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THE UNIVERSITY OF ALBERTA

THE SYNTHESES AND PROPERTIES OF N-HYDROXYBENZOTHIAZINES AND RELATED COMPOUNDS

by

© NORMAN JACK POUND, B.S.P., M.Sc.

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

Faculty of Pharmacy and
Pharmaceutical Sciences

EDMONTON, ALBERTA

FALL, 1970

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Syntheses and Properties of N-Hydroxybenzothiazines and Related Compounds" submitted by Norman Jack Pound in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

R. T. Coutts
Supervisor

A. Casy

R. Bodnaryk C.

John W. Steele
External Examiner

Date May 20, 1970.

ABSTRACT

The primary objective of the research described in this thesis was the study of the syntheses and properties of N-hydroxy compounds, prior to their pharmacological evaluation.

Three 1,3-disubstituted 4-(o-nitrophenylthio)-2-pyrazolin-5-ones were prepared, then reduced with sodium borohydride and palladium-charcoal. These reactions yielded 9,9a-dihydro-9-hydroxy-1H-pyrazolo-[4,3-b]-1,4-benzothiazines and novel 2-pyrazolin-4-spiro-2'-benzothiazoline derivatives.

The reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one with catalyzed sodium borohydride, and subsequent treatment with hydrochloric acid gave rise to an unexpected product, 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. Closer investigation revealed that the action of hydrochloric acid on 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and on 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one yielded chlorinated compounds. An extention of this reaction to the treatment of benzothiazine and benzoxazine hydroxamic acids with hydrochloric acid was found to give lactam derivatives which contained chlorine.

During the course of this work, an occasion arose to prepare 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine

from the hydroxamic acid, 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine. It was found that the reaction of this hydroxamic acid with acetyl chloride gave the desired 4-acetoxy derivative; however, when acetic anhydride was employed as the acetylating agent, the 2-acetoxy lactam was formed. Similar reactions were carried out on 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine. In this instance it was found that treatment of this hydroxamic acid with acetyl chloride yielded the 4-acetoxy derivative, whereas the action of acetic anhydride unexpectedly gave rise to 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine. Rearrangements involving the acetoxy groups of these acetylated hydroxamic acids were also investigated.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. R.T. Coutts for his able supervision and personal interest throughout the course of this research.

The financial assistance, in the form of a studentship, from the Medical Research Council of Canada is gratefully acknowledged.

Finally, thank you to Miss V. McLeod for the very capable typing of this thesis.

TO MY WIFE, JANICE -

HER PATIENCE, FORBEARANCE AND UNDERSTANDING

MADE THE COMPLETION OF THIS THESIS POSSIBLE.

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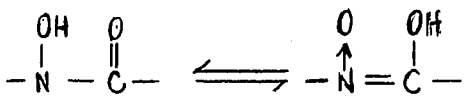
INTRODUCTION

INTRODUCTION

The initial purpose of the project described in this thesis was to determine whether reductive cyclizations of appropriate aromatic nitro compounds would yield new cyclic N-hydroxy compounds which were required for pharmacological evaluation. A brief review of the information available on cyclic N-hydroxylamines is now given.

The most commonly known cyclic N-hydroxy compounds are the hydroxamic acids. These compounds are characterized by the presence of the hydroxamate grouping (1), i.e., they are N-hydroxy lactams. Reviews on these compounds have appeared recently in the literature (Coutts, 1967, 1967a; Bapat, Black, and Brown, 1969). Since this information is readily available, the discussion which follows will be restricted to those N-hydroxy derivatives which may be more correctly defined as cyclic N,N-dialkylhydroxylamines (2).



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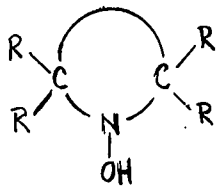


2

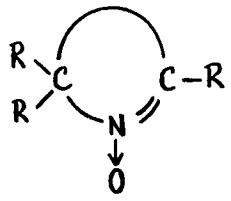
Because these compounds are indexed in abstracts under the name of the parent cyclic amine, a complete literature search for N-hydroxy compounds is nearly impossible. As a result, the following discussion, while extensive, is not to

be considered as an exhaustive review. It is meant to be simply an outline of the methods of synthesis and some of the chemical properties of cyclic hydroxylamines.

Syntheses

Reduction of Nitrones

A common method of synthesizing cyclic hydroxylamines involves the reduction of a class of N-oxide derivatives generally known as nitrones (3).

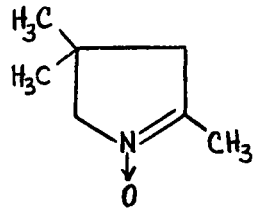


3

Nitrones, recently the subject of a review themselves, (Delpierre and Lamchen, 1965) are readily prepared by the oxidation of heterocyclic compounds, by the alkylation of oximes, or by the reduction of suitably substituted nitro aldehydes and ketones. It is of interest that one synthetic route is by mild oxidation of N,N-disubstituted hydroxylamines.

Bonnett and co-workers (1959) found that Δ'-pyrroline 1-oxides were readily reduced to cyclic secondary hydroxylamines with aqueous potassium borohydride. For example, whereas the reduction of 2,4,4-trimethyl- Δ'-pyrroline 1-oxide (4) with tin and hydrochloric acid gave 2,4,4-trimethylpyrrolidine (5), and milder agents such as zinc dust and

acetic acid, or sulfur dioxide in chloroform yielded the Δ^{1}-pyrroline derivative (6), reduction in aqueous potassium borohydride gave a good yield of 1-hydroxy-2,4,4-trimethyl-pyrrolidine (7).



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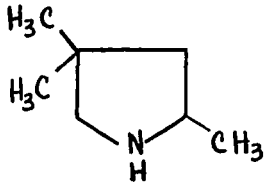

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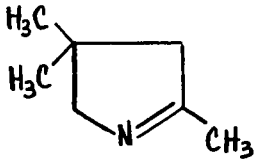

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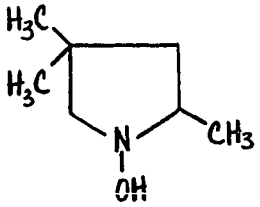
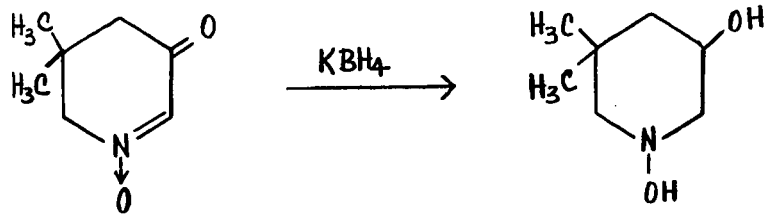


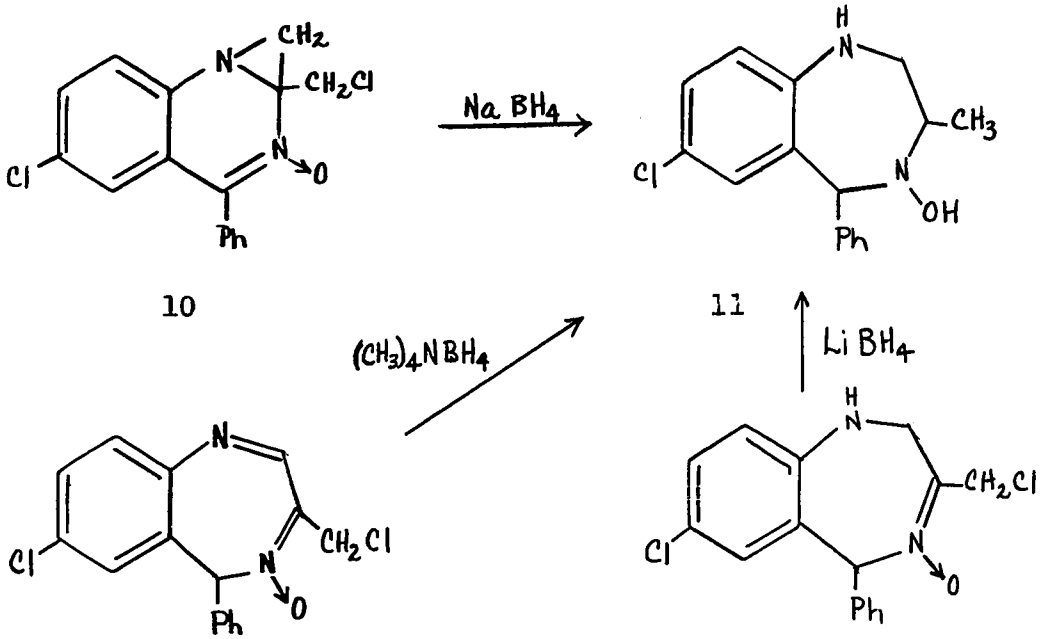
7

Similarly, 1,5-dihydroxy-3,3-dimethylpiperidine (8) was prepared by the potassium borohydride reduction of 1,2,3,4-tetrahydro-3,3-dimethyl-5-oxo-pyridine 1-oxide (9) (Brown, Clark and Todd, 1959a).



9 8

Other borohydrides have also been used for this purpose. During the synthesis of benzodiazepine derivatives, it was found that sodium borohydride in diglyme could be used in a ring-expanding reduction procedure to convert 10 to the N-hydroxy compound (11) (Hoffmann - La Roche, 1966). The same compound (11) was also prepared by the action of tetramethyl ammonium borohydride and lithium borohydride on compounds 12 and 13 respectively. Other related N-hydroxy derivatives have also been reported (Field, Zally and Sternbach, 1966).

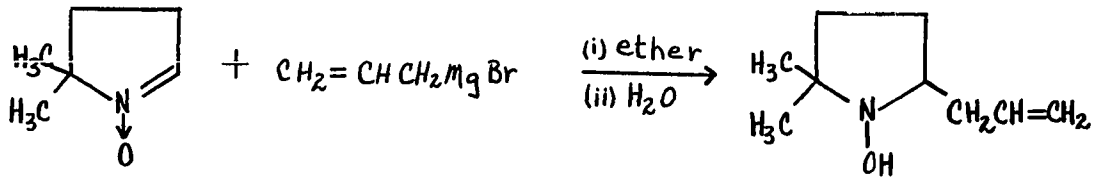


10 11 12 13

Addition to Nitrones

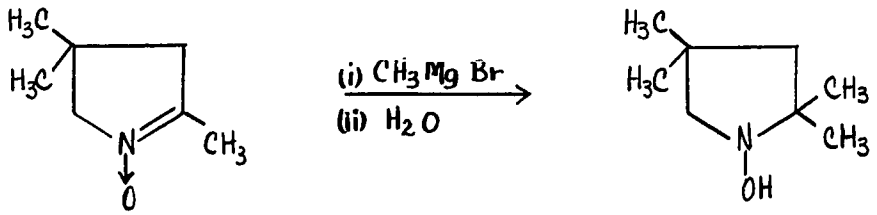
Cyclic hydroxylamines can also be prepared by adding various reagents across the double bond of the nitrone. Grignard reagents are the ones most commonly used. Allylmagnesium bromide, for example, reacts with 5,5-dimethyl-

△'-pyrroline 1-oxide (14) to form 2-allyl-1-hydroxy-5,5-dimethylpyrrolidine (15) (Delpierre and Lamchen, 1963).



14 15

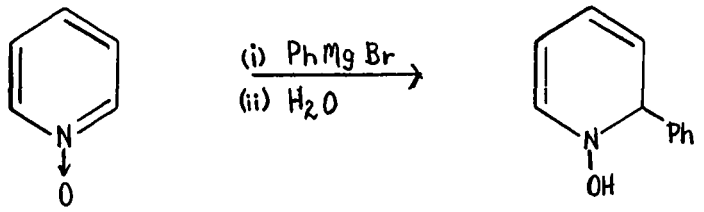
In a similar manner, Bonnett and co-workers (1959) prepared 1-hydroxy-2,2,4,4-tetramethylpyrrolidine (16) from 2,4,4-trimethyl-△'-pyrroline 1-oxide (4) and methylmagnesium bromide. The 2-ethyl-2-methyl derivative of 16 was also prepared by using ethylmagnesium bromide.



4 16

Kato and Yamanaka (1965) were able to prepare 1-hydroxy-2-phenyl-1,2-dihydropyridine (17) and 1-hydroxy-2-phenyl-1,2-dihydroquinoline (18) by the action of phenylmagnesium bromide on pyridine 1-oxide (19) and quinoline 1-oxide (20) respectively. It should be noted that attempts to repeat these reactions using 4-substituted quinoline 1-oxides (21) failed

to yield any 1-hydroxy compounds. Only derivatives of 2-phenylquinoline (22) and 2-phenylquinoline 1-oxide (23) were isolated.



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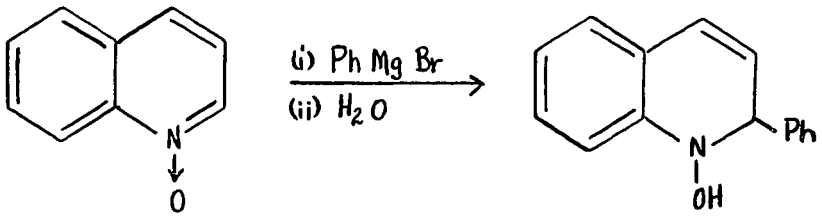

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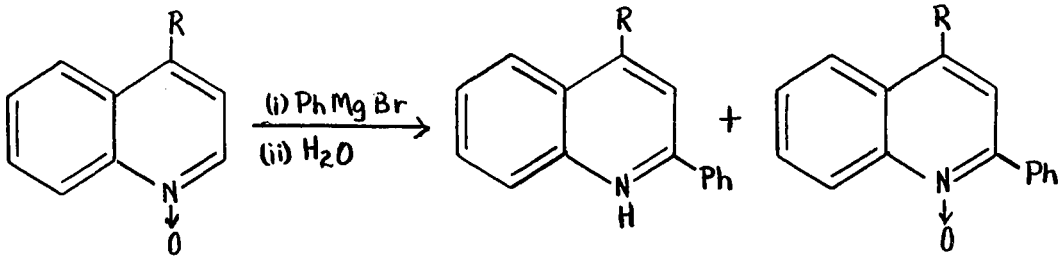
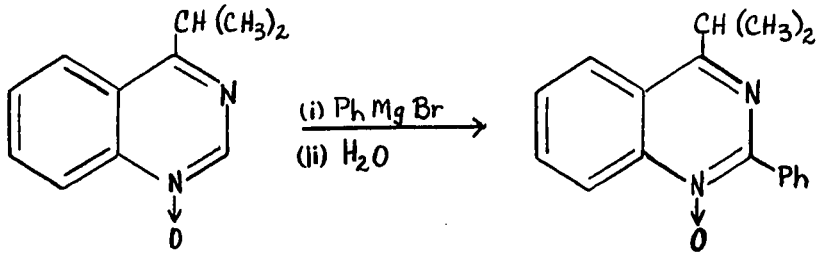


21 22 23

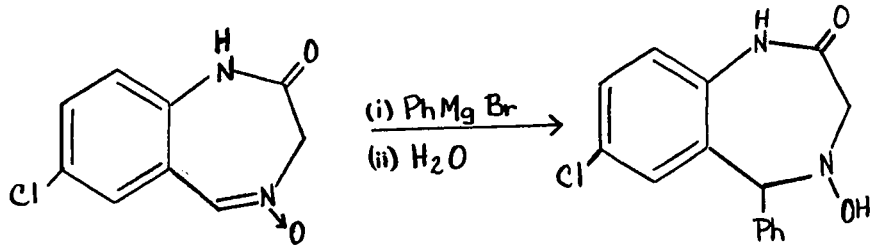
These observations are in agreement with similar results obtained by Hayashi and Higashino (1964). These investigators found that the reaction of 4-isopropylquinazoline 1-oxide (24) with phenylmagnesium bromide gave rise to 2-phenyl-4-isopropylquinazoline 1-oxide (25). No N-hydroxy

derivatives were reported.



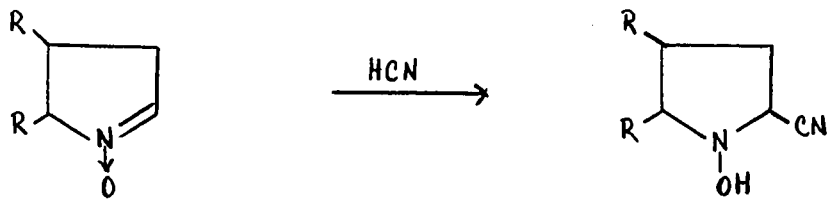
24 25

4-Hydroxy-5-phenyl-7-chloro-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (26), a compound structurally related to the previously described benzodiazepines (11), has been prepared by the action of phenylmagnesium bromide on the N-oxide, 27 (Grindstedvaerket, 1967).



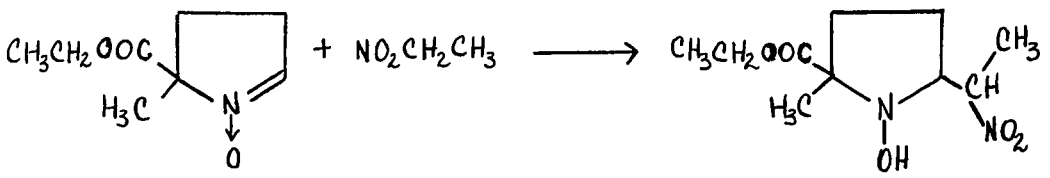
27 26

Other reagents have been found to add across the N-oxide function of nitrones. Hydrogen cyanide is reported to react with △'-pyrroline 1-oxides (28) and give rise to 2-cyano-1-hydroxypyrrolidines (29) (Bonnett et al, 1959).



28 29

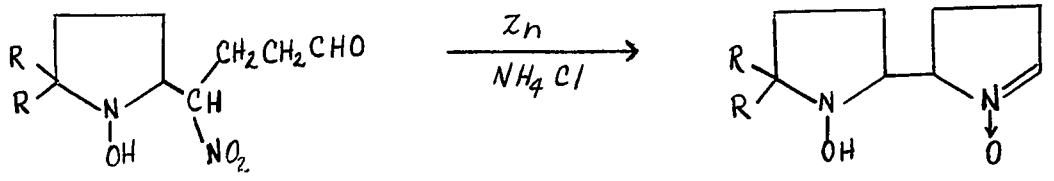
Bowering and co-workers (1963) have found that base catalyzed addition of nitro alkanes to nitrones gives 2-substituted N-hydroxy compounds. An example of this is the addition of nitroethane to 5-carbethoxy-5-methyl-Δ'-pyrroline 1-oxide (30) in the presence of Triton B (aqueous benzyltrimethylammoniumhydroxide) which results in the preparation of 5-carbethoxy-1-hydroxy-5-methyl-2-(1-nitroethyl)-pyrrolidine (31).



30 31

The same investigators have reported that reduction of a nitrobutyraldehyde derivative (32) by means of zinc dust and aqueous ammonium chloride resulted in the formation of a nitrone-hydroxylamino compound (33). Similar nitrone-hydroxylamines have also been prepared by a base catalyzed aldol type of condensation involving two nitrones. While most nitrones show little tendency to dimerize on storage,

Brown and co-workers (1959) found that 2,4,4-trimethyl-Δ'-pyrroline 1-oxide (4) would react with 4,5,5-trimethyl-Δ'-pyrroline 1-oxide (34) or 3,3,5,5-tetramethyl-Δ'-pyrroline 1-oxide (35) in the presence of triphenylmethylsodium to yield two nitrone-hydroxylamines. These products were identified as 2-(1'-hydroxy-4',5',5'-trimethylpyrrolidin-2'-ylmethyl)-4,4-dimethyl-Δ'-pyrroline 1-oxide (36) and 2-(1'-hydroxy-3',3',5',5'-tetramethylpyrrolidin-2'-ylmethyl)-4,4-dimethyl-Δ'-pyrroline 1-oxide (37) respectively.



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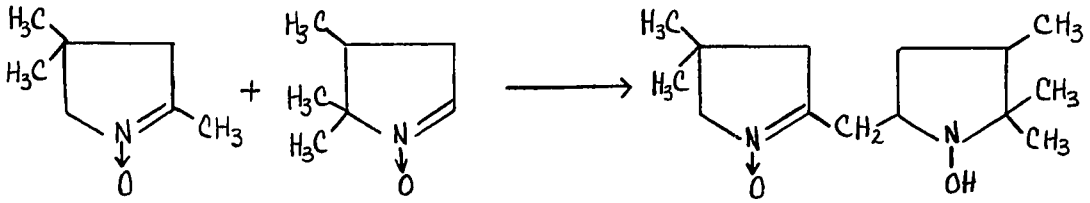
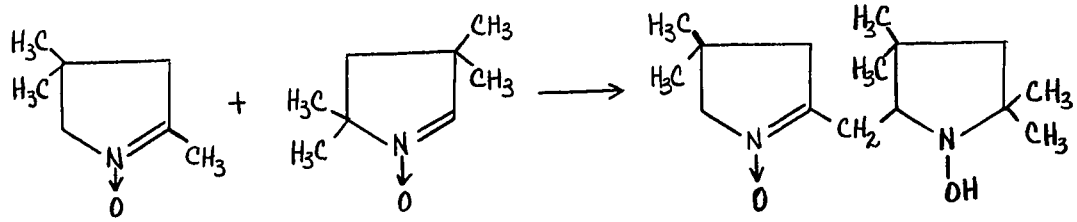
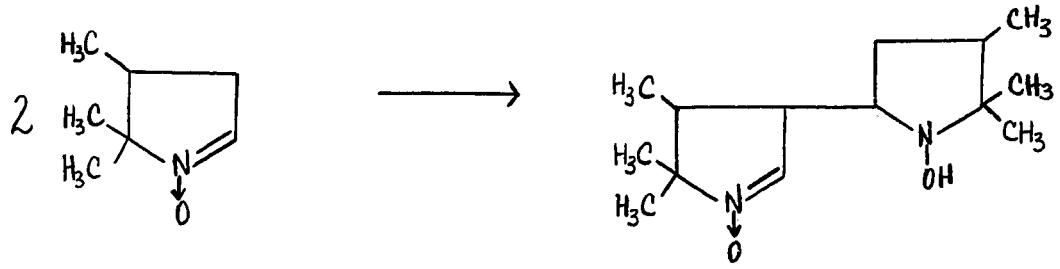


4 34 36



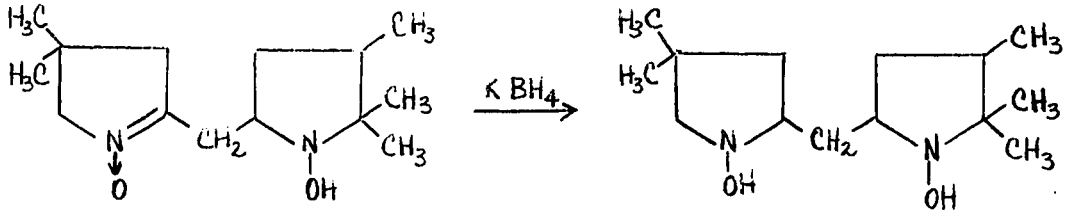
4 35 37

Similarly, the treatment of 4,5,5-trimethyl-Δ'-pyrrolidine 1-oxide (34) with triphenylmethylsodium gave a low yield of 3-(1'-hydroxy-4',5',5'-trimethylpyrrolidin-2'-yl)-4,5,5-trimethyl-Δ'-pyrroline 1-oxide (38).



34 38

These investigators have also reported that a dihydroxy derivative, 1,1'-dihydroxy-4,4,4',5',5'-pentamethyl-2,2'-dipyrrolidinylmethane (39), can be prepared by the reduction of 36 with aqueous potassium borohydride.



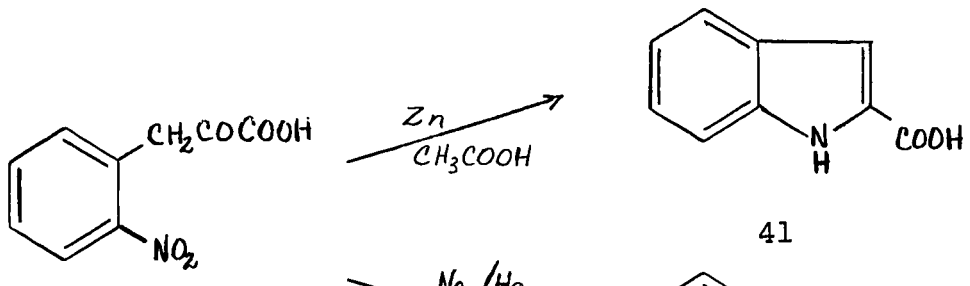
36 39

Reductive Cyclizations

Cyclic hydroxylamines have also been prepared by reductive cyclization of suitable precursors. It is well known that oximes are readily synthesized from the inter-

action of hydroxylamine with aldehydes and ketones. Nitrones are formed if N-substituted hydroxylamines are used. If the hydroxylamine and carbonyl functions are suitably orientated in the same molecule, the products are usually cyclic nitrones. In fact, the reduction of ɣ-nitro-aldehydes or ketones with zinc dust and aqueous ammonium chloride can be considered as a general synthesis of five-membered cyclic nitrones (Bonnett et al, 1959). However, there have also been several reports in which the reduction of nitro carbonyl compounds have given rise to cyclic hydroxylamines rather than the expected nitrones.

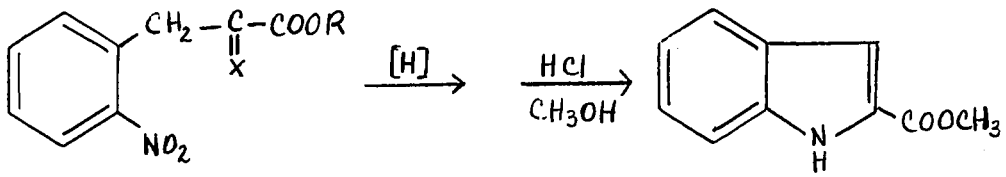
Reissart (1897) investigated the reduction of 2-nitrophenylpyruvic acid (40) and found that whereas reduction with zinc and acetic acid gave indole-2-carboxylic acid (41), reduction with sodium-amalgam gave a good yield of 1-hydroxyindole-2-carboxylic acid (42). Similar results were obtained when 4-methyl-2-nitrophenylpyruvic acid was reduced.



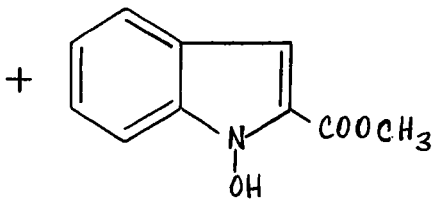
40 41 42

The preparation of 1-hydroxyindole-2-carboxylic acid (42) by the reduction of either o-nitrophenylpyruvic acid or its methyl ester with sodium borohydride in the presence of palladium-charcoal has also been reported (Coutts and Wiberley, 1963).

Several N-hydroxyindole derivatives are obtained when the oximes of 2-nitrophenylpyruvic acid and its ethyl ester (43) are catalytically hydrogenated (Baxter and Swan, 1967). For example, when oxime 43 (R=H; X=NOH) was hydrogenated over Adam's catalyst, and the product esterified, the methyl esters of indole-2-carboxylic acid (44) and 1-hydroxyindole-2-carboxylic acid (45) were isolated. The esters, present in a ratio of 2:3, were separated by chromatography.



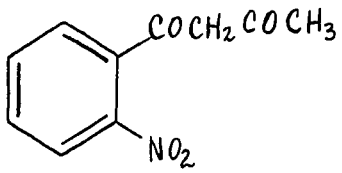
43 44



45

Gabriel and Gerhard (1921) have reported the results of reducing o-nitrobenzoylacetone (46) with stannous chloride and hydrogen iodide. This gave rise to an oxygenated prod-

uct which these investigators felt could be represented by one of the following structures, 47, 48 or 49.



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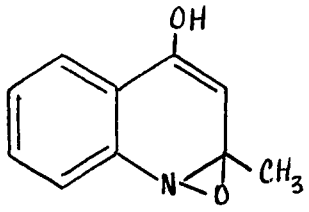

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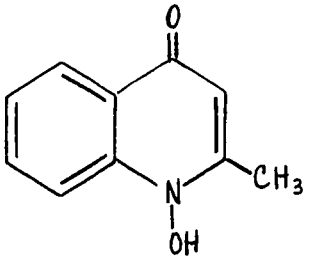

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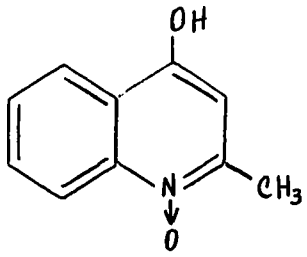
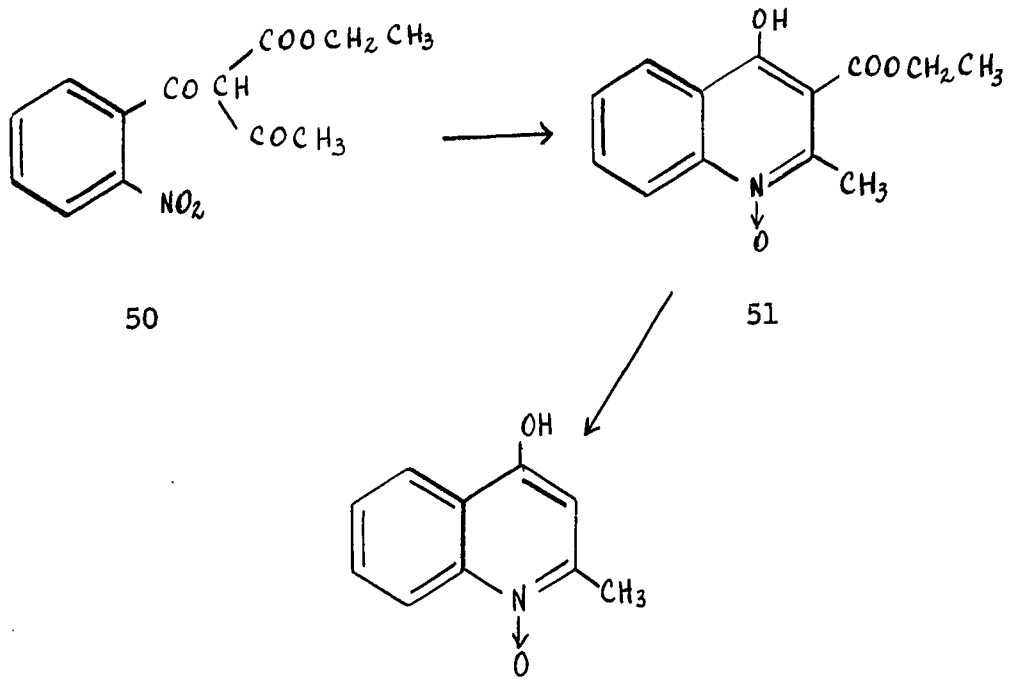


49

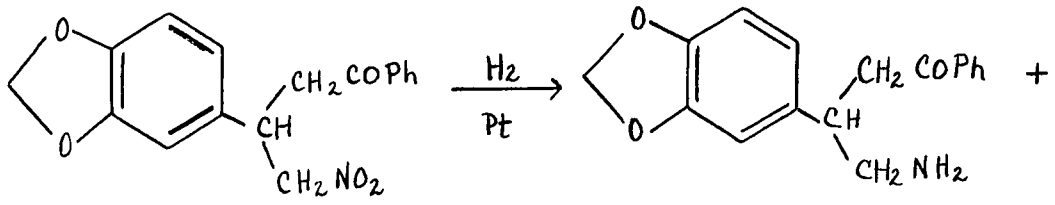
This work was investigated further by McCluskey (1922), who was able to reduce ethyl o-nitrobenzoylacetoacetate (50) with stannous chloride and hydrochloric acid in acetic acid to 3-carbethoxy-4-hydroxy-2-methylquinoline 1-oxide (51). By hydrolysis and decarboxylation of 51, McCluskey was able to prepare 4-hydroxy-2-methylquinoline 1-oxide (49) which was found to be identical to the oxygenated compound reported by Gabriel and Gerhard.



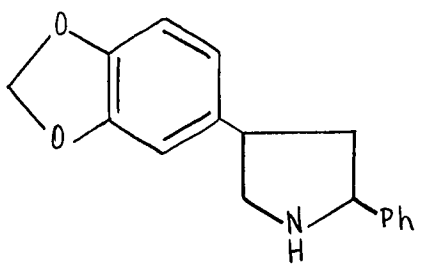
50 51

49

The hydrogenation of 3-(3,4-methylenedioxyphenyl)-4-nitro-1-phenyl-1-butanone (52) over platinum black resulted in three products, the amino ketone (53), the pyrrolidine (54), and a hydroxylated pyrroline, which Kohler and Drake (1923) identified as either 55 or 56.

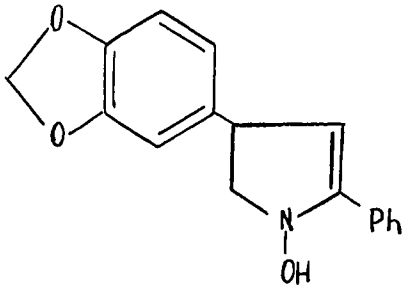


52 53



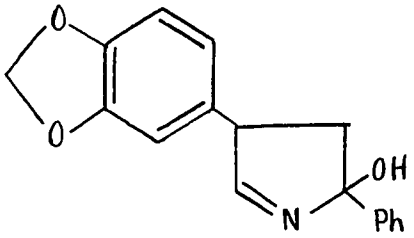
54

+



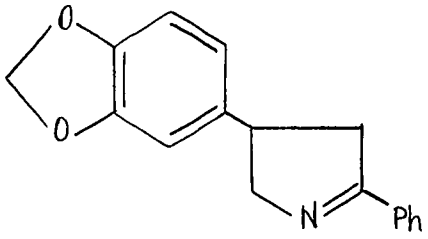
55

OR

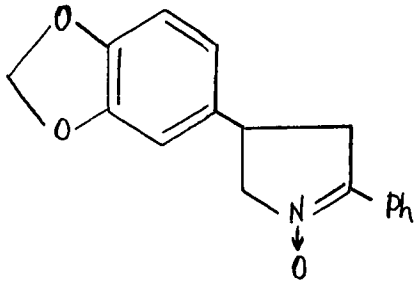


56

These results were questioned by Kloetzel and Pinkus (1958) who reduced 52 with hydrogen over platinum black and Raney nickel and with zinc dust and aqueous ammonium chloride, but they were able to isolate only one product, 4-(3,4-methylenedioxyphenyl)-2-phenyl-Δ'-pyrroline (57).



57

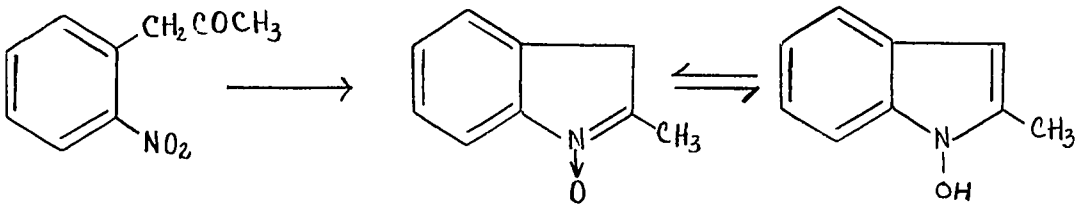


58

In an attempt to clarify these reports, Bonnett and co-workers (1959) investigated further the reduction of 52 with zinc dust and aqueous ammonium chloride. These workers

obtained a 40% yield of 4-(3,4-methylenedioxyphenyl)-2-phenyl-Δ'-pyrroline 1-oxide (58). Physical data confirmed that this compound was identical to the oxygenated compound reported by Kohler and Drake.

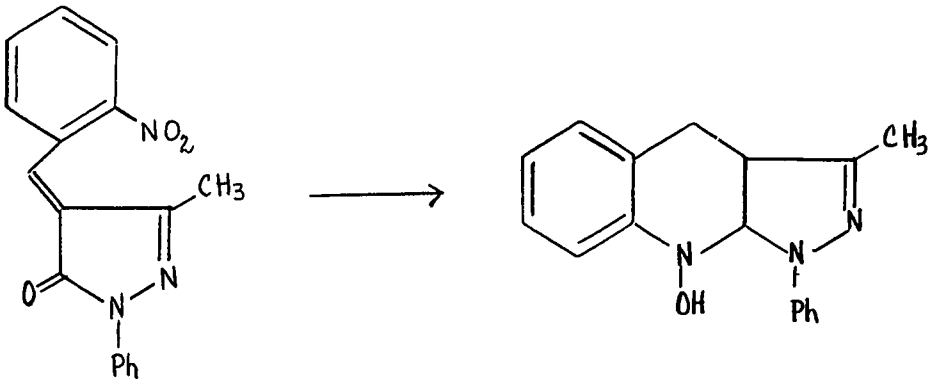
Mausseron-Canet, Boca and Tabacik (1967) isolated an oxygenated product, which they identified as 2-methylindolenine 1-oxide (59), from the reduction of o-nitrobenzylmethylketone (60) with zinc and ammonium chloride. Extensive n.m.r. studies by these workers have shown that the nitrone (59) and the enolic tautomer (61) exist in an equilibrium. The relative proportions of the two tautomers that are present in solution depends on the nature of the solvent. In very polar solvents, such as phenol, for example, the solution contains 100% of the nitrone (59), while in less polar solvents such as acetonitrile, only the 1-hydroxy tautomer (61) is present.



60 59 61

Narang, Ray, and Singh (1934) were able to prepare an N-hydroxy compound, 3a,4,9,9a-tetrahydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[3,4-b]-quinoline (62) by reducing 3-methyl-4-(o-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (63)

with either aluminum-amalgam or with zinc dust and acetic or hydrochloric acid.



63 62

Coutts and Edwards (1966) extended this work to study the reduction of related 4-(o-nitrobenzylidene)-2-pyrazolin-5-one derivatives. These investigators found that while a reducing system of either zinc dust and acetic acid or sodium borohydride and palladium-charcoal did yield some N-hydroxy derivatives, consistent results were obtained only when cyclohexene and palladium-charcoal were employed as the reducing agent. A fourth method, using hydrazine hydrate and palladium-charcoal, was abandoned when it was found that this reagent caused the degradation of the pyrazolone ring.

Syntheses from o-Substituted Nitrobenzenes

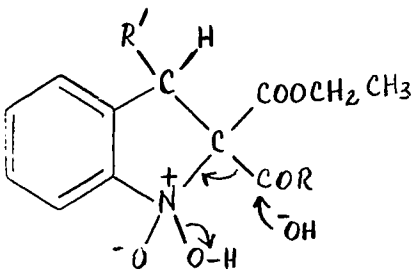
The rather extensive studies on the substituent interactions of o-substituted nitrobenzenes have been the subject of a review (Loudon and Tennant, 1964). Frequently the products arising from these acid and base catalyzed reactions

have been identified as N-hydroxy compounds.

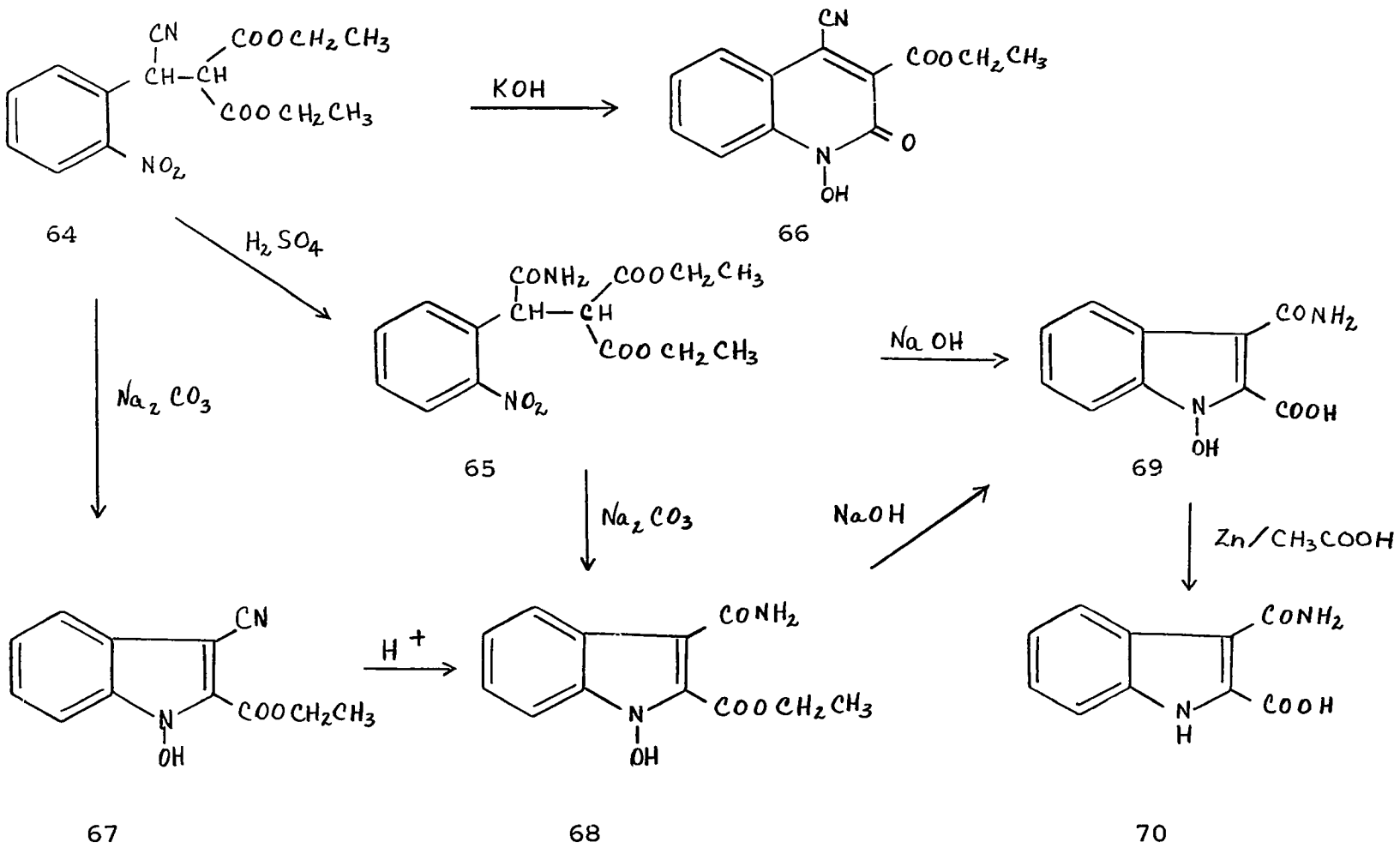
Cyclizations involving alkali

Loudon and Wellings (1960) investigated some base catalyzed reactions of diethyl ∝-cyano-∝-2-nitrobenzylmalonate (64) and its hydrolysis product, diethyl ∝-carbamoyl-∝-2-nitrobenzylmalonate (65). They found that the action of ethanolic potassium hydroxide on 64 gave the hydroxamic acid (66); however, when 64 was treated with sodium carbonate, ethyl 3-cyano-1-hydroxyindole-2-carboxylate (67) was obtained. Similarly, the action of aqueous sodium carbonate on 65 gave rise to the corresponding amide-ester (68), whereas, the amide-acid derivative (69) was obtained when aqueous sodium hydroxide was employed. The N-hydroxy indole ester (67) is readily hydrolyzed with dilute acid to the amide-ester (68), which in turn may be converted to the amide-acid (69) with aqueous sodium hydroxide. The action of zinc dust and acetic acid readily converted 3-carbamoyl-1-hydroxyindole-2-carboxylic acid (69) to 3-carbamoylindole-2-carboxylic acid (70) (Scheme 1).

It was suggested by these investigators that the formation of the N-hydroxyindoles involved an intermediate of the type shown below (71).

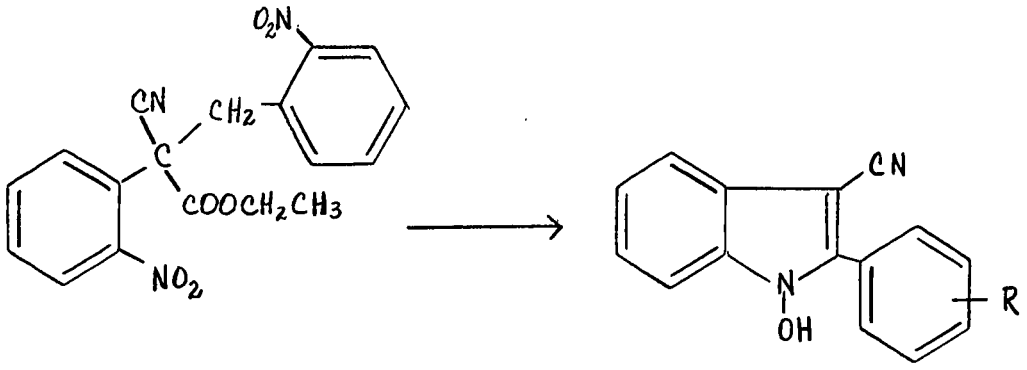


71


CN
COOCH2CH3
CH—CH
COOCH2CH3
NO2
64
KOH
CN
COOCH2CH3
O
N
OH
66
H2SO4
CONH2
COOCH2CH3
CH—CH
COOCH2CH3
NO2
65
Na2CO3
NaOH
CONH2
COOH
N
OH
69
Na2CO3
NaOH
Zn/CH3COOH
CN
COOCH2CH3
N
OH
67
H+
CONH2
COOCH2CH3
N
OH
68
CONH2
COOH
N
H
70

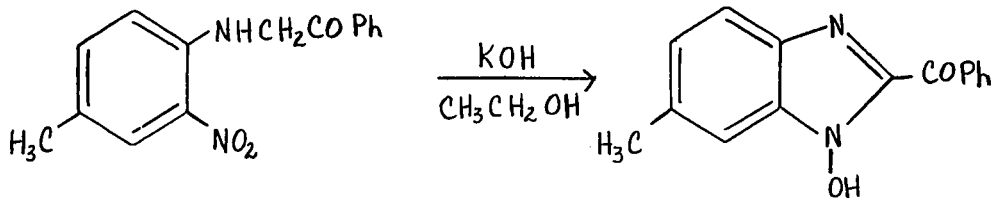
Scheme 1

A modification of the procedure described above has been used for the synthesis of substituted 3-cyano-1-hydroxy-2-phenylindoles (72) (Petracek, 1967). For example, treatment of an ethanolic solution of ethyl ∝-(o-nitrophenyl)-∝-(o-nitrobenzyl)cyanoacetate (73) with aqueous potassium carbonate yielded 3-cyano-1-hydroxy-2-(o-nitrophenyl)-indole (72; R=o-NO_2).



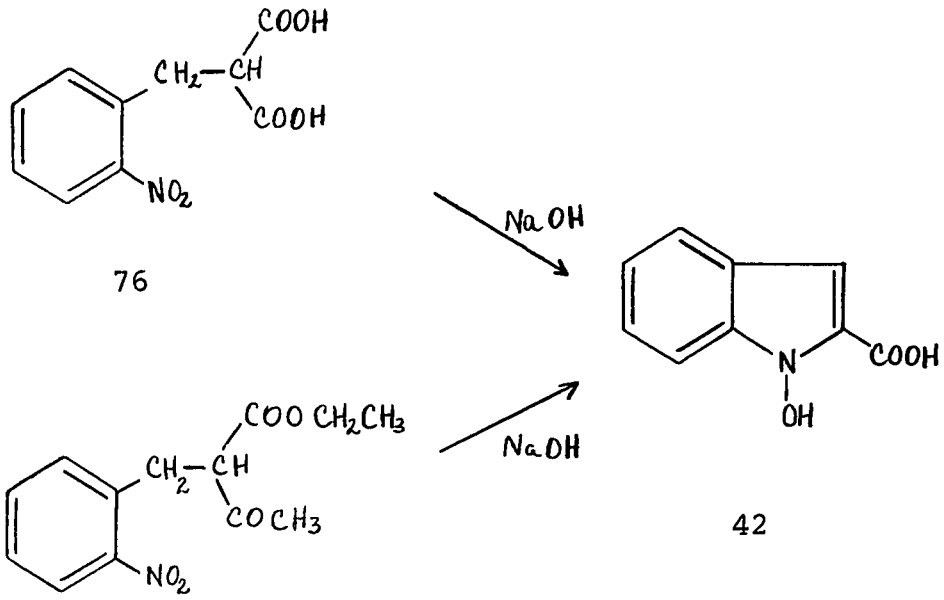
73 72

Similar base catalyzed reactions have been adapted to the synthesis of benzimidazoles (Loudon and Tennant, 1963). Treatment of 2-nitro-4-phenylacyl-p-toluidine (74) with ethanolic potassium hydroxide produced 2-benzoyl-1-hydroxy-6-methylbenzimidazole (75).



74 75

Other base catalyzed reactions have been reported. Reissart (1896) found that the action of aqueous sodium hydroxide on 2-nitrobenzylmalonic acid (76) gave rise to 1-hydroxyindole-2-carboxylic acid (42). Gabriel, Gerhard and Wolter (1923) have also described the formation of 1-hydroxyindole-2-carboxylic acid (42) by treating ethyl ∝-(2-nitrobenzyl)acetoacetate (77) with aqueous sodium hydroxide.



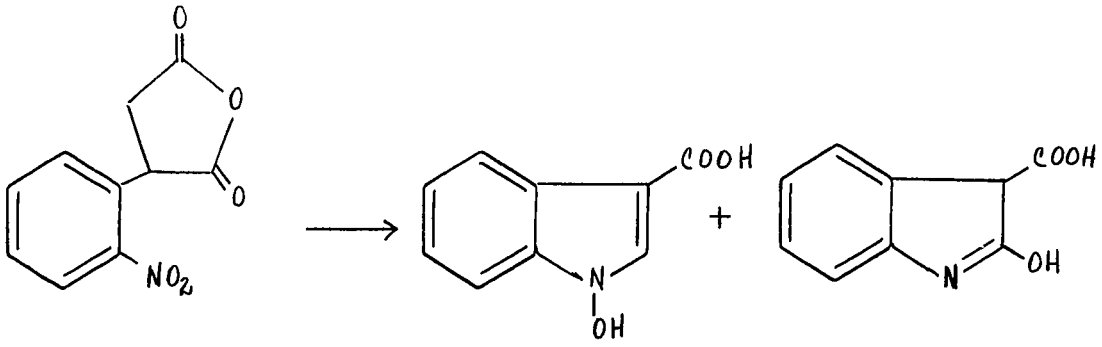
76

42

77

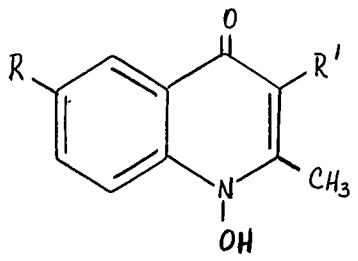
Cyclizations involving acid

An acid catalyzed cyclization procedure has also been reported for the synthesis of 1-hydroxyindole-3-carboxylic acid (79) (Askam and Deeks, 1968). The action of fluorosulfonic acid on o-nitrophenylsuccinic anhydride (78) gives rise to both 1-hydroxyindole-3-carboxylic acid (79) and oxindolic acid (80).



78 79 80

o-Nitrobenzaldehyde reacts with ethyl acetoacetate and acetylacetone in the presence of hydrogen chloride to give derivatives of 6-chloro-1-hydroxy-2-methyl-4-quinolone (81a) (Loudon and Wellings, 1960a). In this way, 3-acetyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline (81b) was obtained from o-nitrobenzaldehyde and acetylacetone. When, however, hydrogen bromide was used, the result was the formation of a halogen-free 1-hydroxy derivative (81c) (Loudon and Tennant, 1962).



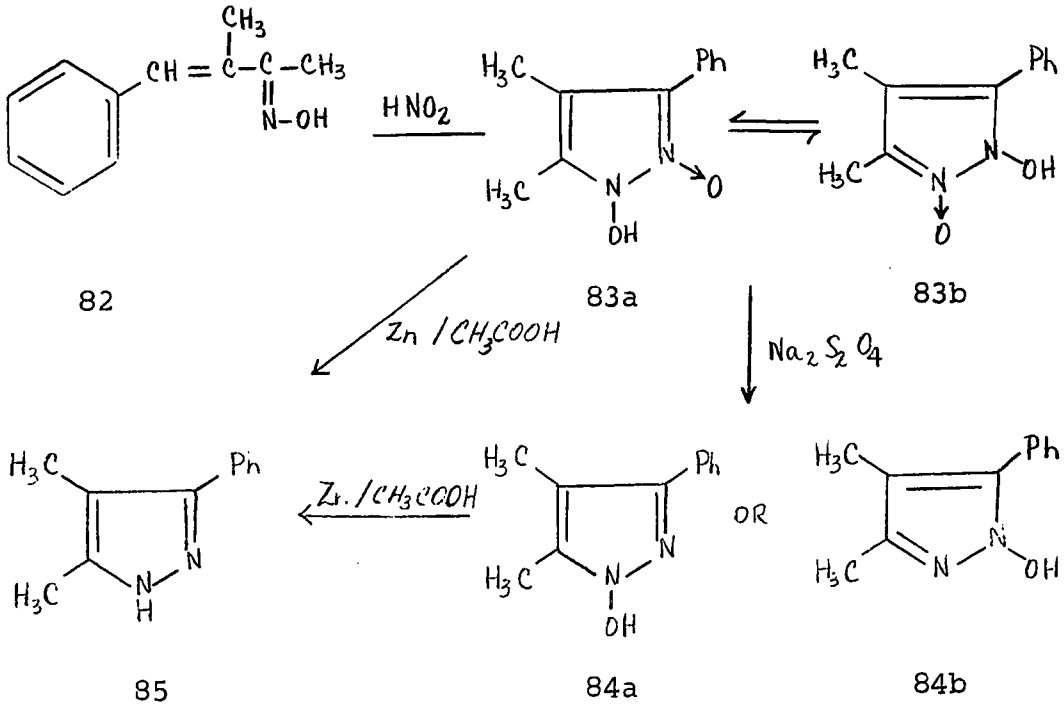
81 a) R=Cl; R'=H

b) R=Cl; R'=$COCH_3$

c) R=H; R'=$COCH_3$

The synthesis of a novel N-hydroxypyrazole derivative

has recently been reported in the literature. Freeman and Gannon (1966) found that nitrosation of 2-methyl-1-phenyl-but-1-on-3-one oxime (82) produced 1-hydroxy-4,5-dimethyl-3-phenylpyrazole-2-oxide (83a) which can also exist as the 2-hydroxy-1-oxide tautomer (83b). This compound was soluble in dilute alkali, chelated readily with metals, and could be reduced with sodium hydrosulfite to an N-hydroxypyrazole (84a or b). While the substitution pattern of this pyrazole was not determined, only one product was formed. Reduction of 83 with zinc and acetic acid gave rise to 4,5-dimethyl-3-phenylpyrazole (85). This product was also obtained from the zinc and acetic acid reduction of 84.



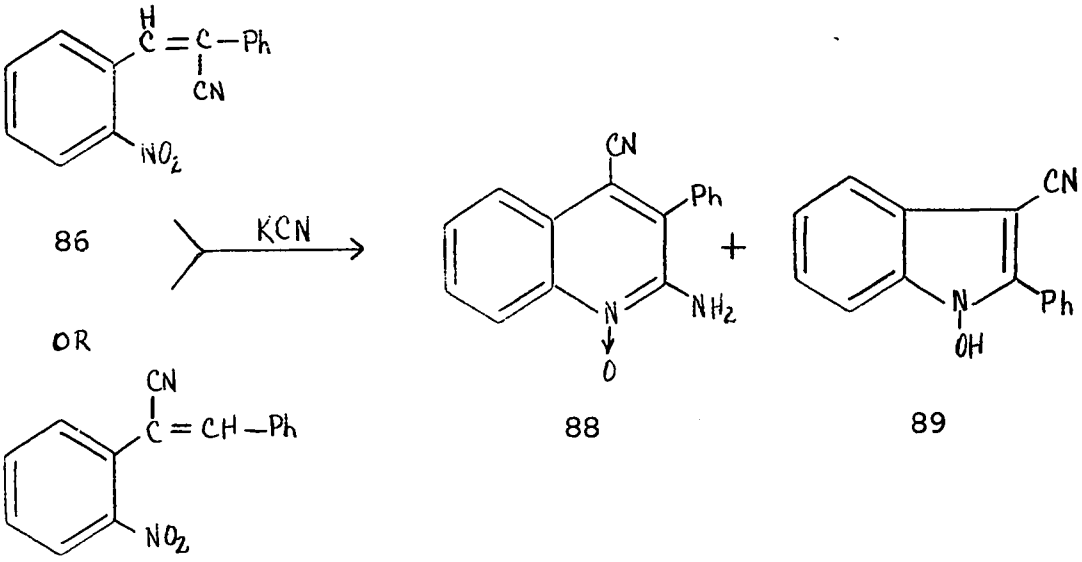
82 83a 83b

85 84a 84b

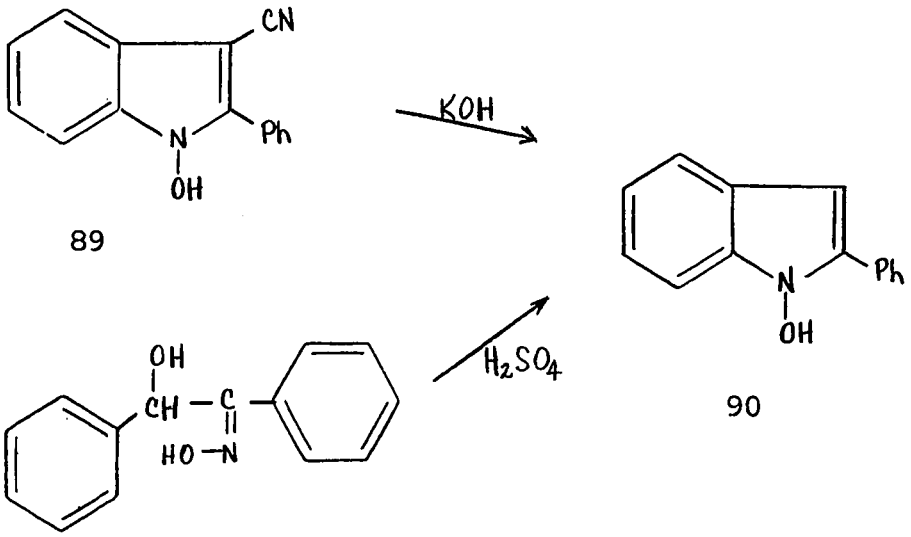
Cyclizations involving potassium cyanide

The action of potassium cyanide on o-substituted

nitro compounds has also been shown to produce N-hydroxy derivatives. A typical example is the treatment of o-nitro-∝-phenylcinnamonitrile (86) or ∝-o-nitrophenyl-cinnamonitrile (87) with aqueous potassium cyanide which yielded a mixture of 2-amino-4-cyano-3-phenylquinoline N-oxide (88) and 3-cyano-1-hydroxy-2-phenylindole (89) (Loudon and Tennant, 1960). By carefully controlling the reaction conditions, either of these products could be obtained at will.

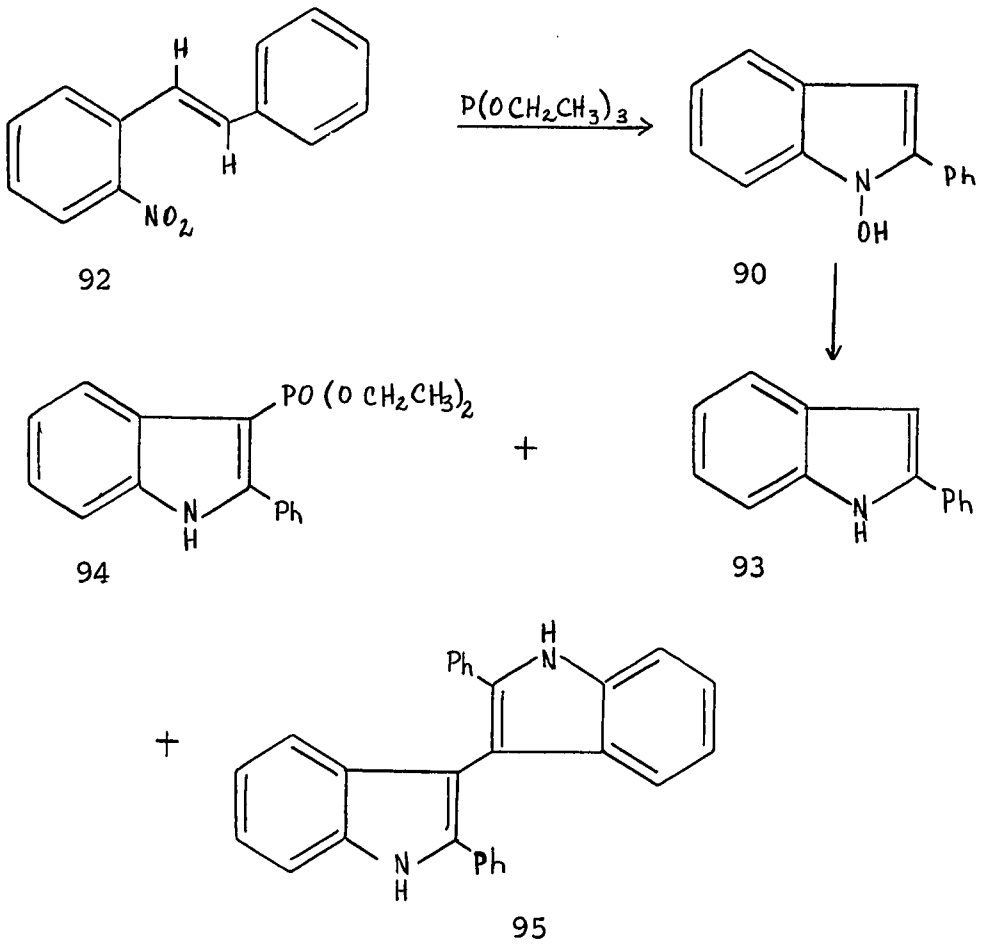


Alkaline hydrolysis of the N-hydroxyindole (89) also resulted in decarboxylation and gave rise to 1-hydroxy-2-phenylindole (90). This indole had originally been prepared by Fischer and Hütz (1895) by treating benzoin oxime (91) with concentrated sulfuric acid.



89 91 90

An additional means of synthesizing 1-hydroxy-2-phenylindole (90) has been reported more recently. Sundberg (1965), during his investigations of trivalent phosphorous compounds, found that the action of triethylphosphite on trans-2-nitrostilbene (92) yielded 2-phenylindole (93) as well as traces of two other compounds (94 and 95). 1-Hydroxy-2-phenylindole (90) was postulated as an intermediate in the formation of these reaction products. When the reaction was interrupted after one hour and extracted with dilute sodium hydroxide and then the alkaline solution acidified, 1-hydroxy-2-phenylindole (90) was precipitated.



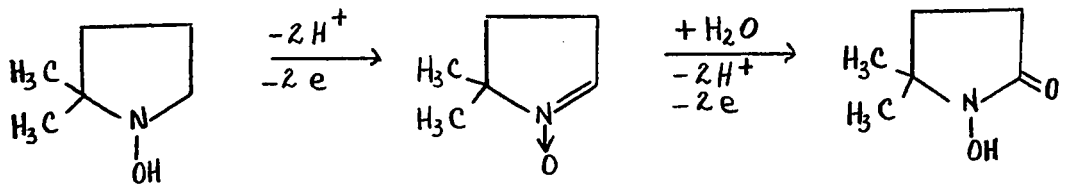
92 90 94 93 95

Chemical Properties

No extensive studies on N-hydroxy compounds have been performed, and as a result little is known about their chemical behaviour. They are acidic; therefore, they are readily soluble in dilute alkali and are re-precipitated with acid. Due to their highly polar character they tend to be high melting solids with a relatively low solubility in organic solvents.

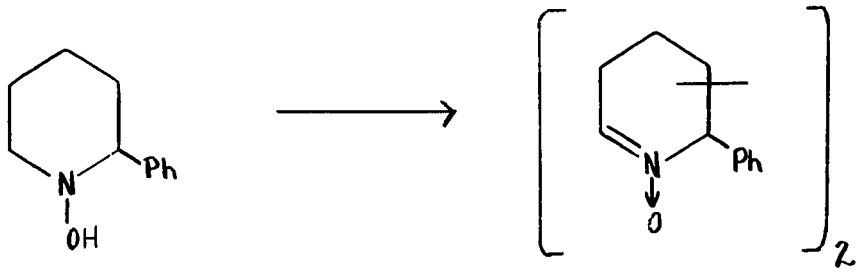
These compounds can be synthesized by the reduction of nitrones, and relatively mild oxidation will convert them back to nitrone derivatives. Frequently the passage

of oxygen (air) into an aqueous solution of the hydroxylamine in the presence of a suitable catalyst, such as a copper-ammonia complex, is sufficient to oxidize these compounds (Brown et al, 1959). Other oxidizing agents such as mercuric oxide, hydrogen peroxide and potassium ferricyanide have also been used successfully (Delpierre and Lamchen, 1965). Ferric chloride has been found to oxidize the hydroxylamine (96) to the corresponding hydroxamic acid (97) via a nitrone intermediate (Elsworth and Lamchen, 1966).

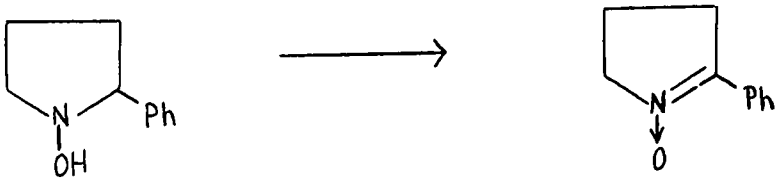


96 97

Cyclic hydroxylamines readily reduce Tollen's reagent (Habib and Rees, 1962). In some cases the stability of the cyclic hydroxylamine and the course of the oxidation have been found to be dependent on subtle steric effects (Delpierre and Lamchen, 1965). The mercuric oxide oxidation of 1-hydroxy-2-phenylpiperidine (98), for example, gave a nitrone dimer (99) in which the N-oxide group was not in conjugation with the aromatic ring, whereas, the same reagent oxidized 1-hydroxy-2-phenylpyrrolidine (100) to a nitrone (101) in which the nitrone double bond and the phenyl ring were conjugated.



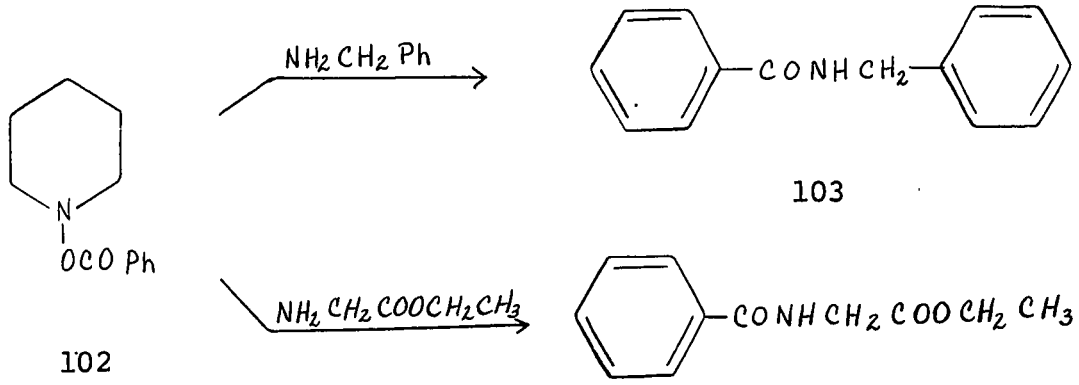
98 99



100 101

These N-hydroxy compounds react with acetyl, benzoyl, and toluene-p-sulfonyl chlorides to form acetates, benzoates, and toluene-p-sulfonates. Acetic anhydride has also been used as an acetylating agent (Loudon and Wellings, 1960). Studies have shown that the cyclic N-acetoxy carbonyl group absorbs infrared radiation in the region of 1800 cm^{-1}. As few functional groups absorb strongly in this region, the presence of such an absorption band in a spectrum is very diagnostic (Loudon and Tennant, 1960; Loudon and Wellings, 1960, 1960a; Coutts et al, 1968; Paquette, 1965; Ohta and Ochiai, 1962). Sammes in 1965 investigated the possibility of employing o-acyl-N,N-dialkylhydroxylamines as acetylating and benzoylating reagents. N-Benzoyloxypiperidine (102), prepared by the action of benzoyl peroxide on piperidine, was found to

react with benzylamine and ethyl aminoacetate producing N-benzylbenzamide (103) and ethyl hippurate (104) respectively. N-Acetoxypiperidine was shown to be a more reactive acetylating agent.

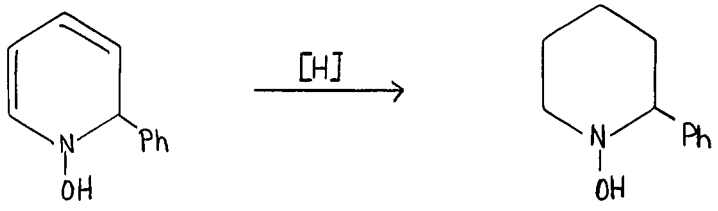


102

103

104

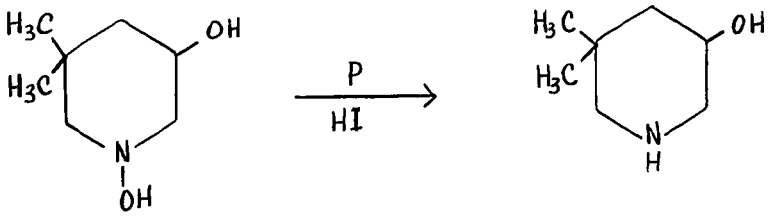
The N-hydroxy function of cyclic hydroxylamines is resistant to catalytic reduction. This is illustrated by the results of the catalytic hydrogenation of 1-hydroxy-2-phenyl-1,2-dihydropyridine (17) with palladium-charcoal which yielded 1-hydroxy-2-phenylpiperidine (98) (Kato and Yamanaka, 1965). However, hydrogenation of the acetate, benzoate, or toluene-p-sulfonate derivatives of cyclic hydroxylamines results in the formation of cyclic amines.



17

98

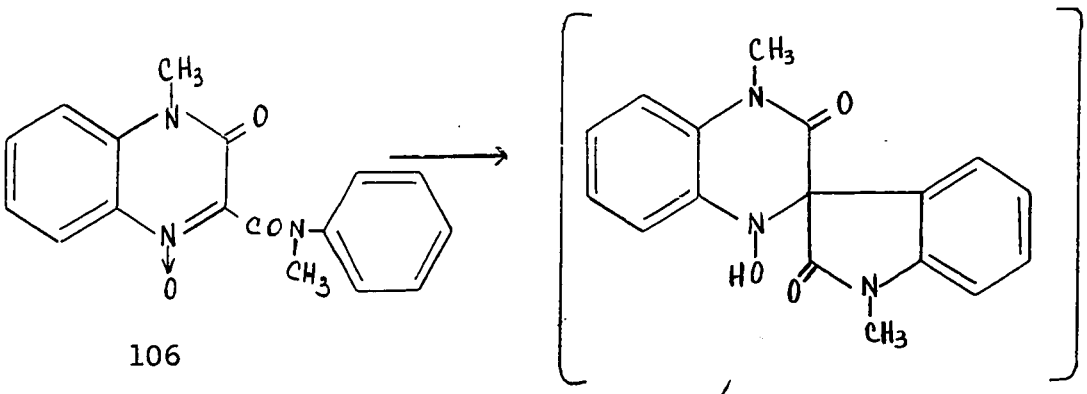
On the otherhand, chemical reagents will reduce cyclic N-hydroxy groups. Treatment of 1,5-dihydroxy-3,3-dimethylpiperidine (8) with phosphorous and hydriodic acid results in the formation of 5-hydroxy-3,3-dimethylpiperidine (105) (Brown, Clark, and Todd, 1959a). The usefulness of zinc and acetic acid as a reagent for the reduction of N-hydroxy compounds was mentioned earlier in this discussion.



8 105

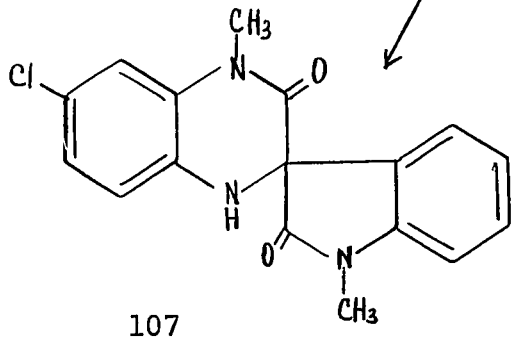
What appears to be a rather complex reaction of the cyclic hydroxylamines is their interaction with mineral acid. The work of Loudon and co-workers (Loudon and Wellings, 1960; Loudon and Tennant, 1962) on the interaction of o-nitrobenzaldehyde derivatives with hydrogen chloride or hydrogen bromide has been mentioned previously in this discussion. A related reaction has been reported by Clark-Lewis and Katekar (1959). These investigators found that the treatment of 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-N-methylanilide 1-oxide (106) with ethanolic hydrogen chloride gave a good yield of a spiro compound, 6-chloro-1,2,3,4,2',3'-hexahydro-4,1'-dimethyl-3,2'-dioxoquinoxaline-2-spiro-3'-indole (107). In view of the work

described by Heller, Hughes and Ingold (1951) on the interaction of N-phenylhydroxylamines with hydrochloric acid, these workers proposed that the conversion of 106 to 107 proceeded via an N-hydroxy intermediate (108).



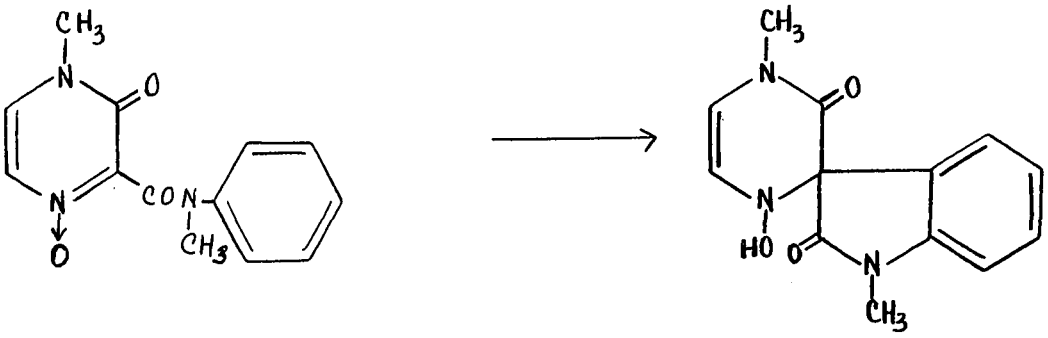
106

108



107

This reaction was reinvestigated by Habib and Rees (1962) but attempts by these workers to isolate or prepare the N-hydroxy intermediate (108) failed. They did find, however, that the action of ethanolic hydrogen chloride on 3,4-dihydro-4-methyl-2-(N-methyl-N-phenylcarbamyl)-3-oxopyrazine 1-oxide (109) yielded the spiro-N-hydroxy derivative (110) which is structurally related to the proposed quinoxaline intermediate (108).



109 110

Pharmacological Properties

It is well known that hydroxamic acids possess many pharmacological properties (Coutts, 1967; 1967a). Several of these compounds are now being used as chemotherapeutic agents. Desferrioximine (Desferol) (111), for example, is used as a chelating agent for the treatment of iron poisoning, and hydroxyurea (112) is used in the treatment of leukemia. Studies have shown that the biological activity of the hydroxamic acids is in many cases dependent on the presence of the N-hydroxy function.

$H_2N(CH_2)_5N(OH)CO(CH_2)_2CONH(CH_2)_5$
NOH
$CH_3COCON(OH)(CH_2)_5NHCO(CH_2)_2CO$

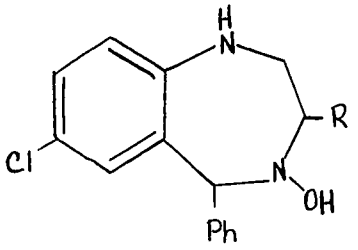
111

$H_2NCONHOH$

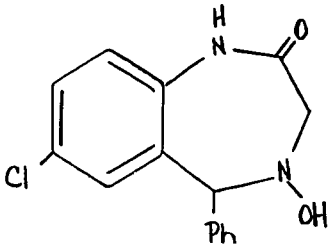
112

To date, little is known about the pharmacological properties of the cyclic N,N-disubstituted hydroxylamines, although a few reports have recently begun to appear in the literature.

N-Hydroxy-benzodiazepine derivatives (11) have been prepared for screening as potential anticonvulsants (Hoffmann - La Roche, 1966). Similar compounds, such as 26, are also being investigated for potential central nervous system depressant activity (Grindstedvaerket, 1967).

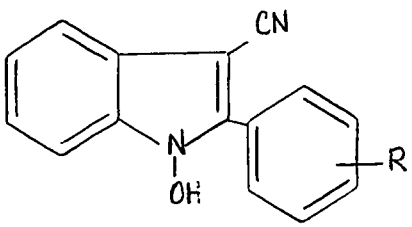


11

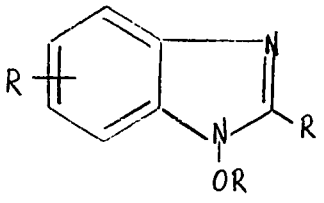


26

Petracek (1967) found that N-hydroxyindole derivatives (72) not only possess central nervous system depressant activity but that they are also active adrenolytic agents. A number of related N-hydroxybenzimidazole derivatives (113) have also been prepared to evaluate their action as central nervous system depressants, muscle relaxants and tranquillizers (Ciba, 1966).



72



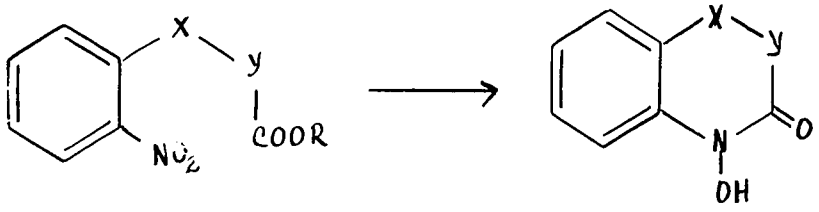
113

It is apparent from these preliminary reports that further investigation of the pharmacological properties of

N-hydroxy compounds is justified.

Scope of the Present Investigation

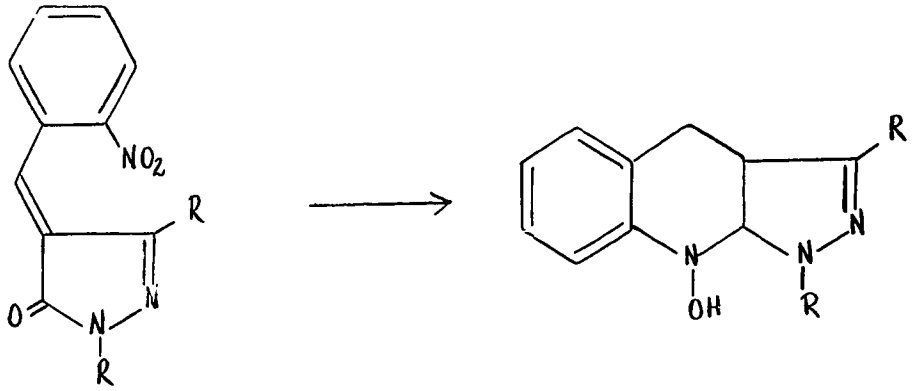
Extensive studies by Coutts and co-workers (Coutts and Wibberley, 1963; Coutts, Noble and Wibberley, 1964; Coutts, Peel, and Smith, 1965; Coutts and Hindmarsh, 1966; Coutts, Barton and Smith, 1966; Coutts and Smith, 1967) have shown that aromatic nitro compounds with a suitably orientated side chain carbonyl group can be reductively cyclized by means of sodium borohydride and palladium-charcoal. This work primarily involved the reduction of aromatic nitro compounds in which the carbonyl group was that of an ester or acid. In most cases these reactions gave rise to hydroxamic acids (114). It was also found that the reduction of o-nitroketones yielded N-oxide derivatives. (Coutts and Wibberley, 1963).



114

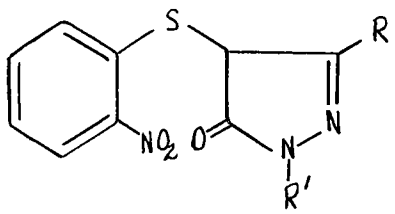
These results led to an investigation of the reduction of aromatic nitro compounds in which the side chain possessed a lactam carbonyl group. As mentioned previously, Coutts and Edwards (1966) have investigated the reduction of 4-(o-nitrobenzylidene)-2-pyrazolin-5-one derivatives (115). The reduction of these compounds with cyclohexene and palladium-charcoal did yield the desired N-hydroxy com-

pounds (116); however, the catalyzed sodium borohydride reductions were less successful. It was felt that the failure of these sodium borohydride/palladium-charcoal reductions was due to the fact that cyclization required the reduction of both the double bond and the nitro group of these compounds.



115 116

For this reason the reduction of 4-(o-nitrophenylthio)-2-pyrazolin-5-one derivatives (117) was undertaken. These compounds were chosen since, unlike the benzylidene compounds (115), they do not possess a rigid geometry. It is possible for the lactam and the nitro functions of these compounds to be freely orientated in close proximity to each other, a situation which, it was hoped, would facilitate reductive cyclization to N-hydroxy products.



117

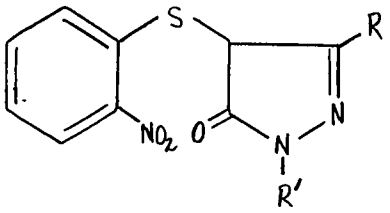
The synthesis and the catalyzed sodium borohydride reduction of these pyrazolone derivatives (117) was the initial purpose of the project described in this thesis. These reductions led to a study of the interaction of hydrochloric acid with aromatic hydroxylamines and hydroxamic acids, which in turn, resulted in a preliminary investigation of a novel reaction involving hydroxamic acids and acetic anhydride. This work is described in detail in the following discussion.

DISCUSSION

DISCUSSION

Reduction of Some 4-(o-Nitrophenylthio)pyrazolin-5-ones

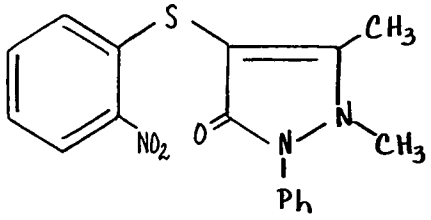
As previously mentioned, the initial purpose of this project was to study the sodium borohydride and palladium-charcoal reduction of 4-(o-nitrophenylthio)pyrazolin-5-ones (117) to see whether cyclic N-hydroxy compounds could be prepared in this way. The four pyrazolone derivatives that were chosen for this investigation were 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a), 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b), 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c), and 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118).



117 a) $R=CH_3$; $R'=Ph$

b) $R=R'=Ph$

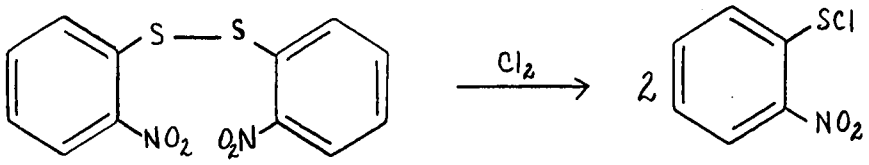
c) $R=CH_3$; $R'=H$



118

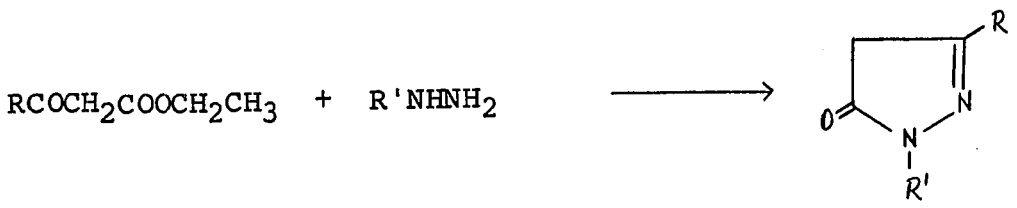
Preparations of the 4-(o-nitrophenylthio)-2-pyrazolin-5-ones (117a-c) have been reported (Coutts, Hindmarsh, and Pound, 1966). One method involved the condensation of o-nitrobenzenesulfenyl chloride with the appropriate pyrazolone derivative, and this method was employed in the present study.

o-Nitrobenzenesulfenyl chloride (119) was readily prepared by the cleavage of bis-(o-nitrophenyl)disulfide (120) with dry chlorine gas (Hubacher, 1935). The disulfide (120) itself, was prepared from o-nitrochlorobenzene, sulfur, and sodium disulfide following the procedure reported by Bogart and Stull (1928).



120 119

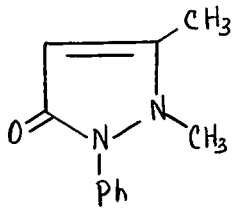
Four pyrazolones were required for these syntheses. 3-Methyl-1-phenyl-2-pyrazolin-5-one (121a) and 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (122) are commercially available; 1,3-diphenyl-2-pyrazolin-5-one (121b) was prepared by treating ethyl benzoylacetate (123a) with phenylhydrazine (124a), and a similar reaction involving ethyl acetoacetate (123b) and hydrazine (124b) gave rise to 3-methyl-2-pyrazolin-5-one (121c).



123 a) R=Ph
b) $R=CH_3$

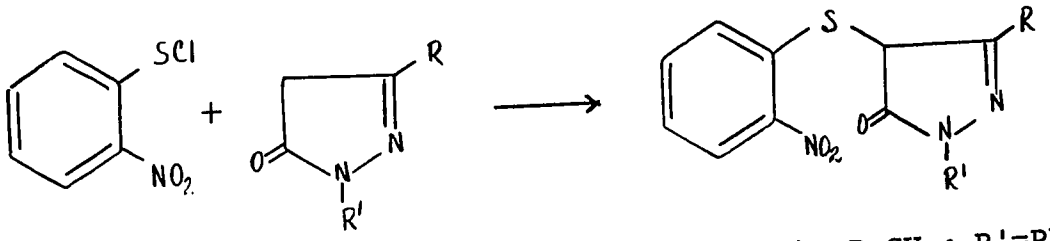
124 a) R'=Ph
b) R'=H

121 a) $R=CH_3$; R'=Ph
b) R=R'=Ph
c) $R=CH_3$; R'=H



122

3-Methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) was obtained as a bright yellow solid by reacting o-nitrobenzenesulfenyl chloride (119) with 3-methyl-1-phenyl-2-pyrazolin-5-one (121a). Similarly, the condensation of o-nitrobenzenesulfenyl chloride (119) with 1,3-diphenyl-2-pyrazolin-5-one (121b) and with 3-methyl-2-pyrazolin-5-one (121c) gave good yields of 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b) and 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c) respectively. 2,3-Dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) was also prepared from the interaction of o-nitrobenzenesulfenyl chloride (119) and 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (122) in acetonitrile.



119 121

117 a) $R=CH_3$; $R'=Ph$

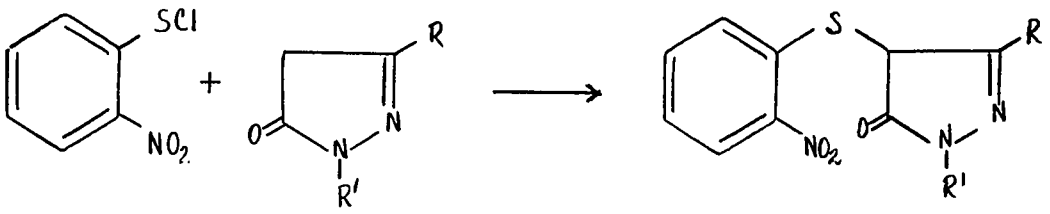
b) $R=R'=Ph$

c) $R=CH_3$; $R'=H$

Reduction of 3-Methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a)

Most reactions using metal hydrides are carried out in organic solvents, frequently under anhydrous conditions. The course of the reaction is often influenced by the nature of the solvent employed (Brown, 1962). Diglyme and dioxane are two organic solvents that are commonly used. Coutts and co-workers found dioxane to be a suitable solvent for their catalyzed sodium borohydride reductions (Coutts and Wibberley, 1963; Coutts and Hindmarsh, 1966), although ethanol and methanol were also used successfully (Coutts, Barton and Smith, 1966; Coutts and Smith, 1967). The previously mentioned reductions of (o-nitrobenzylidene)-pyrazolones (115) (Coutts and Edwards, 1966) were all performed in dioxane.

In the present study, dioxane was used initially as the solvent in the catalyzed sodium borohydride reductions



119 121

117 a) $R=CH_3$; $R'=Ph$

b) $R=R'=Ph$

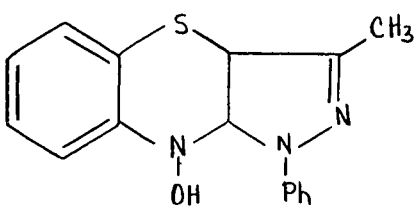
c) $R=CH_3$; $R'=H$

Reduction of 3-Methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a)

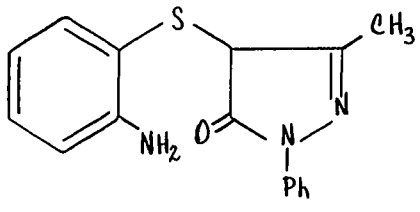
Most reactions using metal hydrides are carried out in organic solvents, frequently under anhydrous conditions. The course of the reaction is often influenced by the nature of the solvent employed (Brown, 1962). Diglyme and dioxane are two organic solvents that are commonly used. Coutts and co-workers found dioxane to be a suitable solvent for their catalyzed sodium borohydride reductions (Coutts and Wibberley, 1963; Coutts and Hindmarsh, 1966), although ethanol and methanol were also used successfully (Coutts, Barton and Smith, 1966; Coutts and Smith, 1967). The previously mentioned reductions of (o-nitrobenzylidene)-pyrazolones (115) (Coutts and Edwards, 1966) were all performed in dioxane.

In the present study, dioxane was used initially as the solvent in the catalyzed sodium borohydride reductions

of the 4-(o-nitrophenylthio)-2-pyrazolin-5-ones (117a-c). These reductions met with only limited success in that the reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) in dioxane was the only reaction from which any product was recovered. The product isolated from this reaction was soluble in dilute sodium hydroxide solution, and its infrared spectrum was devoid of any carbonyl absorption. These facts, together with the elemental analysis of this compound, suggested that it might well be the desired N-hydroxy derivative (125). However, subsequent work in the present project involved the reduction of the nitro compound (117a) using sodium hydroxide solution as solvent. This reaction yielded another product which was also soluble in sodium hydroxide solution. A microanalysis of this compound showed that it was isomeric with the above reduction product. It was, therefore, imperative that the identity of the product obtained from the reduction performed in dioxane be positively established at this stage. This compound has been identified as 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (126) for the reasons which follow.



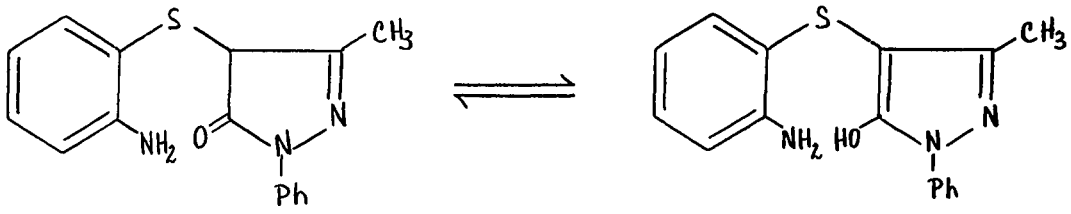
125



126

The product analyzed satisfactorily for $C_{16}H_{15}N_3OS$, a formula supported by its mass spectrum. It was soluble in cold dilute sodium hydroxide solution and was reprecipitated as the pyrazolone (126) by the addition of acetic acid, or as the hydrochloride salt of 126 by adding dilute hydrochloric acid. It formed a monoacetate when reacted with acetic anhydride. As expected, reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) with iron and ferrous ammonium sulfate also produced the amine (126). It is known that aromatic nitro compounds are fully reduced to amines by this type of reducing system (Hickinbottom, 1959; Hodgson and Hathaway, 1944). The infrared spectrum of 126 showed two absorption maxima at 3145 and 3295 cm^{-1}. Although these peaks were at unusually low wavenumbers, they were considered to be indicative of a primary amine. The possibility that the amine function is strongly hydrogen bonded to the lactam carbonyl may account for this shift (Bellamy, 1968b). The infrared spectrum of the hydrochloride salt of this product displayed a broad absorption band with maxima at 2640 and 2900 cm^{-1}, which was attributed to the presence of a protonated primary amino function in the molecule (Nakanishi, 1964). The absence of a carbonyl stretching band in the spectrum of this compound was not surprising. It has been found that the 4-(o-nitrophenylthio)-2-pyrazolin-5-ones (117a-c) exist in enolic forms in the solid state (Coutts, Hindmarsh and Pound, 1966). This implies that the structure of 4-(o-

aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (126) can be more correctly written as the enolic tautomer (126a).



126 126a

The nuclear magnetic resonance (n.m.r.) spectrum of the product also supports structure 126. This spectrum possesses a three-proton singlet at τ7.79 (CH_3) and a broad multiplet between τ2.10 and 3.54 which integrated for twelve protons. When this aromatic portion of the spectrum was expanded, it was possible to detect a broad two-proton signal, centered at τ3.19, which exchanged when the sample was treated with deuterium oxide.

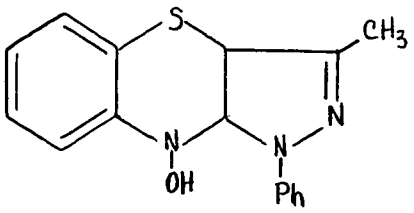
The use of dioxane as a solvent for the sodium borohydride and palladium-charcoal reduction of 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b) and 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c) proved to be quite unsatisfactory. Only trace amounts of solid products were recovered from these reactions. It was felt that the low solubility of these nitro compounds in dioxane was the primary reason for these low yields of products.

Because of their ability to enolize, the three pyrazolones (117a-c) are soluble in dilute alkali. In view of

this, the catalyzed sodium borohydride reductions were repeated using dilute sodium hydroxide solution as the solvent, and in all instances, good yields of a reduction product were obtained. The most effective way of reducing 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) was to dissolve it in dilute sodium hydroxide solution and to add this solution slowly to an aqueous solution of sodium borohydride in which palladium-charcoal was suspended. Acidification of the filtered reaction mixture with either hydrochloric or acetic acid yielded a copious cream-colored product. Purification of this compound proved difficult. When the product was treated with any of the common organic solvents such as ethanol, benzene, or dioxane, it would not crystallize. Only dark oily semi-solids were recovered, although on one occasion a small amount of relatively pure product was obtained by recrystallization from acetic acid. Eventually a method of purification involving adsorption chromatography on a silica gel column was perfected. When benzene/ether (3:2) was used as the solvent, two wide pale yellow bands moved down the column very close together. When the eluate containing the first band was concentrated on a film evaporator, a yellow solid (product A) precipitated in low yield. The eluate containing the second band was collected and evaporated leaving a yellow oil. Trituration of this oil with ethanol yielded a second yellow crystalline product (product B). Only small amounts of dark oils were recovered by

further elution of the column with more polar solvents. These were not investigated.

Evidence is now presented which enables the identification of products A and B as 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) and 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) respectively.



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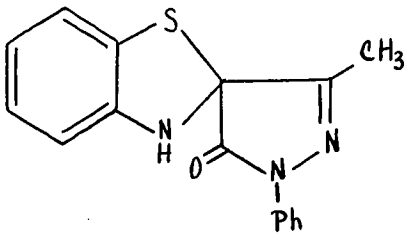
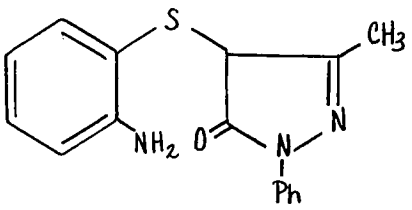


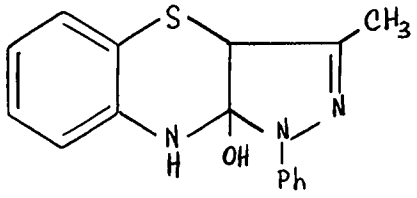
127

Product A gave an elemental analysis which satisfied a molecular formula of $C_{16}H_{15}N_3OS$. This formula was substantiated by an accurate mass determination of the molecular ion (m/e 297) in the mass spectrum of this product (Figure 3; Scheme 3; page 59). The infrared spectrum of A was different from that of the pyrazolone (117a) from which it was derived, and the absence of any absorption peaks that could be attributed to a nitro function suggested that the reduction of the nitro group had occurred. Since it is known that the 2-pyrazolin-5-ones are relatively resistant to both reduction and the action of alkali, it can be assumed that the pyrazole ring system remained intact in the reduction product (A). The heterocyclic ring of the 2-

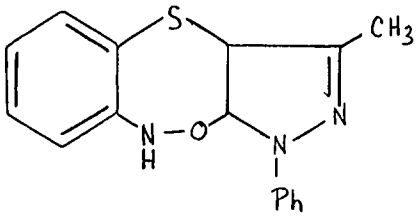
pyrazolin-5-ones is stable, for example, to catalytic reduction. In fact, aromatic substituents can be catalytically reduced to cyclohexyl groups without reduction of the heterocyclic ring occurring (Wiley and Wiley, 1964). The 2-pyrazolin-5-ones are also stable in alkali. It has been shown that this ring system is resistant to hydrolysis by means of sodium hydroxide solution (Seibert, 1947). The presence of a three-proton singlet (CH_3) at τ 7.97 in the n.m.r. spectrum of the N-hydroxy compound (A) is also consistent with an intact pyrazole ring. The corresponding methyl group in the starting material (117a) came to resonance at τ 7.85, and the same group in the primary amino derivative (126) gave a singlet at τ 7.79. It can be concluded that there are only four possible structures for this reduction product. These are compounds 126, 128, 129, and 125, all of which possess the molecular formula, $C_{16}H_{15}N_3OS$.



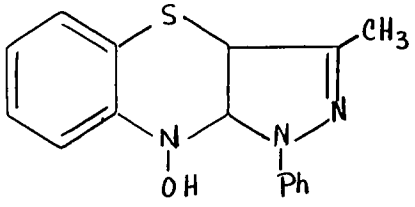
126



128



129



125

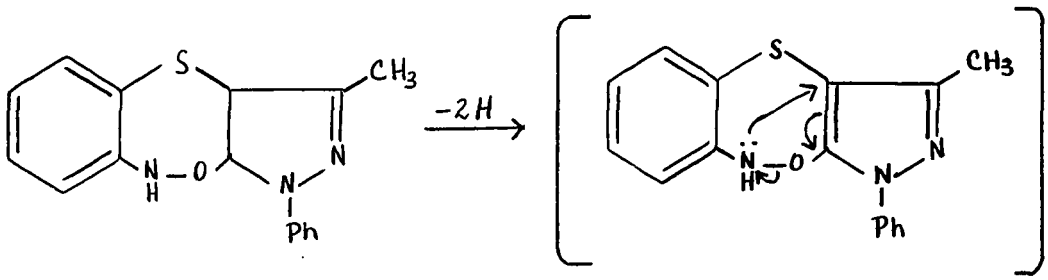
The possibility of product A possessing structure 126 is readily eliminated. Compound 126 was isolated and characterized as described earlier. Its melting point, infrared spectrum and physical characteristics differed greatly from those of A.

Structure 128 was also considered to be an unlikely possibility. The fact that the reduction product was readily soluble in cold dilute sodium hydroxide solution and was reprecipitated unchanged by acidification with either hydrochloric or acetic acid suggested this. Compound 128 is a tertiary alcohol and it is unlikely that this product would be soluble in alkali without structural modification.

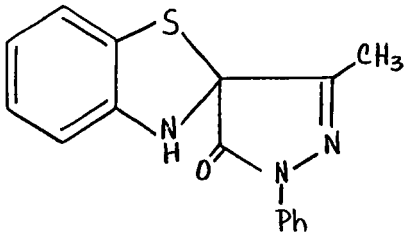
Product A is easily converted into the spiro compound, 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127). (This conversion is discussed in detail on page 57). Structure 129 was given serious consideration at this point since a mechanism for its conversion to the spiro-compound (127) is readily apparent, as shown below.

However, the fact that product A was acidic and easily dissolved in cold dilute alkali suggested that structure 129 was not appropriate. It is known that the isoxazolidines (cyclic 5-membered -NH-O- compounds) are strong bases (Quilico, 1962). From this it seems unlikely that compound 129 would exhibit acidic properties. It is conceivable that this compound (129) could be soluble in alkali due to the rupture of the nitrogen to oxygen bond,

however, it is unlikely that the compound would be reprecipitated unchanged on acidification of the alkaline solution.



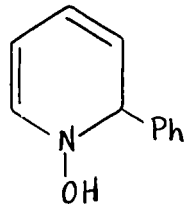
129



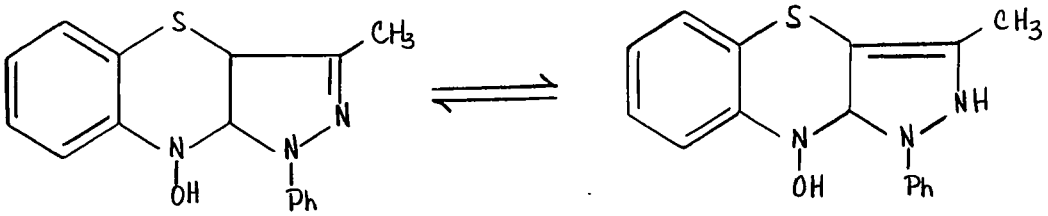
127

Therefore, based on the above observations, compounds 126, 128 and 129 were eliminated as possible structures of the reduction product. This leaves structure 125 as the most acceptable one. The infrared spectrum of product A was in full agreement with this conclusion. The broad adsorption band from 2400 to 3500 cm^{-1} has been attributed to the presence of the N-hydroxy function. This assignment is supported by unpublished work of Coutts and El-Hawari which involved the preparation of 1-hydroxy-2-phenyl-1,2-dihydropyridine (17). The infrared spectrum of

this compound possesses a broad absorption band from 2400 to 3450 cm^{-1} with a maximum at 3180 cm^{-1} which must be due to the presence of the N-hydroxy group. The presence of a weak maximum at 3220 cm^{-1} in the spectrum of product A, suggestive of an NH grouping, does not contradict the assumption that product A possesses structure 125. This can be explained by the fact that 125 could easily exist in a tautomeric form (125 ⇋ 125a), since it is known that the pyrazolones do exist as tautomers (Katritsky and Lagowski, 1963).



17



125 125a

Attempts were made to prepare a chemical derivative of product A. Efforts to acetylate this product with acetic anhydride were unsuccessful. This reaction yielded only black oils which would not crystallize. It was pos-

sible, however, to benzoylate A. A solution of this reduction product (A) in cold dilute sodium hydroxide solution, was treated with benzoyl chloride and in this way a red oil was formed. Chromatography of this semisolid gave several dark oils, one of which solidified on repeated trituration with petroleum ether (product C). Mass spectral analysis of C revealed that tribenzoylation of A had occurred (Figure 1). This spectrum possessed two ions at m/e 609 and 399. Accurate mass determinations indicated that these ions possessed molecular formulae $C_{37}H_{27}N_3O_4S$ and $C_{23}H_{17}N_3O_2S$ respectively.

It is seen that a tribenzoyl derivative of A (130) would have a molecular weight of 609, and that the loss of two benzoyl groups (PhCO) from such a derivative could give rise to the formation of an ion of m/e 399. The loss of two benzoyl groups (PhCO) from 130 could give rise to such a fragment (Scheme 2); however, the possibility of benzoylation having occurred at the nitrogen of the pyrazoline ring or even in the aromatic ring must not be overlooked.

The significant fact is that product C does possess an N-benzoyloxy function. Evidence found in the mass spectrum and infrared spectrum of C indicates this.

The mass spectrum of C (Figure 1) displayed a peak at m/e 488. A strong metastable peak at m/e 391.0 indicated that this fragment arose from the direct loss of 121 mass units from the molecular ion (m/e 609). It is seen that the loss of a benzoyloxy radical (PhCOO·) from 130 would account

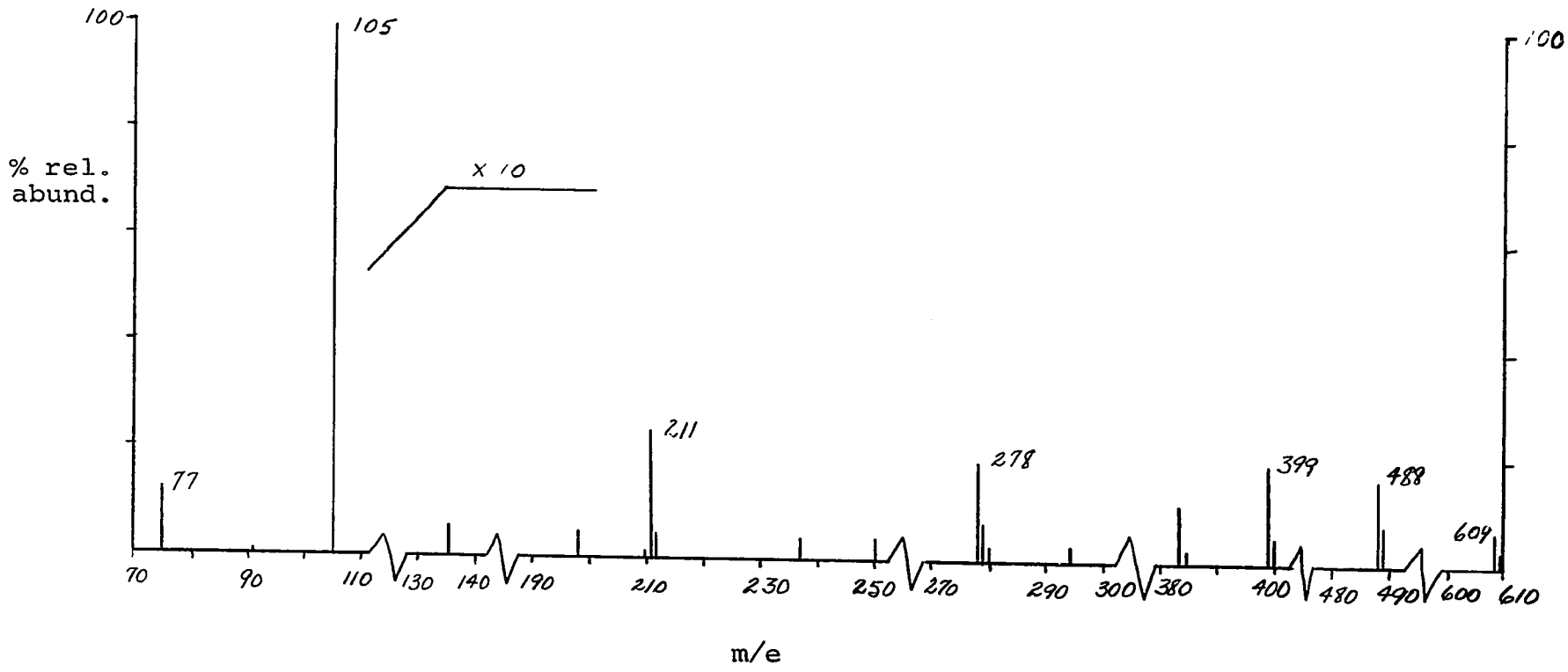
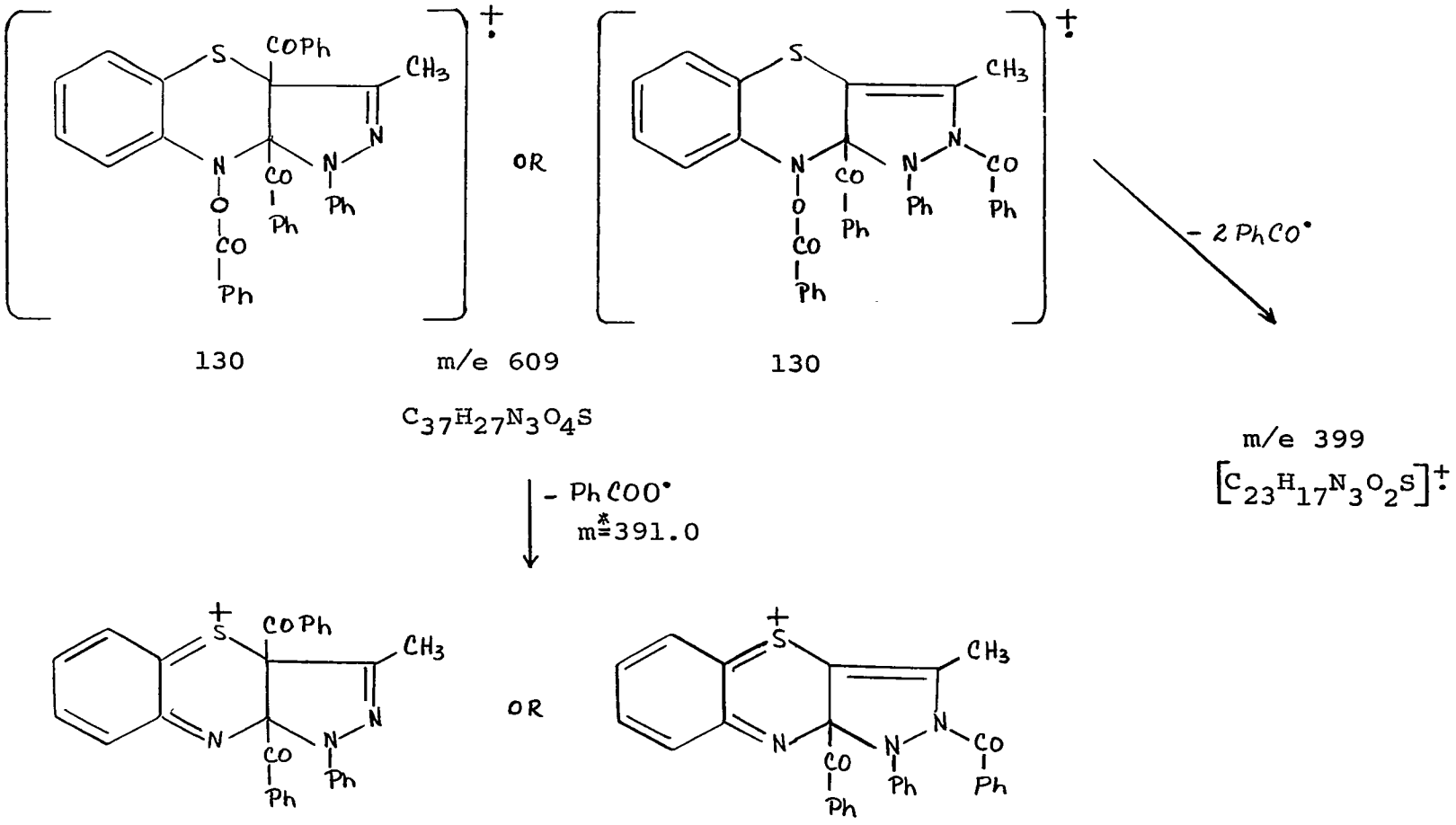


Figure 1: A portion of the mass spectrum of the tri-benzoate derivative of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-2-pyrazolo-[4,3-b]-1,4-benzothiazine (C).


COPh
CH3
S
N
O
CO
Ph
OR
- 2 PhCO•
130
m/e 609
C37H27N3O4S
130
m/e 399
[C23H17N3O2S]+
- PhCOO•
m*=391.0
OR
m/e 488

Scheme 2

for this fragmentation.

This conclusion is also supported by the infrared spectrum of product C. This spectrum showed a strong carbonyl absorption band at 1758 cm^{-1}. This peak may be attributed to the presence of an N-benzoyloxy function because the infrared spectrum of 1-benzoyloxy-2-phenyl-1, 2-dihydropyridine* (131) possesses carbonyl stretching at 1755 cm^{-1} which must obviously be due to the N-benzoyloxy carbonyl function. It is known that the carbonyl absorption band of benzoates ($PhCOOCR_3$) appears in the region of 1720 cm^{-1} (Bellamy, 1968). The carbonyl stretching band of n-propylbenzoate, for example, is located at 1720 cm^{-1} (Coutts, 1969a). Benzamides (PhCONH-) absorb at even lower wavenumbers (Bellamy, 1968a). The infrared spectrum of benzamide itself, possesses carbonyl absorption at 1655 cm^{-1} (Coutts, 1969). The fact that the carbonyl peak in the spectrum of product C appears above either of these values eliminates the possibility that the absorption band at 1758 cm^{-1} in the spectrum of C could be due to benzoate or benzamide absorption.

This evidence indicates that product C does possess an N-benzoyloxy function. Product A, therefore, must contain an N-hydroxy group as shown in 125.

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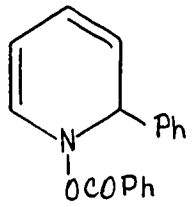
* Prepared by El-Hawari by the reported procedure (Kato and Yamanaka, 1965).



131

The n.m.r. spectrum of the reduction product (A) displayed only two signals; a three-proton singlet at τ 7.97 (CH_3) and a broad twelve-proton multiplet between τ 1.92 and 3.75 which is in full agreement with structure 125. The integral of the aromatic multiplet indicates that this signal must be masking the signals of the protons of both the N-hydroxy function and the pyrazole ring. The pyrazole ring protons might be expected to appear far downfield due to the electron-withdrawing properties of the adjacent sulfur and nitrogen atoms. This suggestion is supported by the fact that no separate signals for the pyrazolone protons are detected in the n.m.r. spectrum of either the nitro compound (117a) or the amine derivative (126). Several reports in the literature support the conclusion that the N-hydroxy proton comes to resonance in this region. Kato and Yamanaka (1965) have reported the presence of a one-proton singlet at τ 0.8 in the n.m.r. spectrum of 1-hydroxy-2-phenyl-1,2-dihydropyridine (17), which they attributed to the N-hydroxy function. Mousseron-Canet and co-workers

(1967) found that the hydroxyl proton signal in the n.m.r. spectrum of 1-hydroxy-2-methylindole (61) appeared within the region τ 3.95 to 4.31. The position of the signal was dependent on the nature of the solvent used. For example, in acetonitrile the proton came to resonance at τ 3.95, while in carbon tetrachloride the signal was found at the other extreme, τ 4.31. Attempts to detect the N-hydroxy proton in the aromatic signal in the spectrum of product A by exchange with deuterium oxide were unsuccessful.

Infrared and n.m.r. data, therefore, are in agreement with the product (A), isolated from the catalyzed sodium borohydride reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a), being 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125).

As mentioned before, a second product, (product B) was isolated during the purification of the crude product from the reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) with sodium borohydride and palladium-charcoal. The identification of this product as 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) was based on the following data. An elemental analysis and an accurate mass determination of the molecular ion (m/e 295) in the mass spectrum of product B supported a molecular formula of $C_{16}H_{13}N_3OS$ (Figure 2). Its n.m.r. spectrum possessed a three-proton singlet at τ 7.78 (CH_3), a broad one-proton signal at τ 5.26 (NH), which ex-

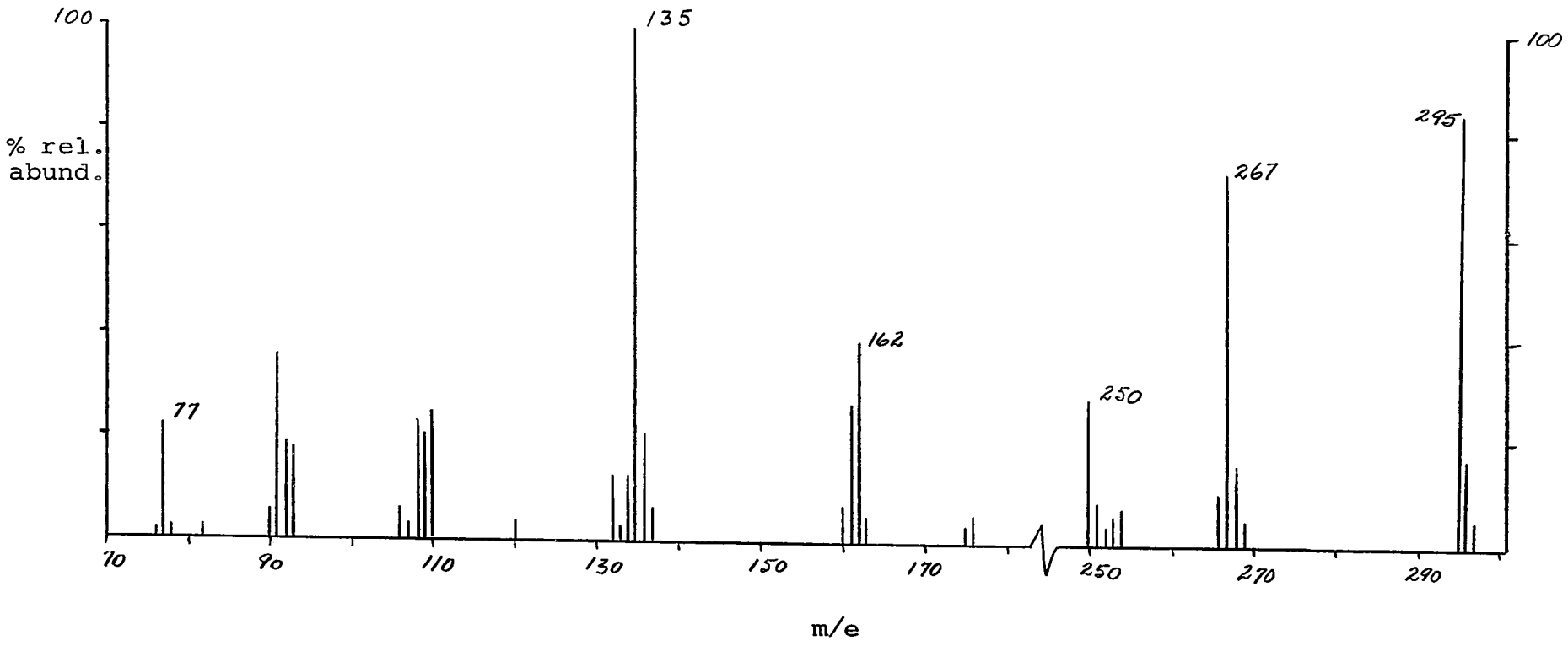
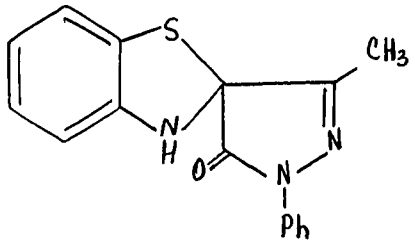


Figure 2: A portion of the mass spectrum of 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127).



127

changed on the addition of deuterium oxide, and a complex nine-proton aromatic signal between τ 1.98 and 3.43. The infrared spectrum of B contained a strong absorption band at 1705 cm^{-1} and a sharp peak at 3265 cm^{-1}. Since neither the infrared spectrum of the crude product obtained from the catalyzed sodium borohydride reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) nor that of compound 125 possessed any carbonyl absorption, it was felt that product B must have formed from 125 on the column during the purification process. The ability of the N-hydroxy derivative (125) to convert to the spiro compound (B) was illustrated by a closer examination of the n.m.r. spectrum of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125). This spectrum displayed a small peak at τ 7.73 which, with time, slowly increased in size as the methyl singlet at τ 7.97 decreased in size. This suggested that the rearrangement was occurring in dimethyl sulfoxide at room temperature. The rearranged sample from the n.m.r. analysis was recovered and shown to be identical to product B. A low yield of B was

the only product obtained when 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) was heated with dilute hydrochloric acid. The conversion of the N-hydroxy compound (125) to the spiro derivative (B) also occurred in the mass spectrometer (Figures 2 and 3). The mass spectrum of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) (Figure 3) possessed a molecular ion at m/e 297 ($C_{16}H_{15}N_3OS$) and a strong peak at m/e 295, corresponding to a molecular formula of $C_{16}H_{13}N_3OS$. This $[M-2]^+$ ion was present even at an ionizing potential of 12 eV, and as the temperature of the probe (Figure 4) or the length of time of bombardment was increased, the intensity of the peak at m/e 295 increased. This suggested that the N-hydroxy compound (125) was being rapidly converted to the spiro pyrazolone (B) in the probe of the spectrometer.

A provisional fragmentation pathway has been outlined for compound 125 (Scheme 3). The fragmentation pattern of this compound is similar to that of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (Scheme 4, p. 73). One significant difference is the presence of an ion at m/e 250 in the spectrum of 125. Since this ion appears in the spectrum of both compound 125 (Figure 3) and the spiro derivative (127) (Figure 2), it is not an artifact. Presumably its formation is due to a rearrangement involving the methyl group, but at the present time no structure can be proposed for it.

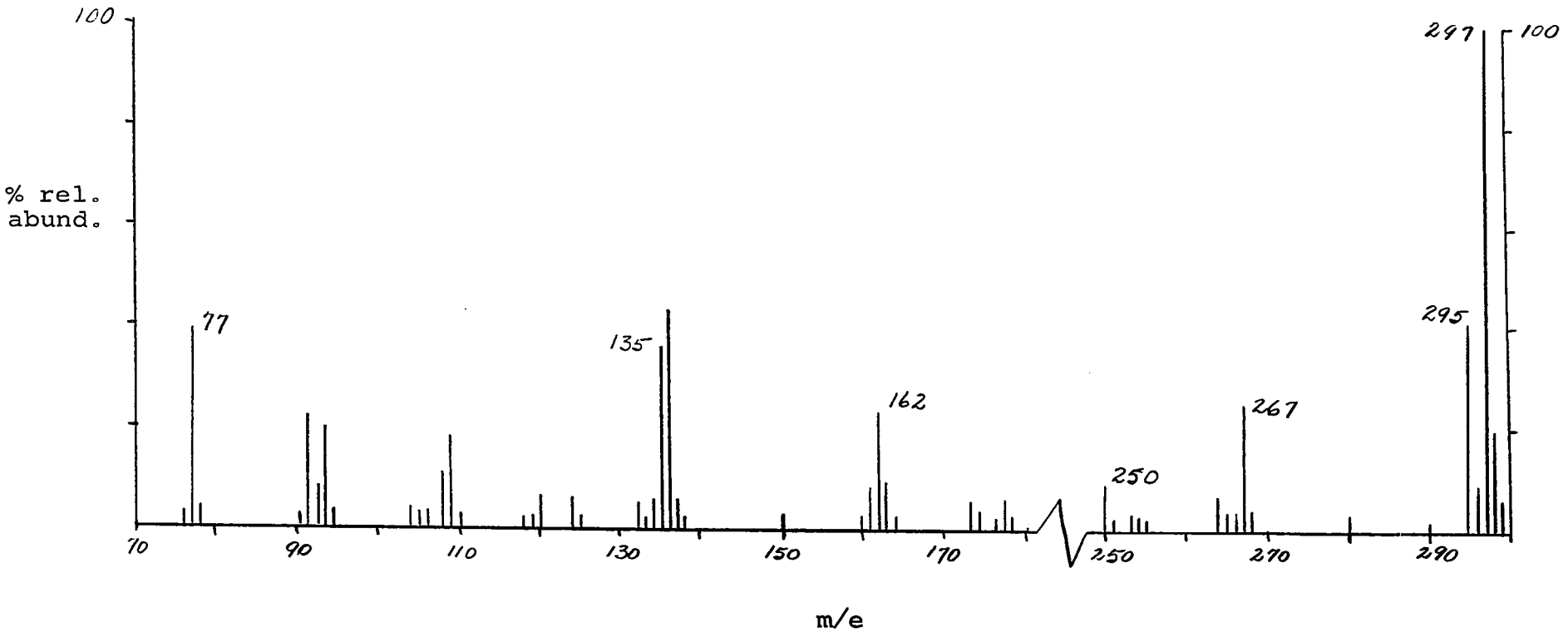
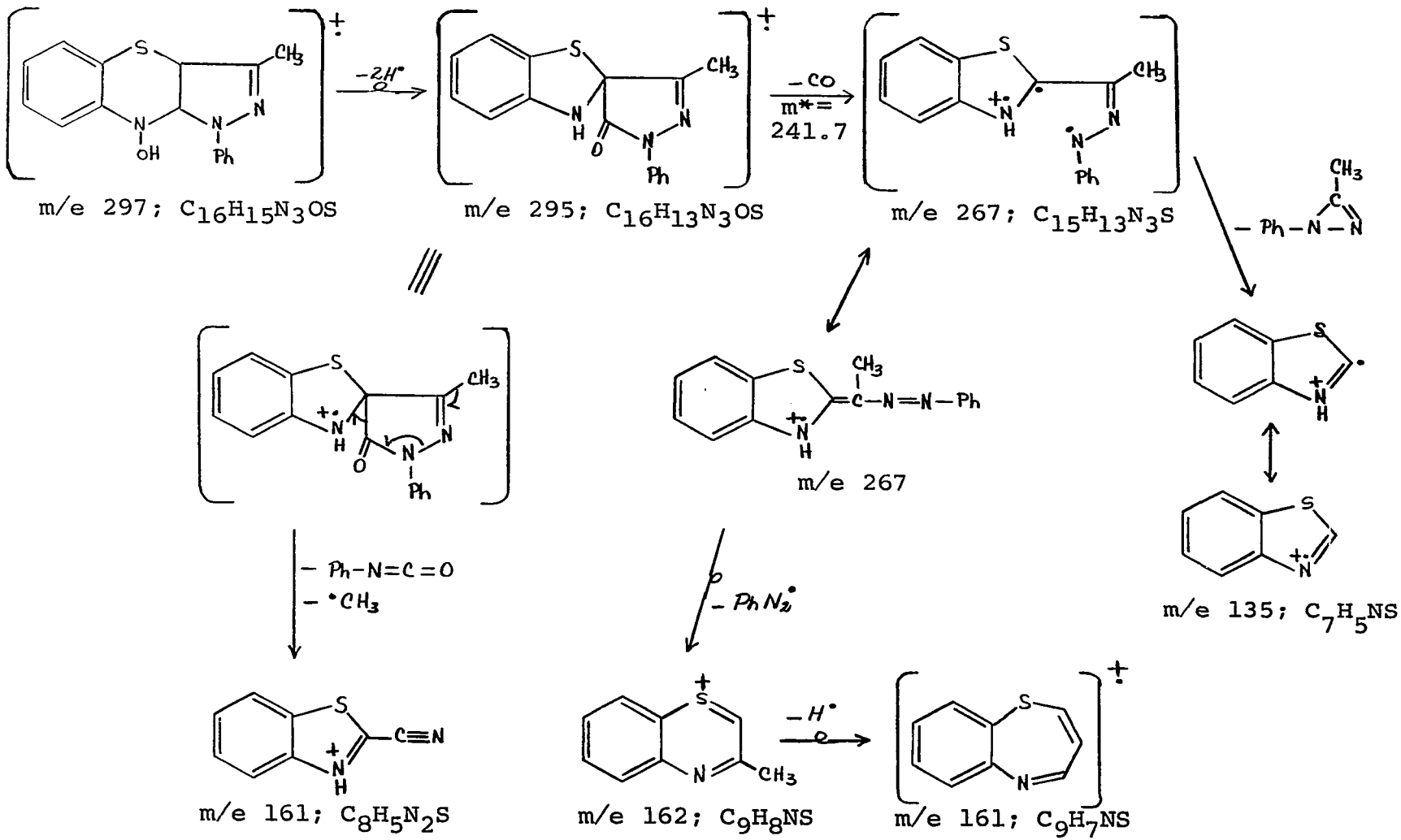


Figure 3: A portion of the mass spectrum of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125).


m/e 297; $C_{16}H_{15}N_3OS$
m/e 295; $C_{16}H_{13}N_3OS$
m/e 267; $C_{15}H_{13}N_3S$
m/e 267
m/e 135; C_7H_5NS
m/e 161; $C_8H_5N_2S$
m/e 162; C_9H_8NS
m/e 161; C_9H_7NS

Scheme 3

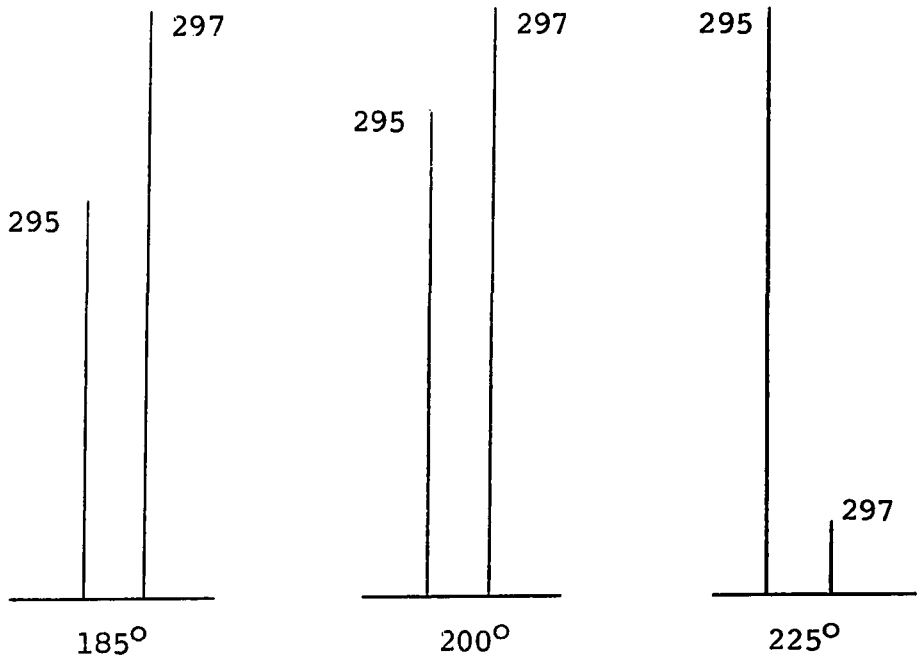
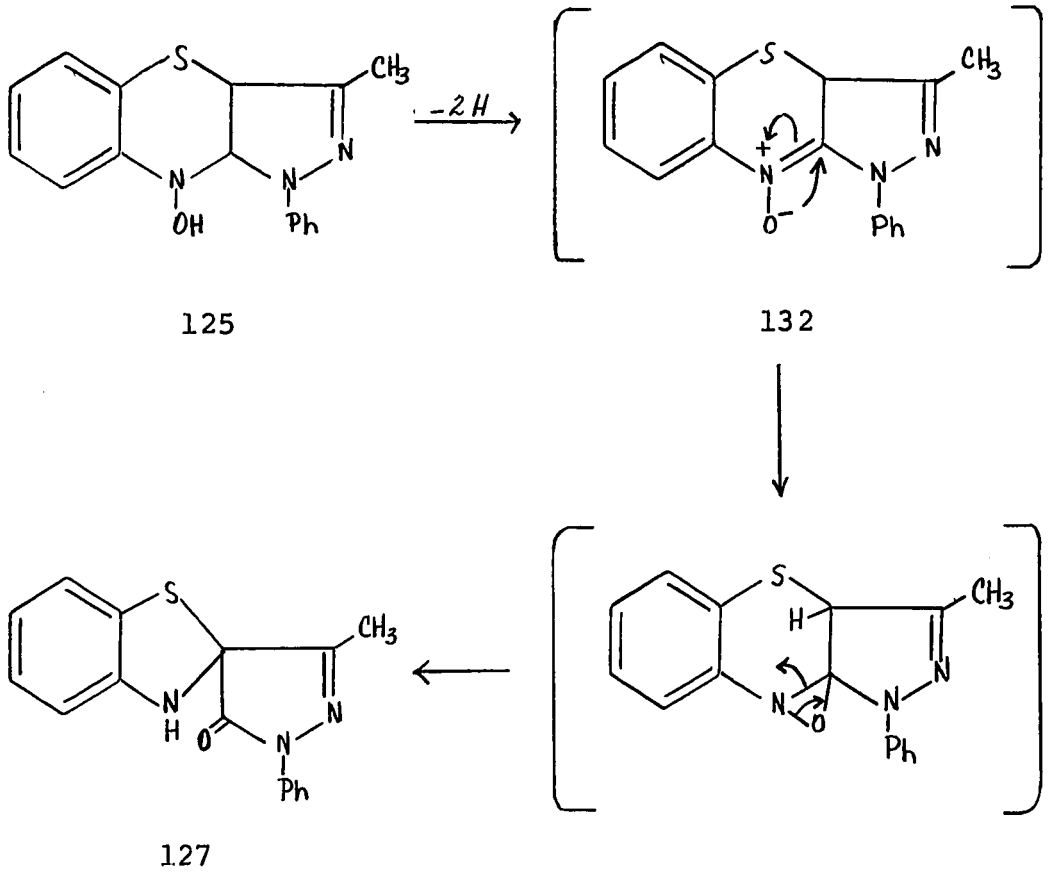


Figure 4: Ratio of the intensity of the ions at m/e 295 and 297 in the mass spectrum of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) at varying temperatures.

From these observations, it can be seen that the rearrangement of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) to 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) involves the loss of two hydrogen atoms; i.e., oxidation is involved. Since the spiro compound (127) possesses a pyrazolone ring system, this rearrangement must involve an oxygen migration as well. These facts can be explained by the following mechanism.



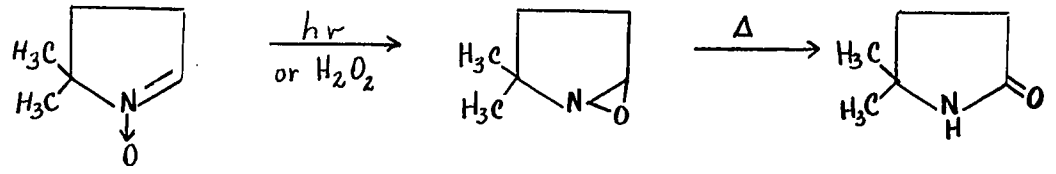
125 132

127

This postulated mechanism is supported by several references which appear in the literature. The first step in the rearrangement involves the oxidation of the N-hydroxy compound (125) to the N-oxide derivative (132). It has been reported that N-hydroxy compounds are readily oxidized by aerial oxygen in the presence of a suitable catalyst (Bonnett et al, 1959), and by various other mild oxidizing agents such as ferric chloride and mercuric oxide (Delpierre and Lamchen, 1965). It is also known that dimethyl sulfoxide is an oxidizing agent (Epstein and Sweat, 1967). The tendency of 9,9a-dihydro-9-hydroxy-3-methyl-

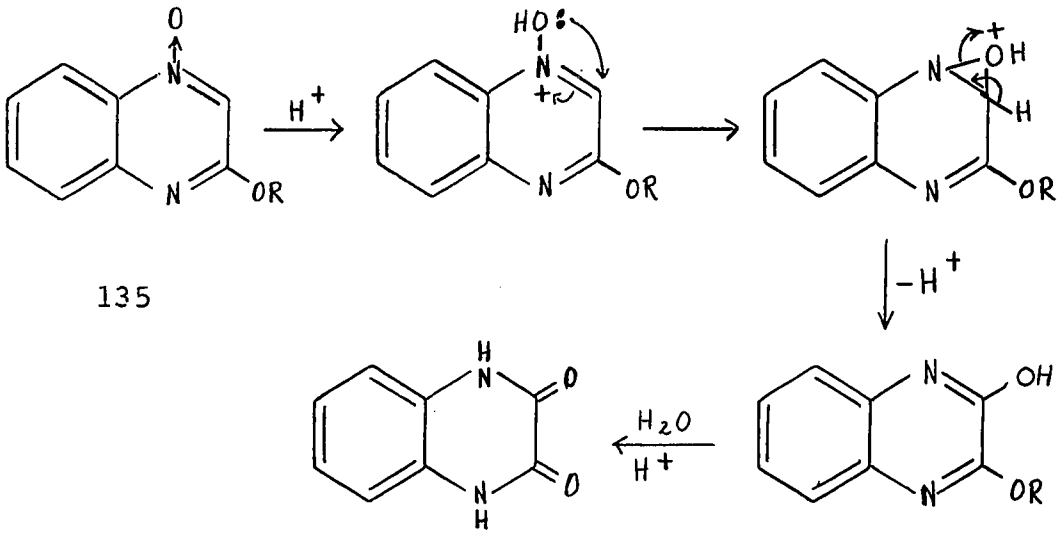
1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) to rapidly discolor on exposure to the atmosphere suggests that it might be susceptible to aerial oxidation. Several attempts were made to convert this compound (125) to the spiro compound (127) by oxidation with hydrogen peroxide. These were unsuccessful. The only product obtained from these reactions was a thick black oil which failed to crystallize. It was assumed that these failures were due to the known sensitivity of the pyrazolone ring itself to oxidation (Veibel and Linholt, 1954, 1954a, 1955). Strong oxidizing agents such as potassium permanganate are known to completely destroy the 2-pyrazolin-5-one ring (von Rothenburg, 1893).

The type of nitrogen to carbon migration involved in the above mechanism is not new. Examples of similar migrations in N-oxides have been reported. Bonnett, Clark, and Todd (1959a) found that treatment of 5,5-dimethyl-Δ'-pyrroline 1-oxide (14) with either ultraviolet light or hydrogen peroxide resulted in the formation of an epoxide derivative (133). Heating this epoxide (133) did not regenerate the starting material (14). Instead, rearrangement occurred giving rise to the amide, 5,5-dimethyl-2-pyrrolidone (134).



14 133 134

A similar reaction has been reported by Cheeseman (1961). This investigator has shown that 3-ethoxy- or 3-methoxyquinoxaline 1-oxide (135), on treatment with hydrochloric acid, undergoes an intramolecular rearrangement and hydrolysis, yielding quinoxaline-2,3-dione (136) via the following pathway.

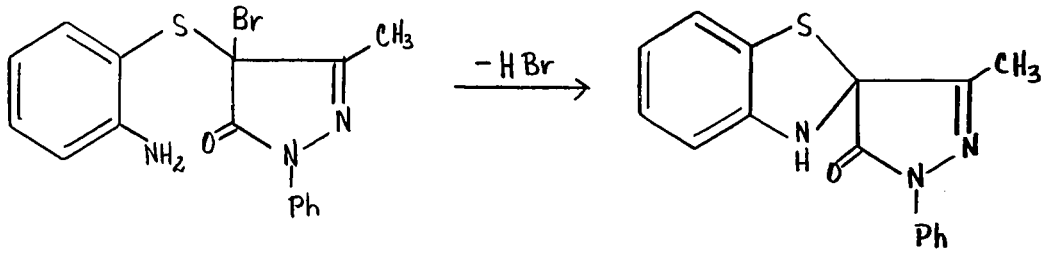


135

136

The synthesis of 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) by an alternate route was attempted. This met with little success.

Westöö (1952) has reported the synthesis of 4-mono- and 4-dihalopyrazolones. This investigator also found that the treatment of 4-alkyl-2-pyrazolin-5-ones with halogens resulted in the formation of 4-alkyl-4-halopyrazolones. From this it was felt that 4-(o-aminophenylthio)-4-bromo-3-methyl-1-phenyl-2-pyrazolin-5-one (137) could be prepared in a similar manner, and that it should be possible to dehydrohalogenate this compound to form the desired spiro pyrazolone (127).

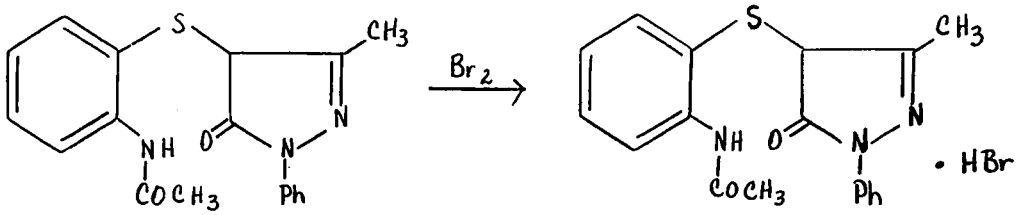


137 127

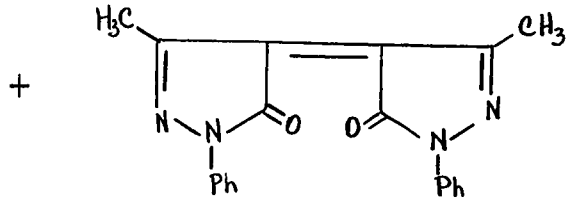
4-(o-Aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (126) was acetylated with acetic anhydride prior to bromination to reduce the possibility of bromine attacking the aromatic ring. The acetate derivative (138), on treatment with an equimolar quantity of bromine in glacial acetic acid, yielded a semisolid product. Recrystallization of this solid from ethanol and acetone gave two compounds. One of these, a black solid, which was isolated in milligram quantities only, has been identified as 3,3'-dimethyl-1,1'-diphenyl-[$\Delta^{4,4'}$-bi-2-pyrazoline]-5,5'-dione

(139). The identification of this product is discussed below. A good yield of the second product was recovered. The following evidence led to the identification of this product as the hydrobromide salt of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-pyrazolin-5-one (140).

The infrared spectrum of the salt (140) possessed a peak at 3305 cm^{-1} which was attributed to amide NH stretching, and a strong broad absorption band between 2000 and 3500 cm^{-1} with maxima at 2550, 2600 and 2680 cm^{-1}, which



138 140



139

was indicative of the presence of a protonated nitrogen function (Nakanishi, 1964). The mass spectrum of this product (140) had a molecular ion at m/e 339, which would suggest that the product was identical to or isomeric with the starting material (138), as well as two strong peaks

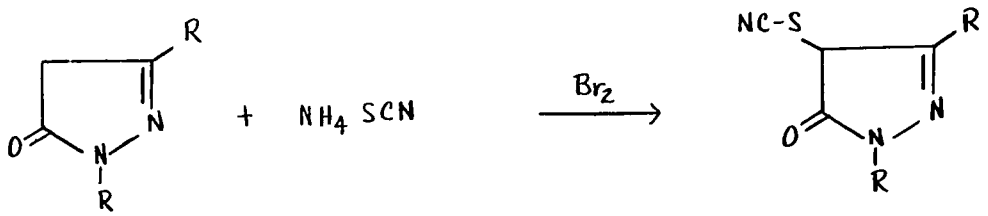
at m/e 80 and 82, which indicated the presence of hydrogen bromide in the compound. The microanalysis of this product satisfied the formula $C_{18}H_{18}BrN_3O_2S$. When the hydrobromide (140) was taken up in sodium carbonate solution and the solution acidified with glacial acetic acid, 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (138) was recovered. The identity of the hydrobromide was further supported by the fact that 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrobromide (140) was precipitated when an acetone solution of the acetate (138) was saturated with hydrogen bromide.

Similar results were obtained when 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (138) was reacted with pyridinium bromide perbromide. A nearly quantitative yield of the hydrobromide salt (140) was obtained. In this reaction none of the bis-pyrazolone derivative (139) was detected.

One other synthesis was attempted at this time. This reaction involved the treatment of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) with pyridinium bromide perbromide. The same black product as described above, together with some unreacted starting material, was recovered from this reaction. Recrystallization of the black product yielded a compound which proved to be 3,3'-dimethyl-1,1'-diphenyl-[$\triangle^{4,4'}$-bi-2-pyrazoline]-5,5'-dione (Pyrazole Blue) (139). The identity of this compound was based on the following observations. The elemental analysis was sat-

isfactory for $C_{20}H_{16}N_4O_2$. The mass spectrum of the product (139) indicated a molecular weight of 344, and the $[M+2]^+/[M]^+$ ratio suggested the absence of sulfur in the molecule. It is known that the action of mild oxidizing agents on the 2-pyrazolin-5-ones will result in the formation of bis-derivatives of this type (Wiley and Wiley, 1964a). Shirai and Yashiro (1955) have reported that some 2-pyrazolin-5-ones can be converted to bis-pyrazolones merely by recrystallizing them from water. Pyrazole Blue (139) itself, was prepared by Knorr (1887) by treating 3-methyl-1-phenyl-2-pyrazolin-5-one (121a) with such mild oxidizing agents as platinic chloride or ferric chloride solutions.

These reactions suggest that the 4-position of the 4-(phenylthio)-2-pyrazolin-5-ones is resistant to attack by bromine. This observation is reminiscent of the work performed by Kinugawa and Ochiai (1964), who found that the reaction of ammonium thiocyanate with 2-pyrazolones and 2-pyrazolins in the presence of bromine resulted in the formation of 4-thiocyanate derivatives (e.g. 141 ⟶ 142) of these compounds. The fact that no halogen derivatives were reported is consistent with the results obtained in this thesis.

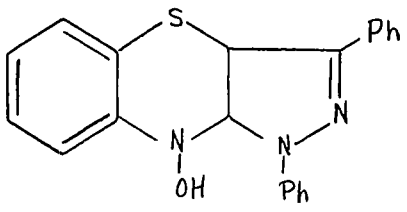


141 142

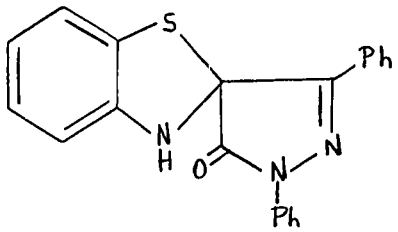
Reduction of 4-(o-Nitrophenylthio)-1,3-diphenyl-2-pyrazolin-one (117b)

When 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b) was reduced with sodium borohydride and palladium-charcoal using sodium hydroxide solution as solvent, a good yield of an off-white solid was recovered. Purification of this product on a silica gel column yielded a yellow solid which was purified further by recrystallization from ethanol. Elemental and mass spectral analysis (Figure 5) confirmed the molecular formula of this compound as being $C_{21}H_{17}N_3OS$. The infrared spectrum and the solubility properties of this product were similar to those of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125). These observations led to the conclusion that this product was 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143).

While the N-hydroxy compound (143) was the only product isolated from the chromatography process, the mass spectrum of this product indicated that rearrangement to the spiro pyrazolone, 5-oxo-1,3-diphenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (144), did occur in the mass spectrometer (cf. Figures 5 and 6).



143



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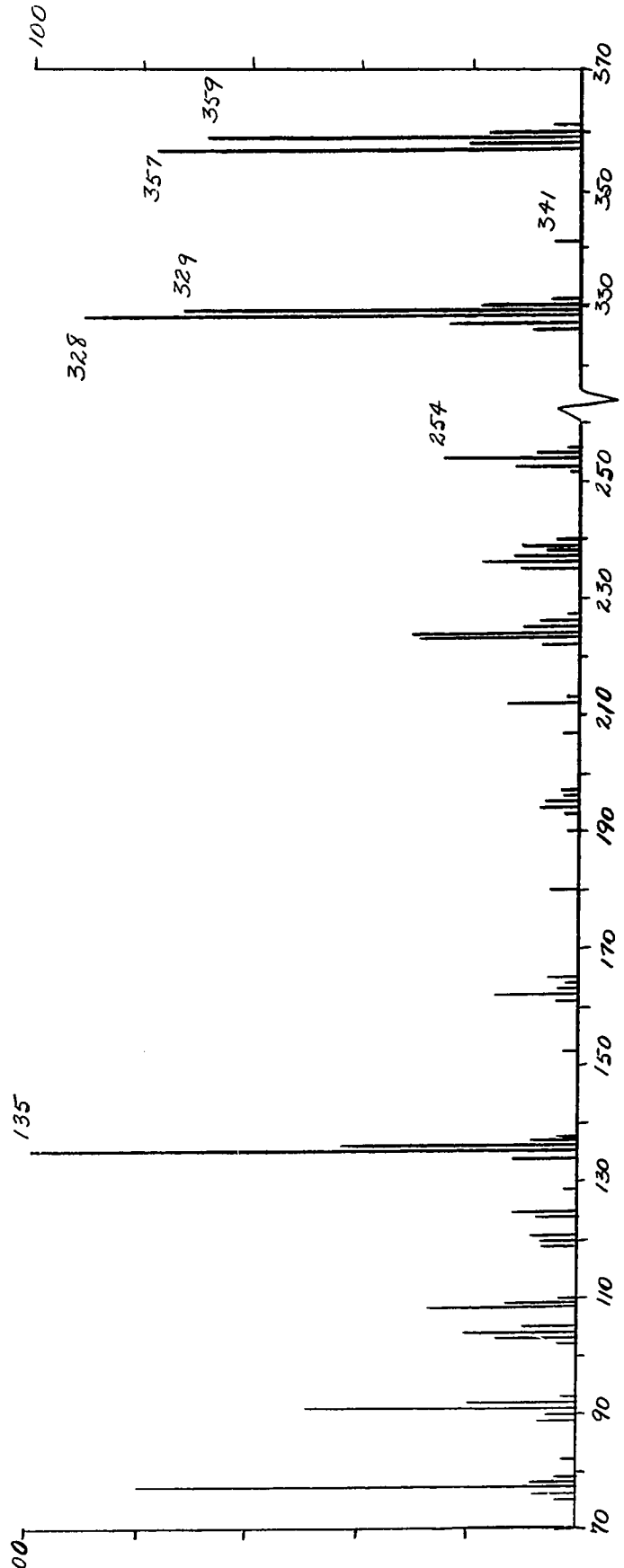


Figure 5: A portion of the mass spectrum of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143).

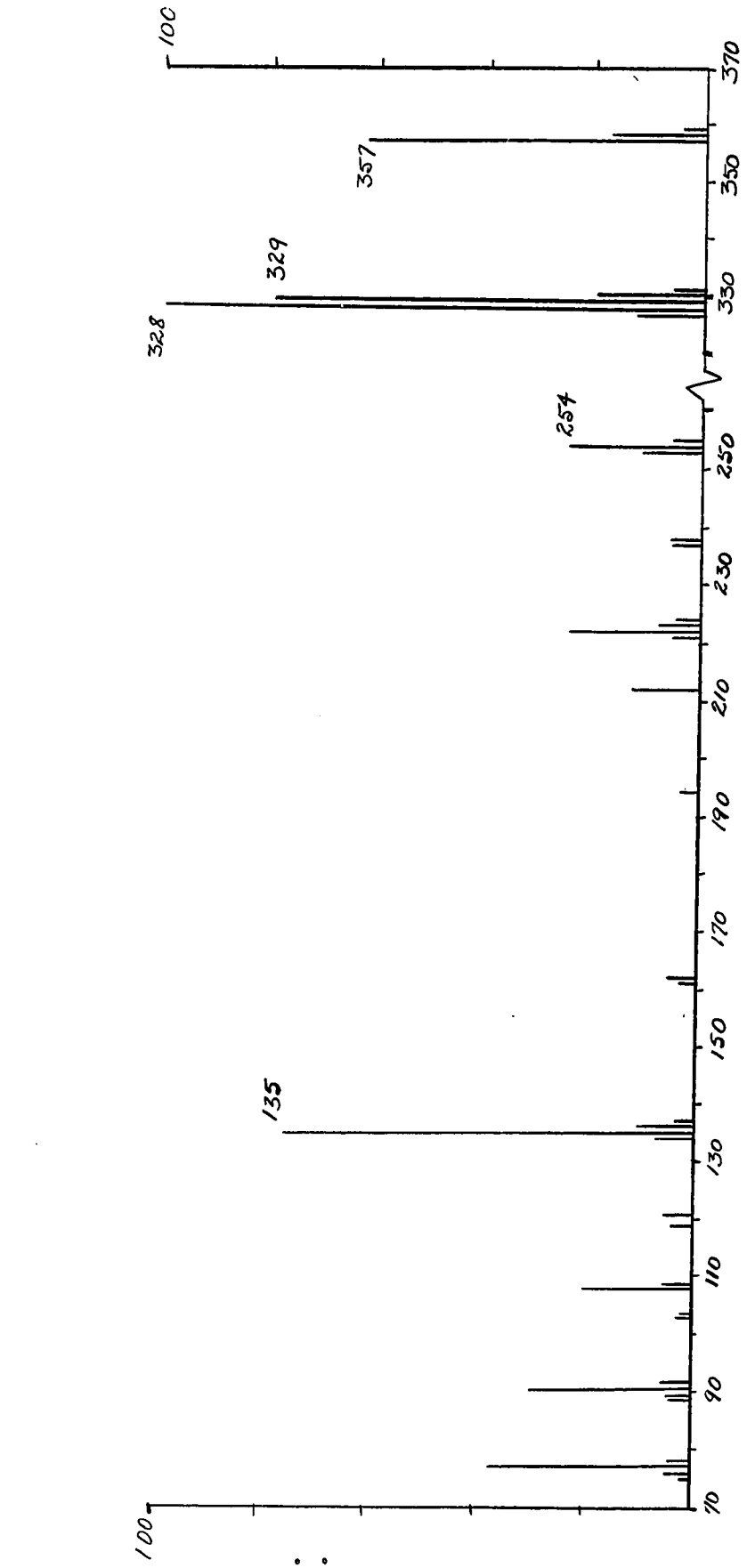
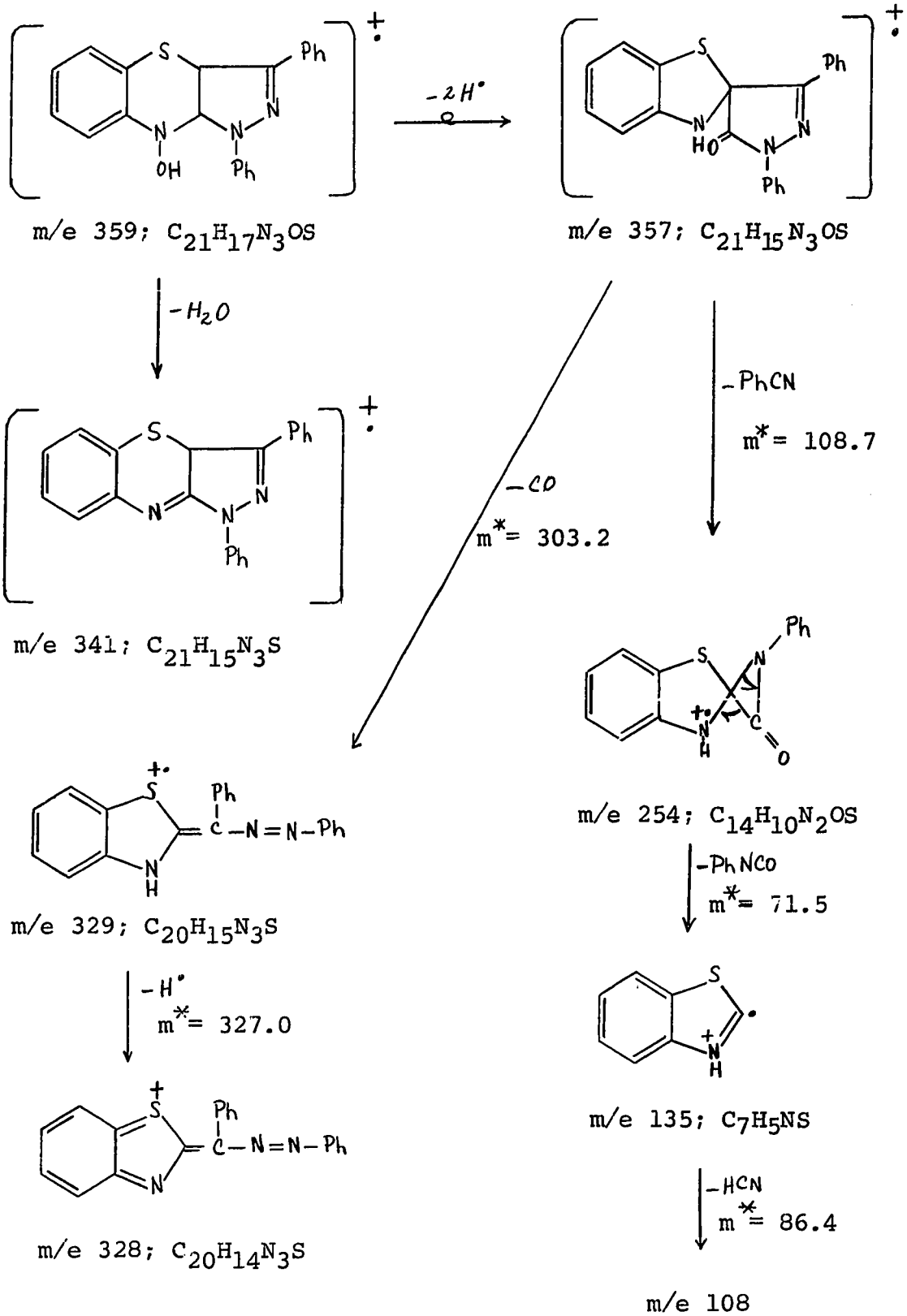


Figure 6: A portion of the mass spectrum of 5-oxo-1,3-diphenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (144).

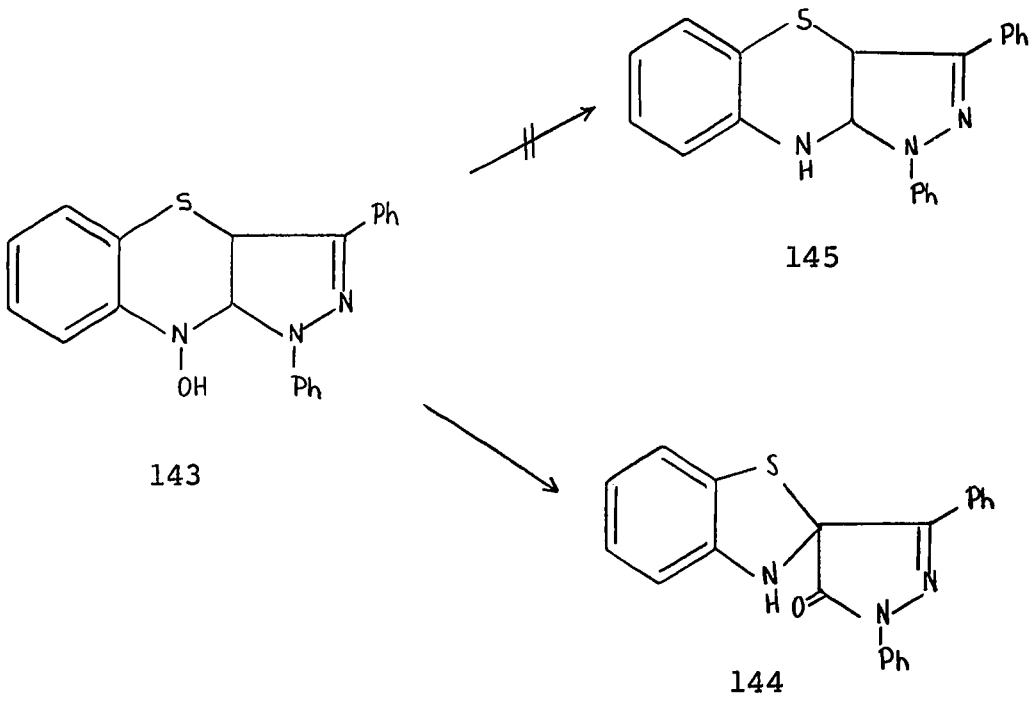
The mass spectrum of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143) (Figure 5) possessed abundant ions at m/e 359 ($[M]^+$), 357, 341, 329, 328, 254, and 135. Accurate mass determinations indicated that these peaks corresponded to ions of the following elemental composition: $C_{21}H_{17}N_3OS$, $C_{21}H_{15}N_3OS$, $C_{21}H_{15}N_3S$, $C_{20}H_{15}N_3S$, $C_{20}H_{14}N_3S$, $C_{14}H_{10}N_2OS$, and C_7H_5NS. A tentative identity of each fragment ion is given in Scheme 4.

It is known that the reduction of many N-hydroxy derivatives with zinc dust and acetic acid gives rise to the corresponding amino compound (Loudon and Wellings, 1960). An attempt to prepare an amine derivative (145) by the zinc and acetic acid reduction of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143) was unsuccessful. The only compound isolated from this reaction was the spiro pyrazolone, 5-oxo-1,3-diphenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (144). This product was identified from its elemental analysis, which was satisfactory for a molecular formula of $C_{21}H_{15}N_3OS$, its mass spectrum, ($[M]^+$ at m/e 357) (Figure 6), and its infrared spectrum which possessed a strong carbonyl absorption band at 1718 cm^{-1} and NH stretching at 3370 cm^{-1}.

Since it has already been proposed that the rearrangement of these N-hydroxy compounds to the spiro pyrazolones involves an initial oxidation to the N-oxide derivative, the above rearrangement under reducing conditions can only be explained if the conversion occurred before zinc dust


-2H°
m/e 359; $C_{21}H_{17}N_3OS$
m/e 357; $C_{21}H_{15}N_3OS$
$-H_2O$
$-PhCN$
m^*= 108.7
-CO
m^*= 303.2
m/e 341; $C_{21}H_{15}N_3S$
m/e 254; $C_{14}H_{10}N_2OS$
$-PhNCO$
m^*= 71.5
m/e 329; $C_{20}H_{15}N_3S$
$-H^\bullet$
m^*= 327.0
m/e 135; C_7H_5NS
$-HCN$
m^*= 86.4
m/e 328; $C_{20}H_{14}N_3S$
m/e 108

Scheme 4



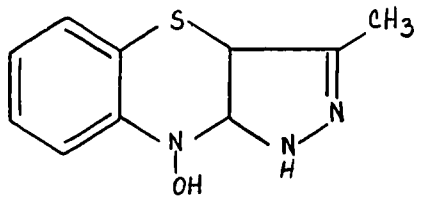
143 145 144

was added to the hot acid solution. This conclusion was confirmed by heating a sample of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143) in glacial acetic acid. A good yield of the spiro pyrazolone (144) was recovered.

Reduction of 3-Methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c)

Reduction of 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c) with sodium borohydride and palladium-charcoal, using sodium hydroxide solution as solvent, gave a good yield of a pale yellow solid which rapidly darkened in color on exposure to air. Attempts to purify this product were unsuccessful. While it was not possible to ob-

tain reproducible microanalyses of the product at this time, the solubility properties and infrared spectrum of the reduction product suggested that it was, in fact, 9,9a-dihydro-9-hydroxy-3-methyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (146).



146

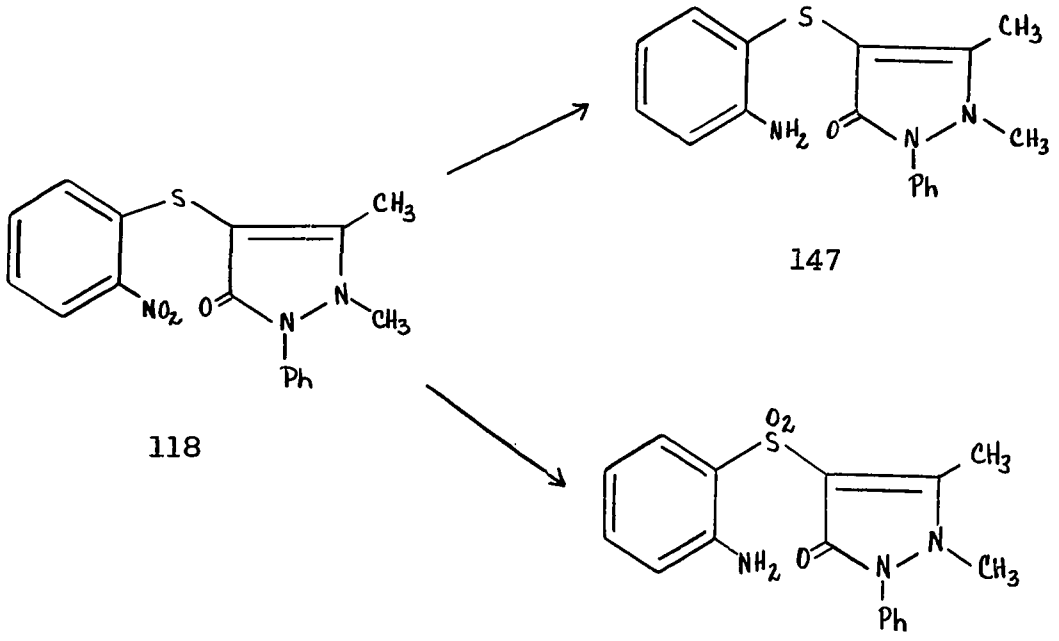
Reduction of 2,3-Dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118)

Due to its inability to enolize, 2,3-dimethyl-4-(o-nitrophenylthio)-3-pyrazolin-5-one (118) was insoluble in sodium hydroxide solution. Attempts to reduce a suspension of this compound in dilute sodium hydroxide solution with sodium borohydride and palladium-charcoal yielded only starting material. As a result, dioxane was used as solvent in this reduction. Acidification of the filtrate from this reaction yielded an off-white product (designated as product D), the infrared spectrum of which possessed a carbonyl absorption band at 1642 cm^{-1} and two peaks at 3220 and 3400 cm^{-1}, which were indicative of the presence of a primary amino function. This suggested that reduction had taken place, but that cyclization had not occurred. The product (D), on diazotization and coupling

with β-naphthol, gave a red colored dye. This, together with the fact that the compound readily reacted with acetic anhydride to form a monoacetate derivative, confirmed that product D was a primary amine. However, a direct comparison with authentic material indicated that it was not 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (147).

The authentic sample of 147 was prepared by reducing 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) with iron and ferrous ammonium sulfate. The elemental analysis and mass spectrum of this amine (147) corresponded to a molecular formula of $C_{17}H_{17}N_3OS$. Its infrared spectrum which was similar to, but not identical with the spectrum of the amine (D) isolated above, possessed carbonyl and primary amine absorption bands. This compound (147), which formed a monoacetate derivative on treatment with acetic anhydride, could also be diazotized, then coupled with β-naphthol to form a red dye.

The elemental analysis of product D isolated from the catalyzed sodium borohydride reduction of 118 was not consistent with a molecular formula $C_{17}H_{17}N_3OS$. It apparently satisfied a formula for $C_{17}H_{17}N_3O_3S$, and for this reason, the possibility of D being the sulfone, 4-(o-aminophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (148) was considered. Later work proved this conclusion to be incorrect. Initially, however, this assumption was not unrealistic, since Coutts, Barton, and Smith (1967) had reported

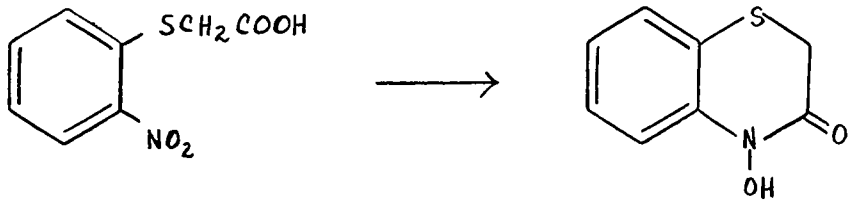


118

147

148

previously that the reduction of (o-nitrophenylthio)acetic acid (149) with sodium borohydride and palladium-charcoal yielded three products (150, 151, and 152), one of which (152) was unexpected and deduced to be 3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide.



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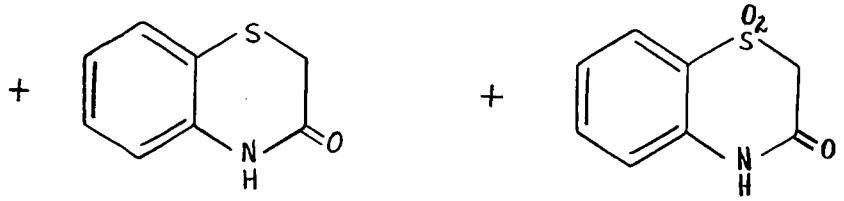
150

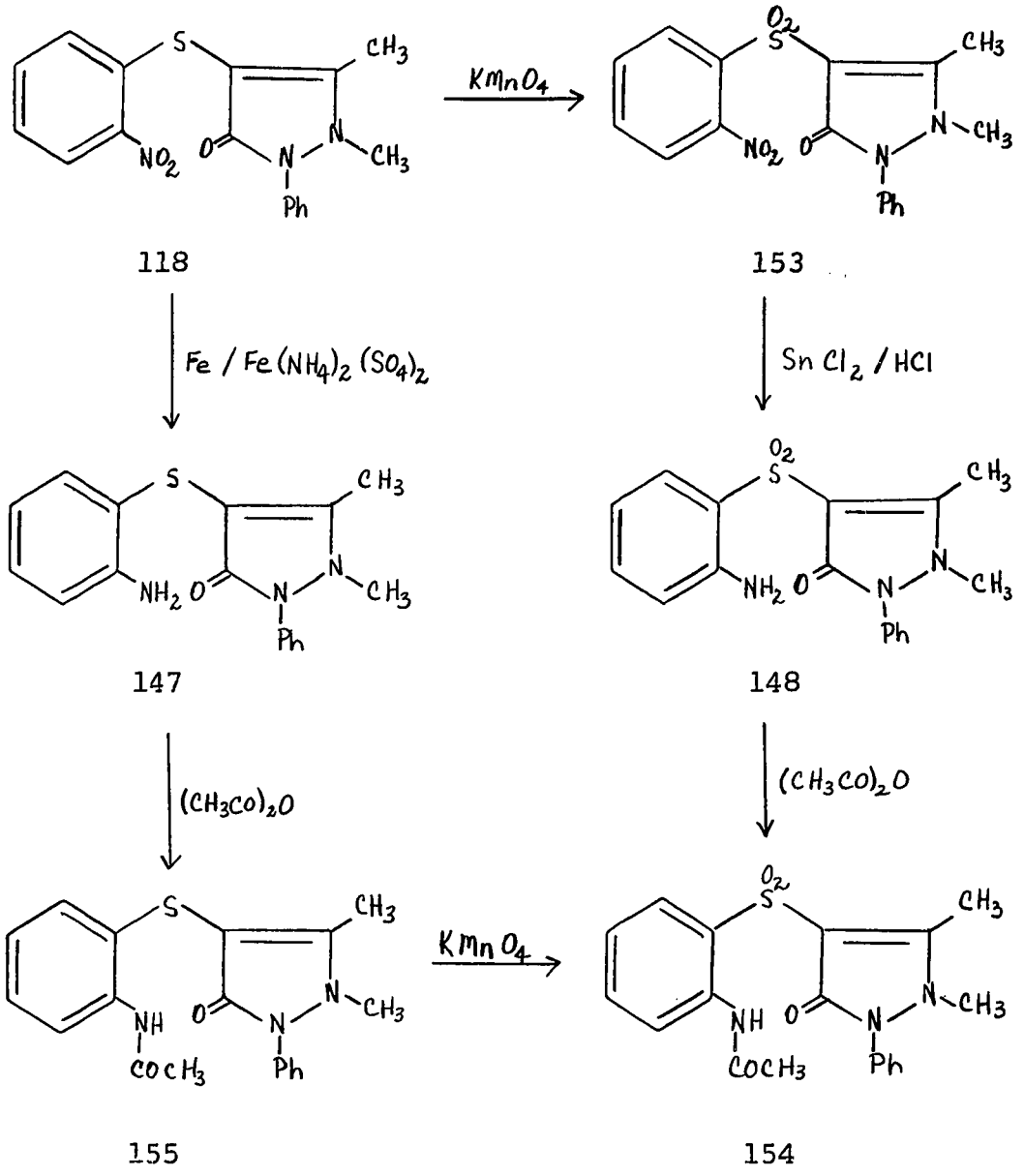


151

152

An authentic sample of 4-(o-aminophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (148) was prepared by an unambiguous synthesis. Oxidation of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) with potassium permanganate in glacial acetic acid gave 2,3-dimethyl-4-(o-nitrophenylsulfonyl)-1-phenyl-3-pyrazolin-5-one (153). The identity of this compound was inferred from its microanalysis, its infrared spectrum and its mass spectrum. This product (153) was readily reduced with stannous chloride and hydrochloric acid to the primary amine, 4-(o-aminophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (148), which was similarly characterized. The authenticity of these products was confirmed when it was shown that 4-(o-acetamidophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (154) was identical to the product obtained from the potassium permanganate oxidation of 4-(o-acetamidophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (155) (Scheme 5).

The amino sulfone isolated from the stannous chloride reduction of 2,3-dimethyl-4-(o-nitrophenylsulfonyl)-1-phenyl-3-pyrazolin-5-one (153) was not the same as the primary amine (D) obtained from the catalyzed sodium borohydride reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118). In view of this, product D was reinvestigated. An examination of its mass spectrum revealed that the molecule contained a chlorine atom. The spectrum possessed a molecular ion at m/e 345 and a strong

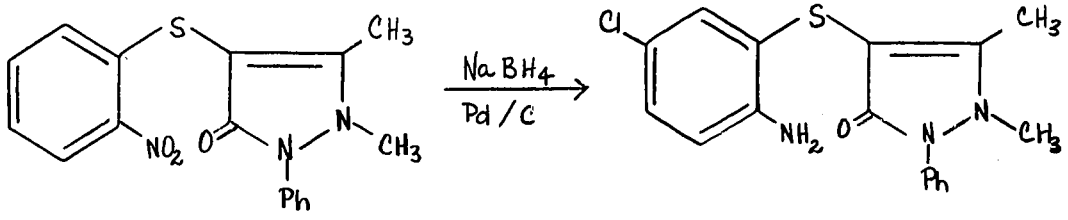


Scheme 5

$[M+2]^+$ ion which had a relative abundance equal to approximately 40% of the molecular ion. An accurate mass determination of the molecular ion corresponded to a molecular formula of $C_{17}H_{16}ClN_3OS$. A recalculation indicated that this formula was also compatible with the microanalysis obtained for the reduction product. The presence of chlor-

ine in the molecule was further confirmed by performing a chlorine analysis on the acetate derivative of the reduction product (D).

Chlorination must have occurred when hydrochloric acid was added to the reaction mixture to decompose the excess sodium borohydride used in the reduction of 118. From this, and the following evidence, it was concluded that the reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) resulted in the formation of 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156).



118 156

The position of the chlorine atom in the reduction product (156) was inferred primarily from the n.m.r. spectrum (Figure 7). Although this spectrum readily eliminated the possibility that chlorination had occurred at either the 3- or 6-position of the benzene ring, it did not differentiate between substitution at either the 5- or 4-position (156 and 157 respectively).

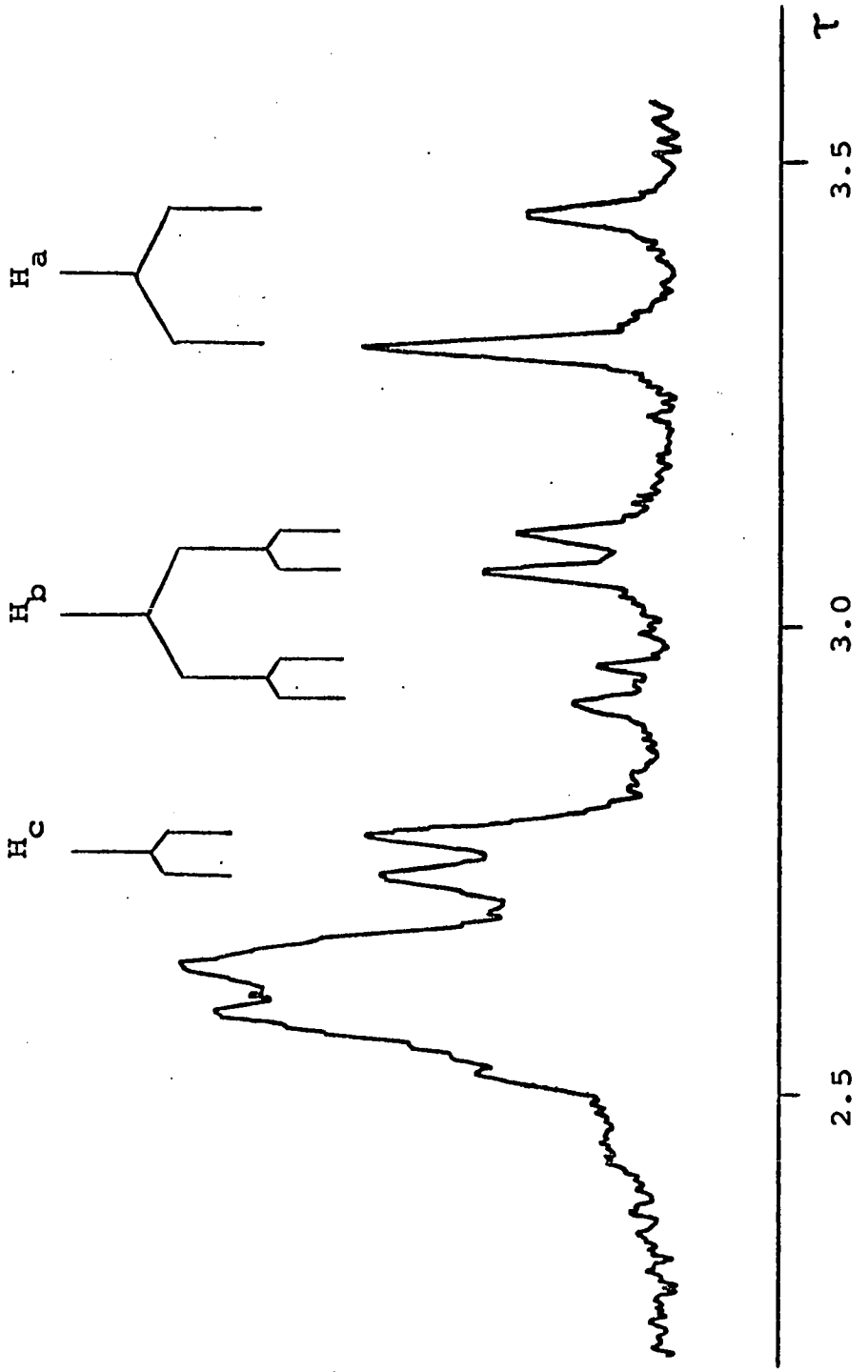
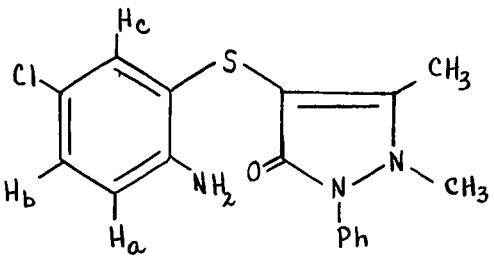
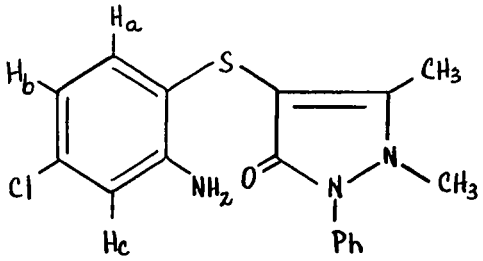


Figure 7: N.m.r. Spectrum (aromatic ring protons) of 4-(2-amino-5-chloro-phenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156).



156

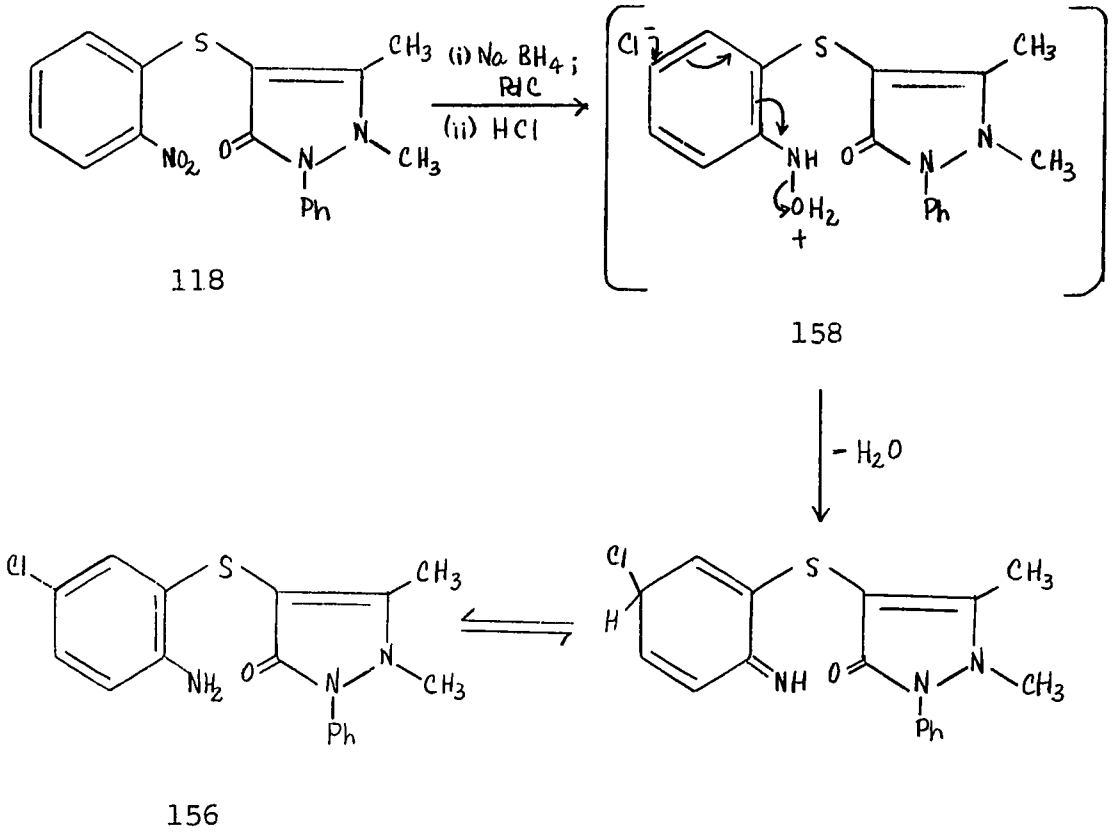


157

In the spectrum of either 156 or 157 the signal for proton H_a would be o-coupled with proton H_b and p-coupled with proton H_c. Similarly, the signal for proton H_b would be o-coupled with H_a and m-coupled with H_c, while the signal for proton H_c would in turn be m-coupled with H_b and p-coupled with H_a. It should be possible to identify these protons (H_a, H_b and H_c) by their coupling constants. The normal ranges of coupling constants for aromatic protons are: ortho, 6.5-9.4 c.p.s.; meta, 0.8-3.0 c.p.s.; and para, 0.4-1.0 c.p.s. (Bovey, 1969). While coupling constants vary somewhat depending on the nature of the substituents present in the ring, they generally fall within these ranges. Therefore, provided that the chemical shifts between these proton signals are large enough to permit an interpretation of these signals, it should be possible to identify all three of the protons in the chlorinated ring. This was the case. The signals of the amine protons and the aromatic protons of the pyrazolone did not overlap with the signals from the protons of the

chlorinated ring. The coupling constants were readily determined, and the protons H_a, H_b, and H_c were identified as shown in Figure 7. This information does not differentiate between 156 and 157 and so the fact that substitution had taken place in the 5-position (156) was substantiated by the following evidence.

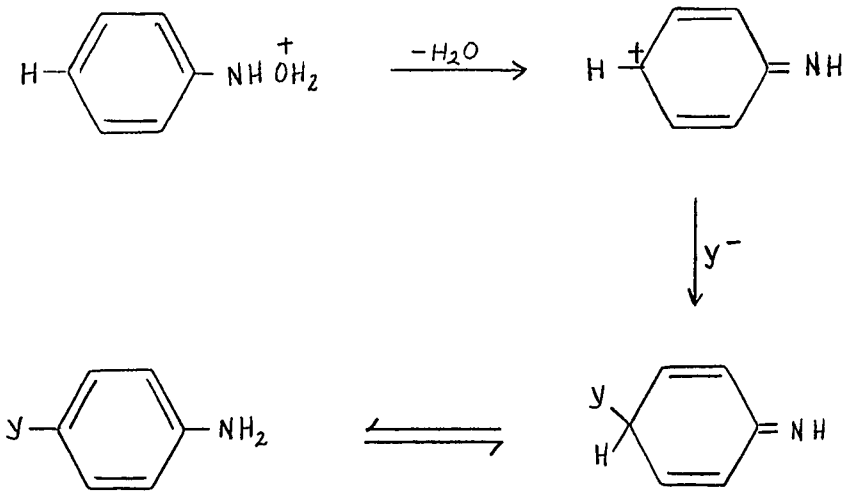
The formation of the chlorinated compound can be readily explained if reduction of 118 had occurred only as far as the hydroxylamino stage, and the resulting hydroxylamine (158) was subsequently attacked by the hydrochloric acid to yield the chloro-amino derivative (156) as shown in Scheme 6.



118 158 156

Scheme 6

This mechanism, which is similar to that described by Heller, Hughes and Ingold (1951) as an explanation of the rearrangement of hydroxylamines to substituted amines and is commonly referred to as the Bamberger rearrangement, could not give rise to a 4-chlorinated compound (Scheme 7).



Scheme 7

Bamberger (1921, 1921a, 1925) reported that chloride ion and other nucleophilic species such as methoxy, ethoxy, and hydroxyl radicals react with aromatic hydroxylamines and aromatic azides to yield p-substituted amines as the major products. The prolonged action of hydrochloric acid on phenylhydroxylamine, for example, yielded p-chloroaniline, o-chloroaniline and smaller amounts of o,p-disubstituted aniline, azoxybenzene, and aniline. Although traces of o-aminophenol and trichloroaniline were

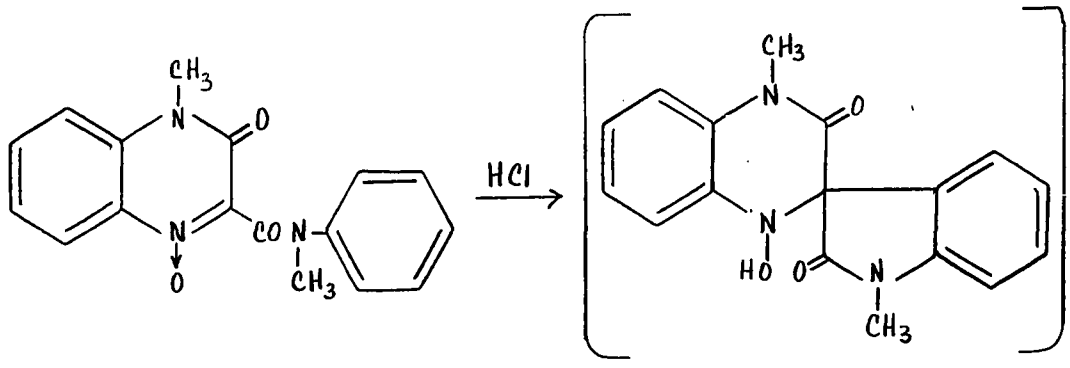
also isolated, no m-substituted amines were reported. When hydrogen bromide was used, similar observations were made except that a somewhat larger yield of aniline was isolated. Similar reactions have also been observed by Kock (1887) and Robertson and Evans (1940), who have reported the formation of p-chloroaniline as a by-product in the reduction of nitrobenzene with zinc and hydrochloric acid.

Other reactions of this type have also been reported. Clark-Lewis and Katekar (1959) found that the action of hydrochloric acid on 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-N-methylanilide 1-oxide (106) yielded 6-chloro-1,2,3,4,2',3'-hexahydro-4,1'-dimethyl-3,2'-dioxoquinoxaline-2-spiro-3'-indole (107). These investigators postulated a mechanism which involved the formation and chlorination of a hydroxylamine intermediate (108).

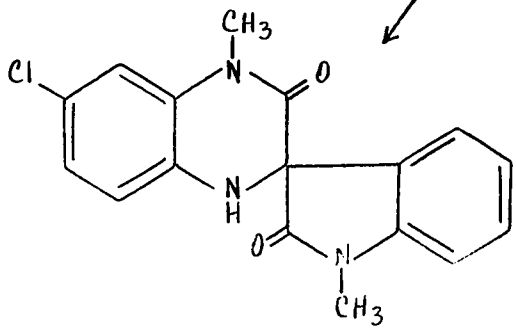
Loudon and Wellings (1960a) have shown that the reaction of ethyl acetoacetate and related compounds with o-nitrobenzaldehyde in the presence of hydrochloric acid also gives rise to chlorinated products, i.e., 6-chloro-1-hydroxy-4-quinolones (159).

From this evidence, and later work discussed in this thesis, it was concluded that the catalyzed sodium borohydride reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) had given rise to 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-

3-pyrazolin-5-one (156).



106 108



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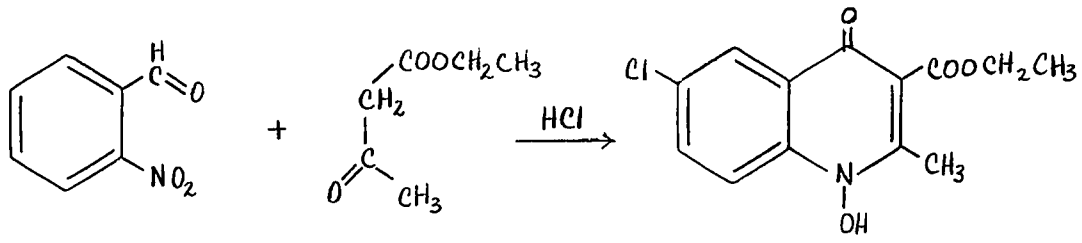
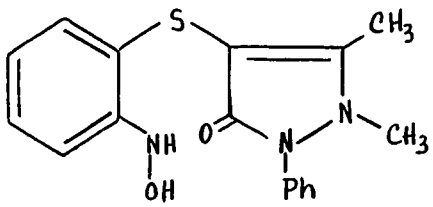


159

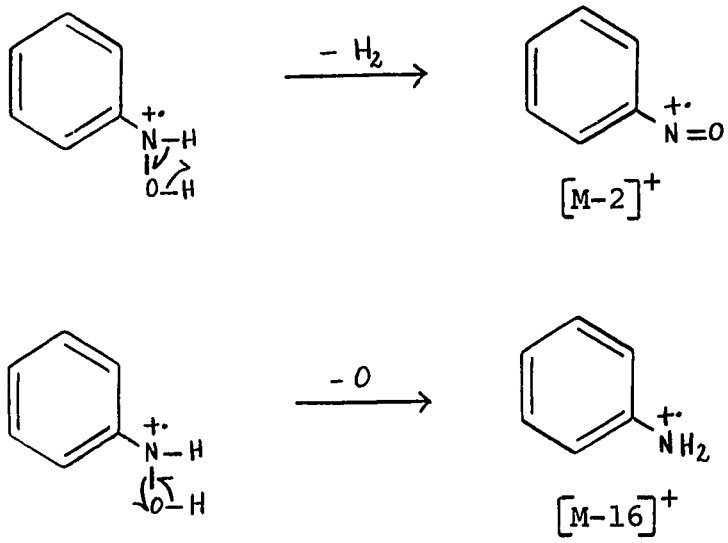
If the mechanism, shown in Scheme 6, for the formation of 156 was correct, it should be possible to isolate the intermediate hydroxylamine (158) by excluding hydrochloric acid from the reaction, and to convert this compound to the chloro amine (156) by subsequent treat-

ment with hydrochloric acid. To confirm this, the reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) with sodium borohydride and palladium-charcoal was repeated, and the filtrate was acidified with acetic acid. The expected hydroxylamine (158) was isolated as a pale yellow solid.



158

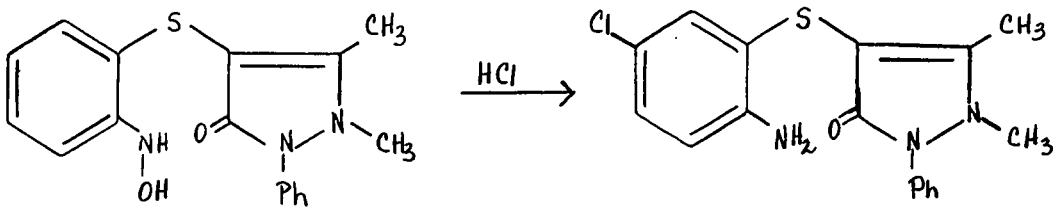
Structure 158 was assigned to this product for the following reasons. The compound readily reduced Tollen's reagent, it analyzed satisfactorily for $C_{17}H_{17}N_3O_2S$, and its mass spectrum possessed a molecular ion at m/e 327. The mass spectrum also contained $[M-2]^+$ and $[M-16]^+$ fragment ions of significant intensity. Coutts and Mukherjee (1970) have shown that this type of fragmentation pattern is characteristic of aromatic hydroxylamines (Scheme 8). The infrared spectrum of 158 also possessed strong carbonyl stretching at 1619 cm^{-1} and a broad peak at 3245 cm^{-1} which was attributed to both NH and OH absorption.



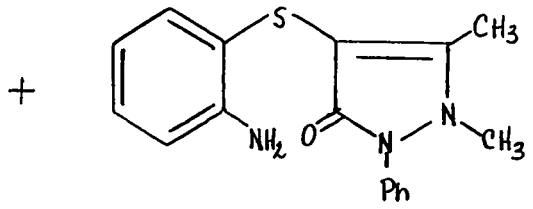
Scheme 8

4-(o-Hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158) was treated with hydrochloric acid. Extraction of the neutralized reaction mixture yielded a grey solid, which proved to be a mixture of 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (147) and 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156).

Although recrystallization failed to raise the melting point of this product, and thin layer chromatography gave only one spot, its mass spectrum indicated the presence of both compounds 147 and 156. The mass spectrum possessed a molecular ion at m/e 345 and an abundant fragment ion at m/e 311. The intensity of the peaks at m/e 347 and 313 indicated that the ion at m/e 345 contained chlorine while, the one at m/e 311 did not.



158 156

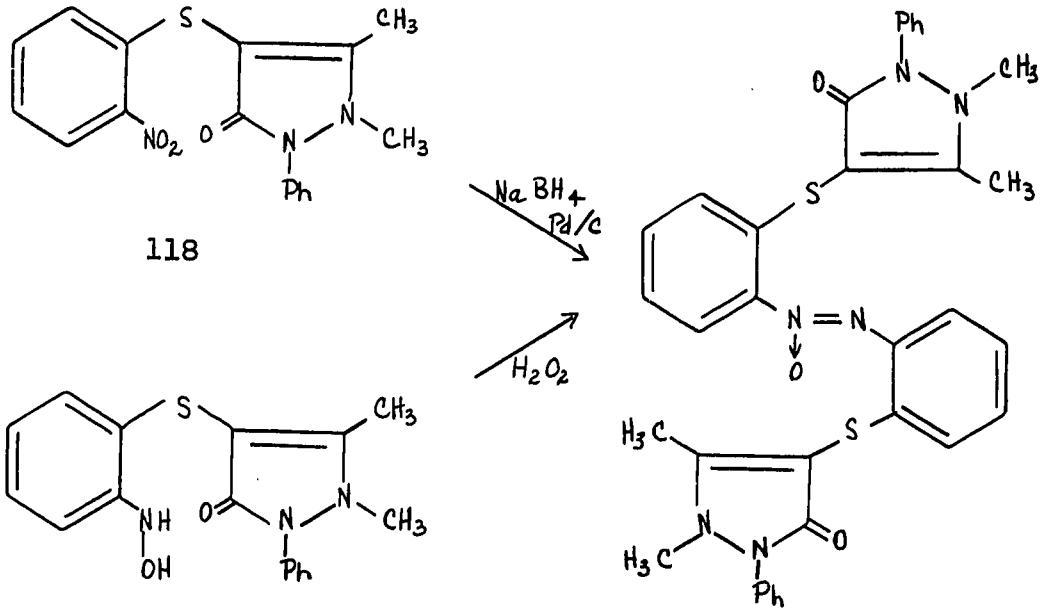


147

Since the fragment at m/e 311 could not be formed by the loss of chlorine from the ion at m/e 345, it must represent the molecular ion of another compound, namely, 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (147).

The formation of the non-chlorinated amine (147) in the above reaction was not unexpected in view of the report by Heller, Hughes and Ingold (1951) who explained the reported (Bamberger, 1921, 1921a, 1925) formation of aniline from phenylhydroxylamine as being due to the irrelevant oxidation-reduction of the starting material. Presumably in this case, the hydroxylamine, 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158) undergoes a similar auto oxidation-reduction reaction.

As a matter of interest, the catalyzed sodium borohydride reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) was repeated, and the filtered reaction mixture was evaporated to dryness without acidification. Recrystallization of the resulting semi-solid with a dimethyl sulfoxide/ethanol solvent system gave rise to a product which has been identified as 2,2'-bis [(2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl) thio]-azoxybenzene (160).



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158

160

The elemental analysis of this product (160) satisfied a molecular formula of $C_{34}H_{30}N_6O_3S_2$. The infrared spectrum, which possessed a carbonyl peak at 1668 cm^{-1}, did not contain any absorption due to the presence of an NH function. The appropriateness of structure 160 was also

supported by the mass spectrum which displayed a molecular ion at m/e 434, and a strong $[M-16]^+$ fragment at m/e 418. The presence of the $[M-16]^+$ peak was attributed to the loss of oxygen from the azoxy function. It is known that the mass spectrum of azoxybenzene possesses a prominent $[M-16]^+$ peak (Budzikiewicz, Djerassi and Williams, 1967a).

The azoxybenzene (160) was also prepared by the oxidation of 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158) with hydrogen peroxide.

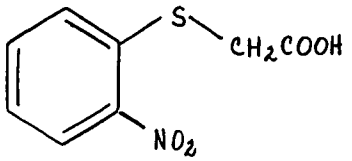
Similar reactions involving hydroxylamine derivatives which also give rise to azoxy compounds have been reported (Parisi, Bovina and Quilico, 1962; Ochiai, Ohta and Nomura, 1957).

Interaction of Cyclic Hydroxamic Acids and Aromatic Hydroxylamines with Hydrochloric Acid

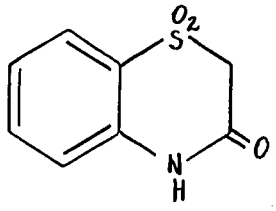
Previous mention was made of the report by Coutts, Barton, and Smith (1966) that the reduction of (o-nitrophenylthio)acetic acid (149) gave rise to three products, one of which (designated as product E), was thought to be 3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (152). Since the infrared spectrum and analytical data of product E were consistent with structure 152, the possibility of this compound being a chlorinated compound had not been considered.

In view of the unexpected chlorination observed

during the reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118), the identity of product E was now questioned. A sample was submitted for mass

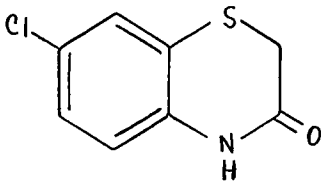


149



152

spectral analysis and this revealed that the product was not the sulfone. The spectrum contained molecular ions at m/e 199 and 201, indicating that the molecule contained chlorine. This observation made possible the suggestion that E was 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (161). This conclusion was supported by the following evidence.

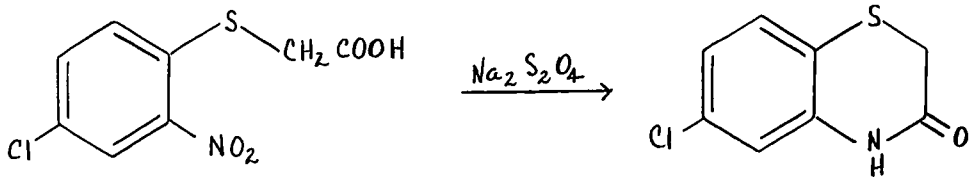


161

The elemental analysis of E was consistent also with the molecular formula C_8H_6ClNOS. Its infrared spectrum showed carbonyl absorption and an NH stretching band typ-

ical of a lactam ring system. The n.m.r. spectrum of this compound contained signals which could be ascribed to a methylene group, an NH proton, and three aromatic protons. Using the principles described earlier in this discussion, it was possible to measure the coupling constants of the proton signals and thus identify the individual protons of the aromatic signal (Figure 8). This confirmed the presence of a 1,2,4-trisubstituted benzene ring in the compound. Two structures (161 and 162) were theoretically possible, but in the light of the previous work involving 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158), the possibility that E was 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (162) was considered very unlikely. However, since the reported melting point of the 6-chloro derivative (162) was identical with that of 161, an authentic sample of 162 was prepared for direct comparison with product E.

The product reported by Prasad and Tietje (1966) was used to prepare 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (162). This involved the sodium hydrosulfide reduction of (4-chloro-2-nitrophenylthio)acetic acid (163).



163 162

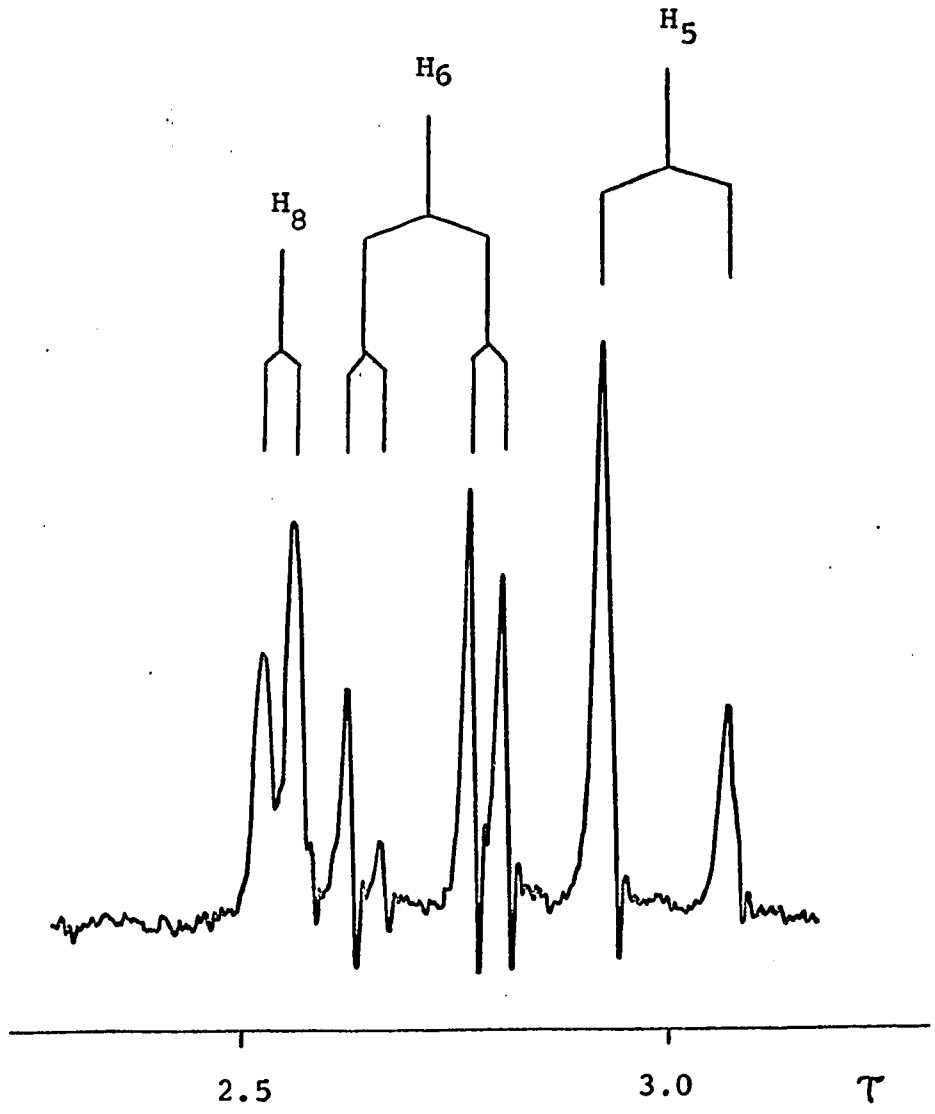


Figure 8: N.m.r. Spectrum (aromatic ring protons) of 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (161).

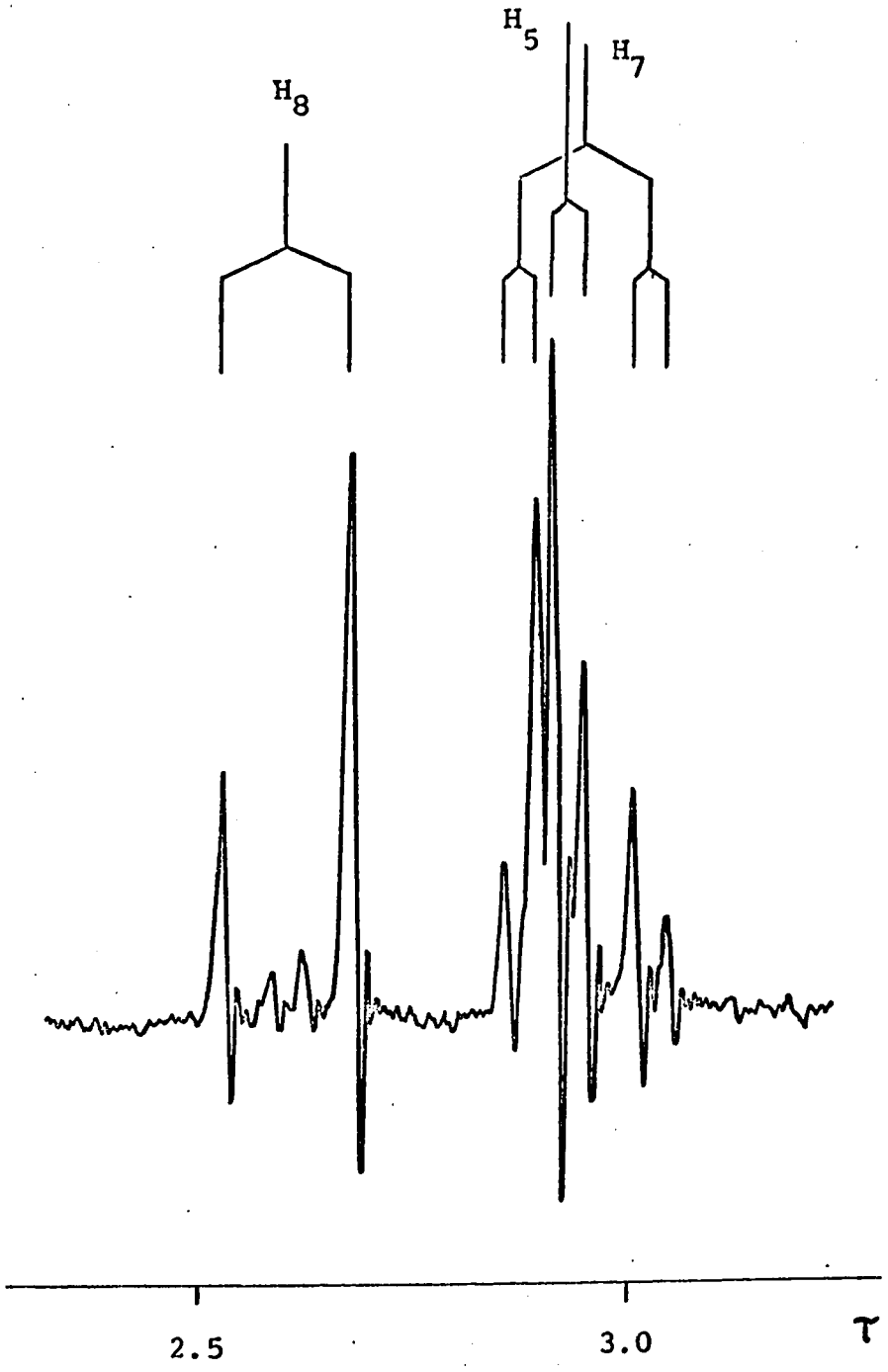
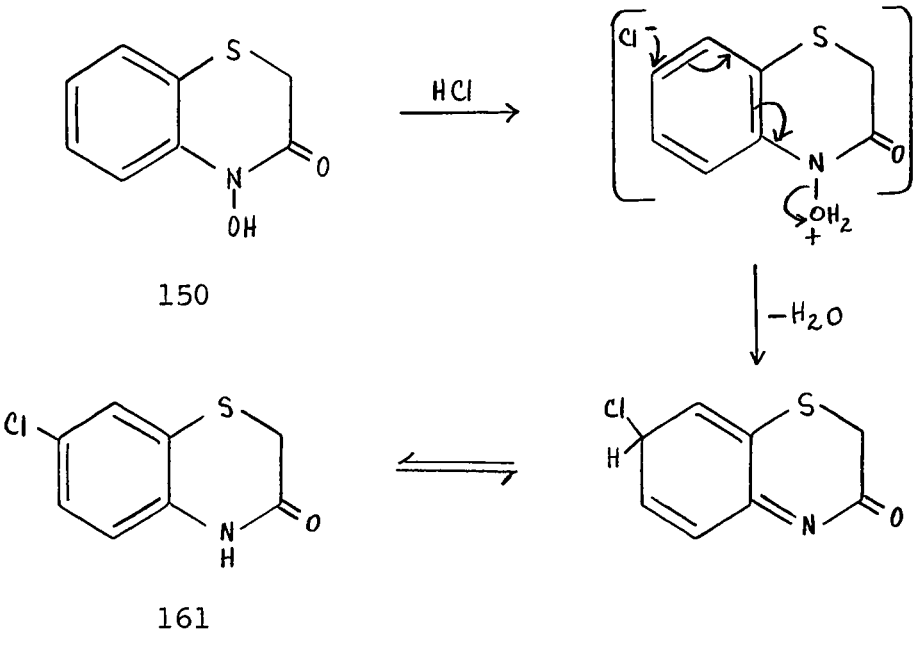


Figure 9: N.m.r. Spectrum (aromatic ring protons) of 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (162).

The infrared spectrum of this product (162) showed carbonyl absorption at 1670 cm^{-1} and NH stretching at 3185 cm^{-1}, and differed significantly from that of the 7-chloro derivative (161). A mixed melting point of the two products was depressed. The n.m.r. spectrum of 162 was similar to that of the isomer 161, but the aromatic signals of both compounds, while each still possessing the characteristic 1,2,4-trisubstituted benzene pattern, (cf. Figures 8 and 9) differed significantly.

The formation of the 7-chloro lactam (161) can be explained by a mechanism similar to that proposed for the formation of 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156) during the catalyzed sodium borohydride reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118). Presumably this reaction involves the nucleophilic attack of chloride ion on the protonated hydroxamic acid as shown below.

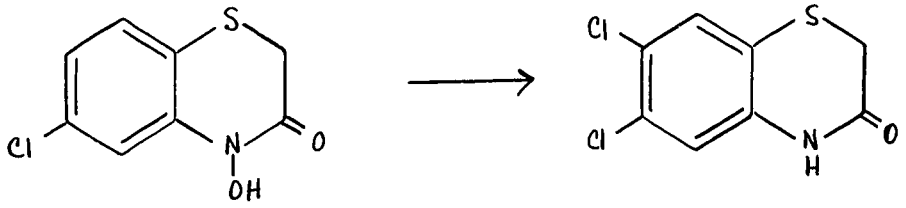


150

161

The authenticity of this mechanism was substantiated by treating a pure sample of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) with hydrogen chloride. This yielded a grey solid, which, on recrystallization from ethanol, proved to be 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (161).

The fact that attack had occurred at the 7-position was further confirmed when it was found that the action of hydrogen chloride on 6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (164) resulted in the formation of a product, $C_8H_5Cl_2NOS$, that was identified as 6,7-dichloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (165).



164 165

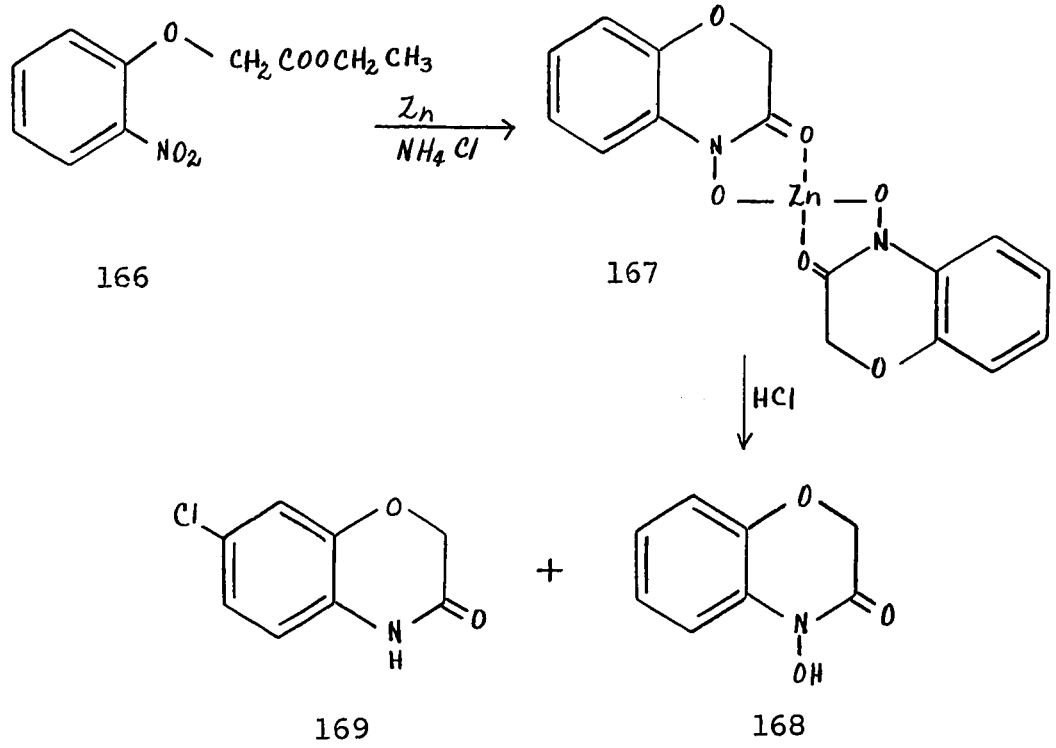
The infrared spectrum of 165 displayed both carbonyl and NH stretching bands. Its n.m.r. spectrum possessed signals due to the methylene group and the NH function. Of more importance was the aromatic signal, which consisted of two one-proton signals at τ2.32 and τ2.80 that were attributed to protons at the 5- and 8-positions in the molecule, i.e., positions which would not permit ortho- or meta-coupling.

The significance of this chlorination reaction is that it provides a means of preparing 7-chlorobenzothiazines which are not readily available by conventional reductive methods. The synthesis of 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (161) for example, would require (2-nitro-5-chlorophenylthio)acetic acid as a starting material. This acid is not readily available by the action of thioglycollic acid on 2,4-dichloronitrobenzene because of the reactivity of both chlorine atoms.

It has been found that the formation of chlorinated lactams is not restricted to the 1,4-benzothiazine series. The action of hydrochloric acid on 1,4-benzoxazine hydroxamic acids also yields 7-chloro lactam derivatives.

When Coutts and Hindmarsh (1966; Hindmarsh, 1970) were investigating the synthesis of benzoxazine hydroxamic acids, they found that the reduction of ethyl (o-nitrophenoxy)-acetate (166) with zinc dust and ammonium chloride yielded a zinc chelate of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (167) and a second product that was insoluble in sodium carbonate solution and gave a negative ferric chloride test. The second product has now been identified as 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (169). It analyzed satisfactorily for $C_8H_6ClNO_2$, a molecular formula supported by its mass spectrum. The infrared spectrum of this compound was consistent with this structure. While the aromatic signal in the n.m.r. spectrum of 169 was too complex for complete interpretation, even

when the spectrum was recorded on a 100 Mc. instrument, it did integrate for three protons. The spectrum also possessed a two-proton methylene singlet and an NH signal which exchanged with deuterium oxide. The n.m.r. spectrum, therefore, supported structure 169.

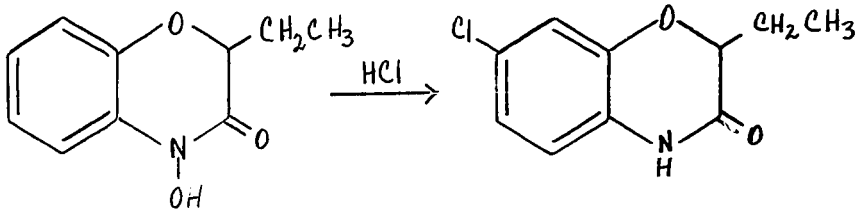


166 167 169 168

A purified sample of the zinc chelate (167) analyzed satisfactorily for a molecular formula of $C_{16}H_{12}N_2O_6Zn$. Hydrolysis of this product (167) with acetic acid yielded only the hydroxamic acid (168). It was also found that heating 3,4-dihydro-4-hydroxy-3-oxo-1,4-benzoxazine (168) itself, under reflux with dilute hydrochloric acid gave a good yield of 7-chloro-3,4-dihydro-3-oxo-1,4-benzoxazine (169).

A similar chlorination reaction occurred on prolonged

treatment of 2-ethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (170) with dilute hydrochloric acid at room temperature, and gave rise to a neutral compound. The infrared spectrum of this product possessed carbonyl and NH absorption bands. Its mass spectrum contained a molecular ion at m/e 211 and a strong $[M+2]^+$ peak indicating the presence of chlorine in the compound. From this and its microanalysis, it was concluded that this product was 7-chloro-2-ethyl-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (171).

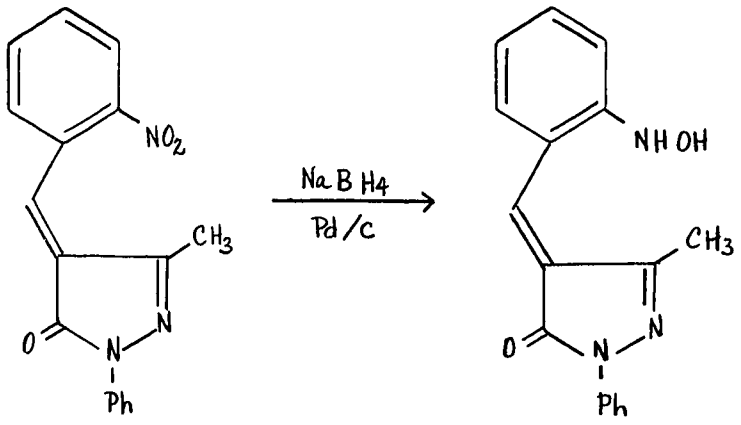


170 171

Bamberger (1921, 1921a, 1925) has reported that nucleophilic reagents such as methanol, ethanol, hydrogen bromide, phenol, and aniline also react with phenylhydroxylamine, giving rise to p-substituted anilines. This would suggest that these nucleophilic reagents might also react at the 7-position of the hydroxamic acids, making possible the preparation of a number of 7-substituted lactam derivatives.

Interest in the properties of N-hydroxy compounds was extended to a study of the action of hydrochloric acid on 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyra-

zolin-5-one (172). The catalyzed sodium borohydride reduction of 3-methyl-4-(o-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (63) yielded a colorless compound which was not characterized by Coutts and Edwards (1966). This product has now been purified and identified as 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (172). The identity of this compound was based on the observation that it reduced Tollen's reagent and that it gave an elemental analysis that corresponded to a molecular formula of $C_{17}H_{15}N_3O_2$. Its mass spectrum displayed a molecular ion at m/e 293 and an abundant $[M-16]^+$ fragment ion. The infrared spectrum of 172 possessed carbonyl stretching and a broad absorption band between 3100 and 3400 cm^{-1} with a maximum at 3275 cm^{-1}, which was attributed to the OH and NH absorption bands of the hydroxylamine function.

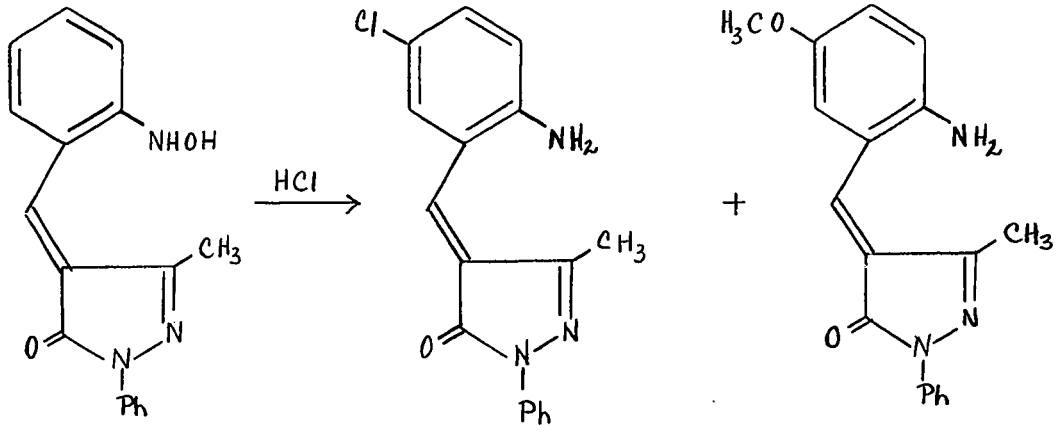


63 172

This hydroxylamine (172) was treated with hydrogen

chloride. Initially methanol was used as a solvent for this reaction. The solid that was left on evaporation of the reaction mixture was shown to be a mixture of 4-(2-amino-5-chlorobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (173) and 4-(2-amino-5-methoxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (174).

The mass spectrum of the mixture possessed a molecular ion at m/e 311 and an intense ion at m/e 307. Accurate mass determinations revealed that these ions



172 173 174

possessed molecular formulae of $C_{17}H_{14}ClN_3O$ and $C_{18}H_{17}N_3O_2$ respectively. It is seen that these formulae correspond to structures 173 and 174. Thin layer chromatography of this product indicated the presence of two compounds possessing R_f values of 0.61 and 0.30. These values were found to be identical to the R_f values of authentic samples of 173 and 174 chromatographed under the same conditions.

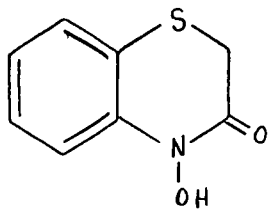
Authentic 4-(2-amino-5-chlorobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (173) was prepared by treating a solution of 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (172) in tetrahydrofuran with hydrogen chloride. This gave a black semisolid which, when chromatographed on a silica gel column, yielded 4-(2-amino-5-chlorobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (173). The infrared spectrum of this product possessed absorption bands that were attributed to carbonyl and NH absorption, as well as a strong peak at 812 cm^{-1} that was indicative of aromatic CH bending. Elemental analysis showed that the compound was a monohydrate, $C_{17}H_{14}ClN_3O.H_2O$, and prolonged drying at elevated temperatures failed to remove all of the water of crystallization. The mass spectrum of this compound contained a molecular ion at m/e 311 ($C_{17}H_{14}ClN_3O$) and the expected strong $[M+2]^+$ peak, characteristic of the presence of chlorine in the molecule.

Treatment of a methanolic solution of 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (172) with concentrated sulfuric acid produced a brown oil which was chromatographed and gave an authentic sample of 4-(2-amino-5-methoxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (174) as a white solid. The mass spectrum and microanalysis of this product supported a molecular formula of $C_{18}H_{17}N_3O_2$. The significant difference between the infrared spectrum of 174 and that of the 2-amino-

5-chloro derivative (173) was the absence of any absorption at 812 cm^{-1}.

Interaction of Benzothiazine and Benzoxazine Hydroxamic Acids with Acetic Anhydride

The preparation of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) was mentioned in the preceding section (see page 97). To aid in the characterization of this compound, an acetate derivative was prepared by reacting the hydroxamic acid (150) with acetyl chloride. This yielded a product which was isomeric with, but not identical to, the acetate prepared by the interaction of 150 with acetic anhydride (Coutts et al, 1968). This observation led to a detailed study of the acetylation of the benzothiazine hydroxamic acid (150) and the related hydroxamic acids, 175, 176, and 168.



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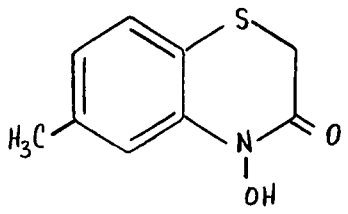

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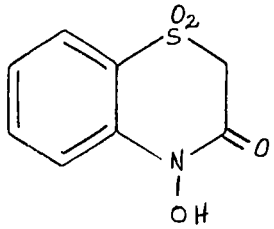

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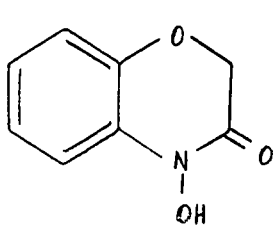
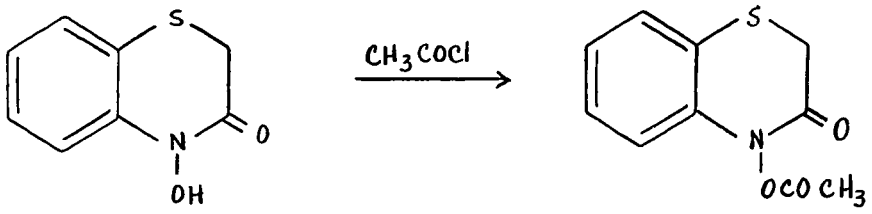


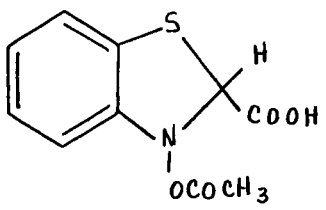
168

The treatment of a solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) in dry benzene with excess acetyl chloride yielded 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (177). The identity of this product was based on the following observations. This compound (177) gave an elemental analysis which corresponded to a molecular formula of $C_{10}H_9NO_3S$. Its mass spectrum possessed a molecular ion at m/e 223 and a $[M-42]^+$ ion at m/e 181. The presence of a metastable ion at m/e 146.9 supported the direct fragmentation of a ketene molecule (CH_2CO) from the molecular ion, and the presence of a fragment ion at m/e 43 (CH_3CO^+) also supported structure 177. This type of fragmentation is very common in the mass spectra of acetate derivatives (Budzikiewicz, Djerassi and Williams, 1967). The presence of two carbonyl bands at 1705 and 1802 cm^{-1} in the infrared spectrum was also indicative of structure 177. Carbonyl stretching in the region of 1800 cm^{-1} in the infrared spectrum is characteristic of the N-acetoxy group (Loudon and Wellings, 1960, 1960a; Loudon and Tennant, 1960; Ohta and Ochiai, 1962; Paquette, 1965; Coutts et al, 1968). Final confirmation of the authenticity of structure 177 was obtained by examining its n.m.r. spectrum. The three-proton singlet at τ 7.66, the two-proton singlet at τ 6.43 and a four-proton multiplet between τ 2.55 and τ 3.20 were signals which could be associated respectively with the methyl group, the methylene group, and the four aromatic protons of structure 177.

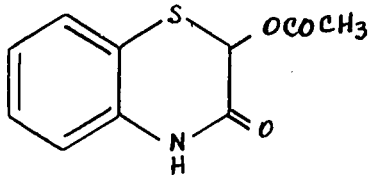


150 177

The reaction of acetic anhydride with 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) was repeated and yielded a product that was identical to the one reported in the literature (Coutts et al, 1968). Elemental analysis and mass spectral data again supported a molecular formula of $C_{10}H_9NO_3S$ for this derivative. The presence of fragment ions at m/e 43 and $[M-42]^+$ and a metastable ion of mass 146.7 in the mass spectrum indicated that this compound was also an acetate derivative of 150, i.e., an isomer of 177. The n.m.r. spectrum of this compound contained a three-proton singlet at τ 8.0 (CH_3), a one-proton singlet at τ 3.69 (CH), a four-proton aromatic signal in the τ 2.58 to 3.18 region and a broad one-proton signal at τ -0.1 which exchanged with deuterium oxide. The absence of a two-proton singlet near τ 6.5 indicated that the reaction must have occurred at the active methylene group in the 2-position of the molecule. Two structures can be written which might be expected to give an n.m.r. spectrum of this type (178 and 179).



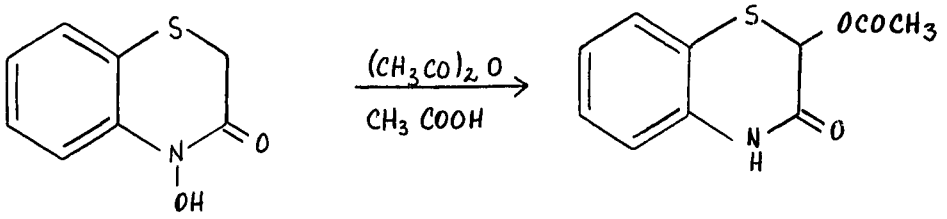
178



179

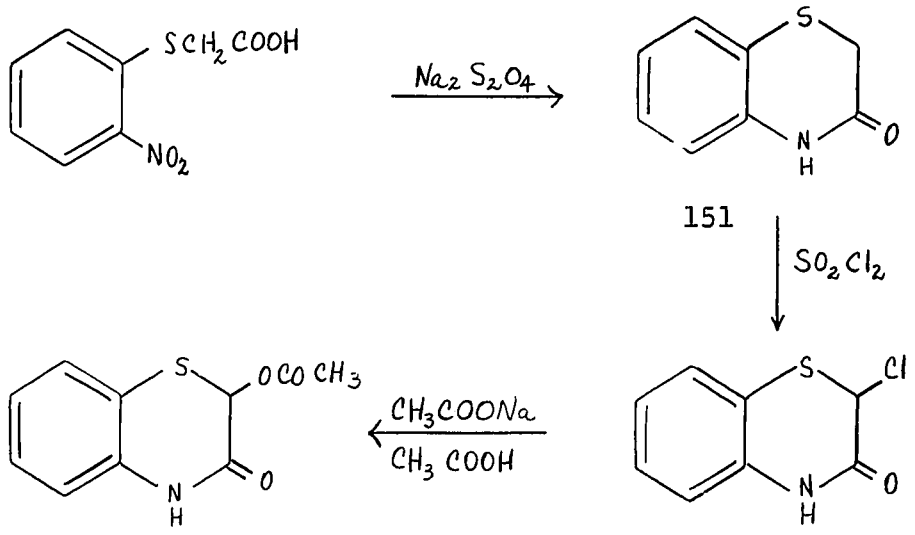
A closer look at the other properties of the acetate immediately eliminated structure 178. The acetate was insoluble in dilute sodium carbonate solution and, therefore, was not a carboxylic acid. For this reason the singlet at τ-0.1 in the n.m.r. spectrum was deduced to be due to an NH rather than an acidic OH group. Structure 179 is also supported by the infrared spectrum of this product, which displays carbonyl peaks at 1680 and 1758 cm^{-1} and a sharp band at 3200 cm^{-1} which was attributed to NH stretching. The fact that there were no carbonyl bands in the region of 1800 cm^{-1} in this spectrum indicated that the N-acetoxy function was not present in the molecule. From this, it is proposed that acetoxylation, not acetylation, had occurred during the treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) with acetic anhydride, giving rise to 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (179).

Compound 179 is known, and its reported melting point was the same as that of the product isolated from this reaction. An authentic sample of 2-acetoxy-3,4-dihydro-



150 179

3-oxo-2H-1,4-benzothiazine (179) was prepared by the literature method (Zahn, 1923) (Scheme 9) to confirm the identity of the compound prepared in the present study. A comparison of the infrared data and a mixed melting point of the two compounds proved that they were identical.



179

Scheme 9

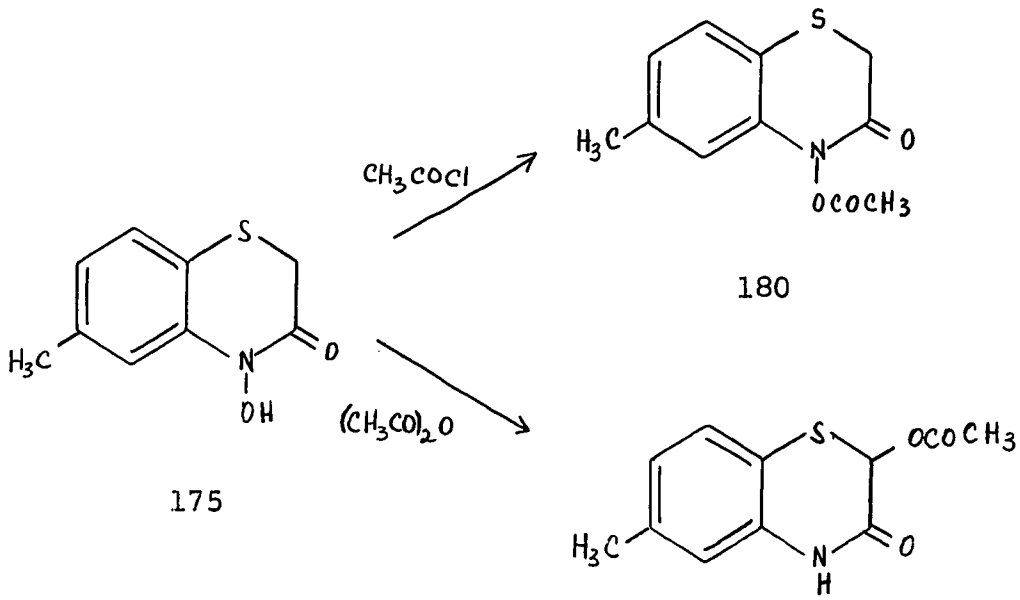
Further investigation revealed that the treatment of

4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (177) with glacial acetic acid gave a good yield of 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (179). The mechanism of this reaction is discussed later (Scheme 10). It was also found that acetic acid did not react with the hydroxamic acid (150) itself. Only starting material was recovered from this reaction. No reaction occurred either when 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (151) was heated with acetic anhydride in acetic acid.

Analogous results were obtained with 3,4-dihydro-4-hydroxy-6-methyl-3-oxo-2H-1,4-benzothiazine (175). Treatment of this hydroxamic acid with acetyl chloride yielded 4-acetoxy-3,4-dihydro-6-methyl-3-oxo-2H-1,4-benzothiazine (180). The identity of this product was inferred from its microanalysis, $C_{11}H_{11}NO_3S$, its n.m.r. which indicated the presence of both protons of the methylene group, and its infrared spectrum which possessed two carbonyl bands at 1705 and 1795 cm^{-1}.

When 3,4-dihydro-4-hydroxy-6-methyl-3-oxo-2H-1,4-benzothiazine (175) was heated under reflux with acetic anhydride, the 2-acetoxy derivative (181) was isolated. The microanalysis of this product satisfied a molecular formula of $C_{11}H_{11}NO_3S$, and its infrared spectrum lacked carbonyl stretching bands above 1755 cm^{-1}. Its n.m.r. spectrum contained a one-proton singlet at τ3.82 which indicated that attack had taken place at the 2-position and showed this compound to be 2-acetoxy-3,4-dihydro-6-

methyl-3-oxo-2H-1,4-benzothiazine (181).

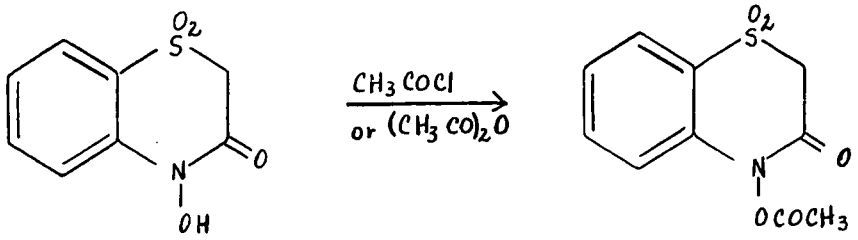


180

175

181

Coutts and co-workers (1968) had reported that the action of acetic anhydride on 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (176) produced 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (182). In view of the above results this reaction was reinvestigated. It was found that treatment of the hydroxamic acid (176) with acetyl chloride or acetic anhydride gave only one product, 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (182), even on prolonged heating. This product was identical to that reported by Coutts et al (1968).

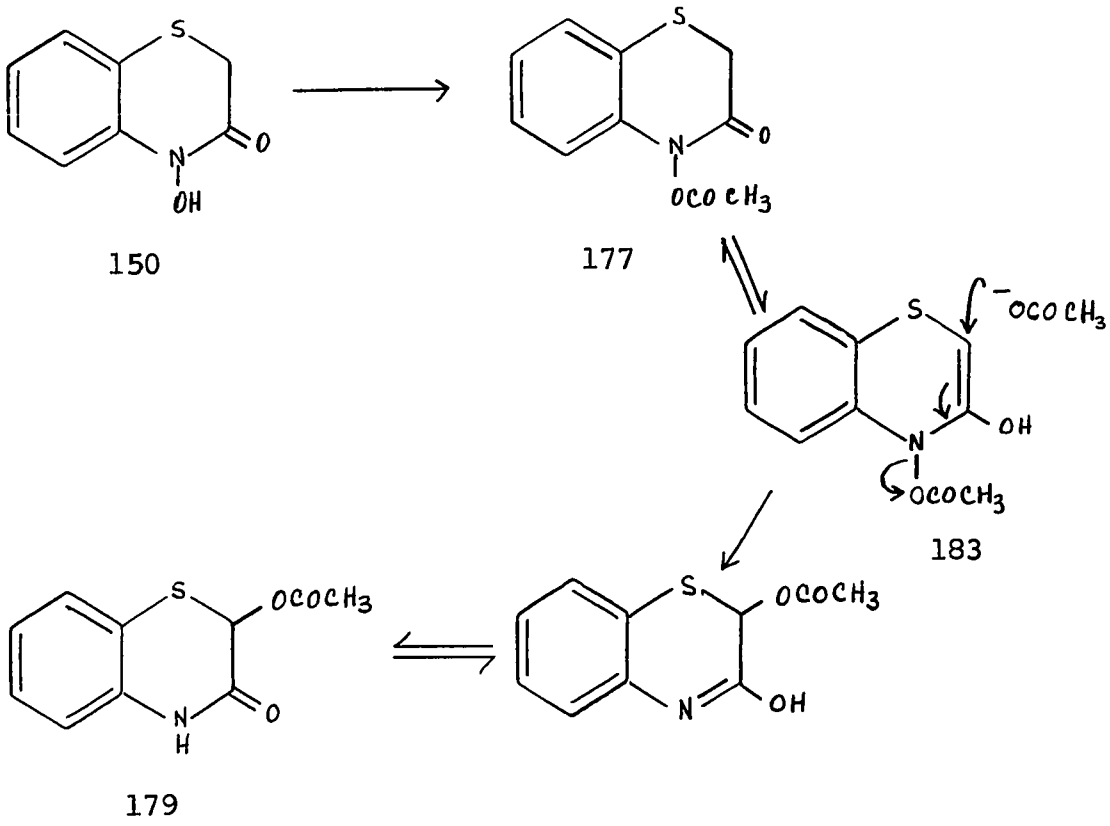


176 182

The formation of the 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazines can be explained by the mechanism in Scheme 10. This involves an initial acetylation of the N-hydroxy function of the hydroxamic acid followed by a nucleophilic attack by the acetate anion at the 2-position of the enolized tautomer (183), and the subsequent expulsion of the 4-acetoxy group. The acetate anion probably arises from the solvent; however, an intermolecular rearrangement could also be involved.

A related reaction is the α-acetoxylation of certain steroidal ketones which also involves the formation of an enol intermediate (Fieser and Romero, 1953; Clarke, 1960).

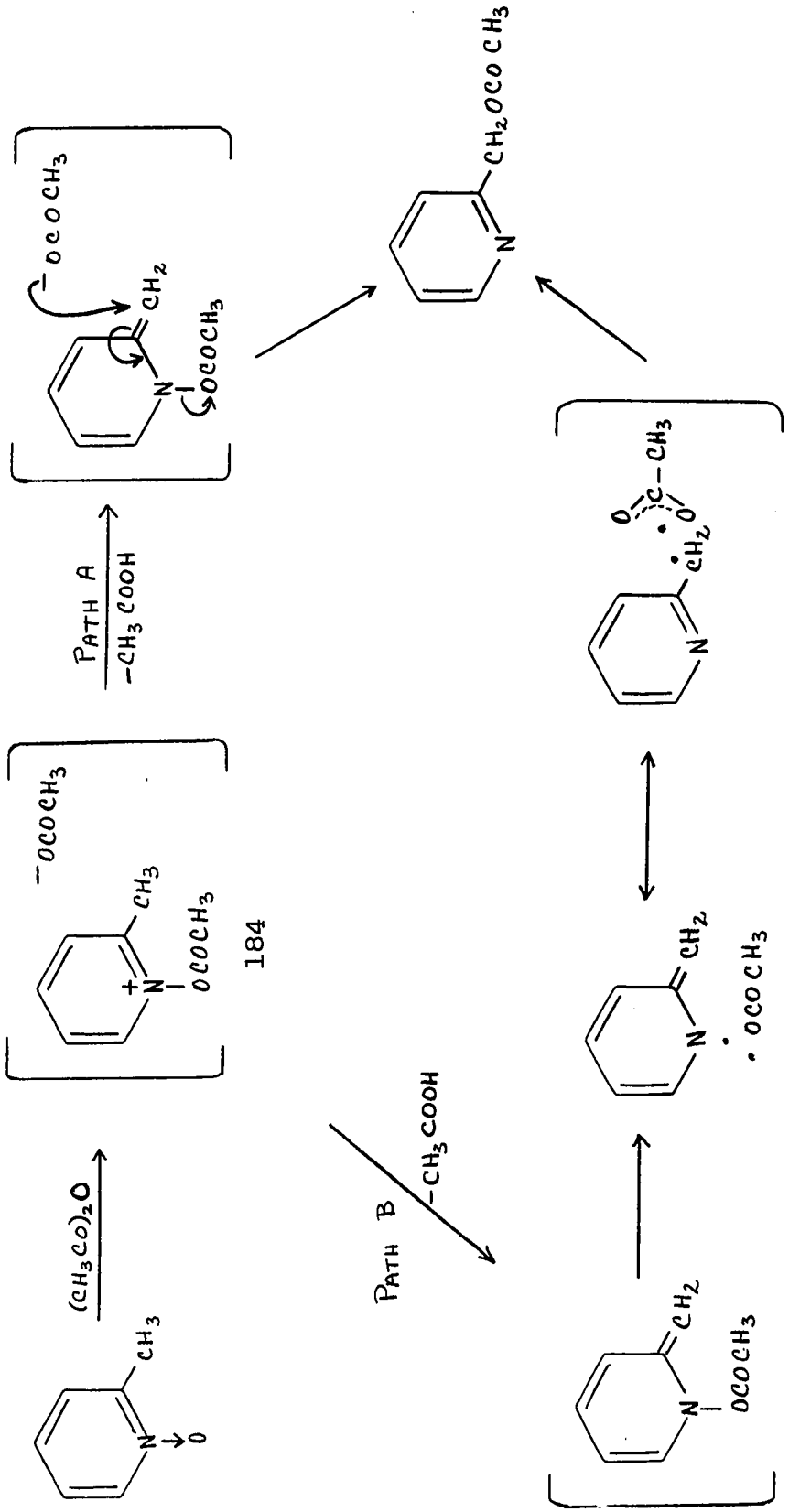
The proposed mechanism (Scheme 10) has been written as an ionic reaction. This is a reasonable suggestion; however, in view of recent studies on the acetoxylation of 2- and 4-picoline 1-oxides (e.g. Scheme 11) (Paquette, 1968) the possibility of a free radical mechanism should not be overlooked. Although it is generally agreed that the first step in the acetoxylation of picoline 1-oxides



Scheme 10

is the formation of 184, conclusive evidence pertaining to the fate of 184 remains to be provided. Two mechanisms, involving ion-pairs (path A) or radical-pairs (path B) are being studied by current investigators. The formation of smaller quantities of 3-acetoxypyridines during these reactions can also be rationalized in terms of either polar or radical intermediates.

The fact that the sulfone (176) does not acetylate in the 2-position is attributed to steric hindrance. The size of the sulfone group, together with the tendency of

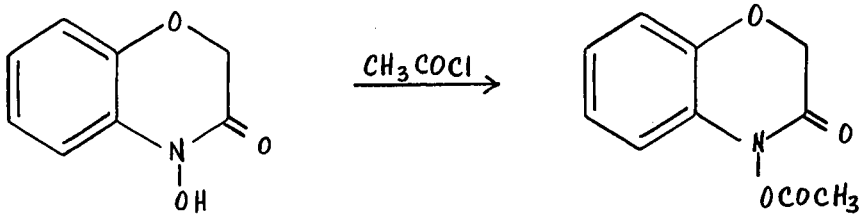


Scheme 11

the oxygen atoms to repel the attacking anion, presumably block this reaction.

These acetylation reactions were repeated using the benzoxazine hydroxamic acid, 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (168). This led to the isolation of an unexpected product as described below.

Treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (168) with acetyl chloride gave a product, $C_{10}H_9NO_4$, which proved to be 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185). Its infrared spectrum possessed carbonyl absorption at 1700 and 1803 cm^{-1}, and its n.m.r. spectrum displayed signals which could be attributed to the methyl, methylene and aromatic protons of structure 185.

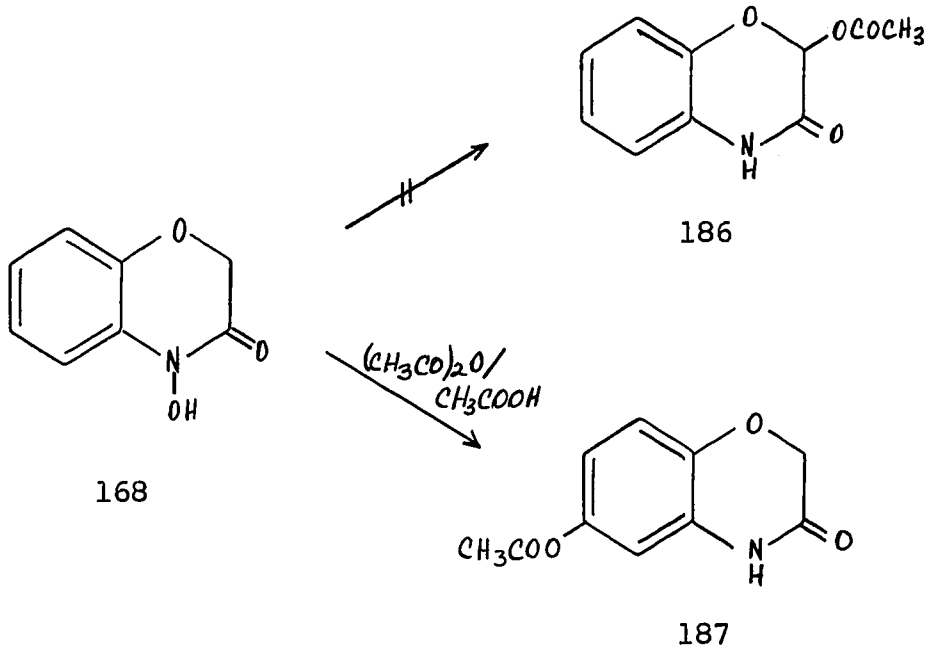


168 185

However, heating a solution of the hydroxamic acid (168) with acetic anhydride and acetic acid did not yield the expected 2-acetoxy derivative (186). The following information revealed that the product isolated (designated as product F) was, in fact, 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187).

This compound (F) gave an elemental analysis which

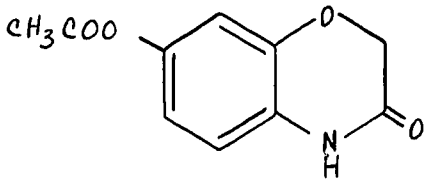
corresponded to $C_{10}H_9NO_4$, a formula which was also supported by the mass spectrum. This spectrum contained a molecular ion at m/e 207 and strong fragment ions at m/e 165 ($[M-42]^+$) and m/e 43, all of which indicated that this compound was isomeric with the 4-acetoxy derivative (185). The infrared spectrum of F displayed carbonyl absorption bands at 1695 and 1760 cm^{-1} as well as NH



stretching at 3200 cm^{-1}. The fact that product F was not the expected 2-acetoxy derivative (186) was evident from the n.m.r. spectrum. The presence of a two-proton methylene signal at τ5.43 in the spectrum, and the fact that the aromatic signal integrated for only three protons, indicated that the substitution had occurred in the aromatic ring rather than at the 2-position.

In view of the results obtained from the previous

work involving the action of hydrochloric acid on these hydroxamic acids, it was felt that the acetoxylation had probably involved nucleophilic attack of the acetate ion (CH_3COO^-) at the 7-position of the aromatic ring, giving rise to 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188), but, further investigation proved this assumption to be incorrect.

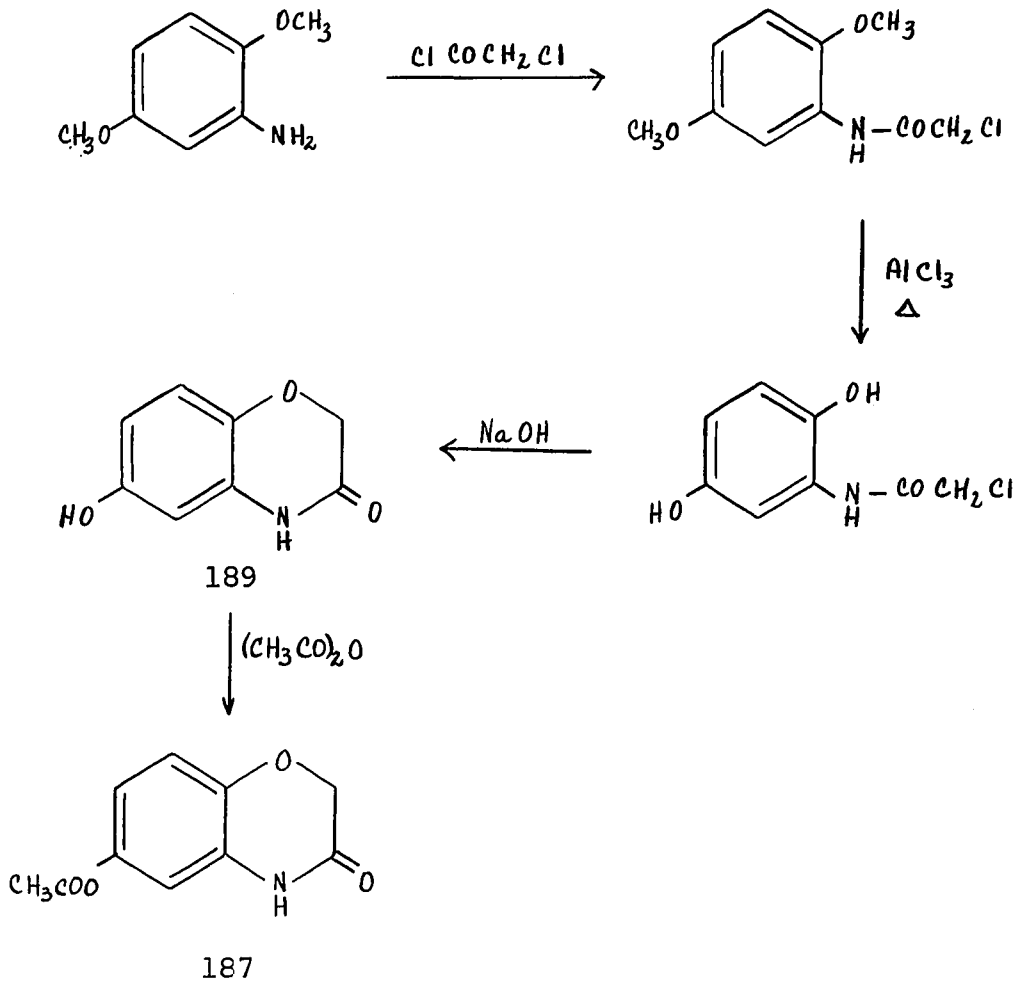


188

A literature search revealed that both 6-acetoxy- (187) and 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188) were known. The melting point of the acetoxy derivative (F) isolated in the above reaction did not correspond to that reported for the 7-acetoxy derivative (188). Instead it was the same as the melting point recorded for 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187). It was also found that hydrolysis of this acetoxy compound (F) yielded a phenol which had a melting point and ultraviolet spectrum that were the same as those quoted for 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (189). From this it was concluded that the product isolated from the treatment of 3,4-dihydro-4-

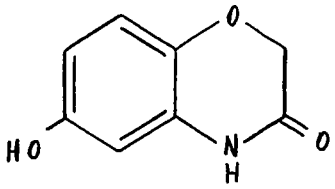
hydroxy-3-oxo-2H-1,4-benzoxazine (165) with acetic anhydride and acetic acid was 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187).

Since acetoxylation in the 6-position of the hydroxamic acid was totally unexpected, a sample of 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188) was prepared by the unambiguous synthesis reported previously by Loudon and Ogg (1955) (Scheme 12). The 6-acetoxy derivative prepared by this method was identical to the pro-

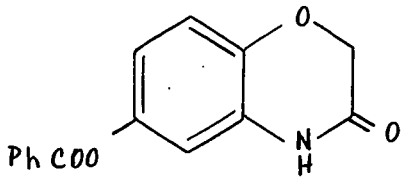


Scheme 12

duct formed by the treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (165) with acetic anhydride. The fact that these two compounds were identical was further confirmed when it was shown that hydrolysis of both with sodium hydroxide solution yielded the same product, 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzothiazine (189), and that the benzoate derivatives, 6-benzoyloxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (190), of these 6-hydroxy lactams (189) were also identical.



189



190

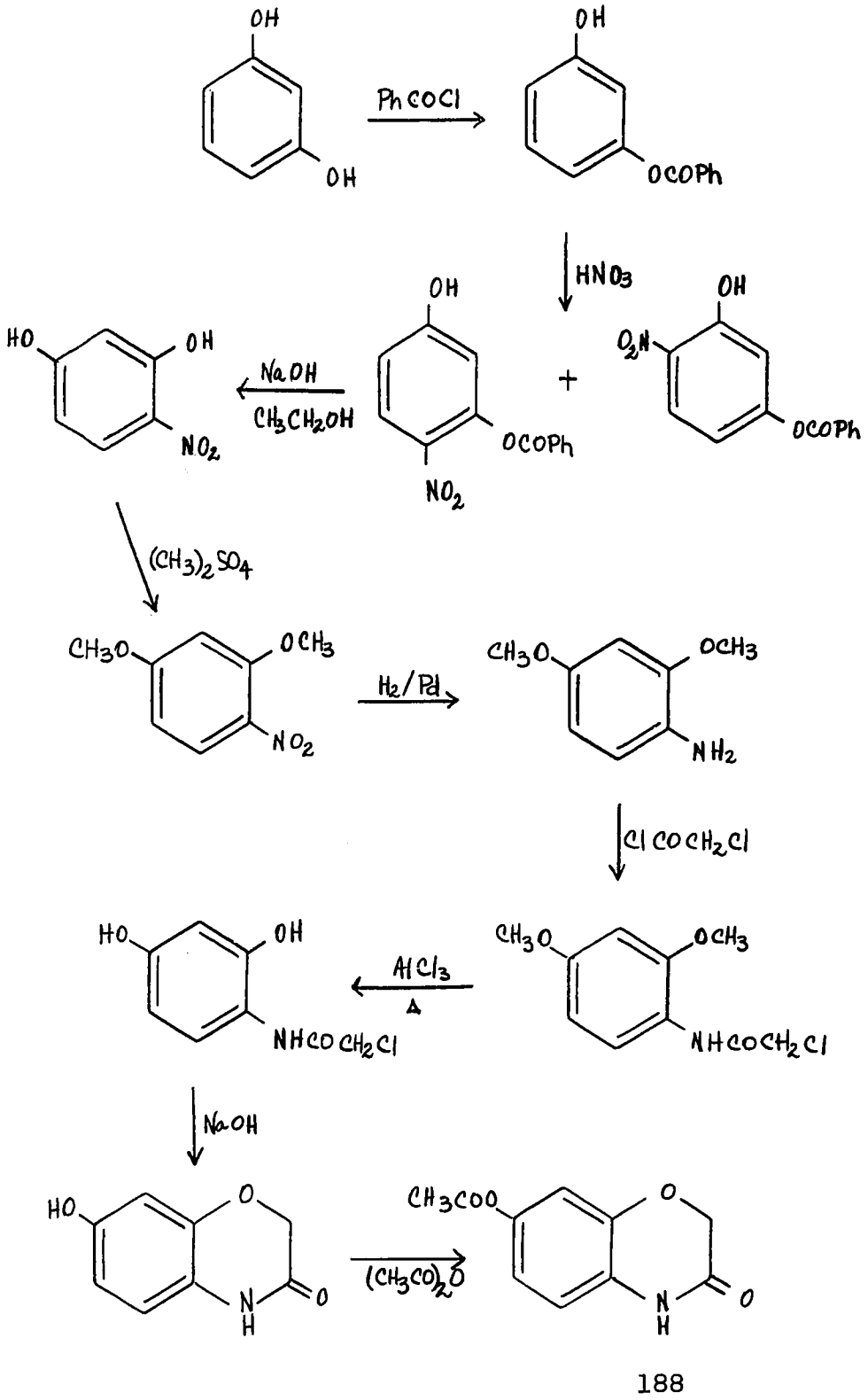
It was then established that the 4-acetoxy benzoxazine (185) could be converted mainly to the 6-acetoxy derivative (187), together with trace amounts of 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188) and an additional unidentified compound.

Treatment of 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185) with glacial acetic acid gave a product which, on repeated recrystallization, yielded 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187). When the filtrates from these recrystallizations were bulked and evaporated to dryness, a residue was left. This solid was

further investigated. Its infrared spectrum was nearly identical to that of the pure 6-acetoxy derivative (187) and it gave only one spot on thin layer chromatography, but repeated recrystallization and column chromatography failed to raise its melting point to that of 187. On one occasion, however, a small amount of compound was obtained which had a melting point that suggested that it might be 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (188). The infrared spectrum of F was similar to, but not identical with, that of the 6-acetoxy derivative (187). Its n.m.r. spectrum also possessed a three-proton aromatic signal which differed significantly from that of the 6-acetoxy lactam. It was then found that the infrared and n.m.r. spectra of this compound were superimposable on those of an authentic sample of 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (188) prepared by the method outlined by Loudon and Ogg (1955) (Scheme 13).

Attempts to isolate more of this compound from the reaction mixture were unsuccessful, but when a sample of the mixture was subjected to gas-liquid chromatography, a chromatographic trace was obtained which indicated the presence of three products represented by peaks I, II, and III as shown in Figure 10.

The largest of these peaks (II) was increased in size when a sample of pure 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (187) was added to the mixture prior to chromatography. Similarly, peak III was augmented when the



188

Scheme 13

7-acetoxy derivative (188) was added. Peak I was not identified at this time. From this it was determined

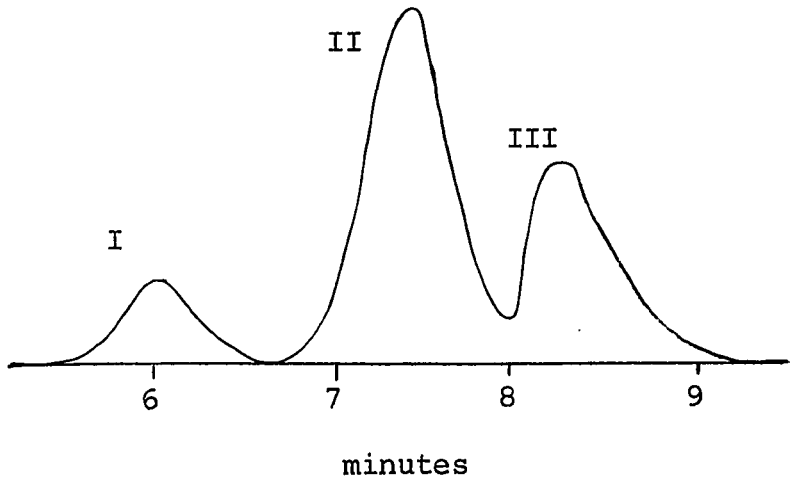
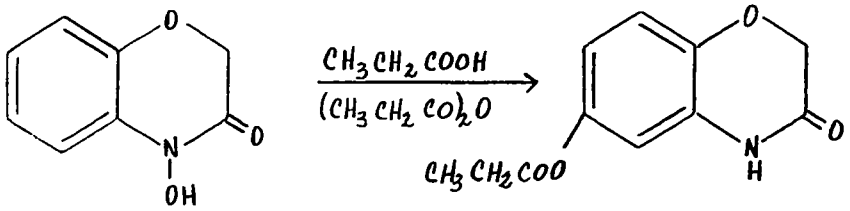


Figure 10: Chromatographic trace of the product from the reaction of acetic acid with 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine.

that the treatment of 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185) with acetic acid gave rise to 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187), 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188), and a third, as yet unidentified, product in yields of approximately 85, 10, and 5% respectively.

To confirm that the N-acetoxy group was involved in these reactions, the hydroxamic acid (168) itself, was treated with glacial acetic acid. This yielded only starting material. Similarly, the lactam, 3,4-dihydro-3-oxo-2H-1,4-benzoxazine was recovered unchanged after heating with acetic anhydride.

When 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (168) was heated with propionic anhydride in propionic acid, a crystalline solid was obtained. This product proved to be 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine (191).

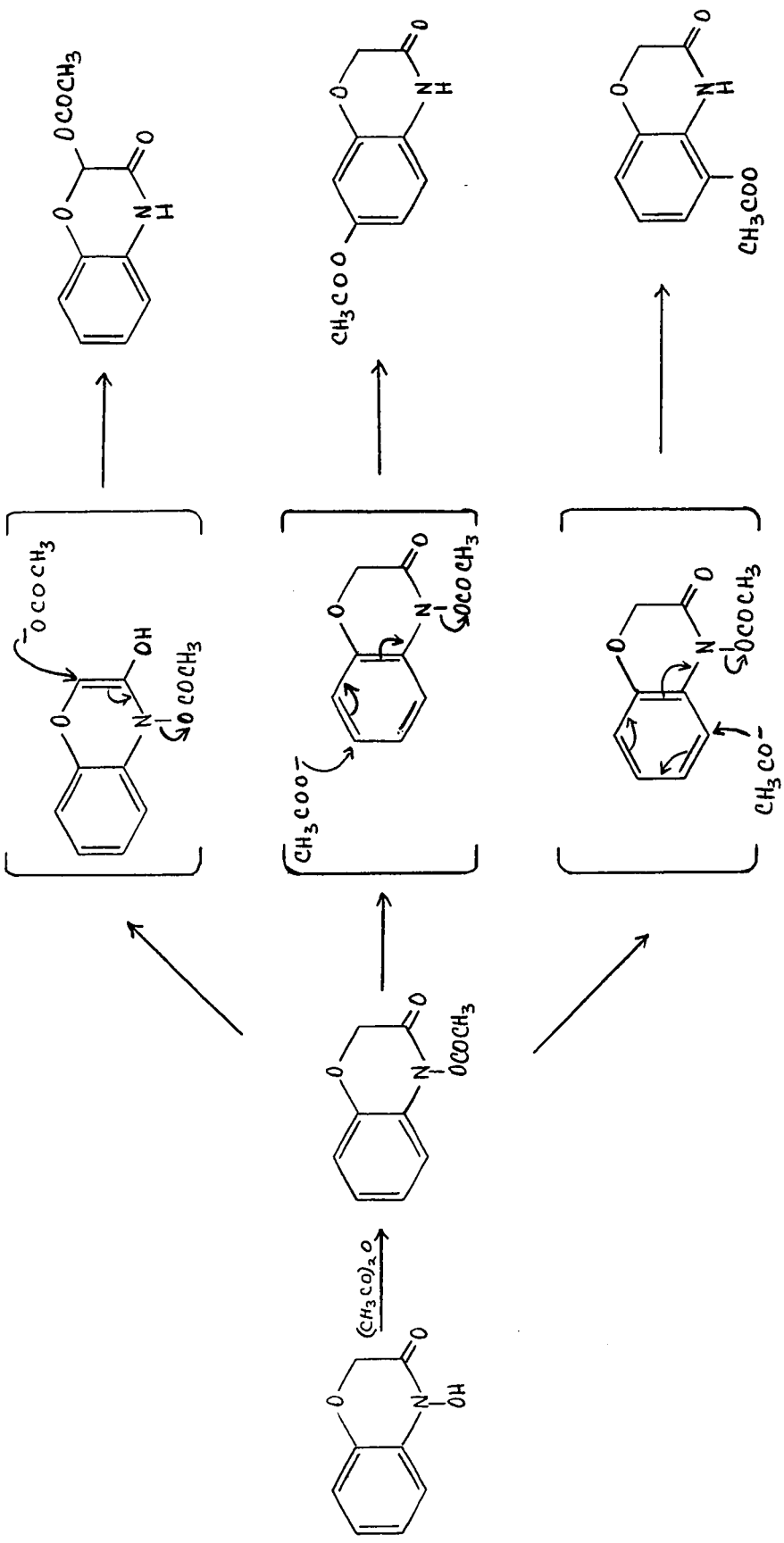


168 191

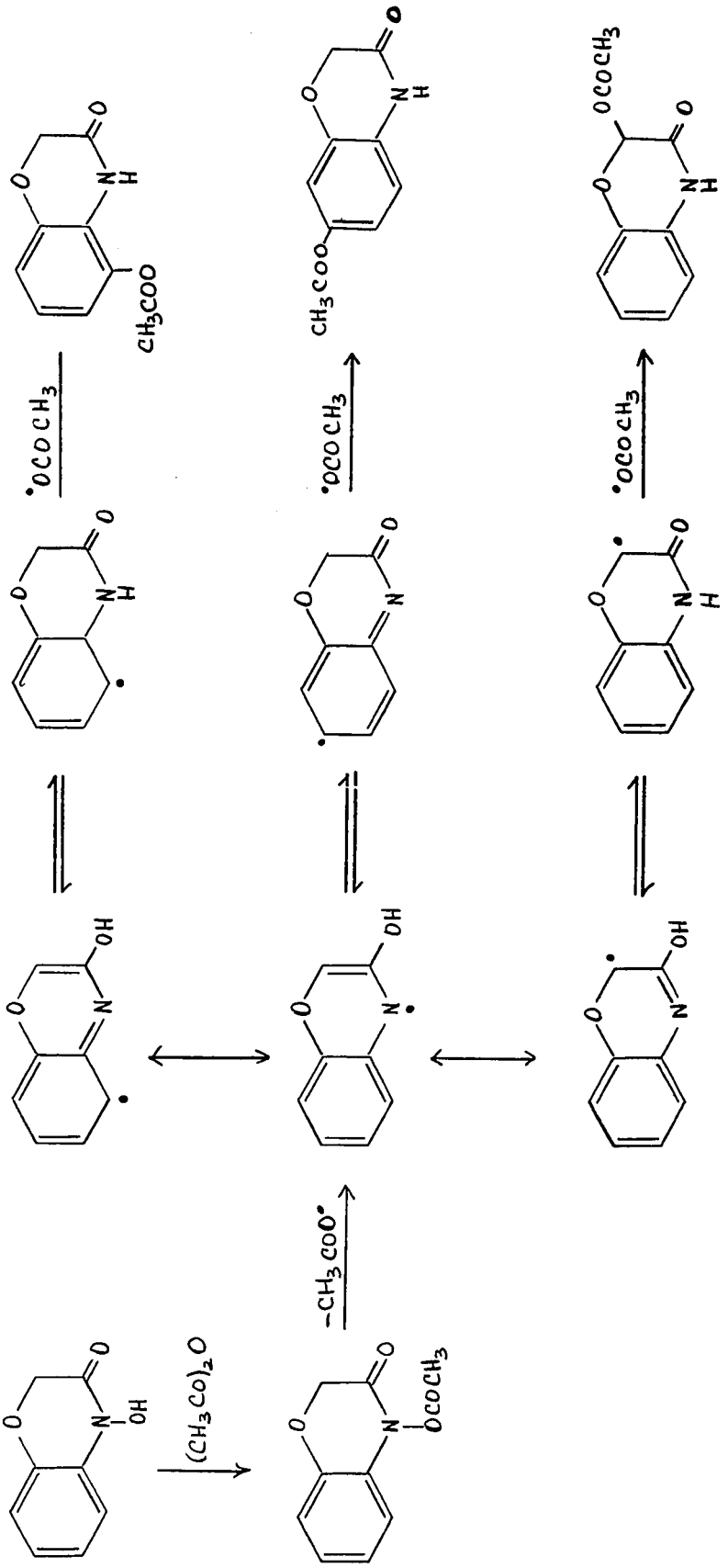
The microanalysis of this compound (191) satisfied a molecular formula $C_{11}H_{11}NO_4$; its infrared spectrum and n.m.r. spectrum were in agreement with this formula. Hydrolysis of 191 yielded 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (189).

It was also found that 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine (191) was formed when 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185) was heated with propionic acid; in contrast, the action of propionic acid on the 6-acetoxy derivative (187) yielded only starting material.

Obviously, this reaction involves more than simple nucleophilic attack by the acetate anion. If this were so, one might expect substitution to occur at the 2-, 7-, and possibly the 5-position in the hydroxamic acid (Scheme



Scheme 14



Scheme 15

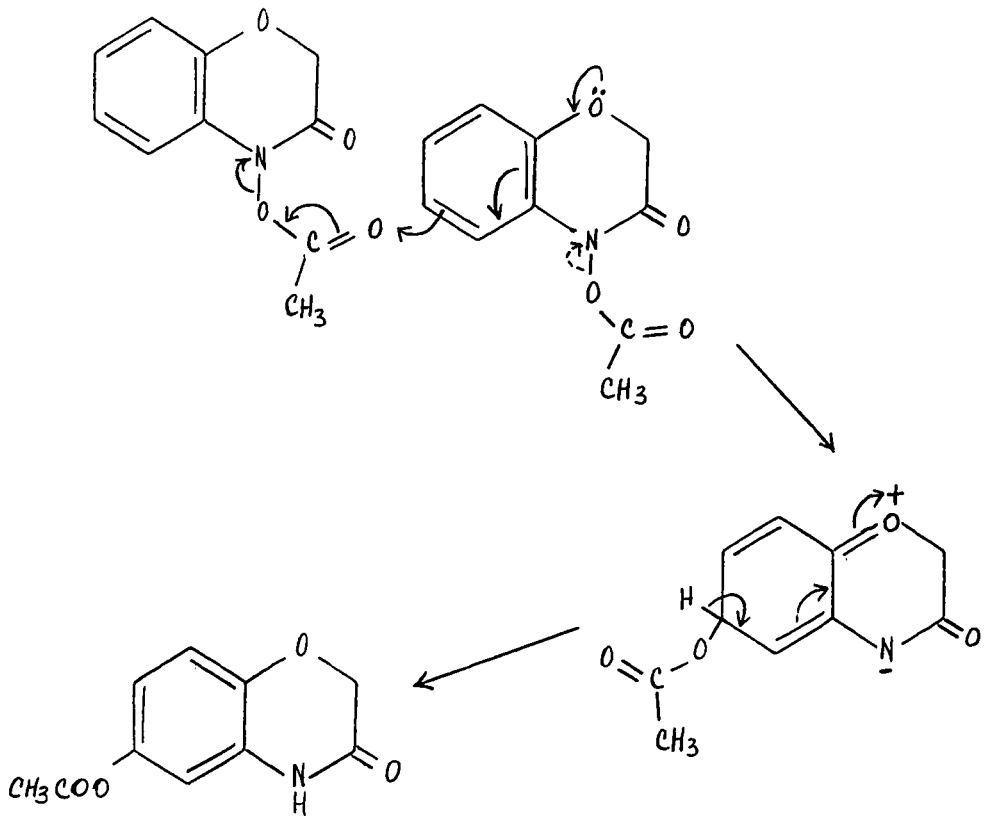
14).

Even if a free radical, rather than an ion-pair, mechanism was involved, the formation of the 6-acetoxy compound is not explained. One would also expect a free radical mechanism to give rise to 2-, 7-, and possibly 5-substituted compounds (Scheme 15).

It has been confirmed that the presence of the N-acetoxy function is necessary for the rearrangement to occur. If this reaction did not involve this group, the same type of reaction should occur in the lactam series. As mentioned, when either the benzothiazine or benzoxazine lactams were treated with acetic anhydride only starting material was recovered.

From these observations a tentative mechanism is proposed (Scheme 16). This involves an intermolecular rearrangement as shown below. The rearrangement is presumably influenced by the presence of the ring oxygen atom, which might be responsible for the reaction occurring at the 6-position.

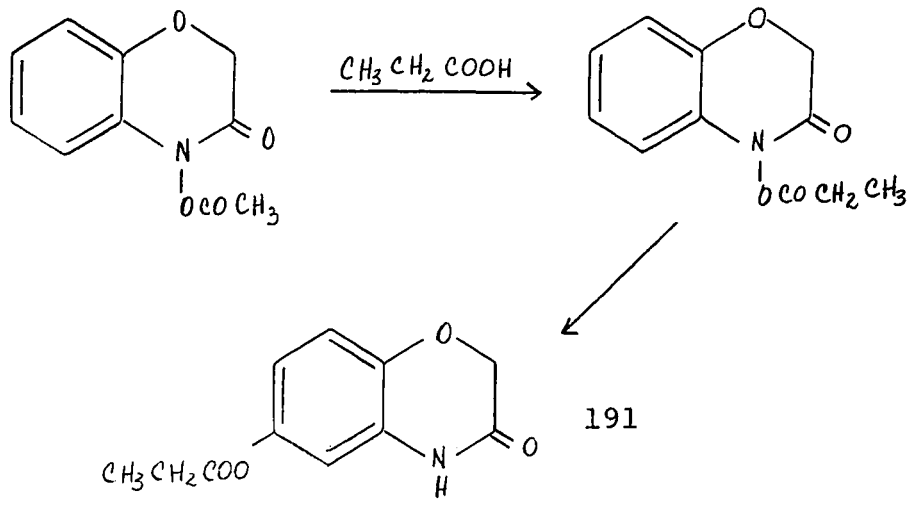
The conversion of 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185) to 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine (191) by the action of propionic acid can also be explained by this mechanism only if the conversion involves an ester exchange (Scheme 17) before the rearrangement takes place, since it has been shown that an ester exchange does not occur when 6-acetoxy-



187

Scheme 16

3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187) is heated under reflux in propionic acid.



191

Scheme 17

From the above discussion it is seen that more work will be required to clarify this mechanism and to fully investigate the scope of the reactions of hydroxamic acids. Such studies are now in progress.

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting poirt apparatus. All melting points are uncorrected. Infrared (i.r.) spectra were recorded as nujol mulls on a Beckman IR-10 spectrophotometer unless otherwise specified. Nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A-60 Spectrometer, using trimethylsilane as an internal standard and deuterated dimethyl sulfoxide as solvent unless otherwise stated. Mass spectra were determined by Dr. A.M. Hogg and his associates, Department of Chemistry, University of Alberta, with an A.E.I. MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct probe technique. Elemental analyses were performed by the Department of Chemistry and the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta.

The author wishes to thank Dr. R.T. Coutts and coworkers for furnishing authentic samples of the following compounds: methyl (4-methyl-2-nitrophenylthio)acetate (Coutts, Peel, and Smith, 1965); (4-chloro-2-nitrophenylthio)acetic acid and methyl (4-chloro-2-nitrophenylthio)-acetate (Coutts, Barton, and Smith, 1966); 3-methyl-4-(o-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (Coutts and Edwards, 1966); zinc chelate of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (Coutts and Hindmarsh, 1966); 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine and 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide

(Coutts et al, 1968); 7-chloro-2-ethyl-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (Hindmarsh, 1970).

General procedure for sodium borohydride and palladium-charcoal reductions

An aqueous solution (10 ml) of sodium borohydride (0.5 g) was carefully added to a suspension of palladium-charcoal (0.05 g) in water (5 ml). A concentrated solution of the nitro compound (1.0 g), in a suitable solvent, was added dropwise to this reducing system over a period of fifteen minutes. Nitrogen was passed through the suspension during the addition of the nitro compound, and for a further fifteen minutes after the addition was completed. If the catalyst tended to precipitate, sufficient water was added to resuspend it. The reaction mixture was then filtered, and the filtrate treated in the manner described in detail in the following procedures.

4-(o-Nitrophenylthio)pyrazolin-5-ones

Bis-(o-nitrophenyl)disulfide (120) (Bogart and Stull, 1928)

A hot ethanolic solution (1.5 l) of sodium disulfide, prepared from sodium sulfide (360 g) and sulfur (48 g), was slowly added to a hot solution of o-chloronitrobenzene (315 g) in ethanol (500 ml). After heating on a water bath for two hours, the reaction mixture was cooled and filtered. The resulting product was washed

with water, leaving the title compound, as a yellow solid (180 g), m.p. 189-190°. Reported (Bogart and Stull, 1928) m.p. 192-195°.

o-Nitrobenzenesulfenyl chloride (119) (Hubacher, 1935)

A stream of dry chlorine gas was passed slowly through a warmed suspension of bis-(o-nitrophenyl) disulfide (77 g) and iodine (0.25 g) in dry carbon tetrachloride (300 ml) for one to two hours. The reaction mixture was cooled and filtered, leaving a yellow solid. A second crop of crystals was obtained by concentrating the mother liquors. These products were combined and recrystallized from carbon tetrachloride leaving yellow needles of o-nitrobenzenesulfenyl chloride (70 g), m.p. 73-75°. Reported (Hubacher, 1935) m.p. 73-74°.

1,3-Diphenyl-2-pyrazolin-5-one (121b) (Hinton and Mann, 1959)

Phenylhydrazine (11.9 g) was slowly added to ethyl benzoylacetate (21.4 g) and the mixture warmed on a water bath for five minutes. This solution was then poured into ether (75 ml) and stirred for a further two hours. The precipitate, which formed slowly during this time, was the title compound. It was an off-white solid (18.2 g), m.p. 136-138° (ethanol). Reported (Hinton and Mann, 1959) m.p. 135-138°.

3-Methyl-2-pyrazolin-5-one (121c) (Carpino, 1958)

Hydrazine hydrate (17.0 g) was added slowly, with

stirring, to a solution of ethyl acetoacetate (44.5 g) in ether (150 ml). A vigorous exothermic reaction occurred. The suspension, which formed almost immediately, was filtered, and the precipitate was washed with water and ether to yield 3-methyl-2-pyrazolin-5-one (25.3 g), m.p. 223-226°. Reported (Carpino, 1958) m.p. 221.5-224.5°.

3-Methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) (Coutts, Hindmarsh, and Pound, 1966)

A solution of o-nitrobenzenesulfenyl chloride (3.0 g) in acetonitrile (20 ml) was added to a suspension of 3-methyl-1-phenyl-2-pyrazolin-5-one (3.0 g) in the same solvent (20 ml). The pyrazolone immediately dissolved and a bright yellow solid began to precipitate. This suspension was stirred under reflux for four hours, then cooled and filtered leaving 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (4.6 g), m.p. 209-211° (decomp) (ethanol). Reported (Coutts, Hindmarsh, and Pound, 1966) m.p. 207° (decomp).

I.r. spectrum: 1330, 1510 (NO_2); 1625 (CN); 3040-3720 with a maximum at 3450 (OH) cm^{-1}.

N.m.r. spectrum: τ7.85 (3-proton singlet) (CH_3); 1.71-2.93 (10-proton multiplet).

4-(o-Nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b) (Coutts, Hindmarsh, and Pound, 1966)

o-Nitrobenzenesulfenyl chloride (1.61 g) and 1,3-diphenyl-2-pyrazolin-5-one (2.0 g) were dissolved in

acetonitrile (60 ml) and heated under reflux for five hours. The resulting dark amber solution was evaporated to dryness leaving a thick brown oil which slowly solidified. Recrystallization of this solid from benzene gave 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (2.91 g), m.p. 184-186° (decomp). Reported (Coutts, Hindmarsh, and Pound, 1966) m.p. 182-183° (decomp).

I.r. spectrum (Unican SP-200) (KBr disc): 1340, 1525 (NO_2); 2100-3200 with maxima at 2260 and 3080 (OH) cm^{-1}.

3-Methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c) (Coutts, Hindmarsh, and Pound, 1966)

A solution of o-nitrobenzenesulfenyl chloride (2.01 g) in acetonitrile (75 ml) was added to a suspension of 3-methyl-2-pyrazolin-5-one (1.15 g) in the same solvent (15 ml), and the reaction mixture heated under reflux for five hours. The resulting suspension was cooled and filtered leaving a yellow solid (2.12 g). This product was dissolved in 10% sodium hydroxide solution and the solution washed with ether. Acidification of this solution with dilute hydrochloric acid yielded 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one, m.p. 272-274° (decomp) (ethanol). Reported (Coutts, Hindmarsh, and Pound, 1966) m.p. 273-274° (decomp).

I.r. spectrum (Perkin-Elmer, Model-21) (KBr disc): 1345, 1525 (NO_2); 2000-3300 with maxima at 2600 (OH) and

3390 (NH) cm^{-1}.

2,3-Dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118) (Coutts and Storey, 1967)

o-Nitrobenzenesulfenyl chloride (5.51 g) and 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (5.07 g) were dissolved in acetonitrile (250 ml) and the solution heated under reflux for thirty minutes. The resulting suspension was cooled and filtered, leaving the title compound as a yellow precipitate (8.84 g), m.p. 223-225° (ethanol). Reported (Coutts and Storey, 1967) m.p. 223-224°.

Reduction of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a)

Method A: with sodium borohydride and palladium-charcoal in dioxane

The title compound (2.02 g) was dissolved in dioxane (50 ml) and reduced by the general procedure (p. 129). When the resulting pale brown filtrate was acidified with dilute hydrochloric acid, then diluted with an equal volume of water, a flocculent light brown precipitate (0.88 g) formed and was filtered off. This compound was dissolved in dilute sodium hydroxide, the resulting solution filtered, and the product reprecipitated with acetic acid. This yielded 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (126), m.p. 184-185° (ethanol). Reported (Angelini and Martani, 1955) m.p. 181°.

I.r. spectrum: 1620 (CN); 2100-3350 (OH) with maxima at 3145 and 3295 (NH_2) cm^{-1}.

N.m.r. spectrum: τ 7.79 (3-proton singlet) (CH_3); 2.10-3.54 (12-proton multiplet which exchanged two protons on the addition of deuterium oxide, resulting in the collapse of a broad 2-proton signal centered at τ 3.19).

Mass spectrum: 297 (29) $[M]^+$, m/e (% rel abund).

Accurate mass measurements: 297.0935, $C_{16}H_{15}N_3OS$ requires, 297.0936.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 65.20; H, 5.13; N, 13.81.

An ethanolic solution of 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.25 g) was acidified with concentrated hydrochloric acid (2 drops). 4-(o-Aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrochloride (0.26 g) immediately precipitated, m.p. 243-244° (decomp) (ethanol). Reported (Angelini and Martani, 1955) m.p. 240-241°.

I.r. spectrum (Unicam SP-200G) (KBr disc): 1620 (CN); 2120-3000 with maxima at 2640 and 2900 ($\overset{+}{N}H_3$) cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 57.56; H, 4.83; N, 12.59. Found: C, 58.03; H, 4.95; N, 12.29.

Method B: with iron and ferrous ammonium sulfate

Using a modification of a method outlined by Hodgson and Hathaway (1944), 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (1.02 g) and reduced iron (2.0 g) were suspended in ethanol (50 ml) and the suspension brought

to reflux. An aqueous solution (5 ml) of ferrous ammonium sulfate (0.51 g) was added slowly to the boiling solution. Heating was continued for forty-five minutes, and the hot solution filtered. The colorless filtrate was placed on a water bath. The solution immediately darkened and, as it evaporated, a brick-red precipitate formed. When the solution had been reduced to one-half its original volume, it was first diluted with an equal volume of water, then made basic with dilute sodium hydroxide solution. The ferric oxide was filtered off. The dark solution was washed with ether and acidified with dilute hydrochloric acid, yielding the hydrochloride salt of 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.58 g) as a white solid, m.p. 235-238° (decomp) (ethanol).

A portion of this salt was dissolved in dilute sodium hydroxide solution, and this solution acidified with acetic acid to give rise to 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one, m.p. 183-184° (ethanol). The infrared spectra of these products were identical to those of the compounds prepared in Method A.

Method C: with sodium borohydride and palladium-charcoal in sodium hydroxide solution

Following the general procedure outlined above (p. 129), a solution of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (2.0 g) in 10% sodium hydroxide solution was reduced with sodium borohydride and pallad-

ium-charcoal. The filtered reaction mixture was acidified over ice with concentrated hydrochloric acid. (The same results were obtained when glacial acetic acid was used). Acidification resulted in effervescence and the formation of a copious cream colored precipitate (1.91 g). Purification of this product proved difficult, however, on one occasion a low yield of pure compound was obtained by recrystallization from glacial acetic acid. Chromatography of the crude product (1.42 g) on a silica gel column (1" x 12"; 50 g) using a benzene/ether (3:2) solvent system resulted in the formation of two wide pale yellow bands on the column. When the eluate containing the first band was evaporated on a film evaporator, a yellow precipitate formed. This solid was filtered off and dried under vacuum leaving 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) (0.07 g) as a yellow solid, m.p. 214-215°.

I.r. spectrum: 1625 (CN); 2200-3450 with maxima at 2670 and 3060 (OH) and 3375 (NH) cm^{-1}.

N.m.r. spectrum: τ 7.97 (3-proton singlet) (CH_3); 1.92-3.75 (12-proton multiplet).

Mass spectrum (Figure 3): 297 (100) $[M]^+$; 295 (41); 267 (26); 250 (9); 162 (23); 161 (8); m/e (% rel abund).

Accurate mass measurements: 297.0919, $C_{16}H_{15}N_3OS$ requires, 297.0921; 295.0781, $C_{16}H_{13}N_3OS$ requires, 295.0780; 267.0831, $C_{15}H_{13}N_3S$ requires, 267.0831; 250.0562,

$C_{15}H_{10}N_2S$ requires, 250.0565; 162.0378, C_9H_8NS requires, 162.0378; 161.0300, C_9H_7NS requires, 161.0300; 161.0179, $C_8H_5N_2S$ requires, 161.0174; 135.0146, C_7H_5NS requires, 135.0143.

Anal. $C_{16}H_{15}N_3OS$ requires: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.53; H, 4.93; N, 13.92.

Evaporation of the eluate containing the second yellow band left an oil (0.15 g) which readily solidified. Crystallization of this product from ethanol gave pale yellow needles of 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127), m.p. 154-156°.

I.r. spectrum: 1705 (CO); 3265 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ7.78 (3-proton singlet) (CH_3); 5.26 (1-proton, broad signal; exchanged with deuterium oxide) (NH); 1.98-3.43 (9-proton multiplet) (aromatic protons).

Mass spectrum (Figure 2): 295 (84) $[M]^+$; 267 (73); 250 (28); 135 (100), m/e (% rel abund).

Accurate mass measurements: 295.0781, $C_{16}H_{13}N_3OS$ requires, 295.0780; 267.0828, $C_{15}H_{13}N_3S$ requires, 267.0830; 250.0562, $C_{15}H_{10}N_2S$ requires, 250.0565; 135.0146, C_7H_5NS requires, 135.0143.

Anal. $C_{16}H_{13}N_3OS$ requires: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.40; H, 4.70; N, 14.10.

Further elution of the column with more polar solvents yielded only small amounts of dark brown oils. These were not investigated.

Reduction of 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (117b)

Method A: with sodium borohydride and palladium-charcoal in dioxane

Using the general procedure (p. 129), a dioxane solution (100 ml) of 4-(o-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (1.0 g) was reduced with catalyzed sodium borohydride. The filtrate was acidified with dilute hydrochloric acid, flooded with water (600 ml) and extracted with ether. The ethereal layer was extracted, first with 5% sodium hydroxide solution and then with dilute hydrochloric acid, before it was evaporated to dryness. This yielded a thick black oil (0.79 g). No product was obtained on neutralization of the acid layer, while the alkali fraction gave only a trace of dark-colored solid on acidification.

This reaction was not investigated further.

Method B: with sodium borohydride and palladium-charcoal in sodium hydroxide solution

4-(o-Nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (1.01 g) was moistened with ethanol and dissolved in 10% sodium hydroxide solution (25 ml). This solution was reduced with sodium borohydride and palladium-charcoal as described in the general procedure (p. 129). Acidification of the filtrate with dilute hydrochloric acid yielded a flocculent yellow solid (0.90 g). (The same product was isolated when glacial acetic was used for acidification).

This product was dried under vacuum, then placed on a silica gel column (1" x 12"; 50 g). Elution of the column, first with benzene, then with a mixture of benzene and chloroform yielded small amounts of several dark oils. A solvent system of benzene/chloroform (1:9) produced a broad yellow band on the column. Evaporation of the eluate containing this band left a brittle yellow solid (0.18 g). Recyrstallization of this product from ethanol yielded 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143), m.p. 181-184°.

I.r. spectrum: 1580 (CN); 2100-3400 with maxima at 3060 and 3700 (OH) cm^{-1}.

Mass spectrum (Figure 5): 359 (68) $[M]^+$; 357 (78); 341 (5); 329 (72); 328 (90); 254 (25); 135 (100); 108 (27), m/e (% rel abund).

Accurate mass measurements: 359.1090, $C_{21}H_{17}N_3OS$ requires, 359.1092; 357.0935, $C_{21}H_{15}N_3OS$ requires, 357.0936; 341.0984, $C_{21}H_{15}N_3S$ requires, 341.0987; 329.0986, $C_{20}H_{15}N_3S$ requires, 329.0987; 328.0907, $C_{20}H_{14}N_3S$ requires, 328.0908; 254.0519, $C_{14}H_{10}N_2OS$ requires, 254.0514; 135.0143, C_7H_5NS requires, 135.0143.

Anal. $C_{21}H_{17}N_3OS$ requires: C, 70.17; H, 4.77; N, 11.69. Found: C, 70.26; H, 4.63; N, 12.38.

This was the only significant product isolated from this procedure. Further elution of the column with more polar solvents gave only dark colored oils which were not investigated.

Reduction of 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (117c)

Method A: with sodium borohydride and palladium-charcoal in dioxane

3-Methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (1.3 g) was dissolved in dioxane (125 ml) and the solution reduced as outlined in the general procedure (p.129). The filtered reaction mixture was acidified with concentrated hydrochloric acid, flooded with water (600 ml) and extracted with ether. The ether layer was in turn extracted with 10% sodium hydroxide solution and rejected. Acidification of the alkaline fraction yielded only a trace of flocculent red solid.

This reaction was not investigated further.

Method B: with sodium borohydride and palladium-charcoal in sodium hydroxide solution

A solution of 3-methyl-4-(o-nitrophenylthio)-2-pyrazolin-5-one (2.0 g) in 10% sodium hydroxide solution (25 ml) was reduced by the general procedure (p.129). The filtrate, on acidification with dilute hydrochloric acid, yielded a yellow solid (1.4 g). Attempts to purify this product by recrystallization resulted only in the formation of dark yellow to brown solids. A sample of the crude product, thought to be 9,9a-dihydro-9-hydroxy-3-methyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (146), m.p. 242-245° (decomp), was dried for analysis.

I.r. spectrum (Unicam SP-200) (KBr disc): 2100-3500

with maxima at 2740 (OH) and 3400 (NH) cm^{-1}.

Anal. $C_{10}H_{11}N_3OS$ requires: N, 18.98; S, 14.49. Found: N, 18.52; S, 14.28. Poor values were obtained for C and H.

Reduction of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (118)

Method A: with sodium borohydride and palladium-charcoal in dioxane

This reduction involved a modification of the general procedure (p. 129). An aqueous solution (15 ml) of sodium borohydride (1.02 g) was added in three equal portions at five minute intervals to a suspension of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (2.01 g) and palladium-charcoal (0.12 g) in dioxane (100 ml). After thirty minutes the suspension was filtered and the filtrate acidified with dilute hydrochloric acid. This solution was concentrated to near dryness on a film evaporator, then diluted with dilute hydrochloric acid (100 ml), and extracted with chloroform. The chloroform layer was then extracted with 10% sodium hydroxide solution and evaporated to dryness, leaving a dark brown oil (0.21 g). The alkaline layer was acidified with hydrochloric acid and extracted with chloroform. Evaporation of the organic layer left only a trace of oil (0.03 g). The original acid fraction was neutralized with 50% sodium hydroxide solution over ice and the resulting suspension extracted with chloroform. Removal of the chloroform left

a light brown solid (1.4 g). Recrystallization of this product from ethanol and benzene yielded 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156), m.p. 180-181°. Thin layer chromatography on alumina using ether as the developing solvent gave only one spot, R_f 0.78.

I.r. spectrum: 1642 (CO); 3320, 3400 (NH_2) cm^{-1}.

N.m.r. spectrum (Figure 7): τ 7.58 and 6.80 (3-proton singlets) (CH_3); 4.26 (2-proton, broad singlet; exchanged with deuterium oxide (NH_2); 2.30-3.50 (8-proton multiplet) (aromatic protons).

Mass spectrum: 347 (25) $[M+2]^+$; 345 (62) $[M]^+$, m/e (% rel abund).

Anal. $C_{17}H_{16}ClN_3OS$ requires: C, 59.04; H, 4.66; N, 12.15. Found: C, 59.41; H, 5.12; N, 11.60.

Method B: with iron and ferrous ammonium sulfate

An aqueous solution (25 ml) of ferrous ammonium sulfate (0.57 g) was added to a suspension of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (1.02 g) and iron (2.07 g) in hot ethanol (80 ml). The reaction mixture was heated under reflux for ninety minutes, then filtered while hot. The filtrate was evaporated to dryness leaving an off-white solid (0.8 g) which, on recrystallization from ethanol, gave 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (147), m.p. 204-207°. Thin layer chromatography of this product on alumina using ether as the developing solvent gave one spot, R_f

0.76.

I.r. spectrum: 1642 (CO); 3318, 3400 (NH_2) cm^{-1}.

Mass spectrum: 311 (63) $[M]^+$, m/e (% rel abund).

Anal. $C_{17}H_{17}N_3OS$ requires: C, 65.57; H, 5.50; N, 13.50. Found: C, 65.55; H, 5.84; N, 13.41.

Method C: with sodium borohydride and palladium-charcoal in sodium hydroxide solution

A solution of sodium borohydride (0.5 g) in water (10 ml) was added slowly to a suspension of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (1.04 g) and palladium-charcoal (0.05 g) in 10% sodium hydroxide solution. Nitrogen was passed through the suspension for forty minutes. At the end of this time the suspension was filtered leaving some yellow solid on the filter with the charcoal. The filtrate was acidified with acetic acid and extracted with chloroform. Evaporation of the organic layer left only a trace of black oil (0.03 g). The solid on the filter was stirred with chloroform and the charcoal removed by filtration. Removal of the chloroform left a solid (0.89 g) which on recrystallization from ethanol proved to be the starting material, m.p. 220-223°.

Attempted acetylation of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125)

The title compound (0.11 g) was heated under reflux with acetic anhydride in glacial acetic acid for fifteen minutes. The reaction mixture was poured into ice and a

dark oil was deposited. The suspension was extracted with chloroform, giving rise to a thick black oil (0.09 g) that would not crystallize.

x,x-Dibenzoyl-9-benzoyloxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (130)

A sample of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (1.27 g) was dissolved in dilute sodium hydroxide solution (40 ml) and stirred in an ice bath. Benzoyl chloride (1.5 ml) was added dropwise to the cold solution. A soft semisolid mass formed slowly. After forty-five minutes, more benzoyl chloride (1.0 ml) was added and the ice bath removed. Stirring was continued for a further forty-five minutes. The reaction mixture was then diluted with 10% sodium hydroxide solution (15 ml) and extracted with chloroform. Evaporation of the organic layer left a brown semisolid (1.65 g). This product was chromatographed on a silica gel column (1" x 14"; 60 g). Elution with benzene/chloroform (1:2) yielded a fraction which, on evaporation, left a reddish-brown oil (0.52 g). Repeated trituration of this oil with petroleum ether yielded the title compound, m.p. 102-104° (decomp), sinters at 85°.

I.r. spectrum: 1677, 1758 (CO) cm^{-1}.

Mass spectrum (Figure 1): 609 (6) $[M]^+$; 488 (16); 399 (18), m/e (% rel. abund.).

Accurate mass determinations: 609.1724, $C_{37}H_{27}N_3O_4S$ requires, 609.1723; 300.1039, $C_{23}H_{17}O_2S$ requires, 399.1042.

Anal. $C_{37}H_{27}N_3O_4S$ requires: C, 72.89; H, 4.46; N, 6.89. Found: C, 72.72; H, 4.77; N, 6.94.

Treatment of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]1,4-benzothiazine (125) with dimethyl sulfoxide

The title compound (0.06 g) was dissolved in dimethyl sulfoxide (1.0 ml) and the solution was set aside to evaporate. After one week the brown solid that remained was crystallized from ethanol. This yielded 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) (0.04 g), m.p. 152-154°. The infrared spectrum of this product was superimposible on that of a sample of the spiro compound isolated as described previously (p. 137).

Treatment of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) with hydrochloric acid

9,9a-Dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (0.41 g) was heated under reflux with concentrated hydrochloric acid (2.0 ml) in dioxane (20 ml). The reaction mixture, which turned black in color almost immediately, was heated for thirty minutes, then chilled and diluted with water (50 ml). No precipitate formed. The reaction mixture was evaporated to dryness leaving a dark brown oil. This product was dissolved in chloroform and the solution extracted with di-

lute sodium hydroxide solution. Evaporation of the organic layer left 3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (127) (0.06 g), m.p. 152-153°. Infrared analysis confirmed that this product was identical to the spiro compound isolated in the previous procedure.

The alkaline layer was acidified with dilute hydrochloric acid and extracted with chloroform. The organic layer left a dark brown oil (0.31 g) on evaporation. This product, which failed to crystallize, was not investigated.

Attempted oxidation of 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (125) with hydrogen peroxide

Hydrogen peroxide solution (30%) (0.5 ml) was added to a suspension of the title compound (0.54 g) in glacial acetic acid. The reaction mixture turned black in color as the temperature of the solution was raised to 85°. After thirty minutes at this temperature, the solution was diluted with water (30 ml) and extracted with chloroform. The organic fraction was washed with dilute sodium hydroxide solution and dilute hydrochloric acid, then evaporated to dryness leaving a thick black oil (0.48 g) which would not crystallize.

The reaction was repeated at room temperature but, again, only a black oil was obtained after twenty-four hours.

This reaction was not investigated further.

4-(o-Acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (138)

A suspension of 4-(o-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (5.05 g) in glacial acetic acid (75 ml) was treated with excess acetic anhydride (8.0 ml) and heated under reflux for fifteen minutes. Water (25 ml) was added and the reaction mixture evaporated to dryness on a film evaporator leaving a light brown oil. Repeated trituration of this oil with acetone yielded the title compound (5.14 g), m.p. 170-172° (acetone).

I.r. spectrum: 1665 (CO); 2400-3350 with a maximum at 3160 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 7.87 (3-proton singlet) (CH_3); 7.82 (3-proton singlet) (CH_3); 1.95-3.12 (10-proton multiplet) (aromatic protons); 0.05 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Mass spectrum: 339 (59) $[M]^+$, m/e (% rel abund).

Anal. $C_{18}H_{17}N_3O_2S$ requires: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.74; H, 4.99; N, 12.01.

Attempted bromination of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (138)

Method A: with bromine in acetic acid

Bromine (0.23 g) in glacial acetic acid (10 ml) was added dropwise to a solution of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.51 g) in glacial acetic acid (20 ml) over a period of fifteen minutes. After another ten minutes the pale yellow reaction mix-

ture was poured over ice and stirred. The resulting solution was extracted with a large volume of chloroform and ether. The organic layers were combined and evaporated to dryness leaving a thick oil (0.56 g). This product was stirred with ethanol (8 ml) and filtered leaving 3,3'-dimethyl-1,1'-diphenyl-[$\Delta^{4,4'}$-bi-2-pyrazoline]-5,5'-dione (139) (0.02 g) as a black solid, m.p. 229-231° (decomp) (benzene). Reported (Knorr, 1887) m.p. 230-240° (decomp). The identity of this product was confirmed by comparing its infrared spectrum with that of another sample of this compound prepared by the action of pyridinium bromide perbromide on 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (p.150).

Evaporation of the ethanolic filtrate gave a light brown oil (0.43 g) which, on trituration with acetone, yielded 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrobromide (140), m.p. 193-194° (decomp) (acetone), identical with an authentic sample prepared as described below.

I.r. spectrum: 1650 (CO); 2000-3500 with maxima at 2550, 2600, and 2680 ($^{+}$NH) and 3305 (NH) cm^{-1}.

Mass spectrum: 339 (7) $[M]^{+}$; 82 (100); 80 (100), m/e (% rel abund).

Anal. $C_{18}H_{18}BrN_3O_2S$ requires: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.21; H, 4.26; N, 9.70.

Method B: with pyridinium bromide perbromide

Pyridinium bromide perbromide (1.13 g) was added in four equal portions to a solution of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.72 g) in glacial acetic acid (35 ml) over a period of ninety minutes. The resulting suspension was stirred for eighteen hours, then filtered leaving the hydrobromide salt of 4-(o-acetamidophenyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (140) (0.71 g) as a white solid, m.p. 192-193° (decomp) (acetone). Infrared analysis indicated that this product was identical to the salt isolated in Method A.

4-(o-Acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrobromide (140)

Hydrogen bromide was passed through a cooled acetone solution (45 ml) of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.29 g) for two minutes. A white solid slowly precipitated. After thirty minutes the suspension was filtered yielding a white solid (0.27 g). Concentration of the mother liquors gave a second crop of the same product (0.07 g). Recrystallization of the combined solids from acetone yielded 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrobromide, m.p. 193-194° (decomp). Infrared spectra indicated that this product was identical to the products isolated in the two preceding reactions.

Treatment of 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one hydrobromide (140) with sodium carbonate solution

The title compound (0.53 g) was dissolved in 10% sodium carbonate solution. Acidification of this solution with acetic acid yielded 4-(o-acetamidophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (138) (0.40 g), m.p. 170-173°. The infrared spectrum of this product was identical to that of an authentic sample of this compound (p. 147).

Treatment of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (117a) with pyridinium bromide perbromide

Pyridinium bromide perbromide (3.04 g) was added in three equal portions to a suspension of 3-methyl-4-(o-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (2.01 g) in glacial acetic acid (200 ml) over a period of ninety minutes. After stirring for eighteen hours, the volume of the reaction mixture was reduced to approximately 50 ml, diluted with 5% hydrochloric acid (50 ml) and extracted with chloroform. Starting material (0.51 g), m.p. 208-209°, formed in the separatory funnel. The chloroform extract was washed with dilute sodium hydroxide solution. Acidification of the alkaline fraction yielded a second crop of the starting pyrazolone (0.32 g).

Evaporation of the organic layer left a black semisolid (1.04 g) which on recrystallization from benzene yielded 3,3'-dimethyl-1,1'-diphenyl-[$\Delta^{4,4'}$-bi-2-pyr-

azoline]-5,5'-dione (139) as black platelets, m.p. 229-231° (decomp). Reported (Knorr, 1887) m.p. 230-240° (decomp).

I.r. spectrum: 1700 (CO) cm^{-1}.

Mass spectrum: 344 (73) $[M]^+$, m/e (% rel abund).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.63; N, 16.27. Found: C, 70.05; H, 4.31; N, 16.44.

Attempted reduction of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143)

Zinc dust (1.0 g) was added in three equal portions to a solution of the title compound (0.91 g) in boiling glacial acetic acid (30 ml) over a period of forty-five minutes. After one hour the reaction mixture was evaporated to near dryness, then poured into chloroform. This solution was washed, first with 10% sodium carbonate solution, then dilute hydrochloric acid before evaporating it to dryness. Recrystallization of the resulting solid (0.58 g) from benzene and ethanol yielded 5-oxo-1,3-diphenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (144) as a yellow solid, m.p. 183-184°. Thin layer chromatography on ChromAR Sheet 500 (Mallinckrodt) using chloroform as the developing solvent revealed only one component, R_f 0.48.

I.r. spectrum: 1718 (CO); 3770 (NH) cm^{-1}.

Mass spectrum (Figure 6): 357 (63) $[M]^+$, 329 (78); 328 (100); 254 (25); 135 (75) m/e (% rel. abund.).

Anal. $C_{21}H_{15}N_3OS$ requires: C, 70.57; H, 4.23; N,

11.76. Found: C, 70.66; H, 4.32; N, 11.58.

Acidification and extraction of the sodium carbonate fraction left a black oil (0.12 g). The acid layer on neutralization and extraction, yielded only a trace of dark oil (0.01 g). Both semisolids were discarded.

Treatment of 9,9a-dihydro-9-hydroxy-1,3-diphenyl-1H-pyrazolo-[4,3-b]-1,4-benzothiazine (143) with acetic acid

A solution of the title compound (0.02 g) in glacial acetic acid (5 ml) was heated under reflux for ten minutes. The reaction mixture was evaporated to near dryness, then taken up in chloroform. This chloroform solution was washed with dilute sodium carbonate solution and evaporated to dryness leaving a brown solid (0.014 g), m.p. 177-182°. Infrared analysis and thin layer chromatography on ChromAr Sheet 500 (Mallinckrodt) using chloroform as the developing solvent indicated that this product, R_f 0.48, was nearly pure 5-oxo-1,3-diphenyl-2-pyrazolin-4-spiro-2'-benzothiazoline (144).

Acidification and extraction of the sodium carbonate layer yielded only a trace of brown oil.

2,3-Dimethyl-4-(o-nitrophenylsulfonyl)-1-phenyl-3-pyrazoline-5-one (153)

Water (5 ml) and potassium permanganate (4.0 g) were added to a suspension of 2,3-dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (2.03 g) in glacial acetic acid (40 ml). After stirring for three hours the black solu-

tion was decolorized by the addition of excess hydrogen peroxide (30%). The reaction mixture was reduced in volume and neutralized by the addition of solid sodium carbonate. An equal volume of water was added and the solution extracted with chloroform. Evaporation of the organic layer left a dark brown oil (0.98 g). This product was stirred with ethanol (10 ml) and filtered leaving 2,3-dimethyl-4-(o-nitrophenylsulfonyl)-1-phenyl-3-pyrazolin-5-one (0.56 g), as an off-white solid, m.p. 209-211° (ethanol).

I.r. spectrum: 1330, 1529 (NO_2); 1668 (CO) cm^{-1}.

Mass spectrum: 373 (3) $[M]^+$, m/e (% rel abund).

Anal. $C_{17}H_{15}N_3O_5S$ requires: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.67; H, 4.38; N, 11.22.

Evaporation of the ethanolic filtrate left a thick dark oil which would not crystallize. This product was rejected.

4-(o-Aminophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (148)

The stannous chloride reagent used in this synthesis was prepared by the method outlined by Abramovitch and Hey (1954). This procedure involved passing hydrogen chloride through a suspension of stannous chloride dihydrate (9.0 g) in glacial acetic acid (15 ml) until all of the solid dissolved. The volume of the final solution was then made up to 20 ml with glacial acetic acid. 2,3-Dimethyl-4-(o-nitrophenylsulfonyl)-1-phenyl-3-pyrazolin-5-

one (0.5 g) was treated with this reagent (5.5 ml). An exothermic reaction occurred as the starting material dissolved. The reaction was left standing at room temperature for forty-eight hours. The white complex which formed slowly during this time, was filtered off and treated with 50% sodium hydroxide solution over ice. The resulting suspension was again filtered yielding the title compound (0.44 g) as a white solid, m.p. 227-228° (ethanol).

I.r. spectrum: 1650 (CO); 3335, 3430 (NH_2) cm^{-1}.

Anal. $C_{17}H_{17}N_3O_3S$ requires: C, 59.46; H, 4.99. Found: C, 59.10; H, 5.14.

Attempts to prepare this compound using an iron and ferrous ammonium sulfate reducing system were unsuccessful. Only starting material was recovered.

4-(o-Acetamidophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (155)

A suspension of 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1.05 g) in acetic anhydride (4 ml) was heated under reflux for ten minutes. Water (20 ml) was added and heating continued for another fifteen minutes. The reaction mixture was cooled and extracted with chloroform. Evaporation of the chloroform layer left a brown semisolid (0.89 g). Recrystallization of this product from ethanol gave 4-(o-acetamidophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, m.p. 162-164°.

I.r. spectrum: 1650, 1700 (CO); 3250 (NH) cm^{-1}.

Anal. $C_{19}H_{19}N_3O_2S$ requires: C, 64.52; H, 5.42; N, 11.89. Found: C, 64.49; H, 5.61; N, 11.48.

4-(o-Acetamidophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (154)

Method A

A solution of 4-(o-acetamidophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1.6 g) in glacial acetic acid (25 ml) and water (2 ml) was stirred in an ice bath, and solid potassium permanganate (3.5 g) was added slowly. After ten minutes, the ice bath was removed and the solution stirred for thirteen hours at room temperature. Hydrogen peroxide (30%) was added to decolorize the reaction mixture. This solution was neutralized with solid sodium carbonate then extracted with both ether and chloroform. The organic layers were combined and evaporated to dryness leaving a light brown oil (1.1 g) from which 4-(o-acetamidophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, m.p. 212-213° (ethanol), was obtained on trituration with absolute ethanol.

I.r. spectrum: 1645, 1703 (CO); 3340 (NH) cm^{-1}.

Anal. $C_{19}H_{19}N_3O_4S$ requires: C, 59.21; H, 4.98; N, 10.90. Found: C, 58.86; H, 5.08; N, 11.48.

Method B

Acetic anhydride (1.0 ml) was added to a suspension of 4-(o-aminophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-

pyrazoline-5-one (0.4 g) in glacial acetic acid (3 ml). The reaction was heated under reflux for ten minutes, diluted with water (5 ml), then heated for a further ten minutes. The reaction mixture was cooled and filtered leaving a white solid (0.2 g). Crystallization of this product from ethanol gave 4-(o-acetamidophenylsulfonyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, m.p. 213-215°. The infrared spectrum of this product was identical to that of the product prepared by method A.

4-(2-Acetamido-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one

4-(2-Amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (0.17 g) and acetic anhydride (3 ml) were heated under reflux for five minutes. The reaction was diluted with water (5 ml), heated for another five minutes, cooled, and filtered leaving a brown solid (0.14 g). Recrystallization from benzene, then ethanol yielded the title compound, m.p. 202-203°.

I.r. spectrum: 1640, 1700 (CO); 3315 (NH) cm^{-1}.

Anal. $C_{19}H_{18}ClN_3O_2S$ requires: C, 58.83; H, 4.68; N, 10.83; Cl, 9.14. Found: C, 59.08; H, 5.09; N, 10.41; Cl, 8.90.

4-(o-Hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158)

2,3-Dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (2.24 g) was reduced with sodium boro-

hydride and palladium-charcoal in dioxane using the procedure described on page 141. In this case, the filtered reaction mixture was acidified with glacial acetic acid. This solution was evaporated to dryness on a film evaporator, leaving a thick oil which solidified on trituration with ethanol. Crystallization of this product from aqueous ethanol yielded 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1.5 g), m.p. 156-157° (decomp).

I.r. spectrum: 1619 (CO); 3245 (broad) (OH and NH) cm^{-1}.

Mass spectrum: 327 (1) $[M]^+$; 325 (5); 311 (25), m/e (% rel abund).

Anal. $C_{17}H_{17}N_3O_2S$ requires: C, 62.36; H, 5.23; N, 12.84. Found: C, 62.24; H, 5.75; N, 12.92.

Treatment of 4-(o-hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (158) with hydrochloric acid

A methanolic solution (30 ml) of the title compound (0.36 g) was chilled in ice and treated with hydrogen chloride for five minutes. After standing for forty-eight hours, the solution was evaporated to dryness leaving a black oil. This oil was poured into chloroform and extracted with hydrochloric acid. Evaporation of the chloroform left a black oil which would not crystallize (0.24 g). Neutralization and extraction of the acid layer yielded a grey solid (0.14 g). Recrystallization of this product from benzene and ethanol yielded

a mixture of 4-(o-aminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (147) and 4-(2-amino-5-chlorophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (156) as an off-white solid, m.p. 168-174°. Chromatography on both ChromAr Sheet 500 (Mallinckrodt) and alumina using chloroform, chloroform/ether, ether, and benzene/ethanol as solvents gave only one spot, R_f (on alumina with ether as a developing solvent) 0.77.

I.r. spectrum: 1638 (CO); 3318, 3400 (NH_2) cm^{-1}.

Mass spectrum: 347 (5); 345 (13); 313 (1); 311 (9), m/e (% rel abund).

2,2'-Bis-[(2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl)thio]-azoxybenzene (160)

Method A

2,3-Dimethyl-4-(o-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one (1.01 g) was reduced by the procedure described on page 141. This time the filtered reaction mixture was evaporated to dryness without acidification leaving a grey semisolid. This product was taken up in hot ethanol and filtered, leaving a grey water-soluble residue which was rejected. Evaporation of the filtrate left a thick oil (0.48 g) which slowly solidified. Recrystallization of this solid from a dimethyl sulfoxide/ethanol solvent system yielded the azoxy compound as a yellow solid, m.p. 272-273° (decomp).

Infrared spectrum: 1668 (CO) cm^{-1}.

Mass spectrum: 634 (0.3) $[M]^+$; 618 (2), m/e (% rel

abund).

Anal. $C_{34}H_{30}N_6O_3S_2$ requires: C, 64.33; H, 4.76; N, 13.24. Found: C, 63.63; H, 4.39; N, 12.71.

Method B

4-(o-Hydroxylaminophenylthio)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (0.48 g) was suspended in dioxane (30 ml) and 30% hydrogen peroxide solution (2.5 ml) was added gradually with stirring. The reaction mixture was stirred for eighteen hours during which time the starting material dissolved and a precipitate formed (0.17 g). Recrystallization of this solid from dimethyl sulfoxide/ethanol gave 2,2'-Bis-[(2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl)thio]azoxybenzene (160), m.p. 272-274° (decomp), the infrared spectrum of which was superimposible on that of the product obtained by method A.

Interaction of Cyclic Hydroxamic Acids and Aromatic Hydroxylamines with Hydrochloric Acid

6-Chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (162) (Prasad and Tietje, 1966)

(4-Chloro-2-nitrophenylthio)acetic acid (2.6 g) (Coutts, Barton, and Smith, 1966) was dissolved with sodium hydroxide (2.6 g) in water (250 ml) and warmed to 45°. Sodium hydrosulfite (7.0 g) was added to the stirring solution and the temperature raised to 95°. After five minutes, activated charcoal was added and the hot reaction mixture filtered. The hot filtrate

was acidified with concentrated hydrochloric acid, cooled, and extracted with chloroform. Evaporation of the chloroform layer yielded the title compound (1.3 g), m.p. 201-203° (ethanol). Reported (Prasad and Tietje, 1966) m.p. 205-206°.

I.r. spectrum: 1670 (CO); 3185 (NH) cm^{-1}.

N.m.r. spectrum (Figure 9): τ 6.50 (2-proton singlet) (CH_2); 2.48-3.10 (3-proton multiplet) (aromatic protons); -0.67 (1-proton, broad singlet; exchanged with deuterium oxide) (NH).

(o-Nitrophenylthio)acetic acid (149) (Brewster, 1968)

o-Nitrochlorobenzene (32.0 g), thioglycollic acid (15.2 g) and sodium carbonate (40.0 g) were dissolved in 50% aqueous ethanol (440 ml) and this solution heated under reflux for three and one-half hours. A portion of the ethanol (200 ml) was removed by distillation. The mother liquors were filtered, cooled, and acidified with dilute hydrochloric acid. The resulting suspension was filtered yielding (o-nitrophenylthio)acetic acid (22.8 g), m.p. 158-162°. Reported (Brewster, 1968) m.p. 164°.

I.r. spectrum: 1330, 1505 (NO_2); 1705 (CO); 2000-3360 with maxima at 2570 and 2675 (OH) cm^{-1}.

Methyl (o-nitrophenylthio)acetate

Concentrated sulfuric acid (20 ml) was added slowly to a hot methanolic solution (200 ml) of (o-nitrophenylthio)acetic acid (18 g). This solution was heated under

reflux for six hours, cooled, and filtered leaving a yellow solid (12.3 g). Concentration of the mother liquors yielded a second crop of the same product (4.2 g). Recrystallization of these solids from ethanol yielded the title compound as yellow needles, m.p. 88-89°. Reported (Coutts and Wibberley, 1963) m.p. 89-90°.

I.r. spectrum: 1328, 1503 (NO_2); 1723 (CO) cm^{-1}.

3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150)

Following the general procedure (p. 129), a solution of methyl (o-nitrophenylthio)acetate (2.5 g) in dioxane (50 ml) was reduced with sodium borohydride and palladium-charcoal. The filtrate from the reaction was acidified with acetic acid and reduced in volume to approximately 30 ml on a film evaporator. The resulting suspension was filtered leaving 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (1.13 g) as a white solid, m.p. 148-150° (ethanol). Reported (Coutts, Barton, and Smith, 1966) m.p. 151-152°.

I.r. spectrum: 1627, 1672 (CO); 2400-3280 (OH) cm^{-1}.

N.m.r. τ 6.37 (2-proton singlet) (CH_2); 2.50-3.19 (4-proton multiplet) (aromatic protons); -0.47 (1-proton, very broad signal; exchanged with deuterium oxide) (NH).

7-Chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (161)

A stream of hydrogen chloride was passed through an ice cold methanolic solution (15 ml) of 3,4-dihydro-4-

hydroxy-3-oxo-2H-1,4-benzothiazine (0.35 g) for ninety seconds. The solution was left standing at room temperature for three and one-half hours before the solvent was removed leaving a grey solid. Crystallization of this product gave 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (0.26 g), m.p. 204-206°. Reported (Vasiliu, Major, and Arsenesca, 1963) m.p. 206°.

I.r. spectrum: 1688 (CO); 3180 (NH) cm^{-1}.

N.m.r. spectrum (Figure 8): τ 6.50 (2-proton singlet) (CH_2); 2.45-3.10 (3-proton multiplet) (aromatic protons); -0.68 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Mass spectrum: 201 (35) $[M+2]^+$; 199 (100) $[M]^+$, m/e (% rel abund).

6-Chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (164)

A dioxane solution (40 ml) of methyl (4-chloro-2-nitrophenylthio)acetate (1.08 g) (Coutts, Barton, and Smith, 1966) was reduced with sodium borohydride and palladium-charcoal as outlined in the general procedure (p. 129). The filtered reaction mixture was acidified with glacial acetic acid and evaporated to dryness on a film evaporator. The resulting solid was taken up in ether and the solution was extracted with 10% sodium carbonate solution. Evaporation of the organic layer left a dark brown solid (0.29 g). The alkaline layer was neutralized with acetic acid and extracted with

ether. The ether layer yielded the desired hydroxamic acid (0.51 g) on evaporation, m.p. 177-178° (ethanol). Reported (Coutts, Barton, and Smith, 1966) m.p. 179-180°.

I.r. spectrum: 1622, 1663 (CO); 3150 (broad) (OH) cm^{-1}.

6,7-Dichloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (165)

6-Chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (0.22 g) was dissolved in methanol (10 ml) and the ice cold solution saturated with hydrogen chloride. After standing for three hours the reaction mixture was reduced to dryness leaving a grey solid, which on recrystallization from ethanol yielded 6,7-dichloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (0.15 g), m.p. 249-251°.

I.r. spectrum: 1678 (CO); 3170 (NH) cm^{-1}.

N.m.r. spectrum: τ 6.47 (2-proton singlet) (CH_2); 2.80 (1-proton singlet) (C_8-H); 2.32 (1-proton singlet) (C_5-H); -0.75 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Anal. $C_8H_5Cl_2NOS$ requires: C, 41.04; H, 2.15; N, 5.98. Found: C, 40.94; H, 2.42; N, 5.99.

Purification of the zinc chelate of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (167)

A sample of the title compound (Coutts and Hindmarsh, 1966) was dissolved in dimethyl sulfoxide, filtered, and the complex reprecipitated by flooding the filtrate with ethanol. Repeating this procedure several times

yielded a pure sample of the zinc chelate, m.p. >360°.

I.r. spectrum: 1631 (chelated CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O_6Zn$: C, 48.82; H, 3.07; N, 7.12. Found: C, 48.99; H, 2.81; N, 7.04.

3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (168)

Method A

A sample of the zinc chelate of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (0.18 g) was suspended in glacial acetic acid (5 ml) and stirred for two and one-half hours. The reaction mixture was evaporated to near dryness on a film evaporator, then poured into chloroform. This solution was washed with water and evaporated to dryness leaving a grey solid (0.08 g). Crystallization of this product from aqueous ethanol yielded 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine, m.p. 164-166°. Reported (Coutts and Hindmarsh, 1966) m.p. 159-160°.

I.r. spectrum: 1647, 1682 (CO); 2450-3380 with a maximum at 3070 (OH) cm^{-1}.

N.m.r. spectrum: τ 5.26 (2-proton singlet) (CH_2); 2.65-3.15 (4-proton multiplet) (aromatic protons); -0.67 (1-proton singlet; exchanged with deuterium oxide) (OH).

Method B

A solution of ethyl (o-nitrophenoxy)acetate (p.179) (3.16 g) in dioxane (25 ml) was reduced with sodium borohydride and palladium-charcoal according to the general

procedure (p. 129). After twenty minutes the reaction mixture was filtered and the filtrate acidified with glacial acetic acid. This solution was diluted with water (50 ml) and extracted with chloroform. The chloroform layer was, in turn, extracted with 10% sodium carbonate solution, then evaporated to dryness leaving 3,4-dihydro-3-oxo-2H-1,4-benzoxazine (0.23 g) as a light brown solid, m.p. 170-172° (aqueous ethanol). Reported (Loudon and Ogg, 1955) m.p. 171-172°.

I.r. spectrum: 1700 (broad) (CO); 3128 (NH) cm^{-1}.

N.m.r. spectrum: τ 5.46 (2-proton singlet) (CH_2); 3.10 (4-proton singlet) (aromatic protons); -0.57 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

The sodium carbonate layer was acidified with acetic acid and the resulting suspension filtered leaving a white solid (1.02 g). Crystallization of this product from aqueous ethanol yielded 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine, m.p. 162-163°. The infrared spectrum of this product was identical to that of the compound prepared in method A.

7-Chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (167)

A suspension of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (0.7 g) in dilute hydrochloric acid (15 ml) was heated under reflux for two and one-half hours. The reaction mixture was cooled, then extracted with chloroform. The organic layer was extracted with dilute sodium

carbonate solution and evaporated to dryness leaving a grey solid (0.61 g). Crystallization of this product from aqueous ethanol yielded 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (169), m.p. 195-196°.

I.r. spectrum: 1684 (CO); 3175 (NH) cm^{-1}.

N.m.r. spectrum: τ 5.42 (2-proton singlet) (CH_2); very broad 1-proton signal centered at 4.25 which exchanged with deuterium oxide (NH); 2.90-3.12 (3-proton multiplet) (aromatic protons).

Mass spectrum: 185 (35) $[M+2]^+$; 183 (100) $[M]^+$, m/e (% rel abund).

Anal. $C_8H_6ClNO_2$ requires: C, 52.43; H, 3.29; N, 7.63. Found: C, 52.67; H, 3.52; N, 7.67.

Neutralization and extraction of the sodium carbonate layer yielded only a trace of brown oil.

7-Chloro-2-ethyl-3,4-dihydro-3-oxo-2H-1,4-benzoxazine* (171)

A solution of 2-ethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (10 mg) in aqueous sodium carbonate solution (20 ml) was acidified with concentrated hydrochloric acid and allowed to stand for fifteen hours. The crystalline product which separated (5 mg), m.p. 143-144°, was 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (171).

I.r. spectrum: 1696 (CO); 3190 (NH) cm^{-1}.

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*K.W. Hindmarsh carried out this reaction.

Mass spectrum: 213 (20) $[M+2]^+$; 211 (67) $[M]^+$, m/e (% rel abund).

Anal. $C_{10}H_{10}ClNO_2$ requires: N, 6.62. Found: N, 6.30.

4-(o-Hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (172)

A solution of 3-methyl-4-(o-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (3.12 g) (Coutts and Edwards, 1966) in dioxane (50 ml) was reduced with sodium borohydride and palladium-charcoal as outlined in the general procedure (p. 129). The filtered reaction mixture was acidified with dilute hydrochloric acid, flooded with water (250 ml) and extracted with chloroform and ether. The organic layers were combined and reduced to dryness, leaving a dark yellow oil (2.9 g). This product was eluted from a silica gel column (1" x 8"; 35 g) using chloroform/ether (9:1). Evaporation of this eluate gave the title compound (1.03 g) as a yellow solid, m.p. 183-185° (ethanol).

I.r. spectrum: 1690 (CO); 3100-3400 (OH) with a sharp band at 3275 (NH) cm^{-1}.

Mass spectrum: 293 (21) $[M]^+$; 277 (27), m/e (% rel abund).

Anal. $C_{17}H_{15}N_3O_2$ requires: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.74; H, 5.49; N, 14.27.

Treatment of 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (172) with hydrogen chloride

The title compound (0.25 g) was dissolved in methanol (25 ml) and the solution chilled in ice, then saturated with hydrogen chloride. Evaporation of the reaction mixture left a brown oil which solidified on trituration with ethanol. This product (0.13 g) was crystallized from aqueous ethanol as a light brown solid, m.p. 144-146°. Thin layer chromatography on ChromAR Sheet 500 (Mallinckrodt) using chloroform as the developing solvent revealed two components, R_f 0.61 and 0.29.

I.r. spectrum: 1708 (CO); 3360 (broad) (NH_2) cm^{-1}.

Mass spectrum: 313 (33); 311 (100); 307 (91), m/e (% rel abund).

4-(2-Amino-5-chlorobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (173)

A stream of hydrogen chloride was passed through a solution of 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.34 g) in tetrahydrofuran (5 ml) for thirty seconds at 0-5°. The dark red solution was set aside for fifteen hours then evaporated to dryness. The resulting black semisolid was placed on a silica gel column (0.25" x 4"; 8 g) and eluted with petroluem ether then benzene. Evaporation of the benzene solution (100 ml) gave a dark yellow solid (0.16 g). Crystallization of this product from ethanol yielded the title compound monohydrate, as a white solid, m.p. 152-154°. R_f [ChromAR

Sheet 500 (Mallinckrodt) with chloroform], 0.61.

I.r. spectrum: 1708 (CO); 3365 (NH_2) cm^{-1}.

Mass spectrum: 313 (32) $[M+2]^+$; 311 (100) $[M]^+$, m/e (% rel abund).

Anal. $C_{17}H_{14}ClN_3O.H_2O$ requires: C, 61.91; H, 4.89; N, 12.74. Found: C, 62.10; H, 4.81; N, 12.68.

4-(2-Amino-5-methoxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (174)

Concentrated sulfuric acid (0.5 ml) was added dropwise to a suspension of 4-(o-hydroxylaminobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.4 g) in hot methanol (15 ml). The solid dissolved immediately and the resulting solution was heated under reflux for two hours, then left standing at room temperature for twelve hours. Dilute sodium hydroxide solution (10 ml) was added, then the solution was reacidified with glacial acetic acid and extracted with chloroform. The washed and dried ($MgSO_4$) chloroform solution was evaporated to dryness to give an oil which was chromatographed on a silica gel column (0.25" x 8"; 15 g) using benzene (100 ml), benzene/chloroform (1:1) (100 ml), and then chloroform (325 ml) as solvent. Evaporation of the chloroform eluate gave a brown oil which solidified when triturated with ethanol. The product (0.21 g) was crystallized from ethanol (charcoal) to yield 4-(2-amino-5-methoxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one as an off-white solid, m.p. 136-137°. R_f [ChromAR Sheet 500 (Mallinckrodt) with chloroform], 0.29.

I.r. spectrum: 1711 (CO); 3280, 3300 (NH_2) cm^{-1}.

Mass spectrum: 307 (100) $[M]^+$, m/e (% rel abund).

Anal. $C_{18}H_{17}N_3O_2$ requires: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.14; H, 5.44; N, 13.49.

Interaction of Benzothiazine and Benzoxazine Hydroxamic Acids with Acetic Anhydride

4-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (177)

A solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (1.08 g) in hot dry benzene (75 ml) was treated with acetyl chloride (3.0 ml), and the solution heated under reflux for two and one-half hours. The reaction mixture was reduced to dryness, leaving a colorless oil which yielded 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (1.01 g) when triturated with ethanol, m.p. 89-90° (aqueous ethanol).

I.r. spectrum: 1705, 1802 (CO) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 7.66 (3-proton singlet) (CH_3); 6.43 (2-proton singlet) (CH_2); 2.55-3.20 (4-proton multiplet) (aromatic signal).

Mass spectrum: 223 (41) $[M]^+$; 181 (100); 43 (59), m/e (% rel abund).

Anal. $C_{10}H_9NO_3S$ requires: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.65; H, 4.18; N, 6.43.

2-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (179)

Method A

Acetic anhydride (2.5 ml) was added to a suspension

of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (1.0 g) in glacial acetic acid (5 ml), and the reaction mixture was heated under reflux for thirty minutes. The hot solution was poured into ice and the resulting suspension neutralized with solid sodium carbonate. This mixture was extracted with ether. Evaporation of the organic layer yielded a yellow solid (0.9 g). Crystallization of this product from ethanol yielded the title compound, m.p. 172-174°. Reported (Zahn, 1923) m.p. 172-173°.

I.r. spectrum: 1675, 1753 (CO); 3198 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ8.00 (3-proton singlet) (CH_3); 3.60 (1-proton singlet) (CH); 2.58-3.18 (4-proton multiplet) (aromatic protons); -0.10 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Mass spectrum: 223 (30) $[M]^+$; 181 (61); 43 (100); m/e (% rel abund).

Method B

A solution of 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (0.53 g) in glacial acetic acid (3 ml) was heated under reflux for thirty minutes. The reaction mixture was diluted with water (10 ml) and extracted with chloroform. Evaporation of the chloroform layer on a film evaporator left a brown solid (0.50 g). Crystallization of this product from benzene gave 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine, m.p. 170-173°. The infrared spectrum of this product was superimposible on that of the compound prepared by method A.

Method C (Zahn, 1923)

A suspension of 2-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (0.92 g) and anhydrous sodium acetate (0.52 g) in glacial acetic acid (8 ml) was stirred under reflux for forty-five minutes. The hot suspension was filtered and the filtrate was poured over ice. Stirring and filtration of the resulting suspension yielded a white solid (0.85 g), which on recrystallization from ethanol gave 2-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine, m.p. 171-173°. Reported (Zahn, 1923) m.p. 172-173°. The infrared spectrum of this compound was superimposible with the spectrum of the product isolated from the treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine with acetic anhydride in glacial acetic acid. A mixed melting point of the two compounds was not depressed.

3,4-Dihydro-3-oxo-2H-1,4-benzothiazine (151) (Prasad and Tietje, 1966)

Sodium hydrosulfite (11.75 g) was slowly added to a warm solution of (o-nitrophenylthio)acetic acid (4.75 g) and sodium hydroxide (4.0 g) in water (250 ml). After the exothermic reaction had ceased, the temperature of the reaction mixture was raised to 90° for five minutes. The hot solution was filtered and the filtrate acidified with concentrated hydrochloric acid. As the solution cooled a flocculent yellow precipitate of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine formed (1.6 g), m.p. 174-177°. Reported (Coutts, Barton, and Smith, 1966) m.p. 179-180°.

I.r. spectrum: 1662 (CO); 3190 (NH) cm^{-1}.

2-Chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (Zahn, 1923)

A solution of sulfuryl chloride (0.5 g) in dry benzene (10 ml) was slowly added to a hot solution of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (1.05 g) in the same solvent (50 ml). A grey precipitate slowly formed, and after twenty minutes the resulting suspension was chilled and filtered, leaving 2-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (1.03 g) as a grey solid, m.p. 215-218°. Reported (Zahn, 1923) m.p. 215°.

I.r. spectrum: 1673 (CO); 3195 (NH) cm^{-1}.

Treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (150) with acetic acid

3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (0.31 g) was dissolved in hot glacial acetic acid (10 ml), and the solution heated under reflux for forty minutes. The solvent was removed on a film evaporator leaving a solid. This compound was dissolved in 10% sodium carbonate solution, the solution washed with chloroform, then the product reprecipitated with acetic acid. Extraction of this suspension with chloroform and evaporation of the chloroform layer left a white solid which proved to be the starting material (0.28 g), m.p. 149-151° (ethanol). Reported (Coutts, Barton, and Smith, 1966) m.p. 151-152°. The infrared spectrum of the product was superimposible on the spectrum of the starting material.

Treatment of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (151) with acetic acid

A suspension of the title compound (0.53 g) in glacial acetic acid (5 ml) was treated with acetic anhydride (3 ml) and heated under reflux for twenty-five minutes. The reaction mixture was poured over ice and the resulting suspension filtered leaving 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (0.47 g), m.p. 174-176° (ethanol). Reported (Coutts, Barton, and Smith, 1966) m.p. 179-180°. The infrared spectrum of this product was the same as that of the starting material.

3,4-Dihydro-4-hydroxy-6-methyl-3-oxo-2H-1,4-benzothiazine (175)

A solution of methyl (4-methyl-2-nitrophenylthio)-acetate (Coutts, Peel, and Smith, 1965) (3.01 g) in dioxane (60 ml) was reduced with sodium borohydride and palladium-charcoal as described in the general procedure (p.129). The filtrate was acidified with acetic acid and the solution reduced to approximately one-third volume on a film evaporator. The resulting suspension was filtered leaving the title compound as a white solid (1.52 g), m.p. 106-108°. Reported (Coutts, Peel, and Smith, 1965) m.p. 105-107°.

I.r. spectrum: 1628, 1673 (CO); 2500-3390 with a maximum at 3125 (OH) cm^{-1}.

N.m.r. spectrum: τ 7.69 (3-proton singlet) (CH_3); 6.41 (2-proton singlet) (CH_2); 2.67-3.30 (3-proton multi-

plet) (aromatic protons); -0.47 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

4-Acetoxy-3,4-dihydro-6-methyl-3-oxo-2H-1,4-benzothiazine (180)

Acetyl chloride (2 ml) was added to a solution of 3,4-dihydro-4-hydroxy-6-methyl-3-oxo-2H-1,4-benzothiazine (0.43 g) in dry benzene (30 ml). This solution was heated under reflux for ninety minutes, then reduced to dryness leaving a dark oil. Trituration of this oil with ethanol yielded a grey solid (0.37 g). Recrystallization of this product from ethanol (charcoal) gave 4-acetoxy-3,4-dihydro-6-methyl-3-oxo-2H-1,4-benzothiazine, m.p. 97-98°.

I.r. spectrum: 1701, 1793 (CO) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 7.68 (3-proton singlet) (CH_3); 7.64 (3-proton singlet) (CH_3); 6.46 (2-proton singlet) (CH_2); 2.68-3.30 (3-proton multiplet) (aromatic protons).

Anal. $C_{11}H_{11}NO_3S$ requires: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.43; H, 4.71; N, 5.89.

2-Acetoxy-3,4-dihydro-6-methyl-3-oxo-2H-1,4-benzothiazine (181)

A suspension of 3,4-dihydro-4-hydroxy-6-methyl-3-oxo-2H-1,4-benzothiazine (0.47 g) in glacial acetic acid (6 ml) was treated with acetic anhydride (2.5 ml) and heated under reflux for thirty minutes. The reaction mixture was stirred with ice, then filtered leaving a

yellow solid (0.41 g). Crystallization of this product from ethanol (charcoal) left the title compound as a white precipitate, m.p. 187-189°.

I.r. spectrum: 1678, 1757 (CO); 3200 (NH) cm^{-1}.

N.m.r. spectrum: τ 8.01 (3-proton singlet) (CH_3); 7.74 (3-proton singlet) (CH_3); 3.82 (1-proton singlet) (CH); 2.66-3.27 (3-proton multiplet) (aromatic protons); -1.00 (1-proton singlet; exchanged with deuterium oxide) (NH).

Anal. $C_{11}H_{11}NO_3S$ requires: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.72; H, 4.73; N, 6.01.

Methyl (o-nitrophenylsulfonyl)acetate (Coutts and Smith, 1967)

Potassium permanganate (20 g) was stirred with a solution of methyl (o-nitrophenylthio)acetate (10 g) in glacial acetic acid (150 ml) and water (25 ml). After stirring for two hours, a thick black gel formed. This was left standing for twelve hours, then decolorized with hydrogen peroxide (30%). The suspension which formed was filtered and the solid dissolved in chloroform. The organic layer was washed with water, then evaporated to dryness leaving methyl (o-nitrophenylsulfonyl)acetate (8.1 g), m.p. 118-120°. Reported (Coutts and Smith, 1967) m.p. 120-121°.

I.r. spectrum: 1750 (CO) cm^{-1}.

3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (176)

Following the general procedure (p. 129) a solution of methyl (o-nitrophenylsulfonyl)acetate (3.1 g) in dioxane (75 ml) was reduced with sodium borohydride/palladium-charcoal. The filtered reaction mixture was acidified over ice with dilute hydrochloric acid. This solution was flooded with water (350 ml) and extracted with chloroform. Removal of the chloroform left a colorless oil which solidified on trituration with ethanol. Recrystallization of this product yielded 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (1.72 g) as an off-white solid, m.p. 147-148°. Reported (Coutts et al, 1968) 149-150°.

I.r. spectrum: 1655 (broad) (CO); 2400-3450 with a maximum at 3090 (OH) cm^{-1}.

4-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (182)

Method A

A solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (0.49 g) in dry benzene (50 ml) was treated with acetyl chloride (2.5 ml) and heated under reflux for two and one-half hours. Evaporation of the reaction mixture left an oil. Trituration of this oil with ethanol gave a white solid (0.41 g) which proved to be the title compound, m.p. 159-161°. Reported (Coutts et al, 1968) m.p. 161-162°.

I.r. spectrum: 1705, 1806 (CO) cm^{-1}.

N.m.r. spectrum: τ 7.57 (3-proton singlet) (CH_3); 4.84 (2-proton singlet) (CH_2); 1.96-2.72 (4-proton multiplet) (aromatic protons).

Method B

Acetic anhydride (3 ml) was added to a solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (0.51 g) in glacial acetic acid (7 ml). After heating under reflux for thirty-five minutes, the reaction mixture was poured over ice. The resulting suspension was filtered leaving a white solid (0.50 g). Crystallization of this product from ethanol left 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide, m.p. 159-160°. The infrared spectrum of this product was identical to that of the product isolated in method A.

This reaction was repeated except that the solution of the hydroxamic acid (0.51 g) in acetic anhydride (6 ml) was heated for twenty-two hours. The reaction mixture was left standing for a further eighteen hours then poured into ice. Stirring yielded a solid (0.44 g) which was recrystallized from ethanol (charcoal) leaving 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide, m.p. 160-161°. The infrared spectrum of this compound was superimposible on those of the products isolated in both of the preceding reactions.

Ethyl (o-nitrophenoxy)acetate

The sodium salt of o-nitrophenol was prepared by adding slowly o-nitrophenol (20.8 g) to a solution of sodium hydroxide (10.5 g) in ethanol (125 ml). A thick suspension formed immediately, and after stirring for fifteen minutes this was filtered leaving the sodium salt (23.0 g) as a bright red solid.

This salt (20.1 g) was suspended in acetone (250 ml) and treated with ethyl bromoacetate (22.5 g). The suspension was stirred under reflux for fourteen hours. During this time a pale yellow suspension formed. The hot reaction mixture was filtered and the filtrate evaporated to dryness, leaving an oil (29.3 g) which solidified on cooling. Crystallization of this product from ethanol yielded yellow needles of ethyl (o-nitrophenoxy)-acetate, m.p. 45-47°. Reported (Minton and Stephen, 1922) m.p. 46-47°.

I.r. spectrum: 1733 (CO) cm^{-1}.

4-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (185)

A suspension of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (1.92 g) in benzene (80 ml) was treated under reflux with acetyl chloride (2.8 ml) for three hours. Evaporation of the reaction mixture left a brown oil which, on repeated trituration with ethanol, yielded a grey solid (1.44 g). Recrystallization of this product from benzene/petroleum ether and aqueous ethanol gave 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine, m.p. 64-65°.

I.r. spectrum: 1705, 1803 (CO) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 7.54 (3-proton singlet) (CH_3); 5.25 (2-proton singlet) (CH_2); 2.93-3.26 (4-proton multiplet) (aromatic protons).

Anal. $C_{10}H_9NO_4$ requires: C, 57.98; H, 4.37; N, 6.76. Found: C, 58.01; H, 4.30; N, 6.70.

6-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187)

Method A

Acetic anhydride (5 ml) was added to a solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (1.03 g) in glacial acetic acid (10 ml), and the reaction mixture heated under reflux for thirty-five minutes. The reaction mixture was poured into ice and the resulting suspension filtered. Recrystallization of this product (0.73 g) from benzene and ethanol yielded 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine, m.p. 162-164°. Reported (Loudon and Ogg, 1955) m.p. 162-163°.

I.r. spectrum: 1691, 1760 (CO); 3200 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 7.74 (3-proton singlet) (CH_3); 5.43 (2-proton singlet) (CH_2); 2.96-3.44 (3-proton multiplet) (aromatic protons); -0.27 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Anal. $C_{10}H_9NO_4$ requires: C, 57.98; H, 4.37; N, 6.76. Found: C, 57.84; H, 4.33; N, 6.74.

Method B

A solution of 4-acetoxy-3,4-dihydro-3-oxo-2H-1,4-

benzoxazine (0.45 g) in glacial acetic acid (3 ml) was heated under reflux for thirty minutes. The reaction mixture was poured into ice, and the suspension that formed was filtered leaving a white solid (0.35 g). The filtrate was neutralized with solid sodium carbonate and extracted with chloroform. Evaporation of the chloroform left a white product (0.09 g). These two solids were combined and recrystallized from benzene. This yielded 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (0.25 g), m.p. 159-161°. The infrared spectrum of this product was identical to that of the compound isolated in procedure A.

The filtrates from these recrystallizations were evaporated to dryness leaving a white solid (0.16 g), m.p. 135-140°. The infrared spectrum of this solid was similar to, but not identical with, that of the 6-acetoxy lactam, and the solid gave only one spot on thin layer chromatography, R_f 0.56 [ChromAR Sheet 500 (Mallinckrodt) using chloroform/ether (1:1) as a developing solvent] which was the same as the R_f value of 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine under the same conditions; however, repeated recrystallization failed to increase the melting point of this product. Attempts to purify this solid by column chromatography using a silica gel column were also unsuccessful. Gas chromatography of a methanolic solution of this product on a 0.25" x 6' glass column of 3% silicone rubber O.V. - 17 on chromasorb (80-100 G) at 185° gave three peaks with retention times of 6.0, 7.4, and 8.3 minutes

which were present in a ratio of 2:16:7 respectively. The addition of authentic samples of 6-acetoxy- and 7-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine resulted in the augmentation of the second and third peaks.

Method C (Loudon and Ogg, 1955)

A solution of 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (0.35 g) in ice cold 5% sodium hydroxide solution (5 ml) was treated with excess acetic anhydride (1 ml). A suspension formed almost immediately and after five minutes this was filtered, leaving 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (0.36 g) as a white solid, m.p. 162-163° (benzene). Reported (Loudon and Ogg, 1955) m.p. 162-163°. [R_f 0.56 when chromatographed on ChromAR Sheet 500 (Mallinckrodt) using a developing solvent of chloroform/ether (1:1)]. The infrared spectrum of this product and those of the compounds prepared by methods A and B were identical. The mixed melting points of these compounds were not depressed.

α-Chloro-2,5-dimethoxyacetanilide (Loudon and Ogg, 1955)

A solution of chloroacetyl chloride (4.5 ml) in dry benzene (15 ml) was added slowly to a solution of 2,5-dimethoxyaniline (8.4 g) and pyridine (4.7 ml) in the same solvent, (225 ml) keeping the temperature below 15°. A precipitate slowly formed. After one hour more chloroacetyl chloride (2 ml) was added and the reaction mixture stirred at room temperature for twenty-four hours. The

suspension was washed with 5% hydrochloric acid yielding a clear amber benzene layer. The organic layer was dried ($MgSO_4$) and evaporated to dryness leaving a grey solid (13.22 g). Crystallization of this product from petroleum ether gave ∝-chloro-2,5-dimethoxyacetanilide, m.p. 72-75°. Reported (Loudon and Ogg, 1955) m.p. 76-77°.

I.r. spectrum: 1676 (CO); 3395 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 6.24 and 6.16 (3-proton, singlets) (CH_3); 5.85 (2-proton singlet) (CH_2); 3.43 (1-proton, doublet of doublets; J=9 and 3 c.p.s.); 3.18 1-proton, doublet; J=9 c.p.s.); 1.99 (1-proton doublet, J=3 c.p.s.); 1.17 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

∝-Chloro-2,5-dihydroxyacetanilide (Loudon and Ogg, 1955)

A mixture of ∝-chloro-2,5-dimethoxyacetanilide (3.06 g), anhydrous aluminium chloride (10.1 g) and sodium chloride (4.1 g) was stirred on an oil bath at 140-145° for ten minutes. During this time a thick grey mass formed. This was cooled, then stirred with 5% hydrochloric acid over ice. Filtration of the resulting suspension yielded ∝-chloro-2,5-dihydroxyacetanilide (1.87 g) as a white solid, m.p. 195-196° (aqueous ethanol). Reported (Loudon and Ogg, 1955), 196-197°.

I.r. spectrum: 1655 (CO); 2400-3540 with maxima at 3290 (OH) and 3365 (NH) cm^{-1}.

N.m.r. spectrum: τ5.86 (2-proton singlet) (CH_2); 3.70 (1-proton, doublet of doublets; J= 8.5 and 3 c.p.s.); 3.34 (1-proton doublet; J= 8.5 c.p.s.); 2.56 (1-proton

doublet; J= 3 c.p.s.); broad 3-proton signal with peaks at 1.30, 0.94 and 0.79; all three exchanged with deuterium oxide (OH and NH).

3,4-Dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (189)

Method A (Loudon and Ogg, 1955)

∝-Chloro-2,5-dihydroxyacetanilide (1.05 g) was stirred with 5% sodium hydroxide solution (7 ml) for fifteen minutes. The solid dissolved and a precipitate slowly formed. The resulting suspension was neutralized with acetic acid and filtered, leaving an off-white solid (0.71 g). Crystallization of this product from ethanol (charcoal) yielded 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine, m.p. 251-253° (decomp). Reported (Loudon and Ogg, 1955) m.p. 249-250°.

I.r. spectrum: 1672 (CO); 2500-3440 (OH) with a maximum at 3195 (NH) cm^{-1}.

N.m.r. spectrum: τ 5.53 (2-proton singlet) (CH_2); 3.06-3.78 (3-proton signal) (aromatic protons); 0.90 and -0.5 (two 1-proton, broad signals; both exchanged with deuterium oxide) (OH and NH).

U.v. spectrum (ethanol): λ_{max}: 3020 Å (log ϵ: 3.68).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.23; H, 4.37; N, 9.04.

Method B

6-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (1.22 g) was dissolved in 10% sodium hydroxide solution (10 ml)

by stirring at room temperature. A black solution formed almost immediately. After five minutes, the reaction mixture was acidified with glacial acetic acid and filtered, leaving an off-white solid (1.1 g). Recyrstallization of this product from ethanol (charcoal) gave 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine, m.p. 252-254° (decomp). The infrared and n.m.r. spectra of this product were identical to those of the compound isolated in method A. A mixed melting point of the two compounds was not depressed.

6-Benzoyloxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (190)

A solution of 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (0.25 g) in 10% sodium hydroxide solution (4 ml) was shaken with benzoyl chloride (1 ml) and left standing for five minutes. Excess sodium hydroxide was added and the suspension, which had formed almost immediately, was filtered. The resulting solid (0.22 g) was crystallized from ethanol leaving 6-benzoyloxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine, m.p. 201-202°.

I.r. spectrum: 1698, 1738 (CO); 3200 (NH) cm^{-1}.

N.m.r. spectrum: τ 5.41 (2-proton singlet) (CH_2); 1.80-3.34 (8-proton multiplet) (aromatic protons); -0.71 (1-proton singlet; exchanged with deuterium oxide) (NH).

Anal. $C_{15}H_{11}NO_4$ requires: C, 66.91; H, 4.12; N, 5.20. Found: C, 67.07; H, 4.40; N, 5.51.

Resorcinol-3-benzoate (Barton, Linnell, and Senior, 1945)

Benzoyl chloride (56 g) was added, dropwise, to a mechanically stirred solution of resorcinol (44 g), sodium carbonate (88 g), and sodium hydrosulfite (5 g) in water (1300 ml) over a period of six hours, and stirring was continued for a further three hours. The resulting suspension was filtered, yielding resorcinol-3-benzoate (54.5 g), m.p. 131-133°, without further purification. Reported (Barton, Linnell, and Senior, 1945) m.p. 132-133°.

I.r. spectrum: 1708 (CO); 3430 (OH) cm^{-1}.

Nitration of resorcinol-3-benzoate (Kauffmann and Kugel, 1911)

A solution of the title compound (53 g) in glacial acetic acid (500 ml) was cooled to 20°, then treated with 35% aqueous nitric acid (sp. gr. 1.2) (55 ml). The acid was added over a period of two hours at a rate such that the temperature did not exceed 37°. The reaction mixture was stirred for a further three hours, then filtered, leaving a pale yellow solid (57 g), which was assumed to be a mixture of 4-nitroresorcinol-3-benzoate and 6-nitroresorcinol-3-benzoate.

2,4-Dimethoxynitrobenzene

Method A

A portion (3.42 g) of the mixture of the two isomers prepared in the preceding reaction was heated with sodium hydroxide (2.5 g) in 70% ethanol (100 ml) for ten minutes,

then cooled to 20°. An ethanolic solution (15 ml) of dimethyl sulfate (8 ml) was added dropwise to the reaction mixture. This solution was heated under reflux for twenty minutes, diluted with 10% sodium hydroxide solution (25 ml), then heated for a further four hours. The reaction mixture was concentrated to a volume of approximately 50 ml on a film evaporator and extracted with chloroform. Evaporation of the chloroform layer gave a low yield of the desired 2,4-dimethoxynitrobenzene (0.45 g), m.p. 74-75°. Reported (Kauffmann and Kugel, 1911) m.p. 75°.

Method B

The mixture of the two isomers (23.5 g) was stirred with sodium hydroxide (70 g) in hot ethanol (100 ml) for ten minutes. The resulting suspension was cooled and filtered, yielding what was assumed to be the disodium salt of 2,4-dihydroxynitrobenzene (16.1 g). This product was stirred with dry toluene (60 ml) and the resulting slurry heated under reflux on an oil bath (110°). Excess dimethyl sulfate (16 ml) was added dropwise to the solution over a thirty minute period, then the solution was heated for a further two hours. During this time the orange solid slowly dissolved. Dilute sodium hydroxide solution was added, and heating continued for another forty-five minutes. The reaction mixture was cooled, diluted with 10% sodium hydroxide solution (100 ml) and extracted with chloroform. Evaporation of the chloroform

layer yielded the desired 2,4-dimethoxynitrobenzene (8.6 g), m.p. 73-75°. The infrared spectrum of this compound was superimposible on that of the product prepared in method A.

2,4-Dimethoxyaniline (Loudon and Ogg, 1955)

Palladium-charcoal (1.5 g) was added to a solution of 2,4-dimethoxynitrobenzene (10.9 g) in glacial acetic acid (150 ml), and the reaction mixture hydrogenated until the uptake of hydrogen had ceased (approximately 4.2 l). The catalyst was removed and the volume of the filtrate reduced to approximately 50 ml on a film evaporator. The solution was neutralized with 50% sodium hydroxide solution and extracted with chloroform. The chloroform layer was then extracted with dilute hydrochloric acid and evaporated to dryness leaving a black solid (0.62 g). The acid layer was basified with 50% sodium hydroxide solution and re-extracted with chloroform. Removal of the chloroform left 2,4-dimethoxyaniline (8.04 g) as a light brown oil.

I.r. spectrum: 3365, 3450 (NH_2) cm^{-1}.

This product was characterized as its hydrochloride salt, m.p. 223-225° (decomp). Reported (Bechhold, 1889) m.p. 224° (decomp).

I.r. spectrum: 2400-3220 with maxima at 2570 and 2625 ($^{+}NH_3$) cm^{-1}.

α-Chloro-2,4-dimethoxyacetanilide (Loudon and Ogg, 1955)

Chloroacetyl chloride (4 ml) in benzene (15 ml) was slowly added to a benzene solution (225 ml) of 2,4-dimeth-

oxyaniline (8.04 g) and pyridine (5 ml) over a period of ten minutes, keeping the temperature of the reaction below 15°. After thirty minutes more chloroacetyl chloride (4 ml) was added and the suspension stirred at room temperature for forty-eight hours. The reaction mixture was then washed with dilute hydrochloric acid and evaporated to dryness leaving a brown solid (11.8 g). Recrystallization of this product from ethanol gave ∝-chloro-2,4-dimethoxyacetanilide, m.p. 87-90°. Reported (Loudon and Ogg, 1955) m.p. 90°.

I.r. spectrum: 1670 (CO); 3415 (NH) cm^{-1}.

∝-Chloro-2,4-dihydroxyacetanilide (Loudon and Ogg, 1955)

A mixture of ∝-chloro-2,4-dimethoxyacetanilide (4.05 g), sodium chloride (8.1 g) and anhydrous aluminium chloride (20.04 g) was fused at 140-145° for twenty minutes on an oil bath, resulting in the formation of a dark colored melt. This was cooled, then stirred with dilute hydrochloric acid over ice. The suspension was filtered leaving a grey solid which was crystallized from water and yielded ∝-chloro-2,4-dihydroxyacetanilide (2.82 g) m.p. 179-180°. Reported (Loudon and Ogg) m.p. 179-180°.

I.r. spectrum: 1643 (CO); 2400-3420 with maxima at 3110 (OH) and 3385 (NH) cm^{-1}.

3,4-Dihydro-7-hydroxy-3-oxo-2H-1,4-benzoxazine (Loudon and Ogg, 1955)

∝-Chloro-2,4-dihydroxyacetanilide (2.01 g) was dissolved in 10% sodium hydroxide solution (20 ml) and

the solution stirred for one hour. The reaction mixture was acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted with a large volume of ether. Evaporation of the ether layer left a purple solid (1.52 g) which on recrystallization from water yielded 3,4-dihydro-7-hydroxy-3-oxo-2H-1,4-benzoxazine as an off-white solid, m.p. 233-234° (decomp). Reported (Loudon and Ogg, 1955) m.p. 208-209°.

I.r. spectrum: 1678 (CO); 2500-3600 (OH) with a maximum at 3190 (NH) cm^{-1}.

N.m.r. spectrum: τ 5.50 (2-proton singlet) (CH_2); 3.09-3.70 (3-proton multiplet) (aromatic protons); 0.88 and -0.33 (1-proton singlet and 1-proton, broad signal; both exchanged with deuterium oxide) (OH and NH).

7-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (188)
(Loudon and Ogg, 1955)

A solution of 3,4-dihydro-7-hydroxy-3-oxo-2H-1,4-benzoxazine (0.28 g) in ice cold 5% sodium hydroxide solution (5 ml) was treated with excess acetic anhydride (0.75 ml). A precipitate began to form almost immediately, and after forty-five minutes the suspension was filtered leaving the title compound (0.30 g) as a white solid, m.p. 215-217° (water). Reported (Loudon and Ogg, 1955) m.p. 216-217°.

I.r. spectrum: 1685, 1757 (CO); 3190 (NH).

N.m.r. spectrum: τ 7.78 (3-proton singlet) (CH_3), 5.40 (2-proton singlet) (CH_2); 2.92-3.41 (3-proton multi-

plet) (aromatic protons); -0.72 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (168) with acetic acid

A solution of the title compound (0.63 g) was heated under reflux in glacial acetic acid for three hours. The reaction mixture was evaporated to dryness on a film evaporator leaving a grey solid. This product was dissolved in 10% sodium carbonate solution, and the solution washed with chloroform. Evaporation of the organic layer left a black oil (0.09 g).

The sodium carbonate layer was acidified with acetic acid and extracted with chloroform. Evaporation of the chloroform layer gave starting material as a grey solid (0.52 g), m.p. 163-164°. The infrared spectrum of this compound was identical to that of the starting material.

Treatment of 3,4-dihydro-3-oxo-2H-1,4-benzoxazine with acetic anhydride and acetic acid

Acetic anhydride (2 ml) was added to a solution of 3,4-dihydro-3-oxo-2H-1,4-benzoxazine (0.64 g) in acetic acid (5 ml), and the reaction mixture was heated under reflux for fifty minutes. The reaction mixture was poured into ice, stirred, and filtered, leaving the starting material (0.47 g) as a pale yellow solid, m.p. 169-171° (ethanol). The infrared spectrum of this product was the

same as that of the starting compound.

3,4-Dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine (191)

Method A

A solution of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzoxazine (1.65 g) in propionic anhydride (7 ml) and propionic acid (15 ml) was heated under reflux for thirty minutes. The reaction mixture was poured into ice, stirred, and the resulting suspension filtered, leaving an off-white solid (1.13 g). The filtrate was neutralized with solid sodium carbonate and extracted with chloroform. Removal of the chloroform left a solid (0.41 g). These products were combined and recrystallized from ethanol yielding 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine, m.p. 146-147°.

I.r. spectrum: 1703, 1762 (CO); 3200 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): τ 8.78 (3-proton triplet) (CH_3); 7.44 (2-proton quartet) (CH_2); 5.45 (2-proton singlet) (CH_2); 3.00-3.46 (3-proton multiplet) (aromatic protons); 0.5 (1-proton, broad signal; exchanged with deuterium oxide) (NH).

Anal. $C_{11}H_{11}NO_4$ requires: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.54; H, 4.75; N, 6.37.

Method B

4-Acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (0.61 g) was dissolved in propionic acid (5 ml) and the reaction heated under reflux for thirty-five minutes.

The reaction mixture was poured into ice, stirred, then filtered leaving a white solid (0.39 g). The filtrate was neutralized with solid sodium carbonate and extracted with chloroform. Evaporation of the chloroform layer left more product (0.21 g). These products were combined and recrystallized from ethanol yielding 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine, m.p. 143-145°. The infrared spectrum of this product was identical to the spectrum of the compound isolated in method A.

Hydrolysis of 3,4-dihydro-3-oxo-6-propionoxy-2H-1,4-benzoxazine (191)

A black solution slowly formed as a suspension of the title compound (0.79 g) in 10% sodium hydroxide solution (25 ml) was stirred at room temperature. After twenty minutes the reaction mixture was acidified with glacial acetic acid over ice, and filtered leaving a grey solid (0.59 g). Crystallization of this product from ethanol yielded 3,4-dihydro-6-hydroxy-3-oxo-2H-1,4-benzoxazine (189) as a white solid, m.p. 255-257° (decomp). Reported (Loudon and Ogg, 1955) m.p. 249-250°. The infrared spectrum of this compound was superimposible on the spectrum of an authentic sample of the 6-hydroxy derivative (p. 184).

Treatment of 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (187) with propionic acid

A solution of 6-acetoxy-3,4-dihydro-3-oxo-2H-1,4-

benzoxazine (0.34 g) in propionic acid was heated under reflux for thirty-five minutes. The reaction mixture was cooled, diluted with water, neutralized with solid sodium carbonate and extracted with chloroform. The chloroform layer yielded a white solid (0.33 g) on evaporation to dryness. This product was starting material, m.p. 157-160°. The infrared spectra of the product and the starting compound were superimposible.

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