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

Elena Secara

Institute of Chemistry of the Academy of Sciences of Moldova, 3 Academiei str., Chisinau MD-2028, Republic of Moldova
e-mail: esecara8@gmail.com

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).

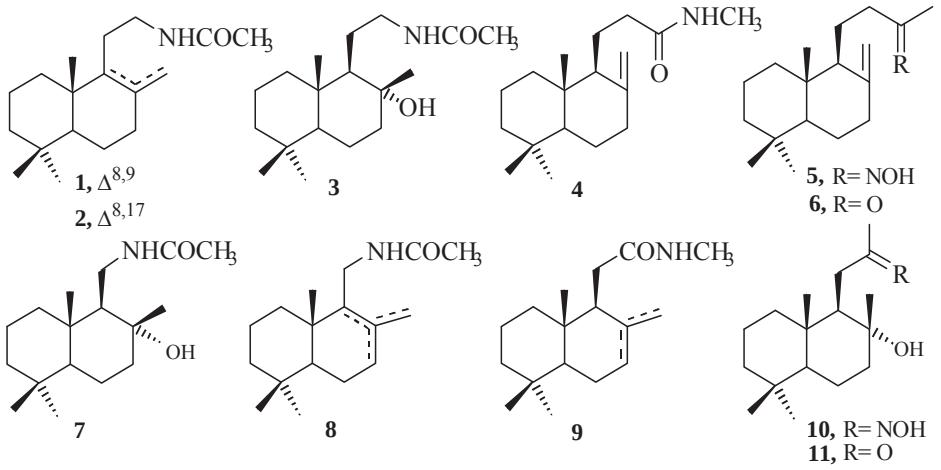


Figure 1. Tri-, tetra- and pentanorlabdane amides obtained by the Beckmann rearrangement and their precursors.

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].

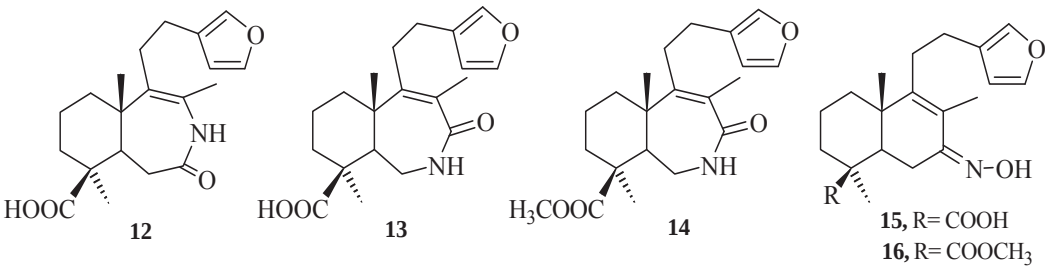
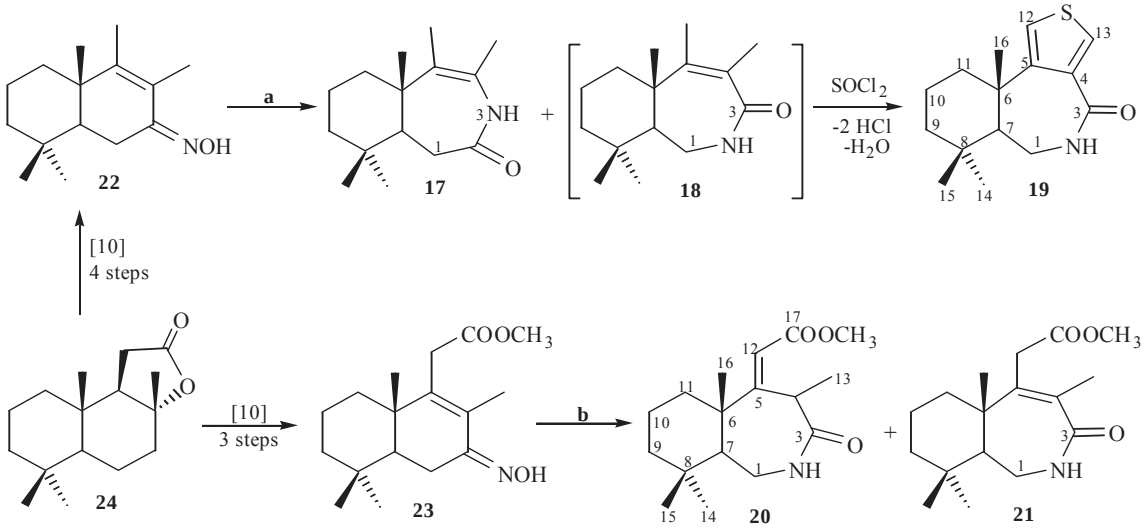


Figure 2. Furanolactams obtained by the Beckmann rearrangement of 7-oxo-phlomisoic acid ketoximes and their precursors.

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].

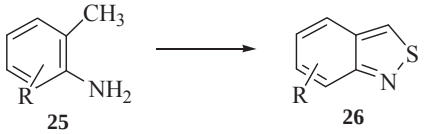
The treatment of ketoxime **22** with thionyl chloride in anhydrous dioxane according to the literature procedure [9,12] resulted in a mixture of isomeric lactams **17** and **19**. The Beckmann rearrangement of oxime **23** under these conditions gave a mixture of lactams **20** and **21** (Scheme 1).



Scheme 1. Synthesis of new drimane and homodrimane lactams.
Reagents and conditions: a) $SOCl_2$, dioxane, 50-60 °C, 9h; b) $SOCl_2$, dioxane, 60-65 °C, 17 h.

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].



Scheme 2. Synthesis of 2,1-benzisothiazoles from *o*-toluidines.
Reagents and conditions: $SOCl_2$/xylene, reflux.

The structures of all new compounds were confirmed by the IR, ^{1}H, ^{13}C, ^{15}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 (^{1}H, ^{13}C, DEPT-135°) and 2D homo- ($^{1}H/^{1}H$ COSY-45°, $^{1}H/^{1}H$ NOESY) and heteronuclear ($^{1}H/^{13}C$ HSQC, $^{1}H/^{15}N$ HMQC and $^{1}H/^{13}C$ HMBC, $^{1}H/^{15}N$ HMBC) correlation spectra. According to the NMR spectral data, compound **20** is a homodrimane lactam. An analysis of ^{1}H, ^{13}C, $^{1}H/^{1}H$ COSY and $^{1}H/^{13}C$ HSQC NMR spectra suggested the presence of three isolated spin systems: $CH_2CH_2CH_2$ (C-11 to C-9), $CHCH_2NH$ (C-7 to NH), and $CHCH_3$ (C-4 to C-13) (Figure 3). Key $^{1}H/^{13}C$ HMBC and $^{1}H/^{15}N$ 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 $^{1}H/^{13}C$ 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 $^{1}H/^{15}N$ 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 $^{1}H/^{15}N$ HMBC and $^{1}H/^{13}C$ HMBC spectra. Thus, the H-7/N-2 cross-peak in the $^{1}H/^{15}N$ HMBC spectrum, as well as H_3-13/C_3, H_3-13/C_4 and H_3-13/C_5 in the $^{1}H/^{13}C$ HMBC spectrum, prove the localization of a lactam function as depicted in Figure 3.

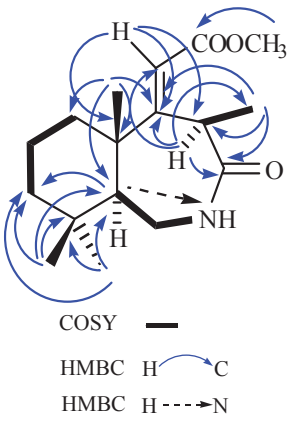


Figure 3. Key COSY and HMBC correlations in lactam 20.

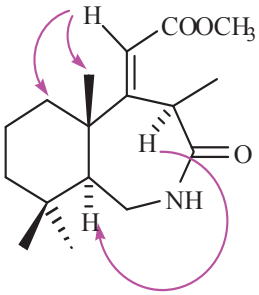


Figure 4. Key NOESY correlations in lactam 20.

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 α-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 ^{1}H, 100.62 MHz for ^{13}C and 40.55 MHz for ^{15}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}C of $CDCl_3$) and relative to $MeNO_2$ in the ^{15}N NMR spectra. Coupling constants (J) are recorded in Hertz. Signals in the ^{1}H and ^{13}C NMR spectra have been assigned using the DEPT-135, $^{1}H/^{1}H$ COSY-45, $^{1}H/^{13}C$ HSQC, $^{1}H/^{13}C$ HMBC, and $^{1}H/^{1}H$ NOESY experiments whereas the $^{1}H/^{15}N$ HMBC experiments have been used for the assignment of the ^{15}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 $SOCl_2$ (0.185 mL). Then the reaction mixture has been heated at 50-60°C for 9 h, cooled, diluted with H_2O (100 mL), and extracted with Et_2O (3x50 mL). The extract has been washed with water (3x20 mL) and dried over anhydrous $MgSO_4$. 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 $C_{15}H_{25}NO$: C 76.54, 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. ^{1}H NMR (δ, ppm): 0.88 (3H, s, CH_3-14), 0.94 (3H, s, CH_3-15), 1.19 (3H, s, CH_3-16), 1.47 (1H, t, J=3.8, J=3.66, H-7), 1.74 (3H, d, J=1, CH_3-12), 1.90 (3H, d, J=0.96, CH_3-13), 3.08-3.11 (2H, m, H-1a, H-1b). ^{13}C NMR (δ, ppm): 17.91 (q, C-12), 18.58 (q, C-13), 18.76 (t, C-10), 20.88 (q, C-16), 22.39 (q, C-15), 33.27 (q, C-14), 34.40 (s, C-8), 38.09 (t, C-11), 39.27 (t, C-1), 40.83 (t, C-9), 45.59 (s, C-6), 58.22 (d, C-7), 124.7 (s, C-4), 151.64 (s, C-5), 174.49 (s, C-2). ^{15}N NMR (δ, ppm): 121.0 (NH).

14,15,16-Trimethyl-4,5-(3,4-thiopheno)-3-oxo-2,3,6,7,8,9,10,11-octahydro-1H-benzo[c]azepine (**19).** M.p. 188-190°C (from $CHCl_3$ – MeOH (1:1)). Calculated, % for $C_{15}H_{23}NOS$: C 67.88, H 8.73, N 5.27, S 12.08. Found, %: C 67.85, H 8.75, N 5.25, S 12.03. IR (ν, cm^{-1}): 3323, 3133, 2924, 2862, 1645, 1606, 1496, 1461, 1392, 1377, 1354, 1304, 1129, 1036, 893, 819, 774, 724. ^{1}H NMR (δ, ppm): 0.91 (3H, s, CH_3-15), 1.03 (3H, s, CH_3-14), 1.40 (3H, s, CH_3-16), 1.69 (1H, dd, J=5.64, 2.52, H-7), 2.28 (2H, m, H-1a, H-1b), 7.05 (1H, d, J=3.72, H-12), 8.17 (1H, d, J=3.68, H-13). ^{13}C NMR (δ, ppm): 19.18 (t, C-10), 22.08 (q, C-15), 25.93 (q, C-16), 33.12 (q, C-14), 34.33 (s, C-8), 39.84 (t, C-1), 41.14 (t, C-9), 41.86 (s, C-6), 42.64 (t, C-11), 55.35 (d, C-7), 121.45 (d, C-12), 133.87 (d, C-13), 135.01 (s, C-4), 152.31 (s, C-5), 167.34 (s, C-3). ^{15}N NMR (δ, ppm): 118.0 (NH).

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 $SOCl_2$ (0.180 mL). Then the reaction mixture has been heated at 60-65°C for 17 h, cooled, diluted with H_2O (75 mL), and extracted with Et_2O (3x35 mL). The extract has been washed with water (3x15mL) and dried over anhydrous $MgSO_4$. 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 (3:2) gives pure lactam **20** (55 mg, 37%) as white solid. The elution with EtOAc/light petroleum ether mixture (4:1) gives lactam **21** (28 mg, 19%) as oil.

5-Carbomethoxymethinyl-13,14,15,16-tetramethyl-3-oxo-2,3,6,7,8,9,10,11-octahydro-1H-benzo[c]azepine (20). M.p. 127-129°C (from MeOH). Calculated, % for $C_{17}H_{27}NO_3$: C 69.59, H 9.27, N 4.77. Found, %: C 69.57, H 9.30, N 4.74. IR (ν, cm^{-1}): 3290, 3239, 3099, 2929, 1722, 1664, 1620, 1468, 1458, 1379, 1170, 1029, 867, 769. ^{1}H NMR (δ, ppm): 0.91 (3H, s, CH_3-14), 1.01 (3H, s, CH_3-15), 1.22 (1H, td, J=13.2, 4.7, H-9a), 1.23 (1H, dd, J=6.3, 1.5, H-7α), 1.38 (3H, s, CH_3-16), 1.44 (3H, d, J=7.1, CH_3-13), 3.29 (1H, ddd, J=15.9, 6.6, 1.5, H-1a), 3.41 (1H, dd, J=15.9, 6.4, H-1b), 3.73 (3H, s, OCH_3), 4.69 (1H, q, J=7.1, H-4α), 5.84 (1H, s, H-12), 5.93 (1H, brt, J=5.8, NH). ^{13}C NMR (δ, ppm): 19.19 (q, C-16), 19.59 (t, C-10), 19.71 (q, C-13), 22.67 (q, C-15), 33.41 (q, C-14), 35.18 (s, C-8), 38.88 (t, C-11), 39.40 (t, C-1), 41.24 (d, C-4), 41.53 (t, C-9), 45.05 (s, C-6), 51.27 (q, OCH_3), 56.89 (d, C-7), 112.56 (d, C-12), 167.14 (s, C-17), 169.56 (s, C-5), 176.66 (s, C-3). ^{15}N NMR (δ, ppm): 110.0 (NH).

5-Carbomethoxymethyl-13,14,15,16-tetramethyl-3-oxo-2,3,6,7,8,9,10,11-octahydro-1H-benzo[c]azepine (21). Calculated, % for $C_{17}H_{27}NO_3$: C 69.59, H 9.27, N 4.77. Found, %: C 69.56, H 9.30, N 4.75. IR (ν, cm^{-1}): 3293, 3223, 3083, 2945, 1716, 1661, 1616, 1464, 1434, 1391, 1359, 1169, 1032, 916, 731. ^{1}H NMR (δ, ppm): 0.95 (3H, s, CH_3-14), 0.97 (3H, s, CH_3-15), 1.33 (3H, s, CH_3-16), 1.65 (1H, m, H-7), 1.89 (3H, s, CH_3-13), 3.30 (2H, s, H-12a, H-12b), 3.71 (3H, s, OCH_3), 6.07 (1H, brt, J=5.6, NH). ^{13}C NMR (δ, ppm): 17.89 (q, C-13), 18.90 (t, C-10), 22.18 (q, C-16), 22.49 (q, C-15), 33.57 (q, C-14), 34.83 (s, C-8), 35.67 (t, C-12), 38.75 (t, C-11), 39.57 (t, C-1), 40.71 (t, C-9), 44.09 (s, C-6), 52.05 (q, OCH_3), 57.13 (d, C-7), 121.90 (s, C-4), 146.43 (s, C-5), 171.73 (s, C-17), 174.69 (s, C-3). ^{15}N NMR (δ, ppm): 108.0 (NH).

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