A New Synthesis of Indoloquinolizines by Pictet–Spengler Reaction of Tryptamine Type 1,2-Dihydropyridines Utilizing sec-Nitrodienamine

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The Pictet–Spengler reaction of tryptamine type 1,2-dihydropyridine 5c derived from the cycloaddition of the sec-nitrodienamine 3c with acetaldehyde afforded the indoloquinolizine derivatives 6 and 7.

Key words nitrodienamine; tryptamine; 1,2-dihydropyridine derivative; indoloquinolizine; Pictet–Spengler reaction

The reactivities of tert-nitrodienamines [ex. 1-(N,N-di-methylamino)-4-nitro-1,3-butanediole (1)] and sec-nitrodienamines [ex. 4-nitro-1-phenylethyl-1,3-butanediole (3a)] have been studied because of their potentially useful synths in organic synthesis. The chemistry of nitrodienamines exploits the enaminic, dienic, and electronic “push pull” character of these molecules, and leads to interesting cycloaddition reactions as well as aminodialenyl esters and aminocarbonyl compounds.1–4) Dihydropyridine chemistry is of interest from the point of view of pure research on heterocyclic compounds and also from a biological standpoint.5)

Here, we studied the reactivities of aryl and alkylethylidenamines, especially indolethylidenamine derivative and the Pictet–Spengler reaction of tryptamine type 1,2-dihydropyridine derivative 5c. We earlier found that the reaction of sec-nitrodienamine 3a with acetaldehyde (4) provided 2-methyl-3-nitro-1-phenylethyl-1,2-dihydropyridine (5a) in 92% yield.6,7) Similarly, the sec-nitrodienamines 3a–c were prepared by the reaction of the tert-nitrodienamine 1 with 2-phenylethylamine (2a), propylamine (2b), and tryptamine (2c), respectively (Chart 1, Table 1). The 2-methyl-3-nitro-1,2-dihydropyridine derivatives 5a–c were prepared from the corresponding sec-dienamines 3a–c.

We investigated the Pictet–Spengler reaction of tryptamine type 1,2-dihydropyridine derivative 5c and expected to get information on indole alkaloid synthesis.8a) The Pictet–Spengler reaction is the most important and powerful method of alkaloid chemistry. It has been applied in numerous cases for the construction of β-carboline and indoloquinolizine of natural products.8b) Refluxing treatment of tryptamine type 1,2-dihydropyridine derivative 5c in 10% H2SO4/tetrahydrofuran (THF) provided (±)-rel-(2S,3S,4S,12bS)-2-methoxy-4-methyl-3-nitro-1,2,3,4,6,7,12,12b-octahydropindolo[2,3-a]quinolizine (7) in 18% yield. Compound (7) has an axial methyl group at C-4, which may provide less steric interference to a nitro group than an equatorial methyl group. On the other hand, refluxing treatment of 5c in 10% H2SO4/tetrahydrofuran (THF) provided (±)-rel-(4R,12bS)-4-methyl-3-nitro-1,4,6,7,12,12b-hexahydropindolo[2,3-a]quinolizine (7) in 18% yield. Compound (7) has an axial methyl group at C-4, which may provide less steric interference to a nitro group than an equatorial methyl group. On the basis of our earlier report on the formation of 2-methyl-3-nitro-1,2-dihydropyridines 5 by the reaction of sec-nitrodienamines 3 with acetaldehyde (4),9a,b) we attempted to prepare the product 3-nitro-1,2-dihydropyridines 10a,b by cycloaddition reaction of the sec-nitrodienamine 3a with ace...
Table 1. Physical Data of Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Appearance [solvent, mp (°C)]</th>
<th>(^1^H)-NMR, δ (ppm)</th>
<th>IR (cm(^{-1}))</th>
<th>Formula, HR-MS m/z or Analysis (%) Calcd (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>71</td>
<td>Brown oil</td>
<td>0.99 (3H, t, J=7.3 Hz, Me), 1.52—1.80 (2H, m, methylene H), 3.04—3.26 (2H, m, methylene H), 5.17 (1H, s, NH), 5.33 (1H, t, J=12.3 Hz, olefinic H), 7.00 (1H, d, J=12.3 Hz, olefinic H), 7.00 (1H, d, J=12.3 Hz, olefinic H), 7.80 (1H, t, J=12.3 Hz, olefinic H), [CDCl(_3)]</td>
<td>3219, 1609, 1582, 1543, 1468, 1433, (neat)</td>
<td>C(_9)H(_8)N(_2)O, 115.0901 (156.0899)</td>
</tr>
<tr>
<td>5b</td>
<td>85</td>
<td>Dark red oil</td>
<td>0.94 (3H, t, J=12.2 Hz, Me), 1.71 (2H, s, Me), 2.16 (3H, s, Me), 2.80 (2H, t, J=7.3 Hz, olefinic H), 5.16 (1H, dd, J=7.3, 6.2 Hz, olefinic H), 5.16 (1H, q, J=6.2 Hz, methine H), 6.71 (1H, d, J=6.2 Hz, olefinic H), [CDCl(_3)]</td>
<td>1616, 1516, 1481, 1435, 1358, 1290, (neat)</td>
<td>C(_5)H(_4)N(_2)O, 182.1054 (182.1074)</td>
</tr>
<tr>
<td>3c</td>
<td>95</td>
<td>Dark yellow prisms [AcOEt–MeOH, 125—126]</td>
<td>0.98 (2H, m, methylene H), 3.45—3.62 (2H, m, methylene H), 5.45 (1H, t, J=12.2 Hz, olefinic H), 6.91 (1H, d, J=12.2 Hz, olefinic H), 6.97—7.62 (6H, m, aromatic and olefinic H), 7.76 (1H, t, J=12.2 Hz, olefinic H), 10.11 (1H, brs, NH)</td>
<td>3329, 1605, 1570, 1530, 1439, 1416, (KBr)</td>
<td>C(_4)H(_6)N(_2)O, 283.1319 (283.1347)</td>
</tr>
<tr>
<td>5c</td>
<td>85</td>
<td>Dark red oil</td>
<td>1.16 (3H, t, J=6.6 Hz, Me), 3.17 (2H, t, J=7.0 Hz, methylene H), 3.74 (1H, dt, J=13.8, 7.0 Hz, methylene H), 3.90 (1H, t, J=13.8, 7.0 Hz, methylene H), 4.84 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 5.22 (1H, q, J=6.2 Hz, methine H), 6.89 (1H, d, J=7.4 Hz, olefinic H), 7.02 (1H, t, J=7.5 Hz, aromatic H), 7.10 (1H, t, J=7.5 Hz, aromatic H), 7.14 (1H, s, aromatic H), 7.38 (1H, d, J=7.5 Hz, aromatic H), 7.48 (1H, d, J=6.2 Hz, olefinic H), 7.61 (1H, d, J=7.5 Hz, aromatic H), 10.09 (1H, brs, NH), [CD(_3)COCD(_3)]</td>
<td>3330, 1610, 1550, 1510, 1490, 1430, (neat)</td>
<td>C(_5)H(_4)N(_2)O, 182.1054 (182.1074)</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Colorless prisms [ether–hexane, 148—150]</td>
<td>1.29 (3H, d, J=6.1 Hz, Me), 1.64 (1H, q, J=12.1 Hz, methylene H), 2.54 (1H, ddd, J=12.1, 5.0, 2.4 Hz, methylene H), 2.59 (1H, ddd, J=11.5, 8.9, 5.0 Hz, methylene H), 2.77 (1H, ddd, J=15.3, 5.0, 1.5 Hz, methylene H), 2.82—2.88 (1H, m, methylene H), 3.06 (1H, dq, J=10.1, 6.1 Hz, methine H), 3.08 (1H, dt, J=11.5, 5.0 Hz, methylene H), 3.40 (1H, S, OMe), 3.70 (1H, dd, J=12.1, 2.4 Hz, methine H), 3.98 (1H, ddd, J=12.1, 10.1, 5.0 Hz, methine H), 4.38 (1H, t, J=10.1 Hz, methine H), 7.11 (1H, t, J=7.6 Hz, aromatic H), 7.17 (1H, t, J=7.6 Hz, aromatic H), 7.32 (1H, d, J=7.6 Hz, aromatic H), 7.48 (1H, dd, J=7.6, 1.5 Hz, aromatic H), 7.73 (1H, brs, NH), [CD(_3)COCD(_3), (^1^H)-NMR)]</td>
<td>3400, 1550, 1480, 1470, 1460, 1395, (KBr)</td>
<td>C(_7)H(_8)N(_2)O, 264.67 (264.66)</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>Colorless prisms [ether–hexane, 196 (dec.‧)]</td>
<td>1.37 (3H, d, J=4.1 Hz, Me), 2.52 (1H, ddd, J=22.1, 10.1, 2.8 Hz, methylene H), 2.75 (1H, dt, J=22.1, 4.6 Hz, methylene H), 2.83—2.94 (2H, m, methylene H), 3.06 (1H, ddd, J=15.0, 8.6, 4.9 Hz, methylene H), 3.34 (1H, dt, J=15.0, 4.9 Hz, methylene H), 4.16 (1H, dd, J=10.1, 4.6 Hz, methine H), 4.35 (1H, q, J=4.1 Hz, methine H), 7.12 (1H, t, J=7.6 Hz, aromatic H), 7.18 (1H, t, J=7.6 Hz, aromatic H), 7.33 (1H, d, J=7.6 Hz, aromatic H), 7.34 (1H, dd, J=4.6, 2.8 Hz, olefinic H), 7.51 (1H, d, J=7.6 Hz, aromatic H), 7.73 (1H, brs, NH), [CD(_3)COCD(_3), (^1^H)-NMR)]</td>
<td>3390, 1680, 1620, 1550, 1510, 1470, (KBr)</td>
<td>C(_7)H(_8)N(_2)O, 283.1319 (283.1299)</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>Yellow oil</td>
<td>2.16 (3H, s, Me), 2.60 (3H, s, Me), 2.80 (2H, t, J=7.5 Hz, methylene H), 2.96 (2H, t, J=7.5 Hz, methylene H), 7.38 (1H, t, J=7.8 Hz, aromatic H), 7.41 (1H, d, J=7.8 Hz, aromatic H), 7.79 (1H, s, aromatic H), 7.79 (1H, d, J=7.8 Hz, aromatic H), [CD(_3)COCD(_3)]</td>
<td>1715, 1682, 1610, 1585, 1520, 1485, (neat)</td>
<td>C(_8)H(_8)O, 190.0992 (190.0965)</td>
</tr>
</tbody>
</table>

a) Compounds 3a and 5a were reported in reference 1d.
tone (dimethyl ketone) (8) and methyl vinyl ketone (9), respectively. Although the reaction of 3a with acetone (8) did not proceed, the reaction of 3a with methyl vinyl ketone (9) unexpectedly afforded 4-(3-acetylphenyl)butan-2-one (11) in 10% yield. The formation of 11 can be explained as follows. Initially, the reaction of 3a with 9 may generate intermediate 12, and following elimination of the amino group in 12 and the subsequent condensation reaction of 13 with another methyl vinyl ketone (9) would give intermediate 14. Then, the aromatization reaction of 15 with denitration would provide compound 11 as shown in Chart 3.

Next, we attempted to prepare compound 16 by intramolecular Diels–Alder reaction of 1-[2-(3-indolyl)ethylamino]-4-nitro-1,3-butadiene (3c). Unexpectedly, refluxing treatment of 3c in xylene afforded 1-[2-(3-indolyl)ethyl]-2-methyl-3-nitro-1,2-dihydropyridine (5c), 1,3-dinitrobenzene (17) and 3-nitrobenzaldehyde (18) in 11%, 37% and 14% yields, respectively, as shown in Chart 4. The self-cycloaddition reactions of 3c can be explained as follows. Initially, the self-condensation reaction of 3c might generate the intermediates 19 and 21, and following aromatization with deamination it affords the 3-nitrobenzaldehyde (18), 1,3-dinitrobenzene (17) and acetaldehyde (4), respectively. Then, the condensation reaction of 3c with acetaldehyde (4) might generate the intermediate 22, followed by an intramolecular ring closure with dehydration, which could lead to 1,2-dihydropyridine 5c, as shown in Chart 5.

These results indicate a new synthetic method of indoloquinolizines 6 and 7 by the Pictet–Spengler reaction of tryptamine type 1,2-dihydropyridine derivative 5c utilizing sec-ni-
trodiename 3c.

**Experimental**

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on either a JASCO FT/IR-200 or JASCO FT/IR-8000 spectrometer, and 1H-NMR and 13C-NMR spectra on either a JEOL EX-90 or JEOL JNM-α500 spectrometer with tetramethylsilane as an internal standard. NOESY spectra were obtained with the usual pulse sequence and data processing was performed with the standard JEOL software. MS spectra were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. Wakogel C-200 (silica gel) and Merck Kieselgel G nach Stahl (silica gel) and NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysia Chemical, Ltd.) were used for column chromatography and thin layer chromatography (TLC), respectively. All runs were carried out under an argon atmosphere.

**General Procedure for Reactions of tert-Nitrodiename 1 with Primary Amines 2** A solution of the tert-nitrodiename 1 (40 mg, 0.28 mmol) and an amine 2 (0.98—14.5 mmol) in benzene (8 ml) or THF (4 ml) was stirred at room temperature for an appropriate period until the disappearance of 1 (checked by TLC). The reaction mixture was concentrated in a vacuum, then the residue was subjected to silica gel column chromatography with appropriate solvents. The properties of the prepared compounds 3 are shown in Table 1.

4-Nitro-1-phenethylamino-1,3-butadiene (3a) and 2-methyl-3-nitro-1-phenethyl-1,2-dihydropyridine (5a) were synthesized by the previously reported method.14

4-Nitro-1-propylamino-1,3-butadiene (3b): Substrate: propylamine (2b) (856 mg, 14.5 mmol). Reaction solvent: benzene. Reaction time: 1.2 h. Sol-
vent for chromatography: 30% ethyl acetate in hexane. Product 3b: 31 mg.

1-[2-(3-Indolyl)ethylamino]-4-nitro-1,3-buta diene (3c): Substrate: tryptamine (2e) (450 mg, 2.81 mmol). Reaction solvent: THF. Reaction time: 4.5 h. Solvent for chromatography: 20% hexane in ethyl acetate. Product 3c: 69 mg.

General Procedure for Reactions of sec-Nitrodiene 3 with Aldehyde (4). A solution of a sec-nitrodiene 3 (0.214 mmol) and acetaldehyde (4) (0.4 ml, 7.16 mmol) in THF (3 ml) in a sealed tube was stirred at room temperature for an appropriate period until 3 disappeared (checked by TLC). The reaction mixture was concentrated in a vacuum, then the residue was subjected to silica gel column chromatography [solvent: 50% ethyl acetate in hexane]. Product: 6 mg (11%) of 4.

The Reaction of 4-Nitro-1-phenethylamino-1,3-butadiene (3a) with Methyl Vinyl Ketone (9). A solution of 3a (40 mg, 0.183 mmol) with methyl vinyl ketone (9) (1.5 ml, 18.3 mmol) and phenethylamine (2 drops) in liquid reaction mixture (no solvent) in a sealed tube was stirred at room temperature for 16 h. The reaction mixture was concentrated in a vacuum, then the residue was subjected to silica gel column chromatography [solvent: 30% ethyl acetate in hexane]. Product: 4 mg of 4-(3-acetyloxy)butan-2-one (11).

The Self-Cycloaddition Reaction of 1-[2-(3-Indolyl)ethylamino]-4-nitro-1,3-buta diene (3c) A solution of 3c (50 mg, 0.195 mmol) in xylene (10 ml) was refluxed for 12 h in a sealed tube. The reaction mixture was concentrated in a vacuum, then the residue was subjected to silica gel column chromatography [solvent: 50% ethyl acetate in hexane]. Product: 6 mg (37%) of 1,3-dinitrobenzene (17), light yellow plates (AcOEt-hexane), mp 89 °C (lit. 45 mp 88—90 °C) and 2 mg (14%) of 3-nitrobenzaldehyde (18), yellow needles (AcOEt-hexane), mp 58 °C (lit. 17 mp 57—59 °C) and 6 mg (11%) of 5e, red oil. These products were identical with authentic samples on the basis of IR, MS, and NMR spectral comparisons.

References and Notes
8) This product was identified by comparison with an authentic sample obtained from a commercial supplier.