Chemistry of Heterocyclic Compounds, Vol. 39, No. 6, 2003

NON-STEREOSPECIFIC REDUCTIVE CLEAVAGE OF 2-ISOXAZOLINES

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Under conditions of reductive cleavage 13,15-isoxazolinoprostanoids with a bicycloheptane unit in the ω-chain underwent epimerization at atom $C_{(2)}$ of this unit to give non-stereospecific products of hydrogenolysis of the heterocycle.

Keywords: bicycloheptane, derivatives of isoxazoline, reductive cleavage of the isoxazoline ring.

Reductive cleavage of 2-isoxazolines, like their synthesis by 1,3-dipolar cycloaddition, is a stereospecific process which makes isoxazoline technology for the generation of bifunctional fragments of compounds favorable for the synthesis of polychiral molecules [1, 2].

We noted previously the formation of a product of non-stereospecific hydrogenolysis of the heterocycle of isoxazolinbicyclo[2.2.1]heptanes, when three isomeric ketones **2a-c** were obtained from a mixture of two isomeric isoxazolines **1a,b** with *exo*-coupling of the carbo- and heterocycles [3].

In the present work this reaction was studied more thoroughly and with new examples. It was shown that, when a mixture of compounds **1a** and **1b** was reduced with hydrogen *in situ* in the presence of Ni–Ra/$AlCl_3$–H_2O–MeOH by a known method [4], the keto ester **5** was formed in addition to the previously described products **2a-c** [3]. Analogously, a mixture of the isomeric ketols **4a-c** and the keto ester **6** were obtained from a mixture of the 2',6'-di-*exo*-isoxazolinobicyclo[2.2.1]heptanes **3a** and **3b**.

Reductive cleavage of the isoxazoline **3a** proceeds stereospecifically with retention of the stereochemistry, since only ketol **4a** is formed. In the reaction of the isoxazoline **3b** a mixture (3:1) of the isomeric ketols **4b,c** and the ketone **6** was obtained. Compounds **5** and **6** are evidently the products of the dehydration of the *endo*-ketols **2b** and **4b** respectively, and subsequent reduction produces the enones **7** and **8** from them. It should be noted that attempts to dehydrate the ketol **2a** to the corresponding enone **7** *via* the methyl ester **9** were unsuccessful. The difficulty of dehydrating such *cis*-ketols has been noted previously [6]. The composition and structures of the compounds synthesized were confirmed by elemental analysis and ^{1}H NMR spectroscopy.

Demonstration of the relative configurations of the *endo*-protons at positions 2' and 3' and the *exo*-configuration of the hydroxy groups in the isomers **4a,b** follows from the ^{1}H NMR spectra. Since in the *endo*-orientated bicycloheptane protons the number of interactions is limited, the 2'-H and 3'-H protons appear in the spectrum as doublets with vicinal couplings $J_{2',3'}$ = 6.8 -7.0 Hz with an additional more distant coupling $J \sim 1$ Hz to the bridge proton 7', confirmed by the broadening of the signals of these protons, which corresponds to literature data compounds with analogous structures [5, 6].

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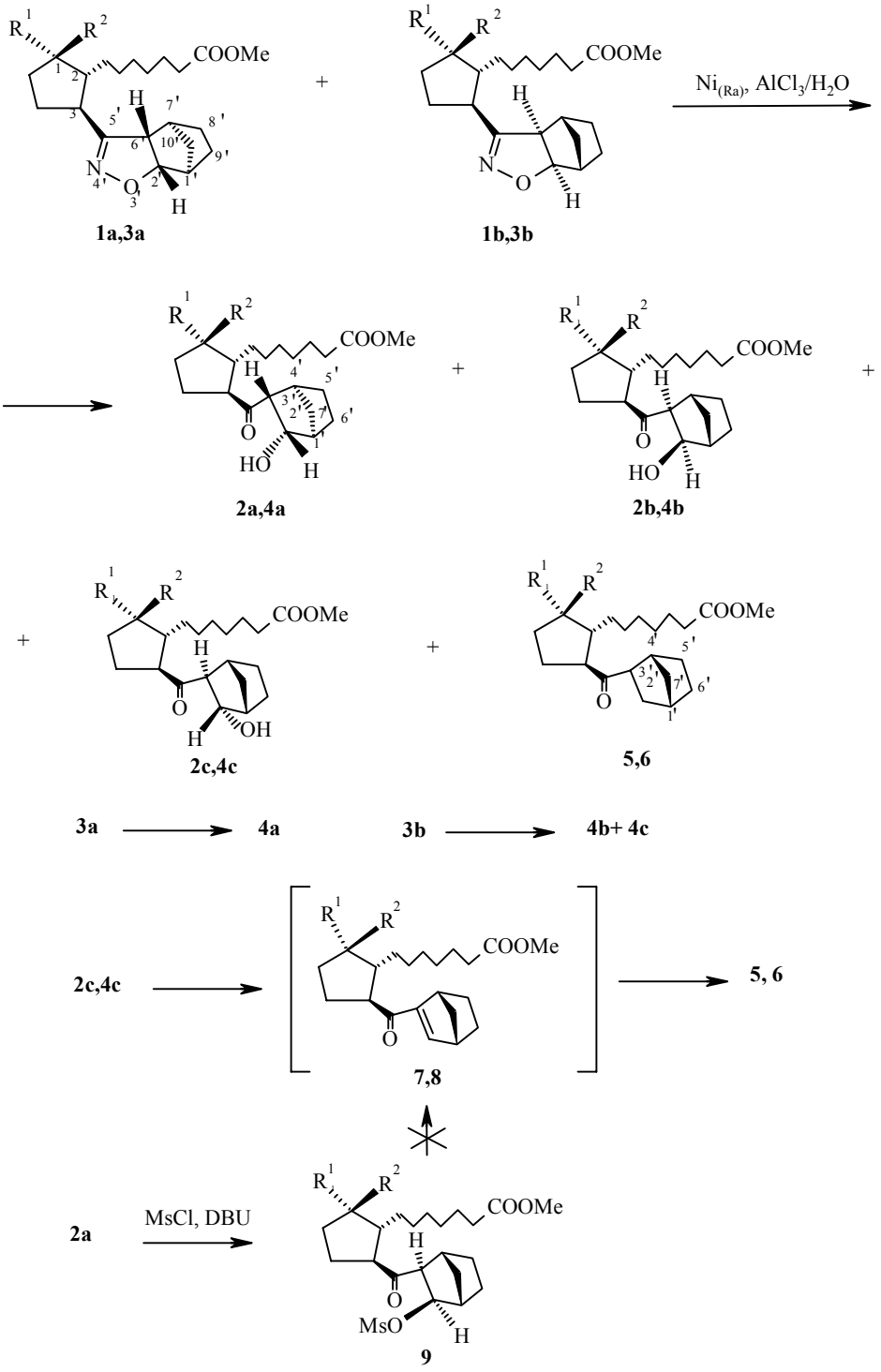
 0009-3122/03/3906-0780$25.00



1, 2, 5, 7, 9 R^1, R^2 = O; **3, 4, 6, 8** R^1 = OH, R^2 = H

In the ^{1}H NMR spectrum of compound **4c** the signal of proton 2'-H is observed as a broad triplet at 4.06 ppm with $J_{2',3'} = J_{2',1'} = 6.8$ Hz, but the signals of the protons 3'-H (3.15 ppm, d) and 1'-H (2.74 ppm, d) are deshielded by 0.2-0.4 ppm in comparison with the signals of the corresponding protons in isomers **4a** and **4b**, which indicates the change in the relative configuration of the proton 2'-H and the OH group. Thus the OH

group in isomer **4c** has the *endo* configuration. The ketol **4c** with the *endo-exo* configuration of protons 3'- and 2'-H may be either the product of non-stereospecific cleavage of the isoxazoline ring in compound **3** or of *exo-endo* isomerization of the hydroxy ketone **4**. In our view, epimerization at atom $C_{(2')}$ of the bicycloheptane fragment under the reaction conditions is the more likely source for the *endo*–ketone.

EXPERIMENTAL

IR spectra of films of the substances were recorded with a UR-20 spectrophotometer. ^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Bruker AC-200 (200 MHz) spectrometer. Mass spectra were obtained with a Varian MAT-311 mass spectrometer with an ionizing voltage of 70 eV. Column chromatography was carried out on 40/100 μ silicagel (Czech Republic). TLC was carried out on Silufol UV-254 (Serva) and Kieselgel 60 F_{254} (Merck) with 85:15 chloroform–methanol eluent and development with anisaldehyde. Preparative TLC was carried out on glass plates with Kieselgel L5/40 μ with 5% methanol in chloroform as eluent.

Starting materials **1a**, **1b**, **3a**, and **3b** were prepared as describe elsewhere [3].

Reductive Cleavage of Isoxazolines (General Method). To a solution of the isoxazoline derivative **1** or **3** (0.5 mmol) in methanol (10 ml) Raney nickel (0.60 g), $AlCl_3$ (0.10 g), and water (2 ml) were added consecutively and the mixture was stirred for 12-24 h until the starting material had disappeared (monitored by TLC). The reaction mixture was filtered through a layer of silicagel, the filtrate was evaporated , the residue was washed with water, extracted with ether, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the extract was chromatographed on a column of silicagel with methanol–chloroform as eluent.

From the mixture of compounds **1a** and **1b** (1:1) a mixture of products **2a-c** and **5** (2:2:1:1) was obtained in 60% overall yield; from the mixture of compounds **3a** and **3b** (1:1) a mixture of products **4a-c** and **6** (2:2:1:1) was obtained in 60% overall yield. Compounds **2a-c** were described elsewhere [3]. The characteristics of the newly synthesized compounds are given below.

2-(6-Carbomethoxyhexyl)-3-(2'-*exo*-hydroxybicyclo[2.2.1]heptan-3'-*exo*-carbonyl)cylopentan-1α-ol (4a). "*Erythro*"-isomer. Yield 20%. IR spectrum, ν, cm^{-1}: 1450, 1600, 1720, 1738, 3380-3500. $[M]^+$ = 366. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (1H, dd, J_1 = 10.0, J_2 = 1.0 , 7'-H); 1.26-2.45 (20H, m, 10 CH_2); 2.32 (2H, t, *J* = 8.0, $\underline{CH_2}$COOMe); 2.40 (1H, br. s, 4'-H); 2.54 (1H, br. s, 1'-H); 2.74 (1H, d, *J* = 6.5, 3'-H); 2.92 (1H, br. q, *J* = 10.5, 3-H); 3.64 (3H, s, OCH_3); 4.06 (1H, d, *J* = 6.5 , 2'-H); 4.28 (1H, t, *J* = 3.0, 1β-H). Found, %: C 68.88; H 9.35. $C_{21}H_{34}O_5$. Calculated, %: C 68.82; H 9.35.

2-(6-Carbomethoxyhexyl)-3-(2'-*exo*-hydroxybicyclo[2.2.1]heptan-3'-*exo*-carbonyl)cylopentan-1α-ol (4b). "*Threo*"-isomer. Yield 20%. IR spectrum, ν, cm^{-1}: 1450, 1600, 1720, 1738, 3380-3500. $[M]^+$ = 366. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 and 1.92 (2H, dd and d, J_1 = 10.0, J_2 = 1.0, 7'-H); 1.26-2.20 (20 H, m, 10 CH_2); 2.33 (2H, t, *J* = 8.0, $\underline{CH_2}$COOMe); 2.38 (1H, br.s, 4'-H); 2.50 (1H, br. s, 1'-H); 2.74 (1H, d, *J* = 7.0, 3'-H); 2.94 (1H, td, J_1 = J_2 = 10.5, J_3 = 7.0, 3-H); 3.64 (3H, s, OCH_3); 4.02, 1H, d, *J* = 7.0, 2'-H); 4.28 (1H, t, *J* = 4.0, 1β-H). Found, %: C 68.98; H 9.38. $C_{21}H_{34}O_5$. Calculated, %: C 68.82; H 9.35.

2-(6-Carbomethoxyhexyl)-3-(2'-*endo*-hydroxybicyclo[2.2.1]heptan-3'-*exo*-carbonyl)cyclopentan-1α-ol (4c). *Threo*-isomer. Yield 10%. IR spectrum, ν, cm^{-1}: 1450, 1600, 1720, 1738, 3400-3500. $[M]^+$ = 366. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (1H, d, *J* = 10.0, 7'-H); 1.10 -1.25 (20H, m, 10 CH_2); 2.32 (2H, t, *J* = 8.0, $\underline{CH_2}$COOMe); 2.40 (1H, br. s, 4'-H); 2.74 (1H, d, *J* = 6.8, 1'-H); 2.84 (1H, td, J_1 = J_2 = 10.5, J_3 = 5.0, 3-H); 3.15 (1H, d, *J* = 6.8, 3'-H); 3.68 (3H, s, OCH_3); 4.06 (1H, t, *J* = 6.8, 2'-H); 4.30 (1H, t, *J* = 4.0, 1β-H). Found, %: C68.89, H 9.32. Calc. for $C_{21}H_{34}O_5$, %: C 68.82, H 9.35.

2-(6-Carbomethoxyhexyl)-3-(bicyclo[2.2.1]heptan-3'-carbonyl)cyclopentan-1-one (5). Yield 10-15%. IR spectrum, ν, cm^{-1} 1720, 1740, 3450. $[M]^+$ = 348. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (2H, dd, J_1 = 20.0, J_2 = 10.5, 7'-H); 1.20-2.00 (18H, m, 9CH_2); 2.32 (2H, t, *J* = 8.0, $\underline{CH_2}$COOMe); 2.40-2.60 (4H, m, 1'-, 3'-, 4'-,

2-H); 2.94 (1H, ddd, $J_1 = J_2 = 10.5$, $J_3 = 6.0$, 3-H); 3.66 (3H, s, OCH_3); 3.52 (2H, d, $J = 6.5$, 2'-H). Found, %: C 72.38; H 9.26. $C_{21}H_{32}O_4$. Calculated, %: C 72.42; H 9.32.

2-(6-Carbomethoxyhexyl)-3-(bicyclo[2.2.1]heptan-3'-carbonyl)cyclopentan-1α-ol (6). Yield 10-15%. IR spectrum, ν, cm^{-1}: 1600, 1710, 1740, 3450. $[M]^+ = 350$. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (2H, dd, $J_1 = 11.0$, $J_2 = 9.5$, 7-H); 1.18-2.00 (18H, m, 9-CH_2); 2.18 (2H, m, 3'-H, 2-H); 2.32 (2H, t, $\underline{CH_2}$COOMe); 2.48 (1H, d, $J = 2.0$, 4'-H); 2.52 (1H, d, $J = 3.0$, 1'-H); 2.82 (1H, td, $J_1 = J_2 = 10.5$, $J_3 = 7.0$, 3-H); 3.54 (2H, d, $J = 6.5$, 2'-H); 3.64 (3H, s, OCH_3); 4.28 (1H, t, $J = 4.0$, 1β-H). Found, %: C 72.04; H 9.80. $C_{21}H_{34}O_4$. Calculated, %: C 71.93; H 9.76.

Dehydration of Ketol 2a *via* the Mesyl Ether (9). Mesyl chloride (0.024 mmol) was added to a solution of ketol **2a** (0.014 mmol) in pyridine (0.5 ml) at 0°C. The mixture was stirred at this temperature for 1 h. Ether was added to the reaction mixture, which was then washed with water and dried over $MgSO_4$. The residue, after evaporation, but without chromatography, was dissolved in methylene chloride (5 ml). 1,8-Diazobicyclo[5.4.0]undec-7-ene (0.07 mmol) was added to the solution, which was stirred for 10 h at room temperature, washed with saturated sodium chloride solution and water, and dried over $MgSO_4$. After column chromatography on silicagel a mixture of compounds was isolated, the basic one of which was the starting material **2a**.

The authors thank candidate of chemical science N. F. Bondar' for valuable discussion and comments.

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