Tetrahedron Vol. 49, No. 36, pp. 8139-8146, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

A PRACTICAL SYNTHESIS OF 1H-PYRROLO[2,3-c]PYRIDINE-5-CARBOXYLIC ACID DERIVATIVES FROM PYRROLE-2-CARBOXALDEHYDES

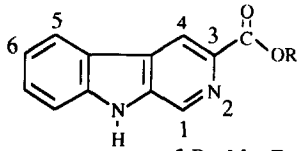
Mouloud Dekhane, Pierre Potier and Robert H. Dodd*

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette Cedex, France

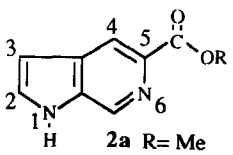
(*Received in USA* 22 *March* 1993; *accepted* 20 *May* 1993)

Abstract: *As part of a study concerning benzodiazepine receptor-ligand interactions, an efficient synthesis of 1H-pyrrolo[2,3-c]pyridine-5-carboxylates (i.e., 6-azaindole-5-carboxylates, 2), structurally related to the highly active β-carboline-3-carboxylates (1), was developed. Thus, condensation of 1-(p-toluenesulfonyl)pyrrole-2-carboxaldehyde (4) and ethyl α-amino-β,β-diethoxypropionate (6) followed by reduction of the resulting imine bond gave the amino intermediate 13 which cyclized cleanly in the presence of titanium (IV) chloride to furnish, after detosylation, 2b in preparatively useful yields. This route is potentially applicable to the preparation of multiply-substituted 6-azaindole derivatives.*

Esters of β-carboline-3-carboxylic acids (1) are well-described high affinity ligands of the benzodiazepine receptors of the central nervous system.[1] Although molecules of type 1 have been shown to possess activities opposite to those of the commonly prescribed 1,4-benzodiazepines (i.e., they are convulsant and anxiogenic instead of anticonvulsant and anxiolytic),[2] introduction of various alkyl and aryl substituents at the 4- and 5- or 6-positions leads to ligands having therapeutically useful benzodiazepine-like pharmacological profiles.[3] In an effort to further explore the structural requirements for β-carboline binding to the benzodiazepine receptor and to better understand the factors which determine whether a ligand is, for example, convulsant rather than anticonvulsant, we desired to investigate substituted derivatives of 1H-pyrrolo[2,3-c]pyridine-5-carboxylic acids (hereinafter referred to as 6-azaindole-5-carboxylic acids for clarity) (e.g., 2). Esters of 6-azaindole-5-carboxylic acids (**2a**, **2b**) contain all the structural features of β-carbolines 1 except for the aromatic A-ring. While **2a** and **2b** themselves have only relatively modest affinities for the benzodiazepine receptor,[4] it was hoped, moreover, that by introducing two substituents known to favor receptor binding in the β-carboline series at the 4- and 2- or 3-positions, a new class of high affinity benzodiazepine receptor ligands could be developed.



1 R= Me, Et ...



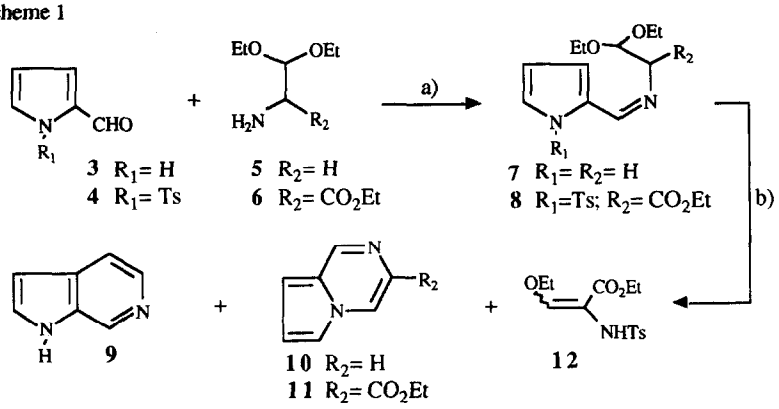
2a R= Me
2b R= Et

This paper is dedicated to Professor Sir Derek Barton on the occasion of his 75th birthday.

In this context, we have previously described the synthesis of 5-carboxy- and 2,5-dicarboxy-6-azaindoles from trisubstituted pyridine precursors.[5] However, this strategy was not amenable to the preparation of 6-azaindoles substituted at positions other than C-2 and C-5. We thus sought to develop an alternative method of synthesizing 6-azaindoles which would allow easy access to derivatives substituted at various ring positions. One such possibility involved the use of pyrroles as starting material for azaindole synthesis. This route seemed particularly attractive in view of the plethora of multiply substituted pyrrole derivatives which can be prepared.

The preparation of 6-azaindoles from pyrroles has, in fact, received only scant attention in the literature[6] and, with the notable exception of 6-azaindole precursors used in the synthesis of porphobilinogen,[7] only monosubstituted derivatives have been formed in this way. The synthesis of 6-azaindole-4,5-dicarboxylates has recently been reported ;[8] however, the strategy employed also resulted in substitutions at the 1- and 7-positions, incompatible with prospective benzodiazepine receptor binding.[9] Herz and Tocker[10] described many years ago the synthesis of the completely unsubstituted 6-azaindole **9** by condensation of pyrrole-2-carboxaldehyde (**3**) with aminoacetaldehyde diethyl acetal (**5**) followed by cyclization of the resulting imine **7** under Pommeranz-Fritsch conditions (PPA-$POCl_3$) (Scheme 1). However, the expected 6-azaindole **9** was only formed in approximately 2% yield, the

Scheme 1



a) Et_3N, 4 Å molecular sieve, CH_2Cl_2, rt; b) PPA, $POCl_3$, toluene, 120°C.

major product being pyrrolo[1,2-a]pyrazine (**10**) arising from nucleophilic attack of the acetal group by the pyrrole NH. Nevertheless, since compound **6**, the ethyl carboxylate analogue of the aminoacetaldehyde derivative **5** utilized by Herz and Tocker, has been described[11] (thereby allowing incorporation of the requisite 5-carboxylate function in **9**), it appeared to us to be particularly worthwhile to reinvestigate this reaction. We now report that by combining a number of major modifications to the scheme originally described by Herz and Tocker, pyrrole-2-carboxaldehyde is, in fact, an excellent precursor for the preparation of derivatives of 6-azaindole-5-carboxylic acids **2**.

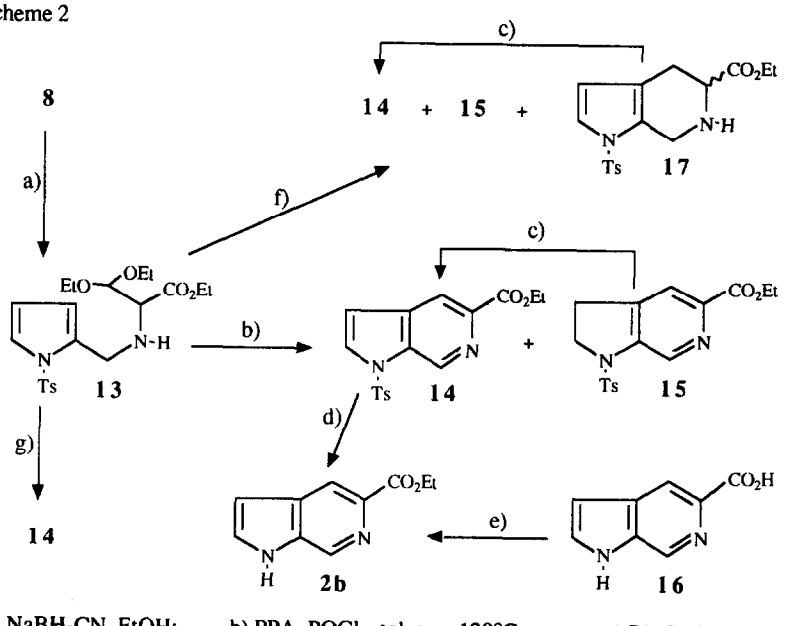
RESULTS AND DISCUSSION

An obvious way of preventing competitive formation of pyrrolopyrazines of type **10** under Pommeranz-Fritsch cyclization conditions is to use an N-protected pyrrole-2-carboxaldehyde, for example, the N-tosyl derivative **4**,[12] as starting material. When the latter was condensed with the diethyl acetal derivative of α-formylglycine ethyl ester **6** in the presence of 4 Å molecular sieves and triethylamine,[13] imine **8** was formed. Although the reaction went to completion only slowly (2 days at room temperature), attempts to accelerate product formation by use of higher temperatures led to

extensive decomposition. The sensitive imine **8** was nevertheless heated at 110°C in a mixture of PPA and phosphorus oxychloride to give two major products, **11** and **12**. The NMR spectrum of **11** showed absence of both the tosyl group and of a pyrrole NH, indicating that pyrazine formation had occurred as in the case of **3** + **5**, despite the precautions taken. This surprising result was explained by the identification of the N-tosylaminoacrylate derivative **12** as the second reaction product. This compound most probably arises from cleavage of the imine bond of **8** to give starting amine **6** to which the tosyl group is transferred from intact **8**. Subsequent elimination of ethanol from this product yields **12**. The detosylation of **8** which occurs during this process then permits formation of pyrrolopyrazine **11**. The structure of **12** was assigned on the basis of ^{1}H-NMR data which indicated, in addition to the presence of a tosyl group, a vinylic proton as a singlet at δ 7.38 as well as two dissimilar ethoxy groups. Moreover, the IR spectrum of **12** showed a single carbonyl absorption at 1697 cm^{-1}, characteristic of an α,β-unsaturated ester. Although **12** apparently exists as a single geometrical isomer, we have not yet established whether this novel enol ether derivative of α-formylglycine has the E or Z configuration.

In view of the observed sensitivity of the imine bond of intermediate **8**, responsible for formation of undesired **11** and **12**, it was decided to saturate this bond in order to form its more stable amine. Thus, treatment of **8** with sodium cyanoborohydride in ethanol gave **13** (Scheme 2). This was immediately subjected to the same cyclization conditions (PPA-$POCl_3$) as **8**. In this case, two compounds, **14** and **15**, were isolated. Compound **14**, formed in 23% yield, showed a ^{1}H-NMR spectrum compatible with the desired 6-azaindole structure, showing singlets at δ 8.37 and 9.38 for H-4 and H-7, respectively, as well as coupled doublets for H-2 and H-3. The structure of **14** was firmly established by its detosylation using sodium in ethanol, giving **2b**. The latter was identical in all respects with the compound prepared by esterification of 6-azaindole-5-carboxylic acid **16**, previously synthesized via an unambiguous route from a pyridine precursor.[5c]

Scheme 2



a) $NaBH_3CN$, EtOH; b) PPA, $POCl_3$, toluene, 120°C; c) DDQ, dioxane, Δ;
d) NaOEt, EtOH, rt; e)EtOH, HCl, Δ; f) p-TSA, benzene, Δ; g) $TiCl_4$,benzene, Δ.

The second (and minor) product obtained from this reaction, **15**, was clearly the 2,3-dihydro derivative of **14**. Thus, the mass spectrum of **15** showed two mass units more than **14** whereas its ^{1}H-NMR spectrum indicated that the vinylic H-2 and H-3 protons of **14** had been replaced by two higher field triplets. Moreover, dihydro compound **15** could be transformed into the fully aromatic azaindole **14** by treatment with DDQ in dioxane. Saturation of the 2,3-double bond of **14** presumably occurs via disproportionation of the 4,5,6,7-tetrahydropyridine ring, initially formed upon cyclization of **13**.

Although these results served to demonstrate that amine **13** was indeed a viable precursor for the synthesis of 6-azaindole-5-carboxylates (the formation of compounds **11** and **12** being completely suppressed), the overall yield of **14** and **15** (33%) was still somewhat too low to make this a preparatively useful route. Other cyclization conditions were thus investigated. It was found that by refluxing **13** in benzene in the presence of p-toluenesulfonic acid, higher overall yields of **14** and **15** (45%) were obtained but in addition, the 4,5,6,7-tetrahydro-6-azaindole-5-carboxylate derivative **17** (15% yield) was also formed. In contrast to the 2,3-dihydro analogue **15**, the ^{1}H-NMR spectrum of **17** showed, in particular, two doublets at δ 7.11 and 6.08, corresponding to the vinylic protons at C-2 and C-3, while H-4 was now observed as part of an ABM system with H-5. The presence of an alkyl NH group was also evident from the NMR and IR spectra of **17**. As a final proof of structure, the latter was dehydrogenated using 2 eq of DDQ to give exclusively the fully aromatic 6-azaindole **14**.

Finally, it was found that cyclization of **13** was best effected using a Lewis acid (i.e., titanium (IV) chloride) in benzene. In this case, an 80% yield of the desired azaindole **14** was obtained, with no traces of the dihydro or tetrahydro derivatives **15** and **17**, respectively. Application of these reaction conditions to imine **8** led to decomposition products, again pointing to the necessity of working with the saturated precursor **13**.

Thus, by bringing three major modifications to the originally conceived synthetic route to 6-azaindoles using pyrrole-2-carboxaldehyde precursors (i.e., a protected pyrrole amine function, saturation of the intermediate imine bond and milder cyclization conditions), it is now possible to obtain these compounds in preparatively useful quantities. Extension of this newly developed methodology to the synthesis of 2-, 3- and(or) 4-substituted 6-azaindole-5-carboxylates is currently being studied.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets (for solids) or as films (for oils) with a Nicolet 205 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker 250 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High-resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm). All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Ethyl pyrrolo(1,2-a)pyrazine-3-carboxylate (11) and ethyl 2-(p-toluenesulfonylamino)-3-ethoxyacrylate (12). To a solution of 1-(p-toluenesulfonyl)pyrrole-2-carboxaldehyde **4**[12] (498 mg, 2 mmol) and triethylamine (303 mg, 3 mmol) in anhydrous dichloromethane (8 mL) was added 4 Å molecular sieve (1.5 g) followed by a solution of ethyl α-amino-β,β-diethoxypropionate **6**[11] (1.23 g, 6 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 48 h at room temperature and then filtered through a pad of Celite. The filtrate was washed with water, dried (Na_2SO_4) and the solvents were evaporated under vacuum, leaving a dark brown, oily residue corresponding to imine **8**

(830 mg, 95%) : IR (ν_{max} cm^{-1}) 1627 (C=N), 1740 (C=O) ; EIMS : m/z 436 (M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.04 (t, 3H, $OCH_2\underline{CH_3}$), 1.20 (t, 3H, $OCH_2\underline{CH_3}$), 1.29 (t, 3H, $OCH_2\underline{CH_3}$), 2.39 (s, 3H, CH_3 of tosyl), 3.43-3.86 (m, 4H, 2 x $O\underline{CH_2}CH_3$), 4.06 (d, 1H, J = 7.4 Hz, $\underline{CH}CO_2$), 4.22 (q, 2H, $O\underline{CH_2}CH_3$), 4.90 (d, 1H, $\underline{CH}CHCO_2$), 6.30 (t, 1H, J = 3.2 Hz, H-4'), 7.02 (dd, 1H, J = 1.5 Hz and 3.2 Hz, H-3'), 7.27 (d, 2H, H_{arom}), 7.40 (dd, 1H, H-5'), 7.69 (d, 2H, H_{arom}), 8.67 (s, 1H, $\underline{CH}$=N) ; ^{13}C-NMR ($CDCl_3$) : δ 14.31, 15.28, 15.40, 21.68, 61.09, 63.59, 63.85, 77.23, 102.55, 112.89, 117.79, 126.14, 127.13, 130.19, 132.19, 136.20, 145.45, 155.15, 169.58. This crude material, more than 95% pure and containing no trace of starting material (as evaluated by NMR and MS) was used without further purification in the following step. Thus, imine **8** (1 g, 2.3 mmol) was dissolved in toluene and this solution was added over a period of 10 min to a mixture of polyphosphoric acid (10 g) and phosphorus oxychloride (1 mL, 11 mmol) held at 120°C. The reaction mixture was then stirred for 5 min at 120°C, cooled to 0°C and ice-water (30 mL) was slowly added. After 1 h, the solution was made basic with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), the solvents were removed under vacuum and the residue was purified by column chromatography (heptane-ethyl acetate, 1:1), yielding first **12** (250 mg ; 35%) followed by **11** (31 mg ; 7%).

Compound **12** : mp 89-91° (ether) ; IR (ν_{max} cm^{-1}) : 1628 (C=C), 1697 (C=O), 3400 (NH) ; EIMS : m/z 313 (M^+), 158 (M^+ - Tos) ; ^{1}H-NMR ($CDCl_3$) : δ 1.11 (t, 3H, $CH_2\underline{CH_3}$), 1.19 (t, 3H, $CH_2\underline{CH_3}$), 2.39 (s, 3H, CH_3 of Tos), 3.97 (q, 2H, $C\underline{H_2}CH_3$), 4.03 (q, 2H, $C\underline{H_2}CH_3$), 5.88 (br s, 1H, exchangeable with D_2O, NH), 7.27 (d, 2H, H_{arom}), 7.38 (s, 1H, H-3), 7.77 (d, 2H, H_{arom}) ; ^{13}C-NMR ($CDCl_3$) : δ 14.02, 14.93, 21.34, 60.71, 71.19, 106.65, 127.47, 128.99, 137.43, 143.18, 156.23, 165.17. Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.67 ; H, 6.07 ; N, 4.47. Found : C, 53.88 ; H, 6.05 ; N, 4.50.

Compound **11** : IR (ν_{max} cm^{-1}) : 1719 (C=O) ; EIMS : m/z 190 (M^+), 145 (M^+-OC_2H_5) ; ^{1}H-NMR ($CDCl_3$) : δ 1.43 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 4.49 (q, 2H, $C\underline{H_2}CH_3$), 6.90 (d, 1H, J = 4.5 Hz, H-7), 7.02 (dd, 1H, J = 2.2 Hz and 4.5 Hz, H-6), 7.55 (d, 1H, H-5), 8.78 (s, 1H, H-1 or H-4), 8.87 (s, 1H, H-4 or H-1). High resolution EIMS : Calcd for $C_{10}H_{10}N_2O_2$: m/z 190.0740. Found : m/z 190.0751.

Ethyl 2-[1-p-toluenesulfonylpyrrol-2-yl)methyl]amino-3,3-diethoxypropionate (13). A solution of crude iminoacetal **8** (872 mg, 2 mmol) (prepared as above) in ethanol (6 mL) was treated at 0°C with sodium cyanoborohydride (138 mg, 2.2 mmol). After 10 min, the reaction mixture was neutralized with aqueous 2N hydrochloric acid and extracted with 5% ethanolic dichloromethane (3 x 20 mL). The organic phase was dried (Na_2SO_4) and the solvents were removed under vacuum, leaving **13** as a brown syrup (95% yield) which was used in the following steps without further purification. A small quantity of this sensitive compound was purified by column chromatography (cyclohexane-ethyl acetate 1:1) for analytical purposes : IR (ν_{max} cm^{-1}) : 1735 (C=O), 3350 (NH) ; CIMS m/z 439 $(M+1)^+$; ^{1}H-NMR ($CDCl_3$) : δ 1.13-1.24 (m, 6H, 2 x $CH_2\underline{CH_3}$), 1.27 (t, 3H, J = 7.5 Hz, $CO_2CH_2\underline{CH_3}$), 3.36 (br s, 1H, exchangeable with D_2O, NH), 3.39 (s, 3H, tosyl $C\underline{H_3}$), 3.43 (d, 1H, J = 6.5 Hz, -$\underline{CH}CO_2$), 3.53 (q, 2H, J = 7.75 Hz, -$O\underline{CH_2}CH_3$), 3.62 (d, 1H, J_{gem} = 15.0 Hz, -$\underline{CH_A}NH$), 3.68 (m, 2H, -$OC\underline{H_2}CH_3$), 3.98 (d, 1H, -$\underline{CH_B}NH$), 4.17 (q, 2H, -$CO_2C\underline{H_2}$), 4.62 (d, 1H, O-C$\underline{H}$), 6.19 (m, 2H, H-3, H-4 of pyrrole), 7.26 (br d, 3H, J = 8.0 Hz, H-5 of pyrrole + H_{arom}), 7.68 (d, 2H, H_{arom}) ; ^{13}C-NMR ($CDCl_3$) : δ 11.13, 14.31, 21.66, 43.86, 60.92, 62.29, 62.51, 63.72, 102.48, 111.55, 115.39, 123.38, 126.84, 130.05, 132.37, 136.26, 144.99, 171.62. High resolution CIMS : Calcd for $C_{21}H_{30}N_2O_6S$: m/z 439.1903 (M^+ + 1). Found : m/z 439.1902.

Cyclization of compound 13 : Preparation of ethyl 1-(p-toluenesulfonyl)pyrrolo[2,3-c]pyridine-5-carboxylate (14), ethyl 2,3-dihydro-1-(p-toluenesulfonyl)pyrrolo[2,3-c]pyridine-5-carboxylate (15) and ethyl 4,5,6,7-tetrahydro-1-(p-toluenesulfonyl)pyrrolo[2,3-c]pyridine-5-carboxylate (17).

a) Using PPA/$POCl_3$: A solution of the crude acetal **13** (65 mg, 0.15 mmol) in toluene (1 mL) was added over a period of 1 min to a stirring mixture of PPA (1.5 g) and $POCl_3$ (100 µL, 1 mmol) held at 120°C. The reaction mixture was left at 120°C for 3 min, then cooled to 0°C and treated as above (see preparation of **11** and **12**). Compounds **14** (12 mg ; 23%) and **15** (5 mg ; 10%) were isolated by preparative chromatography of the crude reaction mixture (cyclohexane-ethyl acetate 1:1).

Compound **14** : mp 126-128°C (ethanol) ; IR (ν_{max} cm^{-1}) : 1357 (N-SO_2), 1715 (C=O) ; EIMS : m/z 344 (M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.44 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3 of tosyl), 4.47 (q, 2H, $\underline{CH_2}CH_3$), 6.77 (d, 1H, J = 3.3 Hz, H-3), 7.25 (d, 2H, J = 7.7 Hz, H_{arom}), 7.76 (d, 1H, H-2), 7.81 (d, 2H, H_{arom}), 8.37 (s, 1H, H-4), 9.38 (s, 1H, H-7) ; ^{13}C-NMR ($CDCl_3$) : δ 14.09, 21.24, 61.40, 108.15, 118.39, 126.71, 130.00, 130.20, 132.54, 134.34, 135.18, 136.34, 141.42, 146.15, 165.20. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.30 ; H, 4.65 ; N, 8.13. Found : C, 59.14 ; H, 4.57 ; N, 7.98.

Compound **15** : mp 128°C (ethyl acetate-cyclohexane) ; IR (ν_{max} cm^{-1}) : 1739 (C=O), 1357 (N-SO_2) ; EIMS : m/z 346 (M^+), 274 (M^+ - CO_2Et) ; ^{1}H-NMR ($CDCl_3$) : δ 1.42 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 2.39 (s, 3H, $\underline{CH_3}$ of tosyl), 3.09 (t, 2H, J = 8.6 Hz, H-3), 3.98 (t, 2H, H-2), 4.43 (q, 2H, $\underline{CH_2}CH_3$), 7.27 (d, 2H, J = 8.0 Hz, H_{arom}), 7.72 (d, 2H, H_{arom}), 7.89 (s, 1H, H-4), 8.96 (s, 1H, H-7) ; ^{13}C-NMR ($CDCl_3$) : δ 14.37, 21.58, 27.54, 49.81, 61.85, 122.15, 127.36, 130.10, 133.39, 135.14, 141.39, 142.16, 143.30, 145.06, 164.79. Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.95 ; H, 5.20 ; N, 8.09. Found : C, 58.79 ; H, 5.13 ; N, 7.89.

b) Using *p*-toluenesulfonic acid : A solution of *p*-toluenesulfonic acid monohydrate (10 g, 52.6 mmol) in benzene (30 mL) was refluxed in a Dean-Stark apparatus until no more water co-distilled. A solution of crude acetal **13** (5 g, 11.5 mmol) in benzene (5 mL) was then added dropwise and the mixture was refluxed for 1.5 h. The reaction mixture was cooled, the solvent was removed under reduced pressure and the residue was taken up in ethyl acetate (50 mL). The solution was carefully neutralized with solid sodium hydrogen carbonate before washing with water (20 mL) and drying (Na_2SO_4). Removal of the organic solvent under reduced pressure left an oily residue which was purified by column chromatography (ethyl acetate-heptane 2:7 followed by 1:1). In addition to compounds **14** (1.1 g, 36%) and **15** (356 mg, 9%) was isolated the tetrahydro derivative **17** (595 mg, 15%) ; mp 84-86°C (ethanol) ; IR (ν_{max} cm^{-1}) : 3340 (NH), 1735 (C=O), 1368 (N-SO_2) ; EIMS : m/z 348 (M^+), 275 (M^+-CO_2Et) ; ^{1}H-NMR ($CDCl_3$) : δ 1.22 (t, 3H, J = 7.2 Hz, $CH_2\underline{CH_3}$), 2.12 (bs, 1H, NH), 2.37 (s, 3H, $\underline{CH_3}$ of tosyl), 2.51 (dd, 1H, $J_{4a,4b}$ = 15.8 Hz, $J_{4a,5}$ = 9.6 Hz, H-4a), 2.84 (dd, 1H, $J_{4b,5}$ = 4.6 Hz, H-4b), 3.50 (dd, 1H, H-5), 3.94 (d, 1H, $J_{7a,7b}$ = 16.6 Hz, H-7a), 4.16 (d, 1H, H-7b), 4.15 (q, 2H, $\underline{CH_2}CH_3$), 6.08 (d, 1H, J = 3.2 Hz, H-3), 7.11 (d, 1H, H-2), 7.25 (d, 2H, J = 8.3 Hz, H_{arom}), 7.63 (d, 2H, H_{arom}) ; ^{13}C-NMR ($CDCl_3$) : δ 14.22, 21.62, 27.06, 42.48, 55.31, 61.16, 112.31, 120.78, 121.14, 126.78, 127.13, 130.15, 136.18, 145.04, 172.66. Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.62 ; H, 5.74 ; N, 8.04. Found : C, 58.68 ; H, 5.61 ; N, 7.99.

c) Using titanium (IV) chloride : A solution of acetal **13** (26 mg, 0.06 mmol) in anhydrous benzene (0.5 mL) containing titanium (IV) chloride (50 µL, 0.5 mmol) was refluxed for 10 h under nitrogen with exclusion of moisture. The reaction mixture was then cooled, ethyl acetate (2 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$. After drying of the organic phase over Na_2SO_4, the solvents were removed under reduced pressure and the crude product was purified by chromatography on silica gel (ethyl acetate-heptane, 1:1), yielding compound **14** (16 mg, 80%), identical in all respects to that obtained by methods a) and b).

Preparation of 14 via dehydrogenation of dihydro derivative 15 or tetrahydro derivative 17. A solution of **15** (25 mg, 0.072 mmol) and DDQ (22 mg, 0.093 mmol) in dioxane (2.5 mL) was refluxed for 24 h under nitrogen. The reaction mixture was cooled, water (5 mL) was added and excess dioxane was removed under vacuum. The aqueous residue was then extracted with dichloromethane (2 x 5 mL), the combined organic extracts were dried over Na_2SO_4 and the solution was concentrated under vacuum. Purification of the residue by chromatography on silica gel (ethyl acetate-heptane, 1:1) gave compound **14** (20 mg, 81%).

Similarly, refluxing of a solution of compound **17** (22 mg, 0.063 mmol) and DDQ (34 mg, 0.15 mmol) in dioxane (2 mL) gave, after 2 h, compound **14** (21 mg, 96%), isolated as described above.

Ethyl 1H-pyrrolo[2,3-c]pyridine-5-carboxylate (2b).

a) From deprotection of **14** : A solution of the tosyl derivative **14** (10 mg, 0.029 mmol) in anhydrous ethanol (0.5 mL) at 0°C was treated with a 0.17 M solution of sodium in ethanol (0.5 mL). After 30 min, water (3 mL) was added, the solution was made acidic by addition of acetic acid and then brought to pH 9 by addition of saturated, aqueous $NaHCO_3$. The reaction mixture was then extracted with dichloromethane-ethanol (95:5) (3 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvents were removed under vacuum, leaving **2b** as a white powder in 90% yield. The material was crystallized from ethanol, mp 218-220°C ; IR (ν_{max} cm^{-1}) : 3407 (NH), 1715 (C=O) ; CIMS : m/z 191 $(M+1)^+$; ^{1}H-NMR (DMSO-d_6) : δ 1.42 (t, 3H, J = 7.0 Hz, CH_3), 4.42 (q, 2H, CH_2), 6.80 (d, 1H, $J_{2,3}$ = 2.3 Hz, H-3), 7.83 (d, 1H, H-2), 8.48 (s, 1H, H-4), 8.93 (s, 1H, H-7), 12.13 (s, 1H, exchangeable with D_2O, NH) ; ^{13}C-NMR (DMSO-d_6) : δ 14.0, 60.3, 102.2, 117.9, 130.6, 131.8, 134.0, 134.3, 136.7, 165.8. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15 ; H, 5.25 ; N, 14.73. Found : C, 62.96 ; H, 5.14 ; N, 14.86.

b) From esterification of **16** : A solution of carboxylic acid **16**[5c] (37 mg, 0.22 mmol) in anhydrous ethanol (5 mL) previously saturated with HCl gas at 0°C, was refluxed for 3 h. The reaction mixture was cooled and saturated aqueous $NaHCO_3$ was added until CO_2 evolution ceased. The mixture was then extracted with dichloromethane-ethanol (9:1) (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4. Removal of the solvents under reduced pressure yielded compound **2b** (33 mg, 80%), identical in all respects with that obtained above.

ACKNOWLEDGEMENT

We thank the Algerian Ministry of Education and Universities for a fellowship (M.D.).

REFERENCES AND NOTES

1. Braestrup, C.; Nielsen, M.; Olsen, C. E. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2288.
2. a) Prado de Carvalho, L.; Grecksch, G.; Chapouthier, G.; Rossier, J. *Nature*, **1983**, *301*, 64. b) Belzung, C.; Misslin, R.; Vogel, E.; Dodd, R. H.; Chapouthier, G. *Pharmacol. Biochem. Behav.* **1987**, *28*, 29. c) Prado de Carvalho, L.; Grecksch, G.; Cavalheiro, E. A.; Dodd, R. H.; Chapouthier, G.; Rossier, J. *Europ. J. Pharmacol.* **1984**, *103*, 287. d) Oakley, N. R.; Jones, B. J. *Europ. J. Pharmacol.* **1980**, *68*, 381.
3. a) Stephens, D. N.; Kehr, W.; Wachtel, H.; Schmiechen, R. *Pharmacopsychiatry* **1985**, *18*, 167. b) Meldrum, B. *Neuropharmacology* **1984**, *23*, 845. c) Petersen, E. N.; Jensen, L. H.; Honoré, T.; Braestrup, C.; Kehr, W.; Stephens, D. N.; Wachtel, H.; Seidelman, D.; Schmiechen, R. *Psychopharmacologia*, **1984**, *83*, 240.

4. The *in vitro* affinities of compounds **2a** and **2b** for the benzodiazepine receptor are approximately 500-fold inferior to those of β-carbolines of type **1** (unpublished results from this laboratory).
5. a) Dodd, R. H.; Ouannès, C.; Robert-Gero, M.; Potier, P. *J. Med. Chem.* **1989**, *32*, 1272. b) Dodd, R. H.; Doisy, X.; Potier, P.; Potier, M.-C.; Rossier, J. *Heterocycles* **1989**, *28*, 1101. c) Dellouve-Courillon, C.; Dorey, G.; Poissonnet, G.; Doisy, X.; Potier, P.; Dodd, R. H. *Tetrahedron* **1990**, *46*, 3245.
6. For reviews concerning the preparation and reactions of azaindoles, see : a) Willette, R. E. In *Advances in Heterocyclic Chemistry :* Katritzky, A. R., Boulton, A. J., Eds.; Academic Press : New York, 1968 ; Vol. 9, p. 27. b) Yakhontov, L. N. *Russ. Chem. Rev.* **1968**, *37*, 551. c) Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428.
7. a) Frydman, B.; Reil, S.; Despuy, M. E.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 2338. b) Demopoulos, B.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1983**, *61*, 2415.
8. Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1993**, *58*, 516.
9. Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C., Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081.
10. Herz, W.; Tocker, S. *J. Am. Chem. Soc.* **1955**, *77*, 6355.
11. Doyle, T. W.; Belleau, B.; Luh, B.-Y.; Ferrari, C. F.; Cunningham, M. P. *Can. J. Chem.* **1977**, *55*, 468.
12. Prinzbach, H.; Bingmann, H.; Fritz, H.; Markert, J.; Knothe, L.; Eberbach, W.; Brokatzky-Geiger, J.; Sekutowski, J. C.; Kruger, C. *Chem. Ber.* **1986**, *119*, 616.
13. Scott, M. K.; Martin, G. E.; DiStefano, D. L.; Fedde, C. L.; Kukla, M. J.; Barrett, D. L.; Baldy, W. J.; Elgin, R. J.; Kesslick, J. M.; Mathiasen, J. R.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1992**, *35*, 552.