SPIROCYCLIC BETAINES OR 2-AMINO-Δ^2-1,3,4-THIADIAZOLINE-5-ACETIC ACID AND THEIR REARRANGEMENT IN ACETIC ANHYDRIDE

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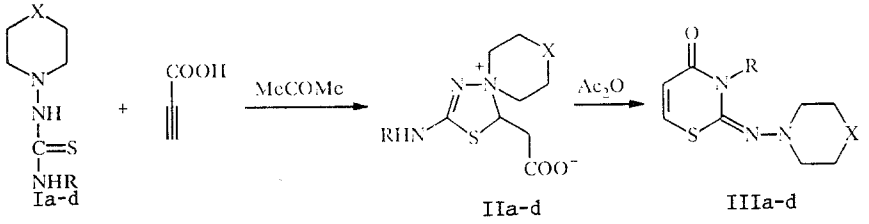
Reaction of N-(1-pyrrolidinyl)-, N-(1-piperidinyl)-, N-(4-morpholinyl)-, and N-(1-hexahydroazepinyl)-thioureas with propiolic acid gives hetero-N-spiro-4'-(2'-amino-Δ^2-1',3',4'-thiadizolin-4'-io-5'-acetates), which rearrange in acetic anhydride to 2-(N-heteryl)imino-2,3-dihydro-4H-1,3-thiazin-4-ones.

We have previously synthesized Δ^2-1,3,4-thiadizolin-5-acetic acid betaines which rearrange in acetic anhydride to 1,3-thiazin-4-ones [1]. The aim of this work was to prepare similar spirocyclics in which the spiro atom is the N_4 atom of 1,3,4-thiadiazoline and to investigate the opening of the spirocycle in acetic anhydride.

The starting thiosemicarbazides Ia-d were prepared from the corresponding N-amino heterocycles and isothiocyanates as reported in [2]. The reaction of the thiosemicarbazides with propiolic acid was carried out in acetone, which partially suppresses side reactions relating to opening of the $C_{(3)}-S$ bond of the intermediate isothiosemicarbazide and formation of β,β'-thiodiacrylates. The physicochemical parameters of the spirocycles IIa-d do not differ significantly from the 4,4-dimethyl-Δ^2-1,3,4-thiadiazolinium analogs [1] (Tables 1 and 2).



I-IIIa R = $CH_2CH{=}CH_2$, X = −; b, c, d R = Ph; b X = CH_2; c X = 0; d X = CH_2CH_2

Rearrangement of IIa-d in acetic anhydride gives 2,3-dihydro-4H-1,3-thiazin-4-ones IIIa-d. Products of the fission of the N^+-C_α azacyclanes were not observed. It should be noted that opening of the spirocycles at the $N_{(4)}-C_{(5)}$ bond of the 1,3,4-thiadiazoline ring occurs no more readily than opening of the 4,4-dimethyl analogs.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90 instrument in $CDCl_3$, DMSO-D_6, or D_2O solvent with TMS or DSS internal standards. IR spectra were taken on a Perkin−Elmer 580B in Nujol. Reaction monitoring and product purities were monitored by TLC using Silufol UV-254 plates and hexane−ethyl acetate (2:1) or chloroform−methanol−water (8:6:1) as eluents.

N-Amino heterocycles were obtained by nitrosation of the corresponding azacyclanes with subsequent reduction of the nitroso group by zinc in hydrochloric acid.

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TABLE 1. Parameters for Compounds Synthesized

Compound	Empirical formula	Mp, °C	IR spectrum, cm^{-1}	Yield, %
IIa	$C_{11}H_{17}N_3O_2S$	153...154	3180, 1608, 1585	62
IIb	$C_{15}H_{19}N_3O_2S$	205...207 (decomp.)	3200, 1600, 1583	70
IIc	$C_{14}H_{17}N_3O_2S$	200...202 (decomp.)	3200, 1600, 1564	69
IId	$C_{16}H_{21}N_3O_2S$	170...172 (decomp.)	3225, 1614, 1590	72
IIIa	$C_{11}H_{15}N_3OS$	62...63	1672, 1600, 818	57
IIIb	$C_{15}H_{17}N_3OS$	136...138	1698, 1607, 808	67
IIIc	$C_{14}H_{15}N_3OS$	125...127	1690, 1607, 818	66
IIId	$C_{15}H_{17}N_3OS$	106...107	1674, 1609, 813	66

TABLE 2. PMR Spectra of Spirocycles IIa-d (in D_2O)

Compound	Chemical shift, δ, ppm					Spin–spin coupling, Hz		
	$-(CH_2)_2 \times (CH_2)_2-$	RNH	H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}
IIa	2,0...2,4 (4H, m); 3,4...3,75 (4H, m)	3,8...3,95 (2H, m NCH_2); 5,0...5,3 (2H, m); 5,6...6,1 (1H, m, =CH)	2,78	3,19	5,63	15,0	10,0	4,0
IIb	1,4...2,3 (6H, m); 3,6...3,85 (4H, m)	7,0...7,75 (5H, m)	2,87	3,25	5,54	16,0	11,0	4,0
IIc	3,6...4,0 (4H, m); 4,0...4,35 (4H, m)	7,1...7,6 (5H, m)	2,93	3,33	5,69	16,0	10,0	4,0
IId*	1,35...2,2 (8H, m); 3,35...3,75 (4H, NH)	3,77 (2H, m); 4,95...5,3 (2H, m); 5,5...6,0 (1H, m); 8,64 (1H, m)	2,47	2,93	5,49	14,0	11,5	4,0

*Spectrum recorded in DMSO-D_6.

TABLE 3. PMR Spectra of 1,3-Thiazin-4-ones IIIa-d (in DMSO-D_6)

Compound	R	$-(CH_2)_2 \times (CH_2)_2-$	C(5)-H	C(6)-H
IIIa	4,45...4,6 (2H, m); 4,9...5,2 (2H, m); 5,55...6,0 (1H, m)	1,6...1,85 (4H, m); 2,55...2,8 (4H, m)	6,18 (1H, d)*	7,60 (1H, d)
IIIb	7,1...7,5 (5H, m)	1,32 (2H, m; 1,54 (4H, m); 2,41 (4H, t, $N(CH_2)_2$)	6,32 (1H, d)	7,74 (1H, d)
IIIc**	7,0...7,5 (5H, m)	2,5....2,65 (2H, m); 3,2...3,35 (2H, m); 3,6...3,8 (4H, m)	6,33 (1H, d)	7,30 (1H, d)
IIId	7,0...7,5 (5H, m)	1,35...1,65 (8H m); 2,4...2,7 (4H, m)	6,24 (1H, d)	7,67 (1H, d)

*J_{HH} = 10 Hz for IIIa-d.
**Spectrum recorded in $CDCl_3$.

Elemental analytical data for the compounds synthesized agreed with those calculated.

Pyrrolidine-1-spiro-4'-(2'-allylamino-Δ^2-1',3',4'-thiadiazolin-4'-io-5'-acetate) (IIa). Propiolic acid (0.77 g, 11 mmoles) was added to thiosemicarbazide Ia (1.85 g, 10 mmoles) in acetone (30 ml) and refluxed with stirring for 6 h (monitored by TLC). The mixture was cooled to 5-10°C and the crystalline precipitate filtered and washed with acetone. An additional

portion separated from the filtrate which was evaporated, treated with water (10 ml), and filtered. After evaporation of water, the residue was crystallized from ethanol, filtered, and dried to give IIa (1.33 g, 62%).

Similarly, Ib gave **piperidine-1-spiro-4′-(2′-phenylamino)-Δ^2-1′,3′,4′-thiadiazolin-4′-io-5′-acetate (IIb)** and Ic gave **morpholine-4-spiro-4′-(2′-phenylamino-Δ^2-1′,3′,4′-thiadiazolin-4′-io-5′-acetate (IIc)**.

Id gave **hexahydroazepin-2-spiro-4′-(2′-phenylamino-Δ^2-1′,3′,4′-thiadiazolin-4′-io-5′-acetate (IId)**.

2-(1-Pyrrolidinyl)-imino-3-allyl-2,3-dihydro-4H-1,3-thiazin-4-one (IIIa). Acetic anhydride (10 ml) was added to betaine IIa (2.55 g, 10 mmoles). The mixture was refluxed for 2.5 h (TLC monitoring) and evaporated in vacuo. The residue was dissolved in ethyl acetate and filtered through aluminum oxide. The solution was refluxed with activated charcoal, filtered, the ethyl acetate evaporated, and the residue crystallized from isopropanol and dried to give thiazine IIIa (1.35 g, 57%).

Similarly IIb gave **2-(1-piperidinyl)imino-3-phenyl-2,3-dihydro-4H-1,3-thiazin-4-one (IIIb)**, IIc gave **2-(4-morpholinyl)imino-2,3-dihydro-4H-1,3-thiazin-4-one (IIIc)**, and IId gave **2-(1-hexahydroazepinyl)imino-3-phenyl-2,3-dihydro-4H-1,3-thiazin-4-one (IIId)**.

Parameters for the compounds prepared are given in Tables 1-3. The most distinctive IR bands are given in Table 1.

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