Recent Studies in the Field of Indole Compounds

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1. Introduction

Interest in the study of indole-containing compounds in biological systems has increased dramatically over the past decade. Tangible evidence for this interest is the fact that this chapter has been preceded by two earlier ones in the second and third volumes of this series. These reviews have discussed, respectively, the naturally occurring indoles isolated from plant and animal sources [35][1]) and the effects of serotonin and other tryptamines on biological systems [56]. The latter chapter contains over 1300 references to papers published in the preceding six years, clearly pointing out the remarkable variety of target organs which respond to members of this class of compounds.

Another review of the above types is certainly not warranted. We have chosen, instead, to report in admittedly a rather disjointed manner, some chemical, biological and clinical findings from our own as well as other laboratories, illustrating the way scientists of varied disciplines seek to enlarge our knowledge by the use of a combination of logic, intuition, and blind trial and error. It may be of interest to the reader to observe by what tenuous threads and chance observations one progresses from the knowledge of today into totally unexpected areas of research tomorrow. Our presentation, much of it representing unpublished data, is in no sense intended to be a comprehensive review. It will differ from other chapters in this series in containing, in addition to structure-activity correlations, more information on the syntheses of the indole compounds to be discussed. Progress in drug research is the result of the combined efforts of chemists, biologists and clinicians. The rate of this progress is directly related to the extent that each of these disciplines understands and appreciates the problems, approaches and accomplishments of the other two.

2. Approaches to Tryptamine Synthesis

2.1 *Early Tryptamine Studies*

The demonstration [155, 44, 55, 176] by RAPPORT, ERSPAMER, and others that tryptamines such as serotonin and bufotenine play some part in mammalian, reptilian and plant physiology resulted in no less than thirteen synthetic approaches to serotonin itself [95, 53, 175, 11, 99, 172, 18, 174, 26, 111, 1, 214, 146, 31, 152, 12] and many studies aimed at versatile syntheses of tryptamines in general. We have made considerable use of the method involving the heating, without solvent, of indole magnesium iodide with an α-chloro N-substituted acetamide [203], followed by lithium aluminum hydride reduction to a 3-(2-substituted aminoethyl)indole. In spite of evidence from the literature [33] that benzyloxyindoles would resinify under the conditions of this reaction,

[1]) Numbers in brackets refer to References, page 145

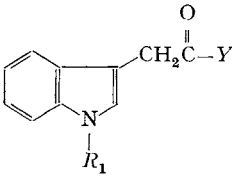
we were able to apply this method to the preparation, in good yield, of 5-hydroxytryptamines [172, 173]. The method was most successful with di-substituted amides, less so with mono-substituted amides and failed with α-chloroacetamide itself. The reduction of the amides was best conducted in tetrahydrofuran since their low solubility in ether made a continuous extraction technique necessary when this solvent was used. Some of the amides and tryptamines prepared by this method are listed in Tables 1 and 2 (Method B), respectively.

2.2 *Oxalyl Chloride Procedure*

2.21 1-Unsubstituted Indoles

By far the most versatile synthesis of tryptamines which contain no substituent on either the indole nitrogen or on the α-carbon of the tryptamine side chain is that of Speeter and Anthony [174], illustrated in Flowsheet 1, involving the condensation of indoles with oxalyl chloride, conversion of the resulting 3-indole-glyoxylyl chloride to the desired glyoxamide (I) followed by

Table 1
Indole Acetamides



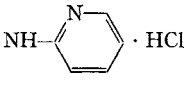
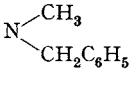
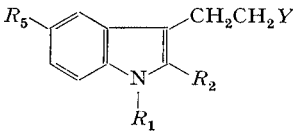
No.	R_1	Y	m.p. °C	Empirical formula	LD_{50}
1	H	NHC_6H_5	149·5–150	$C_{16}H_{14}N_2O$	1778
2	H	 · HCl	102–104	$C_{15}H_{14}ClN_3O$	562
3	H		148–149	$C_{18}H_{18}N_2O$	>1000
4	H	$N(n\text{-}C_4H_9)_2$	66–67	$C_{18}H_{26}N_2O$	562
5	CH_3	$N(CH_2C_6H_5)_2$	117·5–119	$C_{25}H_{24}N_2O$	>1000

Table 2a *Tryptamines*



R_1, R_5 = H

No.	R_2	Y	m.p. °C	Emp rical formula	Toxicology		Other significant activity	Method of prepa-ration[1])
					LD_{50}	Suggested activity[4])		
1	H	$NH_2 \cdot CH_3CO_2H$	134·5–135·5	$C_{10}H_{12}N_2 \cdot C_2H_4O_2$	233	None	Sleep potentiation: 1/5–1/7 chlorpromazine	F
2	H	$NHCH_3 \cdot HCl$	176–177	$C_{11}H_{15}ClN_2$	200	None		F
3	H	NHC_2H_5	b.p. 144–146/0·8 mm	$C_{12}H_{16}N_2$	562	CNS stimulant	MAOI[3]): I_{50} $4\times10^{-4}M$	E
4	H	$NHC_2H_5 \cdot HCl$	180–181	$C_{12}H_{17}ClN_2$	167	CNS stimulant		F
5	H	$NHC_3H_7 \cdot HCl$	182–183·5	$C_{13}H_{19}ClN_2$	77	None		F
6	H	$NH{-}CH(CH_3)_2 \cdot HCl$	236–237	$C_{13}H_{19}ClN_2$	205	None	MAOI: I_{50} $3\times10^{-4}M$	D
7	H	$NHC_4H_9 \cdot HCl$	196–197	$C_{14}H_{21}ClN_2$	65	None		F
8	H	$NHCH_2{-}CH(CH_3)_2 \cdot HCl$	172–173	$C_{14}H_{21}ClN_2$	167	None	MAOI: inactive at $10^{-3}M$	F
9	H	$NHCH(CH_3){-}CH_2CH_3 \cdot HCl$	180–181	$C_{14}H_{21}ClN_2$	167	None		F
10	H	$NHCH_2CH_2CH(CH_3)_2 \cdot HCl$	192–194	$C_{15}H_{23}ClN_2$	100	Depressant		D
11	H	$NHCH_2C_6H_5 \cdot HCl$	232–233	$C_{17}H_{19}ClN_2$	200	None		D
12	H	$NHCH_2C_6H_{11} \cdot HCl$	205–207	$C_{17}H_{25}ClN_2$	100	None		D
13	H	$NH(CH_2)_7CH_3 \cdot HBr$	182·5–183	$C_{18}H_{29}BrN_2$	32	None		C

Table 2a (Continued)

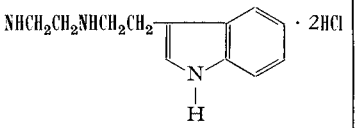
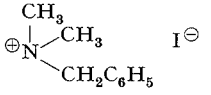
No.	R_2	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity	Method of preparation[1])
					LD_{50}	Suggested activity[4])		
14	H	$NHCH_2CH(C_2H_5)-(CH_2)_2CH_3 \cdot HCl$	172–174	$C_{18}H_{29}ClN_2$	200	None		F
15	H	$NHCH_2CH_2C_6H_5 \cdot HCl$	211–212	$C_{18}H_{21}ClN_2$	100	None	Some infilt. anesthesia; sl. bl. press. fall; MAOI: inactive at $10^{-3}M$	B
16	H	$NHC_5H_9 \cdot HCl$	209–210·5	$C_{15}H_{21}ClN_2$	200	Depressant	MAOI: inactive at $10^{-3}M$	D
17	H	$NHC_6H_{11} \cdot HCl$	264·5–266	$C_{16}H_{23}ClN_2$	200	None		F
18	H		299–301	$C_{22}H_{28}Cl_2N_4$	167	Sedative		F
19	H	$N(CH_3)_2$	47–48	$C_{12}H_{16}N_2$	167	None		B
20	H	$N(CH_3)(CH_2C_6H_5) \cdot HCl$	169–170	$C_{18}H_{21}ClN_2$	200	Convulsant	MAOI: inactive at $10^{-3}M$	B
21	H		177–179	$C_{19}H_{23}IN_2$	200	None		B
22	H	$N(C_2H_5)_2 \cdot HCl$	166·5–167·5	$C_{14}H_{21}ClN_2$	77	None	$^1/_2$–1 ergometrine as oxytocic	F
23	H	$N(C_3H_7)_2 \cdot HCl$	169–171	$C_{16}H_{25}ClN_2$	56	CNS stimulant	MAOI: inactive at $10^{-3}M$	B
24	H	$N(CH_2CH=CH_2)_2$	b.p. 138–142/0·5 mm	$C_{16}H_{20}N_2$	178	CNS stimulant	Slight bronochodilator activity	C

Table 2a (Continued)

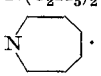
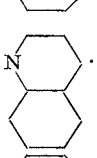
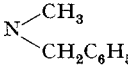
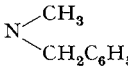
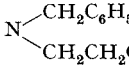
No.	R_2	Y	m.p. °C	Empirical formula	Tocixology		Other significant activity	Method of preparation[1])
					LD_{50}	Suggested activity[4])		
25	H	$N(C_4H_9)(CH_2C_6H_5 \cdot HCl)$	204–205	$C_{21}H_{27}ClN_2$	200	Local anesthetic	MAOI: inactive at $10^{-3}M$	F
26	H	$N(CH_2C_6H_5)(C_6H_{11} \cdot HCl)$	216–218	$C_{23}H_{29}ClN_2$	>1000	None	MAOI: inactive at $10^{-3}M$	F
27	H		111–112	$C_{14}H_{18}N_2$	167	CNS stimulant	Slight bl. press. fall; some antihistamine activity	C
28	H		148–150	$C_{15}H_{20}N_2$	100	CNS stimulant		C
29	H		221–222	$C_{15}H_{21}ClN_2$			2/3 ergometrine as oxytocic; MAOI: inactive at $10^{-3}M$	C
30	H		212–213	$C_{14}H_{19}ClN_2O$	200	Sedative	MAOI: inactive at $10^{-3}M$	F
31	CH_3	$N(C_2H_5)_2$	79–81	$C_{15}H_{22}N_2$	65	None		F
32	CH_3	$N(C_2H_5)_2 \cdot HCl$	207–208·5	$C_{15}H_{23}ClN_2$	65	None	$^1/_2$ ergometrine as oxytocic	B
33	CH_3		252–254	$C_{17}H_{25}ClN_2$	110	Sedative	$^1/_2$ chlorpromazine as inhibitor of motor act.; MAOI: inactive at $10^{-3}M$	F
34	CH_3		284–286	$C_{20}H_{29}ClN_2$	200	None	MAOI: inactive at $10^{-3}M$	F
35	C_6H_5		118–120	$C_{22}H_{26}N_2$	167	Sedative	$^1/_2$ chlorpromazine as inhibitor of motor activity	F

Table 2b

R_1 or R_5 other than H

No.	R_1	R_2	R_5	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity	Method of preparation[1]
							LD_{50}	Suggested activity[4]		
36	H	H	OH	$N(C_4H_9)_2 \cdot HCl$	212–213	$C_{18}H_{29}ClN_2O$	178	Vasoactive	Prolonged bl. press. fall; slight bl. press. fall in DCA rat	B
37	H	H	$C_6H_5CH_2O$	$NHC_6H_5 \cdot HCl$	184–185	$C_{23}H_{23}ClNO$	1778	None		B
38	H	H	$C_6H_5CH_2O$		77–78	$C_{25}H_{26}N_2O$	178	None		B
39	H	H	$C_6H_5CH_2O$		110–112	$C_{25}H_{27}ClN_2O$	200	None		B
40	H	H	$C_6H_5CH_2O$	$N(CH_2C_6H_5)_2 \cdot HCl$	232–233	$C_{31}H_{31}ClN_2O$	1000	None		B
41	H	H	$C_6H_5CH_2O$		214–215	$C_{32}H_{33}ClN_2O$	1778	None		B
42	H	CH_3	$C_6H_5CH_2O$	$N(CH_2C_6H_5)_2 \cdot HCl$	242–243	$C_{32}H_{33}ClN_2O$	>1000	Analgetic		B
43	CH_3	H	H	$NH_2 \cdot HCl$	203–204	$C_{11}H_{15}ClN_2$	200	CNS stim.		F[2]
44	CH_3	CH_3	H	$NH_2 \cdot HCl$	239–240	$C_{12}H_{17}ClN_2$	167	CNS stim.		A[2]

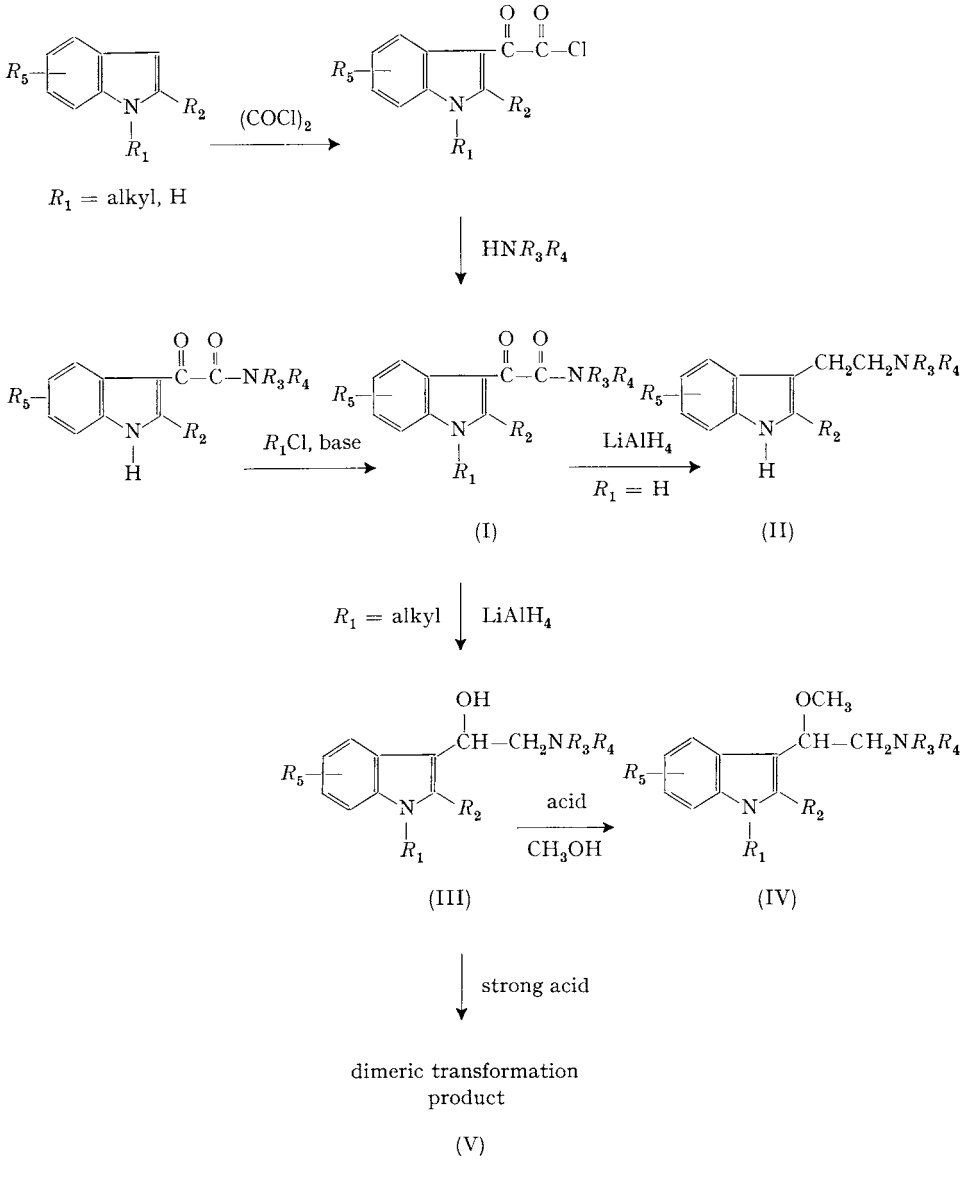
[1] Method A: $LiAlH_4$ reduction of the indoleacetonitrile.
Method B: $LiAlH_4$ reduction of the indoleacetamide.
Method C: Reaction of the bromoethylindole with an amine.
Method D: Formation of a Schiff base from the tryptamine and a ketone followed by catalytic hydrogenation.
Method E: Formation of an acyltryptamine from tryptamine and a mixed anhydride followed by reduction with $LiAlH_4$.
Method F: Reaction of the indole with oxalylchloride, then with an amine, followed by reduction of the glyoxamide with $LiAlH_4$.
In the above methods, when benzyl groups were used as protecting groups, these were removed by catalytic hydrogenation using Pd/C.

[2] Followed by alkylation on the indole nitrogen using CH_3I and $NaNH_2$.

[3] MAOI = monoaminoxidase inhibition.

[4] For explanation see text, Section 3.1.

Flowsheet 1



lithium aluminum hydride reduction to the corresponding tryptamine (II). (The structures of compounds designated by Roman numerals are shown in the text, while those designated by Arabic numerals are shown in Tables.) Many of the glyoxylylchlorides are surprisingly stable, possibly due to hydrogen bonding between the indole nitrogen and the carbonyl group (infrared evidence) and, although they can be used without purification, they can often be re-

crystallized from ethylene dichloride. Yields of tryptamines decreased in going from disubstituted through monosubstituted to unsubstituted amides, probably due to formation of some glycolamides as by-products when amide hydrogens were present. This problem was particularly serious when the mono-substituent was lower alkyl. Such compounds could be prepared satisfactorily by use of the appropriate N-benzyl-N-alkyl glyoxamide which could be reduced, first with lithium aluminum hydride, then using palladium on charcoal to effect debenzylation.

This method of tryptamine synthesis has since found wide application [30, 210, 16, 34]. Some of the glyoxamides and tryptamines produced in this manner in our laboratories are listed in Tables 3 and 2 (Method F), respectively.

2.22 1-Substituted Indoles; Formation of β-Hydroxytryptamines

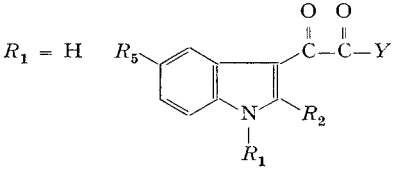
When the above indoleglyoxamide procedure was applied to 1-substituted indoles [171, 173] the hydrogenolysis reaction was blocked and the reaction proceeded only as far as the carbinol stage (III), Flowsheet 1. Apparently the carbonyl group has now lost come of its amidic character. These β-hydroxytryptamines give highly colored products with strong acids, the nature of which will be discussed below (3.242). The hydroxyl group does not show typical reactions of simple carbinols. Attempts at acetylation by the usual means were unsuccessful, though an acetoacetate was obtained by direct refluxing of one member with methylacetoacetate. A hydrochloride could be obtained from (III) by precipitation from ether with less than one equivalent of hydrogen chloride in isopropyl alcohol, but recrystallization of the salt from methanol-ether caused the formation of the ether (IV) (cf. [124] in the case of 3-indolemethanol). A similar β-hydroxytryptamine structure is compatible with the analytical and acid sensitivity data obtained for the by-product, m.p. 157–159°C, formed by lithium aluminum hydride reduction of 2-(benzylmethylamino)-1-indol-3-yl-1-propanone.

The 1-alkylated indole glyoxamides presented in Table 4 were prepared by two methods. The first involved alkylation of 1-unsubstituted glyoxamides with alkyl halides in absolute alcohol in the presence of sodium methoxide in a pressure flask at 60–75°, or using potassium carbonate in 98% alcohol at reflux temperature for 18 hours. Since efforts to use this method to alkylate N-isopropyl-3-indoleglyoxamide resulted in very low yields, some 1-alkylated glyoxamides were made by reaction of the appropriate 1-alkyl indole with oxalyl chloride and then with the amine. A single effort to alkylate a 3-indoleglyoxamide with dimethyl sulfate and sodium hydroxide resulted in the formation of 1-alkyl-3-indoleglyoxylic acid.

The β-hydroxytryptamines obtained by lithium aluminum hydride reduction of the glyoxamides of Table 4 are shown in Table 5. An alternate method was catalytic reduction of the glyoxamides (palladium on charcoal) to glycolamides, followed by lithium aluminum hydride reduction of the amide function. Compound 1 (Table 5), having no substituent on the indole nitrogen, was pre-

Table 3

Glyoxamides



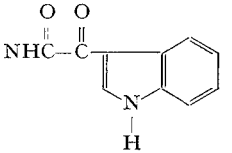
No.	R_2	R_5	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1])
						LD_{50}	Suggested activity[3])	
1	H	H	NH_2	246–248	$C_{10}H_8N_2O_2$	>1000	Sedative	Low potency hypnotic and anticonvulsant – $LRRD_{50}$ >1000; NTD_{50} 248; electroshock: ED_{50} = 177[2])
2	H	H	$NHNH_2$	216 dec.	$C_{10}H_9N_3O_2$	533	Sedative	Poor to fair inhibitor of motor activity; 5-hydroxytryptophane decarboxylase inhibition: $I_{50} = 10^{-4} M$
3	H	H		>300	$C_{20}H_{14}N_4O_4$	>1000	None	
4	H	H	$NHCH_3$	218–219	$C_{11}H_{10}N_2O_2$	>1000	Analgetic	
5	H	H	NHC_2H_5	199–200	$C_{12}H_{12}N_2O_2$	1778	CNS stim.	
6	H	H	$NHCH_2CH_2OH$	199–201	$C_{12}H_{12}N_2O_3$	1778	Sedative	
7	H	H	NHC_5H_{11}-*n*	150–151	$C_{15}H_{18}N_2O_2$	422	None	

Table 3 (Continued)

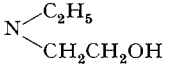
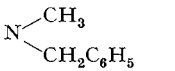
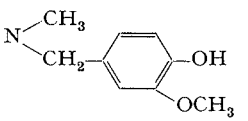
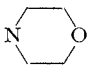
No.	R_2	R_5	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1])
						LD_{50}	Suggested activity[3])	
8	H	H	$NHCH_2CH=CH_2$	180–182	$C_{13}H_{12}N_2O_2$	>1000	Sedative; muscle relaxant	Sleep potentiation: $^1/_4$ chlorpromazine; motor activity: poor to fair; classical avoidance: some activity; rat sleep >6 hrs at 500 mg/kg IP
9	H	H	$NHCH_2C_6H_5$	172–173·5	$C_{17}H_{14}N_2O_2$	>1000	None	
10	H	H	NHC_6H_5	242–243	$C_{16}H_{12}N_2O_2$	>1000	None	
11	H	H	$N(CH_3)_2$	159–160	$C_{12}H_{12}N_2O_2$	1000	Sedative; laxative; muscle paralysis	$LRRD_{50}$ 378; NTD_{50} 189; strychnine antagonism: ED_{50} 77; sleep potentiation: fair
12	H	H	$N(C_2H_5)_2$	168·5–169·5	$C_{14}H_{16}N_2O_2$	>1000	Sedative	
13	H	H		138–139	$C_{14}H_{16}N_2O_3$	750	None	
14	H	H		172·5–173·5	$C_{18}H_{16}N_2O_2$	>1000	None	
15	H	H		201–202	$C_{19}H_{18}N_2O_4$	1778	Sedative	
16	H	H		184–185	$C_{14}H_{14}N_2O_3$	250	None	

Table 3 (Continued)

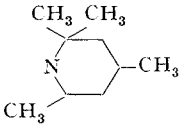
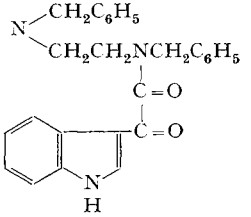
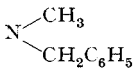
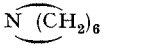
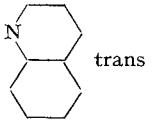
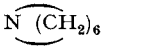
No.	R_2	R_5	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1)]
						LD_{50}	Suggested activity[3)]	
17	H	H		203–204	$C_{19}H_{24}N_2O_2$	1778	None	
18	H	H		307–309	$C_{36}H_{30}N_4O_4$	167	Local anesthetic	
19	H	H	N-phenothiazinyl	283	$C_{22}H_{14}N_2O_2S$	>1000	None	
20	H	$OCH_2C_6H_5$		152–157 dec.	$C_{25}H_{22}N_2O_3$	>1000	None	
21	H	CH_3O	$N(CH_2C_6H_5)_2$	184–186	$C_{25}H_{22}N_2O_3$	>1000	None	
22	H	OCH_3, 6-OCH_3	$N(CH_2C_6H_5)_2$	1 3–194	$C_{26}H_{24}N_2O_4$	>1000	None	
23	H	OCH_3, 6-OCH_3		196·5–198	$C_{18}H_{22}N_2O_4$	>1000	None	

Table 3 (Continued)

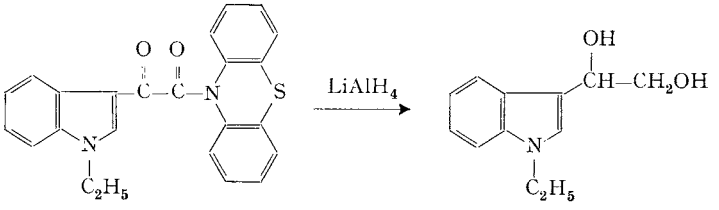
No.	R_2	R_5	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1]
						LD_{50}	Suggested activity[3]	
24	CH_3	H	$N(CH_3)_2$	169–170	$C_{13}H_{14}N_2O_2$	1000	Analgetic; diuretic	Motor activity: fair to poor; morphine potentiation: fair; sleep potentiation: equal to chloropromazine (orally active)
25	CH_3	H	$N(C_2H_5)_2$	171–174	$C_{15}H_{18}N_2O_2$	>1000	Sedative	Sleep potentiation: equal to or better than chlorpromazine (orally active)
26	CH_3	H		157–158	$C_{17}H_{20}N_2O_2$	650	Sedative	
27	CH_3	H	 trans	211–213	$C_{20}H_{24}N_2O_2$	>1000	None	
28	CH_3	OH	$N(CH_3)_2$	Variable	$C_{13}H_{14}N_2O_3$	>1000	None	
29	C_6H_5	H		164–165	$C_{22}H_{22}N_2O_2$	>1000	None	

[1]) Comparisons with chlorpromazine on sleep potentiation were made at equitoxic doses and hence represent relative therapeutic ratios and not relative absolute potencies.

[2]) LRRD = loss of righting reflex dose (mouse); NTD = neurotoxic dose (lowest dose showing some neurologic deficit); ED = effective dose.

[3]) For explanation, see text, Section 3.1.

pared by sodium borohydride reduction of 3-(dimethylaminoacetyl)indole. It is interesting that whereas the lithium aluminum hydride reduction of indole glyoxylyl chlorides or glyoxylic esters yields tryptophols [74, 75] the reduction of the corresponding 1-alkyl compounds results in the formation of glycols, by direct analogy with the β-hydroxytryptamine formation above. An effort to reduce the phenothiazine derivative (VI) to a tryptamine [7] also yielded only the glycol (VII) whose structure was established by periodate oxidation to 1-ethylindole-3-carboxaldehyde.



(VI) (VII)

Although the synthesis of a few indole analogs of the well-known sympathomimetic amines has been reported, no pharmacological data have been published. MAJIMA and KOTAKE [131] have reported the synthesis of β-hydroxytryptamine itself. Although efforts in our laboratory and elsewhere [5] have failed to duplicate this work, the successful preparation of this compound as its picrate has been accomplished [5] by lithium borohydride reduction of 3-(N-carbobenzoxyglycyl)indole, followed by catalytic hydrogenolysis of the carbobenzoxyl group. Attempts to isolate the free base or hydrochloride were unsuccessful, solutions of the latter rapidly turning red even in the cold (compare acid instability of our β-hydroxytryptamines discussed in Section 3.242). To our knowledge no β-hydroxytryptamines have been found in nature. YANOFSKY [211, 212] has suggested that indole-3-glycerolphosphate is an intermediate in the synthesis of indole be *E. coli*. The occurrence in nature of indole-3-glycolic acid has been claimed [62] but is not supported by more recent studies [82].

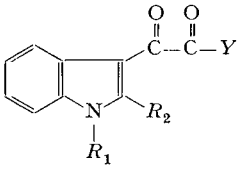
3. Biological Studies With Tryptamines

3.1 *Testing Procedures*

The indoleacetamides (Table 1), glyoxamides (Tables 3 and 4) and tryptamines (Tables 2 and 5) were subjected to a number of tests aimed at detecting central nervous system (CNS) activity. Among these were: gross observation of behavior at various dose levels [114], potentiation of hexobarbital-induced sleep [140, 163], inhibition of motor activity in an actophotometer [163, 45], antagonism of the characteristic pawing ('piano-playing') syndrome in the rat produced by bufotenine [70], the potentiation or antagonism of a number of

Table 4

1-Alkylindoleglyoxamides



No.	R_1	R_2	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1])
						LD_{50}	Suggested activity[2])	
1	CH_3	H	NH_2	185–187	$C_{11}H_{10}N_2O_2$	—	—	Weak depressant
2	CH_3	H	$NHCH_3$	206–207	$C_{12}H_{12}N_2O_2$	>1000	None	Very weak depressant
3	CH_3	H	$NHCH(CH_3)_2$	103–104·5	$C_{14}H_{16}N_2O_2$	1000	None	Very weak depressant; sleep potentiator: $^1/_4$–$^1/_2$ chlorpromazine
4	CH_3	H	NHC_6H_5	150–152	$C_{17}H_{14}N_2O_2$	1000	None	Very weak depressant
5	CH_3	H	$N(CH_3)_2$	107·5–108·5	$C_{13}H_{14}N_2O_2$	1000	Sedative; anti-convulsant	Fair depressant; sleep potentiator: equal to chlorpromazine; fair anti-convulsant (electroshock)
6	CH_3	H	$N(C_2H_5)_2$	109–110	$C_{15}H_{18}N_2O_2$	>1000	None	Inactive as depressant
7	CH_3	H	$N(CH_2C_6H_5)_2$	109–111	$C_{25}H_{22}N_2O_2$	>1000	None	Very weak depressant
8	CH_3	H		177–178·5	$C_{15}H_{16}N_2O_3$	650	Sedative	Moderate depressant; sleep potentiator: $^1/_8$–$^1/_4$ chlorpromazine

Table 4 (Continued)

No.	R_1	R_2	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1])
						LD_{50}	Suggested activity[2])	
9	CH_3	CH_3	$N(CH_3)_2$	127–129	$C_{14}H_{16}N_2O_2$	650	Sedative	Fair depressant; sleep potentiator: equal to chlorpromazine (moderately active orally)
10	CH_3	CH_3	$N(C_2H_5)_2$	102–103·5	$C_{16}H_{20}N_2O_2$	650	Sedative	Fair depressant; sleep potentiator: $^1/_{20}$–$^1/_3$ chlorpromazine
11	CH_3	C_6H_5	NH_2	194–196	$C_{17}H_{14}N_2O_2$	1334	None	
12	CH_3	C_6H_5	$N(CH_2C_6H_5)_2$	171–172	$C_{31}H_{26}N_2O_2$	>1000	None	Very weak depressant
13	CH_3	C_6H_5	OH	175–176	$C_{17}H_{13}NO_3$	750	None	Inactive as depressant
14	C_2H_5	H	NH_2	173–176	$C_{12}H_{12}N_2O_2$	>1000	None	Very weak depressant; sleep potentiator: $^1/_4$ chlorpromazine
15	C_2H_5	H	$NHCH_3$	125–127	$C_{13}H_{14}N_2O_2$	>1000	Sedative; diuretic	Good depressant (rats slept >6 hrs. at 300 mg/kg orally); sleep potentiator: $^1/_4$–$^1/_2$ chlorpromazine; fair inhibitor of motor activity; strychnine antagonist; poor oral activity
16	C_2H_5	H	$N(CH_3)_2$	140–142·5	$C_{14}H_{16}N_2O_2$	1000		Sleep potentiator: $^1/_2$ chlorpromazine
17	C_2H_5	H	$N(CH_3)_2$ 5-$OCH_2C_6H_5$	104–106·5	$C_{21}H_{22}N_2O_3$	1800	None	Weak depressant
18	C_2H_5	H	N-phenothiazinyl	273·5–274·5	$C_{24}H_{18}N_2O_2S$	650	Sedative; muscle paralysis	Fair depressant; sleep potentiator: $^1/_{15}$–$^1/_4$ chlorpromazine

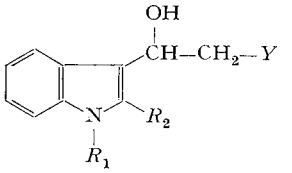
Table 4 (Continued)

No.	R_1	R_2	Y	m.p. °C	Empirical formula	Toxicology		Other significant activity[1])
						LD_{50}	Suggested activity[2])	
19	C_2H_5	CH_3	$N(CH_3)_2$	111–113	$C_{15}H_{18}N_2O_2$	1000	None	Weak depressant; fair motor activity inhibitor; sleep potentiator: 1–2 times chlorpromazine (not an inhibitor of hexobarbital metabolism); moderate oral activity
20	$CH(CH_3)_2$	H	$N(CH_3)_2$	113–114·5	$C_{15}H_{18}N_2O_2$			Fair depressant
21	n-C_4H_9	H	$N(CH_3)_2$	57·5–59	$C_{16}H_{20}N_2O_2$	650	Sedative	Fair depressant (mice slept 3 hrs. at $^1/_2$ LD_{50})
22	n-C_6H_{13}	H	$N(CH_3)_2$	59·5–61	$C_{18}H_{24}N_2O_2$	1000	CNS stimulant; muscle paralysis	Weak depressant; sleep potentiator: $^1/_4$ chlorpromazine
23	$C_{16}H_{33}$	H	$N(CH_3)_2$	61·5–63·5	$C_{28}H_{44}N_2O_2$	>1000	None	Inactive as depressant
24	CH_3	COOH	$NHCH_3 \cdot CH_3NH_2$	187 dec.	$C_{13}H_{12}N_2O_4 \cdot CH_5N$	>1000	Analgetic; diuretic	Inactive as depressant
25	CH_3	$CH_2N(CH_3)CO-CO_2C_2H_5$	OC_2H_5	67–68	$C_{19}H_{22}N_2O_6$	>1000	Analgetic; sedative	Slight depressant activity

[1]) 'Depressant' activity is determined qualitatively from gross behavior in rats and mice; see Table 3, Footnote 1.
[2]) For explanation see text, Section 3.1.

Table 5

β-Hydroxytryptamines

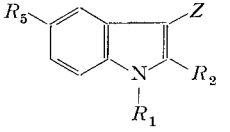


No.	R_1	R_2	Y	m.p. °C	Empirical formula	LD_{50}	Diuretic activity at 10 mg/kg[1]	Hypotensive Activity[2]
1	H	H	$N(CH_3)_2$	118–121	$C_{12}H_{16}N_2O$		—	—
2	CH_3	H	$NHCH_3$	138–140	$C_{12}H_{16}N_2O$	650	++[3]	++
3	CH_3	H	$NHCH(CH_3)_2$	114·5–115·5	$C_{14}H_{20}N_2O$	sl. >1000	—	++
4	CH_3	H	$NHCH_2C_6H_5$	111–113	$C_{18}H_{20}N_2O$	200	—	+
5	CH_3	H	$N(CH_3)_2$	94–95	$C_{13}H_{18}N_2O$	744	++	—
6	CH_3	H	$N(CH_3)_2 \rightarrow O$	148–152	$C_{13}H_{18}N_2O_2$	>1000	++	—
7	CH_3	H	$N(CH_2C_6H_5)_2$	120·5–122	$C_{25}H_{26}N_2O$	>1000	+	—
8	CH_3	H		99–100	$C_{15}H_{20}N_2O_2$	417	—	—
9	CH_3	C_6H_5		154·5–156	$C_{22}H_{26}N_2O$	1000	+	+
10	C_2H_5	H	NH_2	83–85	$C_{12}H_{16}N_2O$			++

Table 5 (Continued)

No.	R_1	R_2	Y	m.p. °C	Empirical formula	LD_{50}	Diuretic activity at 10 mg/kg[1])	Hypotensive Activity[2])
11	C_2H_5	H	$NHCH_3$	139–140	$C_{13}H_{18}N_2O$	30	—	++
12	C_2H_5	H	$N(CH_3)_2$	82–83	$C_{14}H_{20}N_2O$	133	+	++
13	C_2H_5	H	$\overset{O}{\uparrow}N(CH_3)_2 \cdot H_2O$	74–84	$C_{14}H_{20}N_2O_2$ H_2O	650	++	—
14	C_2H_5	H	$N(CH_3)_2 \cdot CH_3I$	166–167	$C_{15}H_{23}IN_2O$		—	—
15	C_2H_5	CH_3	$N(CH_3)_2$	86–87	$C_{15}H_{22}N_2O$		+	
16	C_2H_5	CH_3	$\overset{O}{\uparrow}N(CH_3)_2$	110–114	$C_{15}H_{22}N_2O_2$	>300	+	
17	$CH(CH_3)_2$	H	$N(CH_3)_2$	66–67	$C_{15}H_{22}N_2O$	14	—	++
18	C_4H_9	H	$N(CH_3)_2$	Oil, n_D 1·5478	$C_{16}H_{24}N_2O$	200	+	+
19	C_6H_{13}	H	$N(CH_3)_2$	Oil, n_D 1·5370	$C_{18}H_{28}N_2O$	200	—	++
20	$C_{16}H_{33}$	H	$N(CH_3)_2$	50·5–51·5	$C_{28}H_{48}N_2O$	77	—	++
21	H	H	$CH_2N(CH_3)_2$	149–151	$C_{13}H_{18}N_2O$	767	—	+
22	CH_3	H	$CH_2N(CH_3)_2$	87·5–88·5	$C_{14}H_{20}N_2O$	237	—	

Table 5 (Continued)



No.	R_1	R_2	R_5	Z	m.p. °C	Empirical formula	LD_{50}	Diuretic activity at 10 mg/kg[1]	Hypotensive activity[2]
23	H	H	H	$C_6H_5C(OH)-CH_2CH_2N(CH_3)_2$	150–151·5	$C_{19}H_{22}N_2O$	650		+
24	H	H	H	$Cl-C_6H_4-C(OH)-CH_2CH_2N(CH_3)_2$	142–143	$C_{19}H_{21}ClN_2O$	200		
25	CH_3	H	H	$C_6H_5C(OH)-CH_2CH_2N(CH_3)_2$	147–148·5	$C_{20}H_{24}N_2O$	200	—	—
26	H	H	H	$CH_3CH_2C(OH)-CH_2CH_2N(CH_3)_2$	177–181	$C_{15}H_{22}N_2O$	533		—
27	C_2H_5	H	$C_6H_5CH_2O$	$CH(OH)-CH_2-N(CH_3)_2$	76·5–77	$C_{21}H_{26}N_2O_2$	237		

[1]) Diuretic activity determined after oral administration to hydrated rats using a modification of the procedure of LIPSCHITZ *et al*; J. Pharmacol. Exp. Therap. 79 (1943), 97. Criteria for activity: + + good to excellent, or >50 % over controls; + slight, mild or fair activity, or 20–50 % over controls; — inactive, or <20 % over controls.

[2]) Hypotensive activity determined in rats given 0.2 mg DCA subcutaneously daily for five weeks, using those rats whose systolic blood pressure had risen to 140 mm (average rise, 112 mm to 153 mm); significant response is more than a 20 mm fall. Criteria for activity: + + response of >25 mm obtained in $^1/_2$ hour, and lasting >4 hrs; + response not clearly — or + +; — insignificant reduction in blood pressure or a significant drop which returns to the predrug level in less than 4 hrs.

[3]) Excellent diuretic at 5 mg/kg but antidiuretic at 10 mg/kg and 20 mg/kg, probably due to toxicity.

agents such as thiosemicarbazide, strychnine, reserpine and norepinephrine [114], and the *in vitro* inhibition of enzymes [86] which might be expected to affect brain levels of serotonin or catecholamines, e.g., monoamine oxidase [20], 5-hydroxytryptophan decarboxylase [36] and tryptophan 5-hydroxylase [66]. Only those compounds showing significant CNS depression or stimulation in some of these tests were subjected to all the tests. In addition, various of the compounds were tested in one or more of a number of other biological procedures such as diuretic, hypotensive, pharmacodynamic, antiinflammatory, hypoglycemic, uterine relaxant and antifertility assays, such that any pattern of activity present would be clearly discernible.

The LD_{50} data [114] recorded in Tables 1 to 5 represent only approximate values, intraperitoneally in the mouse, having 95% confidence limits of +100% to −50%. The 'suggested activity' column represents the evaluation of the gross behavior observed during the LD_{50} determinations in relationship to behavior produced by known drugs. Patterns of CNS activity not reminiscent of any useful drug or not suggestive of a specific type of CNS action are recorded as 'none'. In the column 'other activity', data are reported only when a significant level of activity was observed, or when absence of a particular activity was itself significant.

3.2 *Testing Results*

3.21 Acetamides

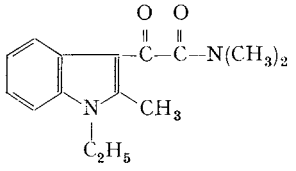
As a class the acetamides (Table 1) possess little significant biological activity and no member of the series merited detailed study. Compound (2) was the only member which caused any CNS depression and even this activity was minimal.

3.22 Glyoxamides

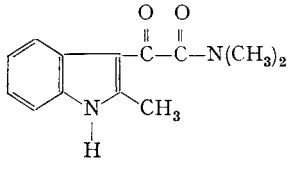
When one turns to the glyoxamides (Tables 3 and 4) it may be said that no consistent effects were apparent other than CNS depression. An attempt to discern trends in CNS activity with structure is not very conclusive. In Table 3 the compounds with some order of CNS activity are: 1, 2, 8, 11, 24, and 25. Of these the last two are the most interesting. Comparison of compounds 11 and 24 on one hand and 12 and 25 on the other suggests that an alkyl group in the 2-position enhances CNS activity. Comparison of 24 and 25 with 26 and 27, respectively, suggests further that, while disubstituted amides are preferred, the substituents should be dialkyl groups rather than being incorporated into a heterocyclic ring.

It would seem from Table 4, that in the series, $R_1 = CH_3$, disubstituted amides are more potent than unsubstituted or monosubstituted members (compare 5 with 1 through 4), and among the disubstituted amides, dialkylamides are again preferable to heterocyclic amides (compare 5, 6 with 8). Among the alkyl substituents, dimethyl appears better than diethyl in the two cases available (compare 5 with 6, 9 with 10). Although few examples are available,

a 2-methyl substituent either does not affect CNS activity (compare 5 with 9) or enhances it (compare 10 with 6 or 19 with 16). With regard to R_1, methyl and ethyl groups appear to be superior to hydrogen or higher alkyl groups, with ethyl somewhat preferred. However, it should be pointed out that oral activity may be better in the series $R_1 = H$ than with $R_1 = C_2H_5$ [compare 19, Table 4, structure (VIII) below, with compound 24, Table 3, or (IX) below].



(VIII)



(IX)

Compounds (VIII) and (IX) were selected for more intensive study in animals. For example these compounds were compared with chlorpromazine in the sleep-potentiation assay (I.P., mice) [140, 163], and the results are shown in Table 6.

Table 6

Dose % of LD_{50}	Chlorpromazine		(VIII)		(IX)	
	Dose (mg/kg)	Increase in sleep (%)	Dose (mg/kg)	Increase in sleep (%)	Dose (mg/kg)	Increase in sleep (%)
20 %	33	1104	200	2383	200	1106
10 %	17	752	100	748	100	560
5 %	8	447	50	707	50	531
2·5 %	4	387	25	436	25	136

The results of Table 6 indicate that (VIII) is slightly more active than (IX) and about one to two times as active on a therapeutic index basis or one fifth as active on a weight basis as chlorpromazine. In order to determine the oral absorption of (VIII) and IX) the sleep potentiation assay was carried out orally, allowing different times for absorption of the drug prior to the administration of hexobarbital. The results in Table 7 indicate that (IX) is fairly rapidly absorbed and more completely absorbed than (VIII).

Table 7

Time for absorption	% Increase in sleep			
	(VIII)		(IX)	
	400 mg/kg	200 mg/kg	400 mg/kg	200 mg/kg
30 min	245	250	1232	818
60 min	493	173	943	436
120 min	332	226	584	460

These compounds produced no significant avoidance behavior effects, analgesia or skeletal muscle relaxation. Compounds (VIII) and (IX) produced an approximately 50% inhibition of motor activity intraperitoneally in mice at 120 mg/kg and 200 mg/kg respectively. This activity is relatively weak and is comparable with that obtained with meprobamate and much less than that with chlorpromazine.

3.221 Clinical Results

Compound (IX) was well tolerated for several weeks orally in rats at daily doses up to 300 mg/kg and in dogs up to 100 mg/kg [123]. In normal human volunteers [198] (IX) produced no definite pattern of CNS effects or side effects. Mild daytime drowsiness was common in the 500–1000 mg/day range with nausea and vomiting showing up at 1000–1500 mg/day. Thirteen chronically psychotic patients received the compound orally at doses up to 250 mg four times a day (1000 mg/day). There were no reports of clinical improvement and several patients seemed to hallucinate more and display more bizarre speech.

3.23 Tryptamines

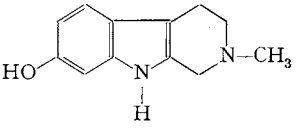
The tryptamines of Table 2 display a wide range of toxicity, extending from approximately 32 mg/kg to over 1000 mg/kg, intraperitoneally in the mouse. By and large it is the higher molecular weight (and usually less soluble) compounds which are least toxic. Presence or absence of gross CNS effects is not, however, dependent on solubility since, for example, compound 13, the most toxic of the series, showed no significant CNS activity. Gross observations made during LD_{50} determinations indicated eight compounds to be depressants, nine to be stimulants and twenty-three to show no CNS activity. It will be seen that only two of the compounds tested for *in vitro* inhibition of monoamine oxidase activity showed significant activity and these (compounds 3 and 6) were secondary amines. Two compounds (33 and 35), both 2-substituted heterocyclic tryptamines, showed appreciable activity in inhibiting spontaneous motor activity of mice in the actophotometer (light box). Three compounds (22, 29, 32), all tertiary amines, share the oxytoxic activity present in some of the indole-containing natural products.

In spite of the fact that it showed no interpretable CNS effects during the toxicity screening, compound 19, dimethyltryptamine, was studied further. This compound has been reported to occur in several plant species [64, 105, 79]. It differs structurally from bufotenine in not having a 5-hydroxyl substituent and might therefore be expected to cross the blood–brain barrier more easily. Since Fabing [58] has found bufotenine, which also shows little if any interpretable CNS effects in the toxicity screen, to have hallucinogenic properties, it was considered possible that dimethyltryptamine might possess more of this activity. After administration of 5 mg/kg of compound 19 to a mongrel dog, panting and muscular rigidity occurred before the needle was withdrawn from the vein. Typical bufotenine symptoms developed with the same rapidity and

within one minute the dog was howling and baying. It assumed a spread-eagle stance, with its abdomen pressed to the floor, and resisted efforts to disturb its equilibrium. The hair did not stand erect. Pulse and respiration were rapid, pupils were dilated and the eyes were open but the animal did not appear to see. The dog did not respond to calling but the ears twitched when fingers were snapped close to them. Immediately after injection the animal defecated and urinated and thereafter had frequent soft stools. After an hour the symptoms became less severe and the dog howled only occasionally. Two hours later he appeared weak but otherwise normal. An oral dose of 50 mg/kg produced similar effects. In the monkey doses up to 36 mg/kg intravenously caused clonic spasms followed by loss of equilibrium, erection of hair, mild ptyalism, loss of perception with no loss of consciousness. A dose of 53 mg/kg was fatal [71].

3.231 Clinical Results

Compound 19 (dimethyltryptamine) as well as its homolog, 3-(3-dimethylaminopropyl)indole, were supplied to W. J. TURNER and S. MERLIS for comparison in humans with bufotenine. Their conclusions [194] were that bufotenine, in spite of its profound physiological effects, did not appear to be an hallucinogen [cf. 58], whereas dimethyltryptamine, having less physiological activity, nevertheless produced typical hallucinatory responses in schizophrenics. Its homolog was without effect. Other reports of the hallucinogenic properties of dimethyltryptamine have appeared [178, 10, 161, 25]. SZARA has reported [179, 180] that dimethyltryptamine is metabolized to monomethyltryptamine and 6-hydroxydimethyltryptamine, and attributed to the latter the hallucinogenic properties of the parent compound. His more recent findings with α-methyltryptamine [112] cast some doubt on this conclusion. It is interesting to speculate that if another metabolite is responsible for the CNS activity of dimethyltryptamine, this might indeed be the tetrahydro-β-carboline (X), which would arise via the metabolite monomethyltryptamine in a manner analogous to that observed for the related compound, α-ethyltryptamine (see Section 4.11).

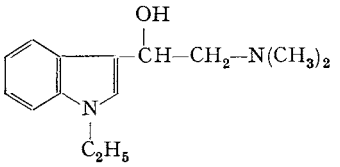


(X)

There have been conflicting reports regarding the excretion of bufotenine in man [32, 159]. Recently FISCHER *et al.* reported the excretion of bufotenine in schizophrenic subjects but not in normal controls. The observations of AXELROD [13] indicate that in the rabbit there is an enzymatic mechanism for the formation of bufotenine and dimethyltryptamine from normally occurring precursors, serotonin and tryptamine. This N-methylating enzyme transfers the methyl group of S-adenosylmethionine.

3.24 β-Hydroxytryptamines

The β-hydroxytryptamines of Table 5 have been screened widely for pharmacological effects and many of these have shown potent oral and parenteral hypotensive activity in DCA-hypertensive rats [40] with a duration of action lasting six hours or more. Angiotensin blocking activity, using the aortic strip assay of Furchgott [73], was minimal or absent. Oral diuretic activity in the hydrated rat [81] was variable, with antidiuretic activity showing up in some cases, probably due to toxicity. In general other standard pharmacological assays, such as those measuring central nervous system and pharmacodynamic effects, showed little, if any, activity. Compounds 7 and 12 (Table 5) were active as uterine stimulants in the cat while compound 11 was a uterine relaxant. Table 5 summarizes the approximate LD_{50} intraperitoneally in the mouse as well as the diuretic and hypotensive effects of these compounds. Notable is the extreme variability of the LD_{50} values. Although not invariably so, the least toxic compounds tended to be fairly insoluble; some are amine oxides which frequently show reduced toxicity relative to the parent amines. N-oxidation clearly enhanced the diuretic activity, a pattern which has shown up in other compounds [139]. Very few generalizations can be made concerning the structural requirements for hypotensive activity. It appears that the indole nitrogen substituent R_1 can be varied widely, with perhaps slightly increased activity with larger alkyl substituents. Again the number of alkyl substituents on the tryptamine nitrogen does not appear critical, though benzyl groups are disadvantageous and tertiary amines and N-oxides are inactive. The activity of compounds 19 and 21 demonstrates the fact that a 3-carbon side chain and even a tertiary alcohol may be present in an active compound. There is no relationship between diuretic and hypotensive activity.



(XI)

Compound 12 (XI) was studied more extensively preparatory to human testing. This agent was able to maintain a reduced blood pressure in a DCA-hypertensive rat when given daily for 40 days at 15 mg/kg orally. The pressure would then return to normal within a short time if the drug were stopped, but could again be lowered on renewed therapy. The dose required to lower the blood pressure of a DCA-hypertensive rat at least 25 mm for at least 6–8 hours was 5–10 mg/kg intraperitoneally and 10 mg/kg orally [40]. (XI) showed no evidence of autonomic activity at 4 mg/kg intravenously in the dog. This compound displayed the species variability of toxicity characteristic of the series, and to some extent of indoles in general. It had an LD_{50} of about 133 mg/kg (I.P., mouse), 233 mg/kg (oral, mouse) and 80 mg/kg (oral, rat). Monkeys could

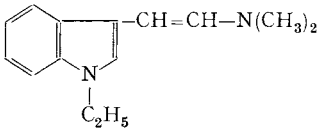
tolerate 100 mg/kg/day orally for 21 days with no lesions apparent on microscopic section. After a daily dose of 15 mg/kg orally for 40 days rats displayed as their only toxic manifestation very slight renal lesions which were reversible. In contrast to the above data, a single oral dose of 1 mg/kg was lethal to a dog, the gross toxic signs being depression and hemorrhage of the digestive tract [39].

3.241 Clinical Results

Compound (XI) has been studied orally in humans with severe hypertension in doses of 12·5 to 100 mg four times a day for up to fourteen days [215]. There resulted a disconcerting variety of side-effects including abdominal pains, diarrhea, nausea and vomiting, urinary urgency, tenesmus, penile erection and ejaculation, chills and fever, paresthesias, arthralgia, pruritis and hives. It is not clear whether the failure to note a blood pressure drop was due to inactivity in man or to the inability to assess blood pressure effects in the face of the above side effects.

3.242 Acid Instability

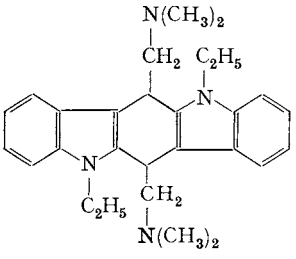
During the chemical studies on the β-hydroxytryptamines it was early noted that these substances were very sensitive to strong aqueous acid, and in most cases attempts to dissolve them in excess mineral acid caused the formation of a deep red solution. These solutions were found by FREYBURGER [70] to be more hypotensive than those of the original amines. For example, the acid transformation product of (XI) (compound 12, Table 5) produced clear-cut hypotensive activity in the DCA rat at 1 mg/kg. Since this new material might well be the active form of the drug, attempts were made to isolate and identify it. It was immediately apparent that the colored material was not simply the dehydration product (XII).



(XII)

By careful treatment of 40 g of (XI) (compound 12, Table 5) with cold aqueous hydrochloric acid, basification of the resulting red solution, extraction with chloroform followed by chromatography over neutral alumina (activity III), using benzene with increasing amounts of acetone (up to 7·5%), there was obtained an ether-insoluble material. Recrystallization from methanol-benzene resulted in 110 mg of a tan crystalline compound, m.p. 350° (Kofler), which had excellent hypotensive activity. The material absorbed in the ultraviolet at 233, 284 (shoulder), 298 and 308 mμ (shoulder) and in the infrared at 2755 cm^{-1} (tertiary amine); 1616, 1573, 1537, 1487 cm^{-1} (C=C); and 733, 762 and 783 cm^{-1}. There was no OH absorption. Analytical and titration data, along with the spectral values, suggested a dimeric compound with a molecular weight of 428·6 compatible with loss of the elements of water and the formation of com-

pound (XIII). Efforts to synthesize (XIII) have been unsuccessful and so this structure must remain speculative [181].

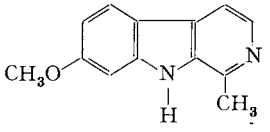


(XIII)

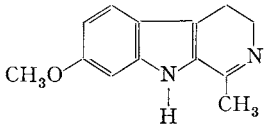
In unanesthetized mongrel dogs as little as 1 mg of the above acid-transformation product caused marked generalized erythema with biting, scratching, muzzle edema and hive-like cutaneous eruptions, suggestive of histamine release. Accordingly, dogs were dosed with this material twice daily for a week in an attempt to deplete histamine stores. The final dose produced a reduced but still marked effect. Therefore, if the compound does act by the liberation of histamine, it does not succeed in depleting the histamine stores [70]. It is interesting to note the remarkable similarity of these effects to those produced by an alkaloid oxypanamine, isolated from the seeds of a Central American tree, Ormosia panamensis [142].

4. Conversion of Tryptamines to β-Carbolines

β-Carbolines such as harmine (I) and harmaline (II) may be looked upon as tryptamine derivatives in which the side chain has been incorporated into the elements of a third ring. Just as several tryptamines, for example, bufotenine [58], dimethyltryptamine [194] and psilocybin [106] have been reported to



Harmine (I)



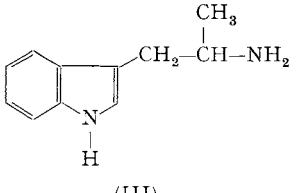
Harmaline (II)

produce hallucinogenic states in man, so also have a number of the related naturally-occurring β-carbolines. Harmine, for example, is reported to be the active principle responsible for the bizarre effects produced by the Indian ritual potion *caapi* [43]. In the sections to follow is reported some of the evidence and speculation implicating endogenous β-carbolines as agents responsible for behavioral changes sometime seen in man.

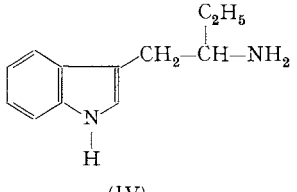
4.1 *Evidence for Metabolic Conversion of Tryptamines to β-Carbolines*

4.11 Metabolism of α-Methyltryptamine and α-Ethyltryptamine

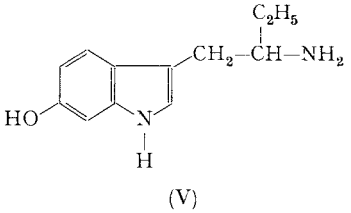
It has been reported that these α-substituted tryptamines, (III) and (IV) [100], are not oxidatively deaminated *in vitro* by monoamine oxidase but, instead, are potent inhibitors of this enzyme and cause an elevation of endogenous amines in the brain of rats [90, 89]. In man these compounds, especially (IV), have been found to resemble other monoamine oxidase inhibitors in displaying antidepressant properties [157]. There is some evidence that they possess delayed stimulant properties typical of the hydrazine monoamine oxidase inhibitors, but, in addition, have more immediate and direct effects, somewhat reminiscent of amphetamine [104, 133, 112, 76]. Szara has shown that some tryptamines such as diethyltryptamine and (III) are metabolized to the corresponding 6-hydroxy derivatives. He has suggested that it is the latter metabolites which are responsible for their more delayed central action, and further, that these 6-hydroxylated metabolites are indeed hallucinogenic substances [180; cf. however 112]. Eberts and Daniels have studied in detail the human metabolism of the more potent α-ethyltryptamine (IV). It is significant that they found no appreciable difference in the amount or type of metabolites formed when acute or chronic doses (14 days) were given (cf. [38]). They have reported [52] that the major metabolites are the sulfate and glucuronide conjugates of 3-(2-aminobutyl)-6-hydroxyindole (V), along with smaller amounts of unconjugated material. Compound (V) was synthesized by Hester [101] and injected into several animal species. Its psychotropic properties were reported to be much less than those of the parent compound [52]. An additional urinary metabolite more recently isolated by Eberts and Daniels, and one which occasionally appeared to be formed in considerable quantities, was postulated



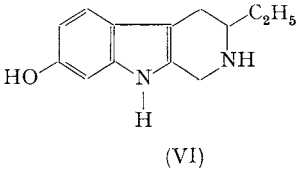
(III)



(IV)



(V)



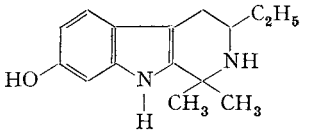
(VI)

by them to have the tetrahydro-β-carboline structure (VI) [51]. This was confirmed by comparison with a synthetic sample [101]. It is interesting to speculate whether (VI) is an artifact produced in the isolation or is formed enzyma-

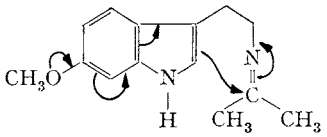
tically in the human by condensation with a formaldehyde precursor. Available data support the latter viewpoint. It is possibly such further metabolites of 6-hydroxytryptamines which are responsible for some of the 'hallucinogenic' properties attributed to tryptamines by SZARA [180, 112] and MURPHEE [143].

As far as we are aware, metabolite (VI) and FARRELL's adrenoglomerulotropin (see Section 4.13) are the only β-carbolines which have been isolated from animal tissues. It is interesting that of all the β-carbolines produced in plants or animals, (VI) is the only one which does not contain a 1-methyl group and hence is, formally at least, formed from a tryptamine and formaldehyde rather than acetaldehyde.

In the course of attempts to convert synthetic (V) to its creatinine sulfate complex in aqueous acetone there was isolated a compound which was found to have the structure (VII) [101], resulting from condensation of (V) with a



(VII)

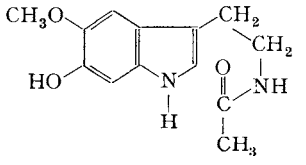


(VIII)

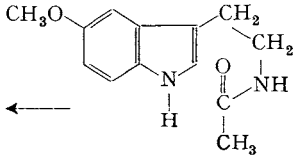
molecule of acetone. Studies aimed at determining the structural requirements for this facile condensation under 'physiologic conditions' with unactivated ketones indicated [101] that electron-donating substituents at position 6 of the indole nucleus (cf. VIII), and presumably at position 4 also, are needed to produce the necessary nucleophilicity at position 2. Thus 6-hydroxy- and 6-methoxytryptamine hydrochlorides (but not tryptamine and 5-methoxytryptamine hydrochlorides) were readily converted into the corresponding tetrahydro-β-carbolines when allowed to stand at room temperature in the presence of aqueous acetone and pH 4·7 acetate buffer. It is worthy of note that many of the naturally occurring indole alkaloids contain an activating group in the position required for facile cyclization of the above type. However, such activation is less important when the carbonyl reagent is an aldehyde or a more reactive ketone such as pyruvic acid (see adrenoglomerulotropin formation, Section 4.13).

4.12 METABOLISM OF MELATONIN

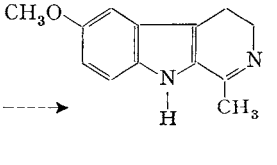
Melatonin, the most potent agent known in lightening frog skin, has been isolated by LERNER from bovine pineal glands and from peripheral nerves of man, monkey and cattle [129, 128, 125]. Its structure has been shown to be



(X)



Melatonin (IX)

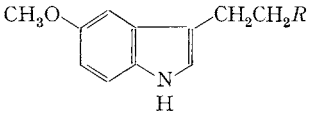


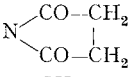
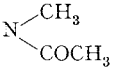
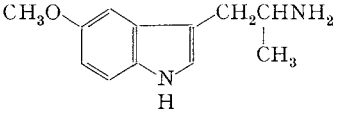
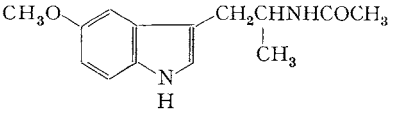
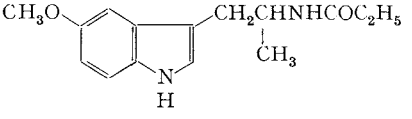
(XI)

N-acetyl-5-methoxytryptamine (IX) [127]. The physiological function of melatonin in man is not yet clear. The possibility that it is involved in color changes of human skin and as a vitiligo factor remains to be proven [125, 126]. Its presence in nerve tissue suggests that it may play some role in nerve function.

Table 8

Lightening of Frog Skin by Derivatives of 5-Methoxytryptamine



R	m.p. °C[1])	*C*[2])
NH_2	[189]	2×10^{-1} [3])
NHCHO	95–96°	1×10^{-4} [3])
$NHCOCH_3$	[189]	1×10^{-7} [3])
$NHCOC_3H_7$-*n*	120–121°	1×10^{-7} [3])
$NHCOC_5H_{11}$-*n*	56–57°	1×10^{-7} [4,5])
$NHCOC_8H_{17}$-*n*	76–77°	1×10^{-7} [4,5])
$NHCOC_{15}H_{31}$-*n*	98–99.5°	1×10^{-7} [4,5])
	168–169.5°	ca. 1×10^{-7} [4,5])
	117°; 123–124°	1×10^{-3} [4])
	[151a][1])	5×10^{-2} [4])
	118–119°	2×10^{-3} [4])
	90–92°	1×10^{-7} [3])

[1]) J. SZMUSZKOVICZ and W. C. ANTHONY, The Upjohn Company, unpublished results.

[2]) *C* = the minimum effective concentration in μg per ml required to lighten frog skin (Rana pipiens) previously darkened with MSH.

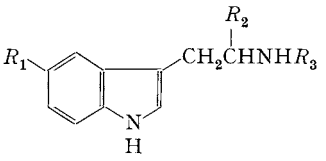
[3]) A. B. LERNER and J. D. CASE, Federation Proc. *19* (1960), 590.

[4]) A. B. LERNER, Yale University Medical School, unpublished results.

[5]) Slower to react than melatonin, but maximum lightening activity was obtained with 1×10^{-7} μg per ml.

Table 9

Lightening of Frog Skin by Other Derivatives of Tryptamine



R_1	R_2	R_3	m.p. °C	C[1]
H	H	H		2×10^{-1} [2]
H	H	$COCH_3$		5×10^{-2} [2]
H	CH_3	$COCH_3$	Oil[3]	Inactive[4]
H	CH_3	COC_2H_5	80–82°[3]	Inactive[4]
OH	H	H		1[2]
OH	H	$COCH_3$		6×10^{-3} [2]
$OCOCH_3$	H	$COCH_3$	Oil[3] [137]	5×10^{-3} [4]
OC_2H_5	H	H		5×10^{-2} [2]
OC_2H_5	H	$COCH_3$		1×10^{-5} [2]

[1]) C = minimum effective concentration in μg per ml required to lighten frog skin (Rana pipiens) previously darkened with MSH.

[2]) A. B. Lerner and J. D. Case, Federation Proc. *18* (1960), 590.

[3]) W. C. Anthony, The Upjohn Company, unpublished results.

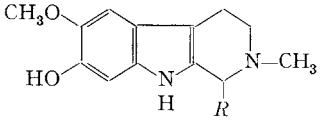
[4]) A. B. Lerner, Yale University Medical School, unpublished results.

A number of related derivatives of 5-methoxytryptamine were prepared [188] for comparison with melatonin in lightening frog skin. These compounds and their lightening activity are listed in Table 8, while Table 9 shows the activity of other tryptamine derivatives. It may be seen that extremely high lightening activity is limited to compounds which have a methoxyl group in the 5-position of the indole nucleus and an acetyl or large acyl substituent on the side-chain nitrogen. McIsaac [134] has reported that '10-methoxyharmalan' (XI) is also potent in this assay, a fact which may be of interest relative to the metabolism of melatonin.

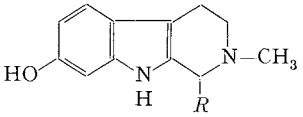
Melatonin is formed from serotonin by N-acetylation followed by O-methylation [137, 204, 14, 15]. Its major metabolic pathway involves 6-hydroxylation to (X), followed by conjugation [119, 122]. A minor non-indolic metabolite is also produced, possibly by cyclodehydration of melatonin to form 3,4-dihydro-6-methoxy-1-methyl-9H-pyrido-[3,4-b]indole (XI) [122]. Depending on the numbering system used, this compound has been variously named '10-methoxyharmalan' [122], '6-methoxyharmalan' and '7-methoxyharmalan'. An interesting hypothesis concerning the cause of mental disease has been proposed by McIsaac [134] who suggests that in certain cases of mental disease the normal metabolism of serotonin is blocked, causing forma-

tion of abnormally large amounts of melatonin and, hence, of its hypothetical metabolite (XI). The latter, a powerful monoamine oxidase inhibitor, would further inhibit the normal metabolism of serotonin and, by a chemical feedback mechanism, ultimately cause its own accumulation. Furthermore, (XI) was shown to be both a potent serotonin antagonist and a 'psychotomimetic agent', as evidenced by its effect on avoidance escape behavior in rats [136, 134].

If one were to attempt to invoke β-carboline formation from endogenous tryptamines to explain hallucinations in schizophrenics, it would seem that one should attempt to offer a similar explanation for the hallucinogenic properties of N,N-disubstituted tryptamines such as bufotenine and dimethyltryptamine (see Section 3.231). N,N-disubstituted tryptamines are not deaminated by monoamine oxidase [80] and instead are 6-hydroxylated [179]. The resulting compounds, being tertiary amines, cannot themselves cyclize to β-carbolines, but would have to first undergo enzymatic demethylation [64a, 65, 179] fol-



(XII)

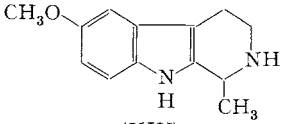


(XIII)

lowed by cyclization to β-carbolines such as (XII) and (XIII) (R = H or CH_3). The pharmacology of such compounds has not been studied.

4.13 Formation of Adrenoglomerulotropin

From pineal tissue there has recently been isolated yet another compound which, in certain preparations, stimulates aldosterone secretion and which has been named adrenoglomerulotropin [59, 60]. The structure of this compound was proposed to be 2,3,4,9-tetrahydro-6-methoxy-1-methyl-1H-pyrido[3,4-b]-indole (XIV), and the formation of (XIV) *in vivo* from 5-methoxytryptamine and acetaldehyde was demonstrated [135]. It will be noted that (XIV) differs from McIsaac's '10-methoxyharmalan' (XI) only in the state of hydrogenation. Subsequent studies have suggested that the structure of adrenoglomerulotropin may not be as formulated above, and experiments are in progress to clarify this point [60a].

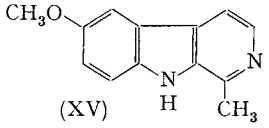


(XIV)

4.2 *Synthetic Compounds Related to the Naturally Occurring β-Carbolines*

We had become interested in the possible cyclodehydration of melatonin independently as soon as the structure of this hormone became known [127]. At that time we prepared and studied the pharmacological properties of (XI), (XIV) and the completely aromatic structure, 6-methoxy-1-methyl-9H-pyrido[3,4-b]indole (XV), as well as a number of related compounds some of

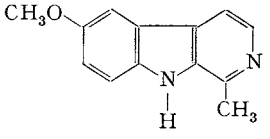
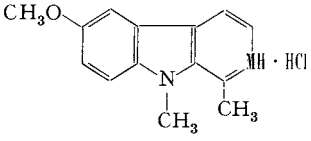
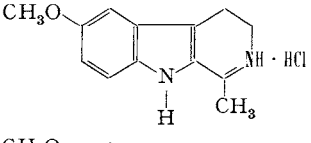
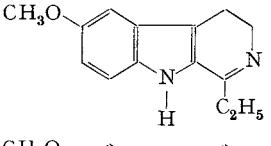
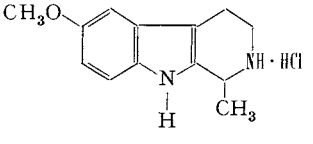
which are listed in Table 10. The aromatic compounds are characterized by excellent diuretic activity in the hydrated rat, and little if any inhibition of the enzymes, monoamine oxidase and pseudocholinesterase. On the other hand the dihydro and tetrahydro compounds are relatively potent as inhibitors of both these enzymes. It is interesting that (XIV) had, in the hydrated rat, no effect on water or electrolyte balance [81], in spite of its reported aldosterone-stimulating effects [60].



(XV)

Table 10

Pharmacological Activity of Various 6-Methoxy-1-Substituted-9H-Pyrido[3,4-b]indoles

Structure	m.p. °C	LD_{50}[4]	Activity
	273–274°[1]	650	Excellent diuretic activity[5] at 10 and 20 mg/kg
	287–288°[3,2]	53	Mild diuretic activity[5] at 5 and 10 mg/kg; excellent at 20 mg/kg
	266–267°[7,1]	53	Inhibition of MAO[6]: $[I]_{50}$ $3.8 \times 10^{-5} M$; inhibition of pseudocholinesterase[6]: $[I]_{50}$ 7×10^{-5}
	160–165°[3]	56	Inhibition of MAO[6]: $[I]_{50}$ $6.0 \times 10^{-4} M$; inhibition of pseudocholinesterase[6]: $[I]_{50}$ 1×10^{-4}
	249-251°[7] [135]	65	Inhibition of MAO[6]: $[I]_{50}$ $2.5 \times 10^{-4} M$

[1] E. Späth and E. Lederer, Ber. *63* (1930), 2102.
[2] J. H. Cook, J. D. Loudon and P. McCloskey, J. Chem. Soc. *1951*, 1203.
[3] J. B. Hester, The Upjohn Company, unpublished results.
[4] Determined in mice intraperitoneally by W. Veldkamp of the Upjohn Company.
[5] Determined in rats orally by B. E. Graham of the Upjohn Company.
[6] M. E. Greig, The Upjohn Company, unpublished results. MAO = monoamine oxidase.
[7] J. Szmuszkovicz and J. B. Hester, The Upjohn Company, unpublished results.

5. Enzyme Inhibitory Activity of 3-(2-Aminobutyl)indole Derivatives

5.1 *Discussion and Results*

3-(2-Aminobutyl)indole [168, 100, 190] (etryptamine, Monase) (compound 11, Table 11) has been shown to be a clinically efficacious drug for treating some types of depressions [138]. It was, therefore, of interest to study [102] the relative pharmacology of several analogous compounds. Early pharmacologic studies clearly demonstrated that etryptamine was a reversible inhibitor of monoamine oxidase *in vitro*, with about the same potency as iproniazid, and that it had no effect on 5-hydroxytryptophane decarboxylase activity at a concentration of 10^{-2} molar [90]. At low doses (<2 mg/kg) etryptamine inhibited both rat brain and rat liver monoamine oxidase activity [89]; it caused a significant increase of endogenous brain serotonin and greatly enhanced 5-hydroxytryptophan potentiation of rat brain serotonin [89, 76]. At high doses (2–10 mg/kg), in chronic experiments, etryptamine was found to depress brain serotonin levels below those observed with lower doses of the drug [88, 85]. This result indicated that, although etryptamine inhibits serotonin metabolism, at high doses it also interferes with serotonin formation. Since the absence of appreciable 5-hydroxytryptophan decarboxylase inhibition had already been demonstrated, the effect of etryptamine on tryptophan-5-hydroxylation was investigated. The results of these experiments, which have been reported by GREIG *et al.* [88, 85] and are summarized in Figure 1, strongly support the view

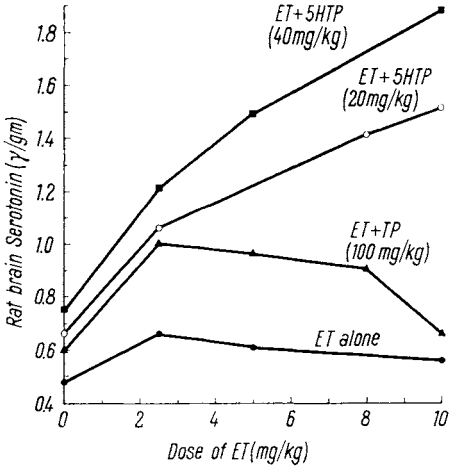


Figure 1

Effect of Etryptamine (ET) on Rat Brain Serotonin (TP = Tryptophan; 5-HTP = 5-Hydroxytryptophan)

that etryptamine *does* inhibit tryptophan-5-hydroxylase. Since the antidepressant effects of etryptamine have usually been ascribed to its activity as a monoamine oxidase inhibitor (cf. arguments presented in References [76 and

197]), we sought to prepare an analog that would not interfere with serotonin synthesis but would still inhibit serotonin metabolism by monoamine oxidase.

Recently HALL and coworkers [94] were able to show that both 7-methyltryptophan and 7-chlorotryptophan were poorly adsorbed on *Escherichia coli* tryptophanase, an enzyme that converts L-tryptophan to indole. This phenomenon was attributed to the fact that 7-substituents on the indole nucleus would sterically inhibit adsorption of the indole nitrogen to an enzyme surface. These workers proposed that three point attachment, required for stereospecific enzyme adsorption, in this case involved the side chain carboxyl and amine groups as well as the indole nitrogen—a conclusion that was supported by the work of GOODER and HAPPOLD [78]. Since tryptophan-5-hydroxylase is specific for the L-amino acid [67] it appeared to us that three point attachment would be required for enzyme interaction, and that a likely point of attachment would be the indole nitrogen. Since enzyme inhibition usually involves adsorption of the inhibitor on the active site of the enzyme, we speculated that indole substituents which would block the approach of the indole nitrogen of etryptamine to the enzyme surface would prevent the inhibition of tryptophan-5-hydroxylase by the resulting compound. These substituents were not expected to affect the monoamine oxidase inhibitory characteristics of the compound, since we had already found that both optical enantiomers of etryptamine had similar activity as monoamine oxidase inhibitors, indicating that a three point attachment of the inhibitor to this enzyme was evidently not required.

Inhibition of monoamine oxidase by 2,7-dimethyl-etryptamine (compound 2, Table 11), the first compound in this series to be investigated, was inferior to that of etryptamine both *in vitro* and *in vivo*. It did, however, potentiate the effects of both tryptophan and 5-hydroxytryptophan on rat brain serotonin levels (Figure 2). Further investigation showed that 2-methyl-etryptamine (compound 9) had little effect on monoamine oxidase *in vitro* and did not

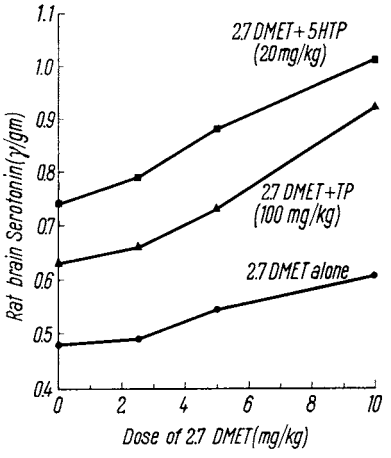


Figure 2

Effect of 2,7-Dimethyl-Etryptamine (2,7-DMET) on Rat Brain Serotonin

potentiate the effect of either tryptophan or 5-hydroxytryptophan on rat brain serotonin (Figure 3). Thus the 2-methyl substituent in these compounds markedly inhibits formation of the enzyme-inhibitor complex, an effect which may be rationalized by a consideration of steric factors. On the other hand the inhibition of monoamine oxidase by 7-methyl-etryptamine (compound 10) was striking. Its *in vitro* activity was ten times that of etryptamine, and it was two to four times as effective as etryptamine in increasing endogenous rat brain serotonin *in vivo*. It also caused a marked increase of rat brain serotonin when

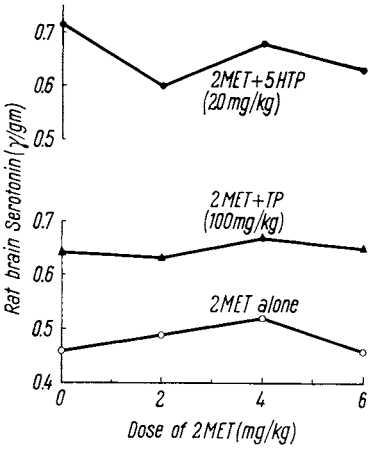


Figure 3
Effect of 2-Methyl-Etryptamine on Rat (2-MET) Brain Serotonin

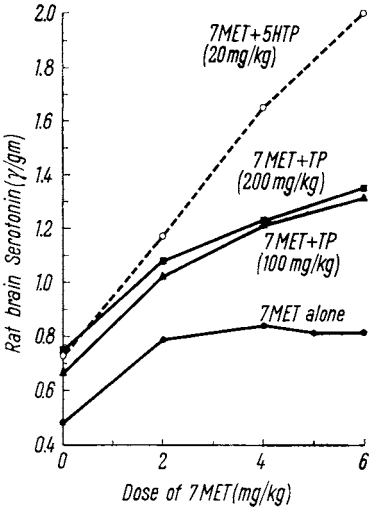


Figure 4
Effect of 7-Methyl-Etryptamine (7-MET) on Rat Brain Serotonin

followed by either tryptophan or 5-hydroxytryptophan. In both cases there was a direct relationship between dose and response (Figure 4). These data offer support for the view that tryptophan-5-hydroxylase, like tryptophanase, requires unhindered approach to the indole nitrogen for substrate complex formation.

It has been found that etryptamine, like many other indole derivatives, is metabolized primarily by 6-hydroxylation [52]. Since SZARA and HEARST [180] had shown that 6-hydroxy-N,N-diethyltryptamine, the major metabolite of N,N-diethyltryptamine, was a potent psychotomimetic agent and probably accounted for the observed activity of its precursor, we were surprised to find that 6-hydroxy-etryptamine (compound 5) had little activity on the central nervous system of intact animals and did not inhibit monoamine oxidase *in vitro* [87]. Recently KALIR and SZARA [112] reported results similar to ours for 3-(2-aminopropyl)-6-hydroxyindole, the major metabolite of 3-(2-aminopropyl)indole.

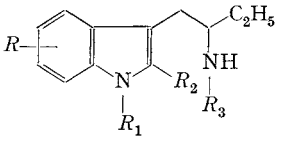
Since etryptamineis metabolized rapidly *in vivo* it was of interest to prepare a 3-(2-aminobutyl)indole that was substituted at the 6-position in the hope that such a compound would retain the activity of etryptamine and resist metabo-

lism by the 6-hydroxylation mechanism. 6-Fluoro-etryptamine (compound 6) was therefore prepared. This compound was, however, a poor monoamine oxidase inhibitor in both *in vivo* and *in vitro* assays.

The 3-(2-aminobutyl)indoles, prepared for this study, are listed in Table 11 along with their *in vitro* monoamine oxidase and 5-hydroxytryptophan decarboxylase inhibitory activities.

Table 11

3-(2-Aminobutyl)Indoles



No.	R	R_1	R_2	R_3	Monoamine oxidase: % inhibition/molar drug concentration [84]	5-Hydroxytryptophan decarboxylase: % inhibition at 10^{-2} molar [84]
1	H	H	H	C_2H_5	$50/7 \times 10^{-4}$	0
2	7-CH_3	H	CH_3	H	$54/10^{-3}$	6
3	5-OCH_3	H	H	H	$10/10^{-3}$	7
4	6-OCH_3	H	H	H	$48/10^{-3}$	58
5	6-OH	H	H	H	$0/10^{-3}$	58
6	6-F	H	H	H	$44/10^{-3}$	0
7	H	CH_3	H	H	$35/10^{-3}$	0
8	H	CH_3	CH_3	H	$0/10^{-3}$	14
9	H	H	CH_3	H	$22/10^{-3}$	13
10	7-CH_3	H	H	H	$50/3 \times 10^{-5}$	0
11[1]	H	H	H	H	$50/2{\cdot}6 \times 10^{-4}$	0

[1] Described in References [168, 100, 190].

5.2 *Pharmacological Results* [84]

Monoamine oxidase activity was determined manometrically by the method of BHAGVAT *et al.* [20]. The source of enzyme was guinea pig liver. The substrate use dwas serotonin in a concentration of 6×10^{-3} *M*. Compounds tested for inhibitory activity were added to the manometer vessel for initial testing in concentrations to give a final molarity of 10^{-3}. For compounds inhibiting more than 50% at this concentration, $[I]_{50}$ determinations were carried out. It is obvious that for monoamine oxidase inhibitors, such as etryptamine (ET), which compete with the substrate the $[I]_{50}$ values are valid only with the substrate concentration used.

5-Hydroxytryptophan (5-HTP) decarboxylase activity was measured manometrically by the method of CLARK *et al.* [36].

In vivo enzyme inhibiting activity was assessed by determining brain serotonin as follows. Four to 10 rats were dosed intraperitoneally with the tryptamine derivative either alone or followed in 10 minutes by tryptophan (100 mg/kg) or 5-hydroxytryptophan (20 or 40 mg/kg). One hour later they were decapitated and brain tissue serotonin was determined by the method of BOGDANSKI *et al.* [23] using the Aminco Bowman spectrophotofluorometer.

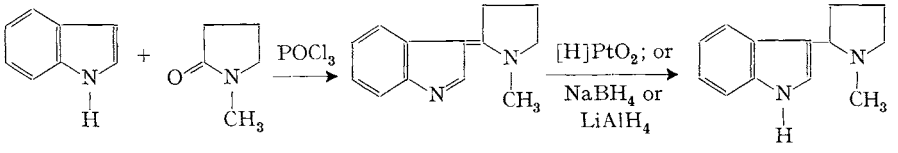
5.3 *Methods of Chemical Syntheses*

Most of the amines listed in Table 11 were prepared [102] by reducing the corresponding nitrobutyl indoles which, in turn, were prepared by allowing the requisite gramine to react with 1-nitropropane under the conditions described by SNYDER and KATZ [168]. In most cases the nitrobutyl indoles were not crystalline. Satisfactory results were obtained when the crude oils were reduced either catalytically with Raney nickel or palladium on carbon, or chemically with lithium aluminium hydride. 3-(2-Ethylaminobutyl)indole (compound 1) was prepared by lithium aluminum hydride reduction of the corresponding N-acetyl derivative, which was prepared by the reaction of etryptamine with acetic anhydride. Alkylation of the indole nitrogen to obtain compounds 7 and 8 was achieved with sodium amide and methyl iodide in liquid ammonia. 3-(2-Aminobutyl)-6-hydroxyindole (compound 5) was prepared by palladium catalyzed hydrogenolysis of the corresponding benzyloxy derivative.

6. Synthesis and Pharmacological Activity of 3-(2-Pyrrolidinyl)Indoles

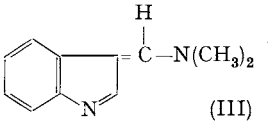
6.1 *Synthesis of 3-(2-Pyrrolidinyl)Indoles*

Recently we have prepared indole 3-C^{14}-carboxaldehyde [190] by the method of SMITH [167] from indole, dimethylformamide and phosphorous oxychloride, as an intermediate to radioactive 3-(2-aminobutyl)indole (etryptamine, Monase; see Section 5). In this connection an attempt has been made [7] to circumvent the inefficient use of radioactive dimethylformamide as the reaction solvent by replacement with N-methyl-2-pyrrolidone. This attempt led to the observation



that under certain conditions the pyrrolidone participated in the reaction, and allowed the development of a general method for the synthesis of 3-(2-pyrrolidinyl)indoles illustrated below in the case of compound (II) [217].

The ultraviolet spectra of (I) and its various substituted derivatives are quite similar to those reported for (III) [167] and other related indolenine

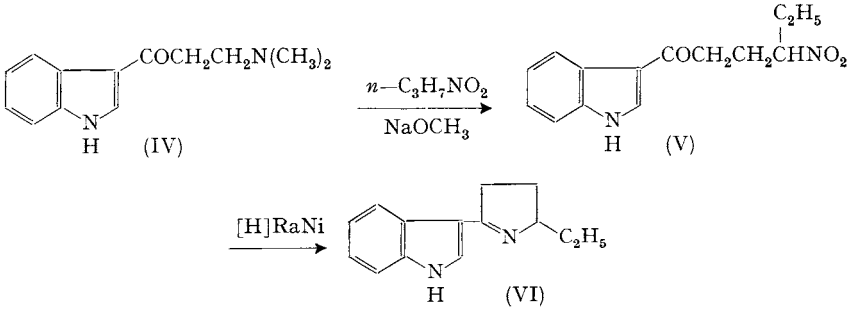


(III)

derivatives [205], and all have a band at 336–361 mμ with an extinction coefficient of 7800–20700. Additional support for the indolenine (I) over the 3-(2-pyrrolin-2-yl)indole structure is provided by the absence of an NH band in the infrared spectrum of compound (I) in both nujol mull and chloroform solution.

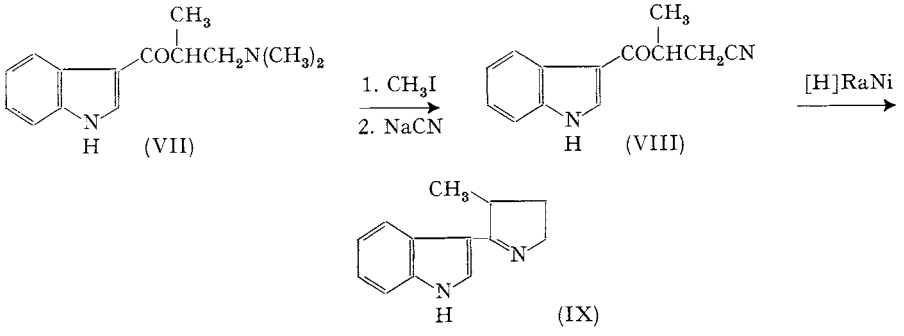
The various indolenines (e.g. I) could be reduced to the desired indoles (e.g. II) by catalytic hydrogenation (PtO_2), and by reduction with either sodium borohydride or lithium aluminium hydride. The only 3-(2-pyrrolidinyl)indole compound which had been reported to date is the parent member of this class prepared by FUHLHAGE and VANDERWERF [72] from indole and 1-pyrroline.

Another method for the synthesis of 3-(2-pyrrolidinyl)indoles was developed employing the Mannich bases derived from 3-acetylindoles [184]. The Mannich base (e.g. IV) was reacted with a nitroalkane in presence of sodium methoxide,



(IV) (V) (VI)

and the resulting 3-indolyl nitroketone (e.g. V) was subjected to hydrogenation in the presence of Raney nickel to give the corresponding 1-pyrroline (e.g. VI)



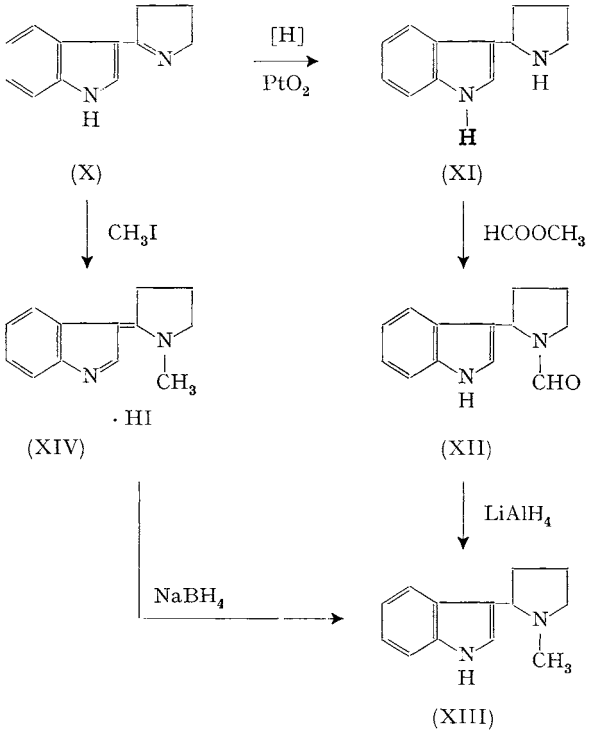
(VII) (VIII) (IX)

[cf. 115]. This method was not successful in the case of the Mannich base (VII) derived from 3-propionylindole. To circumvent this difficulty the methiodide of (VII) was subjected to reaction with sodium cyanide, and the resulting

nitrile (VIII) hydrogenated in the presence of Raney nickel to the desired 1-pyrroline (IX).

The formulation of these products (e.g. VI) as 1-pyrrolines rather than indolenines is strongly supported by the ultraviolet spectra which show maxima not higher than 296 mμ. On the other hand, conversion of (VI) to the hydrochloride brought about a shift to 329 mμ most likely due to formation of the indolenine system.

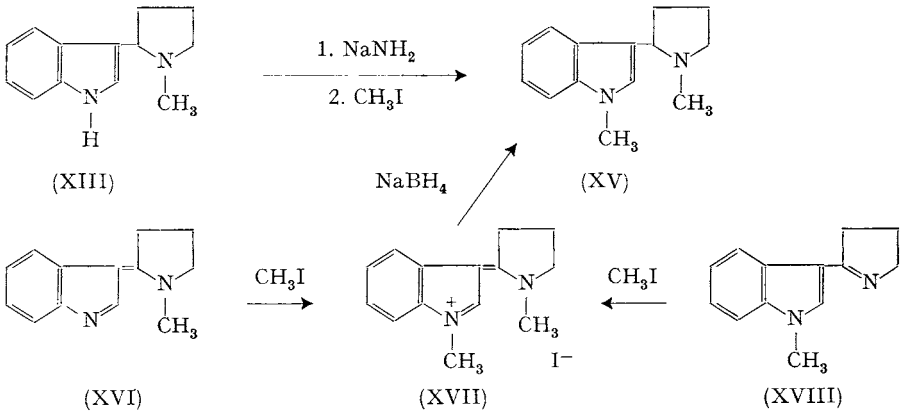
The 1-pyrroline compounds were converted by several methods to 3-(2-pyrrolidinyl)indoles. Catalytic hydrogenation in the presence of platinum oxide afforded the pyrrolidine-N-unsubstituted compounds (e.g. X → XI). Treatment of (XI) with methyl formate or acetic anhydride led to the 1-formyl product (XII) or 1-acetyl compound, respectively, which could be reduced with lithium



aluminum hydride to the 1-methyl (XIII) or 1-ethyl products. Alternatively, treatment of pyrroline (X) with methyl iodide led to the indolenine hydroiodide (XIV) which was reduced to (XIII) with sodium borohydride.

In cases where N-indole substituted compounds were desired several methods were applied. Thus compound (XV) was prepared by reaction of (XIII) with sodium amide followed by methyl iodide, and also by treatment of (XVI) with methyl iodide followed by reduction of the intermediate (XVII) with sodium borohydride. The same intermediate (XVII) resulted from the reaction of (XVIII) (obtained via the Mannich base method) with methyl iodide. The

fact that the identical product (XV) was obtained from these reaction sequences establishes unequivocally the position of methylation in the processes (XVI) → (XVII) and (XVIII) → (XVII).



(XIII) (XV) (XVI) (XVII) (XVIII)

The various 3-(2-pyrrolidinyl)indoles prepared for this study [217] are listed in Tables 12 and 13. Details of the chemical syntheses will be described in the future.

6.2 *Pharmacology*

The results of the pharmacological testing of the 3-(2-pyrrolidinyl)indole derivatives are listed in Tables 12 and 13.

The classical avoidance test, using rats, a five hour test period, and a noise warning-stimulus, was carried out by ANGER [6] and will be described in a future publication. This test, based on the method of VERHAVE *et al.* [199], indicates chloropromazine-like activity; + + = high chloropromazine (CPZ)-like activity (maximum avoidance loss without escape loss > 60% CPZ), + = low CPZ-like activity (40–60% CPZ), ± = weak, doubtful or variable activity (20–40% CPZ), and — = negligible activity (< 20% CPZ).

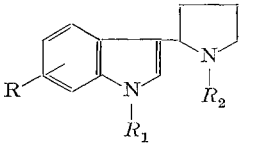
Four compounds showed a high degree of activity: the pyrrolidine-N-methyl derivative (compound 3), 4-chloro-pyrrolidine-N-methyl (compound 9), 7-methyl-pyrrolidine-N-methyl (compound 11), and pyrrolidine-N,5-dimethyl (compound 26) derivatives.

The antiaggressive behavior assay was carried out by DA VANZO [42] and will be described in detail in his future publication. It was similar to the procedure described by YEN *et al.* [213]. This method utilizes isolation stress to induce fighting behavior in mice, and the compounds are tested for their ability to effectively reverse this behavior. Criteria for activity were 40% protection at 10% of the LD_{50} or 40% protection or better at 14 mg/kg.

The most active derivatives in this test were compounds 2, 3, 9, 10, 11, 12, and 15. It is interesting that relatively small modifications in structure either decreased or eliminated the activity in the classical avoidance and antiaggressive behavior tests, as will be readily seen in Tables 12 and 13.

Table 12

3-(2-Pyrrolidinyl)-Indoles



No.	R	R_1	R_2	LD_{50}[1] Mouse mg/kg	Antiaggressive behavior [42] % Protection (1 hr)	Antiaggressive behavior [42] Dose (mg/kg)	Monoamine oxidase inhibition [83] % at 10^{-3} M	Monoamine oxidase inhibition [83] $[I]_{50}$	Pseudocholinesterase inhibition [83] % at 10^{-3} M	Pseudocholinesterase inhibition [83] $[I]_{50}$	LD_{50}[1] Rat mg/kg	Classical avoidance [6] at 28 % of Rat LD_{50}
1	H	H	H	200	20	20	30		67		171	—
2[4]	H	CH_3	H	56	50	8	31			2×10^{-4} M	100	—
3	H	H	CH_3	129	100 50 0	28 14 7		4×10^{-4} M	52		176	+ +
4	5-OCH_3	H	CH_3	65	Inactive		34		17		55	—
5	5-CH_3	H	CH_3	129	Inactive		39		52		92	±[2]
6	5-OCH_2-C_6H_5	H	CH_3	100	40	10	15			6×10^{-5} M	71	—
7	5-OH	H	CH_3	178			0			3×10^{-5} M	282	—
8	5-Cl	H	CH_3	130	100 30	50 25					40	+[3]
9	4-Cl	H	CH_3	354	60 20	14 5·6		4×10^{-4} M			71	+ +
10	5-Br	H	CH_3	105	40	5·6					35	±

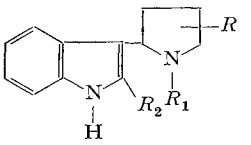
Table 12 (Continued)

No.	R	R_1	R_2	LD_{50}[1] Mouse mg/kg	Antiaggressive behavior [42] % Protection (1 hr)	Dose (mg/kg)	Monoamine oxidase inhibition [83] % at 10^{-3} M	$[I]_{50}$	Pseudocholinesterase inhibition [83] % at 10^{-3} M	$[I]_{50}$	LD_{50}[1] Rat mg/kg	Classical avoidance [6] at 28% of Rat LD_{50}
11	7-CH_3	H	CH_3	154	100	38		$2\times10^{-5}M$		$1\times10^{-4}M$	126	++
					80	14						
					0	9·6						
12	H	CH_3	CH_3	56	100	28	0			$2\times10^{-4}M$	140	—
					50	14						
					0	7						
13[5]	H	$CH_2C_6H_5$	CH_3	133	Inactive		48			$1\times10^{-5}M$	93	—
14[6]	H	$(CH)_2N$-$(C_2H_5)_2$	CH_3	100	Inactive		0			$6\times10^{-6}M$	280	—
15[4]	H	H	C_2H_5	58	100	14		$5\times10^{-4}M$		$5\times10^{-5}M$	71	±
					10	5·6						
16[7]	H	H	n-C_4H_9	56	Inactive		15			$2\times10^{-5}M$	71	—
17	H	H	$CH_2C_6H_5$	224	60	33	7			$6\times10^{-5}M$	55	—
18[4]	5-Br	H	$CH_2C_6H_5$	100	Inactive		0			$2\times10^{-5}M$		
19[4]	5-Cl	H	$CH_2C_6H_5$	75	Inactive		0			$4\times10^{-5}M$		
20	7-CH_3	H	$CH_2C_6H_5$	178	Inactive							

[1]) Determined intraperitoneally by J. W. VELDKAMP of the Upjohn Company.
[2]) + at 40% and + at 56% of rat LD_{50}.
[3]) + at 40% and ++ at 56% of rat LD_{50}.
[4]) As hydrochloride.
[5]) As cyclohexanesulfamate.
[6]) As dihydrochloride.
[7]) As cyclohexanesulfamate ethanol solvate.

Table 13

3-(2-Pyrrolidinyl)Indoles



No.	R	R_1	R_2	LD_{50}[1] Mouse mg/kg	Antiaggressive behavior [42] % Protection (1 hr)	Antiaggressive behavior [42] Dose (mg/kg)	Monoamine oxidase inhibition [83] % at 10^{-3} M	Monoamine oxidase inhibition [83] $[I]_{50}$	Pseudocholinesterase inhibition [83] % at 10^{-3} M	Pseudocholinesterase inhibition [83] $[I]_{50}$	LD_{50}[1] Rat mg/kg	Classical avoidance [6] at 28% of Rat LD_{50}
21[3]	5-CH_3	H	H	56	Inactive			4×10^{-4} M		4×10^{-5} M	42	—
22[3]	5-C_2H_5	H	H	178	Inactive			4×10^{-4} M		7×10^{-5} M	141	—
23[3]	5,5-di-CH_3	H	H	56	Inactive			2×10^{-4} M		1×10^{-4} M	92	—
24[3]	3-CH_3	CH_3	H	56	Inactive		0		90		71	—
25[3]	4-CH_3	CH_3	H	75	100 0 0	28 14 7·5	41		85		126	±[2]
26	5-CH_3	CH_3	H	178	30	17·8		2×10^{-4} M		1×10^{-4} M	125	++
27	5-C_2H_5	CH_3	H	100	Inactive			1×10^{-4} M		1×10^{-5} M	140	+
28	5,5-di-CH_3	CH_3	H	56	Inactive			3×10^{-5} M		8×10^{-5} M	71	±
29	5,5-di-CH_3	C_2H_5	H	56	Inactive		50			3×10^{-6} M	71	—
30	H	CH_3	CH_3	65	Inactive		0		50		92	—

[1] Determined intraperitoneally by W. VELDKAMP of the Upjohn Company. [2] ++ at 40% of rat LD_{50}. [3] As hydrochloride.

The monoamine oxidase inhibition test was carried out by GREIG [83] using a method described in Section 5.2. High degree of activity was obtained in the case of compound 11 and the highly substituted compound 28. On the other hand, thirteen compounds were highly active as pseudocholinesterase inhibitors [83]. The pseudocholinesterase inhibitory activity was determined by the manometric method using human serum as a source of enzyme and acetyl choline as a substrate in a concentration of 0·01 *M* with bicarbonate as the buffer.

One of the compounds in this series, namely 3-(1-methyl-2-pyrrolidinyl)-indole (compound 3), is currently undergoing clinical testing on the basis of its selective depressant activity in the classical avoidance assay.

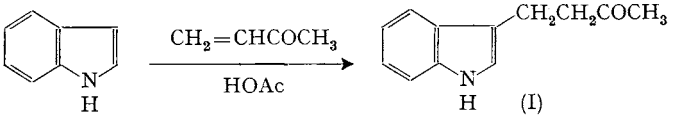
7. Indolic Compounds Bearing Ketonic or Alcoholic Groups at the 3-Position

7.1 *Condensation of Indoles With Methyl Vinyl Ketone*

There are a number of examples in the literature which illustrate the behavior of the indole nucleus toward electrophilic components in the Michael type reaction.

In the case of C_3-unsubstituted indoles, under acidic conditions, the negatively polarized C_3 undergoes reaction, e.g., with acetamidoacrylic acid in acetic acid solution containing acetic anhydride [169], with nitroethylene in benzene solution [145], with propiolactone in the absence of solvent [97], with diketene in the absence of solvent [96], and with acrylonitrile in acetic acid solution in the presence of copper borate [156].

On the other hand, the base catalyzed Michael type reaction occurs at the 1-position. Thus, in a benzene solution containing potassium hydroxide, indole and acrylonitrile react to give 1-(β-cyano)-ethylindole [191], 2-phenylindole reacts with acrylonitrile in the presence of trimethylbenzylammonium hydroxide to give 1-(2-cyanoethyl)-2-phenylindole [22], indole and methacrylonitrile in ethanolic sodium ethoxide solution gives rise to 1-(2-cyano-2-methyl)-ethylindole [54], ethyl α-(3-indolyl)-isobutyrate afforded 1-(2-carboxypropyl)-3-indoleisobutyric acid on reaction with methacrylonitrile in ethanolic sodium methoxide and subsequent hydrolysis [54], 2,3-dimethylindole reacts with acrylonitrile and sodium methoxide to give 1-(2-cyanoethyl)-2,3-dimethylindole [3]; in some cases 1,3-dicyanoethylindoles are obtained as by-products from the reaction of 2-substituted indoles with acrylonitrile [160].

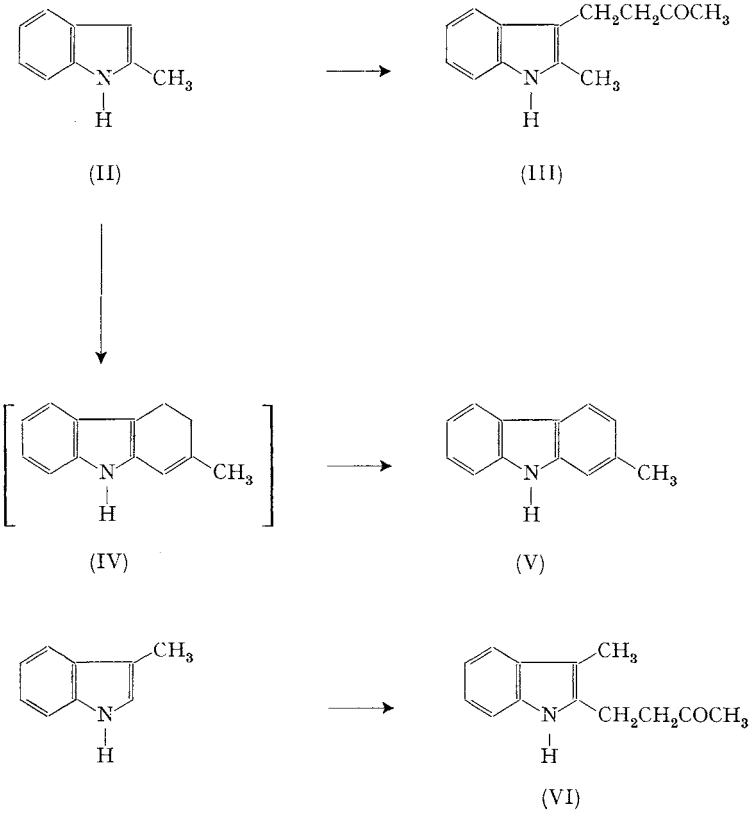


(I)

Some time ago we found that indole reacts with methyl vinyl ketone in acetic acid medium to give 75% yield of 1-(3-indolyl)-butanone-3 (I) [182].

HOLLAND and NAYLER [107] prepared (I) by treatment of gramine methosulfate with ethyl sodioacetoacetate in ethanol, the product subsequently being hydrolyzed with sodium hydroxide.

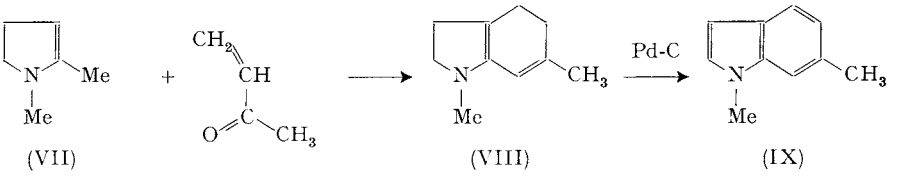
2-Methylindole (II) reacted with methyl vinyl ketone at 160° in the absence of solvent [182] to give a 29% yield of 1-[3-(2-methyl)-indolyl]-butanone-3 (III). In acetic acid solution containing acetic anhydride the yield advanced to 84%. When hydroquinone was added to the two reactants and the temperature raised to 280°, 2-methylcarbazole (V) was isolated in 10% yield. The reaction probably proceeded through an intermediate (IV) which was not isolated.



Skatole did not react with methyl vinyl ketone in the absence of solvent even on prolonged heating. On the other hand, in acetic acid solution containing acetic anhydride, a moderate yield of 1-[2-(3-methyl)-indolyl]-butanone-3 (VI) was obtained. It is interesting to note that acetic anhydride seems to be essential for the reaction of skatole with methyl vinyl ketone, especially in view of a similar observation of SNYDER and MACDONALD [169] in the case of indole and α-acetamidoacrylic acid.

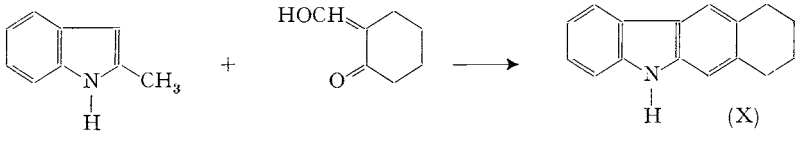
Another interesting case of a reaction of a cyclic enamine with methyl vinyl ketone was reported by IRELAND [109]. 1,2-Dimethyl-2-pyrroline (VII) and

methyl vinyl ketone reacted to give the product (VIII) of C-alkylation and dehydration. Compound (VIII) was dehydrogenated to 1,6-dimethylindole (IX).



(VII) (VIII) (IX)

A related reaction leading to carbazole derivatives was reported by NOLAND and JOHNSON [147] who studied the condensation of 2-methylindole derivatives with α-hydroxymethylene ketones. In this case aromatization was effected by dehydration rather than be dehydrogenation; e.g., reaction of 2-methylindole with 2-hydroxymethylenecyclohexanone led to carbazole derivative (X).



(X)

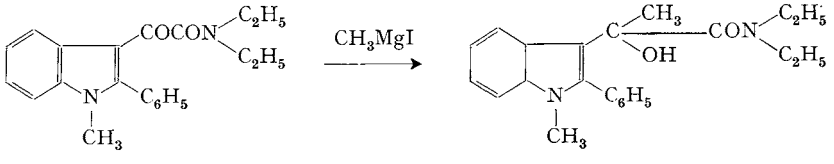
7.2 *Reaction of Ethyl Indole-3-glyoxylate With Methylmagnesium Iodide*

In connection with our studies of the reaction of indoleglyoxylates with Grignard reagents we found that the reaction of ethyl 3-indoleglyoxylate (XI) with four equivalents of methylmagnesium iodide gave rise, after two hours of refluxing, to a 57% yield of 1-(3-indolyl)-2-hydroxy-2-methyl-1-propanone (XII) [186]. Compound (XII) gave an oxime; it also showed the expected ultraviolet spectrum of the 3-acyl-N-unsubstituted indole system characterized by maxima at 243, 255·5 and 300 mμ and the appearance of a new maximum at 336 mμ in alkaline solution. The infrared spectrum showed a strong (cf. Footnote 1 in Reference [186]) band at 1607 cm^{-1} typical of the vinylogous amide system [184, 183].

When the solution of (XI) in tetrahydrofuran was refluxed for four hours with eight equivalents of methylmagnesium iodide a 53% yield of 2-(3-indolyl)-3-methyl-2,3-butanediol (XIII) was obtained.

Clearly, (XI) shows considerable specificity when condensed with methylmagnesium iodide. The carbethoxy group is more reactive, and therefore undergoes the reaction before the carbonyl function of the N-unsubstituted vinylogous amide system becomes involved.

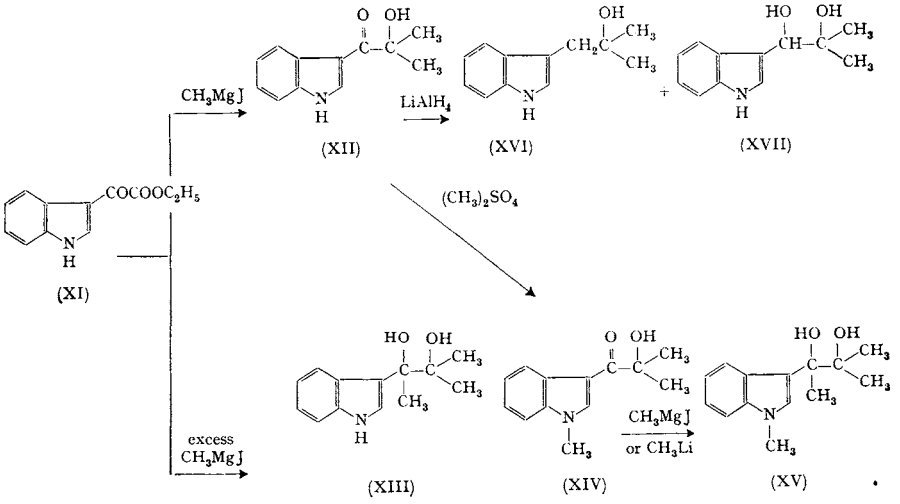
AMES *et al.* [4] reported that N,N,-dimethyl(or diethyl)-1-methyl-2-phenyl-(or *p*-chlorophenyl)-3-indolylglyoxylamides react with Grignard reagents to give hydroxyamides; e.g.,



This system illustrates how much the ketonic character of the first carbonyl group in the side chain varies as a function of substituents on nitrogen and C-2 of the indole nucleus. The methyl group on nitrogen prevents anion formation which otherwise would destroy some of the ketonic character. The phenyl group sterically inhibits conjugation of the carbonyl group with the indole nucleus, and thus forces the carbonyl group to behave like a normal ketone. As a result, the ketonic function reacts much faster than the amidic group, although tertiary amides can react readily with Grignard reagents [117].

Several simple transformations of the acyloin (XII) were carried out. Alkylation with dimethyl sulfate gave 1-[3-(1-methyl)indolyl]-2-hydroxy-2-methyl-1-propanone (XIV) which, in turn, afforded 2-[3-(1-methyl)indolyl]-3-methyl-1,4-butanediol (XV) on reaction with either methylmagnesium iodide or, preferably, with methyllithium.

Reduction of (XII) with lithium aluminium hydride afforded a mixture of the C—O cleavage product, 1-(3-indolyl)-2-methyl-2-propanol (XVI), and of the normal addition product, 1-(3-indolyl)-2-methyl-1,2-propanediol (XVII). Compound (XVI) proved identical with an authentic sample of the substance prepared by condensation of ethyl 3-indoleacetate and methylmagnesium iodide.



Reduction of (XII) with sodium borohydride gave a 59% yield of diol (XVII) and a small yield of a compound isomeric with (XVI). Possibly this compound ($C_{12}H_{15}NO$) is a rearrangement product, perhaps of the Tiffeneau type [192]. A reasonable structure for this product is represented by 3-indole-isopropylcarbinol. Attempts to prepare this substance by reduction of 3-indolylisopropylketone with lithium aluminum hydride or sodium borohydride were not successful. An excess of lithium aluminum hydride produced 3-iso-

butylindole, whereas a stoichiometric amount afforded some polymer and unchanged ketone.

7.3 *Reaction of Ethyl Indole-3-Glyoxylate With Phenylmagnesium Bromide*

When ethyl indole-3-glyoxylate (XVIII) was treated with four moles of phenylmagnesium bromide, hydroxydiphenylmethyl 3-indolyl ketone (XIX) was obtained in 63% yield [187]. The product was the acyloin (XIX) as shown by spectroscopic evidence, formation of an oxime, reaction with methyllithium to give (XXIII), and the reduction with methylmagnesium iodide to give (XXIV).

When eight moles of phenylmagnesium bromide were used, the yield of (XIX) did not change significantly. The reaction probably stops at the stage of the acyloin because of extensive enolization and steric hindrance.

Compound (XIX) was readily methylated with methyl iodide and sodium methoxide and afforded the N-alkylated material—hydroxydiphenylmethyl 1-methyl-3-indolyl ketone (XX).

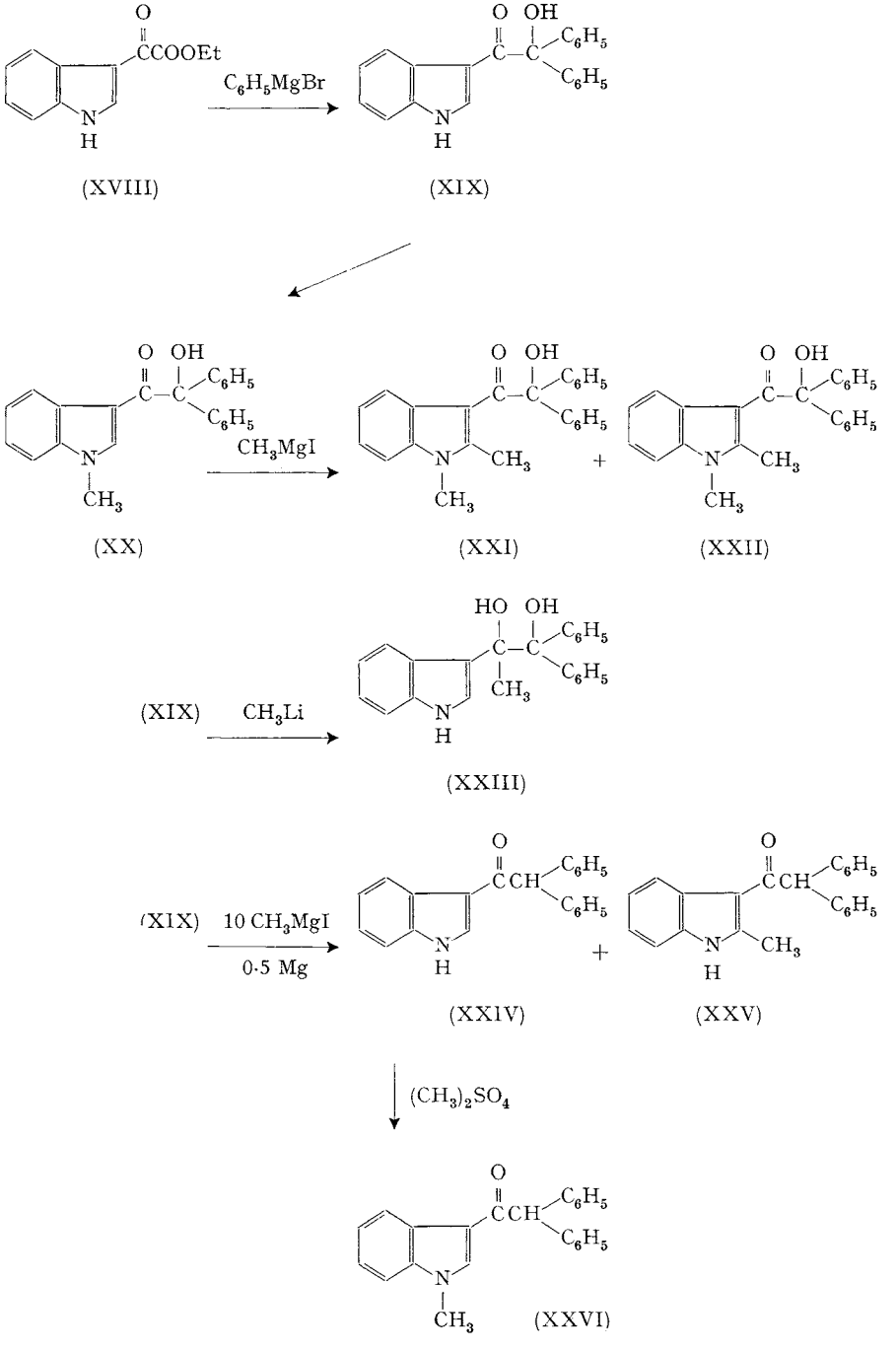
When (XX) was subjected to reaction with methylmagnesium iodide, two compounds were isolated for which structures (XXI) and (XXII) are proposed. Compound (XXI) gave an ultraviolet spectrum typical of an indoline (λ_{max} 250; 8625 and λ_{max} 300; 3050) and infrared indicated a saturated ketone function at 1713 cm^{-1}. This product (XXI) was formed by 1,4-addition of the Grignard reagent, a phenomenon which we have observed previously in the case of 1-methyl-3-benzoylindole [185]. The second compound (XXII) was very likely formed by dehydrogenation of (XXI) perhaps during chromatography, as we have previously demonstrated that this type of transformation occurs very readily in the case of 1-methyl-2-phenyl-3-benzoylindoline [185].

When acyloin (XIX) was treated with methyllithium, the 1,2-product, 2-(3-indolyl)-1,1-diphenyl-1,2-propanediol (XXIII), was obtained in 51% yield.

Reaction of acyloin (XIX) with methylmagnesium iodide was tried initially under the usual conditions, namely the reagent was prepared from 10 equivalents of methyl iodide and 10·5 equivalents of magnesium. Subsequently it was found [187] that the 0·5-equivalent excess of metallic magnesium was quite critical with regard to obtaining the unusual reduction phenomenon [cf. 116, 77] which led to benzhydryl 3-indolyl ketone (XXIV) in 63% yield. Compound (XXIV) was also prepared for comparison from indole, N,N-dimethyldiphenylacetamide, and phosphorus oxychloride and the two samples were identical.

A second product, obtained in 4% yield from the reaction of (XIX) with methylmagnesium iodide in the presence of excess magnesium, proved to be benzhydryl 2-methyl-3-indolyl ketone (XXV). The structure was unequivocally established by an independent synthesis from 2-methylindole, methylmagnesium iodide, and diphenylacetyl chloride.

Alkylation of (XXIV) with dimethyl sulfate afforded benzhydryl 1-methyl-3-indolyl ketone (XXVI) in 98% yield.

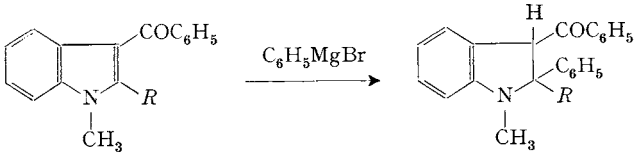


7.4 *Reaction of 3-Acylindoles With Grignard Reagents*

Condensation of 1-methyl-3-benzoylindole (XXVII) (C=O band at 1620 cm^{-1}) with phenylmagnesium bromide afforded 1-methyl-2-phenyl-3-benzoylindoline (XXIX) instead of the expected tertiary carbinol [185]. The structure of the indoline is supported by the characteristic ultraviolet spectrum (λ_{max} 248, plateau 288) and the shift of the C=O band to 1678 cm^{-1}. Dehydrogenation of (XXIX) with palladium gave 1-methyl-2-phenyl-3-benzoylindole, identical with an authentic sample prepared from 2-phenylindole by reaction with dimethylbenzamide and phosphorus oxychloride [cf. 9], followed by alkylation with dimethyl sulfate.

Similarly, 1,2-dimethyl-3-benzoylindole (XXVIII) gave 1,2-dimethyl-2-phenyl-3-benzoylindoline (XXX).

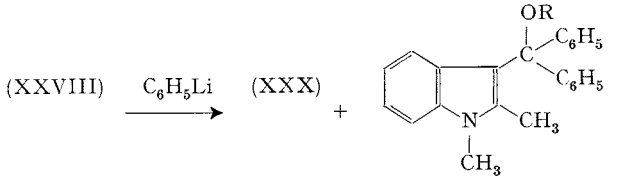
Molecular models of (XXVII) and (XXVIII) show considerable steric crowding of the carbonyl especially by the hydrogen atom at C-4. However, C-2 is relatively unhindered even when substituted by a methyl group. Thus, with phenylmagnesium bromide, 1,4-addition predominates.



(XXVII) $R = H$
(XXVIII) $R = CH_3$

(XXIX) $R = H$
(XXX) $R = CH_3$

Since phenyllithium is reported (cf. Reference [116], p. 223, and [218]) to give 1,2- in preference to 1,4-addition, the reaction of 1,2-dimethyl-3-benzoylindole (XXVIII) with this reagent was carried out, and afforded a mixture. The first product was identical with 1,2-dimethyl-2-phenyl-3-benzoylindoline (XXX). Structure (XXXI) is proposed for the second product on the basis of ultraviolet and infrared spectra and the presence of a methoxyl group. Methyl ether formation very likely occurred during chromatography since the acetone used contained 0·05% methanol.

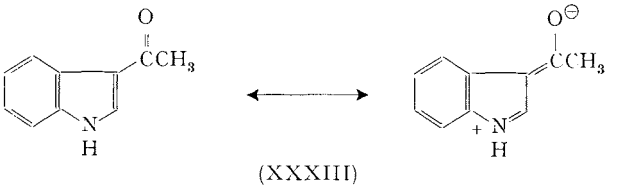


(XXXI) $R = OCH_3$
(XXXII) $R = H$

When this reaction was repeated using methanol-free acetone during chromatography and avoiding methanol during crystallization, the unstable 1,2-dimethyl-α,α-diphenylindole-3-methanol (XXXII) was obtained.

7.5 *3-Acylindole Mannich Bases*

The 3-acetylindole molecule (XXXIII) appeared to be a good candidate for the study of the Mannich reaction. The carbonyl function gives rise to the hybrid formulated as (XXXIII), in which ketonic and vinylogous amide structures contribute. The chemical and physical properties of this system correlate well with the properties expected from this formulation. Thus, 3-acetylindole forms a phenylhydrazone [150], a hydrazone [2], an oxime [154] and a thiosemicarbazone [193]. On the other hand, it undergoes hydrogenolysis with

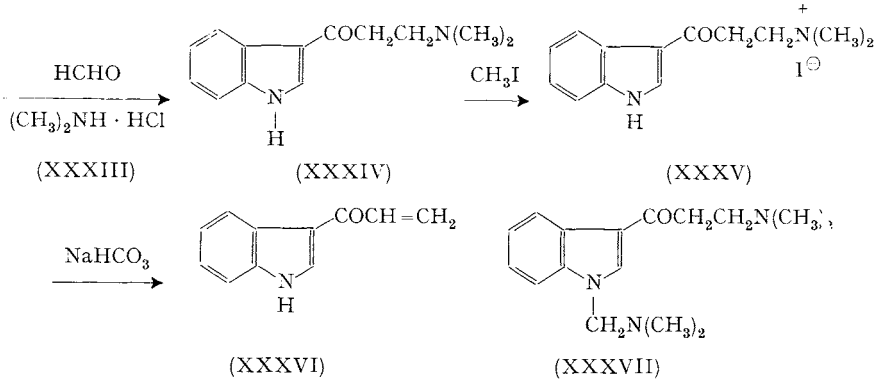


(XXXIII)

lithium aluminum hydride [124] and the ultraviolet spectrum in alkaline solution shows a new maximum at higher wave length (332 mμ) [184].

When compound (XXXIII) was subjected to reaction with dimethylamine hydrochloride and paraformaldehyde in ethanol, a 78% yield of 3-(β-dimethylaminopropionyl)indole (XXXIV) was obtained. The infrared spectrum showed NH and amide C=O absorption (1629 cm^{-1}); ultraviolet maxima were at 242, 257, and 299 mμ and a new maximum at 330·5 mμ was obtained on addition of alkali, which indicated an unsubstituted indolic nitrogen. The reaction was applied to various substituted 3-acylindoles and proved to be quite general [184].

When the Mannich base condensation with 3-acetylindole was repeated using a large excess of reagents, the corresponding bis-Mannich base (XXXVII) was obtained in good yield. Compound (XXXVII) contains an N-dimethylaminomethyl group which is not uncommon [177]. Unlike the case of simple methylenedialkylamines [130] this group in (XXXVII) is somewhat stabilized due to the nature of the indolic nitrogen.



(XXXIII) (XXXIV) (XXXV)

(XXXVI) (XXXVII)

The methiodide (XXXV) could be converted via a reverse Michael reaction to 3-indolylvinyl ketone (XXXVI), and the best yield was obtained employing

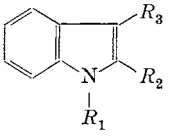
sodium bicarbonate under controlled conditions [184]. The infrared spectrum of the vinyl ketone showed NH, amide C=O and strong C=C absorption. The ultraviolet spectrum indicated additional conjugation (λ_{max} 258, 269·5, 274·5, 324 mμ) [cf. 24] as compared to 3-propionylindole. The chemical properties of (XXXVI) agree with the proposed structure. Thus, on addition of dimethylamine the Mannich base (XXXIV) was isolated, and on reduction with lithium aluminum hydride a mixture resulted from which 3-propionyl-indole was isolated in small yield [cf. 28, 69].

7.6 *Anticonvulsant Activity*

Structures and anti-electroshock activities (relative to phenobarbital) of various 3-acylindoles are listed in Table 14. These compounds were tested by KEASLING [113] by determining the current intensity (milliamperes) necessary to induce maximal tonic extensor seizures following the administration of the compound. Groups of 15 Carworth Farms male mice (or Sprague Dawley rats) were treated with the compound intraperitoneally and 30 minutes later the current strength necessary to induce tonic extensor seizures in 50% of the mice (rats) was determined by the up–down procedure described by KIMBALL *et al.* [118]. In each experiment, phenobarbital at 10 and 20 mg/kg I.P. (mice) or 9 and 18 mg/kg I.P. (rats) and vehicle-treated controls were tested simultaneously. The activity is listed as 0 if the threshold for treated mice (rats) was not significantly elevated over untreated controls. Compounds significantly elevating thresholds are reported relative to the phenobarbital-treated animals in the same experiment.

Table 14

Structures and Anti-Electroshock Activities (Relative to Phenobarbital) of Various 3-Acylindoles



No.	R_1	R_2	R_3	Activity [113][4]		References to source or method of synthesis
				Mice[1]	Rats[2]	
1	H	H	$\overset{O}{\overset{\|\|}{C}}H$	0	–	[5]
2	H	H	$\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[5]
3	CH_3	H	$\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[184]

Table 14 (Continued)

No.	R_1	R_2	R_3	Activity [113][4]		References to source or method of synthesis
				Mice[1]	Rats[2]	
4	H	CH_3	$\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[5]
5	CH_3	CH_3	$\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[181]
6	$\overset{O}{\overset{\|\|}{C}}CH_3$	H	$\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[162]
7	H	H	$CH_2CH(CH_3)_2$	<10	–	[186]
8	H	H	$CH_2\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[27]
9	H	H	$CH_2\overset{OH}{\overset{\|}{C}}(CH_3)_2$	0	0	[186]
10	H	H	$\overset{O}{\overset{\|\|}{C}}CH_2CH_3$	>10	<9	[184]
11	CH_3	H	$\overset{O}{\overset{\|\|}{C}}CH_2CH_3$	>10	0	[184]
12	H	H	$\overset{O}{\overset{\|\|}{C}}CH=CH_2$	0	–	[184]
13	CH_3	H	$\overset{O}{\overset{\|\|}{C}}CH(CH_3)_2$	>20	=9	[181]
14	CH_2CH_3	H	$\overset{O}{\overset{\|\|}{C}}CH(CH_3)_2$	<10	–	[181]
15	H	H	$\overset{O}{\overset{\|\|}{C}}CH(CH_3)_2$	=10	<9	[186]
16	H	CH_3	$\overset{O}{\overset{\|\|}{C}}C(CH_3)_3$	0	0	[8]
17	H	H	$\overset{O}{\overset{\|\|}{C}}C(CH_3)_3$	<10	0	[7]
18	H	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}-(CH_3)_2$	<10[3]	<9	[186]
19	CH_3	H	$\overset{OH}{\overset{\|}{C}}H-\overset{OH}{\overset{\|}{C}}(CH_3)_2$	<10	–	[186]
20	CH_2CH_3	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_3)_2$	<10	<9	[208]
21	H	H	$\overset{OH}{\overset{\|}{C}}H-\overset{OH}{\overset{\|}{C}}(CH_3)_2$	>10	0	[185]

Table 14 (Continued)

No.	R_1	R_2	R_3	Activity [113][4]		References to source of method of synthesis
				Mice[1]	Rats[2]	
22	H	H	$\overset{NOH}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_3)_2$	0	<9	[186]
23	CH_3	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_3)_2$	>10[3]	<9	[186]
24	CH_2CH_3	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_2CH_3)_2$	<10	=9	[208]
25	CH_3	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_2CH_3)_2$	>10	<9	[208]
26	H	H	$\overset{O}{\overset{\|\|}{C}}-\overset{OH}{\overset{\|}{C}}(CH_2CH_3)_2$	<10[3]	–	[208]
27	H	H	$\overset{O}{\overset{\|\|}{C}}CH_2CH_2CH_3$	<10	–	[181]
28	H	H	$CH_2\overset{O}{\overset{\|\|}{C}}CH_2CH_3$	<10	–	[216]
29	H	CH_3	$\overset{O}{\overset{\|\|}{C}}CH_2CH(CH_3)_2$	<10	–	[8]
30	H	CH_3	$\overset{O}{\overset{\|\|}{C}}-\overset{CH_3}{\overset{\|}{C}}HCH_2CH_3$	<10	–	[8]
31	H	H	$CH_2CH_2\overset{O}{\overset{\|\|}{C}}CH_3$	<10	–	[182]
32	H	H	$\overset{O}{\overset{\|\|}{C}}C_6H_5$	0	–	[185]
33	CH_3	H	$\overset{O}{\overset{\|\|}{C}}C_6H_5$	0	–	[185]
34	H	CH_3	$\overset{O}{\overset{\|\|}{C}}C_6H_5$	0	–	[185]
35	CH_3	CH_3	$\overset{O}{\overset{\|\|}{C}}C_6H_5$	<10	–	[185]
36	H	H	$\overset{O}{\overset{\|\|}{C}}CH(C_6H_5)_2$	0	–	[187]
37	CH_3	H	$\overset{O}{\overset{\|\|}{C}}CH(C_6H_5)_2$	<10	–	[187]

Table 14 (Continued)

No.	R_1	R_2	R_3	Activity [113][4]		References to source or method of synthesis
				Mice[1]	Rats[2]	
38	CH_3	C_6H_5	$\overset{O}{\overset{\|}{C}}C_6H_5$	0	–	[187]
39	H	H	$\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{\|}{C}}(C_6H_5)_2$	<10	–	[187]
40	CH_3	H	$\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{\|}{C}}(C_6H_5)_2$	0	–	[187]

[1]) 100 mg/kg intraperitoneally 30 minutes before electroshock.

[2]) 25 mg/kg intraperitoneally 30 minutes before electroshock.

[3]) In separate tests in mice at 30, 60, and 90 minutes after administration it was found that 30 minutes was peak effect time.

[4]) – = not tested; 0 = tested but not different from control; <9 etc. significant threshold increase but less than phenobarbital at the indicated dose; =10 not significantly different from phenobarbital at the indicated dose; >10 more active than phenobarbital at the stated dose.

[5]) Available from Aldrich Chemical Company, Milwaukee, Wisconsin.

7.7 *Structure vs. Anticonvulsant Activity Relationship*

Effect of Substitution on the Indole Nitrogen Examination of Table 14 shows that methylation of the indole nitrogen decreased activity in two cases (compare 21 and 19; 39 and 40), had no effect in four cases (4 and 5; 2 and 3; 10 and 11; 32 and 33) and increased activity in five cases (36 and 37; 34 and 35; 15 and 13; 18 and 23; 26 and 25). Replacement of methyl by ethyl decreased activity in all three cases (13 and 14; 23 and 20; 25 and 24). Replacement of hydrogen by acetyl was without effect (6 and 2).

Effect of Substitution on the 2-Position of the Indole Ring Methylation of the 2-position decreased activity in one case (17 and 16); was without effect in three cases (2 and 4; 32 and 34; 3 and 5) and increased activity in one case (33 and 35). Replacement of methyl by phenyl decreased activity (35 and 38).

Effect of Substitution on the 3-Position of the Indole Ring Although in the 4 carbon straight alkyl chain compounds the location of the carbonyl in relation to the indole ring did not seem to influence activity (compare 27, 28, 31) in the 3 carbon chain α-carbonyl was superior (10 and 8). The α-carbonyl was also superior in branched compounds (compare 15, 9, 7, and 18, 22). Three

carbons appeared the optimum in the straight α-carbonyl sidechain (compare 1, 2, 10, 27). However, if the chain was branched an additional carbon increased activity (10, 15), but two additional carbons decreased activity (15, 17). Hydroxyl on the β-carbon (of a 4 carbon branched side chain) increased activity in mice only if the α carbonyl was reduced to hydroxyl (21, 18, 15). However, in rats, the second hydroxyl reduced activity (15, 21, 18, and 13, 23). Increasing the substituents on the β-carbon to ethyl (18, 26), or phenyl (15, 36 or 18, 39) decreased activity when the indole nitrogen was unsubstituted. With methyl on the indole nitrogen β-dimethyl and β-diethyl compounds were equivalent (23, 25), while β-diphenyl was much less active than the corresponding β-dimethyl (37, 13 or 23, 40).

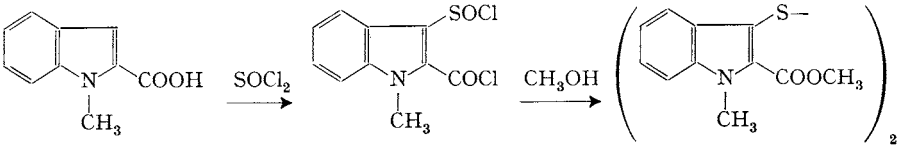
The optimum structure tested was 3-isobutyryl-1-methylindole (compound No. 13). This compound was 0·36 as active as phenobarbital in rats and 0·28 as active in mice.

8. Indole Derivatives Containing Sulfur

8.1 *Reaction of Indole Derivatives With Thionyl and Sulfuryl Chlorides*

1-Methylindole-2-carbonyl chloride has been prepared in the literature from the corresponding acid (I) with phosphorous pentachloride in ether [110]. During an attempted preparation of this acid chloride from (I) and thionyl chloride we have made the observation that, under certain conditions (namely first heating with thionyl chloride and then in benzene), a sulfur containing compound was produced for which structure (II) is proposed [181]. This type of structure is similar to that preferred for the product obtained from the reaction of anhydrous chlorine and *o*-thiolbenzoic acid [49].

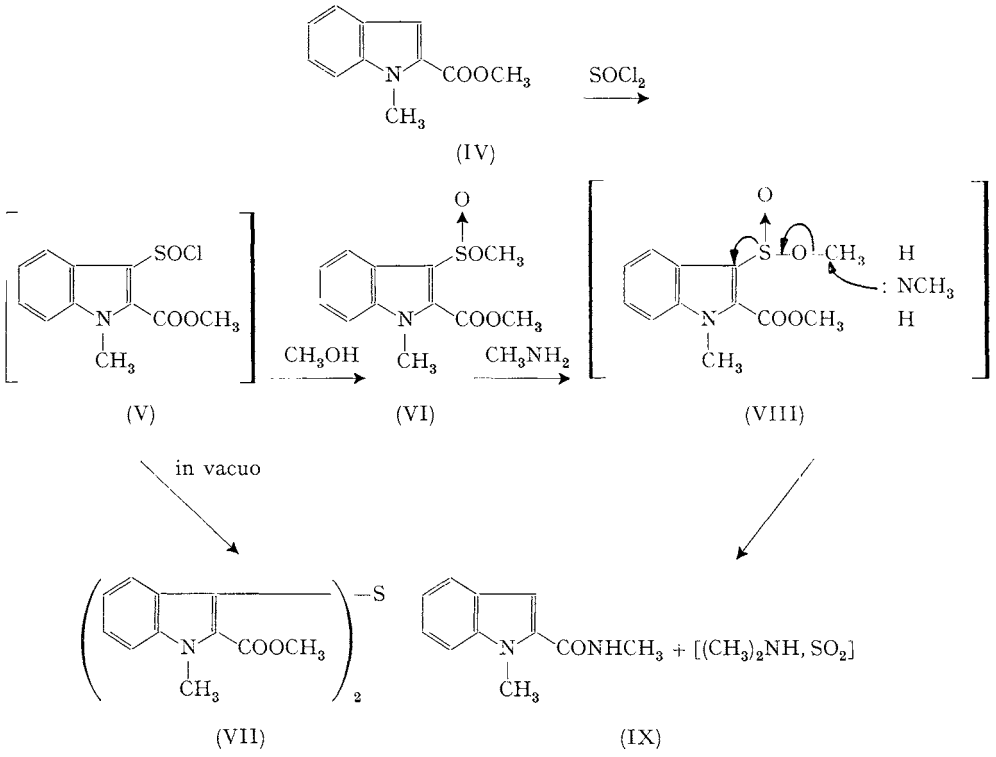
Treatment of (II) with methanol brought about a disproportionation and led to disulfide (III) which was identical with an authentic sample.



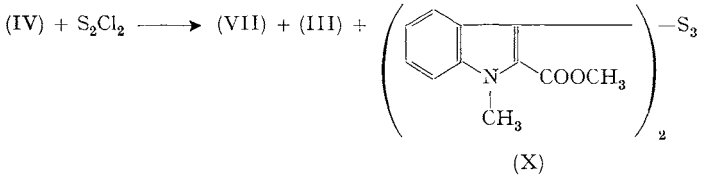
(I) (II) (III)

Extension of the thionyl chloride reaction to methyl 1-methylindole-2-carboxylate (IV) gave the sulfinyl chloride (V) in excellent yield. Compound (V), unlike (II), on treatment with methanol afforded the dimethyl ester (VI). On

the other hand, (V) underwent disproportionation in vacuo to give monosulfide (VII) which was identical with an authentic sample. The authentic monosulfide



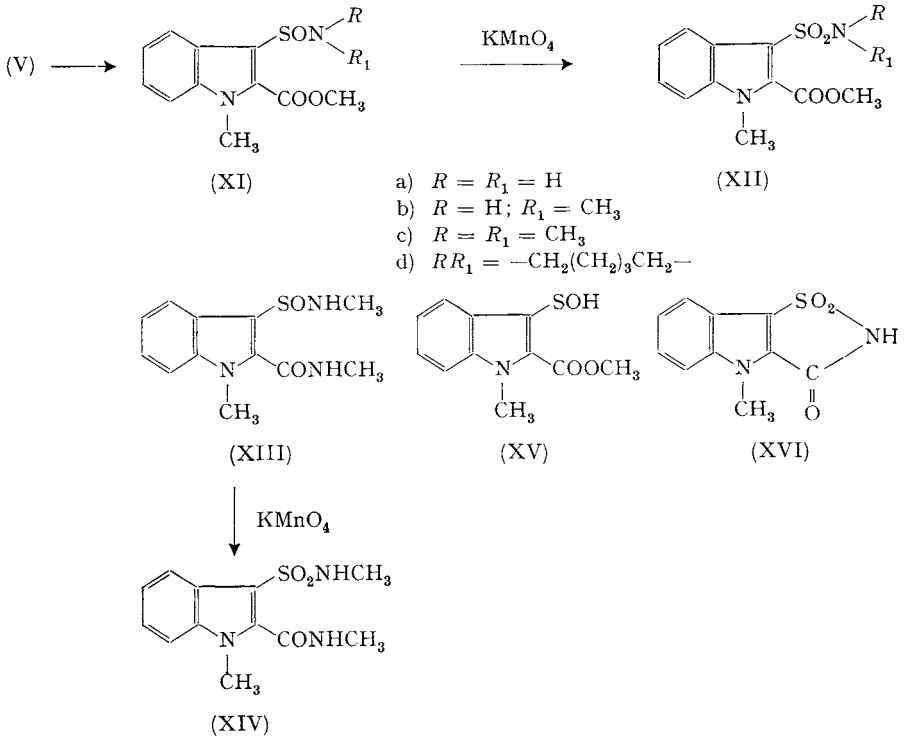
(VII) and disulfide (III) along with trisulfide (X) were obtained from reaction of (IV) with sulfur monochloride [cf. 206, 121].



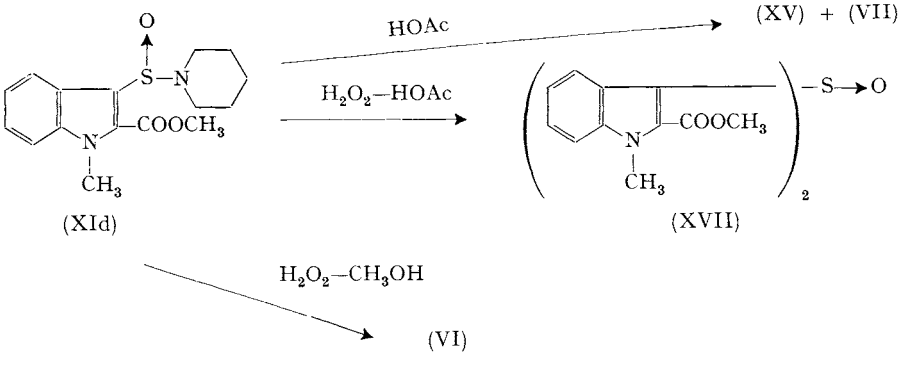
No reaction occurred between dimethyl ester (VI) and methanolic ammonia or dimethylamine. On the other hand, methylamine, under the same conditions, produced N,1-dimethylindole-2-carboxamide (IX), probably via the process indicated in (VIII).

Reaction of sulfinyl chloride (V) under anhydrous conditions with ammonia, methylamine, dimethylamine and piperidine afforded sulfinamides (XIa), (XIb), (XIc), and (XId), respectively. In the case of methylamine some conversion to the bis-methylamide (XIII) also occurred. Reaction of (V) with aqueous dimethylamine afforded 1-methyl-2-carbomethoxyindole-3-sulfenic

acid (XV) along with sulfinamide (XIc). Sulfenic acid (XV) was also isolated from an attempted condensation of (V) with acetamide in pyridine.



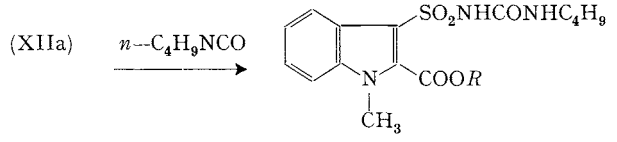
Several additional reactions were carried out with sulfinamide (XId). In acetic acid solution (XId) underwent disproportionation to give sulfenic acid (XV) and monosulfide (VII). Conversion of (XId) to sulfoxide (XVII) occurred with hydrogen peroxide in acetic acid, and with hydrogen peroxide in methanol (XId) afforded diester (VI).



Oxidation of sulfinamides (XIa), (XIb), (XIc), (XId), and (XIII) with potassium permanganate in aqueous acetone afforded sulfonamides (XIIa), (XIIb), (XIIc), (XIId), and (XIV), respectively.

In the case of sulfinamide (XIa), imide (XVI) was also isolated from the oxidation reaction by acidification of the alkaline filtrate.

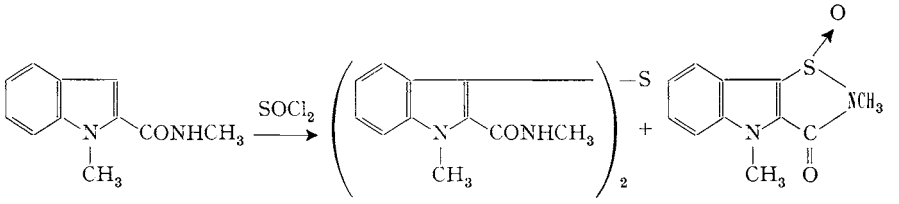
Sulfonamide (XIIa) reacted with butyl isocyanate to give urea derivative (XVIIIa), which was hydrolyzed with aqueous base to the corresponding acid (XVIIIb).



a) $R = CH_3$ b) $R = H$

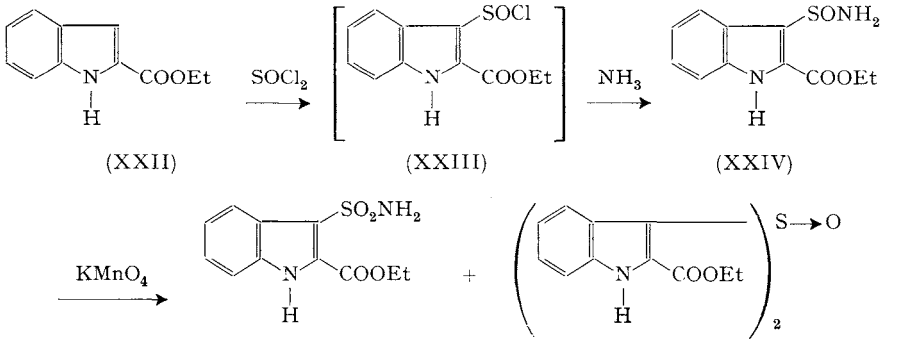
(XVIII)

Extension of the thionyl chloride reaction to N,1-dimethylindole-2-carboxamide (XIX) led to sulfide (XX) and imide-sulfoxide (XXI). Thionyl chloride



(XIX) (XX) (XXI)

also reacted with ethyl indole-2-carboxylate (XXII) and afforded the corresponding sulfinyl chloride (XXIII) which was converted to sulfinamide (XXIV) in 87% overall yield. Oxidation of (XXIV) with permanganate led to sulfonamide (XXV), accompanied by a small quantity of sulfoxide (XXVI).



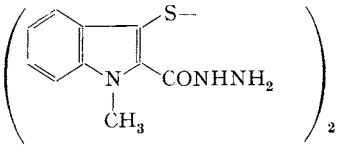
(XXII) (XXIII) (XXIV)

(XXV) (XXVI)

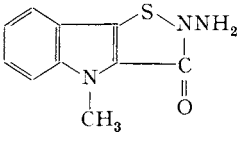
It is interesting to note that recently KUNORI [120] isolated only disproportionation products and not (XXIII) from the reaction of (XXII) with thionyl chloride. This was undoubtedly due to the more drastic nature of the conditions which this author used for his reaction. Our work in this area [181]

was complete prior to the appearance of KUNORI's paper in Chemical Abstracts [120].

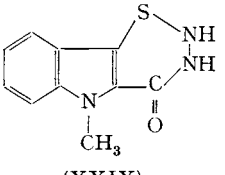
Sulfinyl chloride (V) was very smoothly converted with hydrazine in the cold to disulfide (III) in 70% yield. On refluxing with hydrazine hydrate (III) was transformed to a new compound for which structure (XXVII) is postulated. Compound (XXVII) formed a bis-benzylidene derivative, a tetra-acetyl



(XXVII)

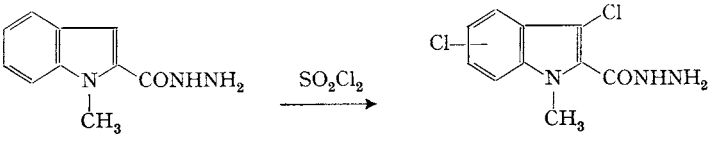


(XXVIII)

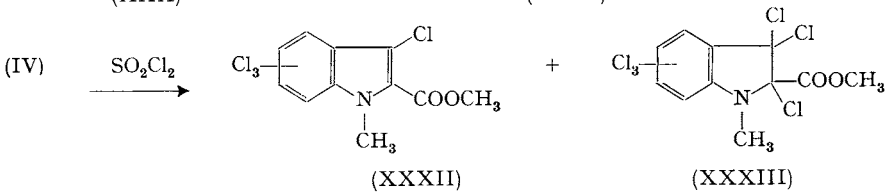


(XXIX)

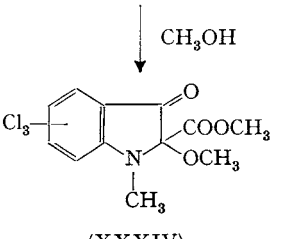
derivative and a bis-isopropylidene derivative. The nuclear magnetic resonance spectrum of the tetra-acetyl compound was run with a Varian HR 60 spectrometer and deuterated dimethyl sulfoxide as solvent, and was interpreted by G. SLOMP and F. A. MACKELLAR of the Upjohn Company. It showed $COCH_3$ hydrogens at 127 cps downfield from internal tetramethylsilane (area 6), NCH_3 at 230 cps (area 3), aromatic hydrogens at 415 to 462 cps (area 4), and NH at 645 (area 0·9). The presence of hydrogen typical of the NH grouping provides strong support for structure (XXVII) in preference to tricyclic structures (XXVIII) and (XXIX), assuming that no skeletal change occurred during the mild acetylation reaction.



(XXX) (XXXI)



(XXXII) (XXXIII)



(XXXIV)

Two reactions were carried out with sulfuryl chloride. Treatment of 1-methylindole-2-carboxylic acid hydrazide (XXX) with sulfuryl chloride af-

Table 15

Antifungal Results Obtained by the Agar Plate Dilution Method[1,2])

	Trichophyton rubrum	*Histoplasma capsulatum*	*Sporotrichum Schenckii*	*Balstomyces dermatitidis*	*Nocardia asteroides*	*Hormodendrum campactum*	*Phialophora verrucosa*	*Trichophyton interdigitale*	*Microsporum canis*
XIa	100	100	100						
XIc	10 *P*	100	100	10 *P*		100 *P*			
XId	100 *P*								
XIId	10 *P*								
XVIIIb	100								
XXVII	10 *P*			100	100				
Bis-isopropylidene derivative of XXVII	100			100	100	100 *P*	100 *P*	100	100
XXX	100			100					

[1]) A. DIETZ, The Upjohn Company, unpublished results.
[2]) Numbers indicate mcg/ml required to inhibit the test organism; *P* = partial inhibition.

forded dichloro derivative (XXXI). Reaction of (IV) with sulfuryl chloride led to a mixture of tetrachloro compound (XXXII) and hexachloro compound (XXXIII). On refluxing with methanol (XXXIII) afforded trichloro derivative (XXXIV). The structures of the last three compounds are postulated on the basis of analytical data, ultraviolet and infrared spectra.

8.2 *Antifungal Activity*

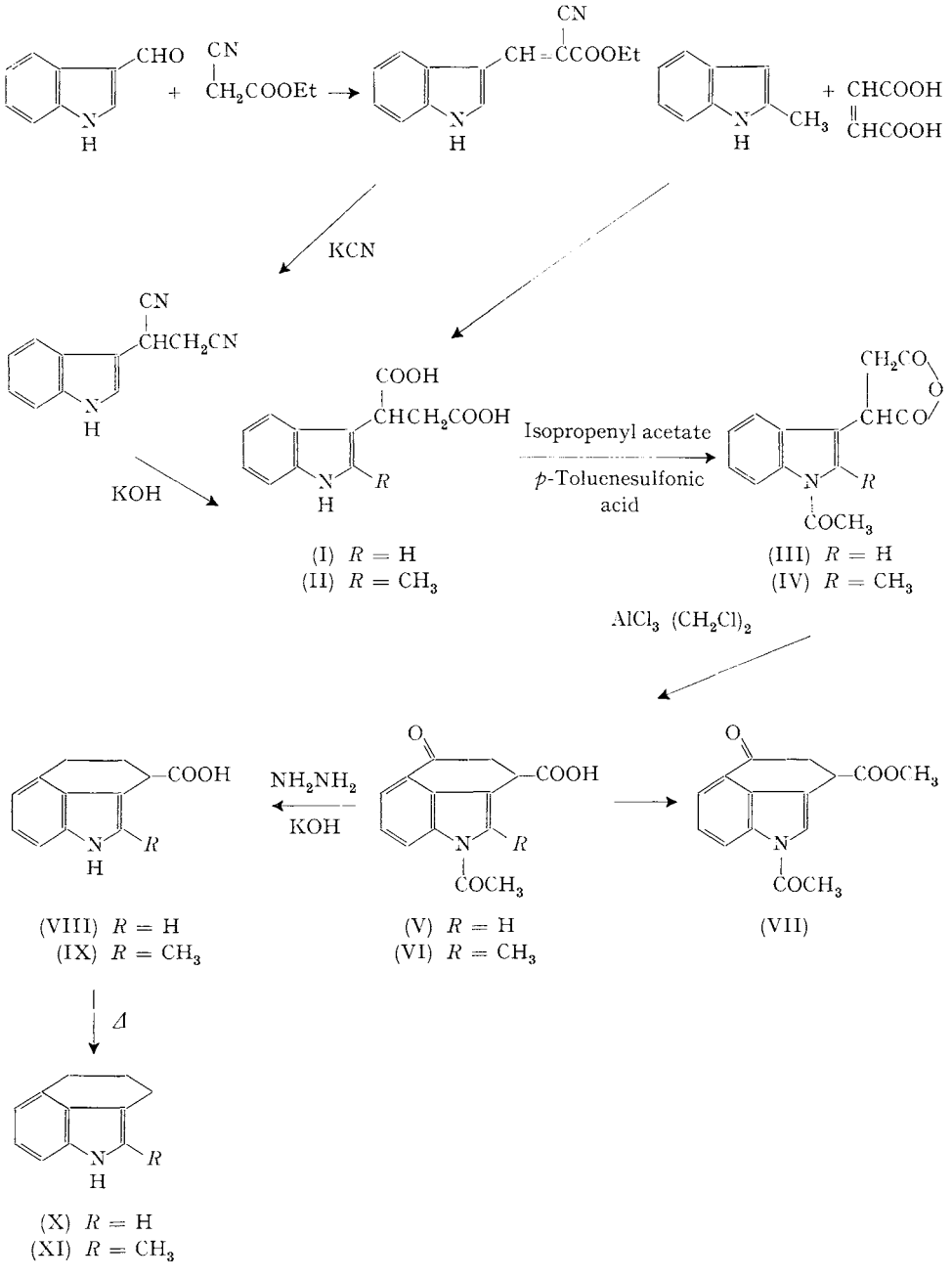
Some of the compounds described in the previous section were tested for antifungal activity by the agar plate dilution method [47] and the results are shown in Table 15. All the compounds shown in this Table were effective against *Trichophyton rubrum*, and sulfinamide (XIc), sulfonamide (XIId), and disulfide-dihydrazide (XXVII) were the most outstanding in this respect. Sulfinamide (XIc) also displayed the best activity against *Blastomyces dermatitidis*.

9. Derivatives of 1,3,4,5-Tetrahydrobenz[cd]indole

Interest in the tetracyclic ergoline system has been stimulated over the years by the potent physiological activity of compounds in this series. For recent reviews on this subject see References [50, 200, 57, and 21]. Subsequent papers include References [202, 141, and 92]. In this section we describe a method for the synthesis of 2-unsubstituted and 2-methyl substituted tricyclic compounds in the 1,3,4,5-tetrahydrobenz[cd]indole series [181] which is relatively simple, and which made possible the introduction of a carboxylic acid function in the hitherto inaccessible 3-position.

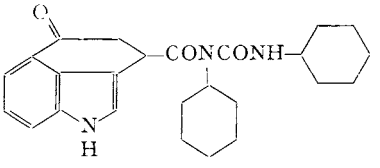
The synthesis of 1-acetyl-1,3,4,5-tetrahydro-5-oxobenz[cd]indole-3-carboxylic acid (V) was accomplished starting from indole-3-carboxaldehyde. Condensation of indole-3-carboxaldehyde with ethyl cyanoacetate, followed by reaction with potassium cyanide, and then hydrolysis with potassium hydroxide led to 3-indolesuccinic acid (I) as described previously [151]. Reaction of (I) with isopropenyl acetate and *p*-toluenesulfonic acid brought about concomitant acetylation and anhydride formation, and led to 1-acetyl-3-indolesuccinic anhydride (III). Compound (III) underwent a facile cyclization in 1,2-dichloroethane with aluminum chloride to give the tricyclic N-acetyl keto-acid (V).

The ring structure of this cyclization product was proved by deacetylation and reduction of (V) with hydrazine [108] under mild conditions, followed by thermal decarboxylation of the resulting acid (VIII) to 1,3,4,5-tetrahydrobenz[cd]indole (X) [195, 17, 196]. This compound (X) was identical with an authentic sample kindly sent to us by F. C. UHLE, of Harvard University.



Acid (V) was best converted to the corresponding methyl ester (VII) by treatment with oxalyl chloride followed by methanol. An attempted esterification with methanol in the presence of N,N′-dicyclohexylcarbodi-imide led to addition product (XII).

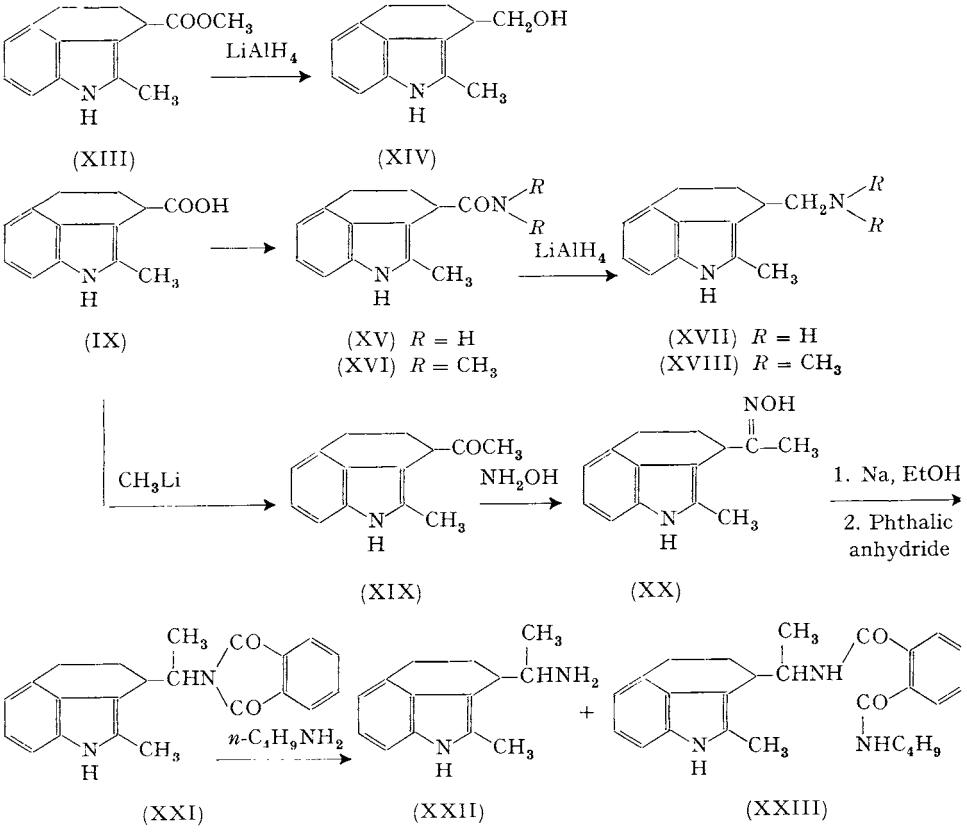
The same type of adduct, namely phthaloyl-L-threonyl-N,N'-dicyclohexylurea, was isolated in addition to the desired peptide derivative from the reaction of phthaloyl-L-threonine with amino acid esters and N,N'-dicyclohexylcarbodi-



(XII)

imide in dioxane or tetrahydrofuran [166]. The ultraviolet spectrum of (XII) was similar to that of 1,3,4,5-tetrahydro-5-oxobenz[cd]indole [91].

In the 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole series the required starting material, 2-methyl-3-indolesuccinic acid (II), was prepared by condensation of 2-methylindole with maleic acid. Compound (II) was previously prepared by hydrolysis of the adduct obtained from 2-methylindole and maleic anhydride [46] (cf. also Reference [144]). The last two steps were analogous to those described above and led via anhydride (IV) to 1-acetyl-2-methyl-1,3,4,5-tetrahydro-5-oxobenz[cd]indole-3-carboxylic acid (VI). The assignment of



(XIII) (XIV)

(IX) (XV) R = H; (XVI) R = CH_3 (XVII) R = H; (XVIII) R = CH_3

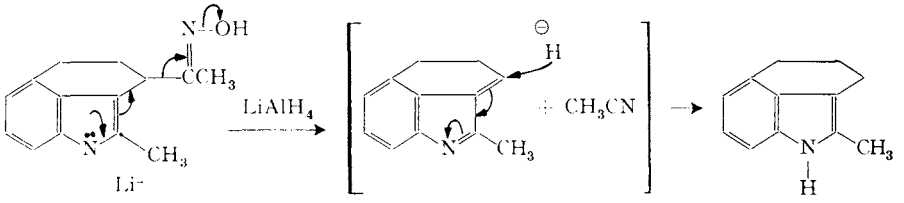
(XIX) (XX)

(XXI) (XXII) (XXIII)

structure to this compound is supported by the ultraviolet and infrared spectra. Additional evidence was provided by isolation of 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole (XI) from the decarboxylation of acid (IX), which in turn was obtained from (VI) by treatment with hydrazine. The ultraviolet and infrared spectra of (XI) were similar to those of the known compound (X).

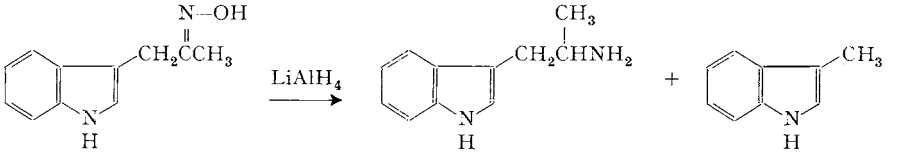
Several transformations of acid (IX) were carried out. Lithium aluminum hydride ($LiAlH_4$) reduction of methyl ester (XIII), prepared by the oxalyl chloride procedure, led to carbinol (XIV). Compound (IX) was also converted via its acid chloride to amide (XV) and dimethylamide (XVI) which were in turn reduced with $LiAlH_4$ to amines (XVII) and (XVIII), respectively.

Reaction of acid (IX) with methyl lithium led to methyl ketone (XIX), which was converted to oxime (XX). Reduction of (XX) with $LiAlH_4$ afforded a basic product, which appeared to be the hydroxylamine derived from (XX), and a neutral compound (XI) which was identical with the decarboxylation product of acid (IX). The formation of (XI) from (XX) can be rationalized in terms of a second-order Beckmann rearrangement [103, 68], and likely proceeds via the indolenine (XXIV). The driving force for this reaction probably derives from negative charge on the indolic nitrogen in salt (XXa).



(XXa) (XXIV) (XI)

This type of cleavage followed by reduction was also demonstrated to occur with the model oxime (XXV), which on treatment with $LiAlH_4$ afforded a small yield of skatole (XXVII) along with the product of simple reduction, α-methyltryptamine (XXVI).

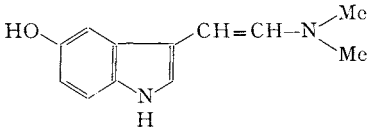


(XXV) (XXVI) (XXVII)

The above fragmentation was circumvented by reduction of oxime (XX) with sodium and ethanol to give a mixture of two diastereoisomeric amines, which were separated by chromatography of their phthalimido derivatives (XXI). Treatment of the two phthalimido compounds (XXI) with butyl amine afforded the corresponding amines (XXII). The product of partial aminolysis (XXIII) was also isolated from the reaction of one of the phthalimido derivatives, and it was readily converted to the corresponding amine.

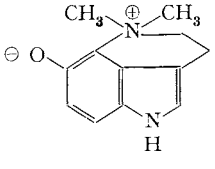
10. Synthesis of the Ring System of Dehydrobufotenine

Dehydrobufotenine was isolated from the parotid glands of the South American toad *(Bufo marinus)*. The original assignment of structure (I) [207] to this compound has been in doubt since the close similarity of its ultraviolet spectrum to that of serotonin was observed [209; cf. also 41]. The recent revi-

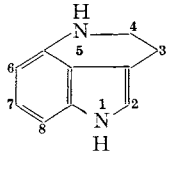


(I)

sion of the dehydrobufotenine structure to (II), based on nuclear magnetic resonance studies [132, 158], stimulated HESTER [101] to prepare the 1,3,4,5-tetrahydropyrrolo-[4,3,2-de]-quinoline ring system (III) for biological evaluation.



(II)



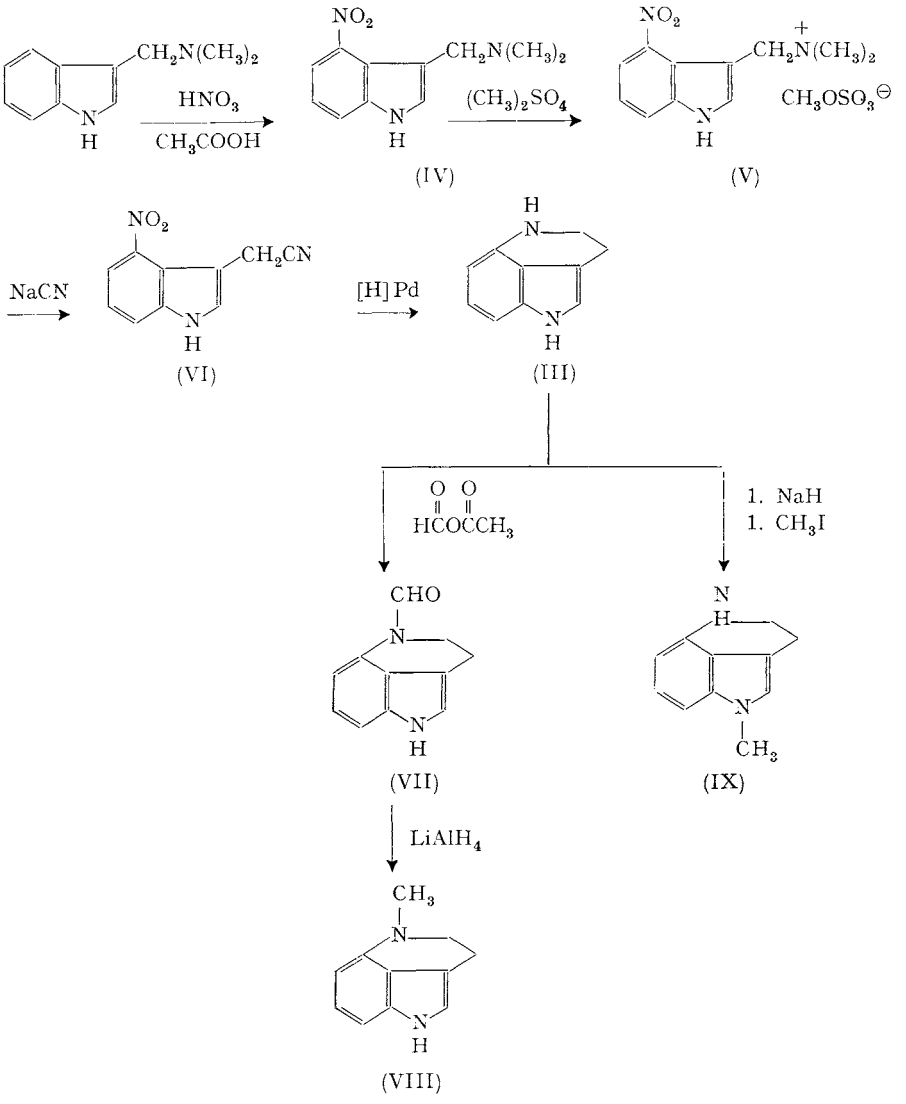
(III)

The starting material for this synthesis, 4-nitrogramine (IV), was obtained by direct nitration of gramine [19]. It was converted to the methosulfate (V) and subsequently treated with sodium cyanide. The resulting 4-nitroindol-3-yl-acetonitrile (VI) was subjected to catalytic hydrogenation, and afforded the desired 1,3,4,5-tetrahydropyrrolo-[4,3,2-de]-quinoline (III). This type of cyclization has been observed previously [201, 153, 170].

The N-formyl derivative (VII) was obtained on treatment of (III) with formic acetic anhydride [164]. Reduction of (VII) with lithium aluminum hydride gave rise to the N-methyl derivative (VIII). Methylation of the indole nitrogen in (III) to compound (IX) was accomplished by treatment of the sodium salt of (III) with methyl iodide.

The nuclear magnetic resonance spectrum of (III) showed two well defined triplets centered at 177 cps and 203·5 cps (J = 5·5 cps) downfield from tetramethylsilane, which have been assigned to the methylene protons on C-3 and C-4, respectively [132, 158]. A sharp singlet at 231 cps was assigned to the proton at N-5. When this nitrogen was methylated the 231 cps peak was replaced by a strong singlet at 175 cps, which was assigned to N-methyl protons of compound (VIII). Structure (III) was also supported by the ultraviolet spectrum which was similar to that reported for 4-amino-2,3-dimethylindole [165].

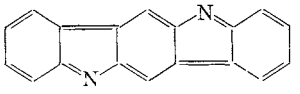
In preliminary pharmacological evaluation (III), (VIII), and (IX), like dehydrobufotenine, showed none of the pronounced central nervous system effects characteristic of bufotenine.



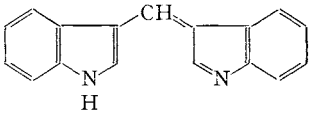
11. Urorosein and Indolo[3,2-b]carbazoles

Early literature on the nature of the urine pigment urorosein was summarized by FEARON and BOGGUST [61]. These authors prepared urorosein sulfate by heating indole-3-carboxaldehyde with sulfuric acid and proposed struc-

ture (I) for the free base. On the other hand, HARLEY-MASON and BU'LOCK [98] presented evidence which favored structure (II) for urorosein (cf. also Reference [167]). More recently VON DOBENECK *et al.* [48] disagreed with the formulation of urorosein as (II).

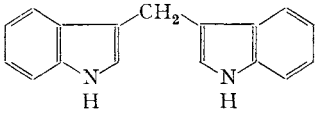


(I)



(II)

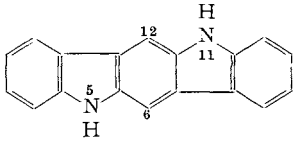
We had occasion to subject urorosein sulfate, prepared according to FEARON and BOGGUST [61], to lithium aluminum hydride reduction in tetrahydrofuran and isolated 3,3'-methylene bisindole (III) in good yield [181]. Compound (III)



(III)

was identical with an authentic sample prepared according to LEETE and MARION [124] from indole, paraformaldehyde and zinc chloride. This result provides support for the formulation [98] of urorosein sulfate as a salt of structure (II).

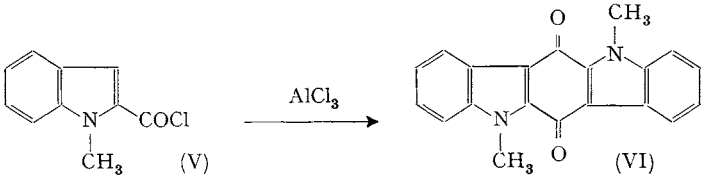
The experimental observation of GROTTA *et al.* [93], who obtained 60 mg of 5,11-dihydroindolo[3,2-b]carbazole (IV) by tin-hydrochloric acid reduction of 1 g of urorosein sulfate, can perhaps be interpreted as resulting from an impurity present in the starting material.



(IV)

Compound (IV) is a derivative of indolo[3,2-b]carbazole (I). Efforts in the indolocarbazole area have already been summarized [93, 29]. Compound (IV) was recently prepared [93] by cyclodehydrogenation of N,N'-diphenyl-*p*-phenylenediamine. NOLAND *et al.* [148, 149] suggested that the condensation products resulting from the reaction of 1-methylindole with methyl isobutylketone, and that of indole with acetophenone may be derivatives of 5,6,11,12-tetrahydroindolo[3,2-b]carbazole.

We found that a derivative of this difficultly accessible ring system resulted readily when a solution of 1-methylindole-2-carbonyl chloride (V) [110] in 1,2-dichloroethane was treated with aluminum chloride. This reaction led to 5,11-dimethylindolo[3,2-b]carbazole-6,12(5H,11H)-dione (VI) in 41% yield [181].



This condensation may be compared with the reaction of benzoyl chloride with aluminum chloride, which afforded a low yield of anthraquinone [37].

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