vea.. that the aromatic substituent effects on MAO inhibition are essentially the same in various sets of inhibitors against enzyme from the same origin. It is also suggested that the inhibition against enzymes from various origins involves similar physicochemical mechanism. Although the electronic effect of substituents does not seem to contribute significantly in some series of inhibitors, the most probable role of the aromatic moiety would be to interact as an electron acceptor with the noncatalytic electron-rich site of the enzyme surface. These findings would not have been uncovered unless the structure-activity relationships were described in the form of equations so that the various features among them could be compared quantitatively. The present work also supports the use of E_S parameters in explaining intermolecular steric interactions in biomedical systems developed by Hansch and Kutter.[10,23] It is hoped that the role of side chain structure in the mechanism of MAO inhibitors could be delineated in physicochemical as well as quantitative terms so that a comprehensive structure-activity picture for MAO inhibitors can be drawn.

Acknowledgments. The author expresses his sincere thanks to Dr. Takashi Ban for his cooperation and Professor Minoru Nakajima for his support during the course of this work.

References

(1) C. Kaiser and C. L. Zirkle, "Medicinal Chemistry," 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 1483.
(2) B. Belleau and J. Moran, *Ann. N. Y. Acad. Sci.*, **107**, 822 (1963).
(3) C. L. Zirkle and C. Kaiser, "Psychopharmacological Agents," M. Gordon, Ed., Vol. 1, Academic Press, New York, N. Y., 1964, p 445.
(4) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *J. Med. Pharm. Chem.*, 5, 1265 (1962).
(5) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).
(6) C. Hansch, "Drug Design," Vol. I, E. J. Ariëns, Ed., Academic Press, New York, N. Y., 1971, p 271.
(7) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).
(8) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 551 (1971).
(9) M. S. Tute, *Advan. Drug Res.*, **6**, 1 (1971).
(10) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
(11) C. Hansch, E. J. Lien, and F. Helmer, *Arch. Biochem. Biophys.*, **128**, 319 (1968).
(12) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957).
(13) B. M. Bloom, *Ann. N. Y. Acad. Sci.*, **107**, 878 (1963).
(14) R. A. Abramovitch and I. D. Spencer, *Advan. Heterocycl. Chem.*, **3**, 187 (1964).
(15) C. Hansch, E. W. Deutsch, and N. R. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965).
(16) T. Fujita, *Advan. Chem. Ser.*, **No. 114**, 1 (1972).
(17) B. T. Ho, *J. Pharm. Sci.*, **61**, 821 (1972).
(18) P. R. Wells, "Linear Free Energy Relationships," Academic Press, London, 1968, p 24.
(19) E. A. Zeller, *Ann. N. Y. Acad. Sci.*, **107**, 811 (1963).
(20) T. Fujita, C. Takayama, and M. Nakajima, *J. Org. Chem.*, **38**, 1623 (1973).
(21) A. H. Neims, D. C. DeLuca, and L. Hellerman, *Biochemistry*, **5**, 203 (1966).
(22) J. A. Mazrimas, P. S. Song, L. L. Ingraham, and R. D. Draper, *Arch. Biochem. Biophys.*, **100**, 409 (1963).
(23) E. Kutter and C. Hansch, *ibid.*, **135**, 126 (1969).

A New Nonsteroidal Antiinflammatory Agent. 2-Substituted 5- or 6-Benzothiazoleacetic Acids and Their Derivatives

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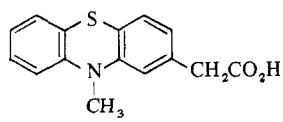
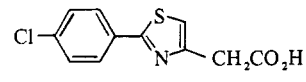
Synthesis of 34 2-substituted benzothiazole compounds with an acetic acid function at the 5 or 6 position was carried out and their antiinflammatory activity was investigated. It was found that the presence of an acetic acid function was important for antiinflammatory activity and also that 2-substituted 5-benzothiazoleacetic acids (**6**) were better than 2-substituted 6-benzothiazoleacetic acids (**7**) in antiinflammatory activity.

Many aromatic and heteroaromatic acetic acids have been reported[1-3] as nonsteroidal antiinflammatory agents. Among them, Messer, *et al.*,[4] recently reported on 10-methyl-2-phenothiazinylacetic acid (metiazinic acid, I) and Hepworth, *et al.*,[5] reported on 2-(4-chlorophenyl)thiazol-4-ylacetic acid (fenclozic acid, II), both of which contain nitrogen and sulfur atoms in their skeleton.

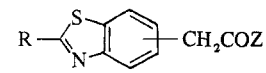


methiazinic acid (I)



fenclozic acid (II)

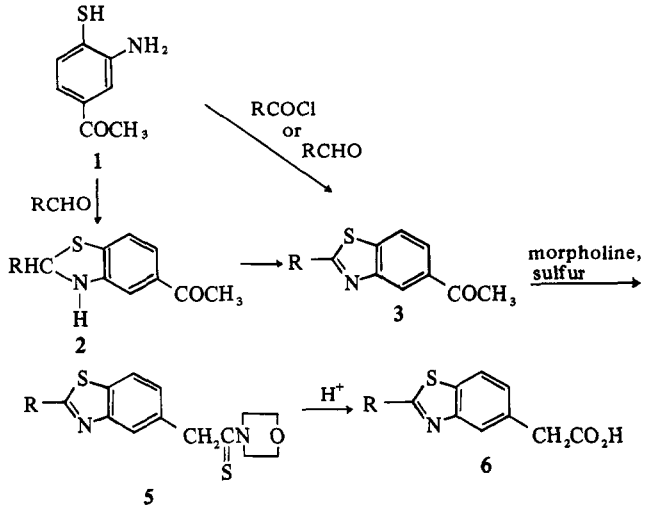
Little is known about the antiinflammatory activity of the benzothiazole ring system[6] and, moreover, a compound which has an acetic acid function in such a system has not yet been reported at all. Therefore, novel 2-substituted 5- or 6-benzothiazoleacetic acids (**6** and **7**) and their derivatives were synthesized and their antiinflammatory activities and LD_{50} values were examined.



R = phenyl, mono- or disubstituted phenyl, pyridyl, naphthyl, furyl, benzyl, phenetyl, styryl, and phenoxymethyl; Z = -OH, -OEt, $-NH_2$, or -NHOH

Chemistry. 3-Amino-4-mercaptoacetophenone (**1**), which was obtained by the reaction of 4-chloro-3-nitroacetophenone with sodium sulfide nonahydrate in water, was condensed with arylcarboxylic acid chlorides or aldehydes to yield the 2-substituted 5-acetylbenzothiazoles (**3**). 5-Acetylbenzothiazole derivatives **3** were allowed to react with sulfur and morpholine in a Willgerodt-Kindler reaction and the morpholides **5** were isolated as intermediates. These morpholides **5** were hydrolyzed with concentrated hydrochloric acid or 10% aqueous sodium hydroxide solution to yield the 2-substituted 5-benzothiazoleacetic acids (**6**). In the ring closure with aryl aldehydes, benzothiazoline derivatives **2** were often obtained, but these (**2**) were easily oxidized to a benzothiazole **3** by refluxing in the presence of

Scheme I. General Synthetic Route to 2-Substituted 5-Benzothiazoleacetic Acids (6) Using the Willgerodt-Kindler Reaction

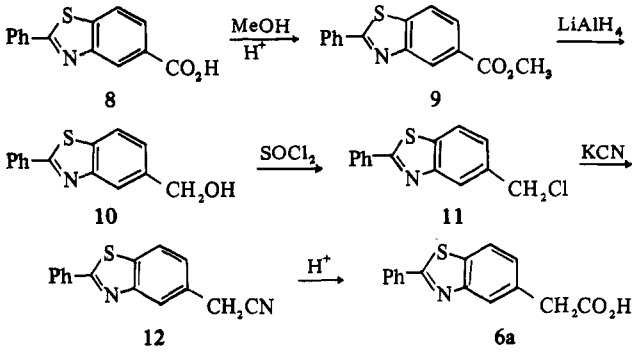


R = phenyl, mono- or disubstituted phenyl, pyridyl, naphthyl, furyl, benzyl, phenetyl, styryl, and phenoxymethyl, etc.

a small amount of $FeCl_3$ in EtOH (Scheme I, Table I).

The 2-substituted 6-benzothiazoleacetic acids (**7**) were synthesized, using the Willgerodt-Kindler reaction[7] as above, from 2-substituted 6-acetylbenzothiazoles (**4**), prepared by the method of Burger, *et al.*[8] (Table II). By another route (Scheme II), 2-phenyl-5-benzothiazoleacetic acid (**6a**) was synthesized as follows. 2-Phenyl-5-benzothiazolemethanol (**10**) was prepared by the esterification of 2-phenyl-5-benzothiazolecarboxylic acid[9] (**8**), followed by reduction with lithium aluminum hydride. Chlorination and cyanation of the hydroxymethyl derivative **10** gave 2-phenyl-5-benzothiazoleacetic acid (**6a**) after hydrolysis. The melting point and nuclear magnetic resonance and infrared data of **6a** obtained by this route agreed with that of the product obtained by

Scheme II. Another Synthetic Route to 2-Phenyl-5-benzothiazoleacetic Acid (6a)

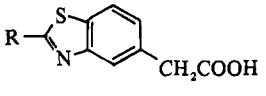


the Willgerodt-Kindler reaction on 2-phenyl-5-acetylbenzothiazole (**3**).

2-Phenyl-5-vinylbenzothiazole (**16**) was prepared in four steps from 2-phenyl-5-benzothiazoleacetonitrile (**12**), described above, and the benzothiazoleacetic acid (**6a**) was prepared by treating the vinyl derivative **16** with sulfur and morpholine (Scheme III). The physical data of **6a** obtained by this third route were identical with the data of **6a** obtained by Schemes I and II.

The 2-phenyl-5- and -6-benzothiazoleacetamides (**18a** and **18b**, respectively) were prepared by heating 2-phenyl-5- or -6-acetylbenzothiazole (**3** or **6**) or 2-phenyl-5-vinylbenzothiazole (**16**) with ammonium polysulfide solution (yellow) in a sealed tube. Alternatively, the acetamides **18a,b** were prepared by amination of the corresponding ethyl 2-phenylbenzothiazoleacetate (**17a,b**). The acetamide **18a** was also prepared by hydrolysis of 2-phenyl-5-benzothiazoleacetonitrile (**12**) (Scheme IV, Table III). The physical, spectral, and analytical data of each acetamide, obtained by the different routes, were identical. 2-Phenyl-5-benzothiazoleacetohydroxamic acid (**19**) was obtained from the reaction of ethyl 2-phenyl-5-benzothiazoleacetate (**17a**) with hydroxylamine.

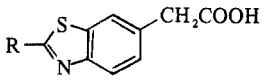
Table I. 2-Substituted 5-Benzothiazoleacetic Acids



Compd no.	R	Yield, %	Mp, °C	Crystn solvent	Formula[a]	Antiinflammatory activity (inhibition of edema, %) po (100 mg/kg)	ip (30 mg/kg)	LD_{50}, mg/kg
6a	C_6H_6	62.9	178–179	*i*-PrOH–H_2O	$C_{15}H_{11}NO_2S$	46.7		800 ip, 1365 po
6b	2-HOC_6H_4	52.2	215–216	Dioxane–C_6H_6	$C_{15}H_{11}NO_3S$	44.5	20.8	450 ip
6c	3-HOC_6H_4	45.6	211–212	Dioxane–C_6H_6	$C_{15}H_{11}NO_3S$	16.9		
6d	4-HOC_6H_4	47.1	231–233	Dioxane–C_6H_6	$C_{15}H_{11}NO_3S$	22.1		
6e	4-$CH_3OC_6H_4$	44.9	182–184	*i*-PrOH–H_2O	$C_{16}H_{13}NO_3S$	17.7		
6f	3,4-$(HO)_2C_6H_3$	40.7	256–268	Dioxane–C_6H_6	$C_{15}H_{11}NO_4S$	27.5		
6g	3,4-$(CH_3O)_2C_6H_3$	49.6	206–208	Dioxane–*i*-PrOH	$C_{17}H_{15}NO_4S$	18.0		
6h	4-ClC_6H_4	45.8	213–215	*i*-PrOH–H_2O	$C_{15}H_{10}ClNO_2S$	35.3		100 ip
6i	3-ClC_6H_4	47.0	164–166	*i*-PrOH–H_2O	$C_{15}H_{10}ClNO_2S$	25.0		
6j	4-$(CH_3)_2NC_6H_4$	43.0	230–233	Dioxane–C_6H_6	$C_{17}H_{16}N_2O_2S$	52.0	34.5	500 ip, 900 po
6k	4-isoPrC_6H_4	46.7	145–148	*i*-PrOH–H_2O	$C_{18}H_{17}NO_2S$	20.2	16.5	400 ip
6l	2-Pyridyl	35.2	194–196	Dioxane–C_6H_6	$C_{14}H_{10}N_2O_2S$	20.5	50.0	435 ip
6m	2-Furyl	64.5	175–176	Dioxane–C_6H_6	$C_{13}H_9NO_3S$	43.0		
6n	1-Naphthyl	39.6	145–146	Dioxane	$C_{19}H_{13}NO_2S$		38.0	
6o	$C_6H_5CH{=}CH$	44.7	168–170	Dioxane	$C_{17}H_{13}NO_2S$	-0.9		
6p	$C_6H_5CH_2$	43.8	139–140	Dixaone–C_6H_6	$C_{16}H_{12}NO_2S$	1.0		
6q	$C_6H_5OCH_2$	45.1	158–159	Dioxane–C_6H_6	$C_{16}H_{13}NO_3S$	16.6	26.5	
6r	$C_6H_5CH_2CH_2$	48.3	113–114	Dioxane–C_6H_6	$C_{17}H_{15}NO_2S$	17.8		
	Phenylbutazone					45.3	56.2	372

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

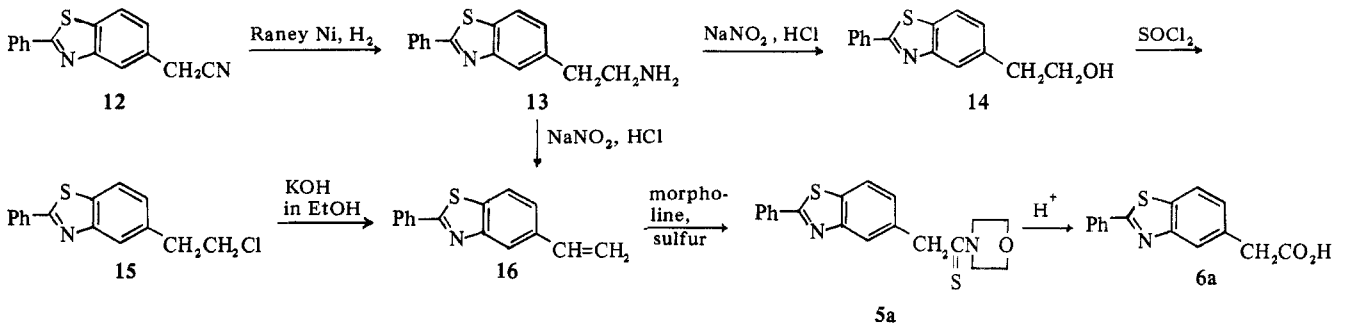
Table II. 2-Substituted 6-Benzothiazoleacetic Acids



Compd no.	R	Yield, %	Mp, °C	Crystn solvent	Formula[a]	Antiinflammatory activity (inhibition of edema, %) po (100 mg/kg)	Antiinflammatory activity (inhibition of edema, %) ip (30 mg/kg)	LD_{50}, mg/kg ip
7a	C_6H_5	58.8	173–175	Dioxane–C_6H_6	$C_{15}H_{11}NO_2S$	33.5		450
7b	4-HOC_6H_4	45.8	248–250	EtOH–H_2O	$C_{15}H_{11}NO_3S$	2.9		
7c	2-HOC_6H_4	48.1	206–207	EtOH–H_2O	$C_{15}H_{11}NO_3S$	0		
7d	4-$CH_3C_6H_4$	50.1	198–200	Dioxane–C_6H_6	$C_{16}H_{13}NO_2S$	3.5		
7e	4-*i*-PrC_6H_4	49.6	162–163	Dioxane–C_6H_6	$C_{18}H_{17}NO_2S$	34.5		400
7f	4-$(CH_3)_2NC_6H_4$	41.4	212–214	Dioxane	$C_{17}H_{16}N_2O_2S$	7.0		
7g	2-HO-3-$CH_3C_6H_4$	60.7	206–207	Dioxane	$C_{16}H_{13}NO_3S$	25.0		450
7h	3,4-$(CH_3O)_2C_6H_3$	49.3	177	Dioxane–C_6H_6	$C_{19}H_{15}NO_4S$	16.9		225
7i	4-$CH_3OC_6H_4$	40.5	151–153	EtOH–H_2O	$C_{16}H_{13}NO_3S$	0		

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

Scheme III. A Synthetic Route of 2-Phenyl-5-benzothiazoleacetic Acid (**6a**) from 2-Phenyl-5-vinylbenzothiazole (**16**) Using the Willgerodt–Kindler Reaction



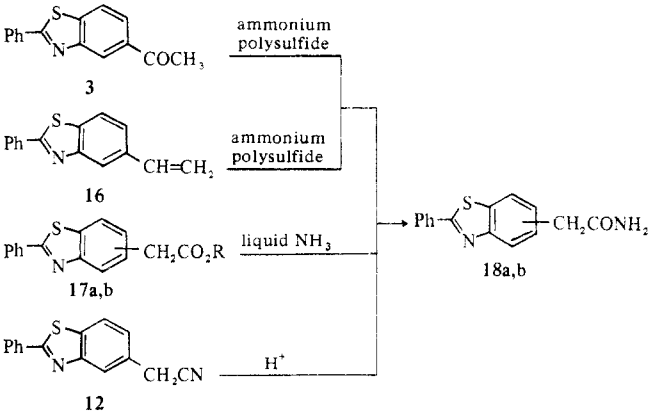
Pharmacology. Antiinflammatory activity was assessed by the inhibition of edema formation in the hind paw of the rat (Wistar strain male rat, body wt 150–180 g, five rats per group) in response to a subplantar injection of carrageenan. The experimental procedure followed that of Winter, *et al.*[10] Edema formation was measured 3 hr after oral or intraperitoneal administration of the test chemical as a CMC suspension (100 or 30 mg/kg, respectively). The response of drug-treated animals was compared with that of carrageenan alone, some receiving vehicle alone and others receiving phenylbutazone (100 or 30 mg/kg). LD_{50} values after 72 hr were determined by oral or intraperitoneal administration to groups of five ICR mice.

Discussion

2-Phenylbenzothiazole[11] (**20**), the parent skeletal compound, showed considerable antiinflammatory activity. Although introduction of a carboxylic acid function at the 5 position increased the activity only slightly, substitution of the acetic acid function markedly increased the activity to a level equal to or better than that of phenylbutazone. Introduction of the acetic acid function at the 6 position did not affect the activity relative to the 5-acetic acid (Tables II and IV).

Introduction of a hydroxyl group into the 2 position or a dimethylamino group into the 4 position of the phenyl group in **6a** gave compounds (**6b** and **6j**, respectively) with about the same or higher activity as **6a**, but these compounds had greater acute toxicity. Replacement of the phenyl group with the 2-furyl, 1-naphthyl, or 2-pyridyl groups gave compounds (**6m**, **6n**, and **6l**, respectively) with appreciable activity. Derivation of the acetic acid group to esters **17a** and **21**, amides **18a** and **18b**, or hydroxamic acid (**19**) was found to reduce the activity of the original compound **6a** to about one-half. This would indicate that the acetic acid function plays an important role for the retention of antiinflammatory activity.

Scheme IV. A Synthetic Route of 2-Phenyl-5- or -6-benzothiazoleacetamides (**18a,b**)

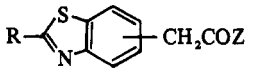


In general, activity of the 5-acetic acid analog was better than that of the 6-acetic acid analog. The introduction of a dimethylene or a methyleneoxy group between the benzothiazoleacetic acid skeleton and the phenyl group at the 2 position (**6r** and **6q**, respectively) lowered the activity relative to that of **6a** and that of a methylene or an ethylene group (**6p** and **6o**, respectively) did not affect the activity relative to that of **6a**.

Experimental Section

Melting points were determined on a Mitamura Riken melting point apparatus and are corrected. The ir (KBr) and nmr ($CDCl_3$,

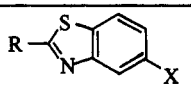
Table III. 2-Phenyl-5- or -6-benzothiazoleacetamides and 2-Substituted 5-Benzothiazoleacetate Esters



Compd no.	R	Z	5 or 6	Yield, %	Mp, °C	Crystn solvent	Formula[a]	Antiinflammatory activity (inhibition of edema, %) po (100 mg/kg)	Antiinflammatory activity (inhibition of edema, %) ip (30 mg/kg)	LD_{50}, mg/kg ip
18a	C_6H_5	NH_2	5	82.1	206-207	Dioxane-C_6H_6	$C_{15}H_{11}N_2OS$	23.6		
18b	C_6H_5	NH_2	6	80.6	229-230	Dioxane-C_6H_6	$C_{15}H_{12}N_2OS$	3.3		
17a	C_6H_5	OEt	5	92.4	89-90	EtOH	$C_{17}H_{15}NO_2S$	28.1	41.0	600
21	4-$CH_3OC_6H_4$	OEt	5	89.7	128-130	EtOH	$C_{18}H_{17}NO_3S$	24.1	30.5	1000
19	C_6H_5	NHOH	5	75.0	172-175	Dioxane-H_2O	$C_{15}H_{12}N_2O_2S$	17.8		

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

Table IV. 2,5-Disubstituted Benzothiazoles



Compd no.	R	X	Yield, %	Mp, °C	Crystn solvent	Formula[a]	Antiinflammatory activity (inhibition of edema, %) po (100 mg/kg)	Antiinflammatory activity (inhibition of edema, %) ip (30 mg/kg)	LD_{50}, mg/kg ip
24[b]	C_6H_5	H		114		$C_{13}H_9NS$	31.4		1800
25[c]	C_6H_5	COOH		273		$C_{14}H_{10}NO_2S$	35.0		
3a	C_6H_5	$COCH_3$	89.2	104-105	EtOH	$C_{15}H_{11}NOS$	0	36.5	1500
23	4-$H_2NCOC_6H_4$	$COCH_3$	74.2	237-240	Dioxane	$C_{16}H_{12}N_2O_2S$	36.7	35.5	1200

[a] All compounds were analyzed for C, H, and N. [b] Reference 12. [c] Reference 9.

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.

General Methods for Acetyl Compounds. A. Acetyl compounds **3b-m** were prepared from the appropriate aldehyde and 3-amino-4-mercaptoacetophenone (**1**) in pyridine. A mixture of **1** (0.05 mol) and aldehyde (0.05 mol) was heated at reflux in pyridine (50 ml) for 3 hr. After evaporation *in vacuo*, the solid (**2b-m**) deposited by addition of Et_2O (20 ml) was collected and suspended in EtOH (100 ml) containing a small amount of $FeCl_3$, and the mixture was heated at reflux with stirring for 2 hr. Cooling of the solution gave a solid which was recrystallized (EtOH) to give the product.

B. Acetyl compounds **4a-i** were prepared from the appropriate aldehyde and 4-amino-3-mercaptoacetophenone[8] in pyridine and worked up in the same manner as A.

C. Compounds **6n-r** were prepared from the appropriate acid chloride and **1** in *N,N*-dimethylaniline. A mixture of **1** (0.05 mol) and acid chloride (0.05 mol) in *N,N*-dimethylaniline (50 ml) was heated at 100° for 1 hr and then at 140° for a further 1 hr. The cooled solution was poured onto ice and concentrated HCl. The solid was collected, washed (H_2O), and recrystallized (EtOH) to give the product.

General Method for Acetic Acids (Table I, 6b-m, Table II, 7a-i). Acetyl compounds **3** and **4** (10 g), sulfur (1.6 g), and morpholine (20 ml) were heated at reflux for 20 hr. The excess solvent was evaporated *in vacuo* to dryness, and the residue was crystallized (EtOH) to give the morpholides. The morpholides were heated at reflux in 10% aqueous NaOH (100 ml) for 20 hr. The cooled solution was acidified (AcOH or dilute HCl), and the resulting solids were collected and recrystallized (C_6H_6-dioxane) to give the products.

3-Amino-4-mercaptoacetophenone (1). A solution of 4-chloro-3-nitroacetophenone[12] (100 g, 0.5 mol) and H_2O (1200 ml) containing $Na_2S \cdot 9H_2O$ (260 g, 1.08 mol) was heated at reflux for 40 hr. The reaction mixture was cooled to 5° and neutralized (AcOH), and the precipitate was recrystallized ($CHCl_3$) to give **1** (37.0 g, 44.4%), mp 67-70°. *Anal.* (C_8H_9NOS) C, H, N.

2-Phenyl-5-acetylbenzothiazole (3a). A mixture of **1** (8.5 g, 0.05 mol) and BzCl (7.2 g, 0.05 mol) in *N,N*-dimethylaniline (50 ml) was heated at 100° for 1 hr and then at 140° for a further 1 hr. The cooled solution was poured onto ice and concentrated HCl. The solid was collected, washed (H_2O), and recrystallized (EtOH) to give **3a** (9.5 g, 89.2%), mp 104-105°. *Anal.* ($C_{15}H_{11}NOS$) C, H, N.

2-(4-*N,N*-Dimethylaminophenyl)-5-acetylbenzothiazole (3j). A mixture of **1** (8.5 g, 0.05 mol) and *p*-(*N,N*-dimethylamino)benzaldehyde (7.6 g, 0.05 mol) was heated at reflux in pyridine (50 ml) for 3 hr. After evaporation *in vacuo*, the solid deposited by addition of Et_2O (20 ml) was collected and suspended in EtOH (100 ml) containing a small amount of $FeCl_3$, and the mixture was heated at reflux with stirring for 2 hr. Cooling of the solution gave a solid which was recrystallized (EtOH) to give **3j** (8.3 g, 66.5%), mp 190-191°. *Anal.* ($C_{17}H_{16}N_2OS$) C, H, N.

2-Phenyl-5-benzothiazoleacetic Acid (6a). Method a. A mixture of **3a** (10 g, 0.04 mol), sulfur (1.6 g, 0.05 mol), and morpholine (20 ml) was heated at reflux for 20 hr. The excess solvent was evaporated to dryness, and the residue was crystallized (EtOH) to give the morpholide (**5a**), mp 157-160°. **5a** was heated at reflux in 10% aqueous NaOH (100 ml) for 20 hr. The cooled solution was acidified (AcOH), and the resulting solid was collected and recrystallized (C_6H_6-dioxane) to give **6a** (6.7 g, 62.9%), mp 178-179°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N (Table I).

Method b. A mixture of 2-phenyl-5-vinylbenzothiazole (**16**, 2 g, 0.007 mol), sulfur (0.8 g, 0.025 mol), and morpholine (4 ml) was heated at reflux for 20 hr. The isolated morpholide was refluxed in concentrated HCl for 15 hr. The reaction mixture was poured into ice-H_2O, and the precipitate was collected and recrystallized (C_6H_6-dioxane) to give **6a** (1.5 g, 69.6%), mp 178-179°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N.

Method c. The nitrile (**12**, 0.6 g, 0.002 mol) in concentrated HCl (25 ml) was heated at reflux for 1 hr; dilution (H_2O) gave a solid (0.61 g, 94.5%), and this was recrystallized (C_6H_6-dioxane) to give **6a**, mp 178-179°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N.

2-(4-Carbamoylphenyl)-5-acetylbenzothiazole (23). A mixture of **1** (16.7 g, 0.1 mol) and *p*-cyanobenzoyl chloride (16.6 g, 0.1 mol) was heated at reflux in *N,N*-dimethylaniline (100 ml) for 2 hr. The reaction mixture was poured onto ice and concentrated HCl and the resulting precipitate was collected and recrystallized (dioxane) to give 2-(4-cyanophenyl)-5-acetylbenzothiazole (**22**, 20.1 g, 73.0%). Into a mixture of **22** (16.0 g, 0.06 mol) and Me_2CO (560 ml) containing 10% aqueous NaOH (160 ml), 30% H_2O_2 (20 ml) was added in small portions, and the solution was heated at reflux for 20 min. The reaction mixture was poured into ice-H_2O, and the precipitate was separated and recrystallized (dioxane) to give **23** (12.0 g, 74.2%), mp 237-240°. *Anal.* ($C_{16}H_{12}N_2O_2S$) C, H, N.

2-Phenyl-5-benzothiazolemethanol (10). This was prepared by reduction of methyl 2-phenyl-5-benzothiazolecarboxylate[9] (**9**) (5.0 g, 0.02 mol, mp 155-156°) with $LiAlH_4$ in THF and worked up in the usual way. The product was recrystallized [C_6H_6-petroleum ether (30-70°)] to give **10** (3.4 g, 72.6%), mp 105-106°. *Anal.* ($C_{14}H_{11}NOS$) C, H, N.

2-Phenyl-5-chloromethylbenzothiazole (11). This was prepared from **10** (2.2 g, 0.009 mol) by treatment with $SOCl_2$. Crystallization (C_6H_6) gave **11** (2.1 g, 88.7%), mp 153–154°. *Anal.* ($C_{14}H_{10}ClNS$) C, H, N.

2-Phenyl-5-benzothiazoleacetonitrile (12). Into a mixture of KCN (94.4 mg, 0.0014 mol), KI (20 mg, 0.0001 mol), H_2O (1.0 ml), and EtOH (10 ml) was added **11** (300 mg, 0.0012 mol), and the mixture was heated at reflux for 4 hr. Dilution (H_2O) gave a solid which was recrystallized (EtOH) to give **12** (230 mg, 79.5%), mp 131.5–132.5°. *Anal.* ($C_{15}H_{10}N_2S$) C, H, N.

2-Phenyl-5-aminoethylbenzothiazole (13). This was prepared by hydrogenation of **12** (10.0 g, 0.04 mol) with Raney nickel in liquid NH_3 and worked up in the usual way. The product was recrystallized (C_6H_6–dioxane) to give **13** (8.2 g, 80.7%), mp 98–100° *Anal.* ($C_{15}H_{14}N_2S$) C, H, N.

2-Phenyl-5-benzothiazoleethanol (14). A solution of **13** (25.4 g, 0.1 mol) in H_2O (100 ml) containing concentrated HCl (30 ml) was cooled to about 0° and treated dropwise over 1-hr period with a solution of $NaNO_2$ (7.0 g, 0.1 mol) in H_2O (5 ml). The product was extracted with $CHCl_3$, washed (H_2O), and dried (Na_2SO_4). After evaporation of the solvent *in vacuo*, the product was isolated with column chromatography on silica gel (silica gel 60, Merck; C_6H_6–AcOBu–AcOH, 16:4:1). The resulting product was crystallized (C_6H_6) to give **14** (0.8 g, 3.1%), mp 123–124°. *Anal.* ($C_{15}H_{13}NOS$) C, H, N.

2-Phenyl-5-(2-chloroethyl)benzothiazole (15). The above compound (**14**, 3 g, 0.012 mol) in excess $SOCl_2$ was heated at reflux for 1 hr. After evaporation of excess $SOCl_2$ *in vacuo*, addition of EtOH (1 ml) gave a solid. After washing with H_2O, 10% aqueous $NaHCO_3$, and H_2O in turn, crystallization (C_6H_6–dioxane) gave **15** (3.3 g, 93.3%), mp 98–99°. *Anal.* ($C_{15}H_{12}ClNS$) C, H, N.

2-Phenyl-5-vinylbenzothiazole (16). Method a. This was obtained as a main product on preparing **14.** Crystallization (EtOH–H_2O) gave **16** (12.5 g, 52.7%), mp 89–90°. *Anal.* ($C_{15}H_{11}NS$) C, H, N.

Method b. A mixture of **15** (0.45 g, 0.0016 mol) and KOH (0.32 g) in EtOH (20 ml) was heated at reflux for 2 hr. The reaction mixture was poured into ice–H_2O and the resulting precipitate was collected and recrystallized (EtOH–H_2O) to give **16** (0.30 g, 76.9%), mp 89–90°. *Anal.* ($C_{15}H_{11}NS$) C, H, N.

2-Phenyl-5-benzothiazoleacetamide (18a). Method a. A mixture of **3a** (2.53 g, 0.01 mol), ammonium polysulfide solution (yellow, 13 ml), and dioxane (10 ml) was heated in a sealed tube at 160° for 10 hr. Upon cooling the yellow solid that crystallized out was dissolved in MeOH with warming, and cooling of the solution crystallized the product. The solid was recrystallized (C_6H_6–dioxane) to give **18a** (2.2 g, 82.1%), mp 206–207°. *Anal.* ($C_{15}H_{11}N_2OS$) C, H, N (Table III).

Method b. The vinyl derivative **16** (3.0 g, 0.01 mol) and ammonium polysulfide solution (yellow, 15.5 ml) in dioxane (12 ml) were heated in a sealed tube at 155–156° for 10 hr. The pure product **18a** (2.9 g, 86.0%) was obtained in the same manner as method a. *Anal.* ($C_{15}H_{11}N_2OS$) C, H, N.

Method c. Ethyl 2-phenyl-5-benzothiazoleacetate (**17a**, 5.94 g, 0.02 mol) and EtOH (50 ml) were placed in an autoclave, cooled with Dry Ice–Me_2CO, and liquid NH_3 (10 ml) was added. The reaction mixture was heated at 85–90° for 15 hr. The solid was collected and recrystallized (C_6H_6–dioxane) to give **18a** (4.37 g, 81.4%). *Anal.* ($C_{15}H_{11}N_2OS$) C, H, N.

Method d. The nitrile **12** (25.0 g, 0.1 mol) in concentrated HCl was heated at 35–40° with stirring for 1 hr. The reaction mixture was poured onto ice and water. The solid was collected, washed (10% aqueous $NaHCO_3$ and water), and recrystallized (C_6H_6–dioxane) to give **18a** (22.8 g, 85.1%). *Anal.* ($C_{15}H_{11}N_2OS$) C, H, N.

2-Phenyl-6-benzothiazoleacetamide (18b). This was prepared in the same manner as method a or c of **18a** described above, mp 229–230°. *Anal.* ($C_{15}H_{11}N_2OS$) C, H, N (method a, see Table III).

Ethyl 2-Phenyl-5-benzothiazoleacetate (17a). This was prepared by esterification of **6a** in EtOH containing a little concentrated H_2SO_4 and worked up in the usual way. Crystallization (EtOH) gave **17a** in a good yield, mp 89–90°. *Anal.* ($C_{17}H_{15}NO_2S$) C, H, N.

Ethyl 2-Phenyl-6-benzothiazoleacetate (17b). This was prepared from **7a** in the same manner as above. Crystallization (EtOH) gave **17b** in a good yield, mp 78–80°. *Anal.* ($C_{17}H_{15}NO_2S$) C, H, N.

2-Phenyl-5-benzothiazoleacetohydroxamic Acid (19). Into a cooled solution of $NH_2OH \cdot HCl$ (23.0 g, 0.33 mol) in absolute MeOH (500 ml), MeONa, prepared from Na (6.9 g, 0.3 mol) and absolute MeOH (70 ml), was added with stirring. NaCl was removed by filtration, and **17a** (58.5 g, 0.197 mol) and additional MeONa, prepared from Na (4.6 g, 0.2 mol) and absolute MeOH (50 ml), were added to the filtrate with stirring. The reaction mixture was then heated at reflux for 1 hr. Upon cooling in ice–H_2O, solids were formed, collected, and dissolved in H_2O–dioxane (2:3, 900 ml) and AcOH (a little) by heating. Cooling of the solution gave a solid which was collected, washed (H_2O), and recrystallized (H_2O–dioxane) to give **19** (42.0 g, 75.0%), mp 172–175°. *Anal.* ($C_{15}H_{12}N_2O_2S$) C, H, N.

2-Phenyl-6-benzothiazoleacetic Acid (7a). A mixture of 2-phenyl-6-acetylbenzothiazole (**4a**)[8] (10 g, 0.05 mol), sulfur (1.6 g, 0.05 mol), and morpholine (20 ml) was heated at reflux for 20 hr. The isolated morpholide was refluxed in 10% aqueous NaOH (100 ml) for 20 hr. The cooled solution was acidified (dilute HCl), and the precipitate was collected and recrystallized (*i*-PrOH–H_2O) to give **7a** (6.2 g, 58.8%), mp 173–175°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N (Table II).

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References

(1) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willet, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. L. Lucas, C. H. Stammer, F. W. Holly, L. H. Sarrett, E. A. Risley, G. W. Nuss, and C. A. Winter, *J. Amer. Chem. Soc.*, **85**, 488 (1963).
(2) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *Nature (London)*, **200**, 271 (1963).
(3) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *J. Pharm. Sci.*, **56**, 1686 (1967).
(4) P. M. Messer, D. Farge, J. C. Guyonnet, C. Jeanmart, and L. Julou, *Arzneim.-Forsch.*, **19**, 1193 (1969).
(5) W. Hepworth, B. B. Newbould, D. S. Platt, and G. J. Stacey, *Nature (London)*, **221**, 582 (1969).
(6) British Patent 1,093,355 (Appl. No. 32438/65).
(7) M. Carmack and M. A. Apielman, *Org. React.*, **3**, 83 (1946).
(8) A. Burger and S. N. Sawhney, *J. Med. Chem.*, **11**, 270 (1968).
(9) M. T. Bogert and H. G. Husted, *J. Amer. Chem. Soc.*, **54**, 3394 (1932).
(10) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962); *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).
(11) M. T. Bogert and A. Stull, *J. Amer. Chem. Soc.*, 47, 3078 (1925).
(12) J. R. Keneford and J. C. E. Simpson, *J. Chem. Soc.*, 227 (1947).