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

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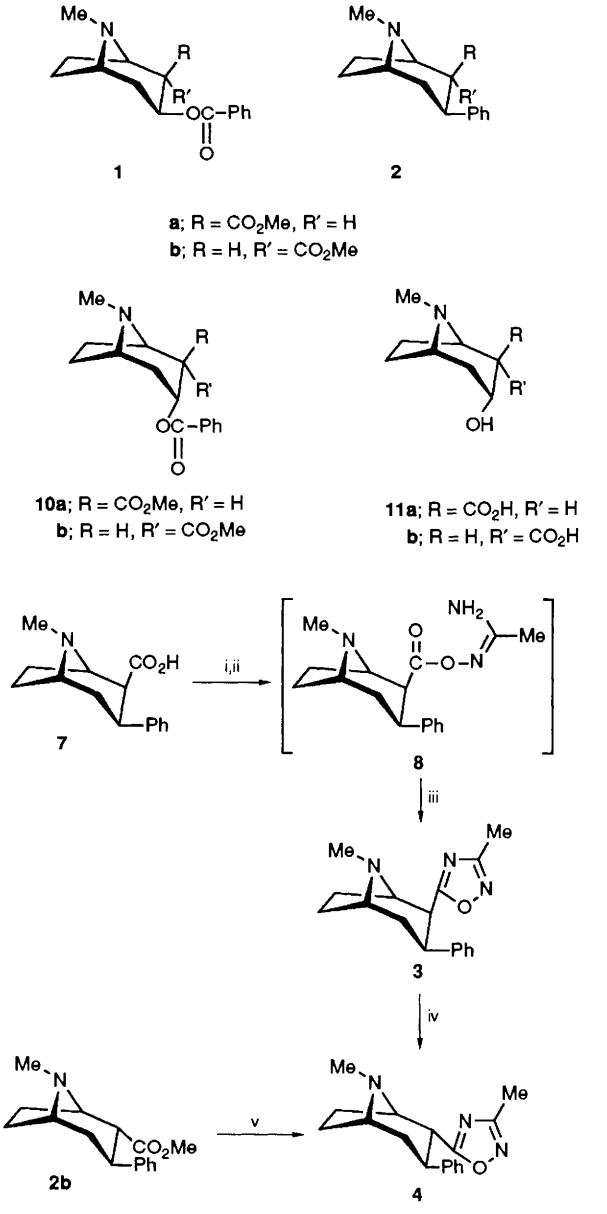
This study reports the synthesis and binding affinities at the cocaine receptor of all four isomers of 3-phenyl-2-(3-methyl-1,2,4-oxadiazole-5-yl)tropane derivable from natural (−)-cocaine.

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]

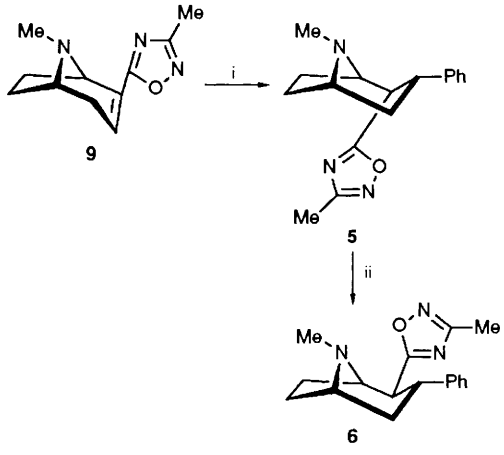
As part of our ongoing structure–activity studies, we now report the synthesis of the 3-methyl-1,2,4-oxadiazole-5-yl derivatives **3–6**. These compounds are of interest since the 1,2,4-oxadiazole ring can be an excellent bioisostere for an ester group.[8] Compounds **3** and **4** are the bioisosteres 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 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.

‡ 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

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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