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Synthesis and Tranquilizing Effect of New Dibenzoxazepines and Pyridobenzoxazepines

S. Botros*, B. H. Naguib and A. N. Osman
Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

A SERIES of new 6,7,8,9-tetrahydrodibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones (3) was prepared by alkylation of salicylamides 1 with 2-chlorocyclohexanone followed by cyclodehydration of the resulting 2-cyclohexyloxybenzamides 2. New pyrido [2,3-*b*] [1,4]benzoxazepin-6(5*H*)-ones (8) were prepared by reacting salicoyl chlorides 4 or their corresponding acids 5 with 3-amino-2-chloropyridines 6 followed by treatment of the resulting amides 7 with sodium methoxide. Some of the new compounds were subjected to preliminary screened for their tranquilizing effect.

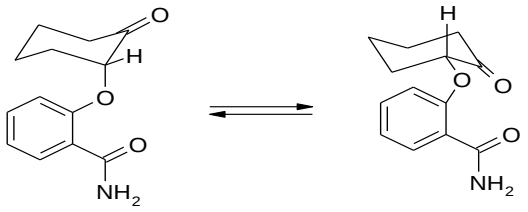
Keywords: Dibenz[b,f][1,4]oxazepin-11(10*H*)-ones, Pyrido [2,3-b] [1,4] benz- oxazepin-6(5*H*)-ones, Tranquilizers and Diazepam.

Tricyclic 1,4-benzoxazepines are reported to have biological activity as anti-inflammatory [(1)], analgesics [(1)], antipyretics [(1)], antidepressants [(2)], HIV-1 reverse transcriptase inhibitors [(3)], antipsychotics [(4,5)] and a few of them have been studied as tranquilizers [(6)]. Therefore, the aim of this work is to synthesize new 6,7,8,9-tetrahydrodibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones and pyrido[2,3-*b*] [1,4] benzoxazepin-6(5*H*)-ones to investigate their tranquilizing effect.

Results and Discussion

The synthesis of the target tetrahydrodibenzoxazepinones 3(a-c) was carried out as depicted in Scheme 1. Alkylation of salicylamides 1(a-c) with 2-chlorocyclohexanone in acetone / potassium carbonate mixture afforded the corresponding 2-cyclohexyloxybenzamides (2a-c). Study of the chemical shift of the α cyclohexyl methine H in different solvents revealed the existence of two conformers for compounds 2; axial conformer A and equatorial conformer B.

*E-mail: Samirbotros@hotmail.com



A B

Conformers of compounds **2**

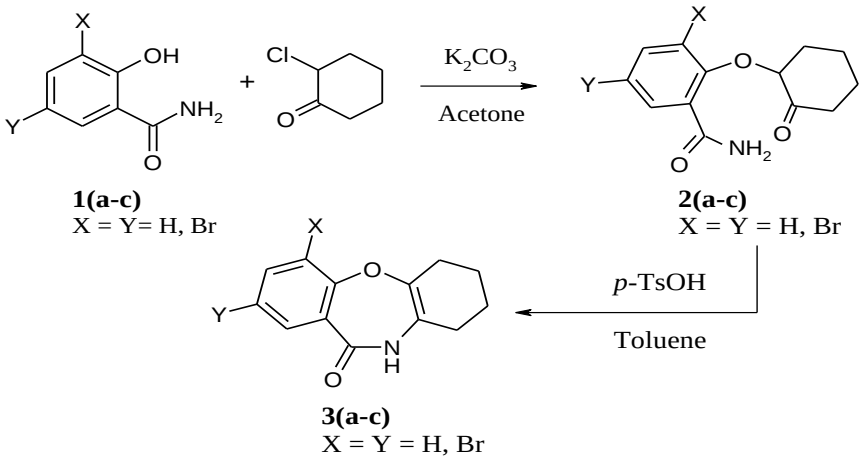
The ^{1}H NMR spectra of compounds 2 in dimethylsulphoxide showed two multiplet signals for the α methine H; one at δ 3.98 due to the equatorial H of the axial conformer A and the other at δ 5.31 due to the axial α H of the equatorial conformer B. On the other hand, the ^{1}H NMR spectra of compounds 2 in the less polar solvent chloroform showed only one multiplet signal at δ 3.88 ppm due to the equatorial α methane H of the axial conformer A. These results indicate predominance of the axial conformer A in solvent chloroform while in the more polar solvent dimethylsulphoxide both conformers A and B exist. These findings are in accordance with that reported for other 2-substituted cyclohexanones [7-9], which showed the preferred existance of the axial conformer in less polar solvents. As the solvent polarity increases the axial form decreases while the equatorial form increases [7, 8]. The decreased stability of the equatorial conformer B may be due to the parallel arrangement of the dipoles of the C=O and C-O (due to dipole - dipole repulsion) [7].

Cyclodehydration of the intermediate 2 in toluene using 4-toluenesulphonic acid as catalyst according to Schenker's procedure [10] yielded the desired tetrahydrodibenzoxazepinones 3 (Scheme 1).

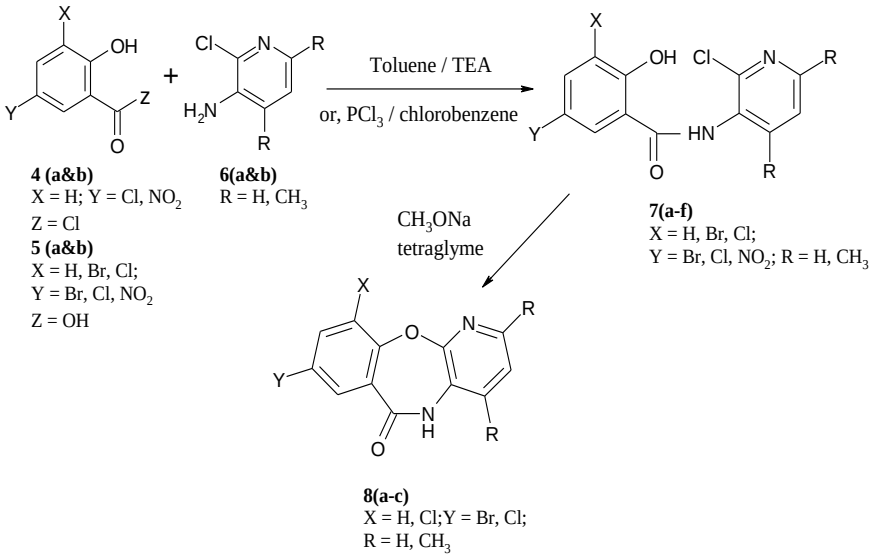
The synthesis of pyridobenzoxazepinones 5 is shown in Scheme 2. The reaction of the appropriate 3-amino-2-chloropyridine 6 with substituted salicylic acids 5a&5b in the presence of PCl_3 or substituted salicoyl chlorides 4a&4b gave substituted -*N*- (substituted -2-chloro -3-pyridyl)-2-hydroxybenzamides (7a-f). Treatment of compounds 7a, 7d &7f with sodium methoxide in tetraglyme under N_2 gave the corresponding pyrido[2,3-b][1,4]benzoxazepin-6(5*H*)-one derivatives (5a-c).

The tranquilizing effect of 1,4-benzoxazepines was examined using the open field test [11-14] and diazepam was used as a standard. The effect of the tested compounds on latency time, ambulation, grooming and rearing frequencies as well as those of diazepam was recorded and presented in Table 1. The results revealed that diazepam, 8a and 8c significantly increased the latency time. The ambulation frequency is significantly reduced with diazepam, 8a and 8c. Furthermore, diazepam, 3a, 8a and 8c significantly reduced the grooming

frequency. The rearing frequency is significantly reduced with only diazepam 8a and 8c.



Scheme 1



Scheme 2

Conclusion

It is observed from Table 1 that pyridobenzoxazepinones 8a & 8c markedely decreased the behavioral activity in mice. However, tetrahydrobenzoxazepines 3a & 3b did not alter the tested behavioral parameters.

TABLE 1. The latency time, ambulation, grooming and rearing frequencies of the tested 1,4-benzoxazepines using the open field test in mice.

Groups	The open field test Mean ± S.E.			
	Latency time (seconds)	Ambulation Frequency Square/3min	Grooming Frequency no/3min	Rearing Frequency no/3min
normal	0.3±0.2	69.3±3.0	7.8±0.9	10.8±0.8
Diazepam	180.0±0.0*	0.0±0.0*	0.0±0.0*	0.0±0.0*
3a	0.6±0.2	55.0±7.8	2.6±0.4*	13.3±3.9
3b	0.1±0.1	50.0±2.8	4.3±1.0	21.6±1.2
8a	140±16.1*	6.6±1.5*	0.0±0.0*	0.0±0.1*
8c	100.1±11.1*	10.1±2.5*	0.4±0.2*	0.0±0.1*

* Significantly different from control at $p \leq 0.05$

Experimental

Melting points were determined with a Griffin or Stuart apparatus in open capillaries and uncorrected. IR spectra (KBr) were recorded using Shimadzu IR 435 spectrophotometer. ^{1}H NMR were measured using Gemini 200 MHz spectrometer using DMSO-d_6 , $CDCl_3$ as solvents and TMS as an internal standard (chemical shifts were recorded in δ, ppm). Mass spectra were run on Hewlett Packard 5988 spectrometer. Elemental analyses were performed at the Microanalytical Center, Faculty of Science, Cairo University, Giza, Egypt. TLC was performed on silica gel (Merck 60 F254) and spots were visualized using UV lamp. The starting materials were purchased from Sigma-Aldrich. The intermediates 5-bromosalicylamide [15], 3,5-dibromo-salicylamide [16], 3-amino-2-chloropyridine [17], 3-amino-2-chloro-4,6-dimethylpyridine [3], 5-bromosalicylic acid [18], 5-nitrosalicylic acid [19], 3,5-dibromosalicylic acid [18], 5-chlorosalicoyl chloride [20] and 5-nitrosalicoyl chloride [21] were prepared according to the reported procedures.

Substituted-2-(2-oxocyclohexyloxy)benzamides (2a-c)

General procedure

A mixture of substituted salicylamide (1a-c) (0.07 mol), 2-chloro-cyclohexanone (10.5 g, 0.08 mol), potassium carbonate (20 g, 0.02 mol), potassium iodide (0.2 g, 0.0012 mol) and dry acetone (175 ml) was heated under reflux with stirring for 14hr. The reaction mixture was evaporated to dryness under reduced pressure. The resultant precipitate was extracted with $CHCl_3$, washed with sodium hydroxide solution (1N) and water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from the suitable solvent.

2-(2-Oxocyclohexyloxy)benzamide (2a)

Crystallized from acetone; yield 10.62 g, 65 %; m.p. 122-124°C; ^{1}H NMR (200MHz, DMSO-d_6), δ, ppm: 1.48-2.17 (m, 8H at C-3,4,5 & 6), 3.98 (m, 1H, α equatorial methine H), 5.31 (m, 1H, α axial methine H), 5.72 (2H, NH_2, D_2O exchangeable), 7.05-8.22 (m, 4H aromatic H's); IR (KBr), cm^{-1}: 3400-3170 (NH_2 str.), 2915-2850 (CH aliphatic str.), 1690 (C=O ketonic str.), 1650 (C=O amidic str.), 1600-1450 (C=C aromatic str.); MS (70eV), *m/z* (%) : 233 [22.2] $(M)^{+\cdot}$; 120 [100]; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.24; H, 6.42; N, 6.11.

5-Bromo-2-(2-oxocyclohexyloxy)benzamide (2b)

Crystallized from methanol; yield 13.77 g, 63 %; m.p. 176-177°C; ^{1}H NMR (200MHz, DMSO-d_6), δ ,ppm: 1.35-2.49 (m, 8H at C-3,4,5 & 6), 4.00 (m, 1H, α equatorial methine H), 5.28 (m, 1H, α axial methine H), 5.74 (2H, NH_2, D_2O exchangeable), 6.93-8.57 (m, 3H aromatic H's); ^{1}H NMR (200MHz, $CDCl_3$): δ =1.56-1.87 (m, 6H at C-3,4 & 5), 2.13(m, 2H ,CH_2 α to carbonyl), 3.88 (m, 1H, α equatorial methine H), 6.68 (2H, NH_2, D_2O exchangeable), 6.92-8.36 (m, 3H aromatic H's); IR (KBr), cm^{-1} : 3400-3170 (NH_2 str.), 2915-2850 (CH aliphatic str.), 1700 (C=O ketonic str.), 1660 (C=O amidic str.), 1600-1450 (C=C aromatic str.); MS (70eV), *m/z* (%) : 311,313 [9.1:9.2] $(M)^{+\cdot}$; 113[100]; Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52; N, 4.48. Found: C, 50.16; H, 4.61; N, 4.38.

3,5-Dibromo-2-(2-oxocyclohexyloxy)benzamide (2c)

Crystallized from ethanol; yield 16.41 g, 60 %; m.p. 190-191°C; IR (KBr), cm^{-1}: 3400-3170 (NH_2 str.), 2915-2850 (CH aliphatic str.), 1710 (C=O ketonic str.), 1670 (C=O amidic str.), 1600-1450 (C=C aromatic str.); Anal. Calcd for $C_{13}H_{13}Br_2NO_3$: C, 39.92; H, 3.35; N, 3.58. Found: C, 40.11; H, 3.35; N, 3.41.

Substituted-6,7,8,9-tetrahydrodibenz[b,f][1,4]oxazepin-11(10H)-ones (3a-c)

General procedure

The appropriate substituted-2-(2-oxocyclohexyloxy)benzamide (2) (0.04 mol) was dissolved in 60 ml dry toluene at 70°C, and then 4-toluenesulphonic acid (0.25 g, 0.0014 mol) was added. The reaction mixture was heated under reflux using water separator for 5-10hr (till all equivalent mol of water was separated). The reaction mixture was cooled, filtered and crystallized from the suitable solvent.

6,7,8,9-Tetrahydrodibenz[b,f][1,4]oxazepin-11(10H)-one (3a)

Crystallized from dioxane; yield 6.81 g, 80 %; m.p. 145-146°C; IR (KBr), cm^{-1}: 3200-3170 (NH str.), 1650 (C=O str.), 1600-1450 (C=C str.); MS (70eV), *m/z* (%): 215 [54.0] $(M)^{+\cdot}$; 105 [100]; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.08; N, 6.50. Found: C, 72.36; H, 5.85; N, 6.31.

2-Bromo-6,7,8,9-tetrahydrodibenz[b,f][1,4]oxazepin-11(10H)-one (3b)

Crystallized from toluene; yield 10.35 g, 88 %; m.p. 194-196^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,ppm:* 1.50-1.65 (m, 4H's at C-7 & C-8) 2.09-2.21 (m, 4H's at at C-6 & C-9), 6.99-7.77 (m, 3H, aromatic H's), 9.35 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3200-3170 (NH str.), 1660 (C=O str.), 1600-1450 (C=C str.); MS (70eV), *m/z:* (293,295 [53.0:56.6] $(M)^{+\cdot}$; Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.21; H, 4.21; N, 4.53.

2,4-Dibromo-6,7,8,9-tetrahydrodibenz[b,f][1,4]oxazepin-11(10H)-one (3c)

Crystallized from toluene; yield 12.23 g, 82 %; m.p. 200-201^{o}C; IR (KBr), cm^{-1}: 3200-3170 (NH str.), 1660 (C=O str.), 1600-1450 (C=C str.); Anal. Calcd for $C_{13}H_{11}Br_2NO_2$: C, 41.85; H, 2.97; N, 3.75. Found: C, 41.83; H, 2.92; N, 3.81.

Substituted-N-(substituted-2-chloro-3-pyridyl)-2-hydroxybenzamides (7a-f)

Method (A): To a stirred suspension of 3-amino-2-chloro-4,6-dimethylpyridine (6a) (0.2 g, 0.0013 mol) and triethylamine (0.129 g, 0.oo128 mol) in dry toluene (5 ml) under nitrogen gas was added dropwise a solution of the appropriate acid chloride 4 (0.0013 mol) in dry toluene (2 ml). After the addition was complete, the mixture was heated under reflux for 3hr. The reaction mixture was then cooled at ambient temperature and shaken well with 1N NaOH (2x10 ml). The aqueous layer was collected, adjusted to pH 5 with 1N HCl, and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with water and saturated aqueous NaCl, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was crystallized from the suitable solvent to give 7(a,b).

5-Chloro-N-(4,6-dimethyl-2-chloro-3-pyridyl)-2-hydroxybenzamide (7a)

Crystallized from methanol; yield 0.14 g, 35 %; m.p. 107-108^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ*, ppm: 2.30 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.08-8.10 (m, 4H, aromatic H's), 10.39 (1H, NH, D_2O exchangeable), 12.06 (1H, OH, D_2O exchangeable); IR (KBr), cm^{-1}: 3310-3290 (NH str.), 3400-2500 (OH hydrogen bonded str.), 1689-1660 (C=O str.), 1610-1580 (C=N str.), 1500-1460 (C=C aromatic str.); MS (70eV), *m/z* (%): 310,312,314 [4.0:3.8:0.8] $(M)^{+\cdot}$; 156,158 [100:33.3]; Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_2$: C, 54.04; H, 3.88; N, 9.00. Found: C, 54.05; H, 4.00; N, 8.89.

5-Nitro-N-(4,6-dimethyl-2-chloro-3-pyridyl)-2-hydroxybenzamide (7b)

Crystallized from methanol; yield 0.12 g, 30 %; m.p. 125-126^{o}C; IR (KBr), cm^{-1}3310-3290 (NH), 3400-2500 (OH hydrogen bonded), 1689-1660 (C=O), 1610-1580 (C=N), 1520, 1340 (NO_2), 1500-1460 (C=C aromatic); MS (70eV), *m/z* (%) : 321,323 [48.9:18.5] $(M)^{+\cdot}$; 165 [100]; Anal. Calcd for $C_{14}H_{12}ClN_3O_4$: C, 52.26; H, 3.75; N, 13.06. Found: C, 52.22; H, 3.64; N, 13.00.

Method (B): A suspension of the appropriate acid 5 (0.02 mol), phosphorus trichloride (0.69 g, 0.005 mol) and 3-amino-2-chloropyridine (6b) (3.85 g, 0.03 mol) in chlorobenzene (100 ml) was heated under reflux for 3hr. The reaction mixture was filtered while hot and then the filtrate was cooled. The precipitate formed was crystallized from the suitable solvent to give 7(c-f).

5-Nitro-N-(2-chloro-3-pyridyl)-2-hydroxybenzamide (7c)

Crystallized from methanol; yield 2.76 g, 47 %; m.p. 216-217^{o}C; IR (KBr), cm^{-1}: 3310-3290 (NH), 3400-2500 (OH hydrogen bonded), 1689-1660 (C=O), 1610-1580 (C=N), 1520, 1340 (NO_2), 1500-1460 (C=C aromatic); MS (70ev), *m/z* (%): 293,295 [0.5:0.1] $(M)^{+\cdot}$; 165 [100]; Anal. Calcd for $C_{12}H_8ClN_3O_4$: C, 49.08; H, 2.74; N, 14.30. Found: C, 49.05; H, 2.90; N, 13.90.

5-Bromo-N-(2-chloro-3-pyridyl)-2-hydroxybenzamide (7d)

Crystallized from methanol; yield 3.07 g, 47 %; m.p. 230-231^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,*ppm: 7.06-8.82 (m, 6H, aromatic H's), 10.96 (1H, NH, D_2O exchangeable), 12.35 (1H, OH, D_2O exchangeable); IR (KBr), cm^{-1}: 3310-3290 (NH str.), 3400-2500 (OH hydrogen bonded str.), 1689-1660 (C=O str.), 1610-1580 (C=N str.), 1500-1460 (C=C aromatic str.); MS (70eV), *m/z* (%): 326,328,330 [24.2:26.8:9.2] $(M)^{+\cdot}$; 128,130 [100:40.2]; Anal. Calcd for $C_{12}H_8BrClN_2O_2$: C, 44.00; H, 2.46; N, 8.55. Found: C, 44.03; H, 2.55; N, 8.59.

3,5-Dibromo-N-(2-chloro-3-pyridyl)-2-hydroxybenzamide (7e)

Crystallized from toluene; yield 3.65 g, 45 %; m.p. 250-251^{o}C; IR (KBr), cm^{-1}: 3310-3290 (NH), 3400-2500 (OH hydrogen bonded), 1689-1660 (C=O), 1610-1580 (C=N), 1500-1460 (C=C aromatic); Anal. Calcd for $C_{12}H_7Br_2ClN_2O_2$: C, 35.46; H, 1.73; N, 6.89. Found: C, 35.52; H, 1.78; N, 7.11.

3,5-Dichloro-N-(2-chloro-3-pyridyl)-2-hydroxybenzamide (7f)

Crystallized from methanol; yield 3.04 g, 48 %; m.p. 210-211^{o}C; IR (KBr), cm^{-1}: 3310-3290 (NH), 3400-2500 (OH hydrogen bonded), 1689-1660 (C=O), 1610-1580 (C=N), 1500-1460 (C=C aromatic); MS (70eV), *m/z* (%) : 316,318,320,322 [10.9:7.2:4.1:0.9] $(M)^{+\cdot}$); 128,130 [100:29.7]; Anal. Calcd for $C_{12}H_7Cl_3N_2O_2$: C, 45.39; H, 2.22; N, 8.82. Found: C, 45.55; H, 2.28; N, 8.87.

Substituted pyrido[2,3-b][1,4]benzoxazepin-6(5H)-ones (8a-c)

Sodium methoxide (0.123 g, 0.00228 mol) was added to a solution of the appropriate amide 7 (0.00152 mol) in tetraethyleneglycol dimethyl ether (4 ml), and the stirred mixture was heated at 220 ^{o}C for 5hr. The reaction mixture was then cooled at room temperature, diluted with water (25ml), and neutralized with 1N HCl. The resultant solid was collected and crystallized from the suitable solvent.

8-Bromopyrido[2,3-b][1,4]benzoxazepin-6(5H)-one (8a)

Crystallized from ethanol; yield 0.13 g, 30 %; m.p. 321-322°C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,ppm*: 7.34-8.07 (m, 6H, aromatic H's), 10.78 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3200-3300 (NH), 1660 (C=O), 1590 (C=N), 1485-1550 (C=C aromatic); Anal. Calcd for $C_{12}H_7BrN_2O_2$: C, 49.51; H, 2.42; N, 9.62. Found: C, 49.60; H, 2.65; N, 9.28.

8,10-Dichloropyrido[2,3-b][1,4]benzoxazepin-6(5H)-one (8b)

Crystallized from ethanol; yield 0.10 g, 25 %; m.p. 340-342°C; IR (KBr), cm^{-1}: 3200-3300 (NH), 1675 (C=O), 1610 (C=N), 1485-1550 (C=C arom); Anal. Calcd for $C_{12}H_6Cl_2N_2O_2$: C, 51.27; H, 2.15; N, 9.96. Found: C, 51.20; H, 2.20; N, 10.01.

8-Chloro-2,4-dimethylpyrido[2,3-b][1,4]benzoxazepin-6(5H)-one (8c)

Crystallized from acetone; yield 0.12 g, 30 %; m.p. 302-304°C; ^{1}HNMR (200MHz, DMSO-d_6), *δ*, ppm: 2.33 (s, 3H, CH_3 at position 4), 2.50 (s, 3H, CH_3 at position 2), 7.07-7.70 (m, 4H, aromatic H's), 10.16 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3200-3300 (NH), 1670 (C=O), 1600 (C=N), 1485-1550 (C=C aromatic); MS (70eV), *m/z* (%): 275,277 [20.3:4.4]; $(M+1)^+$; 274,276 [52.5:24.7] $(M)^{+\cdot}$; 232,243 [100:32.6]; Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.03; N, 10.19. Found: C, 61.20; H, 4.21; N, 10.30.

Pharmacology

Four compounds 3a, 3b, 8a & 8c were suspended in saline using Tween 80. Several groups, each consisting of 6 mice (17-25gm) were injected i.p. with tested compounds at a dose level 25mg/Kg. Another group received diazepam 25mg/Kg as a standard, and the last group received saline containing few drops of Tween 80 and served as normal group. Thirty minutes following the administration, each mouse was observed for 3 min. Effect of the compounds on latency time, ambulation, grooming and rearing frequencies as well as that of diazepam were recorded and presented in Table 1.

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تشييد ودراسة التأثير المطمئن لمركبات جديدة من ثنائي بنزوكسازيبينات وبيريدوبنزوكسازيبينات

سمير بطرس صليب ، باسم حشمت نجيب و عبد الجابر نصر عثمان
.قسم الكيمياء العضوية – كلية الصيدلة – جامعة القاهرة – الجيزة – مصر .

تم تحضير سلسلة من مركبات 6، 7، 8، 9 -رباعى هيدروثنائي بنزو] ب، و[1]، [4أوكسازيبين10) 11-يد)-ونات جديدة عن طريق ألكلة مركبات الساليسلاميدات (1) بمركب 2-بروموهكسانون حلقى متبوعا بحلقنة الاميدات الناتجة .(2) وأيضا تم تحضير مركبات بيريدو [ب،و] [4،1] أوكسازيبين 6-5)يد)-ونات (8) عن طريق تفاعل مركبات كلوريد السليسويل (4 (أو أحماضهما المقابلة (5) مع مركبات4 ، -6ثنائي ميثيل-2-كلورو-3 -بيريدين امين (6) ومعاملة الاميدات (7) الناتجة مع ميثوكسيد الصوديوم .

وبالإضافة إلى ما تقدم، فقد تضمن البحث أيضاً عمل مسح مبدئى لبعض المركبات المنتخبة لتبيان ما قد يكون لها من نشاط حيوى كمطمئنات.