

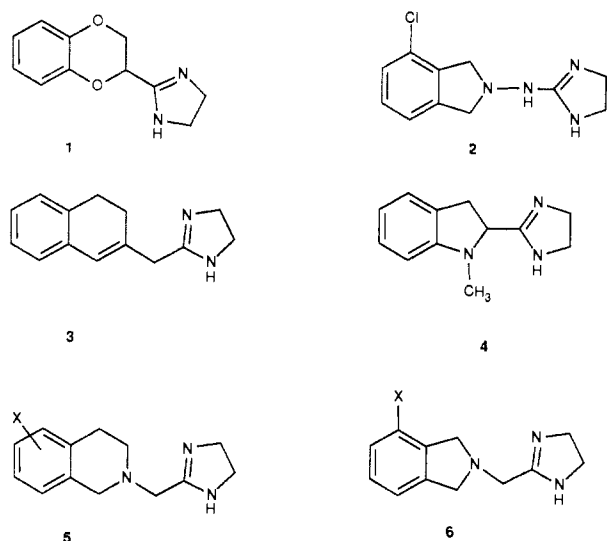
# Affinity of 2-(Tetrahydroisoquinolin-2-ylmethyl)- and 2-(Isoindolin-2-ylmethyl)imidazolines for $\alpha$ -Adrenoceptors. Differential Affinity of Imidazolines for the [ $^3\text{H}$ ]Idazoxan-Labeled $\alpha_2$ -Adrenoceptor vs the [ $^3\text{H}$ ]Yohimbine-Labeled Site<sup>1</sup>

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A series of 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines were prepared and tested for  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor affinity with radioligand binding. Several compounds, 5-fluoro- (5h), 5-chloro- (5j), 5,8-dimethoxy- (5r), and 5,8-dimethoxy-1-methyl- (5s) 2-(tetrahydroisoquinolin-2-ylmethyl)imidazoline, were found to be selective  $\alpha_2$ -adrenoceptor ligands on the basis of displacement of [ $^3\text{H}$ ]yohimbine from rat cerebral cortical membranes. One compound, 2-[(8-chloro tetrahydroisoquinolin-2-yl)methyl]imidazoline (5m), showed a 36-fold difference in affinity for the [ $^3\text{H}$ ]idazoxan-labeled  $\alpha_2$ -adrenoceptor relative to the [ $^3\text{H}$ ]yohimbine-labeled site, which may be evidence for  $\alpha_2$ -adrenoceptor subtypes.

The synthesis and pharmacological evaluation of selective  $\alpha_2$ -adrenoceptor antagonists remains an active area of research.<sup>2</sup> Such selective antagonists will be of use in defining the functional roles of  $\alpha_2$ -adrenoceptors and may ultimately be of therapeutic use, e.g. for the treatment of depression.<sup>3</sup> A number of imidazoline derivatives have been reported to be  $\alpha_2$ -adrenoceptor antagonists with various degrees of selectivity for the  $\alpha_2$  as opposed to the  $\alpha_1$ -adrenoceptor.<sup>2</sup> Among these are the benzodioxane idazoxan (1),<sup>4</sup> the isoindoline BDF-6143 (2),<sup>5</sup> the di-

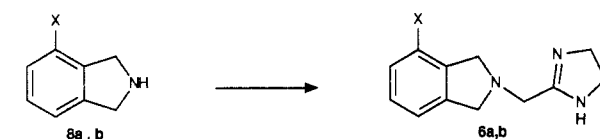
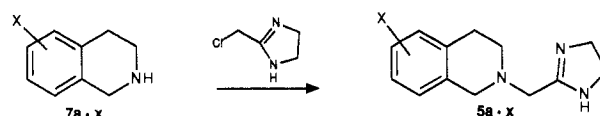


hydronaphthalene napamezole (3),<sup>6</sup> and the indoline 4.<sup>7</sup> On the basis of their structural similarities with some of these agents, we were interested in evaluating 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines (5 and 6,<sup>8</sup> respectively) as  $\alpha_2$ -adrenoceptor antagonists. Reported herein are the results of structure-affinity relationship studies based on ligand-binding methodology which indicate that a number of these compounds are selective, high affinity  $\alpha_2$ -adrenoceptor ligands and that several may differentiate between subtypes of the  $\alpha_2$ -adrenoceptor.

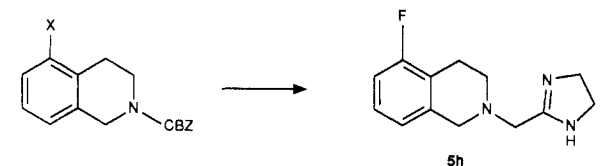
## Chemistry

The 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines 5a-x and 6a,b were prepared by condensation of tetrahydroisoquinolines 7a-x and isoindolines 8a,b, respectively, with 2-(chloromethyl)-

## Scheme I



## Scheme II



9 X = NO<sub>2</sub>

10 X = NH<sub>2</sub>

11 X = F

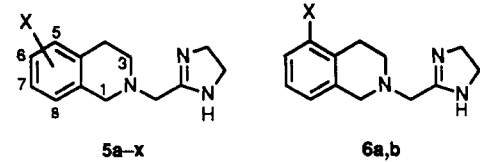
imidazoline<sup>9</sup> (Scheme I). The requisite 1,2,3,4-tetrahydroisoquinolines 7a-x either were known compounds, 7b,<sup>10</sup> 7f,<sup>11</sup> 7i,l-p,<sup>12</sup> 7q,<sup>13</sup> 7r,<sup>14</sup> 7t,<sup>15</sup> 7u,<sup>16</sup> 7v,<sup>17</sup> and 7w,<sup>18</sup> or

- (1) Contribution No. 762 from the Institute of Organic Chemistry.
- (2) Clark, R. D.; Michel, A. D.; Whiting, R. L. *Prog. Med. Chem.* 1986, 23, 2.
- (3) Pinder, R. M. *Drugs Future* 1985, 10, 841.
- (4) Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Doxey, J. C.; Roach, A. G.; Smith, C. F. C. *J. Med. Chem.* 1983, 26, 823.
- (5) Armah, I. B.; Ferry, D. R.; Glossmann, H. *Br. J. Pharmacol.* 1983, 78 (Suppl.), 151P.
- (6) Wentland, M. P.; Bailey, D. M.; Alexander, E. J.; Castaldi, M. J.; Ferrari, R. A.; Haubrich, D. R.; Luttinger, D. A.; Perrone, M. H. *J. Med. Chem.* 1987, 30, 1482.
- (7) (a) Hlasta, D. J.; Luttinger, D.; Perrone, M. H.; Silbernagel, M. J.; Ward, S. J.; Haubrich, D. R. *J. Med. Chem.* 1987, 30, 1555. (b) Fagan, G. P.; Chapleo, C. B.; Lane, A. C.; Myers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* 1988, 31, 944.
- (8) Compounds of formula 6 have independently been the subject of several patent applications: GB Appl. 85-29, 546, 1985. Also see: *Chem. Abstr.* 1987, 107, 176037j.
- (9) Anilkumar, P. P.; Bauer, L. *J. Heterocycl. Chem.* 1966, 3, 472.
- (10) Seebach, D.; Yoshifuji, M. *Helv. Chim. Acta* 1981, 64, 643.
- (11) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* 1984, 32, 2421.
- (12) Bondinell, W. E.; Chapin, F. W.; Girard, G. R.; Kaiser, C.; Krog, A. J.; Pavloff, A. M.; Lam, B. L.; Wellman, G. R.; Pendelton, R. G. *J. Med. Chem.* 1980, 23, 506.

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Table I. Physical Properties and Ligand Binding Data



compd	X	% yield <sup>b</sup>	mp, °C	formula <sup>c</sup>	rat cerebral cortex radioligand binding, pK <sub>i</sub>			selectivity ratio <sup>d</sup> ( $\alpha_2/\alpha_1$ )	ratio I/Y <sup>e</sup>
					[ <sup>3</sup> H]prazosin ( $\alpha_1$ )	[ <sup>3</sup> H]yohimbine ( $\alpha_2$ )	[ <sup>3</sup> H]idazoxan ( $\alpha_2$ )		
5a	H	84	250–254	C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> ·2HCl	5.67	6.32 ± 0.10	7.77 ± 0.11	5	28
5b	1-CH <sub>3</sub>	34	225–228	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> ·2HCl·0.25H <sub>2</sub> O	5.14	7.19 ± 0.09	7.32 ± 0.07	110	1
5c	1-C <sub>2</sub> H <sub>5</sub>	35	indef	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> ·2HCl <sup>f</sup>	<5	6.16 ± 0.05	6.31 ± 0.06	14	1
5d	1-allyl	23	135–137	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> ·2HCl·0.5H <sub>2</sub> O	<5	5.97	6.41 ± 0.03	9	3
5e	1,1-(CH <sub>3</sub> ) <sub>2</sub>	42	220–223	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> ·2HCl	<5	6.00	6.68 ± 0.05	10	5
5f	3-CH <sub>3</sub>	10	210–213	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> ·2HCl <sup>g</sup>	<5	6.90 ± 0.12	7.38 ± 0.15	80	3
5g	5-CH <sub>3</sub>	20	240–241	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> ·2HCl	5.26	6.57 ± 0.15	7.38 ± 0.10	20	6
5h	5-F	22	245–248	C <sub>13</sub> H <sub>16</sub> FN <sub>3</sub> ·2HCl·0.5H <sub>2</sub> O	5.55	7.48 ± 0.12	8.39 ± 0.08	86	8
5i	8-F	50	214–216	C <sub>13</sub> H <sub>16</sub> FN <sub>3</sub> ·2HCl	5.50	7.25 ± 0.07	8.27 ± 0.09	56	10
5j	5-Cl	12	233–234	C <sub>13</sub> H <sub>16</sub> ClN <sub>3</sub> ·2HCl	5.68	7.65 ± 0.08	7.80 ± 0.20	93	1
5k	5-Cl, 1-CH <sub>3</sub>	7	220–221	C <sub>14</sub> H <sub>18</sub> ClN <sub>3</sub> ·2HCl·H <sub>2</sub> O	5.20	6.74 ± 0.08	7.62 ± 0.12	35	8
5l	6-Cl	44	238–239	C <sub>13</sub> H <sub>16</sub> ClN <sub>3</sub> ·2HCl·0.5H <sub>2</sub> O	<5	6.18	6.83 ± 0.13	15	4
5m	8-Cl	55	220–222	C <sub>13</sub> H <sub>16</sub> ClN <sub>3</sub> ·2HCl	5.80	6.67 ± 0.14	8.23 ± 0.08 <sup>h</sup>	7	36
5n	5,8-(Cl) <sub>2</sub>	34	234–237	C <sub>13</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> ·2HCl	5.50	7.14 ± 0.09	8.12 ± 0.06	44	10
5o	5,6-(Cl) <sub>2</sub>	57	247–248	C <sub>13</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> ·2HCl	<5	6.42 ± 0.18	7.67 ± 0.16	26	18
5p	7,8-(Cl) <sub>2</sub>	45	221–222	C <sub>13</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> ·2HCl	<5	6.52 ± 0.10	7.68 ± 0.09	33	14
5q	5-OCH <sub>3</sub>	56	240–241	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> O·2HCl·H <sub>2</sub> O	4.72	7.07 ± 0.07	8.00 ± 0.04	225	9
5r	5,8-(OCH <sub>3</sub> ) <sub>2</sub>	31	232–235	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl·0.5H <sub>2</sub> O	4.80	7.51 ± 0.13	7.80 ± 0.10	502	2
5s	5,8-(OCH <sub>3</sub> ) <sub>2</sub> , 1-CH <sub>3</sub>	76	270–272	C <sub>16</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl	5.19	7.71 ± 0.11	7.02 ± 0.10	332	0.2
5t	5,6-(OCH <sub>3</sub> ) <sub>2</sub>	10	235–236	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl·H <sub>2</sub> O	<5	6.44 ± 0.21	6.24 ± 0.05	28	0.6
5u	6,7-(OCH <sub>3</sub> ) <sub>2</sub>	51	239–240	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl·H <sub>2</sub> O	<5	5.87	6.13 ± 0.29	7	2
5v	6,8-(OCH <sub>3</sub> ) <sub>2</sub>	45	232–233	C <sub>15</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl·0.5H <sub>2</sub> O	<5	6.29	7.20 ± 0.11	20	8
5w	5-NO <sub>2</sub>	41	250–252	C <sub>13</sub> H <sub>16</sub> N <sub>3</sub> O <sub>2</sub> ·2HCl·0.5H <sub>2</sub> O	<5	6.13	7.14 ± 0.21	13	10
5x	5-NH <sub>2</sub>	66	248–250	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> ·3HCl·H <sub>2</sub> O <sup>j</sup>	<5	6.17	6.99 ± 0.14	15	7
6a	H	10	220–224	C <sub>12</sub> H <sub>16</sub> N <sub>3</sub> ·2HCl·0.5H <sub>2</sub> O	5.43	6.91 ± 0.08	8.07 ± 0.08	30	14
6b	Cl	28	231–233	C <sub>12</sub> H <sub>14</sub> ClN <sub>3</sub> ·2HCl	6.05	7.71 ± 0.05	8.38 ± 0.10	46	5
idazoxan					6.10 ± 0.08	7.96 ± 0.04 <sup>k</sup>	8.12 ± 0.05 <sup>k</sup>	72	1
yohimbine					6.40 ± 0.03	7.90 ± 0.03 <sup>k</sup>	7.25 ± 0.07 <sup>k</sup>	32	0.2
rauwolscine						8.15 ± 0.10	7.09 ± 0.07		0.1

<sup>a</sup> Values represent means of three separate determinations ( $n = 3$ ) with SEM unless otherwise noted. Values without SEM are means of two determinations ( $n = 2$ ). <sup>b</sup> Yield refers to the last step in each reaction sequence. <sup>c</sup> Elemental analyses were within 0.4% of theory unless otherwise noted. <sup>d</sup> Antilog of the [<sup>3</sup>H]yohimbine pK<sub>i</sub> minus the [<sup>3</sup>H]prazosin pK<sub>i</sub>. For [<sup>3</sup>H]prazosin pK<sub>i</sub> of less than 5, a pK<sub>i</sub> of 5 was used to calculate the selectivity ratio. <sup>e</sup> Antilog of the [<sup>3</sup>H]idazoxan pK<sub>i</sub> minus the [<sup>3</sup>H]yohimbine pK<sub>i</sub>. <sup>f</sup> C: calcd, 56.97; found, 57.46. <sup>g</sup> C: calcd, 55.63; found, 53.30. <sup>h</sup>  $n = 5$ . <sup>i</sup> N: calcd, 16.37; found, 15.95. <sup>j</sup> C: calcd, 43.65; found, 46.72. <sup>k</sup>  $n = 4$ .

were prepared by standard literature procedures, **7c–e** (alkylation of 2-(bis(dimethylamino)phosphino)-1-lithio-1,2,3,4-tetrahydroisoquinoline<sup>10</sup>), **7g,k,s**<sup>19</sup> (Bischler–Napieralski cyclization<sup>20</sup> followed by sodium borohydride reduction), and **7i** (intramolecular Friedel–Crafts alkylation<sup>21</sup>). The 5-fluoro compound (**5h**) was prepared as shown in Scheme II. The diazonium tetrafluoroborate, prepared from aniline **10** by the boron trifluoride-*tert*-butyl nitrite method,<sup>22</sup> decomposed upon storage at room temperature to give the intermediate fluoro compound **11**. Amino derivative **5x** was prepared by catalytic hydrogenation of **5w**.

Isoindolines **10a,b** were prepared by reduction of the corresponding phthalimides with borane–methyl sulfide.<sup>23</sup>

## Pharmacological Testing

The relative affinities of the imidazolines for  $\alpha$ -adrenoceptors were determined by measurement of radioligand displacement from rat cerebral cortical membrane binding sites. [<sup>3</sup>H]Yohimbine and [<sup>3</sup>H]prazosin were used to label  $\alpha_2$ - and  $\alpha_1$ -adrenoceptors, respectively, and for determination of  $\alpha_2/\alpha_1$  selectivity ratios. The ability of compounds to displace the imidazoline ligand [<sup>3</sup>H]idazoxan from rat cerebral cortical  $\alpha_2$ -adrenoceptors was also determined. The results are presented in Table I.

## Results and Discussion

**Structure–Affinity Relationships Based on  $\alpha_1$ -Adrenoceptor Affinity Assessed by [<sup>3</sup>H]Prazosin Binding and  $\alpha_2$ -Adrenoceptor Affinity Based on [<sup>3</sup>H]Yohimbine Binding.** None of the imidazolines in Table I were potent displacers of [<sup>3</sup>H]prazosin from  $\alpha_1$ -adrenoceptors and only one compound (**6b**) had a pK<sub>i</sub> value of greater than 6.<sup>24</sup>

In the 2-(tetrahydroisoquinolin-2-ylmethyl)imidazoline series (**5a–x**) it was found that while the parent compound

- (13) Durand, S.; Lusinchi, X.; Moreau, R. C. *Bull. Chim. Soc. Fr.* 1961, 270.  
 (14) Goldstein, M.; Saito, M.; Lew, J. Y.; Pendelton, R. G. *Eur. J. Pharmacol.* 1980, 67, 305.  
 (15) 5,6-Dimethoxy-3,4-dihydroisoquinoline: Haworth, R. D. *J. Chem. Soc.* 1927, 2281.  
 (16) Aldrich Chemical Co.  
 (17) Mata, R.; Chang, C. J.; McLaughlin, J. L. *Phytochem.* 1983, 22, 1263.  
 (18) Rao, K. V.; Jackman, D. J. *Heterocycl. Chem.* 1973, 10, 213.  
 (19) The dihydroisoquinoline is known: Sugawara, S.; Shigehara, H. *Chem. Ber.* 1941, 74, 459.  
 (20) Whaley, W. M.; Grovindachari, T. R. *Org. React.* 1951, 6, 74.  
 (21) Mendelson, W. L.; Spainhour, C. B.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* 1980, 21, 1393.  
 (22) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* 1979, 44, 1572.

- (23) Dubois, R. J.; Lin, C. L.; Beisler, J. A. *J. Med. Chem.* 1978, 21, 303.  
 (24) Compound **8b** was subsequently found to be a partial  $\alpha_1$ -agonist in functional assays (contraction of rabbit aortic strip) and to elevate blood pressure directly in pithed rats. Partial  $\alpha_1$ -agonist activity has been reported for idazoxan (**1**) and BDF-6143 (**2**), ref 2 and citations therein, and for compound **4**, ref 7b.

**5a** had a low affinity for the [<sup>3</sup>H]yohimbine-labeled  $\alpha_2$ -adrenoceptor, substituted analogues were considerably more active. Substitution at C-1 with methyl gave a higher affinity compound (**5b**), but larger groups (**5c,d**), 1,1-disubstitution (**5e**), or moving the methyl group to C-3 was detrimental (**5f**). In the aromatic ring, C-5 appeared to be particularly amenable to substitution with fluorine (**5h**), chlorine (**5j**), and to a lesser degree with methoxy (**5q**). Among the disubstituted analogues, substitution at C-5 and C-8 was beneficial in the dimethoxy case (**5r**), although less so in the dichloro compound (**5n**). Any substitution involving C-6 and/or C-7 was clearly not tolerated relative to the C-5 and C-5,8 substituted examples (e.g., **5j** vs **5o**, **5r** vs **5v**). Substitution of methyl at C-1 of the two highest affinity compounds, **5j** and **5r**, was carried out to determine if the enhancement in affinity seen in going from **5a** to **5b** was general. However, while the derived **5s** was of higher affinity than the related **5r**, the trend was the opposite in the chloro case as **5k** was over a log order less active than **5j**. In terms of  $\alpha_2/\alpha_1$  selectivity within this series, the general trend among the C-1 and substituted aromatic derivatives of **5a** was toward increased  $\alpha_2$ -selectivity due to increased  $\alpha_2$ -affinity with a concomitant maintenance (e.g., **5j**) or decrease in  $\alpha_1$ -affinity (e.g., **5r,s**). The highest affinity compound in the series, **5s**, was approximately  $1/2$  as active as idazoxan in the ligand binding assay while displaying a 5-fold-enhanced selectivity for the [<sup>3</sup>H]yohimbine-labeled  $\alpha_2$ -adrenoceptor.

In the 2-(isoinidolin-2-ylmethyl)imidazoline series, 4-chloro derivative **6b** (which corresponds to 5-chlorotetrahydroisoquinoline **5j**) was also of higher affinity than the parent (**6a**). However, this compound was less selective for the  $\alpha_2$ -adrenoceptor than the tetrahydroisoquinoline analogues.

**$\alpha_2$ -Adrenoceptor Affinity Assessed by [<sup>3</sup>H]Idazoxan Binding.** Although many of the compounds had essentially similar potency displacing [<sup>3</sup>H]idazoxan and [<sup>3</sup>H]yohimbine, there were also marked discrepancies with ratios of  $pK_i$  values (Table I, I/Y), ranging from 0.2 (yohimbine selective) to 36 (idazoxan selective). Some of the compounds were very potent in displacing [<sup>3</sup>H]idazoxan, and seven compounds (**5h**, **5i**, **5m**, **5n**, **5q**, **6a**, **6b**) had  $pK_i$  values greater than or equal to 8. In contrast, the most potent ligands in displacing [<sup>3</sup>H]yohimbine (**5s**, **6b**) had  $pK_i$  values of 7.71. In this series the affinity for [<sup>3</sup>H]idazoxan appeared to relate more to functional effectiveness as an  $\alpha_2$ -adrenoceptor antagonist, e.g., **6b** was found to have a  $pA_2$  value of 8.5 as an antagonist of the  $\alpha_2$ -selective agonist UK14304 in the guinea pig ileum. The most [<sup>3</sup>H]idazoxan-selective agent (**5m**, I/Y ratio = 36) had a  $pA_2$  value of 8.2 in this preparation,<sup>25</sup> which was identical with the  $pK_i$  value.

Relative structure-affinity relationships (SAR) based on [<sup>3</sup>H]idazoxan binding were also somewhat different from those based on [<sup>3</sup>H]yohimbine displacement. For example, the enhancement of affinity upon 1-methylation ([<sup>3</sup>H]yohimbine binding) was reversed in several cases (e.g., **5a** vs **5b**, **5r** vs **5s**) based on [<sup>3</sup>H]idazoxan binding. Among the chlorinated 2-(tetrahydroisoquinolin-2-ylmethyl)imidazolines, the 8-substituted isomers (**5m**, **5n**, **5p**) showed a 14–36-fold enhancement in [<sup>3</sup>H]idazoxan binding as compared to virtually no enhancement for the 5-chloro isomer (**5i**). There thus appear to be differences in the selectivity of certain of these imidazolines for the sites

labeled by [<sup>3</sup>H]idazoxan and [<sup>3</sup>H]yohimbine.<sup>26</sup>

On the basis of extensive SAR studies, three major binding sites were proposed for idazoxan type compounds at the  $\alpha_2$ -adrenoceptor.<sup>27</sup> These were a planar hydrophobic area that interacts with the benzene ring, a site which binds one or both of the benzodioxane oxygens, and an imidazoline binding site which is presumably anionic in nature. Aromatic substitution was not tolerated. The ability of the 2-position of idazoxan to accommodate alkyl and methoxy groups with an enhancement in  $\alpha_2$ -affinity has also suggested either an additional binding site or a preferential skewed pseudoequatorial orientation of the imidazoline ring.<sup>27</sup> 2-(Tetrahydroisoquinolin-2-ylmethyl)imidazoline (**5**) fits this model in a general sense with the proviso that either the benzodioxane oxygen binding site is not accommodated or the nitrogen of the tetrahydroisoquinoline binds to this site. However, series **5** differs in that aromatic substitution is allowable for significant binding to the  $\alpha_2$ -adrenoceptor labeled by either [<sup>3</sup>H]yohimbine or [<sup>3</sup>H]idazoxan. This suggests that the additional methylene spacer between the tetrahydroisoquinoline and the imidazoline rings may induce these compounds to bind in a somewhat different manner than idazoxan.

## Conclusion

Previously, both [<sup>3</sup>H]yohimbine and [<sup>3</sup>H]idazoxan have been used as radioligands to define  $\alpha_2$ -adrenoceptor affinity. However, there have been suggestions that there may be different subtypes of  $\alpha_2$ -adrenoceptors.<sup>28–32</sup> On the basis of autoradiographic<sup>31</sup> and pharmacological<sup>32</sup> studies, [<sup>3</sup>H]rauwolscine, an isomer of yohimbine, and [<sup>3</sup>H]idazoxan appear to label different areas of rat brain. This evidence indicates that [<sup>3</sup>H]idazoxan and [<sup>3</sup>H]rauwolscine label a heterogeneous population of  $\alpha_2$ -adrenoceptors.<sup>31–32</sup> It was therefore of interest that the imidazolines reported herein showed a wide spectrum of selectivity ratios in displacing [<sup>3</sup>H]yohimbine and [<sup>3</sup>H]idazoxan from rat cerebral cortex with a rank order of potencies different for the two ligands. This is consistent with the concept that these compounds may have different affinities for subtypes of the  $\alpha_2$ -adrenoceptor, although we cannot exclude the possibility that [<sup>3</sup>H]yohimbine and [<sup>3</sup>H]idazoxan bind at different sites, or affinity states, of a single receptor. Further detailed studies with the most selective compounds may resolve this issue. Nevertheless, this report shows that compounds may have differential affinities

(25) Compound **5m** was also found to be a partial  $\alpha_2$ -adrenoceptor agonist in the guinea pig ileum, but only at high concentrations (1  $\mu$ M, 50% inhibition of electrically evoked contractions at 9  $\mu$ M).

(26) The observed  $pK_i$  differences did not appear to result from the different buffers used in the  $\alpha_2$ -adrenoceptor binding assays (Tris HCl, pH 7.4 for [<sup>3</sup>H]yohimbine binding; physiological salt solution, pH 7.4, for [<sup>3</sup>H]idazoxan binding). For example, in the [<sup>3</sup>H]idazoxan binding assay using physiological buffer,  $pK_i$  values of  $7.25 \pm 0.07$  and  $8.12 \pm 0.05$  were determined for the standards yohimbine and idazoxan, respectively, compared with values of  $7.36 \pm 0.10$  and  $8.09 \pm 0.10$ , respectively, in the Tris HCl buffer. In the same assay, **5m** had  $pK_i$  values of  $8.23 \pm 0.08$  in the physiological buffer and  $8.55 \pm 0.15$  in the Tris HCl buffer.

(27) Stillings, M. R.; Chapleo, C. B.; Butler, R. C.; Davis, J. A.; England, C. D.; Myers, M.; Myers, P. L. Tweddle, N.; Welbourn, A. P.; Doxey, J. C.; Smith, C. F. C. *J. Med. Chem.* 1985, 28, 1054.

(28) Vici, E. S. *Med. Res. Rev.* 1986, 6, 431.

(29) Bylund, D. B. *Pharmacol. Biochem. Behav.* 1985, 22, 835.

(30) Nahorski, S. R.; Barnett, D. B.; Cheung, Y. D. *Clin. Sci.* 1985, 10, 39s–42s.

(31) Boyajian, C. L.; Loughlin, S. E.; Leslie, F. M. *J. Pharmacol. Exp. Ther.* 1987, 241, 1079.

(32) Boyajian, C. L.; Leslie, F. M. *J. Pharmacol. Exp. Ther.* 1987, 241, 1092.

in displacing two ligands which are thought to label the  $\alpha_2$ -adrenoceptor.

### Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were recorded for all compounds with Varian A-60 or Bruker WM 300 instruments and were consistent with the assigned structures. Microanalyses were performed by the Syntex Analytical Department and, where analyses are indicated only by symbols of the elements, results obtained were within  $\pm 0.4\%$  of the theoretical values.

**General Procedure for the Preparation of 5a-x and 6a,b.** 2-[(1,2,3,4-Tetrahydro-5,8-dimethoxy-1-methylisoquinolin-2-yl)methyl]-4,5-dihydro-1H-imidazole Dihydrochloride (5s). Isoquinoline 7s was prepared by Bischler-Napieralski cyclization of *N*-acetyl-2,5-dimethoxyphenethylamine (phosphorus oxychloride, acetonitrile, 60 °C)<sup>20</sup> followed by  $\text{NaBH}_4$  reduction (27%): HCl salt, mp 229–230 °C. A mixture of isoquinoline 7s (5.3 g, 26 mmol), 2-(chloromethyl)imidazoline hydrochloride<sup>9</sup> (4.65 g, 30 mmol), and *N,N*-diisopropylethylamine (10 mL, 60 mmol) in 30 mL of dichloromethane was stirred at room temperature for 12 h. The mixture was added to water and extracted with dichloromethane and the extract was evaporated. After addition of toluene, solvents were removed in vacuo and this procedure was repeated twice to remove *N,N*-diisopropylethylamine. The residue was dissolved in hot ethanol and the resulting hot solution was filtered with charcoal and acidified with ethanolic HCl. The product crystallized upon cooling the solution to room temperature and filtration afforded 7.0 g (76%) of 5s: mp 270–272 °C; NMR ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.38 (d,  $J = 7$  Hz, 3 H), 2.78 (m, 2 H), 3.10 (m, 1 H), 3.28 (m, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.90 (s, 4 H), 3.92 (AB quartet,  $J = 15$  Hz, 2 H), 4.18 (q,  $J = 7$  Hz, 1 H), 6.85 (s, 2 H), 10.5 (br s, 2 H, exchanges with  $\text{D}_2\text{O}$ ).

2-[(4-Chloro-1,3-dihydro-2H-isoindol-2-yl)methyl]-4,5-dihydro-1H-imidazole Dihydrochloride (6b). 3-Chlorophthalic anhydride<sup>33</sup> was converted to 3-chlorophthalimide by heating with aqueous  $\text{NH}_4\text{OH}$ .<sup>34</sup> To a solution of the phthalimide (60 g, 0.33 mol) in 1 L of THF was slowly added 100 mL (1 mol) of borane-methyl sulfide complex and the resulting solution was heated under reflux for 12 h. The solution was cooled in an ice bath and treated carefully with 100 mL of 6 M HCl. The mixture was heated under reflux for 2 h, filtered, and concentrated in vacuo. The residue was partitioned between water and ethyl acetate, and the aqueous layer was basified with  $\text{NH}_4\text{OH}$  and extracted 3 $\times$  with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extracts were combined and evaporated to an oil, which was purified by Kugelrohr distillation, bp 80–85 °C (ca. 1 mm), to afford 15.3 g (30%) of 4-chloroisoindoline (8b) as a white solid mp 48–50 °C, which rapidly darkened at room temperature and was stored in a freezer prior to use. This material was converted to 6b as described for the preparation of 5s.

*N*<sup>2</sup>-(Carbobenzyloxy)-5-amino-1,2,3,4-tetrahydroisoquinoline (10). 5-Nitro-1,2,3,4-tetrahydroisoquinoline<sup>18</sup> was converted to the CBz derivative 9 with benzyl chloroformate (ethyl acetate-aqueous  $\text{K}_2\text{CO}_3$ ): mp 68–69 °C; IR 1685  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ ) C, H, N.

To a solution of 9 (7.3 g, 23 mmol) in 55 mL of acetic acid was added a solution of stannous chloride dihydrate (20 g, 89 mmol) in 25 mL of 10% HCl, and the resulting homogenous mixture was stirred for 48 h at room temperature. The mixture was poured into a mixture of ice-aqueous NaOH and extracted with ethyl acetate. The ethyl acetate was dried ( $\text{K}_2\text{CO}_3$ ) and evaporated to 6.3 g (97%) of 10: mp 75–81 °C. A small sample was converted to the HCl salt (ethanol-ether): mp 193–194 °C. Anal. ( $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\cdot\text{HCl}$ ) C, H, N.

*N*-(Carbobenzyloxy)-5-fluoro-1,2,3,4-tetrahydroisoquinoline (11).<sup>22</sup> Boron trifluoride etherate (1.1 mL, 8.5 mmol) was cooled to  $-15$  °C and a solution of 10 (1.55 g, 5.5 mmol) in 10 mL of dichloromethane was added. To the slightly cloudy mixture was added *tert*-butyl nitrite (0.8 mL, 6.7 mmol) in 4 mL of dichloromethane over a 10-min period at  $-15$  °C. After the

addition was complete, the clear solution was stirred for 25 min at ca. 3 °C. Pentane (20 mL) was added and a gummy precipitate formed. The mixture was allowed to remain at room temperature for 72 h during which time a slow evolution of gas bubbles was noted. The supernatant was decanted from the now-solid precipitate and evaporated to an oil, which was purified by silica gel chromatography (10% ethyl acetate-hexane) to afford 0.55 g (35%) of 11 as an oil: IR (film) 1695  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  2.82 (m, 2 H), 3.72 (t, 2 H), 4.65 (s, 2 H), 5.12 (s, 2 H), 6.88 (apparent t, 2 H, H-7, H-8), 7.14 (q,  $J = 8, 13.5$  Hz, 1 H, H-6), 7.34 (m, 5 H); MS  $m/e$  285 ( $\text{M}^+$ ), 240, 194, 150, 91.

2-[(5-Fluoro-1,2,3,4-tetrahydroisoquinolin-2-yl)methyl]-4,5-dihydro-1H-imidazole Dihydrochloride (5h). A mixture of 11 (0.5 g, 1.75 mmol) and 10% palladium on carbon (80 mg) in 15 mL of ethanol was hydrogenated at atmospheric pressure for 20 min. The catalyst was filtered off and to the filtrate was added 2-chloromethyl-2-imidazoline hydrochloride<sup>9</sup> (0.3 g, 1.9 mmol) and the resulting mixture was heated under reflux for 16 h. The mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and aqueous  $\text{NH}_4\text{OH}$ . The dichloromethane was evaporated and the residue was purified by silica gel chromatography (5% methanol-dichloromethane, 1%  $\text{NH}_4\text{OH}$ ) to afford 130 mg (32%) of free base 5h: mp 129–130 °C. This was converted to the bis HCl salt with ethanolic HCl: mp 245–248 °C.

**Adrenoceptor Binding Assays. Membrane Preparation.** Male Sprague-Dawley rats (150–200 g) were killed by cervical dislocation; the brains were rapidly removed and dissected on ice. Cerebral cortices were homogenized in 25 volumes of Tris buffer (50 mM Tris HCl, 5 mM EDTA; pH 7.4 at 4 °C) using a polytron PT 10 tissue disrupter. The homogenate was then centrifuged at 38000g for 15 min. The pellet obtained was washed 3 $\times$  by resuspension and centrifugation in Tris assay buffer (50 mM Tris HCl, 0.5 mM EDTA; pH 7.4 at 4 °C). The final pellet was resuspended in assay buffer to a protein concentration of 1.0 mg/mL and stored under liquid nitrogen until required.

**[ $^3\text{H}$ ]Yohimbine Binding.** Competition  $\alpha_2$ -adrenoceptor binding assays were performed by incubating washed rat cerebral membranes (500  $\mu\text{g}$  of protein) with 1.5 nM [ $^3\text{H}$ ]yohimbine (New England Nuclear, 80.9 Ci/mmol) in the presence or absence of a range of 12 concentrations of the competing ligand in a total volume of 500  $\mu\text{L}$  of Tris assay buffer (50 mM Tris HCl, 0.5 mM EDTA; pH 7.4 at 25 °C). Nonspecific binding was defined as the concentration of bound ligand in the presence of 10  $\mu\text{M}$  phentolamine. Specific binding represented  $\sim 70\%$  of total binding at 1.5 nM [ $^3\text{H}$ ]yohimbine. Following equilibrium (30 min at 25 °C), bound radioactivity was separated from free by filtration through a Brandel cell harvester. Bound radioactivity on the glass-fiber filters was determined by liquid-scintillation counting.

**[ $^3\text{H}$ ]Idazoxan Binding.** EDTA-free membrane preparations were incubated with 1 nM [ $^3\text{H}$ ]idazoxan (Amersham, 58 Ci/mmol) to equilibrium (30 min) at 25 °C in a final volume of 0.5 mL. The incubations were performed in a physiological salt solution: 118 mM NaCl, 4.7 mM KCl, 1.2 mM  $\text{MgSO}_4$ , 1.2 mM  $\text{KH}_2\text{PO}_4$ , 25 mM  $\text{NaHCO}_3$ , 1.3 mM  $\text{CaCl}_2$ ; pH 7.4; 25 °C. Nonspecific binding was determined using 3  $\mu\text{M}$  phentolamine and represented  $\sim 40\%$  of total binding.

**[ $^3\text{H}$ ]Prazosin Binding.** EDTA-washed membranes (250  $\mu\text{g}$ ) were incubated with 0.5 nM [ $^3\text{H}$ ]prazosin (New England Nuclear 85 Ci/mmol) for 30 min at 25 °C in Tris buffer (50 mM pH 7.4, 0.5 mM EDTA) in a volume of 0.5 mL. Nonspecific binding was defined by 10  $\mu\text{M}$  phentolamine and represented  $\sim 15\%$  of total binding.

Inhibition of specific ligand binding by the test compound was analyzed graphically to estimate the  $\text{IC}_{50}$  (concentration of test compound that displaced 50% specific binding). The inhibitory constant ( $K_i$ ) was calculated from the  $\text{IC}_{50}$  using the equation of Cheng and Prusoff.<sup>35</sup> Hill coefficients were essentially equal to unity for all compounds tested.

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(33) Newman, M. S.; Scheurer, P. G. *J. Am. Chem. Soc.* 1956, 78, 5004.

(34) Noyes, W. A.; Porter, P. K. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, 457.

(35) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* 1973, 22, 3099.

chemistry and Lani Russell and Nicole Grindler for preparing the manuscript.

**Registry No.** 5a, 110706-41-7; 5a·2HCl, 123621-18-1; 5b, 123593-76-0; 5b·2HCl, 123594-09-2; 5c, 123593-77-1; 5c·2HCl, 123594-10-5; 5d, 123593-78-2; 5d·2HCl, 123594-11-6; 5e, 123593-79-3; 5e·2HCl, 123594-12-7; 5f, 123593-80-6; 5f·2HCl, 123594-13-8; 5g, 123593-81-7; 5g·2HCl, 123594-14-9; 5h, 123593-82-8; 5h·2HCl, 123594-15-0; 5i, 123593-83-9; 5i·2HCl, 123594-16-1; 5j, 123593-84-0; 5j·2HCl, 123594-17-2; 5k, 123593-85-1; 5k·2HCl, 123594-18-3; 5l, 123593-86-2; 5l·2HCl, 123594-19-4; 5m, 123593-87-3; 5m·2HCl, 123594-20-7; 5n, 123593-88-4; 5n·2HCl, 123594-21-8; 5o, 123593-89-5; 5o·2HCl, 123594-22-9; 5p, 123593-90-8; 5p·2HCl, 123621-19-2; 5q, 123593-91-9; 5q·2HCl, 123594-23-0; 5r, 123593-92-0; 5r·2HCl, 123594-24-1; 5s, 123593-93-1; 5s·2HCl, 123594-25-2; 5t, 123593-94-2; 5t·2HCl, 123594-26-3; 5u, 123593-95-3; 5u·2HCl, 123594-27-4; 5v, 123593-96-4; 5v·2HCl, 123594-28-5; 5w,

123593-97-5; 5w·2HCl, 123594-29-6; 5x, 123593-98-6; 5x·3HCl, 123594-30-9; 6a, 110706-35-9; 6a·2HCl, 123594-31-0; 6b, 110706-37-1; 6b·2HCl, 123594-32-1; 7a, 91-21-4; 7b, 4965-09-7; 7c, 25939-81-5; 7d, 87443-63-8; 7e, 41565-85-9; 7f, 29726-60-1; 7g, 123593-99-7; 7h, 123594-00-3; 7i, 123594-01-4; 7j, 73075-43-1; 7k, 123594-02-5; 7l, 33537-99-4; 7m, 75416-50-1; 7n, 89315-57-1; 7o, 75416-53-4; 7p, 61563-24-4; 7q, 103030-70-2; 7r, 76019-13-1; 7s, 123594-03-6; 7s·HCl, 123594-05-8; 7t, 52759-09-8; 7u, 1745-07-9; 7v, 88207-92-5; 7x, 115955-90-3; 8a, 496-12-8; 8b, 123594-04-7; 9, 123594-06-9; 10, 123594-07-0; 10·HCl, 123594-33-2; 11, 123594-08-1; 2-(chloromethyl)-2-imidazoline hydrochloride, 13338-49-3; *N*-acetyl-2,5-dimethoxyphenethylamine, 106274-40-2; 5,8-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 105901-26-6; 3-chlorophthalic anhydride, 117-21-5; 3-chlorophthalimide, 51108-30-6; 5-nitro-1,2,3,4-tetrahydroisoquinoline, 41959-45-9; [<sup>3</sup>H]yohimbine, 146-48-5; [<sup>3</sup>H]idazoxan, 79944-58-4; [<sup>3</sup>H]prazosin, 19216-56-9.

## Aporphines as Antagonists of Dopamine D-1 Receptors

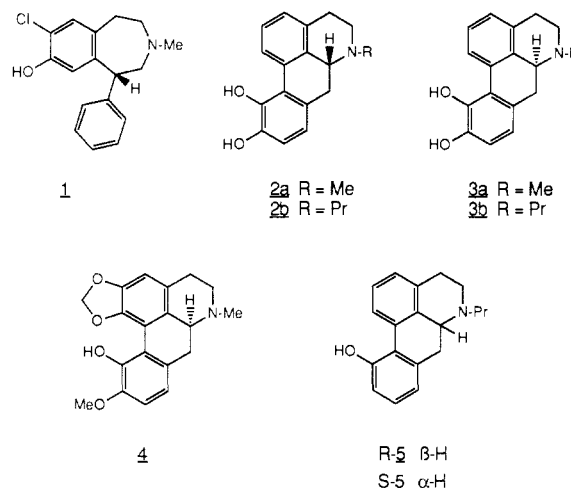
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The aporphine alkaloids are a class of compounds known to possess activity at both D-1 and D-2 dopamine receptors. (*R*)-Apomorphine and (*S*)-bulbocapnine are examples of compounds which have agonist and antagonist activity, respectively, at D-1 receptors. A series of optically pure aporphines was synthesized and their activity at D-1 and D-2 dopamine receptors was studied. The (*R*)-aporphines uniformly had greater affinity for both D-1 and D-2 receptors than their *S* antipodes. Dihydroxy compound (*R*)-apomorphine, in accord with previous studies, was found to be a D-1 agonist. Aporphines possessing a single hydroxy group at C-11 are antagonists at the D-1 receptor. The corresponding methoxy compounds are virtually inactive at dopamine receptors. The most potent compounds, (*R*)-11-hydroxyaporphine (*R*-14) and (*R*)-10-bromo-11-hydroxyaporphine (*R*-26), are more potent than bulbocapnine as D-1 antagonists but are not as selective. A model for binding of aporphines to the D-1 receptor was formulated in which binding interactions between the receptor and the basic nitrogen and the C-11 hydroxy group of the aporphine are required for high-affinity binding to the receptor. The absolute configuration at C-6a determines the orientation of the N-6 lone pair and binding is optimal for the 6a*R* series. The agonist or antagonist activity of an aporphine is determined by the presence or absence, respectively, of a hydroxy group at C-10. A hydrophobic binding site may be present and may account for the high antagonist activity of (*S*)-bulbocapnine.

Studies with dopaminergic agents have led to the identification of two distinct classes of central nervous system (CNS) dopamine receptors, D-1 and D-2. The D-1 receptors are located postsynaptically and are positively linked to adenylate cyclase as its second messenger. In contrast, D-2 receptors are located both pre- and postsynaptically and either are not coupled or are negatively coupled to adenylate cyclase.<sup>1</sup> While much research has concentrated on the function of D-2 receptors in the CNS, until relatively recently, little has been known of the significance of D-1 receptors. The discovery of the D-1 selective antagonist SCH-23390 (1) has greatly facilitated research on the function of D-1 receptors in the CNS.<sup>2</sup>

It is now known that functional interaction exists between D-1 and D-2 receptors in the CNS. In dopamine-depleted mice and rats, administration of either a D-1 or a D-2 agonist alone is ineffective in producing stereotypic behavior and increases in locomotor activity. However, when these agents are given in combination, similar increases in these behavioral indices are seen as when (*R*)-apomorphine (2a), an agonist at both D-1 and D-2 receptors, is given.<sup>3-5</sup> Similarly, climbing behavior in



normal mice identical with that induced by (*R*)-apomorphine is induced by concomitant administration of a D-1 and a D-2 agonist but not by either treatment alone.<sup>6</sup> Locomotor activity and stereotypy induced by either (*R*)-apomorphine or a selective D-1 or D-2 agonist can be blocked by antagonists selective for either D-1 or D-2 receptors.<sup>7</sup>

(1) (a) Leff, S. E.; Creese, I. *Trends Pharm. Sci.* 1983, 4, 463. (b) Stoof, J. C.; Keabian, J. W. *Life Sci.* 1984, 35, 2281.  
(2) Clark, D.; White, F. J. *Synapse* 1987, 1, 347.  
(3) Jackson, D. M.; Hashizume, M. *Psychopharm.* 1986, 90, 147.  
(4) Braun, A. R.; Chase, T. N. *Eur. J. Pharmacol.* 1986, 131, 301.  
(5) Arnt, J.; Bøgesø, K. P.; Hyttel, J.; Meier, E. *Pharmacol. Toxicol.* 1988, 62, 121.

(6) Moore, N. A.; Axton, M. S. *Psychopharmacol.* 1988, 964, 263.  
(7) Molloy, A. G.; O'Boyle, K.; Pugh, M. T.; Waddington, J. L. *Pharmacol. Biochem. Behav.* 1986, 25, 249.