Chemistry of Heterocyclic Compounds, Vol. 43, No. 5, 2007

NOVEL SYNTHESIS OF 2-ISOXAZOLYL STEROIDS

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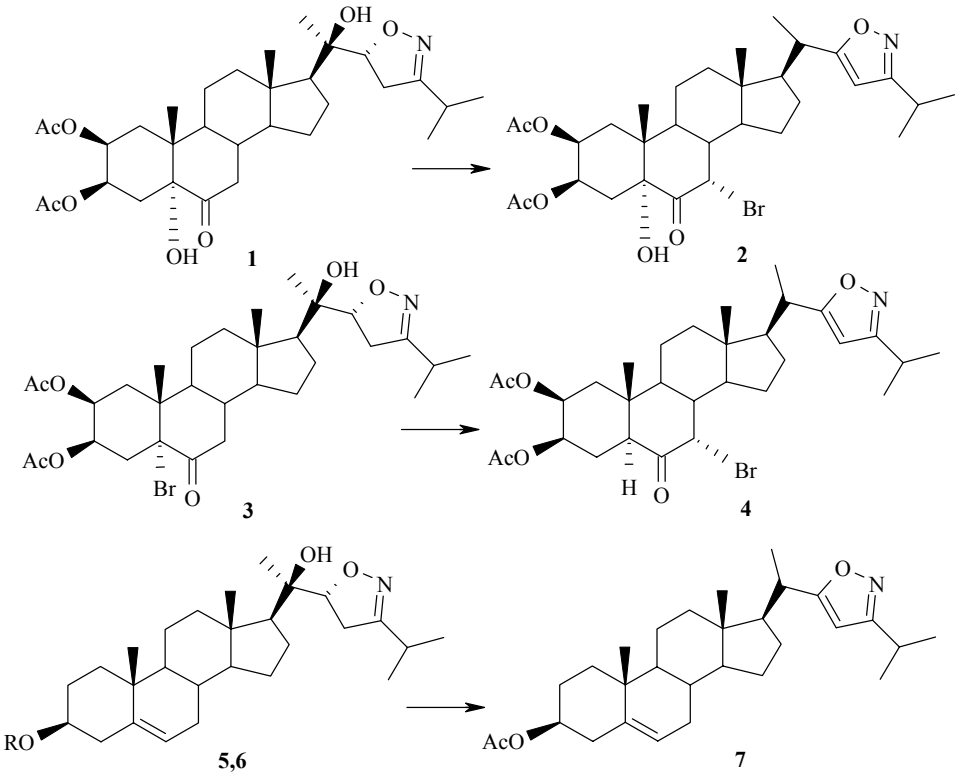
Novel examples of the reaction of 20-hydroxy-20-isoxazolinyl steroids to 20-isoxazolyl steroids using acetic acid in the presence of hydrobromic acid are reported.

Keywords: isoxazoles, isoxazolines, isoxazolinyl steroids.

We recently observed the stereoselective conversion of 20-hydroxy-20-isoxazolinyl steroids to 20-isoxazolyl steroids using lithium perchlorate and trifluoroacetic acid in acetonitrile [1]. The formation of isoxazoles from 20-hydroxy-20-isoxazolinyl steroids has also been noted before in the dehydration of the latter using thionyl chloride in a chloroform and pyridine medium [2].



5 R = H, **6** R= Ac

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0009-3122/07/4305-0637

We unexpectedly found novel examples of the reaction of 20-hydroxy-20-isoxazolinyl steroids to 20-isoxazolyl steroids when attempting to use 20-hydroxy-20-isoxazolinyl steroids in the synthesis of ecdysteroids in conditions similar to those reported by us before [3, 4]. It was hoped to introduce a Δ^7-6-keto group in compound **1** by the conventional method of bromination – dehydrobromination of 6-oxosteroids [5]. However, bromination of ketone **1** [6] by bromine in acetic acid gave both introduction of bromine and the transformation of the 20-hydroxy-20-isoxazolinyl steroid **1** to the 7α-bromo-6-oxo-20-isoxazolyl steroid **2** which ^{1}H NMR spectroscopy showed to be a mixture of the C-20(R)- and C-20(S)-epimers in the ratio of about 2 : 1.

The formation of a 20-isoxazolyl steroid was also observed in the isomerization reaction of the 5α-bromo derivative **3** [7] to the 7α-bromide. Thus the action of a catalytic amount of hydrobromic acid and zinc bromide in acetic acid on compound **3** gave the 7α-bromo-20-isoxazolyl steroid **4** which was also a mixture of epimers at the C-20 center and which could not be separated on silica gel chromatography.

Model experiments carried out by us on the reaction of isoxazolines **5** and **6** in acetic acid with traces of hydrobromic acid gave similar results, the basic product being a chromatographically inseparable mixture of 20-isoxazolyl steroids **7**. It should be noted that refluxing the 20-hydroxy derivative **5** in acetic acid gives only the acetylation product of the 3-hydroxy group and is not accompanied by formation of the isoxazole **7**.

The reaction described can be explained as follows. The acid protonates the tertiary hydroxyl group of compounds **1, 3, 5** and **6** which is readily removed. The carbocation formed rearranges with the participation of the neighboring isoxazoline ring leading to its aromatization. The fact that a $\Delta^{20(21)}$ compound is not found in the reaction products supports such a mechanism. Their formation might infer initial dehydration of the 20-hydroxy group with its subsequent migration and aromatization of the heterocycle.

EXPERIMENTAL

^{1}H NMR spectra were taken on an Avance 500 (500 MHz) instrument using $CDCl_3$ and with TMS as internal standard and IR spectra on a UR-20 instrument (film).

Compound 7 (General Method). Hydrobromic acid (40%, 0.5 ml) was added to a solution of the isoxazoline **5** or **6** (1 mmol) in acetic acid (10 ml) and the reaction mixture was heated at 50-60ºC for 1-2 h. The product was poured into water, extracted with ethyl acetate, the extract dried with anhydrous sodium sulfate, and the solvent was removed. The residue was chromatographed on a silica gel column using toluene as eluent. Isoxazole **7** yield 40-60%. The spectroscopic characteristics of obtained as a mixture of the isomers product agreed with data for the 20-α-methyl-20-isoxazolyl steroid [1] and 20β-methyl-20-isoxazolyl steroid [8].

2β,3β-Diacetoxy-7α-bromo-20-(3'-isopropyl-2'-isoxazolin-5'-yl)pregnan-5α-ol-6-one (2) was obtained by the method indicated from the isoxazoline **1** with the addition of a catalytic amount of zinc bromide. IR spectrum, ν, cm^{-1}: 3440, 1750, 1720, 1240, 1260. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.72 and 0.77 (3H, two s, H-18); 0.98 and 1.02 (3H, two s, H-19); 1.22 (9H, d, *J* = 7, H-21, CH(C$\underline{H}_3$)$_2$); 1.96 and 1.99 (3H, two s, CH_3CO); 2.03 (3H, s, CH_3CO); 2.82 (1H, m, H-20); 3.02 (1H, m, C$\underline{H}$Me$_2$); 4.18 (1H, d, *J* = 4.5, H-7); 5.28 (2H, m, H-2,3); 5.80 and 5.84 (1H, two s, H-4'). Compound **2** has been described by us before [6].

2β,3β-Diacetoxy-7α-bromo-20-(3'-isopropylisoxazol-5'-yl)pregnan-6-one (4) was prepared by the method indicated from the isoxazoline **3** by the addition of 1.3 ml of a 2M solution of bromine in acetic acid. IR spectrum, ν, cm^{-1}: 1755, 1730, 1250, 1260. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.70 and 0.76 (3H, two s, H-18); 0.88 and 0.96 (3H, two s, H-19); 1.22 and 1.28 (3H, two d, *J* = 7, H-21); 1.24 (6H, d, *J* = 7, CH(C$\underline{H}_3$)$_2$); 2.00 and 2.06 (3H, two s, CH_3CO); 2.06 and 2.08 (3H, two s, CH_3CO); 2.82 (1H, m, H-20); 2.91 (1H, m, C$\underline{H}$Me$_2$); 3.34 (1H, m, H-5α); 4.16 (1H, d, *J* = 3, H-7β); 4.84 (1H, m, H-2α); 5.26 (1H, m, H-3α); 5.79 and 5.82 (1H, two s, H-4'). Found, %: C 61.19; H 7.22; Br 13.10; N 2.24. $C_{36}H_{44}N_4O_6$. Calculated, %: C 61.38; H 7.31; Br 13.17; N 2.31.

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