was crystallized from CH_2Cl_2–hexane to give 1.65 g of white crystals, mp 134–144 °C. Recrystallization (three times) from methanol gave 0.96 g of white crystals, mp 138–148 °C. Anal. ($C_{21}H_{16}O_4SCl_2$) C, H, Cl, S.

Methyl 2-(*p*-Chlorophenoxy)-2-[*p*-(*p*-chlorophenoxy)-phenyl]propionate (93). The general procedure of Brocksom et al.[19] and Schlessinger et al.[20] was followed. A solution of 2.02 g (0.02 mol) of dry *N,N*-diisopropylamine and 15 mL of dry THF (distilled from lithium aluminum hydride) was cooled to 0 °C, and 8.5 mL of 2.0 M *n*-butytllithium in hexane was added dropwise, keeping the tempature 0–5 °C. The mixture was then cooled to −70 °C, and 6.51 g (0.015 mol) of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate in 10 mL of THF was added over 15 min. After 15 min, 3.58 g (0.02 mol) of dry HMPA was added. After 0.5 h, 4.26 g (0.03 mol) of methyl iodide was added. The color lightened slowly over 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was then poured into 100 mL of water and extracted with 2 × 75 mL of ether. The combined extracts were washed with 4 × 50 mL of 10% HCl, H_2O, and saturated brine, and then dried. Evaporation of the solvent gave a brown oil, which was filtered through a short silica gel column (benzene) to give 4.3 g (69%) of a light yellow oil.

Dimethyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)-phenyl]malonate (94). The ester enolate of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate was prepared identically as in the previous example. To this solution at −70 °C was added 2.82 g (0.03 mol) of methyl chloroformate. The color of the mixture lightened and the temperature rose to −40 °C. The mixture was stirred overnight at room temperature and worked up as in the previous example to afford a yellow oil containing the desired product and methyl *N,N*-diisopropylcarbamate. The latter was removed by trituration with petroleum ether. The residue was chromatographed on 100 g of silica gel (petroleum ether–benzene, 1:1) to give 4.86 g (70%) of a yellow glass.

Methyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)-phenyl](diethoxyphosphinyl)acetate (98). The ester enolate of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate was prepared as in the preceding two examples, and 5.17 g (0.03 mol) of diethyl chlorophosphonate was added. The reaction mixture was stirred at room temperature for 3 days. Workup as before afforded a brown oil, which was chromatographed on 250 g of silica gel (3:2 benzene–chloroform) to afford an unidentified side product. Further elution with chloroform gave the desired product, which was purified further by preparative TLC to give 1.46 g (18%) of product as a yellow oil.

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Antiinflammatory Agents. 1. Synthesis and Antiinflammatory Activity of 2-Amino-3-benzoylphenylacetic Acid

William J. Welstead, Jr.,* H. Wayne Moran, Harold F. Stauffer, Lennox B. Turnbull, and Lawrence F. Sancilio

A. H. Robins Company, Richmond, Virginia 23220. *Received October 23, 1978*

The synthesis and antiinflammatory activity of 2-amino-3-benzoylphenylacetic acid are described. This compound was postulated to be an active metabolite of 7-benzoylindoline in order to explain the unexpected antiinflammatory activity of the latter compound. Metabolism studies on ^{14}C-labeled 7-benzoylindoline did not confirm this hypothesis. Nevertheless, 2-amino-3-benzoylphenylacetic acid, its ethyl ester, and the sodium salt show potent antiinflammatory activity in pharmacological models.

During the course of synthetic work on a series of tricyclic benzodiazepines, a number of bicyclic amino benzophenones were prepared as intermediates. One compound, 7-benzoylindoline (**1**),[1] demonstrated unexpected antiinflammatory activity comparable to phenylbutazone in the Evans blue carrageenan pleural effusion model in

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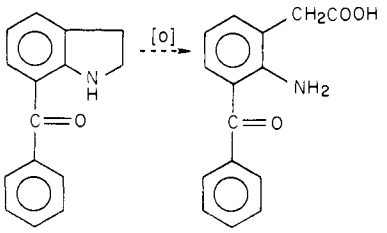


1 10

rats. While activity of this magnitude could be intrinsic, the fact that related compounds such as 8-benzoyl-1,2,3,4-tetrahydroquinoline, 2-aminobenzophenone, and 2-(methylamino)benzophenone were inactive suggested that a metabolite might be responsible for the activity.

Numerous examples of metabolic oxidation α to amino groups have been reported, including the conversion of cyclic amines to amino acids.[2] An analogous oxidation of **1** would lead to 2-amino-3-benzoylphenylacetic acid (**10**), a novel compound for which antiinflammatory activity might be expected. In order to test this active metabolite hypothesis, **10** was prepared for pharmacological evaluation and, in addition, metabolism studies were carried out using ^{14}C-labeled 7-benzoylindoline.

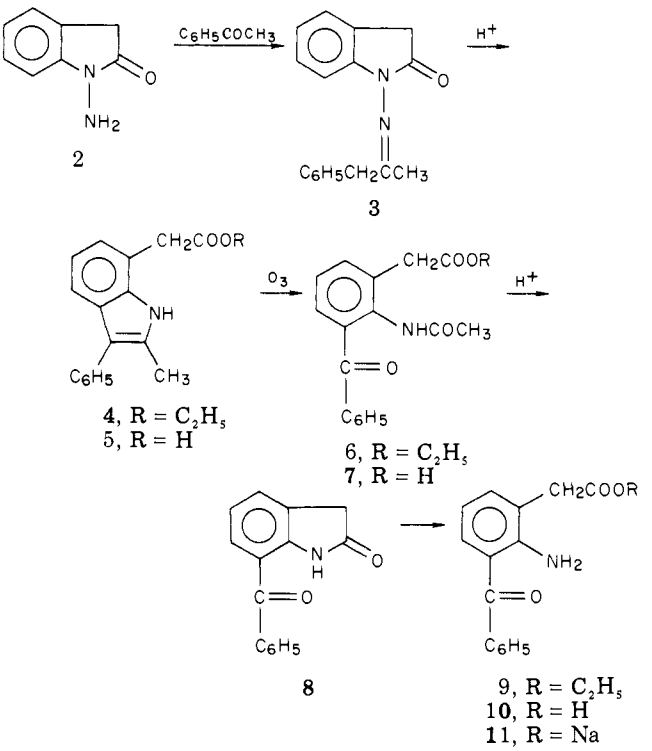
Chemistry. Schemes I and II depict two practical methods for the synthesis of **10** from different starting materials. Scheme I utilizes 1-aminooxindole (**2**), which was prepared from 2-nitrophenylacetic acid by the method of Baumgarten et al.[3] Reaction of **2** with phenylacetone gave hydrazone **3**, which on treatment with ethanolic HCl gave 2-methyl-3-phenylindole-7-acetic acid, ethyl ester (**4**). Ozonization of **4** or the corresponding acid **5** in acetic acid gave **6** and **7**, respectively. Both **6** and **7** were converted to the key intermediate 7-benzoyloxindole (**8**) by acid hydrolysis.

Intermediate **8** was also prepared by an elegant general method for the synthesis of substituted oxindoles developed by Gassman et al.[4] (Scheme II). This method involves the in situ formation of the azasulfonium salt **12** from 2-aminobenzophenone, ethyl methylthioacetate, and *tert*-butyl hypochlorite; the rearrangement of **12** with triethylamine to form **13** (not isolated); an acid-catalyzed cyclization of **13** to give **14**; and a Raney nickel desulfurization of **14** to give **8**. The overall yield is between 25 and 50%. Ring opening of **8** with sodium hydroxide gave the desired 2-amino-3-benzoylphenylacetic acid, which was isolated as the sodium salt **11** or the free acid **10**. The ethyl ester **9** was also prepared for pharmacological comparison.

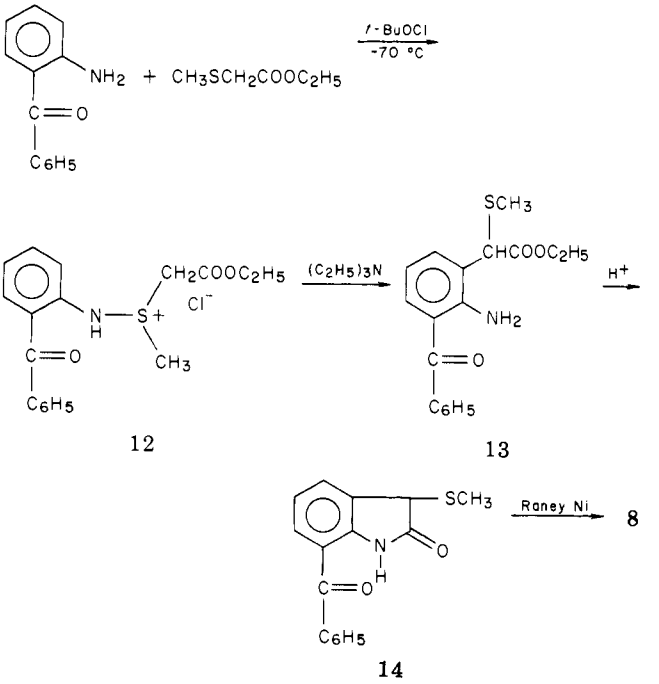
The most satisfactory method developed for the preparation of **1** is essentially the same as the one developed independently by Hester et al.[1] To prepare radiolabeled **1**, however, an alternate method (Scheme III) was developed which utilizes indoline-7-carboxylic acid (**17**)[5] as a key intermediate. The novel metabolites 7-benzoyldioxindole (**19**) and 7-benzoylindole (**20**) were prepared as shown in Schemes IV and V, respectively.

Pharmacology. Acute antiinflammatory activity was determined by sequential analysis using the Evans blue carrageenan pleural effusion assay of Sancilio and Fishman.[6] Compounds were tested initially at 316 mg/kg orally and in parallel with the same dose of acetylsalicylic acid (ASA). Active compounds were tested again in six animals at one or two dose levels and compared with one or more dose levels of phenylbutazone. The compounds were dissolved or suspended in water containing 0.5% Tween 80 and administered by gavage (10 mL/kg). The results described in Table I indicate that compounds **9**–**11** possess potent antiinflammatory activity, warranting additional pharmacological studies. To determine their effectiveness

Scheme I



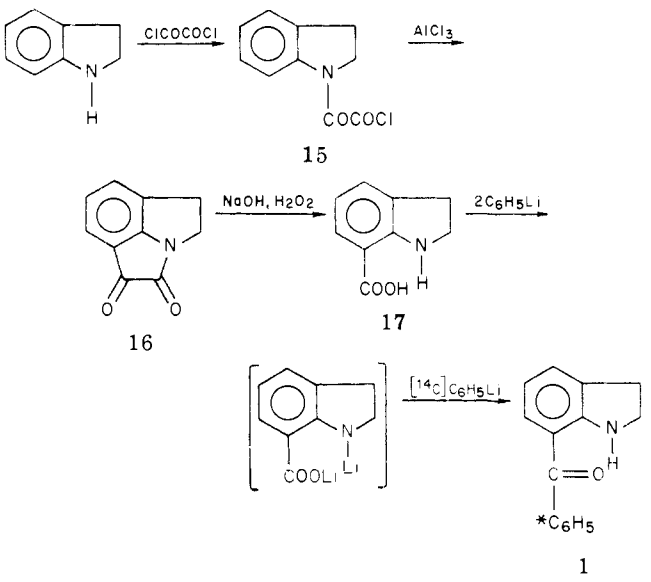
Scheme II



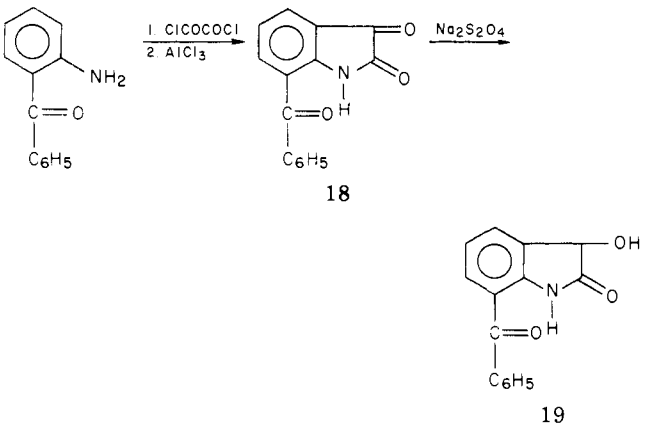
against chronic inflammation, compounds **9** and **11** were tested in the adjuvant-induced arthritic rat model (Waltz et al.[7]) using a therapeutic (dosing animals once daily on days 18–22 and on days 25–28) dosing regimen.[8] Preparations of compounds **9** and **11** were made and administered in the manner described above. Both compounds were comparable or superior to phenylbutazone (Table II).

Metabolism. Biotransformations of ^{14}C-labeled **1** were studied by in vitro experiments using rat liver preparations and by in vivo experiments following oral dosing to rats. In vitro studies involved the incubation of **1** with a 10000*g* fraction of rat liver supernatant, followed by TLC examination of the extract. Two major and two minor

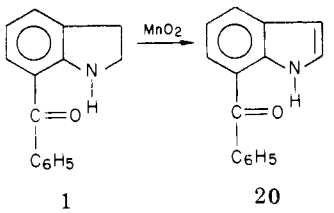
Scheme III



Scheme IV



Scheme V



biotransformation products were detected, along with unchanged 1 (Table III). The metabolite found in greatest concentration (25%) was unstable to workup conditions, but was isolated as an acetate derivative by adding sodium ascorbate as an antioxidant to the system following incubation and then treating the metabolite with acetic anhydride/pyridine after TLC separation. IR, UV and mass spectra identified the compound as the acetate derivative of **19**. The same derivative was also synthesized from an authentic sample of **19**. The other major metabolite was identified as **20** by its IR, UV and mass spectra and by synthesis. The two minor metabolites were not identified but were shown by TLC to be not identical with **10** or its cyclic derivative **8**.

In the in vivo studies, drug-related components from the urine and feces were not identified. However, it was established by TLC that no **10**, **8**, or unchanged **1** were present in the urine. The feces contained only unchanged **1**.

Table I. Relative Antiinflammatory Activity in the 5-h Evans Blue Carrageenan Pleural Effusion Assay in Fasted Male Rats

compd[a]	oral dose, mg/kg	no. of rats	pleural fluid, mL ± SD	% decrease	potency (95% conf limits)
PBZ	10	6	5.5 ± 0.8	11.3	1
	50	5	4.7 ± 0.2[b,c]	24.2	
1	10	6	5.3 ± 0.7	14.5	2.1
	50	6	4.0 ± 0.4[b]	35.5	(1.0-8.0)
control	10[e]	6	6.2 ± 0.8		
PBZ	10	6	5.5 ± 0.6	12.7	1
	50	6	4.5 ± 0.4[b]	28.6	
8	60	6	5.6 ± 0.7	11.1	0.1[d]
	300	6	5.2 ± 0.6[b]	17.5	
control	10[e]	6	6.3 ± 0.4		
PBZ	10	6	6.0 ± 0.8	10.5	1
	50	6	4.9 ± 0.3[b]	26.9	
9	0.8	6	4.9 ± 0.6[b]	26.9	65.6
	4	6	4.2 ± 0.5[b]	37.3	(25.8-604.7)
control	10[e]	6	6.7 ± 0.9		
PBZ	2	6	6.8 ± 1.1	0	1
	10	6	5.9 ± 0.6	13.2	
	50	6	5.0 ± 0.8[b]	26.5	
10	0.8	6	6.1 ± 1.1	10.3	13.3
	4	6	4.5 ± 0.5[b]	33.8	(6.1-41.0)
control	10[e]	6	6.8 ± 0.4		
PBZ	20	6	5.8 ± 0.68	19.4	1
	100	6	4.6 ± 0.63[b]	36.1	
11	0.8	6	6.4 ± 0.58	11.1	16.4
	4	6	4.8 ± 1.01[b]	33.3	(6.4-33.9)
control	10[e]	6	7.2 ± 1.68		
PBZ	100	6	4.9 ± 1.4[b]	31.0	
17	100	6	6.2 ± 0.6	12.6	
control	10[e]	6	7.1 ± 1.4		
ASA	316	2	5.2	31.6	
18	316	2	6.2	18.4	
control	10[e]	8	7.6 ± 1.0		

[a] PBZ = phenylbutazone, ASA = acetylsalicylic acid. [b] $p < 0.05$. [c] A value of 6.4 was rejected as an outlier; $\alpha < 0.005$. [d] Approximation due to lack of significance of slope. [e] In mL/kg.

Discussion

To account for the unexpected antiinflammatory activity of **1**, an active metabolite hypothesis was put forward. Experimentally, however, neither the proposed metabolite **10** nor the more stable cyclic derivative **8** was detected in the metabolic extracts. In addition, compounds **19** and **20**, the major metabolites of **1**, were found to possess little antiinflammatory activity (Table I). Nevertheless, compound **10** and its two derivatives **9** and **11** demonstrated potent antiinflammatory activity against acute inflammation, and **9** and **11** demonstrated comparable or superior activity to the standard, phenylbutazone, in suppressing chronic inflammation. Additional pharmacological studies show compound **11** to possess potent analgesic activity (36.3 times phenylbutazone in suppressing the nociceptive response to bradykinin in dogs) and a higher therapeutic ratio, compared to phenylbutazone, of its potency in suppressing the foot edema of the uninjected feet of adjuvant-induced arthritic rats, to its potency in producing intestinal lesions.[8] Compound **11** is currently being studied clinically.[9]

Experimental Section

Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian A-60 spectrometer, IR spectra were obtained on a Beckman IR8, and mass spectra were

Table II. Relative Antiinflammatory Activity in Adjuvant-Induced Arthritic Rats (Female Lewis Wistar) Using a Therapeutic Dosing Regimen[f]

compd[a]	oral dose, mg/kg	no. of rats	11-day edema, mL ± SD		11-day growth, g ± SD
			inject. foot	uninject foot	
9	0.03	8	0.4 ± 0.5	0.6 ± 0.3	+11 ± 8
	0.316	8	−0.1 ± 0.2[b]	0.1 ± 0.3	+10 ± 11
	3.16	8	−0.6 ± 0.4[b]	−0.1 ± 0.2[b]	+13 ± 14
PBZ	3.16	8	0.3 ± 0.3	0.3 ± 0.3[b]	+16 ± 14
	10.0	8	−0.5 ± 0.2[b]	−0.2 ± 0.4[b]	+20 ± 10
	31.6	8	−0.9 ± 0.4[b]	−0.4 ± 0.4[b]	+26 ± 7[b]
control (neg)	10[g]	8			+29 ± 10[b]
control (pos)	10[g]	8	0.6 ± 0.3	0.8 ± 0.2	+8 ± 6
11	0.0031	7	+0.2 ± 0.2	+0.6 ± 0.3[c]	+12 ± 4
	0.0316	7	+0.2 ± 0.4[c]	+0.4 ± 0.4[c]	+6 ± 5
	0.316	7	−0.3 ± 0.01[b,c]	−0.2 ± 0.1[b,c,d]	+3 ± 16
PBZ	0.316	7	+0.4 ± 0.4[c]	+0.4 ± 0.3[c]	+8 ± 7
	3.16	7	−0.3 ± 0.2[b,c]	0 ± 0.2[b,c]	+8 ± 12
control (neg)	10[g]	7			+8 ± 5
control (pos)	10[g]	7	+0.4 ± 0.3	+0.6 ± 0.4	+8 ± 13

compd	antiedema potency, 95% conf limits	
	inject. foot	uninject foot
PBZ	1	1
9	10.9[e]	5.1 (1.0-15.0)
11	14.2 (5.9-37.7)	23.9 (5.9-88.9)

[a] PBZ = phenylbutazone. [b] $p < 0.05$. [c] Doses used to determine potency. [d] Computed recognizing that the slope for 11 was not significantly different from 0 ($t - 1.79; p > 0.05$). [e] Approximation due to lack of parallelism. [f] Days 18-22 and 25-28. [g] In mL/kg.

Table III. 7-Benzoylindoline Biotransformation Products of Rat Liver Microsomes

compd	% recovery[a]	R_f[b]
1	49	0.72[c]
19	25	0.17
20	16	0.72[c]
unknown no. 1	7	0.51
unknown no. 2	3	0.04
8	ND[d]	0.45
10	ND[d]	0.01

[a] Recovery expressed as percent of total extract radioactivity for one experiment. [b] MeOH/$CHCl_3$, 2:98. [c] 7-Benzoylindole and 7-benzoylindoline zone was resolved using benzene as TLC solvent. [d] ND, not detected.

obtained on a Hitachi Perkin-Elmer RMU-6H mass spectrometer. Elemental analyses for carbon, hydrogen, and nitrogen were obtained using a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory. Spectral data for all compounds were consistent with the proposed structures.

1-(α-Methylphenethylidenimino)oxindole (3). A stirred mixture of 10.0 g (0.07 mol) of 1-aminooxindole[3] and 9.05 g (0.07 mol) of phenylacetone in 65 mL of absolute EtOH was heated until all the oxindole dissolved, treated with 0.5 mL of HOAc, and heated on a steam bath an additional 15 min. After cooling the reaction mixture, the solid which precipitated was filtered and the filtrate was diluted with H_2O to give additional solid. Recrystallization of the solids from absolute EtOH gave 16.0 g (90%) of pure **3**, mp 102–104 °C. Anal. ($C_{17}H_{16}N_2O$) C, H, N.

Ethyl 2-Methyl-3-phenylindole-7-acetate (4). A stirred suspension of 10.0 g (0.04 mol) of **3** in 150 mL of absolute EtOH was heated under a N_2 atmosphere to reflux temperature and then treated with excess dry HCl gas for 40 min. After cooling in ice–H_2O, the mixture was filtered to remove the insoluble 1-aminooxindole and the filtrate was concentrated to give an oil. The oil was dissolved in ligroin and 6.5 g (58%) of **4**, mp 108–109 °C, crystallized. Anal. ($C_{19}H_{19}NO_2$) C, H, N.

2-Methyl-3-phenylindole-7-acetic Acid (5). A stirred suspension of 6.0 g (0.02 mol) of **4** in 80 mL of H_2O containing 8.0 g of KOH was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was treated with an equal volume of H_2O. Acidification of the filtrate with 3 N HCl gave a precipitate, which was filtered and recrystallized from C_6H_6 to give 3.7 g (67%) of **5**, mp 165 °C dec. Anal. ($C_{17}H_{15}NO_2$) C, H, N.

(2-Acetamido-3-benzoylphenyl)acetic Acid (7). A stirred solution of 2.0 g (0.007 mol) of **5** in 60 mL of HOAc was treated with ozone (Wellsbach ozonator) for 15 min. A KI solution was used to indicate when the reaction was complete. The reaction mixture was diluted with 10 mL of H_2O and concentrated. The residue was recrystallized from *i*-PrOH to give 1.6 g (71%) of **7**, mp 188–190 °C. Anal. ($C_{17}H_{15}NO_4$) C, H, N.

Ethyl (2-Acetamido-3-benzoylphenyl)acetate (6). A stirred solution of 5.0 g (0.017 mol) of **4** in 75 mL of HOAc was ozonized as described for **5**. After ozonization was complete, the solution was diluted with H_2O and extracted with Et_2O. The Et_2O extracts were washed with H_2O and 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give a solid residue. Recrystallization of the solid from *i*-PrOH gave 2.6 g (47%) of **6**, mp 133–134 °C. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

7-Benzoyloxindole (8). A. From 6 or 7. A stirred mixture of 2.5 g (0.008 mol) of **6** in 50 mL of 3 N HCl was heated at reflux for 1 h and filtered, and the filtrate was poured onto ice. The resulting precipitate was recrystallized from EtOH–toluene to yield 1.0 g (55%) of **8**, mp 154 °C. Anal. ($C_{15}H_{11}NO_2$) C, H, N. Compound **7** gave **8** in a comparable yield using the same procedure.

B. From 14. A stirred solution of 102 g (0.36 mol) of **14** in 1.2 L of THF at 15 °C under an N_2 atmosphere was treated portionwise with 6.15 g of commercially prepared Raney nickel over 2 h. After the addition was complete, the mixture was stirred for 1.5 h and then filtered. The filter cake was washed with 700 mL of THF and the combined filtrates were treated dropwise with 5 N HCl until the deep red color changed to greenish-yellow (pH ~6). Concentration of the solution under reduced pressure gave 80.0 g (94%) of crude **8**, which could be purified as above.

7-Benzoyl-3-(methylthio)oxindole (14). A stirred solution of 300 g (1.52 mol) of 2-aminobenzophenone in 4 L of CH_2Cl_2 was chilled to −40 °C and treated with a solution of 204 g (1.52 mol) of ethyl 2-(methylthio)acetate in 5 L of CH_2Cl_2. The mixture was cooled to −65 °C and treated dropwise with a solution of 164 g (1.52 mol) of *tert*-butyl hypochlorite in 500 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred at −70 °C for 2 h, treated over several minutes with 182 g (1.8 mol) of Et_3N, and allowed to warm to room temperature. The reaction mixture was washed with H_2O, dried ($MgSO_4$), and concentrated under

reduced pressure to give an oily residue. The oil was dissolved in 1.5 L of MeOH, treated with 1 L of 1 N HCl, and heated at reflux for 2 h. After cooling the solution, 343 g (80%) of crude 14 (containing 5–10% aminobenzophenone) precipitated. An analytical sample, mp 130 °C, was prepared by recrystallization of the solid from toluene. Anal. ($C_{16}H_{13}NO_2S$) C, H, N.

4,5-Dihydropyrrolo[3,2,1-*hil*]indoline-1,2-dione (16). To a stirred solution of 100 g (0.79 mol) of oxalyl chloride in 300 mL of dry ether was added, dropwise, 200 g (1.7 mol) of indoline. The mixture was stirred over a weekend and then concentrated to give a semisolid as residue. Trituration of the residue with ether resulted in the desired acid chloride being dissolved and the insoluble bisamide remaining undissolved. Concentration of the ether extract under reduced pressure gave 90.0 g (58%) of crude acid chloride (**15**). To **15** in a 3-L beaker was added 285 g (2.1 mol) of $AlCl_3$. The reactants were thoroughly mixed and heated rapidly on a hot plate to 100–110 °C. Stirring was continued at 110 °C until the evolution of HCl ceased (15 min). The mixture was cooled, poured onto ice, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. Trituration of the oil with acetone gave a red solid which was recrystallized from benzene to give 23.0 g (8.3% based on starting indoline) of **16**, mp 206–208 °C. Anal. ($C_{10}H_7NO_2$) C, H, N.

Indoline-7-carboxylic Acid (17). A mixture of 22.0 g (0.13 mol) of **16** and 40.0 g (1 mol) of NaOH in 400 mL of H_2O was stirred at room temperature for 30 min and treated with 40 mL of 30% H_2O_2 in 400 mL of H_2O. After the addition was complete, the mixture was stirred for 3 h and then washed with C_6H_6. The pH of the aqueous layer was adjusted to 6.6 with HCl and then the layer was extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil as residue. Trituration of the residue with C_6H_6/isooctane (75:25) gave 15.0 g (73%) of nearly pure **17**, which melted at 164–168 °C. Recrystallization of the solid from acetone gave **17**, which melted at 167–169 °C (lit.[5] mp 162–164 °C). Anal. ($C_9H_9NO_2$) C, H, N.

7-Benzoylindoline (1). A stirred mixture of 27.0 g (0.16 mol) of **17** and 800 mL of dry ether was treated dropwise with a phenyllithium solution prepared from 157 g (0.44 mol) of bromobenzene, 6.94 g (0.87 mol) of lithium wire, and 500 mL of dry ether. After the addition was complete, the reaction mixture was heated at reflux for 3 h and poured onto ice. The mixture was filtered, and the ether layer was separated, washed with 1 N HCl, and extracted with 12 N HCl. Neutralization of the HCl extract with 3 N NaOH caused precipitation of 15.0 g (42%) of **1**, mp 119–122 °C (lit.[1] mp 124–125 °C). Anal. ($C_{15}H_{13}NO$) C, H, N.

7-Benzoylisatin (18). To 450 g (3.5 mol) of oxalyl chloride at 0 °C was added, with stirring, 118 g (0.6 mol) of 2-aminobenzophenone over a 20-min period. A precipitate of bisamide formed. After the addition was complete, 500 mL of toluene was added, and the mixture was stirred for another 30 min and concentrated under reduced pressure to give a semisolid residue. The residue was triturated with petroleum ether, and the mixture was filtered. The filtrate was concentrated under reduced pressure to yield the crude oxaniloyl chloride, yield 165 g (96%).

A stirred mixture of 14.0 g (0.05 mol) of *o*-benzoyloxaniloyl chloride and 70.0 g (0.05 mol) of $AlCl_3$ was heated in an oil bath at 120 °C for 10 min and poured onto ice. The resulting solid was collected by filtration, dissolved in benzene, and chromatographed on a column of Florisil (250 g) using benzene containing increasing amounts of acetone to elute. The product from the column was recrystallized from acetone to yield 1.8 g (14%) of **18** as orange needles, mp 206–208 °C. Anal. ($C_{15}H_9NO_3$) C, H, N.

7-Benzoyldioxindole (19). A solution of 4.0 g (0.016 mol) of **18** in 100 mL of THF was added dropwise to a stirred solution of $Na_2S_2O_4$ (excess) in 100 mL of H_2O. The orange solution rapidly changed color to yellow during the addition. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and concentrated to give 3.6 g of crude product. Recrystallization of the solid from CH_3CN gave 1.6 g (40%) of pure **19**, mp 165–179 °C dec. Anal. ($C_{15}H_{11}NO_3$) C, H, N.

7-Benzoylindole (20). A stirred solution of 3.35 g (0.15 mol) of **1** in 150 mL of C_6H_6 was treated with 12.9 g of active MnO_2 (0.15 mol) and heated at reflux for 18 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give an oil which crystallized on standing. Recrystallization of the solid from C_6H_6–isooctane gave 2.1 g (64%) of **20**, mp 103–104 °C. Anal. ($C_{15}H_{11}NO$) C, H, N.

(2-Amino-3-benzoylphenyl)acetic Acid (10). A mixture of 3.0 g (0.013 mol) of **8** and 50 mL of 3 N NaOH was heated at reflux under a N_2 atmosphere for 45 min, cooled, diluted with an equal volume of H_2O, and filtered. Addition of HOAc to the filtrate until pH 7 was reached caused precipitation of 2.7 g (84%) of **10**, mp 121–123 °C dec. Anal. ($C_{15}H_{13}NO_3$) C, H, N.

Sodium (2-Amino-3-benzoylphenyl)acetate Monohydrate (11). A stirred solution of 111 g (0.43 mol) of **10** in 777 mL of THF was treated with 31.3 g (0.39 mol) of 50% NaOH. After cooling the solution at 0 °C for 3 h, the solid which precipitated was collected by filtration to yield 64.0 g (56%) of **11**, mp 245–252 °C. An analytical sample was obtained by dissolving 1.0 g of crude **11** in 10 mL of 95% EtOH and treating the solution with 5 mL of isopropyl ether. Pure **11** slowly precipitated to yield 0.9 g, mp 254–255.5 °C, of yellow solid. Anal. ($C_{15}H_{14}NO_4Na$) H, N; C: calcd, 61.02; found, 60.19 (compound **11** frequently analyzes for slightly more water than 1 mol).

Ethyl (2-Amino-3-benzoylphenyl)acetate (9). A solution of 2.5 g (0.009 mol) of **11** in 25 mL of dry DMF was treated with 5.0 g (0.035 mol) of EtI and stirred at room temperature for 2 h. The solution was diluted with H_2O and extracted with Et_2O. The combined Et_2O extracts were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was recrystallized from absolute EtOH to give 1.7 g (61%) of **9**, mp 77–78 °C. Anal. ($C_{17}H_{17}NO_3$) C, H, N.

7-[U-^{14}C]Benzoylindoline. This procedure was identical with that used to prepare unlabeled **1**, except indoline-7-carboxylic acid was treated with 2 equiv of nonradioactive phenyllithium to produce a dianion, which was then converted to 7-[U-^{14}C]-benzoylindoline by the addition of 1 equiv of [U-^{14}C]phenyllithium. The overall radioyield from bromo[U-^{14}C]benzene was 81%. Two fractions of product were obtained. One had a specific activity of 1.89 μCi/mg, mp 121.5–124 °C, radiopurity by TLC in acetone/benzene (1:9) 97%. A second fraction, obtained by adding unlabeled carrier to the ^{14}C mother liquor had a specific activity of 0.77 μCi/mg, mp 121.5–124 °C, radiopurity 95%.

Incubation of 7-[U-^{14}C]Benzoylindoline. A 10-mg sample of ^{14}C-labeled **1**, suspended by sonic vibration in 30 mL of 0.1 M, pH 7.4, Na^+/K^+ phosphate buffer, was incubated with 20 mL of the supernatant from 6.5 g of rat liver tissue by the procedure of LaDu et al.[10] Following a 1-h incubation, 50 mg of sodium ascorbate was added to the mixture as an antioxidant. Extraction of the incubation mixture with 3–65-mL portions of ether gave 75% of the radioactivity of the substrate. Immediate TLC (acetone/$CHCl_3$, 2:98) of the extract gave the results described in Table III.

Animal Studies. Three 200-g female Wistar rats were dosed orally with 75 mg/kg of ^{14}C-labeled **1** suspended by sonic vibration in 2 mL of H_2O. Urine and feces were collected at intervals over a 3-day period and analyzed for radioactivity as previously described.[11]

References and Notes

(1) Compound **1** was independently prepared [J. B. Hester, Jr., A. D. Rudzik, and W. Veldkamp, *J. Med. Chem.*, **13**, 837 (1970)] and reported to have antiinflammatory activity [J. B. Hester, Jr., U.S. Patent 3 642 820 (1972)].

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Syntheses of N-Substituted 2(3,4)-Pyridylcarboxylic Acid Hydrazides with Analgesic and Antiinflammatory Activity

Kinfe Redda, Linda A. Corleto, and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada.
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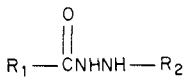
A group of N-substituted 2(3,4)-pyridylcarboxylic acid hydrazides were synthesized to investigate the effects that changes in functionality on the terminal hydrazide nitrogen have on analgesic and antiinflammatory activities. The most active analgesic–antiinflammatory compound was 1-(2-pyridylcarbonyl)-2-(2-pyridyl)hydrazine (**10a**), which was much more potent than dextropropoxyphene and caused a 100% inhibition of carrageenan-induced paw edema up to 5 h. Pyridylcarbonylhydrazides **5a**, **8**, and **10c** exhibited analgesic activity similar to dextropropoxyphene. Although **10b** was an inactive analgesic agent, it exhibited antiinflammatory activity similar to **10a**.

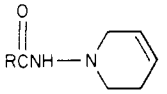
Pyridylcarboxylic acid hydrazide derivatives **1** which



1a, R_1 = 4-pyridyl, R_2 = H
b, R_1 = 4-pyridyl, R_2 = *i*-Pr
c, R_1 = 4-pyridyl, R_2 = $CH_2CH_2CONHCH_2Ph$
d, R_1 = 4-pyridyl, R_2 = CH_2SO_2Na
e, R_1 = 4-pyridyl, R_2 = C_6H_{11}
f, R_1 = 2-pyridyl, R_2 = COMe

exhibit antitubercular (**1a**, isoniazid; **1b**, iproniazid), monoamine oxidase inhibitory (**1b**; **1c**, nialamide), antibacterial (**1d**), CNS depressant (**1e**), and antitumor (**1f**) activities have been reported.[1]

In an earlier study we described a facile method for the synthesis of *N*-[[2(3,4)-pyridylcarbonyl]amino]-1,2,3,6-tetrahydropyridines **2**[2] via the sodium borohydride re-



2, R = 2-, 3-, or 4-pyridyl

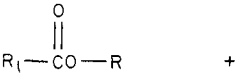
duction of *N*-iminopyridinium ylides, which exhibited significant analgesic and antinflammatory activities.[3] It was therefore of interest to determine what effect replacement of the 1,2,3,6-tetrahydropyridyl ring of **2** by other ring systems and functionality would have on pharmacological activity. We now describe the synthesis and analgesic–antiinflammatory activity of structurally related pyridylcarbonylhydrazides.

Chemistry. Two synthetic procedures were used to prepare pyridylcarbonylhydrazide derivatives in which the terminal hydrazide nitrogen is part of a heterocyclic ring system. For example, reaction of pyridyl esters **3** with the anions of **4**, obtained by addition of *n*-butyllithium, afforded pyridylcarbonylhydrazides **5** (Scheme I).

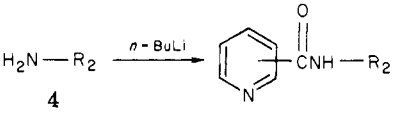
Treatment of *N*-aminoisoquinoliniuim chloride **6**[4] with 4-pyridylcarbonyl chloride gave rise to the *N*-[(4-pyridylcarbonyl)imino]isoquinolinium ylide **7**, which on subsequent reduction with sodium borohydride in ethanol at 0 °C yielded the 1,2,3,4-tetrahydroisoquinoline derivative **8** (Scheme II).

A group of pyridylcarbonylhydrazides, possessing varied functionality at the terminal hydrazine nitrogen, was

Scheme I

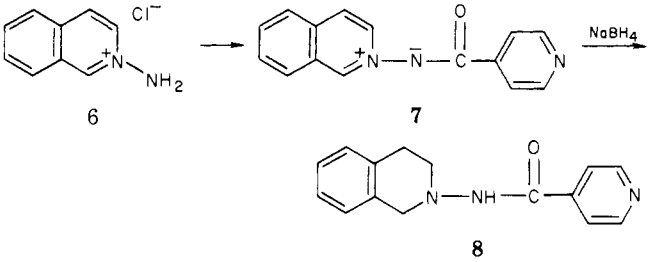


3a, R_1 = 3-pyridyl, R = Et
b, R_1 = 4-pyridyl, R = Me
c, R_1 = 2-pyridyl, R = Et

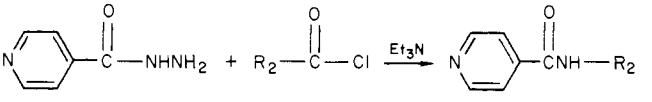


a, R_2 = 1-piperidyl
b, R_2 = 1-morpholinyl
c, R_2 = 1-homopiperidyl
d, R_2 = dimethylamino

Scheme II



Scheme III



a, R_2 = NHCOPh
b, R_2 = $N(COCH_3)_2$

prepared as illustrated by Schemes III and IV and summarized in Table I. Thus, treatment of isonicotinic acid hydrazide **1a** with benzoyl and acetyl chloride using the Schotten–Baumann reaction gave hydrazides **9**. Reaction of pyridyl esters **3b** and **3c** with the anions of 2-pyridyl- and phenylhydrazine **4**, obtained by addition of sodium hydride, afforded pyridylcarbonylhydrazides **10** (Scheme IV).

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