Serotonin Receptor Affinity of Cathinone and Related Analogues[1]

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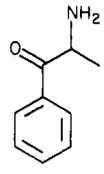
A series of cathinone (α-aminopropiophenone) analogues was examined using the isolated rat fundus preparation. (*S*)-(−)-Cathinone possesses twice the serotonin receptor affinity of (±)-cathinone and four times the affinity of racemic amphetamine. Several derivatives of cathinone were found to either possess a lower affinity than the parent compound or did not interact with the receptors in a competitive manner. Several novel analogues, 1-(aminomethyl)-3,4-dihydronaphthalene hydrochloride (**3**), 4-(aminomethyl)-3-chromene hydrochloride (**4b**), as well as its 6-methoxy derivative, **4a**, interact with serotonin receptors but in a fashion which is, most likely, dissimilar to the interaction of the substituted cathinone analogues.

In an effort to map the serotonin (5-hydroxytryptamine, 5-HT) receptors of the rat fundus, we have determined the receptor affinities of derivatives of several classes of compounds. The 5-HT receptor affinities of phenalkylamines, for example, vary depending upon the presence and location of substituent groups.[2,3] Cathinone (α-aminopropiophenone, **1**) and cathine (1-phenyl-2-aminopropanol or norpseudoephedrine, **2**), isomers of which are naturally occurring psychoactive constituents of the shrub *Catha edulis*,[4] possess a phenylisopropylamine backbone and offer a new series of compounds for evaluation.

In a preliminary investigation, it was found that racemic **1** possesses twice the 5-HT receptor affinity of racemic



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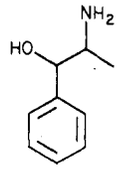

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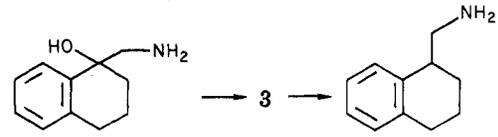
phenylisopropylamine (amphetamine) and that **2** acts in such a manner as to preclude determination of valid affinity data (pA_2 values).[3] Furthermore, the presence of a 2-methoxy substituent decreases affinity severalfold, and it was suggested that this substituent might sterically interfere with a side-chain conformation that is optimal for receptor binding.

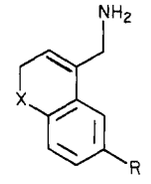
How might cathinone and its derivatives interact with 5-HT receptors? Lysergic acid diethylamide (LSD) contains within its tetracyclic framework both an indolealkylamine and a phenalkylamine component; these may represent the conformations in which the latter two classes of compounds interact with 5-HT receptors.[5] The C_{10} position of LSD and the benzylic carbon atom of **1** are both sp^2 hybridized. This sp^2-hybridized atom may play a role in receptor affinity.

The aims of the present study are (a) to obtain the 5-HT receptor affinities of several additional cathinone analogues, in order to explore their SAR and to determine if similarities exist with the SAR of the phenalkylamines, and (b) to prepare several novel compounds which possess the sp^2-hybridized carbon atom common to LSD and cathinone but which are somewhat more conformationally restricted than **1** (i.e., **3** and **4**) and which might mimic the effect of cathinone at 5-HT receptors.

Scheme I



5 **6**



3, X = CH_2; R = H
4a, X = O; R = OCH_3
4b, X = O; R = H

Chemistry. Compound **3** was conveniently prepared by dehydration of (±)-1-(aminomethyl)-1-hydroxy-1,2,3,4-tetrahydronaphthalene hydrochloride (**5**).[6] The tetrahydro derivative of **3** (i.e., **6**) could be obtained by catalytic reduction of **3** or by hydrogenolysis of **5** using 10% Pd/C and $HClO_4$ (Scheme I).

The synthesis of the chroman and chromene analogues is shown in Scheme II. Conceptually, the chromanols **13a** and **13b** can be dehydrated, in a manner similar to that employed for the preparation of **3**, to afford **4a** and **4b**. Acylation of 4-methoxyphenol (**7**) with 3-chloropropionyl chloride yields **8**, which upon heating with freshly sublimed $AlCl_3$ undergoes Fries rearrangement to **9**. Compound **9** was not isolated but was treated with dilute base to afford **10** (after acidification). Although **12a** might be prepared by methylation of **10**, the yields of **10**, from **7**, were unacceptably low. Alternatively, alkylation of **7** with sodium 3-chloropropionate, followed by cyclization of the resultant product by heating with PPA, gave **12a** in an overall yield of about 60%. Compounds **12a** and **12b** were allowed to react with Me_3SiCN,[6] and the resultant products were reduced with $LiAlH_4$ to give **13a** and **13b**, respectively.

Heating a methanolic solution of **13a** (**13b**) in the presence of HCl effected dehydration to **4a** (**4b**) in low yield. Under these conditions, exocyclic dehydration is apparently a competing reaction, and workup of the reaction results in isolation of varying amounts of NH_4Cl. If the dehydration is performed at room temperature, **14a** (**14b**) is isolated in 70% yield. Using ethanol as solvent, **13b** yields 88% of **14c**. Compound **14a** (**14c**) was dissolved

(1) Presented, in part, at the Southeast Regional American Chemical Society Meeting, Roanoke, VA, 1979.
(2) Glennon, R. A.; Liebowitz, S. M.; Mack, E. C. *J. Med. Chem.* **1978**, *21*, 822.
(3) Glennon, R. A.; Liebowitz, S. M.; Anderson, G. M. *J. Med. Chem.* **1980**, *23*, 294.
(4) United Nations Document MNAR/3, "The Botany and Chemistry of Khat", 1979, 1.
(5) See discussion in Glennon, R. A.; Liebowitz, S. M.; Leming-Doot, D. *J. Med. Chem.* **1980**, *23*, 990.
(6) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

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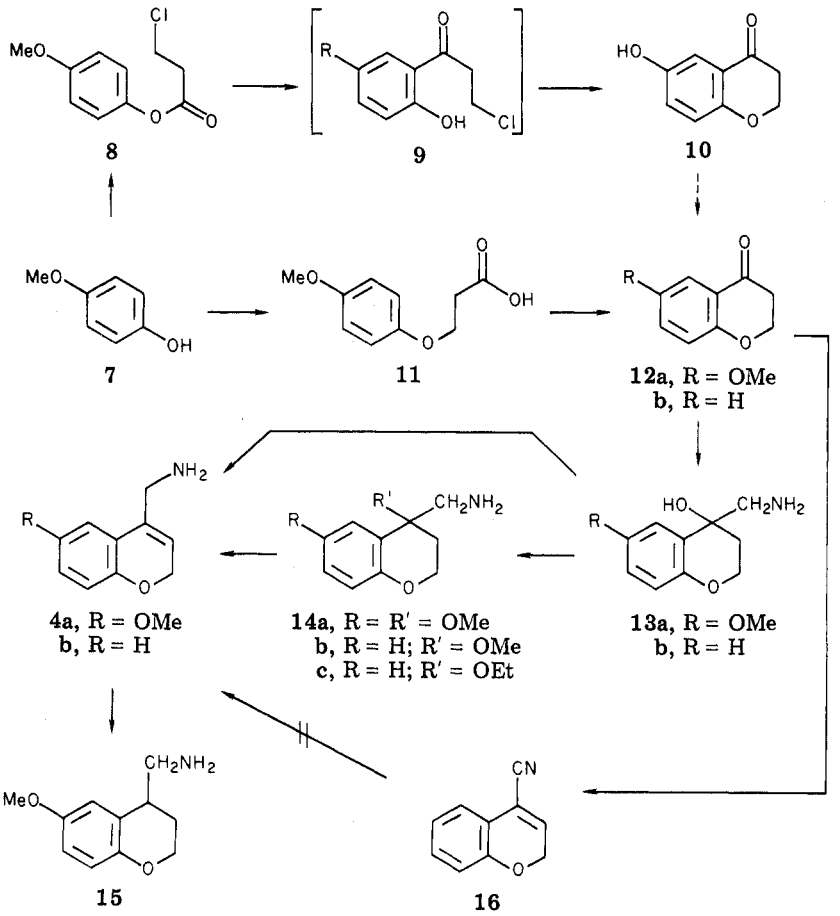
Scheme II



in glacial HOAc to which HCl had been previously added; heating this solution at reflux for 1–2 h gave **4a** (**4b**) in 50% yield. Catalytic reduction of **4a** gave the desired methoxy derivative **15**. In another effort to prepare **4b** and as a model reaction for the preparation of **15**, the unsaturated nitrile **16** was prepared from **12b**. Attempts to reduce **16** with a variety of reducing agents resulted in the formation of complex mixtures from which **4b** could be identified (GC/MS) but not isolated.

Results and Discussion

While certain of the compounds interact with the 5-HT receptors in a competitive manner, as determined by the slopes of their Schild plots (Table I), some (i.e., **1b**, **5**, **6**, **17**, **20**, and **21**) do not. As a consequence, valid pA_2 values could not be obtained for the latter group of compounds. Racemic cathinone (**1**) possesses twice the affinity of (±)-amphetamine (**25**);[3] (−)-cathinone (**1a**) possesses twice the affinity of **1**, while its enantiomer, (+)-cathinone (**1b**), does not interact with the 5-HT receptors in a competitive manner.[7] 4-Methoxylation of **1** (i.e., **18**) has little effect on affinity, whereas demethylation of this methoxy group, to give **19**, halves affinity. The 2,4-dimethoxy derivative **22** has one-fifth the affinity of **1**; the 2-methoxy derivative **17** and the 4-halogenated compounds **20** and **21** result in a noncompetitive interaction. Removal of the α-methyl group of **1**, to give **26** and reduction of the carbonyl group of **26** to the hydroxy derivative **27** also result in a noncompetitive receptor interaction. Interestingly, when the carbonyl group of **26** is replaced by an amino group, the resultant compound, **28** does interact competitively, although it possesses a rather low affinity (pA_2 = 4.90).

The affinity of the dihydronaphthalene analogue **3** (pA_2 = 5.81) is similar to that of (−)-cathinone (**1a**) and twice that of (±)-cathinone (**1**). Inclusion of an oxygen atom in the ring of **3** results in the chromene **4b** (pA_2 = 4.94). Methoxylation of the latter compound para to the oxygen atom (i.e., **4a**) results in a 15-fold increase in affinity; this is similar to the 10- to 20-fold increase in affinity observed for para-methoxylation of the corresponding methoxyphenalkylamines.[3] The tetrahydronaththalene **6** and the hydroxy intermediate **5** do not interact with the 5-HT receptors in a competitive manner. The same is true of the hydroxy (e.g., **13a**) and alkoxy (**14a,b**) analogues in the chroman series; however, the reduced derivative of **4a** (i.e., **15**), unlike the reduced derivative of **3**, interacts with the receptors in a competitive manner and possesses approximately half the affinity of **4a**.

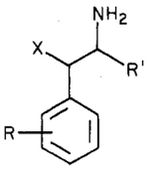
With respect to SAR, very few similarities exist between the cathinone analogues and the phenalkylamines (whose SAR has been previously reported[3]); different modes of receptor interaction may be involved. Whereas the *R* isomers of substituted phenalkylamines usually constitute the eutomeric series with respect to 5-HT receptor affinity,[8] (*S*)-(−)-cathinone possesses twice the affinity of its racemate. Furthermore, removal of the α-methyl group of phenylisopropylamines has no effect on affinity (e.g., compare **24** and **25**), whereas removal of the α-methyl group of **1**, to give **26**, results in a noncompetitive interaction.

The increase in affinity of **3** over that of phenethylamine (**24**; pA_2 = 5.26) might be due (a) to conformational re-

(7) We had previously reported identical pA_2 values for racemic cathinone and (*S*)-(−)-cathinone.[3] It is now thought that the (*S*)-(−)-cathinone used originally was actually mislabeled racemic cathinone.

(8) Glennon, R. A. *Life Sci.* **1979**, *24*, 1487.

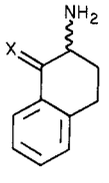
Table I. Serotonin Receptor Affinity Data for Cathinone and Related Analogues



no.	R	R′	X	pA_2[a]	slope[b]	N[c]
1	(±)-H	Me	=O	5.55 (±0.29)[d]	0.89 (±0.09)	5 (23)
1a	(−)-H	Me	=O	5.86 (±0.14)	1.08 (±0.30)	6 (31)
1b	(+)-H	Me	=O	*e*	0.32 (±0.06)	4 (20)
17	(±)-2-OMe	Me	=O	*e*	0.67 (±0.09)	4 (19)
18	(±)-4-OMe	Me	=O	5.65 (±0.07)	0.90 (±0.13)	3 (16)
19	(±)-4-OH	Me	=O	5.30 (±0.15)	1.06 (±0.22)	4 (20)
20	(±)-4-Cl	Me	=O	*e*	0.64[f]	6 (27)
21	(±)-4-F	Me	=O	*e*	0.63 (±0.02)	4 (18)
22	(±)-2,4-$(OMe)_2$	Me	=O	4.95 (±0.09)	0.81 (±0.10)	3 (15)
23	(±)-3,4-$(OMe)_2$	Me	=O	6.14 (±0.18)	0.77 (±0.28)[g]	5 (25)
24	H	H	H	5.26[h]		
25	(±)-H	Me	H	5.27[h]		
26	H	H	=O	*e*	0.53 (±0.09)	4 (20)
27	(±)-H	H	OH	*e*	0.52 (±0.30)	3 (15)
28	(±)-H	H	NH_2	4.90 (±0.40)	0.86 (±0.21)	5 (22)
29a (2-aminotetralin)				5.61		
29b				6.04 (±0.13)	1.07 (±0.21)	5 (22)
3				5.81 (±0.23)	0.92 (±0.14)	8 (39)
4a				6.12 (±0.34)	0.86 (±0.27)	6 (28)
4b				4.94 (±0.32)	0.82 (±0.23)	4 (20)
5				*e*	0.56 (±0.18)	3 (14)
6				*e*	0.67 (±0.21)	5 (20)
15				5.94 (±0.12)	1.10 (±0.02)	3 (15)

[a] pA_2 value followed by standard deviation. Compounds **13a**, **14a**, and **14b** were examined in duplicate determinations; Schild plot slopes ranged from −0.54 to −0.69. Compound **13b** had no effect, on the dose-response curve to 5-HT, at doses of up to 10 μM in one determination and 30 μM in a second determination. [b] Negative slope of Schild plot followed by standard deviation. [c] Number of pA_2 determinations followed by total number of dose-response curves (in parentheses). [d] pA_2 value, but not slope, has been previously reported. [e] Unable to determine valid pA_2 value due to the slope of the Schild plot. [f] Most concentrations of **20** appear to have no effect on the dose-response curve for 5-HT; in one instance, a Schild plot slope of −0.64 was obtained. [g] Compound **23**, most likely, does not interact with 5-HT receptors in a competitive manner; however, insufficient compound precluded additional determinations. [h] pA_2 values for phenethylamine (**24**) and amphetamine (**25**) have been previously reported[3] and are included here only for comparative purposes.

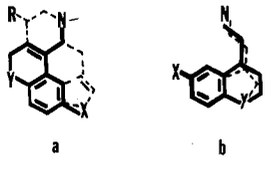
strictions imposed by the ring and/or (b) to some binding feature associated with the ring itself (e.g., the sp^2-hybridized carbon atoms). Because 2-aminotetralin (**29a**),



29a, X = H
b, X = O

an example of a relatively rigid phenalkylamine, possesses twice the affinity of **24**, while **29b**, an analogue of **1**, possesses three times the affinity of **1**, conformational considerations may play a role in the higher affinity of **3** as compared with **24**. On the other hand, reduction of the C_1–C_2 double bond of **3**, to give **6**, results in a noncompetitive interaction. Therefore, the double bond, through an electronic effect or through a conformational effect, also appears to play a role in the interaction of **3** with 5-HT receptors.

The cyclic compounds **3** and **4** appear to behave more like the phenethylamines than like the cathinone derivatives, in that their interaction with 5-HT receptors is competitive even though they lack an α-methyl group. However, because of the lower affinity of **4b** as compared with **3** and because of the differences observed for the reduced analogues **6** and **15**, the mode of interaction even within this series of cyclic derivatives may be dissimilar.



a b

Figure 1. Structure of **3** (Y = CH_2; X = H), **4a** (Y = O; X = OMe), and **4b** (Y = O; X = H) superimposed over a molecule of (a) LSD or (b) tryptamine.

At this time, there are insufficient data to support the suggestion that **1**, **3**, and **4** might mimic a partial structure of LSD as shown in Figure **1a**; an alternative interaction for **3** and/or **4** is also possible (Figure 1b). Additional studies on derivatives of **3** and **4** are necessary to resolve this problem; nevertheless, the sp^2-hybridized atoms (1 position of **3** and 4 position of **4**) appear to play a role in the 5-HT receptor interactions of these compounds.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were obtained on a Perkin-Elmer R-24 spectrometer, and chemical shifts are reported relative to tetramethylsilane (DSS, where D_2O was used as solvent). Infrared and mass spectra were determined using a Perkin-Elmer 257 spectrophotometer and a Finnigan 4000 series GC/MS, respectively. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and values are within 0.4% of theoretical.

1-(Aminomethyl)-3,4-dihydronaphthalene Hydrochloride (3). Dry HCl gas was bubbled into a solution of **5** (4.5 g, 25.4 mmol) in absolute EtOH (100 mL) at 0 °C for 5 min. The solution

was heated at reflux for 4 h and evaporated to dryness under reduced pressure to yield crude **3**. Recrystallization from an absolute EtOH–Et_2O mixture afforded 3.35 g (67%) of **3** as a fluffy white powder: mp 191–193 °C; NMR (Me_2SO-d_6) δ 2.1–2.9 (m, 4 H), 3.85 (s, 2 H, CH_2N), 6.25 (m, 1 H, CH), 7.15–7.45 (m, 4 H). Anal. ($C_{11}H_{13}N$·HCl·0.5H_2O) C, H, N.

4-(Aminomethyl)-6-methoxy-3-chromene Hydrochloride (4a). Method A. Dry HCl gas was bubbled into a solution of **13a** (0.2 g, 0.8 mmol) in absolute EtOH (25 mL) at 0 °C for 2 min. This solution was heated at reflux for 1.5 h; the solvent was evaporated under reduced pressure and was replaced with benzene (25 mL). The benzene was removed in vacuo and the process was repeated twice more to yield a crude yellow product. The product was stirred with Et_2O (25 mL) overnight and collected by filtration. Recrystallization from 2-propanol gave 16 mg (9%) of **4a**, mp 213–215 °C.

Method B. Dry HCl gas was bubbled into a solution of **14a** (0.8 g, 3.08 mmol) in glacial HOAc at 5 °C for 1 min, and the solution was then heated at reflux for 1 h. The solvent was removed under reduced pressure; the residual product was triturated with Et_2O and collected by filtration. The crude off-white product was dissolved in hot absolute EtOH (10 mL), treated with charcoal, and precipitated by the addition of Et_2O (10 mL). The solid material was collected (mp 230–231 °C) and recrystallized from 2-propanol to yield 0.35 g (50%) of **4a** as small white needles, mp 215–216 °C. Approximately 15 mg of 2-propanol-insoluble material was collected and tentatively identified as NH_4Cl (sublimes 335–345 °C). The analytical sample of **4a** melted at 216–217 °C: NMR (Me_2SO-d_6) δ 3.75 (s, 3 H, OCH_3), 3.85 (s, 2 H, CH_2N), 4.70 (d, 2 H, OCH_2), 6.10 (t, 1 H, CH), 6.7–7.0 (m, 3 H, ArH), 8.0 (br signal, 3 H, NH_3); mass spectrum, *m/e* (relative intensity) 191 (70), 173 (100). Anal. ($C_{11}H_{13}NO_2$·HCl) C, H, N.

4-(Aminomethyl)-3-chromene Hydrochloride (4b). Compound **4b** was prepared from **13b** using method A (for **4a**). Recrystallization from 2-propanol gave a 12% yield of **4b**, mp 226–227 °C. Compound **4b** was also prepared from either **14b** or **14c** in 50% yield using method B: mp 227 °C; NMR (Me_2SO-d_6) δ 3.8 (s, 2 H, CH_2N), 4.76 (d, 2 H, OCH_2), 6.05 (t, 1 H, CH), 6.7–7.3 (m, 4 H, ArH), 8.0 (br signal, 3 H, NH_3); mass spectrum, *m/e* (relative intensity) 161 (57), 160 (80), 143 (100). Anal. ($C_{10}H_{11}NO$·HCl) C, H, N.

(±)-1-(Aminomethyl)-1-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrochloride (5). Compound **5** (as the free base) was prepared from 1-tetralone as reported by Evans et al.[6] In our hands however, the product crystallized upon standing to give a white solid, mp 74–76 °C. The hydrochloride salt was prepared, and recrystallization from an absolute EtOH–Et_2O mixture gave **5** as white crystals, mp 165–167 °C. Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

(±)-1-(Aminomethyl)-1,2,3,4-tetrahydronaphthalene Hydrochloride (6). Method A. A solution of **3** (2 g, 10.2 mmol) in absolute ethanol (75 mL) was shaken with 10% Pd/C (0.2 g) in an atmosphere of H_2 at 50 psig for 3.5 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to yield crude **6**. Recrystallization from an absolute EtOH–Et_2O mixture gave 1.2 g (60%) of **6** as a white powder: mp 217–220 °C; NMR (D_2O) δ 1.95 (m, 4 H), 2.85 (m, 2 H), 3.35 (m, 3 H, CH, CH_2N), 7.25–7.40 (m, 4 H).

Method B. A solution of **5** (0.5 g, 2.3 mmol) in absolute EtOH (50 mL) containing 10% Pd/C (0.5 g) and a trace of 70% $HClO_4$ was shaken in an atmosphere of H_2 at 50 psig overnight. The catalyst was removed by filtration, and the filtrate was evaporated to near dryness under reduced pressure. A solution of 5% $NaHCO_3$ (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The solid residue was dissolved in Et_2O (30 mL); the hydrochloride salt was obtained by bubbling HCl gas through the ether solution to yield 82 mg (18%) of **6**, mp 215–217 °C. Anal. ($C_{11}H_{15}N$·HCl) C, H, N.

4-Methoxyphenyl 3-Chloropropionate (8). Freshly distilled (Kugelrohr) 3-chloropropionic acid (25 g, 230 mmol) was heated at reflux with $SOCl_2$ (31 g, 261 mmol; freshly distilled from linseed oil) in benzene (50 mL) for 2.5 h. The clear liquid was evaporated to dryness under reduced pressure; 4-methoxyphenol (22 g, 177 mmol) was added, and the mixture was heated at reflux for 2.5 h. When cool, H_2O (50 mL) was added; the mixture was extracted thrice with CH_2Cl_2 (75 mL), and the combined extracts were washed twice with 10% KOH (100 mL) and twice with H_2O (100 mL), dried (Mg_2SO_4), and evaporated under reduced pressure to a yellow oil. Distillation afforded 24.5 g (64%) of **8** as a pale-yellow liquid, bp 103–104 °C (0.04 mm). Anal. ($C_{10}H_{11}ClO_3$) C, H.

6-Hydroxychroman-4-one (10). Freshly sublimed $AlCl_3$ (45 g, 337 mmol) was added portionwise to a solution of **8** (15 g, 70 mmol) in CH_2Cl_2 (40 mL) at a rate to allow gentle reflux. The mixture was heated to 75 °C (oil bath) to evaporate the CH_2Cl_2; the temperature was slowly increased to 170 °C (2 h), and heating at this temperature was continued for another 1.5 h. The mixture was chilled to 0 °C, and H_2O (150 mL) was slowly added; this was followed by the addition of concentrated hydrochloric acid (50 mL). Benzene (50 mL) was added at room temperature and the mixture was allowed to stir overnight (16 h). The mixture was filtered and the filtrate was extracted with 10% aqueous KOH (3 × 75 mL); the combined aqueous extracts were acidified with hydrochloric acid and extracted with CH_2Cl_2 (3 × 100 mL). After drying (Na_2SO_4), the CH_2Cl_2 solution was evaporated to dryness under reduced pressure to afford crude **10**. Recrystallization from a benzene–ligroin mixture gave 0.5 g (4%) of **10** as bright yellow crystals, mp 129–131 °C (lit.[9] mp 134–135 °C).

3-(4-Methoxyphenoxy)propionic Acid (11). A solution of 4-methoxyphenol (35 g, 282 mmol) in 20% aqueous KOH (100 mL) was added to a solution of 3-chloropropionic acid (30.6 g, 282 mmol) and $NaHCO_3$ (23.6 g, 282 mmol) in H_2O (100 mL). The solution was heated on a steam bath for 3 h, acidified to pH 5 by the addition of 10% HCl, and extracted with Et_2O (3 × 100 mL). The combined ethereal solutions were extracted with 10% $NaHCO_3$ (4 × 100 mL), and the aqueous extract was reacidified to pH 5 by the addition of 10% HCl to yield a white precipitate. The precipitate was dissolved in CH_2Cl_2 (100 mL). The aqueous extract was extracted twice with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 solutions were dried (Na_2SO_4) and evaporated to dryness under reduced pressure to afford crude **11**. Recrystallization from benzene gave 7.1 g (73%, based on recovered 4-methoxyphenol) of **11**, mp 105–107 °C (lit.[10] mp 106–107 °C).

6-Methoxychroman-4-one (12a). A solution of **11** (7 g, 35.7 mmol) in polyphosphoric acid (100 mL) was stirred at 65–75 °C (oil bath) for 1 h. The warm red solution was slowly poured onto ice (50 g) and was stirred for 20 min. The resultant precipitate was collected by filtration and washed several times 10% $NaHCO_3$ and then H_2O. Distillation [Kugelrohr, 65–75 °C (0.14 mm)] yielded 5.2 g (82%) of **12a** as a white solid, mp 47–49° C (lit.[11] mp 47–50 °C).

(±)-4-(Aminomethyl)-6-methoxy-4-chromanol Hydrochloride (13a). Trimethylsilyl cyanide (10 mL) was introduced via syringe to a flask containing 6-methoxychromanone (**12a**; 5.11 g, 28.7 mmol.) and ZnI_2 (100 mg) under an atmosphere of N_2. The solution was stirred at 50 °C (oil bath) for 5 h and cooled to room temperature, and dry THF (100 mL) was added. This solution was added dropwise to a stirred suspension of $LiAlH_4$ (2.28 g, 60 mmol) in dry THF (50 mL) at 0 °C. The mixture was heated at reflux for 2 h and cooled to 0 °C, and Na_2SO_4·10H_2O was added in small portions until the evolution of H_2 ceased. The precipitated material was removed by filtration and was washed with warm THF (30 mL). The combined THF solutions were dried (Na_2SO_4) and evaporated to dryness to give 5.4 g (90%) of the amine as a white solid: mp 105–107 °C; NMR ($CDCl_3$) δ 2.05 (m, 3 H, OH, CH_2), 2.95 (s, 2 H, CH_2N), 3.75 (s, 3 H, OCH_3), 4.2 (t, 2 H, OCH_2), 6.75–7.0 (m, 3 H, ArH); mass spectrum, *m/e* (relative intensity) 209 (8), 137 (100). The hydrochloride salt was prepared and recrystallized from an absolute EtOH–Et_2O mixture, mp 157–158 °C. Anal. ($C_{11}H_{16}NO_3$·HCl) C, H, N.

(±)-4-(Aminomethyl)-4-chromanol (13b). Compound **13b** was prepared in 75% yield from 4-chromanone in the same manner employed for the preparation of **13a**. The hydrochloride salt was recrystallized from a methanol–Et_2O mixture: mp 172–174 °C; NMR (Me_2SO-d_6) δ 2.1 (m, 2 H), 3.05 (s, 2 H, CH_2N), 4.1 (t, 2 H, OCH_2), 6.1 (br signal, 1 H, OH), 6.6–7.3 (m, 4 H, ArH),

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8.3 (br signal, 3 H, NH_3); mass spectrum, m/e (relative intensity) 179 (9), 149 (100). Anal. ($C_{10}H_{13}NO_2$·HCl) C, H, N.

(±)-4-(Aminomethyl)-4,6-dimethoxychroman Hydrochloride (14a). Compound **14a** was prepared from **13a** in 72% yield by the same method employed for the synthesis of **14b**: mp 168–170 °C (dec) after recrystallization from a methanol–Et_2O mixture; NMR (Me_2SO-d_6) δ 2.1 (m, 2 H, CH_2), 2.85 (s, 3 H, OCH_3), 3.05 (s, 2 H, CH_2N), 3.55 (s, 3 H, $ArOCH_3$), 4.05 (t, 2 H, OCH_2), 6.2 (s, 3 H, ArH), 8.2 (br signal, 3 H, NH_3); mass spectrum, m/e (relative intensity) 223 (5), 193 (100). Anal. ($C_{12}H_{17}NO_3$·HCl) C, H, N.

(±)-4-(Aminomethyl)-4-methoxychroman Chloride (14b). Dry HCl gas was bubbled into a solution of **13b** (2 g, 9.28 mmol) in MeOH (100 mL) at 0 °C for 2 min. The exothermic reaction was cooled so as to not allow the temperature to exceed 30 °C; stirring at room temperature was continued for 2 h. The MeOH was evaporated under reduced pressure, and the resultant product was recrystallized from a MeOH–Et_2O mixture to give 1.83 g (71%) of **14b** as white crystals: mp 183–185 °C dec; NMR (Me_2SO-d_6) δ 2.15 (m, 2 H, CH_2), 3.0 (s, 3 H, OCH_3), 3.25 (s, 2 H, CH_2N), 4.3 (m, 2 H, OCH_2), 6.8–7.45 (m, 4 H, ArH), 8.35 (br signal, 3 H, NH_3). Anal. ($C_{11}H_{15}NO_2$·HCl) C, H, N.

(±)-4-(Aminomethyl)-4-ethoxychroman Hydrochloride (14c). Compound **14c** was prepared in the same manner as **14b** except that absolute EtOH replaced the MeOH as reaction solvent. Recrystallization from an absolute EtOH–Et_2O mixture gave an 88% yield of **14c** as white crystals, mp 187–189 °C dec. Compound **14c** was used without further purification for the preparation of **4b**: NMR (Me_2SO-d_6) δ 1.4 (t, 3 H, CH_2CH_3), 2.4 (m, 2 H, CH_2), 3.4 (s, 2 H, CH_2N), 3.55 (m, 2 H, CH_2CH_3), 4.5 (m, 2 H, OCH_2), 7.1–7.85 (m, 4 H, ArH), 8.6 (br signal, 3 H, NH_3).

(±)-1-(Aminomethyl)-6-methoxychroman Hydrochloride (15). A solution of **4a** (0.15 g, 6.6 mmol) in MeOH (25 mL), to which 150 mg of 10% Pd on C had been added, was shaken under an atmosphere of H_2 (40 psig) for 4 h. The solution was filtered and evaporated to dryness, and the crude product was recrystallized from 2-propanol to yield 80 mg (53%) of **15**, mp 177–179 °C. Anal. ($C_{11}H_{15}NO_2$·HCl) C, H.

4-Cyanochromene (16). Trimethylsilylcyanide (2.5 mL) was added via syringe to a mixture of 4-chromanone (3 g, 20.25 mmol) and a catalytic amount of ZnI_2 in CH_2Cl_2, under a nitrogen atmosphere. The mixture was stirred at 50–55 °C (oil bath temperature) for 5 h and then cooled to room temperature, 3 M hydrochloric acid (30 mL) was added, and stirring was continued for an additional 4 h. The solution was extracted three times with Et_2O (25 mL), and the ether portions were combined, dried ($MgSO_4$), and evaporated to dryness. The crude cyanochromanol was dissolved in benzene, to which tosic acid (0.5 g) had been added, and the solution was heated at reflux for 2 h. The solvent was removed under reduced pressure, and the product was distilled (Kugelrohr) to yield 2.55 g (80%) of **16** as a clear colorless liquid, which crystallized upon standing, mp 35–37 °C. Anal. ($C_{10}H_7NO$) C, H, N.

Affinity Assay Studies. Male Sprague–Dawley rats weighing 200–300 g were used; the stomach fundus was dissected and prepared according to the procedure described by Vane.[12] Two strips were cut from the same tissue and were used in parallel 8-mL muscle baths; the muscle baths and wash (Tyrodes) solution were aerated with 95% O_2–5% CO_2 and were maintained at 37 °C. The relative sensitivity of the two strips was determined, after a 1-h equilibration period, by exposure to a dose of 5-HT, which resulted in submaximal contractions. Only one compound was examined per preparation. The ability of each compound to inhibit the contractile response to 5-HT was determined by obtaining cumulative dose–response curves to 5-HT, first in the absence and then in the presence of several increasing concentrations of the agent in question. The ED_{50} for each of the curves was determined, and the apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild.[13] The pA_2 value is actually the negative logarithm of the molar concentration of an antagonist which effectively reduces the effect of the agonist by a factor of two. Determinations of pA_2 values are valid as long as the interaction is of a competitive nature; although the ideal slope of a Schild plot is −1.0 for a competitive antagonist, the interaction is assumed to be competitive when slopes are between −0.8 and −1.2. The number of Schild plots (pA_2 determinations), the number of dose–response curves, and the slopes of the Schild plots are shown in Table I.

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Peptide Sweeteners. 5. Side-Chain Homologues Relating Zwitterionic and Trifluoroacetylated Amino Acid Anilide and Dipeptide Sweeteners

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Side-chain homologues of sweet trifluoroacetyl-α-L-aspartyl-*p*-cyanoanilide have been synthesized and tasted. Removal of the trifluoroacetyl group only changes the potency of sweet taste, not the taste property. These results have been compared with the structure–taste relationships of dipeptide sweeteners. An informative discontinuity of taste effects was found to exist with novel aminomalonyl dipeptide derivatives. The results are explained on topochemical grounds.

An extremely wide variety of structural features are found in sweet tasting compounds. Attempts to determine general characteristics from the great diversity of the structures of sweet compounds have been made, and molecular theories of sweet taste have been proposed.[2,3] Recently, the relationship between structure and taste has been quantitatively analyzed by correlating the potency of sweet taste of L-aspartyl dipeptide analogues to steric, electronic, and hydrophobic parameters.[4] Derivatives

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