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Aroyl- and Arylisoquinolineacetic Acids as Antiinflammatory Agents

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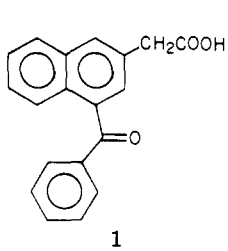
A series of 1-benzoyl- and 1-phenylisoquinolineacetic acid derivatives was prepared and tested for antiinflammatory activity. The most potent compound synthesized, 1-(4-chlorophenyl)-3-isoquinolineacetamide, was as active as phenylbutazone in the Evans blue carrageenan-induced pleural effusion assay but inactive in the adjuvant-induced arthritis model of chronic inflammation.

Since Shen[1] first outlined the structural requirements for indomethacin-type nonsteroidal antiinflammatory agents, a myriad of compounds has been synthesized and tested for this activity.[2] Reports that benzoylnaphthaleneacetic acid (**1**)[3] and phenylnaphthaleneacetic acid (**2**)[4]



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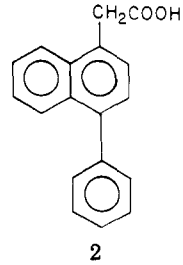

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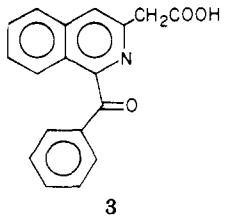

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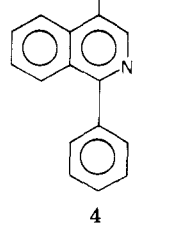

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possessed antiinflammatory activity prompted us to study various substituted isoquinolineacetic acids (**3** and **4**) to determine the effect on activity caused by a change from a naphthalene to a heterocyclic ring system.

Chemistry. The compounds were prepared according to Scheme I. For the synthesis of the acetic acid derivatives, the appropriate methylisoquinoline was treated with 1 mol of *N*-bromosuccinimide (NBS) to effect side-chain bromination. The crude bromomethyl compound was then treated with KCN in EtOH–H_2O and the nitrile was purified by column chromatography. The pure nitrile was stirred with concentrated H_2SO_4 to yield the desired acetamide compound. The amides were chosen for study due to the propensity of 2-pyridineacetic acids to undergo decarboxylation.[5]

The synthesis of the carboxylic acid derivatives involved treatment of the appropriate methylisoquinoline with 2 mol of NBS to give the dibromomethyl derivative. The aldehyde was prepared by heating the dibromomethyl compound with $AgNO_3$ in EtOH. The crude aldehyde was then treated with $AgNO_3$ in base according to the procedure of Shamma and Rodriguez[6] to yield the desired carboxylic acids (Table I).

Discussion

The aroyl- and arylisoquinolineacetic acid derivatives prepared fulfill the structural requirements for the hy-

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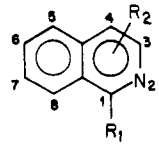
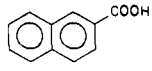
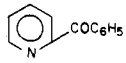
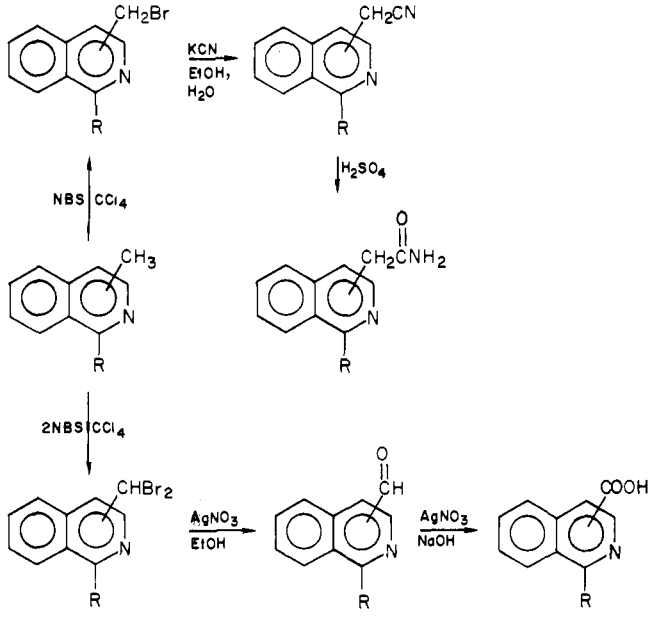
Table I



No.	R_1	R_2	Efficacy ratio at 316 mg/kg: Compd	Efficacy ratio at 316 mg/kg: Aspirin	% decrease in vol of fluid at 100 mg/kg: Compd	% decrease in vol of fluid at 100 mg/kg: Phenylbutazone	Mp, °C	Formula[a]	Recrystn solvent[b]
5[c]			1.13	1.35			185-187	$C_{11}H_8O_2$	
6[d]	H	3-$COOC_2H_5$	1.97	1.87	1	29	203 dec	$C_{12}H_{12}BrNO_2$	x
7	H	3-$CH_2COOC_2H_5$	1.20	1.87			205-207 dec	$C_{13}H_{14}BrNO_2$	y
8[c]			1.23	1.65			195-201 dec	$C_{12}H_{10}BrNO$	x
9[e]	C_6H_5CO	H	0.83	1.65			190-200 dec	$C_{16}H_{12}BrNO$	y
10[f]	C_6H_5CO	3-CH_3	0.93	1.87			222-229 dec	$C_{17}H_{11}BrNO$	wy
11	C_6H_5CO	3-COOH	1.28	1.82			158	$C_{17}H_{11}NO_3$[g]	wy
12	C_6H_5CO	3-CH_2CONH_2	0.90	1.67			185-187	$C_{18}H_{14}N_2O_2$	y
13[h]	C_6H_5	3-COOH	1.26	1.72			222-223	$C_{16}H_{11}NO_2$	z
14	C_6H_5	3-CH_2CONH_2	1.33	1.51	14	29	201-204	$C_{17}H_{14}N_2O$	y
15	C_6H_5	4-CH_2CONH_2			9	40	190-192	$C_{17}H_{14}N_2O$	y
16	4-ClC_6H_4	3-CH_2CONH_2			22	29	219-221	$C_{17}H_{13}ClN_2O$	x
17[i]	C_6H_5	3-$COOC_2H_5$, 4-$OCOCH_3$	1.06	1.35			169-170	$C_{20}H_{17}NO_4$	y

[a] All compounds were analyzed for C, H, and N and results agreed to ±0.4% of theoretical values unless otherwise stated. [b] w = H_2O, x = EtOH, y = *i*-PrOH, z = CH_3CN. [c] Purchased from Aldrich Chemical Co. [d] Reference 7. [e] Reference 8. [f] Reference 9. [g] C: calcd, 73.64; found, 73.21. [h] Reference 10. [i] Reference 11.

Scheme I



R = C_6H_5, -C(=O)C_6H_5

pothetical receptor site for nonsteroidal antiinflammatory agents outlined by Shen.[1] Initial biological results were encouraging since the isoquinoline derivative **6** was about as active as aspirin in the pleural effusion test, while its carbocyclic analogue **5** was inactive.

Houlihan et al.[12] reported that 2-benzoylpyridine (**8**) possessed a good level of antiinflammatory activity in the carrageenan foot edema assay; however, neither **8** nor the benzoylisoquinoline compounds **9** and **10** showed activity in our test system. The acidic benzoylisoquinoline derivatives **12** and **13**, which were direct heterocyclic analogues of **1**, were also inactive.

Compound **15**, a direct heterocyclic analogue of **2**, did not show activity at 100 mg/kg. The most active analogues in this series were the 1-aryl-3-isoquinolineacetamides **14** and **16**. Compound **14** was about as active as aspirin while the 4′-chloro derivative **16** was as active as phenylbutazone in the pleural effusion test. In the chronic inflammation screen, however, **16** was inactive at 31.6 mg/kg, the same dose at which phenylbutazone shows good activity. Walford et al.[13] have found that aza analogues of 5-phenylsalicylic acid were about three times as potent as salicylic acid itself as an antiinflammatory agent. Compound **17**,[11] which contains the isoquinoline ring in place of the pyridine ring, was inactive.

Replacement of a carbon atom in the naphthalene ring with a nitrogen atom should not substantially alter the geometry of **3** with respect to **1**, or **4** with respect to **2**. Physical parameters such as the partition coefficient, pK_a, and rate of absorption could be greatly affected, however. The ease of decarboxylation of 2-pyridylacetic acid systems probably would influence metabolic pathways and help explain the limited antiinflammatory activity of this series of compounds. These biological data reconfirm that, although a molecule must possess the required geometry to interact with the receptor, other factors are also quite important in determining potency.

Experimental Section

Pharmacological Methods. Compounds were tested in the Evans blue carrageenan-induced pleural effusion model and evaluated by sequential analysis as described by Sancilio and

Fishman.[14] Each compound was administered orally at a dose of 316 mg/kg to two rats and the 5-h effusive response to the intrapleural injection of 5 mL of 0.075% Evans blue 0.5% carrageenan type 7 was measured. An efficacy ratio [volume effusion (control)/volume effusion (compound)] was determined and compared with that observed for 316 mg/kg of aspirin. If a compound was considered active (efficacy ratio ≥ 1.30), it was retested at a dose of 100 mg/kg in six rats and compared with the activity observed for 100 mg/kg of phenylbutazone. The data were reported as a percentage decrease in volume of pleural fluid from that of the control group. Compounds which were still considered active were tested at 31.6 mg/kg in the adjuvant-induced arthritic rats, a model of chronic inflammation described by Walz et al.,[15] using a therapeutic rather than a prophylactic dosing regimen. Phenylbutazone at 31.6 mg/kg was used as a standard.

General. Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard on a Varian A-60 spectrometer; IR spectra were run as KBr pellets on a Beckman IR8 spectrophotometer; mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6H mass spectrometer; analytical results for compounds followed by elemental symbols are within ±0.4% for these elements and were determined on a Perkin-Elmer Model 240 C,H,N analyzer. Spectral data for all reported compounds were consistent with assigned structures. A sample of 3-methylisoquinoline was purchased from Columbia Chemical Co.

4-Chloro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)benzamide (18). A solution of 38 g (0.22 mol) of *p*-chlorobenzoyl chloride in 100 mL of CH_2Cl_2 was added dropwise to a stirred slurry of 37.6 g (0.2 mol) of norephedrine hydrobromide, 200 mL of CH_2Cl_2, and 400 mL of 5% NaOH. After the addition was complete, the mixture was stirred at ambient temperature for 4 h. The mixture was filtered and the filter cake was washed successively with H_2O, *i*-PrOH, and Et_2O and then dried to yield 54.5 g (94%) of **18** as a white solid: mp 183–185 °C (*i*-PrOH). Anal. ($C_{16}H_{16}ClNO_2$) C, H, N.

1-(4-Chlorophenyl)-3-methylisoquinoline (19). A mixture of 52 g (0.18 mol) of **18**, 180 g of P_2O_5, and 500 mL of *o*-dichlorobenzene was heated at reflux overnight. The mixture was cooled and most of the solvent was decanted. To the residue was cautiously added 500 mL of H_2O and after the vigorous reaction had subsided, the dark solution was washed with two 150-mL portions of C_6H_6. The aqueous solution was cooled and made basic with 50% NaOH. A gray-green solid precipitated and the solid was collected by filtration, washed with H_2O, dried, and recrystallized from ligroine to yield 23.4 g (51%) of **19** as tan needles, mp 116–118 °C. Anal. ($C_{16}H_{12}ClN$) C, H, N.

3-Dibromomethyl-1-phenylisoquinoline (20). A mixture of 8.8 g (0.04 mol) of 3-methyl-1-phenylisoquinoline,[16] 17.8 g (0.10 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 300 mL of CCl_4 was heated at reflux while being illuminated by a flood lamp for 5 h. The reaction mixture was cooled and filtered, and the filtrate was washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to give 17 g of yellow oil which solidified to give crude product. A portion of the solid was recrystallized from cyclohexane to yield an analytical sample of **20**, mp 159–161 °C. Anal. ($C_{16}H_{11}Br_2N$) C, H, N.

3-Dibromomethyl-1-benzoylisoquinoline (21). A mixture of 12.3 g (0.05 mol) of **10**,[9] 21.3 g (0.12 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 350 mL of CCl_4 was treated as above to give 23.7 g of crude **21** which was used without further purification.

1-Phenyl-3-isoquinolinecarboxaldehyde (22). A solution of 15.1 g (0.04 mol) of crude **20** in 200 mL of EtOH and 100 mL of THF heated at reflux was treated with a solution of 21 g (0.12 mol) of $AgNO_3$ in a small volume of H_2O. The mixture was heated at reflux for 1 h and filtered while hot, and the filter cake was washed with hot THF. The combined filtrates were concentrated to give crude **22** as an orange oil. This oil was used without further purification.

1-Benzoyl-3-isoquinolinecarboxaldehyde (23). A mixture of 20.2 g (0.05 mol) of crude **21** and 25.4 g (0.15 mol) of $AgNO_3$ was treated as above to give crude **23** as a tan solid. The solid was used without further purification.

1-Phenyl-3-isoquinolinecarboxylic Acid (13).[10] To a solution of 9.3 g (0.04 mol) of crude **22** in 200 mL of absolute EtOH was added 16 g (0.095 mol) of $AgNO_3$ in 15 mL of H_2O. To this stirring solution was added dropwise a solution of 13 g (0.325 mol) of NaOH in 200 mL of H_2O. After addition was complete, the black slurry was stirred for 2 h. The mixture was filtered through Celite and the filter cake was washed with Et_2O and then made slightly acidic with concentrated HCl. The solid which precipitated was collected by filtration, washed with a small portion of H_2O, and recrystallized from CH_3CN to yield 5.5 g (55%) of **13** as yellow needles, mp 222–223 °C. Anal. ($C_{16}H_{11}NO_2$) C, H, N.

1-Benzoyl-3-isoquinolinecarboxylic Acid (11). A solution of 3.5 g (0.0134 mol) of crude **23**, 50 mL of acetone, and 5 mL of 30% H_2O_2 was heated at reflux for 5 h.[17] The solution was cooled, an additional 5 mL of 30% H_2O_2 was added, and the mixture was heated at reflux overnight. The solution was concentrated under a stream of nitrogen. Methylene chloride was added to the residue and the solution was dried over Na_2SO_4 and concentrated to give an oil. This oil was further purified by heating it in a solution of 60 mL of 5% NaOH for 1 h. The solution was cooled and filtered and the filtrate made acidic with concentrated HCl. The solid which precipitated was collected by filtration and recrystallized from *i*-PrOH–H_2O to give 0.9 g (24%) of **11** as tan needles, mp 158 °C. Anal. ($C_{17}H_{11}NO_3$) H, N; C: calcd, 73.64; found, 73.21.

1-Phenyl-3-isoquinolineacetonitrile (24). A mixture of 7.5 g (0.034 mol) of 3-methyl-1-phenylisoquinoline,[16] 6.3 g (0.035 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 250 mL CCl_4 was heated at reflux under illumination by a flood light for 2 h. The reaction mixture was cooled and filtered and the filtrate concentrated to give crude 1-phenyl-3-(bromomethyl)isoquinoline as a solid. This solid and 9.8 g (0.15 mol) of KCN in 50 mL of EtOH and 40 mL of H_2O were heated on a steam bath for 2 h. The dark solution was concentrated and 100 mL of 5% NaOH was added to the residue. The mixture was extracted with four 50-mL portions of CH_2Cl_2 and the combined extracts were washed once with H_2O, dried over Na_2SO_4, and concentrated to give 9.0 g of dark oil. The oil was chromatographed on 200 g of neutral alumina. The nitrile was eluted with a 1:1 solution of ligroine–C_6H_6 to give 4.7 g (48%) of an oil which crystallized immediately. This solid was recrystallized from *i*-PrOH to give **24** as pale yellow needles, mp 98–99 °C. Anal. ($C_{17}H_{12}N_2$) C, H, N.

1-Benzoyl-3-isoquinolineacetonitrile (25). Using the above procedure, a mixture of 12.3 g (0.05 mol) of **10**,[9] 8.9 g (0.05 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 300 mL of CCl_4 gave 19.2 g of crude 1-benzoyl-3-(bromomethyl)isoquinoline. This intermediate was treated with 16.2 g (0.25 mol) of KCN in EtOH–H_2O to yield 7.4 g (80%) of **25** as pale yellow needles, mp 107–108 °C (*i*-PrOH). Anal. [$C_{18}H_{12}N_2O$·0.25$(CH_3)_2CHOH$] C, H, N.

1-Phenyl-4-isoquinolineacetonitrile (26). Using the above procedure, a mixture of 16.4 g (0.075 mol) of 4-methyl-1-phenylisoquinoline,[18] 13.3 g (0.075 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 500 mL of CCl_4 gave 18.6 g of crude 4-(bromomethyl)-1-phenylisoquinoline. This intermediate was treated with 22.8 g (0.35 mol) of KCN in EtOH–H_2O to yield 2.4 g (13%) of **26** as buff-colored needles, mp 78–80 °C (cyclohexane–C_6H_6). Anal. ($C_{17}H_{12}N_2$) C, H, N.

1-(4-Chlorophenyl)-3-isoquinolineacetonitrile (27). Using the above procedure, a mixture of 12.6 g (0.05 mol) of **19**, 8.9 g (0.05 mol) of NBS, 0.5 g of dibenzoyl peroxide, and 400 mL of CCl_4 gave 19.7 g of crude 1-(4-chlorophenyl)-3-(bromomethyl)-isoquinoline as a tan solid. This intermediate was treated with 16.3 g (0.25 mol) of KCN in EtOH–H_2O to yield 3.7 g (27%) of **27** as pale yellow needles, mp 130–132 °C (cyclohexane–C_6H_6). Anal. ($C_{17}H_{11}ClN_2$) C, H, N.

Ethyl 3-Isoquinolineacetate Hydrobromide (7). A mixture of 3.2 g (0.019 mol) of 3-cyanomethylisoquinoline,[19] 10 mL of 95% EtOH, and 10 mL of concentrated H_2SO_4 was heated on a steam bath for 5 h and then let stand at ambient temperature overnight. The dark solution was cooled and made basic with 20% NaOH. The resulting oil was extracted with three 25-mL portions of CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 and concentrated to give 2.6 g (63%) of ethyl 3-isoquinolineacetate. The salt, mp 205–207 °C dec (*i*-PrOH), was prepared by bubbling

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

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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.

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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