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SPATIAL STRUCTURE OF DERIVATIVES OF 1-NITROPHENYLPYRROLES

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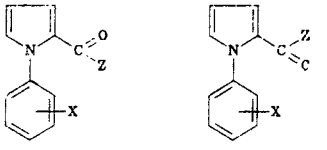
Combined ^1H and ^{13}C NMR data were used to show that 2-carbonyl derivatives of 1-nitrophenylpyrroles (aldehydes, acids, esters, and amides) have primarily the S-trans-configuration. Oximes of 1-nitrophenyl-2-formylpyrroles exist as a mixture of S-trans-syn- and S-cis-anti-isomers.

Lowered IR frequencies for the carbonyl groups in 2-substituted 1-nitrophenylpyrroles suggest strong conjugation of the substituent to the pyrrole ring (Table 1). This raises the barrier to rotation around the single bond between the substituent and the heterocycle. Such conjugation is strongest in the two steric conformations S-cis- and S-trans-.



S-cis S-trans

This work studies the spatial structure of 2-substituted carbonyl derivatives of 1-nitrophenylpyrroles such as acids, esters, amides, and oximes. 1-Nitrophenyl-2-formylpyrroles are the starting materials for synthesis of all these compounds.

The classical method for oxidation of a carbonyl group to a carboxylate is the reaction with silver ions [1, 2]. In the case of 1-nitrophenyl-2-formylpyrrole this method does not give positive results because of the slight solubility of the aldehyde in water. Use of other stronger oxidants leads to polymerization or decomposition of the pyrrole ring [3]. We were able to oxidize the aldehyde group to the carboxylate with potassium permanganate in sulfolane; the reaction in acetone requires too great a volume of solvent. Esters and amides which can be used for identification were synthesized based on these acids. The acids themselves are extremely easily decarboxylated (heating for 15-20 min at the melting point), which is a convenient method for synthesis of the 2-substituted 1-arylpyrroles.

The question of the spatial structure of carbonyl compounds more often than not is decided using ^1H NMR spectra and dipole moments. Thus, it was found in [4, 5] that 2-formyl-, 2-acetyl-, and 2-benzoylpyrroles have dipole moments near to those calculated for the S-trans-position of the carbonyl group. Besides this, it is known [6] that for an S-trans-position of

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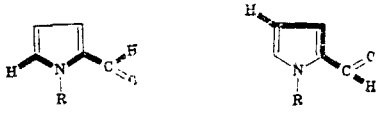
TABLE 1. Carbonyl Group Absorption in the IR Spectra of 2-Substituted 1-Nitrophenylpyrroles

Z	νC=O, cm^{-1}
H	1665
CH_3	1670
C_6H_5	1635
OH	1690
OCH_3	1730
$N(C_2H_5)_2$	1630
NHC_6H_5	1630

TABLE 2. Changes in the Chemical Shifts (ppm) for the Carbonyl Derivatives of Phenylpyrroles

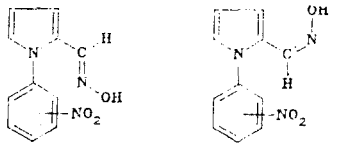
$\Delta=\delta_{2\text{-}X}-\delta_{2\text{-}H}$, ppm	Compound				
	aldehyde	amine	ester, acid	oxime	
				I	II
Δ3-H	0,89	0,17	0,73 (R=H); 0,80 (R=CH_3)	0,33	1,00
Δ3-C	14,26	0,82	9,10 (R=H); 9,38 (R=CH_3)	1,57	2,00

the 2-formyl group the aldehyde proton appears in the ^1H NMR spectra as a doublet (J = 1.0-1.2 Hz) due to interaction with the 5-H proton. For the S-cis-conformation, interaction with the 4-H proton is observed [7].



S-trans S-cis

Introduction of an electron-acceptor group into the 2 position of a 1-nitrophenylpyrrole elicits in the NMR spectrum a weak field shift of the signal for proton 3-H and carbon $C_{(3)}$. We found, comparing these values, that it is possible to draw a conclusion about the preferred conformation of the substituent. The presence of a stereospecific interaction of the aldehyde proton with 5-H [$J_{5\text{-}\alpha}$ = 1.0 (m-NO_2); 0.98 (p-NO_2), and 0.73 Hz (p-CO_2Et), found experimentally by double resonance] allows a conclusion to be made about the S-trans-position of the formyl group in aldehydes. The signals of the hydrogen and carbon atoms in position 3 undergo a strong synchronous weak field shift (Table 2). An analogous situation is observed in acids and esters with correction for the change in the acceptor strength of the substituent. These same factors are strengthened even more in the case of amides which decrease the shifts of the signals for hydrogen and carbon while preserving the synchronicity. Therefore it can be proposed for all indicated acid derivatives, as in the case of aldehydes, that the S-trans-configuration is preferred.



S-trans-syn (I) S-cis-anti (II)

1-Nitrophenyl-2-formylpyrroles easily form oximes upon reaction with hydroxyamine, always giving a mixture of two isomers: S-trans-syn- and S-cis-anti- (for the proof, see below), which can be separated chromatographically. In the case of the oxime of 1-(p-nitrophenyl)-2-

TABLE 3. ^{1}H NMR Spectra for Oximes of 2-Formyl-1-nitrophenylpyrroles, δ, ppm

Proton	Isomer	X		
		m-NO_2	*p*-NO_2	*p*-$COOC_2H_5$
3-H	I	6,66	6.68	—
	II	7.33	7.36	7,32
4-H	I	6.36	6.43	—
	II	6.40	6.39	6.39
5-H	I	7,22	7.20	—
	II	7,22	7.29	7,13
α-H	I	7.94	7.95	—
	II	7.12	7.17	7,10
OH	I	10,85	10,87	—
	II	11,42	11.46	11,41
OH–(α-H)	I	2,91	2,92	—
	II	4,30	4,29	4,31

formylpyrrole, their ratio is 2:1, for the meta-isomer, 4:1, i.e., conjugation of the nitro group to the pyrrole ring stabilizes the S-trans-syn-isomer. In the case of 1-(p-carbethoxyphenyl)-2-formylpyrrole, only the S-cis-antioxime is formed, although traces of the second isomer are observed chromatographically.

It is known from the literature [8] that the syn-anti-isomers of aldehyde oximes have definite chemical shifts for the α-H and OH in DMSO which do not depend on the concentration. It is also known that the difference between the chemical shifts of these signals is characteristic for the syn- and anti-isomers. For the syn-isomer, this difference is about 3 ppm, for the anti- about 4 ppm. As Table 3 shows, for one of the isomers the difference $\delta_{OH}-\delta_{\alpha\text{-}H}$ is 2.91 and 2.92 ppm and for the other 4.30. Thus, the isomers of I are syn-, and those of II, anti-.

Proton 3-H in isomer II (Table 2) absorbs in a significantly weaker field than in isomer I, at the same time the chemical shifts of $C_{(3)}$ for both isomers differ little. This is easily explained if it is accepted that in isomer I the oxime group is located in the S-trans-, and in isomer II in the S-cis-configuration.

These isomers are thermally stable and according to the ^{1}H NMR spectra do not change upon heating to 130°C in DMSO solution.

It can be concluded from the data of Table 3 that the isolated oxime of 1-(p-carbethoxyphenyl)-2-formylpyrrole has the S-cis-anti-configuration.

EXPERIMENTAL

IR spectra were taken on SP-1000 and UR-20 instruments as KBr tablets, UV spectra on a Specord instrument in alcohol, NMR spectra on a FX-90Q instrument. Monitoring of the reaction and the purity of products was done by TLC on UV-254 plates in benzene, separation and purification used columns with Merck 60 silica gel and benzene–methanol, 19:1, as eluent.

Starting p- and m-nitrophenyl-2-formylpyrroles were synthesized according to [9]. Spectral data for 2-carbonyl derivatives of 1-arylpyrroles are in Tables 4-6. Elemental analyses for C, H, and N corresponded to those calculated.

1-(p-Nitrophenyl)-2-formylpyrrole oxime, $C_{11}H_9N_3O_3$. To a mixture of 2 g (28 mmole) hydroxylamine hydrochloride, 3.2 g (36 mmole) sodium acetate, and 4 ml water heated to 40°C was added a solution of 2 g (9.2 mmole) aldehyde. The mixture was boiled for 30 min. Solvent was removed in vacuum to 20-30 ml; the crystals which formed were filtered. A mixture of isomers (1.98 g, 93%) was obtained. After chromatographic separation, 1.4 g of the mixture gave:

S-trans-syn-Oxime. Yield 0.86 g (62%), mp 144-146°C. IR spectrum: 1335, 1510, (NO_2), 3000-3400 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 203 (4.25), 227 sh (4.24), 281 nm (4.25). Mol. wt. 231.

S-cis-anti-Oxime. Yield 0.48 g (34%), mp 168-170°C. IR spectrum: 1340, 1530 (NO_2), 3000-3400 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 205 (4.25), 227 (4.12), 274 nm (4.32). Mol. wt. 231.

TABLE 4. ^{1}H NMR Spectra for Carbonyl Derivatives of 1-(p-Nitrophenyl)pyrroles, δ, ppm, J, Hz

2-R	Solvent	3-H	4-H	5-H	J_{45}	J_{34}	J_{35}	Signals of remaining protons
H	DMSO	6,38	6,38	7,50	—	—	—	7,88 (*o*-H); 8,30 (*m*-H); $J_{o,m}$=9,00
	$CDCl_3$	6,42	6,42	7,16	2,25	2,25	2,25	7,50 (*o*-H); 8,30 (*m*-H)
$CH_\alpha O$	DMSO	7,14	6,34	7,31	2,93	3,52	1,75	7,54 (*o*-H); 8,20 (*m*-H); 9,48 (α-H); $J_{5\alpha}$=1,46, $J_{o,m}$=9,00
	$CDCl_3$	7,20	6,49	7,13	—	—	—	7,52 (*o*-H); 8,32 (*m*-H); 9,62 (α-H); $J_{5\alpha}$=0,98
CH_α=NOH,	DMSO	6,68	6,37	7,20	—	—	—	7,66 (*o*-H); 8,35 (*m*-H); 7,95 (α-H); 10,87 (OH); $J_{o,m}$=9,25
I	$CDCl_3$	6,74	6,40	6,94	2,92	3,91	1,71	7,47 (*o*-H); 8,31 (*m*-H); 7,95 (α-H); 4,76 (OH); $J_{o,m}$=9,19
CH_α=NOH,	DMSO	7,36	6,43	7,29	2,93	3,81	1,76	7,68 (*o*-H); 8,36 (*m*-H); 7,17 (α-H); 11,46 (OH); $J_{o,m}$=9,01
II	$CDCl_3$	6,96	6,47	7,20	—	—	—	7,52 (*o*-H); 8,38 (*m*-H); 7,26 (α-H); 4,00 (OH); $J_{o,m}$=8,96
COOH	DMSO	7,07	6,37	7,30	2,82	3,76	1,75	7,63 (*o*-H); 8,27 (*m*-H)
	$CDCl_3$	7,25	6,38	7,01	2,75	3,85	1,76	7,48 (*o*-H); 8,28 (*m*-H); $J_{o,m}$=8,87
$COOCH_3$	DMSO	7,12	6,40	7,36	2,85	3,95	1,76	7,65 (*o*-H); 8,29 (*m*-H); 3,62 (CH_3); $J_{o,m}$=8,91
	$CDCl_3$	7,16	6,36	6,97	2,81	3,90	1,71	7,46 (*o*-H); 8,23 (*m*-H); 3,74 (CH_3); $J_{o,m}$=8,85
$CON(Et)_2$	DMSO	6,55	6,34	7,32	2,85	3,62	1,53	7,51 (*o*-H); 8,29 (*m*-H); 1,08 (CH_3); 3,39 (CH_2); $J_{o,m}$=8,87
	$CDCl_3$	6,55	6,33	6,96	2,85	3,63	1,53	7,41 (*o*-H); 8,27 (*m*-H); 1,14 (CH_3); 3,46 (CH_2); $J_{o,m}$=8,87

TABLE 5. ^{1}H NMR Spectra for Carbonyl Derivatives of 1-(m-Nitrophenyl)pyrroles, δ, ppm, J, Hz

2-R	Solvent	3-H	4-H	5-H	J_{45}	J_{34}	J_{35}	Signals of remaining carbon protons
H	DMSO	6,38	6,38	7,54	2,30	2,30	2,30	8,03 (6′-H); 7,77 (5′-H); 8,03 (4′-H); 8,34 (2′-H)
	$CDCl_3$	6,40	6,40	7,15	—	—	—	7,71 (6′-H); 7,57 (5′-H); 8,03 (4′-H); 8,27 (2′-H)
$CH_\alpha O$	DMSO	7,22	6,44	7,47	—	—	—	7,83 (6′-H); 7,77 (5′-H); 8,20 (4′-H); 8,16 (2′-H); 9,54 (α-H)
	$CDCl_3$	7,22	6,49	7,13	—	—	—	7,69 (6′-H); 7,62 (5′-H); 8,27 (4′-H); 8,22 (2′-H); 9,61 (α-H); $J_{5\alpha}$=0,98
CH_α=NOH,	DMSO	6,66	6,36	7,22	2,84	3,55	1,72	7,86 (6′-H); 7,77 (5′-H); 8,26 (4′-H); 8,16 (2′-H); 7,94 (α-H); 10,85 (OH)
I	$CDCl_3$	6,72	6,41	6,94	—	—	—	7,71 (6′-H); 7,59 (5′-H); 8,26 (4′-H); 8,22 (2′-H); 7,94 (α-H); 2,86 (OH)
CH_α=NOH,	DMSO	7,33	6,40	7,22	2,88	3,51	1,75	7,89 (6′-H); 7,80 (5′-H); 8,24 (4′-H); 8,14 (2′-H); 7,12 (α-H); 11,42 (OH)
II	$CDCl_3$	7,49	6,46	6,96	—	—	—	7,70 (6′-H); 7,62 (5′-H); 8,28 (4′-H); 8,21 (2′-H); 7,26 (α-H); 5,50 (OH)
COOH	DMSO	7,06	6,38	7,32	2,81	3,91	1,75	7,90 (6′-H); 7,71 (5′-H); 8,22 (4′-H); 8,16 (2′-H)
	$CDCl_3$	7,25	6,38	7,01	—	—	—	7,69 (6′-H); 7,56 (5′-H); 8,23 (4′-H); 8,20 (2′-H)
$COOCH_3$	DMSO	7,13	6,39	7,38	—	—	—	7,86 (6′-H); 7,72 (5′-H); 8,28 (4′-H); 8,19 (2′-H); 3,65 (CH_3)
	$CDCl_3$	7,18	6,38	7,00	2,80	3,96	1,76	7,70 (6′-H); 7,60 (5′-H); 8,27 (4′-H); 8,20 (2′-H); 3,75 (CH_3)

TABLE 6. ^{13}C NMR Spectra for Carbonyl Derivatives of 1-Nitrophenylpyrroles in DMSO, δ, ppm

p-Isomer

2-R	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(1')}$	$C_{(o)}$	$C_{(m)}$	$C_{(p)}$	Signals of remaining carbon atoms
H	119,29	112,22	112,22	119,29	143,57	119,02	125,40	144,23	
CHO	131,70	125,14	111,38	131,89	143,67	123,90	126,39	146,11	178,45 (CO)
CH=NOH, I	126,00	113,38	110,81	125,84	144,64	124,65	126,32	145,83	139,98 (CH=N)
CH=NOH, II	123,56	118,63	110,81	124,71	143,93	125,03	126,71	146,10	134,62 (CH=N)
COOH	124,21	120,06	110,11	129,87	145,34	123,87	126,85	146,03	161,01 (CO)
$COOCH_3$	122,70	120,14	110,41	130,46	145,04	124,00	127,00	146,27	160,14 (CO); 51,16 (CH_3)
$CON(Et)_2$	127,00	112,75	109,77	124,03	144,57	123,73	124,46	145,06	

m-Isomer

2-R	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(6')}$	Signals of remaining carbon atoms
H	119,08	111,17	111,17	119,08	140,54	113,34	148,23	119,25	130,79	125,12	
CHO	131,24	125,43	111,38	131,96	133,01	120,33	147,50	124,16	132,08	130,09	178,59 (CO)
CH=NOH, I	122,14	112,74	110,14	125,85	140,02	120,26	147,62	121,73	132,02	130,24	139,59 (CH=N)
CH=NOH, II	126,09	113,17	110,63	126,15	—	120,52	148,03	128,09	132,29	130,63	140,20 (CH=N)
COOH	124,02	120,27	110,47	130,67	141,29	121,25	147,93	122,66	132,95	130,51	161,66 (CO)
$COOCH_3$	122,35	120,55	109,62	130,20	140,25	119,18	147,36	122,01	132,49	129,56	159,62 (CO); 50,74 (CH_3)
$CON(Et)_2$	126,90	111,79	109,25	123,90	140,29	117,84	147,78	120,87	130,40	129,53	162,09 (CO); 12,84* (CH_3)

*CH_2 group absorbs near 40 ppm and is masked by solvent.

1-(m-Nitrophenyl)-2-formylpyrrole oxime, $C_{11}H_9N_3O_3$. Obtained analogously with a total yield of 1.1 g (92%).

S-trans-syn-Oxime. Yield 0.88 g (80%), mp 179-180°C. IR spectrum: 1350, 1540 (NO_2), 3000-3300 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 204 (4.09), 258 nm (4.18).

S-cis-anti-Oxime. Yield 0.18 g (16%), mp 130-131°C. UV spectrum, λ_{max} (log ε): 286 nm (4.18). Mol. wt. 231.

1-(p-Carbethoxyphenyl)-2-formylpyrrole oxime, $C_{14}H_{14}N_2O_3$. Obtained analogously, yield 88% (S-cis-anti-isomer), mp 138-140°C. IR spectrum: 1715 (C=O), 2800-3300 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 202 (4.07), 2.18 (4.09), 265 (4.44), 280 nm (4.47).

1-(p-Nitrophenyl)-2-carboxypyrrole, $C_{11}H_8N_2O_4$. To a solution of 2 g (9 mmole) 1(p-nitrophenyl)-2-formylpyrrole in 100 ml sulfolane was added dropwise with stirring a solution of potassium permanganate until loss of color stopped. It was heated to 80°C, filtered while hot, and the precipitate washed a few times with hot water. The combined filtrate was acidified with HCl and cooled. The precipitate which formed was filtered, washed on the filter with cold water, and dried. Yield 1.6 g (74%) of acid, mp 240-242°C. IR spectrum: 1350, 1525 (NO_2), 1690 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 204 (4.25), 225 (4.12), 258 (4.15), 298 mm (4.08).

1-(m-Nitrophenyl)-2-carboxypyrrole, $C_{11}H_8N_2O_4$. Obtained analogously, yield 80%, mp 226-228°C. IR spectrum: 1360, 1540 (NO_2), 1690 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 208 (4.14), 257 nm (4.25).

1-(p-Nitrophenyl)-2-carbomethoxypyrrole, $C_{12}H_{10}N_2O_4$. To a solution of 0.5 g (2 mmole) chloroanhydride of 1-(p-nitrophenyl)pyrrole-2-carboxylic acid, obtained by the standard method, in methanol was gradually added 0.3 ml (2 mmole) triethylamine in 5 ml methanol. The mixture was boiled for 1 h. Most of the methanol was removed in vacuum, the resulting precipitate was filtered and washed with water. The ester was recrystallized from methanol. Yield 0.45 g (92%), mp 108-109°C. IR spectrum: 1350, 1515 (NO_2), 1720 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 204 (4.11), 224 (4.06), 260 (4.14), 296 nm (4.05).

1-(m-Nitrophenyl)-2-carbomethoxypyrrole, $C_{12}H_{10}N_2O_4$. Obtained analogously with yield 90%, mp 107-108°C. IR spectrum: 1355, 1535 (NO_2), 1730 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 208 (4.09), 264 nm (4.22).

1-(p-Nitrophenyl)pyrrole-2-carboxylic acid diethylamide, $C_{15}H_{17}N_3O_3$. To a solution of 0.5 g (2 mmole) chloroanhydride of the acid in 30 ml dry benzene was added dropwise with stirring a solution of 0.3 ml (2 mmole) triethylamine in 5 ml benzene at 6°C. The mixture was stirred for 10 min, a solution of 2 mmole diethylamine in 5 ml dry benzene was added dropwise, and the mixture was boiled for 30 min. It was cooled, triethylamine hydrochloride was filtered off, the filtrate was evaporated to dryness in vacuum, and the residue was recrystallized from alcohol with activated carbon. Yield 0.4 g (70%), np 115-116°C. IR spectrum: 1335, 1515 (NO_2), 1625 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 204 (4.26), 221 (4.25), 309 nm (4.05).

1-(m-Nitrophenyl)pyrrole-2-carboxylic acid diethylamide, $C_{15}H_{17}N_3O_3$. Obtained analogously with yield 75%, mp 95-96°C. IR spectrum: 1355, 1535 (NO_2), 1630 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 209 (4.26), 250 nm (4.28). M^+ 287.

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