SYNTHESIS OF NEW DRIMANE AND HOMODRIMANE LACTAMS 
BY BECKMANN REARRANGEMENT OF SOME KETOXIMES

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Abstract. The synthesis of new drimane and homodrimane lactams, derivatives of octahydro-1H-benzo[d]azepine and octahydro-1H-benzo[c]azepine, from norambreinolide is reported. Those compounds were prepared by the Beckmann rearrangement of the corresponding ketoximes.

Keywords: drimane, homodrimane, lactam, ketoxime, synthesis, Beckmann rearrangement.

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Introduction

Many drimane and homodrimane sesquiterpenoids, including those with nitrogen, exhibit various types of a biological activity: antifungal, antibacterial, antiviral, cytotoxic, antifeedant, etc. [1]. Therefore, the development of synthetic methods for these compounds is of a scientific and practical importance.

In a search for new biologically active compounds and in continuation of our group’s investigations of obtaining nitrogen-containing sesquiterpenoids [2-5], in the present paper the synthesis of new drimane and homodrimane lactams by the Beckmann rearrangement of some ketoximes is described.

Earlier Grant et al. reported the preparation of amides 1-4 by the Beckmann rearrangement of Z- and E-isomers of oxime 5 obtained from 14,15-dinorlabd-8(17)-en-13-one 6 [6]. Then, Barrero et al. described a multi-step synthesis of amide 7 from (-)-sclareol [7]. Later, amides 8 and 9 were synthesized by the Beckmann rearrangement of oxime 10 of 11-dihomodriman-8α-ol-12-one 11 [8] (Figure 1).

Figure 1. Tri-, tetra- and pentanorlabdane amides obtained by the Beckmann rearrangement and their precursors.

The Beckmann rearrangement is known to occur stereospecifically as a result of anti-migration of the bulkier radical. Therefore, it has been expected that the major product of the Beckmann rearrangement of oxime 10 would be amide 7. However, in the case of oxime 10, amide 9 is obtained as a result of the migration of CH$_3$- group and concomitant dehydration.

Recently, Kharitonov et al. have obtained a mixture of isomeric furanolactams, derivatives of octahydro-1H-benzo[d]azepine 12 and octahydro-1H-benzo[c]azepines 13 and 14 by the Beckmann rearrangement of the respective 7-oxo-phlomisoic acid ketoxime 15 and its methyl ester 16 (Figure 2) [9].
Results and discussion

Herein, the synthesis of new drimane and homodrimane lactams 17-21 by the Beckmann rearrangement of the corresponding oximes 22 and 23 is described. Oximes 22 and 23 have been obtained earlier [10] from the commercially available norambreinolide 24 according to the procedure [11].

The treatment of ketoxime 22 with thionyl chloride in anhydrous dioxane according to the literature procedure [9,12] resulted in a mixture of isomeric lactams 17 and 19. The Beckmann rearrangement of oxime 23 under these conditions gave a mixture of lactams 20 and 21 (Scheme 1).

It is very likely that thiophenolactam 19 is formed as a result of the interaction of the intermediate lactam 18 with thionyl chloride. The presence of the α,β-unsaturated carbonyl group in the molecule of lactam 18 activated the methyl groups and promoted the reaction of lactam 18 with thionyl chloride.

It is known that the analogous reactions of o-toluidine and ring-substituted o-toluidines 25 with thionyl chloride in xylene at reflux temperature yield 2,1-benzisothiazoles 26 (Scheme 2) [13].
The structures of all new compounds were confirmed by the IR, $^1\text{H}$, $^{13}\text{C}$, $^{15}\text{N}$- NMR spectral data and by elemental analysis.

The NMR data of compound 20 have been assigned (Figures 3, 4) on the base of their 1D (H, $^{13}\text{C}$, DEPT-135°) and 2D homo- (H/H COSY-45°, H/H NOESY) and heteronuclear (H/$^{13}\text{C}$ HSQC, H/$^{15}\text{N}$ HMQC and H/$^{13}\text{C}$ HMBC, H/$^{15}\text{N}$ HMBC) correlation spectra. According to the NMR spectral data, compound 20 is a homodrimane lactam. An analysis of H, $^{13}\text{C}$, H/H COSY and H/$^{13}\text{C}$ HSQC NMR spectra suggested the presence of three isolated spin systems: CH$_2$CH$_2$CH$_2$ (C-11 to C-9), CHCH$_2$NH (C-7 to NH), and CHCH$_3$ (C-4 to C-13) (Figure 3). Key H/$^{13}\text{C}$ HMBC and H/$^{15}\text{N}$ HMBC correlations for lactam 20 are also depicted in Figure 3. The rearranged carbon framework of compound 20 becomes obvious at a detailed analysis of its H/$^{13}\text{C}$ HMBC spectrum. Thus, the observed correlations from H-12 to $sp^2$ hybridized carbon (C-5, δ$_C$ 169.9) are indicative for the $\Delta^{5(12)}$ localization, which was supported also by the correlations H-12/C-4 and H-12/C-6. A signal of a lactam nitrogen atom has been found at δ$_N$ 110 ppm in the H/$^{15}\text{N}$ HMQC spectrum, while its proton resonates at δ$_H$ 5.93 ppm as a broad triplet with J = 5.8 Hz. The position of lactam has been corroborated by both H/$^{13}\text{C}$ HMBC and H/$^{15}\text{N}$ HMBC spectra. Thus, the H-7/N-2 cross-peak in the H/$^{13}\text{C}$ HMBC spectrum, as well as H$_3$-13/C$_3$, H$_3$-13/C$_4$ and H$_3$-13/C$_5$ in the H/$^{13}\text{C}$ HMBC spectrum, prove the localization of a lactam function as depicted in Figure 3.

The migration of a double bond $\Delta^{4(5)}$ in precursor 23 to $\Delta^{5(12)}$, as a result of the reaction, has additionally generated two centres of isomerism: a geometrical centre at C-5/C-12 and an optical one at C-4. The NOESY correlations between H-12 and H$_3$-16, as well as H-12 and H-11, demonstrate the trans nature of the isomer at $\Delta^{5(12)}$. The NOESY correlation between H-4 and H-7 indicates that they are in the $\alpha$-plane and determines the (R) relative configuration at C-4 (Figure 4).

Conclusion

New drimane and homodrimane lactams, derivatives of octahydro-1H-benzo[d]azepine and octahydro-1H-benzo[c]azepine, which are of a scientific and practical importance as compounds with a potential biological activity, were synthesized.

Experimental

General experimental procedure

Melting points (m.p.) have been determined on a Boetius heating stage and were not corrected. The IR spectra have been recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. The NMR spectra have been recorded on a Bruker 400 Avance III spectrometer at 400.13 MHz for H, 100.62 MHz for $^{13}\text{C}$ and 40.55 MHz for $^{15}\text{N}$ in CDCl$_3$, with tetramethylsilane (TMS) as an internal standard. Proton chemical shifts (δ) are reported in parts per million (ppm) and are compared against the residual non-deuterated solvent peak (7.26 ppm for CHCl$_3$ of CDCl$_3$). Chemical shifts of carbon atoms (δ) are reported in ppm and are compared against the deuterated solvent peak (77.00 ppm for $^{13}\text{C}$ of CDCl$_3$) and relative to MeNO$_2$ in the $^{15}\text{N}$ NMR spectra. Coupling constants (J) are recorded in Hertz. Signals in the H and $^{13}\text{C}$ NMR spectra have been assigned using the DEPT-135, H/H COSY-45, H/$^{13}\text{C}$ HSQC, H/$^{15}\text{N}$ HMBC, and H/$^{15}\text{N}$ NOESY experiments whereas the H/$^{15}\text{N}$ HMBC experiments have been used for the assignment of the $^{15}\text{N}$ nuclei chemical shift. The course of reactions has been monitored by the TLC on Silufol plates with the detection by I$_2$ vapours. The column chromatography has been performed on Silica Gel (L 70-230 mesh Fluka). Chemicals have been
of commercially available reagent grades being used without further purification. All solvents have been purified and dried by standard techniques before use.

**Beckmann rearrangement of oxime 22**

A solution of oxime 22 (200 mg, 0.849 mmol) in anhydrous dioxane (10 mL) has been cooled in an ice bath and treated dropwise with freshly distilled SOCl₂ (0.185 mL). Then the reaction mixture has been heated at 50-60°C for 9 h, cooled, diluted with H₂O (100 mL), and extracted with Et₂O (3x50 mL). The extract has been washed with water (3x20 mL) and dried over anhydrous MgSO₄. The evaporation of the solvent under a reduced pressure gives the crude product (220 mg) which has been chromatographed on a column of silica gel (7 g). The elution with a mixture of EtOAc/light petroleum ether (1:1) gives pure lactam 19 (105 mg, 53 %) as white solid. The elution with EtOAc gives lactam 17 (7.3 mg, 4%) as oil.

4,5,14,15,16-Pentamethyl-2-oxo-2,3,6,7,8,9,10,11-octahydro-1H-benzo[d]azepine (17). Calculated, % for C₆H₈NO: C 76.74, H 10.70, N 5.95. Found, %: C 76.51, H 10.67, N 5.93. IR (ν, cm⁻¹): 3329, 2924, 2863, 1647, 1605, 1497, 1460, 1392, 1377, 1354, 1304, 1129, 1036, 893, 819, 774, 716. ¹H NMR (δ, ppm): 0.88 (3H, s, CH₃-14), 0.94 (3H, s, CH₃-15), 1.19 (3H, s, CH₃-16), 1.47 (1H, t, J=3.8, J=3.66, H-7), 1.74 (3H, d, J=1, CH₃-12), 1.90 (3H, d, J=0.96, CH₃-13), 3.08-3.11 (2H, m, H-1a, H-1b), 7.05 (1H, d, J=3.72, H-12), 8.17 (1H, d, J=3.68, H-13).

**Beckmann rearrangement of oxime 23**

A solution of oxime 23 (150 mg, 0.511 mmol) in anhydrous dioxane (7.5 mL) has been cooled in an ice bath and treated dropwise with freshly distilled SOCl₂ (0.180 mL). Then the reaction mixture has been heated at 60-65°C for 17 h, cooled, diluted with H₂O (75 mL), and extracted with Et₂O (3x35 mL). The extract has been washed with water (3x15ml) and dried over anhydrous MgSO₄. The evaporation of the solvent under a reduced pressure gives the crude product (141 mg) which has been chromatographed on a column of silica gel (7 g). The elution with a mixture of EtOAc/light petroleum ether (4:1) gives lactam 21.

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References


