Antiinflammatory Activity of *N*-(2-Benzoylphenyl)alanine Derivatives

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A series of *N*-(2-benzoylphenyl)alanine derivatives were synthesized and tested for antiinflammatory activity in the Evans blue–carrageenan induced pleural effusion assay. The target compounds were envisioned to bind to a receptor site on the cyclooxygenase enzyme by a mechanism first proposed by Appleton and Brown. Of the 21 compounds prepared, two were found to be one-tenth as potent as indomethacin in the pleurisy model and one compound was tested and found to be weakly active in the adjuvant arthritis model.

During the course of the studies of 2-amino-3-benzoylphenylacetic acid (**1**, amfenac), a potent analgesic and antiinflammatory agent,[1] certain topological similarities (Chart I) between **1** and 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone[2] (**2**, proquazone), a potent nonacidic antiinflammatory agent, were noted. Structurally related compounds, 2-(isopropylamino)benzophenone (**3**) and *N*-[3-(4-chlorobenzoyl)-2-methylphenyl]glycine (**6**), were also reported to possess antiinflammatory[3] and analgesic[4] activity, respectively.

Appleton and Brown[5] have recently proposed a model for the binding of nonsteroidal antiinflammatory drugs to the cyclooxygenase enzyme, using the peroxy radical of arachidonic acid (**34**) as a template. This model has been applied to the binding of both the classical arylacetic acids and noncarboxylic acid inhibitors[6,7] and will readily accommodate the binding of **1** as shown in Chart II using a representation suggested by Dewhirst.[7]

The application of Appleton's model to **2** and **3** suggested that no group in **2** or **3** was in position to bind to the enzyme in place of the carboxyl group of **1**.

In an attempt to prepare novel antiinflammatory agents, a carboxyl analogue of **2** (**4**) and a series of derivatives of **3** incorporating a pendant carboxyl group (**5**, **9–14**, **22–31**) were synthesized. These compounds, along with **3** and **6** for comparison, were evaluated in pharmacological models of inflammation.

Chemistry. The acidic derivatives of **3** utilized in this study (Table I and II) were for the most part prepared by a general procedure. Thus, *N*-(2-benzoylphenyl)glycine (**9**) and the substituted *N*-(2-benzoylphenyl)alanines (**5**, **22–31**) were synthesized as illustrated in Scheme I. The 2-aminobenzophenones used as starting materials were prepared by literature procedures.[8] A mixture of sodium carbonate, ethyl bromoacetate (**7**) or ethyl 2-bromopropionate (**8**), and the 2-aminobenzophenone was heated to give the crude ester. The esters were purified by column chromatography on silica gel or by high-pressure liquid chromatography and, without further characterization, were hydrolyzed in aqueous sodium hydroxide to afford the acids. Following the same sequence, compounds **10** and **13** were obtained from the reaction of 2-aminobenzophenone with ethyl 3-bromopropionate and ethyl 3-bromo-2-methylpropionate, respectively. Similarly, the reaction of **8** with 3-aminobenzophenone, 4-aminobenzophenone, 2-benzoylphenol, or 2-phenoxyaniline gave, after hydrolysis, **11**, **12**, **15**, and **16**, respectively.

The preparation of *N*-(2-benzoylphenyl)-*N*-methylglycine (**14**), however, did not follow the standardized procedure. When 2-(methylamino)benzophenone (**17**) was reacted with **7** in the presence of anhydrous sodium carbonate, the N-demethylated ester **18** was obtained (Scheme II). This compound was identical in all respects with the product obtained from the reaction of 2-aminobenzophenone and **7**. Apparently the hydrobromic acid generated in situ was responsible for the N-demethylation[9] since

Chart I

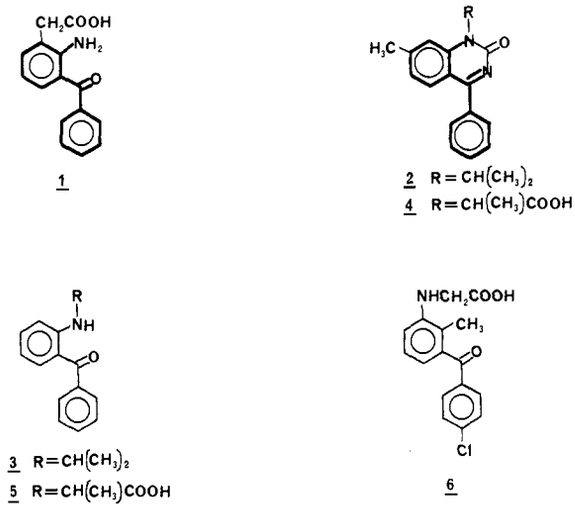
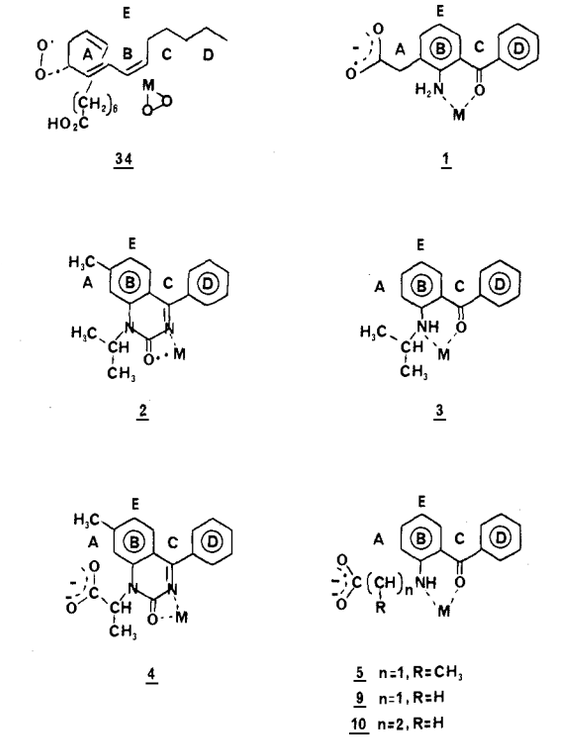


Chart II



†Department of Chemical Research.
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(2) Coombs, R. V.; Danna, R. P.; Denzer, M.; Hardtmann, G. E.; Huegi, B.; Koletar, G.; Koletar, J.; Ott, H.; Jukniewicz, E.; Perrine, J. W.; Takesue, E. I.; Trapold, J. H. *J. Med. Chem.* **1973**, *16*, 1237–45.

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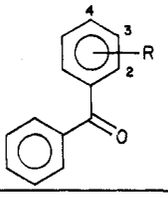
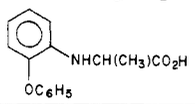
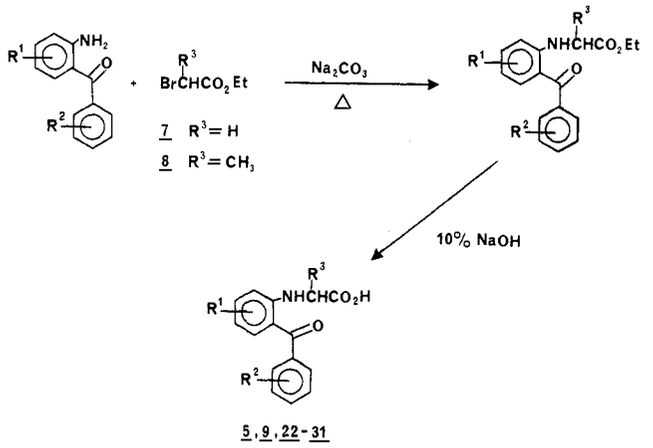
Table I. Oral Antiinflammatory Activity in the 5-h Evans Blue–Carrageenan Pleural Effusion Assay



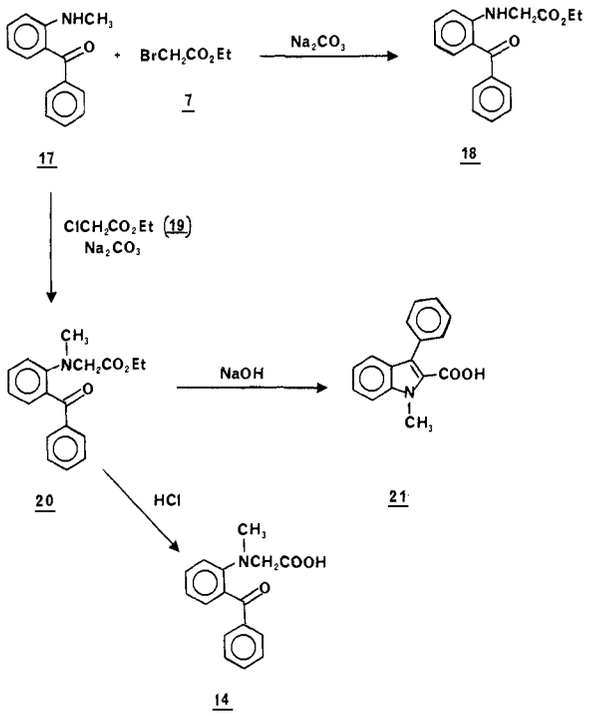
no.	R	mp, °C (solvent[b])	% yield	formula[c]	efficacy ratio[a] at 316 mg/kg compd	efficacy ratio[a] at 316 mg/kg ASA[d]	% change in vol of pleural fluid compd (100 mg/kg)	% change in vol of pleural fluid Indo[e] (4.0 mg/kg)
3	2-NHCH(CH$_3$)$_2$	155–157 dec. (x)	18	$C_{16}H_{18}ClN$[f]	1.13	1.46		
9	2-NHCH$_2$CO$_2$H	197–199 dec (z)	52	$C_{15}H_{13}NO_3$	0.98	1.47		
10	2-NHCH$_2$CH$_2$CO$_2$H	128–130 (pq).	35	$C_{16}H_{15}NO_3$	1.35	1.46	−9	−41[g]
5	2-NHCH(CH$_3$)CO$_2$H	100–102 dec (y)	64	$C_{16}H_{15}NO_3$	1.60[h]	1.66	−28[g]	−20[g]
11	3-NHCH(CH$_3$)CO$_2$H	164–169 dec (wz)	9	$C_{16}H_{16}ClNO_3$[f]	1.38	1.40	−15	−32[g]
12	4-NHCH(CH$_3$)CO$_2$H	163–165 (z)	35	$C_{16}H_{15}NO_3$	1.37	1.91	−4	−31[g]
13	2-NHCH$_2$CH(CH$_3$)CO$_2$H	160–161 dec (wz)	24	$C_{17}H_{18}ClNO_3$[f]	0.97	1.40		
14	2-N(CH$_3$)CH$_2$CO$_2$H	177–178 dec (wz)	8	$C_{16}H_{16}ClNO_3$[f]			−13	−38[g]
15	2-OCH(CH$_3$)CO$_2$H	100–102 (pq)	61	$C_{16}H_{14}O_4$	0.98	1.65		
16		87–89 (wy)	18	$C_{15}H_{15}NO_3$	1.18	1.52		

[a] Efficacy ratio ≤ 1.08, uninteresting; 1.09–1.29, no decision; ≥1.30, study further. [b] p = benzene, q = cyclohexane, w = ethyl ether, x = ethyl acetate, y = hexane, z = 2-propanol. [c] All compounds were analyzed for C, H, and N and results agreed to ±0.4% of theoretical values. [d] Acetylsalicylic acid. [e] Indomethacin. [f] Characterized as the hydrochloride. [g] Significantly different from control group at $p < 0.05$, as determined by the Dunnett's t test. [h] Dose = 100 mg/kg.

Scheme I



Scheme II



the substitution of ethyl chloroacetate (**19**) for **7** and heating the reaction in a steel bomb afforded **20** in good yield. The attempted basic hydrolysis of **20** gave a product that was assigned the structure of an indole derivative (**21**)[10] by NMR and MS. A condensation of the activated amino ester **20** apparently leads to the cyclized **21**. The synthesis of 3-arylindoles from *N*-nitroso-*N*-methyl-2-aminobenzophenones under similar conditions has been reported.[11] The desired acid **14** was obtained from acid hydrolysis of **20**.

Cyclization of *N*-(2-benzoyl-5-methylphenyl)alanine ethyl ester (**32**) with ethyl carbamate following a published general procedure[2] gave, after hydrolysis, quinazolinone **4**.

Results

Table I lists the acute antiinflammatory activity for several aminobenzophenone derivatives and related compounds. Compound **3**, although reported[3] to possess an-

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(5) Appleton, R. A.; Brown, K. *Prostaglandins* **1979**, *18*, 29–33.
(6) Carty, T. J.; Stevens, J. S.; Lombardino, J. G.; Parry, M. J.; Randall, M. J. *Prostaglandins* **1980**, *19*, 671–9.
(7) Dewhirst, F. E. *Prostaglandins* **1980**, *20*, 209–22.
(8) Walsh, D. A. *Synthesis* **1980**, 667–88.
(9) Chambers, R. A.; Pearson, D. E. *J. Org. Chem.* **1963**, *28*, 3144–7.
(10) Borsche, W.; Klein, A. *Justis Liebigs Ann. Chem.* **1941**, *548*, 64–74; *Chem. Abstr.* **1943**, *37*, 2379.
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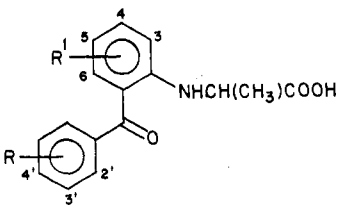
Table II. Oral Antiinflammatory Activity in the 5-h Evans Blue–Carrageenan Pleural Effusion Assay for *N*-(2-Benzoylphenyl)alanine Derivatives



no.	R^1	R^2	mp, °C (solvent[b])	% yield	formula[c]	efficacy ratio[a] at 316 mg/kg: compd	efficacy ratio[a] at 316 mg/kg: ASA[d]	% change in vol of pleural fluid: compd dose, mg/kg	% change in vol of pleural fluid: compd	% change in vol of pleural fluid: Indo[e] (4.0 mg/kg)
5	H	H	100–102 dec (z)	31	$C_{16}H_{15}NO_3$	1.60[f]	1.66	80	−32[g]	−30[g]
								20	+4	
22	4-CH_3	H	143.5–144.5 (qy)	48	$C_{17}H_{17}NO_3$	1.88	1.46	20	−19	−28[g]
23	5-CH_3	H	116–117 (xz)	33	$C_{17}H_{17}NO_3$	1.52	1.52	100	−15	−31[g]
24	5-OCH_3	H	150 (p)	62	$C_{17}H_{18}ClNO_4$[h]	1.06	1.52			
25	5-Cl	H	148–150 (q)	13	$C_{16}H_{14}ClNO_3$	1.96	1.57	100	−28[g]	−18[g]
								4	+6	
26	H	4'-CH_3	144–145 (xz)	52	$C_{17}H_{17}NO_3$	1.39	1.52	100	−21[g]	−35[g]
								4	−8	
27	H	4'-OCH_3	111.5–113 (xz)	40	$C_{17}H_{17}NO_4$	1.80	1.94	100	−22[g]	−35[g]
								4	−9	
28	H	4'-Cl	132–134 (y)	40	$C_{16}H_{14}ClNO_3$	1.62	1.42	80	−33[g]	−30[g]
								20	−5	
29	H	4'-Br	127–129 (w)	22	$C_{16}H_{14}BrNO_3$	1.43	1.46	100	−29[g]	−25[g]
								4	−3	
30	H	2',4'-Cl_2	171–172 (xz)	36	$C_{16}H_{13}Cl_2NO_3$	1.44	1.52	100	−34[g]	−32[g]
								4	−3	
31	5-Cl	4'-Br	162–165 (qy)	19	$C_{16}H_{13}BrClNO_3$	1.10	1.57			

[a] Efficacy ratio ≤ 1.08, uninteresting; 1.09–1.29, no decision; ≥1.30, study further. [b] p = acetone, q = benzene, w = carbon tetrachloride, x = chloroform, y = cyclohexane, z = hexane. [c] All compounds were analyzed for C, H, and N and results agreed to ±0.4% of theoretical values. [d] Acetylsalicylic acid. [e] Indomethacin. [f] Dose = 100 mg/kg. [g] Significantly different from control group at $p < 0.05$, as determined by the Dunnett's t test. [h] Characterized as the hydrochloride.

tiinflammatory activity in the carrageenan-induced edema test in rats, was not active in the pleural effusion assay at 316 mg/kg, a dose at which acetylsalicylic acid (ASA) shows activity. Compounds **5**, **10**, **11**, and **12** showed activity comparable to that of ASA at 316 mg/kg, but only **5** showed significant antiinflammatory activity at 100 mg/kg.

Several derivatives of **5** are listed in Table II. Six of the compounds had activity comparable to the parent **5** at 100 mg/kg, but no derivative showed activity at 4 mg/kg, a dose at which indomethacin is active.

The relative antiinflammatory potency (indomethacin = 1.0) as well as the prostaglandin synthetase inhibition IC_{50} values for several representative compounds are listed in Table III.

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

compd	rel potency	PG synthetase inhib: IC_{50}, μM
indomethacin	1.0	1.1
acetylsalicyclic acid	0.01	1500
1, amfenac	0.7	0.2
2, proquazone	0.4	0.07
4	i[a]	300
6	0.1	>1000
28	0.07	60

[a] Inactive at 316 mg/kg.

Discussion

The current view of the mechanism of action of nonsteroidal antiinflammatory drugs (NSAIDS) is that they may inhibit the conversion of arachidonic acid to the prostaglandins that are mediators in the inflammatory process.[12] Since the introduction of this concept there have been several attempts to describe the binding of arachidonic acid and NSAIDS to the cyclooxygenase enzyme.

1. Gund and Shen[13] have proposed a binding model for NSAIDS using X-ray analysis and computer estimations of the probable conformation of arachidonic acid.

2. Appleton and Brown[5] have based their model on the conformation of the precursor peroxy radical of the cyclic endoperoxide. Using space filling models, they concluded that the carboxyl group of the NSAID competes with the peroxy group of peroxy arachidonic acid for the same site.

3. Peterson et al.[14] have suggested that NSAIDS do not bind to the active site of the cyclooxygenase enzyme but instead chelate with the iron on one side of the heme group of the cyclooxygenase complex. This model may explain why many NSAIDS do not block the lipoxygenase enzyme that does not require the heme complement.

4. Humes et al.[15] presented evidence that NSAIDS react at two sites, a catalytic site and a supplementary site. The degree of interaction with the catalytic site determines the potency of a drug, but interaction with the supplementary site is also obligatory for efficacy as a cyclooxygenase inhibitor.

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(15) Humes, J. L.; Winter, C. A.; Sadowski, S. J.; Kuehl, F. A. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2053–6.

5. Sankawa et al.[16] have recently described a binding model consisting of multiple sites based upon their work with antiinflammatory lichen depsides. This model allows a wide variety of chemical structures to bind to the active site of cyclooxygenase.

Many of the above binding models have been reviewed by Bekemeier et al.[17] The variety of receptor models that have been proposed indicate that a valid general theory of binding to the cyclooxygenase enzyme is not yet at hand. As a working model, these authors have selected the Appleton and Brown[5] approach since it will accommodate diverse chemical structures: the classical arylacetic acids as well as noncarboxylic acid inhibitors.[6,7] The compounds in Table I represent our initial attempt to prepare acidic derivatives of **3** that would better bind to the receptor.

Clearly, the most active compound synthesized in our initial search was **5**, which had antiinflammatory activity at 100 mg/kg in the pleural effusion assay. Eliminating the α-methyl group (**9**), increasing the chain length (**10**, **13**), or shifting the methyl group to the nitrogen (**14**) decreased activity. Derivatives in which the point of attachment of the alanine residue was changed (**11**, **12**) retained some activity at 316 mg/kg but were inactive at 100 mg/kg. Replacing the nitrogen with an oxygen (**15**) or replacing the benzoyl group with a phenoxy group (**16**) eliminated activity.

Several substituted derivatives of **5** were prepared in an attempt to increase potency (Table II). Of these derivatives, **24** and **31** were inactive at 316 mg/kg and the others were equipotent with **5**. Since this chemical series did not exhibit a range of activity as is often observed for this class (aryl acids) of compounds,[18] derivative **30** was chosen as being representative and tested in the adjuvant-induced arthritic rat, a model of chronic inflammation. It was found to be $^1/_{100}$ as potent as indomethacin, a degree of activity that did not warrant further study of this series.

The acidic derivative (**4**) of proquazone (**2**) was then prepared and had an IC_{50} 5 times that of ASA for inhibition of cyclooxygenase, yet it was inactive as an antiinflammatory agent in the in vivo assay (Table III). Compound **6**[4] was $^1/_{10}$ as potent as indomethacin in inhibiting inflammation but was not an inhibitor of cyclooxygenase. These data suggest that **6** inhibits the inflammatory response by a mechanism other than inhibition of cyclooxygenase or that a metabolite of **6** is responsible for the antiinflammatory activity in vivo. Derivative **28** showed moderate activity in both the in vivo and in vitro test systems.

Conclusions

1. Preparing the acidic derivatives of **3** increased antiinflammatory potency of the molecule but did not bring it into the range of that of **1** or **2**.

2. Preparing the acidic derivative of **2** decreased the cyclooxygenase inhibitory activity by 5 orders of magnitude and eliminated the in vivo antiinflammatory activity. In this case, introduction of an acidic function into **2** might well destroy the affinity of **4** for the receptor or **2** may bind in a different manner than that depicted in Chart II.

Experimental Section

Pharmacology. Acute antiinflammatory activity was determined in the Evans blue carrageenan-induced pleural effusion model and evaluated by sequential analysis as described by Sancilio and Fishman.[19] Each compound was administered orally at a dose of 316 mg/kg to two fed 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. An efficacy ratio [average volume of pleural fluid (control)/average volume of pleural fluid (compound)] was determined and compared with that observed for 316 mg/kg of aspirin. If a compound was considered active (efficacy ratio $\geq$ 1.30), it was retested at a dose of 100 mg/kg in six fasted rats and compared with the activity observed for 4.0 mg/kg of indomethacin. The data were reported as a percentage decrease in volume of pleural fluid from that of the control group. Compounds that were still considered active were tested in the adjuvant-induced arthritic rats, a model of chronic inflammation described by Walz et al.[20] using a therapeutic rather than a prophylactic dosing regimen as described by Sancilio et al.[21] Indomethacin at 3.16 mg/kg orally was used as standard. Antiinflammatory potency in acute and chronic models relative to indomethacin was determined by regression analysis. The methodology used for the determination of the inhibition of prostaglandin synthetase obtained from bovine seminal vesicles has been described in detail.[22]

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 on a Varian EM-360L spectrometer; mass spectra were determined on a Varian MAT-44 mass 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 $\pm$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. Proquazone (**2**) was obtained from Sandoz Pharmaceutical Co.; 3- and 4-aminobenzophenone, 2-benzoylphenol, 2-phenoxyaniline, ethyl bromoacetate, ethyl chloroacetate, ethyl 2-bromopropionate, and ethyl-3-bromopropionate were purchased from Aldrich Chemical Co. Ethyl 3-bromo-2-methylpropionate was prepared by literature procedures.[23]

General Procedure for the Preparation of Acid Derivatives of 3. A mixture of 0.04 mol of the appropriate amine or phenol, 0.044 mol of the halo ester, and 4.2 g (0.04 mol) of anhydrous sodium carbonate was heated at 140–170 °C under a nitrogen atmosphere for 5 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude ester, which was purified by column chromatography on silica gel or by high-pressure liquid chromatography with use of a Waters Prep LC-500A apparatus with a Prep PAK-500 silica cartridge. The esters were oils in most cases and were hydrolyzed without further characterization.

A mixture of 0.02 mol of ester and 100 mL of 10% sodium hydroxide solution was heated at reflux under a nitrogen atmosphere for 1 h. The reaction mixture was cooled, diluted with 100 mL of water, and filtered. The filtrate was made acidic with concentrated hydrochloric acid. The solid that precipitated was collected by filtration, dried, and recrystallized to give the acid. In some cases, the acid was dissolved in ethyl ether and the solution was treated with ethereal hydrochloric acid to provide the hydrochloride for characterization. The yields reported in Tables I and II are based on the starting amine or phenol.

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(17) Bekemeier, H.; Böhm, R.; Hagen, V.; Hannig, E.; Henkel, H. J.; Hirschelmann, R.; Wenzel, U. In "Trends in Inflammation Research, 2", Agents and Actions Supplement; Bekemeier, H., Hirschelmann, R., Eds.; Birkhaüser Verlag: Basel, 1982; Vol. 10, pp 17–34.
(18) Shen, T. Y.; Winter, C. A. In "Advances in Drug Research"; Harper, N. J., Simmonds, A. B., Eds.; Academic Press: New York, 1977; Vol. 12, pp 89–245.
(19) Sancilio, L. F.; Fishman, A. *Toxicol. Appl. Pharmacol.* **1973**, *26*, 575–84.
(20) Walz, D. T.; DiMartino, M. J.; Misher, A. *J. Pharmacol. Exp. Ther.* **1971**, *178*, 223–31.
(21) Sancilio, L. F.; Reese, D. L.; Cheung, S; Alphin, R. S. *Agents Actions* **1977**, *7*, 133–44.
(22) Walsh, D. A.; Shamblee, D. A.; Welstead, W. J., Jr.; Sancilio, L. F. *J. Med. Chem.* **1982**, *25*, 446–51.
(23) Pickard, P. L.; Lochte, H. L. *J. Am. Chem. Soc.* **1947**, *69*, 14–6.

N-(2-Benzoylphenyl)-N-methylglycine Hydrochloride (14). A mixture of 10.5 g (0.05 mol) of 2-(methylamino)benzophenone (17), 6.5 g (0.053 mol) of ethyl chloroacetate, and 5.8 g (0.055 mol) of anhydrous sodium carbonate was heated in a steel bomb at 180 °C for 10 h. The reaction mixture was partitioned between methylene chloride and water, and the methylene chloride layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 15.8 g of oil. The oil was purified by chromatography on 300 g of silica gel to yield 7.6 g (51%) of **20** as an oil.

A mixture of 6.5 g (0.022 mol) of **20** and 200 mL of 3 N hydrochloric acid was heated at reflux under a nitrogen atmosphere for 1.5 h. The solution was concentrated under reduced pressure and the residue was partitioned between benzene and 250 mL of a 5% sodium bicarbonate solution. The aqueous layer was made slightly acidic with concentrated hydrochloric acid and was extracted with benzene. The benzene layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 4.3 g of yellow gum. The residue was dissolved in ethyl ether and filtered, and the filtrate was treated with ethereal hydrochloric acid. The solid that crystallized was collected by filtration and recrystallized from 2-propanol–ethyl ether to yield 1.0 g (15%) of 14 as a white solid, mp 177–178 °C, which rapidly loses hydrochloric acid and turns yellow in color when exposed to moisture. Anal. ($C_{15}H_{16}ClNO_3$) C, H, N.

N-(2-Benzoyl-5-methylphenyl)alanine Ethyl Ester (32). By use of the above general procedure, a mixture of 10.5 g (0.05 mol) of 2-amino-4-methylbenzophenone,[5] 9.9 g (0.055 mol) of ethyl 2-bromopropionate, and 5.3 g (0.05 mol) of anhydrous sodium carbonate gave 9.0 g (58%) of **32** as pale yellow needles, mp 76.5–78.5 °C (cyclohexane–benzene). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

α,7-Dimethyl-2-oxo-4-phenyl-1H-quinazoline-1-acetic Acid Ethyl Ester (33). A mixture of 5.0 g (0.016 mol) of **32**, 9.0 g (0.1 mol) of ethyl carbamate, and 0.5 g of zinc chloride was heated under a nitrogen atmosphere at 190 °C for 4 h and then an additional 4.5 g (0.05 mol) of ethyl carbamate and 0.5 g of zinc chloride was added and heating was continued for 3 h. The reaction mixture was cooled, diluted with chloroform (250 mL), and filtered, and the filtrate was washed with water (2 × 500 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was adsorbed onto a silica gel column (40 g). Elution with ethyl ether (500 mL) afforded, after evaporation of the solvent, a light yellow solid, which was recrystallized to yield 1.9 g (35%) of **33** as a white solid, mp 174–175 °C (hexane–tetrahydrofuran). Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

1,2-Dihydro-α,7-dimethyl-2-oxo-4-phenyl-1-quinazolineacetic Acid (4). A suspension of 1.6 g (0.005 mol) of **33** in 50 mL of 6% potassium hydroxide solution was heated at reflux for 45 min. The resulting clear solution was cooled, diluted with water (50 mL), washed with ethyl ether (50 mL), and acidified to pH 5 with dilute hydrochloric acid. The precipitate was collected by filtration and twice recrystallized from ethanol to yield 0.6 g (39%) of 4 as a white solid, mp 249–250 °C dec. Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

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Registry No. 4, 91409-57-3; 5, 76477-50-4; 9, 91409-58-4; 10, 53491-43-3; 11, 72504-22-4; 11·HCl, 91409-59-5; 12, 72504-38-2; 13, 91409-61-9; 13·HCl, 91409-60-8; 14, 91409-63-1; 14·HCl, 91409-62-0; 15, 80099-62-3; 16, 91409-64-2; 17, 1859-76-3; 20, 91409-65-3; 22, 91409-66-4; 23, 91409-67-5; 24, 91409-69-7; 24·HCl, 91409-68-6; 25, 91409-70-0; 26, 91409-71-1; 27, 91409-72-2; 28, 91409-78-8; 29, 91409-73-3; 30, 91423-94-8; 31, 91409-74-4; 32, 91409-75-5; 33, 91409-76-6; ethyl chloroacetate, 105-39-5; 2-amino-4-methylbenzophenone, 4937-62-6; ethyl 2-bromopropionate, 535-11-5; ethyl carbamate, 51-79-6; 2-aminobenzophenone, 2835-77-0; ethyl 3-bromopropionate, 539-74-2; ethyl 3-bromo-2-methylpropionate, 59154-46-0; 3-aminobenzophenone, 2835-78-1; 4-aminobenzophenone, 1137-41-3; 2-benzoylphenol, 117-99-7; 2-phenoxyaniline, 2688-84-8; 2-amino-5-methylbenzophenone, 17852-28-7; 2-amino-5-methoxybenzophenone, 17549-79-0; 2-amino-5-chlorobenzophenone, 719-59-5; 2-amino-4′-methylbenzophenone, 36192-63-9; 2-amino-4′-methoxybenzophenone, 36192-61-7; 2-amino-4′-chlorobenzophenone, 2894-51-1; 2-amino-4′-bromobenzophenone, 1140-17-6; 2-amino-2′,4′-dichlorobenzophenone, 91409-77-7; 2-amino-4′-bromo-5-chlorobenzophenone, 60773-48-0; 2-amino-4′-bromo-5-chlorobenzophenone, 60773-48-0; prostaglandin synthetase, 9055-65-6.

Synthesis and Murine Antineoplastic Activity of Bis[(carbamoyloxy)methyl] Derivatives of Pyrrolo[2,1-*a*]isoquinoline[1]

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The synthesis of 4,5-dihydropyrrolo[2,1-*a*]isoquinolines is reported. A key intermediate in the synthesis of 8-methoxy-4,5-dihydropyrrolo[2,1-*a*]isoquinolines, 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**6**), was prepared by using a regiospecific phenolic cyclization reaction. The P388 lymphocytic activity is reported for 1,2-bis(hydroxymethy)-5,6-dihydro-8-methoxy-3-methylpyrrolo[2,1-*a*]isoquinoline bis(isopropylcarbamate) (**11a**), 1,2-bis(hydroxymethyl)-5,6-dihydro-8-methoxy-3-methylpyrrolo[2,1-*a*]isoquinoline bis(cyclohexylcarbamate) (**11b**), 1,2-bis(hydroxymethyl)-5,6-dihydro-3-methylpyrrolo[2,1-*a*]isoquinoline bis(methylcarbamate) (**13a**), 1,2-bis(hydroxymethyl)-5,6-dihydro-3-methylpyrrolo[2,1-*a*]isoquinoline bis(ethylcarbamate) (**13b**), and 1,2-bis(hydroxymethyl)-5,6-dihydroxy-3-methylpyrrolo[2,1-*a*]isoquinoline bis(cyclohexylcarbamate) (**13c**); all of the compounds were active. Compound **11a** was tested in an expanded tumor panel and was shown to be active against B16 melanocarcinoma, $CD8F_1$ mammary, L1210 lymphoid leukemia, colon 38, and MX-1 human tumor breast xenograft systems.

Recent reports on the significant antitumor activity of bis[(acyloxy)methyl]pyrrolizines and pyrroles have elicited a marked interest in this new class of agents. The rationale employed in the design of these compounds has, in part, been contingent upon the transmission of electronic effects from the phenyl ring to the pyrrole ring in these biaryl systems.[2] Accordingly, the biological activity would be modulated in proportion to the degree of electronic perturbation of the pyrrole.

(1) (a) Vinylogous Carbinolamine Tumor Inhibitors. 12. For part 11 in this series, see: Anderson, W. K.; Chang, C. -P.; McPherson, H. L., Jr. *J. Med. Chem.* **1983**, *26*, 1333. (b) Taken in part from the Ph.D. Dissertation of James S. New.

(2) Anderson, W. K.; Corey, . F. *J. Med. Chem.* **1977**, *20*, 812.

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