Journal of Medicinal Chemistry

Volume 21, Number 11 November 1978

Articles

Novel Analgesic-Antiinflammatory Salicylates

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5-(2,4-Difluorophenyl)salicylic acid, diflunisal (**25**), is the best compound, in terms of both efficacy and safety, from over 500 salicylates investigated in our laboratories. It is a chemically distinct, nonacetylating salicylic acid, more active than aspirin as an analgesic and antiinflammatory agent and superior in duration of action and therapeutic index. Some recent clinical and biochemical observations are briefly discussed.

For 100 years the simplicity of the structure of salicylates has belied the complexity of their biological properties. Clinically, acetylsalicylic acid (aspirin, **2**) is a mild, antiinflammatory, nonnarcotic analgesic and is frequently the first choice in the treatment of arthritic disorders. Its beneficial effects, however, can be accompanied by tinnitus, hypersensitization, interference with blood platelet function, and, most commonly, gastrointestinal bleeding.[1]

The elucidation of the molecular events in aspirin therapy and concomitant toxicity has engendered a multitude of studies which show that it affects physiological function via many sites of action.[1] In particular, its irreversible inhibition of prostaglandin biosynthesis is considered to be a plausible mechanism of its antiinflammatory action.[2-4]

Empirically, the goal of a more potent, less toxic, and longer acting form of aspirin has been pursued in many research institutions, and hundreds of analogues have been prepared,[1,5-8] including a recent series of heterocycles from these laboratories.[9] Adequate potency with good therapeutic ratio, however, has been elusive.

Following our previous study of nonsteroidal antiinflammatory agents, we used antiinflammatory and analgesic assays[10] to reinvestigate the structure–activity relationship of salicylates.

Structure–Activity Relations. Some representative examples of salicylic acids from these studies are presented in Table I. Selected active compounds were also examined in gastric hemorrhage and intestinal perforation assays.[11] Among the first group of compounds evaluated, the higher potency of 5-phenylsalicylic acid in comparison to salicylic acid (**1**) became evident. A special emphasis in our synthetic work was then directed to fluorophenyl substituents because of their pronounced activity-enhancing effects in antiinflammatory structures such as the ring A pyrazolocorticoids[12-14] and substituted phenylpropionic acids.[15]

Substituents on the 5-phenyl ring other than fluorine or chlorine did not increase this activity, which reached a maximum for monosubstitution with fluorine in the para position. Additional groups such as alkyl or halogen on the salicylate ring were of no benefit. However, the activity of compound **16** was improved by the introduction of a second fluorine to give compound **25**.

Biological Results and Discussion. Preliminary laboratory and clinical studies with *O*-acetyl-5-(4-fluorophenyl)salicylic acid (flufenisal, **17**)[16,17] were highly encouraging.

As shown in Table II, the compound was four to five times more potent than aspirin in the antiinflammatory assays in rats.[10] Analgesia was approximately twice that of aspirin with longer duration of action. In the acute gastric hemorrhage test in the rat,[11] the ED_{50} for flufenisal was almost 15 times less irritating than aspirin in the same assay.

In the clinic,[17] single doses of flufenisal of 300–600 mg appeared equal in effectiveness to 600–1200 mg of aspirin in the relief of episiotomy pain and to have double the duration of action. These promising studies were discontinued on completion of the high dose safety assessment in rats and dogs, which showed that at 100 mg/kg/day gastrointestinal lesions and renal papillary necrosis were produced.

After an intensive reinvestigation of related compounds our attention became focused on 5-(2,4-difluorophenyl)-salicylic acid (diflunisal, **25**),[18,19] which was found to be superior in activity to flufenisal in animal assays. A pharmacological profile of diflunisal in comparison with those of flufenisal, aspirin, ibuprofen, sulindac, and indomethacin is presented in Table II. On a weight basis, diflunisal is almost 20 times more potent than aspirin in a yeast-induced hyperesthesia assay and seven to nine times in the adjuvant arthritis and carrageenan-induced foot edema assays. However, it is only slightly more active than aspirin as an antipyretic.

The *O*-acetyl group in aspirin has long been recognized as an important contributor to its antiinflammatory and analgesic action[1,20] and, in particular, has been shown to

0022-2623/78/1821-1093$01.00/0

Table I. Preparation and Antiinflammatory Activity of Substituted Salicylic Acids

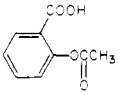
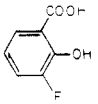
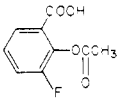
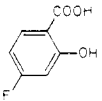
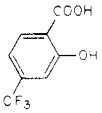
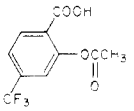
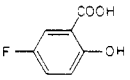
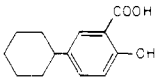
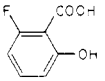
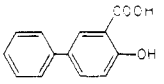
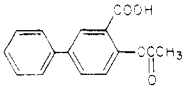
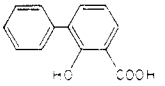
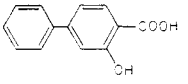
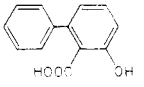
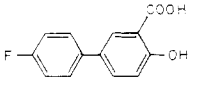
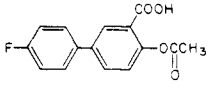
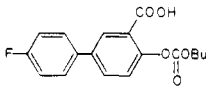
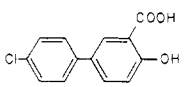
no.	structure	antiinflam efficacy, ED_{50}, mg/kg[a]	formula[b]	mp, °C	recrystn solvent	synthetic[c,d] method
1		77	$C_7H_6O_3$			
2		89	$C_9H_8O_4$			
3		90	$C_7H_5FO_3$[e]			
4		281	$C_9H_7FO_4$	123-125	C_6H_6	Q
5		400	$C_7H_5FO_3$[f]			
6		inact.	$C_8H_5F_3O_3$[g]			
7		155	$C_{10}H_7F_3O_4$[g]			
8		120	$C_7H_5FO_3$[e]	182-183		
9		inact.	$C_{13}H_{16}O_3$[h]			N
10		inact.	$C_7H_5FO_3$[i]	165-165.5	C_6H_6	
11		54	$C_{13}H_{10}O_3$[j]			
12		170	$C_{15}H_{12}O_4$	147-150	$CHCl_3$	A
13		130	$C_{13}H_{10}O_3$[j]			
14		150	$C_{13}H_{10}O_3$[k,l]	207-208	acetone-hexane	N
15		inact.	$C_{13}H_{10}O_3$[m]			
16		14	$C_{13}H_9FO_3$[n]	199-203	CH_3OH-C_6H_6	N
17		24	$C_{15}H_{11}FO_4$	134-137	C_6H_6	Q
18		25	$C_{18}H_{17}FO_5$	95-97	$CHCl_3$-hexane	R
19		24	$C_{13}H_9ClO_3$[n]	219-221	C_6H_6	N

Table I (*Continued*)

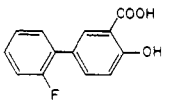
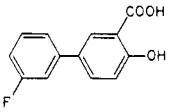
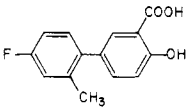
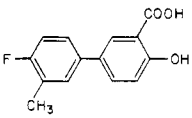
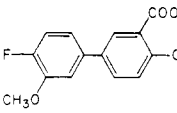
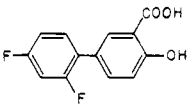
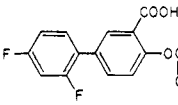
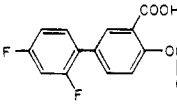
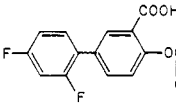
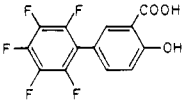
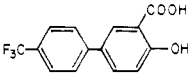
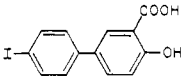
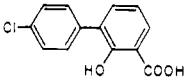
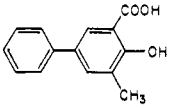
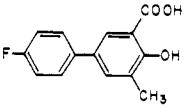
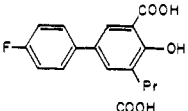
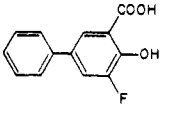
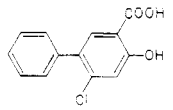
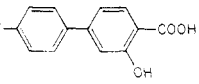
no.	structure	antiinflam efficacy, ED_{50}, mg/kg[a]	formula[b]	mp, °C	recrystn solvent	synthetic[c,d] method
20		20	$C_{13}H_9FO_3$[o]	201-203	C_6H_6	N
21		40	$C_{13}H_9FO_3$	196-197	C_6H_6	V
22		76	$C_{14}H_{11}FO_3$	175-177	C_6H_6	III
23		inact.	$C_{14}H_{11}FO_3$	208-209	C_6H_6	V
24		inact.	$C_{14}H_{11}FO_4$	206-208	C_6H_6-petr ether	II
25		9.8	$C_{13}H_8F_2O_3$	210-211	C_6H_6-petr ether	I, V
26		27	$C_{15}H_{10}F_2O_4$	177-180	acetone-petr ether	Q
27		30	$C_{16}H_{12}F_2O_5$	115-117	acetone-petr ether	R
28		12	$C_{18}H_{16}F_2O_5$	103-104.5	$CHCl_3$-hexane	R
29		20	$C_{13}H_5F_5O_3$	241-243	C_6H_6-hexane	IV
30		50	$C_{14}H_9F_3O_3$	207-209	DMF-H_2O	VI
31		120	$C_{13}H_9IO_3$	211-212	HOAc-dil HCl	V
32		inact.	$C_{13}H_9ClO_3$[p]	218-219	C_6H_6	
33		60	$C_{14}H_{12}O_3$	215-217	C_6H_6-petr ether	O, N
34		60	$C_{14}H_{11}FO_3$	211-212	C_6H_6	O, N
35		inact.	$C_{16}H_{15}FO_3$	188-190	C_6H_6	P
36		110	$C_{13}H_9FO_3$	154-155	C_6H_6	V[q]

Table I (*Continued*)

no.	structure	antiinflam efficacy, ED_{50}, mg/kg[a]	formula[b]	mp, °C	recrystn solvent	synthetic[c,d] method
37		inact.	$C_{13}H_9ClO_3$	218-222	C_6H_6	II
38		400	$C_{13}H_9FO_3$	209-210	aq CH_3OH	S

[a] Antiinflammatory efficacy; carrageenan-induced foot edema. Drugs in aqueous suspension were administered by gastric gavage to six rats at each dose level. The highest dose employed for "inactive" compounds was 400 mg/kg; see ref 10. [b] Analysis of new compounds for C, H, and halogen agreed with theoretical values within 0.4%. Footnotes *e-p* are references for known salicylic acids or for phenols used in synthetic method N. [c] Capital letters refer to synthetic methods in the Experimental Section. [d] Roman numerals refer to sequential synthetic routes outlined in Scheme I. [e] L. N. Ferguson, R. R. Holmes, and M. J. Calvin, *J. Am. Chem. Soc.*, **72**, 5315 (1950). [f] O. Baine et al., *J. Org. Chem.*, **19**, 510 (1954). [g] M. Hauptschein, E. A. Nodiff, and A. J. Sagiomo, *J. Am. Chem. Soc.*, **76**, 1051 (1954). [h] R. R. Burtner and J. M. Brown, *ibid.*, **75**, 2334 (1953). [i] Prepared by the method of W. W. Kaeding and A. T. Shulgin, *J. Org. Chem.*, **27**, 3551 (1962). [j] N. N. Vorozhtzov and A. T. Trosshchonko, *J. Gen. Chem. USSR*, **8**, 427 (1958); *Chem. Abstr.*, **32**, 7097 (1938). [k] P. Jacobsen and A. Loeb, *Ber.*, **36**, 4082 (1903). [l] See ref 48 (phenol). [m] G. Heyl, *J. Prakt. Chem.*, **59** (2), 456 (1899). [n] H. Rowe and H. L. Fleishman, *J. Am. Chem. Soc.*, **69**, 509 (1947) (phenol). [o] A. Angeletti and D. Gatti, *Gazz. Chim. Ital.*, **58**, 630 (1929); *Chem. Abstr.*, **23**, 2961 (1929) (phenol). [p] J. D. Early and J. B. Chupp, Belgian Patent 639 933 (1964); *Chem. Abstr.*, **63**, 16267c (1965). [q] Kolbe reaction on lithium phenolate.

Table II. Pharmacological Profiles of Diflunisal and Other Agents. Effective Dose in mg/kg Given by Oral Route

	aspirin	flufenisal	diflunisal	ibuprofen	sulindac	indomethacin
analgesic to yeast-induced[a,h] inflam (rat)	87	35	4.6	2.6	1.7	2.2
antipyretic (rat)[a,i]	40 (35.9-44.3)	160	27.8 (23.0-33.6)	5.9	2.9 (2.2-4.7)	1.8 (1.4-2.3)
carrageenan-induced foot[a,f,i] edema (rat)	89 (81.8-97.1)	23.9	9.8 (7.1-14.1)	23 (15.2-36.0)	5.5 (4.8-6.5)	2.7 (2.4-3.1)
pain in dog knee joint[b,f,j]	68		24		45	1.7
adjuvant arthritis (rat)[c,f,k]	78	~40	10.4	28	0.55	0.27
PG synthetase inhibn,[d,f] μg/mL	13	10	0.6	0.4	inactive	0.1
intestinal perforating ulcers (rat)[e]	none at 1024	>512	520	<256	69	5.2
gastric hemorrhage (rat)[e]	81[f]	>512	>256[g]	<16	27	5.4

[a] See ref 10. [b] M. E. Rosenthale, J. Kassarich, and F. Schneider, Jr., *Proc. Soc. Exp. Biol. Med.*, **122**, 693 (1966). [c] C. A. Winter and G. W. Nuss, *Arthritis Rheum.*, **9**, 394 (1966). [d] See ref 36. [e] See ref 11; no confidence limit data. [f] ED_{50}, effective dose to achieve 50% inhibition. [g] No erosions at 256 mg/kg; some were evident at 512 mg/kg but about one-half of the rats died at this dose. [h] Dose of drug to elicit threshold response at 30-mm mercury pressure. [i] Confidence limits in parentheses. [j] No confidence limits for aspirin and diflunisal; for sulindac, nine dogs (9-54 mg/kg); for indomethacin, data from 22 dogs. [k] No confidence limits for these data. Number of animals used: for aspirin, 288 rats; for diflunisal, 36 rats; for sulindac, 60 rats; for indomethacin, 55 rats.

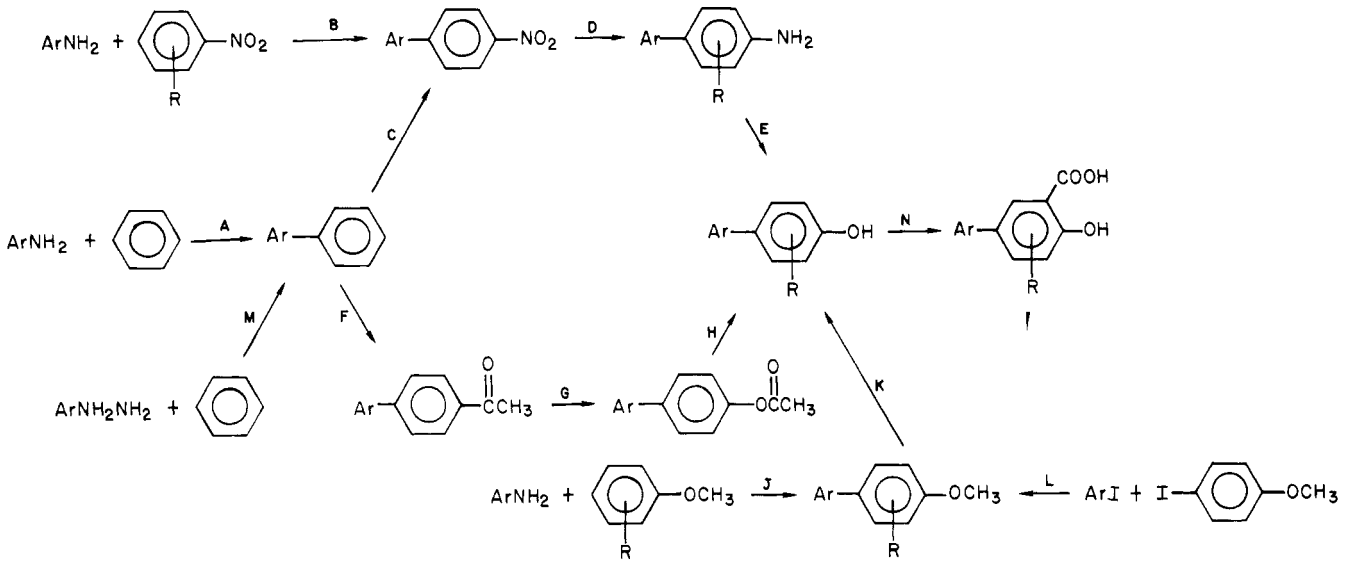
acetylate macromolecules, serum albumin, and platelet membrane both in vitro and in vivo.[21,22] It has also been postulated that there is a connection between this in vivo trans acetylation and the toxicity of aspirin.[23-25] Aspirin, however, exhibits pharmacokinetics superior to salicylic acid and several *O*-carbonate esters have been prepared to retain this advantage with diminished local irritation.[26] Since carbonates would be expected to show less tendency toward trans acylation, the *O*-*n*-butyl carbonate of diflunisal was prepared and, although equipotent on a molar basis, offered no advantage in gastrointestinal assays over the parent compound. It seemed prudent, therefore, to omit any *O*-acyl function, and on the basis of efficacy, long-term safety data, and promising pharmacological behavior,[27,28] diflunisal was chosen for detailed clinical evaluation.

Diflunisal is readily absorbed in man, reaching peak plasma levels of 30 and 99 μg/mL at 2 h after single oral doses of 250 and 500 mg, respectively. The plasma disappearance half-time, as with aspirin, is dosage dependent and varies from about 7.5 h from peak plasma level for a 125-mg dose to 10–12 h for a 500-mg dose.[29] Approximately 95% of diflunisal is excreted in the urine in 96 h, in the form of its ether and ester glucuronides.[30] Diflunisal increases the renal clearance of uric acid in a dose-related manner.[34] It does not affect platelet aggregation, bleeding time, and several hematological parameters at the therapeutic doses of 500–750 mg/day in man.[34,35] Diflunisal is a moderately active reversible inhibitor of prostaglandin synthetase[36] and decreases the production of prostaglandins E and F in vitro and in vivo. The urinary excretion of the major metabolite of PGE_1 and PGE_2, 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid, in normal subjects receiving 375 mg b.i.d. for 5 days was reduced by ca. 70%.[37] However, without an *O*-acetyl group, diflunisal cannot acetylate cyclooxygenase, an irreversible process possibly involved in the prolonged antiplatelet effect of aspirin.[38-40]

These data and information from current clinical trials demonstrate that diflunisal is a more potent analgesic and antiinflammatory agent than aspirin, exhibiting a longer duration of action and reduced toxicity.[31-33]

Chemistry. Most of the compounds prepared for this study were synthesized via the Marasse[41] modification of the Kolbe–Schmitt carbonation of phenols.[42,43] Synthetic routes to the requisite phenolic biphenyls and the con-

Scheme I. Synthetic Routes for Preparation of Arylsalicylic Acids[a]



[a] Route I, AFGHN; route II, BDEN; route III, ACDEN; route IV, MCDEN; route V, JKN; route VI, LKN.

version to 5-arylsalicylic acids are summarized in Scheme I. The interannular bond of the biphenyl structure was formed via the Cadogan[44] adaptation of the Gomberg–Bachman–Hey[45] reaction (methods A, B, and J), the Ullman reaction[46] (method L), or the arylation of benzene with pentafluorophenylhydrazine[47] (method M). In methods B, J, and L, the functionality ($-NO_2$ or $-OCH_3$) which was to be transformed ultimately to phenolic –OH was present at the outset in one of the starting materials. Yields in these methods were diminished markedly by isomer formation. In methods C and F the functionality in the "salicylic" ring was introduced into the biphenyl nucleus by nitration and Friedel–Crafts acylation, respectively. The acylation reaction (method F) was quite efficient in yielding almost exclusively the para isomer. Conversion of the nitro group (methods D and E), the acetyl group (methods G and H), and the methoxyl group (method K) to the phenolic hydroxyl function was accomplished by standard procedures.

The structures of the intermediates obtained in the various methods were verified by NMR when the problem of selecting the required isomer was encountered. Some of the intermediates were used in subsequent reactions without purification to analytical specifications.

The phenols used in the synthesis of compounds **33** and **34** were obtained by the reduction of the carboxyl group of compounds **11** and **16** to methyl groups (method O). Compound **36** was prepared via an ortho Claisen rearrangement of the *O*-allyl ether derivative of compound **16** (method P). Starting from 4-fluoroacetophenone, compound **38** was prepared in a manner analogous to that for 4-phenylsalicylic acid.[48]

Experimental Section

Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Elemental analyses were determined at the Merck Sharp & Dohme Research Laboratories by Mr. Richard Boos and his associates.

Method A. Preparation of Biphenyls by Arylation of Benzene.[44] 2,4-Difluorobiphenyl. In a 12-L flask fitted with thermometer, mechanical stirrer, and reflux condenser, a mixture of 100 g of 2,4-difluoroaniline, 146 mL of isoamyl nitrite, and 9 L of benzene was heated in a water bath until gas evolution began, ca. 67 °C. The bath was removed; the reaction mixture was stirred at ambient temperature for 1.5 h and then heated at reflux for 2 h. After standing at 25 °C for 2 days the mixture was concentrated in vacuo and the residue taken up in ether. After washing with water, aqueous sodium bicarbonate, dilute HCl, and water, the ether phase was dried and evaporated. The crude product was chromatographed on silica gel to yield 76.4 g (51%) of the desired compound, mp 64–67 °C.

Method B. Preparation of 4-Nitrobiphenyls by Arylation of Nitrobenzene. 3-Methoxy-4-fluoro-4′-nitrobiphenyl. A mixture of 38 g of 3-methoxy-4-fluoroaniline, 2000 mL of nitrobenzene, and 53 mL of isoamyl nitrite was warmed on the steam bath until a vigorous reaction with evolution of gas commenced. The reaction was allowed to proceed without heating until the gas evolution subsided, and the mixture was then heated on the steam bath for an additional 2 h. The excess of nitrobenzene was removed by vacuum distillation, the last traces by steam distillation. The residue was chromatographed on a column of silica gel and fractions containing the desired isomer were selected from those eluted by petroleum ether–ether. These combined fractions were rechromatographed on neutral alumina, and the desired isomer was eluted with petroleum ether–ether: yield 0.98 g (2%).

Method C. Preparation of 4-Nitrobiphenyls by Nitration. 2-Fluoro-4′-nitrobiphenyl. To a stirred suspension of 33.3 g of 2-fluorobiphenyl (prepared by method A) in 40 mL of glacial acetic acid was added 39 g of fuming HNO_3 dropwise. The temperature rose gradually to 32 °C and it was then lowered to and kept at ca. 25 °C with a cold water bath during the remainder of the addition. After the addition was complete, the mixture was heated cautiously to 65 °C during which time it became homogeneous. After 2 h at this temperature, the reaction mixture was heated at 75 °C for 3 h. After keeping at 25 °C overnight the mixture was poured into ice–water, and the precipitate was washed several times with water by decantation. The crude product was taken up in ether, washed with sodium bicarbonate solution and water, and dried over sodium sulfate, and the solvent was removed. Chromatography on 1350 g of silica gel using petroleum ether–ether as the eluent yielded 18.1 g (43%) of the desired 2-fluoro-4 -nitrobiphenyl.

Method D. Preparation of 4-Aminobiphenyls. 4-(Pentafluorophenyl)aniline. A solution of 17.3 g of 2′,3′,4′,5′,6′-pentafluoro-4-nitrobiphenyl (prepared by method C) in 250 mL of ethanol was hydrogenated at 25 °C and 40 psi of pressure in the presence of 250 mg of PtO_2. After the required uptake of hydrogen, the mixture was filtered, the filtrate concentrated, and the crude product recrystallized from ether–hexane after treating with charcoal: yield 12.6 g (76%); mp 131–133 °C. Anal. ($C_{12}H_6F_5N$) C, H, F.

Method E. Preparation of 4-Hydroxybiphenyls from the Corresponding Aminobiphenyls. 4-Hydroxy-2′-methyl-

4′-fluorobiphenyl. To a cooled (0 °C) suspension of 5.5 g of 4-amino-2′-methyl-4′-fluorobiphenyl (prepared by method D) in 100 mL of 2 N H_2SO_4 was added slowly a solution of 2.0 g of $NaNO_2$ in 25 mL of H_2O with stirring and continued cooling. After the mixture became homogeneous, it was added slowly to 100 mL of boiling 50% H_2SO_4. The mixture was boiled for an additional 5 min and then allowed to cool to 25 °C. The product was extracted with chloroform; the solution was dried and treated with charcoal. After evaporation of solvent the crude product was chromatographed on silica gel: yield 2.5 g (45%); oil.

Method F. Preparation of 4-Acetylbiphenyls by Friedel–Crafts Acetylation. 4-Acetyl-2′,4′-difluorobiphenyl. To a stirred mixture of 37.5 g of 2,4-difluorobiphenyl (prepared by method A), 250 mL of CS_2, and 100 g of anhydrous $AlCl_3$ was added 22 g of acetic anhydride. The mixture was heated on the steam bath until a vigorous reaction occurred. After the reaction subsided, the mixture was refluxed for 0.5 h and then poured into ice–water. The product was extracted into ether, washed with aqueous potassium carbonate, and dried over $MgSO_4$. Evaporation of the ether yielded 43 g (94%) of crude product, mp 68–71 °C, which was used without purification in the next step.

Method G. Preparation of 4-Acetoxybiphenyls by the Baeyer–Villiger Reaction. 4-Acetoxy-2′,4′-difluorobiphenyl. A solution of pertrifluoroacetic acid was prepared by the dropwise addition of 50.6 mL of trifluoroacetic anhydride into 50 mL of cold dichloromethane containing 8.2 mL of 90% hydrogen peroxide. This cold solution was then added dropwise during 0.5 h to a stirred mixture of 43 g of crude 4-acetyl-2′,4′-difluorobiphenyl (method F), 150 mL of dichloromethane, and 130 g of disodium hydrogen phosphate. The reaction was exothermic and reflux occurred during the addition. After heating at reflux for an additional 0.5 h the mixture was filtered and the filtrate was washed successively with water, 10% aqueous sodium carbonate, saturated aqueous sodium bisulfite, and aqueous ammonium sulfate. Evaporation of the solvent yielded 44 g (95%) of crude product, mp 90–95 °C, which was saponified without further purification. Recrystallization of a sample from ethanol raised the melting point to 100–102 °C.

Method H. Preparation of 4-Hydroxybiphenyls by Saponification of the Corresponding Acetoxy Compounds. 4-Hydroxy-2′,4′-difluorobiphenyl. A mixture of 16.2 g (0.065 mol) of the acetoxy biphenyl compound was heated at reflux with 100 mL of 2.5 N sodium hydroxide for 2 h. After cooling, the mixture was acidified with HCl and the product filtered and dried: yield 13 g (97%); mp 143–148 °C. Recrystallization from benzene gave mp 151–153 °C. Anal. ($C_{12}H_8F_2O$) C, H, F.

Method J. Preparation of 4-Methoxybiphenyls by Arylation of Anisoles. 4-Methoxy-3′-methyl-4′-fluorobiphenyl. A mixture of 56 g of 4-fluoro-3-methylaniline, 2000 mL of anisole, and 85 mL of isoamyl nitrite was warmed on the steam bath until the vigorous evolution of gas began. The reaction was allowed to proceed without heating until it subsided and then the mixture was heated on the steam bath for an additional 2 h. The excess anisole was removed by vacuum distillation and the residue was chromatographed on a column of silica gel using petroleum ether–ether as the eluting solvent. Fractions containing the desired isomer were selected and recrystallized from methanol: yield 4.2 g (4.3%); mp 84–85 °C. Anal. ($C_{14}H_{13}FO$) C, H, F.

Method K. Preparation of 4-Hydroxybiphenyls from the Corresponding Methoxy Compounds. 4-Hydroxy-3′-methyl-4′-fluorobiphenyl. To a solution of 4.2 g of 4-methoxy-3′-methyl-4′-fluorobiphenyl in 150 mL of boiling acetic acid was added 15 mL of 47–51% HI and the boiling continued 3 h. The crude product precipitated upon the addition of water and was recrystallized from ether–hexane: yield 3.7 g (95%); mp 116–117 °C. Anal. ($C_{13}H_{11}FO$) C, H, F.

Method L. Preparation of 4-Methoxybiphenyls via the Ullmann Reaction. 4-Methoxy-4′-trifluoromethylbiphenyl. A mixture of 85 g of 4-iodoanisole and 50 g of 4-iodobenzotrifluoride was heated and stirred at 200 °C for 5 days while a total of 180 g of copper powder was added periodically in portions. The cooled reaction mixture was extracted in a Soxhlet apparatus with heptane. By fractional crystallization of the extract, 11.2 g (24%) of the desired compound was obtained, mp 130–131 °C.

Method M. Preparation of 2,3,4,5,6-Pentafluorobiphenyl. This compound was prepared by the method of Birchall et al.[47]

Method N. Preparation of Salicylic Acids by Carbonation of the Corresponding Phenols. 5-(2′,4′-Difluorophenyl)-salicylic Acid (Diflunisal). A mixture of 2.06 g of 4-hydroxy-2′,4′-difluorobiphenyl and 6.9 g of anhydrous potassium carbonate was exposed to carbon dioxide at 3400 psi at 250 °C for 6 h. The dark mass obtained from the carbonation was dissolved in 500 mL of water and filtered, the filtrate acidified with HCl, and the product filtered. The dried product was recrystallized from toluene: mp 210–211 °C; yield 2.02 g (81%).

Method O. Preparation of 3-Methyl-4-hydroxy-4′-fluorobiphenyl. A solution of 5.0 g of methyl 5-(4′-fluorophenyl)salicylate (method P) in 25 mL of ether was added to a stirred suspension of 1.28 g of lithium aluminum hydride in 100 mL of ether at a rate sufficient to maintain gentle reflux. Heating at reflux temperature was continued for 0.5 h after the addition. The excess hydride was decomposed with ethyl acetate, and sufficient dilute hydrochloric acid was added to make separation of the ether layer possible. The ether phase was washed with water, dried over magnesium sulfate, and concentrated to dryness. Trituration with hexane yielded 3.93 g of 4-(4′-fluorophenyl)-2-hydroxymethylphenol, mp 150–157 °C.

A mixture of 3.0 g of the above compound, 10 mL of acetic anhydride, and 6 mL of pyridine was heated on the steam bath for 1 h. The reaction mixture was poured into ice water and stirred for 0.5 h, and the product was extracted into ether. After drying with magnesium sulfate and treating with activated charcoal, 4-(4′-fluorophenyl)-2-(acetoxymethyl)phenyl acetate was obtained as an oil. The yield was 3.95 g.

A solution of 3.9 g of this diacetate in 30 mL of glacial acetic acid was hydrogenated in the presence of 0.5 g of 5% Pd/C catalyst at 40 psi and 70 °C until the uptake of hydrogen was 1 equiv. The catalyst and solvent were removed, the product was taken up in ether, washed with dilute sodium bicarbonate solution, and dried, and the solution was concentrated to dryness. The crude yield was 2.95 g. Chromatography of 2.6 g of the crude product on 110 g of silica gel furnished 2.1 g (80%) of 4-(4′-fluorophenyl)-2-methylphenyl acetate, which when eluted with benzene gave mp 71–73 °C. Recrystallization from ethanol gave mp 72–73 °C. Anal. ($C_{15}H_{13}FO_2$) C, H, F.

A mixture of 2.01 g of this ester, 10 mL of ethanol, and 10 mL of 1.25 N sodium hydroxide was heated at reflux for 20 min. The reaction mixture was concentrated to dryness in vacuo, and the residue was redissolved in water. After acidification and extraction of the product with ether, 1.6 g (97%) of 3-methyl-4-hydroxy-4′-fluorobiphenyl was obtained, mp 130–131 °C. Anal. ($C_{13}H_{11}FO$) C, H, F.

Method P. Preparation of 3-Propyl-5-(4′-fluorophenyl)salicylic Acid. A mixture of 18 g of 5-(4′-fluorophenyl)-salicylic acid, 60 mL of methanol, and 6 mL of concentrated H_2SO_4 was heated at reflux 21 h. The mixture was concentrated in vacuo and partitioned between water and dichloromethane. The organic layer was washed with dilute $NaHCO_3$ solution, dried with $MgSO_4$, and treated with charcoal, and the solvent was evaporated to yield 16.8 g (85%) of methyl 5-(4′-fluorophenyl)salicylate, mp 51–53 °C. Anal. ($C_{14}H_{11}FO_3$) C, H, F.

A mixture of 6.6 g of this ester, 5.5 g of anhydrous potassium carbonate, 25 mL of acetone, and 4.5 g of allyl bromide was heated at reflux for 2 h and then stirred at room temperature overnight. The mixture was distributed between water and ether and the ether phase was dried and evaporated to yield 6.0 g (78%) of methyl 2-allyloxy-5-(4′-fluorophenyl)benzoate as an oil.

This material, 5.5 g, was heated under an N_2 atmosphere at 235 °C for 35 min. Recrystallization from ethanol yielded 3.76 g (68%) of methyl 3-allyl-5-(4′-fluorophenyl)salicylate, mp 76–77 °C. Anal. ($C_{17}H_{15}FO_3$) C, H, F.

Saponification of the foregoing ester with aqueous methanolic sodium hydroxide yielded 3-allyl-5-(4′-fluorophenyl)salicylic acid, mp 170–172 °C from benzene. Anal. ($C_{16}H_{13}FO_3$) C, H, F.

Hydrogenation of 0.8 g of the above allyl compound in ethanol in the presence of platinum oxide yielded 3-propyl-5-(4′-fluorophenyl)salicylic acid: yield 0.72 g (90%); mp 188–190 °C. Anal. ($C_{16}H_{15}FO_3$) C, H, F.

Method Q. Acetylation of Salicylic Acids. Compound 17 (Flufenisal). A mixture of 3 g of 5-(4′-fluorophenyl)salicylic acid, 12 mL of pyridine, and 3 mL of acetic anhydride was heated on the steam bath for 20 min. The mixture was poured onto ice and

the product extracted with methylene chloride. After drying and evaporation of the solvent, the crude product was recrystallized.

Method R. Preparation of Alkyl Carbonate Esters.[26] **Compound 28.** To a mixture of 17 g (0.068 mol) of 5-(2',4'-difluorophenyl)salicylic acid, 60 mL of benzene, and 17.28 g of dimethylaniline at 25 °C was added 9.28 g (0.068 mol) of *n*-butyl chloroformate. The mixture was stirred for 3 h, washed with 2.5 N HCl and water, dried over $MgSO_4$, and concentrated, and the residue was recrystallized from chloroform–hexane.

4-(4'-Fluorophenyl)salicylic Acid (38). (a) 4-Fluoro-hydroxymethyleneacetophenone Sodium Salt. Sodium hydride oil dispersion (50 g, 53%) was added in portions to a vigorously stirred solution of 4-fluoroacetophenone (100 g) and redistilled ethyl formate (174 mL) in benzene (1 L) at room temperature. The mixture became hot and in 1 h appeared as a thick yellow slurry, which was cooled and filtered. The solid was washed with benzene, with 1:4 ethanol–ether, and finally with ether, yielding a yellow-orange powder (147 g).

(b) 4-Fluoromethoxymethyleneacetophenone. The above crude sodium enolate was dissolved in water (300 mL) and dimethyl sulfate (82 g) added dropwise in 30 min to the vigorously stirred solution at room temperature. After being stirred for 5 h, the mixture was extracted with ether and the ethereal extract washed with aqueous 0.5 N NaOH and then with water to neutrality. The dried ethereal solution was evaporated and the residual oil distilled at reduced pressure, 54.7 g, bp 124 °C (4 mm), crystallizing on cooling. A portion was recrystallized from ether, forming colorless needles (**3**), mp 53–55 °C.

(c) Ethyl 4-(4'-Fluorophenyl)salicylate. Sodium hydride oil suspension (10.0 g, 53%) was added to a solution of ethyl acetoacetate (28.9 g) in benzene (500 mL) forming a slurry of the sodium salt. The mixture was cooled to 10 °C and a solution of 4-fluoromethoxymethyleneacetophenone (40.0 g) (**3**) in benzene (100 mL) added rapidly with vigorous stirring. After 30 min at room temperature, the mixture was boiled under reflux for 1 h and cooled to room temperature, and an orange resinous solid filtered off. This crude sodium salt was triturated with benzene, ether, and petroleum ether, becoming a yellow powder, which was shaken with ether (500 mL) and an excess of aqueous NaH_2PO_4 (200 mL). The ethereal layer was dried and evaporated to ca. 100 mL, and an equal volume of petroleum ether was added to induce crystallization: pale yellow needles (16.7 g) in two crops; mp 69–73 °C. Recrystallization from cyclohexane raised the melting point to 72–74 °C: UV (CH_3OH) 265, 331 nm (ϵ 9400, 14 050); UV (CH_3OH + base) 265, 420 nm (ϵ 11 300, 27 660); IR (Nujol mull) 1658, 1600, 1567 cm^{-1}. Anal. ($C_{15}H_{15}FO_4$) C, H (which is noncyclized, initial adduct).

The above mother liquors were rapidly distilled yielding an oil (4.57 g), bp 170–175 °C (0.5 mm), which crystallized on cooling, mp 85–89 °C. Recrystallization from acetone gave colorless needles of ethyl 4-(4'-fluorophenyl)salicylate: mp 89–90 °C; UV (CH_3OH) 272, 316 nm (ϵ 21 700, 7500); IR, 3165, 1667 cm^{-1}; NMR ($CDCl_3$) δ 7.88 (d, J = 8 Hz, 1 H, H_6), 7.04 (dd, J = 8, 1 Hz, 1 H, H_5), 7.12 (s, 1 H, H_3), 7.9 (t, J = 8, 8 Hz, 2 H, $H_{3'}$), 7.57 (dd, J = 8, 5 Hz, 2 H, $H_{2'}$), 4.43 (q, J = 7 Hz, 2 H), 1.42 (t, J = 7 Hz, 3 H). Anal. ($C_{15}H_{13}FO_3$) C, H, F.

A mixture of the above ester (1.65 g), ethanol (20 mL), and aqueous 2.5 N NaOH (10 mL) was boiled under reflux until homogeneous (ca. 3 min). Half of the ethanol was distilled out and the residual solution was cooled and acidified with aqueous 2.5 N HCl. The precipitate was filtered, washed with aqueous 2.5 N HCl, and recrystallized from aqueous 75% CH_3OH, yielding colorless needles (1.40 g, **38**), mp 204–208 °C. Recrystallization gave mp 209–210 °C; IR 1656 cm^{-1}. Anal. ($C_{13}H_9FO_3$) C, H, F.

Acknowledgment. We wish to thank Drs. A. A. Patchett, D. J. Jacobus, and C. A. Stone for helpful discussions. The gastrointestinal data were obtained by Dr. D. Brodie, Dr. H. J. Jacoby, and Mrs. P. G. Cook.

References and Notes

(1) M. J. H. Smith and P. K. Smith, Ed., "The Salicylates", Wiley-Interscience, New York, N.Y., 1966, and references cited therein.
(2) J. R. Vane, *Nature (London), New Biol.*, **231**, 232 (1971).
(3) J. B. Smith and A. L. Willis, *Nature (London), New Biol.*, **231**, 235 (1971).
(4) P. Needleman, S. Moncada, S. Bunting, J. R. Vane, M. Hamberg, and B. Samuelsson, *Nature (London)*, **261**, 558 (1976).
(5) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).
(6) S. S. Adams and R. Cobb, *Prog. Med. Chem.*, **5**, 59 (1967).
(7) G. L. Walford, H. Jones, and T. Y. Shen, *J. Med. Chem.*, **14**, 339 (1971).
(8) T. Y. Shen, *Angew. Chem., Int. Ed. Engl.*, **11**, 460 (1972).
(9) H. Jones, M. W. Fordice, R. B. Greenwald, J. Hannah, A. A. Jacobs, W. V. Ruyle, G. L. Walford, and T. Y. Shen, *J. Med. Chem.*, following paper in this issue.
(10) (a) C. A. Winter, *Int. Symp. Non-Steroidal Anti-inflammatory Drugs, Proc., 1964*, 190–202 (1965); (b) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(11) D. A. Brodie, C. L. Tate, and K. F. Hooke, *Science*, **170**, 183 (1970).
(12) R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts, and A. A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).
(13) R. F. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963).
(14) R. G. Strachen, N. G. Steinberg, M. Tishler, and R. F. Hirschmann, *J. Med. Chem.*, **7**, 355 (1964).
(15) T. Y. Shen, C. P. Dorn, and B. E. Witzel, U.S. Patent 3 624 142 (1971).
(16) J. Hannah, W. V. Ruyle, K. Kelly, A. Matzuk, W. J. Holtz, B. E. Witzel, C. A. Winter, C. A. Silber, and T. Y. Shen, Joint Conference of the Chemical Institute of Canada and the American Chemical Society, 1970, Abstract, MEDI 18.
(17) S. S. Bloomfield, T. P. Barden, and R. Hille, *Clin. Pharmacol. Ther.*, 11, 747 (1970).
(18) J. Hannah, W. V. Ruyle, H. Jones, A. R. Matzuk, K. W. Kelly, B. E. Witzel, W. J. Holtz, R. W. Houser, T. Y. Shen, and L. H. Sarett, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 7 (1977).
(19) W. V. Ruyle, L. H. Sarett, and A. R. Matzuk, U.S. Patent 3 714 226 (1973).
(20) H. O. J. Collier, *Adv. Pharmacol. Chemother.*, **7**, 333 (1969).
(21) N. R. Pinckard, D. Hawkins, and R. S. Farr, *Nature (London)*, **219**, 68 (1968).
(22) D. Hawkins, R. N. Pinckard, I. P. Crawford, and R. S. Farr, *J. Clin. Invest.*, **48**, 536 (1969).
(23) R. S. Farr, *J. Allergy*, **45**, 321 (1970).
(24) R. S. Farr, "Mechanisms of Toxicity", W. N. Aldridge, Ed., St. Martin's Press, New York, N.Y., 1971, p 87.
(25) S. M. Krane, *N. Engl. J. Med.*, **286**, 317 (1972).
(26) L. W. Dittert, H. C. Caldwell, T. Ellison, G. M. Irwin, D. E. Rivard, and J. V. Swintosky, *J. Pharm. Sci.*, **57**, 828 (1968).
(27) C. A. Stone, C. G. Van Arman, V. J. Lotti, D. H. Minsker, E. A. Risley, W. J. Bagdon, D. L. Bokelman, R. D. Jensen, B. Mendlowski, C. L. Tate, H. M. Peck, R. E. Zwickey, and S. E. McKinney, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 19 (1977).
(28) C. G. Van Arman, E. A. Risley, and V. J. Lotti, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **36**, 1037 (1977).
(29) K. F. Tempero, V. J. Cirillo, and S. L. Steelman, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 31 (1977).
(30) D. J. Tocco, G. O. Breault, A. G. Zacchei, S. L. Steelman, and C. V. Perrier, *Drug Metab. Dispos.*, **3**, 453 (1975).
(31) G. H. Besselaar, S. L. Steelman, K. F. Tempero, W. Honig, Y. Brosens, J. Caudron, and P. DeVroey, *Clin. Pharmacol. Ther.*, **17**, 229 (1975).
(32) L. Inberg, O. Holopainen, and K. F. Tempero, *Scand. J. Rheumatol.*, **4** (Suppl. 8), 117 (1975).
(33) (a) A. Andrew, B. Rodda, L. Verhaest, and C. Van Winzum, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 45 (1977); (b) G. E. Farrer, Ed., "Clinical Therapeutics", Vol. 1, Suppl. A, in press.
(34) K. F. Tempero, S. L. Steelman, G. H. Besselaar, C. Th. Smit-Sibinga, P. DeSchepper, T. B. Tjandramaga, A. Dresse, and F. W. J. Gribnau, *Clin. Res.*, **23**, 224A (1975).

(35) C. Th. Smit-Sibinga, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 37 (1977).
(36) T. Y. Shen, E. A. Ham, V. J. Cirillo, and M. Zanetti, "Prostaglandin Synthetase Inhibitors", J. R. Vane and H. R. Robinson, Ed., Raven Press, New York, N.Y., 1974, pp 19–31.
(37) S. L. Steelman, C. T. Smit-Sibinga, P. Schulz, W. J. H. VandenHeuvel, and K. F. Tempero, *Int. Congr. Intern. Med., 13th*, 215 (1976).
(38) G. J. Roth, N. Stanford, and P. W. Majerus, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 3073 (1975).
(39) L. H. Rome, W. E. M. Lands, G. J. Roth, and P. W. Majerus, *Prostaglandins*, **11**, 23 (1976).
(40) P. W. Majerus and N. Stanford, *Br. J. Clin. Pharmacol.*, **4** (Suppl. 1), 15 (1977).
(41) Marasse, German Patent 73 279 (1893); *Friedl.*, **3**, 821 (see also ref 5).
(42) H. Kolbe, *Justus Liebigs Ann. Chem.*, **113**, 125 (1860).
(43) R. Schmitt, *J. Prakt. Chem.*, **31** [2], 397 (1885).
(44) V. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
(45) M. Gomberg and W. E. Bachman, *J. Am. Chem. Soc.*, **46**, 2339 (1924).
(46) F. Ullman, *Justus Liebigs Ann. Chem.*, **332**, 38 (1904).
(47) J. M. Birchall, R. N. Hazeldine, and A. R. Parkinson, *J. Chem. Soc.*, 4966 (1962).
(48) J. Walker, *J. Chem. Soc.*, 120 (1939).

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

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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

0022-2623/78/1821-1100$01.00/0