1-AMINOCYCLOPROPANECARBOXYLIC ACID AND ITS DERIVATIVES*

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Action of strongly basic reagents on methyl N^{α}-benzyloxycarbonylamino-γ-bromobutyrate leads to 1-aminocyclopropanecarboxylic acid derivatives whose structure was determined by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. According to IR spectroscopy, the urethane CO—NH group in crystalline methyl 1-benzyloxycarbonylaminocyclopropanecarboxylate exists in the *cis*(*E*) conformation which on dissolution is transformed into the *trans*(*Z*) form. NMR spectroscopy showed that the acid-catalyzed esterification of α-amino-γ-bromobutyric acid is accompanied by replacement of the covalently bonded bromine by chlorine.

Methyl N^{α}-benzyloxycarbonylamino-γ-bromobutyrate[1] (*IIc*) was the key intermediate in the preparation of cystathionine derivatives[1–3], suitable for the synthesis of carba-analogues of peptide hormones. The possibility of nucleophilic substitution of the bromine atom in the γ-position made the compound *IIc* useful for preparation of other non-coded amino acids. The bromine atom was replaced by iodine, nitro group, thiocyanate group, hydrogen, hydroxyl[4] and cyano group[5]. The compound *IIc* served also as the starting material for preparation of homolanthionine[4], Se-benzylselenohomocysteine, selenomethionine and selenoethionine (all ref.[6]).

Action of strongly basic reagents such as sodium in ether, sodium ethoxide, sodium salts of C-acids (diethyl malonate, ethyl acetoacetate, diethyl acetamidomalonate) or phenyl lithium on methyl N^{α}-benzyloxycarbonylamino-γ-bromobutyrate (*IIc*) did not afford any of the desired products but, instead, led to the cyclic derivative, 1-aminocyclopropanecarboxylic acid. The reactions resemble the formation of methyl 1-tert-butyloxycarbonylaminocyclopropanccarboxylate from sulfonium salt of methyl N-tert-butyloxycarbonylmethioninate by action of sodium hydride or cesium carbonate[7].

The absence of the characteristic signal due to α-CH proton (δ 4·0–5·0) in the ^{1}H NMR spectra of compounds *Ia–Ic* excludes the formation of the possible dimeric

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product *III*. The compounds *Ia*–*Ic* exhibit a four-spin AA'BB' system in the region δ 1·0–1·6 and compounds *Ia* and *Ib* moreover the $COOCH_3$ and $NHCOOCH_2C_6H_5$ signals. The ^{13}C NMR ^1H-off resonance decoupled spectrum of compound *Ic* displays a triplet at δ 13·56 due to two equivalent CH_2 carbon atoms and singlets due to quaternary carbon atoms at δ 37·12 and 177·18. Therefore, compounds *Ia*–*Ic* must have a cyclic structure with symmetrically equivalent carbon atoms. Neither the proton nor carbon chemical shifts observed represent any unequivocal proof of a cyclopropane ring; this may be due to its substitution. The coupling constants, obtained by simulation-iterative analysis of the spectrum of *Ic* (particularly the low geminal coupling constant $J_{AB} = J_{A'B'} = -5{\cdot}92$ Hz; for complete data see Table I) confirms unequivocally a 1,1-disubstituted cyclopropane structure.

Mass spectrum of the compound *Ia* displayed molecular peak 249, however, also higher peaks due to trace impurities were present. The molecular weight of the compound *Ib* was determined both cryoscopically and by vapour pressure osmometry[8]. The free 1-aminocyclopropanecarboxylic acid (*Ic*) whose synthesis was several times described[7,9–16] was prepared from the derivative *Ib* by acid hydrolysis. Its mass spectrum[17] as well as IR spectra[18,19] (save small differences in the $\delta(NH_3^+)$ and $\nu(COO^-$ bands)) were identical with the published values.

The IR spectra of compound *Ic* revealed two crystalline phases differing apparently only in the arrangement and symmetry of the unit cell but not in molecular conformation. This was obvious from the change of the spectra of both the crystalline phases: the transition from one phase into the other (at 85–95°C) was accompanied only with changes caused by crystal effects[20]. The overall shape of the spectrum, however[4], remained unchanged.

The spectral data for compounds *Ia*–*Ic* are given in Table I (^1H and ^{13}C NMR spectra) and Table II (IR spectra).

Analysis of the reaction mixtures revealed that the unreacted methyl benzyloxycarbonylamino-γ-bromobutyrate was in fact a mixture of two compounds: the γ-bromobutyric acid and γ-chlorobutyric acid derivatives. Using the NMR spectroscopy we found that both these derivatives were already present (though in other ratio) in the starting compound *IIb* (ref.[1]) whereas the derivative *IIa* (ref.[1]) contained only the bromo derivative. It follows thus that the hydrogen chloride catalyzed esterification of α-amino-γ-bromobutyric acid hydrobromide (*IIa*) is accompanied by a partial replacement of bromine by chlorine. The ^1H NMR spectrum of compound *IIc* displayed the expected signals of benzylic protons and NH, $COOCH_3$ and —CH——CH_2—CH_2 groupings (for data see Table III). The doubling of the γ-CH_2 signal (triplets at δ 3·41 and 3·57 with intensity ratio 86 : 14) showed the presence of a small amount (14%) of the chloro derivative in which the replacement of bromine by chlorine affected markedly only the γ-CH_2 protons. Also, the ^{13}C NMR spectrum led to the same conclusion, however, in this case the double signals were observed for γ-, β-, as well as α-carbons (triplets at δ 28·29 and 40·50, triplets at δ 35·33 and

35·06 and doublets at δ 52·80 and 51·76); the intensity ratios were again 86 : 14 (Table III).

In model experiments we studied whether the esterification with methanolic hydrogen chloride was accompanied by halogen substitution also in other bromo acids. Negative results were obtained with both γ-bromobutyric and α-bromopropionic acids. It follows thus that the amino group is essential for this substitution. In nucleophilic substitutions at the halogen atom of compound *IIc* the bromo derivative reacted preferentially and the remaining unreacted compound, isolated after reaction, was invariably enriched in the chloro derivative (in some cases more than 50%). The chloro and bromo derivatives of methyl α-benzyloxycarbonylaminobutyrate

TABLE I

^{1}H NMR and ^{13}C NMR parameters of 1-aminocyclopropanecarboxylic acid and its derivatives

Groups	*Ia* (C^2HCl_3)	*Ib* (C^2HCl_3)	*Ic* (^2H_2O)
		^{1}H NMR	
$-CH_2-CH_2-$ [a]	1·21 m 1·56 m	1·26 m 1·62 m	0·96 m 1·11 m
$-NH-$	5·32 s	5·40 s	[b]
C_6H_5	7·35 m	7·34 m	—
$-CH_2-$ [c]	5·14 s	5·13 s	—
$-COOCH_3$	3·66 s	—	—
$-COOH$	—	6·71 s	[b]
		^{13}C NMR	
$-CH_2-CH_2-$	17·93 t	18·51 t	13·56 t
$-C-$	34·53 s	34·27 s	37·12 s
$-COO-$	173·22 s	178·55 s	177·18 s
$-CO-NH-$	156·50 s	156·73 s	—
$-CH_2-$ [c]	66·92 t	67·10 t	—
C_6H_5- [d]	136·32 s	136·18 s	—
[e]	128·50 d	128·50 d	—
[f]	128·12 d	128·12 d	—

[a] An AA′BB′ system; multiplet centers are given; the parameters for *Ic* were obtained by the simulation iterative procedure: $J_{AA'} = 10{\cdot}65$, $J_{BB'} = 10{\cdot}62$, $J_{AB} = J_{A'B'} = -5{\cdot}92$, $J_{AB'} = J_{A'B} = 7{\cdot}73$ Hz; [b] in ^2H_2O the protons are replaced by deuterium and are thus not observed; [c] benzylic methylene; [d] quaternary aromatic carbon atom; [e] aromatic carbon atoms in *ortho*-positions; [f] aromatic carbon atoms in *meta*- and *para*-positions.

can be separated by HPLC on a reverse phase. Also mass spectrometry revealed that the compound *IIc* exhibited, in addition to two molecular peaks 329 and 331 (in the ratio 1 : 1, corresponding to the population of isotopes ^{79}Br and ^{81}Br), also molecular peaks 285 and 287 (in the ratio 3 : 1, corresponding to the population of isotopes ^{35}Cl and ^{37}Cl) due to methyl benzyloxycarbonylamino-γ-chlorobutyrate.

TABLE II

Infrared data for 1-aminocyclopropanecarboxylic acid and its derivatives (wavenumbers in cm^{-1})

Groups	Approximate assignment	*Ia*	
		$CHCl_3$	KBr
$C_6H_5CH_2$—OCONH—	ν(NH)	3 440 (m)	3 310 (s) 3 295 (s)
	ν(CO)	1 730 (vs) 1 715 (sh)	1 685 (s)
	trans amide II	1 505 (s)	—
	δ(CH)[b]	702 (m)	699 (m)
—$COOCH_3$	ν(CO)	1 740 (sh)	1 732 (sh)
	$\delta(CH_3)$	1 440 (m)	1 440 (m)
	ν(C—O)	1 169 (s)	1 171 (s)
—COOH	ν(OH)	—	—
	ν(CO)	—	—
	δ(—OH) + ν(C—O)	—	—
—COO^-	$\nu(COO^-)$	—	—
$=NH_2^{(+)}$	$\nu(NH_2)^{(+)}$	—	—
	$\delta(NH_2)^{(+)}$	—	—
—NH_3^+	$\nu(NH_3)^{(+)}$	—	—
	combination	—	—
	$\delta(NH_3)^+$	—	—
	δ(CH$_2$) sciss	[d]	[d]

[a] Dicyclohexylammonium salt; [b] phenyl out-of-plane bending; [c] group of bands; [d] cannot be

Methyl 1-benzyloxycarbonylaminocyclopropanecarboxylate (*Ia*) exhibited some interesting IR spectroscopic properties. The spectrum of the crystalline compound *Ia* differed very much from those taken in solutions (in tetrachloromethane, chloroform and bromoform). Spectrum of the crystalline compound exhibits neither *trans*-amide II (1 600–1 500 cm^{-1}) nor *trans*-amide III (1 300–1 200 cm^{-1}) bands

TABLE II
(*Continued*)

Ib		*Ib*.DCHA[a]		*Ic*
$CHCl_3$	KBr	$CHCl_3$	KBr	KBr
3 440 (m)	3 350 (s)	3 440 (m)	3 222 (m)	—
1 738 (vs)	1 695 (sh)	1 730 (vs)	1 733 (sh)	—
1 725 (sh)		1 715 (sh)	1 722 (s)	
1 504 (s)	1 542 (s)	1 505 (s)	1 524 (s)	—
	1 533 (sh)			
702 (m)	698 (m)	702 (m)	705 (m)	—
—	—	—	—	—
—	—	—	—	—
—	—	—	—	—
3 300–2 400 (m)[c]	3 100–2 400 (m)[c]	—	—	—
1 710 (s)	1 700 (s)	—	—	—
	1 715 (sh)			
	1 730 (sh)			
1 419 (m)	1 428 (w)	—	—	—
—	—	1 628 (vs)	1 628 (vs)	1 661 (sh)
		1 396 (vs)	1 405 (vs)	1 612 (vs)
				1 408 (vs)
—	—	2 700–2 200 (m)[c]	2 700–2 200 (m)[c]	—
—	—	1 565 (m)	1 585 (m)	—
—	—	—	—	~3 100 (s)
				~2 500 (m)
—	—	—	—	2 190 (m)
—	—	—	—	1 582 (ws)
				1 490 (vw)
[d]	[d]	[d]	[d]	1 451 (m)

assigned unequivocally since it interfers with bands due to other groups.

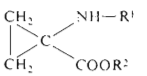
TABLE III

^{1}H and ^{13}C NMR parameters of the γ-bromo- and γ-chlorobutyric acid derivatives *IIa*—*IIc*

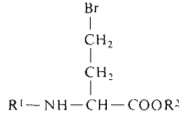
Groups	*IIa* (^2H_2O)[a]	*IIb* (^2H_2O)[b,c]	*IIc* (C^2HCl_3)[c]
		^{1}H NMR	
C_α—H	4·25 t $J_{\alpha,\beta}$ = 6·9; 6·5	4·37 m	4·50 m $J_{\alpha,\beta}$ = 8·5; 5·0 $J_{\alpha,NH}$ = 7·5
C_β—H_2	2·58 m $J_{\beta\beta}$ = −15·3, $J_{\beta\alpha}$ = 6·9 $J_{\beta\gamma}$ = 6·3; 6·4 2·42 m $J_{\beta\beta}$ = −15·3, $J_{\beta\alpha}$ = 6·5 $J_{\beta\gamma}$ = 7·1; 7·0	2·35—2·66 m	2·23 m 2·40 m
C_γ—H_2	3·66 m $J_{\gamma\gamma}$ = −10·8, $J_{\gamma\beta}$ = 6·3; 7·1 3·62 $J_{\gamma\gamma}$ = −10·8, $J_{\gamma\beta}$ = 6·4; 7·0	3·64 t (3·80 t)	3·41 t $J_{\gamma\beta}$ = 7·0; 7·0 (3·57 t)
$COOCH_3$	—	3·87 s	3·74 s
NH	—	—	5·54 bd $J_{NH,\alpha}$ = 7·5
CH_2—O	—	—	5·11 s
C_6H_5	—	—	7·33 m
		^{13}C NMR	
$C_\alpha H$	53·35 d	53·38 d (52·46 d)	52·80 d (51·76 d)
$C_\beta H_2$	34·63 t	34·53 t (34·37 t)	35·33 t (35·06 d)
$C_\gamma H_2$	30·21 t	29·99 t (42·15 t)	28·29 t (40·50 t)
—COO—	172·85 s	171·62 s (171·75 s)	172·01 s
—CH_3	—	55·87 q	52·63 q
—CONH—	—	—	155·97 s
—CH_2O—	—	—	67·12 t
C_6H_5—[d]	—	—	136·05 s
[e]	—	—	128·07 d
[f]	—	—	128·18 d, 128·48 d

[a] Parameters determined by simulation-iterative analysis of the spectrum; [b] the ^{1}H NMR spectrum cannot be analyzed in detail; according to the ^{13}C NMR spectrum the sample is a 63 : 24 mixture of bromo and chloro derivative which, moreover, contains 6% of α-aminobutyrolactone and 6% of other unidentified compound; [c] the presence of the chloro derivative manifests itself by doubling of some signals (for the chloro derivative in parentheses); [d] quaternary aromatic carbon atom; [e] aromatic carbon atoms in *ortho*-positions; [f] aromatic carbon atoms in *meta*- and *para*-positions.

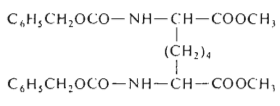
which are typical for the *trans*(*Z*) arrangement of —CONH— in the urethane group[21]. In solution, these bands appear at 1 500 cm^{-1} and 1 222 cm^{-1} (Table IV) whereas bands at 1 465, 1 403 and 1 356 cm^{-1}, present in the spectra of the crystalline compound, disappear. At the same time, further changes in wavenumbers and intensities were observed on going from crystalline phase to solution. After extraction of the compound from the measured KBr pellet with the solvent we obtained a spectrum which was completely identical with that of directly dissolved compound. This shows that during preparation of the pellet no chemical changes took place. Spectra of other studied compounds, containing the —OCONH— group (*i.e. Ib* and its dicyclohexylammonium salt) exhibited both in the crystalline state and in solution the urethane *trans*-amide II bands (Table II).



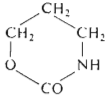
Ia: $R^1 = C_6H_5CH_2OCO$, $R^2 = CH_3$
Ib: $R^1 = C_6H_5CH_2OCO$, $R^2 = H$
Ic: $R^1 = H$, $R^2 = H$



IIa: $R^1 = HBr.H$, $R^2 = H$
IIb: $R^1 = HCl.H$, $R^2 = CH_3$
IIc: $R^1 = C_6H_5CH_2OCO$, $R^2 = CH_3$



III



IV

We measured therefore spectrum of 1-oxa-3-azacyclohexan-2-one (*IV*) (ref.[22,23]) as a model in which the —CONH— urethane group has the *cis*(*E*) conformation thanks to the cyclic system. The transition of the compound *IV* from the crystalline state into solution is accompanied by changes in the spectra which are smaller than those observed in the case of the compound *Ia*. The observed differences concern mainly bands in the regions 1 500–1 400 cm^{-1} and 1 150–1 100 cm^{-1}. These bands are association-sensitive as evident also from comparison of the spectra in tetrachloromethane and chloroform. Thus, intensity of the band at 1 458 cm^{-1} in crystal strongly diminishes on transition to tetrachloromethane solution in which the compound is still predominantly associated. On going to solution in chloroform, in which free NH strongly predominates, this band completely disappears. The same is true for the band at 1 425 cm^{-1} in spectrum of the crystalline compound. In chloro-

TABLE IV

Wavenumbers (in cm^{-1}) of bands in IR spectra of methyl 1-benzyloxycarbonylaminocyclopropanecarboxylic acid (*Ia*) in the region 1600–400 cm^{-1}

Non-deuterated form			Deuterated form
KBr[a]	$CHCl_3$[b]	CCl_4[c]	CCl_4[d]
—	1 502 vs	1 500 vs	—
1 500 vw	[e]	[e]	1 500 vw
1 465 m	1 465 sh	1 465 sh	1 465 sh
1 437 m	1 440 m	1 438 m	1 438 m
1 420 w	1 414 w	1 414 w	[f]
—	—	—	1 410 s
1 403 m	1 400 w	1 395 sh	—
—	1 375 vw	1 375 vw	1 368 vw
1 356 vs	—	—	—
1 344 sh	1 345 m[b]	1 342 m[b]	—
1 335 sh	—	—	—
—	—	—	1 310 s
1 302 m	1 304 m	1 304 m	1 295 sh
1 297 m	—	—	—
1 261 w	—	1 260 sh	1 255 sh
1 248 vw	—	—	—
—	—	1 222 vs	—
1 205 m	—	1 200 m	1 200 m
1 170 s	1 169 s	1 165 s	1 165 s
—	—	—	1 110 m
1 085 sh	1 085 sh	1 085 sh	1 085 sh
1 065 s	1 070 m	1 069 m	1 070 m
1 050 sh		1 055 sh	1 055 sh
1 038 sh	1 040 m	1 040 m	1 040 m
1 030 m	1 030 w	1 030 w	1 030 w
1 005 vw	1 005 vw	1 005 vw	1 005 vw
993 vw	—	—	—
—	988 vw	988 vw	988 vw
970 vw	970 vw	980 vw	980 vw
—	923 w	931 vw	920 vw
915 vw	910 vw	915 vw	908 vw
890 vw	890 vw	892 vw	890 vw
870 vw	880 vw	879 vw	875 vw
823 vw	—	—	—
805 vw	—	—	—
780 vw	—	—	—
760 m	—	—	—
750 m	—	—	—
735 sh	—	—	—

TABLE IV
(*Continued*)

Non-deuterated			Deuterated form
KBr[a]	$CHCl_3$[b]	CCl_4[c]	CCl_4[d]
699 m	699 m	699 m	699 m
—	—	680 vw	660 vw
675 wb	—	—	—
660 m	—	—	—
593 w	592 sh	593 vw	593 vw
—	580 w	580 w	580 w
—	509 m	505 sh	505 sh
485 m	487 m	487 m	485 m
441 wt	450 sh	460 sg	450 sh

[a] 100% association; [b] 3% solution, free NH predominates; [c] saturated solution, about 70% of free NH; [d] saturated solution, about 60% of deuterated NH; [e] ν(C=C) of aromatic nucleus, obscured by *trans*-amide II band; [f] coalescence with the neighbouring strong band.

form in which the compound is almost non-associated, this band is by an order of magnitude weaker. With growing proportion of the non-associated form the intensity of the bands at 1 450 cm^{-1} and 1 417 cm^{-1} increases. In the second association-sensitive region, the spectrum of crystalline compound exhibits a strong band at 1 122 cm^{-1} which, after dissolution, is transformed into two bands at 1 131 and 1 116 cm^{-1}. The intensity of the former decreases with decreasing association, whereas the intensity of the latter increases (Table V). After deuteration, all these association-sensitive bands are shifted to the region 1 250–1 200 cm^{-1} (doublet; from the region 1 500–1 400 cm^{-1}) and 1 050–1 000 cm^{-1} (doublet; from the region 1 150–1 100 cm^{-1}). In the latter doublet the band at 1 036 cm^{-1} is due to associated species whereas that at 1 021 cm^{-1} due to non-associated species. At the same time, the deuteration alters the distribution of the vibrations into the present bands (Table V).

Returning now to spectra of the compound *Ia* we see that on transition from the crystalline state to solution two bands in the region 1 500–1 400 cm^{-1} disappeared. This is the region of δ(NH) in-plane vibration of *cis*-amides (*cis*-amide II bands) in which the model compound *IV* displayed two association-sensitive bands, disappearing on deuteriation. Moreover, after deuteriation of *Ia* in the crystalline state which proceeded only to the extent of several percents, we observed unequivocally detectable changes only with the band at 1 465 cm^{-1} whose intensity decreased

TABLE V

Wavenumbers (in cm^{-1}) of bands in the IR spectra of 1-oxa-3-azacyclohexan-2-one (*IV*) in the region 1 600—400 cm^{-1}

Non-deuterated form			Deuterated form	
KBr[a]	CCl_4[b]	$CHCl_3$[c]	CCl_4[d]	$CHBr_3$[e]
1 536 vw	—	1 529 sh[f]	—	—
1 492 s	1 491 s	1 490 s	1 489 m	1 488 s
—	—	1 483 sh	1 481 sh	1 481 sh
1 458 m	1 458 sh	—	—	—
—	1 450 vw	1 450 m	—	—
1 435 sh	1 438 vw	1 438 m	1 439 s	1 439 s
1 425 m	1 425 m	1 429 w	—	—
—	1 414 sh	1 417 m	—	—
1 380 w	1 380 w	1 378 w	1 386 w	1 386 w
1 345 vw	1 351 vw	1 351 vw	1 350 vw	1 350 vw
1 298 s	1 298 s	1 298 s	1 311 s	1 311 s
—	—	1 294 sh	1 300 sh	1 300 sh
1 280 sh	1 280 sh	1 280 sh	1 279 w	1 279 w
—	—	—	1 235 s	1 235 s
1 228 w	1 230 w	—	[g]	[g]
1 210 vw	1 210 vw	—	1 210 sh	1 210 sh
—	—	—	1 208 s	1 215 s
1 122 s	1 131 s	1 131 s	1 132 vw	—
—	1 117 sh	1 116 s	1 115 vw[h]	—
1 079 s	1 082 s	1 082 s	1 082 s	1 080 s
—	—	—	1 036 m	1 032 w
—	—	—	1 023 sh	1 021 m
996 w	996 w	996 w	986 w	986 w
950 vw	953 vw	951 vw	953 vw	950 vw
912 vw	908 vw	910 vw	900 vw	900 vw
—	—	—	880 vw	878 vw
—	—	—	—	858 m
—	—	—	—	846 vw
820 vw	—	—	—	808 w
780 m	—	—	—	768 m
—	—	—	—	765 sh
684 w	685 w	682 w	682 w	—
550 w	558 w	550 w	555 w	—
—	522 wb	535 shb	—	—
487 m	490 m	488 m	488 m	485 m
—	—	480 sh	—	—
458 w	462 w	461 w	458 w	460 w
450 w	455 sh	451 w	450 sh	447 w
340 w				

in comparison with the neighbouring bands, and also in the region 1 250 – 1 200 cm^{-1} where an additional shoulder at 1 220 cm^{-1} occurred as part of the band at 1 205 cm^{-1}. The spectrum of *Ia* has no bands in the region 1 150 – 1 100 cm^{-1} where the model compound *IV* exhibited a concentration-sensitive doublet. Dissolution of crystalline *Ia* resulted also in disappearance of a band at 1 356 cm^{-1} in the *cis*-amide III band region[24]. Since the spectrum of crystalline compound *Ia* on the one hand does not exhibit any *trans*-amide II and *trans*-amide III bands and on the other hand displays significant bands in the *cis*-amide II region (analogous to those of compound *IV*), we assume that in the crystalline compound the —CONH— urethane grouping has the *cis*(*E*) conformation. On transition to solution, the *cis*-amide bands disappear and are replaced by *trans*-amide II and III bands. At the same time intensity of the 1 065 cm^{-1} band decreases and the shape of the spectrum changes. We thus assume that in solution the —CONH— group of the urethane has the usual *trans*(*Z*) conformation[22,23,25]. (A similar conformational change of an amide group on transition from the crystalline state to solution has already been described[26,27].)

It follows from these facts that the behaviour of the bands in the region 1 500 to 1 400 cm^{-1} is the same for urethane of *cis*(*E*) conformation of the —CONH— group as well as for *cis* amides. The best-defined band in the *cis*-amide II band region in amides is found in the spectrum of 2,5-piperazinedione[28]. In this compound the band is predominant (80%) due to the δ(NH) in-plane vibration[29]. In *cis*-amides with a larger number of $—CH_2—$ groups the δ(NH) in-plane vibration contributes to a larger number of bands in this region, depending on the state of the measured compound. This follows *e.g.* from Table II and III in reference[30]; the situation is even more obvious from a direct comparison of the pertinent spectra and also from the work of the French authors[24]. Also the deuterium-induced shift of the *cis*-amide II bands (δ(NH) in-plane region) due to *cis* —CONH— groups is analogous for both amides and urethanes: in the region 1 250 – 1 200 cm^{-1} one or more bands occur, again depending on the state in which the compound is measured and on the degree of coupling of the δ(NH) in-plane vibration with other vibrations.

Comparison of the behaviour of the *trans*-amide II bands (1 600 – 1 500 cm^{-1}) in amides and in the studied urethane *Ia* (in solution) after deuteration shows that the disappearance of the *trans*-amide II band is accompanied by appearance of a band in the *trans*-amide region. However, whereas in amides there appears a further

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[a] 100% association; [b] saturated solution in tetrachloromethane, about 10% free NH; [c] 0·1M solution in chloroform, predominantly free NH; [d] saturated solution, 100% deuterated, about 10% of free N^2H; [e] 80 – 90% deuteration, about 50% of free N^2H; [f] 7% solution in chloroform, predominantly associated NH; [g] obscured by the neighbouring band; [h] in the non-deuterated compound obscured by a strong doublet.

trans-amide III' band at about 900 cm^{-1}, the spectra of our urethane were more complicated, exhibiting a band at 1 100 cm^{-1} and a shift of several bands in the 1 400–1 100 cm^{-1} region.

The vibrational coupling which gives rise to the *trans*-amide II bands, is thus comparable in both amides and urethane with a *trans* conformation of the —CONH— grouping (ref.[31]). This is true also for the amide II bands in *cis* amides and *cis* urethanes (*i.e. E* conformation of the —CONH— group; in this case more exactly the *EE* conformation of the model urethane) but not for the amide III bands.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Analytical samples were dried at room temperature and 150 Pa for 24 h. Thin-layer chromatography was performed on silica gel plates (Silufol, Kavalier, Czechoslovakia) in the following systems: S1: 2-butanol–98% formic acid–water (75 : 13·5 : 11·5); S3: 1-butanol–acetic acid–water (4 : 1 : 1); S4: 1-butanol–pyridine–acetic acid–water (15 : 10 : 3 : 6); S5: n-heptane–tert-butyl alcohol–pyridine (5 : 1 : 1); S8: 5% methanol in benzene; S14: 2% methanol in benzene. Paper electrophoresis was carried out in a moist chamber in 1M acetic acid (pH 2·4) and in a pyridine–acetate buffer (pH 6·7) on a paper Whatman 3 MM; 20 V/cm, 60 min. Spots were detected by ninhydrin reaction (electrophoresis) and by chlorination method (thin-layer chromatography). Amino acid analysis was performed on an automatic two-column analyzer (Developmental workshops, Czechoslovak Academy of Sciences, type 6020). Column chromatography was carried out on silica gel of particle size 30–60 μ.

Spectral Measurements

The NMR spectra were measured at 23°C in C^2HCl_3 or ^2H_2O on a Varian XL-200 instrument in the FT-mode, the ^1H NMR spectra at 200 MHz and the ^{13}C NMR spectra at 50·3 MHz. Chemical shifts are referenced to tetramethylsilane, either directly or *via* hexadeuteriodimethyl sulfoxide ($\delta_{13C} = 40{\cdot}9$; $\delta_{1H} = 2{\cdot}50$). The multiplicity of signals in the ^{13}C NMR spectra was determined by a ^1H-off-resonance decoupling experiment. Mass spectra were taken on an AEI-MS 902 spectrometer (70 eV, direct inlet). The IR spectra were measured on a Zeiss-Jena UR-20 spectrophotometer (accuracy ±2 cm^{-1}) or on a Perkin–Elmer instrument, model 580 (accuracy ±1·5 cm^{-1}). Compounds in solutions were deuteriated with ^2H_2O with subsequent azeotropic removal of water. The compound *Ic* in the solid state was measured in KBr pellets. On crystallization from aqueous ethanol, *Ic* was obtained in the crystalline phase I. Freeze-drying of its aqueous solution afforded the crystalline phase II, which was prepared also by crystallization directly in the KBr pellet or by heating the phase I. In the range 89–95°C the transparent platelets of the crystalline phase I were transformed into non-transparent platelets of the phase II without change of the crystalline shape. Although the overall shape of the IR spectra is similar for both phases, they differ distinctly, particularly in the $\delta(NH_3^+)$ region.

Methyl 1-Benzyloxycarbonylaminocyclopropanecarboxylate (*Ia*)

Methyl N^{α}-benzyloxycarbonylamino-γ-bromobutyrate[1] (*IIc*; 1·0 g) was added to sodium (70 mg) under ether (10 ml) and the mixture was refluxed for 3 h. Water was added, the mixture was adjusted to pH 4·0–5·0 with 1M-HCl and the product was taken up in ether. The ethereal extract

was washed with water, dried over sodium sulfate and taken down. The residue (0·7 g), which after several days solidified at room temperature, consisted of three or four compounds (R_F 0·37 and 0·21 in S14 for the two main compounds) and was purified by chromatography on a column of silica gel (2 × 30 cm; eluant benzene–2% methanol). The eluates were analyzed by thin-layer chromatography on silica gel (S14). Fractions 85 to 115 ml contained the starting compound *IIc* (R_F 0·37 in S14 and 0·49 in S8), further fractions contained a mixture of *IIc* and the product, and fractions 185—220 ml contained the product. The recovered starting material (72 mg), m.p. 81—83°C, was a mixture of derivatives of γ-bromobutyric and γ-chlorobutyric acids. The product (132 mg) solidified (m.p. 92—94°C) and on crystallization from benzene and light petroleum (110 mg; 15%) melted at 96—98°C. R_F 0·21 (S14), 0·30 (S8). For $C_{13}H_{15}NO_4$ (249·3) calculated: 62·65% C, 6·07% H, 5·62% N; found: 62·41% C, 5·95% H, 5·99% N. Mass spectrum: 249 (M^+).

1-Benzyloxycarbonylaminocyclopropanecarboxylic Acid (*Ib*)

A) *From* IIc *by sodium ethoxide.* Compound *IIc* (1·0 g) was added to a solution of sodium (86 mg) in absolute ethanol (6·5 ml). The mixture was refluxed for 1 h, treated with 1M-NaOH (3 ml) and after stirring for 1 h taken down. The residue was acidified with 1M-HCl and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and taken down. The residue (a mixture of compounds of R_F 0·23, 0·15, 0·00 (S14), 0·46, 0·35, 0·10 (S8), 0·48, 0·16 (S5)) was chromatographed on a column of silica gel (1·8 × 13 cm, eluant n-heptane–tert-butyl–alcohol–pyridine 5 : 1 : 1). The compounds were detected by thin-layer chromatography on silica gel (S5). Fractions 25—45 ml contained two by-products and fractions 55—86 ml contained the desired product, m.p. 135—150°C (220 mg). Crystallization from benzene afforded 150 mg (21%) of the product, m.p. 155—157°C. The analytical sample was recrystallized from water, m.p. 156—159°C; R_F 0·16 (S5) and 0·10 (S8). For $C_{12}H_{13}NO_4$ (235·3) calculated: 61·27% C, 5·57% H, 5·95% N; found: 61·26% C, 5·61% H, 6·16% N. A part of the product was transformed into the dicyclohexylammonium salt, m.p. 149—151°C. For $C_{24}H_{36}N_2O_4$ (416·5) calculated: 69·20% C, 8·71% H, 6·72% N; found: 69·20% C, 8·94% H, 6·99% N.

B) *From* IIc *by action of sodium salt of diethyl acetamidomalonate.* Diethyl acetamidomalonate (2·9 g) was added to a solution of sodium (305 mg) in ethanol (20 ml). After 1 min the derivative *IIc* (4·0 g) was added, the mixture refluxed for 4 h, filtered while hot and diluted with water. The oily layer was separated, dissolved in ether and washed with water. The ethereal layer was taken down, the residue diluted in methanol, mixed with 2M-NaOH (35 ml) and stirred for 1 h. The methanol was evaporated, the solution acidified with 6M-HCl to pH 3·0, refluxed for 1 h and set aside in a refrigerator. The separated crystals were filtered, affording 1·45 g (50%) of the product, m.p. 159—161°C. R_F 0·78 (S1), 0·62 (S4). Found: 61·52% C, 5·49% H, 5·96% N. The IR spectrum was identical with that of the compound prepared according to procedure *A*). The molecular weight was determined cryoscopically in camphor (m.w. 214) in a sealed capillary on a Kofler block and also by vapour pressure osmometry in methyl tert-butyl ether at 28°C (m.w. 230), using a Vapor-Pressure-Osmometer instrument (Hitachi Perkin–Elmer, model 115).

C) *By alkaline hydrolysis of derivative* Ia. A solution of the compound *Ia* (155 mg) in methanol (10 ml) was mixed with 1M-NaOH (1·2 ml), and stirred for 1 h at room temperature. Dowex 50 W (H^+-cycle; 10 ml) was added and the mixture was stirred for 30 min. The Dowex was filtered off, washed with methanol and the filtrates were taken down and azeotropically dried (benzene). The residue was dissolved in benzene, treated with dicyclohexylamine (0·15 ml) and light petroleum. The separated crystals were collected on filter and washed with light petroleum, affording 100 mg (39%) of the product, m.p. 154—155°C. Its IR spectrum was identical with that of the

dicyclohexylammonium salt of *Ib*, prepared under *A*). Also chromatographic properties of both compounds were the same: R_F 0·78 (S1), 0·75 (S3), 0·62 (S4), 0·16 (S5), 0·10 (S8).

1-Aminocyclopropanecarboxylic Acid (*Ic*)

The derivative *Ib* (1·15 g) was refluxed with 6M-HCl (20 ml) for 1 h. After cooling, the reaction mixture was shaken with ether and the aqueous portion was evaporated several times with water to remove excess hydrochloric acid. The residue was dissolved in water and filtered through Dowex 50 W (H^+-cycle; 30 ml). After washing with water the product was eluted with 10% aqueous pyridine, the eluates were evaporated and the product was crystallized from water and ethanol; yield 0·49 g (66%); m.p. 250 – 252°C (decomposition). $E^{Gly}_{2.4}$ 1·16, $E^{His}_{5.7}$ 0·00. For $C_4H_7NO_2$ (101·1) calculated: 47·52% C, 6·98% H, 13·85% N; found: 47·50% C, 7·01% H, 13·91% N. In the amino acid analysis the product had the same elution time as isoleucine (for conditions see ref.[32]), the colour yield of the ninhydrin reaction, compared with leucine, was 0·041. Its IR and mass spectra were identical with those of the authentic compound[17–19]. Reported m.p. above 200°C (ref.[12]), 229–231°C (ref.[7,16]), 233–235°C (ref.[15]) and 248–249°C (ref.[13]).

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