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.

Acknowledgment. We thank David Witty for able assistance in the synthetic work and Ginette Gray for typing the manuscript.

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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Received August 27, 1985

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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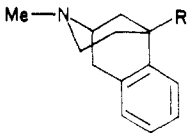
0022-2623/86/1829-1783$01.50/0

Table I. Analgesic Activities of (±)-3-Substituted-6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines

compd	ED_{50},[a] mg/kg
4	14.1 (10.6–18.9)
6	IA[b] (50)
7	9.9 (7.1–13.8)
8	IA[b] (20)
morphine sulfate	1.2

[a] Tested as hydrochloride (sc) in water. Mouse hot-plate test[14] employing Caesarian-derived general-purpose mice at N.I.H., Bethesda. [b] Inactive at the dose level (mg/kg) indicated.

6-alkyl function through ethyl to isopropyl caused no significant change in analgesic potency.



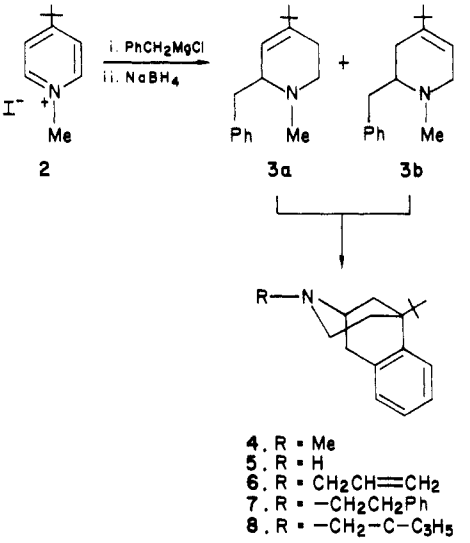
1a. R = Me
b. R = H
c. R = Ph

The presence of a quaternary carbon atom at C-6 was considered, for many years, to be a prerequisite[5] for analgesic responses. However, the development[4,6] of synthetic routes to compounds lacking a 6-substituent indicated that hydrogen at C-6 (**1b**) rather than alkyl gave no difference in analgesic activity.[4] In contrast, a phenyl substituent at C-6 in benzomorphans increased antinociceptive activity in the series,[7,8] with **1c** possessing one-fifth the activity of morphine.

An extensive investigation of 6-phenylbenzomorphans[8] demonstrated that the inclusion of 8-OH and 11β-Me groups in the molecule enhanced analgesic activity to twice that of morphine in the mouse hot-plate assay.

Here we examined, by the synthesis of 6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines, whether molecular bulk is a factor in the enhancement of analgesic actions by the C-6 substituent or if the electronic nature of the substituent dominates.

Chemistry. (±)-3-Methyl-6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**4**) was prepared by a standard Grewe procedure. 4-*tert*-Butylpyridine methiodide (**2**) was reacted with benzylmagnesium chloride, and the resultant unstable dihydropyridine was reduced with sodium borohydride to the mixture of double-bond isomers (**3a** and **3b**). In the ^1H NMR spectrum of crude **3**, the *t*-Bu signals occurred as singlets at δ 0.98 and 1.00 and the alkene signals occurred at δ 5.2 and 5.4. The former, a broad apparent singlet, was assigned to the proton at C-3 in **3a**, and the latter was a multiplet attributable to the X proton of an ABX system at C-5 of **3b**. The ratio of **3a** to **3b** was approximately 2:1. Thus the *tert*-butyl signal at δ 0.98 was assigned to the tetrahydropyridine **3a** and that at δ 1.0 to **3b**.



2 3a 3b

4. R = Me
5. R = H
6. R = $CH_2CH{=}CH_2$
7. R = $-CH_2CH_2Ph$
8. R = $-CH_2-C-C_3H_5$

As both **3a** and **3b** are capable of cyclization to the benzomorphan **4**, they were not separated and the mixture was cyclized with hot H_3PO_4 (158 °C). The cyclization could not be effected under standard conditions with boiling 48% aqueous HBr (126 °C) presumably because a higher temperature was required to overcome hindrance by the *tert*-butyl group.

An interesting feature of the ^1H NMR spectrum of **4** was the presence of a single aromatic proton at δ 7.6 downfield of the three-proton aromatic multiplet centered at δ 7.1. The δ 7.6 signal was assigned to the aromatic hydrogen at C-7, which is subject to an anisotropic effect from the 6-*tert*-butyl group.

Trichloroethyl chloroformate was employed to N-demethylate **4** under standard conditions to **5**, and N-allylation to **6** was effected by direct alkylation with allyl bromide. *N*-Phenethyl and *N*-cyclopropylmethyl derivatives (**7** and **8**, respectively) were prepared easily and in good yield by the reductive alkylation procedure described by Gribble et al.[10] and Marchini et al.[11] This involved reaction of the secondary amine (**5**) with either phenylacetic acid or cyclopropanecarboxylic acid previously treated with $NaBH_4$. An alternative lower yielding and more laborious approach to **7** was via the corresponding 3-phenylacetyl derivative of **5**, followed by LAH reduction.

Biological Results and Discussion

The presence of the bulky *tert*-butyl substituent at C-6 of benzomorphans has little influence on mouse hot-plate antinociceptive responses (Table I). 3-Methyl-6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**4**) had an activity (ED_{50} = 14.1 mg/kg) that differed insignificantly from the corresponding compound bearing a 6-H group (ED_{50} = 11.2 mg/kg).[4] Only a marginal enhancement of activity occurred when the N-substituent was phenethyl (**7**) (ED_{50} = 9.9 mg/kg). As anticipated, *N*-allyl and *N*-cyclopropylmethyl analogues (**6** and **8**) lacked mouse hot-plate antinociceptive actions.

These observations suggest that the π-nature of the phenyl substituent, rather than its bulk, is responsible for enhancing antinociceptive actions in benzomorphan series bearing C-6 substituents. The only other benzomorphans reported that had a C-6 substituent with π-properties were 6-allyl derivatives.[12,13] Although some members of this

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series were good analgesics, the presence of 8-OH and 11β-OH rendered them more akin to butorphanol than to compounds discussed here.

Experimental Section

The infrared spectra (liquids as films and solids as Nujol mulls) were recorded with a Unicam SP1025 spectrometer, and melting points (uncorrected) were taken on a Townson and Mercer melting point apparatus.

^{1}H NMR spectra were recorded with a JEOL PS 100 spectrometer operating at 100 MHz. Samples were prepared in 5-mm-o.d. tubes as ca. 10% solutions in $CDCl_3$ with Me_4Si as internal reference. All short-path distillations were carried out in a Buchi GKR-50.

C, H, N values are within ±0.4% of theory unless otherwise indicated.

6-*tert*-Butyl-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (4). Benzylmagnesium chloride (prepared from 56 g of benzyl chloride) in dry ether (100 mL) was added to a stirred ice-cooled suspension of 1-methyl-4-*tert*-butylpyridinium iodide (57 g, 200 mmol) in dry ether (200 mL) during 15 min. The mixture was stirred for a further 2 h at room temperature and poured onto crushed ice (300 g). After collection of the ethereal layer, the aqueous phase was extracted further with ether (3 × 200 mL). The combined ethereal solutions were extracted with 2 N HCl (3 × 200 mL), and the acid extracts were basified with strong NH_4OH and then extracted with ether (4 × 200 mL). The dried (Na_2SO_4) ethereal extracts were evaporated to yield 32 g of yellow oil.

To this product (32 g) in ethyl alcohol (200 mL) was added a suspension of $NaBH_4$ (8 g) in ethyl alcohol (100 mL), and the mixture was stirred at room temperature overnight. The mixture was evaporated to dryness, the residue dissolved in water, and the solution extracted with ether (3 × 100 mL). The dried (Na_2SO_4) ether extracts were evaporated to yield a crude mixture of **3a** and **3b** (24 g): IR ν_{max} 1370, 1470, 1460, 1505, 1603, 1640 cm^{-1}.

A solution of crude **3a** and **3b** (20 g) in H_3PO_4 (80 mL) was heated (158 °C) under reflux for 24 h. The cooled solution was basified with strong NH_4OH and extracted with ether (3 × 100 mL). The ethereal solution was extracted with 2 N HCl (3 × 100 mL), and the combined acid extracts were basified with strong NH_4OH and extracted with ether (4 × 100 mL). Evaporation of the dried (Na_2SO_4) extracts gave 6-*tert*-butyl-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine as an orange oil (15 g), which was distilled over a short path (98–100 °C and 0.025 mmHg) to a pale yellow oil (10 g, 20%). The hydrochloride separated from acetone as white needles: mp 204–206 °C; ^{1}H NMR (base) δ 1.2 (s, 9 H, 6-C_4H_9), 2.32 (s, 3 H, NCH_3), 6.98–7.25 (m, 3 H, C-8, C-9, C-10 Ar), 7.55–7.73 (m, 1 H, C-7). Anal. ($C_{17}H_{26}NCl$) C, H, N.

6-*tert*-Butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (5). A mixture of **4** (2.6 g, 10.6 mmol), trichloroethyl chloroformate (4.6 mL, 2.0 mmol), and K_2CO_3 (0.5 g) in dry toluene (50 mL) was heated under reflux for 72 h. Ether (50 mL) was added to the cooled mixture and the mixture washed with 3 N HCl (2 × 40 mL) and water (1 × 40 mL). The organic phase was dried (Na_2SO_4) and evaporated to a yellow oil (4.5 g). The oil (4.5 g) was dissolved in acetic acid (50 mL) and stirred at room temperature, Zn dust (3.3 g) was added, and the mixture was stirred for 4 h. After removal of excess Zn by filtration, the filtrate was basified with 5 N NaOH and extracted with ether (3 × 100 mL). The dried (Na_2SO_4) ethereal extracts were evaporated to dryness to yield **5** as a yellow oil, which was purified (colorless plates from EtOH/Et_2O) as its hydrochloride (1.1 g, 39%): mp ~300 °C dec; ^{1}H NMR (base) δ 1.4 (s, 9 H, 6-C_4H_9), 7.08–7.14 (m, 3 H, C-8, C-9, C-10), 7.58–7.80 (m, 1 H, C-7. Anal. ($C_{16}H_{24}NCl$) C, H, N.

3-Allyl-6-*tert*-butyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (6). To a stirred suspension of $NaHCO_3$ (0.5 g) and **5** (0.57 g, 2.5 mmol) in EtOH (15 mL) at room temperature was added allyl bromide (0.213 mL, 2.5 mmol). The mixture was stirred and heated under reflux overnight, and after cooling, the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in ether (20 mL), and the solution was filtered and extracted with 2 N HCl (3 × 30 mL). The combined extracts were basified with strong NH_4OH and extracted with ether (3 × 50 mL). Evaporation of the dried (Na_2SO_4) ethereal extracts gave the product (0.4 g, 60%) as a pale yellow oil. The hydrochloride crystallized from acetone: 250–252 °C dec; IR ν_{max} (base) 1640 cm^{-1}; ^{1}H NMR (base) δ 1.15 (s, 9 H, 6-C_4H_9), 5.15, 5.75 (m, 3 H, —CH=CH_2), 7.1 (m, 3 H, C-8, C-9, C-10), 7.55 (m, 1 H, C-7). Anal. ($C_{19}H_{28}NCl$) C, H, N.

5-*tert*-Butyl-3-(2-phenylethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (7). Method A. A solution of **5** (0.36 g, 1.5 mmol), phenylacetyl chloride (0.25 mL, 1.6 mmol), and triethylamine (2 mL) in dry ether (10 mL) was stirred at room temperature overnight. The triethylamine hydrochloride that separated was removed by filtration and the filtrate was evaporated to dryness to yield crude 6-*tert*-butyl-3-(phenylacetyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine as an oily solid (0.4 g). This intermediate (0.4 g) dissolved in dry ether (20 mL) was added dropwise at room temperature to a stirred suspension of LAH (2 g) in dry ether (20 mL), and the mixture was heated under reflux for 6 h. To the mixture, cooled to 0 °C, was added carefully water (2 mL), 5 N NaOH (1.5 mL), and water (7 mL) in that order. The resultant granular mass was removed by filtration and washed with ether (20 mL), and the combined ethereal filtrate and washings were dried (Na_2SO_4) and evaporated to yield **7** (0.22 g) as a pale yellow oil. The hydrochloride crystallized from acetone/Et_2O as white needles: mp 250 °C dec; IR ν_{max} (base) 1603, 3100 cm^{-1}; ^{1}H NMR (base) δ 1.15 (s, 9 H, 6-C_4H_9. Anal. ($C_{24}H_{32}NCl$), C, H, N.

Method B. $NaBH_4$ (0.42 g, 12.5 mmol) was added slowly with stirring to a solution of phenylacetic acid (5.1 g, 37.5 mmol) in dry toluene (20 mL) while a temperature of 20 °C was maintained. When the evolution of hydrogen had ceased, compound **5** (0.5 g, 2.5 mmol) was added and the mixture heated under reflux for 3 h. The mixture was cooled to 20 °C and shaken with 2 N NaOH (20 mL), and the organic phase was collected, dried (Na_2SO_4), and evaporated to yield **7** (0.4 g) as an oil. The hydrochloride (0.4 g, 50%) separated from acetone/Et_2O and was identical in all respects with that prepared by method A.

5-*tert*-Butyl-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (8). Following the procedure described for compound **6**, method B, **5** (0.46 g, 2.0 mmol) was reacted with $NaBH_4$ (0.37 g, 10 mmol) and cyclopropanecarboxylic acid (28 g, 33 mmol) in dry toluene (20 mL) to give the product (0.38 g). The hydrochloride (0.39 g, 61%) separated from acetone as white needles: mp ~230 °C dec; ^{1}H NMR (HCl salt) δ 0.4–0.9 (m, 5 H, c-C_3H_5), 1.2 (s, 9 H, 6-C_4H_9). Anal. ($C_{20}H_{30}NCl$) C, H, N.

Registry No. **2**, 64326-91-6; (±)-**3a**, 102649-50-3; (±)-**3b**, 102649-51-4; (±)-**4**, 102649-52-5; (±)-**4**·HCl, 102649-53-6; (±)-**5**, 102649-54-7; (±)-**5**-ene, 102649-57-0; (±)-**5**·HCl, 102649-55-8; (±)-**6**, 102682-03-1; (±)-**6**·HCl, 102682-04-2; (±)-**7**, 102682-06-4; (±)-**7** (amide), 102682-05-3; (±)-**7**·HCl, 102682-07-5; (±)-**8**, 102682-08-6; (±)-**8**·HCl, 102682-09-7; $PhCH_2MgCl$, 6921-34-2.

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