MILD SYNTHESIS OF N-ALKYL- AND N-ACYL-β-CARBOLINE ANHYDRO-BASES USING TRIFLUOROMETHANESULFONATES

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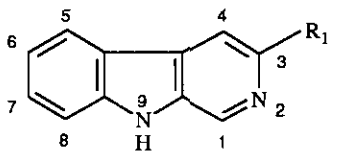
Abstract - Hindered 3-substituted pyrido[3,4-b]indoles (1 - 3) were quaternized in good yield using various alkyl trifluoromethanesulfonates generated **in situ** from the corresponding alcohol and trifluoromethanesulfonic anhydride in the presence of diisopropylethylamine in CH_2Cl_2. The resulting salts (4 - 13) were allowed to react with Cs_2CO_3 in refluxing DME to give the corresponding β-carboline anhydro-bases (14 - 23). While attempts to N-acylate compounds (1 - 3) intermolecularly with different acylating agents failed, intramolecular acylation of the carboxylic acid derivative 24 *using trifluoromethanesulfonic* anhydride and diisopropylethylamine at - 78°C succeeded, to give the 1,4-benzodiazepine 28. The intermediacy of the mixed sulfonic-carboxylic anhydride in this acylation reaction was strongly supported by the novel, direct acylation of benzene with benzoic acid under the same conditions. Relevant spectroscopic data of these new compounds are discussed.

3-Substituted pyrido[3,4-b]indoles (or β-carbolines, e.g. 2 and 3) are known to interact with the benzodiazepine receptor[1] of the mammalian central nervous system.



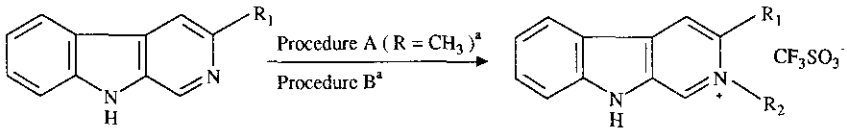
	R_1
1	H
2	CO_2CH_3
3	$CO_2CH_2CH_3$

1 - 3

Various studies of the structure-activity relationships in this series have shown the influence of substitutions on all but the 2-position (pyridinyl nitrogen) of β-carbolines 2 and 3 on their binding affinities. We report herein the results of our attempts to alkylate and acylate 3-substituted β-carbolines in the 2-position.

We first tried to quaternize compound 3 by use of an excess of methyl iodide in dichloromethane at room temperature. However, after 144 hours of reaction, only traces of salt could be detected. This can be easily understood in terms of steric hindrance and electron withdrawing effects of the C-3 substituent. Similar problems have been reported in the quaternization of ortho-substituted pyridines[2,3]. To overcome these difficulties, we decided to use the highly reactive trifluoromethanesulfonate (triflate) group, rather than iodide, as the leaving group. The triflates of various alcohols (R_2OH, *Table I*) were generated *in situ* (except for commer-

Table I



1 - 3 4 - 13

n°	R_1	R_2	time h	temp. °C	yield %	m p (solv.)[b] °C	δ H_1 ppm	δ H_4 ppm	$\nu_{C=N^+}$ cm^{-1}
4	H	CH_3	7	25	80	204 (E)	9.41	8.84	1645
5	CO_2CH_3	CH_3	7	25	96	183 (E)	9.83	9.16	1638
6	$CO_2CH_2CH_3$	CH_3	7	25	91	182 (E)	9.80	9.13	1640
7	$CO_2CH_2CH_3$	$CH_2CH_2CH_3$	22	0 to 25	92	102 (P)	9.71	9.00	1638
8	$CO_2CH_2CH_3$	$CH_2CH=CH_3$	3	0 to 25	99	116 (P)	9.70	8.93	1640
9	$CO_2CH_2CH_3$	$CH_2CH_2OCH_3$	30	0 to 25	88	143 (E)	9.66	8.96	1640
10	$CO_2CH_2CH_3$	$CH_2C_6H_5$	4	-78 to 25	83	127 (E)	9.95	8.96	1638
11	$CO_2CH_2CH_3$	o-$FC_6H_4CH_2$	4	-78 to 25	65	161 (E)	9.83	8.95	1640
12	$CO_2CH_2CH_3$	m-$FC_6H_4CH_2$	4	-78 to 25	68	161 (E)	10.03	9.06	1642
13	$CO_2CH_2CH_3$	p-$FC_6H_4CH_2$	4	-78 to 25	70	160 (E)	10.00	8.96	1640

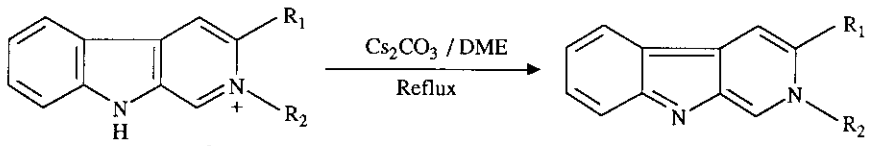
[a]See experimental section.

[b]Recrystallisation solvent : (E) =Ethanol , (P) =Propanol.

cially available methyl triflate) using a published procedure[4] and were allowed to react with 1 equivalent of β-carbolines 1, 2 or 3, giving the quaternized salts[5] in good to excellent yields (65-99%). For example, the quaternization of 3 by methyl triflate could be achieved in 91% yield in 7 hours. It is interesting to note that the allyl and benzyl triflates react more rapidly than their alkyl counterparts. This is possibly explained by the greater stability of the cations formed in the first two cases.

The conversion of the salt 4 (having an iodide as counterion) into its so-called anhydrobase[6] has been achieved using hot 20% sodium hydroxide. Because these drastic conditions were completely incompatible with the ester function present in our salts, we investigated milder methods of generating these anhydro-bases. We found that treatment of the quaternized β-carbolines 4 - 13 with cesium carbonate in dimethoxyethane at reflux gave the corresponding anhydro-bases 14 - 23 in good yield (Table II). These dipoles give a characteristic $C_1=N_2$

Table II



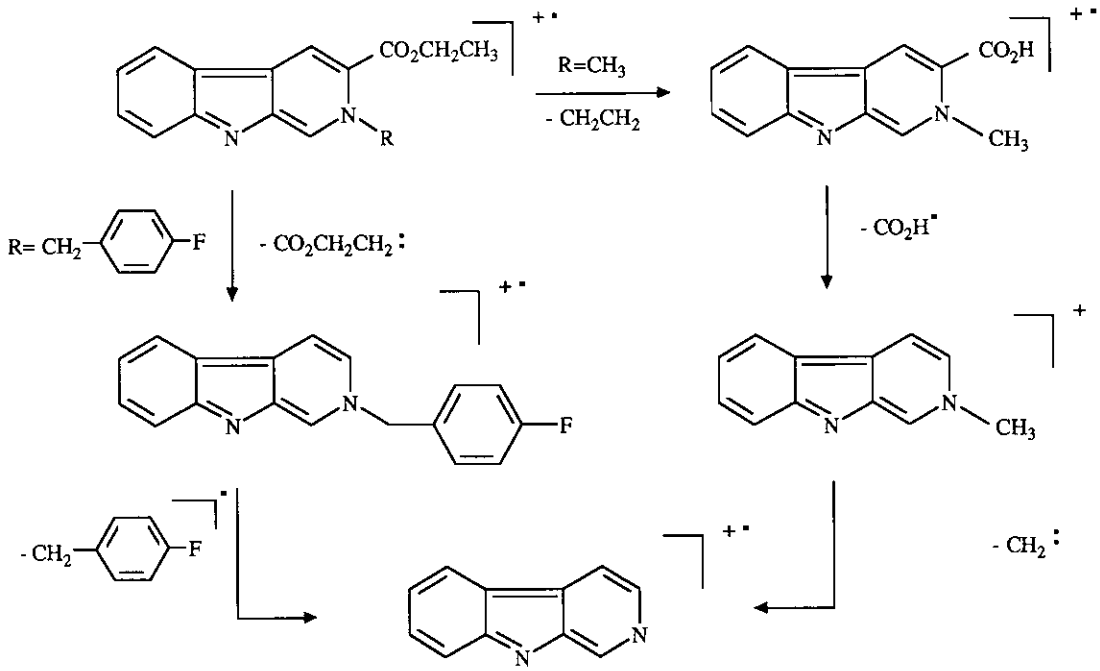
4 - 13 $CF_3SO_3^-$ 14 - 23

n°	R_1	R_2	yield %	δ H_1 ppm	δ H_4 ppm	ν C=N cm^{-1}
14	H	CH_3	63	8.62	8.16	1620
15	CO_2CH_3	CH_3	92	9.02	9.02	1622
16	$CO_2CH_2CH_3$	CH_3	84	9.12	8.78	1620
17	$CO_2CH_2CH_3$	$CH_2CH_2CH_3$	67	9.04	8.78	1622
18	$CO_2CH_2CH_3$	$CH_2CH=CH_3$	65	9.04	8.78	1618
19	$CO_2CH_2CH_3$	$CH_2CH_2OCH_3$	91	9.03	8.83	1620
20	$CO_2CH_2CH_3$	$CH_2C_6H_5$	50	9.00	8.93	1620
21	$CO_2CH_2CH_3$	o-$FC_6H_4CH_2$	55	9.08	8.83	1620
22	$CO_2CH_2CH_3$	m-$FC_6H_4CH_2$	77	9.11	8.85	1620
23	$CO_2CH_2CH_3$	p-$FC_6H_4CH_2$	70	8.72	8.52	1620

stretching vibration (1620 cm^{-1}), mid-way between the C=N stretching vibrations of the parent salts (1640 cm^{-1}) and of the starting β-carbolines (1605 cm^{-1}). The incomplete character of this iminium bond of the dipoles 14 - 23 is also reflected in their nmr spectra (Table II) in which the H-1 protons (and, to a lesser extent, the H-4 protons) are considerably shielded with respect to those in the quaternized salts (Table I).

The mass spectra of anhydro-bases are also quite characteristic (Scheme I). For example, when R is a methyl group, the major fragmentation pathway is initiated by a loss of ethylene

Scheme I

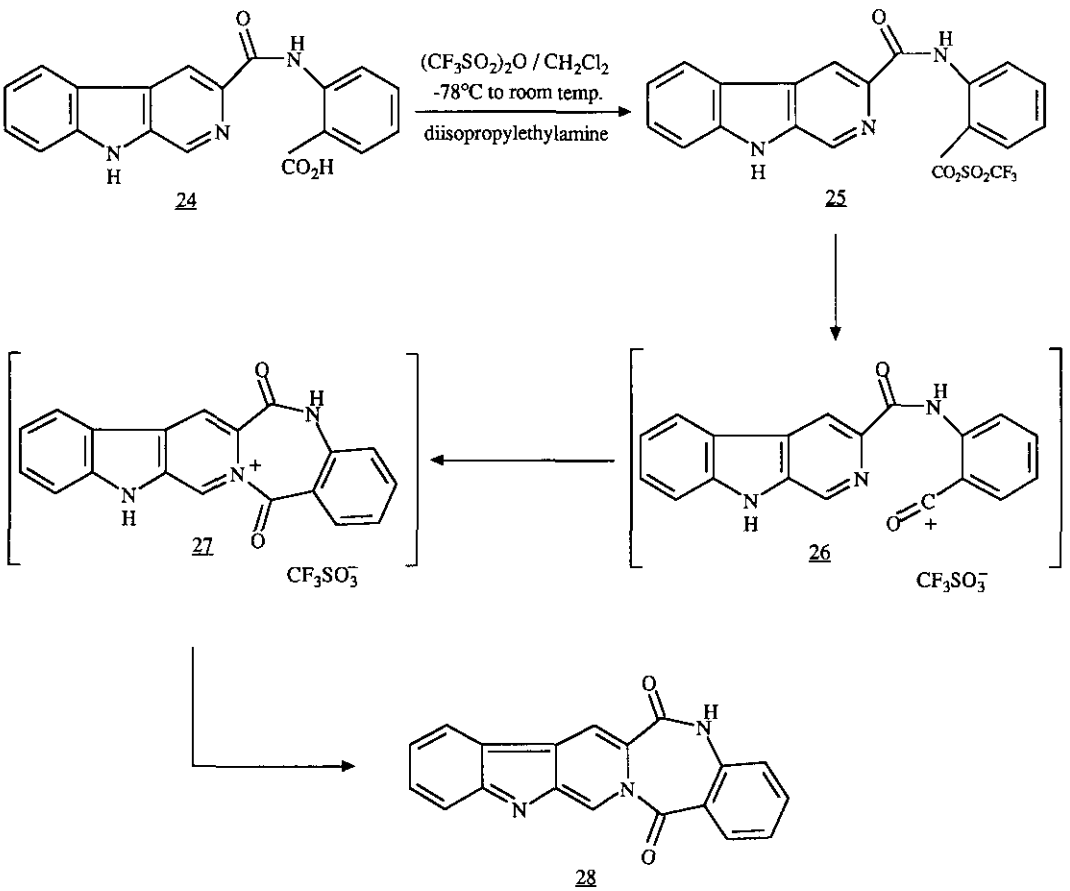


(Calcd for $C_{13}H_{10}O_2N_2$: m/z = 226.0811. Found : m/z = 226.0776) followed by decarboxylation (Calcd for $C_{12}H_9N_2$: m/z = 181.0591. Found : m/z = 181.0678) and the loss of the methylene diradical (Calcd for $C_{11}H_7N_2$: m/z = 167.0551. Found : m/z = 167.0580). On the other hand, when R is for example, a fluorobenzyl group, the first fragmentation occurs at the carbonyl-heterocycle bond (Calcd for $C_{18}H_{13}N_2F$: m/z = 276.1010. Found : m/z = 276.1036). This is followed by loss of the fluorobenzyl radical to also give the ion typical of the anhydro-bases (Calcd for $C_{11}H_7N_2$: m/z = 167.0551. Found : m/z = 167.0505).

We also attempted to acylate the N-2 position of β-carboline. Though such N-acyl compounds are known to be stable in the pyridine series[7], no corresponding products were formed by the

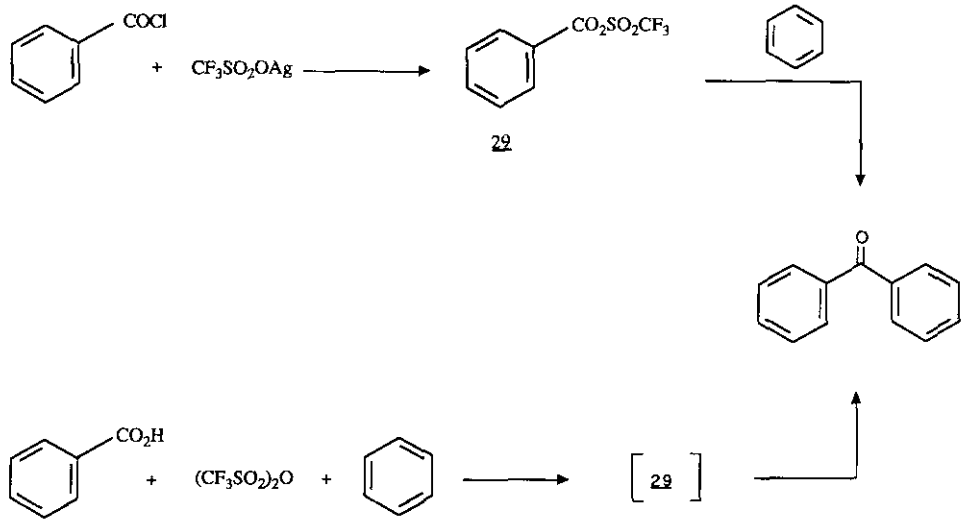
reaction of acetyl chloride, benzoyl chloride or benzoyl triflate[8] with even non-hindered β-carbolines such as 1 ; only starting material and N-9 (indolyl) substituted compounds could be isolated. Nevertheless, with the knowledge that compounds such as 28 are stable[9], it seemed reasonable to assume that an intramolecular acylation of the pyridinyl nitrogen of β-carboline could be achieved. Indeed, when the carboxylic acid derivative 24 was allowed to react at - 78°C with trifluoromethanesulfonic anhydride and a non alkylating base such as diisopropylethylamine, compound 28 was obtained in 95% yield. This compound, which formally can be considered to possess a dipole structure, was identical to that synthesized previously by a different method[9]. Compound 28 is presumably formed via a mixed sulfonic-carboxylic anhydride 25 (Scheme II) which

Scheme II



dissociates into the unstable acylium ion 26. Attack of this ion by the neighboring nitrogen atom leads to the salt intermediate 27 which, under the basic reaction conditions, gives the anhydro-base 28 directly. The intermediacy of salt 27 was confirmed by the negative fast atom bombardment (FAB) mass spectrum of an aliquot of the reaction mixture (m/z = 149).

The use of mixed sulfonic-carboxylic anhydrides in the acylation of aromatic rings has been reported[8,10]. Thus, the reaction of benzene with benzoyl triflate, prepared separately by the action of silver triflate on benzoyl chloride followed by lengthy purification, yielded benzophenone. If the mechanism proposed for the synthesis of 28 is correct, then the direct one-pot



acylation of benzene via the anhydride should be possible using benzoic acid as starting material. Indeed, treatment of benzoic acid with triflic anhydride in benzene at reflux effectively gave benzophenone in 81% yield after work up[11]. The intermediacy of the mixed anhydride 25 in the formation of 28 is thus confirmed.

In conclusion, we have developed a mild and efficient method of quaternizing hindered, pharmacologically important β-carbolines with a variety of alkyl trifluoromethanesulfonates and their consecutive transformation into anhydro-bases. Although analogous intermolecular acylations of the N-2 position of β-carbolines did not succeed, this reaction could be achieved intramolecularly by use of a mixed trifluoromethanesulfonic-carboxylic anhydride intermediate to yield a cyclic N-2 acyl anhydro-base in one step. Biological evaluation of these novel compounds will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Büchi open capillary apparatus. Infrared spectra (ir) were obtained in KBr with a Perkin-Elmer 297 instrument. Ultraviolet (uv) spectra were recorded in methanol on a Perkin Elmer lambda 5 UV/VIS spectrophotometer. Proton nmr spectra were recorded in $CDCl_3$ on a Brüker WP 200 MHz instrument. Chemical shifts are given as δ values relative to tetramethylsilane. Thin-layer chromatography was performed on Merck silica gel 60 or aluminum oxide 60 plates with fluorescent indicator. Merck aluminum oxide 90 was used for all column chromatography unless otherwise indicated. Electron impact (EI) and fast atomic bombardment (FAB) mass spectra were obtained respectively on a AEI MS-50 and on a Kratos MS-80 spectrometer. High resolution mass spectroscopy was performed at the S.C.A., C.N.R.S., Vernaison, France and elemental analyses were determined at the I.C.S.N., C.N.R.S., Gif-sur-Yvette, France.

General procedure for the preparation of the salts 4 - 13.

Procedure A : To a stirred solution of the β-carboline (0.59 mmol) in methylene chloride (CH_2Cl_2, 6 ml) was added dropwise methyl trifluoromethanesulfonate (0.12 ml, 0.71 mmol) under a nitrogen atmosphere. The mixture was stirred for the time shown in Table I. The reaction mixture was then concentrated in vacuo leaving a powder which was crystallized in alcohol (cf. Table I).

Procedure B : To a stirred solution of trifluoromethanesulfonic anhydride (84 µl, 0.50 mmol) in CH_2Cl_2 (2 ml) chilled to the temperature indicated in Table I was added dropwise under a nitrogen atmosphere a solution of diisopropylethylamine (87 µl, 0.50 mmol) and the corresponding alcohol (0.50 mmol) in CH_2Cl_2 (2 ml). Stirring was continued for 15 min after which the β-carboline 3 (0.42 mmol) was added portionwise. The reaction mixture was allowed to gradually warm to room temperature and was then concentrated in vacuo. The resulting brown gum, which solidified on standing, was crystallized in alcohol.

General procedure for the preparation of compounds 14 - 23.

To a hot solution of dimethoxyethane (D.M.E. 2 ml) and cesium carbonate (Cs_2CO_3 , 35.7 mg, 0.11 mmol) was added 0.11 mmol of the quaternized salt. The reaction mixture immediately became orange and was refluxed for 5 h. The mixture was then filtered, the solid was washed with CH_2Cl_2

(4 ml) and the combined filtrate and washings were washed with water (4 ml). The organic layer was recovered, dried over anhydrous sodium sulfate and evaporated leaving an amorphous yellow solid which was either crystallized in the appropriate solvent (see individual compounds) or was subjected to column chromatography.

3-N-(2-Carboethoxy)phenyl-β-carboline-3-carboxamide (24).

A suspension of β-carboline-3-carboxylic acid[12] (0.7 g, 3.3 mmol) in dry tetrahydrofuran (150 ml) was refluxed for 30 min in the presence of triethylamine (0.5 ml, 3.6 mmol). The mixture was cooled to room temperature and a solution of freshly distilled ethyl chloroformate (0.32 ml, 3.3 mmol) in tetrahydrofuran (20 ml) was added dropwise over 1.5 h. After the addition was complete, the solution was stirred for a further hour after which ethyl anthranilate (0.49 g, 3.3 mmol) was added. The reaction mixture was refluxed 3 h, cooled and evaporated to dryness under vacuum. The residue was taken up in chloroform and washed with saturated aqueous sodium hydrogen carbonate and water. The organic phase was then dried with sodium sulfate, the solvent removed in vacuo and the residue was chromatographed on a column of silica gel using toluene/ethanol (9:0.5) as developer, yielding 3-N-(2-carboethoxy)phenyl-β-carboline-3-carboxamide (25%) which was crystallized from ethanol : mp : 234-236°C ; EI mass spectrum, m/z = 359 ; ^{1}H nmr (Me_2SO-d_6) δ 1.52 (t, J = 9 Hz, 3H, CH_3), 4.55 (q, J = 9 Hz, 2H, CH_2), 7.38 (t, J = 7 Hz, 1H), 7.48 (t, J = 7 Hz, 1H), 7.91 - 7.71 (m, 3H), 8.24 (d, J = 8 Hz, 1H), 8.61 (d, J = 8 Hz, 1H), 9.11 (d, J = 9 Hz, 1H), 9.21 (s, 2H, H-1, 4), 10.95 (s, 1H, D_2O exchangeable, NH), 11.68 (s, 1H, D_2O exchangeable, NH). Anal. Calcd for $C_{21}H_{17}N_3O_3 \cdot 1/4\ H_2O$: C, 69.32 ; H, 4.81 ; N, 11.55. Found : C, 69.61 ; H, 4.97 ; N, 11.35. To a solution of this ester (1 g, 0.28 mmol) in 10% aqueous ethanol (20 ml) was added 0.2 N aqueous sodium hydroxide (2 ml). The reaction mixture was refluxed for 1 h, cooled and concentrated in vacuo. The resulting residue was dissolved in a minimum of water and treated slowly with glacial acetic acid until a precipitate formed. This precipitate was collected by filtration, washed with cold water and dried (96%). Recrystallization from ethanol gave pure 24: mp 325-327°C ; EI mass spectrum, m/z = 331 ; ^{1}H nmr (Me_2SO-d_6) δ 3.49 (bs, HDO + CO_2H), 7.35 (t, J = 7 Hz, 1H), 7.48 (t, J = 7 Hz, 1H), 7.92 - 7.68 (m, 3H), 8.21 (d, J = 8 Hz, 1H), 8.61 (d, J = 8 Hz, 1H), 9.11 (d, J = 9 Hz, 1H), 9.15 (s, 1H, H-4), 9.21 (s, 1H, H-1), 12.28 (s, 1H, D_2O exchangeable, NH), 13.34 (s, 1H, D_2O exchangeable, NH). Anal. Calcd. for $C_{19}H_{13}N_3O_3$: C, 68.88 ; H, 3.93 ; N, 12.69. Found : C, 69.07 ; H, 3.91 ; N, 12.75.

8,14-Dioxo-13,14-dihydro-8H-indolo[3',2':4,5]pyrido[2,1-c][1,4] benzodiazepine (28) :

To a stirred solution of compound 24 (3.3 mg, 0.01 mmol) in CH_2Cl_2 (0.5 ml) was added under a nitrogen atmosphere 0.012 mmol of diisopropylethylamine at room temperature. Stirring was continued for 30 min after which the reaction mixture was cooled to - 78°C before the dropwise addition of trifluoromethanesulfonic anhydride (1.8 µl, 0.012 mmol). The resulting solution was stirred 2 h at -78°C. The solution was then allowed to warm to room temperature and was washed with water (1 ml). The organic phase was recovered, dried over anhydrous sodium sulfate and evaporated to give a pale yellow solid (2.7 mg, 0.0095 mmol) which crystallized in dioxane-ethanol : mp 338-340°C (lit.[9] 340-342°C) ; ^1H nmr (DMSO-d_6) δ 7.38 (1H, t, H_2, J = 7 Hz), 7.68 to 7.80 (m, 4H), 8.05 (t, 1H, J = 7 Hz), 8.21 (d, 1H, H-1, J = 8 Hz), 8.54 (d, 1H, H-4, J = 8 Hz), 9.13 (s, 1H, H-15), 9.27 (s, 1H, H-6), 12.28 (1H, s, D_2O exchangeable) ; EI mass spectrum, m/z = 313 ; uv (log ε), 343.9 (4.294), 281.6 (4.438), 231.6 nm (4.467).

Benzophenone.

A solution of trifluoromethanesulfonic anhydride (180 µl, 1.07 mmol) and benzoic acid (0.1 g, 0.82 mmol) in dry benzene (1.5 ml) was refluxed for 4 h. After cooling to room temperature, the solution was taken up in chloroform (10 ml) and washed with aqueous 0.2 N sodium hydroxide and brine. The organic phase was dried with anhydrous sodium sulfate and evaporated leaving a pale oil which was chromatographed on silica gel using dichloromethane/hexane (1:1) as developer to give benzophenone (0.121 g, 0.66 mmol, 81%). Nmr, ir, uv spectra were identical with published spectra. EI mass spectrum, m/z = 182.

2-Methyl-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (4) :

Ir 3170 (N-H), 1645 (C=N^+), 1300-1220, 1160, 1035, 640 cm^{-1} (CF_3-SO_3^-) ; ^1H nmr δ 4.70 (s, 3H, CH_3), 7.50 (t, 1H, H_7, J = 8.3 Hz), 7.85 (m, 2H, H_6 + H_5), 8.50 (d, 1H, H_8, J = 8.3 Hz), 8.70 (d, 1H, H_4, J = 6.6 Hz), 8.80 (d, 1H, H_3, J = 6.6 Hz), between 8.50 and 8.83 (1H, broad, H_9, D_2O exchangeable), 9.41 (s, 1H, H_1) ; FAB mass spectrum, m/z = 183 ; uv (log ε), 377.2 (3.445), 307.5 (4.061), 253.5 (4.256), 218.5 (4.004), 206.9 nm (4.097). Anal. Calcd for $C_{13}H_{11}N_2O_3F_3S$: C, 46.99 ; H, 3.33 ; N, 8.43 ; S, 9.65. Found : C, 47.04 ; H, 3.33 ; N, 8.26 ; S, 9.87.

2-Methyl-3-methoxycarbonyl-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (5) :

Ir 3150 (N-H), 1730 (C=O), 1638 ($C=N^+$), 1300-1220, 1150, 1030, 640 cm^{-1} (CF_3-SO_3^-) ; ^1H nmr δ 4.18 (s, 3H, O-CH_3), 4.76 (s, 3H, N-CH_3), 7.56 (t, 1H, H_6 or H_7, J = 7 Hz), 7.88 (m, 2H, H_6 or H_7 and H_5), 8.31 (d, 1H, H_8, J = 8 Hz), 8.71 (s broad, 1H, H_9, D_2O exchangeable), 9.16 (s, 1H, H_4), 9.83 (s, 1H, H_1) ; FAB mass spectrum, m/z = 241 ; uv (log ε), 379.6 (3.387), 279.3 (4.140), 242.1 (3.812), 216.3 nm (3.900). Anal. Calcd for $C_{15}H_{13}N_2O_5F_3S$: C, 46.15 ; H, 3.36 ; N, 7.17 ; S, 8.21. Found : C, 46.25 ; H, 3.33 ; N, 7.35 ; S, 8.04.

3-Ethoxycarbonyl-2-methyl-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (6) :

Ir 3220 (N-H), 1730 (C=O), 1640 ($C=N^+$), 1290-1210, 1150, 1028, 645 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.56 (t, 3H, CH_3, J = 8 Hz), 4.63 (q, 2H, CH_2, J = 8 Hz), 4.75 (s, 3H, CH_3), 7.58 (t, 1H, H_6 or H_7, J = 7 Hz), 7.73 (m, 2H, H_6 or H_7 and H_5), 8.34 (d, 1H, H_8, J = 8 Hz), 8.76 (s broad, 1H, H_9, D_2O exchangeable), 9.13 (s, 1H, H_4), 9.80 (s, 1H, H_1) ; FAB mass spectrum, m/z = 255 ; uv (log ε), 380.5 (3.836), 278.5 (4.509), 241.4 (4.259), 216 nm (4.359). Anal. Calcd for $C_{16}H_{15}N_2O_5F_3S$: C, 47.52 ; H, 3.74 ; N, 6.92 ; S, 7.93 ; Found : C, 47.48 ; H, 3.92 ; N, 6.72 ; S, 7.85.

3-Ethoxycarbonyl-2-propyl-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (7) :

Ir 3200 (N-H), 1725 (C=O), 1638 ($C=N^+$), 1310-1220, 1160, 1035, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.05 (t, 3H, CH_3, J = 7.5 Hz), 1.53 (t, 3H, CH_3, J = 7.5 Hz), 2.09 (sextet, 2H, CH_2, J = 7.5 Hz), 4.60 (q, 2H, CH_2, J = 7.5 Hz), 5.05 (t, 2H, CH_2, J = 7.5 Hz), 7.50 (t, 1H, H_6 or H_7, J = 8 Hz), 7.80 (m, 2H, H_6 or H_7 and H_5), 8.28 (d, 1H, H_8, J = 8 Hz), 9.00 (s, 1H, H_4), 9.71 (s, 1H, H_1), 12.36 (s broad, 1H, H_9, D_2O exchangeable) ; FAB mass spectrum, m/z = 283 ; uv (log ε), 382.6 (3.461), 279.9 (4.241), 240.8 (3.923), 216.3 nm (4.025). Anal. Calcd for $C_{18}H_{19}N_2O_5F_3S.1H_2O$: C, 47.99 ; H, 4.69 ; N, 6.22 ; S, 7.11 ; Found : C, 48.06 ; H, 4.45 ; N, 6.10 ; S, 7.12.

2-Allyl-3-ethoxycarbonyl-9H-pyrido[3,4b]indolium trifluoromethanesulfonate (8) :

Ir 3180 (N-H), 1720 (C=O), 1640 ($C=N^+$), 1310-1220, 1160, 1035, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.50 (t, 3H, CH_3, J = 7.5 Hz), 4.56 (q, 2H, CH_2, J = 7.5 Hz), 5.40 (d, 1H, J = 15 Hz), 5.45 (d, 1H, J = 7 Hz), 5.63 (d, 2H, J = 6 Hz), 6.08 (m, 1H), 7.46 (t, 1H, J = 8 Hz, H_6 or H_7), 7.76 (m,

2H, H_6 or H_7 and H_5), 8.28 (d, 1H, H_8, J = 8 Hz), 8.93 (s, 1H, H_4), 9.70 (s, 1H, H_1), 12.33 (s, 1H, H_9, D_2O exchangeable) ; FAB mass spectrum, m/z = 281 ; uv (log ε), 387.7 (3.388), 280.3 (4.171), 241.1 (3.841), 216.6 nm (3.946). Anal. Calcd for $C_{18}H_{17}N_2O_5F_3S.1/2\ H_2O$: C, 49.26 ; H, 4.02 ; N, 6.38 ; S, 7.30 ; Found : C, 49.56 ; H, 4.22 ; N, 6.65 ; S, 7.32.

3-Ethoxycarbonyl-2-(1-ethyl-2-methoxy)-9H-pyrido[3,4b]indolium trifluoromethanesulfonate (9) :

Ir 3205 (N-H), 1738 (C=O), 1640 ($C=N^+$), 1300-1220, 1160, 1038, 642 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.53 (t, 3H, CH_3, J = 8 Hz), 3.30 (s, 3H, CH_3), 3.85 (t, 2H, CH_2, J = 5.8 Hz), 4.56 (q, 2H, CH_2, J = 8 Hz), 5.33 (t, 2H, CH_2, J = 5.8 Hz), 7.50 (m, 1H, H_6 or H_7), 7.83 (m, 2H, H_6 or H_7 and H_5), 8.26 (d, 1H, H_8, J = 8 Hz), 8.76 (s broad, 1H, H_9, D_2O exchangeable), 8.96 (s, 1H, H_4), 9.66 (s, 1H, H_1) ; FAB mass spectrum, m/z = 299 ; uv (log ε), 382.4 (3.811), 278.6 (4.537), 241.0 (4.234), 215.9 nm (4.326). Anal. Calcd for $C_{18}H_{19}N_2O_6F_3S$: C, 48.21 ; H, 4.27 ; N, 6.24 ; S, 7.15 ; Found : C, 48.20 ; H, 4.28 ; N, 6.12 ; S, 7.12.

2-Benzyl-3-ethoxycarbonyl-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (10) :

Ir 3220 (N-H), 1730 (C=O), 1638 ($C=N^+$), 1310-1220, 1165, 1032, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.31 (t, 3H, CH_3, J = 8 Hz), 4.40 (q, CH_2, J = 8 Hz), 6.28 (s, 2H, CH_2), 7.25 to 7.46 (m, 6H), 7.66 (m, 2H, H_6 or H_7 and H_5), 8.28 (d, 1H, H_8, J = 8 Hz), 8.73 (s, 1H, H_9-D_2O exchangeable), 8.96 (s, 1H, H_4), 9.95 (s, 1H, H_1); FAB mass spectrum, m/z = 331 ; uv (log ε), 384.8 (3.600), 280.9 (4.418), 240.3 (4.119), 214.7 nm (4.268). Anal. Calcd for $C_{22}H_{19}N_2O_5F_3S.1/2\ H_2O$: C,53.98; H, 4.11 ; N, 5.74 ; S, 6.55 ; Found: C, 53.99 ; H, 3.98 ; N, 6.02 ; S, 6.79.

3-Ethoxycarbonyl-2-(o-fluorobenzyl)-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (11) :

Ir 3118 (N-H), 1722 (C=O), 1640 ($C=N^+$), 1310-1230, 1162, 1038, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.45 (t, 3H, CH_3, J = 8 Hz), 4.53 (q, 2H, CH_2, J = 8 Hz), 6.30 (s, 2H, CH_2), 7 to 7.46 (m, 5H), 7.80 (m, 2H), 8.26 (d, 1H, H_8, J = 8 Hz), 8.70 (s, 1H, H_9, D_2O exchangeable), 8.95 (s, 1H, H_4), 9.83 (s, 1H, H_1) ; FAB mass spectrum, m/z = 349 ; uv (log ε), 384.8 (3.565), 281.6 (4.326), 241.6 (4.003), 212.7 nm (4.187). Anal. Calcd for $C_{22}H_{18}N_2O_5F_4S$: C, 53.01 ; H, 3.64 ; N, 5.62 ; S, 6.43 ; Found : C, 53.31 ; H, 3.63 ; N, 5.52 ; S, 6.62.

3-Ethoxycarbonyl-2-(m-fluorobenzyl)-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (12) :

Ir 3150 (N-H), 1720 (C = O), 1642 ($C=N^+$), 1310-1230, 1168, 1039, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.45 (t, 3H, CH_3, J = 8 Hz), 4.55 (q, 2H, CH_2, J = 8 Hz), 6.31 (s, 2H, CH_2), 7 to 7.73 (m, 5H), 8.11 (m, 2H), 8.43 (d, 1H, d, H_8, J = 8 Hz), 8.85 (s, 1H, H_9, D_2O exchangeable), 9.06 (s, 1H, H_4), 10.03 (s, 1H, H_1) ; FAB mass spectrum, m/z = 349 ; uv (log ε), 386.0 (3.667), 282.0 (4.461), 241.7 (4.135), 215.6 nm (4.303). Anal. Calcd for $C_{22}H_{18}N_2O_5F_4S$: C, 53.01 ; H, 3.64 ; N, 5.62 ; S, 6.43 ; Found : C, 53.05 ; H, 3.47 ; N, 5.52 ; S, 6.22.

3-Ethoxycarbonyl-2-(p-fluorobenzyl)-9H-pyrido[3,4-b]indolium trifluoromethanesulfonate (13) :

Ir 3120 (N-H), 1720 (C=O), 1640 ($C=N^+$), 1320-1220, 1165, 1040, 640 cm^{-1} ($CF_3SO_3^-$) ; ^1H nmr δ 1.45 (t, 3H, 3H, CH_3, J = 8 Hz), 4.51 (q, 2H, CH_2, J = 8 Hz), 6.25 (s, 2H, CH_2), 7.06 (m, 2H), 7.36 (m, 3H), 7.83 (m, 2H), 8.26 (d, 1H, H_8, J = 8 Hz), 8.70 (s, 1H, H_9, D_2O exchangeable), 8.96 (s, 1H, H_4), 10.00 (s, 1H, H_1) ; FAB mass spectrum, m/z = 349 ; uv (log ε), 387.0 (3.350), 271.7 (4.320), 239.7 (4.071), 216.5 nm (4.155). Anal. Calcd for $C_{22}H_{18}N_2O_5F_4S.1/2\ H_2O$: C, 52.07 ; H, 3.77 ; N, 5.52 ; S, 6.31 ; Found: C, 51.98 ; H, 3.68 ; N, 5.76 ; S, 6.59.

2-Methylpyrido[3,4-b]indole (14) :

Ir 1620 cm^{-1} (C=N) ; ^1H nmr δ 4.34 (s, 3H, CH_3), 7.23 (t, 1H, H_6 or H_7, J = 8 Hz), 7.50 (d, 1H, H_5, J = 8 Hz), 7.64 (t, 1H, H_7 or H_6, J = 8 Hz), 7.90 (d, 1H, H_8, J = 8 Hz), 8.16 (t, 2H, H_3 and H_4, J = 7 Hz), 8.62 (s, 1H, H_1) ; EI mass spectrum, m/z = 182 ; uv (log ε), 377.9 (3.328), 307.2 (3.944), 283.1 (3.679), 253.8 (4.123), 217.8 (3.922), 207.5 nm (3.967) ; mp (acetone/hexane), 213-215°C (lit.[6] 212-214).

2-Methyl-3-methoxycarbonylpyrido[3,4-b]indole (15) :

Ir 1725 (C=O), 1622 cm^{-1} (C=N) ; ^1H nmr δ 4.07 (s, 3H, CH_3), 4.62 (s, 3H, CH_3), 7.36 (t, 1H, H_6 or H_7, J = 7 Hz), 7.68 (t, 1H, H_6 or H_7, J = 7 Hz), 7.97 (d, 1H, H_5, J = 7.2 Hz), 8.20 (d, 1H, H_8, J = 7.2 Hz), 9.02 (s, 2H, H_4 and H_9) ; EI mass spectrum, m/z = 240 ; uv (log ε), 374.8 (3.419), 279.5 (4.065), 241.7 (3.832), 217.3 nm (3.934) ; mp(toluene), 222-224°C. Anal. Calcd for $C_{14}H_{12}N_2O_2.1/2\ H_2O$: C, 67.46; H, 5.23 ; N, 11.23 : Found : C, 67.46 ; H, 4.87 ; N, 11.05.

3-Ethoxycarbonyl-2-methylpyrido[3,4-b]indole (16) :

Ir 1720 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.51 (t, 3H, CH_3, J = 8 Hz), 4.56 (q, 2H, CH_2, J = 8 Hz), 4.60 (s, 3H, CH_3), 7.38 (t, 1H, H_{6a} or H_7, J = 8 Hz), 7.73 (t, 1H, H_6 or H_7, J = 8 Hz), 8.11 (d, 1H, H_5, J = 8 Hz), 8.36 (d, 1H, H_8, J = 8 Hz), 8.78 (s, 1H, H_4), 9.12 (s, 1H, H_1) ; EI mass spectrum, m/z = 254 ; uv (log ε), 379.0 (3.107), 278.7 (3.847), 240.6 (3.666), 215.1 nm (3.816) ; mp (toluene/hexane), 158-160°C dec. Anal. Calcd for $C_{15}H_{14}N_2O_2.1/2\ H_2O$: C, 68.43 ; H, 5.74 ; N, 10.63 ; Found : C, 68.79 ; H, 5.79 ; N, 10.38.

3-Ethoxycarbonyl-2-propylpyrido[3,4-b]indole (17) :

Ir 1690 (C=O) 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.05 (t, 3H, CH_3, J = 7 Hz), 1.52 (t, 3H, CH_3, J = 7 Hz), 2.03 (m, 2H, CH_2), 4.50 (q, 2H, CH_2, J = 7 Hz), 4.97 (t, 2H, CH_2, J = 7 Hz), 7.30 (t, 1H, H_6 or H_7, J = 7.5 Hz), 7.65 (t, 1H, H_6 or H_7, J = 7.5 Hz), 8.03 (d, 1H, H_5, J = 8 Hz), 8.27 (d, 1H, H_8, J = 8 Hz), 8.78 (s, 1H, H_4), 9.02 (s, 1H, H_1) ; EI mass spectrum, m/z = 282 ; uv (log ε), 376.9 (3.440), 278.0 (4.191), 240.5 (3.943), 217.2 nm (4.020) ; mp (ethyl acetate), 191-193°C. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32 ; H, 6.42 ; N, 9.92 ; Found : C, 72.11 ; H, 6.37 ; N, 9.74.

2-Allyl-3-ethoxycarbonylpyrido[3,4-b]indole (18) :

Ir 1700 (C=O), 1618 cm^{-1} (C=N) ; ^1H nmr δ 1.51 (t, 3H, CH_3, J = 8 Hz), 4.51 (q, 2H, CH_2, J = 8 Hz), 5.16 (d, 1H, J = 17 Hz), 5.40 (d, 1H, J = 10 Hz), 5.65 (d, 2H, CH_2, J = 4 Hz), 6.16 (m, 1H), 7.35 (t, 1H, H_6 or H_7, J = 7.5 Hz), 7.70 (t, 1H, H_6 or H_7, J = 7.5 Hz), 8.06 (d, 1H, H_5, J = 8 Hz), 8.31 (d, 1H, H_8, J = 8 Hz), 8.78 (s, 1H, H_4), 9.04 (s, 1H, H_1); EI mass spectrum, m/z = 280 ; uv (log ε), 375.8 (3.942), 281.5 (4.275), 242.5 (3.974), 217.7 nm (4.095); mp(ethyl acetate), 166-168°C dec. Anal. Calcd for $C_{17}H_{16}N_2O_2.1/2\ H_2O$: C, 70.57 ; H, 5.97 ; N, 9.70; Found : C, 70.50 ; H, 5.97 ; N, 10.19.

3-Ethoxycarbonyl-2-(1-ethyl-2-methoxy)pyrido[3,4-b]indole (19) :

Ir 1718 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.53 (t, 3H, CH_3, J = 8 Hz), 3.26 (s, 3H, CH_3), 3.86 (t, 2H, CH_2, J = 5 Hz), 4.50 (q, 2H, CH_2, J = 8 Hz), 5.16 (t, 2H, CH_2, J = 5 Hz), 7.31 (t, 1H,

H_6 or H_7, J = 8 Hz), 7.66 (t, 1H, H_6 or H_7, J = 8 Hz), 8.01 (d, 1H, H_5, J = 8 Hz), 8.26 (d, 1H, H_8, J = 8 Hz), 8.83 (s, 1H, H_4), 9.03 (s, 1H, H_1) ; EI mass spectrum, m/z = 298 ; uv (log ε), 381.6 (3.452), 279.5 (4.203), 241.4 (3.872), 215.6 nm (3.963) ; mp (ethyl acetate), 173-175°C. Anal. Calcd for $C_{17}H_{18}N_2O_3.3/4\ H_2O$: C, 65.46 ; H, 6.30 ; N, 8.99 ; Found : C, 65.16 ; H, 6.16; N, 8.99.

2-Benzyl-3-ethoxycarbonylpyrido[3,4-b]indole (20) :

Ir 1700 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.35 (t, 3H, CH_3, J = 8 Hz), 4.38 (q, 2H, CH_2, J = 8 Hz), 6.25 (s, 2H, CH_2), 7.11 (m, 2H), 7.33 (m, 4H), 7.65 (t, 1H, H_6or H_7, J = 7.6 Hz), 8.00 (d, 1H, H_5, J = 8 Hz), 8.26 (d, 1H, H_8, J = 8 Hz), 8.83 (s, 1H, H_4), 9.00 (s, 1H, H_1) ; EI mass spectrum, m/z = 330 ; uv (log ε), 375.7 (3.614), 302.5 (4.328), 284.5 (4.316), 241.6 (4.043), 211.4 nm (4.227) ; mp (diethyl ether) 165-167°C. Anal. Calcd for $C_{21}H_{18}O_2N_2.1\ H_2O$: C, 73.39 ; H, 5.20 ; N, 8.04; Found : C, 73.39, H, 5.20 ; N, 8.51.

3-Ethoxycarbonyl-2-(o-fluorobenzyl)pyrido[3,4-b]indole (21) :

Ir 1700 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.46 (t, 3H, CH_3, J = 8 Hz), 4.50 (q, 2H, CH_2, J = 8 Hz), 7 to 7.36 (m, 5H), 7.70 (t, 1H, H_6 or H_7, J = 8 Hz), 8.03 (d, 1H, H_5, J = 8 Hz), 8.31 (d, 1H, H_8, J = 8 Hz), 8.83 (s, 1H, H_4), 9.08 (s, 1H, H_1) ; EI mass spectrum, m/z = 348; uv (log ε), 376.4 (3.463), 302.2 (4.197), 289.9 (4.150), 244.0 (3.858), 217.6 nm (4.037) ; mp (diethyl ether), 188-190°C. Anal. Calcd for $C_{21}H_{17}N_2O_2F.1/2\ H_2O$: C, 70.57 ; H, 5.07 ; N, 7.83 ; Found : C, 70.66 ; H, 5.40 ; N, 7.90.

3-Ethoxycarbonyl-2-(m-fluorobenzyl)pyrido[3,4-b]indole (22) :

Ir 1700 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.41 (t, 3H, CH_3, J = 8 Hz), 4.42 (q, 2H, CH_2, J = 8 Hz), 6.26 (s, 2H, CH_2), 6.90 to 7.33 (m, 5H), 7.71 (t, 1H, H_6 or H_7, J = 8 Hz), 8.02 (d, 1H, H_5, J = 8 Hz), 8.33 (d, 1H, H_8, J = 8 Hz), 8.85 (s, 1H, H_4), 9.11 (s, 1H, H_1) ; EI mass spectrum, m/z = 348 ; uv (log ε), 376.8 (3.630), 303.4 (4.349), 291.0 (4.314), 242.0 (4.036), 218.4 (4.237), 208.4 nm (4.260) ; mp (diethyl ether), 188-190°C. Anal. Calcd for $C_{21}H_{17}N_2O_2F.1/2\ H_2O$: C, 70.57 ; H, 5.07 ; N, 7.83 ; Found : C, 70.71 ; H, 5.32 ; N, 7.63.

3-Ethoxycarbonyl-2-(p-fluorobenzyl)pyrido[3,4-b]indole (23) :

Ir 1700 (C=O), 1620 cm^{-1} (C=N) ; ^1H nmr δ 1.36 (t, 3H, CH_3, J = 8 Hz), 4.28 (q, 2H, J = 8 Hz), 6.00 (s, 2H, CH_2), 6.78 to 7.10 (m, 5H), 7.41 (t, 1H, H_6 or H_7, J = 8 Hz), 7.75 (d, 1H, H_5, J = 8 Hz), 8.00 (d, 1H, H_8, J = 8 Hz), 8.52 (s, 1H, H_4), 8.72 (s, 1H, H_1) ; EI mass spectrum, m/z = 348 ; uv (log ε), 377.5 (3.611), 300.4 (4.282), 283.3 (4.326), 242.4 (4.031), 210.4 nm (4.245) ; mp (diethyl ether), 188-190°C. Anal. Calcd for $C_{21}H_{17}N_2O_2F.1\ H_2O$: C, 68.84 ; H, 4.22 ; N, 7.64 Found : C, 68.41 ; H, 4.08 ; N, 7.59.

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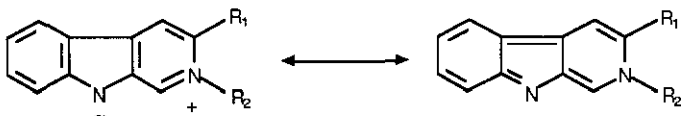

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