dioxane–ether afforded analytically pure **21a** in 36.6% yield. Properties of **21a** are included in Table I.

Biological Methods. Procedural details for the inhibition of synaptosomal biogenic amine uptake,[11] inhibition of monoamine oxidase,[11] prevention of tetrabenazine-induced ptosis,[5] potentiation of 5-hydroxytryptophan-induced stereotypy,[5] and protection against amphetamine aggregation toxicity[12] were previously reported; inhibition of supramaximal electroshock was carried out by the method of Woodbury and Davenport[7] with minor modifications.

Acknowledgment. The authors express their appreciation to Marc N. Agnew and Anastasia Rizwaniuk for spectral data and to Susan Bullock and Mark Szewczak for contributions to the biological evaluation. We also gratefully acknowledge June D. Baird-Strupczewski and Ann Van Dine for library research and Rose Marie Boysen for assistance in preparation of the manuscript.

Registry No. **1a**, 326-62-5; **1b**, 75279-53-7; **2a**, 69584-88-9; **2b**, 75391-75-2; **3a**, 69584-91-4; **3b**, 75391-76-3; 4a, 85422-38-4; **4a** base, 85422-39-5; **5a**, 69585-02-0; **5a**·HCl, 85422-40-8; **6a** maleate, 75391-66-1; **6b** maleate, 75391-81-0; **7a**·HBr, 75391-63-8; **8a** maleate, 75391-70-7; **8b** maleate, 75391-86-5; **9a**, 81049-97-0; **9a** base, 81049-98-1; **10a**, 69584-97-0; **11b** maleate, 75391-78-5; **12a**, 69584-99-2; **13a**, 69584-96-9; **14a**, 69585-08-6; **14b**, 75391-96-7; **15a**·2HCl, 75391-69-4; **15b**, 75391-93-4; **15b** base, 85422-41-9; **16a**, 69585-03-1; **17a**, 75391-72-9; **17b**, 75391-82-1; **18a**, 69585-01-9; **19a**, 81049-94-7; **20a**, 81049-89-0; **20b**, 75391-88-7; **21a**, 81049-99-2; **22b**, 75391-89-8; **23b**, 75391-84-3; **23b** base, 75391-83-2; **24a** maleate, 75391-67-2; **25a** maleate, 81049-96-9; **26a**, 81049-91-4; **26a** base, 81049-90-3; **26a** maleate, 85422-42-0; **26b**, 75391-91-2; **26b** base, 75391-90-1; **27a**·2HCl, 81049-93-6; **27b**·2HCl, 75401-59-1; 2,2′-dichloro-*N*-methyldiethylamine, 51-75-2; fluorobenzene, 462-06-6; 2-fluoropyridine, 372-48-5; *o*-fluoronitrobenzene, 1493-27-2; phenyl chloroformate, 1885-14-9; *o*-difluorobenzene, 367-11-3; *p*-difluorobenzene, 540-36-3; *o*-chlorofluorobenzene, 348-51-6; *p*-chlorofluorobenzene, 352-33-0; *o*-(trifluoromethyl)fluorobenzene, 392-85-8; *m*-(trifluoromethyl)fluorobenzene, 401-80-9; *p*-(trifluoromethyl)fluorobenzene, 402-44-8.

Synthesis and Anticonvulsant Activity of Some Tetracyclic Indole Derivatives

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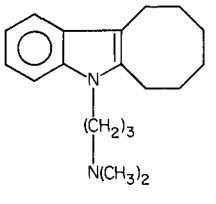
Several related series of cycloalkyl[4,5]pyrrolo[3,2,1-*ij*]quinolines **7a–g**, **8a–c**, **10a–e**, and **16a–f** and indolo[3,2,1-*hi*]indoles **22a–c** and **23a,b** were synthesized and tested for anticonvulsant activity. The key preparative step, a Fischer indole reaction between a bicyclic hydrazine and a cyclic ketone, gave the compounds in 34–96% yield. The products were tested in rat maximal electroshock for anticonvulsant activity. Several compounds showed good activity, with 6-[(dimethylamino)methyl]-4,5,6,8,9,10-hexahydrocyclopenta[4,5]pyrrolo[3,2,1-*ij*]quinoline (**7d**) and *N*-methyl-4,5,6,8,9,10,11,12-octahydrocycloheptа[4,5]pyrrolo[3,2,1-*ij*]quinoline-6-carboxamide (**10c**) having ED_{50}'s of 12.5 and 12.9 mg/kg po, respectively.

After preparing a number of tetracyclic analogues of the antidepressant iprindole (**1**),[1] we found that several of the



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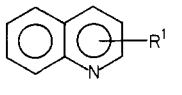
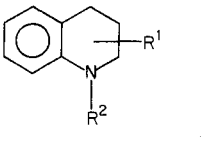
compounds showed activity in an anticonvulsant screen and, therefore, set out to investigate the structural parameters of this activity. In this report we describe the preparation and anticonvulsant activity of these tetracyclic indole derivatives.

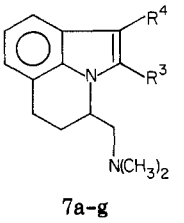
Chemistry. A number of different tetracyclic ring systems were synthesized. One series of indoles, **7**, was prepared starting with quinaldic acid (**2a**). Conversion of **2a** to dimethyl amide **3a**, followed by hydrogenation, gave tetrahydroquinoline **4a**, which was converted to a key hydrazine intermediate, **5a**, by nitrosation with acidic sodium nitrite, followed by lithium aluminum hydride reduction. Fischer indolization of **5a** with cyclic ketones in hot glacial acetic acid afforded a series of indole products, **7a–g**. An isomeric series, **8a–c**, was prepared following the



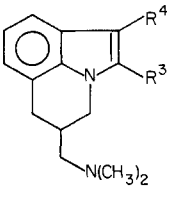
2a, R^1 = 2-CO_2H
b, R^1 = 3-CO_2H
3a, R^1 = 2-$CON(CH_3)_2$
b, R^1 = 3-$CON(CH_3)_2$
12, R^1 = 2-CH_2CH_2Cl
13, R^1 = 2-$CH_2CH_2N(CH_3)_2$



4a, R^1 = 2-$CON(CH_3)_2$; R^2 = H
b, R^1 = 3-$CON(CH_3)_2$, R^2 = H
5a, R^1 = 2-$CH_2N(CH_3)_2$; R^2 = NH_2
b, R^1 = 3-$CH_2N(CH_3)_2$; R^2 = NH_2
6a, R^1 = 2-CO_2CH_3, R^2 = H
b, R^1 = 2-CO_2CH_3; R^2 = NH_2
14, R^1 = 2-$CH_2CH_2N(CH_3)_2$; R^2 = H
15, R^1 = 2-$CH_2CH_2N(CH_3)_2$; R^2 = NH_2



7a–g



8a–c

above route starting with quinoline-3-carboxylic acid (**2b**). Several indolamides, **10a–e**, were also prepared analogously via tetrahydroquinaldic ester **6a**, which was converted to

(1) Gluckman, M. I.; Baum, T. *Psychopharmacologia* **1969**, *15*, 169.

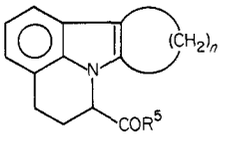
0022-2623/83/1826-0986$01.50/0

Table I. Tetracyclic Indoles

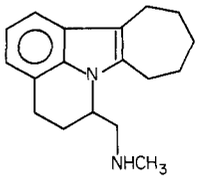
compd	R^3	R^4	emp formula	mp,[a] °C	yield,[b] %	recrystn solvent[c]
7a	$-(CH_2)_6-$		$C_{20}H_{28}N_2 \cdot HCl$	232-233	75	A
7b	$-(CH_2)_5-$		$C_{19}H_{26}N_2 \cdot HCl \cdot 0.25H_2O$	247-249	70	A
7c	$-(CH_2)_4-$		$C_{18}H_{24}N_2 \cdot HCl$	243-245	67	A-B
7d	$-(CH_2)_3-$		$C_{17}H_{22}N_2 \cdot HCl$	215-216	37	C-B
7e	$-CH_2CH_2SCH_2-$		$C_{17}H_{22}N_2S \cdot HCl \cdot 0.25H_2O$	281 dec	74	C
7f	$-C_6H_4CH_2CH_2-$		$C_{22}H_{24}N_2 \cdot HCl$	138-139	55	D
7g	$-C_6H_4SCH_2-$		$C_{21}H_{22}N_2S \cdot HCl$	247-249	37	A
8a	$-(CH_2)_6-$		$C_{20}H_{28}N_2 \cdot C_4H_4O_4$	201-203	62	A-B
8b	$-(CH_2)_5-$		$C_{19}H_{26}N_2 \cdot C_4H_4O_4$	218 dec	62	C
8c	$-CH_2C_6H_4-$		$C_{21}H_{22}N_2 \cdot C_4H_4O_4$	118 dec	57	C
10a	$-(CH_2)_5-$		$C_{19}H_{24}N_2O$	178-180	16	B
10b	$-(CH_2)_5-$		$C_{22}H_{29}N_3O \cdot HCl$	237-238	39	A
10c	$-(CH_2)_5-$		$C_{18}H_{22}N_2O$	186-188	63	D
10d	$-(CH_2)_4-$		$C_{17}H_{20}N_2O$	201-203	62	B
10e	$-(CH_2)_3-$		$C_{16}H_{18}N_2O$	191-192	58	E
11	$-(CH_2)_5-$		$C_{18}H_{24}N_2 \cdot HCl$	271-273	68	C-B
16a	$-(CH_2)_6-$		$C_{21}H_{30}N_2 \cdot C_4H_4O_4$	179-181	54	A
16b	$-(CH_2)_5-$		$C_{20}H_{28}N_2 \cdot C_4H_4O_4$	183-184	46	A
16c	$-(CH_2)_4-$		$C_{19}H_{26}N_2 \cdot C_4H_4O_4$	179-180	67	A
16d	$-(CH_2)_3-$		$C_{18}H_{24}N_2 \cdot C_4H_4O_4$	125-127	62	A
16e	$-CH_2CH_2SCH_2-$		$C_{18}H_{24}N_2S \cdot HCl$	233-234	65	A
16f	$-CH_2CH_2N(CH_3)CH_2-$		$C_{19}H_{27}N_3 \cdot 2C_4H_6O_6 \cdot 2H_2O$	106-108	34	C
22a	$-(CH_2)_6-$		$C_{19}H_{26}N_2 \cdot HCl$	217-218	73	A
22b	$-(CH_2)_5-$		$C_{18}H_{24}N_2 \cdot HCl$	217-218	65	A
22c	$-(CH_2)_4-$		$C_{17}H_{22}N_2 \cdot C_4H_4O_4$	212 dec	96	C
23a	$-(CH_2)_6-$		$C_{19}H_{26}N_2 \cdot C_4H_4O_4$	175-176	55	A
23b	$-(CH_2)_5-$		$C_{18}H_{24}N_2 \cdot C_4H_4O_4$	190-192	55	A

[a] All products were racemic. All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structures. [b] Value indicates isolated yield for final step. [c] Abbreviations are as follows: A = 2-propanol; B = diethyl ether; C = ethanol; D = methanol; E = petroleum ether.

hydrazine **6b** by nitrosation, followed by zinc reduction.[2] Indolization of **6b** with cyclic ketones produced esters **9a–c**. Aminolysis of **9a–c** afforded amide products **10a–e**. Also, **10c** was reduced with lithium aluminum hydride to yield **11**.



	n	R^5
9a	5	OCH_3
b	4	OCH_3
c	3	OCH_3
10a	5	$N(CH_3)_2$
b	5	c-$N(CH_2CH_2)_2N$-CH_3
c	5	$NHCH_3$
d	4	$NHCH_3$
e	3	$NHCH_3$



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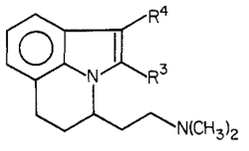


16a-f

A homologous series related to **7** was synthesized starting from 2-(2-chloroethyl)quinoline (**12**). Alkylation of dimethylamine with **12** produced **13**, which was converted to tetrahydroquinoline **14** by catalytic hydrogenation. This amine was then converted as described above via hydrazine **15** to another series of indole products, **16a–f**.

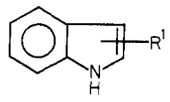
(2) Hartman, W. W.; Roll, L. J. In "Organic Syntheses"; Wiley: New York, 1943; Vol. II, p 418.

Table II. Anticonvulsant Activity of Tetracyclic Indoles

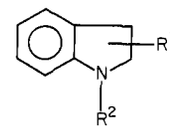
compd	rat max electroshock:[a] reactors/ test group	ED_{50},[b] mg/kg po	rat rotorod performance:[a] reactors/ test group
7a	0/3		0/6
7b	2/3	78.9 (52.2-119.4)	0/6
7c	3/3	14.1 (10.6-18.7)	0/6[c]
7d	3/3	12.5 (9.5-16.6)	0/6
7e	0/3		0/6
7f	1/3		1/6
7g	0/3		0/6
8a	0/3		1/6
8b	0/3		0/6
8c	0/3		1/6
10a	0/3		0/6
10b	0/3		0/6
10c	3/3	12.9 (9.5-17.6)	0/6
10d	0/3		0/6
10e	0/3		0/6
11	0/3		0/6
16a	0/3		0/6
16b	3/3	27.4 (18.0-41.8)	0/6
16c	2/3		0/6
16d	0/3		0/6
16e	0/3		1/6
16f	0/3		0/6
22a	0/3		0/6
22b	0/3		0/6
22c	3/3	19.2 (15.9-23.2)	0/6
23a	0/3		0/6
23b	0/3		0/6
diphenylhydantoin		42.3 (38.8-46.2)	0/6

[a] Test was run at 30 mg/kg po. The results are listed as a ratio of the number of reactors per number in test group. See Experimental Section for details. [b] 95% confidence limits in parentheses. [c] Test was run at 300 mg/kg po.

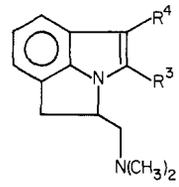
A set of ring-contracted analogues of **7** was synthesized from methyl indole-2-carboxylate (**17**). Conversion of **17** to amide **18**, followed by lithium aluminum hydride re-



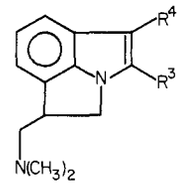
17, R^1 = 2-CO_2CH_3
18, R^1 = 2-$CON(CH_3)_2$
19a, R^1 = 2-$CH_2N(CH_3)_2$
b, R^1 = 3-$CH_2N(CH_3)_2$



20a, R^1 = 2-$CH_2N(CH_3)_2$; R^2 = H
b, R^1 = 3-$CH_2N(CH_3)_2$; R^2 = H
21a, R^1 = 2-$CH_2N(CH_3)_2$; R^2 = NH_2
b, R^1 = 3-$CH_2N(CH_3)_2$; R^2 = NH_2



22a-c



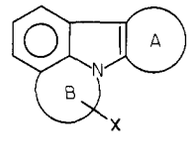
23a,b

duction, led to 2-[(dimethylamino)methyl]indole (**19a**). Reduction of **19a** to indoline **20a** was achieved with sodium borohydride pellets in trifluoroacetic acid.[3] Generation of hydrazine **21a**, followed by indole formation with cyclic ketones, gave the indole targets **22a–c**. An isomeric series **23a,b** was prepared starting with gramine (**19b**). The various tetracyclic indoles prepared by the methods described above are listed in Table I.

Results and Discussion

The anticonvulsant activity of the compounds listed in Table I is summarized in Table II. Each compound was tested orally in rats at 30 mg/kg for protection against maximal electroshock and rotorod performance. For the more active compounds, an ED_{50} was also determined. Compounds **7c**, **7d**, and **10c** were quite potent as anticonvulsants in the rat maximal electroshock test. None of the more active compounds showed any effects on rotorod performance at 30 mg/kg po and compound **7c**, tested at 300 mg/kg po, still showed no effects.

The structure–activity profile of the tetracyclic indoles, depicted in general structure **24**, was investigated by



24

systematic modification of the rings and side chain. As indicated in Table II, it was found that the location of the substituent X was preferable when attached as shown in structures **7**, **10**, or **22** rather than 8 or **23**. Within the series of compounds **7**, variation of ring A resulted in an increase in activity as the ring size contracted from 8 to 5 carbons (compare structures **7a–d**). The effect of changing the size of the B ring can be seen by comparing **7a–c** with **22a–c**, which shows that in the B ring, a six-membered ring is somewhat preferred over a five-membered ring. Keeping rings A (seven membered) and B (six membered) constant, variation of X indicates that X = $CONHCH_3$ gives greatest activity (compare **7b**, **16b**, **10c**, and **11**). However, compound **10e**, which combines the apparently optimal ring sizes for rings A and B (five and six carbons, respectively) with the apparently optimal substituent (X = $CONHCH_3$), was inactive as an anticonvulsant in the maximal electroshock test at 30 mg/kg po. Thus, it would seem that the various tetracyclic indoles described here comprise distinct series, each with their own structure–activity profile. In this light, compound **7d** depicts the lead structure for an amino series, and compound **10c** represents the best of an amide series. Thus, these tetracyclic indole derivatives provide several novel structures with potential anticonvulsant utility.

Experimental Section

NMR spectra were determined on a Varian EM-390 spectrometer with Me_4Si as the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 457 or Model 137 spectrophotometer. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were prepared by methods identical with those described below. Intermediate products were used directly without further purification. During workup, solvent was dried with anhydrous $MgSO_4$, and removal of solvent was carried out with a rotary evaporator.

6-[(Dimethylamino)methyl]-4,5,6,8,9,10-hexahydrocyclopenta[4,5]pyrrolo[3,2,1-*ij*]quinoline (7d). Thionyl chloride (15.6 g, 0.164 mol) and quinaldic acid (**2a**; 22.7 g, 0.131 mol) in 200 mL of toluene were refluxed for 2 h, and 50 mL of solvent was distilled. The reaction was cooled to room temperature, and dimethylamine was bubbled into the reaction until the pH was 11. The reaction was washed with 2 × 100 mL of saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was dissolved in 200 mL of ether, and HCl gas was bubbled through the solution. Filtration gave the hydrochloride salt of **3a** (25.1 g, 86%) as an amorphous solid: IR (Nujol) 3260, 2965, 2890, 1640, 1488, 1362, 1090 cm^{-1}.

A solution of **3a**·HCl (25.1 g, 0.113 mol) in 200 mL of 2-propanol was hydrogenated at atmospheric pressure in the presence of 1.4 g of platinum oxide. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was recrystallized from 2-propanol to give **4a** (13.4 g, 52%): mp 190–191 °C; NMR (Me_2SO-d_6) δ 2.71–3.28 (4 H, m), 3.05 (3 H, s), 3.16 (3 H, s), 4.41 (1 H, m), 4.65 (2 H, br s), 7.60–8.82 (4 H, m); IR (Nujol) 3010, 2865, 1649, 1455, 1088 cm^{-1}.

A solution of $NaNO_2$ (4.38 g, 63.5 mmol) in 20 mL of H_2O was added over 10 min to a solution of **4a** (12.0 g, 52.9 mmol) in 100 mL of 4 N aqueous HCl. The reaction temperature was maintained between 5 and 10 °C with an ice bath. After 1 h the reaction was filtered, washed with H_2O, and dried at 50 °C to give 7.25 g of crude *N*-nitroso compound, which was used directly.

This product was dissolved in 500 mL of ether, and lithium aluminum hydride (4.0 g, 0.104 mol) was added over 15 min. After refluxing for 1 h, the reaction was cooled to 0 °C, and 100 mL of 5% aqueous NaOH was slowly added. The reaction was filtered, and the aqueous layer of the filtrate was washed with 2 × 200 mL of ether. The ether portions were dried and concentrated to give **5a** (4.15 g, 38%) as an oil: NMR ($CDCl_3$) δ 1.82 (2 H, m), 2.38 (6 H, s), 2.76 (3 H, m), 3.48 (2 H, m), 3.78 (2 H, br s), 6.41–7.35 (4 H, m); IR (Neat) 3250, 2895, 1600, 1302, 1032 cm^{-1}.

A solution of **5a** (4.05 g, 19.7 mmol) and cyclopentanone (2.04 g, 24.3 mmol) in 15 mL of acetic acid was refluxed for 1 h and then concentrated. The residue in 75 mL of H_2O was washed with 75 mL of ether, which was discarded. The aqueous layer was made alkaline with 1.5 mL of 20% aqueous NaOH and extracted with 3 × 75 mL of ether. The combined ether portions were dried, and HCl gas was bubbled through the solution, producing a white precipitate. The product was collected by filtration and recrystallized from ethanol–ether to give **7d** (2.14 g, 37%): mp 215–216 °C; NMR (Me_2SO-d_6) δ 1.80–3.65 (18 H, m), 4.85 (1 H, m), 6.81–7.40 (3 H, m), 11.45 (1 H, s); IR (Nujol) 2845, 1590, 1432, 1345, 1182 cm^{-1}; Anal. ($C_{17}H_{22}N_2$·HCl) C, H, N.

***N*-Methyl-4,5,6,8,9,10,11,12-octahydrocyclohepta[4,5]pyrrolo[3,2,1-*ij*]quinoline-6-carboxamide (10c).** To **6a**[4] (22.1

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g, 97.1 mmol) in 150 mL of H_2O, 50 mL of 1 N aqueous HCl, and 300 mL of ether at 5–10 °C was added a solution of $NaNO_2$ (8.04 g, 0.116 mol) in 20 mL of H_2O over 15 min. The reaction was stirred for 1 h at 5–10 °C, the layers were separated, and the organic layer was concentrated. The residue was dissolved in 150 mL of acetic acid and 150 mL of H_2O, and zinc dust (25.4 g, 0.388 mol) was added over 5 min. The reaction temperature was maintained below 60 °C with external cooling. After 1 h, the reaction was filtered, and the filtrate was concentrated. The residue in 125 mL of 1 N aqueous NaOH was extracted with 3 × 100 mL of ether. The combined ether portions were dried and concentrated to give **6b** (11.5 g, 57%) as an oil: NMR (Me_2SO-d_6) δ 2.18 (2 H, m), 2.74 (4 H, m), 3.74 (3 H, s), 4.29 (1 H, t, J = 6 Hz), 7.05 (4 H, m).

Cycloheptanone (6.24 g, 55.6 mmol) and **6b** (11.5 g, 55.6 mmol) in 22 mL of acetic acid were refluxed for 2 h. The solvent was removed, and the residue in 300 mL of ether was washed with 4 × 50 mL of 1 N HCl. The organic layer was dried and concentrated to give **9a** (10.0 g, 63%) as an oil: NMR ($CDCl_3$) δ 1.76 (6 H, m), 2.82 (8 H, m), 3.62 (3 H, s), 4.92 (1 H, m), 6.68–7.35 (3 H, m).

To **9a** (5.77 g, 20.4 mmol) in 25 mL of MeOH containing 1.0 g of sodium methoxide was added 50 mL of saturated aqueous methylamine. The reaction was sealed in a steel container and heated at 110 °C for 6 h. The reaction was cooled to room temperature and partitioned between 300 mL of ether and 100 mL of H_2O. The aqueous layer was washed with 100 mL of ether. The combined organic portions were dried and concentrated, and the residue was recrystallized from MeOH to give **10c** (3.62 g, 63%): mp 186–188 °C; NMR ($CDCl_3$) δ 1.73 (6 H, m), 2.45–2.90 (8 H, m), 2.60 (3 H, d, J = 5 Hz), 4.76 (1 H, m), 5.10 (1 H, s), 6.72–7.32 (3 H, m); IR (Nujol) 3120, 2795, 1645, 1540, 1441, 1152 cm^{-1}. Anal. ($C_{18}H_{22}N_2O$) C, H, N.

5-[(Dimethylamino)methyl]-4,5,7,8,9,10-hexahydroindolo-[3,2,1-*hi*]indole (22c). To *N,N*-dimethylindole-2-carboxamide (18.0 g, 0.103 mol) in 200 mL of trifluoroacetic acid at 0 °C was added $NaBH_4$ pellets (19.5 g, 0.516 mol) at a rate such that the reaction remained below 10 °C. The reaction was stirred for 6 h and then concentrated to 50 mL. The residue was diluted with 300 mL of 10% aqueous NaOH and extracted with 3 × 200 mL of ether. The combined ether portions were dried, and HCl gas was bubbled through the solution, producing a precipitate. The product was collected by filtration and recrystallized from EtOH to give **20a** (17.3 g, 67%): IR (Nujol) 3250, 2910, 1605, 1455, 1261, 1143, 1032 cm^{-1}.

To **20a** (12.5 g, 50.2 mmol) in 100 mL of 4 N aqueous HCl at 5–10 °C was added a solution of $NaNO_2$ (4.33 g, 62.7 mmol) in 10 mL of H_2O. The reaction was stirred for 1 h at 10 °C, made alkaline with 20% aqueous NaOH, and extracted with 2 × 200 mL of ether. The combined ether portions were dried, added slowly to a slurry of lithium aluminum hydride (5.72 g, 0.151 mol) in 100 mL of ether, and refluxed for 1 h. Fifty milliliters of 10% aqueous NaOH was slowly added, and the reaction was filtered. The aqueous layer of the filtrate was washed with 75 mL of ether. The combined organic portions were dried and concentrated to give **21a** (7.9 g, 82%) as an oil: NMR ($CDCl_3$) δ 2.29 (6 H, s), 2.41–3.42 (5 H, m), 3.75 (2 H, s), 6.72–7.35 (4 H, m).

Cyclohexanone (1.75 g, 17.8 mmol) and **21a** (2.84 g, 14.8 mmol) in 10 mL of acetic acid were refluxed for 1 h, cooled to room temperature, diluted with 50 mL of H_2O, made alkaline with 15 mL of 20% aqueous NaOH, and extracted with 3 × 75 mL of ether. The combined ether portions were dried and concentrated to give 4.2 g of crude product. The product was dissolved in 100 mL of ether, and maleic acid (1.87 g, 16.1 mmol) in 50 mL of ether was added. The resulting precipitate was collected by filtration and recrystallized from EtOH to give the maleate salt of **22c** (5.20 g, 96%): mp 212 °C dec; NMR (Me_2SO-d_6) δ 1.85 (4 H, m), 2.35–3.45 (8 H, m), 2.90 (6 H, s), 4.85 (1 H, m), 6.20 (2 H, s), 6.85–7.39 (3 H, m), 10.50 (2 H, s); IR (Nujol) 3050, 2915, 2850, 2650, 1695, 1580, 1488, 1352, 1210 cm^{-1}. Anal. ($C_{17}H_{22}N_2 \cdot C_4H_4O_4$) C, H, N.

6-[2-(Dimethylamino)ethyl]-4,5,6,8,9,10,11,12,13-nonahydrocycloocta[4,5]pyrrolo[3,2,1-*ij*]quinoline (16a). Compound **12** (4.95 g, 25.8 mmol), dimethylamine (8.0 g, 0.177 mol), Na_2CO_3 (10.6 g, 0.10 mol), and KI (0.50 g) in 50 mL of DMF were stirred overnight at room temperature, poured into 200 mL of H_2O, and extracted with 2 × 200 mL of ether. The combined ether portions were washed with 100 mL of H_2O, dried, and concentrated to give 4.42 g (85%) of **13** as an oil: NMR ($CDCl_3$) δ 2.29 (6 H, s), 2.73 (2 H, m), 3.12 (2 H, m), 7.17–8.13 (6 H, m).

Compound **13** (9.00 g, 32.9 mmol) in 200 mL of MeOH containing 5.5 mL of 12 N HCl was hydrogenated under 1 atm pressure in the presence of 0.3 g of PtO_2. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was recrystallized from 2-propanol to give **14**·2HCl (6.31 g, 69%): NMR (Me_2SO-d_6) δ 1.75–2.45 (4 H, m), 2.77 (6 H, s), 2.88 (2 H, m), 3.15–3.82 (3 H, m), 7.26 (4 H, s), 8.45 (2 H, br s).

To **14** (6.00 g, 21.6 mmol) in 75 mL of 2.5 N HCl at 5 °C was added $NaNO_2$ (1.80 g, 25.9 mmol) in 10 mL of H_2O at a rate to maintain the reaction temperature below 10 °C. The reaction was adjusted to pH 9 with 20% NaOH and extracted with 2 × 100 mL of ether. The combined ether portions were dried (K_2CO_3) and added to a suspension of lithium aluminum hydride (2.50 g, 64.8 mmol) in 100 mL of ether. The reaction was refluxed for 2 h, cooled to room temperature, quenched with 21.5 mL of 10% NaOH, and filtered. The filtrate was concentrated to give **15** (3.7 g, 77%) as an oil: NMR ($CDCl_3$) δ 1.48–2.06 (4 H, m), 2.22 (6 H, s), 2.31 (2 H, m), 2.70 (2 H, t, J = 7 Hz), 3.29 (1 H, m), 3.60 (2 H, br s), 6.45–7.11 (4 H, m).

Cyclooctanone (2.31 g, 18.3 mmol) and **15** (3.65 g, 16.6 mmol) in 10 mL of acetic acid underwent the Fischer indole reaction and workup as described for **22c** to give **16a** maleate (3.80 g, 54%): mp 179–181 °C; NMR (Me_2SO-d_6) δ 1.18–2.25 (12 H, m), 2.75 (6 H, s), 2.88 (6 H, m), 3.27 (2 H, m), 4.49 (1 H, m), 6.05 (2 H, s), 6.68–7.31 (3 H, m), 10.3 (2 H, br s); IR (Nujol) 3275, 2990, 2885, 2610, 2390, 1690, 1615, 1567, 1452, 1355, 1200, 1068, 877 cm^{-1}. Anal. ($C_{21}H_{30}N_2 \cdot C_4H_4O_4$) C, H, N.

Rat Rotorod Performance Test. Male Charles River Wistar rats (125–175 g) were fasted 18 h but allowed water ad libitum prior to testing. Rotorod performance was assessed by using a rat treadmill (Model 7700, UGO Basile, Milano, Italy) modified by placing a section of polyethylene material over the bar, which rotated at a speed of 16 rpm. Rotorod performance was determined 45 min after oral adminsitration of test compound. Rats were classified as reactors if they were unable to remain on the rotorod for 30 s within three trials.

Rat Maximal Electroshock Test. Ninety minutes after oral dosing, male Charles River Wistar rats (125–175 g) received a 150-mA shock of 0.2-s duration through corneal electrodes and observed for clonic seizure. Rats were classified as reactors if they showed no seizures. The ED_{50} was calculated by the Berkson logit method.

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Registry No. **2a**, 93-10-7; **3a**·HCl, 85453-80-1; **4a**, 85453-81-2; **4a** (*N*-nitroso derivative), 85453-82-3; **5a**, 85453-83-4; **6a**, 63430-79-5; **6b**, 85453-84-5; **7a**, 85453-85-6; **7a**·HCl, 85453-86-7; **7b**, 85453-87-8; **7b**·HCl, 85453-88-9; **7c**, 85453-89-0; **7c**·HCl, 85453-90-3; **7d**, 85453-91-4; **7d**·HCl, 85453-92-5; **7e**, 85453-93-6; **7e**·HCl, 85453-94-7; **7f**, 85453-95-8; **7f**·HCl, 85453-96-9; **7g**, 85453-97-0; **7g**·HCl, 85453-98-1; **8a** maleate, 85454-00-8; **8b** maleate, 85454-02-0; **8c** maleate, 85454-04-2; **9a**, 85454-05-3; **10a**, 85454-06-4; **10b**, 85454-07-5; **10b**·HCl, 85454-08-6; **10c**, 85454-09-7; **10d**, 85454-10-0; **10e**, 85454-11-1; **11**, 85454-12-2; **12**, 85454-13-3; **13**, 63487-23-0; **14**, 85454-14-4; **14**·2HCl, 85454-15-5; **15**, 85454-16-6; **16a** maleate, 85454-18-8; **16b** maleate, 85454-20-2; **16c** maleate, 85454-22-4; **16d** maleate, 85454-24-6; **16e**, 85454-25-7; **16e**·HCl, 85454-26-8; **16f** ditartrate, 85454-28-0; **20a**, 85454-29-1; **21a**, 85454-40-6; **22a**, 85454-30-4; **22a**·HCl, 85454-31-5; **22b**, 85454-32-6; **22b**·HCl, 85454-33-7; **22c**, 85454-34-8; **22c** maleate, 85454-35-9; **23a** maleate, 85454-37-1; **23b** maleate, 85454-39-3; dimethylamine, 124-40-3; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; *N,N*-dimethylindole-2-carboxamide, 7511-14-0; cyclohexanone, 108-94-1; cyclooctanone, 502-49-8.