Some Spiro Analogues of the Potent Analgesic Ketobemidone

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A series of spiro analogues of the potent narcotic ketobemidone have been prepared and found to be devoid of opiate activity. Additional pharmacology and possible implications for the mode of binding of ketobemidone to the analgesic receptor are discussed.

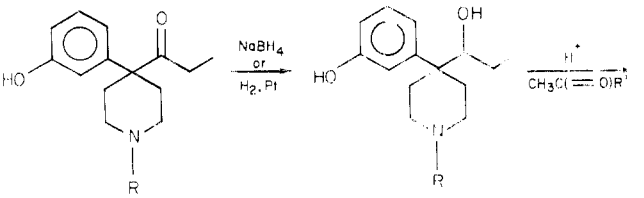
Spiro derivatives of 4-phenylpiperidine analgesics would appear to be interesting receptor probes inasmuch as the rotation of the phenyl ring is restricted in such compounds. A number of examples have appeared in the literature and the importance of the torsional relationship between the aromatic group and the piperidine ring in nonspiro analgesics has received attention.[1a-i] Although biological data are not abundant, in general, spiro examples of 4-phenylpiperidines have been found to be less active or inactive, except for a few examples where the activity is not clearly opiate-like. We report the synthesis and evaluation of several spiro analogues (Scheme I, 1–4) of the potent analgesic ketobemidone (5).

Chemistry. Compound **2** was obtained in an attempt to prepare the HBr salt of **6** (Scheme I). Treatment of an acetone solution of **6** dropwise with 30–32% HBr/acetic acid until acidic at room temperature afforded **2**·HBr.[2] The NMR spectrum of this product exhibited singlets at δ 1.38 and 1.40 and the aromatic region integrated for three protons. Furthermore, the aromatic coupling pattern was consistent with para cyclization to give **2**. Similarly prepared from their respective alcohols in the appropriate ketonic solvent were **1**, **3**, and **4**; **1** and **4** required warming to complete the reaction. Compound **3**, for which diastereomers are possible, appears on TLC to be a single racemate.

Compounds **7** and **8** were prepared from norketobemidone as previously reported.[3] Attempts to prepare **5** from norketobemidone via the Eschweiler–Clarke procedure gave mixtures, but methylation using formaldehyde/sodium cyanoborohydride gave good yields. Reduction of the ketones to give **6**, **9**, and **10** was easily accomplished with either sodium borohydride or hydrogenation over platinum; it was necessary to use the amine salt for hydrogenation.

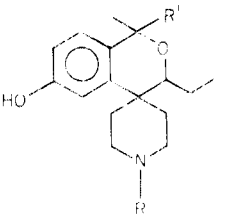
Biological Results. Compounds **1–4** were evaluated for analgesic activity in the hot-plate[4a,b] and Nilsen[5] assays

Scheme I



5, R = CH_3
7, R = $(CH_2)_4CH_3$
8, R = $CH_2CH{=}CH_2$

9, R = CH_3
6, R = $(CH_2)_4CH_3$
10, R = $CH_2CH{=}CH_2$



1, R = CH_3; R' = CH_3
2, R = $(CH_2)_4CH_3$; R' = CH_3
3, R = $(CH_2)_4CH_3$; R' = CH_2CH_3
4, R = $CH_2CH{=}CH_2$; R' = CH_3

and for receptor affinity as determined by the capacity to displace bound, radiolabeled dihydromorphine from rat brain homogenates.[6] Compound **2** was also evaluated in the tail-flick[7] and writhing[8] procedures.

The spiro analogues appear to be essentially devoid of opiate activity. The binding constants for **1**, **2**, **3**, and **4** are 10000, 2000, 5000, and 5000 nM, respectively. In general, **1–4** were only weakly active (ED_{50} > 30 mg/kg) in the hot plate and Nilsen tests and failed to show normal dose–response curves [in the hot plate, ED_{50} of morphine = 1.0 (0.7–1.4) mg/kg and ED_{50} of ketobemidone = 0.8 (0.7–0.9) mg/kg; in the Nilsen, ED_{50} of morphine = 0.7 (0.5–1.1) mg/kg]. For example in the hot-plate assay with **1**, five of ten mice responded at 10 mg/kg and four of ten at 50 mg/kg, while in the Nilsen procedure two of eight responded at 10 mg/kg and none of eight at 20 and 50 mg/kg. Also, solubility problems were encountered at the higher doses. Compound **2** was inactive in the tail-flick assay and had an ED_{50} of 4.2 (1.4–12.5) mg/kg [ED_{50} of morphine = 0.23 (0.20–0.25) mg/kg] in the writhing test.

Compound **2** was examined at 2, 5, and 10 mg/kg in single dose suppression tests in monkeys[9] and was judged to be not morphine-like; however, at 10 mg/kg some CNS depression was noted. Therefore, **2** was examined for

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(2) The synthesis of 1*H*-2-benzopyrans from phenylethanols and carbonyl reagents in the presence of acid has been reported: D. Satoh, T. Hashimoto, and K. Aoyama, *Yakugaku Zasshi*, **95**, 1183 (1975).

(3) T. Oh-ishi and E. L. May, *J. Med. Chem.*, **16**, 1376 (1973).

(4) (a) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); (b) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

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(6) M. E. Rogers, H. H. Ong, E. L. May, and W. A. Klee, *J. Med. Chem.*, **18**, 1036 (1975).

(7) W. L. Dewey and L. S. Harris in "Methods in Narcotic Research", S. Ehrenpreis and A. Neidle, Eds., Marcel Dekker, New York, 1975, p 101.

(8) J. Pearl and L. S. Harris, *J. Pharmacol. Exp. Ther.*, **154**, 319 (1966).

(9) R. L. Balster, *Pharmacology*, in press.

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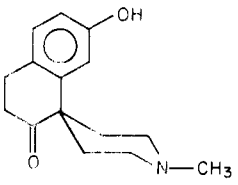
depressant effects in photocell activity cages and the inclined screen and the inverted screen assays.

In activity cages, at 60 mg/kg during the 10–25 min time period after injection, counts were significantly different from nontreated controls ($p > 0.05$). Diazepam used as a positive control was active at 5 mg/kg. In the inclined screen assay, **2** was inactive at 10 and 60 mg/kg up to 1 h after injection. In the inverted screen assay,[9] **2** had an ED_{50} of 38.0 mg/kg (27.1–53.1) with effects most pronounced 5–15 min after injection. One animal died at 60 mg/kg and 50% died when a dose of 80 mg/kg was attempted. Compound **2** did not elicit significant CNS depressant activity in these assays.

Since novel benzopyrans are of potential value as antiglaucoma agents,[10] **2** was administered as a 0.3% aqueous solution to one eye of six normal rabbits. Measuring the intraocular pressure with a pneumotonograph revealed no effect up to 3.5 h.

Discussion

The data would appear to indicate that the failure of **1–4** to induce opiate effects is the result of low receptor affinity. Viewed in this context, explanations for the inactivity include decreased fit due to the greater steric bulk of **1–4** compared to **5**; however, **11**, a previously reported



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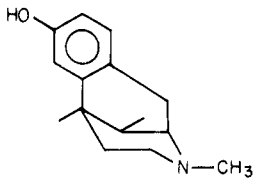

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spiro analogue of **2**, offers less steric bulk but is also inactive.[1a] Furthermore, the diacetylated derivative of the diol **6** which approaches **1–4** in steric bulk has analgesic activity and receptor affinity equivalent to morphine.[11]

Restricted rotation of the aromatic ring appears to be a more reasonable explanation for the observed effects. Molecular models reveal that the preferred orientation of the phenyl moiety in **1–4** and **11** is similar to that in nonspiro 4-phenylpiperidines. This suggests that perhaps the orientation of the phenyl ring of **5** during receptor interaction is one having the aromatic moiety in a nonpreferred orientation. Alternatively, in **1–4** and **11**, not only is the rotation of the phenyl ring restricted, the phenolic hydroxyl moiety is locked into an orientation that differs from that observed in the analgesically active benzomorphan **12**. This may be causal with regard to the inactivity of **1–4** and **11**, whether the phenyl ring is oriented axially or equatorially.

We have begun a program of synthesis to differentiate among the possible explanations for the lack of opiate activity for **1–4** and clearly define the mode of binding of **5** to the analgesic receptor.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt, capillary, melting point apparatus and are uncorrected. IR spectral data were obtained on a Perkin-Elmer 257 or a Beckman Acculab 8, and NMR spectral data were obtained on a Perkin-Elmer R-24. Spectra were obtained on all compounds and these are compatible with the structural assignments. Microanalyses obtained, as indicated by the symbols of the elements, are within ±0.4% of the theoretical values.

Pharmacology. For the hot-plate and Nilsen assays, **1**, **2**, and **4** were administered sc as aqueous solutions of their HBr salts (**3** as Emulphor solution of HBr salt). Compound **2**·HBr was given sc as an aqueous solution in the tail-flick and writhing procedures and sc in 66% propylene glycol for the single dose suppression tests. Compound **2**·HBr was given ip in a propylene glycol–EtOH–saline solution for the activity cage studies and ip in Emulphor–EtOH–saline solution for the inclined screen and the inverted screen assays. The binding constants reported are an average of duplicates.

Spiro[1,1-dimethyl-3-ethyl-7-hydroxy-1*H*-2-benzopyran-4,4′-(1′-methylpiperidine)] (1). To a solution of 1.0 g (4.0 mmol) of **9** in 30 mL of Me_2CO was added dropwise 30–32% HBr/AcOH until the solution was acid to litmus. A precipitate did not form and the volume was reduced one half on a steam bath. The solution was filtered, yielding 0.5 g (34%) of crude **1**·HBr, mp 247–252 °C; three recrystallizations from Me_2CO gave an analytical sample: mp 249–251 °C; ^1H NMR ($CDCl_3$) of free base δ 1.4 (s, 3 H, CH_3), 1.5 (s, 3 H, CH_3), 3.8 (m, 1 H, C-H), 6.6–7.1 (m, 3 H, aromatic); EIMS 289 (M^+), 232 (base). Anal. ($C_{18}H_{27}NO_2Br$) C, H, N.

Spiro[1,1-dimethyl-3-ethyl-7-hydroxy-1*H*-2-benzopyran-4,4′-(1′-pentylpiperidine)] (2). To a solution of 1.0 g (3.3 mmol) of **6** in 25 mL of Me_2CO was added dropwise 30–32% HBr/AcOH until the solution was acid to litmus. The solution was filtered to yield 0.6 g (43%) of **2**·HBr, mp 292–294 °C; recrystallization from absolute EtOH afforded the analytical sample: mp 292–294 °C; ^1H NMR ($CDCl_3$) of free base δ 1.45 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.8 (m, 1 H, C-H), 6.6–7.05 (m, 3 H, aromatic); EIMS 345 (M^+), 289 (base). Anal. ($C_{22}H_{35}NO_2Br$) C, H, N.

Spiro[1,3-diethyl-1-methyl-7-hydroxy-1*H*-2-benzopyran-4,4′-(1′-pentylpiperidine)] (3). To a solution of 0.9 g (3.0 mmol) of **6** in 30 mL of methyl ethyl ketone was added dropwise 30–32% HBr/AcOH until the solution was acid to litmus. The solution was filtered, yielding 0.6 g (46%) of **3**·HBr, mp 283–286 °C; recrystallization twice from absolute EtOH afforded the analytical sample: mp 289–291 °C; ^1H NMR ($CDCl_3$) of the free base δ 1.4 (s, 3 H, CH_3), 3.6 (m, 1 H, C-H), 6.6–7.1 (m, 3 H, aromatic); EIMS 359 (M^+), 302 (base). Anal. ($C_{23}H_{37}NO_2Br$) C, H, N.

Spiro[1,1-dimethyl-3-ethyl-7-hydroxy-1*H*-2-benzopyran-4,4′-(1′-allylpiperidine)] (4). The alcohol **10** was prepared from **8**·HBr (2.0 g, 5.6 mmol) as for **9** to give 0.9 g (58%) of a gum: IR (neat) 3300 cm^{-1} (OH), no carbonyl; ^1H NMR ($CDCl_3$) δ 3.3 (m, 1 H, C-H), 4.9–6.0 (m, 3 H, vinyl), 6.6–7.3 (m, 4 H, aromatic). To a solution of 1.5 g of **10** in 30 mL of Me_2CO was added dropwise 30–32% HBr/AcOH until the solution was acid to litmus. A precipitate did not form and the volume was reduced one-half on a steam bath. The solution was filtered. The acetone was replenished and the above procedure repeated twice more. The three crops were combined to afford 1.0 g of crude **4**·HBr, mp 265–273 °C. Recrystallization from Me_2CO–EtOH gave 0.8 g (37%) of **4**·HBr: mp 266–268 °C; ^1H NMR ($CDCl_3$) of free base δ 1.46 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.8 (m, 1 H, C-H), 5.0–6.2 (m, 3 H, vinyl), 6.5–7.2 (m, 3 H, aromatic); EIMS 315 (M^+), 70 (base). Anal. ($C_{20}H_{30}NO_2Br$) C, H, N.

4-(3-Hydroxyphenyl)-4-(1-hydroxypropyl)-1-pentylpiperidine (6). To a 500-mL Parr hydrogenation bottle containing 500 mg of PtO_2 was added a solution of **7**·HBr (7.5 g, 19.5 mmol) in 250 mL of 95% EtOH. The mixture was shaken at a hydrogen pressure of 55 psi for 24 h. The catalyst was filtered and the filtrate evaporated in vacuo. The residue was dissolved in 75 mL of H_2O and basified with $NaHCO_3$. The mixture was extracted with three 100-mL portions $CHCl_3$. The organic layer was washed (100 mL of saturated NaCl), dried ($MgSO_4$), and evaporated in vacuo to yield 6.0 g (80%) of **6**: IR ($CHCl_3$) 3300 cm^{-1} (OH), no carbonyl; ^1H NMR ($CDCl_3$) δ 3.3 (m, 1 H, C-H), 6.85–7.25 (m, 4 H, aromatic); EIMS 305 (M^+), 248 (base). The oxalate salt was made and recrystallized from Me_2CO, mp 145–147 °C. Anal. ($C_{21}H_{33}NO_6$) C, H, N.

4-(3-Hydroxyphenyl)-4-(1-hydroxypropyl)-1-methylpiperidine (9). The procedure of Borch and Hassid[13] was fol-

(10) A. T. Dren and B. A. Bopp, German Patent 2735046, Feb 8, 1978.
(11) M. E. Rogers, unpublished data.
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lowed for the preparation of **5**. Norketobemidone (23.3 g, 0.1 mol), 40 mL of 37% formaldehyde, sodium cyanoborohydride (10.0 g, 0.16 mol), and 300 mL of MeCN were stirred (**exothermic**) for 15 min. Glacial acetic acid was added to neutrality (wet litmus). The mixture was stirred for 45 min, maintaining neutrality, and then evaporated in vacuo. The residue was dissolved in 100 mL of distilled H_2O and made acidic with 6 N HCl. The mixture was basified with NH_4OH and extracted with three 100-mL portions of $CHCl_3$. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated in vacuo giving 21.2 g of a powder. Recrystallization from EtOAc afforded 17.1 g of **5**, mp 148–151 °C (lit.[14] mp 156–157 °C). The HBr salt was made, mp 191–193 °C (lit.[15] mp 194–196 °C).

A mixture of **5**·HBr (3.4 g, 10.4 mmol), 75 mL of EtOH, 1.4 g of KOH, and a solution of $NaBH_4$ (1.44 g, 38.1 mmol) in 20 mL of H_2O was maintained at 80 °C for 2 h. The mixture was evaporated in vacuo and acidified with 6 N HCl. Basification with NH_4OH and filtration gave 1.5 g of crude solid, mp 109–145 °C. Recrystallization from acetone gave 1.0 g of **9** (38%), mp 187–189 °C. A small sample was recrystallized from acetone for analysis: mp 188–190 °C; IR (KBr) 3250 cm^{-1} (OH), no carbonyl; ^1H NMR (Me_2SO-d_6) δ 3.2 (m, 1 H, C-H), 6.5–7.35 (m, 4 H, aromatic). Anal. ($C_{15}H_{23}NO_2$) C, H, N.

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(14) "The Merck Index", P. G. Stecher, Ed., 8th ed, Merck and Co., Inc., Rahway, N.J., 1968, p 600.
(15) A. W. D. Avison and A. L. Morrison, *J. Chem. Soc.*, 1470 (1950).

Synthesis and Diuretic Profile of 3-(3-Amino-1,2,4-oxadiazol-5-yl)-5-chloro-2,6-pyrazinediamine, an Amiloride-Type Diuretic

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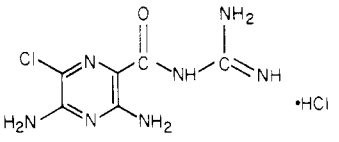
The synthesis of an analogue of amiloride in which the acylguanidine moiety has been replaced by a 1,2,4-oxadiazol-3-amine unit is described. This substance (**3**, CGS 4270) exhibited a diuretic profile similar to that of amiloride when evaluated in the rat and the dog. In the rat, combination with hydrochlorothiazide increased diuresis and saluresis and returned potassium levels to control values. A series of 5-aryl-1,2,4-oxadiazol-3-amines not directly related to amiloride was prepared, but these substances had no diuretic activity.

Amiloride (**1**)[1] is a clinically effective potassium sparing



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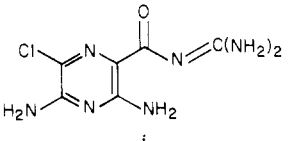
diuretic which is marketed in a number of countries throughout the world. It is especially effective when used in combination with a thiazide diuretic, as the effects of the two agents are additive with respect to the excretion of water and sodium but antagonistic with respect to the excretion of potassium.[3] Of the many analogues of **1** which have been prepared and tested, the carboxamidoguanidine

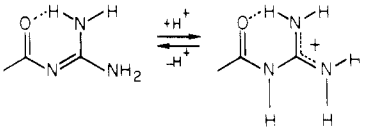
(1) Formulation **1** has been routinely used for amiloride, but the major tautomeric form in Me_2SO is apparently i.[2]



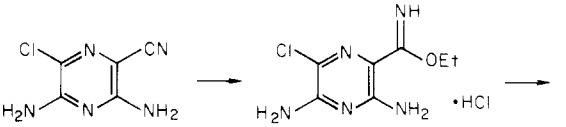
i

(2) R. L. Smith, D. W. Cochran, P. Gund, and E. J. Cragoe, *J. Am. Chem. Soc.*, **101**, 191 (1979).
(3) G. J. Schapel, K. D. G. Edwards, and J. Robinson, *Clin. Exp. Pharmacol. Physiol.*, **2**, 277 (1975), and references cited therein.

Scheme I



Scheme II



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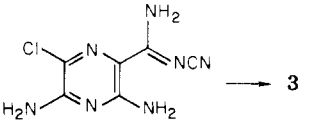

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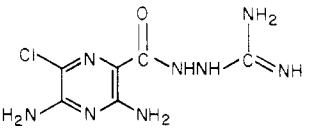
2 is apparently the only one where a significant structural departure did not result in loss of useful diuretic activity.[4,5]



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