Acetylenedicarboxylate - Nucleophile Condensations As A Route To Heterocyclic Compounds.

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ACETYLENEDICARBOXYLATE-NUCLEOPHILE CONDENSATIONS AS A ROUTE TO HETEROCYCLIC COMPOUNDS

by

William P. Fives

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

Lehigh University

1971

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.

William P. Fives

William P. Fives

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.

May 17, 1971
Date

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I would like to recognize the efforts of Mrs. Jonathan Elkus in typing the manuscript.

This dissertation is dedicated with affection to my wife, without whose support this would not have been possible.

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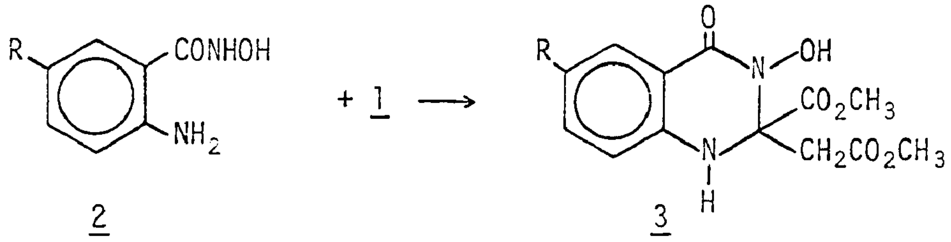
Abstract

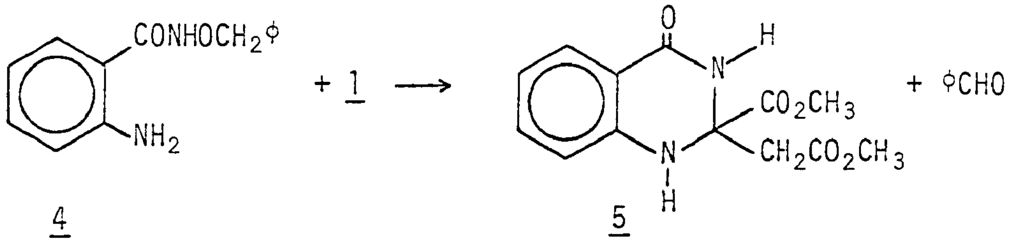
The synthetic utility of dimethyl acetylenedicarboxylate (1) has been demonstrated through the synthesis of 3-hydroxy-2,3-dihydro-4(1H)-quinazolinones, 1,4,2-dioxazoles, and a variety of 3-alkyl and arylamino-2,3-dihydro-4(1H)-quinazolinones.

The condensation of anthranilohydroxamic acids (2) with 1 gives a direct synthesis of 2-carbomethoxy-2-carbomethoxymethyl-3-hydroxy-2,3-dihydro-4(1H)-quinazolinones (3).

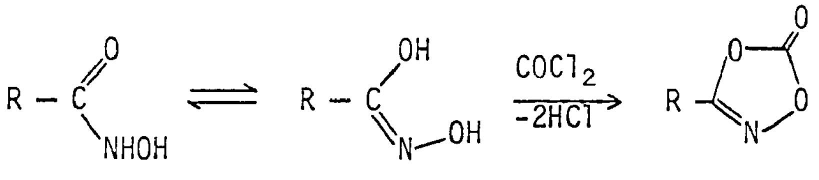


o-Alkylaminobenzohydroxamic acids were found to not yield 3 owing to a possible combination of steric hindrance at the secondary amine and side reactions with the hydroxamic acid portion of the molecule.

The reaction of benzyl O-aminobenzohydroxamate (4) with 1 was found to yield a previously known quinazolinone (5) by the elimination of benzaldehyde.



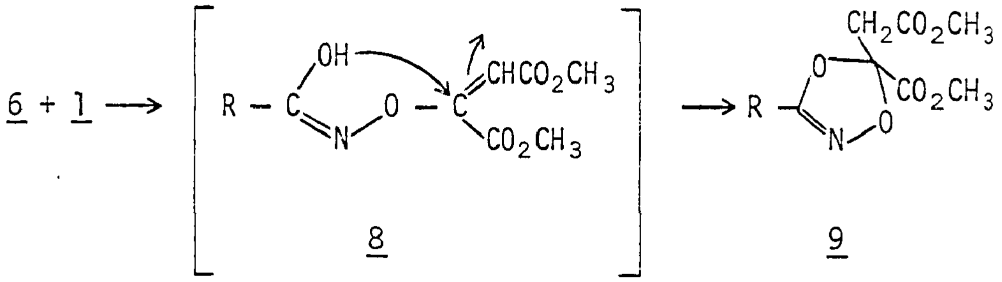
The postulated tautomeric equilibrium of hydroxamic acids (6), shown below, has previously been demonstrated by the reaction with phosgene to produce 1,4,2-dioxazol-5-ones (7).



6

7

When 6 was reacted with 1 the previously unknown 5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazoles (9) resulted. Postulation of 8 as the reaction intermediate was based on its rearrangement to an isocyanate and the presence of vinyl resonances in the nmr.



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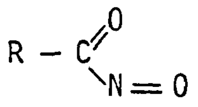
The presence of the nitroso derivative (10) during the reaction was indicated by the appearance of a blue color and the isolation of benzoic acid. Also isolated from the reaction of 6 (R = C_6H_5) was O-phenylcarbamyl benzohydroxamate (11).



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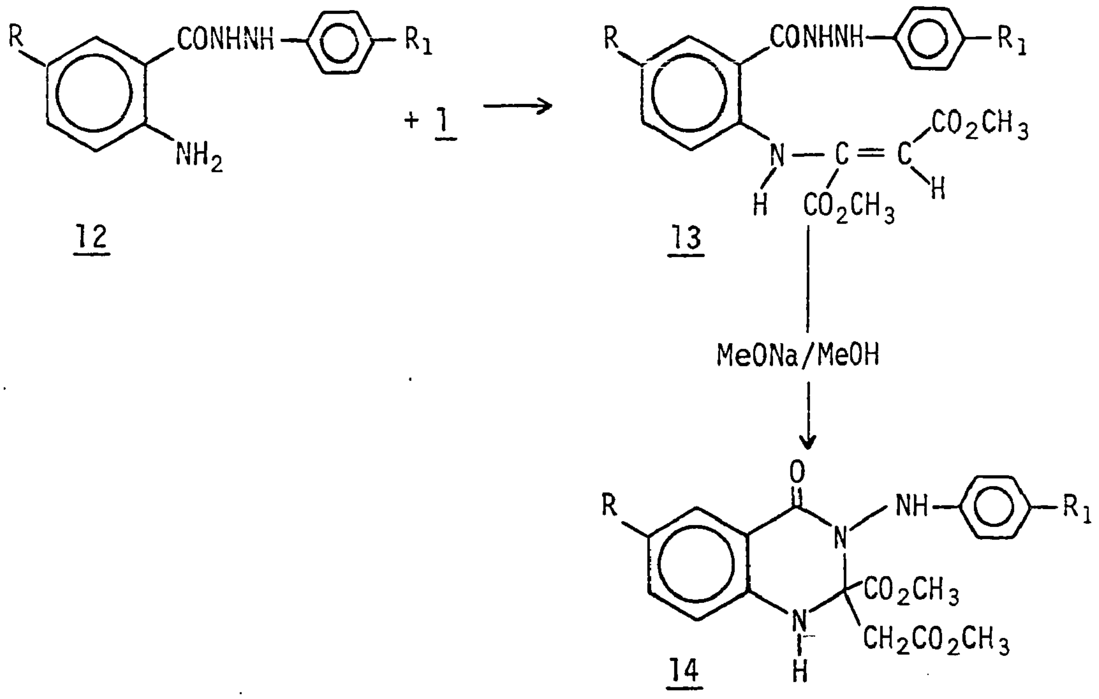
$C_6H_5CONHOCONHC_6H_5$

11

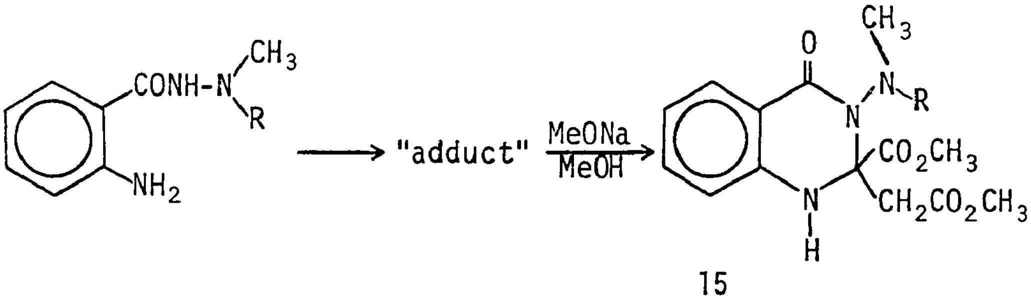
Electron impact studies, as well as nmr and ir, provided a structure proof for the dioxazole ring system (9). The thermal decomposition of 9 by a modified Lossen rearrangement yielded isocyanates.

The reaction of 6, where R = *o*-substituted phenyl, with 1 yielded a mixture of 8 and 9. This "ortho effect" was attributed to a probable combination of hindrance to the tautomerization and steric hindrance to cyclization. In 6, (R = 1-naphtho) a "peri effect" was exhibited and no condensation with 1 resulted.

The treatment of anthranilophenylhydrazides (12) with 1 yielded fumarate Michael adducts (13) which were transformed into 3-anilino-2,3-dihydro-4(1H)-quinazolinones (14) by base-catalysis.



Methylation of 14 (R = R_1 = H), with NaH and CH_3I, gave quinazolinone 15 (R = C_6H_5) which was independently prepared by the synthetic pathway shown below. Compounds of structure 15 also included R = CH_3.



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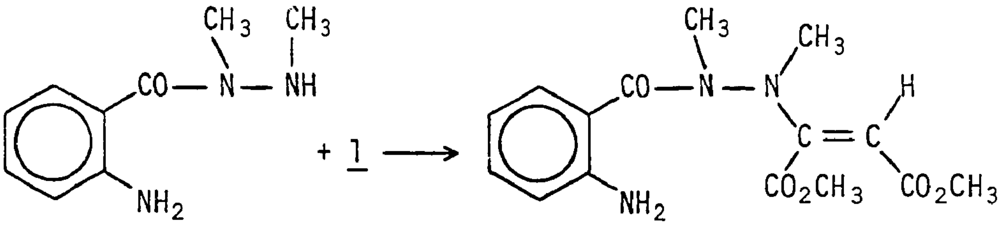
The structure of 14 was further verified by comparison of the mass spectra and ultraviolet spectra of 14 with model compounds known to be of the quinazolinone class.

The reaction of 16 with 1 was of interest because of the inability of 16 to cyclize to the quinazolinone if the primary amine formed a fumarate adduct. However, the product isolated was the maleate adduct (17) which could not be transformed to a cyclized product.



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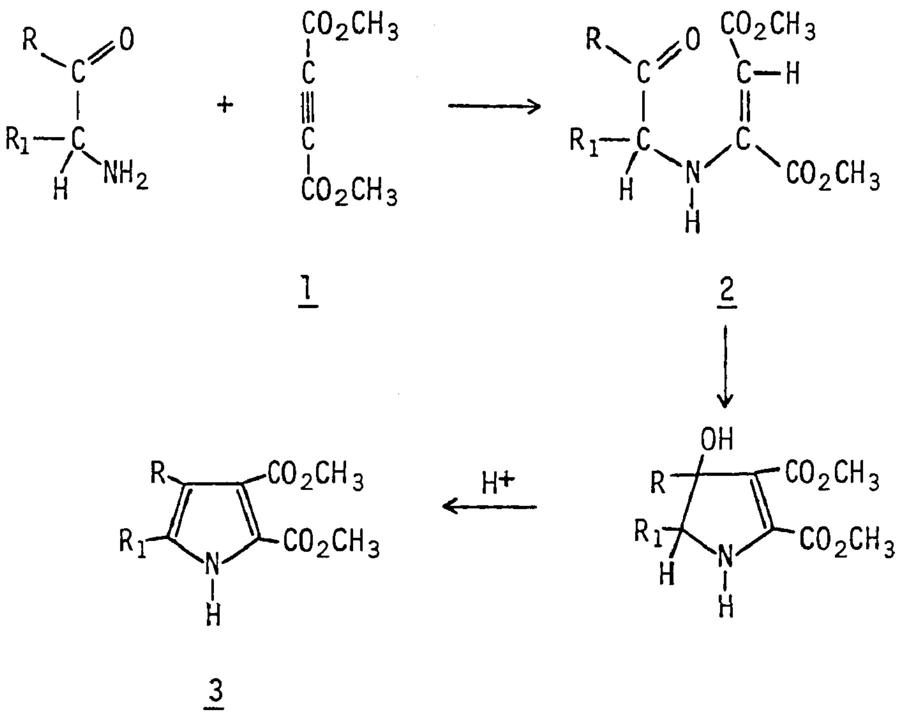
Part I

HYDROXAMIC ACID PRECURSORS

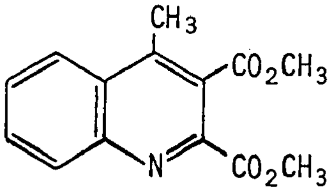
INTRODUCTION

Dimethyl acetylenedicarboxylate (1) has found considerable synthetic utility in its reaction with amines and phenols. The initially formed Michael adducts have been transformed into a variety of heterocyclic compounds. Hendrickson, Rees, and Templeton[1,2] reacted α-aminoketones with dimethyl acetylenedicarboxylate to give the enamine (2) which under acidic conditions



yielded 2,3-dicarbomethoxypyrrole derivatives (3). In this case they combined both a nucleophilic (-NH_2) and an electrophilic center (ketone carbonyl) in the starting compound.

Several six-membered heterocyclics were also synthesized using the above method. 2-Aminoacetophenone with 1 cyclized to the 4-methylquinoline (4) and 2-aminobenzophenone yielded the 4-phenylquinoline (5).[3]



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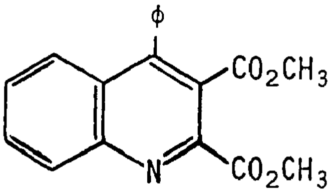

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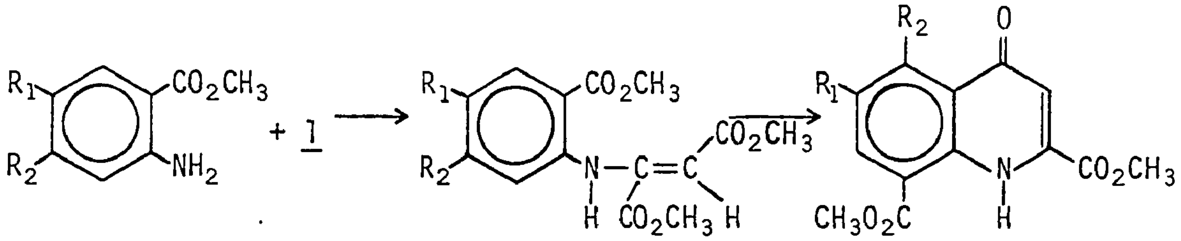
Taylor and Heindel[4] synthesized the adducts (7) of several methyl anthranilates (6) with 1. These adducts were then cyclized to 2,8-dicarbomethoxy-4(1H)-quinolinones (8).



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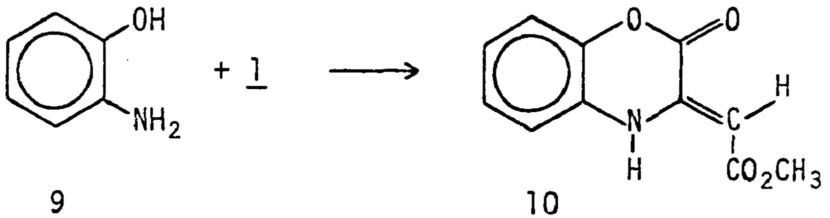
By substituting a nucleophilic species for that of the electrophilic carbonyl Iwanami[5] was able to synthesize several classes of heterocyclic compounds. The reaction of 1 with 2-aminophenol (9) yielded the 1,4-benzoxazine system (10).



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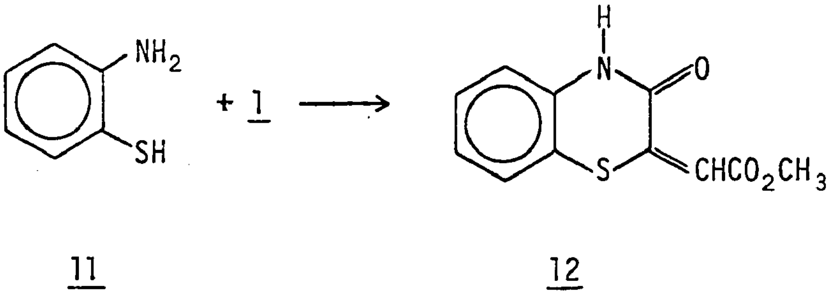
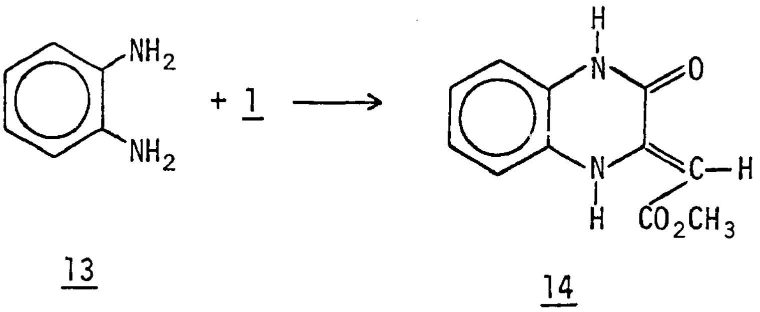
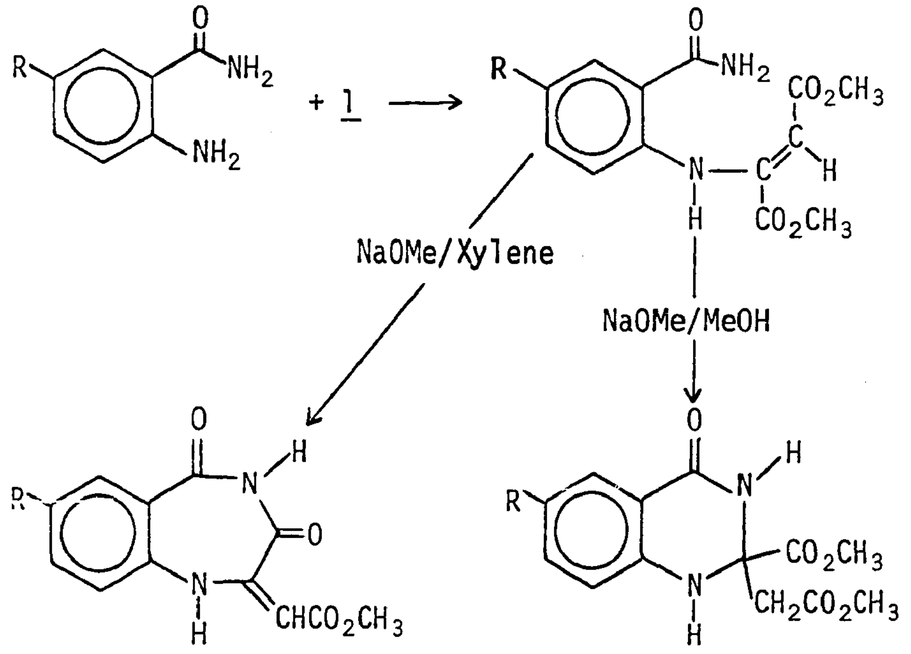
In 10 it was shown that the amine had added to the acetylenic bond and the phenol had displaced the ester. The condensation of 2-aminothiophenols (11) with 1 has recently been shown to yield 2-carboxymethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine derivatives (12).[6,7,8]



Iwanami[9] further extended the use of the dinucleophilic approach to obtain quinoxaline (14) from *o*-phenylenediamine (13) with 1.



A recent extension of the *o*-phenylenediamine reaction with 1 is that of Heindel, Fish, and Lemke[10] utilizing anthranilamide-acetylene-dicarboxylate adducts (15). The initially formed adducts have been shown to be exclusively of the fumarate geometry. The cyclization of the adducts provided either 1,4-benzodiazepine-3,5-diones (16) or quinazolinone diesters (17) depending on the solvent used.



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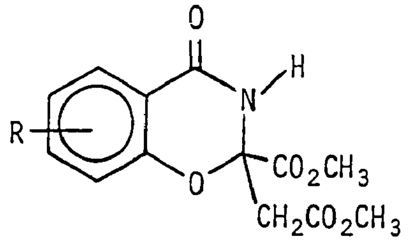
Other difunctional nucleophiles which have shown versatility in this reaction are salicylamides[11] and *o*-mercaptobenzamides[12,13] which lead to only the six membered benzoxazinones (18) and benzothiazinones (19) respectively.



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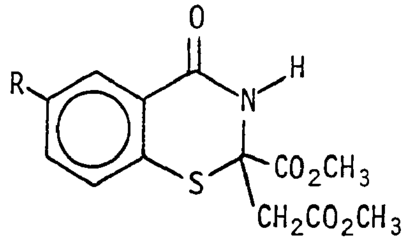

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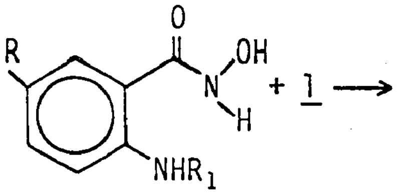
As a logical extension of the above work the reaction of anthranilohydroxamic acids (20) was investigated. These acids can be thought of as being N-hydroxy derivatives of anthranilamides. By the addition of another nucleophilic center the possible modes of cyclization are increased. Below are shown some of these possibilities:



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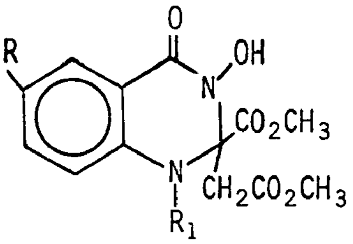

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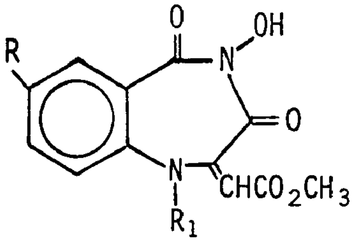

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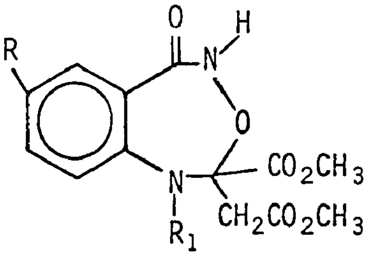

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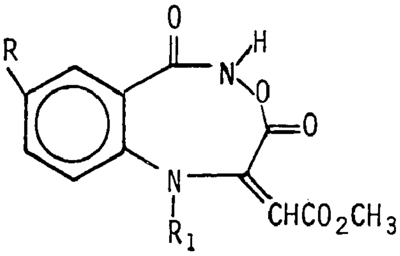

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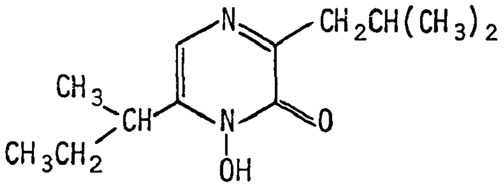
The 1,4-benzodiazepine-3,5-dione (22) belongs to a class of compounds which have shown interesting anti-anxiety activity. Two well known examples are Librium® and Valium®.

Structure 21 which is a cyclic hydroxamic acid of the quinazolinone family would also be expected to have some pharmacological activity. Many examples — both naturally occurring and synthetic — of cyclic hydroxamic acids are available.

Aspergillic acid (25) was the first cyclic hydroxamic acid isolated in 1943 from certain strains of *Aspergillus flavus*.[14,15] On mild reduction, aspergillic acid is converted into the hydroxypyrazine (26) which is relatively ineffective as an antibacterial agent.[16] It would appear that the activity of aspergillic acid as an antibiotic is to be attributed to the cyclic hydroxamic acid grouping.



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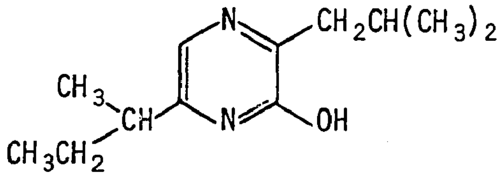

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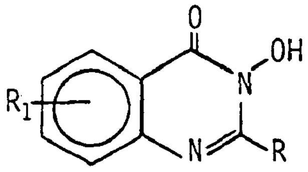
Several quinazolinone hydroxamic acids have been synthesized from esters of anthranilic acid. Included in this group are potential antibacterials (27). A potent diuretic (28) was developed from a substituted anthraniloylhydroxamic acid and several have been reported to influence the central nervous system and to show depressive and antitremor activity.[17]



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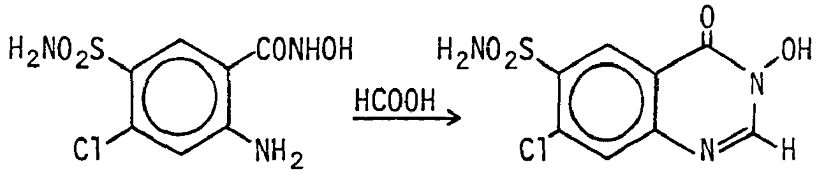
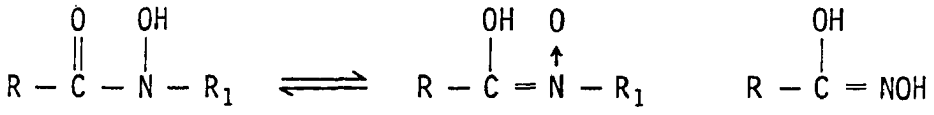


28

Since hydroxamic acids[18] exhibit the tautomerism (29 $\rightleftharpoons$ 30), and when R_1 = H, the additional tautomeric structure 31 is also possible, it appeared reasonable that tautomer 31 could take part in the reaction with dimethyl acetylenedicarboxylate.

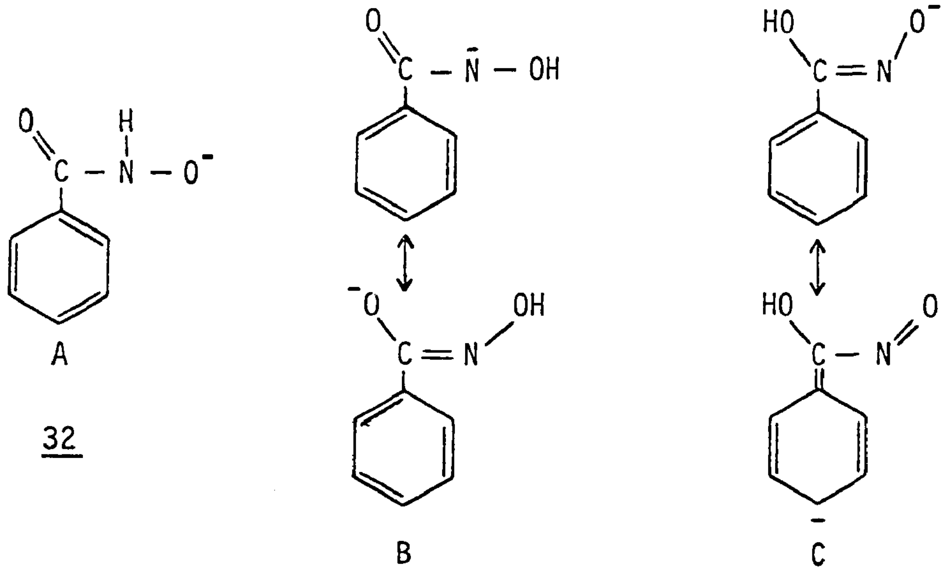


$$R-\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{N}-R_1 \rightleftharpoons R-\overset{\overset{OH}{|}}{C}=\overset{\overset{O}{\uparrow}}{N}-R_1 \qquad R-\overset{\overset{OH}{|}}{C}=NOH$$

29 30 31

Designating 29 as the keto form and 31 as the enol form Plapinger[19] has shown that benzohydroxamic acid (29, R = C_6H_5,R_1 = H) exists predominantly in the keto state. His argument is based on the similarity in the ultraviolet spectra of benzohydroxamic acid and N-methylbenzohydroxamic acid (29, R = C_6H_5,R_1 = CH_3) which can exist only as the keto form and the dissimilarity between the spectra of benzohydroxamic acid and ethylbenzohydroximic acid (tautomer 31 where R = C_6H_5 and the COH is replaced by COEt) the latter which can exist only as the enol form.

Plapinger[19] and later Steinberg and Swidler[20] discussed some interesting studies on the structure of the benzohydroxamate anion (32).



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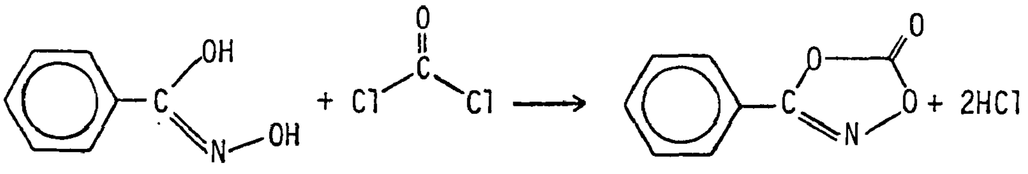
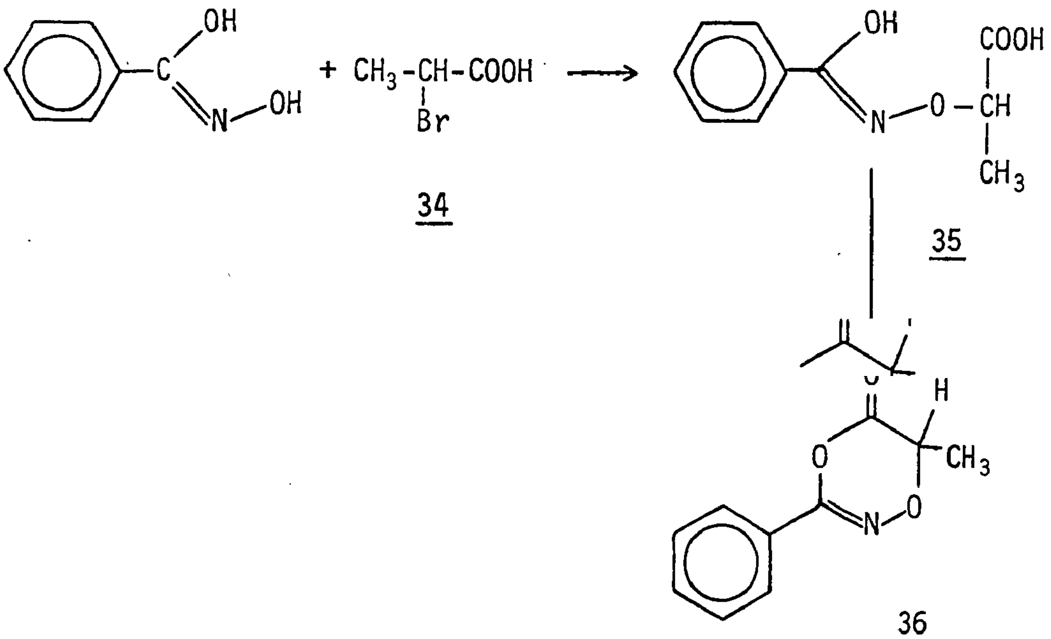
They found that the UV spectrum of the anion exhibited both a bathochromic and a hypsochromic shift compared to that of benzohydroxamic acid. By comparison of model compounds they established that the hypsochromic shift is probably due to the contribution of structure A. The bathochromic shift can be attributed to either structure B or C, but Steinberg and Swidler indicated, by reaction rate studies, that structure B was the predominant form with C perhaps contributing a maximum concentration of 10^{-3} to 10^{-4} times that of the other species.

The addition of phosgene to benzohydroxamic acid (29, R = C_6H_5, R_1 = H) was shown to yield the first known derivative of the 1,4,2-dioxazole ring system (33). This reaction was developed in 1951 by Gerhard Beck[21] using several different hydroxamic acids, including the bis hydroxamic acid terephthaloylhydroxamic acid. In a recent work[22] the same 3-phenyl-1,4,2-dioxazol-5-one (33) was synthesized from the potassium salt of benzohydroxamic acid and phosgene.



33

The tautomerism of benzohydroxamic acid is further illustrated[23] by the addition of α-bromopropionic acid (34) to form the adduct (35). This 35 on heating with acetic anhydride or thionylchloride is converted to the 5-oxo-1,4,2-dioxazine (36).



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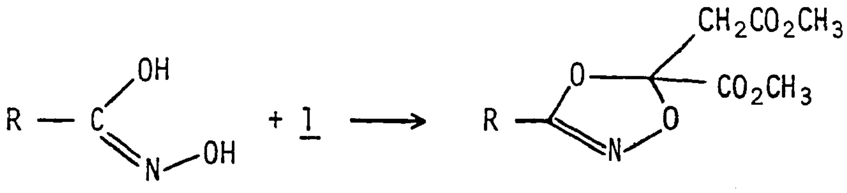
36

In the enol tautomer of hydroxamic acids either the oxime portion or the COH could be expected to add to 1. Both groups are known to add to acetylenic bonds.[11,24] With these reactions in mind benzohydroxamic acid and several other aromatic and alkyl hydroxamic acids were reacted with 1. Although the variety of nucleophilic sites (nitrogen and oxygens) in the hydroxamic acids and the duality of electrophilic sites (the alkyne carbon and the ester carbonyl) in 1 makes plausible a number of modes of product formation, only one type of cyclized product was formed. This product was identified as the 1,4,2-dioxazole (37).



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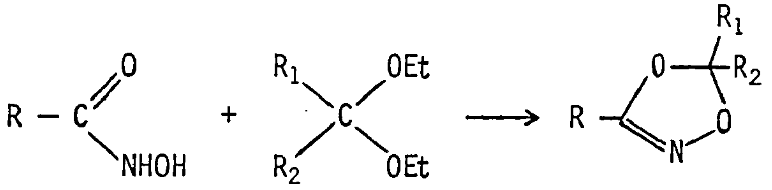
37

A few 1,4,2-dioxazoles appear in the literature including those previously described. Several of the methods of synthesis include the use of hydroxamic acids. The recent work of Nohira and co-workers[25] utilizes the diethylketals (38) of such ketones as acetone and cyclohexanone and benzohydroxamic acids.



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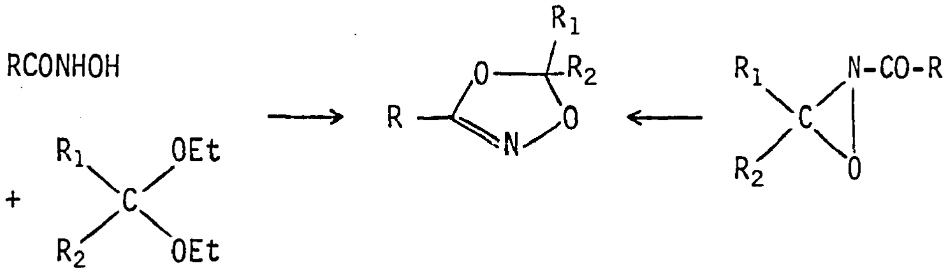
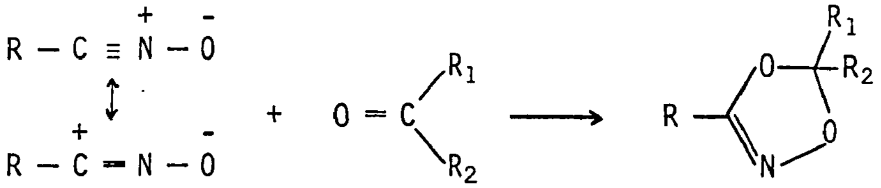
Schmitz, Ohme, and Schramm[26] used both hydroxamic acids and 2-acyloxaziridines (39) in their reaction schemes and were able to synthesize many dioxazoles.

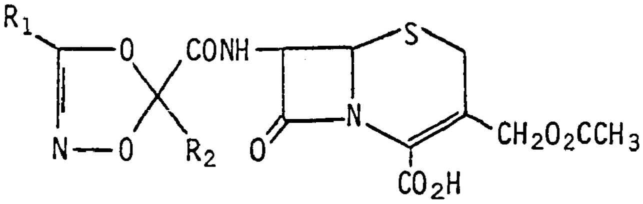


39

Several other synthetic schemes including the work of Huisgen and Mack[27] have involved 1,3-dipolar additions to carbonyl compounds yielding the 1,4,2-dioxazole ring system.



Although a moderate number of 1,4,2-dioxazoles were known there were no reports of any pharmacological studies. In fact, the only references to biological activities were for derivatives of 7-aminocephalosporanic acid (40)[28] and of 6-aminopenicillanic acid (41)[29] claimed as antimicrobial agents. Because of this lack of pharmacological studies an investigation into the variations of the 1,4,2-dioxazole system was undertaken.



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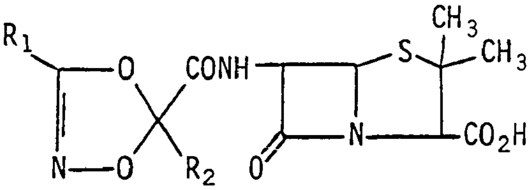

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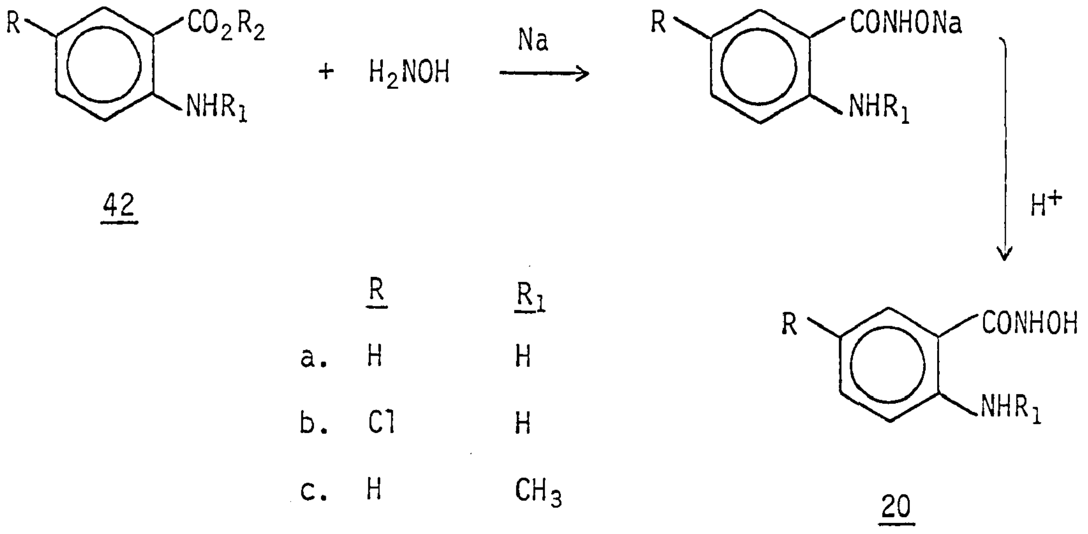
RESULTS AND DISCUSSION

Synthesis of Hydroxamic Acids and Esters

The anthranilohydroxamic acids (20) were prepared by the reaction of anthranilate esters (42) with hydroxylamine. The sodium salts were initially isolated and then neutralized to yield the free anthranilohydroxamic acids.



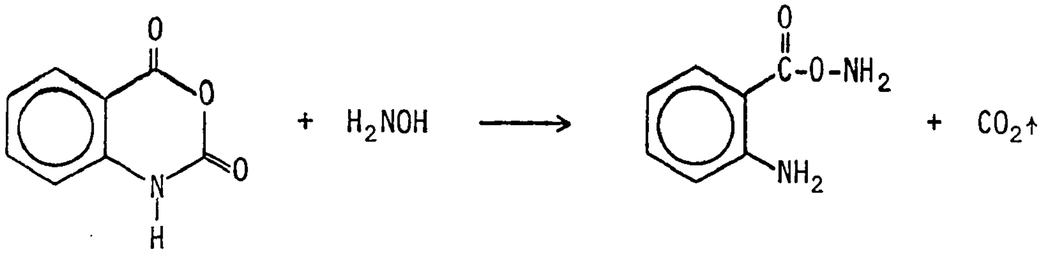
42

20

	R	R_1
a.	H	H
b.	Cl	H
c.	H	CH_3

The reaction of isatoic anhydrides with nucleophiles is a well known synthesis of anthranilic acid derivatives. When ammonia or primary amines are utilized as the nucleophile the corresponding anthranilamides are isolated.[30a,31] Meyer and Bellman[32] published the preparation of anthranilohydroxamic acid from isatoic anhydride and hydroxylamine. This method would eliminate the synthesis of the anthranilate esters (42), but it has since been shown by Scott and

Wood[33] that the product actually isolated is O-(2-aminobenzoyl)-hydroxylamine.



The synthesis of O-substituted anthranilohydroxamic acids from isatoic anhydide by the reaction of O-alkyl or -arylhydroxylamines has proven to be of synthetic utility. The synthesis of benzyl O-aminobenzohydroxamate (43) by this method is described in the experimental section.

The anthranilic acid esters were prepared by the procedure of Staiger[34] using the modification of Heindel and Taylor.[4] Treatment of isatoic anhydrides with methanol or ethanol and catalytic amounts of sodium methoxide produced the desired methyl or ethyl anthranilates (42). All of the esters that were utilized have been previously prepared and characterized.

Benzohydroxamic acids, alkylhydroxamic acids, and phenyl alkylhydroxamic acids were prepared from the appropriate esters and an equimolar quantity of hydroxylamine with either sodium or potassium hydroxide. The initially isolated salt was then neutralized with acetic acid to free the hydroxamic acid (44).

$$R-CO_2R_1 \xrightarrow{H_2NOK \text{ or } Na^+} R-CONHOK \text{ or } Na^+ \xrightarrow{H^+} \underset{\underline{44}}{R-CONHOH}$$

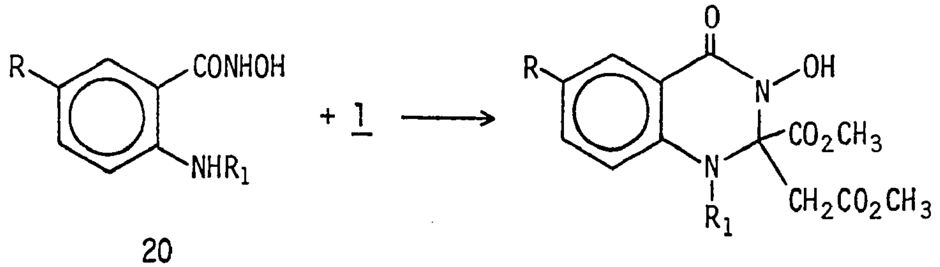
	R		R
a.	C_6H_5	h.	C_6H_{11}
b.	$4-CH_3O-C_6H_4$	i.	$C_6H_5-CH_2$
c.	$3-CH_3O-C_6H_4$	j.	$C_6H_5-CH_2-CH_2$
d.	$2-CH_3O-C_6H_4$	k.	CH_3
e.	$4-Br-C_6H_4$	l.	CH_3-CH_2
f.	$2-Br-C_6H_4$	m.	1 – Naphtho
g.	$3-NO_2-C_6H_4$	n.	$4-HOHNOC-C_6H_4$

The appropriate esters, except ethyl 3-methoxybenzoate, used in the above syntheses were commercially available.

The carbonyl group of the hydroxamic acids absorbed at 1632±12cm.$^{-1}$ Also all of the hydroxamic acids synthesized gave the violet ferric chelates when excess ferric chloride was added to a methanol solution of the hydroxamic acid. This violet color is a positive test for the hydroxamic acid moiety.[35]

Cyclization of the Anthranilohydroxamic Acids with Dimethyl Acetylenedicarboxylate

The condensation of anthranilohydroxamic acids (20) with 1 provided a direct one step synthesis of substituted 3-hydroxy-2,3-dihydro-4(1H)-quinazolinones (21). The isolation of an intermediate open adduct analogous to 15 was not possible in these cases.



20

21

	R	R_1
a.	H	H
b.	Cl	H
c.	H	CH_3

Since the reaction of 20 with 1 can lead to more than one isomeric product it is necessary to establish that 21 is in actuality the product isolated. The mass spectral and elemental analysis established the molecular formula of 21 as being a 1:1 adduct of 20 and 1. This eliminates structures of type 22 and 24 where the molecular ion would show the loss of methanol. A more detailed explanation of the mass spectral data will follow.

Structures 22 and 24 are also eliminated because of the lack of a vinyl H resonance in the nmr. However, the nmr does show a geminally split AB quartet (J = 16.0 Hz) at δ 3.63, 3.13 and 3.45, 3.11ppm for 21a and 21b respectively. The appearance of magnetically non-equivalent methylene protons adjacent to an asymmetric center is well known.[36] The nmr also disproves the loss of methanol because the spectra revealed two methyl ester resonances.

If the N-H of the hydroxamic acid participated in the addition to 1 the quinazolinone (21) would result, while the addition of the O-H would provide 23. Since 21 is a cyclic hydroxamic acid, the identification of this moiety would distinguish 21 from 23. From the information available the direct loss of O or OH from the molecular ion of the cyclic hydroxamic acid is to be expected in the mass spectrum.[37] The spectra of the product obtained made evident the loss of 16 a.m.u. in support of structure 21; the relative abundance of this fragment was low.

Cyclic hydroxamic acids, such as aspergillic acid (25), have been reported to give violet ferric chelates when ferric chloride is added to a solution of the cyclic hydroxamic acid.[35] A methanol solution of 21 was treated with ferric chloride and the characteristic violet color developed, further substantiating the hydroxamic acid structure, 21.

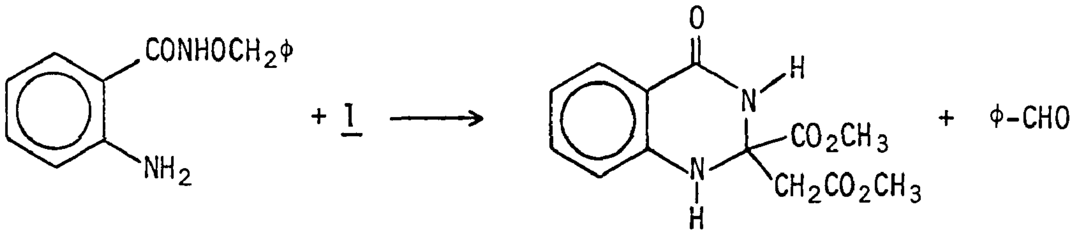
The infrared spectra also support the quinazolinone structure (21). The ir of the anthranilohydroxamic acids (20a, b) have absorbances corresponding to the primary amine and to the NH and OH of the hydroxamic acid. The OH appears as a broad resonance from 3100 to 3260cm^{-1}. In the cyclic structure (21) this broad absorbance is also present. Although it is difficult to distinguish the NH and OH in the ir this does indicate the presence of the OH moiety.

Other absorptions in the ir include the saturated ester carbonyls between 1730 and 1750cm^{-1} and the cyclic hydroxamic acid carbonyl at 1660cm^{-1}. Also of interest is the lack of primary amine absorptions in 21. This eliminates the possibility of the reaction of 1 with only the hydroxamic acid portion of 20. A reaction of this type will be discussed in a later section of this dissertation.

From the above it can be concluded that 21 is a 3-hydroxyquinazolinone. There is also very good precedent in the recent literature for this type of double addition leading to six membered heterocyclic ring systems as exemplified by structures 17, 18, and 19.

When 2-methylaminobenzohydroxamic acid (20c) was reacted with 1 the expected quinazolinone (21c) could not be isolated from the reaction mixture. That 21c was not formed from 20c and 1 can be attributed to steric hindrance at the secondary amine function. There is also the added complication of a side reaction with the hydroxamic acid portion of the molecule. This reaction could lead to the 1,4,2-dioxazole structure, which will be discussed later, and would give a mixture of products.

Benzyl O-aminobenzohydroxamic acid (43) eliminates the possibility of the NO-H reacting with (1). Benzaldehyde was cleaved and the isolated product was identified as the crystalline quinazolinone.



43

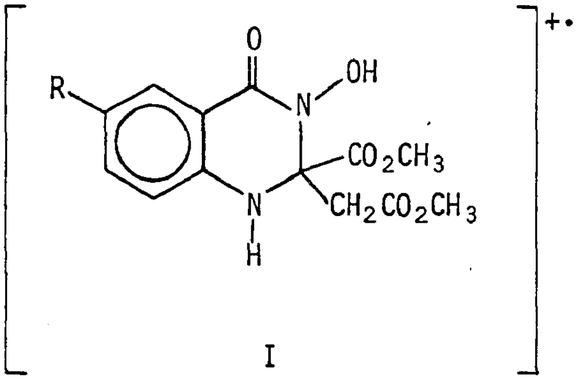
17

Mass Spectral Analysis of 2-Carbomethoxy-2-carbomethoxymethyl-3-hydroxy-2,3-dihydro-4(1H)-quinazolinones*

The mass spectral data here presented fully support the conclusion that 21 represents the reaction product. Although the data are limited they allow one to characterize the fragmentation pattern of this class of compounds.

Table I lists the compounds with their mass spectral fragments and their abundance relative to the most abundant fragment, the base peak.

Both 21a and 21b showed parent molecular ions (I) at the appropriate m/e.



I

The loss of 16 a.m.u. from 21a and b would be expected in view of the cyclic hydroxamic acid structure.[37] Both show this loss although the relative abundance is less than 1% in both cases.

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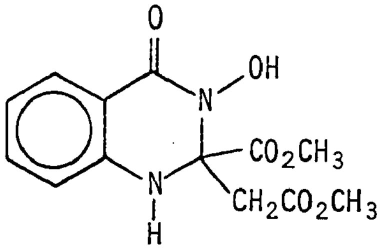
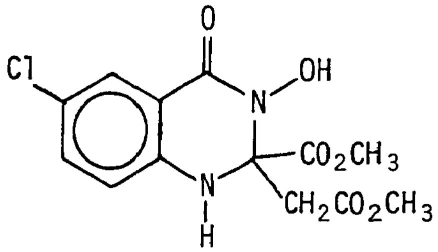
*The spectral data for compounds containing chlorine are based on the chlorine 35 isotope.

TABLE I

Mass Spectra of 21



21a

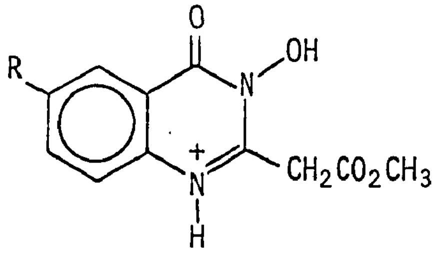


21b

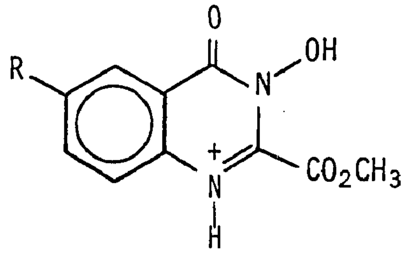
m/e	Relative abundance
294	1.3
278	.8
263	1.6
235	100.
234	1.3
221	10.
220	.8
218	4.2
203	42.
186	6.9
175	11.
161	2.7
145	16.
119	9.3
104	4.4
91	4.5

m/e	Relative abundance
328	1.6
312	.9
297	2.5
269	100.
268	2.5
255	12.
254	3.0
252	3.9
237	38.
220	7.9
209	15.
195	6.2
179	22.
153	18.
138	7.9
125	15.

The cleavage of carbomethoxy ($\cdot CO_2CH_3$, 59 mass units) and carbomethoxymethyl ($\cdot CH_2CO_2CH_3$, 73 mass units) by a "Type A_1"[38] mechanism clearly indicates the substituents on the 2-position. Structures II and III, respectively, represent the resulting ions. Structure II represents the most abundant ion in both cases.

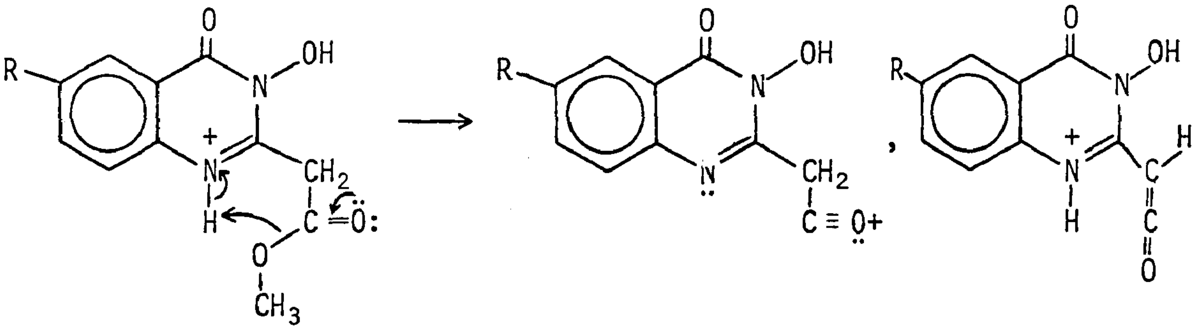


II



III

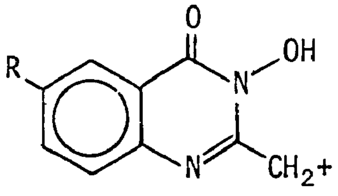
The next most abundant ion resulted from the loss of methanol from II. This could arise from either a cyclic process to give IV or by the direct loss of methanol from the side chain to give V.



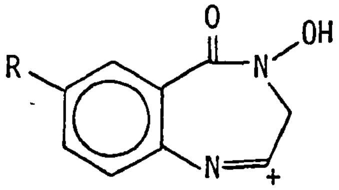
II IV V

Regardless of the mechanism involved the loss of 32 a.m.u. from II was verified by the presence of a metastable ion. For <u>21a</u> the transition from 235 to 203 was verified by a metastable ion at the calculated position of m/e 175.3. Likewise 21b (269 → 237) has a metastable ion at m/e 208.8.

The ion corresponding to either IV or V was fragmented by either the loss of CO (mass 28) or ketene (mass 42). The loss of CO could result in VI or VII; these data cannot discriminate between them. This transition was verified however by metastable ions at the calculated positions (21a, 203 → 175, m/e 150.9 and 21b, 237 → 209, 184.3).

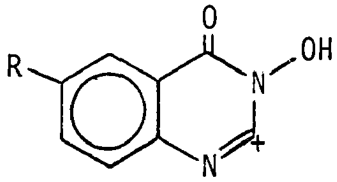


VI



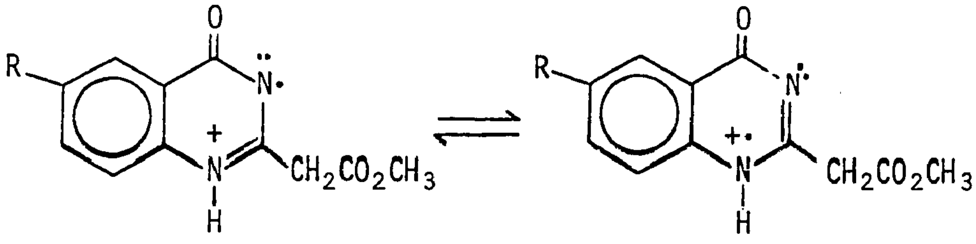
VII

The loss of ketene from IV or V would lead to an ion with a structure of type VIII. Likewise IV or V could lose OH to give m/e 186 for 21a and m/e 220 for 21b.



VIII

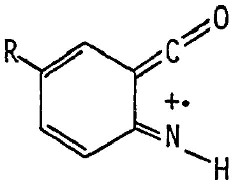
Ions at m/e 218 and m/e 252 for 21a and 21b respectively show the loss of 17 mass units from structure II. In the case of 21a this loss is verified by a metastable ion at m/e 202.2. A probable structure for this ion is IX.



IX

The ions at m/e 145 and m/e 179 for 21a and 21b respectively could result from either VIII by the loss of O (mass 16) or from IX by the elimination of the carbomethoxymethyl fragment (mass 73). No metastable ions are available to establish this point.

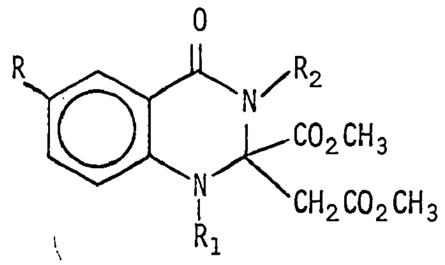
A retro Diels-Alder cleavage, similar to that reported by Budzikiewicz, et al.[39] for a series of quinazolinones, would produce ion X. This ion appears at m/e 119 for 21a and m/e 153 for 21b.



X

Other ions present in the spectra are due to loss of methyl formate (21a, m/e 234 and 21b, m/e 268) and methyl acetate (21a, m/e 220 and 21b, m/e 254) from the molecular ion. The loss of 31 a.m.u. from the molecular ion can be attributed to the loss of $CH_3O\cdot$.

Many of the ions observed in this class of compounds are also seen in the fragmentation of the quinazolinone shown below.[30b] Those additional ones which only appear in 21 are attributable to the presence of the 3-hydroxyl group.



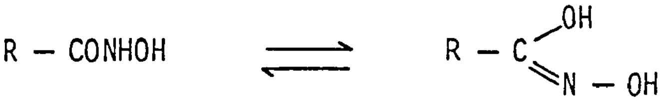
where R = H or Cl

R_1 = H or CH_3

R_2 = H, CH_3, or ϕ

Synthesis and Proof of Structure of 1,4,2-Dioxazoles

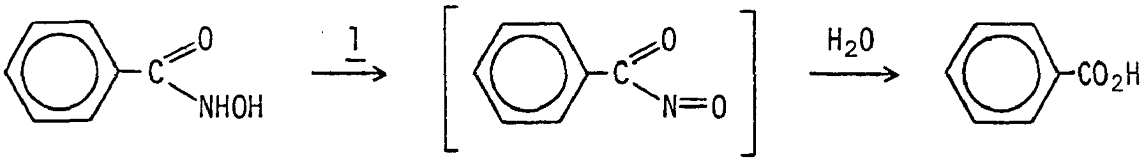
As previously described, anthranilohydroxamic acids condensed with 1 yielded 3-hydroxy-2,3-dihydro-4(1H)-quinazolinones (21). Because of the tautomerism shown below, even hydroxamic acids lacking the *o*-amino function could react with 1, since two nucleophilic sites are available.



44 31

Reactions demonstrating the synthetic utility of tautomer 31 have been discussed *vide infra*. The reaction of the hydroxamic acids with an acetylenic bond was originally demonstrated by Ruhemann and Stapelton.[40,41] They found that phenylpropiolohydroxamic acid could not be isolated, but underwent intramolecular cyclization to 5-phenyl-3-isoxazolone.

When 1 was added to a methanol solution of the hydroxamic acid and subjected to mild heating, the solution became dark blue. The compound producing the blue color was removed in a water extract of a CCl_4 solution of the reaction mixture. In all cases the blue color in the aqueous solution disappeared after several days. In the case of 44a after the blue color disappeared, concentration of the water solution yielded benzoic acid. The isolation of the benzoic acid[42] and the observation of the blue color,[43] might indicate the presence of the nitroso derivative (45) in the reaction medium.



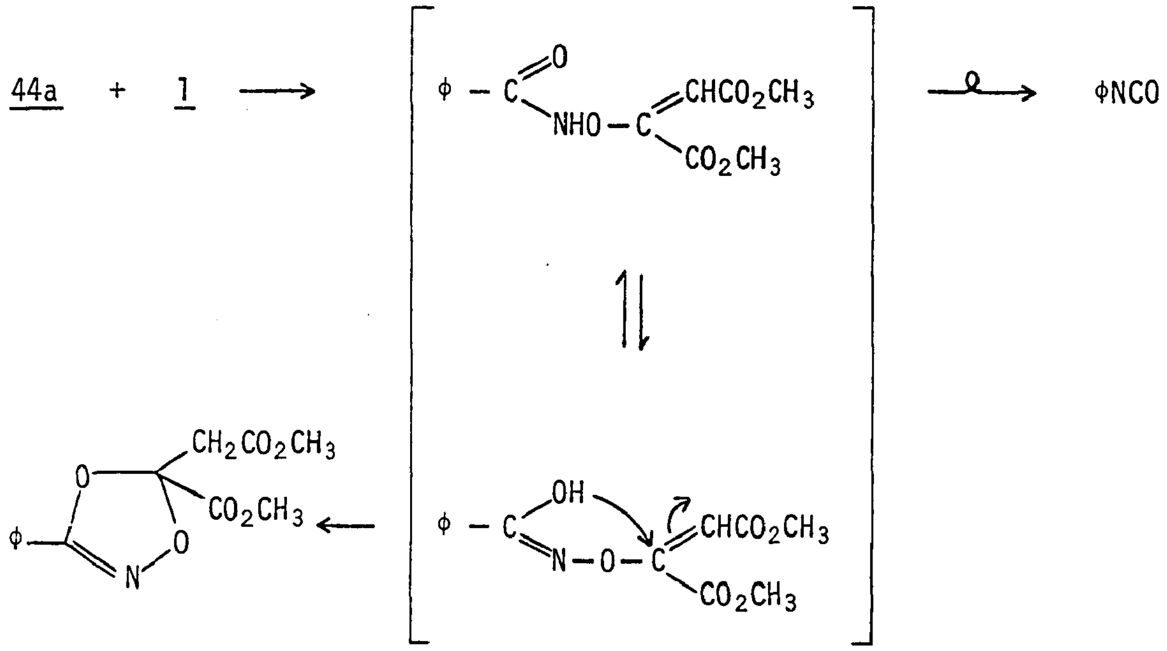
44a 45

The intermediacy of 45 in the reaction of 44a has been previously discussed by Rowe and Ward[42] and references therein. It would appear in this case that 1 was the oxidizing agent since the blue color appeared almost immediately. The abstraction of H• by acetylenedicarboxylic acid was reported to be essentially quantitative and rapid under the one condition studied: aqueous chromous sulfate solution.[44]

Concentrating the CCl_4 solution gave an oil which was vacuum distilled to yield a single product. This product has been identified as a 1,4,2-dioxazole and in this case is specifically 37a. Also isolated from the CCl_4 layer as a flocculent precipitate was O-phenylcarbamyl benzohydroxamate (46).[45] This substance was identified by its melting point and by comparison of the ir with that of authentic 46 (Sadtler Research Laboratories infra-red spectrogram 8136). Also when 46 was melted or refluxed in $CHCl_3/MeOH$ it evolved CO_2 and yielded diphenylurea.[45] Since 46 probably resulted from the following reaction, it is necessary to assume that some phenylisocyanate was present.

$$\underset{\underline{44a}}{\phi - \mathrm{CONHOH}} \; + \; \phi\mathrm{NCO} \; \longrightarrow \; \underset{\underline{46}}{\phi\mathrm{CONHOCONH}\phi}$$

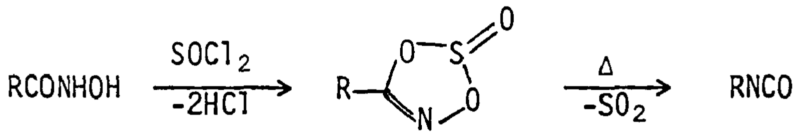
The Lossen rearrangement of O-acylated hydroxamic acids is well known to yield isocyanates.[41] Therefore intermediate 47 can be postulated as leading to both the phenylisocyanate by a Lossen rearrangement and to 37a by tautomerization and addition to the CC double bond. It has also been reported that the N-OH is the most nucleophilic portion of the hydroxamic acid group.[45] Hence initial addition to 1 should occur at this site.



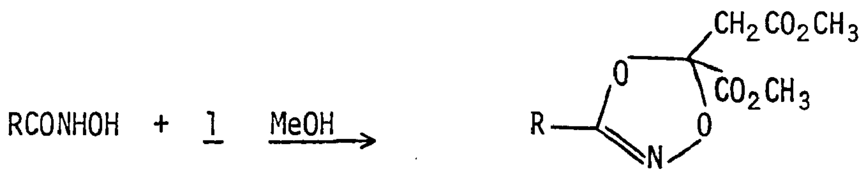
37a

47

It was also shown that heating pure 37a above its boiling point gave a complex mixture of products including phenylisocyanate. This could not have given the necessary phenylisocyanate for the production of 46 because when 37a was refluxed in methanol no decomposition resulted. The thermal decomposition of 1,4,2-dioxazoles is a known reaction of this class of compounds.[25] This reaction can be thought of as a modified Lossen rearrangement. Also of interest for comparison purposes is the thermal rearrangement to isocyanates of dioxathiazole S-oxides derived from hydroxamic acids and thionyl chloride.[46]



The reaction of 44 with 1 yielded the following 1,4,2-dioxazoles (37):

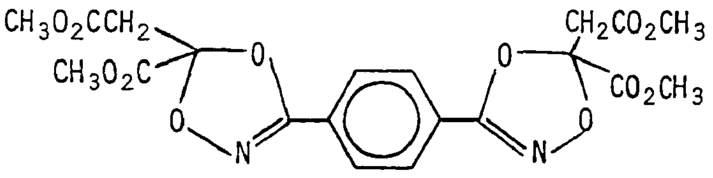


44

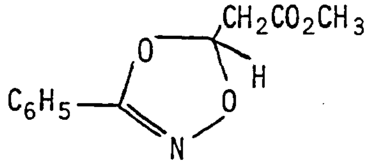
37

	R		R
a.	C_6H_5	h.	C_6H_{11}
b.	$4-CH_3O-C_6H_4$	i.	$C_6H_5-CH_2$
c.	$3-CH_3O-C_6H_4$	j.	$C_6H_5-CH_2-CH_2$
d.	$2-CH_3O-C_6H_4$	k.	CH_3
e.	$4-Br-C_6H_4$	l.	CH_3-CH_2
f.	$2-Br-C_6H_4$	m.	1 – Naphtho
g.	$3-NO_2-C_6H_4$		

Other 1,4,2-dioxazoles synthesized include the bis-dioxazole 37n derived from 44n, and 48 derived from 44a and methyl propiolate.



37n



48

Structure assignment for the product isolated from the reaction of 44 and 1 rests on several analyses. From the elemental analysis and mass spectral data 37 was firmly identified as a 1:1 adduct of 44 and 1. The absence of any absorbances in 37 in the 3100 to 3500cm^{-1} region indicates the absence of N-H or O-H functions and this implies a double addition of tautomer 31 to the acetylenedicarboxylate moiety. Furthermore, compound 37 also gave a negative $FeCl_3$ test.

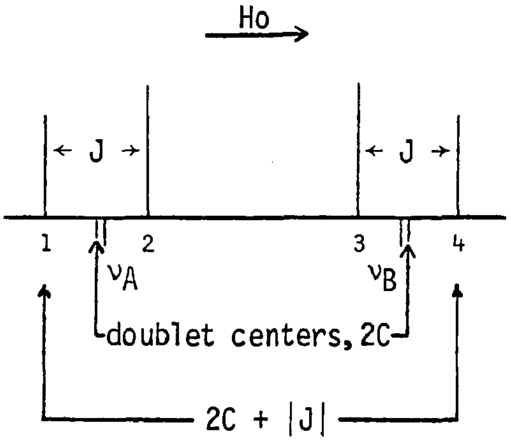
The establishment of 37 as a 1:1 adduct of 44 and 1 excludes any products resulting from an elimination type mechanism. Thus a rearrangement followed by an elimination as found by Heindel and Chun[47] in the case of amidoxime-dimethyl acetylenedicarboxylate adducts, is eliminated. These adducts were found to undergo a Claisen-type rearrangement to yield imidazolones.

Further, the mass spectra of all the products, with the exception of 48, showed the loss of $\cdot CO_2CH_3$ (59 mass units) and $\cdot CH_2CO_2CH_3$ (73 mass units). In the case of 48 only the loss of 73 mass units was seen. This loss of 59 and 73 mass units clearly indicates that a double addition of 44 to 1 has taken place. A more detailed analysis of the mass spectra will be presented *vide infra*.

The nmr also verifies the presence of two methyl esters between δ 3.65 and 3.86ppm in compounds of type 37. The infra-red spectra of all 37 cases, except 37b and 37n, display a broad absorbance at ca. 1750cm^{-1} indicating saturated esters. Both 37b and 37n were solids and each showed two ester carbonyls between 1732 and 1752cm^{-1}.

Further verification of the carbomethoxymethyl as a pendent group is the appearance in the nmr of the $-CH_2-$ as a geminally split AB quartet in all cases of 37. The appearance of magnetically non-equivalent methylene protons adjacent to an asymmetric center is well known.[36] The AB quartets all have coupling constants between 16.5 and 17.0 Hz and all appear on the high field side of the methyl ester resonances.

All of the AB quartets in this dissertation are reported as follows.[48] The two resonances reported in each instance are ν_A and ν_B in the diagram. From



the equation $\Delta\nu = \nu_A - \nu_B$ the value of $\Delta\nu$ can be obtained. Knowing $\Delta\nu$ and the value of J, the value of 2C can be calculated from $2C = (\Delta\nu^2 + J^2)^{\frac{1}{2}}$. With the value of 2C and the fact that $J = \nu_1 - \nu_2 = \nu_3 - \nu_4$ the spacing of the AB quartet can be reproduced.

The ir spectra of 37 and 48 all have the characteristic absorption bands reported for the 1,4,2-dioxazole ring system by Nohira, et al.[25] The C=N stretching modes of the ring system appear at 1631±1cm^{-1} for all cases of 37 in which an aryl group is directly bonded to the 3-position. Compound 48 also falls into this group. In all other cases

(37 h-l) where a non-aromatic substituent is attached at the 3-position this absorption appears at 1654±6cm^{-1}. This observation clearly indicates that the C=N is in direct conjugation with the substituent in the 3-position.

Also present in the ir of 37 and 48 is a broad resonance centered around 1200cm^{-1} which correlates well with the O-C-O-C skeletal vibrations of the ring system. Nohira[25] reported a band in the 1080-90cm^{-1} region as characteristic of 1,4,2-dioxazoles. In all cases of 37 and 48, except 37g where it is a single broad band, this band appears as a doublet between 1060 and 1105cm^{-1}. Moore[49] further characterizes this absorption as an acetal ether doublet.

The above characterizations, as well as the modified Lossen rearrangement of 37 to yield isocyanates, clearly define 37 as a member of the 1,4,2-dioxazole ring system.

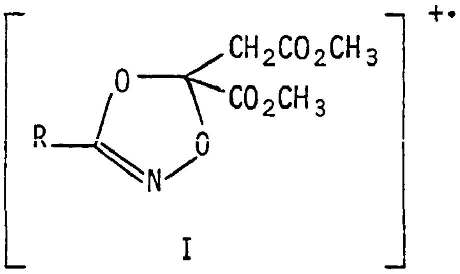
In the reaction of both 44d and 44f with 1 pure 37d and 37f were not isolated, but their presence in the reaction mixture was determined from the AB quartet of the -CH_2- protons. The nmr of 37d also had resonances at δ 6.03 and 5.40ppm which correspond to fumerate and maleate vinyl protons respectively. Compound 37f had similar resonances at δ 5.96 and 5.47ppm. The fact that the vinyl resonances are present indicates that the reaction proceeds via intermediate 47 and implies that the ortho substituent hinders the tautomerization[50] which precedes the second addition or that it provides steric hindrance to the cyclization. If the reaction was initiated by addition of the C-OH to 1 then the ortho substituent should not hinder further cyclization and the presence of vinyl protons would not be expected.

The same results were also obtained in the reaction of 44m with 1. In this case the "peri effect" can provide the hindrance to tautomerization or cyclization.

Mass Spectral Analysis of 1,4,2-Dioxazoles

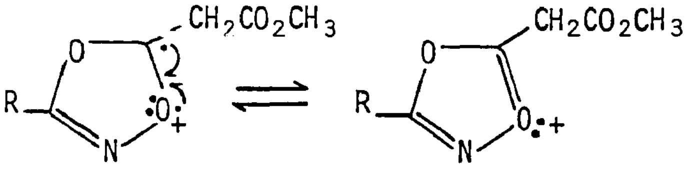
The mass spectral data presented here verify the previous assignment of structure 37 as a 1,4,2-dioxazole. Table II lists the spectral data for the compounds studied. The relative abundances are recorded as a percent relative to the base peak.

All of the compounds studied had a parent molecular ion (I) of expected mass. The relative abundances of these ions were proportional to the ability of the R group to stabilize the positive charge. Compound 37b, containing a para-methoxy group, had the most abundant molecular ion.

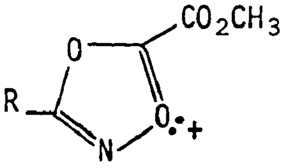


I

The prominent loss of $\cdot CO_2CH_3$ (59 mass units) and $\cdot CH_2CO_2CH_3$ (73 mass units) results in structures of type II and III respectively.



II



III

TABLE II

Mass Spectra of 37 and 48

37a		37b		37c	
m/e	Relative abundance	m/e	Relative abundance	m/e	Relative abundance
279	5.3	309	14.	309	9.1
220	34.	250	13.	250	22.
206	5.1	236	3.6	236	2.9
119	6.2	149	21.	149	18.
105	14.	135	15.	135	11.
103	15.	133	23.	133	13.
101	100.	101	100.	101	100.
77	85.	76	9.4	76	8.3

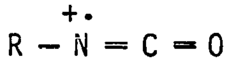
37e		37g		37h	
m/e	Relative abundance	m/e	Relative abundance	m/e	Relative abundance
359(P+2)	4.8	324	2.6	285	3.0
357	4.6	265	31.	226	35.
298	23.	251	2.3	212	13.
284	2.2	205	11.3	125	11.
197	10.	150	4.3	111	8.2
183	12.	148	5.2	109	9.3
181	5.0	104	9.6	108	2.5
101	100.	102	11.	101	100.
76	9.0	101	100.	83	38.
		76	20.		

TABLE II (continued)

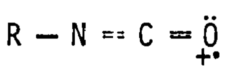
37i		37j		37k	
m/e	Relative abundance	m/e	Relative abundance	m/e	Relative abundance
293	2.8	307	2.6	217	1.4
234	40.	248	42.	158	48.
220	12.	234	15.	144	9.9
133	5.3	147	3.1	101	100.
119	4.1	133	4.9	59	45.
117	6.2	131	5.8	57	35.
101	100.	101	100.	43	41.
91	42.	91	20.	41	12.
77	31.	77	34.		

48	
m/e	Relative abundance
221	8.8
148	12.
119	24.
105	27.
103	100.
77	60.

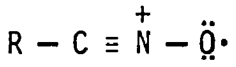
Fragment ions which are indicative of the 1,4,2-dioxazole ring system include m/e 119, 105, and 103 in the case of 37a. The fragment ion at m/e 119 can be formed in several ways, but all of the pathways provide isomers of the same elemental composition. Structures IV, V, and VI all have m/e values of 119 for R = C_6H_5. Precise identification is, of course, impossible,


$R-\overset{+\bullet}{N}=C=O$

IV


$R-N=C=\underset{+\bullet}{\ddot{O}}$

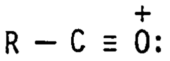
V


$R-C\equiv\overset{+}{N}-\underset{\cdot\cdot}{\ddot{O}}\cdot$

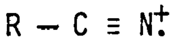
VI

but the presence of ion IV or V would be expected since the 1,4,2-dioxazoles are known to yield isocyanates via a thermal Lossen rearrangement.[25] The ion corresponding to IV, V, or VI is present in all cases of 37 except 37g in which R = 3-nitrophenyl. This is probably due to the inability of the nitro group to stabilize the positive charge. The molecular ion in 37g also has the smallest relative abundance of all the dioxazoles with an aromatic substituent in the 3-position (37a,b,c,e).

The acylium ion (VII) is a result of the fragmentation of the ring system and is present in all cases of 37. In 37a, where R = C_6H_5, this ion is at m/e 105. This ion is also found in 37g, but 37g has an ion of greater relative abundance at m/e 104 which corresponds to the loss of $\cdot NO_2$ (46 mass units) from VII. This increase in abundance is probably due to the scission of the destabalizing nitro group.


$R-C\equiv\overset{+}{O}:$

VII


$R-C\equiv N\overset{+}{:}$

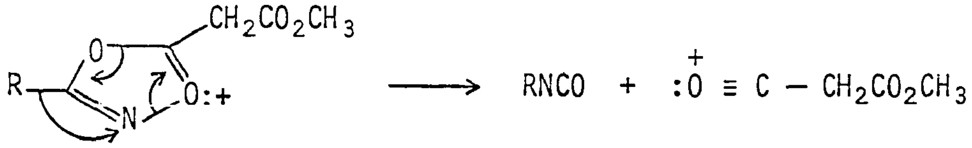
VIII

Also originating from the dioxazole structure is the nitrile ion (VIII). This ion, like that of VII, is found in all cases of 37, appearing at m/e 103 in 37a. As with VII, 37g has an ion corresponding to VIII which must have undergone the initial fragmentation of the nitro group to give a more abundant ion at m/e 102.

The base peak of all of the dioxazoles studied in class 37 was at m/e 101. The fact that this fragment is present in all 37's clearly indicates that it is not a function of the substituent in the 3-position, since varying this substituent has no effect on the m/e 101 ion. This would indicate that this ion is a result of the ring system and/or the 5-position, both of which are not varied in 37.

The only compound, whose spectrum was observed, which did not have an ion at m/e 101 was 48. Since 48 is the only compound with a variation in the 5-position, it becomes evident that m/e 101 must in some way involve the pendent groups in the 5-position.

Further fragmentation of ion II fulfills the above facts; the resulting ion (IX) has a m/e 101. In 37a this fragmentation is further



II IX

supported by a metastable ion at the calculated position of m/e 46.4 (m/e 220 → m/e 101). Several other 37's yield similar metastable ions, including 37c which has a metastable ion at the calculated value of m/e 40.8 (m/e 250 → m/e 101). The spectrum of 48 contains all the peaks in 37a except those attributed to the loss of carbomethoxy (structure II) and its daughter ion, IX. The loss of 31 mass units was observed in nearly all spectra, but its relative abundance was very low. This peak results from the loss of $CH_3O\cdot$ from the esters.

EXPERIMENTAL SECTION

Melting points were determined between glass slide covers on a Fisher-Johns block and are reported uncorrected in degrees centigrade.

Infrared spectra were obtained in Nujol or the neat state with a Perkin-Elmer 257 spectrophotometer. Nmr spectra were recorded on either a Varian Associates A-60 or a Hitachi Perkin-Elmer Model R-20A spectrometer using tetramethylsilane (TMS) as an internal standard. Data are presented in the order δ (multiplicity, number of protons, assignment).

Mass spectra were run by J. 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°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 provided by Dr. G. I. Robertson of Florham Park, New Jersey.

Isatoic anhydrides. The 5-chloroisatoic anhydride and the N-methylisatoic anhydride were graciously provided by the Maumee Chemical Company, Toledo, Ohio.

Methyl 5-chloroanthranilate (42b, R_2=CH_3). A mixture of 25.0 g (0.13 mol) of 5-chloroisatoic anhydride and 0.1 g of NaOMe was added to 200 ml of MeOH with stirring. The reaction temperature was raised to the boiling point with moderate evolution of CO_2. When the anhydride was consumed, *in vacuo* evaporation of the MeOH yielded 20.0 g (86%) of the ester. Recrystallization of the solid from 100 ml of MeOH and 20 ml of H_2O gave pure 42b (R_2=CH_3): mp 72-4°: lit. mp 76°.[4]

Ethyl N-methylanthranilate (42c, R_2=CH_3CH_2). A mixture of 79.0 g (0.45 mol) of N-methylisatoic anhydride and 0.1 g of NaOEt was added to 250 ml of EtOH with stirring. Evolution of CO_2 and solution of the anhydride at the boiling point were followed by *in vacuo* evaporation of the solvent. The resulting oily solid was recrystallized from EtOH/H_2O to afford 52.0 g (65%) of the pure ester: mp 35-8°: lit. mp 39°.[51]

Ethyl 3-methoxybenzoate. A solution of 50.0 g (0.33 mol) of 3-methoxybenzoic acid in 120 ml of abs. EtOH was saturated with HCl gas at reflux for 24 hours. Evaporation of the EtOH yielded an oil which was dissolved in CCl_4. The CCl_4 solution was washed with three 50 ml portions of saturated $NaHCO_3$ and two 50 ml portions of H_2O then dried over $MgSO_4$. Evaporation *in vacuo* of the CCl_4 followed by vacuum distillation of the oil yielded 35.4 g (59%) of the pure ester: bp 77-8°/0.12 Torr: lit. bp 158-60°/43.5 Torr;[52] ir (thin film) 3100-2850 (C-H) and 1725 cm^{-1} (ester C=O); nmr ($DCCl_3$) δ 7.8-6.9 (m, 4, Ar-$\underline{H}$), 4.35 (q, 2, J=7.1 Hz, O-C$\underline{H}_2$), 3.78 (s, 3, O-C$\underline{H}_3$), and 1.35 ppm (t, 3, J=7.1 Hz, CH_2-C$\underline{H}_3$).

General Note on Hydroxamic Acid Syntheses. Although the chemical method for production of the precursor hydroxamic acids was essentially identical in all cases, the experimental procedures required considerable individual variation in order to obtain the free acids. In the interest of total reproducibility of this research by later workers, each individual hydroxamic acid preparation is described, although tabular presentation would obviously be briefer.

5-Chloroanthranilohydroxamic acid (20b). A solution of 5.2 g (0.23 mol) of sodium in 150 ml of MeOH was added to a solution of 7.85 g (0.11 mol) of hydroxylamine hydrochloride in 100 ml of MeOH. The NaCl precipitate was removed by vacuum filtration. 21.0 g (0.11 mol) of 42b (R_2=CH_3) were added to the filtrate. The solution was heated on a steam-bath for 45 minutes, the MeOH was replenished to 250 ml volume, and the medium was cooled for 24 hours at 4°. Since very little precipitate formed, 2.6 g (0.11 mol) of sodium in 75 ml of MeOH and 7.85 g (0.11 mol) of hydroxylamine hydrochloride were prepared as above; this solution was added to the 42b (R_2=CH_3) and heated on a steam-bath for 1 hour. The precipitate formed by cooling the solution was removed by filtration. The filtrate was again heated on a steam-bath with 2.6 g (0.11 mol) of sodium and the resulting solid was combined with the above to give 17.1 g (73%) of the sodium salt of 20b; ir (Nujol mull) 3370, 3280-3100 (N-H) and 1610 cm^{-1} (hydroxamic acid C=O).

The sodium salt was dissolved in 1.25 N HOAc and the precipitate was sublimed at 115°/0.01 Torr to yield 12.9 g (62%) of 20b: mp 152-4°; ir (Nujol mull) 3490, 3400, 3320 (N-H), 3260-3100 (O-H), and 1620 cm^{-1} (hydroxamic acid C=O).

Anal. Calcd. for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 44.76; H, 3.62; N, 14.83.

2-Methylaminobenzohydroxamic acid (20c). After filtering the NaCl from a MeOH solution of 40.5 g (0.58 mol) of hydroxylamine hydrochloride and 35.0 g (0.87 mol) of NaOH, 52.0 g (0.29 mol) of 42c (R_2=CH_3CH_2) were added to the filtrate. The solution was left at ambient temperature for 7 days and the pink solid sodium salt (36.5 g, 67%) was filtered: mp 177-80°; ir (Nujol mull) 3410, 3300 (N-H) and 1620 cm^{-1} (hydroxamic acid C=O).

The sodium salt (20.0 g, 0.11 mol) was dissolved in 1.25 N HOAc and the resulting precipitate, 17.0 g (94%), of the free acid filtered. Recrystallization from 100 ml of hot ethyl acetate gave pure 20c: mp 130-1°; ir (Nujol mull) 3400-3200 (N-H and O-H) and 1628 cm^{-1} (hydroxamic acid C=O).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.10; H, 6.31; N, 16.63.

Benzyl *o*-aminobenzohydroxamate (43). The method of Mamalis, et al.,[53] was utilized to obtain a 90% yield of 43 with mp 103-6°. Recrystallization from ethylacetate-petroleum ether gave pure 43: mp 104-5°: lit. mp 104-6°;[53] ir (Nujol mull) 3420, 3340 (Primary N-H), 3160 (N-H), and 1665 cm^{-1} (hydroxamic acid C=O).

4-Methoxybenzohydroxamic acid (44b). Separate solutions of 38.6 g (0.56 mol) of hydroxylamine hydrochloride in 200 ml of MeOH, and of 47.0 g (0.83 mol) of KOH in 100 ml of MeOH, were prepared at the boiling point of the solvent.[54] Both were cooled to 3°, and the KOH solution was added to the hydroxylamine solution; the temperature was maintained below 20°C by cooling in an ice bath. The precipitated KCl was filtered by suction and 50.0 g (0.28 mol) of ethyl anisate were added with thorough shaking. After 48 hours at ambient temperature the crystals were filtered and dried in air. The yield was 37.9 g (65%) of the potassium salt; ir (Nujol mull) 3250 (N-H) and 1690 cm^{-1} (hydroxamic acid C=0).

A mixture of 25.0 g (0.12 mol) of the potassium salt in 120 ml of 1.25 N HOAc was stirred and heated until a clear solution was obtained. After cooling in an ice bath, the crystals were suction filtered to yield 18.0 g (88%) of the product with mp 152-8°. Recrystallization from ethyl acetate yielded pure 44b: mp 156-8°: lit. mp 156-7°;[55] ir (Nujol mull) 3280 (N-H), 3150-2400 (broad 0-H), and 1640 cm^{-1} (hydroxamic acid C=0); nmr (1:1, $DCCl_3$:DMSO-d_6) δ 14.0 (braod s, 1, 0-H), 7.72 (S, 1, N-H), 7.82, 6.95 (AB quartet, 4, J=9.0 Hz, Ar-H), and 3.85 ppm (S, 3, 0-CH_3).

3-Methoxybenzohydroxamic acid (44c). A MeOH solution of 19.2 g (0.28 mol) of hydroxylamine hydrochloride and 23.2 g (0.42 mol) of KOH was prepared. 25.0 g (0.14 mol) of ethyl 3-methoxybenzoate were added to the filtrate with shaking. After 48 hours at ambient temperature 19.9 g (70%) of the potassium salt were filtered; ir (Nujol mull) 3200 (N-H) and 1629 cm^{-1} (hydroxamic acid C=0).

The potassium salt (15.0 g, 0.07 mol) was neutralized in 1.25 N HOAc to yield 11.0 g (90%) of 44c with mp 100-5° which was utilized without further purification; ir (Nujol mull) 3450-2600 (N-H and 0-H) and 1645 cm^{-1} (hydroxamic acid C=0); nmr (DMSO-d_6) δ 12.5 (broad S, 1, 0-H), 7.6 (S, 1, N-H), 7.8-6.9 (m, 4, Ar-H), and 3.83 ppm (S, 3, 0-CH_3).

2-Methoxybenzohydroxamic acid (44d). A MeOH solution of 42.0 g (0.60 mol) of hydroxylamine hydrochloride and 49.0 g (0.90 mol) of NaOMe was prepared. The NaCl was filtered and 50.0 g (0.30 mol) of methyl

2-methoxybenzoate were added to the filtrate with shaking. Concentration of the solution to one-third volume (130 ml) yielded 31.8 g (56%) of the sodium salt; ir (Nujol mull) 3160 (N-H) and 1640 (hydroxamic acid C=O).

Neutralization of the sodium salt (31.8 g, 0.18 mol) in 1.25 N HOAc yielded 22.3 g (79%) of 44d. Recrystallization from acetone-ether yielded pure 44d: mp 128-30°: lit. mp 129-31°;[56] ir (Nujol mull) 3360, 3330 (N-H), 3140 (O-H), and 1639 cm^{-1} (hydroxamic acid C=O).

4-Bromobenzohydroxamic acid (44e). Ethyl 4-bromobenzoate (50.0 g, 0.22 mol) was added to the MeOH filtrate of 30.4 g (0.44 mol) of hydroxylamine hydrochloride and 26.2 g (0.66 mol) of NaOH. After standing three weeks at ambient temperature 8.5 g of crystals were filtered. Concentration to one-fifth volume (50 ml) yielded 34.2 g (combined yield 81%) of the sodium salt: mp>300°; ir (Nujol mull) 3220 (N-H) and 1615 cm^{-1} (hydroxamic acid C=O).

Neutralization of 25.0 g (0.11 mol) of the sodium salt in 1.25 N HOAc yielded 19.6 g (86%) of 44e. Recrystallization from ethyl acetate yielded pure 44e: mp 190-1°: lit. mp 190-190.5°;[57] ir (Nujol mull) 3290 (N-H), 3100-2600 (broad O-H) and 1645 cm^{-1} (hydroxamic acid C=O).

2-Bromobenzohydroxamic acid (44f). The same procedure as 44e was utilized with 50.0 g (0.22 mol) of ethyl 2-bromobenzoate to yield 38.0 g (72%) of the sodium salt of 44f; ir (Nujol mull) 3200 (N-H) and 1610 cm^{-1} (hydroxamic acid C=O).

The sodium salt (25.0 g, 0.11 mol) was neutralized in 1.25 N HOAc to yield 15.3 g (68%) of 44f. Recrystallization from ethyl acetate yielded pure 44f: mp 174-6°: lit. mp 178-80°;[55] ir (Nujol mull) 3225 (N-H and O-H) and 1630 cm^{-1} (hydroxamic acid C=O).

3-Nitrobenzohydroxamic acid (44g). After filtering the NaCl from a MeOH solution of 35.5 g (0.51 mol) of hydroxylamine hydrochloride and 30.8 g (0.77 mol) of NaOH, 50.0 g (0.26 mol) of ethyl 3-nitrobenzoate were added to the filtrate with shaking. 34.7 g (67%) of the sodium salt were filtered off after 48 hours contact; ir (Nujol mull) 3420 (N-H) and 1622 cm^{-1} (hydroxamic acid C=O).

Neutralization of 25.0 g (0.12 mol) of the sodium salt with 1.25 N HOAc yielded a waxy product. On recrystallization from water at pH 6 it yielded 18.0 g (81%) of pure 44g: mp 144-6°: lit. mp 145°;[58] ir (Nujol mull) 3380 (N-H), 3165 (O-H), 1645 (hydroxamic acid C=O), and 1520, 1355 cm^{-1} (N-O).

Cyclohexylhydroxamic acid (44h). An EtOH solution of 44.5 g (0.64 mol) of hydroxylamine hydrochloride and 15.0 g (0.65 mol) of sodium metal was prepared. After removal of the NaCl and addition of 50.0 g (0.32 mol) of ethyl cyclohexanecarboxylate to the filtrate, it was allowed to stand at ambient temperature for 72 hours and then treated with 7.1 g (0.31 mol) of sodium. After 24 hours standing, the solution deposited 36.0 g (68%) of the sodium salt; ir (Nujol mull) 3230 (N-H) and 1632 cm^{-1} (hydroxamic acid C=O).

The sodium salt (20.0 g, 0.14 mol) was neutralized in 1.25 N HOAc to yield 12.3 g (62%) of 44h. Recrystallization from MeOH yielded the purified acid: mp 125-8°: lit. mp 131-2°;[59] ir (Nujol mull) 3200 (broad N-H and O-H) and 1630 cm^{-1} (hydroxamic acid C=O).

Phenylacetohydroxamic acid (44i). Ethyl phenylacetate (60.0 g, 0.37 mol) was added to the MeOH filtrate of 51.0 g (0.73 mol) of hydroxylamine hydrochloride and 44.0 g (0.10 mol) of NaOH. No crystals were formed during three weeks standing at room temperature. Evaporation of the MeOH *in vacuo* gave 58.2 g (92%) of the sodio salt: mp >300°; ir (Nujol mull) 3250 (N-H) and 1630 cm^{-1} (hydroxamic acid C=O).

Neutralization of 30.0 g (0.17 mol) of the sodium salt with 1.25 N HOAc yielded 20.1 g (77%) of 44i on subsequent recrystallization from ethyl acetate: mp 138-40°: lit. mp 143-4°;[55] ir (Nujol mull) 3200 (broad N-H and O-H) and 1632 cm^{-1} (hydroxamic acid C=O); nmr (DMSO-d_6) δ 9.75 (S, 2, exchangeable N-$\underline{H}$ and O-$\underline{H}$), 7.31 (S, 5, Ar-$\underline{H}$), and 3.30 ppm (S, 2, Ar-C$\underline{H}_2$).

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.20; N, 8.99.

β-Phenylpropionohydroxamic acid (44j). Ethyl β-phenylpropionate (50.0 g, 0.28 mol) was added to the MeOH filtrate of 39.0 g (0.56 mol) of hydroxylamine hydrochloride and 33.7 g (0.84 mol) of NaOH. No crystals had precipitated after 72 hours and evaporation *in vacuo* yielded 45.3 g (86%) of the sodium salt; ir (Nujol mull) 3220 (N-H) and 1630 cm^{-1} (hydroxamic acid C=O).

The sodium salt (20.0 g, 0.12 mol) was neutralized in 1.25 N HOAc to yield 12.2 g (70%) of 44j. Recrystallization from benzene yielded pure 44j: mp 78-80°: lit. mp 78°;[60a] ir (Nujol mull) 3200-2800 (broad N-H and O-H) and 1630 cm^{-1} (hydroxamic acid C=O).

Acetohydroxamic acid (44k). Ethyl acetate (40.0 g, 0.45 mol) was added to the EtOH filtrate of 63.1 g (0.91 mol) of hydroxylamine hydrochloride and 20.0 g (0.91 mol) of sodium metal. After 48 hours 10.4 g (0.45 mol) of metallic sodium were added and the mixture maintained at 4°C for 48 hours. Evaporation of the solvent *in vacuo* yielded 42.1 g (95%) of product. This salt was extremely hydroscopic and was therefore stored in a vacuum oven; ir (Nujol mull) 3240 (N-H) and 1620 cm^{-1} (broad C=O).

Neutralization of 20.0 g (0.21 mol) of the salt with 1.25 N HOAc solution (in EtOH) yielded 7.9 g of NaOAc and evaporation of the ethanolic filtrate gave a solid with mp 120-30°. After Soxhlet extraction of the solid for 72 hours with ethyl acetate, crystals were obtained from the solvent; yield 3.5 g (22%) of pure 44k: mp 88-90°: lit. mp 84-6°;[61] ir (Nujol mull) 3280-2500 (broad N-H and O-H) and 1640 cm^{-1} (broad hydroxamic acid C=O).

Propionohydroxamic acid (44l). A MeOH solution of 23.5 g (0.34 mol) of hydroxylamine hydrochloride and 28.6 g (0.51 mol) of KOH was prepared. Filtration removed the KCl and 30.0 (0.17 mol) of β-phenylethyl propionate were added to the filtrate. Storage at room temperature for 9 days, and subsequent evaporation of the MeOH produced a semi-solid which upon treatment with cyclohexane yielded 12.2 g (58%) of the potassium salt; ir (Nujol mull) 3220 (N-H) and 1630 cm^{-1} (hydroxamic acid C=O).

The potassium salt (5.0 g, 0.04 mol) was treated with 1.25 N HOAc, but no hydroxamic acid was recovered. Therefore, 5.0 g (0.04 mol) of the potassium salt in MeOH were treated with 2.46 g (0.04 mol) of glacial HOAc. This technique produced an insoluble by-product (unidentified) and the filtered MeOH solution of the hydroxamic acid was employed for further reaction without isolating the free acid.

Terephthalohydroxamic acid (44n). Diethyl terephthalate (25.0 g, 0.11 mol) was added to the MeOH filtrate of 23.4 g (0.34 mol) of hydroxylamine hydrochloride and 31.4 g (0.56 mol) of KOH. The crystals which formed in 10 minutes were filtered off to yield 27.8 g (93%) of the dipotassium salt; ir (Nujol mull) 3240 (N-H) and 1605 cm^{-1} (hydroxamic acid C=O).

Neutralization of 15.0 g (0.06 mol) of the dipotassium salt with 1.25 N HOAc gave 10.0 g (81%) of the free acid: mp 228-30°: lit. mp 232;[60b] ir (Nujol mull) 3300 (N-H), 3140-2400 (broad O-H), and 1640 cm^{-1} (broad hydroxamic acid C=O).

2-Carbomethoxy-2-carbomethoxymethyl-3-hydroxy-2,3-dihydro-4(1H)-quinazolinone (21a). A solution of 5.0 g (33.0 mmol) of 20a in 50 ml of MeOH was treated with 4.65 g (33.0 mmol) of 1 in small portions. After heating on a steam-bath for 20 minutes the medium was cooled for 24 hours. Concentration of the reaction mixture *in vacuo* provided a viscous brown oil which when triturated with acetone-cyclohexane crystallized to 7.79 g (82%) of product with mp 145-8°. Recrystallization from acetone-cyclohexane yielded pure white 21a: mp 151-2°; ir (Nujol mull) 3340 (N-H), 3240 (O-H), 1735 (ester C=O) and 1660 cm^{-1} (cyclic hydroxamic acid C=O); nmr ($DCCl_3$) δ 9.0 (broad S, 1, N-$\underline{H}$ or O-$\underline{H}$) 7.91-6.65 (m, 4, Ar-$\underline{H}$), 6.36 (S, 1, O-$\underline{H}$ or N-$\underline{H}$), 3.80 (S, 3, O-$C\underline{H}_3$), 3.73 (S, 3, O-$C\underline{H}_3$), and 3.63, 3.13 ppm (AB quartet, 2, J=16.0 Hz, -$C\underline{H}_2$-CO).

Anal. Calcd. for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.98; H, 4.74; N, 9.72.

2-Carbomethoxy-2-carbomethoxymethyl-3-hydroxy-6-chloro-2,3-dihydro-4(1H)-quinazolinone (21b). Following the above procedure, 9.78 g (52.0 mmol) of 20b and 7.42 g (52.0 mmol) of 1 were reacted in 75 ml of MeOH. Trituration of the resulting oil yielded 14.1 g (82%) of the product with mp 160-2°. Recrystallization yielded white crystals of 21b: mp 176-8°; ir (Nujol mull) 3360, 3320, 3290 (N-H and O-H), 1748 and 1730 (ester C=O), and 1660 cm^{-1} (cyclic hydroxamic acid C=O); nmr ($DCCl_3$) δ 9.66 (broad S, 1, N-H or O-H), 7.80-6.65 (m, 3, Ar-H), 6.90 (S, 1, O-H or N-H), 3.74 (S, 3, O-CH_3), 3.71 (S, 3, O-CH_3), and 3.45, 3.11 ppm (AB quartet, 2, J=16.0 Hz, -CH_2-CO).

Anal. Calcd. for $C_{13}H_{13}ClN_2O_6$: C, 47.50; H, 3.99; N, 8.52. Found: C, 47.65; H, 3.92; N, 8.47.

Attempted reaction of 2-methylaminobenzohydroxamic acid, 20c, with 1. Equimolar quantities (50.0 mmol) of 20c and 1 were reacted as above to yield a dark brown viscous oil which could not be solidified by trituration. This oil showed multiple resonances in the N-CH_3 region. Since attempted purification was unsuccessful the oil was refluxed for 72 hours in xylene with a catalytic amount of NaOMe. Cooling to room temperature did not yield a precipitate and forced precipitation with petroleum ether yielded an amorphous powder. This product could not be purified to yield the desired 21c.

Reaction of benzyl *o*-aminobenzohydroxamate, 43, with 1. Equimolar quantities (41.3 mmol) of 43 and 1 reacted slightly exothermally upon mixing in 60 ml of MeOH. Refluxing for 45 minutes and concentration *in vacuo* yielded a viscous brown oil which had a strong almond odor of benzaldehyde. Trituration with MeOH afforded 4.5 g of solid material. Recrystallization from MeOH gave pure white crystals of 17 (R=H): mp 148-9°: lit. mp 149-50°;[10] the ir and nmr were also identical with pure 17 (R=H).

Reader Note: In the following experimental procedures compounds indicated by numeral 44a-m are the corresponding hydroxamic acids shown on page 19 of this dissertation.

3-Phenyl-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37a). A solution of 5.0 g (36.5 mmol) of 44a in MeOH (ca. 100 mmol/100 ml) was treated with 5.2 g (36.5 mmol) of 1. Heating on a steam-bath for 30 minutes gave a dark blue solution and concentration *in vacuo* provided a dark blue oil. The oil was taken up in CCl_4 and washed with four 50 ml portions of distilled H_2O. The CCl_4 layer was separated, dried over $MgSO_4$, concentrated *in vacuo* to a clear yellow oil, and vacuum distilled to yield 8.15 g (80%) of pure 37a: bp 154-6°/0.5 Torr: $n_D^{21}=1.5182$; ir (neat) 3100-2860 (C-H), 1750 (broad ester C=O), 1630 (C=N), and 1100, 1080 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 7.8-7.3 (m, 5, Ar-$\underline{H}$), 3.86 (S, 3, O-C$\underline{H}_3$), 3.73 (S, 3, O-C$\underline{H}_3$), and 3.44, 3.27 ppm (AB quartet, 2, J=17.0 Hz, -C$\underline{H}_2$-CO).

Anal. Calcd. for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.81; H, 4.61; N, 4.97.

The higher boiling fractions of the distillate (bp 165-70°/0.6 Torr) displayed an ir band at 2260 cm^{-1} identical with N=C=O in authentic phenylisocyanate.

When the CCl_4 layer was separated from the H_2O layer a flocculent solid was present. Filtration yielded 0.6 g of this solid (46): mp 170-3°: lit. mp 176-7°;[45] ir (Nujol mull) 3300 (broad N-H), 1750 (C=O), and 1650 cm^{-1} (C=O). Recrystallization of this solid from $CHCl_3$/MeOH yielded 1,3-diphenylurea: mp after recrystallization from 95% EtOH was 235-7°.[45] A mixed mp with an authentic sample of diphenylurea gave no depression.

On standing several days the blue color of the H_2O disappeared. Concentration to 40 ml yielded 0.2 g of benzoic acid: mp 119-20°: mixed mp 120°.

3-(4-Methoxyphenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37b). Utilizing the above procedure, 5.83 g (34.9 mmol) of 44b were reacted with 4.95 g (34.9 mmol) of 1 to yield 9.8 g (90%) of a yellow oil. On standing the oil solidified. Recrystallization from EtOH gave pure white 37b: mp 50-1°; ir (Nujol mull) 1750, 1735 (ester C=O), 1631 (C=N), and 1103, 1088 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 7.76, 6.95 (AB quartet, 4, J=9.0 Hz, Ar-H), 3.86 (S, 6, O-CH_3), 3.75 (S, 3, O-CH_3), and 3.43, 3.23 ppm (AB quartet, 2, J=17.0 Hz, -CH_2-CO).

Anal. Calcd. for $C_{14}H_{15}NO_7$: C, 54.37; H, 4.89; N, 4.53. Found: C, 54.65; H, 5.09; N, 4.72.

3-(3-Methoxyphenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37c). 44c (10.0 g, 60.0 mmol) was reacted with 8.5 g (60.0 mmol) of 1 as above to yield 12.1 g (66%) of a clear oil. An analytical sample was prepared by two methods. One was prepared by washing the CCl_4 layer with three 50 ml portions of distilled H_2O, twice heating with Norit A, and drying over $MgSO_4$. Concentration *in vacuo* and final drying of the oil gave an analytical sample with n_D^{21}=1.5221. Vacuum distillation of the above analytical sample also yielded pure 37c: bp 120°/0.1 Torr; ir (neat) 3080-2840 (C-H), 1755 (broad ester C=O), 1632 (C=N), and 1105, 1080 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 7.4-6.85 (m, 4, Ar-H), 3.83 (S, 3, O-CH_3), 3.80 (S, 3, O-CH_3), 3.70 (S, 3, O-CH_3), and 3.39, 3.21 ppm (AB quartet, 2, J=16.5 Hz, -CH_2-CO).

Anal. Calcd. for $C_{14}H_{15}NO_7$: C, 54.37; H, 4.89; N, 4.53. Found: C, 54.25; H, 4.80; N, 4.37.

Attempted synthesis of 3-(2-methoxyphenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37d). Equimolar quantities (120 mmol) of 44d and 1 were reacted as above. The yellow oil obtained on *in vacuo* concentration of the CCl_4 layer showed N-H and O-H absorption bands at 3200 cm^{-1}. The nmr ($DCCl_3$) had resonances at δ 10.2 (N-H or O-H), 6.03 and 5.40 (vinylic H), 4.0-3.7 (m, O-CH_3) and 3.41, 3.19 ppm (AB quartet, J=17.2 Hz, -CH_2-CO). These resonances indicated a mixture of open adducts and 1,4,2-dioxazole (37d). Attempted vacuum distillation produced an intense isocyanate absorption at 2280 cm^{-1} in all fractions. Thin layer chromatography on Baker-flex silica gel 1B-F (80 benzene/20 $CHCl_3$) resulted in four distinct spots with R_f values of 6.0, 7.1, 8.4, and 9.2.

3-(4-Bromophenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37e). Equimolar quantities (44.6 mmol) of 44e and 1 were refluxed in 80 ml of MeOH for 72 hours. The reaction mixture was concentrated *in vacuo* to a yellow oil, which on standing precipitated a solid in the oil phase. A CCl_4 solution of the oil was filtered to yield 0.45 g of 44e. The filtrate was treated as in 37c to yield 13.2 g (83%) of 37e: $n_D^{21}=1.5450$; ir (neat) 3030-2920 (C-H), 1750 (broad ester C=O), 1630 (C=N), and 1095, 1072 (O-C-O doublet); nmr ($DCCl_3$) δ 7.72, 7.61 (AB quartet, 4, J=9.0, Ar-H), 3.85 (S, 3, O-CH_3), 3.73 (S, 3, O-CH_3), and 3.40, 3.08 ppm (AB quartet, 2, J=16.5, -CH_2-CO).

Anal. Calcd. for $C_{13}H_{12}BrNO_6$: C, 43.60; H, 3.38; N, 3.91. Found: C, 43.78; H, 3.66; N, 4.01.

Attempted synthesis of 3-(2-bromophenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37f). Equimolar quantities (71.5 mmol) of 44f and 1 were refluxed for 72 hours in 100 ml of MeOH. Work up of the reaction mixture produced 0.3 g of the starting acid (44f) and a yellow oil. The oil showed N-H and O-H absorption at 3230 cm^{-1}. The nmr ($DCCl_3$) had the expected dioxazole resonances plus δ 5.96 and 5.47 ppm (vinylic H). Attempted vacuum distillation led to an isocyanate absorption at 2270 cm^{-1} in all fractions. Also washing the CCl_4 layer with a saturated $NaHCO_3$ solution afforded an oil containing the desired dioxazole contaminated with other N-H and O-H containing products.

3-(3-Nitrophenyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37g). Equimolar quantities (71.5 mmol) of 44g and 1 were stirred in a MeOH solution for 24 hours. Concentration of the reaction mixture *in vacuo* followed by vacuum distillation yielded 10.5 g (45%) of pure 37g: bp 145-8°/0.1 Torr: $n_D^{21}=1.5337$; ir (neat) 3100-2860 (C-H), 1755 (broad ester C=O), 1630 (C=N), 1540 and 1350 (N-O), and 1080 cm^{-1} (broad O-C-O); nmr ($DCCl_3$) δ 9.4-7.5 (m, 4, Ar-H), 3.86 (S, 3, O-CH_3), 3.73 (S, 3, O-CH_3), and 3.40, 3.17 ppm (AB quartet, 2, J=16.5, -CH_2-CO).

Anal. Calcd. for $C_{13}H_{12}N_2O_8$: C, 48.15; H, 3.73; N, 8.64. Found: C, 48.29; H, 3.75; N, 8.60.

3-Cyclohexyl-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37h). Equimolar quantities (80.5 mmol) of 44h and 1 were reacted in 100 ml of MeOH and stirred without heating for 24 hours. *In vacuo* concentration yielded 1.0 g of 44h and a dark blue oil. Product isolation as in previous experiments yielded 17.5 g (76%) of 37h. Vacuum distillation gave pure 37h: bp 123-5°/0.04 Torr: n_D^{21}=1.4687; ir (neat) 3000-2860 (C-H), 1755 (broad ester C=O), 1648 (C=N), and 1080, 1070 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 3.86 (S, 3, O-$C\underline{H}_3$), 3.74 (S, 3, O-$C\underline{H}_3$), 3.35, 3.10 (AB quartet, 2, J=16.5 Hz, -$C\underline{H}_2$-CO), and 2.1-1.1 ppm (m, 11, cyclohexyl-$\underline{H}$).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.58; H, 6.77; N, 4.93.

3-Benzyl-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37i). Equimolar quantities (19.9 mmol) of 44i and 1 were refluxed in 30 ml of MeOH for 1 hour. Work up of the reaction mixture as in 37a yielded a yellow oil (74%). Vacuum distillation gave pure 37i: bp 161-3°/0.3 Torr; ir (neat) 3060-2900 (C-H), 1750 (broad ester C=O), 1650 (C=N), and 1080, 1060 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 7.35 (S, 5, Ar-$\underline{H}$), 3.80 (S, 3, O-$C\underline{H}_3$), 3.73 (S, 2, Ar-$C\underline{H}_2$-), 3.65 (S, 3, O-$C\underline{H}_3$) and 3.29, 3.10 ppm (AB quartet, 2, J=17.0 Hz, -$C\underline{H}_2$-CO).

Anal. Calcd. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.22; H, 5.35; N, 4.62.

3-(β-Phenylethyl)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37j). Equimolar quantities (54.5 mmol) of 44j and 1 were stirred without heating for 24 hours in 50 ml of MeOH. The reaction mixture was treated as in 37a. Vacuum distillation led to considerable decomposition of the product. Therefore a CCl_4 solution of the oil was washed two more times with 50 ml portions of H_2O, concentrated *in vacuo* and thoroughly dried to yield 79% of the pure 37j: $n_D^{21}=1.5032$; ir (neat) 3080-2860 (C-H), 1755 (broad ester C=0), 1650 (C=N), and 1085, 1060 (0-C-0 doublet); nmr ($DCCl_3$) δ 7.20 (S, 5, Ar-H), 3.78 (S, 3, $0-CH_3$), 3.65 (S, 3, $0-CH_3$), 3.27, 3.03 (AB quartet, 2, J=17.0, $-CH_2$ -CO) and 3.1-2.5 ppm (m, 4, $-CH_2-CH_2-$).

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.56; H, 5.53; N, 4.73.

3-Methyl-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37k). Equimolar quantities (37.8 mmol) of 44k and 1 were refluxed for 2 hours in 25 ml of MeOH. Treatment of the reaction mixture in the same manner as 37j yielded 5.65 g (69%) of pure 37k: bp 77-9°/0.07 Torr; ir (neat) 3010-2860 (C-H), 1755 (broad ester C=0), 1660 (C=N), and 1085, 1070 cm^{-1} (0-C-0 doublet); nmr ($DCCl_3$) δ 3.86 (S, 3, $0-CH_3$), 3.73 (S, 3, $0-CH_3$), 3.36, 3.11 (AB quartet, 2, J=16.5 Hz, $-CH_2-CO$), and 2.10 ppm (S, 3, $-CH_3$).

Anal. Calcd. for $C_8H_{11}NO_6$: C, 44.24; H, 5.11; N, 6.45. Found: C, 44.15; H, 5.22; N, 6.45.

3-Ethyl-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37l). Equimolar quantities (4.93 mmol) of 44l and 1 were stirred for 24 hours in 20 ml of MeOH. Treatment of the reaction mixture in the same manner as above, gave a 73% yield of pure 37l: n_D^{21}=1.4461; ir (neat) 3000-2860 (C-H), 1750 (broad ester C=O), 1655 (C=N), and 1080, 1060 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 3.83 (S, 3, O-CH$_3$), 3.70 (S, 3, O-CH$_3$), 3.34, 3.09 (AB quartet, 2, J=16.5 Hz, -CH$_2$-CO), 2.41 (q, 2, J=7.5 Hz, CH$_3$-CH$_2$-), and 1.23 ppm (t, 3, J=7.5 Hz, -CH$_2$-CH$_3$).

Anal. Calcd. for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 47.02; H, 5.58; N, 5.95.

Bis-para-di-[5-carbomethoxy-5-carbomethoxymethyl-3-(1,4,2-dioxazolo)]-benzene (37n). A MeOH solution of 10.0 g (51.0 mmol) of 44n and 14.48 g (102 mmol) of 1 was stirred for 48 hours while a precipitate formed. Filtration of the solid gave 14.2 g (58%) of product with mp 110-2°. Recrystallization from MeOH afforded pure white 37n: mp 112-4°; ir (Nujol mull) 1752, 1732 (ester C=O), 1632 (C=N), and 1105, 1085 cm^{-1} (O-C-O doublet); nmr ($DCCl_3$) δ 7.86 (S, 4, Ar-H), 3.83 (S, 6, O-CH$_3$), 3.70 (S, 6, O-CH$_3$), and 3.42, 3.21 ppm (AB quartet, 4, J=17.0 Hz, -CH$_2$-CO).

Anal. Calcd. for $C_{20}H_{20}N_2O_{12}$: C, 50.00; H, 4.20; N, 5.83. Found: C, 49.94; H, 4.06; N, 5.74.

Attempted synthesis of 3-(1-naphtho)-5-carbomethoxy-5-carbomethoxymethyl-1,4,2-dioxazole (37m). Equimolar quantities (43.0 mmol) of 44m and 1 were refluxed 1 hour in 50 ml of MeOH, then stirred 24 hours at ambient temperature. Because acid could still be detected in the medium the reaction mixture was refluxed an additional 24 hours with 0.1 g of NaOMe added. Concentration *in vacuo* yielded an oil which showed NH and OH bands in the ir and vinyl H plus the dioxazole resonances in the nmr. Attempted separations were unsuccessful and vacuum distillation led to decomposition products including the isocyanate.

3-Phenyl-5-carbomethoxymethyl-1,4,2-dioxazole (48). Equimolar quantities (73.0 mmol) of 44a and methyl propiolate were refluxed for 24 hours in 70 ml of MeOH. Work up as in 37a yielded 76% of 48. Vacuum distillation gave pure 48: bp 134-6°/0.6 Torr: n_D^{21}=1.5344; ir (neat) 3060-2900 (C-H), 1745 (ester C=O), 1630 (C=N), and 1100, 1080 (O-C-O doublet); nmr ($DCCl_3$) δ 8.0-7.2 (m, 5, Ar-$\underline{H}$), 6.51 (t, 1, J=5.5 Hz, $>C\underline{H}-CH_2-$), 3.76 (S, 3, O-$C\underline{H}_3$), and 2.95 ppm (d, 2, J=5.5 Hz, $-C\underline{H}_2-CH<$).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.94; H, 5.02; N, 6.52.

Part II

HYDRAZIDE PRECURSORS

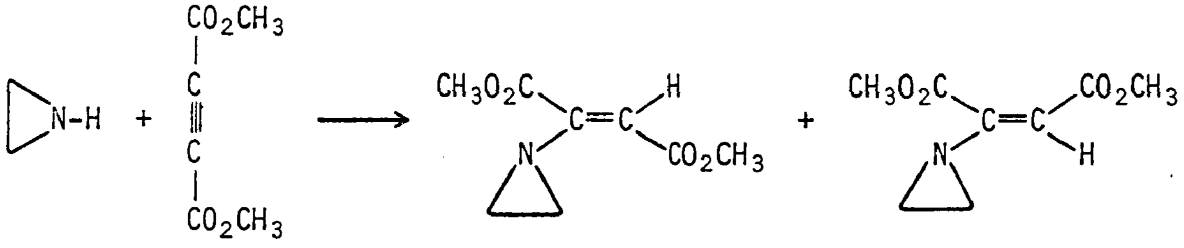
INTRODUCTION

Acetylenic esters have been found to undergo nucleophilic additions with a variety of nucleophiles. Nucleophiles such as thiolates,[1] alkoxides,[2] and phenoxides[3] undergo a Michael-type reaction yielding 1:1 adducts or products indicating a previous 1:1 adduct formation.

The Michael addition of primary, secondary and tertiary amines has been well documented. The stereochemistry of these additions has recently been studied by Dolfini[4] and Huisgen.[5]

The stereochemistry of additions of thiolic nucleophiles has been carefully studied by Truce[1] who has developed a "Rule of Trans-Nucleophilic Addition" in such cases.

Dolfini[4] studied the reaction of equimolar ratios of dimethyl acetylenedicarboxylate (1) and aziridine (2) in methanol at room temperature. Nmr analysis of the product mixture revealed that the *trans* ester (3) comprised 67% of the product and the *cis* ester (4), 33%.

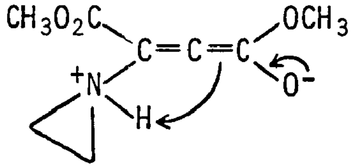


2 1 3 4

When the same reaction was run changing the solvent to dimethyl sulfoxide the product mixture contained 95% *cis* ester (4) and only 5%

of the trans ester (3). An important point not considered by previous authors was the non-isomerization of the cis or trans ester under the reaction conditions.

The formation of the zwitterionic intermediate 5 can account for the difference between the course of amine addition in dimethyl sulfoxide and that in methanol. The common



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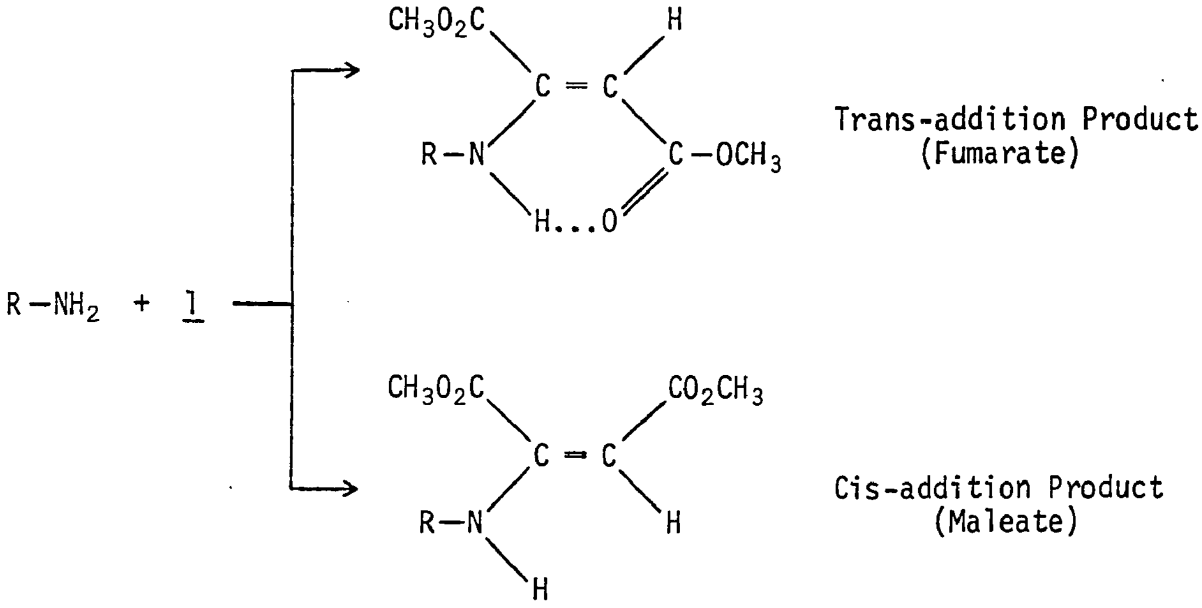
zwitterionic intermediate (5) can pick up a proton internally from the attacking nucleophile, resulting in the formation of the cis ester (4) or externally from the solvent to give the trans addition product (3). In agreement with this view, it was found that the yields of the trans ester varied, depending on the proton-donating ability of the solvent.

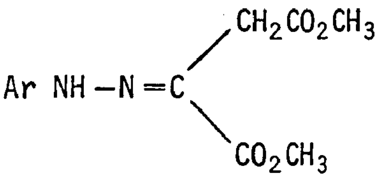
Dolfini also discussed the nmr assignment of the fumerate (3) and maleate (4) vinyl protons. Based on the influence of the adjacent carbonyl functions,[6] Dolfini suggests that the vinyl proton of the fumarate adduct, flanked by two deshielding carbonyl groups, would be expected to be deshielded with respect to the maleate vinyl proton. In the maleate one of the deshielding carbonyls is replaced by a shielding amine moiety.

The nucleophilic addition of an amine with dimethyl acetylenedicarboxylate can proceed by both a trans or cis mechanism giving rise to a mixture of fumarates and maleates respectively. The relative yields of these isomers will depend upon several factors such as the reaction conditions, the thermodynamic stability of the products, the nature of the attacking nucleophiles, and the solvent. Thus, in the reaction of primary amines with 1, a larger ratio of fumarates is formed.[7] It has been suggested that the

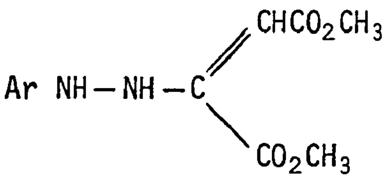


prevalence of the fumarate in these cases is due to their higher relative stability to maleates. This stability is due to the presence of internal hydrogen bonding between the -NH of the amine and the ester carbonyl group of the fumarate. As previously described in the Introduction to Part I[8a] the initially formed Michael adducts have been transformed into a variety of heterocyclic compounds.

Recently Heindel, Kennewell, and Pfau[9] demonstrated the existence of imine-enamine tautomers in the reaction of aryl hydrazine and hydrazine with 1.

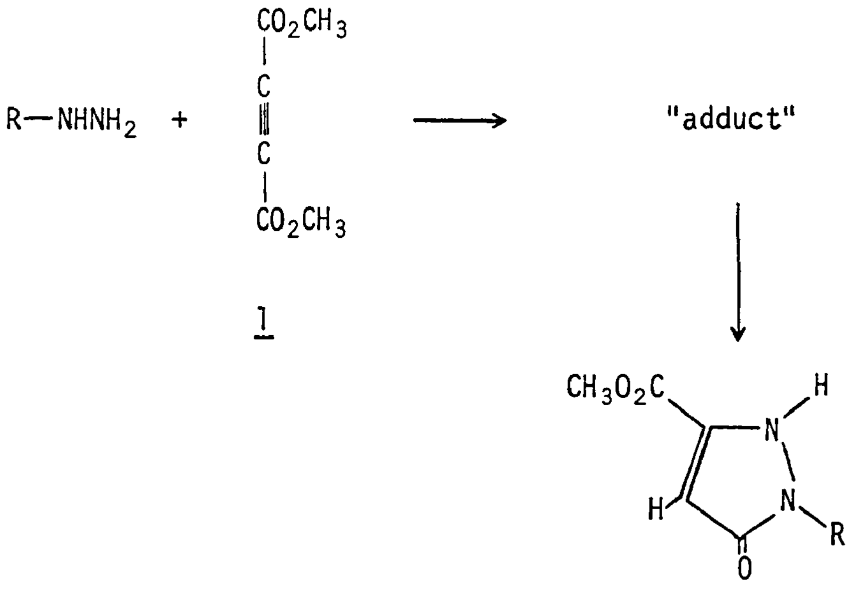


imine



enamine

Both isomers appear to arise directly from the condensation of the coreactants, since in most cases the more stable imine isomer predominates in the product mixture. However, postreaction isomerization, while easily demonstrable, is not sufficiently rapid to explain the isomer balance observed in the direct reaction. The isolable adducts were found to be intermediates in the condensation of hydrazines and dimethyl acetylenedicarboxylate to yield 3-carbomethoxy-5-pyrazolinones (6).^{10}



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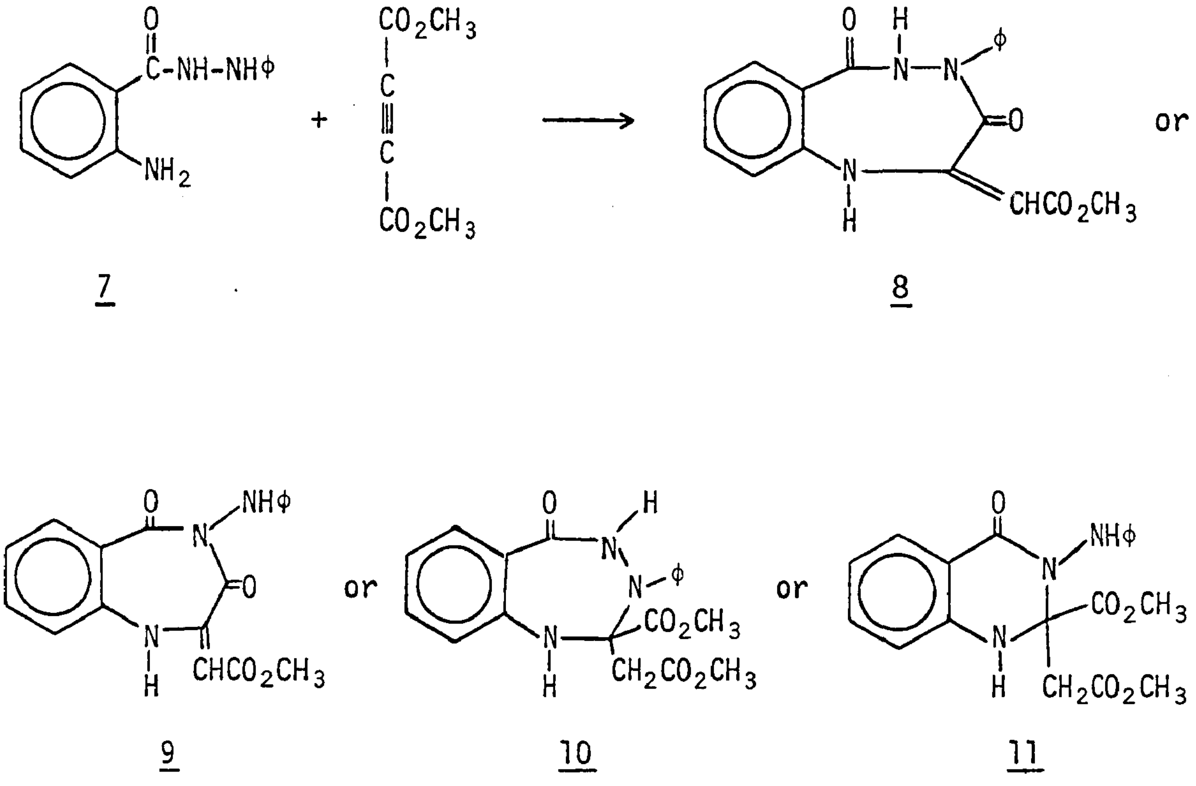
The above reaction of hydrazines, coupled with the previous work of Heindel, Fish, and Lemke[11] involving the base-catalyzed cyclization of anthranilamide-acetylenedicarboxylate adducts to either 1,4-benzodiazepine-3,5-diones or quinazolinone diesters, provided the scientific motivation for this research project.

Anthranilohydrazides (7) provide an additional nucleophilic atom compared to the previously discussed anthranilamides of Heindel, Fish, and Lemke. The addition of this nucleophile increases the number of possible heterocyclic derivatives as shown below.



7 8

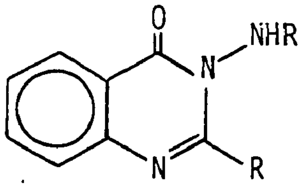
9 10 11

The two displacement products (8 and 9) can be easily distinguished from the double addition systems (10 and 11) by molecular weight determinations. The assignment of a particular structure within either of these classes is not as readily apparent and will be further discussed in this dissertation.

Many pharmacologically active compounds may be considered as hydrazine derivatives. They contain an -N-N-group either in the side chain (isonicotinic hydrazide, thiosemicarbazones of aldehydes) or in a heterocyclic ring (pyrazolones, butazolidine, antipyrine).[12]

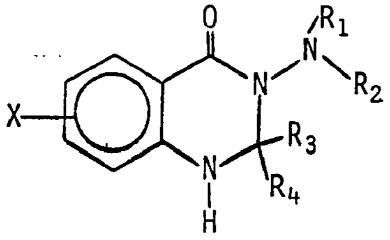
Less attention has been paid to hydrazine derivatives in which only one nitrogen atom is heterocyclic, while the other one belongs to the N-amino group in the side chain.[13] This type would be exemplified by compounds of structure 9 and 11.

One of the compounds with this general structure which has been synthesized is the 3-aminoquinazolinone (12). Compound 12 derived from both an *o*-aminoarylcarboxylic acid (anthranilic acid) and a hydrazine participating with a nitrogen atom in a hetero ring. Several of these compounds have shown useful pharmacological properties such as tranquilizing, analgetic, and hypnotic activity.[14]



12

In a recent disclosure Kirchner and Zalay[15] discussed the potential usefulness of certain alkyl and aryl substituted 3-amino-2,3-dihydro-4(1H)-quinazolinones (13). Their pharmacological evaluation indicated usefulness as adjuvants in the treatment of insomnia, convulsions, and mental disturbances.



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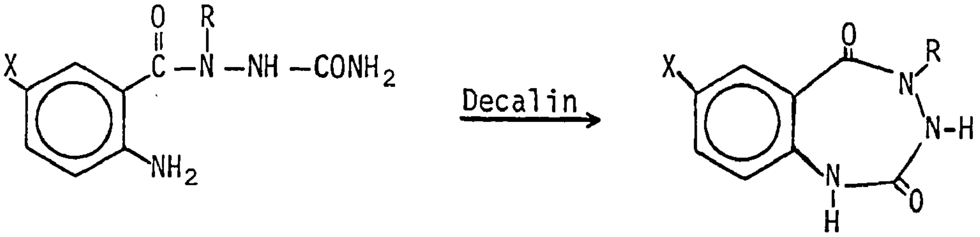
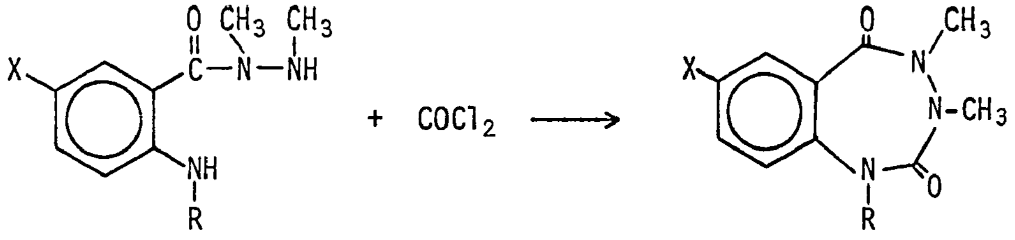
A number of 3-arylamino-, dialkylamino-, and alkylarylamino-1,2-dihydro-4(1H)-quinazolinones have also been synthesized by S. Somasekhara and co-workers.[16] Their biological activities were evaluated.

1,3,4-Benzotriazepines (Structure 10) also represent a class of heterocyclic compounds with medicinal potential. Sulkowski and Childress[17,18] reported 5-aryl-1,3-dihydro-2H-1,3,4-benzotriazepin-2-ones as a new class of psychotherapeutic agents. More recently Langis and Charest[19] reported the synthesis of derivatives of 1,3,4-benzotriazepin-2,5-diones (14).



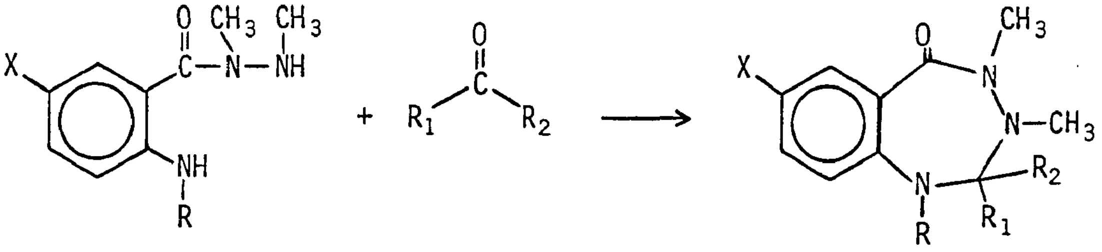
14

Recently Hromatka, Krenmüller, and Knollmüller[20] cyclized 1',2'-dimethylanthranilic acid hydrazides with phosgene to yield the 1,3,4-benzotriazepin-2,5-diones (15).



15

Hromatka and co-workers[21] have also developed a method of synthesis of 1,3,4-benzotriazepin-5-ones (16) involving the reaction of 1',2'-dimethylanthranilic acid hydrazides with aldehydes and ketones. These compounds are also formed from anthranilic acid hydrazides having an unsubstituted amino group which allows the formation of azomethines.

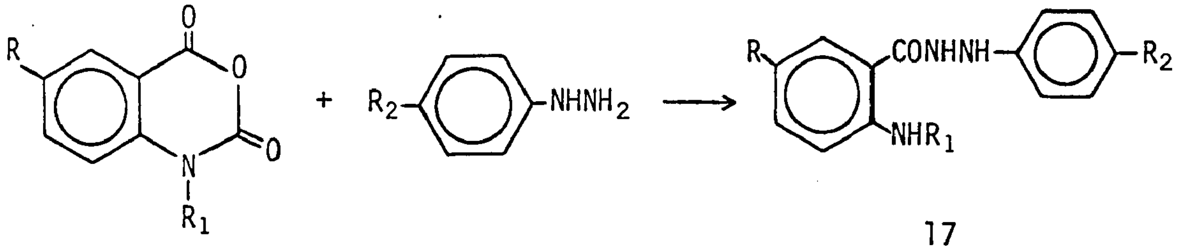


16

RESULTS AND DISCUSSION

Synthesis of Alkyl and Aryl Anthranilohydrazides

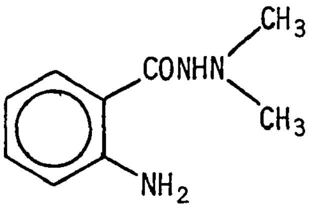
Nucleophilic ring opening of isatoic anhydrides has been shown to yield anthranilic acid derivatives.[22a] By utilizing substituted hydrazines as the nucleophiles toward isatoic anhydrides, substituted anthranilohydrazides (17) can be prepared.



17

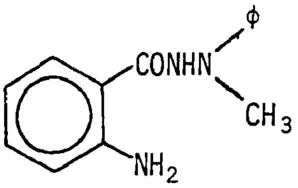
	R	R_1	R_2
a.	H	H	H
b.	Cl	H	H
c.	H	H	Cl
d.	H	H	NO_2
e.	Cl	H	NO_2
f.	H	CH_3	H

The reaction of 1,1-dimethylhydrazine with isatoic anhydride provided 1-(2-aminobenzoyl)-2,2-dimethylhydrazine (18).

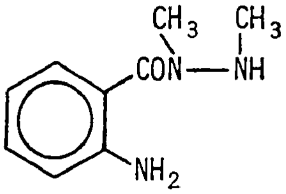


18

Similarly prepared by the reaction of 1-methyl-1-phenylhydrazine with isatoic anhydride was 1-(2-aminobenzoyl)-2-methyl-2-phenylhydrazine (19). By the addition of 1,2-dimethylhydrazine to isatoic anhydride the corresponding 1-(2-aminobenzoyl)-1,2-dimethylhydrazine (20) was synthesized.

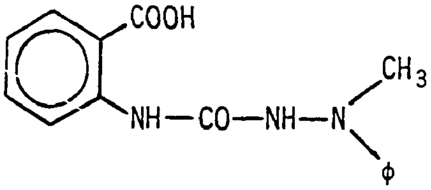


19



20

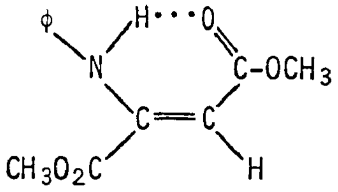
In the synthesis of 19 the product (21) resulting from the ring opening of the isatoic anhydride at the number 2 carbonyl has also been isolated.



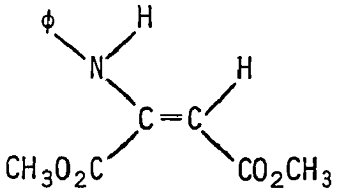
21

Adduct Formation

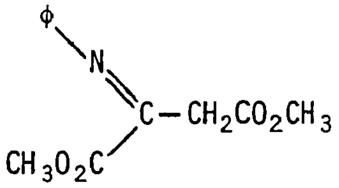
The Michael addition of primary aromatic amines (anilines) with dimethyl acetylenedicarboxylate has been found to yield adducts of several different isomeric species: fumarate (22), maleate (23), or imine (24).



22

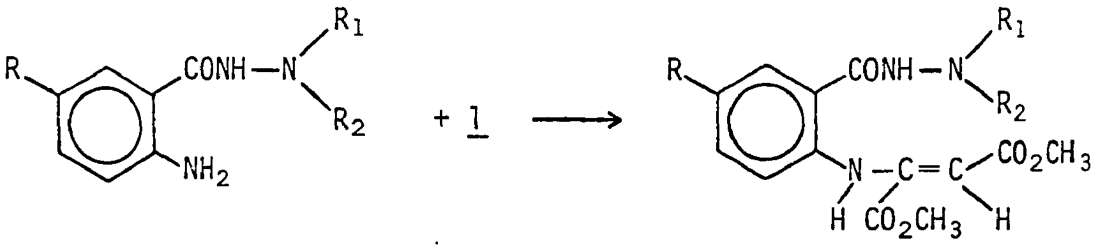


23



24

The reaction of anthranilohydrazides (17, 18, and 19) yielded a product (25) which was found to possess an isomeric homogeneity as evidenced by the appearance of a single vinyl proton resonance in its nmr spectrum. This also indicated that the imine isomer (24) was not present.



17, 18, or 19

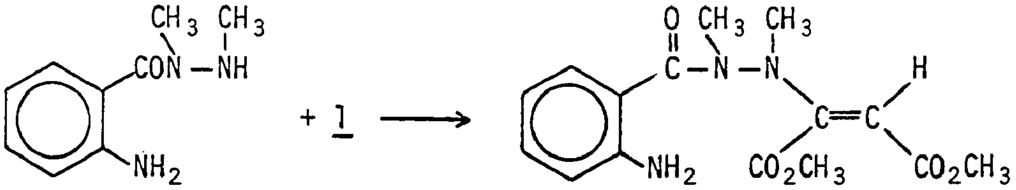
25

	R	R_1	R_2		R	R_1	R_2
a.	H	H	C_6H_5	e.	Cl	H	$4\text{-}NO_2\text{-}C_6H_4$
b.	Cl	H	C_6H_5	f.	H	CH_3	C_6H_5
c.	H	H	$4\text{-}Cl\text{-}C_6H_4$	g.	H	CH_3	CH_3
d.	H	H	$4\text{-}NO_2\text{-}C_6H_4$				

The vinyl proton of the fumarate (22) experiences the deshielding effects of the two carbonyl groups, while the maleate proton is deshielded by only one carbonyl group. Previous nmr data have established that the maleate vinyl proton is upfield from the fumarate. This conclusion has been verified by ir and uv spectral studies.[23]

The infrared spectra of the adducts are also helpful in making a reasonable assignment of the vinyl geometry. The fumarate (22), with its chelated ester, shows one normal ester above 1700 cm^{-1} and one ester absorption below 1690 cm^{-1}. In the maleate geometry (23) the absorption of both ester carbonyls is above 1695 cm^{-1}. The six-membered hydrogen-bonded ring in the fumarate (22) has added importance as it provides the measure of stability that favors the fumarate whenever a primary amine forms a dimethyl acetylenedicarboxylate adduct.[2,23]

However, when secondary amines are reacted with 1 the maleate geometry arises by cis-addition. In this work the reaction of the dimethyl derivative (20) with 1 produces the maleate (26) shown below.



20

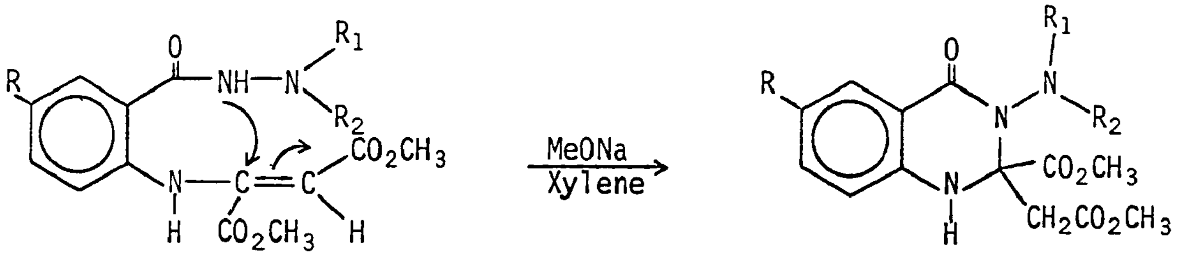
26

The assignment of 25 as the fumarate geometry is entirely in accord with the spectra. The vinyl proton resonance is at δ 5.48±0.06 ppm with that of 25a being at δ 5.42 ppm, which is identical to the previously reported dimethyl (2-carboxamidoanilino) fumarate.[22b] The ester carbonyls appear at 1736±14 cm^{-1} and at 1685±5 cm^{-1} for the normal and chelated ester respectively. The ir spectra of 25 also lack the primary amine absorbances present in 17, 18, and 19 further verifying the reaction of the primary amine to yield the fumarate.

In 26 the vinyl proton resonance is at δ 4.86 ppm, which is 0.56 ppm upfield from the closest fumarate vinyl resonance of 25. The ester carbonyl absorptions are at 1748 and 1697 cm^{-1} indicating the lack of the chelated ester of 25. Also present in 26 is the primary amine absorption at 3470 and 3370 cm^{-1} clearly indicating that reaction took place at the secondary amine to give the maleate (26).

Cyclization of the Anthranilohydrazide-Acetylenedicarboxylate Adducts to 3-Substituted-2,3-dihydro-4(1H)-quinazolinones

The base-catalyzed cyclization of the dimethyl acetylenedicarboxylate adducts (25) in xylene produced a single product (27) in each case. The isolated products are the 2,3-dihydro-4(1H)-quinazolinones (27) shown below.



25

27

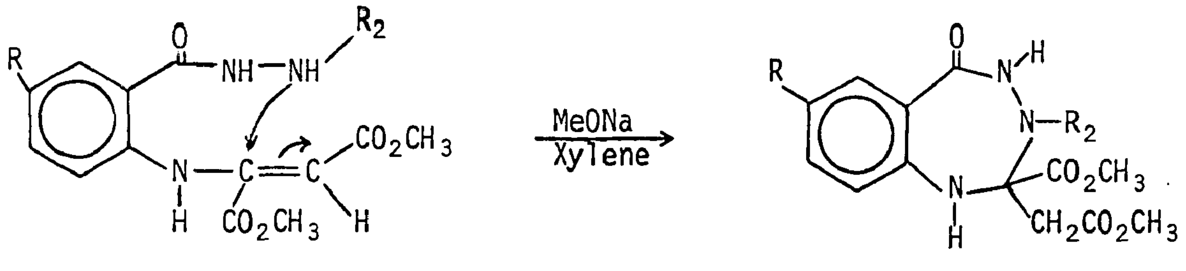
	R	R_1	R_2		R	R_1	R_2
a.	H	H	C_6H_5	e.	Cl	H	4-NO_2-C_6H_4
b.	Cl	H	C_6H_5	f.	H	CH_3	C_6H_5
c.	H	H	4-Cl-C_6H_4	g.	H	CH_3	CH_3
d.	H	H	4-NO_2-C_6H_4				

The elemental analysis and mass spectral data provide proof that 27 is a 1:1 adduct of the hydrazide with 1; thus eliminating any cyclizations involving a displacement type mechanism. The mass spectra of all 27 contain ions representing the loss of carbomethoxy ($\cdot CO_2CH_3$, 59 mass units) and carbomethoxymethyl ($\cdot CH_2CO_2CH_3$, 73 mass units) from the molecular ion. This loss of 59 and 73 mass units clearly indicates that a double addition to 1 has taken place.

The knowledge that base-catalyzed cyclization of 25 has taken place by the addition of the N-H to the CC double bond simplifies the structure elucidation of 27. In the case of 25f,g, where both R_1 and R_2 are alkyl or aryl groups, there is only one N-H (α to the C=O) which can add to the CC double bond. Therefore, this addition can generate only the quinazolinone (27). Hence, the addition is similar to the cyclization of anthranilamide-acetylenedicarboxylate adducts to quinazolinones previously discussed.[11] Other recent examples of acetylenic esters as heterocyclic building blocks include the synthesis of benzothiazines[24] and benzoxazinones[25] from *o*-mercapto- and *o*-hydroxybenzamides.

However, in 25a-e, where R_1=H and R_2=aryl, the duality of the hydrazide type N-H protons can lead to two types of addition products.

By addition of the N-H α to the C=O quinazolinones of type 27 would result, but if the β N-H is involved in the cyclization-addition the benzotriazepinone (28) would result.



25a-e

28

When 17a was condensed with 1 concentration of the reaction mixture after filtration of 25a yielded the cyclized material (27a). This was also observed in the case of 17e to give 25e and 27e.

All attempts at cyclization of the maleate (26) resulted in recovery of 26. Both base-catalyzed and thermal cyclization were unsuccessful. Molecular models of 26 show that the molecular distance between the primary amine and the maleate portion of the molecule appears too great for intramolecular reaction.

Structure Proof of the Quinazolinone Products

Having established that when both R_1 and R_2 are alkyl or aryl, 25 was readily cyclized to quinazolinone (27), and when R_1=H, R_2=aryl the resulting product was either 27 or 28 a more detailed structure elucidation was undertaken. The previously described mass spectral data, indicating double addition, were augmented by the appearance in the nmr of either a broad singlet or an AB quartet for the pendent $-CH_2-$

resonances. The appearance of magnetically non-equivalent methylene protons adjacent to an asymmetric center is well known.[26]

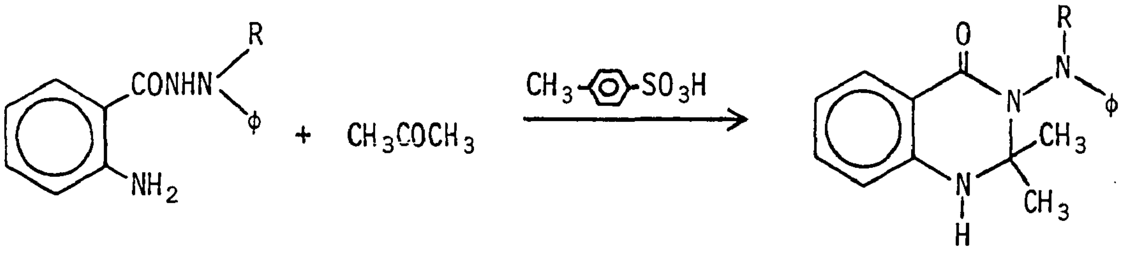
All 27, except 27b with a single broad absorption at 1735 cm^{-1}, have two saturated ester absorbances between 1725 and 1760 cm^{-1}. The cyclic carbonyl appears between 1645 and 1680 cm^{-1} which is consistent with either structure 27 or 28.

The NaH/MeI methylation of 27a provided definite proof that the base-catalyzed condensation of 25 did indeed provide quinazolinone (27) rather than alternate structure 28. Monomethylation of 27a can occur either at the 1-position or on the pendent 3-anilino moiety. If methylation occurs on the anilino moiety the resulting product would be 27f.

The methylation of 27a resulted in the recovery of 50% of 27a and a solid product. Thin layer chromatography of this material, on both silica gel and aluminum oxide, separated a compound with an R_f value identical to 27a from one with an R_f identical to 27f. The presence of 27f in the methylation product of 27a clearly defines 27a as the quinazolinone structure. Two other minor products with R_f values less than 27a or 27f were also separated. These products are probably the result of methylation at the 1-position or more exhaustive methylation. For more details of the TLC see the experimental section.

Examination of the nmr data of the adducts (25) provides additional information that the α N-H would be expected to add to the enamine double bond to provide 27. The nmr of 25a-e all have one N-H proton at δ 11.0±0.1 ppm which is very slowly exchanged with D_2O. A second N-H at δ 10.5±0.2 ppm exchanged with D_2O almost instantly. This difference in exchange rates implies the probable greater acidity of the N-H at δ 10.5±0.2 ppm. In 25f,g, where only the N-H α to the C=O is present, a rapidly exchangeable resonance at δ 10.50±0.03 ppm is present. Hence, by comparison of 25a-e with 25f,g the resonance at δ 10.5±0.2 ppm in 25a-e can be assigned to the α N-H. Since this is the more acidic H it would be expected to condense with the enamine double bond to provide 27.

The method of Kirchner and Zalay[15] was utilized to synthesize the quinazolinones (29) shown below. Both 29, where R=H or CH_3, are known to be of the quinazolinone class and were developed here for comparison as model compounds.



29

TABLE I

UV Spectra of Quinazolinones in EtOH

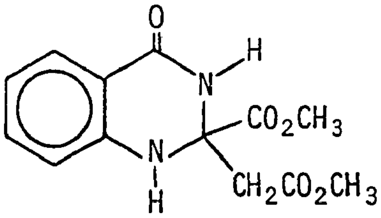
27a		29, R=H		27f	
λ, nm	log ε	λ, nm	log ε	λ, nm	log ε
230	4.46	231	4.43	229	4.43
286	3.30	287	3.24	289	3.34
345	3.30	348	3.34	345	3.30

29,R=CH_3		27g		30	
λ, nm	log ε	λ, nm	log ε	λ, nm	log ε
229	4.45	228	4.44	225	4.49
290	3.26	260	3.60	255	3.61
347	3.38	345	3.30	345	3.36

Table I contains pertinent uv data for several quinazolinones. Comparison of the spectrum of 29 (R=H) with the spectrum of 29 (R=CH_3) clearly indicates that the substitution of the CH_3 group does not markedly alter the uv spectra. In fact, they are nearly superimposable on each other. The striking similarity of 29 (R=H) and 29 (R=CH_3) defines both as being of the quinazolinone class. With this in mind, the spectra of 27a and 27f, which also differ only by a CH_3 group, are also practically superimposable. Likewise, the spectra of 27a and 29 (R=H) are very similar. It can be seen from this comparison of spectra that

27a can be formulated as a quinazolinone.

The uv spectra of 27g, which is a quinazolinone, is very similar to that of the previously reported quinazolinone 30.[11] The spectra of 27a,f and 29 are also strikingly similar to 30, clearly defining them as quinazolinones.



30

Mass Spectral Analysis of 3-Substituted-quinazolinones

The mass spectral data are presented here to substantiate the previously presented assignment of structure 27 as a 2,3-dihydro-4(1H)-quinazolinone. The spectral data are tabulated in Table II, including the relative ion abundances as a percent relative to the base peak. The Roman numerals in column one of Table II correspond to the structures assigned to each m/e.

A molecular ion (I) of expected mass was present in all 27 (see Scheme 1 for ions I-VII). In all cases this ion had a relative abundance greater than 5%.

The loss of 31 a.m.u. from I was also evident in all 27. This ion (II) can be attributed to the fragmentation of a methoxyl group from the ester side chain.

TABLE II

Mass Spectra of Quinazolinones (27)

	27a		27b		27c	
	m/e	Relative abundance	m/e	Relative abundance	m/e	Relative abundance
I	369	16.	403	12.	403	9.5
II	338	3.1	372	2.8	372	2.3
III	310	100.	344	100.	344	100.
IV	296	3.1	330	2.8	330	3.4
V	278	54.	312	60.	312	40.
VI	250	8.3	284	12.	284	6.1
VII	236	16.	270	20.	270	11.
VIII	234	10.	268	7.1	234	27.
IX	219	11.	253	11.	219	20.
X	202	19.	236	23.	202	22.
XI	170	20.	204	15.	170	30.
XII	159	13.	193	13.	159	25.
XIII	144	21.	178	14.	144	22.
XIV	130	8.3	164	7.1	130	9.2
XV	119	17.	153	10.	119	19.

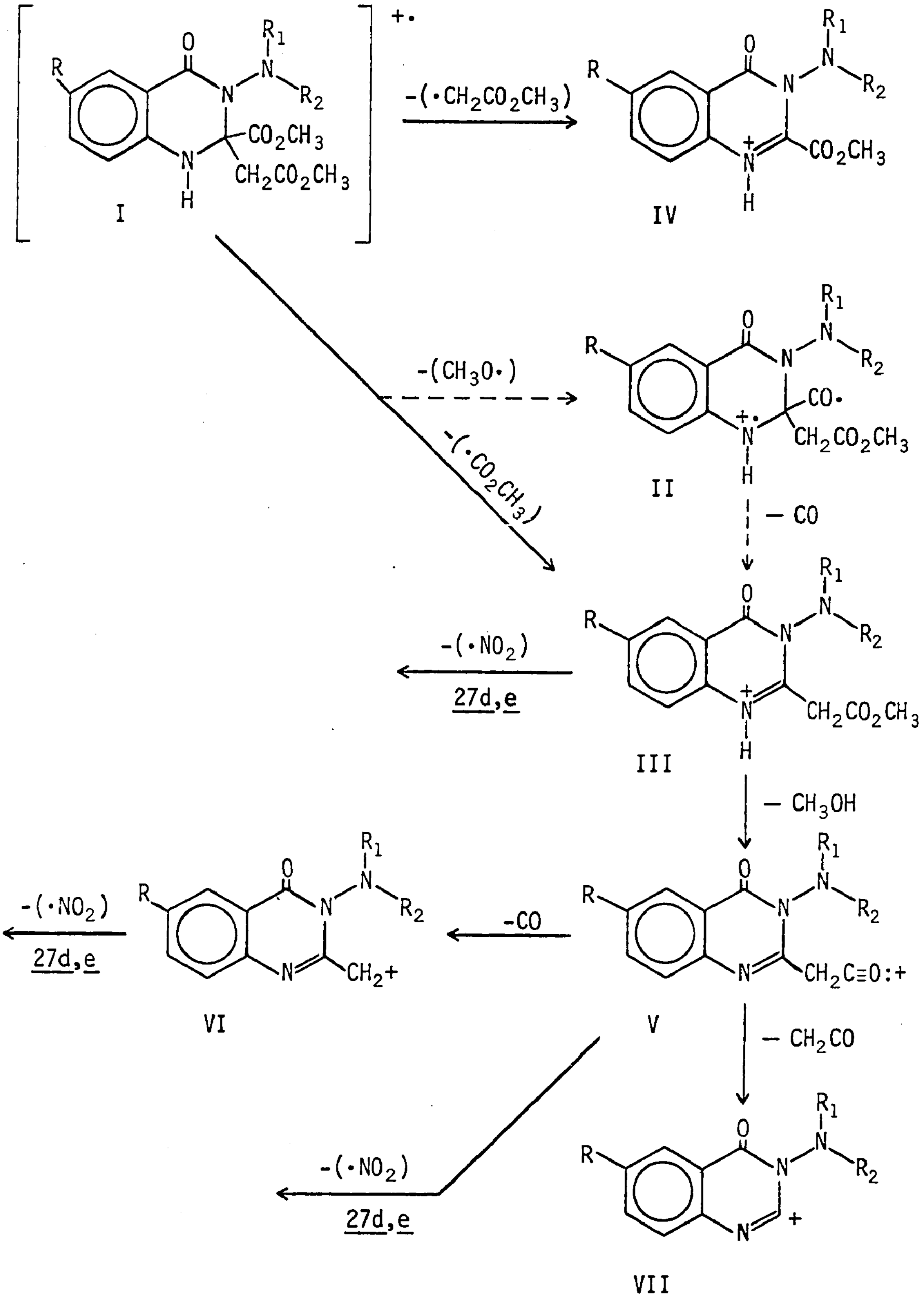
TABLE II (continued)

	27d		27e		27f	
	m/e	Relative abundance	m/e	Relative abundance	m/e	Relative abundance
I	414	6.2	448	5.1	383	43.
II	383	2.6	417	2.2	352	6.4
III	355	100.	389	100.	324	100.
IV	341	2.4	375	2.2	310	6.4
V	323	19.	357	18.	292	7.4
	309	28.	343	32.		
VI	295	4.5	329	2.9	264	4.3
VII	281	5.1	315	2.2	250	9.2
	277	10.	311	3.6		
	249	7.2	283	6.2		
VIII	234	16.	268	4.3	234	52.
IX	219	13.	253	6.2	219	86.
X	202	16.	236	14.	202	78.
XI	170	18.	204	18.	170	64.
XII	159	11.	193	8.7	159	83.
XIII	144	18.	178	8.5	144	42.
XIV	130	7.3	164	5.1	130	42.
XV	119	15.	153	12.	119	54.

TABLE II (continued)

	27g	
	m/e	Relative abundance
I	321	12.
II	290	6.3
III	262	100.
IV	248	14.
V	230	27.
VI	202	71.
VII	188	11.
VIII	234	29.
IX	219	45.
X	202	71.
XI	170	42.
XII	159	59.
XIII	144	26.
XIV	130	22.
XV	119	21.

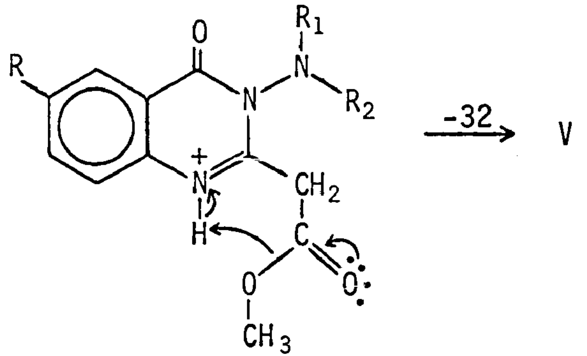
Scheme 1


I
II
III
IV
V
VI
VII
-(•CH2CO2CH3)
-(CH3O•)
-(•CO2CH3)
- CO
-(•NO2)
27d,e
- CH3OH
-CO
- CH2CO

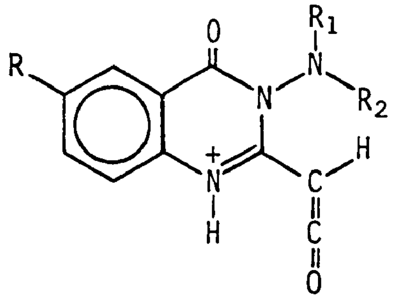
The substitution of a carbomethoxy and carbomethoxymethyl in the 2-position was clearly demonstrated by the presence of ions corresponding to the loss of these pendent groups. The loss of $\cdot CO_2CH_3$ (59 a.m.u.) and $\cdot CH_2CO_2CH_3$ (73 a.m.u.) would result in structures of type III and IV respectively. Whether these ions are the result of a stepwise fragmentation (as indicated by the broken line in Scheme 1) or the direct loss of the pendent group cannot be ascertained from the available data.

In compounds 29d,e ion III is further fragmented by the loss of the nitro group in each case. In 29d this fragmentation is verified by a metastable ion at the calculated value of m/e 268.9 (m/e 355 ⟶ m/e 309). Likewise, the transition from m/e 389 to m/e 343 in 29e is represented by a metastable ion at m/e 302.4.

Ion V which represents the loss of CH_3OH from III can arise by the concerted, cyclic process shown below. The direct loss of CH_3OH from the side-chain ester would lead to the isomeric species V'. The direct loss of methanol from the methyl ester is known in some aliphatic esters.[27]



III



V'

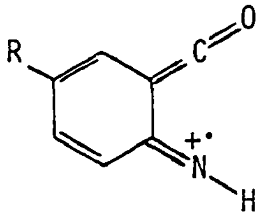
The loss of 32 mass units from III is verified by a metastable ion at the calculated value in nearly all 27. Two representative cases are 27a and 27b with calculated values of m/e 249.3 (m/e 310 ⟶ m/e 278) and m/e 283.0 (m/e 344 ⟶ m/e 312) respectively.

Further fragmentation of V can lead to ions VI and VII. Ion VI represents the loss of CO from V while VII can result from the loss of ketene from V. The loss of CO is verified by a metastable ion at m/e 224.8 (m/e 278 ⟶ m/e 250) for 27a. Several other 27 also have this metastable ion at the appropriate value.

Both ions VI and VII also show the loss of the nitro group (46 a.m.u.) from R_2 in 27d,e. This loss is similar to that seen from ion III.

Ion XIII represents the bare quinazolinone ring system and could result from several different fragmentation pathways. In particular, ion VII could split off the 3-substituent to give XIII.

The retro Diels-Alder cleavage, similar to that of 3-hydroxyquinazolinones previously discussed,[8b] was present in all 27.



XV

A comparison of the fragment ions VIII-XV demonstrates the assignment of the quinazolinone structure to 27. Comparison of 27a,c,d,f, and g shows that ions VIII-XV are independent of the substituent in the

3-position. This is also seen in 27b and e where VIII-XV are increased in value by the substituent in the 6-position as compared to 27a. From this information it can be said that the lower mass fragments VIII-XV contain the quinazolinone portion of the molecule without the 3-substituent.

The fragment ions in the mass spectra of 27a-e are identical to those in the mass spectra of 27f,g which have been proven to be quinazolinones. The identity of the fragment ions clearly substantiates the assignment of 27a-e as quinazolinones.

EXPERIMENTAL SECTION

Melting points were determined between glass slide covers on a Fisher-Johns block and are reported uncorrected in degrees centigrade.

The ultraviolet spectra were recorded on a Perkin-Elmer 402 ultraviolet-visible spectrophotometer. Infrared spectra were obtained in Nujol or the neat state with a Perkin-Elmer spectrophotometer. Nmr spectra were recorded on a Hitachi Perkin-Elmer Model R-20A spectrometer using tetramethylsilane (TMS) as an internal standard. Data are presented in the order δ (multiplicity, number of protons, assignment).

Mass spectra were run by J. 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°C below the melting or boiling point at 80 eV. Peak positions were assigned relative to peaks found in the fragmentation pattern of perfluorokerosene.

The thin layer chromatograms were developed on either silica gel 1B-F or aluminum oxide 1B-F Baker-flex sheets.

Microanalyses were provided by Dr. G. I. Robertson of Florham Park, New Jersey.

Anthranilophenylhydrazide (17a). Phenylhydrazine (39.6 g, 0.36 mol) was slowly added to a stirred suspension of 30.0 g (0.18 mol) of isatoic anhydride in 100 ml of EtOH. The reaction mixture was heated to just below reflux for 2 hours, then stirred for 24 hours. The precipitate was filtered off, washed with 50 ml of EtOH, and recrystallized from EtOH to yield 29.9 g (72%) of white 17a: mp 173-5°: lit. mp 170°;[28]

ir (Nujol mull) 3430, 3340 (primary N-H), 3240 (N-H) and 1650, 1618 cm^{-1} (hydrazide C=O).

1-(2-Amino-5-chlorobenzoyl)-2-phenylhydrazine (17b). A suspension of 31.0 g (0.16 mol) of 5-chloroisatoic anhydride and 34.0 g (0.32 mol) of phenylhydrazine was reacted as above to give 32.5 g (79%) of 17b: mp 203-6°: lit. mp 203-5°;[19] ir (Nujol mull) 3480, 3410, 3360, 3300 (N-H) and 1660, 1610 cm^{-1} (hydrazide C=O).

1-(2-Aminobenzoyl)-2-(4-chlorophenyl) hydrazine (17c). A solution of 7.3 g (0.18 mol) of NaOH in 100 ml of EtOH was added to a slurry of 33.1 g (0.18 mol) of 4-chlorophenylhydrazine in 300 ml of EtOH. The solution was cooled to 4°, the NaCl filtered off by suction, and 30.0 g (0.18 mol) of isatoic anhydride were added to the filtrate with no evolution of CO_2. The reaction mixture was refluxed for 24 hours and then cooled to 4° for 24 hours. The reaction mixture was filtered to remove 16.1 g of 17c, concentrated to one-third volume, and 14.2 g of 17c were filtered to give a combined yield of 63%. Recrystallization from benzene yielded pure 17c: mp 187-8°; ir (Nujol mull) 3460, 3440, 3410, 3570, 3270 (N-H) and 1650, 1615 cm^{-1} (hydrazide C=O).

Anal. Calcd. for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.95; H, 4.63; N, 16.04.

1-(2-Aminobenzoyl)-2-(4-nitrophenyl) hydrazine (17d). Isatoic anhydride (40.0 g, 0.25 mol) was added to a slurry of 4-nitrophenylhydrazine (37.6 g, 0.25 mol) in 250 ml of EtOH. The reaction mixture was refluxed with stirring for 24 hours, during which time solid was continually present. Filtration of the solid yielded 36.8 g (59%) of 17d.

Recrystallization from EtOH afforded pure yellow <u>17d</u>: mp 233-5°; ir (Nujol mull) 3480, 3380, 3350, 3240 (N-H) and 1630, 1610 cm^{-1} (hydrazide CO).

<u>Anal.</u> Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.12; H, 4.55; N, 20.67.

<u>1-(2-Amino-5-chlorobenzoyl)-2-(4-nitrophenyl) hydrazine (17e)</u>. Equimolar quantities (0.20 mol) of 4-nitrophenylhydrazine and 5-chloroisatoic anhydride were reacted as in <u>17d</u> to yield 33.2 g (53%) of <u>17e</u>. Recrystallization from EtOH gave pure yellow <u>17e</u>: mp 258-60°; ir (Nujol mull) 3480, 3380, 3340, 3240 (N-H) and 1630, 1620 cm^{-1} (hydrazide C=O).

<u>Anal.</u> Calcd. for $C_{13}H_{11}ClN_4O_3$: C, 50.90; H, 3.71; N, 18.26. Found: C, 51.02; H, 3.72; N, 17.91.

<u>1-(2-Methylaminobenzoyl)-2-phenylhydrazine (17f)</u>. A mixture of 25.0 g (0.14 mol) of N-methylisatoic anhydride and 30.4 g (0.28 mol) of phenylhydrazine was reacted as in <u>17a</u> to yield 20.4 g (60%) of <u>17f</u>. Recrystallization from benzene yielded pure <u>17f</u>: mp 130-2°; ir (Nujol mull) 3410, 3260 (N-H) and 1630, 1610 cm^{-1} (hydrazide C=O); nmr (DMSO-d_6) δ 10.05 (S, 1, N-$\underline{H}$), 7.8-6.4 (m, 9, Ar-$\underline{H}$), 6.1 (broad S, 2, N-H), and 2.76 ppm (S, 3, N-C$\underline{H}_3$).

<u>Anal.</u> Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.39; H, 6.40; N, 17.15.

<u>1-(2-Aminobenzoyl)-2,2-dimethylhydrazine (18)</u>. An EtOH slurry of 50.0 g (0.30 mol) of isatoic anhydride was reacted with 27.2 g (0.45 mol) of 1,1-dimethylhydrazine. After the evolution of CO_2 ceased the reaction mixture was refluxed for 2 hours. Cooling for 24 hours yielded

24.2 g (44%) of 18. Recrystallization from benzene provided pure 18: mp 140-1°; ir (Nujol mull) 3420, 3300, 3220 (N-H) and 1635, 1620 cm^{-1} (hydrazide C=0).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.26; H, 7.54; N, 23.74.

1-(2-Aminobenzoyl)-2-methyl-2-phenylhydrazine (19). Use of the method of Kirchner and Zalay[15] to prepare 19 resulted only in the isolation of starting material and methyl anthranilate. A modification utilizing 16.8 g (0.10 mol) of isatoic anhydride in 80 ml of 1,4-dioxane was refluxed with 12.6 g (0.10 mol) of 1-methyl-1-phenylhydrazine for 72 hours. Cooling to room temperature resulted in a precipitate with mp 239-41° which evolved CO_2 on heating at the mp. This product was tentatively identified as 21; ir (Nujol mull) 3200 (N-H), 3300-2500 (broad COOH), and 1690, 1675 cm^{-1} (acid and urea C=0). *In vacuo* concentration of the dioxane solution yielded 21.4 g (88%) of a viscous oil which was used subsequently as 19. All attempts to obtain crystalline 19 were unsuccessful.

1-(2-Aminobenzoyl)-1,2-dimethylhydrazine (20). A mixture of 16.3 g (0.10 mol) of isatoic anhydride, 14.6 g (0.11 mol) of 1,2-dimethylhydrazine, and 50.5 g (0.20 mol) of triethylamine was refluxed with stirring for 16 hours in 200 ml of absolute pyridine. During the reflux period there was solid present. After cooling, the salt was filtered with suction and the filtrate was concentrated *in vacuo* to an oil. The oil was dissolved in 100 ml of benzene and extracted 4 times with 100 ml portions of 2N HCl. The combined HCl extracts were neutralized with NaOH with the temperature being maintained below 20°. The neutralized solution was extracted 8 times with 100 ml portions of benzene, the combined benzene layers were dried over $MgSO_4$, and the benzene was removed *in vacuo*. The resulting semisolid was dissolved in 20 ml of toluene and cooled in dry ice/acetone. The solid which initially formed became an oil, but the addition of petroleum ether and agitation while warming to room temperature resulted in 12.1 g (68%) of solid 20. Recrystallization from diethylether yielded pure 20: mp 62-4°: lit. mp 63-5°;[20] ir (Nujol mull) 3420, 3340, 3220 (N-H) and 1635 cm^{-1} (hydrazide C=O); nmr ($DCCl_3$) δ 7.32-6.52 (m, 4, Ar-H), 4.71 (S, 3, N-H, rapidly exchanged with D_2O), 3.14 (S, 3, N-CH_3), and 2.62 ppm (S, 3, N-CH_3).

Reader Note: For the convenience of the reader the structures of the hydrazides (17-20) utilized in the following procedures appear on pages 70-71. Those compounds designated as 27 are 2,3-dihydro-4(1H)-quinazolinones.

Dimethyl 2-[2-(carbonyl-2-N-phenylhydrazino)anilino] fumarate (25a). When 6.25 g (44.2 mmol) of 1 were added in small portions to a MeOH solution (ca. 20 mmol/100 ml) of 10.0 g (44.2 mmol) of 17a a slightly exothermic reaction resulted. While the reaction was stirred for 24 hours a yellow precipitate formed. Suction filtration yielded 12.3 g (76%) of the open adduct (25a). Recrystallization from MeOH gave pure yellow crystals of 25a: mp 176-8°; ir (Nujol mull) 3310 (N-H), 1745 (ester C=O), 1685 (chelated ester C=O), and 1665 cm^{-1} (hydrazide C=O); nmr (DMSO-d_6) δ 11.1 (S, 1, N-H, slowly exchanged with D_2O), 10.3

(S, 1, N-H, rapidly exchanged with D_2O), 7.91-6.60 (m, 10, Ar-H and N-H), 5.42 (S, 1, C=CH), 3.69 (S, 3, CO_2CH_3), and 3.65 ppm (S, 3, CO_2CH_3).

Anal. Calcd. for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.19; N, 11.38. Found: C, 62.01; H, 5.27; N, 11.48.

In vacuo concentration of the reaction mixture to ca. one-third volume resulted in a precipitate of 3.4 g (which combined with 25a accounts for 97% of 17a and 1) of 27a. The base-catalyzed synthesis of 27a is described below.

Dimethyl 2-[2-(carbonyl-2-N-phenylhydrazino)-4-chloroanilino] fumarate (25b). Equimolar quantities (50.0 mmol) of 17b and 1 were reacted as above except that a 2 hour reflux was necessary. The solid which precipitated was approximately 85% 25b and 15% 27b by nmr data. The synthesis of 27b is described below. Attempts to separate the mixture by fractional recrystallization and column chromatography were unsuccessful. The data given below are for the open adduct (25b); ir (Nujol mull) 3240 (N-H), 1750 (ester C=O), 1680 (chelated ester C=O), and 1655 cm^{-1} (hydrazide C=O); nmr ($DMSO-d_6$) δ 10.97 (S, 1, N-H, slowly exchanged with D_2O), 10.48 (S, 1, N-H, rapidly exchanged with D_2O), 7.9-6.4 (m, 8, Ar-H), 5.46 (S, 1, C=CH), 4.55 (broad S, 1, N-H), 3.70 (S, 3, CO_2CH_3), and 3.62 ppm (S, 3, CO_2CH_3).

Dimethyl 2-[2-(carbonyl-2-N-para-chlorophenylhydrazino)anilino] fumarate (25c). Equimolar quantities (45.0 mmol) of 17c and 1 were reacted as in 25a to give a 90% yield of the adduct (25c). Recrystallization from MeOH yielded pure yellow crystals of 25c: mp 153-4.5°;

ir (Nujol mull) 3360, 3320, 3250 (N-H), 1730 (ester C=0), 1690 (chelated ester C=0), and 1670 cm^{-1} (hydrazide C=0); nmr (DMSO-d_6) δ 11.08 (S, 1, N-H, slowly exchanged with D_2O), 10.35 (S, 1, N-H, rapidly exchanged with D_2O), 7.9-6.4 (m, 8, Ar-H), 7.65 (S, 1, N-H), 5.45 (S, 1, C=CH), 3.72 (S, 3, CO_2CH_3), and 3.67 ppm (S, 3, CO_2CH_3).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49; N, 10.41. Found: C, 56.49; H, 4.33; N, 10.49.

Dimethyl 2-[2-(carbonyl-2-N-para-nitrophenylhydrazino)anilino] fumarate (25d). Equimolar quantities (72.0 mmol) of 17d and 1 were reacted as in 25a. The resulting product consisted of approximately 70% 25d and 30% 27d by nmr. The synthesis of 27d is described below. The data given below are for the open adduct (25d); ir (Nujol mull) 3340, 3280 (N-H), 1725 (ester C=0), 1690 (chelated ester C=0), and 1670 cm^{-1} (hydrazide C=0); nmr (DMSO-d_6) δ 11.03 (S, 1, N-H, slowly exchanged with D_2O), 10.60 (S, 1, N-H, rapidly exchanged with D_2O), 8.1-6.6 (m, 9, Ar-H and N-H), 5.46 (S, 1, C=CH), 3.72 (S, 3, CO_2CH_3), and 3.65 ppm (S, 3, CO_2CH_3).

Dimethyl 2-[2-(carbonyl-2-N-para-nitrophenylhydrazino)-4-chloroanilino] fumarate (25e). Equimolar quantities (45.2 mmol) of 17e and 1 were reacted as in 25a to give a 95% yield of the open adduct (25e). Recrystallization from benzene yielded pure yellow crystals of 25e: mp 167-168.5°; ir (Nujol mull) 3310, 3250 (N-H), 1742 (ester C=0), 1690 (chelated ester C=0), and 1670 cm^{-1} (hydrazide C=0); nmr (DMSO-d_6) δ 10.93 (S, 1, N-H, slowly exchanged with D_2O), 10.65 (S, 1, N-H, rapidly exchanged with D_2O), 9.10 (S, 1, N-H, rapidly exchanged with D_2O), 8.15-

6.62 (m, 7, Ar-H), 5.51 (S, 1, C=CH), 3.75 (S, 3, CO_2CH_3), and 3.66 ppm (S, 3, CO_2CH_3).

Anal. Calcd. for $C_{19}H_{17}ClN_4O_7$: C, 50.85; H, 3.82; N, 12.48. Found: C, 51.04; H, 3.87; N, 12.55.

In vacuo concentration of the reaction mixture to ca. one-third volume yielded 5.77 g (which combined with 25e accounts for 95% of 17e and 1) of 27e. An alternate synthesis of 27e is described below.

Attempted reaction of 1-(2-Methylaminobenzoyl)-2-phenylhydrazine (17f) and 1. The reaction of equimolar quantities (52.0 mmol) of 17f and 1 as in 25a resulted in a viscous oil from which the pure adduct could not be isolated. The nmr showed multiple peaks for the N-CH_3 protons indicating more than one product in the oil.

Dimethyl 2-[2-(carbonyl-2,2-N-dimethylhydrazino)anilino] fumarate (25g). Equimolar quantities (56.0 mmol) of 18 and 1 in 70 ml of MeOH were allowed to react exothermically followed by stirring for 24 hours. When the mixture was cooled to 4° and the glass container scratched 12.8 g (72%) of the open adduct precipitated. Recrystallization from MeOH gave pure yellow crystals of 25g: mp 150-2°; ir (Nujol mull) 3240 (N-H), 1742 (ester C=0), 1690 (chelated ester C=0), and 1640 cm^{-1} (hydrazide C=0); nmr (DMSO-d_6) δ 10.47 (S, 1, N-H, rapidly exchanged with D_2O), 7.6-6.6 (m, 4, Ar-H), 7.5 (broad S, 1, N-H, rapidly exchanged with D_2O), 5.51 (S, 1, C=CH), 3.72 (S, 6, CO_2CH_3), and 2.62 ppm (S, 6, N-CH_3).

Anal. Calcd. for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N, 13.08. Found: C, 56.20; H, 6.10; N, 13.03.

Dimethyl 2-[2-(carbonyl-2-N-methyl-2-N-phenylhydrazino)anilino] fumarate (25f). Equimolar quantities (85.0 mmol) of 1 and the oil previously designated as 19 were reacted in 90 ml of MeOH. The slightly exothermic reaction was heated for 1 hour on a steam-bath, cooled for 20 hours, and scratching of the glass beaker crystallized 19.4 g (65%) of the open adduct. Recrystallization from MeOH yielded pure yellow 25f: mp 158-60°; ir (Nujol mull) 3320(N-H), 1723 (ester C=O), 1680 (chelated ester C=O), and 1620 cm^{-1} (hydrazide C=O); nmr ($DCCl_3$) δ 10.52 (S, 1, N-H, rapidly exchanged with D_2O), 8.53 (S, 1, N-H, rapidly exchanged with D_2O), 7.7-6.6 (m, 9, Ar-H), 5.54 (S, 1, C=CH), 3.70 (S, 6, CO_2CH_3), and 3.17 ppm (S, 3, N-CH_3).

Anal. Calcd. for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.53; H, 5.61; N, 10.84.

In vacuo concentration of the reaction mixture to ca. one-third volume yielded 6.25 g (combined with 25f this accounts for 93% of 19 and 1) of a mixture of 25f and 27f. An alternate synthesis of 27f is described below.

Reaction of 20; Preparation of 26. Equimolar quantities (56.0 mmol) of 20 and 1 were reacted in 70 ml of MeOH. The slightly exothermic reaction was allowed to stir for 5 hours, cooled, and 10.1 g (56%) of 26 were collected. Recrystallization from MeOH yielded pure yellow 26: mp 170-2°; ir (Nujol mull) 3470, 3370 (primary N-H), 1748 (ester C=O), 1697 (ester C=O), and 1665 cm^{-1} (hydrazide C=O); nmr ($DCCl_3$) δ 7.35-6.50 (m, 4, Ar-H), 4.86 (S, 1, C=CH), 4.32 (broad S, 3, N-H, rapidly exchanged with D_2O), 3.87 (S, 3, CO_2CH_3), 3.66 (S, 3, CO_2CH_3), 3.17 (S, 3, N-CH_3), and 2.95 ppm (S, 3, N-CH_3).

Anal. Calcd. for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N, 13.08. Found: C, 56.07; H, 6.03; N, 13.01.

Reader Note: The structures of compounds 25a-g appear on page 72 of this dissertation.

2-Carbomethoxy-2-carbomethoxymethyl-3-anilino-2,3-dihydro-4(1H)-quinazolinone (27a). A mixture of 5.0 g (13.4 mmol) of 25a and ca. 0.1 g of NaOMe was slowly added to a refluxing xylene (dried over dry Na) solution (ca. 30 mmol/100 ml). Not all of the solid dissolved immediately, but solution was complete after 1 hour of refluxing. The reaction was refluxed for a total of 18 hours, filtered while hot to remove a small quantity of resinous material, and allowed to cool at 4° for 5 hours. Vacuum filtration and washing of the solid with petroleum ether yielded 4.6 g (92%) of light tan 27a with mp 210-2°. Sublimation at 180°/0.03 Torr gave pure white 27a: mp 212-3°; ir (Nujol mull) 3330, 3290 (N-H), 1758 (ester C=O), 1735 (ester C=O), and 1655 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 7.8-6.5 (m, 9, Ar-H), 7.63 (S, 1, N-H), 7.35 (S, 1, N-H), 3.68 (S, 3, O-CH_3), 3.44 (S, 3, O-CH_3), and 3.12 ppm (S, 2, -CH_2-CO).

Anal. Calcd. for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.19; N, 11.38. Found: C, 62.00; H, 5.17; N, 11.59.

2-Carbomethoxy-2-carbomethoxymethyl-3-anilino-6-chloro2,3-dihydro-4(1H)-quinazolinone (27b). A mixture of 11.0 g (25.3 mmol) of 25b and 27b was reacted as in 27a. The resulting precipitate yielded 10.1 g (92%) of the desired quinazolinone. Recrystallization from MeOH gave pure white crystals of 27b: mp 207-8°; ir (Nujol mull) 3340, 3260 (N-H), 1735 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 7.95-6.55 (m, 8, Ar-H), 7.88 (S, 1, N-H), 7.53 (S, 1, N-H), 3.70 (S, 3, O-CH$_3$), 3.47 (S, 3, O-CH$_3$), and 3.12 ppm (S, 2, -CH$_2$-CO).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49; N, 10.41. Found: C, 56.62; H, 4.42; N, 10.46.

2-Carbomethoxy-2-carbomethoxymethyl-3-(4-chloroanilino)-2,3-dihydro-4(1H)-quinazolinone (27c). A MeOH solution of 7.0 g (17.3 mmol) of 25c was reacted as in 27a. Cooling of the reaction mixture yielded 6.4 g (91%) of crystalline quinazolinone. Recrystallization from MeOH or sublimation at 190°/0.03 Torr gave pure white 27c: mp 221-3°; ir (Nujol mull) 3360, 3320, 3250 (N-H), 1755 (ester C=O), 1725 (ester C=O), and 1665 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 7.72 (S, 2, N-H), 7.65-6.65 (m, 8, Ar-H), 3.69 (S, 3, O-CH$_3$), 3.48 (S, 3, O-CH$_3$), and 3.12 ppm (broad S, 2, -CH$_2$-CO).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49; N, 10.41. Found: C, 56.70; H, 4.65; N, 10.36.

2-Carbomethoxy-2-carbomethoxymethyl-3-(4-nitroanilino)-2,3-dihydro-4(1H)-quinazolinone (27d). A mixture of 20.0 g (48.3 mmol) of 25d and 27d was reacted as in 27a. After refluxing the reaction mixture for 5 hours, 19.25 g (96%) of the desired quinazolinone were obtained. Recrystallization from MeOH provided pure white crystalline 27d: mp 201-3°; ir (Nujol mull) 3342, 3240 (N-H), 1740 (ester C=O), 1732 (ester C=O), and 1670 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 8.98 (S, 1, N-H), 8.02 (S, 1, N-H), 8.26-6.70 (m, 8, Ar-H), 3.71 (S, 3, O-CH$_3$), 3.58 (S, 3, O-CH$_3$), and 3.28, 2.99 ppm (AB quartet, 2, J=16.5 Hz, -CH$_2$-CO).

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 55.31; H, 4.45; N, 13.64.

2-Carbomethoxy-2-carbomethoxymethyl-3-(4-nitroanilino)-6-chloro-2,3-dihydro-4(1H)-quinazolinone (27e). The cyclization of 20.0 g (44.5 mmol) of *25e* in refluxing xylene was effected as above, except that the reaction mixture had to be stirred because the quinazolinone was precipitating and preventing uniform boiling. The resulting precipitate represented 18.75 g (94%) of *27e*. Recrystallization from MeOH gave pure white *27e*: mp 211-2°; ir (Nujol mull) 3360, 3300 (N-H), 1755 (ester C=O), 1735 (ester C=O), and 1680 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 8.86 (S, 1, N-$\underline{H}$), 7.98 (S, 1, N-$\underline{H}$), 8.07, 7.03 (AB quartet, 4, J= 9.5 Hz, Ar-$\underline{H}$ of 4-nitroanilino moiety), 7.67 (d, 1, $J_{5,7}$=2.5 Hz, Ar-$\underline{H}_5$), 7.35 (d of d, 1, $J_{7,5}$=2.5 Hz, $J_{7,8}$=8.5 Hz, Ar-$\underline{H}_7$), 6.93 (d, 1, $J_{8,7}$= 8.5 Hz, Ar-$\underline{H}_8$), 3.73 (S, 3, O-C$\underline{H}_3$), 3.50 (S, 3, O-C$\underline{H}_3$), and 3.25, 3.00 ppm (AB quartet, 2, J=17.0 Hz, -C$\underline{H}_2$-CO).

Anal. Calcd. for $C_{19}H_{17}ClN_4O_7$: C, 50.85; H, 3.82; N, 12.48. Found: C, 51.09; H, 3.92; N, 12.65.

2-Carbomethoxy-2-carbomethoxymethyl-3-dimethylamino-2,3-dihydro-4(1H)-quinazolinone (27g). The cyclization of 9.00 g (28.0 mmol) of *25g* as in *27a* afforded 7.5 g (84%) of the quinazolinone. Recrystallization from diethylether gave pure white crystalline *27g*: mp 137-8°; ir (Nujol mull) 3270 (N-H), 1750 (ester C=O), 1736 (ester C=O), and 1645 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 7.95-6.50 (m, 4, Ar-$\underline{H}$), 5.55 (S, 1, N-$\underline{H}$), 3.71 (S, 6, O-C$\underline{H}_3$), 3.36, 3.00 (AB quartet, 2, J=16.5 Hz, -C$\underline{H}_2$-CO), 2.89 (S, 3, N-C$\underline{H}_3$), and 3.86 ppm (S, 3, N-C$\underline{H}_3$).

Anal. Calcd. for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N, 13.08. Found: C, 56.12; H, 5.99; N, 12.86.

2-Carbomethoxy-2-carbomethoxymethyl-3-(N-methylanilino)-2,3-dihydro-4(1H)-quinazolinone (27f). Treatment of 9.00 g (23.4 mmol) of 25f as in 27a resulted in a precipitate of 7.82 g of the quinazolinone. Recrystallization from MeOH or sublimation at 190°/0.03 Torr afforded pure white 27f: mp 225-7°; ir (Nujol mull) 3295 (N-H), 1752 (ester C=O), 1735 (ester C=O), and 1670 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 9.22 (S, 1, N-H), 7.95-6.55 (m, 9, Ar-H), 3.73 (S, 3, O-CH_3), 3.45 (S, 3, O-CH_3), 3.39, 3.18 (AB quartet, 2, J=17.0 Hz, -CH_2-CO), and 3.01 ppm (S, 3, N-CH_3).

Anal. Calcd. for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.90; H, 5.61; N, 10.74.

Attempted cyclizations of 26. A mixture of 1.0 g (3.2 mmol) of 26 and ca. 0.02 g of NaOMe was added to refluxing xylene as in 25a. Refluxing for 32 hours and cooling to 4° for 20 hours provided 0.87 g (87%) of 26. Concentration of the xylene *in vacuo* and dilution with petroleum ether yielded another 0.1 g of 26.

Because of the unsuccessful attempt at cyclization utilizing NaOMe/xylene, a thermal ring closure was investigated. 1.60 g (5.0 mmol) of 26 were heated to reflux in 90 ml of decalin (bp 190°) for 3 hours. After cooling for several days 1.4 g (88%) of 26 were recovered. Diphenyl ether was also used as above with the same results, i.e., only 26 was recovered.

2,2-Dimethyl-3-anilino-2,3-dihydro-4(1H)-quinazolinone 29, R=H. A solution containing 1.35 g (5.9 mmol) of 17a in 150 ml of acetone and a crystal of *p*-toluenesulfonic acid was refluxed on a steam-bath for 5 hours. *In vacuo* evaporation of the acetone gave a white crystalline solid. Recrystallization from acetone yielded 1.36 g (86%) of pure white 29, R=H: mp 237-40°; lit. mp 235.6-43.6°;[15] ir (Nujol mull) 3320, 3280, 3260 (N-H) and 1625 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 7.85-6.35 (m, 9, Ar-H), 7.63 (S, 2, N-H), and 1.51 ppm (broad S, 6, -CH_3).

2,2-Dimethyl-3-(N-methylanilino)-2,3-dihydro-4(1H)-quinazolinone (29, R=CH_3). A solution containing 10.0 g (41.5 mmol) of 19 in 150 ml of acetone was refluxed on a steam-bath for 1 hour. Cooling of the reaction mixture resulted in a precipitate of 9.50 g (82%) of 29, R=CH_3. Recrystallization from acetone gave white crystalline 29, R=CH_3: mp 231-2°; ir (Nujol mull) 3330, 3300 (N-H) and 1645 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 7.85-6.58 (m, 9, Ar-H), 6.20 (S, 1, N-H), 3.38 (S, 3, N-CH_3), 1.61 (S, 3, -CH_3), and 1.54 ppm (S, 3, -CH_3).

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.44; H, 6.92; N, 14.88.

Attempted formation of HCl salt of 27g. Diethyl ether (30 ml) was saturated with HCl gas. This solution was added with stirring to a solution of 1.00 g (3.12 mmol) of 27g in 150 ml of diethyl ether. After ca. 5 minutes the solution became cloudy and a precipitate began to form. Continued stirring for 24 hours in a stoppered Erlenmeyer flask yielded 0.75 g of a readily water soluble solid; ir (Nujol mull) 3150-2300 (broad N-H) and 1680 cm^{-1} (hydrazide C=O); nmr δ 8.32 (S, 4, N-H, rapidly exchanged with D_2O), 7.90-6.40 (m, 6, Ar-H and N-H, integrates for 4 after D_2O exchange), and 3.22 ppm (S, 6, N-C$\underline{H}_3$). Neutralization of the solid with aqueous NaOH yielded 0.5 g of the starting hydrazide (18). The addition of 2,4-dinitrophenylhydrazine to the ethereal mother liquor did not result in the formation of a hydrazone precipitate.

Methylation of 27a. Following the general procedure of Heindel, et al.[11] a solution of 0.30 g (0.82 mmol) of 27a in 2.5 ml of DMF (freshly distilled from P_2O_5) was added to 0.97 mmol of NaH in 2.0 ml of dry benzene. The dark red solution that resulted was stirred until the evolution of gases ceased (ca. 5 minutes) before the dropwise addition of 0.16 g (1.14 mmol) of MeI was initiated. The reaction mixture was then heated at 80° for 1 hour during which time the red color became a yellow-orange. The reaction was cooled to room temperature, treated with a small amount of MeOH-H_2O, and diluted with ice water until two distinct layers formed. 0.10 g of 27a was removed by filtration and the aqueous layer was separated and extracted two times with 25 ml of benzene. The benzene layers were combined, dried (Na_2SO_4), and concentrated. 0.05 g of 27a was filtered off and the remaining oil was triturated with MeOH to yield 0.10 g of solid material. The ir (Nujol mull) of this material contained a broadening in the N-H and C=O bands from that of 27a. Below are the results of the thin layer chromatography of the methylated material.

Thin layer chromatography (TLC) of the product from the methylation of 27a. The separation of 27a and 27f by TLC was shown in the following manner. The TLC plates were preheated at 120° for 1 hour before the compounds to be separated were applied. The compounds were applied as ca. 1% ethyl acetate solutions with a microcapillary. The size of the spot was limited to 3 mm or less. After the compounds were applied the plates were again heated for 15 minutes at 120°. The plates were developed in an Eastman Chromagram Developing Apparatus (cat. no. 6071). The silica gel plates were developed with 65% benzene/35% ethyl acetate by volume for 30-45 minutes. The aluminum oxide plates were developed with 80% ethyl acetate/20% acetone by volume for 30-45 minutes. Visualization was achieved by using a uv light source on the fluorescent indicator. By simultaneously developing three spots consisting of 27a, 27f, and a mixture of 27a and 27f on both silica gel and aluminum oxide the following data were obtained.

Compound	R_f Value	TLC Composition
27a	0.69±0.04	Silica gel
27f	0.37±0.04	Silica gel
27a	0.72±0.04	Aluminum oxide
27f	0.49±0.04	Aluminum oxide

When the methylation product was developed simultaneously with 27a and 27f on silica gel two major components separated from the methylated mixture. These two compounds had R_f values identical with the R_f values of 27a and 27f. There were also two minor components with R_f values less than 0.30.

On the aluminum oxide the methylated product was also developed simultaneously with 27a and 27f. Here again two major components separated from the mixture with R_f values identical with the R_f values of 27a and 27f. There was also a minor component which had an R_f value of 0.21.

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