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Ring-chain Tautomerism of Oxazolidines Derived from Serine Esters

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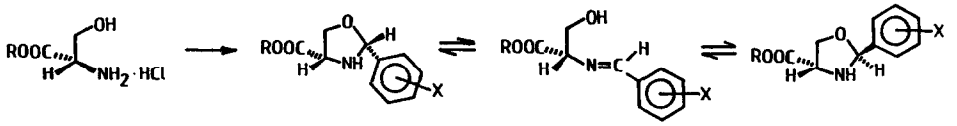
Abstract: *In spite of an earlier statement (Bull. Chem. Soc. Jpn. 1981, 54, 1844), ring-chain tautomeric mixtures were obtained from serine methyl or ethyl ester with aromatic aldehydes. Tautomeric ratios gave a good correlation according to the equation log* $K=\rho\sigma^{+}+\log K_0$. *A clear tendency was also found between the tautomeric ratios and the dielectric constants of the solvents.*

A new technique of serine protection was recently described,[1] which involves the incorporation of serine as oxazolidine-protected "pseudo-proline" in a host peptide. This represents a new tool for modulation of the physico-chemical, the conformational and hence the biological properties of peptides. From the oxazolidine, the "free" aminoacid part can be liberated by hydrolysis. The hydrolytic process *via* the open-chain imminium salt has been studied very thoroughly.[2-5] In this new protection technique, pivalaldehyde was used to build in a bulky apolar group. Our present aim was to study the tautomerism of oxazolidines derived from serine.

The ring-chain tautomerism of oxazolidines[6-9] and related 1,3-oxazines[10,11] has been thoroughly studied, especially because the tautomerism and ring-closure reaction resulting in oxazolidines are disfavoured processes according to the Baldwin rules.[10,12] Although a number of papers have dealt with the synthesis and transformation of oxazolidines (e.g. refs. 13-18), only in very few was the tautomerism mentioned, which strongly determines the reactivity of the compounds. In 1981, Badr *et al.*[16] reported that the ethyl esters of *L*-serine, 3-phenyl-*DL*-serine, *L*-threonine and cysteine, with aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde, *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde, gave the corresponding oxazolidines or thiazolidines. The alternative open-chain structure of the products was excluded by the absence of the NMR signal near to 7.5 ppm, ascribable to azomethine.

Dedicated to **Professor Gábor Bernáth**, Head of the Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, on the occasion of his 60th birthday.

When *L*-serine methyl ester and (±)-serine ethyl ester were reacted with seven different aromatic aldehydes, the presence of a three-component tautomeric equilibrium was evident from the ^{1}H NMR spectra of all products, in $CDCl_3$ at ambient temperature at 400 MHz (Scheme 1, Table 1). In Scheme 1, only the *S*-enantiomer of the (±)-serine ester is shown. Only a negligible difference was found between the methyl and ethyl ester derivatives. Of the two ring forms, one (**A**) always predominated.[15] As concerns the ratio of the C-2 epimers **A** and **C**, a clear tendency was found according to the electronic character of the C-2 aryl substituent (Table 1).



R = Me: **1**	**3A-9A**	**3B-9B**	**3C-9C**
R = Et: **2**	**10A-16A**	**10B-16B**	**10C-16C**

Scheme 1

Figure 1 shows part of the ^{1}H NMR spectrum of an equilibrium mixture of *L*-serine methyl ester derivative **8** in $CDCl_3$. The protons at position 2 give a signal at 5.30 ppm for the *cis* (**8A**) and at 5.62 ppm[15] for the *trans* (**8C**) 2-(*p*-methoxyphenyl)-4-(*R*)-methoxycarbonyloxazolidines. The azomethine singlet at 8.20 ppm provides clear-cut evidence of the predominating open-chain form (**8B**). The ^{1}H NMR data (Table 1) show that serine methyl and ethyl esters both react with aromatic aldehydes to give three-component tautomeric mixtures.

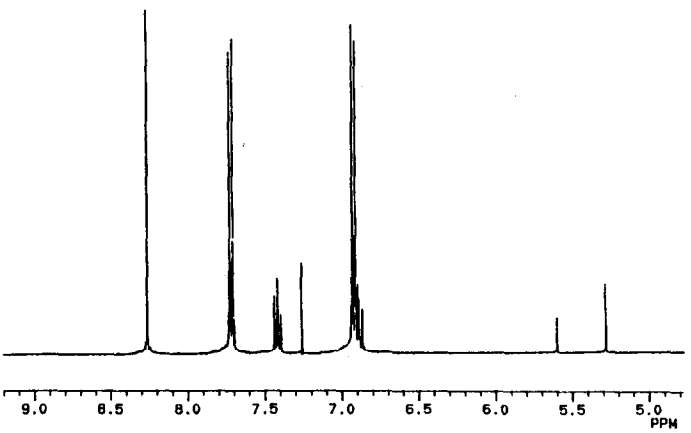


Figure 1. Part of ^{1}H NMR spectrum of compound **8**

Figure 1 and Table 1 clearly demonstrate that Badr *et al.*[16] described the above reactions erroneously, except when thiazolidines were formed. In thiazolidines, the ring form is highly preferred in comparison with oxazolidines, because of the enchanced nucleophilicity and the lower steric strain on the sulphur atom. The relative stability of the thiazolidine ring is estimated to be more than 10^4 times higher than that of the corresponding oxazolidine.[19]

Table 1. Characteristic Data on Tautomeric Mixtures of Oxazolidines[a] Prepared from Serine Esters

No	R	X	σ^+	Ring (%)		log K	Mp (°C) or appearance	Formula	δNC*H*O (*s*)		δN=C*H* (*s*)
				A	C				A	C	B
3	Me	*p*NO_2	0.79	38	35	0.432	oil	$C_{11}H_{12}N_2O_5$	5.44	5.84	8.46
4	Me	*m*Cl	0.399	33	27	0.176	oil	$C_{11}H_{12}ClNO_3$	5.32	5.71	8.32
5	Me	*p*Cl	0.114	29	19	-0.035	oil	$C_{11}H_{12}ClNO_3$	5.32	5.69	8.33
6	Me	H	0	27	17	-0.105	oil	$C_{11}H_{13}NO_3$	5.34	5.68	8.35
7	Me	*p*Me	-0.311	18	11	-0.389	oil	$C_{12}H_{15}NO_3$	5.28	5.60	8.27
8	Me	*p*OMe	-0.778	16	10	-0.454	98-99[b]	$C_{12}H_{15}NO_4$	5.30	5.62	8.29
9	Me	*p*NMe_2	-1.7	4.5	2.5	-1.123	111-113[b]	$C_{13}H_{18}N_2O_4$	5.27	5.57	8.20
10	Et	*p*NO_2	0.79	40	36	0.501	oil	$C_{12}H_{14}N_2O_5$	5.44	5.86	8.46
11	Et	*m*Cl	0.399	36	27	0.231	oil	$C_{12}H_{14}ClNO_3$	5.31	5.72	8.30
12	Et	*p*Cl	0.114	32	22	0.070	oil	$C_{12}H_{14}ClNO_3$	5.31	5.71	8.32
13	Et	H	0	33	19	0.035	oil	$C_{12}H_{15}NO_3$	5.34	5.71	8.36
14	Et	*p*Me	-0.311	26	14	-0.176	oil	$C_{13}H_{17}NO_3$	5.31	5.66	8.37
15	Et	*p*OMe	0.778	17	9	-0.454	70-71[b]	$C_{13}H_{17}NO_4$	5.29	5.64	8.29
16	Et	*p*NMe_2	-1.7	6	3	-1.005	oil	$C_{14}H_{20}N_2O_3$	5.26	5.61	8.20

[a]In $CDCl_3$ solution at ambient temperature. [b]Recrystallized from diethyl ether.

In parallel with earlier findings,[7,8] satisfactory linear correlations were obtained between log K and the Hammett-Brown σ^+ values (Table 2, Figure 2). The slopes and plots correspond within experimental error to those found earlier for oxazolidines. The intercepts show that introduction of a methoxycarbonyl or an ethoxycarbonyl group at position 4 increases the population of the ring form in the tautomeric equilibrium relative to the parent 2-aryl-substituted oxazolidines,[8] *e.g.* from 19% to 85% for *p*-nitrophenyl-substituted oxazolidines.

Table 2. Linear regression analysis data on compounds **3-9**, **10-16** and the parent 2-aryloxazolidines[a]

Compound	**3-9**	**10-16**	Parent compounds[8]
No. of points	7	7	8
Slope[b]	0.61(4)	0.60(1)	0.60(4)
Intercept[b]	-0.09(3)	0.00(1)	-1.10(2)
Correlation coefficient	0.991	0.999	0.989

[a]In $CDCl_3$ solution. [b]Standard errors in brackets.

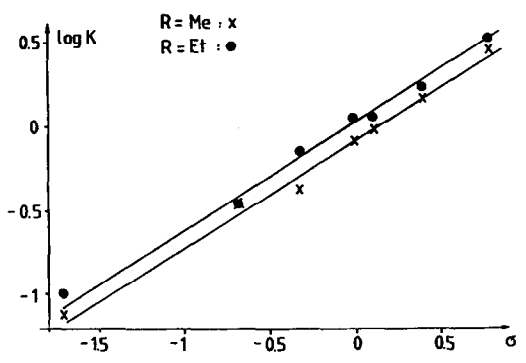


Figure 2. Plots of log K for **3-9** (x) and **10-16** (●) *vs* Hammett-Brown σ^+

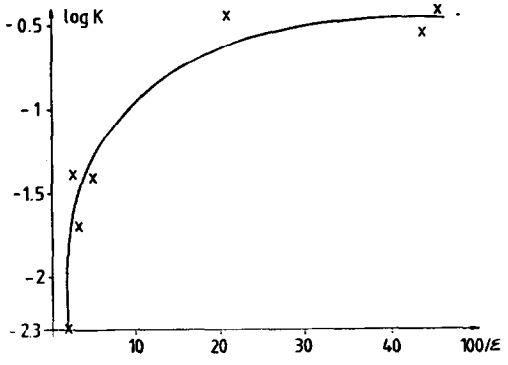


Figure 3. Plot of log K for compound **15** (R = Et, X = *p*OMe) *vs* $100/\varepsilon$

Only a few quantitative data are available[6,8] on the solvent effect on the tautomerism. The equilibrium of compound **15** was investigated in seven different solvents and characteristic differences were found. Table 3 and Figure 3 show the solvent effect on the ring-chain equilibrium of **15**. The plot of log K *vs* dielectric constant clearly demonstrates that more polar solvents prefer the more polar open-chain form. Independently of the tautomeric ratios, the equilibrium mixtures can be used as protected pseudo-prolines, since substitution of the secondary amine group always results in the equilibria being shifted toward the ring form, as proved by different authors (*e.g.* refs. 10, 15, 20).

Table 3. Solvent effect on the tautomeric equilibrium of compound **15**

Solvent	ε	Ring (%)		δNC*H*O(*s*) (ppm)		log K
		15A	**15C**	**15A**	**15C**	
CCl_4	2.24	18	10	5.17	5.62	-0.41
C_6D_6	2.28	13.5	8.5	5.23	5.63	-0.55
$CDCl_3$	4.81	17	9	5.29	5.64	-0.45
$(CD_3)_2CO$	20.7	2	2	5.20	5.52	-1.38
CD_3OD	32.7	1	1	5.25	5.40	-1.69
CD_3CN	37.5	2	2	5.25	5.45	-1.38
DMSO-d_6	46.68	$\Sigma \sim 0.5$		~5.3	~5.45	~-2.3

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JEOL GX 400 FT-NMR spectrometer at ambient temperature 24 h after dissolution of the substances. The number of scans was 40. *L*-Serine methyl ester hydrochloride, (±)-serine ethyl ester hydrochloride and aromatic aldehydes were commercial products.

General procedure of reaction of serine esters with aromatic aldehydes

L-Serine methyl ester hydrochloride (156 mg, 1 mmol) or (±)-serine ethyl ester hydrochloride (170 mg, 1 mmol) was dissolved in 5 ml methanol or ethanol, respectively. The aromatic aldehyde (1 mmol) and triethylamine (202 mg, 2 mmol) were then added, and the mixture was allowed to stand for 2 h at room temperature. The solvent was evaporated off and 30 ml diethyl ether was added to the residue. After a few minutes' stirring, the mixture was dried over Na_2SO_4, filtered and evaporated; the product was recrystallized. If the product was an oil, it was dried for 24 h in a vacuum desiccator. The ^{1}H NMR spectra indicated that the oily products were of higher than 95% purity. The crystalline derivatives gave satisfactory microanalyses (C, H, N).

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