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SYNTHESIS OF PENTACYCLIC β-CARBOLINE AND 1,4-BENZODIAZEPINE HYBRID MOLECULES BY DEHYDROGENATION-TRANSAMIDATION OF QUINAZOLINO-TETRAHYDRO-β-CARBOLINES

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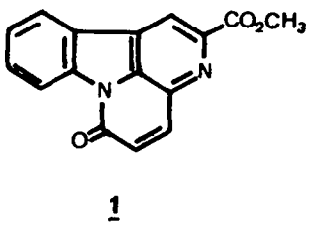
Abstract - Pentacyclic hybrid molecules 2a and 2b possessing both the 3-carbethoxy-β-carboline and the 1,4-benzodiazepine pharmacophores have been synthesized by dehydrogenation - transamidation of quinazolino-tetrahydro-β-carbolines 6 catalyzed by palladium on activated carbon.

The synthesis of β-carboline derivatives, namely methyl or ethyl esters,[1] and the study of their pharmacological activity have been intensified since Braestrup[2] showed that 3-carbethoxy-β-carboline was a potent benzodiazepines antagonist. For instance Guzman et al.[1a] found that 2-carbomethoxy-canthin-6-one 1 bound to benzodiazepine receptors with an affinity comparable to severable pharmacologically active benzodiazepines. Within the framework of our laboratory investigations,[3] we decided to synthesize "hybrid molecules" possessing both the 3-carbethoxy-β-carboline-N-acylindole and the 1,4-benzodiazepine pharmacophores. To our knowledge, the only molecule with an analogous structure already described in the literature is compound 3 which does not have the ester function considered to be essential for pharmacological activity. This molecule has been obtained by rearrangement of the natural quinazolino-carboline euxylophorine B.[4]



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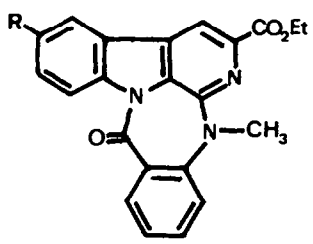
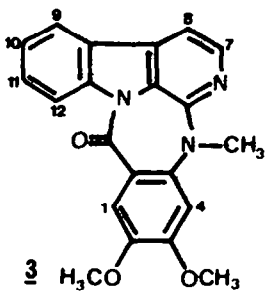


2a R = H
b R = OCH3



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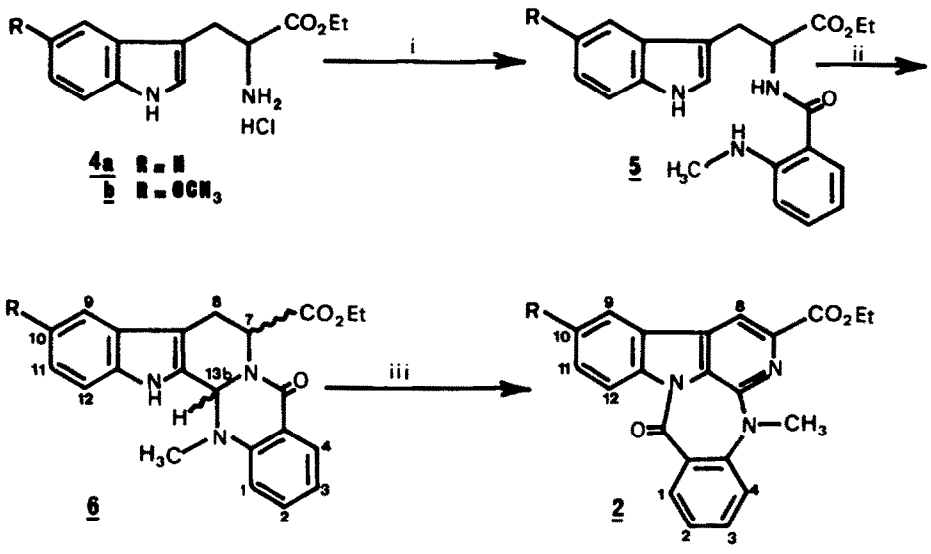
In this report, we describe the synthesis of compounds 2 following the three steps indicated in scheme 1.

The reaction of N-methylisatoic anhydride with the tryptophane and 5-methoxy-tryptophane ethyl ester hydrochlorides 4a and 4b gave amino-esters 5 in excellent yields[5] (scheme 1).



Scheme 1. Reagents : i) N-methylisatoic anhydride-pyridine ; ii) $HC(OEt)_3$, TsOH, toluene ; iii) Pd/C xylene.

The two diastereomeric methyl esters homologous of 6a have been obtained by Danieli et al.[6] from the amido-ester homologous of 6a. Attempts to transform 5 into 6 following the literature procedure reported by these authors, using neat triethyl orthoformate and ammonium chloride, resulted in a poor yield of 6.

Alternatively we performed the preparation of quinazolino-carbolines 6 by reacting 5 with an excess of triethyl orthoformate in refluxing toluene in the presence of p-toluenesulfonic acid as catalyst (≃ 70% yield). Each quinazolinocarboline 6a and 6b was found to be a diastereomeric mixture of trans and cis compounds in the ratio of 9:1 (determined by ^1H NMR) and was used as such in the next step since the isolation of these isomers was not necessary for our further work.

Dehydrogenation of compound 6a with 10% palladium on activated carbon in refluxing xylene gave 1,4-benzodiazepine 2a (42%) and a by-product 8a (10%) (Scheme 2). In order to make the reaction faster, 30% palladium on activated carbon was reacted with 6a. As expected the transformation of 6a indeed occurred more rapidly but the quantity of undesired product 8a (16%) was increased whereas the amount of 2a (31%) decreased. It was checked that 8a was not formed from 2a since this compound remained unchanged after a prolonged heating in the hydrogen donor solvent cyclohexene, in the presence of palladium on activated carbon.

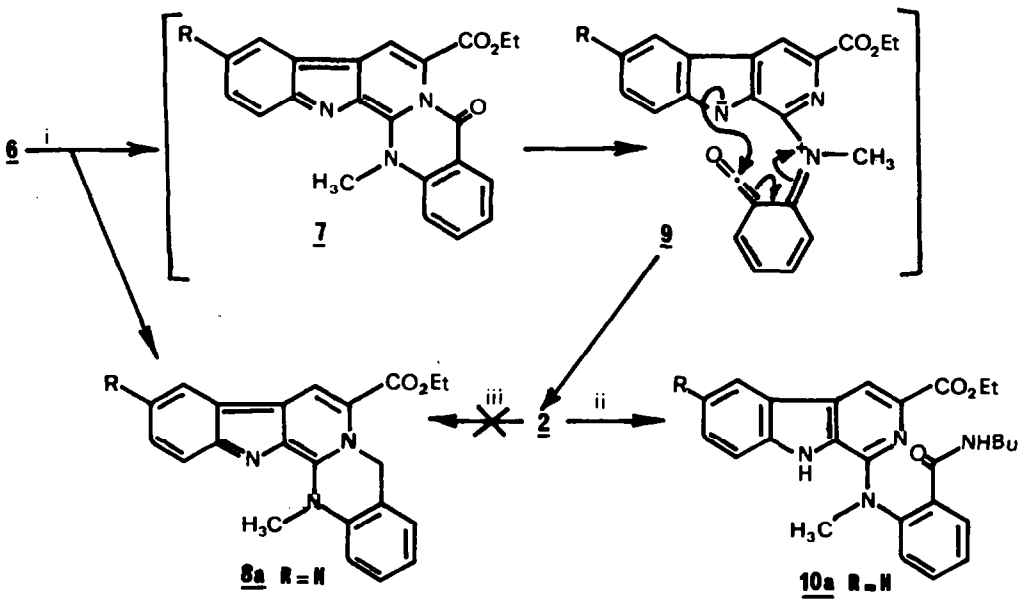
The conversion of methoxy quinazolino-carboline 6b to 1,4-benzodiazepine 2b was achieved using 10% or 30% palladium on activated carbon (71% and 62% yield respectively) ; no product analogous to 8a was detected (the remainder consisting of polymeric material).

The structure assignments of compounds 2 are based on their spectral data UV (2a λ_{max} 236, 266, 292, 300, 335, N-acylindole[7]) IR (2a 1730 ester, 1710 and 1680 lactam) and NMR. The ^1H NMR spectrum of each compound 2 exhibited a doublet (J = 9 Hz) at 8.80 ppm for 2a and 8.70 for 2b.* These low field signals were unambiguously attributed to the proton H-12 by irradiation with spin decoupling which allowed identification of all the aromatic protons. The observed downfield chemical shift for proton H-12 is certainly due to its location in the anisotropy zone of the carbonyl adjacent to the indole nitrogen.

* Danieli et al.[6] have also observed in the ^1H NMR spectrum of 3 a low field signal which they have assigned to the H-12 proton without any additional proof.

Transformation of 6 into 2 could take place through the intermediacy of quinazolino-carboline 7a which on participation of the N-methyl nitrogen lone pair of electrons could lead to an unstable ketene-imine 9. This ketene-imine then undergoes nucleophilic attack by the indole nitrogen to give 2 (Scheme 2).

It has been reported[8,9] that during the dehydrogenation of hydroaromatic compounds catalyzed by palladium on activated carbon, hydrogen abstracted from one part of the molecule may be used intramolecularly for the hydrogenation of another part of the molecule (or either be transferred intermolecularly[10]). By product 8a may well be formed from 6a by such an internal dehydrogenation-hydrogenation process ; the structure proposed for 8a is in agreement with its spectral characteristics.



Scheme 2. Reagents : i) Pd/C ; ii) $nBuNH_2$ dioxane ; iii) Pd/C cyclohexene.

The proposed reaction scheme is in accordance with the fact that 2b is the only product isolated from 6b ; the electrodonating methoxy group para to the indole nitrogen will increase its nucleophilicity in 7b compared to 7a. Therefore it is logical that the transmidation reaction occurs more rapidly than the amide reduction.

The 1,4-benzodiazepines 2 are quite stable compounds, nevertheless the N-acylindole bond may be easily cleaved, thus n-butylamine reacted with 2a to afford n-butylbenzamide derivative 10a.

To our knowledge, the formation of 2 from 6 constitutes the first example of a direct transformation of a quinazolinotetrahydro-β-carboline into a rearranged 1,4-benzodiazepine and β-carboline derivative ; this transformation must be due to the presence of the 7-carbethoxy group in compounds 6. The synthesis described should provide a general route to 2 analogues bearing substituents either on the β-carboline or on the phenyl nucleus. The pharmacological properties of the compounds that have been prepared are under current evaluation.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in chloroform on a Perkin-Elmer 297 spectrometer. UV spectra were determined in methanol on a Perkin-Elmer Lambda 5 instrument. NRM spectra were obtained in deuterochloroform on Brucker 200-MHz or Brucker 400-MHz instruments ; chemical shifts are reported as δ values using TMS as internal standard. Mass spectra were recorded using a AEI-MS-50 spectrometer. Thin layer chromatography was performed on Merck 60 silica gel

plates with fluorescent indicator using methylene chloride-methanol (98:2 or 95:5) as the eluant. Merck silica gel 60 (70-230 mesh or 230-400 mesh) was used for column chromatography.

Ethyl N-(o-N-methylaminobenzoyl)-DL-tryptophane 5a.

A solution of DL-tryptophane ethyl ester hydrochloride (5g, 18.6 mmol) and N-methylisatoic anhydride (3.3. g, 18.6 mmol) in pyridine (25 mL) was refluxed under nitrogen for 5.5 h. After evaporation of pyridine under vacuum, water was added to the oily residue which was triturated and then changed into a light beige powder. Crystallization from cyclohexane-ethyl acetate afforded 5a 6.6.g (97 %) as white crystals. F 164° ; IR 3475, 1730, 1640 cm^{-1} ; MS m/z 365(M^+), 215(M^+-$HNCOC_6H_4NHCH_3$) ; ^1H NMR δ 1.23 (t, J = 7 Hz, 3H, $C\underline{H}_3CH_2$), 2.84 (s, 3H, CH_3N), 3.42 (d, J = 5.5. Hz, 2H, $C\underline{H}_2$-CH), 4.18 (q, J = 7 Hz,2H,$C\underline{H}_2CH_3$), 5.05 (q, J = 5.5 Hz 1H, CH), 6.42-6.72 (m, 3H, Ar-H), 7-7.65 (m, 6H, ArH), 8.15 (br s, 1H, NH indole). Found : C 69.17, H 6.44, N 11.32 ; calcd. for $C_{21}H_{23}N_3O_3$: C 69.02, H 6.34, N 11.50.

Ethyl 5-methoxy-N-(o-N-methylaminobenzoyl)-DL-tryptophane 5b.

5-Methoxy-Dl-tryptophane was esterified following Boissonnas method[11] to give the corresponding ethyl ester hydrochloride 4b. The procedure given for 5a was used. 5-Methoxy-DL-tryptophane ethyl ester hydrochloride 4b (1.45 g, 4.85 mmol) was reacted with N-methylisatoic anhydride (860 mg, 4.85 mmol) and afforded 1.69 g (88 %) of amido-ester 5b. F 132° (cyclohexane-ethyl acetate) ; MS m/z : 395(M^+), 245(M^+-$HNCOC_6H_4NHCH_3$) ; IR 3475, 1730, 1640 cm^{-1} ; ^1H NMR : δ 1.20 (t, J = 7.5 Hz, 3H, $C\underline{H}_3CH_2$), 2.80 (s, 3H, CH_3N), 3.38 (d, J = 5.5. Hz, 2H, $C\underline{H}_2$CH), 3.62 (s, 3H, CH_3O), 4.17 (q, J = 7.5 Hz, CH_2CH_3), 5.04 (q, J = 5.5 Hz, 1H, CH), 6.50-7.33 (m, 7H, ArH), 8.00 (br s, NH indole). Found C 66.98 H 6.23 N 10.53 ; calcd. for $C_{22}H_{25}N_3O_4$: C 66.82 H 6.37 N 10.63.

7-Carbethoxy-14-methyl-8,13,13b,14-tetrahydro-indolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one 6a.

A solution of amido-ester 5a (1.15 g, 3 mmol), triethyl orthoformate (2.22 g, 15 mmol) and p-toluenesulfonic acid monohydrate (30 mg) in toluene (52 mL) was refluxed under nitrogen. After 5.5 h, all the starting material disappeared as checked by thin layer chromatography. The toluene and excess triethyl orthoformate were removed under vacuum, the crude residue was dissolved in methylene chloride and the solution washed with saturated aqueous hydrogen carbonate then dried over magnesium sulfate. After evaporation of the solvent the oily residue was purified by fast column chromatography with methylene chloride as the eluant and gave 740 mg (66%) of 6a as a white foam consisting of a trans and cis diastereomeric mixture. IR 3470, 1740, 1710, 1650 cm^{-1} ; MS m/z 375(M^+), 346(M^+-Et), 302(M^+-CO_2Et) ; ^1H NMR : δ 1.10 and 1.21 (2t, 3H, J = 7 Hz, $C\underline{H}_3CH_2$), 2.44 and 2.91 (2s, 3H, CH_3N), 3.17 (dd, J = 16, 6 Hz, H-8α), 3.55 (d, J = 16 Hz, H-8β), 4.03-4.21 (m, 2H, $C\underline{H}_2CH_3$), 5.73 and 5.20 (2d, J = 6 Hz, H-7), 6.22 (s, 1H, H-13b), 7.15-7.62 (m, 7H, ArH), 8.15 (dd, J = 8, 2Hz, 1H, ArH), 8.37 (br s, 1H indole NH) ; the signals at δ 1.10, 2.44 and 5.73 ppm were assigned to trans-6a[6] and the signals at δ 1.21, 2.91 and 5.20 ppm assigned to cis-6a and integration showed a 9:1 mixture of the two diastereomers. Found : C 69.88, H 5.65, N 10.97 ; calcd. for $C_{22}H_{21}N_3O_3$: C 70.38, H 5.64, N 11.20.

7-Carbethoxy-10-methoxy-14-methyl-8,13,13b,14-tetrahydro-indolo[2',3':3,4]pyrido[2,1-b]7H-quinazolin- one-5 6b.

This compound was prepared according to the procedure described for the preparation of 6a. Amido-ester 5b (1.58 g, 4 mmol) and triethyl orthoformate (2.96 g, 20 mmol) in the presence of p-toluenesulfonic acid monohydrate (50 mg) gave 1.12 g (69%) of 6b as an ivory white foam. SM m/z : 405(M^+), 332(M^+-CO_2Et) ; IR 3470, 1730, 1710, 1650 cm^{-1} ; ^1H NMR : δ 1.12 and 1.23 (2t, J = 7 Hz, 3H, $C\underline{H}_3CH_2$), 2.43 and 2.95 (2s, 3H, CH_3N), 3.17 (dd, J = 16, 6 Hz, H-8α), 3.51 (d, J = 16 Hz, H-8β), 3.88 (s, 3H, CH_3O), 4.05-4.17 (m, 2H, $C\underline{H}_2CH_3$), 5.70 et 5.18 (2d, J = 6 Hz, H-7), 6.19 (s, 1H, H-13b), 6.89 (dd, J = 9, 2 Hz, 1H, H-11), 7.01 (d, J = 2 Hz, 1H, H-9), 7.14-7.31 (m, 3H, 3ArH), 7.51 (dt, J = 8, 2 Hz, 1H, ArH), 8.14 (dd, J = 8, 2 Hz, 1H, ArH), 8.24 (br s, 1H, indole NH) ; the

signals at δ 1.12, 2.43 and 5.70 ppm were assigned to trans 6b and the signals at δ 1.23, 2.95 and 5.18 assigned to cis 6b and integration showed a 9:1 mixture of the two isomers. Found : C 67.89, H 5.61, N 10.53 ; calcd for $C_{23}H_{23}N_3O_4$: C 68.13, H 5.72, N 10.37.

6-Aza-7-carbethoxy-5-methyl-14-one 14H-(1,4)-benzodiazepine [4,3,2-1 m] carbazole 2a.

A solution of quinazolino-carboline 6a (1.116g, 2.97 mmol) in dry xylene (30 mL) was stirred with 10% palladium on activated carbon (553 mg) and refluxed under nitrogen. After 118 h, the catalyst was filtered off and washed with boiling toluene. After removal of the solvents under vacuum the solid residue was purified by column chromatography using methylene chloride-hexane 88:12 as the eluant affording 427 mg (42%) of 2a as pale yellow crystals. Then 96 mg (10%) of 8a and 100 mg of the starting material eluted. 2a was recrystallized from carbon tetrachloride. F 207° ; MS m/z 371(M^+), 297(M^+-CO_2Et-H) ; IR 1730, 1710, 1680 cm^{-1} ; UV 236, 266, 292, 300, 335 (qualitative); ^1H NMR(400 MHz) 1.49 (t, J = 7.5 Hz, 3H, $C\underline{H}_3CH_2$), 3.61 (s, 3H, CH_3N), 4.51 (q, J = 7.5 Hz, 2H, CH_2), 7.14 (t, $J_2^3 = J_1^2 = 7.5$ Hz, 1H, H-2), 7.22 (d, $J_3^4 = 8$ Hz, 1H, H-4), 7.50 (t, $J_{10}^{11} = J_9^{10} = 8$ Hz, 1 H, H-10), 7.55 (dt, $J_3^4 = J_2^3 = 7.5$, $J_1^3 = 2$ Hz, 1H, H-3), 7.67 (dt, $J_{10}^{11} = J_{11}^{12} = 8$, $J_9^{11} = 1.5$ Hz, 1H, H-11), 8.01 (dd, $J_1^2 = 7.5$, $J_1^3 = 2$ Hz, 1H, H-1), 8.06 (dd, $J_9^{10} = 8$ Hz, $J_9^{11} = 1.5$ Hz, 1H, H-9), 8.34 (s, 1H, H-8), 8.80 (d, $J_{11}^{12} = 8$ Hz, 1H, H-12). Found : C 70.82, H 4.49, N 11.27 ; calcd. for $C_{22}H_{17}N_3O_3$: C 71.15, H 4.62, N 11.32.

7-Carbethoxy-14-methyl-indolo[2',3':3,4]pyrido[2,1-b] 7H-quinazoline 8a.

Compound 8a isolated as described above was crystallized from cyclohexane-ethyl acetate. F 203-204°; MS m/z 357(M^+), 283(M^+-CO_2Et-H) ; IR 1710, 1620 cm^{-1} ; UV 242(23700), 282(10900), 346(8100) ; ^1H NMR 1.48 (t, J = 7 Hz, 3H, $C\underline{H}_3CH_2$), 3.69 (s, 3H, CH_3N), 4.50 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 5.47 (s, 2H, CH_2N), 7.07 (dt, J = 7, 2.5 Hz, H-2), 7.25-7.43 (m, 4H, ArH), 7.59-7.61 (m, 2H, 2 ArH), 8.11 (d, J= 8 Hz, 1H, ArH), 8.44 (s, 1H, H-8) ; ^{13}C NMR : 166.4 (CO), 48.0 (C-5). Found : C 73.61 H 5.27 N 11.58 ; calcd. for $C_{22}H_{19}N_3O_2$: C 73.93, H 5.36, N 11.76.

Dehydrogenation of 6a with 30% palladium on carbon.

The same procedure as described above was followed : a solution of quinazolinocarboline 6a (164 mg, 0.43 mmol) in xylene (5 mL) was refluxed with 30% palladium on activated carbon (96 mg) and after 27h heating gave 38 mg (31%) of 2a and 19 mg (16%) of 8a. Then 41 mg of the starting compound 6a eluted, the remaining material consisting of uncompletely dehydrogenated compounds and polymers.

Control experiment.

A solution of 2a (40 mg) in cyclohexene (4 mL) was stirred and boiled under reflux for 24 h in the presence of 10% palladium on carbon (20 mg). After filtration of the catalyst and removal of solvents, compound 2a was recovered unchanged.

Ethyl 1-N-methyl N-(o-N-n-butylamidophenyl)-amino-β-carboline 3-carboxylate 10a.

A solution of benzodiazepine 2a (32 mg, 0.086 mmol) in 1,4-dioxane (7 mL) and n-butylamine (0.3 mL) was refluxed under nitrogen for 6 h. After evaporation of the solvents under vacuum the oily residue was purified by column chromatography with methylene chloride - methanol (95:5) as the eluant. 26 mg of 10a were isolated as colorless crystals. F 206° ; MS m/z : 444(M^+), 371(M^+-CO_2Et), 344 (M^+-CONHBu) ; IR 3450, 1710, 1650 cm^{-1} ; UV 235(29100); 258(23700), 332(10000) ; ^1H NMR : δ 0.860 (t, J = 7 Hz, 3H, $C\underline{H}_3(CH_2)_3$, 1.31 (q, J = 7 Hz, 2H, $(CH_2)_2$ $C\underline{H}_2CH_3$), 1.49 (t, J = 7 Hz et m, 5H, $C\underline{H}_3CH_2$ et $CH_2C\underline{H}_2C_2H_5$), 3.43 (q, J = 7 Hz, 2H, $C\underline{H}_2NH$), 3.51 (s, 3H, CH_3N), 4.51 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 7.08 (dd, J = 7.5, 1 Hz, 1H, ArH), 7.21-7.47 (m, 5H, ArH), 7.59 (br s, NHBu), 8.03-8.07 (m, 2H, ArH), 8.55 (s, 1H, H-8), 8.71 (br s, NH indole). Found : C 69.70 H 6.44 N 12.55 ; calcd. for $C_{26}H_{28}N_4O_3$: C 70.25, H 6.35, N 12.60.

6-Aza-7-carbethoxy-10-methoxy-5 methyl 14-one 14H-(1,4)-benzodiazepine [4, 3, 2-1 m] carbazole 2b.

A solution of quinazolino-carboline 6b (200 mg, 0.49 mmol) in dry xylene (6 mL) was stirred with 30%

palladium on activated carbon (80 mg) and refluxed under nitrogen. After 46 h all the starting material disappeared as checked by thin layer chromatography. The catalyst was filtered from the hot mixture, washed thoroughly with boiling toluene then the solvents were evaporated under vacuum. The crude yellow-brown powder obtained was crystallized from ethyl acetate and afforded 122 mg (62%) of 2b. F 220° ; MS = m/z 401(M^+), 327(M^+-CO_2Et-H) ; IR 1720, 1670 cm^{-1} ; UV 239, 264, 275, 302, 345 (qualitative) ; ^{1}H NMR(400 MHz) : 1.49 (t, J = 7.5 Hz, 3H, CH_3CH_2), 3.60 (s, 3H, CH_3N), 3.95 (s, 3H, CH_3O), 4.50 (q, J = 7.5 Hz, 2H, CH_2), 7.14 (t, J_1^2 = 8 Hz, 1H, H-2), 7.22 (d, J_3^4 = 8 Hz, 1H, H-4), 7.26 (dd, J_{11}^{12} = 9, J_9^{11} = 2.5 Hz, 1H, H-11), 7.48 (d, J_9^{11} = 2.5 Hz, 1H, H-9), 7.55 (t, $J_2^3 = J_3^4$ = 8 Hz, 1H, H-3), 8.03 (d, J_1^2 = 8 Hz, 1H H-1), 8.30 (s, 1H, H-8), 8.70 (d, J_{11}^{12} = 9 Hz, 1H, H-12).
A solution of 6b (95 mg, 0.23 mmol) in dry xylene (4 mL) was stirred with 10% palladium on activated carbon (75 mg) and refluxed for 71 h, then the reaction mixture treated as above gave 67 mg (71%) of 2b.

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