Heteroaromatic Analogues of the α_2-Adrenoreceptor Partial Agonist Clonidine

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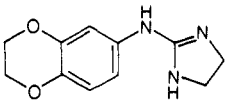
A 1,4-dioxane analogue (1) of the α_2-adrenoreceptor partial agonist clonidine (2) has previously been shown to possess an interesting but complex pharmacological profile. In this study, from a series of other heterocyclic analogues of clonidine, the 1,4-oxazines 6 and 12 were found to resemble 1 in that they are partial α_2-agonists in the periphery and are excluded from the central nervous system. However, when given directly into the brain, they behave as pure α_2-antagonists.

We have previously reported[1] that the 1,4-dioxane analogue 1 (RX 801074) of clonidine (2) is a partial agonist at α_2-adrenoreceptors and that its agonist/antagonist profile was dependent upon the peripheral or central α_2-receptor system examined. For example, in the central



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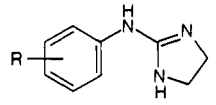


2: R = 2,6-Cl_2
3: R = 3-OH, 4-NHR'; 3-NHR', 4-OH where R' = H, CHO, Ac, SO_2Me

nervous system, whereas clonidine is an α_2-agonist, 1 profiles as a competitive antagonist. Other 1,4-dioxane analogues of known α_2-adrenoreceptor agents were also prepared[2] and were found to possess reduced α-adrenoreceptor affinity and/or a change in pharmacological profile compared to the parent compounds. Our investigations therefore returned to alternative heterocyclic analogues of clonidine. Of interest in this area was a recent report[3] that certain disubstituted derivatives 3 are of potential use in the treatment of peripheral disorders; they are claimed to be potent inhibitors of gastric acid secretion. The compounds, 3, possess α-adrenergic agonist activity even though they lack the distinguishing 2,6-disubstitution generally considered to be responsible for conferring α_2-agonist activity to clonidine and related compounds. We now report our investigations into the synthesis and evaluation of heterocyclic analogues of 3 including some 1,4-oxazine analogues of clonidine.

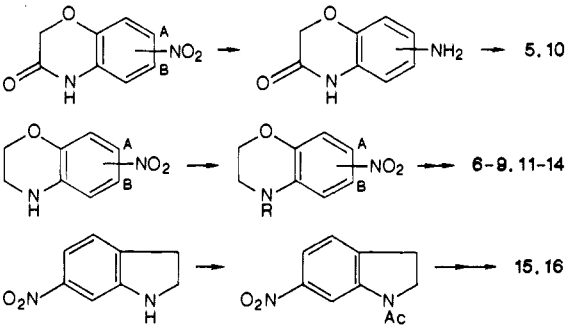
Chemistry

The preparation of the imidazoline products (5–16) (Table I) was carried out following the general routes shown in Scheme I. The oxazines were obtained from either the 6- and 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-ones[4] or the corresponding 1,4-benzoxazines[5] by using standard procedures. Similarly the indolines were prepared from 6-nitroindoline. The dioxole compound 4 was synthesized according to the patent procedure.[6]

Results and Discussions

All compounds were examined for α-adrenoreceptor agonist and antagonist properties using standard testing

Scheme I



procedures[7] and the results are summarized in Table I. The compounds were tested on isolated tissues for α_2 (rat vas deferens) and α_1 (rat anococcygeus) adrenoreceptor activity. A selected number of compounds were also examined in vivo (Table II). Dioxole 4, a lower homologue of 1, has been claimed[6] to possess antihypertensive properties. In this study 4 was found to be a partial α_2-agonist and an α_1-antagonist (in vitro, Table I). However, compared to 1 and clonidine (2), a considerable reduction in α_2-agonist potency (50-fold and 15-fold, respectively) was observed. As an α_2-antagonist, 4 was found to be a low-affinity compound possessing only 2–3% the potency of idazoxan. We have recently reported[7] that idazoxan and yohimbine were equipotent as α_2-antagonists (both compounds $pA_2 = 7.98$). Somewhat surprisingly a recent report[8] has claimed that 4 was found to be a potent and selective α_2-antagonist comparable to yohimbine. No explanation can be offered for these differences especially as very similar testing procedures were used in the two independent studies.

The in vitro results showed that the majority of the heterocyclic analogues, as with 1, profiled as pure α_2-agonists in the rat vas deferens preparation although the potency in all compounds was reduced compared to the dioxane compound 1. Only three analogues, 5, 10, and 15, failed to show α_2-agonist properties. Oxazinones 5 and 10 and indolines 15 and 16 proved to be of no interest. In the limited series of oxazines studied, there was an indication that the "B" position was the favored position of attachment for the aminoimidazoline moiety when considering α_2-agonist potency; cf. 6 $\approx$ 11 but 7 < 12.

Four of the oxazine analogues, 6, 12–14, were investigated in vivo since they demonstrated agonist activity at α_2-adrenoreceptors in vitro with little or no effect at α_1-receptors. As compounds 6 and 12 also failed to increase blood pressure in pithed rats, α_1-activity was not inves-

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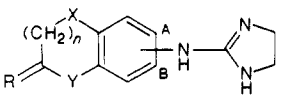
Table I. In Vitro Pharmacological Results[a]



no.	X	Y	R	n	position A/B	mp, °C	formula	RVD α_2-agonist potency[b] (*p*-amino-clonidine = 1)[d]	RVD α_2-antagonist potency[b] (idazoxan = 1)[e]	RA α_1-agonist potency[b] (phenyl-ephrine = 1)[f]	RA α_1-antagonist potency[c] (prazosin = 1)[g]
1	O	O	H_2	1	A	157–159	$C_{11}H_{13}N_3O_2$·maleate	1.5	Ag	0.01	Ag
4	O	O	H_2	0	A	167–169	$C_{10}H_{11}N_3O_2$·HCl	0.03	0.025	0	0.003
5	O	NH	O	1	A	301–303	$C_{11}H_{12}N_4O_2$·HI	0	0.0013	0.006	Ag
6	O	NMe	H_2	1	A	152–154	$C_{12}H_{16}N_4O_2$·HI	0.03	Ag	0.0002	Ag
7	O	NCHO	H_2	1	A	256–260	$C_{12}H_{14}N_4O_2$·HI	0.006	Ag	0.02	Ag
8	O	NEt	H_2	1	A	147–148	$C_{13}H_{18}N_4O$·HI	<0.01	Ag	0.055	Ag
9	O	NCH_2Ph	H_2	1	A	182–186	$C_{18}H_{20}N_4O$·2HCl·H_2O	0.02	Ag	0	0.001
10	O	NH	O	1	B	266–276	$C_{11}H_{12}N_4O_2$·HI	0	0.0005	0.002	Ag
11	O	NMe	H_2	1	B	218–222	$C_{12}H_{16}N_4O$·HI	0.025	Ag	0.5	Ag
12	O	NCHO	H_2	1	B	251–261	$C_{12}H_{14}N_4O_2$·HI	0.02	Ag	0	0.0006
13	O	NAc	H_2	1	B	237–240	$C_{13}H_{16}N_4O_2$·HI[h]	0.10	Ag	0	0.0006
14	O	NSO_2Me	H_2	1	B	167–170	$C_{12}H_{18}N_4O_3S$·HI	0.22	Ag	0	0.0005
15	bond	NEt	H_2	1	B	124–130	$C_{13}H_{18}N_4$·HI[i]	0	0.04	0.17	Ag
16	bond	NAc	H_2	1	B	254–256	$C_{13}H_{16}N_4O$·HI	0.006	Ag	0	0.00002
2	clonidine							0.49	Ag	0.8	Ag

[a] Results are expressed as potencies which were compared directly with that of the standard in the same experiment: Ag = agonist; RVD = rat vas deferens; RA = rat anococcygeus. [b] Dose–response curves of the standards were obtained before and after the dose–response curve of the analogue. There was no difference between the two dose–reponse curves of the standards. [c] Postjunctional antagonism concentration giving a dose–response equal to 2 vs phenylephrine. A minimum of five dose–response curves were obtained for phenylephrine alone, followed by a minimum of four dose–response curves in the presence of the analogue. [d] *p*-Amino IC_{40} = 1.99 ± 0.004 nm. [e] α_2 – pA_2 = 7.98. [f] Phenylephrine IC_{50} = 78 ± 21 nm. [g] α_1 – pA_2 = 9.24. [h] N: calcd, 14.43; found, 13.95. [i] C: calcd, 43.59; found 44.08.

Table II. In Vivo Pharmacological Results[a]

no.	RVD α_2-agonism: ED_{40}	RVD α_2-agonism: max inhibn, %	RVD α_2-antagonism: DR_2, μg/kg per min	antagonism of guanoxabenz-induced mydriasis (rat): AD_{50}, μg/kg, icv
6	6736 ± 2426	65 ± 5	4.62 ± 0.3	58.9
12	385 ± 184	62 ± 5	6.8 ± 2.3	297
13	17.88 ± 2.8	69 ± 5	ND	>200[b]
14	27.3 ± 5.2	70 ± 5	ND	>300[b]
UK-14,304	3.3 ± 0.6	100	NA	NA
idazoxan	NA	NA	2.0 ± 0.6	29.36 ± 3.01

[a] ND = not determined; NA = not applicable; RVD = rat vas deferens. ED_{40} = dose (μg/kg) inhibiting vas deferens contraction by 40%. DR_2 = antagonist dose (μg/kg per min) producing 2-fold shift of UK-14,304 dose–response curve. AD_{50} = dose (μg/kg) reversing guanoxabenz by 50%. All values are expressed as mean ± sem. [b] No activity was observed at the doses indicated.

tigated further in vivo. All four compounds showed α_2-agonist properties in that they inhibited contractions of the vas deferens in pithed rats (Table II). However, the dose–response curves were biphasic with plateaux occurring in the range 62–70% inhibition, indicating a very similar level of intrinsic activity for the four analogues. Two of the compounds **6** and **12** were also examined for α_2-antagonist properties (rat vas deferens) and were found to possess 43% and 29% the potency of idazoxan,[7] respectively. There is an obvious discrepancy between the in vitro (α_2-agonists) and in vivo (α_2-partial agonists) test results for **6** and **12**. The reason why the isolated rat vas deferens (in vitro) is so sensitive to the agonist effect of these compounds is due to a higher receptor reserve of α_2-receptors in this particular model. This results from the different stimulus parameters used for the in vitro and in vivo preparations. Although clonidine is known to be a α_2-partial agonist, it also profiles as a full agonist in the isolated rat vas deferens.[1]

It has been established that centrally acting α_2-adrenoreceptor agonists cause mydriasis as a result of a direct action on central nervous system (CNS) α_2-receptors.[10] None of the compounds **6**, **12–14** possessed mydriatic activity after iv or icv administration. After iv administration they also failed to reverse guanoxabenz-induced mydriasis in the anesthetized rat.[10] However, significant central α_2-antagonist activity was noted with compounds **6** and **12** when given directly into the brain (icv), i.e. 50% and 10% the potency of idazoxan, respectively. Thus, comparison of the α_2-antagonist potencies of **6** and **12** in the periphery and CNS after iv administration indicates that their actions are restricted entirely to the periphery (the peripheral:central ratios being <0.0001).

In summary, the results obtained with benzoxazines **6** and **12** indicate that they resemble the dioxane compound **1** in that they are partial α_2-agonists in the periphery and α_2-antagonists in the CNS after central administration. In addition, the data indicate that they are effectively excluded from the CNS after systemic administration.

Experimental Section

Chemistry. Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded for all compounds on Perkin-Elmer

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700, Varian Associates T-60, and LKB-2091 instruments, respectively, and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. The methods described are numbered as shown in Scheme I.

5-(2-Imidazolin-2-ylamino)-1,3-benzodioxole Hydrochloride (4). The free base was obtained following the published procedure, mp 158–160 °C (lit.[6] mp 157–160 °C), which was converted to 4, mp 167–169 °C (lit.[6] mp 167–169 °C).

3,4-Dihydro-6-(2-imidazolin-2-ylamino)-2*H*-1,4-benzoxazine-4-carbaldehyde Hydriodide (12). A mixture of formic acid (45 mL) and 6-nitro-1,4-benzoxazine[5] (14.0 g, 78 mmol) was heated under reflux for 1 h. After cooling, the mixture was evaporated to leave an oil which was treated with saturated aqueous $NaHCO_3$. A yellow solid which crystallized from the oil was collected and washed with water. Recrystallization from EtOH gave 3,4-dihydro-6-nitro-1,4-benzoxazine-4-carbaldehyde: yield 14.2 g (88%); mp 126–128 °C. A mixture of the above aldehyde (5 g, 24 mmol), 10% Pd–C (0.3 g), and MeOH (100 mL) was shaken in an atmosphere of hydrogen at 39 psi. After 2 h the mixture was filtered and evaporated to leave a pink solid (3.9 g). Recrystallization from EtOH gave 3,4-dihydro-6-amino-1,4-benzoxazine-4-carboxaldehyde: yield 2.8 g (65%); mp 148–149 °C. A mixture of this amine (2.6 g, 15 mmol), 2-(methylthio)-2-imidazoline hydriodide (3.8 g, 16 mmol) and pyridine (20 mL) was heated under reflux for 1.5 h. The cooled reaction mixture was poured into Et_2O and the organic phase decanted to leave an oily residue which was triturated with more Et_2O four times. EtOH (30 mL) was then added to the residue and the solid which formed was collected by filtration to leave impure product (2.6 g). Recrystallization from EtOH gave **12**: yield 1.8 g (33%); mp 251–261 °C. Anal. ($C_{12}H_{14}N_4O_2$·HI) C, H, N. Compound **7** was prepared by the above methods from 3,4-dihydro-7-nitro-1,4-benzoxazine.[5]

3,4-Dihydro-6-(2-imidazolin-2-ylamino)-4-methyl-2*H*-1,4-benzoxazine Hydriodide (11). A solution of 3,4-dihydro-6-nitro-1,4-benzoxazine-4-carbaldehyde (7 g, 34 mmol) in anhydrous THF (130 mL) was treated with dropwise addition of a 1 M BH_3–THF solution (50.5 mL) under an atmosphere of nitrogen. The mixture was heated under reflux for 2 h and then allowed to cool overnight. HCl (5 N, 20 mL) was added cautiously and after 0.25 h solvent was removed under vacuum to leave a solid residue. This residue was treated with 4 N NaOH (300 mL) and the product extracted with CH_2Cl_2. The combined extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to leave a solid (6.0 g). Recrystallization from EtOH gave 3,4-dihydro-4-methyl-6-nitro-1,4-benzoxazine: yield 4.4 g (67%); mp 84–85 °C; MS 194 (M^+) ($C_9H_{10}N_2O_3$ requires M^+ 194). Reduction of the above nitro product with hydrogen over 10% Pd–C (80% yield) followed by reaction with 2-(methylthio)-2-imidazoline hydriodide, using the methods described for **12**, gave **11** in 29% yield: mp 218–222 °C. Anal. ($C_{12}H_{16}N_4O$·HI) C, H, N. Compound **6** was prepared by using the above procedures.

4-Ethyl-3,4-dihydro-7-(2-imidazolin-2-ylamino)-2*H*-1,4-benzoxazine Hydriodide (8). A solution of 3,4-dihydro-7-nitro-1,4-benzoxazine (4.84 g, 26.9 mmol) in acetic anhydride (12 mL, 127 mmol) and EtOAc (50 mL) was heated under reflux for 48 h. Evaporation of the solvent gave impure 4-acetyl-3,4-dihydro-7-nitro-1,4-benzoxazine as a yellow powder, which was used without purification in the next reaction: NMR (Me_2SO-d_6) δ 8.19 (1 H, d, J = 9 Hz, aryl H-5), 7.75 (1 H, dd, J = 9 and 2.6 Hz, aryl H-6), 7.65 (1 H, d, J = 2.6 Hz, aryl H-8), 4.37 (2 H, dd, J = 5.4 and 3.9 Hz, CH_2), 3.94 (2 H, dd, J = 5.4 and 3.9 Hz, CH_2), 2.32 (3 H, s, CH_3CO). A solution of the acetyl product in anhydrous THF (120 mL) was treated dropwise with a 1 M BH_3–THF solution (39 mL, 39 mmol) under an atmosphere of nitrogen. After 14 h EtOH (30 mL) was added cautiously and the mixture was then evaporated to leave an oil which was partitioned between CH_2Cl_2 and 2 N HCl. After the mixture was stirred for 14 h, the organic layer was collected and the aqueous layer extracted with CH_2Cl_2. The combined extracts were washed, dried, and evaporated to leave impure 4-ethyl-3,4-dihydro-7-nitro-1,4-benzoxazine: yield 5.2 g (95%); NMR ($CDCl_3$) δ 6.55 (1 H, d, J = 9 Hz, aryl H-5), 6.19–6.30 (2 H, m, aryl H-6 and H-8), 4.12 (2 H, t, J = 4.4 Hz, CH_2), 3.3 (2 H, br s, NH_2), 3.35–3.12 (4 H, m, 2 CH_2), 1.10 (3 H, t, J = 7 Hz, CH_3).

To a solution of the above impure product (5.13 g, 25 mmol) in EtOAc (55 mL) was added $SnCl_2·H_2O$ (27.9 g, 124 mmol). The mixture was heated under reflux for 4 h. After the mixture was allowed to cool, aqueous 10% Na_2CO_3 was added with shaking followed by EtOAc. The white amorphous solid was removed by filtration and the organic layer collected. The aqueous layer was further extracted with EtOAc, and the combined extracts were then washed with water, dried, and evaporated to leave an oil (3.99 g). Chromatography on silica, eluting with $CHCl_3$, gave crude 7-amino-4-ethyl-3,4-dihydro-1,4-benzoxazine: yield 3.04 g (76%); MS, 178 (M^+) ($C_{10}H_{14}N_2O$ requires M^+ 178). This amine was converted to **8** in 13% yield, using the method described for **12**: mp 147–148 °C. Anal. ($C_{13}H_{18}N_4O$·HI) C, H, N.

4-Acetyl-3,4-dihydro-6-(2-imidazolin-2-ylamino)-2*H*-1,4-benzoxazine Hydriodide (13). 4-Acetyl-3,4-dihydro-6-nitro-1,4-benzoxazine was reduced to the corresponding amino intermediate by using the method already described for **8** (83% yield). Reaction with 2-(methylthio)-2-imidazoline hydriodide gave **13**: yield 45%; mp 237–240 °C. Anal. ($C_{13}H_{16}N_4O_2$·HI) C, H; N: calcd, 14.43; found, 13.95.

4-Benzyl-3,4-dihydro-7-(2-imidazolin-2-ylamino)-2*H*-1,4-benzoxazine Dihydrochloride (9). A stirred suspension of 3,4-dihydro-7-nitro-1,4-benzoxazine (7.2 g, 40 mmol) in triethylamine (4.05 g, 5.6 mL) and benzoyl chloride (11.2 g, 5.6 mL) was heated at 100 °C for 1 h. After the mixture was allowed to cool, 2 N NaOH was added cautiously. The aqueous layer was decanted and the residue triturated with more 2 N NaOH and then with water. EtOH was added to give a solid which was collected (10 g). Recrystallization from MeOH (1 L) gave 4-benzoyl-3,4-dihydro-7-nitro-1,4-benzoxazine: yield 8.0 g (68%); MS 284 (M^+) ($C_{15}H_{12}N_2O_4$ requires M^+ 284). The benzoyl compound was reduced with BH_3–THF as described for **8** to give 4-benzyl-3,4-dihydro-7-nitro-1,4-benzoxazine in 62% yield: mp 92–93 °C.

A mixture of the nitro benzyl compound (4.0 g, 14.8 mmol), granulated tin (8.0 g), 12 N HCl (40 mL), water (40 mL), and EtOH (20 mL) was heated at 100 °C for 3 h. Excess 7 N NaOH was then added to the cooled solution and precipitated solid was removed by filtration. The filtrate was extracted with Et_2O and the solid was also washed well with Et_2O. The combined extracts and washings were washed with water and dried, and the solvent was evaporated to leave impure 7-amino-4-benzyl-3,4-dihydro-1,4-benzoxazine as an oil (3.5 g) which was used without purification in the next reaction. A mixture of the above amine (1.66 g, 6.92 mmol), 1-acetyl-2-imidazolidinone (0.97 g, 7.6 mmol), and $POCl_3$ was stirred at 50 °C for 5 days. Evaporation of $POCl_3$ gave an oily residue to which CH_2Cl_2 was added followed by 2 N NaOH with ice. The mixture was stirred for 1 h. The aqueous layer was extracted, and the combined extracts were washed with aqueous saturated NaCl, dried, and evaporated to leave crude 1-acetyl-2-[(4-benzyl-3,4-dihydro-1,4-benzoxazin-7-yl)imino]imidazolidine: yield 1.67 g (69%). A solution of this unstable product (1.67 g, 4.6 mmol) in MeOH (30 mL) was heated under reflux for 5 h. After a further 14 h at room temperature, the precipitated solid was filtered off and washed with MeOH. The filtrate and washings were combined and evaporated to leave an oil which was chromatographed on silica with MeOH/$CHCl_3$ 1:4 as eluant to give crude product (0.92 g). To a solution of the product in EtOH was added excess ethereal HCl and the precipitated solid was collected and recrystallized from EtOH to give **9**: yield 0.09 g (6%); mp 182–186 °C. Anal. ($C_{18}H_{20}N_4O$·2HCl·H_2O) C, H, N.

3,4-Dihydro-6-(2-imidazolin-2-ylamino)-4-mesyl-2*H*-1,4-benzoxazine Hydriodide (14). Mesyl chloride (1.9 mL, 25 mmol) was added slowly to a stirred solution of 6-nitro-1,4-benzoxazine (4.0 g, 22.2 mmol) in triethylamine (4.6 mL, 33 mmol) and CH_2Cl_2 (205 mL). The solution was stirred for 48 h and then heated under reflux for a further 24 h. The mixture was partitioned between water and CH_2Cl_2. The organic layer was collected and the aqueous layer was reextracted with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated to leave impure 3,4-dihydro-4-mesyl-6-nitro-1,4-benzoxazine: yield 5.1 g (89%); NMR ($CDCl_3$) δ 8.52 (1 H, d, J = 2.2 Hz, aryl H-5), 7.97 (1 H, dd, J = 9.1 and 2.2 Hz, aryl H-7), 7.15 (1 H, d, J = 9.1 Hz, aryl H-8), 4.43 (2 H, t, J = 4.4 Hz, CH_2), 3.90 (2 H, t, J = 4.4 Hz, CH_2), 3.25 (3 H, s, CH_3). The above compound was reduced with $SnCl_2·H_2O$ and converted to the imidazoline product **14** by using

procedures already described: mp 167–170 °C. Anal. ($C_{12}H_{16}N_4O_3S$·HI) C, H, N.

6-(2-Imidazolin-2-ylamino)-2*H*-1,4-benzoxazin-3(4*H*)-one Hydriodide (5). 7-Nitro-2*H*-1,4-benzoxazin-3(4*H*)-one[4] was converted in 43% yield to 7-amino-2*H*-1,4-benzoxazin-3(4H)-one: mp 216–219 °C. The method described for **12** was used to convert this amine to **5**: yield 15%; mp 301–303 °C. Anal. ($C_{11}H_{12}N_4O_2$·HI) C, H, N. Compound **10** was prepared, by using the same methods, from 6-nitro-benzoxazinone.[4]

1-Ethyl- and 1-Acetyl-6-(2-imidazolin-2-ylamino)indoline Hydriodide (15 and 16). 6-Nitroindoline (Aldrich) was converted to the 1-acetyl derivative which was converted by methods already described to give **15** and **16**.

Pharmacology. Details of the in vitro screening procedures have been described in an earlier publication.[7]

Activity at Peripheral α_2-Adrenoreceptors in Vivo. Prejunctional agonist and antagonist activities were studied in the vas deferens of pithed rats. Agonist potency was determined as the dose (μg/kg, iv) required to inhibit the electrical-evoked contractions of the vas deferens by 40% (ED_{40} value). The maximal percent inhibition of the vas deferens was also noted, indicating the intrinsic activity of the test compound. Antagonist potencies were determined as the dose (as an infusion μg/kg per min) required to produce a 2-fold shift of the cumulative dose–response curve to UK-14,304[9] on the twitch response of the vas deferens. Agonist and antagonist studies were performed in separate groups of pithed rats ($n = 6$). Agonists were administered in a cumulative manner and the antagonists were continuously infused (0.03 mL/min, iv) to obtain equilibrium conditions, and a dose–response curve to UK-14,304 was constructed 10 min after the start of the infusion.

Activity at Central α_2-Adrenoreceptors. Agonist activity was determined by measuring the mydriatic effects of the compounds after iv or icv administration to pentobarbitone anesthetized rats. Antagonist potency was determined by the reversal of a maximally effective mydriatic dose of guanoxabenz (300 μg/kg).[10] Compounds were administered 10 min after guanoxabenz, and the cumulative dose reversing guanoxabenz by 50% was calculated (AD_{50}, μg/kg).

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Registry No. 1, 87135-03-3; 1·maleate, 87135-04-4; 2, 4205-90-7; 4, 70183-99-2; 4·HCl, 103124-99-8; 5, 120711-83-3; 5·HI, 120711-66-2; 6, 120711-84-4; 6·HI, 120711-67-3; 7, 120711-85-5; 7·HI, 120711-68-4; 8, 120711-86-6; 8·HI, 120711-69-5; 9, 120711-87-7; 9·2HCl, 120711-70-8; 10, 120711-88-8; 10·HI, 120711-71-9; 11, 120711-89-9; 11·HI, 120711-72-0; 12, 120711-90-2; 12·HI, 120711-73-1; 13, 120711-91-3; 13·HI, 120711-74-2; 14, 120711-92-4; 14·HI, 120711-75-3; 15, 120771-32-6; 15·HI, 120711-76-4; 16, 120771-33-7; 16·HI, 120711-77-5; 6-nitro-1,4-benzoxazine, 120711-78-6; 3,4-dihydro-6-nitro-1,4-benzoxazine-4-carbaldehyde, 120711-79-7; 3,4-dihydro-6-amino-1,4-benzoxazine-4-carbaldehyde, 120711-80-0; 2-(methylthio)-2-imidazoline hydriodide, 5464-11-9; 3,4-dihydro-7-nitro-1,4-benzoxazine, 120711-81-1; 3,4-dihydro-4-methyl-6-nitro-1,4-benzoxazine, 120711-82-2; 3,4-dihydro-4-methyl-7-nitro-1,4-benzoxazine, 120711-93-5; 4-acetyl-3,4-dihydro-7-nitro-1,4-benzoxazine, 120711-94-6; 4-ethyl-3,4-dihydro-7-nitro-1,4-benzoxazine, 120711-95-7; 7-amino-4-ethyl-3,4-dihydro-1,4-benzoxazine, 105297-44-7; 4-acetyl-3,4-dihydro-6-nitro-1,4-benzoxazine, 120711-96-8; 4-acetyl-3,4-dihydro-6-amino-1,4-benzoxazine, 120711-97-9; 4-benzoyl-3,4-dihydro-7-nitro-1,4-benzoxazine, 120711-98-0; 4-benzyl-3,4-dihydro-7-nitro-1,4-benzoxazine, 120711-99-1; 7-amino-4-benzyl-3,4-dihydro-1,4-benzoxazine, 120712-00-7; 1-acetyl-2-imidazolidinone, 5391-39-9; 1-acetyl-2-[(4-benzyl-3,4-dihydro-1,4-benzoxazin-7-yl)imino]imidazolidine, 120712-01-8; 3,4-dihydro-4-mesyl-6-nitro-1,4-benzoxazine, 120712-02-9; 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one, 81721-86-0; 7-amino-2*H*-1,4-benzoxazin-3(4*H*)-one, 26215-14-5; 6-nitrobenzoxazinone, 81721-87-1; 6-nitroindoline, 19727-83-4; 1-acetyl-6-nitroindoline, 22949-08-2.

The Importance of the Orientation of the C9 Substituent to Cannabinoid Activity

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We have found a correlation between cannabinoid psychopharmacological activity and the orientation of the C9 substituent in one class of cannabinoid derivatives. We report here a study of the active cannabinoids Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), and 11β-hexahydrocannabinol (11β-HHC); the minimally active cannabinoid 11α-hexahydrocannabinol (11α-HHC); and the inactive cannabinoids Δ^7-tetrahydrocannabinol (Δ^7-THC) and $\Delta^{9,11}$-tetrahydrocannabinol ($\Delta^{9,11}$-THC). Our working hypothesis is that there are two components of cannabinoid structure which confer upon these compounds reactivity characteristics crucial to activity: the directionality of the lone pairs of electrons of the phenyl group hydroxyl oxygen and the orientation of the carbocyclic ring relative to this oxygen. The structures of these six molecules were optimized by using the method of molecular mechanics as encoded in the MMP2(85) program. Other possible minimum-energy conformations of the carbocyclic ring were calculated by driving one torsion angle in this ring by use of the dihedral driver option in MMP2(85). The rotational energy behavior of the phenyl group hydroxyl in each molecule was studied also by using the dihedral driver option in MMP2(85). We found that the carbocyclic ring in 11α-HHC can exist in either a chair or a twist conformation. The carbocyclic ring in Δ^9-THC, in Δ^8-THC, and in Δ^7-THC was found to exist only in a half-chair conformation, while the carbocyclic ring in 11β-HHC and in $\Delta^{9,11}$-THC was found to exist only in a chair form. The results of the rotational energy profiles indicated that the minimum-energy positions of the phenyl group hydroxyls are nearly identical in all molecules. These molecules, then, were found to differ only in the conformation of the carbocyclic ring in each. This conformation, in turn, determines the orientation of this ring and its C9 substituent relative to the oxygen of the phenyl group hydroxyl. In order to assess the orientation of the carbocyclic ring with respect to the phenyl group hydroxyl oxygen in each optimized structure, the following nonbonded torsion angles were measured: C10–C10a–C1–O, C8–C7–C1–O, C11–C9–C1–O, and C9–Q–C1–O (where Q is a dummy atom placed midway between C8 and C10). A correlation was found between activity and the C11–C9–C1–O angle, an angle that measures the orientation of the C11 methyl group (i.e., the C9 substituent) relative to the oxygen of the phenyl group hydroxyl. C11–C9–C1–O was found to be negative for all active cannabinoids. As C11–C9–C1–O becomes positive, activity is significantly reduced or abolished. These results seem to indicate that there is a critical area near the top of the carbocyclic ring which must not be blocked. Such findings argue strongly for a steric requirement at the site of action of these compounds.

Cannabinoids are the group of C_{21} compounds that are typical of and present in *Cannabis sativa*, their carboxylic acids, analogues, and transformation products.[1] Since Mechoulam et al. reported (−)-*trans*-Δ^9-tetrahydro-

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