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THE PROTON MAGNETIC RESONANCE SPECTRA AND THE STRUCTURE OF 4,6-DIHYDROXY PYRIMIDINE AND ITS DERIVATIVES

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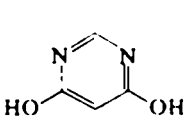
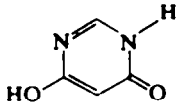
Abstract—PMR spectra of 4,6-dihydroxypirimidine and its 2- and 5-substituted derivatives have been compared with the spectra of their O- and N-methyl derivatives of fixed structures, corresponding to possible tautomeric forms. It was found that in dimethyl sulphoxide medium the compounds exist predominantly in the oxo-hydroxy form. In aqueous solutions of 4,6-dihydroxypyrimidine and its N-methyl derivatives the bipolar-ionic form with delocalized charges probably predominates.

URACIL (2,6-dihydroxypyrimidine) is known to be a cyclic diamide[1] but the structure of its isomer, 4,6-dihydroxypyrimidine, is not certain. The results obtained by UV spectroscopy on aqueous soln of 4,6-dihydroxypyrimidine[2] differ from ours obtained by the same method.[3] In order to decide between possible tautomeric forms I–VII* 4,6-dihydroxypyrimidine and a series of its derivatives were investigated by PMR spectroscopy.

The PMR spectra of tautomeric forms were compared with non-tautomeric O- and N-methylates derivatives.



I



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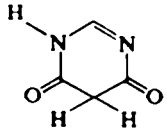

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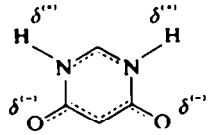

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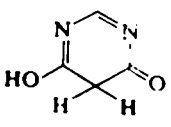
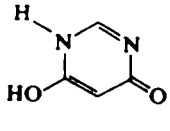
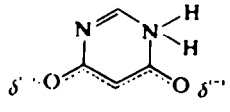


V



VI



VII

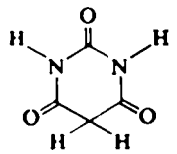
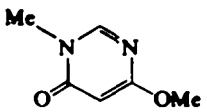
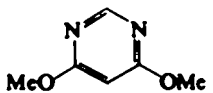
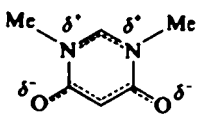
* In structures IV and VII the C_5 and C_6 have also some partial charges δ^+ and δ^- respectively. Nevertheless, most of these charges are localized at the hetero atoms as these structural formulae show.

[1] A. R. Katritzky, *Adv. Heterocycl. Chem.* **1**, 371 (1963).

[2] D. J. Brown and T. Teitei, *Austral. J. Chem.* **17**, 567 (1964).

[3] G. M. Kheifets, N. V. Khromov-Borisov and A. I. Koltsov, *Doklady. Akad. Nauk. USSR* **166**, 635 (1966).

TABLE 1. CHEMICAL SHIFTS OF PROTONS IN THE 4,6-DIHYDROXYPYRIMIDINE DERIVATIVES WITH FIXED STRUCTURES AND IN BARBITURIC ACID

No.	Formula of compd	Model structure	Solvent	Chemical shifts						Method of synthesis Ref.
				N_1H (Me)	C_5—H	N_3—H (Me)	C_4—OCH_3	C_5—H (Me)	C_6—OCH_3	
1[a]		III, V	DMSO	−1·00	—	−1·00	—	6·53	—	
2		II	DMSO D_2O	6·72 6·74	1·62 1·76	— —	6·27 6·33	4·40 4·42	— —	2
3		II	DMSO D_2O	6·74 6·74	1·72 1·98	— —	6·27 6·31	*b* 8·40	— —	6
4		I	DMSO D_2O	— —	1·63 1·90	— —	6·20 6·30	3·85 4·03	6·20 6·30	7
5[c]		IV	D_2O	6·65	0·95	6·65	—	4·90	—	3

[a] Poorly soluble in water. In DMSO the line 6·25 is observed belonging to water contained in the dehydrate of barbituric acid.
[b] Masked by the signal of the solvent.
[c] Poorly soluble in DMSO.

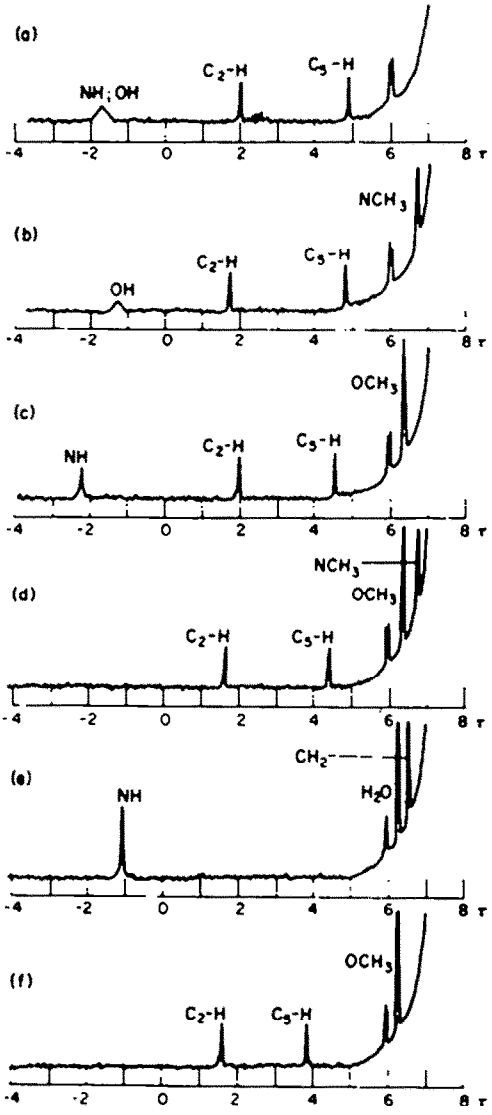


FIG. 1. PMR spectra of the solutions of 4,6-dihydroxypyrimidine and its N- and O-methyl derivatives in DMSO: (a) 4,6-dihydroxypyrimidine; (b) 1-methyl-4-hydroxypyrimidine-6-on; (c) 4-methoxy-6-hydroxypyrimidine; (d) 1-methyl-4-methoxypyrimidine-6-on; (e) barbituric acid; (f) 4,6-dimethoxypyrimidine. The line 5·95 belongs to the DMSO molecules containing C^{13}.

RESULTS AND DISCUSSION

Non-tautomeric O- *and* N-*methylated derivatives of* 4,6-*dihydroxypyrimidine*

Table 1 contains the τ values of O- and N-methylated derivatives with fixed structures and those of the barbituric acid (Figs. 1 and 3), these compounds being the models for the possible tautomeric forms of 4,6-dihydroxypyrimidine. In this paper Roman numerals designate the possible structures of the substances while the substances themselves are designated by arabic numerals.

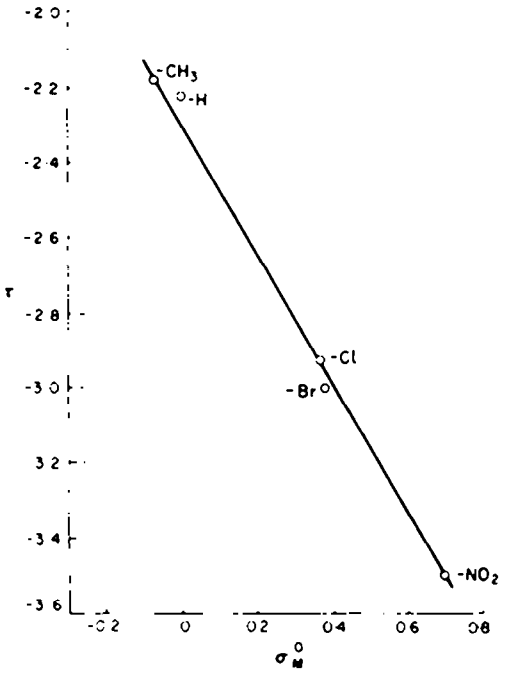


FIG. 2. The dependence of the chemical shifts of the NH group on the Taft constants (σ_M^0) in 5-R-4-methoxy-6-hydroxypyrimidines.

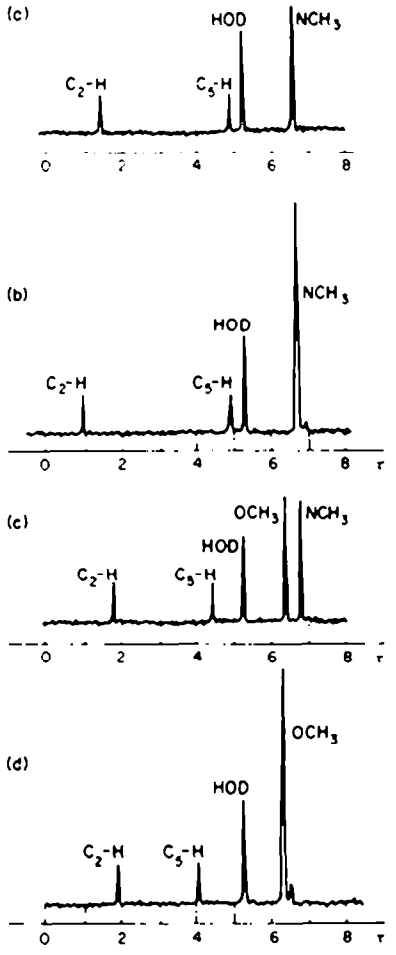


FIG. 3. PMR spectra of freshly prepared solutions in D_2O: (a) 1-methyl-4-hydroxypyrimidine-6-one, (b) anhydro-1,3-dimethyl-4-hydroxy-6-oxopyrimidinium hydroxide; (c) 1-methyl-4-methoxypyrimidine-6-one; (d) 4,6-dimethoxypyrimidine.

The trioxo form of barbituric acid in crystals and aqueous solns was established earlier.[4] The presence of the 6·53 line in the PMR spectrum of methylenic group (No. 1, Table 1) and the absence of the lines corresponding to the protons bonded with unsaturated carbon atoms show clearly that the substance has the same structure in DMSO soln. Barbituric acid can be considered, therefore, as a model for the structures containing a methylene group of C_5 atom (III and V). On addition of D_2O to the soln of barbituric acid in DMSO the line of two protons at C_5 disppears immediately. This phenomenon is due to the exchange of deuterium. This tendency to exchange is a well-known property of β-dicarbonyl compounds. The structure III of the 4,6-dixydroxypyrimidine and its derivatives must possess the same property.

[4] A. R. Katritzky, *Adv. Heterocycl. Chem.* **1**, 375 (1963).

The compounds with fixed structures VI and VII were not obtained. A compound having a tentative structure of 1,4-dihydro-6-methoxy-1-methyl-4-oxopyrimidine (type VI) has been described[2] but this structure was later disproved.[5]

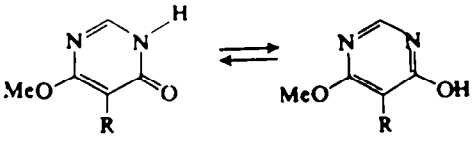
Structure VII is less probable than the bipolar structure IV having lower energy due to the delocalization of the positive charge that leads to symmetry of the molecule.

Table 1 shows that the chemical shifts C_5—H are different in substances serving as models for various tautomeric forms. The protons C_2—H of the form IV in anhydro-1,3-dimethyl-4-hydroxy-6-oxo-pyrimidinium hydroxide (No. 5) absorb at much lower frequency than structures I and II and thus it is possible to determine the substances with potential tautomerism.

By using D_2O instead of DMSO, no marked variation in the chemical shifts of the methyl groups was observed. The position of the C_2—H line in D_2O soln is shifted approximately by 0·2 ppm towards higher fields.

5-Substituted derivatves of the 4-methoxy-6-hydroxypyrimidine

These compounds may have tautomeric forms I and II. (The method of synthesis excludes form VI[6,8] and the absence of methylene protons line (Table 2) eliminates structure V.)



The chemical shift C_5—H in 4-methoxy-6-hydroxypyrimidine (Table 2, No. 6) both in DMSO and in water resembles that in fixed structure II (Table 1, Figs. 1c, 1d and 3c). At the same time this shift is greater (by 0·7 ppm in DMSO) than that

TABLE 2. CHEMICAL SHIFTS IN THE PROTONS OF 5-R-4-METHOXY-6-HYDROXYPYRIMIDINES IN DMSO

No.	R[a]	Chemical shifts			
		NH	C_5—H	O—Me	C_5—H(Me)
6	H[b]	−2·22	2·00	6·35	4·56
		(−)[c]	(2·07)	(6·35)	(4·46)
7	Me	−2·18	2·13	6·34	—[d]
8	Cl	−2·92	1·88	6·20	—
9	Br	−3·00	1·75	6·15	—
10	NO_2	−3·50	1·55	6·05	—

[a] All the substances are obtained by the method described.[6]

[b] The chemical shifts in D_2O are shown in parentheses.

[c] Deuterium is substituted for proton.

[d] Masked by the solvent signal.

[5] G. M. Kheifets, N. V. Khromov-Borisov and A. I. Koltsov *Zn Organ Khim.* **2**, 1516 (1966).

[6] G. M. Kheifets and N. V. Khromov-Borisov, *Zh. Organ Khim.* **2**, 1511 (1966).

[7] N. Okuda, I. Kuniyoshi, Japan Pat. 21,090 (Oct. 10, 1963), Appl. Dec. 24, 1960; *Chem. Abstr.* **60**, 2977 g (1964).

[8] G. M. Kheifets and N. V. Khromov-Borisov, *Zh. Obshch. Khim.* **34**, 3134 (1964).

in the model of dihydroxy form I (No. 4). These facts support structure II both in DMSO and D_2O. We draw the same conclusion from UV[6,8] and IR[9] spectra.

The chemical shift of NH decreases from −2·20 to −3·50 ppm and the band width increases from 3 to 20 c/s as the electronegativity of the substituent in the position 5 increases. Linear dependence observed between the τ values of the NH protons and the Taft constant (σ_M^0)[10] for the *meta*-position in respect to the substituent shows that all the compounds listed in the Table 2 have a type II structure (Fig. 2).

The addition of H_2O in concentrations 1–10% (τ H_2O 6·0–6·5 ppm) does not alter the position and the width of the NH-signals. It shows a relatively slow proton exchange between NH and H_2O.[11] 5-Nitro-4-methoxy-6-hydroxypyrididine (No. 10) is an exception, the exchange occurring here at such rate that the common signal of NH and H_2O is observed.

The exchange rate increases strongly at the addition to the solution of 5-R-4-methoxy-6-hydroxypyrimidine in DMSO of weak acids instead of water; we studied such weak acids as *p*-nitrophenol (τ OH = −1·00 ppm) and N-methylated derivatives of 4,6-dihydroxypyrimidine and 5-methyl-4,6-dihydroxypyrimidine (No. 11 and 12 in Table 3) with pK_a 5·75 and 6·2 respectively.[6] In these cases the common line of exchanging protons is observed. This result is important for the interpretation of the PMR spectra of 4,6-dihydroxypyrimidines described below.

TABLE 3. THE CHEMICAL SHIFTS OF N-METHYLATED DERIVATIVES OF 5-R-4,6-DIHYDROXYPYRIMIDINES IN DMSO

No.	R	Chemical shifts				Method of synthesis
		N_1-Me	C_2-H	OH	C_5—H(Me)	
11	H	6·70	1·76	−1·30	4·75	13
12	Me	6·73	1·84	−1·00	—[a]	6

[a] Masked by the signal of the solvent.

We did not observe any spin–spin splitting between the protons of the neighbouring NH and CH groups neither in the 5-R-4-methoxy-6-oxypyrimidines nor in other substances studied here, in contrast to thymine and 5-bromuracil in DMSO,[12] Fig. 1.

The chemical shift C_2H in No. 6 and 7 in DMSO and D_2O is considerably higher (over 0·4 ppm) than in their N-methylated analogues (No. 2 and 3).

As both kinds of derivatives have the same structure II, this effect can be only caused by the presence of the NCH_3 group.

*The mono-*N*-methylated derivatives of* 4,6*-dihydroxypyrimidine in* DMSO

N-methylated derivatives of 4,6-dihydroxypyrimidine (No. 11, Table 3) and 5-methyl-4,6-dihydroxypyrimidine (No. 12) are compounds with a partly fixed structure. They can exist in the same tautomeric forms as the 4,6-dihydroxypyrimidine except

[9] Ju. M. Bojarchuk, M. V. Volkenstein, G. M. Kheifets and N. V. Khromov-Borisov, *Khim Geterotskil. Soedin. Akad. Nauk Latv. SSR*, in press.

[10] R. W. Taft, *J. Phys. Chem.* **65**, 1 (1961).

[11] J. Pople, V. Shneider and G. Bernstein, *High resolution PMR spectra*, Russ. transl. I. L. Moskowt, 1962.

[12] J. P. Kokko, J. H. Goldstein and L. Mandell, *J. Amer. Chem. Soc.* **83**, 2909 (1961).

[13] G. M. Kheifets and N. V. Khromov-Borisov, *Zh. Organ. Khim.* **1**, 6, 1173 (1965).

forms I and V. It is convenient to consider their structure in DMSO and D_2O solns separately as their spectra in these solutions are different.

Table 3 contains the data of the PMR spectra of these substances.

They are represented by structure II on the basis of the following observations.

The intensity of the line C_5—H is the same as of the line C_2—H, i.e. the intensity corresponds to one proton. The position of the line is typical for the protons in olefins (Fig. 1b). This means that the derivatives No. 11 and 12 do not contain form III in appreciable amount. We have to consider the possibilities of the oxo-hydroxy form II (or VI) and of the bipolar form IV (or VII). In these structures the PMR signals at low fields (−1·00 and −1·30 ppm) can be attributed to the group OH or to the group NH with partial positive charge. The latter possibility seems to be improbable as the NH protons absorb at considerably lower fields (- ·2·20 and - 2·30 ppm, see Table 2) and the positive charge can shift the signals towards still lower fields.

The investigation of the PMR signals of stable protons gives more definite arguments in favour of the oxo-hydroxy form. The τ values of C_2—H and N—CH_3 of both substances (Table 3) are very near to those of the substances with fixed structure II (No. 2 and 3) and are higher than the τ value for the substance with the structure IV (No. 5). (For C_2—H the difference is equal to 0·8 ppm). The same arguments enable us to prefer form II to form VI through the model of the latter structure does not exist. The UV spectral data are also in favour of structure II for the N-methylated 4,6-dihydroxypyrimidine.[3]

The C_5—H group in No. 11 absorbs at higher fields than in the substances with fixed structure II (No. 2), see Fig. 1c and 1d. Perhaps it can be explained by the strong polarization of the OH bond in DMSO medium.

The position of the PMR signals of the OH groups in contrast to the NH groups in the O-methylated derivatives depends on the water content in DMSO. It is determined by rapid proton exchange between OH and H_2O shown by the common PMR line at high fields in comparison with the OH bond in dry DMSO.

2- *and* 5- *derivatives of the* 4,6-*dihydroxypyrimidine in* DMSO

All tautomeric forms are possible for these compounds. The data of their PMR spectra are collected in Table 4. The spectrum of 4,6-dihydroxypyrimidine (No. 13) contains signals of equal intensity corresponding to the protons of C_2—H and C_5—H (Fig. 1a). The chemical shifts of these protons in all derivatives show that they are bonded with unsaturated C atoms. The spectra do not contain the line of methylenic groups or (in 5-derivatives) of the methine groups. Therefore, forms III and V are not present in considerable amounts.

The chemical shifts C_2—H of all 5-derivatives are near to those for the corresponding O-methyl derivatives (Table 2) having structure II, and are considerably different from the chemical shifts for the substances with different structures (I and IV) (Table 1). The C_5—H group of No. 13 absorbs in the same range of τ as in the N-methylated derivatives (No. 11, Table 3) whose existence in form II was established earlier. Thus the chemical shifts of the stable protons favour structure II of all 2- and 5-derivatives of 4,6-dihydroxypyrimidine in DMSO.

Spectra No. 13–21 contain the broad signal at lower fields whose intensity

TABLE 4. CHEMICAL SHIFTS OF 2- AND 5-DERIVATIVES OF 4,6-DIHYDROXYPYRIMIDINE IN DMSO

No.	Derivs of 4,6-dihydroxypyrimidine	Chemical shifts						Method of synthesis
		NH and OH[a]	C_2—H	C_5—H	Me	Aromatic protons		
13	Non-substituted	−1·60	1·90	4·85	—	···		14
14	5-methyl	−1·50	2·04	—	[b]	—		15
15	5-phenyl	1·80	1·90	· ·	·	2·56		16
16	5-chloro	2·30	1·88	—	—	· ·		17
17	5-bromo	−2·30	1·80	—	—	-		18
18	5-nitro	2·60	1·31	· ·	· ·	—		19
19	2-methyl	1·60	·	5·05	[b]	· ·		20
20	2-*p*-methoxy phenyl	1·70	· ·	4·80	6·30	1·94[c]	3·03[d]	—
21	2-phenyl	1·80	· ·	4·72	—	1·90[c]	2·50	21

[a] The common line of mobile protons

[b] Masked by the solvent signal

[c] The signals of lower fields belong to the protons in *ortho*-position pyrimidine ring.

[d] The spin–spin splitting constant of aromatic protons in 8·0 c/s.

corresponds to two protons. Its chemical shift and width decrease as the electronegativity of the substituent increases. The width of the signal in 5-methyl derivatives is equal to some tens of c/s while that in the 5-nitro derivative is 5 c/s only.

A comparison of the τ values of the NH group in O-methyl derivative No. 6 of the OH group is N-methyl derivative No. 13 and of the broad signal in the spectrum of 4,6-dihydroxypyrimidine shows that the latter is an approximate average of the two first values. The same is observed in 5-methyl-4,6-dihydroxypyrimidine (No. 14) and its O- and N-methyl derivatives (No. 7 and 12). The chemical shifts of the broad signals in No. 13 (−1·6 ppm) and No. 14 (−1·5 ppm) are near to the shifts of exchangeable protons of the group NH and OH possessing the common PMR signal in equimolecular mixtures of the corresponding O- and N-methylated analogues (−1·5 ppm) (see above). All these facts attribute the broad signals in the low field region to the exchangeable OH and NH protons of form II.

Forms IV and VII must have the line of protons NH at lower fields than in O-methylated derivatives as in this case the N atoms are charged positively.

We conclude that 4,6-dihydroxypyrimidine and its 2- and 5- derivatives exist in DMSO soln for the most part in the oxy-oxo form II independently of the nature of the substitute. The UV and IR spectra data support this conclusion.[8,9]

The presence of water in DMSO shifts the OH and NH signals towards higher fields as in the case of N-methyl derivatives. This effect is due to rapid exchange of mobile protons with H_2O.

[14] D. J. Brown, *J. Chem. Soc.* 2312 (1956).
[15] G. M. Kheifets and N. V. Khromov-Borisov, *Zh. Obshch. Khim.* **34**, 1321 (1964).
[16] R. Hull, *J. Chem. Soc.* 2214 (1951).
[17] G. M. Kheifets and N. V. Khromov-Borisov, *Zh. Obshch. Khim.* **34**, 3851 (1964).
[18] J. Chesterfield, J. F. W. McOmie and E. R. Sayen, *J. Chem. Soc.* 3478 (1955).
[19] J. W. Daly and B. E. Christensen, *J. Org. Chem.* **21**, 177 (1956).
[20] H. R. Henze, W. J. Clegg and C. Smart, *J. Org. Chem.* **17**, 1370 (1952).
[21] J. A. Hendry and R. F. Homer, *J. Chem. Soc.* 328 (1952).

We have already seen (Tables 1 and 2) that the N-methylation of the O-methyl derivatives No. 6 and 7 shifts the C_2—H signal towards lower fields. The same effect can be observed if we compare the spectra of 4,6-dihydroxypyrimidine and 5-methyl-4,6-dihydroxypyrimidine (No. 13 and 14) with the spectra of their N-methylated derivatives (No. 11 and 12). See Fig. 2.

On the PMR spectra of 2-phenyl-4,6-dihydroxypyrimidine (No. 21), the signals of aromatic protons which are in the *ortho*-position to C_2 of the pyrimidine ring shift considerably towards lower fields in comparison with those of *meta*- and *para*-protons, whereas in the 5-phenyl derivative (No. 15) all aromatic protons absorb in a narrow range of τ. Undoubtedly this difference is connected with lower electronic density at the second C atom of pyrimidine cycle.

4,6-dihydroxypyrimidine and its N-methyl derivatives in water

It was difficult to obtain satisfactory PMR spectra of 4,6-dihydroxypyrimidine and its 2- and 5- derivatives in water because of their low solubility. Therefore we chose the N-methyl derivative of 4,6-dihydroxypyrimidine and of 5-methyl-4,6-dihydroxypyrimidine for the study of tautomerism in D_2O since these substances have sufficient solubility. As mentioned earlier, these substances can possess all tautomeric forms, except structures I and V. The similarity of dissociation constants and UV spectra[3,6] suggest that the conclusions concerning the N-methyl derivatives are valid for 4,6-dihydroxypyrimidine itself.

The chemical shifts of these substances are shown in Table 5. In D_2O medium deuterium is substituted for mobile protons. Spectrum No. 11 (Table 5, Fig. 3a)

TABLE 5. CHEMICAL SHIFTS OF 4,6-DIHYDROXYPYRIMIDINE AND OF SOME OF ITS DERIVATIVES IN D_2O

No. of the substance	Compound	Chemical shifts			
		N—Me	C_2—H	C_5—H	C_5—Me
11	N-methyl derivative of 4,6-dihydroxypyrimidine	6·63	1·46	4·90	—
12	N-methyl derivative of 5-methyl-4,6-dihydroxy-pyrimidine	6·63	1·50	—	8·33
13	4,6-dihydroxypyrimidine	—	1·60	—*	—

* The compound could be dissolved only at elevated temperature. In these conditions the C_5—H proton was substituted for deuterium.

shows the absence of form III in considerable amount both in D_2O and DMSO. In the spectrum of the freshly prepared soln the line of the methylenic group is absent but two lines of equal intensity C_2—H and C_5—H are present absorbing in the region of chemical shifts of olefinic protons. It is an indication of structures II or IV. In time the intensity of C_5—H line decreases exponentially (twofold in 40 min) without any change in the intensities and positions of other lines. It means that the deuteration of C_5—H occurs without a change in the structure of the substances studied. The τ values of N—CH_3 and C_2—H of two other substances (No. 12 and 13) are near to those of No. 11. It suggests the similarity of the structures of all three substances in D_2O medium.

The chemical shifts of the groups N—CH_3 and C_5—H in No. 11 in D_2O are

practically equal to those of the substance No. 5 (Table 1) having structure IV (Fig. 3a, 3b). However, this fact cannot be considered as decisive for the choice of the structure, as these chemical shifts are near to those in DMSO medium where structure II was established.

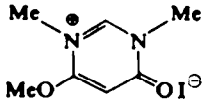
The τ values for C_2—H in substances No. 11, 12 and 13 are lower by 0·3–0·4 ppm than in DMSO (cf. Tables 3–5). Such a decrease (though a smaller one) is observed also for the groups N—CH_3. This decrease cannot be explained by the influence of the solvent, which has an opposite effect in model substances (Table 1). It is probably due to the difference in the structure of the substance in DMSO and D_2O. It is possible that a decrease of the chemical shift of C_2—H and N—CH_3 is determined by the positive charge at the N and C_2 atoms. Structure IV follows from this consideration. But the C_2—H group of No. 11 in D_2O absorbs at higher fields than in the model for structure IV (No. 5). Perhaps this discrepancy is connected with the existence of the second methyl group in No. 5. We have already mentioned that the N-methylation of the substances having structure II lowers the τ values of C_2—H by 0·2–0·4 ppm. It is difficult to explain this effect satisfactorily. Perhaps it is determined by the hydrogen bonds of the group NH, lacking in N-methylated derivatives.

The PMR spectra do not allow us to exclude the rapid establishment of the equilibrium of the structures II $\rightleftarrows$ IV. But the UV spectral data obtained by us[3,5,6] show the predominance of structure IV in aqueous solns regardless of their concentration.

The 4,6-dihydroxypyrimidine derivatives in D_2SO_4

The derivatives of 4,6-dihydroxypyrimidine in 5M D_2SO_4 (Table 6) are protonated and exist in the cationic state. It is shown by decreased τ values of all the

TABLE 6. THE DATA OF PMR SPECTRA OF 4,6-DIHYDROXYPYRIMIDINE AND ITS O- AND N-DERIVATIVES IN 5M D_2SO_4

No.	Compds protonated[a]	Chemical shifts					
		N_1	CH_3	C_2—H	N_3—CH_3	C_4—OCH_3	C_5—H
22	4,6-dihydroxypyrimidine	--		0·90	--	—	—
23	4-methoxy-6-hydroxypyrimidine	—		0·95		5·91	3·88
24	1-methyl-4-hydroxypyrimidine-6-on	6·30		0·90	—	--	—[b]
25	1-methyl-4-methoxypyrimidine-6-on	6·40		0·92		5·98	3·90
26	Anhydro-1,3-dimethyl-4-hydroxy-6-6-oxo-pyrimidinium hydroxide	6·33		0·73	6·33	—	—[b]
27	 1,3-dimethyl-4-methoxy-6-oxo-pyrimidinium methiodide[c]	6·39		0·52	6·26	5·95	3·95

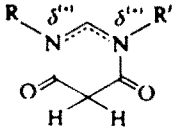
[a] We consider the cations as new substances (salts) hence new numbers.

[b] The absence of C_5—H lines can be explained by rapid exchange with deuterium.

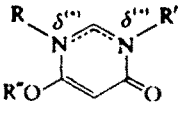
[c] Solutions in neutral D_2O.

protons as compared to neutral molecules. The chemical shifts are near to those in methiodide (No. 27) whose structure was established.[3]

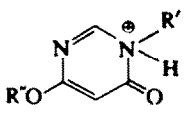
The protonation of the 4,6-dihydroxypyrimidine derivatives, whose structure was discussed above, can give the following reasonable structures for cations of type VIII–X.



VIII



IX



X

The chemical shifts of the groups N—CH_3, O—CH_3 and C_5—H in the cations of 1-methyl-4-methoxypyrimidine-6- on (No. 25) and of 4-methoxy-6-hydroxypyrimidine (No. 23) are practically equal to those in methiodide[3] (No. 27, Table 6). This fact suggests the preference of structure IX to the other possible structure X for No. 23 ($R = R' = H$, $R'' = Me$), and No. 25 ($R = H$, $R' = R'' = Me$). If it were otherwise, the localization of the positive charge at one of the nitrogen atoms, i.e. the change of electronic density distribution in the cycle, could change the chemical shifts in comparison with No. 27. The difference of the τ values for C_2—H in these substances is apparently connected with the presence of the second methyl group in No. 27.

The PMR spectrum of the cation of anhydro-1,3-dimethyl-4-hydroxy-6-oxo-oxopyrimidinium hydroxide (No. 26), whose possible structures are VIII ($R = R' = Me$) and IX ($R = R' = Me$, $R'' = H$) shows that the methyl groups in the cation remain equivalent. This fact suggests a symmetrical structure VIII ($R = R' = Me$). The practically instaneous deutero-exchange of C_5—H is also consistent with structure VIII (see Table 6). We cannot exclude structure IX, but the explanation of the methyl groups equivalence needs the assumption of the rapid proton exchange between the two oxygen atoms. The presence of structure IX in No. 26 is shown by the similarity of the UV spectrum and the spectrum of No. 25 whose structure is apparently IX ($R = H$, $R' = R'' = Me$).[3] However, this structure does not explain the rapid deuteration of C_5—H. Therefore we have to assume the presence of form VIII in sufficient amount.

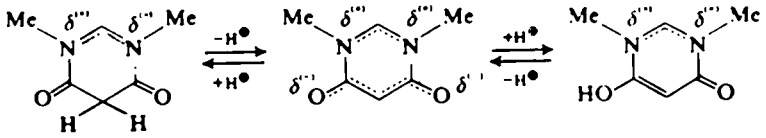
The chemical shifts of the group N—CH_3 in 1-methyl-4-hydroxypyrimidine-6- on (No. 24) in D_2SO_4 are close to those of No. 26. It is possible to suggest that the neutral forms in water and their cations have the same types of structure. This view is supported by the rapid proton exchange in C_5—H and by the close similarity of the UV spectra.[3] The same conclusion is valid for the structure of the cation of 4,6-dihydroxypyrimidine whose UV spectrum is practically the same as that of the cation of N-methylated derivative (No. 24).[3]

Thus the PMR data show that the proton is bonded with C_5. Taking into account the data of UV and PMR spectra it is possible to assume the existence of the equilibrium VIII $\rightleftarrows$ IX in acidic medium for No. 22, 24, 26.

Deuterium exchange at C_5 in some 4,6-dihydropyrimidine derivatives

The deuterium exchange of C_5—H was not observed in the substances having the fixed structure II (No. 2 and 6) either in D_2O or in concentrated D_2SO_4. There is only

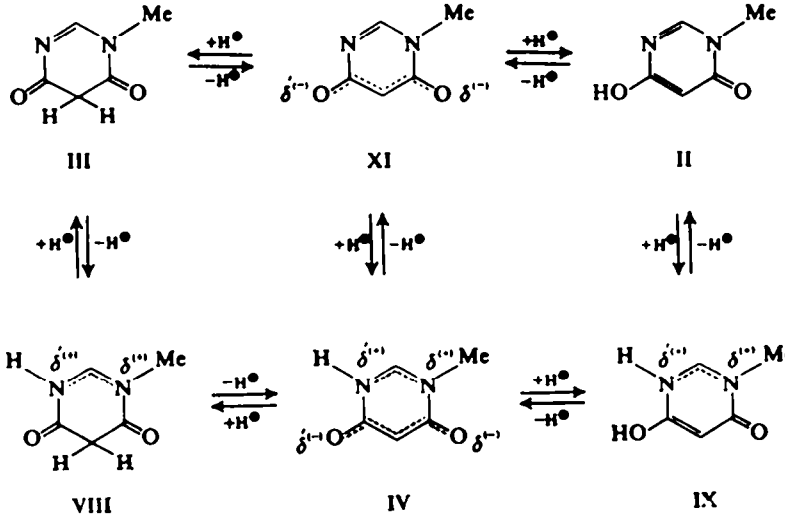
one way for deuteration of the anhydro-1,3-dimethyl-4-hydroxy-6-oxo-pyrimidinium hydroxide ((No. 5) structure IV), passing through cation VIII (see the schemes below)*



VIII IV IX

This compound does not exchange its protons considerably in neutral D_2O (pH $\simeq$ 7). But the deuteration occurs with pH decrease as the concentration of cation VIII increases. One half of C_5—H is deuterated in 35 min at pH 3·72 (acetate buffer) and the exchange is practically instantaneous in 5M D_2SO_4.

Again, we observe instantaneous exchange in the case of 1-methyl-4-hydroxy-pyrimidine-6-on (No. 11) in 5M D_2SO_4. As it has been said before, substance No. 11 is deuterated slowly in neutral D_2O (one half in 40 min at 20°). Being an acid (pK = 5·75) at the concentration 0·8N this substance produces pH = 2·93 as a result of autoprotolysis. In contrast to No. 5 the exchange with deuterium in this case can be explained by the equilibrium between the bipolar form IV and cationic form VIII, and by the equilibrium with dioxoform through the common anion XI. Therefore there are two ways of deuteration.



III XI II

VIII IV IX

The rate of deuteration increases with pH, at first the increase is insignificant ($t_{1/2}$ = 30 min at pH 4·86) and then becomes sharp (at pH 5·94 $t_{1/2}$ is immeasurably small).

These data show that the cationic mechanism of the exchange predominates in concentrated acid. At pH > 5 the anionic mechanism predominates and in the region

* To simplify designations, the deuterium symbol is not used in the schemes.

3–5 where the exchange is slow the effectivity of both mechanisms is of the same order. The existence of the anionic mechanism confirms the presence of the dioxo form III in small amounts.

SUMMARY

The high resolution PMR spectra of solutions of 22 derivatives of 4,6-dihydroxypyrimidine in DMSO, D_2O and D_2SO_4 were obtained and interpreted. It is shown that the hydroxy-oxo form II of the derivatives studied is predominant in the DMSO solutions. In D_2O the bipolar ionic form IV apparently predominates. In the concentrated acid these substances exist in the cationic form with a delocalized positive charge.

The deutero-exchange at measurable rates was observed in 4,6-dihydroxypyrimidine and in some of its derivatives. These facts suggest indirectly the existence of a small quantity of the dioxo form III in water. The possible exchange mechanisms are discussed.

EXPERIMENTAL

References concerning the methods of synthesis are given in Tables. The purity of the compds obtained by the methods described in the lit. was checked by paper chromatography using the following systems: MeOH, HCl, water (7:2:1) and n-BuOH, AcOH, water (4:1:5). Barbituric acid (dihydrate) was analytically pure. 2-*p*-Methoxyphenyl-4,6-dihydroxypyrimidine was obtained by a method similar to its *p*-ethoxy analogue[21] from *p*-methoxybenzamidine hydrochloride[22] and malonic ester; m.p. 289–291°. (Found: N, 12·9, 13·0. Calc. for $C_{11}H_{10}N_2O_3$: N, 12·9%.)

D_2O and DMSO were used as solvents and DMSO was dried ($MgSO_4$) and distilled at 5 mm Hg and 50°. All work with DMSO was performed in an atm. of dry Ar. The spectrum of D_2O showed a weak line due to contamination by HOD. The acetate buffer solns had a concn of 1M and pH 3·75, 4·86 and 5·94. They were prepared from CD_3COOD and NaOD in D_2O For the solns in strong acid D_2SO_4 was used. The concns of the solns investigated were 5–10% by wt.

The PMR spectra: room temp and at 40 Mc/s with a spectrometer JNM-3 (τ-scale). In D_2O solns, water in a capillary was used as standard (5·25 τ). The error of the chemical shift determination was $\pm$0·05 ppm. The changes of the chemical shifts determined by the concn in the 5–10% range are within the limits of experimental error. The interpretation of spectra is shown in Tables and Figs. The spin–spin splitting was only observed in the lines of aromatic protons in substances containing phenyl groups.

[21] J. Tafel and C. Enoch, *Ber. Dtsch. Chem. Ges.* **23**, 107 (1890).