Computational Studies, Synthesis and Biological Investigations of *N*-[(*p*-Bromo)carboxyphenyl]dibenz[*b*,*f*]azepine

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In memoriam to Professor Nicholas Alexandrou

With the aim to find new compounds with superior tranquilizer-antidepressant activity theoretical studies, synthesis, X-ray characterization and pharmacological test of the title compound were carried out. Theoretical studies suggested both tranquilizer and antidepressant activity and pharmacological tests proved it.

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The stereochemistry of biologically active compounds is of critical importance in the formation of substrate-receptor complexes and its resulting biological effects. This fact is valid for 5*H*-dibenz[*b*,*f*]azepines that show a continuous transition of activity in going from structures as the antiepileptic [3] carbamazepine **1** (Figure 1) through the antidepressant imipramine **2** [4]. A tentative stereochemical classification of tricyclic psychotropic drugs has been reported [5]. It has been proposed that the biological activity of these compounds can be determined by three structural elements: the tricyclic skeleton, the side chain and the basic substituent. The steric shape of the tricyclic skeleton has been defined by three angles: α (bending), β (anellation) and γ (torsion) (Figure 2). In general, the tranquilizers have only a bending angle α, but no β and γ angles. The mixed tranquilizer-antidepressants have both a bending (α) and anellation angle β but no γ angle. The pure antidepressants exhibit all three angles [6]. With this information it was deemed of interest to inquire into the behavior of analogous molecules containing the 5*H*-dibenz[*b*,*f*]azepine ring like compounds **3a-k** (Figure 3).

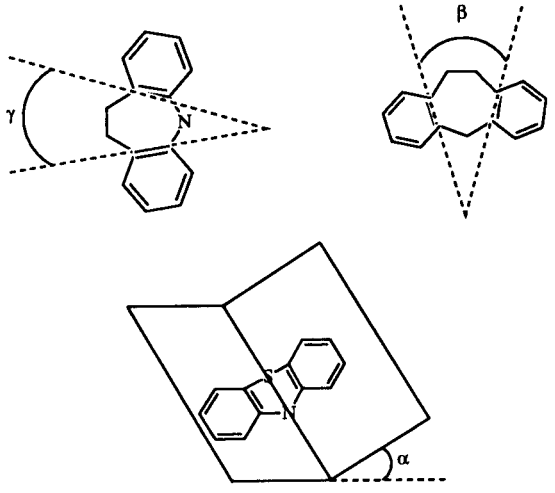

Figure 1. Ring topology of tricyclic psychomimetic drugs (from reference 6).

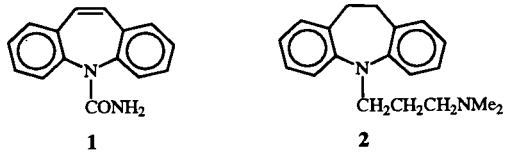

Figure 2. Tricyclic compounds.

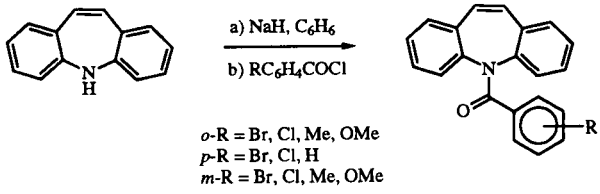

Figure 3.

Table 1

α, β and γ Angles for Compounds **1**, **2** and **3k**

Compound No.	Angle (°) α	β	γ
1 [a]	54.5	92.9	0.1
2 [a]	55.0	40.0	20.0
3k [b]	58.4	29.5	5.2

[a] From ref [4]. [b] These values were obtained from our X-ray data and theoretical calculations.

Table 2

Physical, Analytical and Spectral Data for Compounds **3a-k**

Compound No.	R	Yield %	mp °C	Molecular Formula	Analysis % C	H	Spectral Data
3a	H	39	129-131	$C_{21}H_{15}NO$	84.82 (84.80)	5.09 (5.03)	ir (chloroform): 1625 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.85-7.70 (m, 15 H); ms: M^+ at m/z 297
3b	*o*-Me	38	164-165	$C_{22}H_{17}NO$	84.85 (84.82)	5.51 (5.48)	ir (chloroform): 1655 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.80-7.60 (m, 14 H), 2.31 (*s*, 3H); ms: M^+ at m/z 311
3c	*m*-Me	36	164-166	$C_{22}H_{17}NO$	84.85 (84.83)	5.51 (5.49)	ir (chloroform): 1655 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.81-7.60 (m, 14 H), 2.35 (*s*, 3H); ms: M^+ at m/z 311
3d	*o*-OMe	35	132-134	$C_{22}H_{17}NO_2$	80.70 (80.66)	5.24 (5.22)	ir (chloroform): 1665 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.79-7.50 (m, 14 H), 3.87 (*s*, 3H); ms: M^+ at m/z 327
3e	*m*-OMe	36	140-142	$C_{22}H_{17}NO_2$	80.70 (80.65)	5.24 (5.21)	ir (chloroform): 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.80-7.50 (m, 14 H), 3.9 (*s*, 3H); ms: M^+ at m/z 327
3f	*o*-Cl	37	180-182	$C_{21}H_{14}NOCl$	76.12 (76.07)	4.26 (4.23)	ir (chloroform): 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.75-7.50 (m, 14 H); ms: M^+ at m/z 331
3g	*m*-Cl	34	157-159	$C_{21}H_{14}NOCl$	76.12 (76.09)	4.26 (4.22)	ir (chloroform): 1653 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.77-7.40 (m, 14 H); ms: M^+ at m/z 331
3h	*p*-Cl	36	132-134	$C_{21}H_{14}NOCl$	76.12 (76.08)	4.26 (4.22)	ir (chloroform): 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.76-7.40 (m, 14 H); ms: M^+ at m/z 331
3i	*o*-Br	36	175-177	$C_{21}H_{14}NOBr$	67.20 (67.16)	3.76 (3.73)	ir (chloroform): 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.78-7.50 (m, 14 H); ms: M^+ at m/z 375
3j	*m*-Br	38	143-145	$C_{21}H_{14}NOBr$	67.20 (67.17)	3.76 (3.73)	ir (chloroform): 1665 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.78-7.40 (m, 14 H); ms: M^+ at m/z 375
3k	*p*-Br	38	157-159	$C_{21}H_{14}NOBr$	67.20 (67.18)	3.76 (3.73)	ir (chloroform): 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.77-7.50 (m, 14 H); ms: M^+ at m/z 375

The theoretical results predicted that compound **3k** ought to have sedative and antidepressant activity because it shows the angles α (121.6°), β (29.5°) and γ (5.2°) and as can be seen in Table 1 these values are closely related to compounds with such effects.

Our synthetic strategy to get the compounds **3a-k** is outlined in Figure 3. In a typical procedure 5*H*-dibenz-[*b,f*]azepine was deprotonated by sodium hydride and subsequent addition of substituted benzoyl chlorides produce the target compounds in moderate yields (Table 2). Structural assignment of **3a-k** derivatives was made on spectroscopic grounds. In the infrared spectra of **3a-k** the appearance of absorption bands at 1645-1675 cm^{-1} was consistent with the presence of an amide group. In the ^1H-nmr spectra of the aromatic protons **3a-k** derivatives appeared as unresolved multiplets at 6.85-7.70. Further evidence of the structure of **3a-k** was derived from their mass spectral data. All the compounds showed the molecular ion and their base peak as the ion at m/z (104 + R).

X-ray diffraction of **3k** (Tables 3 and 4) showed that the tricyclic moiety is not planar. The central seven-membered ring adopts a bote conformation with N5(0.639Å), C10(0.582Å) and C11(0.613Å) out of the plane formed by C4A-C5A-C9A-C11A. Amide group N5-C1'-O-C2' and the *para*-bromophenyl ring are no

Table 3

Bond Lengths (Å)

Br-C(5')	1.898(7)	C(7)-C(8)	1.372(12)
O-C(1')	1.217(8)	C(8)-C(9)	1.367(10)
N(5)-C(4A)	1.447(8)	C(9)-C(9A)	1.406(9)
N(5)-C(5A)	1.443(8)	C(9A)-C(10)	1.466(9)
N(5)-C(1')	1.372(10)	C(10)-C(11)	1.339(9)
C(1)-C(2)	1.365(13)	C(11)-C(11A)	1.459(11)
C(1)-C(11A)	1.411(10)	C(1')-C(2')	1.511(10)
C(2)-C(3)	1.362(13)	C(2')-C(3')	1.380(10)
C-(3)-C(4)	1.385(11)	C(2')-C(7')	1.379(10)
C(4)-C(4A)	1.381(10)	C(3')-C(4')	1.380(10)
C(4A)-(11A)	1.394(10)	C(4')-C(5')	1.365(10)
C(5A)-C(6)	1.395(9)	C(5')-C(6')	1.372(10)
C(5A)-C(9A)	1.393(10)	C(6')-C(7')	1.384(10)
C(6)-C(7)	1.384(10)		

Table 4

Bond Angles (°)

C(4A)-N(5)-C(5A)	115.6(6)	C(9)-C(9A)-C(10)	121.0(6)
C(4A)-N(5)-C(1')	120.5(5)	C(9A)-C(10)-C(11)	127.2(7)
C(5A)-N(5)-C(1')	123.3(5)	C(10)-C(11)-(11A)	125.9(6)
C(2)-C(1)-C(11A)	120.8(7)	C(1)-C(11A)-C(4A)	117.3(7)
C(1)-C(2)-C(3)	120.6(8)	C(1)-C(11A)-C(11)	119.8(6)
C(2)-C(3)-C(4)	120.7(8)	C(4A)-C(11A)-(11)	122.9(6)
C(3)-C(4)-C(4A)	119.0(7)	O-C(1')-N(5)	122.3(6)
N(5)-C(4A)-C(4)	120.1(6)	O-C(1')-C(2')	121.3(7)
N(5)-C(4A)-(11A)	118.3(6)	N(5)-C(1')-C(2')	116.3(6)
C(4)-C(4A)-C(11A)	121.6(6)	C(1')-C(2')-C(3')	117.7(6)
N(5)-C(5A)-C(6)	119.7(6)	C(1')-C(2')-C(7')	123.0(6)
N(5)-C(5A)-C(9A)	119.2(5)	C(3')-C(2')-C(7')	119.3(6)
C-(6)-C(5A)-C(9A)	121.1(6)	C(2')-C(3')-C(4')	121.2(7)
C(5A)-C(6)-C(7)	119.6(7)	C(3')-C(4')-C(5')	119.0(6)
C(6)-C(7)-C(8)	120.3(6)	Br-C(5')-C(4')	119.5(5)
C(7)-C(8)-C(9)	119.8(7)	Br-C(5')-C(6')	119.9(6)
C(8)-C(9)-C(9A)	122.1(7)	C(4')-C(5')-C(6')	120.6(6)
C(5A)-C(9A)-C(9)	116.9(6)	C(5')-C(6')-C(7')	120.5(7)
C(5A)-C(9A)-C(10)	122.0(6)	C(2')-C(7')-C(6')	119.4(6)

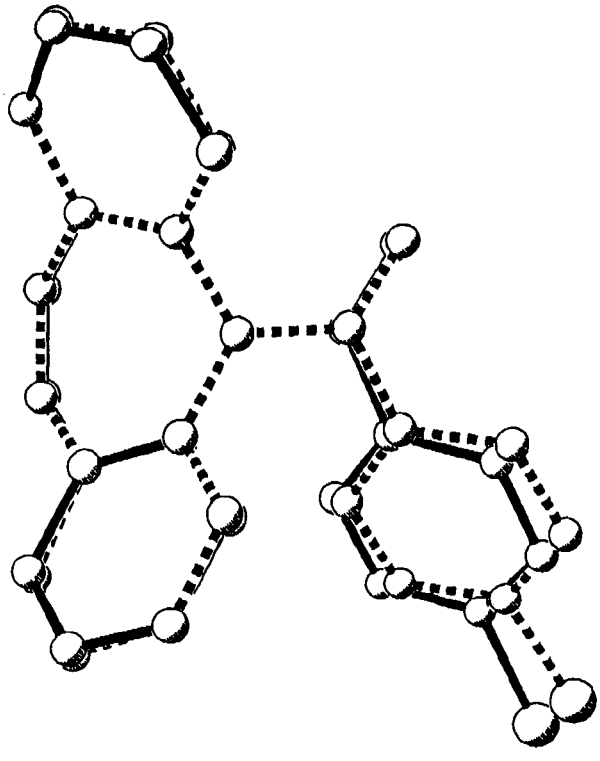

Figure 4. Molecular conformation of compound **3b**. The solid represents the structure determined by X-ray diffraction. The optimized geometry with LDA is represented by dashed lines.

longer coplanar (angle between planes = 47.7°), while the former group makes a dihedral angle of 56.7° with the mean plane of the seven-membered ring. The tricyclic skeleton topology in terms of the parameters defined by Wilhelm and Kuhn [5] are: α = 121.6, β = 29.5, γ = 5.2, δ = 4.79 Å. The GO achieved for this molecule shows an excellent agreement with the experimental bond lengths and angles obtained from X-ray diffraction (Figure 4).

Derivative **3k** was submitted to pharmacological tests using rats to evaluate their depressant and the antidepressant activity. From the three evaluated variables, the Immobility time was the best for the comparison of the effects in the lots. As seen from the values in Table 5 and Figure 5, compounds **1**, **2** and **3k** showed maximal depressor effects at a dosage of 20 mg/Kg. Likewise, compounds **1** and **3k** showed a similar depressor behavior. Statistical studies showed that compound **3** has a 55% depressant activity similar to that of Carbamazepine (**1**) and a 25% antidepressant activity similar to that of Imipramine (**2**).

Table 5

Effect of Different Drugs on the Total Duration of Immobility in Seconds (Mean)

Dose (mg/kg)	Compound **1**	Compound **2**	Compound **3k**	Control
10	25.3 (1.7)	11.2 (1.8)	37.6 (2.0)	41.9
20	37.1 (1.9)	26.6 (2.1)	6.2 (0.8)	41.9
30	33.0 (1.4)	25.2 (1.5)	8.5 (1.9)	41.9
40	27.6 (2.6)	22.7 (1.9)	15.9 (1.4)	41.9
50	20.4 (1.7)	20.2 (2.3)	12.5 (2.0)	41.9
100	9.1 (1.7)	13.17 (1.9)	12.5 (1.5)	41.9

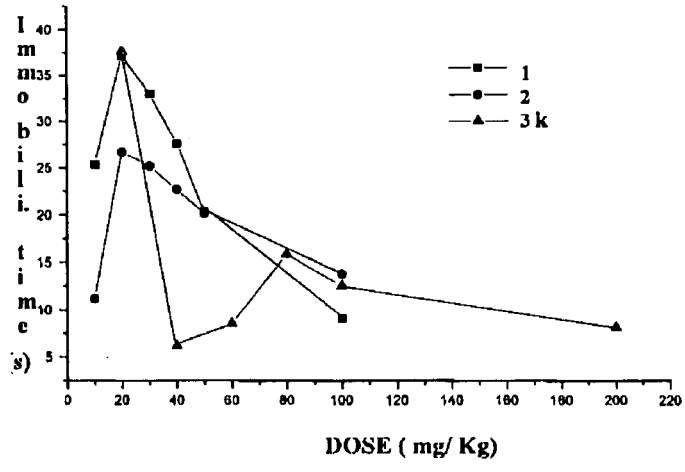

Figure 5. Immobility time in seconds (ordinate) as a function of the drug dose in mg/Kg (abscissa).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H nmr spectra were determined on a Varian Gemini 200 spectrometer. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and were determined in a deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Jeol SX-100 mass spectrometer.

Electronic Structure Calculations.

Molecule **3k** was built and optimized with molecular mechanics using the package Nemesis [7]. Further Geometry Optimization (GO) was carried out first at a semiempirical level using an MNDO approximation and in a second stage at an *ab initio* level, within the Local Density Approximation (LDA) using Dgauss; from this optimized geometry the electronic structure of the molecule was computed by LDA and Hartree-Fock (HF) methods. For HF the Effective Core Potential (ECP) approximation was used, as implemented in Gaussian 92 [8]. All these calculations were done with the suit of programs in Unichem [9]. The basis sets for the LDA calculations were Double Zeta with valence polarization [10]. For the HF calculations the ECP and their associated double Zeta basis sets as in reference were used [11].

Synthesis of *N*-[(*o*-, *m*- and *p*-R)Carboxyphenyl]dibenz[*b*,*f*]azepines **3a-k**.

General Procedure (R= H).

To a solution of 5*H*-dibenz[*b,f*]azepine (0.193 g, 1.0 mmole) dissolved in 50 ml of dry benzene 2 mmoles of sodium hydride (0.048 g) were added. The mixture was refluxed for 2 hours and a solution of benzoyl chloride (0.250 g, 1.8 mmoles) in 2 ml of dry benzene was added dropwise, with stirring, for 15 minutes. The reaction mixture was heated for 2 hours, then it was allowed to cool. The resulting solution was concentrated (rotatory evaporator) to afford a brown solid that was purified by column chromatography (silca-gel, hexane-ethyl acetate, 9:1) to give 0.116 g (39%) of **3a** mp 129-131°. The physical, analytical and spectral data for the synthesized compounds **3a-k** are recorded in Table 1.

X-ray diffraction of *N*-[*p*-Bromo)carboxyphenyl]dibenz[*b,f*]-azepine **3k**.

Crystals of **3k** were grown from methylene chloride-hexane. They were shown to be monoclinic, with a space group $P2_1/c$ (a = 9.950(2) Å, b = 17.201(3)Å, c = 9.783(2)Å; β = 101.45(3)°; V = 1641 $Å^3$, Z = 4; Dc = 1.523 g/cm^3; μ = 2.511 mm^{-1}. X-ray single crystal analysis and data collection were performed on a Siemens P4/PC four circle diffractometer (monochromatic MoKα radiation, λ = 0.71073Å and unit-cell dimensions calculated by least-squares refinement of 23 reflections in the θ range 2.4-9.5°. Two octants (hk1 and hk-1) were measured in the θ range 1.5-25° yielding 2856 independent reflections (Rint = 1.46%, Lp corrections but no absorption). The structure was solved by direct methods [12]. Full matrix least-squares F-refinement on the 1475 reflections with $F > 3\sigma(F)$ was performed with SHELXTL [13]. Refinement of the anisotropic displacement parameters were performed only for non-H atoms. The H atoms were included at idealized positions with a fixed overall isotropic temperature factor equal to 0.06$Å^2$. At convergence, R = 5.83%, Rw = 4.59%, S = 1.064; secondary extinction parameter χ = 0.0034(3).

Pharmacology.

The Forced Swimming Test for inducing a depressed state in a rat was implemented [14]. This test keeps the animal in a reduced space where they are forced to swim, this causes a certain grade of stress resulting in no chance of escape. The drugs were dissolved in dimethylformamide (DMF). Eighth week old Long Evans rats were used and they were distributed in lots of 9 animals. To each lot was given a different dose of carbamazepine (**1**), imipramine (**2**), compound **3k** and to the control of only the solvent. The drugs were administered orally in two steps: the first at 12 hours and the second 1 hour before beginning the observation. The administered doses were 10, 20, 30, 40, 50 and 100 mg/Kg. The time of observation was 15 minutes and the record of the variables was carried out on the first and third block of 5 minutes. Variables measured were Immobiliy time (seconds), plunger number and defecation (number of boli). The control groups were carbamazepine (**1**) and imipramine (**2**) as controls drug and a control group which was administered by the vehicle (DMF), under the same conditions. Results of the experiments were statistically analyzed by the "Dunnett t test" [15] and statistical significance against controls was stimulated as follows: [1] $\rho < 0.05$. Comparison was performed according to the Student's t test.

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[2] Contribution No. 1351 from Instituto de Química UNAM. This work was presented in part at the XIIth International Congress of Pharmacology, Montreal, Canada, July 24-29, (1994).

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