SYNTHESIS OF A NEW BENZOCYCLEHEPTAQUINOLINE SYSTEM

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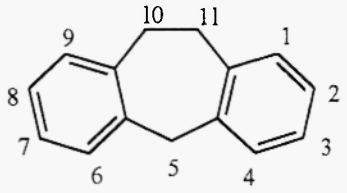
Abstract

The new heterocyclic benzocycloheptaquinoline **8a** was synthetized with 44% yield, starting with dibenzosuberone **3** in five steps. The linear isomer was totaly identified by IR, NMR ^{1}H and ^{13}C and MS, spectroscopic methods.

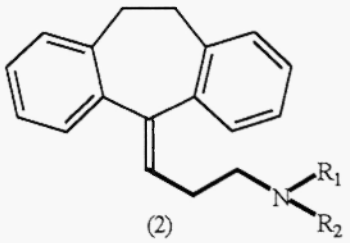
Keywords: dibenzocycleheptane, dibenzosuberone, benzocycleheptaquinoline, antidepressants.

INTRODUCTION

The dibenzocycleheptane **1** have been studied because of its biological properties, particulary in the Central Nervous System studies (CNS). The amitriptyline **2a** and the monomethylated analogous nortriptyline **2b,** for exemple, show activity in those disturbance's treatment.[1,2]



(1)



(2)

2a = R_1=Me R_2=Me

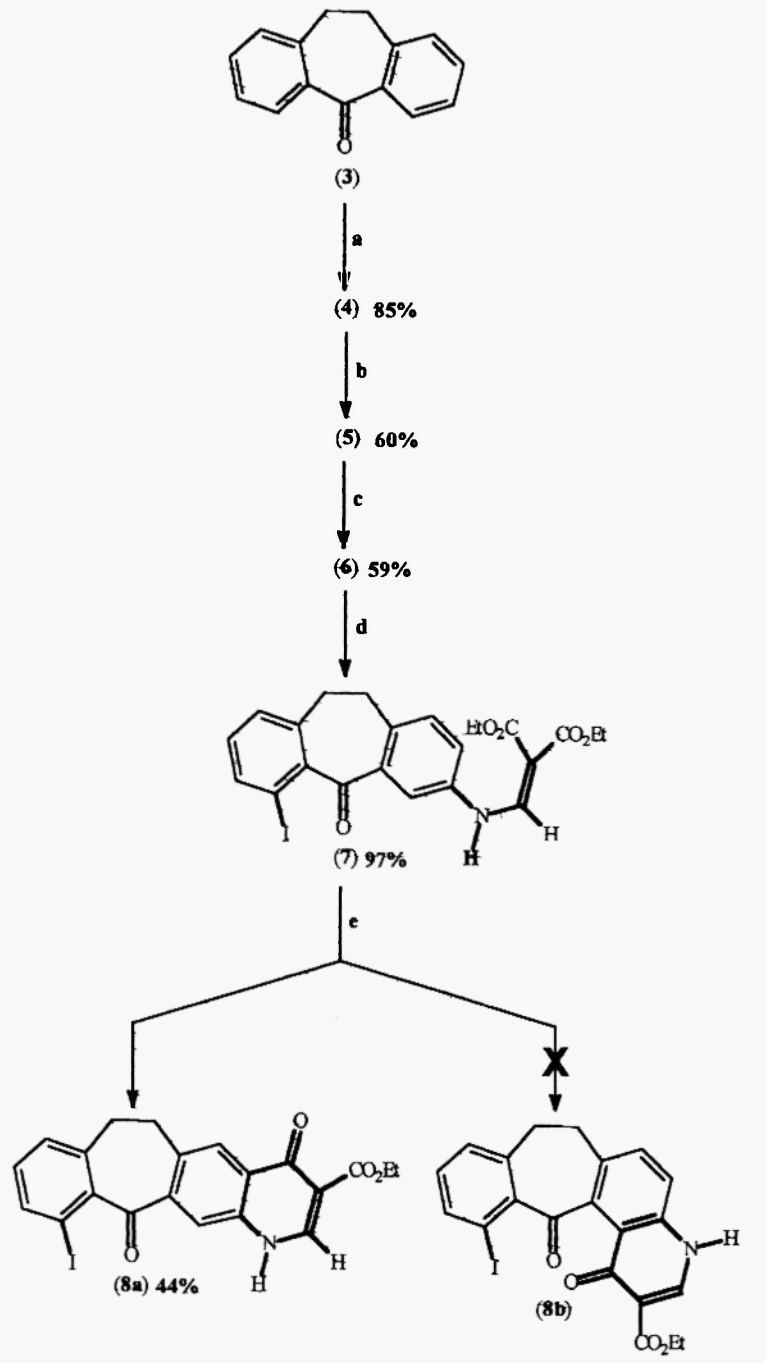
2b = R_1=Me R_2=H

In this work, continuing our researches in antidepressants[3], will be presented the synthesis of new heterocyclic having the pyridine attached to the basic sistem dibenzocycloheptane **1.**

RESULTS AND DISCUSSION

The synthesis of new heterocyclic system **8a** was obtained starting with the reaction of dibenzosuberone **3** with thalium trifluoracetate and potassium iodide, leading to 4-iodo-dibenzosuberone **4** with 85% yield[4]. The compound **4** was then submitted to nitration, reduction[5], condensation and thermical ciclization, leading to the tetracycle system **8a** , Scheme **1.**

SCHEME 1



a) TTFA / ATF / KI ; b) HNO_3 / H_2SO_4 / 0 °C ; c) Fe / HCl / NH_4Cl / CH_3OH / REFLUX 8 h

d) DEEMM / C_2H_5OH / 3h / REFLUX ; e) DOWTHERM / 250 °C / 15'

The last step, ciclization with Dowtherm, can lead to the linear **8a** or **8b** isomer. Spectral data shows with the final product in agreement with the structure 9-carboethoxy-11-iodo-4,12-dioxo-1,4,6,7-tetrahydro-12H-benzo [1',2': 6,7] cyclohepta[3,2-g]quinoline **8a** and not with the angular product **8b**.

The position 2 and 4 in the structure 7 are actived by the nitrogen atom in the position 3, by resonance efect (Fig. **1a**). The ciclization in the position 2 is minimized by the carbonyl group, wich desatives this position.

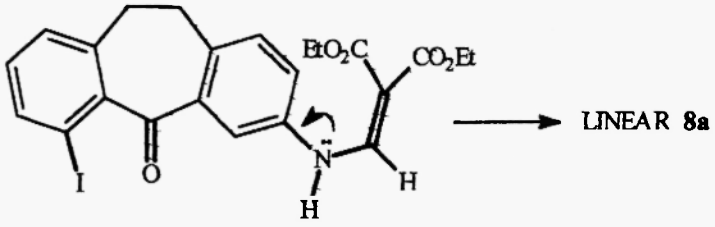


Fig. **1a**

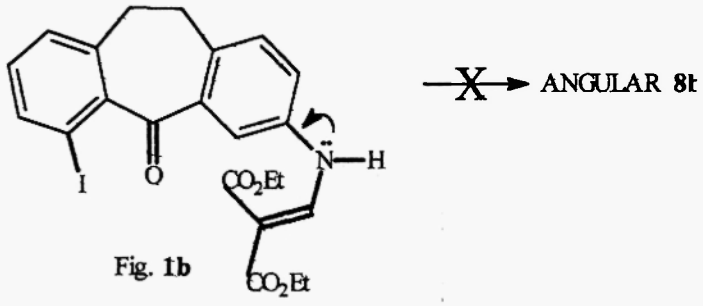


Fig. **1b**

In the Fig. **1b**, the repulsive steric efect of the carbonyl groups, also contribuited negatively for the ciclization.

The structure **8a** was identified by NMR ^1H, that shows only one triplete and one quartete signal for ethyl group, when compared with the precursor 7. The aromatic region shows two singlets corresponding to the protons in the positions 6 and 11, in agreement with the **8a** linear isomer. The coupling constant relative to the protons in the positions 10 and 11, in the angulated isomer **8b**, is not present.

The EIMS 70 eV, shows the molecular ion $[M]^{+\cdot}$ 473 as the base peak. Other significant ions were observed involving lost of C_2H_4 or CO (**28**); HCN (**27**); C_2H_2 (**26**); C_2H_5 (**29**); C_2H_5O. or C_2H_5OH (**45/46**) and CO_2 (**44**) in agreement with the structure.

CONCLUSIONS

All the five stages of the sinthetic rout of the heterocyclic tetracycle **8a**, shows a good yields. This new compound could be an alternative for the treatment of disturbance of the central nervous system.

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EXPERIMENTAL

Melting points, were determined using a Fisher-Jonhs melting point appararus and are uncorrected. The **IR** spectra were recorded on a Perkin-Elmer 1420 spectrometer in potassiun bromide pellets . The **^{1}H** and **^{13}C NMR** spectra were recorded on a 300 MHz, Varian Unity Spectrometer, with TMS as an internal standard, coupling constants are given in Hz. Low-resolution **EI** mass spectra were recorded on a MAT 711^{A} Finningan Instruments, at 70 eV, with source at 200 ^{0}C and the accelerating voltage of 8 KV. The samples were heated and introduced directly into de source area. Analytical thin-layer chomatography (tlc) was performed on silica gel plates, 60F-254 (MERCK, 0,25mm).

3-nitro-6-iodo-10,11-dihydro-5H-dibenzo[a,d]cycloeptane-5-one (**5**).

8 mL of H_2SO_4 conc. were cold at 0 ^{0}C and stirred; after temperature's stabilization, 2,50 g of ketone iodine **4** was added in small quantity. Finished the addition of ketone **4** was added slowly an acid mixture (0,75 mL of HNO_3 conc. and 0,75 mL of H_2SO_4 conc. at 0 ^{0}C), keeping the temperature between 0^{0}C and 10 ^{0}C. After the addition, the solution was left at room temperature for 3 hours; after this time, the reational midle was changed to a cold saturate solution of NaCl, obtaining immediately precipitation of yellow solid. The solid was filtered under low pressure and was washed several times with saturated solution of NaCl until the total remotion of acidity. The dry solid was submited the column chromatography with appropriate solvent, obtain 1,40 g of yellow solid, 60% yield, m.p. 210-11 ^{0}C. **IR.** (KBr cm^{-1}) 3060, 1675 (C=O), 1605, 1575, 1555, 1520, 1475, 1440, 1340, 1310, 1280, 1260, 1250, 1245, 1215, 1185, 1150, 1130, 1110, 1085, 970, 950, 910, 860, 840, 805, 790, 775, 730, 710, 645, 630. **EIMS** (70eV) m/z(%), $[M]^{+\cdot}$ 379(100), 362(7), 349(8), 334(74), 306(10), 281(2), 264(3), 252(10), 235(5), 207(30), 194(6), 178(82), 165(15), 151(25), 140(7), 127(5), 102(6), 89(35), 76(23), 65(20). **^{1}H NMR** δ($CDCl_3$, ppm), 3.13-3.17(m, 2H, $CH_2\phi$), 3.33-3.37(m, 2H,$CH_2\phi$), 7.08(t, J=7.5 Hz, 1H), 7.23(dd, J=7.5 and 1.2 Hz, 1H), 7.38(d, J=8.7 Hz, 1H), 7.81(dd, J=7.8 and 0.9 Hz, 1H), 8.26 (dd, J=8.4 Hz, 1H), 8.74(d, J= 2.4 Hz, 1H). **^{13}C NMR** δ($CDCl_3$, ppm) 32.22, 34.69, 92.20, 125.03, 125.95, 127.50, 131.74, 132.02, 138.58, 138.68, 139.36, 144.37, 146.52, 147.35, 197.35.

3-amino-6-iodo-10,11-dihydro-5H-dibenzo[a,d]cycloeptane-5-one (**6**)[4].

A solution of 2,40 g of nitro compound **5** and methanol 100 mL, was stirred and refluxed. Then was slowly added a solution of NH_4Cl (2,80 g NH_4Cl and 50 mL H_2O). In it finished addition the solution it was refluxed again. The next step was added seven drops of HCl conc. and 1,50 g of the Fe^{0} in a small quantity over the hot solution. Finished the addition,

the resultant solution was refluxed for 8 h. When the time is over, the hot solution was filtered and the residue was washed three times with 30 mL of methanol. The organic solution was concentrated and submited to a column chromatography with appropriate solvent, obtained 1,23 g, yield 56% of yellow-green solid of m.p. 218 °C. **IR.** (KBr cm^{-1}) 3460(NH), 3360(NH), 3075, 3045, 3015, 2970, 2880, 1660(C=O),1625, 1610, 1580, 1555, 1500, 1440, 1430, 1420, 1360, 1325, 1305, 1260, 1250, 1215, 1190, 1180, 1150, 1110, 1030, 980, 945, 920, 860, 845, 820, 800, 790, 780, 750, 715, 705, 645. **EIMS** (70eV) m/z(%), $[M]^{+\cdot}$ 349(3), 223(100), 208(15), 194(75), 180(15), 165(17), 152(7), 139(4), 111(2), 104(4), 97(12), 90(6), 77(6), 65(4). **^{1}H NMR** δ($CDCl_3$, ppm) 3.07-3.19 (m, 6H), 6.79(dd, J= 8.1 and 1.2 Hz, 1H), 6.07(d , J= 8.4 Hz, 1H), 7.00(t, J= 7.8 Hz, 1H), 7.17 (s, 1H), 7.18 (dd, 8.4 and 1.2 Hz, 1H). **^{13}C NMR** δ($CDCl_3$, ppm), 33.56, 34.05, 92.43, 115.49, 120.03, 127.52, 130.78, 131.58, 131.67 138.54, 138.74, 140.50, 144.98, 145.84, 200.16.

3-amineacrilate-6-iodo-10,11dihydro-5H-dibenzo[a,d]cycloeptane-5-one (7).

0,32 g of amine **6**, 0,20 g of diethyl ethoxymethylenemalonate and 10 mL of ethanol were refluxed for 3 h. Then the solution was concentrated under low pressure, obtaining a yellow solid. This solid was recristalized in the mixture EtOH : $CHCl_3$ (3:1), obtaining 0,56 g, 97 % yield of the yellow solid, m.p. 170-1 °C. **IR.** (KBr cm^{-1}) 2980, 2930, 2900, 1685(C=O), 1660(C–O), 1640(C=O), 1590, 1500, 1480, 1435, 1405, 1380, 1340, 1320, 1300, 1250, 1090, 1030, 990, 980, 920, 910, 880, 850, 790, 770. **EIMS** (70eV) m/z(%), $[M]^{+\cdot}$ 519(100), 473(60), 444(3), 428(10), 417(25), 393(50), 373(13), 347(25), 333(3), 302(8), 291(2), 274(17), 257(2), 247(15), 232(5), 217(15), 205(7), 189(12) 178(20), 165(7), 152(4), 130(2), 89(4), 77(2). **^{1}H NMR** δ($CDCl_3$, ppm) 1.33(t, J=7.2 Hz, CH_3), 1.39(t, 7.2 Hz, CH_3), 3.07-3.11(m, 2H, $CH_2\phi$), 3.18-3.22(m, 2H, $CH_2\phi$), 4.26(q, J= 7.2 Hz, 2H, CH_2CH_3), 4.32(q, J=7.2 Hz, 2H, CH_2CH_3) 7.04(t, J=7.8 Hz, 1H), 7.62(d, J=1.8 Hz, 1H), 7.78(dd, J= 7,8 and 1.2 Hz, 1H), 7.18-7,22(m, 3H), 8.52(d, J= 13,5 Hz, 1H), 11.09(d, J=13,5 Hz, 1H, NH). **^{13}C NMR** δ($CDCl_3$, ppm) 14.14, 14.28, 32.76, 33.94, 60.08, 60.34, 92.08, 94.11, 117.74, 120.60, 127.36, 131.58, 131.97, 136.74, 137.79, 138.39, 138.89,139.79, 144.96, 151.38, 165.39, 168.32, 198.88.

3-carboetoxi-11-iodo-4,12-dioxo-1,4,6,7-tetrahydro-12H-benzo[1',2':6,7]ciclohepta[3,2-g]quinoline (**8a**).

5 mL of Dowterm was hot until 250 °C. In this temperature was added 0,50 g of acrilate **7** and the solution is kept at 250 °C for 15 min. After this time, the reactional middle was left colding at room temperature. A precipitation occurs and the solid was filtered, washed with petroleum ether and dichlormethane (twice), dissolved in dimethylformamide and precipited in water. The white solid was filtered and washed with ethanol then dry, obtaining 0,20 g of white solid 44 % yield and m.p. over 250 ° C. **IR.** (KBr cm^{-1}) 3440 (NH), 3080, 3060, 2980, 1700(C=O), 1630(C=O, 1605, 1580, 1520, 1470, 1440, 1420, 1380, 1350, 1310, 1285, 1255, 1200, 1160, 1135, 1110, 1085, 1065, 1020, 960, 940, 930, 840, 800, 775, 755, 730, 715, 690, 640, 615. **EIMS** (70eV) m/z(%), $[M]^{+\cdot}$ 473(100), 454(3), 427(77), 414(7), 401(95), 386(2), 372(15), 347(8), 332(3), 300(24), 274(35), 258(3), 246(30), 232(15), 217(23), 189(30), 177(12), 156(10), 139(4), 128(13), 116(7), 94(7), 75(4). **^{1}H NMR** δ(DMSO, ppm) 1.39(t, J= 7.2 Hz, CH_3), 3.19-3.25 (m, 4H, $CH_2\Phi$),

4.33(q, J= 7,2 Hz, 2H, CH_2CH_3), 7.31(t, J= 7.8 Hz, 1H), 7.53(d, J=7.8 Hz, 1H),7.93(d, 7.8 Hz, 1H), 8.11(s, 1H), 8.16(s, 1H), 8.73(s, 1H). **^{13}C NMR** δ(CF_3CO_2H, $CDCl_3$, ppm) 13.30, 31.84, 34.28, 65.09, 91.47, 105.53, 121.74, 122.10, 127.00, 128.05, 133.33, 137.49, 139.15, 139.74, 142.20, 143.10, 145.76, 146.58, 167.66, 172.82, 200.51.

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