Synthesis of an analogue of the naturally occurring Aristotelia indole alkaloid, fruticosoline

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Received 8 December 1998; accepted (revised) 8 June 1999

A synthesis of an analogue of the rare Aristotelia indole alkaloids is reported. The monoterpene, Pulegone, 1 on nitromethylation give nitromethylpulegone, 2, which on reduction with LiAlH₄ and as well as with NaBH₄ yield the compounds 3, 4 and 5. The amino-alcohol 5 is condensed with indolyloxalyl chloride 6 to furnish the α-ketoamide 7, which is converted to the corresponding monoterpeneoid indole alkaloid 8, an analogue of fruticosoline 9.

A number of Aristotelia alkaloids have been discovered recently in Australia, New Zealand, Chile, Peru, France and Argentina. Synthesis of only a few of these alkaloids isolated in minor amounts from the plants of genus, Aristotelia have been reported. No pharmacological studies have yet been carried out with these alkaloids owing to their occurrence in the plants in minute amount. The simplest indole alkaloid in Aristoteline family is fruticosoline, 9, which was isolated from Aristotelia fruticosa. Our aim was to synthesize some analogues of the monoterpeneoid, fruticosoline in higher yield. The basic skeleton of the two parts forms the alkaloid. For this purpose we have selected pulegone 1 as a source of the monoterpene unit, which, after a few conversions, was condensed with the indole nucleus. The condensed product was then reduced to 8, the analogue of fruticosoline 9.

**Results and discussion**

The Michael addition of nitromethane to pulegone 1 yielded a colourless crystal of compound 2 (Scheme I). Strong absorptions of IR peaks at 1550 and 1380 cm⁻¹ clearly indicate the presence of nitro group in 2. In the ¹H NMR spectra two methylene (Table I) protons attached to NO₂ group appear as two doublets (J=10Hz) at δ 5.02 and 4.27, which indicates that two methylene protons are not equivalent. In the ¹³C NMR spectra the peaks at δ 211 and 83 clearly indicates the carbon of C=O and CH₂-NO₂ respectively.

The reduction of nitromethylpulegone 2 gave compounds 3, 4 and 5 with LiAlH₄ as well as with NaBH₄ (Table II). LiAlH₄ reduction gave almost exclusively the aminomethylpulegone 3 whereas the NaBH₄ reduction in MeOH gave nitromethylpulegol 4 and NaBH₄ in combination with Pd/C in MeOH/H₂O gave the aminomethylpulegol 5. IR spectrum of compound 3 gave a medium broad band for -NH stretching at 3300 cm⁻¹ and a sharp peak at 1735 cm⁻¹ due to C=O stretching. Broad ¹H NMR peak at δ 7.64 for NH₂ confirmed the reduction of keto group. The two methylene protons attached to the carbon containing NH₂ showed absorptions at δ 2.37 and 2.32. Compound 4 is found to be a mixture of two isomers (2:3) on GC which could not be separated. IR absorption at δ 3612 cm⁻¹ indicate the reduction of keto group to alcoholic group. The 500 MHz ¹H NMR spectra clearly indicates two sets of absorption for the isomers of 4. The ¹³C NMR spectrum also showed two sets of carbon signals of eleven carbon each with different intensity ratio. IR spectrum of compound 5 showed the two broad bands at 3300 and 3200 cm⁻¹ which are for -OH and -NH₂ groups respectively. Compound 5 showed two broad absorptions as singlets at δ 3.5 and at δ 2.22 in the ¹H NMR spectra.
These confirmed the presence of -NH₂ and -OH groups in the compound (Table II). The methylene protons attached to the carbon atom containing the NH₂ absorbs at 8 2.84 and 2.75 whereas the methine proton (CHOH) attached to hydroxyl group absorbs at 8 4.1. The ¹³CNMR values also confirm the structure of 5. The stereochemistry of the compound 5 could not be determined.

The reaction of indole with oxalyl chloride in anhyd. ether for 1 hr at 0°C yielded the compound 6 as yellow powder in high yield. The reaction of compound 5 with compound 6 in presence of anhyd. Na₂CO₃ in dry ethyl acetate at room temperature yielded two isomeric condensation products 7a and 7b, the later being the major product. The IR spectrum of both the compounds showed a medium sharp
Table 1 — IR, $^1$H and $^{13}$C NMR, and MS of the isolated compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>IR</th>
<th>$^1$H NMR(δ)</th>
<th>$^{13}$C NMR(δ)</th>
<th>MS: m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2960,2940 m(sh,CH), 1705 s(sh,C=O), 1380 s(sh,C=NO₂)</td>
<td>5.02 (d, 1H, J=10Hz, 8-H), 4.27 (d, 1H, J=10 Hz, 8-H), 2.43 (dd, 1H, J=5, 13Hz), 2.33 (ddd, 1H, J=2, 4, 13 Hz, 2-H), 2.13 (m, 1H, 2-H), 2.07 (dd, 1H, J=1, 13Hz), 1.94 (m, 1H, 6-H), 1.90 (m, 1H, 5-H), 1.49 (dd, 1H, J=3.13, 16 Hz, 6-H), 1.37 (ddq, 1H, J=3.6, 14 Hz, 1-H), 1.12 (s, 3H, 7-CH₃), 1.02 (d, 3H, J=6Hz, 1-CH₃)</td>
<td>211.2 (C=O), 83.6 (8-C), 54.5 (4-C), 51.7(2-C), 36.2 (7-C), 36.0 (1-C), 34.3 (5-C), 28.0 (6-C), 24.6(7-C(Me)), 22.1 (1-C(Me))</td>
<td>198(M'-CH₃, 1), 183(M'-NO₂, 12), 167(M'-NO₂, 22), 151 (M'-H-NO₂-CH₃, 26), 137(M'-NO₂-2xCH₃, 24), 123 (M'-H-NO₂-CH=CO, 46), 112 (58), 109 (50), 83 (58), 69 (100)</td>
</tr>
<tr>
<td>3</td>
<td>3300 (br, NH), 2970, 2935 m (sh,CH), 1735 s(sh, C=O)</td>
<td>7.64 (br, 2H, NH₂), 2.37 (d, 1H, J=10Hz, 8-H), 2.32 (d, 1H, J=10Hz, 8-H), 1.97-2.02 (m, 2H, 1-H, 4-H), 1.84, 1.90 (m, 2H, 2-H, 3-H), 1.72-1.79 (m, 1H, 6-H), 1.25-1.33 (m, 3H, 5, 5', 6-H), 1.23 (s, 3H, 2x7-Me), 1.03 (d, 3H, J=6, 5 Hz, 1-Me)</td>
<td>184 (C=O), 65.6 (8-C), 58.6 (4-C), 52.3 (7-C), 42.2 (2-C), 36.6 (1-C), 24.4(5-C), 25.9(6-C), 24.4(7-Me), 22.3(7-Me), 21.0(1-Me)</td>
<td>183(M'-4), 182 (M'-H), 171, 167(M'-H-CH₃,11), 154 (M'-H-CH₂-O, 1), 138 (M'-CH₃NH₂-CH₃, 14), 111 (M'-CH₂NH₂, 8), 100 (47), 87 (100)</td>
</tr>
<tr>
<td>3a</td>
<td>3612, 3565 m(s,OH), 2960,2910 s (CH), 1550 s(s, C-NO₂, assym. str.), 1378 s(sh, C-NO₂, symm. str.)</td>
<td>5.07 (d, 1H, J=10.5 Hz, 8-H), 4.46 (d, 1H, J=10.5 Hz, 8-H), 3.49-3.58 (m, 1H, 3-H), 2.04 (s, 1H, OH), 1.80-1.84 (m, 1H, 1-H), 1.71-1.74 (m, 2H, 2-H, 3-H), 1.61-1.65 (m, 2H, 5-H, 6-H), 1.40-1.46 (m, 1H, 4-H), 1.30-1.40 (m, 2H, 6-H), 1.08 (m, 3H, 7-Me), 0.91 (d, 3H, J=6 Hz, 1-Me)</td>
<td>83.8 (8-C), 67.2(CH-CH₃), 54.5 (4-C), 41.6(2-C), 39.0 (7-C), 34.0(1-C), 32.6 (5-C), 31.3(6-C), 27.0 (7-C(Me)), 24.0 (7-C(Me)), 20.5 (1-C(Me))</td>
<td>No mole peak</td>
</tr>
<tr>
<td>3b</td>
<td>3612, 3565 m(s,OH), 2960,2910 s (CH), 1550 s(s, C-NO₂, assym. str.), 1378 s(sh, C-NO₂, symm. str.)</td>
<td>4.67 (d, 1H, J=10Hz, 8-H), 4.31 (d, 1H, J=10 Hz, 8-H), 4.12 (d, 1H, J=7.14Hz, 3-H), 1.91-1.98 (m, 1H, 1-H), 1.75-1.80 (m, 2H, 6-H), 1.65-1.69 (m, 2H, 5-H), 1.59 (s, 1H, OH), 1.47-1.56 (m, 2H, 4-H), 1.17-1.26 (m, 1H, 4-H), 1.16 (s, 3H, 7-Me), 1.14 (s, 3H, 7-Me), 0.88(d, 3H, J=6Hz, 1-Me)</td>
<td>83.9 (8-C), 67.3(CH-CH₃), 51.0 (4-C), 43.5(2-C), 38.8 (7-C), 36.0(1-C), 26.5 (7-C(Me)), 26.0 (6-C), 25.5(5-C), 22.5 (7-C(Me)), 22.0 (1-C(Me))</td>
<td>—</td>
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</table>
The IR spectrum of compound 7a showed a band at 3600 and 3450 cm⁻¹ which were assigned to -OH stretching and NH stretching respectively. A strong sharp band at 1710 cm⁻¹ was assigned to C=O stretching. The ¹H NMR spectrum of compound 7a showed a broad peak at δ 9.40 for indolic -NH proton. Absorption at δ 8.12 was for amide -NH. The peak at δ 3.98 corresponds to -OH proton. On the other hand the ¹H NMR spectrum of 7b showed a peak at δ 10.15 for indolic -NH proton and another broad singlet at δ 9.70 for the amide -NH. The singlet at δ 2.02 was assigned to the hydroxyl proton.

Finally the reduction of compound 7b with LiAlH₄
Table II — Reduction of nitromethylpulegone 2 with LiAlH₄ and NaBH₄ to give compounds 3, 4 and 5

<table>
<thead>
<tr>
<th>Reagents and conditions</th>
<th>Percentage of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄, CH₂Cl₂, R.T. 3 hr</td>
<td>44 5 2</td>
</tr>
<tr>
<td>LiAlH₄, THF Reflux, 2 hr</td>
<td>48 21 5</td>
</tr>
<tr>
<td>NaBH₄, MeOH/H₂O Reflux, 12 hr</td>
<td>8 74 2</td>
</tr>
<tr>
<td>(i) NaBH₄, dry ethanol</td>
<td>24 41 30</td>
</tr>
<tr>
<td>(ii) Pd/C, R.T. 4 hr</td>
<td></td>
</tr>
<tr>
<td>(iii) NaBH₄, MeOH/H₂O</td>
<td></td>
</tr>
<tr>
<td>(ii) Pd/C, 2 hr, RT.</td>
<td>5 2 65</td>
</tr>
</tbody>
</table>

in THF gave the reduced product 8. IR of 8 showed no absorptions for the C = O groups. Moreover, the compound 8 showed two triplets on ¹H NMR spectra at δ 3.91 and 3.05 which clearly indicate two methylene groups at position C-9 and C-8, thus confirming that reduction of the keto as well as amide group has taken place. The synthesis of 8, the analogue of fruticosoline, has been achieved in only 5 steps from pulegone 1.

Experimental Section

Fisher-John’s electrothermal melting point apparatus was used for recording the melting points and are uncorrected. IR spectra were recorded either as KBr or as solution in CHCl₃ or CCl₄ or as nujol mull in perkin-Elmer 257 spectrometer. ¹H NMR spectra in CDCl₃ on a Bruker WM-400 spectrometer with TMS as internal standard. ¹³C NMR spectra on a Bruker WH1270 instrument with DEPT Programme in CDCl₃ using TMS as internal standard and mass spectra on a varian MAT-711 (70ev) and varian MAT 445 with GC. Column chromatography was performed on kiesel gel 60GF 254 (E merck). A varian R250 type, GC and TLC were used for reaction monitoring. All reactions were carried out in dry nitrogen atmosphere. All organic solutions after work-up were dried over anhyd. Na₂SO₄. Pet. ether refer to fraction of b.p. 40-60°C. For test of alkaloids Dragendorff and Mayer’s reagents were used.

Preparation of 8-nitromethylparamethan-3-one 2. Pulegone 1 (7.6 g; 0.05 mole), nitromethane (9.15 g; 150 mL, 0.15 mole) and K₂CO₃ (10 g) in the mixture of acetonitrile (45 mL) and methanol (15 mL) was refluxed with continuous stirring at 120°C. TLC examination of the reaction showed the increase of the product with time. After 20 hr reaction the solids were filtered off and the filtrate was evaporated in vacuo. It was extracted with benzene to remove K₂CO₃ and the extract was concentrated to brown coloured liquid (12.97 g). The crude product was chromatographed over a column of kiesel gel using pet. ether : ethyl acetate (24:1) as solvent system to give pure 2 as colourless crystals (9.0226 g; 85%), m.p. 57-58°C.

Reduction of 2 with lithium aluminium hydride. A solution of 2 (1.5 g; 10 mmole) was added dropwise to the suspended LiAlH₄ (3 g) in 30 mL THF and was refluxed for 2 hr with continuous stirring under nitrogen atmosphere. After 2 hr the reaction was worked up by adding dropwise to ice water. THF was then distilled in vacuo. The concentrate was then treated with few drops of dil. H₂SO₄ and stirred for 30 min. The mixture was extracted with dichloromethane (4×30 mL). The organic layer was washed with water, dried and evaporated in vacuo to yield the crude liquid product (1.20 g). The crude on TLC examination gave four spots, of them was reactant 2. The liquid was chromatographed over a column of kiesel gel using initially with pet. ether : ethyl acetate (7:1) solvent system and afterwards with continuous increase of ethyl acetate. From the column chromatography, three pure fractions were collected. Fractions (6-10) yielded the compound 4 (0.390 g; 21%), fractions (15-25) was found to be the compound 3 (0.620 g; 48%) and fractions (30-38) gave the compound 5 (0.063 g; 5%).

The compound 4 was light yellow liquid; its GC analysis showed it to be a mixture of two isomers 4a, 4b, ratio 2:3 respectively. Compound 5 was obtained as colourless crystals m.p. 53-54°C and compound 3 was also obtained as colourless crystals m.p. 156-157°C. The compounds 3, 4 and 5 were characterized by spectral analysis (Table I).

Reduction of 2 with sodium borohydride. In a 2-necked flask a suspension of 125 mg sodium borohydride in 10 mL of water was quickly added to 1.7 g of Pd/C in 10 mL water. The nitro compound 2 (0.5 g, 2.34 mmole) in 20 mL of methanol was then added over a period of 5 min. The reaction was continued for 2 hr. Then the solution was filtered off and the filtrate was extracted with dichloromethane (3×25 mL). The combined organic portion was dried and evaporated in vacuo. A pale yellow coloured crystalline product was
obtained (0.49 g). The crude crystal was then recrystallized from n-hexane : dichloromethane (10 : 1) and a pure colourless crystals of the compound 5 (0.28 g ; 65%) were obtained.

Reduction of 4 to 5 with lithium aluminium hydride. To a stirred solution of 4.7 g LiAlH₄ in 10 mL of dry ether was added dropwise a solution of 4 (0.7 g; 4.7 mmol) in 5 mL of ether at room temperature. Stirring was continued for 2 hr. After completion of the reaction it was added dropwise to ice. The mixture was treated with a few drops of dilute H₂SO₄ and then the whole solution was extracted with dichloromethane (4×30 mL). The extracts were washed with water, dried and evaporated in vacuo to yield the crude product (0.86 g). The crude product was then recrystallized with the solvent systems n-hexane : dichloromethane (10:1) and pure crystals (0.67 g; 77%) of 5 were isolated.

Preparation of 3-indolyloxalyl chloride 6. To a stirred solution of indole (2 g; 17 mmole) in 50 mL anhyd. ether at 0-5°C oxalyl chloride (2.25 g ; 17.71 mmol) was added dropwise during 30 min, stirring and cooling were continued for 1 hr more. The resulting yellow powder was collected, washed with anhyd. ether and dried in vacuo to give the compound 6, a yellow coloured powder (2.4 g ; 72.7% ), m.p. 134-35°C (decom) (Lit. m.p. 135°C)¹¹.

Reaction of compound 5 with 6 to give 7. To a mixture of anhyd. Na₂CO₃ (500 mg ; 4.71 mmole) and compound 5 (225 mg ; 1.22 mmole) in 10 mL freshly distilled dry ethyl acetate, compound 6 (337 mg ; 1.62 mmole) in 20 mL of dry ethyl acetate was added with vigorous stirring at room temperature. The reaction was continued for 12 hr. Then the reaction mixture was filtered off and the filtrate was dried and evaporated in vacuo. Finally a brown coloured gummy product (0.53 g ) was obtained. On TLC examination two spots were found. The crude product was chromatographed over a column of kiesel gel using dichloromethane: ethyl acetate (10:1), when two pure isomeric products were isolated in addition to the mixture. The compound 7a (34 mg; 8%) was a light violet colourd gummy product and compound 7b (260 mg; 60%) was a light green coloured solid m.p. 130-32°C.

Reduction of 7b with lithium aluminium hydride. To a stirred solution of excess LiAlH₄ (141 mg; 3.70 mmole) in 20 mL of dry THF was added dropwise a solution of compound 7b (100 mg; 0.28 mmole) in 5 mL of THF at room temperature. It was refluxed for 5 hr. Then the reaction mixture was added dropwise with stirring to ice-water. The THF was evaporated in vacuo. The concentrate was treated with a few drops of dilute HCl and was extracted with CH₂Cl₂ (4×30 mL). The extracts were washed with water, dried and evaporated in vacuo to yield the crude gummy product (83 mg). The crude product was chromatographed over a column of kiesel gel using pet. ether : ethyl acetate (8:1) and successively eluted with solvent of increasing polarity. First fractions gave the starting material 7b and then compound 8 (45 mg; 49%) as brown coloured gummy product.

Acknowledgement
The authors are thankful to G Cardillo, Department of Chemistry, Bologna University, Italy, for providing instrumental facilities for the spectral analyses.

References