# Synthesis of a New 1,4-Dihydropyridine Containing the Imidazo[1,5-*a*]pyridine Nucleus



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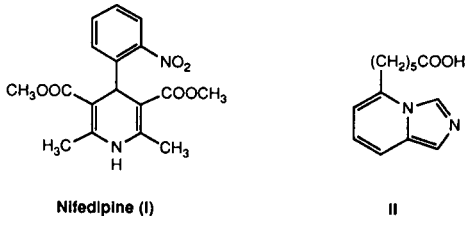
Received November 10, 1992

The synthesis of the new dihydropyridine diethyl 1,4-dihydro-4-(imidazo[1,5-*a*]pyridin-8-yl)-2,6-dimethylpyridine-3,5-dicarboxylate (**1**) is described. After many attempts to prepare the key intermediate aldehyde **2a** by different approaches, this compound has been obtained in good yields from methyl 2-cyano-3-pyridinecarboxylate (**10**). A three-step procedure involving reduction to the amine, formylation with concomitant cyclization and reduction of the ester group was used.

*J. Heterocyclic Chem.*, **30**, 473 (1993).

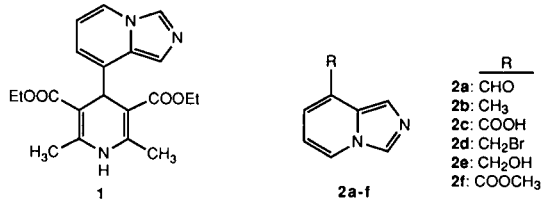
1,4-Dihydropyridines represent the largest and most studied class of calcium channel blockers [1], where nifedipine (**I**) is the prototype. In an attempt to obtain a dual antithrombotic-antihypertensive agent [2] we planned the synthesis of a new dihydropyridine, namely diethyl 1,4-dihydro-4-(imidazo[1,5-*a*]pyridin-8-yl)-2,6-dimethylpyridine-3,5-dicarboxylate (**1**), combining some structural components of nifedipine **I** and compound **II**, a reported $TxA_2$ synthase inhibitor [3] (Figure 1).




Nifedipine (I) II

Figure 1

Since most 4-aryldihydropyridines are obtained by the Hantzsch reaction from the corresponding arylaldehydes, the previously unknown imidazo[1,5-*a*]pyridine-8-carbaldehyde (**2a**) was selected as the key intermediate for the synthesis of **1** (Figure 2).




1 2a-f

Figure 2

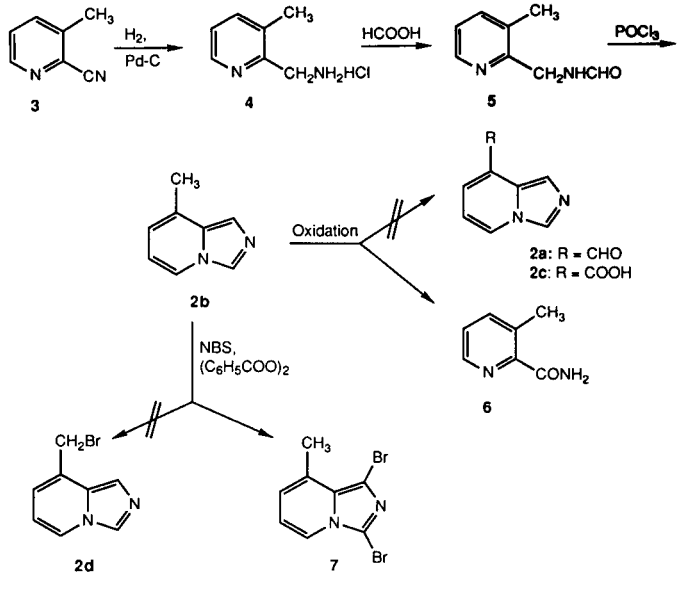
We describe in this paper the different attempts to prepare the aldehyde **2a**, as well as the synthesis of the dihydropyridine **1**.

## Results and Discussion.

The synthesis of the imidazo[1,5-*a*]pyridine system is well established in the literature, starting from pyridine [3] or pyridine-2-carbaldehyde [4]. However, functionalization of the basic nucleus has not been explored to a large extent. In particular, we could not find in literature any derivative containing a formyl group at the C-8 position (compound **2a**) or any other group suitable for its transformation into aldehyde (compounds **2b-f**).

Our initial plan to synthesize **2a** involved the 8-methylimidazo[1,5-*a*]pyridine (**2b**), as depicted in Scheme I. The starting material 3-methylpyridine-2-carbonitrile (**3**) was prepared by literature procedures from 3-methylpyridine [5,6] or 2,3-dimethylpyridine [7-9]. Catalytic hydrogenation of **3** at atmospheric pressure with palladium on charcoal in the presence of hydrochloric acid afforded the corresponding pyridinemethylamine **4** (81%), which was transformed to **5** (83%) by formylation with formic acid at reflux. Subsequent cyclization with phosphorus oxychloride yielded the desired 8-methylimidazo[1,5-*a*]pyridine (**2b**) in 82% yield.

Scheme I




Selenium dioxide has been reported as an effective reagent for allylic oxidation of some methyl-substituted heteroaromatic systems such as methylquinoline [10]. How-

ever, when **2b** was treated with selenium dioxide at reflux in dioxane-water no reaction was observed, whereas the same reagent in the presence of sulfuric acid gave the amide **6**, through oxidation of the imidazole nucleus. Similarly, the reaction of **2b** with chromic acid or potassium persulfate afforded **6** as the only detectable product. Finally, when we employed potassium permanganate in water at room temperature a complex mixture of products was obtained.

When allylic bromination of compound **2b** was attempted with *N*-bromosuccinimide and dibenzoyl peroxide the dibromo derivative **7** was formed instead of the expected bromomethyl derivative **2d**.

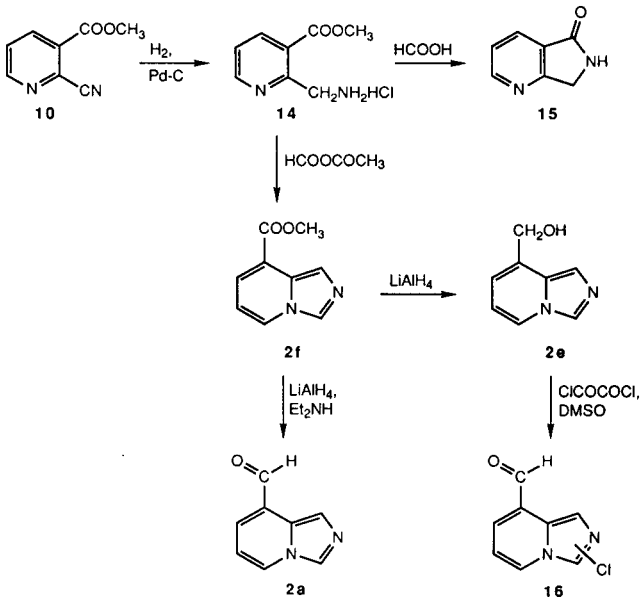
In order to avoid oxidation or bromination of the imidazole ring, we planned a new strategy consisting in the synthesis of the pyridine **11** (Scheme II), containing a hydroxymethyl group in C-3, precursor of the oxidized function present in the imidazopyridine **2e**.

Reaction of **3** with *N*-bromosuccinimide afforded the unstable bromomethyl derivative **8**, which was treated without purification with silver nitrate in acetone-water at room temperature giving the desired 3-hydroxymethylpyridine-2-carbonitrile (**9**) in 48% yield. Several conditions for the reduction of the cyano group of **9** with sodium borohydride or lithium aluminum hydride were investigated without success. In some cases the lactone **12** and the carboxylic acid **13** were formed. The mechanism of this reaction probably involves deprotonation of the hydroxymethyl group, followed by a nucleophilic attack on the cyano group coordinated by the Lewis acid. Subsequent hydrolysis would give the lactone **12** and the carboxylic acid **13**.

The same products were obtained by lithium aluminum hydride reduction (normal or inverse addition) of the cyanoester **10**, which was prepared from methyl 3-pyridinecarboxylate [6,11].

Finally, we explored the alternative synthesis of **2a** *via* cyclization of the aminoester **14** to compound **2f** (Scheme III). This synthetic approach had been initially rejected due to the predictable nucleophilic attack of the amino group upon the carbonyl function of **14** under formylation conditions.

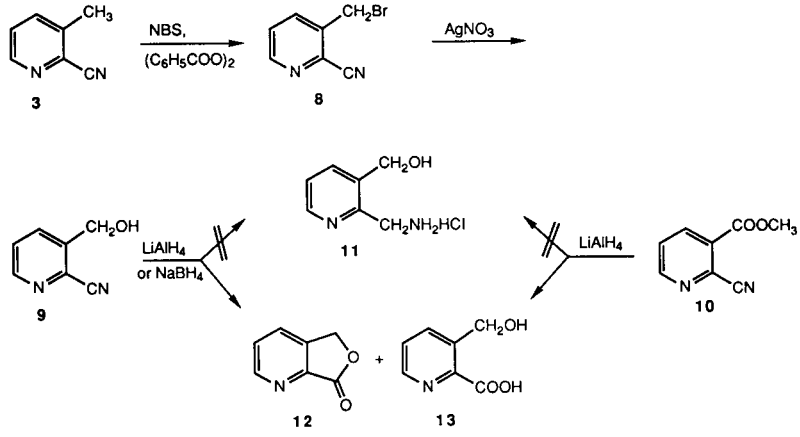
Scheme III




The cyano derivative **10**, was hydrogenated at atmospheric pressure with palladium on charcoal in the presence of hydrochloric acid, giving the amino hydrochloride **14** in 93% yield. As expected, formylation of **14** in the usual conditions gave only the lactam **15** (79%). To overcome this problem, the (aminomethyl)pyridine **14** was formylated with acetic formic anhydride [12] and cyclization took place in the same reaction medium leading to the imidazo[1,5-*a*]pyridine **2f** (76%).

Transformation of methyl ester **2f** into aldehyde **2a** was first attempted *via* the hydroxymethyl derivative **2e**, by

Scheme II



reduction with lithium aluminum hydride followed by Swern oxidation [13] with dimethyl sulfoxide and oxalyl chloride. However, in the latter step only the chlorinated aldehyde **16** could be isolated. Alternatively, treatment of the alcohol **2e** with selenium dioxide at reflux in dioxane-water yielded starting material only.

Finally the aldehyde **2a** was synthesized in good yield (66%) from the ester **2f** through a direct reduction with lithium aluminum hydride and diethylamine in pentane at room temperature [14].

The synthesis of the dihydropyridine **1** was achieved following a modification of the Hantzsch condensation [15] starting from the aldehyde **2a** (27% after crystallization).

Compound **1** showed calcium antagonistic activity when tested *in vitro* ($IC_{50}$ = 1.34 x $10^{-7}$ *M* in the guinea pig ileum contraction assay) although it was devoid of any thromboxane inhibition activity ($TxB_2$ production in rabbit platelets) at concentrations as high as 1 *mM*.

## EXPERIMENTAL

Solvents were made anhydrous as follows: dichloromethane was dried over calcium oxide, tetrahydrofuran and diethyl ether were refluxed over sodium/benzophenone just prior to use. The other solvents were absolute grade and were stored over molecular sieves. Silica gel plates (Merck silica gel 60 $F_{254}$) were used to monitor reactions. MN silica gel 60 (70-230 mesh ASTM) was used for flash chromatography. Organic extracts were dried over sodium sulfate or magnesium sulfate. Melting points were taken in a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Beckman 4210 spectrophotometer. The $^1$H- and $^{13}$C-nmr were taken on a Varian Gemini 300 instrument. Mass spectra were measured with a gc/ms Hewlett-Packard 5988A spectrometer. Elemental analyses were performed by "Centro de Investigación y Desarrollo", C.S.I.C., Barcelona (Spain).

3-Methylpyridine-2-methylamine Hydrochloride (**4**).

A solution of 3-methylpyridine-2-carbonitrile [6] (1 g, 8.55 mmoles) in 70 ml of methanol containing 1.9 ml of concentrated hydrochloric acid was hydrogenated at room temperature and atmospheric pressure with 0.93 g of 10% palladium on charcoal, until no more hydrogen was consumed (about 3 hours). Filtration and evaporation yielded 1.1 g (81%) of 3-methylpyridine-2-methylamine hydrochloride (**4**), mp 195-197°; $^1$H-nmr (tetradeuteriomethanol): δ 2.35 (s, 3H, $CH_3$), 4.28 (s, 2H, $CH_2$), 7.60 (dd, $J_{5,4}$ = 8 Hz, $J_{5,6}$ = 5 Hz, 1H, HC-5), 8.08 (d, $J_{4,5}$ = 8 Hz, 1H, HC-4), 8.48 (d, $J_{6,5}$ = 5 Hz, 1H, HC-6).

*Anal.* Calcd. for $C_7H_{10}N_2 \cdot 2HCl$: C, 43.09; H, 6.19; N, 14.35; Cl, 36.34. Found: C, 42.83; H, 6.17; N, 14.16; Cl, 36.04.

*N*-[(3-Methyl-2-pyridyl)methyl]formamide (**5**).

A solution of 3-methylpyridine-2-methylamine (0.65 g, 6 mmoles) in 6 ml of formic acid was heated at 90° for 20 hours. The mixture was cooled to 0-5° and saturated ammonium hydroxide solution was added until the solution was basic. The reaction mixture was extracted with dichloromethane (3 x 100 ml), the combined organic extracts were dried and solvents were evaporated under reduced pressure to give 0.51 g (83%) of *N*-[(3-methyl-2-pyridyl)methyl]formamide (**5**). This compound was used without further purification in the next step, mp 70-71°; ir (chloroform): 3400 (NH), 1700 (CO) cm$^{-1}$; $^1$H-nmr (deuteriochloroform): δ 2.23 (s, 3H, $CH_3$), 4.45 (s, 2H, $CH_2$), 7.08 (dd, $J_{5,4}$ = 8 Hz, $J_{5,6}$ = 5 Hz, 1H, HC-5), 7.41 (d, $J_{4,5}$ = 8 Hz, 1H, HC-4), 7.63 (s, 1H, NH), 8.28 (s, 1H, CHO), 8.29 (d, $J_{6,5}$ = 5 Hz, 1H, HC-6).

8-Methylimidazo[1,5-*a*]pyridine (**2b**).

A solution of *N*-[(3-methyl-2-pyridyl)methyl]formamide (1 g, 7.7 mmoles) in 20 ml of toluene was refluxed for 3 hours with phosphorus oxychloride (2.05 g, 13.4 mmoles). The mixture was cooled to 0° and then was neutralized with ammonium hydroxide. The reaction mixture was extracted with dichloromethane (3 x 80 ml), the combined organic extracts were dried and solvents were evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ether/dichloromethano, 5:1) to give 0.72 g (82%) of 8-methylimidazo[1,5-*a*]pyridine (**2b**) as an oil; $^1$H-nmr (deuteriochloroform): δ 2.35 (s, 3H, $CH_3$), 6.41 (m, 2H, HC-6 and HC-7), 7.33 (s, 1H, HC-1), 7.75 (d, $J_{5,6}$ = 7 Hz, 1H, HC-5), 8.06 (s, 1H, HC-3); $^{13}$C-nmr (deuteriochloroform): δ 17.90 ($CH_3$), 113.34, 116.27, 119.19, 120.03, 120.44, 123.14, 128.73 (C-Ar); ms: m/z 132 ($M^+$, 100), 131 (28), 105 (22), 104 (38).

3-Hydroxymethylpyridine-2-carbonitrile (**9**).

A solution of 3-methylpyridine-2-carbonitrile [6] (2 g, 17 mmoles), *N*-bromosuccinimide (3 g, 17 mmoles) and dibenzoyl peroxide (0.2 g) in 150 ml of carbon tetrachloride was refluxed for 4 hours. The mixture was cooled, filtered and evaporated under reduced pressure to give 2.5 g of a crude mixture which was added to a suspension of silver nitrate (2.16 g, 17 mmoles) in 60 ml of acetone/water 5:1 and stirred for 4 hours at room temperature. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (3 x 100 ml), the combined organic extracts were dried and solvents were evaporated under reduced pressure to give a crude which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 2:1) affording 1.1 g (48%) of 3-hydroxymethylpyridine-2-carbonitrile (**9**) as an oil; ir (chloroform): 3350 (OH), 2110 (CN) cm$^{-1}$; $^1$H-nmr (deuteriochloroform): δ 5.62 (s, 2H, $CH_2$), 7.56 (dd, $J_{5,4}$ = 7 Hz, $J_{5,6}$ = 4 Hz, 1H, HC-5), 7.92 (d, $J_{4,5}$ = 7 Hz, 1H, HC-4), 8.71 (d, $J_{6,5}$ = 4 Hz, 1H, HC-6); $^{13}$C-nmr (deuteriochloroform): δ 70.16 ($CH_2$), 115.16 (CN), 127.80, 133.65, 134.40, 138.36, 152.23 (C-Ar); ms: m/z 134 ($M^+$, 28), 132 (18), 117 (2), 105 (100).

Methyl 2-(Aminomethyl)-3-pyridinecarboxylate Hydrochloride (**14**).

A mixture of methyl 2-cyano-3-pyridinecarboxylate [6] (0.3 g, 1.84 mmoles), 10% palladium on charcoal (0.25 mg), methanol (30 ml) and concentrated hydrochloric acid (0.5 ml) was hydrogenated at room temperature and atmospheric pressure, until no more hydrogen was consumed (about 3 hours). Filtration and evaporation yielded 0.35 g (93%) of methyl 2-(aminomethyl)-3-pyridinecarboxylate hydrochloride (**14**). This compound was used without further purification in the next step, mp 193-195°; ir (potassium bromide): 1710 (CO) cm$^{-1}$; $^1$H-nmr (tetradeuteriomethanol): δ 3.72 (s, 3H, $CH_3$), 4.45 (s, 2H, $CH_2$), 7.33 (dd, $J_{5,4}$ = 7 Hz, $J_{5,6}$ = 4 Hz, 1H, HC-5), 8.22 (d, $J_{4,5}$ = 7 Hz, 1H, HC-4), 8.58 (d, $J_{6,5}$ = 4 Hz, 1H, HC-6); $^{13}$C-nmr (tetradeuteriomethanol): δ 43.87 ($CH_2$), 53.97 ($CH_3$), 125.94, 126.66, 142.32, 153.20, 154.59 (C-Ar), 167.47 (CO); ms: m/z 166 ($M^+$, 48), 151 (63), 135 (28), 134 (47), 133

(93), 106 (62), 79 (100).

*Anal.* Calcd. for $C_8H_{10}O_2N_2 \cdot 2HCl$: C, 40.18; H, 5.05; N, 11.72; Cl, 29.65. Found: C, 39.80; H, 5.20; N, 11.89; Cl, 29.40.

Methyl Imidazo[1,5-*a*]pyridine-8-carboxylate (**2f**).

A mixture of methyl 2-(aminomethyl)-3-pyridinecarboxylate hydrochloride (0.28 g, 1.36 mmoles) and acetic formic anhydride (4 ml, which was prepared by heating 5.6 ml of acetic anhydride and 2.4 ml of formic acid for 2 hours at 50-60°) was stirred at room temperature for 1 hour. Then, was heated at 35° for 3 hours. The reaction mixture was cooled to 0-5° and neutralized with ammonium hydroxide (30%) at such a rate that the temperature did not rise above 5°. The mixture was extracted with dichloromethane (2 x 50 ml), the combined organic extracts were dried and solvents were evaporated under reduced pressure to give a crude which was purified by column chromatography (silica gel, ethyl acetate) affording 0.18 g (76%) of methyl imidazo[1,5-*a*]pyridine-8-carboxylate (**2f**), mp 76-78°; ir (chloroform): 1725 (CO) $cm^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ 3.90 (s, 3H, $CH_3$), 6.55 (t, $J_{6,5} = J_{6,7} = 7$ Hz, 1H, HC-6), 7.50 (d, $J_{7,6} = 7$ Hz, 1H, HC-7), 7.82 (s, 1H, HC-1), 8.02 (d, $J_{5,6} = 7$ Hz, 1H, HC-5), 8.11 (s, 1H, HC-3); $^{13}$C-nmr (deuteriochloroform): $\delta$ 52.67 ($CH_3$), 111.97, 112.01, 121.67, 122.76, 125.89, 127.06, 128.97 (C-Ar), 162.56 (CO); ms: m/z 176 ($M^+$, 100), 145 (19), 118 (33), 90 (15), 63 (14).

*Anal.* Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.16; H, 4.58; N, 15.77.

Imidazo[1,5-*a*]pyridine-8-methanol (**2e**).

A solution of methyl imidazo[1,5-*a*]pyridine-8-carboxylate (0.5 g, 2.86 mmoles) in 20 ml of ether was heated, lithium aluminum hydride (0.14 g, 3.58 mmoles) was added and the mixture was refluxed for 1 hour, then was cooled and ethyl acetate (10 ml) was added drop by drop. The reaction mixture was filtered and evaporated to give 0.208 g (50%) of imidazo[1,5-*a*]pyridine-8-methanol (**2e**), mp 64-66°; $^1$H-nmr (deuteriochloroform): $\delta$ 4.67 (s, 2H, $CH_2$), 6.38 (t, $J_{6,5} = J_{6,7} = 7$ Hz, 1H, HC-6), 6.68 (d, $J_{7,6} = 7$ Hz, 1H, HC-7), 7.22 (s, 1H, HC-1), 7.65 (d, $J_{5,6} = 7$ Hz, 1H, HC-5), 7.93 (s, 1H, HC-3); $^{13}$C-nmr (deuteriochloroform): $\delta$ 61.17 ($CH_2$), 113.43, 116.40, 118.26, 121.51, 128.33, 129.63, 132.70 (C-Ar); ms: m/z 148 ($M^+$, 100), 131 (10), 119 (28), 92 (46).

Imidazo[1,5-*a*]pyridine-8-carbaldehyde (**2a**).

A mixture of lithium aluminum hydride (0.038 g, 1 mmole), diethylamine (0.146 g, 2 mmoles) and pentane was stirred vigorously, and methyl imidazo[1,5-*a*]pyridine-8-carboxylate (0.176 g, 1 mmole) was added. The reaction mixture was stirred for 1 hour at room temperature and then was cooled to 0°. The precipitate formed was filtered off and washed with ethyl acetate (100 ml). The filtrate was dried and evaporated under reduced pressure. This operation was carried out below 40°. The crude mixture was purified by column chromatography (silica gel, ethyl acetate) affording 0.097 g (66%) of imidazo[1,5-*a*]pyridine-8-carbaldehyde (**2a**), mp 123-125°; ir (chloroform): 1675 (CHO) $cm^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ 6.74 (t, $J_{6,7} = J_{6,5} = 7$ Hz, 1H, HC-6), 7.35 (d, $J_{7,6} = 7$ Hz, 1H, HC-7), 8.09 (s, 1H, HC-1), 8.14 (d, $J_{5,6} = 7$ Hz, 1H, HC-5), 8.19 (s, 1H, HC-3), 9.97 (s, 1H, CHO); $^{13}$C-nmr (deuteriochloroform): $\delta$ 111.97, 112.06, 123.13, 128.33, 128.75, 129.12, 131.43 (C-Ar), 190.15 (CHO); ms: m/z 146 ($M^+$, 100), 119 (33), 91 (39), 63 (39).

Diethyl 1,4-Dihydro-4-(imidazo[1,5-*a*]pyridin-8-yl)-2,6-dimethylpyridine-3,5-dicarboxylate (**1**).

A mixture of imidazo[1,5-*a*]pyridine-8-carbaldehyde (0.14 g, 0.96 mmoles), ethyl acetoacetate (0.26 g, 2 mmoles), ethanol (0.5 ml) and ammonium hydroxide (0.1 ml of 30%) was refluxed for 4 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by crystallization from petroleum ether/ethanol, 7:1, affording 0.1 g (27%) of crystalline compound diethyl 1,4-dihydro-4-(imidazo[1,5-*a*]pyridin-8-yl)-2,6-dimethylpyridine-3,5-dicarboxylate (**1**), mp 217-220°; ir (chloroform): 1675 (CO) $cm^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ 1.12 (t, J = 8 Hz, 6H, $OCH_2CH_3$), 2.30 (s, 6H, $CH_3$), 4.00 (q, J = 8 Hz, 4H, $OCH_2CH_3$), 5.31 (s, 1H, HC-4), 6.50 (t, $J_{6,7} = J_{6,5} = 7$ Hz, 1H, HC-6), 6.70 (d, $J_{7,6} = 7$ Hz, 1H, HC-7), 7.54 (s, 1H, HC-1), 7.76 (d, $J_{5,6} = 7$ Hz, 1H, HC-5), 8.08 (s, 1H, HC-3), 8.50 (s, 1H, NH); $^{13}$C-nmr (deuteriochloroform): $\delta$ 14.42 ($OCH_2CH_3$), 19.02 ($CH_3$), 40.01 (C-4), 59.94 ($OCH_2CH_3$), 101.43 (C-3 and C-5), 113.60, 118.89, 120.11, 120.86, 127.56, 130.94, 137.28 (C-Ar), 146.32 (C-2 and C-6), 168.48 (CO); ms: m/z 369 ($M^+$, 32), 296 (21), 252 (100), 224 (42), 196 (70), 118 (39).

*Anal.* Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.27; N, 11.37. Found: C, 65.27; H, 6.31; N, 11.41.

## REFERENCES AND NOTES

† A preliminary report of this work has been presented at the 7th European Symposium on Organic Chemistry, July 15-19, 1991, Namur, Belgium, (Abstr. 14-THUR-A) and in: F. Boscá, Pd.D. Thesis, Universidad de Valencia, 1992, pp. 114-199.

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