DETERMINATION OF REACTIVITY CONSTANTS OF p-SUBSTITUTED

2- AND 5-PYRIMIDYL GROUPS BY MEANS OF ¹³C NMR

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In [1] we reported on the determination of the σ_I and σ_R° constants of 2- and 4-pyrimidyl groups having substituents in one of the m-positions of the pyrimidine ring, using ¹³C NMR. In a continuation of these studies of electronic effects in substituted pyrimidal groups, we have determined in the present work the constants σ_I and σ_R° of pyrimidyl groups with substituents in the p-position — specifically, 5-substituted 2-pyrimidal groups and 2-substituted 5-pyrimidal groups, by means of ¹³C NMR.

Two series of phenylpyrimidines (I) and (II) were synthesized by known methods; the ¹³C chemical shifts (CS) of these compounds were measured in acetone:



where

 $X = H(a_1, Cl(b), OCH_3(c), NH_2(d), N(CH_3)_2(e), COOC_2H_5(f), CN(g).$

The values obtained for the ¹³C CSs are listed in Table 1. There was no difficulty in assigning the signals of the benzene-ring carbon atoms, since the introduction of various substituents into the pyrimidine ring produces only relatively small changes in the ¹³C CSs of the benzene-ring carbon atoms (see Table 1). These changes do not go beyond the analogous changes in m-substituted phenylpyrimidines of [1] and biphenyls [2]. The assignment of the signals of the pyrimidine-ring carbon atoms in the 2-substituted 5-phenylpyrimidines was performed by the use of the corresponding increments found from the data of [3] for 2-substituted pyrimidines (Table 2). The assignment of the signals of the pyrimidines (2). The assignment of the signals of the pyrimidine for 5-substituted 2-phenylpyrimidines was performed using the increments for 5-substituted pyrimidines [4] and monosubstituted benzenes [2, 5] (Table 3).

In calculating the σ -constants of the substituted pyrimidyl groups, we used correlation equations given in [1] for monosubstituted benzenes, relating the o-constants of the substituents to the relative ¹³C CSs of the m- and p-carbon atoms ($\Delta\delta C^m$ and $\Delta\delta C^p$). The substituted pyrimidyl groups were regarded as substituents on the benzene ring. The relative CSs of the benzene-ring carbon atoms in the phenylpyrimidines, these CSs being used to calculate the $\sigma_{\rm I}$ and $\sigma_{\rm R}^{\circ}$ constants of the substituted pyrimidyl groups, were adjusted by applying anisotropic corrections (-0.15 ppm for $\Delta\delta C^{m}$ and -0.10 ppm for $\Delta\delta CP$) to account for the influence of the ring current of the pyrimidine ring. These corrections were calculated by analogy with biphenyl [2]. In calculating the corrections in the case of the phenyl pyrimidines, consideration was given to data indicating the closeness of magnitudes of the ring currents of benzene and pyrimidine [6] and the similarity of the geometric parameters of biphenyl and phenylpyrimidines. The angle between the planes of the benzene and pyrimidine rings for the 5-phenylpyrimidine was assumed to be $\sim 40^{\circ}$ by analogy with biphenyl [7], and for 2-phenylpyrimidine $\sim 0^{\circ}$, in accordance with data obtained by x-ray structure analysis.* The anisotropic corrections that were obtained remained practically constant when the angle of rotation was varied from 0° to 40°. In Tables 4 and 5 we have listed the values of the relative CSs of the m- and pcarbon atoms of the benzene ring of the substituted phenylpyrimidines, the calculation having taken into account the anisotropic correction and the values found on this basis for the σ constant of 5-substituted 2-pyrimidy1 and 2-substituted 5-pyrimidy1 groups. The constants

*The analysis was performed by Yu. V. Gatilov, using a Syntex P2, diffractometer.

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Compound	C3	ů	C:	ບຶ	co	°,	съ	c ⁱ	Other C
(1a)	164,85	158,10	120,29	158,10	128,71	129,19	131,35	138,58	1
(IP)	162,86	156,44	129,95	156,44	128,71	129,25	131,64	137,24	1
(Ic)	157,81	144,14	153,15	144,14	128,12	129,09	130,34	138,48	56,48
(Id)	155,14	149,69	145,16	149,69	127,95	128,97	130,00	138,20	1
(If)	167,23	158,81	122,61	158,81	129,36	129,36	132,44	137,40	14,36;
									164,32
(Ig)	169,36	160,92	107,33	160,92	129,47	129,53	132,92	136,76	119,16
(IIa)	158,16	155,41	134,69	155,41	127,73	130,05	129,57	135,18	1
(qII)	160,58	158,43	133,72	158,43	127,79	130,11	129,69	133,94	1
(IIc)	165,98	157,89	128,28	157,89	127,19	129,89	128,71	135,29	55,02
(IId)	164,20	156,92	124,66	156,92	126,55	129,84	127,90	136,69	1
(IIe)	162,45	156,32	122,56	156,32	126,33	129,78	127,70	136,74	37,06
(IIf)	156,97	156,05	135,94	156,05	128,06	130,22	130,22	134,48	14,46 62.36
									164,25
(IIG)	143,86	156,70	136,90	156,70	128,17	130,32	130,75	133,51	116,84

TABLE 1. ¹³C Chemical Shifts of Substituted Phenylpyrimidines, ppm

TABLE 2. Changes in ¹³C Chemical Shift under the Influence of Substituent 2-X, ppm

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Substituent X	Com - pound	C2	C4,6	C⁵				
CI	(II) (III)	$2,42 \\ 2,3$	3,02 3,3	-0,97 -0,9				
$\rm NH_2$	(II) (III)	$^{6,04}_{3,7}$	1,51 0,2	-10,03 -12,3				
$N(CH_3)_2$	(II)	4,29	0,91	-12,13				
OCH_3	(II) (III)	7,82 6,7	2,28 2,3	$-6,41 \\ -6,5$				
CN	(II) (III)	-14,30 -14,2	1,29 1,9	2,21 2,9				
$\rm COOC_2H_5$	(II)	-1,19	0,64	1,25				
$\rm COOCH_3$	(III)	-3,2	0,3	1,2				

*According to [3]; solvent (CD₃)₂-CO; for $X = NH_2$, solvent $(CD_3)_3SO$.

TABLE 3. Changes in ¹³C Chemical Shift under the Influence of Substituent 5-X, ppm



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Sub sti tuent X	Series	C²	C4,6	C⁵
Cl	(I) (V)	-1,99 -1,13	$-1,66 \\ 0,18$	9,66 5,60
OCH₃	(I) (IV) (V)	-7,04 -7,49 -7,93	-13,96 -13,66 -14,51	32,86 32,07 31,50
$\rm NH_2$	(I) (IV) (V)	$-9,71 \\ -11,16 \\ -11,51$	8,41 14,43 13,87	24,87 20,73 20,08
$\rm COOC_2H_5$	(I) (V)	$2,38 \\ 4,53$	0,71 0,97	$2,22 \\ 2,38$
CN	(I) (V)	4,51 4,60	2,82 3,72	$-12,96 \\ -16,50$

*According to [4]; solvent CDCl₃ when $X = OCH_3$, and $(CD_3)_2SO$ when $X = NH_2$. +According to [1]; solvent (CH₃)₂CO; for $X = NH_2$, solvent $(CD_3)_2CO$ [5].

 σ_I and σ_R° of the 5-substituted 2-pyrimidal groups indicate a weak electron-acdeptor character of these groups. The 2-substituted 5-pyrimidal groups, in terms of their inductive effect, are electron-acceptor substituents, but in terms of the mesomeric effect they are weak electron-donor substituents; among the 2-substituted 5-pyrimidal groups, the exception is the 2-cyano-5-pyrimidyl group, which is an electron-acceptor substituent in terms of both inductive and mesomeric effect (Table 5).

Previously, in the example of substituted phenyl [2] and pyrimidyl [8] groups, we demonstrated that the electronic effects of such complex substituents can be expressed in terms

TABLE 4. Relative ¹³C Chemical Shifts (ppm) of 5-Substituted 2-Phenylpyrimidines and Derived Values of σ -Constant of 5-Substituted 2-Pyrimidyl Groups

Substituent on pyrimidine ring	$\Delta \delta C^m$	∆8C ^m *	$\Delta \delta C^p$	∆ôC ^p *	σI	σ° _R
$egin{array}{c} H \\ Cl \\ OCH_3 \\ NH_2 \\ COOC_2H_5 \\ CN \end{array}$	0,110,170,01-0,110,280,45	$\begin{array}{r} -0,04\\ 0,02\\ -0,14\\ -0,26\\ 0,13\\ 0,30\end{array}$	2,27 2,56 1,26 0,92 3,36 3,84	$2,17 \\ 2,46 \\ 1,16 \\ 0,82 \\ 3,26 \\ 3,74$	$\begin{array}{c} 0,05\\ 0,07\\ 0,00\\ -0,04\\ 0,11\\ 0,16\end{array}$	0,10 0,11 0,07 0,06 0,14 0,16

 $\delta^{13}C(C_6H_6) = 129.08 \text{ ppm}.$

*With correction for magnetic anisotropy. The σ -constants were calculated by the use of the following equations:

 ${}^{\sigma}I = 0.034 {}^{+}0.315 \Delta \delta \ C^{m} \, {}^{+}0.012 \Delta \delta \ {\rm C}^{p}; \ \ {}^{\sigma}{}^{n}_{R} = 0.003 {}^{-}0.060 \Delta \delta \ {\rm C}^{m} {}^{+}0.045 \Delta \delta \ {\rm C}^{p}.$

TABLE 5. Relative ¹³C Chemical Shifts (ppm) of 2-Substituted 5-Phenylpyrimidines and Derived Values of σ -Constant of 2-Substituted 5-Pyrimidal Groups

Substituent on pyrimidine ring	$\Delta \delta C^m$	ΔδC ^{m∗}	$ extsf{dd}^p$	$\Delta \delta C^{p *}$	σI	σ° _R
H Cl OCH ₃ NH ₂ N(CH ₃) ₂ COOC ₂ H ₅ CN	0,97 1,03 0,81 0,76 0,70 1,14 4,24	0,82 0,88 0,66 0,61 0,55 0,99 4 00	$\begin{array}{r} 0,49\\ 0,61\\ -0,37\\ -1,18\\ -1,38\\ 1,14\\ 4,67\end{array}$	0,39 0,51 -0,27 -1,08 -1,28 1,04 4,57	$\begin{array}{c} 0,30\\ 0,32\\ 0,24\\ 0,21\\ 0,19\\ 0,36\\ 0,40\end{array}$	$\begin{array}{r} -0,03\\ -0,03\\ -0,06\\ -0,09\\ -0,09\\ -0,09\\ -0,01\\ 0,04\end{array}$

 $\delta^{13}C$ (C₆H₆) = 129.08 ppm.

*With correction for magnetic anisotropy.

Equation	Group	a	ь	r	8
(1)		0,14	0,22	0,998	0,007
(2)		0,06	0,11	0,991	0,007
(1)		0,12	0,21	0,996	0,009
(2)		0,05	0,11	0,992	0,006

TABLE 6. Parameters of Correlation Equations

of the effects of their components, i.e., in terms of the effects of the corresponding unsubstituted group and the substituent. In the present work, by means of a two-parameter correlation, we have also found equations that can be used to estimate the σ -constants of substituted 2- and 5-pyrimidyl groups if we know the σ -constants of the unsubstituted 2- or 5pyrimidyl group and the substituent X. The parameters of these correlation equations are listed in Table 6. In the constant $\sigma_{\rm I}({\rm Pym}~{\rm X})$, characterizing the inductive effect of the substituted pyrimidyl groups as defined by Eq. (1), contributions that are comparable in magnitude come from the inductive and mesomeric effects of the substituted pyrimidyl groups as defined by Eq. (2), there is very little dependence on either the inductive or mesomeric effects of the substituent X.

EXPERIMENTAL

The ¹³C NMR spectra were measured at $\sim 28^{\circ}$ C in the pulse regime under conditions of complete spin coupling, with subsequent Fourier transform, in a Bruker NX-90 spectrometer (22.63 MHz). The ¹³C NMR spectra were taken on solutions of the substances, at a concentration of 0.35 mole/liter. TMS was used as in internal standard. Approximately 5% (CD₃)₂CO was added to stabilize the resonance conditions. The pulse width was 15 µsec ($\sim 60^{\circ}$). The time between pulses was 10 sec. The sweep width was 5000 Hz. The number of scans was varied from 300 to 5800. The accuracy of CS measurement was ±0.03 ppm.

2-Dimethylamino-5-phenylpyrimidine (IIe). To a solution of 1.33 g (7 mmoles) of 2chloro-5-phenylpyrimidine (IIb) and 25 ml of absolute acetone, there was added 10 ml of absolute acetone containing 0.63 g (14 mmoles) of $NH(CH_3)_2$. The course of the reaction was followed chromatographically on Silufol (CHCl₃). The reaction mixture was evaporated to dryness, and the residue was recrystallized twice from ethanol. Yield 1.05 g (75%), m.p. 90-91°C. Found: C 72.2, H 6.45, N 21.0%. C₁₂H₁₃N₃. Calculated: C 72.3, H 6.58, N 21.1%.

5-Phenylpyrimidyl-2-trimethylammonium Chloride (VI). To a solution of 1.9 g (10 mmoles) of (IIb) in 25 ml of absolute acetone, was added, with cooling, 20 ml of absolute acetone containing 1.77 g (30 mmoles) of N(CH₃)₃. The reaction mixture was allowed to stand for 7 h at \sim 20°C. The precipitate was filtered off, washed with acetone, and vacuum-dried. Yield 2.28 g (92%). Found: C 62.4, H 6.52, N 16.7%. C₁₃H₁₇ClN₃. Calculated: C 62.5, H 6.46, N 16.8%.

2-Cyano-5-phenylpyrimidine (IIg). A mixture of 1.5 g (6 mmoles) of (VI), 0.78 g (12 mmoles) of KCN, and 25 ml of H₂O was stirred at 70°C for 1 h. The mixture was then cooled to \sim 20°C, and the precipitate was filtered off, washed with water, vacuum-dried, and crystal-lized from ethanol. Yield 0.69 g (63%), m.p. 129-130°C. Found: C 72.8, H 3.81, N 23.2%. C₁₁H₇N₃. Calculated: C 72.9, H 3.89, N 23.2%.

2-Carbethoxy-5-phenylpyrimidine (IIf). To a suspension of 1 g (5 mmoles) of 5-phenylpyrimidyl-2-carboxylic acid in 15 ml of absolute benzene, there was added 1.2 ml of SOCl₂ and 2 drops of DMFA. The mixture was refluxed 1.5 h while stirring. After cooling, the solvent and excess SOCl₂ were driven off under vacuum. To the dry residue of the acid chloride, 30 ml of absolute methanol was added, and the mixture was refluxed for 2 h. The reaction mixture was evaporated to dryness, and the residue was treated with a 5% NaHCO₃ solution. The precipitate was filtered off, washed with water, and crystallized from ethanol. Yield 0.82 g (72%), m.p. 123-125°C. Found: C 68.3, H 5.27, N 12.2%. C₁₃H₁₂N₂O₂. Calculated: C 68.4, H 5.30, N 12.3%.

2-Phenyl-4-hydroxy-5-methoxypyrimidine (VII). To 0.92 g (0.04 g-at) of Na in 12 ml of absolute toluene, a mixture of 4.16 g (40 mmoles) of the methyl ester of methoxyacetic acid and 2.96 g (40 mmoles) of ethyl formate was added dropwise while stirring. The mixture was stirred at \sim 20°C until the Na dissolved completely. The toluene was decanted off, and the yellow, viscous Na derivative was dissolved in 10 ml of absolute ethanol. In a separate operation, 0.92 g (0.04 g-at) of Na was dissolved in 30 ml of absolute ethanol, and 6.26 g (40 mmoles) of benzamidine hydrochloride was added. This mixture was poured into the alcoholic solution of the Na derivative and refluxed for 5 h while stirring. The reaction mixture was evaporated to dryness, and the residue was dissolved in 40 ml of H₂O, filtered, and neutralized with acetic acid. The resulting precipitate was filtered off and crystallized from methyl Cellosolve. Yield 2.59 g (32%), m.p. 215-217°C. Found: C 65.4, H 5.01, N 14.0%. C₁₁H₁₀N₂O₂. Calculated: C 65.3, H 4.98, N 13.9%.

2-Phenyl-4-chloro-5-methoxypyrimidine (VIII). To 30 ml of SOCl₂, 3 ml of DMFA was added dropwise. Over a period of 15 min, 2.02 g (10 mmoles) of (VII) was added in portions. The reaction mixture was refluxed for 2 h, the excess SOCl₂ was distilled off, and the residue was poured over ice (\sim 100 g). The resulting solution was extracted with ether; the extract was washed with NaHCO₃ solution and with H₂O and then dried over calcined MgSO₄. The ether was driven off, and the residue was sublimed under vacuum. Yield 1.72 g (82%), m.p. 157-158°C. Found: C 59.8, H 4.00, N 12.8%. C₁₁H₉ClN₂O. Calculated: C 59.9, H 4.11, N 12.7%.

<u>2-Phenyl-5-methoxypyrimidine (Ic)</u>. A mixture of 0.3 g (1.3 mmoles) of (VIII), 3 g (46 mmoles) of activated zinc dust, 5 ml of ethanol, and 5 ml of H_2O was refluxed while stirring. The course of the reaction was followed chromatographically on Silufol (CHCl₃). Then the hot reaction mixture was filtered, and the filter cake was washed with hot ethanol. The

ethanol was distilled off from the filtrate, and the remaining solution was extracted with benzene. The benzene extract was passed through a column with Al_2O_3 (activity II) and then evaporated to dryness; the residue was crystallized from methyl Cellosolve. Yield 0.11 g (46%), m.p. 58-59°C. Found: C 71.0, H 5.28, N 15.1%. C₁₁H₁₀N₂O. Calculated: C 70.9, H 5.41, N 15.0%.

2-Phenyl-5-carbethoxypyrimidine (If). Obtained, analogous to (Ic), from 2-phenyl-4chloro-5-carbethoxypyrimidine. Yield 20%, m.p. 94-96°C (ethanol). Found: C 68.4, H 5.13, N 12.4%. C13H12N2O2. Calculated: C 68.4, H 5.30, N 12.3%.

2-Phenyl-5-cyanopyrimidine (Ig). Obtained, analogous to (Ic), from 2-phenyl-4-chloro-5-cyanopyrimidine. Yield 27%, m.p. 187-188°C (ethanol). Found: C 72.8, H 3.79, N 23.1%. C₁₁H₇N₃. Calculated: C 72.9, H 3.89, N 23.2%.

CONCLUSIONS

1. ¹³C chemical shifts have been measured for substituted phenylpyrimidines in acetone.

2. The σ and σ_R° constants have been determined for 5-substituted 2-pyrimidyl groups and 2-substituted 5-pyrimidal groups.

3. Relationships have been found for estimation of the σ -constants for any 5-substituted 2-pyrimidyl group or 2-substituted 5-pyrimidyl group.

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