Synthesis and Cocaine Receptor Affinities of 3-Phenyl-2-(3′-methyl-1,2,4-oxadiazole-5′-yl)tropane Isomers

F. Ivy Carroll,*[a] Philip Abraham,[a] Michael A. Kuzemko,[a] Jeffrey L. Gray,[a] Anita H. Lewin,[a] John W. Boja[b] and Michael J. Kuhar[b]

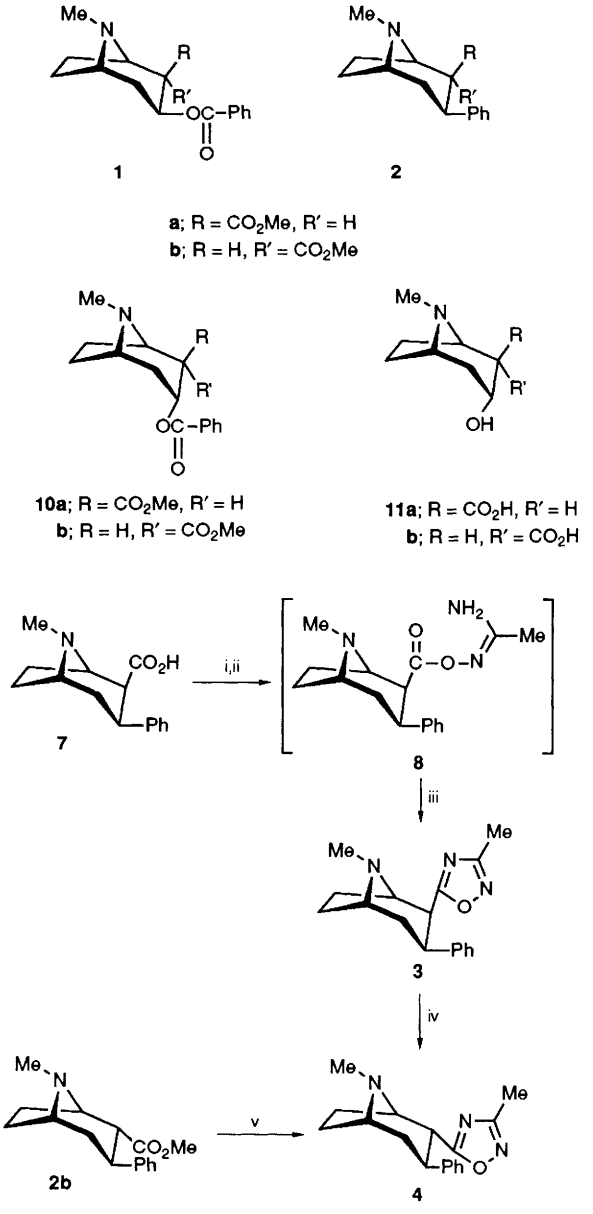
[a] Chemistry and Life Sciences, Research Triangle Institute, PO Box 12194, Research Triangle Park, North Carolina 27709, USA

[a] Neuroscience Branch, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland 21224, USA

This study reports the synthesis and binding affinities at the cocaine receptor of all four isomers of 3-phenyl-2-(3-methyl-1,2,4-oxadiazole-5-yl)tropane derivable from natural (−)-cocaine.

Numerous studies have suggested that the behavioural and reinforcing properties of (−)-cocaine **1a** are related to its ability to inhibit dopamine (DA) reuptake.[1,2] Binding site(s) that correspond to the (−)-cocaine **1a** receptor on the dopamine transporter have been identified using several radioligands.[1] Recently, we reported that 4′- and 3′,4′-substituted analogues of methyl [1*R*-(*exo*,*exo*)]-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**2a**, WIN 35065-2)† possessed high affinity for the cocaine binding site on the dopamine transporter.[3–5] We also showed in separate studies

† The name, 3β-phenyltropan-2β-carboxylic acid methyl ester has largely been used in the literature for naming cocaine analogues of structure **2a**. This system is used for naming structures in this paper.



Scheme 1 *Reagents and conditions*: $(COCl_2)$, CH_2Cl_2; ii, MeC(=NOH)NH_2, pyridine–$CHCl_3$ (1:3), 25 °C; iii, 25 °C for 16 h; iv, MeONa, MeOH; v, MeC(=NOH)NH_2, NaH, THF, molecular sieve, reflux, 12 h

that the 2β-carbomethoxy group and the absolute stereochemistry of **1a** and **2a** play important roles in binding to the dopamine transporter.[1,6,7]

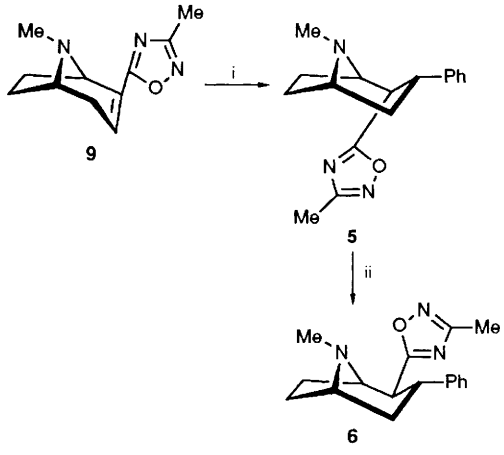
As part of our ongoing structure–activity studies, we now report the synthesis of the 3-methyl-1,2,4-oxadiazole-5-yl derivatives **3–6**. These compounds are of interest since the 1,2,4-oxadiazole ring can be an excellent bioisostere for an ester group.[8] Compounds **3** and **4** are the bioisosteres of **2a** and its 2α-isomer **2b**;[4,9] to our knowledge the esters corresponding to **5** and **6** have not been reported. 3β-Phenyl-2β-(3′-methyl-1,2,4-oxadiazole-5′-yl)tropane **3** and 3β-phenyl-2α-(3-methyl-1,2,4-oxadiazole-5-yl)tropane **4** were prepared from the known acid, 3β-phenyltropan-2β-carboxylic acid **7**[9] and ester **2b**, respectively, as shown in Scheme 1. The hydrochloride salt **3**·HCl had m.p. 177–178 °C, $[\alpha]_D^{23}$ −126.5 (*c* 0.57, MeOH), and the free base **4** had m.p. 58–59 °C and $[\alpha]_D^{23}$ + 114.5 (*c* 1.42, $CHCl_3$).‡ Compound **4** was also obtained by epimerization of **3** (axial 2-oxadiazole group) to **4** (equatorial

‡ All new compounds gave satisfactory analytical and spectral data.

Table 1 Selected ^{1}H NMR assignments and vicinal coupling constants for compounds **3–6** in [$^2H_5$]pyridine[a]

	4	**3**	**5**	**6**
Proton(s)	δ	δ	δ	δ
1	3.4	3.5[b]	3.65	3.55
2	4.0	3.8	4.45	3.45
3	3.5	3.3	3.95	3.9
4ax	2.05	2.9	2.54	2.6
4eq	1.7	1.7	2.07	
5	3.1	3.2[b]	3.25	3.25
	J/Hz	*J*/Hz	*J*/Hz	*J*/Hz
1,2	2.5	~3.8	7.0	0
2,3	12	5	7.8	9.9
3,4ax	12.1	13.0	7.8	9
3,4eq	5.7	5	8.6	10
4ax,4eq		13.0	13.5	15.5
4ax,5		2.6	7.6	8.0

[a] Chemical shifts are relative to $SiMe_4$ at 500 MHz. [b] These assignments might be reversed.



Scheme 2 *Reagents*: i, PhLi; ii, MeONa, MeOH

2-oxadiazole group) using sodium methoxide in methanol. The relative stereochemistries for **3** and **4** follow from the methods of synthesis and are supported by their ^{1}H NMR spectra data (see Table 1). Assignments of the resonances were made using 2D NMR (^{1}H COSY). The observed coupling constants for the C-2, C-3 and C-4 protons (Table 1) 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. It thus appears that both **3** and **4** possess chair conformations.

Since Meyers and coworkers have reported that phenyllithium treatment of α,β-unsaturated oxazolines results in 1,4 addition,[11] we had envisioned that the addition of phenyllithium to (1*R*,5*S*)-2-(3-methyl-1,2,4-oxadiazole-5-yl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene **9**[12] might proceed similarly. In fact, the addition of 2 equiv. of phenyllithium to **9** at −70 °C in dry tetrahydrofuran (THF) followed by quenching with trifluoroacetic acid at −78 °C gave a 70% yield of 3α-phenyl-2α-(3′-methyl-1,2,4-oxadiazole-5′-yl)tropane **5**. The compound had m.p. 124–125 °C, $[\alpha]_D^{23}$ + 32.1 (*c* 0.14, MeOH). Isomerization of **5** with methanolic sodium methoxide or hydrogen chloride provided the remaining possible (3α,2β)-isomer **6** as a clear oil. This isomer was characterized as its hydrochloride salt **6**·HCl, m.p. 201–202 °C, $[\alpha]_D^{23}$ −71.1 (*c* 0.09, MeOH).

Comparison of the ^{1}H NMR spectra of **5** and **6** to those of the 3α-cocaine isomers[10] allococaine **10a** and allopseudococaine **10b** revealed striking differences. In particular, the

magnitude of the coupling constants (Table 1) strongly suggested a boat conformation for the piperidine ring in **5** and **6**. Thus, the large (*ca.* 8 Hz) values observed for the coupling constants between the proton at C-3 and its neighbours 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 axial position. The zero value of $J_{1,2}$ in **6** 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.[13] The assignment of the C-2 proton as axial is also consistent with its upfield chemical shift value relative to the isomer **5**, *i.e.* axial C-2 protons are shielded relative to their equatorial counterparts in the cocaine series[10] as well as in **3** and **4** (Table 1).

Based on these arguments, we conclude that **5** is the 2α,3α isomer and **6** is the 2β,3α isomer. The similar chemical shifts for H-3 and the similar $J_{3,4ax}$ and $J_{3,4eq}$ values for **5** and **6** indicate that both compounds possess flattened boat conformations.

The configurational assignment of **5** (oxadiazole and phenyl group in *cis* orientation) is consistent with phenyllithium adding to the α-face of **9** *via* a mechanism similar to that proposed by Meyers and coworkers for α,β-unsaturated oxazolines.[11] This is striking since phenyl magnesium bromide adds exclusively to the β-face of the carbomethoxy analogue of **9**, anhydroecgonine methyl ester **12**.[9] Additional studies are needed to establish the mechanism and versatility of this reaction. However, this new Michael addition-type reaction, which proceeds in good yield and high selectivity, is of considerable interest and provides entry into an important new class of cocaine analogues.

The isomerization of **5** to **6** may appear to be unexpected since usually isomerization at C-2 proceeds to convert the 2β isomer to the 2α isomer.[14–18] However, isomerization in the opposite direction is not unprecedented, *e.g.* allopseudoecgonine **11b** is known to isomerize to alloecgonine **11a**.[19] The isomerization of **5** to **6** is easily rationalized based on the fact that both exist in boat conformations. In the boat conformations the C-2 substituent in **5** is axial; isomerization to **6** thus gives the more stable, equatorially substituted **6**.

Radioligand binding data revealed that, as expected, the 2α,3β isomer **4** was much less potent (IC_{50} 1030 nmol dm^{-3}) than the 2β,3β isomer **3** (IC_{50} 100 nmol dm^{-3}). Surprisingly, the 3α isomers **5** and **6** were found to have potencies similar to that of **3** (IC_{50} 204 and 148 nmol dm^{-3}, respectively), although, as analogues of allopseudo- and allo-cocaine (**10b** and **10a**, respectively), they were expected to be substantially less potent than **3**, the analogue of cocaine **1a**. This suggests that boat conformations may be favourably recognized by the receptor.

The most active oxadiazole analogue in this group, compound **3**, is clearly less potent than the parent compound **2a** (IC_{50} 23 nmol dm^{-3}). However, these analogues are of considerable interest since the oxadiazole ring at C-2 is more resistant than the carbomethoxy group to metabolic and chemical degradation. Moreover, since substitution of the phenyl group of **2a** has been found to enhance potency,[3–5] substituted phenyl analogues of **3**, and probably of **5** and **6**, might be more potent. Studies along these lines are underway.

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