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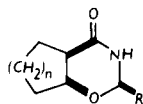
The C=O stretching frequencies of twenty-six *cis*-5,6-polymethylene-2,3,5,6-tetrahydro-1,3-oxazinone derivatives were measured in tetrachloromethane and in chloroform and correlated with the substituent constants  $X^*(R)$  in the sense of the modified and extended Seth-Paul Van Duyse equation. The influence of the fused hydrocarbon ring on the C=O stretching frequency and on the transmission of substituent effects through the six-membered heterocyclic ring is discussed and compared with that in the previously investigated 5,6-polymethylenepyrimidin-4(3*H*)-ones and *cis*-5,6-dihydropyrimidin-4(3*H*)-ones.

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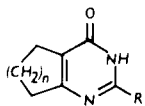
Application of the modified and extended Seth-Paul-Van Duyse equation to various series of compounds containing an exocyclic C=O group of a cyclic 1,3-dicarbonyl system was studied earlier [3-10]. This equation was recently used to investigate the transmission of substituent effects in 5,6-polymethylenepyrimidin-4(3*H*)-one derivatives [2].

The aim of this paper is to study the transmission of substituent effects in further series of six-membered heterocyclic compounds using the modified and extended Seth-Paul-Van Duyse equation [3]. For this purpose, the C=O stretching frequencies of *cis*-5,6-tri-, **1a-1n**, *cis*-5,6-tetra-, **2a-2i** and *cis*-5,6-pentamethylene-2,3,5,6-tetrahydro-1,3-oxazin-4-one, **3a-3c**, derivatives possessing marked anti-inflammatory activity [11-12] were measured.

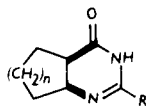
The C=O stretching frequencies of polymethylenetetrahydrooxazinones **1-3** in tetrachloromethane and chloroform are given in Table I.



1a - 1n : n = 1  
2a - 2i : n = 2  
3a - 3c : n = 3



4 : n = 1, 2, 3, 4



5 : n = 1, 2

Analogously to the 5,6-polymethylenepyrimidin-4(3*H*)-one derivatives **4** and **5** reported previously [2], dilute

tetrachloromethane solutions of compounds **1-3** exhibit two absorption bands assignable to the stretching vibration of the free,  $\nu(C=O)_f$ , and hydrogen-bonded,  $\nu(C=O)_b$ , molecules **6**. A similar cyclic structure containing intermolecular hydrogen bonds has been demonstrated in *cis*-2-phenyl-2-methyl-5,6-trimethylene-2,3,5,6-tetrahydro-1,3-oxazinone by X-ray diffraction analysis [13].

The  $\nu(C=O)$  values for both the free and the hydrogen-bonded molecules of **1-3** decrease in the same sequence as the size of the fused hydrocarbon ring increases:

$$\nu(C=O)_n = 1 > \nu(C=O)_n = 2 > \nu(C=O)_n = 3$$

However, the change on passing from  $n = 1$  to  $n = 3$ ,  $\Delta\nu = 4.5 \text{ cm}^{-1}$ , is much smaller than that observed [2] for the pyrimidinones **4** ( $\Delta\nu = 12-19 \text{ cm}^{-1}$ ). The weaker influence of the size of the fused hydrocarbon ring on the  $\nu(C=O)$  values for the tetrahydrooxazinones **1-3** is evidently caused by the lack of conjugation between the hydrocarbon and heterocyclic rings. It is noteworthy that the above sequence of C=O stretching frequencies for 2-(4-chlorophenyl) derivatives **1b** and **2f** is in harmony with the C=O bond lengths and the C-CO-N valence angles found by X-ray diffraction analysis [14,15].

As the compounds under investigation contained various types of substituents R, not describable together by a simple Hammett-type equation, we correlated their  $\nu(C=O)$  values (see Table I) with the substituent constants  $X^*(R)$  of the modified and extended Seth-Paul-Van Duyse equation. The  $X^*(R)$  values were taken from papers [3,8,10,16], and the results of statistical treatment of correlations according to Equation 1 are summarized in Table II.

$$y = \rho X^*(R) + q \quad (1)$$

Table I

The C=O Stretching Frequencies (in  $\text{cm}^{-1}$ ) for *cis*-5,6-Polymethylene-2,3,5,6-tetrahydro-1,3-oxazin-4-ones of Types **1**, **2** and **3**

Compound		in Tetrachloromethane		in Chloroform
		$\nu(\text{C}=\text{O})_b$	$\nu(\text{C}=\text{O})_f$	$\nu(\text{C}=\text{O})_b$
<b>1a</b>	4-ClC <sub>6</sub> H <sub>4</sub>	1672.0	1688.0	1667.5
<b>1b</b>	2-ClC <sub>6</sub> H <sub>4</sub>	1675.0	1688.0	1668.5
<b>1c</b>	3-ClC <sub>6</sub> H <sub>4</sub>	1673.0	1687.5	1668.0
<b>1d</b>	2-OHC <sub>6</sub> H <sub>4</sub>	1650.5 [a]	1669.0 [a]	1646.0 [a]
<b>1e</b>	2-OC <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	—	1680.0 [a]	1659.5 [a]
<b>1f</b>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1671.0	1684.0	1666.5
<b>1g</b>	C <sub>4</sub> H <sub>9</sub> O [b]	1675.0	1689.5	1669.0
<b>1h</b>	C <sub>6</sub> H <sub>5</sub>	1673.0	1686.0	1667.0
<b>1i</b>	4-BrC <sub>6</sub> H <sub>4</sub>	1672.5	1688.5	1667.5
<b>1j</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1674.0	1690.5	1670.0
<b>1k</b>	4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	[c]	1682.5	1664.5
<b>1l</b>	3-FC <sub>6</sub> H <sub>4</sub>	1673.5	1688.5	1668.5
<b>1m</b>	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1673.5	1690.0	1688.5
<b>1n</b>	C <sub>6</sub> H <sub>4</sub> CH=CH [d]	1674.5	1688.5	1669.0
<b>2a</b>	4-BrC <sub>6</sub> H <sub>4</sub>	1671.0	1688.5	1666.5
<b>2b</b>	3-ClC <sub>6</sub> H <sub>4</sub>	1672.0	1689.5	1666.5
<b>2c</b>	3-Br,4-OCH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	1672.0 [a]	1687.5	1666.0
<b>2d</b>	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	1669.0	1686.5	1664.5
<b>2e</b>	C <sub>4</sub> H <sub>9</sub> O [b]	1674.0	1690.5	1669.5
<b>2f</b>	4-ClC <sub>6</sub> H <sub>4</sub>	1670.0	1688.0	1665.5
<b>2g</b>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1676.0	1690.5 [a]	1667.5 [a]
<b>2h</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1673.0	1690.5	1668.0
<b>2i</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1673.0	1691.0	1669.0
<b>3a</b>	C <sub>6</sub> H <sub>5</sub>	1669.0 [a]	1680.5 [a]	1662.0 [a]
<b>3b</b>	4-BrC <sub>6</sub> H <sub>4</sub>	1668.5 [a]	1683.0 [a]	1663.5 [a]
<b>3c</b>	4-ClC <sub>6</sub> H <sub>4</sub>	1668.0 [a]	1683.0 [a]	1663.0 [a]

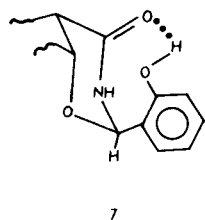
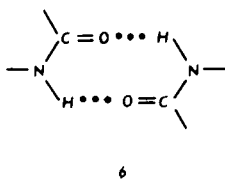
[a] Values not taken into correlations. [b] Furyl; the X\*(R) value for the O,O *cis* conformation was taken. [c] The  $\nu(\text{C}=\text{O})_b$  absorption band was not observed. [d] The X\*(R) value for the *s-cis* conformation was taken.

Table II

Statistical Treatment of Linear Correlations According to Equation 1 for Series of Compounds **1** and **2**

Compound	Solvent	y	r [a]	q	q	s [b]	n [c]
<b>1</b>	tetrachloromethane	(C=O) <sub>b</sub>	0.915	9.9	1661.9	0.5	11
<b>1</b>	tetrachloromethane	(C=O) <sub>f</sub>	0.926	12.3	1673.9	0.9	12
<b>1</b>	chloroform	(C=O) <sub>b</sub>	0.945	7.7	1659.2	0.5	12
<b>2</b>	tetrachloromethane	(C=O) <sub>b</sub>	0.979	13.4	1656.2	0.5	8
<b>2</b>	tetrachloromethane	(C=O) <sub>f</sub>	0.970	11.6	1675.8	0.4	8
<b>2</b>	chloroform	(C=O) <sub>b</sub>	0.913	12.3	1653.0	0.8	8

[a] Correlation coefficient. [b] Standard deviation. [c] Number of compounds used in correlation.



For the 2-(2-hydroxyphenyl) derivative **1d**, the experimental  $\nu(\text{C}=\text{O})$  values were 13-20  $\text{cm}^{-1}$  lower than those

calculated from the expected correlations, and they were therefore not taken into the correlations. These significant deviations, occurring even in dilute tetrachloromethane solutions, can be explained as being due most probably to intramolecular hydrogen-bonding between the C=O and O-H groups, which is rendered possible only by the existence of an *O-inside* conformation of the tetrahydrooxazinone ring **7**. The preference for such a conformation in other tetrahydrooxazinone derivatives **1** has been confirmed previously [11,12,17] by <sup>1</sup>H nmr spectroscopy.

The results in Table II show that for both series of com-

pounds **1** and **2** the slopes ( $\rho$ ) of the correlations  $\nu(\text{C}=\text{O})$  vs  $X^*(\text{R})$  for the hydrogen-bonded  $\text{C}=\text{O}$  group are very close to those for the free  $\text{C}=\text{O}$  group. This indicates that the mechanism of transmission of the substituent effects is probably the same in the free and the hydrogen-bonded molecules. Comparison of the constants  $\rho$  for the above correlations with previously obtained results [2] reveals that the hydrogen-bonded molecules of **1** and **2** transfer the substituent effects approximately twice as readily as the corresponding pyrimidinones **4** ( $n = 1, 2$ ). This demonstrated that in the tetrahydrooxazinones the substituent effects are transmitted to the  $\text{C}=\text{O}$  group directly through the  $\text{NH}$  group. This is different from the situation in the hydrogen-bonded pyrimidinones, in which the substituent effect is transferred *via* the  $\text{C}=\text{N}-\text{C}=\text{C}$  part of the molecule. On the other hand, the value of the constant  $\rho$  for the correlation  $\nu(\text{C}=\text{O})$ , vs  $X^*(\text{R})$  for the tetrahydrooxazinones **1** and **2** is approximately one-half of that for the corresponding pyrimidinone derivatives **4** and **5**. This is caused by the lack of conjugation between the C-2 atom and the  $\text{NH}-\text{CO}$  part of the molecule.

Similarly as in the pyrimidinones **4** [2], the transmission of the substituent effects in hydrogen bonded oxazinones is influenced by the size of the fused hydrocarbon ring. Thus, in the trimethylenetetrahydrooxazinones **1** the substituent effects are transmitted to the  $\text{C}=\text{O}$  group less efficiently than in the corresponding tetramethylene derivatives **2**. A comparison with previously published results [2] reveals that in compounds **1** and **2** the size of the fused hydrocarbon ring influences the transmission of the substituent effect through the heterocyclic ring as significantly as in the case of the pyrimidinones **4**.

Finally, the conclusion can be drawn that the modified and extended Seth-Paul-Van Duyse equation is well applicable to the endocyclic  $\text{C}=\text{O}$  group in tetrahydrooxazinone derivatives and provides a satisfactory method for investigation of the efficiency and mechanism of substituent effect transmission.

## EXPERIMENTAL

The syntheses and some chemical and physical properties of the compounds **1-3** under investigation were reported earlier [11,18].

The ir spectra were recorded on a Zeiss 75 IR Specord grating spectrophotometer. The measurements were carried out at room temperature in sodium chloride cells 0.1, 1.0 and 10 mm in thickness, in tetrachloromethane and chloroform solutions of the compounds. The concentrations of the measured solutions were chosen to give absorption between 70% and 75%. Peak positions were determined by averaging the results of three measurements and are believed to be accurate to  $\pm 0.5 \text{ cm}^{-1}$ . The instrument calibration was verified by using water vapour and indene standard spectra.

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