ANALOGUES OF ANTIDEPRESSANTS - SYNTHESIS OF NEW 4-AMINE DERIVATIVES OF 10,11-DIHYDRO-5H-DIBENZO[a,d]CYCLOHEPTANE

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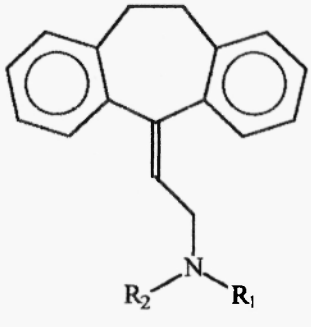
Abstract

In this paper the synthesis of six new 10,11-dihydro-5H-dibenzo[a,d]cycloheptane derivatives, analogues of antidepressants agents are reported. The preparation involved the initial introduction of the iodine atom in the positon 4 of the dibenzosuberone 3 to give the compound 4, which was then treated with different nucleophilic reagents, to produce the compounds 5a to 5f.

Introduction

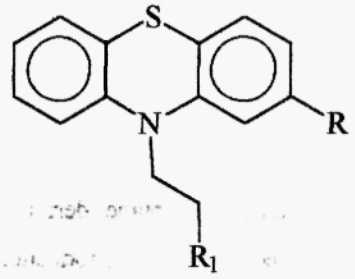
Two benzenoid rings fused to a six or seven membered ring, aromatic or not, and to an alkyl chain with terminal substituted nitrogens, are present in several drugs with activities in the central nervous system. Psycotropics agents include, antipsycotics, anxiolytcs, antidepressants and halucinogenic agents[1]. The 10,11-dihydro-5H-dibenzo[a,d]cycloheptane system exhibit several pharmacological activities. For example: 5-(3-dimethylamine-propilidene)-10,11-dihydro-5H dibenzo[a,d]cycloheptane **1a** and its monomethylated analog, nortripticine **1b**, exhibit antidepressant activity[2].



1

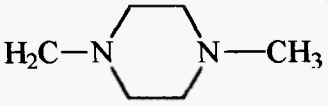
1a- $R_1 = R_2 = CH_3$
1b- $R_1 = CH_3$, $R_2 = H$

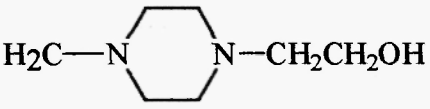
The antipsycotics agents can be divided into different classes: phenotiazinics derivatives, thioxantenics, butirophenones, diphenylbuthylamines and others[1]. Amplictyl **2a**[3], tementyl **2b**[4] and trilaflon **2c**[5] are phenotiazinics drugs commercial antipsycotics agents.



2

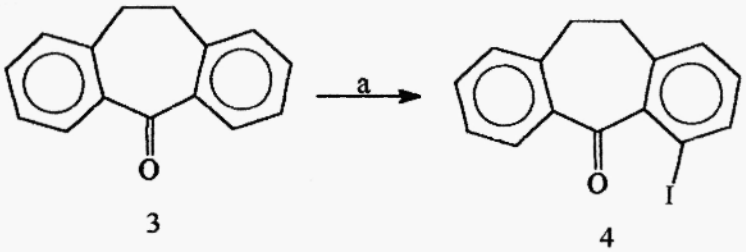
2a- R = Cl, $R_1 = CH_2N(CH_3)_2$

2b- R= Cl, R_1 = 

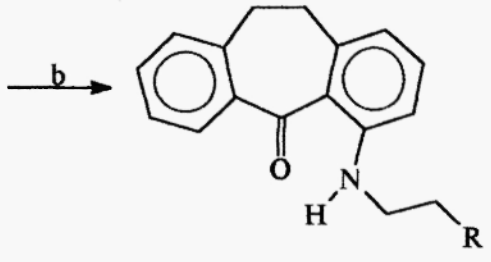
2c- R= Cl, R_1= 

Results and discussion

The first step in synthesis of dibenzocycloheptane derivatives is the introduction of the iodine atom in position 4 of the dibenzosuberone **3** to give compound **4**[6]. The iodineted compound was treated with six different nucleophilic reagents, to produce compounds **5a** to **5f** (Scheme 1).



3 4



5

5a, R= NH_2
5b, R= OH
5c, R= $CH_2N(C_2H_5)_2$
5d, R= $CH_2N(CH_3)_2$
5e, R= Ph
5f, R= $N(CH_3)_2$

Schcmc 1: a) TTFA/TFA/ KI b) RNH_2 / rcflux

When compared with know nervous sistem drugs, the main modifications were the terrminal groups with different electronic density and positions of this nucleophilic moyety.

The compounds **5a** to **5f**, were characterized by infrared, nmr, and mass spectrometry.

Experimental

Melting points, were determined using a Fisher-Johns melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1420 spectrometer in potassium 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 711A Finnigan instrument, at 70 eV with the source at 200 °C and the accelerating voltage of 8 KV. The samples were heated and introduced directly into the source area. Analytical thin-layer chromatography (tlc) was performed on silica gel plates, 60F-254 (MERCK, 0.25mm).

General procedure

A solution of the iodeneted ketone 4 and appropriated amine was stirred under reflux for several hours. The solution was cooled, chloroform added, and washed three times with water. The organic phase was dried with Na_2SO_4 and concentrated. Column chromatography of the residue on silica gel, afforded the product as a yellow oil.

4-amine(2-aminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-one (5a) was isolated with 51% yield. IR(KBr, cm^{-1}) 3500-3300(NH), 3060, 3020, 2920, 2880, 1620(C=O), 1600, 1480, 1450, 1300, 1150, 1090, 790, 760, 740. EIMS(70eV) *m/z*(%), $[M]^{+\cdot}$ 266(2), 247(8), 236(15), 221(44), 220(100), 208(18), 189(8), 178(18), 165(12), 91(8), 77(5). HR calc. 266.1419, found 266.1417. ^{1}H NMR δ($CDCl_3$, ppm) 2.95-3.29 (m, 8H), 6.46-6.48 (d, J= 7.5 Hz, 1H), 6.60-6.63 (d, J= 7.8 Hz, 1H), 7.15-7.40 (m, 4H), 7.72 (brs, 2H), 8.00-8.03 (dd, J= 7.8 Hz, 1H), ^{13}C NMR ($CDCl_3$, ppm)

34.5, 35.3, 40.5, 45.6, 109.6, 115.9, 121.6, 125.9, 128.7, 130.7, 131.4, 132.7, 139.4, 141.3, 142.9, 149.4, 197.3 (C=O).

4-amine-(2-hydroxyethyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-one (5b), was isolated with 79% yield. IR (KBr, cm^{-1}) 3500-3300(NH, OH), 3060, 2960, 2940, 1640(C=O), 1607, 1590, 1560, 1500, 1450, 1260, 1240, 1100, 1060, 930, 780. EIMS(70eV) *m/z*(%), $[M]^{+\cdot}$ 267(20), 249(3), 236(100), 221(3), 206(3), 193(3), 178(12), 91(10), 77(6). HR calc.267.1259, found. 267.1244. ^1H NMR δ($CDCl_3$, ppm) 2.37 (brs, 1H), 3.06-3.38 (m, 4H), 3.34-3.38 (t, J= 5.7 Hz, 2H), 3.82-3.80 (t, J= 5.7 Hz, 2H), 6.48-6.50 (d, J= 8.1 Hz, 1H), 6.62-6.65 (d, J= 8.4 Hz, 1H), 7.14-7.40 (m, 4H), 7.99-8.02 (dd, J= 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, ppm) 34.7, 35.3, 45.5, 60.8, 110.0, 116.4, 122.3, 126.0, 128.9, 130.9, 131.6, 132.8, 139.3, 141.5, 142.9, 149.2, 197.6 (C=O).

4-amine(3-N,N-diethylpropylamine)-10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-one (5c) was isolated with 53% yield. IR (filme cm^{-1}) 3400-3285(NH), 3080, 2960, 2920, 2800, 1630(C=O),1610, 1590, 1570, 1500, 1460, 1290, 1270, 1240, 1170, 1150, 1130, 1100, 1080, 920, 880, 810, 775, 740, 715, 690. EIMS (70eV) *m/z*(%), $[M]^{+\cdot}$ 336(15), 237(09), 220(23), 178(06), 110(13), 86(100), 72(07), 58(09). HR calc.336.2201; found 336.2201. ^1H NMR δ($CDCl_3$, ppm) 1.01-1.06 (t, J= 7.2 Hz, 6H), 1.77-1.87 (qui, J= 7.2 Hz, 2H), 2.51-2.59 (q, J= 7.2 Hz, 4H), 3.08-3.24 (m, 8H), 6.43-6.46 (dd, J= 7.5 Hz, 1H), 6.60-6.62 (dd, 7.5 Hz, 1H), 7.15-7.40 (m, 4H), 7.72 (brs, 1H), 7.96-7.99 (dd, J= 7.8 Hz). $^{13}CNMR$ ($CDCl_3$, ppm) 11.4, 26.3, 34.6, 35.5, 41.5, 46.6, 50.2, 109.6, 115.5, 121.2, 125.9, 128.6, 130.7, 131.3, 132.7, 139.7, 141.3, 142.9, 149.7, 197.1 (C=O).

4-amine(3-N,N-dimethylpropylamine)-10,11-dihydro-5H-dibenzo[a,d]cycloeptane-5-one (5d), was isolated with 55% yield. IR (film cm^{-1}) 3400-3260(NH), 3060, 2940, 2850, 2800, 2760, 1630(C=O), 1610, 1590, 1570, 1500, 1460, 1400, 1350, 1320,1290, 1270, 1240, 1170, 1150, 1100, 1080, 1030, 920, 880, 810, 770, 740, 729, 700. EIMS (70eV) *m/z*(%), $[M]^{+\cdot}$ 308(11), 250(13), 237(20), 220(53), 85(17), 83(12), 81(18), 73(12), 72(13), 71(12), 69(42), 58(100), 57(26), 55(26). HR. calc.308.1888; found 308.1888. ^1H NMR δ($CDCl_3$, ppm)1.78-1.88 (qui, J= 7.2 Hz,

2H), 2.25 (s, 6H), 2.37-2.42 (t, J= 7.2 Hz, 2H), 3.07-3.25 (m, 6H), 6.43-6.45 (d, J= 7.2 Hz, 1H), 6.60-6.62 (d, J= 7.8 Hz, 1H), 7.14-7.40 (m, 4H), 7.73 (brs, 1H), 7.97-8.00 (dd, J= 8.1 Hz, 1H). ^{13}CNMR ($CDCl_3$) 26.9, 34.7, 35.6, 41.6, 45.3, 57.3, 109.7, 115.7, 121.5, 126.0, 128.8, 130.8, 131.5, 132.9, 139.9, 141.4, 143.1, 149.7, 197.5 (C=O).

4-amino(2-phenylethyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-one (5e), was isolated with 44% yield. IR (film cm^{-1}) 3380-3250 (NH), 3060, 3020, 2940, 2920, 2860, 1630(C=O), 1590, 1570, 1500, 1460, 1400, 1350, 1320, 1290, 1270, 1240, 1190, 1150, 1100, 1070, 1030, 920, 890, 810, 780, 750, 720, 700. EIMS (70eV) *m/z*(%), $[M]^{+\cdot}$ 307(6), 237(18), 236(100), 178(4), 91(6). HR calc. 327.1623; found 327.1624. ^{1}H NMR δ($CDCl_3$, ppm) 2.93-2.98 (t, J= 7.2 Hz, 2H), 3.04-3.20 (m, 4H), 3.39-3.44 (t, J= 7.2 Hz, 2H), 6.45-6.47 (dd, J= 7.8 Hz, 1H), 6.61-6.64 (d, 8.4 Hz, 1H), 7.14-7.49 (m, 9H), 7.91-7.94 (dd, J= 7.8 Hz, 1H). ^{13}CNMR ($CDCl_3$) 34.6, 35.3, 35.5, 44.8, 109.7, 115.9, 121.7, 126.0, 126.2, 128.3, 128.6, 128.7, 130.8, 131.5, 132.8, 139.1, 139.8, 141.3, 143.0, 149.2, 197.5 (C=O).

4-amino(2-N,N-diethylethylamine)-10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-one(5f), was isolated with 44% yield. IR (film cm^{-1}) 3350 (NH), 3060, 2960, 2920, 2860, 2800, 1640 (C=O), 1610, 1590, 1570, 1500, 1460, 1420, 1380, 1360, 1350, 1320, 1290, 1260, 1240, 1200, 1170, 1150, 1140, 1100, 1070, 1000, 930, 900, 810, 780, 740, 720, 700. EIMS (70eV) *m/z*(%), $[M]^{+\cdot}$ 322 (5), 236(7), 178(4), 86(100), 58(3). HR. calc.322.2045; found. 322.2047. ^{1}H NMR δ($CDCl_3$, ppm) 1.05-1.10 (t, J= 7.2 Hz, 6H), 2.55-2.62 (q, J= 7.2 Hz, 2H), 2.69-2.73 (t, J= 6.9 Hz, 2H), 3.06-3.24 (m, 6H), 6.44-6.46 (d, J= 6.6 Hz, 1H), 6.57-6.60 (d, J= 8.1 Hz, 1H), 7.14-7.40 (m, 4H), 7.52 (brs, 1H), 7.97-8.00 (dd, J= 7.8 Hz, 1H) ^{13}C NMR ($CDCl_3$), 11.8, 34.8, 35.2, 41.1, 46.9, 51.3, 109.8, 115.7, 122.2, 126.0, 128.9, 130.8, 131.5, 132.7, 138.2, 139.7, 141.4, 142.6, 149.2, 195.5 (C=O).

Acknowledgement

We would like to acknowledge the Thomson Laboratorie Group from Universidade Estadual de Campinas (UNICAMP), Sao Paulo, Brasil and its staff for MS measurements.

References

1-Burckhalter, H,J, e Korolkovas, A. Química Farmacêutica, 223-250, 1982, Ed. Guanabara Dois S/A, Rio de Janeiro, R.J.

2- M. Gordon, ed., Psychopharmacological agents, vol. I e II, Academic Press, N.Y. London, 1964.

3-Buisson et al. U.S. Pat. 2,769,002 (1956 to Rhône – Poulenc).

4-J. Lapierre et al. Can. Psychiat. Assoc. J. 14, 267, 1969.

5-U. Breyer; H. J. Goertner. Adv. Biochem. Psychopharmacol 9, 167, 1974.

6- R.A. Hollins e V.M. Salim; Tese de Mestrado pelo Instituto Militar de Engenharia (1976).

Received on May 10, 2001