Pro) and pipecolic acid (Pip) were synthesized: c(L-Pro-Gly), c(L-Pro-L-Pro), c(D-Pro-L-Pro), c(L-Pro-L-Leu), c(L-Pro-D-Leu), c(L-Pip-L-Pro), c(D-Pip-L-Pro), c(D-Pip-Gly), c(D-Leu-D-Pip), c(D-Pip-L-Leu), c(D-Pip-D-Pip) and c(L-Pip-D-Pip). Infrared and Raman spectra were measured, particularly in the region of ν(CN) and ν(CO) vibrations. The results are discussed in relation to geometric parameters of these molecules.

This laboratory has been involved in a study of spatial relations in peptide molecules using physical and chemical methods[1]. Infrared spectroscopy is a useful tool to analyse the geometry of amide bonds[2]. In the future it will be necessary to quantitate the geometric parameters defined by the spatial arrangement of the amide group and the spectroscopic characteristics of individual vibration modes. Qualitative information of these relations is thus far limited[3] to stretching vibrations of N—H and C=O bonds. A transition to a quantitative level will require study of a large number of molecules with, as far as possible, precisely defined geometry. Polycyclic lactams appeared to fulfill this criterion. Particularly lactams with tertiary amide groups would allow study of stretching vibrations of $C_{(O)}$—N bonds which is difficult in secondary amides due to interference with deformation vibrations of N—H bonds.

In the present paper we will discuss the synthesis and infrared spectra of the first series of selected molecular models – 2,5-piperazinediones containing residues of proline and/or pipecolic acid** (structurally, bi- and tri-cyclic dilactams with two amide groups in the same ring). One of these compounds (*IIIa*) has already been subjected to physicochemical study[4,5] including infrared spectroscopy[6].

The preparation of compounds *IIIa*, *IIIb*, *VI* and *VIIa* has already been described. The isolation of enantiomers of compound *VIIb* from alkaloids ergocryptin[8] and ergosinine[9,10] has also been published. In native alkaloids the 2,5-piperazinedione portion is composed of residues of L-amino acids. However, in thermal degradation or hydrolysis with concentrated hydrochloric

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** Standard abbreviations[7] are used for amino-acid residues and protecting groups; TSI bis(*p*-toluenesulphonyl)amine, Pip pipecolic acid.

acid there occurs inversion of the absolute configuration on C_α of the proline residue. The physical properties of the isolated compound correspond to the enantiomer *VIIb* prepared in this laboratory.

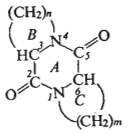
TABLE I

The Properties of Linear Peptide Intermediates

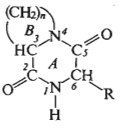
Dipeptide (method)	M.p., °C[a] (yield[d], %)	M.p., °C[b] solvent[e]	Formula (m.w.)	Calculated/Found %C	%H	%N	$[\alpha]_D^{25}$[c] (c)
Nps-L-Pro-Gly-OMe (1)	93— 96 (74)	95— 97 A	$C_{14}H_{17}N_3O_5S$ (339·4)	49·56 49·28	5·05 4·98	12·38 12·54	−100·9° (0·4)
TSI.H-L-Pro-Gly-OMe (1)	119—120 (59)	119—121 B	$C_{22}H_{29}N_3O_7S_2$ (511·6)	51·64 51·75	5·71 5·81	8·21 8·35	− 15·8°[f] (0·5)
TSI.H-L-Pro-L-Leu-OMe (1)	136—138 (62)	138 A	$C_{26}H_{37}N_3O_7S_2$ (567·7)	55·0 55·33	6·57 6·87	7·40 7·07	− 36·5°[f] (0·5)
TSI.H-L-Pro-D-Leu-OMe (1)	109—112 (53)	109—112 A	$C_{26}H_{37}N_3O_7S_2$ (567·7)	55·0 54·67	6·57 6·50	7·40 7·60	+ 3·4°[f] (0·5)
TSI.H-L-Pro-L-Pro-OMe (1)	138—140 (69)	138—140·5 B	$C_{25}H_{33}N_3O_7S_2$ (551·6)	54·43 54·42	6·03 6·0	7·62 7·54	− 71·0°[f] (0·5)
Z-D-Pro-L-Pro-OMe (2)	oil	—	$C_{19}H_{24}N_2O_5$ (360·4)	63·32 63·79	6·71 6·99	7·77 7·58	− 44·8° (0·5)
Z-L-Pip-Gly-OMe (2)	oil	—	$C_{17}H_{22}N_2O_5$ (334·4)	61·07 61·45	6·63 7·17	8·38 7·94	− 45·4° (0·35)
Z-D-Pip-D-Leu-OMe (2)	72— 74 (75)	73— 75 A	$C_{21}H_{30}N_2O_5$ (390·5)	64·60 64·69	7·74 7·70	7·17 7·19	+ 60·0° (0·5)
Z-D-Leu-D-Pip-OMe (2)	oil	—	$C_{21}H_{30}N_2O_5$ (390·5)	64·60 64·84	7·74 7·26	7·17 6·79	+ 61·5° (0·3)
HBr.H-D-Leu-D-Pip-OMe (2)	162—165 (69)	165—169 B	$C_{13}H_{25}BrN_2O_3$ (337·5)	46·33 46·24	7·48 7·61	8·31 7·88	+ 75·1°[f] (0·4)
Z-D-Pip-L-Leu-OMe (2)	oil	—	$C_{21}H_{30}N_2O_5$ (390·5)	64·60 64·37	7·74 8·02	7·17 7·60	+ 12·3° (0·9)
Z-D-Pip-D-Pip-OMe (2)	61— 63 (78)	61—62·5 C	$C_{21}H_{28}N_2O_5$ (388·4)	64·93 64·80	7·27 7·34	7·21 7·02	+ 76·6° (0·4)
Z-L-Pip-D-Pip-OMe (2)	oil[g]	—	$C_{21}H_{28}N_2O_5$ (388·4)	64·93 64·76	7·27 6·82	7·21 7·47	+ 22·6° (0·15)
Z-L-Pip-L-Pro-OMe (2)	oil	—	$C_{20}H_{26}N_2O_5$ (374·4)	64·16 64·47	7·0 7·03	7·48 7·37	− 92·0° (1·4)
Z-D-Pip-L-Pro-OMe (2)	oil	—	$C_{20}H_{26}N_2O_5$ (374·4)	64·16 64·22	7·0 7·36	7·48 7·36	+ 0·8° (0·35)

[a] M.p. of substance in the given yield. [b] M.p. of sample for analysis. [c] In methanol, unless otherwise stated. [d] Based on N-protected amino acids. [e] A ethyl acetate–light petroleum, B methanol–ether, C ether–light petroleum. [f] In water. [g] Derivative of N-acylurea also formed, m.p. 140—141°C (ether–light petroleum); $[\alpha]_D^{25}$ +11·6° (*c* 0·5, methanol); for $C_{27}H_{39}N_3O_4$ (469·6) calculated: 69·05% C, 8·37% H, 8·95% N; found: 69·37% C, 8·58% H, 9·03% N). During reaction carried out at −20°C for 5 h, then 12 h at 4°C, the N-acylurea derivative did not arise.

All the cyclodipeptides were prepared by cyclisation of dipeptide methyl esters in methanol with addition of methanolic ammonia. Cyclisation to compound *Ib* occurred in less than 15 min, *i.e.* more rapidly than this process occurs with previously described dipeptide esters[11,12]. The dipeptide methyl esters were prepared by the dicyclohexylcarbodiimide method using benzyloxycarbonyl or *o*-nitrobenzenesulphenyl protecting groups.



I; n = m = 4
II; n = 4, m = 3
III; n = m = 3



IV; n = 4, R = H
V; n = 4, R = i-C_4H_9
VI; n = 3, R = H
VII; n = 3, R = i-C_4H_9

a cis-disubstituted at $C_{(3)}$ and $C_{(6)}$, *b trans*.

EXPERIMENTAL

Melting points were determined on a Kofler block, unless otherwise stated. Sublimation was carried out at a pressure of 1—3 Torr and at temperature 10°C less than the melting point. Crystalline samples for analysis and physical measurements were dried one day, oily samples 3 days at 0·5 Torr over P_2O_5. Salts were dried over KOH. Optical rotation was measured on a photoelectric polarimeter. The molecular weight of 2,5-piperazinediones (Mass spectrometer MS 902) corresponded to theoretical values.

Linear Peptide Intermediates

a) *Method* 1: To the dicyclohexylammonium salt of *o*-nitrobenzenesulphenyl-L-proline (4·5 g) and the hydrochloride of D-leucine methyl ester (2·0 g) in chloroform (100 ml) at 0°C N,N′-dicyclohexylcarbodiimide (2·15 g) was added. After standing overnight at 4°C chloroform was evaporated off and ethyl acetate was added. The solution was filtered, washed with 0·05M-H_2SO_4, 0·5M-$NaHCO_3$, and water and then dried with Na_2SO_4. Evaporation gave an oil (4 g) which was refluxed with bis(*p*-toluenesulphonyl)amine (3·8 g) in methanol (100 ml) for 30 min after solution of the first precipitated material. The course of the reaction was followed using thin-layer chromatography[13]. The residue after evaporation was ground up several times with light petroleum, then with ether until crystallisation of the salt of the L-prolyl-D-leucine methyl ester with bis(*p*-toluenesulphonyl)amine (Table I). b) *Method* 2: To the solution of benzyloxycarbonyl-D-pipecolic acid (395 mg) and L-proline methyl ester, prepared using ammonia in chloroform from L-proline methyl ester hydrochloride (250 mg) in chloroform (30 ml), N,N′-dicyclohexylcarbodiimide (320 mg) was added at −10°C. After standing overnight at 4°C 4 drops of acetic acid were added, the mixture left for 2 h at room temperature, chloroform was evaporated off, and the residue was dissolved in ethyl acetate. N,N′-Dicyclohexylurea was filtered off and the solution was washed with 1M-HCl, 0·5M-$NaHCO_3$, and water, dried with Na_2SO_4 and evaporated three times with benzene. In order to remove N,N′-dicyclohexylurea the residue was dissolved in ether, the solution filtered and evaporated, the residue dissolved in hot light petroleum and again filtered. Evaporation yielded the oil of benzyloxycarbonyl-D-pipecolyl-L-proline methyl ester.

TABLE II
Properties of Cyclodipeptides

Cyclodipeptide (method)	M.p., °C[a] (yield[d], %)	M.p., °C[b] solvent[e]	Formula (m.w.)	Calculated/Found %C	%H	%N	$[\alpha]_D^{25c}$ (c)
c(D-Pip-D-Pip)	105—107·5	105—108	$C_{12}H_{18}N_2O_2$	64·84	8·16	12·60	+ 50·4°
Ia (2)	(22)	A	(222·3)	64·49	8·34	12·57	(0·45)
c(L-Pip-D-Pip)	225·5—226	227—228	$C_{12}H_{18}N_2O_2$	64·84	8·16	12·60	—
Ib (2)	(34)	B[f]	(222·3)	65·11	8·39	12·61	
c(L-Pip-L-Pro)	143—149	150—154	$C_{11}H_{16}N_2O_2$	63·44	7·74	13·45	— 8·8°
IIa (2)	(50)	C[f]	(208·3)	63·36	7·92	13·39	(0·28)
c(D-Pip-L-Pro)	123—127	125—130	$C_{11}H_{16}N_2O_2$	63·44	7·74	13·45	— 4·3°
IIb (2)	(41)	A	(208·3)	63·62	7·86	13·35	(0·23)
c(L-Pro-L-Pro)[g]	132—141[h]	140—144[h]	$C_{10}H_{14}N_2O_2$	61·84	7·27	14·42	—151·6°[i]
IIIa (2)	(53[j])	D	(194·2)	62·15	7·34	14·14	(0·5)
c(D-Pro-L-Pro)[k]	190—196	194—199	$C_{10}H_{14}N_2O_2$	61·84	7·27	14·42	—
IIIb (2)	(37)	E[f]	(194·2)	61·59	7·29	14·11	
c(D-Pip-Gly)	160—164	161—165	$C_8H_{12}N_2O_2$	57·12	7·19	16·65	+ 8·2°
IV (2)	(43)	B[f]	(168·2)	57·35	7·25	16·69	(0·5)
c(D-Leu-D-Pip)	113—118	113—117	$C_{12}H_{20}N_2O_2$	64·26	8·99	12·49	+ 21·4°
Va (2)	(39[l])	A	(224·3)	64·08	9·15	12·65	(0·5)
c(D-Pip-L-Leu)	149—151	150—151	$C_{12}H_{20}N_2O_2$	64·26	8·99	12·49	— 7·4°
Vb (2)	(43)	B	(224·3)	64·25	8·99	12·49	(0·5)
c(L-Pro-Gly)[m]	208—212	209—210	$C_7H_{10}N_2O_2$	54·53	6·54	18·17	—196·5°[i]
VI (1)	(31)	F	(154·2)	54·38	6·53	17·99	(0·5)
c(L-Pro-L-Leu)[n]	140—162	164—167	$C_{11}H_{18}N_2O_2$	62·83	8·63	13·32	—145·4°[i]
VIIa (1)	(41)	G	(210·3)	62·94	8·65	13·27	(0·5)
c(L-Pro-D-Leu)[o]	144—149	148—151	$C_{11}H_{18}N_2O_2$	62·83	8·63	13·32	— 93·9°[i]
VIIb (1)	(25)	H	(210·3)	62·86	8·51	13·41	(0·5)

[a]M.p. of substance in the given yield; [b]m.p. of the sample for analysis; [c]in methanol, unless otherwise stated; [d]based on N-protected amino acid; [e]A ether–light petroleum, B ethanol–ether, C ethyl acetate–light petroleum, D 2-propanol–ether, E 2-propanol–ether–light petroleum, F ethanol, G acetone; H benzene; [f]first recrystallised and then sublimated; [g]citation[14] gives a m.p. of 146°C and $[\alpha]_D^{20}$ −147·2° (*c* 0·5, water); [h]in sealed capillary on a Thiele apparatus; [i]in water; [j]prepared also by method I with a 33% yield; [k]reference[15] given a m.p. of 179—181°C; [l]prepared also from Z-D-Pip-D-Leu-OMe in a 22% yield; [m]literature gives a m.p. of 213°C (refs[16,17]) and $[\alpha]_D^{20}$ −217·4° (*c* 7·5, water) (ref.[16]), $[\alpha]_D^{20}$ −197·3° (*c* 8·1, water)[17]; [n]literature gives a m.p. of 150—160°C (ref.[16]), 170—171°C[9], $[\alpha]_D^{20}$ −144° (*c* 0·5, water)[9]; [o]reference[7] gives for cyclo(D-Pro-L-Leu) a m.p. of 148—150°C and $[\alpha]_D^{20}$ +92° (*c* 1, water).

Cyclodipeptides

a) *Method I*: To a solution of the salt of the L-prolyl-D-leucine methyl ester with bis(*p*-toluenesulphonyl)amine (2·5 g) in chloroform (20 ml) a saturated solution of ammonia in chloroform was added. The ammonium salt of bis(*p*-toluenesulphonyl)amine was filtered off, the solution was evaporated, 50 ml of methanol were added to the remainder and a saturated solution of ammo-

nia in methanol (1 ml). The next day the solution was evaporated, the product sublimated and recrystallised (Table II). b) *Method 2*: To the benzyloxycarbonyl-D-pipecolyl-L-proline methyl ester (240 mg, oil) 35% HBr in acetic acid (5 ml) was added. After 30 min the reaction mixture was evaporated, the remainder was ground up several times with ether. The further processing was the same as in *a*).

Spectroscopic Measurements

Infrared spectra were measured on a Perkin-Elmer 621 instrument, with a precision of $\pm 1{\cdot}5\ cm^{-1}$. For substances measured in chloroform 3%, or saturated solutions were used. Cell thickness was 0·1 mm; nujol suspensions had a thickness of 0·03 mm. Raman spectra were measured on a DFS 12 instrument.

IIa (3% in chloroform,): 411 m, 419 m, 441 m, 488 sh, 519 vw, 579 m, 623 s, 837 m, 867 s, 888 w, 900 w, 921 vw, 938 vw, 949 w, 986 s, 1015 w, 1025 w, 1056 m, 1070 w, 1115 m, 1139 s, 1156 w, 1174 w, 1185 w, 1256 vs, 1266 m, 1278 m, 1300 vs, 1308 sh, 1332 s, 1347 s, 1366 w, 1443 vs, 1450 sh, 1458 sh.

IIb (in chloroform): 415 m, 420 m, 439 vw, 477 m, 489 m, 550 s, 582 w, 621 s, 843 m, 863 m, 885 w, 900 w, 920 m, 938 vw, 948 w, 972 s, 1011 w, 1019 w, 1059 s, 1069 m, 1085 vw, 1102 m, 1126 s, 1140 m, 1159 w, 1186 m, 1253 vs, 1266 m, 1278 m, 1300 vs, 1310 vs, 1331 w, 1343 vs, 1356 sh, 1440 vs, 1452 vs, 1460 vs.

Ia (nujol): 390 m, 410 w, 433 m, 469 s, 499 m, 551 w, 651 m, 668 w, 681 m, 747 m, 763 m, 807 w, 834 w, 850 s, 871 s, 892 w, 938 sh, 948 s, 978 m, 993 w, 1040 s, 1057 vw, 1081 m, 1119 s, 1144 m, 1179 s, 1231 vs, 1251 s, 1276 vs, 1303 s, 1330 s, 1340 s, 1347 s, 1351 sh.

Ib (nujol): 396 s, 438 m, 486 s, 548 m, 656 m, 747 s, 809 w, 851 s, 890 m, 938 w, 960 s, 1048 s, 1073 vw, 1089 s, 1118 m, 1148 m, 1178 m, 1230 s, 1253 vs, 1279 s, 1299 vs, 1320 vs, 1333 vw, 1343 w, 1348 w. (Raman spectrum, tablet): 452 m, 486 s, 629 s, 671 m, 768 m, 836 m, 857 s, 938 m, 991 s, 1060 s, 1077 vs, 1261 s, 1302 s, 1331 s, 1440 s, 1494 s.

IIIa (nujol): 373 s, 426 m, 471 m, 487 m, 553 s, 594 s, 629 vs. 770 m, 782 vw, 793 w, 841 m, 865 m, 880 s, 891 vw, 910 s, 920 vs, 940 w, 995 w, 969 m, 1000 vs, 1015 vw, 1026 w, 1035 vw, 1050 m, 1069 s, 1085 vw, 1100 vw, 1124 vw, 1136 sh, 1161 vs, 1179 vw, 1190 vw, 1203 s, 1209 s, 1234 s, 1269 s, 1279 s, 1289 s, 1310 vs, 1316 w, 1335 s.

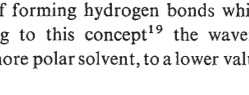
IIIb (nujol): 362 s, 475 s, 609 s, 659 vs, 762 s, 882 m, 917 s, 965 m, 1007 vs, 1074 m, 1143 sh, 1151 vs, 1179 s, 1200 vs, 1215 sh, 1279 sh, 1299 vs, 1328 vs, 1343 m. (Raman spectrum, tablet): 368 s, 439 s, 467 m, 555 vs, 643 w, 928 vs, 1283 s, 1457 s, 1488 s.

Selected data from the 1300—1700 cm^{-1} region of the spectra of substances *I*—*III* in tetrachloromethane are presented in Table III. Wavenumber values of ν(C=O) and ν(N—H) of substances *IV*—*VII* in chloroform are shown in Table IV.

RESULTS AND DISCUSSION

Particular attention in the interpretation of the results is given to the stretching vibrations of the $C_{(O)}$—N and C=O bonds which are typical for the amide group. These vibrations are also the most important contributors to the origin of bands (*e.g.* amide-I, amide-II and amide-III bands) which are usually exploited for conformational studies in peptides.

Whereas the vibration of the C=O bond is always characteristic and occurs isolated from the other vibrational bands, the wavelength of the stretching vibration of the $C_{(O)}$—N bond falls into the region of deformation vibrations of C—H bonds. The $\nu(C_{(O)}—N)$ and $\delta(C—H)$ vibrations can be therefore coupled and one must consider the occurrence of several bands with a greater or lesser contribution of the $\nu(C_{(O)}—N)$ vibration[18]. For the detection of bands, to the origin of which is a contribution from the $\nu(C_{(O)}—N)$ vibration, we used the effect of a change in solvent (tetrachloromethane *vs* chloroform) on the state of the amide bond. A polar solvent shifts the distribution of electrons towards the dipolar structure *A*. Chloroform has an additional effect of forming hydrogen bonds which also increase the weight of structure *A*. According to this concept[19] the wavenumber of $\nu(C=O)$ shifts, during the transition to a more polar solvent, to a lower value, and vibration $\nu(C_{(O)}—N)$ to a higher.



B *A*

Individual vibrational modes can be influenced by changes in molecular geometry. In the present series the source of geometric change is annelation of further 5 and/or 6-membered rings. In comparing the known spatial arrangement of 2,5-piperazinedione[20] or its N,N′-dimethyl derivative[21] there can be seen (Fig. 1): *a*) a change in the conformation of the 2,5-piperazindione ring (change in angles Φ and Ψ), *b*) deformation of valence angles ϱ_1, *c*) a change in the torsion angle ω about the $C_{(O)}$—N bond. In a system of three linearly anneled rings the conformation of the central ring A depends particularly on the relative configuration at the sites of annelation. For both symmetric *trans*-dianneled systems *Ib*, *IIIb*, the A ring, according to analysis of Dreiding models, takes on a planar arrangement, or possibly a slightly deformed one in the direction of a flattened chair[22]. This arrangement is not in disagreement with the general requirement that the conformation of *trans*-3,6-disubstituted 2,5-piperazindiones with equal substituents can show symmetry C_1 or C_i, but not C_2. *cis*-Dianneled compound *IIIa* with two five-membered rings has, on the other hand, its A ring in a boat form; in compound *Ia* we must consider a similar boat conformation or strainless conformation with planar ring A. These arrangements are in agreement with the

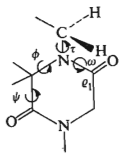


FIG. 1
Angle Designation in a Peptide Group

requirement that *cis*-substituted 2,5-piperazindione with equal substituents can show symmetry C_1 or C_2, but not C_i. The diastereoisomeric pair *II* has in both cases the A ring in boat conformation, in *cis*-isomer *IIa* much deeper than in *trans*-isomer *IIb*. The arrangement of the end rings is given from model inspection only for compound *III*. In the other cases greater or lesser fluctuations in conformation are possible. As shown by NMR measurements[22] the geometric arrangement of substances *I* and *III* in solution are symmetric. The symmetric properties derived for the central ring are therefore in agreement with the symmetric properties of the molecule.

Comparison of the infrared spectra and number of bands contained therein allowed us to show that compounds *I* and *III* have a single conformation both in crystal and solution and that *cis* and *trans* isomers differ in the degree of symmetry. As an example of symmetry C_1 let us take two diastereoisomers of *II*. The spectra of both compounds differ only in the intensity of the individual bands, not in their number. On the other hand, the number of bands in the diastereoisomers of *III* differ in nujol and in chloroform; *cis*-isomer *IIIa* has roughly twice as many bands as *trans*-isomer *IIIb*. Bands which are active in the infrared spectrum of *cis*-isomer *IIIa*, but inactive in that of *IIIb*, occur as active bands in the Raman spectrum of *trans*-isomer *IIIb*. On the other hand, some bands present in the infrared spectrum of *cis*- and *trans*-isomers are missing from the Raman spectrum of *trans*-isomer *IIIb*. An analogous situation exists with the isomers of substance *I*. Both *trans*-isomers *Ib* and *IIIb* therefore must be associated with a higher degree of symmetry than *cis*-isomers *Ia* and *IIIa*.

Vibration $\nu(C_{(0)}—N)$

In the spectra of isomeric pairs *I*—*III* between 1400 and 1500 cm^{-1} there occur two types of bands sensitive to solvent. In compounds with conformation of the A ring near to planarity (all *trans*-isomers and *Ia*) we find a band at about 1455 cm^{-1} in the remaining two *cis*-isomers *IIa* and *IIIa* (with a boat conformation of the A ring) at the lower wavenumber of 1420 cm^{-1} (Table III). The large solvent shift in the bands around 1420 cm^{-1} suggests a large contribution of $\nu(C_{(0)}—N)$ to the band and a small – if any – contribution associated with vibration $\delta(C—H)$. On the other hand the solvent shift of bands around 1455 cm^{-1} in substances *Ia*, *Ib*, *IIb*, *IIIb* is less, and is manifest in more bands as a result of coupling with the deformational C—H vibrations.

The reason for these differences in position and particularly in character of the vibrations $\nu(C—N)$ in individual substances can be sought in a number of factors. The first would be the concept that coupling of vibrations $\nu(C—N)$ and $\delta(C—H)$ depends upon the spatial relation of the amide bond to the C—H bonds of the methylene groups around the N atom, expressed in the value of angle τ. This is an approach principally similar to that used for the analysis of $\nu(OH)$ and $\nu(SH)$ vibrations[23]. Analysis of Dreiding models of the diastereoisomers *III*, however, show (as confirmed also by the NMR spectrum)[22] that there is no great difference

in the τ angle values between the two, even though the bands of vibrations $\nu(C_{(O)}—N)$ in their spectra are quite different. The principal factor cannot be sought even in changes in the valence angles, which are always approximately the same in the pair of diastereoisomers. This is clear also in comparing the spectra of substances *Ib* and *IIb*, which are not associated with a large difference in the conformation of the A ring, but annelation of one six-membered and one five-membered ring results in differences in the valence angles. Whereas the wavenumber of $\nu(C=O)$ in *IIb* is 7 cm^{-1} higher, suggesting a sharper valence angle ϱ_1 than in *Ib*, the wavenumber of $\nu(C_{(O)}—N)$ in both compounds is the same. However, the change in the valence angles might be in relation to the intensity of the band contributed by the $(C_{(O)}—N)$ vibration. (The intensity increases in the order *Ia,b* < *IIa,b* < *IIIa,b* independent of the position of the bands (Fig. 2)). We cannot, however, exclude the effect of

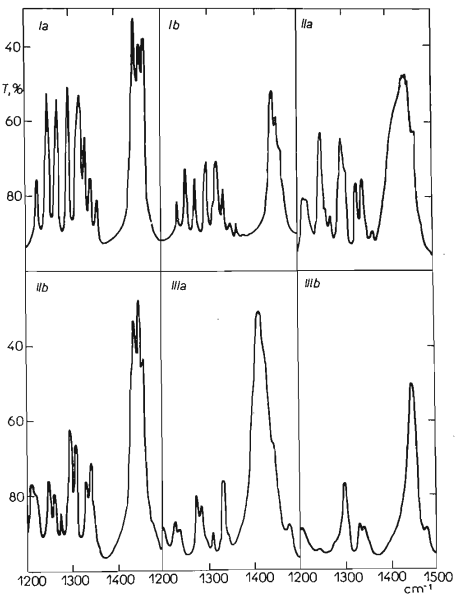


FIG. 2

The Region of Deformation Vibrations of C—H Bonds Ranging from 1300—1500 cm^{-1} for the Compounds *Ia*, *Ib*, *IIa*, *IIb*, *IIIa*, and *IIIb*

changes in the torsion angle ω. The latter would of necessity decrease the wavenumber of $\nu(C_{(O)}—N)$ from values for a planar arrangement (for perdeuterated N,N-dimethylacetamide the vibration at 1430 cm^{-1} is characteristic[24] so that

TABLE III

Wavenumbers of Bands (cm^{-1}) in the Region 1 300—1 700 cm^{-1} for Substances *I—III*

Given are values measured in tetrachloromethane; in brackets are differences (cm^{-1}) in wavenumber when measured in chloroform.

Substance	ν(C═O)[a]	Bands with contribution ν(C—N)[b]			
Ia	1 662·4	1 460 (5);	1 453 (2)	1 321 (2)	
Ib	1 663·0	1 455 (5);	1 441 (2)	1 320 (3)	
IIa	1 668·7	1 425 (18)	—		
IIb	1 669·4	1 455 (5);	1 449 (3)	1 340 (3)	1 297 (3)
IIIa	1 676·8	1 420 (15)[c]	—	1 310 (3)	1 275 (3)
IIIb	1 670·8	1 451 (7·6)[d]		1 341 (3)	

[a]Measured as saturated solution in KBr cells 0·5 mm thick with a precision of ±0·5 cm^{-1}, calibration with water vapour. [b]Measured in saturated solutions, KBr cell 0·5 mm thick, program with precision of ± 1·5 cm^{-1}, calibration with polystyrene; for measurement in chloroform 3% solutions were used (with compounds of lower solubility saturated solutions), KBr cell 0·1 mm. [c]For measurement in KBr disc the literature[6] gives ν(C═O) 1 667 cm^{-1}, ν(C—N) 1 434 cm^{-1}. [d]Measured with a precision of ±0·5 cm^{-1}.

TABLE IV

Main Vibrational Bands (cm^{-1}) of Substances *IV—VII*

Spectra were measured in tetrachloromethane; concentration 4 . 10^{-4}M; cells 1 cm NaCl for the ν(C═O) region, 10 cm infrasil for the ν(N—H) region; calibration with water vapour and ammonia; precision of measurement ±0·5 cm^{-1}.

Substance	ν(C═O) tert-amide	ν(C═O) sec-amide	ν(N—H)
IV[a]	1 668·4	1 699·8	3 411·6
Va	1 662·6	1 693·9	3 404·1
Vb	1 662·4	1 694·0	3 403·3
VI	1 681·9	1 706·4	3 425
VIIa	1 679	1 702·2	3 418
VIIb	1 674	1 699	3 417

[a]Measured in saturated solution.

it is far from the frequency of vibrations with which it should be coupled. In our models this explanation is not very satisfactory because the deviation of the amide group from planarity cannot be large, particularly in substance *IIa*. More plausible would appear to be the possibility of mutual interaction of the $\nu(C_{(O)}-N)$ vibration of both amide groups, which would be different in a planar and in a boat conformation of the 2,5-piperazindione ring.

The ν(C=O) *Vibration*

The conformation of the A ring does not influence the stretching vibration of the carbonyl group. At least in substances *I* and *II*, in each pair the wavenumbers of ν(C=O) are practically the same (Table III) even if between diastereoisomers *IIa* and *IIb* there is a marked difference in conformation of ring A. *cis* and *trans* Annelations are equal in their effect. There is a far greater difference (about 6 cm^{-1} between pairs *I* and *II*) associated with varied size of the anneled ring B. A decrease in size of the anneled ring results in a change of the valence angles in the central ring, which manifests itself in the angle ϱ_1 (both C=O groups) as a sharpening, and thus increases the wavenumber (compare ν(C=O) of cyclanones[25] and lactams[26] with varied ring sizes). The situation in pair *III* is different, since here there is a marked difference in the ν(C=O) wavenumber between the two isomers. The *trans*-isomer *IIIb* is only slightly raised over *trans*-isomer *IIb* (by 1·4 cm^{-1}) which can be interpreted as a further slight sharpening of angle ϱ_1 as a result of the annelation of a further five-membered ring. On the other hand, *cis*-isomer *IIIa* shows an increase over *cis*-isomer *IIa* by 8 cm^{-1}. This relatively large change can hardly be explained as a further – this time of necessity a major – change in angle ϱ_1. More plausible is the assumption that the increase in wavenumber of the ν(C=O) vibration in *cis*-isomer *IIIa* is caused by a deviation of the amide group from planarity. We can appreciate this deviation by comparison with polycyclic lactams with known non-planar amide groups[19]. The resulting values are similar to values found for one of the amide group in *cis*-disubstituted cyclo(L-alanyl-L-alanine)[27,28].

Qualitatively similar behaviour as in isomer pairs *I*–*III* can be observed in pairs *V* and *VII* (Table IV). Pair *V*, containing a six-membered ring of pipecolic acid, has for the ν(C=O) vibration of the tertiary amide group the same wavenumber as pair *I*. Pair *VII* with an anneled 5-membered ring of proline shows a difference in the ν(C=O) wavenumber between both isomers which is less than the difference in the isomers *III*, but of the same sign. Values for the ν(C=O) vibration of secondary amide groups go in parallel with changes for tertiary groups. Annelation of the second 5-membered ring and substitution of an isobutyl group are therefore manifest in the same way; even from this aspect the most attractive explanation of the behaviour of substances *IIIa* and *VIIa* involves a concept of greater torsion on the amide bond in the *cis*-disubstituted isomer.

From comparison of substance *IV* with the isomeric pairs *V*, and substance *VI* with the isomeric pairs *VII*, one can see the influence of the isobutyl substituent on the ν(C=O) wavenumber. In both cases there is a decrease in ν(C=O) wavenumber of the tertiary amide of 6 cm^{-1}, of the same magnitude as introducing a second 6-membered ring (compare substance *IV* with the isomeric pair *I*). The same decrease in wavenumber is manifest in the ν(C=O) of the secondary amide group. The effect of the substituent on the C_α atom of the amino-acid residue is independent of its relative configuration and can be explained as predominantly one of mass[29]. By comparison of the wavenumber of ν(C=O) in substances *IV* and *VI*, and also of the pairs *V* and *VII*, we see a direct effect of the difference in the valence angle ϱ_1 as a result of condensation of the 6-membered or 5-membered ring. The changes described for vibrations ν(C=O) in substances *IV*–*VII* find a parallel also in ν(N—H) vibrations (Table IV).

It would appear that the vibrations of "exo bonds" in the amide group, *i.e.* C=O and N—H bonds, which in lactams appear as exo-cyclic bonds, are governed by other spatial factors than the vibrations of the C—N bond which is always part of the chain. If we glance away from changes in planarity of the amide group, which of necessity change the entire electron structure and influence vibrations of all bonds, then particularly with vibrations of the "exo bonds" (C=O and N—H) the action of valence angles is manifest. On the contrary, the vibration of a $C_{(\alpha)}$—N bond can be influenced by an intrachenar interference with other chromophores in the main chain. In the present work we have been thus far unable to discuss the problem in greater detail – summation of data from a larger group of different molecules may make deeper analysis possible.

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