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(Nitroethenyl)salicylic Acid Anilides and Related Substances, a New Group of Molluscicidal and Microbicidal Compounds

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5-(2-Nitroethenyl)salicyloyl chloride (**2b**) condenses with anilines affording the anilides **3a–h**. The compound **3a** reacts with isocyanates to give the corresponding carbamates **5a–c**, whereas at higher temperatures the anilide **3a** as well as the acid **2a** give the same benzoxazinedione **4a** which affords 5-formyl-*N*-methylsalicylamide (**6**) upon treatment with alkali. **3a** and **3d** react with thionyl chloride to give the corresponding 2-chloro-5-(2-nitroethenyl)benzanilides **8a** and **8b**. Spectral features of the compounds are discussed and their molluscicidal and microbicidal activities are presented.

(Nitroethenyl)salicylsäureanilide und verwandte Substanzen, eine neue Gruppe molluskizider und mikrobizider Verbindungen

5-(2-Nitroethenyl)salicylsäurechlorid (**2b**) wird mit Anilinen zu den Aniliden **3a–h** kondensiert. Mit Isocyanaten liefert **3a** die entsprechenden Carbamate **5a–c**, dagegen ergibt sowohl das Anilid **3a** als auch die Säure **2a** bei höheren Temperaturen dasselbe Benzoxazindion **4a**. Dieses bildet bei der Behandlung mit Alkali 5-Formyl-*N*-methylsalicylamid (**6**). Mit Thionylchlorid reagieren **3a** und **3d** zu den entspechenden 2-Chlor-5-(2-nitroethenyl)-benzaniliden **8a** bzw. **8b**. Die spektroskopischen Merkmale der Verbindungen werden diskutiert, und über die molluskiziden und mikrobiziden Eigenschaften wird berichtet.

Several synthetic organic compounds proved to be toxic to aquatic snails and some of these compounds are now used as molluscicides in prevention of parasitic diseases. An important group of molluscicides are the salicylanilides, the most active member of which turned out to be 2′,5-dichloro-4′-nitrosalicylanilide (**1**) which is now used successfully in combating snails for control of schistosomiasis in endemic areas[1]. On the other hand, it has been shown in our laboratory that some aryl- and heteroaryl-substituted nitroalkenes possess molluscicidal properties characterized by a well defined knock-down effect[2].

In the light of the aforementioned reports and in the course of our program in search of new molluscicides, it was interesting to construct molecules incorporating both the salicylanilide and nitroethenyl moieties in an attempt to obtain compounds which possibly would combine the biological properties of both or synergize any of these activities.

For this purpose, 5-formylsalicylic acid was condensed with nitromethane in acetic acid in the presence of *n*-butylamine[*], to give 5-(2-nitroethenyl)salicylic

[*] This procedure proved to be superior to that previously described using ammonium acetate in acetic acid[3].

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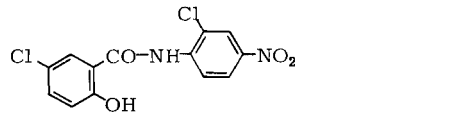
acid (**2a**) in good yield. Refluxing the latter with freshly distilled thionyl chloride, then treating the formed acid chloride **2b** with the appropriate aniline in the presence of triethylamine at low temperature gave the 5-(2-nitroethenyl)salicylanilides **3a–h**.



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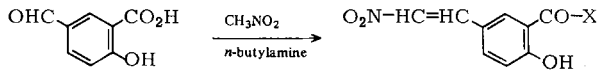
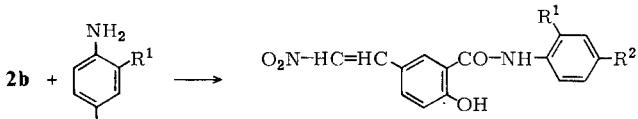


2a: X = OH
2b: X = Cl



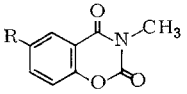
3a-h

3	a	b	c	d	e	f	g	h
R^1	H	Cl	H	Cl	Cl	CF_3	H	H
R^2	H	H	Cl	NO_2	Cl	H	F	$COCH_3$

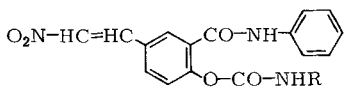
The structure of the compounds **3** is supported by their spectral features in addition to elemental analysis. Thus, the IR spectra show bands in the 3410–3120-cm^{-1} region due to NH and OH stretching vibrations, and C=O bands in the 1650–1640-cm^{-1} region, as well as absorption in the 970-cm^{-1} region due to *trans*-ethylenic, out-of-plane hydrogen deformations. The UV spectra are largely dependent on the solvent used. Thus, when the spectrum of **3a** was determined in benzene, it exhibits one main band (λ_{max} = 335 nm, ε = 15000) which is mainly similar to that of nitrostyrene itself. However, this band is red-shifted (λ_{max} = 345 nm, ε = 15800) accompanied by the appearance of a longer wave absorption (λ_{max} = 430 nm, ε = 10800) if the spectrum is determined in ethanol. The spectrum of **3b** is mainly similar to that of **3a** and shows a similar strong long-wave absorption. This spectral pattern in ethanolic solution is presumably due to a larger contribution of resonance-stabilized dipolar structures involving the hydroxy group and nitroethenyl side chain. The NMR spectrum of **3**, exemplified by **3a** and **b**, exhibits the downfield doublet of doublets centered at δ = 8 and 8.2 for the coupled olefinic protons, similar to nitrostyrene itself.

3a reacts with methyl isocyanate in boiling dioxane under base catalysis to give 3-methyl-6-(2-nitroethenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**4a**) in good yield. However, when the reaction with the isocyanate is performed at lower temperature, the open-chain *N*-methylcarbamate **5a** is readily obtained. *n*-Butyl and isopropyl isocyanate react similarly with **3a** to give the corresponding *N*-alkylcar-

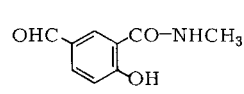
bamates **5b** and **c**. The dione **4a** is also readily obtained by reacting the parent 5-(2-nitroethenyl)salicylic acid (**2a**) with methyl isocyanate*).



4a: R = $CH{=}CHNO_2$
4b: R = H



5a: R = CH_3
5b: R = C_4H_9
5c: R = $CH(CH_3)_2$



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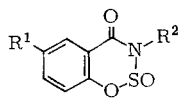
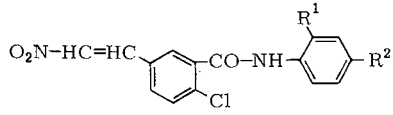


7	**a**	**b**
R^1	$CH{=}NHNO_2$	H
R^2	C_6H_5	CH_3



8	**a**	**b**
R^1	H	Cl
R^2	H	NO_2

The cyclic dione structure **4a** is supported by elemental analysis and by mass as well as IR spectra. The latter exhibits two bands at 1770 and 1700 cm^{-1} for the cyclic carbamoyl and amide carbonyl groups. The UV spectrum shows one main band (λ_{max} = 300 nm, ε = 6700; methanol) which is similar to that of **4b**.

The open-chain carbamate structure assigned to **5** is supported by their IR spectra which exhibit two bands in the 3370- and 3280-cm^{-1} regions due to NH stretching vibrations, as well as bands in the 1730- and 1660-cm^{-1} region for the carbamoyl and amide carbonyl groups, respectively, in addition to strong absorption in the 970-cm^{-1} region for the *trans*-ethylenic out-of-plane hydrogen deformations. The UV spectral pattern of **5** in methanolic solution, exemplified by **5a**, is mainly similar to that of the parent anilide, exhibiting two long-wave bands [λ_{max} (ε) = 350 (16100), 425 nm (11400)].

The dione **4a**, upon treatment with alkali, affords 5-formyl-*N*-methylsalicylamide (**6**). Formation of **6** presumably proceeds with cleavage of the nitroethenyl side chain regenerating the formyl group and attack at C-2 followed by decarboxylation to give the amide.

The IR spectrum of **6** exhibits OH, formyl-C=O, and amide-C=O bands at 3370, 1680, and 1650 cm^{-1}, respectively. The UV spectrum shows two main bands [λ_{max} (ε) = 275 (13300), 310 nm (11300); methanol].

In an attempt to obtain the corresponding benzoxathiazinone **7a** by reacting the anilide **3a** with thionyl chloride, as described for the preparation of **7b** from salicylamide itself[5], 2-chloro-5-(2-nitroethenyl)benzanilide (**8a**) was produced in good yield, but no benzoxathiazinone could be isolated. In a similar manner, from **3d** the 2′-chloro-4′-nitro-5-(2-nitroethenyl)benzanilide (**8b**) could be prepared. The IR spectra of **8** lack OH and include NH bands in the 3200-cm^{-1} region and

*) The parent benzoxazinedione **4b** has been previously prepared by the action of methyl isocyanate on methyl salicylate[4], however, no spectral data have been given.

C=O absorption in the 1630-cm^{-1} region. Apparently, the presence of the strong electron withdrawing nitroethenyl side chain in **3** is mainly responsible for enhancing this interesting replacement of the phenolic hydroxy group by chlorine. However, in contrast to the anilides, the hydroxy group of the parent acid **2a** proved to be resistant to this substitution when similarly treated with thionyl chloride presumably due to intramolecular hydrogen bond involving the hydroxy and carboxy groups.

Molluscidial activity

The toxicity of the products to *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni* in Egypt were evaluated. From the results given in Table 1, it is clear that the nitroethenylsalicylanilides are the most effective members, two of which (**3c, d**) proved to be toxic in concentrations down to 1 ppm. Meanwhile, all the 2-nitroethenyl derivatives tested showed knock-down effects which are characteristic of aryl-substituted nitroalkenes in general. The toxicity of the anilides to Cercariae exemplified by **3a** showed activity in concentrations down to 5 ppm.

Table 1. Molluscicidal activity[a] of the products

Compd.	Number of snails killed after an expossure period of 24 h by a concentration of			
	10 ppm	5 ppm	2 ppm	1 ppm
2	8	2	–	–
3a	10	10	4	0
3b	10	10	2	0
3c	10	10	10	3
3d	10	10	10	5
4a	10	8	0	0
5a	10	10	9	0
5b	10	10	8	0

[a] The test was carried out by dissolving 0.1 g of the compound in 10 ml of acetone and adding the appropriate volume of the solution to one litre of water to get the required concentration. Ten snails were used in each experiment. Reference experiments were carried out using the same volume of acetone added to one litre of water.

Microbicidal activity

The toxicity of the compounds to various types of bacteria and phytopathogenic fungi has been evaluated. The majority of the products exhibited interesting activity in high dilutions especially to fungi as shown in Table 2. The results obtained prompted us to test some of the products on a larger number of fungi species as shown in Table 3. From the results obtained, **3g** and **8a** are apparently the most active members of the nitroethenyl derivatives tested. The results are rather interesting since the fungi are responsible for some diseases which affect economic crops in Egypt.

Table 2. Microbicidal activity of the products expressed as minimum inhibitory concentrations (μg/ml)

Microorganism	**2**	**3a**	**3b**	**3c**	**3d**
Fusarium moniliforma	–	12.5	12.5	50	12.5
Fusarium oxysporum	–	12.5	12.5	50	12.5
Aspergillus flavus	12.5	12.5	25	50	12.5
Sarcina leuitia	–	12.5	12.5	50	12.5
Bacillus cereus	–	12.5	12.5	50	12.5
Bacillus subtilis	12.5	12.5	12.5	50	12.5
Candida albicans	–	12.5	–	50	12.5
Pseudomonas aeroginosa	–	–	–	–	–
Escherichia coli	–	12.5	12.5	50	12.5
Staphylococcus aureus	–	12.5	12.5	50	12.5

Table 3. Fungicidal activity of the products expressed as minimum inhibitory concentrations (μg/ml)

Microorganism	**3g**	**3h**	**8a**
Alternaria tenius	12.5	–	12.5
Aspergillus flavus	12.5	100	12.5
Aspergillus fumigatus	12.5	100	12.5
Aspergillus niger	12.5	100	12.5
Aspergillus ochraceus	12.5	100	12.5
Aspergillus paraziticus	12.5	100	12.5
Aspergillus tamarir	12.5	100	12.5
Aspergillus terreus	12.5	100	12.5
Aspergillus versicular	12.5	100	12.5
Botrytis allii	50	–	12.5
Cephalosporium acromorium	50	–	12.5
Fusarium moniliform	50	–	12.5
Fusarium oxysporum	50	–	12.5
Fusarium solani	50	–	12.5
Newrospora sp.	50	–	12.5
Penicillium crysogenium	50	100	12.5
Rhizopus nigricans	50	100	12.5
Trichoderma viridi	50	100	12.5
Trichothecium roseum	50	100	12.5

Mutagenic Activity

The observed molluscicidal and microbicidal activity of the prepared anilides prompted us to test their mutagenicity. Some of the compounds proved to be not mutagenic (*e. g.* **2, 3a, 3c**, and **3e**) whereas, **3b** and **3d** are mutagenic. Actually, it is difficult to correlate between structures and activity.

The authors thank Professor Dr. *M. Nagib* for the microbicidal and Dr. *A. Farahat* for the fungicidal tests and Professor Dr. *F. Youssef*, Theodor Bilharz Institute, Cairo, for screening the toxicity of **3a** to Cercariae. They also are indepted to the *Naval Bioscience Laboratory*, Oakland, Cal., for the mutagenic tests. Furthermore, the authors thank the *Office of Naval Research*, U.S.A., for a grant supporting this work, Mrs. *R. Swellem*, and Mr. *W. Basyouni* for experimental assistance in preparing compound **2a**.

Experimental

5-(2-Nitroethenyl)salicylic acid (**2a**): To a suspension of 5-formylsalicylic acid (8.3 g; 0.05 mol) in glacial acetic acid (30 ml) was added nitromethane (4.5 g; 0.075 mol) and *n*-butylamine (3 ml), then the mixture was heated under reflux for 3 h. After cooling, the mixture was poured into ice-cold water, and the precipitated solid was filtered off and crystallized from ethanol (90%) to give 5.0 g (48%) of **2** with m. p. 230–232°C.

5-(2-Nitroethenyl)salicyloyl chloride (**2b**): A solution of the acid **2a** (10.4 g; 0.05 mol) in redistilled thionyl chloride (25 ml) was refluxed for 20 min. The excess thionyl chloride was evaporated under reduced pressure, and the crude acid chloride obtained was dissolved in dry benzene and used as such for further work.

5-(2-Nitroethenyl)salicylanilides **3a–h**. – *General procedure:* The acid chloride **2b** [prepared from 10.4 g (0.05 mol) of the acid **2a**] in dry benzene (150 ml) was cooled in an ice-bath. A solution of the appropriate aniline (0.05 mol) and triethylamine (17.8 g; 0.15 mol) in dry benzene*) (50 ml) was added dropwise while stirring to the acid chloride solution at such a rate that the temp. did not rise above 5°C. The stirring was continued at the bath temp. for 1 h, then at room temp. for 2 h. When a solid precipitate was formed, it was filtered off, washed with water, dried, then recrystallized. If no precipitate was formed, the reaction solution was evaporated to dryness under reduced pressure, and the residue was triturated with water. The solid product obtained was then filtered off, dried, and crystallized from the appropriate solvent (Table 4) to give the anilide **3** as yellow crystals. Characteristic data are shown in Table 4.

3-Methyl-6-(2-nitroethenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4a**). – (a) *From* **3a**: A solution of **3a** (1.4 g; 0.005 mol), methyl isocyanate (0.6 g; 0.01 mol), and a few drops of triethylamine in dry dioxane (20 ml) was heated on a boiling water bath for 4 h. The solution was concentrated, and a few millilitres of methanol was added and cooled. The separated solid was recrystallized from dioxane-methanol (1:1) to give 0.7 g (57%) of **4a** as almost colourless crystals with m. p. 240°C.

$C_{11}H_8N_2O_5$ (248.2) Calc. C 53.23 H 3.25 N 11.29 Found C 53.10 H 3.00 N 10.50

(b) *From* **2a**: A mixture of **2a** (4.0 g; 0.02 mol) and methyl isocyanate (2.3 g; 0.04 mol) was treated dropwise while shaking with triethylamine (2 ml). After the exothermic reaction had ceased, the resulting red syrup was left at room temp. for a few hours. The solid mass obtained was triturated with methanol (10 ml) and the solid obtained was filtered off and crystallized from dioxane-methanol (1:1) to give 2.5 g (60%) of **4a** with m. p. 240°C.

5-Formyl-N-methylsalicylamide (**6**): The dione **4a** (1.0 g) was heated at 40°C in 10% aqueous sodium hydroxide for 4 h and left to cool. The solution was neutralized with cold dilute hydrochloric acid, and the solid precipitated was filtered off, washed with water, dried, and crystallized from cyclohexane to give 0.5 g (70%) of **6** as almost colourless crystals with m. p. 148–150°C.

$C_9H_9NO_3$ (179.2) Calc. C 60.33 H 5.06 N 7.82 Found C 59.55 H 4.93 N 7.90

2-(Alkylcarbamoyl)-5-(2-nitroethenyl)benzanilides **5a–c**: A solution of the anilide **3a** (0.005 mol) and of the alkyl isocyanate (0.006 mol) was treated with a few drops of triethylamine. – In the case of methyl isocyanate, the solution was stirred at room temp. for 1 h. The crystalline solid separated was filtered off and recrystallized to give **5a**. – In the case of *n*-butyl and isopropyl isocyanate, the solution was heated on a boiling water bath for

*) In the case of 4-aminoacetophenone, benzene-dioxane mixture (1:1) was used.

Table 4. Characteristic data of the products **3**, **5**, and **8**

No.	...-5-(2-nitroethenyl)-benzamide	M. p. [°C] (solvent)[a]	% Yield	Mol. formula (mol. mass)		Elemental analysis C	H	N
3a	2-Hydroxy-*N*-phenyl-...	209–211 (A)	68	$C_{15}H_{12}N_2O_4$ (284.3)	Calc.	63.38	4.26	9.85
					Found	63.70	3.90	10.5
3b	*N*-(2-Chlorophenyl)-2-hydroxy-...	217 (A)	60	$C_{15}H_{11}ClN_2O_4$ (318.7)	Calc.	56.53	3.48	8.79
					Found	56.6	3.4	8.37
3c	*N*-(4-Chlorophenyl)-2-hydroxy-...	260–262 (B)	67	$C_{15}H_{11}ClN_2O_4$ (318.7)	Calc.	56.53	3.48	8.79[b]
					Found	56.4	3.63	8.86
3d	*N*-(2-Chloro-4-nitrophenyl)-2-hydroxy-...	256–258 (B)	45	$C_{15}H_{10}ClN_3O_6$ (363.7)	Calc.	49.53	2.77	11.55[c]
					Found	49.02	2.91	10.99
3e	*N*-(2,4-Dichlorophenyl)-2-hydroxy-...	232–234 (C)	37	$C_{15}H_{10}Cl_2N_2O_4$ (353.2)	Calc.	51.01	2.85	7.93[d]
					Found	51.24	3.07	7.5
3f	2-Hydroxy-*N*-[2-(trifluoromethyl)phenyl]-...	183–184 (B)	73	$C_{16}H_{11}F_3N_2O_4$ (352.3)	Calc.	54.55	3.15	7.95
					Found	54.66	3.10	7.9
3g	*N*-(4-Fluorophenyl)-2-hydroxy-...	234–235 (A)	40	$C_{15}H_{11}FN_2O_4$ (302.3)	Calc.	59.61	3.67	9.27[e]
					Found	59.80	3.60	8.80
3h	*N*-(4-Acetylphenyl)-2-hydroxy-...	266–267 (C)	25	$C_{17}H_{14}N_2O_5$ (326.3)	Calc.	62.57	4.32	8.59
					Found	62.32	3.91	8.95
5a	2-(Methylcarbamoyl)-*N*-phenyl-...	212–214 (D)	71	$C_{17}H_{15}N_3O_5$ (341.3)	Calc.	–	–	12.31
					Found			12.31
5b	2-(Butylcarbamoyl)-*N*-phenyl-...	225–226 (D)	74	$C_{20}H_{21}N_3O_5$ (383.4)	Calc.	–	–	10.96
					Found			11.44
5c	2-(Isopropylcarbamoyl)-*N*-phenyl-...	213–214 (E)	60	$C_{19}H_{19}N_3O_5$ (369.4)	Calc.	–	–	11.38
					Found			11.30
8a	2-Chloro-*N*-phenyl-...	150 (F)	60	$C_{15}H_{11}ClN_2O_3$ (302.7)	Calc.	59.52	3.66	9.25
					Found	59.6	3.7	9.74
8b	2-Chloro-*N*-(2-chloro-4-nitrophenyl)-...	200–202 (F)	55	$C_{15}H_9Cl_2N_3O_5$ (382.2)	Calc.	47.14	2.37	11.00
					Found	47.64	2.73	10.64

[a] Solvent of crystallization: A = methanol, B = ethanol, C = tetrahydrofuran-methanol, D = tetrahydrofuran, E = dioxane, F = benzene. – [b] Calc. Cl 11.12, found Cl 10.8. – [c] Calc. Cl 9.75, found Cl 9.0. – [d] Calc. Cl 20.08, found Cl 20.3. – [e] Calc. F 6.29, found F 6.20.

3 h and then evaporated to dryness. The residue was heated with a few millilitres of methanol and the separated solid was filtered off and crystallized to give **5b** and **5c**, respectively, as almost colourless crystals (cf. Table 4).

2-Chloro-5-(2-nitroethenyl)benzanilides **8a** *and* **b**. – *General procedure:* The anilide **3a** or **3d** (0.01 mol) was heated under reflux with thionyl chloride (15 ml) for 3 h. The excess of thionyl chloride was evaporated under reduced pressure and the residue was recrystallized to give **8a** and **8b**, respectively, as yellow crystals (cf. Table 4).

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