(±)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9a-hexahydro-1*H*-pyrido[4,3-*b*]indole, 8.5 g (42.5 mmol) of 4-bromobutyronitrile, 19.1 g (182 mmol) of anhydrous Na_2CO_3, and 100 mg of KI in 100 mL of methyl isobutyl ketone was heated at 70 °C overnight. The cooled reaction mixture was poured into 200 mL of water, and the resulting mixture was extracted twice with 200-mL portions of $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and evaporated to a yellow oil. This oil was dissolved in acetone, and a solution of HCl(g) in acetone was added, precipitating a white solid. This solid was separated by filtration and washed well with acetone to give 8.5 g (72%) of the desired product, mp 245–249 °C.

***trans*-(±)-2-(4-Aminobutyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Dihydrochloride (2).** A 1.82-g (48-mmol) portion of lithum aluminum hydride (LAH) was stirred under N_2 while 8.5 g (21.8 mmol) of compound 1 was added portionwise over a 1-h period. The resulting reaction mixture was allowed to stir at room temperature for 1 h. An excess of Glauber's salt was added carefully and stirred until the excess LAH had decomposed, and then the salts were filtered off and washed with dry ether. A solution of HCl(g) in ether was added, and the solid that precipitated was collected by filtration and dried to give 706 mg (90%) of the desired product, mp 224–227 °C.

***trans*-(±)-2-(4-Acetamidobutyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Hydrochloride (3).** A suspension of 315 mg (0.8 mmol) of compound 2 in 10 mL of CH_2Cl_2 was stirred with 0.44 mL (32.1 mmol) of triethylamine to give a pale yellow solution. To this was added, under N_2, 0.063 mL (0.88 mmol) of acetyl chloride in 5 mL of CH_2Cl_2. This solution was allowed to stir at ambient temperature for 2 h and was then poured into 20 mL of saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2, and the extracts were dried over $MgSO_4$ and evaporated. The residual yellow gum was dissolved in ether and treated with a saturated solution of HCl(g) in ether. A gummy tan solid precipitated. The solvent was evaporated, and the residual solid was slurried with acetone to give a white crystalline solid in 82% yield. An analytical sample was crystallized from hot acetonitrile, mp 245–248 °C.

***trans*-(±)-8-Fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-2-[4-(2-oxo-3-oxazolidinyl)butyl]-1*H*-pyrido[4,3-*b*]indole Hydrochloride (11).** A suspension of 1 g (3.49 mmol) of *trans*-(±)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydropyrido[4,3-*b*]indole, 0.93 g (5.23 mmol) of 3-(4-chlorobutyl)oxazolidin-2-one, 1.46 g (14 mmol) of anhydrous Na_2CO_3, and a trace of KI in 50 mL of methyl isobutyl ketone was heated at 95 °C overnight. A second 0.93 g (5.73 mmol) of oxazolidinone was added, and the reaction was heated a further 24 h at 95 °c. The solvent was then evaporated in vacuo, and the residues were partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous layer was extracted with a second 100-mL portion of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to a yellow gum, which was dissolved in 30 mL of 2:1 2-propanol/acetone. An ethereal solution of HCl(g) was added, and a white crystalline product separated. This was filtered off to give the desired product: 1.1 g (74%); mp 197–199 °C.

Registry No. (±)-1, 77378-64-4; (±)-1·HCl, 77378-79-1; (±)-**2**, 98651-79-7; (±)-**2**·HCl, 103422-28-2; (±)-**3**, 77378-66-6; (±)-**3**·HCl, 77378-81-5; (±)-**4**, 103422-29-3; (±)-**4**·HCl, 77378-69-9; (±)-**5**, 103422-30-6; (±)-**5**·HCl, 77400-06-7; (±)-**6**, 103422-31-7; (±)-**6**·HCl, 77400-07-8; (±)-**7**, 103422-32-8; (±)-**7**·HCl, 77378-70-2; (±)-**8**, 103422-33-9; (±)-**8**·HCl, 77378-71-3; (±)-**9**, 103422-34-0; (±)-**9**·HCl, 77378-75-7; (±)-**10**, 103422-35-1; (±)-**10**·HCl, 77378-74-6; (±)-**11**, 103422-36-2; (±)-**11**·HCl, 83502-51-6; (±)-**12**, 103437-39-4; (±)-**12**·HCl, 83502-34-5; (±)-**13**, 103422-37-3; (±)-**13**·HCl, 77378-77-9; (±)-**14**, 103422-38-4; (±)-**14**·HCl, 83502-53-8; (±)-**15**, 103422-39-5; (±)-**15**·HCl, 83514-69-6; $Br(CH_2)_4CN$, 5332-06-9; (±)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4.3-*b*]indole, 69623-07-0; 3-(4-chlorobutyl)oxazolidin-2-one, 15026-71-8.

3,7-Diazabicyclane: A New Narcotic Analgesic

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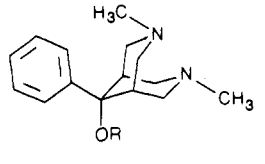
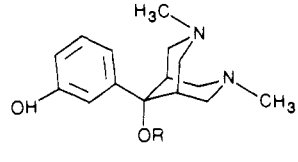
The synthesis of a series of 9-phenyl-3,7-diazabicyclanes and 9-(*m*-hydroxyphenyl)-3,7-diazabicylanes is described. Members of both series were tested for antinociception in rat tail withdrawal and mouse acetic acid writhing assays. Their affinities for opiate receptors in rat brain homogenate were also determined. The 9-phenyl compounds, **1a–c**, were inactive. However, the 9-(*m*-hydroxyphenyl) analogues, **2a–c**, were found to possess significant activity in the writhing assay, comparable to that of morphine. All activity was reversed by naloxone.

In 1976, the 3,7-dimethyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonane compounds **1a–c** were reported to be devoid of antinociceptive activity in the Haffner tail clamp test at doses of up to 100 mg/kg po.[1] However, this diazabicyclane structure continues to appear in the literature as a model to explain the different activity profiles of narcotic analgesics that have their aromatic rings in a phenyl-equatorial rather than a phenyl-axial orientation.[2-6] In this model, the aromatic ring is considered to be the most important element for binding to the narcotic receptor. Acting as the anchor, it determines the orientation of the rest of the molecule at the receptor. The protonated nitrogens can still interact with a common anionic site, albeit from different directions, but their alkyl substituents would be projected to very different areas of the receptor. This model can also explain why N-allyl and similar groups induce opiate antagonist activity in phenyl-axial opiates but not phenyl-equatorial opiates.[7-9] If this model is valid,



1a-c



2a-c

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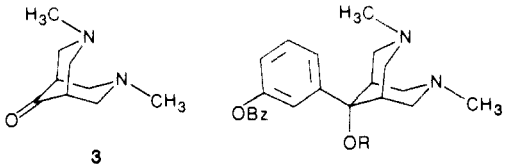
we felt that the relatively simple diazabicyclane structure should possess narcotic analgesic activity. The initial investigators reported the apparent pK_a's of **1a–c** and found them to be exceptionally high (11.03–11.73) for monoprotonated amines.[1] The diazabicyclanes are therefore very highly charged molecules at physiological pH. This charged character might make it difficult for the diazabicyclanes to cross the blood–brain barrier in significant concentration and thus appear to be inactive as antinociceptives. We have resynthesized the original diazabicyclanes **1a–c** by a slightly different method and their new 9-(*m*-hydroxyphenyl) analogues **2a–c** and investigated their analgesic properties by administering them directly into the CNS, obviating the blood–brain barrier.

Chemistry. The synthesis of the diazabicyclanes started with the preparation of 3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (**3**).[10] This was condensed with phenylmagnesium bromide to yield **1a**. Treatment of **1a** with *n*-butyl lithium followed by propionyl chloride or methyl *p*-toluenesulfonate yielded **1b** and **1c**, respectively. Similarly, **3** was condensed with 3-benzyloxyphenylmagnesium bromide[11] to yield the intermediate **4a**, which was debenzylated with hydrogen on 10% Pd/C catalyst to give **2a**, or first derivatized (**4b**, **4c**) then debenzylated to yield **2b** and **2c**.



3

4a, R = H
b, R = $COCH_2CH_3$
c, R = CH_3

Pharmacology. Affinities (IC_{50}) of **1a–c** and **2a–c** and **2a–c** for opiate receptors in rat brain were determined by using [^{3}H]etorphine (sp act. 46 Ci/mmol, Amersham, 0.3 nmol) as the ligand.[12] All compounds were administered as methanesulfonic acid salts. They were given intracerebroventricularly (icv) and tested for analgesia in a rat tail withdrawal assay.[13] The compounds were also administered subcutaneously and tested for analgesia in a mouse acetic acid writhing assay.[14] ED_{50}'s and 95% confidence limits were obtained by the method of Litchfield and Wilcoxon.[15]

Results and Discussion

The pharmacological data on the diazabicyclanes is presented in Table I. Compounds **1b,c** are indeed inactive as antinociceptives, regardless of the route of administration. However, introduction of a hydroxyl group at the meta position of the aromatic ring, **2a–c**, produces significant increases in receptor affinity and introduces analgesic activity. The most potent compound in the series, **2c**, is significantly more potent than morphine in the writhing assay. The lack of activity in **1a–c** is therefore not due to an inability to enter the CNS as first thought but rather to their lack of affinity for narcotic receptors as evidenced by their own IC_{50} values and by the activity of sc administered **2a–c**. In fact, the inactive diazabicyclanes **1a–c** are more lipophilic as measured by their HPLC retention indexes, and therefore have better bioavailability to the CNS than the active compounds **2a–c**.[16]

Table I. Opiate Receptor Affinities and Analgesic Activities

compd	IC_{50},[a] nM	ED_{50} analgesic testing: writhing,[b] μmol/kg	ED_{50} analgesic testing: tail flick,[c] nmol[d]
1a	*e*	*e*	*e*
1b	7600	inactive at 460	inactive at 760
1c	7200	inactive	inactive
2a	3000	5.8 (4.5–6.8)	*e*
2b	530	0.85 (0.25–2.8)	25 (12–37)
2c	2300	0.56 (0.21–1.5)	*e*
morphine	160	3.0 (2.5–3.6)	23 (11–70)

[a] Expressed as the concentration of compound required to inhibit stereospecific [^{3}H]etorphine by 50%. [b] The compounds were administered subcutaneously to mice in deionized water. [c] The compounds were administered intracerebroventricularly to rats in artificial cerebrospinal fluid. [d] This was the total amount administered. [e] Not tested.

It is known that a *m*-hydroxyl group increases receptor affinity and analgesic activity in other narcotic structures.[17] This substitution produces particularly dramatic results in the case of the diazabicyclanes, transforming an inactive structure into a very active one. This seems to add further credence to the premise that the aromatic ring, particularly a *m*-OH substituted one, is the most important structural element in determining a compound's affinity for and orientation at narcotic receptors. In conclusion, the 3,7-diazabicyclane structure is not intrinsically inactive as a narcotic analgesic as first reported, but rather, the 3,7-diazabicyclanes have been shown to be potent, naloxone-reversible narcotic analgesics when properly substituted.

Experimental Section

Pharmacology. For the icv injections, stainless-steel cannulae (25 g, thin-wall tubing) were stereotaxically implanted into the lateral ventricles of rats anesthetized with Equi-Thessin (3 mL/kg, ip). The cannulae were cemented in place with dental cement. The coordinates were AP 0.0, L 2.0 using bregma as the reference.[18] The cannulae were implanted 3.5 mm below the dura, and the rats were allowed 2 weeks to recover from surgery prior to drug evaluation. Injections were made with 31-g needles attached to a microliter syringe and a short piece of flexible polyethylene tubing for attachment to the cannulae. All compounds were dissolved in rat artificial cerebrospinal fluid (CSF)[19] and injected slowly (30 s) in a volume of 10 μL. Artificial rat CSF alone was injected to obtain control values. Rats were placed in specially designed restraint devices and were allowed 0.5-h acclimation period prior to testing. Rats were tested for analgesia 5, 10, 15, and 20 min after injection by immersion of the tail 5 cm into a cup of water maintained at 55 °C. The latency to withdrawal of the tail was determined with a stopwatch using a maximum cutoff of 30 s. The values of three observations on the same animal were averaged. For the acetic acid writhing assay the compounds were dissolved in deionized water.

Naloxone reversal of analgesia was carried out in the following manner. In the tail withdrawal assay, an ED_{50} dose of agonist

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was given icv. Ten minutes later, naloxone hydrochloride (1 mg/kg) was given sc. Latency, determined 10 min later, returned to control values. In the acetic acid writhing assay, an ED_{50} dose of agonist was given sc 20 min prior to sc injection of 1 mg/kg naloxone hydrochloride. Acetic acid was administered ip 10 min after the antagonist. Latency was indistinguishable from control values.

Chemistry. Melting points were determined in a Thomas-Hoover Unimelt apparatus and are uncorrected. All compounds were characterized by IR (Beckman Acculab 3 or a Beckman 620 MX spectrophotometer) and NMR (Hitachi Perkin-Elmer R-24B spectrometer with Me_4Si internal standard) and MS (AEI MS-9 spectrometer). Hydrogenolyses were carried out in a Parr 3911 medium-pressure, shker-type reduction apparatus. Where analyses are indicated by symbols of the elements, results obtained were within ±0.4% of theoretical values.

3,7-Dimethyl-9-phenyl-9-hydroxy-3,7-diazabicyclo[3.3.1]nonane (1a). A solution of **3**[10] (5.0 g, 0.03 mol) in 100 mL of THF was added dropwise to a 100-mL THF solution of freshly prepared phenylmagnesium bromide (0.03 mol). The mixture was stirred for 1 h at room temperature, refluxed for 8 h, and poured onto a solution of NH_4Cl (250 mL). The THF was evaporated. The mixture was made strongly alkaline, filtered through Celite, and extracted with Et_2O. This organic solution was washed with 10% NaOH and water, dried over Na_2SO_4, filtered, and evaporated to yield 7.0 g (0.028 mol, 95%) as a solid. This crude product was decolorized and crystallized from petroleum ether (35–60 °C): mp 126–128 °C. Anal. ($C_{15}H_{22}N_2O$) C, H, N. The monoperchlorate salt crystallized from 95% EtOH: mp 251–252 °C. Anal. ($C_{15}H_{22}N_2O\cdot HClO_4$) C, H, N. The monomethanesulfonate salt crystallized from EtOH/EtOAc: mp 254–255 °C. Anal. ($C_{15}H_{22}N_2O\cdot CH_3SO_3H$), C, H, N.

3,7-Dimethyl-9-phenyl-9-(propionyloxy)-3,7-diazabicyclo[3.3.1]nonane (1b). A solution of **1a** (1.0 g, 4.1 mmol) in 25 mL of THF was cooled to −5 °C and treated with *n*-butyl lithium (1.1 equiv). The mixture was stirred for 0.5 h. A 25-mL THF solution of propionyl chloride (1.1 equiv) was added slowly, and the reaction was heated to reflux for 2 h. The reaction was poured on ice and the THF evaporated. The mixture was chilled, made alkaline with chilled 10% NaOH, and extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4, filtered, and evaporated to yield crude **1b** (1.2 g, 4.0 mmol, 98%) as a white solid, which was crystallized from petroleum ether: mp 118–119 °C. Anal. ($C_{18}H_{26}N_2O_3$) C, H, N. The monoperchlorate salt crystallized from EtOH/Et_2O: mp 191–192 °C. Anal. ($C_{18}H_{26}N_2O_3\cdot HClO_4$) C, H, N. The monomethanesulfonate salt crystallized from EtOH/Et_2O: mp 194–195 °C. Anal. ($C_{18}H_{26}N_2O_3\cdot CH_3SO_3H$) C, H, N. The sesquimethanesulfonate salt crystallized from EtOH/EtOAc: mp 153–154 °C. Anal. ($C_{18}H_{26}N_2O_3\cdot 1.5CH_3SO_3H$) C, H, N.

3,7-Dimethyl-9-phenyl-9-methoxy-3,7-diazabicyclo[3.3.1]nonane (1c). A solution of **1a** (1.0 g, 4.1 mmol) in 25 mL of THF was cooled to −5 °C and treated with *n*-butyl lithium (1.1 equiv). The mixture was stirred for 0.5 h at −5 °C and then for 0.5 h at room temperature. Methyl *p*-toluenesulfonate (1.1 equiv) in 25 mL of THF was added slowly, and the reaction was heated to reflux for 8 h. The reaction was poured onto ice and the THF evaporated. The solution was made strongly alkaline with solid NaOH and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, filtered, and evaporated to give crude **1c** (1.0 g, 3.8 mmol, 94%), which could be sublimed (80 °C, 0.01 mmHg) or crystallized from petroleum ether: 85–86 °C. Anal. ($C_{16}H_{24}N_2O$) C, H, N. The monoperchlorate salt crystallized from EtOH: mp 210–212 °C, 220–226 °C dec. Anal. ($C_{16}H_{24}N_2O\cdot HClO_4$) C, H, N. The monomethanesulfonate salt crystallized from MeOH/EtOAc (1:60): (hygroscopic) mp 243–245 °C. Anal. ($C_{16}H_{24}N_2O\cdot CH_3SO_3H\cdot 0.75H_2O$) C, H, N.

3,7-Dimethyl-9-(*m*-hydroxyphenyl)-9-hydroxy-3,7-diazabicyclo[3.3.1]nonane (2a). A solution of **3** (5.0 g, 0.03 mol) in 100 mL of THF was added dropwise to a 100-mL THF solution of freshly prepared *m*-(benzyloxy)phenyl magnesium bromide[11] (0.03 mol). In a manner identical to that for the preparation of **1a**, the above reaction yielded crude **4a** (9.0 g, 25 mmol, 95%) as an off-white solid, which crystallized from Et_2O: mp 122–123 °C. Anal. ($C_{22}H_{28}N_2O_2$) C, H, N. The monoperchlorate salt crystallized from EtOAc/acetone: mp 204–205 °C. Anal. ($C_{22}H_{28}N_2O_2\cdot HClO_4$) C, H, N. The monomethanesulfonate salt crystallized from acetone: mp 150–151 °C. Anal. ($C_{22}H_{28}N_2O_2\cdot CH_3SO_3H\cdot H_2O$) C, H, N.

Hydrogenolysis of **4a** (1.5 g, 4.25 mmol) in 95% EtOH afforded **2a** (1.1 g, 4.1 mmol, 98%) as a white solid crystallized from petroleum ether: mp 190–191 °C dec. The monomethanesulfonate salt crystallized from absolute EtOH: mp 269–270 °C. Anal. ($C_{15}H_{22}N_2O_2\cdot CH_3SO_3H$) C, H, N.

3,7-Dimethyl-9-(*m*-hydroxyphenyl)-9-(propionyloxy)-3,7-diazabicyclo[3.3.1]nonane (2b). By using the same procedure as was used for the preparation of **1b**, **4a** (1.2 g, 3.4 mmol) yielded crude **4b** (1.1 g, 2.69 mmol, 79%) as a solid, which crystallized from hexane: mp 120–121 °C.

Hydrogenolysis of **4b** (0.70 g, 1.71 mmol) yielded **2b** (0.44 g, 1.38 mmol, 81%) crystallized from Et_2O or Me_2CO: mp 157–158 °C. Anal. ($C_{18}H_{26}N_2O_3$) C, H, N. The monomethanesulfonate salt crystallized from Me_2CO/MeOH (80:1): mp 201–202 °C. Anal. ($C_{18}H_{26}N_2O_3\cdot CH_3SO_3H$) C, H, N.

3,7-Dimethyl-9-(*m*-hydroxyphenyl)-9-methoxy-3,7-diazabicyclo[3.3.1]nonane (2c). By using the same procedure as was used for the preparation of **1c**, **4a** (1.3 g, 3.7 mmol) yielded crude **4c** (1.2 g, 3.3 mmol, 90%) as a white solid, which was crystallized from Me_2CO/Et_2O: mp 140–142 °C.

Hydrogenolysis of **4c** (1.12 g, 3.05 mmol) yielded **2c**, (0.87 g, 3.15 mmol, 97%) as a white solid crystallized from Et_2O: mp 154–155 °C. The monmethanesulfonate salt crystallized from Me_2CO/EtOAc: mp 210–212 °C. Anal. ($C_{16}H_{24}N_2O_2\cdot CH_3SO_3H$) C, H, N.

Acknowledgment. We acknowledge financial support from the National Institute on Drug Abuse, MHA, USPHS, under Grant DA-01612.

Registry No. **1a**, 57209-56-0; **1a**·$HClO_4$, 57209-57-1; **1a**·CH_3SO_3H, 103366-69-4; **1b**, 57209-58-2; **1b**·$HClO_4$, 57209-63-9; **1b**·CH_3SO_3H, 103346-58-3; **1b**·$1.5CH_3SO_3H$, 57209-61-7; **1c**, 57209-59-3; **1c**·$HClO_4$, 57209-60-6; **1c**·CH_3SO_3H, 103346-59-4; **2a**, 92643-18-0; **2a**·CH_3SO_3H, 103346-62-9; **2b**, 92643-19-1; **2b**·CH_3SO_3H, 103346-64-1; **2c**, 103346-66-3; **2c**·CH_3SO_3H, 103346-67-4; **3**, 14789-54-9; **4a**, 103346-60-7; **4a**·$HClO_4$, 103366-70-7; **4a**·CH_3SO_3H, 103346-61-8; **4b**, 103346-63-0; **4c**, 103346-65-2; phenylmagnesium bromide, 100-58-3; propionyl chloride, 79-03-8; methyl *p*-toluenesulfonate, 80-48-8; *m*-(benzyloxy)phenylmagnesium bromide, 36281-96-6.