Chemistry and Biology of the 2β-Alkyl-3β-phenyl Analogues of Cocaine: Subnanomolar Affinity Ligands That Suggest a New Pharmacophore Model at the C-2 Position

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Received March 27, 1995®

A series of 2β-alkyl-3β-phenyltropanes (i.e., the 2β-alkyl analogues of the WIN series) were prepared as analogues of cocaine and tested for their ability to displace [^{3}H]mazindol binding and to inhibit high-affinity dopamine uptake into striatal nerve endings (synaptosomes). These 2β-alkyl analogues were readily prepared in optically pure form starting from cocaine by proceeding through the 2β-phenyl-bearing aldehyde **6** as a key intermediate. Wittig reaction of **6** with the appropriate phosphorane and hydrogenation delivered the final products. All new compounds with the exception of **8e** were found to exhibit nanomolar or subnanomolar affinity for the cocaine binding site in the rat striatum. These results are in apparent opposition to the binding model previously proposed which suggests a hydrogen bond donor-acceptor interaction to be present in the vicinity of the C-2 substituent. Taken together with our previous reports and recent findings from other laboratories, we suggest a new pharmacophore model in which 2β-substituents lacking H-bond acceptors enhance affinity to the binding site through hydrophobic interactions. The new SAR data contained herein may be relevant to the design of possible cocaine antagonists.

Cocaine (**1**), a naturally occurring local anesthetic first isolated from the plant *Erythroxylum coca* in 1860, has been recognized to be a potent central nervous system stimulant since the days of Sigmund Freud. This alkaloid was considered to be a relatively "safe" drug until about 1914 when its toxic dependence-producing properties were publicized.[1] The ready availability of cocaine and its tremendous abuse liability have led to the current epidemic of cocaine use in the United States and other countries. Indeed, cocaine abuse is one of the greatest concerns of the American public today. As a consequence of the need to curb the cocaine problem, considerable effort has been put into acquiring a better understanding of the chemistry and the pharmacology of this drug. As a result of these research efforts, our knowledge of the mode of action of cocaine has improved dramatically. While cocaine inhibits the reuptake of the monoamine neurotransmitters dopamine,[2] serotonin,[3] and noradrenaline,[4] the rewarding properties of cocaine clearly require activation of the dopaminergic system. The recent cloning of the human dopamine transporters[5,6] will undoubtedly provide further molecular insights into the mechanism by which cocaine is capable of inhibiting neurotransmitter reuptake.

From the medicinal chemistry perspective, the synthesis and biological evaluation of cocaine analogues can provide valuable information as to the structural elements of cocaine which are essential for recognition by the cocaine binding site as well as to give possible clues as to the design of cocaine-like molecules possessing an antagonist action. On the basis of the results obtained from the chemical synthesis and biological evaluation of a host of cocaine analogues, Carroll and co-workers had previously arrived at the following conclusions concerning the binding interactions of cocaine:[7] (1) an important binding interaction involving a hydrophobic pocket occurs in the vicinity of cocaine's C-3 benzoate group, and replacement of this group by phenyl or substituted phenyl dramatically increases binding affinity;[8,10,25] (2) the suggestion was made that one or possibly two hydrogen bond donor groups are localized in the vicinity of cocaine's C-2 ester group;[9] and (3) the basic nitrogen atom present in cocaine's one-atom bridge is fundamental to its activity, and this nitrogen probably engages in a hydrogen bond or an electrostatic interaction.[10]

In our own efforts to acquire a better understanding of the topology of the cocaine receptor with the aim toward identifying a possible cocaine antagonist, we have investigated modifications to various regions of this molecule.[11] A previous paper disclosed our findings about the requirements for the binding at the nitrogen bridge.[12] The present paper is an extension of our previous communication concerning the nature of the binding interactions of cocaine's C-2 substituent with the cocaine recognition site. We now report the synthesis of other C-2 alkyl-substituted analogues of 2β-carbomethoxy-3β-phenyltropane **4** (a member of the WIN series) together with their ability to displace [^{3}H]-mazindol binding and to inhibit high-affinity dopamine uptake into striatal nerve endings (synaptosomes).

Chemistry

The structures of the compounds selected for synthesis and biological evaluation are shown in Table 1. All compounds described herein were prepared from natural (−)-cocaine, and therefore they all possess the same absolute configuration as (−)-cocaine. The synthetic approach we adopted was based upon our previous report[11b] and is displayed in Scheme 1. Anhydroecgo-

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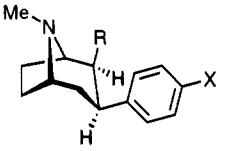
® Abstract published in *Advance ACS Abstracts*, July 15, 1995.

0022-2623/95/1838-3086$09.00/0

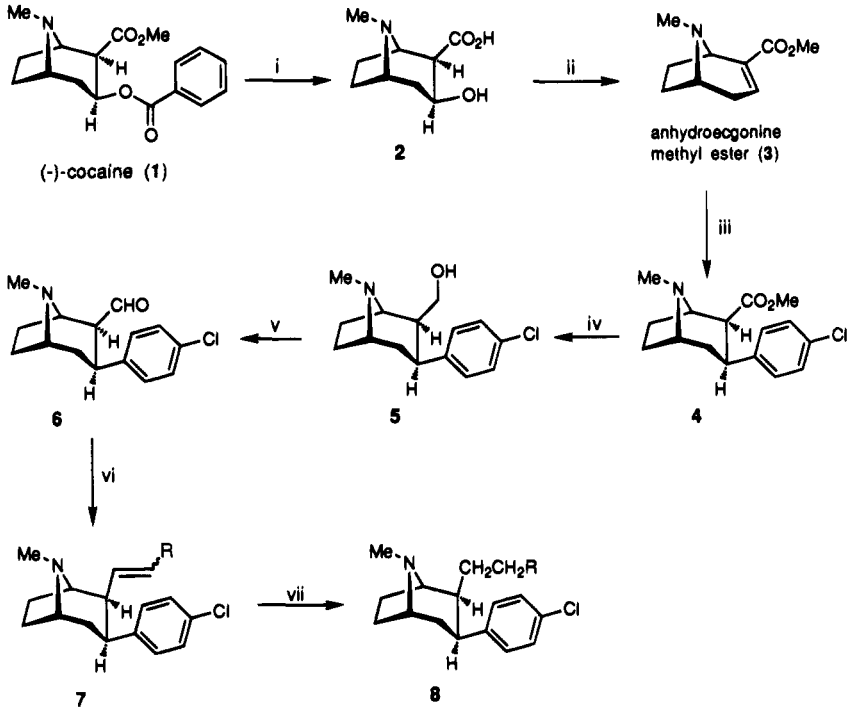
Table 1. Physical Properties of the 2β-Alkenyl- and 2β-Alkyl-3β-(4-substituted phenyl)tropanes



compd	optical rotation[a] $[\alpha]^{25}_D$ (CH_2Cl_2)	mp[b] (°C)	molecular formula	^{1}H NMR δ ($CDCl_3$) NCH$_3$	1-H	5-H	2-H
8a	−60.3	77−79	$C_{16}H_{22}NCl$	2.24	3.25	3.21	2.19
8b	−67.4	74−77	$C_{17}H_{24}NCl$	2.27	3.34	3.06	2.21
8c	−56.1	89−90	$C_{17}H_{25}N$	2.25	3.30	3.09	2.28
8d	−78.6	82−83	$C_{18}H_{27}NCl$	2.24	3.31	3.12	2.17
8e	−123.2	75−77	$C_{20}H_{30}NCl$	2.24	3.33	3.15	2.20
8f	−112.9	154−156	$C_{22}H_{26}NCl$	2.28	3.28	3.23	2.51
7a	−63.1	91−92	$C_{16}H_{20}NCl$	2.25	3.28	3.18	2.23
7b	−118.3	103−105	$C_{16}H_{19}NCl_2$	2.22	3.27	3.05	2.19
7c	+71.4	111−112	$C_{16}H_{19}NCl_2$	2.21	3.31	3.19	2.21
7g	−161.3	133−135	$C_{22}H_{24}NCl$	2.24	3.31	3.16	2.42
7h	+130.9	149−150	$C_{22}H_{24}NCl$	2.26	3.34	3.18	2.89

[a] The optical rotations (deg) are reported for the free base at $c = 1$ in MeOH. [b] The melting points are for the hydrochloride salts.

Scheme 1. General Method for the Preparation of the 2β-Alkyl-Substituted WIN Analogues[a]



Reagents and conditions: (i) 1 N HCl, reflux 15 h; (ii) (a) $POCl_3$, reflux; (b) MeOH, 0 °C; (iii) 4-ClPhMgBr, Et_2O, −40 °C; (b) −78 °C, 1.1 equiv of TFA; (c) silica gel chromatography; (iv) Dibal-H, toluene, −78 °C; (v) ClCOCOCl, CH_2Cl_2, −78 °C, DMSO, 30 min, Et_3N; (vi) $Ph_3P^+CH_2R\ Br^-$, *n*-BuLi, THF, room temperature; (vii) H_2, Pt/C, 40 psi, cyclohexane; see the Experimental Section for individual yields.

nine methyl ester (**3**) was prepared following previously described methods.[10,13] The intermediate WIN analogue (**4**) was prepared in accordance with Carroll's modification[10] of the original procedure of Clarke et al.[13] The mixture of C-2 epimeric products resulting from the conjugate addition reaction was separated to obtain the pure 2β-carbomethoxy isomer. The methyl ester (**4**) was then reduced to the alcohol **5** in 93% yield using Dibal-H in toluene at 0 °C. The resulting alcohol was subjected to a Swern oxidation.[14] Attempts to purify the resulting aldehyde **6** by use of silica gel chromatography were unsuccessful due to the facile epimerization of this material. Accordingly, the crude aldehyde was used without further purification in the subsequent Wittig reactions. As an aside, we note that a variety of reducing agents were examined for their ability to transform the methyl ester **4** to the corresponding aldehyde in a single step. These reagents included lithium tri-*tert*-butoxyaluminum hydride,[15] diisobutylaluminum hydride,[16] sodium aluminum hydride,[17] bis-(4-methyl-1-piperazinyl)aluminum hydride,[18] and Li-AlH_4−$HNEt_2$.[19] In all cases, the ester was reduced directly to the alcohol stage, or it was recovered unchanged with only traces of the desired aldehyde being detectable.

The aldehyde **6** was reacted in turn with the appropriate Wittig reagent prepared by treatment of the corresponding phosphonium salt with *n*-butyllithium. In cases where the required phosphonium salt was not commercially available, it was prepared by refluxing triphenylphosphine with the corresponding alkyl bromide in ether. In general, Wittig reaction of the

aldehyde **6** gave rise to a cis/trans mixture of the alkenes **7** in 35–61% isolated yield. The ratio of the cis/trans isomers was in the range of 20:80 in favor of the trans isomer.

Some attempts were made to increase the reaction yields and to improve the isomer ratio in the Wittig reaction. By lowering the reaction temperature from room temperature to −20 °C, −45 °C, or −78 °C, the reaction rate was slowed, but no significant effect on the isomer ratio was observed. Variations in the order of the addition, stoichiometry, counterion, and reaction time failed to improve the overall yield. Recently, Schlosser[20] described a highly cis-selective Wittig reaction employing α-heterosubstituted ylides. Thus, the *o*-(methoxymethoxy)phenyl-armed ylide was prepared and reacted with the aldehyde **6**. This armed ylide was found to give solely the cis-olefin product but, unfortunately, exclusively of the α-configuration at the C-2 position with no trace of the β-isomer. The result is likely due to the basicity of the phosphorane which promotes the formation of the more stable α-isomer through enolate formation.

Contamination of the β-cis/trans isomers by the α-cis/trans isomers conspired to make purification of these products rather difficult. However, by following the protocol in which a one-pot Swern oxidation of **5** is carried out, and then the crude aldehyde is subjected to the Wittig olefination reaction, it is possible to consistently obtain the desired olefins **7** with no detectable epimerization of the C-2 position. This procedure has been adapted from the work of Luly[21] et al. who previously reported on the Wittig olefination reactions of stereochemically sensitive amino aldehydes derived from α-amino acids, wherein the question of the racemization in this reaction had been addressed. This procedure provides acceptable yields of the pure β-isomers as long as the aldehyde is used immediately without additional purification.

In the case of the olefins **7d**–**f** (R = Me, Et, and *n*-Bu, respectively), the separation of the cis and trans isomers proved to be difficult by silica gel chromatography or by HPLC of the trifluoroacetate salts. Thus, it was decided to evaluate the biological activity of the saturated analogues in such cases.

Accordingly, the reduction of the double bond in compound **7d** was attempted in the presence of Pd/C in absolute ethanol under 40 psi of H_2. Unfortunately, these reaction conditions failed to provide **8b**. Instead, the reduction occurred with loss of the chlorine atom from the aromatic ring, giving rise to **8c**. The presence of cocaine's tertiary amino group may contribute to the hydrogenolysis of the halogen substituent.[22] The use of Pt/C instead of Pd/C reduced the extent of hydrogenolysis and gave rise to a 60% yield of the desired product. Finally, it was found that if the hydrogenation reaction is carried out in the presence of Pt/C in cyclohexane as solvent,[23] the reduction of the double bond occurs smoothly in 95% yield without any detectable trace of the product of hydrogenolysis.

Because of our interest in examining the biological activity of the saturated C-2 carbon chain analogues, we also briefly examined the possibility of preparing these compounds by a more direct route. Tosylation of the alcohol **5** followed by reaction of the derived tosylate with the appropriate organocuprate was thus pursued. Unfortunately, this investigation proved disappointing, for none of the desired coupling product was detected upon examining several different cuprates. Surprisingly, even the characteristic ^{1}H NMR signals of the tropane skeleton were absent in the products isolated, suggesting that some rearrangement/elimination reaction may have ensued. We therefore chose to prepare all of the saturated chain analogues by the Wittig olefination–hydrogenation protocol.

In regard to stereochemical assignments, the β-configuration of the C-2 substituent of the new analogues was generally assigned on the basis of the ^{1}H NMR chemical shift of the *N*-methyl group[24] which resonated at about 2.24 ppm; in the C-2 α-configured compounds, this chemical shift was about 2.4 ppm.

The cis–trans isomers were assigned on the basis of the coupling constants of the olefinic protons. The cis isomers showed a characteristic coupling constant of 11.7 Hz while the trans isomers showed a larger coupling constant of 16 Hz.

A striking difference was noted in the ^{1}H NMR chemical shifts of the proton at C-2 in compounds **7g** and **7h**: the chemical shift of H-2 was 2.92 ppm in the cis isomer whereas it was 2.42 ppm in the case of the trans isomer. This large difference can presumably be attributed to the fact that H-2 lies within the deshielding region of the aromatic ring of the C-2 cis-configured olefinic appendage. Another interesting observation from the ^{1}H NMR spectra of these two compounds concerns the chemical shifts of the aromatic rings of compounds **7g** and **7h**. In the case of the trans isomer **7g**, the aromatic protons are found at 7 ppm, while these same protons occur at 6.85 ppm in the cis isomer. The shielding effect observed in the cis isomer can be explained by the existence of a $\pi-\pi$ interaction between the two aromatic rings. A parallel plane arrangement of the two aromatic rings in **7h** is thus probable.[25] Although an edge–face interaction between these two rings is also possible, such an interaction would disrupt the resonance between the aromatic ring of the C-2 substituent and the adjacent olefinic group. Molecular modeling studies on this entire series of structures are underway and will be reported separately.

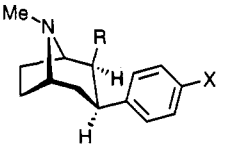
Pharmacological Results

The new cocaine analogues were tested for their ability to displace [^{3}H]mazindol binding, a compound which has been shown to label the cocaine binding sites on the dopamine transporter of rat striatal membranes.[11a,26] This ligand binds with high affinity to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier. Additionally, the new compounds were tested for their ability to inhibit high-affinity uptake of [^{3}H]dopamine into striatal nerve endings (synaptosomes) in accordance with protocols previously described.[2a] The results of the pharmacological studies are presented in Table 2. As is apparent from a perusal of this table, the majority of these new analogues bind with significantly high affinity and in some cases better than the WIN analogue **4** itself, a compound first reported by Carroll and co-workers.

Discussion

Previous reports from this laboratory[11a,b,27] and others[9b,28,29] have already disclosed some structure–

Table 2. [^{3}H]Mazindol Binding and Dopamine Uptake Activity of the Cocaine Analogues



			K_i (nM), mean ± SEM[a]	
compd	R	X	[^{3}H]mazindol binding	[^{3}H]dopamine uptake
4	CO_2Me	Cl	0.83 ± 0.07	2.85 ± 0.09
7a	$CH{=}CH_2$	Cl	0.59 ± 0.15	2.47 ± 0.52
7b	(*E*)-CH=CHCl	Cl	0.42 ± 0.04	1.13 ± 0.27
7c	(*Z*)-CH=CHCl	Cl	0.22 ± 0.02	0.88 ± 0.05
7g	(*E*)-CH=CHPh	Cl	0.31 ± 0.04	0.66 ± 0.01
7h	(*Z*)-CH=CHPh	Cl	0.14 ± 0.07 (N = 2)	0.31 ± 0.09
8a	CH_2CH_3	Cl	2.17 ± 0.20	2.35 ± 0.52
8b	$(CH_2)_2CH_3$	Cl	0.94 ± 0.08	1.08 ± 0.05
8c	$(CH_2)_2CH_3$	H	1.87 ± 0.22	1.61 ± 0.05
8d	$(CH_2)_3CH_3$	Cl	1.21 ± 0.18	0.84 ± 0.05
8e	$(CH_2)_5CH_3$	Cl	155.7 ± 15.5	271.0 ± 3.2
8f	CH_2CH_2Ph	Cl	1.46 ± 0.03	1.54 ± 0.08

[a] Data are mean ± standard error of three experiments unless noted otherwise.

activity data concerning the nature of the substituent located at the C-2 position of cocaine. Carroll and others have, of course, already shown the profound effect of the stereochemistry of this substituent on binding affinity at the dopamine transporter. Furthermore, it has been suggested previously by Carroll that the C-2 ester group of cocaine interacts with the cocaine recognition site through its acceptance of two hydrogen bonds. Reasonable evidence in support of this notion derives from the following observations: (a) the *N*-methylamide derivative of cocaine binds with considerably reduced affinity and is about 30-fold less potent than cocaine and (b) the 2β-hydroxymethyl analogue **9** which is capable of accepting only one hydrogen bond was found to be 5−6-fold less active than cocaine.[28]

For purposes of comparison, we have included in Table 2 data concerning several compounds we had reported on previously, specifically compounds **7a**−**c**. The 2β-vinyl analogue **7a** inhibits mazindol binding with a K_i of 0.59 nM while inhibiting dopamine uptake at 2.5 nM. Saturation of the double bond of **7a** provided the 2β-ethyl analogue **8a** which inhibits mazindol binding with a K_i of 2.2 nM. The binding affinity of **8a** is only a factor of 2.6-fold weaker than the WIN analogue **4**. Substitution of the double bond by a chlorine atom provided the *trans*- and *cis*-vinyl chlorides **7b** and **7c**, respectively. Both of these compounds proved to be more potent displacers of mazindol binding than the WIN compound **4**, with the cis isomer being about 2-fold more potent than the trans isomer. Analogue **8b** with an *n*-propyl group at the C-2 position inhibited mazindol binding with a K_i of 0.94 nM and had similar potency in inhibiting dopamine uptake. Remarkably, this saturated three-carbon chain analogue, which is incapable of engaging in any type of hydrogen bonding to the amino acid residues comprising the C-2 binding region of the cocaine recognition site, is about 3-fold more potent than the WIN analogue **4** in inhibiting dopamine reuptake. Examination of the activity of compound **8c**, which lacks the chlorine atom present in the para position of the phenyl ring of **8b**, reveals that this substitutent makes only a modest contribution to binding, since **8c** is only about 2-fold less potent than its chlorinated counterpart. Elongation of the C-2 substituent of **8b** by one additional carbon atom to provide the *n*-butyl analogue **8d** results in a structure which is comparable in activity to the *n*-propyl derivative; the K_i for mazindol binding is 1.21 nM and that for dopamine uptake is 0.84 nM. This *n*-butyl analogue is about 2-fold more active than its two-carbon lower homologue **8a** in both binding and dopamine reuptake, thus suggesting the existence of a hydrophobic pocket in the vicinity of the C-2 position.

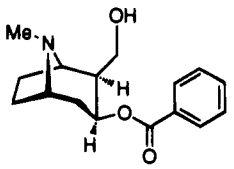
The ability to further enhance binding potency by further elongating the C-2 substituent does, however, have its limits; compound **8e** possessing a C-2 *n*-hexyl chain is about 128-fold less potent than the *n*-butyl analogue **8d**. The rationalization of these data may, however, not be sraightforward, for the decreased binding and uptake potencies may be related to factors other than the size of the hydrophobic pocket. For example, the greater lipophilicity of **8e** may limit its solubility in the test medium, whereas coiling of the alkyl chain[30] may result either in obstruction with certain residues comprising the C-2 binding pocket or in hindering the tropane nitrogen or the C-3 phenyl ring from freely interacting with their binding counterparts in the cocaine recognition site.

To investigate if this putative hydrophobic pocket can more easily accommodate a structurally rigid aromatic residue in contrast to the more conformationally flexible alkyl chain, we tested compounds **7g**, **7h**, and **8f**. The *cis*- and *trans*-phenyl analogues were in fact found to represent some of the most potent analogues in this series with K_i's for binding of 0.14 and 0.31 nM, respectively. Compound **7h** is thus 6-fold more potent than the WIN analogue **4** in mazindol binding and 9-fold more potent in the dopamine reuptake experiments. The improvement in activity which is seen with compounds **7g** and **7h** is certainly further supportive of the notion that a hydrophobic pocket exists in the vicinity of the C-2 position. Indeed, it is even possible that this hydrophobic pocket is lined with aromatic residues much like the gorge region of acetylcholinesterease and that the aryl rings of **7g** and **7h** engage in π-interactions with such residues.

Removal of the double bond of either **7g** or **7h** by simple hydrogenation provided the saturated analogue **8f**. As expected, this analogue was still reasonably active, exhibiting K_i's of about 1.5 nM in the binding and dopamine uptake experiments. The 5−10-fold diminution in the activity of **8f** as compared to **7g** or **7h** can, of course, be attributed to the greater flexibility of the C-2 side chain appendage of the former, and thus to the entropy penalty that will be incurred upon the binding of this compound to the cocaine recognition site. Nonetheless, it is noteworthy that this analogue again possesses an activity which is close to that of the WIN compound **4**, in spite of the absence of H-bond accepting heteroatoms.

In a recent report,[29] Carroll and co-workers have rationalized the good potency of the *cis*-vinyl chloride by invoking William's proposal[31,32] that the total free energy for the association of a ligand to its binding site via a hydrogen bond is partitioned among four separate energy terms. Thus the vinyl chloride would contribute to the binding through the hydrophobic component of

hydrogen bonding. This interesting suggestion fails to explain, however, how compounds such as **8a**, **8b**, **8c**, and **8d** which lack a functional group able to act as a hydrogen bond donor and/or acceptor still retain high affinity for the dopamine transporter. Unless these compounds bind to the dopamine transporter at a site which is different from that of the ester **4**, the only satisfactory explanation for the foregoing observations is the existence of a hydrophobic pocket in the vicinity of the C-2 position of cocaine. The observed lower affinity of the hydroxymethyl derivative **9**, on which the hydrogen bond interaction model was in part based, may simply be due to the unfavorable interaction of the polar hydroxyl group with the hydrophobic pocket. Furthermore, while acetylation of the primary hydroxyl group of **9** to provide **10** has been shown to restore activity, this result may also be due to enhancement of the hydrophobic interaction by masking of the more polar hydroxy group. While the differences in binding affinities of **9** and **10** were ascribed earlier to the difference in the number of potential hydrogen bond acceptor atoms, this notion must be re-evaluated in light of the new findings.



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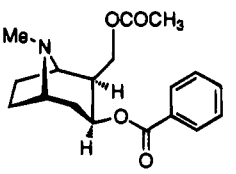

10

More recently, a report from Meltzer[33] et al. described difluropine as a new cocaine analogue with an IC_{50} of 10.9 nM. On the basis of the data obtained with such compounds, these authors arrived at conclusions similar to our own, specifically the necessity for proposing the existence of a hydrophobic pocket in the vicinity of the C-2 position. This pocket significantly contributes to the overall binding of the analogues as seen especially for compounds **7g** and **7h** and is further suggestive of the idea that even more potent analogues might be designed through the introduction of other C-2 appendages bearing multiple aryl rings.

We also note that our findings are in contrast to the conclusions of Crippen[34] et al. who performed an analysis of the cocaine receptor site by three-dimensional Voronoi site modeling. From the modeling efforts, these researchers postulated that the 2-substituent does not impart significant activity to cocaine analogues, a conclusion that must be gauged as being somewhat untenable in light of the recent body of SAR data. It is also pertinent to point out that, in a recent modeling paper,[35] a point was made regarding the contribution that solvation effects may have in binding and the importance of taking such effects into account when analyzing structure–activity relationships. Indeed, it is certainly possible to rationalize in a relatively simplistic way the foregoing data on the basis of differences in aqueous solvation of the various analogues. One would anticipate, however, that the binding difference between compounds **7a** and **7g** should be larger than the only 4-fold difference observed. Thus, other factors clearly come into play, and a truly comprehensive understanding of the individual contribution of each of the relevant factors will require, among other things, considerably more detail at the atomic level of the nature of cocaine's interaction with its recognition site(s).

Lastly, in regard to other applications of the C-2 alkyl and arylalkyl compounds, these may find use for *in vivo* studies where analogues exhibiting a long duration of action are required. Since such analogues are devoid of any ester bonds, they are not subject to the action of esterases which result in the generation of inactive structures. Experimental evidence in support of this statement derives from some of our earlier work in which compound **7c** was examined in animal self-administration studies, with a duration of action of almost 3 days being noted.

Conclusions

An SAR study of the 2β-alkyl-substituted 3β-(chlorophenyl)tropanes has been described. This series of compounds has provided additional valuable information concerning the structural requirements of the C-2 position to the binding of cocaine to its recognition site. It is noteworthy that among all known C-2 modified analogues of the WIN compound **4** presenting possibilities for altered or improved hydrogen bond capacity (such as the hydroxytrifluoroethyl analogue[27] or the oxadiazole analogues[29]), none of these compounds showed an affinity for the dopamine transporter which was better than the parent methyl ester. All such results when taken together suggest that in the absence of H-bond acceptors in the ligand hydrophobic interactions are important in the region of the cocaine recognition site which surrounds the C-2 substituent. Cocaine analogues that bear simple alkyl chains or, even better, arylvinyl groups at the C-2 position have comparable or improved affinities for the dopamine transporter relative to the analogues which contain potential hydrogen bond acceptor groups at the same position. We would accordingly suggest another pharmacophore model for the cocaine recognition site wherein a hydrophobic 2β substituent enhances binding affinity through interactions with a hydrophobic pocket.

Experimental Section

All reactions were carried out in oven- or flame-dried glassware under a dry argon atmosphere unless otherwise noted. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl. Toluene was distilled over calcium hydride. Methylene chloride was distilled over calcium hydride and stored over molecular sieves (4 Å). Triethylamine (TEA) was distilled over calcium hydride and stored over potassium hydroxide. Dimethyl sulfoxide (DMSO) was distilled over calcium hydride under reduced pressure and stored under argon. All other reagents were used as supplied unless otherwise stated.

^1H and ^{13}C NMR spectra were recorded at 300 and 75.46 MHz (Bruker AC-300), respectively, in $CDCl_3$. ^1H chemical shifts (δ) were reported with TMS (δ = 0.00 ppm) or $CDCl_3$ (δ = 7.26 ppm) as internal standards. ^{13}C chemical shifts were reported with $CDCl_3$ (central peak, δ = 77.0 ppm) as internal standard. Elemental analyses were carried out by Oneida Research Services, Inc. Melting points are uncorrected. All optical rotations were determined at the sodium D line. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F-254 (0.25 mm, precoated on glass). Measurements of optical rotation were carried out at c = 1 in methanol as solvent unless noted otherwise.

(***R***)-(−)-**Anhydroecgonine Methyl Ester (3).** (−)-Cocaine (10 g, 32.7 mmol) was dissolved in 1 N HCl (120 mL), and the mixture was heated for 16 h at reflux. The resulting yellow

solution was cooled to room temperature and extracted with ether (100 mL). The aqueous phase was concentrated and then lyophilized to dryness. $POCl_3$ (40 mL) was added to the residue, and the mixture was heated to reflux for 4 h. The excess $POCl_3$ was removed under reduced pressure, and the resulting dark oil was cooled to −40 °C and carefuly treated with 50 mL of anhydrous MeOH. The mixture was then warmed to room temperature, stirred for additional 20 min, and concentrated under reduced pressure. The residue was dissolved in water (60 mL), and the resulting solution was adjusted to a pH of 9, extracted with methylene chloride, and dried over Na_2SO_4. The organic phase was concentrated and distilled under reduced pressure to afford 4.6 g of a clear oil (76% yield): ^{1}H NMR ($CDCl_3$) δ 6.87 (m, 1H, H-3), 3.77 (m, 1H, H-1), 3.75 (s, 3H, CO_2CH_3), 3.23 (m, 1H, H-5), 2.62 (m, 1H, H-4ax), 2.34 (s, 3H, NCH_3), 2.13 (m, 1H, H-4eq), 1.86–1.49 (m, 4H, H-6 and H-7).

2β-Carbomethoxy-3β-(4-chlorophenyl)tropane (4). Into a 500 mL flask dried under argon was added 120 mL of anhydrous ether and (4-chlorophenyl)magnesium bromide (1 M, 40 mL, 40 mmol). The solution was cooled to −40 °C, and anhydroecgonine methyl ester (3.62 g, 20 mmol) in 120 mL of anhydrous ether was added slowly. The reaction mixture was stirred for 2 h at −40 °C, cooled to −78 °C, quenched with trifluoroacetic acid, and allowed to warm to room temperature. The yellow mixture was then diluted with water, basified with NH_4OH, and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and purified by silica chromatography using Et_2O–Et_3N (95:5) to give 0.98 g of the β-isomer as a white solid: mp 120–121 °C; $[\alpha]^{20}_D$ −89.3°; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 3.54 (m, 1H, H-1), 3.44 (s, CO_2CH_3), 3.23 (m, 1H, H-5), 2.91–2.76 (m, 2H, H-2 and H-3), 2.53 (m, 1H, H-4-ax), 2.22 (s, 3H, NCH_3), 2.20 (m, 1H, H-4-eq), 2.18–1.64 (m, 6H). Anal. ($C_{16}H_{20}NO_2Cl$) C, H, N.

2β-(Hydroxymethyl)-3β-(4-chlorophenyl)tropane (5). Intermediate **4** (4 mmol, 1.17 g) was dissolved in 50 mL of freshly distilled toluene and cooled to 0 °C. A 1 M solution of Dibal-H (8 mmol, 8 mL) in hexanes was added dropwise, and the mixture was stirred for 0.5 h. The reaction mixture was quenched by adding 10 mL of a saturated Rochelle salt solution, and the resulting white slurry was stirred for an additional 0.5 h, diluted with water, and extracted several times with chloroform. The combined organic phases were dried over sodium sulfate and purified by column chromatography using Et_2O–Et_3N (9:1) as eluent. The title alcohol was obtained as white crystals (1 g, 90%): mp 189 °C; $[\alpha]^{20}_D$ −51.2°; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 3.41 (m, 1H), 3.22–3.10 (m, 4H), 2.26 (s, 3H, NCH_3), 2.25–2.10 (m, 3H), 2.05–1.75 (m, 4H). Anal. ($C_{15}H_{20}NOCl$) C, H, N.

2β-Formyl-3β-(4-chlorophenyl)tropane (6). Oxalyl chloride (1.5 mmol, 0.13 mL) was dissolved in 10 mL of anhydrous methylene chloride, and the solution was cooled to −78 °C. Dimethyl sulfoxide (3 mmol, 0.22 mL) was added, after 5 min the alcohol **5** (1.5 mmol, 440 mg) was added in 2 mL of CH_2Cl_2, and stirring was continued for 30 min. The reaction mixture was quenched by adding 1.95 mL of Et_3N, and the resulting solution was warmed to room temperature, washed with water, and extracted several times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo while the temperature was kept below 40 °C to provide aldehyde **6** in essentially quantitative yield. The NMR and GC–MS data were consistent with the assigned structure, and the compound was used in the following step without further purification.

General Procedure for the Preparation of 2β-Alkenyl-3β-(4-chlorophenyl)tropanes (7). A solution of n-butyllithium (3 mmol, 1 M in hexane, 3 mL) was dissolved in 10 mL of freshly distilled THF and cooled to 0 °C. The phosphonium salt (3 mmol) of desired chain length was added slowly under argon. The resulting yellow-orange to black solution was stirred for 30 min, and then the cooling bath was removed. The crude aldehyde **6** (1 mmol, 265 mg) was added in 2 mL of THF, and the reaction mixture was stirred for 16 h at room temperature. The salts were then removed by filtration over Celite, and the resulting solution was diluted with water and extracted with ether (3 × 5 mL). The ethereal extracts were concentrated by rotary evaporation, and the residue was purified by chromatography on silica gel using Et_2O–Et_3N (95:5) as eluent. Selected physical parameters are provided in Table 1.

2β-Vinyl-3β-(4-chlorophenyl)tropane (7a): yield 38%; $[\alpha]^{25}_D$ −63.1° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 5.65 (m, 1H), 5.27–5.19 (m, 2H), 3.28 (m, 1H), 3.18 (m, 1H), 3.12–2.99 (m, 2H), 2.25 (s, 3H), 2.23–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.8, 138.9, 131.4, 129.3, 128.0, 115.6, 68.4, 62.0, 52.0, 42.1, 35.9, 34.5, 26.4, 25.0. Anal. ($C_{16}H_{20}NCl$) C, H, N.

2β-(*E*-2-chlorovinyl)-3β-(4-chlorophenyl)tropane (7b): yield 33%; $[\alpha]_D^{25}$ −118.3° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 6.15 (dd, 1H, J = 13.4, 10 Hz), 5.47 (d, 1H, J = 13.4 Hz), 3.26 (m, 1H, H-1), 3.03 (m, 1H, H-5), 3.01 (m, 1H), 2.28 (m, 1H), 2.22 (s, 3H), 2.18–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.1, 133.8, 131.7, 129.3, 128.2, 117.6, 67.3, 62.0, 49.6, 42.0, 36.6, 34.5, 26.4, 25.0. Anal. ($C_{16}H_{19}NCl_2$) C, H, N.

2β-((*Z*)-2-Chlorovinyl)-3β-(4-chlorophenyl)tropane (7c): yield 18%; $[\alpha]^{25}_D$ +71.4° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 5.91 (dd, 1H, J = 7.3 and 9 Hz), 5.83 (d, 1H, J = 7.2 Hz), 3.31 (m, 1H), 3.19–2.99 (m, 3H), 2.22 (s, 3H), 2.19–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.1, 131.9, 131.7, 128.8, 128.1, 117.6, 66.5, 62.0, 45.0, 42.0, 34.9, 34.4, 26.4, 24.9. Anal. ($C_{16}H_{19}NCl_2$) C, H, N.

2β-(1-Propenyl)-3β-(4-chlorophenyl)tropane (7d): isolated as a cis/trans mixture, yield 57%; $[\alpha]^{25}_D$ = −13.2° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 4H), 7.08 (m, 4H), 5.62 (m, 2H), 5.32 (m, 1H), 4.99 (m, 1H), 3.35 (m, 2H), 3.05 (m, 4H), 2.65 (m, 2H), 2.25 (s, 3H, NCH_3), 2.24 (s, 3H, NCH_3), 2.24–2.10 (m, 8H), 1.73 (m, 2H), 1.55 (m, 1H), 1.44 (m, 1H), 1.25 (m, 6H). Anal. ($C_{17}H_{22}NCl$) C, H, N.

2β-(1-Butenyl)-3β-(4-chlorophenyl)tropane (7e): isolated as a cis/trans mixture, yield 43%; $[\alpha]^{25}_D$ −19.8° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 4H), 7.02 (m, 4H), 5.5 (m, 2H), 5.19 (m, 1H), 4.95 (m, 1H), 3.28 (m, 2H), 3.02 (m, 4H), 2.60 (m, 2H), 2.23 (s, 3H, NCH_3), 2.22 (s, 3H, NCH_3), 2.20–2.05 (m, 8H), 1.73–1.50 (m, 3H), 1.44 (m, 1H), 1.20–0.8 (m, 4H), 0.70–0.60 (m, 6H). Anal. ($C_{18}H_{24}NCl$) C, H, N.

2β-(1-Hexenyl)-3β-(4-chlorophenyl)tropane (7f): isolated as a cis/trans mixture, yield 34%; $[\alpha]^{25}_D$ −21.6° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 4H), 7.04 (m, 4H), 5.53 (m, 2H), 5.13 (m, 1H), 4.90 (m, 1H), 3.19 (m, 2H), 3.00 (m, 4H), 2.53 (m, 2H), 2.23 (s, 3H, NCH_3), 2.22 (s, 3H, NCH_3), 2.12–1.98 (m, 8H), 1.73–1.40 (m, 8H), 1.20–0.63 (m, 14H). Anal. ($C_{20}H_{28}NCl$) C, H, N.

2β-((*E*)-2-Phenylvinyl)-3β-(4-chlorophenyl)tropane (7g): yield 41%; $[\alpha]^{25}_D$ −161.3° (c = 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.25–7.12 (m, 9H), 7.04 (d, 1H, J = 8.5 Hz), 6.49–6.41 (dd, 1H, J = 16.3 and 16.0 Hz), 5.92–5.87 (d, 1H, J = 16.0 Hz), 3.33–3.31 (m, 1H, H-1), 3.17–3.15 (m, 1H, H-5), 3.14–2.99 (m, 1H, H-3), 2.42 (m, 1H, H-2), 2.24 (s, 3H), 2.21–2.16 (m, 1H, H-4ax), 1.75–1.62 (m, 5H); ^{13}C NMR ($CDCl_3$) 141.4, 139.8, 131.1, 130.6, 129.1, 127.9, 127.6, 125.7, 67.8, 61.8, 51.3, 41.7, 34.6, 26.2, 24.7. Anal. ($C_{22}H_{24}NCl$) C, H, N.

2β-((*Z*)-2-Phenylvinyl)-3β-(4-chlorophenyl)tropane (7h): yield 19%; $[\alpha]^{25}_D$ +130.9° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.30–7.14 (m, 3H, Ph), 6.98 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 6.8 Hz), 6.33 (d, 1H, J = 11.9 Hz), 5.95 (dd, 1H, J = 10.8 Hz and 11.7 Hz), 3.34 (m, 1H, H-5), 3.18 (m, 1H, H-1), 3.02 (m, 1H, H-3), 2.91 (m, 1H, H-2), 2.26 (s, 3H), 2.28–2.11 (m, 1H, H-4eq), 1.68–1.62 (m, 5H); ^{13}C NMR ($CDCl_3$) 137.4, 132.4, 128.8, 127.8, 127.5, 125.7, 67.4, 61.7, 44.4, 41.7, 35.5, 34.0, 26.1. Anal. ($C_{22}H_{24}NCl$) C, H, N.

2β-Ethyl-3β-(4-chlorophenyl)tropane (8a). To a solution of **7a** (240 mg, 0.9 mmol) in 50 mL of absolute ethanol was added 15 mg of 10% Pd/C. The mixture was stirred at room temperature for 2 h under 40 psi of hydrogen. The reaction mixture was filtred over Celite, and the filtrate was evaporated to dryness. The resulting colorless oil was purified by flash chromatography on silica gel using hexane–ethyl acetate–triethylamine (90:8:2) as eluent to afford the title compound in 95% yield: $[\alpha]^{25}_D$ −60.3° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$)

δ 7.24 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.1 Hz), 3.33 (m, 2H, H-1 and H-5), 3.08 (m, 1H), 2.28 (m, 3H), 2.24 (s, 3H), 2.11 (m, 1H), 1.73 (m, 2H), 1.52 (m, 3H), 0.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 142.4, 131.3, 129.1, 128.1, 63.8, 61.9, 47.9, 42.1, 36.1, 33.6, 26.4, 24.8, 19.7, 12.1. Anal. ($C_{16}H_{22}NCl$) C, H, N.

2β-n-Propyl-3β-phenyltropane (8c): yield 83%; $[\alpha]^{25}_D$ −118° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 6.15 (dd, 1H, J = 13.4, 10 Hz), 5.47 (d, 1H, J = 13.4 Hz), 3.26 (s, 1H), 3.03 (m, 2H), 2.28 (m, 1H), 2.22 (s, 3H), 2.18−1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 139.8, 128.6, 128.0, 127.0, 66.6, 64.4, 45.6, 35.2, 30.9, 28.2, 26.4, 23.7, 20.8, 13.7. Anal. ($C_{17}H_{25}N$) C, H, N.

General Procedure for the Preparation of the Other 2β-Alkyl-3β-(4-chlorophenyl)tropanes 8. To a solution of **7** (1 mmol) in 50 mL of freshly distilled cyclohexane was added 50 mg of 5% Pt/C. The mixture was stirred at room temperature for 0.5 h under a hydrogen atmosphere at 40 psi. The resulting solution was filtered over Celite and evaporated to dryness. The resulting colorless oil was purified by flash chromatography on silica gel using ether−triethylamine as eluent. Selected physical parameters are provided in Table 1.

2β-n-Propyl-3β-(4-chlorophenyl)tropane (8b): yield 96%; $[\alpha]^{25}_D$ −67.4° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H), 7.05 (d, 2H, J = 8.4 Hz), 3.32 (m, 1H, H-1), 3.28 (m, 1H, H-5), 3.05 (m, 1H), 2.26 (s, 3H), 2.18−2.04 (m, 2H), 1.62−1.40 (m, 5H), 1.32−1.10 (m, 4H), 1.0−0.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.2, 128.2, 64.8, 62.1, 46.3, 42.1, 36.0, 33.7, 30.1, 26.7, 26.5, 24.8, 22.8, 14.1. Anal. ($C_{17}H_{24}NCl$) C, H, N.

2β-n-Butyl-3β-(4-chlorophenyl)tropane (8d): yield 98%; $[\alpha]^{25}_D$ −78.6° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 7.02 (d, 2H, J = 8.4 Hz), 3.30 (m, 1H, H-1), 3.21 (m, 1H, H-5), 3.10 (m, 1H), 2.24 (s, 3H), 2.15−2.00 (m, 2H), 1.65−1.35 (m, 5H), 1.35−1.05 (m, 6H), 0.9−0.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.1, 128.4, 65.1, 62.4, 46.1, 42.0, 36.1, 33.7, 28.9, 26.1, 25.8, 24.7, 21.3, 16.4. Anal. ($C_{18}H_{26}NCl$) C, H, N.

2β-n-Hexyl-3β-(4-chlorophenyl)tropane (8e): yield 96%; $[\alpha]_D^{25}$ −123.2° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 2H), 7.0 (m, 2H), 3.29 (m, 1H, H-1), 3.20 (m, 1H, H-5), 3.07 (m, 1H), 2.24 (s, 3H), 2.10−1.95 (m, 2H), 1.62−1.30 (m, 5H), 1.25−0.7 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 130.0, 129.1, 65.1, 62.2, 46.9, 42.7, 36.3, 34.0, 30.0, 26.8, 26.5, 26.1, 24.2, 21.7, 19.2, 18.0. Anal. ($C_{20}H_{30}NCl$) C, H, N.

2β-(2-Phenylethyl)-3β-(4-chlorophenyl)tropane (8f): yield 98%; $[\alpha]^{25}_D$ −112.9° (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H), 7.06 (m, 4H), 3.24 (m, 2H, H-1 and H-5), 3.03 (m, 1H, H-3), 2.51 (m, 1H, H-2), 2.22 (s, 3H), 2.19−2.06 (m, 5H), 1.65 (m, 2H), 1.50 (m, 1H), 1.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 128.6, 127.9, 127.8, 127.7, 125.0, 64.5, 61.6, 45.2, 35.3, 33.5, 27.9, 25.9, 24.3. Anal. ($C_{22}H_{26}NCl$) C, H, N.

Acknowledgment. We are indebted to the National Institute on Drug Abuse for their support of our research program. We also acknowledge valuable discussions with Drs. F. Ivy Carroll and Anita Lewin of the Research Triangle Institute.

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JM950218+