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CYANOGEN CONDENSATIONS AS A NEW ROUTE TO BENZO-(1,3)-THIAZINONES OF MEDICINAL INTEREST

by

Lee A. Schaeffer

A Dissertation
Presented to the Graduate Committee
of Lehigh University
in Candidacy for the Degree of
Doctor of Philosophy
in
Chemistry

Lehigh University
1972

CERTIFICATE OF PRESENTATION

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Lee A. Schaeffer

Lee A. Schaeffer

CERTIFICATE OF APPROVAL

This dissertation is approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

September 14, 1972
Date

Ned D. Heindel
Professor in Charge

Special committee directing the doctoral work of Mr. Lee A. Schaeffer.

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I would also like to thank Joyce Gordon for her efforts in typing the manuscript.

This dissertation is dedicated to my wife, without whose understanding this work would not have been possible.

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ABSTRACT

The synthetic utility of cyanogen (N≡C-C≡N) has been demonstrated through the synthesis of 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones (10), 5-substituted-2-amino-2-cyano-2,3-dihydro-1,3,4-oxadiazoles (39), and bis-2,2'-(4-oxo-benzothiazinyl) compounds (59).

The condensation of thiosalicylhydrazides with cyanogen provided a direct synthesis of 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones. The reactivity of the 3-amino group was demonstrated by the formation of benzylidene and hydrochloride derivates. Also the spacial proximity of the amino and imino moieties was demonstrated by the condensation of 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones with such electrophiles as phosgene and benzoyl chloride to yield 1,2-dihydro-S-triazolo [5,1-b] benzo-[1,3] -thiazin-2,9-dione and 2-phenyl-S-triazolo [5,1-b] benzo-[1,3]-thiazin-9-one.

The reaction of alkyl and aryl hydrazides was found to give 5-substituted-2-amino-2-cyano-2,3-dihydro-1,3,4-oxadiazoles which could be converted to 5-substituted-2-amino-1,3,4-oxadiazoles by thermal elimination of HCN.

Thiosalicylic acids were found to condense with cyanogen in a 2:1 mole ratio in the presence of a vast

excess of cyanogen with concomitant loss of two molecules of water to yield a series of unique bis-2,2'-(4-oxobenzothiazinyl) compounds.

The reaction of thiosalicylhydrazide and salicylhydrazides with ethyl chloroformate yielded initially β-carbethoxyhydrazides which could be cyclized to 5-substituted-2,3-dihydro-1,3,4-oxadiazolones by thermal elimination of ethanol.

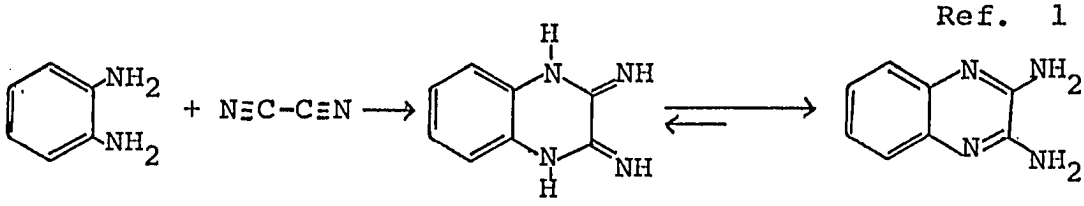
Condensation of thiosalicylhydrazide with the novel electrophile, cyanoacetylene, gave an almost quantitative yield of 3-amino-2-cyanomethyl-3,4-2H-1,3-benzothiazin-4-one. The reactivity of the 3-amino moiety was indicated by formation of a benzylidene derivative. An acid catalyzed cyclization demonstrated the spacial proximity of the 3-amino and 2-cyanomethyl groups by formation of two tricyclic compounds 2-amino-1H-pyrazolo [5,1-b] benzo-[1,3]-thiazin-9-one and 2-methoxy-1H-pyrazolo [5,1-b] benzo-[1,3]-thiazin-9-one.

A series of representative 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones and their derivatives were screened in mice in a neuropharmacological battery according to a standardized procedure. Several compounds in this series were found to have modest activity as central nervous system (CNS) depressants and sedatives.

INTRODUCTION

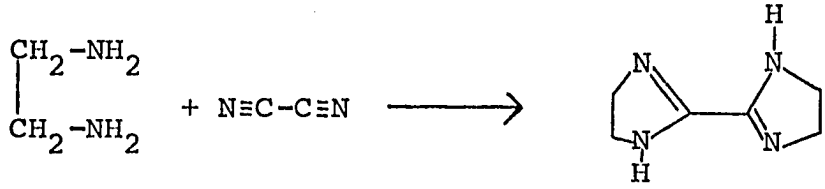
Interest in the cyanogen condensation with o-mercaptobenzhydrazides (thiosalicylhydrazides) arises from two main focuses. First, cyanogen has not been extensively investigated as a building block in heterocyclic syntheses, but sufficient precedent exists to anticipate <u>three</u> possible cyclization pathways with di-functional nucleophiles:

a) insertion of two carbon atoms into the cycle (<u>e.g.</u>)



Ref. 1

b) insertion of one carbon atom into the cycle (<u>e.g.</u>)



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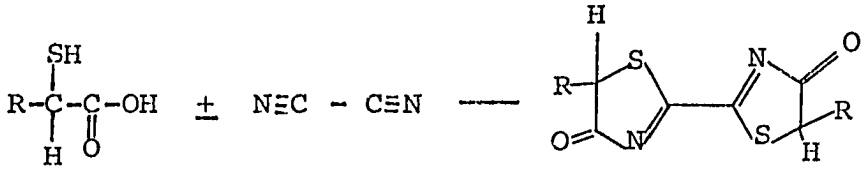
and c) insertion of one carbon and a nitrogen into the cycle (<u>e.g.</u>)



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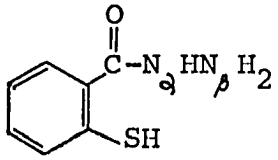
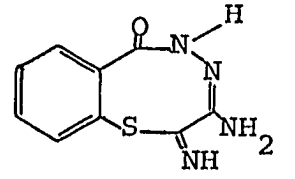
Since thiosalicylhydrazides are really tetranucleophilic in that both nitrogen atoms, the carbonyl oxygen, and the mercapto function possess lone electron pairs, one might expect a host of possible condensation products with cyanogen. A few of the more probable types of condensation products are listed below.

Type 1



1



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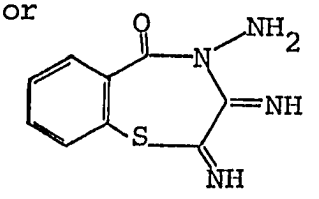

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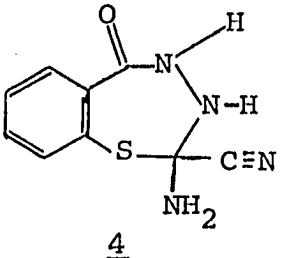
Type 2

1 



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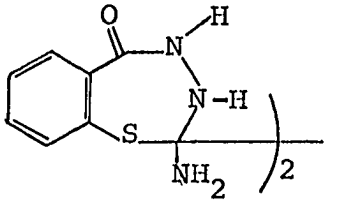

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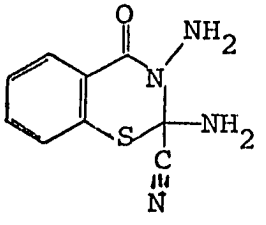

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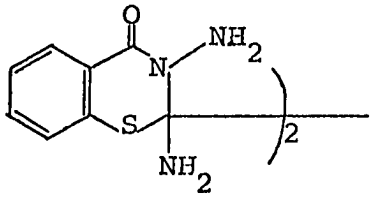

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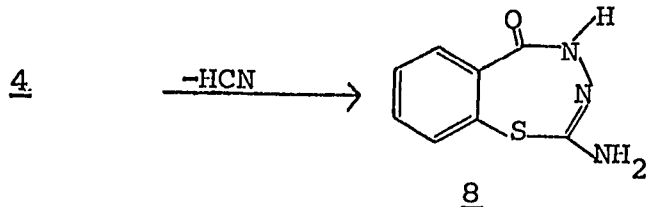
Type 3 (Elimination reaction on initially formed heterocycles 4 and 6)



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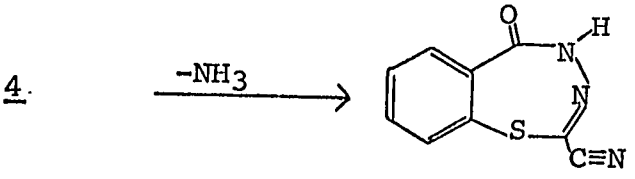

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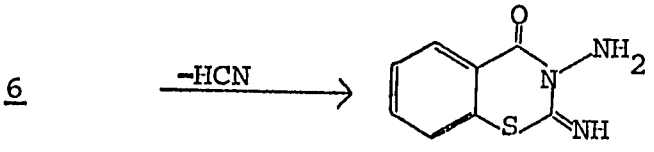

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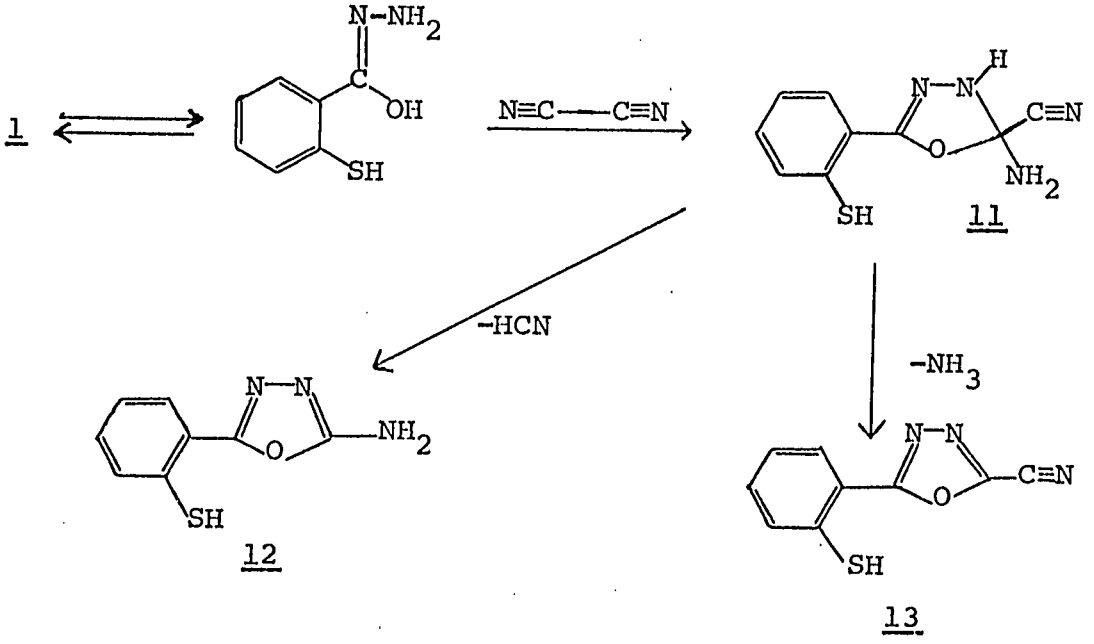
Type 4



Basically, one can envision all possible "insertions" of the cyanogen (in the "one carbon", "two carbon" or in the "carbon + nitrogen mode") between all possible pairs of nucleophilic centers, N_{α}, N_{β}, O, or S plus some products in which HCN or NH_3 are extruded from the initially formed species, plus higher molecular weight dimers and trimers, etc., formed by a second addition, further addition of cyanogen or further condensations of the parent heterocyclics. The illustrations above are not intended to be complete.

The second and equally important focus which motivated this project is the realization that no matter which product or products speculated upon actually did form, all would be of interest as potential pharmaceuticals. Seven and eight-membered heterocyclics containing multiple heteroatoms have come under recent scrutiny as central nervous system (CNS) depressants and minor tranquillizers[4], benzo-1,3-thiazinones as bio-isosteres of the important benzo-1,3-oxaxinones class of sedatives[5] should also be interesting therapeutic candidates and indeed some members have displayed modest activity.[6] Lastly, 1,3,4-oxadiazoles have been reported to possess anti-bacterial potency.[7]

Thus, cyanogen condensations with thiosalicylhydrazides offer a mechanistic, a structural, and a pharmacological challenge to the chemist. We have further extended the

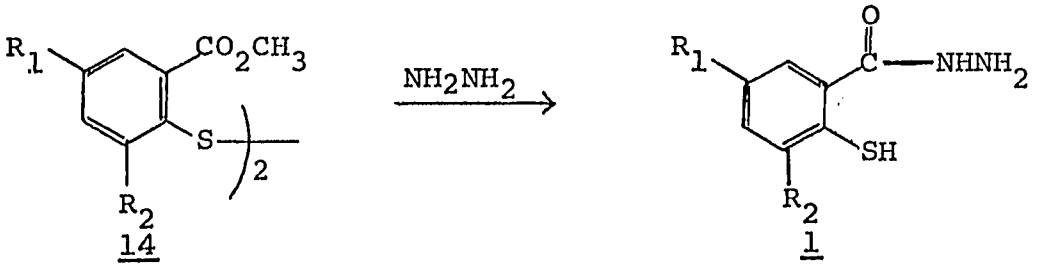
work to include reaction of other significant electrophiles (such as propiolonitrile, phosgene, ethyl chloroformate and dimethyl acetylenedicarboxylate) with thiosalicylhydrazide, condensation of cyanogen with other non-mercapto hydrazides, and condensation of cyanogen with thiosalicyclic acids and esters. The results obtained and the conclusions drawn, are the object of the discussion to follow.

RESULTS AND DISCUSSION

Thiosalicylhydrazide Condensations with Cyanogen

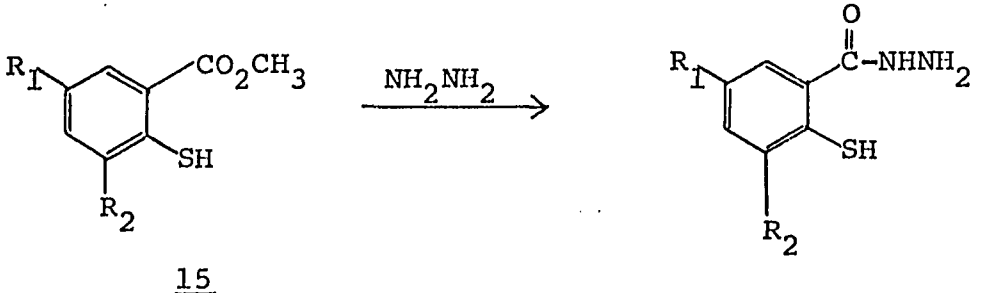
Studies on thiosalicylhydrazide as a nucleophile are limited to one key paper by Katz and coworkers at the E. I. duPont de Nemours Company.[8] This starting material is a readily oxidized mercaptan which has a limited shelf-life by virtue of oxidation to the disulfide. A number of substituted thiosalicylhydrazides were prepared, however several of these were isolated as the oxidized, dithiosalicylhydrazides due to instability of the mercapto group to air oxidation. The two modes of synthesis are outlined below.

1)



14 1

2)

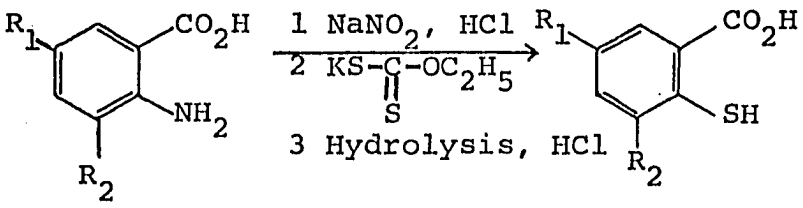


15

In this work we have prepared several analogs of 1 using the second of these two methods and can consistently obtain yields in the 75 to 90% range. In each case the ester (14) or (15) is refluxed in an excess of hydrazine hydrate and the hydrazide is collected from an aqueous solution after acidification with concentrated hydrochloric acid. The thiosalicylhydrazides (1) prepared by this method are listed below.

	R_1	R_2
1a	H	H
1b	Cl	H
1c	CH_3	H
1d	Cl	Cl
1e	NO_2	H

The starting esters (14) and (15), used in the preparation of (1a) through (1d), were prepared from the corresponding anthranilic acids through several steps. The anthranilic acids (16) were diazotized and the diazonium salts thiolated with potassium ethyl xanthate. Subsequent alkaline hydrolysis and acidification with concentrated hydrochloric acid produced the thiosalicylic acids 17a through 17d listed below.

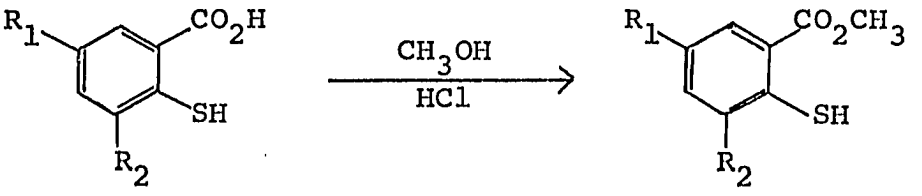


16 17

	R_1	R_2
17a:	H	H
17b:	Cl	H
17c:	CH_3	H
17d:	Cl	Cl
17e:	NO_2	H

These thiosalicylic acids were then esterified in a solution of methanol saturated with anhydrous hydrochloric acid by refluxing for several hours. The esters could generally be obtained in yields ranging from 80 to 90%. An exception was the esterification of 5-methylthiosalicylic acid (17c) in which the yield was 43% of (15c). The low yield was found to be due to the contamination of (17c) by the 5,5'-dimethyldithiosalicylic acid (18c) resulting from air oxidation of (17c) to (18c). The sample of (17c) used in this reaction was found to contain approximately 30% of (18c). The methyl thiosalicylates (15a through 15d) that were prepared are

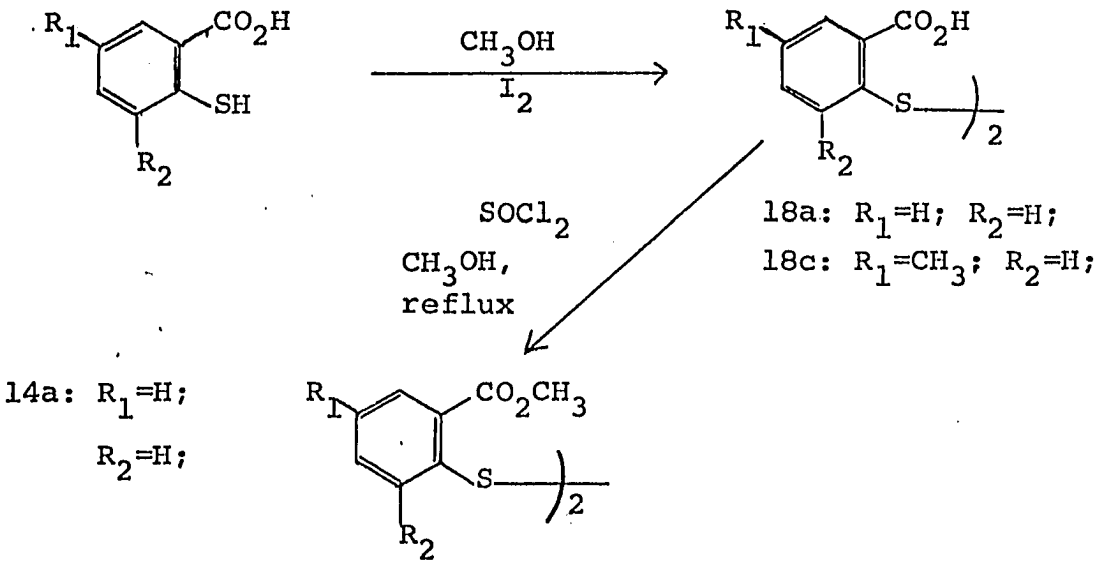
listed below.



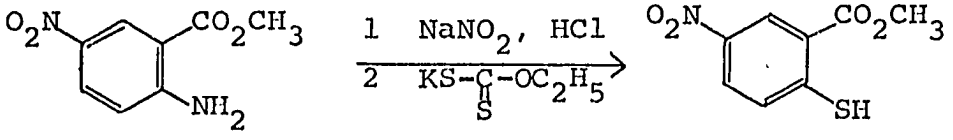
17 15

	R_1	R_2
15a:	H	H
15b:	Cl	H
15c:	CH_3	H
15d:	Cl	Cl
15e:	NO_2	H

An alternate method of preparation of thiosalicylhydrazides involved oxidation of mercapto groups to the disulfide, subsequent esterification and conversion to the thiosalicylhydrazide. Thiosalicylic acids (17) were converted to the dithiosalicylic acids (18) by oxidation with elemental iodine in methanol. The conversion of (17) to (18) is quantitative. The dithiosalicylic acids (18) were then esterified by conversion to the diacid chloride with thionyl chloride *in situ* and subsequent refluxing in methanol to give the dimethyl dithiosalicylates (14) in 61% yield.

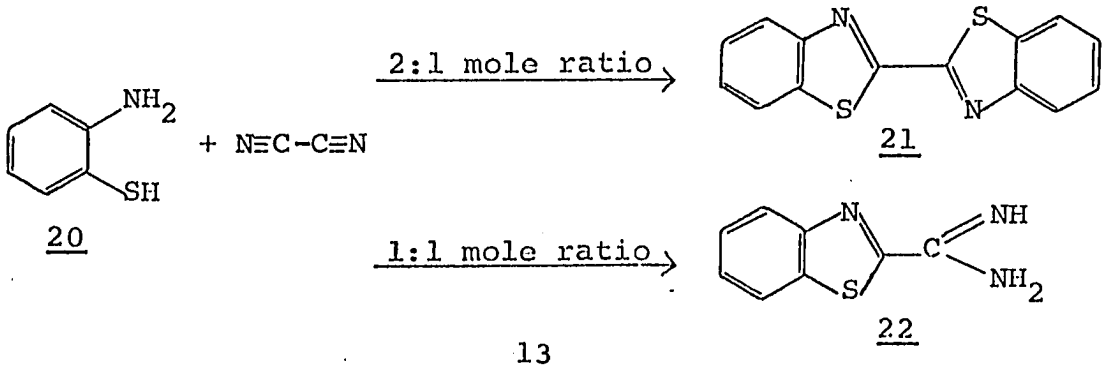


An alternate synthesis of thiosalicylate esters involves the direct conversion of methyl anthranilates to the methyl thiosalicylates. As shown below, methyl 5-nitro anthranilate (19) was converted directly to methyl 5-nitro thiosalicylate (15e) by diazotization and thiolation of the resulting diazonium salt. The thiosalicylate ester (15e) was isolated in 81% yield along with a small amount of the acid (17e).



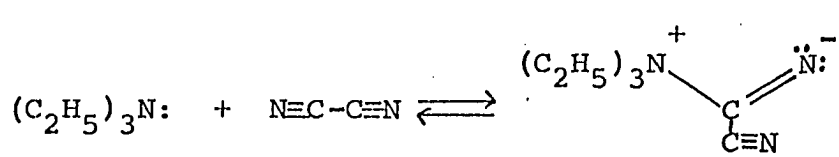
19 15e

As a toxic compressed gas, cyanogen was always handled in condensed phase dissolved in tetrahydrofuran (THF) and transferred in a well-vented hood. In most cases the heterocyclic products precipitated directly from the THF solution and were readily isolated by evaporation of the gas at ambient temperatures. A safety trap of aqueous sodium hydroxide was utilized to hydrolyze excess cyanogen to sodium oxalate. Concentration of the mother liquor *in vacuo* gave additional product in many cases. Because examples do exist of double condensations of the same nucleophile on a cyanogen, both nitrilo carbons being electrophilic, almost all of the reactions were carried out at a 2/1 ratio of cyanogen to thiosalicylhydrazide or greater. An excess of cyanogen was used with the intention to maximize the yield of products containing a 1:1 ratio of thiosalicylhydrzide to cyanogen. It has been reported[9] that the reaction of 2-aminothiophenol (20) yields two products, bis-benzothiazole (21) and benzothiazole-2-carboxamidine (22), the latter being obtained when only 1 mole of aminothiophenol is used per mole of cyanogen.



20 21 22

In the reaction of thiosalicylhydrazides (1) with cyanogen, in all cases a solution of the hydrazide in THF was added dropwise to a solution of cyanogen dissolved in THF. The yields from this manner of addition were significantly better in that it was difficult to isolate any product due to formation of tars when addition was performed in the reverse manner. The method of addition as employed, further assures that cyanogen will always be present in excess. Also the cyanogen solution was cooled to 0-5° before, during and after addition and continued until approximately one hour after the product began to precipitate. It was noted the warming of the reaction mixture to ambient temperatures resulted in slightly lower yields and darker colored products. Triethylamine was added in catalytic amount to the cyanogen solution just prior to addition of the hydrazide substrate. Immediately following the addition of the catalyst a white suspension appeared in the mixture indicating possible formation of a complex. The amount of suspended haziness appeared to be directly related to the amount of triethylamine added. Since triethylamine is the only nucleophile present and cyanogen the only electrophile, it is tempting to speculate upon the formation of a charge-transfer complex as shown below.



Triethylamine is known to catalyze additions to cyanogen by nucleophiles[10] and one possible reason for such catalysis would be the "activation" of C_2N_2 through prior complex formation. Approximately 1-2 hours after the completion of hydrazide addition, the product began to precipitate. The product was found to be less soluble in benzene than in THF and dilution of the reaction mixture with benzene helped precipitate the product more quickly resulting in purer products and better yields. Yields were generally in the range of 70-90% and could be increased by concentration of the benzene-THF mother liquor in vacuo without heating. The additional material, although nearly identical to the precipitated product by ir comparison was more darkly colored, lower melting and very difficult to purify.

Evidence for Structural Assignment:

In order to assign a structure to the product arising from the reaction of thiosalicylhydrazide and cyanogen, it is necessary to consider compounds (2) through (13) as possible structures. On the basis of elemental analyses alone, it is possible to reject all but (8), (10) and (12) as reasonable structures.

a) Spectral Characterization of the Product:

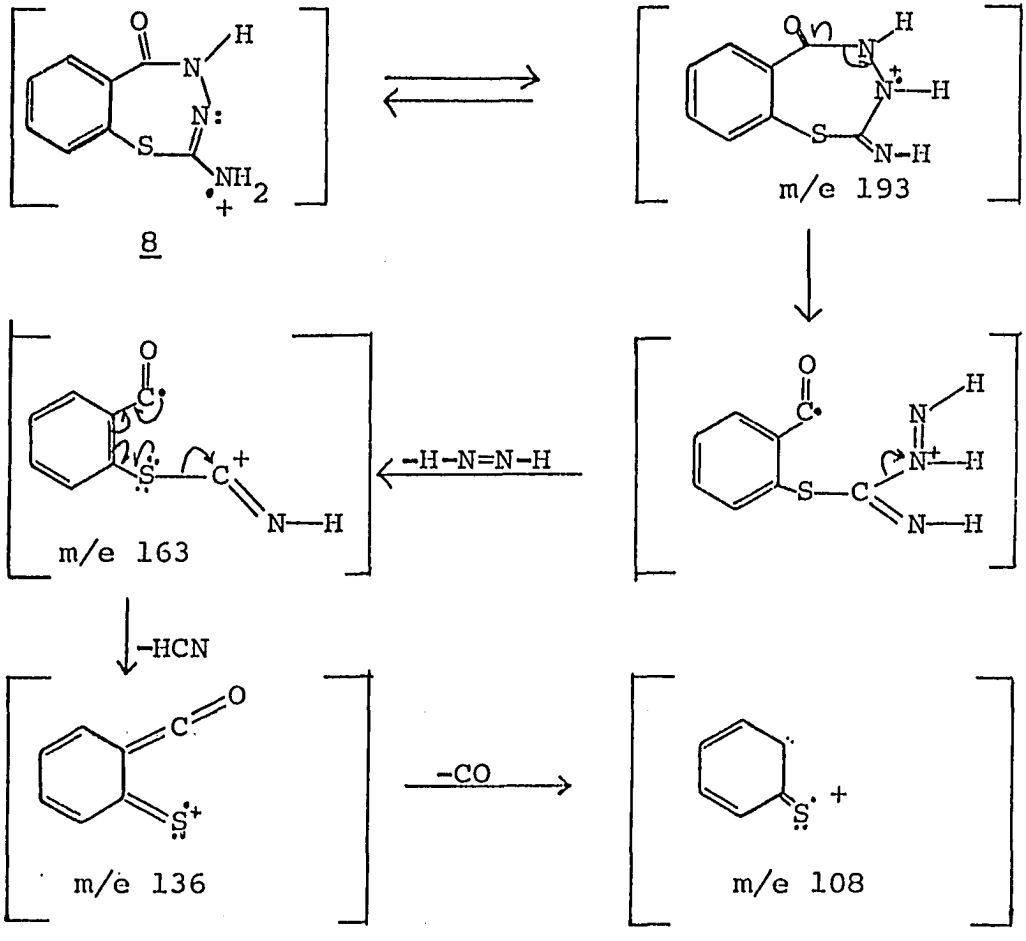
Mass spectral analysis confirms the combustion

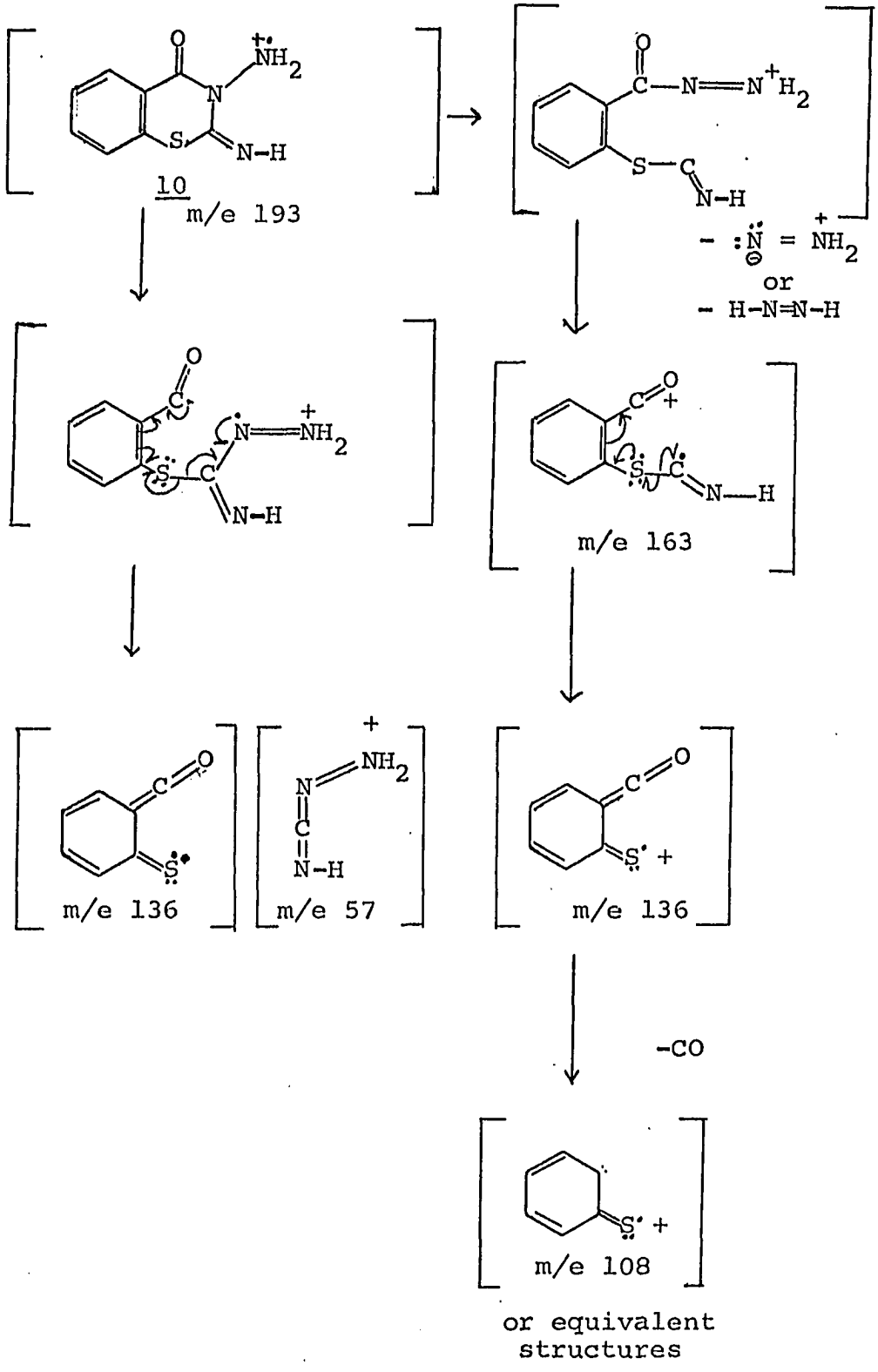
analysis data, in that the possible products 8, 10, and 12 result from a 1:1 combination of the thiosalicylhydrazide and cyanogen with the loss of a mole of HCN. Infrared spectra were more helpful in what structures they eliminated rather than in what they supported. The mercapto SH (at 2520 cm^{-1}) had disappeared and the hydrazide C=O (at 1645 cm^{-1}) still remained thereby eliminating 12 as a likely product of the reaction. Furthermore, no nitrile bands were present at 2250 cm^{-1} but primary amine absorptions were evident at 3295 and 3235 cm^{-1} for the symmetric and the asymmetric N-H stretch. The two most likely structures are 8 and 10.

Nuclear magnetic resonance studies were not particularly useful since the nmr bands could be easily rationalized with either structure. Each of two structures has four aromatic protons which would be expected to exist in nearly identical magnetic environments. Both 8 and 10 have a primary amino group whose protons would be expected to be rapidly exchanged with D_2O. Each would also have a single proton which is either an amide ($-\overset{O}{\overset{\|}{C}}-NH-$) or imino ($=N-H$) type. It is not possible to unequivocally assign the chemical shift of any of these protons as that arising from either structure 8 or 10.

Similarly, the mass spectral studies did not provide any clue toward differentiating between the two possi-

bilities. The electron impact fragmentation pattern could be consistent with either structure. The mass spectrum shows only four significant peaks (m/e 193, 163, 136, and 108), each of which might be found in the expected cracking patterns of both compounds. The m/e 193 peak is the molecular ion. Extrusion of diimide (H-N=N-H m/e 30) gives rise to the m/e 163 peak. The loss of first HCN (m/e 27) and then CO (m/e 28) easily accounts for m/e 136 and m/e 108 respectively. The possible mechanisms accounting for these fragments from compounds 8 and 10 are included below.

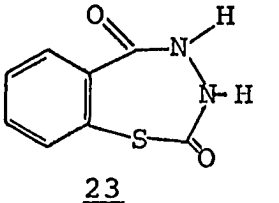




b) Chemical Characterization of the Product:

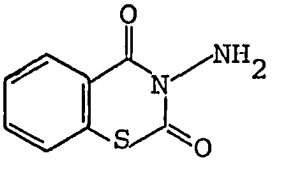
The evidence from reaction studies fully supports the six-membered 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one structure (10) as opposed to the seven-membered 2-amino-4,5-dihydro-1,3,4-benzothiadiazepin-5-one structure (8). The key to structural assignment arises from the hydrolysis of the product in an aqueous solution containing chloroacetaldehyde/ethanol as the solvents and containing a catalytic amount of acetic acid. The reaction is shown below with the possible products.

8 $\xrightarrow[C_2H_5OH,\ CH_3CO_2H]{ClCH_2CHO}$



23

10 $\xrightarrow[C_2H_5OH,\ CH_3CO_2H]{ClCH_2CHO}$

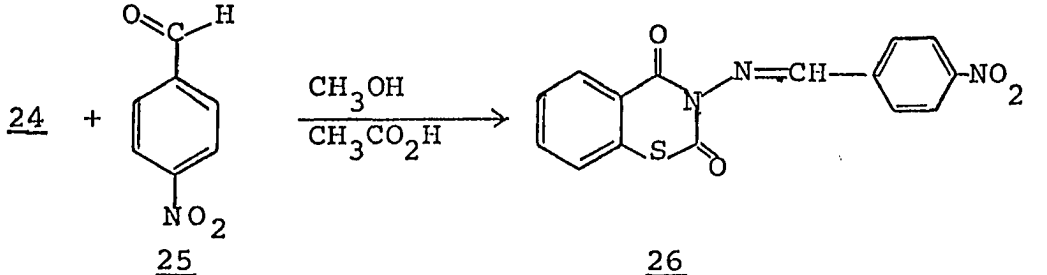


24

Elemental and mass spectral analysis indeed confirmed that the products 23 or 24 arise from the hydrolysis of 8 or 10, however neither of these methods could shed any light as to which isomer was obtained. Likewise, the nmr spectrum was of no value since only the four aromatic

protons and two N-H protons could be observed. Assignment of structure on this basis would be extremely difficult since the two types of protons could be expected to have very similar chemical shifts in 23 and 24. The ir spectrum however provided a hint that the actual structure was 24, in that it showed the presence of a primary amino group with absorptions at 3310 and 3250 cm^{-1} for the symmetric and asymmetric N-H stretch in addition to a carbonyl at 1688 cm^{-1}.

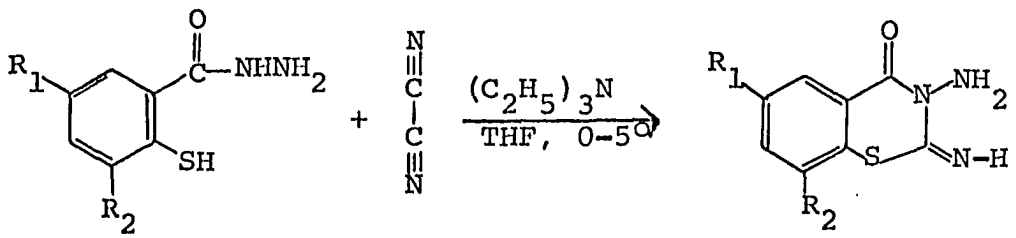
The presence of the primary amino group was confirmed by the following reaction in which 24 was reacted with p-nitrobenzaldehyde (25) by boiling a methanol solution containing a catalytic amount of acetic acid.



25 26

The 3-(4'-nitrobenzylideneimino)-3,4-dihydro-2H-1,3-benzothiazin-2,4-dione (26) was confirmed by elemental analyses and ir analysis. In the ir spectrum of 26 the primary amino bands had disappeared and the carbonyl at 1690 cm^{-1} remained. Mass spectral analysis provided further confirmation of structure 26.

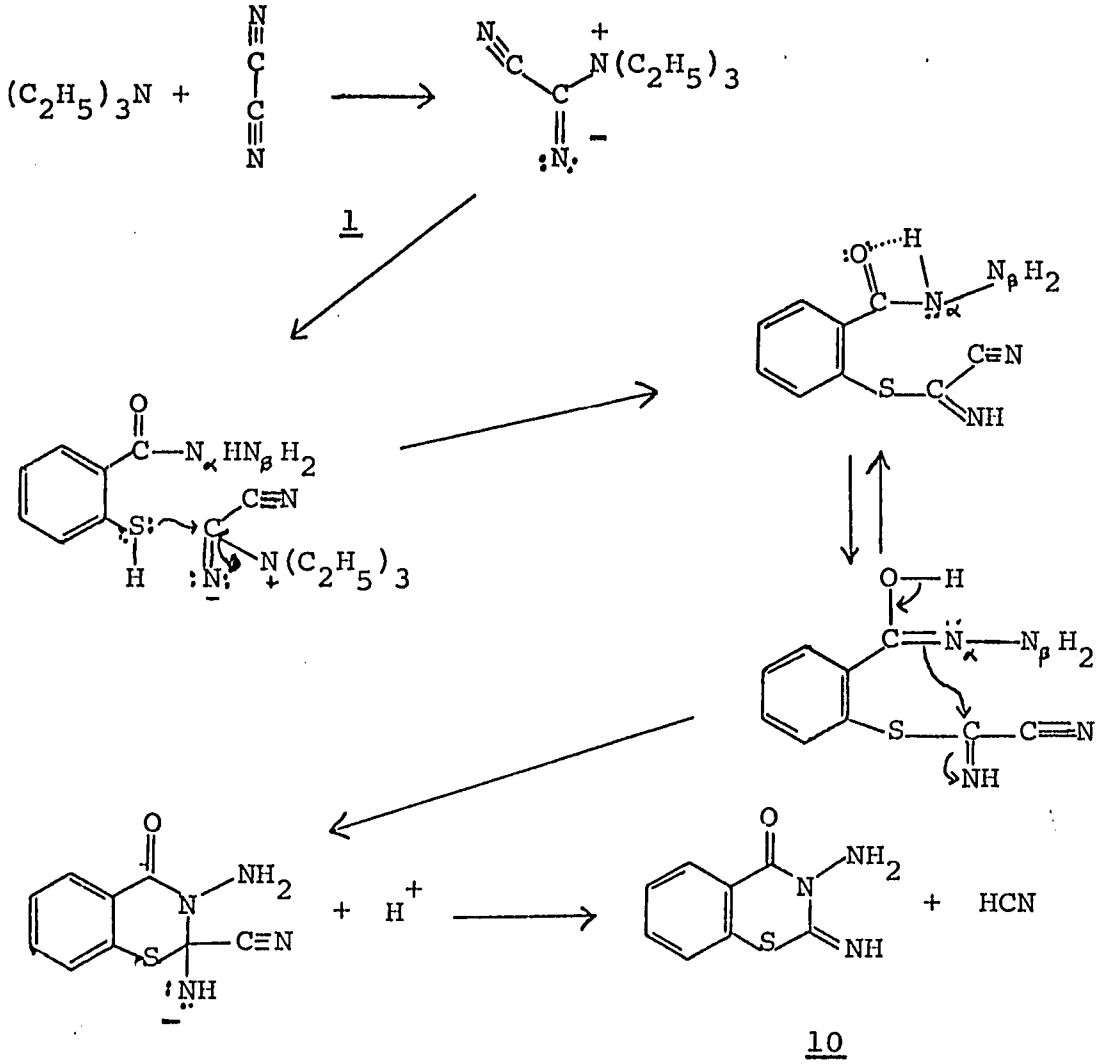
Based upon the above evidence, we have concluded that the reaction of thiosalicylhydrazides with cyanogen yields 3-amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones (10a-c) as shown below.



where 10a: R_1=H; R_2=H;
10b: R_1=Cl; R_2=H;
10c: R_1=CH_3; R_2=H;

A possible mechanism leading to the formation of 10 involves the activation of cyanogen by initial formation of a cyanogen-triethylamine complex followed by nucleophilic attack of the sulfur and subsequent departure of triethylamine. Attack upon imino carbon by N_α and subsequent elimination of HCN lead to the formation of 10. Attack by N_α in preference to N_β can be rationalized in two ways. First, it has been shown that in the formation of 1,3,4-oxadiazoles from hydrazide an enol-amide tautomerism exists[11] and formation of such an enol in this case could lead to attack by N_α. Secondly, it has been reported that attack by the less nucleophilic center can occur

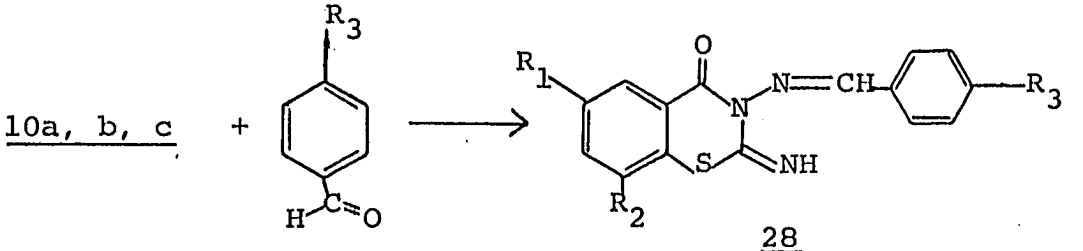
to form a six-membered ring in preference to a seven-membered ring. In addition, several preferential formations of six-membered over seven-membered rings have been reported in cases in which the seven cycle would involve condensation at a more electrophilic seat than would the six cycle. The steric considerations can obviously outweigh the electronic factors in some situations.



1

10

Additional reaction studies served to confirm structure 10 as the product. Reaction with p-dimethylaminobenzaldehyde (27) or 25 produced the anil derivatives (28) as shown below.



28

25: $R_3 = NO_2$

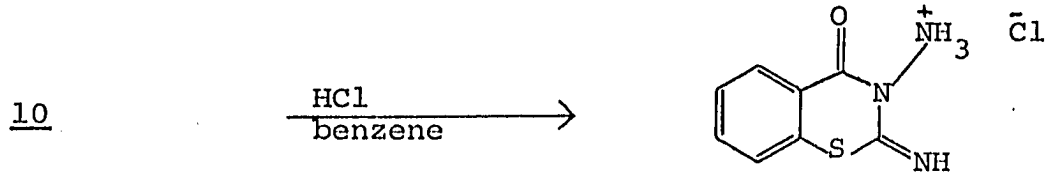
27: $R_3 = N(CH_3)_2$

	R_1	R_2	R_3
28a	H	H	NO_2
28b	H	H	$N(CH_3)_2$
28c	Cl	H	NO_2
28d	Cl	H	$N(CH_3)_2$
28e	CH_3	H	NO_2
28f	CH_3	H	$N(CH_3)_2$

These derivatives are of no structural merit in confirmation of 8 or 10 since both systems would carry pendant amino groups which would condense with aromatic amines. Nevertheless, the benzylidene formations do confirm the infrared spectral indications that an NH_2 function is present. The amino function is obviously of high nucleophilicity since it reacts rapidly and in high yield with

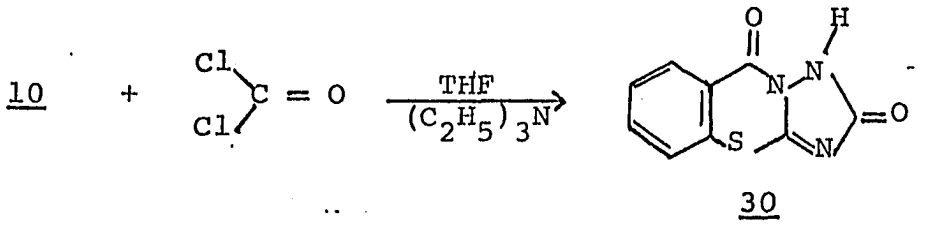
aldehydes carrying donor grouping (p-dimethylamino) and with aldehydes carrying withdrawing moieties (p-NO_2). To a first approximation, hydrazino NH_2's are often more nucleophilic than carbon bound NH_2's but that distinction is too qualitative to serve for structure characterization.

Further support for the basic amino function was the formation of a water soluble hydrochloride. The hydrochloride was formed by passing anhydrous HCl into a hot benzene solution of 10. The white hydrochloride (29) precipitated immediately and was identified by infrared and elemental analyses and a positive Beilstein test.



29

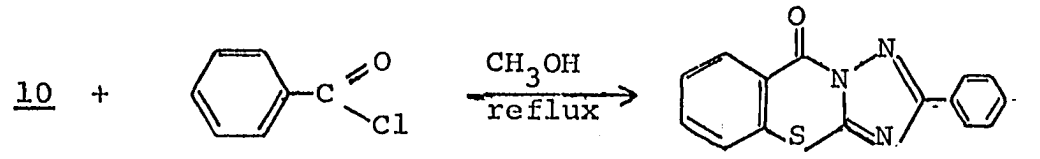
Additional evidence for the six-membered isomer was obtained by reaction of 10 with phosgene and benzoyl chloride. Each of these reactions "spanned" the two nitrogenous centers and thus demonstrated their spacial proximity. The reaction of 10 with phosgene produced the tricyclic 1,2-dihydro-s-triazolo[5,1-b]benzo-[1,3]-thiazin-2,9-dione (30).



30

The compound 30 was identified by its elemental analysis and infrared spectrum. The ir showed a carbonyl at 1695 cm^{-1} and the loss of primary amino bands.

The reaction of 10 with benzoyl chloride also yielded a tricyclic system, 2-phenyl-s-triazolo[5,1-b] benzo-[1,3] -thiazin-9-one (31).

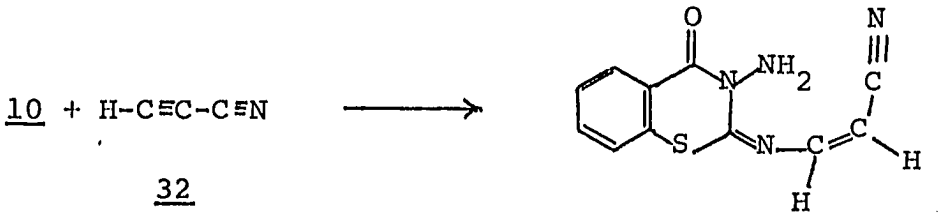


31

The structure of 31 was confirmed by elemental analysis and the loss of all N-H absorption bands in the infrared spectrum. A mass spectrum showing a molecular ion at m/e 279 and a strong peak due to a Retro-Diels-Alder fragment at m/e 136 provided additional confirmation of structure 31.

In order to further study the reactivity of 10, it was reacted with cyanoacetylene (32) and dimethyl acetylene-dicarboxylate (33) and in each case an adduct was obtained

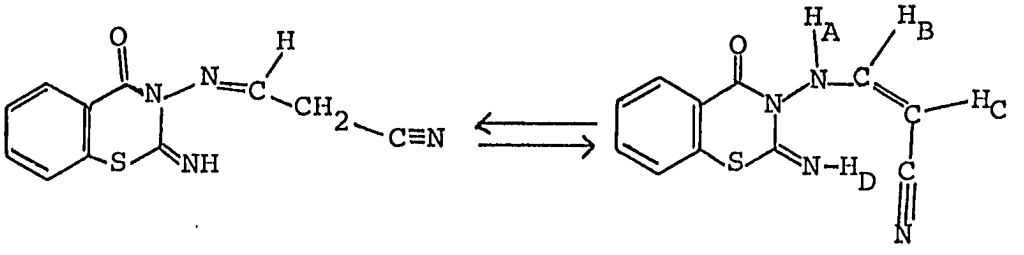
which was found to contain a 1:1 ratio of 10 to 32 or 33 as confirmed by elemental analysis. The reaction with 32 could give two possible adducts as shown below.



10 + H-C≡C-C≡N → 34

32

or



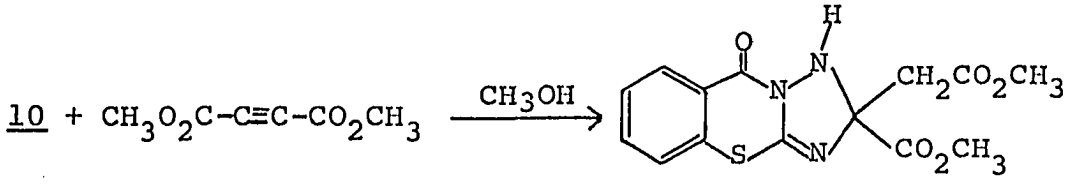
36 ⟷ 35

Interpretation of spectral data indicated that the isomer actually isolated was 34. An ir spectrum showed that the primary amine absorptions were retained at 3300 and 3230 cm^{-1} for the symmetric and asymmetric N-H stretch as well as the appearance of a nitrile band at 2210 cm^{-1}. An nmr spectrum showed two vinyl protons which were split into doublets by each other (J = 8 Hz). The coupling

constant indicates these protons are cis to each other and therefore result from trans-addition. There is no sign of long range splitting between H_A and H_C or splitting between H_A and H_B. Normally an 8 to 10 Hz coupling is observed between N-H protons and an adjacent C-H in propiolate adducts of primary amines.[14] Likewise, the methylene group characteristic of tautomer 36 is not observed. Furthermore, a broad N-H peak was observed at 6.35 δ which integrated for two protons and is comparable to the position of the NH_2 protons at 5.55 δ in 10. It seems unlikely that two protons as chemically different as H_A and H_D would be found to have the same chemical shift especially when it is noted that the =N-H proton found in 10 is observed at 9.0 δ.

Structural assignment of the adduct arising from the reaction of 10 and dimethyl acetylenedicarboxylate (33) is based largely upon spectral evidence. Both combustion and mass spectral analysis confirmed that the compound was a 1:1 adduct of 10 and 33. The ir spectrum revealed a strong bonded N-H absorption at 3260 and 3180 cm^{-1} and the typical hydrazide C=O at 1635 cm^{-1}. The nmr revealed a five proton complex (one of these exchangeable in D_2O between 7.3 and 8.2 ppm δ which could be rationalized as 4 aromatic protons and one N-H signal. Two ester methoxyl groups were detected at δ 3.65 and 3.72.

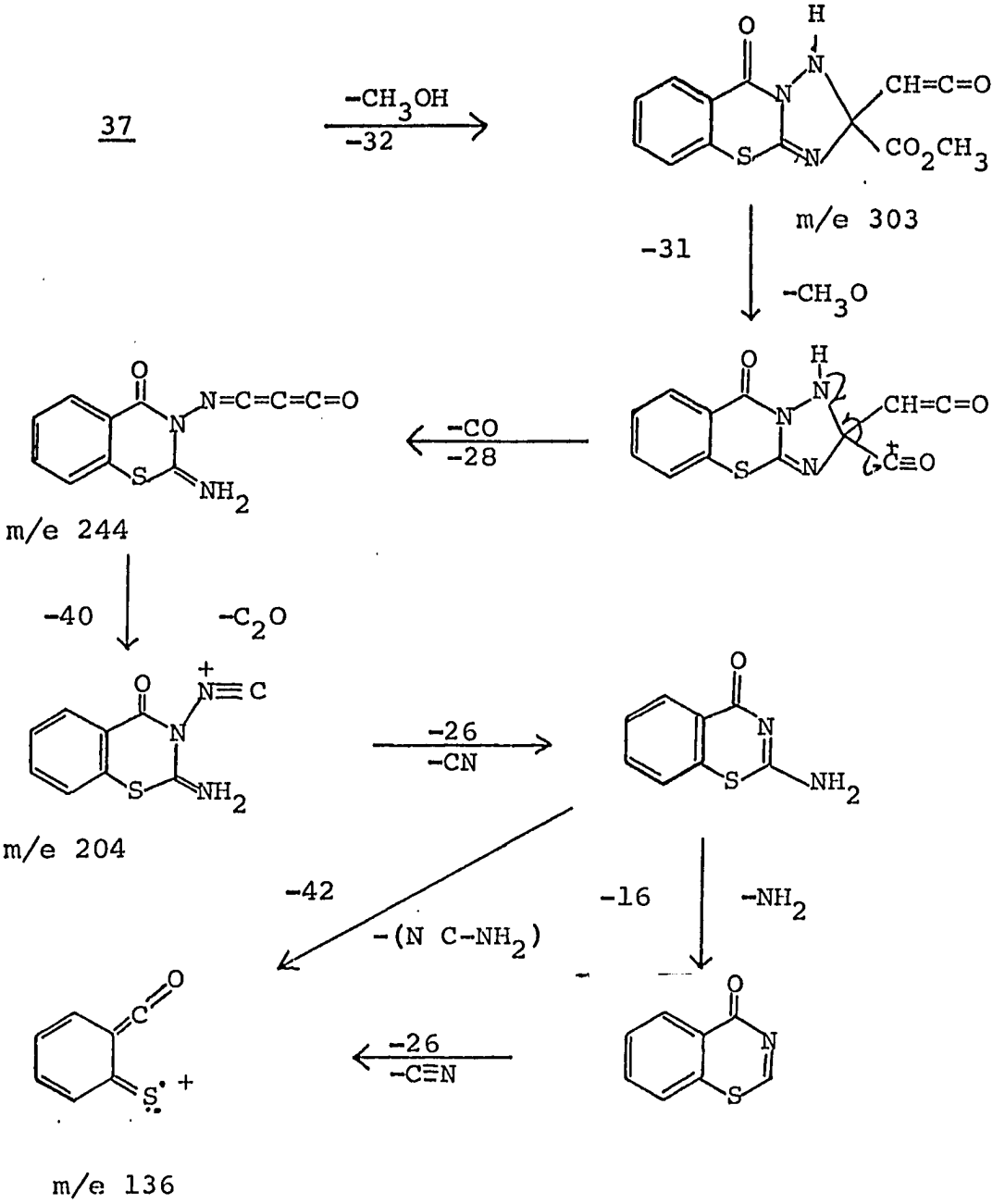
with a superimposed methylene doublet at δ 3.62. Previous research in these laboratories has often led to the observation that such CH_2 groups alpha to tertiary centers appear as widely spaced AB quartets normally detected as doublets due to the invisibility of the outer arms.[13] Based upon this information the structure 37 is suggested for the product of the following reaction.



33 37

The electron impact fragmentation seemed to support the assigned structure and a postualted pathway is shown below. Lemke has recently reported a detailed analysis of the mass spectra of some quinazolinones derived from the addition of 33 to anthranilamides and the parallels in fragment ions are striking.[15] The p-91 ion (in this case m/e 244) is characteristic of such addition compound and was shown by metastables, in Lemke's cases, to be due to stepwise loss of CH_3OH, CH_3O, CO.[15] The subsequent scission of a ketene fragment, denuded of its two protons, has been reported by McLafferty in cumulative pi systems

related to carbon suboxide and such a pathway is envisioned in the m/e 244 to m/e 204 cleavage.[16] Further cleavages to the base peak of m/e 136 are shown. This retro-Diels Alder route has been termed a "Type-D cleavage" by McLafferty and is a characteristic of many C=O containing heterocycles.[17]



All species shown and intended to represent monopositive ions. In most cases alternative structures could be drawn and exact mass assignment was not performed on these ions.

Physiological Evaluation of the N-Aminobenzothiazinones

Screening in a neuropharmacoligical battery was carried out by a professional pharmacologist (Dr. Richard J. Matthews of Pharmakon Labs) according to a standardized procedure - the Irwin mouse profile.[18] Each candidate drug was dissolved or suspended in aqueous methylcellulose (0.25% by weight) and injected intraperitoneally to each of four mice at dose levels of 300 mg/kg and lower, if biological effects were detected at the upper dose range.

Animals were observed for approximately 1.5 hours post-dosing and physiological signs such as relative depression, loss of righting reflex, ataxia, and loss of spontaneous motor activity were rated on a scale of 0 to 8 arbitrary units. Professional interpretation of the data was provided by Dr. Matthews but structure-activity correlations are the work of this researcher.

Both the parent heterocyclic, 10a, and its hydrochloride salt, 29, gave virtually identical profiles with the exception of the rapidity of onset of physiological signs. These agents effected tonic convulsions and death

at any dose above 30 mg/kg and the measured LD_{50} as 18 mg/kg. The agents were apparently acting within the central nervous system since marked hypothermia of 4°C, salivation, body drop and Staub tail phenomenon were detected. The hydrochloride salt, 29, was more rapidly acting than the free base probably due to more rapid absorption from the peritoneal cavity. Death ensued after only 3 minutes with the salt but required 10 minutes for the free base at the 300 mg/kg level.

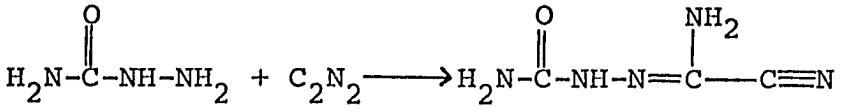
The chloro analog, 10b, was virtually inactive and non-toxic at doses up to 300 mg/kg but at that level it did cause a modest loss of motor activity and modest hypothermia (3°C). The methyl counterpart, 10c, however, while toxic at 300 mg/kg and inducing marked convulsions at that level gave an interesting profile at 100 mg/kg. The LD_{50} was 178 mg/kg and no deaths at all occurred at 100 mg/kg. Slow-acting (60 minutes) depression and sedation were present. The magnitude of activity was not sufficiently high to merit further study. Thus, although 3 analogs of this family do not permit extensive structural conclusions, one can note that the group in the six-position does influence potency and possibly electron donating moieties would be worthy of further study.

The active site of the molecule may well involve the imino (C=NH) function since the hydrolyzed analog, 24, was non-toxic, having an LD_{50} of 7500 mg/kg, as compared to the highly toxic parent compound, 10a. Analog, 24, showed depression, catatonia, hypothermia of 4°C and lacrimation at 300 mg/kg and depression with reduced motor activity at 100 mg/kg. The dimethyl acetylene-dicarboxylate adduct, 37, was non-toxic and totally devoid of activity. Generation of the benzylidene attachments at the N-amino site, i.e. compounds 28a and 28b, likewise affected the potency but not nearly as much as modification at the imino site. For example, 28b, although non-toxic at 300 mg/kg did induce mild catatonia and loss of spontaneous motor activity while, 28a, retained a profile more like the original unsubstituted heterocyclic, 10a. The p-nitro compound, 28a, had an LD_{50} of 237 mg/kg and caused severe depression, catatonia, and reduced motor activity at 300 mg/kg but little activity remained at lower dose levels. Thus, it did not merit further investigation because the therapeutic index was not favorable. Doses of 300 mg/kg were needed to bring about the sedation effects but at this dosage 3 out of 4 mice failed to wake-up.

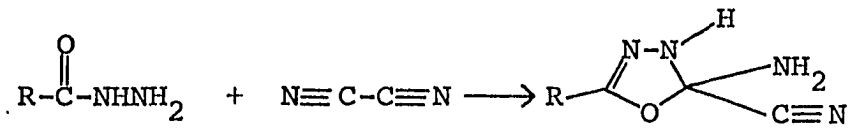
Other Hydrazide Condensations with Cyanogen

In order to further investigate the reactivity of cyanogen with the hydrazide functionality itself, a series of hydrazides (38) lacking the ortho mercapto moiety was reacted with C_2N_2. The reaction was carried out in the same experimental matter as that utilized for the thiosalicylhydrazides (namely an excess of the cyanogen at all times) with the exception that no triethylamine catalyst was employed.

Previous workers have studied semicarbazide and cyanogen and have claimed that addition of the hydrazino N-H to the cyanide does not require catalyst. It has further been reported that a non-cyclic 1:1 adduct is generated.[9]

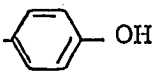


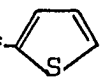
The hydrazides employed in this work were found to give cyclized products which are assigned the structure of 5-substituted-2-amino-2-cyano-2,3-dihydro-1,3,4-oxadiazoles (39) as shown below. Structure proof of these previously unreported oxadiazoles was based in part on spectral data and in part on their conversion to known oxadiazoles.



38 39

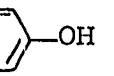
38a R = 

38b R = 

38c R = 

38d R = -CH_2 

39a R = 

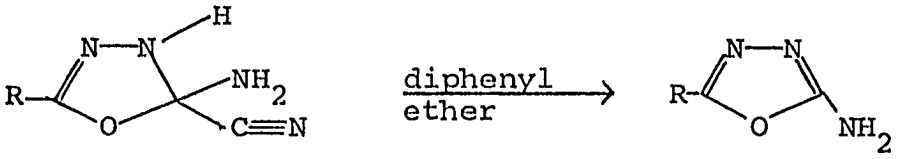
39b R = 

39c R = 

39d R = -CH_2 

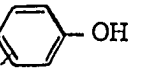
An ir spectrum of 39a showed the presence of N-H absorption bands at 3400, 3270, and 3140 cm^{-1} nitrile absorption at 2240 cm^{-1}, and the absence of C=O bands. An nmr spectrum showed the presence of five aromatic protons from 7.3-8.0 δ, two protons due to NH_2 buried beneath the aromatic protons in the region of 7.6 δ and a single N-H proton at 10.5 δ. Elemental and mass spectral analysis showed 39a to be composed of cyanogen and 38a in a 1:1 mole ratio. In addition the mass spectral cracking pattern showed a strong molecular ion at m/e 188 followed by a strong fragment ion at m/e 161 due to loss of cyanamide (NH_2-C≡N) at m/e 119 and due to the Retro-Diels Alder at m/e 105 are also found. Further evidence for structure 39 was obtained by thermal elimination of HCN. This was accomplished by heating 39 in

diphenyl ether at 200-230°C.



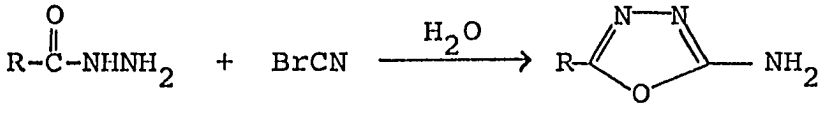
39 40

40a: R = 

40b: R = 

40c: R = 

The identification of 5-substituted-2-amino-1,3,4-oxadizoles (40) was confirmed by independent synthesis since a number of these have been prepared by alternate routes.[19] It has been reported that 5-substituted-2-amino-1,3,4-oxadiazole can be prepared directly from the corresponding hydrazides by reaction with cyanogen bromide (41).[20] As confirmation of structure, 40b, was



38 41 40

prepared using this alternative route. The two samples were identical in physical properties and spectra.

The difference in reactivity of the semicarbazide and the aryl hydrazides, i.e. lack of cyclization in the

$H_2NCONHNH_2$ situation, might possibly be related to the resonance stabilization by the aromatic group of the final ring-closed system (i.e., 39a-c). Alternatively, one might speculate that resonance participation by the aryl ring imparts a higher nucleophilicity to the carbonyl oxygen in the hydrazides, viz-a-viz the semicarbazides and thereby promotes cyclization.

Condensations of Thiosalicylhydrazides and other Hydrazides with a Series of Electrophilic Centers

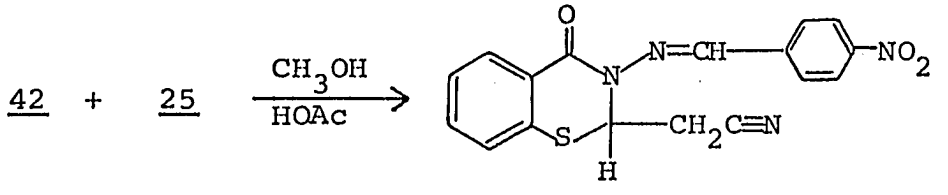
To further elucidate the reactivity of thiosalicylhydrazides 1 and hydrazides in general with electrophic centers, these agents were reacted with a variety of electrophiles to yield a number of unusual and interesting products.

Thiosalicyclhydrazide (1a) was reacted with cyanoacetylene (32) to give an almost quantitative yield of 3-amino-2-cyanomethyl-3,4-dihydro-2H-1,3-benzothiazin-4-one (42). Although a host of other isomeric possible products could be envisioned by "bridging" any of the nucleophilic centers in 1a with any of the electrophilic carbons in 32, the sole product was 42. Its structure was established as follows.

32 42

Elemental analysis confirmed that 42 contained 1a and 32 in a 1:1 mole ratio. An ir spectrum showed presence of a primary amino group with absorptions at 3280 and 3190 cm^{-1}, nitrile absorption at 2245 cm^{-1} and carbonyl absorption at 1620 cm^{-1}. Analysis of the nmr spectrum

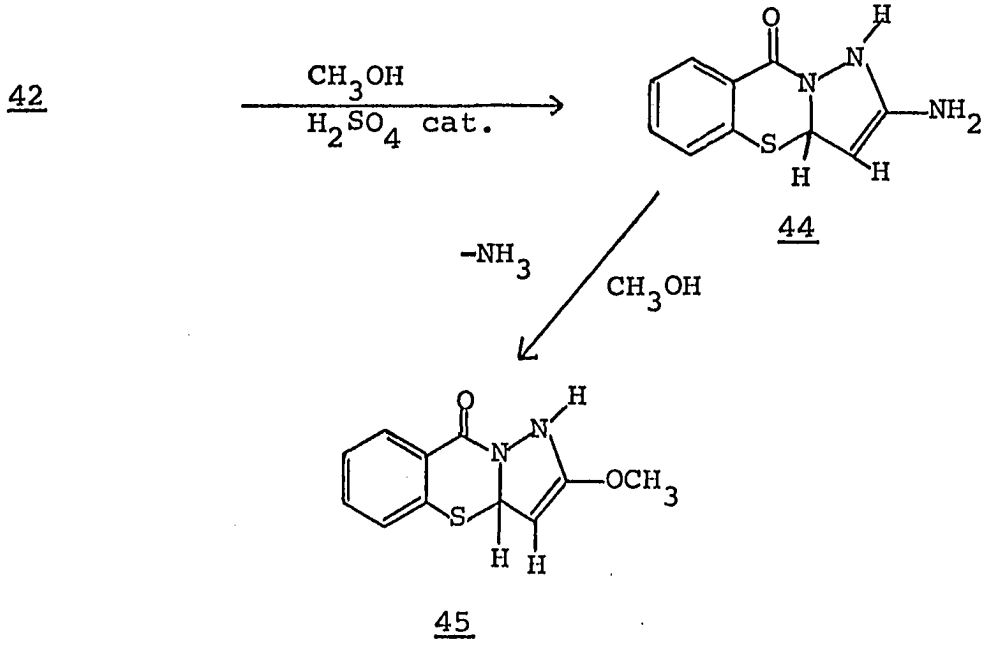
showed the presence of 4 aromatic protons at 7.1-8.4 δ. In addition the presence of a methinyl proton observed as a double doublet due to an ABX splitting pattern (J_{AB}= 6Hz) was detected at 5.1 δ. The adjacent methylene (two protons) was observed at 3.05 δ as a multiplet resulting from ABX splitting. This complex splitting pattern arises by virtue of the diastereoisomeric nature of the two geminal methylene protons. Since they are vicinal to a "tertiary carbon" with three different attachments they become magnetically non-equivalent and self-coupling.[21] Both of these then couple to the adjacent methinyl. Additional evidence for the presence of a primary amino group was obtained by reacting 42 with p-nitrobenzaldehyde (25) to obtain the benzylidene derivative, 43. This derivative, 43, was identified through elemental analysis and the disappearance of primary amino absorption bands in the infrared spectrum.



43

The spacial proximity of the 3-amino and the 2-cyano-methyl groups in 42 was demonstrated by the acid catalyzed

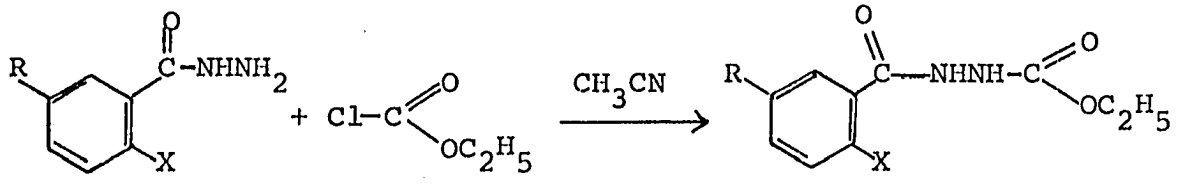
closure of the two functionalities. Compound 42 was dissolved in methanol and refluxed with a catalytic amount of concentrated H_2SO_4. Two products, 44 and 45, were isolated from the reaction mixture and in each case the nitrile absorption was absent from the infrared spectrum.



Both compounds could be identified by elemental analysis and their infrared spectra. Compound 44 showed the

presence of N-H absorption bands in the ir spectrum at 3400, 3270 and 3210 cm^{-1}. In the ir spectrum of compound 45 the N-H absorptions were absent and a strong absorption at 1185 cm^{-1} due to C-O-CH_3 was observed. Product 45 may arise by methanolysis of 44 through the intermediacy of the tautomeric imino form.

The condensation of ethyl chloroformate (46) with thiosalicylhydrazide (1a) and with ortho-hydroxy hydrazides might lead to either new seven-membered compounds of therapeutic interest or to other structural possibilities. The reaction was observed to proceed stepwise via initial formation of β-carbethoxyhydrazides (48).



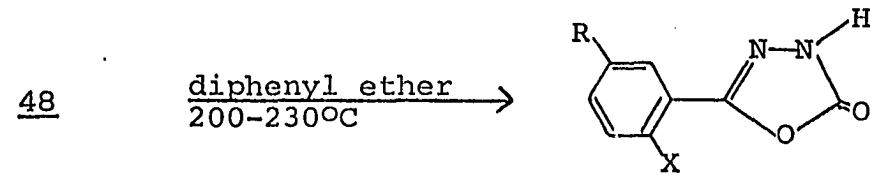
47 46 48

1a:	R=H;	X=SH;	48a:	R=H;	X=SH
47a:	R=H;	X=OH;	48b:	R=H;	X=OH
47b:	R=Br;	X=OH;	48c:	R=Br;	X=OH
47c:	R=OCH_3;	X=OH;	48d:	R=OCH_3;	X=OH
47d:	R=H;	X=H;	48e:	R=H;	R=H

The products 48 were obtained in yields ranging from 65 to 94% by simply refluxing 1a or 47 with (46) in acetonitrile

containing 10-20% water by volume. Elemental analysis was used to confirm the stoichiometry of the reaction and infrared spectra provided additional confirmation. In each analog (48a - 48e), the ir clearly showed absorptions for bonded NH in the region of 3200-3300 cm^{-1}, ester carbonyl absorption at 1710-1730 cm^{-1} and hydrazide carbonyl absorptions at 1640-1655 cm^{-1}. In addition, compound 48a showed a distinct S-H absorption at 2590 cm^{-1}. In the nmr spectra each compound clearly showed the two proton methylene quartet at 4.1-4.2 δ and the methyl triplet at 1.2 δ resulting from the ethyl ester. Also two distinct singlets due to N-H were observed and these were rapidly exchanged with D_2O. In products, 48b-d, the O-H peak could also be observed and this too rapidly exchanged with D_2O. The presence of the free OH could be clearly shown by a positive $FeCl_3$ test. The presence of free SH could be shown by precipitation of a yellow lead mercaptide when a solution containing 48a in ethanol was added to a saturated solution of lead acetate in ethanol.

The compounds, 48a-c , were of particular interest in that each had the option of forming a five-membered, 49, or a seven-membered, 50, heterocycle. Ring-closure was effected by heating the β -carbethoxy hydrazides in diphenyl ether at 200-230°C for 1-2 hours and the products were isolated in yields ranging from 63 to 91%.



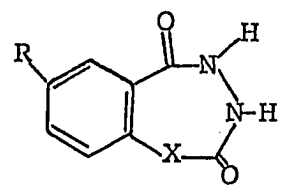
49 or

49a: R=H; X=SH;

49b: R=H; X=OH;

49c: R=Br; X=OH;

49d: R=H; X=H;



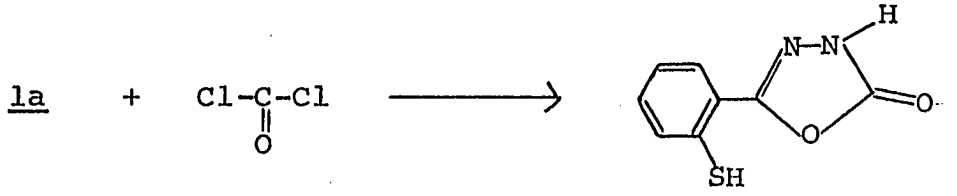
50

Combustion analyses confirmed the loss of ethanol concomitant with cyclization but, of course, this would be true for either structural option 49 or 50. Infrared spectra did not provide significant information as to the actual structure except in the case of 49a which clearly showed the presence of an SH absorption at 2530 cm^{-1}. The nmr spectra were useful mostly in that they demonstrated the loss of the ethyl ester group.

Once again the $FeCl_3$ test for phenolic OH provided substantiation for structure 49b and 49c. Also the ready solubility of 49a-c in cold 5% NaOH suggested the presence of an acidic proton such as that in phenols and thiophenols. Additional proof for 49a was demonstrated

by formation of the lead mercaptide with lead acetate indicating a mercapto group was present.

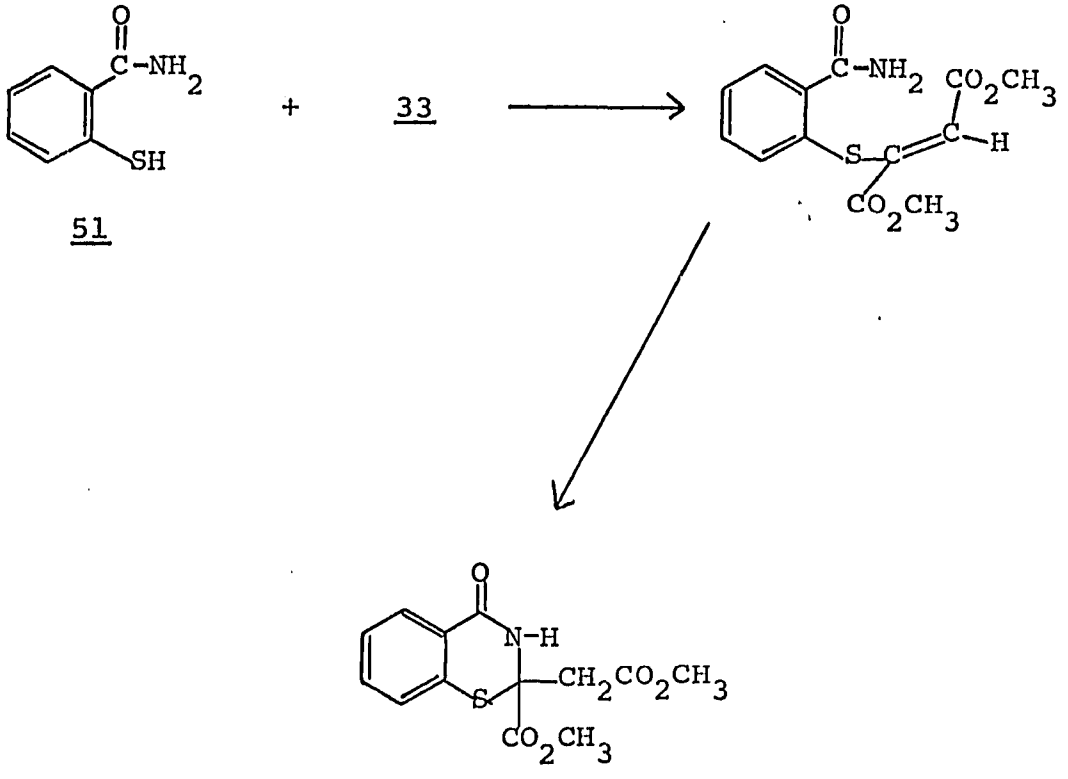
Strong precedent exists to support the expectation that the final product should be 49 since it has been reported that the condensation of p-aminosalicylhydrazide with the more reactive and electrophilic substrate, phosgene, yields a 1,3,4-oxadiazolone.[11] Therefore, as an alternative synthesis the reaction of thiosalicyl-hydrazide (1a) with phosgene was carried out to give 49a in 41% yield. The two samples were identical in physical properties and spectra.



49a

In previous papers from these laboratories, dimethyl acetylenedicarboxylate (33) has been found to generate five-, six-, and seven-membered heterocyclic systems by bridging of nucleophilic centers. Therefore it seemed pertinent to investigate the reaction of thio-salicylhydrazide (1a) with 33. It has been reported that thiosalicylamides (51) when reacted with 33 lead to high

yields of 1,3-benzothiazinones (52) via an intermediate SH addition to the alkyne linkage.[22]



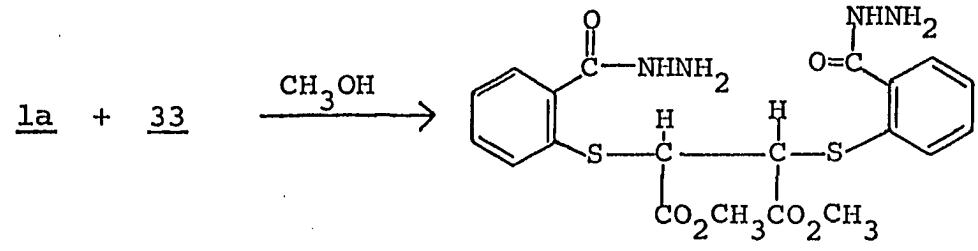
51

52

In like manner, one could envision that the hydrazide might produce six- or seven-membered products by subsequent addition of the α or β nitrogen across the intermediate olefinic bond.

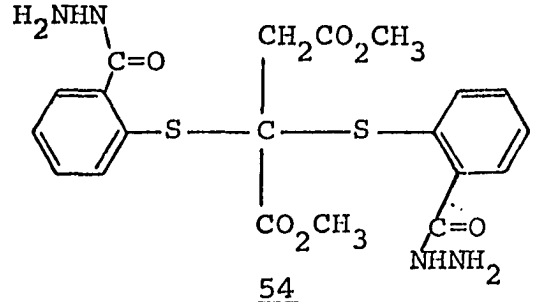
When thiosalicylhydrazide 1a was condensed with 33 in 1:1 molar equivalents a rather labile 2:1 product, 53,

was produced by SH addition to each of the two alkyne carbons (see below).



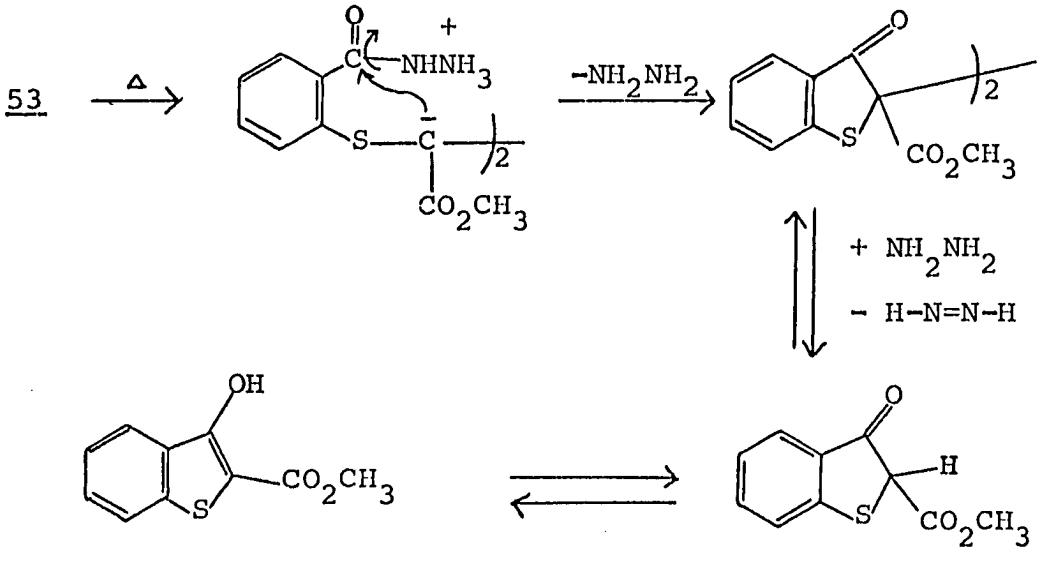
53

This adduct was identified by combustion analysis (for C, H, N, and S) and by spectral studies. No SH absorption remained in the infrared spectrum and the ester functions were now attached to saturated carbon atoms (C=O at 1731 cm^{-1}). The nmr spectrum obtained in trifluoroacetic acid due to the insoluble nature of this intermediate) revealed 2 equivalent ester methoxyls at 3.75 δ and a two proton singlet at 4.33 δ. These resonances eliminate from consideration the alternative di-addition product (54) formed by SH attack at the same alkyne carbon.



54

Under a variety of solvent conditions this labile intermediate underwent ring closure to 2-carbomethoxy-3-hydroxybenzo[b] thiophene (55) which has been previously reported in the literature and was prepared by an alternative synthesis.[23] A suggested mechanism for formation of 55 would involve nucleophilic attack upon the hydrazide C=O with expulsion of hydrazine and subsequent reduction of the strained ethane-linkage by that same hydrazine. Katz has shown that hydrazine is an effective reducing agent for -S-S- bonds.[8] There is also considerable precedent for the reduction of alcohols (to hydrocarbons), epoxides (to alcohols), and thioketals (to hydrocarbons) by refluxing in hydrazine containing solutions.[24] However, previous examples of reductive cleavage of a C-C bond do not appear to have been reported.

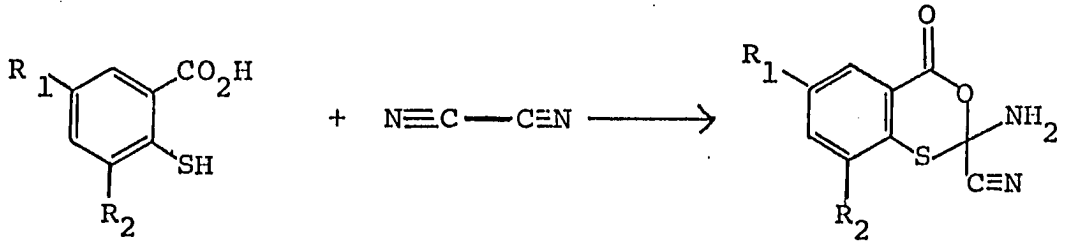


55

Condensations of Cyanogen with o-Mercaptobenzoic Acids (Thiosalicylic Acids)

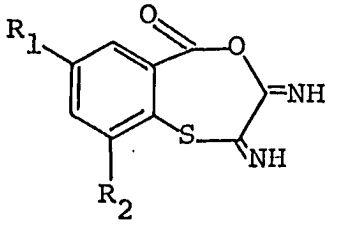
In a parallel manner to the thiosalicylhydrazides, it should be possible to bring about heterocyclic ring formation from a 1:1 combination of o-mercaptocarboxylic acids (17) and cyanogen. Thus one might envision several modes of ring closure in which nucleophilic attack of the SH upon cyanogen would be followed by either addition of the carboxylic OH or displacement by the transient imino function. The pathways and possible products are outlined below. Other less plausible routes are possible and these will not be detailed.

Pathway 1



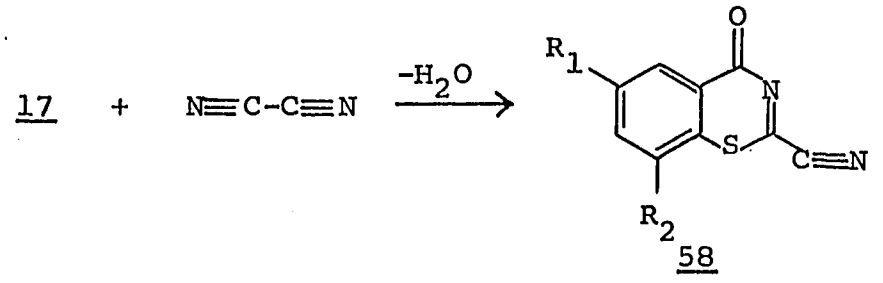
17 56

or



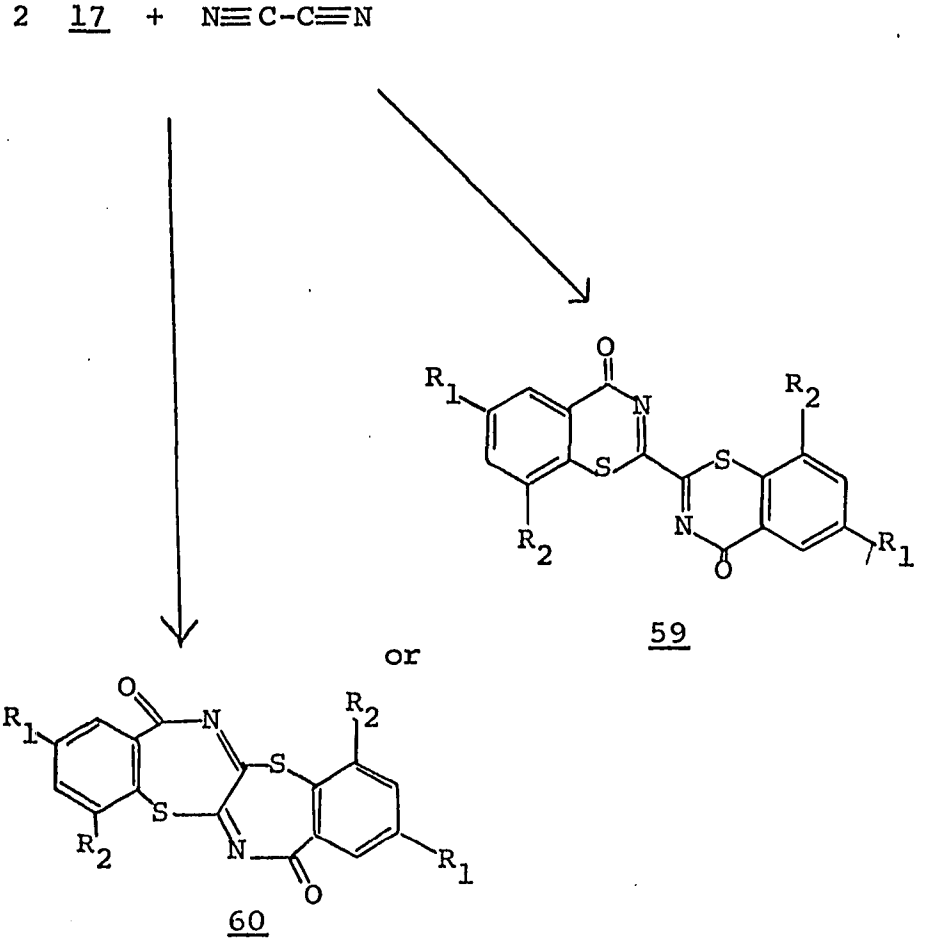
57

Pathway 2



58

Pathway 3 (2:1 mole, thiosalicylic acid:cyanogen)

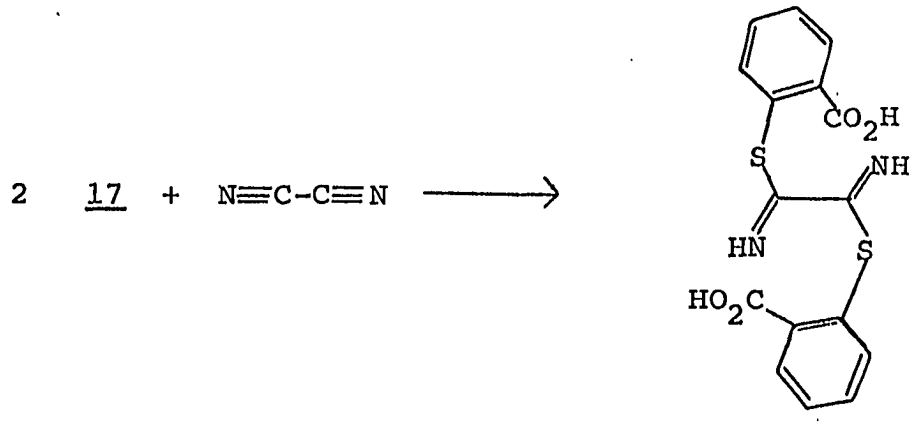


59

60

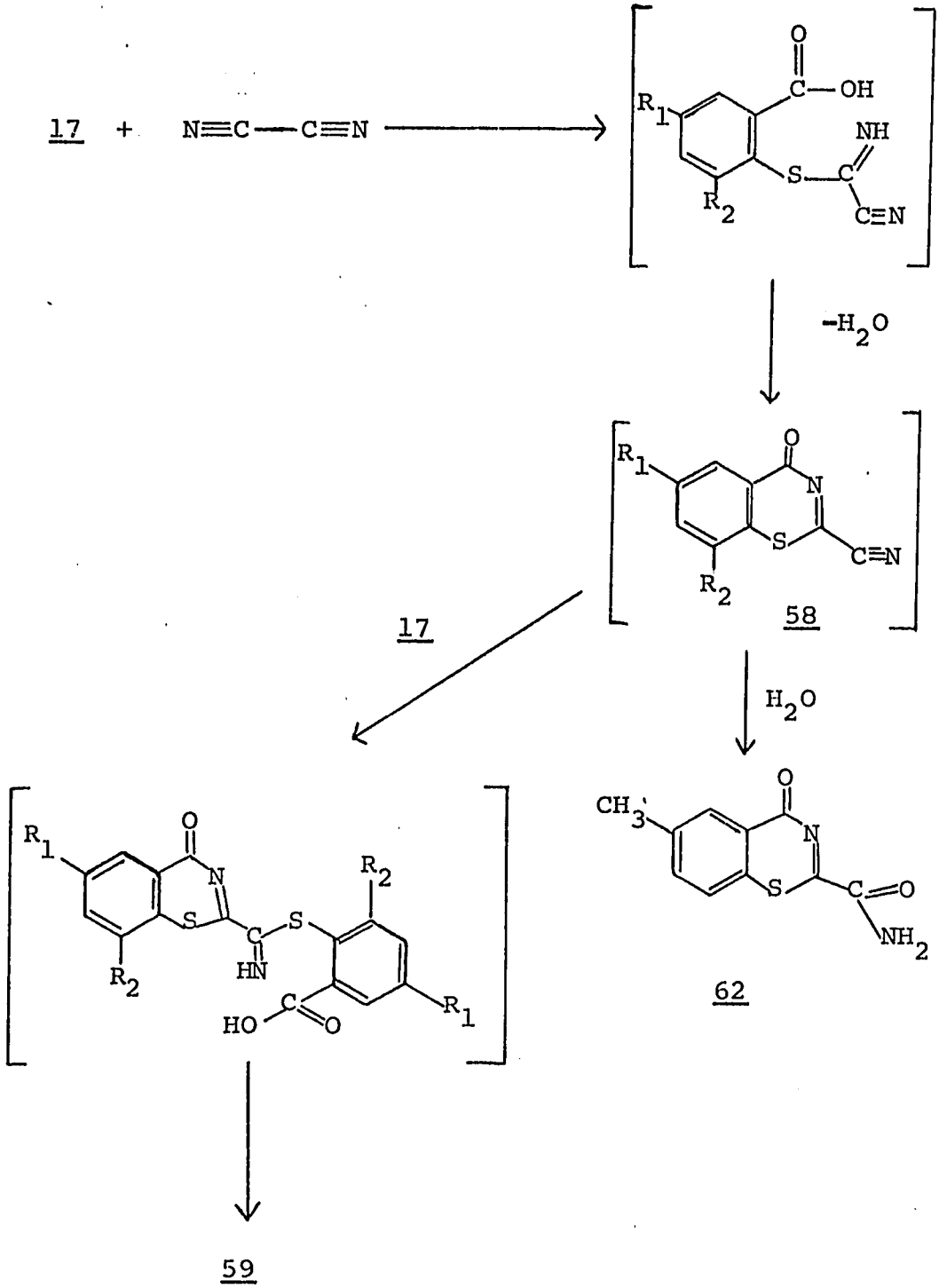
Mass spectra and elemental analyses readily demonstrated that the products represented 2:1 mole combinations of 17 with cyanogen with concomitant loss of two molecules of water. This 2:1 reaction was surprising in that the cyanogen was present in vast excess in the reaction mixture. Although unusual, the isolation of products such as these has been reported in the reaction of α-mercaptoacetic acids with cyanogen.[3] Infrared spectra displayed no nitrile nor NH absorption bands and thus eliminated the 1:1 products 56, 57, and 58. The combustion analysis supported this contention and could be consistent with either 2:1 product from pathway 3, i.e., 59 or 60. However, the mass spectra clearly indicated the greater likelihood of the bis-system (59) over the tetracyclic fused ring system (60). In addition to the molecular ion, an intense fragment ion occurred at exactly half-mass and corresponding to the scission of the C-C single bond. An intense peak was also found from loss of CN in a Retro-Diels Alder process.

While such fused systems have been postulated as possible products of other related cyanogen condensations, none has yet been observed. Furthermore, the generation of the fused system would probably require the intermediacy of a vicinal bis thio-imide intermediate (61).



61

In this intermediate 61 each = NH would displace upon the most distant -COOH. Such a mechanistic pathway, while by no means impossible, would be more complicated than the stepwise condensation via a 2-cyano-4H-1,3-benzothiazin-4-one (58). Although no such intermediate 58 was detected or isolated, it was possible in one case to isolate 2-carboxamido-6-methyl-1,3-benzothiazin-4-one (62). This compound could arise from hydroylsis of 58 which is postulated as an intermediate in the proposed mechanism.



It is suggested that since 58 was not detected, the cyano moiety in 58 might be more activated toward accepting a second nucleophilic attack by another thiosalicylic acid molecule than a cyano in cyanogen itself.

Elemental and mass spectral analysis confirmed the composition of 62 to be a 1:1 mole ratio of 17c and cyanogen. An infrared spectrum demonstrated the absence of nitrile absorption and the presence of bonded N-H bands at 3200-3400 cm^{-1}. A mass spectrum showed a molecular ion at 220 m/e followed by a P-44 fragment at m/e 176 due to loss of the carboxamido moiety.

The reaction of 17 with cyanogen was carried out by the same method as that used in the reaction of thiosalicylhydrazides and cyanogen. The reaction gave yields of 59 ranging from 6 to 96%. Low yields in some cases were attributed to poor solubility differentials between starting material and product leading to difficulty in purification of the product. Also several of the reactions were accompanied by a significant amount of tar formation. The products (59) were all high melting (380°C and up) and extremely stable to thermal decomposition. The analogs of 59 that were prepared are listed below.

59a:	R_1 = H;	R_2 = H;
59b:	R_1 = Cl;	R_2 = H;
59c:	R_1 = I;	R_2 = H
59d:	R_1 = Cl;	R_2 = Cl;
59e:	R_1 = CH_3;	R_2 = H;

All members of this class were too highly insoluble in aqueous medium to consider in vivo pharmacological evaluation.

EXPERIMENTAL SECTION

Melting points were determined in melting point capillaries on a Mel-Temp and are reported uncorrected in degrees centigrade.

Infrared spectra were obtained on a Perkin-Elmer 257 grating infrared spectrophotometer. Liquid samples were run neat as a thin layer between two KBr plates. Solid samples were run as 1-2% KBr discs prepared using a Wilkes Mini-Press.

Nmr spectra were determined on a Hitachi Perkin-Elmer R-20A at 60 MHz using tetramethylsilane as an internal standard in samples whose concentration was 10-20% w/v. The data was presented in the order δ(multiplicity, number of protons, assignment).

Mass spectra were run by Dr. James E. Sturm and Jay E. Rowe on a Hitachi Perkin-Elmer RMU-6E double focusing sector mass spectrometer with a direct solids inlet system. Spectra were obtained at approximately 20^{o}C below the melting or boiling point at 80 eV. Peak positions were assigned relative to peaks found in the fragmentation pattern of perfluorokerosene.

Microanalyses were performed by Dr. George I. Robertson, Jr. of Florham Park, New Jersey.

Preparation of Thiosalicylic acids:

5-Chlorothiosalicylic acid (17b):

A solution of 41.2 g (0.24 mol) of 5-chloroanthranilic acid, 10 g (0.25 mol) of NaOH, and 16.6 g (0.24 mol) of $NaNO_2$ in 350 ml of water was added slowly with vigorous stirring to a mixture of 70 ml of concentrated HCl and 90 g of ice. The temperature of the solution was maintained at 0-5°C by cooling in an ice-bath and by addition of ice. Upon completion of addition, stirring was continued for 0.5 hour and then the mixture was neutralized to pH 7 with potassium acetate. The cold diazonium solution was added slowly with vigorous stirring to a solution of 110.6 g (0.69 mol) of potassium ethyl xanthate in 400 ml of water which was maintained at 75-80°C. During the addition a vigorous evolution of nitrogen was observed. The reaction mixture was acidified with concentrated HCl to pH 3 and the aqueous supernatant liquid was decanted. The sludge remaining was dissolved in 10% NaOH and heated on a steam bath for 2 hours. In order to minimize oxidation to disulfide, 17.4 g (0.10 mol) of sodium dithionite was added and the solution was heated at 80-90°C for 15 minutes. The solution was filtered hot, cooled and then acidified to pH 4 with concentrated HCl to precipitate 24.4 g (54.0%) of light yellow 17b: mp 190-193°; lit. mp 193-4°;[8] ir (KBr) 3100-2500 (broad COOH), 2550 (S-H), and 1690 cm^{-1} (acid C=O).

5-Methylthiosalicylic acid (17c):

A solution of 25.2 g (0.17 mol) of 5-methylanthranilic acid, 6.8 g (0.17 mol) of NaOH and 11.7 g (0.17 mol) of $NaNO_2$ in 200 ml of water was added to a solution of 50 ml concentrated HCl and 70 g of ice with vigorous stirring. The solution was stirred for 0.5 hour after the addition was completed and then neutralized with potassium acetate. The cold diazonium solution was added slowly with vigorous stirring to a solution of 77.0 g (0.48 mol) of potassium ethyl xanthate in 250 ml of water which was maintained at 75-80°C. Acidification of the solution to pH 3 with concentrated HCl yielded a sludge which was worked up as above to yield 21.70 g (81.7%) of tan 17c: mp 200° with decomposition; ir (KBr) 3100-2500 (broad COOH), 2550 (S-H), and 1665 cm^{-1} (acid C=O).

3,5-Dichlorothiosalicylic acid (17d):

A solution of 41.2 g (0.20 mol) of 3,5-dichloroanthranilic acid, 8.0 g (0.2 mol) of NaOH and 13.8 g (0.2 mol) of $NaNO_2$ in 240 ml of water was added to a solution of 55 ml concentrated HCl and 75 g ice. After stirring for 0.5 hour the solution was neutralized with potassium acetate. The cooled diazonium solution was added slowly to a solution of 92.0 g (0.57 mol) of potassium ethyl xanthate in 300 ml water maintained at 75-80°C. Acidification to pH 4 yielded a sludge which was worked up as above to yield

36.8 g (89.4%) of grey 17d: mp 175-180°: lit. 196-8°;[8] ir (KBr) 3100-2500 (broad COOH), 2540 (S-H), and 1688 cm^{-1} (acid C=O).

Preparation of Methyl thiosalicylates:

Methyl thiosalicylate (15a):

A solution of 30.8 g (0.20 mol) of thiosalicylic acid in 200 ml CH_3OH was refluxed for 12 hours during which anhydrous HCl was passed through the mixture. After refluxing the mixture was cooled, concentrated in vacuo, and dissolved in benzene. The benzene solution was washed twice with water, twice with 10% $NaHCO_3$, and twice with water, then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was distilled to yield 30.3 g (90.2%) of pale yellow 15a: bp 76-79° @ 0.1 mm: lit. bp 262-3° @ 728 mm;[8] ir (film) 3070, 3030, 3000, 2960, 2850 (C-H), 2560 (S-H), and 1712 cm^{-1} (ester C=O).

Methyl 5-chlorothiosalicylate (15b):

A solution of 11.3 g (0.06 mol) of 5-chlorothiosalicylic acid in 150 ml of CH_3OH was refluxed for 4 hours while passing anhydrous HCl into the mixture. After refluxing the reaction mixture was worked up as above to yield 9.9 g (81.1%) of white 15b: mp 42-45°: lit. mp 44-45°;[8] ir (film) 3100, 3070, 3000, 2955, 2845 (C-H), 2550 (S-H), and 1715 cm^{-1} (ester C=O).

Methyl 5-methylthiosalicylate (15c):

A solution of 16.7 g (0.10 mol) of 5-methylthiosalicylic acid in 220 ml CH_3OH was refluxed for 3 hours while passing anhydrous HCl into the mixture. During reflux a tan solid precipitated and was collected by filtration before cooling of the mixture. The tan solid was identified as 5,5'-dimethyl-2,2'-dithiosalicylic acid, mp 265-267°, by ir. The filtrate was worked up as in previously reported esterifications to yield 7.8 g (43.0%) of a brown solid 15c: mp 45°; ir (Nujol) 3010 (C-H), 2550 (S-H), and 1703 cm^{-1} (ester C=O).

Methyl 3,5-dichlorothiosalicylate (15d):

A solution of 26.8 g (0.12 mol) of 3,5-dichlorothiosalicylic acid in 200 ml CH_3OH was refluxed for 4 hours while anhydrous HCl was passed into the solution. Cooling precipitated a brown oil which subsequently solidified and was dissolved in benzene. The benzene solution was worked up as in previous esterifications to yield 25.3 g (89.0%) of yellow 15d: mp 50-55°C; ir (film): 3080, 3060, 3020, 2990, 2940, 2840 (C-H), 2490 (S-H), and 1720 (broad ester C=O).

Methyl 5-nitrothiosalicylate (15e):

A solution of 19.6 g (0.10 mol) of methyl 5-nitroanthranilate in 250 ml of concentrated HCl was cooled to 0-5°C and a solution of 8.6 g (0.125 mol) of $NaNO_2$ in 40 ml of water was added over 0.5 hour at 0-5°C. The mixture was stirred

for 1 hour and then neutralized with $NaHCO_3$ added as a slurry. The mixture was then made acidic to Congo red paper and added to a solution of 32.1 g (0.20 mol) potassium ethyl xanthate in 60 ml of water heated to 40-50°C. During addition a mixture of an oil and a yellow solid precipitated. After cooling to ambient temperature the solid was collected and dried under vacuum to remove water. The mixture was extracted with Et_2O to yield 17.3 g (81.3%) of a dark oil 15e: ir (film) 3090, 2980, 2950, 2890, 2860 (C-H) and 1724 cm^{-1} (ester C=O). The yellow solid remaining after Et_2O extraction was recrystallized from CH_3OH, dissolved in water and acidified to precipitate 0.9 g of 5-nitrothiosalicylic acid (17e): mp 330°; ir 3150-2500 (broad COOH) and 1685 cm^{-1} (acid C=O).

Anal. Calcd. for $C_7H_5NO_4S$: N, 7.03; Found: N, 7.07.

Dimethyl dithiosalicylate (14a):

A mixture of 56.3 g (0.18 mol) of dithiosalicylic acid and 85.7 g (0.72 mol) of thionyl chloride was refluxed for 24 hours. After reflux, the excess thionyl chloride was removed in vacuo. A mixture of CH_3OH and THF was used to dissolve the intermediate diacid chloride and the solution was refluxed for 14 hours. The solution was concentrated to yield 40.8 g (61.2%) of yellow 14a: mp 131.5-

133.5°: lit. mp 131-133° [8]; ir (KBr) 3085, 3025, 3000, 2955, 2850 (C-H), and 1705 cm^{-1} (ester C=O).

Preparation of Thiosalicylhydrazides:

Thiosalicylhydrazide (1a) - Method 1:

A solution of 42.1 g (0.25 mol) of methyl thiosalicylate, 22 ml of isopropyl alcohol and 90.0 g (1.80 mol) of hydrazine hydrate was refluxed for 4 hours and cooled to room temperature. The solution was diluted with 290 ml of cold water and then acidified to pH 6-7 with 3 M H_2SO_4 to yield 31.5 g (74.9%) of light yellow 1a: mp 115-117°: lit. mp 115-116; [8] ir (KBr) 3300, 3220 (N-H), 2520 (S-H), and 1625 cm^{-1} (hydrazide C=O).

Thiosalicylhydrazide (1a) - Method 2:

A mixture of 20.4 g (0.06 mol) of dimethyl dithiosalicylate and 20.0 g (0.40 mol) of hydrazine hydrate (85% solution) was refluxed for 7 hours. The clear yellow solution was cooled to room temperature and diluted with 70 ml of 10% NaCl solution. The solution was adjusted to pH 4 with 30 ml of concentrated HCl to yield 16.4 g (81.5%) of light yellow 1a: mp 110-113°: lit. mp 115-116; [8] ir (KBr) as above.

5-Chlorothiosalicylhydrazide (1b):

A mixture of 7.6 g (0.04 mol) of methyl 5-chlorothiosalicylate, 13.7 g (0.27 mol) of hydrazine hydrate (85% solution) and

4 ml of isopropyl alcohol was refluxed for 4 hours. After cooling to room temperature, the solution was diluted with cold water and acidified to pH 5 with 3 M H_2SO_4 to yield 5.9 g (77.3%) of yellow 1b: mp > 200°; ir (KBr) 3270 (N-H), 2560 (S-H), and 1608 cm^{-1} (hydrazide C=O).

5-Methylthiosalicylhydrazide (1c):

A mixture of 7.8 g (0.04 mol) of methyl 5-methylthiosalicylate (15c), 18.0 g (0.3 mol) of hydrazine hydrate (85% solution) and 5 ml of isopropyl alcohol was refluxed for 18 hours. After cooling the amber solution to room temperature, the solution was diluted with 50 ml of 10% NaCl solution and then acidified to pH 4 with concentrated HCl to yield 5.8 g (75.2%) of yellow needles 1c: mp 145.5-148.0°; ir (KBr) 3240 (broad N-H), 2560 (S-H), and 1610-1580 cm^{-1} (broad hydrazide C=O); nmr (DMSO-d_6) δ 7.62-6.92 (m, 3, Ar-H), 5.35 (S, 3, N-H, rapidly exchanged with D_2O), and 2.22 ppm (S, 3, Ar-CH_3).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.58; H, 5.57; N, 15.36.

3,5-Dichlorothiosalicylhydrazide (1d):

A mixture of 23.7 g (0.10 mol) of methyl 3,5-dichlorothiosalicylate, 35.0 g (0.70 mol) of hydrazine hydrate (85% solution) and 15 ml of isopropyl alcohol was refluxed

for 24 hours. After cooling to room temperature, the solution was diluted with 100 ml of 10% NaCl and acidified to pH 4 with 45 ml of concentrated HCl to yield 21.1 g (89.1%) of yellow 1d: mp 162.5-163.0°: lit. mp 162-169°;[3] ir (KBr) 3260 (N-H), 2570 (S-H), and 1600 cm^{-1} (hydrazide C=O).

5-Nitrothiosalicylhydrazide (1e):

A mixture of 14.9 g (0.07 mol) of methyl 5-nitrothiosalicylate, 25.0 g (0.50 mol) of hydrazine hydrate (85% solution) and 50 ml of isopropyl alcohol was refluxed for 3 hours. After cooling to room temperature, 50 ml of CH_3OH were added to yield 7.6 g (51.1%) of light yellow 1e: mp 196-198°; ir (KBr) 3350-3000 (broad N-H) and 1670 cm^{-1} (hydrazide C=O).

Preparation of 3-Amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-ones:

3-Amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (10a):

A solution of 5.2 g (0.10 mol) of cyanogen in 20 ml of THF was cooled to 0°C and several drops of Et_3N were added. A solution of 6.3 g (0.04 mol) of thiosalicylhydrazide 1a in 60 ml of THF was added dropwise over 0.5 hour at 0-5°C. The mixture was stirred at 0-5°C for 1 hour after addition was completed. During this period a yellow solid began

to precipitate and 100 ml of benzene were added to complete precipitation. The solid was collected by filtration to yield 5.4 g (73.6%) of 10a. Recrystallization from benzene yielded white crystalline 10a: mp 141.5-142.5°; ir (KBr) 3295, 3235 (N-H) 1660 (C=NH) and 1645 cm^{-1} (C=O). Nmr (DMSO-d_6) δ 8.25-8.05, 7.8-7.2 (m, 4, Ar-H), 9.0 (broad S, 1, N-H, rapidly exchanged with D_2O), and 5.56 ppm (S, 2, N-H, rapidly exchanged with D_2O).

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75. Found: C, 49.63; H, 3.54; N, 22.47.

3-Amino-6-chloro-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (10b):

A solution of 3.0 g (0.06 mol) of cyanogen in 20 ml of THF was cooled to 0°C and several drops of Et_3N were added. A solution of 1.9 g (9.0 mmol) of 5-chlorothiosalicylhydrazide (1b) in 60 ml of THF was added dropwise over 1.0 hour at 0-5°C. After stirring at 0-5°C for 4 hours, the mixture was allowed to warm slowly to room temperature at which time an off-white solid precipitated. Recrystallization from benzene yielded 1.02 g (50.0%) of 10b: mp 144.5°; ir (KBr) 3320, 3280, 3235, 3180, 3100 (N-H) and 1665 cm^{-1} (C=O, C=NH).

Anal. Calcd. for $C_8H_6ClN_3OS$: C, 42.20; H, 2.66; N, 18.46. Found: C, 42.26; H, 2.62; N, 18.76.

3-Amino-2-imino-6-methyl-3,4-dihydro-2H-1,3-benzothiazin-4-one (10c):

A solution of 1.6 g (0.03 mol) of cyanogen in 15 ml of THF was cooled to 0°C and several drops of Et_3N were added. A solution of 2.9 g (0.02 mol) of 5-methylthiosalicylhydrazide 1c in 65 ml THF was added dropwise over 0.5 hour at 0-5°C. After stirring for 4.5 hours a yellow solid precipitated and the solution was then diluted with 40 ml of benzene. The precipitated solid was collected by filtration to yield 3.13 g (94.4%) of 10c. Recrystallization from benzene gave light yellow 10c: mp 154.5°; ir (KBr) 3310, 3270, 3210 (N-H) and 1658 cm^{-1} (C=O and C=NH). Nmr (DMSO-d_6) δ 8.95 (broad S, 1, N-H), 7.95, 7.6-7.2 (m, 3, Ar-H), 5.55 (S, 2, NH_2), and 2.35 ppm (S, 3, Ar-CH_3).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27. Found: C, 52.01; H, 4.35; N, 20.56.

3-Amino-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one hydrochloride (29):

A solution prepared by dissolving 0.40 g (2.0 mmol) of 10a in 35 ml of hot benzene was blown with anhydrous HCl gas to precipitate white 29 : mp 206-209°; ir (KBr) 3300-2600 (broad N-H), 1700 (C=O) and 1610, 1585 cm^{-1} (C=O).

Anal. Calcd. for $C_8H_8ClN_3OS$: Cl, 15.44. Found: Cl, 15.15.

3-(4'-Nitrobenzylideneimino)-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (28a):

A solution of 0.97 g (50 mmol) of 10a, 0.76 g (5.0 mmol) of p-nitrobenzaldehyde, and 0.3 ml of acetic acid in 20 ml CH_3OH was refluxed for 15 minutes on a steam bath. Filtration of the precipitated yellow solid yielded 1.2 g (76.1%) of yellow 28a: mp 307.5-308.5°; ir (KBr) 3150-2750 (C-H), 1690 (C=NH), and 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{10}N_4O_3S$: C, 55.21; H, 3.09; N, 17.17. Found: C, 54.95; H, 3.10; N, 17.35.

3-(4'-Dimethylaminobenzylideneimino)-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (28b):

A solution of 0.97 g (5.0 mmol) of 10a, 0.75 g (5.0 mmol) of p-dimethylaminobenzaldehyde, and 0.5 ml of acetic acid in 50 ml of CH_3OH was refluxed for 2 hours and then filtered hot to collect the yellow precipitate. Recrystallization from hot DMSO gave 0.8 g of yellow 28b: mp 264-267°; ir (KBr) 3150-2750 (C-H) and 1670 cm^{-1} (C=NH, C=O).

Anal. Calcd. for $C_{17}H_{16}N_4OS$: N, 17.27. Found: N, 17.55.

3-(4'Nitrobenzylideneimino)-6-chloro-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (28c):

A solution of 0.3 g (2.0 mmol) of p-nitrobenzaldehyde, 0.46 g (2.0 mmol) of 10b, and several drops of acetic acid in 30 ml of CH_3OH was refluxed for 45 minutes to yield yellow 28c: mp 331.5-332.0°; ir (KBr) 3260-2800 (C-H), 1690 (C=NH) and 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_9ClN_4O_3S$: C, 49.94; H, 2.51; N, 15.53. Found: C, 49.91; H, 2.44; N, 15.68.

3-(4'-Dimethylaminobenzylideneimino)-6-chloro-2-imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (28d):

A solution of 0.78 g (3.4 mmol) of 10b, 0.51 g (3.4 mmol) of p-dimethylaminobenzaldehyde, and several drops of acetic acid in 40 ml of CH_3OH was refluxed for 20 hours and the dark yellow solid collected by filtering the hot mixture. Recrystallization from hot DMSO yielded 0.4 g of 28d: mp 265.5-267.0°; ir (KBr) 3200-2800 (C-H) and 1768 cm^{-1} (C=NH, C=O).

Anal. Calcd. for $C_{17}H_{15}ClN_4OS$: N, 15.61. Found: N, 15.67.

3-(4'-Nitrobenzylidineimino)-2-imino-6-methyl-3,4-dihydro-2H-1,3-benzothiazin-4-one (28e):

The concentrated mother liquor from recrystallization of 10c, 0.15 g (1.0 mmol) of p-nitrobenzaldehyde, and

several drops of acetic acid dissolved in 25 ml CH_3OH were refluxed for 0.5 hours and precipitated 0.13 g of yellow 28e. Recrystallization from DMSO-CH_3OH yielded pure yellow 28e: mp 312.5-313.0°; ir (KBr) 3150-2800 (C-H) and 1688, 1680 cm^{-1} (C=NH, C=O).

Anal. Calcd. for $C_{16}H_{12}N_4O_3S$: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.23; H, 3.41; N, 16.58.

3-(4'-Dimethylaminobenzylideneimino)-2-imino-6-methyl-3,4-dihydro-2H-1,3-benzothiazin-4-one (28f):

A solution of 1.04 g (5.0 mmol) of 10c, 0.75 g (5.0 mmol) of p-dimethylaminobenzaldehyde, and several drops of acetic acid in 50 ml of CH_3OH was refluxed for 24 hours and then filtered hot to obtain 0.6 g (35.5%) of brown solid. Recrystallization from hot DMSO yielded pure tan 28f: mp 273.5-275.0°; ir (KBr) 3160-2780 (C-H) and 1680 cm^{-1} (C=NH, C=O).

Anal. Calcd. for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.55. Found: C, 63.59; H, 5.51; N, 16.71.

3-Amino-3,4-dihydro-2H-1,3-benzothiazin-2,4-dione (24):

A solution of 1.9 g (0.01 mol) of 10a, 20 g (0.10 mol) of chloracetaldehyde (40-45% aqueous solution), and 2.0 ml of acetic acid in 35 ml of C_2H_5OH was heated for 20 hours at 45-55°C. An off-white solid precipitated during heating

and was collected by filtration to yield 1.07 g (55.3%) of crude 24. Recrystallization yielded pure tan 24: mp 199.0-199.5°; ir (KBr) 3310, 3245, 3070, 3010 (N-H) and 1688, 1610 cm^{-1} (C=O).

Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.48; H, 3.11; N, 14.42. Found: C, 49.85; H, 3.22; N, 14.80.

3-(4'-Nitrobenzylideneimino)-3,4-dihydro-2H-1,3-benzothiazin-2,4-dione (26):

A solution of 0.15 g (1.0 mmol) of p-nitrobenzaldehyde, 0.19 g (1.0 mmol) of 24, and several drops of acetic acid in 20 ml of CH_3OH was refluxed for 45 minutes and then the solution was filtered hot. The first crop of crystals was identified as 24 and the second crop was collected to give white crystalline 26: mp 220.5-221.5°; ir (KBr) 1690 (C=O) and 1640 cm^{-1} (-C=N-).

Anal. Calcd. for $C_{15}H_9N_3O_4S$: C, 55.04; H, 2.77; N, 12.84. Found: C, 54.87; H, 2.81; N, 12.79.

3-Amino-2-cyanomethyl-3,4-dihydro-2H-1,3-benzothiazin-4-one (42):

Cyanoacetylene (0.72 g, 0.014 mol) was dissolved in 25 ml of DMF and treated to the portion wise addition of 2.02 g (0.012 mol) of thiosalicylhydrazide added over 2 minutes. An exothermic reaction resulted increasing

the temperature from 28 to 56°. The mixture was heated at 95° for 2 hours and then the DMF solvent was removed *in vacuo*. The resulting oil (2.6 g, 98%) was allowed to crystallize from CH_3OH to yield 0.4 g of white crystalline 42: mp 98.5-100.0°; ir (KBr) 3280, 3190 (N-H), 2960 (C-H), 2245 (C≡N) and 1618 cm^{-1} (C=O). Nmr ($CDCl_3$) δ 8.25-8.05, 7.60-7.15 (m, 4, Ar-H), 4.88 (S, 2, $-NH_2$), ABX pattern not resolved, δ_A and δ_B centered at 3.04 (m, 2, CH_2), δ_X 5.10 ppm (dd, 1, CH).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.78; H, 4.25; N, 19.37.

2-Cyanomethyl-3-(-4'-nitrobenzylideneimino)-3,4-dihydro-2H-1,3-benzothiazin-4-one (43):

A solution of 0.11 g (0.5 mmol) of 42, 0.08 g (0.5 mmol) of p-nitrobenzaldehyde, and several drops of acetic acid in 20 ml of CH_3OH was refluxed for several hours and then cooled to room temperature. The yellow crystals which precipitated from the mixture were collected by filtration and recrystallized from CH_3OH to yield crystalline yellow 43: mp 169-170°; ir (KBr) 3100-2950 (C-H), 2270 (C≡N) and 1660 cm^{-1} (C=O and -C=N-).

Anal. Calcd. for $C_{17}H_{12}N_4O_3S$: C, 57.95; H, 3.43; N, 15.90. Found: C, 57.89; H, 3.54; N, 15.86.

3-Amino-2-(cis-2-cyanoethenyl)imino-3,4-dihydro-2H-1,3-benzothiazin-4-one (34):

Cyanoacetylene (1.1 g, 0.02 mol) and 10a (3.9 g or 0.02 mol) were dissolved in 25 ml of DMF and heated at 95°C for 2 hours. After cooling to room temperature, the DMF solvent was removed in vacuo and the residue extracted with benzene to yield 2.13 g (43.6%) of brown 34 . Recrystallization from CH_3OH yield tan 34 : mp 144.5-146.0°; ir (KBr) 3305, 3230, 3070 (N-H), 2210 (C≡N), and 1665 cm^{-1} (C=O). Nmr (DMSO-d_6) δ 8.35-8.15, 7.95-7.40 (m, 4, ArH), 7.56 (d, 1, = CH-, J = Hz), 6.35 (S, 2, NH_2), and 5.41 ppm (d, 1, = CH-, J = 8 Hz).

Anal. Calcd. for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94. Found : C, 54.15; H, 3.35; N, 23.20.

1,2-Dihydro-s-triazolo[5,1-b]benzo-[1,3]-thiazin-2,9-dione (30):

A solution of 0.97 g (5.0 mmol) of 10a and 1.5 g (15 mmol) of Et_3N in 50 ml of THF was stirred at room temperature. A solution of 0.74 g (7.5 mmol) of phosgene in benzene (12.5% solution) was added dropwise over 15 minutes and the reaction was exothermic from 30 to 38°. The white solid which precipitated was extracted with CH_3OH and the residual white solid recrystallized from 1,4-dioxane to yield 0.56 g (50.9%) of white crystalline 30 : mp 310°;

ir (KBr) 3100-2500 (NH, free and bonded) and 1695 cm^{-1} (C=O). Nmr (DMSO-d_6) δ 8.55-8.35, 8.0-7.5 (m, 4, ArH).

Anal. Calcd. for $C_9H_5N_3O_2S$: C, 49.31; H, 2.30; N, 19.17. Found: C, 49.25; H, 2.42; N, 19.12.

2-Phenyl-s-triazolo[5,1-b]benzo-[1,3]-thiazin-9-one (31): A solution of 0.97 g (5.0 mmol) of 10a and 1.4 g (0.01 mol) of benzoyl chloride in 65 ml of CH_3OH was refluxed for several hours. The mixture was filtered hot to collect 0.15 g (11%) of white 31. Recrystallization from 1,4-dioxane gave white crystalline 31: mp 281-282°; ir (KBr) 1710 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_9N_3OS$: C, 64.50; H, 3.25; N, 15.04. Found: C, 64.26; H, 3.64; N, 14.82.

2-Amino-1H-pyrazolo[5,1-b]benzo-[1,3]-thiazin-9-one (44) and 2-methoxy-1H-pyrazolo[5,1-b]benzo-[1,3]-thiazin-9-one (45):

A solution of 42 in 25 ml of CH_3OH containing several drops of concentrated H_2SO_4 and several drops of H_2O was refluxed for 24 hours. The mixture was extracted into benzene and H_2O washed. A yellow solid precipitated during the H_2O wash and upon recrystallization from benzene-THF yielded pure yellow 44: mp 201-202°; ir (KBr) 3400, 3270, 3210, 3070 (N-H), and 1635 cm^{-1} (C=O).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.87; H, 4.46; 18.88.

The benzene layer was concentrated to yield a yellow solid which upon recrystallization twice from benzene gave pure yellow 45 : mp 212.0-212.5°; ir (KBr) 3060 (N-H), 1650 (C=O), 1615 (C=N) and 1185 cm^{-1} (C-O-CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30; N, 11.96. Found : C, 56.23; H, 4.46; N, 11.90.

Preparation of 1,3,4-oxadiazol-2-ones:

5-Phenyl-2,3-dihydro-1,3,4-oxadiazol-2-one (49d):

A solution of 2.1 g (0.01 mol) of 48e in 25 ml of diphenyl ether was heated for 2 hours at 225-240°. Upon cooling to room temperature a white solid was precipitated. The mixture was diluted with pet ether (20-40°) to precipitate additional white solid. Recrystallization of the white solid from benzene yielded 1.4 g (86.5%) of crystalline white 49d: mp 136-138°: lit. mp 139°; ir (KBr) 3210, 3150 (N-H), 2820 (C-H), 1765 (C=O) and 1735 cm^{-1} (C=N). Nmr (DMSO-d_6) δ 8.3-7.1 ppm (m, 5, ArH).

5-(2'-Hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazol-2-one (49b):

A solution of 2.2 g (0.01 mol) of 48b dissolved in 40 ml of diphenyl ether was heated at 220-230° for 1.5 hours. Cooling precipitated a white solid which was collected by

filtration to give 1.6 g (88.8%) of 49b. Recrystallization from benzene gave white crystalline 49b: mp 201.0-201.5°; ir (KBr) 3320-3120 (broad N-H), 1790, 1770, 1750 (C=O) and 1625 cm^{-1} (C=N). Nmr (DMSO-d_6) δ 7.75-6.80 (m, 4, ArH) and 10.7-9.7 ppm (broad S, 1, NH, rapidly exchanged with D_2O).

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found: C, 53.78; H, 3.46; N, 15.49.

5-(5'-Bromo-2'-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazol--2-one (49c):

In 25 ml of diphenyl ether a solution of 2.1 g (7.0 mmol) of 48c was heated at 225-240° for 1 hour. Cooling and diluting with petroleum ether precipitated 1.6 g (91.1%) of 49c. Recrystallization from CH_3OH gave pure 49c: mp 242.5-243.5°; ir (KBr) 3280-3120 (broad N-H), 1790-1720 (broad C=O) and 1625 cm^{-1} (C=N). Nmr (DMSO-d_6) δ 7.8-6.9 (m, 3, ArH) and 13-10 ppm (broad, 2, OH and NH, rapidly exchanged with D_2O.

Anal. Calcd. for $C_8H_5BrN_2O_3$: C, 37.38; H, 1.96; N, 10.90. Found: C, 37.63; H, 2.12; N, 10.63.

5-(2'-Mercaptophenyl)-2,3-dihydro-1,3,4-oxadiazol-2-one (49a): Method A:

A solution of 2.4 g (0.01 mol) of 48a in 25 ml of diphenyl ether was heated at 200-220° for 0.5 hour.

Cooling precipitated 1.2 g (63.3%) of 49a.

Method B:

A solution of 1.7 g (0.01 mol) of thiosalicylhydrazide in 35 ml of THF was cooled to 0°. A solution of 11.8 g (0.015 mol) of phosgene (12.5%) in benzene was added dropwise over 1 hour at 0-10°. After warming to room temperature, the mixture was refluxed for 2 hours and then concentrated in vacuo to yield 0.8 g (41.3%) of yellow 49a. Recrystallization from THF-benzene gave white 49a: mp 158-159°; ir (KBr) 3140-3040 (broad N-H), 2820 (C-H), 2530 (S-H), 1805, 1735 (C=O), and 1595 cm^{-1} (C=N).

Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.48; H, 3.11; N, 14.42. Found: C, 49.70; H, 3.12; N, 14.49.

Preparation of β-Carbethoxybenzhydrazides:

β-Carbethoxybenzhydrazide (48e):

Benzhydrazide (6.8 g, 0.05 mol) was dissolved in 55 ml of acetonitrile (CH_3CN) containing 10% H_2O and was heated to 60°C. Ethyl chloroformate 5.4g (0.05 mol) was added drop wise over 15 minutes and was noted to be slightly exothermic. The mixture was refluxed for 24 hours and then the CH_3CN was removed in vacuo. The residue was extracted into benzene and H_2O washed. Concentration of the benzene solution yielded white 48e. Recrystallization from benzene gave 3.1 g (29.8%) of white 48e: mp 128.0-130.5°;

ir (KBr) 3220-3180 (broad N-H), 3020-2980 (broad C-H), 1710 (C=O carbethoxy), and 1660, 1650 cm^{-1} (C=O, hydrazide). Nmr (DMSO-d_6) δ 10.35 (s, 1, N-H), 9.17 (s, 1, N-H), 8.05-7.85, 7.65-7.45 (m, 5, ArH), 4.12 (q, 2, $-CH_2-$), and 1.20 ppm (t, 3, CH_3).

β-Carbethoxysalicylhydrazide (48b):

A solution of 6.1 g (0.04 mol) of salicylhydrazide in 55 ml of CH_3CN was heated to reflux and 4.3 g (0.04 mol of ethyl chloroformate was added dropwise. A white solid precipitated from the mixture and was collected by filtration. This solid was partially soluble in water. The water insoluble material was filtered and dried to give 4.7 g (51.8%) of white 48b. Recrystallization from benzene with decolorizing charcoal gave pure white 48b: mp 120.5-122.0°; ir (KBr) 3260-3180 (broad N-H), 3070-3010 (C-H), 1720, 1710 (C=O carbethoxy) and 1638 cm^{-1} (C=O hydrazide). Nmr ($CDCl_3$-DMSO-d_6) δ 11.61 (S, 1, O-H), 10.06 (S, 1, N-H), 8.17 (S, 1, N-H), 7.92-6.60 (m, 4, ArH), 4.10 (q, 2, $-CH_2-$), and 1.19 ppm (t, 3, $-CH_3$).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.72; H, 5.53; N, 12.78.

β-Carbethoxy-5-bromosalicylhydrazide (48c):

5-Bromosalicylhydrazide (2.3 g, 0.01 mol) in CH_3CN-H_2O (4:1 w) was heated to reflux and 1.1 g (0.01 mol) of

ethyl chloroformate was added. After refluxing for 2 hours, the mixture was cooled to room temperature and a white solid 48c precipitated. Recrystallization from benzene yielded 2.3 g (74.9%) of white 48c: mp 180.5-181.5°; ir (KBr) 3290 (N-H), 3040, 2995, 2980 (C-H), 1730 (C=O, carbethoxy) and 1640 cm^{-1} (C=O hydrazide). Nmr (DMSO-d_6) δ 11.97 (S, 1, O<u>H</u>, rapidly exchanged with D_2O), 10.45 (S, 1, N-<u>H</u>, rapidly exchanged with D_2O), 9.34 (S, 1, N-<u>H</u>, rapidly exchanged with D_2O), 8.08 (d, 1, Ar<u>H</u>, J_m = 3 Hz), 7.62 (dd, 1, Ar<u>H</u>, J_o = 9 Hz, J_m = 3 Hz), 6.98 (d, 1, Ar<u>H</u>, J_o = 9 Hz), 4.13 (q, 2, -C<u>H</u>$_2$-), and 1.22 ppm (t, 3, -C<u>H</u>$_3$).

<u>Anal</u>. Calcd. for $C_{10}H_{11}BrN_2O_4$: C, 39.63; H, 3.66; N, 9.24. Found: C, 39.90; H, 3.68; N, 9.32.

<u>β-Carbethoxy-5-methoxysalicylhydrazide (48d)</u>:

A solution of 1.6 g (9.0 mmol) of 5-methoxysalicylhydrazide dissolved in 55 ml CH_3CN containing 10% H_2O was heated to reflux and 1.0 g (9.0 mmol) of ethyl chloroformate was added dropwise over 10 minutes. After refluxing for 18 hours, the mixture was concentrated <u>in vacuo</u> to give a white solid residue which was water-washed and dried to give 2.2 g (94.3%) of white 48d. Recrystallization from 95% EtOH gave pure white 48d: mp 162.5-163.5°; ir (KBr) 3235 (broad N-H), 3070, 3030, 3000 (C-H), 1708 (C=O carbethoxy) and 1641 cm^{-1} (C=O hydrazide). Nmr (DMSO-d_6) δ 11.51 (S,

1, O-H, rapidly exchanged with D_2O), 10.45 (S, 1, N-H, rapidly exchanged with D_2O), 9.26 (S, 1, N-H, rapidly exchanged with D_2O), 7.44 (d, 1, ArH, J_m = 3 Hz), 7.11 (dd, 1, ArH, J_o = 9 Hz, J_m = 3 Hz), 6.88 (d, 1, ArH, J_o = 9 Hz), 4.11 (q, 2, $-CH_2-$), 3.75 (S, 3, $-OCH_3$), and 1.20 ppm (t, 3, $-CH_3$).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.69; H, 5.74; N, 10.88.

β-Carbethoxythiosalicylhydrazide (48a):

Thiosalicylhydrazide 1a (5.1 g, 0.03 mol) was dissolved in 55 ml of CH_3CN containing 20% water, heated to 45°, and 3.3 g (0.03 mol) of ethyl chloroformate was added dropwise. The addition was completed over 0.5 hour and the mixture was then refluxed for 12 hours. The solution was diluted with water and extracted with benzene. The benzene solution was dried over $MgSO_4$ and concentrated in vacuo to yield 5.9 g (81.7%) of white solid 48a. Recrystallization from benzene gave pale yellow 48a: mp 120-122°; ir (KBr) 3315, 3250 (N-H), 3010, 2985 (C-H), 2590 (S-H) 1733 (C=O, carbethoxy), and 1653 cm^{-1} (C=O, hydrazide). Nmr (DMSO-d_6) δ 10.35 (d, 1, N-H, rapidly exchanged with D_2O), 9.27 (broad S, 1, N-H, rapidly exchanged with D_2O), 7.9-7.1 (m, 4, ArH), 5.3-5.1 (broad S, 1, S-H, rapidly exchanged with D_2O), 4.12 (q, 2, $-CH_2-$), and 1.22 ppm (t, 3, $-CH_3$).

Preparation of Salicylhydrazides:

5-Bromosalicylhydrazide (47b):

A solution of 9.2 g (0.04 mol) of methyl 5-bromosalicylate and 3.0 g (0.06 mol) of hydrazine hydrate (85% solution) in 80 ml of C_2H_5OH were refluxed for 21 hours. Upon cooling white crystalline 47b precipitated. Recrystallization from CH_3OH gave 9.1 g (98.8%) of white crystalline 47b: mp 221-223°: lit. mp 217-218°;[26] ir (KBr) 3400, 3320 (N-H) and 1635 cm^{-1} (C=O, hydrazide).

Preparation of 2-Amino-2-cyano-2,3-dihydro-1,3,4-oxadiazoles:

2-Amino-2-cyano-5-phenyl-2,3-dihydro-1,3,4-oxadiazole (39a):

Benzhydrazide (5.5 g, 0.04 mol) was dissolved in 50 ml of THF and was added dropwise at 0-5° over 0.5 hour to a solution containing 4.7 g (0.09 mol) of cyanogen in 20 ml of THF. The white solid which precipitated was collected by filtration and washed with benzene to yield 7.2 g (95.7%) of dried white 39a. Recrystallization from 1,4-dioxane gave pure 39a: mp 210-211°; ir (KBr) 3400, 3270, 3140 (N-H), 2245 (C≡N) and 1635 cm^{-1} (C=N). Nmr (DMSO-d_6) δ 10.48 (S, 1, N-H), 8.00-7.35 (m, 5, ArH), and 7.5 ppm (S, 2, $-NH_2$).

Anal. Calcd. for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.27; H, 4.22; N, 29.68.

2-Amino-2-cyano-5-(4'-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazole (39b):

A solution of 6.1 g (0.04 mol) of p-hydroxybenzhydrazide dissolved in 50 ml THF and 45 ml of DMSO was added to a solution of 4.4 g (0.08 mol) of cyanogen in 20 ml THF. After stirring at RT for 4 hours, the precipitated solid was collected to yield 6.2 g (76.0%) of 39b. Recrystallization from benzene - CH_3OH gave light yellow 39b: mp 242-245°; ir (KBr) 3400-3260 (broad N-H), 3140-3120 (N-H), 2245 (C≡N) and 1640 cm^{-1} (C=N).

Anal. Calcd. for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.06; H, 4.02; N, 27.70.

2-Amino-2-cyano-5-(2'-thiopheno)-2,3-dihydro-1,3,4-oxadiazole (39c):

2-Thiophenecarboxylic acid hydrazide (5.7 g, 0.04 mol) was dissolved in 50 ml of THF and was added to a solution of 5.0 g (0.10 mol) of cyanogen in 20 ml of THF at 0°C. After stirring at room temperature for 2 hours, the precipitated yellow solid was collected to yield 5.8 g (75.1%) of 39c. Recrystallization from benzene CH_3OH gave pure light yellow 39c: mp 209.0-210.5°; ir (KBr) 3400-3340, 3250 (N-H), 3000, 2920 (C-H), 2250 (C≡N) and 1665 cm^{-1} (C=N).

Anal. Calcd. for $C_7H_6N_4OS$: C, 43.29; H, 3.11; N, 28.85. Found: C, 43.25; H, 3.15; N, 29.07.

2-Amino-2-cyano-5-benzyl-2,3-dihydro-1,3,4-oxadiazole (39d):

A solution of 6.0 g (0.04 mol) of phenylacetic acid hydrazide in 25 ml of THF was added to a solution of 4.3 g (0.08 mol) of cyanogen in 20 ml of THF. After stirring for several hours at room temperature, the solid precipitate was collected to yield 3.8 g (47.5%) of 39d. Recrystallization from THF gave pure 39d: mp 188-189°; ir (Nujol) 3470, 3300, 3240, 3200 (N-H), 2260 (C≡N), and 1665, 1645 cm^{-1} (C=N).

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.65; H, 5.17; N, 27.67.

Preparation of 2-Amino-1,3,4-oxadiazoles:

2-Amino-5-phenyl-1,3,4-oxadiazole (40a):

A solution of 0.94 g (5.0 mmol) of 39a in 25 ml of diphenyl ether was heated at 195° for 1.5 hours. Dilution of the mixture with petroleum ether precipitated 0.7[illegible] g (92.5%) of yellow 40a. Recrystallization from ethanol gave yellow 40a: mp 240°: lit. mp 242°;[27] ir (KBr) 3300, 3120 (broad N-H) and 1652, 1642 cm^{-1} (C=N).

2-Amino-5-(4'-hydroxyphenyl)-1,3,4-oxadiazole (40b):

2.0 g (0.01 mol) of 39b in diphenyl ether was heated at 200° for 2 hours. Dilution and washing with petroleum ether gave 0.7 g (39.0%) of light yellow 40b. Recrystal-

lization from benzene - CH_3OH gave yellow 40b: mp 260-262°; ir (Nujol) 3430, 3160 (N-H) and 1648 cm^{-1} (C=N).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.52; H, 4.25; N, 22.78.

2-Amino-5-(2'-thiopheno)-1,3,4-oxadiazole (40c):

A solution of 1.5 g (8.0 mmol) of 39c in 100 ml of diphenyl ether was heated at 220° for 2 hours. Dilution of the mixture with petroleum ether gave 0.6 g (50.0%) of brown 40c. Recrystallization from 1,4-dioxane gave tan 40c: mp 228-230°; ir (KBr) 3270, 3120 (N-H) and 1648 cm^{-1} (C=N).

Anal. Calcd. for $C_6H_5N_3OS$: C, 43.10; H, 3.01; N, 25.13. Found: C, 43.33; H, 3.15; N, 25.20.

Preparation of 2,2'-Bis(4-oxo-1,3-benzothiazinyl) Compounds:

2,2'-Bis(4-oxo-1,3-benzothiazinyl) (59a):

A solution of 6.2 g (0.12 mol) of cyanogen in 25 ml of THF was cooled to 0°C. Several drops of triethylamine (Et_3N) were added and a solution of 3.1 g (0.02 mol) of thiosalicylic acid (17a) dissolved in 25 ml of THF was added dropwise over 0.5 hour at 0°C. After stirring at 0°C for several hours, the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for several hours, the solution precipitated 3.1 g (95.7%) of yellow 59a. Recrystallization from boil-

ing DMF yielded yellow needles of 59a: mp 408-410°; ir (KBr) 1669 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_8N_2O_2S_2$: C, 59.24; H, 2.49; N, 8.64; S, 19.77. Found: C, 59.10; H, 2.43; N, 8.35; S, 20.04.

2,2'-Bis(6-chloro-4-oxo-1,3-benzothiazinyl) (59b):
Several drops of Et_3N were added to a solution of 5.2 g (0.10 mol) of cyanogen in 30 ml of THF and cooled to 0°C. A solution of 3.8 g (0.02 mol) of 5-chlorothiosalicylic acid (17 b) in 50 ml of THF was added dropwise over 1 hour at 0-5°C. After stirring at 0-5°C for several hours, the mixture was allowed to warm to room temperature and upon stirring overnight precipitated 3.42 g (87.2%) of yellow-brown 59b. Extraction with CH_3OH in a Soxhlet extractor yielded a yellow residue of 59b: mp > 430°C; ir (KBr) 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_6Cl_2N_2O_2S_2$: C, 48.87; H, 1.54; N, 7.12; S, 16.31. Found: C, 48.94; H, 1.78; N, 7.18; S, 16.26.

2,2'-Bis(6-iodo-4-oxo-1,3-benzothiazinyl) (59c):
A solution of 1.6 g (0.03 mol) of cyanogen in 20 ml of THF was cooled to 0°C and several drops of Et_3N added. A solution containing 2.8 g (0.01 mol) of 5-iodothiosalicylic acid in 15 ml of THF was added dropwise over 0.5

hours at 0-5°C. After stirring at room temperature, the THF solvent was partially evaporated and CH_3OH added to precipitate 0.2 g (6.6%) of orange-brown 59c: mp > 410°C; ir (KBr) 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_6I_2N_2O_2S_2$: C, 33.35; H, 1.05; N, 4.86. Found: C, 33.47; H, 1.32; N, 5.34.

2,2'-Bis(6,8-dichloro-4-oxo-1,3-benzothiazinyl) (59d):
A solution of 3.6 g (0.07 mol) of cyanogen in 20 ml of THF was cooled to 0°C and several drops of Et_3N were added. A solution of 4.5 g (0.02 mol) of 3,5-dichlorothiosalicylic acid in 30 ml of THF was added dropwise over 0.75 hour at 0-5°C. The yellow solution was stirred at 0-5°C for 4 hours then allowed to warm to room temperature. Upon warming the solution became reddish and precipitated 2.9 g (75.6%) of tan solid upon addition of benzene. Recrystallization from benzene yielded yellow 59d: mp > 410°; ir (KBr) 1666 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_4Cl_4N_2O_2S_2$: C, 41.58; H, 0.87; N, 6.06. Found: C, 41.56; H, 1.16; N, 5.86.

Reaction of 5-Methylthiosalicylic acid (17c) with cyanogen; Preparation of 2,2'-Bis(6-methyl-4-oxo-1,3-benzothiazinyl) (59e) and 2-Carboxamido-6-methyl-1,3-benzothiazin-4-one (62):
A solution of 6.1 g (0.12 mol) of cyanogen in 20 ml of THF

was cooled to 0°C and several drops of Et_3N were added. A solution of 2.9 g (0.02 mol) of 5-methylthiosalicylic acid (17c) dissolved in 30 ml THF was added dropwise over 1 hour at 0-5°C. After stirring for 12 hours at room temperature, the solvent was evaporated and the brown residue extracted with benzene - THF (3:2 v). The yellow residue was recrystallized from DMF to yield 0.6 g (21.0%) of crystalline yellow 59e: mp 380-381°; ir (KBr) 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95; S, 18.20. Found: C, 61.54; H, 3.48; N, 8.09; S, 17.94.

The benzene - THF extract was boiled with Norit A, cooled and then filtered to give a reddish solution which precipitated a yellow solid on standing. Recrystallization from benzene yielded tan crystalline 62: mp 266.5-268.5°; ir (KBr) 3400-3100 (broad amide N-H), 1705 (amide C=O), 1675 and 1655 (C=O).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72. Found: C, 54.30; H, 3.41; N, 13.00.

Reaction of 17a with 33 to yield 53 and 55:

Dimethyl acetylenedicarboxylate (33) (2.8 g, 0.02 mol) was added dropwise over 20 minutes to a solution of 17a in 30 ml CH_3OH. The addition was exothermic and the temperature ranged from 22 to 36°C during which time a white solid precipitated. Collection of the white solid by filtration gave 1.3 g (13.6%) of 53: mp 158.5°; ir (KBr) 3305 (N-H), 3060, 3010, and 2960 (C-H), 1731 (saturated ester C=O) and 1610 cm^{-1} (hydrazide C=O). Nmr (TFA) δ 7.67 (S, 8, ArH), 4.33 (S, 2, -CH), and 3.75 ppm (S, 6, OCH_3).

Anal. Calcd. for $C_{20}H_{22}N_4O_6S_2$: C, 50.20; H, 4.63; N, 11.71; S, 13.40. Found: C, 50.09; H, 4.68; N, 11.64; S, 13.93.

The mother liquor from 53 was concentrated in vacuo to give 2.5 g (60.0%) of 55 which was the purified by sublimation to give crystalline yellow 55: mp 100-103°C: lit. mp 104-105.5°C;[28] ir (KBr) 3280 (broad enol OH), 2960 (C-H) and 1670 cm^{-1} (unsaturated ester C=O).

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