Structure and Activity in Molluscicides IV: New Substituted Tetralins with Potential Molluscicidal Effect

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Abstract □ Upon a rational biochemical and biological basis, a series of new compounds related to the tetralin system was synthesized. Biological testing showed their molluscicidal activity at very high dilutions.

Keyphrases □ Tetralins, substituted—synthesized and tested as potential molluscicides, structure–activity relationships □ Molluscicides, potential—synthesis and biological testing of new substituted tetralins, structure–activity relationships □ Structure–activity relationships—substituted tetralins and molluscicidal effect

In a previous article (1), the structure–activity relationship in molluscicides of the phenolic type was discussed. In this group of compounds, certain specific structural features regarding the nature of substituents on the aromatic ring govern the biological activity of the candidate compound. The presence of an enzyme system of the peroxidase type within the snail body was identified through specific systemic reactions and assay measurements for activity in some species of economic importance (2). The biological transformation of the active phenols to the corresponding quinones through this enzymatic system could explain the molluscicidal effectiveness of the former. The latter are highly toxic (3).

DISCUSSION

The main source of energy in snails, required for the metabolism of living cells, is liberated due to oxidation of many compounds. The most important energy-yielding reactions are those of the oxidation–reduction type. Snails, schistosomiasis intermediate hosts, appear to respire aerobically. In typical aerobic respiration, the hydrogen and electrons of substrate are transferred to molecular oxygen through enzymatic protein catalysts (4, 5). Quinones uncouple phosphorylation by diverting electrons from the enzyme to molecular oxygen; *e.g.*, 2,4-dichloronaphthoquinone reacts by binding the enzyme to the quinone molecule through substitution or addition at the double bond, an oxidative effect on sulfhydryl enzymes, or changing the redox potential in some systems.

Pentachlorophenol, a widely used molluscicidal agent, could undergo biological transformation through enzymatic peroxidase catalysis to furnish 2,2′,3,3′,5,5′,6,6′-octachlorobiphenylquinone, a polysubstituted quinone of potential molluscicidal activity (6).

Generally, the molluscicides of the phenolic and salicylanilide types that are now in common use are still unsatisfactory. The phenolics are toxic during applications, not easily handled, and unstable during storage. The salicylanilides exhibit a water-insolubility problem (a major one in molluscicides), and they are immiscible with water during application. Thus, the rate of distribution is not satisfactory.

Because of these considerations, new synthetic work is necessary to obtain efficient molluscicides of higher activity and fewer disadvantages. In this work the synthesis of new compounds that may undergo biological transformations to quinoidal systems is emphasized. Substituted compounds related to tetralin were chosen to be common structural moieties in these agents. These types of compounds could be oxidized to give products related to naphthoquinones, which are known to possess potent molluscicidal activity (3). In addition, it was of concern to include the salicylanilide type of structure, since these compounds exert their molluscicidal activity through a different mechanism. They act through chelation with the important metals (*e.g.*, iron and magnesium) present and necessary for the biological functions within the snail body[1].

Compounds of Structures I–V were desired.

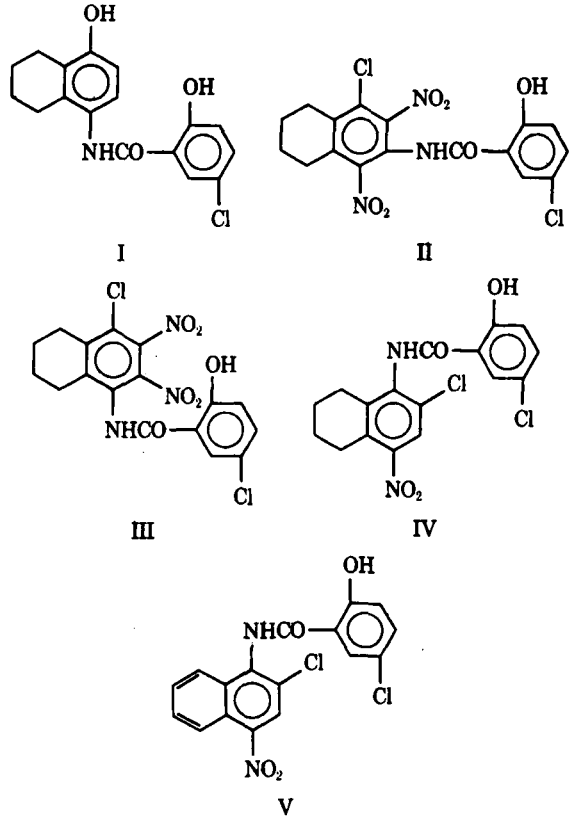
Through the condensation of 5-hydroxy-8-aminotetralin (VI) with 5-chlorosalicylic acid (VII) in the presence of phosphorus pentachloride, 5-hydroxy-8-*N*-(5′-chlorosalicylanilido)tetralin (I) was obtained.

Diazotization of 5-amino-7-nitrotetralin (VIII), followed by subsequent halogenation at the 5-position, reductive acetylation at the 7-position, and nitration at both the 6- and 8-positions, gave 5-chloro-7-amino-6,8-dinitrotetralin (IX). Condensation of VII with IX gave 5-chloro-6,8-dinitro-7-*N*-(5′-chlorosalicylanilido)-tetralin (II).

Chlorination of 8-acetaminotetralin in chloroform gave the 5-chloro derivative (7). Upon nitration (sulfuric acid–nitric acid at −10°), this gave 5-chloro-6,7-dinitro-8-acetaminotetralin (X). Hydrolysis and condensation with VII gave 5-chloro-6,7-dinitro-8-*N*-(5′-chlorosalicylanilido)tetralin (III).

Chlorination of 5-acetamino-8-nitrotetralin (8), followed by hydrolysis, gave 5-amino-6-chloro-8-nitrotetralin (XI). Upon condensation with VII, this gave 5-*N*-(5′-chlorosalicylanilido)-6-chloro-8-nitrotetralin (IV).

Amination of α-nitronaphthalene with hydroxylamine hydrochloride and methanolic potassium hydroxide at 50° gave 4-nitro-1-



[1] This laboratory, to be published.

naphthylamine. Upon acetylation, chlorination, and hydrolysis, this gave 1-amino-2-chloro-4-nitronaphthalene (9). Upon condensation of this amine with VII, the product 1-*N*-(5'-chlorosalicylanilido)-2-chloro-5-nitronaphthalene (V) was obtained.

BIOLOGICAL TESTING

In all tests, the fresh water snails, *Biomphalaria alexandrina*, vector of *Schistosoma mansoni*, were the test animals. Young adult snails (8–11-mm. diameter) were used. Water, freshly boiled to avoid any interference by contaminated chlorine present in tap water (pH 6–6.5), was used as the test medium. Each aquarium was fitted with a glass cover to prevent the accidental dropping of foreign material into test medium. Compounds I–V were tested; they were diluted in volumetric flasks with water to the desired parts per million (p.p.m.). In each test, five snails were used in 200 ml. of the test chemical at each concentration (10, 5, 3, and 1 p.p.m.) and five snails were used as the control in the same volume of water. The exposure period was 24 hr. At the end of each contact period, the snails were removed from the chemically treated water, washed thoroughly, and transferred to fresh water. Food (lettuce) was made available to the snails. On the following day, the mortality rate was determined. Snails that were not fully recovered at the time of the examination were held for future daily observations until death or recovery occurred. Determination of recovery was based on the ability of the snails to move about or cling to the bottom and sides of the glass container.

The concentration effects of different compounds upon *B. alexandrina* (within the 24-hr. exposure period at 25°) are recorded in Table I.

Table I—Effects of Compounds I–V upon Snails of *B. alexandrina* Type

Compound	Concentration, p.p.m. 10	5	3	2	1
I	++[a]	++	++	++	++
II	++	++	++	++	++
III	++	++	++	++	++
IV	++	++	++	++	++
V	++	++	++	++	+

[a] + + = average mortality of 100% and + = average mortality of 80%.

EXPERIMENTAL[1]

5-Hydroxy-8-*N*-(5'-chlorosalicylanilido)tetralin (I)—A mixture of 5-chlorosalicylic acid (VII) (1.06 g.) and 5-hydroxy-8-aminotetralin (VI) (1 g.) (10) in 10 ml. of dry chlorobenzene was refluxed for 10 min. at 160°; then 0.2 g. of phosphorus pentachloride was added to the reaction mixture. Reflux continued for 3 hr., and then the chlorobenzene was steam distilled. The product formed upon cooling was filtered, washed with hot diluted hydrochloric acid (to remove traces of unreacted amine), and then washed with water to give 1.5 g. (79% yield) of I. This compound was purified by dissolving in dilute sodium hydroxide solution and filtering; it was then neutralized with dilute hydrochloric acid, and a dark-brown product formed. Upon recrystallization from ethanol, it melted at 230–232°; IR: 1390 (—OH), 1650 (—CONH—), and 720 (Ar—Cl) cm.$^{-1}$.

Anal.—Calc. for $C_{17}H_{16}ClNO_3$: Cl, 11.16; N, 4.40. Found: Cl, 11.28; N, 4.32.

5-Chloro-7-amino-6,8-dinitrotetralin (IX)—To 8 ml. concentrated sulfuric acid was added 8 g. of 5-chloro-7-acetaminotetralin (11). The mixture was cooled to 0° and nitrated, dropwise, with a nitrating mixture of nitric acid (4 ml.) and concentrated sulfuric acid (12 ml.). The mixture was allowed to stand overnight at room temperature; it was then poured over ice water and the crude dinitro product precipitated. This product was filtered and washed thoroughly with cold water. After drying, it gave 5.2 g. (72% yield) of IX. Upon recrystallization from alcohol, it gave white flakes, m.p. 300°; IR: 1540 (—NO_2), 1680 (—NHCOCH$_3$), and 725 (Ar—Cl) cm.$^{-1}$.

Anal.—Calc. for $C_{12}H_{12}ClN_3O_5$: C, 45.94; H, 3.83; Cl, 11.32; N, 13.39. Found: C, 45.94; H, 4.05; Cl, 11.41; N, 13.41.

The acetamino product was then submitted to acid hydrolysis (hydrochloric acid–ethanol) to give the free amine IX. Due to difficulties encountered in the preparation of an analytical sample, the crude amine, m.p. 162–165°, was used for the condensation reaction in the following step.

5-Chloro-6,8-dinitro-7-*N*-(5'-chlorosalicylanilido)tetralin (II)—A mixture of VII (1.27 g.) and the amine IX (2 g.) was dissolved in 20 ml. of chlorobenzene and heated to 160°. Then 0.4 g. of phosphorus pentachloride was added during reflux, which continued for 2 hr. The solvent was removed through steam distillation. The product was filtered, washed with sodium carbonate solution and then with water, and dried to give 2.2 g. of II (yield 70%). After recrystallization from alcohol, it melted at 194–196°.

Anal.—Calc. for $C_{17}H_{13}Cl_2N_3O_6$: C, 48.00; H, 3.06; Cl, 16.47; N, 9.88. Found: C, 48.46; H, 3.13; Cl, 16.67; N, 9.50.

5-Chloro-6,7-dinitro-8-acetaminotetralin (X)—A mixture of 5-chloro-8-acetaminotetralin (8) (2.36 g.) and 4 ml. of concentrated sulfuric acid was cooled to −10° and then nitrated by the addition of a cold mixture of nitric acid (2 ml.) and concentrated sulfuric acid (6 ml.). The mixture was allowed to stand overnight at room temperature and was then poured over ice. The formed yellow precipitate was filtered and washed with water. After drying, it gave 2.68 g. (82% yield) of X. Upon recrystallization from ethanol, it gave yellow needles, m.p. 250–251°; IR: 1550 (—NO_2), 1685 (—NHCOCH$_3$), and 725 (Ar—Cl) cm.$^{-1}$.

Anal.—Calc. for $C_{12}H_{12}ClN_3O_5$: C, 45.93; H, 3.83; Cl, 11.32; N, 13.39. Found: C, 45.97; H, 3.92; Cl, 11.18; N, 13.19.

5-Chloro-6,7-dinitro-8-aminotetralin—A mixture of X (1.5 g)., ethanol (30 ml.), and concentrated hydrochloric acid (8 ml.) was refluxed for 5 hr., cooled, and poured over ice water. The precipitate was collected, washed with water, and dried to give 1.06 g. of the free amine. After recrystallization from dilute ethanol, it melted at 140–142°.

Anal.—Calc. for $C_{10}H_{10}ClN_3O_4$: C, 44.28; H, 3.69; Cl, 13.10; N, 15.44. Found: C, 44.38; H, 3.73; Cl, 13.20; N, 15.23.

5-Chloro-6,7-dinitro-8-*N*-(5'-chlorosalicylanilido)tetralin (III)—The condensation between the above-mentioned free amine (1 g.) and the acid VII (0.64 g.) was carried out as described for II. The yield (75%) was 1.2 g. After recrystallization from benzene–*n*-hexane, it melted at 187–190°.

Anal.—Calc. for $C_{17}H_{13}Cl_2N_3O_6$: C, 48.00; H, 3.06; N, 9.88. Found: C, 48.26; H, 3.13; N, 9.86.

5-Amino-6-chloro-8-nitrotetralin (XI)—In glacial acetic acid (35 ml.) was chlorinated 9 g. of 5-acetamino-8-nitrotetralin (8) at 100° with a dry stream of chlorine gas for about 15 min. After cooling, the formed yellow precipitate was collected, washed with water, and dried. It weighed 6 g. (90% yield). Recrystallization from ethanol gave white needles, m.p. 181–183°.

Anal.—Calc. for $C_{12}H_{13}ClN_2O_2$: C, 53.53; H, 4.84; Cl, 13.22; N, 10.43. Found: C, 52.97; H, 4.83; Cl, 13.27; N, 10.44.

The free amine XI was obtained through acid hydrolysis of this product. It was recrystallized as yellow crystals (from ethanol), m.p. 110–112°.

Anal.—Calc. for $C_{10}H_{11}ClN_2O_5$: C, 52.98; H, 4.86; Cl, 15.67; N, 12.36. Found: C, 53.11; H, 4.92; Cl, 16.05; N, 12.22.

5-*N*-5'-(Chlorosalicylanilido)-6-chloro-8-nitrotetralin (IV)—The same method of condensation between the free amine (XI) (1 g.) and the acid VII (0.76 g.) was followed as described for II. The product IV, 1.2 g. (70% yield), was recrystallized from benzene–petroleum ether, m.p. 156–158°.

Anal.—Calc. for $C_{17}H_{14}Cl_2N_2O_4$: Cl, 18.42; N, 7.37. Found: Cl, 18.43; N, 7.43.

1-*N*-(5'-Chlorosalicylanilido)-2-chloro-5-nitronaphthalene (V)—The condensation described for II was followed for the acid VII (0.78 g.) and 1-amino-2-chloro-4-nitronaphthalene (1 g.) (9). The product V, 1.3 g. (75% yield), was recrystallized from benzene–petroleum ether, m.p. 210–212°.

Anal.—Calc. for $C_{17}H_{10}Cl_2N_2O_4$: C, 54.26; H, 2.66; Cl, 18.62; N, 7.45. Found: C, 53.98; H, 2.68; Cl, 18.51; N, 7.41.

[1] Melting points were taken in open capillary tubes with a Gallenkamp melting-point apparatus and are uncorrected. The IR spectra were recorded with a Carl-Zeiss Infracord spectrophotometer, model UR 10. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., and the Microanalytical Laboratory, National Research Center, Cairo, Egypt.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 1, 1972, from the *National Research Center, Dokki, Cairo, Egypt.*

Accepted for publication August 3, 1972.

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Anticonvulsant Properties of Mannich Base Derivatives of 2-Phenylsuccinimide III

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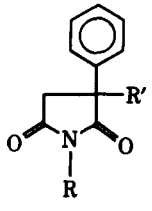
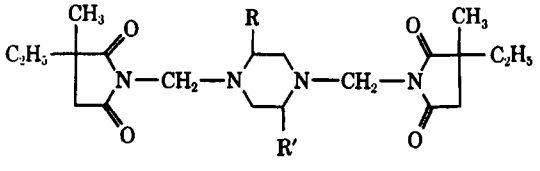
Abstract □ Several Mannich base derivatives of 2-phenylsuccinimide were synthesized and screened for anticonvulsant activity. All products were evaluated by maximal electroshock seizure and pentylenetetrazol seizure threshold tests.

Keyphrases □ 2-Phenylsuccinimide, Mannich base derivatives—synthesis, screened for anticonvulsant properties □ Anticonvulsants, potential—synthesis and screening of Mannich base derivatives of 2-phenylsuccinimide

The preceding papers (1, 2) of this series reported the preparation and anticonvulsant properties of several derivatives of phensuximide[1], *N*-methyl-2-phenylsuccinimide (I). One series of compounds (II), consisting of C-Mannich base derivatives of I, proved interesting since several members were more effective than the parent molecule in eliminating the tonic extensor component of electroshock seizures.



I: R = CH_3, R′ = H
II: R = CH_3, R′ = *tert*-aminomethyl
III: R = *tert*-aminomethyl, R′ = H



IV: R = CH_3, R′ = H
V: R = CH_3, R′ = CH_3

Some researchers (3, 4) reported the preparation of mono- and bis-Mannich bases of succinimides (III–V). These compounds were shown to possess significant anticonvulsant properties.

In view of the foregoing, it was of interest to prepare for evaluation the *N*,2-bis-Mannich bases of 2-phenylsuccinimide (Compounds 1–6 in Table I). The corresponding mono bases (Compounds 7–12 in Table I) were also prepared for comparison purposes. All products were subjected to preliminary pharmacological screening, and the results are presented in Tables II and III.

EXPERIMENTAL[2]

2-Phenylsuccinimide—The title compound was prepared from 2-phenylsuccinic acid and concentrated ammonium hydroxide according to Miller and Long's (5) procedure. It was obtained as a white solid in a yield of 78%, m.p. 79–81° [lit. (6) m.p. 90°].

Preparation of Bis-Mannich Bases (Table I)—To 0.05 mole of the appropriate amine, 5.0 ml. of 40% formalin (2.0 g., 0.067 mole formaldehyde) was added slowly with cooling. This mixture was added immediately to 4.4 g. (0.025 mole) of 2-phenylsuccinimide in 50 ml. of 95% ethanol, after which it was heated at reflux for various periods of time (Table I). The solvent was removed *in vacuo*, leaving either a solid or an oil, which usually solidified upon standing. Occasionally, extraction of the oil with petroleum ether and evaporation of the solvent *in vacuo* yielded solid material. If this procedure failed, an ethereal solution of the oil was washed with 10% NaOH and then with water until the washings were neutral to litmus. The solution was dried (magnesium sulfate), and the ether was removed *in vacuo* to give a solid product.

[1] Milontin, Parke, Davis and Co., Detroit, MI 48232

[2] All melting points were determined on a Thomas-Hoover melting-point apparatus and are corrected. IR spectra were obtained on a Beckman IR-8 spectrophotometer using KBr pellets. The two carbonyl stretching bands, which are characteristic of imides, were present in all products. NMR spectra were obtained on a Varian Associates A-60A spectrometer and are consistent with the assigned structures. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del. Intermediates used in this work are available commercially unless specified otherwise.