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Synthesis of 8-Oxa Analogues of Norcocaine Endowed with Interesting Cocaine-like Activity

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Abstract: In order to further explore the importance of cocaine's bridge nitrogen atom in binding to the dopamine transporter (DAT), we have synthesized the previously known racemic 8-oxa-norcocaines **3-6** in which the nitrogen atom has been replaced by oxygen. Additionally, to avoid incorrect interpretations of biological data that may stem from the use of racemic materials, several of these analogues were synthesized and tested in non-racemic form. (-)-8-Oxa-norcocaine (**3**) was found to bind to the cocaine recognition site and to inhibit the dopamine transporter with potencies only about 8-fold and 4-fold, respectively, less than those of norcocaine (**2**). (-)-8-Oxa-pseudonorcocaine (**4**) as well as (+)-8-oxa-norcocaine (**3**) were found to be comparable in activity to (-)-oxa-norcocaine. These pharmacological findings support our earlier suggestion that cocaine is likely to bind in its neutral form to the DAT.

Cocaine abuse is one of the greatest concerns of the public today, and in the United States alone one to three million cocaine abusers are estimated to be in need of treatment, six times the number of heroin addicts.[1] With the aim to obtain cocaine antagonists or "partial agonists" for possible use in abuse treatment, particular attention has been devoted recently to the discovery of cocaine analogues that show high affinity binding to the cocaine recognition site on the dopamine transporter, but low potency in the inhibition of dopamine uptake.[2-5] The study of cocaine analogues differing sterically or electronically from the parent structure is a logical starting point in this quest of such molecules.[5] In particular, in terms of exploring new areas of structural alteration to cocaine, we believed that it would be informative to examine the effect of replacing cocaine's bridge nitrogen atom by an oxygen atom.

This alteration was deemed valuable to pursue, for we felt that it might not only lead to compounds of altered biological activity, but moreover, that such molecules would provide relevant information to the question of whether cocaine binds to its recognition site in its protonated or non-protonated form.[6]

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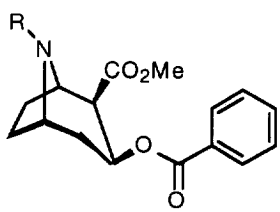
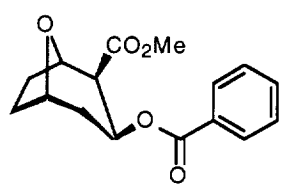
This avenue of research appeared particularly attractive in light of our previous demonstration that certain N-sulfonyl analogues of cocaine exhibited an affinity for the dopamine transporter comparable to that of cocaine itself, in spite of the fact that these sulfonylated derivatives would not exist in their protonated forms.[7] To this regard Madras and Meltzer[8] have discolsed recently the synthesis of 8-oxa analogues of the WIN series of cocaine and they conclude that the protonated form of cocaine is not a perequisite for binding to the dopamine transporter. However, notwithstanding that a number of highly potent cocaine analogues, together with informations concerning their structure-activity relationships (SAR) at the DAT, have been reported,[3-7] the precise details of the binding interactions between cocaine and its analogues and the dopamine transporter is still a matter of much discussion.

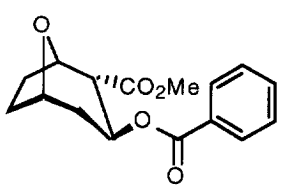
In this communication we wish to report our findings on 8-oxa-norcocaine and its stereoisomers which, when compared to norcocaine and cocaine, showed activity not substantially less potent than the parent compounds in their ability to interact with the DAT. We think that data reported in this communication further expand the understanding of cocaine's structure-activity relationships, and may provide very useful informations to aid the discovery of cocaine antagonists or "partial agonists" for possible use in abuse treatment.



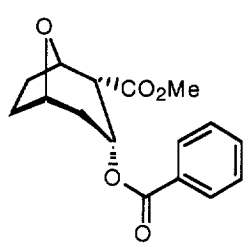
Cocaine, R = Me (**1**)
Norcocaine, R = H (**2**)



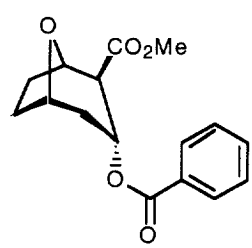
(±)-Oxa-norcocaine (**3**)



(±)-Oxa-pseudonorcocaine (**4**)



(±)-Oxa-allopseudonorcocaine (**5**)



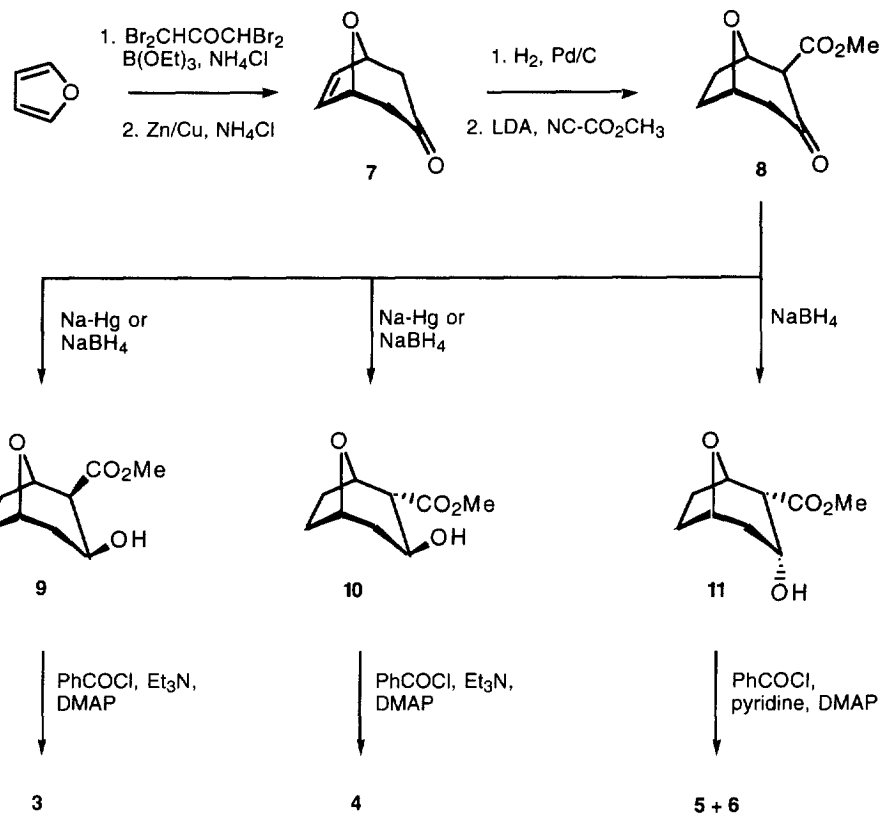
(±)-Oxa-allonorcocaine (**6**)

Chemical synthesis

The 8-oxa analogues **3-6** of cocaine (**1**) were firstly prepared in racemic form. Moreover, we have investigated methods aimed at procuring derivatives **3** and **4** in non-racemic form. A search of the literature revealed that the oxygen analogues of cocaine had, in fact, been known for some time with the first synthesis of racemic oxa-norcocaine being reported by Brownbridge and Chan[9] in 1979, and a second route being reported in 1990 by Kainz and Eiden.[10] In the latter report, these authors actually generated all four possible

diastereomeric products. However, in spite of this earlier synthetic work, we found no reports concerning the enantioselective synthesis and the biological activity of any of these products and in particular nothing is known about their enantiomers.

Scheme

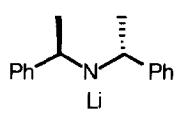


In our own work, we followed a chemical route akin to that of Kainz and Eiden, although with some modifications. First, the well known unsaturated ketone **7** was prepared using the established [4 + 3] cycloaddition reaction of tetrabromoacetone and furan as described by Ansell and Mason.[11] The bicyclic intermediate was hydrogenated to provide the saturated ketone, the ketone was deprotonated in turn with LDA, and the resulting enolate reacted with Mander's reagent to deliver the expected β–keto ester **8**. Subjection of the β–keto ester to reduction with sodium amalgam gave rise to two major alcohols, compounds **9** and **10**. The reduction of the β–keto ester with sodium borohydride was also tried: after some experimentation aimed to optimize the reaction conditions, we found that a mixture of the alcohols **9** and **11** were generated when the reaction was carried out at -30°C, whereas at 0°C a mixture of **9**, **10**, and **11** was produced. The desired alcohols were isolated in pure form by use of flash chromatography. Benzoylation of **9** and **10** was performed using benzoyl chloride, triethylamine, and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) to provide

3 and **4**. Starting from alcohol **11**, benzoylation provided **5** in addition to small amounts of **6**, the latter product being formed by epimerization of the allopseudococaine-like derivative, a result that mirrors that found in the cocaine series itself. Structural assignments of these analogues were made by analysis of their ^{1}H and ^{13}C NMR spectra and by comparison with the spectral data reported by Carroll for cocaine and its isomers.[12]

In order to avoid potential problems stemming from the study of racemic materials, we needed access to the enantiomers of the previously synthesized oxa-norcocaines. Indeed, it has been well documented by Carroll and other that stereochemistry plays an important role in the binding of cocaine and its analogues to the recognition site on the DA transporter and, for example, the seven stereoisomers of cocaine are less potent than the natural product.[3] Therefore, we have investigated methods aimed at obtaining the oxa-norcocaine (**3**) and its diastereomer **4** in non-racemic form.

Homochiral lithium amide (HCLA) bases have been found to serve as important new reagents for asymmetric synthesis, allowing kinetically controlled deprotonations of cyclic ketones to afford good discrimination between enantiotopic α-hydrogens.[13-15] In particular, Bunn *et al.* have described the asymmetric transformation of the dihydro derivative of the ketone **7** into non-racemic enol silanes by use of HCLA bases.[14] Also, Majewski and Lazny have used such a desymmetrisation process as the starting point in the synthesis of a number of alkaloids and natural cocaine-related structures.[15] Thus, use of the HCLA methodology therefore appeared to offer an attractive means for procuring the non-racemic oxa-norcocaine. Deprotonation of the dihydro derivative of **7** by means of the two chiral bases **12** and **13** and subsequent reaction with methyl cyanoformate allowed facile preparation of the enantiomers of **8**. Reduction of the latter enantiomers and benzoylation afforded both the optical antipodes of the oxa-cocaine analogues **3** and **4**.[16] Of interest, in light of the chemical correlations reported by Majewski and Lazny[15] in the conversion of tropinone to cocaine-related products, and the chemical correlations carried out by Bunn *et al.*[14] using 8-oxabicyclo [3.2.1] octan-3-one as substrate, it was possible to assign the absolute stereochemistry of (-)-8-oxa-norcocaine and (+)-8-oxa-pseudonorcocaine to be the same as (-)-norcocaine and (+)-pseudonorcocaine respectively.



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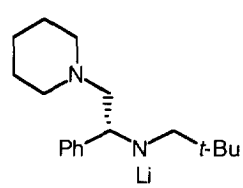

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Pharmacology.

The oxa-norcocaines were examined for their ability to displace [^{3}H] mazindol binding. Mazindol has been shown to label the cocaine binding sites on the dopamine transporter of rat striatal membranes. This ligand binds with high affinity to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier.[17] Additionally, these compounds were tested for their ability to inhibit high-affinity uptake of [^{3}H] dopamine into striatal nerve endings (synaptosomes). The data are provided in the table along with comparison data for (-)-cocaine, its C-2 isomer (+)-pseudococaine, and (-)-norcocaine.

Compound	[^{3}H]Dopamine Uptake, K_i (μM)	[^{3}H]Mazindol Binding, K_i (μM)
(-)-cocaine (**1**)	0.32 ± 0.01	0.28 ± 0.06
(+)-pseudococaine	13.8 ± 1.5	10.4 ± 0.3
(-)-norcocaine (**2**)	2.0 ± 0.1	0.54 ± 0.04
(-)-oxa-norcocaine (**3**)	8.5 ± 1.0	4.2 ± 0.03
(+)-oxa-norcocaine (**3**)	9.4 ± 0.6	3.1 ± 0.03
(-)-oxa-pseudonorcocaine (**4**)	6.0 ± 0.3	4.7 ± 2.1
(+)-oxa-pseudonorcocaine (**4**)	47.7 ± 3.4	29.4 ± 3.4
(±)-oxa-allopseudonorcocaine (**5**)	35 ± 3	38 ± 21
(±)-oxa-allonorcocaine (**6**)	23 ± 10	34 ± 10

Discussion.

It is clear from the data presented in table that the oxygen analogue of cocaine, while less active than either cocaine or norcocaine, still retains activity both in the binding and dopamine uptake inhibition studies, in spite of the fact that this compound lacks the bridge nitrogen generally believed to be so essential for cocaine's interaction with its recognition site within the DAT. For comparison purposes, it is more appropriate to compare these oxa-norcocaines with norcocaine itself, since cocaine's N-methyl group also contributes to binding affinity.[3] Using the binding data obtained for (-)-oxa-norcocaine, which is of 85% ee, the experimental difference is about 8-fold. This difference in the experimental K_i's corresponds to a binding energy difference of about 1 Kcal/mol. These data, taken together with our previous findings of the good binding affinity shown by certain N-sulfonylated derivatives of cocaine,[7] might accordingly suggest that cocaine binds to its recognition site in its unprotonated form.[18-20]

It is our further interest to note that while cocaine and pseudococaine exhibit an 37- to 43-fold spread in activities, (-)-oxa-norcocaine in comparison to (+)-oxa-pseudonorcocaine shows a smaller spread in activities.[3] Using the K_i values determined from the binding data, the difference in activity is about 7-fold. Both (+)-oxa-norcocaine and (-)-oxa-pseudonorcocaine were found to be comparable in activity to (-)-oxa-norcocaine. Since the optical antipode of (-)-cocaine itself has shown a decrease in binding affinity by a factor of 140 fold,[21] it is perhaps surprising that the difference between the (+)- and the (-)-isomers of oxa-norcocaine is not larger.

In summary, the present work reveals that oxa-norcocaine (**3**) is not substantially less potent than norcocaine in its ability to interact with the DAT. The two stereisomers **5** and **6** are about 9 times less potent than the isomer possessing tha natural cocaine-like stereochemistry. It appears evident from these data that introduction of the oxygen markedly diminishes the enantioselectivity of the compounds' binding to the DAT. Moreover, it is surprising that (-)-oxa-pseudococaine (**4**) have binding properties substantially similar to the (-)-oxa-norcocaine. Thus, the new oxa-cocaine series seems to lose, unlike the cocaine isomers, both the enantioselectivity and diastereoselectivity properties toward the DAT binding. It is also surprising that the (+)-oxa-cocaine (**4**) is slightly more active in the binding test than the (-)-oxa-pseudococaine (**4**). Lastly, we note that Madras and Meltzer[8] have disclosed recently the synthesis of the oxa analogues of the WIN series of compounds (8-oxabicyclo-3-aryl-[3.2.1]-octanes), in which the benzoate group is replaced by a phenyl. As expected, these compounds bind with higher affinity than the oxa-norcocaines reported here, and these authors also conclude

that a nitrogen atom is not a requirement for blockade of monoamine transporters. The oxa analogue of WIN-35,428 was found to bind to DAT with an affinity about 73-fold less than that of WIN-35,428.[21] This difference is larger than that found between oxa-norcocaine and cocaine (14-fold).

Therefore, data emerging from our work demonstrate that substitution of the nitrogen atom with oxygen in cocaine affords compounds which hold similarities with cocaine and its isomers, this in particular regarding the binding to the DAT and the reupake inhibition. However, as reported above, the new oxa-cocaine series presents a marked difference in the binding stereoselectivity.

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16. Full details of this chemistry will be reported separately.

    (-)-**3**, $[\alpha]_D$ -43.9° (*c* 0.5, $CHCl_3$), 85 % ee; (+)-**3**, $[\alpha]_D$ +41.7° (*c* 0.5, $CHCl_3$), 83 % ee; (+)-**4**, $[\alpha]_D$ +60.4° (*c* 0.5, $CHCl_3$), 89 % ee; (-)-**4**, $[\alpha]_D$ -58.6° (*c* 0.5, $CHCl_3$), 86 % ee.
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21. Binding affinities (μM) of (+)-cocaine, WIN 35,428 and its oxa-analogue: 15.8, 0.0075, 0.546.