SYNTHESIS OF HETEROCYCLIC COMPOUNDS STARTING FROM 3-AMINO AND 3-HYDROXYTHIOACRYLAMIDES

A Thesis
Presented to
The School of Graduate Studies
Addis Ababa University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Chemistry

By
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June 1982

ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

Synthesis of Heterocyclic Compounds Starting from 3-Amino and 3-Hydroxythioacrylamides

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To

Muluberhan

and

Addis

ACKNOWLEDGMENTS

Profound gratitude is expressed to Dr. J. Liebscher, my advisor. He gave of his time, energy and advice with no reservations. I also express my thanks to Dr. Ermias Dagne who took the burden of reading my paper and gave invaluable comments. To Dr. E. Klienpeter for his advice and help in interpreting some of the NMR spectra.

I extend my thanks to W/t Abrhi-tsion Seyoum who did an excellent typing, and to Ato Abdu Detango and Ato Adenew without whose co-operation no work would have been succesful. I am very greatful to Ato Zewdu Gebeyehu, Ato Wakgari Hirpo, Ato Wondimagne Mamo, Ato Yilma Mamo, and Ato Gizatchew Alemayehu for their symphaty and encouragement.

I extend my deepest gratitude to members of the Technical University of Dresden, Chemistry Section (GDR) who kindly did the elemental analyses and U.V of all componds synthesized. The Swedish Agency for Research Co-operation with Developing Countries (SAREC) is thanked for the financial aid obtainedd through the Commission for Science and Technology and Addis Ababa University.

Finaly, I cannot adequately express my deep appreciation and gratitude to my wife, Wzo. Muluberhan who shared all my problems and took care of our home.

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ABBREVIATIONS

The following abbreciations are used in the text.

Ac	Acetyl
Ar.	Aryl
Cpd.	Compound
DMF,	Dimethyl formamide
Et.	Ethyl
Fig:	Figure
M.P.	Melting point
IR.	Infrared
NMR.	Nuclear magnetic resonance
MS.	Mass spectrum (Spectra)
UV.	Ultra violet
M.W.	Molecular weight
Ph.	Phenyl
Pet.	Petroleum
Nu	Nucleophile
E	Electrophile

Abstract
Synthesis of Hetecrocyclic Compounds
Starting from 3-Amino and
3-Hydroxythioacrylamides

by

Alemayehu Areda
Advisor Dr. J. Liebscher

The 3-amino- and 3-hydroxythioacrylamides were obtained by deprotonation and hydrolysis of 1-mercapto-trimethinium perchlorates respectively. In this research both the thioacrylamides and the mercapto salts were used as starting materials to implement the synthesis of 2-amino-5-nitrothiophenes, 5-aminopysazoles, amino-thiopyrylium salts and 5-aminoisoxazoles. For the amino itrothiophenes and aminopyrazoles attempts made to solate reaction intermediates were successful and acceptable mechanisms have been suggested. In almost all cases reactions were rapid and yields were high.

I. INTRODUCTION

Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways.[1] Most members of the sugars and their derivatives and most of the Vitamin B group[2] possess heterocyclic rings containing oxygen or nitrogen. Many antibiotics[3,4,5] and antibacterial agents also contain heterocyclic ring systems. A large number of heterocyclic compounds, obtainable only by laboratory synthesis, have valuable properties as chemotherapeatic agents, dyestuffs and co-polymers.

The growing interest in the field has led many researchers to design several synthetic routes to heterocyclic molecules. These include synthetic processes such as the following:

a. Cycloaddition reactions
b. Valence bond isomerization reaction
c. Cyclocondensation reactions or enamine condensation reaction

One of the common features of all of these synthetic procedures is that, they involve ring-closure reactions which may be effected by either of the following two ways:

a. By a head to tail connection[6,7] of a bifunctional compound. (Eq.1)

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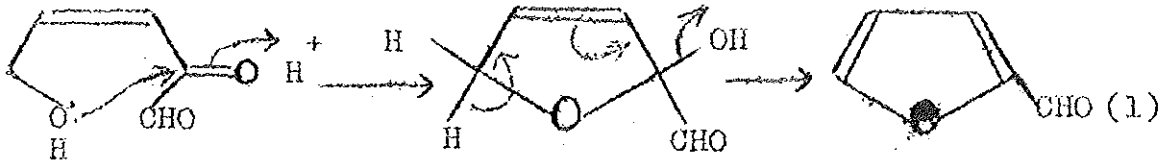
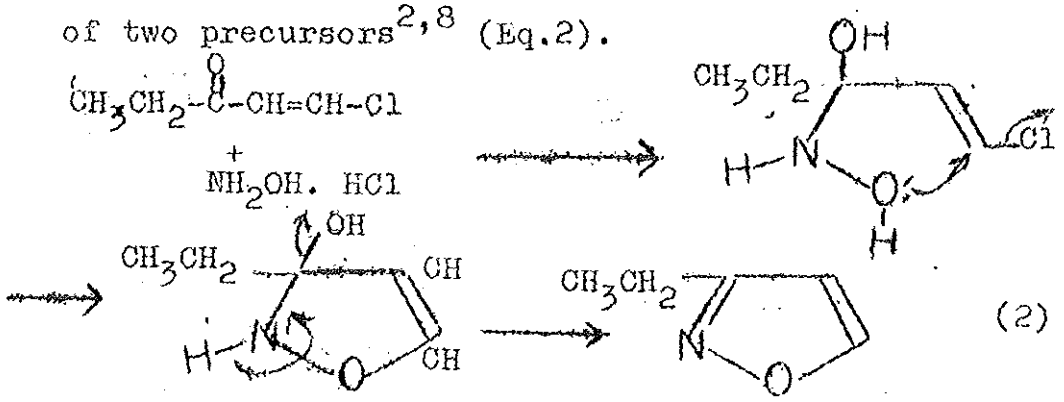


(1)

A nucleophilic attack takes place at the carbonyl carbon because it is the most electrophilic carbon in the structure.

b. By a cyclization reaction effected by an interaction of two precursors[2,8] (Eq.2).



(2)

In the later type of synthesis, bifunctional compounds like β-dicarbonyl compounds and their heteroanalogous thioamides, nitroenamines, hydrazines, hydroxylamines and others are included.

The one problem involved in the synthesis of heterocyclic compounds with one or more heteroatoms is the requirement of a suitably functionalized starting material. Relevant to the research described in this thesis, Liebscher *et al.*[14] synthesized a new series of 3-amino- and 3-hydroxythioacrylamides, 1 and 2, respectively (Fig.1). In essence our work is a continuation of an earlier program[14] which made available the starting materials, 1, 2 and 11.

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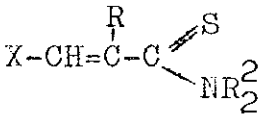

1, X = - NR_2^1

2, X = - OH

Fig.1 The Thioacrylamides

The thioacrylamides 1 and 2 are heteroanalogs of -dicarbonyl compounds, but since the sulfur can be kept for a subsequent cyclization reaction, these intermediates can be used to synthesis sulfur containing heterocycles. This was demonstrated[9], for example, with aminovinylthioketones 3 that resemble 1 or 2 as shown in scheme I. Infact, the synthesis of S-heterocycles could be effected by making use of -dicarbonyl compounds, but one needs sulfur containing reagents for the cyclization reaction.

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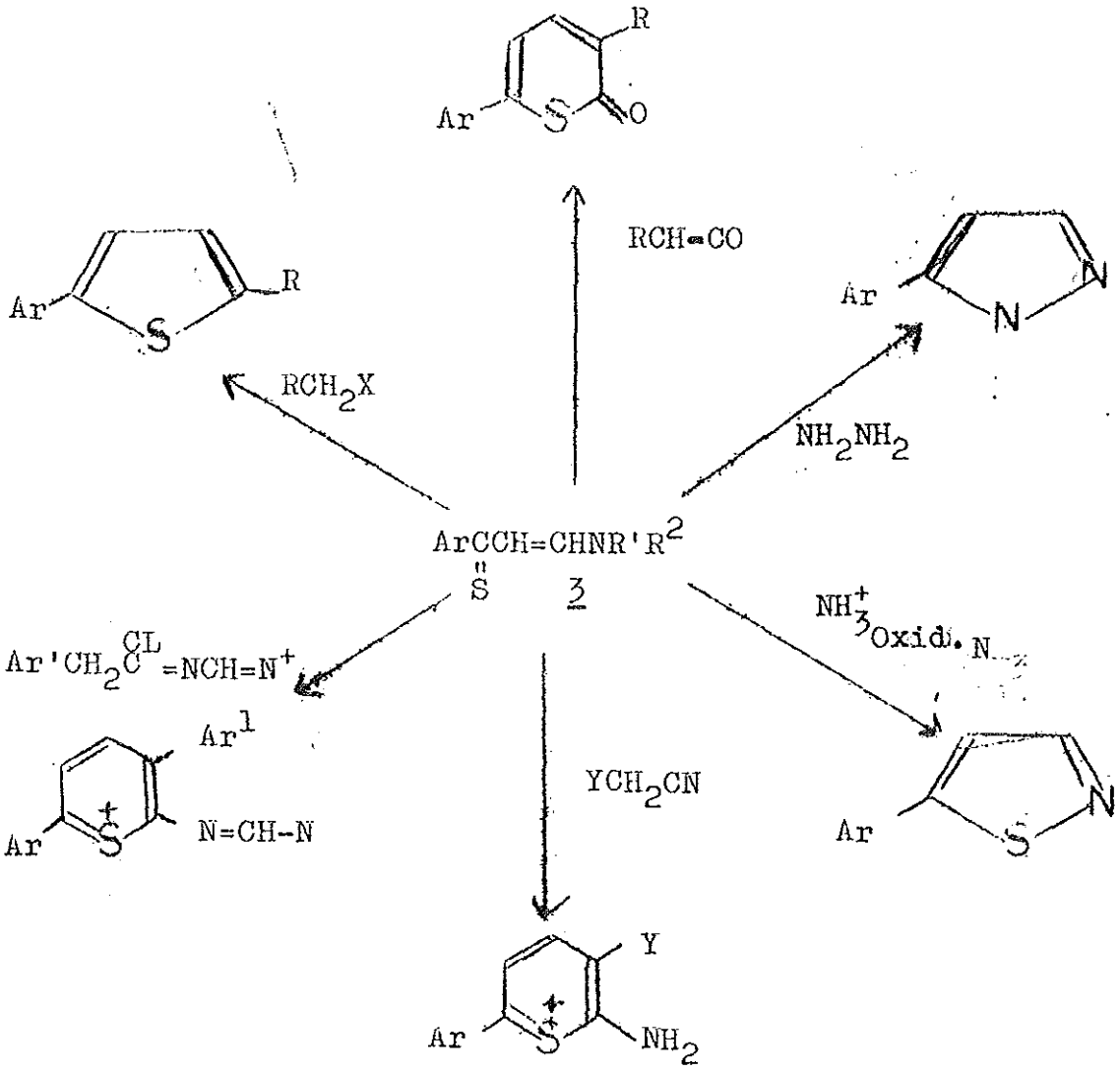
Scheme I: Reactions of Aminovinylthioketones 3



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II. THEORETICAL BACKGROUND

1. Synthesis of 3-Amino- and 3-Hydroxythioacrylamides

The reaction of various active methylene compounds with the electrophilic Vilsmeier reagent, formed from dimethylformamide and various acid chlorides provides an acid-catalyzed procedure for the introduction of a formyl group.[10,11,12] Based on this fact formamido chlorides 4 (Scheme II), prepared by the reaction of formamides and phosphoryl chloride $POCL_3$, thionyl chloride $SOCL_2$, or Oxalyl chloride $COCL_2$, were shown to react with acetamides 5 or 7 by iminoformylation and chlorination to give the 3-chloro-2-propeniminium salts 6[13] and 3-chloro-2-azapentamethinium salts 8.[14] Here it was observed that, along with the introduction of one or two iminocarbonyl groups, the carbonyl oxygen is substituted by a chloro group. These compounds, 6 and 8, were found to be versatile 1, 3- or 1,5-bifunctional electrophiles which makes them suitable for the synthesis of heterocyclic compounds.[9,15,16]

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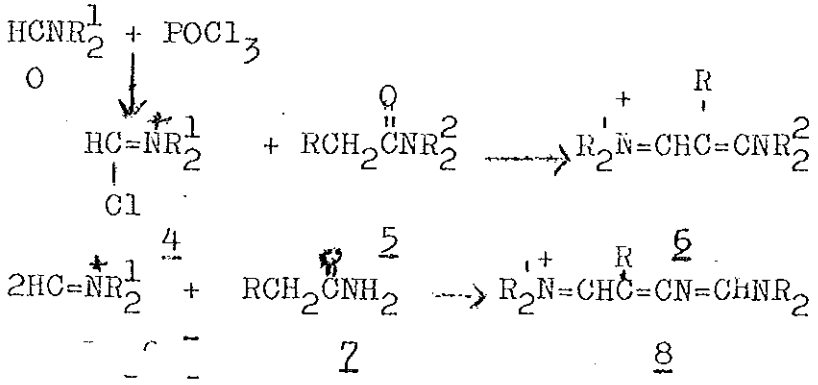
Scheme II. Iminoformylation Reactions of Acetamides



Liebscher et al[17] allowed formamido chlorides 4 to react with substituted thiocetamides 9 (Scheme III), which could be obtained from the Willgerodt-Kindler reaction of methyl ketones 10. In this case, though there is an introduction of the iminocarbonyl group, no substitution of the thiocarbonyl moiety by the chloride ion is observed. As a result instead of the expected 3-chloro-2-propeniminium salts, it was possible to isolate novel 1-mercapto-2-propeniminium salts 11 as colorless, crystalline perchlorates ($X^- = ClO_4^-$).

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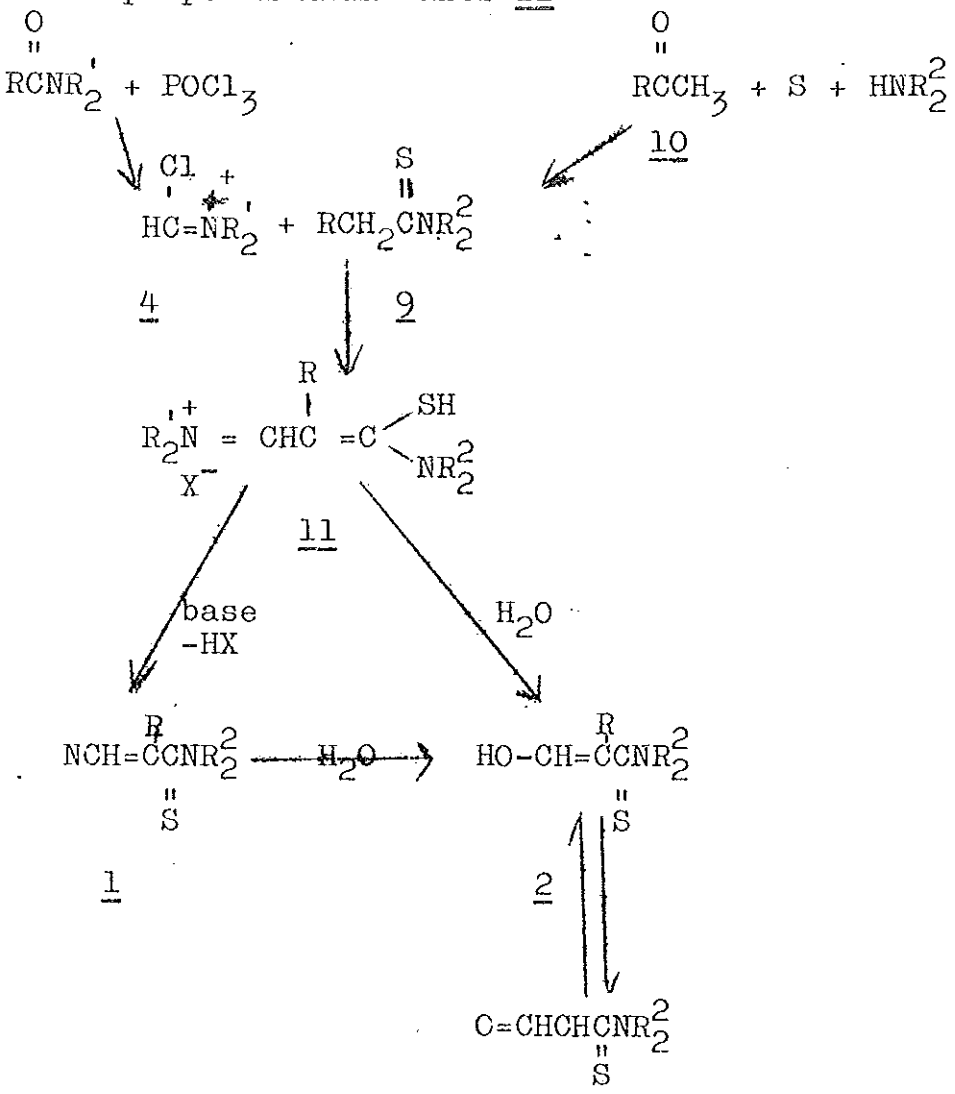
Scheme III. Synthesis of 1-Mercapto-2-propeniminium salts 11



The mercapto compounds 11, on further treatment with a base gave, the deprotonated products, 3-aminothioacrylamides, 1[17] as shown in scheme III above. On the other hand, hydrolysis or 11 of 1 yielded the 3-hydroxythioacrylamides 2.

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2. Reactions of 3-Amino- and 3-Hydroxythioacrylamides 1 and 2

Consideration of the structures of the thioacrylamides will make clear that these compounds are polyfunctional and possess many reactive sites (Fig.2).

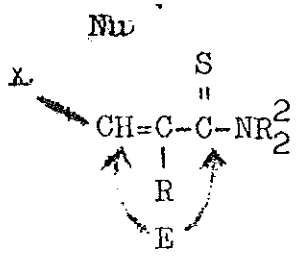

Fig.2 Thioacrylamides, polyfunctional nature.

This polyfunctionality determines the general reactivity of thioacrylamides in both cyclization and substitution reactions. For instance, due to the fact that carbon atoms 1 and 3 of the thioacrylamides 1 and 2 are electrophilic, a binucleophilic (Nu-Nu) compound such as hydrazine can react with them effecting a heterocyclic ring-closure as indicated by (Eq.3).

The thioacrylamides 1 and 2 also possess nucleophilic sites at groups X and S.

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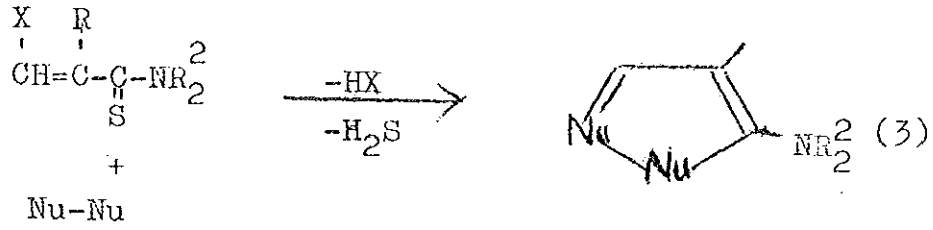
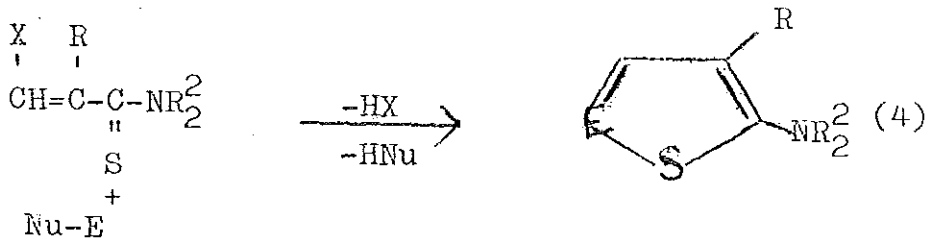
Therefore reaction between these compounds and a bi-functional compound, i.e. (E-Nu), also can lead to a ring-closure product as shown by (Eq.4):



(3)



(4)

The amino group $-NR_2$ in 11 and 1, or the hydroxy group in 2 could be substituted by primary amines and hydrazines[13] 12 ($R^{14} = NH_2$), giving rise to 3-aminothioacrylamides or 3-hydrazinothioacrylamides 13 as shown in Scheme IV.

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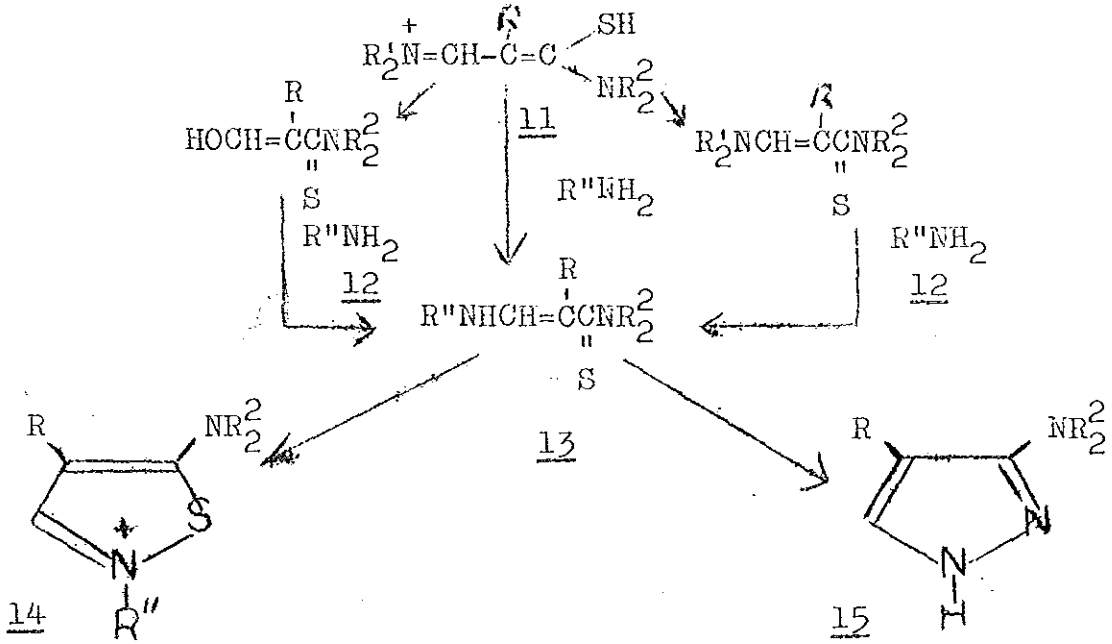
Scheme IV. Substitution and Cyclization Reactions of the thioacrylamide derivatives.



Oxidation of the 3-aminothioacrylamides 13 in acidic medium led to 5-aminoisothiazolium perchlorates 14 (Table 1).[17] On the other hand, the 3-hydrazinothioacrylamides 13 (R'' = NH_2) could undergo further cyclization by elimination of H_2S leading to 3-aminopyrazoles 15 (Table 1).[18]

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Table 1 5-Aminoisothiazolium salts 14(NR_2^2 =Morpholino) and 3-Aminopyrazoles 15 (NR_2^2 = Morpholino)

Cpd.	R	R"	Yield %
14a	C_6H_5	C_6H_5	84
14b	C_6H_5	m-$NO_2C_6H_4$	65
14c	C_6H_5	p-BrC_6H_4	67
14d	C_6H_5	$C_6H_5CH_2$	81
14e	p-$CH_3C_6H_4$	p-BrC_6H_4	67
14f	α-$C_{10}H_7$	p-$CH_3OC_6H_4$	50
15a	C_6H_5	-	53
15b	p-$CH_3C_6H_4$	-	49

1 , 2 and 11 also were shown[17] to react with halomethylene compounds 16 (R"' CH_2X). In this reaction (Eq.5), S-alkylation probably takes place first and is

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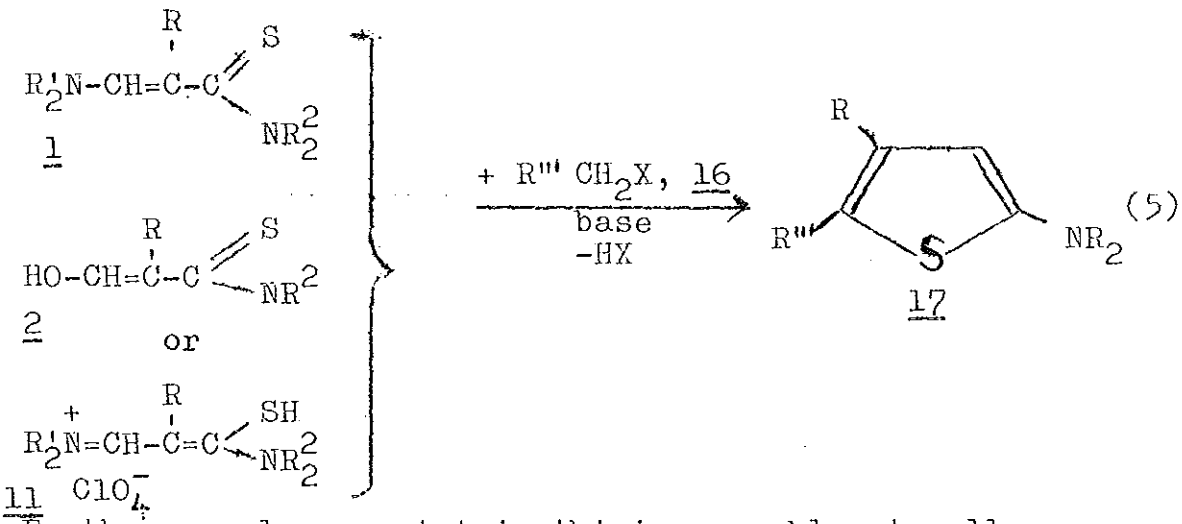
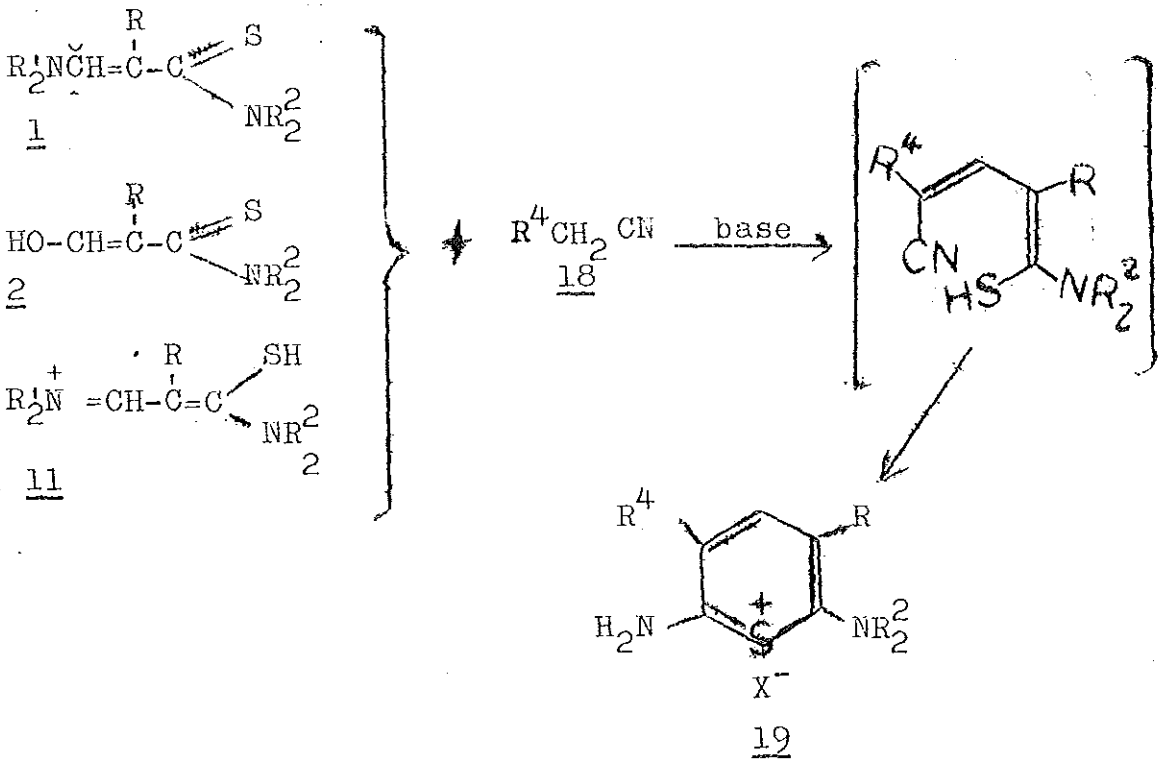
followed by the elimination of HNR'_2 to form 2-aminothiophenes 17 (Table 2).



(5)

Furthermore 1-mercaptotrimethinium perchlorates 11 or the 3-amino-and 3-hydroxythioacrylamides react with substituted acetonitriles, R^4CH_2CN, 18, to give 2, 6-diaminothiopyrylium salts 19 (Eq.6)[18] (Table 2).



Finally, the mercapto salt 11 was shown[18] to react with p-benzoquinone (Eq.7) to give 5-hydroxy-1,3-benzoxathiol derivatives 20 (Table 2). In contrast to the other reactions of 11 mentioned above, only the amino group, NR_2^2, is substituted in this case.

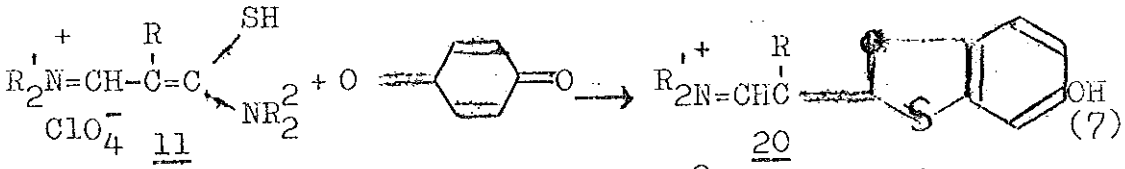


Table 2: 2-Aminothiophenes, 17 (NR_2^2=morpholino), 2,6-diaminothiopyrylium salts 19 (NR_2^2=morpholino), 5-hydroxy--1,3-benzoxathiol derivative 20 (R_2^1=$(CH_3)_2$

Cpd.	R	R"	Yield %
17a	C_6H_5	C_6H_5CO	91
17b	"	p-BrC_6H_4CO	93
17c	"	CH_3CO	53
19a	C_6H_5	CO_2Et	56
19b	C_6H_5	benzimidazol-2-yl	92
19c	p-Cl-C_6H_4	CO_2Et	61
20a	C_6H_5	-	58
20b	"	-	58
20c	p-Cl-C_6H_4	-	49
20d	p-CH_3O-C_6H_4	-	57

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In this research, by making use of the mercapto salts 11 or the thiocrylamides, 1 and 2, and other reagents, various reactions were performed to effect the synthesis of the following heterocyclic compounds:

1. 2-Amino-5-nitrothiophenes - by reaction with bromonitromethane

2. 5-Aminopyrazoles - by reaction with hydrazines

3. Aminoformamidinothiopyrylium salts - by reaction with 3-chloro-2-azatrimethinium salts and 3-chloro-2-azapentamethinium salts.

4. 5-Aminoisoxazoles-by reaction with hydroxylamine hydrochloride.

The results obtained are discussed in the following section. Every subsection starts with what is known about the compounds under discussion. This is followed by what we have done, The schemes and tables accompaning these discussions summarize the synthetic approaches and the compounds synthesized. Elemental analyses, melting points, yields and spectroscopic data are included in the Experimental Section. Additionally, selected spectra are appended to the thesis.

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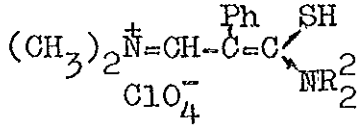
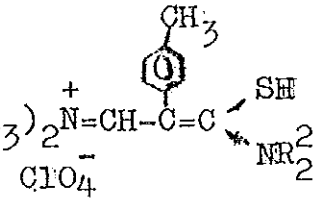
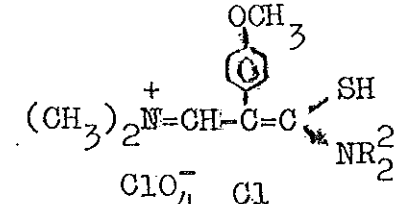
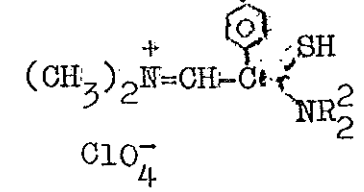
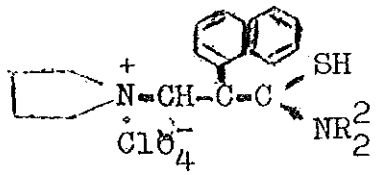
III. RESULTS AND DISCUSSIONS

4. Synthesis of Starting Materials

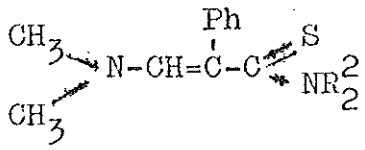
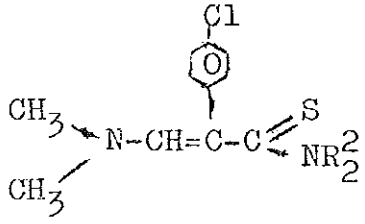
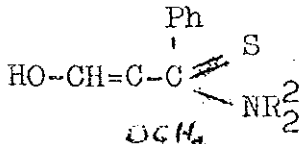
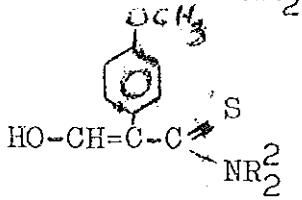
The 3-Amino- and 3-Hydroxythioacrylamides were obtained by deprotanation and hydrolysis of the 1-mercaptotrimethinium perchlorates respectively. The procedure towards the synthesis of the mercapto salts was adopted from earlier reports.[17] Below are given tables that include the structures of 11, 1 and 2 made use of in this project.

Table 3 : 1-Mercaptotrimethinium perchlorates 11, (NR_2^2 = Morpholino)

Cpd	Structure	M.P °C+	Yield %
11a		141	76
11b		139	51
11c		157	69
11d		173	73
11e		154	60

+Recrystallized from acetic acid

Table 4. 3-Amino- and 3-Hydroxythioacrylamides 1 and 2 (NR_2^2 = morpholino)

Cpd	Structure	M.P °C	Yield %
1a		107-108(MeOH)	79
1b		97(cyclohexane)	99
2a		116-118(n-propanol)	81
2b		110-111(MeOH)	96

2. Synthesis of 2-Amino-5-nitrothiophenes

The synthesis of 2-amino-5-nitrothiophenes have been reported by various workers. D.Spinelli et al.,[19] for instance, reported the reaction of the 2-bromo-5-nitrothiophenes 21 with piperidine in ethanol, (Eq.8). This nucleophilic substitution reaction led to 2-amino-5-nitrothiophenes 22.

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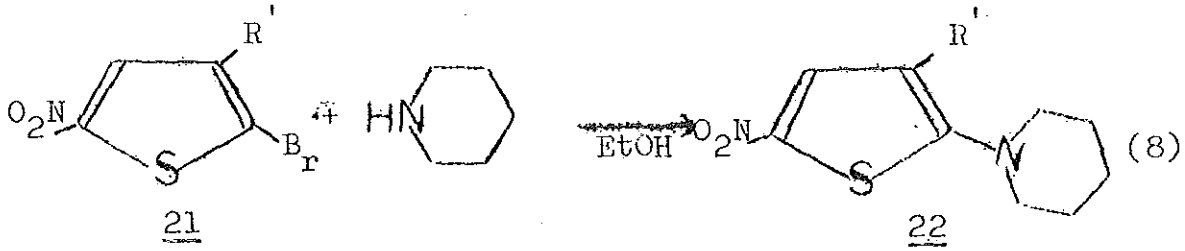
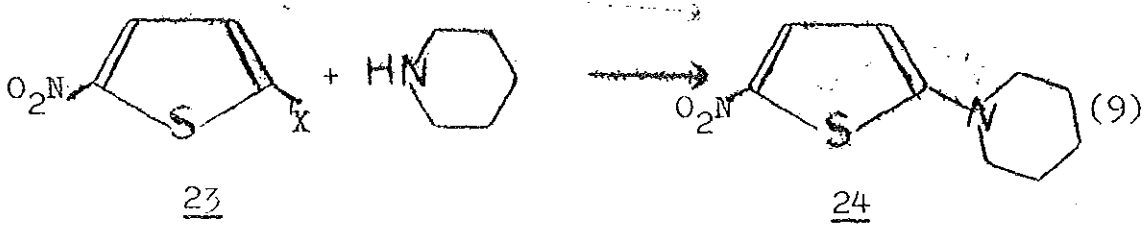


21 22 (8)

22a ; R' = H
22b ; R' = CH_3
22c ; R' = CH_3CH_2
22d ; R' = $CH_3(CH_2)_5$
22e ; R' = $(CH_3)_2CH$

Other workers[20,21,22] in an effort to determine the kinetics of the reaction of halonitrothiophenes with piperidine in ethanol and benzene, carried out nucleophilic substitution reactions on 2-halo-5-nitrothiophenes 23 and obtained 2-amino-5-nitrothiophenes 24 (Eq.9).



23 24 (9)

X = Cl, Br, I.

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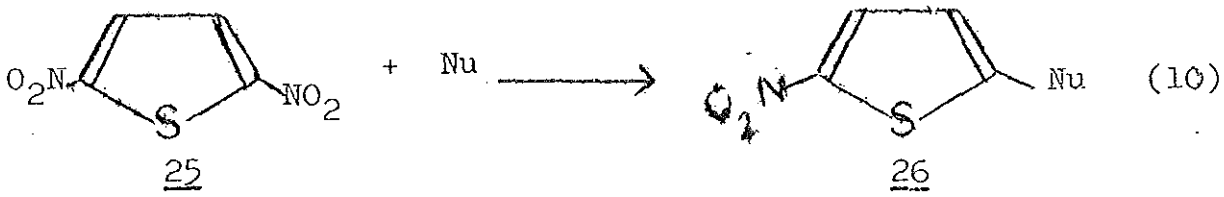
Another nucleophilic reaction[23] on 2,5-dinitrothiophene 25 with various amine nucleophiles led to 2-amino-5-nitro-thiophenes 26 (Eq.10).



25 (10) 26

26a; Nu = Morpholino

26b; Nu = NEt_2

26c; Nu = NHC_6H_5

26d; Nu = p-$CH_3C_6H_4NH$

Even though the results quoted above could lead to the N,N-disubstituted 2-amino-5-nitrothiophenes by nucleophilic substitution, all of these reactions start from an already nitrated thiophene ring.

As far as the 2-aminothiophenes are concerned, N-unsubstituted 2-amino-thiophenes 27 were synthesized[24] by the reaction of substituted acetonitriles 28 with carbonyl compounds 29 and sulfur in the presence of secondary amine bases (Eq.11).

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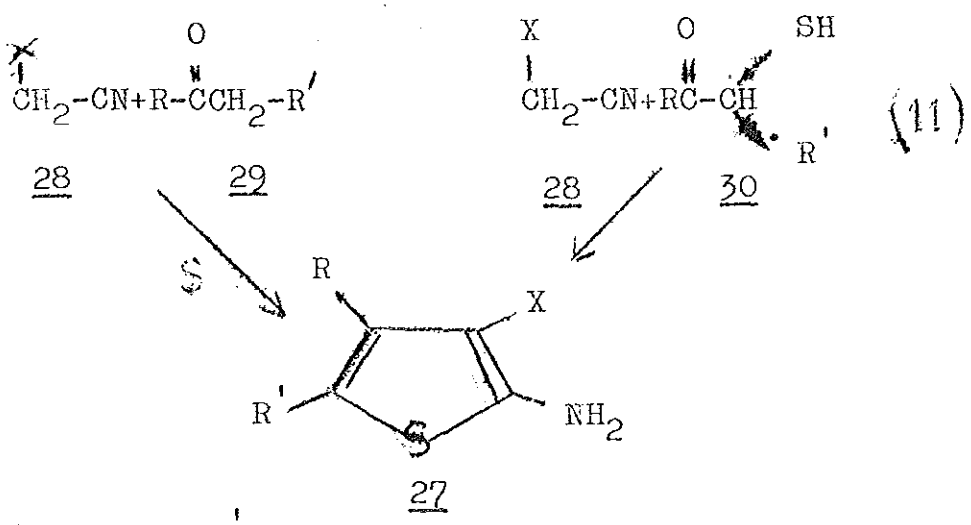
Similar products were obtained[25] by a reaction of a mercapto compound 30 and 28 (Eq.11).



(11)

28 29 28 30

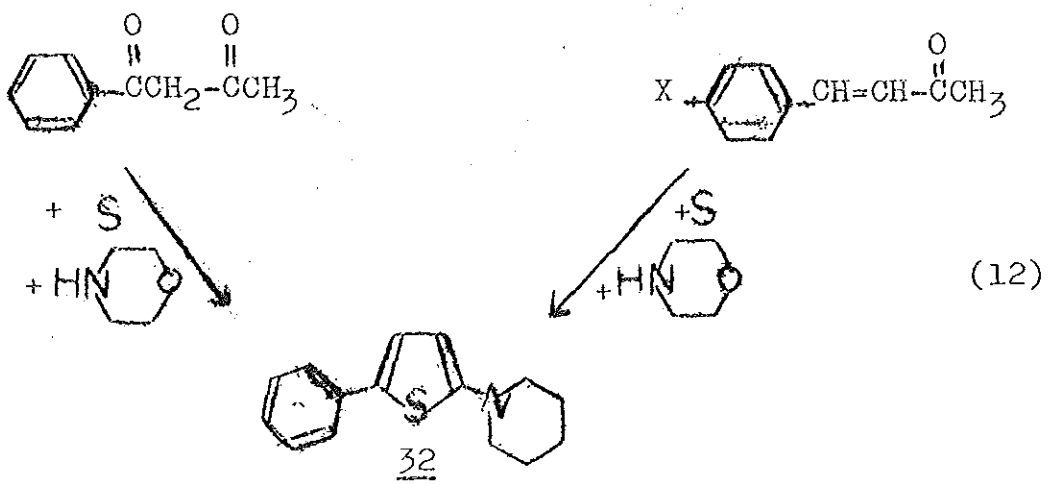
27

27a; R = CH_3, R' = CH_3, X = CN

27b; R = CH_3, R' = CH_3, X = CO_2Et

27c; R = CH_3CH_2, R' = CH_3, X = CO_2CH_3

Furthermore N,N-disubstituted 2-aminothiophenes like 2-morpholino -5-phenylthiophes 32 were synthesised[26,27,28,29] by cyclization reactions of the Willgerodt-Kindler type (Eq.12)



(12)

32

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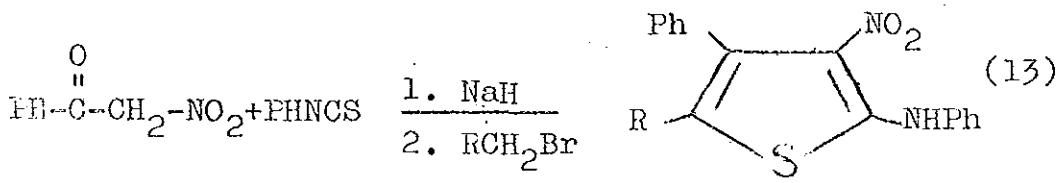
N-Monosubstituted 2-amino-5-nitrothiophenes were sythesized by methods that involve cyclization reactions between two or more reactants. Rudorf,[30] for instance, synthesized N-monosubstituted 2-amino-5-nitrothiophenes 33 by making use of a nitroacetophenone 34, phenylisothiocyanate 35 and a substituted bromomethylene derivative in the presence of bases like sodium hydride as shown by (Eq.13).



(13)

34 35 33

33a ; R = C_6H_5

33b ; R = CH_3CO

33c ; R = C_6H_5CO

33d ; R = NO_2

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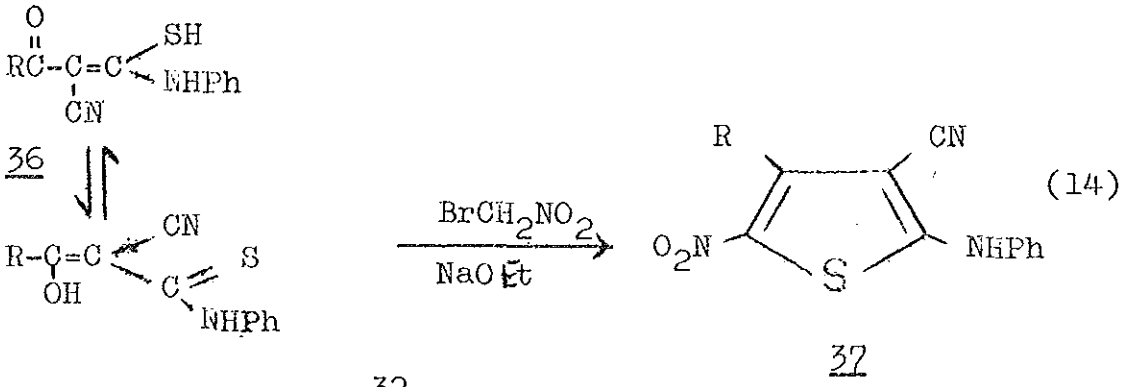
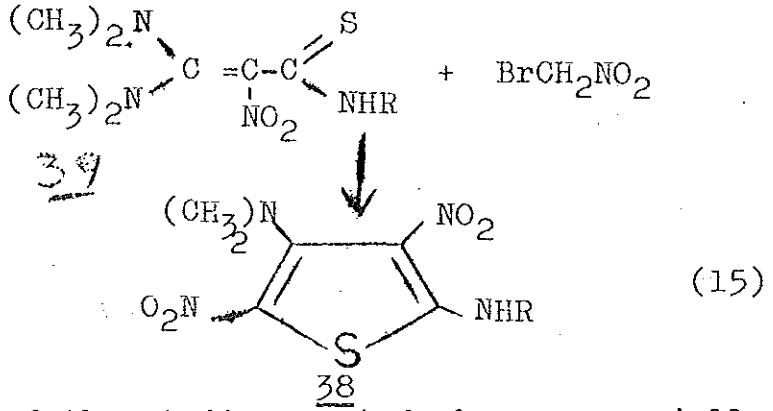
Augustin et al.,[31] used sulfur containing starting materials 36 and bromonitromethane to synthesis N-mono-substituted 2-amino-5-nitrothiophenes 37 (Eq. 14).



(14)

37

Rajappa et al.[32] Synthesized 2,4-diamino-3,5-dinitro-thiophenes 38 by making use of aminothioacrylamide derivatives 39 and bromonitromethane (Eq.15).



(15)

38

A few of the studies quoted above, especially that of Rajappa's[32] established that the cyclization of amino-thioacrylamides with bromonitromethane or substituted bromomethylene compounds is in principle known. Unfortunately no N,N-disubstituted 2-aminonitrothiophenes were synthesized by any of the methods that employed the types of cyclization reactions described here.

../

In the research conducted here, cyclization reactions that made use of the thioacrylamides or their mercapto salts and substituted bromomethylene compounds (in particular bromonitromethane) were carried out in order to obtain the N,N-disubstituted 2-amino-5-nitrothiophenes.

As far as the N,N-disubstituted 2-amino-5-nitrothiophenes synthesized by nucleophilic substitution reactions. (Eq. 8 - 10) are concerned, it is clear that they do not employ the cyclization reactions described here. Above all, their substitution pattern is completely different from those obtained in this research. This then makes for a novel approach to the synthesis of the title compounds. The following reaction scheme summarizes the attempt made here.

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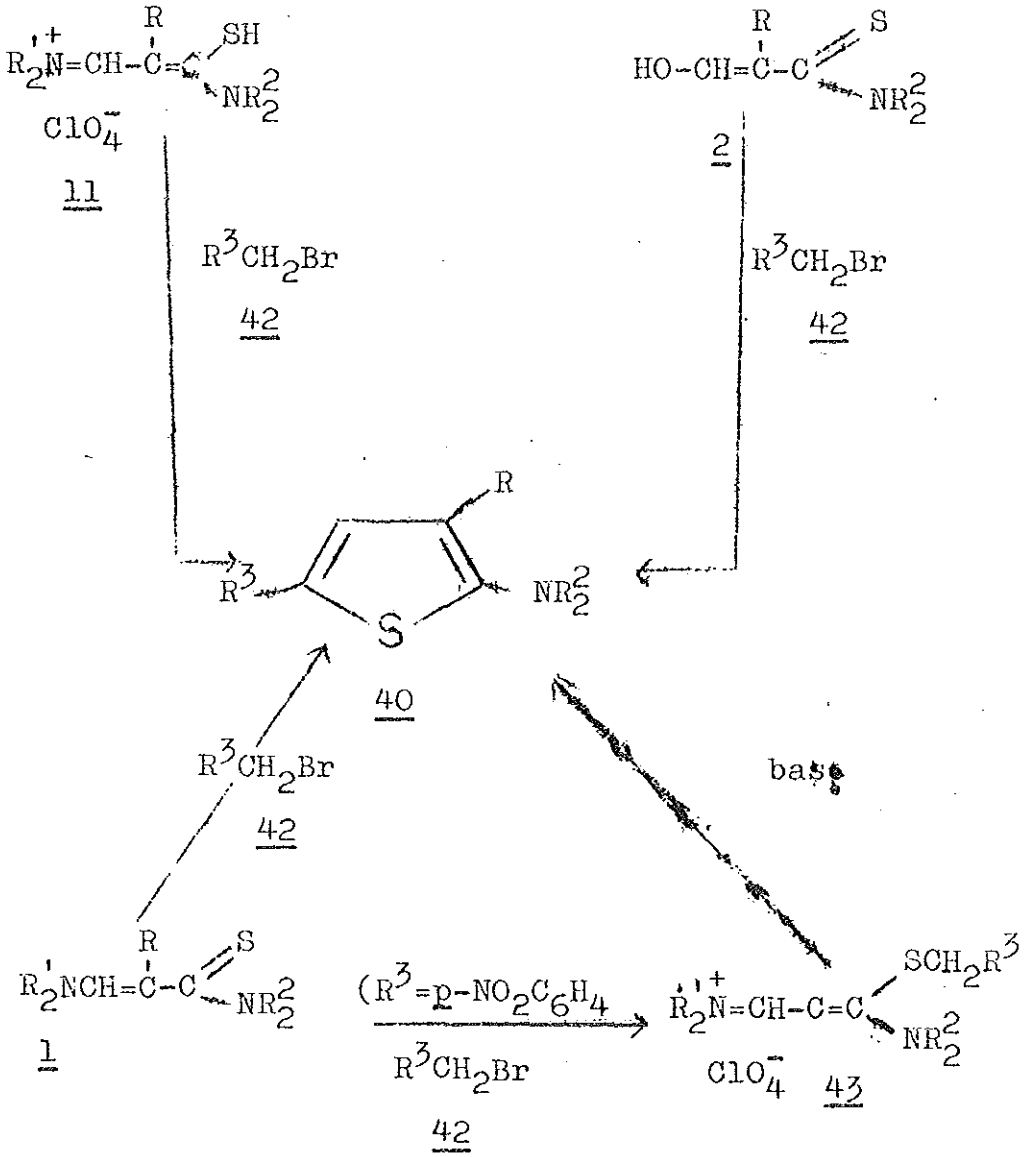
Scheme V Synthesis of 2-Amino-5-nitrothiophenes from the thioacrylamide derivatives ($X^- = ClO_4^-$ or $X^- = Br^-$)



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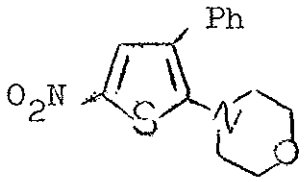
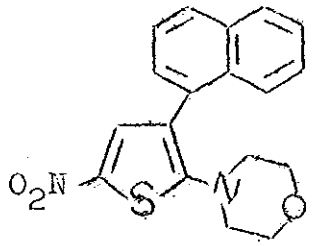
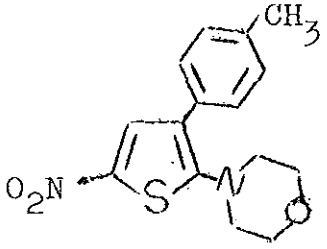
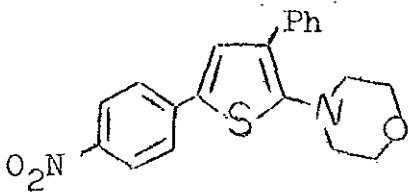
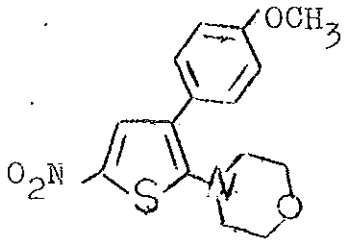
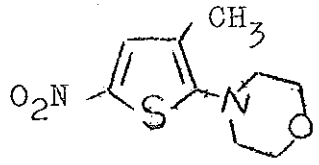
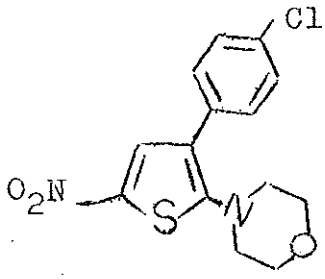
Based on Scheme V, the synthesized aminonitrothiophenes of different R and R^3 groups are given in the table below.

Table 5: 2-Amino-5-nitrothiophenes (NR_2^2 = morpholino)

Cpd.	Structure	Cpd.	Structure
40a		40e	
40b		40f	
40c		40g	
40d			

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The reactions between the thioacrylamides 1 and 2 or the mercapto salts 11 with bromonitromethane (42, $R^3 = NO_2$), under basic conditions, were rapid and yields were high. With an aim of isolating an intermediate for this reaction and to study its mechanism, the same reaction was performed under neutral conditions. This did not lead to any isolable intermediates except pasty like mixture.

Analysis of the products obtained under basic condition indicated that the sulfur was retained in the products. Additionally, no evolution of H_2S was noticed during the reaction. So it was logical to assume that the cyclization reactions could be initiated by nucleophilic attack of the sulfur at the methylene active carbon of bromonitromethane, and under basic conditions the reaction could possibly proceed towards the end product rapidly.

The methylene group in bromonitromethane is highly active so as to contribute to the speed of the reaction. Therefore it was necessary to use a less activated halomethylene compound in order to isolate an intermediate of the reaction. To this effect P-nitrobenzylbromide (42, $R^3 = P\text{-}NO_2C_6H_4$) was allowed to react with 1a under neutral conditions and the S-alkylated mercapto salts (43, $R^3 = P\text{-}NO_2C_6H_4$, $X^- = Br^-$ or ClO_4^-) were isolated and characterized. Moreover the intermediate 43 when heated under reflux for 30 minutes in a basic medium gave the cyclized product 40f in quantitative yield.

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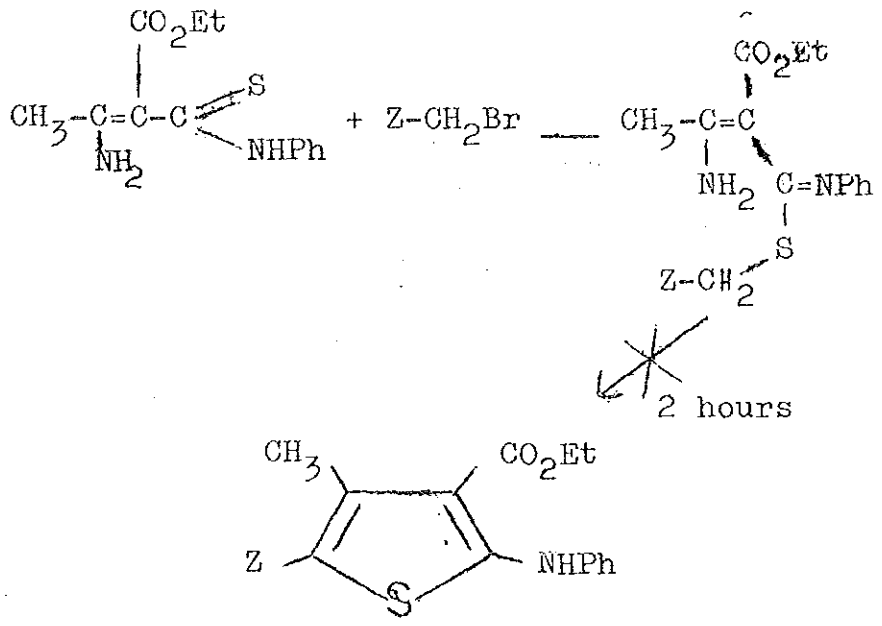
At this juncture, it is worth mentioning that Rajappa *et al.*[27] allowed *p*-nitrobenzylbromide to react with a 3-aminothioacrylamide but could not isolate the cyclized product even after 2-hours of heating under reflux (Eq.16).



Z= *p*-$NO_2C_6H_4$

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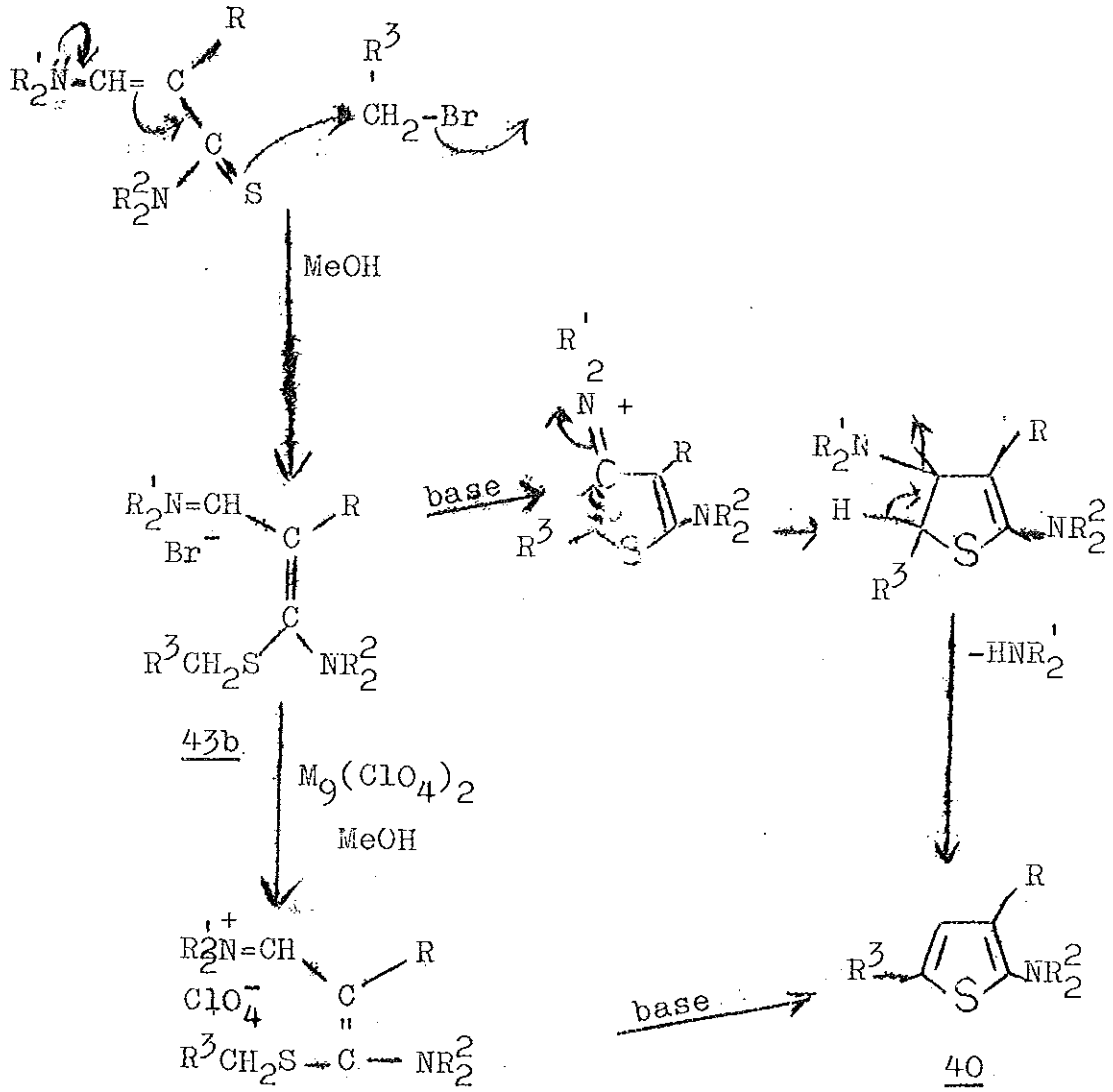
The most probable mechanism for the formation of the aminonitrothiophenes synthesized here is depicted in the following scheme.

Scheme VI: Mechanism of the 2-Amino-5-nitrothiophenes 40 synthesis.



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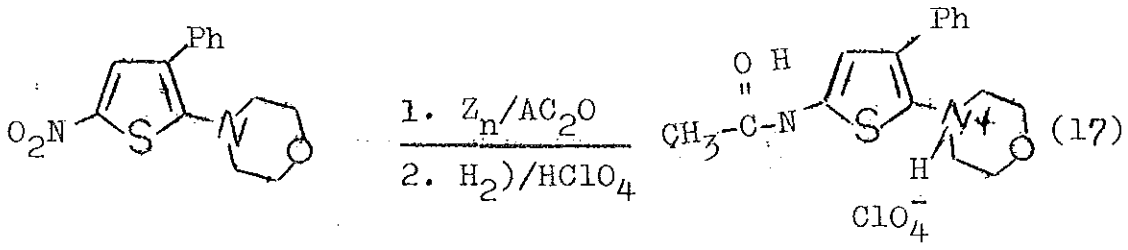
As depicted above the reaction proceeds by a prior S-alkylation whose product is isolated[+] as the bromide or perchlorate salt. Deprotonation by means of base is followed by a nucleophilic attack at carbon 3 of the salt and aromatisation with an elimination of the amine group, R_2N- (or OH if 2 is used) to yield the final product 40.

The structures of the aminonitrothiophenes 40 were confirmed by elemental analysis and spectroscopic data. Moreover 2-morpholino-5-nitrothiophene 40a was reduced by means of zinc and acetic anhydride to the corresponding 2,5-diaminothiophene 41 (Eq.17) which is only stable as the N-acetylated hydroperchlorate 41a. The aminonitrothiophenes 40 are crystalline, stable compounds that usually exhibit a yellow color.



40a

41a

[+]When 42 = NO_2CH_2Br is used no intermediate is isolated.

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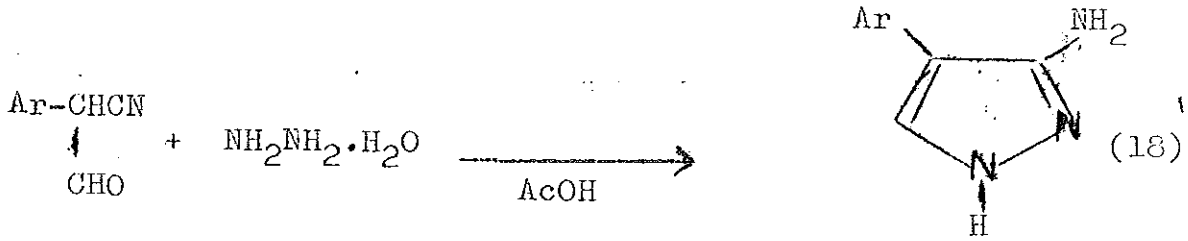
3. Synthesis of 5-Aminopyrazoles

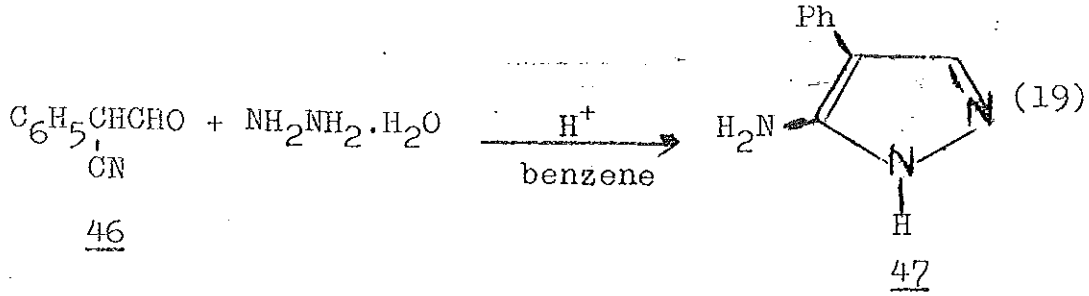
Various reports indicate that aminopyrazoles have been sunthesized from hydrazines and different open chain nitriles by nitrile cyclization. For instance, in one case[34] α- formylacetonitriles 44 were allowed to react with hydrazine hydrate in glacial acetic acid to give 3-amino-4-arylpyrazoles 45 (Eq.18). In another study[35] hydrazine hydrate was allowed to react with phenylcyanoacetaldehyde 46 in benzene containing p-toluensulfonic acid to give 5-amino-4-phenylpyrazole 47 (Eq.19).



44 45

45a; Ar = C_6H_5

45b; Ar = p-ClC_6H_4



46 47

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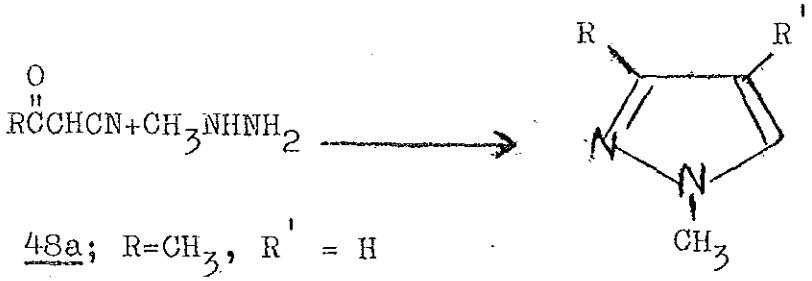
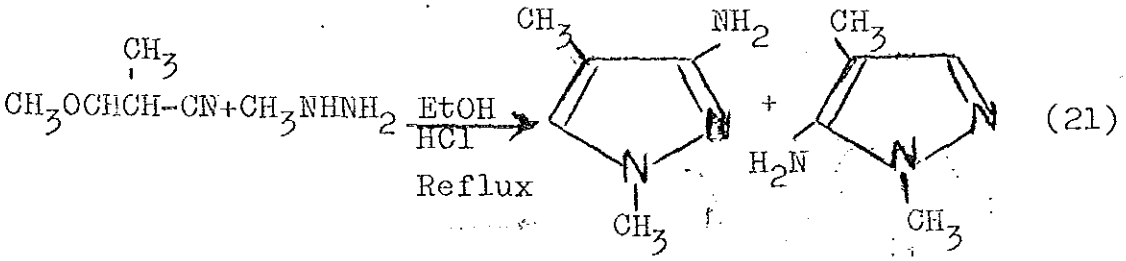
Reactions of methylhydrazine with suitable starting materials giving 1-methylaminopyrazoles have also been reported[36,37,38] (Equns. 20 - 22).



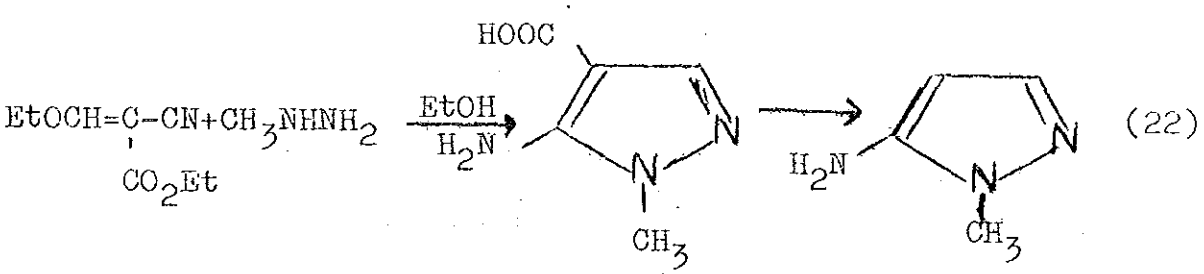
(20)

48a; $R=CH_3$, $R' = H$

48b; $R=Ph$, $R'=CH_3$



(21)



(22)

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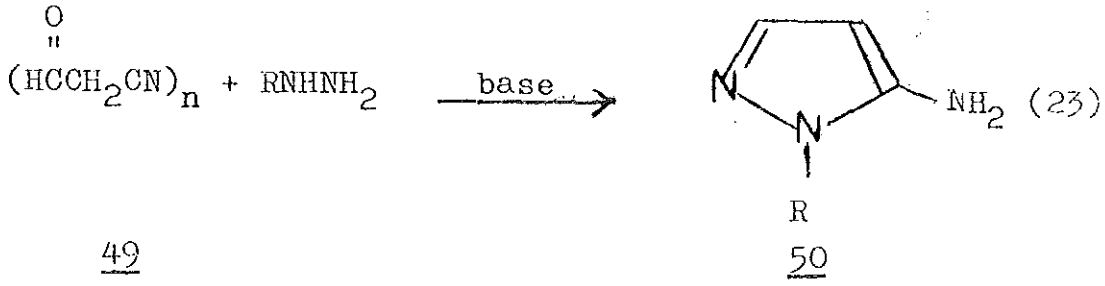
In a study on the reaction products of cyanoacetaldehyde derivatives 49 with various substituted hydrazines, $RNHNH_2$, different 1-(R-substituted)-5-aminopyrazoles 50 were obtained [39,40] (Eq.23).



(23)

49 50

50a ; R = C_6H_5

50b ; R = p-$NO_2C_6H_4$

50c ; R = p-$CH_3C_6H_4$

50d ; R = p-Cl C_6H_4

50e ; R = 2-HO_2C C_6H_4

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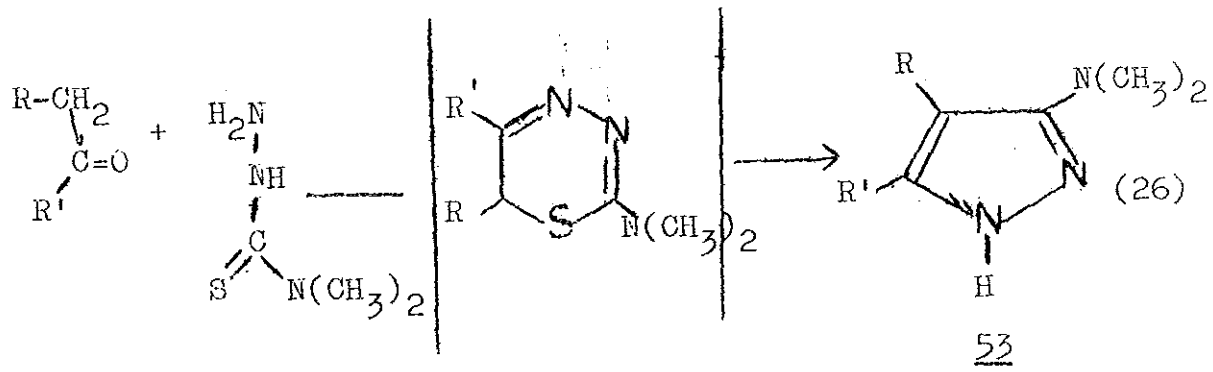
One could trace only one report[43] on the synthesis of N,N-disubstituted aminopyrazoles 53 (Eq.26). Here it is claimed that the reaction proceeds by prior formation of an unstable six-membered sulfur containing intermediate which, with eventual extrusion of the sulfur group leads to the aminopyrazoles 53.



(26)

53

53a ; R = H , R' = Aryl

53b ; R = Ph, R' = Aryl

With few exceptions, most known methods cited above led to the N-unsubstituted aminopyrazoles. In these methods, the major disadvantage is that mixtures of isomeric products are formed (See Eq.21 above). Besides, in most cases, mechanisms have not been investigated.

../

Once again, in principle the reactions of hydrazine or substituted hydrazines with 3-amino or 3-hydroxythioacrylamides are known[41,42] but in all cases the N-monosubstituted 3-aminopyrazoles were obtained.

In the study conducted here the synthesis of the N,N-disubstituted 5-aminopyrazoles[33] was effected by reaction of the 3-amino and 3-hydroxythioacrylamides 1 and 2 or the mercapto salts 11 with hydrazines (Scheme VII). Here reactions were rapid and yields were high. An attempt to investigate the reaction mechanism has also been made.

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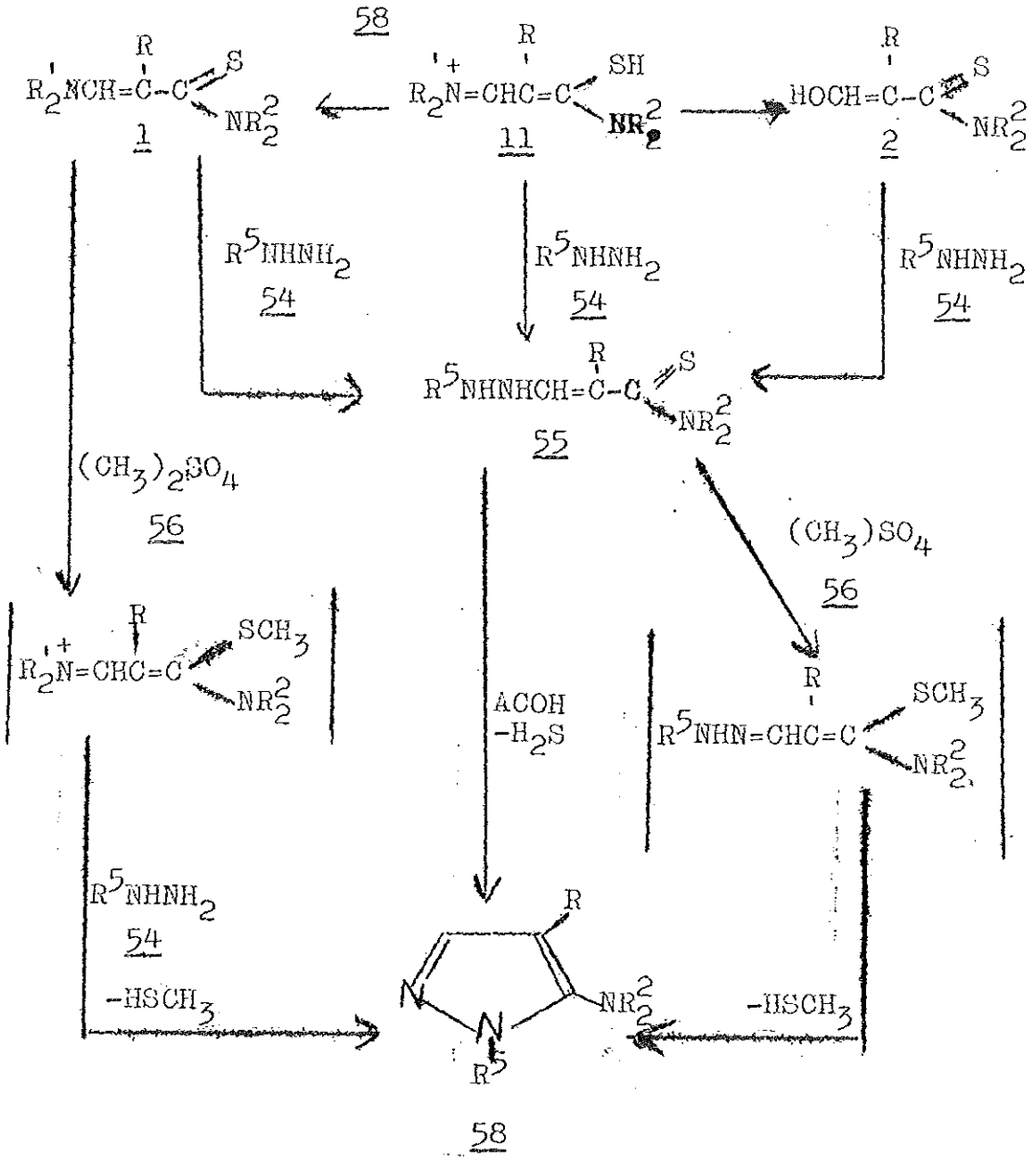
Scheme VII. Synthesis of 5-Aminopyrazoles



Based on the scheme given above the 5-aminopyrazoles, 58 synthesized are included in Table 6.

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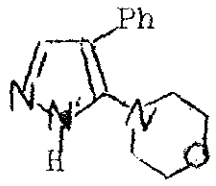
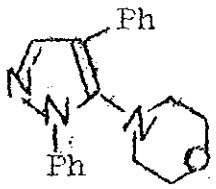
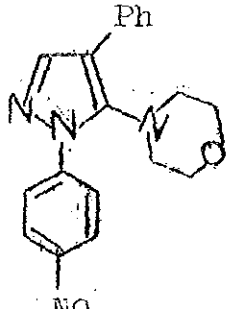
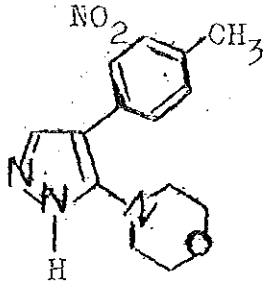
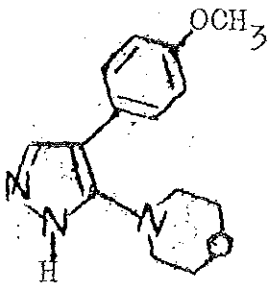
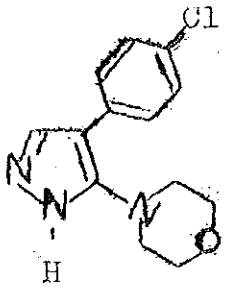
Table 6 : 5-Aminopyrazoles 58

Cpd.	Strucuture
58a	
58b	
58c	
58d	
58e	
58f	

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As shown in Scheme VII, the reactions of the hydrazines R^5NHNH_2, 54 with 3-aminothioacrylamides 1, 3-hydroxythioacrylamides 2 or the mercapto salts, 11 gave 3-hydrazinothioacrylamides, 55, when less basic hydrazines such as phenylhydrazine (54, $R^5 = C_6H_5$), P-nitrophenylhydrazine (54, $R^5 = NO_2\text{-}C_6H_4$) or thiosemicarbazide(54, $R^5 = NH_2\text{-}C$ -) were employed in the reaction. These products were isolated in high yields and were characterized by elemental analyses and NMR.

In some cases, however it was difficult to isolate the corresponding hydrazino products 55. Unsubstituted hydrazine, for instance, formed the corresponding aminopyrazoles 58 (R^5=H) in reactions with 1, 2 or 11. Here the tendency to go towards the cyclized product is high (Method A).

The isolated 3-hydrazinothioacrylamides 55 were further treated in order to get the cyclized products but the cyclization reaction needed either longer reaction time and acidic medium (Method E) or it was totally unsucessful. The isolated 3-hydrazinothioacrylamides were treated with dimethyl sulfate and the resulting S-methylated product were again subjected to cyclization reaction conditions. The methylation in fact reduced the time of the cyclization reaction since the cyclized products could be obtained by the elimination of methylmercaptan(Method D) in a shorter reaction time than in the case of Method E.

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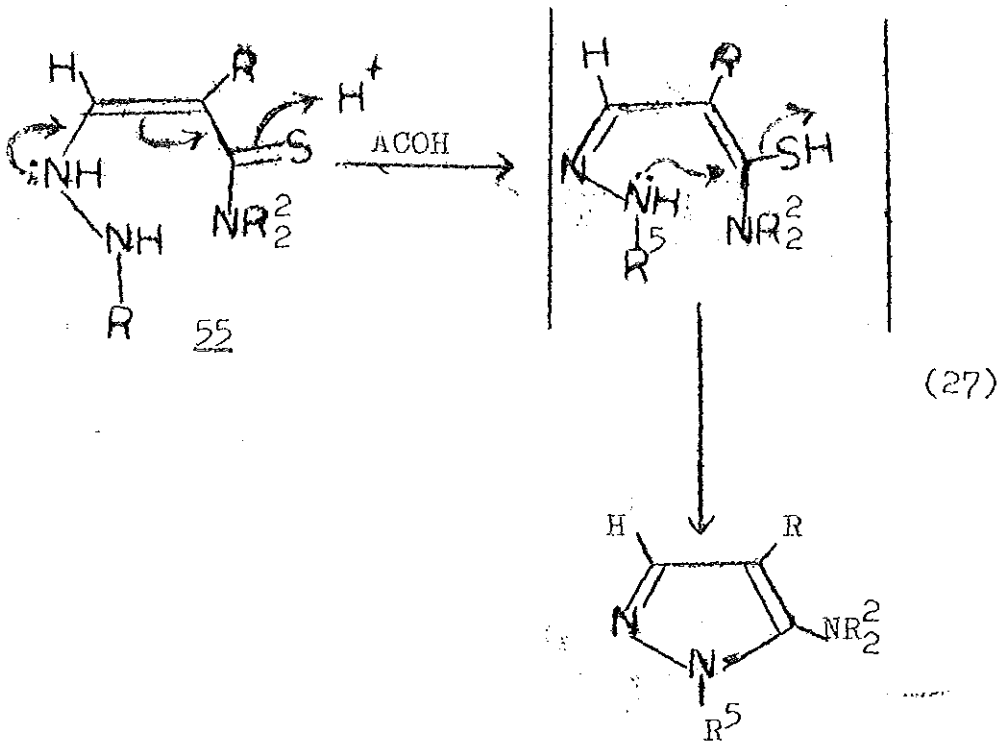
But S-methylation of 1a and further reaction to get the cyclized product could be performed in a relatively shorter time (Method C), than by either Method E or Method D.

The intermediate, 3-hydrazinothioacrylamides 55, as stated above, could be isolated in high yields and cyclized to the respective aminopyrazoles in two different ways as stated above. These reactions are indicated below.

a. The 3-hydrazinothioacrylamides were heated under reflux for seven hours to give 58 as shown by the reactions below (Eq. 27,)



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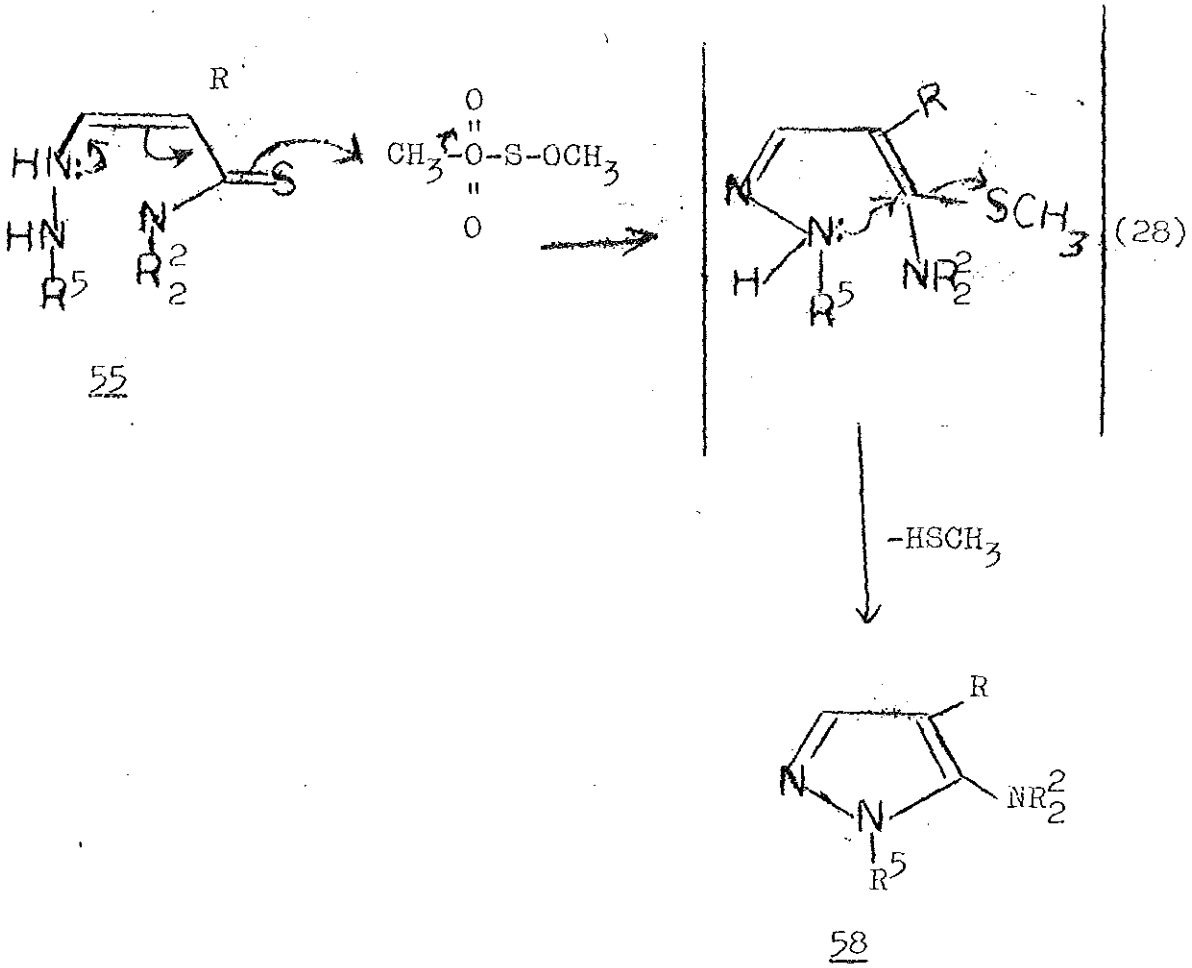
b. The 3-hydrazinothioacrylamides were also treated with dimethyl sulfate and further heated under reflux to give 58.



55

58

Therefore the most probable mechanism of this synthesis seems to be as depicted by the following scheme.

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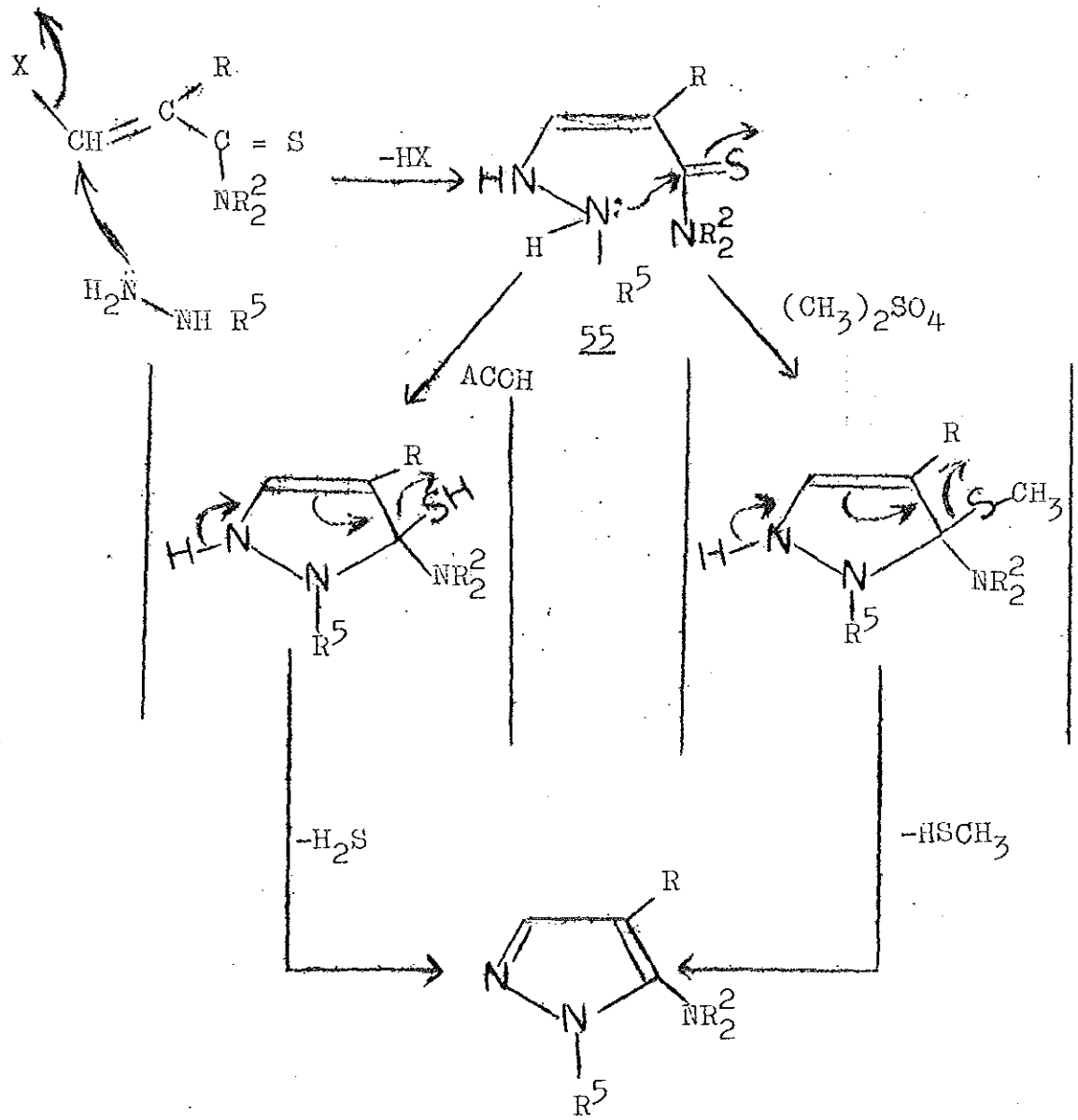
Scheme VIII. Mechanism of the Aminopyrazole Synthesis.



58

As shown above, a nucleophilic attach by the hydrazine derivative on carbon atom 3 of the thioacrylamide derivatives leds to the isolable or (unisolable, in some cases)

../

intermediate 3-hydrazinothioacrylamide 55. A second attack on carbon atom 1 of 55 and an eventual elimination of the H_2S (aromatization) leads to the aminopyrazoles 58.

The structures of the colorless aminopyrazoles 58 was confirmed by elemental analyses and spectroscopic methods which are included in the Experimental Section,

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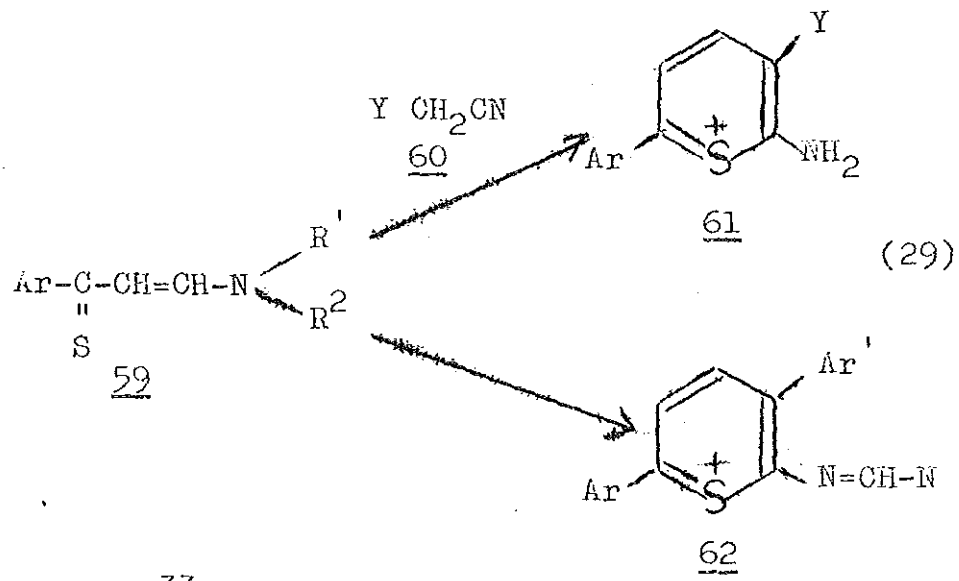
4. 2-Amino-6-formamidinothiopyrylium Salts

Liebscher et al.[43] reported that the reaction of aminovinylthioketones 59 with α - substituted acetonitriles 60 gave 2-aminothiopyrylium salts 61. The aminovinylthioketones 59 also were used in the synthesis of formamidinothiopyrylium salts[44,45] 62 (Eq.29).



(29)

In our work[33] the 2-aminoformamidinothiopyrylium salts were synthesised from the 3-aminothioacrylamides 1 and their mercapto salts 11. The reagents used were 3-chloro-2-azatrimethinium salts 63, the monoiminoformylation products of suitable nitriles. The synthesis also was approached through an independent method. Scheme IX shows both approaches.

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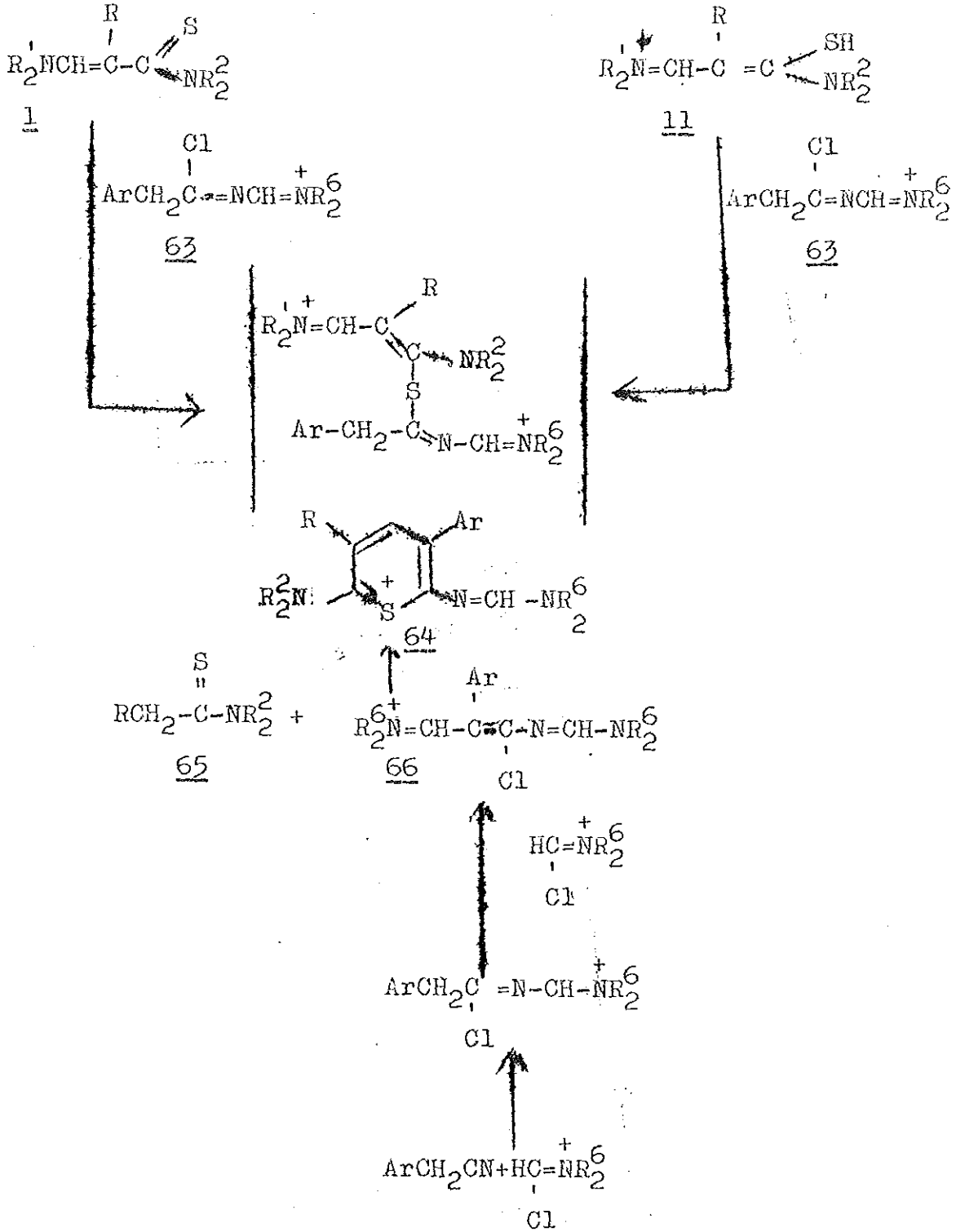
Scheme IX. Synthesis of the 2-amino-6-formamidino-thiopyrylium salts 64



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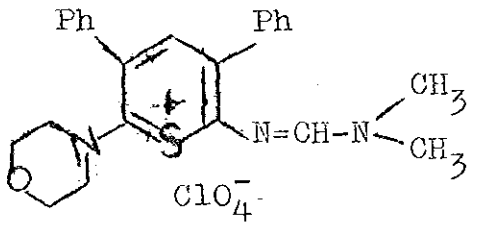
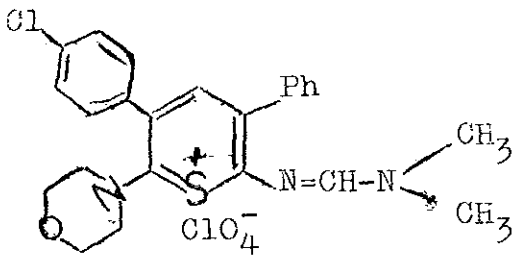
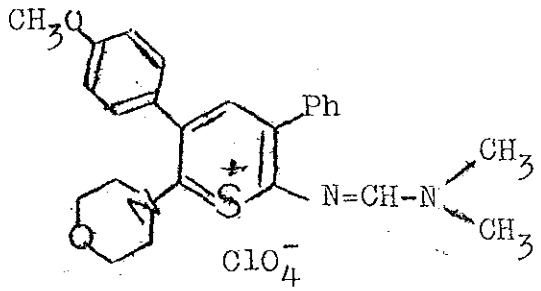
Based on the scheme given above the compounds obtained are given in the following table.

Table 7. 2-Amino-6-formamidinothiopyrylium salts.

Cpd.	Structure
64a	
64b	
64c	

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The reactions of the 3-aminothioacrylamides 1 of their salts 11 with the 3-chloro-2-aza^{trimethinium} salts 63, ($X^- = ClO_4^-$) gave the required brick-red colored 2-amino-6-formamidinothiopyrylium salts 64 (Method A). Apart from the effort to characterize the aminoformamidinothiopyrylium salts 64 by spectroscopic methods and elemental analyses, a trial was made to synthesis 64 by an independent method (Method B). Here thioacetamides 65 were allowed to react with a double iminoformylated product of a substituted acetonitrile, the 3-chloro-2-azapentamethinium salts 66. For R = C_6H_5, or p-ClC_6H_4, Ar= C_6H_5, NR_2^6 = $N(CH_3)_2$, and NR_2^2 = Morpholino, products obtained by Method B showed identical IR and MP with those obtained by Method A. Despite repeated trails reactions with the 3-hydroxythio-acrylamides 2 did not lead to any products.

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5. 5-Aminoisoxazoles

The N-unsubstituted 5-aminoisoxazoles are formed by the action of hydroxylamine on β-Ketonitriles or their imino derivatives and α-acetylenic nitriles or by the action of ammonia on 5-chloroisoxazoles[46] which give aminoisoxazoles that are tautomeric with the 5-iminoisoxazolones. The N-mono and disubstituted 5-aminoisoxazoles were synthesised[47] from nitriloxides and cyanoacetic ester or from nitriloxides and nitroketeneaminals in low yields. Other reports[48] indicate that the 5-aminoisoxazoles could be constructed by the reaction of β-aminopropionitrile with hydrogen peroxide in the presence of solvents like methanol.

In this work, the thioacrylamide derivatives were used to effect the synthesis of the 5-aminoisoxazoles.[33] Similar to the pyrazole formation with hydrazines, attack by the hydroxylamine hydrochloride at carbon atom 3 of the thioacrylamides could lead to the unisolated 3-hydroxylaminothioacrylamides 67 (Scheme X). From the in situ reaction one can assume three possible products (Scheme X).

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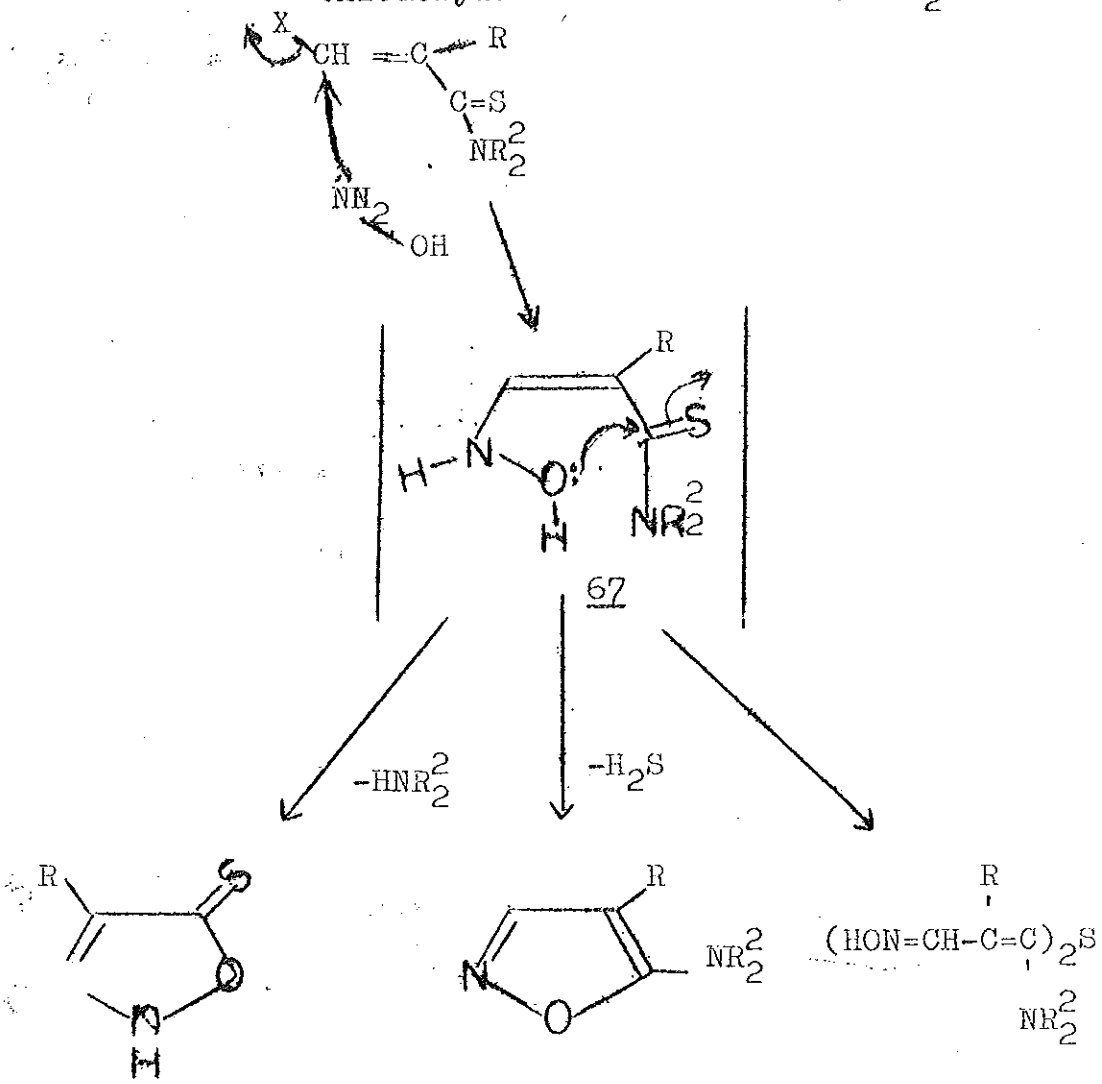
Scheme X. Synthesis of 5-Aminoisoxazoles from the thioacrylamide derivatives(X=NR_2 or OH)



68 69 70

Nucleophilic attack by the oxygen atom of the hydroxyl group 67 at carbon atom 1 can lead to 68 with the elimination of the amino group, $-HNR_2^2$, or to 69 with the elimination of $-H_2S$. Furthermore S-alkylation can take place between two molecules of 67 to give the sulfide 70. Although the assumptions need to be proved, the results obtained so far seem to support the following reaction scheme.

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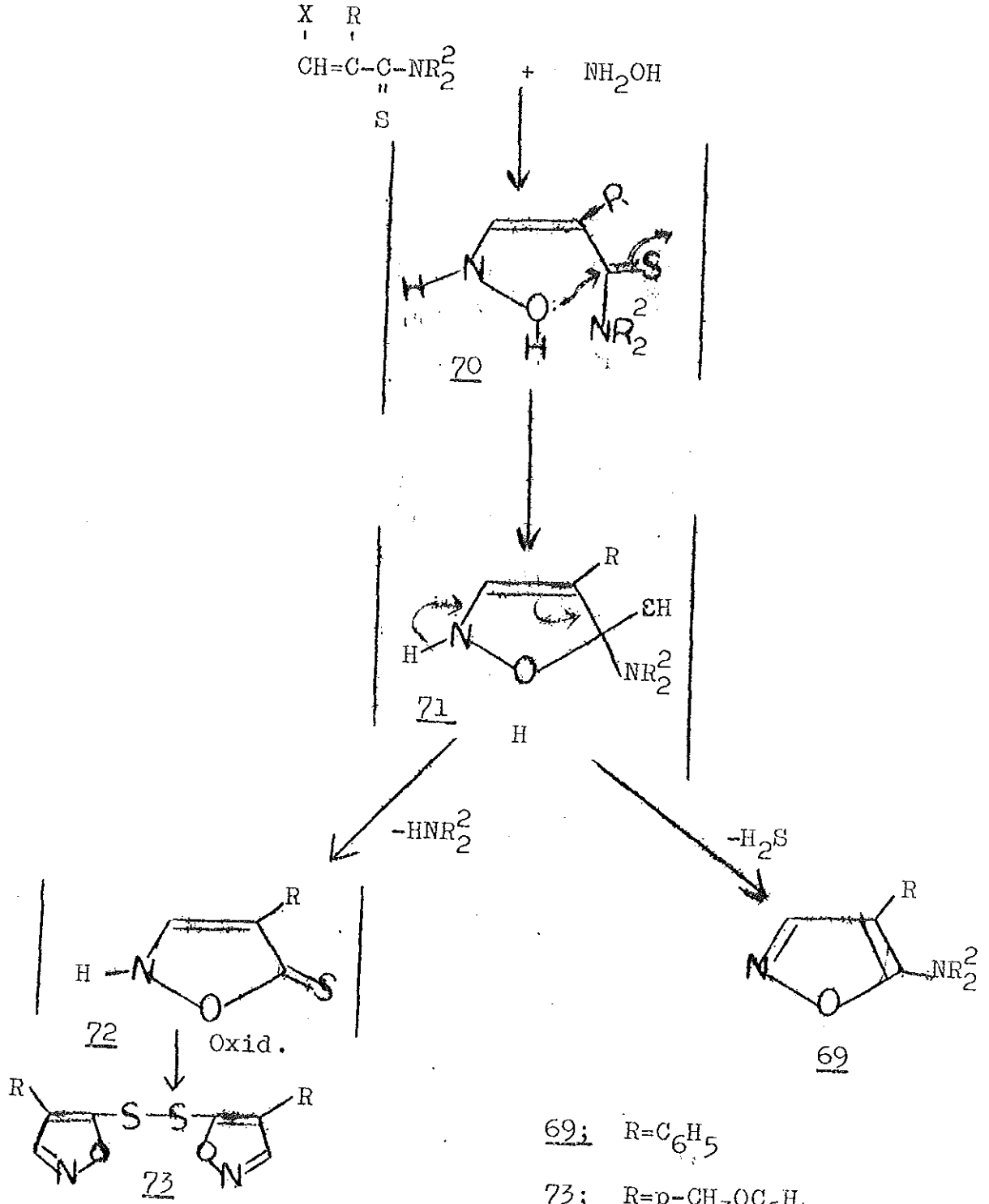
Scheme XI. Synthesis of 5-Aminoisoxazoles and BIS -(4-p-methoxy-5-thioperoxy) isoxazole (X = NR_2 or OH, NR_2^2 = morpholino)



69; R=C_6H_5

73; R=p-$CH_3OC_6H_4$ ../

In the reactions performed, both 1 and 2, with different R groups, were used. For instance, when (1a, R = C_6H_5) was heated under reflux with hydroxylamine hydrochloride in ethanol, the isolated product was found to be 69. Both MS and NMR data confirmed this. On the other hand, when (2b, R=p-$CH_3OC_6H_4$) was used instead of 1a, 73 was the isolated product. It seems then that after the unisolated intermediate 70 is formed in the reaction mixture, the reaction might have gone through 71 to 69 by H_2S elimination or to 72 and through that to the oxidised product 73 by an elimination of HNR_2^2. Since we saw a change in the kind of product formed with a change in R, it seems as if the nature of R determines the type of product obtained. This of course demands further investigation. The aminoisoxazoles 69 are stable, crystalline, yellowish-white compounds. The oxidation products 73 are yellowish fiber-like crystals.

IV. EXPERIMENTAL

Melting Point, M.P, was determined by Uni-Melt Thomas Hover capillary melting point apparatus and uncorrected.

IR: by Perkin-Elmer, Model 727-B infrared spectrophotometer. Values are given in cm^{-1}.

^{1}H-NMR: by Varian T-60 spectrometer. Values are given in (ppm).

UV: by VEB. Carl Zeiss Jena, Model Specord UV-Vis.

MS: Finigan, MS-GC spectrometer.

Elemental Analyses: Was done at the Technical University of Dresden, Section of Chemistry, Department of Elemental Analyses, DDR.

1. Synthesis of Starting Materials

i. 1-Mercaptotrimethinium Salts 11

To a solution prepared by mixing 7.5 gm of dimethylformamide (DMF) and 50 ml CCl_4, 16 gm of phosphorylchloride ($POCl_3$) was added dropwise while cooling in an ice bath. This gave 4 to which was added;

22.1 gm of 9 (R = C_6H_5) or

23.5 gm of 9 (R = p-$CH_3C_6H_4$-) or

25 gm of 9 (R = p-$CH_3OC_6H_4$) or

27 gm of 9 (R = α-$C_{10}H_7$) or

25.5 gm of 9 (R = p-ClC_6H_4) and

refluxed for 30 minutes. The warm mixture was then mixed with an equal amount of glacial acetic acid to which was

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added about 15 ml of perchloric acid. The mixture was diluted with sufficient amount of diethylether and left aside for an hour. The product was filtered by suction and washed with some portions of glacial acetic acid then diethylether. The product was spread in the open air for about two hours (prolonged staying may lead to hydrolysis) placed in a clean and dry container, closed and kept in the fridge.

ii. 3-Aminothioacrylamides 1

Into a beaker containing 15 ml of methanol 0.01 mol, (3.76 gm) of the mercapto salt 11 for (R = C_6H_5 or R = p-ClC_6H_4) was placed and some triethylamine was added to the mixture while stirring. The mixture was kept aside till crystallisation completes and the product was collected by suction filtration.

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2. i. 2-Amino-5-nitrothiophenes 40

Method A

A mixture of 0.01 mole of 3-dialkylaminothioacrylamides 1, or 1-mercaptotrimethenium salts, 11 or 3-hydroxythioacrylamides 2, 8 ml ethanol or acetonitrile and 0.01 mole of bromonitromethane 42 ($R^3 = NO_2$) was heated to boiling. Then 1 gm (2 gm if 11 is used) of triethylamine (TEA) was added. After the exothermic reaction has ceased the mixture was further refluxed for few minutes and cooled. The product was collected by suction filteration and recrystallised and the following data was taken.

Table 8: Data table for 2-Amino-5-nitrothiophenes

cpd.	M.P °C	Yield/method %	IR/KBr $-NO_2/cm^{-1}$	U.V (CH_3CN) $\lambda max(\log \varepsilon)$
40a	143-144 (EtOH)	77/A[1]	1336	230 (4.19)
		91/A[2]	1540	288 (3.91)
		81/A[3]		439 (4.18)
		60/A[4]		
40b	151 (n-PrOH)	73/A[3]	1340	
			1548	-
40c	155 (EtOH)	73/A[3]	1340	-
			1548	

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Table 8: Cont'd

cpd.	M.P °C	Yield/method %	IR/KBr $-NO_2/cm^{-1}$	U.V (CH_3CN) $\lambda max(log\varepsilon)$
40d	139 (EtOH)	82/A[3]	1350 1540	236 (4.26) 293 (4.01) 440 (4.17)
40e	156 (CH_3CN)	85/A[3]	1340 1540	225 (4.85),251s (4.01) 277s (3.95), 308s (3.80) 445 (4.32)
40f	185 (AcOH)	81/A	1320 1505	244 (4.38), 271(4.13) 411 (4.54)

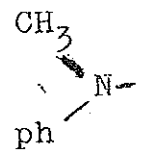
1. The starting material is 1
2. " " " " 2
3. " " " " 11
4. The starting material is different, R'_2N = 

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Table 9: Elemental Analyses for 40

cpd.	Formula (M.W)		C%	H%	N%	S%
40a	$C_{14}H_{14}N_2O_3S$	Calc.	57.90	4.83	9.60	11.05
	(290)	found	56.98	4.74	9.17	11.15
40b	$C_{15}H_{16}N_2O_3S$	Calc,	59.21	5.26	9.21	10.52
	(304)	found	58.57	5.32	8.86	10.50
40c	$C_{15}H_{16}N_2O_4S$	Calc.	56.25	5.04	8.75	10.02
	(320)	found	55.73	5.09	8.64	10.52
40d	$C_{14}H_{13}N_2O_3SCl$	Calc.	51.80	4.01	8.64	9.87
	(324)	found	51.95	4.23	8.47	9.57
40e	$C_{18}H_{16}N_2O_3S$	Calc.	63.58	4.74	8.23	9.43
	(340)	found	63.56	4.74	8.03	9.42

^{1}H-NMR ($CDCl_3$, Internal standard TMS, δ/ppm)

40b. CH_3: 2.37 (s, 3H), CH_2NCH_2: 3.03 (m,4H)

CH_2OCH_2: 3.70 (m, 4H)

C_6H_4: 7.10 (d, 2H) , 7.33 (d, 2H)

CH: 7.73 (s, 1H)

Method B

A mixture of 1-alkylmercaptortimethenium salt 43, 0.01 mole, 15 ml of acetonitrile and 1 gm of TEA, was shortly heated to boiling.

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The mixture was cooled and the product collected by suction filteration and recrystallised.

40f M.P 175°C (CH_3CN)

Yield: 98/B

IR/KB4: 1320 cm^{-1}

1505 cm^{-1}

^{1}H-NMR ($CDCl_3$) Internal standard TMS, δ(ppm):

CH_2NCH_2: 2.93 (m, 4H)

CH_2OCH_2: 3.70 (m, 4H)

CH: 7.30 (s, 1H)

C_6H_5 : 7.33 (m, 5H)

C_6H_4 : 7.47 (d, 2H), 8.03 (d, 2H)

ii. p-Nitrobenzylmercaptotrimethenium Salts 43.

A mixture of 0.01 mole of 1a and 0.01 mole of p-nitrobenzylbromide was refluxed in 15 ml methanol for about five minutes. The homogenous mixture with an equimoloar amount of magnesium perchlorate gave the perchlorate salt 43a. The products were isolated by suction filteration and recrystallised. The following data was obtained.

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43a, M.P = 195° (EtOH)

Yield = 90%

IR/KBr, NO_2, 1345, 1505.

^{1}H-NMR

$N(CH_3)_2$; 3.10 (s, 6H)

$N(CH_2CH_2)_2O$; 3.72 (s, 8H)

CH_2; 4.32 (s, 2H)

C_6H_5; 7.27 (m, 5H)

C_6H_4; 7.53 (d,2H), 8.22 (d, 2H)

CH; 8.10 (s, 1H)

43b. yield: 95%

IR/KBr, NO_2 - 1345, 1505

U.V. (CH_3CN), λ_{max} (log ε)

280 (4.26)

382 (4.31)

^{1}H-NMR. Same as 43a

iii. 2-Acetylamino-5-morpholino-4-phenylthiophene-dihydroperchlorate 41a

A mixture of 2.90 g of 2-morphilino-5-nitro-3-phenyl-thiophene 40a and 80 ml of acetic anhydride was heated to boiling. About 10 gm Zn-dust was added in portions and the reflux continued for 2 hours. The mixture was then filtered and hydrolysed by adding water and neutralised

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by adding aqueous NaOH. A yellow oil separated out which was then dissolved in about 5 ml of acetic acid. When about 2 ml 70% $HClO_4$ and some water was added the product 41a started precipitating. The colorless crystalline product was then filered by suction and recrystalised. The product changes to dark material when exposed to air.

41a M.P = 204 - 206 (AcOH)

yield = 11%

^{1}H-NMR. (DMSO-d_6 internal standard TMS (ppm)

CH_3; 2.07 (s, 3H)

CH_2NCH_2: 2.77 (m, 4H)

CH_2OCH_2: 3.63 (m, 4H)

CH: 6.60 (s, 1H)

C_6H_5: 7.43 (m, 5H)

NH : 5.9 (s, 1H)

3. 5-Aminopyrazoles 58 (NMR_2^2 = Morpholino)

Method A

A mixture of 0.01 mole of 1-mercaptotrimethenium perchlorates 11 (X = ClO_4^-) or 3-dialkylaminothioacrylamides 1 or 3-hydroxythioacrylamides 2, 15 ml ethanol, 0.01 mole of hydrazine (unsubstituted hydrazine was used as 85% hydrazine hydrate) and if the salt 11 is used, 2 ml of TEA was refluxed for 45 minutes. It was cooled to room temperature and about 20 ml water was added.

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The precipitating aminoprazole 58 was filtered by suction and recrystallised.

Table 10: Data table for 5-Aminopyrazoles 58

cpd.	M.P (°C)	Yield/method %	IR/KBR -NH · Cm^{-1}	U.V. CH_3CN λ_{max} (log ε)
58a	112(pet. Ether)	93/A[1] 87/A[2]	3250	222s (4.04), 252 (3.92) 276 (3.93)
58b	207-208 (MeOH/CH_3CN)	79/A[1] 86/A[2]	-	253 (4.23)
58d	137-138 (pet.Ether)	93/A[2]	3410	226 (3.99) 253 (3.96) 266 (3.90)
58e	129-130 (MeOH)	85/a[2]	3400	230 (4.07), 253 (4.12) 265 (4.15)
58f	183-184	91/A[2]	3325	231 (4.01), 252 (3.89) 264 (3.94) 274 (4.01)

1. Starting material is 1 or 2
2. Starting material is 11

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Table 11: Elemental Analyses for 58

cpd.	Formula (M.W)		C%	H%	N%	S%	Hal%
58a	$C_{13}H_{15}N_3O$ (229)	Calc.	68.17	6.60	18.34	-	-
		found	68.77	6.95	18.23	-	-
58b	$C_{19}H_{19}N_3O$ (305)	Calc.	74.75	6.27	13.77	-	-
		found	74.35	6.27	13.94	-	-
58d	$C_{13}H_{14}N_3OCl$ (263)	Calc.	59.36	5.36	15.96	-	13.49
		found	59.65	5.53	15.59	-	13.64
58e	$C_{14}H_{17}N_3O_2$ (259)	Calc.	64.91	6.62	16.21	-	-
		found	65.34	6.88	16.20	-	-
58f	$C_{19}H_{18}N_4O_3$ (350)	Calc.	65.14	5.14	16.00	-	-
		found	65.00	5.28	16.02	-	-

^{1}H-NMR (CF_3COOH; standard TMS, δ/ppm)

58b. CH_2NCH_2; 3.1 (m, 4H), CH_2OCH_2: (3.80/m, 4H)

C_6H_5; 7.4 (s, 5H), 7.6 (s, 5H)

CH; 7.9 (s, 1H)

Mass - spectrum

58a: m/e (relative intensity) 229 (M^+, 52); 198 (18); 172 (20); 171 (27); 170 (100); 115 (18); 89 (15).

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Method B

A mixture of 3-dialkylaminothioacrylamides 1, 0.01 mole 15 ml glacial acetic acid and 0.01 mole of hydrazines, R^5NHNH_2, was heated until boiling. An exothermic reaction takes place. The resulting solution was allowed to cool to room temperature. The precipitation of the product 58 may be completed by the addition of some water. The product was collected by suction and recrystallised.

58b, M.P = 207 - 208 (CH_3CN)

Yield = 66%

Elemental Analyses - See Table 11

^{1}H-NMR is given under Method A

Method C

Dimethylsulfate, 0.01 mole. was added to a solution of 0.01 mole of 3-dialkylaminothioacrylamide 1 in 20 ml methanol. The mixture was heated to boiling for about 3 minutes. The mixture was then treated with 0.01 mole of hydrazines, R^5NHNH_2, while still hot. Methylmercaptan was evolved. The reflux continued for 15 minutes and was cooled to room temperature and the 5-aminopyrazoles 58b, and 58c were filtered by suction and recrystallised.

58b. M.P = 207 - 208°C /MeOH/

Yield = 54/^{1}

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Elemental Analyses and ^{1}H-NMR data are given under Method A.

58c. M.P = 219°C /AcOH/

Yield = 56%[1]

U.V (CH_3CN): λ_{max} (log ε)

231(4.25); 322(4.16)

58c Elemental Analyses

$C_{14}H_{17}N_3O$		C%	H%	N%
(243)	Calc.:	69.13	7.05	17.28
	found:	68.97	7.05	17.12

^{1}H-NMR. (CF_3COOH, standard TMS, δ/ppm)

CH_2NCH_2: 3.15 (m,4H), CH_2OCH_2: 3.78 (m, 4H)

C_6H_5: 7.43 (s, 5H), C_6H_4: 7.92 (d, 2H, 8Hz)

8.50 (d, 2H, 8 Hz)

CH: 8.07 (s, 1H)

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1. Starting material is 1 or 2

Method D

A mixture of 0.01 mole of 3-hydrazinothioacrylamide 52 ($R^5 \neq H$), 15 ml methanol and 0.01 mole of dimethylsulfate 56 was refluxed for 90 minutes. The product 58 was filtered by suction from the cold reaction mixture and recrystallised.

58b. M.P = 207 - 208° (CH_3CN)

Yield = 32%

Elemental Analyses and ^{1}H-NMR data are given under Method A.

58c. M.P = 219(AcOH)

Yield = 57%

Elemental Analyses and ^{1}H-NMR data are given under Method C

Method E

A suspension of 0.01 mole of 3-hydrazinothioacrylamide 55 ($R^5 \neq H$), in 30 ml glacial acetic acid is refluxed for 7 hours. The preipitation of the product 58b was completed by addition of about 20 ml of water to the cold reaction mixture. The product was filtered by suction and recrystallised.

58b. M.P = 208 (MeOH)

Yield = 78%

Elemental Analyses and ^{1}H-NMR data are given under Method A.

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4. i. 2-Amino-6-formamidinothiopyrylium Salts 64 ($X = ClO_4^-$)

Method A

A mixture of 0.01 mole of 1a or 0.01 mole of 11a (1 ml, TEA is added if 11 is used) or 0.01 mole of 1b or 0.01 mole of 11d or 0.01 mole of 11c and 7 ml methanol was taken and 0.01 mole of 3-chloro-2-azatrimethinium salt 63 was added to it. The whole mixture was stirred vigorously and kept aside at room temperature with a label on it for 2 to 3 days. The product was collected by suction filteration and recrystallised.

64a. M.P = 221° (AcOH)

Yield = 64%

Elemental Analyses

	C%	H%	N%	S%	Hal%
$C_{24}H_{26}N_3O_5SCl$, Calc.	57.25	5.16	8.34	6.36	6.95
found	56.62	5.29	8.17	6.42	7.86

64a. U.V (CH_3CN) λ_{max}, ($\log \varepsilon$), 237s (4.35)

253 (4.41), 338 (4.24), 498 (4.27)

64b. M.P = 233° (AcOH)

Yield = 35%

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Method B

3-chloro-2-azapentamethinium salt, 0.01 mole 66 (Ar = C_6H_5, X^- = ClO_4^-) was mixed with an equimoloar amount of thioacetamide 65 (R = C_6H_5, NR_2^2 = Morpholino) and dissolved in 7 ml glacial acetic acid with little warming. The mixture was kept at room temperature for a day and about 1 ml TEA was added to it. On the 3rd day the product was collected by suction filteration and recrystallised.

64a, M.P = 220 - 221° (AcOH)

Yield = 58%

IR - same as 64a obtained by Method A

64b. M.P = 217 - 219°(AcOH)

Yield = 37%

IR = same as 64b obtained by Method A

ii. Preparation of 3-chloro-2-azapentamethinium Sale 63[11] (X^- = ClO_4^-)

To 0.1 mole of dimethyleformamide, 0.1 mole of phosphorylchloride ($POCl_3$) was added drop by drop while cooling (T 30°C) and stirring. To this mixture 0.1 mole of benzylcyanide or p-chlorobenzylcyanide was added and HCl gas (generated by the reaction of H_2SO_4 (Conc.) and (NaCl) was bubbled through the mixture for 90 minutes while cooling in an ice bath and stirring. The cooled reaction mixture was poured into another mixture formed

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by mixing 15 ml of perchloric acid ($HClO_4$) and 100 ml of acetic anhydride. If precipitation did not take place, the whole mixture was diluted with diethylether. Product 63 was collected by suction filtration.

iii. Preparation of 3-Chloro-2-azapentamethinium Salt 66^{11} ($X^- = ClO_4^-$)

To 0.22 mole of dimethylformamide an equivalent amount of phosphorylchloride ($POCl_3$) was added drop by drop while cooling (T 25°C). To this mixture 0.1 mole of benzyl-cyamide is added and HCl gas was bubled through the mixture for 1 hour while cooling and stirring. This is heated for 30 minutes at 90°C. It was cooled down and poured into a mixture of ethanol (2 - 3 times the volume of the mixture) and 10 ml $HClO_4$ while stirring and cooling. The whole mixture was diluted with diethylether. The light yellow precipitate of the product 66, was filtred by suction and washed with diethylether (M.P 117°, 118° (AcOH).

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5. i. 5-Aminoisoxazole 69 (R = C_6H_5, NR_2^2=Morpholino)

A mixture of 0.01 mole of 1a and 0.01 mole of hydroxylamine hydrochloride in 8 ml ethanol was refluxed for 30 minutes. During the reaction H_2S evolution was noticed. The mixture was cooled and the product was collected by suction filteration and recrystallised. The following data taken.

69. M.P = 118° (EtOH)

Yield = 61%

^{1}H-NMR: ($CDCl_3$, internal standard, TMS, δ/ppm)

CH_2NCH_2: 3.3 (m, 4H)

CH_2OCH_2: 3.7 (m, 4H)

C_6H_5: 7.4 (s, 5H)

CH: 8.0 (s,1H)

MS: M/e (relative intensity). 230 (M^+, 81); 144(80); 117(70); 116(70); 115(23); 114(84); 105(66); 104(26); 90(30); 89(89); 86(29); 77(43); 71(24); 70(100); 63(51); (57(64); 56(59) 42(71); 41(65); 38(37); 30(21); 29(25); 28(91); 27(26).

Note. There is a relatively strong peak at 256 that belongs to S_8 elemental sulfur (contamination).

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ii. Bis-(4-paramethoxyphenyl-5-thioperoxyisoxazoles)

73. (R = p-$CH_3OC_6H_4$)

A mixture of 0.01 mole of 2b and 0.01 mole of hydroxylamine hydrochloride in 8 ml ethanol was refluxed for 40 minutes. The mixture was cooled and product collected by suction filteration and recrystallised.

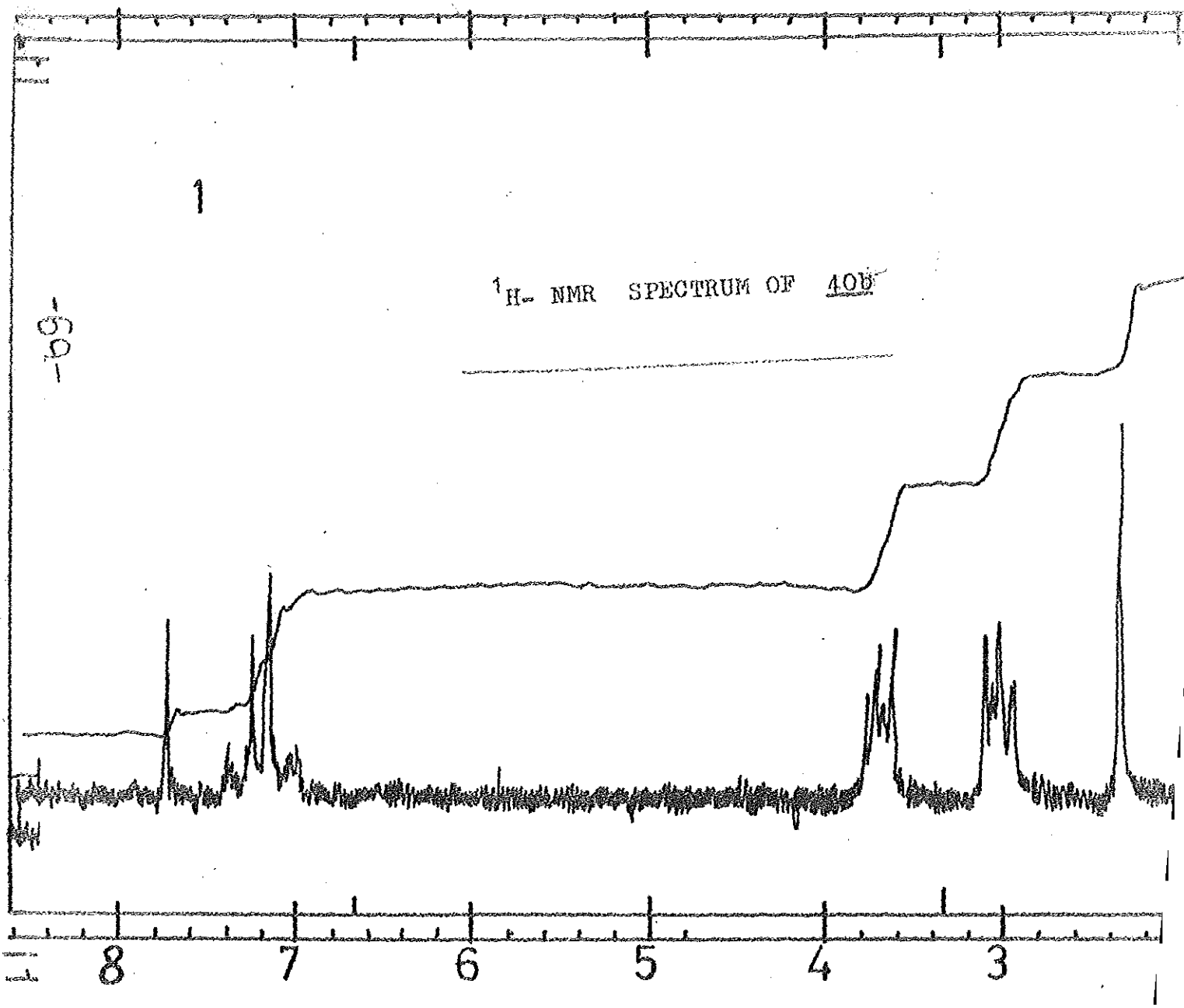
73. M.P = 133° (EtOH)

Yield = 31%

Elemental Analyses

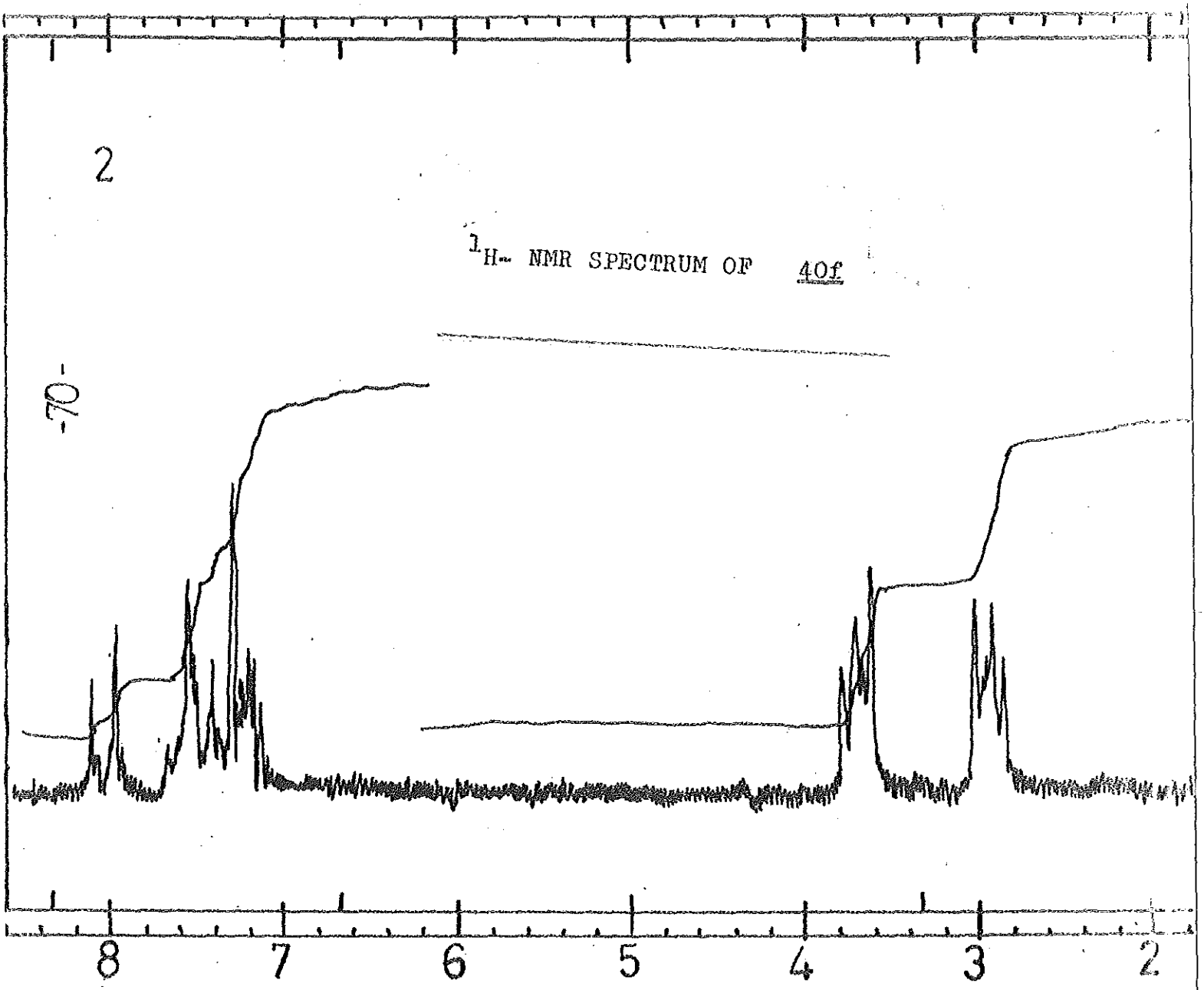
		C%	H%	5%	N%
$C_{20}H_{16}N_2O_4S_2$ (412)	Calc.	58.25	3.88	15.53	6.79
	found	58.56	3.96	10.10	6.66

MS. M/e (relative intensity); 412 (M^+, 100); 381 (16); 380(24); 325(5); 208(10); 207(67); 206(33) ; 192(7); 179(7); 178(13); 174(7); 164(13); 151(16); 146(7); 132(5) 76(5); 60(7); 44(6); 32(24); 28(61); 18(68); 17(28).

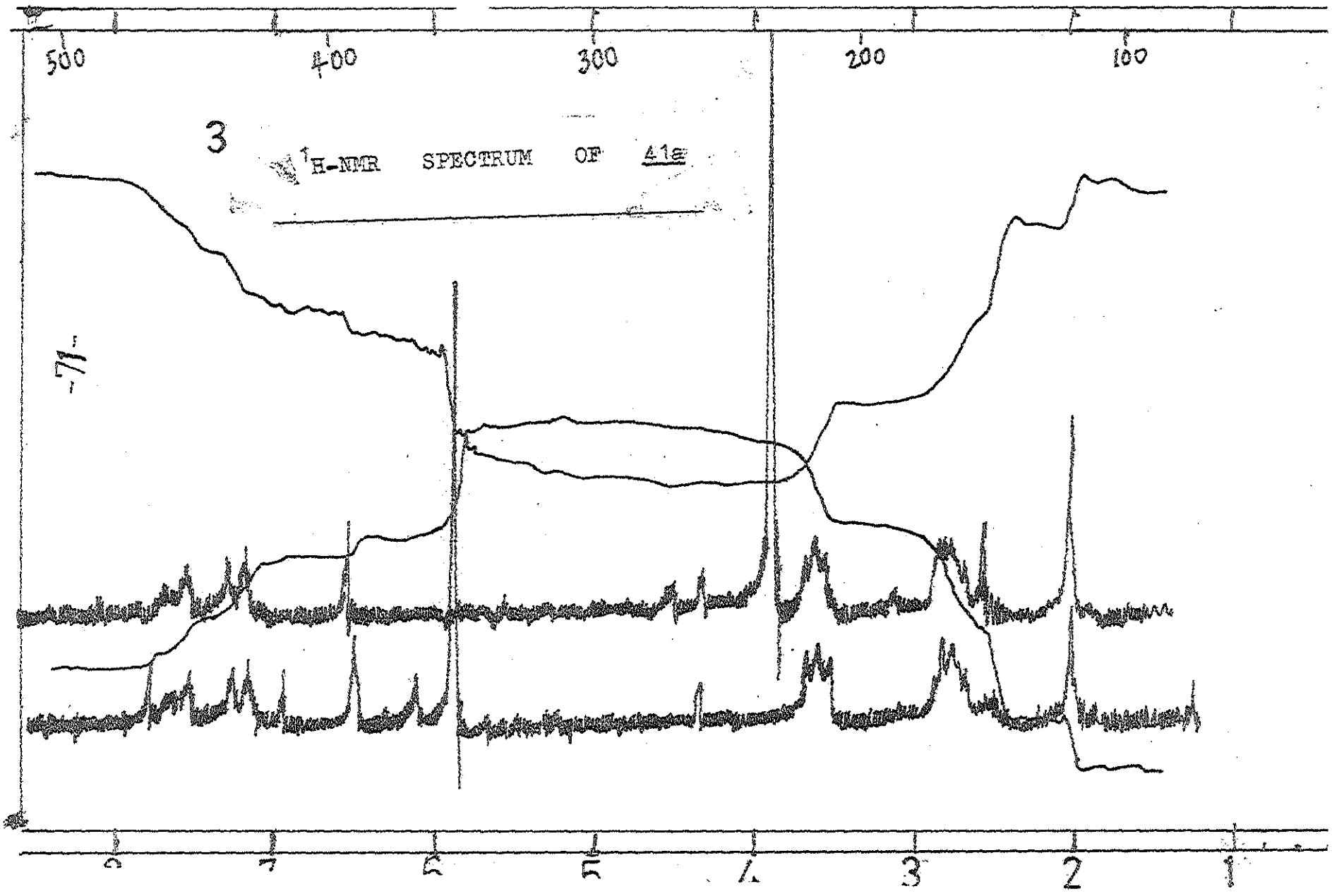

1
^{1}H- NMR SPECTRUM OF 40b
8
7
6
5
4
3

2

^{1}H- NMR SPECTRUM OF 40f

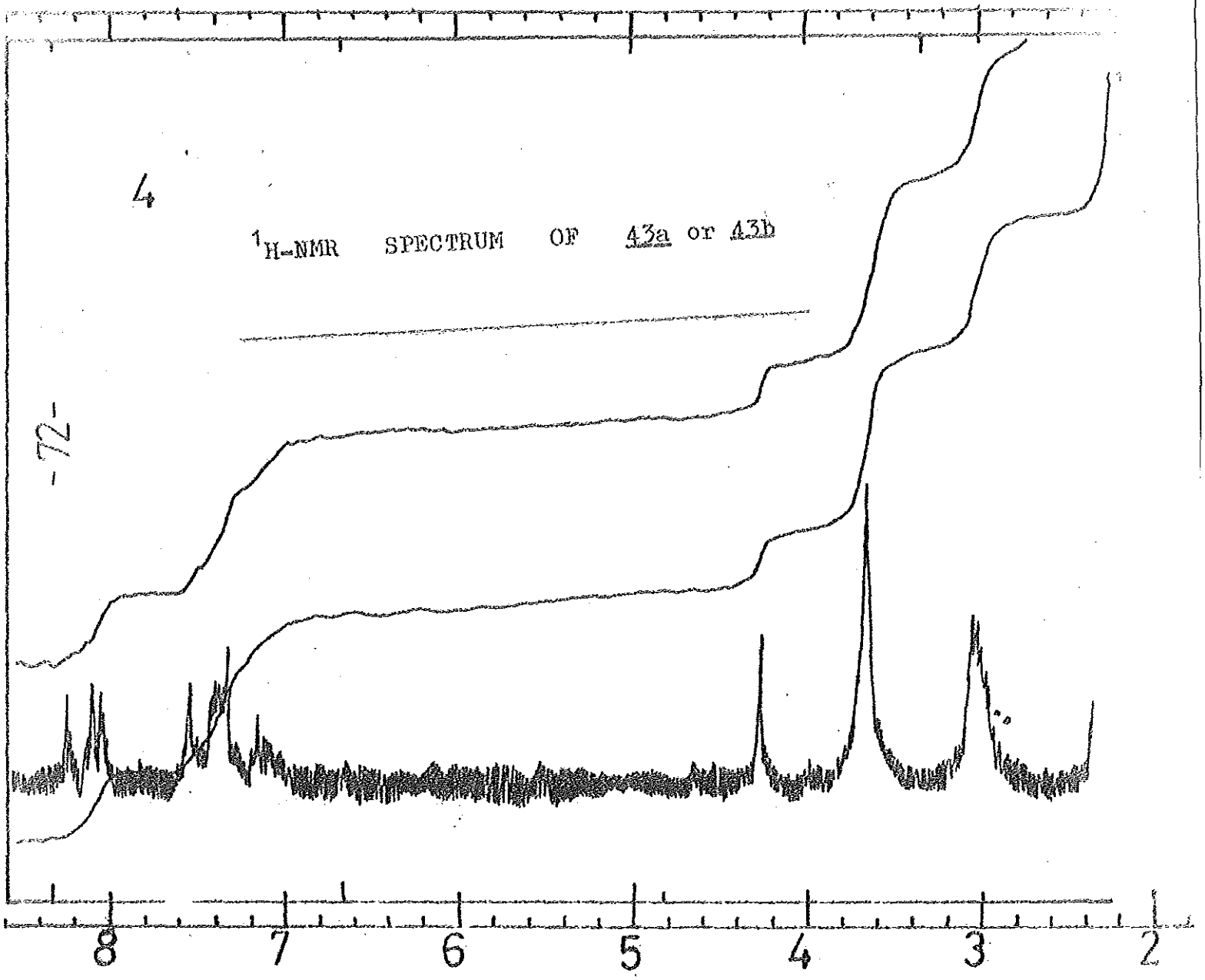


NO2.


500
400
300
200
100
3
^{1}H-NMR SPECTRUM OF 41a
-71-
7
6
5
4
3
2
1

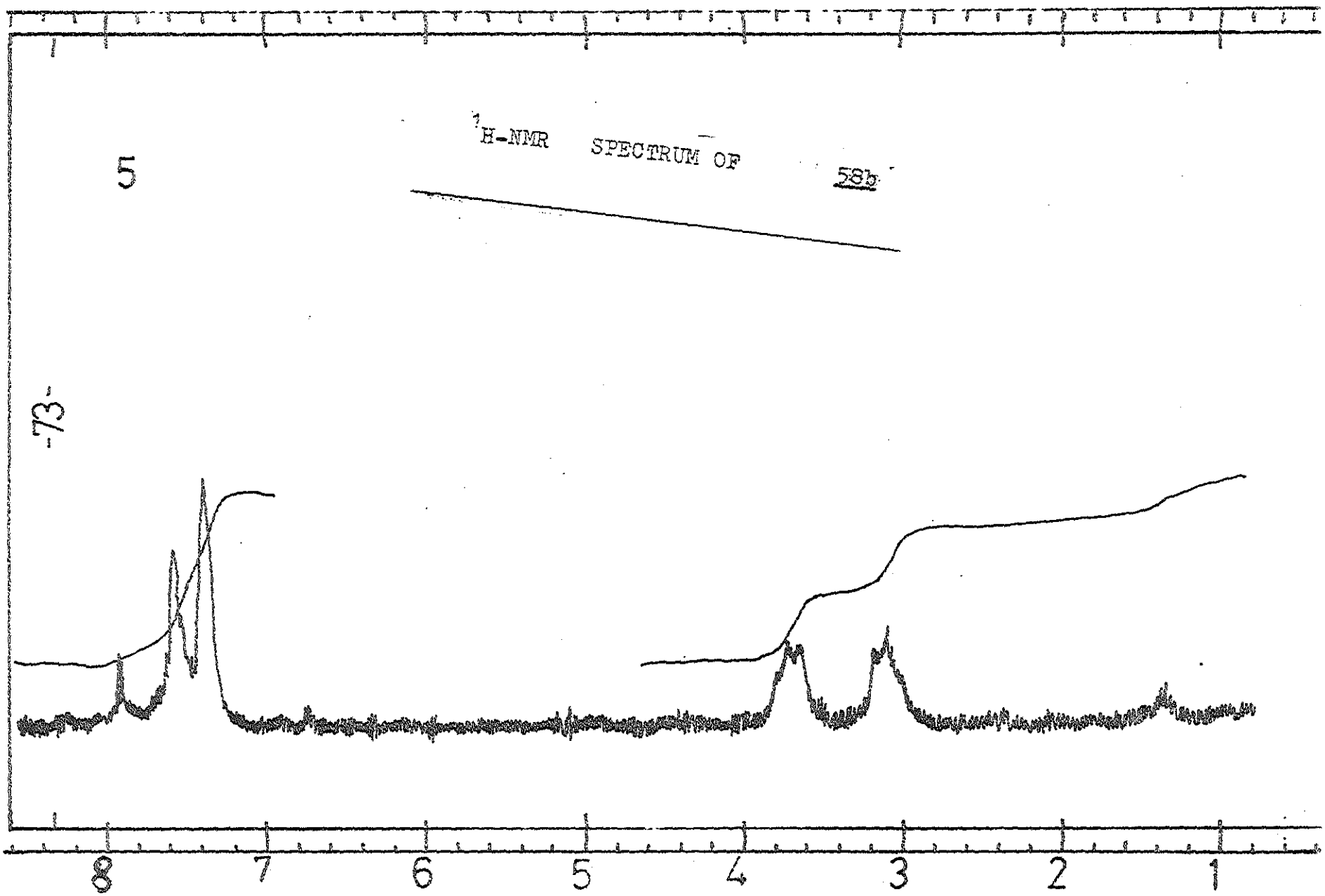
4

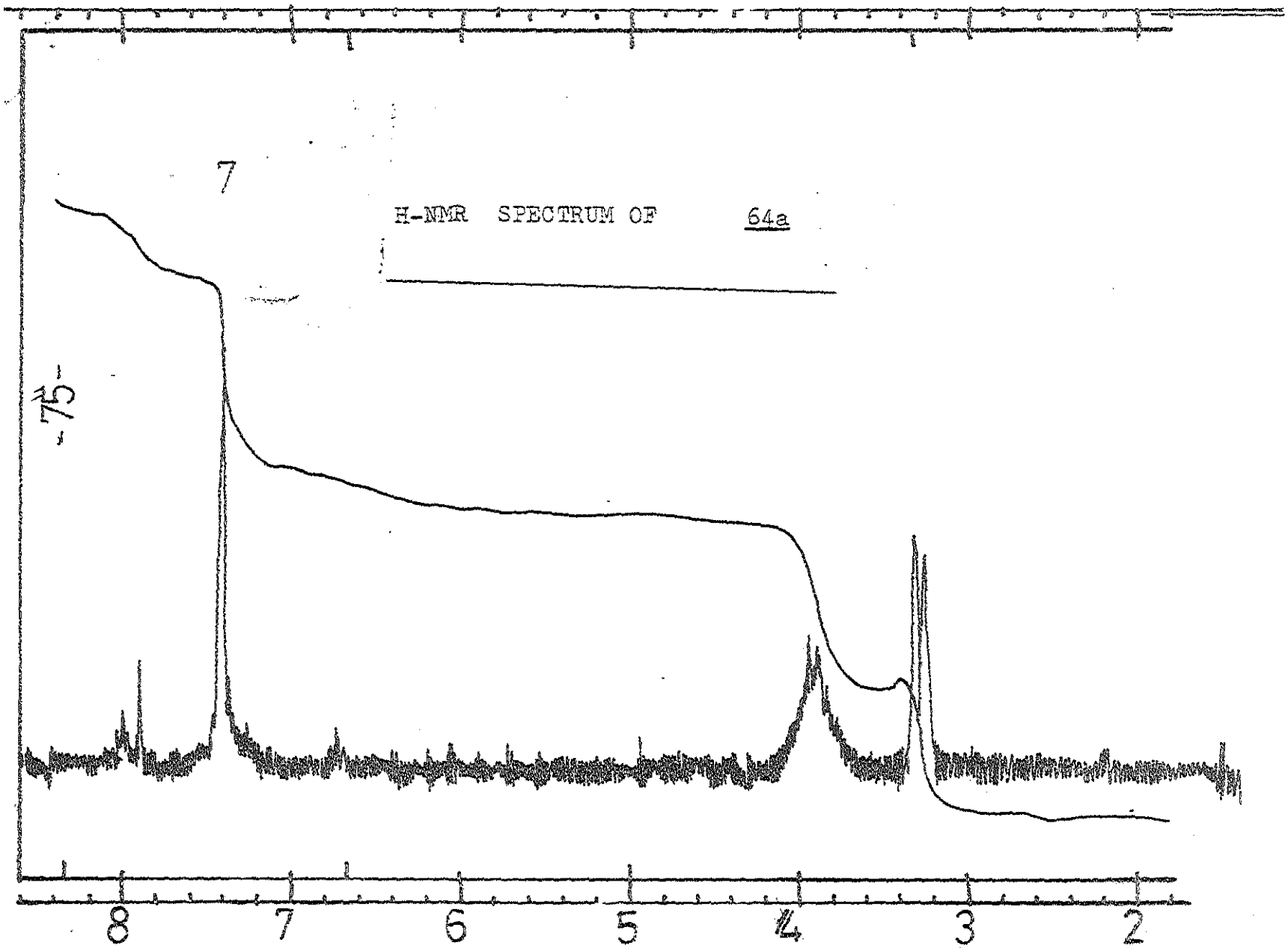
^{1}H-NMR SPECTRUM OF 43a or 43b

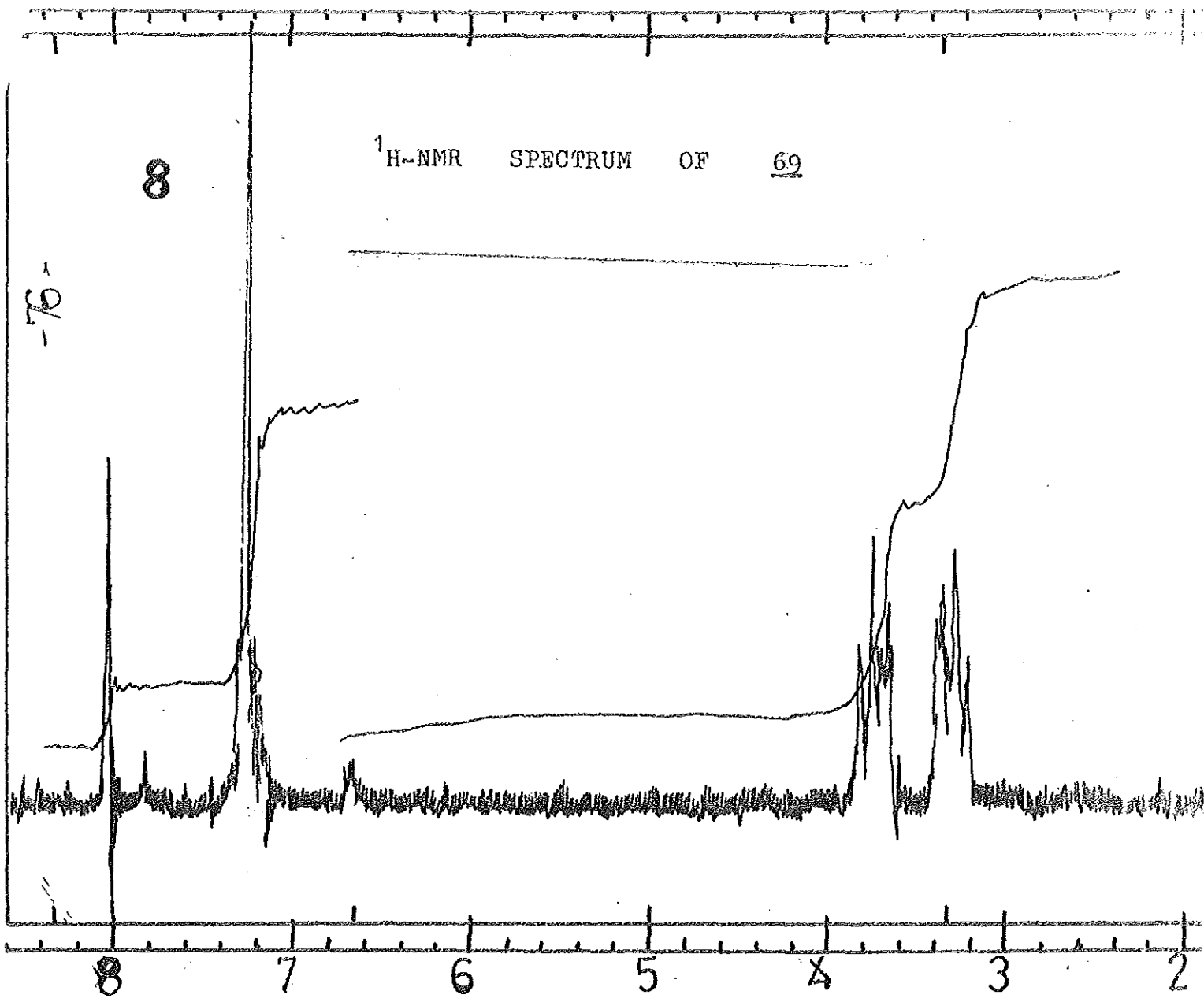


5

^{1}H-NMR SPECTRUM OF 58b




7
H-NMR SPECTRUM OF 64a
8
7
6
5
4
3
2


8
^{1}H-NMR SPECTRUM OF 69
8
7
6
5
4
3
2

REFERENCES

1. R.M.Acheson; "An Introduction to the Chemistry of Heterocyclis Compounds", 3rd ed. 1976, N.Y.

2. L.A.Paquette; "Principles of Modern Heterocyclic Chemistry" 5th printing, 1978.

3. H.C.Koppel; R.H.Springes and R.K.Robins; J.Org. Chem. 1962, 27, 3614

4. J.B.Patrick, R.P.Williams, W.E.Meyer and J.S.Webb; J.Amer.Chem. Soc. 1964, 86, 1889.

5. J.C.Sheehan and K.R.Henery Logan,; J. Amer. Chem. Soc. 1959, 81, 3089.

6. G.Nowlin; J. Amer. Chem. Soc. 1950, 72, 5754

7. D.M. Young and C.F.H. Allen; Org.Syn. 1943, Coll. Vol. 2,219.

8. A.T.Blomquist and H.B.Stevenson; J. Amer. Chem. Soc. 1934, 56, 146.

9. J. Liebscher; D.Sc. Thesis, Technische Universitat, Dresden, DDr, 1977.

10. F.R.Sciaky and U.Pallini, Tetrahedron Letters, 1964, 1839

11. G.K.Ikawa & F.Takami, Tetrahedron Letters, 1969, 3279

12. H.D.Burn and Co-Workers Tetrahedron, 1964, 597

../

13. Z. Arnold; Collect,Czech. Chem. Commum. 1961, 26,3051.

14. J.Liebsche and H.Hartmann; Collect,Czech. Chem. Commun,1976,41,1565.

15. J.Liebscher and H.Hartmann; Synthesis,1979,241

16. H.Bohme,and H.G. Vihe; "Iminium Salts in Organic Chemistry", W.Interscience, N.Y. 1976.

17. J.Liebscher and Berhanu Abegaz, Synthesis in press.

18. J.Liebscher and Berhanu Abegaz; in the "Annual Research Reports"Vol III 1981,A.A.U. Department of Chemistry.

19. G.Consiglio, S.Gronowitz and D.Spinelli, Chem. Scr. 1977, 175-9. C.A. 90; 86494g, 1979.

20. C.Dell'Erba and D.Spinelli; Boll.Sci.Fac. him. Ind. Bologna. 1968 97-101. C.A 69; I06381g, 1968

21. D.Spinelli, C.Dell'Erba and A.Salvemine; Ann.Chim. 1962, 1156-66. C.A. 59, 6219c, 1963.

22. Guanti and Guiseppe; J.Heterocyclic Chem. 1975, 945 C.A. 84, 104666x, 1976

23. D.Spinelli and G.Consiglio; J.Heterocyclic Chem. 1977/ 1325-9, C.A. 88, 120257c.

24. K.Gewald E.Schinke, and H.boettcher; Chem.Ber. 1966 94-100. C.A. 64; 8118c, 1966

25. K.Gewald ;Z.Chem. 1962, 305-6 ,C.A. 58 .6770e ,1963.

../

26. S.Rajappa and B.G. Advani; Indian. J.Chem. 1971, 759

27. Ibide 1974.

28. G.Purrello; Gazz.Chim.Ital. 1967 ,549-56
C.A. 68 ,9577v, 1968.

29. C.D.Slater and D.L.Heywood, J.Heterocyclic.Chem. 1965, 315-16. C.A. 63 ,16341g 1965.

30. W.D.Rudorf. Z. Chem. 1979, 100-1, C.A. 83 ,178681z.

31. M.Augustin, H.Dehne,W.D.Rudorf,DDr.Pat.124,302. C.A.88.74292k, 1978

32. S.Rajappa; Tetrahedron 1981, 1453-80

33. Applied for the DDR. Patent

34. E.L.Anderson and H.E.Reiff; U.S. 2,989,539. C.A56. 4773d ,1962.

35. F.Elden,C.Evers. Arch. Pharm. 1971, 121-5
C.A. 75, 5833g, 1971

36. A.P.Lorette, L.Jean,S.Alain; C.R.Acad.Sci.Ser.C. 1971 203-6, C.A. 74 ,8788v , 1971

37. A.Takamizaua and S.Hayashi; Yakugaku,Zasshi,1963, 313-18. C.A. 59 ,5147e, 1963

38. H.Dorn G.Hilgetag and A.Zubeek; Chem. Ber.1968, 3368-70. C.A. 63., 16331g,1965

39. S.Hans, J.A.Herbert; Justus.Liebigs.Ann. Chem. 1969, 139-45. C.A. 72, 43557r, 1970.

../

40. S.Hans, J.A.Herbert; Ger.Offen. 845.C.A.73, 120617k,1970.

41. H.Beyer,H.Honeck, C.Reichelt. Justus, Liebigs.Ann. Chem.1970, 741-45. C.A. 74 ,31733y,1971.

42. S.Hunig, K.Hubner, Chem.Ber. 1962,937.

43. J.Liebscher and H.Hartmann, Z.Chem. 1974,189

44. Ibide, 1975,16.

45. J.Liebscher and H.Hartmann DDr.Pat.113,911.

46. R.H.Wiley (ed) "The Chemistry of Heterocyclic Coumpounds", Interscience, N.Y. 1962.

47. S.Rajappa, B.G.Advani and R.Sreeniwason; Synthesis 1974,656.

48. Morita,Kei,Hashimoto,Naoto,Japan,68,16,139. C.A. 70 ,57820s, 1969.

D E C L A R A T I O N

I, the undersigned, declare that this thesis is my work and that all sources of material used for the thesis have been duly acknowledged.

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