Short synthesis of 2,3,4,5-tetrahydrocytisine

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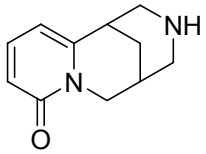
Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract
2,3,4,5-Tetrahydrocytisine (**5**) was synthesized from quinolizidine-2,6-dione in three steps and acceptable yield.

Keywords: Cytisine, quinolizidine-2,6-dione, Mannich condensation, (±)-2,3,4,5-tetrahydrocytisine

Introduction

Due to its ability to affect the nicotinic cholinergic receptors[1] selectively, cytisine **1**, a well known and widespread representative of quinolizidine alkaloids[2] of family *Leguminosae* has attracted considerable attention in the pharmacology[3,4] and in the synthetic chemistry, as well. Especially, the recent results[5,6,7,8] of pharmacological studies stimulated the synthetic research considerably, inspiring the development of new drugs, *e.g.* in smoking cessation. As a result of the numerous trials some different strategies have been elaborated towards its total synthesis starting mainly from properly substituted pyridines[9,10,11], piperidines[12] or bispidines[13], affording the target molecule at the end of multistep procedures in poor or moderate yields. These methods have been surveyed in a comparative manner in an excellent review published recently.[14]



Cytisine (**1**)

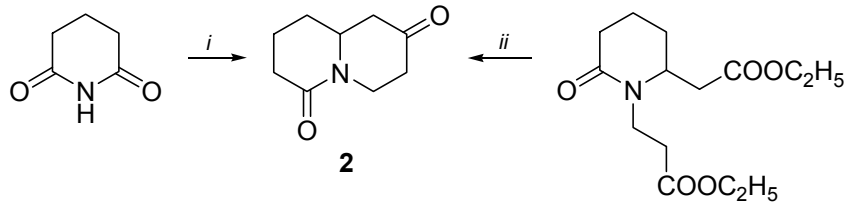
Some saturated compounds including the 3,7-diazatricyclic moiety of cytisine were synthesized from 2-quinolizidone in our laboratory some years ago.[15] Our experiments to convert

these saturated diazatricyclics to cytisine proved, however, unsuccessful, though a wide scale of oxidizing agents, *e.g.* potassium hexacyanoferrate(III), sodium dichromate, mercury(II) acetate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DCCQ), was tried to effect the regioselective tertiary amine → lactam oxidation. Unfortunately, no satisfactory selectivity was observed, and the very complex mixtures obtained in these oxidative transformations made this strategy useless.

Results and Discussion

Due to the difficulties mentioned above quinolizidine-2,6-dione (**2**), a starting compound including the lactam functionality, was subjected to a double Mannich condensation used successfully in our previous work.[15]

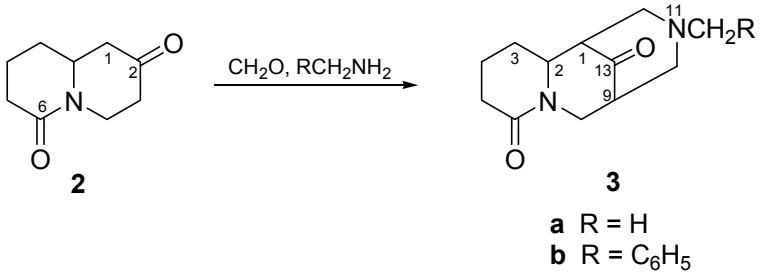
The key intermediate **2** was synthesized using the biomimetic α-acylimmonium cyclization method.[16] Thus, glutarimide was alkylated with 3-butyn-1-ol in a Mitsunobu protocol and reduced with L-Selectride^R, followed by treatment with formic acid, to give the desired product in an acceptable yield. An alternative synthetic route was also used to obtain **2**. The 2-piperidone diester available from simple chemicals in some steps[17] was cyclized, hydrolyzed and decarboxylated in a usual Dieckmann sequence to produce **2** on a multigram scale without need of the chromatographic purification (Scheme 1).



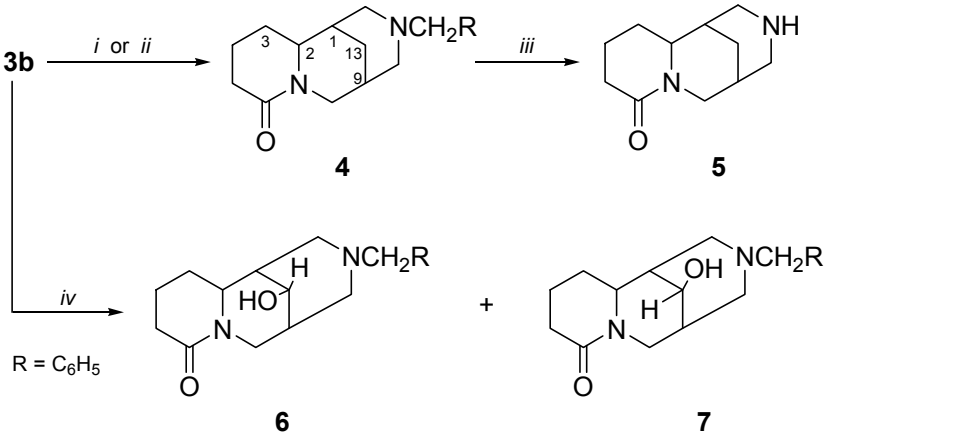
i, acylimmonium cyclization; *ii*, Dieckmann condensation, hydrolysis, decarboxylation

Scheme 1. Synthesis of the key intermediate **2**.

The double Mannich condensation of **2** with formaldehyde and methylamine furnished the ketones **3a,b** in good yield (Scheme 2). The reduction of the C(13) carbonyl group of **3b** was effected through reduction of its tosylhydrazone with sodium cyanoborohydride in sulfolan - dimethyl formamide mixture to yield **4**. The classical Wolff-Kishner procedure gave the same product without any observable damage of the lactam group and in a higher yield (Scheme 3). Removal of the benzyl group of **4** in the usual way (hydrogenation with palladium/charcoal) resulted in 2,3,4,5-tetrahydrocytisine (**5**) as a racemic mixture.



Scheme 2. The double Mannich condensation.



Scheme 3. Transformations of **3b**.

Reduction of the ketolactam **3b** with sodium borohydride led to the formation of an isomeric pair of hydroxylactams **6** (α isomer) and **7** (β isomer) in a ratio 2/8. Based on a previous NMR signal assignment[15,18] the steric position of the C(13)-OH group was determined by ^{13}C NMR spectroscopy.

Conclusions

In this work we demonstrated a new synthetic strategy to construct the diazatricyclic skeleton of cytisine and related compounds. The easy access of the intermediate **2** and the simple transformations provide a short and efficient pathway in total synthesis of cytisine and its derivatives.

Experimental Section

General Procedures. All solvents purchased commercially were redistilled and dried before use. TLC was made with Kieselgel $60F_{254}$ Plastikfolien from Merck. Merck Kieselgel 60 (0.040-0.063 mm) was used for column chromatography. Melting points were measured on a Büchi SMP 20 apparatus and not corrected. IR spectra: Perkin-Elmer FTIR 1600 spectrometer, ^{1}H and ^{13}C NMR spectra: Bruker AM-300 at 300 and 75 MHz, or Varian VXR at 400 and 100 MHz, respectively.

Quinolizidine-2,6-dione (2). Prepared according to the Speckamp's protocol,[16] starting from glutarimide which was N-alkylated with 1-butyn-4-ol in a Mitsunobu reaction, followed by reduction and cyclization to give the target synthon **2** in an acceptable yield. The same substance was obtained in the Dieckmann procedure as described.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.58-2.15 m (4 H), 2.40-2.55 m (6 H), 2.87-2.95 m (1 H), 3.65-3.75 m (1 H), 4.88-4.95 m (1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 18.9, 29.6, 32.7, 40.6, 41.0, 48.1, 54.9 (10-C), 169.5 (6-C), 206.9 (2-C). No NMR data have been reported in the papers[16,17] cited above.

11-Methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecan-6,13-dione (11-Methyl-13-keto-2,3,4,5-tetrahydrocytisine) (3a). To the solution of quinolizidine-2,6-dione (2) (0.5 g, 3.0 mmol and 0.18 g acetic acid in 5 mL of methanol a mixture of methyl amine (0.11 g, 3.0 mmol) and acetic acid (0.18 g, 3.0 mmol) in 3 mL methanol was added dropwise under reflux for six hours. Simultaneously paraformaldehyde (0.2 g, 6.6 mmol) was added in six portions in time intervals of 1 hour. After heating for one hour the reaction mixture was kept at room temperature overnight, then evaporated. Under cooling the residue was made alkaline with 30% potassium hydroxide solution, saturated with potassium carbonate and extracted with 3x20 mL of dichloromethane. The dichloromethane solution was dried and concentrated in vacuum to give 0.76 g of the crude product as a yellow oil. 0.40 g of pure **3a** (57,4%) were obtained with column chromatography, using acetone-methanol 2:3 eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.6-2.7 m (6 H), 2.19 s (N-CH_3, 3 H), 2.9-3.3 m (4 H), 3.7-3.8 m (2 H), 4.1-4.4 m (2 H), 5.13 dd (1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 20.3, 27.1, 32.9, 45.1, 47.4, 48.1, 52.1, 57.0, 59.8, 61.1, 170.0 (6-C), 212.7 (13-C). The fumarate of **3a** recrystallized from 2-propanol melts at 142-43°C.

11-Benzyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecan-6,13-dione (11-Benzyl-13-keto-2,3,4,5-tetra-hydrocytisine) (3b). To the solution of quinolizidine-2,6-dione (**2**) (6,00 g, 358 mmol) in methanol (120 mL)a mixture of benzylamine (4,56 g, 420 mmol), acetic acid (2,52 g, 420 mmol) and methanol (60 mL) was added dropwise under reflux for 6 hrs. Simultaneously paraformaldehyde (2,40 g, 800 mmol) was added to the reaction mixture in six equal portions in time intervals of 1 hour. After standing overnight at room temperature and removal of the solvent in vacuum the residue was made strongly alkaline with 30% potassium hydroxide solution and saturated with solid potassium carbonate. The mixture was extracted with dichloromethane (3x50 mL), the solution was dried (Na_2SO_4) and evaporated to yield a dark viscous liquid (12,48 g).

Trituration with diethyl ether gave 3,81 g of **3b** as a slightly yellow solid. Flash chromatography of the residue (eluent ethyl acetate - acetone 1:1) furnished an additional portion of 1,68 g of **3b**. Overall yield: 51.4%.mp. 133-34°C. IR (KBr): 3060, 3035, 3025, 1724, 1635. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.6-1.8 m (4 H), 2.20-2.55 m (5 H), 2.71-2.76 m (1 H), 3.02-3.06 m (1 H), 3.15-3.76 m (5 H), 5.20 dd (1 H), 7.22-7.37 m (5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 20.3, 26.9, 33.0, 47.7 (CH), 48.1, 51.9 (CH), 53.9, 59.9 (CH), 60.2, 61.8, 127.5, 128.3, 129.0, 138.0, 169.3 (6-C), 212.7 (13-C).

11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one (N-benzyl-2,3,4,5-tetrahydrocytisine) (4). A mixture of **3b** (1.00 g, 3.35 mmol), hydrazine hydrate (0.87 g, 17,4 mmol) and 1.5 g powdered potassium hydroxide in 10 mL diethylene glycol was refluxed for 3.5 hours. After diluting with 25 mL water the mixture was extracted with diethyl ether, the ethereal solution was dried and evaporated to give 0.74 g crude product as a pale yellow oil. The crystalline product separated out from its cold diisopropyl ether solution to yield 5 (0.44 g, 46.3%), and recrystallized from hexane. Mp. 96-101°C. R_f 0.89 (ethyl acetate/isopropyl alcohol/cc. ammonia solution, 45:35:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.40-2.50 m (9 H), 2.80-3.10 m (4 H), 3.40-3.80 m (3 H), 4.76 d (1 H), 7.20-7.30 m (5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 20.3, 26.9, 33.0, 47.7 (CH), 48.1, 51.9 (CH), 53.9, 59.9 (CH), 60.2, 61.8, 127.5, 128.3, 129.0, 138.0, 169.3 (6-C), 212.7 (13-C).

7,11-Diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one (2,3,4,5-tetrahydrocytisine) (5) 4 (0.2 g, 0.70 mmol) in acetic acid (5 mL) was hydrogenated over 10% palladium on charcoal under atmospheric pressure for 30 min. After removal of the catalyst, the usual work-up produced **5** (70 mg, 51.5%) as pale yellow oil. R_f 0.41 (ethyl acetate/isopropyl alcohol/cc. ammonia solution, 45:35:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.55-2.05 m (10 H), 2.35-2.55 m (2 H), 2.85-3.60 m (4 H), 4.55-4.70 m (2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 20.3, 27.9 (CH), 28.1, 32.5 (CH), 32.9, 33.2, 45.8, 46.7, 50.7, 60.0 (CH), 170,6 (C=O)

11-Benzyl-13α- and 13β-hydroxy-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one (6 and 7). To the stirred solution of **3b** (100 mg, 0.335 mmol) in 5 mL methanol sodium borohydride (25 mg, 0.67 mmol) was added at 10°C. After 30 min stirring the reaction mixture was acidified with hydrochloric acid, evaporated, made alkaline, and extracted with dichloromethane. After removal of the solvent and treatment of the yellowish residue with diisopropyl ether a mixture of **6** and **7** (78 mg, 77.5%) was obtained as a white solid. IR (KBr): 3386, 3060, 3030, 3010, 1610. Recrystallization from ethyl acetate provided the major isomer **7**. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40-3.60 m (15 H), 2.61 s (2 H), 3.82 t (1 H), 4.78 dd (1 H), 7.20-7.40 m (5 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 20.2, 27.5, 33.0, 35.5 (CH), 40.5 (CH), 46.2, 47.8, 53.3, 58.8 (CH), 62.9, 70.7 (CH), 127.1, 128.3, 128.9, 138.7, 169.7 (6-C).

Minor isomer **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40-3.60 m (15 H), 2.62 s (2 H), 3.94 t (1 H), 4.08 d (1 H), 7.20-7.40 m (5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 20.2, 27.0, 33.1, 36.2 (CH), 40.3, 40.4 (CH), 51.7 (CH), 52.6, 58.8, 62.6, 70.3 (CH), 128.2, 128.3, 128.9, 138.9, 169.0 (6-C).

Acknowledgements

The authors' thanks are due Prof. G. Habermehl (School of Veterinary Medicine, Hannover) and Dr. M. Kajtár-Peredy (Central Research Institute of Chemistry, Budapest) for providing the NMR facilities. The authors are indebted to Mrs. M. Marton and Mr. B. Molnár for their valuable technical assistance.

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