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Nonsteroidal Antiinflammatory Agents. 1. 2,4-Diphenylthiazole-5-acetic Acid and Related Compounds

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A variety of novel 2,4-diarylthiazole-5-acetic acids and related compounds was prepared by the Hantzsch thiazole synthesis and evaluated as antiinflammatory agents on the carrageenin-induced edema assay in the rat. Two compounds, namely 4-(4-chlorophenyl)-2-phenylthiazole-5-acetic acid (**24**) and 4-(4-chlorophenyl)-2-(3-methylphenyl)-thiazole-5-acetic acid (**31**), were found to possess activity comparable with indomethacin. Derivatives of the acidic side chain such as esters, amides, hydroxamic acid, β-propionic acids, α-propionic acids, and a tetrazole were all less active than the parent compounds. Compound **24** was five times as effective as phenylbutazone against adjuvant-induced polyarthritis.

In 1963 indomethacin, 1-*p*-chlorobenzoyl-5-methoxy-2-methylindole-3-acetic acid, was reported by Shen, *et al.*,[1] to possess antiinflammatory activity against carrageenin-induced edema in the rat hind paw. This knowledge, together with the fact that aspirin and phenylbutazone (two nonsteroidal antiinflammatory drugs of choice at that time) were both acidic compounds, induced many workers to investigate other aryl- and heteroarylalkanoic acids (for a review, see ref 2).

This paper describes studies based upon the discovery that 2,4-diphenylthiazole-5-acetic acid also inhibits carrageenin-induced edema in the rat.[3] Of the 75 related compounds that were synthesized and studied using this assay procedure, only two compounds were found to possess a potency comparable with indomethacin.

Chemistry. The bulk of the compounds were synthesized by the Hantzsch method, which involved reacting together the appropriate thioamide and α-bromo ketone in a solvent. In the course of this work three different solvent systems were investigated.

Initially, we were also interested in testing esters of the acids. Therefore, in some cases, for example, **1**, **10**, and **27**, the reactants were heated together in refluxing EtOH to give the esters **46**, **49**, and **48**, which were then hydrolyzed to the corresponding acids. Although this route gave reasonable yields, some esters were difficult to separate from starting materials and unwanted side products.

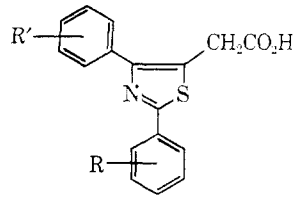
It was decided to obtain the acids directly by heating the reactants in *i*-PrOH at 60° in the presence of Na_2CO_3 essentially according to Knott.[4] Compounds **2–7**, **9**, and **13–22**, for example, were prepared in this way but yields were usually below 50%. It was then found that better yields and cleaner reactions were obtained when the reactants were heated in DMF at 70° without the presence of sodium carbonate, as illustrated for compounds **24–26** and **29–41**.

Derivatives of the acids, such as the amides **52** and **53** and the hydroxamic acid **54**, were prepared in the usual way as indicated in the footnotes of Table II. The α-propionic acid **61** was prepared from the appropriate bromoketo acid but the α-propionic acid **62** was prepared *via* alkylation of the ester **47** with CH_3I, essentially according to Kenyon, Kaiser, and Hauser,[5] and subsequent hydrolysis. The tetrazole **63** was obtained by treating the corresponding acetonitrile derivative **90**, prepared by dehydration of the amide **53**, with NaN_3 in DMF.

Structure-Activity Relationships. Analogs of **1** obtained by substitution in one or both of the phenyl rings are detailed in Table I together with the results on the carrageenin-induced edema test. Because of the variability inherent in this assay procedure, the ED_{40} of each compound is expressed as being within one of the six ranges detailed in the footnotes of Table I. The compounds were prepared essentially in the order shown. The objective was to establish the structure–activity pattern for each phenyl ring and from these data to prepare the appropriate polysubstituted compounds.

Substitution in the 2-phenyl ring resulted in a reduction of activity (compared to **1**) when the group was in the 2 position (**2**, **6**, **9**). When the group was in the 3 or 4 position activity was usually retained. In two cases, however, namely the 4-Cl (**7**) and the 4-$N(CH_3)_2$ (**11**), activity was slightly increased. Substitution in the 4-phenyl ring quickly revealed that the optimum group was chloro in

Table I



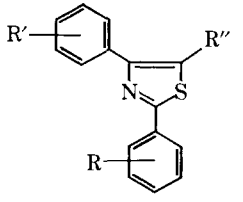
No.	R	R'	Method[a]	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses	Rat paw edema, ED_{40} range[b]
1	H	H	A	89	152–153	C_6H_6	$C_{17}H_{13}NO_2S$	C, H, N, S	4
2	2-CH_3	H	B	34	172–173	C_6H_6–pet. ether	$C_{18}H_{15}NO_2S$	C, H, N, S	6
3	3-CH_3	H	B	30	123–125	C_6H_6–pet. ether	$C_{18}H_{15}NO_2S$	C, H, N, S	4
4	4-CH_3	H	B	51	173–175	C_6H_6	$C_{18}H_{15}NO_2S$	C, H, N, S	6
5	3-CF_3	H	B	23	143–145	C_6H_6–pet. ether	$C_{18}H_{12}F_3NO_2S$	C, H, F, N, S	4
6	2-Cl	H	B	49	169–171	C_6H_6–pet. ether	$C_{17}H_{12}ClNO_2S$	C, H, Cl, N, S	6
7	4-Cl	H	B	44	157–158	C_6H_6	$C_{17}H_{12}ClNO_2S$	C, H, Cl, N, S	3
8	4-Br	H	C	81	174–175	C_6H_6	$C_{17}H_{12}BrNO_2S$	C, H, N	4
9	2-OCH_3	H	B	78	179–181	AcOH–H_2O	$C_{18}H_{15}NO_3S$	C, H, N, S	6
10	4-OCH_3	H	A	68	151–152	C_6H_6	$C_{18}H_{15}NO_3S$	C, H, N, S	4
11	4-$N(CH_3)_2$	H	C	52	154–156	C_6H_6	$C_{19}H_{18}N_2O_2S$	C, H, N, S	3
12	4-$CH(CH_3)_2$	H	C	85	146–147	C_6H_6	$C_{20}H_{19}NO_2S$	C, H, N	4
13	2,6-$(CH_3)_2$	H	B	37	203–205	AcOH–H_2O	$C_{19}H_{17}NO_2S$	C, H, N, S	6
14	2,3-$(CH_3)_2$	H	B	64	143–145	AcOH–H_2O	$C_{19}H_{17}NO_2S$	C, H, N, S	5
15	2,6-Cl_2	H	B	45	210–212	AcOH–H_2O	$C_{17}H_{11}Cl_2NO_2S$	C, H, Cl, N, S	6
16	2,4-Cl_2	H	B	10	158–160	AcOH–H_2O	$C_{17}H_{11}Cl_2NO_2S$	C, H, Cl, N	6
17	2,4-$(OCH_3)_2$	H	B	44	157–159	AcOH–H_2O	$C_{19}H_{17}NO_4S$	C, H, N, S	5
18	2-CH_3, 4-Cl	H	B	58	175–177	AcOH–H_2O	$C_{18}H_{14}ClNO_2S$	C, H, Cl, N	4
19	2-CH_3, 6-Cl	H	B	63	217–219	AcOH–H_2O	$C_{18}H_{14}ClNO_2S$	C, H, Cl, N	6
20	2-CH_3, 4-OCH_3	H	B	28	136–138	AcOH–H_2O	$C_{19}H_{17}NO_3S$	C, H, N, S	4
21	2-OCH_3, 4-Cl	H	B	65	204–205	AcOH–H_2O	$C_{18}H_{14}ClNO_3S$	C, H, Cl, N, S	6
22	H	4-CH_3	B	31	168–169	C_6H_6	$C_{18}H_{15}NO_2S$	C, H, N, S	6
23	H	2-Cl	A	30	178–180	AcOH–H_2O	$C_{17}H_{12}ClNO_2S$	C, H, Cl, N	6
24	H	4-Cl	C	78	162–163	C_6H_6	$C_{17}H_{12}ClNO_2S$	C, H, N, S	1
25	H	4-Br	C	75	178–180	C_6H_6	$C_{17}H_{12}BrNO_2S$	C, H, N	2
26	H	4-F	C	66	173–174	C_6H_6	$C_{17}H_{12}FNO_2S$	C, H, N, S	4
27	H	4-OCH_3	A	85	180–181	C_6H_6	$C_{18}H_{15}NO_3S$	C, H, N, S	4
28	H	3,4-$(OCH_3)_2$	B	34	147–149	C_6H_6	$C_{19}H_{17}NO_4S$	C, H, N, S	6
29	H	4-OH	C	40	214–215	C_6H_6	$C_{17}H_{13}NO_3S$	C, H, N	6
30	2-CH_3	4-Cl	C	61	174–175	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, N	3
31	3-CH_3	4-Cl	C	68	152–153	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, N	1
32	4-CH_3	4-Cl	C	31	188–189	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, N	4
33	3-Cl	4-Cl	C	66	165–166	C_6H_6	$C_{17}H_{11}Cl_2NO_2S$	C, H, N	3
34	4-Cl	4-Cl	C	78	199–201	C_6H_6	$C_{17}H_{11}Cl_2NO_2S$	C, H, Cl, N	2
35	4-Br	4-Cl	C	80	202–203	C_6H_6	$C_{17}H_{11}BrClNO_2S$	C, H, N	3
36	4-OCH_3	4-Cl	C	72	173–174	AcOH–H_2O	$C_{18}H_{14}ClNO_3S$	C, H, N	4
37	4-$N(CH_3)_2$	4-Cl	C	38	205–207	EtOH	$C_{19}H_{17}ClN_2O_2S$	C, H, N	4
38	4-CO_2H	4-Cl	C	22	267–269	EtOH–H_2O	$C_{18}H_{12}ClNO_4S$	C, H, N	6
39	4-Cl	4-Br	C	69	206–207	C_6H_6	$C_{17}H_{11}BrClNO_2S$	C, H, N	3
40	4-Cl	4-F	C	64	194–196	C_6H_6	$C_{17}H_{11}ClFNO_2S$	C, H, Cl, N, S	2
41	4-Br	4-F	C	88	192–193	C_6H_6	$C_{17}H_{11}BrFNO_2S$	C, H, N	4
42	2-CH_3	4-OCH_3	B	45	140–141	AcOH–H_2O	$C_{19}H_{17}NO_3S$	C, H, N, S	6
43	4-Cl	4-OCH_3	B	57	199–201	AcOH–H_2O	$C_{18}H_{14}ClNO_3S$	C, H, N, S	6
44	4-OCH_3	4-OCH_3	B	56	176–178	AcOH–H_2O	$C_{19}H_{17}NO_4S$	C, H, N, S	4
Phenylbutazone									4
Indomethacin									1

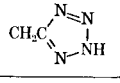
[a]The letters A, B, and C refer to general preparative procedures detailed in the Experimental Section. [b]The numbers 1–6 refer to the following ED_{40} ranges: 1, 1–5 mg/kg; 2, 6–10 mg/kg; 3, 11–25 mg/kg; 4, 26–50 mg/kg; 5, 51–100 mg/kg; 6, >100 mg/kg.

the 4 position (**24**). This compound was comparable in potency to indomethacin in this screen. The corresponding 4-Br (**25**) was only slightly less potent.

A series of analogs with a 4-Cl group in the 4-phenyl ring and a variety of groups in the 2-phenyl ring were then investigated. The most active compound was found to be **31**, which had a methyl group in the 3 position and was comparable in activity with **24**. In terms of activity, this compound was followed by the 4-Cl analog **34** which was comparable to **25**. Surprisingly, the 4-$N(CH_3)_2$ analog **37** only possessed activity similar to **1**. When the compound with a 4-Br group in the 4-phenyl ring and a 4-Cl in the 2-phenyl ring (**39**) was tested, it was found to be slightly less active than **34** as expected (compare **25** and **24**). But

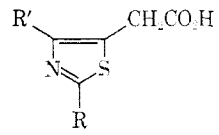
Table II



No.	R	R'	R''	Method[a]	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses	Rat paw edema, ED_{40} range[b]
45	H	H	$CH_2CO_2CH_3$	A	73	122–123	MeOH	$C_{18}H_{15}NO_2S$	C, H, N, S	6
46	H	H	$CH_2CO_2C_2H_5$	A	70	95–96	EtOH	$C_{19}H_{17}NO_2S$	C, H, N, S	6
47	H	4-Cl	$CH_2CO_2C_2H_5$	A	56	69–70	EtOH	$C_{19}H_{16}ClNO_2S$	C, H, Cl, N, S	5
48	H	4-OCH_3	$CH_2CO_2C_2H_5$	A	65	68–69	EtOH	$C_{20}H_{19}NO_3S$	C, H, N, S	6
49	4-OCH_3	H	$CH_2CO_2C_2H_5$	A	62	65–67	EtOH	$C_{20}H_{19}NO_3S$	C, H, N, S	6
50	H	4-Cl	$CH_2CO_2C_4H_9$	*c*	72	68–70	EtOH–H_2O	$C_{21}H_{20}ClNO_2S$	C, H, N	3
51	H	4-Cl	$CH_2CO_2(CH_2)_2N(CH_3)_2 \cdot HCl$	*d*	54	176–178	*i*-PrOH	$C_{21}H_{21}ClN_2O_2 \cdot HCl$	C, H, N	3
52	H	H	CH_2CONH_2	*d*	33	209–210	C_6H_6	$C_{17}H_{14}N_2OS$	C, H, N, S	6
53	H	4-Cl	CH_2CONH_2	*d*	15	223–224	C_6H_6	$C_{17}H_{13}ClN_2OS$	C, H, N, S	6
54	H	4-Cl	$CH_2CONHOH$	*d*	68	176–177	MeOH–H_2O	$C_{17}H_{13}ClN_2O_2S$	C, H, N	6
55	H	H	$CH_2CH_2CO_2H$	A	50	150–151	EtOH	$C_{18}H_{15}NO_2S$	C, H, N, S	6
56	H	4-Cl	$CH_2CH_2CO_2H$	C	36	143–144	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, N	5
57	2-CH_3	H	$CH_2CH_2CO_2H$	A	18	107–109	C_6H_6	$C_{19}H_{17}NO_2S$	C, H, N, S	6
58	4-Cl	H	$CH_2CH_2CO_2H$	C	82	177–178	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, Cl, N, S	6
59	4-OCH_3	H	$CH_2CH_2CO_2H$	A	21	174–175	C_6H_6	$C_{19}H_{17}NO_3S$	C, H, N, S	6
60	4-Cl	4-Cl	$CH_2CH_2CO_2H$	C	44	179–181	C_6H_6	$C_{18}H_{13}Cl_2NO_2S$	C, H, N	4
61	H	H	$CH(CH_3)CO_2H$	B	55	142–144	AcOH–H_2O	$C_{18}H_{15}NO_2S$	C, H, N, S	6
62	H	4-Cl	$CH(CH_3)CO_2H$	*d*	14	135–136	C_6H_6	$C_{18}H_{14}ClNO_2S$	C, H, N	3
63	H	4-Cl		*d*	65	209–210	EtOH–H_2O	$C_{17}H_{12}ClN_5S$	C, H, N	6

[a]See footnote *a*, Table I. [b]See footnote *b*, Table I. [c]Prepared by treating **24** with BuOH in the presence of H_2SO_4 in the usual way. [d]See Experimental Section.

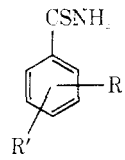
Table III



No.	R	R′	Method[a]	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses	Rat paw edema, ED_{40} range[b]
64	C_6H_5	2-Thienyl	B	48	154–155	C_6H_6	$C_{15}H_{11}NO_2S_2$	C, H, N, S	5
65	2-$CH_3C_6H_4$	2-Thienyl	B	46	136–138	C_6H_6	$C_{16}H_{13}NO_2S_2$	C, H, N, S	5
66	4-ClC_6H_4	2-Thienyl	B	31	137–139	C_6H_6	$C_{15}H_{10}NO_2S_2$	C, H, Cl, N, S	6
67	4-$OCH_3C_6H_4$	2-Thienyl	B	16	149–151	C_6H_6	$C_{16}H_{13}NO_3S_2$	C, H, N, S	6
68	C_6H_5	1-Naphthyl	A	12	166–167	C_6H_6	$C_{21}H_{15}NO_2S$	C, H, N, S	6
69	C_6H_5	2-Naphthyl	A	31	168–169	C_6H_6	$C_{21}H_{15}NO_2S$	C, H, N, S	6
70	2-$CH_3C_6H_4$	2-Naphthyl	B	48	171–172	C_6H_6	$C_{22}H_{17}NO_2S$	C, H, N, S	6
71	4-$OCH_3C_6H_4$	2-Naphthyl	B	44	160–162	AcOH–H_2O	$C_{22}H_{17}NO_3S$	C, H, N, S	6
72	1-Naphthyl	C_6H_5	B	30	145–148	C_6H_6	$C_{21}H_{15}NO_2S$	C, H, N, S	6
73	2-Naphthyl	C_6H_5	B	51	171–172	C_6H_6	$C_{21}H_{15}NO_2S$	C, H, N, S	6
74	2-Pyridyl	4-ClC_6H_4	C	48	202–203	EtOH	$C_{16}H_{11}ClN_2O_2S$	C, H, N	4
75	3-Pyridyl	4-ClC_6H_4	C	23	238–239	EtOH–DMF	$C_{16}H_{11}ClN_2O_2S$	C, H, N	4
76	4-Pyridyl	4-ClC_6H_4	C	8	215–216	EtOH–DMF	$C_{16}H_{11}ClN_2O_2S$	C, H, N	6

[a]See footnote *a*, Table I. [b]See footnote *b*, Table I.

Table IV



No.	R	R′	Rxn time, hr	Yield, %	Mp, °C[a]	Formula[b]
77	2-OCH_3	H	16	66	136–137	C_8H_9NOS
78	3-CF_3	H	4	66	72–73	$C_8H_6F_3NS$
79	2-OCH_3	4-OCH_3	36	68	142–143	$C_9H_{11}NO_2S$
80	2-OCH_3	4-Cl	15	76	149–150	C_8H_8ClNOS
81	2-CH_3	4-OCH_3	15	71	124–126	$C_9H_{11}NOS$
82	2-CH_3	3-CH_3	15	92	137–138	$C_9H_{11}NS$
83	2-CH_3	6-CH_3	204	50	156–157	$C_9H_{11}NS$
84	2-CH_3	4-Cl	15	69	86–87	C_8H_8ClNS

[a]Recrystallized from C_6H_6. [b]All compounds analyzed for C, H, and N.

the corresponding 4-F, 4-Cl analog (**40**) was unexpectedly more active than **39** (compare **26** and **25**).

The effect of altering the acidic side chain was investigated for selected compounds; the results are shown in Table II. In all cases, the esters **45–51**, amides **52** and **53**, hydroxamic acid **54**, β-propionic acids **55–60**, α-propionic acids **61** and **62**, and tetrazole **63** were markedly less active than their parent acetic acid. It was interesting, however, that the butyl ester **50** of **24** was more active than the corresponding ethyl ester **47**.

The replacement of one of the phenyl rings by naphthyl, pyridyl, or thienyl was also investigated as shown in Table III. Disappointingly, none of these compounds was more active than **1**.

Pharmacology. The carrageenin-induced rat paw edema assay was carried out as described by Winter, *et al.*,[6] using rat groups of six animals. The rats were starved for 18 hr before the test compound was orally administrated by gavage. One hour later, the rats received 0.05 ml of 1% carrageenin in one hind paw. After the final paw-volume measurements had been made, the rats were killed, and in some cases, their stomachs were removed and examined for signs of acute gastric erosions, which, if present, were awarded an arbitary severity score. Compound **24**, for example, was considered to be as ulcerogenic as phenylbutazone at an equipotent dose when examined in the edema test. Because of the high activity of this compound against carrageenin-induced edema, it was examined in a variety of other tests.

Against adjuvant-induced polyarthritis in the rat, **24** was found to be five times more effective than phenylbutazone (dose ratio) in inhibiting the swelling of the injected hind paw. This test was carried out essentially as described by Newbould[7] except that rats of the highly reactive Lewis strain were used.

Many acidic antiinflammatory drugs have been shown to block the bronchoconstriction response of the anaesthetized guinea pig to bradykinin. Using the procedure described by Rosenthale and Dervinis,[8] the activity of **24** against bradykinin was found to be similar to that possessed by both indomethacin and phenylbutazone: 1 mg/kg ip of test compound gave 100% block of 8 μg of bradykinin.

Compound **24** was also tested *in vitro* in the albumin heat-denaturation test described by Mizuschima[9] and in the albumin–trinitrobenzaldehyde binding test developed by Skidmore and Whitehouse.[10] In both cases, **24** possessed activity similar to that reported by these authors for phenylbutazone.

Experimental Section

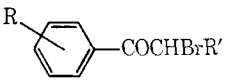
Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. All analytical samples were examined on a Perkin-Elmer 521 infrared spectrophotometer and in every case a spectrum consistent with the proposed structure was obtained. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

Preparation of Substituted Thiobenzamides. The thiobenzamides were prepared by the Fairful, Lowe, and Peak[11] method from nitriles obtained by standard literature procedures. Those compounds not previously reported are detailed in Table IV.

Preparation of the Bromoketo Acids. The appropriate keto acid was suspended in Et_2O at room temperature and 1 equiv of Br_2 was added dropwise. The resulting solution was evaporated and the residue was recrystallized from C_6H_6–petroleum ether (bp 60–80°) to give the desired bromoketo acid. Those compounds not previously reported are detailed in Table V.

The general preparative procedures in Tables I–III are illustrated by the following examples.

Table V



No.	R	R′	Yield, %	Mp, °C[a]	Formula[b]
85	4-Br	CH_2CO_2H	81	137–139	$C_{10}H_8Br_2O_3$
86	4-F	CH_2CO_2H	95	135–136	$C_{10}H_8BrFO_3$
87	4-OH	CH_2CO_2H	76	140–141	$C_{10}H_9BrO_4$
88	3,4-$(OCH_3)_2$	CH_2CO_2H	85	138–141	$C_{12}H_{13}BrO_5$
89	4-Cl	$CH_2CH_2CO_2H$	91	127–129	$C_{11}H_{10}BrClO_3$

[a]Recrystallized from C_6H_6–petroleum ether (bp 60–80°). [b]All compounds analyzed for C and H.

Method **A.** **4-(4-Methoxyphenyl)-2-phenylthiazole-5-acetic Acid (27).** A mixture of 11 g (0.0385 mol) of 3-bromo-3-(4-methoxybenzoyl)propionic acid and 5.25 g (0.0385 mol) of thiobenzamide in 100 ml of EtOH was heated together under reflux for 5 hr. The solvent was then evaporated and the residue was dissolved in Et_2O. The ethereal solution was washed with H_2O and saturated $NaHCO_3$ solution and then dried ($MgSO_4$). Evaporation of the solvent gave a solid, which was recrystallized from EtOH to give 8.5 g of the ester **48** (see Table II). A solution of 5 g (0.01 mol) of 48 in 50 ml of EtOH was then treated with a solution of 2 g (0.035 mol) of KOH in 10 ml of H_2O. After 1 hr at room temperature the solvent was evaporated and the residue was worked up in the usual way to yield 3.9 g of the desired acid **27** (see Table I).

Method **B.** **2-(2-Methylphenyl)-4-(2-thienyl)thiazole-5-acetic Acid (65).** A mixture of 5.7 g (0.0355 mol) of 2-methylthiobenzamide, 10.0 g (0.038 mol) of 3-bromo-3-(2-thenoyl)propionic acid, and 1.8 g (0.017 mol) of Na_2CO_3 in 55 ml of *i*-PrOH was stirred at 60° for 30 min. After a further 60 min at 40°, the mixture was poured into H_2O and made acidic with concentrated HCl. The resulting oily solid was extracted with ether and worked up in the usual way to give 6.7 g of the desired acid **65** (see Table III).

Method **C.** **4-(4-Chlorophenyl)-2-phenylthiazole-5-acetic Acid (24).** A solution of 145.7 g (0.5 mol) of 3-bromo-3-(4-chlorobenzoyl)propionic acid and 68.5 g (0.5 mol) of thiobenzamide in 350 ml of DMF was stirred at 70° for 1 hr. On cooling, the solution was poured into 700 ml of H_2O, and the resulting solid was filtered, washed well with H_2O, and then dried at 60° under vacuum. Recrystallization from C_6H_6 gave 128 g of the desired acid **24** (see Table I).

α-[2-Phenyl-4-(4-chlorophenyl)thiazole]-5-propionic Acid (62). To a stirred suspension of 1.18 g (0.03 mol) of $NaNH_2$ in 120 ml of liquid NH_3 was added 10.75 g (0.03 mol) of the ester **47** in 50 ml of Et_2O. The mixture was stirred for 15 min, 4.26 g (0.03 mol) of methyl iodide was added, and the reaction was worked up according to Kenyon, Kaiser, and Hauser[5] to give 10.6 g of crude ethyl ester of **62** as an orange oil. A solution of this oil in 100 ml of EtOH and 150 ml of 5 *N* NaOH was refluxed for 1 hr before the bulk of the EtOH was evaporated. The resulting solution was washed with Et_2O and then acidified with concentrated HCl to pH 2. The product was extracted into Et_2O and this solution was washed with H_2O and dried ($MgSO_4$) and the solvent was evaporated. The residual oil was triturated with C_6H_6 to yield a solid which was recrystallized from the same solvent to yield 1.4 g of **62** (see Table II).

4-(4-Chlorophenyl)-2-phenylthiazole-5-acetonitrile (90). To a stirred suspension of 20.3 g (0.062 mol) of the amide **53** in 100 ml of dry DMF at 0° was added dropwise 14.6 g (0.124 mol) of redistilled $SOCl_2$. The resulting dark solution was stirred at room temperature overnight and then poured into H_2O. The brown precipitate was filtered and dissolved in Et_2O. This solution was washed with saturated $NaHCO_3$ solution and H_2O and dried ($MgSO_4$). Evaporation of the solvent gave a solid which was recrystallized from EtOH–H_2O to give 11.7 g (61%) of the desired nitrile, mp 119–120°. *Anal.* ($C_{17}H_{11}ClN_2S$) C, H, N.

5-[4-(4-Chlorophenyl)-2-phenylthiazol-5-ylmethyl]tetrazole (63). A mixture of 11.0 g (0.032 mol) of the nitrile **90**, 2.4 g of NH_4Cl (0.045 mol), and 2.9 g (0.045 mol) of NaN_3 in 100 ml of dry DMF was heated at reflux temperature under N_2 with stirring for 24 hr. The solvent was then evaporated and H_2O was added. The mixture was extracted with Et_2O, and the extract was washed with H_2O, dried ($MgSO_4$), and evaporated to a brown solid. Recrystallization from EtOH–H_2O gave 8.1 g of the tetrazole **63** (see Table II).

4-(4-Chlorophenyl)-2-phenylthiazole-5-acetic Acid Dimethylaminoethyl Ester Hydrochloride (51). A mixture of 14.3 g (0.04 mol) of the ester **47**, 50 ml of dimethylaminoethanol, and 0.1 g of Na, in 300 ml of dry benzene, was heated at reflux temperature under a reflux ratio head and the ethanol–benzene azeotrope collected over 3 hr. The solvent was evaporated; dilute HCl was added, which was washed with ether and basified with aqueous NH_4OH. The resulting oil was dissolved in ether, washed with H_2O, dried ($MgSO_4$), and treated with gaseous HCl. The sticky solid which formed was recrystallized from *i*-PrOH to yield 9.4 g of the desired amino ester hydrochloride **51**.

2,4-Diphenyl-5-thiazoleacetamide (52). A solution of 1.9 g (0.006 mol) of the ester **45** and 25 ml of NH_4OH (sp gr 0.88) in 25 ml of methanol was heated at 90° in a sealed tube for 5 hr. On cooling, the crystals which formed were filtered and recrystallized from benzene to yield 0.46 g of the amide **52**.

4-(4-Chlorophenyl)-2-phenyl-5-thiazoleacetamide (53). A solution of 2.0 g (0.006 mol) of the acid **24** in 20 ml of dry THF was cooled to −5°, and 0.68 g (0.0066 mol) of Et_3N followed by 0.73 g (0.0066 mol) of $ClCO_2Et$ was added dropwise, maintaining the reaction temperature below 0°. Then 0.35 g of NH_4OH (sp gr 0.88) was added and the solution stirred at room temperature for 17 hr. The solvent was evaporated; the residue was dissolved in $CHCl_3$, washed with H_2O, HCl, and H_2O, and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the crude product from benzene gave 0.32 g of the amide **53**.

4-(4-Chlorophenyl)-2-phenyl-5-thiazoleacetohydroxamic Acid (54). A solution of 2.56 g (0.037 mol) of hydroxylamine hydrochloride in 40 ml of MeOH was added to NaOMe prepared from 1.25 g (0.054 mol) of Na and 40 ml of MeOH. The resulting mixture was filtered and a solution of 9.7 g (0.027 mol) of the ester **47** in 50 ml of MeOH was added. After 17 hr at room temperature, the solvent was evaporated and the residue recrystallized from MeOH–H_2O to yield 6.3 g of **54**.

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