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AN UNPRECEDENTED 1,8a-BOND FISSION OF AN *N*-FORMYL-1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVE UNDER A NITRATION CONDITION

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Abstract — An unprecedented bond fission between the 1 and 8a positions of an *N*-formyl-1,2,3,4-tetrahydroisoquinoline derivative was observed under nitration conditions using nitric acid and acetic acid. The structures of the products and the proposed reaction mechanism were also described.

INTRODUCTION

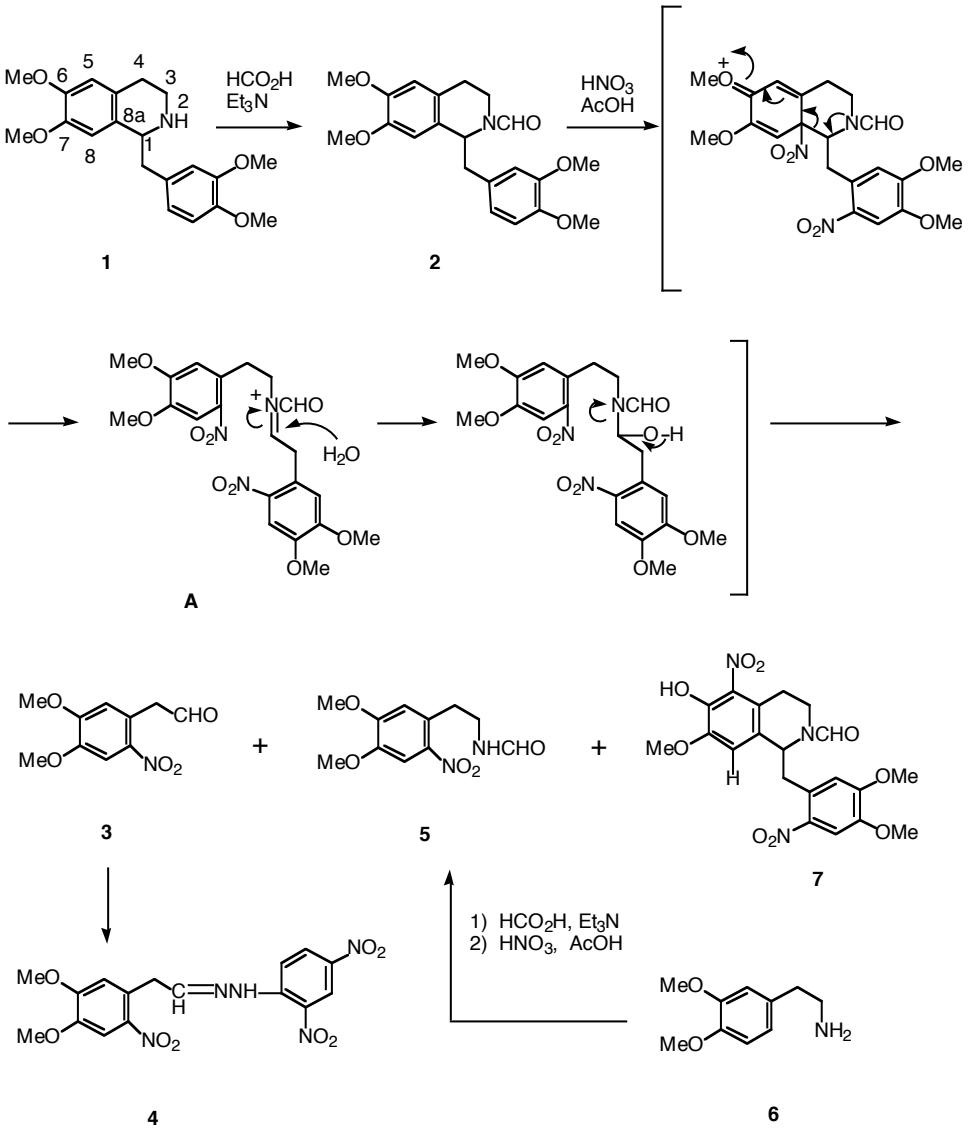
Isoquinoline alkaloids are a large class of natural products that have, over the year, provoked an extraordinary amount of activity by synthetic organic chemists.[1]

During the course of our studies directed toward the total synthesis of isoquinoline alkaloids, we required to synthesize an aminoisoquinoline derivative having an *N*-formyl group on an isoquinoline nitrogen, as an intermediate. It has been well recognized that an amino group played important roles, such as a precursor of a diazo group in the Pschorr reaction or a protecting group in further chemical modification of the aromatic ring, in the synthesis of naturally occurring isoquinoline alkaloids.[2] In order to synthesize an amino-isoquinoline alkaloid, we attempted a nitration reaction of an *N*-formyl-1,2,3,4-tetrahydroisoquinoline derivative using nitric acid and acetic acid, and found that 1,8a-bond was cleaved under such reaction conditions.

RESULTS AND DISCUSSION

The starting material was prepared by formylation of the known 1,2,3,4-tetrahydroisoquinoline derivative

(norlaudanosine) (**1**)[3] with formic acid and triethylamine[4] to afford the *N*-formyl derivative (**2**), as an inseparable mixture of the rotamers,[5] in a ratio of *ca.* 1:1, in 93% yield. The nitration reaction of **2** was carried out as follows. To a stirred solution of *N*-formylnorlaudanosine (**2**) (1.0 mmol) in acetic acid was added 61% nitric acid (12 eq., d = 1.38) at 10 °C and the whole mixture was stirred for a further 10 min at the same temperature. After a usual work-up, the products were purified by column chromatography on silica gel to give three isolable compounds. The first eluate was determined to be 4,5-dimethoxy-2-nitrophenylacetaldehyde (**3**) based on its spectroscopic data and elemental analysis.



Scheme 1

The structure of **3** was further confirmed by its conversion into the corresponding 2,4-

dinitrophenylhydrazone (**4**). The second eluate showed its molecular weight at *m/z* 448 (M^++1) in its MS spectrum, which indicated the presence of two nitro groups, three methoxy groups and one hydroxy group on the aromatic rings. Based on the consideration of reaction mechanism depicted in Scheme 2, two possible structures (**7** and **8**) can be proposed for this product. The reaction mechanism for the formation of **7**, involving a direct nitration at the 5-position and hydrolysis of the methoxy group at the 6-position into the hydroxy group, can easily be assumed. On the other hand, the later (**8**) would be derived from the acyliminium intermediate (**B**) by recyclization at the *ortho*-position to the hydroxy group. Since the NMR spectrum of the second eluate exhibited heavily overlapped signals due to the presence of the rotamers, the *N*-formyl group was removed by hydrolysis with concentrated hydrochloric acid to give the 1,2,3,4-tetrahydroisoquinoline (**9**). In the ^{1}H-^{1}H COSY spectrum of **9**, the proton signal at the 8-position was obviously correlated to the proton at the 1-position (Figure 1), which supported the structure determination of the second compound to be **7**, unambiguously.

The third product was also identified as *N*-formyl-4,5-dimethoxy-2-nitrophenethylamine (**5**), which was identical with the authentic sample prepared from 3,4-dimethoxyphenethylamine (**6**) by two steps involving an *N*-formylation, followed by a nitration of the resulting *N*-formyl-3,4-dimethoxyphenethyl-amine.[6]

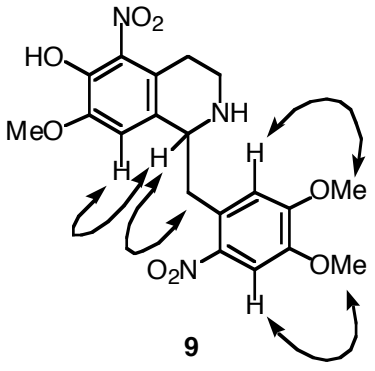


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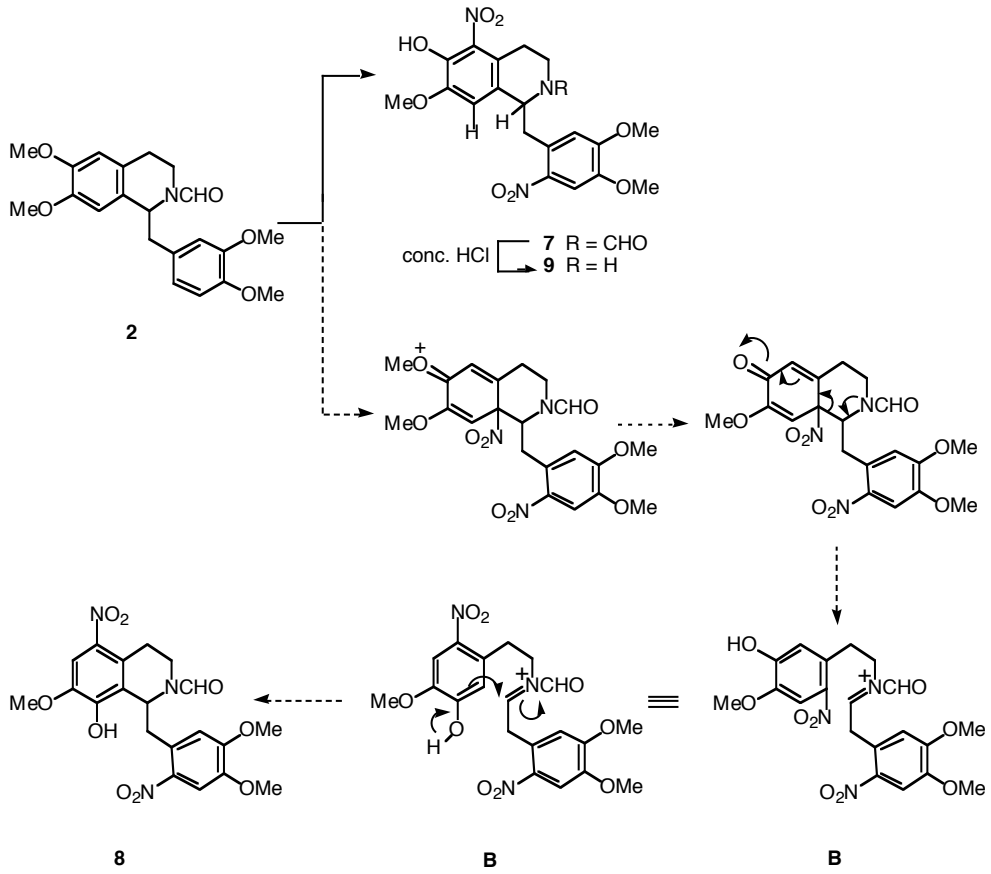
Figure 1 Observed Correlations in COSY Spectrum were indicated as arrows.

The formation of these compounds (**3** and **5**) was reasonably explained by assuming the reaction mechanism as shown in Scheme 1, in which, the first nitration occurred at the 2'-position of the benzene ring of the 1-benzyl moiety, and the second nitration took place at the 8a position. The bond between the 1 and 8a positions was then cleaved to give the acyliminium intermediate (**A**), which on hydrolysis might give the compounds (**3**) and (**5**).



Scheme 2

CONCLUSION

Although the formation of **8**, an interesting compound from the mechanistic point of view, might provide an alternative way to the synthesis of 7,8-dioxygenated isoquinoline alkaloids, none of the compounds with 7,8-dioxygenated substituents could be isolated, unfortunately. However, the nitration at the 8a position of 1,2,3,4-tetrahydroisoquinoline derivatives is very rare, and the subsequent bond fission between 1 and 8a positions of 1,2,3,4-tetrahydroisoquinoline derivative under usual nitration conditions, observed here, would be the first example to the best of our knowledge.

EXPERIMENTAL

General Experimental Procedures. All melting points are uncorrected. IR spectra were recorded for thin films unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were obtained for a solution in $CDCl_3$ or DMSO-d_6, and chemical shifts are reported on the δ-scale from TMS as an internal standard. ^{13}C

Multiplicities were determined with the aid of a APT sequence, separating methylene and quaternary carbons = up, from methyl and methine carbons = down.

*2-Formyl-1,2,3,4-tetrahydro-1-(3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (**2**)* ----- To a stirred solution of a mixture of formic acid and triethylamine, prepared by the dropwise addition of 96% formic acid (45 mL, 1.15 mol) to ice-cooled triethylamine (33 mL, 0.24 mol), was added the tetrahydroisoquinoline (**1**) (8.0 g, 23.3 mmol) in small portions. After complete addition, the mixture was heated at 100 °C for 18 h. The solvent was evaporated and the residue was basified with 10% ammonium hydroxide, and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to give a formyl compound, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$:MeOH (20:1) gave **2** as colorless prisms (8.5 g, 98%); mp 135-135.5 °C (recrystallized from MeOH), IR 1660, 1440, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55-3.35 (5H, m), 3.51-3.61 (0.5H, m), 3.68 (1.5H, s), 3.76 (1.5H, s), 3.85 (6H, s), 3.86 (1.5H, s), 3.87 (1.5H, s), 4.40-4.52 (0.5H, m), 4.57 (0.5H, dd, *J* = 6.1 and 8.5 Hz), 5.52 (0.5H, t, *J* = 6.7 Hz), 6.33 (0.5H, s), 6.53-6.70 (4H, m), 6.74 (0.5H, d, *J* = 8.6 Hz), 6.82 (0.5H, d, *J* = 8.0 Hz), 7.72 (0.5H, s), 8.14 (0.5H, s); ^{13}C NMR ($CDCl_3$) δ up: 27.4, 28.8, 33.9, 40.6, 41.3, 42.8, 125.2, 125.9, 126.8, 127.1, 129.5, 129.7, 147.1, 147.6, 147.8, 148.0, 148.4, 148.8; down: 51.8, 55.5, 55.6, 55.8, 58.7, 109.6, 110.1, 110.7, 111.0, 111.1, 111.4, 112.2, 112.6, 121.5, 121.7, 161.6. MS *m/z* 371 (M^+). HRMS: Calcd for $C_{21}H_{25}NO_5$: 371.1733. Found: 371.1735. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.09; H, 6.66; N, 3.95.

*4,5-Dimethoxy-2-nitrophenylacetaldehyde (**3**), N-Formyl-4,5-dimethoxy-2-nitrophenethylamine (**5**), and 2-Formyl-1,2,3,4-tetrahydro-1-(4',5'-dimethoxy-2'-nitrobenzyl)-6-hydroxy-7-methoxy-5-nitro-isoquinoline (**7**)* ----- To a stirred solution of the *N*-formyltetrahydroisoquinoline (**2**) (2.0 g, 5.39 mmol) in acetic acid (20 mL) was added portionwise 61% nitric acid (5 mL, *d* = 1.38) at 10 °C, and the resulting solution was stirred for a further 10 min at the same temperature. The mixture was poured into ice-cooled water and extracted with $CHCl_3$. The organic layer was washed with water, saturated $NaHCO_3$, and water, and dried over Na_2SO_4. Evaporation of the solvent gave a viscous syrup, which was subjected to column chromatography on silica gel. Elution with chloroform afforded the aldehyde (**3**) (143 mg, 12%), as the first eluant; mp 105-106 °C; IR 1730, 1580, 1500, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (3H, s),

3.97 (3H, s), 4.08 (2H, s), 6.68 (1H, s), 7.76 (1H, s), 9.84 (1H, s); ^{13}C NMR ($CDCl_3$) δ up: 48.7, 123.4, 148.3, 151.4, 153.5; down: 56.4, 56.5, 108.4, 114.5, 197.2. MS *m/z* 225 (M^+). HRMS: Calcd for $C_{10}H_{11}NO_5$: 225.0636. Found: 225.0631. Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.80; H, 4.84; N, 6.44. The structure of the aldehyde was further confirmed by its conversion into the corresponding hydrazone as follows.

A mixture of the aldehyde (**3**) (55 mg, 0.24 mmol) and 2,4-dinitrophenylhydrazine (58 mg, 0.29 mmol) in the presence of conc. hydrochloric acid (2 drops) was heated at reflux for 5 min and the mixture was cooled to rt to give the solid, which was recrystallized from EtOH to yield the hydrazone (**4**) (83 mg, 85%); mp 204-205 °C; IR (KBr) 1620, 1590, 1520, 1340, and 1270 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.75 (3H, s), 3.78 (3H, s), 3.93 (2H, d, *J* = 4.3 Hz), 7.01 (1H, s), 7.53 (1H, d, *J* = 9.7 Hz), 7.57 (1H, s), 8.06 (1H, t, *J* = 4.3 Hz, 6-H), 8.19 (1H, dd, *J* = 2.7 and 9.7 Hz), 8.69 (1H, d, *J* = 2.7 Hz), 11.29 (1H, s); ^{13}C NMR (DMSO-d_6) δ up: 65.1, 126.2, 129.0, 136.8, 141.1, 147.6, 153.2; down: 56.2, 56.4, 108.3, 114.7, 116.2, 123.1, 129.9, 153.2. MS *m/z* 405 (M^+). HRMS: Calcd for $C_{16}H_{15}N_5O_8$: 405.0920. Found: 405.0921. Anal. Calcd for $C_{16}H_{15}N_5O_8$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.17; H, 3.94; N, 17.59.

Further elution with the same solvent gave the dinitroisoquinoline derivative (**7**) (723 mg, 30%) as the second eluant; mp 242-243 °C (recrystallized from MeOH); IR (KBr) 3430, 1650, 1580, 1520, 1330, and 1272 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.43-2.80 (1H, m), 3.14-3.50 (2H, m), 3.55-3.85 (8/3H, m), 3.84 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 4.20-4.35 (1/3H, m), 4.97 (1/3H, br d, *J* = 7.6 Hz), 5.50 (2/3H, dd, *J* = 3.0 and 10.0 Hz), 6.55 (1/3H, s), 6.85 (2/3H, s), 6.93 (2/3H, s), 6.98 (1/3H, s), 7.52 (1/3H, s), 7.62 (2/3H, s), 7.68 (1/3H, s), 7.90 (2/3H, s), 10.35 (1H, br s); Anal. Calcd for $C_{20}H_{21}N_3O_9$: C, 53.69; H, 4.73; N, 9.39. Found: C, 53.73; H, 4.86; N, 9.12. MS(CI) *m/z* 448 (M^++1).

N-Formyl-4,5-dimethoxy-2-nitrophenethylamine (**5**) (210 mg, 15%) was obtained as the third eluant; mp 122-122.5 °C (recrystallized from benzene); IR 1680, 1620, 1580, 1490, and 1320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.17 (2H, t, *J* = 6.8 Hz), 3.64 (2H, dt, *J* = 6.7 and 6.7 Hz), 3.95 (3H, s), 3.98 (3H, s), 5.94 (1H, br s), 6.78 (1H, s), 7.61 (1H, s), 8.19 (1H, s); ^{13}C NMR ($CDCl_3$) δ up: 33.3, 38.5, 128.9, 141.2, 147.6, 153.2; down: 56.2, 108.1, 113.6, 161.4. MS *m/z* 254 (M^+). HRMS: Calcd for $C_{11}H_{14}N_2O_5$: 254.0902. Found: 254.0887. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.62; H, 5.32; N, 10.86.

*Alternative preparation of N-formyl-4,5-dimethoxy-2-nitrophenethylamine (**5**)* ----- To a stirred solution of *N*-formyl-3,4-dimethoxyphenethylamine (1.0 g, 4.78 mmol) in acetic acid (8 mL) was added portionwise nitric acid (2.3 mL, d = 1.38) at 10 °C, and the resulting solution was stirred for a further 10 min at the same temperature. The mixture was poured into ice-cooled water and extracted with $CHCl_3$. The organic layer was washed with water, saturated $NaHCO_3$, and water, and dried over Na_2SO_4. Evaporation of the solvent gave a viscous syrup, which was subjected to column chromatography on silica gel. Elution with chloroform afforded the nitro compound (**5**) (1.01 g, 83%), which was identical with the sample obtained above.

*1,2,3,4-Tetrahydro-1-(4',5'-dimethoxy-2'-nitrobenzyl)-6-hydroxy-7-methoxy-5-nitroisoquinoline (**9**)* ----- A solution of the *N*-formyl compound (**7**) (130 mg, 0.29 mmo) in conc. hydrochloric acid (5 mL) was heated at reflux for 18 h. After evaporation of hydrochloric acid, the esidue was basified with 10% ammonium hydroxide and extracted with $CHCl_3$. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a viscous syrup, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$:MeOH (99:1) gave **9** (103 mg, 85%); mp 230 °C (decomp) (recrystallized from methanol); IR (KBr) 3450, 1520, 1470, 1330, and 1270 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.27-2.45 (2H, m), 2.73-2.87 (1H, m), 2.94-3.07 (1H, m), 3.13 (1H, dd, J = 10.0 and 13.5 Hz), 3.64 (2H, dd, J = 3.5 and 13.5 Hz), 3.82 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 4.04 (1H, dd, J = 3.3 and 9.7 Hz), 6.95 (1H, s), 7.09 (1H, s), 7.58 (1H, s); ^{13}C NMR (DMSO-d_6) δ up: 23.3, 37.7, 38.6, 118.8, 129.4, 130.3, 137.2, 140.5, 141.6, 146.6, 146.9, 152.3; down: 55.1, 55.9, 56.1, 56.3, 107.9, 111.5, 115.4. MS m/z 419 (M^+). HRMS: Calcd for $C_{19}H_{21}N_3O_8$: 419.1328. Found: 419.1332. Anal. Calcd for $C_{19}H_{21}N_3O_8$: C,54.41; H, 5.05; N, 10.02. Found: C, 54.37; H,5.17; N, 9.82.

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