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The Synthesis of Tricyclic Cocaine Analogs *via* the 1,3-Dipolar Cycloaddition of Oxidopyridinium Betaines.

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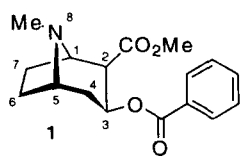
Abstract: Tricyclic cocaine analogs with a spatially fixed nitrogen lone pair were synthesized as structural probes of the dopamine transporter. A tandem cycloaddition/radical cyclization protocol was used to gain access to analog **12** with a two carbon linker between C-2 and N-8. On the other hand, the intramolecular dipolar cycloaddition reaction of betaine **13** was used to procure cocaine analog **18** and its C-3 epimer **19** in which an extra ring links N-8 to C-6. Binding studies reveal **12c** and **18** to be potent DAT ligands.

Cocaine (**1**) has long been recognized to act as a potent central nervous system stimulant.[1] Addicts may lose the ability to function at work or in interpersonal interactions. As a result, cocaine is one of the greatest concerns of the American public today. It is clear that immediate therapies are needed for the treatment of individuals who have become addicted to this powerful reinforcing drug.[2] A growing body of evidence points to the ability of cocaine to bind to the dopamine transporter (DAT) and to inhibit the reuptake of dopamine (DA) as being responsible for the reinforcing properties of this drug.[3] A number of highly potent cocaine analogs together with information concerning their structure-activity relationships (SAR) at the DAT have been reported.[4] However, the precise details of the binding interactions between these analogs and the DAT is still a matter of much discussion.[5]



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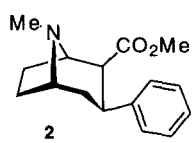

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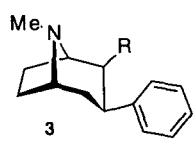

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Previously it has been shown that replacement of the C-3 benzoate by phenyl leads to higher potency cocaine analogs (**2**; these phenyl bearing structures are often referred to as the WIN series).[6] Additionally, we have shown that cocaine's C-2 ester group can be replaced by alkyl and alkenyl groups as in **3** and still retain high binding affinity.[7] A number of *N*-modified cocaine analogs have been reported.[8] For example, replacement of the methyl group of cocaine by electronically similar but sterically larger groups has marginal effect on binding activity. Replacement of the 8-methyl group by propyl has almost no effect, while replacement by allyl or benzyl reduces activity by a factor of 7-fold or less. *N*-substitution with electron-withdrawing groups can significantly decrease activity, however, a basic amine or nitrogen is not always required for potent activity.[9] Little is known experimentally about the spatial requirements of the nitrogen lone pair of these

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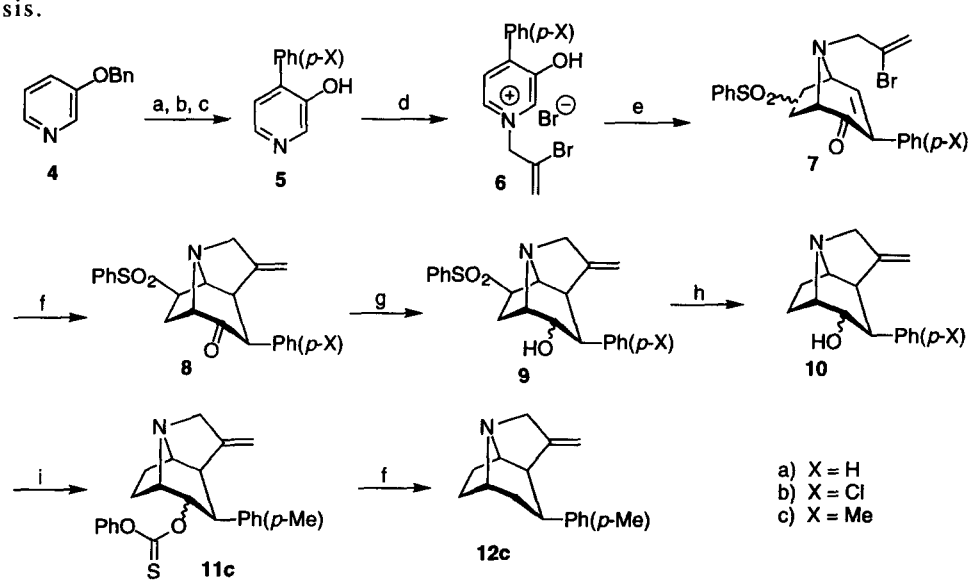
cocaine analogs. The directionality of the nitrogen lone pair is, however, likely to be of some consequence to binding affinity.[10] Conformational analysis of a series of methylphenidate derivatives and their *N*-methyl analogs showed that the reduced binding affinities of the latter could be explained by the spatial requirements at nitrogen. The added *N*-methyl group was shown to preferentially occupy the space presumed to be preferred by the lone pair of cocaine.[10a] Semi-empirical quantum chemistry (PM3) calculations[10b] along with mutational data[10c] suggest that cocaine binds in its neutral form to the dopamine transporter forming a weak hydrogen bond involving a protonated aspartate (Asp 79) residue from the dopamine transporter. Herein we report the synthesis of conformationally restricted cocaine analogs that may be used to further map the cocaine/receptor interactions.

The synthetic route employed in the present study (Scheme 1) exploited the versatile 1,3-dipolar cycloaddition of 3-hydroxypyridinium betaines with electron deficient olefins for the synthesis of the tropane skeleton.[11] This synthesis commences with the preparation of the 4-(*p*-substituted)phenylpyridines **5b** and **c** (X = Cl, Me) by the route previously reported for the unsubstituted (X = H) analog **5a**.[12] *N*-Alkylation with 2,3-dibromopropene in THF afforded the pyridinium bromide salts **6b** and **6c** in 95% yield. The tandem cycloaddition/radical cyclization methodology reported by Ghosh and Hart[8] was used to produce the desired tricyclic ketones **8b** and **8c**. Thus, the dipolar cycloaddition of the betaine of **6b** or **6c** (generated *in situ* with Et_3N) with phenyl vinyl sulfone afforded a mixture of the 6- and 7-*exo*-phenylsulfonyl regiosomers **7b** or **7c** (in 60 and 21% isolated yield, respectively, from **6**). Radical cyclization of **7b** afforded the tricyclic ketone **8b** as a white crystalline solid in 54% yield (75% for the analogous transformation of **7c** into **8c**). The structure of **8b** was unequivocally confirmed by X-ray analysis.

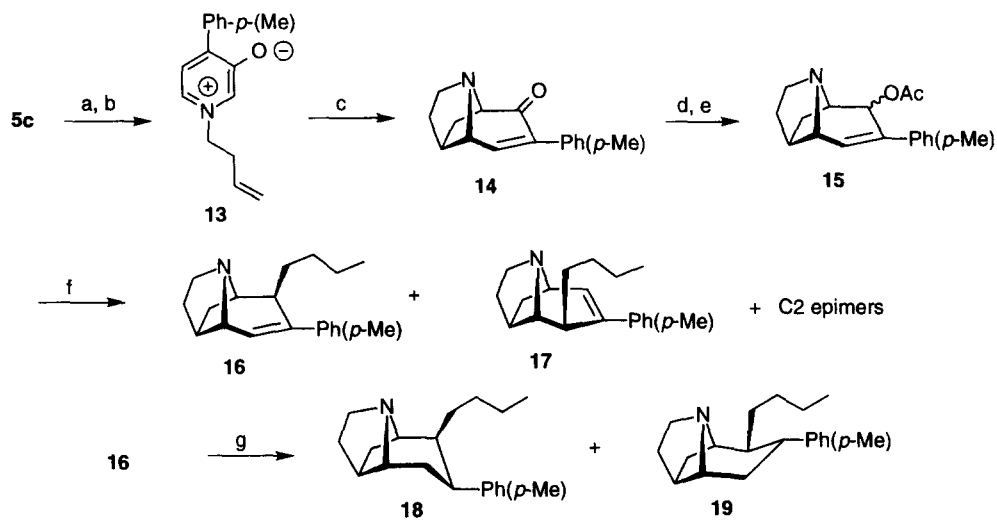


Scheme 1. *Reagents and conditions:* (a) CuI, LiCl, PhOC(O)Cl, Et_2O then *p*-XPhMgBr; (b) *o*-chloranil, toluene; (c) 20% $Pd(OH)_2/C$, H_2, MeOH; (d) 2,3-dibromopropene, THF; (e) phenyl vinyl sulfone, Et_3N, MeCN, reflux; (f) *n*-Bu_3SnH, AIBN, toluene; (g) DIBAL, CH_2Cl_2; (h) 6% Na(Hg), Na_2HPO_4, MeOH; (i) *n*-BuLi, THF then PhOC(S)Cl.

Reduction of the ketone **8b** or **8c** at -78 °C afforded a single isomer in good yield (84 and 79%, respectively). Reductive desulfonylation of **9b** resulted in the partial reduction of the aromatic chloride to afford an inseparable mixture of **10a** and **10b**. The

reductive desulfonylation of **9c** readily afforded alcohol **10c** in 63% yield. Barton deoxygenation then afforded the desired cocaine analog **12c** (in 16% yield for 2 steps).[13] In this rigid analog, the direction of the nitrogen lone pair is fixed so as to point toward the two carbon bridge of the tropane skeleton. The tether also provides an olefinic C-2 substituent. The subnanomolar affinity of the related 2β-vinyl-3β-(*p*-chlorophenyl) analog of cocaine has been reported.[10]

The tricylic cocaine analog containing a tether to the two carbon bridge of the tropane skeleton was prepared, exploiting the intramolecular dipolar cycloaddition[14] of betaine **13**. Compound **13** was readily prepared in 98% yield from pyridine **5c**. The intramolecular cycloaddition was regioselective to afford the 6-bridged tropenone isomer **14** as the only cycloadduct detected (isolated in 36% yield). The structure of **14** was again confirmed by X-ray analysis. Luche reduction of the enone afforded a mixture of alcohols that were directly acylated to afford the epimeric allyl acetates **15**. These acetates could be separated, or more conveniently the mixture (ca. 3:1 by NMR) was directly utilized in the CuCN catalyzed cross coupling as previously reported.[9] This cross coupling afforded a complex mixture in which all four possible isomeric products could be detected (28:11:1:1, by GC/MS).[15] Two major cross coupling products were isolated and tentatively assigned as **16** and **17** (42 and 20% yield), respectively, arising from β-addition of the butyl group. The reduction of the double bond of **16** under acidic conditions afforded a separable mixture of the cocaine analogs **18** and **19** (3:1 by GC/MS). The structure of **19** was confirmed by conversion to the *p*-toluenesulfonate salt and X-ray analysis.



Scheme 2. *Reagents and conditions:* (a) 4-bromo-1-butene, THF; (b) Amberlite IRA-400 (OH), MeOH; (c) xylenes, reflux; (d) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH; (e) Ac_2O, pyridine; (f) CuCN, *n*-BuMgBr, ether; (g) *p*-TsOH, 10% Pd/C, H_2, EtOAc.

In conclusion, synthetic pathways for the construction of cocaine analogs whose nitrogen lone pairs are spatially defined have been delineated. Preliminary biological experiments reveal that **12c** and **18** exhibit substantial affinity for the DAT, with a binding affinity (K_i) of 25 ± 3 nM for **12c** and 17 ± 1 nM for **18** as compared to 280 ± 60 nM for (-)-cocaine. These data would suggest that the directionality of the nitrogen lone pair is not a crucial determinant of high affinity binding.[16] Studies to further address this issue are currently underway, and full details of this work will be reported separately.

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13. All compounds described were purified by chromatography on silica gel, and were characterized by NMR and mass spectra. Spectroscopic data for selected compounds: **12c**: ^{1}H NMR ($CDCl_3$) δ 1.39 (dd, 1 H), 1.77 (m, 1 H), 2.01-2.23 (m, 5 H), 2.34 (s, 3 H), 2.47 (s, 1 H), 3.26 (m, 1 H), 3.45 (m, 1 H), 3.35 (m, 2 H), 3.61 (s, 2 H), 4.25 (s, 1 H), 4.78 (s, 1 H), 7.07 (d, 2 H), 7.12 (d, 2 H). **18**: (*p*-toluenesulfonate salt) ^{1}H NMR (CD_3OD) δ 0.75 (t, 3 H), 1.04-1.16 (m, 3 H), 1.25-1.34 (m, 3 H), 1.70-1.84 (m, 3 H), 2.02-2.16 (m, 4 H), 2.29 (s, 3 H), 2.36 (s, 3 H), 2.53 (m, 1 H), 2.67 (s, 1 H), 3.24 (m, 1 H), 3.47 (m, 1 H), 3.70 (m, 1 H), 3.83 (d, 1 H), 7.11 (s, 4 H), 7.25 (d, 2 H), 7.74 (d, 2H). **19**: (*p*-toluenesulfonate salt) ^{1}H NMR ($CDCl_3$) δ 0.71 (t, 3 H), 0.74-1.00 (m, 3 H), 1.09-1.15 (m, 2 H), 1.57-1.83 (m, 4 H), 1.91 (m, 1 H), 2.07 (m, 1 H), 2.32 (s, 3 H), 2.37 (s, 3 H), 2.40 (m, 1 H), 2.80 (m, 2 H), 2.95 (m, 1 H), 3.17 (m, 1 H), 3.34 (ddd, 1 H), 3.81 (d, 1 H), 3.89 (s, 1 H), 4.09 (dd, 1 H), 6.95 (d, 2 H), 7.09 (d, 2 H), 7.14 (d, 2 H), 7.82 (d, 2 H).
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15. The same isomeric mixture (by GC/MS) was also obtained using either of the isolated allyl acetates.
16. The K_i values were determined by displacement of [^{3}H]mazindol binding. We thank Dr. Kenneth M. Johnson for providing the binding data.