Synthesis of Carboxyarylindoles and Benzofurans as Nonsteroidal Antiinflammatory Agents

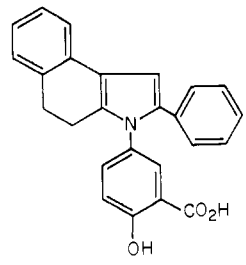
Richard C. Effland

Chemical Research Department, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876. *Received April 7, 1977*

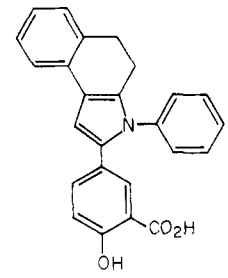
2-Carboxyaryl-substituted dihydrobenz[*e*]indoles, tetrahydroindoles, and tetrahydrobenzofurans have been synthesized as structural analogues of fendosal, a new antiinflammatory agent, and tested in the carrageenan-induced rat paw edema assay. Two of these, 2-(3-carboxy-4-hydroxyphenyl)-3-phenyl-4,5-dihydrobenz[*e*]indole and 1-(*n*-butyl)-2-(3-carboxy-4-hydroxyphenyl)-4,5,6,7-tetrahydroindole, were found to have significant activity, albeit of a lower order than fendosal.

The recently reported antiinflammatory agent, 3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4,5-dihydro-3*H*-benz[*e*]indole (fendosal) (**11**),[1] was selected as the most promising compound from a fairly extensive series of carboxyarylindoles. Requirements for optimal antiinflammatory activity in this series were found to be relatively specific: a central pyrrole nucleus with (a) a 3-carboxy-4-hydroxyphenyl moiety substituted directly on the nitrogen, (b) a 2-phenyl group, (c) absence of a substituent in the 3 position, and (d) a system fused across the 4,5 positions (X, Table I) which is lipophilic, quasiplanar, and does not interact sterically with the *N*-phenyl group.

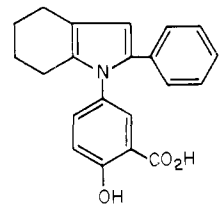
The loss of activity resulting from insertion of a methylene group between the 3-carboxy-4-hydroxyphenyl and the pyrrole nitrogen had indicated the necessity of this ring being attached directly to the pyrrole ring.[1] However, it was not known if the 3-carboxy-4-hydroxyphenyl moiety could be attached to an atom in the pyrrole ring other than nitrogen and still retain activity. Thus, to further explore the structure–activity relationships of this system, a number of related heteroaryl analogues were prepared in which the 3-carboxy-4-hydroxyphenyl moiety has been transposed from the heteroatom to the adjacent α position of the heteroaromatic ring. Of particular interest was the reverse isomer **2**, in which the unsubstituted phenyl and the carboxyaryl rings have been interchanged. Examination of structures **11** and **2** clearly shows that the corresponding aromatic portions of each—the fused aromatic ring, the salicylic acid moiety, the unsubstituted phenyl, and the pyrrole ring—are superimposable. Only the position of the nitrogen and the saturated two-carbon ring portion varies. In addition to **11**, compound **12** has been previously shown to possess good antiinflammatory activity.[1] Therefore, compound **4** was prepared as the reverse isomer of **12**. Finally, to further explore the necessity of an aromatic-substituted pyrrole nitrogen, the *N*-aryl system was replaced with *N*-alkyl; to determine the necessity for a pyrrole ring, the pyrrole nitrogen was replaced with oxygen to give the corresponding furans.



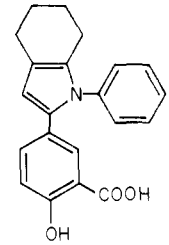
11



2



12



4

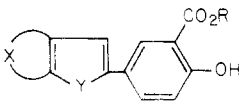
Chemistry. Synthesis of the desired compounds was achieved according to Scheme I. Reaction of methyl 5-bromoacetylsalicylate[2] with an appropriate enamine in dimethylformamide followed by hydrolysis afforded the corresponding 1,4-diketones. While condensation of the enamine with methyl 5-bromoacetylsalicylate and the corresponding methyl ether proceeded smoothly, reaction with the free acid, 5-bromoacetylsalicylic acid, failed completely. Subsequent reaction of the 1,4-diketones with a primary amine (butylamine or aniline) in glacial acetic acid gave the 2-carboxyarylindole methyl esters (**1**, **3**, and **5**) which on hydrolysis afforded the desired 2-carboxyarylindoles (**2**, **4**, and **6**). Refluxing the 1,4-diketone **10** in acidic methanol provided the tetrahydrobenzofuran methyl ester **7** which on hydrolysis afforded the corresponding acid **8**.

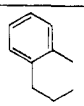
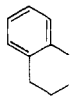
Antiinflammatory Activity. The test for antiinflammatory activity was adapted from the rat paw edema test of Winter et al.[3]

Groups of eight fasted male Wistar strain rats were given experimental drugs or placebo orally at 200 mg/kg as a saline–Tween 80 suspension (10 mL/kg). Thirty minutes later, 0.1 cm^3 of 1% carrageenan in distilled water was injected subcutaneously into the plantar surface of the left hind paw and the paw volume was measured by displacement in a mercury bath. Three hours later, paw volume was measured again. The mean increase in paw volume was compared between placebo and drug-treated groups for calculations of percent inhibition. Results are given in Table I.

Only two compounds, **6** and **2**, showed significant reduction at 200 mg/kg po compared with controls. Despite their structural closeness to **11** and **12**, compounds **2** and **4**, respectively, were considerably less active. Somewhat surprisingly, the *N*-alkyl-substituted **6** was more active than the aromatic substituted **4**. These data may reflect a different mode of binding for compounds of this series as compared to the series from which **11** and **12** originate.[1] The esters **1** and **7** were devoid of activity, indicating the necessity of a free carboxylic acid group. Although the N-substituted pyrrole acids **6**, **2**, and **4** were all more active than the furan **8**, the difference in activity between **4** and **8** was not significant. Thus structural modification of the central heteroatom in this series did not result in pronounced differences in activity. However, the overall lower activity seen with this series confirms the structural specificity found in the fendosal series.

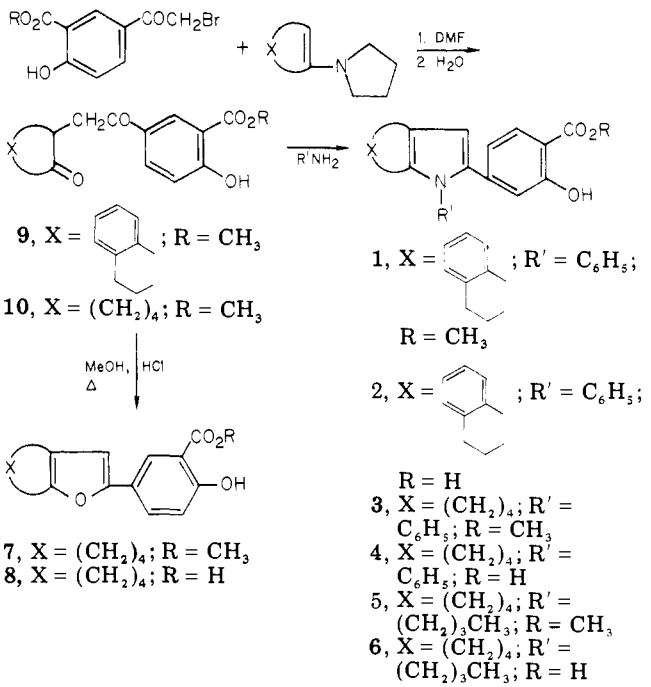
Table I. Carboxyarylindoles and Benzofurans and Derivatives



No.	X	Y	R	Mp, °C	% yield	Procedure[a]	Recrystn solvent	Emp formula	Analyses[b]	CPE[e]
1		N-C_6H_5	CH_3	179–180.5	93.2	A	Acetone	$C_{26}H_{21}NO_3$	C, H, N	21.7[f]
2		N-C_6H_5	H	198–200	60	B	Ligroine (bp 60–90 °C)	$C_{25}H_{19}NO_3$	C, H, N	37.5**
4	$-(CH_2)_4$	N-C_6H_5	H	163–166	56	B	Ether–hexane	$C_{21}H_{19}NO_3$	C, H, N	25.8
6	$-(CH_2)_4$	$N(CH_2)_3CH_3$	H	145–148	52	B	Benzene	$C_{19}H_{23}NO_3$	H, N; C[c]	41*
7	$-(CH_2)_4$	O	CH_3	88	70	*a*	Methanol	$C_{16}H_{16}O_4$	C, H	9.8[f]
8	$-(CH_2)_4$	O	H	237	59	B	Acetonitrile	$C_{15}H_{14}O_4$	H; C[d]	21.5
11										64.2
12										64.0
Aspirin										65.3

[a] See Experimental Section. [b] Unless otherwise indicated, the analyses were within ±0.4% of the theoretical values. [c] C: calcd, 72.80; found, 73.30. [d] C: calcd, 69.75; found, 68.96. [e] CPE = carrageenan paw edema (rat), percent inhibition of edema at 200 mg/kg po; * = result significant on Student's *t* test at $p < 0.001$; ** = $p < 0.01$. [f] Percent increase.

Scheme I



Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Labs, Skokie, Ill. The structures of all compounds are supported by their IR (Perkin-Elmer 457) and NMR (JEOL C60HL) spectra.

Procedure A. Carboxyarylindoles. A mixture of amine (0.05 mol) and the appropriate 1,4-diketone (0.05 mol) in glacial acetic acid (40 mL) was refluxed for 2 h, cooled to effect precipitation, and recrystallized as indicated in Table I.

Procedure B. Hydrolysis of the esters was accomplished by refluxing with 2 equiv of KOH in methanol–water (3:2, 30 mL/0.01 mol of ester), followed by acidification, filtration, crystallization, and recrystallization as indicated in Table I to give the desired acids.

Methyl 2-Hydroxy-5-(1-phenyl-4,5,6,7-tetrahydroindol-2-yl)benzoate (3). This compound was prepared from methyl 2-hydroxy-5-[(2-oxocyclohexyl)acetyl]benzoate (**10**) and aniline by procedure A. Recrystallization of the crude solid from ethanol afforded 50% of the desired product, mp 159–162 °C. Anal. ($C_{22}H_{21}NO_3$) C, H.

Methyl 2-Hydroxy-5-(1-*n*-butyl-4,5,6,7-tetrahydroindol-2-yl)benzoate (5). A mixture of **10** (2.9 g, 0.01 mol) and *n*-butylamine (0.73 g, 0.01 mol) in methanol (50 mL) was stirred at room temperature overnight. Removal of the methanol gave an orange solid that was dissolved in dichloromethane and filtered. Removal of the dichloromethane gave 2.9 g of tan solid which was recrystallized from methanol to give 1.65 g (50%) of pure product, mp 92–93 °C. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

Methyl 2-Hydroxy-5-(4,5,6,7-tetrahydrobenzofuran-2-yl)benzoate (7). A suspension of methyl 2-hydroxy-5-[(2-oxocyclohexyl)acetyl]benzoate (**10**) (5 g, 0.017 mol) in methanolic HCl (50 mL) was refluxed for 1 h and then cooled to room temperature. A light yellow oil precipitated initially, followed by a white crystalline solid which was decanted off (1.3 g), mp 88–88.5 °C. Recrystallization of the oil portion from methanol gave an additional 1.8 g of solid with the same melting point (~70%).

Methyl 2-Hydroxy-5-[(2-oxo-1,2,3,4-tetrahydro-1-naphthyl)acetyl]benzoate (9). A solution of methyl 5-bromoacetylsalicylate (27.31 g, 0.01 mol) in dry DMF (60 mL) was added dropwise to a cooled solution of 1-(3,4-dihydro-2-naphthyl)pyrrolidine (19.93 g, 0.01 mol) in DMF (100 mL), and the mixture was stirred under nitrogen at room temperature overnight. The mixture was stirred with water (200 mL) for 2 h to effect hydrolysis and then extracted with chloroform. The chloroform solution was dried (saturated sodium chloride, $MgSO_4$) and the chloroform removed to give a dark oil, which was warmed under high vacuum to remove any DMF. The remaining dark oil was dissolved in methanol–ether and stored in the cold to give 21.6 g of crystalline product (64%), mp 111–112 °C. Recrystallization of 4.16 g from methanol afforded 2.95 g of light yellow crystals, mp 110–113 °C. Anal. ($C_{20}H_{18}O_5$) C, H.

Methyl 2-Hydroxy-5-[(2-oxocyclohexyl)acetyl]benzoate (10). A solution of methyl 5-(bromoacetyl)salicylate (54.62 g, 0.02 mol) in dry DMF (100 mL) was added dropwise to a cooled solution of 1-pyrrolidino-1-cyclohexene (30.25 g, 0.02 mol) in dry DMF (100 mL). After stirring at room temperature for 5 h, the reaction mixture was hydrolyzed with 360 mL of water for 3 h, then extracted with chloroform, and dried (saturated NaCl, $MgSO_4$). Removal of the chloroform followed by removal of the DMF under high vacuum gave a reddish oil that solidified at room temperature, 44.9 g (77.3%). Treatment with methanol–ether gave 12.8 g of pale yellow solid that recrystallized from methanol–ether to give 8.45 g, mp 113–114.5 °C. The filtrate yielded an orange semisolid which gave an additional 5.1 g of off-white solid from acetone (mp 112–114 °C).

An additional recrystallization from a mixture of acetonitrile, methanol, and ether gave yellow crystals, mp 115–116.5 °C. Anal. ($C_{16}H_{18}O_5$) C, H.

Acknowledgment. The author wishes to express his gratitude to Mrs. Irene Tsina for determination of NMR spectra, to Ms. Adrienne Minet and Mr. Jeff Wilker for performing pharmacological assays, and to Ms. Linda Cuiskelly for assistance in preparation of the manuscript.

References and Notes

(1) V. B. Anderson, M. N. Agnew, R. C. Allen, J. C. Wilker, H. B. Lassman, and W. J. Novick, Jr., *J. Med. Chem.*, **19**, 318 (1976).
(2) (a) D. Lesieur, Y. Blain, and J. P. Bonte, *Chim. Ther.*, **6**, (3), 215 (1971); (b) A. Buzas, Belgium Patent 616045; *Chem. Abstr.*, **58**, 481e (1963).
(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Hypolipidemic Activity of 5-Aryl-3-methylvaleric Acid Derivatives

John H. Dygos,* Charlene M. Jett, Leland J. Chinn, and James E. Miller

Departments of Chemical and Biological Research, Searle Laboratories, Chicago, Illinois 60680. *Received April 29, 1977*

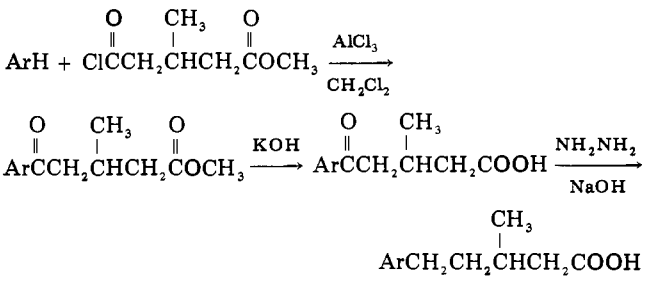
Several 5-aryl-3-methylvaleric acid derivatives have been shown to be more potent hypolipidemic agents than the previously reported 5-(4-biphenylyl)-3-methylvaleric acid (**1**). The most active compound in this series was 5-(4-phenylsulfonylphenyl)-3-methylvaleric acid (**10**) which lowered serum cholesterol levels 45% and serum triglyceride levels 60% in normal rats. Significant lowering of the serum triglyceride levels was the predominant effect noted with most of the compounds tested.

Several *p*-biphenylyl-substituted acids have been reported[1] to exhibit hypocholesterolemic activity in both animal and human studies. Eades and Solberg[2-4] have reported the synthesis of a number of *p*-biphenylyl derivatives, the most potent of which was 5-(4-biphenylyl)-3-methylvaleric acid (**1**).[5] Although this compound exhibited excellent in vitro and in vivo activity in rat studies, it was inactive as a hypolipidemic agent when tested in the dog. More recently, Boots and co-workers[6-9] have reported the synthesis of a large number of *p*-biphenylyl derivatives which have shown potent in vitro inhibition of yeast and rat liver β-hydroxy-β-methylglutaryl coenzyme A reductase (HMG Co A reductase).

As part of a structure–activity study designed to find competitive inhibitors of HMG Co A reductase, we have prepared a series of 5-aryl-3-methylvaleric acids. Inhibition of cholesterol biosynthesis at the HMG Co A reductase stage appears to be an ideal approach for the treatment of hyperlipemia, and the reasons for this have been enumerated by Boots and co-workers.[6] We have found that the biphenyl group in **1** can be replaced by a variety of ring systems without loss of the hypolipidemic activity observed when this compound is administered to rats. Several of the arylvaleric acid derivatives have shown in vitro inhibition of [^{14}C]acetate incorporation into lipids and have also exhibited good in vivo hypolipidemic activity in normal rats.

Chemistry. The compounds reported in this study were prepared by the general sequence outlined in Scheme I where Ar represents the various aryl groups described in Tables I and II.

Scheme I



Acylation of the appropriate aromatic derivatives with 4-chlorocarbonyl-3-methylbutanoic acid methyl ester under Friedel–Crafts conditions gave the corresponding keto esters in moderate yields. Hydrolysis of the esters with aqueous methanolic potassium hydroxide gave the keto acids **2–7** which were reduced via a modified Wolff–Kishner[10] procedure to give the title compounds. The sulfones **10** and **13** were prepared by oxidation of the corresponding sulfides **9** and **12** using either *m*-chloroperbenzoic acid or peracetic acid.

Friedel–Crafts acylation[11] of 9,10-dihydrophenanthrene, dibenzofuran, and dibenzothiophene is known to give substitution predominantly in the 2 position. In order to ensure the absence of undesired isomers, the keto esters derived from these ring systems were purified by column chromatography on silica gel prior to hydrolysis. The crude keto esters derived from biphenyl, diphenyl ether, and diphenyl sulfide, however, could be hydrolyzed without prior purification since acylation[11] of these ring systems is known to give substitution exclusively in the 4 position.

Results and Discussion

All of the aryl-substituted acids listed in Tables I and II were tested in vitro for their capacity to inhibit total lipid, nonsaponifiable lipid and fatty acid biosynthesis when the microsomal–cytosol fraction of rat liver was used as the source of the enzyme systems. It was anticipated that a competitive inhibitor of HMG Co A reductase would exhibit a specificity for the nonsaponifiable fraction while having little or no effect on the fatty acid fraction. While all the compounds demonstrated some capacity to inhibit lipogenesis when tested in the millimolar concentration range, a comparison of the IC_{50} values (see Table III) indicated that none of the compounds appeared to be as potent as **1** in their ability to inhibit nonsaponifiable lipid biosynthesis. However, compounds **7–10** and **13** proved to be at least as potent as **1** in their inhibition of fatty acid biosynthesis.

Although the desired separation of activities was not observed in vitro, the compounds were tested in vivo in male rats to determine their hypolipidemic activity in the intact animal. The results are listed in Table III. With the exception of compounds **5**, **7**, and **12**, all of the