HETERO ANALOGS OF ALLOXAZINES.

2.* STRUCTURE AND TAUTOMERISM OF 6,8-DIMETHYL-7,9-DIOXO-5H-6,7,8,9-TETRAHYDROPYRIMIDO[4,5-b][4',5'-e][1,4]THIAZINES

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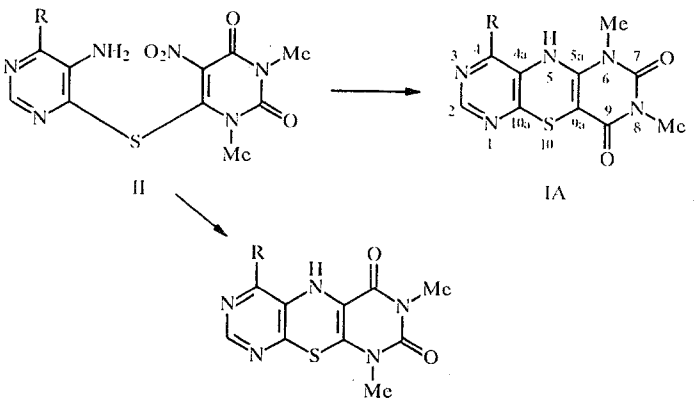
It is demonstrated by ^{13}C NMR spectroscopy that the dipyrimidothiazines that are formed in the reaction of 1,3-dimethyl-5-nitro-6-chlorouracil with 4-R-5-amino-6-mercaptopyrimidines are dipyrimido[4,5-b][4',5'-e][1,4]thiazines. The tautomeric transformations of these compounds were studied.

We have previously reported [2] that the reactions of 5-amino-6-mercaptopyrimidines with 1,3-dimethyl-5-nitro-6-chlorouracil lead to derivatives of a new heterocyclic system, viz., the dipyrimido[4,5-b][4',5'-e][1,4]thiazine (I) system.

The proposed method for the synthesis of I suggests the formation of dipyrimidyl sulfides II in the first step with their subsequent S → N Smiles rearrangement, which also leads to dipyrimido[4,5-b][4',5'-e][1,4]thiazine derivatives IA. A similar sequence of the occurrence of the reactions was also adopted in the case of obtaining 5-thiaisoalloxazines [3]. At the same time, one cannot exclude the cyclization of II without a Smiles rearrangement to give derivatives with an isomeric structure, viz., dipyrimido[4,5-b][5',4'-e][1,4]thiazine derivatives IB [4].



II IA IB

Ia,b

Ia R = OMe, b R = NMe_2

As a rule, chemical methods of proof, which in our case cannot be deemed to be sufficient, were used in [5-7], which were devoted to the synthesis of benzo analogs of structures A and B to confirm their structure.

*For communication 1, see [1].

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TABLE 1. Data from the ^{13}C NMR Spectra of Ia, b and III* in DMSO-d_6

Compound	δ, (ppm) J (Hz)	$C_{(2)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(5a)}$ (I) or $C_{(6)}$ (III)	$C_{(7)}$ (I) or $C_{(2)}$ (III)	$C_{(9)}$ (I) or $C_{(4)}$ (III)	$C_{(9a)}$ (I) or $C_{(5)}$ (III)	$C_{(10a)}$	NCH_3	R
Ia[2*]	δ	152,6	156,4	119,3	146,2	151,1	157,7	78,9	152,8	30,0; 30,6	54,6
Ib	δ	152,5 d	154,8 m	116,9 br s	143,7 q	150,4 m	158,1 q	79,5 s	155,9 d	28,2; 30,7 q	39,6 q
	J	$^1J_{CH}$ = 203,0	ΣJ^{3*} ~28,0	$^4J_{C_{4a},C_2H}$ ~1,0	$^3J_{C_{5a},NCH_3}$ = = 3,0	$^3J_{C_7,NCH_3}$ ~2,6	$^3J_{C_9,NCH_3}$ = = 2,6	—	$^3J_{C_{10a},C_2H}$ = = 12,0	$^1J_{CH_3}$ = = 141,0; 142,0	$^1J_{CH_3}$ = 141,0
Ib[4*]	δ	144,8 d	155,7 m	121,6 s	142,3[4*] br signal	149,8[4*] br m	161,8[4*]br signal	37,1 d	140,3[4*]br d	29,0; 30,9 q	41,6 q
	J	$^1J_{CH}$ = 215,0	ΣJ^{3*} ~28,0	—	$^3J_{C_{5a},NCH_3}$ = = 2,6	$^3J_{C_7,NCH_3}$ = 2,6	$^3J_{C_9,NCH_3}$ = = 2,5	$^1J_{C_{9a},H}$ = 149,6	$^3J_{C_{10a},C_2H}$ = = 8,6	$^1J_{CH_3}$ = = 143,0; 144,0	$^1J_{CH_3}$ = 147,3
III	δ	—	—	—	155,1 br q	151,8 m	161,8 q	75,1m	—	27,3; 29,5	—
	J	—	—	—	$^3J_{C_6,NCH_3}$ = = 2,3	$^3J_{C_2,NCH_3}$ = 2,8	$^3J_{C_4,NCH_3}$ = = 2,5	$^1J_{C_5,H}$ = 169,0; $^3J_{C_5,NH_2}$ = 4,2	—	$^1J_{CH_3}$ = = 140,0; 141,5	—

*δ is the ^{13}C chemical shift, and J is the ^{13}CH spin–spin coupling heteroconstant.

2*The $J_{^{13}CH}$ SSCC were not determined for Ia because of its limited solubility.

3*For the $C_{(4)}$ atom of Ib, $\Sigma J = {}^3J_{C_4,C_2H} + {}^3J_{C_4,R}$.

4*For Ib the medium $CDCl_3$ + CF_3COOH corresponds to an approximately equimolar ratio of the concentrations of the acid and Ib. The signals of the $C_{(5a)}$, $C_{(7)}$, $C_{(9)}$, and $C_{(10a)}$ atoms noted by 4* are broadened due to spin–spin coupling with $C_{(9a)}H$ (J ~ 1-2 Hz); the SSCC for these carbon atoms were determined by a selective-decoupling experiment [the signal of the proton attached to $C_{(9a)}$ was irradiated].

TABLE 2. ^1H Chemical Shifts (δ, ppm) and Ratios of the Tautomeric Forms of Ia and Ib in Various Media at 23°C

Compound	Form	R	NCH_3	C_2H	N_5H	$C_{(9a)}H$	Amt. of the form, %	Solvent
Ia	A	4,02	3,31; 3,49	8,12	5,76	—	100	$CDCl_3$
	A	3,96	3,11; 3,37	8,17	8,06	—	100	DMSO-d_6
	A+D	2,83	3,32; 3,52	8,18	5,54	—	66	$CDCl_3$
	C	3,26	3,37; 3,51	8,19	—	4,63	34	
	A+D	2,82	3,27; 3,48	8,14	5,56	—	74	CD_2Cl_2
	C	3,24	3,34; 3,50	8,12	—	4,70	26	
Ib	A+D	2,99	3,13; 3,40	7,97	8,09	—	100	DMSO-d_6
	A+D	2,84	3,32; 3,52	8,19	*	—	56	$CDCl_3$ +
	C	3,27	3,33; 3,53	8,21	—	4,63	44	+ CH_3COOH [2*]
	E	3,50	3,37; 3,54	8,29	—	4,93	100	$CDCl_3$ +
								+ CF_3COOH [3*]
	E	3,53	3,42; 3,59	8,27	—	4,98	70	$CDCl_3$ +
	E [5*]	3,40	3,41; 3,60	8,11	—	—	30	+ CF_3COOH [4*]

*The NH group participates in exchange with the COOH group (the overall signal at ~10 ppm).

[2*]The medium $CDCl_3$ + CH_3COOH corresponds to a concentration ratio of 0.1 mole of the acid per mole of Ib.

[3*]The medium $CDCl_3$ + CF_3COOH corresponds to a concentration ratio of 1.0-1.5 moles of the acid per mole of Ib.

[4*]The medium $CDCl_3$ + CF_3COOH corresponds to a concentration ratio of ~20 moles of the acid per mole of Ib.

[5*]The product of acylation of the E ion.

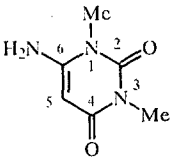
TABLE 3. Mass Spectra of Ia and Ib*

Compound	m/z (I_{rel}, %)
Ia	294 (16), 293 (100), 292 (15), 278 (10), 237 (12), 236 (17), 207 (17), 195 (32), 180 (17), 167 (14), 128 (10), 122 (12), 119 (13), 93 (10), 70 (10), 69 (13), 57 (15), 54 (14), 53 (15), 41 (17)
Ib	307 (18), 306 (100), 305 (13), 291 (18), 277 (37), 220 (4), 206 (7), 193 (3), 192 (11), 191 (7), 179 (6), 178 (5), 167 (14), 165 (7), 152 (5), 126 (5), 82 (11), 67 (5)

*The mass numbers of the ions with $I_{rel} > 3\%$ are presented.

To solve the problem of the structure of dipyrimidothiazines I it became necessary to draw upon physical methods of investigation. The most informative method proved to be ^{13}C NMR spectroscopy.

In the analysis of the spectra of Ia, b, the synthesis of which was described in [2] (with DMSO-d_6 as the solvent), we carried out the assignment of all of the signals, including those corresponding to quaternary carbon atoms. It was based chiefly on the character of their long-range spin–spin coupling with the protons (Table 1). Thus the signals at ~153-156 ppm were assigned to the $C_{(10a)}$ atoms, while the signals at ~117-119 ppm were assigned to the $C_{(4a)}$ atoms: Recording of the spectra of Ib under conditions without proton suppression and the use of the method of selective proton decoupling showed that the signal of the $C_{(10a)}$ carbon has the form of a doublet with $^3J_{C(10a),C2H}$ = 12.0 Hz, while the $C_{(4a)}$ carbon is represented by a broad singlet with $^3J_{C(4a),C2H}$ = 1.0 Hz. Of the two remaining signals of quaternary carbon atoms, one, observed at ~79 ppm, was a singlet under the indicated recording conditions, while the other (δ 144-146 ppm) is the quartet that is typical for coupling of a carbon atom with the protons of an o-oriented methyl group. It was possible to make the assignment of the indicated signals to the $C_{(9a)}$ and $C_{(5a)}$ atoms by comparison of the spectra of the investigated compounds with the ^{13}C NMR spectrum of 1,3-dimethyl-6-aminouracil (III), in which the $C_{(5)}$ atom is structurally similar to the $C_{(9a)}$ atom in form A.



III

Data from the ^{13}C NMR spectra of model compound III are presented in Table 1. Since the chemical shift of the $C_{(5)}$ atom in III (75.1 ppm) is close to the chemical shift of the singlet signal at ~79 ppm of Ia, b, it is natural to assign the latter signal to the $C_{(9a)}$ atom of structure A. The singlet character of the $C_{(9a)}$ signal in the spectrum of Ib and the quaternary character of the signal at 144-146 ppm, corresponding to the 5*a* carbon atom, which couples with the closely located N—CH_3 group [$^3J_{C(5a),NCH3}$ = 3.0 Hz], are understandable in the case of this assignment. Thus the data from the ^{13}C NMR spectra unequivocally indicate that dipyrimidothiazines Ia, b have structure A.

It is interesting that the signals of the $C_{(9a)}$ carbon atoms in Ia, b are shifted substantially to strong field as compared with the signals of the remaining aromatic carbon atoms in the molecules. Since a similar situation is also observed for the $C_{(5)}$ atom in III, one should assume that this strong-field shift is due to the presence of sufficiently high electron density on the $C_{(9a)}$ (Ia, b) and $C_{(5)}$ (III) atoms. This, in turn, should facilitate the occurrence of electrophilic substitution reactions at the given carbon atoms. In the case of dipyrimidothiazines Ia, b this is responsible for a number of their chemical properties, including, in particular, the tautomerism of the investigated compounds and the ease of oxidation in the $C_{(9a)}$ position. The tautomerism of the investigated dipyrimidothiazines was studied by means of NMR spectroscopy and mass spectrometry. One set of narrow signals* that is in complete agreement with enamino ketone structure A of this compound previously proposed on the basis of IR spectral data [2]† is present in the ^1H NMR spectrum of Ia recorded at 23°C in both $CDCl_3$ and DMSO-d_6. The signals at 5.76 ppm (in $CDCl_3$) and 8.06 ppm (in DMSO-d_6, Table 2) were assigned to the signals corresponding to $N_{(5)}H$ in the ^1H NMR spectra.

In contrast to the spectrum of Ia, the ^1H NMR spectrum of dipyrimidothiazine Ib in $CDCl_3$ contains a double set of all of the signals. An increase or decrease in the temperature gives rise, respectively, to their broadening or narrowing. This indicates the participation of the two forms observed in the spectra in exchange processes. The predominant form is characterized by a strong-field location of the signal of the dimethylamino group (2.83 ppm) and by the presence of a broad signal at 5.54 ppm (a labile proton of the NH or OH type). In the minor form the signal of the $N(CH_3)_2$ group is located at appreciably weaker field (3.26 ppm), and, in addition, a rather narrow singlet at 4.63 ppm (with an intensity of one proton unit) is present in the spectrum. The addition of a small amount of CD_3OD to the investigated solution immediately leads to virtually complete disappearance of the signal at 5.54 ppm and to a decrease in the intensity of the singlet at 4.63 ppm (by ~70% of the initial value); this constitutes evidence for a different, although rather high, rate of exchange of these protons. The addition of one to two drops of acetic acid to a solution of Ib in $CDCl_3$ gives rise to a substantial weak-field shift of the NH signal at 5.54 ppm, while the singlet at 4.63 ppm retains its location.

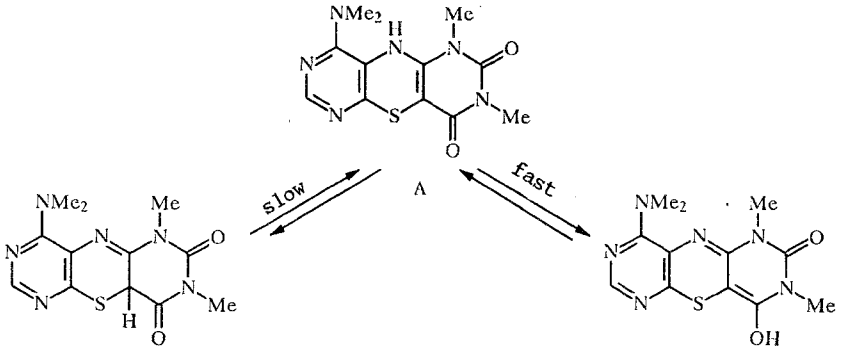
The ratio of the intensities of the signals and, consequently, the ratio of the concentrations of the observed forms depend on the solvent (see Table 2). In pure DMSO-d_6 the predominant form becomes the only form, and the NH value in this form coincides with the chemical shift of the $N_{(5)}H$ group of Ia. All of this makes it possible to assume that the predominant form is enamino ketone form A. It follows from the above-described experiment with the addition of acid to the solution that a methylidyne proton (narrow signal at 4.63 ppm), which has sufficient lability, is present in the second (minor) form. This sort of proton can be present only in a molecule of the imino ketone tautomeric form of Ib — the $C_{(9a)}$ proton in form C.

The results make it possible to assume that enamine–imine tautomerism occurs for Ib. In addition to the indicated tautomeric forms A and C, one cannot exclude the participation in the tautomeric equilibrium of imino enol form D, in which the proton is located in the hydroxy group attached to the $C_{(9)}$ atom. It is natural that tautomeric forms A and D should undergo interconversion at a very high rate, and the spectrum that we previously assigned to enamino form A is therefore possibly, in fact, the averaged spectrum of forms A and D.

*A decrease in the temperature at which the sample was recorded ($CDCl_3$, $t < -20°C$) did not lead to broadening of the lines in the spectrum or a change in their form.

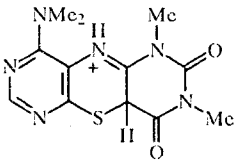
†IR spectra for Ia: ν_{NH} = 3435 cm^{-1} (crystals); ν_{NH} = 3448 cm^{-1} (0.5% solution in $CHCl_3$) [2].

Just as in the ^1H NMR spectrum, one set of signals is observed in the ^{13}C NMR spectrum of dipyrimidothiazine Ib in DMSO-d_6 (see Table 1). An examination of the multiplicity of the signals of the carbon atoms in the spectrum recorded without proton suppression confirms the idea of fast exchange between forms A and D. Thus spin–spin coupling of the N_5H proton with the $C_{(9a)}$ and $C_{(10a)}$ atoms should have occurred for structure A, whereas spin–spin coupling of the proton of the $C_{(9)}$—OH group with the $C_{(9a)}$ atom should have occurred in the case of structure D. However, in the analyzed spectra the $C_{(9a)}$ signal has the form of a narrow singlet, whereas the $C_{(10a)}$ signal has the form of a distinct doublet (spin–spin coupling with C_2H) (see Table 1), which indicates participation of the protons of the NH and OH groups in fast exchange.



It was of interest to examine the protonation process for dipyrimidothiazine Ib. When we added a small amount of acetic acid (~0.1 mole per mole of Ib) to a solution of Ib in $CDCl_3$, in the ^1H NMR spectrum we observed the same pattern as in the case of pure $CDCl_3$ (see Table 2) [with the exception of the above-noted shift of the N_5H signal (δ 5.54 ppm)] due to exchange of the protons of this group with the proton of the COOH fragment. Thus protonation of Ib does not occur under these conditions.

A different situation occurs when CF_3COOH is added to a solution of Ib in $CDCl_3$. One set of signals is present in the spectrum in the case of an equimolar ratio of the acid and the substance, and all of the signals are shifted to weak field to a greater or lesser extent (see Table 2). The retention in the spectrum of the signal of a methylidyne proton [δ $C_{(9a)}H$ 4.93 ppm] makes it possible to assume that the protonated form has structure E.



E

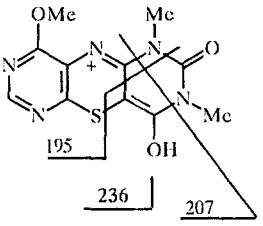
The above-indicated assumption was confirmed by recording the ^{13}C NMR spectra of the investigated solution of Ib in $CDCl_3$ + CF_3COOH (the ratio of the concentrations of the acid and the substance was approximately equimolar) (see Table 1). A signal at 37.1 ppm, which becomes a doublet with spin–spin coupling constant (SSCC) $^1J_{CH}$ = 149.5 Hz under conditions of recording without proton suppression, is observed in the spectrum. It was demonstrated by a selective-decoupling experiment that the methylidyne proton (δ 4.93 ppm) is attached to this carbon atom and, consequently, that this signal is the $C_{(9a)}$ signal. It is interesting to note the increase in the $^1J_{CH}$ direct SSCC for the dimethylamino group in this compound ($^1J_{CH}$ = 147.3 Hz) as compared with the analogous value in the spectrum of Ib recorded in DMSO-d_6 ($^1J_{CH}$ = 141.0 Hz). This sort of increase in $^1J_{CH}$ for the $N(CH_3)_2$ group is in good agreement with the ionic character of structure E [8].

Signals of yet another compound, the spectrum of which does not contain a signal of a methylidyne proton, while the signals of the pyrimidine proton and the dimethylamino group are shifted to stronger field as compared with form E (see Table 2), develop and increase in intensity with a further increase in the amount of CF_3COOH in solution (up to and above 10 moles of the acid per mole of Ib). It may be assumed that the resulting compound is the product of acylation of the E ion with trifluoroacetic acid.

The mass spectra of Ia and Ib (Table 3) are characterized by the presence of maximally intense molecular-ion peaks with m/z 293 and 306, respectively, and an overall fragmentation pathway that is associated with stepwise fragmentation of

*Because of its low solubility, we could not record the ^{13}C NMR spectrum of Ib in $CDCl_3$.

the dimethyluracil ring. An analysis of the daughter ions shows that the molecular ion of Ia preferably undergoes fragmentation from imino hydroxy form D. This is primarily indicated by the presence in the spectrum of an intense (I_{rel} 32%) ion peak with m/z 195, vis-à-vis, the absence of ions corresponding to the detachment of $CON(CH_3)CO$ and $2CONCH_3$ groups from the dimethyluracil ring. A diagram of the fragmentation of the molecular ion of Ia is presented below.



The presence of a dimethylamino group in the pyrimidine ring of Ib is responsible for the preferred elimination of $—CH_3$ and $—NCH_3$ from this group in the first stage of the fragmentation of the molecular ion, which is specific for compounds of this sort [9], and the subsequent fragmentation of the dimethyluracil ring via a scheme similar to that examined above for Ia. Ions at 220 ($[M - NCH_3 - CONCH_3]^+$), 191 ($M - NCH_3 - CH_3NCONCH_3]^+$), and 179 ($[M - NCH_3 - CON(CH_3)COCH]^+$) are observed in the spectrum. However, the specific character of this fragmentation is less pronounced for this compound; as a rule, the intensities of the corresponding ions do not exceed 10%. At the same time, it is interesting to note the development of ions at 206 and 192, which correspond to the detachment of 2CO and an NCH_3 group from the $[M - CH_3]^+$ and $[M - NCH_3]^+$ ions, respectively. The presence of these ions can be explained by the partial existence of the molecular ion of Ib prior to fragmentation either in amino ketone form A or in imino oxo form C.

EXPERIMENTAL

The electron-impact (EI) mass spectra were obtained with a Varian MAT-112 mass spectrometer with direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, and the temperature of the ionization chamber was 200°C.

The ^1H and ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard.

REFERENCES

1. M. P. Nemeryuk, N. I. Traven', T. G. Arutyunyan, E. A. Shatukhina, O. S. Anisimova, N. P. Solov'eva, Yu. N. Sheinker, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, No. 8, 1129 (1992).
2. M. P. Nemeryuk, N. I. Traven', T. G. Arutyunyan, E. A. Shatukhina, N. A. Nersesyan, O. S. Anisimova, N. P. Solov'eva, E. M. Peresleni, Yu. N. Sheinker, A. G. Sokol, V. M. Kazakova, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, No. 2, 258 (1989).
3. Yoshifumi Maki, Tokiyuki Hiramitsu, and Mikio Suzuki, *Chem. Pharm. Bull.*, **22**, 1265 (1974).
4. V. N. Knyazev, V. N. Drozd, and T. Ya. Mozhaeva, *Zh. Org. Khim.*, **15**, 2561 (1979).
5. Yoshifumi Maki, Magoichi Sako, Miyoki Tanabe, and Mikio Suzuki, *Synthesis*, No. 6, 462 (1981).
6. Yoshifumi Maki, Tokiyuki Hiramitsu, and Mikio Suzuki, *Tetrahedron*, **36**, 2097 (1980).
7. Isumeo Hon, Yosuo Tomi, Takayuki Naiton, Minako Yamamura, Ichiro Ishikawa, Yoshihisa Mizuno, and Haruo Ogura, *Chem. Pharm. Bull.*, **37**, 2197 (1989).
8. P. E. Hansen, *Progress in Nuclear Magnetic Resonance Spectroscopy*, Vol. 14, New York (1981), p. 271.
9. N. S. Vul'fson, V. G. Zaikin, and A. I. Mikaya, *Mass Spectrometry of Organic Compounds* [in Russian], Khimiya, Moscow (1986), p. 134.