(c) Cyclization. The nitrosamino acid (0.075 mol) was dissolved in 300 ml of Ac_2O and allowed to stand at ambient temperature under nitrogen for 4 days. The solution was poured into 600 ml of H_2O and stirred. When hydrolysis was complete, the 2-phase mixture was extracted with CH_2Cl_2. The combined extracts were washed with H_2O, aqueous $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated to dryness. Crystallization from the appropriate solvent gave the pure sydnone.

2-Phenylthioethylaminoacetonitrile Hydrochloride (i). 2-Phenylthioethylamine (37 g, 0.24 mol) was dissolved in 20 ml (0.24 mol) of concentrated HCl and stirred while 11.8 g (0.24 mol) of NaCN and 22 g (0.27 mol) of formalin were added at once. After 3 hr, 100 ml of 1 *N* aqueous HCl was added and the solution washed with benzene, basified with 50% aqueous NaOH to pH 10, and extracted with benzene. The benzene solution was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The residual yellow oil was dissolved in Et_2O and treated with saturated HCl-*i*-PrOH. Filtration and washing with Et_2O gave 16 g (28%) of i as white plates: mp 125–126°. *Anal.* ($C_{10}H_{13}ClN_2S$) C, H, N.

Barium 2-Phenylthioethylaminoacetate (ii). A solution of i (16 g, 0.07 mol) and 43 g (0.14 mol) of $Ba(OH)_2$ in 400 ml of 1:1 MeOH–H_2O was heated at reflux for 5 hr. On cooling and standing, the solution deposited 30 g of white solid which partially melted at 200°. Fractional crystallization from H_2O gave 9.8 g of ii as white rosettes: mp 193–196°. *Anal.* ($C_{10}H_{12}NO_2S \cdot 0.5$ Ba) C, H, N.

3-(2-Phenylthioethyl)-4-bromosydnone (6). A solution of 4 g (0.018 mol) of 5 and 4 g of KOAc in 40 ml of HOAc was stirred while 2.8 g (0.018 mol) of Br_2 in 10 ml of HOAc was added dropwise. Stirring continued for 30 min, then the reaction mixture was poured into H_2O, filtered, and washed with H_2O to give 2.2 g of crude 6. Recrystallization from acetone–Et_2O gave 1.72 g of pure 6.

3-(2-Phenylthioethyl)sydnone-4-carboxylic Acid (7). A solution of 6 g (0.027 mol) of 5 in 100 ml of THF was stirred at 0° under N_2 while 23 ml (0.069 mol) of 3 *M* EtMgBr (Et_2O) was added dropwise. The solution was stirred for 1 hr and poured onto crushed Dry Ice, diluted with H_2O, and extracted with Et_2O. The aqueous layer was acidified to pH 2 and extracted with EtOAc. The extracts were washed with H_2O and then with $NaHCO_3$. The rated to dryness. The tan solid residue was recrystallized from $CHCl_3$–EtOAc to give 3.4 g of 7 as white needles.

3-[2-(*p*-*tert*-Butylphenyl)thioethyl]sydnone-4-acetic Acid (9). A solution of 3 g (0.01 mol) of 8 in 90 ml of THF and 30 ml of 3% aqueous H_2SO_4 was heated at 35–40° under N_2 for 72 hr. The mixture was diluted with H_2O and then extracted with benzene. The extracts were washed with H_2O and then with $NaHCO_3$. The basic washes were acidified to pH 2, extracted into benzene, dried (Na_2SO_4), and evaporated to dryness. Recrystallization of the residue (2.1 g) from i-PrOH–H_2O gave 1.1 g of 9 as a white powder.

Pharmacological Method. A modification of the method of Pearson, *et al.*,[12] was employed to induce an arthritic syndrome in rats which resembles rheumatoid arthritis.

Intact, male Sprague–Dawley rats initially weighing approximately 170 g were divided into groups of 12 each and inoculated intradermally on the base of the tail with a suspension of 0.6 mg of dry, heat-killed *Mycobacterium butyricum* (Difco) in 0.05 ml of paraffin oil to which 2% digitonin had been added.

Test compounds were suspended in saline with 1 drop of Tween 80 added per 20 ml as a suspending agent. Daily, intragastric treatment was initiated on the day of inoculation and continued for 19 days. Inoculated control groups received the saline vehicle only (with Tween 80 added).

After the last injection (24 hr), the rats were sacrificed and weighed; their hind paw volumes were measured by mercury displacement and the per cent inhibition of arthritic swelling was determined for each group. Hydrocortisone-treated groups, run simultaneously, served as a standard. Treated groups were rated active if there was a significant reduction in arthritic swelling from the control group ($p \leq 0.05$, one-tailed, Wilcoxon rank sum method).

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2-Aryl-5-benzoxazolealkanoic Acid Derivatives with Notable Antiinflammatory Activity[1]

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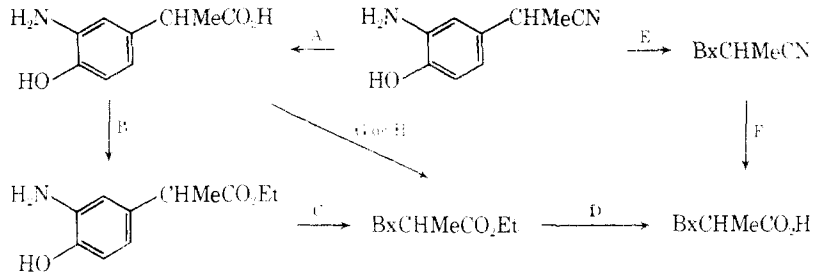
The synthesis and antiinflammatory activity of 5-substituted 2-arylbenzoxazoles are described. Initial screening on carrageenin-induced rat paw edema showed that α-methylacetic substitution in the 5 position was preferable to substitutions with the equivalent esters, amides, alcohols, amines, or tetrazoles. Halogen substitution in the aryl ring led to the most active compounds which were 2-(4-chlorophenyl)-α-methyl-5-benzoxazoleacetic acid (14) and 2-(4-fluorophenyl)-α-methyl-5-benzoxazoleacetic acid (29). These compounds were three to five times more active than phenylbutazone as assessed from ED_{30} values determined on rat paw edema 5 hr after single oral doses.

Aryl and heteroaryl alkanoic acids are well known as nonsteroidal antiinflammatory agents. Most active compounds of this type will fit hypothetical "receptor sites" such as those described by Shen[2] for indomethacin and Scherrer and his coworkers[3] for *N*-arylanthranilic acids. Both these models incorporate a large flat area, a trough to accommodate an out-of-plane group, and a cationic site to accommodate an acid anion. However, there are many

Scheme I. Preparation of 2-Arylbenzoxazole-5-alkanoic Acids[a]



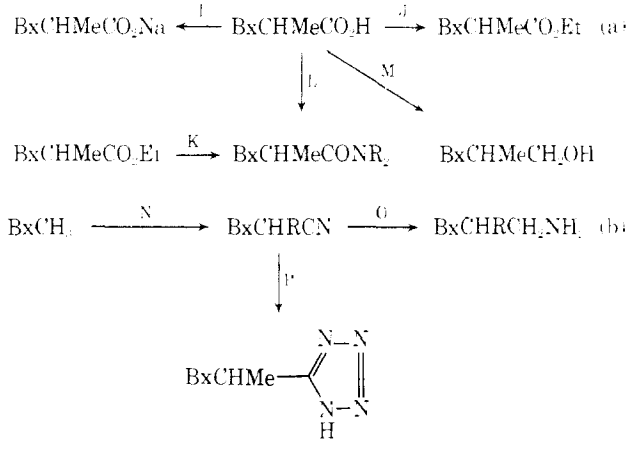
[a]Reagents for method A, concentrated HCl; B, EtOH + HCl; C, ArCOCl, heat; D, NaOH, HCl; E, ArCOCl, heat; F, concentrated HCl, G, ArCHO, $Pb(OAc)_4$; H, ArC(NH)OEt. Bx = 5-substituted 2-arylbenzoxazole

instances[4] in which inactive members of chemical series conform to these structural requirements, indicating that more subtle chemical properties are necessary for useful biological activity. These include the type and position of substituents, which control the physicochemical characteristics of the molecule and influence its duration of action.

It is our experience that chemical changes which confer activity in one series do not necessarily do so in another. In this paper, we define the substituents associated with good antiinflammatory activity in a series of 2-aryl-5-benzoxazolealkanoic acids, some of which proved to be several times more potent than phenylbutazone.

Chemistry. The compounds were prepared by the methods outlined in Schemes I and II. Further details are given in the Experimental Section.

Scheme II. Preparation of Derivatives of 2-Arylbenzoxazole-5-alkanoic Acids[a]



[a]Reagents for method I, $NaHCO_3$; J, EtOH + 4-$MeC_6H_4SO_3H$; K, NH_3; L, $SOCl_2$, Et_2NH; M, B_2H_6; N, NBS, NaCN; O, H_2 + Ni; P, NaN_3. Bx = 5-substituted 2-arylbenzoxazole

Antiinflammatory Activity. The tests for antiinflammatory activity were adapted from the rat paw edema test of Winter, *et al.*[5]

The doses of test compounds used were 2 × 50 mg/kg or 2 × 100 mg/kg. Usually, about one-fourth of the approximate oral LD_{50}, previously determined in groups of two mice given doses of 100–1600 mg/kg, was given. This procedure was adopted to minimize the occurrence of unwanted toxic effects.

Groups of four female Wistar rats, bred in these laboratories and weighing 140–170 g, were dosed orally with the compounds 3 and 0.5 hr prior to the injection of 0.1 ml of a 1% suspension of carrageenin† in 0.9% saline into the plantar surface of the right hind foot of each rat. The injected (right) and noninjected (left) foot volumes were measured with a mercury displacement plethysmograph 2.5 hr after carrageenin injection and the difference was taken to reflect the degree of inflammation produced. The mean increase in volume for each group was calculated and the results were expressed as a per cent inhibition of swelling, compared to a control group of ten rats dosed with saline and tested concurrently. A Student's t test was carried out and acidic compounds showing a significant reduction in swelling ($p < 0.02$) were selected for further testing.

The above test was modified for assessment of the relative potency and duration of action of the compounds. For this test, the compounds were given in increasing single oral doses (usually 10, 33, and 100 mg/kg) to groups of four rats, 1 hr before carrageenin injection, and edema was measured at 2.5 and 5 hr after the injection as described previously. The 5-hr reading distinguishes long-acting compounds which are preferable for the treatment of chronic diseases such as rheumatoid arthritis. From the results ED_{30} values (dose necessary to reduce swelling by 30%) were calculated and used to express relative potency. For comparative purposes, we included phenylbutazone in many of the tests and the mean result with this compound was calculated.

Results and Discussion

The antiinflammatory test results are given in Table I. Compounds 12, 14, and 29 have activity superior to that of phenylbutazone at both 2.5 and 5 hr after a single oral dose while compounds 4, 11, 20, 33, and 40 have activity of the same order. All these compounds are α-methylacetic acid derivatives which we found to be more active than the acetic acid analogs in the two cases where direct comparisons could be made (*cf.* 1 and 4; 3 and 14). The corresponding esters, amides, alcohols, amines, and tetrazoles of the α-methylacetic acids did not show increased potency in terms of activity on the initial screen and they were not examined in detail. For the α-methylacetic acids, substitution of the 2-aryl ring markedly altered activity. Compounds substituted solely in the 3 and/or 5 position possessed low or negligible activity (13, 23, 28, 31, and 34). In the remaining compounds, hydrophilic substituents or ones expected to be readily metabolized, such as hydroxy (25), nitro (26, 44), methyl (34 and 35), methylsulfonyl (38), acetyl (42), and *tert*-butyl (43), also resulted in compounds of low potency. The 2-methyl and 3,4-methylenedioxy substituents appear to be exceptions since compounds 33 and 40 are active. Substitution with halogen in the 2 and/or 4 position produced the most active compounds and the 4-substituted derivatives were more active than the corresponding 2-halogeno derivatives (*cf.* 14 and 12; 29 and 27). This difference may be due to dif-

†Gelozone ST-1, Wiffen and Son Ltd., Loughborough, England.

ferent rates of elimination of unchanged compound since separate experiments in our biochemistry laboratories‡ showed that plasma concentrations of the 4-halogenated compounds were maintained at a relatively high level over 24 hr whereas the 2-halogenated compounds were rapidly eliminated from the blood stream. The 4-fluoro (**29**) and 4-chloro (**14**) derivatives were more active than the 4-bromo (11) and 4-iodo (**30**) analogs and this could be a reflection of changes in physicochemical properties and/or the size of the substituent. The latter possibility may in part explain the low activity of the trifluoromethyl analog (**32**).

These results lead us to conclude that the compounds of choice in this series are the 4-chloro- and 4-fluorophenyl-α-methylacetic acids 14 and **29** and subsequent testing on rat adjuvant arthritis[6] has confirmed this view. Compound 14 gave more reproducible results and is presently undergoing detailed pharmacological and toxicological investigations prior to clinical trial.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak, Eli Lilly & Company, Indianapolis, Ind. Where the analyses are indicated by the symbols of the elements, analytical results were obtained for those elements which were within ±0.4% of the theoretical values. Ir and nmr spectra were obtained for all of the compounds and were consistent with the given structures. The ir spectra were recorded on a Perkin-Elmer 457 spectrophotometer and the nmr spectra on a Varian A-60A spectrometer.

All of the prepared compounds are new.

3-Amino-4-hydroxyphenyl-(α-methylacetonitrile. (a) **4-Hydroxyphenyl-α-methylacetonitrile.** Finely ground 4-aminophenyl-α-methylacetonitrile[7] (73 g, 0.5 mol) was suspended in concentrated HCl (125 ml). The stirred suspension was diazotized at 0–5° by the dropwise addition of a solution of $NaNO_2$ (36.23 g, 0.525 mol) in H_2O (60 ml) during 1–2 hr. The almost clear solution was stirred for a further 20 min at 5–10° and poured into a stirred, boiling solution of concentrated H_2SO_4 (250 ml) in H_2O (2.5 l.). After 6 min it was cooled in an ice bath and extracted with Et_2O (×4). The extracts were extracted with 2 *N* NaOH (×6). The combined alkaline extracts were cooled in an ice bath, acidified with concentrated HCl, and extracted with Et_2O (×3). The extracts were washed with a saturated NaCl solution (×3), dried (Na_2SO_4), and evaporated to leave a dark brown oil (66.7 g) which on distillation gave 4-hydroxyphenyl-α-methylacetonitrile (59.58 g, 81%): bp 118–122° (0.125 mm); mp 42–46°. *Anal.* (C_9H_9NO) C, H, N.

(b) **4-Hydroxy-3-nitrophenyl-α-methylacetonitrile.** A solution of 4-hydroxyphenyl-α-methylacetonitrile (7.79 g, 0.053 mol) in glacial HOAc (10 ml) was added at 7–10°, with stirring, to 12 *N* HNO_3 (8 ml) during 45 min. A further volume (10 ml) of glacial HOAc was added during this period. The resulting yellow suspension was stirred for a further 30 min at 7–10° and then for 30 min at −10 to −15°. The suspension was diluted with H_2O (~90 ml). Filtration yielded 4-hydroxy-3-nitrophenyl-α-methylacetonitrile as a yellow solid (8.43 g, 82%): mp 78–81°. *Anal.* ($C_9H_8N_2O_3$) C, H, N.

(c) **3-Amino-4-hydroxyphenyl-α-methylacetonitrile.** (i) 4-Hydroxy-3-nitrophenyl-α-methylacetonitrile (123.8 g, 0.64 mol) was suspended in absolute EtOH (950 ml) and added during 20 min, with cooling, to a solution of $SnCl_2 \cdot 2H_2O$ (437.8 g, 1.94 mol) in concentrated HCl (591 ml, 7 mol). The addition was made at such a rate that the temperature of the reaction mixture did not exceed 20°. Stirring of the mixture was continued for a further 19 hr at room temperature. The resulting solution, together with ice (1.75 kg), was added during 1 hr to a cooled solution of NaOH (650 g) in H_2O (600 ml). The temperature of the reaction mixture was maintained at 15–20° during the addition. The mixture was stirred for a further 1 hr and the pH then adjusted to 6 by the addition of concentrated HCl. The resulting suspension was filtered and the filtrate was saturated with NaCl and extracted with Et_2O (×6). The extracts were dried (Na_2SO_4) and evaporated to give a solid (69.15 g) which was suspended in $CHCl_3$ and extracted with 2 *N* HCl (×6). The combined acid extracts were neutralized to pH 7–8 by the addition of $NaHCO_3$. The resulting suspension was extracted with Et_2O (×4). The extracts were washed twice with H_2O, dried (Na_2SO_4), and evaporated to yield 3-amino-4-hydroxyphenyl-α-methylacetonitrile as a light brown solid (62.85 g, 66%): mp 110–112°. *Anal.* ($C_9H_{10}N_2O$) C, H, N.

(ii) 3-Amino-4-hydroxyphenyl-α-methylacetonitrile was also prepared as follows. 4-Hydroxy-3-nitrophenyl-α-methylacetonitrile (38.4 g, 0.2 mol) was suspended in absolute EtOH (250 ml) and hydrogenated in a Parr apparatus at 60 psi and room temperature over 10% palladium on charcoal. Hydrogenation was complete in 3.8 hr. The catalyst was removed by filtration. Evaporation of the filtrate yielded 3-amino-4-hydroxyphenyl-α-methylacetonitrile (32.4 g, 100%), mp 110°, undepressed by addition of authentic material.

Methods A–P. Typical examples are given below. Further details of the individual compounds are noted in Table I.

Method A. 3-Amino-4-hydroxyphenyl-α-methylacetic Acid. A suspension of 3-amino-4-hydroxyphenyl-α-methylacetonitrile (10 g, 0.06 mol) in concentrated HCl (100 ml) was refluxed for 2.25 hr. The resulting solution was cooled and the pH adjusted to 5 by the addition of 2 *N* NaOH. The precipitated solid was filtered off. Recrystallization of the solid from MeOH yielded 3-amino-4-hydroxyphenyl-α-methylacetic acid (6.0 g, 54%): mp 167–169°. *Anal.* ($C_9H_{11}NO_3$) C, H, N.

Method B. Ethyl 3-Amino-4-hydroxyphenyl-(α-methylacetate. A solution of 3-amino-4-hydroxyphenyl-α-methylacetic acid (13.82 g, 0.076 mol) in absolute EtOH (50 mol) was saturated with dry hydrogen chloride. The solution was refluxed for 5.5 hr. During the first 1.75 hr of reflux, hydrogen chloride was admitted to the solution. The solution was evaporated under reduced pressure to give an oil. The oil was dissolved in H_2O (50 ml) and the pH of the solution adjusted to 8 by the addition of $NaHCO_3$. The solution was extracted with Et_2O (×3). The extracts were dried (Na_2SO_4) and evaporated to give an oil. Distillation of the oil yielded ethyl 3-amino-4-hydroxyphenyl-α-methylacetate (8.43 g, 53%): bp 154–156° (0.25 mm); mp 79–82°; ν_{CO} (KBr) 1728 cm^{-1}. *Anal.* ($C_{11}H_{15}NO_3$) C, H, N.

Method C. Ethyl 2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetate (16). A solution of ethyl 3-amino-4-hydroxyphenyl-α-methylacetate (4.4 g, 0.021 mol) in dry pyridine (15 ml) was added to cooled *p*-chlorobenzoyl chloride (3.35 g, 0.019 mol) during 5 min. After addition was complete, the mixture was heated at 100° for 1 hr. It was then evaporated under reduced pressure to give an oil (9.85 g) which was heated at 240° for 10 min. Recrystallization of the cooled residue from aqueous EtOH gave **16** as white crystals (7.5 g, 90%): mp 59–61°; ν_{CO} (KBr) 1730 cm^{-1}.

Method D. 2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetic Acid (14). A solution of **16** (7.85 g, 0.024 mol) and NaOH (5 g, 0.125 mol) in 90% aqueous EtOH (955 ml) was stirred at room temperature for 4.5 hr. The solution was evaporated at 55° under reduced pressure to give a viscous oil. The oil was stirred in H_2O (50 ml). The resulting solid was removed by filtration and stirred in concentrated HCl (10 ml). The mixture was filtered and the solid was washed with water until the washings were neutral. This process after recrystallization from EtOH gave 14 as a cream solid (3.15 g, 44%): mp 189–190°; ν_{CO} (KBr) 1701 cm^{-1}.

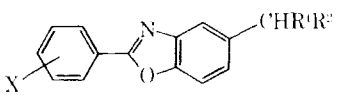
Method E. 2-Phenyl-α-methyl-5-benzoxazoleacetonitrile (9). Benzoyl chloride (27.09 g, 0.19 mol) was added, with cooling, during 20 min to a stirred solution of 3-amino-4-hydroxyphenyl-α-methylacetonitrile (28.35 g, 0.175 mol) in dry pyridine (200 ml) at 0–3°. After addition was complete, the mixture was heated at 100° for 1 hr. It was then evaporated under reduced pressure to yield crude 3-benzamido-4-hydroxyphenyl-α-methylacetonitrile [ν_{CO} (KBr) 1640 cm^{-1}] as an oil. The oil was boiled for 30 min during which time the temperature of the vapor above the oil rose to 200°. On cooling, the residue solidified. Recrystallization of the solid from MeOH yielded **9** (27.65 g, 63.6%): mp 118–120°.

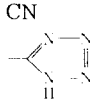
Method F. 2-Phenyl-α-methyl-5-benzoxazoleacetic Acid (4). A solution of **9** (24 g, 0.096 mol) in concentrated HCl (220 ml) was refluxed for 2.5 hr. The mixture was poured into ice-H_2O (1 l.). The precipitated 4 was removed by filtration, washed with water, and recrystallized from aqueous Me_2CO. The dry acid (23 g, 89%) had mp 177–179°; ν_{CO} (KBr) 1720 cm^{-1}.

Method G. 2-(4-Chloro-3-nitrophenyl)-α-methyl-5-benzoxazoleacetic Acid (26). A solution of 4-chloro-3-nitrobenzaldehyde (0.925 g, 0.005 mol) and 3-amino-4-hydroxyphenyl-α-methylacetic acid (0.9 g, 0.005 mol) in EtOH (25 ml) was heated under reflux for 3.5 hr. The solution was evaporated to give a solid which was dissolved in hot HOAc (50 ml). Lead tetraacetate (2.8 g, 0.0063

‡Plasma concentrations of 2-arylbenzoxazoles were determined by Dr. D. H. Chatfield using uv spectrophotometry.

Table I. 5-Substituted 2-Arylbenzoxazoles



No.	X	R^1	R^2	Mp, °C	Method	Recrystn solvent[a]	Formula	Analyses	Approx LD_{50}, mg/kg	Antiinflammatory act. vs. carrageenin: Initial screen[b] Dose, mg/kg × 2	% redn[f]	Dose response,[c] ED_{36}, mg/kg: 2.5 hr	5 hr
1	H	H	CO_2H	175–176	N, F	I	$C_{15}H_{11}NO_3$	C, H, N	1200	100	68**	52.5 ± 8.1	61.1 ± 10.2
2	H	H	$CH_2NH_2 \cdot HCl$	277–278	O	II	$C_{15}H_{15}ClN_2O$	C, H, N	800	100	64**	NT	
3	4-Cl	H	CO_2H	241–242	H	III	$C_{15}H_{10}ClNO_3$	C, H, N	>1600	NT		>200	>200
4	H	Me	CO_2H	177–179	E, F	V–IV	$C_{16}H_{13}NO_3$	C, H, N	800	50	55**	20.0 ± 5.6	48.0 ± 5.7
5	H	Me	CO_2Et	44–45	J		$C_{18}H_{17}NO_3$	C, H, N	>1600	100	29	NT	
6	H	Me	$CONH_2$	202–204	K	II	$C_{16}H_{14}N_2O_2$	C, H, N	>1600	100	50**	NT	
7	H	Me	$CONEt_2$	108–110	L	II	$C_{20}H_{22}N_2O_2$	C, H, N	>1600	100	0	NT	
8	H	Me	CH_2OH	100–103	M		$C_{16}H_{15}NO_2 \cdot 0.25 H_2O$	C, H, N	800	100	44**	NT	
9	H	Me	CN	118–120	E	VI	$C_{16}H_{12}N_2O$	C, H, N	>1600	100	12	NT	
10	H	Me	$CH_2NH_2 \cdot C_4H_6O_4$[d]	158–159	O		$C_{16}H_{16}N_2O \cdot C_4H_6O_4$	C, H, N	1200	100	28	NT	
11	4-Br	Me	CO_2Na	>300	E, F, I	II–IV	$C_{16}H_{11}BrNO_3Na$	C, H, N	1200	100	58**	19.3 ± 11.5	54.7 ± 23.0
12	2-Cl	Me	CO_2H	100–103	C, D		$C_{16}H_{12}ClNO_3$	C, H, N	1200	100	53**	13.6 ± 6.4	24.9 ± 2.8
13	3-Cl	Me	CO_2H	173–175	E, F	V–IV	$C_{15}H_{12}ClNO_2$	C, H, N	1200	100	40**	89.1 ± 50.2	>200
14	4-Cl	Me	CO_2H	189–190	C, D; also E, F	II	$C_{16}H_{12}ClNO_3$	C, H, N	800	50	78**	13.4 ± 2.9	10.6 ± 7.0
15	4-Cl	Me	CO_2Na	312–314	I		$C_{16}H_{11}ClNO_3Na \cdot H_2O$	C, H, N	1200	50	52**	NT	
16	4-Cl	Me	CO_2Et	59–61	C, also J	II–IV	$C_{18}H_{16}ClNO_3$	C, H, N	1600	100	51**	NT	
17	4-Cl	Me	$CONH_2$	245–246	K		$C_{16}H_{13}ClN_2O_2$	C, H, N	>1600	50	46**	NT	
18	4-Cl	Me	CN	150–153	E	II	$C_{16}H_{11}ClN_2O$	C, H, N	>1600	100	12	NT	
19	4-Cl	Me		232–234	P	II	$C_{12}H_{12}ClN_5O$	C, H, Cl, N	1200	100	0	NT	
20	2,4-Cl_2	Me	CO_2H	153–154	C, D	V	$C_{16}H_{11}Cl_2NO_3$	C, H, N	800	100	74**	15.3 ± 9.6	126.9 ± 29.4

21	2,5-Cl	Me	CO_2H	144–146	C, D	V	$C_{16}H_{11}Cl_2NO_3$	C, H, N	>1600	50	0	NT	
22	3,4-Cl_2	Me	CO_2H	170–173	C, D	V	$C_{16}H_{11}Cl_2NO_3$	C, H, N	600	50	37**	37.8 ± 32.9	58.7 ± 10.8
23	3,5-Cl_2	Me	CO_2H	161–165	C, D	II	$C_{16}H_{11}Cl_2NO_3$	C, H, N	600	50	56**	82.7 ± 26.6	156 ± 90.4
24	4-Cl, 2-OH	Me	CN	143–145	E	VII–II[e]	$C_{16}H_{11}ClN_2O_2$	C, H, N	NT	NT		NT	
25	4-Cl, 2-OH	Me	CO_2H	197–200	F	V	$C_{16}H_{12}ClNO_4$	C, H, N	>1600	50	9	NT	
26	4-Cl, 3-NO_2	Me	CO_2H	210–213	G		$C_{16}H_{11}ClN_2O_5$	C, H, N	NT	NT		>200	>200
27	2-F	Me	CO_2H	180–183	C, D	V	$C_{16}H_{12}FNO_3$	C, H, N	1600	100	50**	15.1 ± 3.3	31.5 ± 13.7
28	3-F	Me	CO_2H	137–141	C, D	V	$C_{16}H_{12}FNO_3$	C, H, N	800	100	41**	53.1 ± 7.3	69.0 ± 22.2
29	4-F	Me	CO_2H	162–164	E, F	V–IV	$C_{16}H_{12}FNO_3$	C, H, N	1200	100	41**	17.7 ± 6.5	18.7 ± 6.6
30	4-I	Me	CO_2H	205–208	C, D		$C_{16}H_{12}INO_3$	C, H, I, N	1200	100	40**	32.7 ± 9.0	37.0 ± 16.7
31	3-CF_3	Me	CO_2H	144–147	C, D	II–IV	$C_{17}H_{12}F_3NO_3$	C, H, N	1200	100	0	>200	>200
32	4-CF_3	Me	CO_2H	165–168	C, D	II–IV	$C_{17}H_{12}F_3NO_3$	C, H, N	300	100	27	106 ± 66.1	55.3 ± 53.8
33	2-Me	Me	CO_2H	107–110	E, F	V–IV	$C_{17}H_{15}NO_3$	C, H, N	600	100	70**	26.2 ± 7.9	60.8 ± 11.4
34	3-Me	Me	CO_2H	155–157	E, F	V–IV	$C_{17}H_{15}NO_3$	C, H, N	1200	100	40**	>200	178 ± 39
35	4-Me	Me	CO_2H	166–168	F	V–IV	$C_{17}H_{15}NO_3$	C, H, N	1600	100	69**	77.5 ± 17.5	>200
36	4-Me	Me	CN	129–130	E		$C_{17}H_{14}N_2O$	C, H, N	NT	NT		NT	
37	4-MeO	Me	CO_2H	189–191	E, F	V–II	$C_{17}H_{15}NO_4$	C, H, N	>1600	100	40**	NT	
38	4-$MeSO_2$	Me	CO_2H	236–237	C, D		$C_{17}H_{15}NO_5S$	C, H, N	>1600	NT		176.9 ± 52.5	>200
39	4-$MeSO_2$	Me	CO_2Et	141–142	C		$C_{19}H_{19}NO_5S$	C, H, N	NT	NT		NT	
40	3,4-OCH_2O	Me	CO_2H	185–188	C, D	V	$C_{17}H_{13}NO_5$	C, H, N	800	100	48**	23.3 ± 9.4	44.7 ± 11.6
41	3,4-OCH_2O	Me	CO_2Et	76–79	C, D		$C_{19}H_{17}NO_5$	C, H, N	NT	NT		NT	
42	4-MeCO	Me	CO_2H	208–209	E, F	V	$C_{18}H_{15}NO_4$	C, H, N	1600	NT		>200	>200
43	4-Me_3C	Me	CO_2H	150–152	C, D	II–IV	$C_{20}H_{21}NO_3$	C, H, N	1200	50	0	NT	
44	4-NO_2	Me	CO_2H	211–217	G		$C_{16}H_{12}N_2O_5$	C, H, N	1600	NT		>200	>200
45	Phenylbutazone											23.8 ± 12.1	52.6 ± 7.6

[a]I, toluene; II, EtOH; III, industrial methylated spirit; IV, H_2O; V, Me_2CO; VI, MeOH; VII, DMF. [b]Doses were given orally at 3 and 0.5 hr prior to carrageenin. [c]Doses were given orally at 1 hr prior to carrageenin. ED_{30} = dose ± standard error calculated to give 30% reduction of foot swelling. The highest dose used in the determination of ED_{30} values was 100 mg/kg. ED_{30} values much greater than this dose, requiring extensive extrapolation of the dose-response curve, are quoted as >200 mg/kg. NT = not tested. [d]Succinate. [e]4-Chloro-2-methoxybenzoyl chloride was used as the starting material. Demethylation occurred during the reaction. [f]** = result significant on Student's t test at $p > 0.02$.

mol) was added and the reaction was allowed to cool to room temperature. Next morning, water (200 ml) was added which resulted in the deposition of a sticky solid. The latter was dried (40°) and triturated with a small amount of $CHCl_3$ to yield pure **26** (0.5 g, 29%): mp 210–213°; ν_{CO} (KBr) 1720 cm^{-1}.

Method H. 2-(4-Chlorophenyl)-5-benzoxazoleacetic Acid (3). A suspension of ethyl 4-chlorobenzimidate hydrochloride[8] (16.5 g, 0.08 mol) and 3-amino-4-hydroxyphenylacetic acid[9] (12.53 g, 0.075 mol) in MeOH (75 ml) was refluxed for 2 hr. After standing overnight at room temperature, the white solid was removed by filtration. Recrystallization from industrial methylated spirit gave the required acid (17.5 g, 80%): mp 241–242°; ν_{CO} (KBr) 1695 cm^{-1}.

Method I. Sodium 2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetate (15). Sodium bicarbonate (1.95 g, 0.023 mol) was added to a solution of 14 (7 g, 0.023 mol) in a mixture of MeOH (100 ml), $CHCl_3$ (50 ml), and H_2O (60 ml). The resulting solution was evaporated to give a white solid. The solid was washed with $CHCl_3$ (100 ml), filtered, and dried to yield the desired sodium salt as a monohydrate: mp 312–314°; $\nu(CO_2^-)$ (KBr) 1570, 1405 cm^{-1}.

Method J. Ethyl 2-Phenyl-α-methyl-5-benzoxazoleacetate (5). The acid 4 (10 g, 0.037 mol) and toluene-*p*-sulfonic acid (0.5 g) were dissolved in a mixture of C_6H_6 (60 ml) and absolute EtOH (25 ml). The solution was refluxed for 12 hr and cooled. The solution was washed twice with 2 *N* NaOH and several times with water. After being dried (Na_2SO_4), the organic solution was evaporated under reduced pressure to yield 5 (8 g, 72.5%) as an oil which solidified on cooling: mp 44–45°; ν_{CO} (KBr) 1730 cm^{-1}.

Method K. 2-Phenyl-α-methyl-5-benzoxazoleacetamide (6). The ester 5 (8.6 g, 0.026 mol) and a saturated solution of NH_3 in glycerol (100 ml) were heated at 150° for 17 hr in a bomb. The cooled reaction mixture was poured into H_2O (200 ml). The resulting precipitate was removed by filtration, dried, and recrystallized from EtOH. The amide (6.3 g, 82%) had mp 202–204°; ν_{CO} (KBr) 1650 cm^{-1}.

Method L. *N,N*-Diethyl-2-phenyl-α-methyl-5-benzoxazoleacetamide (7). The acid 4 (50 g, 0.188 mol) and $SOCl_2$ (50 ml) were heated together on a steam bath for 20 min. The excess of $SOCl_2$ was removed by evaporation under reduced pressure. The residue was cooled to 0° and an excess of Et_2NH was added cautiously. After 1 hr the reaction mixture was equilibrated between water (100 ml) and Et_2O (100 ml). The Et_2O layer was washed three times with water (50 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel and recrystallized from a small volume of EtOH to yield the required diethylamide (5.5 g, 92%): mp 108–110°.

Method M. 2-Phenyl-β-methyl-5-benzoxazoleethanol (8). An approximately 1 *M* solution (15 ml) of diborane in dry THF was added during 5 min to a stirred suspension of 4 (3 g, 0.011 mol) in dry THF (10 ml) at room temperature. The resulting solution was stirred for 3.75 hr at room temperature and then poured into concentrated HCl (75 ml) containing crushed ice (35 g). The mixture was extracted with $CHCl_3$ (×2). The combined extracts were washed twice with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated under reduced pressure to give 8 containing 0.25 mol of H_2O which could not be removed by drying *in vacuo*. The solid (2.56 g, 88%) had mp 100–103°.

Method N. 2-Phenyl-5-benzoxazoleacetonitrile. A mixture of *N*-bromosuccinimide (45 g, 0.253 mol), 5-methyl-2-phenylbenzoxazole[10] (47 g, 0.0225 mol), and CCl_4 (400 ml) was heated under reflux for 4 hr in the presence of uv radiation (366 mμ). Azobis(isobutyronitrile) (300 mg) was added in three portions after 0.5, 1, and 1.5 hr. More hot CCl_4 (200 ml) was added and the solution was filtered. The crystals which formed on cooling were removed by filtration yielding 5-bromomethyl-2-phenylbenzoxazole (40 g) of 90% purity by nmr analysis.

A stirred suspension of the above product and NaCN (60 g, 1.22 mol) in dimethylacetonitrile (700 ml) was stirred for 6 hr at room temperature. The solution was filtered and diluted with water (2 l.). The resulting solid was removed by filtration and dissolved in $CHCl_3$. This solution was dried (Na_2CO_3), treated with charcoal, and evaporated. Crystallization of the residue from EtOAc yielded crystals (18.9 g), mp 154–156°, which were 95% pure by nmr spectroscopy; ν_{CO} (KBr) 2241 cm^{-1}.

Method O. 2-Phenyl-β-methyl-5-benzoxazoleethylamine Hydrogen Succinate (10). A solution of 9 (10 g, 0.04 mol) in a 12% solution of NH_3 in EtOH (100 ml) was hydrogenated at 60 psi at room temperature in a Parr apparatus for 65 hr over Raney nickel W-5 (~2 g). After removal of the catalyst by filtration, the solution was evaporated to give an oil (9.7 g). The oil was dissolved in EtOH (15 ml) and added to a warm solution of succinic acid (4.54 g, 0.038 mol) in EtOH (35 ml). On standing overnight at 4°, a solid separated. The latter was removed by filtration and washed with ether to give 10 (11.9 g, 80%): mp 158–159°.

Method P. 2-(4-Chlorophenyl)-5-[1-(5-tetrazolyl)ethyl]benzoxazole (19). A mixture of 18 (5.1 g, 0.018 mol), NaN_3 (1.31 g, 0.02 mol), NH_4Cl (1.08 g, 0.02 mol), and DMF (20 ml) was heated at 125° for 24 hr. The mixture was evaporated to dryness and the residue stirred with water. The solid was removed by filtration and recrystallized twice from EtOH yielding the white crystalline tetrazole derivative (2.4 g, 41%): mp 232–234°.

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