Attempted Esterification of 2-Diethylaminoethanol. The procedure was similar to that of **2b**. Evaporation and column chromatography of the reaction mixture gave various fractions which contained at least five short-wave uv-absorbing products, which were dark brown intractable oils which could not be obtained crystalline upon further chromatography (column and preparative tlc).

Attempted Esterification of Veracevine. The esterification of veracevine† (which contains seven hydroxyl groups, three of which are normally acylable) in a manner similar to the procedures described above was not selective and gave a complex mixture of products, none of which were fully characterized.

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A New Nonsteroidal Antiinflammatory Agent. 3.[1] Analogs of 2-Substituted 5-Benzothiazoleacetic Acids and Their Derivatives

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Compounds of 5-benzothiazole-α-alkylacetic acid with substitutions at the 2 position and/or the alkyl function were synthesized and their pharmacological activities studied. Introduction of a methyl group α to the acetic acid function of 2-phenyl-5-benzothiazoleacetic acid lowered toxicity and enhanced antiinflammatory activity relative to that of phenylbutazone employed as a standard.

We previously reported the synthesis of a series of 2-substituted 5-benzothiazoleacetic acids and studied their antiinflammatory activities.[1] It was found that the most active and the least toxic compound among them was 2-phenyl-5-benzothiazoleacetic acid (**9**). We therefore further synthesized several compounds with varied substituents on the α carbon of the acetic acid function in order to investigate whether such modification affected the pharmacological activities. For the same purpose, some benzothiazolineacetic acids were also synthesized.

Chemistry. General schemes for the synthesis of 2-phenyl-5-benzothiazole-α-alkylacetic acid (**1a–j, 2, 3**) are shown in Schemes I and II.

The many synthetic routes could be classified into two general categories. In the first category (type I), the benzothiazole skeleton was synthesized previous to alkylating the active methylene of the acetic acid at the 5 position. The second category (type II) involved the initial alkylation of the carbon α to the nitrile function of *p*-chlorophenylacetonitrile (**16**) followed by subsequent condensation with an appropriate moiety to form the benzothiazole skeleton.

Routes A–F in Scheme I belonged to the type I synthesis. The α-alkylacetic acid moiety was achieved by alkylating the carbon α to any of three functional groups: nitrile, ester, and acid.

Synthesis from the nitrile was achieved by methylating 2-phenyl-5-benzothiazoleacetonitrile (**4**) with methyl iodide using sodium amide. The product, α-(2-phenyl-5-benzothiazolyl)-α-methylacetonitrile (**5**), could be hydrolyzed directly (route A) or by means of an initial conversion to its amide **6** followed by hydrolysis to yield the desired product **1a** (route B). Higher yields of **1a** were obtained if ethyl carbonate was used to obtain **7** followed by methylation and hydrolysis *via* the amide.

Ethyl 2-phenyl-5-benzothiazolemalonate (**12**), obtainable from the ester **11** by reaction with ethyl carbonate in sodium ethoxide, was alkylated with subsequent hydrolysis to yield either **1a** or **2** (route C). Compound **11** could also be methylated directly at room temperature and hydrolyzed to the product **1a** (route D) but the yield was only 25%. Furthermore, at reflux the disubstituted α-(2-phenyl-5-benzothiazolyl)-α-methylpropionic acid (**3**) was obtained in 50% yield when **11** was subjected to methylation (route E). Ethylation of **11** at elevated temperature yielded **2** in 80% yield (route D).

The acid **9**, when treated with *n*-butyllithium and methyl iodide in the presence of diisopropylamine, gave the lithium salt which was immediately suspended in water and acidified to afford **1a** in 45% yield (route F). Ethylation by this route proved to be difficult.

Type II synthesis included route G in Schemes I and II.

Scheme I. A Synthetic Route to 2-Phenyl-5-benzothiazole-α-alkylacetic Acid (1a, 2, 3)

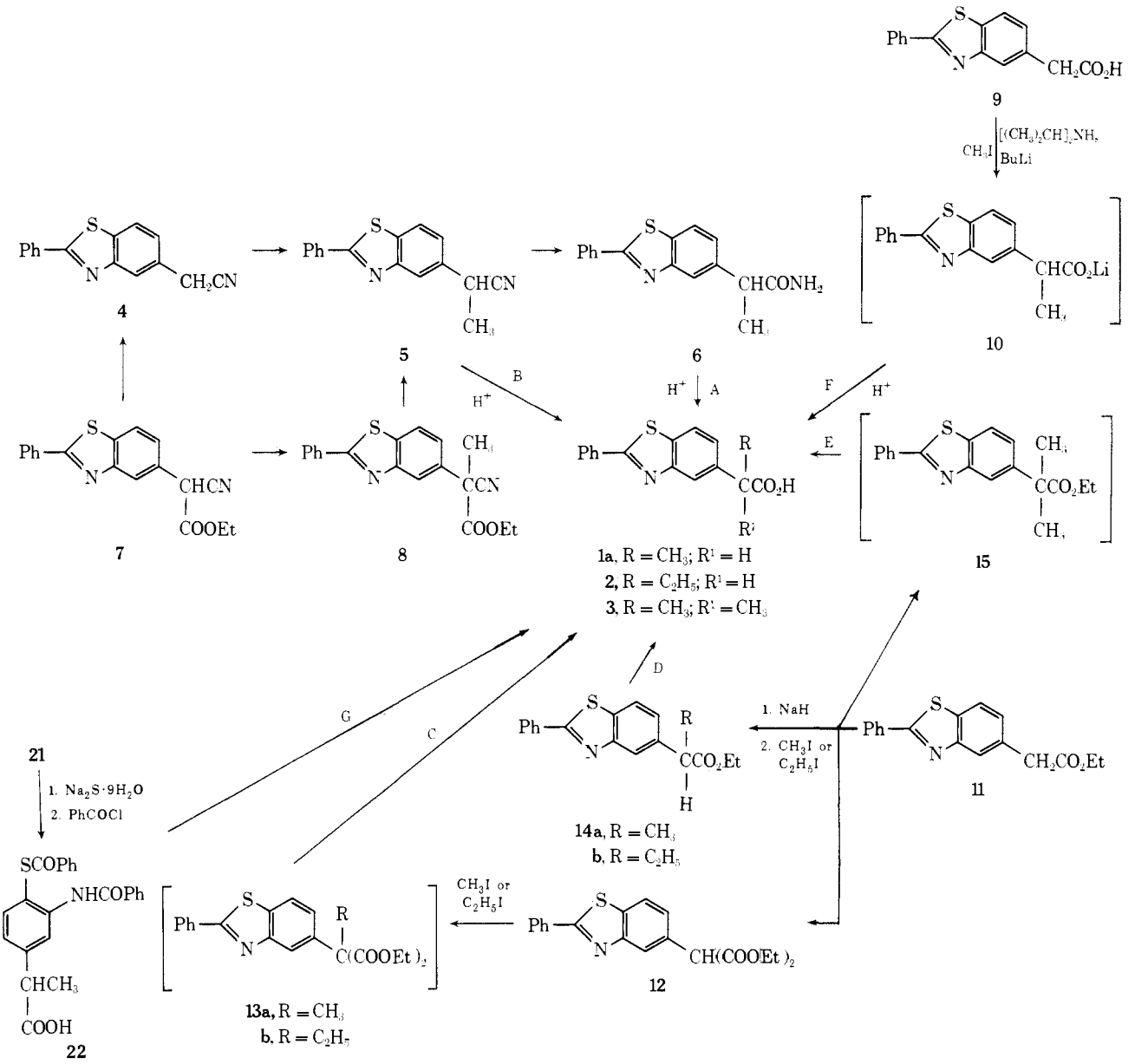
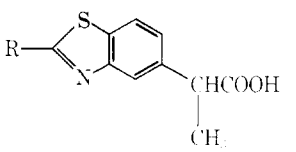


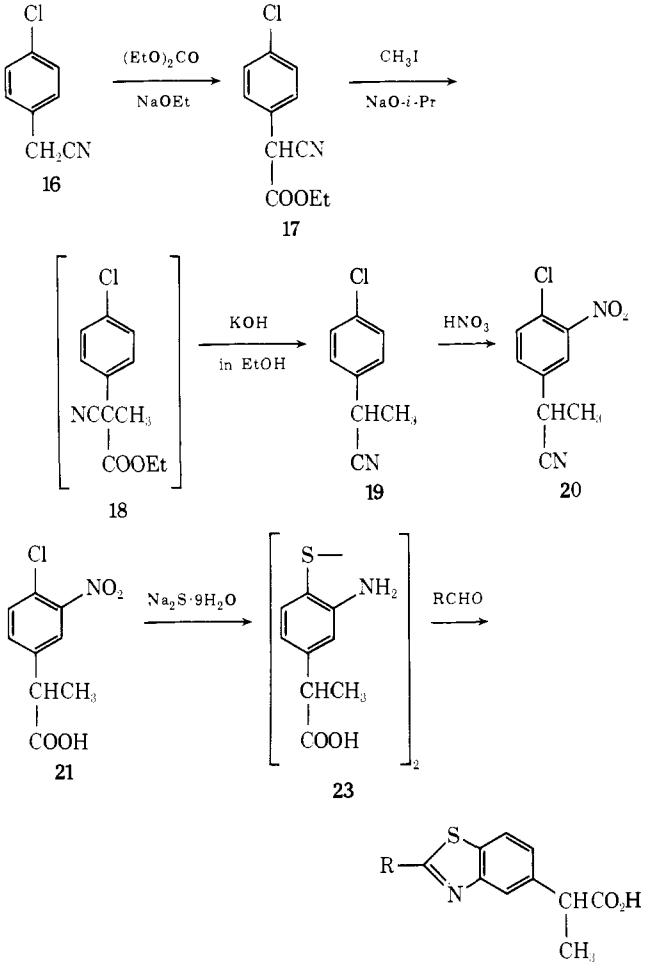
Table I. 2-Substituted 5-Benzothiazole-α-methylacetic Acids



Compd no.	R	Yield, %	Mp, °C	Crystn solvent	Formula[a]	Antiinflam act. (% inhibition of edema) (100 mg/kg po)
1a	C_6H_5	62.0	142–143	$CHCl_3$–ligroine	$C_{16}H_{13}NO_2S$	59.9
1b	2-ClC_6H_4	38.5	134–136	$CHCl_3$–ligroine	$C_{16}H_{12}ClNO_2S$	22.5
1c	4-*i*-PrC_6H_4	29.7	132–133	$CHCl_3$–ligroine	$C_{19}H_{19}NO_2S$	24.3
1d	2-HOC_6H_4	42.4	162–163	$CHCl_3$–ligroine	$C_{16}H_{13}NO_3S$	17.0
1e	4-HOC_6H_4	34.3	208–210	THF–ligroine	$C_{16}H_{13}NO_3S$	18.3
1f	4-$CH_3OC_6H_4$	40.6	147–148	$CHCl_3$–ligroine	$C_{17}H_{15}NO_3S$	31.7
1g	3,4-$(CH_3O)_2C_6H_3$	45.0	194–195	$CHCl_3$–ligroine	$C_{18}H_{17}NO_4S$	27.4
1h	4-$(CH_3)_2NC_6H_4$	37.0	201–203	*i*-PrOH	$C_{18}H_{18}N_2O_2S$	45.7
1i	4-$CH_3C_6H_4$	48.4	166–167	$CHCl_3$–ligroine	$C_{17}H_{15}NO_2S$	37.0
1j	1-Naphthyl	28.5	150–151	$CHCl_3$–ligroine	$C_{20}H_{15}NO_2S$	42.1
Phenylbutazone						56.0

[a] All compounds were analyzed for C, H, and N.

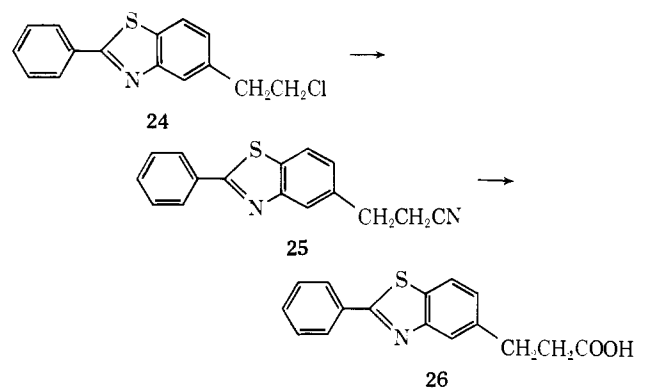
Scheme II. General Synthetic Route to 2-Substituted 5-Benzothiazole-α-methylacetic Acid (1a–j)



Route G involved reaction of **21** with an aqueous solution of sodium sulfide nonahydrate followed by condensation with benzoyl chloride at low temperature to give 3-benzoylamino-4-benzoylthiophenyl-α-methylacetic acid (**22**). Subsequent ring closure converted **22** in good yield to the product **1a**.

The preferred method of synthesis of **1a** was that illustrated in Scheme II. Thus, α-(4-chlorophenyl)-α-methylacetonitrile (**19**) was obtained in three steps from the readily available *p*-chlorophenylacetonitrile (**16**). Nitration of **19** followed by hydrolysis afforded **21** which was then allowed to react with sodium sulfide nonahydrate to yield bis[2-amino-4-(1-carboxy)ethylphenyl] disulfide (**23**). The desired product **1a** was obtained by condensing **23** with benzaldehyde. Furthermore, this route proved more versatile since **1b–j** could be obtained by condensing **23** with appropriate aldehydes.

Scheme III. A Synthetic Route for 2-Phenyl-5-benzothiazolepropionic Acid (**26**)



Scheme III depicts the synthesis of 2-phenyl-5-benzothiazolepropionic acid (**26**). The starting material, 2-phenyl-5-(2-chloroethyl)benzothiazole (**24**),[1] was allowed to react with KCN in DMSO to afford the corresponding nitrile **25** which was subsequently hydrolyzed to yield the product **26**.

3-Methyl-2-phenyl-5-benzolineacetic acid (**29**) was synthesized by heating **9** in an autoclave containing an acidic solution of methyl iodide in methanol. The product was then reduced and hydrolyzed to yield **29** (Scheme IV).

Pharmacology and Results. Antiinflammatory activities were assessed by the inhibition of edema formation in the hind paw of rats (Wister Strain male rat, body wt 150–180 g, five rats per group) in response to a subplanter injection of carrageenin (1%, 0.05 ml). The experimental procedure followed that of Winter, *et al.*[2] Carrageenin was injected 1 hr after oral administration of the test compound as a CMC suspension (100 mg/kg) and edema formation was measured 3 hr after injection. The response of the drug-treated animals was compared with that of carrageenin alone, some receiving vehicle alone and others receiving phenylbutazone (100 mg/kg).

Surveying the various derivatives, it was found that when one of the α hydrogens of the acetic acid function of **9** was replaced with an alkyl group, only the methyl-substituted compound **1a** showed an enhancement of antiinflammatory activity (Table IV). All other alkyl substitutions yielded compounds which had only half of the antiinflammatory activity of phenylbutazone (Tables I–III). On the other hand, changing the chain length of the carboxylic acid function from an acetic to a propionic (**26**) resulted in a compound that had almost the same antiinflammatory activity as **9**.

Placement of another carboxylic function α to the carbonyl (*e.g.*, **12**) dramatically reduced activity. However, it should be noted that it was the carboxylic ester **12** which was tested and not the carboxylic acid.

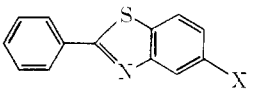
Compound **29** which has a methyl function at the 3 position of the benzothiazoline ring demonstrated only half of the antiinflammatory activity of either phenylbutazone or **9**.

Analgesic activity was determined by the repeated characteristic stretching movements of the mouse (ICR-JCL male mouse, body wt 15–20 g, ten mice per group) in response to an intraperitoneal injection of 0.6% acetic acid. The experimental procedure followed that of Koster, *et al.*[3] The stretching movement was measured at four time intervals (10–15, 25–30, 40–45, and 55–60 min) after injection of acetic acid. The test compounds were administrated as a CMC suspension (30, 50, 100, 200, and 300 mg/kg, respectively). The response of drug-treated animals was compared with that of acetic acid alone, some receiving vehicle alone and others receiving phenylbutazone and aminopyrine (30, 50, 100, 200, and 300 mg/kg, respectively). The results were calculated according to the method of Litchfield and Wilcoxon[4] (Table V).

It was found that **1a** and **29** were equal to or more effective than either aminopyrine or **9** as analgesic agents. They could be arranged in a descending order of activity: **29**, aminopyrine, **1a**, and **9**; however, the difference between the first three was small.

LD_{50} values after 72 hr were determined by oral administration to groups of ten mice (ICR) (Table VI). Three compounds were found to have lower toxicity than **9**. Compound **1a** showed a slight reduction in toxicity, whereas **26** and **29** were found to be only half as toxic as **9**.

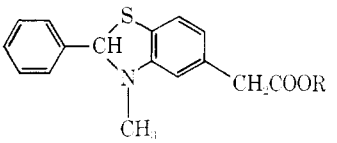
Table II. 5-Substituted 2-Phenylbenzothiazoles



Compd no.	X	Yield, %	Mp, °C	Formula[a]	Antiinflam act. (% inhibition of edema) (100 mg/kg po)
14a	$-C(CH_3)HCOOC_2H_5$	25.2	43–44	$C_{18}H_{17}NO_2S$	50.0
30	$-C(CH_3)HCOOCH(CH_3)_2$	90.5	51–53	$C_{18}H_{18}NO_2S$	34.9
2	$-C(C_2H_5)HCOOH$	96.4	139–140	$C_{17}H_5NO_2S$	30.7
12	$-CH(COOC_2H_5)_2$	78.2	132–134	$C_{20}H_{19}NO_4S$	8.1
3	$-C(CH_3)_2COOH$	57.7	150–151	$C_{17}H_{15}NO_2S$	25.1
26	$-CH_2CH_2COOH$	70.2	148–150	$C_{15}H_{13}NO_2S$	52.8
9	$-CH_2COOH$	75	178–179	$C_{15}H_{11}NO_2S$	57.2

[a] All compounds were analyzed for C, H, and N.

Table III. 3-Methyl-2-phenyl-5-benzothiazolineacetic Acid and Its Methyl Ester



Compd no.	R	Yield, %	Mp, °C	Formula[a]	Antiinflam act. (% inhibition of edema) (100 mg/kg po)
28	CH_3	82.6	88–90	$C_{17}H_{17}NO_2S$	21.0
29	H	95.0	129–130	$C_{16}H_{15}NO_2S$	29.7

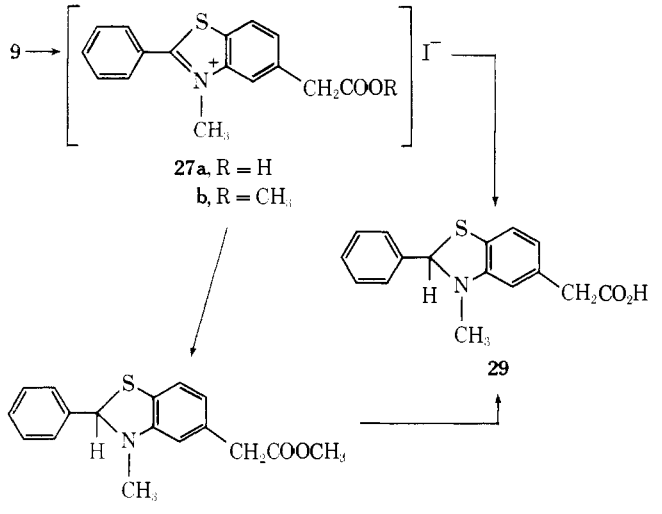
[a] All compounds were analyzed for C, H, and N.

Table IV. Inhibitory Effects of 2-Phenyl-5-benzothiazoleacetic Acid (**9**) and 2-Phenyl-5-benzothiazole-α-methylacetic Acid (**1a**) on the Swelling of the Rat Hind Paw Induced by Carrageenin

Compd no.	Group	Dose, mg/kg po	Swelling, %	Inhibition, %
	Control		75.6 ± 4.44[a]	
1a	2-Phenyl-5-benzothiazole-α-methylacetic acid	50	45.2 ± 2.95	40.2
		100	39.2 ± 2.54	48.2
		200	29.3 ± 2.60	61.2
9	2-Phenyl-5-benzothiazoleacetic acid	50	55.2 ± 2.00	27.0
		100	39.8 ± 1.92	47.4
		200	30.2 ± 2.54	60.1

[a] Mean ± S.E.

Scheme IV. A Synthetic Route to 3-Methyl-2-phenyl-5-benzothiazolineacetic Acid (**29**) and Its Methyl Acetate 28



Therefore, judging from the three criteria, **1a** and **29** could be suitable for further research as possible low toxicity, antiinflammatory, and/or analgesic drugs.

Experimental Section

Melting points were determined on a Mitamura Riken melting point apparatus and are corrected. The ir (KBr) and nmr ($CDCl_3$ or DMSO-d_6) spectra of all the new compounds were consistent with their structures. Where analysis is indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of their theoretical values.

Ethyl α-(2-Phenyl-5-benzothiazolyl)-α-cyanoacetate (7). Into a mixture of 2-phenyl-5-benzothiazoleacetonitrile[1] (4, 1.31 g, 0.005 mol) and ethyl carbonate (excess), NaOEt [prepared from Na (0.14 g) and absolute EtOH] was added dropwise with stirring. The reaction mixture, after removal of solvent under reduced pressure at 80–90°, was poured into ice-H_2O. The resulting solution was extracted with ether and the ethereal layer was then washed with 10% aqueous NaOH. The alkaline extracts were acidified (AcOH) to pH 5 to give a white solid. Recrystallization from EtOH gave pure 7 (1.42 g, 84.1%), mp 118–119°. *Anal.* ($C_{18}H_{14}N_2O_2S$) C, H, N.

Ethyl α-(2-Phenyl-5-benzothiazolyl)-α-cyanopropionate (8). Into sodium isopropoxide [prepared from Na (0.1 g) and *i*-PrOH (2.5 ml)] was added dropwise with stirring compound 7 (1.3 g,

Table V. Analgesic Effects of 3-Methyl-2-phenyl-5-benzothiazolineacetic Acid and Analogs of 2-Phenyl-5-benzothiazoleacetic Acid on Acetic Acid Stretching in Mice by Koster's Method

Compd no.	Drugs	ED_{50}, mg/kg[a]
1a	2-Phenyl-5-benzothiazole-α-methylacetic acid	95.0 (166.3–54.3)
29	3-Methyl-2-phenyl-5-benzothiazolineacetic acid	75.0 (127.5–44.1)
9	2-Phenyl-5-benzothiazole-acetic acid	145.0 (216.0–104.2)
	Phenylbutazone	160.0 (232.0–110.3)
	Aminopyrine	86.0 (126.4–58.5)

[a] 95% confidence limits.

0.004 mol) dissolved in absolute *i*-PrOH. MeI (0.95 g) was then added dropwise and, after 10 min, more MeI (0.95 g) was added. After refluxing for 20 min, the mixture was poured into ice-H_2O and extracted with Et_2O. The ether layer was washed with aqueous $NaHCO_3$, H_2O in turn, and dried over Na_2SO_4. Removal of the Et_2O *in vacuo* gave a solid which was recrystallized (EtOH) to give 8 (1.1 g, 82.1%), mp 49–51°. *Anal.* ($C_{19}H_{16}N_2O_2S$) C, H, N.

α-(2-Phenyl-5-benzothiazolyl)-α-methylacetonitrile (5). Method A. 8 (1.32 g, 0.004 mol) dissolved in 10% KOH-MeOH solution (10 ml) was allowed to stand for 3 hr at room temperature and then poured into H_2O (7 ml). The solution was neutralized (6 *N* HCl) to pH 7, and the deposited solid was collected and recrystallized (EtOH) to give **5** (0.98 g, 94.5%), mp 108–109°. *Anal.* ($C_{16}H_{12}N_2S$) C, H, N.

Method B. $NaNH_2$ (0.4 g, 0.01 mol) in dry C_6H_6 (5 ml) was added to **4** (2.5 g, 0.01 mol) in dry C_6H_6 (10 ml) and the mixture was heated at reflux for 3 hr with stirring. The reaction mixture was then transferred into an autocalve and MeI (2.13 g, 0.015 mol) was added. The mixture was heated at about 60° with shaking for 4 hr. After the addition of H_2O to the reaction mixture, the benzene layer was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo* to give a solid. It was recrystallized (petroleum ether, 35–80°) twice to give **5** (0.98 g, 37.1%), mp 108–109°. *Anal.* ($C_{16}H_{12}N_2S$) C, H, N.

α-(2-Phenyl-5-benzothiazolyl)-α-methylacetamide (6). 5 (2.64 g, 0.01 mol) in concentrated HCl (15 ml) was stirred at 25–30° for 1 hr and then poured into ice-H_2O. The deposited solid was collected, washed (10% aqueous $NaHCO_3$, H_2O in turn), and recrystallized (Me_2CO-$CHCl_3$) to give **6** (2.36 g, 88.1%), mp 191.5–192°. *Anal.* ($C_{16}H_{14}N_2OS$) C, H, N.

Ethyl 2-Phenyl-5-benzothiazolemalonate (12). Into a mixture of **11** (51.3 g, 0.173 mol) and ethyl carbonate (70 ml) was dropwise added NaOEt [prepared from Na (3.7 g) and 70 ml of EtOH], with stirring at 100°, after which time EtOH and ethyl carbonate were removed by distillation. The residue was allowed to cool and a mixture of AcOH (12 ml) and H_2O (50 ml) was poured into the reaction mixture with stirring to give a white solid, which was recrystallized (EtOH) to give **12** (50 g) (Table II).

Hydrolysis of 12. A mixture of **12** (1.23 g, 0.0036 mol) and NaOEt [prepared from Na (0.1 g) and EtOH (10 ml)] was stirred at room temperature for 1 hr. The mixture was then poured into ice-H_2O and acidified (2 *N* HCl) to pH 4, and the precipitate was collected, washed (H_2O), and recrystallized (dioxane-C_6H_6) to give **9** (0.9 g, 92.8%), mp 178–179°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N.

Ethyl α-(2-Phenyl-5-benzothiazolyl)butyrate (14b). Into a mixture of **11** (5 g, 0.017 mol), NaH (65% in liquid parrafin, 0.73 g, 0.02 mol), and anhydrous monoglyme (50 ml), excess EtI was added dropwise and the mixture was heated at 55° for 2 hr. The mixture was poured onto ice to give a solid which was recrystallized (ether-petroleum ether, bp 30–70°) to give **14b** (4.06 g, 79.0%), mp 55–60°. *Anal.* ($C_{19}H_{19}NO_2S$) C, H, N.

2-Phenyl-5-benzothiazole-α-methylacetic Acid (1a). Route A. **6** (2.82 g, 0.01 mol) in concentrated HCl (15 ml) was heated at reflux for 1 hr. The reaction mixture was poured into ice-H_2O and the deposited solid was collected, washed (H_2O), and recrystallized (C_6H_6) to give **1a** (2.58 g, 92.1%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

Route B. 5 (0.95 g, 0.0028 mol) dissolved in a mixture of dioxane (15 ml) and concentrated HCl (15 ml) was heated at reflux for 4 hr. The mixture was evaporated *in vacuo*, diluted (H_2O), neutralized (aqueous $NaHCO_3$) to pH 4, extracted ($CHCl_3$), washed (H_2O), and dried (Na_2SO_4). The solvent was evaporated *in vacuo*, and the resulting residue was recrystallized ($CHCl_3$-ligroine) to give **1a** (0.51 g, 58.0%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

Route C. Into NaOEt [prepared from EtOH (26 ml) and Na (0.6 g, 0.026 mol)], **12** (8.6 g, 0.023 mol) was added. Excess MeI (7 ml) was then introduced and the mixture was refluxed for 2 hr. Evaporation *in vacuo* gave an oily product **13a**, which was heated at reflux in a mixture of NaOH (4 g), H_2O (30 ml), and EtOH (30 ml) for 1 hr. After evaporation of EtOH *in vacuo*, neutralization (2 *N* HCl) gave a solid. It was collected and recrystallized ($CHCl_3$-ligroine) to give **1a** (4.7 g, 71.3%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

Route D. Into a mixture of ethyl 2-phenyl-5-benzothiazoleacetate (**11**, 5.94 g, 0.02 mol), NaH (65% pure, liquid paraffin, 0.9 g, 0.024 mol), and anhydrous monoglyme (50 ml), excess MeI was added and heated at 50–53° with stirring for 3 hr. The mixture was poured onto ice to give an oily product which was extracted (Et_2O) and dried (Na_2SO_4), followed by evaporation *in vacuo* to give a solid. Recrystallization (EtOH) gave ethyl α-(2-phenyl-5-benzothiazolyl)propionate (**14a**, 1.56 g) (Table II).

14a (1.24 g, 0.04 mol) was heated at reflux in 10% aqueous NaOH for 1.5 hr, followed by acidification (AcOH) to pH 5 to give a white solid. It was collected, washed (H_2O), and recrystallized ($CHCl_3$-ligroine) to give **1a** (1.08 g, 95.6%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

Route F. Into a mixture of absolute THF (10 ml) and diisopropylamine (4 g, 0.04 mol), butyllithium in hexane (25.6 ml, 0.04 mol, 1.0 g of BuLi/10 ml of hexane) was added dropwise with stirring at 0–5° under nitrogen atmosphere. After which time the temperature was kept at 0° and **9** (5.58 g, 0.02 mol) in absolute THF (15 ml) was dropwise added and stirring was continued for a further 30 min at 0°. Excess MeI was then added into the resulting mixture and the reaction mixture was stirred at room temperature for 2 hr to give a white solid **10** (2.7 g). **10** (1.45 g, 0.005 mol) was dissolved in H_2O (5 ml), followed by acidification (AcOH) to give a solid. Recrystallization ($CHCl_3$-ligroine) gave **1a** (1.38 g, 97.2%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

2-Phenyl-5-benzothiazole-α-ethylacetic Acid (2). Route C. Into NaOEt [prepared from EtOH (26 ml) and Na (0.6 g, 0.026 mol)] **12** (8.6 g, 0.023 mol) was added. Excess EtI (8 ml) was then added dropwise to the mixture and the reaction mixture was refluxed for 2 hr. Evaporation *in vacuo* gave an oily product (**13b**), which was heated at reflux in a mixture of NaOH (4 g), H_2O (30 ml), and EtOH (30 ml) for 1 hr. After evaporation of EtOH *in vacuo*, neutralization (2 *N* HCl) gave a solid which was collected and recrystallized (AcOEt) to give **2** (4.96 g, 75.4%), mp 139–140°. *Anal.* ($C_{17}H_{15}NO_2S$) C, H, N.

Route D. 14b (3.25 g, 0.01 mol) was heated at reflux in 10% aqueous NaOH for 1.5 hr, followed by acidification (AcOH) to pH 4 to yield a white solid. This was collected, washed (H_2O), and recrystallized (AcOEt) to give **2** (2.86 g) (Table II).

α-(2-Phenyl-5-benzothiazolyl)-α-methylpropionic Acid (3). Route E. **11** (1.0 g, 0.0034 mol) was dissolved in absolute monoglyme (15 ml). Into the stirred mixture, NaH (65% pure, 0.6 g, 0.017 mol) and then excess MeI were added. The mixture was heated at reflux for 1 hr, followed by pouring onto ice to give an oily product (**15**). The oil was extracted with Et_2O and dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was heated at reflux in 10% aqueous NaOH for 1.5 hr, followed by acidification (HCl) to give **3** (0.58 g) (Table II).

Ethyl α-(4-Chlorophenyl)-α-cyanoacetate (17). Into a mixture of *p*-chlorophenylacetonitrile (**16**, 400 g, 2.66 mol) and ethyl car-

Table VI. Oral LD_{50} Values in Mice

	Compd	LD_{50}, mg/kg[a]
1a	2-Phenyl-5-benzothiazole-α-methylacetic acid	1500 (1695–1327)
29	3-Methyl-2-phenyl-5-benzothiazolineacetic acid	2900 (3451–2437)
26	2-Phenyl-5-benzothiazolepropionic acid	2700 (3240–2250)
9	2-Phenyl-5-benzothiazoleacetic acid	1365 (1406–1050)

[a] 95% confidence limits.

bonate (3000 ml), sodium ethoxide [prepared from Na (60 g, 2.66 mol) and absolute EtOH (1440 ml)] was added and the reaction mixture was kept at 80–90° under reduced pressure using an aspirator for 3.5 hr. The mixture was poured into ice–H_2O (10 l.) and acidified (AcOH) to pH 5. The oily product was separated and the aqueous layer was shaken with C_6H_6. The C_6H_6 solution and previous oily product was combined and extracted with 10% aqueous NaOH solution. The alkaline layer was acidified (AcOH) to pH 5 and the organic layer was separated. The aqueous layer was extracted (C_6H_6) and the benzene solution was again combined with the previous organic layer. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was distilled under reduced pressure to yield **17** (457 g, 77.0%), bp 144–148° (1.0–1.5 mm). *Anal.* ($C_{11}H_{10}ClNO_2$) C, H, N.

α-(4-Chlorophenyl)-α-methylacetonitrile (19). A mixture of Na (39.6 g, 1.72 mol) and *i*-PrOH (660 ml) was heated at reflux for 30 min and then cooled to room temperature. Into the reaction, a mixture of **17** (352 g, 1.57 mol) and MeI (387 g, 2.53 mol) in *i*-PrOH (480 ml) was added with stirring. After 10 min, MeI (387 g, 2.53 mol) was again added and the mixture was heated at reflux for 15 min. The reaction mixture was poured into H_2O (10 l.), followed by extraction into C_6H_6 (6 l.). After drying (Na_2SO_4), the solvent was evaporated *in vacuo* and the residue was added into a mixture of EtOH (1750 ml) and KOH (212 g) and the mixture was allowed to stand at room temperature with stirring for 3 hr. K_2CO_3 deposited was filtered out. The filtrate was neutralized (concentrated HCl) to pH 7, followed by concentration *in vacuo* after drying (Na_2SO_4). The concentrate was distilled under reduced pressure to yield **19** (210 g, 80.5%), bp 84–86° (0.45 mm). *Anal.* (C_9H_8ClN) C, H, N.

α-(4-Chloro-3-nitrophenyl)-α-methylacetonitrile (20). Into **19** (260 g, 1.57 mol) fuming HNO_3 (*d* 1.52, 1240 g, 19.7 mol) was added dropwise with vigorous stirring for 3.5 hr while the temperature was kept below 5°. After the complete addition of HNO_3, stirring was continued for 3.5 hr at room temperature. The mixture was poured into ice–H_2O (10 l.) to give a solid, which was collected, washed (H_2O), and recrystallized (ether) to give **20** (235 g, 73.0%), mp 34–35° *Anal.* ($C_9H_7ClN_2O_2$) C, H, N.

α-(4-Chloro-3-nitrophenyl)propionic Acid (21). 20 (100 g, 0.6 mol) was heated at reflux in concentrated HCl (1.5 l.) for 13 hr and then for 12 hr more after an addition of 1 l. of concentrated HCl. The mixture was poured into ice–H_2O (10 l.) to give a crystalline solid which was collected, washed (H_2O), and recrystallized (ligroine–C_6H_6) to give **21** (104 g, 95.9%), mp 82.5–83.5°. *Anal.* ($C_9H_8ClNO_4$) C, H, N.

3-Benzoylamino-4-benzoylthiophenyl-α-methylacetic Acid (22). 21 (40 g, 0.174 mol) was dissolved in a mixture of NaOH (7 g) and H_2O (130 ml). Into the resulting mixture was added dropwise $Na_2S·9H_2O$ (104 g, 0.433 mol) in H_2O (170 ml) and the reaction mixture was heated at reflux for 10 hr. After which time the reaction mixture was chilled to below 5° and benzoyl chloride (53.0 g, 0.377 mol) was added with stirring. After the addition of benzoyl chloride, stirring was continued for 5.5 hr at room temperature. The reaction mixture was allowed to stand in refrigerator overnight; the precipitate was collected and suspended in H_2O (200 ml). The suspension was acidified (AcOH) and the deposited solid was collected, washed (H_2O), and recrystallized (*n*-PrOH) to give **22** (43.1 g, 61.0%), mp 158–159°. *Anal.* ($C_{23}H_{19}NO_4S$) C, H, N.

Route G. 22 (2.0 g, 0.005 mol) was dissolved in a mixture of NaOH (0.59 g, 0.014 mol), H_2O (1.7 ml), and MeOH (17 ml). The resulting mixture was allowed to stand overnight at room temperature and acidified (2 *N* HCl) to pH 2–3. The precipitate was collected, washed (hot water), and recrystallized ($CHCl_3$–ligroine) to give **1a** (1.0 g, 72.0%), mp 142–143°. *Anal.* ($C_{16}H_{13}NO_2S$) C, H, N.

Bis[2-amino-4-(1-carboxy)ethylphenyl] Disulfide (23). 21 (40 g, 0.18 mol) was dissolved in H_2O (130 ml) containing NaOH (8.0 g, 0.2 mol) and into the mixture $Na_2S·9H_2O$ (108 g, 0.45 mol) in H_2O was dropwise added, followed by heating at reflux for 10 hr. The mixture was cooled to 5°, acidified (AcOH) to pH 6.5, and filtered with charcoal. The filtrate was acidified (AcOH) to pH 4, followed by extraction with ether. The ethereal layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a crude solid which was recrystallized (dioxane–ligroine) to give **23** (7.0 g, 88.5%), mp 167–168°. *Anal.* ($C_{18}H_{20}N_2O_4S_2$) C, H, N.

General Method for 2-Substituted 5-Benzothiazole-α-methylacetic Acids (1a–j). A mixture of **23** (0.002 mol), the corresponding aldehyde (0.004 mol), and pyridine (5 ml) was heated at reflux for 4 hr. The mixture was poured onto ice and concentrated HCl (15 ml) to yield a solid which was collected, washed (H_2O), and recrystallized from appropriate solvents to give the product in a moderate yield as shown in Table I.

Isopropyl α-(2-Phenyl-5-benzothiazolyl)propionate (30). **1a** (2.83 g, 0.01 mol) was heated at reflux in the presence of a few drops of concentrated H_2SO_4 in *i*-PrOH (15 ml). The mixture was treated as above and recrystallized from MeOH to give **30** (2.94 g) (Table II).

2-Phenyl-5-benzothiazolepropionitrile (25). A mixture of 2-phenyl-5-(2-chloroethyl)benzothiazole[1] (**24**, 55 g, 0.02 mol), KCN (1.6 g, 0.025 mol), and DMSO (20 ml) was heated at 105–110° for 2 hr. Ice was added into the mixture to give a solid which was collected, washed (H_2O), and recrystallized ($CHCl_3$) to give **24** (4.2 g, 86.8%), mp 144–145°. *Anal.* ($C_{16}H_{12}N_2S$) C, H, N.

2-Phenyl-5-benzothiazolepropionic Acid (26). 25 (2.64 g, 0.01 mol) was heated at reflux in concentrated HCl (20 ml) for 2.5 hr, and the mixture was poured into ice-H_2O to give a solid. This was collected, washed (H_2O), and recrystallized ($CHCl_3$) to give **26** (1.99 g) (Table II).

5-Carboxymethyl-3-methyl-2-phenylbenzothiazolium Iodide (27a). A mixture of **9** (2.69 g, 0.01 mol) and MeI (40 g, 0.26 mol) was heated at 100° in an autoclave for 3 hr. A crystalline solid precipitated on cooling. It was recrystallized (MeOH) to give **27a** (1.88 g, 45.7%), mp ~200° dec. *Anal.* ($C_{16}H_{14}INO_2S$) C, H, N.

Methyl 3-Methyl-2-phenyl-5-benzothiazolineacetate (28). A mixture of **9** (2.69 g, 0.01 mol), MeOH (60 ml), and excess MeI was heated at 100° in the presence of a few drops of concentrated H_2SO_4 in an autoclave for 3 hr. Upon cooling, a solid (**27b**) was obtained which was collected and suspended in MeOH (30 ml). Into the stirring suspension, excess $NaBH_4$ was added and then the mixture was heated at reflux for 15 min. After evaporation *in vacuo*, an excess of water was added, and the crystals precipitated were collected and recrystallized (MeOH) to give **28** (2.47 g) (Table III).

3-Methyl-2-phenyl-5-benzothiazolineacetic Acid (29). Method A. 27a (410 mg, 0.001 mol) was suspended in a mixture of absolute Et_2O (10 ml) and dioxane (5 ml), and into the stirred suspension excess $NaBH_4$ was added followed by heating at 40° on an oil bath for 20 min. After evaporation *in vacuo*, an excess of water was added, and the precipitated crystals were collected and recrystallized (C_6H_6) to give **29** (180 mg, 63.1%), mp 129–130°. *Anal.* ($C_{16}H_{15}NO_2S$) C, H, N.

Method B. 28 (2 g, 0.006 mol) in a mixture of KOH (1.5 g) and MeOH (50 ml) was heated at reflux for 2 hr. After evaporation of the solvent *in vacuo*, the resulting residue was suspended in H_2O, and the suspension acidified (AcOH) to give a white solid. It was recrystallized (C_6H_6) to give **29** (1.8 g) (Table III).

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