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Reversible Interconversion of Thiazolidine-Tetrahydrothiazine in the Thiadiazabicyclooctanone System**

Mirjana Tomić, Jure J. Herak, and **Miće Kovačević***

Research Institute PLIVA, YU-41000 Zagreb, Croatia, Yugoslavia

Summary. The interconversion of thiazolidine-tetrahydrothiazine in some derivatives of thiadiazabicyclooctanone in aqueous HCl has been studied. In the case of 6- and 7-substituted hydroxy or methoxy thiadiazabicyclooctanone a reversible rearrangement was found. The sulfoxide of thiadiazabicyclooctanone under the same reaction conditions undergoes epimerisation, while reaction with PCl_5 – via a corresponding sulfenyl chloride – affords a mixture of 6- and 7-substituted hydroxy or methoxy derivatives of thiadiazabicyclooctanone.

Keywords. Thiadiazabicyclooctanone derivatives; Reversible interconversion thiazolidine-tetrahydrothiazine; Sulfoxide epimerization.

Die reversible Umwandlung von Thiazolidin-Tetrahydrothiazin im Thiadiazabicyclooctanon-System

Zusammenfassung. Es wurde die Interkonversion von einigen Thiazolidin-Tetrahydrothiazin-Derivaten von Thiadiazabicyclooctanon in wäßriger HCl studiert. Im Fall von 6- und 7-substituierten Hydroxy- oder Methoxy-Thiadiazabcyclooctanonen wurde eine reversible Ringumlagerung gefunden. Die Sulfoxide von Thiadiazabicyclooctanon werden unter analogen Reaktionsbedingungen epimerisiert, während bei der Reaktion mit PCl_5 über entsprechende Sulfenylchloride eine Mischung von 6- und 7-substituierten Hydroxy- oder Methoxy-Derivaten von Thiadiazabicyclooctanon entsteht.

Introduction

The interconversion of thiazolidine-tetrahydrothiazine has been described for an isolated ring and for a bicyclic system. An interconversion of an isolated ring was observed in the reversible rearrangement of 5,6-dihydro-1,4-thiazine and 2-substituted thiazolidine [3, 4]. In the bicyclic system the interconversion was demonstrated by the rearrangement of the *penam* and *cepham* systems. The ring expansion of thiazolidine in the *penam* system has received particular attention, since it has been the key reaction in the transformation of penicillins into cephalosporins [5].

In a previous paper we described the ring expansion of thiazolidine into tetrahydrothiazine by the action of PCl_5 or SO_2Cl_2, which give rise to a rearrangement of 6-thia-3,8-diazabicyclo[3.2.1]octan-2-one into 7-thia-2,5-diazabicy-

** The authors dedicate this paper to Dr. B. Gašpert for his 60th birthday

clo[2.2.2]octan-3-one [6]. Now we wish to report the reversible interconversion of the thiazolidine-tetrahydrothiazine ring in some derivatives of the thiadiazabicyclooctanone system which occurs in acid medium [1, 2].

Results and Discussion

The required compounds 4-hydroxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one (**1**), 5-acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5-diazabicyclo[2.2.2]octan-3-one (**2**), 4-methoxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one (**3**) and 5-acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5-diazabicyclo[2.2.2]octan-3-one (**4**) were prepared as described in Ref. [6].

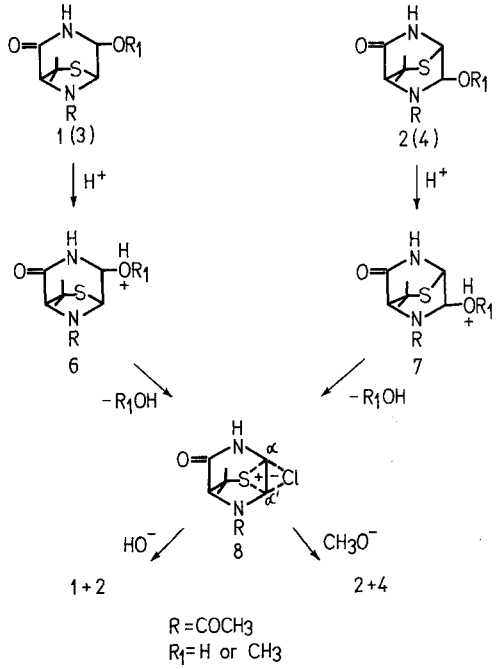
Heating of the methoxy derivatives **3** or **4** in methanol in the presence of diluted acid (0.002 *M* HCl) at 50°C gave a mixture of the isomers **3** and **4** in ratio ca. 3 : 1. The same mixture was obtained when the hydroxy derivatives **1** or **2** were treated under the same reaction conditions. The products were separated by chromatography over silica gel and the structures confirmed in correlation with compounds **1** and **2** or **3** and **4**.

When **3** or **4** was heated without methanol in 0.002 *M* HCl, a mixture of hydroxy derivatives **1** and **2** was obtained. On the other hand, the hydroxy derivatives **1** or **2** treated in the same concentration of acid did not undergo any reaction.

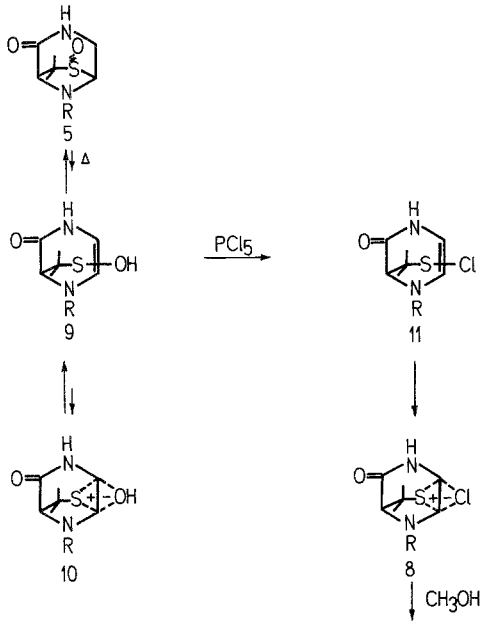
In principle, two different pathways have been proposed for the mechanistic interpretation of the thiazolidine-tetrahydrothiazine interconversion.

One with an $R-CH=CH-NH-CHR'-CHR''-SH$ intermediate, formed by opening of the thiazolidine or thiazine ring, as in the interconversion of 5,6-dihydro-1,4-thiazine and thiazolidine [4].

The second one includes the thiiranium ion as an intermediate, which operates in the case when nitrogen is substituted for a group which prevents ring opening, e.g. *penam-cepham* or thiadiazabicyclooctanone systems [7].



Scheme 1



Scheme 2

In our case, the formation of the thiiranium ion **8** by participation of the neighboring thio group, may also be postulated as an intermediate in the reversible interconversion of thiazolidine-tetrahydrothiazine in the thiadiazabicyclooctanone system (Scheme 1). Nucleophilic attack of OH^- or CH_3O^- on carbon at position *a* or *a'* to sulphur in the proposed structure **8** may explain the generation of thiazolidine **1** (**3**) and tetrahydrothiazine **2** (**4**) derivatives.

In order to provide some more evidence for this interconversion, the behaviour of the sulfoxide of thiadiazabicyclooctanone **5** was also examined.

For this purpose, the monoacyl derivative of 7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one was prepared as outlined in Ref. [8]; subsequent oxidation with hydrogen peroxyde in acetic acid afforded the (2 : 1)-mixture of the corresponding epimeric sulfoxides **5**, which was separated by crystallisation from water-acetone (epimer **5a** with R_f 0.42 and epimer **5b** with R_f 0.51, system B).

On heating of **5a** or **5b** in methanol in the presence of aqueous HCl the corresponding hydroxy (**1** and **2**) or methoxy derivatives (**3** and **4**) could not been detected. Instead, only the starting mixture was recovered besides small amounts of decomposition products. Finally, the methoxy derivatives **3** and **4** were obtained when the sulfoxide **5** was treated with PCl_5 in methanol.

It is known that the sulfoxide-sulfenic acid equilibrium is a thermal process and in some cases the isolation of sulfenic acid in crystalline form is possible [9]. In the case of the epimerisation of **5** under the reaction conditions described, generation of corresponding sulfenic acid **9** may also be proposed, but there seems no possibility of its transformation to hydroxy derivatives **1** and **2** via structure **10**.

On the other hand, the reaction of the sulfoxide **5** with PCl_5 shows that the formation of a sulfenyl chloride **11** as intermediate is necessary, which with OH^- or CH_3O^- gives the corresponding hydroxy or methoxy derivatives **1** and **2** or **3** and **4**.

Acknowledgement

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Experimental

Melting points are uncorrected. IR spectra were recorded in potassium bromide with a Model 257 G Perkin-Elmer spectrometer. The ^{1}H NMR spectra were recorded in *DMSO-d_6*, with *TMS* as internal standard on a JEOL FX 90 Q spectrometer. TLC was performed on Merck, Kieselgel HF_{254}; CH_2Cl_2-*Me*OH (10 : 1; A) or $CHCl_3$-*Me*OH (5 : 1; B); detection: iodine-vapour/UV.

Reaction of 4-methoxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one (**3**), *5-acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5-diazabicyclo[2.2.2]octan-3-one* (**4**)

(a) In methanol. To a suspension of **3** (or **4**) (2.44 g, 0.01 mol) in methanol (120 ml), 0.1 *M* HCl (2.4 ml) was added, to give 0.002 *M* acid solution. After addition of acid the suspension was warmed at 50 °C for 2 h. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The dry residue was dissolved in methanol and again evaporated to dryness. Yield: 2.44 g (100%), with two spots on TLC, R_f 0.45 and 0.38 (system A).

Chromatography of the crude product on silicagel column in dichloromethane and methanol gave 65% of **3** (m.p. 206°C, R_f 0.45) and 21% of **4** (m.p. 225–230°C, R_f 0.38). M.p., R_f, IR and ^{1}H NMR spectral data correspond to those given in Ref. [6].

(b) In water. To a suspension of **3** (or **4**) (2.44 g, 0.01 mol) in water (120 ml), 0.1 *M* HCl (2.4 ml) was added, to give 0.002 *M* acid solution. The suspension was warmed at 75°C for 1 h. The reaction mixture was cooled, neutralised with satd. solution of $NaHCO_3$ and evaporated to dryness. The dry residue was suspended in water (5 ml) filtered and the precipitate dried. Yield: 2.25 g (97%), m.p. 197–205°C, R_f 0.28 (system A). The R_f value is identical to those of hydroxy derivatives **1** and **2**. M.p., IR and ^{1}H NMR spectral data correspond to those obtained for the sample prepared by mixing the hydroxy derivatives **1** and **2** in ratio 3 : 1.

Reaction of 4-Hydroxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one (**1**) *5-acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5-diazabicyclo[2.2.2]octan-3-one* (**2**)

(a) In methanol. According to the above procedure a) **1** (or **2**) (2.3 g, 0.01 mol) was treated with 0.002 *M* HCl and warmed at 50°C for 2 h. The crude product (2.3 g, 94%) showed two spots on TLC, R_f 0.45 and 0.38 (system A).

Chromatography of the crude product on a silica gel column in dichloromethane and methanol gave 63% of **3** (m.p. 210°C, R_f 0.45) and 22% of **2** (m.p. 225–230°C, R_f 0.38).

(b) In water (0.002 M HCl). According to the above procedure (b) **1** (or **2**) treated with 0.002 *M* HCl gave the product in 95% yield, with the same m.p., R_f, IR and ^{1}H NMR spectrum as the starting compound.

(c) In water (0.02 M HCl). To a suspension of **1** (or **2**) (2.3 g, 0.01 mol) in water (120 ml) 1 *M* HCl (2.4 ml) was added, to give a 0.02 *M* acid solution. The suspension was isolated as described above. Yield: 2.18 g (94%) with one spot on TLC, R_f 0.28 (system A). The R_f value was identical to hydroxy compounds **1** and **2**. M.p., IR and ^{1}H NMR spectral data correspond to those obtained for the sample prepared by mixing the hydroxy derivatives **1** and **2** in ratio 3 : 1.

Reaction of 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one sulfoxide (**5**)

8-Acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one (4.28 g, 0.02 mol) was dissolved in the mixture of hydrogen peroxide (2.5 ml, 0.022 mol) and acetic acid (20 ml). The solution was mixed 3 h at room temperature and then neutralized with sodium carbonate. In the mixture dichloromethane

(15 ml) was added and filtered. The organic layer was separated, dried ($MgSO_4$) and evaporated to dryness. Yield: 4.277 g (93%), m.p. 184–187°C. Thin layer chromatography indicated two products, one of which had R_f 0.42 and the other R_f 0.51 (system B). Recrystallization from chloroform-hexane gave an analytical sample with m.p. 194–195°C.

Anal. $C_9H_{14}N_2SO_3$ (230.28). Calcd.: C 46.94, H 6.13, N 12.16%. Found: C 46.94, H 5.96, N 12.36%.

The crude mixture of sulfoxides (4.277 g, m.p. 184–187°C) was suspended in acetone-water (3 : 1, 12 ml), mixed for 10 min at +5°C and then filtered. The filtrate was evaporated to dryness under reduced pressure and the procedure was repeated. The solid (2.851 g, m.p. 192–194°C) was recrystallized from chloroform-hexane m.p. 194–195°C; R_f 0.42 (system B).

IR: 3 480–3 320 (s, b), 1 670 (vs), 1 415 (s), 1 330 (m), 1 250 (m), 1 045 (vs) cm^{-1}.

^1H NMR, δ: 7.87 (s, NH), 6.26–5.93 (m, CH − S), 4.45–4.37 (m, CH − N), 3.60–3.26 (m, CH_2 − N), 2.18 and 2.03 (2s, $COCH_3$), 1.33, 1.25, 1.16 [3s, $(CH_3)_2$] ppm.

The filtrate (acetone-water), after separation of the isomer with m.p. 192–194°C, was evaporated to dryness under reduced pressure. Yield: 1.295 g, m.p. 183–185°C. Recrystallization from acetone-hexane gave an analytical sample with m.p. 188–189°C; R_f 0.51 (system B).

IR: 3 220 (s), 1 670 (vs), 1 415 (s), 1 340 (m), 1 290 (m), 1 050 (vs) cm^{-1}.

^1H NMR, δ: 7.96 (s, NH), 5.28–5.53 (m, CH-S), 4.72–4.63 (m, CH − N), 3.53–3.26 (m, CH_2 − N), 2.21 (s, $COCH_3$), 1.43, 1.25, 1.18 [3s, $(CH_3)_2$] ppm.

Reaction of 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one sulfoxide (**5**)

(a) With PCl_5. To a solution of PCl_5 (0.63 g, 0.003 mol) in dry benzene (20 ml) 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one sulfoxide (**5 a** or **5 b**), (0.69 g, 0.003 mol) was added and the reaction mixture was refluxed 1 h. The solution was cooled and evaporated to dryness under reduced pressure. To the dry residue methanol was added (5 ml), stirred at 25°C for 30 minutes, and then filtered. Yield: 0.53 g (72.4%), m.p. 203–208°C, with two spots on TLC. The crude product was chromatographed on a silica gel column in dichloromethane-methanol giving 0.29 g (54.7%) of **3**; (m.p. 205°C, R_f 0.46) and 0.19 g (35.8%) of **4**; (m.p. 225–230°C, R_f 0.38; system A). M.p., R_f, IR and ^1H NMR spectral data correspond to those given in Ref. [6].

(b) In methanol. According to the procedure a) 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octane-2-one sulfoxide (**5 a** or **5 b**), (2.3 g, 0.01 mol) was treated with 0.02 *M* HCl and warmed at 50°C for 5 h. The crude product (2.2 g, 96%) was chromatographed on a silica gel column in dichloromethane − methanol giving 68% of starting sulfoxide (m.p. 183–187°C, R_f 0.42) and 17% of the other isomer of sulfoxide (m.p. 166–172°C, R_f 0.51; system B). M.p., R_f, IR and ^1H NMR spectra identical to m.p., R_f and spectra of **5 a** or **5 b**.

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