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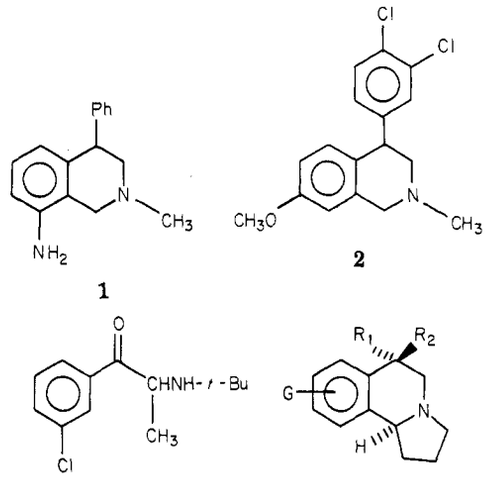
Communications to the Editor

Pyrroloisoquinoline Antidepressants. Potent, Enantioselective Inhibition of Tetrabenazine-Induced Ptosis and Neuronal Uptake of Norepinephrine, Dopamine, and Serotonin

Sir:

Inhibitors of brain norepinephrine (NE) and/or serotonin (5-HT) uptake increase the concentration of biogenic amine neurotransmitters in synaptic regions of the brain, a property that appears to be important in the expression of antidepressant activity.[1] More recently, a role for dopamine (DA) in depression has received some attention, partly because of dopaminergic properties observed with the new antidepressants nomifensin (**1**), diclofensin (**2**), and bupropion (**3**).[2] In our CNS screening program, we have discovered a novel series of hexahydropyrrolo[2,1-*a*]isoquinolines (viz., **4**) that comprises compounds representing the most potent uptake inhibitors presently known for each of these three neurotransmitters, NE, 5-HT, and DA. Furthermore, we report that high enantioselectivity is exhibited in this series with respect to pharmacological and biochemical activities.[3]

Two main synthetic approaches were generally used to obtain target compounds, the *N*-acyliminium cyclization route (Scheme I) and the 2-arylpyrrolidine route (Scheme II). Since the acyliminium chemistry is the subject of separate articles,[4] discussion here is abbreviated. Suffice it to say that the reaction is highly stereoselective for the trans (viz., **4a**) relative stereochemistry; so, the cis (viz., **4b**) diastereomers were obtained by base-catalyzed equilibration of the final amine products or the lactam intermediates.[4b] Series prototypes **5a** and **5b** were synthesized by the acyliminium route (in a 93:7 ratio, respectively; 80% overall), and equilibration gave a 1:1 mixture that was separated by preparative HPLC (Waters Prep 500, silica gel, 95% ethyl acetate/5% methanol). The arylpyrrolidine route is subdivided into mandelic acid or styrene oxide based methods. As an example of the styrene oxide procedure, 2-phenylpyrrolidine was reacted with *m*-(trifluoromethyl)styrene oxide (ethanol, reflux, 82%) and the crude amino alcohol product was cyclized in polyphosphoric acid (PPA) at 100 °C to afford **6** (69%), as a mixture of trans and cis diastereomers (**6a** and **6b**) in a 3:1 ratio, respectively. The isomers were separated by preparative HPLC. To exemplify the mandelic acid procedure, 2-phenylpyrrolidine was condensed with *p*-chloromandelic acid in xylene with azeotropic removal of water. The mandelamide (two diastereomers, 90%) was cyclized in PPA at 100 °C to give a mixture of diastereomeric lactams (91%), which were separated by preparative HPLC and reduced with borane–THF to give target amines **7a** and **7b** (1:2 ratio, respectively, 81%). Demethylation of methoxy groups in **9** and **11** was accomplished



(1) (a) Fuller, R. W. In "Antidepressants: Neurochemical, Behavioral, and Clinical Perspectives"; Enna, S. J., Malick, J. D., Richelson, E., Eds.; Raven Press: New York, 1981; pp 1–12. (b) Hollister, L. E. *Drugs* **1981**, *22*, 129. (c) Schildtkraut, J. In "Psychopharmacology: A Generation of Progress"; Lipton, M. A., Di Mascio, A., Killam, K. F., Eds.; Raven Press: New York, 1978; pp 1223–1234. (d) Sulser, F. In "Typical and Atypical Antidepressants: Molecular Mechanisms"; Costa, E., Racagni, G., Eds.; Raven Press: New York, 1982; pp 1–20. (e) Kostowski, W. *Trends Pharmacol. Sci.* **1981**, *2*, 314. (f) Maj, J. *Trends Pharmacol. Sci.* **1981**, *2*, 80. (g) Kaiser, C.; Setler, P. E. In "Burger's Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1979; Part III, pp 997–1067.

(2) Nomefensin: (a) Algeri, S.; Ponzio, F.; Achilli, G.; Perego, C. In "Typical and Atypical Antidepressants: Molecular Mechanisms"; Costa, E.; Rocagni, G., Eds.; Raven Press: New York, 1982; pp 219–234. (b) Raiteri, M.; Maura, G.; Cerrito, F. *Ibid.*; pp 199–217. Diclofensin: (c) Keller, H.; Schaffner, R.; Carruba, M.; Burkard, W.; Pieri, M.; Bonetti, E.; Scherschlicht, R.; Da Prada, M.; Haefely, W. *Ibid.*; pp 249–263. Bupropion: (d) Ferris, R. M.; Maxwell, R. A.; Cooper, B. R.; Soroko, F. E. *Ibid.*; pp 277–286. (e) Ferris, R. M.; Cooper, B. R.; Maxwell, R. A. *J. Clin. Psychiat.* **1983**, *44:5* (*Sect. 2*), 74. General: (f) Keller, H. H.; Burkard, W. P.; Da Prada, M. *Adv. Biochem. Psychopharmacol.* **1980**, *24*, 175.

(3) High enantioselectivity has not been commonly reported for antidepressant agents. For examples of it, see: (a) Smith, D. F., Ed., "Handbook of Stereoisomers: Drugs in Psychopharmacology"; GRC Press: Boca Raton, FL, 1983; pp 220–227. (b) Waldmeier, P. C. *Trends Pharmacol. Sci.* **1983**, *4*, 448. (c) Footnote 12, herein.

(4) (a) Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, 3797. (b) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.

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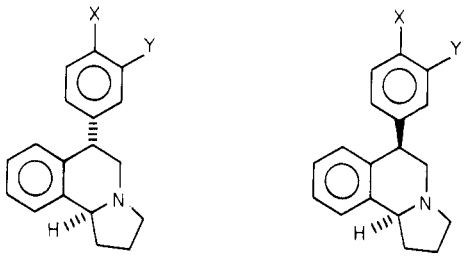


a b

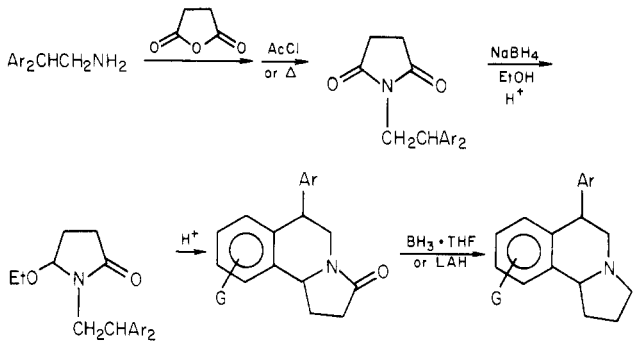
5, X = Y = H
6, X = H; Y = CF_3
7, X = Cl; Y = H
8, X = Y = Cl
9, X = OCH_3; Y = H
10, X = OH; Y = H
11, X = Y = OCH_3
12, X = Y = OH
13, X = NO_2; Y = H
14, X = NH_2; Y = H
15, X = SCH_3; Y = H

with 48% HBr in acetic acid at reflux or with boron tribromide in methylene chloride at −65 °C. The amino derivatives **14** were prepared from already separated (HPLC) nitro compounds **13** by catalytic hydrogenation over platinum.

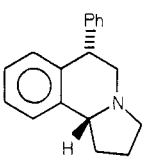
The compounds in this series were evaluated for their effects in the tetrabenazine (TBZ) assay, on antagonism of TBZ-induced depression of motor activity (MA) and TBZ-induced ptosis (Table I).[5] The ptosis parameter was found to be more reliable for comparison of activity because effects on 5-HT, seen with many of the compounds, can disproportionately influence the MA parameter.[6] Compounds **5**–**15** of the **b** set (cis isomers) were very active in the TBZ test, based on ptosis, whereas those of the **a** set (trans isomers) were relatively inactive (e.g., cf. **5a**/**5b** and **6a**/**6b**), except for **14a**. However, in this latter case, **14b** was so potent (ED_{50} of ca. 0.02 mg/kg ip) that the minor quantity of it present in **14a** (ca. 2% by GLC) imparted strong pharmacological activity to an otherwise weakly active material. Aniline **14b** (McN-5908) is probably the most potent inhibitor of TBZ-induced ptosis ever examined; but it is also rather toxic [its LD_{50} (in mice, ip) is in the range of 1–3 mg/kg]. Many of these compounds (**5b**, **7b**–**10b**, **12b**, and **14b**) showed strong stimulant properties in general behavior tests (in mice, ip), which is probably undesirable for a clinical candidate. An especially promising reduction in stimulant character was achieved with three derivatives, **6b**, **13b**, and **15b**, which we are examining for potential development.

The compounds were tested for their ability to inhibit the uptake of tritiated NE, DA, and 5-HT into rat brain synaptosomes (Table I).[7] In these in vitro assays the cis isomers again were much more active than the trans isomers (e.g., cf. the isomers of **5** and **6**). In fact, potent inhibition of uptake of all three monoamines was evident for most of the cis derivatives studied. Compounds worthy of particular note are those that, to our knowledge, are the most potent inhibitors of DA, NE, and 5-HT uptake ever reported: **8b**/**14b**, **7b**/**14b**, and **15b**, respectively.[8] Although most of the compounds are active against all three neurotransmitters, **6b** (McN-5558) has a fairly high selectivity for NE over DA (57-fold) and 5-HT (24-fold), and **15b** (McN-5652-Z) has selectivity for 5-HT over NE (4-fold) and DA (54-fold). The deemphasis of DA activity, relative to NE and 5-HT activity, with these two agents may be responsible for their attenuated stimulant properties, and enhances the prospect of their further development.

Scheme I



Given the interesting biological activity of this series, we resolved the prototype compound **5b** (McN-4612-Z) into its two enantiomers by means of diastereomeric di-*p*-toluoyltartrate salts.[9] Virtually all the activity, both pharmacological and biochemical, resided in (+)-**5b** (Table I). The enantiomeric purity was established by the synthesis of (+)-**5b** from (+)-2-phenylpyrrolidine[10] of known enantiomeric purity[11] by the styrene oxide method (vide supra) and, since the absolute configuration of (+)-2-phenylpyrrolidine was already determined to be *R*,[10] we obtained as a welcome bonus the absolute configuration of (+)-**5b**: 6*S*,10b*R* (illustrated in formula **16**). The



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pyrroloisoquinoline antidepressants thus represent one of the few examples of high enantioselectivity in TBZ antagonism and inhibition of DA/NE/5-HT uptake.[12]

(5) (a) Vernier, V. G.; Hanson, H. M.; Stone, C. A. In "Psychosomatic Medicine"; Nodine, J. H., Moyer, J. H., Eds.; Lea and Febiger: Philadelphia, 1962; p 683. (b) Binesova, O.; Nahunek, K. *Psychopharmacologia* **1971**, *20*, 337.

(6) Maj, J.; Rogoz, Z.; Seuza, G. *J. Pharm. Pharmacol.* **1983**, *35*, 128 and references cited.

(7) Horn, A. S.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1972**, *180*, 523.

(8) (a) Some of the more potent inhibitors reported follow. DA: LR-5182 (3 nM, ref 1a); amfonelic acid (7.2 nM, determined by us); compound **99** in ref 8b (2.3 nM). NE: DMI (0.65 nM, Table I); compound **103** in ref 8b (0.3 nM). 5-HT: clomipramine (6.3 nM, ref 2c); RO-11-2465 (1.5 nM, ref 8c). (b) Bogeso, K. P. *J. Med. Chem.* **1983**, *26*, 935. (c) Da Prada, M.; Keller, H.; Burkard, W.; Schaffner, R.; Bonetti, E.; Launay, J.; Haefly, W. In "Typical and Atypical Antidepressants: Molecular Mechanisms"; Costa, E., Racagni, G., Eds.; Raven Press: New York, 1982; pp 235–248.

(9) The (−)-enantiomer was separated first by fractional crystallization of the natural (+)-tartrate salt (mp 153–153.5 °C dec); the mother liquor supplied the (+)-enantiomer via the (−)-tartrate salt (mp 145–146.5 °C dec).

(10) Morlacchi, F.; Losacco, V.; Tortorella, V. *Gazz. Chim. Ital.* **1975**, *105*, 349.

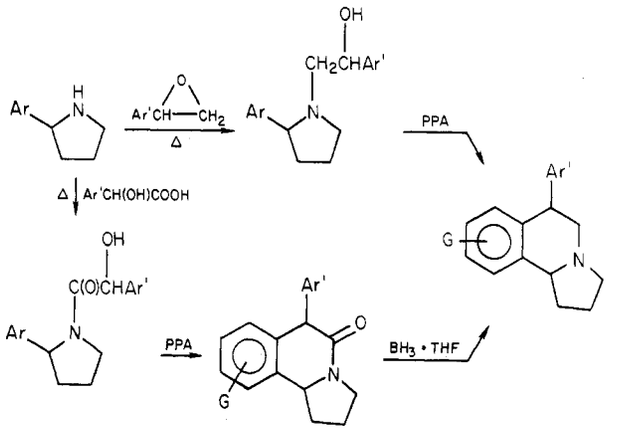
(11) The enantiomeric purity of the (+)-2-phenylpyrrolidine was established by HPLC analysis of Mosher's amide derivatives (Dale, J.; Dull, D.; Mosher, H. *J. Org. Chem.* **1969**, *34*, 2543); the 100% optical purity in ref 10 corresponded to 100% enantiomeric purity.

Table I. Chemical and Biological Data

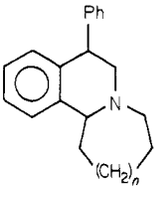
compd[a]	HX[b]	mp, °C	TBZ ED_{50},[c] mg/kg		uptake inhib,[d] K_i, nM		
			MA	ptosis	DA	NE	5-HT
5a	HCl	236–241	>30	>30	160	64.9	2748
5b	fum	170–172	0.34	0.07	11.3	0.60	23.5
(+)-**5b**[e]	HCl	232–242	0.59	0.05	4.4	0.37	12.4
(−)-**5b**[e]	HCl	230–238	>30	8.3	1345	411	4809
6a	HCl	204–206	>60	>60	>1000	>100	>1000
6b	HCl	180–183	1.2	0.43	54.3	0.95	23.0
7b	HBr	290–293	0.55	0.34	1.7	0.16	1.5
8b	fum	196–201	0.39	0.14	0.99	0.68	1.8
9b	HBr	241–244	0.27	0.03	5.2	0.79	1.7
10b	HBr	257–260	0.4	0.09	5.1	0.74	3.2
11b	HBr	235–237	0.45	0.11	71.9	3.4	18.1
12b	HBr	244–248	0.19	0.11	10.1	0.81	33.1
13b	HBr	227–229	0.34	0.14	94.2	3.4	5.0
14a	HBr	252–258d	1.4	0.4	~30	~10	>500
14b	HBr	242–249	>1	0.02	0.86	0.20	44
15b	$HClO_4$	202–203	>30	0.40	36.8	2.89	0.68
17b	fum	195–203	>30	>30	>500	~20	>500
18b	HBr	252–258	~30	>30	>100	~100	>500
DMI[f]	HCl		0.07[g]	0.05[g]	6532	0.65	182
IMIP[f]	HCl		0.58	0.98	>10000	12.0	41.8
MIAN[f]	none		>30	9.7	>10000	26.0	>1000
1[f]	mal		0.27	0.16	79	3.8	874
2[f,h]					14.6	4.4	18.4

[a] The new compounds were fully characterized by IR, ^1H NMR, and elemental analysis (±0.4% for C, H; N or halogen). [b] Compounds were tested by us as the acid-addition salts shown (fum = fumarate, mal = maleate). [c] Tetrabenazine antagonism was measured by the published method in mice.[5] The compounds were administered ip. For relatively inactive compounds the maximum dose tested, which may have been limited by toxicity, is given. 95% confidence ranges are contained in the supplementary material. [d] Inhibition of monoamine uptake was measured in rat brain synaptosomes according to standard procedures.[7] K_i values are reported. 95% confidence ranges are contained in the supplementary material. [e] The sign of rotation refers to the HCl salt in methanol at 589 nm. [f] Reference drug (DMI = desmethylimipramine, IMIP = imipramine, MIAN = mianserin). [g] Administered by sc route. [h] Testing data were taken from the literature (ref 2c). Their values for 1 were 200/9.6/1500 (DA/NE/5-HT).

Scheme II



Our pyrroloisoquinoline series bears some structural resemblance to the tetrahydroisoquinoline antidepressants nomifensin (**1**) and diclofensin (**2**) and shares some common biological properties (Table I).[13] Simplistically, one could suppose that adding the third ring to the tetrahydroisoquinoline structure would be likely to afford antidepressant activity. However, when the pyrrolidine ring was modified to one of larger size, as in the cis (**b**) and trans (**a**) isomers of **17** and **18**, the compounds were only



17, $n = 1$
18, $n = 2$

weakly active at best (see data for **17b** and **18b** in Table I). These results and the stereoselectivity observed in our series indicate that subtle, unobvious structural features are at work in the determination of activity for the isoquinoline antidepressants.

Acknowledgment. We thank Martin Mutter and Nancie Senko for spectroscopic data; Deena DiStefano and Elizabeth Griffin for technical assistance; Linda Labinsky, Yolanda Roman, Joanne Mathiasen, Direese Cooper, and June Hultgren for assistance with biological experiments.

Registry No. (±)-**5a**, 90390-51-5; (±)-**5a**·HCl, 90390-67-3; (±)-**5b**, 90390-52-6; (±)-**5b**·fum, 90390-68-4; (6*S*,10b*R*)-**5b**, 90457-59-3; (+)-(6*S*,10b*R*)-**5b**·HCl, 90527-78-9; (6*R*,10b*S*)-**5b**, 90457-60-6; (−)-(6*R*,10b*S*)-**5b**·HCl, 90527-84-7; (±)-**6a**, 90390-53-7; (±)-**6a**·HCl, 90390-69-5; (±)-**6a** (amino alcohol), 90390-90-2; (±)-**6b**, 90390-54-8; (±)-**6b**·HCl, 90390-70-8; (±)-**6b** (amino alcohol), 90390-82-2; (±)-**7a** (mandelamide), 90412-51-4; (±)-**7a** (lactam), 90390-88-8; (±)-**7b**, 90390-55-9; (±)-**7b**·HBr, 90390-71-9; (±)-**7b** (mandelamide), 90390-83-3; (±)-**7b** (lactam), 90390-89-9; (±)-**8b**, 90390-56-0; (±)-**8b**·fum, 90390-72-0; (±)-**9b**, 90390-57-1; (±)-**9b**·HBr, 90390-73-1; (±)-**10b**, 90390-58-2; (±)-**10b**·HBr, 90390-74-2; (±)-**11b**, 90390-59-3; (±)-**11b**·HBr, 90390-75-3; (±)-**12b**, 90390-60-6; (±)-**12b**·HBr, 90390-76-4; (±)-**13b**, 90390-61-7; (±)-**13b**·HBr, 90390-77-5; (±)-**14a**, 90390-62-8; (±)-**14a**·HBr, 90390-78-6; (±)-**14b**, 90390-63-9; (±)-**14b**·HBr, 90390-79-7; (±)-**15b**, 90390-64-0; (±)-**15b**·$HClO_4$, 90390-80-0; (±)-*cis*-**17**, 90390-65-1; (±)-*cis*-**17**·fum,

(12) (a) Some other examples of enantioselective uptake inhibitors have been reported: see ref 1g, 8b, 12b (oxaprotiline), 12c (YM-08054-1), and 12d (mianserin). (b) Delini-Stula, A.; Hauser, K.; Baumann, P.; Olpe, H.-R.; Waldmeier, P.; Storni, A. In "Typical and Atypical Antidepressants: Molecular Mechanisms"; Costa, E.; Racagni, G.; Eds.; Raven Press: New York, 1982, pp 265–275. (c) Tachikawa, S.; Harada, M.; Maeno, H. *Arch. Int. Pharmacodyn.* **1979**, *238*, 81. (d) Schoemaker, H.; Berendsen, H. H. G.; Stevens, H. J. T.; Nickolson, V. J. *Psychopharmacology (Berlin)* **1981**, *74*, 137.

(13) Full details of the biological activity and SAR for our pyrroloisoquinoline series, which is being explored at length, will be published in due course.

90412-50-3; (±)-*trans*-17, 90390-84-4; (±)-*trans*-17·fum, 90390-86-6; (±)-*cis*-18, 90390-66-2; (±)-*cis*-18·HBr, 90390-81-1; (±)-*trans*-18, 90390-85-5; (±)-*trans*-18·HBr, 90390-87-7; DA, 51-61-6; NE, 51-41-2; 5-HT, 50-67-9; (±)-2-phenylpyrrolidine, 56586-11-9; (±)-*m*-trifluoromethylstyrene oxide, 53631-36-0; (±)-*p*-chloromandelic acid, 7138-34-3.

Supplementary Material Available: Table I, 95% confidence limits for the data presented (1 page). Ordering information is given on any current masthead page.

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Synthetic CNS Agents. 1. (±)-1,2,3,4,4a,5,10,10a-Octahydro-5,10[1′,2′]-benzenobenz[*g*]isoquinoline Hydrochloride. A New, Highly Potent, Potential Antidepressant

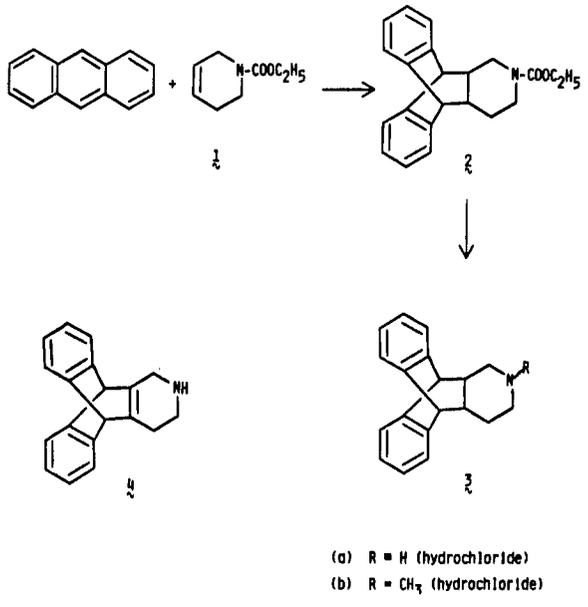
Sir:

In our search for new types of antidepressants, we had occasion to synthesize the title compound (**3a**), which, on the basis of tests with animals, seems to possess potent antidepressant-like properties.

The biological data on **3a**, and its *N*-methyl derivative (**3b**), are listed in Table I along with those of amitriptyline and imipramine, two tricyclic antidepressants in clinical practice.

As is evident from the table, **3a** is thrice as potent in mice and several times as potent in rats as amitriptyline and imipramine in reversing the ptosis induced by tetrabenazine (TBZ)[1] in these species. It exhibits neither stimulation nor dose-induced depression in mice and rats[1] and is not a monoamine oxidase inhibitor in vitro or in vivo. The outstanding feature of its profile is that it lacks both peripheral and central anticholinergic activity as borne out by the oxotremorine antagonism test[2] in mice in which it is inactive in contrast to both amitriptyline and imipramine. In a 12-day subacute toxicity study with rats, **3a** was well tolerated up to a dose of 50 mg/kg po, which represents 100 times the ED_{50} value.[3]

The *N*-methyl derivative (**3b**) of **3a**, while equipotent to amitriptyline and imipramine in mice, is however less active than **3a**. Besides, it is fairly potent in the oxotremorine antagonism test[2] indicative of undesirable anticholinergic side effects and is, therefore, less interesting than **3a**.



(a) R = H (hydrochloride)
(b) R = CH_3 (hydrochloride)

Compound **3a** was synthesized by the Diels–Alder reaction of anthracene with 1-(ethoxycarbonyl)-1,2,3,6-tetrahydropyridine (**1**) to yield **2**, the best condition for which was the use of a large excess of **1** as the solvent and heating the mixture at reflux for 18 h under nitrogen. Removal of the excess of **1** under reduced pressure furnished, in an almost quantitative yield, **2**, which, on hydrolysis with KOH in boiling *t*-butyl alcohol with concomitant loss of CO_2, afforded **3** (R = H) as a colorless crystalline solid (mp 161–162 °C, from hexane). It was converted to its hydrochloride **3a** (mp 339–340 °C dec, from methanol) for screening purposes. Reduction of **2** with lithium aluminum hydride yielded **3** (R = CH_3), which was isolated as its hydrochloride, **3b** (mp 173–175 °C, from THF). The structures of **3a** and **3b** were confirmed by elemental analysis and by the NMR and mass spectra of the corresponding bases.

At the time the compounds **3a** and **3b** were synthesized, the parent heterocyclic ring system was unknown. The synthesis of **4**, a dehydro derivative of **3** (R = H), has recently been described and follows an entirely different

Table I. Biological Evaluation of Compounds **3a** and **3b**

compd	TBZ antagonism[a]		MAO inhibition		oxotremorine antagonism[a]		pressor response (dog)[d]		acute toxicity[f] (mouse)
	mouse	rat	in vitro[b]	in vivo[c]	tremors	lacrimation	↑NE	↓PE	
3a	0.41 (0.26–0.65)	0.5 (0.21–1.21)	>1 × 10^{-3}	>81	>243	>243	0.22	1.2	320
3b	1.0	[e]	[e]	[e]	100[g]	36 (22.9–56.7)	[e]	[e]	126
amitriptyline	1.3 (0.59–2.86)	12 (6.2–23.4)	>1 × 10^{-3}	>135	21 (12.2–36.2)	27 (18.5–40.3)	1.0	1.1	177
imipramine	1.3 (0.96–1.8)	4.12 (2.78–6.11)	>1 × 10^{-3}	>135	70 (43.1–113)	130	3.0	1.5	300

[a] ED_{50}, mg/kg po. [b] KI_{50}, mol/L, with 5-HT as substrate (mouse brain). [c] ED_{50}, mg/kg po, tryptamine potentiation test (mouse).[1] [d] ED_{50}, mg/kg iv; ↑NE refers to potentiation of the response to norepinephrine; ↓PE refers to inhibition of the response to phenethylamine.[1] Confidence limits not determined. [e] Not determined. [f] 24 h LD_{50}, mg/kg po. Confidence limits not determined. [g] Extrapolated value.

(1) Smith, D. H.; Vernier, V. G. "New Drugs—Discovery and Development"; Rubin, A. A., Ed.; Marcel Dekker: New York, 1978; pp 203–261.
(2) Brimblecombe, R. W.; Green, D. M. *Int. J. Neuropharmacol.* **1968**, *7*, 15.
(3) Unpublished results.