

# Indolizine Derivatives with Biological Activity IV: 3-(2-Aminoethyl)-2-methylindolizine, 3-(2-Aminoethyl)-2-methyl-5,6,7,8-tetrahydroindolizine, and Their *N*-Alkyl Derivatives

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Received June 9, 1978, from the *Istituto di Chimica Farmaceutica e di Chimica Organica, Università di Camerino, 62032 Camerino (MC), Italy.* Accepted for publication August 21, 1978. \*Istituto di Farmacologia, Farmacognosia e Tecnica Farmaceutica della Università di Camerino, 62032 Camerino (MC), Italy.

**Abstract** □ In a continuing search for new biologically active agents derived from indolizine, 3-(2-aminoethyl)-2-methylindolizine, 3-(2-aminoethyl)-2-methyl-5,6,7,8-tetrahydroindolizine, and some mono- and di-*N*-substituted derivatives were prepared. Initial pharmacological screening showed that these compounds possess anti-5-hydroxytryptamine, antihistamine, antiacetylcholine, and CNS-depressant activities.

**Keyphrases** □ Indolizines, substituted—series synthesized, evaluated for pharmacological activity □ Anti-5-hydroxytryptamine activity—series of substituted indolizines evaluated □ Antihistaminic activity—series of substituted indolizines evaluated □ Antiacetylcholine activity—series of substituted indolizines evaluated □ CNS activity—series of substituted indolizines evaluated □ Structure-activity relationships—series of substituted indolizines evaluated

A previous paper (1) reported the synthesis of 3-(3-aminopropyl)-2-methylindolizine, 3-(3-aminopropyl)-2-methyl-5,6,7,8-tetrahydroindolizine, and some *N*-alkyl derivatives. These compounds showed anti-5-hydroxytryptamine, antihistamine, antiacetylcholine, and central nervous system (CNS)-depressant activities.

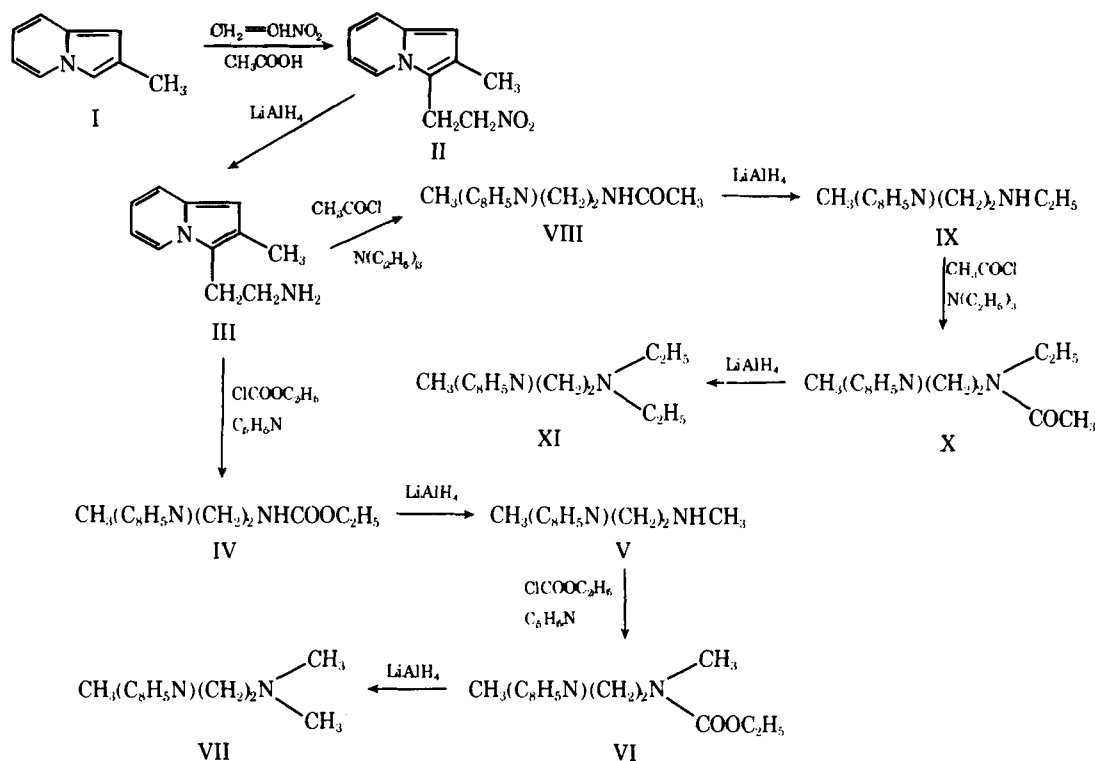
To explore further the structure-activity relationships of indolizine compounds, 3-(2-aminoethyl)-2-methylindolizine, 3-(2-aminoethyl)-2-methyl-5,6,7,8-tetrahydroindolizine, and some *N*-substituted derivatives were synthesized. The *in vitro* anti-5-hydroxytryptamine, antihistamine, and antiacetylcholine activities, as well as the *in vivo* effect on the CNS, were studied.

## EXPERIMENTAL

**Chemistry**—The 3-(2-alkylaminoethyl)indolizine derivatives (Table I) were prepared as shown in Scheme I.

2-Methyl-3-(2-nitroethyl)indolizine (II) was obtained by the reaction of 2-methylindolizine (I) with nitroethylene. The structure of II was established on the basis of its NMR spectrum, which showed a singlet at  $\delta$  6.22 (1-H) ppm and signals at  $\delta$  7.85–7.55 (m, 5-H), 7.45–7.07 (m, 8-H), and 6.85–6.37 (m, 7-H and 6-H) ppm.

Reduction of II with lithium aluminum hydride gave 3-(2-aminoethyl)-2-methylindolizine (III). Treatment of III with ethyl chloroformate, followed by reduction of the 3-ethoxycarbonylaminoethyl derivative (IV), afforded 3-(2-methylaminoethyl)-2-methylindolizine (V). It was converted into the dimethyl derivative (VII) by the same reaction.

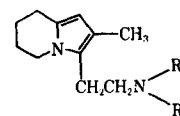


Scheme I

**Table I—Characteristics of 3-(2-Aminoethyl)-2-methylindolizines**

Compound	Boiling Point/mm or Melting Point	Yield, %	Maleate Melting Point	Formula	Analysis, %		Maleate Analysis, %			
					Calc.	Found	Calc.	Found		
III	81°/0.05	84	163–164° <sup>a</sup>	C <sub>11</sub> H <sub>14</sub> N <sub>2</sub>	C	75.82	76.03	C	62.05	62.09
					H	8.10	8.21	H	6.25	6.22
					N	16.08	16.07	N	9.65	9.57
IV	65–66° <sup>b</sup>	83	—	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	C	68.27	68.13	—	—	—
					H	7.37	7.19	—	—	—
					N	11.37	11.34	—	—	—
V	85°/0.05	90	163–164° <sup>c</sup>	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub>	C	76.55	76.48	C	63.14	63.22
					H	8.57	8.51	H	6.62	6.59
					N	14.88	14.92	N	9.21	9.17
VI	122°/0.05	80	—	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	C	69.20	69.26	—	—	—
					H	7.74	7.71	—	—	—
					N	10.76	10.69	—	—	—
VII	84°/0.05	86	131–132° <sup>a</sup>	C <sub>13</sub> H <sub>18</sub> N <sub>2</sub>	C	77.18	77.13	C	64.13	64.05
					H	8.97	8.90	H	6.97	6.88
					N	13.85	13.81	N	8.80	8.73
VIII	124–125° <sup>d</sup>	47	—	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O	C	72.19	72.14	—	—	—
					H	7.46	7.40	—	—	—
					N	12.95	12.89	—	—	—
IX	105°/0.05	81	148–149° <sup>c</sup>	C <sub>13</sub> H <sub>18</sub> N <sub>2</sub>	C	77.18	77.21	C	64.13	64.21
					H	8.97	8.86	H	6.97	6.84
					N	13.85	13.77	N	8.80	8.86
X	124°/0.1	88	—	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O	C	73.73	73.69	—	—	—
					H	8.25	8.27	—	—	—
					N	11.47	11.46	—	—	—
XI	88°/0.1	83	94–95° <sup>c</sup>	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub>	C	78.21	78.15	C	65.87	65.72
					H	9.63	9.58	H	7.57	7.49
					N	12.16	12.19	N	8.09	8.12

<sup>a</sup> Recrystallized from ethanol. <sup>b</sup> Recrystallized from *n*-hexane. <sup>c</sup> Recrystallized from isopropanol. <sup>d</sup> Recrystallized from benzene.


**Table II—Characteristics of 3-(2-Aminoethyl)-2-methyl-5,6,7,8-tetrahydroindolizines**

Compound	R <sub>1</sub>	R <sub>2</sub>	Boiling Point/mm	Yield, %	Maleate Melting Point	Formula	Analysis, %		Maleate Analysis, %			
							Calc.	Found	Calc.	Found		
XII	H	H	77°/0.03	72	135–137° <sup>a</sup>	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub>	C	74.11	74.02	C	61.20	61.18
							H	10.18	10.15	H	7.53	7.47
							N	15.71	15.73	N	9.52	9.56
XIII	H	C <sub>2</sub> H <sub>5</sub>	86°/0.1	78	143–145° <sup>b</sup>	C <sub>13</sub> H <sub>22</sub> N <sub>2</sub>	C	75.67	75.61	C	63.33	63.37
							H	10.75	10.77	H	8.13	8.18
							N	13.58	13.56	N	8.69	8.62
XIV	H	CH <sub>3</sub>	73°/0.05	78	170–172° <sup>c</sup>	C <sub>12</sub> H <sub>20</sub> N <sub>2</sub>	C	74.95	74.98	C	62.31	62.30
							H	10.48	10.44	H	7.85	7.79
							N	14.57	14.53	N	9.09	9.12
XV	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	90°/0.1	73	— <sup>d</sup>	C <sub>15</sub> H <sub>26</sub> N <sub>2</sub>	C	76.86	76.89	C	65.11	65.13
							H	11.18	11.10	H	8.63	8.61
							N	11.95	11.93	N	7.99	7.94
XVI	CH <sub>3</sub>	CH <sub>3</sub>	83°/0.1	75	153–155° <sup>b</sup>	C <sub>13</sub> H <sub>22</sub> N <sub>2</sub>	C	75.67	75.62	C	63.33	63.38
							H	10.75	10.79	H	8.13	8.17
							N	13.58	13.51	N	8.69	8.63

<sup>a</sup> Recrystallized from ethanol and anhydrous ether. <sup>b</sup> Recrystallized from isopropanol. <sup>c</sup> Recrystallized from anhydrous ethanol. <sup>d</sup> The maleate decomposed when heated in solution and is highly hygroscopic.

Again, acetylation of III gave the *N*-acetyl derivative (VIII), which was converted by reduction into 3-(2-ethylaminoethyl)-2-methylindolizine (IX).

Compound IX, again by acetylation followed by reduction, yielded 3-(2-diethylaminoethyl)-2-methylindolizine (XI). The 5,6,7,8-tetrahydroindolizines (XII–XVI, Table II) were prepared by catalytic hydrogenation of the corresponding indolizines III, V, VII, IX, and XI. All NMR spectra showed the signal of the 1-proton as a singlet whose position varied between  $\delta$  5.27 and 5.94 ppm. Moreover, the typical signals of the pyridine moiety protons, between  $\delta$  7.9 and 5.8 ppm in the unreduced products, had disappeared. All amines were converted to maleates.

**Syntheses<sup>1</sup>—2-Methyl-3-(2-nitroethyl)indolizine (II)**—Nitroethylene (0.06 mole) in dry benzene (25 ml) was added dropwise to a stirred

and cooled (0–5°) solution of I (0.057 mole) (2) in acetic acid (5 ml) and dry benzene (50 ml). Stirring was continued for 2 days at room temperature. The solution was filtered on silica gel and then carefully made alkaline with 2 *N* NaOH; the solvent layer was separated and dried. Solvent evaporation gave a dark oily residue from which a solid product was precipitated by ethanol.

The solid was filtered and recrystallized from ethanol, mp 78–80°, in a 57% yield; IR:  $\nu_{\max}$  (mineral oil) 1535 and 1350 (NO<sub>2</sub>) cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>):  $\delta$  7.85–7.55 (m, 1H, 5-H), 7.45–7.07 (m, 1H, 8-H), 6.85–6.37 (m, 2H, 6,7-H), 6.22 (s, 1H, 1-H), 4.42 (t, 2H, CH<sub>2</sub>NO<sub>2</sub>), 3.52 (t, 2H, ArCH<sub>2</sub>), and 2.25 (s, 3H, 2-CH<sub>3</sub>) ppm.

*Anal.*—Calc. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.37; H, 5.79; N, 13.83.

**3-(2-Aminoethyl)-2-methylindolizine (III)**—Slowly, with stirring, a solution of II (0.01 mole) in dry ether (70 ml) was added to a suspension of lithium aluminum hydride (0.031 mole) in dry ether (25 ml). After the solution was stirred for 24 hr at room temperature, the lithium aluminum hydride excess was destroyed with aqueous ethanol, and 2 *N* NaOH (15

<sup>1</sup> Boiling points are uncorrected. Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 257 spectrophotometer. NMR spectra were recorded on a Jeol C-60 HL instrument.

ml) was added. The solid was filtered off; after drying, the ethereal solution was evaporated.

The oil residue was distilled; IR:  $\nu_{\max}$  (liquid film) 3350 and 3280 (NH<sub>2</sub>) cm<sup>-1</sup>; NMR (CCl<sub>4</sub>):  $\delta$  7.8–7.5 (m, 1H, 5-H), 7.3–6.97 (m, 1H, 8-H), 6.6–6.15 (m, 2H, 6,7-H), 6.05 (s, 1H, 1-H), 3.07–2.7 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.22 (s, 3H, 2-CH<sub>3</sub>), and 0.82 (s, 2H, NH<sub>2</sub>) ppm.

**3-(2-Ethoxycarbonylaminoethyl)-2-methylindolizine (IV) and 3-(N-Ethoxycarbonyl-2-methylaminoethyl)-2-methylindolizine (VI)**—With stirring, a solution of ethyl chloroformate (0.05 mole) in chloroform (10 ml) was added dropwise to an ice-cooled solution of III or V (0.048 mole) in chloroform (50 ml). After 1 hr, water (20 ml) was added; stirring was continued for 3 hr. The chloroform layer was recovered, washed with 2 N NaOH, dried, and evaporated. Compound III yielded a solid, which was crystallized; V gave an oil residue, which was distilled.

**3-(2-Methylaminoethyl)-2-methylindolizine (V) and 3-(2-Dimethylaminoethyl)-2-methylindolizine (VII)**—To a suspension of lithium aluminum hydride (0.05 mole) in dry ether (20 ml) was slowly added 0.024 mole of IV or VI in dry ether (50 ml). The mixture was heated under reflux for 14 hr. Aqueous ethanol was added to destroy excess lithium aluminum hydride, and then 2 N NaOH (20 ml) was added. After filtration, the solution was dried and evaporated, and the residue was distilled.

**3-(2-Acetylaminoethyl)-2-methylindolizine (VIII) and 3-(N-Acetyl-2-ethylaminoethyl)-2-methylindolizine (X)**—With stirring, acetyl chloride (0.038 mole) in dry ether (10 ml) was slowly added to a solution of III or IX (0.038 mole). Triethylamine (0.038 mole) in dry ether (20 ml) was added, and then the ether was separated off. The aqueous solution was again extracted with ether. The extracts were dried, and the solvent was driven off. Compound III afforded a solid, which was recrystallized from benzene. The liquid obtained from IX was distilled.

**3-(2-Ethylaminoethyl)-2-methylindolizine (IX)**—A solution of VIII (0.025 mole) in dry tetrahydrofuran (90 ml) was added to a suspension of lithium aluminum hydride (0.050 mole) in dry tetrahydrofuran. The mixture was refluxed for 6 hr; then aqueous ethanol and 2 N NaOH (30 ml) were added. After filtration, the solution was dried and evaporated. The residue was distilled.

**3-(2-Dimethylaminoethyl)-2-methylindolizine (XI)**—To a suspension of lithium aluminum hydride (0.04 mole) in anhydrous ether (20 ml) was added a solution of X (0.019 mole) in dry ether (50 ml). The mixture was refluxed for 12 hr; aqueous ethanol and 2 N NaOH (25 ml) were added. After filtration, the ethereal solution was dried and evaporated. The residue was distilled.

**3-(2-Aminoethyl)-2-methyl-5,6,7,8-tetrahydroindolizine (XII) and N-Alkyl Derivatives (XIII–XVI)**—A mixture of the suitable indolizine, III, V, VII, IX, or XI (0.023 mole), in absolute ethanol (100 ml), 1 g of 5% palladium-on-charcoal, and a few drops of acetic acid was hydrogenated at room temperature at 0.027 atm. Hydrogenation was stopped when 2 moles of hydrogen/mole of compound had been absorbed (7 days). The catalyst was filtered off, and the solution was made alkaline with 3 N NaOH and extracted with ether.

The ethereal extract was dried and evaporated, and the residue was distilled. For XII, the IR spectrum showed  $\nu_{\max}$  (liquid film) 3350 and 3280 (NH<sub>2</sub>) cm<sup>-1</sup>; NMR (CCl<sub>4</sub>):  $\delta$  5.3 (s, 1H, 1-H), 3.7 (t, 2H, 5-CH<sub>2</sub>), 2.8–2.2 (m, 6H, 8-CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>), 2–1.6 (m, 7H, 2-CH<sub>3</sub>, 7-CH<sub>2</sub>, 6-CH<sub>2</sub>), and 0.93 (s, 2H, NH<sub>2</sub>) ppm.

**Maleates of Indolizines III, V, VII, IX, and XI–XVI**—The suitable base in dry ether was added slowly to a stirred equimolar solution of maleic acid in dry ether. After cooling, the solid was collected and recrystallized. The maleate of base XV is highly hygroscopic and uncrystallizable; it was used in the pharmacological test after drying under vacuum. All compounds, with the exception of II, are unstable to light and air but can be stored for several months in an inert atmosphere in a refrigerator.

**Biological Activities**—*In vitro*, the anti-5-hydroxytryptamine, antihistamine, and antiacetylcholine activities of compounds were determined on the isolated guinea pig ileum or the isolated uterus of estrous rats. A previously described technique (1) was employed without any modification.

As comparison standards, tryptamine hydrochloride<sup>2</sup> and specific inhibitors of 5-hydroxytryptamine (metergoline maleate<sup>3</sup>), histamine (diphenhydramine<sup>4</sup>), and acetylcholine (atropine sulfate<sup>5</sup>) were used. In addition, the following agonists and doses were used: 5-hydroxytryptamine (creatinine sulfate<sup>6</sup>), 0.011  $\mu$ g/ml; histamine dihydrochloride<sup>6</sup>, 0.016  $\mu$ g/ml; and acetylcholine chloride<sup>7</sup>, 0.043  $\mu$ g/ml. The synthesized products were used as maleates.

**Table III—*In Vitro* ID<sub>50</sub> Values on Guinea Pig Ileum Smooth Muscle Preparation<sup>a</sup>**

Compound	Acetylcholine	Histamine
Atropine	0.0027 (15.9)	
Diphenhydramine		0.0072 (2.22)
Tryptamine	86.8 (0.0005)	10.83 (0.0014)
III	9.99 (0.0043)	11.19 (0.0014)
V	10.3 (0.0041)	2.88 (0.0055)
VII	15.24 (0.0028)	0.16 (0.1)
IX	17.34 (0.0024)	2.54 (0.0062)
XI	8.84 (0.0048)	0.43 (0.037)
XII	64.56 (0.0006)	32.28 (0.0005)
XIII	38.39 (0.0011)	25.59 (0.0006)
XIV	37.41 (0.0011)	17.83 (0.0008)
XV	89.14 (0.0004)	4.45 (0.0035)
XVI	34.12 (0.0012)	1.49 (0.01)

<sup>a</sup> All concentrations (micrograms per milliliter) refer to the free base. The numbers in parentheses are the antagonistic activity rates (agonist concentration/antagonist concentration ratio).

tamine (creatinine sulfate<sup>6</sup>), 0.011  $\mu$ g/ml; histamine dihydrochloride<sup>6</sup>, 0.016  $\mu$ g/ml; and acetylcholine chloride<sup>7</sup>, 0.043  $\mu$ g/ml. The synthesized products were used as maleates.

For each substance, the agonist to antagonist ratio was calculated. It was the ratio between a constant dose of the agonist and the dose of the antagonist that reduced by 50% the response evoked by the agonist.

*In vivo* experiments were carried out on Swiss male albino mice. The LD<sub>50</sub> values and the effects on the CNS were determined after intravenous administration. The LD<sub>50</sub> value was calculated by the Weil (3) method 14 days after treatment.

To study the CNS effects, the following tests were employed: potentiation of the hypnotic effect of barbiturates (4), grip strength (5), grooming (6), and exploratory activity both in an open field (7) and in a hole board (8). For this last test, the number of rearing reactions (open field) or of holes explored (hole board) during a 3-min period was considered. In these experiments, mice that received simple saline solution acted as controls.

Since this work investigated the effect of replacement of the indole with the indolizine system on pharmacological activity, tryptamine was employed as reference indole derivative.

## RESULTS AND DISCUSSION

The results of the *in vitro* experiments are summarized in Table III. All substances tested possessed anti-5-hydroxytryptamine, antihistamine, and antiacetylcholine activities.

The antihistamine effect was clearly more intense in the indolizine than in the tetrahydroindolizine derivatives. In both series of compounds, the activity increased in the following order: unalkylated, monoalkylated, and dialkylated amines. In some instances, the antihistamine activity was compared to that of 3-(3-aminopropyl)-2-methylindolizine derivatives, whose synthesis and pharmacological properties were described previously (1).

In these experiments, all compounds except XIII appeared less effective than the corresponding 3-(3-aminopropyl)-2-methylindolizines in inhibiting the spasmogenic effect of histamine on the isolated guinea pig ileum. The agonist to antagonist ratios of diphenhydramine and

**Table IV—Acute Toxicity<sup>a</sup>**

Compound	LD <sub>50</sub> (Confidence Limits), mg/kg
Tryptamine	228.6 (203.4–246.2)
III	89.3 (104–76)
V	126 (144–111)
VII	138 (155–122)
IX	70.8 (79–63)
XI	102.9 (114–92)
XII	52.1 (60–45)
XIII	40 (47–33)
XIV	96.9 (103–90)
XV	100 (109–91)
XVI	66.5 (76–58)

<sup>a</sup> All values refer to the free base.

<sup>6</sup> Ibis, Florence, Italy.

<sup>7</sup> Roche, Milan, Italy.

<sup>2</sup> Fluka.

<sup>3</sup> Farmitalia, Milan, Italy.

<sup>4</sup> Parke-Davis.

<sup>5</sup> Merck.

Table V—Effects on the CNS<sup>a</sup>

Compound	Dose, mg/kg <sup>b</sup>	Grip Strength <sup>c</sup>	Grooming <sup>d</sup>	Behavior in Open Field <sup>e</sup>	Barbiturate Narcosis Potentiation <sup>f</sup>	Hole Board <sup>g</sup>
Controls		208.3 ± 9.3	15.1 ± 3.5	20.6 ± 3.1	0	26.6 ± 2.9
Tryptamine	76.2	181.2 ± 6.9	131.2 ± 21.5	0.12 ± 0.1	90	3.25 ± 0.63
III	30	120 ± 9.3	146.5 ± 19.5	0	90	0.4 ± 0.34
V	42	178.3 ± 9.3	59.4 ± 19.5	0.3 ± 0.34	50	9.7 ± 3.1
VII	46	173.3 ± 9.3	110.7 ± 19.5	0.1 ± 0.1	70	3 ± 1.1
IX	23.5	160 ± 9.3	63.2 ± 19.2	2.7 ± 1.65	0	16.6 ± 4.1
XI	34.5	205 ± 9.3	49.2 ± 19.5	0.4 ± 0.34	20	5.1 ± 1
XII	17.6	190.7 ± 13	85.3 ± 20.5	0	60	2.2 ± 0.6
XIII	13.4	212.5 ± 10.4	13 ± 3.1	6.75 ± 1.65	10	8.12 ± 1.5
XIV	32.4	175 ± 3.5	30.7 ± 10	0.75 ± 0.75	0	3.37 ± 1.25
XV	33.4	220.8 ± 10.4	14.3 ± 4.6	2.37 ± 0.88	0	7.6 ± 1.64
XVI	22.2	220.8 ± 10.4	13.25 ± 5	1.75 ± 1.14	10	6.37 ± 1.14

<sup>a</sup> Figures are the mean ± SE of the results obtained on 10–15 mice. <sup>b</sup> All values refer to the free base. <sup>c</sup> Arbitrary units. <sup>d</sup> Latency time of the reflex. <sup>e</sup> Rearing reaction (during a 3-min observation). <sup>f</sup> Percentage of mice that lost the righting reflex. <sup>g</sup> Number of holes explored (during a 3-min observation).

tryptamine were 2.22 and 0.0014, respectively. The agonist to antagonist ratios of VII and XVI were 0.1 and 0.01, respectively; for the other compounds, this ratio ranged between 0.037 (XI) and 0.0005 (XII). Thus, the antihistamine activity of VII and XVI was about 20 and 200 times less, respectively, than that of diphenhydramine while that of the other compounds was up to about 4500 times inferior.

The antiacetylcholine effect of the indolizine derivatives was generally larger than that of the corresponding tetrahydroindolizines. All compounds except XV were up to about eight to 10 times (III, V, and XI) more effective antiacetylcholine agents than tryptamine, but their antiacetylcholine effect proved to be negligible when compared to that of atropine. In fact, the agonist to antagonist ratio of atropine was 15.9 while that of the other compounds ranged between 0.0048 (XI) and 0.0004 (XV). Thus, the substances tested were about 3000–40,000 times less active than atropine in inhibiting acetylcholine activity.

The anti-5-hydroxytryptamine activity of the compounds was negligible and was evident only at doses that irreversibly damaged the isolated uterus.

The results of *in vivo* experiments are summarized in Tables IV and V. The LD<sub>50</sub> value of tryptamine was 228.6 mg/kg. All other compounds were more toxic than the reference standard, with the LD<sub>50</sub> value ranging between 40 (XIII) and 138 (VII) (Table IV).

All compounds showed a more or less intense depressive effect on the CNS. Exploratory activity in a open field or in a hole board was strongly depressed by all substances tested except IX, which reduced rearing reactions but did not significantly alter the number of holes explored by mice.

Grooming was inhibited by III, VII, and, to a lesser extent, XII, V, and IX but was not reduced significantly or was left unmodified by the remaining substances.

The hypnotic action of barbiturates was strongly potentiated by III, XII, V, and VII but was only slightly increased or was left unmodified by the others.

Muscular strength was practically never altered.

Among the tested substances, III and, to a lesser extent, V, VII, and XII proved to be very effective CNS depressants, but their effects could not be considered specific since they inhibited all of the central activities studied to the same extent. However, XV could be considered a more specific inhibitor of the CNS since its effect was limited to the inhibition of exploratory activity.

On the whole, the indolizine derivatives proved to be more effective in inhibiting CNS activity than the corresponding tetrahydroindolizines. The effect of the latter appeared to be more specific, however, since these compounds mainly affected explorative behavior and practically did not modify grip strength, grooming, and the hypnotic action of barbiturates.

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#### ACKNOWLEDGMENTS

Supported by a grant from the Consiglio Nazionale delle Ricerche, Rome, Italy.

The authors are indebted to Professor M. Cardellini and Professor G. De Caro for helpful discussions.