Synthesis of 3β-Aryl-8-azabicyclo[3.2.1]octanes with High Binding Affinities and Selectivities for the Serotonin Transporter Site

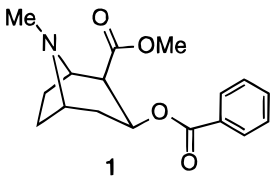
Huw M. L. Davies,*[,†] Lisa A. Kuhn,[‡] Craig Thornley,[‡] Julius J. Matasi,[†] Tammy Sexton,[§] and Steven R. Childers*[,§]

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14260-3000, Department of Chemistry, Wake Forest University, P.O. Box 7486, Winston-Salem, North Carolina 27109, and Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157

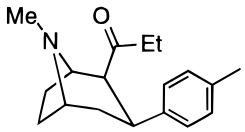
Received January 16, 1996[⊗]

A novel entry to tropane analogs of cocaine was developed based on the reaction of rhodium-stabilized vinylcarbenoids with pyrroles. These analogs were tested in binding to dopamine, serotonin (5-HT), and norepinephrine transporters in membranes from rat striatum and frontal cortex. In all the analogs, the aryl group at the 3 position was directly bound to the tropane ring and an ethyl ketone moiety was present at the 2 position. By appropriate modification of the aryl and nitrogen substituents, highly potent and 5-HT selective tropanes were prepared. The most potent and selective compound was 3β-[4-(1-methylethenyl)phenyl]-2β-propanoyl-8-azabicyclo[3.2.1]octane (**13b**) which had a K_i of 0.1 nM at 5-HT transporters and was 150 times more potent at 5-HT vs dopamine transporters and almost 1000 times more potent at 5-HT vs norepinephrine transporters.

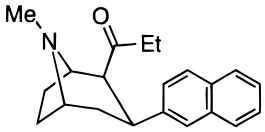
Although the biological actions of cocaine (**1**) are thought to occur primarily through inhibition of dopamine uptake, cocaine also has moderately high binding affinity to serotonin (5-HT) and norepinephrine transporters.[1] Therefore, a complete description of the cocaine pharmacophore will depend upon the synthesis of tropanes with defined selectivities at each of these three transport sites. We have recently described studies that explore the structure-activity relationships of various tropanes with particular emphasis on their binding affinities to both the dopamine and 5-HT transport sites.[2,3] This work expanded on earlier studies on 3β-aryl-8-azabicyclo[3.2.1]octane-2β-carboxylates[4,5] by using a new synthetic approach to the tropane[6] that allowed a more diverse group of derivatives to be prepared.[7] The *p*-tolyl derivative **2a** represents the prototypical member of the class of tropanes that can be derived from this chemistry and has undergone extensive biological evaluation.[8] During the course of these studies it was discovered that introduction of a 2-naphthyl derivative at the 3β position as in **3a** resulted in the most potent tropane analogs to date.[2,3] Furthermore, introduction of bulky aryl substituents, as seen with the 4-isopropylphenyl derivative **4a**, resulted in analogs that were quite selective for the 5-HT transporters. The 5-HT selectivity observed with **4a** is in sharp contrast to that of most of the previously prepared tropane analogs as these tended to be selective for the dopamine transporters.[5,9] Another approach that leads to tropanes with increased 5-HT selectivity has been the use of N-demethylated derivatives.[10] The purpose of the current study was to develop novel tropanes that would have structural elements such that the increased potency obtained with naphthyl derivatives would be combined with the increased 5-HT selectivity seen in bulky aryl-substituted and N-demethylated derivatives.



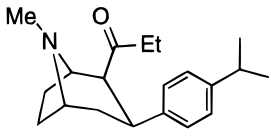
1



2a



3a



4a

Chemistry

The general strategy for the synthesis of tropane derivatives is summarized in Scheme 1. The flexible approach to the tropane skeleton **7** that we have developed is based on the rhodium(II) octanoate-catalyzed decomposition of the vinyldiazomethane **6** in the presence of *N*-BOC-pyrrole (**5**).[6] Selective hydrogenation and deprotection of **7** resulted in the N-H derivative **8** which was readily methylated to produce **9**. The synthesis of the N-methylated aryl derivatives ("**a**" series) was achieved by a copper-catalyzed 1,4-addition of the appropriate Grignard reagent following an established literature procedure.[4] The N-H derivatives ("**b**" series) were expected to be readily prepared by demethylation of the **a** series using standard procedures,[10,11] but all attempts at carrying out such reactions resulted in either no reaction or, under more forcing conditions, demethylation accompanied by epimerization at C-2. Consequently, an alternative approach was developed in which the cuprate addition was carried out directly on the N-demethylated derivative **8**. By using an excess of Grignard reagents and an acid quench of the reaction at low temperature, the N-demethylated derivatives (**b** series) were produced in 40−60% yield with excellent control of the 2β,3β relative stereochemistry.

† State University of New York at Buffalo.
‡ Department of Chemistry, Wake Forest University.
§ Bowman Gray School of Medicine, Wake Forest University.
⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

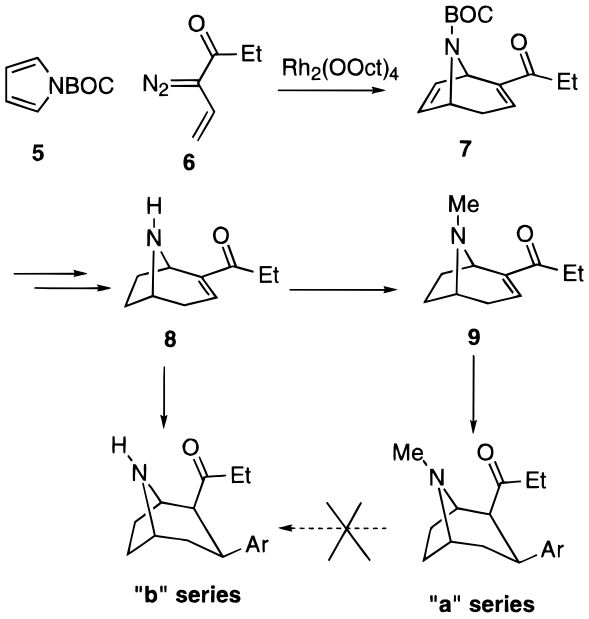
S0022-2623(96)00050-7 CCC: $12.00

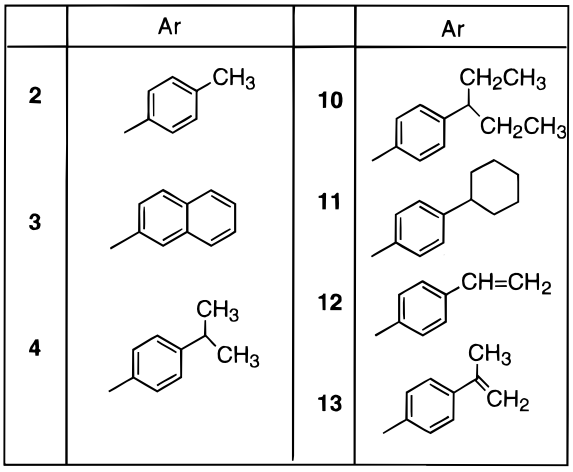
Table 1. IC_{50} and K_i Values of Tropane Analogs in Displacing Binding of [^{125}I]RTI-55, [^{3}H]Paroxetine, and [^{3}H]Nisoxetine Binding in Rat Brain Membranes

analog	[^{3}H]paroxetine (5-HT) K_i (nM)	[^{125}I]RTI-55 (DA) IC_{50} (nM)	[^{3}H]nisoxetine (NE) K_i (nM)	ratios[c]		
				DA/5-HT	NE/5-HT	NE/DA
2a[a]	130 ± 10	8.2 ± 1.6	160 ± 1.6	0.063	1.2	20
2b	19 ± 1.4	4.7 ± 0.58	5.5 ± 2.0	0.25	0.29	1.2
3a[a]	0.39 ± 0.07	0.12 ± 0.02	2.9 ± 0.5	0.31	7.4	24
3b	0.22 ± 0.16	0.069 ± 0.01	2.0 ± 0.09	1	50	50
4a[a]	36 ± 4.4	440 ± 41	>10 000	12	>280	>23
4b	5.3 ± 1.0	380 ± 110	3400 ± 270	72	640	8.9
10a	540 ± 51	270 ± 38	>10 000	0.5	>19	>37
10b	150 ± 50	190 ± 17	5100 ± 220	1.27	34	27
11a	97 ± 12	320 ± 55	>10 000	3.3	>100	>31
11b	85 ± 16	490 ± 120	4300 ± 1100	5.8	51	8.8
12a[b]	3.2 ± 1.3	0.90 ± 0.34	78 ± 31	0.28	24	87
12b	0.32 ± 0.06	1.5 ± 1.1	10.9 ± 1.5	4.7	34	7.3
13a	0.82 ± 0.38	7.2 ± 2.1	794 ± 110	8.8	970	110
13b	0.11 ± 0.016	16 ± 4.9	94 ± 18	150	850	5.9

[a] Reference 2. [b] Analyzed as its fumarate salt. [c] DA/5-HT, NE/5-HT, and NE/DA are ratios of K_i (or IC_{50}) values.

Scheme 1





Pharmacology

Methods. Binding of tropane analogs at biogenic amine transporters was determined as previously described.[3] Affinities of analogs at dopamine transport sites were determined by displacement of [^{125}I]RTI-55 binding in membranes from rat striatum, using 0.5 mg (original wet weight) of membranes and 10 pM [^{125}I]-RTI-55. Nonspecific binding was determined in the presence of 1 μM WF-23 (analog **3a**). Affinities of analogs at 5-HT transport sites were determined by displacement of [^{3}H]paroxetine binding in membranes from rat frontal cortex, using 50 mg (original wet weight) of membranes and 0.4 nM [^{3}H]paroxetine. Nonspecific binding was determined in the presence of 10 μM fluoxetine. Binding of analogs at norepinephrine transport sites was determined by displacement of [^{3}H]-nisoxetine binding in membranes from rat forebrain, using 0.7 nM [^{3}H]nisoxetine. Nonspecific binding was determined in the presence of 1 μM desipramine.

Potencies were calculated from displacement curves using 7−10 concentrations of unlabeled analogs. Because binding of tropanes at dopamine transporters is generally regarded as multiphasic,[12] potencies in inhibiting [^{125}I]RTI-55 binding are reported as IC_{50} values. For [^{3}H]paroxetine and [^{3}H]nisoxetine binding assays, K_i values were calculated using the Cheng−Prusoff equation.[13] All data are mean values ± SEM of at least three separate experiments, each of which was conducted in triplicate. For the sake of convenience in analyzing binding results, any analog that displayed greater than 10-fold difference in potency at any one of the three biogenic amine sites was considered selective; differences less than 10-fold were not considered sufficiently different to provide any selectivity between the three biogenic amine transporters.

Results and Discussion

Table 1 demonstrates the potencies of seven *N*-methyl analogs (**a** series) and seven N-demethylated analogs (**b** series) in displacing radioligand binding at dopamine, 5-HT, and norepinephrine transport sites. The potencies for three of the *N*-methyl analogs (**2a**, **3a**, and **4a**) have been reported previously.[2,3] All of these transporter binding data were obtained in rat striatal membranes, and there is no guarantee that the pharmacological specificity observed in these experiments would be the same across all species. Nevertheless, there is a close correlation reported between cloned rodent and human dopamine transporters for a variety of dopamine transporter inhibitors (Giros et al.[14]), and there is little reason to suspect that the pharmacological specificity reported for these N-demethylated tropanes will be unique to rat.

The 3β-tolyl **2a** was moderately potent at the dopamine transporter, with an IC_{50} value of 8 nM. As is

typical of most of the tropane derivatives that have been evaluated previously,[5] this analog was relatively selective for the dopamine transporter, being 16 times more potent at dopamine vs 5-HT transporters. The demethylated 3β-tolyl derivative **2b** retained similar binding affinity at the dopamine transporter, but its potency at the 5-HT transporter was increased by a factor of 7 compared to the methylated analog **2a.** Therefore, **2b** was relatively nonselective in its binding to the two transporters.

The 2-naphthyl derivative **3a** was extremely potent at both dopamine and 5-HT transporters[2,3] and relatively nonselective. In contrast to the 3β-tolyl analogs **2a**,**b**, the N-demethylated compound **3b** retained similar potency to both transporters. Apparently, the presence of the 2-naphthyl substituent has such a favorable effect on transporter binding that no enhancement in selectivity is observed in **3b** over **3a**.

The 4-isopropylphenyl derivative **4a** has generated a great deal of interest because it is the first reported *N*-methyltropane to have reasonable selectivity for the 5-HT transporters compared to the dopamine transporters,[2,3] since it was 12 times more potent in binding to 5-HT transporters vs dopamine transporters. The demethylated derivative **4b** displayed an even greater selectivity and binding affinity for the 5-HT transporter. As was seen in the case of the tolyl derivatives **2a**,**b**, demethylation resulted in a 7-fold increase in 5-HT transporter potency, while the dopamine transporter binding remained virtually unchanged. This resulted in a compound with an IC_{50} value of 5 nM in binding to 5-HT transporters and over 70 times more potent in binding to 5-HT transporters than dopamine transporters. Interestingly, this trend was not extended to other para-substituted alkyl derivatives. Both the 3-pentyl and cyclohexyl derivatives **10a** and **11a** were less potent at 5-HT transporters than the isopropyl derivative **4a**, and the demethylated derivatives **10b** and **11b** had only a moderate improvement of 5-HT versus dopamine selectivity over **10a** and **11a**.

The choice of the final set of compounds was based on the observation that extended sp^2 functionality on the 3β-aryl ring, as seen with 2-naphthyl or biphenyl,[2,3] resulted in extremely potent compounds. Similar high potency was seen with the vinyl derivative **12a.** The potencies of **12a** at 5-HT and dopamine transporters were 3 and 0.9 nM, respectively; thus, **12a** was relatively nonselective at the two transporters. The change of **12a** to the demethylated derivative **12b** once again resulted in a 10-fold increase in potency at 5-HT transporters with little change in potency at the DA transporters. This resulted in the first example of a tropane with sub-nanomolar binding to the 5-HT transporters (0.32 nM) with a slight tendency for 5-HT transporter selectivity. Although its selectivity for 5-HT transporters improved compared to that of **12a**, it remained relatively nonselective for the two transporters. A significant improvement in selectivity was made possible by using the slightly bulkier derivatives **13** with an isopropenyl substituent. Even the N-methylated compound **13a** displayed sub-nanomolar binding affinity at 5-HT (0.8 nM) and was 9 times more potent at 5-HT vs dopamine transporters. The selectivity was further enhanced in the N-demethylated derivative **13b,** leading to a compound with a K_i of 0.1 nM at 5-HT transporters and 150 times more potent at 5-HT vs dopamine transporters.

As seen in Table 1, most of these compounds (with the exception of the tolyl analogs **2a**,**b**) were significantly less potent in binding to norepinephrine transporters than 5-HT transporters. The most selective of these analogs were the isopropenyl derivatives **13a**,**b**, which were almost 1000 times less potent at norepinephrine vs 5-HT transporters. Overall, the effect of demethylation on 5-HT:norepinephrine selectivity was not dramatic. For most of these compounds, the removal of the methyl group caused increased potency for both 5-HT and norepinephrine transporters such that there was little effect on their relative potencies at 5-HT and norepinephrine transporters.

In general, these results confirm the suggestion previously made by Boja et al.[10] that N-demethylation of tropanes increases potency at 5-HT transporters compared to dopamine transporters. For example, compounds which were relatively selective at dopamine transporters were transformed into nonselective compounds by N-demethylation. Moreover, two analogs which were already somewhat selective for 5-HT transporters (**4a** and **13a**) were significantly increased in terms of both 5-HT transporter potency and selectivity by removal of *N*-methyl groups. One set of compounds, the 2-naphthyl derivatives **3**, appear to be so potent at both dopamine and 5-HT transporters that N-demethylation had no significant effect on selectivity. A particularly interesting set of analogs was represented by **13a**,**b**, which demonstrated that a slight modification of the isopropyl moiety (which was successful in producing the first 5-HT selective N-methylated tropane **4a**) to an isopropenyl group significantly increased potency at 5-HT transporters. When that strategy was combined with N-demethylation, a compound (**13b**) with very high selectivity for 5-HT transporters was produced. These data suggest that a combination of chemical strategies can be extremely effective in producing selective tropanes at defined biogenic amine sites.

Experimental Section

Ether and THF were distilled from sodium benzophenone ketal under Ar. Petroleum ether refers to that fraction boiling in the range 40−60 °C. Flash chromatography was carried out on silica gel (grade 60, 230−400 mesh). ^1H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ at 200 and 50.3 MHz, respectively, on a Varian VXR200 instrument. Chemical shifts are quoted in ppm relative to TMS. The *N*-methyl derivatives, **a** series, were prepared from **9** by the general procedure described previously.[2] The experimental data for the synthesis of compounds **2a**, **3a**, **4a**, and **8** have been reported previously.[2,3]

General Procedure for the NH Derivatives (b series). The arylmagnesium bromide (10−15 equiv) in THF was added to thoroughly dried copper bromide−dimethyl sulfide complex (1−2 equiv). The mixture was stirred at room temperature for 10−45 min and then cooled to 0 °C. A solution of 2-propanoyl-8-azabicyclo[3.2.1]oct-2-ene (**8**; 1 equiv) in dry THF was added dropwise. The solution was allowed to stir at 0 °C for 4−6 h and then overnight at room temperature. The solution was next cooled to −75 °C, and a solution of HCl_g dissolved in dry ether (pH = 2) was added very carefully keeping the temperature below −70 °C at all times. Upon completion of the quench, the reaction mixture was poured on to ice and the mixture was allowed to warm to room temperature. The organic layer was separated and washed thoroughly with aqueous HCl. The combined aqueous solution

was basified with aqueous NH_4OH, saturated with NaCl, and extracted fully with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), evaporated, and subjected to flash chromatography on a silica gel column (5 in. × 1 in.) using the eluent indicated to give the following tropanes.

3β-(4-Methylphenyl)-2β-propanoyl-8-azabicyclo[3.2.1]-octane (2b): ether as reaction solvent, 5% triethylamine:45% ether:50% pentane and then 5% triethylamine:95% ether, 46% yield; IR ($CDCl_3$) 3687, 3605, 2925, 1699, 1602, 1377, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03 (d, 2 H, J = 6.3 Hz), 7.02 (d, 2 H, J = 6.1 Hz), 3.71 (m, 1 H), 3.58 (br d, 1 H, J = 5.3 Hz), 3.18 (ddd, 1 H, J = 13.1, 5.3, 5.3 Hz), 2.88 (br d, 1 H, J = 5.3 Hz), 2.40 (ddd, 1 H, J = 13.1, 13.1, 2.8 Hz), 2.28 (s, 3 H), 2.21−2.00 (m, 3 H), 1.79−1.50 (m, 4 H), 0.67 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 215.3, 139.0, 136.1, 129.1, 127.4, 56.2, 55.8, 53.6, 38.8, 36.2, 33.8, 29.0, 27.5, 21.0, 7.0; MS *m/z* (rel intensity) 257 (M^+, 29), 239 (30), 210 (32), 200 (39), 148 (10), 128 (15), 118 (26), 105 (20), 91 (30), 83 (86), 69 (76), 68 (100). Anal. ($C_{17}H_{23}NO$) C, H, N.

3β-(2-Naphthyl)-2β-propanoyl-8-azabicyclo[3.2.1]-octane (3b): 5% triethylamine:95% ether, 49% yield; IR ($CDCl_3$) 3692, 3607, 2940, 1695, 1602, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (m, 3 H), 7.56 (br s, 1 H), 7.42 (m, 2 H), 7.30 (dd, 1 H, J = 8.5, 1.8 Hz), 3.75 (ddd, 1 H, J = 6.3, 3.1, 3.1 Hz), 3.60 (br d, 1 H, J = 5.7 Hz), 3.37 (ddd, 1 H, J = 12.9, 5.7, 5.7 Hz), 3.01 (br d, 1 H, J = 5.7 Hz), 2.57 (ddd, 1 H, J = 12.9, 12.9, 2.9 Hz), 2.47 (br s, 1 H), 2.19 (dq, 1 H, J = 18.2, 7.2 Hz), 2.10 (dq, 1 H, J = 18.2, 7.2 Hz), 2.09 (m, 1 H), 1.84−1.50 (m, 4 H), 0.59 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 214.9, 139.9, 133.4, 132.2, 127.9, 127.8, 127.5, 126.2, 126.0, 125.5, 56.3, 55.9, 53.6, 38.7, 36.8, 34.0, 29.2, 27.7, 7.0; MS *m/z* (rel intensity) 293 (M^+, 43), 275 (11), 236 (49), 222 (9), 178 (19), 165 (23), 152 (27), 128 (16), 83 (100), 82 (80), 69 (80), 68 (97). Anal. ($C_{20}H_{23}NO·0.7H_2O$) C, H, N.

3β-[4-(1-Methylethyl)phenyl]-2β-propanoyl-8-azabicyclo-[3.2.1]octane (4b): 5% triethylamine:45% ether:50% pentane, 48% yield; IR ($CDCl_3$) 3691, 3607, 2963, 1695, 1602, 1460, 1406, 1377, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, 2 H, J = 8.4 Hz), 7.05 (d, 2 H, J = 8.4 Hz), 3.69 (m, 1 H), 3.55 (br d, 1 H, J = 5.2 Hz), 3.19 (ddd, 1 H, J = 12.9, 5.6, 5.6 Hz), 2.87 (br d, 1 H, J = 5.6 Hz), 2.83 (septet, 1 H, J = 7.0 Hz), 2.45 (br s, 1 H), 2.40 (ddd, 1 H, J = 12.9, 12.9, 2.9 Hz), 2.17 (dq, 1 H, J = 18.2, 7.3 Hz), 2.08 (dq, 1 H, J = 18.2, 7.3 Hz), 2.05 (m, 1 H), 1.77−1.48 (m, 4 H), 1.18 (d, 6 H, J = 7.0 Hz), 0.64 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 215.3, 147.1, 139.5, 127.4, 126.3, 56.3, 55.8, 53.5, 38.7, 36.1, 33.8, 33.6, 29.1, 27.6, 24.0, 23.9, 6.9; MS *m/z* (rel intensity) 285 (26, M^+), 238 (3), 228 (35), 187 (5), 131 (11), 128 (12), 115 (12), 83 (100), 68 (74). Anal. ($C_{19}H_{27}NO·0.25H_2O$) C, H, N.

3β-[4-(1-Ethylpropyl)phenyl]-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10a): pentane−(49% ether:49% pentane:2% triethylamine), 27% yield; IR (neat) 2957, 2931, 1713, 1457, 1362 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 2 H, J = 8.2 Hz), 7.01 (d, 2 H, J = 8.2 Hz), 3.43 (br d, 1 H, J = 6.9 Hz), 3.37 (m, 1 H), 2.98 (m, 2 H), 2.59 (ddd, 1 H, J = 12.3, 12.3, 2.8 Hz), 2.31−2.06 (m, 4 H), 2.20 (s, 3 H), 1.80−1.41 (m, 8 H), 0.79 (t, 3 H, J = 6.9 Hz), 0.72 (t, 6 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.8, 143.1, 140.3, 127.5 (2 CH), 127.0 (2 CH), 64.6, 62.4, 59.5, 49.2, 42.0, 35.6, 34.3, 33.6, 29.2, 29.1, 26.5, 25.2, 12.2 (2 CH_3), 7.7; MS *m/z* (rel intensity) 327 (26, M^+), 270 (48), 128 (8), 115 (8), 107 (13), 97 (70), 96 (54), 83 (100), 82 (90), 57 (28). Anal. ($C_{22}H_{33}NO$) C, H, N.

3β-[4-(1-Ethylpropyl)phenyl]-2β-propanoyl-8-azabicyclo-[3.2.1]octane (10b): 49% ether:49% pentane:2% triethylamine and then 98% ether:2% triethylamine, 46% yield; IR (neat) 3309, 2961, 2931, 1698, 1460, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (d, 2 H, J = 7.7 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 3.71 (br s, 1 H), 3.56 (br d, 1 H, J = 6.0 Hz), 3.24 (ddd, 1 H, J = 12.9, 5.7, 5.7 Hz), 2.85 (br d, 1 H, J = 5.7 Hz), 2.85 (br s, 1 H), 2.42 (ddd, 1 H, J = 12.9, 12.9, 2.8 Hz), 2.30−2.15 (m, 1 H), 2.13−1.96 (m, 3 H), 1.78−1.40 (m, 8 H), 0.70 (t, 6 H, J = 7.3 Hz), 0.61 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 215.4, 143.9, 139.5, 127.8 (2 CH), 127.3 (2 CH), 56.4, 55.7, 53.4, 49.2, 38.9, 36.3, 33.6, 29.3, 29.2, 29.1, 27.5, 12.0 (2 CH_3), 6.8; MS *m/z* (rel intensity) 313 (17, M^+), 295 (10), 266 (16), 256 (31), 215 (11), 175 (3), 148 (6), 128 (9), 117 (14), 83 (50), 82 (31), 69 (100). Anal. ($C_{21}H_{31}NO·0.3H_2O$) C, H, N.

3β-(4-Cyclohexylphenyl)-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (11a): pentane and then 49% ether: 49% pentane:2% triethylamine, 27% yield; IR (neat) 2925, 2850, 1718, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (d, 2 H, J = 8.4 Hz), 7.07 (d, 2 H, J = 8.4 Hz), 3.46 (br d, 1 H, J = 6.3 Hz), 3.36 (br s, 1 H), 2.98 (m, 2 H), 2.58 (ddd, 1 H, J = 12.2, 12.2, 2.9 Hz), 2.46−2.05 (m, 4 H), 2.20 (s, 3 H), 1.84−1.52 (m, 9 H), 1.47−1.17 (m, 5 H), 0.84 (t, 3 H, J = 7.3 Hz); MS *m/z* (rel intensity) 339 (25, M^+), 282 (51), 241 (3), 200 (2), 173 (3), 153 (8), 115 (10), 97 (76), 96 (62), 83 (100), 82 (90), 55 (35). Anal. ($C_{23}H_{33}NO$) C, H, N.

3β-(4-Cyclohexylphenyl)-2β-propanoyl-8-azabicyclo-[3.2.1]octane (11b): 49% ether:49% pentane:2% triethylamine and then 98% ether:2% triethylamine, 31% yield; IR (neat) 3332, 2922, 1709, 1694, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, 2 H, J = 8.5 Hz), 7.05 (d, 2 H, J = 8.5 Hz), 3.70 (br s, 1 H), 3.56 (br d, 1 H, J = 5.9 Hz), 3.21 (ddd, 1 H, J = 13.0, 5.7, 5.7 Hz), 2.89 (d, 1 H, J = 5.7 Hz), 2.56 (br s, 1 H), 2.42 (ddd, 1 H, J = 13.0, 13.0, 2.9 Hz), 2.51−2.34 (m, 1 H), 2.23−1.91 (m, 3 H), 1.83−1.69 (m, 5 H), 1.73−1.52 (m, 4 H), 1.48−1.15 (m, 5 H), 0.65 (t, 3 H, J = 7.2 Hz); MS *m/z* (rel intensity) 325 (4, M^+), 307 (68), 278 (99), 276 (76), 224 (5), 194 (10), 155 (6), 148 (33), 128 (20), 118 (32), 91 (23), 83 (30), 69 (43), 55 (65), 41 (100). Anal. ($C_{22}H_{31}NO·0.5H_2O$) C, H, N.

3β-(4-Ethenylphenyl)-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (12a): 49% ether:49% pentane:2% triethylamine, 52% yield; IR (neat) 3082, 2940, 1714, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J = 8.4 Hz), 7.18 (d, 2 H, J = 8.3 Hz), 6.66 (dd, 1 H, J = 17.6, 10.8 Hz), 5.67 (d, 1 H, J = 17.6 Hz), 5.16 (d, 1 H, J = 10.8 Hz), 3.48 (br d, 1 H, J = 6.9 Hz), 3.36 (br s, 1 H), 2.96 (m, 2 H), 2.58 (ddd, 1 H, J = 12.7, 12.7, 3.0 Hz), 2.44−2.01 (m, 3 H), 2.21 (s, 3 H), 1.82−1.55 (m, 4 H), 0.85 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 143.1, 136.7, 135.0, 127.2, 125.9, 112.8, 64.5, 62.3, 59.3, 42.0, 35.1, 34.2, 33.8, 26.4, 25.2, 7.7; MS *m/z* (rel intensity) 283 (14, M^+), 226 (58), 153 (2), 128 (10), 97 (40), 96 (47), 83 (68), 82 (100), 42 (61).

12a Fumarate Salt. 12a (0.10 g, 0.35 mmol) and fumaric acid (0.039 g, 0.33 mmol) were dissolved in 2-propanol (8 mL). The solvent was removed, and the residue was triturated with ether to give the salt as a white solid: 0.044 g, 57% yield; ^1H NMR (D_2O, DSS) δ 7.49 (d, 2 H, J = 8.2 Hz), 7.23 (d, 2 H, J = 8.3 Hz), 6.77 (dd, 1 H, J = 17.7, 10.8 Hz), 6.69 (s, 2 H), 5.84 (d, 1 H, J = 17.7 Hz), 5.31 (d, 1 H, J = 10.9 Hz), 4.06 (m, 2 H), 3.63 (ddd, 1 H, J = 14.1, 6.5, 6.5 Hz), 3.49 (br d, 1 H, J = 6.5 Hz), 2.83 (s, 3 H), 2.68 (br t, 1 H, J = 14.1 Hz), 2.56−1.94 (m, 6 H), 1.43 (dq, 1 H, J = 12.7, 6.9 Hz), 0.59 (t, 3 H, J = 6.9 Hz). Anal. ($C_{23}H_{29}NO_5·0.25H_2O$) C, H, N.

3β-(4-Ethenylphenyl)-2β-propanoyl-8-azabicyclo[3.2.1]-octane (12b): 5% triethylamine:45% ether:50% pentane and then 5% triethylamine:95% ether, 34% yield; IR ($CDCl_3$) 3854, 3689, 3155, 2978, 1793, 1734, 1696, 1653, 1630, 1602, 1512, 1466, 1405, 1383, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8.2 Hz), 7.10 (d, 2 H, J = 8.2 Hz), 6.64 (dd, 1 H, J = 17.6, 10.8 Hz), 5.70 (d, 1 H, J = 17.6 Hz), 5.19 (d, 1 H, J = 10.8 Hz), 3.70 (ddd, 1 H, J = 6.4, 3.2, 3.2 Hz), 3.56 (br d, 1 H, J = 5.6 Hz), 3.19 (ddd, 1 H, J = 12.9, 5.6, 5.5 Hz), 2.90 (br d, 1 H, J = 5.6 Hz), 2.42 (ddd, 1 H, J = 12.9, 12.9, 2.9 Hz), 2.22 (dq, 1 H, J = 18.3, 7.2 Hz), 2.13 (dq, 1 H, J = 18.3, 7.2 Hz), 2.13−1.91 (m, 2 H), 1.78−1.51 (m, 4 H), 0.68 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 214.9, 142.0, 136.4, 135.8, 127.7, 126.2, 113.4, 56.3, 55.8, 53.5, 38.7, 36.4, 33.8, 29.1, 27.6, 7.0; MS *m/z* (rel intensity) 269 (48, M^+), 251 (8), 212 (61), 197 (9), 171 (19), 128 (20), 115 (17), 83 (58), 69 (100), 57 (34). Anal. ($C_{18}H_{23}NO·0.5H_2O$) C, H, N.

8-Methyl-3β-[4-(1-methylethenyl)phenyl]-2β-propanoyl-8-azabicyclo[3.2.1]octane (13a): 49% ether:49% pentane:2% triethylamine, 10% yield; IR (neat) 3086, 2937, 1717, 1689, 1227, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, 2 H, J = 8.4 Hz), 7.18 (d, 2 H, J = 8.4 Hz), 5.32 (br s, 1 H), 5.01 (br s, 1 H), 3.50 (br d, 1 H, J = 7.1 Hz), 3.37 (br s, 1 H), 3.00 (m, 2 H), 2.60 (ddd, 1 H, J = 12.1, 12.1, 3.0 Hz), 2.45−2.01 (m, 3 H), 2.21 (s, 3 H), 2.11 (s, 3 H), 1.82−1.55 (m, 4 H), 0.86 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 143.0, 142.6, 138.4, 126.9,

125.1, 111.5, 64.6, 62.4, 59.3, 42.1, 35.1, 34.2, 33.7, 26.4, 25.3, 21.7, 7.8; MS *m/z* (rel intensity) 297 (29, M^+), 240 (62), 128 (15), 97 (55), 96 (56), 83 (78), 82 (100), 57 (23), 55 (17), 42 (59). Anal. ($C_{20}H_{27}NO \cdot 0.3H_2O$) C, H, N.

3β-[4-(1-Methylethenyl)phenyl]-2β-propanoyl-8-azabicyclo[3.2.1]octane (13b): 5% triethylamine:45% ether: 50% pentane and then 8% triethylamine:92% ether, 46% yield; IR ($CDCl_3$) 3690, 3605, 2972, 1697, 1602, 1406, 1261, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, 2 H, $J = 8.2$ Hz), 7.09 (d, 2 H, $J = 8.2$ Hz), 5.33 (br s, 1 H), 5.02 (br s, 1 H), 3.70 (br s, 1 H), 3.57 (br d, 1 H, $J = 5.6$ Hz), 3.20 (ddd, 1 H, $J = 13.0$, 5.7, 5.7 Hz), 2.91 (br d, 1 H, $J = 5.7$ Hz), 2.56 (br s, 1 H), 2.43 (ddd, 1 H, $J = 13.0$, 13.0, 2.7 Hz), 2.23 (dq, 1 H, $J = 18.2$, 7.2 Hz), 2.14 (dq, 1 H, $J = 18.2$, 7.2 Hz), 2.13−1.94 (m, 1 H), 2.10 (s, 3 H), 1.79−1.52 (m, 4 H), 0.68 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 214.9, 142.7, 141.6, 139.2, 127.4, 125.4, 112.0, 56.3, 55.8, 53.5, 38.7, 36.2, 33.8, 29.2, 27.6, 21.7, 7.0; MS *m/z* (rel intensity) 285 (35, M^+), 265 (28), 236 (31), 226 (48), 185 (15), 128 (20), 115 (20), 83 (51), 69 (100), 57 (29). Anal. ($C_{19}H_{25}NO \cdot 0.2H_2O$) C, H, N.

Acknowledgment. This research was supported by PHS grants DA-06301 and DA-06634 from the National Institute on Drug Abuse.

References

(1) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223.

(2) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of novel 2β-acyl-3β-aryl-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites in rat striatum and frontal cortex. *J. Med. Chem.* **1994**, *37*, 1262−1268.

(3) Bennett, B. A.; Wichems, C. H.; Hollingsworth, C. K.; Davies, H. M. L.; Thornley, C.; Sexton, T.; Childers, S. R. Novel 2-substituted cocaine analogs: uptake and ligand binding studies at dopamine, serotonin and norepinephrine transport sites in the rat brain. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 1176−1186.

(4) Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, N. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. Compounds affecting the central nervous system. 4. 3β-phenyltropane-2-carboxylic esters and analogs. *J. Med. Chem.* **1973**, *16*, 1260−1267.

(5) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: biochemical characterization and structure-activity relationships of cocaine analogues at the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969−981.

(6) Davies, H. M. L.; Saikali, E.; Young, W. B. Synthesis of (±)-ferruginine and (±)-anhydroecgonine methyl ester by a tandem cyclopropanation/Cope rearrangement. *J. Org. Chem.* **1991**, *56*, 5696−5700.

(7) For other approaches to tropanes with varied functionality, see: (a) Kozikowski, A. P.; Roberti, M.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. SAR of cocaine: further exploration of structural variations at the C-2 center provides compounds of subnanomolar potency. *Biorg. Med. Chem. Lett.* **1993**, *3*, 1327−1332. (b) Kozikowski, A. P.; Xiang, L.; Tanaka, J.; Bergmann, J. S.; Johnson, K. M. Use of nitrile oxide cycloaddition (NOC) chemistry in the synthesis of cocaine analogs; mazindol binding and dopamine uptake studies. *Med. Chem. Res.* **1991**, *1*, 312−321. (c) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. Structure-activity relationship studies of cocaine: replacement of the C-2 ester group by vinyl argues against H-bonding and provides an esterase-resistant high-affinity cocaine analogue. *J. Med. Chem.* **1992**, *35*, 4764−4766. (d) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. Synthesis, cocaine receptor affinity, and dopamine uptake inhibition of several new 2β-substituted 3β-phenyl tropanes. *J. Med. Chem.* **1994**, *37*, 3875−3877. (e) Carroll, F. I.; Gary, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. 3-Aryl-2-(3′-substituted-1′,2′,4′,-oxadiazol-5′-yl)tropane analogues of cocaine: affinities at the cocaine binding site at the dopamine, serotonin and norepinephrine transporters. *J. Med. Chem.* **1993**, *36*, 2886−2890.

(8) (a) Porrino, L. J.; Migliarese, K.; Davies, H. M. L.; Saikali, E.; Childers, S. R. Behavioral effects of the novel tropane analog, 2β-propanoyl-3β-(4-tolyl)tropane (PTT). *Life Sci.* **1994**, *54*, 511−517. (b) Hemby, S. E.; Co, C.; Reboussin, D.; Davies, H. M. L.; Dworkin, S. I.; Smith, J. E. Comparison of a novel tropane analog of cocaine, 2β-propanoyl-3β-(4-tolyl)tropane (PTT) with cocaine HCl in rats: Nucleus accumbens extracellular dopamine concentration and motor activity. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 1176−1186. (c) Porrino, L. J.; Davies, H. M. L.; Childers, S. R. Behavioral and local cerebral metabolic effects of the novel tropane analog, 2β-propanoyl-3β-(4-tolyl)tropane (PTT). *J. Pharmacol. Exp. Ther.* **1995**, *272*, 901.

(9) (a) Carroll, F. I.; Abraham, P.; Lewin, A. H.; Parham, K. A.; Boja, J. W.; Kuhar, M. J. Isopropyl and phenyl esters of 3β-(4-substituted phenyl)tropane-2β-carboxylic acids. Potent and selective compounds for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 2497−2500. (b) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogues. New high affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, *38*, 379−388.

(10) Boja, J. W.; Kuhar, M. J.; Kopaltic, T.; Yang, E.; Abraham, E.; Lewin, A. H.; Carroll, F. I. Secondary amine analogues of 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester and N-norcocaine exhibit enhanced affinity for serotonin and norepinephrine transporters. *J. Med. Chem.* **1994**, *37*, 1220−1223.

(11) (a) Baldwin, S. W.; Jeffs, P. W.; Natarajan, S. Preparation of norcocaine. *Synth. Commun.* **1977**, *7*, 79−84. (b) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-phenyltropane analogs of cocaine: Synthesis, inhibition of binding at cocaine recogition sites, and positron emission tomography imaging. *J. Med. Chem.* **1993**, *36*, 855−862.

(12) Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. I. [^3H] Cocaine binding sites in caudate-putamen. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 132−141.

(13) Cheng, Y.-C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor that causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099.

(14) Giros, B.; El Mestikawy, S.; Godinot, N.; Zheng, K.; Han, H.; Yang-Fen, T.; Caron, M. G. Cloning, pharmacological characterization, and chromosome arrangement of the human dopamine transporter. *Mol. Pharmacol.* **1992**, *42*, 383−390.

JM9600508