Acetylenic esters. II. Further addition reactions with sulfur- and nitrogen-containing compounds

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Substituted thiosemicarbazides react with dimethyl acetylenedicarboxylate to give 3-amino-2,3-dihydrothiazin-4-ones. Confirmation of the structures is provided by catalytic hydrogenation and by characteristic mass spectral fragmentations. 4-Substituted thiosemicarbazides react with methyl propiolate in the same way as monosubstituted hydrazines and hydrazides to give hydrazones, whereas 1-substituted thiosemicarbazides undergo smooth removal of the sulfur with the production of an equal mixture of *cis–trans* and *cis–cis* dimethyl-β-thiodiacrylic esters. Bicyclic heterocyclic structures are formed by reaction of dimethyl acetylenedicarboxylate with imidazolidone thione and with 5,5-dimethyl-2-thiohydantoin. Substituted guanidines react with dimethyl acetylenedicarboxylate in an analogous fashion, yielding substituted 2,3-dihydrodiazinones. The high-resolution mass spectra of the latter show many similarities to the spectra of the sulfur analogues. Thioamides, despite previous claims to the contrary, react with dimethyl acetylenedicarboxylate to give thioethers of fumarate ester or 1,3-thiazin-4-ones. In contrast, thioamides react with methyl propiolate to give an equal mixture of *cis–trans* and *cis–cis* dimethyl-β-thiodiacrylic esters.

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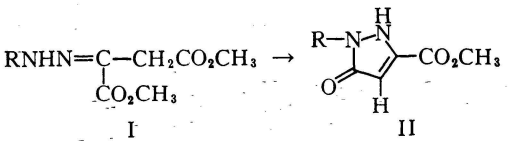
The chemistry of the addition reactions of acetylenic esters has been developed considerably since the pioneering researches of Diels and his co-workers (1). A recent review attests to the versatility of these compounds (2). Although interest has been concentrated upon the reactions with nitrogen-containing heterocycles (these condensations have been investigated fully by Acheson and by Johnson), comparatively little attention has been paid to the reactions of acetylenic esters with simple nitrogen- and sulfur-containing compounds such as hydrazines, thioureas, and thiosemicarbazides.

With a view to extending the synthetic utility of dimethyl acetylenedicarboxylate (DAD), we have investigated its reactions with substituted hydrazines, hydrazides, thiosemicarbazides, guanidines, and imidazolidine thione derivatives, and reinvestigated its reaction with thioamides.

Substituted Hydrazines

A number of monosubstituted hydrazines reacted readily with DAD in methanol solution to give hydrazones which, from their physical data, possessed structures similar to I. In two representative cases, the derivatives of phenylhydrazine and *p*-nitrophenylhydrazine, the structures were confirmed by cyclization to the pyrazolones II, the former by refluxing the solution of the hydrazone in xylene and the latter by treatment with a basic catalyst α-picoline. Table I summarizes the analytical and spectroscopic data of these compounds.



I II

Substituted Hydrazides

Monosubstituted hydrazides reacted readily with DAD in methanol solution to give *N*-acylhydrazones. The analytical and spectroscopic data for these compounds are summarized in Table II.

Substituted Thiosemicarbazides

In contrast to the simple condensations observed with hydrazines and hydrazides, substituted thiosemicarbazides react rapidly with DAD to give cyclic products. In this regard, they resemble thioureas (3). The presence of the C=S group considerably enhances the reactivity compared with that of hydrazines and hydrazides.

(*i*) 4-Methylthiosemicarbazide reacted with 1 *M* equivalent of DAD in methanol, yielding a crystalline solid, $C_7H_9N_3SO_3$.

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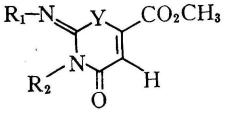
TABLE I

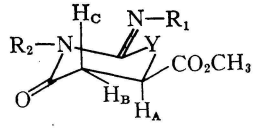
Characteristic mass spectral peaks of 2,3-dihydro-1,3-thiazin-4-ones and 2,3-dihydro-1,3-diazinones



				Common fragmentation								Substitution					
R_1	R_2	Y		Molecular ion	M-31	M-59	144	116	86	85	59	58	R_1	M—R_2	R_1NCNR_2	R_1NCN	$R_1N{\equiv}C$	R_1—N
CH_3	NH_2	S	*m/e*	215	184	156								199	71	55	(42)	
			%	100	10	2	11	11	81	45	22	7		13	41	5	65	
CH_2CHCH_2	NH_2	S	*m/e*	241	210	182							41	225	97	81	67	53
			%	37	8	3	7	15	6	25	16	5	100	17	7	81	4	11
C_6H_5	NH_2	S	*m/e*	277	246	218							77	261	133	117	(104)	91
			%	100	4	5	3	7	4	14	8	3	41	1	15	9	12	13
—CH_2—CH_2—		S	*m/e*	212	181	153									68			
			%	100	30	6	10	8	4	17	8	2			43			
—$C(CH_3)_2$—C(=O)—		S	*m/e*	254	223	195									110			
			%	75	10	7	39	20	29	22	14	4			97			
C_6H_5	C_6H_5	C_6H_5N	*m/e*	397	366	338		175	145	144		117	77		194	117	103	91
			%	100	3	59		41	3	33	1	7	55		57	7	4	13
C_6H_5	H	C_6H_5N	*m/e*	321	290	262		175	145	144		41	77		194	117	(104)	91
			%	7	1	1		3	3	8	1	2	36		1	2	1	4

TABLE II

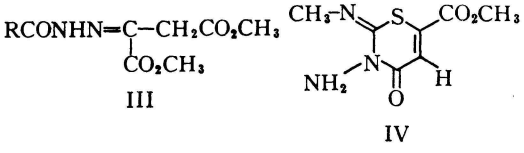
Characteristic mass spectral peaks of perhydrothiazinones and perhydrodiazinones



				Common fragmentation									Substitution						
R_1	R_2	Y		Molecular ion	M-31	M-59	M-60	118	88	87	60	59	R_1	M—R_2	R_1NCNR_2	RNCNH	RNCH	RNCS	R—N
CH_3	NH_2	S	*m/e*	217	186	158	157							201	71	55	42	73	
			%	91	6	100	3	2	3	9	3	51		27	18	98	54	8	
$CH_3CH_2CH_2$	NH_2	S	*m/e*	245	214	186	185						43	229	99	85	70	101	57
			%	32	13	9	9	7	4	20	28	56	98	28	5	26	21	20	29
C_6H_5	NH_2	S	*m/e*	279	248	220	219						77	264		118	104	135	91
			%	99	2	20	55	10	2	3	4	40	100	2		10	20	84	11
—CH_2—CH_2—		S	*m/e*	214	183	155	154								68				
			%	100	26	88	81	5	1	2	4	29			33				
C_6H_5	C_6H_5	C_6H_5N	*m/e*	399	368	340	339	117	148	146	119		77	322	194	118	104		91
			%	100	2	19	2	22	7	2	2	2	78	2	34	12	79		18
C_6H_5	H	C_6H_5N	*m/e*	323	292	264	263	177	147	146	119		77		194	118	104		91
			%	100	2	32	16	6	2	6	12	5	82		7	20	73		14

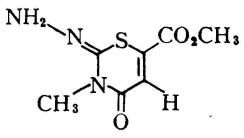
Infrared bands characteristic of NH_2, cyclic amide, ester, and a trisubstituted double bond, and nuclear magnetic resonance (n.m.r.) bands attributable to methyl ester, vinyl proton, and NH, are observed.

These data are consistent with four possible six membered ring structures (IV, V, VI, and VII), an analogous set of five membered ring structures such as VIII, and less likely structures in which the $—NH_2$ is part of a seven-membered ring (IX).

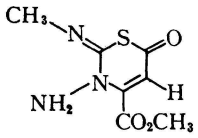


III

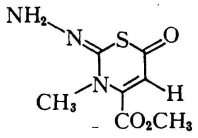
IV



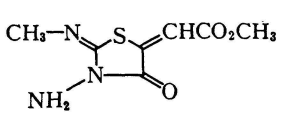
V



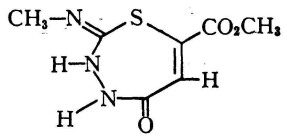
VI



VII

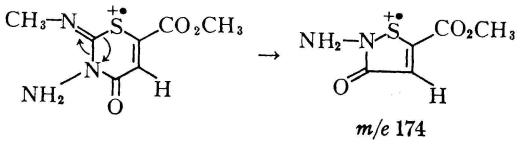


VIII



IX

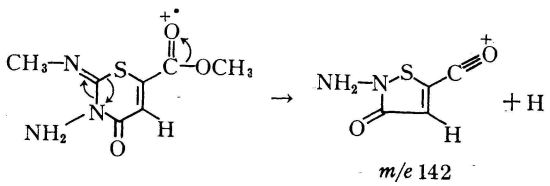
The high-resolution mass spectrum was particularly valuable in assigning a structure (see Fig. 1). A molecular ion peak at *m/e* 215, which was also the base peak, corresponded to $C_7H_9N_3SO_3$. Conventional 'simple' fragmentations such as loss of $—OCH_3$ and CO_2CH_3 confirm the gross structural features, and significant peaks occur at *m/e* 199, 174, 142, and 74. The *m/e* 199 peak can correspond only to loss of $—NH_2$. This was confirmed by peak measurement, thus proving that one of the nitrogens is exocyclic; therefore, structure IX can be discounted. The peak at *m/e* 174 corresponds to loss of $CH_3—N{\equiv}C$, which can be explained satisfactorily in terms of IV or VI but not V or VII. Confirmatory



m/e 174

evidence of the position of the methyl group is provided by the peak at *m/e* 74 corresponding to loss of $CH_3—N{=}C{=}S$ and H, again consistent only with IV or VI.

Measurement of the peak at *m/e* 142 confirms the composition to be $C_4H_2N_2SO_2^+$. This provides an interesting example of an ion which cannot be represented by a con-



m/e 142

ventional structure. Additional confirmation is provided by reference to Tables I and II, when it is seen that the adducts of thiosemicarbazides with DAD show all the features characteristic of 2,3-dihydro-1,3-thiazin-4-ones, i.e. peaks at *m/e* 144, 116, 86, 85, and 58, which have been shown by peak measurement to correspond to the ions shown in Scheme 1. Other peaks which are characteristic of these adducts are those corresponding to separation of the resonance-stabilized substituted carbodiimide ions, and to nitrile ions which are analogous to similar ions found in the spectra of the substituted thiourea – DAD adducts (3) and in substituted Δ^2-thiazolines (4, 5).

The peak measurements listed in Table III confirm the composition of the daughter ions.

An immediate decision between five and six membered ring structures in favor of the latter can be reached on the basis of the n.m.r. spectrum of the hydrogenated adduct $C_7H_{11}N_3O_3S$, which clearly shows an ABC spectrum because of the protons at the C-5 and C-6 positions. The magnitudes of the coupling constants are consistent with a

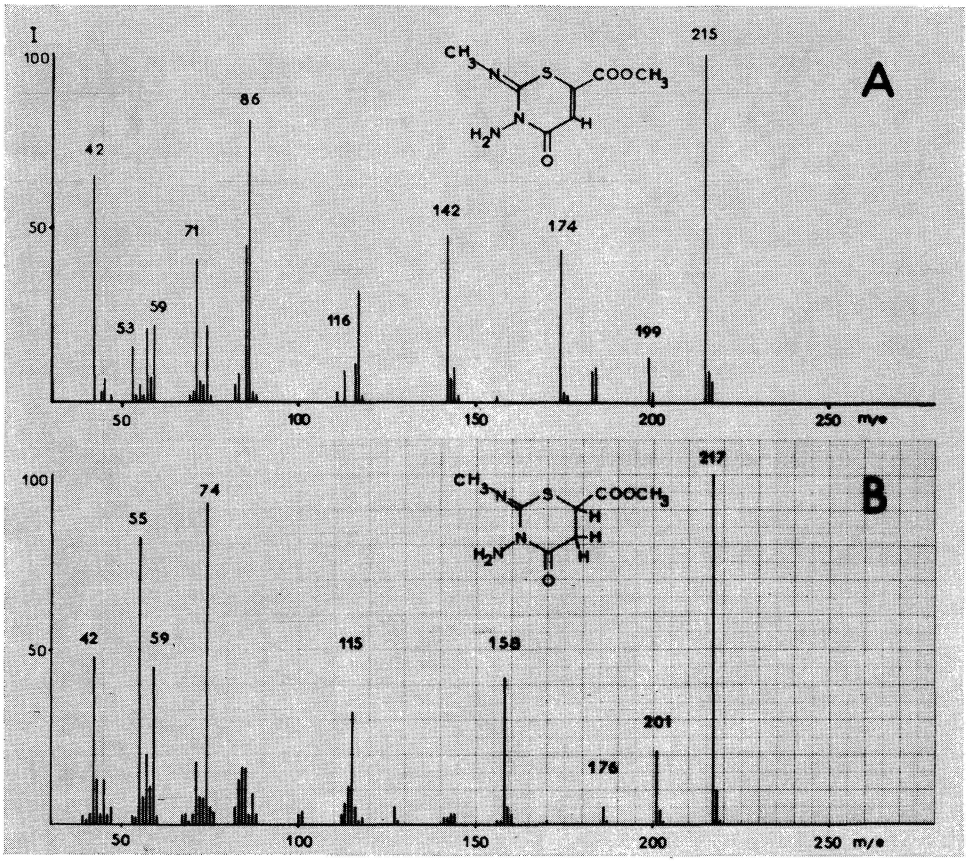
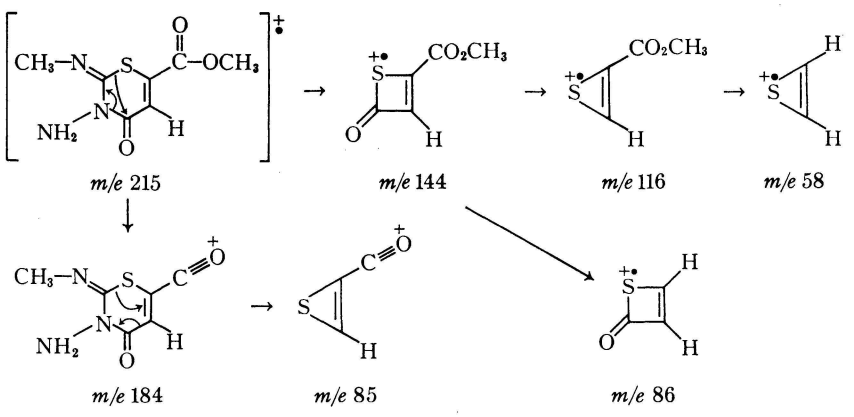


FIG. 1. The high-resolution mass spectra of (A) 2-methylimino-3-amino-6-carbomethoxy-2,3-dihydro-1,3-thiazin-4-one and (B) 2-methylimino-3-amino-6-carbomethoxyperhydro-1,3-thiazin-4-one.



SCHEME 1.

TABLE III

High-resolution mass spectrum of 2-methylimino-3-amino-6-carbomethoxy-2,3-dihydro-1,3-thiazin-4-one

Ion	*m/e* calculated	*m/e* found
$C_5H_6N_2O_3S^+$	174.0099	174.0101
$C_4H_2N_2O_2S^+$	141.9837	141.9851
$C_7H_7N_2O_3S^+$	199.0177	199.0166
$C_2H_4NS^+$	74.0064	74.0063
$C_2H_5N_3^+$	71.0484	71.0482

chair conformation of the type X, whereas a five membered ring structure such as VIII would give rise to an AB_2 pattern on hydrogenation. Final confirmation of this point is provided by base-catalyzed enolization and equilibration of the configuration at C-6 in other representative adducts. The mass spectrum of the hydrogenated adduct is in accordance with prediction, again showing a peak at *m/e* 201 (= M-16) arising from loss of $—NH_2$, and a peak at *m/e* 158 arising from loss of CO_2CH_3 (in all respects it resembles the spectra of perhydrothiazinones; see Fig. 1B).

The selection of IV as the correct structure from the remaining alternatives IV and VI is made on mechanistic grounds by analogy with the reaction of thioureas with DAD (3).

(*ii*) 4-Allylthiosemicarbazide reacts similarly in methanol with 1 *M* equivalent of DAD, giving a yellow crystalline solid, $C_9H_{11}N_3O_3S$, the elemental composition being checked by peak measurement. Structures analogous to IV–IX were considered on the basis of the spectral evidence. High-resolution mass spectrometry immediately provides an answer in favor of structure IV, because of an ion at *m/e* 225 ($—NH_2$) and other ions characteristic of 2,3-dihydro-1,3-thiazin-4-ones (see Table I). The very stable allyl ion is the most abundant in the whole spectrum. The n.m.r. spectrum of the fully hydrogenated adduct is consistent with a six-membered chair conformation.

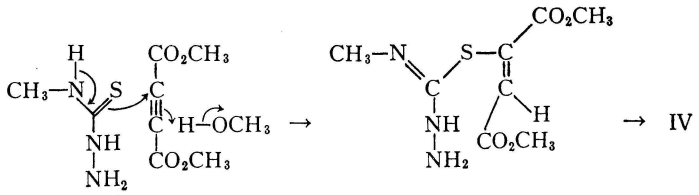
(*iii*) 4-Phenylthiosemicarbazide gives a similar adduct, $C_{12}H_{11}N_3O_3S$, with DAD. Reference to the tables summarizing the physical data will confirm that the structure is quite analogous to IV.

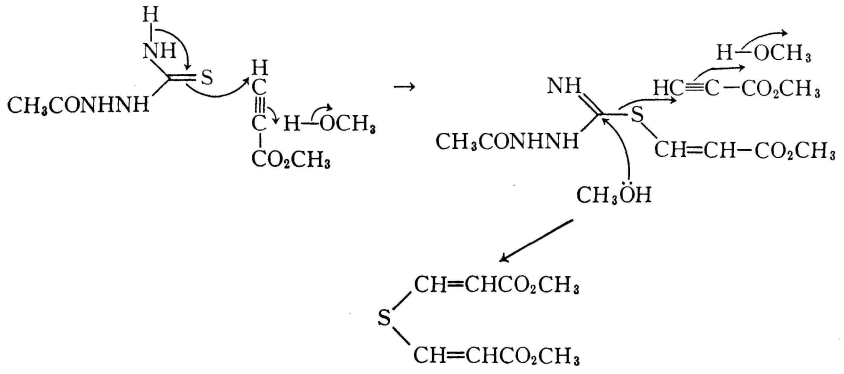
(iv) Reaction of Thiosemicarbazides with Methyl Propiolate

Although not strictly necessary from the standpoint of proof of structure, it was thought desirable to react substituted thiosemicarbazides with methyl propiolate in the expectation that products of the type XI would be formed, to which IV, for example, could be related in principle by saponification and decarboxylation. Such was not the case. However, a potentially important reaction was uncovered. 4-Substituted thiosemicarbazides react with methyl propiolate to give thiosemicarbazones; this result is analogous to the behavior of hydrazines and hydrazides. However, 1-substituted thiosemicarbazides undergo smooth removal of the sulfur with the production of an equal mixture of isomeric *cis–trans* and *cis–cis* dimethyl-β-thiodiacrylic esters. Preliminary work on this reaction indicates that it is widely applicable to thiocarbonyl compounds and that the stereochemistry of the thioester depends on the reaction conditions and the precise structure of the starting material. The details of our findings will be reported in a subsequent publication.

Bicyclic Structures

In view of our experience with substituted thioureas and thiosemicarbazides, it was to be expected that heterocyclic compounds containing the functional groups common to these acyclic systems would undergo reaction with DAD with the production of bicyclic heterocyclic compounds, and so this useful synthetic reaction was studied with imidazolidine thione. The

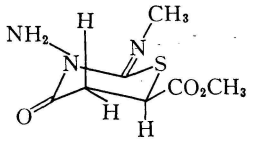




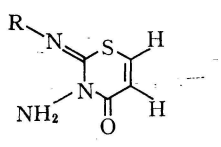
1:1 *cis–cis* and *cis–trans*

latter reacted readily with DAD in methanol, giving a crystalline solid, m.p. 198°, $C_8H_8N_2O_3S$. That the compound contains two methylene groups flanked by two nitrogens differing considerably in their basicity is shown by the behavior of the corresponding n.m.r. absorptions in $CDCl_3$ and in CH_3COOH–CF_3COOH. In the former solvent, the methylene resonances are distinct at 4.5 and 3.93 δ (branches of an A_2B_2 pattern). In the latter solvent, the CH_2 group adjacent to the basic nitrogen (now protonated) suffers a paramagnetic shift (6) and the A_2B_2 pattern collapses together at 5.5 δ. This, together with other physical data, is consistent with structures XII and XIII. The six-membered structure of the new ring is confirmed by catalytic hydrogenation, which yields a compound, $C_8H_{10}N_2O_3S$, the n.m.r. spectrum of which shows an ABC pattern with coupling constants in agreement with those of a perhydrothiazinone structure. Structure XII is preferred on mechanistic grounds, and the assignment is confirmed by the very close similarity of the high-resolution mass spectra of both the adduct and the product of catalytic hydrogenation to the spectra of many 2,3-dihydro-1,3-thiazin-4-ones and perhydro-1,3-thiazinones, respectively.

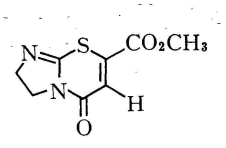
(*vi*) 5,5-Dimethyl-2-thiohydantoin reacts similarly to give a 1:1 adduct, $C_{10}H_{10}N_2O_4S$.



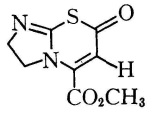
X



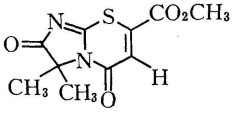
XI



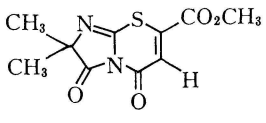
XII



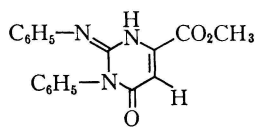
XIII



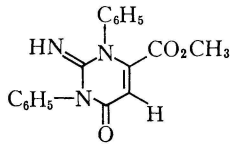
XIV



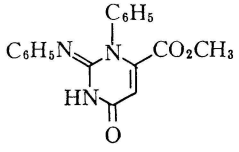
XV



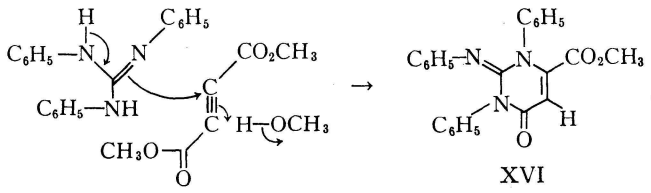
XVII



XVIII



XIX



XVI

Consideration of the physical data and chemical evidence as discussed above leaves two alternative structures, XIV and XV. The observation of an unusual imide band in the infrared at 1 762 cm^{-1}, for which good model compounds are available in the literature (7, 8), is in better accordance with structure XV. When the 1-position is blocked, as in 1-acetyl-2-thiohydantoin, no reaction with DAD takes place.

Substituted Guanidines

By analogy with the facile nucleophilic attack of thiocarbonyl compounds on acetylenic esters, guanidines might be expected to react in a similar fashion. Triphenylguanidine does add readily to DAD to give a crystalline solid, $C_{24}H_{19}N_3O_3$, the spectroscopic data of which corresponded to the substituted pyrimidinone structure XVI. Absorption of 1 mole of hydrogen in the presence of palladium, and the observation of an ABC pattern in the n.m.r. spectrum with coupling constants corresponding to a six-membered chair conformation, confirmed structure XVI.

Because of the general similarity of XVI to structures such as IV, it was of interest to see if the fragmentation patterns characteristic of the dihydrothiazinones have analogies in the guanidine derivatives. As can be seen, many fragmentations are retained when allowance is made for the additional substituent on the nitrogen atom. The assignment of structures to the daughter ions is supported by the peak measurements listed in Table IV.

Examination of the perhydro compounds shows that fragmentations characteristic of the sulfur analogues are also evident here.

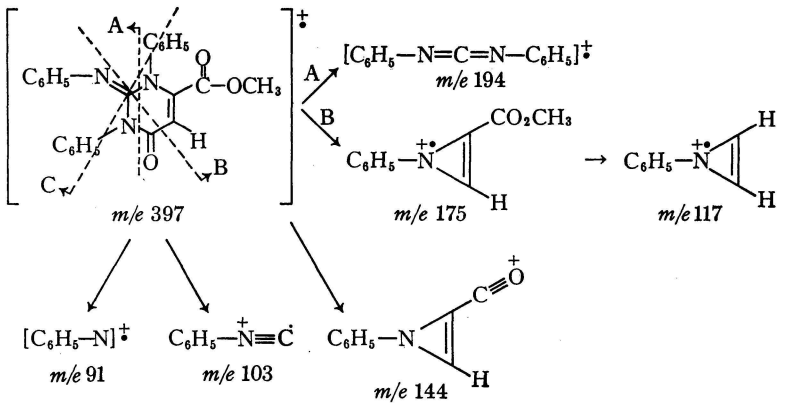
The analogous adduct formed from 1,3-diphenylguanidine can have one of three alternative structures (XVII, XVIII, or XIX), n.m.r. evidence on the perhydro compound having established a six membered ring structure. Direct analogy with the mechanism proposed for the additions of thioureas and thiosemicarbazides would predict structure XVII. Examination of the high-resolution mass spectrum of the perhydrodiazinone (Fig. 3B) shows a peak at *m/e* 194 corresponding to the diphenylcarbodiimide ion in Scheme 3 (confirmed by peak measurement), favoring XVII or

TABLE IV

High-resolution mass spectra of dihydrodiazinones and perhydrodiazinones

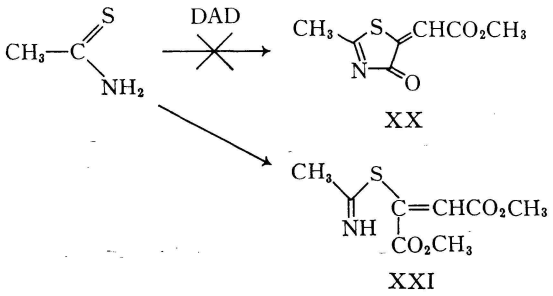
Structure of parent compound	Ion	*m/e* calculated	*m/e* found
$R_1 = C_6H_5$, $R_2 = C_6H_5$, $Y = NC_6H_5$*	$C_{10}H_9NO_2^+$	175.0633	175.0632
	$C_9H_6NO^+$	144.0449	144.0450
	$C_8H_7N^+$	117.0578	117.0580
	$C_7H_5N^+$	103.0422	103.0418
$R_1 = C_6H_5$, $R_2 = C_6H_5$, $Y = NC_6H_5$†	$C_{24}H_{21}N_3O_3^+$	399.1583	399.1576
	$C_{10}H_{11}NO_2^+$	177.0789	177.0789
	$C_8H_8N^+$	188.0657	118.0655
	$C_6H_5N^+$	91.0422	91.0425
	$C_7H_7^+$	91.0549	91.0551
$R_1 = C_6H_5$, $R_2 = H$, $Y = NC_6H_5$*	$C_6H_5N^+$	93.0578	93.0578
$R_1 = C_6H_5$, $R_2 = H$, $Y = NC_6H_5$†	$C_{13}H_{10}N_2^+$	194.0844	194.0840
	$C_{10}H_{12}NO_2^+$	178.0868	178.0859

*See Table I for the structural formula.
†See Table II for the structural formula.



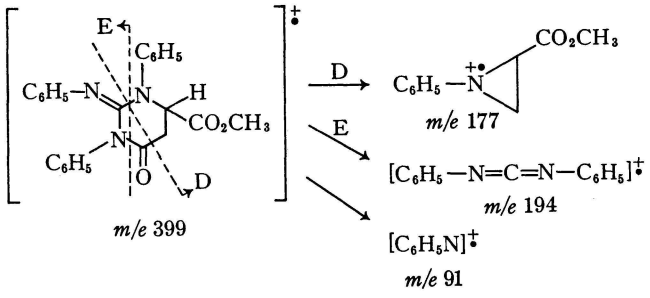
SCHEME 2.

XIX. This conclusion is supported by the peak at *m/e* 104, which corresponds to $[C_6H_4—N=CH]^+$ and which can arise by a fragmentation similar to C in Scheme 2. A decision between the two alternatives XVII and XIX in favor of the latter is made on the basis of the peak at *m/e* 177 (analogous to fragmentation D in Scheme 3), which definitely places a phenyl group adjacent to the carbon bearing the carbomethoxy group.



Thioamides

Previously published reports of the addition of thioamides to acetylenic esters were at variance with the results presented here (9). It is claimed, for example, that thioacetamide reacts with DAD in methanol to give XX, and that thioamides react with propiolic esters to give 1,3-thiazin-4-ones. Reexamination of the product of the reaction of thioacetamide with DAD shows that it contains two ester methyl groups and analyzes for $C_8H_{11}NSO_4$; accordingly, it is assigned structure XXI. Since it contains a sulfur bonded to the carbon–carbon double bond of the fumarate residue, one would predict the mass spectrum to show all the sulfur-containing daughter ions shown in Scheme 1. This is found to be the case. In contrast, both thioacetamide and thiobenzamide react with methyl propiolate to give a 1:1 mixture of *cis–trans* and *cis–cis* dimethyl-β-thiodiacrylic esters. Thiobenzamide is said to react with ethyl propiolate to give 2-phenyl-1,3-thiazin-4-one; however, since no structural proof was offered, and in view of our result, this conclusion is strongly suspected (9).



SCHEME 3.

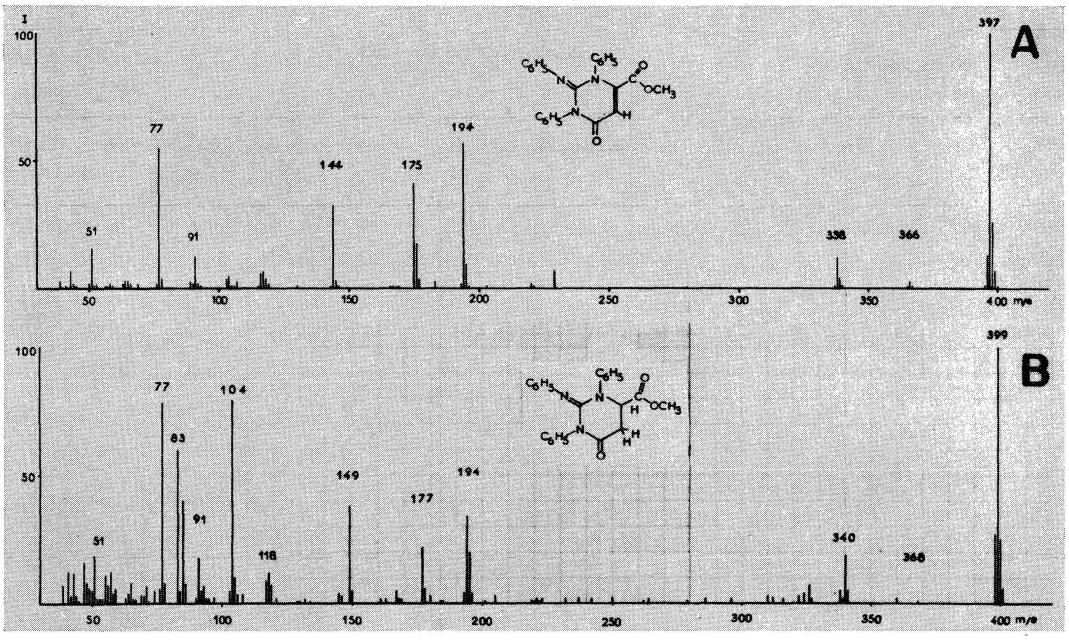


FIG. 2. The high-resolution mass spectra of (A) 2-phenylimino-1,3-diphenyl-6-carbomethoxy-2,3-dihydro-1,3-diazin-4-one and (B) 2-phenylimino-1,3-diphenyl-6-carbomethoxyperhydro-1,3-diazin-4-one.

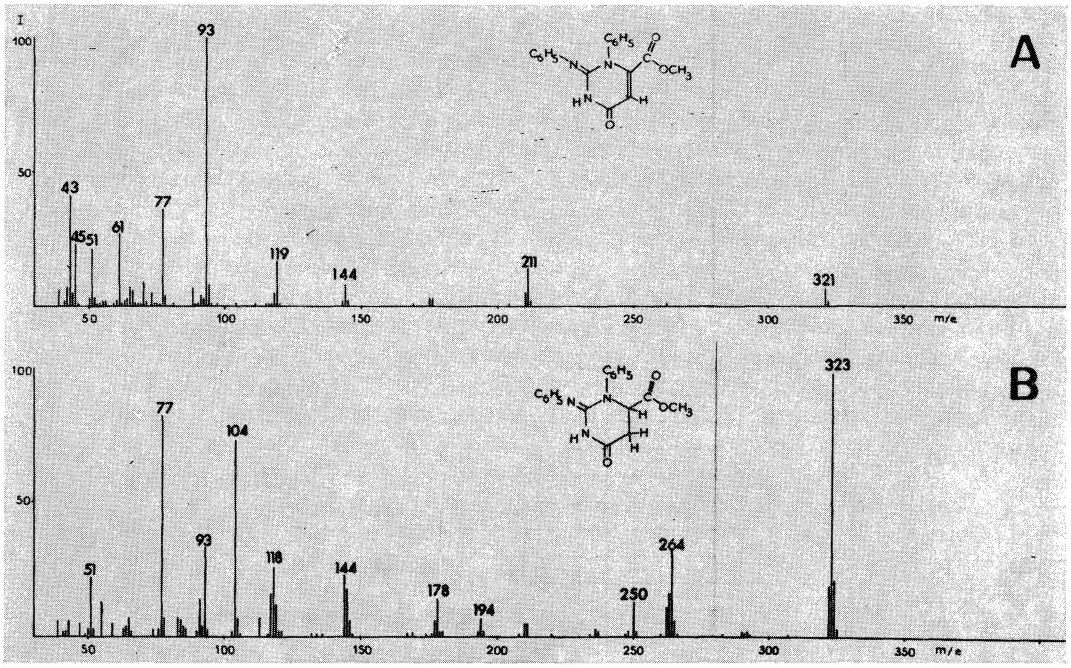


FIG. 3. The high-resolution mass spectra of (A) 2-phenylimino-1-phenyl-6-carbomethoxy-2,3-dihydro-1,3-diazin-4-one and (B) 2-phenylimino-1-phenyl-6-carbomethoxyperhydro-1,3-diazin-4-one.

Thiobenzamide reacts with DAD to give a crystalline solid, $C_{12}H_9NSO_3$. Although this could not be hydrogenated to provide convincing proof of a six membered ring structure, the close similarity of the mass spectrum to those of the other structures previously discussed leaves little doubt that this is 2-phenyl-6-carbomethoxy-1,3-thiazin-4-one, and not a 4-thiazolidinone as claimed (9).

EXPERIMENTAL

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer model 421 spectrophotometer, and only the principal, sharply defined peaks are reported. Nuclear magnetic resonance spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in an appropriate solvent, with tetramethylsilane as a standard. Line positions are reported in parts per million from the reference. Mass spectra were determined on an Associated Electronic Industries MS-9 double-focusing high-resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15 000. Kieselgel DF-5 (Camag, Switzerland) was used for thin-layer chromatography. Microanalyses were carried out by Dr. C. Daesslé, Organic Microanalysis Ltd., Montreal, Quebec, and by Miss D. Roberts of this department.

General Procedure for Preparation of Adducts

All the new compounds, the physical data of which are summarized in tabular form, were prepared according to the following procedure. Approximately 0.012 mole of DAD dissolved in 25 ml of warm methanol was added in portions to a magnetically stirred solution of ca. 0.01 mole of substrate (thiosemicarbazide, hydrazine, guanidine, etc.) in 25 ml of warm methanol.

Usually there was little evolution of heat or color change, and the mixture was set aside at room temperature for 24 h. The excess solvent was allowed to evaporate on a clock-glass in the fume hood, and the resulting crystalline adduct was collected, washed with a little cold methanol, and purified by recrystallization from an appropriate solvent as indicated in the tables. In general, two recrystallizations were sufficient to provide a sample of analytical purity, but thin-layer chromatography on silica gel under a variety of eluents was performed before the sample was analyzed by mass spectrometry.

General Procedure for Hydrogenation of Adducts

The primary adducts were usually hydrogenated smoothly at atmospheric pressure over 5% palladium on charcoal in ethyl acetate or methanol. In some experiments the uptake of hydrogen was quite slow, presumably because of partial poisoning of the catalyst by the sulfur or nitrogen heterocycles. Monitoring of the reaction by thin-layer chromatography provided a convenient check on the purity of the product, which usually crystallized well. In those few cases where hydrogenation by this procedure could not be accomplished, the limiting factor was insolubility. The catalyst was cleanly removed by filtration through silica-impregnated filter paper (Whatman SG-81 containing 22% silica gel.)

General Conditions for Equilibration of Epimers of Perhydro Adducts

The conditions have been described previously (3), and in representative cases the appearance of the second epimer was recognized by additional lines in the n.m.r. spectrum, in particular new ABC systems. The fact that the only chemical change as a result of treatment with base had been epimerization at C-6 is confirmed by the identity of the high-resolution mass spectrum before and after such treatment.

2-Phenyl-5-carbomethoxypyrazolone

Dimethyloxaloacetate phenylhydrazone (0.52 g) was dissolved in 10 ml of dry xylene and the mixture boiled momentarily. After the solution was allowed to cool, thick crystals (0.425 g, 95%) of the pyrazolone, m.p. 225°, separated.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.58; N, 12.89. Found: C, 60.37; H, 4.60; N, 12.91.

2-(p-Nitrophenyl)-5-carbomethoxypyrazolone

Dimethyloxaloacetate *p*-nitrophenylhydrazone (0.596 g) was dissolved in 10 ml of α-picoline, the solution was refluxed for 30 min and then cooled, and the solvent was allowed to evaporate, giving a brown gum which readily crystallized from methanol as a tan microcrystalline solid, m.p. 253° (decomp.), 0.41 g (91% yield).

Anal. Calcd. for $C_{11}H_9N_3O_5$: C, 50.2; H, 3.42; N, 15.98. Found: C, 50.11; H, 3.30; N, 15.85.

Reaction of 4-Phenylthiosemicarbazide with Methyl Propiolate

A solution of 6.68 g of 4-phenylthiosemicarbazide and 3.60 g of methyl propiolate in 50 ml of warm acetonitrile was set aside for 3 days; then the yellow crystalline solid which had separated was collected, washed with a little solvent, and purified by recrystallization from ethyl acetate, giving methyl formylacetate 4-phenylthiosemicarbazone, 6.5 g (65% yield), m.p. 101.5°.

Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76; mol. wt. 251. Found: C, 52.31; H, 5.15; N, 16.71; S, 12.76; mol. wt. (mass spectrum) 251.

Infrared spectrum: ν_{max} (Nujol) 1 740 (s) (ester C=O) and 3 300 and 3 120 cm^{-1} (br) (NH). Nuclear magnetic resonance spectrum ($CDCl_3$): 3.75 (3H, singlet, ester methyl), 3.40 (2H, $-CH_2-$), and 7.5 (8H, complex, aryl protons, NH and =CH).

Reaction of 4-Methylthiosemicarbazide with Methyl Propiolate

A solution of 2.0 g of 4-methylthiosemicarbazide and 1.70 g of methyl propiolate in 100 ml of methanol

TABLE V

Hydrazones

$RNHN{=}C(CO_2CH_3){-}CH_2CO_2CH_3$

R	Yield (%)	Melting point (°C)	Calculated (%) C	H	N	Cl	Molecular weight	Found (%) C	H	N	Cl	Molecular weight (by mass spectrometry)	
$2,4,6\text{-}Cl_3C_6H_2$	42	125	40.79	3.14	7.93	30.11	352	40.86	3.21	7.91	29.57	352	^{35}Cl
$2,4\text{-}(NO_2)_2C_6H_3$	72.5	158	42.36	3.56	16.47	—	340	42.82	3.78	16.40	—	340	—
$2\text{-}NO_2C_6H_4$	61	70	48.81	4.44	14.23	—	295	48.92	4.29	13.51	—	295	—
$4\text{-}NO_2C_6H_4$	75.5	182–183	48.81	4.44	14.23	—	295	48.42	4.69	14.36	—	295	—
$2,5\text{-}Cl_2C_6H_3$	84	126	45.16	3.79	8.78	22.22	318	45.34	3.90	9.02	21.96	318	^{35}Cl
$4\text{-}CH_3C_6H_4CO$	38	151	57.60	5.47	9.58	—	292	57.73	5.37	9.66	—	292	—
$CNCH_2CO$	57	125	45.50	4.30	19.90	—	241	45.21	4.67	17.36	—	241	—
PhCO	71	147–148	59.99	5.49	12.72	—	220	59.74	5.48	12.85	—	220	—

TABLE VI

2,3-Dihydro-1,3-thiazin-4-ones and 2,3-dihydro-1,3-diazin-4-ones*

R_1	R_2	Y	Yield (%)	Melting point (°C)	Calculated (%) C	H	N	S	Integral molecular weight	Found (%) C	H	N	S	Molecular weight (by mass spectrometry)
CH_3	NH_2	S	56.6	188	39.06	4.21	19.52	14.90	215	39.33	4.40	19.53	14.95	215
CH_2CHCH_2	NH_2	S	58.5	125	44.80	4.60	17.18	13.29	241	44.86	4.72	16.99	13.48	241
Ph	NH_2	S	72	162	51.97	4.00	15.15	11.56	277	52.36	4.14	15.09	11.83	277
$-CH_2-CH_2-$		S	65	198	45.27	3.80	13.20	15.11	212	45.44	3.54	13.12	15.41	212
$-C(CH_3)_2-\overset{O}{\overset{\|}{C}}-$		S	23	197–198	47.23	3.96	11.01	12.61	254	47.28	4.22	11.13	12.63	254
C_6H_5	C_6H_5	C_6H_5N	75	225	72.53	4.82	10.57	—	397	72.81	4.74	10.23	—	397
C_6H_5	H	C_6H_5N	74.8	155	67.28	4.71	13.08	—	321	67.35	4.83	13.17	—	321

*See Table I for the structural formula.

TABLE VII

Characterization of the molecular ion from perhydro-1,3-thiazin-4-ones and perhydro,1-3-diazin-4-ones*

R_1	R_2	Y	Melting point (°C)	Ion M^+	*m/e* calculated	*m/e* found
CH_3	NH_2	S	38	$C_7H_{11}N_3O_3S$	217.0521	217.0522
$CH_3CH_2CH_2$	NH_2	S	Liquid	$C_9H_{15}N_3O_3S$	245.0834	245.0833
C_6H_5	NH_2	S	87	$C_{12}H_{13}N_3O_3S$	279.0678	279.0671
—CH_2—CH_2—		S	108	$C_8H_{10}N_2O_3S$	214.0410	214.0413
C_6H_5	C_6H_5	C_6H_5N	127	$C_{24}H_{21}N_3O_3$	399.1583	399.1576
C_6H_5	H	C_6H_5N	186	$C_{18}H_{16}N_3O_3$	323.1270	323.1268

*See Table II for the structural formula.

was refluxed for 24 h and cooled, and the solvent was allowed to evaporate in the fume hood. The crystalline residue was collected, washed with a little cold methanol, and purified by recrystallization from ethyl acetate, giving methyl formylacetate 4-methylthiosemicarbazone, 2.1 g (58.4% yield), m.p. 123–125°.

Anal. Calcd. for $C_6H_{11}N_3O_2S$: C, 38.08; H, 5.86; N, 22.20; S, 16.94; mol. wt. 189. Found: C, 38.26; H, 5.88; N, 22.48; S, 17.28; mol. wt. (mass spectrum) 189.

Infrared spectrum: ν_{max} (Nujol) 1 735 (s) (ester C=O) and 3 300 cm^{-1} (NH). Nuclear magnetic resonance spectrum ($CDCl_3$): 3.18 (3H, *N*-methyl), 3.76 (3H, ester methyl), 3.33 (2H, —CH_2), and 7.44 (1H, =CH).

Reaction of 1-Acetylthiosemicarbazide with Methyl Propiolate

A solution of 2.5 g of 1-acetylthiosemicarbazide in 30 ml of warm methanol was added to a solution of 3.05 g of methyl propiolate in 30 ml of methanol; the mixture was shaken and set aside. After 20 min a mass of white crystals separated; these were collected, washed with a little cold methanol, and purified by recrystallization from methanol, giving dimethyl-β-thiodiacrylic ester, 1.95 g (55% yield), m.p. 115–117°.

Anal. Calcd. for $C_8H_{10}O_4S$: C, 47.51; H, 4.98; S, 15.86; mol. wt. 202. Found: C, 47.55; H, 4.88; S, 15.80; mol. wt. (mass spectrum) 202.

Infrared spectrum: ν_{max} (Nujol) 1 695 cm^{-1} (s) (ester C=O). Nuclear magnetic resonance spectrum ($CDCl_3$): 3.73 (12H, ester methyl); pair of AB quartets of the same intensity centered at (*a*) 7.69 and 6.04 (2H, J_{AB} = 15.5 c.p.s.) and at (*b*) 7.20 and 6.00 (2H, J_{AB} = 10.0 c.p.s.), corresponding to the *trans–cis* isomer; and an AB quartet centered at 7.13 and 5.96 (4H, J_{AB} = 10.5 c.p.s.), corresponding to the *cis–cis* isomer. Thin-layer chromatography on Camag Kieselgel DF-5 in chloroform showed two spots, R_f 0.46 and 0.58.

Reaction of Thioacetamide with DAD

A solution of 3.75 g of thioacetamide and 7.10 g of DAD in 50 ml of methanol was set aside at room temperature for 2 days, and the crystals which had separated were collected, washed with cold methanol, and purified by recrystallization from ethyl acetate, giving (1′-iminoethyl)thiodimethyl fumarate, 8.5 g (81% yield), m.p. 149° (decomp.).

Anal. Calcd. for $C_8H_{11}NO_4S$: C, 44.23; H, 5.10; N, 6.45; S, 14.76; mol. wt. 217. Found: C, 44.34; H, 5.24; N, 6.40; S, 14.82; mol. wt. (mass spectrum) 217.

Infrared spectrum: ν_{max} (Nujol) 1 692 (ester C=O) and 1 606, 3 155, and 3 050 cm^{-1} (s) (NH). Nuclear magnetic resonance spectrum ($CDCl_3$): 1.96 (3H, CH_3—C=NH), 3.24 and 3.78 (3H each, ester CH_3), 6.72 (1H, vinyl proton), and 8.30 (br, 1H, NH). Mass spectrum: *m/e* 217 (molecular ion), 5%; 144, 54%; 116, 94%; 86, 57%; 85, 100%; and 58, 18%.

Reaction of Thioacetamide with Methyl Propiolate

A solution of 1.5 g of thioacetamide and 3.36 g of methyl propiolate in 20 ml of methanol was shaken and set aside. After 10 min heat was evolved and a mass of crystals precipitated. The solid was collected, washed with a little cold methanol, and purified by recrystallization from ethyl acetate, giving a 1:1 mixture of *cis–trans* and *cis–cis* dimethyl-β-thiodiacrylic esters, the analytical and spectroscopic data of which were identical in all respects with those obtained from 1-acetylthiosemicarbazide as described above, 2.86 g (71% yield), m.p. 115–117°.

Reaction of Thiobenzamide with DAD

A solution of 7.63 of DAD in 20 ml of methanol was added, with stirring, to a solution of 6.03 g of thiobenzamide in 60 ml of methanol. After 3 min a yellow crystalline mass separated; this was collected, washed with a little cold methanol, and purified by recrystallization from acetonitrile, giving 2-phenyl-6-carbomethoxy-1,3-thiazin-4-one, 6.8 g (55% yield), m.p. 153°, as shiny golden plates.

Anal. Calcd. for $C_{12}H_9NSO_3$: C, 58.29; H, 3.67; N, 5.67; S, 12.97; mol. wt. 247. Found: C, 58.39; H, 3.90; N, 5.80; S, 12.99; mol. wt. (mass spectrum) 247.

Infrared spectrum: ν_{max} (Nujol) 1 710 (s) (ester C=O) and 1 695 (s) (amide C=O). Nuclear magnetic resonance spectrum ($CDCl_3$): 3.88 (3H, ester CH_3), 7.07 (1H, vinyl proton), and 7.5–8.2 (5H, complex aryl proton bands). Mass spectrum: *m/e* 247, 11%; 216, 4%; 188, 7%; 144, 55%; 116, 100%; 86, 33%; 85, 60%; 77, 12%; 59, 25%; and 58, 18%. All of these peaks can be interpreted satisfactorily in terms of the proposed structure by reference to Scheme 1 and Table I.

Reaction of Thiobenzamide with Methyl Propiolate

The reaction of 1.37 g of thiobenzamide and 1.68 g

TABLE VIII

Spectroscopic data on 2,3-dihydro-1,3-thiazin-4-ones and 2,3-dihydro-1,3-diazin-4-ones*

			Infrared (cm^{-1}) (Nujol)			Nuclear magnetic resonance† (δ) ($CDCl_3$)			
R_1	R_2	Y	NH	Ester C=O	Amide C=O	NH	Vinyl	Ester methyl	$=NR_1$
CH_3	NH_2	S	3 290	1 735	1 660	4.35 (2)§	6.93 (1)	3.86 (3)	3.31 (3)
CH_2CHCH_2	NH_2	S	3 600	1 722	1 652	4.84 (2)§	6.95 (1)	3.87 (3)	4.15 (CH_2) 5.25 ($=CH_2$) 5.90 ($=CH-$)
C_6H_5	NH_2	S	3 305	1 735	1 650	4.90 (2)§	6.95 (1)	3.80 (3)	6.9–7.45 (15)
$-CH_2-CH_2-$ O ‖		S	—‡	1 720	1 750	—	6.95 (1)	3.91 (3)	A_2B_2 at 4.5 (2) and 3.93 (2)‖
$-C(CH_3)_2-C-$		S	—	1 732	1 762	—	7.16 (1)	3.95 (3)	1.68 (6)
C_6H_5	C_6H_5	C_6H_5N	—	1 712	1 650	—	5.97 (1)	3.18 (3)	7.20 and 6.5 (15)
C_6H_5	H	C_6H_5N	3 400	1 705	1 685	6.65 (1)§	6.76 (1)	3.20 (3)	7.5–6.8 (10)

*See Table I for the structural formula.
†The numbers in parentheses indicate the number of protons.
‡Spectrum in $CHCl_3$.
§Exchangeable with D_2O.
‖A_2B_2 collapses to a single band at 5.5 p.p.m. in CF_3CO_2H.

TABLE IX

Spectroscopic data on perhydrothiazinones*

			Infrared (cm^{-1}) (Nujol)			Nuclear magnetic resonance† (δ) ($CDCl_3$)									
R_1	R_2	Y	NH	Ester C=O	Amide C=O	NH	Ester methyl	N—R	Aryl protons	δ_A‡ —CH—	δ_B‡ —CH_2—	δ_C‡ —CH_2—	J_{AB} (c.p.s.)	J_{AC} (c.p.s.)	J_{BC} (c.p.s.)
CH_3	NH_2	S	3 320	1 730	1 650	4.68 (2)§	3.68 (3)	3.08 (3)	—	4.32 (1)	3.22 (1)	2.82 (1)	4.0	9.5	17.5
n-C_3H_7	NH_2	S	3 410	1 732	1 642	4.73 (2)§	3.70 (3)	0.94 (3) (CH_3) ~1.6 (4) ($-CH_2-CH_2$)	—	4.32 (1)	3.30 (1)	2.82 (1)	4.0	9.7	17.7
C_6H_5	NH_2	S	3 280	1 730	1 635	4.50 (2)	3.75 (3)	—	7.5–7.0 (5)	4.25 (1)	3.33 (1)	2.99 (1)	4.0	9.0	17.5
$-CH_2-CH_2-$		S	—	1 725	1 622	—	3.71 (3)	~3.8 (2) ~4.3 (2)	—	4.7 (1)	3.21 (1)	2.97 (1)	4.0	9.0	18.0
C_6H_5	C_6H_5	C_6H_5N	—	1 740	1 653	—	3.61 (3)	—	7.5–6.5 (15)	4.52 (1)	3.0 (1)	2.70 (1)	3.5	6.5	17.0
C_6H_5	H	C_6H_5N	3 265	1 743	1 650	—	3.44 (3)	—	~7.3 (10)	4.58 (1)	2.87 (1)	2.67 (1)	4.5	6.0	16.5

*See Table II for the structural formula.
†The numbers in parentheses indicate the numbers of protons.
‡Estimated centers of gravity of the multiplets of the ABC systems.
§Exchangeable with deuterium oxide.

TABLE X

Additional confirmatory mass spectral peak measurements

Structure of parent compound	Ion	*m/e* calculated	*m/e* found
R_1,R_2 = —$C(CH_3)_2$—CO—, Y = S*	C_2NSO^+	85.9701	85.9694
	$C_4H_6N_2^+$	82.0531	82.0530
R_1 = CH_2=CH—CH_2—, R_2 = NH_2, Y = S*	$C_9H_{11}N_3O_3S^+$	241.0531	241.0527
	$C_9H_9N_2O_3S^+$	225.0334	225.0339
	$C_8H_7N_3O_2S^+$	209.0259	209.0259
I, R = 2,4-$(NO_2)_2C_6H_3$	$C_{11}H_8N_4O_7^+$	308.0393	308.0399
	$C_4H_5O_3^+$	101.0239	101.0237
I, R = 2,5-$Cl_2C_6H_3$	$C_5H_3Cl_2^+$	133.9613	133.9615

*See Table I for the structural formula.

of methyl propiolate in 25 ml of methanol according to the method described above yielded a 1:1 mixture of *cis–cis* and *cis–trans* dimethyl-β-thiodiacrylic esters identical in all respects with that obtained from 1-acetylthiosemicarbazide and methyl propiolate as described above, 1.40 g (69% yield), m.p. 115–117°.

Additional Confirmatory Mass Spectral Peak Measurements

These are listed in Table X.

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