and the precipitate was removed by filtration and washed with water to give 1.3 g (94%) of a product that was identical to the compound obtained in experiment A.

LITERATURE CITED

1. Yu. V. Koshchienko, G. M. Suvorova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 111 (1977).
2. G. V. Kovalev, S. M. Gofman, S. V. Ivanovskaya, M. V. Pan'shina, V. I. Petrov, A. M. Simonov, and I. N. Tyurenkov, Farmakol. Toksikol., 36, 232 (1973).
3. Yu. K. Fomin, Author's Abstract of Master's Dissertation, Kazan (1975).
4. A. M. Simonov, V. A. Anisimova, and T. A. Borisova, Khim. Geterotsikl. Soedin., No. 1, 111 (1973).
5. Yu. M. Yutilov, V. A. Anisimova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 3, 416 (1965).
6. F. Krohnke and E. Borner, Ber., 69, 2012 (1936).
7. V. A. Anisimova, N. I. Avdyunina, A. M. Simonov, G. V. Kovalev, and S. M. Gofman, Khim. Geterotsokl. Soedin., No. 12, 1660 (1976).
8. A. M. Simonov, V. A. Anisimova, and L. E. Grushina, Khim. Geterotsikl. Soedin., No. 6, 838 (1970).
9. V. A. Anisimova, N. I. Avdyunina, A. M. Simonov, G. V. Kovalev, and S. M. Gofman, Khim. Geterotsikl. Soedin., No. 1, 126 (1976).

NMR SPECTRA OF PYRIMIDINES.

EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFT OF THE PARA PROTONS IN 2- AND 5-SUBSTITUTED PYRIMIDINES

O. P. Shkurko and V. P. Mamaev

UDC 543.422.25:547.853:541.67

The chemical shifts of the protons of the pyrimidine ring in the 2 position for a series of 5-substituted pyrimidines and in the 5 position for a series of 2-substituted pyrimidines in solutions in dimethyl sulfoxide were determined. The correlation equations that link the relative chemical shifts with the F and R substituent constants were calculated. The correlation equations were analyzed by comparison with the corresponding correlation equation for a series of monosubstituted benzenes. The reasons for the change in the conductivity of the electronic effects of the substituents via inductive and conjugation mechanisms in the pyrimidine ring as compared with the conductivity in the benzene ring are discussed.

Gronowitz and co-workers [1] in a study of the PMR spectra of 2- and 5-substituted pyrimidines pointed out the nonequivalence of the effect of substituents on the chemical shifts of the protons in the para positions relative to the substituent. However, the insufficiently extensive set of investigated compounds and the small differences in the chemical shifts have made it impossible to draw an unambiguous conclusion regarding the nature of this effect.

Continuing our research on the transmission of the effects of substituents in the pyrimidine ring [2, 3] we determined the chemical shifts of the protons of the pyrimidine ring in the 2 position (δ_{2-H}) for 5-substituted pyrimidines and in the 5 position (δ_{5-H}) for 2-substituted pyrimidines (Table 1). The relative chemical shifts presented in [1] for acetone solutions were found to be close to the values that we found for solutions of the same compounds in dimethyl sulfoxide (DMSO). A qualitative comparison of the values presented in both columns of Table 1 confirms the conclusion [1] regarding the different effects of substituents in each of the series presented. This difference is displayed most distinctly for strong electron-donor or strong electron-acceptor substituents. For example, the presence

---

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 526-529, April, 1978. Original article submitted April 12, 1977.

0009-3122/78/1404-0432$07.50

TABLE 1. Chemical Shifts of the Para Protons of 2- and 5-Substituted Pyrimidines in Dimethyl Sulfoxide Solutions

Substituent	2-Substituted		5-Substituted	
	$\delta_{5\text{-H}}$, Hz	$\Delta\delta_{6\text{-H}}$, Hz *	$\delta_{2\text{-H}}$, Hz	$\Delta\delta_{2\text{-H}}$, Hz *
$N(CH_3)_2$	392,5	59	509	43
OCH_3	427	24,5	529	23
CH_3	438	13,5	538,5	13,5
C_6H_5	445,5	6 (8†)	550,5	1,5 (3,5†)
H	451,5	0	552	0
F	453	−1,5	546	6
Cl	454	−2,5	549,5	2,5
Br	456,5	−5	551	1
$COOCH_3$	463	−11,5	—	—
CN	471,5	−20	567	−15
SO_2CH_3	471,5	−20	573	−21
NO_2	—	—	572,5	−20,5

*Positive values correspond to a shift of the resonance signal to strong field.

†With allowance for a correction for the magnetic anisotropy of the phenyl group calculated for the para proton in diphenyl [4].

in the pyrimidine ring of a dimethylamino group, which has a considerable +M effect, leads to stronger shielding of the 5-H proton of pyrimidine as compared with the 2-H proton. The presence of halogen atoms or a cyano group, which display a considerable −I effect, leads to stronger deshielding of the 5-H proton. However, as in the case of the methoxy group, these two effects substantially compensate one another for this substituent. In cases such as this the specific characteristics of the electronic effect of a substituent may be ascertained only under the condition of separation of the overall electronic effect into two components — the inductive and conjugation components.

It is known that in the benzene series the chemical shift of the para protons is determined primarily by the magnitude of the diamagnetic shielding of the resonating proton, which correlates satisfactorily with the electronic effects of substituents [5-8]. The existence of a relationship between the chemical shifts of the protons and the individual charges in the molecules has also been shown [9] for a number of six-membered nitrogen-containing heteroaromatic systems under the condition that a correction is made for the chemical shifts with allowance for the effects of the magnetic anisotropy of the ring, the diamagnetic and paramagnetic anisotropy of the heteroatoms, and the electrical field created by the p orbitals of the nitrogen atoms. Assuming that the contribution of the indicated components remains virtually constant for each of the series under consideration [10], one may suppose that the relative chemical shift of the para protons in the pyrimidine series also is determined by the electronic effects of the substituents.

To determine the contributions of the inductive and conjugation components to the overall electronic effect exerted by a substituent on the diamagnetic shielding of the para protons in 2- and 5-substituted pyrimidines we made a two-parameter correlation of the relative chemical shifts $\Delta\delta_{5\text{-H}}$ and $\Delta\delta_{2\text{-H}}$ (Table 1) with the modified [11] Swain–Lupton F and R substituent constants [12]. The experimentally found relative chemical shifts of the protons without correction for the effects of the magnetic anisotropy of the substituents were used for the correlation, just as in the case of substituted benzenes [8]. We disregarded the effect of the magnetic anisotropy of the pyrimidine ring associated with the circulation of the induced "ring current," since the "ring currents" of pyrimidine and benzene are very close [13, 14]. Considerable deviation of the point for the fluoro derivative was revealed during correlation of the chemical shifts for the series of 2-substituted pyrimidines. The reasons for this are not clear, and the corresponding value was disregarded in the correlation. The following correlation dependences were found:

$$\Delta\delta_{5\text{-H}} = 4.1 - 28.7F - 58.1R;\quad R = 0.988,\quad s = 4.2\ \text{Hz} \tag{1}$$

$$\Delta\delta_{2\text{-H}} = 3.1 - 23.2F - 46.6R;\quad R = 0.993,\quad s = 2.5\ \text{Hz} \tag{2}$$

The presence in Eqs. (1) and (2) of free terms that exceed the experimental error and have positive values may attest to the manifestation of unaccounted for contributions of the magnetic anisotropy of the heteroaromatic ring and the substituents.

It has been shown [12] that the Swain–Lupton correlation equation can successfully describe diverse chemical or physical characteristics (P) of aromatic systems if these characteristics change linearly as the free energy of the system changes; in this case the overall constant of a substituent that reflects its electronic effect on the "reaction center," is expressed in the form of a linear combination of inductive (F) and conjugation (R) constants of the substituent:

$$\sigma = fF + rR.$$

It is obvious that the ratio of the corresponding effects $\lambda = r/f$ is of substantial significance for the correlation:

$$\Delta P = \rho f(F + \lambda R).$$

Since the ρ value remains constant for reaction series of the same type in the case of standardization of the conditions, the f parameter in the latter equation can be replaced by parameter φ, which is proportional to it:

$$\Delta P = \varphi(F + \lambda R).$$

If we select one of the series as a standard, i.e., $\Delta P_0 = \varphi_0(F + \lambda_0 R)$, for correlation series of the same type the changes in the conductivity of the inductive and conjugation effects relative to the standard series can be expressed in terms of transmission factors γ_I and γ_R, respectively:

$$\Delta P = \varphi_0(\gamma_I F + \gamma_R \lambda_0 R),$$

where $\gamma_I = \varphi/\varphi_0 = f/f_0$, and $\gamma_R = \varphi\lambda/\varphi_0\lambda_0 = r/r_0$.

In order to discuss the parameters of the correlation equations that we obtained it seems expedient to select as a standard a series that examines the dependence of the relative chemical shift of the para proton in monosubstituted benzenes on the electronic nature of the substituent. Consequently, the correlation equations for series of the same type in the benzene and pyrimidine series can be represented as follows:

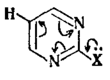
$$\Delta\delta_{n\text{-H}} = 0.7 - 32.3(F + 1.63R), \qquad (3)^*$$

$$\Delta\delta_{5\text{-H}} = 4.1 - 32.3(0.9F + 1.8R), \qquad (4)$$

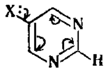
$$\Delta\delta_{2\text{-H}} = 3.1 - 32.3(0.7F + 1.4R) \qquad (5)$$

Comparison of the coefficients of F and R in correlation equations (3)-(5) makes it possible to estimate the strengthening or weakening of the conductivity of the electronic effects of substituents in the pyrimidine ring as compared with the benzene ring. This approach enables one to draw some conclusions regarding the specific character of the effect of substituents on the "reaction center" in the pyrimidine ring.

Despite the identical ratios of the inductive and conjugation components ($\lambda = 2$) in both pyrimidine series, the effects of substituents from the 2 and 5 positions of the ring on the chemical shift of the para proton prove to be nonequivalent; whereas transmission of the conjugation component from the 2 position of the pyrimidine ring increases 10% as compared with the para position of the benzene ring, transmission from the 5 position of the pyrimidine ring is weakened by 12%. This is due to the difference in the properties of the π-electron systems of benzene and pyrimidine and to the unsymmetrical character of the 2 and 5 positions of the latter. Because of the higher electronegativity of the nitrogen atoms as compared with the carbon atoms, the polarization of the π electrons in the pyrimidine ring under the influence of substituent X is facilitated in a direction towards the nitrogen atoms (structure A) and is hindered in the reverse direction (structure B). A similar pattern of nonequivalence of the transmission of the electronic effects of substituents via a mechanism involving conjugation through the C═N bond is also observed in the case of substituted benzylideneanilines [16].



A



B

---

*For solutions in dimethylacetamide. However, the identical character of the chemical shifs of the aromatic protons of monosubstituted benzenes in dimethylacetamide and dimethyl sulfoxide solutions is pointed out in [15].

A comparison of Eqs. (3)-(5) indicates the close magnitudes of the contributions of the F components for substituted benzenes and 2-substituted pyrimidines. From the point of view of the concept of the primarily field nature of the inductive effect, this fact is in agreement with the results of structural analysis [17], which indicates approximately equal distances between the 2 and 5 positions in the pyrimidine ring and the para positions in the benzene ring. However, the contribution of the F component turns out to be appreciably lower in the case of 5-substituted pyrimidines. The reason for this may consist in the creation by the p orbitals of the nitrogen atoms of an electrical field that is most appreciable in the position of the pyrimidine ring adjacent to the heteroatoms; this leads to a decrease in the "field" component of the inductive effect of the substituent.

EXPERIMENTAL

The PMR spectra of the compounds in dimethyl sulfoxide (DMSO) (4 mole % solutions) were recorded with a Varian A 60/56 A spectrometer at 60 MHz and 37-38°C with the ^{13}C—H satellite of DMSO (221 Hz from the signal of tetramethylsilane) as the internal standard. The chemical shifts were determined with an accuracy of ±0.5 Hz. The DMSO was dried over molecular sieves. The sample of commercial pyrimidine (Chemapol. Czechoslovakian Socialist Republic) was distilled prior to recording of the spectra. 5-Fluoropyrimidine was obtained by the method in [18], and 2-methylsulfonylpyrimidine was obtained by the method in [19]. The physical constants and methods for the preparation of 2-methoxycarbonylpyrimidine were presented in [20], whereas those of the remaining pyrimidine derivatives were presented in [21].

LITERATURE CITED

1. S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson, and R. Hoffman, Ark. Kemi, 22, 65 (1964).
2. O. P. Shkurko and V. P. Mamaev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2173 (1971).
3. V. P. Mamaev and O. A. Zagulyaeva, Zh. Org. Khim., 8, 583 (1972).
4. C. W. Haigh and R. B. Mallion, Org. Magn. Reson., 4, 203 (1972).
5. H. Spiesecke and W. G. Schneider, J. Chem. Phys., 35, 731 (1961).
6. P. Diehl, Helv. Chim. Acta, 44, 829 (1961).
7. K. Hayamizu and O. Yamamoto, J. Mol. Spectrosc., 29, 183 (1969).
8. O. P. Shkurko, Zh. Org. Khim., 13, 918 (1977).
9. P. J. Black, R. D. Brown, and M. L. Heffernan, Austral. J. Chem., 20, 1305 (1967).
10. T. B. Cobb and J. D. Memory, J. Chem. Phys., 50, 4262 (1969).
11. C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. Lien, J. Med. Chem., 16, 1207 (1973).
12. C. G. Swain and E. C. Lupton, J. Am. Chem. Soc., 90, 4328 (1968).
13. G. G. Hall, A. Hardisson, and L. M. Jackman, Disc. Faraday Soc., 34, 15 (1962).
14. B. Bock, M. Kuhr, and H. Musso, Chem. Ber., 109, 1184 (1976).
15. Y. Yukawa, Y. Tsuno, and N. Shimizu, Bull. Chem. Soc. Jpn., 44, 2843 (1971).
16. N. Inamoto, S. Masuda, K. Tokumaru, K. Tori, and M. Yoshida, Tetrahedron Lett., 43, 3701 (1975).
17. P. J. Wheatley, Acta Crystallogr., 13, 80 (1960).
18. C. Reichardt and K. Halbritter, Ann., No. 3, 470 (1975).
19. D. J. Brown and P. W. Ford, J. Chem. Soc., C, No. 7, 568 (1967).
20. V. P. Mamaev and É. A. Gracheva, Khim. Geterotsikl. Soedin., No. 6, 1086 (1969).
21. V. A. Koptyug (editor), Atlas of the Spectra of Aromatic and Heterocyclic Compounds [in Russian], Nauka, Novosibirsk (1975), No. 8.