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Synthesis and Analgesic–Antiinflammatory Activity of Some 4- and 5-Substituted Heteroarylsalicylic Acids

Howard Jones,* Michael W. Fordice, Ronald B. Greenwald, John Hannah, Arlene Jacobs, William V. Ruyle, G. Lyn Walford, and T. Y. Shen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received September 19, 1977*

We have made a series of 4- and 5-aryl- and 4- and 5-heteroarylsalicylic acid derivatives with the objective of reducing gastric irritation and increasing potency. Here we describe a series of 4- and 5-heterocyclic salicylic acids and their antiinflammatory–analgesic potencies measured in comparison to aspirin. An improvement of the therapeutic index over aspirin of 100 was achieved; however, the heterocyclic salicylic acids lacked antipyretic activity. Some physicochemical parameters which may bear on the antiinflammatory activity of these compounds are discussed.

As an extension of our synthetic study of 4- and 5-arylsalicylic acids,[1] a group of 4- and 5-heteroarylsalicylic acids were also investigated. Although these compounds were less potent in antiinflammatory–analgesic assays than arylsalicylic acids, some encouragement was obtained from their relatively low, gastric toxicities as compared with aspirin.

The synthesis of aza analogues of 5-(*p*-fluorophenyl)-salicylic acid in which the heteroaryl ring replaced the phenyl ring of salicylic acid was reported previously.[2] We now wish to report on our work in synthesizing 4- and 5-heteroarylsalicylic acids.

Chemistry. The heterocyclic salicylic acids were synthesized by different routes as described in the Experimental Section. Generally, a substituted anisole was synthesized which was cleaved to a phenol. Kolbe–Schmitt carboxylation then gave the salicylic acid. The substituted anisoles were sometimes obtained by direct displacement (e.g., **5** and **7**). *p*-Bromoanisole and the parent heterocycle were reacted with cuprous cyanide in nitrobenzene.

In other cases (e.g., **8**, **18**, and **26**) the substituted anisole was synthesized containing the linear components in the meta or para position that would eventually be cyclized to give the desired heterocyclic system. For example, the 5-(2-imidazolyl) derivative **8** was made through *N*-(2,2-dimethoxyethyl)-*p*-methoxybenzamidine by cyclization with sulfuric acid followed by deblocking and carboxylation. *p*-(4-Oxazolyl)anisole was made from *p*-methoxyphenacyl bromide and formamide. *p*-(4-Thiazolyl)anisole was made from *p*-methoxy-α-(thioformamido)acetophenone[19] and concentrated sulfuric acid.

At other times the heterocyclic salicylic acids were obtained by direct ring formation on an appropriately substituted salicylic acid derivative. For example, **1** was made through the product obtained by the reaction of ethyl 5-cyanosalicylate with sodium azide and ammonium chloride in hot dimethylformamide. Compound **4** was obtained directly by the reaction of 5-aminosalicylic acid and diformylhydrazine with phosphorus pentoxide. While compound **11** was obtained similarly but using 2,5-dimethoxytetrahydrofuran in place of the hydrazine derivative, compound **28** was obtained from ethyl 5-acetyl-2-methoxybenzoate through the sodium enolate derivative of ethyl 5-(formylacetyl)-2-methoxybenzoate, followed by cyclization with hydroxylamine hydrochloride to give **28** after removing the methyl-protecting group.

The heterocyclic-substituted anisoles were cleaved to the corresponding phenols with either 48% hydrobromic acid or boron tribromide. In some cases, reasonable yields of phenol could only be achieved by using one procedure. On many occasions the heterocyclic ring was cleaved during this procedure and carefully controlled conditions had to be developed.

In the case of **20**, the phenol was prepared from the corresponding nitro compounds by reduction and diazotization.

In many cases, the presence of an electronegative heterocyclic ring is disadvantageous for the carboxylation reaction. Consequently, high carbon dioxide pressures, high temperatures, and long periods of time were required for this reaction to be run successfully. Decomposition was common and each reaction was individually developed. Prior to this work, of the 4-heterocyclic phenols previously described in the literature, none had ever been carboxylated.

Physical Properties. As a separate exercise, simple Hückel molecular orbital calculations were done on all of the described compounds. Electronegativities, total π energies, ionization potentials, and superdelocalizabilities[3,4] were all used in a regression analysis in an attempt to correlate edema or analgesic activity with these calculated constants. No good correlations could be obtained.

Hansch[5,6] π values were also measured for most of the compounds and no correlation was found between this and

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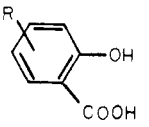
Table I. ED_{50} in Carrageenan Edema[b] Together with the ED_{50} in the Hyperesthesia Assay[c] of the More Edema Active Members



R	compd no.	ED_{50}[a] in edema[b]	ED_{50}, mg/kg, in hyperesthesia[c]
5-[5-(1,2,3,4-tetrazolyl)]	1	110	
5-[1-(1,2,3-triazolyl)]	2	150	
5-[2-(1,2,3-triazolyl)]	3	150	
5-[1-(1,3,4-triazolyl)]	4	>250	
5-[1-(1,2,4-triazolyl)]	5	200	
5-(3-pyrazolyl)	6	>250	
5-(*N*-pyrazolyl)	7	200	
5-(2-imidazolyl)	8	200	
5-(4-imidazolyl)	9	100	
5-(*N*-imidazolyl)	10	75	65
5-(*N*-pyrryl)	11	50	30
4-(*N*-pyrryl)	12[d]	200	
5-(2-pyrimidyl)	13	100	
5-(4-pyrimidyl)	14	>200	
5-(3-pyridyl)	15[e]	>250	
5-(2-pyridyl)	16[e]	200	
5-(2-oxazolyl)	17	100	
5-(4-oxazolyl)	18	110	
5-(5-oxazolyl)	19	>200	
4-(2-oxazolyl)	20[d]	>250	
5-(2-thienyl)	21	60	
5-(2-thiazolyl)	22[e]	>250	
4-(2-thiazolyl)	23[d]	110	
5-(4-thiazolyl)	24	95	90
4-(4-thiazolyl)	25[d]	70	>80
5-(5-thiazolyl)	26	>200	
5-(5-isothiazolyl)	27	80	>80
5-(5-isooxazolyl)	28	110	
5-[4-(1,2,3-thiadiazolyl)]	29	>200	
O-acetyl-5-pyrryl	30	42	35
n-butyl 5-pyrryl carbonate	31	52	38
aspirin		90	90
diflunisal[f] (R = $C_6H_3F_2$)		9.8	4.6
salicylic acid (R = H)		200	>150

[a] Dose in milligrams per kilogram to give 50% reduction in size of edematous paw compared to edematous control. Obtained graphically from dose-response curves at three or four dose levels. [b] See ref 7. Drugs administered orally in 0.5% Methocel to six rats. p values ≤ 0.01. [c] See ref 8. Drugs administered orally in 1% Methocel to six rats. p values ≤ 0.01. [d] See U.S. Patent 3 687 971 (1972). [e] See U.S. Patent 3 558 641 (1971). [f] See ref 1.

the biological activity in this series of compounds.

From the pK_a values of the parent heterocycles present in these compounds, it was apparent to us that absorption from the gastric system would be a problem. A model of such absorption was therefore developed and consists of measuring the movement of the compound along silica gel chromatoplates. The R_f values of the heterocyclic salicylic acids were measured on silica gel chromatoplates (see the Experimental Section) in a 95:5 chloroform–acetic acid solution. The pH of the acetic acid solution is ca. 2.5 and therefore could well mimic the human contents (pH 1–3). Heterocyclic salicylic acids which have pK_a values of the conjugate acids of the bases >4.75 would not be expected to be well absorbed from the gut, nor would these compounds have high R_f values in the TLC system described above.

It was found that salicylic acids prepared from strongly basic heterocycles had very low R_f values and were only biologically weakly active. Strongly basic heterocycles are very likely in their zwitterionic form and this probably explains their lack of mobility in the TLC system. 5-(*N*-Pyrryl)salicylic acid (**11**) must have a pK_a of the conjugate acid lower than −3.8 (the pK_a of pyrrole) and thus would be expected to move on the TLC system (R_f 0.46) and be absorbed in the gut. Compound **11** was found to be the most potent antiinflammatory compound in this series.

Table II. Summary of Most Active Heterocyclic Salicylic Acids and Their R_f Values[a] and Water Solubilities[b]

compd no.	R_f	water solubility
1	0.1	1.7
9	0.2	1.1
10	0.1	2.0
11	0.5	8.6
13	0.2	6.0
17	0.18	6.0
21	0.6	7.0
24	0.24	2.7
25	0.35	8.7
27	0.23	7.3

[a] Rate of flow of salicylic acids compared to solvent front on silica gel chromatoplates using 5% HOAc-$CHCl_3$ as solvent. [b] Solubility in water at pH 7.0 phosphate buffer, in milligrams per milliliter.

Water solubility was also found to be a requirement for good activity. Some of these 4- and 5-heterocyclic salicylic acids are extremely insoluble in aqueous solutions. Presumably absorption from the gut requires solubility of the organic compound in an almost completely aqueous environment.

Biological Assays. The rat carageenan edema model of Winter and Risley[7] and the rat hyperesthesia assay of Winter and Flataker[8] were used to generate the biological data (see Table I). Only edema-active compounds were tested in the rat hyperesthesia analgesic assay. Table III contains all other biological data of significance on compound **11** compared with aspirin.

Discussion of Results. It can be seen that the most edema active heterocyclic salicylic acid that was made was **11**, 5-(*N*-pyrryl)salicylic acid (ED_{50} = 50 mg/kg). Its activity may be a reflection of its high R_f and water solubility compared to other 4- or 5-heterocyclic salicylic acids, since, within the group of acids listed in Table II, **11** has the highest R_f and water solubility. This relationship may be completely fortuitous of course; however, we wish to point out that such a relationship does exist.

It is also interesting to note that **11** is much more active in the edema assay than 4-(*N*-pyrryl)salicylic acid (**12**). However, 4-(2-thiazolyl)salicylic acid (**23**) is more active than 5-(2-thiazolyl)salicylic acid (**22**) and the 4-(4-thiazolyl) compound **25** is more active than 5-(4-thiazolyl)salicylic acid (**24**), indicating that both water solubility and R_f contribute to the activity.

It can be seen from Table I that the most active compound in the hyperesthesia assay[8] was also compound **11** which has an ED_{50} of 30 mg/kg (aspirin has an ED_{50} of 90 mg/kg).

It can be seen from the results in Table III that compound **11** is a more potent antiinflammatory–analgesic agent than aspirin with less gastric toxicity. However, it does lack the antipyretic potency of aspirin.

The acetate derivative **30** of the phenolic residue compound **11** was made without improving the activity or decreasing the toxicity of the compound. There was some suggestion that the antipyretic potency increased.

It has been reported that preparation of carbonates of salicylic acid improves the gastric toxicity of these compounds. The *n*-butyl carbonate derivative **31** of compound

Table III. Comparison of Pharmacological Activities of 5-(*N*-Pyrryl)salicylic Acid (11) and Aspirin

assay[i]	11	aspirin
PG synthetase,[a] ID_{50}, μg/mL	0.3	5
adjuvant arthritis[b] established lesion, ED_{50}, mg/kg	35	25
adjuvant arthritis[c] delayed dosing, ED_{50}, mg/kg	58	46
adjuvant arthritis,[d] ED_{50}, mg/kg	64	33
gastric hemorrhage,[e] ED_{50}, mg/kg	>800	16
antipyretic,[f] ED_{10}, mg/kg	401[g]	43
urate synovitis in the dog,[h] ED_{50}, mg/kg	39	68

[a] Method described in Ham et al., "Mode of Action of Non-Steroidal Antiinflammatory Agents on Prostaglandins and Cellular Biology", Ramwell and Pharrise, Eds., Plenum Press, New York, N.Y., 1972, p 345. [b] Method based on Staerk et al., *Am. J. Pathol.*, 30, 616 (1954). Compounds given orally suspended or dissolved in 0.5% Methocel on days 17–20 to six rats. Read on day 20. [c] See Newbould, *Br. J. Pharmacol.*, 24, 632 (1965). Compound administered as in footnote *b* above on days −1 through 1 to six rats. Read on days 0 and 14. [d] See Staerk et al. in footnote *b* above. Compound administered as in footnote *b* above on days −1 through 14 to six rats. Read on days 0 and 14. [e] See Brodie and Chase, *Gastroenterology*, 53, 604 (1967). Compound administered as in footnote *b* above by stomach tube to six rats. [f] Method based on Smith and Hambourger, *J. Pharmacol.*, 54, 346 (1935), and Barin et al., *J. Pharm. Pharmacol.*, 4, 872 (1952). Compound administered as in footnote *b* above to eight rats. [g] The effective dose in milligrams per kilogram to produce a drop in body temperature of 1 °C. [h] Modified procedure of Rosenthale et al., *Proc. Soc. Exp. Biol. Med.*, 122, 693 (1966). Compound given orally in 1% Methocel to three dogs. Read after 2 h. [i] All ED_{50} values were graphically calculated from statistically ($p \leq 0.05$) significant values.

11 was prepared by the described procedure,[9,10] but the analgesic–antiinflammatory potency was not improved. There was some evidence that gastric hemorrhage was reduced; however, compound **11** has so little gastric toxicity (ED_{50} = >800 mg/kg) that improvement is difficult to measure. If one defines the therapeutic index in these compounds as ED_{50} in edema over ED_{50} in gastric hemorrhage, it can be seen that compound **11** has a beneficial ratio of 100 over aspirin.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Where analyses are indicated by the symbols of the elements, analytical results obtained for these elements were ±0.4% of theoretical values.

Hansch[6] π values as defined by log $[K_{R\text{-}Y}/K_{R\text{-}H}]$ (where $K_{R\text{-}Y}$ is the distribution coefficient of the heterocyclic salicylic acid and $K_{R\text{-}H}$ is the distribution coefficient of salicylic acid itself, between 1-octanol and water) were measured.

5-[5-(1,2,3,4-Tetrazolyl)]salicylic Acid (1). Ethyl 5-bromosalicylate (24.5 g, 0.1 mol) and CuCN (8.95 g, 0.1 mol) were heated at 180 °C in *N*-methylpyrrolidine (100 mL) for 5 h. The reaction mixture was cooled to 80 °C and concentrated HCl (60 mL) and ferric chloride (20 g) were added. After 15 min, the precipitated solid was filtered, dried, and recrystallized from hexane to give ethyl 5-cyanosalicylate (14.6 g), mp 57–59 °C. Ethyl 5-cyanosalicylate (6.2 g, 0.032 mol), sodium azide (2.16 g, 0.033 mol), and ammonium chloride (1.69 g) were heated at 120 °C in dimethylformamide (25 mL) for 16 h. The solution was evaporated to dryness and mixed with water (50 mL). The precipitated solid was collected and recrystallized from EtOH to give ethyl 5-[5-(1,2,3,4-tetrazolyl)]salicylate (**1a**) (4.3 g), mp 233–240 °C dec. Ester **1a** (3.8 g) was dissolved in H_2O (50 mL) containing KOH (8 g) and refluxed for 1 h. The filtered solution was cooled and acidified with HCl. The precipitated solid was collected, dried, and recrystallized from MeOAc to give 5-[5-(1,2,3,4-tetrazolyl)]salicylic acid (2.4 g), mp 253–255 °C dec. Anal. ($C_8H_6N_4O_3$) C, H, N.

5-[1-(1,2,3-Triazolyl)]salicylic Acid (2). *p*-Methoxyphenyl azide (5 g) and vinyl acetate (15 mL) were kept in an oil bath at 85 °C for 44 h. The crude product isolated by evaporation was extracted with hot cyclohexane from which crystals of 4-[1-(1,2,3-triazolyl)]anisole (4.2 g), mp 75.5–77.5 °C, came out on cooling. The anisole (567 mg) was dissolved in dry CH_2Cl_2 (15 mL) and kept at 0–10 °C while BBr_3 (0.2 mL) was added over 5 min. The solution was allowed to warm to room temperature over 30 min and evaporated to dryness. The 4-[1-(1,2,3-triazolyl)]phenol (246 mg), mp 216–220 °C, crystallized out on addition of dilute $NaHCO_3$ solution. The phenol (636 mg, 3.95 mmol) was ground up with dry powdered K_2CO_3 (5 g) and carboxylated under 4300 psi of carbon dioxide pressure and 250 °C for 12 h. The product was dissolved in hot water (100 mL) and filtered. The filtrate was acidified with concentrated HCl and filtered, and the solid was dried at 80 °C under vacuum to yield 5-[1-(1,2,3-triazolyl)]salicylic acid (430 mg), mp 269.5–271.5 °C, which was crystallized from EtOAc. Anal. ($C_9H_7N_3O_3$) C, H, N.

5-[2-(1,2,3-Triazolyl)]salicylic Acid (3). 2-(*p*-Anisyl)-1,2,3-triazole[11] (1.5 g, 0.0086 mol) was dissolved in CH_2Cl_2 (15 mL); BBr_3 (4.3 g, 0.017 mol) was added and allowed to stand for 20 min at 0 °C. The reaction mixture was poured into saturated $NaHCO_3$ solution containing a slurry of ice and filtered, and the aqueous layer was separated and evaporated to a small volume. The phenol crystallized, mp 84–86 °C (940 mg).

The carboxylation reaction was run with the phenol (99 mg, 0.00062 mol) and dry powdered K_2CO_3 (0.3 g, 0.0022 mol) at 250 °C and 6500 psi of carbon dioxide pressure for 6 h as for compound **2**. The usual workup gave 5-[2-(1,2,3-triazolyl)]salicylic acid (52 mg), mp 238–240 °C. Anal. ($C_9H_7N_3O_3$) C, H, N.

5-[1-(1,3,4-Triazolyl)]salicylic Acid (4). A mixture of 5-aminosalicylic acid (17.5 g, 0.114 mol), symmetrical diformylhydrazine (5.0 g, 0.057 mol), and P_2O_5 (8.1 g, 0.057 mol) was heated together in an oil bath at 250 °C for 1 h. The crude reaction mixture was added to saturated $NaHCO_3$ solution (200 mL) and filtered. The filtrate was neutralized with concentrated HCl and the solid collected. The dry solid was powdered, suspended in hot dimethylformamide, filtered hot, and crystallized from the filtrate to give 5-[1-(1,3,4-triazolyl)]salicylic acid (6.2 g), mp 265–270 °C dec. Anal. ($C_9H_7N_3O_3$) C, H, N.

5-[1-(1,2,4-Triazolyl)]salicylic Acid (5). *p*-Bromoanisole (56.1 g, 0.3 mol), 1,2,4-triazole (13.8 g, 0.2 mol), and K_2CO_3 (27.6 g, 0.2 mol) were refluxed in nitrobenzene (60 mL) together with CuBr (1.0 g). After 48 h, the reaction mixture was filtered and acidified with dilute HCl, and the nitrobenzene was steam distilled. The residue was made basic with 2.5 N KOH and the organic material extracted with $CHCl_3$. Isolation gave a blue oil (8.1 g). The crude anisole (8 g) in 48% HBr (25 mL) was refluxed for 1 h, evaporated to small volume, and poured onto saturated $NaHCO_3$. The precipitated phenol was filtered and dried (6.7 g), mp 216–220 °C. *p*-[1-(1,2,4-Triazolyl)]phenol (0.3 g, 0.0019 mol) prepared above and K_2CO_3 (0.8 g, 0.0058 mol) were reacted under carboxylation conditions at 5600 psi of carbon dioxide pressure and 250 °C for 8 h. The usual workup gave 5-[1-(1,2,4-triazolyl)]salicylic acid (0.12 g), mp 263–265 °C dec. Anal. ($C_9H_7N_3O_3$) C, H, N.

5-(3-Pyrazolyl)salicylic Acid (6). 3-(*p*-Anisyl)pyrazole[12] (1.0 g) was refluxed in 48% HBr (5 mL) for 1 h. The cooled reaction mixture was poured onto saturated $NaHCO_3$-ice. The precipitated solid was filtered, dried, and crystallized from EtOH to give *p*-(3-pyrazolyl)phenol (865 mg), mp 165–168 °C.

The above phenol (1.0 g, 0.0062 mol) and dry powdered K_2CO_3 (2.5 g, 0.018 mol) were combined under carboxylation conditions at 200 °C and 3500 psi of carbon dioxide pressure for 6 h. The reaction was worked up in the usual way and gave 5-(3-pyrazolyl)salicylic acid (0.82 g), mp 257–260 °C. Anal. ($C_{10}H_8N_2O_3$) C, H, N.

5-(*N*-Pyrazolyl)salicylic Acid (7). *p*-Bromoanisole (208 g, 1.12 mol), pyrazole (50 g, 0.735 mol), K_2CO_3 (100 g, 0.735 mol), and CuCN (2 g) were combined and refluxed in nitrobenzene (75 mL) for 24 h. The crude solution was acidified with concentrated HCl and nitrobenzene steam distilled off. The solution was then made neutral with KOH solution and extracted with $CHCl_3$ (3 × 200 mL). The crude isolate was distilled under reduced pressure

to give one fraction of pure 1-(*p*-anisyl)pyrazole, bp 138–140 °C (0.5 mm).

1-(*p*-Anisyl)pyrazole (3.7 g, 0.021 mol) and BBr_3 (10.7 g, 0.042 mol) were stirred at room temperature in dry CH_2Cl_2 (35 mL). At the end of 5 h, water, saturated $NaHCO_3$ solution, and then $CHCl_3$ (100 mL) were added. The $CHCl_3$ layer was separated, dried ($MgSO_4$), and filtered. Isolation gave *p*-(*N*-pyrazolyl)phenol (1.9 g), mp 94–96 °C.

The carboxylation reaction was run at 250 °C and 5100 psi of carbon dioxide pressure for 6 h with the phenol (0.2 g, 0.0012 mol) and K_2CO_3 (0.3 g, 0.0043 mol) The usual workup (see compound **2**) gave 5-(*N*-pyrazolyl)salicylic acid (0.12), mp 249–250 °C. Anal. ($C_{10}H_8N_2O_3$) C, H, N.

5-(2-Imidazolyl)salicylic Acid (8). *p*-Methoxybenzonitrile (11.9 g, 0.1 mol) in MeOH (3.2 g, 0.1 mol) was added to ether (75 mL) and saturated with dry HCl gas at 5 °C. After 8 h, the precipitate was filtered off and washed with ether to give 12.6 g, mp 170 °C.

The iminoether prepared above (10.8 g, 0.05 mol) was dissolved in MeOH (55 mL). β-Aminoacetaldehyde dimethyl acetal (5.3 g, 0.05 mol) was added to this solution in MeOH (20 mL) over 70 min. The reaction mixture was stirred for 36 h and evaporated to leave an oil. This oil was dissolved in $CHCl_3$ and a little ether. The crystalline dimethyl acetal hydrochloride **8a** (3.7 g), mp 144–146 °C, was collected. Anal. ($C_{12}H_{18}ClN_2O_3$) C, H, N.

The crude hydrochloride above (12 g) was mixed with concentrated H_2SO_4 (16 mL), keeping the temperature at 10 °C. At the end of the addition, the temperature was raised to 50 °C for 5 min, cooled, and diluted with water (60 mL). The aqueous solution was made basic with 2.5 N KOH solution and extracted with $CHCl_3$ (2 × 100 mL) Isolation of the $CHCl_3$ extract gave a red oil (6.1 g) The crude oil was recrystallized from water to give 2-(4-anisyl)imidazole (10.5 g) (**8b**), mp 152–154 °C. Anal. ($C_{10}H_{10}N_2O$) C, H, N. The anisylimidazole (8 g) above, in 48% HBr (50 mL), was refluxed for 3 h, cooled, and filtered. The solid was dissolved in water (50 mL) and made basic with saturated $KHCO_3$ solution. The precipitated solid was collected and dried (3.4 g), mp 225–226 °C.

4-(2-Imidazolyl)phenol (2.0 g) prepared above was ground with dry K_2CO_3 (8.0 g) and subjected to 2900 psi of carbon dioxide pressure for 8 h in a sealed tube at 250 °C. The usual workup as for compound **2** gave a solid which was recrystallized from EtOH to give 5-(2-imidazolyl)salicylic acid (0.85 g), mp 263–265 °C dec. Anal. ($C_{10}H_8N_2O_3 \cdot 2H_2O$) C, H, N.

5-(4-Imidazolyl)salicylic Acid (9). 4-(4-Anisyl)imidazole (1.6 g)[13] was refluxed in 48% HBr (15 mL) for 1.5 h. The cooled reaction mixture was filtered and the solid dropped into ice-cold aqueous $NaHCO_3$. The precipitated imidazole was filtered, dried, and recrystallized from EtOH to give the phenol **9a** (1.3 g), mp 231–232 °C. Anal. ($C_7H_6N_4O$) C, H, N.

4-(4-Imidazolyl)phenol (1.0 g, 0.06 mol) was powdered with dry K_2CO_3 (2.6 g) and heated at 250 °C in a sealed tube under a dry CO_2 pressure of 1350 psi for 8 h. The usual workup (compound **2**) gave a crude product which was dried and recrystallized from DMF to give 5-(4-imidazolyl)salicylic acid (2.7 g), mp 290–292 °C dec. Anal. ($C_{10}H_8N_2O_3 \cdot H_2O$) C, H, N.

5-(1-Imidazolyl)salicylic Acid (10). *p*-(1-Imidazolyl)phenol[14] was reacted on the conditions of carboxylation as described for compound **2**. The usual isolation and recrystallization from EtOH gave 5-(1-imidazolyl)salicylic acid, mp 255–257 °C dec. Anal. ($C_{10}H_8N_2O_3 \cdot 2H_2O$) C, H, N.

5-(*N*-Pyrryl)salicylic Acid (11). 5-Aminosalicylic acid (15.3 g, 0.1 mol) and 2,5-dimethoxytetrahydrofuran (13.2 g, 0.1 mol) in dry DMF (350 mL) were heated and stirred at reflux for 0.3 h with *p*-TsOH (0.7 g). The reaction was cooled, diluted with cold H_2O (150 mL), and extracted with ether (2 × 200 mL), and the aqueous layer was warmed to remove ether. On cooling, the crude salicylic acid crystallized. The crude solid was recrystallized from EtOAc (600 mL) to give 5-(*N*-pyrryl)salicylic acid (11.4 g), mp 229–230 °C. Anal. ($C_{11}H_9NO_3$) C, H, N.

5-(2-Pyrimidyl)salicylic Acid (13). 2-(4-Anisyl)-2-chloropyrimidine[15] (6.6 g, 0.03 mol) was hydrogenated in MeOH (200 mL) containing a 10% aqueous NaOH solution (20 mL) and Pd on barium sulfate catalyst at 41.25 psi of H_2 pressure. After 6 h, the hydrogenation had taken up 0.03 mol of H_2, the catalyst was filtered, and the filtrate was evaporated to a small volume. After addition of water, the crystalline material was filtered (5.3 g), mp 55–57 °C.

4-(2-Pyrimidyl)phenol was prepared from 2-(4-anisyl)pyrimidine by the procedure described for compound **5**. The product, **13a**, was recrystallized from $CHCl_3$, mp 194–196 °C. Anal. ($C_{10}H_8N_2O$) C, H, N.

The above phenol was reacted in the carboxylation reaction as described for compound **2** at 250 °C and 2700 psi of carbon dioxide pressure for 8 h. The phenol (1.5 g) gave 1.7 g of crude salicylic acid. This was recrystallized from aqueous DMF to give 0.9 g of 5-(2-pyrimidyl)salicylic acid, mp 292 °C. Anal. ($C_{11}H_8N_2O_3$) C, H, N.

5-(4-Pyrimidinyl)salicylic Acid. 4-(*p*-Anisyl)pyrimidine[16] (6.0 g) was refluxed in 48% HBr for 10 min. The solution was evaporated to near dryness and poured into an ice-cold saturated $NaHCO_3$ solution. The precipitate was collected, dried, and crystallized from acetone (4.8 g), mp 193–196 °C. The phenol (202 mg, 2.91 mmol) was carboxylated using conditions described for compound **2** with dry powdered K_2CO_3 (1.2 g, 8.73 mmol) at 200 °C and 5000 psi of carbon dioxide pressure for 12 h. The described isolation and crystallization from EtOH gave 5-(4-pyrimidyl)salicylic acid (250 mg), mp 286–287 °C. Anal. ($C_{11}H_8N_2O_3$) C, H, N.

5-(2-Oxazolyl)salicylic Acid (17). To a stirred solution of *p*-(2-oxazolyl)aniline[17] (480 mg) in 2 N H_2SO_4 (10 mL) immersed in an ice bath was added a solution of $NaNO_2$ (230 mg) in cold H_2O (5 mL), the addition being made dropwise during ca. 5 min. The ice bath was not replenished, and the solution was allowed to warm to room temperature with continued stirring for 1 h.

The solution was then warmed on the steam bath until N_2 evolution ceased, allowed to cool, and then filtered. The filtrate was treated with 2.5 N NaOH to pH ~5, affording a brown solid precipitate which was washed with water and air-dried to give 385 mg (80%), mp ~155–170 °C, of *p*-(2-oxazolyl)phenol (**17a**). Anal. ($C_{10}H_7NO_4$) H, N; C: calcd, 58.54; found, 57.95. The above crude phenol (403 mg, 2.5 mmol) and powdered K_2CO_3 (2 g) were reacted under carboxylation conditions as for compound **2** at 200 °C and 7500 psi of carbon dioxide pressure for 15 h. The standard isolation followed by crystallization from EtOH gave 5-(2-oxazolyl)salicylic acid (395 mg), mp 253–256 °C. Anal. ($C_{10}H_7NO_4$) C, H, N.

5-(4-Oxazolyl)salicylic Acid (18). *p*-Methoxy-α-bromoacetophenone (50 g) in formamide (200 mL) was heated at reflux for 4 h, cooled to room temperature, and filtered. The filtrate was evaporated to dryness and chromatographed on silica gel using mixtures of MeOH–$CHCl_3$ (10:90) as eluate. The initial fraction yielded 5-(*p*-anisyl)oxazole (**18a**), mp 72–76 °C.

The crude product from the above reaction (1.6 g) was reacted in CH_2Cl_2 (200 mL) and BBr_3 (2 g) as for compound **2** to give *p*-(4-oxazolyl)phenol (**18b**) (4.2 g), mp 141–142.5 °C. Anal. ($C_9H_7NO_2$) C, H, N.

p-(4-Oxazolyl)phenol (210 mg) and powdered K_2CO_3 (0.8 g) were reacted under carboxylation conditions as for compound **2** at 4600 psi of carbon dioxide pressure and 200 °C for 5 h. The usual workup gave 5-(4-oxazolyl)salicylic acid (160 mg), mp 236–237.5 °C dec. Anal. ($C_{10}H_7NO_4$) C, H, N.

5-(5-Oxazolyl)salicylic Acid (19). *p*-(5-Oxazolyl)phenol[18] (370 mg) and dry powdered K_2CO_3 (1.4 g) were reacted under carboxylation conditions as described for compound **2** at 240 °C and 3500 psi of carbon dioxide pressure for 12 h. The usual workup gave 5-(5-oxazolyl)salicylic acid (289 mg), mp 259.5–261 °C dec. Anal. ($C_{10}H_7NO_4$) C, H, N.

5-(4-Thiazolyl)salicylic Acid (24). *p*-Anisyl bromide (34 g), P_2S_5 (9.9 g), formamide (9.9 g), and 3 drops of piperidine were heated on a steam bath for 20 min. After cooling, the reaction mixture was made basic with 2.5 N Na_2CO_3 solution (200 mL). The product was extracted with CH_2Cl_2 (2 × 150 mL). Isolation gave 20 g of crude 4-(*p*-anisyl)thiazole.

The crude product from above was refluxed in 48% HBr in the usual way. Isolation gave 10.8 g of *p*-(4-thiazolyl)phenol, mp 250–252 °C.

Carboxylation on 1.3 g of the above product in the usual way gave 1.4 g of 5-(4-thiazolyl)salicylic acid, mp 258–261 °C. Anal. ($C_{10}H_7NO_3S$) H, N; C: calcd, 54.34; found, 54.86.

5-(5-Thiazolyl)salicylic Acid (26). *p*-Methoxy-α-(thioformamido)acetophenone[19] (3.0 g) in concentrated H_2SO_4 (9 mL)

was stirred at room temperature for 30 min, put into water (50 mL), and neutralized with dilute NH_4OH. The precipitate was filtered and the crude 5-(*p*-anisyl)thiazole (**26a**) was collected. The crude product (2 g) was cleaved in 48% HBr solution (8 mL). The usual workup gave 5-(5-thiazolyl)phenol (1.8 g), mp 230–233 °C. *p*-(5-Thiazolyl)phenol (1.2 g, 0.006 mol) and dry powdered K_2CO_3 (3.4 g, 0.024 mol) were reacted under carboxylation conditions at 200 °C and 5100 psi of carbon dioxide pressure for 6 h. The usual workup gave 5-(5-thiazolyl)salicylic acid (0.89 g), mp 294–295 °C. Anal. ($C_{10}H_7NO_3S$) C, H, N.

5-(5-Isothiazolyl)salicylic Acid (27). 5-(*p*-Anisyl)isothiazole[21] (6.0 g) was refluxed in 48% HBr solution as for compound **5**. *p*-(5-Isothiazolyl)phenol (**27a**) (5.3 g) was recrystallized from MeOH, mp 215–216 °C. Anal. (C_9H_7NSO) C, H, N. A carboxylation reaction on the above crude product (0.5 g, 0.0028 mol) at 225 °C and 4450 psi of carbon dioxide pressure for 8 h gave, after the usual workup, 5-(5-isothiazolyl)salicylic acid (0.3 g), mp 241–244 °C. Anal. ($C_{10}H_7NO_3S$) C, H, N.

5-(5-Isooxazolyl)salicylic Acid (28). Ethyl 5-acetylsalicylate (21.3 g, 0.1 mol) and $(CH_3)_2SO_4$ (25 g, 0.2 mol) were stirred together in hot 2.5 N NaOH solution (100 mL). The reaction mixture was allowed to stand at room temperature for 1 h and then it was refluxed for 6 h. The reaction mixture was cooled and acidified with HCl, and the precipitate was collected and dried. 5-Acetyl-2-methoxybenzoic acid (18.6 g), mp 137 °C, was obtained.

The acid (18.6 g) in absolute EtOH (200 mL) was saturated with HCl gas over 8 h. The reaction mixture was evaporated to 50 mL, water (300 mL) was added, and the ethyl ester was extracted with CH_2Cl_2 (2 × 100 mL). After drying and filtering, the solution was evaporated to give ethyl 5-acetyl-2-methoxybenzoate (12.9 g).

Ethyl 5-acetyl-2-methoxybenzoate prepared above (6.9 g, 0.031 mol) was reacted under conditions described[20] using sodium metal (0.7 g, 0.031 mol) and ethyl formate (2.3 g, 0.03 mol). The reaction mixture was refluxed overnight. The precipitate was filtered, dried (7.5 g), and used without further purification.

The sodium salt above (7.9 g, 0.039 mol) was added to EtOH (40 mL) to which $NH_2OH·HCl$ (2.8 g, 0.04 mol) had been added. The mixture was heated and sufficient water added to keep solution. After 1 h, Na_2CO_3 (2.1 g, 0.02 mol) dissolved in water (15 mL) was added dropwise during the next 3 h. The whole reaction was then refluxed for 7.5 h. The EtOH was evaporated off and the solution extracted with $CHCl_3$ (2 × 100 mL). Isolation gave an amber oil (4.0 g). The crude material (3.0 g) from the above reaction was refluxed in 48% HBr (15 mL) for 3 h. The crude precipitate was filtered and dried. It was recrystallized from acetic acid to give 5-(5-isooxazolyl)salicylic acid (1.8 g), mp 220–223 °C dec. Anal. ($C_{10}H_7NO_4$) C, H, N.

5-[4-(1,2,3-Thiadiazolyl)]salicylic Acid (29). Ethyl 5-acetyl-2-methoxybenzoate prepared as for compound **28** above (6 g, 0.027 mol) was added to a solution of ethyl hydrazinocarboxylate (2.8 g, 0.027 mol) in toluene (25 mL). The solution was then allowed to stand overnight at room temperature. The precipitate was filtered and dried (6.6 g), mp 84–86 °C.

The hydrazone (2.0 g, 0.0065 mol) prepared above was stirred in ether (10 mL) as $SOCl_2$ (5 mL) was added dropwise. At the end of 30 min, the ether was evaporated off and the solid recrystallized from benzene (1.2 g), mp 54–56 °C.

Ethyl 2-methoxy-5-[4-(1,2,3-thiadiazolyl)]benzoate (1.2 g) prepared above was refluxed in 48% HBr (8 mL) as described earlier. In this way 5-[4-(1,2,3-thiadiazolyl)]salicylic acid recrystallized from acetone (0.8 g), mp 243–244 °C dec, was obtained. Anal. ($C_9H_6N_2O_3S$) C, H, N.

***O*-Acetyl-5-pyrrylsalicylic Acid (30).** Acetic anhydride (1.2 g, 0.012 mol) was added to a stirred solution of the salicylic acid 11 (1.2 g, 0.0059 mol) in pyridine (10 mL) at room temperature. After 8 h the mixture was poured into ice water (40 mL). The aqueous solution was extracted with $CHCl_3$ (3 × 30 mL), and the extracts were combined and washed consecutively with dilute HCl (2 × 10 mL) and water (10 mL). The product was dried and crystallized from benzene, mp 171–173 °C (0.8 g). Anal. ($C_{13}H_{11}NO_4$) C, H, N.

***n*-Butyl 5-Pyrrylsalicoyl Carbonate (31).** *n*-Butyl chloroformate (1.37 g, 0.01 mol) was added at 0 °C to a stirred solution of the salicylic acid 11 (2.0 g, 0.01 mol) in benzene (10 mL) containing dimethylaniline (1 mL) over 10 min. The mixture was stirred for 12 h and then washed consecutively with 2.5 N HCl (4 × 20 mL) and water (2 × 10 mL) from benzene (100 mL). The benzene layer was dried, filtered, and evaporated to dryness. The residue was crystallized from chloroform, mp 158–160 °C (2.1 g). Anal. ($C_{16}H_{17}NO_5$) C, H, N.

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