tions during 45 min. Additional stirring for 15 min and cooling precipitated crude **102**. Redissolving in hot saturated $NaHCO_3$, charcoaling, and acidification with AcOH precipitated **102**.

4-R_3-3-R_4-5-Sulfamoylbenzoic Acids 6-11, 103-150, and 168-183 (Table I). Method S. **5** was in AcOH solution hydrogenated using PtO_2 as catalyst.

Method T. **6** was alkylated adapting a described procedure (see ref 3, method 3A), in the case of **7** using $CH_3CH{=}CHCH_2Br$ instead of $C_6H_5CH_2Br$. The intermediate Et esters were saponified (2 *N* NaOH) without purification.

Method U. **7** was in EtOH solution hydrogenated using PtO_2 as catalyst.

Method V. **6** was reductively alkylated adapting a method described in ref 3, method 4K.

Method W. 4-Vinylpyridine was in MeOH solution allowed to react with **6**, using AcOH as catalyst.

Method X. A solution of the appropriate amino derivative (3 mmol) and KNO_2 or $LiNO_2{\cdot}H_2O$ (3.3-3.5 mmol) in 1 *N* KOH or LiOH (6.5-7.5 ml) was added at −2-2° dropwise to a stirred mixture of concentrated HCl (7-10 ml) and AcOH (7-10 ml). To the diazonium mixture was added AcOH saturated with SO_2 (10 ml) and containing $CuCl_2{\cdot}2H_2O$ (0.3-0.4 g) in H_2O (1-1.5 ml). The stirring was continued for a further 2-4 hr at room temperature to precipitate the sulfochloride, if necessary after cooling and/or dilution with H_2O. It was added at 10-15° in portions to stirred concentrated aqueous NH_3 (about 10 ml/g of sulfochloride). Additional stirring at room temperature for 16-20 hr followed by cooling precipitated the NH_4 salt. Redissolving in 1 *N* NaOH (about 10 ml/g of salt) and acidification with a slight excess of ice-cold 1 *N* AcOH or HCl gave the crude reaction product. For **106**, 120-121, 130-133, and 135-138 the reaction mixture after the amidation process was acidified without isolation of an NH_4 salt.

Method Y. A described process given under method D was adapted except that the solvent was a mixture of concentrated HCl and AcOH. The crude reaction product was (except in the case of **110**, **112**, and **139**) dissolved in hot saturated $NaHCO_3$ (about 10 ml/g of sulfamoyl derivative) and, after cooling, the Na salt thus obtained was worked up as described under method X for similar NH_4 salts.

Method Z. The Wolff-Kishner reduction described in ref 5, method G, was adapted.

Method ZA. **164**[2] or **165**[2] (0.1 mol) was diazotized according to method X using $NaNO_2$ (7.0 g, 0.1 mol) and 1 *N* NaOH (150 ml). The filtered diazonium solution at 60-70° was carefully added to a vigorously stirred solution of $KSCSOC_2H_5$ (24 g, 0.15 mol) and $NaHCO_3$ (250 g) in H_2O (900-1100 ml). Stirring at 60-70° for a further 1-1.5 hr, cooling, and cautious acidification with concentrated HCl precipitated the crude xanthate, which was dissolved in 2 *N* NaOH (about 10 ml/g of xanthate) and in a N_2 atmosphere heated on a steam bath for 1-1.5 hr. Cooling and acidification with a slight excess of 4 *N* HCl (in a N_2 atmosphere) precipitated crude **166** (80-85% based on **164**) or crude **167** (30-35% based on **165**) contaminated with various amounts of the corresponding disulfides. The crude thiol (**166** or **167**, 5 mmol) was dissolved in stirred saturated $NaHCO_3$ (12-15 ml) followed by addition of $NaHCO_3$ (1.0 g, 12 mmol) and, in small portions, $Na_2S_2O_4$ (1.0 g, 6 mmol). The appropriate alkyl iodide or alkyl bromide, for **178** 4-chloromethylpyridine and for **179** 4-vinylpyridine (6-10 mmol), was added, and the mixture was stirred at room temperature for 2-4 hr. In the case of **178**, **180**, and **181** the reaction time was extended to 18-20 hr and in the case of **169**, **170**, **172**, **173**, and **179** the reaction was performed at 65-70° for 3-4 hr. After cooling, the separated Na salt was worked up as described under method X for similar NH_4 salts. For **179** the reaction mixture was acidified (4 *N* AcOH) without isolation of a salt.

Method ZB. **164**[2] (6.12 g, 20 mmol) was diazotized as given in method ZA. The filtered diazonium solution was added to a stirred mixture of furfurylmercaptan (3.8 g, 33 mmol), Cu powder (2.0 g), and 2 *N* NaOH (125 ml). After additional stirring at room temperature for 1 hr, the mixture was heated on a steam bath for 1.5 hr, charcoaled, and, after cooling, acidified with AcOH (12 ml) to precipitate an oil. Redissolving in hot saturated $NaHCO_3$ (35 ml) and cooling yielded the Na salt of **176**, which was worked up as described under method X for similar NH_4 salts.

3-Aryl-4-R_4-6-carboxy-1,2-benzisothiazole 1,1-Dioxides 151-158 and 160-163 (Table II). Method ZC. A pure sample (25-100 mg) of the appropriate 4-aroyl-5-sulfamoyl derivative was heated for 5-10 min in an oil bath kept at the temperature defined in Table II. On cooling, the pure anhydro compound usually crystallized in quantitative yield. In a few cases (see Table II) where an amorphous material resulted, crystallization from C_6H_6 was performed.

Hydrolytic Ring Cleavage of 153. To **153** (10 mg) was added phosphate buffer of pH 7.4 (10 ml) preheated to 37°, and the mixture was stirred at 37 ± 0.5°; **153** dissolved within 1-2 min. After 1.5, 5, 15, 30, and 60 min samples (2.0 ml) were rapidly cooled in ice, acidified with 4 *N* AcOH (0.3 ml), and extracted with EtOAc (0.5 ml). The extracts were analyzed by tlc [silica gel (HF 254, Merck), $CHCl_3$ (80), AcOH (10), C_6H_{12} (10), MeOH (2.5)]. As reference compounds were used **107** and **153** both proved to be stable under the chromatographical conditions. Examination of the plates in uv (254 and 366 nm) revealed that all time samples had the same composition in showing only **107** besides traces of **153**.

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Antiinflammatory Sydnones. 2

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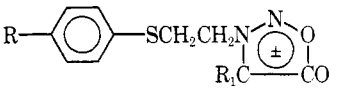
A series of derivatives of 3-(2-phenylthio)ethylsydnone has been synthesized. Several of these compounds are more potent than hydrocortisone and phenylbutazone *vs.* adjuvant arthritis.

We have recently reported that sydnone **1** and several closely related analogs possess potent antiarthritic activity as measured in the adjuvant arthritis assay. It was shown that the structural features consistent with maximum activity included an aromatic ring at R_2, X = S or SO, and a two-carbon link between sulfur and the sydnone ring. Where X = SO_2 or O, activity was maintained but at diminished levels. The study described here was designed to determine the structural limits on R_1 and R_2 consistent with biological activity and to determine which of these impart maximum potency.

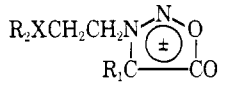
The sydnones were synthesized according to the general

Table I



Compd	R_1	R	Mp, °C	Crystn solvent	Formula	Analyses	Activity[a]	ED_{50}[b]
1[c]	CH_3	H					2.5 (++)	5
2	Ph	H	81–82	Et_2O–Me_2CO	$C_{16}H_{14}N_2O_2S$	C, H, N, S	25 (0)	
3	Pr	H	50–52	Et_2O	$C_{13}H_{16}N_2O_2S$	C, H, N	10 (++)	10
4	*t*-Bu	*t*-Bu	86–87	Et_2O–EtOH	$C_{18}H_{26}N_2O_2S$	C, H, N, S	7.5 (++)	
5[c]	H	H					2.5 (++)	2
6	Br	H	86–88	Et_2O–Me_2CO	$C_{10}H_9BrN_2O_2S$	C, H, N, S, Br	25 (+)	
7	CO_2H	H	132–133	$CHCl_3$–EtOAc	$C_{11}H_{10}N_2O_4S$	C, H, N, S	16 (0)	
8	CH_2CO_2Et	*t*-Bu	80–81	Et_2O	$C_{17}H_{22}N_2O_4S$	C, H, N, S	30 (+)	
9	CH_2CO_2H	*t*-Bu	136–137	*i*-PrOH–H_2O	$C_{16}H_{20}N_2O_4S$	C, H, N, S	30 (+)	
10	H	Cl	66–68	Et_2O–Me_2CO	$C_{10}H_9ClN_2O_2S$	C, H, N, S	5 (++)	2.5
11	H	2,4,6-CH_3	136–137	EtOH	$C_{13}H_{16}N_2O_2S$	C, H, N	4 (++)	5
12	CH_3	2,4,6-CH_3	93–94	EtOH–Et_2O	$C_{14}H_{18}N_2O_2S$	C, H, N, S	7.5 (+++)	2.1
Hydrocortisone								6.5
Phenylbutazone								5

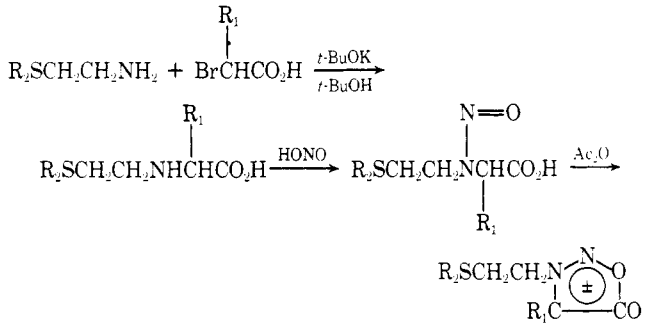
[a]Lowest dosage (mg/kg) at which the compound was tested in the adjuvant arthritis assay and the degree of activity at that dose level. Inhibition of arthritic swelling: 70–100% (+++), 40–69% (++), 25–39% (+). [b]mg/kg. [c]Described in ref 2.



1, $R_1 = CH_3$; $R_2 = Ph$; X = S

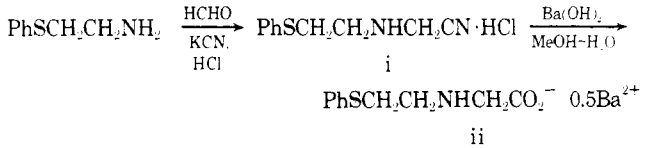
sequence[1-3] outlined in Scheme I. Compounds 2–4 (Table I) were obtained simply by varying the α-halo acid.

Scheme I

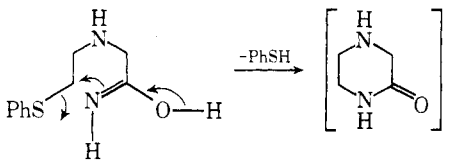


The 4-H sydnone 5 was best prepared *via* the aminonitrile (Scheme II).

Scheme II



Basic hydrolysis is required because thiophenol is eliminated under acidic conditions, presumably *via* attack of the partially hydrolyzed nitrile to form a cyclic intermediate (eq 1).



(1)

Bromination[4] of 5 afforded 6 and carbonation of the Grignard[5] furnished 7. The 4-acetic acid derivative 9 was synthesized *via* the ester 8 because the corresponding diacid would be expected to cyclize to the anhydride rather than to the sydnone.[6] Attempts to hydrolyze 8 with an acidic resin in boiling water[6] were unsuccessful. A mixture of dilute sulfuric acid–THF gave good yields with no evidence of attack on the sydnone ring.

Variation of R_2 in 13–33 (Tables II and III) was achieved by treating the appropriate thiol with ethylenimine,[7] bromoethylamine hydrobromide,[8] or ethanolamine–propionic acid[9] and submitting the resulting β-alkyl- or arylthioethylamine to the usual series of reactions (Scheme I). The nitrosation must be carried out in a short period of time (see Experimental Section) since the sulfoxide is obtained directly, as in the case of 13 and 19, if the mixture is allowed to stand at 0° overnight.

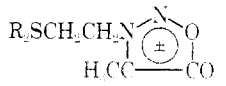
It can be seen from Table I that potency is maximum when R_1 is methyl or hydrogen (1, 5). Increasing steric bulk (3, 4) gradually diminishes the level of activity, as does replacement with an electronegative substituent (6) or introduction of an aromatic ring (2). Carboxylic acid substituents (7, 9) greatly reduce potency, a somewhat surprising result in view of the well-known activity of arylcarboxylic acids.[10] In fact, the acid 9 has essentially the same activity as the corresponding ester 8.

Methyl was chosen as the substituent at the 4 position because such sydnones are more stable than the 4-H analogs and the two show similar potency (compare 1 and 5, 10 and 20, 11 and 12). The effects of variations in R_2 can be seen in Tables II and III.

Insertion of a methylene bridge between sulfur and the aromatic ring (13–15) or substitution of a saturated ring for benzene (16) results in greatly reduced potency. The moderately high activity shown by the adamantyl analog (17) indicates that lipophilic groups in this portion of the molecule have a beneficial effect. In all, it is clearly preferable that R_2 be an aromatic ring.

Considering modifications of this ring, in 18–23 (Table III) potency increases with increasing electronegativity of the substituent, although differences are not great. The *tert*-butyl substituent (24) violates this tendency but the enhanced lipophilicity is probably responsible, as in the adamantyl case.

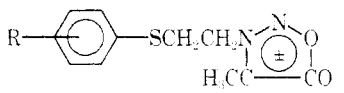
Table II



Compd	R_2	Mp, °C	Crystn solvent	Formula	Analyses	Activity[a]	ED_{50}[b]
13[c]	$PhCH_2-$	82–84	Me_2CO	$C_{12}H_{14}N_2O_3S$	C, H, N, S	25 (0)	
14	p-$CH_3OC_6H_4CH_2-$	57–59	Et_2O	$C_{13}H_{16}N_2O_3S$	C, H, N, S	25 (0)	
15	Ph_3C-	126–127	Me_2CO	$C_{24}H_{22}N_2O_2S$	C, H, N, S	25 (0)	
16	$C_6H_{11}-$	82–83	Et_2O–EtOH	$C_{11}H_{17}N_2O_2S$	C, H, N, S	30 (++)	
17	1-Adamantyl	92–93	Me_2CO	$C_{15}H_{22}N_2O_2S$	C, H, N, S	7.5 (++)	9.4

[a]Lowest dosage (mg/kg) at which the compound was tested in the adjuvant arthritis assay and the degree of activity at that dose level. Inhibition of arthritic swelling: 70–100% (+++), 40–69% (++), 25–39% (+). [b]mg/kg. [c]Sulfoxide.

Table III



Compd	R	Mp, °C	Crystn solvent	Formula	Analyses	Activity[a]	ED_{50}[b]
18	p-CH_3O	60–61	Et_2O–Me_2CO	$C_{12}H_{14}N_2O_3S$	C, H, N, S	5 (+)	
19[c]	p-CH_3	102–103	Me_2CO	$C_{12}H_{14}N_2O_3S$	C, H, N, S	7.5 (+)	9.7
20	p-Cl	77–78	Et_2O–Me_2CO	$C_{11}H_{11}ClN_2O_2S$	C, H, N	2.5 (++)	3.2
21	p-F	92–93	Et_2O–Me_2CO	$C_{11}H_{11}FN_2O_2S$	C, H, N, S	3 (++)	3.7
22	p-Br	78–80	Et_2O–Me_2CO	$C_{11}H_{11}BrN_2O_2S$	C, H, N, S, Br	8 (++)	
23	p-NO_2	111–112	EtOAc	$C_{11}H_{11}N_3O_4S$	C, H, N, S	2.5 (++)	4.8
24[d]	p-t-Bu					2.5 (+++)	1.7
25[e]	3,4-Benzo	81–82	Et_2O–Me_2CO	$C_{15}H_{14}N_2O_2S$	C, H, N, S	2 (++)	1.9
26[f]	2,3-Benzo	85–87	Et_2O–Me_2CO	$C_{15}H_{14}N_2O_2S$	C, H, N	16 (+)	12.8
27	3,4-Cl_2	84–85	EtOAc	$C_{11}H_{10}Cl_2N_2O_2S$	C, H, N, S	8 (−)	7.9
28	2,5-Cl_2	74–75	Et_2O–Me_2CO	$C_{11}H_{10}Cl_2N_2O_2S$	C, H, N, S	2 (+++)	2.4
29	2,6-Cl_2	106–107	Me_2CO	$C_{11}H_{10}Cl_2N_2O_2S$	C, H, N, S, Cl	1 (++)	1.1
30	o-CH_3[c]	91–92	Et_2O	$C_{12}H_{14}N_2O_3S$	C, H, N, S	4 (+++)	3.7
31	m-OCH_3	55–56	Et_2O	$C_{12}H_{14}N_2O_3S$	C, H, N, S	30 (+++)	
32	3-CH_3, 4-Br	76–77	Et_2O	$C_{12}H_{13}BrN_2O_2S$	C, H, N, Br	7.5 (+)	
33	2,3,4,5,6-Cl_5	109–110	AcOH–H_2O	$C_{11}H_7Cl_5N_2O_2S$	C, H, N, S	0.5 (++)	

[a]Lowest dosage (mg/kg) at which the compound was tested in the adjuvant arthritis assay and the degree of activity at that dose level. Inhibition of arthritic swelling: 70–100% (+++), 40–69% (++), 25–39% (+). [b]mg/kg. [c]Sulfoxide. [d]Described in ref 2. [e]2-Naphthyl. [f]1-Naphthyl.

Substitution of 2-naphthyl (**25**) for phenyl (**1**) results in increased potency while replacement by 1-naphthyl (**26**) causes a 50% decrease. It is probable that chloro or *tert*-butyl substituents in the 2-naphthyl nucleus would further decrease the ED_{50}.

The effect of the position of substitution was also examined. Comparing **20** and **27**, introduction of the additional chloro substituent in the meta position has a negative effect on potency. In the case of **27** and **28**, which both have a chloro substituent in the meta position, **28** is more active indicating that ortho substitution is more beneficial than para. This relationship also holds for methyl substituents as can be seen from **19** and **30**.

From these data we can conclude that R_1 should preferably be a small, nonpolar group and that R_2 should be an aromatic ring, not necessarily phenyl. Maximum potency is achieved by introducing electronegative substituents at the ortho positions of this ring but the improvement is at best a four- or fivefold increase over unsubstituted phenyl.

Together with our previous observations, the requirements listed above delineate the structural features necessary for antiarthritic activity in this series. Compounds incorporating the requisite features are at least as active as hydrocortisone or phenylbutazone, thus representing the first group of sydnones to possess consistent activity at a usefully high level.[11] Investigations aimed at determining the nature of this antiarthritic activity and the possible utility of these compounds in the treatment of rheumatoid arthritis are in progress.

Experimental Section†

General Synthesis of Sydnones. (a) Alkylation. The appropriately substituted α-bromoacetic acid (0.1 mol), 2-arylthioethylamine (0.1 mol), and *t*-BuOK (0.1 mol) in 600 ml of *t*-BuOH were heated at reflux under nitrogen overnight. The solvent was removed under reduced pressure and the residue was taken up in 250 ml of 2% aqueous NaOH. The aqueous solution was extracted with Et_2O and acidified to pH 5 with concentrated HCl. Filtration and washing with H_2O gave the amino acid sufficiently pure for nitrosation.

(b) Nitrosation. The amino acid (0.08 mol) and $NaNO_2$ (0.09 mol) in 400 ml of 1:1 CH_2Cl_2–H_2O were stirred at 0° while 8 ml of concentrated HCl was added dropwise over a 1-hr period. Stirring was continued for 2 hr and the CH_2Cl_2 layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residual oil was cyclized without further purification.

† Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Elemental analyses, indicated by symbols of the elements, were within ±0.4% of the theoretical values. Ir, uv, and nmr spectra of all new compounds were consistent with the proposed structures.

(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