conclude that they are the same on this evidence alone. Structural evidence based on physical and chemical methods is also needed.

These tentative forecasts have two common factors. On the one hand they point toward a new generation of more potent, specific, effective therapeutic agents with less toxicity, reduced side effects, and fewer aberrant responses, which is what people and society at large are seeking. On the other hand, they also point toward more costly research, which is the price that must be paid. Apart from that, one last conclusion seems very probable. Mountaineers climb because the mountains are there and offer them a worthwhile challenge, and scientists will try to design drugs to fit receptors for similar reasons.

Acknowledgment. I thank the Wellcome Foundation at Beckenham, the Laboratory of Molecular Biophysics at Oxford, and all my colleagues for their advice, encouragement, and support. My debt to them is very large, and I am also grateful to the authors who have allowed me to reproduce their figures, and the copyright holders for their permission to do so.

Articles

Biomimetic Approach to Potential Benzodiazepine Receptor Agonists and Antagonists

Filadelfo Guzman,† Michael Cain,† Paul Larscheid,† Tim Hagen,† James M. Cook,*,† Margaret Schweri,‡ Phil Skolnick,‡ and Steven M. Paul§

Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201, Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205, and Clinical Neuroscience Branch, National Institute of Mental Health, Bethesda, Maryland 20205. *Received March 4, 1983*

Several β-carbolines, isoquinolines, imidazopyridines, and canthin-6-ones prepared in biomimetic fashion were tested for their ability to bind to the benzodiazepine receptor. Methyl isoquinoline-3-carboxylate (**3a**), methyl 6,7-dimethoxyisoquinoline-3-carboxylate (**3b**), 1-phenyl-3-carbomethoxyimidazopyridine (**6b**), and canthin-6-one (**13a**) bound with moderate affinities, while 2-carbomethoxycanthin-6-one (**13b**) bound to benzodiazepine receptors with an affinity comparable to several pharmacologically active benzodiazepines. The potency of **13b** suggests that the benzodiazepine receptor(s) can tolerate substitution at positions 1 and 9 of a β-carboline without loss of activity if the substituents are trigonal and maintain a planar topography. Moreover, displacement of the carbonyl group by two atoms (**17**) from the aromatic ring (C) of the β-carboline skeleton caused a marked decrease in binding to the benzodiazepine receptor. This observation supports the hypothesis that maximum binding affinity of β-carbolines is achieved when the carbonyl group at position 3 is attached directly to the aromatic pyridine ring.

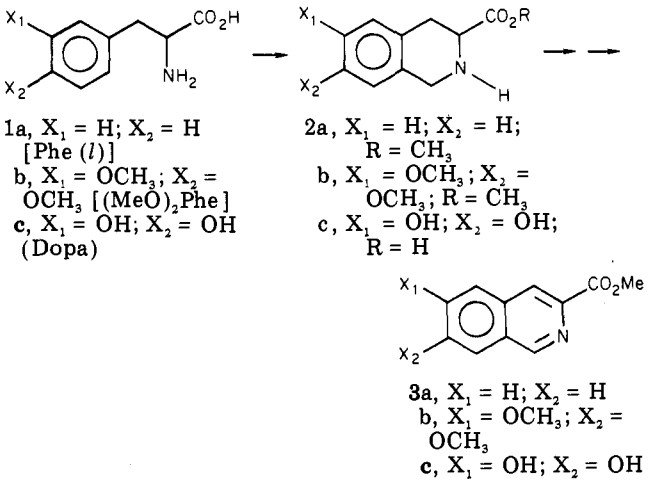
The demonstration of high-affinity, saturable and stereospecific binding sites for benzodiazepines (viz., receptors) in the CNS[1,2] has radically altered concepts of the molecular mechanisms of benzodiazepine action. Benzodiazepines, the most widely prescribed psychoactive drugs in current therapeutic use,[3] exhibit four principle pharmacological actions: anticonvulsant, anxiolytic, muscle relaxant, and sedative effects.[4,5] Evidence for the multiplicity of benzodiazepine receptors has been reported,[6] and by analogy to the progression of events in the opiate–receptor–enkephalin area,[7,8] the first reports that benzodiazepines have selective and specific high-affinity binding sites in the CNS stimulated a search for an "endogenous ligand" that physiologically acts at these receptors.[9,12] Ethyl β-carboline-3-carboxylate (β-CCE) was first identified in human urine[12a] and found to inhibit potently ($K_i \approx 1$ nM) the in vitro binding of [^{3}H]diazepam to brain benzodiazepine receptors. The potent biological activity of this β-carboline led to the hypothesis that β-CCE or a related compound could be an endogenous ligand of the benzodiazepine receptor. However, subsequent reports suggested that β-CCE was formed during the extraction and isolation procedure employed, since identical treatment of many proteins resulted in the formation of

† University of Wisconsin-Milwaukee.
‡ National Institutes of Health.
§ National Institute of Mental Health.

(1) Squires, R. F.; Braestrup, C. *Nature (London)* **1977**, *266*, 732.
(2) Mohler, H.; Okada, T. *Science* **1977**, *198*, 849.
(3) Greenblatt, D. J.; Shader, R. I. "Benzodiazepines in Clinical Practice"; Raven Press: New York, 1974. Williams, M. *J. Med. Chem.* **1983**, *26*, 619.
(4) Randall, L. O.; Kappel, B. In "The Benzodiazepines"; Garattini, S.; Mussini, E.; Randall, L. O. Eds.; Raven Press, New York, 1973; pp 27–51.
(5) Mohler, H.; Okada, T.; Heitz, H. P.; Ulrich, J. *Life Sci.* **1978**, *22*, 985.
(6) Nielsen, M.; Schou, H.; Braestrup, C. *J. Neurochem.* **1981**, *36*, 276.
(7) Pert, C.; Snyder, S. *Science* **1973**, *179*, 1011.
(8) Hughes, J.; Smith, T. W.; Kosterlitz, H. W.; Fothergill, L. A.; Morgan, B. A.; Morris, H. R. *Nature (London)* **1975**, 258, 577.
(9) Mohler, H.; Polc, P.; Cumin, R.; Pieri, L.; Kettler, R. *Nature (London)* **1979**, *278*, 563. Collelo, C. D.; Hockenberry, D. M.; Bosmann, D. M.; Fuchs, H. B.; Folkers, K. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 6319. Skolnick, P.; Marangos, P. J.; Goodwin, F.; Edwards, M.; Paul, S. *Life Sci.* **1978**, *23*, 1473. Ally, A.; Manku, M. S.; Horrobin, D. F.; Karmali, R. A.; Karmazyn, M.; Morgan, R. O. *Neurosci. Lett.* **1978**, *7*, 31. Asano, T.; Spector, S. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 977. Davis, L. G.; Cohen, R. K. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 141. Davis, L. G.; McIntosh, H.; Reker, D. *Pharmacol. Biochem. Behav.* **1981**, *14*, 839.

0022-2623/84/1827-0564$01.50/0

Scheme I



1a, X_1 = H; X_2 = H [Phe (*l*)]
b, X_1 = OCH_3; X_2 = OCH_3 [$(MeO)_2$Phe]
c, X_1 = OH; X_2 = OH (Dopa)

2a, X_1 = H; X_2 = H; R = CH_3
b, X_1 = OCH_3; X_2 = OCH_3; R = CH_3
c, X_1 = OH; X_2 = OH; R = H

3a, X_1 = H; X_2 = H
b, X_1 = OCH_3; X_2 = OCH_3
c, X_1 = OH; X_2 = OH

large quantities of substances that potently inhibit [^{3}H]-diazepam binding to benzodiazepine receptors.[6,10,12b,13] Nonetheless, the observation that β-CCE and other β-carbolines[10,11] possess a high affinity for the benzodiazepine receptor provided impetus for further pharmacological studies.

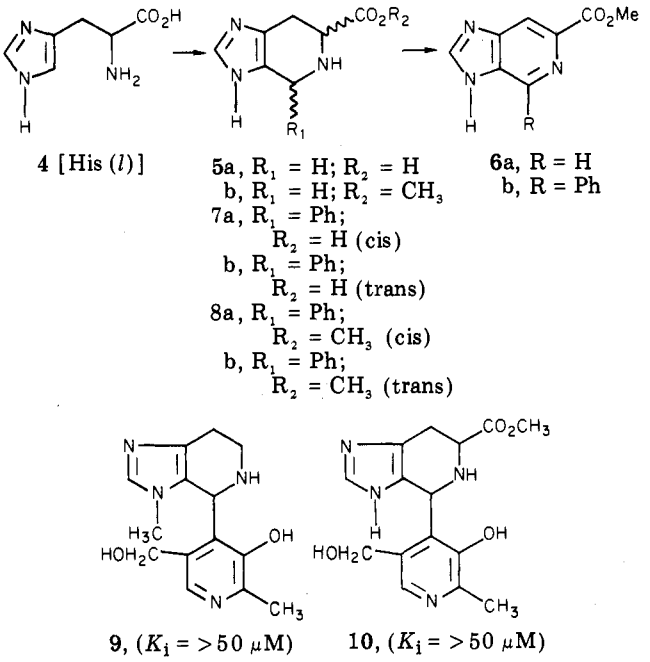
Recently, it has been demonstrated[14-16] that β-CCE antagonizes the anticonvulsant actions of diazepam, lowers the seizure threshold of the convulsant pentylenetetrazole (PTZ), antagonizes the sedative actions of flurazepam, and is anxiogenic.[17] A closely related compound, 3-(hydroxymethyl)-β-carboline,[10] was shown to antagonize both the anticonvulsant and anxiolytic actions of diazepam at doses that do not exert overt behavioral effects. Furthermore, Mendelson et al.[18] demonstrated that 3-(hydroxymethyl)-β-carboline not only antagonizes the hypnotic properties of flurazepam but also increases sleep latency and reduces total and non-REM sleep in rats.[18]

We have previously reported structure–activity relationships in the β-carboline series,[10] and four structural parameters dramatically affected the affinity for the receptor. The fully aromatic β-carbolines were more active than their tetrahydro congeners, and a carbonyl group adjacent to the pyridine nitrogen greatly augmented binding to the receptor; moreover, the receptor site would not tolerate large substituents attached at either position 1 or 9 of the β-carboline nucleus.

It is now known that many C-3 substituted β-carbolines are benzodiazepine receptor antagonists.[10] Schweri et al.[19] observed subtle pharmacological and neurochemical distinctions among classes of compounds generally termed "benzodiazepine antagonists". Seizures induced by 3-carbomethoxy-β-carboline can be blocked by benzodiazepine receptor antagonists R015-1788 and CGS-8216.[19] In contrast to the methyl ester, neither the ethyl nor propyl esters of β-carboline-3-carboxylic acid elicit frank convulsions at similar doses in rats, although at higher doses some convulsions are observed with the ethyl ester in primates.[20]

The formation of these potent β-carboline-3-carboxylates could be derived from the amino acid tryptophan and a C-1 unit. Pandit[21] has shown that tetrahydro-β-carbolines can be synthesized, in a biomimetic sense, from N^5,N^{10}-methylenetetrahydrofolate models, which suggests that the biosynthetic machinery for the synthesis of the C-1 unit of β-carbolines may be present in vivo. Moreover, tryptophan need not be considered the only amino acid involved in such a process. Other amino acids, such as

Scheme II



4 [His (*l*)]

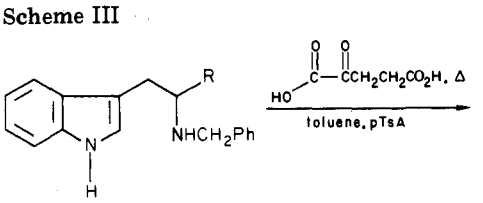
5a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
7a, R_1 = Ph; R_2 = H (cis)
b, R_1 = Ph; R_2 = H (trans)
8a, R_1 = Ph; R_2 = CH_3 (cis)
b, R_1 = Ph; R_2 = CH_3 (trans)

6a, R = H
b, R = Ph

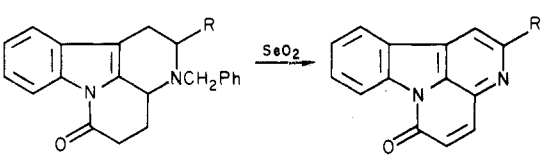
9, (K_i = >50 μM)

10, (K_i = >50 μM)

Scheme III



11a, R = H
b, R = CO_2Me

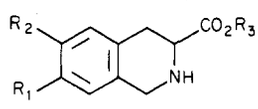


12a, R = H
b, R = CO_2Me

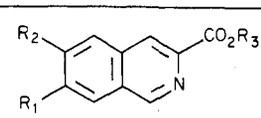
13a, R = H
b, R = CO_2Me

(10) Cain, M.; Weber, R.; Guzman, F.; Cook, J.; Barker, S.; Rice, K.; Crawley, J.; Paul, S.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081. Skolnick, P.; Paul, S.; Crawley, J.; Rice, K.; Barker, S.; Weber, R.; Cain, M.; Cook, J. *Eur. J. Pharmacol.* **1981**, *69*, 525.
(11) Cain, M.; Guzman, F.; Cook, J.; Rice, K.; Skolnick, P. *Heterocycles* **1982**, *19*, 1003.
(12) (a) Nielsen, M.; Gredal, O.; Baestrup, C. *Life Sci.* **1979**, *25*, 679. (b) Braestrup, C.; Schmiechen, R.; Neef, G.; Nielsen, M.; Peterson, E. N. *Science* **1982**, *216*, 1241.
(13) Squires, R. "GABA and Benzodiazepine Receptors"; Costa, E.; DiChiara, G.; Gessa, G., Eds.; Raven Press: New York, 1980; pp 129–138.
(14) Tenen, S.; Hirsch, J. *Nature (London)* **1980**, *288*, 609.
(15) Oakley, N.; Jones, B. *Eur. J. Pharmacol.* **1980**, *68*, 381.
(16) Cowen, P.; Green, A.; Nutt, D.; Martin, I. *Nature (London)* **1981**, *290*, 54.
(17) Ninan, P. T.; Insel, T. M.; Cohen, R. M.; Cook, J. M.; Skolnick, P.; Paul, S. M. *Science* **1982**, *218*, 1332.
(18) Mendelson, W. B.; Cain, M.; Cook, J. M.; Paul, S. M.; Skolnick, P.; Williams, E.; Rice, K.; Crawley, J. "Beta-Carbolines and Tetrahydroisoquinolines"; Usdin, E.; Alan R. Liss: New York, 1982; p 233.
(19) Schweri, M.; Cain, M.; Cook, J.; Paul, S.; Skolnick, P. *Pharmacol. Biochem. Behavior* **1982**, *17*, 457.
(20) Schweri, M.; Martin, J.; Mendelson, W.; Barrett, J.; Paul, S.; Skolnick, P. *Life Sci.*, in press.
(21) Bierdugel, H.; Plemp, R.; Hiemstra, H. C.; Pandit, U. K. *Heterocycles* **1979**, *13*, 221.

Table I. In Vitro Binding of Isoquinolines and Imidazopyridines

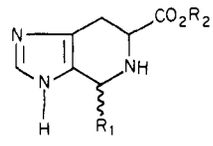


2

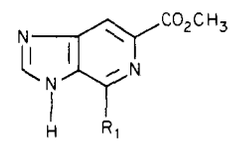


3

no.	R_1	R_2	R_3	K_i,[a] μM
2a	H	H	CH_3	>50[b]
2b	OCH_3	OCH_3	CH_3	32
2c	OH	OH	H	>50[b]
3a	H	H	CH_3	13.2[b]
3b	OCH_3	OCH_3	CH_3	10
3c	OH	OH	CH_3	



5, 7, 8



6

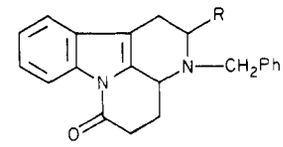
5a	H	H	>50
5b	H	CH_3	
7a (cis)	Ph	H	>50
7b (trans)	Ph	H	>50
8a (cis)	Ph	CH_3	>50
8b (trans)	Ph	CH_3	>50
6a	H		>50
6b	Ph		10

[a] For inhibition of [^{3}H]diazepam binding to rat cerebral cortical membranes as described under Experimental Section. Values X of two experiments. [b] See reference 10.

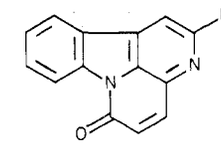
phenylalanine, tyrosine, Dopa and histidine, might well condense in vivo with a C-1 unit to provide 3-carboxy-substituted systems similar to β-carbolines. In fact, Barker et al. have recently reported the isolation of 6,7-dimethoxytetrahydroisoquinoline and 6,7-dihydroxytetrahydroisoquinoline from mammalian systems.[22] Our studies in this area are illustrated in Schemes I through III.

Preliminary results on isoquinolines that could be derived from the amino acids phenylalanine and dihydroxyphenylalanine and a C-1 unit in vivo are outlined in Scheme I; 2,3-dimethoxyphenylalanine was also employed in this study. We have previously reported that methyl isoquinoline-3-carboxylate (**3a**, prepared from Phe) binds to benzodiazepine receptors with moderate affinity (Table I, K_i = 13.2 μM).[10,11] However, this isoquinoline **3a** is about four orders of magnitude less active than its β-carboline congener β-CCM ($K_i \approx 5$ nM), and isoquinoline itself was inactive,[10] suggesting that a carbonyl next to the pyridine ring also augments binding to the receptor in the isoquinoline series. In order to examine the binding affinity of the stable 3-substituted analogues of the isoquinolines, we prepared the bases methyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2b**), methyl 6,7-dimethoxyisoquinoline-3-carboxylate (**3b**), and methyl 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2c**) via the Pictet–Spengler reaction.[10] Of these three compounds, the tetrahydro analogue **2b** bound less tightly to the receptor than the planar fully aromatic **3b** (Table I); moreover, as in the β-carboline series, substitution of oxy groups on the aromatic ring had little or no effect[10] on binding (compare **3a** to **3b**). The corresponding dihydroxy acid **2c** was inactive up to 50 μM, in complete

Table II. In Vitro Binding of Canthin-6-one Derivatives



12



13

no.	R	K_i,[a] μM
12a	H	11.2
12b	CO_2CH_3	17% inhibn at 50 μM
13a	H	10
13b	CO_2CH_3	0.1 (100 nM)

[a] For inhibition of [^{3}H]diazepam binding to rat cerebral cortical membranes as described under Experimental Section.

agreement with the low affinity of β-carboline-3-carboxylic acid for the receptor.[10] Although the isoquinolines **3a** (K_i = 13.2 μM) and **3b** (K_i = 10 μM) had only moderate activities, the report of an isoquinoline derivative that binds to the "peripheral benzodiazepine receptor" is noteworthy.[23] Of the limited number of isoquinolines tested (Table I), the planar **3a** and **3b** were the most potent, and structure–activity relationships (SAR) were similar to those obtained for the β-carbolines.[10]

In Table I are illustrated the SAR data for imidazopyridines that could be generated from a C-1 unit and histidine, in vivo. The 1-phenylimidazopyridine derivative **6b** had moderate affinity for the receptor (10 μM), whereas the tetrahydro derivatives **8a** and **8b** were virtually inactive. The trend toward decreased activity in the tetrahydro derivatives was also observed in the β-carboline series.[10] We have reported that a planar aromatic ring adjacent to the pyridine nitrogen is necessary for potent activity.[10] This principle is supported by comparison of the affinities of methyl β-carboline-3-carboxylate (β-CCM) and isoquinoline **3a** with 2-acetylpyridine or pyridine-2-carboxaldehyde, which are inactive.[10] The more potent activity of the 1-phenyl derivative **6b** when compared to **6a** is puzzling and may be due to several factors. For example: (1) The imidazo moiety is too hydrophilic, and the phenyl group serves as a hydrophobic group, as well as behaving as the required planar aromatic function adjacent to the pyridine ring. (2) The imidazo moiety is more basic than the indole portion of β-carbolines or the phenyl portion of isoquinolines. It should be mentioned here that the 1-phenyl derivative **6b** is approximately equipotent to its β-carboline congener, methyl 1-phenyl-β-carboline-3-carboxylate (3.89 μM).[10] These results taken together indicate that the basicity and hydrophobicity of the planar aromatic portion of these molecules also have an effect on binding to the receptor.

Since vitamin B_6 is an essential cofactor for many enzymatic reactions of amino acids, similarly the Pictet–Spengler products **9** and **10** of *N*-methylhistamine and histidine, respectively, with pyridoxal have been obtained, according to the method of Casella.[24] Neither of these molecules, prepared in a biomimetic fashion, bound to the receptor with any noticable affinity (K_i > 50 μM).

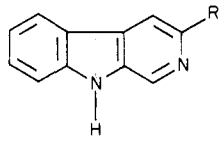
Although the results with isoquinolines and imidazopyridines did not provide compounds that bound with high affinity, analogues resulting from tryptophan and α-ke-

(22) Barker, S. A.; Monti, J. A.; Tolbert, L. C.; Brown, G. B.; Christian, S. T. *Biochem. Pharmacol.*, in press.

(23) Le Fur, G.; Perrier, M. L.; Vaucher, N.; Imbault, F.; Flamier, A.; Benavides, J.; Uzan, A.; Renault, C.; Dubroeucq, M. C.; Gueremy, C. *Life Sci.* **1983**, *32*, 1839.

(24) Casella, L.; Gullotti M. *J. Am. Chem. Soc.* **1981**, *103*, 6338.

Table III. Effect of the 3-Substituent on in Vitro Binding



no.	R	K_i,[a,b] nM
14a	$CO_2CH_2CH_3$	1
14b	CO_2CH_3	1
15	$C(=O)CH_3$	58
16	$C(=O)NH_2$	68
17	$CH_2OC(=O)CH_3$	750

[a] For inhibition of [^{3}H]diazepam binding to rat cerebral cortical membranes as described under Experimental Section. The K_d of diazepam under the experimental conditions employed was 5.6 nM.[40] [b] Values presented here are the X of two experiments. IC_{50} values were graphically estimated with five to eight concentrations of compound. The K_i was determined by the following formula: $K_i = IC_{50}/(1 + [L]/K_d)$.

toglutaric acid, available from the Krebs cycle, were somewhat more exciting. It was felt that not only could tryptophan or tryptamine condense with a C-1 unit to form potentially active compounds, but these amines could also condense with other aldehydes in vivo. It was therefore decided to explore the reaction of α-ketoglutaric acid with these compounds, as depicted in Scheme III. The natural product canthin-6-one (**13a**) prepared from **11a**[25] demonstrated a slight affinity for the receptor (Table II), as was the case with the N^{α}-benzyltetrahydro analogue **12a**;[26] however, substitution of tryptophan for tryptamine in the sequence resulted in the preparation of gram quantities of 2-(methoxycarbonyl)canthin-6-one (**13b**) in virtually a two-step sequence (see Experimental Section for details). The 2-carbomethoxy derivative **13b** was 100 times more potent than **13a**; moreover, the affinity (K_i = 100 nM) was comparable to that demonstrated for some clinically active benzodiazepines. The carbonyl group adjacent to the pyridine nitrogen augments the binding in the canthin-6-one series analogous to the increase in activity observed in the corresponding β-carbolines and isoquinolines.

In fact, recent results from our laboratory shed further light on this important point. As illustrated in Table III, β-carbolines (i.e., **14a** and **14b**) that contain an ester carbonyl adjacent to the pyridine ring (position 3) are known to displace [^{3}H]diazepam from benzodiazepine receptors with a potency comparable to that of some benzodiazepines. Moreover, the analogous 3-acetyl (**15**) and 3-amido (**16**) derivatives bound to the receptor(s) with high affinity, although it appears the ester oxygen systems are necessary in order to achieve optimum activity. Nevertheless, if 3-(hydroxymethyl)-β-carboline (K_i = 1470 nM) is converted into the acetyl derivative **17**, the binding affinity is doubled with respect to 3-(hydroxymethyl)-β-carboline but is greatly diminished in comparison to the activity of the esters **14a** or **14b**. This maneuver is equivalent to displacing the carbonyl function in space over the distance of two atoms, yet this compound **17** is sevenfold less active than the methyl ester **14b** and 100 times less active than the acetyl derivative **15**. This fully supports the hypothesis put forth earlier with regard to the position of the carbonyl vis a vis the most potent affinity for the receptor;[10,11] the carbomethoxy derivatives **13b** and **14b** could potentially behave as bidentate ligands with metals in the same fashion as methyl picolinate.[27] The importance of the ability of the compounds described here to behave as bidentate ligands at the receptor site remains to be determined.

It has been demonstrated that large substituents located on either position 1 or 9 of β-carbolines greatly decreased binding potency;[10] however, 2-carbomethoxycanthin-6-one (**13b**) demonstrated high affinity for the receptor. This is, presumably, due to the trigonal nature of the enone functionality, which permits planarity to a greater degree than in the corresponding β-carboline series (substituents at C-1 and N-9). This result also clearly indicates that the benzodiazepine receptors involved in this process can accept a β-carboline analogue of considerably larger size if the topography of the system remains planar. Although the results with isoquinolines and imidazopyridines did not yield compounds that bound with high affinity, the discovery of a canthin-6-one derivative (**13b**), via the biomimetic approach, that binds to the benzodiazepine receptor tighter than chlorodiazepoxide strongly supports the approach toward potential benzodiazepine agonists and antagonists described herein.

Chemistry. Isoquinolines that can be derived from amino acids are of interest as potential endogenous ligands, and some of these are illustrated in Scheme I. Several target isoquinolines have been prepared previously.[10,11] Phenylalanine (**1a**) was converted to the tetrahydroisoquinoline **2a** via a Pictet–Spengler reaction with formaldehyde, followed by esterification of the resulting acid with methanolic hydrogen chloride. The desired methyl isoquinoline-3-carboxylate (**3a**) was obtained by heating **2a** with palladium on carbon in refluxing xylene. The 6,7-dimethoxy-3-methoxycarbonyl analogue **2b** was synthesized by the standard Pictet–Spengler technology[10] and was converted into the fully aromatic methyl 6,7-dimethoxyisoquinoline-3-carboxylate (**3b**) on treatment with sulfur in nitrobenzene at 140 °C.

Imidazopyridines that can be derived from the amino acid histidine are illustrated in Scheme II. The alkaloid spinacine (**5a**) was prepared in 90% yield by heating an aqueous solution of the hydrochloride salt of **4** with formaldehyde. The ester **5b** was then prepared on heating **5a** in the presence of methanolic hydrogen chloride. Oxidation of **5b** to produce **6a** was accomplished by heating **5b** with selenium dioxide in acetic acid. The 1-phenyl derivatives **7a** and **7b** were synthesized by the method of Wille[28] by way of a base-catalyzed Pictet–Spengler reaction of histidine (**4**) with benzaldehyde. To determine the stereochemistry of the carboxylic acids **7a** and **7b**, reported by Wille,[28] we prepared the methyl esters **8a** and **8b**, and assignments were made based on ^{13}C NMR spectroscopy, a method previously employed in our laboratories under

(25) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.

(26) The tetrahydrocanthin-6-one analogues **12a** and **12b** (Table II) were examined for their affinity for the benzodiazepine receptor. Although both tetrahydro derivatives were less active than their planar counterparts **13a** and **13b**, surprisingly the 3-protio derivative **12a** was more active than the 3-methoxycarbonyl compound **12b**. Although the reasons for this are not understood at the present time, it is felt the 2- and 3-substituents in **12b** distort ring C from planarity to a greater extent than that which occurs in the 2-substituted case, **12a**. Distortion from planarity in the β-carboline series is known to decrease binding affinity for the receptor site.[10]

(27) Paul, R. C.; Chopra, R. S.; Singh, G. *Inorgan. Chim. Acta* **1975**, *14*, 105. Masuko, A.; Nomura, T.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 511. Kidani, Y.; Noji, M.; Koike, H. *Ibid.* **1975**, *48*, 239.

(28) Wille, Myles Albert Ph.D. Thesis, University of Pennsylvania, 1969.

similar circumstances in the tetrahydro-β-carboline series.[29] The signals for carbon-1 and carbon-3 in the diastereomer (**8b**, 53.83 and 51.98 ppm) designated trans appeared upfield from those of the cis isomer (**8a**, 57.37 and 56.06 ppm) in similar fashion to that observed in the tetrahydro-β-carboline series.[29] Aromatization of the tetrahydroimidazopyridine derivatives **5b** and **8b** was attempted unsuccessfully with palladium on carbon or with sulfur; however, oxidation with selenium dioxide readily afforded bases **6a** and **6b**, respectively.

Canthin-6-one (**13a**) has been isolated from a variety of plants[30] and has been synthesized by a number of investigators.[31-33] Since this natural product can assume planarity analogous to simple β-carbolines, a short, simple synthesis of this alkaloid **13a** and the corresponding 2-carbomethoxy derivative **13b** was developed. The present preparation of **13a** and **13b** was based on observations made earlier on the Pictet–Spengler reaction in aprotic media.[34] Facile entry into the hexahydrocanthin-6-one skeleton was accomplished simply by heating N^{α}-benzyltryptamine (**11a**) or N^{α}-benzyltryptophan (**11b**) and 2-ketoglutaric acid in refluxing toluene for several days.[35,36] Although the 1-propionic acid intermediates were also isolated, they could be converted into **12a** and **12b** on further heating in the presence of *p*-toluenesulfonic acid. Compounds **12a** and **12b** could be obtained from **11a** and **11b** in high yield in a one pot reaction by monitoring the reaction by TLC. The choice of selenium dioxide as the oxidant for the preparation of **13a** and **13b** was guided by observations made previously,[35] wherein *N*-benzyl groups were cleaved with this reagent to give benzaldehyde. The final step therefore corresponds to removal of the N^{α}-benzyl group from **12a** or **12b** and incorporation of three double bonds into the molecule. The bases **13a** and **13b** were obtained in 33 and 66% yields, respectively. The two step sequence reported here should prove to be general for the synthesis of substituted canthine-6-ones. Finally, the synthesis of several 3-substituted β-carbolines, including compounds **14a–16** listed in Table III, have been previously reported elsewhere,[10,12] while the carboxamide **16** was prepared by bubbling anhydrous ammonia through a solution of the ester (**14b**), which had been dissolved in anhydrous methanol.

Experimental Section

Microanalyses were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. NMR spectra were recorded on Varian T-60 and EM-360 spectrometers and a Varian CFT-20 ^{13}C NMR spectrometer. IR spectra were taken on a Beckman Acculab-1 instrument, while electron-impact (EI) mass spectra were recorded on a Hitachi RMU-6 spectrometer. Chemical ionization (CI) mass spectra were obtained on either a Finnigan GC/MS or Hewlett Packard 5855 GC/MS mass spectrometer.

Analytical TLC plates used were E. Merck Brinkman UV active silica gel or alumina on plastic. Silica gel 60 and aluminum oxide for chromatography were purchased from EM Laboratories and J. T. Baker, respectively. Tryptamine, tryptophan, phenylalanine, Dopa, histidine, selenium dioxide, and 2-ketoglutaric acid were purchased from Aldrich Chemical Co., while 2,3-dimethoxyphenylalanine was acquired from Vega Fox Biochemical Co. The preparation of methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**),[10] 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2c**),[10] methyl isoquinoline-3-carboxylate (**3a**),[10] canthin-6-one (**13a**),[25] and 3-substituted β-carbolines **14–16**[10] have been reported elsewhere. The tetrahydropyrido[3,4-*d*]imidazoles **9** and **10** were obtained according to the method of Casella et al.[24] Authentic samples of **9** and **10** were kindly provided by Professor Casella.

6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (2c). Racemic 3-(3,4-dihydroxyphenyl)alanine (**1c**; 2 g, 11.5 mmol) and formaldehyde (37%, 12 mL) were added to sulfuric acid (0.5 N, 120 mL), and the solution was stirred at room temperature for 24 h. The mixture was cooled in an ice bath, and aqueous sodium hydroxide (2 N, 25 mL) was added. The solution became turbid, and a white precipitate formed, which was filtered and dried to give **2c** (2 g): mp 280–285 °C (lit.[38] mp 293–294 °C). Care must be taken not to add excess base, which results in the formation of an orange solution and excessive decomposition.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Hydrogen Sulfate. 3,4-Dimethoxy-DL-phenylalanine (**1b**; 5.70 g, 25.3 mmol) and formaldehyde (37%, 30.0 mL) were added to sulfuric acid (0.15 N, 300 mL), and the solution was stirred at room temperature for 24 h. The mixture was then cooled in an ice bath, followed by the addition of 1 N sodium hydroxide until a precipitate formed. The pH of the solution that resulted was 3. The precipitate was filtered and dried to give **2** (4.30 g, 12.8 mmol, 50.7%): mp 260–264 °C; IR 3680–2340, 1630 cm^{-1}; ^1H NMR δ (D_2O) 3.30 (m, 1 H), 4.10 (s, 6 H, m, 1 H), 4.20 (s, 2 H), 4.45 (br, s, 1 H), 5.85 (s, 2 H), 7.45 (m, 2 H); mass spectrum (CI, CH_4) 238 (M + 1, 100), 220 (18), 208 (13.3), 190 (51.8). Anal. ($C_{12}H_{15}O_4N \cdot H_2SO_4 \cdot H_2O$) N; C: calcd, 40.80; found, 39.49; H: calcd, 5.07; found, 4.39. This material was converted directly into the methyl ester **2b** without further purification.

Methyl 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (2b·HCl). The carboxylic acid from the previous experiment (5.55 g, 17.0 mmol) was dissolved in saturated methanolic hydrogen chloride (1.5 L), and the solution was held at reflux for 72 h. The volume of solvent was reduced under vacuum, and the crystals that formed were filtered from the medium and recrystallized from methanol to furnish **2b**·HCl (3.98 g, 81.5%). This material was homogeneous on TLC (SiO_2, 97% CH_3OH/3% CH_3CO_2H, R_f 0.34): mp 251–253 °C; IR 1728 cm^{-1}; ^1H NMR, (D_2O/DCl) δ 3.65 (s, 2 H), 4.15 (s, 6 H), 4.25 (s, 3 H), 4.85 (m, 3 H), 7.51 (m, 2 H); mass spectrum (EI, 15 eV), 251 (M^+, 60), 192 (100). Anal. ($C_{13}H_{18}O_4NCl$) N; C: calcd, 54.22; found, 53.65; H: calcd, 6.26; found, 6.98. High-resolution mass spectrum, *m/e* 251.1157 ($C_{13}H_{17}O_4N$ requires 251.1157).

Methyl 6,7-Dimethoxyisoquinoline-3-carboxylate (3b). The hydrochloride salt of **2b** (5.00 g, 17.39 mmol) was dissolved in H_2O (20 mL), and then $CHCl_3$ (20 mL) was added. The solution was brought to pH 10 with saturated K_2CO_3 solution with cooling (ice). The mixture was then extracted with $CHCl_3$ (4 × 30 mL) and dried (K_2CO_3). The solvent was then removed under reduced pressure to provide methyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2b**; 4.36 g, 100%): mp 54–56 °C; CI mass spectrum identical with that of the hydrochloride salt of **2b**. The free base (**2b**; 4.36 g, 17.39 mmol) was then dissolved in nitrobenzene (500 mL), and sulfur (1.38 g, 43.2 mmol) was added. The mixture was then stirred at 140 °C for 14 h. The solvent was removed under reduced pressure, and the solid material that remained was taken up in 100 mL of ice-cold 1 N HCl and filtered to remove sulfur. The aqueous layer was then extracted with benzene (5 × 50 mL). The aqueous layer was brought to pH 10

(29) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976.
(30) Haynes, H. F.; Nelson, E. R.; Price, J. R. *Aust. J. Sci. Res., Ser. A* **1952**, *A5*, 387. Cannon, J. R.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1953**, *6*, 86. Lassak, E. V.; Polonsky, J.; Jacquemin, H. *Phytochemistry* **1977**, *16*, 1126. Awad, A. T.; Beal, J. L.; Talapatra, S. K.; Cava, M. P. *J. Pharm. Sci.* **1967**, *56*, 279. Fish, F.; Waterman, P. G. *Phytochemistry* **1971**, *10*, 3325. Scheuer, P. J.; Pattabhiraman, T. R. *Lloydia* **1965**, *28*, 95. Guise, G. B.; Ritchie, E.; Senior, R. G.; Taylor, W. C. *Aust. J. Chem.* **1968**, *20*, 2429.
(31) Rosenkranz, H. J.; Batyos, G.; Schmidt, H. *Liebigs Ann. Chem.* **1966**, *691*, 159.
(32) Mitscher, L. A.; Shipchandler, M.; Showalter, M. D. H.; Bathala, M. S. *Heterocycles* **1975**, *3*, 1.
(33) Oehl, R.; Lohzer, G.; Rosenmund, P. *Chem. Ber.* **1976**, *109*, 705.
(34) Sandrin, J.; Soerens, D.; Hutchins, L.; Richfield, E.; Ungemach, F.; Cook, J. M. *Heterocycles* **1976**, *4*, 1101.
(35) Campos, O.; DiPierro, M.; Cain, M.; Mantei, R.; Gawish, A.; Cook, J. M. *Heterocycles* **1980**, *14*, 975.
(36) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.

with saturated K_2CO_3, with cooling (ice). The aqueous layer was then extracted with $CHCl_3$ (3 × 75 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the solid that remained was recrystallized from ethyl acetate to provide methyl 6,7-dimethoxyisoquinoline-3-carboxylate (**3b**; 4.19 g, 97.5%): mp 209–210 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.40 (s, 9 H), 7.75 (s, 1 H), 7.85 (s, 1 H), 9.15 (s, 1 H), 9.85 (s, 1 H); mass spectrum (CI, CH_4) m/e 248 (M + 1, 100%). Anal. ($C_{13}H_{13}O_4N$) C, H, N.

***cis*- and *trans*-1-Phenyl-1,2,3,4-tetrahydroimidazo[4,5-*c*]pyridine-3-carboxylic Acid (7a,b).** To a solution of L-histidine hydrochloride hydrate (**4**; 12.5 g, 60 mmol) in water (30 mL) was added a solution of potassium hydroxide (6.7 g) in water (30 mL) and benzaldehyde (6.36 g, 60 mmol) in ethanol (30 mL). The resultant solution was stirred under reflux for 1 h and cooled, and the solvent volume was reduced under reduced pressure. The solution was adjusted to pH 6 with the addition of 1 N sulfuric acid. While the solution was cooling, the white crystalline trans isomer **7b** precipitated from the mixture and was filtered from the medium to give **7b** (8.6 g, 59%): mp 255–257 °C (lit.[28] 267–268 °C); mass spectrum (70 eV), m/e (relative abundance) 243 (36), 198 (78), 169 (100); IR (KBr) was identical with the published spectrum of **7b**.[28] The solvent volume of the mother liquor was reduced, and the cis isomer precipitated to give **7a** (3.25 g, 22%): mp 212–213 °C (lit.[28] mp 212–213 °C).

Methyl *trans*-1-Phenyl-1,2,3,4-tetrahydroimidazo[4,5-*c*]-pyridine-3-carboxylate (8b). The carboxylic acid **7b** (7.5 g, 29 mmol) prepared in the previous experiment was added to a solution of saturated methanolic hydrogen chloride (100 mL) and held at reflux overnight. The suspension that resulted was filtered, and the filtrate was reduced in volume under reduced pressure to furnish an oil **8b** (11.25 g). The oil was dissolved in water and brought to pH 8 with 1 N sodium hydroxide. A thick white precipitate formed and was filtered to give *trans*-**8b** (4.0 g, 50%): mp 217–218 °C; IR (KBr) 3350 (br), 1735 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.85 (m, 1 H), 2.90 (m, 1 H), 3.70 (s, 3 H), 3.75 (m, 1 H), 5.10 (s, 1 H), 7.30 (s, 5 H), 7.45 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) 26.18 (d), 51.59 (q), 51.98 (d), 53.83 (d), 126.39, 126.70, 127.85, 128.25, 130.78, 133.93, 143.29, 173.28 ppm; mass spectrum (CI, CH_4), m/e 258 (M + 1, 100). Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

Methyl *cis*-1-Phenyl-1,2,3,4-tetrahydroimidazo[4,5-*c*]-pyridine-3-carboxylate (8a). The carboxylic acid **7a** (2 g, 7.7 mmol) was dissolved in saturated methanolic hydrogen chloride and heated to reflux for 20 h. The solvent was evaporated under reduced pressure, and the residue was brought to pH ~8 with aqueous sodium hydroxide (1 N). The white precipitate that formed was filtered to furnish **8a** (400 mg, 20%): mp 196–199 °C; IR (KBr) 1735 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.75 (m, 1 H), 2.90 (m, 1 H), 3.70 (s, 3 H, OCH_3), 3.90 (m, 1 H), 5.00 (s, 1 H), 7.30 (s, 5 H), 7.35 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) 26.87 (t), 51.68 (q), 56.06 (d), 57.35 (d); 126.83, 127.15, 127.86, 128.24, 131.73, 133.92, 142.60, 172.47 ppm; mass spectrum (CI, CH_4), m/e 258 (M + 1, 100). Anal. ($C_{14}H_{15}N_3O_2$) C, H.

A sizeable portion (40%) of **8a** remained in the mother liquors and was not isolated, since **8a** did not demonstrate potent affinity for the benzodiazepine receptor.

Spinacine Hydrochloride (5a).[37] L-Histidine hydrochloride hydrate (**4**; 1 g, 4.76 mmol) was dissolved in water (10 mL). Formaldehyde (37%, 0.54 mL) was added, and the solution was held at reflux for 1 h. The solvent was removed under reduced pressure, and the residue was crystallized from methanol to provide **5a** (950 mg, 95%): mp 285 °C (lit.[37] mp 276 °C); IR (KBr) 3600–3200, 1620, 1370 cm^{-1}; ^1H NMR (D_2O) δ 3.20–3.40 (m, 2 H), 4.35 (m, 2 H), 8.30 (s, 1 H); mass spectrum (70 eV), m/e 167 (M^+, 30), 122 (69), 94 (100). Anal. ($C_7H_{10}N_3O_2Cl$) C, H, N.

Methyl Imidazo[4,5-*c*]pyridine-3-carboxylate (6a). Spinacine hydrochloride (**5a**; 10 g, 49 mmol) was dissolved in saturated methanolic hydrochloric acid (1 L) and was held at reflux for 3 h. The solvent was evaporated, and sodium carbonate (6.5 g) in water (40 mL) was added. The solvent was removed under reduced pressure. The residue was dissolved in acetic acid (250 mL), and SeO_2 (11 g) was added. The mixture was heated to reflux for 15 min. The black selenium was filtered from the medium over Celite, and the solvent was evaporated under reduced pressure. The residue was chromatographed on SiO_2 (150 g) and eluted with NH_4OH/MeOH/dioxane (3:30:67) to give **6a** (1.4 g, 16%): mp 248 °C; IR (KBr) 3150 (br), 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90 (s, 3 H), 8.38 (s, 1 H), 8.55 (s, 1 H), 9.05 (s, 1 H). High-resolution mass spectrum, m/e 177.0538 ($C_8H_7N_3O_2$ requires 177.0537). This material proved to be homogeneous by TLC (SiO_2; NH_4OH/CH_3OH/dioxane, 10:40:50), R_f 0.87.

No attempt to maximize this yield was carried out, since **6a** did not demonstrate potent affinity for the benzodiazepine receptor.

Methyl 1-Phenylimidazo[4,5-*c*]pyridine-3-carboxylate (6b). The trans amine **8b** (300 mg, 1.17 mmol) and SeO_2 (600 mg, 5.4 mmol) were dissolved in acetic acid (25 mL), and the mixture was heated to reflux for 22 h. The reaction was cooled, additional amounts of SeO_2 (500 mg, 4.5 mmol) were added, and reflux continued for an additional 7 h. The solvent was removed under reduced pressure, and the residue was chromatographed on SiO_2 [eluent, NH_4OH/MeOH/EtOAc (1:1:8)] to give **6b** (150 mg, 50%): mp 227–229 °C (MeOH); IR (KBr) 3150 (br), 1705 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90 (s, 3 H), 7.40–7.60 (m, 5 H), 8.25 (s, 1 H), 8.40 (s, 1 H), 8.70–8.90 (m, 1 H); mass spectrum (CI, CH_4), m/e 254 (M + 1, 100). Anal. ($C_{14}H_{11}N_3O_2$) C, H, N.

2-Carbomethoxycanthin-6-one (13b). The amine **12b**[36] (2.0 g, 5.35 mmol) and SeO_2 (4.1 g, 37 mmol) were added to dioxane (250 mL), and the mixture was heated to reflux for 3 days. The black selenium that precipitated was filtered from the medium over Celite, and the solvent was removed in vacuo. The slurry that resulted was diluted with methanol, and the solid that crystallized was removed by filtration to furnish **13b** (980 mg, 66%). This material proved to be homogeneous by TLC (SiO_2, 10% CH_3OH/EtOAc) R_f 0.82: mp 249–250 °C; IR (Nujol) 1670, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (s, 3 H), 7.10 (d, 1 H, J = 10 Hz), 7.40–8.00 (m, 2 H), 8.00–8.50 (m, 2 H), 8.60–8.90 (m, 1 H), 9.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.14, 117.26, 118.33, 122.77, 124.03, 125.93, 129.98, 130.78, 131.26, 135,57, 139.48, 139.75, 144.15, 159.18, 165.54. High-resolution mass spectrum, m/e 278.0684 ($C_{16}H_{10}N_2O_3$ requires 278.0691).

β-Carboline-3-carboxamide (16). The methyl ester **14b** (100 mg, 0.43 mmol) was dissolved in dry methanol (20 mL) and anhydrous ammonia was bubbled through the solution for 2 days. The mixture of **14b** and **16** was chromatographed on SiO_2 ($MeOH/CH_2Cl_2$, gradient) to give **16** (50 mg, 50%). This material was homogeneous by TLC (SiO_2, 10% $CH_3OH/CHCl_3$), R_f 0.79: mp 318–319 °C (MeOH); IR (KBr) 3450 (br), 1680, 1645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.00–7.70 (m, 5 H), 7.80–8.00 (m, 1 H), 8.20 (d of d, J_1 = 7 Hz, J_2 = 1 Hz, 1 H), 8.72 (s, 1 H), 8.75 (s, 1 H). High-resolution mass spectrum, m/e 211.0737 ($C_{12}H_9N_3O$ requires 211.0745).

Pharmacology. Measurement of [^{3}H]diazepam binding to rat cerebral cortical membranes was accomplished by previously described methods.[10,40] In brief, rats were killed by decapitation, and the cerebral cortex was removed. Tissue was distributed in 100 vol of Tris-HCl buffer (50 mM, pH 7.4) with a Polytron (15s, setting 6, Brinkman Instruments, Westbury, NY) and centrifuged (4 °C) for 20 min at 20000g. Tissue was resuspended in an equal volume of buffer and recentrifuged. This procedure was repeated until the tissue was washed a total of three times. The tissue was then resuspended in 100 vol of buffer (protein concentrations: 0.5–0.6 mg/mL), and 1 mL was added to 0.4 mL of buffer and 0.0375 mL of test compound. Incubations (4 °C) were initiated by the addition of [^{3}H]diazepam (2 nM, 0.0625 mL) and terminated after 30 min by the addition of 5 mL of ice-cold Tris buffer, followed by filtration on Whatman GF/B under vacuum and an additional washing of the filter with 5 mL of buffer. Filters were suspended in 10 mL of Hydrofluor (National Diagnostics, Summerville, NJ) and then shaken vigorously for 30 min, and the radioactivity was measured in a Packard B-2450 liquid scintillation counter. Nonspecific binding was determined by substituting nonradioactive diazepam (final concentration 3 μM) or clonazepam

(37) Wellisch, J. *Biochem. Z.* **1913**, *49*, 173.
(38) Brossi, A.; Focella, A.; Teitel, S. *Helv. Chim. Acta* **1972**, *55*, 15.
(39) Paul, S.; Skolnick, P. *Science* **1978**, *202*, 892.
(40) Skolnick, P.; Lock, K.; Paul, S.; Marangos, P.; Jonas, R.; Irmscher, K. *Eur. J. Pharmacol.* **1980**, *67*, 179.

(final concentration 1 μM) for the test compound. Nonspecific binding was less than 10% of total binding under these conditions. Specific binding was defined as the difference in binding in the presence and absence of a large excess of nonradioactive benzodiazepine. Data were expressed as percent inhibition of specific binding, and IC_{50} values were estimated from semilogarithmic plots (see Figure 1 in ref 10). Inhibitory constants of compounds under study were calculated by the equation $K_i = IC_{50}/(1 + [L]/K_D)$, where [L] is the ligand concentration (2 nM), and the K_D for [^{3}H]diazepam was estimated to be 5.6 ± 0.34 nM in thrice washed cerebral cortical membranes.[40]

Acknowledgment. We thank Frank Laib and Judith Siegrist for their very able technical assistance.

Registry No. **1b**, 33522-62-2; **1c**, 63-84-3; **2**, 88980-04-5; **2a**, 79815-19-3; **2b**, 88932-16-5; **2b**·HCl, 88932-15-4; **2c**, 88980-05-6; **3a**, 27104-73-0; **3b**, 88932-17-6; **3c**, 88932-18-7; **4**, 645-35-2; **5a**, 88980-06-7; **5b**, 88932-19-8; **6a**, 82523-07-7; **6b**, 82523-11-3; **7a**, 88980-07-8; **7b**, 88980-08-9; **8a**, 88980-09-0; **8b**, 88980-10-3; **12a**, 65284-99-3; **12b**, 60702-98-9; **13a**, 479-43-6; **13b**, 84133-31-3; **14a**, 74214-62-3; **14b**, 69954-48-9; **15**, 82596-93-8; **16**, 88932-13-2; **17**, 88932-14-3.

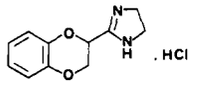
α-Adrenoreceptor Reagents. 2. Effects of Modification of the 1,4-Benzodioxan Ring System on α-Adrenoreceptor Activity

Christopher B. Chapleo,* Peter L. Myers, Richard C. M. Butler, John A. Davis, John C. Doxey, Stanley D. Higgins, Malcolm Myers, Alan G. Roach, Colin F. C. Smith, Michael R. Stillings, and Anthony P. Welbourn

Departments of Medicinal Chemistry and Pharmacology, Reckitt and Colman Ltd., Kingston upon Hull, HU8 7DS, United Kingdom. *Received August 11, 1983*

Modification of the 1,4-benzodioxan ring present in RX 781094 (1) has not previously been considered. This paper describes a number of analogues of this ring system, including compounds in which one of the oxygen atoms has been replaced by a methylene group and also those in which the ring size has been changed to give, for example, furan and thiophene derivatives. The dihydrobenzofuranylimidazoline compound **7** is the only analogue possessing presynaptic antagonist potency and selectivity comparable to that of **1**. In view of this result, a number of derivatives was prepared to determine the structure–activity relationships within this series. Many derivatives, as well as the parent compound **7**, were found to possess presynaptic α_2-adrenoreceptor antagonist and postsynaptic α_1-adrenoreceptor partial agonist properties. Two of the selective presynaptic antagonists, **13** and **14**, possess greater potency and selectivity than that possessed by **1**. The 5-chloro derivative **25** is twice as potent as **1** after oral administration but only about half as potent when given intravenously.

The rational design of idazoxan (**1**, RX 781094), a new

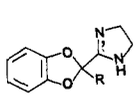


(1) Idazoxan (RX 781094)

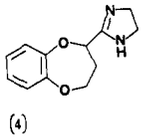
potent and selective antagonist of α_2-adrenoreceptors, has been described, and the effects of substituents on the aromatic or imidazoline ring, as well as modification of the imidazoline moiety, have been discussed.[1] Such modifications resulted in a reduction or loss of both the selectivity and potency of the parent compound **1** and in some examples lead to a change in profile. Modification of the 1,4-dioxan ring present in **1** has not been previously considered, and we discuss here the synthesis of a number of analogues of this ring system.

Chemistry. The preparation of the imidazoline products was carried out following one of the routes shown in Scheme I by using the intermediate ester or acid chloride **2**. The analogues were obtained as described in the following paragraphs.

Variation of Ring Size. The benzodioxole **3b** was



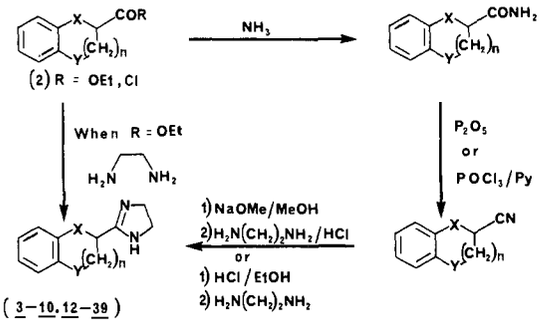
(3) a) R = H
b) R = CH_3



(4)

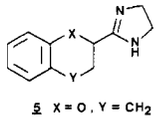
isolated by the procedure first described in the patent[2] to

Scheme I



Olin Mathieson Chemical Corp., which claimed the "benzodioxan ring–idazoxan structure".[3] The corresponding demethylbenzodioxole **3a** and the seven-membered ring analogue **4** were prepared from catechol and the appropriate dihalo esters via the intermediates **2** (n = 0; R = OEt; X = Y = 0)[4] and **2** (n = 2; R = OEt; X = Y = 0),[5] respectively (Scheme I).

Replacement of One Oxygen Atom by a Methylene Group. The two isomeric chromans **5** and **6** were prepared



5 X = O, Y = CH_2
6 X = CH_2, Y = O

(1) 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.
(2) Krapcho, J.; Lott, W. A. U.S. Patent 2 979 511.
(3) Chapleo, C. B.; Myers, P. L. *Tetrahedron Lett.* **1981**, 22, 4839. Chapleo, C. B.; Myers, P. L. British Patent 2 068 476.
(4) Christiansen, W. G.; Dolliver, M. A. *J. Am. Chem. Soc.* **1944**, *66*, 312.
(5) Geigy, J. R. Belgium Patent 613 210.

0022-2623/84/1827-0570$01.50/0