PMR SPECTRA AND cis-trans ISOMERISM OF 2-METHYLENEPYRROLIDINE AND 2-METHYLENETETRAHYDROFURAN DERIVATIVES

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A number of secondary enamines and cyclic enol ethers (2-methylenetetrahydrofuran derivatives) were synthesized by the reaction of O-methylbutyrolactim and 2,2-dieth-oxytetrahydrofuran, respectively, with compounds that have an active methylene link. The absence of reversible cis-trans isomerization was established in a study of the PMR spectra of these compounds. The configuration of the secondary enamines is determined by the possibility of the formation of a strong intramolecular hydrogen bond between the carbonyl-containing substituent and the NH group. In the case of the cyclic enol ethers it was shown that the energy barrier to cis-trans isomerization is greater than 25 kcal/mole and that, as a consequence of this, the geometrical isomers can be separated preparatively.

It has been previously shown by means of PMR spectroscopy that reversible cis-trans isomerization is characteristic for derivatives of cyclic enamines, viz., l-methyl-2-methylenepyrrolidines (I). The free energy of activation ( $\Delta G^{\vec{7}}$ ) ranges from 9.4 to 19.7 kcal/mole, depending on the nature of substituents R and R'; this was explained primarily by stabilization of the dipolar transition state of isomerization at the C-C bond [1, 2].



 $\mathbf{R}$ .  $\mathbf{R}' = \mathbf{CN}$ ,  $\mathbf{COOCH}_3$ ,  $\mathbf{COOC}_2\mathbf{H}_5$ ,  $\mathbf{CONH}_2$ ,  $\mathbf{C}_6\mathbf{H}_5$ 

The aim of the present research was to study the cis-trans isomerization of secondary enamines II and enol ethers III and to compare the results with data for tertiary enamines I.

Pyrrolidine and tetrahydrofuran derivatives II and III were synthesized by the reaction of O-methylbutyrolactim (IV) and butyrolactone diethylacetal (V) with the appropriate compounds with an active methylene link:



II, III a R=CN,  $R'=COOC_2H_5$ ; b R=CN,  $R'=CONH_2$ ; c  $R=COCH_3$ ,  $R'=COOC_2H_5$ ; d R=CN,  $R'=COOCH_3$ ; e R=R'=CN; f  $R=R'=COCH_3$ ; g  $R=R'=COOCH_3$ ; h  $R=R'=COOC_2H_5$ 

It should be noted that, in contrast to N-methylpyrrolidone diethylacetal [3], lactone acetal V undergoes condensation under relatively severe conditions and only with sufficiently strong CH acids. Thus we were unable to carry out the reaction of acetal V with acetophenone and phenylacetic ester.

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TABLE 1. PMR Spectra of Secondary Enamines II

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Com- pound	δ, ppm								
	3-H	4-H	5-H	NH	соосн₃	СОСН₃	$C_2H_5$ or $NH_2$	solvent	
IIa IIb IIc	2,96 2,85 3,15 2,96	2,15 2,03 2,02 2,15	3,74 3,67 3,64 3,73	8,98 9,75 11,68 8,92	 	2,40	$\begin{array}{c} 1,30 \ (CH_3), \\ 4,21 \ (CH_2) \\ 6,50 \ (NH_2) \\ 1,32 \ (CH_3), \\ 4,21 \ (CH_2) \\ \end{array}$	CDCl₃ d <sub>7</sub> -DMF CDCl₃ CDCl₃	
Ile Ilf Ilg	2,93 2,91 3,08 3,13	2,19 2,14 2,06 2,04	3,69 3,72 3,68 3,64	7,52 9,50 11,45 9,50	 3,72 3,75	2,38		CDCl <sub>3</sub> d <sub>7</sub> -DMF CDCl <sub>3</sub> CDCl <sub>3</sub>	

TABLE 2. PMR Spectra of Enol Ethers III

Com-				Equilib-	0					
pound	3-H	4-H	5-H	соосн3	COCH₃	$C_2H_5$	NH2	concn.,	Sorvent	
IIIa	3,32	2,27	4,60			1,32 CH <sub>3</sub> 4,23 CH <sub>2</sub>	~	87	CDCl <sub>3</sub>	
	3,14	2,23	4,71	-		1,31 CH₃ 4,24 CH₂		13		
	3,27	2,18	4,60	-		1,25 CH <sub>3</sub> 4,18 CH <sub>2</sub>		100	d <sub>6</sub> ,DMSO	
IIIb	3,13	2,26	4,73	_	_		7,08	60	i i i	
	3,29	2,20	4,53				7,08	40	d <sub>7</sub> -DMF	
	3,05	2,13	4,63				6,88 7,33	100	d <sub>6</sub> -DMSO	
IIIc	3,14		4,38		2,33	1,31 1,26 CH₃		50	CDCL	
I	3,10	2,11	4,39		2,21	4,18 CH <sub>2</sub> 4,26	-	50	CDCI3	
	3,06	0.05	4,39	-	2,25	1,20 1,24 CH <sub>3</sub>		50	d <sub>6</sub> , DMSO	
	3,01	2,05	4,35		2,13	4,11 4,18 CH <sub>2</sub>		50		
IIId	3,33	2,28	4,61	3,78				90	CDCl₃	
	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$		3,71	-	-	-	100	d <sub>6</sub> -DMSO		
IIIe	3,14 3,15	2,34 2,23	4,75	-	-	_	-		CDCI3 d <sub>6</sub> -DMSO	
IIIf	3,14	2,13	4,45		2,43			·	CDCI3	
	3,02	2,06	4,44	-	2,24 2,35 2,12		_	_	d <sub>s</sub> -DMSO	
IIIg	3,18	2,15	4,42	3,72					CDCI3	
	3,08	2,07	4,36	3,65 3,62	-	_	-	-	d <sub>6</sub> -DMSO	
IIIh	2,88	1,84	4,10			0,96 1,00 CH <sub>3</sub> 3,90 CH <sub>2</sub>	·		CDCl <sub>3</sub>	

Data from the PMR spectra of II and III are presented in Tables 1 and 2. One set of signals was present in the PMR spectra of secondary enamines II. Neither prolonged heating of the solutions (at 70°C for 10 h) nor varying the solvent led to the appearance of signals of the second isomeric form. The configuration of the isomer was determined on the basis of a comparison of the data from the PMR spectrum of the unsymmetrically substituted compound with the corresponding data for symmetrical derivatives. Thus the chemical shifts of the 3-H protons in the dicyano and dicarbomethoxy derivatives (IIe, g) and in enamine IId are, respectively, 2.93, 3.13, and 2.96 ppm, which made it possible to unambiguously assign to IId a structure in which the ester group approaches the ring NH group. A similar configuration was assigned to IIa.

In the case of IIb,c the type of configuration of the isomer was established on the basis of a comparison of the chemical shift of the proton of the NH group. Recording the spectra at -60 to +60°C showed that the  $\delta_{\rm NH}$  value remains virtually unchanged, which constitutes evidence for the presence of a strong intramolecular hydrogen bond in the molecule. A comparison of the  $\delta_{\rm NH}$  value for IIc with the  $\delta_{\rm NH}$  values for symmetrically substituted enamines IIf,g made it possible to establish that an intramolecular hydrogen bond is realized in enamine IIc through the keto carbonyl group rather than through the ester carbonyl group.



The configuration of IIb was similarly established from the presence of an intramolecular hydrogen bond in the molecule.

The presence of a chelate hydrogen bond in secondary enamines IIa-d explains the great energic favorability of this isomer and the complete absence of the second possible isomeric form.

In an investigation of the PMR spectra of enol ethers III it was found that either two isomers are present in the sample immediately (IIIc) or that a freshly prepared solution initially contains one isomeric form, and the second form develops in it after prolonged heating (at 70°C for 10 h) (IIIa,b,d).

Data on the equilibrium concentrations of the isomers were obtained for IIIa-d (Table 2). An examination of these values makes it possible to conclude that the principal factor that determines the composition of the isomeric mixture is the steric factor, and the isomer in which the bulkier group is remote from the methylene group in the 3 position of the ring is therefore more favorable. Thus, for example, the isomeric form in which the ester group is cis-oriented relative to the ring oxygen atom predominates for IIIa,d (90% IIIa and 87% IIId). When the volumes of substituents R and R' are equal, the percentage of the second isomeric form increases; this also occurs for enol ethers IIIb,c.

Broadening of the signals of the isomers was not observed in the PMR spectra of the enol ethers recorded at high temperatures (up to  $180^{\circ}$ C in d<sub>6</sub>-DMSO); this constituted evidence for a high activation barrier to cis-trans isomerization of the investigated compounds ( $\Delta G^{\neq} > 25$ kcal/mole). This made it possible to assume that separation of the mixture of isomers into individual components could be realized in this case. In fact, we were able to accomplish this for IIIc, which is a mixture of geometrical isomers (1:1), by means of preparative chromatography on Silufol UV-254 plates (elution with ethyl acetate).

The higher barrier to isomerization of 2-methylenetetrahydrofuran III as compared with tertiary enamines I is evidently due to the considerably greater energy of the ground state and, chiefly, transition state A\* (see [1,2] for the large role of the transition state in such cases) because of the lower degree of favorability of localization of the positive charge on the oxygen atom than on the nitrogen atom (B).

<sup>\*</sup>In transition states A and B the anionic center and the vacant orbital are situated in mutually perpendicular planes.

Com-	bp, °C (mm)	Found, %			Empirical	Calc., %			Yield,
pouna		с	н	N	formula	с	н	N	1%
IIe* Ilg IIId IIIe IIIf IIIg IIIh	155-156 (2) 186-187 (3) 166-167 (2) 123-124 (2) 141-142 (2) 162-163 (3)	63,1 54,6 57,6 62,8 64,1 54,0 58,0	5,1 7,1 5,5 4,9 7,1 6,0 7,1	31,7 6,7 8,1 20,7 —	$\begin{array}{c} C_7 H_7 N_3 \\ C_9 H_{13} N O_4 \\ C_8 H_9 N O_3 \\ C_7 H_6 N_2 O \\ C_9 H_{12} O_3 \\ C_9 H_{12} O_5 \\ C_1 H_2 O_5 \\ C_1 H_2 O_5 \end{array}$	$\begin{array}{c} 63,2\\ 54,3\\ 57,5\\ 62,7\\ 64,3\\ 54,0\\ 57,9\end{array}$	5,3 6,5 5,4 4,5 7,1 6,0 7,0	31,6 7,0 8,4 20,9 —	92 72 63 83 67 54 41

TABLE 3. Characteristics of IIe,g and IIId-h

\*This compound had mp 167-168°C.



## EXPERIMENTAL

The PMR spectra were recorded with an XL-100 A spectrometer with tetramethylsilane as the internal standard.

Compounds IIa-c,f and IIIa,b were synthesized by known methods [4-6].

<u>2-(Methoxycarbonylcyanomethylene)pyrrolidine (IId)</u>. A 1.98-g (20 mmole) sample of 0methylbutyrolactim (IV) was added to 1.98 g (20 mmole) of methyl cyanoacetate. After spontaneous heating was complete, the reaction mixture was allowed to stand for 1 h. The precipitate was removed by filtration, washed with ether, and dried to give 3 g (90%) of IId with mp 130-132°C (from alcohol). Found: C 57.7; H 6.21; N 16.8%.  $C_8H_{10}N_2O_2$ . Calculated: C 57.8; H 6.0; N 16.9%.

Compounds IIe, g were similarly synthesized (see Table 3).

2-(Acetylethoxycarbonylmethylene)tetrahydrofuran (IIIc). A mixture of 2.6 g (20 mmole) of ethylacetoacetate and 3.2 g (20 mmole) of butyrolactone diethylacetal (V) was refluxed for 5 h with removal of the liberated alcohol by distillation. The reaction mixture was then distilled to give 3 g (76%) of IIIc with bp 160-161°C (5 mm). Found: C 60.7; H 7.4%. C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>. Calculated: C 60.6; H 7.1%.

Compounds IIId-g were similarly obtained (see Table 3).

## LITERATURE CITED

- N. P. Kostyuchenko, V. G. Granik, A. M. Zhidkova, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 9, 1212 (1974).
- 2. J. Shvo and H. Shanan-Atidi, J. Am. Chem. Soc., <u>91</u>, 6683, 6689 (1969).
- 3. A. M. Zhidkova, V. G. Granik, N. S. Kuryatov, V. P. Pakhomov, O. S. Anisimova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 8, 1389 (1974).
- 4. A. Etienne and Y. Correia, Bull. Soc. Chim. Fr., No. 10, 3704 (1969).
- 5. V. A. Azimov, V. G. Granik, R. G. Glushkov, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 355 (1978).
- 6. N. B. Marchenko and V. G. Granik, Khim. Geterotsikl. Soedin., No. 1, 68 (1982).