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Synthesis of Substituted 1-Hydroxy-2-naphthanilides as Potential Cestodicidal Agents[1]

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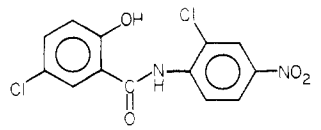
A series of substituted 1-hydroxy-2-naphthanilides 4–14 has been synthesized by treating 1-hydroxy-2-naphthoic acids **2** with substituted anilines **3**. The nitronaphthanilides, on reduction and subsequent treatment with thiophosgene, gave the corresponding substituted 2-naphthanilide isothiocyanates **30–33**. Substitution of the chlorine of **8** by various cyclic amines gave 3′-nitro-4′-substituted 1-hydroxy-2-naphthanilides **15–21**. Various 3-aryl-4-oxo-2,3-dihydro-1,3-naphthoxazine-2-thiones **34–43** and 3-aryl-2,4-dioxo-2,3-dihydro-1,3-naphthoxazines **44–51** have been prepared by reacting the corresponding naphthanilides with thiophosgene and ethyl chloroformate, respectively. All the compounds were tested for their cestodicidal activity against *Hymenolepis nana* infection in rats; **30** was found to be the most active compound of the series, showing 100% clearance of infection at a single oral dose of 7.5 mg/kg.

During the course of structure–activity relationship studies carried out in the analogues of 2′,5-dichloro-4′-nitrosalicylanilide (niclosamide, **1**),[2] we have reported the



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synthesis and biological activity of a large number of substituted salicylanilides of which many showed powerful cestodicidal activity.[3-5] In a further probe in this direction, the synthesis of various substituted 1-hydroxy-2-naphthanilides **4–33** and some of their cyclic analogues, viz., 3-aryl-4-oxo-2,3-dihydro-1,3-naphthoxazine-2-thiones **34–43** and 3-aryl-2,4-dioxo-2,3-dihydro-1,3-naphthoxazines **44–51**, has been undertaken. All these compounds have been screened for their cestodicidal activity against *Hymenolepis nana* in rats, and the results are reported in this communication.

Chemistry. Condensation of substituted 1-hydroxy-2-naphthoic acids **2** with different mono- and disubstituted anilines **3** in the presence of PCl_3 in refluxing xylene or toluene gave substituted 1-hydroxy-2-naphthanilides **4–14**.[6,7] The nitronaphthanilides, thus obtained, were reduced to the corresponding aminonaphthanilides **22–29** which were smoothly converted into the respective naphthanilide isothiocyanates **30–33** by treatment with thiophosgene. Various 3′-nitro-4′-substituted 1-hydroxy-2-naphthanilides **15–21** were prepared by treating 4′-chloro-3′-nitro-1-hydroxy-2-naphthanilide (**8**) with different cyclic amines. The synthesis of 3-aryl-4-oxo-2,3-dihydro-1,3-naphthoxazine-2-thiones **34–43** and 3-aryl-2,4-dioxo-2,3-dihydro-1,3-naphthoxazines **44–51** was accomplished by treating the corresponding naphthanilides with thiophosgene and ethyl chloroformate, respectively, in the presence of triethylamine[8] (see Scheme I).

Biological Activity. All the compounds were tested for their in vivo cestodicidal activity against *H. nana* infection in rats by the technique of Steward,[9] and the results are summarized in Tables I and II. The compounds were given orally at dosages of 250, 100, 50, 13, and 7.5 mg/kg, using three rats per experimental group. For all the control experiments, **1** was used as the standard drug. The active compounds of this series were **14** and **30**, showing 100% clearance of worm load at a single oral dose of 13 and 7.5 mg/kg, respectively, while **10** was equipotent to **1**. Compounds **12**, **31**, and **32** were active at a dose of 100 mg/kg, and **11**, **13**, and **33** showed activity at 250 mg/kg. The other compounds were inactive at 250 mg/kg.

In view of the marked cestodicidal activity exhibited by **30**, its efficacy was assessed against a related cestode species *Hymenolepis diminuta* in rats and also against *Taenia* sp. in naturally infected dogs. A single oral dose of 10 mg/kg of the compound caused 100% reduction of worm load in both of the above-mentioned hosts. The standard compound **1** produced similar results when given orally at a dose of 50 mg/kg.[10] The detailed toxicity studies of **30** in rats and mice have also been carried out. At a dose of 5 g/kg given orally or intraperitoneally to uninfected rats, **30** was found to be tolerated well without any mortality. The young rats infected with *H. nana* also tolerated 1 g/kg of **30**. The acute toxicity experiments carried out on *Mastomys natalensis* and dogs showed **30** to be safe when given orally or intraperitoneally. Further chronic toxicity studies in rats, dogs, and monkeys are in progress.

The cestodicidal testing results of **4–51** establish a definite structure–activity relationship. Among various

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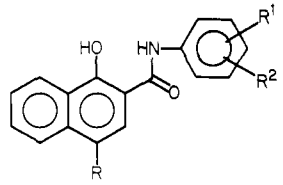
Table I



compd no.	R	R¹	R²	formula[a]	mp, °C	yield, %	cestodicidal act., MED[b] in mg/kg
1	niclosamide						50
4	H	2-Cl	4-Cl	$C_{17}H_{11}Cl_2NO_2$	174	67	i[c]
5	H	2-Cl	4-NO_2	$C_{17}H_{11}ClN_2O_4$	233	72	i
6	H	H	4-NO_2	$C_{17}H_{12}N_2O_4$	225[d]	70	i
7	H	2-NO_2	H	$C_{17}H_{12}N_2O_4$	190[d]	69	i
8	H	4-Cl	3-NO_2	$C_{17}H_{11}ClN_2O_4$	243	70	i
9	H	4-Cl	2-NO_2	$C_{17}H_{11}ClN_2O_4$	225	62	i
10	Br	2-Cl	4-Cl	$C_{17}H_{10}BrCl_2NO_2$	190	65	50
11	Br	4-Cl	2-NO_2	$C_{17}H_{10}BrClN_2O_4$	182	63	250
12	Br	H	4-NO_2	$C_{17}H_{11}BrN_2O_4$	250	68	100
13	Br	2-NO_2	H	$C_{17}H_{11}BrN_2O_4$	174	67	250
14	Br	2-Cl	4-NO_2	$C_{17}H_{10}BrClN_2O_4$	224	70	13
15	H	3-NO_2	4-c-NC_4H_8	$C_{21}H_{19}N_3O_4$	192	90	i
16	H	3-NO_2	4-c-NC_5H_{10}	$C_{22}H_{21}N_3O_4$	205	87	i
17	H	3-NO_2	4-c-NC_5H_9-3′-CH_3	$C_{23}H_{23}N_3O_4$	173	81	i
18	H	3-NO_2	4-c-NC_5H_9-4′-CH_3	$C_{23}H_{23}N_3O_4$	215	91	i
19	H	3-NO_2	4-c-$N(CH_2CH_2)_2NCH_3$	$C_{22}H_{22}N_4O_4$	236	80	i
20	H	3-NO_2	4-c-$N(CH_2CH_2)_2NC_6H_5$	$C_{27}H_{24}N_4O_4$	202	85	i
21	H	3-NO_2	4-c-$N(CH_2CH_2)_2O$	$C_{21}H_{19}N_3O_5$	227	84	i
22	H	2-Cl	4-NH_2	$C_{17}H_{13}ClN_2O_2$	200	83	i
23	H	H	4-NH_2	$C_{17}H_{14}N_2O_2$	178	78	i
24	H	2-NH_2	H	$C_{17}H_{14}N_2O_2$	210	80	i
25	H	4-Cl	3-NH_2	$C_{17}H_{13}ClN_2O_2$	212	70	i
26	H	4-Cl	2-NH_2	$C_{17}H_{13}ClN_2O_2$	206	80	i
27	Br	2-NH_2	H	$C_{17}H_{13}BrN_2O_2$	172	76	i
28	Br	H	4-NH_2	$C_{17}H_{13}BrN_2O_2$	190	67	i
29	Br	2-Cl	4-NH_2	$C_{17}H_{12}BrClN_2O_2$	180	80	i
30	H	2-Cl	4-NCS	$C_{18}H_{11}ClN_2O_2S$	180	72	7.5
31	H	H	4-NCS	$C_{18}H_{12}N_2O_2S$	172	78	100
32	H	4-Cl	3-NCS	$C_{18}H_{11}ClN_2O_2S$	180	78	100
33	Br	2-Cl	4-NCS	$C_{18}H_{10}BrClN_2O_2S$	175	76	250

[a] All the compounds were analyzed for C, H, and N, and the results were within ±0.4% of the theoretical values. [b] Minimum effective dose given orally to clear 98–100% of *H. nana* infection in rats. [c] Inactive at 250 mg/kg. [d] See ref 7.

structural requirements the presence of pharmacophores with electron-pulling ability in naphthalene (**10–14** and **33**) and benzene (**30–32**) rings, situated preferably at positions 4, 2′, and 4′, respectively, is the most essential parameter for optimal cestodicidal activity. However, in all cases the presence of a phenolic OH, responsible for introducing hydrogen-bonding ability in the molecule, is required. This relationship is proven by the fact that introduction of electron-donating groups in the benzene ring (**15–29**) or incorporation of phenolic oxygen in cyclic structures (**34–51**) causes loss of activity in the molecules.

Experimental Section

All the compounds were checked routinely by IR on Perkin-Elmer 137, 337, or 177 Infracord spectrophotometers. Melting points were taken in a sulfuric acid bath and are uncorrected.

4-Bromo-1-hydroxy-2-(2-chloro-4-nitro)naphthanilide (14). PCl_3 (0.6 mL, 0.006 mol) was added dropwise to a refluxing solution of 4-bromo-1-hydroxy-2-naphthoic acid (**2**, R = Br, 4 g, 0.015 mol) and 2-chloro-4-nitroaniline (2.6 g, 0.015 mol) in dry xylene (80 mL). Refluxing was continued until HCl evolution ceased (~1 h). The reaction mixture was cooled and the excess of PCl_3 decomposed by adding water. Xylene was removed by steam distillation and the residual solid crystallized from THF–water: yield 4.2 g (70%).

Other naphthanilides, **4–13**, were prepared in a similar manner.

3′-Nitro-4′-pyrrolidyl-1-hydroxy-2-naphthanilide (15). A mixture of **8** (3.4 g, 0.01 mol) and pyrrolidine (0.85 g, 0.012 mol) in dry pyridine (30 mL) was refluxed for 24 h. Solvent was removed from the reaction mixture and the residue washed with 0.5 N HCl (25 mL). The resulting solid was dried and crystallized from acetone: yield 3.4 g (90%).

Compounds **16–21** were prepared using the same procedure.

4-Bromo-1-hydroxy-2-(2-chloro-4-amino)naphthanilide (29). A suspension of **14** (4.2 g, 0.01 mol) in THF (100 mL) was shaken with Raney nickel (3 g) and hydrogen at 2.5 kg/cm² in a Parr hydrogenator for 24 h. The catalyst was filtered off, the solvent was removed in vacuo, and the solid which separated was crystallized from THF–water: yield 3.1 g (80%).

Other naphthanilides, **22–28**, were prepared in the same way from the corresponding nitro compounds.

1-Hydroxy-2-(2-chloro-4-isothiocyanato)naphthanilide (30). A solution of thiophosgene (0.88 mL, 0.01 mol) in dry acetone (10 mL) was added dropwise to a stirred solution of **22** (3.2 g, 0.01 mol) in dry acetone (100 mL) and the reaction mixture stirred for 6 h at room temperature. The solvent was removed from the reaction mixture and the separated solid filtered to give 3.5 g of crude **30** which was crystallized from acetone: yield 3 g (85%).

Compounds **31–33** were synthesized similarly.

3-Aryl-4-oxo-2,3-dihydro-1,3-naphthoxazine-2-thiones 34–43. A general procedure for the synthesis of naphthoxazine-2-thiones (Table II) is typified by the preparation of 3-(2,4-dichlorophenyl)-2,3-dihydro-4-oxo-1,3-naphthoxazine-2-thione (**34**). A solution of thiophosgene (0.88 mL, 0.01 mol) in dry $CHCl_3$ (20 mL) was added dropwise to a stirred suspension of **4** (3.32 g, 0.01 mol) and triethylamine (2.8 mL, 0.02 mol) in dry $CHCl_3$ (50 mL) at 0 °C. Stirring was continued for 4 h at

Scheme I

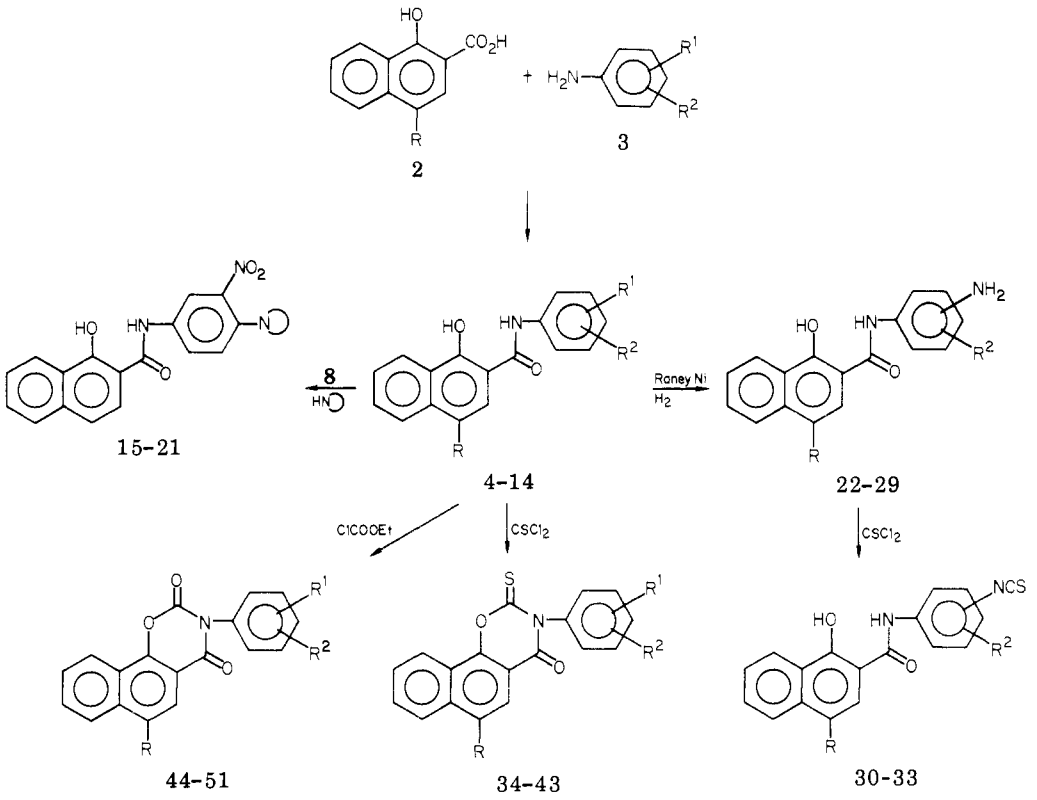
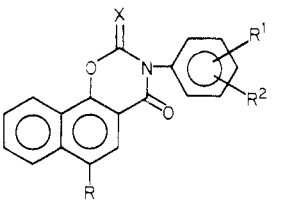


Table II[a]



compd no.	X	R	R^1	R^2	formula[b]	mp, °C	yield, %
34	S	H	2-Cl	4-Cl	$C_{18}H_9Cl_2NO_2S$	170	63
35	S	H	2-Cl	4-NO_2	$C_{18}H_9ClN_2O_4S$	190	65
36	S	H	H	4-NO_2	$C_{18}H_{10}N_2O_4S$	250	67
37	S	H	2-NO_2	H	$C_{18}H_{10}N_2O_4S$	185	62
38	S	H	4-Cl	3-NO_2	$C_{18}H_9ClN_2O_4S$	210	68
39	S	H	4-Cl	2-NO_2	$C_{18}H_9ClN_2O_4S$	175	64
40	S	Br	2-Cl	4-NO_2	$C_{18}H_8BrClN_2O_4S$	217	65
41	S	Br	H	4-NO_2	$C_{18}H_9BrN_2O_4S$	226	70
42	S	Br	2-NO_2	H	$C_{18}H_9BrN_2O_4S$	270	68
43	S	Br	4-Cl	2-NO_2	$C_{18}H_8BrClN_2O_4S$	296	60
44	O	H	2-Cl	4-Cl	$C_{18}H_9Cl_2NO_3$	238	59
45	O	H	2-Cl	4-NO_2	$C_{18}H_9ClN_2O_5$	260	68
46	O	H	H	4-NO_2	$C_{18}H_{10}N_2O_5$	158	62
47	O	H	2-NO_2	H	$C_{18}H_{10}N_2O_5$	112	67
48	O	H	4-Cl	3-NO_2	$C_{18}H_9ClN_2O_5$	275	61
49	O	Br	2-Cl	4-Cl	$C_{18}H_8BrCl_2NO_3$	140	70
50	O	Br	2-Cl	4-NO_2	$C_{18}H_8BrClN_2O_5$	122	72
51	O	Br	4-Cl	2-NO_2	$C_{18}H_8BrClN_2O_5$	150	68

[a] All the compounds were found to be inactive when given orally at a dose of 250 mg/kg against *H. nana* infection in rats. [b] All the compounds were analyzed for C, H, and N, and the results were within ±0.4% of the theoretical values.

room temperature and then the mixture refluxed for 0.5 h. The solvent was washed successively with water (20 mL), 0.5 N NaOH (20 mL), and water (10 mL) and dried (Na_2SO_4), the solvent removed, and the residue crystallized from acetone–water: yield 2.4 g (63%).

3-Aryl-2,4-dioxo-2,3-dihydro-1,3-naphthoxazines 44–51. Various 2,4-dioxonaphthoxazines listed in Table II were prepared by the following method described for 3-(2,4-dichlorophenyl)-2,4-dioxo-2,3-dihydro-1,3-naphthoxazine (**44**). Ethyl chloroformate (0.4 mL, 0.004 mol) in dry THF (20 mL) was added dropwise to a stirred solution of **4** (1.3 g, 0.004 mol) in dry THF (60 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and then refluxed for 3 h. The solvent was removed from the reaction mixture, and the residue was washed with water and crystallized from ethanol: yield 0.75 g (59%).

Cestodicidal Screening. Newly weaned male rats (25–30 g) of the University of Freiburg strain were infected by feeding them with 200 viable ova of *H. nana*. On day 15 after intubation of

viable ova, rats found positive for *H. nana* ova in feces were treated after being starved overnight. Initially a single dose of 250 mg/kg of the compound was given orally to three animals and three were kept as controls. All animals including the controls were again starved overnight before being sacrificed on day 3 posttreatment. The small intestine of each animal was removed separately and washed, and the worms were collected and scored. The minimum dose of the compound bringing down the score to 10% of the control or less was considered as the minimum effective dose.

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(1) Communication No. 2420 from the Central Drug Research Institute, Lucknow.
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Book Reviews

Chemical Transmission in the Mammalian Central Nervous System. Edited by C. H. Hockman and D. Bieger. University Park Press, Baltimore, Md. 1976. x + 442 pp. $34.50.

According to their preface, the editors of this volume have attempted to produce a "systematic account of the various substances which qualify as transmitters at mammalian central nervous system synapses" in a "comprehensive yet manageable volume that would encompass biochemical, pharmacological, physiological, and behavioral aspects of neural transmission". It seems extremely doubtful that such an objective is attainable in a single volume. (Consider that the "Handbook of Psychopharmacology", which covers largely the same material, runs to nine volumes, excluding clinical chapters.) Certainly "Chemical Transmission in the Mammalian Central Nervous System" does not adequately fulfill this goal. For one thing, the treatment of different "putative" transmitters is extremely uneven. The two chapters on dopamine and serotonin comprise half of the book, leaving the remaining pages to four chapters on acetylcholine, norepinephrine, and inhibitory and excitatory amino acids and an introductory chapter on the relationship between the structure and function of synapses. There is no discussion of substance P or enkephalin, perhaps the most hotly debated transmitter candidates during the past several years. Furthermore, the material which is discussed differs radically for different transmitters. The chapter by Marczynski on serotonin is concerned primarily with the role of serotonin in mediating various behavioral and physiological processes (e.g., sleep, thermoregulation, gonadotropin secretion, and sexual behavior), while the chapter by Phillis on acetylcholine concentrates on the effects of acetylcholine applied iontophoretically near identified neurons in the brain and spinal cord.

In terms of reviewing the evidence for particular substances being transmitters, perhaps the most successful chapter is that by Johnston. In it he presents a concise summary of the evidence that γ-aminobutyric acid (GABA), glycine, and taurine are inhibitory transmitters in the central nervous system. Johnston considers the transmitter roles of these compounds to be "established", "highly probable", and "possible", in that order. He reviews data on their distribution, metabolism, uptake, release, and postsynaptic actions and discusses related drugs which seem to act at the same receptor sites as these amino acids. One of the pieces of evidence often cited to support the argument that a compound is a neurotransmitter in a region of the central nervous system is the demonstration of a high-affinity uptake system for the compound in that region (see Chapters 2, 3, and 5–7). In this regard, it is important to remember as pointed out here that not only neurons but also glial cells possess such an uptake system for GABA and glycine. In fact, glial cells take up GABA in areas of the nervous system, such as in sympathetic ganglia, where there is no suggestion of the existence of GABA-ergic nerves.

While this book contains some interesting chapters, it would have been a more useful volume if the authors had agreed on a common set of guidelines for approaching the various transmitter candidates.

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Neurotoxicology. Volume 1. Edited by Leon Roizin, Hirotsugu Shiraki, and Nenad Grčevič. Raven Press, New York, N.Y. 1977. xxviii + 658 pp. 18 × 26 cm. $55.00.

This volume is an updated collection of papers from the First International Symposium on Neurotoxicology, held in New York City during May 16–19, 1976. There are 61 articles by 129 contributors, covering such diverse topics as tranquilizers; narcotics and anesthetics; stimulants, antidepressants, and hallucinogens; heavy and trace metals; antimicrobials; industrial chemicals; pesticides; and anorexic agents. A final section on pathogenic considerations includes a variety of papers not fitting conveniently into one of the above chemical categories.

Since the book is a symposium volume rather than a text or treatise, there is a lack of integration of topics, and coverage is uneven in depth and extent. For example, there are 12 articles on metals but only two on pesticides. The chapter on industrial neuropathies was disappointingly short, and the article on TOCP neuropathy mentioned only briefly the current research on neurotoxic esterase as the primary biochemical target in the development of the lesion. The important question of the relationship of drugs or environmental agents to neurologic disease is well represented by several articles dealing with clioquinol intoxication and subacute myeloopticoneuropathy (SMON) and an interesting account of the possible role of aluminum in senile and presenile dementias.

Researchers having the common aim of seeking to understand adverse effects of chemical agents on the nervous system represent an incredible diversity of backgrounds and approaches. Yet, because of this similarity of purpose, a certain melding has begun to take place. Neurotoxicology is beginning to be recognized as a distinct field of investigation. The appearance of this book should aid in that recognition. The major emphasis in this volume