Effect of Methoxy Substitution on the Adrenergic Activity of Three Structurally Related α_2-Adrenoreceptor Antagonists

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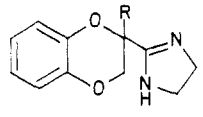
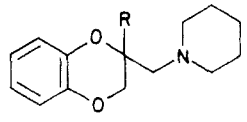
We have recently reported the synthesis and α_2-antagonist activity of the methoxy derivative 2 [2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline] and described the enhanced potency of this compound over the parent 1,4-benzodioxan, idazoxan, in reversing the inhibition caused by α_2-adrenoreceptor agonists of the electrically induced twitch in the rat or mouse vas deferens. It was of interest to us to discover whether a similar substitution in the structurally related α_2-adrenoreceptor antagonists piperoxan, prosympal, and fenmetazole would similarly enhance potency. We subsequently discovered that this was not so and potency was decreased markedly. In particular, that of the methoxy derivative of piperoxan was ca. 220 times less than the parent structure.

Following the discovery of the potent and selective adrenoreceptor antagonist idazoxan (1),[1] a search was initiated for related compounds of even greater potency. It

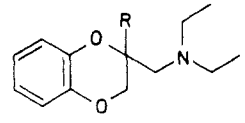


1, R = H (idazoxan)
2, R = OCH_3 (RX821002)

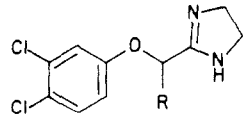
was observed that substitution in any but the 2-position resulted in compounds of greatly reduced potency as antagonists at the α_2-adrenoreceptor. The 2-position was unique in that it could accommodate certain relatively large groups[2] with little or no reduction in potency and, in addition, the introduction of small alkyl and alkoxy side chains resulted in compounds having increased affinity for the α_2-receptor. In particular the 2-methoxy derivative (2, RX821002) was between 10 and 50 times more potent than idazoxan, depending on the test situation used. We were interested therefore in determining if a similar structure–activity relationship existed in other structurally related α_2-adrenoreceptor antagonists. Three compounds were chosen for investigation, piperoxan (3), prosympal (4), and fenmetazole (5), and this paper describes the synthesis and pharmacological evaluation of the methoxy derivatives (6–8) of these classical antagonists.



3, R = H (piperoxan)
6, R = OCH_3



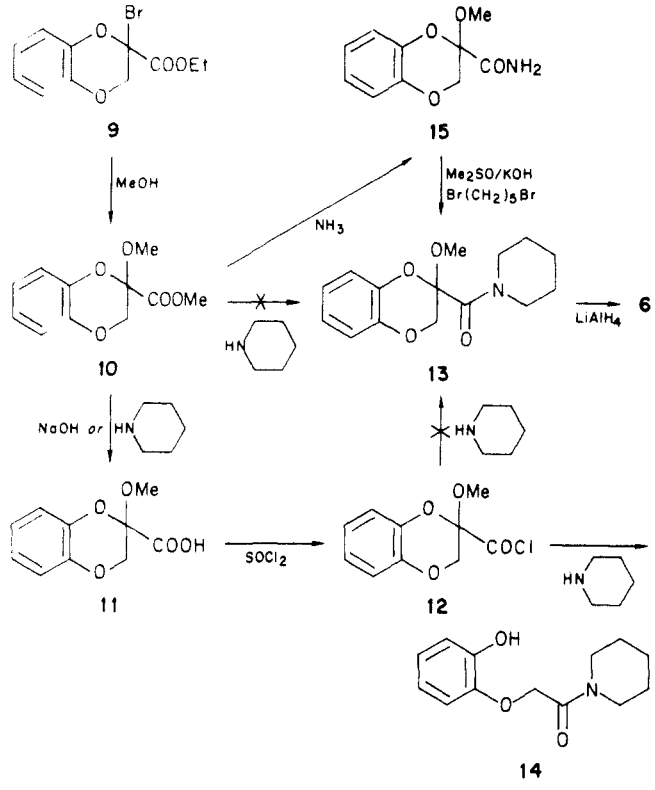
4, R = H (prosympal)
7, R = OCH_3



5, R = H (fenmetazole)
8, R = OCH_3

Chemistry. The chemistry can be conveniently divided into two sections. The first (section A) deals with the synthesis of the methoxy derivatives (6 and 7) of the two 1,4-benzodioxans piperoxan and prosympal, and the second

Scheme I



(section B) describes the synthesis of the methoxy derivative (8) of fenmetazole.

Section A. Scheme I shows a number of approaches that were undertaken in order to synthesize compound 6. The first attempt involved the reaction of the methyl ester (10) with piperidine. Unexpectedly this gave the corresponding carboxylic acid (11), and it was subsequently discovered that this type of reaction does have precedence in the literature.[3] The saponification is thought to be due to excessive steric crowding at the proposed site of interaction. In order to increase the reactivity at this center, the corresponding acid chloride (12) was prepared; reaction of this with piperidine again failed to give the desired amide (13), however. In this instance, the major product was the ring-opened phenol (14) containing one less carbon atom than the starting acid chloride (12). Diethylamine also gave a corresponding ring-opened product in its re-

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(2) Stillings, M. R.; Chapleo, C. B.; Butler, R. C. M.; Davis, J. A.; England, C. D.; Myers, M.; Myers, P. L.; Tweddle, N.; Welbourn, A. P.; Doxey, J. C.; Smith, C. F. C. *J. Med. Chem.* **1985**, *28*, 1054.
(3) Zaugg, H. E.; Helgren, P. F.; Schaefer, A. D. *J. Org. Chem.* **1963**, *28*, 2617.
(4) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1959**, *14*, 48.

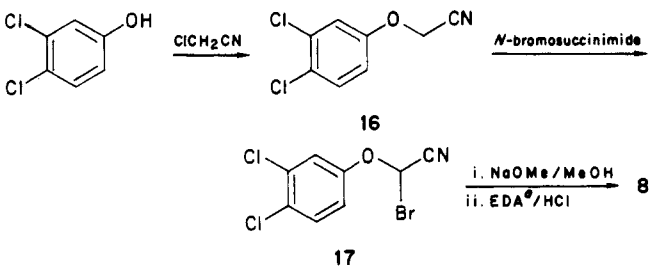
0022-2623/86/1829-1780$01.50/0

Table I

compound	pharmacological testing results[a] prejunctional ag[b]	prejunctional antag[c]	postjunctional ag[d]	postjunctional antag[e]
2	0	11.3 ± 1.3	0	8.3 ± 1.3
idazoxan	0	1.0	0	1.0
6	0	0.00065 ± 0.00015	0	<0.012
piperoxan	0	0.29 ± 0.04	0	4.8 ± 1.8
7	0	0.0037 ± 0.0006	0	<0.012
prosympal	0	0.033 ± 0.004	0	0.52 ± 0.16
8	0	0.0021 ± 0.0004	0	0.063 ± 0.017
fenmetazole	<0.0008	0.018 ± 0.005	0.16 ± 0.05	agonist

[a] Minimum of three determinations. [b] Agonist potency cf. clonidine in the mouse isolated electrically stimulated vas deferens (clonidine $pD_2 = 8.8$). [c] Antagonist potency cf. idazoxan in the mouse electrically stimulated vas deferens (idazoxan $pA_2 = 7.9 \pm 0.1$). [d] Agonist potency cf. phenylephrine in the rat isolated anococcygeus muscle (phenylephrine $pD_2 = 6.54$). [e] Antagonist potency cf. idazoxan vs. phenylephrine in the rat isolated anococcygeus muscle (pA_2 idazoxan = 6.3 ± 0.04).

Scheme II



action with the acid chloride (**12**). The mechanism of this unusual reaction has not been investigated. The target compound (**6**) was eventually synthesized via the alkylation of the primary amide (**15**) followed by conventional reduction. A similar route also provided the corresponding diethylamino derivative (**7**).

Section B. The methoxy derivative (**8**) of fenmetazole was synthesized in three steps from 3,4-dichlorophenol as described in Scheme II.

Results and Discussion

The in vitro results on the three methoxy derivatives together with their parent compounds are present in Table I. In addition the corresponding results for idazoxan and its methoxy derivative (**2**, RX821002) are also included for comparison purposes. The compounds were tested on isolated tissues for presynaptic α_2 (mouse vas deferens) and postsynaptic α_1 (rat anococcygeus) adrenoreceptor agonist activity. The values are given in terms of potency relative to clonidine ($pD_2 = 8.8$) (α_2) and phenylephrine ($pD_2 = 6.54$) (α_1). The ability of the compounds to antagonize the inhibitory effect of clonidine on the vas deferens and the contractile effect of phenylephrine on the anococcygeus were used to assess respective pre-α_2 and post-α_1 antagonist activity. In this case values are quoted as potencies relative to idazoxan.

The table shows quite clearly that while the introduction of a methoxy group into the 2-position of idazoxan increases potency at least 10-fold, a corresponding decrease is seen in the methoxy derivatives of prosympal and fenmetazole. In the case of piperoxan, however, this decrease is more pronounced, compound **6** being some 450 times less potent at the α_2-adrenoreceptor than piperoxan. In order to verify this result, the pA_2 values of compounds **2** and **6** together with those of idazoxan and piperoxan were evaluated using the rat vas deferens (α_2) with *p*-aminoclonidine as the agonist and the rat anococcygeus (α_1) using phenylephrine as the agonist. The results presented in Table II confirm both the significant increase in α_2-adrenoreceptor antagonist potency seen on 2-methoxylation of idazoxan (~50 times) and the marked decrease in potency (~220 times) when piperoxan is similarly substituted.

Table II

compound	rat vas deferens: α_2 pA_2 values[a,b] vs. *p*-aminoclonidine	rat anococcygeus: α_1 pA_2 values[b] vs. phenylephrine
idazoxan	8.29 ± 0.1 (7)[c]	6.30 ± 0.04 (10)
2	9.92 ± 0.01 (5)	7.43 ± 0.3 (2)
piperoxan	7.54 ± 0.09 (3)	7.16 ± 0.12 (5)
6	5.19 ± 0.2 (3)	<4.48 (2)

[a] pA_2 values were calculated according to Arunlakshana and Schild.[4] [b] The values for idazoxan and compound **2** are somewhat different from those presented in ref 2. The only difference in the testing procedure was that clonidine and noradrenaline were used as agonists in the previous experiments. [c] Number of tests, results expressed as mean ± SEM.

It is possible that the increase in potency seen in compound **2** is due to a strong hydrogen bond between the protonated imidazoline ring and the methoxy oxygen atom, enabling it to maintain an orientation in which the interaction of the non-hydrogen-bonded amino function with the α_2-adrenoreceptor is optimized. If an analogous hydrogen bond is formed with the protonated piperidine ring in compound **6**, however, it would remove an important site of drug–receptor interaction, thus significantly reducing the affinity of the compound for the α-adrenoreceptor. If this were the sole factor contributing to the dramatic decrease in the potency of compound **6**, then a similarly large decrease would also be expected for the 2-methoxy derivative (**7**) of prosympal. The results show that this is not the case, which implies that steric factors may also be important, and despite the relatively small size of the methoxy group, the synthetic problems described earlier indicate that it introduces into the environment around the 2-position of the benzodioxan ring a significant degree of steric congestion in compounds **6** and **7**. We suggest therefore that the decrease in potency of all three methoxylated derivatives is due to a combination of both steric and electronic factors, these being particularly unfavorable in the case of compound **6**.

Experimental Section

Chemistry. Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and mass spectra were recorded on Perkin-Elmer 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 value.

Methyl 2-Methoxy-1,4-benzodioxan-2-carboxylate (10) and 2-Methoxy-1,4-benzodioxan-2-carbonyl Chloride (12). A mixture of ethyl 1,4-benzodioxan-2-carboxylate[5] (60.0 g, 0.288 mol),

N-bromosuccinimide (NBS, 51.0 g, 0.287 mol), benzoyl peroxide (catalytic quantity), and carbon tetrachloride (700 mL) was stirred and heated at reflux for 5 h. The mixture was cooled and filtered, and the filtrate was evaporated to give ethyl 2-bromo-1,4-benzodioxan-2-carboxylate (**9**) as a yellow oil: yield 87.4 g (>100%, compound contaminated with carbon tetrachloride). NMR ($CDCl_3$) δ 6.8–7.3 (4 H, m, Ar H), 4.8–4.1 (4 H, m, ester CH_2 + benzodioxan CH_2), 1.4 (3 H, t, CH_3).

The bromo ester **9** (87.4 g, 0.3 mol) was dissolved in dry methanol (400 mL) and allowed to stand at room temperature for 14 days. The methanol was removed by evaporation, and the residual oil was purified via column chromatography (Kieselgel 60, 70–230 mesh, ASTM) by eluting with 5% diethyl ether/petroleum ether (bp 40–60 °C) to give **10**: yield 28.4 g (42%); mp 71–72 °C. Anal. ($C_{11}H_{12}O_5$) C, H.

A mixture of the methoxy ester **10** (15.0 g, 0.067 mol) and 2 N NaOH solution (200 mL) was stirred at room temperature overnight. The resulting solution was washed with diethyl ether and then acidified with 2 N HCl solution. The acid layer was extracted with dichloromethane, and the extracts were washed with water, dried, and evaporated to give 2-methoxy-1,4-benzodioxan-2-carboxylic acid (**11**): yield 13.2 g (93.9%); mp 122–125 °C. Anal. ($C_{10}H_{10}O_5$) C, H; C: calcd, 57.14; found, 57.57.

A solution of the acid **11** (13.0 g, 0.0519 mol), thionyl chloride (23.0 g, 0.193 mol), and dry toluene (250 mL) was heated under reflux for 3.5 h. The reaction mixture was evaporated to dryness, further toluene (120 mL) added, and the mixture reevaporated to give **12**: yield 12.2 g (86.3%); IR (thin film) ν_{max} 1790 cm^{-1}, MS, 228 (M^+) ($C_{10}H_9ClO_4$ requires M^+ 228).

Reaction of Methyl 2-Methoxy-1,4-benzodioxan-2-carboxylate (10) with Piperidine. A solution of the methoxy ester **10** (1.0 g, 0.0045 mol) in dry piperidine (4.3 g, 5 mL, 0.051 mol) was heated at 100 °C for 0.5 h. The mixture was then poured into 2 N HCl solution and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give a brown solid, which was partitioned between a saturated solution of $NaHCO_3$ and dichloromethane. The aqueous phase was separated and acidified with 2 N HCl solution and then extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give **11**: yield 0.3 g (32%), identical with the product isolated from saponification of the corresponding ester (**10**).

Reaction of 2-Methoxy-1,4-benzodioxan-2-carbonyl Chloride (12) with (a) Piperidine and (b) Diethylamine. (a) Piperidine (6.0 g, 7.0 mL, 0.071 mol) was added dropwise over 5 min to a stirred solution of the acid chloride **12** (4.0 g, 0.0175 mol) in dry toluene (50 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. It was then poured into 2 N HCl solution, which was subsequently extracted with dichloromethane. The organic layer was washed with Na_2CO_3 solution, dried, and evaporated to give a yellow oil, which slowly crystallized. The oily solid was triturated with diethyl ether and filtered; the filtered solid was dried to give 2-(2-hydroxyphenoxy)-*N*,*N*-pentamethylenacetamide (**14**): yield 2.5 g (61%); mp 95–97 °C; NMR ($CDCl_3$) δ 8.8 (1 H, brs, OH), 7.2–6.6 (4 H, m, Ar H), 4.7 (2 H, s, CH_2CO), 3.6 (2 H, brs, CH_2N), 3.2 (2 H, brs, CH_2N), 1.8–1.4 (6 H, m, CH_2); IR ($CHBr_3$) ν_{max} 1640 cm^{-1}. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

(b) The reaction of diethylamine (4.9 g, 7.0 mL, 0.068 mol) with the acid chloride **12** (4.0 g, 0.0175 mol) was carried out in essentially the same manner as that described in the reaction with piperidine to give a crude sample of *N*,*N*-diethyl-2-(2-hydroxyphenoxy)acetamide as a brown viscous oil: yield 3.7 g (95%); NMR ($CDCl_3$) δ 6.9 (4 H, s, Ar H), 4.9–3.0 (7 H, m, OH, CH_3); IR (thin film) ν_{max} 1650 cm^{-1}.

2-Methoxy-2-(1-piperidinylmethyl)-1,4-benzodioxan Hydrochloride (6). A solution of the 2-methoxy ester **10** (7.0 g, 0.0313 mol) in dry ethanol (100 mL) was cooled to 0 °C, and gaseous ammonia was then bubbled into the mixture until saturation was achieved. The reaction was allowed to warm to room temperature and kept at this temperature for 48 h. The ethanol was evaporated off to give 2-methoxy-1,4-benzodioxan-2-carboxamide (**15**): yield 6.5 g (99%). A small quantity was crystallized from ethyl acetate/petroleum ether bp 40–60 °C to give an analytically pure sample: mp 164–166 °C; IR ($CHBr_3$) ν_{max} 3420, 1660 cm^{-1}. Anal. ($C_{10}H_{11}NO_4$) C, H, N.

A solution of powdered potassium hydroxide (6.25 g, 0.089 mol) in dimethyl sulfoxide (50 mL) was stirred at room temperature for 0.5 h. The 2-methoxy carboxamide **15** (2.5 g, 0.0120 mol) was added followed by 1,5-dibromopentane (11.02 g, 0.048 mol), and the reaction mixture was allowed to stir at room temperature for 2 h and then poured into water and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated, and the residue was purified via column chromatography (Kieselgel 60, 70–230 mesh, ASTM) eluting with chloroform. This gave, as a yellow oil, 2-methoxy-*N*,*N*-pentamethylene-1,4-benzodioxan-2-carboxamide (**13**): yield 1.0 g (30%); NMR ($CDCl_3$) δ 6.9 (4 H, s, Ar H), 4.4 (2 H, AB q (J = 12 Hz), OCH_2), 4.1–3.4 (4 H, m, NCH_2), 3.3 (3 H, s, OCH_3), 1.7 (6 H, brs, CH_2). MS, 277 (M^+) ($C_{15}H_{19}NO_4$ requires M^+ 277).

The 2-methoxy-*N*,*N*-pentamethylene carboxamide **13** 0.85 g, 0.00307 mol) was dissolved in dry THF (20 mL) and added dropwise to a stirred mixture of $LiAlH_4$ (0.4 g, 0.011 mol) in dry THF (10 mL) at 0 °C over 2 min. The stirred mixture was heated under reflux for 3 h and then cooled, and wet THF was added. The resulting mixture was partitioned between ethyl acetate and water, and the organic layer was extracted with 2 N HCl solution. The acid layer was then basified with $NaHCO_3$ solution, and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated, and the residue was converted to the hydrochloride salt with ethereal HCl. The salt was recrystallized from ethanol/diethyl ether to give **6**: yield 0.85 (91%); mp 216–218 °C. Anal. ($C_{15}H_{21}NO_3 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

2-[(*N*,*N*-Diethylamino)methyl]-2-methoxy-1,4-benzodioxan Hydrochloride (7). Iodoethane (14.6 g, 7.5 mL, 0.094 mol) was added at room temperature to a stirred mixture of 2-methoxy-1,4-benzodioxan-2-carboxamide (**15**) (2.5 g, 0.012 mol), powdered potassium hydroxide (6.25 g, 0.10 mol), and dimethyl sulfoxide (50 mL), and the suspension was stirred for 2 days. The subsequent workup was identical with that in the preparation of the corresponding *N*,*N*-pentamethylene amide (**13**) and gave a yellow oil, which was purified via column chromatography (Kieselgel 60, 70–230 mesh, ASTM) by eluting with chloroform to give *N*,*N*-diethyl-2-methoxy-1,4-benzodioxan-2-carboxamide as a colorless oil: yield 2.9 g (92%); IR (thin film) ν_{max} 1650 cm^{-1}.

The diethyl carboxamide (2.9 g, 0.0109 mol) was reduced in THF solution (100 mL) with $LiAlH_4$ (1.5 g, 0.039 mol) in the same manner as that described in the preparation of **6**. The crude product was purified via column chromatography (Kieselgel 60, 70–230 mesh, ASTM) by eluting with chloroform. The hydrochloride salt was prepared with ethereal HCl and was crystallized frim ethanol/diethyl ether to give **7**: yield 2.1 g (67%); mp 190–192 °C. Anal. ($C_{14}H_{21}NO_3 \cdot HCl$) C, H, N.

2-[(3,4-Dichlorophenoxy)methoxymethyl]-2-imidazoline Hydrochloride (8). A mixture of 3,4-dichlorophenol (4.37 g, 0.0268 mol), potassium iodide (0.061 g, 0.00037 mol), potassium carbonate (3.15 g, 0.0288 mol), and acetone (15 mL) was stirred at room temperature during the dropwise addition of chloroacetonitrile (2.01 g, 0.0266 mol) over 0.5 h. The mixture was then stirred and heated at reflux for 36 h. The suspension was allowed to cool and then evaporate to dryness; the resulting brown solid was partitioned between diethyl ether and water, and the organic layer was washed successively with 2 N NaOH solution, sodium thiosulfate solution, and water, dried, and evaporated to give (3,4-dichlorophenoxy)acetonitrile (**16**) as a yellow oil: yield 4.3 g (79%); MS, 202 M^+ ($C_8H_5Cl_2NO$ requires M^+ 202).

A mixture of the phenoxyacetonitrile (4.1 g, 0.0203 mol), NBS (3.6 g, 0.0202 mol), benzoyl peroxide (0.05 g), and carbon tetrachloride (100 mL) was stirred and heated at reflux for 16 h. The mixture was then cooled and filtered and the filtrate was evaporated to dryness to give 2-bromo-2-(3,4-dichlorophenoxy)-acetonitrile (**17**): yield 6.4 g (>100%, IR showed that the product was contaminated with succinimide).

A mixture of the bromo nitrile (5.7 g, 0.020 mol), sodium methoxide (1.2 g, 0.022 mol), and dry methanol (50 mL) was stirred at 0 °C for 10 min and then at room temperature for 16 h. The solution was cooled to 0 °C, and ethylenediamine (1.4 g, 1.6 mL,

(5) Koo, J.; Avakian, S.; Martin, G. J. *J. Am. Chem. Soc.* **1955**, *77*, 5373.

0.024 mol) was added followed by the dropwise addition of methanolic HCl (5.6 M, 7.3 mL, 0.041 mol). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 16 h, after which it was evaporated to low bulk and partitioned between dichloromethane and $NaHCO_3$ solution. The organic layer was extracted with 2 N HCl, and the acidic phase was then basified with Na_2CO_3 solution and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give the free base of 8 as a brown oil. This was purified via column chromatography (Kieselgel 60, 70–230 mesh, ASTM) by eluting with chloroform/5% methanol, and the pure fractions were combined, evaporated, dissolved in 2 N HCl, and reevaporated to give 8: yield 0.71 g (11%). Crystallization from ethanol/diethyl ether gave an analytically pure sample, mp 173–175 °C. Anal. ($C_{11}H_{12}Cl_2N_2O_2 \cdot HCl \cdot {}^1/_3H_2O$) C, H, N.

Pharmacology. Preparations. Rat Vas Deferens. Vasa deferentia were removed from male Sprague–Dawley rats weighing 200–250 g. The prostatic half of the vas deferens was cleaned of connective tissue and suspended under an initial tension of 0.5 g in an organ bath of 8–10-mL capacity. The tissue was bathed in Krebs solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 0.6 mM; $NaHCO_3$, 25 mM; dextrose, 11.1 mM), which was gassed with 95% O_2 and 5% CO_2 and maintained at a temperature of 30 °C. The intramural nerves of the vas deferens were stimulated by rectangular pulses of 3-ms duration, 40 V, at a frequency of 0.1 Hz, and the resultant contractions of the tissue were recorded isometrically.

Mouse Vas Deferens. Vasa deferentia from adult male mice (MFI > 30 g) were set up, under an initial tension of 0.5 g in an organ bath of 50-mL capacity that contained magnesium-free Krebs solution. The physiological solution was maintained at 30 °C and gassed with 95% O_2 and 5% CO_2. The preparations were field-stimulated between platinum electrodes at 0.1 Hz with rectilinear pulses of 3-ms duration. The voltage (100–140 V) was adjusted to give a twitch response of ca. 100-mg tension. Contractions of the tissue were recorded isometrically.

In Vitro Screening. Presynaptic α_2-Adrenoreceptor Agonist Activity. Vas Deferens. The mouse vas deferens was used in these studies. Repeated cumulative concentration–response curves were constructed to the presynaptic α_2-adrenoreceptor agonist clonidine until consistent ID_{50} values were obtained. The effect of the test compound was then examined, and if inhibition of the twitch was obtained, an ID_{50} value was determined, i.e., presynaptic potency of the new analogue was compared directly with that of clonidine in the same experiment. The compound was then removed from the bathing fluid and the responsiveness of the tissue to clonidine reassessed.

Presynaptic α_2-Adrenoreceptor Antagonist Properties. Vas Deferens. Tissues taken from the mouse were used to determine presynaptic α_2-adrenoreceptor antagonist potency. Contractions of the vas deferens were inhibited by including clonidine (110 nM) in the Krebs solution. The concentration of compound required to produce 50% reversal of the inhibitory effects of clonidine was determined and compared with the value determined for idazoxan in the same tissue. Presynaptic α_2-adrenoreceptor antagonist potency was therefore expressed with respect to idazoxan as the standard.

Postsynaptic α_1-Adrenoreceptor Agonist Activity. Rat Anococcygeus. Postsynaptic α_1-adrenoreceptor agonist activity was determined on the rat anococcygeus muscle. Cumulative concentration–response curves to the contractile effects of phenylephrine were constructed until the responses were reproducible. The effects of test compounds were then studied, and the potencies of compounds with agonist activity were compared directly with that of phenylephrine in the same tissue.

Postsynaptic α_1-Adrenoreceptor Antagonist Properties. Rat Anococcygeus. Cumulative concentration–response curves to phenylephrine were constructed in the absence and presence of a fixed concentration of idazoxan or one of the test compounds. From the dose ratios produced the concentration of agonist producing a dose ratio of 2 was calculated and thus, the α_1-antagonist potency relative to idazoxan was determined.

Determination of pA_2 Values for Competitive Antagonists. The pA_2 values of selected compounds were determined at presynaptic α_2-adrenoreceptors and postsynaptic α_1-adrenoreceptors. Antagonism of the inhibitory effects of *p*-aminoclonidine on the vas deferens and antagonism of phenylephrine contractions on the anococcygeus muscle were used to determine pA_2 values at presynaptic α_2-adrenoreceptors and postsynaptic α_1-adrenoreceptors, respectively. pA_2 is the negative log of the antagonist concentration required to maintain a constant response when the concentration of the agonist is doubled.

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Registry No. **1**, 79944-58-4; **2**, 102575-24-6; **3**, 59-39-2; **4**, 952-37-4; **5**, 41473-09-0; **6**, 102575-20-2; **6**·HCl, 102575-10-0; **7**, 102575-22-4; **7**·HCl, 102575-11-1; **8**, 102575-23-5; **8**·HCl, 102575-12-2; **9**, 102575-13-3; **10**, 102575-14-4; **11**, 102575-15-5; **12**, 102575-16-6; **13**, 102575-17-7; **14**, 34919-95-4; **14** (diethylamide), 34919-94-3; **15**, 102575-18-8; **15** (diethylamide), 102575-21-3; **16**, 38949-69-8; **17**, 102575-19-9; $HN(CH_2Me)_2$, 109-89-7; NH_3, 7664-41-7; $Br(CH_2)_5Br$, 111-24-0; H_3CCH_2I, 75-03-6; $ClCH_2CN$, 107-14-2; NaOMe, 124-41-4; $H_2NCH_2CH_2NH_2$, 107-15-3; ethyl 1,4-benzodioxan-2-carboxylate, 4739-94-0; piperidine, 110-89-4; 3,4-dichlorophenol, 95-77-2.

Analgesic Actions of 3-Substituted 6-*tert*-Butyl-1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines

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The synthesis of four 3-substituted 6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines is described. Derivatives with *N*-Me (**4**) or *N*-phenethyl (**7**) substituents do not differ significantly in their antinociceptive properties from compounds bearing 6-H or 6-Me; however, they are less active than 6-Ph analogues.

Although variation of the C-6 substituent in 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (6,7-benzomorphans) has not been extensively studied,[2] some interesting observations regarding the analgesic potencies of such compounds have been made. Major synthetic routes to the benzomorphans dictated that an alkyl function, usually Me, was located at the 6-bridgehead position. Where the benzomorphan ring possessed only a *N*-Me substituent, the presence of 6-Me (**1a**) afforded an analgesic about one-tenth as potent as morphine in the mouse hot-plate antinociceptive assay.[3,4] Extension of the

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(2) Eddy, N. B.; May, E. L. *Synthetic Analgesics*; Pergamon: London, 1966; Part IIB.

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