Azepinoindoles. I. Hexahydroazepino[4,5-*b*]indoles

J. B. HESTER, A. H. TANG, H. H. KEASLING, AND W. VELDKAMP

Biochemical Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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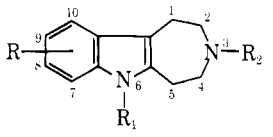
A series of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles has been prepared *via* the formic acid catalyzed cyclization of phenylhydrazones of 1-benzoylhexahydroazepin-4-one. The pharmacologic activity of these compounds on the mammalian central nervous system is discussed.

Our continued interest in the pharmacologic activity of indole derivatives on the mammalian central nervous system[1] led us to prepare a series of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles (**1**). Formally, these



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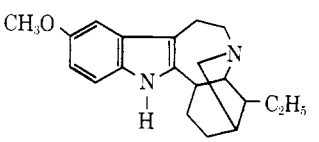

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compounds may be considered to be tryptamine derivatives in which the spatial orientation of the basic nitrogen is limited by the conformational restrictions of the seven-membered ring. If, therefore, we postulate that the complex physiologic activity of tryptamine and tryptamine derivatives[2,3] is due in part to the interaction of the amine with different receptor sites or enzymes involving different orientations of the ethylamine side chain, we would expect the subject compounds to interact with a restricted number of tryptamine receptors and, thus, to have a more specific activity. Moreover, if compounds of this type were found to have certain specific tryptamine-like activities, they might be useful for the study of the spatial configuration of tryptamine as it interacts with the site(s) responsible for the particular activity observed. In addition, we would hope that any tryptamine-like activity of the hexahydroazepino[4,5-*b*]indoles would be prolonged as compared to that of tryptamine, since monoamine oxidase, the enzyme responsible for most tryptamine metabolism,[4] would probably not oxidize these heterocyclic amines. Prolonged tryptamine-like activity has been observed[5] with the α-alkyltryptamines which are not oxidized by monoamine oxidase and actually serve as competitive inhibitors of the enzyme.[6] It is also noteworthy that several β-carboline derivatives, structurally related to the azepinoindoles under discussion, are reversible inhibitors of monoamine oxidase.[7] Our interest in the subject compounds was enhanced by the reported[8] central-stimulant activity of ibogaine (**2**), an alkaloid which incorporates the hexahydroazepino[4,5-*b*]indole system in its rather complex structure.

Recent activity in several laboratories[9-11] toward synthetic approaches to the iboga alkaloids has yielded a variety of substituted 1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]indole derivatives. Several indolobenzazepines[12,13] have also been prepared. Approaches to the unsubstituted ring system have been limited in scope[14] or unsuccessful.[15]

Our synthetic approach to the 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles (**1**) may be illustrated by the preparation of the unsubstituted derivatives. This was initiated by the acetic acid catalyzed condensation of phenylhydrazine with 1-benzoylhexahydroazepin-4-one (**3**), a ketone which was available to us *via* the biological oxidation of 1-benzoylhexahydroazepine[16] (Scheme I). Fisher cyclization of the crude phenylhydrazone thus obtained was accomplished with refluxing formic acid.[17,18] Although we expected two products from this reaction, alumina chromatography of the crude product gave only 3-benzoyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**4**) in moderate yield. The structural assignment was based on the ultraviolet and infrared spectra, which substantiated the indole chromophore and the benzamide moiety and on the nmr spectrum[19a] (*vide infra*). Reduction of the benzamide with lithium aluminum hydride gave the expected benzylamine (**5**). Catalytic hydrogenation of **5** with palladium gave **6** which was isolated as its hydrochloride. Selective methylation[20] of the indole nitrogen to give **7** was achieved with sodium hydride and methyl iodide in dimethylformamide. Methylation of **4** was accomplished in a like manner to give **8**. Reductive cleavage of this benzamide (**8**) to give **7** constitutes a structure proof of the latter compound. We converted both **6** and **7** to their N-3 methyl derivatives, **9** and **12**, respectively, by acylation with formic–acetic anhydride[21] followed by lithium aluminum hydride reduction of the formamides.

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(19) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) $CDCl_3$, (b) CD_3SOCD_3, or (c) D_2O. The chemical shifts are recorded in cps downfield from TMS.
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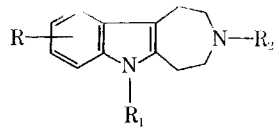
TABLE I

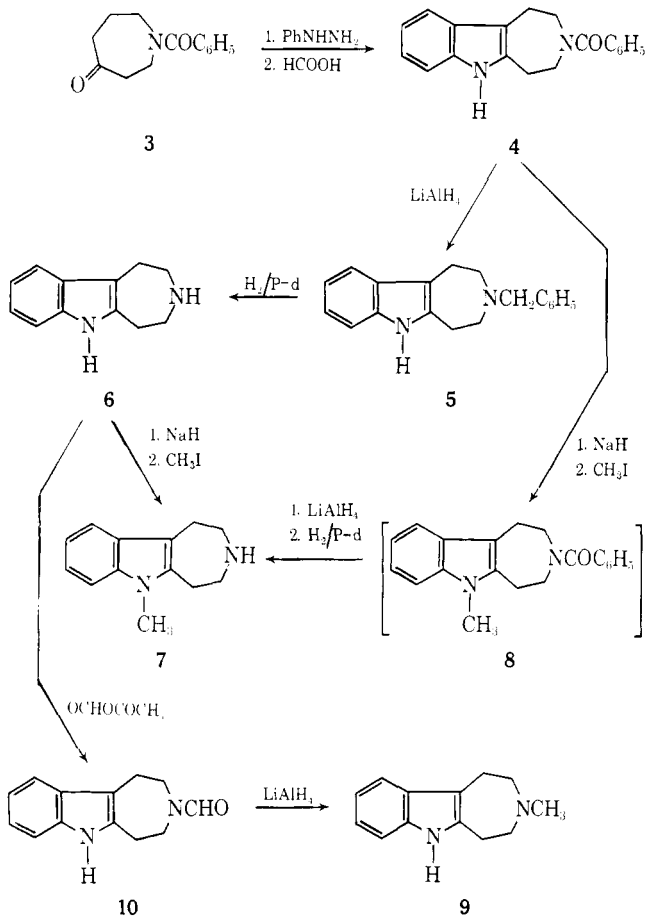
1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-*b*]INDOLES



No.	R	R_1	R_2	Yield, %	Procedure	Mp, °C	Recrystn solvent	Formula	% calcd C	% calcd H	% calcd N	% calcd Cl (F)	% found C	% found H	% found N	% found Cl (F)
4	H	H	C_6H_5CO	36.9	A	169–170	MeOH–H_2O	$C_{19}H_{18}N_2O$	78.59	6.25	9.65		78.26	6.22	9.43	
5	H	H	$C_6H_5CH_2$	59.0	B	116–117	EtOAc–Skelly B	$C_{19}H_{20}N_2$	82.57	7.30	10.14		82.34	7.52	10.04	
6	H	H	H	93.5	C	247.5–248.5	MeOH–EtOAc	$C_{12}H_{14}N_2 \cdot HCl$	64.71	6.79	12.58	15.92	64.93	7.08	12.70	16.10
7	H	CH_3	H	75.3	D, E	214–215	MeOH–EtOAc	$C_{13}H_{16}N_2 \cdot HCl$	65.95	7.24	11.84	14.98	66.35	6.99	11.78	14.90
9	H	H	CH_3	91.3	G	165–166.5	EtOAc	$C_{13}H_{16}N_2$	77.96	8.05	13.99		77.69	8.08	13.72	
10	H	H	CHO	89	F	221–222.5	CH_2Cl_2–CH_3OH	$C_{13}H_{14}N_2O$	72.87	6.59	13.08		72.90	6.74	12.84	
11	H	CH_3	CHO		F	125–128.5	CH_2Cl_2–MeOH	$C_{14}H_{16}N_2O$	73.65	7.06	12.27		73.57	7.05	12.55	
12	H	CH_3	CH_3	68.5	G	251–251.5	MeOH–EtOAc	$C_{14}H_{18}N_2 \cdot HCl$	67.05	7.64	11.17	14.14	67.18	7.70	11.37	14.28
13	H	C_2H_5	H	76.5	D	253–254 dec	MeOH–EtOAc	$C_{14}H_{18}N_2 \cdot HCl$	67.05	7.64	11.17	14.14	67.10	7.90	11.47	14.38
14	H	$C_6H_5CH_2$	$C_6H_5CH_2$		D	85.5–86.5	Skelly B	$C_{26}H_{26}N_2$	85.20	7.15	7.65		84.80	7.25	7.74	
15	H	$C_6H_5CH_2$	H		D	212–213	MeOH–EtOAc	$C_{19}H_{20}N_2 \cdot HCl$	72.95	6.77	8.96	11.35	72.51	6.75	9.21	11.41
16	7-OCH_3[b]	H	C_6H_5CO	6.69	A	205–206	CH_2Cl_2–MeOH	$C_{20}H_{20}N_2O_2$	74.97	6.29	8.74		75.00	6.45	8.92	
17	7-OCH_3	H	$C_6H_5CH_2$	91.5	B	247–248 dec	MeOH–EtOAc	$C_{20}H_{22}N_2O \cdot HCl$	70.06	6.76	8.17	10.34	70.15	6.94	8.12	10.32
18	7-OCH_3	H	H	85.4	C	275–275.5 dec	MeOH	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	11.09	14.03	61.83	6.71	10.92	13.85
19	9-F[b]	H	C_6H_5CO	34.8	A	165–167	EtOAc–Skelly B	$C_{19}H_{17}FN_2O$	74.00	5.56	9.09	(6.16)	73.57	6.02	8.89	(5.93)
20	9-F	H	$C_6H_5CH_2$	83.6	B	143–144	EtOAc	$C_{19}H_{19}FN_2$	77.52	6.51	9.52	(6.45)	77.81	6.52	9.25	(6.25)
21	9-F	H	H	86.7	C	179–180	EtOAc	$C_{12}H_{13}FN_2$	70.56	6.41	13.72	(9.30)	70.70	6.09	13.60	(9.09)
22	7-CH_3[b]	H	C_6H_5CO	37.9	A	189–190	EtOAc	$C_{20}H_{20}N_2O$	78.92	6.62	9.20		78.70	6.79	8.99	
23	7-CH_3	H	$C_6H_5CH_2$	41.9	B	210.5–212	MeOH–EtOAc	$C_{20}H_{22}N_2 \cdot HCl$	73.49	7.09	8.57	10.85	73.09	7.27	8.18	10.60
24	7-CH_3	H	H	75.0	C	271 dec	MeOH	$C_{13}H_{16}N_2 \cdot HCl$	65.95	7.24	11.84	14.98	65.93	7.26	11.53	14.90
25	9-CH_3[b]	H	C_6H_5CO	40.6	A	210–211	CH_2Cl_2–MeOH	$C_{20}H_{20}N_2O$	78.91	6.62	9.21		78.30	6.80	9.10	
26	9-CH_3	H	$C_6H_5CH_2$	93	B	142.5–143.5	EtOAc–Skelly B	$C_{20}H_{22}N_2$	82.72	7.64	9.65		82.38	7.91	9.96	
27	9-CH_3	H	H	95.2	C	243.5–245 dec	CH_2Cl_2–MeOH	$C_{13}H_{16}N_2$	77.96	8.05	13.99		77.76	8.38	13.93	
28	9-OCH_3	CH_3	CH_3		D	270 dec	MeOH	$C_{15}H_{20}N_2O \cdot HCl$	64.16	7.54	9.98	12.63	64.20	7.73	9.82	12.78
29	9-OCH_3	CH_3	H		D	272 dec	MeOH	$C_{14}H_{18}N_2O \cdot HCl$	63.03	7.18	10.50	13.29	62.89	7.25	10.36	13.25
30	10-OCH_3	CH_3	C_6H_5CO	85.5	E	187.5–188.5	CH_2Cl_2–MeOH	$C_{21}H_{22}N_2O_2$	75.42	6.63	8.38		75.36	6.80	8.36	
31	10-OCH_3	CH_3	$C_6H_5CH_2$		E	246–247.5	MeOH–EtOAc	$C_{21}H_{24}N_2O \cdot HCl$	70.67	7.06	7.85	9.94	70.49	7.45	7.78	10.03
32	10-OCH_3	CH_3	H		E	276.5–278	MeOH	$C_{14}H_{18}N_2O \cdot HCl$	63.03	7.18	10.50	13.29	62.93	7.36	10.52	13.35
33	10-OCH_3[c]	H	C_6H_5CO	6.82	A	264.5–266.5	CH_2Cl_2–MeOH	$C_{20}H_{20}N_2O_2$	74.97	6.29	8.74		74.49	6.63	9.01	
34	10-OCH_3	H	$C_6H_5CH_2$	83.3	B	163.5–164.5	EtOAc–Skelly B	$C_{20}H_{22}N_2O$	78.40	7.24	9.14		78.80	7.42	9.03	
35	10-OCH_3	H	H	75.6	C	236	MeOH–EtOAc	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	11.09	14.03	61.95	6.49	10.98	14.06
36	8-OCH_3	H	C_6H_5CO	23.6	A	202–203.5	CH_2Cl_2–MeOH	$C_{20}H_{20}N_2O_2$	74.97	6.29	8.74		74.77	6.50	8.62	
37	8-OCH_3	H	$C_6H_5CH_2$	77.4	B	146.5–147	EtOAc	$C_{20}H_{22}N_2O$	78.40	7.24	9.14		78.25	7.44	9.33	
38	8-OCH_3	H	H	72.4	C	276–276.5 dec	H_2O	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	11.09	14.03	62.03	6.87	11.17	14.12
39	9-OCH_3[c]	H	C_6H_5CO	9.37	A	126.5–127.5	EtOAc	$C_{20}H_{20}N_2O_2 \cdot 0.25CH_3CO_2C_2H_5$	73.66	6.48	8.18		73.58	6.68	7.89	
40	9-OCH_3	H	$C_6H_5CH_2$	84	B	127.5–129.5	EtOAc–Skelly B	$C_{20}H_{22}N_2O$	78.40	7.24	9.14		78.54	7.35	9.42	
41	9-OCH_3	H	H	92.3	C	235–235.5	MeOH	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	11.09	14.03	61.30	6.85	10.99	14.11

[a] 3-Methoxyphenylhydrazine hydrochloride was prepared by the method of M. W. Bullock and J. J. Hand, *J. Am. Chem. Soc.*, **78**, 5856 (1956). [b] 2-Methoxyphenylhydrazine hydrochloride, 4-fluorophenylhydrazine hydrochloride, and 2- and 4-tolylhydrazine hydrochlorides were obtained from Aldrich Chemical Company, Inc., Milwaukee, Wis. [c] 4-Methoxyphenylhydrazine was obtained from Chemicals Procurement Laboratories, Inc., College Point, N. Y.

SCHEME I



1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indoles with substituents at C-7 to C-10 were obtained by employing appropriately substituted phenylhydrazines in the reaction scheme described above. These compounds have been listed in Table I. Cyclization of the 3-methoxyphenylhydrazone of 1-benzoylhexahydroazepin-4-one gave two isomeric products: 3-benzoyl-10-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**33**) and 3-benzoyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**36**) which were separated by silica gel chromatography and identified by nmr. Alkoxy and hydroxy substituents on the indole nucleus normally increase the magnetic shielding of the hydrogens adjacent to them.[22] For 3-benzoyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole[19b] this effect produced a well-defined coupling pattern characteristic of 1,2,4-trisubstituted benzenes of this type. The following assignments for the aromatic protons were made: H-7, a doublet centered at δ 6.84 (apparent $J_{7,9}$ = 2 cps); H-9, a pair of doublets centered at δ 6.65 (apparent $J_{7,9}$ = 2 cps and $J_{9,10}$ = 8 cps); H-10 a doublet centered at δ 7.27 (apparent J = 8 cps). The nmr spectrum of 10-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole hydrochloride (**35**),[19c] on the other hand, had a pair of doublets centered at δ 6.52 for H-9 and a complex multiplet at δ 6.92–7.15 for H-7 and H-8.

Pharmacology

Methods.—Male, albino mice of Upjohn strain (Rockland Farm ancestry, 18–25 g) were used in all of the studies reported here. Unless specified otherwise, drugs were suspended or dissolved in 0.25% aqueous methylcellulose solution and administered intraperitoneally.

Procedures for measuring the acute toxicity (LD_{50}) and the influence of test compounds on simple reflexes and behavior—righting reflex, traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), fighting mouse (FM_{50}), and antagonism of nicotine-induced running (R), tonic-extensor convulsions and death (TE–D)—have been described.[23] Other test procedures used for this series of compounds were the following.

Pit-Avoidance Test (P_{50}).[24]—The pit avoidance is a conditioned-response procedure in which the apparatus ("pit") serves as the conditioning stimulus. Mice avoid shocks through a grid floor by jumping out of the pit before the current is turned on. High doses of central depressants render the mouse unable to leave the pit even when the current is on: "escape loss." Mice treated with multiple doses (0.5 log intervals) of the test compound (3–5 animals/dose) were tested for 12 trials 10 min after drug administration. The dose that caused 50% loss of avoidance without escape loss was estimated from the dose–response relationship.

Anorexigenic Test.—Groups of eight mice were weighed, housed together, and allowed to eat, *ad lib*, a ground diet (Upjohn BA) mixed with 0.03, 0.1, and 0.3% of the test compound for 24 hr. At the end of the test period, food consumption and weight change were measured. Controls run with the test compounds consisted of two groups without drug and one group on a 0.03% *d*-amphetamine diet. The anorexigenic potencies were expressed as a ratio of the *d*-amphetamine potency.

Tryptamine Symptoms.—Groups of four mice were injected intravenously with a solution of the test compound in saline, starting at 100 mg/kg and decreasing at 0.3 log intervals. Presence or absence of tremors (t), clonus of the forepaws (p), and hind-leg spread (hls) within 15 min were recorded and the 50% effective dose (ED_{50}) for each symptom was calculated by the method of Spearman and Karber.[25]

Results.—The pharmacological activities demonstrated with the hexahydroazepino[4,5-*b*]indoles in mice belong to three categories: (1) depression of some covert behaviors (inhibition of fighting and positive dish test, pit avoidance, etc.), (2) appetite suppression, and (3) induction of tryptamine-like symptoms after intravenous injections.

(1) Depression of Covert Behaviors.—The ED_{50}'s of selected members of the present series of compounds on tests measuring covert behaviors are presented in Table II. The corresponding ED_{50}'s for chlorpromazine and α-methyltryptamine are included for comparison. While none of the compounds in Table II is especially toxic ($LD_{50} \geq 75$), some members compare very favorably with chlorpromazine and are much more potent than α-methyltryptamine in depressing the covert behaviors. Thus, compounds **35**, **7**, and **32** are more potent than chlorpromazine on a milligram per kilogram

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TABLE II

PHARMACOLOGICAL ACTIVITIES OF HEXAHYDROAZEPINO[4,5-*b*]INDOLES[a]

Compd	LD_{50}	FM_{50}	Ch_{50}	Tr_{50}	D_{50}	P_{50}	R	TC-10
4	>1000	>20	79	>200	50	...[d]	>200	178
5	422	>20	>200	>200	63	...	>200	>200
6	178	2.2	45	100	11	30	>100	11
7	112	1.1	9.9	25	2.8	6	>100	5.6
9	142	14	>100	>100	50	...	>100	>100
10	>200	>20	>200	>200	178	...	>200	>200
12	126	14	45	50	18	>30	>50	40
13	100	7	40	>50	15	15	>50	13
14	>1000	>20	200	>200	89	...	>200	>200
15	142	16	>50	79	32	...	>50	20
18	>200	9	>200	89	25	>30	>200	36
21	75	5	100	100	7.9	30	>100	14
24	562	9	>100	126	10	>30	>100	7
27	178	4.4	63	50	12.5	10	>100	22
28	142	>20	79	>100	32	>30	>100	79
29	100	9	>25	32	18	15	>25	18
32	142	1.8	0.8	20	1	6	>25	9
35	178	0.56	6.3	14	3.9	3	>50	4.4
38	178	8.8	100	200	20	20	>100	25
41	75	7.1	25	40	12.5	15	>50	12
b	215	2.8	5.6	12	5.6	3	3.5	1.3
c	159	5.6	>50	40	12	30	>50	3.1

[a] See text for an explanation of the symbols. Values are expressed in mg/kg. [b] Chlorpromazine hydrochloride. [c] α-Methyltryptamine. [d] Not tested.

basis in FM and D. The high FM and D potency of these compounds becomes more significant when it is noted that none shows parallel potency in Ch and Tr which measure skeletal muscle strength and coordination. Thus, unlike chlorpromazine, none of these compounds produced gross behavioral depression or loss of righting reflex even at toxic doses. In addition to the unsubstituted molecule (**6**), the most active compounds in FM and D have a methoxyl substituent at C-10 (**35**) and/or a methyl group at N-6 (**32**, **7**). Comparable but slightly less active are compounds with substituents at C-9 (**27**, **21**, **41**, and **29**), C-8 (**38**), and C-7 (**18**, **24**). In contrast, substitution of the azepino nitrogen (**4**, **5**, **10**, **9**, and **28**) or the indole nitrogen with groups larger than ethyl (**14**, **15**) decreases the activity in covert behavioral tests in mice.

Compared to chlorpromazine, the azepino indoles are less active in the pit avoidance test; only **35** has a potency similar to that of chlorpromazine. Also weaker than chlorpromazine is the antagonism of the convulsions and death induced by the intravenous injections of nicotine. In sharp contrast to chlorpromazine, none of the compounds tested antagonizes nicotine-induced running.

(**2**) **Appetite Suppression.**—A number of the compounds in the present series depress food intake and cause body weight loss comparable to *d*-amphetamine (Table III). The most active compounds in addition to the parent compound (**6**) have a substituent at C-7 to C-10 and/or a small alkyl group on the indole nitrogen (**7**, **24**, **32**, **21**, and **13**). Methylation of the azepino nitrogen decreases the anorexigenic activity (compare **12** with **7** and **28** with **29**).

(**3**) **Induction of Tryptamine-like Symptoms.**—Tedeschi, *et al.*,[26] reported that tryptamine, injected intravenously into rats, produced a characteristic pattern of involuntary movements including tremors of the body, forepaw clonus, and hunching of the back. 5-Hydroxytryptamine, injected in the same manner, produced only inactivity and flaccid paralysis of the hind limbs (hind-leg spread). We have observed in this laboratory that higher doses of tryptamine and some of its structural analogs injected intravenously into mice produced similar symptoms (unpublished observations). This relatively specific test offers a simple means to compare the likeness of the present series of compounds with tryptamine.

For producing t and hls after intravenous injection, the parent compound **6** has a potency equal

TABLE III

ANOREXIGENIC AND TRYPTAMINERGIC ACTIVITIES OF SELECTED HEXAHYDROAZEPINO[4,5-*b*]INDOLES

	Potency				
	Anorexigenic[a]		Tryptaminergic[b]		
Compd	Food intake	Body wt loss	t	p	hls
6	0.53	0.53	57.5	>100	57.5
7	1.0	0.59	16	57.5	21.8
9	...[c]	...	73	>100	>100
12	0.15	0.13	12.3	26.3	26.3
13	0.48	0.67	>100	>100	26.3
18	...	...	>100	>100	>100
21	0.56	0.20	100	>100	>100
24	1.0	0.63	>100	>100	>100
27	0.33	0.27	>100	>100	>100
28	<0.1	<0.1	26.3	34	26.3
29	0.15	0.14	34	>100	>100
32	0.71	0.67	12.6	>46	16
35	0.24	0.30	17.8	>100	14.8
38	0.23	0.33	34	>100	>100
41	<0.1	<0.1	26.3	>100	>100
d	...	...	73	>100	83.2
e	0.38	0.40	57.5	>100	69.2
f	0.50	0.42	...	...	...

[a] Relative to *d*-amphetamine (= 1). [b] For an explanation of the symbols see the text. Expressed as ED_{50} (mg/kg iv). [c] Not tested. [d] Tryptamine hydrochloride. [e] α-Methyltryptamine. [f] Chlorpromazine hydrochloride.

(26) D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **126**, 223 (1959).

to α-methyltryptamine and better than tryptamine (Table III). Methoxyl substitution at C-10 (**35**), C-9 (**41**), and C-8 (**38**), but not at C-7 (**18**) increases the tremor-inducing potency and is more effective than methyl (**27**) or fluoro (**21**) substitution at C-9. Methylation of the indole nitrogen enhanced the tryptamine-like activity of some compounds (**7**, **32**, but not **29**). A similar effect was obtained by methylating the azepino nitrogen (**28**, **12** but not **9**).

Comments.—In view of the relationship of this series of compounds to tryptamine, it was interesting to find that **6** was at least as active as α-methyltryptamine in inducing tremors and hind-leg spread in mice after an intravenous injection. Furthermore, methoxylation of C-8, -9, and -10, but not C-7, enhanced this phenomenon; substitution with methoxyl was more favorable than with methyl or halogen. This specificity of ring substitution is in accord with the smooth muscle stimulant activities of the hydroxytryptamines.[27]

In this series of compounds, the potency of depressing covert behaviors (FM, D, and P) roughly parallels that for inducing tryptamine-like overt symptoms in mice after intravenous injection. While the role of 5HTP in brain function is still ill-defined, experimental evidence in laboratory animals tends to suggest a depressant type of activity.[28] More specifically 5HTP has been shown to abolish intraspecific aggressive behavior[29,30] with a wide spread between effective and toxic doses. The present series of compounds is expected to have therapeutic usefulness in mental disease. One of these compounds (**7**) is now being tested in the clinic.

Experimental Section[31]

3-Benzoyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (4). Procedure A.—A stirred solution of 1-benzoylhexahydroazepine-4-one (228.0 g, 1.05 moles), phenylhydrazine (127.2 g), and HOAc (18.4 ml) in absolute EtOH (2.4 l.) was refluxed under N_2 for 30 min, then cooled in an ice bath for 5 hr. The crystalline product was collected by filtration, washed with EtOH, and dried in a vacuum oven to give 279.4 g (86.6%) of crude hydrazone, mp 178–186°. Additional product (21.6 g, mp 178–186°) was obtained by concentrating the filtrate *in vacuo*. The combined product was added under N_2 with stirring to 88% formic acid (2 l.) which had been preheated to 80° on the steam bath. Heating was continued during the addition and for an additional 30 min, and the hot reaction mixture was poured into 10–15 l. of a stirred mixture of ice and H_2O. The resulting pink precipitate was collected, washed with H_2O, and dissolved in CH_2Cl_2. The CH_2Cl_2 was washed with H_2O, dried ($MgSO_4$), and poured onto a column of 5.4 kg of neutral alumina. Elution of the column with 75% EtOAc–Skellysolve B gave 105.3 g (36.9%) of **4**, mp 168–169°. The analytical sample had λ_{max} 225, 282, and 290 mμ (ε 38,700, 6950, and 6050), inflection at 275 mμ (ε 6600). The infrared spectrum showed NH, 3260, 3240, 3200, and C=O, 1605 cm^{-1}. The nmr spectrum had peaks at δ 6.98–7.50 (9 H multiplet, aromatic), 8.17 (broad singlet, NH), 3.84 (4 H broad singlet, C-2 and C-4), and 2.97 (4 H broad singlet, C-1 and C-5).

3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (5). Procedure B.—To a stirred mixture of $LiAlH_4$ (6.0 g) in dry THF (400 ml) was added, under N_2 during 1 hr, **4** (6.0 g, 20.6 mmoles) in 150 ml of THF. The resulting mixture was stirred at room temperature for 4 hr, refluxed for 18 hr, cooled in an ice bath, and treated successively with H_2O (6.0 ml), 15% NaOH (6 ml), and H_2O (18 ml). This mixture was stirred for 2 hr and filtered. The filtrate was concentrated under reduced pressure, and the residue was crystallized from EtOAc–Skellysolve B to yield 3.4 g (59%) of **5**, λ_{max} 227, 283, 290 mμ (ε 37,300, 7250, 6600), inflection at 275 mμ (ε 6550).

1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole (6) Hydrochloride. Procedure C.—A mixture of **5** (73.9 g, 0.27 mole), 95% EtOH (700 ml), HOAc (300 ml), and 10% Pd–C (8.0 g) was hydrogenated at an initial pressure of 2.1 kg/cm^2 for 2 hr. The filtered solution (vacuum filtration through Celite) was concentrated *in vacuo*. The residue in H_2O was decolorized with Darco G-60, cooled in an ice bath, and made alkaline with 50% NaOH. The solid was collected, washed with H_2O, dried under reduced pressure at 40°, and crystallized from MeOH–EtOAc to give 40.5 g, mp 193–195°, and 5.95 g, mp 190–193° (93.5% yield), of **6**. This amine (7.6 g) in MeOH–EtOAc was acidified with methanolic HCl. Crystallization of the resulting hydrochloride gave 6.74 g (74.4%) of **6** hydrochloride, mp 250.5–251.5°. The analytical sample had λ_{max} 223, 282, and 289 mμ (ε 34,950, 7400, 6400), inflections at 274 and 279 mμ (ε 7000 and 7300).

6-Methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (7) Hydrochloride. From 6. Procedure D.—To an ice-cold, stirred solution of **6** (3.7 g, 0.02 mole) in dry DMF (200 ml) was added under N_2, 0.96 g (0.2 mole) of a 55% suspension of NaH in mineral oil. This mixture was allowed to warm to 25° and stand for 2 hr. It was then cooled in an ice bath and treated, during 30 min, with MeI (1.4 ml, 0.02 mole) in Et_2O (25 ml). The resulting solution was left for 18 hr at 25°, concentrated under reduced pressure to about 50 ml, and poured into H_2O. This solution was extracted four times with Et_2O. The ether extract was washed with brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue in EtOAc was acidified with methanolic HCl, and the resulting hygroscopic salt was crystallized from MeOH–EtOAc to give 3.2 g (75.3%) of **7**·HCl, mp 211–213°.

The dimethyl derivative **12** which was occasionally obtained as a by-product in this reaction could easily be separated from **7** by silica gel chromatography using 2% Et_2NH–20% MeOH–78% EtOAc as eluent.

From 8. Procedure E.—A 57.1% mineral oil suspension of NaH (28.2 g) was added under N_2 to a stirred solution of 3-benzoyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (177 g) in dry DMF (7.56 l.). This mixture was stirred for 2 hr at room temperature. MeI (41.8 ml) was added dropwise to the cold (ice bath) mixture during 20 min. The resulting mixture was left at room temperature for 18 hr. The DMF was removed on the rotating evaporator (7 mm, bath temperature 55–60°). The residue was suspended in H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (K_2CO_3), and concentrated under reduced pressure. The residual oil was dissolved in C_6H_6, and the resulting solution was concentrated to dryness. The resulting oil in THF (1 l.) was added slowly, under N_2, to an ice-cold, stirred suspension of $LiAlH_4$ (145 g) in THF (7 l.). The mixture was warmed slowly to reflux temperature, refluxed for 18 hr, cooled in an ice bath, and treated successively with H_2O (145 ml, dropwise), 15% NaOH (145 ml), and H_2O (435 ml). This mixture was stirred for about 30 min and filtered. The solid was washed well with THF and the combined filtrates were concentrated *in vacuo*. The residual oil in C_6H_6 (1 l.) was concentrated to dryness (reduced pressure). Thin layer chromatography of the resulting oil on silica gel with 2% Et_2NH–15% MeOH–83% EtOAc indicated that it was a mixture of 3-benzyl-1,2,3,4,5,6-hexahydro-6-methylazepino[4,5-*b*]-indole and **7**. It was, therefore, mixed with 95% EtOH (1.5 l.), HOAc (50 ml), and 10% Pd–C and hydrogenated on a Parr apparatus for 1.5 hr. The catalyst was removed by vacuum filtration through Celite, and the filtrate was concentrated (reduced pressure). The residue in H_2O was washed with Et_2O, cooled in an ice bath, made alkaline with 50% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried (K_2CO_3), and concentrated *in vacuo*. A MeOH solution of the residue was cooled in an ice bath and acidified with methanolic HCl. Crystallization of the resulting salt from MeOH–EtOAc gave 110.7 g (76.8%) of **7**·HCl, mp 214–216°.

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(31) Melting points, taken in a capillary tube, are corrected. Ultraviolet spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Infrared spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Skellysolve B is commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Celite is a filter aid manufactured by Johns-Manville, New York 16, N. Y. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck A. G., Darmstadt, Germany.

3-Formyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (10). Procedure F.—A stirred mixture of Ac_2O (9.5 ml) and 98% formic acid (4.0 ml) was allowed to stand at 25° for 1 hr, cooled in an ice bath, and treated with 5.6 g (0.03 mole) of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole. As the amine went into solution, a second precipitate formed. Ether (25 ml) was added to this mixture which was left at room temperature under N_2 for 18 hr and poured into H_2O. The solid was collected, washed with H_2O, and dried *in vacuo* to give 6.3 g of crude product, mp 220–221.5°. Recrystallization of this material from MeOH–EtOAc yielded in three crops, 5.7 g (89%), of **10**. The infrared spectrum showed C=O, 1655, 1645 cm^{-1}.

3-Methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (9). Procedure G.—To a stirred suspension of $LiAlH_4$ (1.0 g) in ice-cold THF (100 ml) was added **10** (1.0 g, 0.005 mole), and the mixture was refluxed under N_2 for 18 hr, cooled in an ice bath, and treated successively with H_2O (1 ml), 15% NaOH solution (1 ml), and H_2O (3 ml). The resulting mixture was stirred for 1 hr and filtered. Concentration of the filtrate (reduced pressure) gave a solid which was recrystallized from EtOAc to yield 0.85 g (91.3%) of **9**, mp 162–166°.

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Bisquaternary Ammonium Indolines and Perhydroindoles in Ganglionic Blockade[1]

MATHIAS P. MERTES, SUBHASH A. NERURKAR,

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

AND EDWARD J. WALASZEK

Department of Pharmacology, School of Medicine, University of Kansas, Kansas City, Kansas

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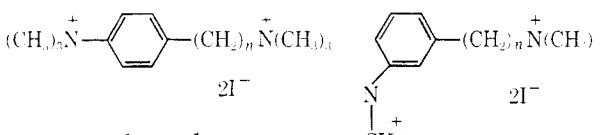
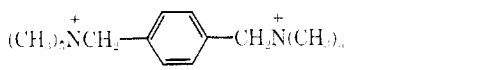
The indoline derivatives, 1-methyl-6-dimethylaminoindoline dimethiodide (**4**) and 1-methyl-5-dimethylaminoindoline dimethiodide (**5**), were synthesized by methylation of 6-aminoindoline and 5-aminoindoline. 1-Methyl-6-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (**7**) and 1-methyl-6-*anti*-dimethylamino-*cis*-octahydroindole dimethiodide (**6**) were obtained by reduction of 6-aminoindoline to the corresponding octahydro compounds followed by reductive methylation and quaternization. 1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (**8**) was synthesized in a similar manner from 5-aminoindoline. Preliminary biological results on the guinea pig ileum indicate that dimethiodide **7**, with only three carbons separating the onium heads, is as active as hexamethonium.

The discovery by Paton and co-workers[2] of potent ganglionic-blocking activity in the bisquaternary alkyls was followed rapidly by investigations into the nature of the blockade, in particular the effect of distance between the onium heads on activity. Compounds of the general structure **1** and **2** are reported to have considerable activity, particularly **1b** which is



1a, $n = 1$
b, $n = 2$
c, $n = 3$

2a, $n = 1$
b, $n = 2$
c, $n = 3$



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four times as active as hexamethonium on the isolated guinea pig ileum.[3,4] However, the isomeric bisquaternary *p*-xylylene **3** has been found to be inactive.[5] Reduction of the benzene ring of **1b** to the cyclohexyl analogs afforded the opportunity of examining the geometric isomers. One of the isomers was reported to be as active a ganglion-blocking agent as the corresponding phenyl analog **1b**, whereas the other isomer was only one-tenth as active; the author failed to assign the isomeric structure.[6]

The dependence of activity on chain length in the polymethylene bisoniums and in **1** and **2** was interpreted by assuming that the blocking agent made simultaneous contact with two anionic receptor groups and that the length of the most active compounds was a measure of the interreceptor distance.[6,7]

Gill[8] has calculated the interquaternary distance probability distributions for the polymethylene compounds (n = 4–8) and for **1a**–**c**. From these calculations for the most active members of each series (6–8 Å) it was assumed that the interreceptor distance would lie within these limits. The qualitative agreement between these calculated and observed activities of the individual members of the two series of compounds was taken as proof for the validity of the "two-point contact" hypothesis. Gill's[8] explanation for the inactivity of **1a** and **3** is that there is not a range of interquaternary distances in these compounds, but this

(1) This work was generously supported in part by the University of Kansas Graduate School and by Research Grant 1K3-CA 10739 of the National Institutes of Health, U. S. Public Health Service.

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