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The Hantzsch condensation of 2-hydroxy-5-nitrobenzaldehyde, ethyl acetoacetate and ammonia gave the hitherto unknown 2-methyl-3-ethoxycarbonyl-4-ethoxycarbonylmethyl-6-(2-hydroxy-5-nitrophenyl)-pyridine *via* an unusual condensation and oxidation *in situ*.

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1,4-Dihydropyridines are  $\text{Ca}^{2+}$  antagonists with wide-spread pharmacological use [3]. Among the methods for the preparation of 1,4-dihydropyridines, the Hantzsch cyclization [4] is one of the oldest and most versatile; it is widely used, specifically in pharmaceuticals [5]. As part of our program on drug design [6] we became interested in the Hantzsch condensation of 5-nitrosalicylaldehyde **1** with ethyl acetoacetate **2** and ammonia (Scheme 1). The new compound **3** is a pale yellow solid of mp 176°. The molecular formula  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_7$  was assigned by high resolution mass spectrometry ( $\text{M}^+$ ,  $m/z$  388, 100%) to **3**. Its ir spectrum showed absorption for a phenolic hydroxyl ( $3600\text{--}3350\text{ cm}^{-1}$ ) and carbonyl ester groups ( $1700, 1680\text{ cm}^{-1}$ ). The  $^1\text{H}$  nmr spectrum of **3** showed four signals for the ethyl ester groups instead of the two expected signals at  $\delta$  1.30 (t, 3H), 1.43 (t, 3H), 4.21 (q, 2H) and 4.44 (q, 2H). Two singlets at 2.75 (3H) and 3.92 (2H) were assigned to the methyl group joined to C-2 and the methylene group linked to C-4 of the pyridine ring, respectively. Likewise, it showed a series of five signals in the aromatic region as follows: a doublet at 7.06 ( $J = 9.3\text{ Hz}$ ) for H-5', a singlet at 7.78 for H-5, a partially split doublet at 8.20 ( $J = 9.3, 2.4\text{ Hz}$ ) for H-4', a doublet at 8.76 ( $J = 2.4\text{ Hz}$ ) for H-2' and one singlet at 15.56 for the phenolic hydroxyl group. The  $^{13}\text{C}$  nmr spectrum of **3** and  $^1\text{H}$ - $^{13}\text{C}$  correlation (HETCOR) confirmed the structure proposed. The final elucidation of the tridimensional structure was achieved by X-ray diffraction of a single-crystal (Figure 1). The single-

Scheme 2

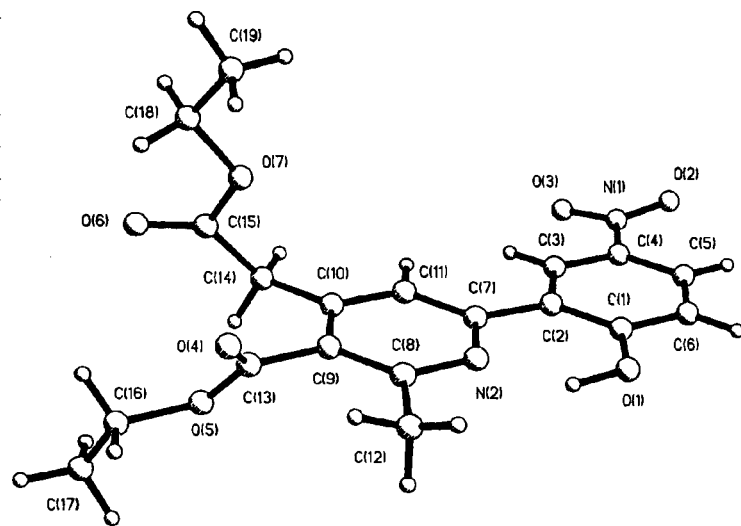
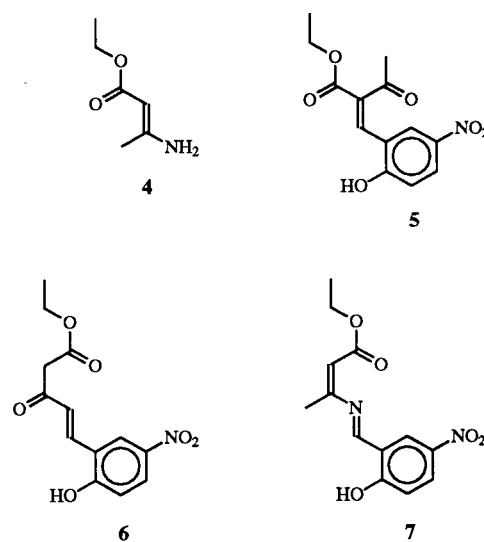
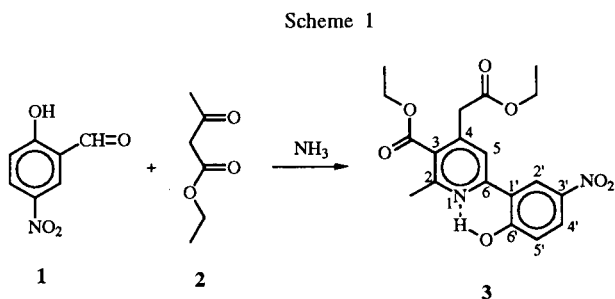


Figure 1. Crystal structure of compound 3.



crystal analysis showed the ethyl ester groups joined to C-3 and C-4 in different magnetic environments. This can explain the different chemical shift of the methyl and methylene groups in the  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra of **3**; also there is a hydrogen bond between the phenolic hydrogen and the pyridine ring nitrogen atom. The Hantzsch synthesis of dihydropyridines [7] has generally been assumed to proceed through the intermediacy of the aminocrotonate **4** and the  $\alpha,\beta$ -unsaturated ketone **5** with Michael addition of **4** to **5** being the rate determining stage (Scheme 2). In our case the aminocrotonate **4** and the chalcone-like intermediate **6** can be the two possible intermediates to obtain **3**; another possible intermediate can be **7** and the kinetic enol of ethyl acetoacetate. To the best of our knowledge, this kind of ring closure and oxidation *in situ* on the Hantzsch condensation has never been described. On preliminary biological tests **3** has shown analgesic and anti-inflammatory activity. Further investigation of the general course of this reaction is presently being carried out with substituted salicylaldehydes.

## EXPERIMENTAL

The melting point is uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The  $^1\text{H}$  and COSY nmr spectra were determined on a Varian Gemini-200 instrument; the  $^{13}\text{C}$  and  $^1\text{H}$ - $^{13}\text{C}$  nmr spectra were determined on a Varian VXR-300S instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and were determined in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts ( $\delta$ ) expressed downfield from TMS. Mass spectra were obtained with a Jeol SX-100 mass spectrometer. The X-ray diffraction of the single crystal was determined on the Nicolet R3m diffractometer.

Synthesis of 2-Methyl-3-ethoxycarbonyl-4-ethoxycarbonylmethyl-6-(2-hydroxy-5-nitrophenyl)pyridine **3**.

A mixture of 16.7 g (0.1 mole) of 5-nitrosalicylaldehyde, 25.2 g (0.21 mole) of ethylacetoacetate and 3.85 g (0.11 mole) of ammonia hydroxide in ethanol (50 ml) was stirred under reflux for 8 hours. The solution was concentrated (rotatory evaporator) to afford a solid. Crystallization of this material from dichloromethane-hexane gave 11.6 g (30%) of **3**, mp 176°; ir (chloroform):  $\nu$   $\text{cm}^{-1}$  3600-3350, 1700, 1680;  $^1\text{H}$ -nmr (deuteriochloroform):  $\delta$  1.3 (t, J = 7.5 Hz, 3H), 1.43 (t, J = 7.5 Hz, 3H), 2.75 (s, 3H,  $\text{CH}_3$ -Ar), 3.92 (s, 2H,  $\text{CH}_2$ -CO), 4.21 (q, J = 7.5 Hz, 2H,  $\text{CH}_2$ -O), 4.44 (q, J = 7.5 Hz, 2H,  $\text{CH}_2$ -O), 7.06 (d, J = 9.3 Hz, 1H, H-5'), 7.78 (s, 1H, H-3), 8.2 (dd, J = 9.3, 2.4 Hz, 1H, H-4'), 8.76 (d, J = 2.4 Hz, 1H, H-2'), 15.56 (s, 1H, -OH);  $^{13}\text{C}$ -nmr (deuteriochloroform):  $\delta$  169.2 (C=O), 166.2 (C=O), 155.7 (Cq), 154.4 (Cq), 144.7 (Cq), 139.7 (Cq), 127.6 (Cq), 127.2 (C-4'), 123 (C-2'), 119.3 (C-3'), 119.2 (C-5'), 117.2 (Cq), 62 (-OCH<sub>2</sub>), 61.5 (-OCH<sub>2</sub>), 39.8 [-CH<sub>2</sub>-(C-4')], 23.3 (CH<sub>3</sub>-py), 14.1 (CH<sub>3</sub>-CH<sub>2</sub>), 14.08 (CH<sub>3</sub>-CH<sub>2</sub>).

Anal. Calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: C, 58.76; H, 5.19; N, 7.21.

Table 1  
Bond Lengths (Å)

O(1)-C(1)	1.346 (8)	O(2)-N(1)	1.225 (8)
O(3)-N(1)	1.212 (8)	O(4)-C(13)	1.187 (10)
O(5)-C(13)	1.307 (10)	O(5)-C(16)	1.437 (12)
O(6)-C(15)	1.190 (9)	O(7)-C(15)	1.312 (9)
O(7)-C(18)	1.449 (10)	N(1)-C(4)	1.451 (9)
N(2)-C(7)	1.342 (8)	N(2)-C(8)	1.342 (8)
C(1)-C(2)	1.396 (8)	C(1)-C(6)	1.409 (9)
C(2)-C(3)	1.388 (9)	C(2)-C(7)	1.472 (8)
C(3)-C(4)	1.371 (9)	C(4)-C(5)	1.381 (9)
C(5)-C(6)	1.352 (10)	C(7)-C(11)	1.389 (8)
C(8)-C(9)	1.397 (9)	C(8)-C(12)	1.487 (9)
C(9)-C(10)	1.403 (9)	C(9)-C(13)	1.486 (10)
C(10)-C(11)	1.390 (8)	C(10)-C(14)	1.507 (8)
C(14)-C(15)	1.490 (9)	C(16)-C(17)	1.269 (21)
C(18)-C(19)	1.316 (15)		

Table 2  
Bond Angles (°)

C(13)-O(5)-C(16)	117.9 (7)	C(15)-O(7)-C(18)	117.2 (6)
O(2)-N(1)-O(3)	121.8 (6)	O(2)-N(1)-C(4)	119.0 (6)
O(3)-N(1)-C(4)	119.1 (6)	C(7)-N(2)-C(8)	121.0 (5)
O(1)-C(1)-C(2)	122.3 (5)	O(1)-C(1)-C(6)	116.6 (5)
C(2)-C(1)-C(6)	121.1 (6)	C(1)-C(2)-C(3)	117.1 (5)
C(1)-C(2)-C(7)	122.1 (5)	C(3)-C(2)-C(7)	120.8 (5)
C(2)-C(3)-C(4)	121.2	N(1)-C(4)-C(3)	119.3 (6)
N(1)-C(4)-C(5)	119.4 (6)	C(3)-C(4)-C(5)	121.2 (6)
C(4)-C(5)-C(6)	119.5 (6)	C(1)-C(6)-C(5)	119.9 (6)
N(2)-C(7)-C(2)	115.9 (5)	N(2)-C(7)-C(11)	120.4 (5)
C(2)-C(7)-C(11)	123.7 (5)	N(2)-C(8)-C(9)	120.9 (6)
N(2)-C(8)-C(12)	115.8 (6)	C(9)-C(8)-C(12)	123.3 (6)
C(8)-C(9)-C(10)	119.4 (5)	C(8)-C(9)-C(13)	119.6 (6)
C(10)-C(9)-C(13)	121.0 (5)	C(9)-C(10)-C(11)	117.8 (5)
C(9)-C(10)-C(14)	123.1 (5)	C(11)-C(10)-C(14)	119.1 (5)
C(7)-C(11)-C(10)	120.5 (5)	O(2)-C(13)-O(5)	124.2 (7)
O(4)-C(13)-C(9)	124.3 (7)	O(5)-C(13)-C(9)	111.5 (6)
C(10)-C(14)-C(15)	115.8 (5)	O(6)-C(15)-O(7)	123.3 (7)
O(6)-C(15)-C(14)	123.8 (7)	O(7)-C(15)-C(14)	112.9 (6)
O(5)-C(16)-C(17)	114.1 (11)	O(7)-C(18)-C(19)	111.5 (8)

Found: C, 58.80; H, 5.21; N, 7.19.

Crystallography.

X-Ray Analysis Data for 2-Methyl-3-ethoxycarbonyl-4-ethoxycarbonylmethyl-6-(2-hydroxy-5-nitrophenyl)pyridine **3**.

Crystals were grown from hexane-dichloromethane; C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>, M = 388.4, monoclinic space group P2<sub>1</sub>/c, a = 7.301(2), b = 33.186(7), c = 7.704(2) Å,  $\beta$  = 92.51(3)°, U = 1864.9(9) Å<sup>3</sup>, F(000) = 816, Z = 4, D<sub>c</sub> = 1.383 g cm<sup>-3</sup>,  $\mu$  = 9.00 cm<sup>-1</sup> (Cu-K $\alpha$ ). Intensities were recorded for 1919 unique reflections by an  $\omega$  scan,  $2\theta_{\text{max}}$  100° on a Nicolet P3F four circle diffractometer with Cu-K $\alpha$  radiation (Ni-filter,  $\lambda$  = 1.54178 Å) at 293K. Intensity data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and full-matrix least-squares refinement with SHELXTL [8] converged at R = 0.073, Rw = 0.090 for 1336 terms with  $F \geq 4\sigma F$ . The non-H atoms were given anisotropic temperature factors and the H-atoms were added at idealized positions with common fixed isotropic temperature factor U = 0.06 Å<sup>2</sup>. The function minimized was  $\Sigma w(|F_o| - |F_c|)^2$  with  $w^{-1} = \sigma^2(F_o) + 0.0057F^2$ . At convergence  $(\Delta\rho)_{\text{max}}$ ,  $(\Delta\rho)_{\text{min}}$  +0.24, -0.36 eÅ<sup>-3</sup> (Tables 1 and 2).

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