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# COMPOSITION OF REDUCTIVE CLEAVAGE PRODUCTS OF CYCLOPENTA[*d*]ISOXAZOLINES

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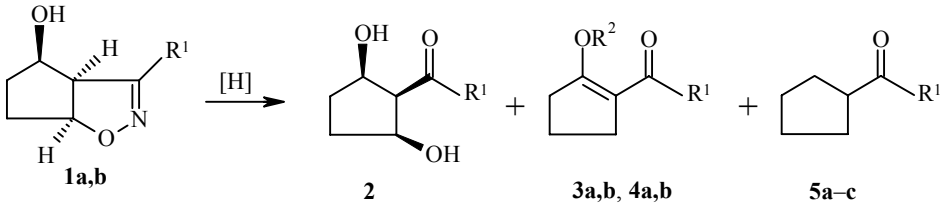
*The composition of the reductive cleavage products of cyclopenta[d]isoxazolines in acid medium depends on the acid, Raney nickel, and solvent used. Depending on the reaction conditions, we obtained β-hydroxy ketones, α,β-unsaturated ketones, or 2-acylcyclopentanes as the major products.*

**Keywords:** acyl cyclopentanes, isoxazolines, Raney nickel, prostanoids, reduction.

Reductive cleavage of 2-isoxazolines has been widely used in synthesis of many natural compounds, including prostaglandins and their analogs [1-3]. Among the various methods for accessing the latent bifunctionality of the isoxazoline heterocycle in the scheme involving introduction of a prostaglandin side chain into 2-cyclopentenone by a 1,3-dipolar cycloaddition, the most convenient approach from our standpoint is reductive cleavage upon treatment with Raney nickel in acid medium [2]. Under these conditions, the following processes occur in succession: cleavage of the N–O bond of the cyclopenta[*d*]isoxazoline **1**, acid hydrolysis of the intermediate hydroxy imine to form diol **2**, the dehydration of which in the presence of strong acids leads to the enol **3** [2].




**1a,b** **2** **3a,b**, **4a,b** **5a–c**

**1-5 a** $R^1 = (CH_2)_4COOMe$; **1**, **3-5 b** $R^1 = (CH_2)_5COOMe$; **5 c** $R^1 = (CH_2)_4COOH$; **3** $R^2 = H$, **4** $R^2 = Me$

We note that in the case of opening of isoxazolines **1**, the diol **2** is the sole product under catalytic hydrogenation conditions on Raney nickel in the presence of boric acid by the Curran method [4]. On the other hand, carrying out this reaction in aqueous 75% trifluoroacetic acid usually has resulted in moderate yields, leading mainly to enols **3** along with fairly low amounts of diols **2** [2].

During a detailed study, we observed that when using Raney nickel* obtained immediately before the reactions, the composition and ratio of the products change considerably, and specifically we isolated ketones of type **5** as the major products. As a result of treatment of isoxazoline **1a** with such Raney nickel in aqueous 75%

* In the reaction, we used a reagent prepared by the standard procedure for obtaining W-2 Raney nickel, and as specified by the procedure it was carefully washed with distilled water until the pH was neutral [5].

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trifluoroacetic acid, from the reaction mixture we isolated 20% ketone **5a**, 16% of the corresponding acid **5c**, 10% enol **3a**, and 1% diol **2a**. The analogous reaction with isoxazoline **1b** in an aqueous methanol solution of trifluoroacetic acid led to 27% ketone **5b**, 16% enol **3b**, and 5% of its methyl ester **4b**. The physicochemical characteristics of diol **2a** and enols **3a,b** match those obtained earlier. Formation of products of type **5** may be represented as the following processes occurring in succession under the reaction conditions: reduction of the double bond of enol **3**, dehydration of the hydroxyl group, and reduction of the newly formed double bond.

## EXPERIMENTAL

The IR spectra were taken on a UR-20, in a thin film for liquids; the $^1$H and $^{13}$C NMR spectra were taken on a Bruker AC-200 (200 MHz and 50 MHz) in $CDCl_3$, internal standard TMS. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct injection of the sample into the source, with ionizing radiation energy 70 eV. The course of the reaction and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates. For the column chromatography, we used Silicagel L 100/160 from Chemapol.

The procedure for reductive cleavage of isoxazolines **1** is described in [2].

**Methyl Ester of 7-(2-Methoxycyclopent-1-enyl)-7-oxoheptanoic Acid (4b).** IR spectrum, ν, cm$^{-1}$: 1743 (COOMe); 1675 (C=O); 1620 (C=C). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.95 (1H, t, *J* = 2.5, H-2'); 4.69 (1H, dt, *J* = 6.5, *J* = 2.5, H-5'); 3.67 (3H, s, $COOCH_3$); 3.36 (3H, s, $OCH_3$-5'); 2.64-2.84 (3H, m, $COCH_2$ + H-4'); 2.41-2.56 (1H, m, H-4'); 2.33 (2H, t, *J* = 7.0, $CH_2COOMe$); 1.58-1.73 + 1.31-1.43 (4H + 2H, m, –$CH_2$–). Found: *m/z* 254 $[M]^+$. $C_{14}H_{22}O_4$. Calculated: M 254.326.

**Methyl Ester of 6-Cyclopentyl-6-oxohexanoic Acid (5a).** IR spectrum, ν, cm$^{-1}$: 1740 (COOMe); 1710 (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, $COOCH_3$); 2.88 (1H, m, *J* = 7.5, H-1'); 2.49 (2H, t, *J* = 7.0, $COCH_2$); 2.33 (2H, t, *J* = 7.0, $CH_2COOMe$); 1.54-1.84 (12H, m, –$CH_2$–). $^{13}$C NMR spectrum, δ, ppm: 212.76 (C=O); 173.86 (COOMe); 51.47 (C-1'); 51.39 ($COO\underline{C}H_3$); 41.30 ($CO\underline{C}H_2$); 33.88 ($\underline{C}H_2COOMe$); 28.95 (C-2'); 26.04 (C-3'); 24.58 (C-3); 23.28 (C-4).

**Methyl Ester of 7-Cyclopentyl-7-oxoheptanoic Acid (5b).** IR spectrum, ν, cm$^{-1}$: 1743 (COOMe), 1715 (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.66 (3H, s, $COOCH_3$); 2.85 (1H, m, *J* = 7.5, H-1'); 2.45 (2H, t, *J* = 7.2, $COCH_2$); 2.31 (2H, t, *J* = 7.2, $C\underline{H}_2COOMe$); 1.51-1.82 (12H, m, –$CH_2$–) + 1.24-1.38 (2H, m, –$C_4H_2$–). $^{13}$C NMR spectrum, δ, ppm: 213.15 (C=O); 174.09 (COOMe); 51.41 ($COO\underline{C}H_3$); 41.48 ($CO\underline{C}H_2$); 33.87 ($\underline{C}H_2COOMe$); 28.93 (C-2'); 26.01 (C-3'); 28.77 (C-4); 24.76 (C-3); 23.40 (C-5). Found: *m/z* 226 $[M]^+$. $C_{13}H_{22}O_3$. Calculated: M 226.317.

**6-Cyclopentyl-6-oxohexanoic Acid (5c).** IR spectrum, ν, cm$^{-1}$: 1700 (C=O); 3070-3030, 2700-2675 (OH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 10.71 (1H, br. s, OH); 2.89 (1H, m, *J* = 7.5, H-1'); 2.52 (2H, t, *J* = 6.5, $COCH_2$); 2.39 (2H, t, *J* = 6.5, $CH_2COOH$); 1.54-1.85 (12H, m, –$CH_2$–). $^{13}$C NMR spectrum, δ, ppm: 213.54 (C=O); 179.07 (COOH); 51.43 (C-1'); 41.30 ($CO\underline{C}H_2$); 33.87 ($\underline{C}H_2COOH$); 28.96 (C-2'); 26.00 (C-3'); 24.29 (C-3); 23.17 (C-4).

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