Synthesis and Spectral Properties of Isomeric [(12-*N*-Methyl) and (10-*N*-methyl)]-11-(*o*, and *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines

Eduardo Cortés Cortés*[1], Pedro Muñoz Islas, Marcos Martínez García and Mayra O. Zepeda Romero

Instituto de Química [2], Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510 México, D.F.

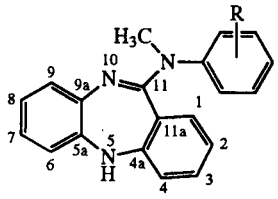
Received August 21, 1995

The preparation of sixteen novel substituted [(10-*N*-methyl) and (12-*N*-methyl)]-11-(*o*-, and *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines which have potentially useful pharmacological properties is described. The structure and the isomeric differences in all products was corroborated by ir, ^{1}H-nmr, ^{13}C-nmr, and mass spectra.

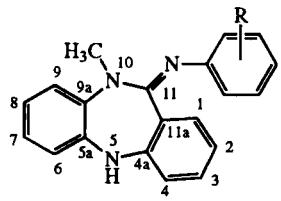
J. Heterocyclic Chem., **33**, 1723 (1996).

Clozapine, an atypical neuroleptic dibenzodiazepine, [3-5] is particularly significant because it lacks extrapyramidal side-effects in man [6]. Recently, research has been carried out on this compound to confirm its pharmacological activity as an antipsychotic drug [7-11]. This has given renewed momentum to the search for new psychotropic drugs with diminished side effects. As a part of a program directed towards the synthesis and spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report the synthesis of novel compounds **VIIa**, 1-8 and **VIIb**, 9-16 (Scheme 1), following the five steps indicated in Scheme 2.

Scheme 1



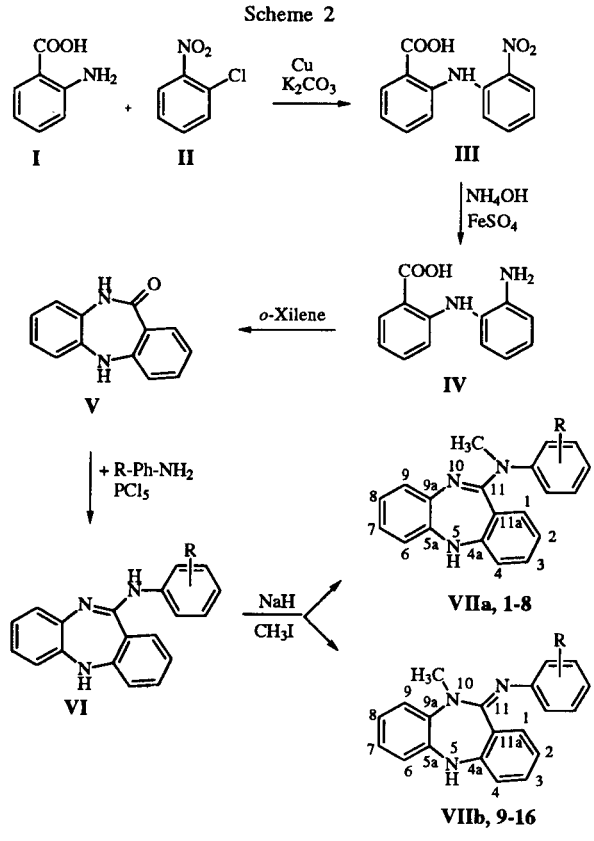
VIIa, 1-8



VIIb, 9-16

1	H	**9**	H
2	*o*-CH_3	**10**	*o*-CH_3
3	*o*-OCH_3	**11**	*o*-OCH_3
4	*o*-Cl	**12**	*o*-Cl
5	*o*-Br	**13**	*o*-Br
6	*p*-CH_3	**14**	*p*-CH_3
7	*p*-Cl	**15**	*p*-Cl
8	*p*-Br	**16**	*p*-Br

Scheme 2



The *o*-chloronitrobenzene **II** was dissolved in nitrobenzene and treatment with antranilic acid **I** in the presence of potassium carbonate and powder copper, with magnetic stirrer and heating at 195° for eight hours afforded compound **III** in 55% yield.

To an aqueous ferrous sulfate solution was added *N*-(*ortho*-nitrophenyl)anthranilic acid **III** dissolved in a mixture of amonium hydroxide/water (1:1) with magnetic stirring. The mixture was stirred at reflux for twenty minutes, the reaction mixture was filtered and the solution was concentrated *in vacuo* to afford compound **IV**, brown needles in 70% yield. Compound **IV** was converted to 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11-one **V**, by refluxing in dry xylene for twenty two hours in 89% yield as gray needles.

Treatment of diazepin-11-one **V** with the corresponding substituted-phenylamine in the presence of phosphorus pentachloride and refluxing benzene for seventeen hours [12], afforded compound **VI**. The infrared spectrum of compound **VI** displayed absorptions at 3430-3200 cm^{-1} for N-H stretching, at 1630-1638 cm^{-1} for C=N stretching, at 1240-1285 cm^{-1} for C-N stretching, and the corresponding absorptions

for the substituent. In the ^{1}H-nmr spectra of derivatives **VI** the presence of two-proton broad signal at δ 5.34, and δ 6.3-7.8, with exchanges with deuterium oxide, was consistent with the presence of two amine groups; the aromatic protons appeared as an unresolved multiplet at δ 6.6-7.4. The mass spectrum of the compounds showed the molecular ion and its fragmentation is in accordance with the assigned structure.

Compound **VI** was converted to 12-*N*-methyl-11-(*o*-, and *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines **VIIa**, **1-8**, and 10-*N*-methyl-11-(o and *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines **VIIb**, **9-16** by refluxing in dry benzene in presence of sodium hydride and methyl iodide for thirty six hours. The isomeric compounds **VIIa**, **1-8** and **VIIb**, **9-16** were separated by silica gel chromatography column and elution with dichloromethane/ethyl acetate (90:10) to yield **VIIa**, **1-8** (30-51%) and **VIIb**, **9-16** (20-51%).

The infrared spectrum of compounds **1-16** displayed absorptions at 3360-3375 cm^{-1} for N-H stretching; at 1615-1597 cm^{-1} for C=N stretching; at 1243-1253 cm^{-1} for C-N stretching and the corresponding absorptions for aromatic and substituents. In the ^{1}H-nmr spectra of derivatives **1-16** the presence of three proton singlet signals at δ 3.35-3.60 singlet were assigned to the methyl protons joined to N; the presence of a broad one-proton signal at δ 4.90-5.05, which exchanges with difficulty with deuterium oxide, was consistent with the presence of an amino group; the aromatic protons appeared as an unresolved multiplet; an AA'BB' system at δ 6.60-7.25, and the signal for the substituent on the aromatic anilino group.

The ^{13}C nmr spectra of compounds **7** and **15** are given in Table 1.

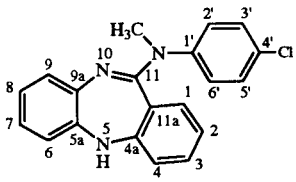
The mass spectrum of the compounds **1-16** exhibit an abundant molecular ion which probably reflects the stable nature of the 5*H*-dibenzodiazepine ring under electron impact. The relative abundance of the principal fragment ions of the isomeric compounds **1-8** and **9-16** have some common features, the only difference being in the base peak.

The main fragmentation pathways of **1-16** include the elimination of the substituent on the anilino group from the molecular ion to produce the base peak [M-substituent]$^+$ for **1-5**; loss of an hydrogen atom occurs in all the mass spectra giving rise to the base peak for **6-8**. In compounds **9-16** the ion at m/z 195 is the base peak. In contrast to compounds **9-16** the ion at m/z 195 in compounds **1-8** is not favoured.

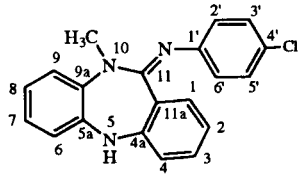
The main fragmentation pathways of **1-16** include ions at m/z [M-1]$^+$; m/z [M-substituent]$^+$, m/z 283, 269, 207, 195, 192, 181 and 180, was consistent with the assigned structures.

Table 1

^{13}C NMR Spectral Data for Compounds **7** and **15**



VIIa, 7



VIIb, 15

Carbon	Chemical shifts (ppm)	
	7 (N-CH_3,R = *p*-Cl)	**15** (1O-CH_3, R = *p*-Cl)
C-1 (CH=)	124.4	133.5
C-2 (CH=)	122.7	122.5
C-3 (CH=)	131.4	130.6
C-4 (CH=)	119.3	119.0
C-4a (C-N5)	152.9	152.1
C-5a (C-N5)	141.7	145.3
C-6 (CH=)	119.5	120.0
C-7 (CH=)	131.2	124.7
C-8 (CH=)	124.3	124.4
C-9 (CH=)	127.6	124.7
C-9a (C-C=C)	140.1	137.7
C-11 (C=N_{10})(C=N)	160.5	156.6
C-11a (C-C=C)	124.9	122.2
C-13 (C-N)	146.4	149.9
C-14 (CH-)	126.5	123.6
C-15 (CH=)	128.9	128.4
C-16 (C-Cl)	129.5	125.9
C-17 (CH=)	128.9	128.4
C-18 (CH=)	126.5	123.6
C-19-(CH_3-N_{12}) (CH_3-N_{10})	40.6	40.5

Note: The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbons in ^{13}C NMR spectra.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian Unity-300 Spectrometer operating at 300 MHz and the ^{13}C-nmr spectra were recorded on a Varian Unity Plus-500. Spectrometer operating at 500 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from TMS. The mass spectra were measured on a JEOL JMS-AX505 and JEOL JMS-SX 102A High Resolution Mass Spectrometer with accurate mass determination of the molecular ion, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190°and ionizing electron energy of 70 eV.

Synthesis of 10,11-Dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one **V**.

To a stirred solution of *N*-(*o*-aminophenyl)anthanilic acid **IV**, 1.98 g (8.7 x 10^{-3} mole) in 50 ml of anhydrous *o*-xylene was refluxed for 22 hours followed by cooling to room temperature and the *o*-xylene was evaporated *in vacuo* to yield **V**, (89%), as gray needles, mp 245°; ir (chloroform): ν -NH-C=0 3230, -NH-3170, C=O 1640, C-N 1250 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.8 (bs, 1H, 10-NH, deuterium oxide exchangeable), 7.85 (bs, 1H, 5-NH, deuterium oxide exchangeable), 6.80-8.00 (m, 8H, phenyl protons); ms: m/z 210 (M$^+$).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.26; H, 4.80; N, 13.33. Found: C, 74.39; H, 4.71; N, 13.45.

Synthesis of 11-(*o*; *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]-diazepines **VI**.

To 100 ml of benzene was added 3.96 g (1.9 x 10^{-2} mole) of phosphorus pentachloride and the mixture was stirred and heated at reflux for two hours. Subsequently was added 1.99 g (9.5 x 10^{-3} mole) of diazepin-11-one **V** and the reflux was continued for two hours, then was added 19.0 x 10^{-3} mole of substituted-aniline and stirring at reflux was continued for seventeen hours. The reaction mixture was cooled with ice-water, filtered and washed with benzene (3 x 10 ml). The solid residue was dissolved in ethanol and ammonium hydroxide was added until basic *p*H, to yield **VI** (45-83%) as yellow needles; ir (chloroform): ν -NH-3300-3400; -C=N- 1625-1640; C-N 1320-1370 and 1210-1260 cm^{-1}. In addition, bonds for the anilino-substituents are also shown; ^1H nmr (deuteriochloroform): δ 7.83-8.32 (bs, 1H, 12-NH, deuterium oxide exchangeable), 5.25-5.34 (bs, 1H, 5-NH, deuterium oxide exchangeable); 6.6-7.4 (m, 12H, phenyl protons, R = H). The mass spectral fragmentation patterns, physical and analytical data for compound **VI** was reported by us [13].

Synthesis of Isomeric (12-*N*-Methyl) and (10-*N*-methyl)]-11-(*o*, and *p*-substituted-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines, **VIIa**, **1-8**, and **VIIb**, **9-16**.

To 100 ml of benzene was added 1.2 x 10^{-3} moles of 5*H*-dibenzo[*b*,*e*][1,4]diazepines **VI** and heated at reflux with magnetic stirring, subsequently was added 1.6 x 10^{-3} moles of sodium hydride and the mixture was stirred and heated at reflux for two hours. Then methyl iodide (1.6 x 10^{-3} moles) was added dropwise with stirring. The mixture was stirred at reflux for thirty five hours followed by cooling to room temperature, filtered and the organic solution was dried (sodium sulfate) and evaporated *in vacuo* to yield a solid. The residual solid was purified on a silica gel chromatography column and elution with dichlorometane-ethyl acetate 9:1 to yield the compounds **VIIa**, **1-8** and **VIIb**, **9-16**.

12-*N*-Methyl-11-anilino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**1**).

This compound was obtained as yellowish needles in 51% yield, mp 70°; ir (chloroform): ν N-H 3370; C=N 1614; C-N 1252 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.58 (s, 3H, 19-H), 5.01 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.50-7.30 (m, 13H, phenyl protons); ms: m/z 299 (M^+).

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.30; H, 5.65; N, 14.10.

12-*N*-Methyl-11-[(*ortho*-methyl)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**2**).

This compound was obtained as yellowish needles in 49% yield, mp 55°; ir (chloroform): ν N-H 3368, C=N 1614, C-N 1252 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, 20-H), 3.39 (s, 3H, 19-H), 4.92 (bs, 1H, 5-H, deuterium oxide exchangeable) 6.50-7.25 (m, 12H, phenyl protons); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.29; H, 6.28; N, 13.49.

12-*N*-Methyl-11-[(*ortho*-methoxy)anilino]-5*H*-dibenzo[*b*,*e*]-[1,4]diazepine (**3**).

This compound was obtained as yellowish needles in 30% yield, mp 62-63°; ir (chloroform): ν N-H 3365, C=N 1612, C-N 1252, C-O 1320 and 1355 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50 (s, 3H, 19-H), 3.70 (s, 3H, 20-H), 4.96 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.60-7.29 (m, 12H, phenyl protons); ms: m/z 329 (M^+)

Anal. Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.50; H, 5.71; N, 12.87.

12-*N*-Methyl-11-[(*ortho*-chloro)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**4**).

This compound was obtained as yellowish needles in 48% yield, mp 63-65°; ir (chloroform): ν N-H 3359; C=N 1616; C-N 1246 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.40 (s, 3H, 19-H), 4.96 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.50-7.25 (m, 12H, phenyl protons); ms: m/z 333 (M^+); 335 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.88; H, 4.92; N, 12.67.

12-*N*-Methyl-11-[(*ortho*-bromo)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**5**).

This compound was obtained as yellow needles in 44% yield, mp 163; ir (chloroform): ν N-H 3360, C=N 1610, C-N 1250 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.41 (s, 3H, 19-H), 4.95 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.58-7.33 (m, 12H, phenyl protons); ms: m/z 377 (M^+); 379 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Br$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.59; H, 4.38; N, 11.04.

12-*N*-Methyl-11-[(*para*-methyl)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**6**).

This compound was obtained as yellowish needles in 38% yield, mp 210°; ir (chloroform): ν N-H 3345, C=N 1615, C-N 1240 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, 20-H), 3.54 (s, 3H, 19-H), 4.97 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.56-7.22 (m, 12H, phenyl protons); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.56; H, 6.03; N, 13.34.

12-*N*-Methyl-11-[(*para*-chloro)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**7**).

This compound was obtained as yellowish needles in 30% yield, mp 202-204°; ir (chloroform): ν N-H 3370, C=N 1612, C-N 1248 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50 (s, 3H, 19-H), 4.98 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.60-7.27 (m, 12H, phenyl protons); ms: m/z 333 (M^+), 335 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.99; H, 4.70; N, 12.45.

12-*N*-Methyl-11-[(*para*-bromo)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**8**).

This compound was obtained as yellowish needles in 34% yield, mp 193-195°; ir (chloroform): ν N-H 3375; C=N 1614; C-N 1251 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.54 (s, 3H, 19-H), 4.98 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.60-7.27 (m, 12H, phenyl protons); ms: m/z 377 (M^+); 379 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Br$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.42; H, 4.34; N, 11.15.

10-*N*-Methyl-11-anilino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**9**).

This compound was obtained as yellowish needles in 35% yield, mp 195°; ir (chloroform): ν N-H 3373, C=N 1604, C-N 1243 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, 19-H), 5.22 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.50-7.30 (m, 13H, phenyl protons); ms: m/z 299 (M^+).

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.17; H, 5.79; N, 14.00.

10-*N*-Methyl-11-[(*ortho*-methyl)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**10**).

This compound was obtained as yellowish needles in 40% yield, mp 135%; ir (chloroform): ν N-H 3374, C=N 1607, C-N 1244 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.38 (s, 3H, 20-H), 3.68 (s, 3H, 19-H), 5.13 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.50-7.29 (m, 12H, phenyl protons); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.38; H, 6.23; N, 13.33.

10-*N*-Methyl-11-[(*ortho*-methoxy)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**11**).

This compound was obtained as yellowish needles in 50% yield, mp 41-42°; ir (chloroform): ν N-H 3365; C=N 1610, C-N 1249, C-O 1320 and 1360 cm^{-1}, ^1H nmr (deuteriochloroform) δ 3.69 (s, 3H, 19-H), 3.73 (s, 3H, 20-H), 5.11 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.46-7.27 (m, 12H, phenyl protons); ms: m/z 329 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.65; 5.71; N, 12.67.

10-*N*-Methyl-11-[(*ortho*-chloro)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**12**).

This compound was obtained as yellowish needles in 39% yield, mp 143-145°; ir (chloroform): ν N-H 3355; C=N 1605, C-N 1245 cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.69 (s, 3H, 19-H), 5.12 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.40-7.30 (m, 12H, phenyl protons); ms: m/z 333 (M^+), 335 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.87; H, 4.97; N, 12.48.

10-*N*-Methyl-11-[(*ortho*-bromo)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**13**).

This compound was obtained as yellow needles in 30% yield, mp 77-79°; ir (chlorofrom): ν N-H 3360; C=N 1610, C-N 1240 cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, 19-H), 5.13 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.50-7.30 (m, 12H, phenyl protons); ms: m/z 377 (M^+), 379 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Br$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.55; H, 4.32; N, 11.06.

10-*N*-Methyl-11-[(*para*-methyl)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**14**).

This compound was obtained as yellowish needles in 29% yield, mp 45-46°; ir (chloroform): ν N-H 3373; C=N 1602, C-N 1245 cm^{-1}, ^1H nmr (deuteriochloroform): δ 2.19 (s, 3H, 20-H), 3.66 (s, 3H, 19-H), 5.10 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.4-7.3 (m, 12H, phenyl protons); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.43; H, 6.07; N, 13.51.

10-*N*-Methyl-11-[(*para*-chloro)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**15**).

This compound was obtained as yellowish needles in 20% yield, mp 158°; ir (chloroform): ν N-H 3375, C=N 1600, C-N 1245 cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.67 (s, 3H, 19-H), 5.12 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.45-7.28 (m, 12H, phenyl protons); ms: m/z 333 (M^+), 335 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.49. Found: C, 71.90; H, 4.90; N, 12.65.

10-*N*-Methyl-11-[(*para*-bromo)anilino]-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (**16**).

This compound was obtained as yellow needles in 20% yield, mp 140°; ir (chloroform): ν N-H 3374, C=N 1599, C-N 1245 cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.66 (s, 3H, 19-H), 5.12 (bs, 1H, 5-H, deuterium oxide exchangeable), 6.40-7.27 (m, 12H, phenyl protons); ms: m/z 377 (M^+), 379 $[M+2]^+$.

Anal. Calcd. for $C_{20}H_{16}N_3Br$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.46; H, 4.32; N, 11.19.

REFERENCES AND NOTES

[1] Author to whom correspondence should be addressed.

[2] Contribution No. 1461 from Instituto de Química, UNAM.

[3] J. Schmutz, *Arzneim.-Forsch.*, **25**, 712 (1965).

[4] J. Schmutz, *Chim. Ther.*, **2**, 424 (1967).

[5] F. Hunziker, E. Fisher and J. Schmutz, *Helv. Chim. Acta*, **50**, 1588 (1967).

[6] J. Angst. D. Bente, P. Berwer, H. Heimann, H. Helmohen and H. Hippus, *Pharmakopsychiatr. Neuro-Psychopharmakol.*, **4**, 201 (1971).

[7] J. F. Nash, H. Meltzer and G. A. Gudelsky, *Eur. J. Pharmacol.*, **151**, 463-9 (1988).

[8] M. Picker, *Pharmacol. Biochem. Behav.* **30**, 603 (1988).

[9] M. Picker and J. Mitchell, *Pharmacol. Biochem. Behav.*, **31**, 953 (1988).

[10] C. Kilts, C. Anderson, G. Bissette, T. Elg and C. Nemeroff, *Biochem. Pharmacol.*, **37**, 1547-54 (1988).

[11] B. McMillen, A. Brian, E. Davanzo, A. Song, S. Scott and M. Rodríguez, *Eur. J. Pharmacol.*, **160**, 149 (1989).

[12] E. Cortés Cortés, E. Cortés Romero and A. Domínguez Taylor, *J. Heterocyclic Chem.*, **31**, 725 (1994).

[13] E. Cortés, R. Martínez and A. Zarza, *J. Heterocyclic Chem.*, **20**, 1615 (1983).