Synthesis of Some 3-Indenealkylamines. Comparison of the Biological Activity of 3-Indenealkylamines and 3-Benzo[*b*]thiophenealkylamines with Their Tryptamine Isosteres[1a,b]

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The synthesis of a series of indene isosteres of substituted tryptamines is described. The activity of these compounds, 3-(3-aminopropyl)indene and a number of benzo[*b*]thiophene isosteres of substituted tryptamines was compared to that of the isosteric indole compounds by determining, in the rat stomach fundus, their intrinsic activity relative to 5-hydroxytryptamine and their affinity. The majority of the indenes, tryptamines, and benzo[*b*]thiophenes have a greater intrinsic activity than 5-hydroxytryptamine, but none has a higher affinity. A high degree of correlation exists between isosteres with respect to these drug parameters. These correlations lead to the conclusion that the substitution of a methylene carbon or of sulfur for the indole ring nitrogen of tryptamine does not appreciably alter contractile activity in the rat stomach fundus.

The indole nucleus is found in a variety of compounds of interest to the physiologist and pharmacologist. For example, a number of tryptamines possess psychotomimetic properties. The occurrence of such compounds in human blood and urine has been reported,[2-4] but remains controversial.[5] 5-Hydroxytryptamine (5-HT) is a neurotransmitter in invertebrates[6] and probably in vertebrates.[7-9] These observations have resulted in a large number of investigations being undertaken in this area. However, few studies have been directed toward the elucidation of the nature of the receptor for 5-HT and other tryptamines. Using the rat stomach fundus preparation,[10] Barlow and Khan[11] and Vane[12] examined the changes in pharmacological activity of tryptamine derivatives resulting from alterations in the position and nature of the substituents on the indole ring. Vane[12] proposed two points of attachment of 5-HT to its receptor site, the hydroxyl group at the 5 position and the terminal amino group at the 3 position. As Vane[12] pointed out, however, other areas of the 5-HT molecule could be important for its interaction with the receptor. One of these is the nitrogen in the 1 position of the indole ring. To test the importance of the ring nitrogen the principle of biological isosterism can be employed. Lewis, *et al.*,[13] Beck, *et al.*,[14] and Campaigne, *et al.*,[15] have reported on the pharmacological effect of replacing the nitrogen in the 1 position by sulfur. The benzo[*b*]thiophene derivatives prepared by Lewis, *et al.*,[13] were isosteric with relatively inactive indole compounds, hence it is difficult to draw conclusions regarding the effect of this replacement. These authors did observe, however, that this substitution leads to a reduction of agonistic activity in a variety of smooth muscle preparations and to the emergence of variable nonspecific antagonistic properties toward 5-HT, acetylcholine, and histamine. Beck and co-workers[14] reported the CNS effect of some benzo[*b*]thiophenes as measured by the quantitative EEG in rabbits.[16] In all cases the drugs were tested for their ability to reverse pentobarbital sedation. Comparison of tryptamine and α-methyltryptamine with their benzo[*b*]thiophene isosteres revealed that α-methyltryptamine was considerably more potent in pentobarbital reversal than was tryptamine, while the corresponding benzo[*b*]thiophenes were both very much like tryptamine in potency. Using the same assay system[16] Campaigne, *et al.*,[15] found the benzo[*b*]thiophene isostere of 5-hydroxytryptamine to be somewhat less active than 5-hydroxytryptophan. Although replacement of the ring nitrogen of indolealkylamines by oxygen has been achieved, no detailed pharmacological results have been reported.[17] We have investigated the effect of replacing the indolealkylamine ring nitrogen by either a methylene carbon[18] or sulfur[19] on the ability of these compounds to contract an isolated smooth muscle.

Substitution of an aminoalkyl side chain at the 3 position of indene may be accomplished by treating the indene with the appropriate aminoalkyl halide in the presence of a basic reagent such as sodamide[20] or butyllithium.[21] The mechanism of the reaction (Scheme I, R = H) is considered to involve formation of an indenyl ion (II), substitution at the 1 position (III), and a subsequent intramolecular proton migration to give the 3-substituted derivative (IV).[22] In the

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(18) We are indebted to Dr. Hans Dressler (Koppers Co., Inc.) for the gift of 3-(3-aminopropyl)indene.

(19) We are indebted to Mr. Raymond A. Beck, Dr. Edward S. Neiss, and Dr. Ernest Campaigne for the gift of the benzo[*b*]thiophenes.

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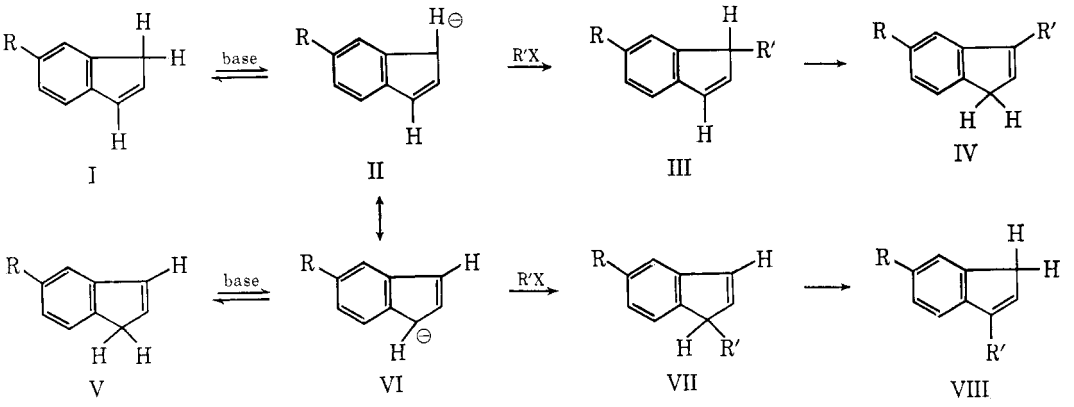
SCHEME I



present study 3-substitution of the product indenealkylamine has been unambiguously established by use of nmr spectroscopy. When 5- or 6-methoxyindene (Scheme I, I or V, R = OCH_3) is used as the starting material in the synthesis of indenealkylamines, the resonance of forms II and VI should lead to isomerization of the starting material. Thus the same mixture of products IV and VIII would result irrespective of whether the starting material was I or V. However, Winter, *et al.*,[23] have shown that 5- and 6-methoxyindenes fail to isomerize when exposed to trimethylamine or boiling KOH. In the present study we have further observed that 5-methoxyindene does not tautomerize to the 6-methoxyindene when treated with sodamide, although some tautomerization of the 6-methoxyindene does occur under these conditions. Thus, it was anticipated that 5-methoxyindene, when treated with N,N-diethylaminoethyl chloride in the presence of sodamide, would give rise to a single disubstituted product (V, R = OCH_3; R′ = $CH_2CH_2NEt_2$). A single product, a disubstituted indene with one vinyl and two methylene protons, was, in fact, obtained and was assigned the structure of 3-(N,N-diethyl-2-aminoethyl)-6-methoxyindene. The same product was also obtained when butyllithium was used instead of sodamide. This raises the question, which we have not resolved, as to whether an indenyl ion is formed in this reaction or whether the reaction takes place by a concerted mechanism. Under similar conditions, 6-methoxyindene was rather unreactive, most of the starting material being recovered unchanged. Small amounts of five basic products were obtained. None of these corresponded to 3-(N,N-diethyl-2-aminoethyl)-6-methoxyindene on thin layer chromatography, although the spectrum of the major component was compatible with that of an impure disubstituted indene.

The pharmacological activity of the indenealkylamines, benzo[*b*]thiophenes, and, whenever possible, the corresponding tryptamines was investigated by obtaining cumulative dose–response curves[24] to the drugs using the rat stomach fundus preparation of Vane.[10] The pharmacological parameters calculated were the intrinsic activity (the ratio of the maximum contraction obtained with the stated drug to that obtained with the reference compound, 5-HT) and the affinity, expressed as the pD_2 value.[25]

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Experimental Section[26]

Chemistry.—The indenealkylamines synthesized are listed in Table I along with yield, physical constants, and analytical data.

Method A. 3-(N,N-Diethyl-2-aminoethyl)-6-methoxyindene.—This preparation will illustrate modifications from the procedure of Eisleb.[20] A benzene solution of 1.53 g (10.5 mmoles) of 5-methoxyindene and 1.39 g (10.3 mmoles) of N,N-diethylethylamine hydrochloride was heated under reflux for 4 hr with 0.42 g (10.8 mmoles) of sodamide. The reaction mixture was cooled and washed with water, and the solvent was removed under reduced pressure. The dark liquid remaining was put on a silica gel column (Will Scientific, grade 923, 25:1 ratio). Elution with $CHCl_3$ removed 0.11 g of unreacted 5-methoxyindene. Subsequent elution with MeOH gave 2.17 g of a dark liquid which distilled at a temperature (bath) of 140–180° (0.1 mm) to give the product as an amber liquid in 37% yield. Tlc (silica gel; HOAC–H_2O, 1:1) gave a single green spot (R_f 0.68) when sprayed with HCHO–H_2SO_4.[27]

Method B. 3-(2-Aminoethyl)indene.—All reactions were carried out under N_2. An ether solution of 2 g (17.2 mmoles) of indene was treated with 12 ml of 1.6 *M* butyllithium in hexane (19.2 mmoles) at −10°. After 2 hr the mixture was cooled to −30°, an additional 19 mmoles of butyllithium was added, and an ether suspension of 2 g (17.2 mmoles) of 2-chloroethylamine hydrochloride was then introduced over a period of 0.5 hr. After warming to room temperature, the basic fraction was separated from the neutral and acidic components and converted to the oxalate, a pale yellow solid, mp 173–178°. Sublimation at a bath temperature of 142–149° (0.7 mm) gave a white solid which after recrystallization from absolute alcohol melted at 176.5–178°.

Pharmacology.—Van Rossum's methods for obtaining cumulative dose–response curves were used.[24] The rat stomach fundus preparation of a Vane[10] was employed with the following modifications: (a) the bathing solution was that of Armitage and Vane,[28] (b) no hyoscine was added to the bathing fluid, (c) responses were recorded using a pendulum auxitronic lever[29] with a magnification of 8 and resting load on the muscle of 1 g, (d) two strips were cut from the same organ and used in parallel, (e) the relative sensitivity of the two strips was determined by the use of 5-HT doses giving submaximal contractions, (f) the intrinsic activity on the test compound was determined by comparison of the maximum contraction occasioned by this compound on one strip with a maximum contraction occasioned by 5-HT on the parallel strip.

Only one drug was tested on each preparation, at least five dosages of the drug being used. Each drug was tested in at least three preparations, the actual number being given in Table II. The affinities and the slopes of the common regression line of the response metameter[30] on the logarithm of the dose was calculated

(26) For all analytical data and physical constants, see Table I. Melting points were taken on a Kofler micro hot stage apparatus and are corrected.

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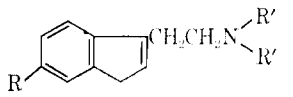
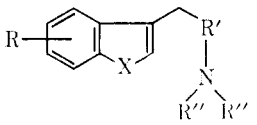
TABLE I[a]
3-INDENEALKYLAMINES



R	R′	Form	Method	Yield, %	Bp (mm) or mp, °C[b]	Formula	C	H	N	C	H	N
							——% calcd——			——% found——		
H	H	Oxalate	B	22	176.5–178	$C_{13}H_{15}NO_4$	62.24	6.07	5.62	62.34	6.12	5.76
H	CH_3	Base	A	32	140–142 (9)	$C_{13}H_{17}N$	83.37	9.15	7.48	83.14	8.92	7.68
H	C_2H_5	Base	A	58	104–105 (0.6)	$C_{15}H_{21}N$	83.66	9.83	6.51	83.49	9.67	6.74
H	$CH(CH_3)_2$	Base	A	62	135–145 (0.7)	$C_{17}H_{25}N$	83.89	10.35	5.76	83.95	10.47	5.90
OCH_3	CH_3	Base	B	51	140 (bath) (0.5)							
OCH_3	CH_3	Oxalate			138–140	$C_{16}H_{23}NO_5$	62.52	6.89	4.56	62.18	6.82	4.75
OCH_3	C_2H_5	Base	A, B	37	140–180 (bath) (0.1)	$C_{16}H_{23}NO$	78.31	9.45	5.71	78.51	9.60	5.83

[a] Melting points were taken on a Kofler micro hot stage apparatus (A. H. Thomas Co.) and are corrected. Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DB spectrophotometer. Nmr spectra were obtained with a Varian A-60 high-resolution spectrometer. The samples were run in CCl_4 solution using

TABLE II
ACTIVITY OF AMINES ON RAT STOMACH FUNDUS PREPARATION



No.	Compd	X	R	R′	R″	No. of expt	Rel intrinsic act. (SE)	pD_2 (SE)	Slope
1	5-Hydroxytryptamine	NH	5-OH	CH_2	H	62	1.00	7.72 (0.08)	1.00
2	3-(2-Aminoethyl)indene	CH_2	...	CH_2	H	3	0.98 (0.02)	5.02 (0.09)	0.96
3	Tryptamine	NH	...	CH_2	H	19	1.32[a] (0.17)	5.84 (0.09)	0.64
4	3-(2-Aminoethyl)benzo[*b*]thiophene	S	...	CH_2	H	4	1.10 (0.08)	4.78 (0.09)	0.95
5	3-(3-Aminopropyl)indene	CH_2	...	CH_2CH_2	H	3	0.49 (0.05)	4.68 (0.05)	1.27
6	3-(3-Aminopropyl)indole	NH	...	CH_2CH_2	H	3	0.72 (0.06)	4.24 (0.12)	0.82
7	α-Methyltryptamine	NH	...	$CH(CH_3)$	H	3	1.18 (0.12)	5.13 (0.12)	0.66
8	3-(1-Methyl-2-aminoethyl)benzo[*b*]-thiophene	S	...	$CH(CH_3)$	H	4	0.68 (0.05)	5.38 (0.15)	0.82
9	3-(N,N-Dimethyl-2-aminoethyl)indene	CH_2	...	CH_2	CH_3	8	1.27 (0.04)	4.02 (0.08)	1.50
10	N,N-Dimethyltryptamine	NH	...	CH_2	CH_3	3	1.32 (0.23)	3.52 (0.16)	1.87
11	3-(N,N-Dimethyl-2-aminoethyl)benzo-[*b*]thiophene	S	...	CH_2	CH_3	4	0.84 (0.08)	4.07 (0.56)	1.49
12	3-(N,N-Diethyl-2-aminoethyl)indene	CH_2	...	CH_2	C_2H_5	6	1.39 (0.10)	4.68 (0.06)	1.04
13	N,N-Diethyltryptamine	NH	...	CH_2	C_2H_5	4	1.01 (0.13)	4.03 (0.32)	1.28
14	3-(N,N-Di-*n*-propyl-2-aminoethyl)-[*b*]thiophene	S	...	CH_2	$(CH_2)_2CH_3$	4	0.91 (0.12)	4.85 (0.10)	1.58
15	3-(N,N-Diisopropyl-2-aminoethyl)-indene	CH_2	...	CH_2	$CH(CH_3)_2$	4	0.91 (0.12)	4.85 (0.10)	1.58
16	N,N-Diisopropyltryptamine	NH	...	CH_2	$CH(CH_3)_2$	3	1.51 (0.10)	4.92 (0.18)	1.23
17	3-[2-(1-Pyrrolidyl)ethyl]benzo[*b*]-thiophene	S	...	CH_2	...[b]	3	1.43 (0.11)	5.42 (0.13)	0.89
18	3-[2-(1-Piperidyl)ethyl]benzo[*b*]-thiophene	S	...	CH_2	...[b]	4	1.19 (0.06)	4.44 (0.29)	1.58
19	3-(N,N-Diethyl-2-aminoethyl)-6-methoxyindene	CH_2	6-OCH_3	CH_2	C_2H_5	6	1.11 (0.07)	4.81 (0.17)	1.06
20	6-Methoxy-N,N-diethyltryptamine	NH	6-OCH_3	CH_2	C_2H_5	3	0.10 (0.01)	3.58 (0.29)	2.24
21	5-Methoxy-N,N-diethyltryptamine	NH	5-OCH_3	CH_2	C_2H_5	3	1.98 (0.16)	5.88 (0.14)	0.49

[a] Calculated on the basis of five experiments. [b] Side-chain nitrogen forms part of a heterocyclic.

by the use of a Fortran IV computer program for probit analysis based on the method of Finney.[31]

Results and Discussion

Table II summarizes the parameters calculated from the dose–response curves of the compounds investigated in this study. For each drug are listed the intrinsic activity, the value of pD_2, and the slope of the common regression line after probit transformation. All values of intrinsic activity are relative to 5-HT which is assigned a value of 1.00. The aim of the present investigation was to evaluate the importance of the indole ring nitrogen in the pharmacological activity of the tryptamines. The data of Table II provide the means for such an evaluation in terms of the contractile effects of the tryptamines on the rat stomach fundus. To facilitate comparison of the ring unsubstituted compounds in the indene–indole series the agents have been ranked in terms of their affinity (Table III).

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Uv spectra[c]		Nmr spectra					
λ_{max}, mμ	log ε	CH_2	OCH_3	Vinyl protons	Aromatic protons	Ratio vinyl/CH_2 protons	Ir spectral lines, cm^{-1}
...	...	...	...	...	...	..	
251	5.34						3000, 2820, 1465, 1045, 772, 720
252	5.00	6.82	...	3.87	2.99–2.56	2	3040, 2880, 1475, 1390, 1210, 1075, 774, 721
251	4.81						3010, 1465, 1362, 1168, 772, 718
260	5.05	6.82	6.24	3.87	3.48–2.66	2	2950, 2770, 1475, 1255, 1240, 863, 812
...	...	...	...	...	...	..	
258	4.94	6.87	6.31	3.97	3.56–2.78	2	3000, 2810, 1470, 1062, 1017, 858, 842, 808

tetramethylsilane as the reference standard. Chemical shifts are reported as τ values. Microanalyses were performed by the Galbraith Laboratories, Inc., Knoxville 21, Tenn. [b] Recrystallizations from ethanol. [c] In absolute ethanol.

TABLE III
COMPARISON OF MEAN pD_2 VALUES FOR ISOSTERIC INDOLE–INDENE PAIRS

Indoles	5-HT >	T	> (*i*-Pr)$_2$	> PrAM	> Et_2	> Me_2
	7.72	5.84	5.42	4.24	4.03	3.52
Indenes		EtAM	> (*i*-Pr)$_2$	> PrAM	= Et_2	> Me_2
		5.02	4.92	4.68	4.68	4.02

It can be seen (Table III) that in both series the affinity (pD_2) is greatest in the primary ethylamines (tryptamine and indene-3-ethylamine) and declines thereafter in the order diisopropyl, propylamine, diethyl, dimethyl. While the range of pD_2 values is greater in the indoles (3.52–5.84 *vs.* 4.02–5.02 for the indenes), the mean pD_2 values for the two isosteric series are remarkably similar, 4.61 and 4.66 for the indoles and indenes, respectively. Consideration of the drugs in terms of relative intrinsic activity reveals, with the exception of **2** and **3**, only minor variations between the intrinsic activities of the indoles and their isosteric indenes.

Only two isosteric indene–indole–benzo[*b*]thiophene sets are present (**2**, **3**, **4** and **9**, **10**, **11**). In each case replacement of the nitrogen in the 1 position of the indole ring by either a methylene carbon or by sulfur leads to parallel changes in both affinity and intrinsic activity. The relative high affinity of **8** parallels that of **7** and could be due to the ability of **7** and probably **8** to block monoamine oxidase.[32]

The disubstituted compounds, **19**–**21**, present results which are somewhat puzzling. We see that introduction of a methoxy group at the 5 position of N,N-diethyltryptamine results in a dramatic increase in affinity (from 4.03 to 5.88) and intrinsic activity (from 1.01 to 1.98). In contrast, 6-methoxy-N,N-diethyltryptamine is nearly inactive (intrinsic activity = 0.10, pD_2 = 3.58). In view of the marked similarity in activity between the other isosteric pairs studied, we might expect 3-(N,N-diethyl-2-aminoethyl)-6-methoxyindene, the isostere of 6-methoxy-N,N-diethyltryptamine, to be likewise relatively inactive. Instead, the relative intrinsic activity for the indene was found to be 1.11 with pD_2 = 4.81.

The values for affinity and intrinsic activity reported in Table II strongly suggest that, for tryptamines unsubstituted in the benzene ring, replacement of the indole ring nitrogen with a methylene group or a sulfur atom does not appreciably alter their ability to cause contraction of the isolated rat stomach fundus. This can be taken as an indication that the ring NH group of such tryptamines is not a binding site in the smooth muscle of the rat stomach fundus. In contrast, the activities of 6-methoxy-N,N-diethyltryptamine and its isostere, 3-(N,N-diethyl-2-aminoethyl)-6-methoxyindene, are markedly different. This raises the possibility that there is a fundamental difference in the mode of action of tryptamines substituted in the benzene ring and ones not so substituted.

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