SYNTHESIS OF 5-ALKYLPYRROLIZIDIN-3-ONES FROM THE LUKES-ŠORM LACTAM BY GRIGNARD REACTION AND RECYCLIZATION OF INTERMEDIATE 5-BROMOALKYLPYRROLIDIN-2-ONES

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Abstract - Synthesis of 5-alkylpyrrolizidin-3-ones 7 and 8 from pyrrolizidin-3,5-dione 1 is described. Grignard reaction of 1 gave 5-(3'-oxobutyl)pyrrolidin-2-one 2. Reduction of 2 with sodium borohydride, followed by mesylation, bromination, and cyclization afforded a diastereomeric mixture 7a and 8a, which were separated by chromatography. The same procedure with 3, also obtained from 1 by a Grignard reaction, afforded 7b and 8b.

Lukes-Šorm's[1] dilactam 1 is a valuable compound in medicine and in chemistry. Under the generic name rolziracetam, 1 has recently been reported to have amnesia-reversal activity and was subject of a multicenter, phase 2 clinical study in memory-impaired elderly patients, as well as in individuals with primary degenerative dementia (PDD)[2]. We reported[3] a synthesis of cis-5-n-propylpyrrolizidine (9), whose analogs are found among ant toxins[4,5]. Recently, we reported a conversion of 1 into trans-2,5-dialkylpyrrolidine[6], also found among natural ant toxins, and an improved synthesis of 1 and ring opening reaction of 1 with Grignard reagents and other nucleophiles[7]. We now report a simple conversion of 1 into cis-5-alkylpyrrolizidin-3-ones (7a,b) and trans-isomers 8a,b.

Reaction of 1 with methylmagnesium bromide and n-propylmagnesium chloride gave ketolactams 2 and 3, respectively, in good yields[7]. Reduction of ketone 2 with sodium borohydride on silica gel gave the alcohol 4a as a mixture of stereo-

isomers. Because hydroxylactam **4a** is soluble in water, supported borohydride gave better result. Mesylation of the alcohol **4a** and treatment of the mesylate **5a** with lithium bromide in acetone gave the bromide **6a** in 64% yield. The same procedure with **3** yielded **6b**. Reaction of the bromide **6a** with sodium hydride in tetrahydrofuran gave a mixture of cis-5-methylpyrrolizidin-3-one (**7a**) and trans-isomer **8a**, in 37% and 35% yield, respectively. Although the synthesis described

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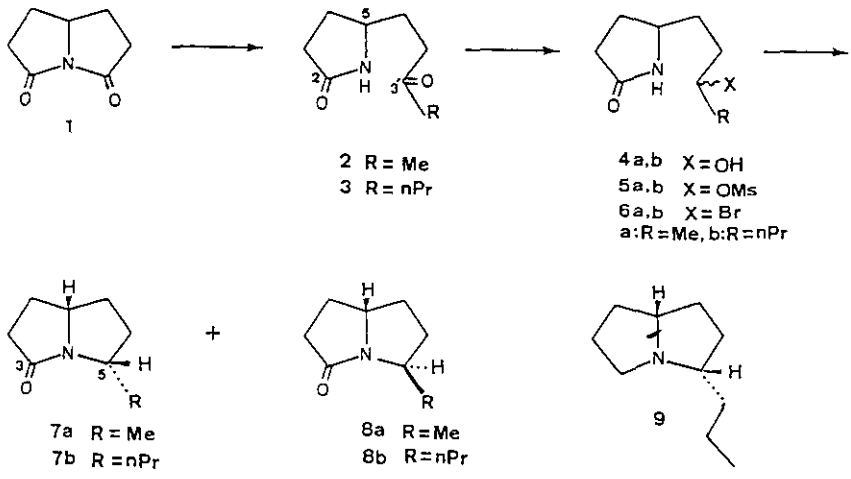

here is not stereoselective, the isomers are effectively separated by flash chromatography affording the cis-isomer as the less polar material. Bromide **6b** when similarly treated with sodium hydride afforded cis-5-n-propylpyrrolizidin-3-one (**7b**) and trans-isomer **8b**, in 34% and 32% yields, respectively, which were identical with the samples prepared by the reported procedure[3]. The cis-isomer **7b**, whose stereochemistry was confirmed by X-ray analysis[3] of the thioketal of cis-5-acetonylpyrrolizidin-3-one, shows the nmr signals of C_5- and C_8-protons at 3.55 and 3.88 ppm, respectively. On the other hand, the nmr signals of the protons at C_5- and C_8-positions of trans-isomer **8b** were observed at 3.55-4.10 ppm as a multiplet[3]. The nmr comparison of **7a** and **8a** allowed to assign to **7a** the cis- and to **8a** the trans-configuration.

Ketones **2** and **3** obtained from dilactam **1** by Grignard reaction were used for synthesis of 5-alkylpyrrolidin-2-ones and derived pyrrolidine ant alkaloids. It is now shown that these ketolactams are also versatile intermediates for synthesis of 5-alkylpyrrolizidin-3-ones and derived pyrrolizidine ant alkaloids[8,9].

EXPERIMENTAL

Ir spectra were determined by using a Beckman 4230 instrument in chloroform solution. ^{1}H-Nmr spectra were determined in deuterochloroform by using a Varian HR-220 spectrometer or a Jeol FX-100 spectrometer. Ms were obtained with a V. G. Micromass 7070F spectrometer with a Perkin-Elmer Sigma 3 gas chromatograph equipped with 2% OV-1 column, or a Hitachi-Perkin-Elmer RMU-6E spectrometer (70 eV). Chemical ionization (CI) Ms were obtained by using a Finnigan 1015D spectrometer. Silica gel (230-400 mesh) for flash chromatography was from EM Laboratories.

5-(3'-Hydroxy-n-butyl)pyrrolidin-2-one (4a). A mixture of the ketone 2 (155 mg, 1.0 mmol), $NaBH_4$ on silica gel (Aldrich, 8%, 160 mg) in CH_2Cl_2 (2.0 ml) was stirred at 25°C for 10 min. The mixture was diluted with 5% MeOH in CH_2Cl_2, filtered through a silica gel column to give 4a (101 mg, 64%) as an oil: Ir 3440 and 1695 cm^{-1}; nmr 7.25 (1H, br s, NH), 3.77 and 3.64 (each 1H, each br s), 2.72 (1H, br s), 2.39- 2.05 (4H, m), 1.81-1.36 (6H, m), and 1.16 (3H, d, J = 6 Hz, C-Me); CI-Ms (NH_3, m/z) 158 (M^++1) and 174 (M^++17).

5-(3'-Hydroxy-n-hexyl)pyrrolidin-2-one (4b). The ketone 3 (1.50 g, 8.2 mmol) was treated with $NaBH_4$ on silica gel (Aldrich, 8%, 1.60 g) in CH_2Cl_2 (50 ml) as above to give 4b (1.32 g, 97%) as an oil: Ir 3440 and 1680 cm^{-1}; nmr 7.25 (1H, br s, NH), 3.80-3.32 (2H, m), 2.95-2.65 (1H, m), 2.45-1.10 (12H, m), and 0.87 (3H, br t, J = 6 Hz, C-Me); ms (m/z) 185 (M^+).

5-(3'-Bromo-n-butyl)pyrrolidin-2-one (6a). MsCl (573 mg, 5.0 mmol) was added to a stirred solution of the alcohol 4a (985 mg, 5.0 mmol) and Et_3N (505 mg, 5.0 mmol) in CH_2Cl_2 (30 ml) at 0°C. The mixture was stirred at 0°C for 1 h, washed with brine, dried ($MgSO_4$), and evaporated to give 5a as an oil: Nmr 8.00 (1H, br s, NH), 4.95-4.65 (1H, m), 3.95-3.70 (1H, m), 3.00 (3H, s, Ms), 2.70-1.50 (8H, m), and 1.42 (3H, d, J = 6 Hz, C-Me), which was used in the next step without further purification. A mixture of the mesylate 5a, LiBr (1.00 g, 11.5 mmol), and acetone (50 ml) was stirred at 25°C for 15h. The mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated to give 6a (705 mg, 64%) as an oil: Ir 3440 and 1680 cm^{-1}; nmr 7.65 (1H, br s, NH), 4.30-3.80 and 3.80-3.35 (each 1H, each m), 2.45-1.40 (8H, m), and 1.76 (3H, d, J = 6 Hz, C-Me); ms (m/z) 219 and 221 (M^+).

5-(3'-Bromo-n-hexyl)pyrrolidin-2-one (6b). The alcohol 4b (1.85 g, 10 mmol) was treated with MsCl (1.14 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in CH_2Cl_2 (50

ml) as above to give 5-(3'-mesyloxy-n-hexyl)pyrrolidin-2-one (**5b**): Nmr 7.65 (1H, br s, NH), 4.90-4.35 (1H, m), 3.85-3.35 (1H, m), 3.00 (3H, s, Ms), 2.70-1.10 (12H, m), and 0.92 (3H, br t, J = 6 Hz, C-Me). Reaction of the mesylate **5b** and LiBr (3.0 g, 34.5 mmol) in acetone (50 ml) carried out as above yielded **6b** (1.56 g, 63%): Ir 3440 and 1690 cm^{-1}; nmr 7.30 (1H, br s, NH), 4.15-3.30 (2H, m), 2.55-1.10 (12H, m), and 0.89 (3H, br t, J = 6 Hz, C-Me); ms (m/z) 247 and 249(M^+).

cis-5-Methylpyrrolizidin-3-one (7a) and trans-5-Methylpyrrolizidin-3-one (8a). A mixture of the bromide **6a** (220 mg, 1.0 mmol) and NaH (50% dispersion in mineral oil, 48 mg, 1.0 mmol) in THF (2.0 ml) was stirred at 25°C for 15 h. The mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on silica gel with CH_2Cl_2/MeOH= 95/5 as the eluent yielding **7a** (53 mg, 37%) as an oil: Ir 1680 cm^{-1}; nmr 3.95 (1H, m, C_8-H), 3.55 (1H, m, C_5-H), 3.10-1.00 (8H, m), and 1.05 (3H, d, J = 6 Hz, C-Me); ms (m/z) 139 (M^+), and oily **8a** as the more polar compound (49 mg, 35%): Ir 1680 cm^{-1}; nmr 4.16-3.55 (2H, m, C_5- and C_8-H), 3.00-1.00 (8H, m), and 1.05 (3H, d, J = 6 Hz, C-Me); ms (m/z) 139 (M^+).

cis-5-n-Propylpyrrolizidin-3-one (7b) and trans-5-n-Propylpyrrolizidin-3-one (8b). A mixture of the bromide **6b** (1.00 g, 4.0 mmol), NaH (50% dispersion in mineral oil, 192 mg, 4.0 mmol) in THF (30 ml) was stirred at 25°C for 15 h. Work-up as mentioned above yielded **7b** (228 mg, 34%) and **8b** as the more polar compound (216 mg, 32%), which were both identical with authentic samples[9] by TLC, ir, and nmr comparison.

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REFERENCES AND NOTES

The compounds described in this paper are racemic, and only one series of enantiomers is depicted for convenience.

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