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SYNTHESIS AND EVALUATION OF THE ANTICONVULSANT ACTIVITY OF A SERIES OF 2-AMINO-1-PHENYL-1-PROPANOLS DERIVED FROM THE METABOLITES OF THE ANTIDEPRESSANT BUPROPION

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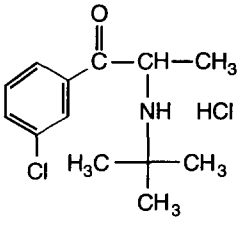
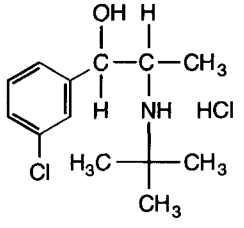
Abstract: A series of 2-amino-1-phenyl-1-propanols that are structurally related to known metabolites of bupropion,**1** (Wellbutrin®) were synthesized and evaluated as potential anticonvulsants. The (**R*,R***)-2-*tert*-butylamino-1-(3-trifluoromethylphenyl) propanol **20** had an ED_{50} of 16.5 ± 2.8 mg/kg ip in mice in the maximal electroshock screen and was chosen for further evaluation.

Introduction

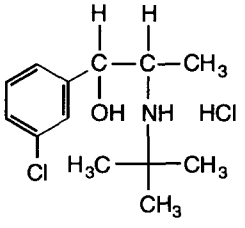
Studies of the metabolic fate[2] of the clinically efficacious antidepressant bupropion,[3] **1** (Wellbutrin®, 2-*tert*-butylamino-3′-chloropropiophenone) identified the **R*,R*** (threo) and **R*,S*** (erythro) aminoalcohols **2** and **3**, respectively. In an earlier report we described the preparation of **2** and **3** and their enantiomers.[4] This paper describes the potent anticonvulsant activity of **2** as compared to **3** and the structure-anticonvulsant activity relationship of this class of compounds.



1, Bupropion



2, R*,R* (threo)

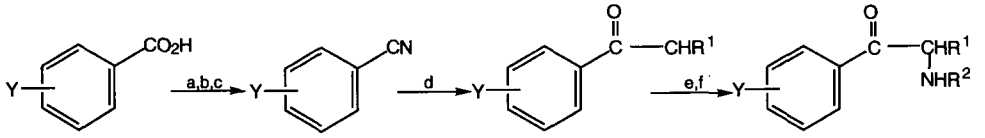


3, R*,S* (erythro)

Chemistry

The aminoalcohols were prepared by reduction of the appropriately substituted aminoketones with borane-tetrahydrofuran or sodium borohydride in ethanol. The general method for the synthesis of aminoketones, such as bupropion, is shown in Scheme I. The benzonitriles were either commercially available or prepared from the corresponding benzoic acids by conversion to the benzamides,[5] followed by treatment with thionyl chloride.[6] The arylketones were prepared from the corresponding benzonitriles by reaction with alkylmagnesiumbromides or iodides.[7,8] Bromination of the arylketones, with either dioxane dibromide[9] or bromine in methanol,[10] followed by treatment with the desired amines gave the aminoketones. The reduction of the aminoketones is shown in Scheme II.[11] Borane-tetrahydrofuran reduction[4] gives a

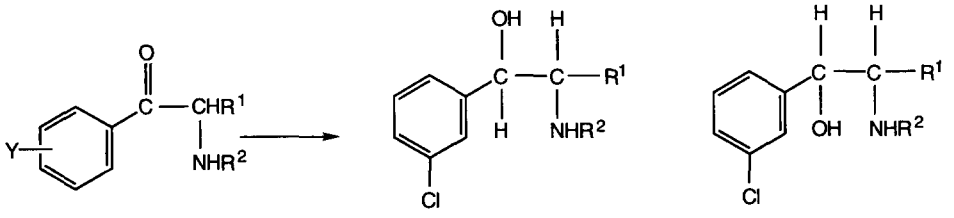
Scheme I



(a) $SOCl_2$ or oxalyl chloride; (b) NH_4OH/dioxane; (c) $SOCl_2/\Delta$; (d) R^1MgX/Et_2O; (e) Br_2/MeOH or dioxane dibromide/dioxane; (f) H_2NR^2/CH_3CN.

diastereomeric mixture that is approximately 80% **R*,R*** and 20% **R*,S***, as determined by NMR studies.[12] Sodium borohydride reduction gives approximately 80% **R*,S*** and 20% **R*,R***. The diastereomers can

Scheme II



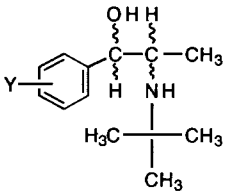
		2, R*R* (threo)	**3**, R*S* (erythro)
Reagent :	BH_3-THF	~80%	~20%
	$NaBH_4$/95%EtOH	~20%	~80%

be separated by preparative HPLC, as described in the literature.[13] Resolutions were carried out according to previously published procedures.[4]

Biological Discussion

The discovery of the potent anticonvulsant activity of the metabolite of bupropion prompted us to intitate a structure–activity relationship (SAR) study of phenylaminoalcohols. The SAR study was partially based on the Topliss tree approach.[14] The compounds were evaluated in the maximal electroshock (MES) assay[15] for potential anticonvulsant activity; the results of the assay are presented in Tables 1-3. In the (**R*,R***) series the unsubstituted analogue **5** had an ED_{50} of 14 mg/kg ip in mice in the MES screen. The 4-Cl derivative **7** is two times less active than **5**. The 4-OMe derivative was not evaluated in the **R*,R*** series. However, the 3-Cl metabolite of bupropion (**2**) was equipotent with **5** with an ED_{50} of 14 ± 2.3 mg/kg ip mice. The 3-CF_3 (**20**), 3-Br (**15**), and 3,4-Cl_2 (**24**) derivatives were equipotent with **2**, while the 3-NO_2 analogue **17** lost all activity. The 4-Me (**10**) analogue was approximately twofold less potent than **2**. In the **R*,S*** series, the unsubstituted (**4**) and the 4-Cl (**6**) analogues were of equal activity, which led us to evaluate the 4-Me derivative **9**. This compound was inactive; thus the Topliss approach would require evaluation of the 3-Cl metabolite of bupropion **3**. Compound **3** is more active than **9** with an ED_{50} of 26 mg/kg ip mice in the MES screen. The 3-CF_3 analogue (**19**) is equipotent with **3** while the 3-Br derivative (**16**) is approximately twofold more active than **3**. The 3-NO_2 (**18**) and 4-OMe (**8**) analogues lost all activity.

Table 1. Anticonvulsant Activity of Phenylaminopropanols.

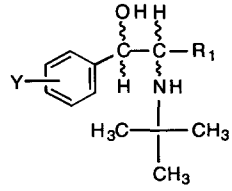


Compd	Y	Isomer[a]	Anticonvulsant Activity Maximal Electroshock (MES) ED_{50} mg/kg ip mice
2	3-Cl (rac)[b,c]	T	14 ± 2.3
3	3-Cl (rac)[d]	E	26
4	H[16]	E	25
5	H[16]	T	14
6	4-Cl	E	25
7	4-Cl	T	29
8	4-OMe	E	IA@70[e]
9	4-Me	E	IA@40
10	4-Me	T	33
11	3-Cl (+)[e]	T	14
12	3-Cl (-)[e]	T	11
13	3-Cl (+)[e]	E	-
14	3-Cl (-)[e]	E	28
15	3-Br	T	11
16	3-Br	E	16
17	3-NO_2	T	IA @ 40
18	3-NO_2	E	IA @ 40
19	3-CF_3 (rac)	E	25
20	3-CF_3 (rac)	T	16 ± 2.8
21	3-CF_3 (+)	T	22
22	3-CF_3 (-)	T	17
23	3,4-Cl_2[17]	E	31
24	3,4-Cl_2	T	13
phenyltoin[18]			8.5

[a]E = erythro (**R*,S***) and T = threo (**R*,R***). [b]rac = racemate. [c]Ref 3. [d]Ref 11. [e]IA = inactive at indicated dose.

Next, we investigated the effect of the length of the aryl side chain on anticonvulsant activity (see Table 2). Comparing the analogues that contained a 3-Cl substituent on the aryl ring, the phenylethanol analogue **25** was equipotent with **3** and approximately two times less active than **2**. Chain extension to the phenylbutanol derivative (**27**) in the **R*,R*** series had little effect on activity as compared to **2**. In the **R*,S*** series, the phenylbutanol analogue **26** and the phenylpentanol derivative **30** were equipotent with **3**. When the aryl substituent is 3-CF_3 in the (**R*,R***) series, increasing the chain length to the phenylbutanol derivative (**29**) resulted in a twofold loss in activity. In the (**R*,S***) series chain extension to the phenylbutanol analogue (**28**) resulted in a loss of activity while the phenylpentanol derivative (**31**) was equipotent with **3**.

Table 2. Anticonvulsant Activity of Side Chain Variations.



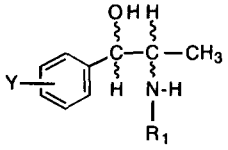
Compd	Y	Isomer[a]	R_1	Anticonvulsant Activity Maximal Electroshock (MES) ED_{50} mg/kg ip mice
25	3-Cl	NA	H[19]	28
26	3-Cl	E	Et	26
27	3-Cl	T	Et	15
28	3-CF_3	E	Et	40
29	3-CF_3	T	Et	31
30	3-Cl	E	Pr	31
31	3-CF_3	E	Pr	31

[a]NA =not applicable, E = erythro (**R*,S***), and T = threo (**R*,R***).

Examination of the effect that various amines had on anticonvulsant activity (see Table 3), while keeping the 3-Cl aryl substituent, indicates that several branched amines such as the *tert*-butyl **2**, *tert*-amyl **38**, and cyclohexyl **42** substituents are compatible with activity. In the **R*,S*** series the primary amine (**32**) was inactive while the *tert*-butyl (**3**), isopropyl (**33**), and *tert*-amyl (**37**) analogues are all equipotent. However, when the aryl substituent was 3-CF_3 in the **R*,R*** series, the isopropyl (**34**) and sec-butyl (**36**) derivatives, as well as the unbranched amino substituent n-butyl (**35**), resulted in loss of activity as compared to **20**. Comparison of **3** with **41** indicates that an aminoalcohol group was not tolerated.

Finally, resolution of the 3-Cl threo isomer (**R*,R*;2**) to give **11** and **12**, of the erythro isomer (**R*,S*;3**) to give **13** and **14**, and of the 3-CF_3 threo isomer (**R*,R*;20**) to give **21** and **22**, did not significantly improve activity in the maximal electroshock screen as compared to the racemates.

Table 3. Anticonvulsant Activity of Amine Variations.



Compd	Y	Isomer[a]	R_1	Anticonvulsant Activity Maximal Electroshock (MES) ED_{50} mg/kg ip mice
32	3-Cl	E	H	@60[b]
33	3-Cl	E	$CHMe_2$[20]	20
34	3-CF_3	T	$CHMe_2$[20]	40
35	3-CF_3	T	n-C_4H_9	IA @ 13
36	3-CF_3	T	EtCHMe	31
37	3-Cl	E	CMe_2Et	23
38	3-Cl	T	CMe_2Et	11
39	3-CF_3	E	CMe_2Et	28
40	3-CF_3	T	CMe_2Et	18
41	3-Cl	E	CMe_2CH_2OH[21]	IA@30
42	3-Cl	T	C_6H_{11}	13

[a]E = erythro (**R*,S***) and T = threo (**R*,R***). [b]IA = inactive at indicated dose.

Conclusion

In general, the **R*,R*** diastereomers were more potent than the corresponding **R*,S*** diastereomers in the MES screen. Side chain extension resulted in derivatives that were equipotent or less potent than the metabolites of bupropion **2** and **3**. Incorporation of the *tert*-butyl and *tert*-amyl amino groups gave some of the most active analogues. Compound **20** had an ED_{50} of 16.5 ± 2.8 mg/kg ip mice in the MES screen and compared favorably with the standard anticonvulsant phenytoin (ED_{50} = 8.5 mg/kg ip mice[18]). Compound **20** was chosen for further evaluation.

Acknowledgment

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