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An Easy and Simple Synthesis of Ricinine and its Analogues

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Abstract: Ricinine is an alkaloid of *Ricinus communis* displaying numerous biological properties. Ricinidine **(1-Methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile)** and new N-analogues of Ricinidine were obtained by the reaction of ethyl α-ethoxyethylidenecyanoacetate with various amines. Earlier, the ethyl α-ethoxyethylidenecyanoacetate was easily prepared from ethyl cyanoacetate. Biologically amines as tryptamine and histamine were used in order to introduce a second pharmacophore on the target molecule.

Keywords: ricinine; alkaloid; pyridinone

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1. Introduction

Ricinine (1,2-Dihydro-4-methoxy-1-methyl-2-oxo-3-pyridinecarbonitrile) is a simple pyridinone alkaloid isolated by Tuson in 1864 [1] from castor-oil seed (*Ricinus communis*). Ricinine is very poorly toxic in comparison to the protein Ricin also present in castor-oil seed. Ricinine exhibits insecticidal properties and is used against leaf-cutting ant (*Atta sexdens rubropilosa*) [2–4]. In the field of medicine, Ricinine inhibits the cellular entry of calcium ions and displays cardiotonic properties [5], in addition to analgesic [6] and anti-leukemic ones [7,8].

Ricinine is a cyanopyridinone according to Späth and Köler [9], many other cyanopyridinone alkaloids are well known such as nudiflorine and ricinidine [10] (Figure 1).

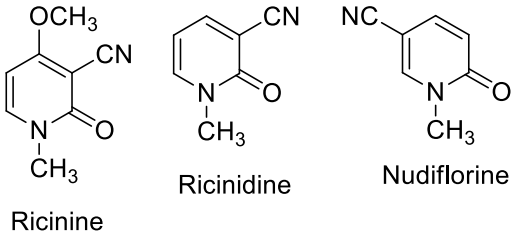
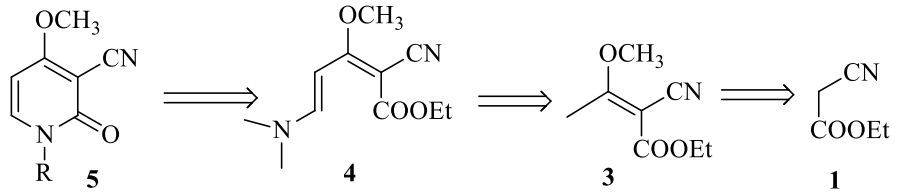


Figure 1. Structure of Ricinine and two natural cyanopyridines, Ricinidine and Nudiflorine.

Many syntheses of Ricinine are described in the literature [11], the earliest syntheses were based on the pyridine ring transformation in many steps. Moreover, cyanopyridin-2(1H)-one analogues of Ricinine which are important chemical intermediates, were the subject of many synthetic approaches [11]. On the other side, we have previously described the formation of the pyridinone cycle in the synthesis of Cerpegin, by the reaction

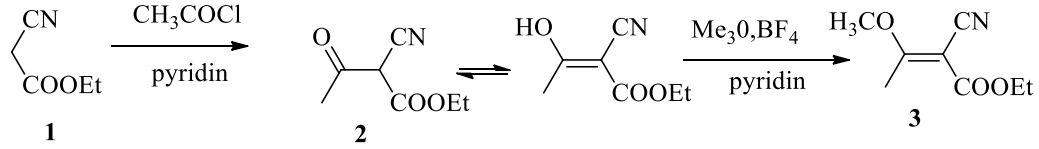
of amines with (dimethylamino)pentadienoate, obtained by a sequence involving the reactant DMF-DEA [12]. Other analogous syntheses of cyanopyridinones using DMF-DMA were described in literature [13], but not the synthesis of Ricinine.

We propose herein the synthesis of Ricinidine and N-derivatives according to the retrosynthetic Scheme 1.



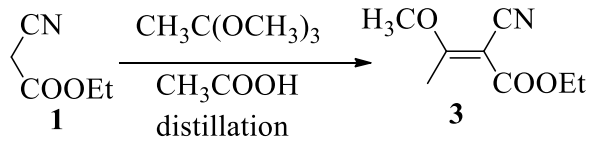
Scheme 1. Retrosynthesis and N-derivatives derivatives.

Initially, our attempts to synthesize 2-cyano-3-methoxybut-2-enoate (**3**) by acylation of ethyl cyanoacetate (**1**) according to the former literature [14] were unsuccessful. We have obtained a mixture of enol and acetyl derivatives which was methylated by trimethyloxonium fluoroborate into (**3**). (Scheme 2)

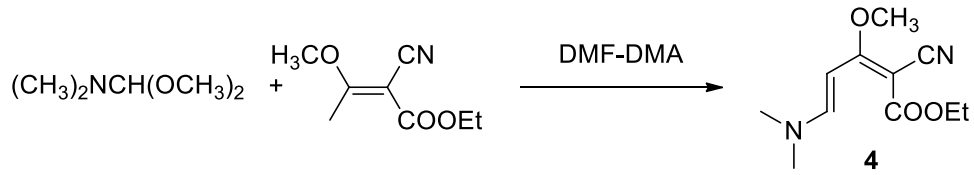


Scheme 2. Synthesis of 2-cyano-3-methoxybut-2-enoate (**3**) by acylation of ethyl cyanoacetate followed by methylation with Me_3O, BF_4.

A better method to obtain the cyanobutenoate (**3**) was to apply the one-step reaction of trimethoxyethane with ethyl cyanoacetate (**1**) catalyzed by acetic acid, according to a modified process described by Nicholl with malonitrile [15]. This approach leads to the compound (**3**).

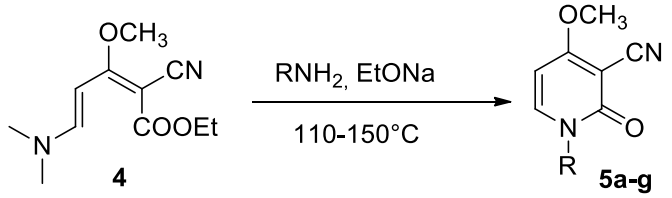


By the reaction of the commercially available dimethyl formamide dimethylacetal (DMFDMA), the cyanobutenoate (**3**) was then converted into (**4**) according to Kasum and Prager in the synthesis of Perloline [16].



Scheme 4. Synthesis of (dimethylamino)pentadienoate (**4**) with DMF-DMA.

The reaction of (dimethylamino)pentadienoate (**4**) in the presence of sodium ethoxide as catalyst affords the synthesis of Ricinine with methylamine or N-derivatives with other primary amines, according to the Scheme 5.

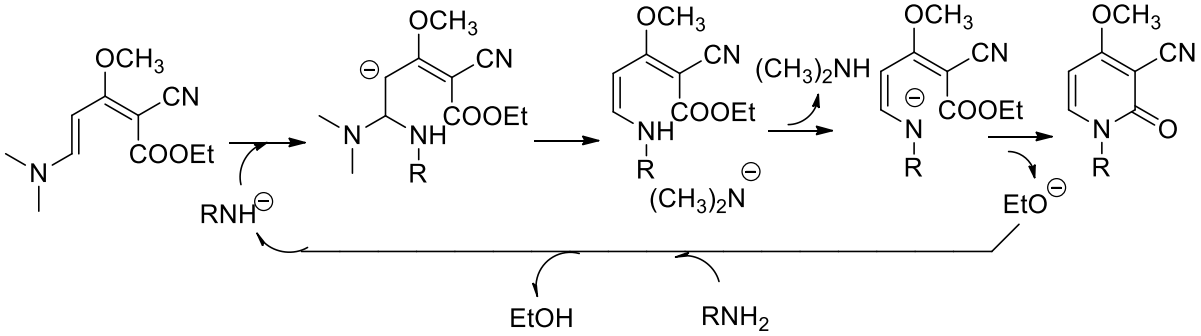


R= CH_3 (**a**), C_4H_9 (**b**), C_8H_{17} (**c**), $CH_2C_6H_5$ (**d**), $CH(CH_3)C_6H_5$ (**e**), $CH_2CH_2C_3H_3N_2$ (**f**), CH_2CH_2 C_8H_5N (**g**)

Scheme 5. Synthesis of Ricinidine (**5a**) and N-analogues of Ricinidine (**5b**–**g**).

This method allows the preparation of the butyl, octyl, benzyl, methylbenzyl and the derivatives of biologically active tryptamine and histidine permitting the introduction of a second pharmacophore group in the target molecule.

We propose the mechanism of formation of the pyridinone cycle by a basic catalysis according to the scheme:

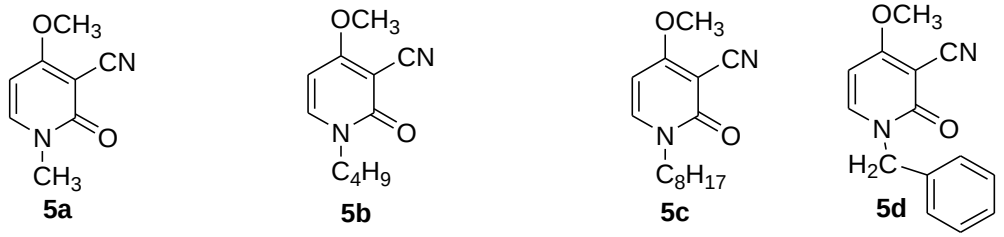


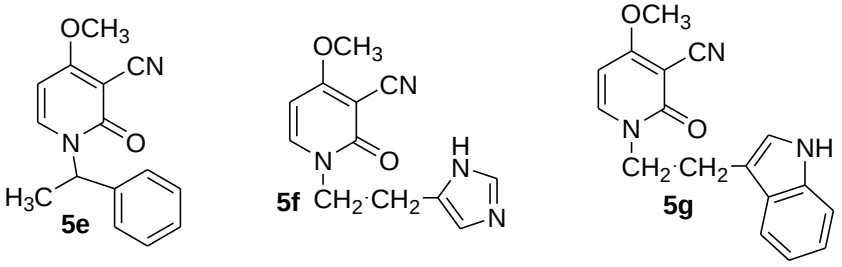
Scheme 6. Mechanism of formation of the pyridinones.

Results obtained are reported Table 1. New compounds were characterised by ^{1}H and ^{13}C NMR and mass spectroscopy.

Table 1. Synthesis of Ricinidine (**5a**) and N-analogues of Ricinidine (**5b**–**g**).

Entry	Amine	Product	Yield (%)
a	methylamine	**5a**	61
b	n-butylamine	**5b**	92
c	n-octylamine	**5c**	95
d	benzylamine	**5d**	92
e	α-methylbenzylamine	**5e**	87
f	histamine	**5f**	60
g	tryptamine	**5g**	58





As the two final steps of the sequence are thermal reaction, the multicomponent approach from ethyl cyanomalonate (**3**) (1 eq), DMF-DMA (1.2 eq), benzylamine (1 eq) have been investigated, but in these conditions, a mixture of different products with only a very poor yield of Ricinine derivative (**5d**) was obtained.

In conclusion, the reaction of primary amines with the ethyl 2-cyano-1-methoxy-5-(dimethylamino)pentadienoate in the presence of sodium ethoxide conducts to N-derivative of Ricinidine. This reaction allows a simple and easy synthesis of a variety of N-substituted Ricinidine derivatives. The biological properties of these new compounds (**5b–g**) are being tested.

2. Experimental

Melting points were measured on a Kofler apparatus and are reported uncorrected. IR spectra were obtained with a Fourier transform Perkin-Elmer Spectrum One with ATR accessory. The frequencies of absorption are given in cm^{-1}. Only significant absorptions are listed. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded while using $CDCl_3$ with TMS as an internal standard on a Bruker DPX 400 NMR spectrometer. Chemical shifts are reported in ppm. Mass spectra were recorded on a Xevo G2- XS QTof WATERS, mass range (50–1000 *m*/*z*), source temperature 120 °C, desolvatation temperature 500 °C.

(1) Synthesis of ethyl 2-cyano-3-methoxybut-2-enoate (3)

A mixture of 1,1,1-trimethoxyethane (0.3 mol, 37,5 mL), ethyl cyanoacetate (0.2 mol, 21 mL) and acetic acid (0.5 mL) was stirred and distillated. Three portions of 0.5 mL of acetic acid were added when approximately 6. 9 and 12 mL of ethanol was collected After the recovery of ethanol, the solution is cooled and evaporated under vaccuo. The mixture was crystallized in ethyl acetate.

Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): 4.20 (q, J = 6.8 Hz, 2H), 4.01 (s, 3H), 2.61 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 184.5, 163.8, 115.1, 85.8, 58.1, 15.1, 15.1.

(2) Synthesis of ethyl 2-cyano-5-(dimethylamino)-3-methoxypenta-2,4-dienoate (4)

Under a stream of nitrogen, a mixture of ethyl 2-cyano-3-methoxybut-2-enoate (29.6 mmol, 5.02 g) and dimethylformamide dimethyl acetal (44.4 mmol, 4 mL) was stirred and refluxed for 1 h. The reaction is followed by TLC (eluent 50% diethylether/50% ethyl acetate). After cooling under a stream of nitrogen, a viscous red solution was obtained by evaporation under vaccuo. The mixture was crystallized in ethyl acetate/diethylether. Mp = 97 °C (lit = 98–100 °C [16]).

^{1}H NMR (400 MHz, $CDCl_3$): 7.21–7.72 (m, 2H, CH=CH), 4.10 (q, J = 6.8 Hz, 2H), 4.02 (s, 3H), 3.11 (s, 3H), 2.90 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 181.8, 157.5, 153.1, 119.7, 91.7, 62.6, 60.9, 45.7, 14.5.

(3) Synthesis of 2-cyano-3-methoxy-2-pyridones

1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (5a) (Ricinine)

A mixture of enamine (1.12 g, 5 mmol), methylamine in ethanol (33%) (21 mmol) and sodium ethoxide (0.1 mmol) in dry DMF under argon was stirred and refluxed for 15 min.

A viscous red solution is obtained. Purification using a preparative thin layer chromatography on silica with $CHCl_3$ /n-butanol/acetic acid (25/10/1) as eluant (Rf = 0.20, pale red) visualized in UV light.

White crystals, Mp = 196–197 °C (ethanol) (Lit Mp = 197 °C [9]). IR: 2220 cm^{-1} (CN). ^1H NMR ($CDCl_3$) δ: 7.39 (d, 1 H, *J* = 8.0 Hz, CH); 5.94 (d, 1 H, *J* = 8.0 Hz, CH); 3.86 (s, 3H, OCH_3); 3.43 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$) δ 186.3; 157.4 (CO); 134.2; 115.8 (CN); 99.7; 67.9; 57.7 (CH_3); 38.9 (CH_3)

HRMS (ESI-QTOF):calcd for $C_8H_9N_2O_2$ (M + H) 165.0664; found 165.0666.

General procedure: A mixture of enamine (2 mmol), primary amine (2.1 mmol) and sodium ethoxide (0.1 mmol) in dry DMF under argon was stirred and refluxed for 15 min. The viscous red-brown solution was chromatographed on silica with a mixture of diethyl ether/ ethyl acetate /methanol = 1/1/0 to 1/1/0.5.

1-butyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5b)

With 1-butylamine

White crystals, Mp = 249°C. ^1H NMR ($CDCl_3$) δ: 7.39 (d, 1 H, *J* = 8.0 Hz, CH); 5.94 (d, 1 H, *J* = 8.0 Hz, CH); 3.86 (s, 3H, OCH_3); 3.30 (t, 2H, NCH_2);1.70 (m, 2H, CH_2); 1.37 (m, 2H, CH_2); 0.98 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 186.3; 157.4 (CO);134.2; 115.8 (CN); 99.7; 67.9; 57.7 (CH_3); 47.6; 30.1; 20.2; 13.8. HRMS (ESI-QTOF): calcd for $C_{11}H_{15}N_2O_2$ (M + H) 207.2490; found 207.2501.

4-methoxy-1-octyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (5c)

With 1-Octylamine

White crystals, Mp = 319 °C. ^1H NMR ($CDCl_3$) δ: 7.39 (d, 1 H, *J* = 8.0 Hz, CH); 5.93 (d, 1 H, *J* = 8.0 Hz, CH); 3.86 (s, 3H, OCH_3); 3.30 (t, 2H, NCH_2); 1.75–1.48 (m, 10H, $(CH_2)_5$); 1.38 (m, 2H, CH_2); 1.08 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 186.3; 157.4 (CO); 134.2; 115.8 (CN); 99.7; 67.8; 54.7 (CH_3); 47.9; 31.9; 30.8; 29.3; 27.2; 22.8; 14.1. HRMS (ESI-QTOF): calcd for $C_{15}H_{23}N_2O_2$ (M + H) 263.1759; found 263.1756.

1-benzyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5d)

With Benzylamine

Mp = 325 °C (dec). ^1H NMR ($CDCl_3$) δ: 7.39 (d, 1H, *J* = 8.0 Hz, CH); 7.28–7.12 (m, 5H, H_{aro}); 5.94 (d, 1H, *J* = 8.0 Hz, CH); 4.68 (s, 2H, CH_2); 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 186.3; 157.4 (CO); 136.5; 134.2; 128.9; 128.5; 126.7; 115.8 (CN); 99.7; 67.9; 57.7 (CH_3); 50.4 (CH_2). HRMS (ESI-QTOF): calcd for $C_{14}H_{13}N_2O_2$ (M + H) 241.0977; found 241.0980.

α-Methyl-1-benzyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5e)

With methylbenzylamine

White crystals, Mp > 300 °C (dec). ^1H NMR ($CDCl_3$) δ: 7.39 (d, 1H, *J* = 8.0 Hz, CH); 7.28–7.12 (m, 5H, H_{aro}); 5.94 (d, 1H, *J* = 8.0 Hz, CH); 6.24 (q, *J* = 8.0 Hz, CH); 3.86 (s, 3H, OCH_3; 1.30 (d, *J* = 8.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 186.3; 157.4 (CO); 140.0; 134.2; 128.9; 128.5; 126.7; 115.8 (CN); 99.7; 67.9; 57.7 (CH_3); 50.4; 18.3 (CH_3). HRMS (ESI-QTOF) calcd for $C_{15}H_{15}N_2O_2$ (M + H) 255.1133. Found 255.1132.

1-(21H-imidazol-5-yl)ethyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5f)

With histidine

White crystals, Mp > 240 °C (dec). ^1H NMR ($CDCl_3$) δ: 8.45 (1H, broad s, NH); 7.44 (1H, s, NCHN); 7.39 (d, 1H, *J* = 8.0 Hz, CH); 5.94 (d, 1H, *J* = 8.0 Hz, CH); 6.86 (1H, CH=C); 3.86 (s, 3H, OCH_3); 3.58 (t, *J*= 6.4 Hz, 2H, NCH_2); 3.22 (t, *J*= 6.4 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 186.3; 157.1 (CO); 135.5; 134.2; 133.5; 118.6; 115.8 (CN); 99.7; 67.9; 57.7; 48.5; 26.5. HRMS (ESI-QTOF) calcd for $C_{12}H_{13}N_4O_2$ (M + H) 245.1038. Found 245.1037.

1-(2-(1H-indol-3-yl)ethyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5g)

With Tryptamine

White crystals, Mp > 250 °C (dec). ^1H NMR ($CDCl_3$) δ: 10.11 (broad s, 1H, NH_{indol}); 7.39 (d, 1H, *J* = 8.0 Hz, CH); 7.25–7.14 (m, 4H, H_{aro}); 6.44 (s, 1H, CH); 5.94 (d, 1H, *J* = 8.0 Hz, CH); 3.87 (t, *J* = 6.4 Hz, 2H, NCH_2); 3.86 (s, 3H, OCH_3); 3.13 (t, *J* = 6.4 Hz, 2H, CH_2). ^{13}C: δ: 186.3; 157.1 (CO); 136.5; 134.2; 127.4; 122.9; 121.7; 115.9; 115.8 (CN); 111.1; 99.7; 67.9; 57.7;

51.9 (CH_2); 26.7 (CH_2). HRMS (ESI-QTOF) calcd for $C_{17}H_{16}N_3O_2$ (M + H) 294.12425; found 294.1242.

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