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Synthesis and Biological Activity of 2-Carbomethoxy-3-catechol-8-azabicyclo[3.2.1]octanes

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Abstract—Cocaine inhibits the dopamine transporter and the consequent elevation of dopamine is thought to contribute to the addictive properties of cocaine. Tropane analogues of cocaine, targeted to the dopamine transporter (DAT), are a significant focus of drug design for cocaine addiction medications. Herein, we report the function of the ortho hydroxy substituents in dopamine with respect to the azabicyclo[3.2.1]octane skeleton. The introduction of the *o*-dihydroxyl functionality led to reduced binding potency at monoamine transporters, rather than enhanced interaction with the DAT. It is therefore likely that the binding site for these compounds on the DAT is not the same as that for dopamine. Notwithstanding the moderate potency of the free catechols (>100 nM), **7** manifested stimulant activity with a duration of effect that exceeded 4 h in a rat locomotor activity assay. Compound **10**, a diacetoxy prodrug for **7**, substituted fully for cocaine in a rat drug-discrimination paradigm and is now undergoing further investigation as a potential medication for cocaine abuse.

Synaptic dopamine levels are regulated by release and uptake into dopamine neurons. Dopamine is transported into presynaptic neurons by the dopamine transporter (DAT), a 12-transmembrane protein localized in extracellular membranes. Cocaine is an effective inhibitor of the DAT and raises extracellular dopamine levels several-fold above basal levels. The consequent prolonged activation of postsynaptic dopamine (DA) receptors[1–3] contributes significantly to the psychomotor stimulant, reinforcing effects and addictive potential of cocaine. The search for DAT-based medications for cocaine addiction includes compounds with different pharmacokinetic properties to function as cocaine replacements (agonists) as well as cocaine antagonists. A fundamental challenge of antagonist compounds is that they block cocaine binding to the dopamine transporter but permit the transport of dopamine. The underlying premise of this antagonist concept is that the binding site(s) for cocaine and dopamine differ.

A lead compound that mimics the effects of cocaine on the DAT, and that offers greater biological stability than cocaine, was first reported by Clarke et al. in 1973.[4] This compound [WIN35,428: 2β-carbomethoxy-3β-(4-fluorophenyl)-8-azabicyclo[1.2.3]octane] has now served as a template for many research groups including our own.[5–10] As the molecular binding site of cocaine or WIN35,428 on the DAT is still unknown, a cocaine antagonist that fulfills this profile remains challenging. Kitayama et al.[11] postulated that the dopamine binding site was located between Transmembrane Domains (TMD) 1 and 7 and they showed that the TMD 1 Asp^{79} and TMD 7 Ser^{356} and Ser^{359} were required for DA binding. The catechol moiety of dopamine was postulated to interact with the two serine residues while the aspartic acid bound ionically to the amine functionality of DA. They suggested that cocaine and WIN35,428 might bind similarly.[11,12] Later, Edvardsen and Dahl[13] suggested that these serine residues may not play a part in DA binding, and Vaughan and Kuhar[14] suggested that the two serines may not provide a general site for binding by DAT inhibitors. We had also questioned the universality of this binding domain to other DAT inhibitors such as the 8-oxatropanes[15] or 8-carbatropanes.[16,17] To further examine this premise, we investigated the role of the *ortho* hydroxy substituents in dopamine with respect to the azabicyclo[3.2.1]octane (tropane) skeleton. This manuscript describes the synthesis of tropanes designed to explore the possibility

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that a tropane with a C3-catechol may interact with the three residues, Asp[79], Ser[356] and Ser[359] (Fig. 1).

It has been shown[8,18,19] that selectivity of inhibition of monoamine uptake systems (dopamine, serotonin, norepinephrine) can be obtained by altering the relative stereochemistry at C2 and C3 on the tropane skeleton. Thus, tropanes with a 'flattened' skeleton (2,3-enes) or with a boat configuration (3α-aryl) were generally more selective for DAT inhibition than were the chair configured 3β-aryl analogues. Our route to these compounds is shown in Scheme 1.

The protected catechol boronic acid **2**[20–22] was reacted with the enol triflate **3**[19] under palladium catalysis[23] to provide **4** in 74% yield. Reduction of the double bond

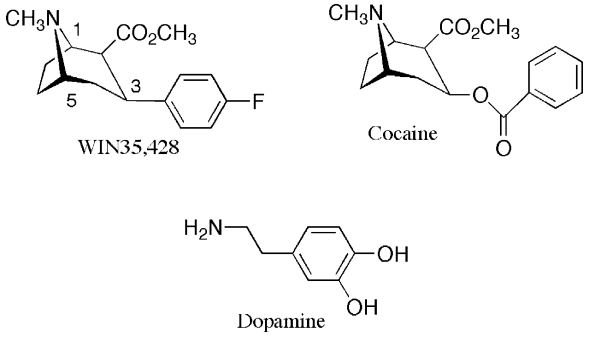
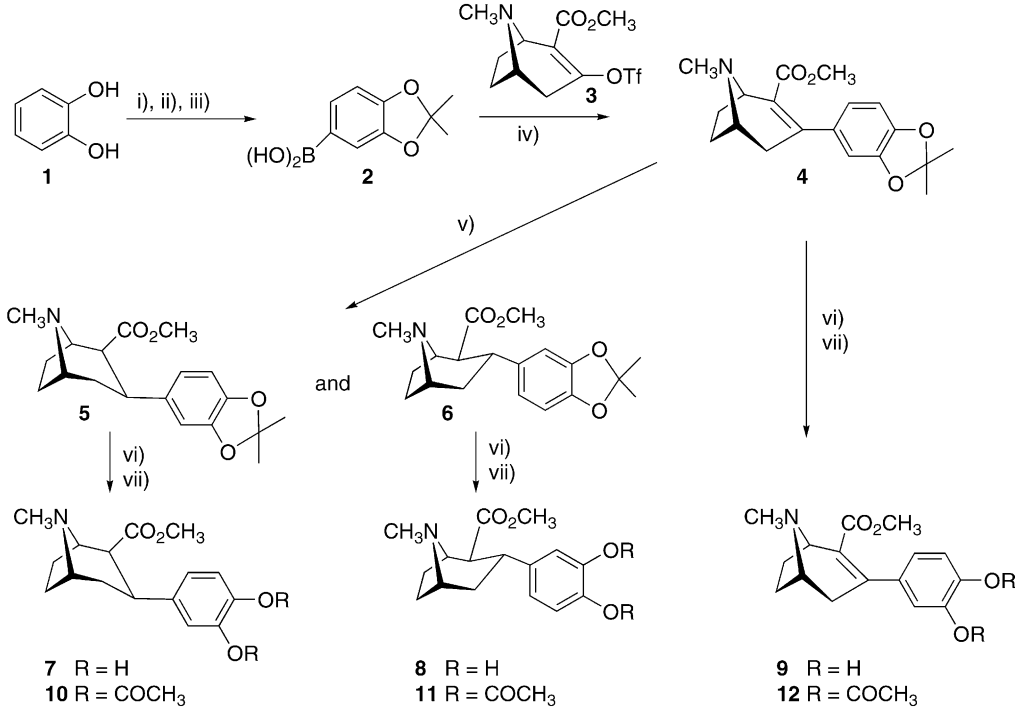


Figure 1.

was conducted with samarium iodide[19] to provide the 3β (**5**: chair: 31%) and 3α (**6**: boat: 42%) configured tropanes in 73% overall yield. Characterization of the 2,3-ene, 3α-aryl and 3β-aryl compounds was conducted by ^{1}H NMR spectroscopy.[15,18] The resonances for the $H_{4\alpha}$ and $H_{4\beta}$ protons are diagnostic in the tropanes. In the case of the 2,3-ene **4**, the $H_{4\alpha}$ appears as a double doublet ($J = 19.2$, 4.7 Hz) at δ 2.72 and the $H_{4\beta}$ appears as a doublet ($J = 19.2$ Hz) at δ 2.03. In boat configured compounds such as **6**, the $H_{4\beta}$ proton (δ 2.40) shows the characteristic geminal coupling ($J = 10.2$ Hz). The $H_{4\alpha}$ in 3α-aryl tropanes generally appears upfield with a characteristic pattern showing transdiaxial, geminal and vicinal coupling. In **6**, the $H_{4\alpha}$ appears at δ 1.26. There are no resonances this far upfield for the 3β-configured chair compounds. Deprotection of **4**–**6** to provide the catechols as the hydrochloride salts **7**–**9** was effected with HCl in methanol in excellent yield. These compounds were then converted quantitatively to their diacetylated derivatives **10**–**12** with acetyl chloride.

We had expected that the free catechols **7**–**9** would be unlikely to cross the blood brain barrier (BBB) and enter the brain in reasonable amounts. Therefore protected catechols would be required for BBB penetration. We anticipated that the diacetoxy tropanes **10**–**12** would permeate the BBB, undergo ester cleavage, and release the free catechols **7**–**9** in the brain. In fact, inhibitory potency [inhibition of [^{3}H]RTI55 of the three monoamine uptake mechanisms (DAT, SERT, NET)] of



Scheme 1. Synthetic route to 3,4-dioxyphenyl tropanes. Reagents: (i) $(CH_3)_2C(OCH_3)_2$, p-TSA, 93%; (ii) Dioxan.Br_2, 94%; (iii) *n*-BuLi, (*i*PrO)$_3$B, −78 °C, 3.5 h, 60% **3**, $CH_2(OCH_2CH_3)_2$, LiCl, Na_2CO_3, $Pd(PPh_3)_4$, reflux 15 h, 74%; (v) SmI_2, MeOH, 1 h, H_2O, **5**: 31%, **6**: 42%; MeOH, HCl, 55 °C, 0.5 h, 98–100%; (vii) CH_3COCl, 22 °C, 40 min, 90–100%.

Table 1. Inhibition of [^{125}I]RTI55 binding in HEK-hDAT, HEK-hSERT and HEK-hNET cells by dihydroxylated aryl tropanes, and inhibition of [^{3}H]dopamine (DA), [^{3}H]serotonin (SER), [^{3}H]norepinephrine (NE), respectively[a]

	Compd[b]	C3-Aryl	DAT K_i (nM)	DA IC_{50} (nM)	SERT K_i (nM)	SER IC_{50} (nM)	NET K_i (nM)	NE IC_{50} (nM)
	Cocaine		419±86	330±58	297±32	325±71	645±87	192±61
	Dopamine[c]		6400±590	460±110	>1100 μM	>30,000	>28,000	6.63±0.26
7	O-506	3β-$(OH)_2$Ph	1370±510	509±44	271±99	308±15	2960±630	122±13
8	O-2005	3α-$(OH)_2$Ph	970±290	406±45	>10,000		3060±290	173±66
9	O-2003	3-$(OH)_2$Ph-2,3-ene	>10,000		>10,000		>10,000	
13	O-906	3β-$(OCH_3)_2$Ph	1536±254	1568±405	46±8.5	23±3.2	4500±165	1452±82
10	O-509	3β-$(OAc)_2$Ph	>10,000		168±47	330±140	>10,000	
11	O-2006	3α-$(OAc)_2$Ph	>10,000		704±64		>10,000	
12	O-2004	3-$(OAc)_2$Ph-2,3-ene	>10,000		>10,000		>10,000	

[a]Data obtained through the auspices of National Institute on Drug Abuse (NIDA). Numbers represent the means from at least three independent experiments each conducted in duplicate (binding assays) or triplicate (uptake assays) determinations. Where $K_i > 10{,}000$ nM, IC_{50}s were not determined. See ref 28.
[b]All compounds had satisfactory elemental analyses (± <0.4%).[27]
[c]From ref 28.

these catechols (Table 1) followed the lines manifested by other tropanes.[8] More specifically, the chair configured compound **7** is less selective, but of similar potency to the boat configured **8**, at the DAT. The unprotected catechols **7**–**8** inhibited [^{3}H]RTI55 binding at the DAT and NET weakly (K_i = 1–3 μM). Catechol **7** manifested moderate inhibition at the SERT ($K_i = 271 \pm 99$ nM). However, **8** had no effect upon the SERT. The 2,3-ene **9** is inactive at the DAT, SERT and NET.[24] The diacetoxy ('prodrug') compounds proved, as anticipated, ineffective at DAT and NET in vitro. Moderate inhibition (170–700 nM) was seen for **10** and **11** at the SERT. The dimethoxy compound **13** (prepared analogously from 3,4-dimethoxyphenylboronic acid) was a reasonably potent and selective inhibitor of the SERT ($K_i = 46 \pm 8.5$ nM). The potencies (IC_{50}s) of **7** and **8** for inhibiting [^{3}H]DA and [^{3}H]NE transport were higher than their potencies for inhibiting binding of the compounds to sites labeled by [^{3}H]RTI55. In the case of [^{3}H]NE uptake, potencies differed by an order of magnitude. In contrast, potencies for inhibiting [^{3}H]SER transport or [^{3}H]RTI55 binding were the same. In comparison with other 3β-(3,4-disubstituted aryl)tropanes, it is interesting to note that introduction of the *o*-dihydroxyl functionality has led to a substantial reduction in binding inhibition at all three transporters. For example the 3β-aryl analogues, 3,4-dichlorophenyl-, 3-methyl-4-chlorophenyl-, or 3-methyl-4-fluorophenyltropanes all inhibit DAT, SERT and NET with high potency (IC_{50} = 0.8–36 nM).[6] The monohydroxy analogue, 4-hydroxyphenyltropane was reportedly a potent inhibitor of monoamine uptake[25] with DAT $IC_{50} = 12.1$ nM. Therefore, although K_i values of inhibition of [^{3}H]RTI55 have been utilized here (Table 1) in contrast to IC_{50}s of [^{3}H]WIN35,428 (DAT), [^{3}H]paroxetine (SERT) and [^{3}H]nisoxetine (NET) for the examples cited above, it is clear that introduction of a second hydroxyl group leads to a reduction in binding affinity compared with that of WIN35,428 or cocaine. We conclude that the C3-catechol in these tropanes does not enhance interaction of tropanes with the three putative residues, Asp^{79}, Ser^{356} and Ser^{359} on the DAT.

Of the diacetoxy prodrugs **10**–**12**, the 3α-catechol **11** and 2,3-ene **12** proved inactive in an intraperitoneal (ip) assay of locomotor activity in rats. In contrast, the 3β-catechol **10** suppressed locomotor activity within 1 h (ID_{50} = 44.8 mg/kg). It did not attenuate locomotor activity induced by cocaine (20 mg/kg). In an 8 h assessment of locomotor activity in rats (ip), stimulant effects of **10** (100 mg/kg) occurred within 40 min of injection ($ED_{50} \geq 38.1$ mg/kg) with a duration of action of about 4 h. This observation is not unanticipated, as stimulant drugs such as amphetamine suppress locomotor activity in rats at low doses and increase activity at higher doses. Notwithstanding the moderately weak inhibitory potency of the free catechols **7**–**9** in a rat locomotor activity assay (ip), **7** was a stimulant in the 1 h assay (ED_{50} = 6.9 mg/kg). In an 8-h assay, it manifested stimulant activity over about 4 h ($ED_{50} \geq 29.6$ mg/kg). It was however extremely weak in a drug discrimination paradigm in rats administered either ip or orally (po). Kimmel et al. have reported that for non-selective tropane analogues in their 8-azabicyclo-[3.2.1]octane series, increases in locomotor activity were positively and significantly correlated with binding potencies at all three monoamine transporters.[26] The non-selective compounds we report herein are comparatively weak inhibitors of all three monoamine uptake systems, yet **10** (100 mg/kg), the prodrug for **7**, substituted partially (75%) for cocaine (10 mg/kg) in the rat drug discrimination assay by the ip route, and substituted fully (within 45 min following 100 mg/kg) for cocaine in a rat drug discrimination paradigm when administered orally (ED_{50} = 46.8 mg/kg). The ability of **10**, but not **7**, to generalize partially or fully to the cocaine discriminative stimulus cue within the same time frame, supports our initial contention that BBB penetration would be enhanced by protection of the free catechol moiety. Assuming cleavage occurs, the potency of the pro-drug is not unanticipated, as the product **7** and cocaine display similar potencies for the [^{3}H]DA transport assay. Compound **10** is now undergoing further investigation as a potential medication for cocaine abuse.

Elemental Analyses

Biological assays

Compd		Calculated C	H	N	Cl	Found C	H	N	Cl	Calculated for formula
O-506	7	56.75	6.91	4.14	10.47	56.60	6.89	3.99	10.64	$C_{16}H_{22}O_4ClN{\cdot}0.6H_2O$
O-2005	8	58.62	6.76	4.27	10.82	58.39	6.93	4.14	10.66	$C_{16}H_{22}O_4ClN$
O-2003	9	56.49	6.40	4.12	10.42	56.40	6.09	3.92	10.46	$C_{16}H_{20}O_4ClN{\cdot}0.8H_2O$
O-509	10	55.41	6.60	3.23	8.18	55.36	6.62	3.03	8.37	$C_{20}H_{26}O_6ClN{\cdot}1.2H_2O$
O-2006	11	58.32	6.36	3.40	8.61	58.27	6.37	3.22	8.38	$C_{20}H_{26}O_6ClN$
O-2004	12	56.14	6.12	3.27	8.29	56.07	6.02	3.20	8.55	$C_{20}H_{24}O_6ClN{\cdot}1.0H_2O$
O-906	13	67.69	7.89	4.39	—	67.60	7.92	4.32	—	$C_{18}H_{25}O_4N$

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27. **(2,2-Dimethylbenzo[1,3]dioxol-5-yl)boronic acid (2)**. Mp 187–189 °C; R_f 0.51 (10% hexanes in EtOAc); ^{1}H NMR δ 1.70 (s, 6H), 6.85 (d, 1H), 7.52 (s, 1H), 7.74 (d, 1H); ^{13}C NMR δ 25.9, 108.3, 114.2, 118.0, 123.2, 130.5, 147.3, 151.2. (1R)-2-**Carbomethoxy-3-(2,2-dimethylbenzo[1,3]dioxol-5-yl)tropene (4)**. Mp 71–73 °C; R_f 0.30 (10% MeOH in EtOAc); ^{1}H NMR δ 1.55–1.70 (m, 1H), 1.67 (s, 6H), 1.90–2.05 (m, 2H), 2.03 (d, J = 19.2 Hz, 1H), 2.05–2.25 (m, 1H), 2.42 (s, 3H), 2.72 (dd, J = 19.2, 4.7 Hz, 1H), 3.33 (t, J = 4.9 Hz, 1H), 3.54 (s, 3H), 4.80 (d, J = 4.7 Hz, 1H), 6.55 (s, 1H), 6.57 (d, 1H), 6.66 (d,1H); **(1*R*)-2β-Carbomethoxy-3α-(2,2-dimethylbenzo[1,3]dioxol-5yl)trop-ane (6)** and **(1*R*)-2β-carbomethoxy-3β-(2,2-dimethylbenzo [1,3]dioxol-5-yl)tropane (5)**. **5**: R_f 0.85 (10% Et_3N in Et_2O); ^{1}H NMR δ 1.55–1.75 (m, 3H), 1.64 (s, 3H), 1.65 (s, 3H), 2.02–2.26 (m, 2H), 2.24 (s, 3H), 2.53 (td, J = 12.4, 2.7 Hz, 1H), 2.81–2.86 (m, 1H), 2.92 (dt, J = 12.9, 4.9 Hz, 1H), 3.34–3.39 (m, 1H), 3.51–3.57 (m, 1H), 3.53 (s, 3H), 6.58–6.72 (m, 3H). **6**: R_f 0.38 (EtOAc); ^{1}H NMR δ 1.26 (ddd, 1H), 1.41–1.65 (m, 2H), 1.64 (s, 6H), 2.07–2.25 (m, 2H), 2.24 (s, 3H), 2.40 (dd, 1H), 2.36–2.50 (m, 1H), 3.16–3.33 (m, 3H), 3.60 (s, 3H), 6.58–6.64 (m, 3H). **(1*R*)-2β-Carbomethoxy-3β-(3,4-dihydroxyphenyl)tropane hydrochloride (7)**. Mp 228–230 °C; R_f = 0.07 (10% Et_3N in Et_2O); ^{1}H NMR (MeOH-d_4) δ 1.92 (dt, J = 14.8, 2.6 Hz, 1H), 2.13–2.31 (m, 2H), 2.31–2.52 (m, 2H), 2.64 (td, J = 14.8 Hz, 0.8H), 2.85 (s, 3H), 3.01–3.06 (m, 1H), 3.36–3.48 (m, 1H), 3.41 (s, 3H), 3.96–4.05 (m, 1H), 4.07–4.15 (m, 1H), 6.53 (dd, 1H), 6.65 (d,1H), 6.69 (d,1H). **(1*R*)-2β-Carbomethoxy-3α-(3,4-dihydroxyphenyl)tropane hydrochloride (8)**. Mp 204–206 °C; R_f 0.15 (10% MeOH in $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 1.94–2.08 (m, 2H), 2.19–2.4 (m, 3H), 2.46–2.58 (m, 1H), 2.81 (s, 3H), 3.21–3.35 (m, 2H), 3.70 (s, 3H), 3.88–3.95 (m, 1H), 4.09–4.15 (m, 1H), 6.67–6.83 (m, 3H). **(1*R*)-2-Carbomethoxy-3-(3,4-dihydroxyphenyl)tropene hydrochloride (9)**. Mp 146–150 °C; R_f 0.13 (10% MeOH in $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 1.90–2.03 (m, 1H), 2.15–2.43 (m, 3H), 2.52 (brd, J = 22 Hz, 1H), 2.72 (s, 3H), 2.95 (brd, J = 22 Hz, 1H), 3.44 (s, 3H), 3.85 (brs, 1H), 4.34 (brs), 1H), 6.44 (dd,1H), 6.53 (d, 1H), 6.64 (d,1H). **(1*R*)-2β-Carbomethoxy-3β-(3,4-diacetoxyphenyl)tropane hydrochloride (10).** Mp 158–161 °C; R_f 0.35 (10% MeOH in $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 1.96–2.07 (m, 1H), 2.17–2.37 (m, 2H), 2.26 (s, 3H), 2.27 (s, 3H),

2.37–2.54 (m, 2H), 2.67 (td, $J = 14.1$, 3.4 Hz, 1H), 2.87 (s, 3H), 3.16 (dd, $J = 6.7$, 2.0 Hz, 1H), 3.39 (s, 3H), 3.61–3.72 (m, 1H), 4.01–4.08 (m, 1H), 4.13–4.19 (m, 1H), 7.08–7.24 (m, 3H). **(1*R*)-2β-Carbomethoxy-3α-(3,4-diacetoxyphenyl)tropane hydrochloride (11)**. Mp 185–187 °C (dec); R_f 0.52 (10% MeOH in $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 1.97–2.06 (m, 2H), 2.25–2.45 (m, 3H), 2.27 (s, 6H), 2.53–2.63 (m, 1H), 2.83 (s, 3H), 3.38–3.49 (m, 2H), 3.71 (s, 3H), 3.94 (t, $J = 6$ Hz, 1H), 4.18 (d, $J = 7.1$ Hz, 1H), 7.21 (d, $J = 8.7$ Hz, 1H), 7.34 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H). (1R)-2-Carbomethoxy-3-(3,4-diacetoxyphenyl)tropene hydrochloride (12). Mp 90–92 °C; R_f 0.45 (10% MeOH in $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 2.08–2.17 (m, 1H), 2.27 (s, 6H), 2.37–2.54 (m, 3H), 2.70 (d, $J = 19$ Hz, 1H), 2.90 (s, 3H), 3.14 (dd, $J = 22$, 5.2 Hz, 1H), 3.52 (s, 3H), 4.03 (brs, 1H), 4.58 (brs, 1H), 7.10 (d, 1H), 7.13 (dd,1H), 7.23 (d,1H).

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