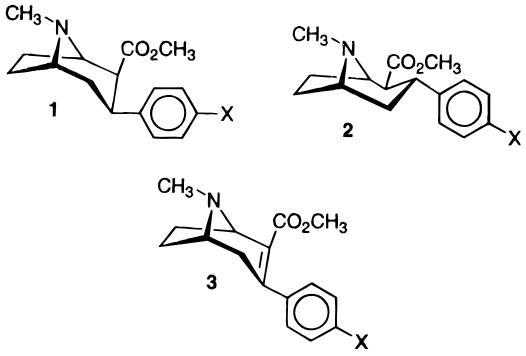
3α-(4′-Substituted phenyl)tropane-2*β*-carboxylic Acid Methyl Esters: Novel Ligands with High Affinity and Selectivity at the Dopamine Transporter

Christopher R. Holmquist,[†]
Kathryn I. Keverline-Frantz,[†] Philip Abraham,[†]
John W. Boja,[‡] Michael J. Kuhar,[‡] and
F. Ivy Carroll*,[†]

Chemistry and Life Sciences, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, North Carolina 27709, and National Institute on Drug Abuse, Addiction Research Center, P.O. Box 5180, Baltimore, Maryland 21224

Received July 16, 1996

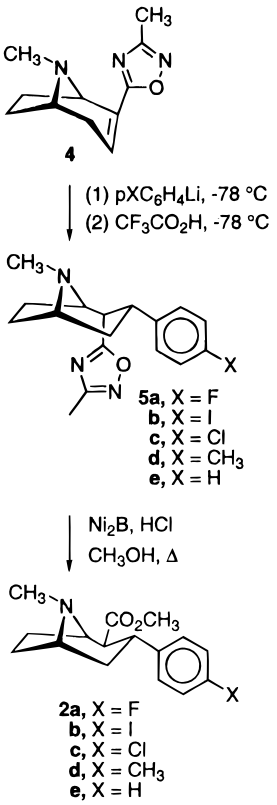
Since their initial preparation by Clarke and coworkers[1] over 23 years ago, the 3*β*-(substituted phenyl)tropane-2*β*-carboxylic acid methyl ester class of compounds **1** have been widely employed in structure−activity relationship (SAR) studies at the cocaine binding site on the dopamine transporter (DAT).[2] Since neither Clarke's nor any other reported method provided the 3α-phenyl analogs, the SAR studies did not include this isomer. Recently, we reported the synthesis of the first 3α-(substituted phenyl)tropane-2*β*-carboxylic acid methyl esters **2** by samarium iodide reduction of 3-aryl-2-carbomethoxytropenes **3**.[3] In this paper we describe a more efficient synthesis of several new 3α-(substituted phenyl)tropane-2*β*-carboxylic acid methyl esters **2** and present the results of the first monoamine transporter binding studies on this series of compounds.



The route used to synthesize the 3α-(substituted phenyl)tropane-2*β*-carboxylic acid methyl ester (**2a**−**e**) analogs is shown in Scheme 1, and the physical properties are listed in Table 1. Addition of a solution of (1*R*,5*S*)-2-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (**4**)[4] in anhydrous tetrahydrofuran or ether to a −78 °C solution of the appropriate aryllithium followed by quenching with trifluoroacetic acid at −78 °C formed 3α-(substituted phenyl)tropane-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropanes **5**. In some cases (X = CH_3, I) the 2α,3*β*-isomer was also formed; this isomer could either be removed by flash column chromatography or carried through the next reaction.

Conversion of the oxadiazole to the methyl ester was accomplished by reduction with nickel boride and hydrochloric acid in refluxing methanol. Under the

Scheme 1



reaction conditions, complete epimerization at C-2 to form the 2*β*,3α-stereoisomer is observed. This is in agreement with previously reported observations on 3α-phenyl-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane (**5e**, X = H)[5] and is presumably driven by the ability of the piperidine ring to adopt an equatorially substituted twist-boat conformation (Figure 1).

Analysis of the ^{1}H NMR and COSY spectra of methyl esters **2a**−**e** (Table 2), using pyridine-d_5 for chemical shift dispersion, shows weak coupling between H_1 and H_2 ($J_{1,2}$ = ∼1.7 Hz), while H_2 couples to H_3 with a coupling constant of 9.4−9.7 Hz. These observations are consistent with a twist-boat conformation in which H_2 is close to orthogonal with H_1 and has a near trans-diaxial relationship to H_3. This contrasts sharply with allococaine (**6**) where the ^{1}H and ^{13}C NMR data show that this compound possesses a chair conformation.[6] As in the 2*β*,3*β*-isomers **1**, the equatorial proton at C-4 of the 2*β*,3α-isomers **2** is deshielded relative to its axial

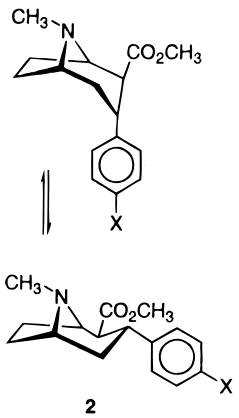


Figure 1.

[†] Research Triangle Institute.
[‡] National Institute on Drug Abuse.

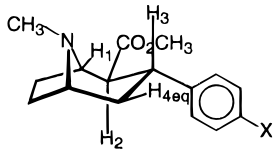
S0022-2623(96)00515-8 CCC: $12.00

Table 1. Chemical Yields and Physical Properties for Oxadiazoles **5** and Methyl Esters **2**

synthesis oxadiazole	yield (%)	methyl ester	yield (%)	molecular formula[a,b]	melting point[a] (°C)	$[\alpha]_D$ (deg) (*c*, CH_3OH)
5a	85	**2a**	86	$C_{20}H_{26}FNO_8 \cdot 0.5H_2O$[c]	65 dec	−34.4 (0.54)
5b	23[d]	**2b**	45	$C_{23}H_{28}INO_5S$	204.6−205.3	−38.9 (1.30)
5c	81	**2c**	54	$C_{23}H_{28}ClNO_5S$	182.4−183.8	−39.9 (0.45)
5d	65[e]	**2d**	51	$C_{24}H_{31}NO_5S$	174.8−175.4	−43.1 (0.55)
5e	86	**2e**	60	$C_{16}H_{22}ClNO_2$[f]	178−179	−48.1 (1.38)

[a] Compounds were characterized as the tosylate salts unless otherwise noted. [b] C, H, and N analyses were within 0.4% of their theoretical values. [c] Characterized as the tartrate salt. [d] The 2α,3*β*-isomer was recovered in 20% yield. [e] The 2α,3*β*-isomer was recovered in 15% yield. [f] Characterized as the HCl salt.

Table 2. ^1H NMR Selected Chemical Shifts and Coupling Constants for the Free Bases of Compounds **2a**−**d**



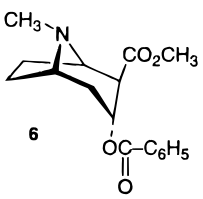
		chemical shifts (ppm)[a]						coupling constants (Hz)		
compd	X	1	2	3	4_{eq}	4_{ax}	5	$J_{1,2}$	$J_{2,3}$	$J_{3,4_{eq}}$
2a	F	3.41	2.65	3.63	2.37	1.32	3.09	1.8	9.7	7.9
2b	I	3.40	2.66	3.57	2.35	1.29	3.07	1.7	9.4	7.9
2c	Cl	3.41	2.65	3.59	2.35	1.30	3.08	1.7	9.4	8.0
2d	CH_3	3.42	2.72	3.65	2.40	1.35	3.09	1.7	9.3	8.1
2e	H	3.43	2.73	3.68	2.41	1.40	3.10	1.6	9.5	8.1

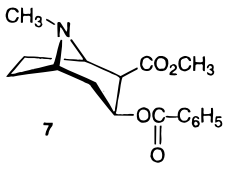
[a] Chemical shifts are reported relative to $Si(CH_3)_4$ in pyridine-d_5 at 500 MHz.

counterpart, indicating that the aromatic ring lies perpendicular to the axis of the piperidine ring.

The IC_{50} values for the inhibition of ligand binding to the dopamine, serotonin, and norepinephrine transporters by 3α-(*p*-substituted phenyl)tropane-2*β*-carboxylic acid methyl esters **2a**−**e** are listed in Table 3. For comparison, the previously reported IC_{50} values for the corresponding 2*β*,3*β*-isomers **1a**−**e**, as well as values for cocaine (**7**) and allococaine (**6**), are also listed. The IC_{50} values for dopamine and serotonin represent inhibition of 0.5 nM [^{3}H]WIN 35,428 and 0.2 nM [^{3}H]paroxetine, respectively, as previously described.[7] Norepinephrine IC_{50} values represent inhibition of 0.5 nM [^{3}H]nisoxetine binding to the norepinephrine transporter.[8,9]

The substituted aryl 2*β*,3α-isomers **2a**−**d** are more selective for the DAT relative to the 5-HT transporter than the 2*β*,3*β*-isomers **1a**−**d**. The unsubstituted analog **2e** possessed DAT selectivity similar to WIN 35,065-2. Furthermore, the 2*β*,3α-isomers are only 1.5−5.9 times less potent at the DAT than the analogous 2*β*,3*β*-isomers. These results contrast sharply with allococaine (**6**), the 2*β*,3α-stereoisomer of cocaine (**7**), which is 60 times less potent than cocaine at the DAT.[10] Apparently, the preference of 2*β*,3α-esters **2** for the twist-boat conformation allows the amino, aryl, and carbomethoxy groups to adopt similar positions to the corresponding groups in **1** and may explain the relatively high dopamine binding affinities exhibited by esters **2** relative to allococaine (**6**). It is interesting to note that the *p*-iodophenyl analog **2b** (RTI-352) is only slightly less potent than **1b** (RTI-55) but 7 times more selective for the DAT relative to the 5-HT transporter. Since [^{123}I]-RTI-55 has proven to be a valuable SPECT (single-photon emission-computed tomography) imaging agent,[11] we plan to conduct further studies with **2b** to determine if it possesses properties that would make it a better SPECT imaging agent than [^{123}I]RTI-55.





Acknowledgment. This research was supported by the National Institute on Drug Abuse, Grant DA05477.

Supporting Information Available: Experimental data for **5a**−**d** and **2a**−**d** (7 pages). Ordering information is found on any current masthead page.

Table 3. Comparison of Transporter Binding Potencies for Stereoisomers of WIN 35,065-2 Analogs

			IC_{50} (nM)[a]			ratio[b]	
compd	X	isomer	DA [^{3}H]WIN 35,428	NE [^{3}H]nisoxetine	5-HT [^{3}H]paroxetine	NE/DA	5-HT/DA
6 (allococaine)[c]			6160 ± 900				
7 (cocaine)[d]			89.1 ± 4.8	3298 ± 293	1045 ± 89		
1a[e,f]	F	2*β*,3*β*	14 ± 1.4	835 ± 45	810 ± 59	60	58
2a	F	2*β*,3α	21 ± 0.57	1230 ± 91	5060 ± 485	59	241
1b[e]	I	2*β*,3*β*	1.26 ± 0.04	36 ± 2.7	4.21 ± 0.3	29	3.3
2b	I	2*β*,3α	2.85 ± 0.16	52.4 ± 4.9	64.9 ± 1.97	18	23
1c[e]	Cl	2*β*,3*β*	1.12 ± 0.1	37 ± 2.1	44.5 ± 1.3	33	40
2c	Cl	2*β*,3α	2.4 ± 0.2	60.1 ± 2.4	998 ± 120	25	415
1d[e]	CH_3	2*β*,3*β*	1.71 ± 0.31	60 ± 0.53	240 ± 27	35	140
2d	CH_3	2*β*,3α	10.2 ± 0.8	275 ± 24	4250 ± 422	27	417
1e[g,h]	H	2*β*,3*β*	23 ± 5	920 ± 73	2000 ± 64	40	87
2e	H	2*β*,3α	101 ± 16	2080 ± 285	5700 ± 721	21	57

[a] Data are mean ± standard error of three or four experiments performed in triplicate. [b] Ratios of IC_{50} values. [c] IC_{50} values taken from ref 10. [d] IC_{50} values taken from ref 7. [e] IC_{50} values taken from ref 12. [f] This compound is WIN 35,428. [g] This compound is WIN 35,065-2. [h] IC_{50} values taken from ref 13.

References

(1) Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. Compounds affecting the central nervous system. 4. 3β-Phenyltropane-2-carboxylic esters and analogs. *J. Med. Chem.* **1973**, *16*, 1260−1267.

(2) Carroll, F. I.; Lewin, A. H.; Kuhar, M. J. Dopamine Transporter Uptake Blockers: Structure Activity Relationships. In *Neurotransmitter Transporters: Structure and Function*; Reith, M. E. A., Eds.; Human Press: Totowa, NJ, in press.

(3) Keverline, K. I.; Abraham, P.; Lewin, A. H.; Carroll, F. I. Synthesis of the 2β,3α- and 2β,3β-isomers of 3-(*p*-substituted phenyl)tropane-2-carboxylic acid methyl esters. *Tetrahedron Lett.* **1995**, *36* (18), 3099−3102.

(4) Triggle, D. J.; Kwon, Y. W.; Abraham, P.; Rahman, M. A.; Carroll, F. I. Synthesis of 2-(3-Substituted-1,2,4-oxadiazol-5-yl)-8-methyl-8-azabicyclo[3.2.1]octanes and 2α-(3-substituted-1,2,4-oxadiazol-5-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-enes as potential muscarinic agonist. *Pharm. Res.* **1992**, *9* (11), 1474−1479.

(5) Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J.W.; Kuhar, M. J. 3-Aryl-2-(3′-substituted-1′,2′,4′-oxadiazol-5′-yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.* **1993**, *36* (20), 2886−2890.

(6) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. Synthesis and conformational analysis of isomeric cocaines: A proton and carbon-13 nuclear magnetic resonance study. *J. Org. Chem.* **1982**, *47*, 13−19.

(7) Boja, J. W.; Kuhar, M. J.; Kopajtic, T.; Yang, E.; Abraham, P.; Lewin, A. H.; Carroll, F. I. Secondary amine analogues of 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters and *N*-norcocaine exhibit enhanced affinity for serotonin and norepinephrine transporters. *J. Med. Chem.* **1994**, *37* (8), 1220−1223.

(8) Tejani-Butt, S. M. [^{3}H]Nisoxetine: A radioligand for quantitation of norepinephrine uptake sites by autoradiography or by homogenate binding. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 427−436.

(9) Tejani-Butt, S. M.; Brunswick, D. J.; Frazer, A. [^{3}H]Nisoxetine: A new radioligand for norepinephrine uptake sites in brain. *Eur. J. Pharmacol.* **1990**, *191*, 239−243.

(10) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. Synthesis and ligand binding of cocaine isomers at the cocaine receptor. *J. Med. Chem.* **1991**, *34*, 883−886.

(11) Carroll, F. I.; Scheffel, U.; Dannals, R. F.; Boja, J. W.; Kuhar, M. J. Development of Imaging Agents for the Dopamine Transporter. *Med. Res. Rev.* **1995**, *15* (15), 419−444.

(12) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3β-(3′-substituted phenyl)-, 3β-(4′-substituted phenyl)-, and 3β-(3′,4′-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.

(13) Carroll, F. I.; Abraham, P.; Lewin, A. H.; Parham, K. A.; Boja, J. W.; Kuhar, M. J. Isopropyl and phenyl esters of 3β-(4-substituted phenyl)tropan-2β-carboxylic acids. Potent and selective compounds for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 2497−2500.

JM960515U