modified JEOL JNM-PS-100 FT-NMR interfaced with a Nicolet 1085 Fourier transform computer system. Spectra were obtained in either 5- or 10-mm tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock signal.[9] All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.538-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000-Hz sweep-width spectra. Typical pulse widths were 12.5 μs (45° flip angle), and the delay time between pulses was fixed at 1.0 sec. Normally 1012 (twice as many for single-frequency off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The chemical shifts reported are believed accurate to within ±0.05 ppm.

5-Alkyl-5-(2'-pentyl)-2-thiobarbituric Acids (2).[5] The title compounds were prepared by a procedure previously reported for similar 5-alkyl-5-(2'-pentyl)-2-thiobarbituric acids.[10] The following new compounds were prepared. 5-Methyl-5-(2'-pentyl)-2-thiobarbituric acid (2, R = CH_3) was recrystallized from EtOAc–hexane and had mp 85–86°. Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N, S. 5-*n*-Pentyl-5-(2'-pentyl)-2-thiobarbituric acid (2, R = C_5H_{11}) was recrystallized from EtOAc–hexane and had mp 97–100°. Anal. ($C_{14}H_{24}N_2O_2S$) C, H, N, S. (*S*)-5-(2'-Pentyl)-2-thiobarbituric acid (2, R = H) was recrystallized from EtOH–H_2O and had mp 140–141°: $[\alpha]^{24}D$ +2.45° (*c* 0.204, CH_3OH). Anal. ($C_9H_{14}N_2O_2S$) C, H, N, S.

Acknowledgment. This work was carried out under Contract No. PH-43-65-1057 with the Pharmacology–Toxicology Program, National Institute of General Medical Sciences, National Institutes of Health.

References and Notes

(1) H. D. Christensen and I. S. Lee, *Toxicol. Appl. Pharmacol.*, **26**, 495 (1973), and references cited therein.
(2) L. G. Mark, Columbia University, personal communication, 1975.
(3) R. I. Freudenthal and J. Martin, *J. Pharmacol. Exp. Ther.*, **193**, 664 (1975), and references cited therein.
(4) F. I. Carroll and A. Sobti, *J. Am. Chem., Soc.*, **95**, 8512 (1973).
(5) Both 2'-pentyl and 1'-methylbutyl have been used to name the group $C_3H_7CHCH_3$.
(6) F. I. Carroll and C. G. Moreland, *J. Chem. Soc., Perkin Trans.*, 374 (1974).
(7) C. Yeh and F. S. Richardson, University of Virginia, personal communication, 1975.
(8) W. J. Doron, "Medicinal Chemistry", Vol. IV, Wiley, New York, N.Y., 1959.
(9) When nondeuterated solvents were used, a 5-mm tube containing the sample and solvent was placed in a 10-mm tube containing $CDCl_3$ which was used as the deuterium lock.
(10) F. I. Carroll and R. Meck, *J. Org. Chem.*, **34**, 2676 (1969).

Syntheses of Heterocyclic Fused Thiazole Acetic Acids. 2

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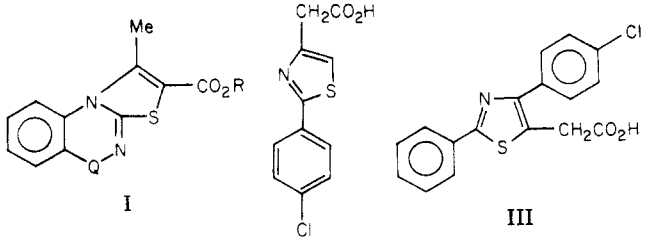
A number of tricyclic and bicyclic fused thiazole-2-acetic acid derivatives were prepared and the chemistry and biological properties of these compounds are discussed. Many of the esters exhibited antitubercular activity. The bicyclic thiazole-2-acetic acids had antidepressant activity. Interesting antimetastatic activity against Lewis lung tumor in mice was found with several compounds, in particular, the thiazolo[3,2-*a*]benzimidazole-2-acetic acid derivative XI.

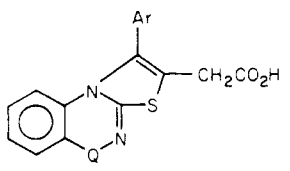
We recently described the syntheses of fused heterocyclic thiazole carboxylic acids I as potential pharmacological agents.[1] The reports of thiazole acetic acid derivatives II (Myalex)[2] and III[3] as potential antiinflammatory agents prompted us to expand our series of compounds from fused heterocyclic thiazolocarboxylic acid to acetic acid derivatives such as IV and V.



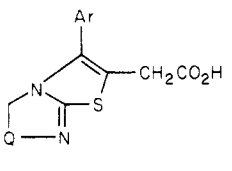
I

II

III



IV



V

In order to prepare compounds of type IV and V, appropriate 2-mercapto heterocycles were allowed to react with 3-aroyl-3-bromopropionic acids and esters. The nature of the products was quite dependent on the reaction conditions and the type of intermediates employed. In all cases the products were identified by spectral data, particularly infrared, as well as analytical data. The compounds were screened in a variety of tests for biological activities, and these results are discussed.

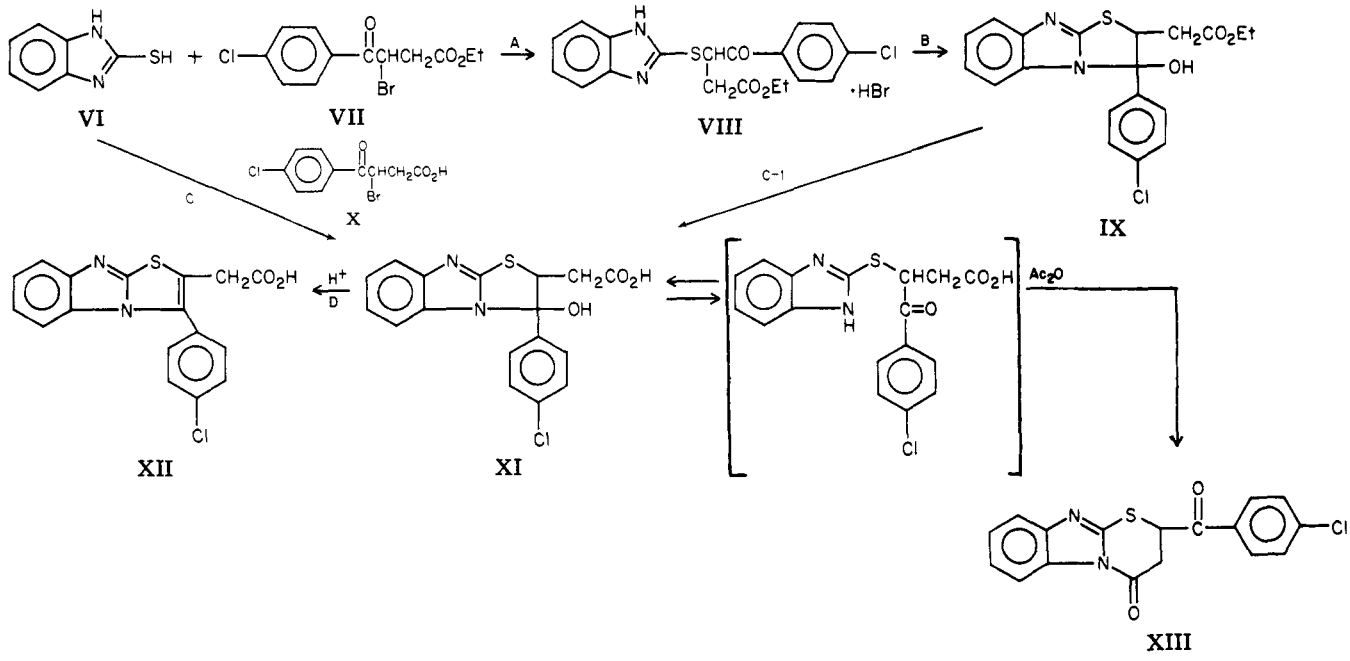
Chemistry. When, for example, 2-mercaptobenzimidazole VI was allowed to react with ethyl 3-bromo-3-*p*-chlorobenzoylpropionate VII in boiling methanol (Scheme I, procedure A) the resultant product was sulfide VIII, isolated as the HBr salt. Upon stirring compound VIII in water or dilute $NaHCO_3$ (procedure B), ring closure took place to form the fused hydroxythiazolo[2,3-*a*]-benzimidazoleacetic acid ethyl ester IX.

When the starting 3-bromo acid X, rather than its ester VII, was allowed to react with VI in a solvent such as hot dimethoxyethane or acetic acid, the fused hydroxythiazoloacetic acid XI HBr (procedure C) was obtained directly in one step. Neutralization of this salt formed the free acid XI. Compound XI was also prepared from IX by alkaline hydrolysis of the ester group (procedure C-1).

Treatment of XI with aqueous hydrochloric acid resulted in dehydration (procedure D) to the thiazolo-[3,2-*a*]benzimidazoleacetic acid XII. The reaction of XI with acetic anhydride produced a rearranged thiazinone XIII, apparently arising from ring opening of the thiazole ring of XI followed by ring closure of the carboxy group onto the nitrogen.[4]

The infrared absorption spectra (KBr) of IX and XI showed one carbonyl peak (carboxy group) at 5.78 and 5.88 μ, respectively, indicating that the compounds exist in the

Scheme I



tricyclic form. However, the NMR spectra of IX and XI showed that the methine proton adjacent to the sulfur atom had unusually high values, δ 5.88 (a,b,x) and 5.82 (a,b,x), respectively, suggesting that the methine proton was adjacent to a carbonyl group and that, therefore, IX and XI exist in the opened chain form. These absorptions were, in fact, similar to the methine protons of the ring opened VIII HBr (δ 5.95, a,b,x) and the cyclic thiazinone XIII (δ 5.75, t). The NMR values for the methine proton of the opened nitro derivative VIIIc and its closed tricyclic form IXd were somewhat higher, each at δ 6.15 in an a,b,x pattern.

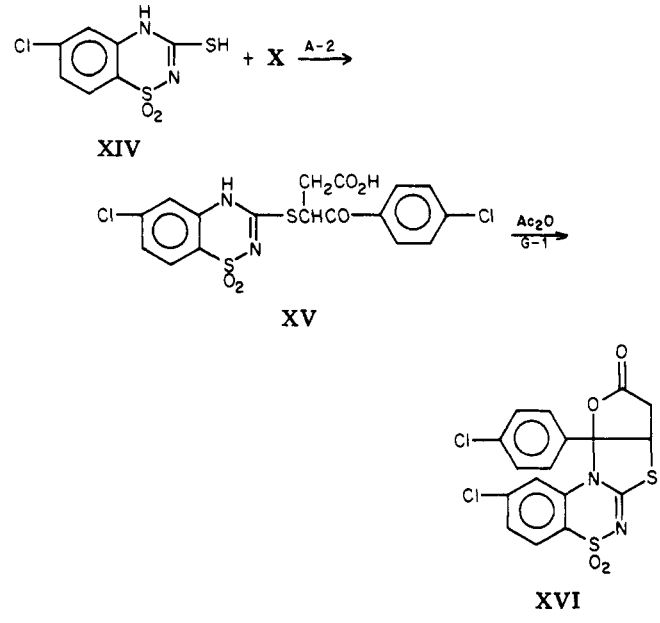
When infrared spectra of compounds XI and IXd were run in solution ($CHCl_3$, dioxane) there were now two carbonyl peaks [XI, 5.78 (ester), 5.92 μ (ketone); IXd, 5.80 (ester), 5.95 μ (ketone)]. Uv spectra of XI in ethanol at pH 12 and 7 showed several maxima. The most intense, at ~250 mμ, was indicative of the benzoyl group; however, at pH 2 the maximum at 250 mμ was no longer present.

Thus, it was concluded that in the solid state, benzo compounds of type IX and XI exist in the tricyclic form and, in solution, they exist as the open form at neutral and high pH and as the closed tricyclic form in acid medium.[4]

The reaction of the 3-mercapto[1,2,4]thiadiazine 1,1-dioxide XIV with X in the presence of excess alkali produced the corresponding sulfide XV (Scheme II, procedure A-2) which upon heating in acetic anhydride gave the tetracyclic lactone XVI (procedure G-1). It seems likely that first ring closure of XV to the hydroxythiazoline acetic acid took place followed by dehydration to the lactone XVI.[4]

Our interests were directed to the preparation of bicyclic fused diazolothiazole acetic acids V. Thus, for example, the 2-mercaptotetrahydropyrimidine XVII (x = 2) was allowed to react with either compound VII or X in hot acetic acid (Scheme III, procedure C) producing the fused hydroxythiazole acetic acids XVIII and XX, respectively. When the reaction between VII and XVII in hot acetic acid took place over an extended period of time (procedure F), dehydration took place forming the unsaturated thiazole acetic acid ester XIX (cf. preparation of compound XII from XI). Upon heating with acetic anhydride (procedure G), XVIII did not undergo a rearrangement as in the case of XI to XIII but instead formed the lactone XXII.[4]

Scheme II



Scheme III

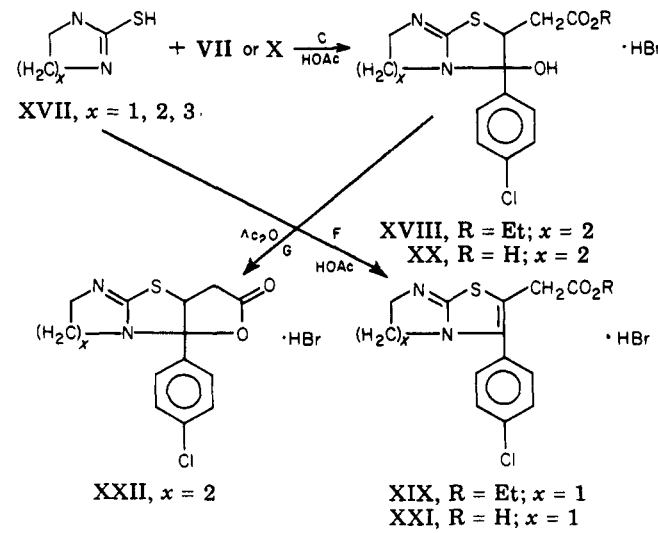
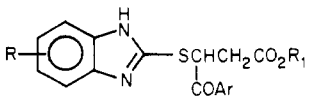
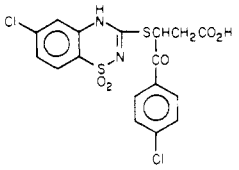
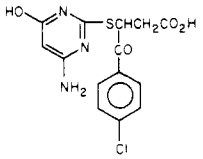


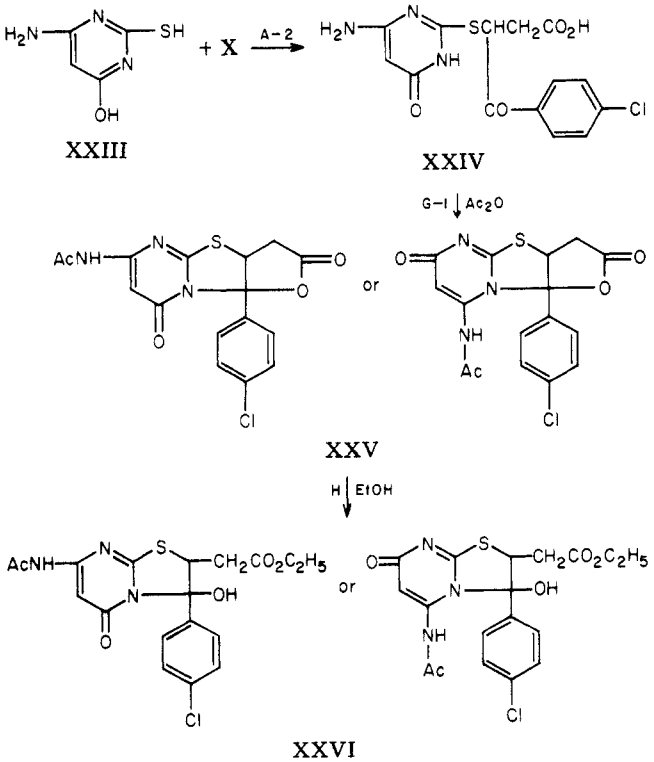
Table I



No.	R	R_1	Ar	Mp, °C	Yield, %	Procedure	Recrystn solvent	Infrared (μ)	Emp formula	Analyses[a]
VIII	H	Et	*p*-ClC_6H_4	168-170	55	A	EtOH	5.75 (ester), 5.92 (ketone)	$C_{19}H_{17}ClN_2O_3S$·HBr	C, H, N
VIIIa	H	Et	C_6H_5	126-127	67	A	Me_2CO	5.72 (ester), 5.90 (ketone)	$C_{19}H_{18}N_2O_3S$·HBr	C, H, Br, N, S
VIIIb	H_2N	Et	*p*-ClC_6H_4	250 dec	72	A	EtOH-Me_2CO	5.75 (ester), 5.91 (ketone)	$C_{19}H_{18}ClN_3O_3S$·HBr	C, H, Cl, N, S; Br[b]
VIIIc	NO_2	Et	*p*-ClC_6H_4	218-220	63	A-1	EtOH	5.80 (ester), 5.97 (ketone), 6.73, 7.50 (NO_2)	$C_{19}H_{16}ClN_3O_5S$·HBr	C, H, Br, Cl, N, S
VIIId	H	Me	*p*-ClC_6H_4	182-185	50	A	MeOH, Me_2CO	5.73 (ester), 5.92 (ketone)	$C_{18}H_{15}ClN_2O_3S$·HBr	C, H, Br, Cl, N, S
XV				237-239	44	A-2	Dimethoxyethane-C_6H_6	5.85 (CO_2H), 5.95 (keto)	$C_{17}H_{12}Cl_2N_2O_5S_2$	C, H, Cl, N
XXIV				Not isolated		A-2				

[a] Most compounds had all analyses within 0.3%. Analyses over 0.4% are noted. [b] Br: calcd, 16.52; found 16.00.

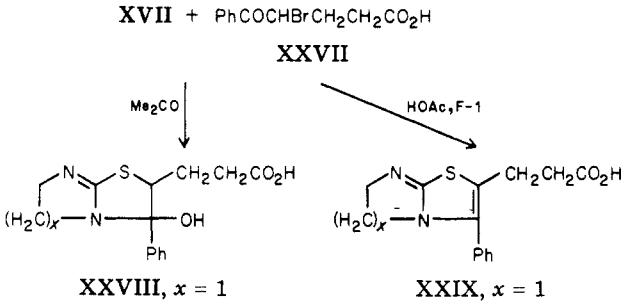
Scheme IV



XXIII XXIV XXV XXVI

The NMR spectra for the methine protons of compounds of type XVIII and XX were at the expected δ 4.3-4.75 region and were in an a,b,x pattern. Their ir spectra, both in solid (KBr) and solution ($CHCl_3$), exhibited only one carbonyl peak. Thus, unlike the benzo analogs, these compounds do not exist in the open form in solution.[4]

Scheme V



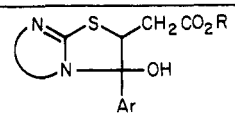
XXVIII, $x = 1$ XXIX, $x = 1$

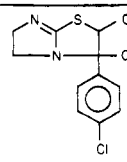
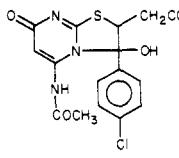
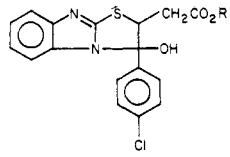
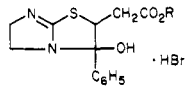
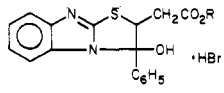
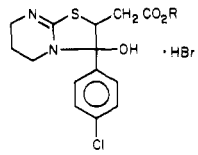
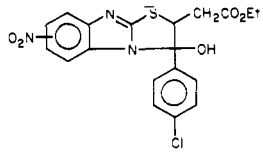
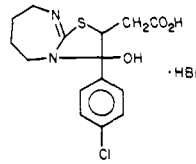
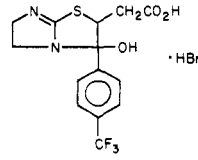
In order to prepare a fused diazolothiazole acetic acid with functional groups, 4-amino-6-hydroxy-2-mercaptopyrimidine XXIII was allowed to react with compound X in the presence of excess alkali (Scheme IV, procedure A-2) resulting in the sulfide XXIV. Treatment of XXIV with acetic anhydride produced the tricyclic lactone XXV[4] (procedure G-1) and then refluxing XXV in ethanol caused ring opening by the ethanol (procedure H) to the hydroxythiazole acetic acid ester XXVI. As discussed previously,[1] we were unable to establish the relative positions of the substituents on the pyrimidine ring of XXV and XXVI.

As a means of preparing the propionic acid homologs of compounds of type V, 2-mercaptodiazines such as XVII were allowed to react with 4-benzoyl-4-bromobutyric acid XXVII in acetone at room temperature. The reaction product was the hydroxythiazole propionic acid XXVIII, a higher homolog of XX. In hot acetic acid the reaction of XVII and XXVII (Scheme V, procedure F-1) went directly to XXIX, presumably via the dehydration of the intermediate XXVIII.[4]

The compounds described in Schemes I-V are listed in Tables I-IV. In instances where reaction conditions are

Table II



No.	Structure	Mp, °C	Yield, %	Procedure	Recrystn solvent	Infrared (μ)	Emp formula	Analyses[a]
XXa, R = H		273-277	100	C	Dimethoxyethane	5.78 (CO_2H)	$C_{13}H_{13}ClN_2O_3S\cdot HBr$	C, H, Br, Cl, N, S
XVIIIa, R = Me		173-174	69	C	MeOH	5.80 (ester)	$C_{14}H_{15}ClN_2O_3S\cdot HBr$	C, H, Br, Cl, N, S
XVIIIb, R = Et		163-164	78	C	MeCN	5.82 (ester)	$C_{15}H_{17}ClN_2O_3S\cdot HBr$	C, H, Br, Cl, N, S
XXVI		172-174	65	H	MeCN	5.85 (ester), 6.10 (amide)	$C_{18}H_{18}ClN_3O_5S$	C, H, N
XI, R = H		163-165	75	C, C-1	Dioxane-MeCN	5.88 (CO_2H)	$C_{17}H_{13}ClN_2O_3S$	C, H, N, S
IXa, R = Me		132-134	55	E	Me_2CO	5.78 (ester)	$C_{18}H_{15}ClN_2O_5S$	H, Cl, N, S; C[b]
IX, R = Et		140-142	83	B	Me_2CO	5.78 (ester)	$C_{19}H_{17}ClN_2O_3S$	C, H, N
XVIIIc, R = Et		150-151	58	C	Me_2CO	5.82 (ester)	$C_{15}H_{18}N_2O_3S\cdot HBr$	C, H, Br, N, S
XVIIId, R = Me		169-170	75	C	MeCN	5.80 (ester)	$C_{14}H_{16}N_2O_3S\cdot HBr$	C, H, Br, N, S
IXb, R = Et		129-131	67	E	Me_2CO	5.82 (ester)	$C_{19}H_{18}N_2O_3S$	C, H, N, S
IXc, R = Me		145-147	53	B	Me_2CO	5.80 (ester)	$C_{18}H_{16}N_2O_3S\cdot HBr$	C, H, Br, N, S
XX, R = H		158-160	80	C	MeCN	5.78 (CO_2H)	$C_{14}H_{15}ClN_2O_3S\cdot HBr$	C, H, Br, Cl, N, S
XVIII, R = Et		180-182	84	C	MeCN	5.77 (ester)	$C_{16}H_{19}ClN_2O_3S\cdot HBr$	C, H, Br, N, S
IXd		99-101	95	E	C_6H_6-MeCN	5.78 (ester), 6.83, 7.65 (NO_2)	$C_{19}H_{16}ClN_3O_5S$	C, H, N, S; Cl[c]
XXb		163-165	44	C	MeCN	5.75 (CO_2H)	$C_{15}H_{17}ClN_2O_3S\cdot HBr$	C, H, Br, Cl, N, S
XXc		278-280	83	C	MeCN	5.74 (CO_2H)	$C_{14}H_{13}F_3N_2O_3S\cdot HBr$	C, H, Br, N, S

[a] See footnote *a*, Table I. [b] C: calcd, 57.68; found, 57.20. [c] Cl: calcd, 8.17; found, 8.64.

similar, a procedure for one of the compounds is described in the Experimental Section. Listed in Tables I–IV are structure, melting point, yield, procedure, recrystallization solvent, infrared, empirical formula, and analyses.

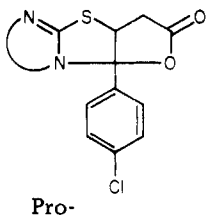
Biological Activities. The compounds described herein were found to have activities in a number of screening procedures. The most interesting activities are described below.

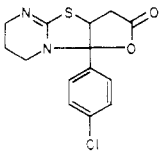
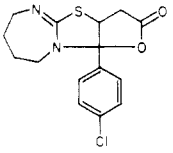
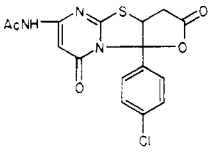
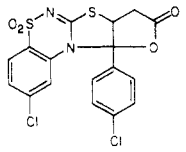
A. Many of the bicyclic thiazole acetic acids (type XX) and esters (type XVIII) exhibited potent antidepressant activity in mice in the antagonism to reserpine ptosis screen. These activities are listed in Table V.

B. Numerous compounds were found to be active at 0.1–5 μg/ml when tested against H 37RV human TB strain (INH used as a standard was active at 0.05–0.005 μg/ml). The benzo derivatives seemed more active and the esters were considerably more potent than the corresponding acid. The most active esters are listed in Table VI.

C. Since many of the compounds described in this paper have a part of the basic structure of levamisole, an anthelminthic drug also reported effective in inhibiting Lewis lung tumor in mice,[5] these compounds were also tested

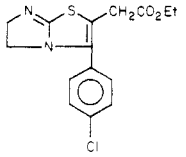
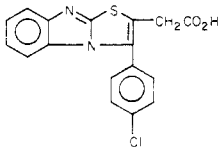
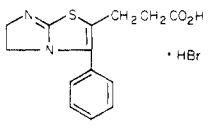
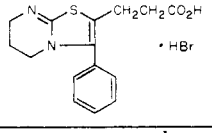
Table III



No.	Structure	Mp, °C	Yield, %	Procedure	Recrystn solvent	Infrared (μ)	Emp formula	Analyses[a]
XXII		200-202	32	G	MeCN	5.56 (γ-lactone)	$C_{14}H_{13}ClN_2O_2S\cdot HBr$	C, H, Cl, N, S
XXIIa		183-185	45	G	MeCN	5.55 (γ-lactone)	$C_{15}H_{15}ClN_2O_2S\cdot HBr$	C, H, N
XXV		170-180	86	G-1	Dimethoxyethane–Et_2O	5.50 (γ-lactone), 5.90 (amide)	$C_{16}H_{12}ClN_3O_4S$	C, H, S; N[b]
XVI		295-300	70	G-1	Dimethoxyethane	5.50 (γ-lactone), 7.60, 8.50 (SO_2N)	$C_{17}H_{10}Cl_2N_2O_4S_2$	C, H, Cl, N

[a] See footnote a, Table I. [b] N: calcd, 11.12; found, 10.69.

Table IV

No.	Structure	Mp, °C	Yield, %	Procedure	Recrystn solvent	Infrared (μ)	Emp formula	Analyses[a]
XIX		217-218	88	F	MeCN	5.75 (ester), 6.35 (C=N) (C=C)	$C_{15}H_{15}ClN_2O_2S\cdot HBr$	C, H, N, S
XII		242-243	23	D	Dimethoxyethane	5.81 (CO_2H)	$C_{17}H_{11}ClN_2O_2S$	C, H, N, S; Cl[b]
XXIX		236-238	71	F-1	MeCN	5.81 (CO_2H)	$C_{14}H_{14}N_2O_2S\cdot HBr$	C, H, Br, N, S
XXIXa		285-287	81	F-1	HOAc	5.80 (CO_2H)	$C_{15}H_{16}N_2O_2S\cdot HBr$	C, H, Br, N, S

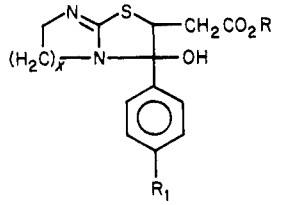
[a] See footnote a, Table I. [b] Cl: calcd, 10.34; found, 11.00.

against Lewis lung tumor.[6] Several of the thiazolobenzimidazoleacetic acids were found to have significant antimetastatic activity against virulent Lewis lung tumor in BDF_1 black mice.

The most potent of these compounds, XI, had a T/C of 37% at 150 mg/kg ($p < 0.001$) and was found to be more active and less toxic than levamisole. Compound XI was also found to be noncytotoxic but did have a synergistic effect with cytotoxic agents such as 5-fluorouracil and cytotoxin.[7] The esters of XI and IX and the dehydrated derivative XII were also active but less potent.

The pyrimidinethiazole acetic acid derivative XXVI was

Table V



No.	x	R	R_1	ED_{50}, mg/kg po
XXa	1	H	Cl	0.22
XVIIIa	1	Me	Cl	0.5
XVIIId	1	Me	H	0.5
XX	2	H	Cl	0.25
XVIIIc	1	Et	Cl	0.27
XVIII	2	Et	Cl	0.118

Table VI

No.	Act. vs. H 37RV TB, μg/ml	No.	Act. vs. H 37RV TB, μg/ml
IXd	0.1	IXa	2
XXVI	1	VIIIb	3
IX	1	XVIIIc	5
XVIIIa	1	XVIIIb	5
VIIId	1	IXc	5
VIII	1	XVIIId	5

also quite effective in inhibiting Lewis lung tumor. While many of the benzo compounds of type IX and XI were active the debenzo compounds of type XX were ineffective in inhibiting Lewis lung tumor.

Experimental Section

Melting points were taken in a Thomas-Hoover oil bath and are uncorrected. Infrared spectra were obtained in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were obtained in Me_2SO-d_6 on either a Varian A-60 or Jeolco HL60 spectrometer.

Preparation and Reactions of 3-(*p*-Chlorophenyl)-2,3-dihydro-3-hydroxythiazolo[3,2-*a*]benzimidazole-2-acetic Acid (XI). Procedure A. 3-(Benzimidazol-2-ylthio)-3-(*p*-chlorobenzoyl)propionic Acid Ethyl Ester Hydrobromide (VIII). An alcoholic solution of 16 g of ethyl 3-bromo-3-(*p*-chlorobenzoyl)propionate (VII) and 7.5 g of 2-mercaptobenzimidazole (VI) was refluxed on the steam bath for 5 h. After most of the solvent was evaporated in vacuo the solid was precipitated by the addition of C_6H_6.

Procedure B. 3-(*p*-Chlorophenyl)-2,3-dihydro-3-hydroxythiazolo[3,2-*a*]benzimidazole-2-acetic Acid Ethyl Ester (IX). The finely ground suspension of 21.8 g of VIII was stirred in 500 ml of H_2O for 5 h and filtered.

Procedure C. A mixture of 6.0 g of VI and 11.6 g of X in HOAc was heated on a steam bath for 3 h. On cooling there was obtained 15 g of the HBr salt of XI.

Similarly, reaction of 10 g of VI and 17.4 g of X in dioxane gave 25 g of XI·HBr, mp 203–205°.

The HBr salt of XI (17.0 g) dissociated upon stirring in water and the free acid was collected by filtration. Recrystallization gave 12.0 g of XI.

Procedure C-1. A suspension of IX (3.8 g, 0.01 mol) in an aqueous solution containing 0.60 g (0.015 mol) of NaOH was heated on the steam bath until all the solid had dissolved. After cooling, the solution was acidified with HOAc and the solid was filtered. The infrared was identical with that of the compound prepared above.

Procedure D. 3-(*p*-Chlorophenyl)thiazolo[3,2-*a*]benzimidazole-2-acetic Acid (XII). A mixture of 5.0 g (0.0139 mol) of XI in 200 ml of dioxane and 100 ml of 6 N HCl solution was heated to reflux for 20 h. The reaction mixture was concentrated to a small volume (50 ml) and to the residue was added 200 ml of water. The mixture was made distinctly alkaline by adding a 4 N NaOH solution. A small amount of insoluble material was filtered off. The alkaline solution was acidified with HOAc. The resulting yellow precipitate was collected, washed with water, and dried. NMR showed a methylene singlet ($-CH_2CO_2H$) at δ 3.70.

2-(4-Chlorobenzoyl)-2,3-dihydro-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-one (XIII). A mixture of XI (10.0 g, 0.0277 mol) in 200 ml of Me_2CO was heated to reflux in the presence of 30 ml of Ac_2O for 3 h. The solution was treated with Darco, the solvent was removed, and the residual solid was dissolved in 50 ml of Me_2CO. After some insoluble material was filtered off, the filtrate was diluted with 150 ml of Et_2O. The resulting precipitate was collected in a yield of 8.7 g, mp 189–191°. Infrared exhibited no NH or OH band; there were two carbonyl bands, 5.79 (ketone) and 5.96 μ (lactam). Anal. ($C_{17}H_{11}ClN_2O_2S$) C, H, N, Cl, S.

Procedure E. 2,3-Dihydro-3-hydroxy-3-phenylthiazolo[3,2-*a*]benzimidazole-2-acetic Acid Ethyl Ester (IXb). To a mixture of C_6H_6–H_2O was added 9.0 g of 3-(benzimidazol-2-ylthio)-3-benzoylpropionic acid ethyl ester hydrobromide (VIIIa) and the mixture was stirred vigorously and neutralized with dilute $NaHCO_3$ solution. The C_6H_6 layer was separated, dried over anhydrous $MgSO_4$, and evaporated to dryness.

Procedure A-1. 3-(*p*-Chlorobenzoyl)-3-[5- (or 6-) nitrobenzimidazol-2-ylthio]propionic Acid Ethyl Ester Hydrobromide (VIIIc). A glacial HOAc solution of 12.7 g of VII and 7.8 g of 5-nitro-2-mercaptobenzimidazole was heated on the steam bath for 15 h. On concentration of the mixture and cooling there was collected 13 g of pure product.

Procedure A-2. 3-(*p*-Chlorobenzoyl)-3-(6-chloro-4*H*-1,2,4-benzothiadiazin-3-ylthio)propionic Acid 5,5-Dioxide (XV). To an alkaline solution of 7-chloro-2-mercapto-1,2,4-benzothiadiazine 5,5-dioxide (XIV) (5.3 g, 0.0216 mol) and KOH (3.8 g, 0.067 mol) was added 6.6 g (0.0226 mol) of X. The solution was stirred at room temperature for about 4 h and left to stand overnight. A small amount of impurities was filtered off and the filtrate acidified with 6 N HCl solution yielding 8.0 g of crude material.

Procedure F. 3-(*p*-Chlorophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-acetic Acid Ethyl Ester Hydrobromide (XIX). A solution of 6.4 g of VII and 2.2 g of XVII in glacial HOAc was heated on the steam bath for 24 h. The reaction mixture was filtered from insoluble material, the solvent removed in vacuo, and the product (7.5 g) precipitated out with dimethoxyethane.

Procedure F-1. 5,6-Dihydro-3-phenylimidazolo[2,1-*b*]thiazole-2-propionic Acid Hydrobromide (XXIX). A glacial HOAc solution of 8.1 g of 4-benzoyl-4-bromobutyric acid (XXVII) and 3.1 g of 2-mercaptoimidazoline (XVII) was heated on the steam bath for 4 h. After cooling, the precipitate was filtered and washed with HOAc and then Et_2O.

Procedure G. 3-(*p*-Chlorophenyl)-2,3,6,7-tetrahydro-3-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidine-2-acetic Acid γ-Lactone Hydrobromide (XXII). To a solution of 100 ml of HOAc and 25 ml of Ac_2O was added 11.64 g of X and 4.64 g of 2-mercapto-3,4,5,6-tetrahydropyrimidine (XVIIa) and the mixture was heated on the steam bath for 15 min. After removal of the solvent in vacuo, the residue was washed with Et_2O, then dimethoxyethane, and then MeCN giving the crude material (8.0 g).

Procedure G-1. *N*-[9a-(4-Chlorophenyl)-2,3,3a,9a-tetrahydro-2,6- (or 8-) dioxo-6*H*- (or 8*H*-) furo[2',3':4,5]thiazolo[3,2-*a*]pyrimidin-8- (or 6-) yl]acetamide (XXV). A mixture of 28.0 g (0.079 mol) of XXIV, prepared from X and XXIII according to procedure A-2, in 200 ml of Ac_2O was heated to gentle reflux for 26 h. After a small amount of insoluble material was filtered off, the filtrate was concentrated to dryness. The residual solid was dissolved in 80 ml of dimethoxyethane and the dimethoxyethane solution was added to 300 ml of anhydrous Et_2O, precipitating 24 g of XXV.

Procedure H. 5- (or 7-) Acetamido-3-(*p*-chlorophenyl)-2,3-dihydro-3-hydroxy-7- (or 5-) oxo-5*H*- (or 7*H*-) thiazolo[3,2-*a*]pyrimidine Acetic Acid Ethyl Ester (XXVI). XXV (5.0 g) was dissolved in EtOH and, after standing, a precipitate developed which was collected yielding 3.0 g of product.

2,3,5,6-Tetrahydro-3-hydroxy-3-phenylimidazo[2,1-*b*]thiazole-2-propionic Acid (XXVIII). A solution of 150 ml of Me_2CO containing 2.7 g of XXVII and 1.0 g of XVII was stirred for 20 h. The resultant solid (2.7 g) was filtered, washed with Me_2CO and then Et_2O, and recrystallized from MeCN giving pure product: mp 237–241° (72%); infrared, carboxyl at 5.75 μ. Anal.

($C_{14}H_{16}N_2O_3S$·HBr) C, H, N, Br.

Acknowledgment. The authors are indebted to the Analytical Section, under the supervision of Mr. Bruce Hofmann, for the analyses and interpretation of the spectra and to Elizabeth A. Lilley for assistance in preparation of the manuscript.

References and Notes

(1) For paper 1, see *J. Heterocycl. Chem.*, in press.
(2) W. Hepworth, B. B. Newbould, D. S. Platt, and G. J. Stacy, *Nature (London)*, **221**, 582 (1969).
(3) K. Brown, J. F. Cavalla, D. Green, and A. B. Wilson, *Nature (London)*, **219**, 164 (1968).
(4) The tendency of the fused thiazole ring to exist in the open form in solution appears to depend on electronic effects due to the presence of the benzo ring and the nature of the substituents on the benzo ring. Thus, when compounds exist as the open form in solution, they tend to cyclize under dehydration conditions to the thiazinone (for example, XIII), whereas when they are in the cyclic thiazoline form they undergo dehydration to either the thiazole ring (for example, XII, XIX) or the lactone (for example, XVI, XXII, XXV).
(5) *Chem. Eng. News*, 14 (Dec 23, 1974).
(6) R. Fenichel, F. J. Gregory, and H. E. Alburn, *Br. J. Cancer*, in press. Compound XI is Wy-13876 (NSC-D 208828).
(7) R. L. Fenichel, H. E. Alburn, W. E. Tucker, G. H. Warren, and F. J. Gregory, paper presented during the Proceedings of the 66th Annual Meeting of the American Association of Cancer Research and the 11th Annual Meeting of the Society of Clinical Oncology, May 7–11, 1975, San Diego, Calif.

(Vinylaryloxy)acetic Acids. A New Class of Diuretic Agents. 1. (Diacylvinylaryloxy)acetic Acids

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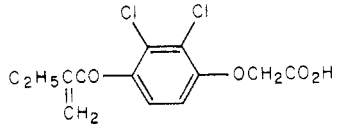
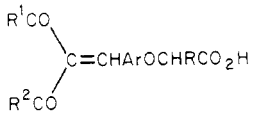
A series of (diacylvinylaryloxy)acetic acids was synthesized and tested in dogs for saluretic and diuretic activity. Several compounds exhibit a high order of activity, the most active being [2,3-dichloro-4-(2,2-diacetylvinyl)-phenoxy]acetic acid (**3**). This compound is about three times as potent as [2,3-dichloro-4-(2-methylenebutyryl)-phenoxy]acetic acid (ethacrynic acid) but is qualitatively similar in causing a prompt increase in the excretion of water and in the excretion of sodium and chloride ions in approximately equimolar amounts. Saturation of the double bond of **3** virtually abolishes activity lending support to the hypothesis that the saluresis induced by these compounds, like that of ethacrynic acid, is related at least in part to a chemical reaction with protein-bound sulfhydryl groups. Four mercaptan adducts of **3** were prepared; these probably function as prodrugs in producing saluresis. The adduct with mercaptoacetic acid is as active as **3** itself.

The high saluretic and diuretic activity of ethacrynic acid,[1,2] [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (I), apparently is associated with the presence of the double bond in conjugation with the carbonyl group. It has been proposed that this compound acts by the binding of renal sulfhydryl-containing enzymes by means of this electrophilic center.[1,3] This paper is a report of the synthesis and renotropic properties of a series of (diacylvinylaryloxy)acetic acids of general structure II which incorporate a double bond activated toward nucleophilic attack by two carbonyl groups.

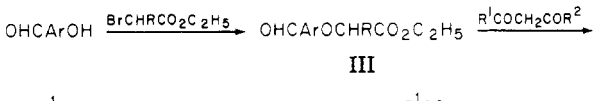


I

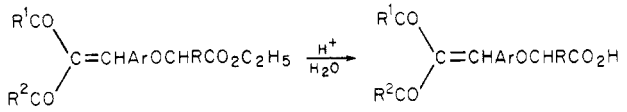


II

Chemistry. The (diacylvinylaryloxy)acetic acids presented in Table I were prepared by a process outlined below involving the piperidine or piperidine acetate catalyzed Knoevenagel condensation of ethyl (formylaryloxy)acetates (III) (Table II) with β-diketones followed by acid hydrolysis of the resulting ethyl (diacylvinylaryloxy)acetates (IV) (Table III).

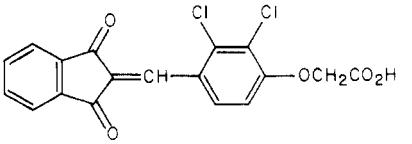


III

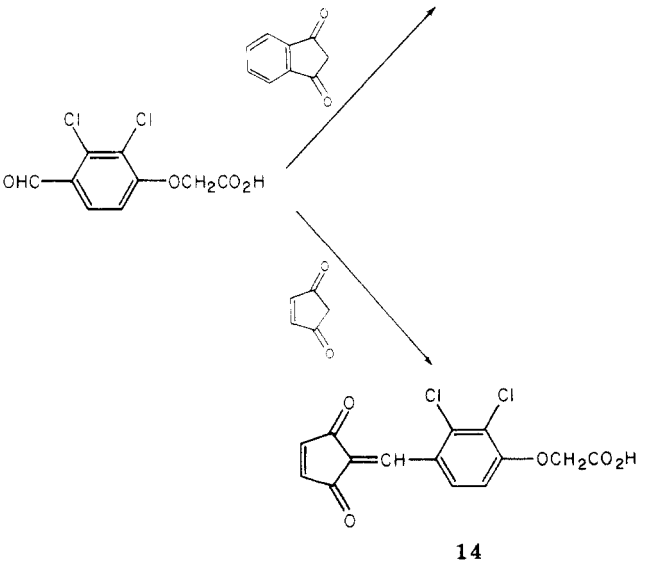


IV II

In an alternate procedure, (2,3-dichloro-4-formylphenoxy)acetic acid, obtained by hydrolysis of the ethyl ester, was condensed under acidic conditions with the cyclic diketones 1,3-indandione and 4-cyclopentene-1,3-dione to yield products **13** and **14**.



13



14

Geometrical isomers of acids **5** and **12** can exist since