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FACILE ENTRY TO ETHYL TETRAHYDRO-1*H*-PYRROLIZIN-7a(5*H*)-YLACETATE: A VERSATILE PHARMACEUTICAL INTERMEDIATE

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Abstract – An improved synthesis of ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H)*-ylacetate is reported. This valuable pharmaceutical intermediate was easily obtained from 1,7-diiodo-4-heptanone in 46% yield, thus improving the procedure reported in the literature (23% yield) which starts from 1,7-dichloro-4-heptanone. Moreover, 1,7-diiodo-4-heptanone was obtained as an easily manageable solid, in this being preferable to its 1,7-dichloro isologue, which is a quite unstable oil. The former was synthesized in high overall yield (75%) starting from the commercially available diethyl 4-oxoheptanedioate, thus overtaking the well-known problems related to the use of γ-butyrolactone.

INTRODUCTION

The pyrrolizidine ring system – 1-azabicyclo[3.3.0]octane or perhydropyrrolizine – represents a part of the structure of several drugs with different pharmacological properties. A series of compounds bearing 7a-substituted pyrrolizidine ring are shown in Figure 1. Pilsicainide (**1**) is an antiarrhythmic belonging to class I_c currently used in therapy in Japan,[1,2] while its oxymethylene analogue **2** proved to be a 4-fold more potent use-dependent blocking agent on human skeletal muscle voltage-gated sodium channels.[3] Piracetam analogs **3**[4] and SK-946[5,6] have been proposed as nootropic agents acting through the activation of the muscarinic M_1 receptor.[6,7] Affinity for M_1 receptors was also found in the heterocyclic derivatives **4**[8] and **5**,[7] while SK-951 has been proposed as a prokinetic agent[9] acting as a 5-HT_4 receptor agonist.[10]

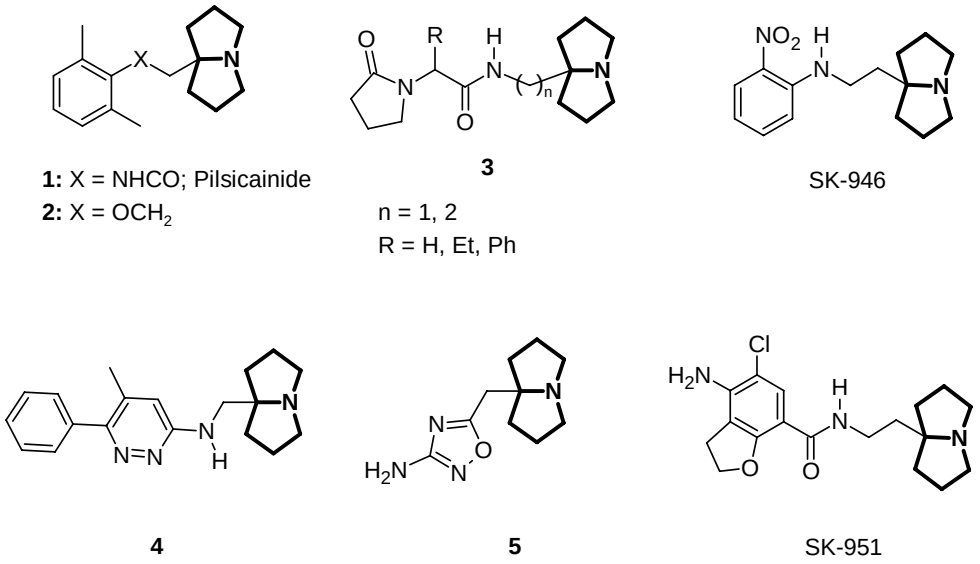


Figure 1. Pharmacological relevant compounds containing the 1-azabicyclo[3.3.0]octane moiety

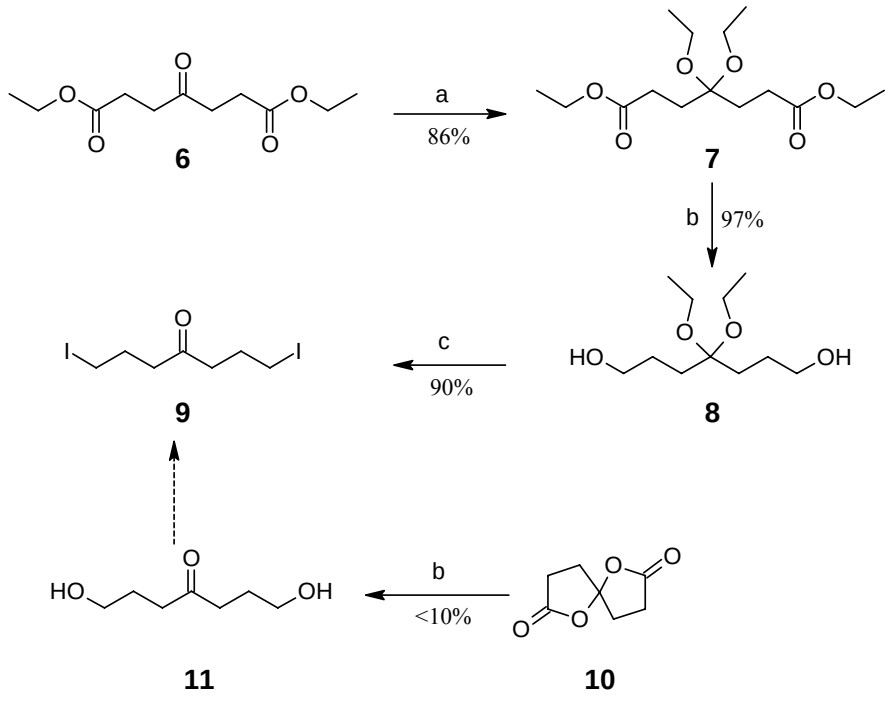
There are two possible conformers for the pyrrolizidine ring, i.e. the *trans*- and *cis*-fused form, the latter being favoured in that it is free from strong angular strains; in aqueous solution, unstrained pyrrolizidines show high basicity and are apparently the strongest bases among saturated tertiary amines, being the unshared electron pair of the nitrogen more accessible for protonation in the *cis*-fused geometry than in the *trans*-fused one.[11] 7a-Substitution is generally preferred when complex stereochemical items are to be avoided — that is a golden rule in drug research.[12]

Some of the methods reported so far for the synthesis of perhydropyrrolizine-7a-derivatives present disadvantages such as a high number of steps[13] and the use of either electrogenerated reactants[13] or high pressure hydrogenation devices.[14] More conveniently, perhydropyrrolizine-7a-derivatives are generally obtained by either the use of 1,7-dichloro-4-heptanone[15–17] or 4-(2-oxopyrrolidin-1-yl)butanoic acid,[18,19] both obtained starting from γ-butyrolactone.[18,20–22] However, some of the reported procedures use the sodium salt of 2-pyrrolidinone at high temperature[18] and pass through unstable pyrrolizine intermediates[18,19] which have to be purified as the corresponding perchlorates. Both the above procedures are tainted by the hazard of explosions.[23,24] A recently reported synthesis of both pilsicainide and its bioisostere (**1**, and **2**, respectively, Figure 1)[3] passes through ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate, which was obtained from 4-(2-oxopyrrolidin-1-yl)butanoic acid, in turn prepared starting from alternative commercially available compounds which are not included in the regulated substance list. However, the routes reported passed through several steps and gave the key intermediate in overall moderate yields. Moreover, they did not overtake the use of perchloric acid to convert an unstable pyrrolizine intermediate into the corresponding perchlorate. In this paper, we propose the use of

1,7-diiodo-4-heptanone, in lieu of 1,7-dichloro-4-heptanone, as a reagent for the synthesis of ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate. Unlike its dichloro analogue, 1,7-diiodo-4-heptanone is a solid that can be easily weighed and stored for some days in the refrigerator. It is mentioned in the Patent literature,[25] but the only preparation we could find was unpractical and inefficient in that it gave the desired intermediate in low yield (29%) as a by-product of an attempt of deprotection run on 7,7-dimethoxy[3]triangulane.[26] Herein, we report a simple synthetic route to 1,7-diiodo-4-heptanone (**9**, Scheme 1) which starts from commercially available diethyl 4-oxoheptanedioate (**6**). Ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate (**15**) was obtained starting from **9**, as shown in Scheme 2.

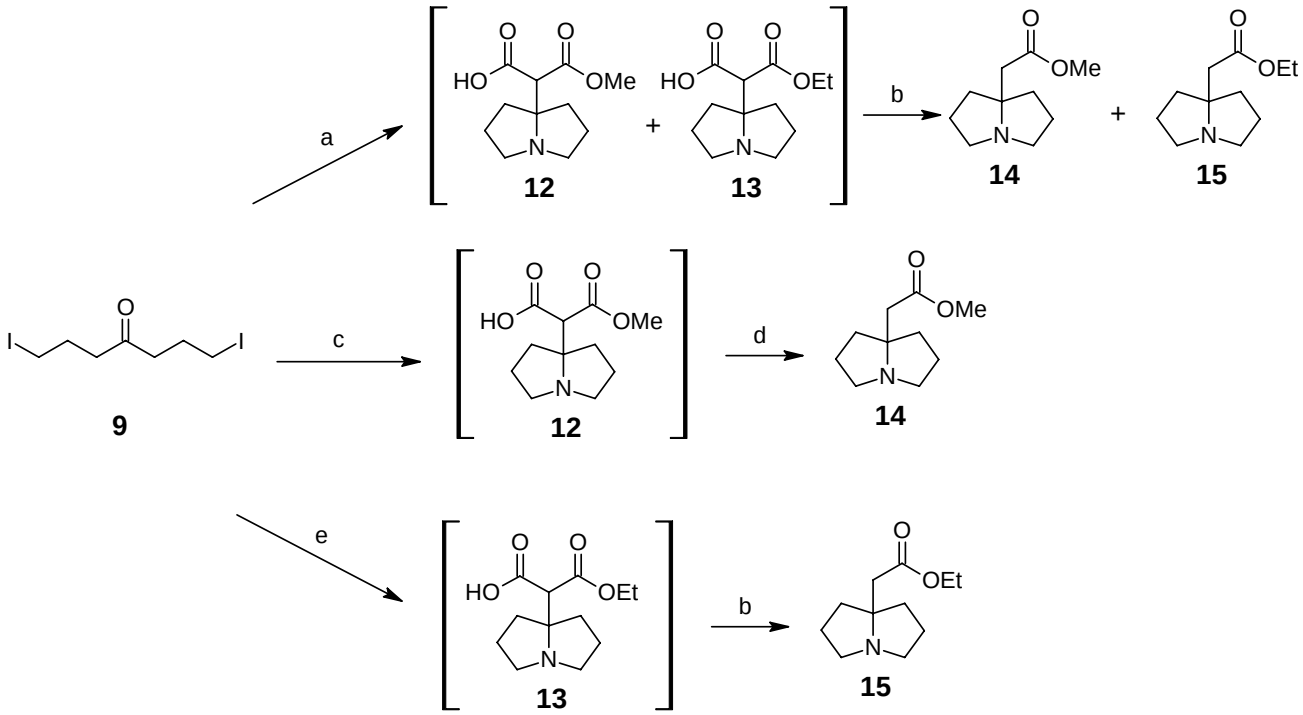
RESULTS AND DISCUSSION

Protection of the carbonyl group of the commercially available diethyl 4-oxoheptanedioate (**6**) with triethyl orthoformate in the presence of Amberlyst® 15[27] gave the ketal **7**, which was submitted to reduction with $LiAlH_4$ to give the diol **8**. Finally, the hydroxy groups of **8** were replaced by iodine in the presence of triphenylphosphine.[28] The conditions of this reaction were able to remove the protection of the carbonyl group to give **9** in 75% overall yield from **6**. An alternative route to **9** envisaged the spirolactone **10**, which underwent reduction with $LiAlH_4$ to give dihydroxyketone **11**. Unfortunately, **11** was only obtained in a complex mixture in very low yield (EIMS) and this route was abandoned.



Scheme 1. *Reagents and conditions:* (a) triethyl orthoformate, Amberlyst 15, 0 °C, 12 h; (b) $LiAlH_4$, anhyd. THF, 0 °C, 1 h; (c) I_2, triphenylphosphine, anhyd. toluene, 130 °C, 1 h.

The diiodoketone **9** represents the key intermediate for the synthesis of methyl and ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetates (**14** and **15**, respectively, Scheme 2).[1] Reaction of **9** with ethyl potassium malonate in MeOH in the presence of an excess of gaseous ammonia gave a mixture of **15** and its inferior homologue **14** in 40% and 10% yield, respectively, as assessed by GC/MS analysis. Possible intermediates **13** and **12**, respectively, are reported in square brackets. The same reaction carried out using methyl potassium malonate in MeOH gave pure **14** in 45% yield. Pure **15** was obtained in 46% yield by reacting **9** with ethyl potassium malonate in absolute EtOH in the presence of an excess of gaseous ammonia.



Scheme 2. *Reagents and conditions:* (a) gaseous NH_3, ethyl potassium malonate, MeOH, rt, 24 h; (b) EtOH, 70 °C, 2 h; (c) gaseous NH_3, methyl potassium malonate, MeOH, rt, 24 h; (d) MeOH, 70 °C, 2 h; (e) gaseous NH_3, ethyl potassium malonate, abs. EtOH, rt, 24 h.

CONCLUSIONS

A facile synthesis of ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate (**15**) is reported. It consists of only four steps, gave **15** in acceptable (35%) overall yield, and uses compounds that are not included in the regulated substance lists. Furthermore, the route proposed herein avoids the risk of explosions[23,24] that makes some of the early proposed methods[3,18,19] less attractive. The conversion of **9** into **15** (46% yield) was performed more efficiently than the previously reported reaction carried out on 1,7-dichloro-4-heptanone (23% yield).[15] Moreover, 1,7-diiodo-4-heptanone is a solid, easy to handle and store, that can be prepared starting from the commercially available diethyl 4-oxoheptanedioate (**6**). The

ester **15** represents the intermediate for the synthesis of a large variety of drugs bearing the 1-azabicyclo[3.3.0]octane moiety, such as nootropic agents, drugs effective against Alzheimer disease,[4] prokinetics,[9,10] antiarrhythmics, and skeletal muscle sodium channel blockers.[1–3] The facile route to **15** proposed herein might facilitate the access to further analogues.

EXPERIMENTAL

General. All chemicals were purchased from Sigma-Aldrich or Lancaster in the highest quality commercially available. Solvents were RP grade unless otherwise indicated. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Melting points were determined on a Gallenkamp apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-VX spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: δ 7.26 (^{1}H NMR) and δ 77.3 (^{13}C NMR). *J* values are given in Hz. EIMS spectra were recorded on a Hewlett-Packard 6890-5973 MSD gas chromatograph/mass spectrometer at low resolution. ESI$^{+/-}$/MS/MS analyses were performed with an Agilent 1100 series LC-MSD trap system VL Workstation. GC was performed on a Varian 3800 gas chromatograph equipped with a flame ionization detector and a Jew Scientific DB-5 capillary column (30 m, 0.25 mm i. d., 0.25 μm film thickness). Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040−0.063 mm, Merck, Darmstadt, Germany) as described by Still et al.[29] TLC analyses were performed on precoated silica gel on aluminium sheets (Kieselgel 60 F_{254}, Merck).

Diethyl 4,4-diethoxyheptanedioate (7). 0.25 g of Amberlyst® 15 were added to **6** (1.00 g, 4.34 mmol). The suspension was cooled to 0 °C, then triethyl orthoformate (3.61 mL, 21.7 mmol) was added. The mixture was stirred for 12 h, then it was filtered and purified by silica-gel flash chromatography (petroleum ether/EtOAc = 9:1) to give **7** (1.09 g, 86%) as a colorless oil: IR (neat) 1740 (C=O); ^{1}H NMR: δ 1.14 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$O), 1.24 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$OCO), 1.87–1.92 (m, 4H, C*H*$_2$CH$_2$CO), 2.26–2.32 (m, 4H, C*H*$_2$CO), 3.41 (q, *J* = 7.1 Hz, 4H, C*H*$_2$O), 4.10 (q, *J* = 7.1 Hz, 4H, C*H*$_2$OCO); ^{13}C NMR: δ 14.5 (2C), 15.6 (2C), 29.0 (2C), 29.5 (2C), 55.8 (2C), 60.7 (2C), 101.9 (1C), 173.5 (2C); MS (70 eV) *m/z* (%) 185 (M^+– 119, 21), 101 (100); ESI$^+$/MS *m/z*: 327 $(M+Na)^+$; ESI$^+$/MS/MS *m/z*: 281 (100).

4,4-Diethoxyheptanediol (8). To a stirred solution of **7** (0.96 g, 3.16 mmol) in dry THF (20 mL), $LiAlH_4$ (0.36 g, 9.48 mmol) under N_2 atmosphere was added. The mixture was stirred at 0 °C for 1 h. The reaction was quenched by careful addition of few drops of water until the end of gas evolution. The residue was removed by filtration and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give **8** (0.67 g, 97%) as a white solid: mp 94–95 °C; IR (KBr): 3284, 3157 (OH); ^{1}H NMR: δ 1.23 (t, *J* = 7.1 Hz, 6H, C*H*$_3$), 1.55 (bs, 2H, O*H*), 1.85–2.09 (m, 8H, CH_2CH_2), 3.71 (q, *J* = 7.1 Hz, 4H, CH_2CH$_3$), 3.81–3.97 (m, 4H, CH_2OH); ^{13}C NMR: δ 18.6 (2C), 24.9 (2C), 35.0 (2C), 58.6 (2C), 67.4 (2C), 115.0 (1C); MS (70 eV) *m/z* (%) 128 (M^+– 92, 8), 87 (100); ESI$^+$/MS *m/z*: 243 $(M+Na)^+$; ESI$^+$/MS/MS *m/z* (%): 197 (100); ESI$^-$/MS *m/z*: 219 $(M–H)^-$; ESI$^-$/MS/MS *m/z* (%): 173 (100); Anal. Calcd for $C_{11}H_{24}O_4$ (220.30): C, 59.97; H, 10.98. Found C, 59.59; H, 10.81.

1,7-Diiodoheptan-4-one (9). To a stirred solution of **8** (0.30 g, 1.36 mmol) in dry toluene (15 mL) under N_2 atmosphere, triphenylphosphine (0.93 g, 3.54 mmol) was added. The reaction mixture was brought to 130 °C and then iodine (0.90 g, 3.54 mmol) was added portionwise. The mixture was refluxed for 1 h, then absolute EtOH (0.3 mL) was added in two portions at ca. 30 min intervals. After evaporation of the solvent, the residue was taken up with $CHCl_3$ and washed twice with saturated $Na_2S_2O_3$ aqueous solution and then twice with H_2O. The organic layer was dried (Na_2SO_4) and concentrated under vacuum, then EtOAc was added and the precipitate formed was filtered off. The filtrate was evaporated and the residue was purified by silica-gel flash chromatography (petroleum ether/ EtOAc = 9:1) to give **9** (0.45 g, 90%) as a yellowish solid, which was recrystallized from Et_2O: mp 47–48 °C (lit.,[26] 43–45 °C, Et_2O); IR (KBr): 1706 (C=O) 565 (C-I); MS (70 eV) *m/z* (%) 238 (M^+– 128, 22), 84 (100). Other spectroscopic data were in agreement with the literature.[26]

Ethyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate (15). Method A. Gaseous ammonia (7 g) was added to 40 mL of MeOH at 0 °C. To this solution compound **9** (2.20 g, 6.01 mmol) and ethyl potassium malonate (5.11 g, 30.0 mmol) were added. The mixture was stirred for 24 h at rt, then it was concentrated under vacuum and the residue was taken up with absolute EtOH. This mixture was heated at 70 °C for 2 h. The solvent was evaporated and the residue was submitted to distillation (70 °C, 2 mmHg) to give a colorless oil consisting of a mixture of **15** (40%) and **14** (10%) as assessed by GC/MS analysis. **Method B.** Gaseous ammonia (2.5 g) was added to 20 mL of absolute EtOH at 0 °C. To this solution compound **9** (0.50 g, 1.37 mmol) and ethyl potassium malonate (1.16 g, 6.83 mmol) were added. The mixture was stirred for 24 h at rt, then it was concentrated under vacuum and the residue was taken up with absolute EtOH. This mixture was heated at 70 °C for 2 h. The solvent was evaporated and the residue was submitted to distillation (70 °C, 2 mmHg) to give **15** (0.12 g, 46%) as a colorless oil. Spectroscopic data were in agreement with the literature.[1]

Methyl tetrahydro-1*H*-pyrrolizin-7a(5*H*)-ylacetate (14). Gaseous ammonia (3 g) was added to 20 mL of MeOH at 0 °C. To this solution compound **9** (1.60 g, 4.37 mmol) and methyl potassium malonate (3.1 g, 21.8 mmol) were added. The mixture was stirred for 24 h at rt, then it was concentrated under vacuum and the residue was taken up with methanol. This mixture was heated at 70 °C for 2 h. The solvent was evaporated and the residue was submitted to distillation (70 °C, 2 mmHg) to give **14** (0.36 g, 45%) as a colorless oil. IR (neat): 1736 (C=O); ^{1}H NMR: δ 1.59–1.68 (m, 2H, C*H*HC), 1.77 (apparent octet, *J* = 6.3 Hz, 4H, $CH_2CH_2CH_2$), 1.93–2.01 (m, 2H, CH*H*C), 2.48 (s, 2H, CH_2CO)(lit.,[30] 2.44, s, 2H, CH_2CO), 2.56 (d t, *J* = 10.4, 6.5 Hz, 2H, C*H*HN), 3.07 (d t, *J* = 10.4, 5.9 Hz, 2H, CH*H*N), 3.63 (s, 3H, CH_3) (lit.,[30] 3.60, s, 3H, COO*Me*); ^{13}C NMR: δ 25.2 (2C), 37.7 (2C), 45.8 (1C), 51.5 (1C), 55.4 (2C), 72.3 (1C), 172.4 (1C); MS (70 eV) *m/z* (%) 183 (M^+, 1), 110 (100).

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