Salicylamides Containing Amino Acid or Pyran Moieties with Molluscicidal Activity

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Salicylamide amino acid conjugates were prepared utilizing 5-formyl-, 5-dicyanoethenyl-, and 5-nitroethenylsalicylic acid. 5-Substituted salicylanilides were treated with glycine and formaldehyde in a *Mannich* type reaction affording the corresponding 3-(*N*-glycino)salicylanilides. The reactions of anilines with pyrans containing the salicylyl moiety yielded the corresponding salicylanilides. The obtained compounds were tested for molluscicidal activity.

Molluskizide Salicylamide mit Aminosäure- oder Pyran-Bausteinen

Die Titelverbindungen wurden aus 5-Formyl-, 5-Dicyanoethenyl- und 5-Nitroethenylsalicylsäure hergestellt. C-5-substituierte Salicylanilide wurden mit Glycin und Formaldehyd im Sinne einer *Mannich*-Reaktion zu den entspr. 3-(*N*-Glycino)-salicylaniliden umgesetzt. Pyran-substituierte Salicylsäuren gaben die entspr. Salicylanilide. Die so hergestellten Verbindungen wurden auf molluskizide Wirkung geprüft.

An important group of molluscicides are the salicylanilides[1,2] the most active member of which is 2,5'-dichloro-4-nitrosalicylanilide (**9b**)[1] which is also known for its anthelmintic action[3]. However, the toxicity of **9b** towards fish[4] is its main disadvantage as molluscicide.

In the course of our programme aiming to synthesize new molluscicides[5] we constructed new salicyloylamino acid conjugates, as amino acid conjugations are known to improve the pharmacokinetics and toxicity of active drug[6]. This work also deals with the synthesis of salicylanilides incorporating the pyran moiety which may synergize the activity.

Results and Discussion

Thus, 5-formylsalicylic acid (**1a**) underwent condensation with hippuric acid (2) in presence of sodium acetate to give a product $C_{19}H_{13}NO_6$ (m/z = 351) which is compatible with the salicylylidene oxazolinone **3**. Its IR spectrum showed three C=O absorptions at 1760, 1705, and 1660 cm^{-1}. Similar condensation of hippuric acid with aromatic aldehydes has been reported[7].

When the acid chloride of **3** was treated with 2-chloro-4-nitroaniline, the salicylanilide **4a** was obtained.

The reaction with 4-bromoaniline afforded product **4b**, $C_{23}H_{15}BrN_2O_4$ (m/z = 462/464). Deacetylation which occurred in compounds **4a,b** may be due to aminolysis by the anilines present in the reaction media.

Treatment of compounds **4a,b** with 10% NaOH hydrolysed the oxazolinone ring affording the salicylanilide derivatives **5a,b**. Structure **5** was established by analytical and spectral data; the mass spectrum of **5a** showed $M^{+\cdot}$ at m/z = 481 for ^{35}Cl-$C_{23}H_{16}ClN_3O_7$.

Reaction of 5-(2,2-dicyanoethenyl)salicylic acid (**1b**)[5] with *N*-hydroxysuccinamide in presence of dicyclohexyl carbodiimide (DCC), followed by the addition of the amino acid **7e** in presence of triethylamine, afforded the corresponding *N*-substituted salicylamide **8f**. Its ^{1}H-NMR revealed protons pattern of 1,2,5-trisubstituted benzene with a d at 7.0 ppm (J_o = 9 Hz), a d at 8.1 ppm (J_m = 3 Hz) and a dd at 7.9 ppm (J_o = 9 Hz, J_m = 3 Hz) along with two m at 2.1 ppm (1H) and 4.8 ppm (1H) and a d at 1.0 (6H) (J = 7 Hz, valine moiety), in addition to a s at 7.7 ppm (1H) (ylidene-H). Adopting the same experimental conditions, derivatives **8a-e** could be obtained on reacting **1b,c** with the corresponding amino acids (**7a-d**).

The formation of **8** is assumed to proceed *via* the intermediacy of the active imide **6** which reacts with the amino acids affording **8**. A similar assumption for amide formation in peptide chemistry has been reported[8]. It is worth to mention that the direct coupling of **1b** with **7a** in presence of DCC afforded the corresponding *N*-[5-(2,2-dicyanoethenyl)salicyloyl]dicyclohexylurea[5].

In our molluscicidal assay, the salicylyl-hippuric acid derivatives **4,5,8** showed no activity in spite of the presence of the salicylanilide moiety which is present in the known mollusicide **9b**[1]. So, it was interesting to construct salicylanilides having amino acid residue but still keeping the activity. For this purpose, the active salicylanilides **9a,b**, prepared following lit. procedures[1-9], reacted with formaldehyde and glycine in a *Mannich* type reaction to yield the corresponding salicylanilide derivatives **10a,b**; their ^{1}H-NMR spectra revealed the *N*-benzyl-CH_2 as s at δ = 3.3 ppm and the *N*-glycino-CH_2 at δ = 4.2 ppm. The mass spectrum of **10b** revealed $M^{+\cdot}$ at m/z = 413 (^{35}Cl-$C_{16}H_{13}Cl_2N_3O_6$).

We have reported a simple synthesis of pyran derivatives containing the salicylyl moiety from the reaction of the corresponding α,β-unsaturated nitriles with active methylenes[5]. In continuation to this study, compound **1e** was reacted with $SOCl_2$ with subsequent treatment with 2-chloro-4-nitroaniline in order to prepare the corresponding

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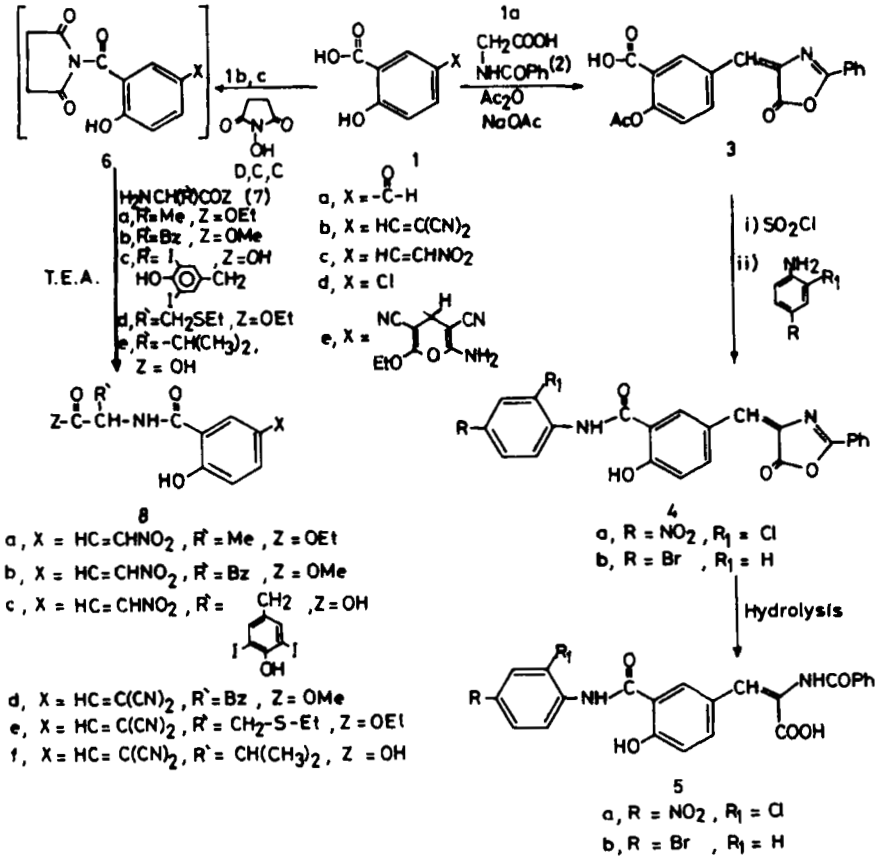
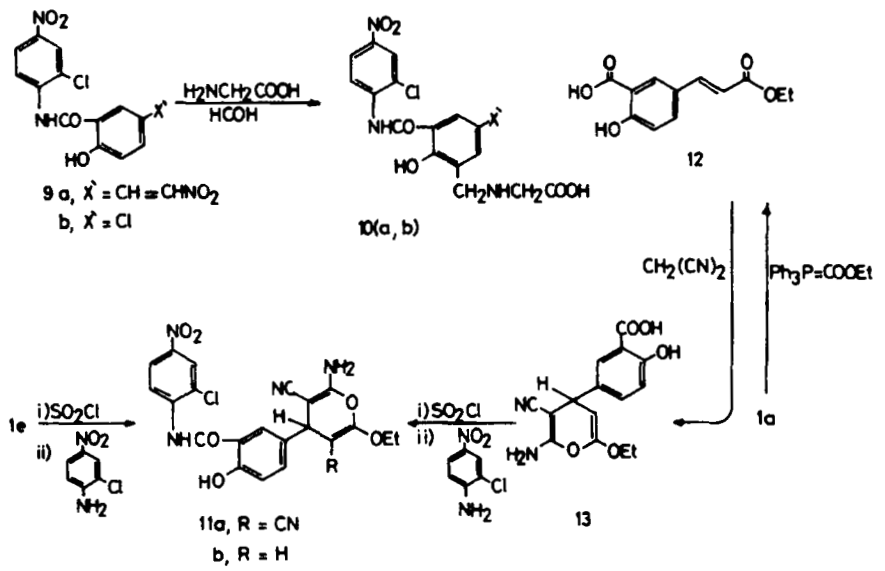


Scheme 1



Scheme 2

salicylanilide **11a**: its mass spectrum gave $M^{+\cdot}$ for ^{35}Cl-$C_{22}H_{16}ClN_5O_6$ (m/z = 481) and its ^{1}H-NMR spectrum showed the pyran 4-H at δ = 5.1 ppm [5].

Treatment of the new ethylcinnamate derivative **12** - prepared by a Wittig reaction of **1a** with [ethyl(triphenylphosphor anylidene)acetate]- with malononitrile in ethanol in the presence of triethylamine, afforded 2-amino-4*H*-pyran **13**: its ^{1}H-NMR-spectrum shows the pyran 4-H as a d (J = 10 Hz) at δ = 5.0 ppm and its IR-spectrum reveals a CN-absorption at $\tilde{\nu}$ = 2220 cm^{-1}.

When the pyran derivative **13** reacted with $SOCl_2$ followed by treatment with 2-chloro-4-nitro aniline, the corresponding salicylanilide **11b** was obtained.

Molluscicidal activity

The toxicity of the products to Biomphalaria alexandria snails, the intermediate host of schistosoma mansoni in Egypt, was evaluated. The results (Table 1) show that the salicylanilides containing the *N*-glycino moiety **10** are the most effective, especially derivative **10b** which proved to be toxic in concentration down to 1 ppm. - The two types of salicyloylamino acid conjugates **5** and **8** surprisingly lacked any molluscicidal acitivity although they possess all the structural features present in their corresponding active salicylanilides[1,2,5].

The salicylanilides containing the pyran moiety [11] showed activity inferior to the stander molluscicide **9b**[10].

Table 1: Molluscidal activity[a] of the tested products.

Compound No.	Number of snails killed after an exposure period of 24 h by a concentraiton of:			
	10 ppm	5 ppm	2 ppm	1 ppm
9b	10	10	10	10
4a	4	1	0	0
4b	4	1	0	0
5a,b	0	0	0	0
8a-f	0	0	0	0
10a	10	10	5	2
10b	10	10	10	10
11a	6	3	0	0
11b	6	3	1	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 L of water to get the required concentration. Ten snails were used in each experiment. 2,5'-Dichloro-4-nitrosalicylanilide (**9b**) was used as a standard[10]. Reference experiments: 10 ml of acetone/L water.

Experimental Part

Melting points: uncorrected. - IR spectra (KBr): Pye Unicam Sp-1000. - ^{1}H-NMR spectra: Varian EM 390 (90 MHz) and GEMINI-200 spectrometer, DMSO, TMS as internal standard, chemical shifts in δ (ppm). - Mass spectra: 70 eV, Varian MAT 311A. - Analytical data: Central Service Laboratory at National Research Centre.

Compounds **9a-d** were prepared following lit. procedures[1,9].

*Acetyl 5-(2-phenyl-Δ^2-oxazolin-5-one-4-ylidene) salicylate (**3**)*

A mixture of **1a** (0.01 mol) and hippuric acid (0.01 mol) was boiled under reflux in acetic anhydride (30 ml) in the presence of sodium acetate (0.01 mol) for 3 h. The mixture was cooled, poured into crushed ice and the solid was crystallized from methanol as yellow crystals; 72%; m.p. 185°C. - IR: 3480-3300 (phenolic OH, carboxylic OH), 1750 (CO oxazolinone), 1705 (CO acetyl), 1705 (CO carboxylic), 1660 (C=N). - ^{1}H-NMR: 2.2 (s, 3H, acetyl), 7.2-7.7 (m, 7H, C_6H_5, salicylate 3-H and ylidene H), 8.1 (m, 2H, salicylate 4-6, H-6), 8.8 (s, 1H, OH). - $C_{19}H_{13}NO_6$ (351.3) Calc. C 64.9 H 3.7 N 4.0 Found C 64.7 H 3.4 N 3.7.

*Salicylanilide derivatives **4** and **11**, General Procedure*

Compounds **3**, **11b,f**, and **13** (0.01 mol) were each heated in $SOCl_2$ (20 ml) at 80°C for 2 h. $SOCl_2$ was evaporated *in vacuo* and the acid chloride, thus formed, was dissolved in dry benzene (20 ml) and cooled in an ice bath. A solution of the appropriate aniline (0.01 mol) and triethylamine (1 ml) in dry benzene (20 ml) was added dropwise while stirring at such a rate that the temp. did not rise above 5°C. Stirring was continued at ice bath temp. for 1 h, then at room temp. for 2 h. When a solid precipitate was formed, it was washed with water, then recrystallized. If no precipitate was formed, the solution was evaporated to dryness *in vacuo*, and the residue was triturated with water. The solid product obtained was then crystallized from an appropriate solvent.

*5-(2-Phenyl)Δ^2-oxazolin-5-one-4-methylidene)-2'-chloro-4'-nitrosalicylanilide (**4a**)*

Yellow crystals from toluene; 45%; m.p. 280°C. - IR: 3400 (OH), 3300 (NH), 1750 (CO lactam), 1660 (CO amide). - ^{1}H-NMR: 7.1-7.8 (m, 8H, C_6H_5, aniline 6-H, salicylate 3-H, =CH), 8.0 (m, 2H, salicylate 4-H, 6-H), 8.3 (m, 2H, aniline 3-H, 5-H). - $C_{23}H_{15}ClN_3O_6$ (464.8) Cal. C 59.4 H 3.25 N 9.0 Found C 59.18 H 3.2 N 8.8.

*5-(2-Phenyl-Δ^2-oxazolin-5-one-4-methylidene)-4'-bromosalicylanilide (**4b**)*

Yellow crystals from toluene; 50%; m.p. 274°C. - IR: 3400 (OH), 3300 (NH), 1800 (CO oxazolinone), 1660 (CO amide). - $C_{23}H_{15}BrN_2N_4$ (463.3) Calc. C 59.6 H 3.3 Br 17.2 N 6.0 Found C 59.3 H 3.0 Br 16.8 N 5.6.

*2-Ethoxy-3,5-dicyano-6-amino-4-[5-(2'-chloro-4'-nitro)salicylanilide]-4H-pyran (**11a**)*

Yellow crystals from dioxane; 65%; m.p. 218°C. - IR: br 3450-2800 (OH, NH, NH_2), 2325 (CN), 1650 (CO). - ^{1}H-NMR: 1.5 (t, J = 7 Hz, 3H, CH_2-CH_3), 3.0 (br s, 2H, NH_2), 4.2 (m, 2H, CH_2), 5.1 (s, 1H, pyran 4-H), 7.3-8.0 (m, 4H, salicylate 3-H, 4-H, aniline 6-H, 5-H), 8.1 (dd, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 3 Hz, salicylate 5-H), 8.4 (s, 1H, OH), 8.5 (d, $J_{6,4}$ = 3 Hz), 1H, salicylate 6-H), 8.7 (d, $J_{3,5}$ = 3 Hz, aniline 3-H). - $C_{22}H_{16}ClN_5O_6$ (481.8) Calc. C 59.1 H 3.35 N 14.5 Found C 58.9 H 3.5 N 15.2.

*2-Ethoxy-5-cyano-6-amino-4-[5-(2'-chloro-4'-nitro)salicylanilide]4H-pyran (**11b**)*

Yellow crystals from CH_3OH; m.p. 202°C. - ^{1}H-NMR: 7.3-8.0 (m, 5H, salicylate 3-H, 4-H, aniline 5-H, 6-H, pyran 3-H), 8.3 (s, 1H, OH), 8.5 (d, $J_{6,4}$ = 3 Hz, 1H, salicylate 6-H), 8.7 (d, $J_{3,5}$ = 3 Hz, 1H, aniline 3-H). $C_{23}H_{17}ClN_4O_6$ (422.4) Calc. C 59.7 H 4.3 N 13.3 Found C 59.5 H 4.1 N 13.0.

*5-(2-Benzamidoacrylic acid)-4'-substituted salicylanilides **5**, General Procedure*

A solution of **4a** or **4b** in 10% aqueous NaOH (25 ml) was stirred at 25°C for 5 h. The solution was acidified with dil. HCl, then extracted with ethyl acetate. The org. layer was washed with water, dried (Na_2SO_4), then concentrated; the solid precipitate obtained was crystallized from the appropriate solvent.

5-(2-Benzamidoacrylic acid)-2'-chloro-4'-nitrosalicalanilide (**5a**)

Yellow crystals from dioxane; 50%; m.p. 178°C. - IR: br 3500-3200 (phenolic OH, carboxylic OH, NH), 1700 (CO carboxylic), 1650 and 1635 (N-benzoyl, CO amide). - $C_{33}H_{16}ClN_3O_7$ (481.8) Calc. C 57.3 H 3.3 Cl 7.4 N 8.7 Found C 57.1 H 3.1 Cl 7.1 N 8.3.

5-(2-Benzamidoacrylic acid)-4'-bromosalicylanilide (**5a**)

Yellowish crystals from dioxane; 60%; m.p. 195°C. - IR: br 3500-3200 (phenolic OH, carboxylic OH, NH), 1700 (CO carboxylic). 1650 and 1635 (N-benzoyl, CO amide). - $C_{23}H_{17}BrN_2O_5$ (481.3) Calc. C 57.4 H 3.6 Br 16.6 N 5.8 Found C 57.3 H 3.3 Br 16.2 N 5.4.

Salicylanilide derivatives **8**, *General Procedure*

To a solution of **1b** or **1c** (0.01 mol) and *N*-hydroxysuccimide (0.01 mol) in tetrahydrofuran (50 ml), a solution of dicyclohexyl carbodiimide (0.01 mol) in tetrahydrofuran (25 ml) was added dropwise, while stirring for 15 min at 0-5°C. After further 2 h of stirring at room temp., the mixture was cooled at 0°C and the precipitate of dicyclohexylurea was filtered off. To the remaining filtrate, a solution of the appropriate amino acid or amino acid ester (**7a-e**) (0.01 mol) and triethylamine (0.01 mol) in tetrahydrofuran (30 ml) was dropped while stirring at 0-5°C for 15 min. Stirring was kept for further 3 h at 25°C, then the mixture was extracted with toluene after adding 150 ml of water. The toluene phase was washed with Na_2CO_3 (20%) followed by acetic acid (50%) and finally with water, then it was concentrated; the separated solid product was crystallized from the proper solvent.

Ethyl N-(5-nitroethenylsalicyloyl)alanine (**8a**)

Yellowish white crystals from ethyl acetate/n-hexane 1:1; 66%; m.p. 96°C. - IR: 3300-2290 (OH and NH), 1735 (CO ester), 1680 (NO_2), 1650 (CO amide). - $C_{14}H_{16}N_2O_6$ (308.3) Calc. C 54.5 H 5.2 N 9.1 Found C 54.3 H 5.0 N 8.7.

Methyl N-(5-nitroethenylsalicyloyl)phenylalanine (**8b**)

Yellowish white crystals from toluene; 62%; m.p. 102°C. - IR: 3440-3350 (OH and NH), 1750 (CO ester), 1675 (NO_2), 1650 (CO amide). - ^{1}H-NMR: 3.1 (m, 2H, CH_2-Ph), 3.8 (s, 3H, OCH_3), 5.0 (m, 1H, N-CH-C=O), 7.0 (d, $J_{3,4}$ = 9 Hz, 1H, salicylate 3-H), 7.2-7.4 (m, 5H, C_6H_5), 7.8 (m, 2H, salicylate 4-H, 6-H), 8.5 and 8.7 AB system, J = 1.5 Hz, 2H, ylidene H), 9.7 (s, 1H, OH). - $C_{19}H_{18}N_2O_6$ (370.3) Calc. C 61.6 H 4.9 N 7.6 Found C 61.3 H 4.7 N 7.2.

N-(5-nitroethenylsalicyloyl)diiodotryrosine (**8c**)

Yellow crystals from ethyl acetate; 40%; m.p. 126°C. - IR: 3450 (OH), 3350-3300 (salicylate OH, carboxylic OH, NH), 1730 (CO ester), 1690 (NO_2), 1650 (CO). - ^{1}H-NMR: 3.1 (d, J = 8 Hz, 2H, CH_2), 5.1 (m, 1H, COOH), 7.0-8.0 (m, 7H, salicylate, tryosine, olefinic H's), 9.8 s, 1H, salicylate OH), 12.1 (s, 1H, tyrosine OH). - $C_{18}H_{14}I_2N_2O_7$ (624.1) Calc. C 34.6 H 2.3 I 40.7 N 4.5 Found C 34.4 H 2.1 I 40.2 N 4.2.

Methyl N-[5-(2,2-dicyanoethenyl)salicyloyl]phenylalanine (**8d**)

Yellowish crystals from toluene; 70%; m.p. 85-87°C. - IR: 3400-3250 (OH, NH), 2240 (CN), 1735 (CO ester), 1650 (CO amide). - ^{1}H-NMR; 3.1 (m, 2H, CH_2-Ph), 3.9 (s, 3H, OCH_3), 5.0 (m, 1H, O=C-CH-N), 7.0 (d, $J_{3,4}$ = 9 Hz, 1H, salicylate 3-H), 7.2-7.4 (m, 5H, C_6H_5), 7.6 (s, 1H, ylidene H), 7.8-7.9 (m, 2H, salicylate 4-H, 6-H), 9.8 (s, 1H, OH). - $C_{21}H_{17}N_3O_4$ (375.4) Calc. C 67.2 H 4.6 H 11.2 Found C 66.9 H 4.3 N 10.9.

Ethyl N-[5-(2,2-dicyanoethenyl)salicyloyl]methionine (**8e**)

Pale yellow crystals from methanol; 65%; m.p. 138°C. - IR: 3450-3350 (OH, NH), 2220 (CN), 1745 (CO ester), 1650 (CO amide). - ^{1}H-NMR: 1.1 (t, J = 7 Hz, 3H, CH_3-CH_2), 1.8 (m, 2H, S-CH_2), 2.1 (s, 3H, SCH_3), 2.2 (m, 2H, CH_2-S), 4.2 (q, 2H, CH_2-CH_3), 4.9 (m, 1H, N-CH-C=O), 7.0 (d, $J_{3,4}$ = 9 Hz, 1H, salicylate 3-H), 7.6 (s, H, ylidene H), 7.8 (dd, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 3 Hz, 1H, salicylate 4-H), 8.1 (m, 2H, salicylate 6-H, phenolic OH). - $C_{18}H_{19}N_3O_4S$ (373.4) Calc. C 57.9 H 5.1 N 11.3 S 8.6 Found C 57.6 H 4.9 N 11.1 S 8.2.

N-[5-(2,2-dicyanoethenyl)salicyloyl]valine (**8f**)

Yellow crystals from methanol; 45%; m.p. 116°C. - IR: 3350-3200 (phenolic OH, carboxylic OH, NH), 2240 (CN), 1700 (CO carboxylic), 1650 (CO amide). - ^{1}H-NMR: 1.0 (d, J = 7 Hz, 6H, $2CH_3$), 2.1 (m, 1H, $CH(CH_3)_2$), 4.8 (m, 1H, CH), 7.0 (d, $J_{3,4}$ = 9 Hz, 1H, salicylate 3-H), 7.7 (s, 1H, ylidene H), 7.9 (dd, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 3 Hz, 1H, salicylate 4-H), 8.1 (d, $J_{6,4}$ = 3 Hz, 1H, salicylate 6-H), 8.5 (br s, 1H, carboxylic OH), 9.8 (s, 1H, phenolic OH). - $C_{16}H_{15}N_3O_4$ (313.30) Calc. C 61.3 H 4.8 N 13.4 Found C 61.0 H 4.6 N 13.1.

3'-(N-glycinomethyl)-2,4,5'-substituted salicylanilides **10**, *General Procedure*

A solution of each of 9a-d (0.003 mol) in ethanol (30 ml) was treated with glycine acetate (0.003 mol) and 40% formalin (0.03 mol). The reaction mixture was refluxed for 5 h, left overnight at room temp., diluted with water (60 ml) and basified with ammonia to pH 8. The product, thus separated, was filtered off and crystallized from the appropriate solvent.

3'-(N-glycinomethyl)-5'-nitroethenyl-2-chloro-4-nitrosalicylanilide (**10a**)

Bright yellow crystals from ethanol; 60%; m.p. 205°C. - IR: 3400-2890 (OH, NH), 1645 (CO). - ^{1}H-NMR: 3.2 (s, 2H, Ph-CH_2-N), 4.1 (s, 2H, CH_2 glycine), 7.3-8.7 (m, 9H aromat. and nitroethenyl H's), 10.0-10.1 (2S, 2H, NH amide, NH glycine), 11.8 (s, 1H, OH). - $C_{18}H_{15}ClN_4O_8$ (450.8) Calc. C 48.0 H 3.5 Cl 7.9 H 12.4 Found C 47.8 H 3.3 Cl 7.4 H 12.1.

3'-(N-glycinomethyl)-2,5'-dichloro-4-nitrosalicylanilide (**10b**)

Bright yellow crystals from ethanol; 65%; m.p. 234°C. - IR: 3400-2890 (OH, NH, *N*-glycinomethylen), 1650 (CO). - ^{1}H-NMR: 3.4 (s, 2H, Ph-CH_2-N), 4.3 (s, 2H, N-CH_2-COOH), 7.9-8.3 (m, 5H, aniline, salicylate H's), 12.2 (s, 1H, OH). - $C_{16}H_{13}Cl_2N_3O$ (414.2) Calc. C 46.4 H 3.2 Cl 17.1 N 10.1 Found C 46.2 H 3.1 Cl 16.9 N 9.8.

Ethyl 4-hydroxy-3-hydroxycarbonylcinnamatey (**12**)

1a (0.01 mol) was boiled under reflux with ethyl (triphenylphosphoranylidene)acetate-ylide (0.01 mol) in dry toluene (40 ml) for 8 h. The mixture was concentrated, cooled and the solid product was crystallized from methanol as brown crystals; 70%; m.p. 48-50°C. - IR: 3500-3450 (OH and NH), 1715 (CO cinnamate). - ^{1}H-NMR: 1.0 (t, 3H, J = 7 Hz, CH_2-CH_3), 4.0 (q, J = 7 Hz, 2H, CH_2-CH_3), 7.0-8.1 (m, 5H, salicylate, olefinic H's), 11.9 (s, 1H, OH). - $C_{12}H_{12}O_5$ (236.2) Calc. C 61.0 H 5.1 Found C 59.8 H 4.9.

2-Ethoxy-4-(salicyl-5-yl)-5-cyano-6-amino-4H-pyran (**13**)

A mixture of **12** (0.01 mol) and malononitrile (0.01 mol) was boiled under reflux in ethanol (35 ml) in the presence of triethylamine (2 ml) for 8 h. The mixture was evaporated and the residual solid dissolved in water then acidified with dil. HCl. The solid product was crystallized from toluene as brown crystals; 60%; m.p. 230°C. - IR: br 3500-2850 (phenolic

OH, carboxylic OH, NH_2), 2220 (CN), 1680 (CO). - ^{1}H-NMR: 1.5 (t, J = 7 Hz, 3H, CH_2-CH_3), 2.9 (br s, 2H, NH_2), 4.2 (q, J = 7 Hz, 2H, CH_2), 5.0 (d, J = 10 Hz, 1H, pyran 4-H), 6.9 (d, $J_{3,4}$ = 9 Hz, 1H, salicylate 3-H), 7.8 (d, J = 10 Hz, 1H, pyran 3-H), 8.1 (dd, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 3 Hz, 1H, salicylate 4-H), 8.3 (s, 1H, OH), 8.6 (d, $J_{6,4}$ = 3 Hz, 1H, salicylate 6-H). - $C_{15}H_{14}N_2O_5$ (302.3) Calc. C 59.6 H 4.7 N 9.3 Found C 59.4 H 4.4 N 8.9.

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