Synthesis, Resolution, and Absolute Configuration of the Isomers of the Neuronal Excitant 1-Amino-1,3-cyclopentanedicarboxylic Acid

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The endogenous amino acids glutamate and aspartate depolarize mammalian neurons to produce excitation, and the rigid glutamate analogue 1-amino-1,3-cyclopentanedicarboxylic acid also has this effect. This compound exists as two pairs of geometric isomers, and in the present study the absolute configuration of the four isomers is assigned. The known (+)-*S* and (−)-*R* isomers of 3-oxocyclopentanecarboxylic acid were used as the basis for the synthesis. The cis and trans amino acids were obtained by fractional crystallization. Spectral data, including optical rotation, circular dichroism, and ^{13}C nuclear magnetic resonance, are presented. The compounds were evaluated as excitants by microiontophoretic ejection into the dendritic region of impaled CA1 pyramidal neurons of rat hippocampal slices. One isomer, cis-1*R*,3*R*, mimicked completely the actions elicited by *N*-methyl-D-aspartic acid; the other three isomers were α-kainic acid like.

Considerable interest has been shown by neuropharmacologists in rigid analogues of the endogenous excitants glutamic and aspartic acids.[1,2] The latter compounds are thought to function as synaptic transmitters in the mammalian central nervous system and elucidation of the receptors involved in their actions has been attempted for many years.

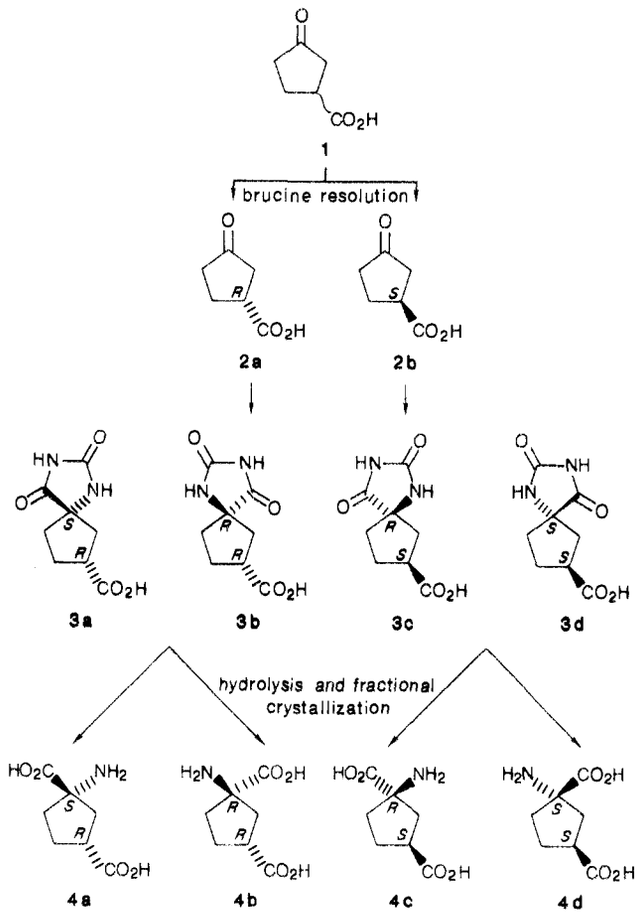
It is currently believed that three subpopulations of receptor exist, each having its own conformational and stereochemical requirements. To characterize these receptors more fully, the cis and trans isomers of 1-amino-1,3-cyclopentanedicarboxylic acid (ACPD) have been tested.[3] However, since the individual optical isomers may be expected to have different pharmacological actions, their use as effective probes of the receptor systems involved has been vitiated.

Toki[4] has described a resolution of the isomers of 3-oxocyclopentanecarboxylic acid using the chiral base brucine as the resolving agent. The absolute configurations of the isomers have been assigned[5] and they are the starting material for the present synthesis. The two chiral centres of ACPD give rise to four stereoisomers that exist as two pairs of geometric isomers. Since resolution of one chiral center is achieved prior to the synthesis of the amino acids, fractional crystallization gives a separation of all four stereoisomers.

Chemistry

Some modifications of the method of Stephani et al.[6] were employed in the synthesis of the starting material 3-oxocyclopentanecarboxylic acid. Esterification of the intermediate compound 1,2,4-butanetricarboxylic acid was facilitated by the use of a Dean and Stark distillation apparatus, increasing the yield of triethyl 1,2,4-butanetricarboxylate from the reported 66% to 90% of the theoretical yield. The Bucherer–Bergs method of hydantoin formation has been described as a conformationally directed reaction in restricted ring systems.[7] This study assigned a difference between the Bucherer–Bergs and

Scheme I



Strecker type formation of the hydantoin intermediates; the reaction can be pushed in the direction of the Strecker product by the modifications outlined below. Selectivity was found in trial experiments where replication of the published synthesis[6] yielded 3:1 trans:cis amino acids as the final products. In the present study as indicated in Scheme I, a higher proportion of the cis Strecker product was obtained by neutralization of the keto acid with aqueous ammonia solution and addition of ammonium chloride to the reaction mixture. A final product ratio of 1:1 trans:cis was obtained. Hydrolysis of the hydantoins with 1 M aqueous sodium hydroxide solution, followed by acidification with hydrochloric acid and fractional crystallization yielded the four stereoisomers of ACPD. The isolated isomers were eluted from a reverse-phase high-performance liquid chromatography (HPLC) column, each isomer showing a single peak with no contamination when

(1) Krogsgaard-Larsen, P.; Honoré, T.; Hansen, J. J.; Curtis, D. R.; Lodge, D. *Glutamate as a Neurotransmitter*; Raven: New York, 1981; p 285.
(2) McLennan, H. *Glutamate as a Neurotransmitter*; Raven: New York, 1981; p 253.
(3) McLennan, H.; Liu, J. R. *Exp. Brain Res.* **1982**, *45*, 151.
(4) Toki, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 333.
(5) Allen, R. D.; Johnston, G. A. R.; Twitchin, B. *Aust. J. Chem.* **1979**, *32*, 2517.
(6) Stephani, R. A.; Rowe, W. B.; Gass, J. D.; Meister, A. *Biochemistry* **1972**, *11*, 4094.
(7) Edward, J. T.; Jitrangsri, C. *Can. J. Chem.* **1975**, *53*, 3339.

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Table I. Pharmacological Characteristics of the Isomers of ACPD Compared with Those of *N*-Methyl-D-aspartic, Kainic, and Quisqualic Acids

compound	firing pattern	APV block	KYN block	repolarization time, ±SD	times different from[a] NMDA	KA
NMDA	bursts 5-mV threshold	yes	yes	8.0 ± 3.5 (35)		$p < 0.001$
KA	spikes 15-mV threshold	no	yes	19.9 ± 5.9 (10)	$p < 0.001$	
QA	spikes 15-mV threshold	no	no	7.8 ± 3.4 (28)	$p > 0.1$	$p < 0.001$
cis-(1*R*,3*R*)-ACPD	bursts 5-mV threshold	yes	yes	10.5 ± 6.4 (6)	$p > 0.1$	$p < 0.01$
trans-(1*R*,3*S*)-ACPD	spikes 15-mV threshold	no	yes	12.7 ± 3.1 (10)	$p < 0.002$	$p < 0.01$
cis-(1*S*,3*S*)-ACPD	spikes 15-mV threshold	no	yes	15.0 ± 6.6 (10)	$p < 0.001$	$p > 0.1$
trans-(1*S*,3*R*)-ACPD	spikes 15-mV threshold	no	yes	17.0 ± 5.3 (10)	$p < 0.001$	$p > 0.1$

[a] Student's *t* test.

an ultraviolet detector was used at 214 nm. The 20-MHz ^{13}C NMR spectra show only slight differences in chemical shift between the cis and trans isomers and have seven peaks for each.

The stereoisomers of the cis compound have been studied previously;[6] in that investigation enzymic formation of the amide permitted a separation of the isomers and it was assumed that the isomer utilized by the enzyme would have the L-configuration at the carbon atom α to the amino and carboxylic acid groups. The study reported a large positive molar rotation $[M]^{25}_{226}$ +425° (0.5 M HCl) for this compound. This corresponds to the cis-1*S*,3*S* amino acid described here, which has a specific rotation of $[\alpha]^{20}_{D}$ +24.5° (6 M HCl).

Circular dichroism (CD) curves for the four isomers gave mirror-image traces for the two pairs of optical isomers, centered at 214 nm for the trans and 199 nm for the cis compounds. Both isomers having the *S* configuration at ring carbon C1 displayed a positive Cotton effect (CE) while the isomers having the *R* configuration had a negative CE.

Pharmacology

The three receptor types for excitatory amino acids are well characterized in the mammalian hippocampus both in terms of the firing patterns induced and of the selective antagonism of these effects by D-(−)-2-amino-5-phosphonovaleric (APV) and kynurenic (KYN) acids.[8] When administered microiontophoretically into stratum radiatum with intracellular recording from CA1 pyramidal neurones, excitants can be classified as resembling quisqualic (QA), α-kainic (KA), or *N*-methyl-D-aspartic (NMDA) acids. QA-like responses are depolarizations that above ca. 15 mV have tetrodotoxin-sensitive action potentials superimposed upon them, and they are unaffected by APV or KYN. The membrane repolarizes within 10 s of cessation of the ejecting current. KA-like responses are also depolarizations with superimposed spikes above a 15-mV threshold; however, further depolarization and firing continue beyond the termination of the current and repolarization is slower (ca. 20 s). The effect is prevented by KYN (ejecting currents <50 nA) but is insensitive to APV. NMDA-like responses begin at a lower level of depolarization (ca. 5 mV) when sudden depolarizing shifts of membrane potential occur, each with a superimposed brief burst of action potentials. If depolarization reaches the 15-mV level, the bursts are replaced by continuous firing. Repolarization occurs in <10 s of the end of ejection and is usually succeeded by a period of hyperpolarization. All of these phenomena are sensitive both to APV (10–20 nA) and KYN (<50 nA).

Table II. Paired Comparisons of the Iontophoretic Currents Required To Elicit Equivalent Excitations (Currents in nA ± SD)

NMDA	1.44 ± 0.49 (7)	*cis*-(1*R*,3*R*)-ACPD	3.70 ± 1.29 (7)
KA	0.56 ± 0.22 (11)	*trans*-(1*S*,3*R*)-ACPD	2.80 ± 0.96 (11)
KA	0.60 ± 0.17 (7)	*cis*-(1*S*,3*S*)-ACPD	6.20 ± 1.80 (7)
KA	0.49 ± 0.19 (9)	*trans*-(1*R*,3*S*)-ACPD	6.70 ± 2.50 (9)

Tables I and II set forth certain characteristics of the excitations elicited by the isomers of ACPD. Table I compares the patterns of firing, blockade by APV and KYN, and the repolarization times with those exhibited by NMDA, QA, and KA. Only the cis-1*R*,3*R* isomer (Scheme I, **4b**) resembles NMDA in all respects, and it differs completely from KA. It should, however, be noted that the trans-1*R*,3*S* compound (Scheme I, **4c**), which in other respects is KA-like, also has a significantly shorter repolarization time than do KA and the other two isomers of ACPD.

Table II presents the results of paired experiments in which the intensities of the ejecting currents required to elicit equivalent excitations were recorded to give a measure of the relative potencies of the compounds. *cis*-(1*R*,3*R*)-ACPD is the only isomer evoking burst firing and is 2.6 times less potent than NMDA. Of the other three, *trans*-(1*S*,3*R*)-ACPD (Scheme I, **4a**) is 5.0 times, *cis*-(1*S*,3*S*)-ACPD (Scheme I, **4d**) 10.3 times and *trans*-(1*R*,3*S*)-ACPD 13.7 times less effective than KA. The results confirm the earlier prediction[8] that a combination of the *R* configuration and cis conformation yield an excitant that is indistinguishable from NMDA: rather unexpectedly all of the remaining isomers of ACPD resembled KA.

Discussion

The use of rigid analogues of known stereochemistry is essential to the elucidation of receptor systems and this principle is amply demonstrated in the excitatory amino acid field. The excitatory action of KA has been well described in several systems.[8-10] Its structure (Figure 1, 1), contains the basic elements required to produce exci-

(8) Peet, M. J.; Curry, K.; Magnuson, D. S. K.; McLennan, H. *Neuroscience* **1987**, *22*, 563.
(9) Shinozaki, H.; Konishi, S. *Brain. Res.* **1970**, *24*, 368.
(10) Biscoe, T. J.; Evans, R. H.; Headley, P. M.; Martin, M. R.; Watkins, J. C. *Br. J. Pharmacol.* **1976**, *58*, 373.

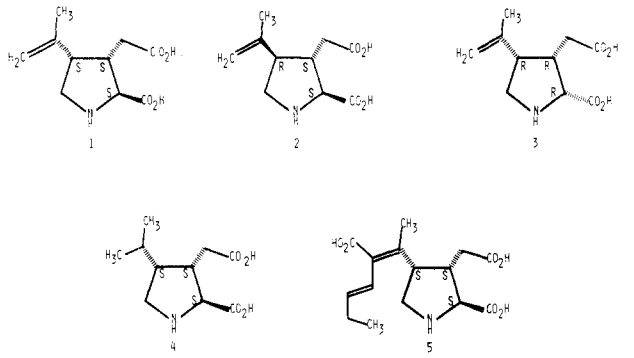

Figure 1. Structural representation of some isomers and analogues of kainic acid: (1) α-kainic acid, (2) α-allokainic acid, (3) β-kainic acid, (4) dihydrokainic acid, and (5) domoic acid.

tation, i.e., an amino group and two carboxyl groups separated by at least one carbon atom. The unsaturated isopropylene group at C4 of KA appears to be essential to its activity since hydrogenation to give dihydro-KA (Figure 1, 4) results in a compound with very little action.[11] Binding studies[12] had led to the conclusion that the reaction of KA with its receptor was dependent upon the presence of a π-electron source on the substituent at C4 of the ring; however, a later electrophysiological study[13] refuted this hypothesis. The present findings are in agreement with the latter report since the ACPD molecule lacks an unsaturated side chain yet three of its isomers are antagonized by KYN but not by APV, as is the case with KA. Three of the eight possible isomers of KA have been studied and of these only KA has any appreciable activity as an excitant. The second known isomer, α-allo KA,[14] has very little activity[9,10] and has the *R* configuration at C4 (Figure 1,2) instead of *S* as in KA. The final isomer that has been examined is β-KA. This isomer also has low activity[15,16] and has the *R* configuration at C2 (Figure 1, 3), placing the two acidic functions in closer proximity than in the KA molecule. These results indicate that, for KA to have an excitatory effect, the specific combination of the four functional groups and their spatial orientation are critical. Hitherto the only other amino acid to resemble KA is domoic acid,[10] which is structurally related and also possesses an unsaturated side chain (Figure 1, 5), although as noted above this no longer seems essential for KA-like activity. Of other rigid compunds examined in the hippocampus, no aromatic amino acid elicited a KA-mimetic response[8] and this may indicate that only aliphatic compounds are active. The intercarboxyl separation does appear to be important however: the effectiveness of *cis*-(1*S*,3*S*)-ACPD and of KA itself indicates that the separation of the carboxyl carbon atoms cannot be less than 0.35 nm. The relatively rigid pyrrolidine rings of KA and domoate and the cyclopentane ring of ACPD are presumably important for maintaining the required conformation. The fact that both isomers of *trans*-ACPD are active suggests that the KA receptor may not be highly stereospecific, and the inactivity of β-KA, which has the *R* configuration at C2, is therefore more likely due to the proximity of its carboxyl groups than to its stereochemistry.

Experimental Section

CD measurements were made with a Jasco 500 ORD/CD spectropolarimeter at 20 °C. Polarimetry was carried out in a Perkin-Elmer 241 polarimeter at the sodium D line, using a 1% solution in a 1-dm tube. HPLC was run in a Waters dual-pump system with a solvent programmer and a variable-wavelength detector. Compounds were eluted from a Waters μ Bondapak C18 reverse-phase column. UV absorbances were determined on an LKB Ultrospec I spectrophotometer. Carbon-13 NMR spectra were obtained on either a Varian CFT20 or a XL300 Fourier transform NMR machine.

3-Oxocyclopentanecarboxylic Acid (1). This compound was synthesized by the method of Stephani et al.[6] Recrystallization from diethyl ether gave a white crystalline solid, mp 62 °C (lit.[5] mp 63–65 °C); 300-MHz ^{13}C NMR (Me_4Si). 26.16, 37.1, 40.38, 40.65, 179.47, 217.33 ppm.

(+)-(*R*)- and (−)-(*S*)-3-Oxocyclopentanecarboxylic Acid (2a and 2b). The keto acid was resolved via its brucine salt, by fractional crystallization from water. Five recrystallizations gave (*R*)-3-oxocyclopentanecarboxylic acid brucine salt. The salt was destroyed by the addition of aqueous ammonia and the free acid isolated by extraction into ether. The free acid was found to have a specific rotation of $[\alpha]^{20}_D$ +22.6° (*c* 1.0, MeOH) (lit.[4] $[\alpha]^{20}_D$ +22.1°). The more soluble salt was isolated and destroyed as above, and the free acid was found to have a specific rotation of $[\alpha]^{20}_D$ −22.0° (*c* 1.0, MeOH) (lit.[4] $[\alpha]^{20}_D$ −22.2°.

***trans*-(1*S*,3*R*)- and *cis*-(1*R*,3*R*)-3-Carboxycyclopentane-1-spiro-5′-hydantoin (3a and 3b).** (*R*)-3-Oxocyclopentanecarboxylic acid (7.8 mmol) was dissolved in 25 mL of 1:1 ethanol–water and the solution neutralized by the addition of ammonium solution. Potassium cyanide (8.46 mmol), ammonium carbonate (15.5 mmol), and ammonium chloride (7.8 mmol) were added, and the mixture was maintained at 55–60 °C for 6 h. The product was isolated by acidification of the reaction mixture with hydrochloric acid. Acidification caused the precipitation of a white solid, which was recrystallized from water several times.

***trans*-(1*R*,3*S*)- and *cis*-(1*S*,3*S*)-3-Carboxycyclopentane-1-spiro-5′-hydantoin (3c and 3d).** These compounds were synthesized from (*S*)-3-oxocyclopentanecarboxylic acid in the same way as **3a** and **3b** above.

***trans*-(1*S*,3*R*)- and *cis*-(1*R*,3*R*)-1-Amino-1,3-cyclopentanedicarboxylic Acids (4a and 4b).** The hydantoins **3a** and **3b** were hydrolyzed by refluxing in 1 M aqueous sodium hydroxide for 12 h. The reaction mixture was acidified by the addition of hydrochloric acid to a pH of 5.0. The solution was filtered and reduced in vacuo to one-third of its original volume. A white crystalline material was precipitated and collected by filtration. This material was eluted on a thin-layer chromatography plate showing two ninhydrin staining spots corresponding to authentic samples of racemic *cis*- and *trans*-ACPD.

Recrystallization of the product from water–ethanol provided pure *trans*-(1*S*,3*R*)-ACPD as microcrystals: mp 248 °C dec (lit.[6] mp 246–250 °C); specific rotation $[\alpha]^{20}_D$ −6.9° (*c* 1.0, H_2O), −10.1° (*c* = 1.0, 6 M HCl); circular dichroism $[\theta]^{20}_{214}$ +1696 L mol^{-1} cm^{-1}; ^{13}C NMR (Me_4Si) 29.19, 35.53, 38.76, 43.91, 64.67, 174.09, and 178.65 ppm.

The mother liquors were combined and carefully reduced to precipitate all of the trans product and finally evaporated to dryness to give the chloride salt of *cis*-ACPD. This salt was taken up into ethanol and destroyed by the addition of propylene oxide. The free *cis* amino acid was collected by filtration: mp 277 °C dec (lit.[6] mp 275–280 °C); specific rotation $[\alpha]^{20}_D$ −8.2° (*c* 1.0, H_2O), −24.0° (*c* 1.0 6 M HCl); circular dichroism $[\theta]^{20}_{199}$ −2076 L mol^{-1} cm^{-1}; ^{13}C NMR (Me_4Si) 29.15, 36.22, 38.62, 43.19, 64.75, 173.86, and 177.29 ppm.

***trans*-(1*R*,3*S*)- and *cis*-(1*S*,3*S*)-1-Amino-1,3-cyclopentanedicarboxylic Acids (4c and 4d).** The hydantoins were hydrolyzed and the amino acids isolated as above. Specific rotation for *trans*-(1*R*,3*S*)-**4c**, $[\alpha]^{20}_D$ +7.1° (*c* 1.0, H_2O), +10.5° (*c* 1.0, 6 M HCl); specific rotation for *cis*-(1*S*,3*S*)-**4d**, $[\alpha]^{20}_D$ +8.4° (*c* 1.0, H_2O), +24.5° (*c* 1.0, 6 M HCl).

The ^{13}C NMR spectra for the 1*R*,3*S* and 1*S*,3*S* compounds were identical with those found for the 1*S*,3*R* and 1*R*,3*R* amino acids.

(11) Johnston, G. A. R.; Curtis, D. R.; Davies, J.; McCulloch, R. M. *Nature (London)* **1974**, *248*, 804.
(12) Slevin, J. T.; Collins, J. F.; Coyle, J. T. *Brain Res.* **1983**, *265*, 169.
(13) King, A. E.; Wheal, H. V. *Eur. J. Pharmacol.* **1984**, *102*, 129.
(14) Takeuchi, H.; Watanabe, K.; Nomoto, K.; Ohfune, Y.; Takemoto, T. *Eur. J. Pharmacol.* **1984**, *102*, 325.
(15) Stone, T. W.; Collins, J. F. *J. Pharm. Pharmacol.* **1985**, *37*, 668.
(16) Shinozaki, H.; Shitaya, I. *Neuropharmacology* **1976**, *15*, 145.

CD studies gave mirro-image curves to those described for the 1*S*,3*R* and 1*R*,3*R* compounds.

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Registry No. 1, 62696-96-2; **2a**, 13012-38-9; **2b**, 71830-06-3; **3a**, 112896-82-9; **3b**, 112965-97-6; **3c**, 112965-98-7; **3d**, 112965-99-8; **4a**, 111900-32-4; **4b**, 111900-33-5; **4c**, 89253-38-3; **4d**, 111900-31-3.

N,N-Di-*n*-propylserotonin: Binding at Serotonin Binding Sites and a Comparison with 8-Hydroxy-2-(di-*n*-propylamino)tetralin

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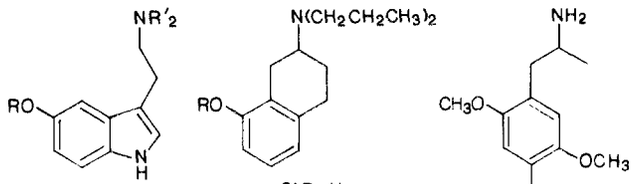
8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) is a serotonergic agonist with high affinity and selectivity for a particular population of central serotonin (5-HT) binding sites (i.e., 5-HT_{1A} sites). Because the selectivity of 8-OH-DPAT may be due to the terminal amine substituents, the di-*n*-propyl analogue of 5-HT (i.e., **4**) and of 5-methoxytryptamine (i.e., **5**) were prepared and compared with 8-OH-DPAT with respect to their binding profile. Unlike 8-OH-DPAT, neither compound **4** nor **5** displays selectivity for 5-HT_{1A} vs 5-HT_2 sites. Consistent with these results, stimulus generalization occurs with **5** both in rats trained to discriminate 8-OH-DPAT from saline and in rats trained to discriminate the 5-HT_2 agonist DOM from saline. The results of this study suggest that it is not the *N,N*-dipropyl groups that account for selectivity, but, rather, it is some feature associated with the pyrrole portion of the indolylalkanamines that is important.

Several different populations of central serotonin (5-hydroxytryptamine; 5-HT) binding sites have been identified in mammalian brain; these include 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 sites.[1] There is now evidence to suggest that members of a new class of anxiolytic agents (i.e., second generation anxiolytics) act as 5-HT_{1A} agonists and that both thermoregulation and appetite control may also involve a 5-HT_{1A} mechanism (see ref 1 for a review). These findings have focused considerable attention on this particular population of sites. The most potent and selective 5-HT_{1A} agonist is 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **6**);[1-3] 8-OH-DPAT binds at 5-HT_{1A} sites with high affinity (K_i = ca. 2 nM[1]), and [^{3}H]-8-OH-DPAT is now commonly used to label these sites.[1] An early report by Hoyer and co-workers[4] showed that the di-*n*-propyl portion of 8-OH-DPAT makes a significant (>50-fold) contribution to its affinity for 5-HT_{1A} sites. The affinity of 5-HT (**1**) for 5-HT_{1A} sites is essentially identical with that of 8-OH-DPAT; however, 5-HT does not enjoy the selectivity displayed by 8-OH-DPAT. Arvidsson and coworkers[5] demonstrated that the two *n*-propyl groups of 8-OH-DPAT are necessary for optimal activity in a biochemical measure of serotonergic activity (i.e., receptor-mediated feedback inhibition of 5-hydroxytryptophan accumulation). Aminotetralin analogues with alkyl groups smaller than *n*-propyl are less active whereas those with larger substituents are essentially inactive.[5] They have also argued that 5-HT and 8-OH-DPAT share common aromatic and terminal amine sites in their binding to serotonin receptors.[5] If this is the case, it may be possible to enhance the affinity and/or selectivity of 5-HT for 5-HT_{1A} sites by incorporating the two *n*-propyl substituents onto its terminal amine. Consequently, *N,N*-di-*n*-propyl-2-[(5-hydroxyindol-3-yl)amino]ethane (i.e., *N,N*-di-*n*-propylserotonin; DiPS) (**4**) and its *O*-methyl ether, **5**, were synthesized and evaluated.

Chemistry. Compound **4** has been previously mentioned in the literature;[6-8] however, details of its synthesis and characterization of the intermediates involved were not provided.[6] Compound **4** was prepared by the Speeter–Anthony method.[9] 5-(Benzyloxy)indole was acylated with oxalyl chloride, and the resultant glyoxylyl chloride was allowed to react with di-*n*-propylamine to afford the di-*n*-propylglyoxylamide; reduction of the glyoxylamide with $LiAlH_4$ provided the benzyl-protected derivative of **4** which was isolated as the hydrochloride salt (i.e., **9**). Deprotection of **9** to **4** was achieved by catalytic hydrogenolysis.



1: R = R′ = H
2: R = Me; R′ = H
3: R = R′ = Me
4: R = H; R′ = *n*-Pr
5: R = Me; R′ = *n*-Pr

6: R = H
7: R = Me

8

Binding Studies. Binding data for 5-HT (**1**), DiPS (**4**), 8-OH-DPAT (**6**), and their *O*-methyl ethers (i.e., **2**, **5**, and **7**, respectively) at 5-HT_{1A}, 5-HT_{1B}, [^{3}H]ketanserin-labeled 5-HT_2, and [^{3}H]DOB-labeled 5-HT_2 sites are shown in Table I. Data for the *N,N*-dimethyl derivative of the

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(1) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.
(2) Middlemiss, D. N.; Fozard, J. R. *Eur. J. Pharmacol.* **1983**, *90*, 151.
(3) Gozlan, H.; El-Mestikawy, S.; Pichat, L.; Glowinski, J.; Hamon, M. *Nature (London)* **1983**, *305*, 140.
(4) Hoyer, D.; Engel, G.; Kalkman, H. O. *Eur. J. Pharmacol.* **1985**, *118*, 13.
(5) Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikstrom, H.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 45.
(6) Barlow, R. B.; Kahn, I. *Br. J. Pharmacol.* **1959**, *14*, 265.
(7) Vane, J. R. *Br. J. Pharmacol.* **1959**, *14*, 87.
(8) Born, G. V. R.; Juengjaroen, K.; Michal, F. *Br. J. Pharmacol.* **1972**, *44*, 117.
(9) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208.

0022-2623/88/1831-0867$01.50/0