Synthesis of 5*H*-pyrido[4,3-*b*]indole by a modification of Pomeranz-Fritsch isoquinoline synthesis

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Abstract: 5*H*-Pyrido[4,3-*b*]indole was obtained from 3-formylindole in 16% overall yield by Jackson and Shannon modification of the Pomeranz-Fristch isoquinoline synthesis. The final cyclisation occurred but the removal of the tosyl group and oxidation of the dihydrocompound was not efficient. Changes in the concentration of the acid catalyst gave 29% as the best yield for the last step. An NMR study of the cyclisation is described.

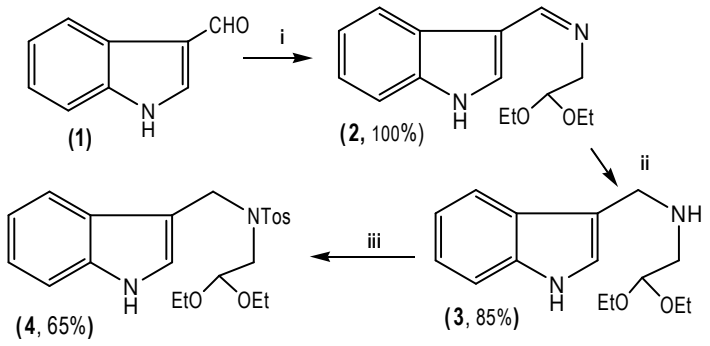
Keywords: pyrido[4,3-*b*]indole, γ-carboline, isoquinoline, Pomeranz-Fritsch

Introduction

Pyrido[4,3-*b*]indoles, commonly known as γ-carbolines, have been studied for their biological activity, namely as antipsychotic and antitumor agents [1]. They may be considered as smaller analogues of the ellipticine /olivacine anticancer agents [2] that contain indole and isoquinoline moieties

One classical way of building the pyridine ring consists in starting from an arylaldehyde and apply the Pomeranz-Fritsch conditions. This method (cyclisation of an iminoacetaldehyde diethyl acetal) was improved by Bobbitt (hydrogenation of the imine to the corresponding amine) and later by Jackson and Shannon. These authors cyclised the tosyl derivative of this amine in smooth conditions: 6N HCl in dioxane [3]. Although consisting of several steps, in general this method gives high yields and the cyclisation occurs in one pot. This method was applied successfully to synthesise ellipticine and olivacine derivatives [4].

In the work described here, starting from 3-formylindole, the modification of Jackson and Shannon of the Pomeranz-Fritsch method was used to build the third ring of the γ-carboline (scheme 1).



i) Toluene, Aminoacetaldehyde diethyl acetal (1,1 eq.); Δ, 1h; **ii)** $NaBH_4$, EtOH; **iii)** TosCl, Pyridine, 2h, RT.

Scheme 1. Synthesis of sulphonamide **4**

Results and Discussion

Azeotropic distillation of a mixture of 3-formylindole **1** with aminoacetaldehyde diethyl acetal in toluene gave the imine **2**, as an orange oil, in quantitative yield. The ^{1}H-NMR spectrum showed a singlet at δ 8.45, corresponding to the Ar*CH*=N, together with other signals due to the acetal side chain.

Due to the instability of the imine it was used as such for the next step and it was reduced with $NaBH_4$ in methanol [5], to the amine **3**, as colourless oil, in 85% yield. In its proton NMR spectrum, it was observed the replacement of the singlet at δ 8.45 ppm by a two proton signal at δ 4.06, corresponding to Ar*CH*$_2$NH and the presence of a large singlet at δ 2.7 corresponding to ArCH$_2$*NH*. Other expected signals were also seen. The structure was further confirmed by ^{13}C spectrometry.

The amine **3** was treated directly with *p*-toluenesulphonyl chloride in pyridine for two hours, giving the sulphonamide 4 as beige crystals, in 65 % yield. Its NMR spectrum showed a singlet at δ 2.43 and 2 doublets at 7.27 and 7.74, due to the CH_3 and aromatic signals, respectively, from the tosyl group. The disappearance of the broad signal due to the NH of the amine **3** and the change in position of the CH_2 signal from δ 4.06 to 4.70 in sulphonamide **4** was also observed.

It was decided to attempt the cyclisation of the sulphonamide by the modification of Jackson and Shannon of the Pomeranz-Fritsch method [4] (scheme 1) by conventional heating or in the microwave oven (MW). The yields were low as shown in the Table 1, entries 1-3.

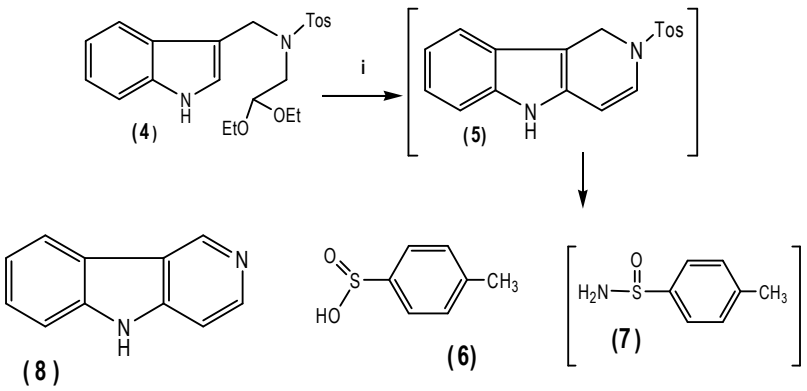
Table 1. Experiments on the cyclisation of the sulphonamide **4**

Experiment	**Reaction conditions**	**By product**	Compound **8** **η**
1	Dioxane, 6N HCl, 4h reflux	-	15% 224-227 ºC**
2	Dioxane, 6N HCl, MW (400 W, 15 min.)	10% (**7**) 101-106ºC*	22% 224-227ºC**
3	Dioxane, 12N HCl, 105 min.reflux	22% (**7**) 110-113 ºC	1% (oil)
4	DMSO-d$_6$, 37% DCl, 66ºC, 1h	Scheme 2 and fig 1	25%
5	1.DMSO, 12N HCl, 70ºC, 5h	TosOH (**6**), 43%	29%

*(lit. mp (R) 115-118 ºC; (S) 118-121ºC) [Aldrich cat.]

**(lit. mp. 230-231 ºC [6], 216-218 ºC [7])

In view of the low yields obtained it was decided to study the reaction by NMR. The sulphonamide **4** was dissolved in DMSO-d$_6$ in an NMR tube, 37% DCl was added and the spectrum was obtained. The reaction mixture was heated, in a water bath, at 66ºC and the NMR spectra were registered at 15, 30, 45, 60, 120, 180, 240 and 300 min.



i) Dioxane, HCl; Δ (conventional and MW)

Scheme 2. Cyclisation of sulphonamide **4**

In the NMR spectrum, which was obtained at room temperature, it was observed that about 12% conversion of the OEt groups, into ethanol, had occurred. A small amount of TosOH **6** was also present. After 15 minutes no signals due the acetal group were seen indicating that cyclisation occurred with the formation of the dihydro compound.

An increase on the signals of TosOH (δ 2.2, s, CH_3; 7.4, d, and δ 7.6, d) was detected, which indicates the formation of the γ-carboline **8** in the same extent. The signal at δ 9.31 corresponding to H-1 of the γ-carboline is seen from 15 min. on, however it was overlapped by another signal.

At 60 minutes both TosOH **6** and the intermediate dihydro **5** reached the maximum and no further changes were detected for compounds **5** and **6**, later on. These observations led us to conclude that the dihydro compound **5** (70-75%) was the major product of the reaction and the yield for γ-carboline was assumed to be 25-30%.

The results obtained in this study are shown in figure 1.

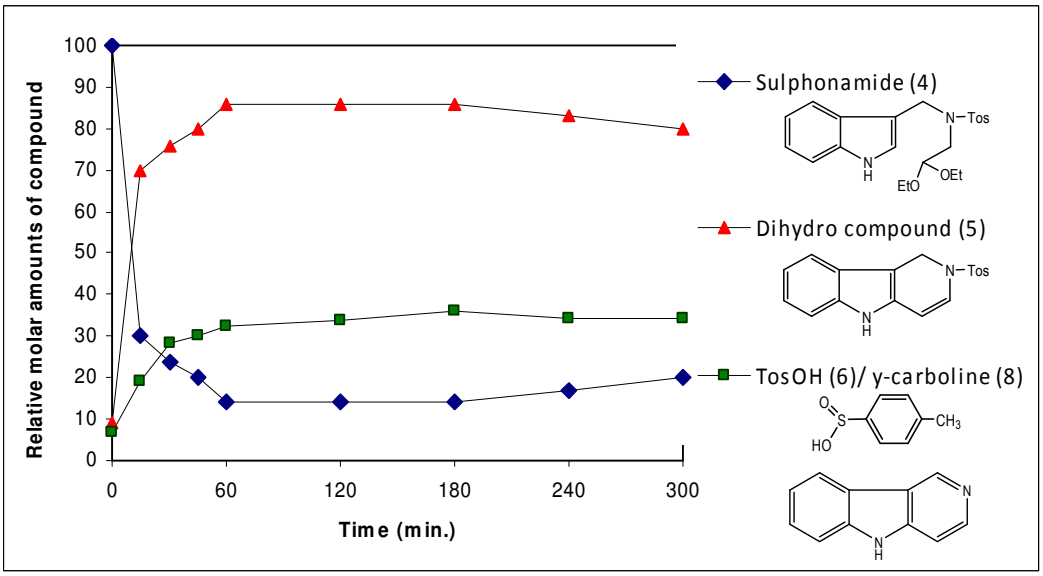


Figure 1. Results of concentration *versus* time, obtained by NMR study.

The most polar product, the γ-carboline **8**, was characterized by mp and ^{1}H and ^{13}C NMR. On the ^{1}H NMR spectrum a singlet at δ 9.3 and a doublet at 8.4 with coupling constant of 5.6 Hz, due to the pyridine ring were observed. The remaining expected signals were also present in both the proton and the carbon spectra, as it is described in the experimental part. The ESI mass spectrum showed the fragment m/*z* 169 $(M+1)^{+}$.

Experimental

All melting points were measured on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR spectra were determined at 75.4 MHz on a Varian Unity Plus or on a Bruker Avance II 400 spectrometer. In the NMR spectra was used TMS as internal reference. Low resolution EI mass spectra were determined on a Unicam GC-MS 120. Elemental analysis data were obtained on a Leco CHNS-932.

3-(2,2-Diethoxyethyliminomethyl)-indole (2). To a solution of formylindole **1** (7.9 g, 54.49 mmol) in toluene (100 mL) aminoacetaldehyde diethyl acetal (8.7 mL, 59.9 mmol) was added and the mixture was refluxed using a Dean & Stark system until no water was formed. Evaporation of the solvent gave the imine as orange oil in quantitative yield.
δ (^{1}H, $CDCl_3$, 300 MHz) 1.22 (6H, t, J=7.2 Hz, 2xOCH$_2$*CH$_3$*), 3.55-3.80 (4H, m, 2xO*CH$_2$*CH$_3$), 3.80 (2H, d, J=6.5 Hz, ArCH=N*CH$_2$*), 4.85 (1H, t, J=6.5 Hz, NCH$_2$*CH*(OEt)$_2$), 7.17-7.30 (2H, m, H-5 and H-6), 7.32-7.40 (1H, m, H-7), 7.46 (1H, s, H-2), 8.24-8.32 (1H, m, H-4), 8.45 (1H, s, Ar*CH*=NCH$_2$). The NH signal was not observed.

3-(2,2-Diethoxyethylaminomethyl)-indole (3). The above imine **2** (15.95g, 61.07 mmol) was dissolved in ethanol (50 mL), $NaBH_4$ (61.07 mmol) was added and the mixture was stirred at room temperature for 1 h. To the reaction mixture water (100 mL) was added and it was extracted with ethyl acetate (3 x 120 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed to give a brownish oil (13.54g, 85%).
δ (^{1}H, DMSO-d_6, 300 MHz) 1.07 (6H, t, J=7.2 Hz, 2xOCH$_2$*CH$_3$*), 2.61 (1H, d J=5.4 Hz, ArCH$_2$NH-*CH$_2$*), 3.20-3.60 (4H, m, 2xO*CH$_2$*CH$_3$, overlapped with H_2O and possibly NH), 3.85 (2H, s, indole-CH$_2$), 4.51 (1H, t, J=5.7 Hz *CH*(OEt)$_2$), 6.96 (1H, dt J=6.9 and 1.2 Hz, H-5) 7.05 (1H, dt J=7.2 and 1.2 Hz, H-6), 7.20 (1H, d J= 2.4 Hz, H-2), 7.33 (1H, d J=7.8 Hz, H-7), 7.58 (1H, d J= 7.8 Hz, H-4), 10.83 (1H, br s, N*H*).
δ (^{13}C, DMSO-d_6, 75.4 MHz) 15.35, 44.21, 51.16, 61.26, 101.73, 111.34, 113.68, 118.26, 118.67, 120.93, 123.42, 126.96, 136.34.

3-(2,2-Diethoxyethyl)-*N*-*p*-tosylaminomethyl)-indole (4). To a solution of the above amine **3** (51.6 mmol, 13.54g) in pyridine (30 mL), TosCl (10.38g, 54.4 mmol) was added and the mixture was stirred at room temperature for two hours. To the reaction mixture water (150 mL) was added and a beije solid precipitated out which was filtered and recrystallised from ethanol to give beige crystals (13.91 g, η= 65%, m.p. 137.3-139.5º C).
δ (^{1}H, DMSO-d_6, 300 MHz) 0.92 (6H, t, J=7.2 Hz, 2xOCH$_2$*CH$_3$*), 2.40 (3H, s, Tos-*CH$_3$*), 3.05 (2H, d, J=5.4 Hz, CH*CH$_2$*), 3.10-3.20 (2H, m, 2xO*CHa*CHbCH$_3$), 3.30-3.44 (2H, m, 2xOCHa*CHb*CH$_3$), 4.28 (1H, t J=5.4 Hz, CH$_2$*CH*), 4.53 (2H, s, indole-*CH$_2$*), 6.96 (1H, dt J=7.8 and 0.9 Hz, H-5), 7.08 (1H, dt J=8.1 and 1.2 Hz, H-6), 7.13 (1H, d

J=2.4Hz, H-2), 7.35 (1H, d J= 8.4 Hz H-7), 7.40 (2H, d J=8.4 Hz Ar-H from Tos), 7.50 (1H, d J= 8.1 Hz H-4), 7.76 (2H, d, J=8.4, Ar-H from Tos), 11.01 (1H, br s, N*H*).
δ (^{13}C, DMSO-d_6, 75.4 MHz) 15.01, 20.98, 43.76, 48.39, 62.10, 100.71, 108.45, 111.52, 118.60, 118.78, 121.31, 125.74, 126.75, 127.03, 129.72, 136.32, 137.14, 143.02.
Anal. calc. for $C_{22}H_{28}N_2O_4S$: C 63.44, H 6.78, N 6.73, S 7.70; found: C 63.41, H 6.88, N 6.91, S 7.22%.

Attempts to cyclize sulphonamide (4)

Conventional heating (method A)
To a solution of the sulphonamide **4** (0.37 g, 0.89 mmol) in dioxane (12 mL) was added HCl (6N, 1mL) at 0-5ºC and the mixture was refluxed for 4h. After cooling, water (40 mL) was added and the mixture was extracted with dichloromethane (3x 30 mL). The aqueous layer was basified with ammonia (25%) until pH= 8 and again extracted with dichloromethane (4 x 25 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a thick oil, that showed two spots on TLC. The mixture was submitted to column chromatography and the most polar compound (Rf=0.35) was eluted with chloroform:ethanol; 9:1) giving the pyridoindole **8** as an off-white solid (22 mg, η=15%, m.p. 224-227 ºC) (lit. m.p. 230-231 ºC [6], 216-218 ºC [7].
δ (^{1}H, $CDCl_3$, 300 MHz) 7.25 (1H, t, J=7.5 Hz, H-8), 7.43-7.48 (2H, m, H-4 and H-7), 7.55 (1H, d, J=7.8 Hz, H-6), 8.21 (1H, d, J=7.8 Hz, H-9), 8.4 (1H, d, J=5.1 Hz, H-3), 9.32 (1H, s, H-1), 11.71 (1H, s, N*H*).
δ (^{13}C, $CDCl_3$, 75.4 MHz) 106.40, 111.49, 119.42, 120.01, 120.64, 120.72, 126.62, 139.54, 142.70, 143.54, 144.45.

Conventional heating (method B)
To a solution of the sulphonamide **4** (1.0 g, 2.4 mmol) in dioxane (10 mL) was added HCl (12N, 5mL) at 0-5ºC and the mixture was refluxed for 105 min. The work-up was identical to that described above for method A and a brown oil (141 mg) resulted which was purified by column chromatography. The first compound eluted (chloroform:ethanol; 9.5:0.5) was the sulphinamide **7**, as a light brown solid (92 mg, 22.4%), m.p. 110-113ºC (lit. mp (R) 115-118 ºC; (S) 118-121ºC) (Aldrich catalogue).
δ (^{1}H, $CDCl_3$, 400 MHz) 2.45 (3H, s, CH_3), 4.75 (2H, br s, ArNH_2), 7.34 (2H, d, J=8.8 Hz, Ar-*H* from Tos), 7.82 (2H, d, J=8.4 Hz, Ar-*H* from Tos).
Further elution with chloroform:ethanol; 9:1, gave the pyridoíndole **8** as a brown solid (30 mg, 1.0%, m.p. 209-216 ºC). Its 1H NMR was identical to that described above. **EM,** *m/z* 169 (100, $[M+1]^+$).

Microwave heating
To a solution of the sulphonamide **4** (0.403 g, 0.97 mmol) in dioxane (10 mL) was added HCl (6N, 2mL) at 0-5ºC and the mixture was heated in the microwave for 15 min. The work-up was identical to that described above and gave a brown oil (93 mg) which was purified by column chromatography. Elution with mixtures of chloroform:ethanol of increasing polarity gave the sulphinamide **7**, as a brown solid (15 mg, 10.0 %), m.p. 101-106ºC, with an NMR identical to the first sample obtained, and the pyridoíndole **8** as a brown solid (36 mg, 22%, m.p. 224-227 ºC). Its ^{1}H NMR was identical to that described above.

^{1}H NMR study of the cyclisation of 3-(2,2-diethoxyethyl-*N*-*p*-tosylaminomethyl)-indole 4

The sulphonamide **4** (10 mg, 0.024 mmol) was dissolved in DMSO-d_6 (0.5 ml) in an NMR tube, 37% DCl (0.075 ml) was added and the spectrum was obtained. The reaction mixture was heated at 66ºC and the NMR spectra registered at 15, 30, 45, 60, 120, 180, 240 and 300 min. The results obtained in this study are discussed above and they are shown in figure 1. Approximate yields were drawn from data: the major product (70-75%) from the reaction was the dihydrocompound **5** and the minor product (25-30%) was the pyridoindole **8**.

Cyclisation of 3-(2,2-diethoxyethyl-*N*-*p*-tosylaminomethyl)-indole 4 in the conditions from the ^{1}H NMR study

To a solution of the sulphonamide **4** (2.0 g, 4.8 mmol) in DMSO (10 mL) was added HCl (12N, 2mL) at 0-5ºC and the mixture was heated at 70ºC for 5 h. Water (100 mL) was added and a solid came out which was filtered and discarded. The aqueous layer was extracted with diethyl ether (4x30 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent was removed to give *p*-toluenesulphinic acid **6** as a beige solid (43%). The aqueous layer was basified with ammonia (25%) until pH= 8 and extracted with ethyl acetate (4 x 50 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a solid whose NMR spectrum showed to be a mixture of pyridoindole slightly contaminated with *p*-toluenesulphinic acid. The yield for the pyridoindole **8** was deduced from the spectrum as 29%. The fact that the yield is lower than that for the *p*-toluenesulphinic acid is possibly due to loss during extraction.

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