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

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Received June 13, 2000; accepted August 23, 2000

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*-dimethylamino)-4-nitro-1,3-butadiene (**1**)] and *sec*-nitrodienamines [*ex.* 4-nitro-1-phenethylamino-1,3-butadiene (**3a**)] have been studied because of their potentially useful synthons 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 aminodienyl esters and aminoacrylate synthons.[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 alkylethyldienamine derivatives, especially indolylethyldienamine 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-phenethyl-1,2-dihydropyridine (**5a**) in 92% yield.[1d] 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.[6a] 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.[6b] Refluxing treatment of tryptamine type 1,2-dihydropyridine derivative **5c** in 10% H_2SO_4/MeOH gave (±)-*rel*-(2*S*,3*S*,4*S*,12b*S*)-2-methoxy-4-methyl-3-nitro-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**6**) in 52% yield. The structure of product **6** was proposed on the basis of the following spectroscopic analyses. The molecular formula of **6** was found to be $C_{17}H_{21}N_3O_3$. The ^{1}H-NMR spectrum of **6** showed the presence of two methyl protons at δ 1.29 (3H, d, J=6.1 Hz), 3.40 (3H, s), three methylene protons at δ 1.64 (1H, q, J=12.1 Hz), 2.54 (1H, ddd, J=12.1, 5.0, 2.4 Hz), 2.59 (1H, ddd, J=11.5, 8.9, 5.0 Hz), 2.77 (1H, dtd, J=15.3, 5.0, 1.5 Hz), 2.82—2.88 (1H, m), 3.08 (1H, dt, J=11.5, 5.0 Hz), four methine protons at δ 3.06 (1H, dq, J=10.1, 6.1 Hz), 3.70 (1H, dd, J=12.1, 2.4 Hz), 3.98 (1H, ddd, J=12.1, 10.1, 5.0 Hz), 4.38 (1H, t, J=10.1 Hz), four aromatic protons at δ 7.11 (1H, t, J=7.6 Hz), 7.17 (1H, t, J=7.6 Hz), 7.32 (1H, d, J=7.6 Hz), 7.48 (1H, dd, J=7.6, 1.5 Hz), and a nitrogen proton of the indole ring at δ 7.73 (1H, br s). The IR spectrum of **6** revealed absorption bands at 3400 cm^{-1} (NH group), 1550 cm^{-1} (NO_2 group), and 1480, 1470, 1460, 1395 cm^{-1} (indoloquinolizine ring). The nuclear Overhauser effect correlation spectroscopy (NOESY) of **6** exhibited the presence of cross-peaks between the methine proton of Hα-12b at δ 3.70 and the methine protons of Hα-2 and Hα-4 at δ 3.98 and 3.06, and cross-peaks between the methine proton of Hβ-3 at δ 4.38 and the methyl protons of OMeβ-2 and Meβ-4 at δ 3.40 and 1.29. It can therefore be deduced that indoloquinolizine **6** has an energically stable equatorial methoxy group, an equatorial nitro group, and an equatorial methyl group in *trans*-decaline type configuration as shown in Chart 2. On the other hand, refluxing treatment of **5c** in 10% H_2SO_4/tetrahydrofuran (THF) provided (±)-*rel*-(4*R*,12b*S*)-4-methyl-3-nitro-1,4,6,7,12,12b-hexahydroindolo[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**),[1d,f] we attempted to prepare the product 3-nitro-1,2-dihydropyridines **10a**, **b** by cycloaddition reaction of the *sec*-nitrodienamine **3a** with ace-

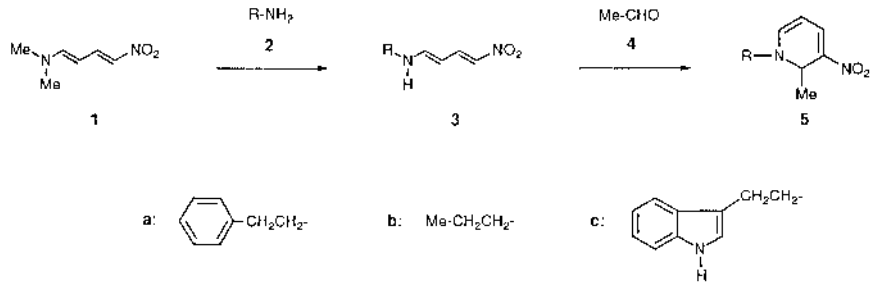

Chart 1

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Table 1. Physical Data of Compounds

Compound[a)]	Yield (%)	Appearance [solvent, mp (°C)]	^{1}H-NMR, δ (ppm)	IR (cm^{-1})	Formula, HR-MS *m/z* or Analysis (%) Calcd (Found)
3b	71	Brown oil	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, br 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), [$CDCl_3$]	3219, 1609, 1582, 1543, 1468, 1433, (neat)	$C_7H_{12}N_2O_2$ 156.0901 (156.0899)
5b	85	Dark red oil	0.94 (3H, t, *J*=7.1 Hz, Me), 1.20 (1H, d, *J*=6.2 Hz, Me), 1.71 (2H, sexet, *J*=7.1 Hz, methylene H), 3.02—3.61 (2H, m, methylene H), 4.94 (1H, d, *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), [$CDCl_3$]	1616, 1516, 1481, 1435, 1358, 1290, (neat)	$C_9H_{14}N_2O_2$ 182.1054 (182.1074)
3c	95	Dark yellow prisms [AcOEt–MeOH, 125—126]	3.04 (2H, t, *J*=6.6 Hz, 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, br s, NH), [CD_3COCD_3]	3239, 1605, 1570, 1530, 1439, 1416, (KBr)	$C_{14}H_{15}N_3O_2$ C, 65.35; H, 5.88; N, 16.33. (C, 65.23; H, 5.90; N, 16.03)
5c	85	Dark red oil	1.16 (3H, d, *J*=6.2 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, dt, *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, br s, NH), [CD_3COCD_3, ^{1}H-NMR]. 15.52, 26.03, 53.17, 55.75, 93. 23, 111.65, 112.25, 119.02, 119.58, 122.23, 124.07, 127.02, 128.15, 133.21, 137.67, 148.50, [CD_3COCD_3, ^{13}C-NMR]	3330, 1610, 1550, 1510, 1490, 1430, (neat)	$C_{16}H_{17}N_3O_2$ 283.1319 (283.1347)
6	52	Colorless prisms [ether–hexane, 148—150]	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, ddt, *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 (3H, 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, br s, NH), [$CDCl_3$, ^{1}H-NMR]. 16.44 (C4-Me), 22.06 (C7), 32.62 (C1), 44.16 (C6), 56.37 (C12b), 56.82 (OMe), 59.01 (C4), 78.88 (C2), 93.24 (C3), 108.93 (C7a), 110.87 (C11), 118.32 (C8), 119.73 (C9), 121.92 (C10), 126.97 (C7b), 133.05 (C12a), 136.20 (C11a), [$CDCl_3$, ^{13}C-NMR]	3400, 1550, 1480, 1470, 1460, 1395, (KBr)	$C_{17}H_{21}N_3O_3$ C, 64.74; H, 6.71; N, 13.33. (C, 64.61; H, 6.72; N, 13.38)
7	18	Colorless prisms [ether–hexane, 196 (dec.)]	1.37 (3H, d, *J*=4.1 Hz, Me), 2.52 (1H, ddt, *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, br s, NH), [$CDCl_3$, ^{1}H-NMR]. 13.31 (C4-Me), 21.91 (C7), 31.10 (C1), 46.01 (12b), 48.12 (C6), 54.08 (C4), 108.88 (C7a), 110.82 (C11), 118.38 (C8), 119.73 (C9), 121.96 (C10), 126.98 (C7b), 131.02 (C2), 133.78 (C12a), 136.44 (C11a), 153.00 (C3), [$CDCl_3$, ^{13}C-NMR]	3390, 1680, 1620, 1540, 1510, 1470, (KBr)	$C_{16}H_{17}N_3O_2$ 283.1319 (283.1299)
11	10	Yellow oil	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), [$CDCl_3$]	1715, 1682, 1610, 1585, 1520, 1485, (neat)	$C_{12}H_{14}O_2$ 190.0992 (190.0965)

a) Compounds **3a** and **5a** were reported in reference **1d**.

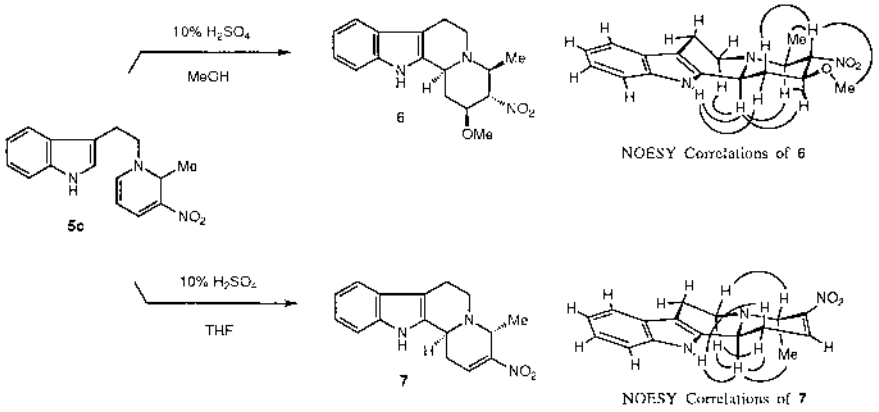
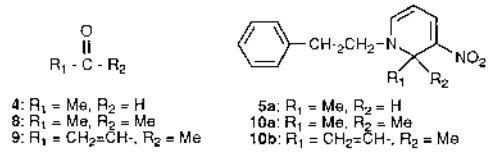


Chart 2



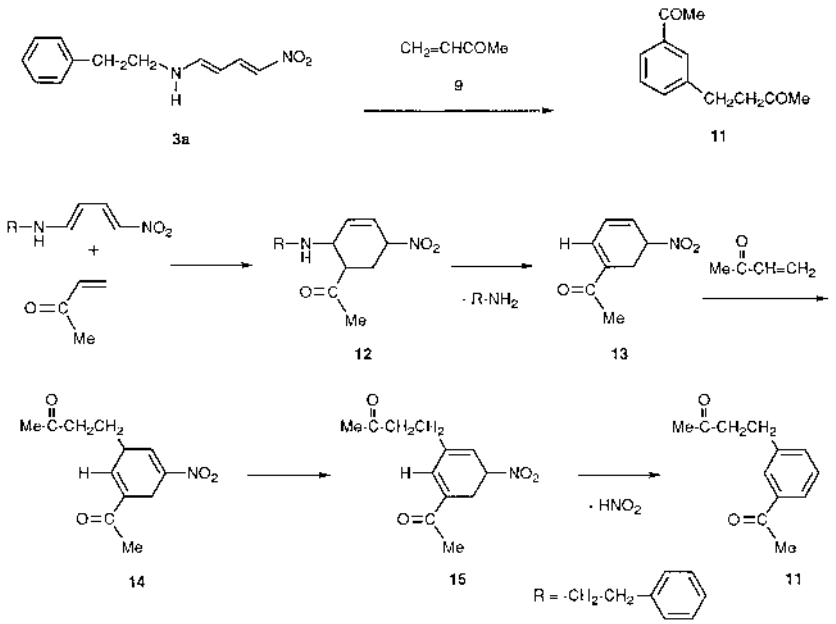


Chart 3

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**).[7] 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-

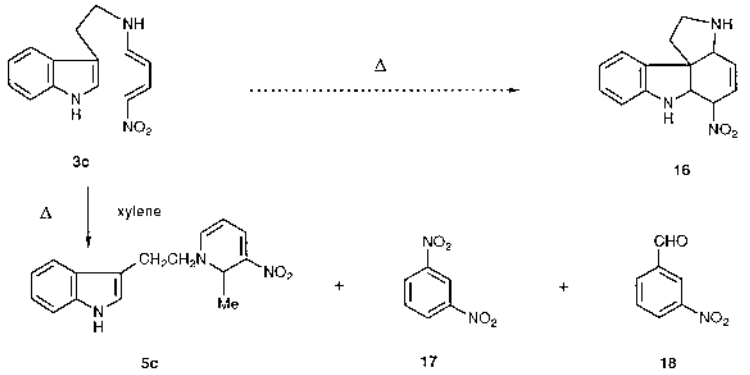


Chart 4

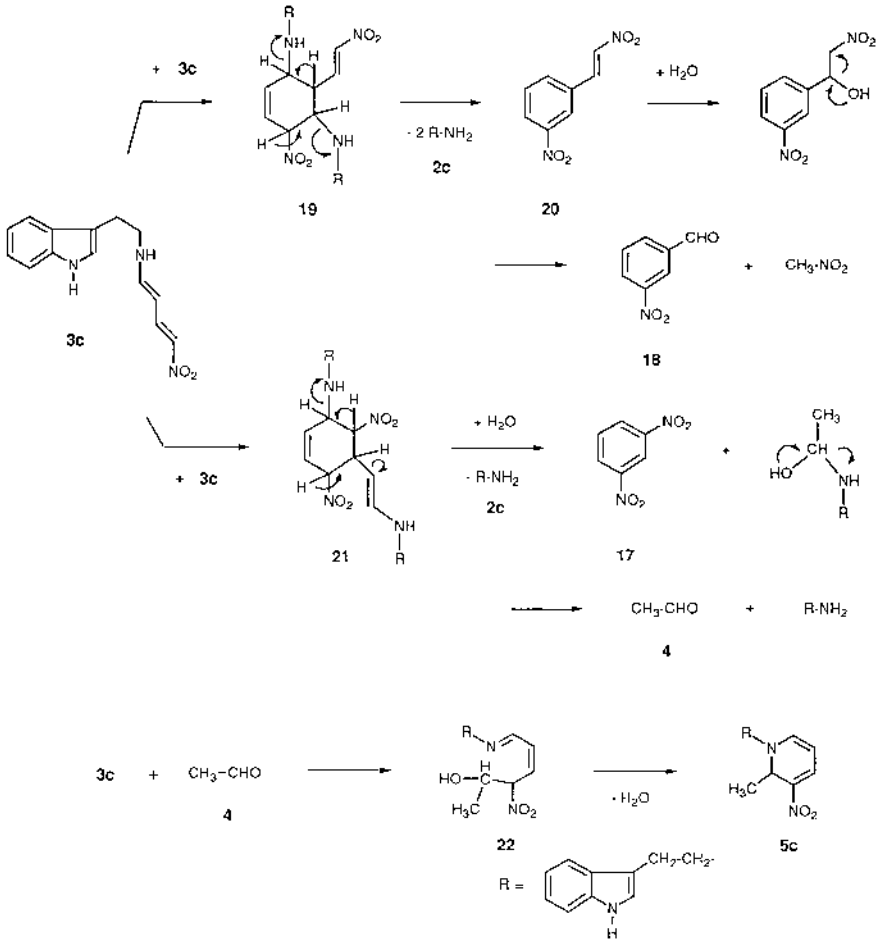


Chart 5

trodienamine **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 ^{1}H-NMR and ^{13}C-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*-Nitrodienamine 1 with Primary Amines 2 A solution of the *tert*-nitrodienamine **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.[1d)]

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-butadiene (**3c**): Substrate: tryptamine (**2c**) (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*-Nitrodienamine 3 with Acetaldehyde (4) A solution of a *sec*-nitrodienamine **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. The properties of the prepared compounds **5** are shown in Table 1.

2-Methyl-3-nitro-1-propyl-1,2-dihydropyridine (**5b**): Substrate: 4-nitro-1-propylamino-1,3-butadiene (**3b**) (33 mg, 0.214 mmol). Reaction time: 1.2 h. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5b**: 33 mg.

1-[2-(3-Indolyl)ethyl]-2-methyl-3-nitro-1,2-dihydropyridine (**5c**): Substrate: 1-[2-(3-indolyl)ethylamino]-4-nitro-1,3-butadiene (**3c**) (55 mg, 0.214 mmol). Reaction time: 1.5 h. Solvent for chromatography: 50% ethyl acetate in hexane. Product **5c**: 52 mg.

The Pictet–Spengler Reactions of 1-[2-(3-Indolyl)ethyl]-2-methyl-3-nitro-1,2-dihydropyridine (5c) A solution of **5c** (40 mg, 0.141 mmol) and 10% H_2SO_4 (0.5 ml) in MeOH (2 ml) was refluxed for 3 h. The reaction mixture was concentrated in a vacuum, and then the residue was made alkaline with a K_2CO_3 solution. The whole was extracted with AcOEt and the organic phase was washed with water, dried and evaporated. The residue was subjected to silica gel column chromatography [solvent: 20% acetone in hexane]. Product: 23 mg of (±)-*rel*-(2*S*,3*S*,4*S*,12b*S*)-2-methoxy-4-methyl-3-nitro-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**6**).

A solution of **5c** (40 mg, 0.141 mmol) and 10% H_2SO_4 (0.5 ml) in THF (2 ml) was refluxed for 3 h. The reaction mixture was concentrated in a vacuum, and then the residue was made alkaline with a K_2CO_3 solution. The whole was extracted with AcOEt and the organic phase was washed with water, dried and evaporated. The residue was subjected to silica gel column chromatography [solvent: 50% ether in hexane]. Product: 7 mg of (±)-*rel*-(4*R*,12b*S*)-4-methyl-3-nitro-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (**7**).

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-acetylphenyl)butan-2-one (**11**).

The Self-Cycloaddition Reaction of 1-[2-(3-Indolyl)ethylamino]-4-nitro-1,3-butadiene (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.[8] mp 88—90 °C) and 2 mg (14%) of 3-nitrobenzaldehyde (**18**),[1f] yellow needles (AcOEt–hexane), mp 58 °C (lit.[8] mp 57—59 °C) and 6 mg (11%) of **5c**, red oil. These products were identical with authentic samples on the basis of IR, MS, and NMR spectral comparisons.

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