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By varying the acidity, solvent polarity, and temperature when thiosemicarbazide reacted with ethyl 4-chloroacetoacetate, ethyl 2-amino-6*H*-1,3,4-thiadiazine-5-acetate hydrochloride, ethyl 2-hydrazinothiazole-4-acetate, and ethyl 2-imino-3-aminothiazoline-4-acetate hydrochloride were prepared selectively. Double bond migration occurred after neutralizing the thiadiazine and thiazoline hydrochlorides to form the α,β -unsaturated esters: 2-amino-5-carbethoxymethylidene-4,5-dihydro-6*H*-1,3,4-thiadiazine and 2-imino-3-amino-4-carbethoxymethylidene-thiazolidine. Pmr studies revealed that an equilibrium existed in solution between the imine and enamine tautomers of the thiadiazine free base. In the enamine structure, a 6-membered hydrogen bonded ring system promotes stability. The thiadiazine contracted in acidic aqueous acetone to ethyl 2-isopropylidenehydrazonothiazole-4-acetate.

Monobenzoylation at the primary amine of the thiadiazine yielded ethyl 2-benzamido-6*H*-1,3,4-thiadiazine-5-acetate without disruption of the hydrogen bonded ring, but benzoylating the imino functionality of the thiazolidine caused deconjugation of the α,β -unsaturated ester by double bond migration back into the ring, and ethyl 2-benzimido-3-aminothiazoline-4-acetate was produced, dehydration yielded ethyl 2-phenylthiazolo[3,2-*b*]-s-triazole-5-acetate. This compound was also obtained by reacting 3-phenyl-1,2,4-triazole-5-thiol with ethyl 4-chloroacetoacetate, while the monobenzoylated derivative of the hydrazinothiazole, ethyl 2-(2-benzoylhydrazino)thiazole-4-acetate underwent a dehydrative cyclization to ethyl 3-phenylthiazolo[2,3-*c*]-s-triazole-5-acetate.

In chloroform solvent, the second site of benzoylation on the thiadiazine was ring nitrogen 3 while in ethanol or acetonitrile-pyridine ring nitrogen 4 was benzoylated instead. Benzoylation at ring nitrogen 3 resulted in deconjugation of the α,β -unsaturated ester moiety and formed the endocyclic imine, ethyl 2-benzimido-3-benzoyl-2,3-dihydro-6*H*-1,3,4-thiadiazine-5-acetate. However, deconjugation of the unsaturated ester did not occur after benzoylation at ring nitrogen 4; the product was *trans*-2-benzamido-4-benzoyl-5-carbethoxymethylidene-4,3-dihydro-6*H*-1,3,4-thiadiazine.

The hydrogen bonded oximes, *syn*-2-amino-5-ethyloxalyl-6*H*-1,3,4-thiadiazine oxime, 3,3-dimethyl-5-ethyloxalyl-2*H*-1,2,4-triazolo[3,4-*b*]thiazole oxime, and 2-(2-benzoylhydrazino)-4-ethyloxalylthiazole oxime were synthesized by nitrosation.

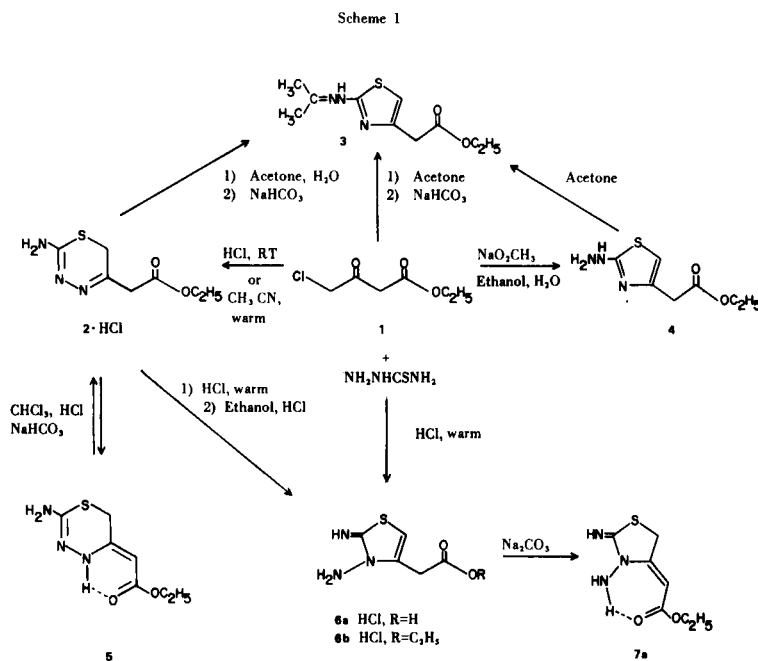
2-Amino-5-ethyloxalyl-6*H*-1,3,4-thiadiazine oxime benzoate, 2-benzamido-5-ethyloxalyl-6*H*-1,3,4-thiadiazine oxime dibenzoate, and the tribenzoylated derivatives, 2-benzimido-3-benzoyl-5-ethyloxalyl-2,3-dihydro-6*H*-1,3,4-thiadiazine oxime benzoate and 2-benzamido-4-benzoyl-5-ethyloxalyl-4*H*-1,3,4-thiadiazine oxime benzoate, of the thiadiazine oxime were prepared. The oxime benzoylated first, the primary amine second, and the number 3 and 4 ring nitrogens last.

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Thiosemicarbazide condensed with an α -halo carbonyl compound may result in the formation of one or more of a number of five and six membered heterocyclic isomers (3). The hydrogen ion concentration of the medium, substituents present, and temperature favor the formation of specific structural isomers. Cyclizing thiosemicarbazide with phenacyl bromide (4) or chloroacetone (3) might possibly produce a thiazole, a thiazoline, or a thiadiazine. With phenacylbromide, the stable ring was the thiadiazine; however, with chloroacetone the thiazoline was more stable (5). Many difficulties were encountered when structural characterizations were attempted and some erroneous references do exist in the literature. Beyer has outlined the historical experimentation concerned with

this subject in a recent review on 1,3,4-thiadiazine chemistry (5).

Although γ -haloketo esters have been reacted with thiourea (6), they had not been condensed with thiosemicarbazide. We have now demonstrated that cyclization of ethyl 4-chloroacetoacetate (1) with thiosemicarbazide occurs, but the products are somewhat more complex. By varying the conditions, ethyl 2-amino-6*H*-1,3,4-thiadiazine-5-acetate (2) hydrochloride, ethyl 2-hydrazinothiazole-4-acetate (4), and ethyl 2-imino-3-aminothiazoline-4-acetate (6*b*) hydrochloride, each having an acetic ester side chain, were obtained. Neutralizing the thiadiazine (2) and thiazoline (6*b*) hydrochlorides allowed double bond migration, thus yielding 2-amino-5-carbeth-



oxymethylidene-4,5-dihydro-6*H*-1,3,4-thiadiazine (5) and 2-imino-3-amino-4-carbethoxymethylidenethiazolidine (7a) respectively. Both of these free bases (5 and 7) contained an *alpha*, *beta*-unsaturated ester moiety. Since most former studies pertained only to the simple methyl and phenyl substituted heterocycles, this phenomenon had not been observed before. Products and conditions are outlined in Scheme 1.

Rearrangements of one ring system to another could also occur as shown in Scheme 1. For example, the thiadiazine 2 hydrochloride contracted in acidic acetone solution to generate ethyl 2-isopropylidenehydrazonothiazole-4-acetate (3). However, the thiazoline 6b hydrochloride did not isomerize under these conditions.

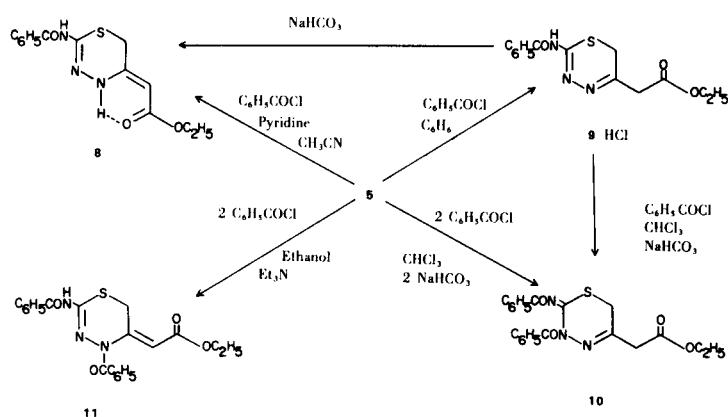
When Bose (4) first attempted the synthesis of a 2-hydrazinothiazole by reacting phenacyl bromide with thiosemicarbazide in ethanol a complex product mixture resulted. Similarly, refluxing or stirring ethyl 4-chloroacetoacetate (1) and thiosemicarbazide in ethanol at room temperature produced a dark colored mixture from which impure 2 hydrochloride reluctantly crystallized. The yields were low and numerous recrystallizations from ethanol were necessary to obtain pure 2 hydrochloride. The reaction was demonstrated to be quite sensitive to the acidity and polarity of the medium; yield and purity of the product was significantly influenced by the choice of solvent. Chloroform or ethers as solvents at room temperature gave better yields of crude 2 hydrochloride. These reactions, being heterogeneous, needed a large excess of solvent. Concentrated hydrochloric acid produced white 2 hydrochloride in good yield; however acetonitrile was by far the most desirable solvent.

Practically pure compound precipitated from solution on cooling.

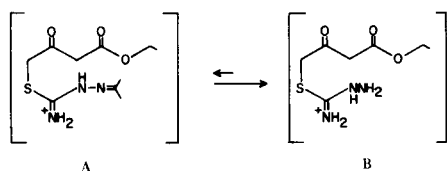
The electronic spectrum of 2 hydrochloride revealed an absorption maximum very similar to that of a model 2-aminothiazole hydrochloride (7). Neutralizing 2 hydrochloride in aqueous acetone produced the acetone thiazolohydrazone 3. This data suggested that the compound was actually the hydrochloride of the thiazolohydrazine 4. However, the pmr spectrum conclusively proved that 2 with a 4,5-double bond was indeed the correct structure; there was no evidence for a 5,6-double bond. Two singlets (2 protons each) were observed at δ 3.73 and 3.83 due to the methylenes on the acetate branching and on the ring itself (C_6). Such a spectrum was not consistent with a thiazole isomer since vinylic resonance did not occur. Having the double bond in the 5,6-position would have also created a vinyl proton in the thiadiazine. Since insertion of an extra doubly bound nitrogen into a S-heterocycle rarely has much effect on the ultraviolet spectrum even though loss of fine structure and shifts to slightly longer wavelengths may occur (8), the similarity of electronic spectra of the thiadiazine 2 hydrochloride and the thiazole model is not surprising.

Ring contraction of 2-amino-thiadiazines in the presence of carbonyl compounds in acidic solution to produce hydrazones of 2-hydrazinothiazoles has previously been observed (9). The reaction of thiosemicarbazide and 1 in acetone produced the hydrochloride salt of 3 in good yield; no trace of 2 hydrochloride could be detected. Refluxing the hydrochloride of 2 in acetone did not cause isomerization to 3; the 2 salt was recovered unchanged. Refluxing acetonethiosemicarbazone with 1 in acetone

Scheme 2



also gave an excellent yield of pure **3** hydrochloride. However, refluxing acetoneithiosemicarbazone and **1** in ethanol produced a mixture of **2** and **3** hydrochlorides, but refluxing either **2** hydrochloride or **3** hydrochloride in ethanol did not produce a mixture, each compound being recovered unchanged on cooling. These observations are consistent with a mechanism involving initial formation of an acetoneisothiosemicarbazonium salt (A) which in ethanol is partially solvolized to the isothiosemicarbazonium salt (B). Since this solvolysis cannot occur in acetone, cyclization of A leads to pure **3** hydrochloride, but in ethanol a mixture is obtained. The salts of **2** and **3**, once formed, are apparently stable in these solvents and are not in equilibrium with intermediates A or B, since refluxing pure samples of either in acetone or ethanol did not change them.



Treatment of **3** hydrochloride with bicarbonate solution precipitated the free base **3**, but similar treatment of **2** hydrochloride caused isomerization to the exocyclic double-bonded thiadiazine **5**. The *cis*-ester carbonyl in a hydrogen-bonded structure, shown for **5**, is indicated by

the spectra characteristics: a vinyl proton at δ 4.45, and a downfield chemical shift to δ 10.5 for a hydrogen-bonded proton on nitrogen in the nmr (**10**), conjugated carbonyl stretching at $1670\text{--}1560\text{ cm}^{-1}$ in the ir spectrum, and a conjugated *alpha, beta*-unsaturated carbonyl absorption at 345 nm in the uv, consistent with the calculated value for this chromophore (**11**).

Actually the pmr revealed that an equilibrium existed in solution between **5** and **2** free bases, compound **5** usually being in higher concentration. A singlet with two adjacent bands (δ 3.30 and δ 3.65) appeared at δ 3.45 (in deuteriochloroform on a 60 MHz instrument) corresponding to the ring methylene of **5**. It was first assumed that the methylene protons were chemical shift non-equivalent and coupled to produce a superimposed AB quartet which resembled the oddly shaped triplet. Resolution of an AB quartet was unsuccessful on a 220 MHz spectrometer; the two adjacent bands remained but were unevenly displaced from the singlet. Since the pmr samples were analytically pure, these bands were attributed to the two methylene resonances of the tautomeric free base **2**, similar to the methylene absorptions of **2** hydrochloride in hexadeuteriodimethylsulfoxide. The solvent in which **5** and **2** were dissolved did affect the relative amounts of each (table 1), free base **5** being quantitatively converted to the salt of **2** in trifluoroacetic acid. Although an equilibrium between **2** and **5** existed in solvents (table

Table 1

Tautomeric Equilibria Between **2** and **5**

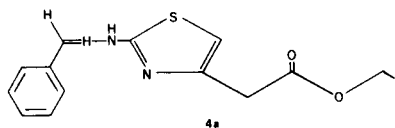
Solvent	% 2 (a)	% 5 (a)	2 δ (CH ₂ CO)	5 δ (SCl ₂)
deuteriochloroform	18	82	3.30	3.45
hexadeuterioacetone	22	78	3.20	3.50
hexadeuteriodimethylsulfoxide	25	75	3.25	3.52
tetradeteriomethanol	38	62	3.15	3.25
trifluoroacetic acid	100	0	3.40	---

(a) The concentrations were determined by relative peak intensities in the pmr at room temperature.

1), the collected precipitate obtained when **2** hydrochloride was neutralized showed no unconjugated carbonyl infrared bands characteristic of **2**. Addition of concentrated hydrochloric acid to a chloroform solution of **5** regenerated **2** hydrochloride.

The reaction of **1** with thiosemicarbazide in aqueous ethanolic potassium acetate produced a red oil, which proved to be a mixture of **4** and **5** and could be separated on a silica gel column. Compound **4** was a red oil which could not be crystallized, but was identified by a characteristic mass ion, the pmr spectrum and conversion to the known acetonethiazolohydrazone **3**. Compound **5** did not condense with acetone unless the mixture was acidified.

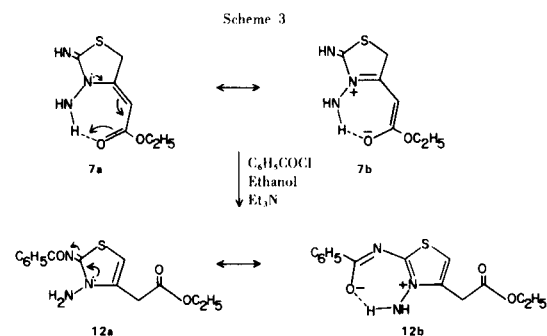
The benzaldehydehydrazone derivative of **4**, ethyl 2-benzylidenehydrazonothiazole-4-acetate (**4a**), was also prepared by reacting benzaldehydethiosemicarbazone with **1**.



In warm concentrated hydrochloric acid, **2** hydrochloride isomerized to 2-imino-3-aminothiazoline-4-acetic acid (**6a**) hydrochloride. Compound **6a** hydrochloride was also obtained by simply warming **1** and thiosemicarbazide in concentrated hydrochloric acid. In both of these reactions, the ester was hydrolyzed. After refluxing in acidic ethanol **6b** hydrochloride crystallized upon cooling. No isomerization to the hydrazone **3** was observed when **6a** or **6b** hydrochloride was dissolved in aqueous acetone. Unlike the thiadiazine, **2** hydrochloride, the thiazoline ring did not open in aqueous acidic solution to form **3**. Here, the thiazoline **6b** hydrochloride was the most stable salt structure, as opposed to the case where the phenyl substituted thiadiazine was more stable (**5**).

Another isomerization occurred when **6b** hydrochloride was neutralized. The double bond migrated to give an *alpha, beta*-unsaturated ester (**7a**). Vinylic proton resonance was observed at δ 4.45, identical to the vinylic proton chemical shift of the thiadiazine free base (**5**). Electronic (290 nm, $\log \epsilon$ 25.6) and ir (1675 cm^{-1} , C=O) data supported structure **7a**. In both **5** and **7a** the ester moiety substituted on the double bond was situated *cis* to the ring nitrogen in contrast to a later example (to be discussed) where the ester carbonyl is forced to be *trans* to the ring nitrogen. Weak hydrogen bonding (unlike that in **5**) may exist between the amino group substituted on the ring nitrogen and the ester carbonyl. This would favor formation of the *cis* structure **7a**. As illustrated spectrally, and by physical appearance compound **7a** (white) was less conjugated than **5** (yellow). Free base **7a** did not react with acetone.

Benzoylation Experiments.



The benzoylation experiments are outlined in Schemes 2 and 3. Using a stoichiometric amount of benzoyl chloride, yellow monobenzoylated 2-benzamido-5-carbomethoxymethylene-4,5-dihydro-6H-1,3,4-thiadiazine (**8**) was prepared in acetonitrile-pyridine solvent. The vinylic proton of **8** absorbed at δ 4.45 the same as the vinylic protons of **5** and **7**. Bands were observed at $1625\text{-}1550 \text{ cm}^{-1}$ (C=O) and 360 nm ($\log \epsilon$ 11.2) in the ir and uv spectra. Because the pmr showed amide-hydrogen resonance at δ 11.50, compound **5** must have benzoylated at the primary nitrogen. Also spectral results indicated that the 6-membered hydrogen bonded ring was still intact.

Refluxing **5** and benzoyl chloride in benzene yielded the hydrochloride of ethyl 2-benzamido-6H-1,3,4-thiadiazine-5-acetate (**9**). The unconjugated acetate carbonyl appeared at 1725 cm^{-1} in the ir, and the methylenes (ring and acetate) had chemical shifts at δ 3.70 and δ 3.70 and δ 3.85 in the pmr. Isomerization to **8** took place after neutralization of **9** hydrochloride. In solution, pmr revealed that all of the free base was in the conformation of **8**.

When **5** was heated with an excess of benzoyl chloride in a chloroform-sodium bicarbonate suspension, dibenzoylated ethyl 2-benzimido-3-benzoyl-2,3-dihydro-6H-1,3,4-thiadiazine-5-acetate (**10**) resulted. Methylene absorptions were at δ 3.65 (S-CH₂) and δ 3.75 (CH₂CO) while acetate carbonyl stretching occurred at $1720\text{-}25 \text{ cm}^{-1}$ in the ir. The double bond of **5** isomerized back into the ring after benzoylating the ring 3 nitrogen. Heating **9** hydrochloride under the same conditions also gave **10**. No hydrogen-nitrogen absorptions were observed in the pmr or ir spectra of **10**.

However, 2-benzamido-4-benzoyl-5-carbomethoxymethylene-4,5-dihydro-6H-1,3,4-thiadiazine (**11**) was obtained after stirring **5** and excess benzoyl chloride in hot pyridine-acetonitrile or ethanol-triethylamine solvents. The amide hydrogen had a chemical shift of δ 11.70, and hydrogen-nitrogen stretching was at 3220 cm^{-1} in the ir. Indications of an *alpha, beta*-unsaturated ester arose from electronic (295 nm, $\log \epsilon$ 20.1) and vibrational (1690 cm^{-1} , C=O) data. The ester group was assigned *trans* to the ring nitrogen in structure **11**, on the basis of a vinylic proton

at δ 6.00. Steric and electronic repulsions between the ethyl and benzoyl ester carbonyls would be expected to favor the *trans* structure. Substitution of benzoyl on the 4-nitrogen in **11** may be responsible for the chemical shift of the vinylic proton, but several *cis* compounds, **5**, **7** and **8**, show a consistent vinylic proton resonance at δ 4.45.

The strong intramolecular hydrogen bonding in **5** could prevent benzoylation at the 4-nitrogen in chloroform. In ethanol and pyridine-acetonitrile intermolecular hydrogen attractions likely disrupted the hydrogen bonded 6-membered ring and allowed for increased nucleophilicity of the 4-nitrogen, thus giving product **11**. Nonpolar solvents would favor adduct **10** while more polar systems could produce **11**.

Compound **7a** was selectively benzoylated at the imino functionality to yield ethyl 2-benzimido-3-aminothiazoline-4-acetate (**12a**) (Scheme 3). Double bond migration back into the ring, out of conjugation with the ester carbonyl, also occurred; the ir spectrum exhibited unconjugated carbonyl stretching at 1725 cm^{-1} . A reasonable explanation for the presence of the *alpha*, *beta*-unsaturated ester originally in **7** would be conjugation of the lone pair of electrons on the ring nitrogen with the ester carbonyl (resonance structure **7b**). However, in the benzoylated derivative **12a**, the lone pair favors conjugation with the benzimide branching rather than with the ester carbonyl and the endocyclic double bond tautomer (**12a**) with the ionic resonance structure (**12b**) becomes the more stable conformer. No evidence for an equilibrium between *endo* and *exo* double bond tautomers was uncovered by pmr studies.

Instead of benzoylating the hydrazinothiazole (**4**), isolated only by tedious chromatographic separation, good yields of ethyl 2-(2-benzoylhydrazino)thiazole-4-acetate (**14**) hydrochloride, the thiazole isomer of mono-benzoylated thiadiazine **8**, were achieved by refluxing 1-benzoyl-3-thiosemicarbazide (**13**) and **1** in ethanol, and this was readily neutralized to **14** (Scheme 4). Following a procedure similar to that used by Potts (12), the free

base **14** underwent a dehydrative cyclization in phosphoryl chloride-xylene to ethyl 3-phenylthiazolo[2,3-*c*]-s-triazole-5-acetate (**16**) in low yield. The corresponding structural isomer, ethyl 2-phenylthiazolo[3,2-*b*]-s-triazole-5-acetate (**17**) was obtained either by dehydrating the 2-benzimido-3-aminothiazole (**12**) or by reacting 3-phenyl-1,2,4-triazole-5-thiol (**15**), readily prepared from **13** (**13**), with **1**. Consistent with past results (**12**, **14**), these dehydration reactions required vigorous conditions and gave low yields. Interestingly, the phenyl protons on **16** resonated as a singlet at $7.45\ \delta$ (acetone- d_6) while the aromatic protons on **17** exhibited a multiplet at δ 8.03-8.52 (deuteriochloroform), as seen in analogs (**12**).

Nitrosation Experiments.

Treatment of either **2** hydrochloride or **5** with nitrous acid produced a mixture of *syn* (**18a**) and *anti* (**18b**) 2-amino-5-ethoxalyl-6*H*-1,3,4-thiadiazine oximes (Scheme 5). Although analyzed correctly, thin layer chromatography detected two substances being present. Benzoylating this mixture did not yield any isomeric derivatives other than those from **18a** or **18b**.

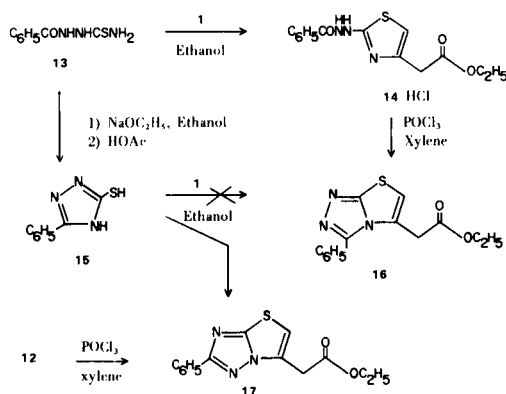
One of the oximes was obtained pure from acetone; it exhibited a carbonyl stretching in the ir solely at 1725 cm^{-1} while the mixture absorbed at 1725 and 1690 cm^{-1} . This compound was characterized as **18a** since the hydrogen bonded carbonyl of the *anti* **18b** would be shifted to longer wavelength (1690 cm^{-1}), as compared to that of **18a**. The original mixture was probably the two isomeric *syn* and *anti* oximes, **18a** and **18b**.

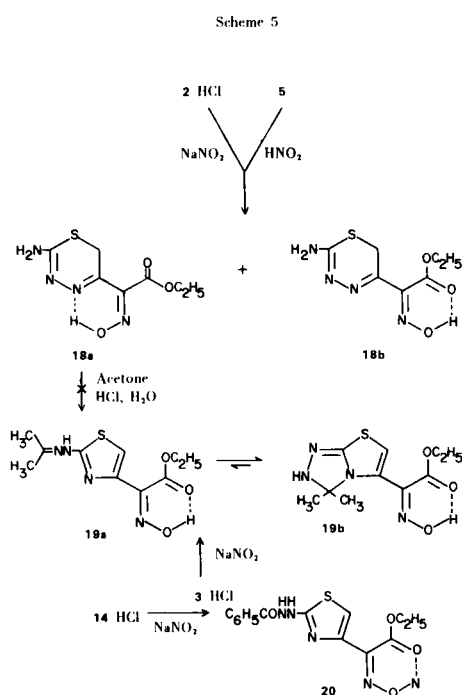
The ir spectrum of **18a** revealed a strongly hydrogen bonded oxime, but a 6-membered ring could be formed by intramolecular hydrogen bonding in either **18a** or **18b**. Due to decomposition in solution, evidence of an equilibrium between **18a** and **18b** was not obtained.

Compound **18a** was soluble in aqueous acid, and reprecipitated when the solution was made basic. Heating **18a** in aqueous acidic acetone did not convert it to the acetonylhydrazone **19a**, as was the case for the analogous 2-hydrochloric acid which was converted to **3** (*vide supra*). However, an isomer of **19a** (**19b**) was obtained when **3** was nitrosated. The tautomeric structure **19b**, 3,3-dimethyl-5-ethoxalyl-2*H*-1,2,4-triazolo[3,4-*b*]thiazole oxime, was assigned on the basis of a single methyl resonance, different from the doublet seen for **3**, and the fact that hydrolysis of the acetonylhydrazone did not occur in dilute hydrochloric acid (Scheme 5).

The 2-(2-benzoylhydrazino)-4-ethoxalylthiazole oxime (**20**) was prepared by nitrosating **14** hydrochloride. The carbonyl stretching in the ir (1680 cm^{-1} , C=O) indicated the oxime was hydrogen bonded to the ester carbonyl. In all of these mentioned examples, the oxime product (**18**, **19**, or **20**) was capable of forming an intramolecular hydrogen bonded 6-membered ring system.

Scheme 4





A mixture of 2-amino-5-ethoxy-1,3,4-thiadiazine oxime benzoate (**21**), 2-benzamido-5-ethoxy-1,3,4-thiadiazine oxime benzoate (**22**), 2-benzamido-4-benzoyl-5-ethoxy-1,3,4-thiadiazine oxime benzoate (**23**) and 2-benzimido-3-benzoyl-5-ethoxy-1,3,4-thiadiazine oxime benzoate (**24**) arose after reacting the oxime **18** with excess benzoyl chloride in acetonitrile-pyridine solvent. These compounds were separated by silica gel chromatography, but an experimental procedure was later devised so that high yields of all four could be directly obtained without chromatographic techniques (Scheme 6).

The monohydrate hydrochloride of **21** separated after stirring **18** and benzoyl chloride at room temperature in acetonitrile. This salt was neutralized to the free base **21**

with sodium bicarbonate. Spectral data confirmed that **21** was indeed benzoylated at the oxime; there was no oximic stretching in the ir and a broad singlet (2 proton) at δ 5.10 corresponded to the primary amine on the thiadiazine.

If **21** was dissolved in acetonitrile-pyridine at 0° and benzoyl chloride titrated slowly into the reaction, a white pyridinium complex precipitated. Insolubility in chloroform was one characteristic of this complex. When it was recrystallized from a methanol-chloroform-petroleum ether mixture analytically pure **22** was isolated; this free base was readily soluble in chloroform. Benzamide-hydrogen resonance at δ 9.60 in the pmr of **22** confirmed that the primary amine was the second site of benzoylation.

Refluxing the free base **22** or pyridinium complex with benzoyl chloride in acetonitrile-pyridine resulted in the preparation of the tri-benzoylated adducts, which were easily separated on basis of solubility, and assigned structures **23** and **24** on the basis of spectral data.

EXPERIMENTAL

Melting points were taken on a Mel-temp melting point apparatus and are uncorrected. Infrared spectra were determined on Perkin-Elmer models 137-B and 467 infrared spectrometers using potassium bromide pellets unless stated otherwise. With deuteriochloroform or hexadeuteriodimethylsulfoxide as solvents, nuclear magnetic resonance spectra were determined on a Varian Associates Model EM-360 spectrometer; the high resolution experiment was performed on a Varian HR 220 MHz High Resolution spectrometer. The electronic spectra were obtained in ethanol on a Bausch and Lomb 505 spectrometer, with molar absorptions recorded to only two significant figures. At 70 eV a Varian Mat CH-7 spectrometer recorded the mass spectra. Elemental analysis were performed at Midwest Micro Labs Inc., Indianapolis, Indiana.

In thin layer chromatography separations, Kodak silica gel sheets were utilized. Chromatographic columns were constructed of silica gel pellets. Usually based on the first crystallization, the % yields are not considered optimum.

Ethyl 2-Amino-6H-1,3,4-thiadiazine-5-acetate (**2**) Hydrochloride.

To a stirred suspension of thiosemicarbazide (14.0 g., 0.15 mole) in acetonitrile (450 ml.), 26.5 g. (0.15 mole) of ethyl 4-chloroacetoacetate (**1**) was added. Heating caused solution, and after 6 hours at 60° , the white hydrochloride of **2** (24 g., 67%) precipitated upon cooling. The product was washed thoroughly with chloroform after filtration and recrystallized from ethanol, m.p. 147-148; ir (potassium bromide): 3220-2640 (N-H^+), 1730 (C=O), 1600, 1560 (C=N) cm^{-1} ; uv λ max (ethanol) nm (log ϵ): 220 (14.3), 258 (9.5), 344 (7.1); pmr (deuteriodimethylsulfoxide, deuteriochloroform): δ 1.22 (t, 3H, $-\text{CH}_3$), 3.73 (s, 2H, S-CH_2), 3.83 (s, 2H, CH_2CO), 4.20 (q, 2H, OCH_2^-).

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}$: C, 35.36; H, 5.10; Cl, 14.92; N, 17.68; S, 13.47; m.w. $-\text{HCl}$, 201. Found: C, 35.48, H, 5.15; Cl, 15.17; N, 17.91; S, 13.77; M^+ , 201.

With chloroform, ethyl ether, or tetrahydrofuran as solvents, the above condensation was carried out at room temperature. Since these reaction mixtures were heterogeneous throughout, a large excess of solvent was needed. The product was usually colored yellow and had to be recrystallized several times from

Table 2

Condensation of **1** with Thiosemicarbazide in Various Solvents

Solvent	2·HCl, % yield	Appearance	M.p.
Ethanol, reflux	34	dark yellow	137-143°
Ethanol, room temperature	37	yellow	138-143°
Chloroform, room temperature (a)	40	yellow	138-143°
Tetrahydrofuran, room temperature (a)	50	yellow tinted	140-144°
Ethyl ether, room temperature (a)	55	yellow tinted	142-145°
Concentrated hydrochloric acid, room temperature (a)	60	off white	143-146°
Acetonitrile, warming	67	colorless	146-148°

(a) These reactions were heterogeneous and the % yield was based on the amount of product obtained after the first crystallization from ethanol.

ethanol Refluxing or stirring at room temperature in ethanol produced a complex mixture out of which impure **2** crystallized. The reaction also occurred in concentrated hydrochloric acid at room temperature (as a suspension). The percent yields and melting points for the crude product from various solvent systems are given in Table 2.

A solution of **5** (1.0 g., 5.0 mmoles) in 35 ml. of chloroform was acidified with 6 drops of concentrated hydrochloric acid and stirred for 2 hours at room temperature. Gradually a solid separated (1.0 g., 84%). When filtered and dried it melted at 146-148° identical to **2** hydrochloride in melting point and ir spectrum.

Ethyl 2-Isopropylidenehydrazonothiazole-4-acetate (**3**) Hydrochloride.

A suspension of thiosemicarbazide (4.5 g., 50.0 mmoles) and **1** (8.2 g., 50.0 mmoles) in 175 ml. of acetone was magnetically stirred at room temperature for 18 hours. The insoluble white hydrochloride of **3** was separated (11.9 g., 86%) from the milky white mixture and dissolved in ethanol by heating. Upon cooling, colorless **3** hydrochloride crystallized, m.p. 171-173° dec.; ir (potassium bromide): 3120-2640 (N-H⁺), 1725 (C=O), 1590 (C=N) cm⁻¹; nmr (deuteriodimethylsulfoxide, deuterochloroform): δ 1.30 (t, 3H, CH₃), 2.10 (d, 6H, (CH₃)₂C=N, J = 3 Hz), 3.80 (s, 2H, CH₂CO), 4.15 (q, 2H, OCH₂), 6.88 (s, 1H, vinyl).

Anal. Calcd. for C₁₀H₁₆ClN₃O₂S: C, 43.23; H, 5.82; Cl, 12.77; N, 15.13; S, 11.53; m.w. -HCl, 241. Found: C, 42.95; H, 5.88; Cl, 13.29; N, 15.30; S, 11.94; M⁺, 241.

Analogous results were obtained when reacting acetone-thiosemicarbazone with **1** in acetone. Stirring at room temperature 2.9 g., (25.0 mmoles) of acetone-thiosemicarbazone and 4.1 g., (25.0 mmoles) of **1** in acetone (100 ml.) for 15 hours yielded 5 g., (72%) of **3** hydrochloride.

Ethyl 2-Isopropylidenehydrazonothiazole-4-acetate (**3**).

The hydrochloride of **3** (4.0 g., 14.4 mmoles) was dissolved in 125 ml. of water and neutralized with 5% sodium bicarbonate solution at room temperature. After complete neutralization, white product gradually formed (2.7 g., 78%). When first isolated after filtration and washed with water, the precipitate was off-white but upon setting in air turned yellow. Crystallization (ethanol, water) yielded the yellow free base **3**. Both the white and yellow products gave identical melting points and matching spectral properties. Gas chromatography produced a single peak for the yellow free base **3** but showed a slight impurity for the initial white product, m.p. 68-69°; ir (potassium bromide): 3330 (N-H), 1725 (C=O), 1570 (C=N) cm⁻¹; pmr (deuteriochloroform): δ 1.35 (t, 3H, CH₃), 1.94 (d, 6H, J = 12 Hz, N=C(CH₃)₂), 3.82 (s, 2H, CH₂CO), 4.22 (q, 2H, OCH₂), 6.50 (s, 1H, vinyl).

Anal. Calcd. for C₁₀H₁₅N₃O₂S: C, 49.76; H, 6.28; N, 17.42; S, 13.27; m.w., 241. Found: C, 49.55; H, 6.17; N, 17.23; S, 13.14; M⁺, 241.

The hydrochloride of **2** (2.0 g., 8.4 mmoles) was dissolved in 80 ml. of water and 10 ml. of acetone and heated on a steam bath for 10 minutes. The free base of **3** (1 g., 49%) was isolated after neutralized at 0° with 10% sodium bicarbonate.

Reaction of **1** and Acetonethiosemicarbazone in Ethanol.

Compound **1** (4.0 g., 25.0 mmoles) was slowly added to 2.9 g. (25.0 mmoles) of acetonethiosemicarbazone dissolved in 100 ml. of ethanol. The solution was warmed with constant stirring until the original green color turned yellow (approximately 1 hour). Only a small amount (0.6 g., 9%) of the white **3** hydrochloride precipitated after cooling. Refluxing the filtrate for 2 hours produced a deep-red solution, and upon cooling, impure crystals of **2** hydrochloride separated (1.1 g., 19%), identified by m.p. and ir.

Ethyl 2-Hydrazinothiazole-4-acetate (**4**).

Potassium acetate (1.3 g., 12.5 mmoles) was dissolved in 40 ml. of an aqueous ethanol mixture (1:1). With stirring, thiosemicarbazide (1.1 g., 12.5 mmoles) and **1** (2.0 g., 12.5 mmoles) were introduced. After 3 hours of stirring at room temperature a red oil settled out. The reaction mixture was diluted with water and extracted several times with methylene chloride (total 100 ml.). Combined extracts were dried (calcium chloride), filtered, and concentrated under reduced pressure to approximately 2.0 g. of oily residue. Thin layer chromatography (chloroform) revealed the presence of two compounds. This oil was then chromatographed on a silica gel column using methylene chloride as the eluent. Compound **5** was in the first few fractions while the latter fractions contained a single component (0.6 g.) characterized as **4** by pmr. Although **4** was chromatographically pure, it would not crystallize. Simple addition of acetone converted this oil to the hydrazone **3**; ir (mull): 3450-3200 (N-H), 1725 (C=O), 1620, 1580 (C=N) cm⁻¹; pmr (deuteriochloroform): δ 1.20 (t, 3H, CH₃), 3.55 (s, 2H, CH₂CO), 4.15 (q, 2H, OCH₂), 5.80-6.20 (s-broad, 3H, N-H), 6.30 (s, 1H, vinyl); ms: (m/e) 201 (M⁺).

Ethyl 2-Benzylidenehydrazonothiazole-4-acetate (**4a**).

To 3.0 g. (18.1 mmoles) of benzaldehyde thiosemicarbazone, prepared as reported (15) m.p. 162-163°, and 1.82 g. of triethylamine in 125 ml. of ethanol, **1** (2.96 g., 18.1 mmoles) was added. Immediately the reaction turned black; this dark solution was heated with constant stirring for 8 hours. Yellow **4a** separated (4.4 g., 86%) after water was added dropwise to the chilled reaction solution, m.p. 134-136° (ethanol, water); ir (potassium bromide): 3440 (N-H), 1725 (C=O), 1570 (C=N) cm⁻¹; uv λ max (ethanol) nm (log ϵ): 248 (14.2), 344 (18.4); pmr (deuterio-

chloroform): δ 1.25 (t, 3H, CH₃), 3.72, (s, 2H, CH₂CO), 4.20 (q, 2H, OCH₂), 6.50 (s, 1H, vinyl), 7.20-7.75 (m, 5H, ArH), 7.85 (s, 1H, benzylidene-H), 8.35 (s, 1H, N-H).

Anal. Calcd. for C₁₄H₁₅N₃O₂S: C, 58.10; H, 5.24; N, 14.53; S, 11.07; m.w., 289. Found: C, 57.88; H, 5.23; N, 14.57; S, 11.03; M⁺, 289.

2-Amino-5-carbathoxymethylidene-4,5-dihydro-6H-1,3,4-thiadiazine (5).

A 4.0 g. sample of **2** hydrochloride (17.0 mmoles) was dissolved in 60 ml. of distilled water and chilled to 0°. Sodium bicarbonate solution (10%) was slowly titrated into the stirred aqueous solution until neutrality was reached, detected with pH paper. A white precipitate eventually settled out. After filtering, washing with water, and drying under vacuum at 60°, the yellow free base **5** was isolated (2.4 g., 70%). The original white precipitate isomerized to a mixture of **2** and **5** in solution, as monitored by pmr. Crystallization of **5** from benzene generated yellow diamond shaped crystals, m.p. 123-125°; ir (potassium bromide): 3450, 3350 (N-H), 1670-1560 (C=O, C=N) cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 248 (5.7), 345 (10.1); pmr (deuteriochloroform): δ 1.25 (t, 3H, CH₃), 3.45 (s, 2H, SCH₂), 4.15 (q, 2H, OCH₂), 4.45 (s, 1H, vinyl), 4.70 (s, 2H, NH₂), 10.50 (s, 1H, hydrogen bonded N-H).

Anal. Calcd. for C₇H₁₁N₃O₂S: C, 41.77; H, 5.52; N, 20.88; S, 15.91; m.w., 201. Found: C, 42.12; H, 5.62; N, 20.60; S, 15.62; M⁺, 201.

If an aqueous solution of **2** hydrochloride was neutralized with 10% sodium bicarbonate before addition of acetone, only the formation of **5** free base resulted.

2-Imino-3-aminothiazoline-4-acetic Acid (6a) Hydrochloride.

Addition of the thiadiazine (**2**) hydrochloride (23.0 g., 97.0 mmoles) to concentrated hydrochloric acid (70 ml.), followed by heating (20 minutes) gave a clear solution. Eventually white hydrochloride **6a** (16.0 g., 79%) crystallized. Collected on a glass filter and washed several times with chloroform, the product (**6a** hydrochloride) was crystallized from a methanol mixture. The dried thiazoline (**6a**) hydrochloride melted at 220-223° dec.; ir (potassium bromide): 3300-2630 (N-H⁺), 1720-1690 (C=O), 1625-1580 cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 262 (3.50); pmr (deuteriodimethylsulfoxide, deuteriochloroform): δ 3.83 (s, 2H, CH₂CO), 6.50 (s-broad, 3H, N-H), 6.80 (s, 1H, vinyl), 9.70 (s-broad, 1H, OH).

Anal. Calcd. for C₅H₈ClN₃O₂S: C, 28.64; H, 3.86; Cl, 16.92; N, 20.04; S, 15.27. Found: C, 28.51; H, 3.85; Cl, 17.12; N, 20.26; S, 15.08.

Ethyl 2-Imino-3-aminothiazoline-4-acetate (6b) Hydrochloride.

Suspended in 250 ml. of ethanol, 7.0 g. (30.0 mmoles) of the acid **6a** hydrochloride and 4 ml. of 6N hydrochloric acid were refluxed for 35 hours; a solution gradually formed. Ester **6b** hydrochloride was precipitated (5.0 g., 67%) by slowly adding ethyl ether into the concentrated solution. At shorter reaction times, a mixture of the acid **6a** hydrochloride and ester **6b** hydrochloride was obtained. Since the vinylic proton of **6a** hydrochloride and **6b** hydrochloride both resonated at δ 6.80 in the pmr, termination of the reaction had to be determined by measuring the relative intensities (by integration) of the ring vinyl and the ester protons.

Compound **6b** hydrochloride melted at 154-155° (ethanol-ethyl ether); ir (potassium bromide): 3320-2700 (N-H⁺), 1725-1690 (C=O), 1625-1580 (C=N) cm⁻¹; uv, λ max (ethanol): δ 1.15 (t, 3H, CH₃), 3.83 (s, 2H, CH₂CO), 4.20 (q, 2H, CH₂O), 6.80 (s, 1H, vinyl), 9.60 (s-broad, 1H, NH).

Anal. Calcd. for C₇H₁₂ClN₃O₂S: C, 35.36; H, 5.10; Cl,

14.92; N, 17.68; S, 13.47. Found: C, 35.64; H, 5.17; Cl, 14.85; N, 17.87; S, 13.42.

2-Imino-3-amino-4-carbathoxymethylidene-thiazolidine (7a).

In an ice bath, 3.0 g. (12.7 mmoles) of **6b** hydrochloride dissolved in 60 ml. of distilled water was neutralized with 5% sodium carbonate solution. The aqueous solution was extracted 3 times with ethyl ether (30 ml. portions). The extracts were combined, washed with water, dried (calcium chloride) and evaporated under reduced pressure, leaving a white solid. Free base **7a** (1.4 g., 55%) was obtained after crystallization from isopropanol, and melted at 135-137°; ir (potassium bromide): 3230 (N-H), 1675 (C=O), 1550-1650 (C=N) cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 290 (25.6); pmr (deuteriochloroform): 1.27 (t, 3H, CH₃), 4.00-4.41 (m, 4H, N-H, OCH₂), 4.45-4.55 (m, 3H, SCH₂, vinyl), 5.75 (s-broad, 1H, =NH).

Anal. Calcd. for C₇H₁₁N₃O₂S: C, 41.77; H, 5.52; N, 20.88; S, 15.91. Found: C, 41.42; H, 5.68; N, 20.49; S, 15.72.

2-Benzamido-5-carbathoxymethylidene-4,5-dihydro-6H-1,3,4-thiadiazine (8).

To a solution of the thiadiazine **5** (4.0 g., 20.0 mmoles) dissolved in 100 ml. of acetonitrile and 2.5 ml. of pyridine, benzoyl chloride (2.8 g., 20.0 mmoles) in acetonitrile (80 ml.) was added dropwise over a period of 1.5 hours at 0°. The yellow solution was stirred for 8 hours at room temperature then heated 2 hours. A small amount of **2** hydrochloride was filtered after sitting 2 hours at room temperature. Concentrated, the filtrate was transferred to a separatory funnel, and ether (250 ml.) and water were added. The aqueous layer was separated, and the organic layer washed several more times with water to remove traces of pyridine. When the ether solution was dried (calcium chloride) and concentrated; 2.4 g. (40%) of **8** crystallized, m.p. 149-151° after recrystallization from ethanol; ir (potassium bromide): 3220 (N-H), 1625-1550 (C=O, C=N) cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 255 (6.6), 360 (11.2); pmr (deuteriochloroform): δ 1.13 (t, 3H, CH₃), 3.50 (s, 2H, SCH₂), 3.72 (q, 2H, CH₂CO), 4.45 (s, 1H, vinyl), 7.35-7.75 (m, 3H, ArH), 7.95-8.20 (m, 2H, ArH), 10.23 (s, 1H, hydrogen bonded N-H), 11.50 (s, 1H, amide N-H).

Anal. Calcd. for C₁₄H₁₅N₃O₃S: C, 55.05; H, 4.96; N, 13.77; S, 10.49. Found: C, 55.10; H, 4.91; N, 13.52; S, 10.27.

Compound **9** hydrochloride (1.0 g., 3.0 mmoles) in a 300 ml. round bottom flask was dissolved in 50 ml. of an ethanol-water mixture (4:1) and chilled in an ice bath. Sodium bicarbonate (10%) was added while the reaction mixture was being stirred. After a white product began to form additional water was introduced. Filtration and vacuum drying yielded yellow crystals (0.65 g., 71%) with an identical melting point and ir spectrum to **8** free base.

Ethyl 2-Benzamido-6H-1,3,4-thiadiazine-5-acetate (9) Hydrochloride.

A mixture of **5** (3.0 g., 15.0 mmoles) and benzoyl chloride (5.0 g., 35.7 mmoles) in 100 ml. of benzene was refluxed for 14 hours. After cooling, the organic solution was washed with water (to remove traces of **2** hydrochloride), dried over calcium chloride, filtered, and concentrated under reduced pressure. Upon addition of a small amount of petroleum ether to the final reaction solution, white **9** hydrochloride slowly separated from solution (3.0 g., 59%). Thin layer chromatography revealed a number of compounds present in the filtrate. The hydrochloride of **9** was fairly soluble in chloroform but not so in water, m.p. 156-158° (ethanol); ir (potassium bromide): 3200-2300 (N-H⁺), 1725, 1675 (C=O), 1590-1490 (C=N) cm⁻¹; pmr

(deuteriochloroform): δ 1.40 (t, 3H, CH₃), 3.70 (s, 2H, SCH₂), 3.85 (s, 2H, CH₂CO), 7.55-7.85 (m, 3H, ArH), 8.30-8.65 (m, 2H, ArH).

Anal. Calcd. for C₁₄H₁₆ClN₃O₃S: C, 49.18; H, 4.73; Cl, 10.38; N, 12.29; S, 9.37. Found: C, 48.92; H, 4.75; Cl, 10.57; N, 12.39; S, 9.18.

Ethyl 2-Benzimido-3-benzoyl-2,3-dihydro-6*H*-1,3,4-thiadiazine-5-acetate (**10**).

The thiadiazine **5** (1.0 g., 5.0 mmoles) was dissolved in 40 ml. of chloroform and an excess of sodium bicarbonate (1.5 g., 18.0 mmoles) was introduced. An excess of benzoyl chloride (3.5 g., 25.0 mmoles) was then added, the suspension refluxed for 8 hours, and then allowed to stand for several hours at room temperature. The insoluble salts were filtered and the filtrate concentrated under reduced pressure. With slow addition of a petroleum ether-isopropanol mixture (1:1), white **10** immediately precipitated (1.6 g., 78%). Colorless leaflets of **10** melted at 146-148° (2-propanol); *ir* (potassium bromide): 1715-1720 (C=O), 1650-1580 (C=N) cm⁻¹; *uv* λ max (ethanol): nm (log ϵ) 255 (19.2), 265 (20.0); *pmr* (deuteriochloroform): δ 1.33 (t, 3H, CH₃), 3.65 (s, 2H, SCH₂), 3.75 (s, 2H, CH₂CO), 4.25 (q, 2H, OCH₂), 7.00-8.20 (m, 10H, ArH).

Anal. Calcd. for C₂₁H₁₉N₃O₄S: C, 61.59; H, 4.69; N, 10.26; S, 7.82; m.w., 409. Found: C, 61.31; H, 4.70; N, 10.26; S, 7.60; M⁺, 409.

2-Benzamido-4-benzoyl-5-carbethoxymethylidene-4,5-dihydro-6*H*-1,3,4-thiadiazine (**11**).

A solution of 10 g. (0.071 mole) of benzoyl chloride in 70 ml. of acetonitrile was added dropwise to an ice cold solution of 6 g. (30 mmoles) of **5** and 8 ml. of pyridine in 125 ml. of acetonitrile with stirring. The clear orange solution was refluxed for 12 hours, concentrated, taken up in ether (250 ml.) and washed several times with water. The ether was then dried (calcium chloride) and evaporated, leaving an oily brown residue, which when triturated in hot ethanol (150 ml.), solidified to a yellow solid (3.0 g.). Approximately 1.5 g. of impure **8** was isolated from the ethanol filtrate on concentration. Colorless crystals of **11** (1.9 g., 16%) m.p. 187-189°, were obtained after recrystallizing the yellow solid from a methanol-chloroform-petroleum ether mixture: *ir* (potassium bromide): 3220 (N-H), 1690, 1670, 1640, 1580 (C=O, C=N) cm⁻¹; *uv*, λ max (ethanol): nm (log ϵ) 258 (20.1), 295 (20.1); *pmr* (hexadeuteriodimethylsulfoxide, deuteriochloroform): 1.30 (t, 3H, CH₃), 3.80 (s, 2H, SCH₂), 4.13 (q, 2H, OCH₂), 6.00 (s, 1H, vinyl), 7.35-8.25 (m, 10H, ArH), 11.70 (s-broad, 1H, N-H).

Anal. Calcd. for C₁₂H₁₁N₃O₄S: C, 61.59; H, 4.69; N, 10.26; S, 7.82. Found: C, 61.73; H, 4.64; N, 10.28; S, 7.60.

When **5** (2.0 g., 10 mmoles) was refluxed with an excess of benzoyl chloride in ethanol (100 ml.) and triethylamine (2.0 g., 20.0 mmoles) for 10 hours, concentrated and cooled, 1.5 g. (36%) of **11** crystallized. Dropwise addition of ethyl ether to the ethanol concentrate promoted precipitation of the product.

Ethyl 2-Benzimido-3-aminothiazoline-4-acetate (**12a**).

At room temperature, 3.5 g. (30.0 mmoles) of benzoyl chloride was added at once to 6.0 g. (30.0 mmoles) of thiazoline **6b** hydrochloride suspended in 100 ml. of ethanol and 7.0 g. of triethylamine. After stirring for 2.5 hours (room temperature) the clear yellow solution was refluxed 8 hours, then concentrated to 50 ml. and water slowly added until the white product precipitated. Compound **12a** (8.0 g., 87%) was collected, dried, and crystallized from 2-propanol as colorless needles melting at 130-132°; *ir* (potassium bromide): 3300-2850 (H₂N-N), 1725 (C=O), 1550-1500 (C=N, C=O) cm⁻¹; *pmr* (deuteriochloroform):

δ 1.25 (t, 3H, CH₃), 3.70 (s, 2H, CH₂CO), 4.15 (q, 2H, OCH₂), 5.2 (s-broad, 2H, NH₂), 6.33 (s, 1H, vinyl), 7.20-7.50 (m, 3H, ArH), 8.15-8.40 (m, 2H, ArH).

Anal. Calcd. for C₁₄H₁₅N₃O₃S: C, 55.05; H, 4.96; N, 13.77; S, 10.49. Found: C, 54.92; H, 5.00; N, 13.80; S, 10.26.

1-Benzoyl-3-thiosemicarbazide (**13**).

The procedure followed that reported by Hoggarth (13). Powdered semicarbazide (3.0 g., 33.0 mmoles) was suspended in dry pyridine (33 ml.) and cooled to 0°. Benzoyl chloride (5.0 g., 35.7 mmoles) was added dropwise at 0° for 1.5 hours. After 14 hours of stirring at room temperature, 170 ml. of water were added and the pyridine removed under reduced pressure. The oily precipitate was dissolved in hot water, filtered, and allowed to cool to give 4.0 g. (62%) of colorless leaflets melting at 196-198° (lit. (13) melting point, 196-198°), after several crystallizations. The 1,4-dibenzoylated adduct was not soluble in hot water.

Ethyl 2-(2-Benzoylhydrazino)-thiazole-4-acetate (**14**) Hydrochloride.

A mixture of **13** (3.0 g., 15.0 mmoles) and **1** (2.48 g., 15 mmoles) were refluxed 6 hours in 100 ml. of absolute ethanol, to form a clear yellow solution. By slowly adding ethyl ether to the chilled concentrated solution, 4.0 g. (78%) of white **14** hydrochloride settled out. The compound was recrystallized, (ethanol, ether) **14** hydrochloride melted at 172-196° dec.; *ir* (potassium bromide): 3330-2500 (N-H⁺), 1725 (C=O), 1675, 1630 (C=O, C=N) cm⁻¹; *pmr* (deuteriodimethylsulfoxide, deuteriochloroform): δ 1.25 (t, 3H, CH₃), 3.72 (s, 2H, CH₂CO), 4.18 (q, 2H, OCH₂), 6.9 (s, 1H, vinyl), 7.50-7.80 (m, 3H, ArH), 8.05-8.33 (m, 2H, ArH).

Anal. Calcd. for C₁₄H₁₅O₃N₃SC: C, 49.32; H, 4.45; N, 12.33; S, 9.40; m.w., -HCl, 305. Found: C, 49.53; H, 4.59; N, 12.38; S, 9.69; M⁺, 305.

Ethyl 2-(2-Benzoylhydrazino)-thiazole-4-acetate (**14**).

Neutralization at 0° of 4.0 g. (11.7 mmoles) of **14** hydrochloride in aqueous-methanol solution (100 ml., 1:4) with 10% sodium bicarbonate, precipitated 3.0 g. (84%) of the free base **14**. More water (100 ml.) was added, the product collected and crystallized from propanol to give colorless crystals melting at 151-153°; *ir* (potassium bromide): 3330 (N-H), 1725, 1688 (C=O), 1600 (C=N) cm⁻¹; *uv*, λ max (ethanol): nm (log ϵ) 240 (26.9), 263 (13.8); *pmr* (deuteriochloroform): δ 1.24 (t, 3H, CH₃), 3.65 (s, 2H, CH₂CO), 4.18 (q, 2H, OCH₂), 6.52 (s, 1H, vinyl), 7.35-8.25 (m, 5H, ArH).

Anal. Calcd. for C₁₄H₁₅N₃O₃S: C, 55.05; H, 4.96; N, 13.77; S, 10.49; m.w., 305. Found: C, 54.96; H, 5.00; N, 13.70; S, 10.38; M⁺, 305.

3-Phenyl-1,2,4-triazole-5-thiol (**15**).

As previously reported (13) compound **13** (3.9 g., 20.0 mmoles) was added to a solution of sodium (1.5 g.) in ethanol (50 ml.) and refluxed 12 hours. After evaporation to dryness under reduced pressure, the residue was dissolved in water (100 ml.), filtered, and acidified with 10% acetic acid. The precipitate crystallized from water, yielded 2.8 g. of **15** as colorless leaflets (m.p. 254-256°). A melting point of 256° was reported for **15** (16).

Ethyl 3-Phenylthiazolo[2,3-*c*]-s-triazole-5-acetate (**16**).

This procedure corresponded closely to that described by Potts (12). Phosphoryl chloride (6.0 ml.) and the 2-(2-benzoylhydrazino)thiazole **14** (3.0 g., 10.0 mmoles) were added to 35 ml. of xylene and heated to form a bright orange solution. After

refluxing for 8 hours with constant stirring, an insoluble black residue settled to the bottom of the flask. The chilled reaction mixture was diluted with petroleum ether and the liquid then decanted. Sodium bicarbonate solution (10%, 150 ml.) and methylene chloride (60 ml.) dissolved the dark residue, after which the organic layer was separated. Two successive methylene chloride extractions (2 x 50 ml.) were combined, washed twice with water (2 x 50 ml.), and dried over magnesium sulfate. After twice treating the methylene chloride solution with Norite, the clear solution was evaporated to yield 0.8 g. (28%) of impure product **16**. Pure **16** was obtained after several crystallizations from benzene, m.p. 157-160°; ir (potassium bromide): 1715 (C=O), 1460-1450 (C=N) cm^{-1} ; pmr (acetone- d_6): δ 0.85 (t, 3H, CH_3), 3.40-3.70 (m, 4H, OCH_2 , CH_2CO), 7.15 (s, 1H, vinyl), 7.45 (s, 5H, ArH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$: C, 58.51; H, 4.57; N, 14.63; S, 11.14; m.w., 287. Found: C, 58.26; H, 4.53; N, 14.57; S, 11.15; M^+ , 287.

Ethyl 3-Phenylthiazolo[3,2-*b*]-s-triazole-5-acetate (**17**).

A solution of 3.0 g. (16.9 mmoles) of **15** in 80 ml. of absolute ethanol was stirred while 3.0 g. of triethylamine (17.0 mmoles) and 2.8 g. of the ester **1** (17.0 mmoles) were added. The clear solution which resulted was refluxed for 12 hours. When cooled, 2.0 g. (62%) of **17** crystallized, m.p. 131-133° (ethanol); ir (potassium bromide): 1760 (C=O), 1560-1640 (C=N) cm^{-1} ; uv, λ max (ethanol): nm (log ϵ) 268 (20.0); pmr (deuteriochloroform): 1.30 (t, 3H, CH_3), 4.25 (s, 2H, CH_2CO), 4.40 (q, 2H, OCH_2), 7.15 (s, 1H, vinyl), 7.30-7.85 (m, 3H, ArH), 8.03-8.52 (m, 2H, ArH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{N}_3\text{S}$: C, 58.51; H, 4.57; N, 14.63; S, 11.14; m.w., 287. Found: C, 58.71; H, 4.52; N, 14.41; S, 10.94; M^+ , 287.

Using a procedure analogous to that used for the preparation of compound **16**, 1.0 g. (3.0 mmoles) of the 2-benzimido-3-aminothiazoline (**12**) in dry xylene (20 ml.) and phosphoryl chloride (7 ml.) was refluxed 12 hours. Following the previously described workup, 0.33 g. (37%) of **17**, as identified by spectroscopy and m.p., was obtained.

2-Amino-5-ethyloxalyl-6H-1,3,4-thiadiazine Oxime (**18a**).

Sodium nitrite (6.9 g., 0.10 mole) in 70 ml. of water was added dropwise to a reaction flask containing 24.0 g. (0.10 mole) of **2** hydrochloride dissolved in 150 ml. of water, chilled in an ice bath. Stirring gradually produced a light yellow solution at which time off-white product began to precipitate. This product was constantly filtered off throughout the reaction at varying intervals of time. If the precipitate was allowed to set in the reaction medium, it turned brown. The filtered portions of the crude material were combined to give 18 g. of product. Recrystallized from aqueous ethanol, colorless crystals which analyzed correctly for $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_3\text{S}$ were obtained, but thin layer chromatography (methanol-2*N* hydrochloric acid, 8:1) demonstrated the presence of two substances. Successive crystallizations from aqueous methanol did not remove the impurity, nor could it be separated by column chromatography. When the material (1.10 g.) was refluxed in acetone for 20 hours (never going completely into solution), 0.7 g. of pure white product, characterized as **18a**, was collected.

The original recrystallized product mixture exhibited carbonyl stretchings at 1725 and 1690 cm^{-1} in the ir. Compound **18a**, insoluble in acetone, absorbed solely at 1725 cm^{-1} , while the impure yellow material isolated by concentrating the bright acetone filtrate showed an enhanced absorption at 1690 cm^{-1} , along with the 1725 cm^{-1} band.

Compound **18a** melted at 188-191° (methanol); ir (potassium bromide): 3450, 3330 (N-H), 2870-2230 (=N-OH), 1725 (C=O), 1610 (C=N) cm^{-1} ; uv, λ max (ethanol); nm (log ϵ) 268 (9.9), 312 (7.4), 337 (6.2); pmr (deuteriodimethylsulfoxide, deuteriochloroform): δ 1.30 (t, 3H, CH_3), 3.50 (s, 2H, SCH_2), 4.40 (q, 2H, OCH_2).

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_3\text{N}_4\text{S}$: C, 36.51; H, 4.39; N, 24.34; S, 13.91; m.w., 230. Found: C, 36.74; H, 4.63; N, 24.17; S, 13.62; M^+ , 230.

Nitrosating the yellow free base **5** with an equivalent of hydrochloric acid in aqueous solution under the same reaction conditions yielded the same product mixture.

3,3-Dimethyl-5-ethyloxalyl-2*H*-1,2,4-triazolo[3,4-*b*]thiazole Oxime (**19b**).

A solution of sodium nitrite (0.5 g., 7.2 mmoles) in 20 ml. of water was slowly added to a magnetically stirred aqueous solution (40 ml.) of **3** hydrochloride (2.0 g., 7.2 mmoles) at 0°. The mixture was allowed to reach room temperature with stirring for 7 hours. By that time, 1.8 g. (90%) of yellow **19b** had settled out of solution and was collected. This compound was quite hygroscopic, vacuum drying caused a 10% weight loss after oven drying for several days. Crystallization was achieved in benzene-chloroform, m.p. 175-177° dec.; ir (potassium bromide): 3330 (N-H), 3200-3780 (=N-OH), 1675-1575 (C=O, C=N); uv, λ max (ethanol): nm (log ϵ) 257 (12.5), 346 (19.4); pmr (deuteriochloroform): 1.25 (t, 3H, CH_3), 2.05 (s, 6H, $(\text{CH}_3)_2\text{C}'$), 4.24 (q, 2H, OCH_2), 5.83 (s, 1H, vinyl), 10.61 (s-broad, 2H, N-H).

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$: C, 44.42; H, 5.23; N, 20.73; S, 11.85; m.w., 270. Found: C, 44.61; H, 5.22; N, 20.67; S, 11.67; M^+ , 270.

2-(2-Benzoylhydrazino)-4-ethyloxalylthiazole Oxime (**20**).

Slow addition of aqueous (20 ml.) sodium nitrite (0.8 g., 12.0 mmoles) to a stirred solution (150 ml., 1:1 methanol-water mixture) of **14** hydrochloride (4.0 g., 12.0 mmoles) was carried out in an ice bath. A few drops of 6*N* hydrochloric acid was added during the addition. The mixture was then stirred for 10 hours at room temperature, while precipitation of impure yellow **20** (3.0 g., 75%) gradually occurred. After recrystallizing several times from ethanol, off-white crystals of **20** were obtained, which melted at 194-198° dec.; ir (potassium bromide): 3220-2700 (N-H, =N-OH), 1680 (C=O), 1640-1580 (C=O, C=N) cm^{-1} ; uv, λ max (ethanol) nm (log ϵ): 237 (14.7), 327 (17.2); pmr (hexadeuteriodimethylsulfoxide, deuteriochloroform): δ 1.25 (t, 3H, CH_3), 4.22 (q, 2H, OCH_2), 5.70 (s, 1H, vinyl), 7.20-8.18 (m, 5H, ArH), 12.85 (s-broad, 2H, N-H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$: C, 50.28; H, 4.23; N, 16.76; S, 9.58; m.w., 334. Found: C, 50.21; H, 4.24; N, 16.55; S, 9.37; M^+ , 334.

2-Amino-5-ethyloxalyl-6*H*-1,3,4-thiadiazine Oxime Benzoate (**21**) Hydrate Hydrochloride.

Without further purification, the crude oxime mixture (**18a** and **18b**), thoroughly dried, (16.0 g., 70.0 mmoles) was suspended in 300 ml. of acetonitrile. Benzoyl chloride (10.0 g., 70.0 mmoles) diluted with acetonitrile (50 ml.) was added at room temperature. After stirring the clear yellow solution for 1 hour at room temperature, white product began to precipitate. The reaction mixture was allowed to sit for 12 hours, then filtered to give 20 g. (74%) of **21** hydrochloride which melted at 182-185° dec. following crystallization from chloroform-methanol. A hydrochloride hydrate was indicated by the elemental analysis and spectra: ir (potassium bromide): 3330-2500 (N-H⁺), 1735 (C=O), 1625-1610 (C=N) cm^{-1} ; pmr (deuteriodimethylsulfoxide,

deuteriochloroform): δ 1.32 (t, 3H, CH₃), 4.34 (s, 2H, S-CH₂), 4.53 (q, 2H, OCH₂), 7.40-8.15 (m, 5H, ArH).

Anal. Calcd. for C₁₄H₁₇ClN₄O₅S: C, 43.23; H, 4.42; N, 14.41; S, 8.23; m.w., -HCl, 334. Found: C, 43.36; H, 4.49; N, 14.34; S, 7.82; M⁺, 334.

2-Amino-5-ethyloxalyl-6H-1,3,4-thiadiazine Oxime Benzoate (21).

In an aqueous ethanol solution (200 ml., 2:1) the hydrochloride hydrate of **21** (10 g., 26.0 mmoles) was neutralized dropwise at room temperature with 10% sodium bicarbonate. Almost instantaneously a greenish-yellow free base precipitated from solution. Complete neutralization, filtering, and drying resulted in 8 g. (92%) of **21**, which decomposed at 156-159° after recrystallizing from 2-propanol; ir (potassium bromide): 3450-3100 (N-H), 1735 (C=O), 1625-1610 (C=N) cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 251 (10.0), 280 (10.0), 372 (6.3); pmr (deuteriochloroform): δ 1.39 (t, 3H, CH₃), 3.73 (s, 2H, SCH₂), 4.45 (q, 2H, OCH₂), 5.10 (s-broad, 2H, NH₂), 7.43-7.75 (m, 3H, ArH), 7.95-8.20 (m, 2H, ArH).

Anal. Calcd. for C₁₄H₁₄N₄O₄S: C, 50.28; H, 4.23; N, 16.76; S, 9.58; m.w., 334. Found: C, 49.98; H, 3.97; N, 16.74; S, 9.54; M⁺, 334.

2-Benzamido-5-ethyloxalyl-6H-1,3,4-thiadiazine Oxime Benzoate (22).

Benzoyl chloride (1.26 g., 9.0 mmoles) in acetonitrile (40 ml.) was dropped into a chilled suspension of the monobenzoylated oxime **21** (3.0 g., 9.0 mmoles), in acetonitrile (100 ml.), containing 2 ml. of pyridine over a period of 1.5 hours with stirring. Addition of all the acid chloride caused formation of a clear yellow solution. A white precipitate settled after continual stirring for 2 hours. After standing for 10 hours at room temperature, 3.6 g. of a pyridinium complex was filtered, which melted at 154-157° and was insoluble in chloroform. When recrystallized from a methanol-chloroform-petroleum ether system, the dibenzoylated free base **22** was isolated (2.9 g., 73%). Readily soluble in chloroform, compound **22** melted at 195-197° dec.; ir (potassium bromide): 3250 (N-H), 1730-1720 (C=O), 1620-1560 (C=O, C=N) cm⁻¹; uv, λ max (ethanol): nm (log ϵ) 258 (22.0), 351 (21.0); pmr (deuteriochloroform): δ 1.45 (t, 3H, CH₃), 3.90 (s, 2H, SCH₂), 4.53 (q, 2H, OCH₂), 7.35-7.85 (m, 6H, ArH), 8.00-8.50 (m, 5H, ArH, N-H).

Anal. Calcd. for C₂₁H₁₈N₄O₅S: C, 57.51; H, 4.15; N, 12.78; S, 7.30; m.w., 438. Found: C, 57.14; H, 4.20; N, 12.49; S, 7.20; M⁺, 438.

2-Benzamido-4-benzoyl-5-ethyloxalyl-4H-1,3,4-thiadiazine Oxime Benzoate (23).

To a suspension of 3.0 g. (6.90 mmoles) of **22** in acetonitrile (100 ml.) and pyridine (3.0 ml.) an excess of benzoyl chloride (10.0 g., 7.20 mmoles) was added. The resulting yellow solution was refluxed for 35 hours. After cooling, the tribenzoylated adduct (**23**) separated from solution and was filtered, washed and dried to give 2.0 g. (53%) of the crude white precipitate. After recrystallizing from ethanol, **23** melted at 215-218°; ir (potassium bromide): 3150-3300 (NH), 1710-1725 (C=O), 1630-1650, 1560 (C=O, C=N) cm⁻¹; pmr (hexadeuteriodimethyl-sulfoxide): δ 1.35 (t, 3H, CH₃), 4.40 (q, 2H, OCH₂), 8.30-7.30 (m, 16H, ArH, vinyl).

Anal. Calcd. for C₂₈H₂₂N₄O₆S: C, 61.97; H, 4.10; N, 10.33; S, 5.90. Found: C, 61.73; H, 4.00; N, 10.12; S, 5.69.

2-Benzimidazo-3-benzoyl-5-ethyloxalyl-2,3-dihydro-6H-1,3,4-thiadiazine Oxime Benzoate (24).

After concentrating the filtrate from the previous experiment

(from which **23** crystallized) under reduced pressure, 150 ml. of ethyl ether were added and the resulting suspension allowed to sit for 0.5 hour. Solid material was filtered off and the ether filtrate washed with 5% sodium bicarbonate (1 x 100 ml.) and water (2 x 150 ml.). The ether was dried (magnesium sulfate), filtered and concentrated under reduced pressure. Slow addition of a petroleum ether-ethanol mixture (1:1) precipitated 1.0 g. (27%) of the colorless tribenzoylated adduct **24**, m.p. 173-175° (ethanol, chloroform); ir (potassium bromide): 1770-1710 (C=O), 1625 (C=N) cm⁻¹; pmr (deuteriochloroform): δ 1.35 (t, 3H, CH₃), 4.14 (s, 2H, S-CH₂), 4.50 (q, 2H, OCH₂), 7.35-7.70 (m, 9H, ArH), 7.85-8.25 (m, 6H, ArH).

Anal. Calcd. for C₂₈H₂₂N₄O₆S: C, 61.97; H, 4.10; N, 10.33; S, 5.90. Found: C, 61.76; H, 4.13; N, 10.56; S, 6.16.

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- (1) Contribution No. 3059. This work was partially supported by Grant GM-10366, General Medical Sciences, U.S. Public Health Service, to Indiana University.
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195	α,β -unsaturated carboxylic acids and esters
12	γ ring residue
5	exo double bonds
95	β amino substituent
30	double bond (or lone pair electron on nitrogen) extending conjugation

 337nm (calculated maximum wavelength) (a)
 345nm (experimental value)
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