Synthesis and Preliminary Screening of *N*-Ethyltryptamine Derivatives Related to Reserpine and Lysergic Acid

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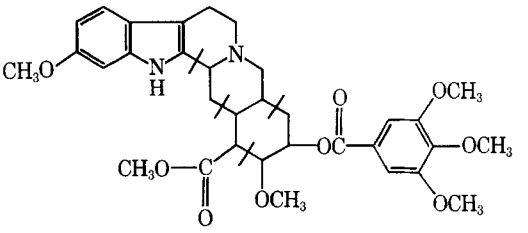
Abstract □ Fourteen derivatives of *N*-ethyltryptamine, structurally related to reserpine and lysergic acid, were synthesized. These compounds plus two intermediates were screened for gross pharmacologic activity in unanesthetized rats. Reserpinelike activity was absent, while LSD-like activity was found in those compounds most closely related to lysergic acid.

Keyphrases □ *N*-Ethyltryptamine derivatives—synthesized, screened for reserpinelike, LSD-like activity □ LSD-like activity—*N*-ethyltryptamine derivatives synthesized, screened □ Reserpinelike activity—*N*-ethyltryptamine derivatives synthesized, screened

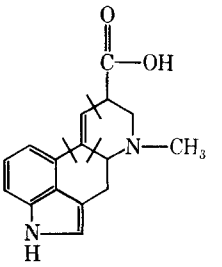
For many years, medicinal chemists have been attempting to determine the active moieties of complex medicinal agents. The first and most important reason for such determinations is to develop newer and more potent drugs with a lower incidence of side effects. The second is to reveal information concerning the mechanism of action of these drugs and possibly their site of action. Reserpine and lysergic acid are typical complex medicinal agents to which these general considerations have already been applied by other investigators with considerable success. By disjunction, both reserpine and lysergic acid can be shown to possess an *N*-alkyl substituted tryptamine fragment and an additional alkyl chain terminating with a carboxy group (III). In the case of reserpine, this alkyl group consists of four methylene groups and terminates with a carbomethoxy group; in the case of lysergic acid, this alkyl group consists of two methylene groups terminating with a carboxyl group.

Examination of the structures of reserpine and lysergic acid diethylamide indicated potential activity of compounds that incorporated certain features of each. The title compounds are aliphatic esters and amides attached at the omega position to the aliphatic nitrogen of tryptamine. Psychotomimetic activity would be anticipated in those compounds that had a two-carbon chain separating the tryptamine and carbonyl function as in lysergic acid diethylamide. Those compounds having a four carbon chain between the two functional groups would be expected to exhibit CNS depression. The length of the chain was varied from two to four carbons. The carbonyl function was a methyl or ethyl ester or an *N*,*N*-dimethyl or diethyl amide. A few compounds were substituted with a 6-methoxy group to resemble more the reserpine molecule.



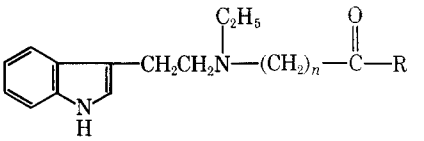
reserpine

I



lysergic acid

II



III

$n = 2,3,4$

$R = OCH_3,\ OC_2H_5,\ N(CH_3)_2,\ N(C_2H_5)_2$

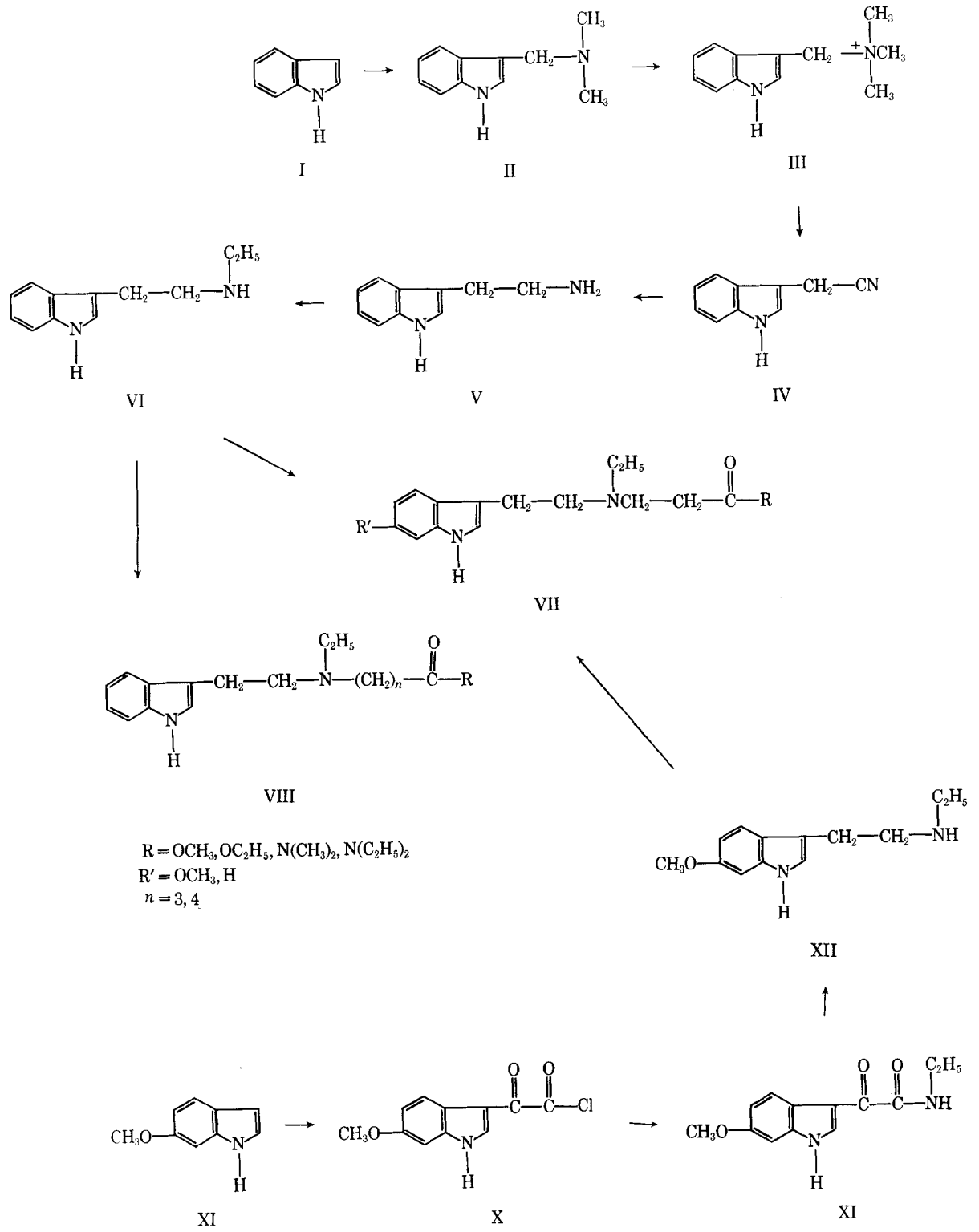
Disjunction of reserpine and lysergic acid

EXPERIMENTAL

N-Ethyltryptamine and *N*-ethylethyl-6-methoxytryptamine were synthesized by the use of published procedures, the former compound by the procedure of Snyder *et al.* (1) and the latter compound by the procedure of Woodward *et al.* (2) (Scheme I). The title compounds were prepared by one of the two following procedures.

Preparation of Amides and Esters of *N*-Ethyl-*N*-(3-indolylethyl)-ω-aminoalkyl Carboxylic Acid—*Procedure A*—The *N*-ethyltryptamine derivative was dissolved in approximately 40 times its weight of absolute methanol. To this solution was added a 10% molar excess of the acrylic acid derivative. The mixture was allowed to stand at room temperature for 4 days. The solvent was removed with reduced pressure and replaced with an equal amount of ether. After the ether solution was washed twice with 10% saline solution, it was dried over anhydrous sodium sulfate. TLC on silica using 5% diethylamine in chloroform and detection using chromic acid or Dragendorff's reagent revealed only one spot with an R_f different than the starting amine. The yields of the reactions ranged between 75 and 90%. Analytical samples were obtained by adding a saturated solution of picric acid in ether to the ethereal solution of the product and recrystallizing the picrate from absolute ethanol.

Procedure B—*N*-Ethyltryptamine (0.3 g.) was dissolved in 10 ml. of dimethyl sulfoxide. To this solution was added an equimolar quantity of the ω-chlorovaleric acid or butyric acid derivative and 0.5 g. of sodium bicarbonate. The suspension was stirred and warmed to 50° (ω-chlorovaleric acid derivatives) or 70° (butyric acid derivatives) and monitored with TLC using the system described previously. After 2 hr. an additional quantity of the chloroacid was added. Further monitoring with TLC was conducted until the reaction reached completion. Water was added to the mixture, and the resulting suspension was extracted with ether. The ethereal extract



Scheme I

was dried and treated with acetic anhydride (2 ml.) at reflux for 30 min. to acetylate any remaining tryptamine derivative. The ethereal solution was extracted with 20% aqueous acetic acid to remove the amines as acetate salts. Hydrochlorides formed from pure amines isolated on preparative TLC were extremely hygroscopic. Analytical samples were obtained by dissolving the hydrochlorides in water to which was added a concentrated solution of disodium pamoate monohydrate (Table I).

Hippocratic Screening—Using the method of Malone and Robichaud (3), a gross observational screen was performed on the compounds using male and female, nonfasted, intact, unanesthetized rats[1] ranging in weight from 210–480 g. Qualitative and semiquantitative symptomatology after intraperitoneal injection was observed at the required time intervals (controls; 5, 10, 15, and 30 min.; 1, 2, 4, and 6 hr.; and 1, 2, 4, and 7 days) using the standardized worksheet (3) to record data. A constant injection volume of 5 ml./kg. was used with 0.25% agar as the diluting and suspending vehicle. All animals surviving the observational period of 1 week

[1] Wistar strain; E. G. Steinhilber, Oshkosh, Wis.

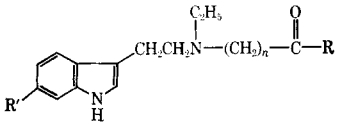


Table I—Amides and Esters of *N*-Ethyl-*N*-(3-indolylethyl)-ω-aminoalkyl Carboxylic Acid

Compound	Free Bases					Derivatives[b]		
	Procedure	*n*	R′	R	R_f Value[a]	M.p.	Calcd., % N	Found, % N
XIII	A	2	H	OCH_3	0.61	148–149.5°	13.95	14.13
XIV	A	2	H	OC_2H_5	0.59	148–149°	13.55	13.29
XV	A	2	H	$N(CH_3)_2$	0.46	166–167°	16.2	16.01
XVI	A	2	H	$N(C_2H_5)_2$	0.54	169–170°	15.45	15.19
XVII	A	2	OCH_3	OC_2H_5	0.61	155–156°	12.8	12.62
XVIII	A	2	OCH_3	$N(C_2H_5)_2$	0.54	174–176°	14.65	14.89
XIX	B	3	H	OCH_3	0.60	>250°	4.01	4.30
XX	B	3	H	OC_2H_5	0.61	>250°	3.94	4.24
XXI	B	3	H	$N(CH_3)_2$	0.53	>250°	5.92	5.99
XXII	B	3	H	$N(C_2H_5)_2$	0.56	>250°	5.79	5.70
XXIII	B	4	H	OCH_3	0.64	>250°	3.93	4.11
XXIV	B	4	H	OC_2H_5	0.66	>250°	3.86	3.75
XXV	B	4	H	$N(CH_3)_2$	0.41	>250°	5.80	5.57
XXVI	B	4	H	$N(C_2H_5)_2$	0.43	>250°	5.68	5.11

[a] R_f values are taken on thin-layer silica plates using 5% diethylamine–chloroform as a developer. [b] Compounds XIII–XVIII are picrates and XIX–XXVI are monosodium pamoates.

were sacrificed by cranio-vertebral dislocation, and a necropsy was performed to detect any grossly apparent latent toxicity. All test compounds as well as the reference materials were coded to conceal identity during screening for activity.

RESULTS AND DISCUSSION

The qualitative nature of the observable symptoms exhibiting dose–response relationships (1–2 rats/dosage level) permits tentative predictions as to possible pharmacologic relationships of the test compounds with reserpine or lysergic acid when these two reference compounds also have been screened by the same procedure. Reserpine- and lysergic acid-like activities can be differentiated easily by Hippocratic screening.

Rats receiving reserpine acetate (0.3–31 mg./kg.) are characterized by the relatively slow onset of miosis, enophthalmos, palpebral ptosis, pilomotor erection, tail grasping, hypothermia, diarrhea, reduction of motor activity, tremors, and passive reactions to both body grasp and head tap challenges (3). Stereotypy and screen grip loss are absent. While reserpinized animals assume statue positions (3), this is associated with profound sedation and decrease of motor activity.

The characteristic symptomatology produced by *d*-lysergic acid diethylamide tartrate (0.1–5.0 mg./kg.) is manifested as a rapid onset of profound mydriasis, pilomotor erection, and hypothermia associated with spontaneous statue positions and stereotypy at doses that do not affect the animal's motor performance significantly. At doses of 1.0–5.0 mg./kg., hyperactivity, hyperreflexia, and tremors are apparent as well as fearful–aggressive reaction patterns to body grasp and head tap challenges. Death following a dosage of 5.0 mg./kg. occurs within 30–45 min. and is associated with cardiac irregularities and general rigidity of musculature, while reserpine-induced lethality is of slow onset (8–24 hr.) and associated with loss of body weight (dehydration due to diarrhea), loss of skeletal muscle tone, and eventually respiratory arrest.

In this series of compounds, reserpinelike activity was totally absent. All methoxy derivatives (XIII, XIX, and XXIII) and ethoxy derivatives (XIV, XX, and XXIV) were essentially inactive, including Compound XVII. However, the diethylamino derivatives appeared to possess some qualitatively similar lysergic acid-like activity, with Compound XVI being the most potent, Compound XXII of intermediate potency, and Compound XXVI possessing only equivocal activity at dosages of 100–178 mg./kg. Compound XVI, in the equivocally effective-to-lethal dosage range of 1.0–10.0 mg./kg., produced dose–response patterns of strong mydriasis, hyperreflexia, tremors, hypothermia, increased motor activity, hyperemia of skin, and evidences for stereotypy and disorientation. Fearful reaction patterns to the head tap and body grasp challenges were observed uniformly. Compound XVII appeared to be active in the same dosage range as XVI and displayed the same qualitative symptomatology except that hyperthermia instead of hypothermia was recorded.

SUMMARY

Fourteen amides and esters of *N*-ethyl-*N*-(3-indolylethyl)-ω-aminoalkyl carboxylic acid were synthesized. These derivatives were formulated to represent a disjunctured reserpine and lysergic acid diethylamide molecule with the hope that the compounds more closely resembling reserpine would possess depressant activity and those resembling LSD would possess LSD-like activity. All synthesized compounds were found to be completely devoid of reserpinelike activity. Each amide showed various degrees of LSD-like activity. The molecule derived directly from the disjuncture of LSD, that is, the diethylamide of the compound where the alkyl chain possesses two carbons, was quantitatively the most potent, showing the desired activity at levels of 1.0–10.0 mg./kg. As the alkyl chain was lengthened, potency decreased. The dimethyl amides were active but to a lesser degree.

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