AROMATIC DERIVATIVES OF 2H-PYRIMIDINO[5,6-b]-1,4-THIAZINE

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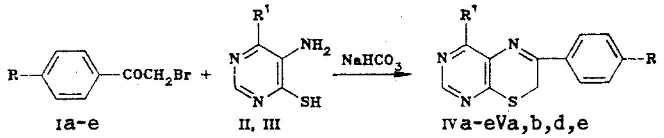
5-R^1-3-(4-R-Phenyl)-2H-pyrimidino[5,6-b]-1,4-thiazines [R^1 = $N(CH_3)_2$ or OCH_3], which exist primarily in the 2H form, were synthesized by the reaction of ω-bromoacetophenones with 4-R^1-5-amino-6-thiopyrimidines.

It is known [1] that ω-bromoacetophenones participate in reactions with o-aminothiophenol which lead to the formation of 3-aryl-2H-1,4-benzothiazines. We have now shown that this sort of process is also possible in the 5-amino-6-thiopyrimidine series. The reactions of p-substituted ω-bromoacetophenones Ia-e with 4-R^1-5-amino-6-thiopyrimidines II and III, which is realized in alcoholic medium by heating and is base-catalyzed, leads to the formation of 5-R^1-3-(4-R-phenyl)-2H-pyrimidino[5,6-d]-1,4-thiazines IV and V (Table 1):

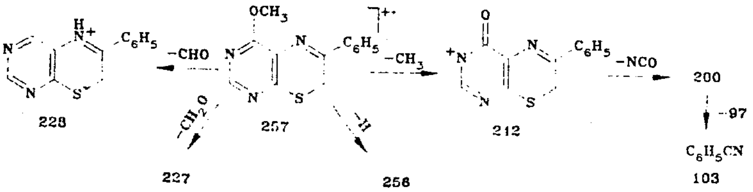


I, IV, Va R=H, b R=CH_3, c R=OCH_3, d R=Cl, e R=NO_2; II, IV R^1=$N(CH_3)_2$; III, V R^1=OCH_3

The yields of products IVa-e and the rates of their formation are appreciably higher than in the case of their OCH_3 analogs V; this is most likely due to the significant electron-donor effect of the dimethylamino group, which increases the basicity of the 5-amino group of II. Intermediate products of nucleophilic substitution could not be isolated, probably because of their high rate of cyclization.

Compounds IV and V were identified by means of spectral methods and the results of elementary analysis. Thus signals of methyl groups of substituents R and R^1, a singlet peak of the protons of the CH_2 group, and a multiplet of aromatic protons are unequivocally identified in the PMR spectra. The δCH_2 values of pyrimidinothiazines IV are 0.06-0.10 ppm lower than those of pyrimidinothiazines V. This phenomenon can be explained by the fact that the dimethylamino group in IV, by increasing the electron density on the azomethine group, promotes an increase in its shielding effect on the adjacent methylene group.

A peak of a molecular ion with m/z 257 (100%), the scheme of the fragmentation of which is in complete agreement with the proposed structure, is observed in the mass spectrum of Va:



One should particularly dwell on the electronic absorption spectra (Table 1). As compared with the spectra of 3-aryl-2H-1,4-benzothiazines [2], they are shifted substantially to the long-wave region (for example, Δλ is 23 nm for Va). A significant bathochromic shift of the long-wave absorption band (by ~40 nm) is also observed when the methoxy group (V) is replaced by a dimethylamino group (IV) in the pyrimidine ring.

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TABLE 1. 3-Aryl-5-R^1-2H-pyrimidino[5,6-b]-1,4-thiazines

Compound	T_{mp} deg C	UV spectrum (in methanol), λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	PMR spectrum (in $CDCl_3$), δ, ppm			N found, %	Empirical formula	N. calc. %	Yield, %
			CH_2	H*	R^1				
IVa	140	384 (8,0), 281 (21,3), 247 (21,7)	3,68	8,16	3,30	20,8	$C_{14}H_{14}N_4S$	20,7	60
IVb	127—128	385 (8,8), 280 (22,3), 250 (18,3)	3,70	8,19	3,27	20,0	$C_{15}H_{14}N_4S$	19,7	50
IVc	131—132	387 (8,5), 285 (18,4), 249 sh.				18,8	$C_{15}H_{16}N_4OS$	18,6	48
IV d	176—177	391 (9,2), 278 (23,6), 253 (22,9)	3,71	8,20	3,31	18,5	$C_{14}H_{13}ClN_4S$	18,4	65
IVe	220 (dec).	421 (9,7), 274 (20,9), 230 sh.				22,2	$C_{14}H_{13}N_5O_2S$	22,0	60
Va	181—182	344 (7,7), 270 (18,2), 231 sh.	3,82	8,40	4,23	16,0	$C_{13}H_{11}N_3OS$	16,3	35
Vb	184—186	349 (9,5), 274 (18,2), 237 (14,1)	3,78	8,37	4,11	15,5	$C_{14}H_{13}N_3OS$	15,5	29
Vd	184—185	350 (8,6), 272 (19,2), 236 (13,9),	4,11	8,44	4,02	14,5	$C_{13}H_{10}ClN_3OS$	14,4	30
Ve	205 (dec.)	364** sh.				18,7	$C_{13}H_{10}N_4O_3S$	18,5	30

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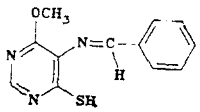
*Proton of the pyrimidine ring.

**The ε value of this compound is not presented because of its insufficient solubility.

TABLE 2. Data from the Calculation of the Planar Model of the



Molecule

Electron transition	Band of UV spectrum	Calc.		Exptl.		Localization of the transition, %					Charge transfer, eV				
		E, eV	f	E, eV	f	S	Pyr	N=C	Ph	Ö	S	Pyr	N=C	Ph	Ö
1	1	3,60	0,76	3,60	0,97	9,1	34,4	33,9	19,0	3,6	−0,16	−0,31	0,37	0,16	−0,06
2		4,25	0,06			6,6	73,9	10,9	3,5	5,1	−0,1	0,01	0,09	0,04	−0,04
3		4,51	0,03			0,5	3,4	10,0	85,9	0,2	−0,005	−0,02	0,1	−0,07	−0,005
4	2	4,93	0,41	4,59	0,88	17,8	47,6	19,7	8,7	6,2	−0,32	0	0,28	0,12	−0,08
5	3	5,20	0,32	5,35	0,35	4,5	18,5	31,1	43,1	2,8	−0,08	0,05	0,36	−0,28	−0,05

Quantum-chemical calculations for a planar model of Va (Table 2) show that the S_0–S_1 electron transition is localized on the S–Pyr–N=C–Ph fragment. According to the calculations, substantial charge transfer from the S atom through the pyrimidine ring to the azomethine bond is observed. This charge transfer is experimentally confirmed, particularly by the electronic effect of substituent R on the position of the long-wave absorption band in the spectrum. Thus acceptor substituents, by favoring transfer of electron density, shift this band bathochromically, while the role of electron-donor substituents is insignificant. It follows from the data in Table 2 that the electron density on the oxygen atom of the R^1 group is decreased, and intensification of the electron-donor properties of substituent $R^1 = N(CH_3)_2$ therefore accordingly gives rise to a bathochromic shift of the long-wave band.

An interesting point that arises in the study of 1,4-thiazines is the question of the existence of an equilibrium between the 2H and 4H tautomers [3]. The IR spectra of KBr pellets and solutions of the compounds in $CHCl_3$ do not contain ν_{N-H} bands at 3200-3400 cm^{-1}. A signal of a CH_2 group is always observed in the PMR spectra of solutions of these compounds in $CDCl_3$ or d_6-DMSO, and a signal of an imino group is not displayed. This makes it possible to conclude that the pyrimidino[4,5-b]-1,4-thiazine derivatives that we synthesized exist primarily in the 2H-tautomeric form.

EXPERIMENTAL

The electronic absorption spectra of ethanol solutions [c = $(2-3)\cdot 10^{-5}$ mole/liter] were recorded with a Specord UV-vis spectrophotometer. The electronic characteristics of the excited states of the Va molecule were calculated by the MO LCAO SCF CI method in the Pariser-Parr—Pople (PPP) variant with the standard set of parameters; an estimate of the contribution of the fragments to the "general molecular" excitation was given for each electron transition with the use of quantitative locality criteria [4] (Table 2). The PMR spectra of solutions in $CDCl_3$ and $(CD_3)_2SO$ were recorded with a Tesla BS-2487-B spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The IR spectra of KBr pellets were obtained with an IR-75 spectrometer. The mass spectrum of Va was recorded with a Varian MAT-212 spectrometer (at an ionizing voltage of 70 eV).

5-Dimethylamino-3-phenyl-2H-pyrimidino[5,6-b]-1,4-thiazine (Va). An equimolar amount (1.0 g) of ω-bromoacetophenone and 0.21 g (25 mmole) of $NaHCO_3$ were added to a solution of 0.85 g (5 mmole) of 6-dimethylamino-5-amino-4-thiopyrimidine in 15 ml of methanol, and the reaction mixture was refluxed for 2 h. The hot solution was filtered and cooled to precipitate 0.81 g (60%) of yellow crystals with mp 140°C (from methanol). Mass spectrum, m/z (%): 257 (100), 256 (33), 242 (16), 227 (12), 200 (27), 199 (11), 169 (17), 141 (16), 104 (10), 103 (45), 97 (6), 89 (10), 77 (29).

The remaining IV and V were similarly obtained.

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