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

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Abstract □ The syntheses and a preliminary pharmacological evaluation of some aminopropylindolizines and aminopropyltetrahydroindolizines are reported. All compounds showed anti-5-hydroxytryptamine, antihistamine, and antiacetylcholine activities. Some also exhibited weak CNS activity.

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

Among the biologically active compounds with an indole structure, various indolylalkylamines are of particular importance. Interest in such substances suggested the synthesis and the study of their isosteres with indan, indene, benzisoxazole, benzofuran, and benzothiophene systems and other structures.

Investigations on derivatives related to gramine showed that the replacement of the indole by the benzothiophene system reduced the agonistic activity in various types of smooth musculature and led to the appearance of variable, nonspecific, antagonistic properties toward 5-hydroxytryptamine, acetylcholine, and histamine (1). Comparative studies on tryptamines and analogs with a benzothiophene and indene structure suggested the hypothesis that the NH group of the indolylalkylamines does not react significantly with the receptors. In fact, the activity [contractile on the rat stomach (2) and stimulating on the central nervous system (CNS) (3)] of the compounds examined did not generally undergo appreciable variations in comparison with the indole isosteres.

In investigations on compounds with an indolizine structure (4), some indolizinylalkylamine analogs of the well-known indolylalkylamines were synthesized and their pharmacological activities were tested. Few alkylaminoalkylindolizines have been prepared (5–9). Some revealed CNS activity; however, it is not possible at the moment to indicate any correlation between structure and activity.

The present paper reports the syntheses and a preliminary pharmacological screening of a series of 3-(3-alkylaminopropyl)-2-methylindolizines and their tetrahydro derivatives. These compounds were synthesized in view of the pharmacological activities of aminopropyl analogs such as 3-(3-aminopropyl)indole (2, 10), 3-(3-aminopropyl)indene (2), and 1-(3-dimethylaminopropyl)-2-phenylindolizine (5). The presence of a methyl group at the 2-position of indolizine derivatives suggests a favorable influence. In fact, various studies on derivatives related to tryptamine (11) or other substituted indoles (12) indicated that the anti-5-hydroxytryptamine activity is potentiated by the introduction of a methyl group at the 2-position.

EXPERIMENTAL

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

2-Methyl-3-indolizinepropionitrile (II) was obtained by reaction of 2-methylindolizine (I) with acrylonitrile. The structure of II was established on the basis of the NMR spectrum, which showed a singlet at δ 6.13 (1-H) ppm and signals at δ 7.63–7.33 (m, 5-H), 7.26–6.97 (m, 8-H), and 6.6–6.26 (m, 7- and 6-H) ppm.

Reduction of II with lithium aluminum hydride gave 3-(3-aminopropyl)-2-methylindolizine (III). Treatment of III with ethyl chloroformate, followed by reduction of the 3-ethoxycarbonylaminopropyl derivative (IV), afforded the 3-(3-methylaminopropyl)-2-methylindolizine (V).

Compound V was converted into the dimethyl derivative (VII) by the same system. Again, acetylation of III gave the *N*-acetyl derivative (VIII), which was converted by reduction into 3-(3-ethylaminopropyl)-2-methylindolizine (IX). Compound IX, again by acetylation followed by reduction, yielded 3-(3-diethylaminopropyl)-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) in the presence of palladium-on-charcoal. All of the NMR spectra showed the signal of the 1-proton as a singlet whose position varied, depending on the compound, between δ 5.26 and 5.60 ppm. However, the typical signals of the pyridine moiety protons, between δ 7.9 and 5.8 ppm in the unreduced products, had disappeared. All amines were transformed into maleates.

Syntheses[1]—*2-Methyl-3-indolizinepropionitrile (II)*—A solution of 0.152 mole of I (13), 0.60 mole of acrylonitrile, and 0.237 mole of acetic acid was stirred for 20 hr at room temperature. It was then made alkaline with 2 *N* NaOH and extracted with ether. The extracts were dried over anhydrous calcium sulfate. Evaporation of the ethereal solution gave a dark oily residue from which a solid product was precipitated by the addition of ethanol. The nitrile crystallized from ethanol, mp 70–72°; IR: ν_{max} (mineral oil) 2240 (C≡N) cm^{-1}; NMR (CCl_4): δ 7.63–7.33 (m, 1H, 5-H), 7.26–6.97 (m, 1H, 8-H), 6.6–6.26 (m, 2H, 6,7-H), 6.13 (s, 1H, 1-H), 3.16 (t, 2H, CH_2CN), 2.46 (t, 2H, $ArCH_2$), and 2.26 (s, 3H, 2-CH_3) ppm.

Anal.—Calc. for $C_{12}H_{12}N_2$: C, 78.25; H, 6.57; N, 15.2. Found: C, 78.16; H, 6.42; N, 15.47.

3-(3-Aminopropyl)-2-methylindolizine (III)—Slowly, with stirring, a solution of 0.054 mole of II in 200 ml of anhydrous ether was added to a suspension of 0.105 mole of lithium aluminum hydride in 50 ml of anhydrous ether. The mixture then was stirred at room temperature for 15 hr. Excess lithium aluminum hydride was destroyed with aqueous ethanol, and 30 ml of 2 *N* NaOH was added. The solid formed was filtered off, and the ethereal solution was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which was distilled; IR: ν_{max} (liquid film) 3270 and 3245 (NH_2) cm^{-1}; NMR (CCl_4); δ 7.8–7.47 (m, 1H, 5-H), 7.23–6.9 (m, 1H, 8-H), 6.52–6.13 (m, 2H, 6,7-H), 6.03 (s, 1H, 1-H),

[1] Boiling points are uncorrected. Melting points were determined on a Büchi melting-point 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.

Table I—Characteristics of 3-(3-Aminopropyl)-2-methylindolizines

Compound	Boiling Point/mm	Yield, %	Maleate Melting Point	Recrystallization Solvent	Formula	Analysis, % Calc.	Analysis, % Found	Maleate Analysis, % Calc.	Maleate Analysis, % Found
III	98°/0.05	78	141–142°[a,b]	Ethanol–ether	$C_{12}H_{16}N_2$	C 76.55 H 8.57 N 14.88	76.71 8.43 14.62	C 63.14 H 16.62 N 9.21	63.41 6.71 9.04
IV	115°/0.05	73	—	—	$C_{15}H_{20}N_2O_2$	C 69.20 H 7.74 N 10.76	69.31 7.69 10.85	—	—
V	105°/0.05	73	115–116°[b]	Ethanol–ether	$C_{13}H_{18}N_2$	C 77.18 H 8.97 N 13.85	77.24 9.03 13.65	C 64.13 H 6.97 N 8.80	64.21 7.22 8.67
VI	131°/0.1	90	—	—	$C_{16}H_{22}N_2O_2$	C 70.04 H 8.08 N 10.21	69.96 8.1 10.26	—	—
VII	95°/0.05	31	94–96°[b]	Ethanol–ether	$C_{14}H_{20}N_2$	C 77.73 H 9.32 N 12.95	77.84 9.21 13.06	C 65.04 H 7.28 N 8.43	64.84 7.59 8.19
VIII	142°/0.05	87	—	—	$C_{14}H_{18}N_2O$	C 73.01 H 7.88 N 12.17	73.18 8.03 12.24	—	—
IX	104°/0.1	92	112–113°[b]	Ethanol–ether	$C_{14}H_{20}N_2$	C 77.73 H 9.32 N 12.95	77.54 9.36 12.88	C 65.04 H 7.28 N 8.43	65.26 7.24 8.69
X	125°/0.05	80	—	—	$C_{16}H_{22}N_2O$	C 74.38 H 8.58 N 10.84	74.25 8.42 10.96	—	—
XI	104°/0.05	—	—[c]	—	$C_{16}H_{22}N_2$	C 78.63 H 9.90 N 10.84	78.45 9.86 10.96	C 63.47[d] H 7.99 N 7.40	63.25 7.73 7.54

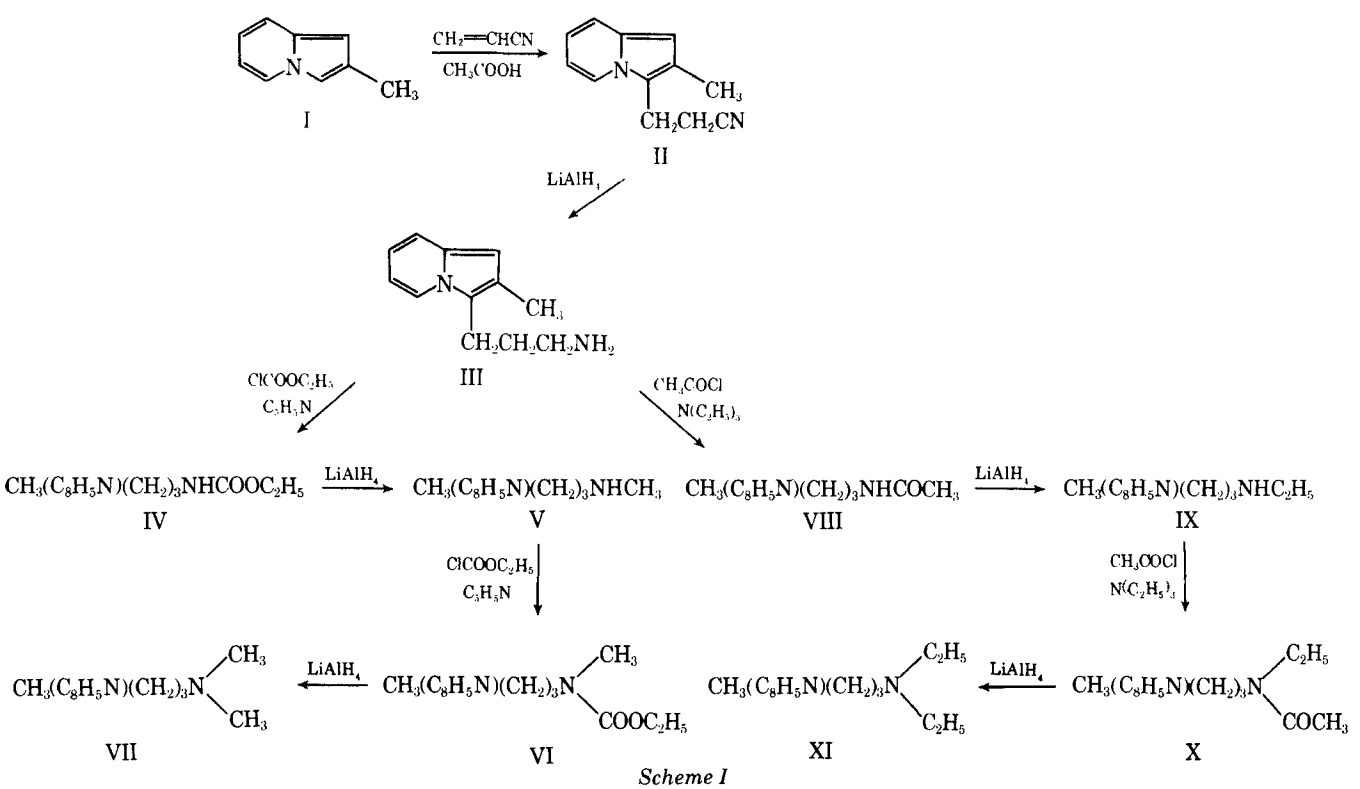
[a] Picrate: mp 193–194°. Recrystallization solvent: ethanol. Formula: $C_{18}H_{19}N_5O_6$. Calc.: C, 53.86; H, 4.77; N, 17.46. Found: C, 54.12; H, 4.85, N, 17.21. [b] Anhydrous solvents. [c] This maleate decomposed when heated in solution and is highly hygroscopic. [d] With 1 mole of water.

2.91–2.44 (m, 4H, CH_2CCH_2), 2.19 (s, 3H, 2-CH_3), 1.56 (q, 2H, CCH_2C), and 0.79 (s, 2H, NH_2) ppm.

3-(3-Ethoxycarbonylaminopropyl)-2-methylindolizine (IV) and 3-(N - Ethoxycarbonyl -3- methylaminopropyl)-2-methylindolizine (VI)—With stirring, a solution of 0.064 mole of ethyl chloroformate in 30 ml of chloroform was added slowly to an ice-cooled solution of 0.053 mole of III or V and 0.053 mole of pyridine in 200 ml of chloroform. After 2.5 hr, 50 ml of water was added; stirring was continued for 3 hr. The chloroform layer was recovered, washed with 2 *N* NaOH, and dried over anhydrous calcium sulfate. Evaporation of the solvent gave an oil, which was distilled.

3-(3-Methylaminopropyl)-2-methylindolizine (V) and 3-(3-Dimethylaminopropyl)-2-methylindolizine (VII)—To a suspension of 0.014 mole of lithium aluminum hydride in 50 ml of anhydrous ether was slowly added 0.067 mole of IV or VI in 300 ml of anhydrous ether. The mixture was heated under reflux for 10 hr and then stirred at room temperature for 5 hr. Aqueous ethanol was added to destroy excess lithium aluminum hydride, and then 30 ml of 2 *N* NaOH was added. The ethereal solution was filtered and dried over anhydrous calcium sulfate. Evaporation of the solvent gave an oil, which was distilled.

3-(3-Acetylaminopropyl)-2-methylindolizine (VIII) and 3-(N-Acetyl-3-ethylaminopropyl)-2-methylindolizine (X)—With stirring, 0.011 mole of acetyl chloride in 10 ml of anhydrous ether was slowly added to a solution of 0.011 mole of III or IX and 0.011 mole of triethylamine



Scheme I

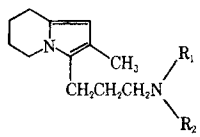


Table II—Characteristics of 3-(3-Aminopropyl)-2-methyl-5,6,7,8-tetrahydroindolizines

Compound	R_1	R_2	Boiling Point/mm	Yield, %	Maleate Melting Point	Recrystallization Solvent	Formula	Analysis, % Calc.	Analysis, % Found	Maleate Analysis, % Calc.	Maleate Analysis, % Found
XII	H	H	76°/0.05	81	128–130°	Ethyl acetate	$C_{12}H_{20}N_2$	C 74.95	74.88	C 62.31	62.62[b]
								H 10.48	10.52	H 7.85	7.76
								N 14.57	14.63	N 9.09	9.15
XIII	H	C_2H_5	78°/0.05	67	93–95°	Ethyl acetate	$C_{14}H_{24}N_2$	C 76.31	76.47	C 60.99	60.78[b]
								H 10.98	10.87	H 8.53	8.34
								N 12.71	12.83	N 7.90	8.15
XIV	H	CH_3	82°/0.05	65	—[a]	—	$C_{13}H_{22}N_2$	C 75.67	75.51	C 59.98	59.73[b]
								H 10.75	10.69	H 8.29	8.17
								N 13.58	13.64	N 8.23	8.31
XV	C_2H_5	C_2H_5	75°/0.05	69	78–79°	Anhydrous ether	$C_{16}H_{28}N_2$	C 77.36	77.24	C 62.80	62.59[b]
								H 11.36	11.23	H 8.96	8.85
								N 11.28	11.13	N 7.32	7.35
XVI	CH_3	CH_3	81°/0.05	43	—[a]	—	$C_{14}H_{24}N_2$	C 76.31	76.45	C 60.99	60.85[b]
								H 10.98	10.86	H 8.53	8.41
								N 12.71	12.84	N 7.90	7.84

[a] The maleate decomposed when heated in solution and is highly hygroscopic. [b] With 1 mole of water.

Table III—*In Vitro* ID_{50} Values on Different Smooth Muscle Preparations[a]

Compound	Guinea Pig Ileum, Acetylcholine	Guinea Pig Ileum, Histamine	Rat Uterus, 5-Hydroxytryptamine
Atropine	0.025 (7.9)	—	—
Metergoline	—	—	7×10^{-7} (24.2×10^3)
Diphenhydramine	—	0.00578 (2.75)	—
Tryptamine	23.7 (0.0084)	8.69 (0.0018)	—[b]
III	3.86 (0.05)	6.18 (0.0025)	1.23 (0.014)
V	1.3 (0.153)	1.27 (0.0125)	0.31 (0.055)
VII	8.64 (0.023)	0.0354 (0.44)	0.195 (0.088)
IX	2.68 (0.074)	2.14 (0.0074)	0.32 (0.054)
XI	11.23 (0.017)	0.186 (0.085)	—[c]
XII	10.35 (0.019)	—[d]	3.1 (0.0055)
XIII	2.7 (0.074)	34.91 (0.0004)	2.62 (0.0066)
XV	72.59 (0.0027)	2.64 (0.006)	13.62 (0.0012)
XVI	21.77 (0.0091)	0.108 (0.146)	6.54 (0.0026)

[a] All concentrations (micrograms per milliliter) refer to the free base. The numbers in parentheses are the antagonistic activity rates (agonist concentration/antagonist concentration ratio). [b] Doses up to 3.3 μg/ml stimulated the uterus contraction. [c] Doses of 2.7 μg/ml yielded inhibition; 4 μg/ml sensitized the rat uterus toward 5-hydroxytryptamine. [d] Doses of 16.6 μg/ml showed an inhibition of 15%. Increasing doses (progression factor = 2) yielded the same response.

in 20 ml of anhydrous ether at 0°. The mixture was stirred for 15 min, water (20 ml) was added, and the ether was separated off. The aqueous solution was again extracted with ether. The extracts were dried with anhydrous sodium sulfate, and the solvent was driven off. The liquid obtained was distilled.

3-(3-Ethylaminopropyl)-2-methylindolizine (IX) and 3-(3-Diethylaminopropyl)-2-methylindolizine (XI)—A solution of 0.025 mole of VIII or X in 50 ml of anhydrous ether was slowly added to a suspension of 0.052 mole of lithium aluminum hydride in 50 ml of ether. The mixture was stirred at room temperature for 18 hr; then aqueous ethanol and 30 ml of 2 *N* NaOH were added. After filtration, the ethereal solution was dried over calcium sulfate, and the solvent was driven off. The liquid obtained was distilled.

Table IV-Acute Toxicity[a]

Compound	LD_{50} (Confidence Limits), mg/kg
Intravenous Administration	
III	24.76 (18.37–33.38)
VII	26.26 (24.24–28.46)
Intraperitoneal Administration	
Tryptamine	223.2 (208.2–260.13)
V	106.10 (90.67–124.14)
IX	102.11 (94.38–110.5)
XI	126.32 (107.91–147.92)
XII	52.97 (47.76–58.48)
XIII	28.89 (24.73–33.89)
XV	62.54 (55.7–70.14)
XVI	19.44 (17.38–21.74)

[a] All values refer to the free base.

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

For Compound XII, the IR spectrum showed ν_{max} (liquid film) 3350 and 3280 (NH_2) cm^{-1}; NMR (CCl_4): δ 5.26 (s, 1H, 1-H), 3.6 (t, 2H, 5-CH_2), 2.92–2.23 (m, 6H, 8-CH_2, CH_2CCH_2), 2–1.9 (m, 2-CH_3, 7-CH_2, 6-CH_2, CCH_2C); and 0.89 (s, 2H, NH_2) ppm.

Maleates of Indolizines III, V, VII, IX, and XI–XVI—The suitable base in anhydrous ether was added slowly to a stirred equimolar solution of maleic acid in anhydrous ether. The maleate precipitated and was then filtered off and recrystallized. The maleates of bases XI and XIV–XVI are highly hygroscopic, and it was not possible to crystallize them; they were used in the pharmacological tests after drying in vacuum. The other maleates and the indolizines synthesized, with the exception of the nitrile, are unstable to light and air but can be kept for several months in an inert atmosphere in a refrigerator.

Biological Activities—The following properties of the synthesized compounds were studied: (*a*) *in vitro*, the anti-5-hydroxytryptamine action, using the uterus of the rat in estrus, and the antihistamine and antiacetylcholine activities, using the isolated terminal guinea pig ileum; and (*b*) *in vivo*, the effects on the CNS. In addition, the LD_{50} after administration of a single drug dose was determined.

Uterus of Estrous Rat—The technique described by Erspamer (14)

Table V—Effects on the CNS[a]

Compound	Dose[b], mg/kg	Grip Strength[c]	Grooming[d]	Behavior in Open Field[e]	Barbiturate Narcosis Potentiation[f]
		Intravenous Administration			
Controls		221.1 ± 9.3	51.8 ± 19.7	9.5 ± 2.1	0
III	8.03	178 ± 7	76.1 ± 18.3	4.3 ± 1.3	0
VII	8.45	207 ± 17.2	82.8 ± 19.4	5.4 ± 1	0
		Intraperitoneal Administration			
Controls		169 ± 12.4	17.8 ± 4.3	17.4 ± 1.8	0
Tryptamine	76.6	140.19 ± 10.59	128.9 ± 15.46	1.3 ± 0.44	90
V	34.92	150.73 ± 11.33	51.8 ± 21.4	8.84 ± 2	20
IX	32.5	198.39 ± 13.1	33.1 ± 22.2	3.39 ± 2	30
XI	41.97	137 ± 7.75	133.9 ± 18.9	2.81 ± 0.93	20
XII	17.44	133.9 ± 13	108.38 ± 21.42	17.69 ± 4.6	40
XIII	9.82	121.77 ± 13.5	61.94 ± 17.29	8.7 ± 2.35	0
XV	20.43	152 ± 6.2	135.5 ± 18.9	4.33 ± 0.24	0
XVI	6.54	183 ± 7	68.3 ± 17.8	11.42 ± 1.75	0

[a] Figures are the mean ± *SE* of the results obtained on 10–15 mice. [b] All values refer to the free base. [c] Arbitrary units. [d] Latency time of the reflex. [e] Rearing reaction (during a 3-min period of observation). [f] Percentage of mice that lost the righting reflex.

was followed. The organ was suspended in 15 ml of Tyrode nutrient solution (15) oxygenated by bubbling air and kept at 32°.

Guinea Pig Ileum—A segment of terminal guinea pig ileum was immersed in 15 ml of Krebs liquid (16), aerated, and kept at 32°. The technique described by Zamboni and Vitali was followed (17).

Determination of Antagonistic Activity—The dose of drug capable of reducing by 50% the response evoked by a standard dose of 5-hydroxytryptamine (0.017 μg/ml), histamine (0.016 μg/ml), and acetylcholine (0.2 μg/ml) was determined. The time of contact of the antagonists with the organ was always 2 min for the guinea pig ileum and 4 min for the rat uterus (Table III).

As comparison standards, tryptamine hydrochloride[2] and specific inhibitors of 5-hydroxytryptamine (metergoline maleate[3]), histamine (diphenhydramine[4]), and acetylcholine (atropine sulfate[5]) were used. In addition, the following agonists were used: 5-hydroxytryptamine creatinine sulfate[5], histamine dihydrochloride[6], and acetylcholine chloride[7].

The products synthesized were used as maleates. Compound XIV was not tested because of its rapid decomposition in solution.

In Vivo *Tests*—The experiments were performed on 25–35-g Swiss male albino mice. The drugs were dissolved in distilled water and injected in a fixed volume of 1 ml/100 g ip. Compounds III and VII, available only in very small amounts, were injected intravenously.

The LD_{50} was determined by Weil's method (18), evaluating the effect of the drugs 14 days after administration (Table IV). The effects on the CNS were studied by the following tests on groups of at least 10 animals: grip strength (19), grooming (20), exploratory activity in an open field (rearing reaction) (21), and potentiation of the hypnotic action of barbiturates (22). In these experiments, the drugs were always injected at a concentration of one-third of the LD_{50} (Table V).

A control test was performed on groups of animals to which pure distilled water was administered under the same conditions. As the comparison standard, tryptamine hydrochloride was used.

RESULTS AND DISCUSSION

Since the scope of this work was to investigate whether the replacement of the indole by the indolizine system led to particular variations in pharmacological activity, tryptamine as a reference indole derivative was included. As can be seen from Table III, all compounds showed *in vitro* inhibitory action toward 5-hydroxytryptamine, histamine, and acetylcholine.

The action was always more pronounced in the indolizine derivatives than in the corresponding tetrahydroindolizine derivatives. The degree of alkylation of the nitrogen atom of the chain had some influence on the magnitude of the pharmacological activity. Thus, the antihistamine activity decreased in the following sequence: dialkyl, monoalkyl, and unalkylated amines; the antiacetylcholine activity decreased in the sequence: monosubstituted, unsubstituted, and disubstituted amines.

The anti-5-hydroxytryptamine activity was most marked in the dimethylated product among the indolizine derivatives and in the monoethylated product among the tetrahydroindolizine derivatives. In the tests on the guinea pig ileum, the activity of 3-(3-aminopropyl)-2-methylindolizine and its derivatives was always greater than that of tryptamine. On the other hand, some reduced products appeared more active and some less active than tryptamine.

All compounds showed weaker activity than that of the specific antagonists such as metergoline, atropine, and diphenhydramine. The products proved to be moderate depressors of the CNS, as shown by reduction in the exploratory activity in the open field and by potentiation of the hypnotic activity of barbiturates (Table V). The reflexes were not appreciably changed; muscular force and motor coordination were not affected. On the whole, the activity of the compounds in the various trials was less than that shown by tryptamine under the same conditions.

The acute toxicity was always greater than that of tryptamine, except for XI (Table IV).

In conclusion, this preliminary investigation showed that the type of activity found in tryptamine persists on the whole, particularly in *in vitro* experiments with the terminal guinea pig ileum. In fact, in this test, all compounds showed a pronounced inhibitory action toward both acetylcholine and histamine. Furthermore, the ratios between the concentrations of agonist to indolizine derivatives were always higher than concentration ratios of agonist to tryptamine.

The tests on the rat uterus showed a stimulating action for tryptamine, as reported in the literature (23). Among the new compounds, a similar activity was found in XI; a clear anti-5-hydroxytryptamine activity was shown by all other compounds, particularly by the *N,N*-dimethyl derivative (VII). Similarly, in a study on tryptamine analogs, the most active compounds as antagonists of 5-hydroxytryptamine were those with a dimethyl group in the side chain (23).

These first results appear to confirm that the NH group of indole is not indispensable for pharmacological activity. Hence, the indolizine system may be considered as a basis for biologically active compounds. Investigation will be extended to other series of analogous compounds.

[2] Fluka.
[3] Farmitalia, Milan, Italy.
[4] Parke-Davis.
[5] Merck.
[6] Ibis, Florence, Italy.
[7] Roche, Milan, Italy.

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Dissolution Kinetics of Soluble Nondisintegrating Disks

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Abstract □ An equation describing the isotropical dissolution of soluble nondisintegrating disks was developed. It was equivalent to the cube root law only if the height and diameter of the disk were equal. The dissolution kinetics of sodium chloride disks were examined, using a beaker equipped with a centrifugal stirrer as the dissolution chamber. The fit of the experimental data to the cube root law had a coefficient of variation of about 4–5%. It was demonstrated statistically that a fit to a square root of mass *versus* time relation was significantly better. With increasing porosity, the dissolution process proceeded faster than predicted on the basis of the diffusion–convection model. An explanation is proposed by assuming an increased effective dissolution surface.

Keyphrases □ Dissolution kinetics—soluble nondisintegrating disks, equation developed, related to cube root law □ Kinetics, dissolution—soluble nondisintegrating disks, equation developed, related to cube root law

Dissolution kinetics have been studied mainly by applying film theory. Recently, the subject was reviewed for monodisperse particles (1) and polydisperse particle systems (2). Larger bodies such as tablets, which have received little attention so far, have had a constant surface exposed to the dissolution fluid when studied (3). Completely exposed 1-cm sodium chloride cubes were studied (4), as were benzoic acid spheres (5).

The present article discusses the validity of the cube root law for completely exposed water-soluble bodies; the role of tablet porosity was investigated.

THEORETICAL

In the derivation of the cube root law (6), the changing surface during dissolution is expressed in terms of mass change. This approach is possible only for symmetrical bodies; disks do not lend themselves to treatment requiring a fixed ratio between surface and mass. Such treatment requires the inversion of the third-order expression: mass = $2\pi\rho r^3 + a\pi\rho r^2$, in which ρ is the tablet density, r is the radius, and a is a constant equal to height (H) minus $2r$.

The root $r = f(M)$ is such that no procedure for the integration of dM/dt is available. Therefore, another approach was followed based on the zero-order decrease rate of linear dimensions of isotropically dissolving particles. In this way, an equation was derived (7) that describes the dissolution kinetics of small spheres and one arrives at the cube root law.

If a flat cylindrical disk is assumed, the following expressions for isotropical dissolution ensue:

$$\text{mass } M = \pi\rho r_t^2 H_t \qquad \text{(Eq. 1)}$$

$$dr/dt = b \qquad \text{(Eq. 2)}$$

$$dH/dt = 2b \qquad \text{(Eq. 3)}$$

$$r_t = r_0 - bt \qquad \text{(Eq. 4)}$$

$$H_t = H_0 - 2bt \qquad \text{(Eq. 5)}$$

where subscripts 0 and t stand for time zero and t, respectively, and b is a constant. Therefore:

$$dM/dt = \pi\rho\, d(r_t^2 H_t)/dt \qquad \text{(Eq. 6a)}$$

$$dM/dt = \pi\rho r_t^2\, dH/dt + \pi\rho H_t\, dr_t^2/dt \qquad \text{(Eq. 6b)}$$

$$dM/dt = \pi\rho r_t^2\, dH/dt + 2\pi\rho H_t r_t\, dr/dt \qquad \text{(Eq. 6c)}$$

Substitution of Eqs. 2–5 in Eq. 6c gives:

$$dM/dt = 2\pi\rho b(r_0 - bt)^2 + 2\pi\rho b(H_0 - 2bt)(r_0 - bt) \qquad \text{(Eq. 7)}$$

which can be rewritten as:

$$dM/dt = C_1 + C_2 t + C_3 t^2 \qquad \text{(Eq. 8)}$$

with $C_1 = 2\pi\rho b r_0(H_0 + r_0)$, $C_2 = -2\pi\rho b^2(H_0 + 4r_0)$, and $C_3 = 6\pi\rho b^3$. Integration of Eq. 8 results in:

$$M_t = C_1 t + 0.5C_2 t^2 + 0.33C_3 t^3 + M_0 \qquad \text{(Eq. 9a)}$$

or:

$$M_t/M_0 = 1 + C_4 t + C_5 t^2 + C_6 t^3 \qquad \text{(Eq. 9b)}$$

Equation 9b describes the dissolution of flat nondisintegrating disks; it is equivalent to the Hixson–Crowell cube root law if a cube root of Eq. 9b can be found. Thus, if its coefficients are related as in $(x + y)^3$, then $(C_4)^3 = 27C_6$ and $(C_4)^2 = -3C_5$. Writing $C_4 = C_1/M_0$ and then substituting C_1 (Eq. 8) and M_0 (Eq. 1) give:

$$C_4 = \frac{2(bH_0 + br_0)}{r_0^2 H_0} \qquad \text{(Eq. 10)}$$

Similarly, C_5 and C_6 can be elaborated. This approach shows that the