NEW METHOD FOR THE SYNTHESIS OF THE 1,3-THIAZINE SYSTEM.

2-PHENYLAMINO-5,6-DIHYDRO-4H-1,3-THIAZIN-5-ONES

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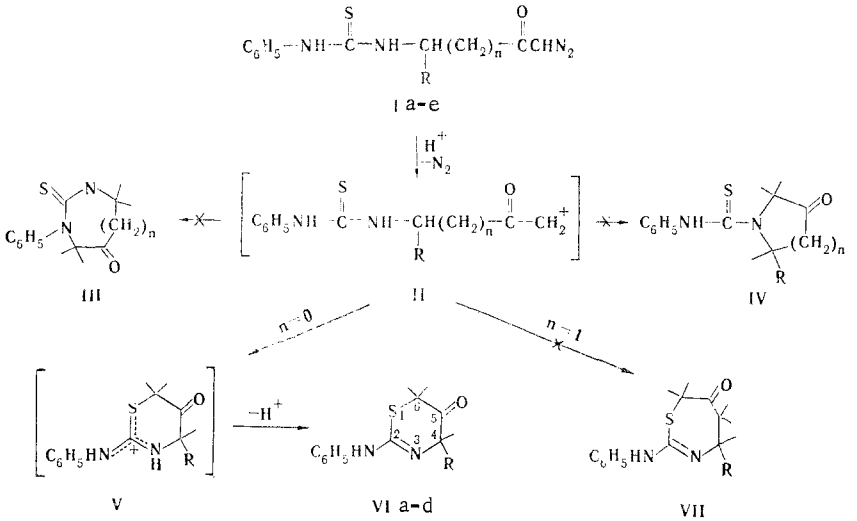
Treatment of N-phenylthioureidoalkyl-α-diazo ketones with acids leads to 2-phenylamino-5,6-dihydro-4H-1,3-thiazin-5-ones.

The 1,3-thiazine system is included in the composition of various biologically active compounds such as cephalosporin antibotics [1] and antimicrobial and antihelminthic preparations [2].

The usual methods for the synthesis of 1,3-thiazines are confined primarily to condensation reactions of thioamides with the appropriate halo derivatives [3, 4].

In order to expand the methods that lead to the 1,3-thiazine system we investigated the possibility of the synthesis of 2-phenylamino-5,6-dihydro-4H-1,3-thiazin-5-one derivatives on the basis of intramolecular cyclization of thioureide derivatives of α-diazo ketones. We recently reported an analogous cyclization in the case of the preparation of N-tosylpyrrolidin-3-ones, which proceeds with the participation of acidic agents [5]. In the reaction of diazo ketones with acids the diazo carbonyl fragment is protonated and an unstable diazonium ion is formed [6]; the latter eliminates a molecule of nitrogen and is converted to a reactive carbonium ion of the II type. Subsequent attack at one of the heteroatoms in the molecule may lead to the corresponding heterocyclic system [7, 8].

In the investigation of analogous transformations in the case of N-phenylthioureidoalkyl-α-diazo ketones (I) we were unable to state *a priori* which of the heteroatoms of the thioureide grouping would undergo cyclization. Carbonium ion II, which is formed under acidic conditions, can be stabilized through the pair of electrons of either the nitrogen atoms or the sulfur atom. Pyrimidine (III) or azetidine (IV) systems should be formed in the case of Ia-d, whereas a diazepine or pyrrolidine system should be formed in the case of Ie. Ring closing at the sulfur atom should lead to 1,3-thiazine (when n = 0) and 1,3-thiazepine (when n = 1) systems.



I, VI a R = H; b R = CH_3; c R = C_2H_5; d R = $CH_2C_6H_5$; I e R = H, n = 1; I a-d n = 0

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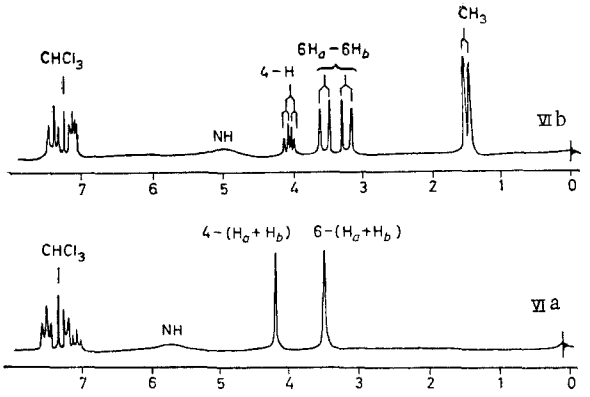

Fig. 1

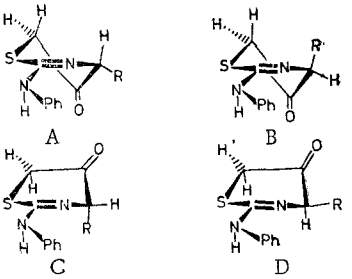

Fig. 2

Fig. 1. PMR spectra of thiazines VIa, b (in $CDCl_3$).

Fig. 2. Possible conformations of 2-phenylamino-5,6-dihydro-4H-1,3-thiazin-5-ones.

The reactions of diazo ketones Ia-e were carried out with a twofold to threefold amount of concentrated sulfuric acid in $CHCl_3$ solution (method A) or in glacial acetic acid (method B) at room temperature. We found that exclusively thiazines VIa-d are formed in high yields when n = 0, whereas cyclization at the nitrogen atoms does not occur at all. This selectivity in the cyclization can be explained by both the greater nucleophilicity of the sulfur atom as compared with both nitrogen atoms and the high stability of cation intermediate V due to the possibility of considerable localization of the positive charge in it. Intramolecular cyclization does not occur when n = 1.

The structure of thiazines VIa-d was proved by the spectral data and the results of elementary analysis (see Tables 1 and 2). Thus intense absorption bands of an NH group at 3130-3200 cm^{-1} and of carbonyl groups at 1710 cm^{-1}, as well as weak bands of stretching vibrations of C=N and C=C bonds at 1580-1610 cm^{-1}, are observed in the IR spectra of VIa-d. The UV spectra of thiazines VIa-d are similar to the spectrum of the previously described isomeric 2-phenylamino-5,6-dihydro-4H-1,3-thiazin-4-one [4]. In addition of signals of five aromatic protons at 7.05-7.32 ppm and a broad signal of an NH proton at 5.57 ppm, two singlets of methylene protons at 4.10 ppm ($4\text{-}H_a$ + $4\text{-}H_b$) and 3.44 ppm ($6\text{-}H_a$ + $6\text{-}H_b$) are observed in the PMR spectrum of VIa (Fig. 1). The introduction of a substituent in the 4 position of the thiazine ring (VIb-d) leads to nonequivalence of the $6\text{-}H_a$ and $6\text{-}H_b$ protons, the signals of which are observed in the form of doublets with geminal spin–spin coupling constants $J_{a,b}$ of 15.4 (VIb), 15.2 (VIc), and 14.85 Hz (VId). The development of nonequivalence of the protons of methylene groups that are remote from an asymmetric center is known [9]; however, this effect has not been described for compounds of the thiazine series.

Thiazines VIa-d can exist in half-chair (A, B) or distorted boat (C, D) conformations (see Fig. 2). However, one cannot form a preference for any of the conformations from the spectral data for VIa-d, although it is known that some derivatives of 1,3-thiazines have a distorted boat conformation [10, 11].

The fragmentation of the molecular ions of thiazines VIa-d under the influence of electron impact is also characteristic (Table 2). The most typical processes are the loss of hydrogen and ejection of ketene from the M^+ and $[M - H]^+$ ions with the subsequent loss of an SH radical. The process $M^+ - RCH{=}C{=}O$ is also observed for VIb-d. The most intense ions are the $[M - CH_2CO]^{+\bullet}$, $PhHN{-}C{\equiv}N^{+\bullet}$ (m/e 118, which is characteristic for the fragmentation of 2-phenylamino-1,3-thiazines [4]), $PhNCSN^{+\bullet}$ (m/e 136), and $PhNCH^+$ (m/e 104).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord IR-75 spectrometer. The UV spectra of solutions of the compounds in methanol were recorded with a Specord UV-Vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Bruker WH-360 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with a Finnigan-3200 mass spectrometer with direct introduction of the samples into the ion souce at an ionizing-electron energy of 70 eV and an emission current

TABLE 1. Characteristics of 2-Phenylamino-5,6-dihydro-4H-1,3-thiazin-5-ones (VI)

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm multiplicity, J, Hz (No. of protons)	N found, %	Empirical formula	N calc., %	Yield, %
VIa	134—135	208 (4,18), 229 (3,83) i*, 269 (3,90)	3180, 3130 (NH), 1710 (C=O), 1610 (C=N), 1580 (C=C)	3,44, s (2H); 4,10, s (2H); 5,57, br s† (1H); 7,05—7,32, m (5H)	13,7	$C_{10}H_{10}N_2OS$	13,6	A. 61 B. 80
VIb	138—140 (dec)	207 (4,22), 228 (3,91) i 272 (4,02)	3180, 3140 (NH), 1710 (C=O), 1610 (C=N), 1580 (C=C)	1,47, d (3H); 4,08, q 6,6 (1H); 3,37and3,54, dd, 15,4 (2H); 5,00 br s (1H); 7,04—7,31, m (5H)	12,8	$C_{11}H_{12}N_2OS$	12,7	A. 57 B. 82
VIc	102—103	207 (4,14), 230 (3,91) i 272 (3,91)	3180, 3140 (NH), 1710 (C=O), 1610 (C=N), 1580 (C=C)	1,02, t 7,7 (3H); 1,91, m (2H); 3,38and3,48, dd, 15,2 (2H); 3,89, q 6,8 (1H); 5,0, brs (1H); 7,03—7,30, m (5H)	12,1	$C_{12}H_{14}N_2OS$	12,0	A. 51 B. 80
VId	94—96	208 (4,37), 231 (3,92) i 276 (4,04)	3200, 3160 (NH), 1700 (C=O), 1575 (C=C)	3,05, m (2H); 3,39, m 14,85 (2H); 4,21, q 5,8 (1H); 5,0, brs (1H); 6,92—7,34, m (10H)	9,5	$C_{17}H_{16}N_2OS$	9,5	A. 70 B. 85

*The abbreviation "i" indicates an inflection.
†The abbreviation "br" indicates broad.

TABLE 2. Mass Spectra of VI

Compound	m/e values (relative intensities, %)*
VIa	207 (14), 206 (87), 205 (42), 178 (5), 177 (38), 166 (5), 165 (12), 164 (100), 163 (35), 150 (11), 145 (5), 137 (8), 136 (56), 135 (38), 132 (16), 131 (69), 119 (8), 118 (39), 117 (5), 110 (9), 109 (8), 106 (23), 105 (10), 104 (75), 103 (12), 92 (8), 91 (15), 78 (15), 77 (82), 76 (12)
VIb	222 (6), 221 (13), 220 (77), 219 (5), 192 (6), 191 (12), 180 (6), 179 (13), 178 (84), 177 (69), 164 (5), 163 (31), 150 (8), 149 (11), 146 (14), 145 (74), 138 (5), 137 (15), 136 (57), 135 (89), 134 (5), 120 (16), 119 (12), 118 (33), 117 (9), 110 (12), 109 (9), 105 (10), 104 (88), 103 (11), 93 (37), 92 (13), 91 (20), 86 (19), 85 (7), 83 (8), 78 (16), 77 (100), 76 (13)
VIc	235 (12), 234 (73), 193 (12), 192 (87), 191 (16), 179 (5), 178 (12), 177 (100), 173 (6), 164 (17), 160 (6), 159 (44), 150 (5), 149 (11), 145 (9), 137 (14), 136 (47), 135 (85), 134 (10), 133 (10), 132 (17), 131 (8), 119 (15), 118 (29), 117 (11), 110 (7), 109 (6), 105 (6), 104 (54), 103 (7), 100 (6), 93 (33), 92 (15), 91 (15), 78 (9), 77 (71), 76 (8)
VId	297 (9), 296 (42), 254 (26), 221 (18), 207 (5), 206 (12), 205 (51), 179 (5), 178 (5), 177 (40), 173 (5), 136 (20), 135 (40), 131 (7), 130 (15), 128 (12), 119 (33), 118 (18), 117 (6), 105 (9), 104 (100), 103 (18), 102 (13), 93 (7), 92 (9), 91 (32), 78 (9), 77 (39)

*The peaks with intensities less than 5% and m/e values less than 76 are not presented.

of 0.4 μA. The purity of the substances was monitored by thin-layer chromatography (TLC) in an ethyl acetate—benzene system on Silufol UV-254 plates.

2-Phenylamino-5,6-dihydro-4H-1,3-thiazin-5-ones (VIa-d, General Method). A) A 0.1-mole sample of acetic acid was added at 20°C to 0.03 mole of diazo ketone I. Vigorous nitrogen evolution and gradual dissolving of the ketone were observed. After 1 h, the excess acetic acid was evaporated *in vacuo*, and the residue was neutralized with a saturated aqueous solution of sodium bicarbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was separated and dried over Na_2SO_4. The chloroform was removed, and the residue was washed with cold ether and dried.

B) A 2-mmole sample of diazo ketone I was dissolved in 6 ml of chloroform, and 400 mg (4 mmole) of concentrated H_2SO_4 was added to the solution. The mixture was shaken vigorously. Nitrogen evolution and decolorization of the solution were observed. After 15-20 min, the mixture was neutralized with sodium bicarbonate and treated with 3 ml of water. The chloroform layer was separated and dried over Na_2SO_4, the chloroform was removed, and the residue was washed with cold ether and dried.

The compounds obtained by methods A and B were chromatographically individual and did not require further purification. Their properties are presented in Tables 1 and 2.

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