Synthesis of New Thieno and Pyrazolo[2,1]benzothiazepine Derivatives with Potential Antidepressant Properties

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In this paper we describe a series of new thieno and pyrazolo[2,1]benzothiazepine derivatives **7a-o** which were synthesized by two different methods both starting from the previously described tricyclic alcohols **1-3**. Several components of this series were effective p. o. (per os, orally) in different pharmacological tests currently employed in the evaluation of antidepressant activity.

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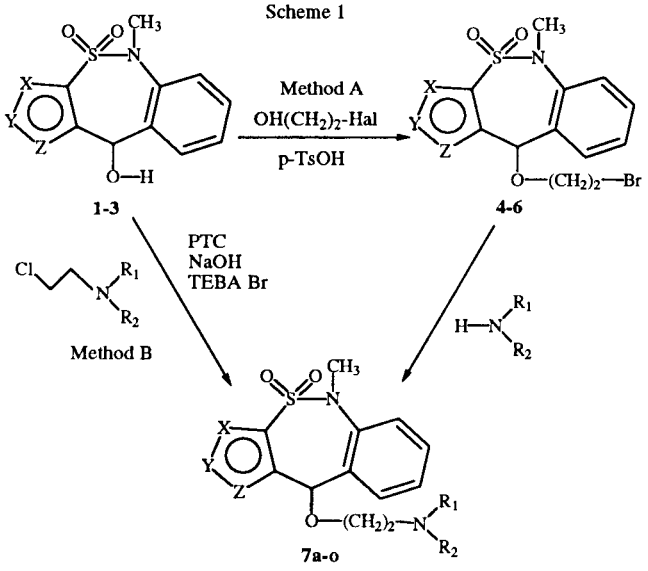
As a part of a research project directed to the discovery of novel psychotropic agents, we have already described the synthesis of a number of hetero[2,1]benzothiazepines which displayed noticeable antidepressant activity in several classical screening tests [1]. These compounds are thiophene and pyrazole bioisosteres of the antidepressant tianeptine and contain in their structures several oxime ether side chains which form part of other tricyclic drugs like amineptine, fluvoxamine, demexiptilina, etc. Tianeptine also possesses a tricyclic structure and, unlike its tricyclic analogues, increases the uptake of serotonin [2].

In an attempt to improve the activity of such compounds, we have prepared a series of new derivatives of these ring systems in which different aminoethoxy side chains were included. The introduction of these types of side chains in some psychotropic agents was a useful recourse frequently employed to retain or enhance the central nervous system activities of these drugs. Thus, for instance, the aminoether derivatives of classical antidepressants show not only the antidepressant effects of imipramine-like compounds but also the antihistaminic actions of phenothiazines [3]. In this paper, the synthesis and the results of a preliminary pharmacological evaluation of the new derivatives are reported [4].

Scheme 1



The hitherto unknown series of the 2-[(5,10-dihydro-4,4-dioxo-5-methyl-thieno[3,4-*c*][2,1]benzothiazepin-10-yl)oxy]-*N*-alkylethylamines **7a-e**, 2-[(5,10-dihydro-4,4-dioxo-5-methyl-thieno[3,2-*c*][2,1]benzothiazepin-10-yl)oxy]-*N*-alkylethylamines **7f-j**, and 2-[(4,9-dihydro-2,9-dimethyl-10,10-dioxo-2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepin-4-yl)oxy]-*N*-alkylethyl amines **7k-o** (Scheme 1), were synthesized by methods A and B both starting from the previously described tricyclic alcohols **1-3** [5].

Method A consisted of the reaction of these alcohols with 2-bromoethanol and the subsequent nucleophilic attack to the formed bromoether derivatives by primary or secondary amines. The first step was carried out by heating alcohols **1-3** at reflux temperature with the 2-haloethanol and catalytic amounts of *p*-toluenesulfonic acid in toluene. The water released in the reaction was removed by azeotropic distillation and the bromoethers **4-6** were isolated by elimination of the solvent. Due to the irritating nature of these compounds they were used in the next reaction without further purification. Reaction of **4-6** with the chosen amines in tetrahydrofuran at room temperature afforded the desired benzothiazepin-*N*-alkylethyl amines **7a-o** in good yields.

Except for **7n** and **7o**, which were solids, all the benzothiazepine derivatives were oily compounds in their free base form. They were transformed into the corresponding salts by precipitation with maleic or succinic acid. Table 1 lists the yields obtained and their main physical and analytical characteristics. Spectral data are compiled in Table 2. Only the thieno[3,2-*c*]benzothiazepine derivatives **7f-j** gave the expected hydrochloride salts when treated with a saturated solution of hydrogen chloride in ethanol. The

rest of the components of the series afforded, in these conditions, the respective ethoxy-thieno[2,1]benzothiazepines in a transetherification reaction similar to that described for diphenylmethane ethers [6].

Method B was a modification of the phase-transfer catalysis procedures more commonly utilized in the alkylation of alcohols [7,8] which was adapted to our needs. In a typical experiment, the starting hydroxy compound and the aminoethylchloride were heated in a heterogeneous mixture of toluene and aqueous sodium hydroxide with triethylbenzylammonium bromide as the catalyst. In this way, compounds **7e-d** and **7l-n** were prepared from the alcohols **1** and **3** respectively. Yields were lower than those obtained with Method A (Table 1).

motor activity, but without reaching the low value elicited by diazepam (Table 3). Compounds **7e**, **7h**, **7l** and **7m** showed a rather psychostimulating effect at 25 mg/kg p. o. which was not confirmed at a dose four times higher. None of them, however, reached the effects produced by amphetamine, the psychostimulant of reference. Some of these compounds also produced a slight hypothermia at the first hour (Table 4). However, compound **7l**, at the dose of 25 mg/kg p. o., significantly increased the normal body temperature of mice. Besides, some of them significantly increased at 100 mg/kg p. o. the sleep induced in mice by a hypnotic dose of sodium pentobarbital (Table 5). In this respect, the compound **7h** confirmed its sedative effect since it induced the sleep in 60% of the

Table 1

Compounds **7a-o** synthesized.

Compound	R_1	R_2	Yield (%) Method A	Yield (%) Method B	Mp (°C) Maleate salt*	Formula	Analysis Calc./Found (%) C	H	N	S
7a	H	CH_3	58		172-175	$C_{19}H_{22}N_2O_7S_2$	50.20	4.88	6.16	14.10
							50.23	4.92	6.30	13.97
7b	CH_3	CH_3	73	54	172-174	$C_{20}H_{24}N_2O_7S_2$	51.26	5.16	5.98	13.78
							51.56	4.99	5.82	13.41
7c	$(CH_2)_4$		92	71	156-157	$C_{22}H_{26}N_2O_7S_2$	53.42	5.30	5.66	12.97
							53.68	4.96	5.71	13.08
7d	$(CH_2)_5$		79	42	142-145	$C_{23}H_{28}N_2O_7S_2$	54.31	5.55	5.51	12.61
							54.58	5.35	5.64	12.59
7e	$(CH_2)_2$-NH-$(CH_2)_2$		83		121-124 [a]	$C_{26}H_{31}N_3O_{11}S_2$	49.90	4.99	6.71	10.25
							49.46	5.05	6.64	9.91
7f	H	CH_3	70		167-169 dec	$C_{19}H_{22}N_2O_7S_2$	50.20	4.88	6.16	14.10
							50.45	4.82	5.98	14.11
7g	CH_3	CH_3	63		151-152 dec	$C_{20}H_{24}N_2O_7S_2$	51.26	5.16	5.98	13.78
							51.13	5.19	6.17	13.69
7h	$(CH_2)_4$		83		130-132 dec	$C_{22}H_{26}N_2O_7S_2$	53.42	5.30	5.56	12.97
							53.60	5.20	5.50	12.63
7i	$(CH_2)_5$		70		193-195 [b]	$C_{19}H_{25}ClN_2O_3S_2$	53.19	5.87	6.53	14.95
							53.13	5.86	6.30	15.23
7j	$(CH_2)_2$-NH-$(CH_2)_2$		70		122-125 [a]	$C_{26}H_{31}N_3O_{11}S_2$	49.90	4.99	6.71	10.25
							49.71	4.91	6.63	10.32
7k	H	CH_3	40		143-146	$C_{19}H_{24}N_4O_7S$	50.43	5.35	12.38	8.09
							50.59	5.43	12.02	8.28
7l	CH_3	CH_3	59	48	152-154	$C_{20}H_{26}N_4O_7S$	51.49	5.62	12.01	6.87
							51.71	5.52	11.97	6.97
7m	$(CH_2)_4$		88	53	130-133 [c]	$C_{22}H_{30}N_4O_7S$	53.42	6.11	11.33	6.48
							53.53	6.01	11.11	6.15
7n	$(CH_2)_5$		90	75	49-53 [d]	$C_{19}H_{26}N_4O_3S$	58.43	6.71	14.35	8.21
							58.79	6.51	13.98	8.53
7o	$(CH_2)_2$-NH-$(CH_2)_2$		76		57-60 [d]	$C_{18}H_{25}N_5O_3$	55.22	6.44	17.89	8.19
							55.58	6.20	18.24	8.31

* Recrystallization solvent: Ethanol. [a] Dimaleate. [b] Hydrochloride. [c] Succinate. [d] Free base (purified by flash chromatography, silicagel or alumina-MeOH).

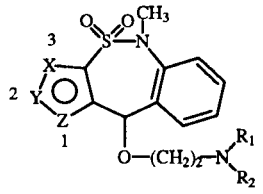
The compounds under study were originally evaluated for their possible antidepressant effects. Potentiation of pentobarbital sleeping time, effects on spontaneous motility and body temperature were first studied in male mice [9]. Tables 3-5 summarize the results obtained for compounds which were significantly different from the control.

The majority of the screened compounds showed, at the highest dose assayed, a decrease of the spontaneous locoanimals treated with a subhypnotic dose (20 mg/kg i. p.) of the barbituric.

In summary, starting from the previously described tricyclic alcohols **1-3**, a series of new thieno and pyrazolo[2,1]benzothiazepine derivatives were synthesized and pharmacologically evaluated. Several components of this series were found effective p. o. in different pharmacological tests currently employed in the evaluation of the antidepressant activity of chemical products. The most

Table 2

^{1}H nmr data of compounds **7a-o**.



Compound[a]	δ H1 (d)	δ H2 (s) or δ $CH_3$2 (s)	δ H3 (d)	δ N-CH_3 (s)	δ H8 (s)	δ $(CH_2)_2$ (t)	R_1 and R_2	δ Benzene (m)
7a	7.85		8.35	3.35	5.85	3.75; 3.20	2.60 (s)	7.50
7b	7.85		8.35	3.40	5.85	3.80; 3.35	2.80 (s)	7.50
7c	7.85		8.35	3.60-3.10 (m)	5.85	3.80; 3.35	3.60-3.10 (m); 1.90 (m)	7.50
7d[b]	7.60-7.20 (m)		8.00	3.40	5.70	3.95; 3.30	3.00 (m); 1.90 (m)	7.60-7.20
7e	7.80		8.30	3.90	5.75	3.65; 3.30-2.95 (m)	3.30-2.95 (m); 2.90-2.40 (m)	7.50
7f		7.35	7.75	3.45	6.15	3.90; 3.30	2.65 (s)	7.70-7.40
7g		7.35	7.75	3.40 (m)	6.20	4.00; 3.40 (m)	2.90 (m)	7.60-7.40
7h[b]		7.30	7.30	3.50 (m)	5.95	4.10; 3.50 (m)	2.10 (m)	7.60-7.35
7i[b]		7.30	7.30	3.50	6.00	4.30 (m); 3.30 (m)	3.10-2.60 (m); 2.45-1.65 (m)	7.65-7.35
7j		7.35	7.70-7.45 (m)	3.45	6.15	3.85; 3.15 (m)	2.75 (m)	7.70-7.45
7k	8.05 (s)	3.90		3.40	5.60	3.60; 3.15	2.60 (s)	7.65-7.35
7l	8.05 (s)	3.95		3.40	5.65	3.70; 3.35	2.80 (s)	7.50
7m	8.00 (s)	3.90		3.40	5.55	3.55; 2.75	2.60 (m); 2.40 (s); 2.65 (m)	7.50
7m[b]	7.50 (s)	3.80		3.45	5.50	3.60; 2.55	2.40 (m); 1.45 (m)	7.40
7o[b]	7.50	3.90		3.50	5.45	3.65; 2.60	2.90 (m); 2.50 (m)	7.45

[a] Solvent: DMSO-d_6. [b] Solvent: deuteriochloroform.

Table 3

Effect of some compounds **7** on spontaneous locomotor activity (mean ± SEM).

Compound	Dose mg/kg p.o.	Horizontal activity 60 min	Total distance (cm) 60 min	Number of movements 60 min
Control	-	2108.30 ± 69.28	955.80 ± 44.48	161.60 ± 4.81
7e	25	2381.83 ± 282.44	1318.50 ± 244.08*	188.50 ± 15.37*
7h	25	2417.50 ± 199.32	1287.50 ± 198.23*	187.83 ± 13.08*
7l	25	2281.33 ± 144.33	1401.67 ± 218.40**	191.50 ± 11.47*
7m	25	2446.60 ± 42.03*	1436.20 ± 104.87**	186.20 ± 10.95*
Amphetamine	5	3244.00 ± 196.79**	1928.83 ± 179.25**	243.66 ± 9.10**
Diazepam	20	466.16 ± 135.41**	356.20 ± 102.86**	40.60 ± 11.32**
Control	-	2840.00 ± 201.52	1160.27 ± 65.71	165.60 ± 7.48
7b	100	1964.67 ± 260.73*	709.50 ± 61.22**	125.83 ± 13.87*
7c	100	3050.80 ± 451.59	1454.83 ± 504.41	141.67 ± 27.32
7d	100	1851.50 ± 199.31*	719.67 ± 105.31**	128.83 ± 16.85*
7e	100	2192.50 ± 309.13	912.33 ± 218.91*	157.17 ± 13.74
7h	100	1654.83 ± 197.98**	750.66 ± 60.29**	155.16 ± 11.07**
7j	100	1673.50 ± 250.72**	719.83 ± 163.16**	109.00 ± 16.37**
7k	100	2002.00 ± 139.27*	846.50 ± 51.65*	137.16 ± 16.64
7l	100	1791.33 ± 157.29**	903.16 ± 163.72	128.83 ± 15.89*
7m	100	2332.00 ± 300.00	1048.00 ± 157.96	155.33 ± 11.52
7n	100	1713.00 ± 213.81*	763.83 ± 364.59	112.16 ± 29.06*
Diazepam	20	725.00 ± 90.45**	468.88 ± 65.37**	49.53 ± 7.05**

* $p < 0.05$; ** $p < 0.01$ (Student's t-test).

Table 4
Effect of some compounds **7** on body temperature (mean ± SEM).

Compound	Dose mg/kg p.o.	Mean decrease in rectal temperature (°C) 1 h	2 h	4 h	8 h	24 h
Control	-	0.18 ± 0.29	0.76 ± 0.23	1.46 ± 0.28	1.18 ± 0.28	0.11 ± 0.23
7d	25	1.02 ± 0.21	2.12 ± 0.15**	2.10 ± 0.10	1.42 ± 0.20	0.44 ± 0.16
7e	25	0.92 ± 0.27	2.06 ± 0.34**	2.12 ± 0.17	1.74 ± 0.27	0.44 ± 0.22
7i	25	1.78 ± 0.34*	1.00 ± 0.21	2.04 ± 0.18	2.24 ± 0.39	—0.28 ± 0.27
7j	25	1.82 ± 0.17**	1.02 ± 0.29	2.46 ± 0.51	2.58 ± 0.36*	—0.02 ± 0.35
7l	25	—1.08 ± 0.20*	0.50 ± 0.10	—0.28 ± 0.26**	0.70 ± 0.16	—1.00 ± 0.19*
Diazepam	20	2.32 ± 0.22**	2.96 ± 0.27**	3.88 ± 0.39**	1.54 ± 0.24	0.35 ± 0.29
Imipramine	25	—0.14 ± 0.66	1.58 ± 0.51	1.86 ± 0.77	0.70 ± 0.57	—0.50 ± 0.38
Control	-	—0.07 ± 0.24	0.21 ± 0.33	1.65 ± 0.30	1.70 ± 0.24	0.17 ± 0.29
7a	100	1.34 ± 0.27**	1.52 ± 0.44	2.00 ± 0.40	1.76 ± 0.55	0.88 ± 0.19
7f	100	1.36 ± 0.19**	0.86 ± 0.27	2.18 ± 0.30	1.58 ± 0.47	0.80 ± 0.46
7g	100	0.90 ± 0.26*	0.16 ± 0.51	2.30 ± 0.22	2.06 ± 0.39	0.04 ± 0.09
7h	100	1.58 ± 0.17**	0.42 ± 0.21	2.10 ± 0.38	1.98 ± 0.41**	0.04 ± 0.12
7j	100	1.98 ± 0.38**	0.92 ± 0.35	0.78 ± 0.42	2.08 ± 0.30	0.64 ± 0.34
7k	100	1.52 ± 0.23**	1.02 ± 0.15	2.02 ± 0.33	1.22 ± 0.22	0.44 ± 0.31
Imipramine	100	2.66 ± 0.64*	1.32 ± 0.37	0.50 ± 0.42	1.70 ± 0.23	0.57 ± 0.42

* $p < 0.05$; ** $p < 0.01$ (Student's t-test).

Table 5
Effect of some compounds **7** on pentobarbital-induced sleeping time.

Compound	Dose mg/kg p.o.	Sleeping time (min) x ± SEM Control	Test drug	Variation (%)
7e	25	48.45 ± 6.54	33.00 ± 2.14*	—31.89
	100	40.33 ± 1.67	60.03 ± 4.17**	48.84
7f	25	48.45 ± 6.54	59.43 ± 3.86	22.66
	100	40.33 ± 1.67	75.36 ± 2.39**	86.86
7g	25	48.45 ± 6.54	58.21 ± 8.69	20.14
	100	40.33 ± 1.67	72.57 ± 3.17**	79.94
7h	25	48.45 ± 6.54	56.38 ± 6.01	16.37
	100	40.33 ± 1.67	79.15 ± 7.60**	96.25
7j	25	48.45 ± 6.54	46.05 ± 2.17	—4.95
	100	40.33 ± 1.67	65.92 ± 7.53*	63.45
Diazepam	15	48.45 ± 6.54	154.81 ± 7.22**	219.52

* $p < 0.05$; **$p < 0.01$ (Student's t-test).

active compounds in these tests will be assayed in other animal models, like the antagonism to tetrabenazine-induced effects and the Porsolt test, which are more predictive of antidepressant activity.

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Ir spectra were recorded using a Shimadzu IR-435 instrument. ^{1}H nmr spectra were measured with a Bruker AM-200 and a Varian XL-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane in appropriate solvents. The purity of compounds was verified by thin-layer chromatography (tlc) which was run on silica gel GF_{254} (E. Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents. Medium-pressure chromatography was performed using 230-400 mesh silica gel purchased from E. Merck, Inc. Microanalysis were performed at the Centro Nacional de Química Orgánica on a Perkin-Elmer 2400 CHN analyzer.

[(Hetero[2,1]benzothiazepinyl)oxy]-1-bromoethanes **4-6**.

General Procedure.

A solution of 2-bromoethanol (6.25 g, 3.54 ml, 0.05 mol), *p*-toluenesulfonic acid (0.5 g) and the corresponding tricyclic alcohol **1-3** (0.05 mol) in toluene (300 ml) was heated at reflux temp. for 1 hour. The water produced in the reaction was removed by azeotropic distillation. The mixture was washed with water, a 10% solution of sodium bicarbonate and water again. The organic layer was dried (magnesium sulfate) and the solvent evaporated *in vacuo* to give the desired bromoethers.

2-[(5,10-Dihydro-4,4-dioxo-5-methyl-thieno[3,4-*c*][2,1]benzothiazepin-10-yl)oxy]-1-bromoethane (**4**).

This compound was synthesized in 72% yield by reaction of 5,10-dihydro-4,4-dioxo-10-hydroxy-5-methyl-thieno-[3,4-*c*][2,1]benzothiazepine (**1**) with 2-bromoethanol as a white solid which was used as such in the next reaction; ir (potassium bromide): 1310, 1140 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 3.45 (s, 3H, CH_3), 3.55 (t, J = 6.0 Hz, 2H, CH_2), 3.95 (t, J = 6.0 Hz, 2H, CH_2), 5.75 (s, 1H, CH), 7.20-7.60 (m, 5H, 4H benzene and 1H thiophene), 7.95 (d, J = 3.7 Hz, 1H, thiophene).

2-[(5,10-Dihydro-4,4-dioxo-5-methyl-thieno[3,2-*c*][2,1]benzothiazepin-10-yl)oxy]-1-bromoethane (**5**).

This compound was synthesized in 76% yield from 5,10-dihydro-4,4-dioxo-10-hydroxy-5-methyl-thieno[3,2-*c*][2,1]benzothiazepine (**2**) as a white solid which was used as such in the next reaction; ir (potassium bromide): 1315, 1140 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 3.50 (s, 3H, CH_3), 3.60 (t,

J = 6.0 Hz, 2H, CH_2), 4.05 (t, J = 6.0 Hz, 2H, CH_2), 5.95 (s, 1H, CH), 7.20-7.70 (m, 6H, 4H benzene and 2H thiophene).

2-[(4,9-Dihydro-2,9-dimethyl-10,10-dioxo-2*H*-pyrazolo[3,4-*c*]-[2,1]benzothiazepin-4-yl)oxy]-1-bromoethane (**6**).

This compound was prepared in 94% yield from 4,9-dihydro-2,9-dimethyl-10,10-dioxo-4-hydroxy-2*H*-pyrazolo[3,4-*c*]-[2,1]benzothiazepine (**3**) as a white solid which was used as such in the next reaction; ir (nujol): 1330, 1160 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 3.45 (m, 5H, CH_3 and CH_2), 3.80 (t, J = 6.0 Hz, 2H, CH_2), 3.95 (t, J = 6.0 Hz, 2H, CH_2), 5.75 (s, 1H, CH), 7.20-7.60 (m, 5H, 4H benzene and 1H thiophene), 7.95 (d, J = 3.7 Hz, 1H, thiophene).

[(Hetero[2,1]benzothiazepinyl)oxy]-N-alkylethylamines **7a-o**.

Method A.

To a solution of bromoethers **4-6** (5 mmol) in tetrahydrofuran (15 ml) was added an excess of the corresponding amine (or an ethanolic solution in the case of gaseous amines). The mixture was kept 24 hours at room temperature and then evaporated to dryness. The residue was dissolved in toluene (40 ml) and the solution was washed with water. The organic layer was extracted four times with 20% aqueous acetic acid and the extracts were basified with 20% aqueous sodium hydroxide. The precipitated product was extracted with ethyl acetate or ethyl ether. After evaporation of solvent, the oily crude material was transformed into the corresponding maleate, succinate or hydrochloride salt which was recrystallized from ethanol.

Method B.

A mixture of sodium hydroxide (4 g, 0.1 mol), water (20 ml), toluene (50 ml), the corresponding tricyclic alcohol **1-3** (0.01 mol), the desired 2-chloro-*N,N*-dialkylethylamine hydrochloride (0.01 mol) and triethylbenzylammonium bromide (0.54 g, 0.002 mol) was stirred at reflux temperature for 20 hours. After cooling, the organic layer was separated, washed with water and dried (magnesium sulfate). The toluene was evaporated *in vacuo* and the oily products obtained were converted, as in Method A, to the respective maleate, succinate or hydrochloride salts.

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