CROATICA CHEMICA ACTA CCACAA 55 (3) 327—335 (1982)

YU ISSN 0011-1643
CCA-1338 UDC 541.124:547.6
Original Scientific Paper

Ring Expansion of Thiazolidine and Nucleophilic Substitution in *N*-Acyl Derivatives of 6-Thia-3,8-diazabicyclo[3.2.1.]octan-2-one[1]

J. J. Herak, M. Kovačević, and B. Gašpert

Research Institute PLIVA, Zagreb, Croatia, Yugoslavia

Received September 29, 1981

Reaction of N^3,N^8-diacyl 6-thia-3,8-diazabicyclo/3.2.1./octan-2--one (I) with PCl_5 or SO_2Cl_2 gave 6-chloro substituted N^2,N^5-diacyl 7-thia-2,5-diazabicyclo/2.2.2./octan-3-one (II). Treatment of II with water yielded the 6-hydroxy derivative (III) while reaction with methanol gave the 6-methoxy derivative (IV). Under the same reaction conditions the mono N^8-acyl derivative (V) gave a mixture of 6-substituted 7-thia-2,5-diazabicyclo/2.2.2./octan-3-one and 4--substituted 6-thia-3,8-diazabicyclo/3.2.1./octan-2-one derivatives (XIV and XV; VI and VII; VIII and IX). It was proposed that ring expansion of thiazolidine and nucleophilic substitution occured via the thiiranium ion XIII as a common intermediate.

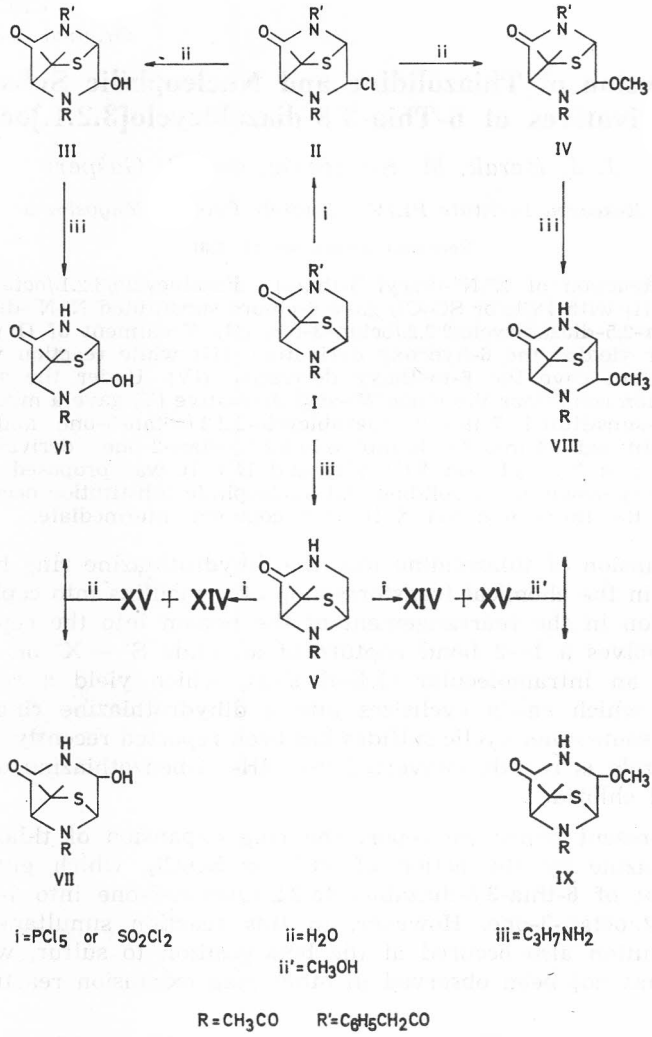
The expansion of thiazolidine into the dihydrothiazine ring has been the key reaction in the chemical transformation of penicillins into cephalosporins[2]. Ring expansion in the rearrangement of the penam into the cephem system generally involves a 1—2 bond rupture of an ylide $S^+ — X^-$ on thiazolidine, probably by an intramolecular (1,4)-H shift, which yield a secoceph-2-em intermediate which easily cyclisizes into a dihydrothiazine ring[3]. The ring expansion of some other cyclic sulfides has been reported recently; 2,3-dihydro-1,3-benzothiazole is readily converted into 4H-1,4-benzothiazine by treatment with sulfuryl chloride[4].

In the present paper we report 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-diazabicyclo/2.2.2./octan-3-one. However, in this reaction simultaneous nucleophilic substitution also occured at the beta-position to sulfur, which to our knowledge, has not been observed in other ring expansion reaction of cyclic sulfides.

The preparation of N^8-acyl 6-thia-3,8-diazabicylclo/3.2.1./ostan-2-ones was described earlier[5], but recently its formation by stereospecific cyclization of c i s *N*-acyl 2-amidomethyl-thiazolidine-4-carboxylic acids has been demonstrated[6]. In an attempt to prepare N^3,N^8-diacylderivatives of 6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (I) from corresponding mono N^3-acyl derivatives (V) by Mumm's method[7], we observed an unusual reaction with PCl_5,

The PCl_5, known as one of the effective agents for the conversion of a secondary amide into an imidoyl chloride group[8], gave in the reaction with

V, a novel reactive chloro derivative different from the expected imidoyl chloride, which, upon addition of water, yielded a product also different from V. Since the N^3,N^8-diacyl derivative (I) reacted on analogous way, it was obvious that a functional group other than the secondary amide reacted with PCl_5.



It has been reported that sulfides, one of the groups also present, treated with PCl_5 undergo a chlorination at the alfa position[9]; it has been claimed that further excess of reagent and prolonged heating may give rise to alkylthiovinyl and chlorovinyl phosphoric acid dichlorides[10].

The analysis of the crude chloro product obtained by heating of I with PCl_5 or SO_2Cl_2 at 50 °C for 1 hour, revealed the presence of only one chloro

atom in the molecule. The ^{1}H NMR spectrum showed the absence of duplicated signals of two conformers, a notable feature of *N*-acyl thiazolidine[11], the presence of a singlet at δ 5.13, attributed to a bridgehead proton, and two doublets at δ 6.06 and 6.20 ($J = 1$ Hz), assignated to another bridgehead proton and a proton adjacent to the halogen, respectively. This indicated a new bicyclic ring system (II) with tetrahydrothiazine and introduction of halogen at the beta position to sulfur. Sensitivity to moisture prevented attepmts to prepare the pure chloro compound II, therefore a crude product was immediately submmited to further reaction with water and the product obtained was isolated and analysed.

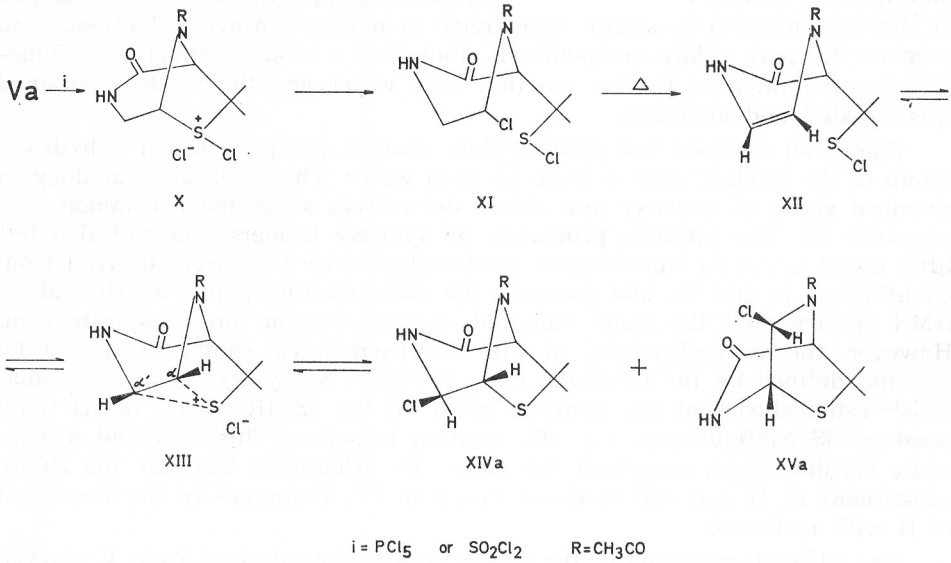
Elemental analysis and spectral data showed the presence of a hydroxy group in the product after a work up with water. The fairly close analogy in chemical shifts of hydroxy and chloro derivatives suggested a common ring structure III. The physical properties of hydroxy isomers IIIa and IIIb left little doubt about its enantiomeric relationship, since they were derived from enantiomers Ia and Ib, and possesed the same melting point, R_f, IR and ^{1}H NMR spectra, and the same value of optical rotation but of oposite sign. However, the stereochemistry of the new asymmetric center in II and III was not defined by the foregoing data. A recent X-ray crystallographic analysis[12] established that the hydroxy group in the 1S, 4R isomer of III (IIIa) possesed 6S configuration, i. e. »E« position to sulfur. This data and mechanistic considerations suggested the same »E« orientation also for the chloro substituent in II and the methoxy group in IV, prepared by the treatment of II with methanol.

The ^{1}H NMR spectrum of the chloro intermediate derived from V, showed much more complicated features, in which duplicated signals of two conformers of *N*-acyl thiazolidine derivatives could be distinguished, indicating at least a chloro derivative of a parent ring structure V. To obtain a reference material for the products to be formed in the reaction of the chloro intermediate with water and alcohol, the compounds III and IV were selectively deacylated. It was found that the acyl group at the N^2-position can be removed selectively by treatment of III or IV with primary or secondary amines in nonaqueous solution, to give VI and VIII respectively, in high yield and purity.

The work up of the product, obtained by treatment of the chloro intermediate derived from V with water, gave a crystalline compound with the same molecular formula and R_f value as product VI, but different melting point, IR, ^{1}H NMR spectra and [α]. Duplication of ^{1}H NMR signals, due to the presence of two conformers of N^8-acyl thiazolidine derivatives, doublet at δ 4.65 (C_4—H) and 5.45 (C_5—H) with ($J = 1.5$ Hz) and a broad signal at δ 5.8—6.5 (—OH) suggested the isomer of the parent ring structure V, substituted with a hydroxy group at the C-4 position (VII). Compound VI was detected in the crude reaction product and in the residue after isolation of VII. Although homogenous on TLC, they showed an ^{1}H NMR spectrum in which the isomers VI and VII could be clearly distinguished.

The same chloro intermediate (from V) treated with methanol gave a crystalline product, consisting of two compounds with R_f 0.45 and 0.36, not separable by crystallization but isolated by preparative TLC. The product with R_f 0.36 (30%) was identical to the product obtained by selective deacylation of IV. The molecular formula of the product with R_f 0.45 (60%) was the

same as that of VIII. The ^1H NMR spectrum resembles that of VII, with two exceptions; the signal of the OH group at δ 5.8—6.5 was absent and the signal at δ 3.26 and 3.35 of the OCH_3 group was present. These data strongly argue in favor of the structure IX.



The most likely mechanism for the reaction of I and V with PCl_5 or SO_2Cl_2, which gives rise to nucleophilic substitution at the beta position to sulfur and ring expansion of thiazolidine, is one which involves the thiiranium ion as a common intermediate. In general, the thiiranium ion has been postulated and propossed as an intermediate in several reactions concerning the thio group, specially in the neighboring group participation reactions of beta aryl and alkyl groups in nucleophilic displacement reactions[13].

The process leading to the formation of thiiranium ion XIII probably involves S-chloro sulfonium chloride X as one intermediate, since it has been proposed to be the first step in the reaction of alkylsulfides with PCl_5 or SO_2Cl_2[9,10,14]. The next reaction step suggests itself, the intermediate X may undergo opening of the thiazolidine ring to give sulfenylchloride XI. The analogous reaction of S-chloro sulfonium chloride on the penam ring, and electrophilic opening of thiazolidine with formation of the corresponding sulfenylchloride was proposed by Kukolja[15]. During heating, XI may eliminate HCl, which gives rise to unsaturated sulfenyl chloride XII, an intermediate with two functional groups ready to form a thiiranium ion XIII[13].

In theory, the attack by nucleophiles of the thiiranium ion can occure at four different sites[13]. In our case the nucleophilic attack at carbons alfa to sulfur can explain the formation of isomers XIV and XV. The attack at the alfa C-atom will give a C-6 substituted tetrahydrothiazine ring (XV), while reaction at the alfa' C-atom will yield a C-4 substituted thiazolidine ring XIV.

It seems that regioselectivity of nucleophilic attacks depends more upon the structure of the thiiranium ion than on the nature of the nucleophiles. When nearly the same nature of amide group was attached to the alfa and alfa' C-atoms in the thiiranium ion (XIII), the mixture of the isomers in the reaction product was obtained in the same ratio (about 3 : 1; XIV and XV; VII and VI; IX and VIII). On the contrary, when nitrogen at the N^3-position was acylated to form an imide group, nucleophilic attack at the thiiranium ion derived from I occured predominantly at the alfa C-atom (90%)[16] to give an adduct with anti-Markovnikov orientation (II, III and IV). It follows, that the same nature of the thiiranium ion gave nearly the same ratio of isomers (3 : 1 or 90%) in the reactions with different nucleophiles.

Finally, the study of the ring expansion of thiazolidine was latter extended to interconversion of thiazolidine and tetrahydrothiazine. A similar mechanism with the thiiranium ion as intermediate will also hold for the interconversion reaction of VI, VII, VIII and IX. This will be presented in detail in our next publication.

EXPERIMENTAL

Melting points are uncorrected.

IR spectra were recorded in potassium bromide plates with a Model 257G Perkin-Elmer spectrometer and are reported as wavelength, followed by relative intensities in brackets.

The ^{1}H NMR spectra were recorded in DMSO-d_6, with TMS as the internal standard, on a Varian A-60 spectrometer. All chemical shifts are given in ppm downfield from TMS.

TLC was performed on original plates (Merck, Kieselgel HF_{254}) followed by detection with iodine vapor and UV absorption in a solvent system as stated:

/A/ Dichlormethane : methanol (10 : 1)

/B/ Benzene : acetone (4 : 1)

Optical rotations were measured on an Opton 372149 polarimeter at ambient temperature.

1S,4R,6S-2-Phenylacetyl-5-acetyl-6-hydroxy-8,8-dimethyl-7-thio-2,5--diazabicyclo/2.2.2./octan-3-one (IIIa))

To a solution of phosphorus pentachloride (6.25 g, 0.03 mol) or sulfuryl chloride (4.05 g, 0.03 mol) in dry benzene (50 ml) warmed to 40 °C, 1R,5R-3-phenylacetyl-8--acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./-octan-2-one (Ia; 9.96 g, 0.03 mol) was added and the mixture was stirred at 50 °C for 1 hour. The reaction solution was cooled and evaporated under reduced pressure. The dry residue was suspended in water (50 ml) and stirred at 25 °C for 30 minutes. IIIa was collected by filtration and washed with water, dried and recrystallized from ethylacetate; yield 8.8 g (84%); m. p. 210—2 °C; $[\alpha]_D^{25} + 62^0$ (c = 1, CH_2Cl_2); R_f 0.78 (solvent system A).

Recrystallization from ethylacetate gave an analytical sample with the same m. p. and $[\alpha]$.

Anal. $C_{17}H_{20}N_2O_4S$ (348.21) calc'd: C 58.64; H 5.75; N 8.04%
found: C 58.43; H 5.88; N 8.25%

IR spectrum: 3340(s), 1740(vs), 1710(vs), 1650(vs), 1415(s), 1350(vs), 1320(s), 1300(m), 1270(s), 1255(vs) cm^{-1}.

^{1}H NMR spectrum δ: 1.30 (s, C_8—$(CH_3)_2$), 2.22 (s, $COCH_3$), 4.25 (s, CH_2CO), 4.96 (s, C_4—H), 5.34 (dd, J = 3Hz and J = 8Hz, C_6—H), 5.86 (d, J = 3Hz, C_1—H), 6.88 (d, J = 8Hz, C_6—OH), 7.30 (s, C_6H_5).

1R,4S,6R-2-Phenylacetyl-5-acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5--diazabicyclo/2.2.2./octan-3-one (IIIb)

According to the above procedure, 1S,5S-3-phenylacetyl-8-acetyl-7,7-dimethyl--6-thia-3,8-diazabicyclo-/3.2.1./octan-2-one (Ib) gave 84% of IIIb; $[\alpha]_D^{25} - 65^0$ (c = 1. CH_2Cl_2).

M. p., R_f, IR and ^1H NMR spectra identical to m. p., R_f and spectra of IIIa.

1S,4R,6S-2-Phenylacetyl-5-acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5--diazabicyclo/2.2.2./octan-3-one (IVa)

To a solution of phosphorus pentachloride (6.25 g, 0.03 mol) or sulfuryl chloride (4.05 g, 0.03 mol) in dry benzene (50 ml) warmed to 40 °C, 1R,5R-3-phenylacetyl--8-aceytl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Ia; 9.96 g, 0.03 mol) was added and the mixture was stirred at 60 °C for 1 hour. Methanol (20 ml) was added to the reaction solution which was then stirred for an additional 30 minutes at 25 °C, and cooled to 0 °C. IVa crystallized from the solution and was collected by filtration; yield 9.30 g (85%); m. p. 232—4 °C; $[\alpha]_D^{25} + 47^0$ (c = 1, CH_2Cl_2); R_f 0.55 (solvent system B).

Recrystallization from methanol gave an analytical sample with the same m. p. and [α].

Anal. $C_{18}H_{22}N_2O_4S$ (362.43) calc'd: C 59.72; H 6.12; N 7.73%
found: C 59.89; H 6.02; N 7.99%

IR spctrum: 1720(vs), 1710(vs), 1660(vs), 1385(s), 1370(vs), 1310(vs), 1305(vs), 1260(vs) cm^{-1}.

^1H NMR spectrum δ: 1.30 (s, $C_8(CH_3)_2$), 2.15 (s, COCH3), 3.30 (s, OCH_3), 4.25 (s, CH_2CO), 4.96 (s, C_4—H), 5.15 (d, J = 3Hz, C_6—H), 6.28 (d, J = 3Hz, C_1—H), 7.22 (s, C_6H_5).

1R,4S,6R-2-Phenylacetyl-5-acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5--diazabicyclo/2.2.2./octan-3-one (IVb)

According to the above procedure, 1S,5S-3-phenyl-acetyl-8-acetyl-6-thia-3,8--diazabicyclo/3.2.1./octan-2-one (Ib) gave 83% of IVb; $[\alpha]_D^{25} - 45.96^0$ (c = 1, CH_2Cl_2).

M. p., R_f, IR and ^1H NMR spectra identical to m. p., R_f and spectra of IVa.

1R,5R-8-Acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Va)

To a suspension of 1R,5R-3-phenylacetyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Ia: 9.96 g, 0.03 mol) in benzene (50 ml), propylamine (3.54 g, 0.06 mol) was added dropwise over 15 minutes with stirring and cooling of the reaction mixture. After the addition, the suspension was stirred at 25 °C for an additional hour. Va was collected by filtration; yield 6.25 g (97.2%); m. p. 228—230 °C; $[\alpha]_D^{25} - 88^0$ (c = 1, CH_2Cl_2). Lit.[6] m. p. 228—230 °C; $[\alpha]_D^{23} - 87.7^0$ (c = 0.5, CH_2Cl_2).

^1H NMR and IR spectral data correspond to spectral data given in the literature.

1S,5S-8-Acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Vb)

According to the above procedure, 1S,5S-3-phenylacethyl-8-acetyl-7,7-dimethyl--6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Ib) gave 95% of Vb; m. p. 228—230 °C; $[\alpha]_D^{25} + 98.5^0$ (c = 1, CH_2Cl_2). Lit.[6] m. p. 228—230 °C; $[\alpha]_D^{25} + 98.3^0$ (c = 0.5, CH_2Cl_2).

IR and ^1H NMR spectral data correspond to spectral data given in the literature.

1S,4R,6S-5-Acetyl-6-hydroxy-8,8-dimetyl-7-thia-2,5--diazabicyclo/2.2.2./octan-3-one (VIa)

According to the above procedure, 1S,4R,6S-2-phenylacetyl-5-acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5-diazabicyclo/2.2.2./octan-3-one (IIIa) treated with propylamine gave 91.3% of VIa; m. p. 165 °C; $[\alpha]_D^{25} + 15.11^0$ (c = 1, MeOH); R_f 0.28 (solvent system A).

Recrystallization from methanol gave an analytical sample with the same m. p. and [α].

Anal. $C_9H_{14}N_2O_3S$ (230.31) calc'd: C 47.35; H 6.12; N 12.16%
found: C 47.60; H 5.97; N 12.20%

IR spectrum: 3320(m), 3190(m), 1690(s), 1630(vs), 1400(s), 1320(m), 1300(m), 1055(s) cm^{-1}. ^1H NMR spectrum δ: 1.25 and 1.30 (2s, C_8—$(CH_3)_2$), 2.17 (s, $COCH_3$), 4.62 (dd, J = 3Hz and J = 5Hz, C_1—H), 4.64 (s, C_4—H), 5.18 (dd, J = 3Hz and J = 7Hz, C_6—H), 6.67 (d, J = 7Hz, C_6—OH), 9.06 (d, J = 5Hz, N_2—H).

1R,4S,6R-5-Acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5-diazabicyclo[2.2.2.]octan-3-one (VIb)

According to the above procedure, 1R,4S,6R-2-phenylacetyl-5-acetyl-6-hydroxy-8,8-dimethyl-7-thia-2,5-diazabicyclo/2.2.2./octan-3-one (IIIb) treated with propylamine gave 93% of VIb; $[\alpha]_D^{25} - 17^0$ (c = 1, MeOH).

M. p., R_f, IR and ^1H NMR spectra identical to m. p., R_f and spectra of VIa.

5-Acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5-diazabicyclo/2.2.2./octane-3-one (VIII)

According to the above procedure 2-phenylacetyl-5-acetyl-6-methoxy-8,8-dimethyl-7-thia-2,5-diazabicyclo-/2.2.2./octan-3-one (IV) treated with propylamine gave 95% if VIII; m. p. 225—230 °C; R_f 0.35 (solvent system A).

Recrystallization from ethanol gave an analytical sample with the same m. p. and R_f.

Anal. $C_{10}H_{16}N_2O_3S$ (244.15) calc'd: C 49.19; H 6.56; N 11.47%
found: C 48.96; H 6.23; N 12.01%

IR spectrum: 3230(s), 1660(vs), 1385(s), 1320(s), 1065(vs), 780(m) cm^{-1}.
^1H NMR spectrum δ: 1.23 and 1.30 (2s, C_8—$(CH_3)_2$), 2.13 (s, $COCH_3$), 3.33 (s, OCH_3), 4.64 (s, C_4—H), 4.90 (d, J = 2Hz, C_6—H), 5.13 (dd, J = 2Hz and J = 6Hz, C_1—H), 9.04 (d, J = 6Hz, N_2—H).

1R,4R,5R-4-Hydroxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (VIIa)

To a solution of PCl_5 (2.08 g, 0.01 mol) or SO_2Cl_2 (1.35 g, 0.01 mol) in dry benzene (20 ml) 1R,5R-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (Va; 2.14 g, 0.01 mol) was added and the suspension was warmed at 40 °C for 1 hour. The reaction mixture was cooled and evaporated to drynes under reduced pressure. The dry residue was dissolved in water (30 ml) and concentrated to 1/3 volume under reduced pressure. VIIa crystallized from the solution and was collected by filtration; yield 1.06 g (46%); m. p. 220 °C (decomp.); $[\alpha]_D^{25} - 30.7^0$ (c = 1, MeOH); R_f 0.28 (solvent system A).

Recrystallization from ethyl acetate gave an analytical sample with the same m. p., [α] and R_f.

Anal. $C_9H_{14}N_2O_3S$ (230.31) calc'd: C 47.35; H 6.12; N 12.16%
found: C 47.21; H 6.42; N 11.76%

IR spectrum: 3250(s), 1660(s), 1615(vs), 1440(s), 1315(m), 1295(m), 1250(m), 1040(m) cm^{-1}. ^1H NMR spectrum δ: 1.32 and 1.42 (2s, C_7—$(CH_3)_2$), 2.10 and 2.15 (2s, $COCH_3$), 4.36 and 4.60 (2s, C_1—H), 4.65 (d, J = 1.5Hz, C_4—H), 5.45 and 5.72 (2d, J = 1.5Hz, C_5—H), [5.8—6.5 (broad, C_4—OH) and 8.33 (d, J = 2Hz, N_8—H) disapeared after shaken with D_2O].

The filtrate, after isolation of VII, was evaporated to dryness under reduced pressure; the mixture of VIIa and VIa was detected by ^1H NMR in ratio 1 : 1.

1S,4S,5S-4-hydroxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octane-2-one(VIIb)

According to the above procedure 1S,5S-8-acetyl-6-thia-7,7-dimetyl-3,8-diazabicyclo/3.2.1./octan-2-one (Vb) gave 52% of VIIb; $[\alpha]_D^{25} + 30.1^0$ (c = 1, MeOH).

M. p., R_f, IR and ^1H NMR spectra identical to m. p., R_f and spectra of VIIa.

4-Methoxy-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (IX)

To a solution of PCl_5 (2.08 g, 0.01 mol) or SO_2Cl_2 (1.35 g, 0.01 mol) in dry benzene (20 ml) warmed to 40 °C, 8-acetyl-7,7-dimetyl-6-thia-3,8-diazabicyclo/3.2.1./octan-2-one (V; 2.4 g, 0.01 mol) was added and the suspension was warmed at 40 °C for 1 hour. The reaction mixture was evaporated under reduced pressure. Methanol (20 ml) was added to the dry residue and stirred at 25 °C for 30 minutes. Upon cooling to 0 °C, a product crystallized from the solution and was collected by filtration; yield 2.2 g (91%) with two spots on TLC, R_f 0.45 and 0.38 (solvent system A).

Chromatography of the product on a preparative TLC plate in solvent system A, gave 60% yield of IX; m. p. 210 °C; R_f 0.45.

Anal. $C_{10}H_{16}N_2O_3S$ (244.15) calc'd: C 49.19; H 6.56; N 11.49%
found: C 49.48; H 6.32; N 12.00%

IR spectrum: 3220(m), 1640(vs), 1410(vs), 1310(s), 1250(s), 1110(m), 1070(s) cm^{-1}.
^1H NMR spectrum δ: 1.37 and 1.45 (2s, C_7—$(CH_3)_2$), 2.08 and 2.12 (2s, $COCH_3$), 3.26 and 3.35 (2s, OCH_3), 4.32 (dd, J = 1.5Hz and J = 3Hz, C_4—H), 4.47 and 4.53 (2s, C_1—H), 5.7 and 5.91 (2d, J = 1Hz, C_5—H), 8.87 (d, J = 3Hz, N_3—H).

The same method was used to isolate the product with R_f 0.38, in 30% yield; m. p., R_f, IR and ^1H NMR spectra identical to compound VIII.

Acknowledgment. — The authors thank the members of the Organic Chemistry Department of Research Institute PLIVA for recording the IR spectra and for the microanalyses.

The ^1H NMR spectra were recorded by NMR service of the Institute »Ruđer Bošković«.

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16. Presence of minor duplicate signals in ^1H NMR spectrum of II, at δ 1.40 and 2.19, probably indicated traces of the 4-chloro derivative of I.

SAŽETAK

Proširenje prstena tiazolidina i nukleofilna supstitucija N-acyl derivata 6-tia-3,8-diazabiciklo/3.2.1./oktan-2-ona

J. J. Herak, M. Kovačević i B. Gašpert

Reakcijom N^3,N^8-diacil 6-tia-3,8-diazabiciklo/3.2.1./oktan-2-ona sa PCl_5 ili SO_2Cl_2 nastaje 6-klor derivat N^2,N^5-diacil 7-tia-2,5-diazabiciklo/2.2.2./oktan-3-ona(II). Djelovanjem vode na II nastaje 6-hidroksi derivat III, dok je u reakciji sa metanolom dobiven odgovarajući 6-metoksi derivat IV. U jednakim reakcijskim uvjetima mono N^8-acil derivat V daje smjesu 6-supstituiranih derivata 7-tia-2,5-diazabiciklo/2.2.2./-oktan-3-ona i 4-supstituiranih derivata 6-tia-3,8-diazabiciklo/3.2.1./oktan-2-ona (XIV i XV; VI i VII; VIII i IX). Pretpostavlja se da je tiiranium ion XIII, zajednički međuprodukt u reakciji nukleofilne supstitucije kao i proširenja prstena tiazolidina.