RECYCLIZATION OF 2-AMINO-4,4-DIMETHYL-Δ^2-1,3,4-THIADIAZOLIN-4-IO-5-ACETATES INTO 2-DIMETHYLHYDRAZONO-2,3-DIHYDRO-4H-1,3-THIAZIN-4-ONES

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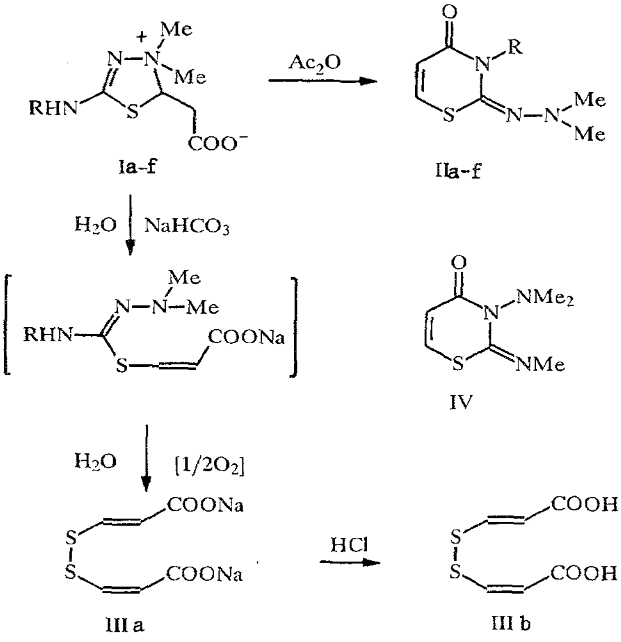
2-Amino-4,4-dimethyl-Δ^2-1,3,4-thiadiazolinio-5-acetates were found to recyclize into 2-dimethylhydrazono-2,3-dihydro-4H-1,3-thiazin-4-ones. The similar mass fragmentation of these compounds is explained by the occurrence of a rearrangement under electron impact which is analogous to the chemical recyclization thiadiazolinioacetates.

A characteristic of some amino acid betaines is reaction of the carboxyl group with trifluoroacetic anhydride to give decarboxylation and diacylation of the α-carbon of the amino acid [1]. To study the applicability of this reaction to the betaines Ia-f we had prepared [2], the latter were boiled in acetic anhydride for 1-4 h. However the compounds isolated appeared to be products of the rearrangement of 2-amino-4,4-dimethyl-Δ^2-1,3,4-thiadiazolin-4-io-5-acetates. It was established by ^1H and ^{13}C NMR and mass spectroscopy that the reaction products are the 2-dimethylhydrazono-2,3-dihydro-4H-1,3-thiazin-4-ones IIa-f.



I, IIa R = H; bR = Me; cR = CH_2=CH-CH_2;d R = p-Ph; eR = C_6H_5; fR = $C_{16}H_{15}$(adamantyl)

It is known that N-methyl-3-pipecolinic acid rearranges into a lactam containing an α-exomethylene group under the influence of acetic anhydride [3]. It was established that the reaction occurred via zwitterionic structure of the amino acid. The β-proton relative to the nitrogen atom is removed at the same time as the acetate ion is formed [4].

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TABLE 1. ^{1}N NMR Spectra of the 1,3-thiazin−4−ones IIa−f*

Compound	δ, ppm (in DMSO d_6)			
	R	$N(CH_3)_2$	=CHCO	=CHS
IIa**	10,0	2,64 and 2,67	6,34	7,23
IIb	3,28	2,41	6,24	7,76
IIc	4,5...4,6 (NCH_2), 4,95...5,25 (=CH_2), 5,6...6,05 (=CH)	2,39	6,22	7,66
IId	0,92 (3H, t), 1,1...1,8 (4H, m), 4,08 (2H, t)	2,44	6,17	7,08
IIe	7,00...7,48 (C_6H_5)	2,24	6,30	7,73
IIf	1,55...1,80 (6H, м), 1,85...2,25 (9H,)	2,85	6,21	7,00

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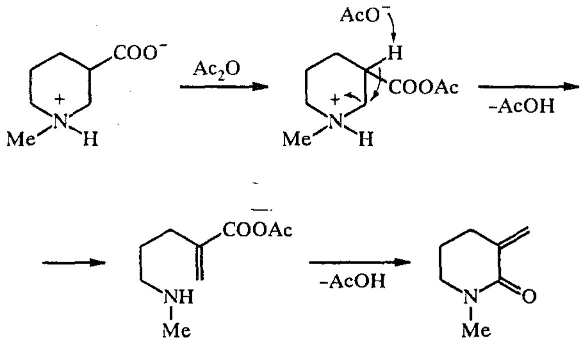
*$^{3}J_{HH}$ ≈ 10 Hz for IIa−f.

**Spectrum recorded in $CDCl_3$.

TABLE 2. Characteristic Ions in the Mass Spectra of Compounds Ia−f

Compound	m/z (I_{rel}, %)			
	$[M-H_2O]^+$	$[M-H_2O-NC_2H_4]^+$	$RNCNN(CH_3)_2$	other (> 10%)
Ia	171 (27)	129 (34)	85 (39)	87 (18), 86 (23), 85 (39), 61 (34), 60 (64), 59 (100), 58 (32), 57 (14), 44 (93), 43 (78), 42 (52)
I	185 (69)	143 (20)	99 (36)	128 (10), 75 (11), 60 (82), 59 (100), 58 (75), 57 (13), 56 (13), 45 (51), 44 (75), 43 (98), 42 (40)
I	211 (5)	169 (17)	125 (6)	153 (24), 60 (100), 59 (71), 58 (14), 45 (35), 44 (33), 43 (28), 42 (19), 41 (26)
I	247 (26)	205 (14)	161 (18)	179 (12), 136 (16), 118 (14), 93 (21), 77 (37), 65 (18), 60 (100), 59 (81), 58 (39), 51 (16), 45 (40), 44 (31), 43 (79), 42 (21)
I	—	263 (2)	219 (48)	135 (100), 119 (56), 107 (99), 103 (36)



Ac = MeCO

It can be proposed that zwitterionic structure, necessary for recyclization, in the betaines we synthesized makes it possible for the reaction to occur via the mechanism described for the β−amino acid. Compounds Ia−f may be described as derivatives of cyclic β−amino acids.

We noted that thiazines IIa−f were not produced when compounds Ia−f were boiled in glacial acetic acid. Ring opening did not occur when compounds Ia−f were heated in hydrochloric acid. The chlorides were formed instead [2]. It was expected, by analogy with the scission of quaternary ammonium salts in the Hofmann reaction, that possibly α,β−unsaturated compounds would be formed as intermediates in the recyclization of betaines Ia−f in the presence of base. In fact, salts of *E,Z*−dithiodiacrylic acid were formed when compound Ib was heated with aqueous sodium hydrogen carbonate or treated with aqueous base at room temperature.

So scission of the $N_{(4)}-C_{(5)}$ bond occurred in both acetic anhydride and in basic media. The difference is that in acetic anhydride the intermediate acyclic isothiosemicarbazide cyclizes to the thiazinone II, whereas in the presence of base the

TABLE 3. Characteristic Ions in the Mass Spectra of the 2-Dimethylhydrazono-2,3-dihydro-4H,1,3-thiazin-4-ones IIa-f

Compound	m/z (I_{rel}, %)				
	M^+	$[M-NC_2H_4]^+$	$[M-C_2H_5N_2]^+$	$RNCNN(CH_3)_2$	other (> 10%)
IIa	171 (100)	129 (11)	114 (11)	85 (43)	128 (16), 87 (23), 86 (16), 58 (52), 44 (61), 43 (83), 42 (29)
IIb	185 (91)	143 (5)	128 (13)	99 (44)	58 (80), 56 (13), 43 (100), 42 (22)
IIc	211 (20)	169 (15)	154 (10)	125 (13)	196 (15), 168 (22), 167 (13), 153 (85), 141 (13), 128 (10), 99 (52), 87 (13), 86 (13), 84 (100), 83 (10), 82 (10), 81 (20), 59 (25), 58 (25), 45 (17), 44 (25), 43 (50), 42 (30), 41 (30)
IIe	247 (62)	205 (15)	—	161 (38) —	118 (15), 77 (30), 69 (10), 58 (91), 57 (15), 55 (13), 43 (100), 42 (10), 41 (10)
IIf	—	263 (16)	—	—	136 (12), 135 (100), 107 (17), 102 (12), 93 (35), 92 (10), 91 (14), 81 (14), 79 (35), 77 (16), 67 (15), 55 (12), 43 (16), 41 (14)

$C_{(3)}-S$ bond of the isothiosemicarbazide is broken with subsequent formation of dithiodiacrylic acid salt as a result of oxidation of the mercapto group by aerial oxygen.

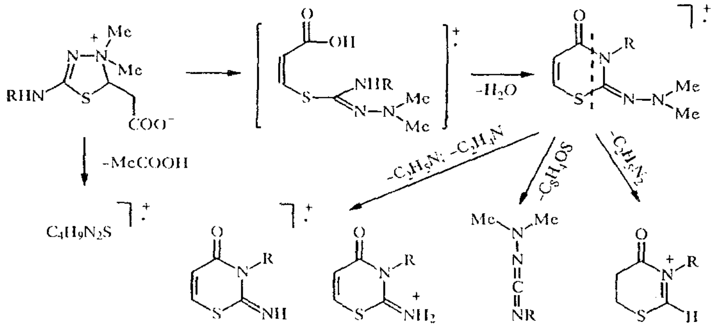
The 1,3-thiazin-4-one ring systems of compounds IIa-f are relatively easily analyzed by ^1H NMR spectroscopy (Table 1). The presence of the endocyclic vinyl fragment is confirmed by the vicinal coupling $^3J_{H,H} \sim 10$ Hz, which is characteristic of *cis*-protons of a vinyl system. However it is not possible to decide between structures II and IV on the basis of the chemical shifts of the dimethylamino groups (2.24-2.85 ppm), so the ^{13}C NMR spectrum of compound IIb ($R = CH_3$) was analyzed. The following couplings were revealed by selective decoupling from the NCH_3 protons: $^3J_{C(2)H(6)} = 7.7$ Hz, $^3J_{C(4)H(6)} = 11.3$ Hz, and $^2J_{C(4)H(5)} = 2.1$ Hz. The presence of structure II is confirmed by the observation of spin-spin coupling between the NCH_3 protons and both $C_{(4)}$ and $C_{(2)}$.

The following characteristic stretching vibrations were observed in the IR spectra of the thiazinones IIa-f (Nujol mulls): $C=O$ 1672-1680 cm^{-1}, $C=N$ 1600-1607 cm^{-1}, and $C=C$ 1550-1560 cm^{-1}.

The rearrangement of betaines Ia-f into thiazinones was also confirmed by mass spectrometry (Table 2). The betaines do not give molecular ions in the mass spectra because of their high polarity and low volatility. The presence of the $[M - H_2O]^+$ peak shows that a carboxylic acid as an intermediate in the gas phase, which then fragments in a characteristic manner for such a compound. In essence the $[M - H_2O]^+$ ion radical is the analog of the molecular ion of tazinone and further fragmentation occurs analogously.

Thus the gas phase decomposition of betaines Ia-f initiated by electron impact has similarities to the chemical conversion to the thiazinones II.

The mass spectra of the thiazinones (Table 3) show that they are highly stable to electron impact. The intensity of the molecular ion peak varies from 20-100% depending on the nature of R. The formation of the ions $[M-C_2H_5N]^+$ and $[M - C_2H_5N_2]^+$ with hydrogen rearrangement in the molecular ion (see scheme). The latter is also characteristic for the mass fragmentation 2-dimethylhydrazonothiazolidinones [5]. Bond scission in the thiazine ring occurs with retention of the charge on the nitrogen containing part of the molecule, $[RN=CNN(CH_3)_2]^+$.



A characteristic difference between the mass fragmentation pattern of the betaines Ia – f and that of the thiazines IIa – f is the formation of the ions $[M - CH_3COOH]^+$ which results from scission of the side chain. The peak with *m/z* 60 (CH_3COOH) has maximum intensity.

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^{1}H NMR spectra were recorded with a Bruker WH – 90 (90 MHz) instrument in $CDCl_3$, DMSO – d_6, or D_2O with TMS or DSS as internal standard. IR spectra were obtained in Nujol mulls with a Perkin Elmer 580 B spectrophotometer. Mass spectra were recorded with an AEI MS – 50 with an ionizing voltage of 70 eV and an ionizing chamber temperature of 200°C. The course of the reactions and the purity of products were monitored by TLC on Silufol UV – 254 strips with 2:1 hexane – ethyl acetate or 8:6:1 chloroform – methanol – water as eluents.

Elemental analyses of the compounds synthesized agreed with calculated values.

2 – Dimethylhydrazono – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IIa, $C_6H_9N_3OS$) (General method). Compound Ia (1.89 g, 10 mmol) was boiled for 3 h in acetic anhydride (20 ml). The reaction was monitored by TLC with ethyl acetate as eluent. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and filtered through aluminum oxide. The filtrate was boiled with activated charcoal, filtered, the solvent removed under reduced pressure, and the residue recrystallized from isopropanol to give IIa (1.25 g, 73 %), m.p. 179 – 180°C.

2 – Dimethylhydrazono – 3 – methyl – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IIb, $C_7H_{11}N_3OS$) was obtained analogously from Ib. Yield 86%, m.p. 90 – 91°C. ^{13}C NMR spectrum (DMSO – D_6): 30.22 (NCH_3), 46.58 ($N(CH_3)_2$, 115.74 ($C_{(5)}$), 138.25 $C_{(6)}$, 156.77 ($C_{(2)}$), and 161.14 ppm ($C_{(4)}$).

2 – Dimethylhydrazono – 3 – allyl – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IIc, $C_9H_{13}N_3OS$) was obtained analogously from Ic, but crystallized only after column chromatography on silica gel with ethyl acetate eluent. Yield 76%, m.p. 39 – 40°C.

2 – Dimethylhydrazono – 3 – *n* – butyl – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IId, $C_{10}H_{17}N_3OS$) was obtained as a colorless oil even after chromatographic purification. Yield 63%.

2 – Dimethylhydrazono – 3 – phenyl – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IIe, $C_{12}H_{13}N_3OS$). Yield 77%, m.p. 147 – 148°C.

2 – Dimethylhydrazono – 3 – adamantyl – 2,3 – dihydro – 4H – 1,3 – thiazin – 4 – one (IIf, $C_{16}H_{23}N_3OS$). Yield 73%, m.p. 135 – 136°C.

Reaction of betaine Ib with sodium hydrogen carbonate. Betaine Ib (1.0 g, 5 mmol) and sodium hydrogen carbonate (0.7 g) were dissolved in water (10 ml) and boiled for 30 min. The solvent was evaporated and the residue treated with ethanol to give disodium β,β' – ((*E,Z*) – dithiodiacrylate IIIa (0.8 g, 63%), m.p.240°C (dec.). ^{1}H NMR spectrum (D_2O): 5.95 and 7.11 (1H, d, $J = 10$ Hz (*Z*) – (CH=CH)), 6.07 and 7.42 ppm (1H, d, $J = 15.5$ Hz, (*E*) – (CH=CH)).

Treatment of IIIa with dilute hydrochloric acid gave β,β' – ((*E,Z*) – dithiodiacrylic acid IIIb, m.p. 250°C (dec.). ^{1}H NMR spectrum (DMSO – d_6): 5.78 and 6.96 (1H, d, $J = 9.5$ Hz (*Z*) – (CH=CH)), 5.98 and 7.49 ppm (1H, d, $J = 15$ Hz (*E*) – (CH=CH)).

Reaction of Betaine Ib with Potassium Hydroxide. Betaine Ib (1.0 g, 5 mmol) was dissolved in water (40 ml) and potassium hydroxide solution (3 ml, 15%) was added. The mixture was stirred at 20°C for 8 h. The solution was neutralized with hydrochloric acid and evaporated to dryness. The residue was treated with acetonitrile, filtered, and the filtrate evaporated to give IIIb (0.4 g, 60%).

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