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C-ALKYLATED SPIRO[BENZOFURAN-3(2H),4'-1'-METHYL-PIPERIDINE-7-OLS] AS POTENT OPIOIDS: A CONFORMATION-ACTIVITY STUDY

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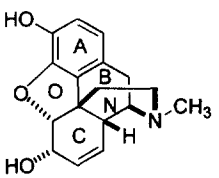
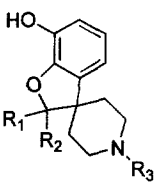
Abstract: Among a series of C-alkylated analogs of the weak μ opioid ligand spiro[benzofuran-3(2H),4'-1'-methylpiperidine-7-ol] (**1**), the 2-methyl, 2-ethyl, and *cis* 3'-methyl analogs, namely compounds (±)**2**, (±)-**3**, and (±)-**4**, showed much enhanced μ-affinities, with (±)-**4** being almost as potent as (-)-morphine; while the *trans* 3'-methyl analog (±)-**5** remained a weak μ-binder. Energy calculations and nmr data indicated that compounds **2-4** favor phenyl-axial conformations, while compounds **1** and **5** favor phenyl-equatorial conformations.

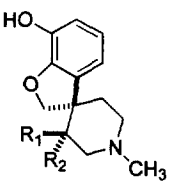
Morphine is a potent analgesic alkaloid, its rigid structure consisting of five rings (ABCNO). Many centrally acting synthetic analgesics are structurally related to morphine in that they possess partial structures of morphine.[1] These include morphinans such as levorphanol (ABCN), benzomorphans such as pentazocine (ABN), 4-phenylpiperidines such as meperidine (AN), cyclohexylbenzene derivatives such as tramadol (AC), and 3-phenylpropylamines such as methadone (A). However, the oxide-containing morphine fragments, namely spiro[benzofuran-3(2H),4'-piperidines] (ANO), octahydro-*1H*-benzofuro[3,2-*e*]isoquinolines (ACNO), and *3H*-2a,6-methano-*2H*-furo[4,3,2-*f,g*][3]benzazocines (ABNO), have remained relatively less explored. Recently we have developed efficient methodologies for the construction of morphine ANO and ACNO fragments via either intramolecular radical cyclization[2] or palladium-catalyzed cyclization.[3] However, the ANO fragment compound **1** thus prepared was found to retain only weak binding affinity towards the μ opioid receptor ($K_{i,\mu}$ = 1.6 μM).[3]



Morphine



1 : $R_1 = R_2 = H$; $R_3 = CH_3$
(±)-**2** : $R_1 = R_3 = CH_3$; $R_2 = H$
(±)-**3** : R_1 = Et ; $R_2 = H$; $R_3 = CH_3$
6 : $R_1 = R_2 = CH_3$; R_3 = 



(±)-**4** : $R_1 = CH_3$; $R_2 = H$
(±)-**5** : $R_1 = H$; $R_2 = CH_3$

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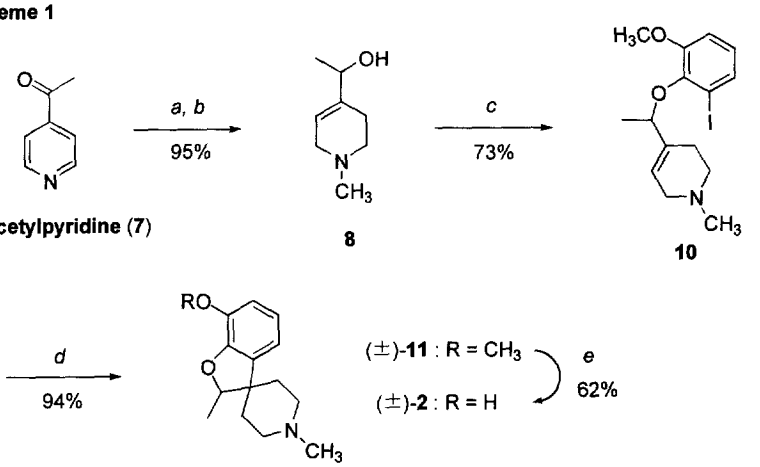
In order to further delineate the structure activity relationships embodied in the ANO fragment of morphine, we have now synthesized a series of C-alkylated analogs of compound **1**, namely compounds **2-5**. It was gratifying to find that the opioid activity of the ANO fragment can be effectively enhanced with a suitably situated alkyl substituent, resulting in the *cis* 3'-methyl analog (±)-**4** being a potent μ opioid ligand ($K_{i,\mu}$ = 54 nM) comparable to morphine. Conformational analysis was then performed on these analogs to help interpret the opioid receptor binding data. The structure-activity studies of a related series of spiro[tetralin-1,4-piperidines] have been reported.[4] A 2,2-dimethyl analog of compound **1**, namely compound **6**, has been documented to be a mixed opioid agonist-antagonist.[5] However, the relevant chemistry or SAR data was not available.

Scheme 1

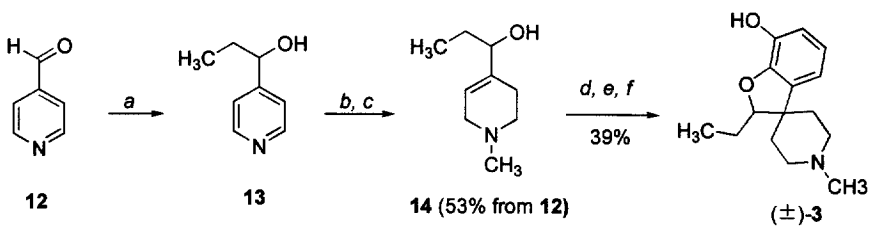


Scheme 1 (*a*) CH_3I, CH_2Cl_2, r.t. (*b*) $NaBH_4$, MeOH, r.t. (*c*) **9**, Diethyl azodicarboxylate, PPh_3,THF, r.t. (*d*) $AIBN_{(cat.)}$, Bu_3SnH, Benzene, 130°C (*e*) BBr_3-$(CH_3)_2S$, $ClCH_2CH_2Cl$

The 2-alkyl analogs of compound **1** are readily accessible via our radical methodology[2] as illustrated in Scheme 1 for the preparation of compound **2**. The starting 4-acetylpyridine (**7**) was first treated with methyl iodide, followed by simultaneous reduction of the resultant pyridinium ring and the keto group to give tetrahydropyridine **8**. Mitsunobu coupling[6] of **8** with iodoguaiacol[3] (**9**) then provided the key intermediate **10**, which cyclized under radical reaction conditions to the desired spiro compound **11**. The target compound (±)-**2**[7] was obtained via O-demethylation of **11** with boron tribromide-dimethylsulfide complex. The 2-ethyl analog compound (±)-**3**[7] was prepared in a similar fashion from the tetrahydropyridine intermediate **14**, which in turn was obtained from 4-pyridylcarboxaldehyde (**12**) via a 3-step sequence of Grignard reaction with ethylmagnesium bromide, N-methylation, and $NaBH_4$ reduction. (Scheme 2) For the synthesis of 3'-methylated analogs, literature procedure for the preparation of 3-methyl-4-phenylpiperidines[8] was adopted.

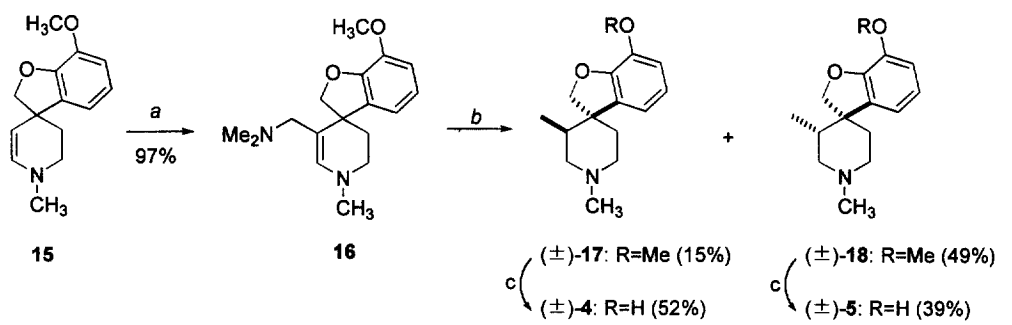
Therefore, spiro-tetrahydropyridine intermediate **15**, a Heck product described previously,[3] underwent Mannich reaction with formaldehyde and dimethylamine to give **16**, which was hydrogenated to give the diastereomeric pair of **17** and **18** in a ratio of 3:10. The assignment of **17** and **18** was based on NMR NOESY experiment and energy minimization. The protons at C-2' and C-6' were observed to have nOe effect with the aromatic H-4 in **17** and the furan protons in **18** respectively. (Figure 1) The conformational preference as shwon, namely phenyl-axial for **17** and phenyl-equatorial for **18**, was supported by energy calculation. (Table 1) The selectivity observed in the above hydrogenation can be explained by the conformational preference of **16** as indicated in Figure 1, with its phenyl ring in a pseudo-equatorial position, and an axial attack by H_2. Compounds **17** and **18** were then treated with BBr_3, and provided the target compounds **4** and **5** respectively.[7] (Scheme 3)

Scheme 2



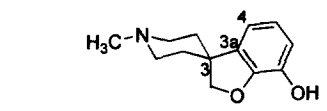
Scheme 2 (a) C_2H_5MgBr, THF, -63°C (*b*) CH_3I, CH_2Cl_2, r.t. (*c*) $NaBH_4$, MeOH, r.t. (*d*) **9**, Diethyl azodicarboxylate,PPh_3,THF, r.t. (*e*) $AIBN_{(cat.)}$, Bu_3SnH, Benzene, 130°C (*f*) BBr_3-$(CH_3)_2S$, $ClCH_2CH_2Cl$

Scheme 3



Scheme 3 (*a*) CH_2O, $HNMe_2$, H_2SO_4, Hexane (*b*) Pd/C, H_2, 5 bar, Ethanol (*c*) BBr_3-$(CH_3)_2S$, $ClCH_2CH_2Cl$

The opioid receptor binding affinities of target compounds were determined with brain membrane preparations from male Hartley guinea-pigs as described previously.[9] The 2-alkylated analogs, compounds (±)-**2** and (±)-**3**, and the *cis* 3'-methyl analog (±)-**4** showed potent affities towards the μ opioid receptor, with the potency of (±)-**4** approaching that of (-)-morphine; while compound **1** and the *trans* 3'-methyl analog (±)-**5** showed much reduced binding at the μ opioid receptor. (Table 1)



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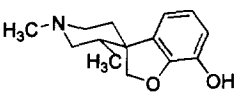
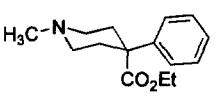
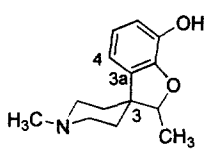


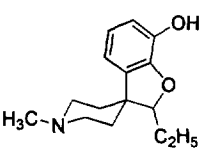
(±) **5**



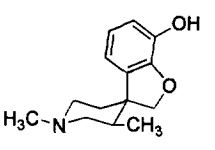
Meperidine



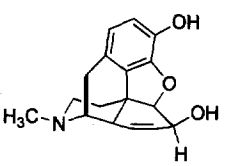
(±) **2**



(±) **3**



(±) **4**

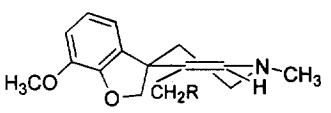


(-)-**Morphine**

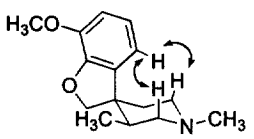
Table 1. Opioid Receptor Binding Affinities and Conformational Energies of Spiro[benzofuran-3(2H),4'-piperidine-7-ols]

	(Ki, nM)[a]			Conformation			△ E[e]
Compound	μ	κ	δ	(*phenyl*)[b]	τ^c	d^d (Å)	kcal/mol.
1	1654 ± 52	$>10^4$	$>10^4$	eq.		5.67	0.7 (1.27)
(±)-**2**	124 ± 2.7	$>10^4$	2409 ± 524	ax.	-10.3°	5.04	-0.83 (-0.84)
(±)-**3**	102 ± 4.0	$>10^4$	853 ± 47	ax.	-11.4°	5.04	-2.99 (-4.88)
(±)-**4**	54 ± 1.4	177 ± 17	—	ax.	-3.8°	5.07	-1.48 (-2.77)
(±)-**5**	1015 ± 118	505 ± 110	—	eq.	-2.7°	5.67	3.42 (5.99)
(-)-**Morphine**	38 ± 4	1870 ± 83	510 ± 55	ax.	28.4°	4.37	
Meperidine	451 ± 40	$>10^4$	—	eq.[11]			

a. Data represents the mean of three experiments each performed in duplicate.
b. Preferred conformation for the phenyl group
c. τ = C4C3a-C3N with clockwise rotation of the plane defined by C4C3aC3 into the plane defined by C3aC3N.
d. Distance between nitrogen atom and center of the phenyl ring.
e. Calculated energy differences between phenyl-axial and phenyl-equatorial conformers. Values in parentheses were obtained on the protonated ammonium species.



(±)-**16** : R = $N(CH_3)_2$
(28.98 vs. 29.56 kcal/mole)[10]



17

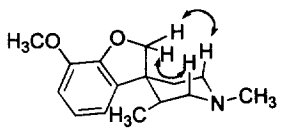


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Figure 1. Favored conformation of compound **16** and NOE effects in compounds **17** and **18** based on NOESY spectra.

Conformational analysis[10] was then performed on these analogs. As indicated in Table 1, compounds with higher affinities at the μ opioid receptor, namely **2**, **3**, and **4**, prefer to adopt phenyl-axial conformations, mimicking the rigid μ-agonist morphine; while those with reduced μ-affinities, including compound **1**, compound **5**, and the flexible 4-phenylpiperidine derivative meperidine, prefer phenyl-equatorial conformations. Compound **4**, and to a lesser extent its *trans* isomer **5**, also demonstrated significant binding at the κ opioid receptor. Whether this can be correlated to the small values of the torsion angle (τ) between the phenyl ring and the piperidine ring in their energy-minimized structures remains to be confirmed. Also listed in Table 1 are *d* values, the distances between the nitrogen atom and the phenyl ring for these analogs in their preferred conformations. Weak μ-binders such as compounds **1** and **5** gave larger *d* values; while the more potent compounds **2-4** have smaller *d* values in between that of morphine and compound **1** or **5**. Since the δ-affinities of compounds **4** and **5** have not been determined, no conclusion can be drawn concerning the structural requirements for binding to the δ opioid receptor.

In conclusion, we have demonstrated that the opioid activity of compound **1** can be drastically enhanced by suitable C-alkyl substituents, e.g. a methyl group at C-3' cis to the phenyl ring. The observed differences in opioid receptor affinities of compound **1** and its C-alkylated analogs can be largely attributed to the conformational preferences induced by the substituents. It is likely that compound **4** or its analogs with suitable N-substituents may be developed as useful opioid analgesics or narcotic antagonists. Further synthetic work and pharmacological testing towards the above goal are in progress.

Acknowledgement: This research was supported by the National Science Council of the R.O.C. under Grant No. NSC 86-2113-M002-013.

References and Notes

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7. Selected spectral and analytical data: **2** : ^{1}HNMR (200MHz, $CDCl_3$) δ 1.29 (d, J = 6.4 Hz, 3H), 1.76 (t, J = 5.6 Hz, 2H), 1.86 (t, J = 5.2 Hz, 2H), 2.35 (s, 3H), 2.35-2.50 (m, 2H), 2.76 (m, 2H), 4.58 (q, J = 6.3 Hz, 1H), 6.69-6.81 (m, 3H); ^{13}CNMR (50Hz, $CDCl_3$) δ 16.0, 30.3, 36.3, 46.1, 46.6, 52.8, 87.8, 115.9, 116.1, 121.4, 136.4, 141.6, 145.8; MS (EI, 70 ev) m/e Calc'd for $C_{14}H_{19}NO_2^+$: 233.1416, found 233.1409. **3** : ^{1}HNMR (200MHz, $CDCl_3$) δ 1.02 (t, J = 7.0 Hz, 3H), 1.49-1.60 (m, 2H), 1.75-1.78 (m, 5H), 2.35 (s, 3H), 2.51-2.54 (m, 1H), 2.66-2.78 (m, 2H), 4.25 (t, J = 6.4 Hz, 1H), 6.68-6.77 (m, 3H); ^{13}CNMR (50Hz, $CDCl_3$) δ 11.7, 14.1, 23.1, 30.2, 36.3, 46.0, 46.5, 52.8, 93.3, 115.9, 116.2, 121.3, 136.8, 141.7, 146.0; MS (EI, 70 ev) m/e Calc'd for $C_{15}H_{21}NO_2^+$: 247.1572, found 247.1567. **4** : ^{1}HNMR (200MHz, $CDCl_3$) δ 0.70, 1.89-2.00, 2.29 (t, J = 11.6 Hz, 1H), 2.37 (s, 3H), 2.62-2.76 (m, 3H), 4.12 (d, J = 8.9 Hz, 1H), 4.37 (d, J = 8.9 Hz, 1H), 6.68 (d, J = 3.4 Hz, 1H), 6.69 (d, J = 5.2 Hz, 1H), 6.88-6.92 (m, 1H); ^{13}CNMR (50Hz, $CDCl_3$) δ 14.6, 38.7, 46.3, 48.0, 52.4, 59.2, 83.4, 116.3, 117.5, 120.9, 132.0, 142.2, 149.1; MS (EI, 70 ev) m/e Calc'd for $C_{14}H_{19}NO_2^+$: 233.1416, found 233.1418. **5** : ^{1}HNMR (200MHz, $CDCl_3$) δ 0.61(d, J = 6.8 Hz, 3H), 1.67-1.82 (m, 2H), 1.92 (d, J = 11.7 Hz, 1H), 2.02-2.22 (m, 2H), 2.30 (s, 3H), 2.84 (dd, J = 12.0, 2.6 Hz, 1H), 2.95 (d, J = 11.5, 1H), 4.12 (d, J = 9.3, 1H), 4.54 (d, J = 9.3, 1H), 6.52 (dd, J = 6.5, 2.0 Hz, 1H), 6.65-6.76 (m, 2H); ^{13}CNMR (50Hz, $CDCl_3$) δ 13.9, 38.0, 38.5, 46.2, 49.1, 53.3, 60.4, 76.5, 114.4, 116.4, 121.9, 134.4, 141.4, 147.6; MS (EI, 70 ev) m/e Calc'd for $C_{14}H_{19}NO_2^+$: 233.1416, found 233.1401.
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