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

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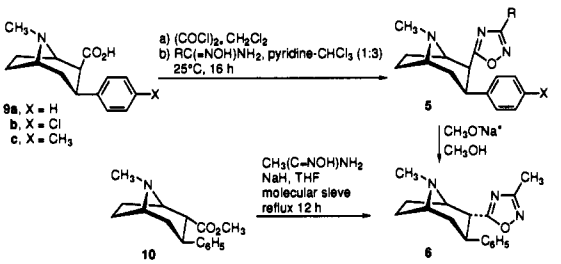
Previous studies have shown that 3β-(substituted phenyl)tropan-2β-carboxylic acid esters possess high affinity for the cocaine binding site on the dopamine transporter both in vitro and in vivo and inhibit dopamine uptake in vitro. Since 1,2,4-oxadiazoles are excellent bioisosteres of ester groups, we have prepared several 3β-(substituted phenyl)-2β-(3-substituted 1',2',4'-oxadiazol-5'-yl)tropanes (**5b-h**) and all four stereoisomers of (1*R*,5*S*)-3 phenyl-2-(3-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**5a** and **6-8**). The 3α-phenyl-2α-(3'-methyl-1',2',4'-oxadiazole) isomer **7** was prepared from a stereoselective addition of phenyllithium to (1*R*,5*S*)-2-(3'-methyl-1',2',4'-oxadizol-5-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (**11**). The binding affinities for **5a-h** and **6-8** at the dopamine, serotonin, and norepinephrine transporters were obtained. In general these bioisosteres showed potencies for the dopamine transporter similar to those of their parent esters. 3β-(4'-Chlorophenyl)-2β-(3'-phenyl-1',2',4'-oxadiazol-5'-yl)tropane (**5d**) was the most potent analogue with an IC_{50} of 1.62 nM. However, 3β-(4'-chlorophenyl)-2β-(3'-methoxyphenyl-1',2',4'-oxadiazol-5'-yl)tropane (**5e**) with an IC_{50} of 1.81 nM was the most selective analogue for the dopamine transporter showing NE/DA and 5-HT/DA ratios of 461 and 186, respectively. The *cis*- and *trans*-3α-phenyl-2-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropanes (**7** and **8**), which exist in a boat conformation, have IC_{50} values only slightly greater than that of the 3β,2β-isomer (**5a**) which possesses the cocaine stereochemistry.

A correlation between the affinities of a number of cocaine (**1a**) analogs for a binding site on the dopamine transporter and their potency for reinforcing effects in animal models of drug self-administration has led to the hypothesis that cocaines action at this site may be responsible for its reinforcing properties.[1,2] Several biochemical and pharmacological studies have supported this hypothesis.[3,4] In previous studies, we reported that several 3β-(substituted phenyl)tropan-2β-carboxylic acid methyl esters (**2b-e**) were more potent than cocaine in inhibiting WIN-35,428 binding to this site.[5] We also reported that the isopropyl and phenyl esters (**3a-c** and **4a-c**) were potent and selective for this site.[6] These 3β-phenyltropane analogs of cocaine are lacking the esteratic link between the phenyl and tropane ring but retain the ester moiety at the 2β-position. Since the 1,2,4-oxadiazole ring can be an excellent bioisostere of ester groups,[7] we now report the syntheses and binding properties of several 3β-(substituted phenyl)-2β-(3'-substituted-1',2',4'-oxadiazol-5'-yl)tropanes (**5b-h**). We also report the syntheses and binding properties of all four stereoisomers of (1*R*,5*S*)-3-phenyl-2-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**5a** and **6-8**).[8]

Chemistry

The 3β-(substituted phenyl)-2β-(3'-substituted-1',2',4'-oxadiazol-5'-yl)tropanes (**5a-h**) were prepared by the general route shown in Scheme I. Thus, treatment of the appropriate 3β-(substituted phenyl)tropane-2β-carboxylic acid (**9a-c**)[6,9] with oxalyl chloride in methylene chloride gave the acid chloride which was treated in situ with the appropriate amide oxime in a 3:1 mixture of pyridine and chloroform at 25 °C to afford **5a-h**. The physical properties of **5a-h** are listed in Table I. The 2α-isomer of **5a**, 3β-phenyl-2α-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**6**), was obtained by epimerization of **5a** using sodium methoxide in methanol or by the condensation of the methyl ester of the 2α-isomer, **10**,[9] with acetamide oxime (see Scheme I). The stereochemical assignments for **5a-h** and **6** follow from the methods of synthesis and are supported by their ^1H NMR spectral data (see Tables I and II). Assignments of the resonances were made using 2D NMR (^1H-COSY). The observed coupling constants for the C-2, C-3, and C-4 protons (Table I) were in good agreement with those previously reported for cocaine (**1a**) and pseudococaine (**1b**)[10] as were the multiplicities and the chemical shift differences between the isomers **5a** and **6**.

Scheme I



Scheme II outlines the route used to prepare 3α-phenyl-2α-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**7**) and 3α-phenyl-2β-(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (**8**). The addition of 2 equiv of phenyllithium to (1*R*,5*S*)-2-

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Table I. Physical Properties of 1,2,4-Oxadiazole Derivatives **5a–h** and **6–8**[a]

compd	mp[b] (°C)	$[\alpha]^{23}_D$ (c) CH_3OH	^1H NMR (free base in $CDCl_3$) 1	2	3	5	4 ax	N-CH_3	other		aromatic	molecular formula[c]
5a	177–178	−126.5 (0.57)	3.50	3.82	3.32	3.24	2.86	2.02	2.03	(3′-CH_3)	7.10–7.57 (m, 5)	$C_{17}H_{22}ClN_3O_2$[d]
5b	153	−154° (0.10)	2.43–3.36	3.42–3.66	3.25	3.42–3.66	2.62	2.15	2.27	(3′-CH_3)	7.09–7.28 (m, 5)	$C_{17}H_{21}Cl_2N_3O$[e]
5c	184 (dec)	−162° (0.1)	3.47–3.53	3.47–3.53	3.21–3.48	3.41–3.48	2.63	2.18	1.13–1.26 2.96	(CH_3) (3′-CH)	7.09–7.18 (m, 4)	$C_{19}H_{25}Cl_2N_3O$[f]
5d	246 (dec)	−200.9 (0.11)	3.57–3.62	3.56–3.61	3.30	3.41	2.74	2.17			7.16–7.21 (m, 5), 7.41 (m, 2), 7.04 (m, 2)	$C_{22}H_{23}Cl_2N_3O$[g]
5e	171	−274 (0.1)	3.56–3.61	3.56–3.61	3.28	3.48	2.71	2.14	3.84	(OCH_3)	6.91 (d, 2), 7.18 (m, 4), 7.87 (d, 2)	$C_{23}H_{25}Cl_2N_3O_2$[e]
5f	183	−282 (0.1)	3.54–3.62	3.54–3.62	3.35	3.42	2.71	2.16			7.18 (m, 4), 7.39 (2, d), 7.87 (d, 2)	$C_{22}H_{22}Cl_3N_3O$[e]
5g	202	−264 (0.1)	3.53–3.62	3.56–3.62	3.35	3.42	2.71	2.16			7.19 (m, 4), 2.54 (d, 2), 7.80 (d, 2)	$C_{22}H_{22}BrCl_2N_3O$[e]
5h	245	−242.2 (1.02)	3.53	3.61	3.30	3.41	2.76	2.22	2.17	(Ar–CH_3)	6.92 (d, 2), 7.04 (d, 2), 7.51 (m, 3), 8.46 (m, 2)	$C_{23}H_{26}ClN_3O$
6[h]	58–59	+114.5° (1.42)	3.40	4.0	3.51	3.1	2.05	2.13			7.12 (t, 1), 7.25 (t, 2), 7.39 (d, 2)	$C_{17}H_{21}N_3O$
7[h]	124–125	+32.1° (0.14)	3.65	4.45	3.95	3.25	2.54	2.27	2.32	(3′-CH_3)	7.19 (t, 1), 7.29 (t, 2), 7.56 (t, 2)	$C_{17}H_{21}N_3O$
8	201–202	−71.1° (0.90)	3.55	3.45	3.90	3.25	2.60	2.26	2.99	(3′-CH_3)	7.27 (d, 1), 7.37 (d, 2), 7.45 (d, 2)	$C_{17}H_{22}ClN_3O$[f]

[a] A general procedure for the synthesis of compounds **5a–h** is given in the experimental section. [b] Mp's for the hydrochloride salts. [c] All compounds were analyzed for C, H, N. The results agreed to ±0.4% with theoretical values. [d] This salt was hydrated with 0.25 mol of water. [e] This salt was hydrated with 1.0 mol of water. [f] This salt was hydrated with 1.25 mol of water. [g] This salt was hydrated with 1.5 mol of water. [h] The mp and $[\alpha]_D$ are for the free base.

Scheme II

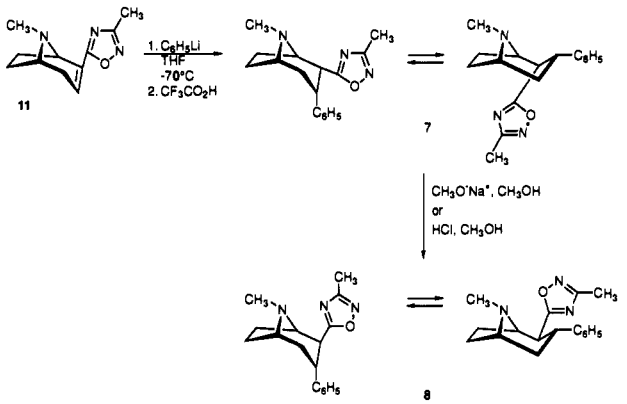
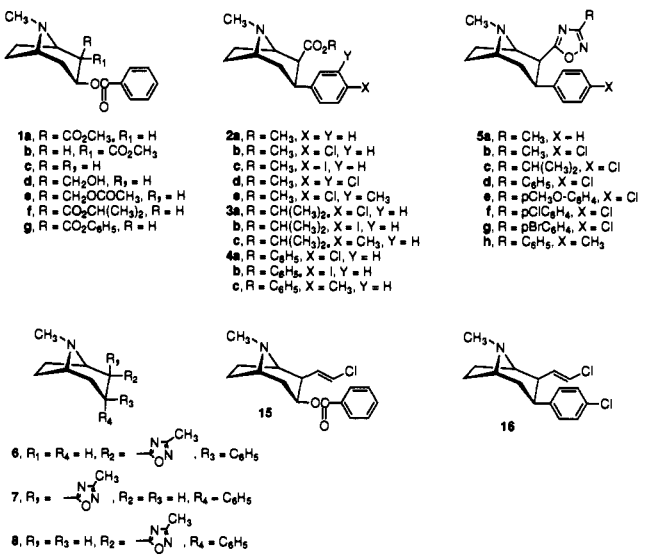
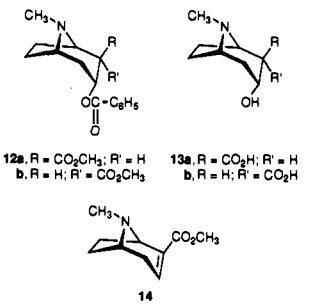


Chart I



(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (**11**)[11] at −70 °C in dry tetrahydrofuran followed by quenching with trifluoroacetic acid at −78 °C gave a 70% yield of **7** along with 5% of the 3α,2β-isomer **8**. Since **7** readily isomerized to **8** on treatment with methanolic sodium methoxide or hydrogen chloride, **8** was probably formed during the workup of the reaction.

Chart II



Comparison of the ^1H NMR spectra of **7** and **8** to those of the 3α-cocaine isomers[10] allococaine (**12a**) and allopseudococaine (**12b**) revealed striking differences. In particular, the magnitude of the coupling constants (Table II) strongly suggested a boat conformation for the piperidine ring in **7** and **8**. Thus, the large (ca. 8 Hz) values observed for the coupling constants between the proton at C-3 and its neighbors at C-2 and C-4 could not be reconciled with its occupying an equatorial position but are consistent with a boat conformation, which would place it in an axial position. The zero value of $J_{1,2}$ in **8** requires that the proton at C-2 be axial; this situation is analogous to that in [2.2.1]bicycloheptane where the value of the vicinal coupling constant between the endo and bridgehead protons is zero.[12] The assignment of the C-2 proton as axial is also consistent with its upfield chemical shift value relative to the isomer **7**, i.e., axial C-2 protons are shielded relative to their equatorial counterparts in the cocaine series[10] as well as in **5a** and **6** (Table II). Based on these arguments, we conclude that **7** is the 2α,3α isomer and **8** is the 2β,3α isomer. The similar chemical shifts for H-3 and the similar $J_{3,4ax}$ and $J_{3,4eq}$ values for **7** and **8** indicate that both compounds possess flattened boat conformations.

Table II. ^{1}H NMR Chemical Shifts and Coupling Constants for Compounds **5a** and **6–8** in Pyridine-d_5[a]

	chemical shifts (ppm)						coupling constants (Hz)					
compd	1	2	3	4_{ax}	4_{eq}	5	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{4ax,4eq}$	$J_{4ax,5}$
5a	3.5[b]	3.8	3.3	2.9	1.7	3.2[b]	~3.8	5	13.0	5	13.0	2.6
6	3.4	4.0	3.5	2.1	1.7	3.1	2.5	12	12.1	5.7		
7	3.65	4.45	3.95	2.54	2.07	3.25	7.0	7.8	7.8	8.6	13.5	7.6
8	3.55	3.45	3.9	2.6		3.25	0	9.9	9.0	10	15.5	8.0

[a] Chemical shifts are reported as δ values in parts per million (ppm) relative to $Si(CH_3)_4$ at 500 MHz. [b] These assignments might be reversed.

Table III. Binding Data for 3β-(Substituted phenyl)-2β-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropanes and Reference Compounds[a]

compd	R	X	Y	DA [^{3}H]WIN 35,428 IC_{50}[b] (nM)	NE [^{3}H]nisoxatine IC_{50}[b] (nM)	5-HT [^{3}H]paroxetine IC_{50}[b] (nM)	NE/DA[f] ratio	5-HT/DA[f] ratio
2a	CH_3	H	H	23.0 ± 5[c]	920 ± 73	2000 ± 60[c]	40	87
2b	CH_3	Cl	H	1.12 ± 0.1[c,d]	37.3 ± 2.1	44.5 ± 1.3[c]	32	38
3a	$CH(CH_3)_2$	Cl	H	1.41 ± 0.131c	778 ± 21	1400 ± 7[c]	551	993
4a	C_6H_5	Cl	H	1.99 ± 0.05[c]	2960 ± 220	2340 ± 2[c]	1490	1176
4c	C_6H_5	CH_3	H	3.27 ± 0.06[c]	5830 ± 370	24 500 ± 1520[c,e]	1783	7490
5a	CH_3	H		100 ± 6	7880 ± 551	3830 ± 420	79	38
5b	CH_3	Cl		4.05 ± 0.57	363 ± 36	2580 ± 800	90	637
5c	$CH(CH_3)_2$	Cl		6.00 ± 0.55	135 ± 13	3460 ± 250	23	577
5d	C_6H_5	Cl		1.62 ± 0.02	245 ± 13	195 ± 5	151	120
5e	p-CH_3O-C_6H_4	Cl		1.81 ± 0.19	835 ± 8	337 ± 40	461	186
5f	p-ClC_6H_4	Cl		4.06 ± 0.22	4070 ± 180	404 ± 56	1000	100
5g	p-BrC_6H_4	Cl		3.44 ± 0.36	1830 ± 170	106 ± 10	532	31
5h	C_6H_5	CH_3		2.33 ± 0.26	60 ± 2	1070 ± 130	26	459
6				1030 ± 70	71 000 ± 3560	33 100 ± 5400	69	32
7				204 ± 29	35 800 ± 6250	29 400 ± 2300	176	144
8				167 ± 13	6990 ± 635	40 600 ± 9400	42	243

[a] All the compounds except 6 and 7 were assayed as their hydrochloride salts. Compounds 6 and 7 were tested as the free bases. [b] Mean ± standard error of four experiments performed in triplicate. [c] Taken from ref 6. [d] The IC_{50} value reported in ref 6 was 1.17 ± 0.1. [e] The IC_{50} value reported in ref 6 was 29 666 ± 4989. [f] Note that ratios do not reflect actal molar ratios of activity; also binding ratios can be quite different than the ratios of uptake inhibitory potencies.

The isomerization of **7** to **8** may appear to be unexpected since usually isomerization at C-2 in cocaine analogs proceeds to convert the 2β isomer to the 2α isomer.[13-17] However, isomerization in the opposite direction is not unprecedented, e.g., allopseudoecgonine (**13b**) is known to isomerize to alloecgonine (**13a**).[18] The isomerization of **7** to **8** is easily rationalized based on the fact that both exist in boat conformations. In the boat conformations the C-2 substituent in **7** is axial; isomerization thus gives the more stable, equatorially substituted **8**.

Meyers and co-workers have reported that phenyllithium adds to α,β-unnatural oxazolines to give the cis product resulting from 1,4-addition.[19] The configurational assignment of **7** (oxadiazole and phenyl group in cis orientation) suggests that phenyl lithium adds to the α-face of **11** via a mechanism similar to that proposed by Meyers and coworkers for α,β-unsaturated oxazolines.[19] This is striking since phenyl magnesium bromide adds exclusively to the β-face of the carbomethoxy analog of **11**, anhydroecgonine methyl ester (**14**).[9]

Biochemical

The IC_{50} values for inhibiting ligand binding to the dopamine, serotonin, and norepinephrine transporters for the 1,2,4-oxadiazole analogs **5a-h** and **6-8**, along with several previously reported 3β-(substituted phenyl)tropan-2β-carboxylic acid esters, are listed in Table III. 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 binding, respectively, as previously described.[20] Norepinephrine IC_{50} values represent inhibition of 0.5 nM [^{3}H]nisoxetine binding to the norepinephrine transporter.[21,22]

At the dopamine transporter the potency of the 3′-phenyl-1′,2′,4′-oxadiazoles **5d** and **5h** were nearly equal to the potency of the parent esters **4a** and **4c**, respectively. The 3′-alkyl analogs **5a-c** were approximately four times less potent at the dopamine transporter than their parent esters **2a**, **2b**, and **3a**, respectively. Substitution of the 3′-phenyl of **5d** with an electron donating *p*-methoxy group resulted in compound **5e** which had essentially the same potency at the dopamine transporters as **5d**. The *p*-chloro (**5f**) and *p*-bromo (**5g**) analogues were about one-half as potent at the dopamine transporter as the unsubstituted analogue **5d**. As expected, the 3β,2α-analogue **6** was much less potent than the 2β,3β-isomer **5a** which possesses the same stereochemistry as cocaine (**1a**) and WIN 35,065-2 (**2a**). Surprisingly, the IC_{50} values at the dopamine transporter of the 3α-analogues **7** and **8** were only 1.7- and 2 times greater than the IC_{50} values for the 2β,3β-isomer **5a**.

None of the 1,2,4-oxadiazole analogues were highly selective for the dopamine transporter. The 3β-(*p*-chlorophenyl)-2β-(3′-methyl-1′,2′,4′-oxadiazole) analogue **5b** was more selective for dopamine than its parent ester **2b**; however, the oxadiazoles **5a**, **5c**, **5d**, and **5h** were all less selective than the corresponding esters **2a**, **3a**, **4a**, and **4b**, respectively. The highest selectivity for the dopamine transporter relative to the serotonin transporter was compound **5c** with a 5-HT/DA ratio of 577, whereas, analogue **5h** with a NE/DA ratio of 1002 demonstrated the highest selectivity relative to the norepinephrine transporter.

Discussion

Previous reports from this laboratory, and others, have shown that the presence of a 2β-substituent contributes substantially to the binding affinity of cocaine analogues at the dopamine transporter.[3,23-26] Replacement of the 2β-

carbomethoxy group of cocaine by a hydrogen to give **1c**, or epimerization to give **1b**, results in a 50- to 200-fold loss in potency.[25,26] Replacement of the 2β-carbomethoxy group with a 2β-hydroxymethyl group to give **1d** resulted in a 5.6-fold loss in potency which could be partially restored (2.7) by acetylation to give **1e**.[25] These results may suggest a pharmacophore model in which the 2β substituent enhances affinity to the binding site by an electrostatic interaction, probably serving as a hydrogen bond acceptor. In agreement with this possibility, we had noted that replacement of the carbomethoxy methyl group in both cocaine and 3β-(substituted phenyl)tropan-2β-carboxylic acids methyl esters by the more lipophilic isopropyl and phenyl groups (structures **1f-g** and **3-4**, respectively) usually resulted in a small reduction in potency. However, we had also noted that, by contrast, the isopropyl ester **3b** has an IC_{50} of 0.43 nM compared to 1.26 nM for the methyl ester **2c**.[5,6] This apparent discrepancy is accommodated by the proposal by Williams and co-workers[27,28] that the total free energy for the association of a ligand to its binding site via a hydrogen bond is partitioned among four separate energy terms. In this case, changing of the C-2 substituent affects more than one of these terms. The recent report by Kozikowski and co-workers that the 2β-chlorovinyl analogues **15** and **16** of cocaine and **2b**, respectively, were 2.6 and 2.3 times more potent than cocaine and **2b** in inhibition of [^{3}H]mazindol binding to the dopamine transporter[29] are similarly accounted for. Since the chlorovinyl group would be expected to be a weaker substrate for electrostatic interaction than an ester group, the hydrophobic term of hydrogen bonding may contribute more to the total free energy of binding and thus to the potency of these compounds. The results of the present study which shows that 3-alkyl- and 3-aryl-1,2,4-oxadiazoles have binding potencies similar to their parent esters and that the 3-aryl analogue **5e** possessing an electron donating methoxy group is more potent than analogues **5f** and **5g** containing electron withdrawing chloro and bromo groups, respectively, are consistent with our suggestion of an electrostatic contribution in the region of the 2β-substituent.

Since the 3α-phenyl analogues **7** and **8** possess stereochemical structures analogous to allococaine and allopseudococaine, **12a** and **12b**, respectively, they were expected to show IC_{50} values substantially higher than the 3β-phenyl-2β-isomer **5a**, the analogue of cocaine. Since ^{1}H NMR suggests that **7** and **8** exist predominantly in boat conformations, it is possible that such conformations may be favorably recognized by the receptor, although a rapid equilibrium in which the minor chair conformers are potently bound cannot be excluded. In any event, the data suggest that 3α-(substituted phenyl) analogues might be more potent and worthy of additional study.

Ritz and co-workers have shown that the inhibition of [^{3}H]mazindol binding to the dopamine transporter was highly correlated with drug-reinforcing behavior in animals.[2] It has been suggested that the abuse liability of reinforcing drugs is greater for those drugs that enter the brain and occupy receptors rapidly.[30,31] If this is correct, the powerful reinforcing properties of cocaine could be due to its rapid delivery to the brain. Compounds that enter the brain more slowly than cocaine might have lower abuse liability and therefore might be useful as a substitute medication for treating cocaine abuse. Using in vivo labeling studies, Scheffel et al.[32] showed that [^{3}H]cocaine reached peak levels in the brain in less than 5 min following intravenous injection. In contrast, peak brain levels of the cocaine analogues [^{3}H]-3β-phenyltropan-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,065-2) and [^{3}H]-3β-(4-fluorophenyl)tropan-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) were reached at 45 min. The slow onset of action and the low nanomolar potency of the 2β-(1,2,4-oxadiazole) analogues **5b-5h** combined with their complete protection against esterases suggest that these compounds may be desirable as potential medications.

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 (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 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. [^{3}H]3β-(*p*-Fluorophenyl)tropan-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-(Substituted phenyl)-2β-(3′-substituted-1′,2′,4′-oxadiazol-5′-yl)tropane (5a-h). To a stirred suspension or solution of 1 mmol of the appropriate 3β-(4-substituted phenyl)-2β-carboxylic acid (**9a-c**)[6,9] in CH_2Cl_2 (8 mL/mol) was added dropwise a solution of oxalyl chloride (2 mL of 2 M solution, 2 mmol) in CH_2Cl_2. After gas evolution ceased, the mixture was stirred for another 1.5 h and evaporated to dryness under reduced pressure. A solution of the appropriate amide oxime (1.1 equiv) in dry pyridine (8.5 mL/mmol of oxime) was added to the acid chloride solution in $CHCl_3$ (3 mL/mmol), and the mixture was heated to reflux for 1.5 h. The reaction mixture was diluted with H_2O (15 mL/mol) and made basic with 3 N NaOH. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). The residue obtained after removal of the solvent was purified by column chromatography on silica gel to give the target oxadiazoles which were characterized as their HCl salts. Physical data for **5a-h** are given in Table I.

3β-Phenyl-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane (6). Method A. A mixture of NaH (50% suspension, 120 mg, 2.5 mmol, washed with hexane) and acetamide oxime (222 mg, 3 mmol) in dry THF (50 mL) was heated to reflux under N_2 for 1 h. The mixture was cooled to room temperature. Powdered molecular sieve 4 Å, and the ester **10**[26] (518 mg, 2 mmol) in THF (10 mL) were added and continued heating to reflux for 3 h followed by stirring overnight at room temperature. The residue was removed by filtration and washed with THF. The filtrate and washing were combined and evaporated to dryness and purified by flash chromatography. The product was evaporated and crystallized from CH_2Cl_2/hexane to give 305 mg (54%) of **6**: mp 58–59 °C, $[\alpha]^{23}_D$ +111.4 (*c*, 1.42, CH_3OH).

Method B. A solution of **5a** (142 mg, 0.5 mmol) in 3% NaOMe in MeOH (15 mL) was heated to reflux for 45 min. The cooled solution was diluted with water (40 mL) and was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine and evaporated to dryness under vacuum. The residue was purified by flash chromatography to give 107 mg (75%) of **6**: mp 58–59 °C.

3α-Phenyl-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane (7). To an oven-dried, round-bottom flask equipped with a rubber septum and N_2 inlet was added oxadiazole **11**[11] (261 mg, 1.27 mmol) in 25 mL of dry THF. The reaction vessel was cooled to ~ −78 °C before dropwise addition of phenyllithium (1.4 mL of 2 M Et_2O solution). Stirring was continued for 2 h when the reaction was quenched with cooled trifluoroacetic acid, warmed to 0–5 °C, and diluted with CH_2Cl_2 (50 mL). The mixture was basified

with dilute NH_4OH (6 N). The organic fraction was separated, and the aqueous fraction was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fraction was washed with brine and evaporated to dryness. The sample was purified by flash chromatography to give 17 mg (5%) of 8 as an oil. Continued elution gave 243 mg (70%) of 7. Recrystallization of 7 from hexane gave 225 mg of analytically pure sample: mp 124–125 °C. The oily 8 was converted to the HCl salt: mp 202 °C. The physical and ^1H NMR data for these compounds are given in Tables I and II.

3α-Phenyl-2β-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane (8). Method A. Compound 7 (50 mg) in 5 mL of MeOH containing 3% HCl was heated on a steam bath for 5 min. The sample was evaporated to dryness and crystallized from MeOH/Et_2O to give 47 mg (83%) of 8·HCl: mp 202 °C.

Method B. A solution of 7 (50 mg) was heated to reflux in 5% solution of NaOMe in MeOH (5 mL) for 30 min. The cooled mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic fraction was washed with brine. The dried (Na_2SO_4) solution was evaporated under reduced pressure. The oily residue was converted to HCl salt to give 43 mg (76%) of 8·HCl: mp 202 °C.

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 are conducted in assay tubes containing 0.5 mL 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 [^3H]WIN 35,428 and 0.1 mg striatal tissue (original wet weight). The nonspecific binding of [^3H]WIN 35,428 was defined using 30 μM (−)-cocaine. Ligand binding experiments for the serotonin transporter are 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 [^3H]paroxetine and 1.5 mg of midbrain tissue (original wet weight). Nonspecific binding of [^3H]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 [^3H]nisoxetine and 8 mg of rat cerebral cortex. The nonspecific binding of [^3H]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% polyethylenimine. Results were analyzed using the Equilibrium Binding Data Analysis software (EBDA, Biosoft).

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