Notes

Secondary Amine Analogues of 3β-(4′-Substituted phenyl)tropane-2β-carboxylic Acid Esters and *N*-Norcocaine Exhibit Enhanced Affinity for Serotonin and Norepinephrine Transporters

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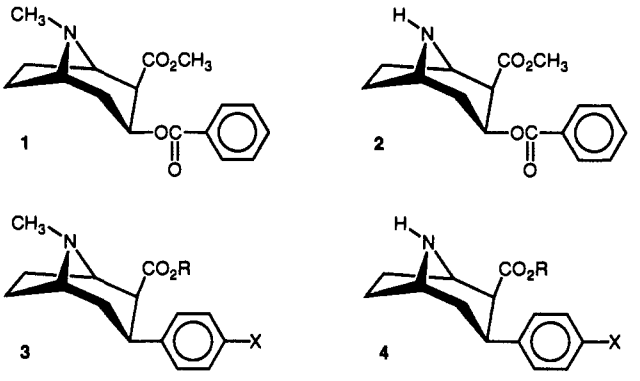
Received December 2, 1993•

N-Norcocaine (**2**) and six *N*-nor-3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters (**4a-f**) were synthesized by N-demethylation of cocaine (**1**) and the appropriate 3β-(substituted phenyl)-tropane analogues (**3a-f**) with α-chloroethyl chloroformate. Radioligand binding affinities of **2** and **4a-f** at the DA, 5-HT, and NE transporter were measured and compared to those of **1** and **3a-f**. N-Demethylation produced relatively small effects at the DA transporter. In contrast, 4–19-fold and 2–44-fold enhanced affinity at the serotonin and norepinephrine transporter resulted from demethylation. *N*-Nor-3β-(4′-iodophenyl)tropane-2β-carboxylic acid methyl ester (**4d**) with an IC_{50} = 0.36 nM showed the greatest affinity for the serotonin transporter. However, *N*-nor-3β-(4′-ethylphenyl)tropane-2β-carboxylic acid methyl ester (**4e**) showed the greatest selectivity for the serotonin transporter.

Cocaine (**1**) is an inhibitor of the neuronal transport of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) at roughly similar concentrations, i.e., with K_i's between 220 and 310 nM.[1] Biochemical binding studies indicate slight DA selectivity.[2,3] In recent years, structure–activity relationships of cocaine (**1**) analogues and binding at monoamine transporters, particularly at the dopamine transporter, have been explored,[2-7] and some structural modifications that result in selectivity for the dopamine transporter over the norepinephrine and serotonin transporters have been reported.[8-10] Such selectivity is useful in developing biochemical probes for behavioral studies and for receptor imaging.

In addition, it had been shown that replacement of the *N*-methyl group by hydrogen in **3a** (WIN 35,065-2) to give **4a** (WIN 35,981) resulted in enhanced affinity at the 5-HT and NE transporters with virtually no change in the affinity at the DA transporter, leading to diminished selectivity for the DA over 5-HT and NE transporters.[3,11] An analogous effect was observed upon replacement of the N-methyl group in cocaine (**1**) by hydrogen to give *N*-norcocaine (**2**); in this case affinity at NE and 5-HT transporters was enhanced while it was decreased at the DA transporter, resulting in slight selectivity for 5-HT and NE transporters over the DA transporter.[3,11,12] These findings prompted examination of the relative potency of several *N*-nor-3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters (**4b-f**) to determine whether replacement of the *N*-methyl group by hydrogen generally enhances selectivity for 5-HT and NE relative to DA transporters.



(a) R = CH_3, X = H
(b) R = CH_3, X = F
(c) R = CH_3, X = Cl
(d) R = CH_3, X = I
(e) R = CH_3, X = C_2H_5
(f) R = $(CH_3)_2CH$, X = I

Results

Chemistry. *N*-Norcocaine (**2**) and the *N*-nor analogues **4a-f** were prepared by treating cocaine, or the corresponding 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester analogues **3a-f**, with α-chloroethyl chloroformate[13] to give an (α-chloroethyl)urethane, which was not isolated, but converted directly to the *N*-nor analogue by solvolysis with methanol. Table 1 lists the physical constants for the compounds prepared. Other methods for preparing *N*-norcocaine,[14-18] as well as **4a-b** and **4f**, have been reported.[4,19-22] The *N*-methyl precursors **3a-c** and **3f** were prepared as previously reported.[8,23] The 4-iodo analogue **4d** (RTI-55) was prepared by direct iodination of the solution of **4a** in a mixture of acetic and perchloric

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• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

0022-2623/94/1837-1220$04.50/0

Table 1. Physical Properties of *N*-Nor-3β-(4′-substituted phenyl)tropane-2β-carboxylic Acid Methyl Esters[a]

compd	molecular formula[b]	yield (%)	mp (°C)	optical rotation $[\alpha]^{25}_D$ (deg) (*c* 1, $CHCl_3$)
2	$C_{15}H_{19}NO_4$	71	81–83[c]	−54.6[c]
4a[d]	$C_{17}H_{25}NO_8$	60	117–119[e]	−89.8
4b	$C_{15}H_{18}FNO_2$	66	114–115[f]	−108.9[f]
4c	$C_{15}H_{18}ClNO_2$	64	104–105	−94.5
4d	$C_{15}H_{18}INO_2$	54	116–117[g]	−86.5
4e[d]	$C_{21}H_{29}NO_8$	48	148–150	−99.6[h]
4f	$C_{17}H_{22}INO_2$	65	110–111	−72.0

[a] A general procedure for the synthesis of compounds is given in the text. [b] All compounds were analyzed for C, H, N. The results agreed to ±0.4% with theoretical values. [c] Borne et al.[18] reports mp 82–83 °C and $[\alpha]^{25}_D$ −41° (*c* 1, $CHCl_3$). [d] This compound was analyzed as the tartrate salt; the mp and $[\alpha]_D$ are for tartrate salt. [e] Clarke et al.[21] reports mp 79–80 °C and $[\alpha]^{25}_D$ −110° (1% in H_2O) for the hydrochloride salt. [f] Meltzer et al.[4] reports mp 115–116 °C and $[\alpha]^{21}_D$ −102.1° (*c* 1, CH_3OH). [g] Neumeyer et al.[22] reports mp 149–151 °C and $[\alpha]^{25}_D$ −67.4° (*c* 1, $CHCl_3$). [h] (*c* 1, CH_3OH).

acid containing mercuric oxide. The 4′-ethylphenyl analogue **3e** was prepared by adding (4-ethylphenyl)-magnesium bromide to anhydroecgonine methyl ester.

Biological. The IC_{50} values for inhibition of radioligand binding at the dopamine, serotonin, and norepinephrine transporters for compounds **1**, **2**, **3a-f**, and **4a-f** are listed in Table 2. The IC_{50} values are for inhibition of 0.5 nM [^{3}H]WIN 35,428 (for DA), 0.2 nM [^{3}H]paroxetine (for 5-HT), and 0.5 nM [^{3}H]nisoxetine (for NE) binding, respectively.[24,25]

Discussion

Examination of cocaine (**1**) and *N*-norcocaine (**2**), as well as six of the 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters (**3a-f**) and their N-demethylated derivatives (**4a-f**), for binding affinity at dopamine, serotonin and norepinephrine transporters revealed findings in agreement with previously reported data.[2,12] N-Demethylation produced only relatively small effects at the DA transporter (Table 2). In two pairs of compounds, **1**/**2** and **3f**/**4f**, an approximately 2-fold decrease in potency was observed, while in two other pairs, **3a**/**4a** and **3e**/**4e**, there was no significant effect, and in the remaining three pairs, **3c**/**4c**, **3d**/**4d**, and **3b**/**4b**, a 2–4-fold increase in potency was recorded. Much larger effects on potency were found at the 5-HT and NE transporters where N-demethylation invariably resulted in increased affinity. For 5-HT, the effect ranged from 4- to 19-fold while for the NE transporter, 2–44-fold enhancements of potency were observed (Table 2).

A consequence of these results is that whereas cocaine (**1**) and the analogues **3a-d,f** all exhibited some selectivity for binding at the DA transporter relative to the 5-HT and NE transporters, the N-demethylated derivatives **2**, **4a-f** exhibited less DA selectivity. In fact, one compound, **4e**, has 5-fold binding selectivity for the 5-HT transporter relative to the DA transporter. The *N*-nor-4′-chlorophenyl and *N*-nor-4′-iodophenyl analogues **4c** and **4d** with IC_{50}'s of 5.45 and 7.54 nM, respectively, showed the highest affinity for the NE transporter. However, examination of the NE/DA ratio (Table 2) shows that none of the compounds possess appreciable selectivity for the NE transporter.

These preliminary data suggest that highly potent, relatively selective ligands for the 5-HT transporter may be derived from N-demethylation of 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters (**3**). In particular, it appears that affinity for the 5-HT transporter can be increased by N-demethylation of the lipophilic 4′-ethylphenyl analogue **3e** to the *N*-nor analogue **4e**. The data also highlight the disparate requirements for binding at the DA, 5-HT, and NE transporters. A working model for the DA pharmacophore has been defined;[23] studies are underway in our laboratories to characterize the binding requirements for the 5-HT and NE transporters. The results of these studies will be useful in the design of specific, high-affinity ligands and behavioral tools for these transporters. Finally, even though ester hydrolysis is the major metabolic pathway for cocaine, norcocaine (**2**) is a known minor metabolite. Since compounds **3** have only one ester group, N-demethylation may be a more significant metabolic pathway, and thus the contribution of the *N*-nor compounds **4** to the in vivo activity of **3** may be important.

Experimental Section

Melting points were determined on a Thomas Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III Polarimeter

Table 2. Comparison of Inhibition of Transporter Binding for Cocaine (**1**), 3β-(4′-Substituted phenyl)tropane-2β-carboxylic Acid Esters (**3a-f**) and Their *N*-Nor Analogues (**2** and **4a-f**)

compd	DA[a] [^{3}H]WIN 35,428 IC_{50} (nM)	(pair ratio)[c]	5-HT[a] [^{3}H]Paroxetine IC_{50} (nM)	(pair ratio)[c]	NE[a] [^{3}H]Nisoxetine IC_{50} (nM)	(pair ratio)[c]	5-HT/DA[b] ratio	NE/DA[b] ratio
1	89.1 ± 4.8		1045 ± 89		3298 ± 293		12	37
2	206 ± 29	(0.4)	127 ± 13	(8)	139 ± 9	(24)	0.6	0.7
3a[d]	23 ± 5		1999 ± 64		920 ± 73		87	40
4a	30.8 ± 2.3	(0.8)	156 ± 8	(13)	84.5 ± 7.5	(11)	5	3
3b[b]	15.7 ± 1.4		759 ± 47		834.0 ± 45		48	53
4b	4.39 ± 0.20	(4)	68.6 ± 2.0	(11)	18.8 ± 0.7	(44)	16	4
3c	1.12 ± 0.10		44.5 ± 1.3		37.3 ± 2.1		40	33
4c	0.62 ± 0.09	(2)	4.13 ± 0.62	(11)	5.45 ± 0.21	(7)	7	9
3d[d]	1.26 ± 0.04		4.21 ± 0.34		36.0 ± 2.7		3	29
4d	0.69 ± 0.2	(2)	0.36 ± 0.05	(12)	7.54 ± 3.19	(5)	0.5	11
3e	55.0 ± 2.1		28.4 ± 3.8		3907 ± 381		0.5	71
4e	49.9 ± 7.3	(1)	8.13 ± 0.30	(4)	122 ± 12	(32)	0.2	2
3f	0.43 ± 0.05[d]		66.8 ± 6.5[e]		285 ± 8		155	662
4f	1.06 ± 0.12	(0.4)	3.59 ± 0.27	(19)	132 ± 5	(2)	3	125

[a] Data are mean ± standard error of three or four experiments performed in triplicate. [b] 5-HT/DA and NE/DA are ratios of IC_{50} values. [c] The pair ratios show the ratio: **1**/**2** and **3**/**4** analogue IC_{50} values, and reflect the potency change occurring upon demethylation. [d] The IC_{50} values were taken from ref 8. [e] The IC_{50} value in ref 8 was 310 ± 77 nM.

(1-dm cell). NMR spectra were recorded on a Bruker WM-250 or AM-500 spectrometer using tetramethylsilane as an internal standard. Thin-layer chromatography was carried out on Whatman silica gel 60 TLC plates using hexane–Et_2O–Et_3N (10:9:1). Flash chromatography was conducted on silica gel 60 (230–400 mesh) using hexane–Et_2O–Et_3N (30:9:1) as the eluent. Visualization was accomplished under UV or in an iodine chamber. Since all of the compounds described were prepared starting from natural cocaine, they are all optically active and have the absolute configuration of natural cocaine. Microanalyses were carried out by Atlantic Microlab, Inc. Cocaine was provided by the National Institute on Drug Abuse. [^{3}H]-3β-(*p*-Fluorophenyl)-tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428), and [^{3}H]paroxetine were purchased from Dupont-New England Nuclear (Boston, MA), and [^{3}H]nisoxetine was purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO).

3β-(4′-Iodophenyl)tropane-2β-carboxylic Acid Methyl Ester (3d). 3β-Phenyltropane-2β-carboxylic acid methyl ester[23] (5.72 g, 0.022 mol) was dissolved in acetic acid (75 mL) containing perchloric acid (25 mL) and mercuric oxide yellow (4.77 g, 0.022 mol). Iodine (13.96 g, 0.055 mol) in CH_2Cl_2 (200 mL) and acetic acid (100 mL) were added in portions over 10 min. The mixture was stirred at room temperature overnight. The solid was separated by filtration, and the filtrate was diluted with H_2O (100 mL) and CH_2Cl_2 (200 mL) and cooled to 0 °C in an ice bath. Concentrated NH_4OH was added dropwise to the stirred mixture over 45 min to basify the aqueous phase. The organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (4 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The crude product was placed on a silica gel flash column (300 g) and eluted with Et_2O–Et_3N–hexane (9:1:10) . The pure product from the column was crystallized from Et_2O–petroleum ether to give 5.01 g (59%) of pure free base: mp 107–108 °C; $[\alpha]^{25}_D$ +4.13° (*c* 1, $CHCl_3$) [lit.[22] mp oil; $[\alpha]^{25}_D$ −2.0° (*c* 0.85, $CHCl_3$)], ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 3), 2.14 (m, 2), 2.22 (s, 3), 2.54 (m, 1), 2.91 (m, 2), 3.35 (m, 1), 3.51 (s, 3), 3.56 (m, 1), 7.01 (d, 2), and 7.58 (d, 2). Anal. Calcd for $C_{16}H_{20}INO_2$: C, H, N.

The tartrate salt had mp 128–129 °C; $[\alpha]^{24}_D$ −82.9° (*c* 1, MeOH) [lit.[23] mp 72–74 °C dec; $[\alpha]^{24}_D$ −73.8° (*c* 0.32, MeOH)].

3β-(4′-Ethylphenyl)tropane-2β-carboxylic Acid Methyl Ester (3e). A solution of anhydroecgonine methyl ester[21] (500 mg, 2.8 mmol) in dry ether (5 mL) was added dropwise to a stirred solution of (4′-ethylphenyl)magnesium bromide (prepared from 200 mg of Mg and 1.14 mL of 4-ethylbromobenzene). The mixture was stirred for 2 h at that temperature, then cooled to −78 °C, and treated with TFA (0.25 mL) in dry Et_2O (5 mL). The mixture was allowed to warm to 0 °C, diluted with water, and made acidic with 2 N HCl to dissolve all the solids. The aqueous layer was separated, made basic with concentrated NH_4OH, saturated with NaCl, and extracted with ether (3 × 10 mL). The dried ether solution ($MgSO_4$) was evaporated to give the crude product which was purified by flash chromatography on silica gel column eluting with Et_2O–Et_3N (9:1) to give 76 mg (10%) of **3e** as an oil. This material was converted to 103 mg of D-tartaric acid salt as white crystals: mp 112–113 °C; $[\alpha]^{25}_D$ −93.7° (*c* 0.205, MeOH); ^{1}H NMR (free base) (250 MHz, $CDCl_3$) δ 1.20 (m, 3), 1.67 (m, 3), 2.15 (m, 2), 2.20 (s, 3, NCH_3), 2.55 (m, 3), 2.87 (m, 1, H-2), 2.93 (m, 1, H-3), 3.35 (m, 1, H-5), 3.49 (s, 3, OCH_3), 3.55 (m, 1, H-1), 7.09 (dd, 4, C_6H_4). Anal. Calcd for $C_{22}H_{31}NO_8 \cdot 0.5H_2O$: C, H, N.

General Procedure for Demethylation of 3β-(4′-Substituted phenyl)tropane-2β-carboxylic Acid Esters and Cocaine. A solution of the appropriate *N*-methyl analogue in 1,2-dichloroethane (20 mL/mmol) under nitrogen atmosphere at room temperature was treated with 3 equiv 1-chloroethyl chloroformate and heated to reflux. After 24 h, the volatiles were evaporated. The residue was taken up in MeOH (20 mL/mmol) and refluxed for 4 h. The solvent was evaporated, and the residue was partitioned between dilute aqueous NH_4OH and CH_2Cl_2. The aqueous phase was further extracted with CH_2Cl_2. Evaporation of the dried (Na_2SO_4) organic extract gave the crude product which was chromatographed on a silica gel flash column, eluting with 10% Et_3N in ether. Products obtained as solids were recrystallized from heptane and characterized. Products obtained as oils were converted to the tartaric acid salt (1 equiv in MeOH) and recrystallized from MeOH/ether for characterization. Physical data are listed in Table 1.

Ligand Binding. Brains from male Sprague–Dawley rats weighing 200–250 g (Harlan Labs, Indianapolis, IN) were removed, dissected, and rapidly frozen. Ligand binding experiments for the dopamine transporter were conducted in assay tubes containing 0.5 mL of buffer (10 mM sodium phosphate containing 0.32 M sucrose, pH 7.40) on ice for 120 min. Each assay tube contained 0.5 nM [^{3}H]WIN 35,428 and 0.1 mg of striatal tissue (original wet weight). The nonspecific binding of [^{3}H]WIN 35,428 was defined using 30 μM (−)-cocaine. Ligand binding experiments for the serotonin transporter were conducted in assay tubes containing 4 mL of buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, pH 7.4 at 25 °C) for 90 min at room temperature. Each assay tube contained 0.2 nM [^{3}H]paroxetine and 1.5 mg of midbrain tissue (original wet weight). Nonspecific binding of [^{3}H]paroxetine was defined by 1 μM citalopram. Ligand binding experiments for the norepinephrine transporter were conducted in Tris buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, pH 7.4 at 4 °C) at a total volume of 0.5 mL. Each assay tube contained 0.5 nM [^{3}H]nisoxetine and 8 mg of rat cerebral cortex. The nonspecific binding of [^{3}H]nisoxetine was defined using 1 μM desipramine. Incubations were terminated by filtration with three 5-mL washes of ice-cold buffer through GF/B filters that were previously soaked in 0.05% poly(ethylenimine). Results were analyzed using the Equilibrium Binding Data Analysis software (EBDA, Biosoft).

Acknowledgment. This research was supported by Grant DA05477 from the National Institute on Drug Abuse and by intramural funds of the Addiction Research Center.

References

(1) Hytell, J. Citalopram-Pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1982**, *6*, 277–295.
(2) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: Biochemical characterization and structure-activity relationships for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969–981.
(3) Ritz, M. C.; Cone, E. J.; Cone, M. J. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: A structure-activity study. *Life Sci.* **1990**, *46*, 635–645.
(4) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-phenyltropane analogs of cocaine: Synthesis, inhibition of binding at cocaine recognition sites, and positron emission tomography imaging. *J. Med. Chem.* **1993**, *36*, 855–862.
(5) Davies, H. M. L.; Saikali, E.; Sexton, T.; Childers, S. R. Novel 2-substituted cocaine analogs: Binding properties at dopamine transport sites in rat striatum. *Eur. J. Pharmacol.-Mol. Pharmacol. Sec.* **1993**, *244*, 93–97.
(6) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. Structure-activity relationship studies of cocaine: Replacement of the C-2 ester group by vinyl argues against H-bonding and provides an esterase-resistant, high-affinity cocaine analogue. *J. Med. Chem.* **1992**, *35*, 4764–4766.
(7) Kline, R. H., Jr.; Wright, J.; Fox, K. M.; Eldefrawi, M. E. Synthesis of 3-arylecgonine analogues as inhibitors of cocaine binding and dopamine uptake. *J. Med. Chem.* **1990**, *33*, 2024–2027.
(8) 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.
(9) Boja, J. W.; McNeill, R. M.; Lewin, A. H.; Abraham, P.; Carroll, F. I.; Kuhar, M. J. Selective dopamine transporter inhibition by cocaine analogs. *NeuroReport* **1992**, *3*, 984–986.
(10) Scheffel, U.; Dannals, R. F.; Wong, D. F.; Yokoi, F.; Carroll, F. I.; Kuhar, M. J. Dopamine transporter imaging with novel, selective cocaine analogs. *NeuroReport* **1992**, *3*, 969–972.
(11) Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. I. [^{3}H]Cocaine binding sites in caudate-putamen. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 132–141.
(12) Abraham, P.; Pitner, J. B.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. N-Modified analogues of cocaine: Synthesis and inhibition of binding to the cocaine receptor. *J. Med. Chem.* **1992**, *35*, 141–144.
(13) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. A new reagent for the selective, high-yield N-dealkylation of tertiary amines: Improved syntheses of naltrexone and nalbuphine. *J. Org. Chem.* **1984**, *49*, 2081–2082.

(14) Werner, G.; Hackel, R.; Mohammad, N.; Seiker, N.; Storr, K. H. *Ann. Chem.* **1967**, *708*, 210.
(15) Stenberg, V. I.; Narain, N. K.; Singh, S. P.; Parmar, S. S. An improved synthesis of norcocaine. *J. Heterocycl. Chem.* **1976**, *13*, 363–364.
(16) Stenberg, V. I.; Singh, S. P.; Narain, N. K.; Parmar, S. S. Novel photochemical demethylation of cocaine and related compounds. *J. Chem. Soc., Chem. Commun.* **1976**, 262–263.
(17) Baldwin, S. W.; Jeffs, P. W.; Natarajan, S. Preparation of norcocaine. *Synth. Commun.* **1977**, *7*, 79–84.
(18) Borne, R. F.; Bedford, J. A.; Buelke, J. L.; Craig, C. B.; Hardin, T. C.; Kibbe, A. H.; Wilson, M. C. Biological effects of cocaine derivatives. I: Improved synthesis and pharmacological evaluation of norcocaine. *J. Pharm. Sci.* **1977**, *66*, 119–120.
(19) Naseree, T. M.; Abraham, P.; Kepler, J. A.; Carroll, F. I.; Lewin, A. H.; Kuhar, M. J. Synthesis of [^{3}H]WIN 35,065–2; A new radioligand for cocaine receptors. *J. Label. Compd. Radiopharm.* **1990**, 1011–1016.
(20) Milius, R. A.; Saha, J. K.; Madras, B. K.; Neumeyer, J. L. Synthesis and receptor binding of N-substituted tropane derivatives. High-affinity ligands for the cocaine receptor. *J. Med. Chem.* **1991**, *34*, 1728–1731.
(21) 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.
(22) Neumeyer, J. L.; Wang, S.; Milius, R. A.; et al. [^{123}I]-2β-Carbomethoxy-3β-(4-iodophenyl)tropane: high affinity SPECT radiotracer of monoamine reuptake sites in brain. *J. Med. Chem.* **1991**, *34*, 3144–3146.
(23) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, QSAR, and CoMFA study of 3β-(p-substituted phenyl)tropan-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1991**, *34*, 2719–2927.
(24) Boja, J. W.; Rahman, M. A.; Philip, A.; Lewin, A. H.; Carroll, F. I.; Kuhar, M. J. Isothiocyanate derivatives of cocaine: Irreversible inhibition of ligand binding at the dopamine transporter. *Mol. Pharmacol.* **1991**, *39*, 339–345.
(25) 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′-oxadiazole-5′-yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.* **1993**, *36*, 2886–2890.