HETERO ANALOGS OF ALLOXAZINES.

3.* REARRANGEMENTS OF 6,8-DIMETHYL-9*a*-HYDROXY-7,9-DIOXO-9*a*H-6,7,8,9-TETRAHYDRODIPYRIMIDO[4,5-b][4′,5′-e][1,4]THIAZINES

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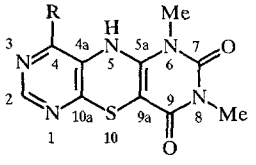
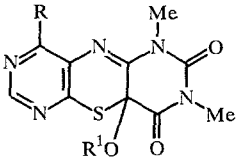
The structures of 6,8-dimethyl-9a-hydroxy-7,9-dioxo-9aH-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazines were studied by NMR spectroscopy and mass spectrometry. The transformation of these compounds in solution in DMSO was investigated. A spiro structure of the resulting rearrangement products was established by means of ^{13}C NMR spectroscopy.

In a previous investigation of the reaction of 5-amino-6-mercaptopyrimidines with 1,3-dimethyl-5-nitro-6-chlorouracil we observed that the resulting dipyrimido[4,5-b][4′,5′-e][1,4]thiazines Ia, b are readily converted to 9*a*-hydroxy-substituted II when oxidizing agents are present. The structures of these compounds were established on the basis of IR spectral data [2]. In the present research we investigated the NMR and mass spectra of both II and III, which are O-methyl derivatives of II.



Ia,b



IIa,b; IIIa,b

Ia, IIa, IIIa R = OMe; Ib, IIb, IIIb R = NMe2; IIa,b R^1 = H; IIIa,b R^1 = Me

The ^{13}C NMR spectra of IIa, b and IIIa, b are similar to one another (Table 1; data from the ^1H NMR spectra of IIa, b and IIIa, b are presented in Table 2) and are extremely similar to the spectra of starting dipyrimidothiazines Ia, b [1], which indicates the invariability of the three-membered ring of these molecules. One might have expected this, since the starting heterocyclic system should be retained in obtaining II by oxidation of dipyrimidothiazines I. The signal of the C_{5a} atom under conditions of recording the spectra without proton decoupling in II and III has the form of a quartet due to spin-spin coupling with the adjacent NCH_3 group (see Table 1) as in the case of the observed quartet for $C_{(5a)}$ in dipyrimidothiazine Ib [1].

The fundamental difference between II and II and I consists in the fact that the quaternary sp^2-hybridized C_{9a} atom in starting dipyrimidothiazines I is converted to the quaternary sp^3-hybridized C_{9a} atom, to which substituents such as OH (IIa, b) and OCH_3 (IIIa, b) groups are attached. In ^{13}C NMR spectra of this type the signals of the C—O carbon atom are usually observed at 65-85 ppm [3]. In the hydroxy derivative IIa that we investigated the signal of the C_{9a} atom has the form of a singlet at 73.2 pp,† whereas in the spectra of O-methyl compounds IIIa, b this signal is observed at $\approx$78 ppm in the form of a quartet due to spin-spin coupling with the protons of the OCH_3 group.

*For Communication 2 see [1].

†The signal of the analogous carbon atom in a hydroxy derivative of the flavine series has a chemical shift of 71.0 ppm [4].

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TABLE 1. Data from the ^{13}C NMR Spectra of II-IV*

Compound	δ (ppm), J (Hz)	$C_{(2)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(5a)}$	$C_{(7)}$	$C_{(9)}$	$C_{(9a)}$	$C_{(10)}$	C_{10a} (IIa, IIIa, b) and C_{11a} (IVa)	NCH_3	R
IIa	δ	153,1 d.	162,2m.	122,6 increased s	145,8 br. q	149,8m.	165,1 q	73,2 s	—	151,3 d.	28,9; 30,8 q	54,6 q
	J	$^1J_{C_2H}$ 206,0	$^3J_{C_4C_2H}$ 10,5	$^4J_{C_{4a},C_2H}$ 1,2	$^3J_{C_{5a},NCH_3}$ 2,4	$^3J_{C_7,NCH_3}$ 2,7	$^3J_{C_9,NCH_3}$ 2,7	—	—	$^3J_{C_{10a},C_2H}$ 12,7	$^1J_{NCH_3}$ 143,1; 142,7	$^1J_{OCH_3}$ 147,5
IIIa[2*]	δ	153,3	162,1	122,9	143,8	149,4	162,2	78,6	—	149,5	28,9; 30,9	54,6
IIIb[4*]	δ	153,3 d.	157,0m.	120,0 increased d	139,6 q.	149,8m	162,5 q.	77,9 d.	—	149,9 d.	29,1; 31,1 q	40,8 q
	J	$^1J_{C_2H}$ 201,3	Σ^3J^{3*} ~23,0	$^4J_{C_{4a},C_2H}$ 1,2	$^3J_{C_{5a},NCH_3}$ 2,5	$^3J_{C_7,NCH_3}$ 2,7	$^3J_{C_9,NCH_3}$ 2,7	$^3J_{C_{9a},OCH_3}$ 5,1	—	$^3J_{C_{10a},C_2H}$ 12,2	$^1J_{NCH_3}$ 142,8; 142,6	$^1J_{NCH_3}$ 139,0
IVa	δ	154,5 d.	162,1 m.	132,8 d	86,2 br.m	155,2 m.	169,9 q.	—	166,8 d.	165,0 d.	24,7; 25,3 q	54,8 q
	J	$^1J_{C_2H}$ 208,0	Σ^3J^{3*} ~ 23,0	$^4J_{C_{4a},C_2H}$ 1,0	ΣJ^{5*} ~ 8,0	$^3J_{C_7,NCH_3}$ 3,0	$^3J_{C_9,NCH_3}$ 3,0	—	$^3J_{C_{10},NH}$ 9,0	$^3J_{C_{11a},C_2H}$ 13,1	$^1J_{NCH_3}$ 140,0; 141,5	$^1J_{OCH_3}$ 148,0

*With d_6-DMSO as the solvent; δ is the ^{13}C chemical shift, and J is the ^{13}CH spin-spin coupling hetero constant.

2*The $J_{^{13}CH}$ SSCC were not determined because of the limited solubility; δR^1 = 51.2 ppm.

3*For C_4, $\Sigma^3J = {}^3J_{C_4,C_2H} + {}^3J_{C_4,R}$.

4*For IIIb, δR^1 = 51.6 ppm (q, $^1J_{CH}$ = 145.4 Hz).

5*For C_{5a} of IVa, $\Sigma J = {}^3J_{C_{5a},NCH_3} + {}^2J_{C_{5a},NH}$; in experimentation involving selective resonance with suppression of the NH signal (δNH = 8.63 ppm) the broad multiplet is converted to a quartet with $^3J_{C_{5a},NCH_3}$ = 2.5 Hz.

TABLE 2. ^1H Chemical Shifts of IIa, b, IIIa, b, and VIa, b (δ, ppm) in d_6-DMSO

Compound	R	NCH_3	C_2H	OH or NH
IIa	4,03	3,22; 3.45	8,46	8,69
IIb	3,26	3,21; 3,40	8,15	8,45
IIIa*	4,03	3,18; 3,46	8,47	—
IIIb*	3,27	3,22; 3,43	8,17	—
VIa	4,15	2,80; 3,05	8,77	8,63
VIb	3,22	2,76; 2,97	8,39	8,43

*For IIIa and IIIb, $\delta_{C_{(9a)}OCH_3} = 3.22$ ppm.

TABLE 3. Characteristics of the Peaks in the Spectra of IIa-f and IIIa

Ion	m/z (Irel, %)						
	IIa	IIb	IIc	IId	IIe	IIf	IIIa
M^+	309 (55)	322 (33)	308 (100)	336 (100)	364 (17)	362 (270	323 (43)
$[M-O]^+$	293 (10)	306 (45)	292 (8)	320 (43)	348 (17)	346 (18)	—
$[M-OH]^+$	292 (6)	305 (67)	291 (25)	319 (73)	347 (33)	345 (29)	292* (100)
$[M-SH]^+$	—	—	275 (11)	303 (84)	331 (5)	329 (11)	—
F_1	167 (100)	180 (14)	166 (29)	194 (24)	222 (11)	220 (7)	— .
F_2	154 (10)	167 (100)	153 (23)	181 (23)	209 (100)	207 (91)	—

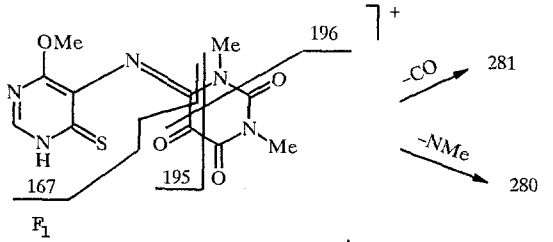
*$[M - OR]^+$.

TABLE 4. Mass Spectra of IIa, b and IIIa*

Compound	m/z (I_{rel}, %)
IIa	310 (8), 309 (55), 293 (10), 292 (6), 281 (29), 280 (63), 207 (8), 196 (5), 195 (42), 194 (10), 183 (13), 168 (29), 167 (100), 154 (10), 139 (12), 138 (4), 137 (25), 113 (9), 110 (12), 84 (21), 70 (24), 61 (180, 59 (59), 45 (37), 44 (34)
IIb	322 (33), 306 (45), 305 (67), 291 (19), 276 (160, 264 (10), 246 95), 207 (12), 206 (14), 194 (4), 191 (6), 180 (14), 179 (15), 178 (24), 167 (100), 151 (14), 136 (15), 125 (11), 67 (10), 44 (25)
IIIa	323 (43), 308 (17), 292 (100), 251 (28), 235 (15), 223 (6), 210 (14), 209 (4), 208 (9), 195 (4), 194 (7), 180 (6), 179 (20), 178 (6), 167 (3), 153 (4), 151 (11), 150 (9), 113 (14), 71 (12), 68 (11), 42 (46)

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

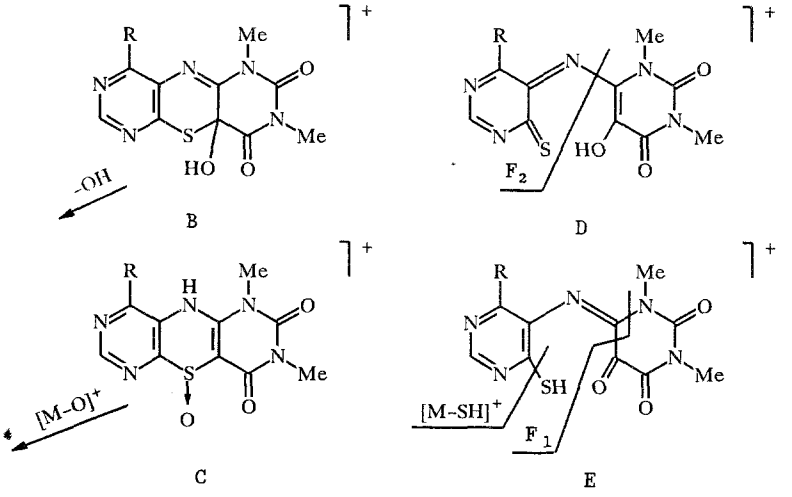
An intense peak of a molecular ion with a mass number of 309, which corresponds to the structure of the hydroxy derivative, is observed in the mass spectrum of IIa. For this compound one should have expected the appearance of an intense peak of an $[M - OH]^+$ ion, which is associated with the advantageousness of the elimination of an angular substituent and subsequent localization of the charge on the sulfur atom of the thiazine ring. However, the intensity of this peak in the spectrum of IIa does not exceed 6%. At the same time, one observes intense peaks of ions with mass numbers 281, 280, 196, 195, 168, and 167, of which the latter (F_1) has the maximum intensity in the spectrum. The sort of fragmentation depicted in the scheme is in good agreement with the idea of open form A of the molecular ion of IIa.



A

As in the cases that we previously studied, conversion to the open form for this compound evidently occurs either during vaporization of the sample [5] or during ionization.

In contrast to IIa, IIb has a mass spectrum in which intense peaks of $[M - OH]^+$ and $[M - O]^+$ ions are observed, while fragmentation of the dimethyluracil ring is markedly suppressed.* This indicates that the molecular ion of IIb remains to a significant extent in three-membered form B prior to fragmentation; partial conversion to sulfoxide C occurs. In addition, in the spectrum of IIb one observes a maximally intense peak at 167, which could not be interpreted as an F_1 ion. Since the assignment of this ion (F_2) raised serious difficulties, we compared the mass spectra of IIb with the spectra of a number of derivatives IIIc-f, which contain alkylamino substituents in the 4 position of the pyrimidine ring [6]. We found that all of the investigated compounds have to a significant extent similar character of their fragmentation. Just as for IIb, fragmentation with the elimination of O and an OH group from M^+ is characteristic for them, and one observes an intense peak of an F_2 ion, the mass number of which depends on the amino group in the 4 position (Table 2). Peaks of an F_1 ion and other ions previously noted in the spectrum of IIa are also observed in the spectra; however, their intensities are considerably lower than in the case of IIa. In addition, the presence of peaks of $[M - SH]^+$ ions and products of their subsequent fragmentation was found to be characteristic for the spectra of IIc, IId, and IIf. All of this makes it possible to assume that the investigated 9*a*-hydroxy derivatives IIb-f undergo fragmentation from several forms of the molecular ion (B-E), as presented in the scheme.



IIb R=NMe_2; c R=NHMe; d R=NHC_3H_7; e R= –N⟨⟩; f R= –N⟨O⟩

The ratio of the intensities of the peaks related to a given form depends quite markedly on substituent R (see Table 3). Thus the $[M - O]^+$ and $[M - OH]^+$ ions have high intensities in the case of IIb and IId, while fragmentation to give F_2 ions proves to be more preferable for morpholino- and piperidino-substituted IIe and IIf.

The correctness of the proposed schemes of the fragmentation of IIa-f is confirmed by an examination of the mass spectra of their transformation products. Fastening of the cyclic form by methylation of the OH group (IIIa) leads to the disappearance in the mass spectra of ions (of the F_1 and F_2 type) and other products of fragmentation of the open form. The fragmentation of this compound is determined virtually completely by the elimination of the angular substituent from the molecular ion.

For hydroxy derivatives II it was established from the ^1H and ^{13}C NMR spectra that the investigated substances undergo substantial changes in solution in d_6-DMSO upon prolonged storage or heating. In the case of IIa we investigated a solution in d_6-DMSO, which was heated for 20 h at 90°C. In the case of IIb we analyzed a solution in d_6-DMSO that had been stored for a long time (more than 15 days) at 23°C. Stronger-field signals of $N(CH_3)$ groups ($\delta_{NCH_3} \approx 2.8$-3.0 ppm and $\Delta\delta_{NCH_3} \approx 0.4$-0.5 ppm) and weaker-field signals of the proton of the pyrimidine ring (δ 8.77 ppm for IVa and 8.39 ppm for IVb) as compared with the analogous signals in starting IIa, b additionally appear in the ^1H NMR spectra of solutions of II

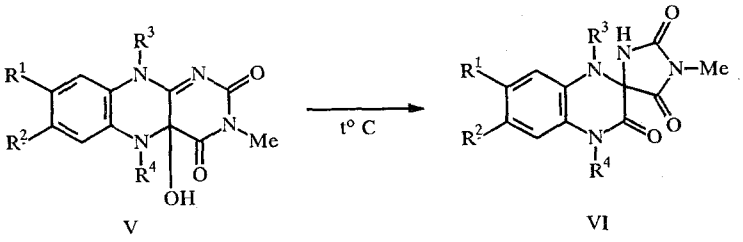
*In the mass spectrum of IIa intensity $I_{[M-O]^+} \approx 10\%$ (see Table 2).

(Table 2). Broad signals at 8.63 ppm (solution of IIa) and 8.43 ppm (solution of IIb), which disappear from the spectra virtually immediately when a small amount of CD_3OD is added to solutions in d_6-DMSO, appear at weak field in the spectra. As a rule, this is characteristic for labile protons of the NH or OH type and is associated with their rapid exchange for D. Judging from the ^1H NMR spectra, the amounts of the products formed as a result of the transformation of starting IIa, b are 45% (IVa) and 20% (IVb).

The ^{13}C NMR spectra of a solution of IIa in d_6-DMSO recorded after prolonged heating and prior to it differ substantially. The most characteristic new signal is the signal of a carbonyl group, which, judging from the magnitude of the chemical shift (δ 166.8 ppm), is bonded to a heteroatom (see Table 1). Spin-spin coupling with the N—CH_3 protons (as occurs in the case of the uracil fragment) is not observed for the carbon atom of this C=O group, but there is coupling with a proton of the NH or OH type (δ 8.63 ppm), which was established in experiments involving selective decoupling of the signal at 8.63 ppm. Instead of the four signals of quaternary carbon atoms that are present in the ^{13}C NMR spectrum of IIa prior to heating, in the spectrum of a solution subjected to heating one observes three analogous signals, one of which (at 86.2 ppm) couples with both the protons of the NCH_3 group and with the labile proton (δ 8.63 ppm).

The mass spectrum of a sample of IIa containing up to 45% IVa does not display the development of additional peaks of molecular and fragment ions. Only a certain redistribution of their intensities is observed. For a more reliable determination of the molecular mass of the transformation product we obtained the secondary-ion emission mass spectra (SIMS) of samples of IIa before and after heating. In both cases only a peak of a quasi-molecular MH^+ ion with a mass number of 310 is observed in the spectra, which proves an isomerization transformation process.

It is known that hydroxy derivatives of isoalloxazines V undergo rearrangement to spiro products of the VI type quite readily [7].

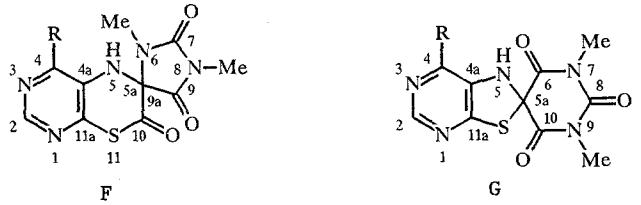


V VI

$R^1=R^2=Me$, $R^3=m$-$MeOC_6H_4CH_2CH_2$, $R^4=Et$

The hydrolysis of flavines (isoalloxazines) also leads to spiro compounds of the VI type [8].

In analogy with the information set forth above, spiro structure F was assigned to transformation product IV, which is formed upon prolonged storage of a solution of hydroxy product II in DMSO or when it heated.



F G

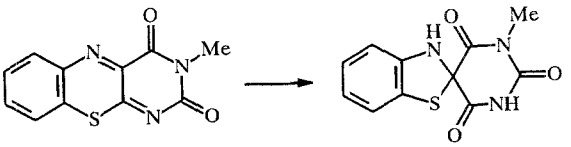
IVa R=OMe, б R=NMe_2

This sort of structure of transformation product IV is in good agreement with the chemical shifts of the carbon atoms, their multiplicities, and the spin-spin coupling hetero constants $J_{^{13}CH}$, which were determined for transformation product IVa in experiments involving recording of spectra without proton decoupling and with selective proton decoupling (see Table 1).

A strong-field shift of the NCH_3 signals in the ^1H NMR spectra as compared with these signals in the spectra of hydroxyflavines V ($\Delta\delta_{NCH_3} \approx 0.5$ ppm) was observed for the spiro system of hydroxyflavines VI [7]. As indicated above, we also noted a similar strong-field shift of the signals of the NCH_3 groups in the spectra of spiro products IVa, b as compared with IIa, b (see Table 2). The mass-spectral data are also in agreement with spiro structure F for product IV.*

*The authors sincerely thank A. P. Pleshakova (Plastmassy NPO) for recording the secondary-ion emission mass spectra (SIMS).

A similar rearrangement of 10-thiaisoalloxazines VII was previously investigated [9, 10], and a different structure (VIII) was proposed for the spiro compound.



VII VIII

In our opinion, the proposed structure VIII was not proved unequivocally, since ^{13}C NMR spectra were not investigated for it, and the information obtained by means of other spectral methods is inadequate. As applied to the dipyrimidothiazines II that we investigated, the resulting IV(a and b), according to [9], could have structure G. However, the data from the ^{13}C NMR spectra of IVa [particularly the multiplicities of the signals of the $C_{(5a)}$ (δ 86.2 ppm) and $C_{(10)}$ (δ 166.8 ppm) atoms] are not in agreement with this sort of structure.

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 secondary-ion emission mass spectra (SIMS) were obtained with a Hitachi M-80A mass spectrometer. Ionization was accomplished with a beam of Xe ions; the energy of the primary beam of ions was keV, and the density of the current of the primary ions was 10^{-7} A/cm^2. The samples were analyzed in a glycerine matrix on a gold target.

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

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