HBr gas through an EtOH–Et_2O solution of the base. Anal. ($C_{13}H_{14}BrNO_2$) C, H, N.

1-Phenyl-3-isoquinolineacetamide (14). A solution of 3.7 g (0.0154 mol) of **24** in 15 mL of concentrated H_2SO_4 was stirred at ambient temperature under a N_2 atmosphere overnight. The solution was poured onto ice and made basic with 50% NaOH. The solid which precipitated was collected by filtration, washed with H_2O, and recrystallized from *i*-PrOH to yield 2.0 g (54%) of 14 as a yellow powder, mp 201–204 °C. Anal. ($C_{17}H_{14}N_2O$) C, H, N.

1-Benzoyl-3-isoquinolineacetamide (12). Using the above procedure, a mixture of 5.4 g (0.02 mol) of **25** and 25 mL of concentrated H_2SO_4 gave 2.6 g (46%) of 12 as tan needles, mp 185–187 °C (*i*-PrOH). Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

1-Phenyl-4-isoquinolineacetamide (15). Using the above procedure, a mixture of 1.9 g (0.008 mol) of crude **26** and 10 mL of concentrated H_2SO_4 gave 0.5 g (25%) of 15 as a tan powder, mp 190–192 °C (*i*-PrOH). Anal. ($C_{17}H_{14}N_2O$) C, H, N.

1-(4-Chlorophenyl)-3-isoquinolineacetamide (16). Using the above procedure, a mixture of 3.0 g (0.11 mol) of **27** and 15 mL of concentrated H_2SO_4 gave 2.2 g (69%) of 16, mp 219–221 °C (EtOH). Anal. ($C_{17}H_{13}ClN_2O$) C, H, N.

Ethyl 4-Acetyloxy-1-phenyl-3-isoquinolinecarboxylate (17). To a solution of 110 mL of glacial HOAc and 110 mL of concentrated H_2SO_4 was added 11.1 g (0.04 mol) of 1-oxo-3-phenyl-1*H*-2-indenecarboxylic acid.[20] The red mixture was heated to 50 °C and 6.5 g (0.10 mol) of NaN_3 was added in portions so that the internal temperature did not rise above 60 °C. After the addition was complete the mixture was heated at 50–60 °C with stirring for 20 min and then poured onto ice. The cold mixture was made basic with concentrated NH_4OH and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, treated with charcoal, and concentrated to give 9.3 g of a dark gum. A 1:1 mixture of C_6H_6–ligroine was added to the gum and a solid precipitated after the solution was let stand overnight. The solid was collected by filtration and recrystallized twice from *i*-PrOH to yield 1.7 g (15%) of 17 as white needles, mp 169–170 °C. Anal. ($C_{20}H_{17}NO_4$) C, H, N.

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Synthesis of Spiro[tetralin-2,2′-pyrrolidine] and Spiro[indan-2,2′-pyrrolidine] Derivatives as Potential Analgesics

Peter A. Crooks* and Howard E. Rosenberg

Department of Pharmacy, University of Manchester, Manchester M13 9PL, United Kingdom. *Received November 17, 1977*

Spiro[tetralin-2,2′-pyrrolidine] (13) and spiro[6-methoxytetralin-2,2′-pyrrolidine] (17) were prepared by initial Michael condensation of 2-nitrotetralin and 6-methoxy-2-nitrotetralin, respectively, with methyl acrylate to give 7 and 8, both of which could be reductively cyclized to 10 and 11, followed by $LiAlH_4$ reduction. Spiro[indan-2,2′-pyrrolidine] (15) was prepared in an analogous manner from 2-nitroindan, and spiro[6-hydroxytetralin-2,2′-pyrrolidine] (19) was prepared by O-demethylation of 17. Compound 13 and its *N*-methyl derivative, 14, both showed good analgesic activity. Compounds 13–16 all possessed weak antidepressant properties, but neither 19 nor its *N*-methyl derivative 20 had any significant CNS activity.

The 2-aminotetralin moiety is a common structural unit in many potent analgesic molecules, including morphine, the morphinans, and the benzomorphans. Recently,[1-3] some simple 2-aminotetralins have been reported to possess good analgesic properties and the ring contracted analogue, 2-aminoindan, has been shown to be a potent analgesic.[4,5] In order to determine some of the structural requirements for analgesic activity, we have synthesized a number of compounds in which the amino group at position 2 of the tetralin and indan ring systems has been rotationally restricted by incorporating it into a spiro 2,2′-pyrrolidine structure, thus retaining the nitrogen in a relatively fixed phenethylamine conformation. We now report the results from the synthesis and initial central nervous system (CNS) screening of some novel spiro[tetralin-2,2′-pyrrolidine] and spiro[indan-2,2′-pyrrolidine] derivatives.

*Address correspondence to this author at the Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510.

Chemistry. Oxidation of 2-tetralin oxime (1) with peroxytrifluoroacetic acid, followed by Michael condensation of the resulting 2-nitrotetralin (4) with methyl acrylate in the presence of benzyltrimethylammonium methoxide, afforded the nitro ester 7. Compound 7 was reductively cyclized with Raney nickel in ethanol to give spiro[tetralin-2,2′-(5′-oxopyrrolidine)] (10), the structure

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Table I. 2-Nitrotetralin and 2-Nitroindan Derivatives 4-9

No.	R^1	R^2	n	Formula[b]	Yield,[a] %	Mp, °C
4	H	H	2	$C_{10}H_{11}NO_2$	63	34-41
5	OMe	H	2	$C_{11}H_{13}NO_3$	47	89-92
6	H	H	1	$C_9H_9NO_2$	67	30.5-32
7	H	$CH_2CH_2CO_2Me$	2	$C_{14}H_{17}NO_5$	72	c
8	OMe	$CH_2CH_2CO_2Me$	2	$C_{15}H_{19}NO_5$	74	67.5-68.5
9	H	$CH_2CH_2CO_2Me$	1	$C_{13}H_{15}NO_4$	83	35-38.5

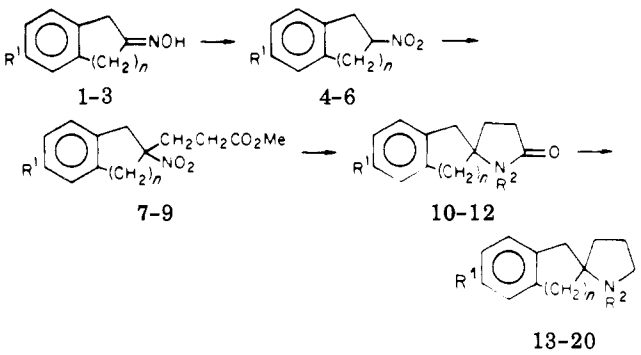
[a] Yields are of purified product and are not maximal. [b] All compounds were analyzed for C, H, and N. [c] Obtained as a liquid, bp 164-174 °C (0.8 mmHg).

Table II. Spiro[tetralin-2,2'-pyrrolidine] and Spiro[indan-2,2'-pyrrolidine] Derivatives 10-20

No.	R^1	R^2	X	n	Formula[b]	Yield,[a] %	Mp, °C
10	H	H	O	2	$C_{13}H_{15}NO$	85	160-162
11	H	H	O	2	$C_{14}H_{17}NO_2$	76	134-137
12	H	H	O	1	$C_{12}H_{13}NO$	89	153-155
13	H	H	H_2	2	$C_{13}H_{17}N \cdot HCl$	82	214-216
14	H	Me	H_2	2	$C_{14}H_{19}N \cdot HCl$	51	186-192
15	H	H	H_2	1	$C_{12}H_{15}N \cdot HCl$	76	148-150
16	H	Me	H_2	1	$C_{13}H_{17}N \cdot HCl$	92	139.5-141
17	OMe	H	H_2	2	$C_{14}H_{19}NO \cdot HCl$	95	236-238
18	OMe	Me	H_2	2	$C_{15}H_{21}NO \cdot HBr$	69	176-179
19	OH	H	H_2	2	$C_{13}H_{17}NO \cdot HBr$	69	224-230
20	OH	Me	H_2	2	$C_{14}H_{19}NO \cdot HBr$	72	230-235

[a, b] See corresponding footnotes in Table I.

Scheme I



of which was confirmed from its NMR spectrum. Reduction of **10** with $LiAlH_4$ afforded spiro[tetralin-2,2'-pyrrolidine] (**13**) in good yield (see Scheme I).

Compounds **15** and **17** were prepared in an analogous manner utilizing 2-indanone oxime (**3**) and 6-methoxy-2-tetralone oxime (**2**), respectively, in the above procedure. N-Methylation of compounds **13**, **15**, and **17** was carried out in HCO_2H-HCHO solution, and O-demethylation of compounds **17** and **18** was accomplished in refluxing hydrobromic acid. Attempts to prepare spiro[5-hydroxyindan-2,2'-pyrrolidine] were unsuccessful (see Tables I and II).

Pharmacology. Analgesia was determined by the acetic acid writhing test[6] in groups of six mice. Each group was dosed orally with either vehicle or compound under test and injected intraperitoneally 30 min later with dilute acetic acid (0.4 mL, 0.25%). The total number of squirming movements was recorded and the protection afforded expressed as a percentage of control values according to the following scale: ++++, 100% inhibition; +++, 75% inhibition; ++, 50% inhibition; +, 25% inhibition. Compounds active at 10 mg/kg in the above test were also determined by the hot-plate method[7] (see Table III).

Antidepressant activity was assessed by the ability to reverse reserpine-induced hypothermia.[8] Groups of six mice were pretreated with reserpine (2 mg/kg sc) and 17 h later with the test compound. Gastric temperatures were recorded immediately before dosing with the test compound (t_0) and at intervals of 2, 4, and 6 h thereafter (t_2, t_4, and t_6). The cumulative temperature rise (T) was then calculated according to the formula: $T = (t_2 + t_4 + t_6) - 3t_0$.

Table III

Compd	Writhing test, mg/kg po	Hot-plate test, ED_{50}, mg/kg	Antagonism of reserpine hypothermia, av temp rise (T) at 30 mg/kg, °C
13·HCl	10, ++++	7.1 (5.2-9.2)[a]	4.5
14·HCl	10, ++++	7.4 (6.6-8.3)[a]	2.7
15·HCl	10, ++	>30	5.1
16·HCl	100, ++	ND[b]	5.1
17·HCl	30, ++	ND[b]	0.2
18·HBr	30, +++	ND[b]	1.2
19·HBr	30, 0	ND[b]	0.7
20·HBr	30, +++	ND[b]	0.7
Morphine hydrochloride	10, ++++	1.5 (1.1-1.7)[a]	0.3
Imipramine	30, ++	ND[b]	8.0

[a] Confidence limits. [b] Not determined.

None of the compounds tested possessed any other significant CNS activity as determined by maximal electroshock, metrazole shock, locomotor activity, and stationary rod tests.

Thus, restricting the rotation of the C-2–N bond in 2-aminoindan and 2-aminotetralin by structural modification has given rise to two compounds (**13** and **14**) with good analgesic activity in initial CNS screening tests. In this respect, the lack of analgesic activity of compounds **19** and **20** is surprising, since these compounds have structural features common to many analgesic molecules, and molecular model examination shows that the rigid tyramine moiety in both compounds is stereosuperimposable with the same structural moiety found in the morphine molecule. However, differences in absorption, distribution, and metabolism may exist between these two pairs of compounds and may play a significant role. The weak antidepressant activity of compounds **13-16** is of additional interest.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Manchester. Analytical results obtained for all compounds were within ±0.4% of the theoretical values. NMR spectra were recorded on a Perkin-Elmer R12B spectrometer with Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer 235 grating spectrophotometer. Mass spectra were recorded on an AEI MS12 spectrometer at a probe temperature of 200 °C.

2-Nitrotetralin (4). A solution of peroxytrifluoroacetic acid prepared from 87% H_2O_2 (2.75 mL) and trifluoroacetic anhydride (20 mL) in CH_3CN (20 mL) was added slowly over a period of 1 h to a mixture of urea (1.0 g), anhydrous Na_2HPO_4 (39 g), 2-tetralone oxime[9] (7.4 g), and CH_3CN (100 mL) maintained at a gentle reflux. After addition was over the mixture was heated under reflux for 1 h. The insoluble inorganic salts were then filtered off and the filtrate was evaporated under vacuum to low volume. A mixture of water (600 mL) and CH_2Cl_2 (300 mL) was added to the resulting solution and the aqueous liquors were separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with Na_2CO_3 solution and dried ($MgSO_4$), and the solvent was evaporated to yield 6.1 g of crude 4, which was distilled in vacuo to give 4.5 g of a pure sample of 4 as a yellow oil, bp 113 °C (0.6 mmHg), which solidified on cooling to afford yellow crystals: mp 34–41 °C; IR (neat) 1550, 1380 cm^{-1} (C-NO_2); NMR ($CDCl_3$) δ 2.22–2.59 (m, 2, C-3 H_2), 2.94 (m, 2, C-4 H_2), 3.35 ("d", 2, C-1 H_2), 4.79 (m, 1, C-2 H), 7.11 (s, 4, Ph); mass spectrum *m/e* 131 (M − NO_2).

Compounds **5** and **6** (Table I) were prepared from the corresponding 2-oximino derivatives **2** and **3** in a manner similar to the above procedure.

Methyl 3-[2-(2-Nitrotetralyl)]propionate (7). A magnetically stirred solution of **4** (4.5 g) and benzyltrimethylammonium methoxide (0.2 mL) in 1-butanol (30 mL) was warmed to 70 °C and freshly distilled methyl acrylate (3.3 mL) added. The solution was maintained with stirring at 73 °C for 2 h, after which time further quantities of benzyltrimethylammonium methoxide (0.3 mL) and methyl acrylate (2.8 mL) were added. The reaction was then cooled to 44 °C and stirred at this temperature overnight. After cooling, 5% HCl (30 mL) was added and the mixture extracted with CH_2ClCH_2Cl (1 × 100 mL, 1 × 50 mL). The combined organic liquors were washed (H_2O) and dried ($MgSO_4$), the solvent was evaporated in vacuo, and the resulting oil was distilled to give 4.8 g of a pure sample of **7** as an orange oil: bp 164–174 °C (0.8 mmHg); IR (neat) 1745 cm^{-1} (CO_2Me); NMR δ 1.97–2.64 (m, 2, C-3 H_2), 2.35 ("s", 4, $-CH_2CH_2CO_2-$), 2.67–3.27 (m, 3, C-4 H_2 and C-1 H trans to NO_2 group), 3.64 (d, J_{gem} = 16 Hz, 1, C-1 cis to NO_2 group), 3.66 (s, 3, CO_2Me), 7.13 (s, 4, Ph); mass spectrum *m/e* 217 (M − NO_2).

Compounds **8** and **9** (Table I) were prepared from the corresponding 2-nitro derivatives **5** and **6** in a manner analogous to the above procedure.

Spiro[tetralin-2,2′-(5′-oxopyrrolidine)] (10). Compound **7** (2.6 g) was dissolved in absolute EtOH (250 mL), Raney nickel (0.5 g moist) added, and the mixture hydrogenated at atmospheric pressure and 60–65 °C overnight. After cooling, the catalyst was removed by filtration and the solvent evaporated in vacuo to yield a white solid (2.0 g), which on recrystallization from ether afforded pure **10** (1.38 g): mp 153–155 °C; IR (Nujol) 3380 (NH), 1715 cm^{-1} (NHCO); NMR ($CDCl_3$) δ 1.64–2.20 (m, 4, C-3′ H_2 and C-4′ H_2), 2.10–2.63 (m, 2, C-3 H_2), 2.78–2.89 (m, 4, C-1 H_2 and C-4 H_2), 6.40 (br s, 1, exchangeable with D_2O, NH), 7.10 (s, 4, Ph); mass spectrum *m/e* 201 (M^+).

Compounds **11** and **12** (Table II) were prepared from the corresponding nitro esters **8** and **9** in a manner analogous to the above procedure.

Spiro[tetralin-2,2′-pyrrolidine] (13) and *N*-Methylspiro[tetralin-2,2′-pyrrolidine] (14). A suspension of **10** (1.7 g) and $LiAlH_4$ (1.3 g) in dry ether was stirred magnetically and heated under reflux overnight. The reaction was then cooled and the excess $LiAlH_4$ decomposed with H_2O. The ether solution was dried ($MgSO_4$), filtered, and evaporated to yield a green oil which on distillation in vacuo afforded 1.3 g of pure **13** as a clear oil: bp 109 °C (0.8 mmHg); IR (neat) 3260–3010 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.40–2.13 (m, 7, decreasing to 6 on exchange with D_2O, C-3 H_2, C-3′ H_2, C-4′ H_2, and NH), 2.53–3.20 (m, 6, C-1 H_2, C-4 H_2, and C-5′ H_2), 7.04 (s, 4, Ph); mass spectrum *m/e* 188 (M^+).

Compound **13** (1.0 g), HCO_2H (2.5 mL), and HCHO (37%, 1.0 mL) were heated on a water bath for 7 h. After evaporation to dryness, the residual oil was dissolved in 5% HCl, washed with ether, basified with 10% NaOH, extracted with ether, and dried ($MgSO_4$). After evaporation of the solvent, the residual oil was distilled in vacuo to give 0.55 g of **14**: bp 118–119 °C (1.5 mmHg); NMR ($CDCl_3$) δ 1.40–2.17 (m, 6 H, C-3 H_2, C-3′ H_2, and C-4′ H_2), 2.26–3.12 (m, 6, C-1 H_2, C-4 H_2, and C-5′ H_2), 2.35 (s, 3, NMe), 7.10 (s, 4, Ph); mass spectrum *m/e* 201 (M^+).

Spiro[indan-2,2′-pyrrolidine] (15): bp 86–88 °C (0.77 mmHg); IR (neat) 3250–3040 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.65–2.0 (m, 5, reducing to 4 on exchange with D_2O, C-3′ H_2, C-4′ H_2, and NH), 2.79–3.15 (m, 6, C-1 H_2, C-3 H_2, and C-5′ H_2), 7.05 (s, 4, Ph); mass spectrum *m/e* 173 (M^+).

***N*-Methylspiro[indan-2,2′-pyrrolidine] (16):** bp 68–69 °C (0.05 mmHg); NMR ($CDCl_3$) δ 1.66–1.98 (m, 4, C-3′ H_2 and C-4′ H_2), 2.12 (s, 3, NMe), 2.59 (d, J_{gem} = 16 Hz, 2, C-1 H and C-3 H trans to N atom), 2.60–3.0 (m, 2, C-5′ H_2), 3.09 (d, J_{gem} = 16 Hz, 2, C-1 H and C-3 H cis to N atom), 7.05 (s, 4, Ph); mass spectrum *m/e* 187 (M^+).

Spiro[6-methoxytetralin-2,2′-pyrrolidine] (17): IR (neat) 3200–3020 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.54–2.19 (m, 7, reducing to 6 on exchange with D_2O, C-3 H_2, C-3′ H_2, C-4′ H_2, and NH), 2.53–3.20 (m, 6, C-1 H_2, C-4 H_2, and C-5′ H_2), 3.73 (s, 3, OMe), 6.55–6.83 (m, 2, C-5 H and C-7 H), 6.99 (d, $J_{8,7}$ = 8 Hz, 1, C-8 H); mass spectrum *m/e* 217 (M^+).

***N*-Methylspiro[6-methoxytetralin-2,2′-pyrrolidine] (18):** NMR ($CDCl_3$) δ 1.48–2.11 (m, 6, C-3 H_2, C-3′ H_2, and C-4′ H_2), 2.18–3.08 (m, 6, C-1 H_2, C-4 H_2, and C-5′ H_2), 2.33 (s, 3, NMe), 3.74 (s, 3, OMe), 6.50–6.81 (m, 2, C-5 H and C-7 H), 7.08 (d, $J_{8,7}$ = 7 Hz, 1, C-8 H); mass spectrum *m/e* 231 (M^+).

Spiro[6-hydroxytetralin-2,2′-pyrrolidine] (19) and *N*-Methylspiro[6-hydroxytetralin-2,2′-pyrrolidine] (20). Compound **17** (0.56 g) and 48% HBr (10 mL) were refluxed for 1.25 h under nitrogen. Evaporation and recrystallization from EtOH gave 0.49 g of **19**·HBr as buff-colored crystals: mp 224–230 °C; IR (Nujol) 3300–2920 (OH), 2850–2780 cm^{-1} (≡N^+H); NMR (C_5D_5N–D_2O) δ 1.72–2.48 (m, 6, C-3 H_2, C-3′ H_2, and C-4′ H_2), 2.70–3.40 (m, 4, C-1 H_2 and C-4 H_2), 3.54–3.07 (m, 2, C-5′ H_2), 6.88–7.17 (m, 3, Ph); mass spectrum *m/e* 203 (M^+). By the above procedure, compound **18**·HBr (0.35 g) afforded 0.24 g of **20**·HBr as buff-colored crystals: mp 230–235 °C; IR (Nujol) 3170–2940 (OH), 2860–2740 cm^{-1} (≡N^+H); NMR (C_5D_5N–D_2O) δ 1.74–2.50 (m, 6, C-3 H_2, C-3′ H_2, and C-4′ H_2), 2.75–3.09 (m, 6, C-1 H_2, C-4 H_2, and C-5′ H_2), 2.83 (s, 3, ≡N^+Me), 6.83–7.15 (m, 3, Ph); mass spectrum *m/e* 217 (M^+).

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