benzene–MeOH). The nitrosoureas (33–64) thus obtained were usually unstable light yellow amorphous powders and are listed in Table II together with the yields and some characteristic data.

Preparation of the Heptaacetate (65) of 1-(2-Chloroethyl)-3-isobutyl-3-β-maltosyl-1-nitrosourea (37). A mixture of 37 (2.65 g, 0.005 mol), acetic anhydride (15 mL), and pyridine (30 mL) was stirred at room temperature for 2 days. The reaction mixture was poured into water and extracted three times with 50 mL of ethyl acetate. The organic layer was washed with cold aqueous hydrochloric acid, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residual oil was stirred with ether to give a colorless powder, which was collected by filtration and dried. The crude product was crystallized from methanol–ethanol to afford pure 65 as light yellow fine needles: 61.5% yield; mp 131 °C dec; $[\alpha]^{15}_D$ +48.0° (c 1.0, MeOH); IR (Nujol) 1750, 1700 (C=O) cm^{-1}; mass spectrum, m/e 825 (M^+), 795 (M^+ – NO). Anal. ($C_{33}H_{48}O_{19}N_3Cl$) C, H, N, Cl.

Decomposition of the Maltosylnitrosourea (37) in Phosphate-Buffered Solution (pH 7.4). The nitrosourea 37 (1.0 g) was dissolved in 30 mL of 1 M phosphate-buffered solution (pH 7.4) at 5 °C, and the mixture was stirred for 30 min. Then the solution was allowed to stand at room temperature for 20 h. The mixture was saturated with ammonium sulfate and extracted twice with a mixture of ethyl acetate and tetrahydrofuran (1:4). The organic layer was dried over $MgSO_4$ and concentrated. The residual colorless caramel which gave only a single spot on TLC was purified by short-column chromatography on silica gel to give 1-(isobutylamino)-1-deoxy-β-maltose-1,2-carbamate (66) in 75% yield as colorless crystals: mp 207–210 °C (ethanol); $[\alpha]^{15}_D$ +104.5° (c 0.98 MeOH); IR (Nujol) 1755 (C=O) cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 0.86 [d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 1.7–2.1 [m, 1 H, $CH(CH_3)_2$], 4.65 (d, J = 8.5 Hz, 1 H, C_1 H), 5.10 (d, J = 3 Hz, 1 H, $C_{1'}$ H). Anal. ($C_{17}H_{29}NO_{11}$) C, H, N.

Heptaacetate (67) of 66: mp 180–181 °C; $[\alpha]^{15}_D$ +81.6° (c 1.0, MeOH); IR (Nujol) 1790, 1740 (C=O) cm^{-1}. Anal. ($C_{29}H_{41}NO_{17}$) C, H, N.

Preparation of Active Controls (CCNU, ACNU, and GANU) and Unsubstituted Analogues (68 and 69). These active controls were synthesized in our laboratory by the method reported in the previous paper.[10] The unsubstituted analogues 68 and 69 were prepared according to the method described in the literature.[12] Compound 68 had mp 95 °C dec and $[\alpha]^{29}_D$ +62° (c 0.5, H_2O) [lit. mp 96 °C dec; $[\alpha]^{23}_D$ +60° (c 0.5, H_2O)]. Compound 69 had mp 129–131 °C dec and $[\alpha]^{28}_D$ +4.7° (c 1.0, H_2O) [lit. mp 131 °C dec; $[\alpha]^{23}_D$ +4.0 (c 0.5, H_2O)].

Acknowledgment. The authors thank Dr. S. Saito, Director of this laboratory, and Drs. M. Takeda and N. Itoh for encouragement and helpful discussions. Thanks are also due to the staff of the Analytical Center of this company for spectral measurements and elemental analyses.

Antiinflammatory Agents. 2.[1] Syntheses and Antiinflammatory Activity of Substituted 2-Aminophenylacetic Acid Derivatives

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Several substituted 2-aminophenylacetic acid derivatives were prepared and tested for in vitro prostaglandin synthetase inhibition activity and for in vivo antiinflammatory activity. The 2-amino substituent is beneficial to potency in the inhibition of prostaglandin synthetase for the 3-phenoxy, 4-phenyl, and 3-benzoyl series, but only the 3-benzoyl series shows increased antiinflammatory potency in the in vivo assay.

The synthesis and potent antiinflammatory and analgesic activities of 2-amino-3-benzoylphenylacetic acid (1, amfenac) have recently been reported.[1] Since there are few nonsteroidal antiinflammatory drugs (NSAIDs) containing an NH_2 group described in the literature, it became of interest to determine if the NH_2 moiety was responsible for the unexpected potency of 1.

Shen,[2,3] Scherrer,[4] and Appleton[5] have all proposed models in which NSAIDs bind with prostaglandin synthetase and, thus, inhibit prostaglandin production and concomitant inflammation. Compound 1 also inhibits prostaglandin synthetase in vitro,[6] and the NH_2 group could provide an additional point of attachment in binding to the receptor. Three series of compounds, the 2-amino-4-biphenylacetic acids and 2-amino-3-phenoxyphenylacetic acids, in addition to analogues of 1, were synthesized, and their antiinflammatory activities and prostaglandin synthetase inhibitory properties were determined to ascertain the influence of the NH_2 moiety on potency.

Chemistry. Scheme I illustrates a general method for the preparation of o-aminophenylacetic acids utilizing Gassman's procedure[7] for the synthesis of oxindoles. Using 3-aminobiphenyl (4), we obtained two isomers, 10 and 11, in a ratio of ~2:1 (by ^1H NMR), respectively. These isomers could be separated by fractional crystallization, but the procedure was quite tedious. Since the desired isomer (11) was the minor component of the mixture, an unequivocal synthesis of 17 was sought and is presented in Scheme II.

Compounds 24 (Scheme III) and 26 (Scheme IV) were synthesized by standard procedures for pharmacological comparison.

Pharmacology. Acute antiinflammatory activity was determined in the Evans blue–carrageenan induced pleural effusion model as described by Sancilio and Fishman.[8] Each compound was dissolved or suspended in water

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(1) For part 1 in this series, see W. J. Welstead, Jr., H. W. Moran, H. F. Stauffer, L. B. Turnbull, and L. F. Sancilio, *J. Med. Chem.*, **22**, 1074 (1979).
(2) T. Y. Shen, in "Non-steroidal Anti-inflammatory Drugs", S. Garattini and M. N. G. Dukes, Eds., Excerpta Medica Foundation, New York, 1965, p 13.
(3) P. Gund and T. Y. Shen, *J. Med. Chem.*, **20**, 1146 (1977).
(4) R. A. Scherrer, in "Antiinflammatory Agents: Chemistry and Pharmacology", Vol. 1, R. A. Scherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, p 29.
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(6) L. F. Sancilio, W. N. Dannenburg, C. A. Leonard, A. J. Collins, and D. Crook, *Eur. Congr. Rheumatol.*, Abstr. 30 (1979).
(7) P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974).
(8) L. F. Sancilio and A. Fishman, *Toxicol. Appl. Pharmacol.*, **26**, 575 (1973).

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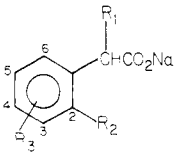
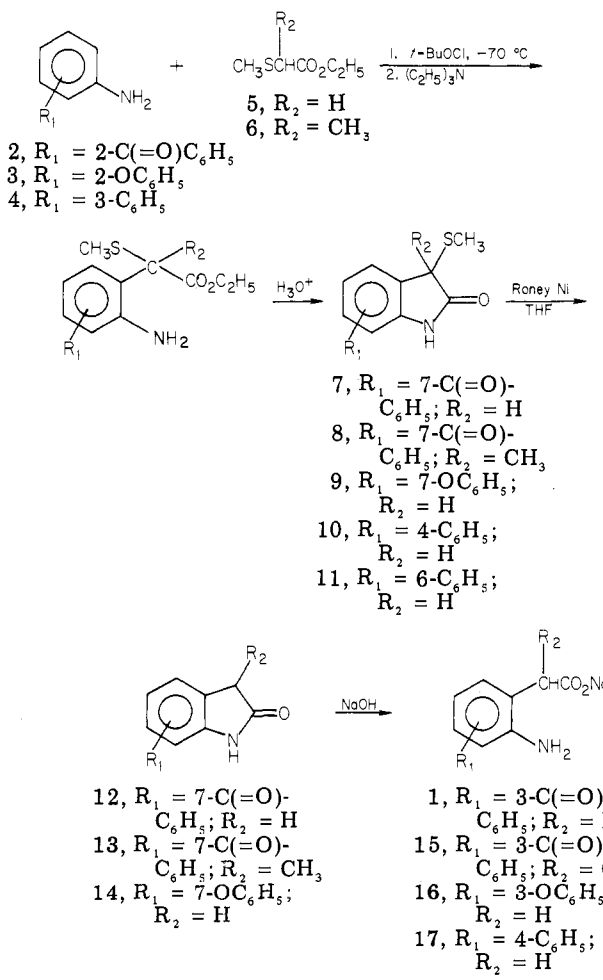
Table I. Antiinflammatory Activity in the 5-h Evans Blue–Carrageenan Pleural Effusion Assay and Inhibition of Prostaglandin Synthetase



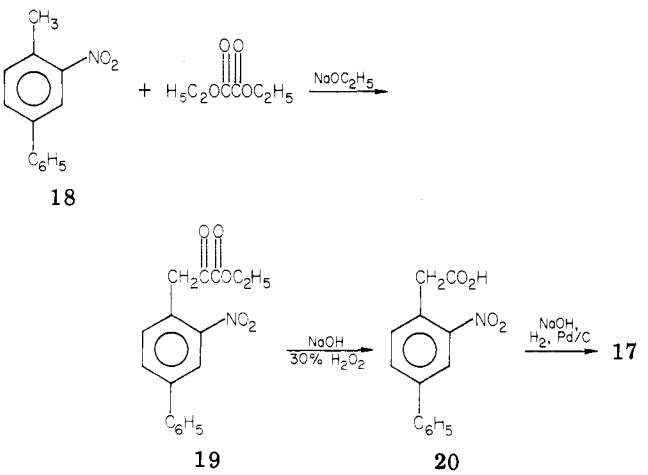
compd	R_1	R_2	R_3	dose, mg/kg	pleural fluid, mL ± SD	% change	IC_{50}, μM
control					5.5 ± 0.5		
INDO[a]				4.0	4.0 ± 0.5[b]	−28	1.1
27	H	H	3-OC_6H_5	20.0	4.9 ± 0.7	−11	>1000
				4.0	5.1 ± 0.7	−7	
28	CH_3	H	3-OC_6H_5	20.0	3.9 ± 0.7[b]	−29	98
				4.0	5.2 ± 0.7	−6	
16	H	NH_2	3-OC_6H_5	20.0	5.1 ± 0.5	−7	420
				4.0	5.7 ± 0.6	+4	
control					6.0 ± 0.3		
INDO				4.0	3.5 ± 1.0[b]	−42	
29	H	H	4-C_6H_5	20.0	3.9 ± 0.4[b]	−35	420
				4.0	4.7 ± 0.7[b]	−21	
30	CH_3	H	4-C_6H_5	20.0	2.9 ± 0.2[b]	−52	12
				4.0	3.4 ± 0.2[b]	−42	
17	H	NH_2	4-C_6H_5	20.0	3.9 ± 0.3[b]	−34	170
				4.0	5.4 ± 0.3	−9	

[a] INDO = indomethacin. [b] Significantly different from control group at $p < 0.05$, as determined by the Dunnett's t test.

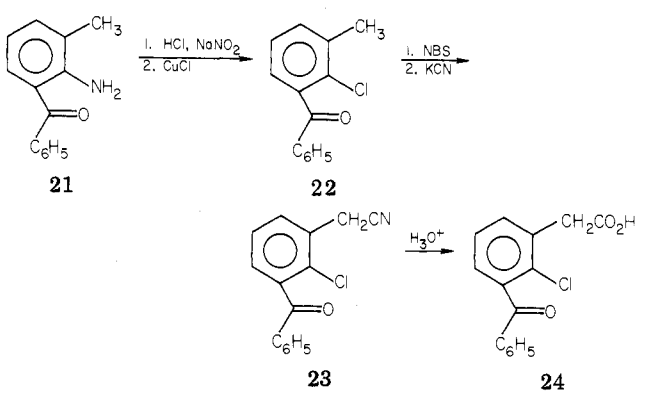
Scheme I



Scheme II

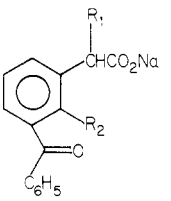


Scheme III



containing 0.5% Tween 80 and administered by gavage (10 mL/kg) to six fasted male rats, and the 5-h effusive response to the intrapleural injection of 5 mL of 0.075% Evans blue–0.5% carrageenan type 7 was measured. The data were reported as a percentage change in volume of pleural fluid from that of a control group. Indomethacin at 4.0 mg/kg was used as the standard. The inhibition of prostaglandin synthetase obtained from bovine seminal vesicles was determined as described under Experimental Section.

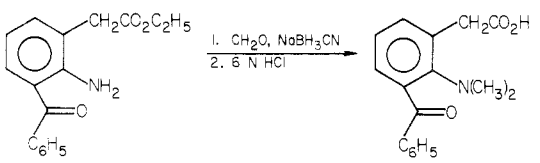
Table II. Antiinflammatory Activity in the 5-h Evans Blue-Carrageenan Pleural Effusion Assay and Inhibition of Prostaglandin Synthetase



compd	R_1	R_2	dose, mg/kg po	pleural fluid, mL ± SD	% change	IC_{50}, μM
control				6.4 ± 0.7		
INDO[a]			4.0	3.9 ± 0.9[b]	−38	1.1
31	H	H	4.0	5.9 ± 0.7	−7	40
control				6.0 ± 0.5		
INDO			4.0	4.3 ± 0.7[b]	−30	
32	CH_3	H	4.0	3.6 ± 0.4[b]	−41	3.4
			0.8	4.6 ± 0.6[b]	−24	
			0.16	5.8 ± 0.6	−4	
1	H	NH_2	4.0	4.5 ± 0.4[b]	−25	0.2
			0.8	5.0 ± 0.5[b]	−17	
			0.16	5.1 ± 0.3[b]	−15	
control				6.2 ± 0.6		
INDO			4.0	4.4 ± 0.6[b]	−30	
15	CH_3	NH_2	100	3.4 ± 0.4[b]	−38	1.0
			4.0	6.0 ± 0.8	−4	
control				6.2 ± 0.6		
INDO			4.0	4.6 ± 0.4[b]	−26	
26	H	$N(CH_3)_2$	100	3.9 ± 0.5[b]	−36	>1000
			20.0	5.2 ± 1.2	−16	
			4.0	5.9 ± 0.7	−5	
control				6.2 ± 0.2		
INDO			4.0	5.0 ± 0.5[b]	−20	
24	H	Cl	100	5.7 ± 0.6	−8	>100

[a] INDO = indomethacin. [b] Significantly different from control group at $p < 0.05$ as determined by the Dunnett's t test.

Scheme IV



25 26

Results

Table I lists the acute antiinflammatory and prostaglandin synthetase inhibitory activities of two series of substituted arylacetic acids. When 3-phenoxyphenylacetic acid (**27**)[9] and 2-(3-phenoxyphenyl)propionic acid (**28**, fenoprofen)[9] were compared with **16**, it was observed that **27** and **16** were inactive at 20 mg/kg. Only **28** showed antiinflammatory potency at 20 mg/kg comparable with indomethacin at 4.0 mg/kg. The in vitro data paralleled the in vivo data for this series of compounds. When 4-biphenylacetic acid (**29**) and 2-(4-biphenyl)propionic acid (**30**)[10] were compared with **17**, all three compounds were active at 20 mg/kg, while **17** was inactive at 4.0 mg/kg. For this series, addition of an *o*-NH_2 group decreased antiinflammatory potency but slightly increased the prostaglandin synthetase inhibitory properties.

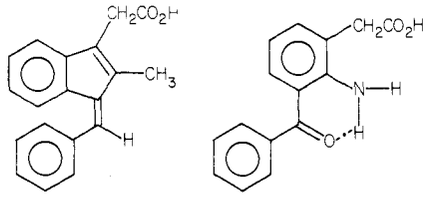
Table II lists the acute antiinflammatory and prostaglandin synthetase inhibitory activities of 3-benzoylphenylacetic acid (**31**),[11] 2-(3-benzoylphenyl)propionic acid (**32**, ketoprofen)[12], **1**, and some derivatives of **1**. At 4.0 mg/kg, **31** was inactive, while addition of an α-methyl (**32**) or an *o*-amino (**1**) group significantly increased antiinflammatory activity. A combination of an α-methyl and an *o*-amino group in the same molecule (**15**) decreased potency relative to that of **1** or **32**. Replacement of an amino group with a dimethylamino group (**26**) also reduced potency, while replacement of the amino group with a chloro group (**24**) abolished antiinflammatory activity. The in vitro results were consistent with the in vivo data for all the compounds except for **15**, which had no antiinflammatory activity at 4.0 mg/kg but did show prostaglandin synthetase inhibitory activity equivalent to indomethacin.

Discussion

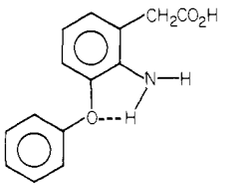
The addition of an *o*-amino moiety slightly increases the ability to inhibit prostaglandin synthetase of both the 3-phenoxyphenyl- and 4-biphenylacetic acids (Table I). The in vivo data for **17** indicate that addition of an *o*-amino group decreases antiinflammatory potency. For a given series of compounds, in vitro and in vivo data may not necessarily be expected to correlate, since the addition of an amino group could substantially alter absorption, distribution, metabolism, and other parameters. However, the addition of an *o*-amino substituent appears to have approximately the same effect on antiinflammatory potency as does the addition of an α-methyl substituent in

(9) W. S. Marshall, U.S. Patent 3600437 (1971); *Chem. Abstr.*, **75**, 48707*m* (1971).
(10) T. Y. Shen, C. P. Dorn, Jr., and B. E. Witzel, *Neth. Appl.* 6508194 (1966); *Chem. Abstr.*, **67**, 21689*e* (1967).
(11) D. E. Bays and R. V. Foster, U.S. Patent 3828093 (1974).
(12) A. Allais, G. Rousseau, J. Meier, R. Dersadt, J. Benzoni, and L. Chifflat, *Eur. J. Med. Chem. Chim. Ther.*, **9**, 381 (1974).

Chart I. Favorable Conformations for Binding of Antiinflammatory Agents



more potent isomer 1



16

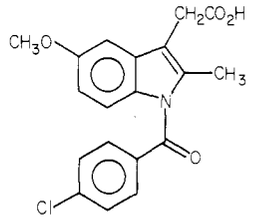
the 3-benzoylphenylacetic acid series (Table II) and has an even larger relative effect on the prostaglandin synthetase inhibiting properties of this series. It is of interest to speculate on the reasons why an amino substituent has a greater beneficial effect on potency in certain chemical series and not in others.

(1) One possible explanation is that 2-aminobenzophenones can form intramolecular hydrogen bonds between the amino hydrogen and the oxygen of the carbonyl.[13,14] This hydrogen bond could hold the aryl group in a more favorable conformation for binding as suggested by Shen[15] from his work on indenes (Chart I). This effect would be most pronounced in **1**, since the hydrogen bond to a carbonyl is one of the strongest,[13] less pronounced in **16** (six-membered ring > five-membered ring), and nonexistent for **17**.

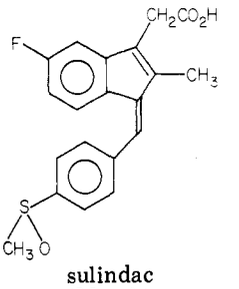
(2) Of the six antiinflammatory aryl acids that are currently marketed in the U.S., three are acetic acids and three are propionic acids (Chart II). Each acetic acid has an *o*-methyl substituent, while the propionic acids do not. It is well documented[16] that in the many arylacetic acid NSAIDs, the addition of an α-methyl substituent increases potency by an order of magnitude, with the *S* configuration being more potent than the *R* configuration; however, if an ortho substituent already exists, addition of an α-methyl substituent may slightly increase or in some cases decrease antiinflammatory activity. Clearly, the binding of the NSAID with the receptor in prostaglandin synthetase is quite sensitive to changes about the carboxylic acid. Apparently, certain ortho substituents will fulfill the same requirement as does an α-methyl substituent.

Allais[12] et al. have reported on a systematic study of the effects of an α-methyl vs. an *o*-methyl substituent in the ketoprofen (**32**) series. Their antiinflammatory data show that **32** is about 10 times as potent as **31** and that 3-benzoyl-2-methylphenylacetic acid is about 5 times as potent as **31**. Our antiinflammatory data in Table II are consistent with their results. When both an α-methyl and an *o*-methyl group are present in the same molecule, Allais observed that there is a decrease in potency. Compound **15** is less potent than **1**, and this result is consistent with an hypothesis of a steric requirement for binding. The dimethylamino substituent increases steric hinderance and

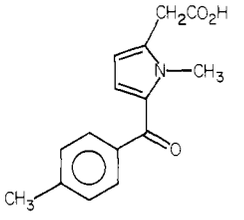
Chart II. Antiinflammatory Drugs Currently Marketed in the U.S.



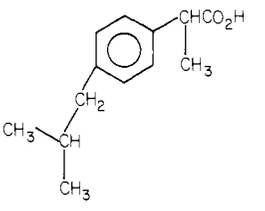
indomethacin (Merck)



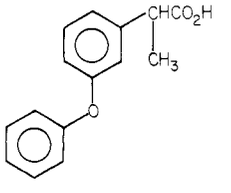
sulindac (Merck)



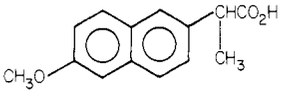
tolmetin (McNeil)



ibuprofen (Upjohn)



fenoprofen (Lilly)



naproxen (Syntex)

eliminates hydrogen bonding, and as a consequence **26** is less potent than **1**.

(3) Farge[17] et al. have indicated that an *o*-OCH_3 or *o*-OH also provides active compounds in this series. From the literature, the ortho substituents attached to active NSAIDs are CH_3, OCH_3, OH, NH_2, and $N(CH_3)_2$. All of these substituents are electron donating, so there may also be an electronic component to binding. A methyl group and a chloro group have approximately the same steric bulk[18] (E_s for CH_3 = 0; E_s for Cl = 0.27), and their contributions to the partition coefficient are similar[18] (π for CH_3 = 0.56; μ for Cl = 0.71), but the chloro group is electron withdrawing. The *o*-chloro compound (**24**) was prepared to test this hypothesis and was found to be devoid of antiinflammatory activity at 100 mg/kg and prostaglandin synthetase inhibition activity at 10^{-4} M (Table II). These results indicate that a steric requirement for binding may not be as important as an electronic component to binding in this series of compounds.

Shen's model[2,3] for the binding of an arylacetic acid to prostaglandin synthetase has served as a useful working hypothesis for several years for the development of many NSAIDs. Recently, Appleton and Brown[5] have proposed a binding model which is markedly different from that of Shen. From the data presented here and in the literature, it is evident that the area around the carboxyl group in an arylacetic acid is very sensitive to steric and electronic changes, while the lipophilic "tail" can be widely varied (Chart II). Shen's[3] model has the relatively insensitive "tail" near the position in the enzyme where oxidation of arachidonic acid occurs. Brown's[5] model has the sensitive

(13) A. N. Hombly and B. V. O'Grady, *Aust. J. Chem.*, **16**, 459 (1963).
(14) T. Axenrod and M. J. Wieder, *J. Am. Chem. Soc.*, **93**, 3541 (1971).
(15) T. Y. Shen and C. A. Winter, *Adv. Drug Res.*, **12**, 160 (1977).
(16) T. Y. Shen, *Angew. Chem., Int. Ed. Engl.*, 460 (1972).
(17) D. Farge, M. N. Messer, and C. Moutonnier, South African Patent 6 800 524 (1968); *Chem. Abstr.*, **70**, 77597c (1969).
(18) K. L. Chu, in "The Basis of Medicinal Chemistry", M. E. Wolff, Ed., Wiley, New York, 1980, Part I, p 401.

carboxylic acid portion of the NSAID bound to the same portion of the enzyme that oxidizes the Δ^{11} double bond of arachidonic acid and, to us, is the intuitively more appealing representation. This latter model is also more consistent with existing experimental results for nonacidic cyclooxygenase inhibitors and will accommodate diverse chemical structures,[19,20] which is a limitation of the Shen model.

Conclusions

(1) The addition of an *o*-amino group to 4-biphenylacetic acid or 3-phenoxyacetic acid slightly increased the prostaglandin synthetase inhibitory properties of these series of compounds. The in vivo results did not show an increase in antiinflammatory potency. Thus, there appears to be no substantial steric or electronic requirements of the enzyme that are fulfilled by an *o*-amino group for these series of compounds.

(2) The addition of an *o*-amino group to 3-benzoylphenylacetic acid (**31**) gives **1**, which is an extremely potent prostaglandin synthetase inhibitor and also shows potent antiinflammatory activity in vivo. Hydrogen bonding between the *o*-amino group and the benzoyl carbonyl may hold the molecule in a favorable conformation for binding to the prostaglandin synthetase receptor.

(3) For many series of antiinflammatory agents, an *o*-methyl substituent may have approximately the same positive effect on potency as does an α-methyl substituent. In some cases, the *o*-methyl substituent may be replaced with other electron-donating groups and antiinflammatory activity will be retained.

(4) For 3-benzoylphenylacetic acid there may be an electronic and a steric requirement about the carboxylic acid portion of the molecule for binding to the prostaglandin synthetase receptor. The data reported herein indicate that the electronic requirement may overshadow any steric requirement.

Experimental Section

Prostaglandin Synthetase Inhibition Determination. Enzyme Preparation. Bovine seminal vesicles stored at −20 °C was used to prepare crude prostaglandin synthetase. This enzyme complex containing cyclooxygenase was prepared according to Saeed et al.[21] Approximately 40 g of BSV was thawed overnight in the refrigerator, and isolation procedures were performed at 4–6 °C. Lean tissue was cut into small pieces, weighed, and homogenized in a Waring blender in 2 volumes of 0.05 M phosphate buffer, pH 7.8. The homogenate was filtered through two layers of gauze, and the filtrate was centrifuged at 600*g* for 15 min at 4 C. The supernatant was refiltered through a double layer of gauze, and 1 mL of the filtrate was transferred to 5-mL vials, lyophilized, and stored at −20 °C. Protein was determined by the method of Lowry et al.[22]

Procedure. Cyclooxygenase activity was assayed according to the procedure of Marnett and Wilcox[23] using a biological oxygen monitor (Yellow Springs Instruments, Model 53) equipped with a circulating water bath and a strip-chart recorder.[24,25] The assay mixture consisted of 0.1 M phosphate buffer, pH 7.8, 2.48 mL; 0.075 M 1-epinephrine, 0.01 mL; 7.5 mg/mL enzyme protein, 0.40 mL; 3×10^{-1} to 3×10^{-6} M test drug, 0.01 mL; and 0.33 Mm arachidonic acid, 0.01 mL for a total volume of 3 mL.[26] Phosphate buffer, epinephrine, enzyme, and test, control, or reference article were sequentially added to the reaction vessel and equilibrated at 30 °C for 3 min. After equilibration, oxygen utilization was determined under basal conditions for 2 min. Arachidonic acid was added, and oxygen consumption under substrate conditions was determined for 3 min. Bias was reduced by randomization[27] of the test, reference, or control article used to determine the inhibition of cyclooxygenase.

Test, reference, and control articles were done in triplicate. Cyclooxygenase activity was determined as the difference between the initial rates of oxygen utilization recorded under basal and substrate conditions. The IC_{50} was calculated by regressing the percent drug inhibition in terms of the control article on the log of the molar drug concentration or by plotting these parameters on graph paper.

Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; ^1H NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard or in D_2O with sodium 3-(trimethylsilyl)-propionate-d_4 as internal standard on a Varian A-60 spectrometer; IR spectra were run as KBr pellets on a Beckman IR8 or on a Perkin-Elmer 297 IR spectrophotometer; analytical results for compounds followed by elemental symbols are within ±0.4% of theory and were determined on a Perkin-Elmer Model 240 CHN analyzer. Spectral data for all reported compounds were consistent with assigned structures. Fenoprofen (**28**) was obtained from Eli Lilly Co., and ketoprofen (**32**) was obtained from Rhone-Poulenc SA.

7-Benzoyl-1,3-dihydro-3-methyl-3-(thiomethyl)-2*H*-indol-2-one (**8**). A solution of 98 g (0.5 mol) of **2** (Eastman) and 74 g (0.5 mol) of **6**[28] in 2 L of CH_2Cl_2 was cooled to −70 °C and treated dropwise with 56 g (0.5 mol) of 95% *tert*-butyl hypochlorite (Frinton Labs) at such a rate that the temperature did not exceed −65 °C. One hour after the addition was complete, 51 g (0.5 mol) of Et_3N was added, and the mixture was allowed to warm to ambient temperature. The solution was diluted with 800 mL of 3 N HCl, and the mixture was stirred for 1 h. The layers were separated, and the organic layer was dried (Na_2SO_4) and evaporated under reduced pressure at 50 °C to give a gummy solid as residue. The residue was triturated with Et_2O, and the powder was collected by filtration. The solid was recrystallized from absolute EtOH to yield 92 g (62%) of **8** as a white powder, mp 135–137 °C. Anal. ($C_{17}H_{15}NO_2S$) C, H, N.

1,3-Dihydro-3-(methylthio)-7-phenoxy-2*H*-indol-2-one (**9**). When the above procedure was used, 21.8 g (0.12 mol) of **3** (Aldrich Chemical Co.), 15.8 g (0.12 mol) of **5** (Fairfield Chemical Co.), 13.4 g (0.12 mol) of *t*-BuOCl and 12.4 g (0.12 mol) of Et_3N in 400 mL of CH_2Cl_2 gave 16.5 g (51%) of **9** as white needles, mp 152–153 °C (2-propanol). Anal. ($C_{15}H_{13}NO_2S$) C, H, N.

1,3-Dihydro-3-(methylthio)-4-phenyl-2*H*-indol-2-one (**10**) **and 1,3-Dihydro-3-(methylthio)-6-phenyl-2*H*-indol-2-one** (**11**). When the above procedure was used, 25.5 g (0.15 mol) of **4** (K & K laboratories), 23.0 g (0.17 mol) of **5**, 18.9 g (0.18 mol) of *t*-BuOCl, and 17.2 g (0.17 mol) of Et_3N in 400 mL of CH_2Cl_2 gave 22.8 g (52%) of yellow solid as a residue. An NMR analysis showed that the residue was a mixture of **10** and **11** in a ratio of 2:1, respectively. Three recrystallizations of the solid from C_6H_6 gave 8.5 g (19%) of **10** as a white solid, mp 182–185 °C. Anal. ($C_{15}H_{13}NOS$) C, H, N.

The mother liquors from the above recrystallization were combined and evaporated under reduced pressure at 50 °C, and the solid residue was recrystallized from acetone. The solid was then recrystallized twice from C_6H_6 to give 3.5 g (8%) of **11** as a tan solid, mp 177–178 °C. Anal. ($C_{15}H_{13}NOS$) C, H, N.

7-Benzoyl-3-methyl-2*H*-indol-2-one (**13**). A stirred solution of 8.0 g (0.03 mol) of **8** in 80 mL of THF was treated with 40 g of a commercial Raney nickel preparation over a 2-h period. The

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mixture was cautiously filtered, and 2 drops of concentrated HCl was added to the filtrate. The filtrate was evaporated under reduced pressure at 50 °C, and the resulting oil crystallized upon standing. The residue was recrystallized twice from 2-propanol to give 6.0 g (89%) of **13** as a white solid, mp 125–127 °C. Anal. ($C_{16}H_{13}NO_2$) C, H, N.

3-Methyl-7-phenoxy-2*H*-indol-2-one (14). When the above procedure was used, 15.0 g (0.06 mol) of **9** and 60 g of Raney nickel in 300 mL of the THF gave 8.2 g (70%) of **14** as tan needles, mp 170–173 °C (2-propanol). Anal. ($C_{14}H_{11}NO_2$) C, H, N.

Sodium 2-Amino-3-benzoyl-α-methylbenzeneacetate Dihydrate (15). A mixture of 4.0 g (0.02 mol) of **13** and 60 mL of 3 N NaOH was heated at reflux under a nitrogen atmosphere for 16 h. The solution was cooled, diluted to 200 mL with H_2O, and titrated to pH 8.0 with concentrated HCl. The mixture was let stand overnight and then filtered through Celite. The filtrate was evaporated under reduced pressure at 70 °C, and the remaining water in the residue was azeotroped twice with absolute EtOH. The residue was recrystallized twice from 2-propanol and then allowed to equilibrate with atmospheric moisture. A 2.2 g (42%) sample of **15** as a yellow powder, mp 95–103 °C, was obtained. Anal. ($C_{16}H_{14}NNaO_3 \cdot 2H_2O$) H, N; C: calcd, 58.71; found, 59.14.

Sodium 2-Amino-3-phenoxybenzeneacetate Hydrate (4:1) (16). When the above procedure was used, 6.0 g (0.03 mol) of **14** and 65 mL of 3 N NaOH gave 7.0 g (100%) of **16** as a white powder, mp 213–216 °C (2-propanol). Anal. ($C_{14}H_{12}NNaO_3 \cdot 0.25H_2O$) C, H, N.

2-Nitro-4-phenylbenzeneacetic Acid (20) To a solution of sodium ethoxide prepared from 3.4 g (0.15 g-atom) of sodium metal in 75 mL of absolute ethanol was added 21.3 g (0.1 mol) of 4-methyl-3-nitrobiphenyl[29] and 21.9 g (0.15 mol) of diethyl oxalate, and the mixture was heated at reflux for 15 min. The dark solution was poured into 1 L of ice–H_2O and extracted with three 300-mL portions of Et_2O. The aqueous layer was made acidic with concentrated HCl, and a solid precipitated. The solid was collected by filtration and dried to give 16.2 g (57%) of crude **19**.

This solid was dissolved in 300 mL of 2% NaOH, and the solution was treated dropwise with 100 mL of 30% H_2O_2 over 1-h period. The solution was filtered, and the filtrate was made acidic with concentrated HCl. The solid that precipitated (foaming occurred) was collected by filtration, washed with H_2O, dried, and recrystallized from 2-propanol to yield 11.5 g (79%) of **20** as a tan solid, mp 186–189 °C dec. Anal. ($C_{14}H_{11}NO_4$) C, H, N.

Sodium 2-Amino-4-phenylbenzeneacetate Hydrate (4:1) (17). A solution of 7.2 g (0.03 mol) of **20** and 1.2 g (0.03 mol) of NaOH in 150 mL of H_2O was hydrogenated at 40 psi over 0.5 g of 10% Pd/C overnight in a Parr hydrogenation apparatus. The mixture was filtered through Celite, and the pH of the filtrate was adjusted to 7 with concentrated HCl. The mixture was filtered, and the filtrate was evaporated under reduced pressure at 70 °C to give a gum as residue. The remaining H_2O in the residue was azeotroped twice with absolute EtOH to give a white powder. The solid was recrystallized from 95% EtOH to yield 5.5 g (79%) of **17** as white plates, mp 271–273 °C. Anal. ($C_{14}H_{12}NNaO_2 \cdot 0.25H_2O$) C, H, N.

(2-Chloro-3-methylphenyl)phenylmethanone (22). A mixture of 6.3 g (0.03 mol) of **21**[30] in 70 mL of concentrated HCl was warmed until all solids dissolved. The solution was cooled to 0–5 °C and treated dropwise with a solution of 2.1 g (0.03 mol) of $NaNO_2$ in 5 mL of H_2O over a 3-h period while maintaining the temperature below 10 °C. This diazonium salt solution was then poured into a stirred solution of 3.5 g (0.04 mol) of CuCl in 17 mL of H_2O and 17 mL of concentrated HCl. The mixture was stirred at ambient temperature for 1 h. The solid that precipitated was collected by filtration, washed with H_2O, and recrystallized from 2-propanol to yield 3.3 g (48%) of **22**, mp 62–63 °C. Anal. ($C_{14}H_{11}ClO$) C, H.

3-Benzoyl-2-chlorobenzeneacetonitrile (23). A mixture of 25 g (0.11 mol) of **22**, 19.6 g (0.11 mol) of *N*-bromosuccinimide, 0.1 g of dibenzoyl peroxide, and 100 mL of CCl_4 was heated at reflux under illumination of a white light for 1.5 h. The mixture was cooled and filtered, and the filtrate was washed with dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the crude bromomethyl derivative.

A mixture of 33 g (0.11 mol) of the above solid, 33 g (0.51 mol) of KCN, 125 mL of dioxane, and 100 mL of H_2O was heated at reflux under a nitrogen atmosphere for 5 h. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was evaporated under reduced pressure at 50 °C to give 30 g of crude product as a syrup. The syrup was purified by chromatography on 600 g of Merck silica gel 60 eluted with 10% acetone in benzene to give 5.8 g (21%) of **23** as white crystals, mp 74–75 °C (2-propanol). Anal. ($C_{15}H_{10}ClNO$) C, H, N.

3-Benzoyl-2-chlorobenzeneacetic Acid (24). A mixture of 4.8 g (0.02 mol) of **23**, 50 mL of dioxane, and 30 mL of concentrated HCl was heated on a steam bath for 20 h. The mixture was evaporated under reduced pressure at 50 °C, and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was evaporated under reduced pressure at 50 °C, and the residue was crystallized from 2:1 benzene/cyclohexane to give 3.1 g (60%) of **24** as a white powder, mp 125–127 °C. Anal. ($C_{15}H_{11}ClO_3$) C, H.

3-Benzoyl-2-(dimethylamino)benzeneacetic Acid (26). A stirred solution of 13.0 g (0.08 mol) of **25**,[1] 100 mL of 37% formaldehyde, and 15 g (0.24 mol) of $NaBH_3CN$ in 400 mL of CH_3CN was treated dropwise with 15 g (0.25 mol) of HOAc. The mixture was treated twice more at 1-h intervals with 20 mL of 37% formaldehyde, 5 g (0.08 mol) of $NaBH_3CN$, and 5 g (0.08 mol) of HOAc. After a total reaction time of 6 h, the solution was made basic with dilute NaOH solution, and the mixture was extracted with Et_2O. The Et_2O extracts were passed through a short silica gel column. The eluant was evaporated under reduced pressure at 50 °C, the residue was dissolved in 95% EtOH, and a few drops of concentrated HCl were added to the solution. The solution was heated on a steam bath for 0.5 h, cooled, and filtered to remove **12**. The filtrate was neutralized with solid Na_2CO_3 and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O, and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure at 50 °C to give 16.5 g (65%) of crude *N,N*-dimethyl ethyl ester.

A mixture of the crude ethyl ester of **26**, 100 mL of dioxane, and 50 mL of 6 N HCl was heated on a steam bath for 2 h. The mixture was concentrated, and the residue was partitioned between dilute NaOH solution and CH_2Cl_2. The aqueous layer was separated and acidified with HOAc. The mixture was extracted with CH_2Cl_2, and the organic extracts were evaporated under reduced pressure at 50 °C. The crystalline residue was recrystallized from isopropyl ether to give 6.3 g (40%) of **26** as white crystals, mp 144–145 °C. Anal. ($C_{17}H_{17}NO_3$) C, H, N.

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