5, 127130-99-8; 6, 127131-00-4; 7, 127131-01-5; 8, 127131-02-6; 9, 127131-03-7; 10, 127131-04-8; 11, 127154-02-3; 12, 16553-22-3; 13, 127131-05-9; 14, 127131-06-0; 15, 127131-07-1; 16, 127131-08-2; 17, 127131-09-3; 18, 127131-10-6; 19, 127131-11-7; 20, 127131-12-8; 21, 127131-13-9; 22, 639-47-4; 23, 127131-14-0; 24, 127131-15-1; 25, 127131-16-2; 27, 127131-17-3; 28, 127131-18-4; 29, 127131-19-5; 30, 57093-46-6; 31, 127131-20-8; 32, 127131-21-9; 33, 127131-22-0; 34, 127131-23-1; 35, 127131-24-2; 36, 127131-25-3; 37, 127154-03-4.

Antiinflammatory Agents. 4.[1] Syntheses and Biological Evaluation of Potential Prodrugs of 2-Amino-3-benzoylbenzeneacetic Acid and 2-Amino-3-(4-chlorobenzoyl)benzeneacetic Acid

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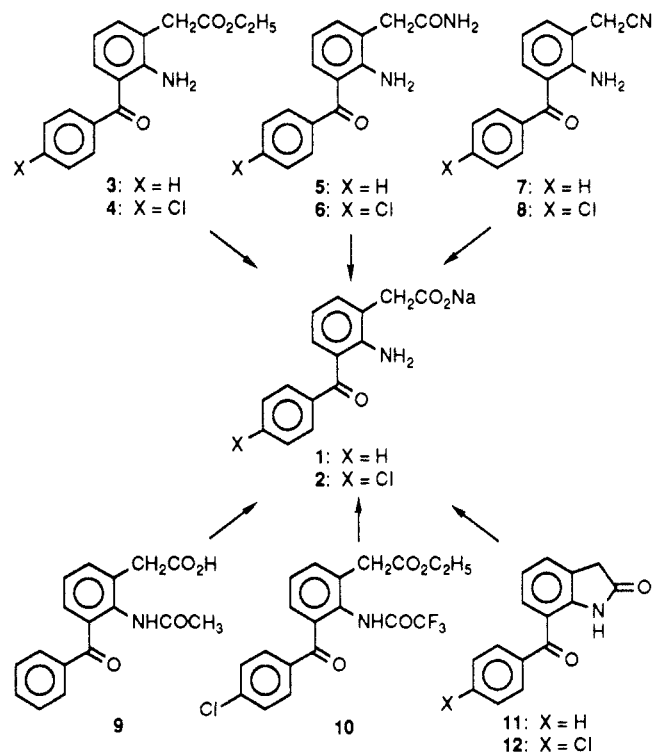
A series of potential prodrugs of 2-amino-3-benzoylbenzeneacetic acid (amfenac) and 2-amino-3-(4-chlorobenzoyl)benzeneacetic acid were synthesized and evaluated for their cyclooxygenase inhibiting properties, antiinflammatory potency, and gastrointestinal irritation liability. One compound, 2-amino-3-(4-chlorobenzoyl)benzeneacetamide, possessed a therapeutic index 1 order of magnitude greater than that of indomethacin.

In general one of the most prevalent and serious side effects of the use of nonsteroidal antiinflammatory drugs (NSAIDS) is the occurrence of gastrointestinal damage.[2] Gastric upset and irritation are a major stumbling block to patient compliance with a prescribed dosage regimen. There have been several attempts to improve the gastric tolerance of NSAIDS which have met with varying degrees of success such as formulation (e.g., buffered, sustained-release, or enteric-coated), chemical manipulation such as esterification[3,4] and coadministration of agents in an attempt to protect the stomach.[5]

As part of a continuing effort to prepare NSAIDS with minimal or no gastrointestinal side effects, several compounds (Charts I–IV) were synthesized which may be metabolically converted to 2-amino-3-benzoylbenzeneacetic acid (1, amfenac),[6] a potent cyclooxygenase inhibitor and clinically useful antiinflammatory drug,[7] or its 4-chloro derivative 2.[1] Ideally these precursors should have no inherent cyclooxygenase inhibiting activity so that when orally administered there would be no gastric side effects before absorption. They would then be metabolically converted to active species 1 or 2 and undergo enterohepatic recirculation[8] to exert the desired antiinflammatory effect. The approach used was to chemically modify 1 and 2 to provide compounds which could be broken down in vivo enzymatically or by non-enzymatic processes to release the active moiety. The term "drug latentiation" was used by Harper[9] to describe this approach.

The synthesized compounds are arbitrarily classified into four categories: compounds which may be converted to 1 or 2 by (a) hydrolysis (Chart I), (b) an oxidative process (Chart II), (c) a reductive process (Chart III), and (d) a multistep process (Chart IV). Since 1 and 2 are potent cyclooxygenase inhibitors,[1] it was assumed that a prodrug that did not possess cyclooxygenase inhibiting properties was inherently devoid of antiinflammatory activity, and any in vivo activity could be ascribed to a metabolic conversion to a cyclooxygenase inhibitor. The compounds initially were tested in vivo in the Evans blue–carrageenan-induced pleural effusion assay,[10] a model of acute inflammation (Table I), and then tested in vitro for cyclooxygenase inhibiting properties (Table II).

Chart I. Compounds That May Be Converted to 1 or 2 by Hydrolysis



(1) For part 3 in this series, see: Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Uwaydah, I. M.; Welstead, W. J., Jr.; Sancilio, L. F.; Dannenburg, W. N. *J. Med. Chem.* **1984**, *27*, 1379–1388.
(2) Rainsford, K. D. *Agents Actions* **1977**, *7*, 573–577.
(3) Rainsford, K. D.; Whitehouse, M. W. *Agents Actions* **1980**, *10*, 451–456.
(4) Whitehouse, M. W.; Rainsford, K. D. *J. Pharm. Pharmacol.* **1980**, *32*, 795–796.
(5) Leyck, S.; Dereu, N.; Etschenberg, E.; Ghyczy, M.; Graf, E.; Winkelmann, J.; Parnham, M. J. *Eur. J. Pharmacol.* **1985**, *117*, 35–42.
(6) Sancilio, L. F.; Reese, D. L.; Cheung, S.; Alphin, R. S. *Agents Actions* **1977**, *7*, 133–144.

[†] Department of Chemical Research.
[‡] Department of Pharmacology.
[§] Department of Molecular Biology.

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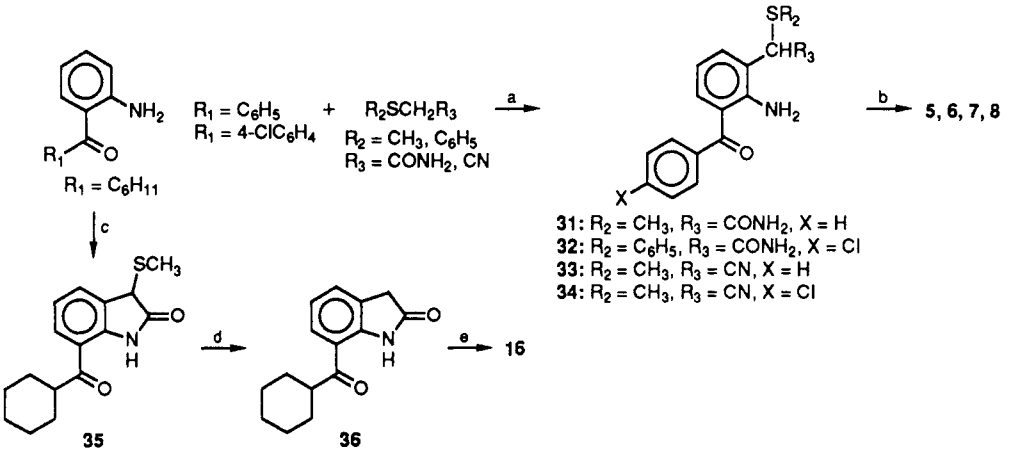
Scheme I[a]



[a] (a) 1. CH_2Cl_2, $(CH_3)_3COCl$, −65 °C; 2. $(C_2H_5)_3N$, −65 °C; (b) Raney nickel, THF; (c) 1. CH_2Cl_2, $CH_3SCH_2CO_2C_2H_5$, $(CH_3)_3COCl$, −65 °C; 2. $(C_2H_5)_3N$, −65 °C; 3. 4 N HCl, 25 °C; (d) C_2H_5OH, Sn, concentrated HCl, Δ, 6 h; (e) 3 N NaOH, N_2, Δ, 16 h.

Chart II. Compounds That May Be Converted to 1 or 2 by an Oxidative Process

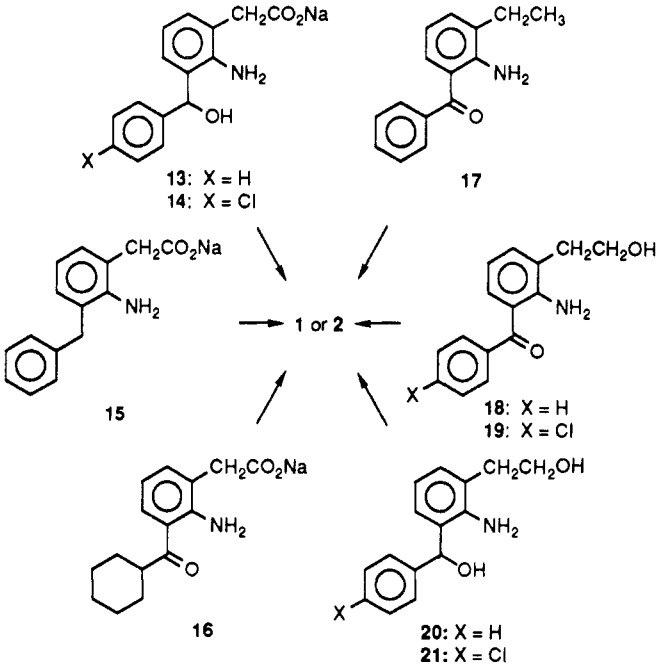
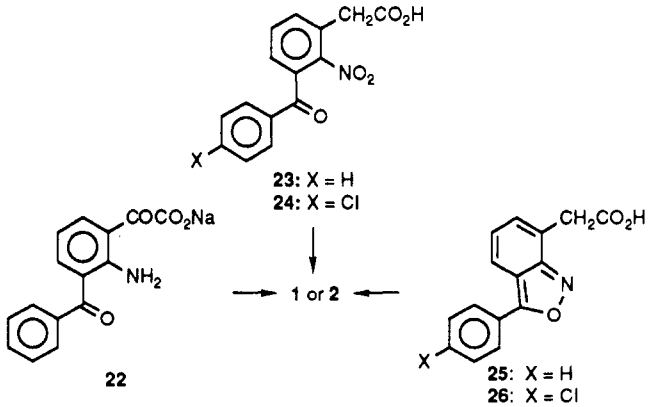
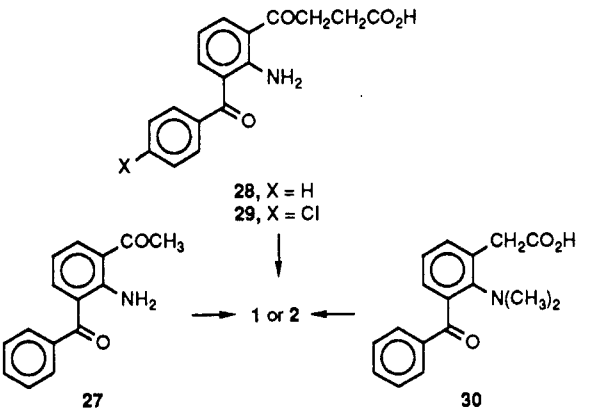


Chart III. Compounds That May Be Converted to 1 or 2 by a Reductive Process



Compounds that were inactive as inhibitors of cyclooxygenase, but possessed in vivo activity in the acute model

Chart IV. Compounds That May Be Converted to 1 or 2 by a Multistep Process



were then compared to indomethacin in the adjuvant-induced arthritic rat model,[6] a model of chronic inflammation, and in a chronic rat intestinal toxicity model.[1] A therapeutic index, the ratio of the potency (versus indomethacin) in the adjuvant-induced arthritis assay divided by the potency (versus indomethacin) in the intestinal toxicity assay, was determined to assess any relative improvement in the irritation profile of the prodrugs when compared to 1 or 2 (Table II).

Whenever prodrugs are assessed in animal models there are at least two caveats that should be considered. One is that the results from tests conducted in rats may not be directly transferable to the human situation, since it is well-known that species to species variations in absorption, distribution, and metabolism exist. In addition, the possibility exists that in the conversion of prodrugs to active drugs, reactive chemical intermediates could be released into the biological system and a toxic response could be elicited.[11] In the final analysis only toxicological and human clinical studies will answer these questions.

Chemistry

Compounds **5**–**8** and **16** were synthesized by using Gassman's procedure,[12] or a modification, for the prepa-

(7) *Drugs Today* **1987**, *23*, 439–440.

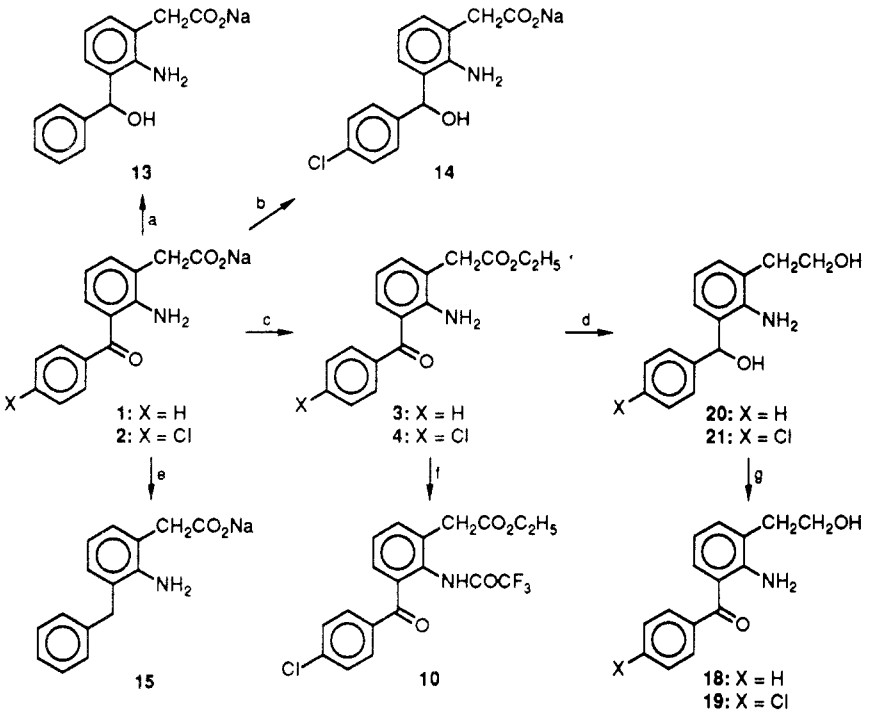
(8) Duggan, D. E.; Hooke, K. F.; Noll, R. M.; Kwan, K. C. *Biochem. Pharmacol.* **1975**, *25*, 1749–1754.

(9) Harper, N. J. In *Absorption and Distribution of Drugs*; Binns, T. B., Ed.; Williams and Wilkins: Baltimore, MD, 1964; p 103.

(10) Sancilio, L. F.; Fishman, A. *Toxicol. Appl. Pharmacol.* **1973**, *26*, 575–584.

(11) Gorrod, J. W. *Chem. Ind.* **1980**, 457–461.

Scheme II[a]

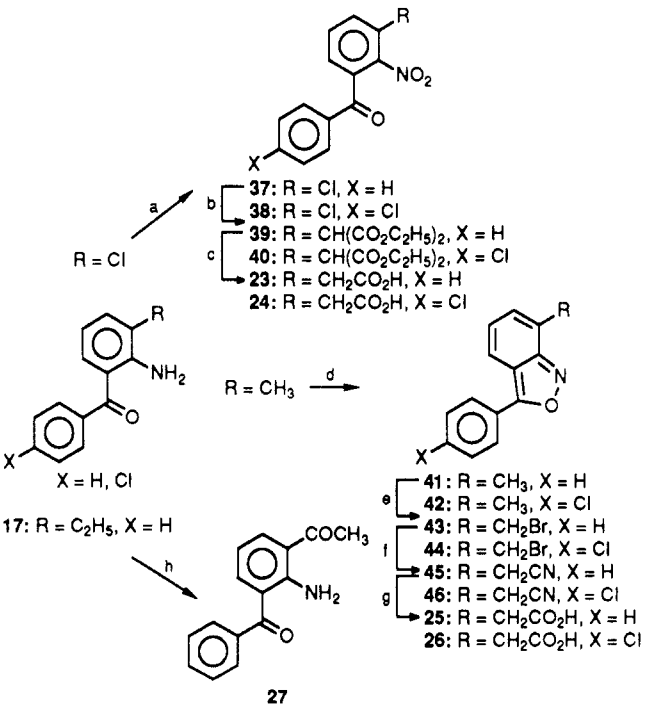


[a] (a) H_2O, H_2, 10% Pd/C, 18 h; (b) 1. H_2O, $NaBH_4$; 2. CH_3CO_2H; 3. NaOH; (c) $(CH_3)_2NCHO$, IC_2H_5; (d) THF, $LiAlH_4$, N_2, Δ, 2.5 h; (e) H_2O, H_2, 10% Pd/C, 60 °C, 32 h; (f) CH_2Cl_2 $(CF_3CO)_2O$; (g) CH_2Cl_2–THF, MnO_2, Δ, 18 h.

ration of oxindoles (Scheme I). An appropriately substituted aniline was reacted with a substituted thiol derivative in the presence of *tert*-butyl hypochlorite at low temperature to give an azasulfonium salt. The azasulfonium salt was treated with triethylamine to cause ylide formation and a Sommelet–Hauser-type rearrangement to yield the 2,6-disubstituted aniline derivatives **31–34** in a one-pot sequence. When ethyl methylthioacetate was used, the resulting intermediate was relatively unstable and readily cyclized in the presence of acid to the oxindole (**35**). Gassman reported that if methylthioacetamide was used as a sulfide, the stable intermediate (such as **31**) could be isolated. It was observed that (methylthio)acetonitrile could also be used as the sulfide to generate stable intermediates (**33, 34**). (Methylthio)acetamide is relatively insoluble in methylene chloride at −70 °C and yields were variable when this reagent was used. Improved yields could be obtained if the methyl substituent on the sulfur was replaced with a more lipophilic alkyl or aryl group. (Phenylthio)acetamide gave a good yield of **32**, and in other examples,[13] 2-(2-propylthio)acetamide was the reagent of choice. Raney nickel desulfurization of **31–34** gave **5–8**, respectively. Removal of the methylthio group from **34** to give **36** was accomplished with tin and HCl. Base hydrolysis of **36** gave **16**.

Scheme II shows several compounds derived from **1** or **2** by various reductive processes. Catalytic hydrogenation of **1** with 10% palladium on carbon can result in production of **13** or **15** depending on length of reaction. Since a chloro substituent can be removed by catalytic hydrogenolysis, **2** was reduced with $NaBH_4$ to give **14**. Reduction of esters **3** and **4** with $LiAlH_4$ gave the diols **20** and **21**, respectively. Reaction of **20** and **21** with activated MnO_2 resulted in selective oxidation of the benzylic hydroxyl to yield **18** and **19**, respectively.[14]

Scheme III[a]

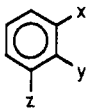


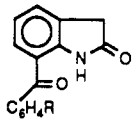
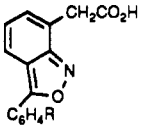
[a] (a) CH_2Cl_2, 90% H_2O_2, $(CF_3CO)_2O$; (b) $(CH_3)_2SO$, NaH, $CH_2(CO_2C_2H_5)_2$, 100 °C, 2 h; (c) CH_3CO_2H, 20% H_2SO_4, Δ, N_2, 16 h; (d) CH_3CO_2H, 30% H_2O_2, 3 days; (e) CCl_4, *N*-bromosuccinimide, Δ, $h\lambda$; (f) H_2O, dioxane, KCN, Δ, N_2, 2.5 h; (g) C_2H_5OH, 20% NaOH, Δ, N_2, 17 h; (h) CH_2Cl_2, $(C_2H_5)_3N(CH_2C_6H_5)MnO_4$, 16 h.

The synthesis of **23–27** utilizing the oxidation of substituted 2-aminobenzophenone derivatives[15] is depicted in

(12) Gassman, P. G.; van Bergan, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508–5517.
(13) Shanklin, J. R., Jr.; Shamblee, D. A.; Walsh, D. A. U.S. Patent 4 313 949, 1982; *Chem. Abstr.* **1981**, *95*, 42702x.
(14) Moran, H. W.; Welstead, W. J., Jr.; U.S. Patent 4 568 695, 1988; *Chem. Abstr.* **1986**, *104*, 224707q.
(15) Walsh, D. A. *Synthesis* **1980**, 677–688.

Table I. Oral Antiinflammatory Activity in the 5-h Evans Blue–Carrageenan Pleural Effusion Assay for Potential Prodrugs of 1 and 2



no.	x	y	z	formula[a]	mp, °C (solv[b])	ref or method of prep[c]	% yield	% change in average volume of pleural fluid: dose, mg/kg 100	4.0	indo[d] dose, mg/kg: 4.0
1	CH_2CO_2Na	NH_2	$C_6H_5C(O)$	$C_{15}H_{12}NNaO_3 \cdot H_2O$	248–252 (mn)	1	80	−35	−26	−33
2	CH_2CO_2Na	NH_2	4-$ClC_6H_4C(O)$	$C_{15}H_{11}ClNNaO_3 \cdot 0.75H_2O$	265 (m)	1	67	−38	−29	−33
3	$CH_2CO_2C_2H_5$	NH_2	$C_6H_5C(O)$	$C_{17}H_{17}NO_3$	77–78 (n)	23	61		−24	−25
4	$CH_2CO_2C_2H_5$	NH_2	4-$ClC_6H_4C(O)$	$C_{17}H_{16}ClNO_3$	101–102 (n)	E	81		−22	−23
5	CH_2CONH_2	NH_2	$C_6H_5C(O)$	$C_{15}H_{14}N_2O_2$	178.5–180 (o)	A	73	−39	−23	−37
6	CH_2CONH_2	NH_2	4-$ClC_6H_4C(O)$	$C_{15}H_{13}ClN_2O_2$	212–215 (n)	A	84		−27	−32
7	CH_2CN	NH_2	$C_6H_5C(O)$	$C_{15}H_{12}N_2O$	137.5–139 (o)	A	72	−17[e]	−3[e]	−29
8	CH_2CN	NH_2	4-$ClC_6H_4C(O)$	$C_{15}H_{11}ClN_2O$	181–182 (p)	A	56	i[f]		
9	CH_2CO_2H	$NHCOCH_3$	$C_6H_5C(O)$	$C_{17}H_{15}NO_4$	188–190 (o)	23	71	i[f]		
10	$CH_2CO_2C_2H_5$	$NHCOCF_3$	4-$ClC_6H_4C(O)$	$C_{19}H_{15}ClF_3NO_4$	68–70	H	78	−39	−30	−33
										
11	R = H			$C_{15}H_{11}NO_2$	154 (nq)	23	94	i[f]		
12	R = 4-Cl			$C_{15}H_{10}ClNO_2$	191–192 (q)	1	74	i[f]		
13	CH_2CO_2Na	NH_2	$C_6H_5CH(OH)$	$C_{15}H_{14}NNaO_3$	273 (mn)	C	53	−34	−1[e]	−25
14	CH_2CO_2Na	NH_2	4-$ClC_6H_4CH(OH)$	$C_{15}H_{13}ClNNaO_3 \cdot 0.25H_2O$	138 (dec) (m)	D	47	−24	−12[e]	−29
15	CH_2CO_2Na	NH_2	$C_6H_5CH_2$	$C_{15}H_{14}NNaO_2 \cdot 0.25H_2O$	204–206 (mn)	G	56	−10[e]		−37
16	CH_2CO_2Na	NH_2	$C_6H_{11}C(O)$	$C_{15}H_{18}NNaO_3 \cdot 0.5H_2O$	235–240 (dec) (mo)	B	17	−29	−9[e]	−30
17	CH_2CH_3	NH_2	$C_6H_5C(O)$	$C_{15}H_{15}NO \cdot HBr$	206–209 (dec) (o)	15	54	−13[e]		−30
18	CH_2CH_2OH	NH_2	$C_6H_5C(O)$	$C_{15}H_{15}NO_2$	107–108 (nr)	I	16	−40	−21	−19
19	CH_2CH_2OH	NH_2	4-$ClC_6H_4C(O)$	$C_{15}H_{14}ClNO_2$	129–131.5 (o)	I	64	−43	−25	−42
20	CH_2CH_2OH	NH_2	$C_6H_5CH(OH)$	$C_{15}H_{17}NO_2$	101 (q)	F	62	−27		−19
21	CH_2CH_2OH	NH_2	4-$ClC_6H_5CH(OH)$	$C_{15}H_{16}ClNO_2$	132–134 (s)	F	45	−37	−21	−42
22	$COCO_2Na$	NH_2	$C_6H_5C(O)$	$C_{15}H_{10}NNaO_4 \cdot 0.25H_2O$	270 (mnt)	O	55	−16[e]	−2[e]	−30[g]
23	CH_2CO_2H	NO_2	$C_6H_5C(O)$	$C_{15}H_{11}NO_5$	160–162 (mo)	J	48	−44	−18	−24
24	CH_2CO_2H	NO_2	4-$ClC_6H_4C(O)$	$C_{15}H_{10}ClNO_5$	164–165 (mo)	J	61		−21	−40
										
25	R = H			$C_{15}H_{11}NO_3$	180.5–183.5 (o)	K	66	−31	−13[e]	−27
26	R = 4-Cl			$C_{15}H_{10}ClNO_3$	200–202 (dec) (o)	K	38	−26	−15[e]	−25
27	$COCH_3$	NH_2	$C_6H_5C(O)$	$C_{15}H_{13}NO_2$	92–93 (uv)	L	29	i[f]		
28	$COCH_2CH_2CO_2H$	NH_2	$C_6H_5C(O)$	$C_{17}H_{15}NO_2$	161–162.5 (tw)	M	67	−37	−26	−29
29	$COCH_2CH_2CO_2H$	NH_2	4-$ClC_6H_4C(O)$	$C_{17}H_{14}ClNO_4$	172–177	N	89	−39	−17[e]	−40
30	CH_2CO_2H	$N(CH_3)_2$	$C_6H_5C(O)$	$C_{17}H_{17}NO_3$	144–145 (t)	24	40	−38	−5[e]	−26

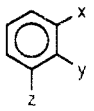
[a] All compounds were analyzed for C, H, and N and results agreed to ±0.4% of theoretical values. [b] m = water, n = absolute ethanol, o = 2-propanol, p = acetonitrile, q = toluene, r = petroleum ether (30–60 °C), s = ethyl acetate, t = isopropyl ether, u = hexane, v = ethyl ether, w = benzene. [c] Numbers refer to references where a preparation is reported and letters refer to procedures described in the Experimental Section. [d] Indomethacin. [e] Not significantly different from control group at $p < 0.05$, as determined by the Dunnett's t test. [f] Inactive at 316 mg/kg. [g] Phenylbutazone at 100 mg/kg was used as reference standard.

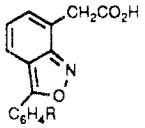
Scheme III. The desired 2-nitro derivatives[16] **23, 24** were prepared by a synthetic route previously described[17] for the 5-nitro isomer. The required 3-chloro-2-nitrobenzophenones **37, 38** were obtained by the oxidation of the 3-chloro-2-aminobenzophenone derivatives with use of peroxytrifluoroacetic acid.[18,19] The activated chloro group was then displaced with diethyl malonate anion, and adducts **39** and **40** were hydrolyzed and decarboxylated with acid.

The oxidation of 2-aminobenzophenone derivatives with peroxyacetic acid stopped at the 3-aryl-2,1-benzisoxazole (**41, 42**) stage[19] in contrast to the more drastic conditions of peroxytrifluoroacetic acid which oxidized to the nitro derivatives **37, 38**. Bromination of the methyl substituents (**43, 44**), displacement of the bromo substituents with cyanide anion (**45, 46**), and base hydrolysis of the nitriles gave the desired 2,1-benzisoxazoleacetic acids **25, 26**.[20]

(16) Walsh, D. A. U.S. Patent 4 254 146, 1981; *Chem. Abstr.* **1981**, *95*, 115064c.
(17) Zinic, M.; Kolbah, D.; Blazevic, N.; Kajfez, F.; Sunjic, V. *J. Heterocycl. Chem.* **1977**, *14*, 1225–1230.
(18) Emmons, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 3470–3472.
(19) Rachlin, A. I. U.S. Patent 3 261 870, 1966; *Chem. Abstr.* **1966**, *65*, 15277e.
(20) Walsh, D. A.; Uwaydah, I. M. Eur. Pat. Appl. EP 260 924, 1988; *Chem. Abstr.* 1988, *108*, 221693d.

Table II. Cyclooxygenase Inhibition Data and Pharmacological Potency Relative to Indomethacin for Selected Prodrug Candidates



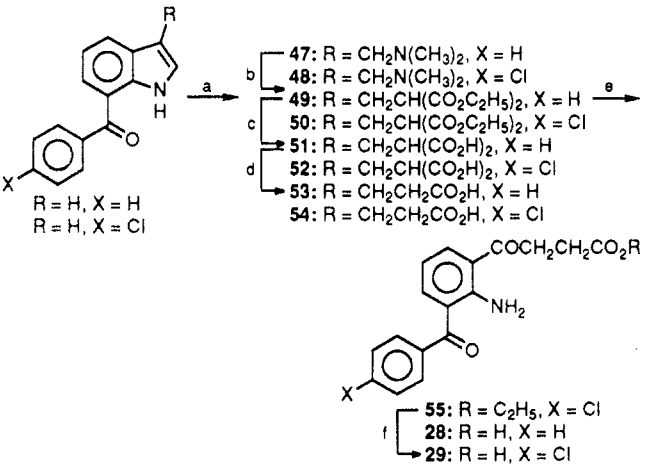
compd	x	y	z	cyclooxygenase inhib: IC_{50}, μM	adjuvant arthritis	intestinal toxicity	therapeutic index[a]
indo[b]				0.2	1	1	1
1	CH_2CO_2Na	NH_2	$C_6H_5C(O)$	0.1	1.1	0.4	2.8
2	CH_2CO_2Na	NH_2	$4\text{-}ClC_6H_4C(O)$	0.1	2.2[c]	1.4	1.6
3	$CH_2CO_2C_2H_5$	NH_2	$C_6H_5C(O)$	~50	0.3	0.7[d]	0.4
4	$CH_2CO_2C_2H_5$	NH_2	$4\text{-}ClC_6H_4C(O)$	73	1.0	0.6[d]	1.7
5	CH_2CONH_2	NH_2	$C_6H_5C(O)$	>100	0.09[d]	–	–
6	CH_2CONH_2	NH_2	$4\text{-}ClC_6H_4C(O)$	>1000	0.8	0.08[d]	10
10	$CH_2CO_2C_2H_5$	$NHCOCF_3$	$4\text{-}ClC_6H_4C(O)$	>1000	1.0[d]	0.3[c]	3.3
13	CH_2CO_2Na	NH_2	$C_6H_5CH(OH)$	>1000	0.001[c]	–	–
14	CH_2CO_2Na	NH_2	$4\text{-}ClC_6H_4CH(OH)$	>1000	0.002[d]	–	–
16	CH_2CO_2Na	NH_2	$C_6H_{11}C(O)$	0.4	0.004[c]	–	–
18	CH_2CH_2OH	NH_2	$C_6H_5C(O)$	>100	0.05[c]	–	–
19	CH_2CH_2OH	NH_2	$4\text{-}ClC_6H_4C(O)$	>1000	0.8	0.24[d]	3.3
20	CH_2CH_2OH	NH_2	$C_6H_5CH(OH)$	>500	0.005[c]	–	–
21	CH_2CH_2OH	NH_2	$4\text{-}ClC_6H_5CH(OH)$	>1000	0.05[c]	–	–
23	CH_2CO_2H	NO_2	$C_6H_5C(O)$	>1000	0.5	0.1[c]	5
24	CH_2CO_2H	NO_2	$4\text{-}ClC_6H_4C(O)$	>1000	1.7	0.5[c]	3.4
							
25	R = H			>1000	0.6[d]	0.24[d]	2.5
26	R = 4-Cl			>500	1.0	1.0	1
28	$COCH_2CH_2CO_2H$	NH_2	$C_6H_5C(O)$	>1000	0.4[c]	0.16[d]	2.5
29	$COCH_2CH_2CO_2H$	NH_2	$4\text{-}ClC_6H_4C(O)$	>1000	0.9	0.3[d]	3.0
30	CH_2CO_2H	$N(CH_3)_2$	$C_6H_5C(O)$	>1000	0.009[c]	–	–

[a] Therapeutic index = potency in adjuvant-induced arthritis assay/potency in intestinal toxicity assay. [b] Indomethacin. [c] 95% confidence limits do not overlap 1.0; thus the compound is significantly different than indomethacin. [d] Approximation; regression lines are not parallel.

The reaction of 2-amino-3-ethylbenzophenone[15] with benzyltriethylammonium permangenate[21] gave oxidation at the benzylic position and yielded the diketone **27**.

Scheme IV outlines the synthesis of substituted γ-oxobenzenebutanoic acids **28**, **29**[22] from 7-benzoylindole derivatives. A Mannich-type reaction with a substituted 7-benzoylindole gave the 3-(dimethylamino)methyl adducts **47**, **48**. The dimethylamino group could be displaced with the diethyl malonate anion to yield **49** and **50**. Base hydrolysis (**51**, **52**) followed by decarboxylation induced by heat led to the substituted indole-3-propanoic acids **53**, **54**. When **53** was subjected to ozonolysis, **28** was isolated directly from the reaction mixture. Under similar reaction conditions, the chloro-substituted derivative **54** gave the intermediate ester **55**. Base hydrolysis of **55** resulted in the desired **29**.

Scheme IV[a]



[a] (a) CH_3CO_2H, H_2O, C_2H_5OH, $(CH_3)_2NH$, CH_2O, 100 °C, 0.5 h; (b) xylene, NaH, $CH_2(CO_2C_2H_5)_2$, Δ, 17 h; (c) 3 N NaOH, Δ, 18 h; (d) 190–200 °C, vacuum; (e) 1. $CH_3CO_2C_2H_5$, C_2H_5OH, O_3; 2. C_2H_5OH, 6 N HCl, Δ, 18 h; (f) C_2H_5OH, 4 N NaOH, Δ, 18 h.

Results and Discussion

The goal of this research project was to determine if a prodrug of **1** or **2** could be found that had a high therapeutic index, yet had a rapid onset of action. Candidates **3**–**30** were tested in the pleural effusion rate assay, an acute model of inflammation (Table I). Activity in this model indicated that the compound possessed inherent antiinflammatory activity or was rapidly metabolized to an active species. Most of the compounds tested showed activity in this model. Of the group of compounds (**2**–**12**) which could be hydrolyzed to **1** or **2**, only the nitriles (**7**, **8**) and the oxindoles (**11**, **12**) were inactive. When amides **9** and **10** were compared, the more labile trifluoroacetyl-substituted amide **12** was active while the acetyl-substituted amide **11** was inactive. Of the group of compounds (**13**–**21**) which must be oxidized to give **1** or **2**, only **15** and **17** were inactive at 100 mg/kg. Metabolic reduction of **22**–**26** could give **1** or **2** but only **22** was inactive. Compounds **27**–**30** require a multistep chemical conversion to **1** or **2** and should be the least likely group to have a quick onset of

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action. However only 27 was inactive while 28–30 showed good activity at 100 mg/kg.

Compounds which were active at 100 mg/kg in the pleural effusion assay were then tested as cyclooxygenase inhibitors (Table II). If a compound had no activity against cyclooxygenase at the dose tested it was considered to have no inherent antiinflammatory activity and to be a true prodrug. Only three compounds (3, 4, 16) which possessed in vivo activity in the pleural effusion assay showed any activity against cyclooxygenase. It is difficult to assess whether esters 3 and 4 are inherently active, or whether a small amount of hydrolysis occurs and the acids 1 and 2 are liberated in the testing medium.

In order to assess whether a therapeutic advantage was achieved through use of the produrg, each compound was tested in the adjuvant-induced arthritis rate assay, a chronic model of inflammation, and a potency determined versus indomethacin. Compounds which possessed good activity in the chronic inflammation model were tested for intestinal toxicity in a rat intestinal lesion assay, and a potency compared to indomethacin was determined. A chronic therapeutic index was calculated (Table II), and this number was used to select candidates for further study.

Eleven (3, 4, 6, 10, 19, 23–26, 28, 29) compounds showed good activity (potency >0.1 × indomethacin) in the adjuvant-induced arthritis assay. All 11 compounds were equivalent to or less than indomethacin in their ability to induce intestinal lesions. It is interesting to note that of the compounds 13–21 which were required to be oxidized to be converted to 1 or 2, only 19 showed good activity in the chronic inflammatory assay. All the prodrugs (except 3) tested had a better index than indomethacin. Clearly 6 stood out from the other candidates by virtue of the value of 10 for its therapeutic index, an order of magnitude improvement over indomethacin. Compound 6 has undergone extensive pharmacological evaluation, the results of which will be reported in a separate communication.

The data in Table II point out that it is difficult to draw generalizations concerning which chemical modifications will produce a prodrug with a high therapeutic index. When amides 5 and 6 are compared, it is observed that the chloro-substituted 6 retains good activity in the adjuvant-induced arthritis assay while 5 is weakly active. A similar observation can be made for alcohols 18 and 19. In all cases studied, chloro-substituted compounds had greater in vivo activity (albeit small in some cases) than their unsubstituted counterparts. The relationship between systematic changes in chemical substituents and the resulting biological variation has been the backbone of much of the study in medicinal chemistry. However when the combination of absorption, distribution, and metabolism must be considered to determine the efficacy and safety of a prodrug, each compound must be considered as unique, and structure–activity generalizations are to date extremely difficult to assess.

Experimental Sectiion

A. Antiinflammation. 1. Acute antiinflammatory activity was determined in the Evans blue–carrageenan-induced pleural effusion model by a modification of the method of Sancilio and Fishman.[10] Each compound was administered orally at doses of 100 and 4.0 mg/kg to six fasted rats, and the 5-h effusive response to the intrapleural injection of 5 mL of 0.075% Evans blue–0.5% carrageenan type 7 at 37 °C was measured. Indomethacin at 4.0 mg/kg orally was used for comparison. The data were reported as a percentage decrease in the average volume of pleural fluid from that of the control group. Statistical differences between control and various treated groups were determined by the Dunnett's t test.[25]

2. Chronic antiinflammatory activity was determined in the adjuvant-induced arthritic rat model of Walz et al.[26] with use of a therapeutic rather than a prophylactic dosing regimen as described by Sancilio et al.[6] Female Lewis Wistar rats that weighed between 151 and 236 g were used. On day 0 a tattoo was made on each leg at the point where the Achilles tendon enters the gastronemius muscle. This served as a reference point for measuring the limb volume plethysmographically. Several hours later 0.05 mL of a suspension of 1.5% *Mycobacterium butyricum* in mineral oil was injected into the subplantar surface of the right hind paw. On day 18 the hind limb volumes of both paws were determined. Animals with significant swelling of the uninjected paws were randomized by block design into groups of 7 or 8. They were dosed orally (po) 5 days/week starting on day 18 with the last dose being given on day 28. Twenty-four hours after the last dose, the animals were weighed and the edema of the injected and uninjected paws was determined by difference. On day 29 each animal was examined for the presence of secondary lesions. A score of 1 was given for each of the following observations: ankylosis of the uninjected paw, modules on the ears and/or tail, and swelling of the forepaws. Linear regression analysis, potency, and 95% confidence limits were determined by the method described by Bliss and White.[27]

B. Chronic Intestinal Toxicity (Multiple Oral Doses).[28] Male and female Sprague–Dawley rats, weighing between 160 and 200 g, were randomly divided into groups of eight. Excluding the weekend, compounds were orally administered on a daily basis for 11 days. Twenty-four hours after the last dose, the rats were killed with chloroform or carbon dioxide, and the intestines were examined for the presence of ulcers. The severity of lesions was scored in increments of 10, from 0 for no damage to +40 for maximum damage, plus 10 for perforations and/or adhesions, and an additional 10 if the animal died. Growth of the animals was also monitored during the course of the experiment.

C. Cyclooxygenase Inhibition. Cyclooxygenase activity was determined polarographically wth a YSI Model 50 Oxygen Monitor.[29] Standard assays were conducted at 30 °C in 3.0 mL of reaction buffer, containing 100 mM Tris-HCl buffer (pH 8.0), 1.0 mM phenol, 2.0 μM hematin, and detergent-solubilized sheep vesicular gland microsomal powder (70 μg). Reactions were initiated by addition of 300 nmol of an aqueous suspension of ammonium arachidonate. The instrument signal was digitized by a Beckman Instruments Co. digimetry instrument coupler and acquired by a Hewlett-Packard Model 1000 minicomputer. Cyclooxygenase optimal velocities were calculated either from recorder tracings of oxygen concentration or from the digitized, differentiated instrument signal by using the RSMTH program of CALS (Computer Automated Laboratory System; Beckman Instruments Co.). Assays were conducted in triplicate.

General Procedures. Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; ^{1}H NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard on a Varian A-60 or Varian EM-360L spectrometer; ^{13}C NMR spectra were obtained in the same solvents on a Varian FT-80A spectrometer; mass spectra were determined on a Varian MAT-44 mass spectrometer; IR spectra were run as KBr pellets on a Beckman IR8 or Perkin-Elmer 297 IR spectrophotometer. Spectral data for all reported compounds were consistent with assigned structures. Purifications were done by column chromatography on silica gel or Florisil and by high-pressure liquid chromatography with use of a Waters Prep LC-500A apparatus with a PrepPAK-500 silica cartridge. Analytical results for compounds followed by elemental

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symbols are within ±0.4% of theory and were determined on a Perkin-Elmer Model 240 CHN analyzer or on a Control Equipment Corporation 240-XHA CHN analyzer. Indomethacin was obtained from Merck and Co., Inc.

2-Amino-3-benzoyl-α-(methylthio)benzeneacetamide (31). To a cold (−70 °C) solution of 19.7 g (0.1 mol) of 2-aminobenzophenone in 300 mL of CH_2Cl_2 was added a solution of 11.5 g (0.1 mol) of 95% *tert*-butyl hypochlorite in 30 mL of CH_2Cl_2, followed in 10 min by the addition of a solution of 10.5 g (0.1 mol) of (methylthio)acetamide in 300 mL of THF. The temperature was maintained at or below −55 °C during these additions. After 1 h at −60 °C, the mixture was allowed to warm to ambient temperature, and the precipitates were collected by filtration. This solid was slurried in 200 mL of CH_2Cl_2 and 11 g (0.11 mol) of $(C_2H_5)_3N$ was added. The mixture was stirred for 5 min and then the yellow-orange solution was washed twice with 100-mL portions of H_2O. The organic phase was dried ($MgSO_4$) and concentrated. The residue was triturated with $(C_2H_5)_2O$, collected by filtration, and dried to yield 13.0 g (43%) of **31** as a light-yellow powder, mp 153–155 °C. Anal. ($C_{16}H_{16}N_2O_2S$) C, H, N.

2-Amino-3-(4-chlorobenzoyl)-α-(phenylthio)benzeneacetamide (32). To a cold (−70 °C) solution of 34.6 g (0.15 mol) of 2-amino-4′-chlorobenzophenone in 500 mL of CH_2Cl_2 was added 17.3 g (0.15 mol) of 95% *tert*-butyl hypochlorite. After 10 min, a solution of 25.0 g (0.15 mol) of (phenylthio)acetamide in 400 mL of THF was added over a period of 20 min while the temperature was maintained below −65 °C. After 2 h, 20 g (0.2 mol) of $(C_2H_5)_3N$ was added, and the mixture was allowed to warm to ambient temperature. The mixture was concentrated, and the residue was partitioned between H_2O and CH_2Cl_2. Material insoluble in either phase was collected by filtration, washed with 20% aqueous C_2H_5OH, and dried to yield 36 g (61%) of **32** as a light-yellow powder, mp 189–191 °C. Anal. ($C_{21}H_{17}ClN_2O_2S$) C, H, N.

2-Amino-3-benzoyl-α-(methylthio)benzeneacetonitrile (33). To a cold (−68 °C) slurry of 29.6 g (0.15 mol) of 2-aminobenzophenone and 13.1 g (0.15 mol) of (methylthio)acetonitrile in 400 mL of CH_2Cl_2 was added dropwise 16.8 g (0.155 mol) of *tert*-butyl hypochlorite at such a rate that the temperature did not exceed −64 °C. The solution was stirred at −69 °C for 1 h, treated with 15.7 g (0.155 mol) of $(C_2H_5)_3N$ in one portion, and allowed to warm to ambient temperature. The solution was washed twice with H_2O, dried (Na_2SO_4), and concentrated to give 45.2 g of dark oil. The oil was purified by column chromatography on 1 kg of silica gel with a gradient elution of 50–100% benzene in petroleum ether (60–110 °C). The appropriate fractions were combined and concentrated to yield 22.5 g (53%) of **33** as tan crystals, mp 107–108 °C (2-propanol). Anal. ($C_{16}H_{14}N_2OS$) C, H, N.

2-Amino-3-(4-chlorobenzoyl)-α-(methylthio)benzeneacetonitrile (34). To a cold (−70 °C) solution of 46.3 g (0.2 mol) of 2-amino-4′-chlorobenzophenone and 17.4 g (0.2 mol) of (methylthio)acetonitrile in 1 L of CH_2Cl_2 was added dropwise 22.2 g (0.21 mol) of *tert*-butyl hypochlorite at such a rate that the temperature did not exceed −65 °C. The solution was stirred at −70 °C for 1 h and then 21.2 g (0.21 mol) of $(C_2H_5)_3N$ was added in one portion. The solution was allowed to warm to ambient temperature, washed twice with H_2O, dried (Na_2SO_4), and concentrated. The residue crystallized when it was triturated with $(C_2H_5)_2O$. The solid was collected by filtration and recrystallized from 2-propanol to yield 43.0 g (68%) of **34** as a tan solid, mp 122 °C dec. Anal. ($C_{16}H_{13}ClN_2OS$) C, H, N.

Method A. 2-Amino-3-benzoylbenzeneacetamide (5). A solution of 9.7 g (0.032 mol) of **31** in 100 mL of THF was treated with 80 g of a commercial (successively washed thrice with H_2O and thrice with THF) preparation of Raney nickel. The mixture was stirred mechanically for 15 min and then cautiously filtered through Celite. The filtrate was concentrated, and the residue was recrystallized from 2-propanol to yield 6.0 g (73%) of **5** as yellow needles, mp 178–180 °C. Anal. ($C_{15}H_{14}N_2O_2$) C, H, N.

7-(Cyclohexylcarbonyl)-1,3-dihydro-3-(methylthio)-2*H*-indol-2-one (35). To a cold (−70 °C) solution of 59 g (0.29 mol) of (2-aminophenyl)cyclohexylmethanone[30] and 40 g (0.30 mol) of ethyl (methylthio)acetate in 1 L of CH_2Cl_2 was added dropwise 34.4 g (0.30 mol) of 95% *tert*-butyl hypochlorite at such a rate that the temperature did not exceed −65 °C. The solution was stirred for 1 h at −70 °C, treated with 40 g (0.4 mol) of $(C_2H_5)_3N$ and allowed to warm to ambient temperature. An 800-mL portion of 4 N HCl was added and the mixture was vigorously stirred for 1 h. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated. The residue was recrystallized from 95% C_2H_5OH to yield 49 g (58%) of **35** as white nnedles, mp 111.5–113.0 °C. Anal. ($C_{16}H_{19}NO_2S$) C, H, N.

7-(Cyclohexylcarbonyl)-1,3-dihydro-2*H*-indol-2-one (36). A mixture of 46 g (0.14 mol) of **35** and 40 g (0.34 mol) of tin powder in 600 mL of 95% C_2H_5OH was heated to reflux and treated with 100 mL of concentrated HCl. The mixture was mechanically stirred and heated at reflux for 6 h and filtered hot. The filtrate was cooled and the resulting precipitate was collected by filtration and recrystallized from 2-propanol to yield 34 g (88%) of **36** as pink needles, mp 122.5–123.5 °C. Anal. ($C_{15}H_{17}NO_2$) C, H, N.

Method B. 2-Amino-3-(cyclohexylcarbonyl)benzeneacetic Acid, Sodium Salt, Hemihydrate (16). A mixture of 20 g (0.08 mol) of **36** in 250 mL of 3 N NaOH was heated at reflux under a nitrogen atmosphere for 16 h. The mixture was cooled, and the resulting precipitate was collected by filtration and recrystallized twice from 1% aqueous 2-propanol to give 4.2 g (17%) of **16** as a light-yellow powder, mp 235–240 °C dec. Anal. ($C_{15}H_{18}NNaO_3 \cdot 0.5H_2O$) C, H, N.

Method C. 2-Amino-3-(hydroxyphenylmethyl)benzeneacetic Acid, Sodium Salt (13). A solution of 14.8 g (0.05 mol) of **1** in 250 mL of H_2O was hydrogenated in a Parr apparatus over 10% Pd/C at ambient temperature overnight. The mixture was filtered through Celite, and the filtrate was concentrated. Absolute ethanol was added to the residue, and the mixture concentrated to azeotropically remove H_2O. This process was repeated twice to give a white solid. The solid was recrystallized successively from $CH_3OH/(C_2H_5)_2O$ and C_2H_5OH/H_2O to yield 7.0 g (53%) of **13** as a white solid, mp 273 °C. Anal. ($C_{15}H_{14}NNaO_3$) C, H, N.

Method D. 2-Amino-3-[(4-chlorophenyl)hydroxymethyl]benzeneacetic Acid, Sodium Salt (14). A mixture of 9.0 g (0.029 mol) of **2** in 200 mL of H_2O and 100 mL of 2% NaOH was filtered through Celite, and the filtrate was treated with 1.1 g (0.03 mol) of $NaBH_4$. The mixture was stirred at ambient temperature for 3 h and then filtered through Celite. The filtrate was made acidic with CH_3CO_2H (foaming). The resulting white solid was collected by filtration and washed with H_2O. The solid was stirred with 150 mL H_2O and 1.1 g (0.03 mol) of NaOH. The solution was filtered, and the filtrate's pH was adjusted to 8.5 with 15% HCl. The mixture was allowed to stand at ambient temperature overnight and then filtered through Celite, and the filtrate was then concentrated. The residue was chased twice with absolute C_2H_5OH to leave a white solid. The solid was recrystallized from H_2O to yield 4.2 g (47%) of **14** as an off-white powder, mp 138 °C dec. Anal. ($C_{15}H_{13}ClNNaO_3 \cdot 0.25H_2O$) C, H, N.

Method E. 2-Amino-3-(4-chlorobenzoyl)benzeneacetic Acid, Ethyl Ester (4). A solution of 14 g (0.045 mol) of **2** in 150 mL of $(CH_3)_2NCHO$ was treated with 30 g (0.19 mol) of C_2H_5I, and the reaction mixture was stirred at ambient temperature for 2.5 h. The solution was poured into 1.5 L of H_2O and allowed to stand. The resulting precipitate was collected by filtration, washed with H_2O, dried, and recrystallized from absolute C_2H_5OH to yield 11.6 g (81%) of **4** as yellow flakes, mp 101–102 °C. Anal. ($C_{17}H_{16}ClNO_3$) C, H, N.

Method F. 2-Amino-3-(hydroxyphenylmethyl)benzeneethanol (20). A mechanically stirred slurry of 5.5 g (0.145 mol) of $LiAlH_4$ in 60 mL of dry (freshly distilled from $LiAlH_4$) THF was treated with a solution of 19.4 g (0.068 mol) of **3**[23] in 120 mL of THF, and the mixture was heated at reflux under a nitrogen atmosphere for 2 h. The mixture was cooled (ice bath) and treated successively with 5.5 mL of H_2O, 5.5 mL of 15% NaOH, and 16.5 mL of H_2O. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was recrystallized from toluene to yield 10.2 g (62%) of **20** as off-white needles, mp 101 °C. Anal. ($C_{15}H_{17}NO_2$) C, H, N.

Method G. 2-Amino-3-(phenylmethyl)benzeneacetic Acid, Sodium Salt (15). A solution of 14.8 g (0.05 mol) of **1** in 250 mL of H_2O was hydrogenated in a Parr apparatus over 10% Pd/C at 50–60 °C for 32 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was recrystallized from 95% C_2H_5OH to yield 7.4 g (56%) of **15** as a white solid, mp 204–206 °C. Anal. ($C_{15}H_{14}NNaO_2 \cdot 0.25H_2O$) C, H, N.

Method H. 3-(4-Chlorobenzoyl)-2-[[(trifluoromethyl)carbonyl]amino]benzeneacetic Acid, Ethyl Ester (10). To a solution of 3.2 g (0.01 mol) of **4** in 100 mL of CH_2Cl_2 was added a solution of 2.1 g (0.01 mol) of trifluoroacetic anhydride in 10 mL of CH_2Cl_2. The reaction mixture was stirred at ambient temperature for 15 min, washed twice with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was triturated with petroleum ether (30–60 °C), collected by filtration and dried to yield 3.2 g (78%) of **10** as a tan solid, mp 68–70 °C. Anal. ($C_{19}H_{15}ClF_3NO_4$) C, H, N.

Method I. [2-Amino-3-(2-hydroxyethyl)phenyl](4-chlorophenyl)methanone (19). A mixture of 8.4 g (0.03 mol) of **21** and 13 g (0.15 mol) of activated MnO_2 in 250 mL of CH_2Cl_2 and 150 mL of THF was heated at reflux for 18 h. The hot mixture was filtered through Celite, and the filtrate was concentrated. The residue was recrystallized from 2-propanol to yield 5.3 g (64%) of **19** as a yellow solid, mp 129–131.5 °C. Anal. ($C_{15}H_{14}ClNO_2$) C, H, N.

(3-Chloro-2-nitrophenyl)phenylmethanone (37). To a cold, stirred mixture of 10.8 mL of 90% H_2O_2 and 250 mL of CH_2Cl_2 was added 100 g (67.6 mL) of trifluoroacetic anhydride dropwise over a 45-min period. The ice bath was removed, and a solution of 23.1 g (0.1 mol) of (2-amino-3-chlorophenyl)phenylmethanone[15] in 100 mL of CH_2Cl_2 was added dropwise over a 45-min period. The dark solution was heated on a steam bath for 1 h, cooled, and washed successively with two 200-mL portions of cold H_2O, two 200-mL portions of cold 10% Na_2CO_3 (emulsion), and once with brine. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on 250 g of silica gel with C_6H_6 as eluent. The appropriate fractions were combined and concentrated to yield 15.3 g (59%) of **37** as a tan solid, mp 67–69 °C (2-propanol). Anal. ($C_{13}H_8ClNO_3$) C, H, N.

(3-Chloro-2-nitrophenyl)(4-chlorophenyl)methanone (38). With use of the above procedure, 10 mL of 90% H_2O_2, 100 g of trifluoroacetic anhydride, and 26.6 g (0.1 mol) of (2-amino-3-chlorophenyl)(4-chlorophenyl)methanone[15] in a total of 350 mL of CH_2Cl_2 gave 11.9 g (40%) of **38** as a white solid, mp 147–148 °C (absolute C_2H_5OH). Anal. ($C_{13}H_7Cl_2NO_3$) C, H, N.

2-(3-Benzoyl-2-nitrophenyl)propanedioic Acid, Diethyl Ester (39). A mixture of 1.9 g (0.044 mol) of washed (petroleum ether, 30–60 °C) 57% NaH/oil in 25 mL of dry $(CH_3)_2SO$ was heated to 100 °C and treated with a solution of 7.0 g (0.044 mol) of diethyl malonate in 25 mL of $(CH_3)_2SO$. The mixture was stirred until all solids had dissolved and then a solution of 5.4 g (0.021 mol) of **37** in 15 mL of $(CH_3)_2SO$ was added. The dark solution was heated at 100 °C for 1 h and then poured into 800 mL of ice/H_2O. The mixture was extracted with three 100-mL portions of C_6H_6, and the combined extracts were washed twice with H_2O and once with brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from 2-propanol to yield 3.1 g (46%) of **39** as an off-white solid, mp 130–131 °C. Anal. ($C_{20}H_{19}NO_7$) C, H, N.

2-[3-(4-Chlorobenzoyl)-2-nitrophenyl]propanedioic Acid, Diethyl Ester (40). With use of the above procedure, 3.9 g (0.08 mol) of 57% NaH/oil, 12.8 g (0.08 mol) of diethyl malonate, and 11.0 g (0.037 mol) of **38** in a total of 100 mL of $(CH_3)_2SO$ gave 8.6 g (55%) of **40** as an off-white solid, mp 96–100 °C (2-propanol). Anal. ($C_{20}H_{18}ClNO_7$) C, H, N.

Method J. 3-Benzoyl-2-nitrobenzeneacetic Acid (23). A solution of 11.5 g of (0.03 mol) of **39** in 50 mL of 20% H_2SO_4 and 50 mL of glacial CH_3CO_2H was heated at reflux under a nitrogen atmosphere overnight. The solution was concentrated, and the residue was made basic with 450 mL of 2 N $KHCO_3$. The mixture was extracted twice with $(C_2H_5)_2O$, and the aqueous layer was made acidic with 20 mL of concentrated H_2SO_4. The solid which precipitated was collected by filtration, washed wtih H_2O, and recrystallized from aqueous 2-propanol to yield 4.1 g (48%) of **23** as an off-white solid, mp 160–162 °C. Anal. ($C_{15}H_{11}NO_5$) C, H, N.

7-Methyl-3-phenyl-2,1-benzisoxazole (41). A solution of 8.4 g (0.04 mol) of (2-amino-3-methylphenyl)phenylmethanone,[15] 150 mL of glacial CH_3CO_2H, and 40 mL of 30% H_2O_2 was allowed to stand at ambient temperature for 3 days. The solution was poured into 800 mL of ice/H_2O, and the solid which precipitated was collected by filtration, washed with H_2O, dried, and recrystallized from 2-propanol to yield 4.1 g (49%) of **41** as tan crystals, mp 73–75 °C. Anal. ($C_{14}H_{11}NO$) C, H, N.

3-(4-Chlorophenyl)-7-methyl-2,1-benzisoxazole (42). With use of the above procedure, 49 g (0.2 mol) of (2-amino-3-methylphenyl)(4-chlorophenyl)methanone,[15] 1 L of glacial CH_3CO_2H, and 200 mL of 30% H_2O_2 gave 16.4 g (34%) of **42** as an off-white solid, mp 134–136 °C (C_6H_{12}). Anal. ($C_{14}H_{10}ClNO$) C, H, N.

7-(Bromomethyl)-3-phenyl-2,1-benzisoxazole (43). A mixture of 23.5 g (0.112 mol) of **41**, 20.0 g (0.112 mol) of *N*-bromosuccimide, and 0.5 g of dibenzoyl peroxide in 400 mL of CCl_4 was heated at reflux while being illuminated by a white light lamp for 3 h. The mixture was filtered, and the filtrate was concentrated. The residue was recrystallized from 2-propanol to yield 25.2 g (77%) of **43** as yellow needles, mp 125.0–125.5 °C. Anal. ($C_{14}H_{10}BrNO$) C, H, N.

3-(4-Chlorophenyl)-7-(bromomethyl)-2,1-benzisoxazole (44). With use of the above procedure, 15.7 g (0.065 mol) of **42**, 11.6 g (0.065 mol) of *N*-bromosuccinimide, and 0.5 g of dibenzoyl peroxide in 400 mL of CCl_4 gave 12.0 g (58%) of **44** as a fluffy, pale-yellow solid, mp 153–155 °C (CH_3CN). Anal. ($C_{14}H_9BrClNO$) C, H, N.

3-Phenyl-2,1-benzisoxazole-7-acetonitrile (45). A mixture of 17.3 g (0.06 mol) of **43**, 17 g (0.26 mol) of KCN, 80 mL of H_2O, and 120 mL of dioxane was heated at reflux under a nitrogen atmosphere for 2 h. The mixture was cooled and diluted with 300 mL of CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was recrystallized twice from absolute C_2H_5OH to give 10.3 g (74%) of **45** as yellow crystals, mp 125–138 °C. Anal. ($C_{15}H_{10}N_2O$) C, H, N.

3-(4-Chlorophenyl)-2,1-benzisoxazole-7-acetonitrile (46). With use of the above procedure, 11.5 g (0.036 mol) of **44**, 9.8 g (0.15 mol) of KCN, 75 mL of H_2O, and 150 mL of dioxane gave 5.8 g (61%) of **46** as a yellow-green powder, mp 165–169 °C (ethyl acetate). Anal. ($C_{15}H_9ClN_2O$) C, H, N.

Method K. 3-Phenyl-2,1-benzisoxazole-7-acetic Acid (25). A mixture of 7.0 g (0.03 mol) of **45**, 25 mL of 20% NaOH, and 75 mL of 95% C_2H_5OH was heated at reflux under a nitrogen atmosphere for 17 h. The mixture was diluted to 500 mL with H_2O, titrated with concentrated HCl to pH 7.0, and filtered. The filtrate was treated wtih charcoal, filtered through Celite, and then acidified with concentrated HCl. The precipitate was collected and recrystallized from 2-propanol to yield 5.0 g (66%) of **25** as yellow needles, mp 180.5–183.5 °C. Anal. ($C_{15}H_{11}NO_3$) C, H, N.

Method L. 1-(2-Amino-3-benzoylphenyl)ethanone (27). A purple solution of 6.8 g (0.03 mol) of **17**[15] and 21.8 g (0.07 mol) of benzyltriethylammonium permanganate[21] in 200 mL of CH_2Cl_2 became a brown-black slurry on stirring for 16 h. The mixture was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate and washings were combined and concentrated, and the residue was purified by column chromatography on 150 g of silica gel with C_6H_6 as eluent. The appropriate fractions were combined and concentrated to yield 2.1 g (29%) of **27** as yellow crystals, mp 92–93 °C (C_6H_{14}/$(C_2H_5)_2O$). Anal. ($C_{15}H_{13}NO_2$) C, H, N.

[3-[(Dimethylamino)methyl]-1*H*-indol-7-yl]phenylmethanone (47). To a solution of 33.1 g (0.15 mol) of (1*H*-indol-7-yl)phenylmethanone[23] in 20 mL of glacial CH_3CO_2H and 100 mL of absolute C_2H_5OH was added a cold solution of 18 g (0.16 mol) of 40% aqueous $(CH_3)_2NH$, 12.2 g (0.15 mol) of 37% formalin, and 25 mL of glacial CH_3CO_2H. The mixture was heated on a steam bath for 0.5 h and concentrated, and the residue was partitioned between CH_2Cl_2 and 5% NaOH. The organic layer was dried (Na_2SO_4) and concentrated and the residue was recrystallized from 2-propanol to yield 29 g (70%) of **47** as light-yellow crystals, mp 111.0–113.5 °C. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

(4-Chlorophenyl)[3-[(dimethylamino)methyl]-1*H*-indol-7-yl]methanone (48). With use of the above procedure, 28.1 g (0.11 mol) of (4-chlorophenyl)(1*H*-indol-7-yl)methanone,[1] 13.5 g (0.12 mol) of 40% aqueous $(CH_3)_2NH$, and 9.3 g (0.115 mol) of 37% formalin in a total of 45 mL of glacial CH_3CO_2H gave 35.3 g (99%) of **48** as a white solid, mp 95–99 °C (2-propanol). Anal. ($C_{18}H_{17}ClN_2O$) C, H, N.

2-[(7-Benzoyl-1*H*-indol-3-yl)methyl]propanedioic Acid, Diethyl Ester (49). A mixture of 19.4 g (0.07 mol) of **47** and 32.5 g (0.2 mol) of diethyl sodiomalonate prepared from 8.5 g (0.2

mol) of 57% NaH in oil and 32 g (0.2 mol) of diethyl malonate in 50 mL of xylene was heated at reflux for 17 h. The mixture was cooled, diluted with $(C_2H_5)_2O$, and washed with H_2O. The solvent and excess reagents were removed by distillation at high vacuum. The pot residue was crystallized successively from 2-propanol and then $[(CH_3)_2CH]_2O$ to give 12.6 g (46%) of **47** as light-yellow powder, mp 86–88 °C. Anal. ($C_{23}H_{23}NO_5$) C, H, N.

2-[[7-(4-Chlorobenzoyl)-1*H*-indol-3-yl]methyl]-propanedioic Acid, Diethyl Ester (50). With use of the above procedure, 4.2 g (0.1 mol) of 57% NaH/oil, 80 g (0.5 mol) of diethyl malonate, and 31.2 g (0.1 mol) of **48** in 30 mL of $(CH_3)_2SO$ gave 28.7 g (67%) of **50** as yellow crystals, mp 102.0–102.5 °C (90% aqueous C_2H_5OH). Anal. ($C_{23}H_{22}ClNO_5$) C, H, N.

2-[(7-Benzoyl-1*H*-indol-3-yl)methyl]-1,3-propanedioic Acid (51). A mixture of 10.0 g (0.025 mol) of **49** in 150 mL of 3 N NaOH was heated at reflux for 18 h and then treated with charcoal, cooled, and filtered. The dark-yellow filtrate was acidified by the dropwise addition of 50 mL of concentrated HCl. The addition of 20 mL of CH_2Cl_2 caused the formation of a precipitate, which was collected and recrystallized from $CHCl_3/CH_3OH$ to give 6.0 g (70%) of **51** as off-white crystals, mp 188–189 °C. Anal. ($C_{19}H_{15}NO_5$) C, H, N.

2-[[7-(4-Chlorobenzoyl)-1*H*-indol-3-yl]methyl]-propanedioic Acid (52). With use of the above procedure, 28.8 g (0.067 mol) of **50** and 600 mL of 3 N NaOH gave 19.5 g (79%) of **52** as pale-yellow crystals, mp 197–201 °C dec ($CHCl_3/CH_3OH$). Anal. ($C_{19}H_{14}ClNO_5$) C, H, N.

7-Benzoyl-1*H*-indole-3-propanoic Acid (53). A 2.4 g (0.07 mol) sample of **51** was heated at 190 °C under vacuum for 0.5 h (until gas evolution ceased). The syrup was cooled to give a quantitative yield of 2.1 g of **53** as a yellow solid, mp 166.5–168.5 °C. Anal. ($C_{18}H_{15}NO_3$) C, H, N.

7-(4-Chlorobenzoyl)-1*H*-indole-3-propanoic Acid (54). With use of the above procedure 18.9 g (0.05 mol) of **52** gave a quantitative yield of 16.6 g of **54** as a dark-yellow solid, mp 190–202 °C. Anal. ($C_{18}H_{17}ClNO_3$) C, H, N.

2-Amino-3-(4-chlorobenzoyl)-γ-oxobenzenebutanoic Acid, Ethyl Ester (55). A solution of 13.1 g (0.04 mol) of **54** in 450 mL of ethyl acetate and 150 mL of absolute C_2H_5OH was treated with ozone (Wellsbach ozonator) until O_3 passed through the solution. The solution was then stirred with an aqueous solution of KI, followed by a wash with aqueous $Na_2S_2O_3$. The organic fraction was concentrated, and the residue was dissolved in 250 mL of 95% C_2H_5OH. The solution was heated to reflux, 150 mL of 6 N HCl was added, and heating was continued for 18 h. The mixture was diluted with 400 mL of H_2O, and a gummy solid was separated. The gum was partitioned between dilute NaOH solution and CH_2Cl_2. The basic aqueous fraction contained only a small amount of acidic material upon acidification, so it was discarded. The CH_2Cl_2 layer was dried (Na_2SO_4) and filtered through a column of silica gel. The yellow-colored eluent was concentrated, and the residue was recrystallized from cyclohexane to give 3.5 g (26%) of **55** as a bright-yellow powder, mp 112–115 °C. Anal. ($C_{19}H_{18}ClNO_4$) C, H, N.

Method M. 2-Amino-3-benzoyl-γ-oxobenzenebutanoic Acid (28). A solution of 8.7 g (0.03 mol) of **53** in 300 mL of ethyl acetate and 100 mL of absolute C_2H_5OH was ozonized (Wellsbach ozonator) until O_3 passed through the solution. The yellow solution was then treated with 16.6 g (0.1 mol) of KI in 30 mL of CH_3CO_2H and 30 mL of H_2O. After 1 h of stirring, the liberated I_2 was removed by washing with a 15% $Na_2S_2O_3$ solution, and the yellow organic layer was concentrated. The residue was dissolved in 100 mL of C_2H_5OH and 20 mL of 6 N HCl and heated at reflux for 16 h. The dark red solution was concentrated, and the residue was partitioned between 5% NaOH and CH_2Cl_2. The layers were separated, and the aqueous layer was made strongly acidic with concentrated HCl. The pH was adjusted to 2–3 by the addition of 5% NaOH, and the precipitate was collected by filtration, washed with H_2O, dried, and recrystallized from $C_6H_6/[(CH_3)_2CH]_2O$ to yield 5.9 g (67%) of **28** as a yellow powder, mp 161.0–162.5 °C. Anal. ($C_{17}H_{15}NO_4$) C, H, N.

Method N. 2-Amino-3-(4-chlorobenzoyl)-γ-oxobenzenebutanoic Acid (29). A solution of 3.3 g (0.009 mol) of **55** in 70 mL of hot C_2H_5OH was treated with 40 mL of 4 N NaOH and the mixture was heated at reflux for 18 h. The hot mixture was filtered, and the insoluble material was discarded. The filtrate was cooled, and the precipitate was collected by filtration. This precipitate was partitioned between 2 N HCl and CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and concentrated to give 2.7 g (89%) of **29** as bright-yellow crystals, mp 172–177 °C. Anal. ($C_{17}H_{14}ClNO_4$) C, H, N.

Method O. 2-Amino-3-benzoyl-α-oxobenzeneacetic Acid, Sodium Salt, Hydrate (4:4:1) (22). A solution of 4 g (0.016 mol) of 7-benzoyl-1*H*-indole-2,3-dione[23] in 100 mL of 1 N NaOH was stirred at ambient temperature for 0.25 h. The resulting precipitate was collected by filtration, washed with acetone, and recrystallized from $C_2H_5OH/H_2O/[(CH_3)_2CH]_2O$ to yield 2.6 g (55%) of **22** as bright-yellow flakes, mp 270 °C. Anal. ($C_{15}H_{10}NNaO_4 \cdot 0.25H_2O$) C, H, N.

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