TAUTOMERISM OF AZINE DERIVATIVES.

III.* TAUTOMERISM OF SUBSTITUTED 4-PYRIMIDINYLMETHANES

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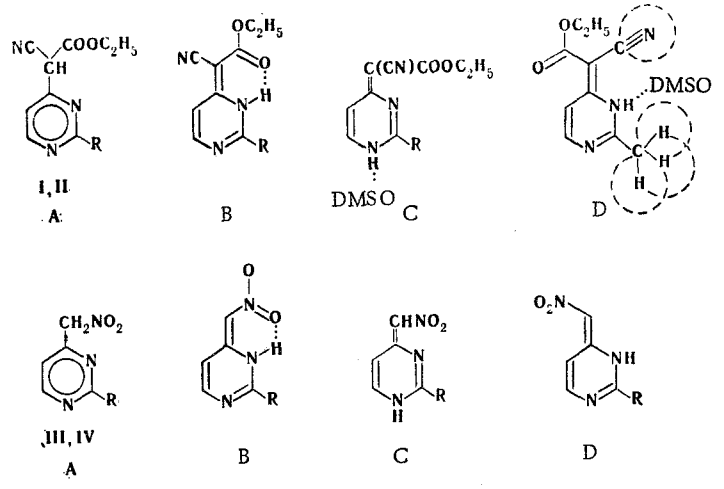
The tautomeric properties of 4-pyrimidinylmethanes were studied in the case of 2-CH_3- and 2-CF_3-4-pyrimidinylcyanoacetic esters, 2-CH_3-4-pyrimidinylnitromethane, and 4-pyrimidinylnitromethane. It was shown by ^1H and ^{13}C NMR spectroscopy that an equilibrium with the participation of three tautomeric forms — pyrimidine form A and pyrimidinylidene forms B and C with "o- and p-quinoid" orientations of the double bonds in the heteroring — may be realized in aprotic dipolar solvents (dimethyl sulfoxide).

During a study of the tautomeric forms of substituted 4-pyrimidinylmethanes I and II we were the first to obtain and separate (in the solid state) tautomeric forms with "o- and p-quinoid" orientations of the double bonds in the heteroring (IB and IIB and IC and IIC, respectively); irreversible C → B isomerization occurs when IC and IIC are melted or dissolved in "neutral" solvents ($CHCl_3$) [1]. The aim of the present research was to ascertain the conditions under which the equilibrium existence (tautomerism) of forms of the B and C type is possible.



I R=CH_3; II R=CF_3; III R=CH_3; IV R=H

We assumed that the development of tautomeric form C, which is not formed in solvents of the $CHCl_3$ type [1], would be promoted by aprotic dipolar solvents [for example, dimethyl sulfoxide (DMSO)]. The latter may stabilize the B form by cleaving the intramolecular hydrogen bond and may stabilize tautomer C by the formation of a strong intermolecular hydrogen bond.† Although migration of a proton between the two heteroatoms is usually a "fast" (on the PMR scale) process [3], the presence of a strong intramolecular hydrogen bond in tautomer B may lead to a "slow" B ⇄ C equilibrium, and this would make it possible to use the PMR method for the direct observation of the individual tautomers.

*See [1, 2] for communications I and II.

†Stabilization by an intermolecular hydrogen bond is sterically hindered for the D form, and its formation is therefore less likely.

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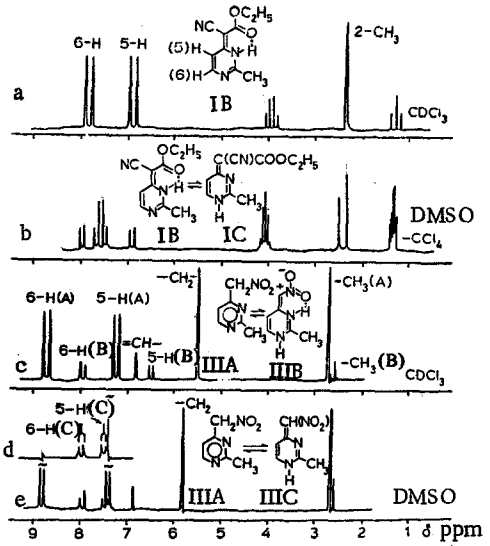

Fig. 1

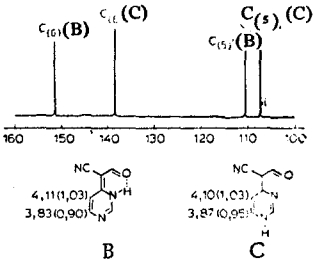

Fig. 2

Fig. 1. PMR spectra of I and III [double resonance (d) makes it possible to expose the doublet of the 5-H proton of form C].

Fig. 2. ^{13}C NMR signals of the $C_{(5)}$ and $C_{(6)}$ atoms of tautomeric forms IB and IC and ($\sigma + \pi$) values and π-electron densities (in parentheses) calculated by the CNDO/2 [5] and PPP [6] methods, respectively.

Compounds I and II exist in tautomeric form B in solution in CCl_4 ($CHCl_3$) (see Fig. 1a) [1]. When dimethyl sulfoxide (DMSO) is added to a solution of I in CCl_4, new signals, the intensity of which increases as the fraction of DMSO is increased and decreases when CCl_4 is added, appear in the PMR spectra (Fig. 1b). The appearance of new signals cannot be ascribed to tautomeric form A (because of the absence of the signal of a methylidyne proton) or to the corresponding anion (comparison with the UV spectrum of the sodium salt of I shows that I is not ionized even in pure DMSO). The substantial change in the position of the signals of the ring protons and of the protons of the methyl group is associated, in our opinion, with rearrangement of the π-electron system of the heteroring and indicates that the tautomer formed in the presence of DMSO has structure C, since changes would be small for structure D.

A more reliable confirmation of the formation of tautomeric form C can be obtained by using the ^{13}C NMR spectra, which not only directly reflect the structure of the heterocyclic framework but also can be interpreted within the framework of the dependence of the magnitude of the chemical shift on the electron density calculated by quantum chemical methods [4]. In the ^{13}C NMR spectrum recorded for I in deuterochloroform the signals of the $C_{(5)}$ and $C_{(6)}$ atoms of tautomeric form B (only this isomer is realized in $CHCl_3$) are located at 110 and 151.6 ppm, respectively. This assignment follows unambiguously from a comparison of the $^{13}C-\{H\}$ double resonance spectra with total suppression of the spin–spin couplings and the double-resonance spectra with extraresonance irradiation of the protons. The doublet splitting in the latter case constitutes evidence that the above-indicated signals belong to the $C_{(5)}H$ and $C_{(6)}H$ fragments, whereas the magnitude of the residual splitting which is lower for the signal at 110 ppm, indicate that it is affiliated with the $C_{(5)}$ atom (the radiofrequency field was set up at a frequency closer to the resonance frequency of the 5-H proton). The position of the above-noted signals is also in agreement with the electron density calculated for a model of tautomer B by the CNDO/2 (complete neglect of differential overlap) [5] and PPP (Pariser–Parr–Pople) [6, 7] methods (see Fig. 2). According to the results of these calculations, the cleavage of the intramolecular hydrogen bond and the conversion to tautomeric form D are not associated with apprecialbe redistribution of the electron density on the carbon atoms (except for the C atom of the carbonyl group).* The conversion to

*Our calculated data are in agreement with the experimental data of Niwa and co-workers [8], who established that cleavage of a strong intramolecular hydrogen bond in six-membered chelates is accompanied by a 4-5 ppm shift of the signal of the C atom of the carbonyl group in the ^{13}C NMR spectra to strong field. The signals of the more remote C atoms are shifted to an even smaller extent.

tautomeric form C, on the other hand, is accompanied by considerable redistribution of the electron density, especially for the $C_{(6)}$ atom. In conformity with the calculated data, the transition from tautomeric form B to form C (in contrast to form D) should lead to a substantial shift of the signal of the $C_{(6)}$ atom to strong field. In fact, in addition to the signals of tautomeric form B, signals of the $C_{(5)}$ and $C_{(6)}$ atoms of tautomeric form C appear in the ^{13}C NMR spectrum of I recorded under conditions of total suppression of the spin–spin coupling of the ^{13}C and ^{1}H nuclei when DMSO is added (Fig. 2); the considerable change in the chemical shifts of the signals of the $C_{(5)}$ and $C_{(6)}$ atoms of tautomeric form C as compared with the corresponding signals of tautomer B is due to rearrangement in the heterocyclic portion of the molecule on passing from B to C. As we assumed, the signal of the $C_{(6)}$ atom undergoes the greatest shift (~14 ppm), and the direction of the shift (to strong field) corresponds to the calculated change in the electron density. Thus the ^{13}C and ^{1}H NMR spectra provide evidence that IB $\rightleftarrows$ IC equilibrium of the pyrimidinylidene tautomers with "o- and p-quinoid" orientations, respectively, of the ring double bonds is realized in CCl_4–DMSO.

According to the PMR spectroscopic data, tautomeric form B is realized for 4-pyrimidinylcyanoacetic ester II in CCl_4. This compound also undergoes reversible conversion to "p-quinoid" form IIC; however, because of the high acidity, the rate of exchange between forms IIB and IIC in this case becomes appreciable as compared with IB and IC. In DMSO–CCl_4 (1:20) the signals of the 5-H and 6-H protons are broadened markedly, and the equilibrium is shifted to favor IIC when the fraction of DMSO is increased (1:10), and the distance between the signals decreases to $\approx$0.2 ppm. A further increase in the percentage of DMSO leads to the appearance in the equilibrium mixture of appreciable amounts of the anion of II (according to the UV spectroscopic data), and II is completely ionized in pure DMSO [1]. The signals of the 5-H and 6-H protons (in the spectrum of a solution in DMSO) appear in the form of a singlet at 7.85 ppm (an AB system with identical chemical shifts), and the signal of the $(CH_3)_2\overset{+}{S}$–OH proton, the position of which depends markedly on the amount of H_2O present in the DMSO, appears at 6.5 ppm. It should be noted that in the case of I and II the transition form the B form to the C form is accompanied by a decrease in the difference in the chemical shifts ($\Delta\delta$H [5, 6]) between the signals of the 5-H and 6-H protons and by conversion of the corresponding AX spin system (the "o-quinoid" form B) to an AB system (the "p-quinoid" form C). This peculiarity is evidently quite general and can be used for the elucidation of the structures of pyrimidinylidene tautomers.

It may be assumed that aprotic dipolar structures would promote the formation of the "p-quinoid" tautomer also in the case of other tautomeric 4-pyrimidinylmethane derivatives that differ with respect to the form of substituents attached to the tautomerized CH fragment. To shed some light on this problem we investigated the tautomeric properties of 4-pyrimidinylnitromethanes III and IV. The tautomerism of 4-pyrimidinylnitromethane has been noted by Feuer and Lawrence [9], who assigned "p-quinoid" structure IVC to the pyrimidinylidene tautomer without, however, presenting specific evidence in favor of this conclusion. This compelled us to investigate the tautomerism of 4-pyrimidinylnitromethanes in greater detail, especially since data on cyanoacetic esters I and II make it possible to expect a considerable dependence of the character of the equilibrium on the solvent for III and IV.

In analogy with I and II we expected that the pyrimidinylidene tautomer would have "o-quinoid" structure IIIB in neutral solvents of the $CHCl_3$ type. In fact, in the PMR spectrum of III in $CHCl_3$ (Fig. 1c) the position of the signals of the 5-H and 6-H ring protons (here and subsequently we have in mind the ring protons of the pyrimidinylidene form) differs by 1.4 ppm, which is close to the value observed for "o-quinoid" tautomer IB ($\Delta\delta H^{5,6}$ = 1.2 ppm). In view of the low concentration ($\approx$1% solution with a ~0.1% concentration of tautomer B) we used pulse Fourier PMR spectroscopy (300-500 scannings were required to obtain the qualitative spectrum). Changes similar to those noted for I and II — the signals of the 5-H and 6-H protons approach one another by a value of 1 ppm (from 1.4 to 0.4 ppm) — occur in the PMR spectrum of III (Fig. 1, spectra d and e) on passing to DMSO, which should facilitate the formation of the "p-quinoid" tautomer. This constitutes evidence for the virtually complete shift of the pyrimidinylidene equilibrium B $\rightleftarrows$ C to favor "p-quinoid" tautomer IIIC. Unsubstituted 4-pyrimidinylmethane IV displays similar properties, and, as for III, form A and "o-quinoid" tautomer IVB are realized for it in $CHCl_3$. The position of the 5-H and 6-H signals of tautomer IVB coincides, within the limits of 0.1 ppm, with the position for IIIB, at the same time that $\Delta\delta H^{5,6}$ retains its earlier value (1.4 ppm). These signals approach one another on passing from $CHCl_3$ to DMSO; however, the $\Delta\delta H^{5,6}$ value in this case is 0.8 ppm,

which is twice the value expected for the "p-quinoid" tautomer (0.4 ppm in the spectrum of III). This difference indicates that "o-quinoid" tautomer IVD, the percentage of which with respect to the sum of pyrimidinylidene tautomers can be estimated

$$\%\,\mathrm{IVD} = \frac{\Delta\delta H^{5,6}(\text{obs.}) - \Delta\delta H^{5,6}(\mathrm{IIIC})}{\Delta\delta H^{5,6}(\mathrm{IVB}) - \Delta\delta H^{5,6}(\mathrm{IIIC})} \cdot 100\% = \frac{(0.8-0.4)\cdot 100\%}{1.4-0.4} = 40\%.$$

by using IIIC as a model, is also present in a solution of IV in DMSO in equilibrium (rapid on the PMR time scale) with the "p-quinoid" tautomer.*

Thus in the case of the 4-pyrimidinylmethanes that we investigated, in addition to pyrimidine form A and pyrimidinylidene form B, previously noted in [2], "p-quinoid" tautomer C is realized on passing from solutions in CCl_4 ($CHCl_3$) to solutions in DMSO. The tautomeric equilibrium between the forms depends markedly on the solvent, and in the case of 4-pyrimidinylnitromethanes has a more complex form than that presented by Feuer and Lawrence [9].

EXPERIMENTAL

The UV spectra of the compounds were recorded with a Specord UV-vis spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer. The ^{13}C NMR spectra of 15-20% solutions of I, 5% solutions of I and II, and of saturated solutions of 4-pyrimidinylnitromethanes III and IV in $CDCl_3$ were recorded under pulse conditions with subsequent Fourier transformation with a Bruker WP-80 spectrometer and tetramethylsilane as the internal standard; the pickup temperature was 40°C. A program provided by I. I. Zakharov was used in the quantum-chemical calculations, which were performed in the Computer Center of the Siberian Branch of the Academy of Sciences of the USSR with a BÉSM-6 computer. The geometry of the molecules was selected in conformity with [10]. 4-Pyrimidinylcyanoacetic esters I and II were previously described in [1], while 4-pyrimidinylnitromethane IV was obtained by the method in [9].

2-Methyl-4-pyrimidinylnitromethane (III). A mixture of 0.58 g (0.024 mole) of sodium hydride and 1.47 g (0.024 mole) of nitromethane in 15 ml of dry DMSO was stirred in an argon atmosphere at 50-60°C for 30 min, after which 1.03 g (0.008 mole) of 2-methyl-4-chloropyrimidine was added, and the mixture was heated at 80-100°C for 2 h. The cooled reaction mixture was then poured into 100 ml of water, 100 ml of CH_2Cl_2 was added, and the mixture was acidified with vigorous stirring with 2 ml of acetic acid. The organic layer was separated, and the aqueous layer was treated twice with 20 ml of CH_2Cl_2. The extracts were combined, washed four times with 15 ml of water, and dried, and the solvent was removed to give 1.1 g (90%) of crude product. Three recrystallization from a small amount of alcohol gave III with mp 116-118°C. Found: C 47.4; H 4.62; N 27.3%. Calculated: C 47.1; H 4.61; N 27.4%.

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*The justification for the use of the $\Delta\delta H^{5,6}$ (IIIC) value instead of the $\Delta\delta H^{5,6}$ (IVC) value follows from the fact that the 2-CH_3 group has a slight effect on the position of the 5-H and 6-H signals and, judging from the PMR data for IIIB and IVB, does not change the $\Delta\delta H^{5,6}$ value.