Novel Tetracyclic Spiropiperidines. 3.[1] 1-Arylspiro[indoline-3,4′-piperidine]s as Potential Antidepressants[2]

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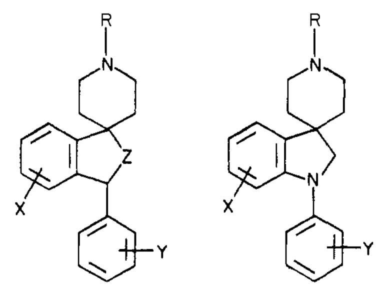
A series of 1-arylspiro[indoline-3,4′-piperidine]s was synthesized and evaluated for potential antidepressant activity by tetrabenazine (TBZ) ptosis prevention and potentiation of 5-hydroxytryptophan (5-HTP) induced head twitching in pargyline-pretreated rats. Marked TBZ activity was observed with analogues bearing an ortho substituent on the pendant aromatic ring, as exemplified by lead compound **25a**, 1-(2-chlorophenyl)spiro[indoline-3,4′-piperidine], which was also very active in potentiating 5-HTP stereotypy and yohimbine toxicity, as well as in inhibiting the muricidal behavior in rats. The potent in vivo activity of **25a**, coupled with weak to moderate in vitro activity with respect to the blockade of neuronal reuptake of biogenic amines, seems to suggest a profile atypical of tricyclic antidepressants.

The search for novel, nontricyclic antidepressants with a fast onset and lower incidence of side effects has continued to stimulate our interest in the tetracyclic spiropiperidines. Earlier reports from these laboratories[4a] described the synthesis and antidepressant-like properties of a series of 3-arylspiro[isobenzofuran-1(3*H*),4′-piperidine]s (I), many of which compared favorably in animal studies with clinically efficacious antidepressants, such as imipramine and desipramine. In a more recent study,[4b] the furan oxygen in I was replaced by sulfur, and

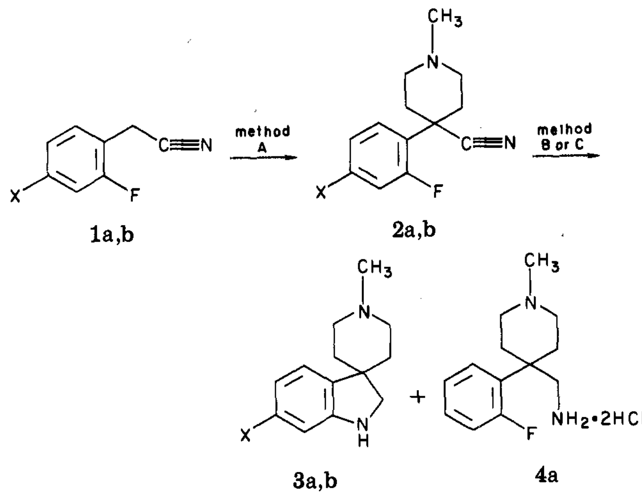


I, Z = O III
II, Z = S

the resultant 3-aryl-1,3-dihydrospiro[benzo[c]thiophene-1,4′-piperidine]s (II) showed significantly reduced anticholinergic liability as a whole, while their range of potencies in the antitetrabenazine assay remained essentially unchanged. The present paper describes the synthesis and pharmacological evaluation of a series of 1-arylspiro[indoline-3,4′-piperidine]s, III, which are related to I and II by "dual isosterism" involving the five-membered heterocyclic ring.

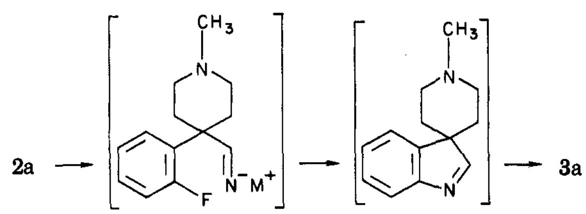
Chemistry. The synthesis of key intermediates **3a,b** is outlined in Scheme I. 2-Fluorophenylacetonitriles, **1a,b**, reacted with 2,2-dichloro-*N*-methyldiethylamine hydrochloride in the presence of sodium hydride to give cyanopiperidines **2a,b** in excellent yields (method A). Initial attempts to effect reductive cyclization of **2a** with lithium aluminum hydride resulted in a 3:1 mixture of **3a** and **4a** (method B), while lithium triethoxyaluminum hydride in refluxing THF (method C) afforded pure **3a** almost quantitatively. The intermediacy of **4a** in the formation of spiroindoline **3a** is considered unlikely, as the former resisted all attempts to cyclize under a variety of conditions normally well suited for nuclear fluorine displacements.

Scheme I[a]



[a] a, X = H; b, X = Cl.

A more plausible mechanism, therefore, would involve the partial reduction of **2a** to the corresponding imino compound, as shown below, which then cyclized to an isoindole derivative readily reducible to the indoline **3a**. An indirect support for this mechanism can be found in the observation that **2a**, when treated with phenylmagnesium bromide



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(1) For paper 2, see Ong, H. H.; Agnew, M. N. *J. Heterocycl. Chem.* 1981, *18*, 815.
(2) This paper has been presented in part; see "Abstracts of Papers", 178th National Meeting of American Chemical Society, Washington, DC; Sept 1979; American Chemcial Society: Washington, DC, 1979, Abstr MEDI 25.
(3) (a) Present address: Miles Laboratories, Elkhart, IN. (b) Present address: McNeil Laboratories, Spring House, PA.
(4) (a) Bauer, V. J.; Duffy, B. J.; Hoffman, D.; Klioze, S. S.; Kosley, R. W., Jr.; McFadden, A. R.; Martin, L. L.; Ong, H. H.; Geyer III, H. M. *J. Med. Chem.* 1976, *19*, 1315. (b) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Kruse, H.; Wilker, J. C.; Geyer III, H. M. *Ibid.* 1981, *24*, 74.

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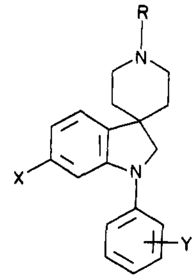
Table I. 1-Arylspiro[indoline-3,4'-piperidine] Derivatives[a]



compd	X	Y	R	starting material	method	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
5a	H	H	CH_3	**3a**	D	70	90-92	H	$C_{19}H_{22}N_2$	C, H, N
6a	H	2-F	CH_3	**3a**	D	63	209-210	A-E	$C_{19}H_{21}FN_2\cdot C_4H_4O_4$[d]	C, H, F, N
6b	Cl	2-F	CH_3	**3b**	D	77	166-168	A-E	$C_{19}H_{20}ClFN_2\cdot C_4H_4O_4$[d]	C, H, F, N
7a	H	4-F	CH_3	**3a**	D	72	267-269	A-E-G	$C_{19}H_{21}FN_2\cdot HBr$	C, H, N
8a	H	2-Cl	CH_3	**3a**	D	56	178-179.5	E-F	$C_{19}H_{21}ClN_2\cdot C_4H_4O_4$[d]	C, H, Cl, N
8b	Cl	2-Cl	CH_3	**3b**	D	73	172-173	A-E	$C_{19}H_{20}Cl_2N_2\cdot C_4H_4O_4$[d]	C, H, N
10a	H	4-Cl	CH_3	**3a**	D	46	123-125	E-H	$C_{19}H_{21}ClN_2$	C, H, Cl, N
11b	Cl	2-CF_3	CH_3	**3b**	D	74	209-211	E-G	$C_{20}H_{20}ClF_3N_2\cdot C_4H_4O_4$[d]	C, H, F, N
12a	H	3-CF_3	CH_3	**3a**	D	61	123-124.5	E-H	$C_{20}H_{21}F_3N_2$	C, H, F, N
13a	H	4-CF_3	CH_3	**3a**	D	58	122-124	H	$C_{20}H_{21}F_3N_2$	C, H F, N
14a	H	2-NO_2	CH_3	**3a**	E	42	132-132.5	I	$C_{19}H_{21}N_3O_2$	C, H, N
14b	Cl	2-NO_2	CH_3	**3b**	E	84	130-131	E-H	$C_{19}H_{20}ClN_3O_2$	C, H, N
15a	H	2-NH_2	CH_3	**14a**	F	85	243-245	E-G	$C_{19}H_{23}N_3\cdot 2HCl$	C, H, N
15b	Cl	2-NH_2	CH_3	**14b**	F	82	*e*	G	$C_{19}H_{22}ClN_3\cdot 2HCl$	C, H, N
16a	H	H	CN	**5a**	G	87	136-138	A-H	$C_{19}H_{19}N_3$	C, H, N
17a	H	2-F	CN	**6a**	G	47	131-132	A-H	$C_{19}H_{18}FN_3$	C, H, F, N
17b	Cl	2-F	CN	**6a**	G	90	*f*	*g*	$C_{19}H_{17}ClFN_3$	*h*
18a	H	4-F	CN	**7a**	G	88	139-140	A-H	$C_{19}H_{18}FN_3$	C, H, N
19a	H	2-Cl	CN	**8a**	G	64	157.5-159.5	A-H	$C_{19}H_{18}ClN_3$	C, H, N
20a	H	2-NO_2	CN	**14a**	G	53	148-150	E-D	$C_{19}H_{18}N_4O_2$	C, H, N
20b	Cl	2-NO_2	CN	**14b**	G	85	163-165	A-H	$C_{19}H_{17}ClN_4O_2$	C, H, N
21a	H	2-NO_2	$CONH_2$	**19a**	L	37	217-219	E-J-K	$C_{19}H_{20}N_4O_3$	C, H, N
22b	Cl	2-NO_2	$COOC_6H_5$	**14b**	J	76	181-182.5	A-H	$C_{25}H_{22}ClN_3O_4$	C, H, N
23b	Cl	2-F	H	**17b**	H	62	174-175.5	E-G	$C_{18}H_{18}ClFN_2\cdot C_4H_4O_4$[d]	C, H, Cl, N
24a	H	4-F	H	**18a**	H	73	185-188	A-E-G	$C_{18}H_{19}FN_2\cdot C_4H_4O_4$[d]	C, H, N
25a	H	2-Cl	H	**19a**	H	80	157.5-158.5	A-E	$C_{18}H_{19}ClN_2\cdot C_4H_4O_4$[d]	C, H, Cl, N
26a	H	2-NO_2	H	**20a**	I	83	222-224	G	$C_{18}H_{19}N_3O_2\cdot HCl$	C, H, N
26b	Cl	2-NO_2	H	**20b**	I	64				
26b	Cl	2-NO_2	H	**20b**	K	77	153-155	A-E	$C_{18}H_{18}ClN_3O_2\cdot C_4H_4O_4$[d]	C, H, Cl, N
27a	H	2-NH_2	H	**26a**	F	79	282.5	G-I	$C_{18}H_{21}N_3\cdot 2HCl$	C, H, N
27b	Cl	2-NH_2	H	**25b**	F	72	270-273	E-G	$C_{18}H_{20}ClN_3\cdot 2HCl$	C, H, Cl, N

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the structures. [b] Isolated yield; no efforts were made to optimize these yields. [c] A = acetone; B = benzene; C = cyclohexane; D = dichloromethane; E = ethyl ether; F = methanol; G = ethanol; H = hexane; I = isopropyl ether; J = dimethyl sulfoxide; K = dioxane. [d] Acid maleate salt. [e] Mp >245 °C. [f] Isolated as a heavy oil. [g] Purified by column chromatography. [h] Mass spectrum, *m/e* 322 (M^+).

in refluxing THF, readily formed 1'-methyl-2-phenylspiro[isoindole-3,4'-piperidine] via an intramolecular fluorine displacement.[1] For the preparation of *N*-methyl target compounds bearing a moderately activating group on the 1-aryl substituent (Scheme II), such as **5a**, **6a**,**b**, **7a**, **8a**,**b**, **10a**, **11b**, **12a**, **13a**, **14a**,**b**, and the 2-pyridyl derivative **9a**, dimsyl sodium was used to effect the direct arylation of **3a**,**b** with the appropriately substituted fluorobenzenes (method D). In the cases of **14a**,**b** where a strongly activating group was involved, coupling of **3a**,**b** with 2-fluoronitrobenzene took place at high temperature even in the absence of a strong base (method E),[5] and further reduction of **14a**,**b** with iron and dilute hydrochloric acid (method F) afforded 1-(2-aminophenyl) derivatives **15a**,**b** in moderate to good yields.

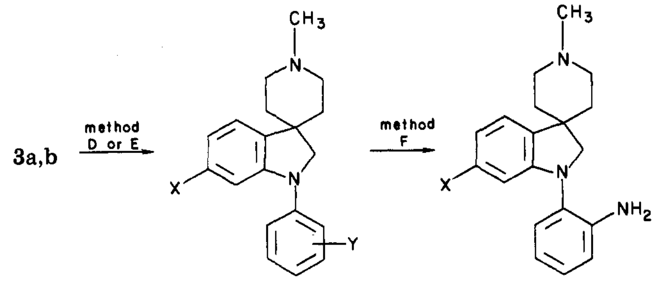
For the preparation of target compounds bearing a secondary amino function on the piperidine ring, compounds **5a**, **6a**,**b**, **7a**, **8a**, and **14a**,**b** were treated with cyanogen bromide in the presence of potassium carbonate to give **16a**, **17a**,**b**, **18a**, **19a**, and **20a**,**b** without noticeable complications arising from the indoline nitrogen (method G). Cyanoamides so formed could be converted to the corresponding secondary amines by reductive elimination with lithium aluminum hydride (method H), as in the cases of **23b**, **24a**, and **25a**, or by hydrolysis with dilute hydrochloric acid (method I). An alternative route to the secondary amines was via the carbamates, as demonstrated by the formation of **22b** from **14b** and phenyl chloroformate (method J), and its subsequent saponification to **26b** (method K). Similar to the tertiary amines, reduction of **26a**,**b** to **27a**,**b** was best carried out with iron powder and dilute hydrochloric acid.

Biological Results and Discussions

The title compounds were evaluated mainly for their potential antidepressant activity by tetrabenazine (TBZ) ptosis prevention in mice and potentiation of head twitching induced by 5-hydroxytryptophan (5-HTP) in pargyline-pretreated rats. While most clinically efficacious antidepressants have shown activity in the TBZ model, augmentation of 5-HTP-induced stereotypy is thought to be associated selectively with agents acting via the serotonergic pathway.

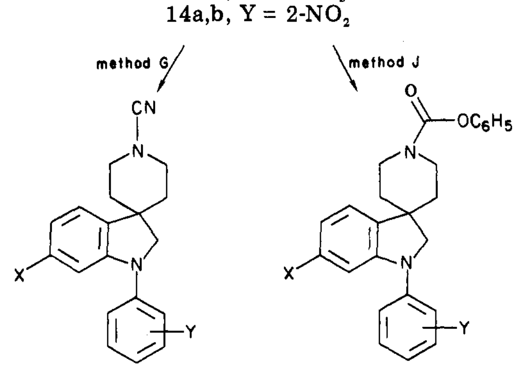
(5) Glamkowski, E. J.; Fortunato, J. M. *J. Heterocycl. Chem.* **1979**, *16*, 865.

Scheme II[a]



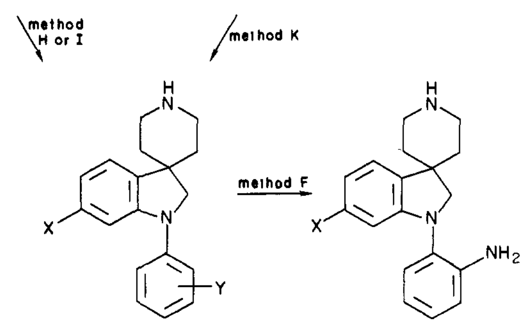
5a, Y = H
6a,b, Y = 2-F
7a, Y = 4-F
8a,b, Y = 2-Cl
10a, Y = 4-Cl
11b, Y = 2-CF_3
12a, Y = 3-CF_3
13a, Y = 4-CF_3
14a,b, Y = 2-NO_2

15a,b



16a, Y = H
17a,b, Y = 2-F
18a, Y = 4-F
19a, Y = 2-Cl
20a,b, Y = 2-NO_2

22b, Y = 2-NO_2



23b, Y = 2-F
24b, Y = 4-F
25a, Y = 2-Cl
26a,b, Y = 2-NO_2

27a,b

[a] a, X = H; b, X = Cl.

With respect to tetrabenazine ptosis prevention, it is apparent from Table II that analogues showing marked activity in this model all carry an ortho substituent on the pendant aromatic ring, as exemplified by **6a,b**, **8a,b**, **14a**, **15a**, and **25a**. Within the subgroup of tertiary amines where there is no additional halogen substituent on the fused aromatic ring (**6a**, **8a**, **14a**, and **15a**, X = H), the magnitude of this ortho effect seems to increase with increasing steric bulk (F < Cl ≃ NH_2 > NO_2) and then declines as the group exceeds its optimum size. Among the few secondary amines studied, it is interesting to note that, again, the most active congener is one with an *o*-chlorine substituent on the pendant nucleus (**25a**).

By application of the computer-aided SCRIPT molecular modeling system,[6a,b] the "roof-angle", or angle of flexure between two aromatic planes, is calculated to be 55.3°, almost identical to that reported for imipramine (55°); the significance of this value to antidepressant activity has been discussed in detail by Finch and by Wilhelm.[7a,b] By contrast, the angle of flexure generated for **5a** is 47.9°,[8] and this compound was only marginally active in the tetrabenazine assay at the screening dose of 20 mg/kg ip.

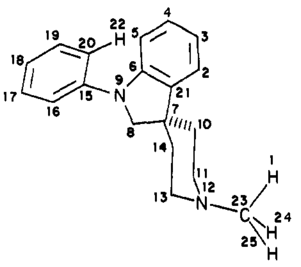
In the 5-HTP model, the spiroindolines in Table II were

Table II. Pharmacology of 1-Arylspiro[indoline-3,4'-piperidine]s

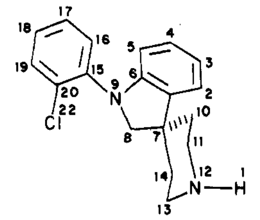
compd[a]	tetrabenazine ptosis: ED_{50},[g] mg/kg ip	5-HTP potentiation: ED_{50},[g] mg/kg ip
5a	>20	>10
6a	15.2 (12.3-20.5)	>10
6b	11.0 (8.5-15.4)	>10
7a	>20	>10
8a	3.4 (2.9-4.0) 3.2 (2.5-3.9)[b]	>10
8b	2.6 (2.2-3.5)	>10
9a	>20	>10
10a	>20	>10
11b	>8[c]	>10
12a	>20	>10
13a	>20	7.8 (4.2-10.0)
14a	4.0 (2.7-6.9) 8.4 (7.1-10.4)[b]	>10
15a	4.0 (3.5-4.6) 1.9 (1.2-2.7)[b]	>10
15b	>20	>10
23b	>8[c]	>10
24a	>20	>10
25a	1.2 (0.89-1.5) 0.37 (0.27-0.45)[b]	4.7 (3.0-7.5)
26a	*d*	>10
27a	>20	>10
27b	>20	>10
HP 505[f]	0.5 (0.3-0.7) 1.0 (1.1-1.3)[b]	1.9 (0.6-3.3)
amitriptyline	1.5 (1.4-1.6) 1.9 (1.4-2.5)[b]	7.1 (3.9-9.1)
despiramine	0.8 (0.6-0.9) 1.6 (1.4-1.8)[b]	>10

[a] The vehicle control used in all biological tests consists of distilled water and a few drops of Tween 80. [b] Determined by oral administration. [c] Poor dose-response relationship. [d] All animals died after tetrabenazine dosing. [e] Not tested. [f] Type I compound (X = Y = R = H), 3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine]. See ref 4a. [g] ED_{50} values were calculated by a linear-regression analysis, with 95% confidence limits given in parentheses.

(6) (a) Cohen, N. C.; Colin, P., Lemoine, G. In "Abstracts of Papers", 181th National Meeting of American Chemical Society, Atlanta, Mar 29–Apr 3, 1981; American Chemical Society: Washington, DC, 1981; Abstr MEDI 13. (b) The logical basis of the SCRIPT molecular modeling system lies on the description of the molecule as the assembly of cyclic and chain fragments having specific torsional constraints, evaluated as a function of the stereochemistry and the hybridations of the atoms concerned. Once these torsional constraints have been identified by the program, the enumeration of all the possible conformers of the molecule becomes possible, thus allowing the direct construction of the corresponding forms in three dimensions without trial and error. The SCRIPT program's exploration of the conformational potential surface is based on a classical molecular mechanics similation procedure.
(7) (a) Finch, N. In "Antidepressants"; Fielding, S.; Lal, H., Eds.; Futura: Mount Kisco, NY, 1975; p 3. (b) Wilhelm, M. In "Depressive Illness"; Kielholz, P., Ed.; Hans Huber: Vienna, 1972; p 129.
(8) The roof angle generated for the demethyl compound of 5a is 47.7°; apparently, N-methylation does not contribute much to conformational changes in this particular area of the molecule.



5a: roof angle, 47.9°; plane (5-3-21), plane (20-18-16)



25a: roof angle, 55.3°; plane (5-3-21), plane (20-18-16)

inactive, except **13a** and **25a**, the latter being almost twice as potent as amitriptyline.

The favorable findings with **25a** emerging from preliminary studies thus prompted further testing in a number of secondary screens, and results are given in Table III. It is readily seen that in potentiating yohimbine-induced toxicity in mice,[9,10] compound **25a** was five times more active than amitriptyline; interestingly, the same potency ratio was also observed for these two compounds in the rat muricide model.[10,11] Thus, the marked in vivo activity of compound **25a** in relation to amitriptyline, in conjunction with similarly moderate activity in blocking in vitro neuronal reuptake of biogenic amines and marginal activity in inhibiting rat brain mitochondrial MAO enzymes,[12] seems to suggest a profile somewhat atypical of tricyclic and MAO-I antidepressants.[13]

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 547) and ^{1}H NMR (JEOLCO C6OHL) (tetramethylsilane) spectra. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectral data were determined with a Finnigan Model 400 GC–MS equipped with a INCOS data system. Where analyses were indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, IL) were within 0.4% of theoretical values.

4-Cyano-4-(2-fluorophenyl)-1-methylpiperidine (2a). Method A. A solution of 6.75 g (50 mmol) of 2-fluorophenylacetonitrile (1a) in 100 mL of Me_2SO was added to 4.4 g of sodium hydride (99%) over 10 min with vigorous stirring. After 30 min, a solution of 8.5 g (43 mmol) of 2,2′-dichloro-*N*-methyldiethylamine hydrochloride (Aldrich Chemical Co.) in 100 mL of Me_2SO was added dropwise, and the mixture was stirred at 75 °C under nitrogen for 4 h. Ice (300 g) was then added, and the mixture was extracted exhaustively with ether. The combined ether solution was shaken with a large excess of 2 N hydrochlorice acid, and the neutral fraction was discarded. Basification of the aqueous solution afforded a thick oil, which crystallized on standing and cooling, mp 67–69 °C. Recrystallization of the crude product from ether–hexane gave 8.55 (91%) of **2a** as rhombic crystals, mp 68–70 °C (lit. 69–71 °C). Anal. ($C_{13}H_{15}N_2F$) C, H, F, N.

4-(4-Chloro-2-fluorophenyl)-4-cyano-1-methylpiperidine (2b) was prepared from **1b** in 75% yield by method A as an off-white solid, mp 85–87 °C. Anal. ($C_{13}H_{14}ClFN_2$) C, H, N.

1′-Methylspiro[indoline-3,4′-piperidine] (3a). Method C. A suspension of lithium triethoxyaluminum hydride was prepared by dropwise addition of 12 mL of absolute ethanol into a chilled (0 °C) suspension of 4.86 g (0.1 mol) of lithium aluminum hydride in 150 mL of glyme. Following total addition, the mixture was slowly heated to reflux, and then 6.98 g (32 mmol) of **2a** in 80 mL of ethylene glycol dimethyl ether (glyme) was added over a period of 30 min. Stirring was continued at reflux for 72 h, and the cooled mixture was decomposed with 5 mL of H_2O, 5 mL of 15% NaOH, and, finally, 15 mL of H_2O. The inorganic precipitate was removed by filtration, and the filter cake was extracted twice with warm CH_2Cl_2. The combined filtrate was washed with water, dried (K_2CO_3), and concentrated in vacuo to give a white crystalline solid, mp 134–136 °C. Recrystallization of the crude product from benzene–hexane gave 6.0 g (92%) of shiny platelets, mp 135–137 °C. Anal. ($C_{13}H_{18}N_2$) C, H, N.

Alternatively, compound **3a** could be prepared in 50% yield by reduction of **2a** with lithium aluminum hydride (method B). Thus, a solution of **2a** (3.27 g, 15 mmol) in 20 mL of glyme was added dropwise to a refluxing slurry of lithium aluminum hydride (0.96 g, 20 mmol) over 15 min. After total addition, the mixture was stirred at reflux for 64 h, cooled, and decomposed with successive portions of H_2O, dilute NaOH, and H_2O. Working up in the usual manner led to a semisolid residue, which recrystallized upon trituration with hexane. The crude product was recrystallized from benzene–hexane to give 1.52 (50%) of colorless prisms identical with **3a** prepared by method C.

4-(Aminomethyl)-4-(2-fluorophenyl)-1-methylpiperidine Dihydrochloride (4a). Method B. The filtrate from the preparation of **3a** via lithium aluminum hydride reduction of **2a** was concentrated in vacuo to a syrup. Trituration of the residue with anhydrous ether, followed by treatment with ethereal HCl, afforded an amorphous white solid. Recrystallization of the crude product from methanol–ether gave 0.81 g (18.3%) of pure **4a**, mp 297.5 °C dec. Anal. ($C_{13}H_{19}FN_2 \cdot 2HCl$) C, H, F, N.

4-Chloro-1′-methylspiro[indoline-3,4′-piperidine] (3b) was prepared by method C from **2b** in 93% yield as white needles (acetone–hexane): mp 172–173 °C. Anal. ($C_{13}H_{17}ClN_2$) C, H, N.

1′-Methyl-1-phenylspiro[indoline-3,4′-piperidine] (5a). Method D. A mixture of **3a** (2.1 g, 11.4 mmol), 3 g of 50% sodium hydride in mineral oil, and 12 mL of fluorobenzene in 18 mL of dimethyl sulfoxide was stirred at 64–70 °C for 4 h. The mixture was poured into water and extracted with 3 × 150 mL of ether. The combined ether solution was washed exhaustively with water, dried over $MgSO_4$, and concentrated to give a brownish oil. The residue was dissolved in 100 mL of anhydrous ether and treated with an excess of ethereal HCl, and the supernatant was removed by decantation. Basification of the gummy hydrochloride, followed by ether extraction, gave rise to a pale yellowish oil, which crystallized on standing. Recrystallization of the crude product from boiling hexane afforded 2.25 g (70%) of **5a** as off-white crystals. Properties of **5a**, and of **6a,b**, **7a**, **8a,b**, **10a**, **11b**, **12a**, and **13a** prepared in a similar manner, are included in Table I.

1′-Methyl-1-(2-pyridyl)spiro[indoline-3,4′-piperidine] Dihydrobromide (9a). Method D. A mixture of **3a** (2.02 g, 10 mmol), 2.6 g of 2-fluoropyridine, and 1.0 g of 50% sodium hydride in 30 mL of dimethyl sulfoxide was stirred under N_2 at 60–65 °C for 1 h. The mixture was cooled, diluted with 150 g of ice–water, and extracted with 3 × 150 mL portions of ether. The combined ethereal solution was shaken with a large excess of 2 N hydrochloric acid to separate neutral materials, and basification of the acidic solution with 40% sodium hydroxide yielded a reddish oil. The crude product was purified by column chromatography over silica gel; elution with 25% methanol–dichloromethane gave a pale yellowish oil, which was converted to **9a** with ethereal hydrobromide. Recrystallization of the crude product from methanol–ether gave 2.3 g (52%) of colorless prisms, mp >280 °C. Anal. ($C_{18}H_{21}Br_2N_3$) C, H, Br, N.

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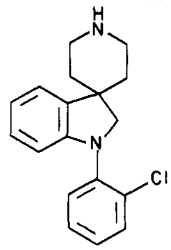
(13) The possibility of an active metabolite is not being excluded.

Table III. Profile of **25a** as a Potential Antidepressant



screening method	25a	amitriptyline
	In Vivo (ED_{50}, mg/kg ip)[a]	
TBZ ptosis prevention[b]	1.2 (0.89-1.5)	1.5 (1.4-1.6)
	0.37 (0.27-0.48)[d]	1.94 (1.40-2.5)[d]
5-HTP potentiation[c]	4.7 (3.0-7.5)	7.1 (3.9-9.1)
yohimbine toxicity potentiation[b]	1.6 (0.60-4.5)	8.0 (4.1-15.6)
muricide[c]	4.9 (2.7-9.1)	22.6 (9.1-56.4)
	In Vitro (IC_{50}, μM)	
inhibn of neuronal uptake[e]		
norepinephrine (WB)	6.5	4.7
dopamine (ST)	8.0	14.0
serotonin (WB)	1.7	2.0
inhibn of MAO[f]	160	

[a] 95% confidence limits are included in parentheses. [b] Mouse. [c] Rat. [d] Administered orally. [e] Rat brain synaptosomes; WB = whole brain; ST = striatum. Values listed are the mean for three separate experiments. [f] Rat whole brain mitochondrial preparation.

1′-Methyl-1-(2-nitrophenyl)spiro[indoline-3,4′-piperidine] (14a). Method E. A mixture of **3a** (12.4 g, 61.1 mmol) and 17.2 g (122 mmol) of o-fluoronitrobenzene was maintained at a temperature of 170–175 °C for 5 h. The resulting product solidified upon cooling to room temperature. The solid was pulverized and triturated with 350 mL of an ether–hexane (1:4, v/v) mixture, and the air-dried product was dissolved in chloroform and treated portionwise with 9.7 mL of triethylamine, leaving a thick slurry. The slurry was thus poured into water, and the organic phase was separated and filtered. The residue was washed with chloroform, and the combined organic portions were washed with water, dried ($MgSO_4$), and concentrated to afford a brown residue. Recrystallization of the crude base from isopropyl ether gave 8.33 g (42%) of pure **14a**. Properties of **14a**, and of **14b** prepared in a similar manner, are included in Table I.

1-(2-Aminophenyl)-6-chloro-1′-methylspiro[indoline-3,4′-piperidine] Dihydrochloride (15b). Method F. A mixture of **14b** (2.5 g, 7 mmol), 4.4 g of iron powder in 30 mL of 95% ethanol, and 7.5 mL of water was acidified with 0.2 mL of concentrated hydrochlorice acid and heated at reflux for 1 h. The inorganics were filtered, and the filtrate was concentrated in vacuo to a heavy syrup, which was triturated with water and basified with ammonium hydroxide. The liberated oil was extracted into ether, dried, and concentrated to a thick oil. Purification of the crude product was effected by column chromatography over alumina packed in ether; elution with ether gave 2.1 g of a colorless oil, which was converted to a crystalline dihydrochloride with ethereal HCl. Recrystallization of the slightly hygroscopic crude salt from methanol–acetone–ether gave 2.3 g (81.9%) of **15b** as off-white granules. Properties of **15b**, and of **15a**, **27a**, and **27b** prepared in a similar manner, are included in Table I.

1′-Cyano-1-phenylspiro[indoline-3,4′-piperidine] (16a). Method G. A mixture of **5a** (0.5 g, 1.8 mmol), 0.5 g of potassium carbonate, and 0.2 g of cyanogen bromide in 10 mL of methylene chloride was stirred at room temperature for 2 h. The mixture was filtered, and the filtrate was evaporated to give a semisolid residue. The crude cyanamide was purified by passing through a short column of silica gel packed in chloroform. Elution with chloroform gave, after concentration, 460 mg (87%) of **16a** as colorless prisms. Properties of **16a**, and of **17a,b**, **18a**, **19a**, and **20a,b** prepared in a similar manner, are included in Table I.

6-Chloro-1-(2-fluorophenyl)spiro[indoline-3,4′-piperidine] Maleate (23b). Method H. A solution of **17b** (3.4 g, 10 mmol) in 50 mL of THF was added dropwise to a refluxing mixture of 1.0 g of lithium aluminum hydride in 50 mL of the same solvent. The mixture was stirred at reflux for 2 h and decomposed in the usual manner with water and 10% NaOH. The inorganics were filtered off, and the filtrate was diluted with ether, washed with water, and dried ($MgSO_4$). Removal of solvents left a pale oil, which was converted to a crystalline maleate in ether. Recrystallization of the crude salt from ethanol–ether gave 2.68 g (62%) of **23b** as off-white granules. Properties of **23b**, and of **24a** and **25a** prepared in a similar manner, are included in Table I.

1-(2-Nitrophenyl)spiro[indoline-3,4′piperidine] Hydrochloride (26a). Method I. A mixture of **20a** (2.5 g, 6.8 mmol) in 40 mL of 3 N hydrochloric acid was refluxed for 16 h under N_2. The cooled solution was basified with 10% NaOH, and the separated oil was extracted with three 150-mL portions of ether. The combined organic solution was washed with water, dried, and concentrated to give a yellowish oil, which was converted to a crystalline maleate in ether. Recrystallization of the crude salt from acetone–ether afforded 2.6 g (83%) of **26a** as orange prisms. Properties of **26a**, and of **26b** prepared in a similar manner, are included in Table I.

6-Chloro-1-(2-nitrophenyl)-1′-(phenoxycarbonyl)spiro[indoline-3,4′-piperidine] (22b). Method J. A mixture of **14b** (12.5 g, 4.2 mmol) and 0.8 g of phenyl chloroformate in 30 mL of CH_2Cl_2 was stirred at room temperature for 16 h. The solution was washed with 10% NaOH and water and dried over $MgSO_4$. Removal of solvent under reduced pressure left a semisolid residue, which was purified by passing through a column of silica gel packed in CH_2Cl_2. Elution with CH_2Cl_2 afforded 1.48 g (76%) of **22b** of analytical purity. Properties of **22b** are included in Table I.

6-Chloro-1-(2-nitrophenyl)spiro[indoline-3,4′-piperidine] Maleate (26b). Method K. A mixture of **22b** (2.32 g, 5 mmol) and 4 g of potassium hydroxide pellets (85%) in 30 mL of ethylene glycol was stirred at 160–170 °C under nitrogen for 2 h. The cooled mixture was diluted with 300 mL of ice–water, and the separated oil was extracted into ether. The ether solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo to a thick oil. Treatment of the crude amine with a 10% acetone–ether solution of maleic acid afforded 1.78 g (77%) of **26b**, identical with that obtained by method I.

1′-Carbamoyl-1-(2-nitrophenyl)spiro[indoline-3,4′-piperidine] (21a). Method L. A solution of **20a** (9.93 g, 29.7 mmol) in 150 mL of glyme and 100 mL of 6 N hydrochloric acid was heated at reflux under N_2 for 1.5 h. The clear solution was cooled to 0 °C, made basic with 50% of NaOH (40 mL), and concentrated to dryness. The residue was dissolved in hot $CHCl_3$, washed with brine, dried over $MgSO_4$, and evaporated to give 9.44 g (90%) of the crude urea. Recrystallization from hot Me_2SO–

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.

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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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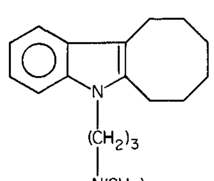
Several related series of cycloalkyl[4,5]pyrrolo[3,2,1-*ij*]quinolines **7a–g**, **8a–c**, **10a–e**, and **16a–f** and indolo[3,2,1-*hi*]indoles **22a–c** and **23a,b** were synthesized and tested for anticonvulsant activity. The key preparative step, a Fischer indole reaction between a bicyclic hydrazine 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-octahydrocyclohepta[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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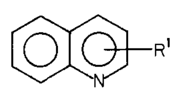
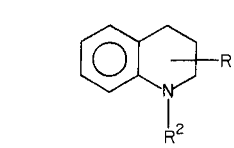
compounds showed activity in an anticonvulsant screen and, therefore, set out to investigate the structural parameters of this activity. In this report we describe the preparation and anticonvulsant activity of these tetracyclic indole derivatives.

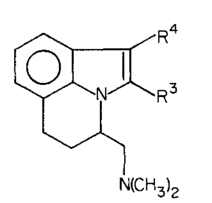
Chemistry. A number of different tetracyclic ring systems were synthesized. One series of indoles, **7**, was prepared starting with quinaldic acid (**2a**). Conversion of **2a** to dimethyl amide **3a**, followed by hydrogenation, gave tetrahydroquinoline **4a**, which was converted to a key hydrazine 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



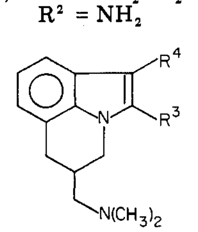
2a, R^1 = 2-CO_2H
b, R^1 = 3-CO_2H
3a, R^1 = 2-$CON(CH_3)_2$
b, R^1 = 3-$CON(CH_3)_2$
12, R^1 = 2-CH_2CH_2Cl
13, R^1 = 2-$CH_2CH_2N(CH_3)_2$



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

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