SELECTIVE HYDROGENOLYSIS OF 3,5-DISUBSTITUTED FUNCTIONALIZED 2-ISOXAZOLINES

F. A. Lakhvich and E. V. Koroleva

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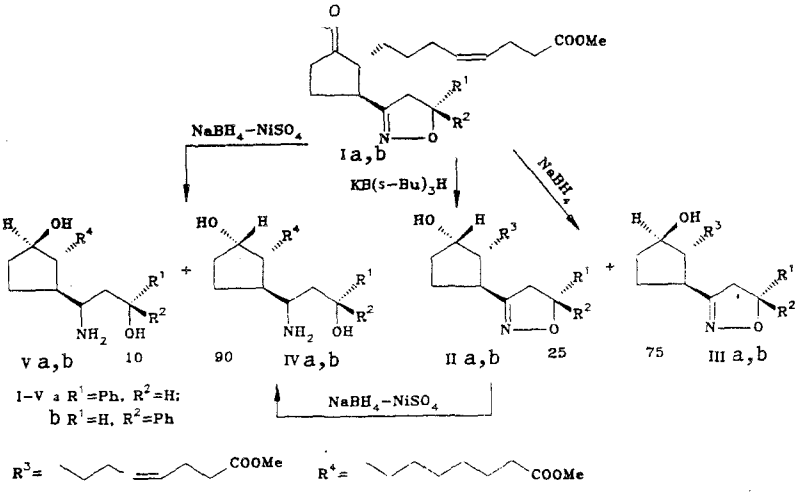
The cleavage of 2-isoxazolines to 1,3-aminoalcohols is most stereoselective when carried out with lithium aluminohydride as the reducing agent [1, 2]. However, the use of this reagent for isoxazolinoprostanoids (I) is inconvenient as a result of concurrent reduction of the carboxy group and nonstereospecific reduction of the carbonyl group.

We have found that the reducing system $NaBH_4$–$NiSO_4$ [3] proposed for the hydrogenolysis of isoxazoles to enaminoketones is a chemo- and stereoselective reductant for the 2-isoxazolines (I) and (II) to the prostanoic acid analogs with a γ-aminoalcohol moiety in the ω-chain. Under the conditions described below, cleavage of the heterocycle in isoxazolines (I) takes place together with α-stereoselective reduction of the cyclic carbonyl group, to give a mixture of 1α-OH (IV) and 1β-OH (V) aminodiols (90:10). Borohydride reduction of the isoxazoline (I) in the absence of $NiSO_4$ proceeds without cleavage of the heterocycle and with β-stereoselective reduction of the carbonyl group to give a mixture of isomers (III) and (II), 75:25, of the corresponding 3-isoxazolinylcyclopentanols:



Hydrogenolysis of the isoxazolines (IIa) and (IIb) after preliminary selective reduction with K selectride of the cyclic carbonyl group in each stereoisomer at $C_{(5)}$ of the heterocycle (IIa) or (IIb) gave as the sole stereoisomer the aminodiol (IVa) or (IVb). Under the reaction conditions, the double bond in the α-chain is saturated. The terminal ester group is unaffected, not even traces of the triol being found in the reaction products. As compared with previously described mixtures of borohydride reductants with metal salts [2], the system $NaBH_4$–$NiSO_4$ is much more stereoselective.

To a solution of 1 mmole of (I) or (II) and 1 mmole of $NiSO_4 \cdot 7H_2O$ in methanol was added at −30 to −25°C 5 mmole of $NaBH_4$. After 5-10 minutes the cooling was withdrawn, the temperature raised to ambient, 15-20 ml of 25% aqueous ammonia added, and the mixture concentrated to 1/3 of its initial volume. It was then extracted with chloroform, and purified by preparative TLC on silica gel in the system hexane–ether–methanol (30:65:5). 2α-(7-Methoxycarbonylheptyl)-3β-[(3-phenyl-3-hydroxy-1-aminopropyl)]cyclopentan-1α-ol (IVa) was obtained in 80% yield from 2α-(7-methoxycarbonylhept-3-enyl)-3β-[3-(5-phenyloxazolinyl)]cyclopentan-1α-ol (IIa). IR spectrum, film: 3500, 3300, 1735 cm^{-1}. PMR spectrum ($CDCl_3$): 1.25-1.90 (20H,

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m, CH_2, CH); 2.3 (2H, t, CH_2COO); 3.11 (1H, m, $\underline{H}C-NH_2$); 3.43 (4H, br. s, OH, NH_2); 3.66 (3H, s, OMe); 4.20 (1H, m, ring $\underline{H}COH$); 5.09 (1H, m, $\underline{H}COH$); 7.33 ppm (5H, m, Ph). M^+ 391. From the stereoisomer (IIb) there was obtained the aminodiol (IVb), yield 85%. IR spectrum, film: 3400, 3250, 1730 cm^{-1}. PMR spectrum, $CDCl_3$: 1.30-1.85 (20H, m, CH_2, CH); 2.32 (2H, t, CH_2COO); 2.8 (4H, br. s, 2OH, NH_2); 3.16 (1H, d.t, J = 11.0; 2.2 Hz, $\underline{H}C-NH_2$); 3.67 (3H, s, OMe); 4.25 (1H, m, ring $\underline{H}COH$); 4.92 (1H, d.d, J = 10.8; 1.8 Hz, $HC-O\underline{H}$); 7.21-7.24 (5H, m, Ph). M^+ 391. A report on the determination of the relative configurations of the isoxazolinocyclopentanes isomeric at $C_{(5)}$ of the heterocycle and of the corresponding aminoalcohols will be published later.

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