sulfate and concentrated in vacuo to give very clean (>90% by HPLC) crude product (77 mg, 89.5%). This material was taken on to the next step as is. HPLC retention time = 9.25 min; MS (FAB) 1118 (M + H), 1140 (M + Na).

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methyl-Pro-Thr-Tyr-4-OH-Pro-Thr-α-*N*-(octyloxybenzoyl)-δ-CBZ-Orn (15e). To a solution of **15d** (75 mg, 0.067 mmol) in 1.5 mL of methyl alcohol was added 1 N NaOH (147 μL, 0.147 mmol, 2.2 equiv). The reaction mixture was stirred under nitrogen for 6 h. HPLC analysis (30:70 H_2O/(90:10 CH_3CN/H_2O), both 0.1% TFA, 1.0 mL/min) showed the reaction to be incomplete. An additional 1.1 equiv of 1 N NaOH was added and the reaction allowed to stir overnight at 0 °C. The following morning the reaction was still incomplete. Another 1.1 equiv of 1 N NaOH was added and the stirring continued for another 6 h. HPLC analysis still showed some starting peptide. Another 0.55 equiv of 1 N NaOH was added and the reaction allowed to warm to room temperature for 6 h. HPLC showed the reaction to be complete. The reaction mixture was partitioned between ethyl acetate (60 mL) and 1 N sodium hydrogen sulfate (20 mL). The organic layer was collected and the aqueous phase back extracted with an additional 2 × 60 mL ethyl acetate and 1 × 60 mL methylene chloride. The combined organics were dried over sodium sulfate and concentrated in vacuo. The gummy residue was redissolved in 20% aqueous acetonitrile and lyophilized to yield a fluffy white solid (67 mg, 90.5%). This material was taken on to the next step as is. HPLC retention time = 6.80 min; MS (FAB) 1126 (M + Na).

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methyl-Pro-Thr-Tyr-4-OH-Pro-Thr-α-*N*-(octyloxybenzoyl)-Orn (15f). A solution of **15e** (60 mg, 0.0544 mmol) in 15 mL of methyl alcohol was degassed and purged with nitrogen. Palladium on carbon (10%, 30 mg) was added and the system flushed with hydrogen. The hydrogenation was carried out overnight at balloon pressure. HPLC analysis (30:70 H_2O/(90:10 CH_3CN/H_2O), both 0.1% TFA, 1.0 mL/min) showed the reaction to be complete. The catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was redissolved in 20% aqueous acetonitrile and lyophilized to yield a fluffy white solid (45 mg, 83%). This material carried on to the cyclization step as is. HPLC retention time = 5.0 min; MS (FAB) 970 (M + H).

***cyclo*-(2*S*,3*S*,4*S*)-3-Hydroxy-4-methyl-Pro-Thr-Tyr-4-OH-Pro-Thr-α-*N*-(octyloxybenzoyl)-Orn (16).** To a −20 °C of **15f** (41 mg, 0.042 mmol) in sieve (3 A, 13 X) dried, degassed DMF under nitrogen was added the DPPA (12.7 mg, 10.0 μL, 0.046 mmol, 1.1 equiv) followed immediately by solid sodium bicarbonate (17.6 mg, 0.21 mmol, 5.0 equiv). The reaction mixture was stirred at −20 °C for 9 h and then warmed to 0 °C for another 9 h. HPLC analysis (45:55 H_2O/(90:10 CH_3CN/H_2O), both 0.1% TFA, 1.0 mL/min) showed the reaction to be complete. The reaction mixture was filtered and the DMF removed in vacuo. Purification was accomplished by HPLC (10 mm × 25 cm Zorbax C8 semi prep column, 45:55 H_2O/(90:10 CH_3CN/H_2O), both 0.1% TFA, 4.0 mL/min flow). Fractions were analyzed by HPLC. Pure cuts were pooled together and lyophilized to give the pure (>95% by HPLC) product as a white fluffy solid (16 mg, 38%). HPLC retention time = 8.50 min; MS (FAB) 952 (M + H).

Registry No. **5**, 141806-00-0; **6**, 141806-01-1; **7**, 123180-69-8; **8**, 106159-24-4; **9a**, 141806-02-2; **9b**, 141806-03-3; **9c**, 141806-04-4; **9d**, 141806-05-5; **9e**, 141806-06-6; **9f**, 141806-07-7; **9g**, 141806-08-8; **10a**, 141806-09-9; **10b**, 141806-10-2; **10c**, 141806-11-3; **10d**, 141806-12-4; **10e**, 141806-13-5; **10f**, 141806-14-6; **10g**, 141806-15-7; **12a**, 110936-12-4; **12b**, 141899-12-9; **12c**, 141806-16-8; **12d**, 141806-17-9; **13a**, 141806-18-0; **13b**, 141806-19-1; **13c**, 141806-20-4; **13d**, 141806-21-5; **13e**, 141806-22-6; **13f**, 141806-23-7; **13g**, 141806-24-8; **14**, 141806-25-9; **15a**, 141806-26-0; **15b**, 141806-27-1; **15c**, 141806-28-2; **15d**, 141806-29-3; **15e**, 141806-30-6; **15f**, 141806-31-7; **16**, 141806-32-8; Cbz-Cl, 501-53-1; Fmoc-Pro-OPfp, 86060-90-4; Fmoc-Thr(Bu-*t*)-ODhbt, 119767-84-9; Fmoc-Tyr(Bu-*t*)-OPfp, 86060-93-7; Boc-Thr(Bn)-OH, 15260-10-3; Boc-Hyp(Bn)-OH, 54631-81-1; Boc-Tyr(BrZ)-OH, 47689-67-8; Boc-Orn(ClZ)-OH, 118554-00-0; Boc-Pro-OH, 15761-39-4; Fmoc-Orn(Boc)-OH, 109425-55-0; 2,6-$Cl_2C_6H_3CH_2Br$, 20443-98-5; 4-[$Me(CH_2)_7O$]C_6H_4COOH, 2493-84-7; (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline methyl ester hydrochloride, 111002-66-5.

Supplementary Material Available: 300-MHz ^1H NMR spectra in CD_3OD of **5**, **10a–g**, **14**, and **16** (10 pages). Ordering information is given on any current masthead page.

2-Substituted 1-Azabicycloalkanes, a New Class of Non-Opiate Antinociceptive Agents

John R. Carson,* Richard J. Carmosin, Jeffry L. Vaught, Joseph F. Gardocki, Michael J. Costanzo, Robert B. Raffa, and Harold R. Almond, Jr.

Drug Discovery Research, The R.W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477-0776.
Received March 4, 1992

2-Substituted 1-azabicycloalkanes (3- and 5-aryloctahydroindolizines **2** and **11**, 3-cyclohexyloctahydroindolizine **12**, 4-aryloctahydroquinolizines **13**, and 3-arylhexahydropyrrolizines **14**) constitute a new class of non-opiate antinociceptive agents. These compounds demonstrated activity in the mouse abdominal constriction test and many were active in the mouse tail-flick test. *trans*-3-(2-Bromophenyl)octahydroindolizine (**2a**) did not bind to the opiate receptor nor did it affect arachidonate metabolism. 3-Aryloctahydroindolizines were prepared by catalytic hydrogenation of 1-aryl-3-(2-pyridinyl)-2-propen-1-ones. The X-ray crystal structure of (−)-**2a** was determined and absolute stereochemistry assigned as 3-*R*,8a-*R*.

Introduction

The mechanisms of pain and its remission (analgesia) have received intensive scientific study. However, despite an ever growing body of knowledge of endogenous nociceptive and antinociceptive systems, clinical treatment of pain today is dominated by two classes of analgesics: the cyclooxygenase inhibitors (aspirin and other NSAIDs) and the opiates (morphine and its synthetic derivatives). The aspirin-like compounds are generally thought of as peripherally acting analgesics with clinical indications for mild to moderate pain. The opiates, on the other hand, produce their action via an interaction with specific receptors in the central nervous system with clinical indications for moderate to severe pain.

The pharmacological profiles of the centrally acting analgesics typically are different from the profiles of peripherally acting analgesics. The mouse abdominal constriction test[1] can be used to detect both peripherally and

* Person to whom correspondence should be addressed.

(1) Collier, H. O. J.; Dinneen, L. C.; Johnson, C. A.; Schneider, C. Abdominal Constriction Response and Its Suppression by Analgesic Drugs in the Mouse. *Br. J. Pharmacol. Chemother.* 1968, *32*, 295–310.

0022-2623/92/1835-2855$03.00/0

Table I. Receptor Binding Profile[7] of 2a

receptor/ uptake	radioligand (μM)	rat brain region	blank determinant (μM)	±2a % response/concn, μM or [K_i, μM]	+2a % response/concn, μM or [K_i, μM]	-2a % response/concn, μM or [K_i, μM]
opiate	[^{3}H]naloxone (20)	whole brain	levorphanol (4)	17/10		
α-1-adrenergic	[^{3}H]WB 4101 (4)	cortex	(-)-norepinephrine (100)	6/1		
α-2-adrenergic	[^{3}H]clonidine (0.4)	cortex	(-)-norepinephrine (10)	[1.12 (0.64-1.71]	[1.20 (0.72-1.84)]	[2.84 (2.36-3.52)]
β-adrenergic	[^{3}H]dihydro-alprenolol (0.2)	cortex	isoproterenol (1)	-3/1	-1/1	-5/1
dopamine D_2	[^{3}H]spiperone (0.05)	striatum	(+)-butaclamol (1)	0/1		
serotonin S_1	[^{3}H]serotonin (1)	cortex	serotonin (10)	7/1		
serotonin S_2	[^{3}H]ketanserin (0.2)	cortex	mianserin (1)	-18/1		
GABA-A	[^{3}H]GABA (60)	cerebellum	GABA (20000)	+2/10	+4/10	-2/10
cannabinoid[10]	[^{3}H]CP-55,940	cortex	desacetyllevonantralol (0.1)	1/10	6/10	2/10

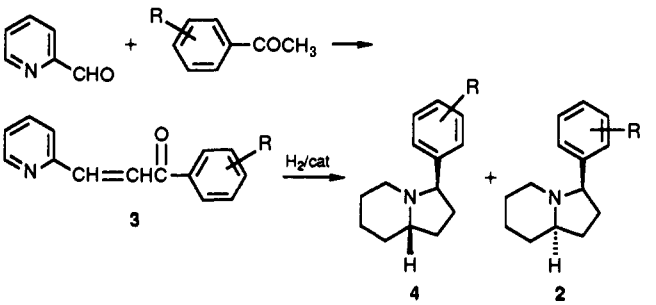
centrally acting analgesics. The hot-plate test,[2] the tail-flick test,[3] and the tail compression test,[4] in combination with the abdominal constriction test, have all been demonstrated to be predictive of centrally acting analgesics.[5] Given the limitations in efficacy of the peripheral analgesics and the reluctance to employ opiates because of their liability toward physical dependence, the quest is to develop an analgesic with the efficacy of morphine without the side effects. Although one may argue that this goal is unachievable, there have been a number of initiatives directed toward a non-NSAID, non-opioid centrally acting analgesic (nefopam, levonantradol, fluradoline, ceruletide, flupertine, THIP, U47476, and SCH30497).

Results and Discussion

Biological Activity. We have found that 2-substituted 1-azabicycloalkanes (1), in particular 3- and 5-aryloctahydroindolizines, 4-aryloctahydroquinolizines, and 3-arylhexahydropyrrolizines, constitute a new class of nonopiate antinociceptive agents.[6] Many of these 2-substituted 1-azabicycloalkanes show activity in assays which detect the centrally active agents as well as in assays which pick up only peripherally active drugs.

The prototypical compound, (±)-**2a** (RWJ-22757, formerly McN-5195), for instance, showed activity in the mouse abdominal constriction test [ED_{50} 20 mg/kg po (14.3-27.9)], the mouse tail-flick assay [ED_{50} 33.9 mg/kg ip (20.9-49.2)], the mouse 48 °C hot-plate test [ED_{50} 30.9 mg/kg ip (20.8-64.7)], the rat abdominal constriction test [ED_{50} 33.2 mg/kg po (14.8-127.3)], and the rat tail-flick test [ED_{50} 33.2 mg/kg ip (14.7-126.90)].[7] Peripherally-acting analgesics, such as aspirin, acetaminophen, and ibuprofen, are active in the abdominal constriction test, but not in the hot-plate or tail-flick test.[7] Diazepam, chlordiazepoxide, meprobamate, imipramine, phenobarbital, haloperidol, or chlorpromazine were inactive or poorly active in the abdominal constriction test and were all inactive in the tail-flick test at doses which do not cause behavioral abnormalities (data not shown). Clonidine, a centrally-acting analgesic in humans,[8] is active in both the abdominal constriction and tail-flick tests.[9]

Scheme I



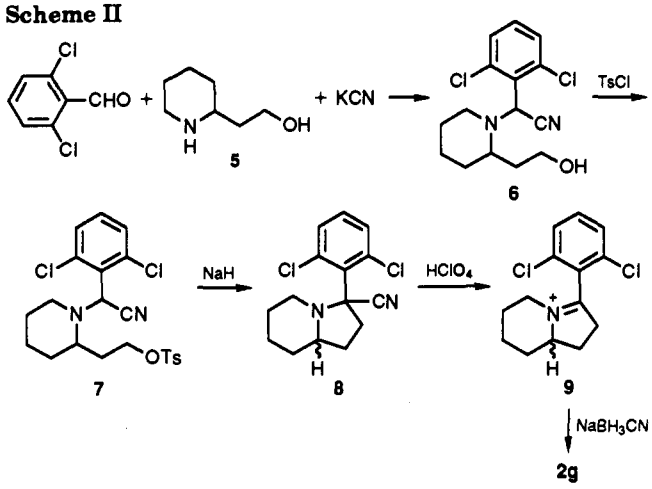
The antinociceptive activity of (±)-**2a** in rats and mice was not blocked by naloxone.[7]

Compound (±)-**2a** did not inhibit the biosynthesis of PGE_2 in vitro. The receptor binding data on compound **2a** are shown in Table I. Compound **2a** did not bind to the opiate, serotonin S_1 or S_2, dopamine D_2, β-adrenergic, GABA-A, or cannabinoid receptors and bound weakly to the α_2-adrenergic receptor. It did not inhibit the synaptic uptake of norepinephrine, serotonin, dopamine, or GABA.[7]

The antinociceptive activity induced by (±)-**2a** was not affected by reserpine (2.5 mg/kg sc) or phentolamine (5 mg/kg ip) pretreatment, and was not reduced in clonidine tolerant animals. The antinociceptive activity of (±)-**2a** was, however, blocked by yohimbine (2 mg/kg ip) or ketanserin (20 mg/kg ip). Compound (±)-**2a** was active in

(2) D'Amour, F. E.; Smith, D. L. A Method for Determining Loss of Pain Sensation. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74-79.
(3) Eddy, N. B.; Leimbach, D. Synthetic Analgesics, II. Dithienylbutenyl and Dithienylbutylamines. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385-393.
(4) Haffner, F. Experimenteile Prufung Schmerzstillender Mittel. *Deut. Med. Wochensche* **1929**, *55*, 731-732.
(5) Fennessy, M. R.; Lee, J. R. The Assessment of and the Problems Involved in the Experimental Evaluation of Narcotic Analgesics. In *Methods in Narcotic Research*; Ehrenpreis, S., Neidle, A., Eds.; Marcel Dekker, Inc.: New York, 1975; pp 73-95.
(6) (a) Carmosin, R. J.; Carson, J. R. Octahydroindolizine Compounds Useful as Analgesics. U.S. Patent 4,582,836, 1986. (b) Carmosin, R. J.; Carson, J. R. Preparation and Formulation of 3-Diphenyl Substituted Octahydroindolizine Analgesic Compounds. U.S. Patent 4,683,239, 1987. (c) Carmosin, R. J.; Carson, J. R. Preparation and Formulation of 5-Substituted Octahydroindolizines as Analgesics. U.S. Patent 4,689,329, 1987. (d) Carmosin, R. J.; Carson, J. R. 4-Substituted Octahydroquinolizine Analgesic Compounds and Octahydroquinolizinium Intermediates. U.S. Patent 4,716,172, 1987. (e) Carmosin, R. J.; Carson, J. R. Hexahydropyrrolizines Useful as Analgesics, and Their Pharmaceutical Compositions and Use. U.S. Patent 4,800,207, 1989.
(7) Vaught, J. L.; Carson, J. R.; Carmosin, R. J.; Blum, P. S.; Hageman, W.; Persico, F. J.; Shank, R.; Raffa, R. B. Antinociceptive Action of McN-5195 in Rodents: A Structurally Novel Analgesic with a Nonopiod Mechanism of Action. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1-10.
(8) Max, M. B.; Schafer, S. C.; Culnane, M.; Dubner, R.; Gracely, R. H. Association of pain relief with drug side effects in postherpetic neuralgia; a single-dose study of clonidine, codeine, ibuprofen, and placebo. *Clin. Pharmacol. Ther.* **1988**, *43*, 363-371.
(9) Raffa, R. B.; Orr, N.; Connelly, C. D.; Hollingworth, R. M. XAMI and DCDM, agonists at cAMP-associated octopamine receptors in cockroach nerve cord, produce centrally mediated antinociception in mice. *Brain Res.* **1991**, *559*, 211-219.
(10) Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. Determination and Characterization of a Cannabinoid Receptor in Rat Brain. *Mol. Pharmacol.* **1988**, *34*, 605-613.

Scheme II



the mouse tail-flick test by intracerebroventricular (icv) administration but was inactive via the intrathecal (it) route. In contrast, morphine was active via both routes. The activity of (±)-**2a** administered ip or icv was attenuated by it administration of phentolamine (2 μg), yohimbine (5 μg), or methysergide.[11]

In addition, electrophysiological techniques were used to study the effect of (±)-**2a** on somatosensory input to neurons in the VPL nucleus of the thalamus. Compound (±)-**2a** blocked the thalamic activity evoked by noxious stimulation (55–57 °C heated probe applied to the contralateral hind limb of an anesthetized rat) but did not alter the thalamic activity during nonnoxious (room temperature probe) stimulation.[7] Thus it is likely that specific antinociceptive effects were being observed and, thus, that RWJ-22757 has a non affect-associated analgesic profile.

On the basis of the evidence from electrophysiological studies and from studies on the route of administration, a hypothesis was advanced that (±)-**2a** exerts its antinociceptive activity supraspinally by activation of descending inhibitory pathways.[11] The evidence at hand does not allow a definite assessment of which receptor or receptors are responsible for the activity of (±)-**2a**. Weak binding activity was observed in the α_2 receptor and activity of (±)-**2a** was blocked by the α_2 antagonist yohimbine, yet (±)-**2a** antinociception was not reduced in clonidine-tolerant animals. No binding to the serotonin S_2 receptor was observed, yet the antinociceptive activity was blocked by the serotonin S_2 antagonist, ketanserin. Further work is in progress to define the mechanism of action.

Chemistry. The chemistry and structure–activity relationship (SAR) of compounds of type **2** was studied in detail. These compounds were prepared by two routes. In the first route (Scheme I), a substituted acetophenone was condensed with 2-pyridinecarboxaldehyde to give a 1-aryl-3-(2-pyridinyl)-2-propen-1-one (**3**) using either Claisen-Schmidt (procedure A) or Knoevenagel (procedure B) conditions. Catalytic hydrogenation of intermediates of type **3** over Pt or Rh afforded the diastereomeric 3-aryloctahydroindolizines **2** (trans) and **4** (cis) in a ratio of approximately 10:1.[12–14] The diastereomers were readily

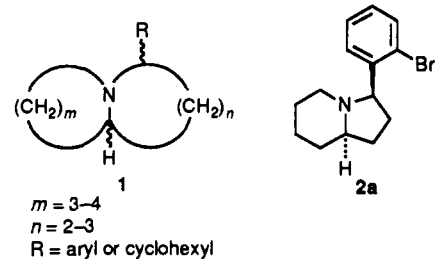


Figure 1.

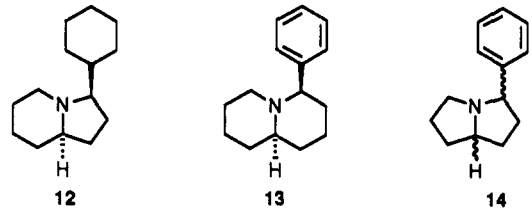


Figure 2.

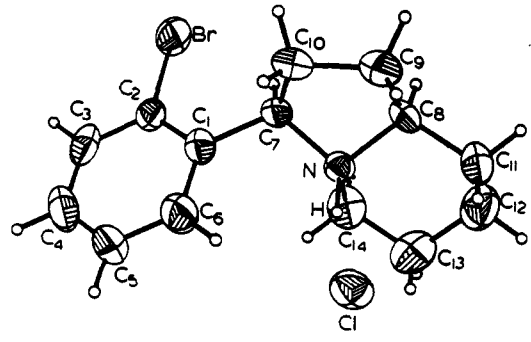
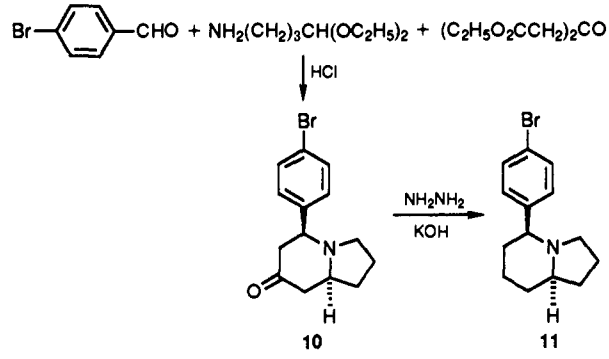


Figure 3.

Scheme III



separated by column chromatography or fractional crystallization. The physical properties of compounds of types **3** and **2** are shown in Tables II and III.

The foregoing method failed in an attempt to prepare the 2,6-dichlorophenyl compound (**2g**); therefore, Scheme II was employed. 2-Piperidineethanol (**5**) was condensed with 2,6-dichlorobenzaldehyde and KCN to give hydroxy nitrile **6**. The hydroxy nitrile was converted by the action of tosyl chloride to tosylate **7**. Treatment of **7** with NaH gave the cyclic nitrile **8**. The action of $HClO_4$ on **8** effected conversion to iminium salt **9**. Reduction of **9** with Na-

(11) Vaught, J. L.; Raffa, R. B. Centrally-Mediated Antinociceptive Action of RWJ-22757 (Formerly McN-5195): Involvement of Spinal Descending Inhibitory Pathways (An Hypothesis). *Life Sci.* **1991**, *48*, 2233–2241.

(12) Murakoshi, I. Studies on the Syntheses of Cyclic Nitrogenous Compounds from Amino Acids (VII). Syntheses of 3-Substituted Indolizidine and Pyrrolizidine Derivatives from dl-3-(2-Piperidinyl)propionic Acid and dl-3-(2-Pyrrolidinyl)propionic Acid. *Yakugaku Zasshi* **1958**, *78*, 598–601.

(13) Nagai, Y.; Uno, H.; Umemoto, S. Studies on Psychotropic Agents, III. Synthesis of 1-Substituted 2-(2-(p-Fluorobenzoyl)ethyl)piperidines and Related Compounds. *Chem. Pharm. Bull.* **1979**, *27*, 1159–1168.

(14) Sam, J.; England, J. D.; Alwani, D. W. Reductive Cyclization of 2-(Picolylidene)-1-indanones to Octahydroindeno [2,1-b]-Indolizine and Indenoisogranatine. *J. Med. Chem.* **1964**, *7*, 732–734.

Table II. 1-Aryl-3-(2-pyridinyl)-2-propen-1-ones

no.	R	procedure[a]	% yield	mp, °C	recryst solvent	formula	anal.
3a	2-Br	A	50	67–69	2-PrOH	$C_{14}H_{10}BrNO$	CHN
3b	H	A	32	59–61	2-PrOH	$C_{14}H_{11}NO$	
3c	4-F	A	68	76–78	2-PrOH	$C_{14}H_{10}FNO$	
3d	4-Br	A	62	208–210	EtOH	$C_{14}H_{10}BrNO{\cdot}HCl{\cdot}0.6H_2O$	CHN
3e	2,4-Cl_2	B	36	62–65	2-PrOH	$C_{14}H_9Cl_2NO$	CHN
3f	2-Cl	B	46	55–59	CH_3CN	$C_{14}H_{10}ClNO$	CHN
3h	2-CH_3O	A	71	166–169	2-PrOH	$C_{15}H_{13}NO2{\cdot}HCl$	CHN
3i	2-CH_3	A	65	152–156	2-PrOH	$C_{15}H_{13}NO{\cdot}HCl$	CHN
3j	2-CF_3	A	31	129–139	2-PrOH	$C_{15}H_{10}F_3NO{\cdot}HCl$	CHN
3k	4-nC_3H_7	A	36	63–65	hexane	$C_{17}H_{17}NO$	CHN
3l	2-C_2H_5O	B	39	61–62	CH_3O-t-C_4H_9	$C_{16}H_{15}NO_2$	CHN
3o	4-($C_6H_5CH_2O$)	A	73	131–134	EtOH	$C_{21}H_{17}NO_2$	CHN
3q	3-Br	B	64	98–100	2-PrOH	$C_{14}H_{10}BrNO$	CHN
3r	2-NO_2	B	71	102–105	EtOAc/Et_2O	$C_{14}H_{10}N_2O_3$	CHN
3s	2,6-F_2	B	35	70–72	2-PrOH	$C_{14}H_9F_2NO$	CHN
3t	2,3,4-Cl_3	B	50	98–100	2-PrOH	$C_{14}H_8Cl_3NO$	CHN
3u	2,5-Cl_2	B	40	180–190	2-PrOH/Et_2O	$C_{14}H_9Cl_2NO{\cdot}HCl$	CHN
3v	2-Cl, 6-F	B	50	70–72	t-BuOH/Et_2O	$C_{14}H_9ClFNO$	CHN
3x	3-CH_3O	A	77	71–73	2-PrOH	$C_{15}H_{13}NO_2$	CHN

[a] See the lettered procedures in the Experimental Section. [b] The nitro compound **3q** was used to make the amino compound **4q**.

BH_3CN afforded a diastereomeric mixture in which **2g** predominated.

Compound **11** was prepared according to Scheme III.[15] 4-Bromobenzaldehyde was condensed with 4-aminobutyraldehyde diethyl acetal and diethyl acetonedicarboxylate. The initially formed 6,8-diester was hydrolyzed and decarboxylated under the reaction conditions and *trans*-**10** was formed directly. Wolff-Kishner reduction of **10** afforded **11**.

Compound **12** was prepared by perhydrogenation of **3b**. Compounds **2m**, **2n**, **2p**, **2r**, **2w**, **2x**, **2y**, and **2z** were prepared by functional group transformation.

The enantiomers of **2a** [(+)-**2a** and (−)-**2a**] were obtained by resolution using the enantiomeric di-*p*-toluoyltartaric acids as resolving agents.

Compounds **13**[16] and **14**[12] (Figure 2) are known compounds. The stereochemistry of **14** could not be rigorously assigned by NMR but analogous reductions in other ring systems gave trans products.

An X-ray crystal structure determination was carried out on (−)-**2a** hydrochloride. The structure is shown in Figure 3. The absolute configurations of the centers at C-3 and C-8a were assigned as *R*,*R* by the technique of anomalous dispersion. The proton at 8a and the aryl ring are trans to one another. The ring fusion is trans. The presence of Bohlmann bands at 2860, 2787, and 2741 cm^{-1} in the IR spectrum of **2a** in $CHCl_3$ indicated a preference for trans fusion for the free base.

Structure–Activity Relationships. Activity of the compounds in the mouse abdominal constriction and tail-flick assays is shown in Table III. The effect of substituents on the aromatic ring of **2** on activity was examined. Compounds with substituents in the meta and para positions tended to show less activity in the tail-flick test (a test indicative of strong centrally mediated activity). Compounds, e.g. **2q** and **2x**, substituted solely in the meta position had reduced or no activity. Compounds with polar substituents, e.g. **2n**, **2p**, and **2r**, had reduced or no activity.

Lipophilic substituents tended to increase duration. For instance, in the mouse abdominal constriction test, **2b** had a duration less than 60 min while **2e** had a duration of greater than 180 min.

At an intermediate stage of our investigation, a QSAR study was carried out on 16 of the analogs (**2a–f,h–k,m–o,r,t,x**) using data from the mouse abdominal constriction test. Significant correlations were found with π (hydrophobicity) and MR (molar refraction, bulk),[17] but not σ (Hammett constant). The activity could be described by the equation: $\log(1/ED_{50}) = -1.089 + 0.12\pi - 0.057MR + 0.0015MR^2$, $n = 16$, $F = 11.5$, $R = 0.74$, $s = 0.11$, and $MR_{min} = 19.3$.[18]

The predicted MR_{min} corresponded to a grouping with about five atoms of average bulk. To maximize potency, the synthesis of compounds with substituents of greater bulk was tried. Consequently **2y** and **2z** were synthesized. These compounds were indeed potent in the mouse abdominal constriction test, but lacked activity in the tail-flick test.

The enantiomers of **2a** showed different profiles of activity. The (−) (*R*,*R*) enantiomer showed enhanced activity in the tail-flick test relative to the racemate and little change in the abdominal constriction test. The (+) (*S*,*S*) enantiomer appeared substantially more potent in the abdominal constriction test and had twice the duration of racemic **2a**. It lacked activity in the tail-flick assay, however. It is not clear whether the enantiomers merely differ quantitatively or whether they have divergent mechanisms.

The pattern of activity seen with (+)-**2a** of potent activity in the mouse abdominal constriction test and little or no activity in the mouse tail-flick test is seen in a number of other analogs. Analogs with a large substituent in the para position of the phenyl ring (**2d**, **2o**, **2y**, and **2z**) or analogs with *o*,*o*′-disubstitution (**2g**, **2v**) on the phenyl ring tended to show this activity pattern. A weaker antinociceptive stimulus is used in the mouse acetylcholine bromide induced abdominal constriction test than in the mouse tail-flick test. The mouse acetylcholine bromide induced body constriction test can show false positive results with several classes of pharmacological agents.[1]

The cis diastereomer of **2a**, **4a**, showed reduced activity.

The activity of the cyclohexyl compound, **12**, indicated that an aromatic ring adjacent to nitrogen was not a prerequisite for activity.

(15) Lions, F.; Willison, A. M. A Synthesis of Octahydropyrrocolines. *Proc. R. Soc. N.S. Wales* **1940**, *73*, 240–252.
(16) Boekelheide, V.; Agnello, E. J. Curariform Activity and Chemical Structure, VIII. Lactones Derived from Quinolizidine. *J. Am. Chem. Soc.* **1950**, *72*, 5005–5009.
(17) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley Interscience: New York, 1979; pp 44–46.
(18) Martin, Y. C. *Quantitative Drug Design*; Marcel Dekker: New York, 1978; p 19.

Table III. Physical Properties and Biological Activity of 2-Substituted 1-Azabicycloalkanes

no.	R	method of synthesis	% yield	recryst solvent	mp, °C	formula	anal.	mouse abdominal constriction: ED_{50}, mg/kg[a] or [% response[b]/dose]	mouse tail flick: ED_{50}, mg/kg ip[a] or [% response/dose]
(±)-2a	2-Br	Scheme I[c]	72	2-PrOH	211.5–213.5	$C_{14}H_{18}BrN\cdot HCl$	CHN	20.1 (14.3–27.9)	33.9 (20.9–49.2)
(+)-2a	2-Br	Exp[d]		MeOH/CH_3CN	243–252	$C_{14}H_{18}BrN\cdot HCl$	CHN	7.9 (4.6–11.5)	IA[e]
(−)-2a	2-Br	Exp		MeOH/CH_3CN	244–253	$C_{14}H_{18}BrN\cdot HCl$	CHN	22.2 (18–27.4)	14.6 (9.8–24.1)
2b	H	Scheme I[f]	30	EtOH	116–118	$C_{14}H_{19}N\cdot HClO_4$	CHN	12.1 (9.5–15.4)	15.0 (10.5–21.5)
2c	4-F	Scheme I[f]	25	CH_3CN	210–212	$C_{14}H_{18}FN\cdot HCl$	CHN	19.1 (16.4–22.4)	22.6 (5.9–50.8)
2d	4-Br	Scheme I[c]	7.6	CH_3CN	234–236	$C_{14}H_{18}BrN\cdot HCl$	CHN	18.8 (13.4–31.9)	IA
2e	2,4-Cl_2	Scheme I[c]	21	CH_3CN	238–240	$C_{14}H_{17}Cl_2N\cdot HCl$	CHN	22.4 (15.5–32.9)	[60%/50]
2f	2-Cl	Scheme I[c]	32	CH_3CN	221–223	$C_{14}H_{18}ClN\cdot HCl$	CHN	28.4 (16.6–47.7)	27.6 (14.1–44.7)
2g	2,6-Cl_2	Scheme II	63	CH_3CN/Et_2O	206–208	$C_{14}H_{17}Cl_2N\cdot HCl$	CHN	3.5 (2.3–5.4)	[60%/100]
2h	2-CH_3O	Scheme I[f]	29	CH_3CN	202–204	$C_{15}H_{21}NO\cdot HCl$	CHN	29.1 (20.9–45.2)	20.6 (17.3–24.9)
2i	2-CH_3	Scheme I[f]	22	CH_3CN	205–208	$C_{15}H_{21}N\cdot HCl$	CHN	28.4 (16.6–47.7)	17.7 (11.1–28.1)
2j	2-CF_3	Scheme I[f]	11	CH_3CN	183–185	$C_{15}H_{18}F_3N\cdot HCl$	CHN	19.7 (17.7–28.4)	55.3 (24.1–212.1)
2k	4-nC_3H_7	Scheme I[f]	15	CH_3CN	158–161	$C_{17}H_{25}N\cdot HCl$	CHN	32.9	[60%/100]
2l	2-C_2H_5O	Scheme I[f]	21	CH_3CN	175–177	$C_{16}H_{23}NO\cdot HCl$	CHN	≥30	<50
2m	2-CH_3S	Exp	71	MeOH/t-BuOH	198–200	$C_{15}H_{21}NS\cdot HBr$	CHN	41.3 (33.9–51.6)	[50%/100]
2n	2-CH_3SO	Exp	32	MeOH	190–218[e]	$C_{15}H_{21}NOS\cdot HClO_4\cdot H_2O$	CHN	59.6 (43.1–77.8)	IA
2o	4-($C_6H_5CH_2O$)	Scheme I[c]	32	EtOH	205–209	$C_{21}H_{25}NO\cdot HCl$	CHN	16.8 (12.1–25.1)	[50%/100]
2p	4-OH	Exp		2-PrOH/Et_2O	239–244	$C_{14}H_{19}NO\cdot HCl$	CHN	>30	IA
2q	3-Br	Scheme I[c]	29	2-PrOH	195–198	$C_{14}H_{18}BrN\cdot HCl$	CHN	IA	[60%/100]
2r	2-NH_2	Exp	64	t-BuOH/H_2O	160–229[d]	$C_{14}H_{20}N_2\cdot 4/3HCl$	CHN	IA	IA
2s	2,6-F_2	Scheme I[c]	27	CH_3CN	228–231	$C_{14}H_{17}F_2N\cdot HCl$	CHN	29.6 (22.1–42.7)	IA
2t	2,3,4-Cl_3	Scheme I[c]	40	MeOH/CH_3CN	219–236	$C_{14}H_{16}Cl_3N\cdot HCl$	CHN	26.7 (10.0–39.8)	<100
2u	2,5-Cl_2	Scheme I[c]	30	MeOH/CH_3CN	230–242[d]	$C_{14}H_{17}Cl_2N\cdot HCl$	CHN	23 (5.0–38.7)	IA
2v	2-Cl, 6-F	Scheme I[c]	12	MeOH/CH_3CN	205–210	$C_{14}H_{17}CFN\cdot HCl$	CHN	16.5 (12.5–23.5)	[60%/100]
2w	2-CN	Exp	58	MeOH/CH_3CN	236–239	$C_{15}H_{18}N_2\cdot HCl$	CHN	IA	28.4 (19.8–39.9)
2x	3-CH_3O	Scheme I[e]	22	EtOH	132–134	$C_{15}H_{21}NO\cdot HCl$	CHN	36.6 (29.5–45.5)	32.2 (20.8–72.6)
2y	4-(4-$CH_3CONHC_6H_4$)S	Exp	30		148–155	$C_{22}H_{26}N_2OS\cdot HCl\cdot 0.5H_2O$	CHN	2.8 (1.6–4.2)	IA
2z	4-(4-Cl-C_6H_4)S	Exp	7	CH_3CN	198–201	$C_{20}H_{22}ClNS\cdot HCl$	CHN	3.2 (2.2–4.5)	IA
4a	Br	Scheme I	1.4		188–190	$C_{14}H_{18}BrN\cdot HCl$	CH	>30	<100
11		Exp	28	2-PrOH	264–267	$C_{14}H_{18}BrN\cdot HCl$	CHN	4.6 (3.3–6.0)	>50
12		Exp	14	CH_2Cl_2/THF	199–202	$C_{14}H_{25}N\cdot HCl$	CHN	[50%/10]	[60%/50]
13		g						15.3 (10.8–20.8)	20.9 (14.8–30.3)
14		h						5.7 (4.3–7.7)	>25
codeine H_3PO_4								11.1 (7.1–20.6)	30.0 (20.9–43)
ibuprofen								15.7 (12.0–21.1)	IA

[a] Value in parentheses refers to 95% fiducial limits. [b] Percentage of animals responding. [c] Rh on C was used as catalyst for the catalytic reduction. [d] Exp indicates that the preparation is shown in the Experimental Section. [e] IA indicates inactive at 100 mg/kg. [f] Pt was used as catalyst. [g] Preparation reported in ref 13. [h] Preparation reported in ref 9.

The nature of the heterocyclic ring system necessary for activity was examined, as well. 4-Phenyloctahydroquinolizine (13) showed activity comparable to the 3-aryloctahydroindolizine series. 5-(4-Bromophenyl)octahydroindolizine 11 showed good activity in abdominal constriction but lacked activity in the tail-flick test. The same pattern was seen with 3-phenylhexahydropyrrolizine 14.

At the current state of the investigation, no definitive assessment of the role of the geometry of the heterocyclic ring on activity can be made. Subtle changes in profile are seen in going from one ring system to another. Overall, however, quite a wide range of heterocycles exhibited activity.

Conclusions

The 2-substituted 1-azabicycloalkane are structurally and pharmacologically unique antinociceptive agents. Two efficient and complimentary synthetic routes were employed for the preparation of compounds of type 2.

Structure–activity relationships were studied with an emphasis on the quantitative effects of substituents on the phenyl group of compounds of type 2. The compounds could be classified into two groups, those such as (−)-2a, which responded to a strong antinociceptive stimulus and those, such as (+)-2a, which did not.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM390 (90 MHz), a Bruker WM-360 (360 MHz), or a Bruker AM-400 (400 MHz) instrument with $(CH_3)_4Si$ as the internal standard. IR spectra were recorded on a Perkin-Elmer 521, 283, or 727B spectrophotometer in KBr pellets. Mass spectra were obtained on a VG Micro Mass 7035 or a Finnegan Model 9500-3300-1600 instrument. Preparative HPLC was carried out on a Waters Prep LC System 500A instrument using PrepPAK-500/Silica columns. TLC separations were carried out on Whatman K6F or on MK6F silica gel plates with visualization by I_2 or UV. The X-ray crystal structure determination was carried out by Crystallytics Co. of Lincoln, NE. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA, or by Scandinavian Labs, Herlev, Denmark.

Stepwise regression calculations for the QSAR were performed with BMDP2R[19] which was modified for interactive input and output.

Statistics. For the mouse abdominal constriction test, 10–20 animals were used for the nontreated control and each of the drug-treated groups. A minimum of three doses was used to determine each dose–response curve and ED_{50} value (that dose which caused a 50% reduction in the number of animals responding). The ED_{50} values and their 95% fiducial limits were calculated by computer-assisted probit analysis.

For tail-flick and hot-plate tests, 10–20 animals were used in each of the drug-treated groups. The reaction time for a drug-treated animal greater than three standard deviations from the mean of the predrug reaction times for the group was the criterion for analgesia. A minimum of three doses was used to determine each dose–response curve and ED_{50} values, their 95% fiducial limits and the comparison between two ED_{50} values were determined by a computer-assisted probit and relatively potency analysis.

X-ray Crystal Structure Determination. A colorless irregularly shaped crystal of the (−)-enantiomer of **2a** from CH_3CN was measured. The space group was $P2_12_12_1$ with a = 10.067 (2), b = 10.679 (3), and c = 13.447 (3) Å. For z = 4, V = 1445.7 (6) Å^3, and a formula mass 316.88 μ, the calculated density was 1.46 g cm^{-1}. Intensity measurements were with Mo Kα radiation (λ 0.710 73 A; graphite monochromator) on a computer-controlled Four Circle Nicolet Autodiffractometer. A total of 1899 reflections were corrected for Lorentz and polarization effects. The solution of the structure was obtained by heavy atom Patterson techniques yielding coordinates for all atoms in the asymmetric unit. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were entered in ideal calculated positions and were not refined. The correctness of the enantiomeric structure of (−)-**2a** was checked by varying the multiplier of Δf for anomalously scattering Br and Cl atoms. After all shifts/esd ratios were less than 0.1, convergence was reached at R = 0.036 (R_w = 0.031). The final difference density map showed no peaks greater than 0.41 e/Å^3.

Mouse Acetylcholine Bromide-Induced Irritant Test. The procedure with minor modifications was that described by Collier et al.[1] Test drugs or appropriate vehicle were administered by the desired route (volume of 10 mL/kg) and, 30 min later, the animals received an ip injection of 5.5 mg/kg of acetylcholine bromide. The mice were then placed into glass bell jars and observed for 10 min for the occurrence of a single writhe (defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hind limbs). The percentage of inhibition of this response (equated to percentage of analgesia) was calculated for each dose as follows:

$$\text{inhibition (\% analgesia)} = 100 - \left(\frac{\text{no. of responders}}{\text{no. of animals in group}} \times 100\right)$$

Mouse/Rat Tail-Flick Assay. The mouse/rat tail-flick assay described by D'Amour and Smith[2] was used with minor modifications. Animals responded to a focused heat stimulus by "flicking" or removing their tail from the path of the stimulus, thereby exposing a photocell located in the apparatus immediately below the tail. The reaction time was then recorded. At designated times after drug administration, the above procedure was repeated and reaction times compared to predrug reaction times. The reaction time for a drug-treated animal greater than three SDs from the mean of the predrug reaction times for the group was the criterion for analgesia. A minimum of three doses was used to determine each dose–response curve and ED_{50}. The ED_{50} values, their 95% fiducial limits, and the comparison between two ED_{50} values were determined by a computer-assisted probit and relative potency analysis. In some instances raw reaction times were utilized to calculate the % MPE, calculated according to the equation:

$$\%\ \text{MPE} = \frac{\text{reaction time in drug-treated animals} - \text{control reaction time}}{\text{cut-off time} - \text{control reaction time}} \times 100$$

The maximum time an animal was exposed to the noxious stimulus (to prevent tissue damage) was 20 s based on control reaction times generally between 5 and 9 s. The ED_{50} values were measured at the time of peak effect (15 or 30 min).

1-(2-Bromophenyl)-3-(2-pyridinyl)-2-propen-1-one (3a) (Procedure A). A 75-g (0.377-mol) sample of 2-bromoacetophenone was added dropwise over 90 min to a mixture of 75 g (0.70 mol) of pyridine-2-carboxaldehyde, 150 mL of 10% NaOH, and 75 mL of MeOH at 10 °C. It was stirred for 90 min and partitioned between H_2O and Et_2O. The Et_2O layer was washed with brine and dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallized from 2-propanol to give 53 g (50% yield) of yellow solid: mp 67–69 °C; ^{1}H NMR ($CDCl_3$) δ 7.26–6.39 (m, 2 H, CH), 7.39–7.57 (m, 5 H, aromatic CH), 7.64 (d, J = 7.8 Hz, 1 H, CH), 7.74 (t, J = 7.0 Hz, 1 H, pyridine CH), 8.67 (d, J = 4.2 Hz, 1 H, CH). Anal. ($C_{14}H_{10}BrNO$) C, H, N.

1-(3-Bromophenyl)-3-(2-pyridinyl)-2-propen-1-one (3q) (Procedure B). A solution of 49 g (0.24 mol) of 3′-bromoacetophenone and 51.2 g (0.047 mol) of pyridine-2-carboxaldehyde was heated on a steam bath for 25 min under N_2. It was partitioned between EtOAc and $NaHCO_3$ solution. The extract was washed with brine, dried ($MgSO_4$), and filtered through SiO_2. The solvent was evaporated from filtrate and the residue recrystallized twice from 2-PrOH to give 44.6 g of yellow solid: mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 7.31–7.41 (m, 2 H, aromatic CH), 7.49 (d, J = 7.7 Hz, 2 H, CH), 7.71–7.81 (m, 3 H, CH), 8.01–8.08 (m, 2 H, CH), 8.22 (s, 1 H, CH), 8.70 (d, J = 4.8 Hz, 1 H, CH). Anal. ($C_{14}H_{10}BrNO$) C, H, N.

(±)-*trans*-3-(2-Bromophenyl)octahydroindolizine Hydrochloride (2a). A solution of 188 g (0.65 mol) of **3a** in 600 mL of glacial HOAc was hydrogenated over 20 g of 5% Rh on C at 60 psi for 72 h. The catalyst was filtered and the residue partitioned between Et_2O and 3 N NaOH. The Et_2O layer was washed with brine and dried (K_2CO_3) and the solvent evaporated. The oily residue was distilled in a Kugelrohr at 115–160 °C (0.5 Torr) to give 143 g of an oil. Preparative HPLC with 5% Et_2O in hexane gave, after evaporation of solvent, 125 g of oil. The hydrochloride was prepared from MeOH/CH_3CN/HCl. The salt crystallized after evaporation of MeOH, 102 g (72% yield) of white solid, mp 210–217 °C. Further recrystallization from CH_3CN afforded material: mp 211.5–213.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.40–1.52 (m, 1 H, CH_2), 1.77 (d, J = 14 Hz, 1 H, CH_2), 2.02 (d, J = 14 Hz, 1 H, CH_2), 2.28–2.66 (m, 6 H, CH_2), 2.73–2.82 (m, 1 H, CH_2), 3.06–3.12 (m, 1 H, 8a-CH), 3.36 (d, J = 12 Hz, 1 H, CH_2), 4.57 (q, J = 10 Hz, 1 H, 3-CH), 7.25 (t, J = 6 Hz, 1 H, aromatic CH), 7.52 (t, J = 7 Hz, 1 H, aromatic CH), 7.58 (d, J = 8 Hz, 1 H, aromatic CH), 8.79 (d, J = 8 Hz, 1 H, aromatic CH), 12.0 (s, 1 H, NH$^+$); mass spectrum (EI) m/z 280, 279, 252, 251, 200, 172,

(19) *BMDP Biomedical Computer Programs*; University of California Press: Berkeley, 1975; p 491.

124. Anal. ($C_{14}H_{18}BrN$·HCl) C, H, N.

(±)-*cis*-3-(2-Bromophenyl)octahydroindolizine Hydrochloride (4a). The HPLC column from the foregoing experiment was eluted with Et_2O. The solvent was evaporated and a hydrochloride salt prepared from the residual oil with MeOH/CH_3CN/HCl. The solvent was evaporated and the residue recrystallized from CH_3CN to give 1.2 g (1.4% yield) of a white solid: mp 188–190 °C; ^1H NMR ($CDCl_3$) δ 1.44–1.61 (m, 1 H, CH_2), 1.62–2.01 (m, 6 H, CH_2), 2.07–2.48 (m, 2 H, CH_2), 2.53–2.70 (m, 1 H, CH_2), 2.71–2.98 (m, 2 H, CH_2), 3.18–3.37 (m, 1 H, CH_2), 4.1 (br s, 1 H, CH), 5.14 (q, J = 10.2 Hz, CH), 7.18–7.65 (m, 3 H, aromatic CH), 8.47 (d, J = 7.8 Hz, aromatic CH), 12.12 (s, 1 H, NH^+). A second set of peaks (some resolved) due to another conformer was present in the ratio of 3.6:1: 1.17–1.35 (m, 1 H, CH_2), 3.1 (m, 1 H, CH_2), 3.47 (d, J = 10.8 Hz, 1 H, CH_2), 5.68 (m, 1 H, CH), 7.0 (d, J = 7.9 Hz, 1 H, CH aromatic), 12.4 (s, 1 H, NH^+). Anal. ($C_{14}H_{18}BrN$·HCl) C, H, N.

(−)-(*R*)-*trans*-3-(2-Bromophenyl)octahydroindolizine [(−)-2a]. A salt was formed from 228 g (0.81 mol) of (±)-**2a** and 329 g of (+)-di-*p*-toluoyl-L-tartaric acid monohydrate in 2-PrOH. The resulting salt was recrystallized seven times. The salt was partitioned between CH_2Cl_2 and NaOH solution. The CH_2Cl_2 was dried. Anhydrous HCl was added and the HCl salt recrystallized three times from MeOH/CH_3CN from which the CH_3OH was evaporated. There was obtained 33.5 g (13% yield) of white solid: mp 244–253 °C; optical purity (^1H NMR), 98.3%;[20] $[\alpha]^{25}_D$ = −43.26° (0.334 g/10 mL of MeOH). Anal. ($C_{14}H_{18}BrN$·HCl) C, H, N.

(+)-(*S*)-*trans*-3-(2-Bromophenyl)octahydroindolizine [(+)-2a]. The mother liquors from the foregoing experiment were evaporated and converted to the free base. The free base, 184.7 g (0.66 mol) of **2a** enriched in the (+) enantiomer, was combined with 216.6 g (0.66 mol) of di-*p*-toluoyl-L-tartaric acid monohydrate in 2-PrOH to give a salt. Resolution was carried out as in the foregoing experiment. There was obtained 34.5 g (16% yield) of the hydrochloride salt as a white solid: mp 243–252 °C; optical purity by NMR, >99%; $[\alpha]^{25}_D$ = +42.79° (0.3368 g/10 mL of MeOH). Anal. ($C_{14}H_{18}BrN$·HCl) C, H, N.

α-(2,6-Dichlorophenyl)-2-(2-hydroxyethyl)-1-piperidineacetonitrile (6). A 71.5-g (0.31-mol) sample of 2,6-dichlorobenzaldehyde was added over 40 min to a solution of 40 g (0.31 mol) of 2-piperidineethanol and 20.2 g (0.31 mol) of KCN in 100 mL of 3 N HCl. The mixture was stirred for 16 h at 25 °C. The mixture was extracted with Et_2O. The Et_2O solution was washed with brine, dried (K_2CO_3), and concentrated. The residue was triturated twice with hexane and the hexane decanted. There was obtained 80.6 g (83% yield) of crude **6** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.33–2.07 (m, 8 H, CH_2), 2.3 (m, 1 H, CH), 2.52 (s, 1 H, OH), 2.8 (m, 40% of 2 H, CH_2) (diastereomer A), 3.1 (m, 60% of 2 H, CH_2) (diastereomer B), 3.5 (m, 2 H, CH_2O), 5.79 (s, 60% of 1 H, CH) (diastereomer A), 5.83 (s, 40% of 1 H, CH) (diastereomer B), 7.36 (m, 1 H, aromatic CH), 7.39 (d, J = 8 Hz, 2 H, aromatic CH); exact mass spectrum (EI) calculated for $C_{15}H_{18}Cl_2H_2O$ 312.0796, found 312.0786.

α-(2,6-Dichlorophenyl)-2-[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]-1-piperidineacetonitrile (7). A 49.0-g (0.257-mol) sample of *p*-toluenesulfonyl chloride was added in portions to a solution of **6** in 83 mL of pyridine at 5–10 °C. The mixture was stirred with cooling for 2.5 h and then allowed to stir at room temperature for 16 h. The mixture was partitioned between Et_2O and $NaHCO_3$. The Et_2O solution was washed with HCl and brine, treated with charcoal, dried ($MgSO_4$), and concentrated. There was obtained 66.3 (55% yield) of crude **7** as an orange oil: ^1H NMR ($CDCl_3$) δ 1.35–1.90 (m, 8 H, CH_2), 2.2 (q, 6.7 Hz, 1 H, CH), 2.48 (s, 3 H, CH_3), 2.75 (m, 2 H, CH_2N), 4.08 (t, J = 6.5 Hz, CH_2O), 5.59 (s, 0.3 of 1 H, CH), 5.63 (s, 0.7 of 1 H, CH), 7.21–7.42 (m, 5 H, aromatic CH), 7.75 (d, J = 8 Hz, 2 H, aromatic CH); exact mass spectrum calculated for $C_{22}H_{24}Cl_2N_2O_3S$ 466.0884, found 466.0824.

3-Cyano-3-(2,6-dichlorophenyl)octahydroindolizine (8). A solution of 64.2 g (0.137 mol) of **7** in 342 mL of dry DMF was added dropwise over 15 min to a suspension of 0.137 mol of NaH (from 6.6 g of 50% NaH from which the oil had been washed with Et_2O) under Ar. The temperature was maintained between 20 and 30 °C with cooling and the mixture was stirred for 1 h. It was partitioned between brine and Et_2O. The Et_2O was dried ($MgSO_4$) and evaporated to give 42 g (100% yield) of crude product as an orange oil: exact mass spectrum (EI) calculated for $C_{15}H_{18}Cl_2N$ 295.0769, found 295.0732.

3-(2,6-Dichlorophenyl)-1,5,6,7,8,8a-hexahydro-2*H*-indolizinium Perchlorate (9). A 13.0-mL (0.14-mol) sample of 70% $HClO_4$ was added to a solution of 42.1 g of crude **8** in 400 mL of 2-PrOH. The atmosphere over the reaction was flushed into a NaOCl trap. After 16 h the solid was collected and recrystallized from MeOH/2-PrOH to give 27.2 g (52% yield) of a white solid. An analytical sample was recrystallized from anhydrous EtOH: mp 145–146 °C; ^1H NMR (Me_2SO-d_6) δ 1.53–1.80 (m, 3 H, CH_2), 1.89 (d, J = 12 Hz, 1 H, CH_2), 1.97 (d, J = 12 Hz, 1 H, CH_2), 2.04–2.15 (m, 1 H, CH_2), 1.97 (d, J = 12 Hz, 1 H, CH_2), 2.04–2.15 (m, 1 H, CH_2), 2.63–2.76 (m, 1 H, CH_2), 3.61 (br s, 2 H, CH_2), 3.86 (br s, 2 H, CH_2), 4.79 (br s, 1 H, CH), 7.70–7.82 (m, 3 H, aromatic CH). Anal. ($C_{14}H_{15}Cl_2N$·$HClO_4$) C, H.

***trans*-3-(2,6-Dichlorophenyl)octahydroindolizine Hydrochloride (2 g).** A 6.9-g (0.11-mol) sample of $NaBH_3CN$ was added to a suspension of **9** in 73 mL of MeOH. MeOH/HCl was added over 20 min until the pH stayed between 3 and 4. After 1 h an additional 4.6 g (0.07 mol) of $NaBH_3CN$ was added and the pH was again adjusted to 3–4. The mixture was stirred for 16 h and then acidified with HCl until gas evolution ceased. The mixture was made basic by the addition of NaOH and extracted with Et_2O. The Et_2O was extracted with HCl. The acidic aqueous extract was made basic with NaOH and extracted with Et_2O. The Et_2O extract was washed with brine, dried (K_2CO_3), and evaporated. The residue was purified by preparative HPLC using 5% Et_2O in hexane. The solvent was evaporated and a salt prepared from CH_3CN/HCl which was recrystallized from CH_3CN/Et_2O to give 14.0 g (63% yield) of a white solid: mp 206–208 °C; ^1H NMR ($CDCl_3$) δ 1.38–1.52 (m, 1 H, CH_2), 1.72 (d, J = 14 Hz, 1 H, CH_2), 2.02 (t, J = 14 Hz, CH_2), 2.26–2.38 (m, 2 H, CH_2), 2.47–2.60 (m, 1 H, CH_2), 2.70–2.86 (m, 2 H, CH_2), 2.92–3.13 (m, 3 H, CH, CH_2), 3.62 (d, J = 10 Hz, 1 H, CH_2), 5.09 (m, 1 H, 3 CH), 7.21–7.31 (m, 1 H, aromatic CH), 7.39 (d, J = 7.5 Hz, aromatic CH), 7.48 (d, J = 7.8 Hz, 1 H, aromatic CH), 11.0 (br s, 1 H, NH^+). Anal. ($C_{14}H_{17}Cl_2N$·HCl) C, H, N.

***trans*-3-[2-(Methylthio)phenyl]octahydroindolizine Hydrobromide (2m).** A solution of 29.8 mL (0.048 mol) of 1.6 M *n*-BuLi in hexane was added over 5 min to a solution of 8.9 g (0.0317 mol) of **2a** in 300 mL of anhydrous Et_2O under N_2. The mixture was stirred for 2 h. An additional 20 mL (0.031 mol) of *n*-BuLi was added. The mixture was stirred for 50 min. The mixture was cooled to 5 °C and 10 mL (0.11 mol) of $(CH_3S)_2$ was added. The mixture was stirred at 25 °C for 16 h and was partitioned between Et_2O and H_2O. The Et_2O layer was washed with brine and dried (K_2CO_3) and the solvent evaporated. The residue was concentrated under reduced pressure for 4 h. A hydrobromide salt was prepared from *t*-BuOH. It was recrystallized twice from MeOH/*t*-BuOH to give 7.4 g (71% yield) of a white solid: mp 198–200 °C; ^1H NMR ($CDCl_3$) δ 1.50 (m, 1 H, CH_2), 1.76 (d, J = 14 Hz, 1 H, CH_2), 2.01 (d, J = 16 Hz, 1 H, CH_2), 2.04 (d, J = 16 Hz, 1 H, CH_2), 2.32 (m, 1 H, CH_2), 2.48 (s, 3 H, CH_3), 2.41–2.53 (m, 4 H, CH_2), 2.55–2.61 (m, 1 H, CH_2), 2.87–2.97 (m, 1 H, CH_2), 3.14–3.21 (m, 1 H, 8a-CH), 3.35 (d, J = 11 Hz, 1 H, CH_2), 4.73 (q, J = 9.5 Hz, 1 H, 3-CH), 7.27–7.41 (m, 3 H, aromatic CH), 8.72 (d, J = 7.5 Hz, aromatic CH), 12.06 (s, 1 H, NH^+). Anal. ($C_{15}H_{21}NS$·HBr) C, H, N.

***trans*-3-[2-(Methylsulfinyl)phenyl]octahydroindolizine Perchlorate (2n).** A solution of 4.2 g of 4m base (0.017 mol), 3.26 g (0.018 mol) of 48% HBF_4, and 8.67 mL (0.085 mol) of 30% H_2O_2 in 200 mL of glacial HOAc was stirred at 25 °C until the **4m** disappeared by TLC. It was treated with $Na_2S_2O_3$ and partitioned between NaOH and CH_2Cl_2. The CH_2Cl_2 was dried (K_2CO_3) and concentrated to dryness. The residue was taken up in Et_2O, filtered, and concentrated to dryness. A perchlorate salt was prepared from EtOH and recrystallized from MeOH. There was obtained 1.83 g (32% yield) of white solid: mp 190–214 °C;

(20) Villani, F. J.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. Determination of Enantiomeric Purity of Tertiary Amines by Proton NMR of α-Methoxy-α-(trifluoromethyl)phenyl Acetic Acid Complexes. *J. Org. Chem.* **1986**, *51*, 3715–3718.

^{1}H NMR (Me_2SO-d_6) δ 1.33–2.00 (m, 7 H, CH_2), 2.01–2.10 (m, 2 H, CH_2), 2.22–2.34 (m, 1 H, CH_2), 2.57–2.70 (m, 1 H, CH_2), 2.72 (s, 26% of 3 H, diastereomeric CH_3), 2.81 (s, 75% of 3 H, diastereomeric CH_3), 2.85–3.0 (m, 1 H, 8a-CH), 3.15 (d, J = 11 Hz, CH_2), 4.64 (q, J = 9 Hz, 26% of 1 H, 3 CH), 4.86 (q, J = 9 Hz, 74% of 1 H, 3 CH), 7.70–7.77 (m, 2 H, aromatic CH), 7.85 (d, J = 7 Hz, 1 H, aromatic CH), 7.97 (d, J = 8.5 Hz, 1 H, aromatic CH), 8.97 (s, 1 H, NH^+). Anal. ($C_{15}H_{21}NOS{\cdot}HClO_4{\cdot}0.25H_2O$) C, H, N.

***trans*-3-(4-Hydroxyphenyl)octahydroindolizine Hydrochloride (2p).** A solution of 9.6 g (0.031 mol) of **2o** in 350 mL of EtOH was hydrogenated at 60 psi in a Parr shaker over 0.7 g of Pd on C for 16 h. An additional 0.7 g of catalyst was added and the hydrogenation was continued for 20 h. The catalyst was filtered, the solvent was evaporated, and the residue was partitioned between NaOH and Et_2O. The NaOH solution was acidified with HCl and then brought to pH 8 with $NaHCO_3$ and extracted with Et_2O. The Et_2O was washed with brine, dried (Na_2SO_4), and evaporated. A hydrochloride salt was prepared from 2-PrOH/HCl. It was recrystallized from MeOH/2-PrOH to give 2.45 g (30% yield) of white solid: mp 239–244 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.32–1.46 (m, 1 H, CH_2), 1.55–2.00 (m, 6 H, CH_2), 2.10–2.40 (m, 3 H, CH_2), 2.78 (q, J = 11 Hz, 1 H, CH_2), 2.94 (d, J = 11 Hz, 1 H, CH_2), 3.13–3.22 (m, 1 H, 8a-CH), 4.17 (q, J = 9 Hz, 1 H, 3-CH), 6.82 (d, J = 8.5, 2 H, aromatic CH), 7.45 (d, J = 8.5, 2 H, aromatic CH), 9.61 (s, 1 H, NH^+), 9.81 (s, 1 H, OH). Anal. ($C_{14}H_{19}NO{\cdot}HCl$) C, H, N.

1-(2-Nitrophenyl)-3-(2-pyridinyl)propan-1-one Hydrochloride (15). A 51.3-mL (0.185-mol) sample of n-Bu_3SnH was added to a solution of 39.2 g (0.154 mol) of 1-(2-nitrophenyl)-3-(2-pyridinyl)-2-propenone, 1.78 g (1.54 mmol) of $[Ph_4P]Pd(0)$, and 9.27 mL (0.162 mol) of glacial HOAc in 525 mL of toluene under Ar at 25 °C.[21] After 90 min the mixture was extracted with 3 N HCl. The extract was made basic with $NaHCO_3$ and extracted with Et_2O. The Et_2O was dried (K_2CO_3) and the solvent evaporated to give 39.5 g (100% yield) of a yellow solid. A portion was converted to the hydrochloride salt with ethereal HCl and recrystallized from 2-PrOH to give a solid: mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (d, J = 5.7 Hz, 2 H, CH_2), 3.75 (d, J = 5.7 Hz, 2 H, CH_2), 7.54–7.67 (m, 2 H, CH), 7.74–7.83 (m, 2 H, CH), 7.98 (d, J = 8 Hz, 1 H, CH), 8.08 (d, J = 8 Hz, 1 H, CH), 8.33 (t, J = 8 Hz, 1 H, CH), 8.66 (d, J = 6 Hz, 1 H, CH), 14.6 (s, 1 H, NH^+). Anal. ($C_{14}H_{12}N_2O_3{\cdot}HCl$) C, H, N.

***trans*-3-(2-Aminophenyl)octahydroindolizine Hydrochloride (2r).** A solution of 37.5 g (0.146 mol) of **15** free base in 3.50 mL of glacial HOAc was hydrogenated over 0.68 g of PtO_2 at 60 psi for 15 h. The catalyst was filtered and the solvent partially evaporated. It was partitioned between Et_2O and NaOH. The Et_2O solution was washed with water and brine, dried (K_2CO_3), and concentrated. The residue was purified by preparative HPLC using 5% EtOAc in hexane as eluant. The solvent was evaporated to give 20.2 g of an oil (64% yield). A portion was converted to the hydrochloride salt from t-BuOH/HCl. It was recrystallized from t-BuOH/H_2O to give a white solid: mp 160–229 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.37–1.50 (m, 1 H, CH_2), 1.60–2.07 (m, 7 H, CH_2), 2.20–2.33 (m, 1 H, CH_2), 2.33–2.44 (m, 1 H, CH_2), 2.92–3.08 (m, 2 H, CH_2), 4.62 (t, J = 9 Hz, 1 H, CH), 6.72 (t, J = 7 Hz, 1 H, aromatic CH), 6.78 (d, J = 8 Hz, 1 H, aromatic CH), 7.13 (t, J = 7 Hz, 1 H, aromatic CH), 7.65 (d, J = 7.5 Hz, 1 H, aromatic CH), 9.5 (br s, 1.3 H, NH^+). Anal. ($C_{14}H_{20}N_2{\cdot}^4/_3HCl$) C, H, N.

***trans*-3-(2-Cyanophenyl)octahydroindolizine Hydrochloride (2w).** A sample of 8.0 g (0.0286 mol) of **2a** was dissolved in 29 mL of dry pyridine under Ar, and 3.84 g (0.042 mol) of CuCN and 0.15 g (0.13 m mol) of $[Ph_4P]Pd(0)$ were added. The mixture was heated under reflux for 65 h. The mixture was partitioned between Et_2O and concentrated NH_4OH. The Et_2O layer was washed with NH_4OH and brine and dried (K_2CO_3). The salt was prepared from CH_3CN/HCl. It was recrystallized twice from MeOH/CH_3CN to give 4.36 g (58% yield) of a white solid: mp 236–239 °C; ^{1}H NMR ($CDCl_3$) δ 1.40–1.55 (m, 1 H, CH_2), 1.80 (d, J = 14 Hz, 1 H, CH_2), 2.04 (d, J = 12 Hz, 1 H, CH_2), 2.30–2.45 (m, 2 H, CH_2), 2.52–2.81 (m, 5 H, CH_2), 3.07–3.21 (m, 1 H, 8a-CH), 3.31 (d, J = 11 Hz, 1 H, CH_2), 4.38 (q, J = 9 Hz, 1 H, 3-CH), 7.54 (t, J = 8 Hz, 1 H, aromatic CH), 7.71 (d, J = 7.5 Hz, 1 H, aromatic CH), 7.83 (t, J = 8 Hz, 1 H, aromatic CH), 8.95 (d, J = 8 Hz, 1 H, aromatic CH). Anal. ($C_{15}H_{18}N_2{\cdot}HCl$) C, H, N.

***trans*-*N*-[4-[[4-(Octahydro-3-indolizinyl)phenyl]thio]phenyl]acetamide Hydrochloride (2y).** A solution of 11.9 g (0.073 mol) of 4-acetamidothiophenol in 180 mL of dry n-BuOH was added to a solution of 0.073 mol of n-BuONa in 60 mL of n-BuOH under Ar. A solution of 26.5 g (0.073 mol) of **2d** and 3.2 g (2.8 mmol) of $[Ph_4P]_4Pd(0)$ in 60 mL of n-BuOH was added and the mixture heated under reflux for 16 h. The solvent was evaporated and the residue was partitioned between Et_2O and H_2O. The Et_2O layer was washed with brine and dried (K_2CO_3) and the solvent evaporated. The residue was flash chromatographed on SiO_2 using 15% acetone in hexane as eluant. The solvent was evaporated and the residual solid was recrystallized from EtOAc–hexane. A hydrochloride salt was prepared from ethereal HCl. There was obtained 11.5 g (30% yield) of a white solid: mp 148–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.37–1.51 (m, 1 H, CH_2), 1.53–1.70 (m, 1 H, CH_2), 1.97 (d, J = 12 Hz, 1 H, CH_2), 2.20 (s, 3 H, CH_3), 2.31–2.64 (m, 7 H, CH_2), 2.90–3.04 (m, 1 H, 8a-CH), 3.11 (d, J = 10 Hz, 1 H, CH_2), 3.80–3.90 (m, 1 H, 3-CH), 7.06 (d, J = 8 Hz, 2 H, aromatic CH), 7.32 (d, J = 8 Hz, 2 H, aromatic CH), 7.56 (d, J = 8 Hz, 2 H, aromatic CH), 7.69 (d, J = 8 Hz, 2 H, aromatic CH), 8.44 (s, 1 H, NH), 11.40 (s, 1 H, NH^+). Anal. ($C_{22}H_{26}N_2OS{\cdot}HCl{\cdot}0.5H_2O$) C, H.

***trans*-3-[4-[(4-Chlorophenyl)thio]phenyl]octahydroindolizine Hydrochloride (2z).** A solution of 4.1 g (0.028 mol) of 4-chlorothiophenol in 40 mL of dry N-methylpyrrolidinone was added to 0.028 mol of NaH (from 1.36 g of 50% NaH washed free of oil with hexane) under N_2. A solution of 5.3 g (0.019 mol) of **2d** in 50 mL of N-methylpyrrolidinone was added. A 1.35-g sample of CuI was added. The mixture was heated under reflux for 16 h. MeOH was added and the solution was filtered. The solvent was evaporated and the residue was flash chromatographed on SiO_2 using 2% acetone in hexane as eluant. The solvent was evaporated, ethereal HCl was added, and the salt was recrystallized from CH_3CN to give 0.77 g (7% yield) of a white solid: mp 198–201 °C; ^{1}H NMR ($CDCl_3$) δ 1.26–1.50 (m, 1 H, CH_2), 1.74 (t, J = 11 Hz, 1 H, CH_2), 1.97 (t, J = 12 Hz, 2 H, CH_2), 2.14–2.58 (m, 6 H, CH_2), 2.60–2.77 (m, 1 H, CH_2), 2.87–3.04 (m, 1 H, 8a-CH), 3.25 (d, J = 10 Hz, 1 H, CH_2), 3.75 (q, J = 9 Hz, 1 H, 3-CH), 7.16–7.39 (m, 6 H, aromatic CH), 7.68–7.87 (m, 2 H, aromatic CH), 11.9 (br s, 1 H, NH^+). Anal. ($C_{20}H_{22}ClNS{\cdot}HCl$) C, H, N.

***trans*-5-(4-Bromophenyl)hexahydro-7(8*H*)-indolizinone Hydrochloride (10).** To a solution of 96.8 g (0.54 mol) of 4-aminobutyraldehyde diethyl acetal (90% technical) in 400 mL of EtOH were added 200 mL of 3 N HCl, 109.2 g (0.54 mol) of diethyl acetonedicarboxylate, and 100 g (0.54 mol) of 4-bromobenzaldehyde. The solution was allowed to stand at 25 °C for 5 days. The mixture was neutralized with 10% aqueous K_2CO_3 and extracted with Et_2O. The Et_2O was extracted with 1 L of 6 N HCl. The acid aqueous solution was heated under reflux for 16 h. The mixture was cooled, made basic with NaOH, and extracted with Et_2O. The Et_2O solution was dried (K_2CO_3) and concentrated. The residue was flash chromatographed on SiO_2 using 5% acetone in hexane as eluant. The solvent was evaporated to give 14.7 g (9% yield) of a solid: mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 1.40–2.05 (m, 5 H, CH_2), 2.20–2.47 (m, 5 H, CH_2), 2.71 (t, J = 10 Hz, 1 H, CH), 3.07–3.30 (m, 1 H, 5-CH), 7.10 (d, J = 9 Hz, 2 H, aromatic CH), 7.35 (d, J = 9 Hz, 2 H, aromatic CH). Anal. ($C_{13}H_{16}BrNO$) C, H, N.

***trans*-5-(4-Bromophenyl)octahydroindolizine Hydrochloride (11).** To a solution of 14.7 g (0.05 mol) of **10** in 150 mL of 2-hydroxyethyl ether was added 3.2 mL (0.1 mol) of anhydrous NH_2NH_2. The solution was heated at 95 °C for 1 h. A 5.6-g (0.1-mol) sample of KOH was added and the mixture was heated until the temperature reached 235 °C. The distillate and the pot residue were diluted with H_2O and extracted with Et_2O. The combined Et_2O solution was dried (K_2CO_3) and evaporated. Volatile materials were removed from the resulting oil by distillation in a Kugelrohr. The pot residue was treated with ethereal HCl and the salt recrystallized from 2-PrOH to give 4.4 g (28% yield) of a white solid: mp 264–267 °C; ^{1}H NMR ($CDCl_3$) δ

(21) Keinen, E.; Glieze, P. A. Organo Tin Nucleophiles IV. Palladium Catalyzed Conjugate Reduction with Tin Hydride. *Tetrahedron Lett.* **1982**, *23*, 477–480.

1.68-1.72 (m, 1 H, CH_2), 1.86-2.01 (m, 1 H, CH_2), 2.04-2.27 (m, 5 H, CH_2), 2.35-2.64 (m, 4 H, CH_2), 2.91-3.05 (m, 1 H, CH), 3.23-3.34 (m, 1 H, CH_2), 3.60-3.68 (m, H, 5-CH), 7.55 (d, J = 8.5 Hz, 2 H, aromatic CH), 7.73 (br s, 2 H, aromatic CH), 12.5 (br s, 1 H, NH^+). Anal. ($C_{14}H_{18}BrN$·HCl) C, H, N.

***trans*-3-Cyclohexyloctahydroindolizine Hydrochloride (12).** A solution of 20 g of **3b** in 96 mL of glacial HOAc was hydrogenated over 2.95 g of 5% Rh on C at 60 psi. Daily additions of 2.95 g of 5% Rh on C were made for 4 days. On day 5, 5.9 g of catalyst was added. After 13 days total, the catalyst was filtered and the solvent evaporated. The residue was partitioned between NaOH solution and Et_2O. The Et_2O solution was washed with brine, dried (K_2CO_3), and evaporated. The residue was distilled in a Kugelrohr at 110-160 °C (1.2 Torr). The distillate was purified by preparative HPLC using 5% EtOAc in hexane as eluant. The solvent was evaporated and a salt prepared from MeOH/EtOAc/HCl. The salt was recrystallized twice from CH_2Cl_2/THF to give 2.74 g (14% yield) of white solid: mp 199-202 °C; ^1H NMR ($CDCl_3$) δ 1.0-2.30 (m, 19 H, CH_2), 2.45-2.90 (m, 5 H, CH, CH_2), 3.8-3.92 (m, 1 H, CH), 11.6 (s, 1 H, NH^+). Anal. ($C_{14}H_{25}$·HCl) C, H, N.

Acknowledgment. We are indebted to Philip Pitis for synthetic assistance, to Roger Scott and Joanne Mathiasen for pharmacological assistance, to Frank Villani for helpful discussions, and to Gary Caldwell and the staff of the spectroscopy group for spectra. We thank Professor Allyn Howlett for determination of binding to the cannabinoid receptor.

Supplementary Material Available: Tables listing atomic coordinates for non-hydrogen and hydrogen atoms in crystalline $BrC_{14}H_{19}NCl$, bond lengths, and band angles (5 pages). Ordering information is given on any current masthead page.

New Antiinflammatory Agents. 2.† 5-Phenyl-3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones: A New Class of Nonsteroidal Antiinflammatory Agents with Potent Activity Like Glucocorticoids

Fumio Suzuki,* Takeshi Kuroda, Tadafumi Tamura, Soichiro Sato, Kenji Ohmori, and Shunji Ichikawa

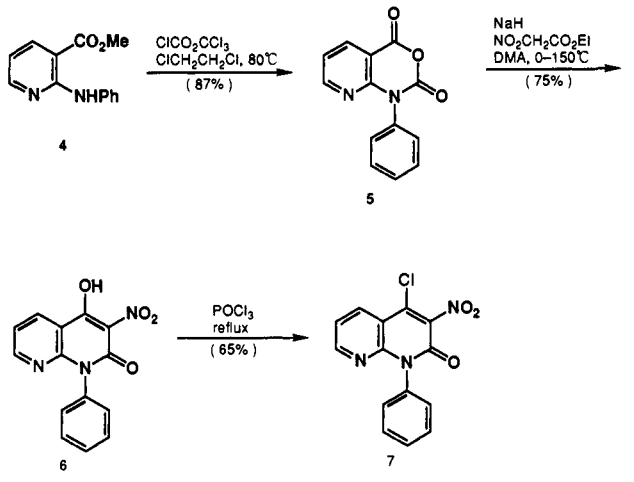
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Company, Ltd., 1188 Shimotogari, Nagaizumi-cho, Shizuoka 411, Japan. *Received January 2, 1992*

We previously described new antiinflammatory agents, 4-hydroxy-2-oxo-1-phenyl-1*H*-1,8-naphthyridine-3-carboxamides 1. Further modification of the compounds bearing 1-phenyl-1,8-naphthyridin-2-one as a mother skeleton led to 5-phenylimidazo[4,5-c][1,8]naphthyridin-4(5*H*)-one derivatives **2** and **3**. Regioselective synthesis of these compounds bearing a substituent at the 1- or 3-position was conducted according to the method shown in Schemes I and II. In this series of compounds, antiinflammatory activities were greatly influenced by the position and nature of substituents on imidazole. 3-Alkyl or 3-benzyl substitution resulted in the potent activity, but 1-substitution did not. Minor modification of the benzyl group reduced or eliminated the activity. Detailed examination of structure–activity relationships led to 3-benzyl-5-phenyl-3*H*-imidazo[4,5-c][1,8]naphthyridin-4(5*H*)-one (**22**), which exhibited potent oral antiinflammatory activities in carrageenan-, zymosan-, and reversed passive Arthus reaction-induced rat paw edemas (ED_{40} = 5.3, 0.37 mg/kg, ED_{50} = 0.47 mg/kg, respectively). This broad activity of **22** was like that of glucocorticoids. Compound **22** did not affect activities of CO and 5-LO enzymes and receptor binding of various ligands. As one of the mechanisms of action, induction of release of glucocorticoids was postulated. These results suggest that **22** represents a novel class of antiinflammatory agents.

Introduction

Glucocorticosteroids are used as useful therapeutic drugs toward patients with severe arthritis, but with systemic side effects often preclude chronic use at efficacious doses.[1] Since the discovery of aspirin, much effort has been devoted to the development of nonsteroidal acidic antiinflammatory drugs (NSAIDs). Although these drugs reduce symptoms of chronic inflammatory diseases and do not show glucocorticosteroid-like side effects, none of them prevent progression of arthritis. This limited effectiveness may be attributed to their mechanism of action, mainly only cyclooxygenase (CO) inhibition.[2] This situation has caused many laboratories to develop a new type of antiinflammatory agents. For example, dual cyclooxygenase-/5-lipoxygenase (CO/5-LO) inhibitors have been discovered,[3] some of which are under clinical evaluation. In addition, as other instances, a new class of antiinflammatory agent, *N*-[(fluorenyl-9-methoxy)carbonyl]amino acids has been recently reported by Burch et al.[4] to possess a broad spectrum of antiinflammatory activity with no CO inhibition and very weak LO inhibition. Gans et al. reported that Dup 697 is a potent orally effective antiinflammatory agent with less toxicity due to tissue selective inhibition of PG synthesis.[5] NE-19550 and NE-28345 are orally active antiinflammatory analgesics derived from the capsaicin class and do not act like conventional NSAIDs via suppression of arachidonic acid metabolism.[6]

Scheme I



† Part 1 in a series of New Antiinflammatory Agents is ref 7.

(1) Silber, R. H.; Busch, R. D.; Oslaps, R. Practical Procedure for Estimation of Corticosteron or Hydrocortisone. *Clin. Chem.* 1958, *4*, 278-285.
(2) (a) Vane, J. R. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin Like Drugs. *Nature (New Biol.)* 1971, *231*, 232-235. (b) Flower, R. J. Drugs which Inhibit Prostaglandin. Biosynthesis. *Pharmacol. Rev.* 1974, *26*, 33-71.

0022-2623/92/1835-2863$03.00/0