HETEROANALOGS OF ALLOXAZINES.

1. PROPERTIES AND CONVERSIONS 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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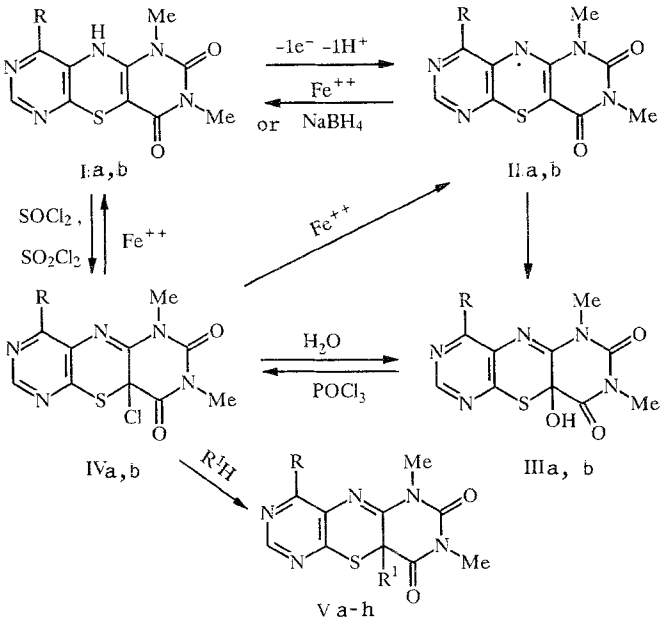
The properties of derivatives of 6,8-dimethyl-7,9-dioxo-5H-6,7,8,9-tetrahydropyrimido[4,5-b][4,5-e][1,4]thiazines have been investigated. These substances are stable in the crystalline form and are readily oxidized in moist solutions in chloroform or methylene chloride, being converted to 9a-hydroxy derivatives. In the example of the 4-dimethylamino derivative, a stagewise mechanism has been shown for the process of one-electron oxidation of the thiazines, proceeding through the formation of a free-radical structure. The thiazinyl radicals have been found to be capable of one-electron redox reactions. A tendency of the thiazines to form 9a-derivatives has been noted.

We had shown previously that the reaction of 5-amino-6-mercaptopyrimidines with 1,3-dimethyl-5-nitro-6-chlorouracil in the presence of bases leads to derivatives of tetrahydrodipyrimidothiazines (I). The 4-amino- or 4-alkylaminodipyrimidothiazines exist predominantly in the free-radical form. Since the systems I can be regarded as diaza analogs of 5-thiaflavins, which are



I-IV: a) R = OMe; b) R = NMe_2. V: a) R = R^1 = OMe; b) R = OMe, R^1 = OEt; c) R = OMe, R^1 = morpholino; d) R = OMe, R^1 = 4-methylpiperazino; e) R = OMe, R^1 = 3-phenylpyrrolidino; f) R = NMe_2, R^1 = morpholino; g) R = NMe_2, R^1 = 4-methylpiperazino; h) R = NMe_2, R^1 = OMe

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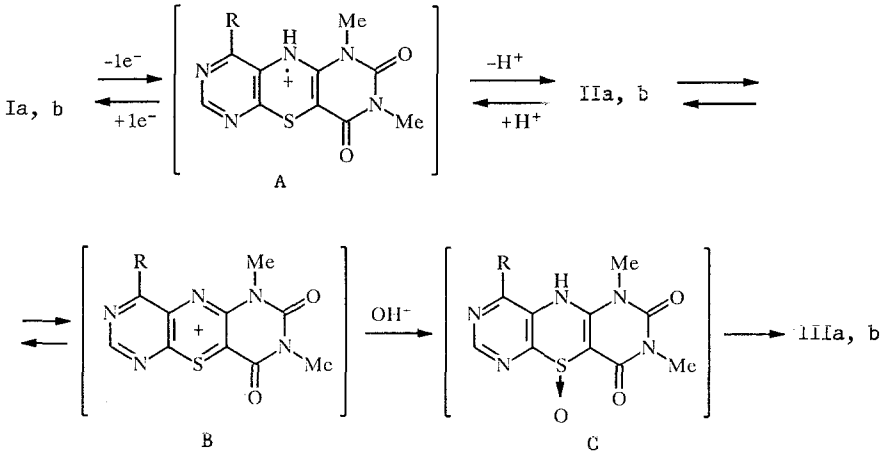
known to be capable of one-electron transfer reactions [2], it could be expected that the dipyrimidothiazines I-III will also tend to undergo mutual conversions governed by reactions of one-electron oxidation and reduction.

We have investigated the properties of the dipyrimidothiazines in detail in the example of the thiazines Ia, b (see above).

It has been shown that compounds Ia, b are stable in the crystalline form; but when solutions of these compounds in moist chloroform or in methylene chloride are allowed to stand at 18-20°C, they are oxidized to the 9*a*-hydroxy derivatives IIIa, b. The thiazine Ib is converted to a mixture of the thiazines IIb and IIIb upon recrystallization from water or ethanol.

The oxidation process Ia, b → IIa, b → IIIa, b proceeds very readily through the action of hydrogen peroxide in acetic acid. The thiazine Ib is converted within 15 min to the radical IIb; and after 30 min, the reaction product is the 9*a*-hydroxy derivative IIIb. The thiazine Ia is converted directly to the thiazine IIIa. The thiazinyl radicals IIa, b are also stable in the crystalline form and are readily oxidized in chloroform or methylene chloride solutions to the thiazines IIIa, b. With a reducing agent present, we have been able to observe the reverse transition of the free-radical form IIa, b to the thiazines Ia, b. For example, by the action of Mohr's salt $FeSO_4(NH_4)_2SO_4 \cdot 6H_2O$ on compounds IIa, b, the thiazines Ia, b are formed; and the action of $NaBH_4$ on IIb brings about the transition IIb → Ib.

On the basis of these findings and data reported in [2], we have concluded tentatively that the thiazines I in solution are capable of undergoing conversions in accordance with the following scheme:



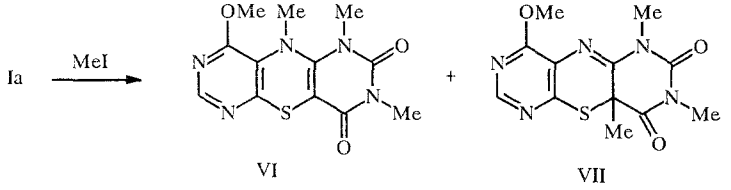
As can be seen from this scheme, the thiazine I is probably converted initially to the ion radical A, which is rapidly transformed to the more stable thiazinyl radical II. This radical, being subjected to the following stage of one-electron oxidation through the intermediate unstable thiazonium cation B, is stabilized by conversion to the sulfoxide C, which then undergoes a Pummerer rearrangement to form the 9*a*-hydroxy derivatives III [3]. Proofs of the structure of the thiazines II and III are given in [1].

The formation of compounds that are angularly substituted at position 9*a* is the preferred direction of conversions of the thiazines I. For example, the chlorine derivatives IVa, b have been isolated from the products obtained by the action of $SOCl_2$ or SO_2Cl_2 on the thiazines Ia, b. In view of the instability of compound IVb, we subjected it to further treatment with very little delay after it had been isolated. The structure of compound IVa was confirmed by elemental analyses and spectroscopic studies. The IR spectrum of the thiazine IVa does not contain any bands of stretching vibrations of the NH group in the 3450 cm^{-1} region. The absorption band of one of the CO groups of the dioxopyrimidine ring is shifted toward higher frequencies (1700-1740 cm^{-1}).

In the mass spectrum of the thiazine IVa, the ratio of intensities of the isotope peaks of the molecular ion indicate that the molecule contains one chlorine atom; and their mass numbers of 327/329 correspond to the proposed structure. The molecular peak (292) pertains to the ion $[M—Cl]^+$, and this indicates the angular position of the chlorine. Subsequent decomposition of the $[M—Cl]^+$ ion is due to stepwise elimination of the 1,3-dimethyl-2,4-dioxopyrimidine ring. The thiazine IVa was also obtained by refluxing the thiazine IIIa with excess $POCl_3$ in benzene. The chlorine atom in position 9*a* is highly mobile, and it reacts readily with nucleophilic agents. Treatment of the 9*a*-chloro derivatives IVa, b with morpholine or N-methylpiperazine leads to the corresponding substituted compounds Vc, d, f, g. Treatment of the thiazine IVa with 3-phenylpyrrolidine leads to the thiazine Ve; treatment of the thiazines IVa, b with methanol leads to the thiazines Va, h. Treatment of the thiazine IVa with ethanol gives the thiazine Vb. The thiazine Va was also obtained from the thiazine IIIa by the action of diazomethane. Compounds IVa, b are readily hydrolyzed, being converted to IIIa, b.

Investigation of the UV spectra of the derivatives IIIa, b, IVa, and Va-h revealed characteristic absorption maxima in the 210, 250, and 320 nm regions, indicating that they are monotypical in structure. In an investigation of the reduction of the thiazine IVa, it was found that it can be reduced to the thiazinyl radical IIa and then to the thiazine Ia by treatment with Mohr's salt in an aqueous medium. The respective reaction times are 2 and 24 h.

Alkylation of the thiazine Ia with methyl iodide in the presence of sodium hydride in dimethylformamide (DMF) leads to the formation of a mixture of the thiazines VI and VII. In the IR spectra of compounds VI and VII, there are no absorption bands corresponding to NH groups; for the 9*a*-CH_3 derivative we observed a shift of the band for one of the CO groups toward higher frequencies, the same as for IIIa.



In the PMR spectra of compounds VI and VII, in comparison with the spectrum of Ia, we observe additional signals of CH_3 groups at 3.11 ppm (5-N-CH_3) (VI) and 1.73 ppm (9*a*-CH_3) (VII).

The mass spectra of compounds VI and VII have basically different modes of decomposition. For the thiazine VII we observe elimination of the angular CH_3 group from the molecular ion. Other paths of decomposition of the molecular ion are almost completely suppressed. As a consequence, the maximum peak in the spectrum of VII is that of $[M-CH_3]^+$. In the spectrum of compound VI the maximum peak is that of the molecular ion; the intensity of the peak for the $[M-CH_3]^+$ ion is only 37%. The main decomposition of M^+ is related to rupture of bonds in the 1,3-dimethyl-2,4-dioxopyrimidine ring and elimination of SH groups. In the spectrum of compound VI we observe the ions $[M-H]^+$ (274), $[M-CONCH_3]^+$ (250), and $[M-2CONCH_3]^+$ (193), which are not present in the spectrum of compound VII. The spectroscopic data confirm unambiguously that compound VI is the 5-NCH_3 derivative of the thiazine Ia, and VII the 9*a*-CH_3 derivative.

Thus, we have noted a tendency of compounds I-III to form 9*a*-derivatives. We can assume that the reactions that we have investigated proceed initially with a short-lived thiazonium cation, with the formation of the corresponding S-substituted compounds, which are unstable and are readily rearranged to the 9*a*-derivatives

We have found that the 5H-thiazines Ia, b and the thiazinyl radicals IIa, b are capable of one-electron redox reactions; this leads us to the conclusion that they are similar to 5-thiaflavins, which are isoelectronic with the reduced and semiquinone forms of alloxazine. At the same time, for the derivatives of the dipyrimidothiazines, in contrast to the 5-thiaflavins, we note a higher stability of the free radical form.

EXPERIMENTAL

The IR spectra of the synthesized compounds were taken in white mineral oil or chloroform in a Perkin—Elmer 457 instrument; the UV spectra were taken in EPS-3 and Specord M-40 spectrophotometers in ethanol or chloroform. The NMR spectra were obtained in Varian XL-100 and XL-200 spectrometers, with TMS internal standard. The mass spectra were obtained in an MAT-112 mass spectrometer (Varian, Germany), with direct introduction of the sample into the ion source.

For compounds Ia, b, IIb, IIIa, b, IVa, Va-h, VI, and VII, the elemental analyses for C, H, N, and S matched the calculated values.

4-Dimethylamino-6,8-dimethyl-7,9-dioxo-9*a*-hydroxy-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (IIIb, $C_{12}H_{14}N_6O_3S$). A. To a suspension of 0.5 g (1.6 mmoles) of the thiazine Ib in 15 ml of acetic acid, 5 ml of a 30% solution of hydrogen peroxide was added; the mixture was stirred for 15 min, and the precipitate was filtered off. Obtained 0.25 g (50%) of the thiazinyl radical IIb, identical to that described in [1]. If the reaction time was extended to 2 h, 0.27 g (54%) of the thiazine IIIb was filtered off as the reaction product.

B. 0.2 g of the thiazine Ib in 20 ml of water was refluxed; filtration gave 0.1 g (50%) of the thiazine IIIb, identical to that obtained by method **A**. Analytical and spectroscopic data: Thiazinyl radical IIb — mp 222-223°C (from DMF); IR spectrum, ν, 1640, 1700 (CO) cm^{-1}; UV spectrum, λ_{max} (log ε): 712 (3.64), 372 (11.03), 315 (4.30), 260 (4.10) (sh), 245 (4.28) nm. Thiazine IIIb — mp 212-214°C (from DMF); IR spectrum, ν 1680, 1740 (CO) cm^{-1}; UV spectrum, λ_{max} (log ε): 220 (4.35), 235 (4.29), 275 (4.22), 360 (3.88) nm.

4-Methoxy-6,8-dimethyl-7,9-dioxo-5H-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Ia, $C_{11}H_{11}N_5O_3S$). To a solution of 0.3 g (0.98 mmole) of the thiazinyl radical IIa in 20 ml of dioxane, a solution of 0.72 g (2.2 mmoles) of

$FeSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$ in 10 m of water was added. The mixture was stirred for 24 h at 20°C, and the precipitate was filtered off, obtaining 0.2 g (74.1%) of the thiazine Ia, identical to that obtained previously in [1].

4-Methoxy-6,8-dimethyl-7,9-dioxo-5H-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Ia, $C_{11}H_{11}N_5O_3S$). To a solution of 0.3 g (0.9 mmole) of the thiazine IVa in 20 ml of dioxane, a solution of 0.72 g (2.2 mmoles) of $FeSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$ in 10 ml of water was added. The mixture was stirred for 24 h at 20°C, and the precipitate was filtered off, obtaining 0.2 g (74.1%) of the thiazine Ia, identical on the basis of analytical and spectral data to the thiazine Ia obtained from the thiazinyl radical IIa.

4-Methoxy-6,8-dimethyl-7,9-dioxo-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazinyl Radical (IIa, $C_{11}H_{10}N_5O_3S$). To a solution of 0.6 g (1.8 mmoles) of the thiazine IVa in 20 ml of dioxane, a solution of 0.72 g (2.2 mmoles) of $FeSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$ in 20 ml of water was added. The mixture was stirred for 1 h at 20°C, and the precipitate was filtered off, obtaining 0.3 g (56.6%) of the thiazinyl radical IIa, identical on the basis of melting point and IR spectrum to the thiazinyl radical IIa obtained by the method given in [1]. Thiazine IIa: mp 190-192°C; IR spectrum, ν, cm^{-1}: 1640, 1700 (CO).

4-Dimethylamino-6,8-dimethyl-7,9-dioxo-5H-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Ib, $C_{12}H_{14}N_6O_2S$). A mixture of 0.4 g (1.4 mmoles) of the thiazinyl radical IIb and 0.1 g (3.3 mmoles) of $NaBH_4$ was stirred with a mixture of 15 ml of dioxane and 15 ml of 99% HCOOH until the dark blue color of the solution had disappeared (~3 h); the solution was evaporated under vacuum at 20-25°C, and the residue was mulled with ethanol and filtered, obtaining 0.35 g (87%) of the thiazine Ib: mp 210-211°C (from ethanol); IR spectrum, ν, cm^{-1}: 3450 (NH), 1640 and 1700 (CO); UV spectrum, λ_{max} ($\log \varepsilon$), nm: 315 (3.78), 280 (3.93), 260 (4.28), 215 (4.26).

4-Methoxy-6,8-dimethyl-7,9-dioxo-9*a*-chloro-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine(IVa,$C_{11}H_{10}N_5ClO_3S$). **A.** A mixture of 1 g (3.4 mmoles) of the thiazine Ia and 20 ml of $SOCl_2$ or SO_2Cl_2 was stirred for 2 h at 20°C; the precipitate was filtered off and washed with dry ether, obtaining 0.6 g (58.7%) of the thiazine IVa, mp 178-180°C (from cyclohexane); IR spectrum, ν, cm^{-1}: 1640, 1740 (CO), 1620 (C=N).

B. A mixture of 1 g (3.2 mmoles) of the thiazine IIIa and 2.5 g (15 mmoles) of $POCl_3$ in 30 ml of dry benzene was refluxed for 3 h; the precipitate (a tarry impurity) was filtered off; the filtrate was evaporated down, 20 ml of benzene was added, and the solution was again evaporated to remove residues of $POCl_3$. The dry residue was mulled with dry ether and filtered, obtaining 0.5 g (51%) of the thiazine IVa, identical on the basis of analytical and spectral characteristics to the compound IVa obtained by method **A**.

4,9-Dimethoxy-6,8-dimethyl-7,9-dioxo-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Va, $C_{12}H_{13}N_5O_4S$). **A.** A 0.89-g quantity (2.7 mmoles) of the thiazine IVa in 30 ml of methanol was stirred for 30 min at 20°C; the precipitate was filtered off, obtaining 0.35 g (39.7%) of the thiazine Va, mp 155-156°C (from methanol); IR spectrum, ν, cm^{-1}: 1680, 1780 (CO), 1620 (C=N); UV spectrum, λ_{max} ($\log \varepsilon$), nm: 215 (4.3), 254 (4.2), 330 (3.9).

B. To a solution of 0.3 g (1 mmole) of the thiazine IIIa in chloroform, a solution of 0.8 g (20 mmoles) of diazomethane in 10 ml of ether was added; the mixture was stirred for 5 h, and the precipitate was filtered off, obtaining 0.1 g of the thiazine Va. The melting point of a mixed sample with the thiazine Va obtained by method **A** did not show any depression.

4-Methoxy-6,8-dimethyl-7,9-dioxo-9*a*-ethoxy-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Vb, $C_{13}H_{13}N_5O_4S$). A mixture of 1.1 g (3.4 mmoles) of the thiazine IVa and 40 ml of ethanol was stirred for 30 min, and the precipitate was filtered off, obtaining 0.6 g (53.1%) of the thiazine Vb, mp 180-181°C (from ethanol); IR spectrum, ν, cm^{-1}: 1680, 1780 (CO), 1620 (C=N); UV spectrum, λ_{max} ($\log \varepsilon$), nm: 215 (4.3), 254 (4.2), 330 (3.9).

4-Methoxy-6,8-dimethyl-7,9-dioxo-9*a*-N-morpholino-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Vc, $C_{15}H_{18}N_6O_4S$). To a solution of 0.6 g (1.8 mmoles) of the thiazine IVa in dry methylene chloride, a solution of 0.32 g (5.2 mmoles) of morpholine in 5 ml of dry methylene chloride was added; the solution was heated to 40°C, stirred for 10 min, cooled, and evaporated under vacuum; the residue was mulled with water, and the precipitate was filtered off, obtaining 0.45 g (75%) of the thiazine Vc, mp 234-236°C (from benzene); IR spectrum, ν, cm^{-1}: 1680, 1730 (CO), 1620 (C=N).

4-Methoxy-6,8-dimethyl-7,9-dioxo-9*a*-N-(N-methyl)piperazinyl-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4-thiazine (Vd, $C_{16}H_{21}N_7O_3S$). Under the same conditions used in preparing the thiazine Vc, starting with 0.4 g (1.2 mmoles) of the thiazine IVa and 1.7 g (17 mmoles) of N-methylpiperazine, obtained 0.4 g (83.7%) of the thiazine Vd, mp 202-204°C (from ethanol); IR spectrum, ν, 1680, 1740 (CO), 1620 (C=N), cm^{-1}; UV spectrum, λ_{max} ($\log \varepsilon$), 215 (4.3), 256 (4.3), 342 (3.8) nm.

4-Methoxy-6,8-dimethyl-7,9-dioxo-9*a*-(3′-phenyl)pyrrolidinyl-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Ve, $C_{21}H_{22}N_6O_3S$). A mixture of 0.8 g (2.4 mmoles) of the thiazine IVa and 0.71 g (4.8 mmoles) of 3-phenylpyrrolidine

in 30 ml of chloroform was stirred for 10 h at 18-20°C; the solution was evaporated, and the residue was mulled with ethanol and filtered, obtaining 0.3 g (28%) of the thiazine Ve, mp 178-180°C; IR spectrum, ν, cm^{-1}: 1680, 1730 (CO), 1620 (C=N)

4-Dimethylamino-6,8-dimethyl-7,9-dioxo-9*a*-morpholino-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Vf, $C_{16}H_{21}N_7O_3S$). A mixture of 0.7 g (2.3 mmoles) of the thiazine Ib and 14 ml of $SOCl_2$ or 14 ml of SO_2Cl_2 was stirred for 3 h at 18-20°C; the reaction mixture was poured into 50 ml of dry ether; the precipitate was separated from the ether by decantation of the ether layer. The residue was dissolved in a solution of 1 g (1.6 mmoles) of morpholine in 40 ml of methylene chloride; the mixture was stirred for 10 h at 18-20°C. The solution was vacuum-evaporated, and the residue was mixed with 20 ml of ether and 10 ml of water; the residue was filtered off, obtaining 0.45 g (53.2%) of the thiazine Vf, mp 212-213°C (from ethanol); IR spectrum, ν, cm^{-1}: 1680, 1730 (CO), 1620 (C=N).

4-Dimethylamino-6,8-dimethyl-7,9-dioxo-9*a*-N-(N′-methylpiperazinyl)-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Vg, $C_{17}H_{24}N_8O_2S$). Under the same conditions used in the preparation of the thiazine Vf, starting with 1 g (3.3 mmoles) of the thiazine Ib and 20 ml of $SOCl_2$, obtained 0.9 g of the thiazine IVb, which was treated without delay with a solution of 1.7 g (17 mmoles) of N-methylpiperazine in 50 ml of dry methylene chloride. The recovery of the thiazine Vg followed procedures similar to those used for the thiazine Vf. Obtained 0.9 g (68.2%) of the thiazine Vg, mp 119-120°C (from benzene); IR spectrum, ν, cm^{-1}: 1680, 1730 (CO), 1620 (C=N).

4-Dimethylamino-6,8-dimethyl-7,9-dioxo-9*a*-methoxy-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (Vh, $C_{13}H_{16}N_7O_3S$). Under the same conditions used in synthesis of the thiazine Vf, starting with 0.5 g (1.6 mmoles) of the thiazine Ib and 10 ml of $SOCl_2$, the thiazine IVb was obtained and then treated, without delay, with 50 ml of methanol; the solution was stirred for 5 h and vacuum-evaporated; the residue was mulled with water and filtered, obtaining 0.21 g (37.5%) of the thiazine Vh. The yields of compounds Vf-h were calculated relative to the thiazine Ib, since the thiazine IVb was not isolated in analytically pure form, in view of its extreme instability. For the thiazine Vh, mp 168-171°C (from ethanol).

4-Methoxy-5-methyl-6,8-dimethyl-7,9-dioxo-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (VI) and 4-Methoxy-6,8,9*a*-trimethyl-7,9-dioxo-6,7,8,9-tetrahydrodipyrimido[4,5-b][4′,5′-e][1,4]thiazine (VII). To a solution of 1 g (3.4 mmoles) of the thiazine Ia at 0-5°C in 25 ml of DMF, a solution of 0.12 g (5 mmoles) of NaH in 5 ml of DMF was added; the mixture was stirred for 20 min, and then a solution of 1 ml of methyl iodide in 5 ml of DMF was added. This mixture was stirred for 5 h, poured into 30 ml of water, and extracted with methylene chloride (3 × 30 ml); the extract was vacuum-evaporated and chromatographed in a column with Al_2O_3 (25 × 2 cm) with second-degree activity; benzene was used as the eluent. The benzene eluate was evaporated, and the residue was mulled with petroleum ether, and filtered, obtaining 0.22 g (21.3%) of the thiazine VI. After recovery of the thiazine VI, ethyl acetate was used as the eluent. The ethyl acetate eluate was vacuum-evaporated; the residue was mulled with petroleum ether and ethanol and then filtered, obtaining 0.26 g (25.2%) of the thiazine VII. Thiazine VI, mp 218-220°C, thiazine VII, 210-212°C. Thiazine VI: IR spectrum, ν, cm^{-1}: 1640, 1700 (CO); UV spectrum, λ_{max} ($\log\varepsilon$), nm: 315 (3.78), 280 (3.93), 260 (4.28), 215 (4.26); PMR spectrum, ppm: 3.49-3.31 (2-NCH_3), 4.02 (OCH_3), 8.12 (2-CH), 3.11 (5-N-CH_3). Thiazine VII: IR spectrum, ν, cm^{-1}: 1680, 1700 (CO); UV spectrum, λ_{max} ($\log\varepsilon$), nm: 328 (3.92), 252 (4.32), 309.2, 295 (3.68); PMR spectrum, ppm: 3.49-3.31 (2-NCH_3), 4.02 (OCH_3), 8.12 (2-CH), 1.73 (9*a*-CH_3).

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