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DISPROPORTIONATION OF 6,8-DIALKYL-3-THIA-2,4,6,8-TETRAAZABICYCLO[3,3,0]OCTAN-7-ONE 3,3-DIOXIDES UNDER CONDITIONS OF ACID HYDROLYSIS AND ACETYLATION*

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Acid hydrolysis and acetylation of 6,8-dialkyl-3-thia-2,4,6,8-tetraazabicyclo[3,3,0]octan-7-one 3,3-dioxides have been studied. 6,8-Dialkyl-3-thia-2,4,6,8-tetraazabicyclo[3,3,0]octan-7-one 3,3-dioxides disproportionate to 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) and sulfamide when treated with acid at pH 1 or with acetyl chloride. The kinetics of the disproportionation have been studied.

Keywords: 4,4'-sulfonyldiiminobis(1,3-dialklylimidazolin-2-ones), 3-thia-2,4,6,8-tetraazabicyclo[3.3.0]-octan-7-one 3,3-dioxides, acetylation, disproportionation, acid hydrolysis.

6,8-Dialkyl- and 2,4,6,8-tetraalkyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxides, the monosulfoanalogs of 2,4-dialkyl- and 2,4,6,8-tetraalkyl-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones, have been obtained previously [2].

2,4,6,8-Tetraazabicyclo[3.3.0]octan-3,7-diones are known to be quite stable to acid hydrolysis. For example, mebikar (2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione) is completely hydrolyzed only after 51 h when refluxed in 25% sulfuric acid. The main products of hydrolysis of mebikar are 1,3-dimethylurea and 1,3-dimethylhydantoin [3].

The dioxides **1a-d** are completely hydrolysed in 12 min to 5 h under analogous conditions. The main products from the hydrolysis of these compounds are analogous to those from mebikar and have been identified as the corresponding 1,3-dialkylhydantoins **2** and sulfamides **3** (scheme 1).

Under milder conditions, pH 1 and 60°C, dioxides **1a** and **1b** do not undergo hydrolysis but instead disproportionate to the 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **4a** and **4b** and the sulfamide **3a**. Increase in the acidity of the medium and increase in the temperature leads to hydrolysis of compounds **4** to sulfamide.

Treatment of dioxides **1a** and **1b** with acetyl chloride also gave products **4a** and **4b**. Apart from compound **4b**, a small amount of N-(1,3-diethyl-2-oxoimidazolidin-4-ylidenaminosulfonyl)acetamide (**5**) (Scheme 1) was isolated from the reaction mixture.

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* For preliminary report see [1].

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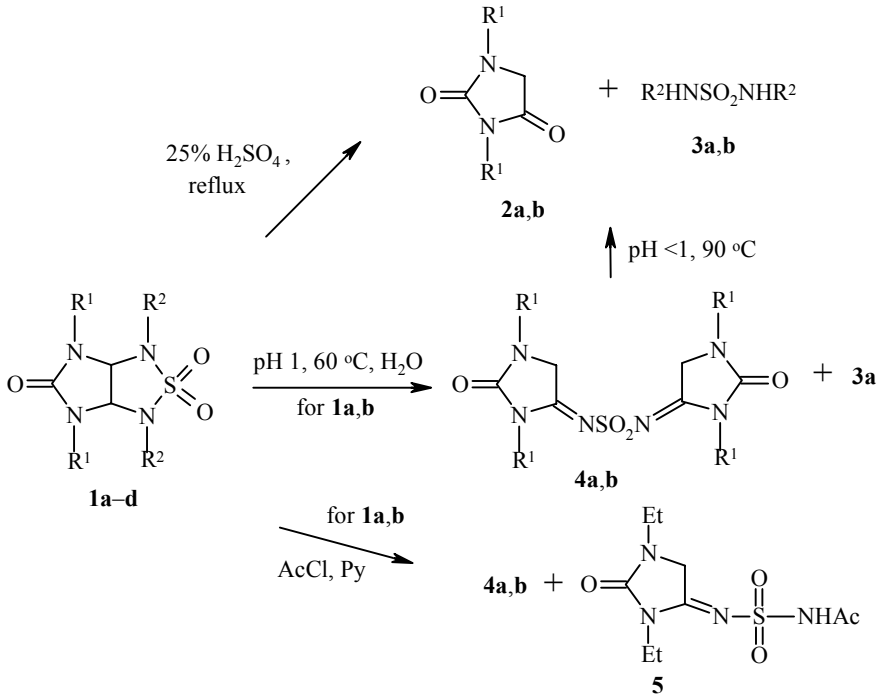
Scheme 1



1 a R^1 = Me, R^2 = H; **b** R^1 = Et, R^2 = H, **c** R^1 = R^2 = Me; **d** R^1 = Et, R^2 = Me; **2**, **4 a** R^1 = Me; **b** R^1 = Et; **3 a** R^2 = H, **b** R^2 = Me

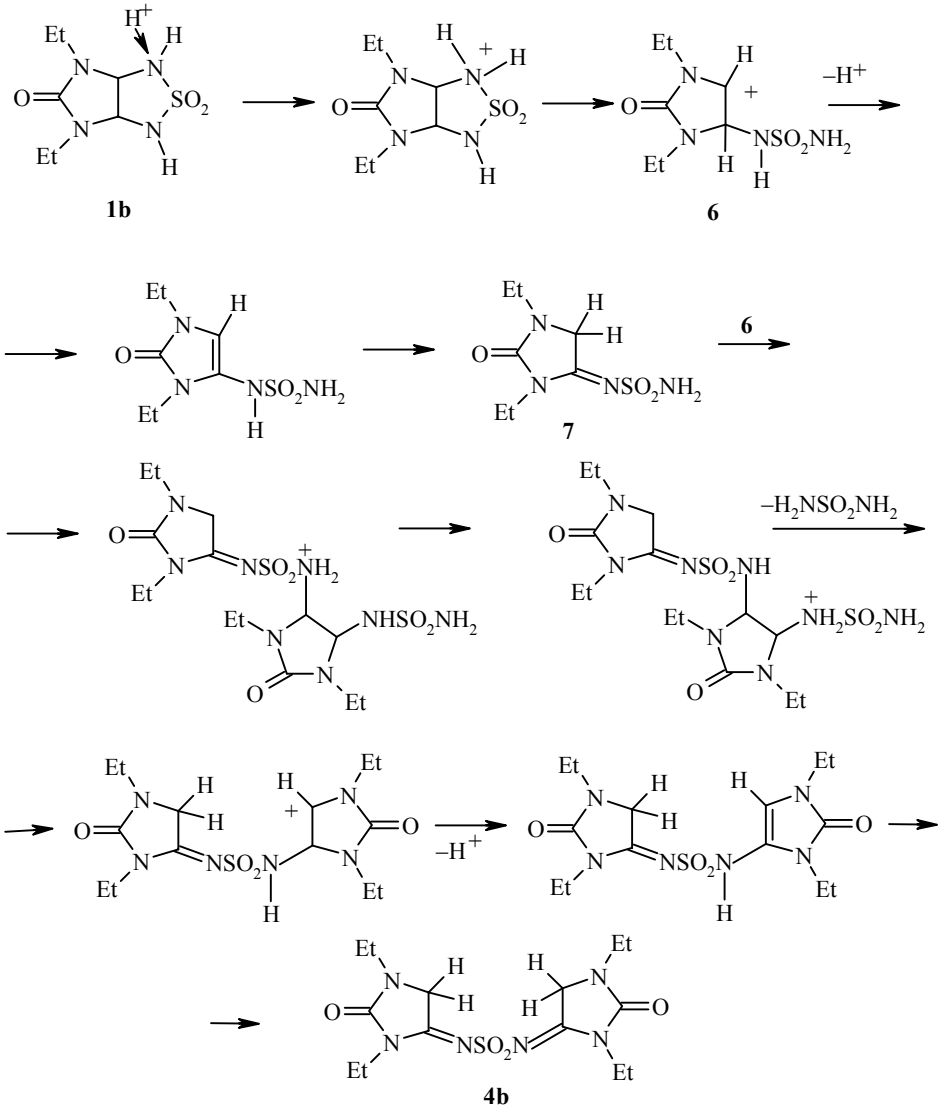
By analogy with the scheme for the formation of products **4** from 4,5-dihydroxyimidazolidin-2-ones and sulfamide in acid media [4], the disproportionation of 6,8-dialkyl-3-thia-2,4,6,8-tetrazaazabicyclo[3.3.0]octan-7-one 3,3-dioxides may be represented by scheme 2, using compound **1b** as an example.

The reactions begin with electrophilic attack by the acid proton on a nitrogen atom of the sulfamide unit of compound **1b**, which leads to ring opening with formation of the carbocation **6**. Deprotonation of **6** leads to the formation of a double bond and then to the intermediate 4-aminosulfonylimino-1,3-diethylimidazolidin-2-one (**7**). Compound **7** undergoes electrophilic attack by the carbocation **6** at the free amino group. The product then loses the sulfamide unit and is deprotonated to form a second double bond in the molecule of the final product **4b**.

Treatment of compounds **1a** and **1b** with acetyl chloride evidently causes scission of the ring with the sulfamide fragment analogously to the reaction with acid to give the acetyl derivative of the carbocation **6** in the first step. Then the proton from the acid formed during acetylation catalyses the conversion **1b** → **4b** according to Scheme 2. That some of the product **4b** is formed from the N-acyl derivative of carbocation **6** by a scheme analogous to Scheme 2 is not excluded.

To confirm the proposed schemes we have obtained some kinetic characteristics of the disproportion of compound **1b** in acidic media. The course of the reaction was followed by ^{1}H NMR in DMSO at 30°C in the presence of trifluoroacetic acid (0.125 mol/l). The rate of conversion of the dioxide **1b** can be judged by the decrease in the integrated intensity of the singlet (δ 5.31 ppm) of the protons of the CH–CH unit. The singlet due to the protons of the CH_2 group in product **4b** at 4.47 ppm appears almost immediately and its intensity increases with time. We also succeeded in detecting another singlet at 4.58 ppm, the intensity of which scarcely changes during the whole reaction time, but it does pass through a maximum. This signal can be assigned to the protons of the CH_2 group of the intermediate iminoimidazolidinone **7** (see Table 1).

Scheme 2



The process can be represented by the following simple scheme:

$$\mathbf{1} \xrightarrow{k_1} \mathbf{6}$$

$$\mathbf{6} \xrightarrow{k_2} \mathbf{7}$$

$$\mathbf{7} + \mathbf{6} \xrightarrow{k_3} \mathbf{4b} + H_2NSO_2NH_2$$

The following equations may be obtained by use of the method of stationary concentrations (k_1[**1b**] = k_2[**6**]):

TABLE 1. Dependence of the Change in Concentration (k) of Compounds **1b**, **7**, and **4b** with Time (τ) in the Presence of CF_3COOH at 30°

τ, min	k, mol/l		
	1b	**7**	**4b**
0	0.123	0	0
10	0.111	0.0043	0.0077
20	0.103	0.0048	0.0151
30	0.098	0.0053	0.0203
40	0.089	0.0055	0.0281
50	0.081	0.0050	0.0360
60	0.072	0.0044	0.0465
90	0.059	0.0046	0.0592
120	0.047	0.0049	0.0711
130	0.044	0.0035	0.0754

$$-d[\mathbf{1b}]/dt = k_1[\mathbf{1b}] \quad (1)$$

$$d[\mathbf{7}]/dt = k_1[\mathbf{1b}](1 - k_3[\mathbf{7}]/k_2) \quad (2)$$

$$d[\mathbf{4b}]/dt = k_1[\mathbf{1b}]k_3[\mathbf{7}]/k_2 \quad (3)$$

Values of the constant k_1 and the ratio k_3/k_2 can be obtained from the kinetic data (Table 1). The experimental "concentration-time" relations were determined by the spline approximation method which permits the simultaneous approximation of this curve and its derivative by the discontinuous functions of minimal curvature. The "SPLAIN-REG3" algorithm was used with a starting parameter pp = 0.9. Calculated values $k_1 = 0.48 \pm 0.03$ h^{-1}, $k_3 / k_2 = 232 \pm 50$, and $k_3 / k_2 = 231 \pm 50$ l/mol were obtained from equations (2) and (3) respectively. It is seen from the ratio k_3 / k_2 that the formation of the final product **4b** occurs several orders of magnitude faster than that of the proposed intermediate compound **7**. These results indicate that the corresponding formal-kinetic model of the experimental relation is satisfactory.

The rate constants calculated at temperatures of 30, 45, and 60°C were 0.48±0.01, 0.90±0.02, and 3.29±0.12 h^{-1} respectively (Fig. 1).

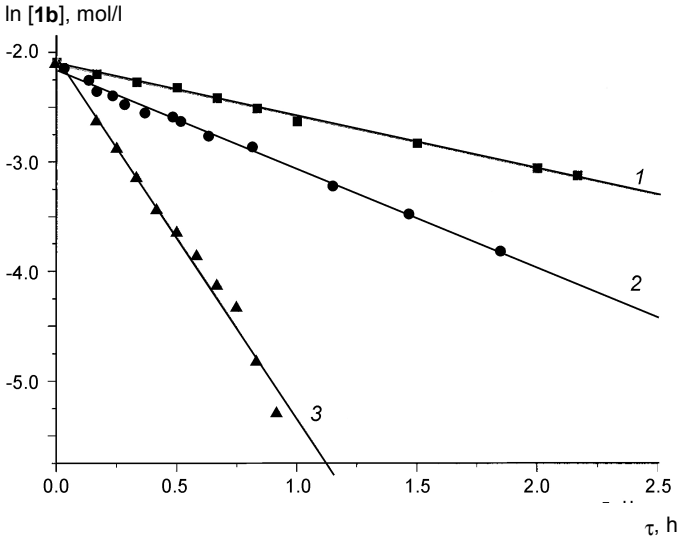


Fig. 1. Dependence of the logarithm of the concentration of compound **1b** on reaction time (τ) in the presence of CF_3COOH at 30 (1), 45 (2), and 60°C (3).

The activation energy (E = 54 ± 12 kJ/mol) and the pre-exponential factor ($k_0 = 7.7\times10^{8\pm2}$ h^{-1} were calculated from the Arrhenius equation.

Thus it has been established from the results of kinetic studies that the reaction is pseudo-first order in dioxide **1b** at constant proton concentration , a probable mechanism and a simplified formal-kinetic model have been proposed.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer. Chemical shifts were measured relative to the residual protons of the solvent DMSO-d_6 (δ 2.50 ppm). IR spectra of KBr tablets were measured on a UR-20 spectrometer and mass spectra on a MS-30 instrument. The course of experiments were monitored by TLC on Silufol UV-254 strips with 9:1 chloroform–methanol as eluent.

Hydrolysis of Compounds 1a-d in 25% Sulphuric Acid (General Method). A solution of compound **1** (0.5 molar) in 25% sulphuric acid (2.5 ml) was maintained on a boiling water bath until the spot corresponding to the starting material had disappeared from the chromatograph (**1a** R_f 0.14, **1b** R_f 0.29, **1c** R_f 0.38, **1d** R_f 0.61). The hydrolysis products were analyzed by TLC, development with iodine vapor. After evaporation of the iodine vapor the strips were treated with alkaline sodium nitroprusside solution to reveal the 1,3-dialkylhydantoins (**2a** R_f 0.37, **2b** R_f 0.69, **3a** R_f 0.22, **3b** R_f 0.31).

Effect of Hydrochloric and Trifluoroacetic Acid on 6,8-Dialkyl-3-thia-2,4,6,8-tetraazabicyclo-[3.3.0]octan-7-one 3,3-Dioxides (1a, 1b). 1 N hydrochloric or trifluoroacetic acid was added to a solution of compound **1a** or **1b** (1 mmol) in water (4 ml) to give pH 1 and the mixture was then maintained on a water bath at 60°C until the spot of the starting material had disappeared (developed in an iodine chamber and with alkaline sodium nitroprusside solution: **1a** R_f 0.14; **1b** R_f 0.29). Complete conversion of compounds **1a** and **1b** took 30-40 min. The water was then partially removed on a rotary evaporator to give precipitates of compounds **4a** and **4b** which were filtered off. Compound **4a**, yield 65 -70%; mp 269-271°C (water), R_f 0.82. Compound **4b**, yield 66 -70%; mp 232-234°C (methanol), R_f 0.88. The IR and ^{1}H NMR spectra and melting points of compounds **4a** and **4b** correspond with those reported in [4].

^{1}H NMR Spectroscopic Study of the Effect of Trifluoroacetic Acid on 6,8-Diethyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-Dioxide (1b). Compound **1b** (12.4 mg, 0.053 mmol) was dissolved in DMSO (0.43 ml) and its ^{1}H NMR spectrum was measured. Trifluoroacetic acid (0.004 ml, 0.054 mmol) was added and the solution was thermostated at 30, 45, and 60°C. The ^{1}H NMR were recorded periodically (see Table 1 and Fig. 1).

Effect of Acetyl Chloride on 6,8-Dialkyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-Dioxides (1a, 1b). A. A solution of compound **1a** or **1b** (1 mmol) in acetyl chloride (2 ml) was refluxed with stirring for 1 h, it was then cooled, the solvent removed on a rotary evaporator, and the oily residue was triturated with ethyl acetate. The precipitated product **4a** (47% yield) or the mixture of **4b** and **5** was filtered off. The mixture of compounds **4b** and **5** was separated by fractional crystallization from methanol: **4b** (0.08 g, 44% yield); **5** (0.05 g, 18.5% yield); mp 156-158°C (methanol). IR spectrum (KBr), ν, cm^{-1}: 1160, 1336 (SO_2), 1604 (C=N), 1708, 1728 (C=O), 3488 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 1.13 (6H, t, J = 6.7, CH_3); 1.96 (3H, s, $COCH_3$); 3.19-3.40 (2H, m, NCH_2); 3.40-3.61 (2H, m, NCH_2); 4.59 (2H, s, CH_2); 11.69 (1H, s, NH). Mass spectrum, m/z (I_{rel}, %): 276 (7.4), 218 (2), 154 (100), 122 (8.5). Found, %: C 38.77; H 5.98; N 20.21; S 11.49. $C_9H_{16}N_4O_4S$. Calculated, %: C 39.12; H 5.84; N 20.28; S 11.60.

B. Acetyl chloride (0.13 ml, 20 mmol) was added dropwise with stirring to a solution of compound **1b** (0.23 g, 1 mmol) in pyridine (4 ml). The colorless compound **4b** which precipitated almost immediately was filtered off, washed with dilute hydrochloric acid and dried in a desiccator over NaOH, Yield 43-55%.

C. Triethylamine (2 drops) was added to a solution of compound **1b** (0.23 g, 1 mmol) in acetonitrile (3 ml). Acetyl chloride (0.13 ml, 20 mmol) was then added dropwise with stirring. A white precipitate of product **4b** deposited almost immediately. It was filtered off, washed with dilute hydrochloric acid and dried in a desiccator over NaOH, Yield 39%.

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