FLUORODEOXYGENATION OF PROLINE, OPTICALLY ACTIVE 2-TRIFLUOROMETHYLPYRROLIDINE, AND ITS CHROMOPHORIC DERIVATIVES

G. V. Shustov, S. N. Denisenko, I. I. Chervin, and R. G. Kostyanovskii

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The fluorodeoxygenation of α-amino acids by the action of sulfur tetrafluoride in hydrogen fluoride [1-3] can be regarded as a path to chiral α-trifluoromethyl-substituted amines, which are of interest for medical biochemistry [4] and as potential resolving agents and chiral solvating additives. However, the stereochemical aspect of this reaction has not been investigated. The retention of optical activity during the fluorodeoxygenation of L-glutamic acid and L-leucine has been reported, but the optical purity of the product was not established [2]. The fluorodeoxygenation of the hydantoin derivatives of amino acids takes place with a considerable degree of racemization (up to 97%) [3]. The latter can occur both in the course of the reaction and during isolation and purification of the products, since the hydantoins readily racemize in the presence of inorganic acids and bases [3]. According to the mechanism proposed in [1, 4], it can be supposed that the fluorodeoxygenation of organic acids is realized without change in the configuration at the α-carbon atom. However, there are no data on the absolute configuration of α-trifluoromethylamines, i.e., the products from the fluorodeoxygenation of optically active α-amino acids [1-3].

We studied the fluorodeoxygenation of (R,S)- and (S)-proline, determined the optical purity of the fluorodeoxygenation product α-trifluoromethylpyrrolidine (−)-(I), and confirmed the retention of the absolute configuration of the chiral α-carbon atom. The reaction of (R,S)- and (S)-proline with sulfur tetrafluoride in hydrogen fluoride at 120°C leads to the racemic (I) and optically active (−)-(I), respectively. In order to determine the optical purity of the latter we obtained the diastereomeric derivative (+)-(IIA) (1) by the action of (S)-α-phenylethyl isocyanate [5], and from the racemic (I) we obtained the authentic mixture of diastereomers (IIA) and (IIB). The ^1H and ^{19}F NMR spectra of these diastereomers differ in the positions of the signals for the PhC<u>H</u>, CF_3, and particularly $CF_3C\underline{H}$ and Me groups. The spectra of (IIA) contain only one set of signals for these groups (Tables 1 and 2). Consequently, the optical purity of (−)-(I) is not less than 96%.

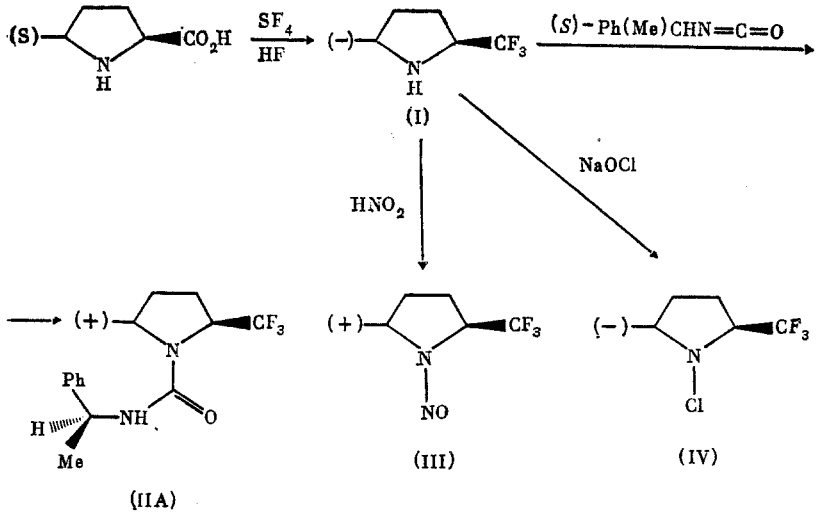

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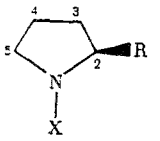
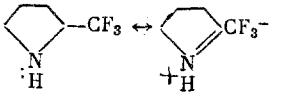
TABLE 1. ^1H (400 MHz) and ^{19}F (75.4 MHz) Chemical Shifts of the Substituted Pyrrolidines



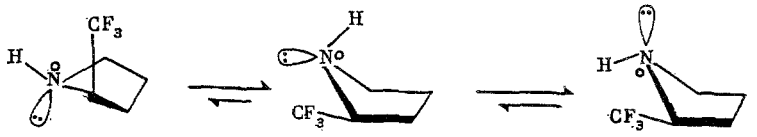
Compound	R	X	δ, ppm (ASIS)[a]					Solvent
			H^2	H^5_a	H^5_e	H^3, H^4	R[b]	
(I)	CF_3	H	3,04	2,62	2,35	1,10–1,58	–1,28	C_6D_6
(IIA)[c]	CF_3	Ph(Me)CHNHCO	4,58	2,64		1,09–1,52	–3,50	C_6D_6
(IIB)	CF_3	Ph(Me)CHNHCO	4,46	2,76		1,09–1,52	–3,72	C_6D_6
(III)[d]	CF_3							
	Preferred isomer		5,16	3,74	3,57	2,05–2,32	–4,20	$CDCl_3$
			(0,69)	(0,60)	(0,61)		(1,24)	
			4,47	3,14	2,96	0,92–1,44	–2,96	C_6D_6
	Less favorable isomer		4,96	4,20	4,69	2,05–2,32	–6,70	$CDCl_3$
			(0,38)	(0,82)	(0,77)		(1,35)	
			4,58	3,38	3,92	0,92–1,44	–5,35	C_6D_6
(IV)	CF_3	Cl	3,18	2,49	3,04	1,20–1,39		C_6D_6
(V)	MeO_2C	NO						
	Preferred isomer		4,43	4,44		2,04–2,31	3,70	$CDCl_3$
			(0,2)	(0,77)			(0,45)	
			4,23	3,66		0,89–1,33	3,25	C_6D_6
	Less favorable isomer		5,27	3,67		2,04–2,31	3,78	$CDCl_3$
			(0,49)	(0,43)			(0,60)	
			4,78	3,24		0,89–1,33	3,18	C_6D_6
(VI)	MeO_2C	Cl	3,55	2,66	3,26	1,25–1,70	3,33	C_6D_6

[a] $\delta\ CDCl_3 - \delta\ C_6D_6$.
[b] The ^{19}F chemical shifts are given for compounds (I)-(IV).
[c] ^1H chemical shifts of remaining groups: (IIA) 1.26 d (Me, ^3J = 7.1 Hz), 4.32 br.d (NH), 5.19 dq (CH, $^3J_{NHCH}$ = 7.9 Hz); (IIB) 1.36 d (Me, ^3J = 7.1 Hz), 4.32 br.d (NH), 5.21 dq (CH, $^3J_{NHCH}$ = 7.9 Hz).
[d] Ratio of isomers according to ^{19}P spectra: 76/24 (deuterochloroform), 83/17 (heptane), 84/16 (hexadeuterobenzene), 86/14 (dioxane), 86/14 (tetradeuteromethanol).

In the CD spectrum of the pyrrolidine (–)-(I) in heptane there is a negative Cotton effect at 207 nm, the magnitude of which decreases greatly if heptane is substituted by methanol (Table 3). This makes it possible to assign the observed absorption to the n–σ* transition. The hypsochromic shift of this band compared with (S)-2-hydroxymethyl- and (R)-2-methylpyrrolidine [6] (Table 3) is due to a decrease in the level of the n orbital of the N atom on account mainly of the negative induction effect of the CF_3 group and to a lesser degree the $n–\sigma_{CC}$*-hyperconjugation (2) [7], since the latter can be realized in the case of the dipseudoaxial orientation of the unshared electron pair of the nitrogen atom and the CF_3 group (the maximum anti-overlap), while the $^3J_{H_2}$ values (Table 2) indicate preferred population of the conformer with the pseudoequatorial CF_3 group (3).



(2)



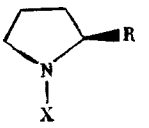
(3)

On the basis of the identical sign of the Cotton effects in (–)-(I) and (S)-2-hydroxymethyl- and (R)-2-methylpyrrolidine (Table 3) it can be supposed that (–)-(I) has the (S) configuration. For a more reliable assignment of the configuration of (–)-(I) we studied the stereochemistry of the chromophoric derivatives: the nitrosoamine (+)-(III) and the

TABLE 2. Spin–Spin Coupling Constants (Hz) of Substituted Pyrrolidines (I)-(VI)

Compound	H^2				H^5_a			H^5_e		Solvent
	aa	*ee*	*ae*	HF	*aa*	*ae*	AB	*ee*	*ea*	
(I)	8,2	–	5,2	8,2	9,8	6,7	–9,8	6,7	9,8	C_6D_6
(IIA)	–	1,0	8,1	8,1			*			C_6D_6
(IIB)	–	1,0	8,1	8,1			*			C_6D_6
(III) Preferred isomer	–	3,4	7,9	7,9	13,9	8,5	–13,9	3,4	8,8	$CDCl_3$
	–	2,4	8,1	8,1	13,7	8,5	–13,7	3,2	8,5	C_6D_6
Less favorable isomer	12,4	–	5,1	7,3	11,7	7,3	–11,7	4,5	7,6	$CDCl_3$
	12,4	–	5,1	7,3	11,7	7,3	–11,7	5,1	8,1	C_6D_6
(IV)	10,1	–	5,2	7,0	10,1	6,7	–10,1	2,4	7,0	C_6D_6
(V) Preferred isomer	–	6,0	6,0	–			*			$CDCl_3$
	–	6,6	6,6	–			*			C_6D_6
Less favorable isomer	–	3,4	8,1	–			*			$CDCl_3$
	–	3,4	8,1	–			*			C_6D_6
(VI)	8,9	–	7,3	–	9,8	8,2	–9,8	4,0	7,9	C_6D_6

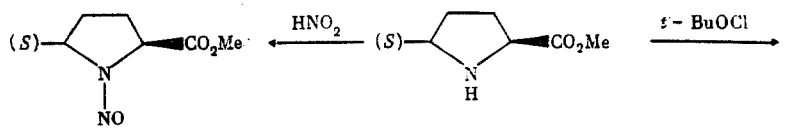
*The spin–spin coupling constant was not determined.

TABLE 3. CD Spectra of Substituted Pyrrolidines 

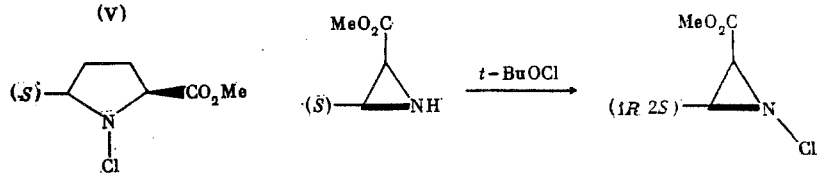
and N-Chloroaziridine (VIII)

R	X	Solvent	λ_{max}, nm($\Delta\varepsilon$)
CF_3	H	Heptane	207 (–1,22)
		MeOH	207 (–0,11)
CH_2OH	H	Hexane	215 (–0,34)
Me	H	Heptane	218 (–1,46)
CF_3	NO	»	396 (+1.20), 380 (+1.06), 365 (+0,59) 242 (–0,89), 210 (+0,27)
		Dioxane	389 (+1,16), 374 (+1,00), 363 (+0,55)
		MeOH	390 (+0,74), 376 (+0,76), 365 (+0,47) 242 (–0,53)
CF_3	Cl	Heptane	269 (–0,42), 206 (–0,87)
		MeOH	267 (–0,49), 204 (–0,77)
MeO_2C	Cl	Heptane	247 (–1,47), 216 (–2,10)
Me	Cl	MeOH	256 (–0,29)
N-Chloroaziridine		Heptane	247 (–1.74), 216 (–2.10)
		MeOH	245 (–1,41), 215 (–1,95)

chloroamine (–)-(IV). The chiroptical characteristics of these compounds and of their closest analogs 1-nitroso-(S)-proline methyl ester (V) [8] and 1-chloro-(S)-proline methyl ester (VI) were compared on the assumption that the CF_3 and MeO_2C groups have similar electronegativity. The N-chloroproline (VI) obtained by the reaction of (S)-proline methyl ester with tert-butyl hypochlorite (4) is only stable at 20°C in solution and was identified by its ^1H NMR (Tables 1 and 2) and CD (Table 3) spectra.



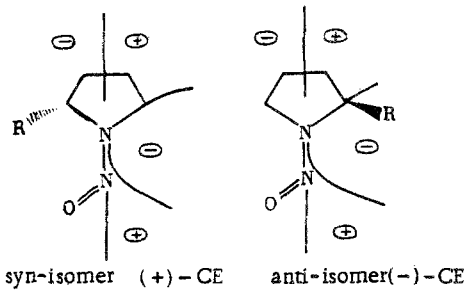
(V) (4)



(VI) (VII) (VIII) (5)

The stereochemistry of (−)-(IV) was also compared with that of other model compounds, i.e., (R)-1-chloro-2-methylpyrrolidine [6] and methyl (1R,2S)-1-chloroaziridine-2-carboxylate (VIII), obtained according to [5].

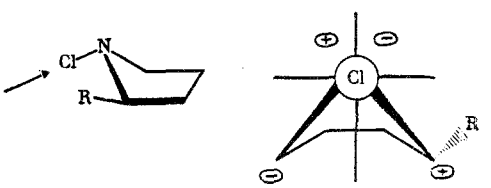
In the CD spectra of the nitrosoamine (+)-(III), as also in the case of (S)-(V) [8], a positive Cotton effect due, evidently, to the $n_a \rightarrow \pi^*$ transition [8] was observed in the region of 370-390 nm. The magnitude of the dichroic absorption decreases with replacement of the aprotic solvents (heptane, dioxane) by methanol (Table 2), and this was also observed for (S)-(V) [8]. In order to determine the absolute configuration of the chiral center in the nitrosoamine on the basis of the sector rule [8] it is necessary to determine the ratio of the syn and anti isomers, due to restricted rotation about the N–N bond, since the indicated regional rule† predicts opposite signs in the Cotton effects for these isomers with one and the same absolute configuration at the chiral center.



(6)

For the nitrosoamine (+)-(III) the isomers are observed from the ^1H and ^{19}F NMR spectra in a ratio which depends little on the solvent (Table 1). The following tests for the assignment of the syn and anti isomers of nitrosoamines in the NMR spectra are well known [9]: Screening of the syn-α-CH_2 (a) and β-Me groups (b); descreening of the syn-α-CH group (c); a larger aromatic solvent induced shift (ASIS) (d) for the anti α-CH_2 and α-CH groups. Test (c) cannot be used for the nitrosoamine (+)-(III), since the chemical shift of the α-CH group depends on the solvent. According to tests (a, d), the nitrosoamine (+)-(III) exists preferentially in the anti form (an upfield shift of 0.6-0.8 ppm for the α-CH_2 group and a larger ASIS effect for the α-CH and a smaller effect for the α-CH_2 groups in the preferred isomer), where test (b) indicates preferred population of the syn isomer (Table 1). The same uncertainty is observed for the nitrosoproline (S)-(V) (Table 1); tests (a, d) indicate preferred population of the syn form and test (c) indicates preferred population of the anti form. Thus, it is not possible to assign the syn and anti isomers of (+)-(III) reliably by means of the ^1H and ^{19}F spectra, and the sector rule was accordingly used for the determination of the absolute configuration of the chiral center. We therefore investigated the chloroamine (−)-(IV) having higher local symmetry in the chromophore.

In the CD spectrum of (−)-(IV) there is a characteristic dichroic absorption band in the region of 270 nm, due to the $n\rightarrow\sigma^*_{NCl}$ transition, and this is confirmed by the hypsochromic shift during replacement of heptane by methanol (Table 3). The negative sign of the $n\rightarrow\sigma^*_{NCl}$ transition is also obtained in the chloroamines (R)-1-chloro-2-methylpyrrolidine and (S)-(VI). This indicates the S configuration for (−)-(IV). According to the $^3J_{H_2}$ values (Table 1), the CF_3 group in (−)-(IV) and MeO_2C in (S)-(VI) have preferred pseudoequatorial orientations. Then, with the most probable trans-pseudoequatorial orientation of the Cl atom [10] in these compounds the observed negative sign of the Cotton effect is not consistent with that predicted on the basis of the previously proposed quadrant rule for the halogenoamine chromophore [11]. From examination of molecular models for (−)-(IV) and (S)-(VI) according to this rule a small positive Cotton effect should be expected, since the perturbing group (R = CF_3, COOMe) lies in the positive quadrant close to the nodal plane.



(7)

†The signs of the upper sectors are shown in scheme (6) [8].

The known trans orientation of the Cl atom and the MeO_2C group is realized in the model (1R,2S)-N-chloroaziridine (VIII) [12]. For this compound the $n_\sigma \rightarrow \sigma_{NCl}^*$ transition is shifted toward the short-wave region compared with the chloroamines (−)-(IV), (S)-(VI), and (R)-1-chloro-2-methylpyrrolidine (Table 3). This is due to the decrease in the contribution from the p-function to the n_σ - and $\sigma_{NCl}^*(\sigma_{NCl}^*)$-MO, as a result of which the energy of the n_σ orbital decreases and that of σ_{NCl}^* increases. The negative sign of the Cotton effect due to the $n-\sigma_{NCl}^*$ transition in N-chloroaziridine (VIII) (Table 3) is also inconsistent with the quadrant rule [10] but confirms the idea of the trans orientation of the Cl atom and the α substituent in the N-chloropyrrolidines (−)-(IV), (S)-(VI), and (R)-1-chloro-2-methylpyrrolidine.

Thus, the data from the CD and ^1H NMR spectra of the pyrrolidine (−)-(I) and its N-chloro derivative (−)-(IV) indicate that the absolute (S) configuration of the carbon chiral sector is preserved during the fluorodeoxygenation of (S)-proline.

EXPERIMENTAL

The CD spectra were measured on a Jasco J-500 A spectropolarimeter with a DP-500N processor. The NMR spectra were obtained on Bruker WP-80SY (^1H, 80 MHz, from HMDS; ^{19}F, 75.4 MHz, from external trifluoroacetic acid) and Bruker WM-400 (^1H, 400 MHz, from TMS) spectrometers. The angles of optical rotation were obtained on a Polamat A polarimeter.

(2S)-2-Trifluoromethylpyrrolidine (I). A mixture of 20 g (0.174 mole) of (S)-proline, 30 g of hydrogen fluoride, and 52 g (0.481 mole) of sulfur tetrafluoride was kept for 8 h in a steel autoclave at 120°C. After cooling to 20°C and removal of the excess of sulfur tetrafluoride and hydrogen fluoride the reaction mixture was diluted with 150 ml of water in a quartz beaker, and the resinous impurities were removed by filtration. The aqueous solution was neutralized to pH ~ 7 with sodium hydroxide, and the product was extracted with ether (5 × 50 ml) and dried over sodium sulfate, and the ether was distilled on a Vigreaux column. After distillation of the residue we obtained 6.55 g (28%) of (I); bp 110-111°C; $[\alpha]_D^{20}$ −1.2°, $[\alpha]_{546}^{20}$ −1.7, $[\alpha]_{366}^{20}$ −12.3° (c 8, hexane). Found, %: C 43.06; H 5.89; N 10.17. $C_5H_8F_3N$. Calculated, %: C 43.17; H 5.80; N 10.07.

The racemate (I) was obtained by this method from (R,S)-proline.

(2S,αS)-1-Phenylethylcarbamoyl-2-trifluoromethylpyrrolidine (IIA). A solution of 0.14 g (1 mmole) of (−)-(I) and 0.15 g (1 mmole) of (S)-α-phenylethyl isocyanate [5] in 3 ml of absolute ether was kept at 20°C for 24 h, and the solvent was evaporated under vacuum. We obtained 0.29 g of (IIA); mp 129-132°C; $[\alpha]_D^{20}$ +10.1, $[\alpha]_{546}^{20}$ + 12.4° (c 3, MeOH). The product was analyzed without further purification by ^1H and ^{19}F NMR (Tables 1 and 2).

A mixture of the diastereomers (IIA) and (IIB) was obtained from the racemic (I) by the previous method. The yield was 92%; mp 121-122.5°C (from heptane); $[\alpha]_D^{20}$ −1.7, $[\alpha]_{546}^{20}$ −2.1° (c 4, MeOH). Found, %: C 58.86; H 6.01; N 9.90. $C_{14}H_{17}F_3N_2O$. Calculated, %: C 58.73; H 5.99; N 9.78.

(2S)-1-Nitroso-2-trifluoromethylpyrrolidine (III). To a solution of 1.39 g (10 mmoles) of (−)-(I) in 20 ml of aqueous hydrochloric acid (pH 1), while cooling to 0 to −3°C and stirring, we added dropwise a solution of 2.07 g (30 mmoles) of sodium nitrite in 5 ml of water. The product was extracted with methylene chloride (4 × 10 ml). After drying over magnesium sulfate the solvent was evaporated under vacuum, and the residue was distilled. We obtained 1.40 g (83%) of (III); bp 48-49°C (1 mm Hg); $[\alpha]_D^{20}$ +1.5° $[\alpha]_{546}^{20}$ +13.7°, $[\alpha]_{436}^{20}$ +356.1° (c 3, heptane). Found, %: C 35.56; H 4.08; N 16.53. $C_5H_7F_3N_2O$. Calculated, %: C 35.72; H 4.20; N 16.66.

(2S)-1-Chloro-2-trifluoromethylpyrrolidine (IV). To a solution of 30 mmoles of sodium hypochlorite in 20 ml of water, while cooling (0 to +3°C) and stirring, we added a solution of 1.39 g (10 mmoles) of (−)-(I) in 15 ml of ether. The stirring was continued at 5°C for 1 h, and the ether solution was separated and dried over magnesium sulfate. After removal of the solvent the residue was distilled under vacuum. We obtained 1.3 g (75%) of (−)-(IV); bp 45-46°C (25 mm Hg); $[\alpha]_D^{20}$ −41.8, $[\alpha]_{546}^{20}$ −50.8° (c 3, heptane). Found, %: C 34.32; H 3.98; N 8.11. $C_5H_7ClF_3N$. Calculated, %: C 34.60; H 4.07; N 8.07.

(2S)-1-Nitrosoproline Methyl Ester (V). Compound (V) was obtained by the method in [8].

(2S)-1-Chloroproline Methyl Ester (VI). To a solution of 0.67 g (5 mmoles) of (S)-proline methyl ester in 10 ml of absolute ether, while cooling (−60°C) and stirring, we added 0.65 g (6 mmoles) of tert-butyl hypochlorite. After holding at the same temperature for 0.5 h the solvent was removed under vacuum at a temperature no higher than 0°C. We obtained 0.78 g (95%) of (VI), which we identified by means of the ^{1}H NMR (Tables 1 and 2) and CD spectra (Table 3).

Methyl (2S)-Aziridine-2-carboxylate (VII). Compound (VII) was obtained by the method in [13]; bp 71-73°C (40 mm Hg), cf. [14]; $[\alpha]_D^{20}$ −22.4, $[\alpha]_{546}^{20}$ −26.1° (c 1.8, MeOH).

Methyl (1R,2S)-1-Chloroaziridine-2-carboxylate (VIII). To a solution of 0.81 g (8 mmoles) of methyl (2S)-aziridine-2-carboxylate (VII) in 10 ml of absolute ether, while cooling (−60°C) and stirring, we added dropwise a solution of 1.08 g (10 mmoles) of tert-butyl hypochlorite in 10 ml of absolute ether. The solvent was evaporated under vacuum. After distillation of the residue we obtained 0.83 g (77%) of (VIII); bp 69-70°C (9 mm Hg); $[\alpha]_D^{20}$ −193.8, $[\alpha]_{546}^{20}$ −232.9° (c 3, MeOH). Found, %: C 35.60; H 4.30; N 10.63. $C_4H_6ClNO_2$. Calculated, %: C 35.45; H 4.46; N 10.34. NMR spectrum (80 MHz, deuterochloroform, δ, ppm, J, Hz): 2.50 (H_A^{cis}, $^3J^{cis}$ = 8.0, $^2J_{AB}$ = 2.5), 2.66 (H_B^{trans}, $^3J^{trans}$ = 5.2), 2.97 (H_C), 3.74 s (MeO).

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CONCLUSIONS

1. The fluorodeoxygenation of (S)-proline by the action of sulfur tetrafluoride in hydrogen fluoride to (−)-2-trifluoromethylpyrrolidine was realized without affecting the carbon of the chiral center.

2. According to PMR data, 2-trifluoromethylpyrrolidine, its N-chloro derivative, and 1-chloro-2-methoxycarbonylpyrrolidine exist preferentially in the conformation with the pseudoequatorial orientation of the substituent at position 2.

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