SYNTHETIC STUDIES IN BIOACTIVE NITROGEN, OXYGEN AND SULFUR HETEROCYCLES

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

BY

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PUNE – 411 008. (INDIA)

MAY 1991


Dedicated to
My
Parents

C E R T I F I C A T E

Certified that the work incorporated in the thesis entitled "Synthetic studies in bioactive nitrogen, oxygen and sulfur heterocycles", submitted by Mrs. S.R. Deshpande was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr.R.B. Mitra)
Research Guide

23·5·91
Pune-411008.

C O N T E N T S

A C K N O W L E D G E M E N T S

I will always remain indebted to Dr.R.B. Mitra, my Research Guide, under whose inspiring and encouraging guidance, the work was successfully carried out.

I owe a word of gratitude to Dr.Z. Muljiani for the keen interest taken in progress of the work. I am thankful to my colleague and friend Dr.Anjali P. Likhite whose assistance enabled me to simplify the work at the bench level.

The assistance rendered by microanalysis and spectroscopy groups is gratefully acknowledged.

I sincerely thank Dr.S. Rajappa, Head, Organic Chemistry Division for his encouragement during the course of my research work.

I acknowledge the help of Mr.H. Nagarajan in typing the manuscript of my thesis and Mr. Kulkarni for drawing figures and charts.

It is my pleasant duty to thank my husband and parents in-laws for their co-operation. Finally, I would like to thank the Director, National Chemical Laboratory, Pune for allowing me to submit this work in the form of a thesis.

S R deshpande

(Mrs. S.R. Deshpande)

National Chemical Laboratory,
Poona-411008.

GENERAL REMARKS

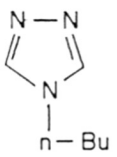
1. All melting points and boiling points are uncorrected.
2. The IR spectra were recorded on a Perkin-Elmer infrared specstrophotometer models 137-B or 599-B using sodium chloride optics.
3. The PMR spectra were taken on Varian-T-60 MHz spectrometer, Varian FT-80 MHz spectrometer and Brucker WH-90 MHz spectrometer and the chemical shifts were measured in δ units, using TMS as internal standard.
4. In the description of PMR signals the abbreviations s, d, t, q, m, dd, mean singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.
5. Mass spectra were recorded on CEC-21-110B mass spectrometer and on Finnigan Mat 1020C mass spectrometer at 70 ev.
6. Pet.ether refers to fraction boiling between 60-80°.
7. Numbers given to the charts, figures and structures in each chapter of the thesis refer to that particular chapter only and compounds described in the present work are only numbered serially.

ABSTRACT of the thesis entitled "Synthetic studies in bioactive nitrogen, oxygen and sulfur heterocycles" submitted by Mrs.S.R. Deshpande to the University of Poona for the degree of Doctor of Philosopy in Organic Chemistry

Chapter I

Section A: General introduction to 1,2,4-triazole fungicides

In the realm of synthetic compounds having biological activity, derivatives of 1,2,4-triazole occupy a unique position. Commercial 1,2,4-triazoles namely n-Butrizole (1), Triadimefon (2)[1], Paclobutrazole (3)[2] and Ribavarin (4) are a few of the active compounds. n-Butrizole and Triadimefon have selective systemic fungicidal activity, Paclobutrazole is a plant growth regulator while Ribavarin is an antiviral drug. It seems that compounds having structural features as in (5) have a great potential as a fungicide.



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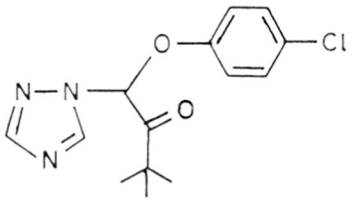

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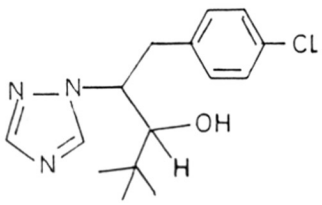

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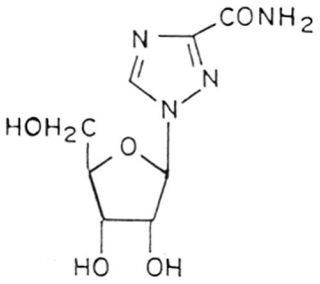

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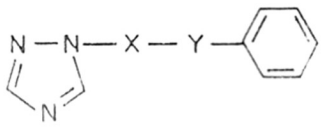

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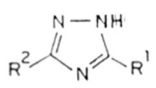
Section B: Properties and methods of synthesis of 1,2,4-triazoles

The heteroaromatic 1,2,4-triazole ring system is best represented as an equilibrium mixture of three regioisomers (6), (7) and (8). As a result of this annular prototropy, when R_1 and R_2 are different, definite assignment of the product of the reactions like alkylation, acylation, ligand formation becomes difficult. Majority of the reactions of 1,2,4-triazoles are the reactions of the substituent group and these are fully diversified as in benzene chemistry.

The ease of forming C-N and C=N bonds as compared to the difficulty in N-N bond formation practically prescribes the use of hydrazines in the synthesis of 1,2,4-triazoles. Hence most of the synthetic schemes use hydrazines[3], acyl hydrazines, amidrazones[4], acyl amidrazones, semicarbazides, thiosemicarbazides[5], amino guanidines, the compounds all of which can be derived from hydrazine as the reactant. Synthesis of 1,2,4-triazoles can also be achieved by transformation of other heterocycles.



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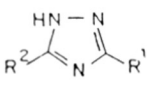

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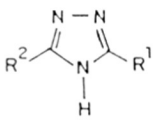

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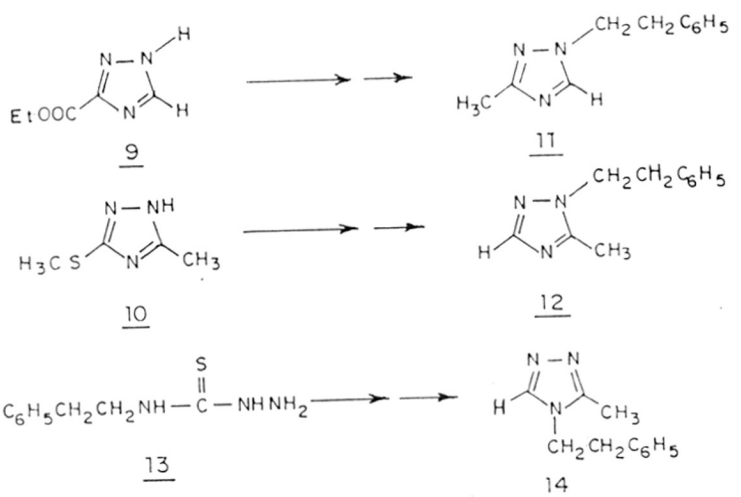
Chapter II

Regiochemistry of alkylation in substituted 1,2,4-triazoles

In alkylation of 1,2,4-triazoles three regioisomers can be formed. It is established in the literature that mainly viciral nitrogens, i.e. N-1 and N-2 are alkylated in preference to N-4[6]. The main studies on alkylation

have been limited to the methylation reaction[7]. No systematic study of regiochemistry with other alkylating agents appear to have been done.

We studied the regiochemical outcome of the phenacylation reaction in ethyl 1,2,4-triazole-3-carboxylate (**9**), 3-methyl-5-methylthio-1,2,4-triazole (**10**) and a few others[8]. Phenacylated product of (**9**) was reduced with lithium aluminium hydride to the diol, which was converted to the dichloro derivative and di(phenylthio) derivative sequentially. Further desulfurisation gave 3-methyl-1-(2-phenylethyl)-1,2,4-triazole (**11**). Similarly (**6**) was converted to 5-methyl-1-(2-phenylethyl)-1,2,4-triazole (**12**). Authentic 3-methyl-4-(2-phenylethyl)-1,2,4-triazole (**14**) was prepared from 4-(2-phenyl ethyl) thiosemicarbazide (**13**). Comparison of the spectroscopic data of compounds (**11**), (**12**) and (**14**) confirmed the structures assigned to the phenacylated product.



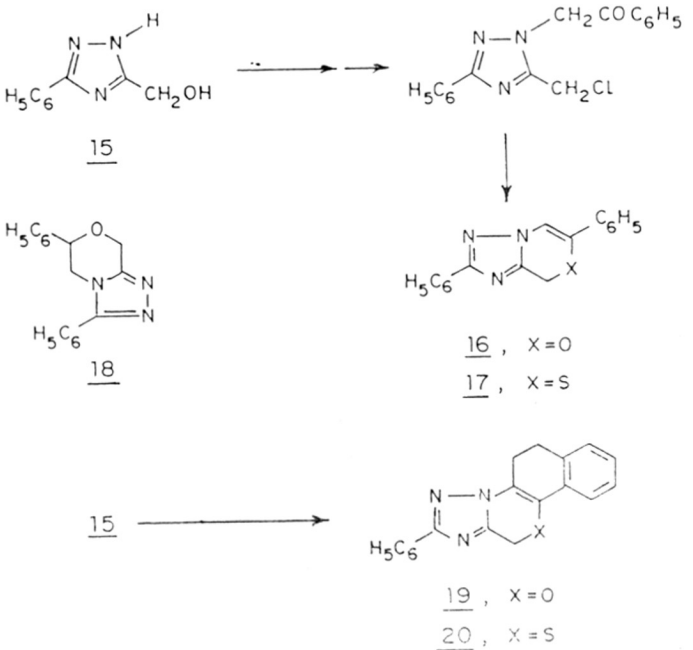
9 11 10 12 13 14

Chapter III

Synthesis of 1,2,4-triazolo fused bicyclic and tetracyclic systems[9]

3-Hydroxymethyl-5-phenyl-1,2,4-triazole (15) was chosen as a substrate for the synthesis of fused heterocycles. Benzamide was converted to benzoyl isocyanate which gave 2-phenyl-4-oxazolone on treatment with diazomethane. Hydrazine hydrate rearranged this oxazolone to the starting compound (15). 5-Hydroxymethyl-1-phenacyl-3-phenyl-1,2,4-triazole was obtained by phenacylation of (15). Thionyl chloride further converted hydroxymethyl functionality to the chloromethyl group. Cyclisation with sodium hydride afforded 2,6-diphenyl-8H-[1,2,4]triazolo[5,1-c][1,4] oxazine (16). The chloro compound on reaction with Lawesson reagent gave the thiazine analogue (17). Compound (16) was hydrogenated to the dihydro derivative which was further compared with the dihydro derivative (18) prepared in an unambiguous way.

Alkylation was also carried out with 2-bromo-1-tetralone on compound (15). Alkylated product was similarly cyclised to tetracyclic compounds (19) and (20).



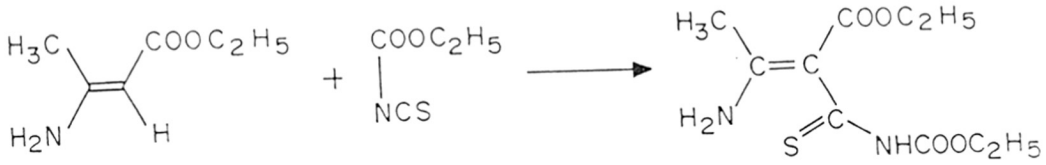
Chapter IV

Synthesis of thiophene derivatives from enamine-isothiocyanate adduct

A versatile route has been developed by Rajappa et al.[10] for thiophene synthesis starting from enamine-isothiocyanate adduct. Effect of strong electron attracting groups like carbethoxy and sulfonyl on the isothiocyanate residue was studied by reacting N-carbethoxy and N-sulfonyl isothiocyanates with an enamine in this synthesis.

Enamine (**21**) was reacted with ethoxycarbonyl isothiocyanate (**22**) and the resulting adduct (**23**) was alkylated with substituted phenacyl bromides to give 2-thiophenecarbamates (**24**).

Arylsulfonyl isothiocyanate (**25**) when reacted with the enamine (**21**) did not give the expected adduct. Structural assignment to the main product of this reaction needs X-ray diffraction analysis.



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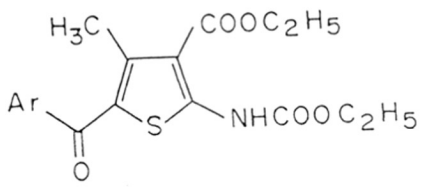

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CHAPTER I

Section A

General Introduction to 1,2,4-triazole fungicides

INTRODUCTION

Food and good health are the basic needs of mankind. To make adequate provision for good and sufficient food one has to overcome the major problems of agriculture, namely, insect pests, weeds and plant diseases. Pesticides play a crucial role in this continuous struggle of man against pests. But with the rapidly increasing world population, one has to search for newer and better pesticides for protection of crops in order to overcome the envisioned food shortage.

Insecticides, herbicides and fungicides are the three main classes of pesticides. Fungicides probably have the longest history. Rust, powdery mildew and smut are the main fungal diseases which are like invisible enemies and spread throughout the fields with an unpredictable fate. Until the accidental discovery of Bordeux in 1882, farmers in the French vinyards had no real possibility of defending their crops against the ravages of these fungal diseases.

A fungicide may broadly be defined as a compound which kills or inhibits the growth of fungi. Those fungicides used to control fungal diseases of plants are frequently divided into three classes.

1] Protective- These provide protection against infection at the site of application.

2] Erradicant- These cure an established infection at the site of application.

3] Systemic- These can prevent the development of diseases on regions of the plant away from the site of application.

Two general approaches for the control of infectious plant disease are prevention and cure. Prevention or propylaxis seeks to prevent infection by inhibiting the pathogen before it penetrates the host gets established within its tissues. Compounds achieving this are called

as protective fungicides or protectants. Cure or therapy seeks to eliminiate pathogen after it is already established within the tissues of its host. Compounds achieving this are chemotherapeutants or curative fungicides.

Systemic fungicides are the compounds which are taken up by plant from the surface to which they are applied and redistributed throughout the plant by normal transport mechanisms, principally the apoplast but also the symplast and exert their activity at places remote from the site of application. But it is necessary that the compound should be toxic to the fungus as opposed to plant cells.

Pioneer fungicides were based on compounds of copper, mercury and sulfur. The organic fungicides of dithiocarbamate and phthalimide type were a breakthrough in 1930's and 1940's. They only have protective activity and hence must be used prophylactically. They find wide applications due to their high plant compatibility and broad disease control spectrum. Though these compounds are still widely used they have some limitations. An established infection cannot be cured as these compounds fail to penetrate the plant tissue. They must be sprayed very carefully to provide maximum cover of the succeptible surface of the plant. Further, surface deposits are exposed to weathering such as wind, rain splash etc. Hence repeated applications are necessary to ensure continued protection.

Discovery of systemic fungicides in 1960's was a milestone in the development of fungicides. Oxathiins used against smuts and rusts, pyrimidine derivatives against powdery mildews and organophosphates

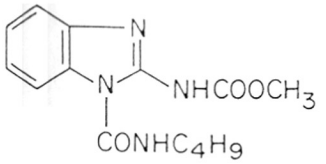
against pyricularia belong to the type of fungicides systemic in nature discovered during 1960's. They are characterised as being absorbed by leaves and often also by seeds and roots, but they possess a very narrow spectrum of disease control.

Benzimidazole fungicides, Benonyl (**1**), Thiabendazole (**2**) had much wider disease control spectrum due to their specific mode of action but resistance appeared quite rapidly.

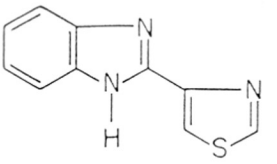
With the class of 1-substituted imidazoles and 1,2,4-triazoles one finds a new group of highly active fungicides and antimycotics. Since their discovery in late 1960's they have been widely used for control of plant diseases and for the treatment of human fungal infections. It was known that tropylium compounds have some biological activity. From the point of view of chemists, they have a stable carbocation which was thought to be interfering with the metabolic processes of biological systems. Different N-tritylimidazoles and 1,2,4-triazoles were prepared and found to be extremely active against powdery mildew fungi[1]. Variation in trityl group does not change the activity and presence of imidazole or 1,2,4-triazole nucleus seems to be the essential component.

Possibly the most selective fungicidal effect observed to date is due to 4-n-butyl-1,2,4-triazole [Butrizole-**3**][2] which is the most active compound of a number of 4-substituted 1,2,4-triazoles. It is active against wheat leaf rust and is effective as a foliar spray and by root uptake at concentrations as low as 1 ppm.

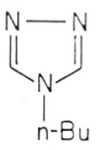
Significant progress was achieved in the control of plant diseases with the discovery of the highly active class of so-called "triazolyl-O,N-acetal" fungicides. It has been observed that compounds belonging



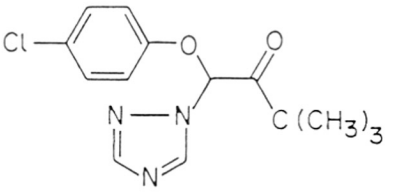
1 BENOMYL



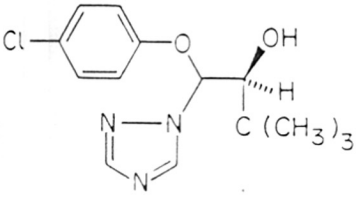
2 THIABENDAZOLE



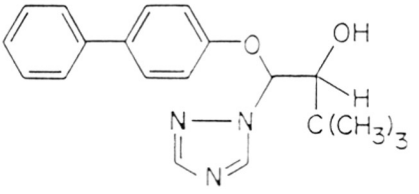
3 BUTRIZOLE



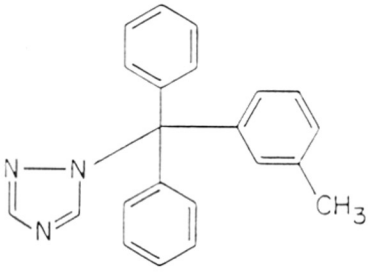
4 TRIADIMEFON



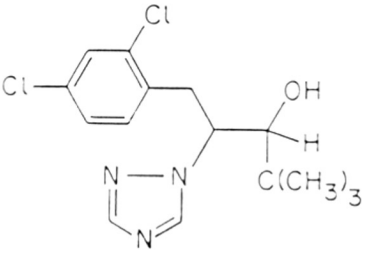
5 TRIADIMENOL



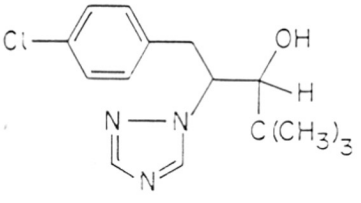
6 BITERTANOL



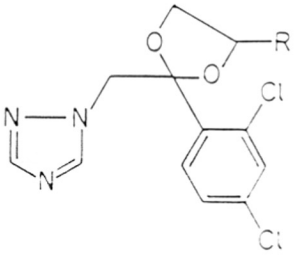
7 FLUOTRIMAZOLE



8 DICHLOBUTRAZOLE



9 PACLOBUTRAZOLE



10 PROPICONAZOLE

R = n-C_3H_7

11 ETACONAZOLE, R = C_2H_5

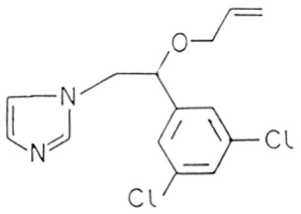
R = C_4H_9

to this class having very close chemical relationship, differ remarkably in their biological and biophysical properties, thus enabling the use of various compounds for specific purpose.

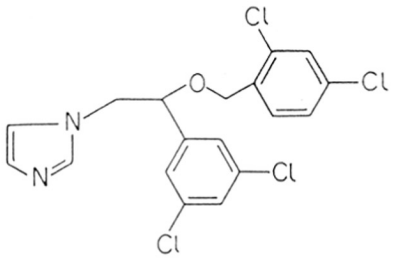
The first commercial triazole compound was triadimefon or Bayleton (4) introduced by Bayer in 1973[3]. This is a potent systemic fungicide with particularly high activity against powdery mildew, rust fungi and seed borne diseases of cereals. Triadimenol or Baytan (5) has excellent systemic activity for control of seed and soil borne fungal organisms and even in infections by wind borne pathogens. Other important member of the "azolyl-O,N-acetal" family that has been marketed so far is Biterfanol or Baycor (6). It is not systemic but penetrates plant tissue and thus posesses curative and eradicative properties combined with protective activity.

Fluotrimazole or Persulon (7) is a non-systemic fungicide developed for the control of powdery mildew in cereals and fruit. It belongs to the first generation class of N-trityl-azole fungicides to reach the market.

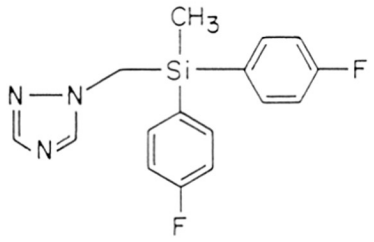
Replacement of the oxygen of the triazolyl-O N-acetals by a methylene group has given compounds like- Dichlobutrazole (8) and Paclobutrazole(9). The compound (8) marketed by ICI was developed for the control of powdery mildew, rust and scab in cereals and Paclobutrazole(9)was the first 1,2,4-triazole derivative introduced in agriculture as a broad spectrum plant growth regulator[4]. It also has good fungicidal activity. 2RS, 3RS Paclobutrazole is the bioactive diastereomer and it has been shown that the (+) 2R, 3R enantiomer possesses good fungicidal activity and the plant growth properties reside with the (-) 2S, 3S enantiomer.



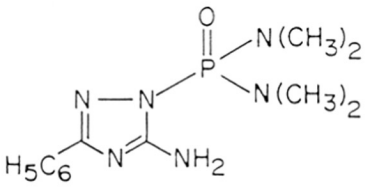
12 IMAZALIL



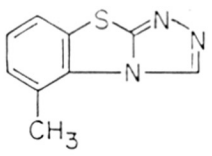
13 MICONAZOLE



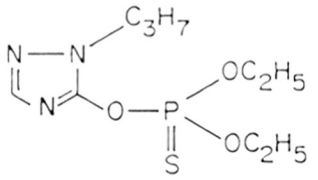
14 DPX-H6573



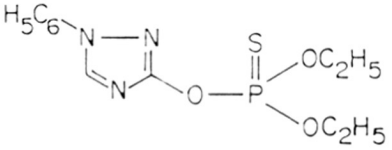
15 TRIAMIPHOS



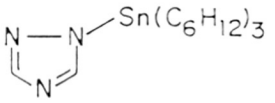
16 TRICYCLAZOLE



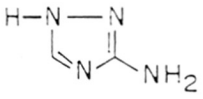
17 ISAZOPHOS



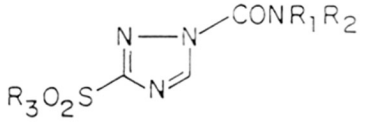
18 TRIAZOPHOS



19 AZACYCLATIN



20 AMITROLE



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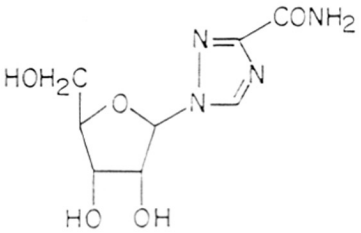
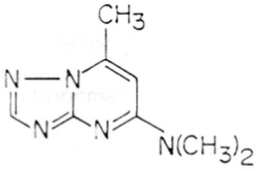
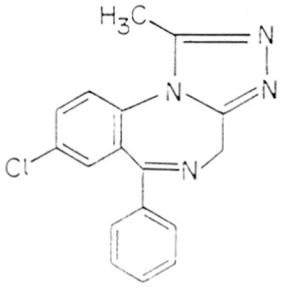


22 RIBAVARIN



23 TRAPYMIN



24 ALPRAZOLAM

Propiconazole (**10**) and etaconazole (**11**) discovered by Janssen and developed under licence by Ciba-Geigy for control of fungal diseases in cereals and fruits, belong to another azole subgroup; azolylmethyl-dioxalanes. Their chemical genesis from the phenethylazoles of imazalil (**12**) and miconazole (**13**) type can be easily recognised.

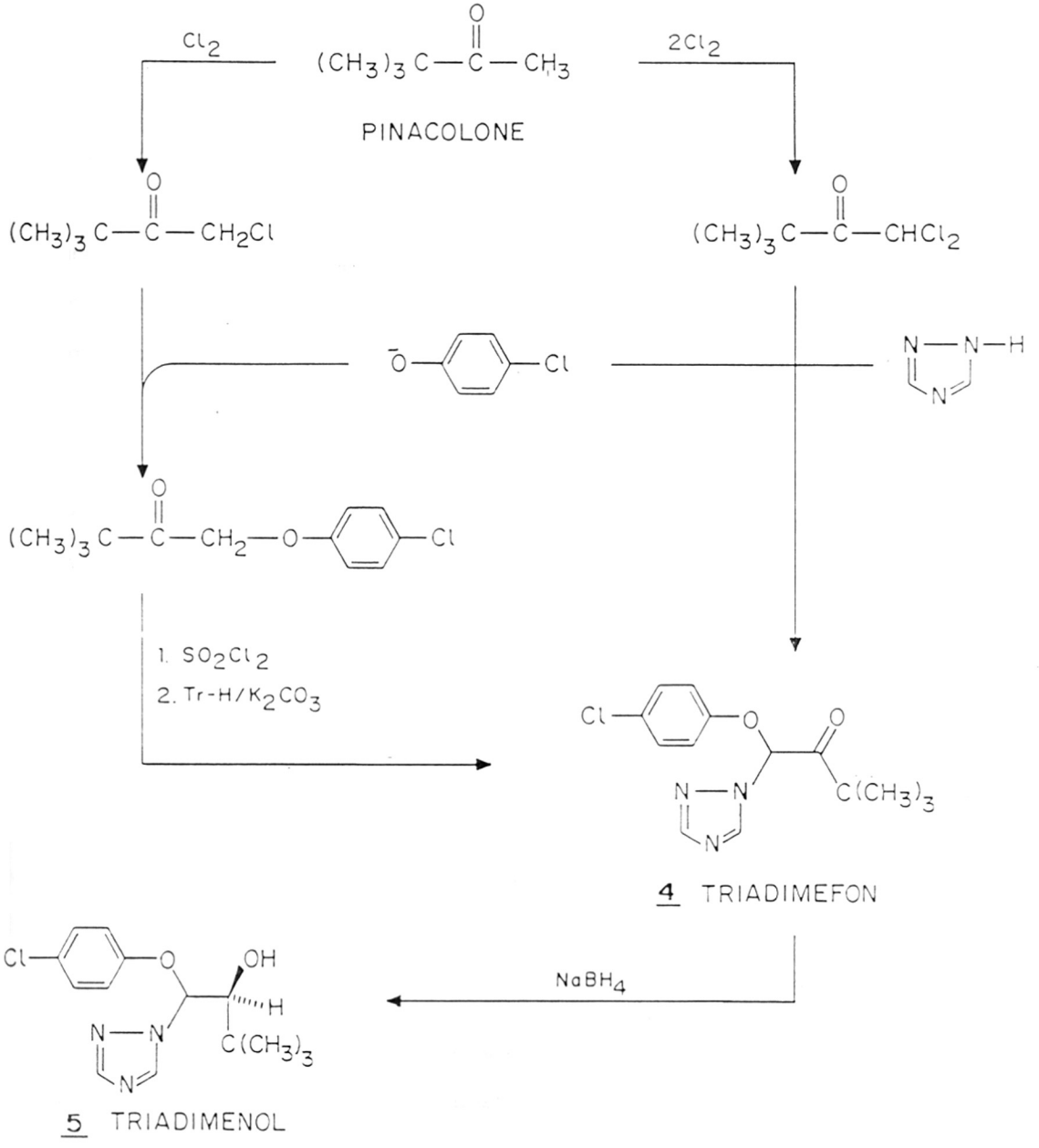
Silylmethyltriazoles represent a new highly active class of triazole fungicides whose success in a wide variety of crops and climatic conditions confirms the utility of organosilicon compounds as agrochemicals. DPX-H6573 (**14**) structurally very close to Triadimefon and Propiconazole, is a new product developed by Du Pont. Triamiphos or Wepsyn (**15**) synthesised by vanden Bos et al.[5] from 3-amino-1,2,4-triazole and bis-(dimethylamido) phosphoryl chloride possesses good fungicidal activity against powdery mildew combined with secondary insecticidal and acaricidal activity.

Tricyclazole (**16**) as the name indicates is a tricyclic triazolo fused compound, used as a systemic fungicide for control of rice blast.

Scheme I gives the preparation of Triadimefon and Triadimenol starting from pinacolone.

It has been accepted that these derivatives of 1,2,4-triazole belong to the group of Ergosterol Biosynthesis Inhibitors. The biosynthesis of ergosterol, the major sterol in most fungi, involves a number of reactions and follows pathways that are more or less typical for a particular organism. Inhibition of the formation of ergosterol at a certain step in the pathway changes the sterol composition of the organism by the accumulation of normal sterol intermediates which are then deviated to side pathways to give abnormal sterols. As a result, a complex

SCHEME - I


Cl2
2Cl2
(CH3)3 C—C—CH3
O
PINACOLONE
(CH3)3 C—C—CH2Cl
(CH3)3 C—C—CHCl2
Cl
N—N—H
N
(CH3)3 C—C—CH2—O—Cl
1. SO2Cl2
2. Tr-H/K2CO3
Cl
O
N—N
C(CH3)3
4 TRIADIMEFON
NaBH4
OH
H
5 TRIADIMENOL

sterol pattern can lead to misinterpretation of the site of inhibition. Triazole compounds are supposed to be interacting with cytochrome-P450 leading to inhibition of the oxidative demethylation of the C-14-methyl group of the lanosterol (scheme II).[6]

The plant growth activity associated with paclobutrazole is due to inhibition of the biosynthesis of gibberellins at the oxidation steps between ent-kaurene and ent-kaurenoic acid .(scheme III)[7].

Isazophos or Miral (17), Triazophos (18) and Azacyclatin (19) are the other commercial triazole compounds belonging to the class of insecticides. Isazophos from Ciba-Geigy is a nematicide and insecticide for the control of imported fire ant and harvester ants in baits. Triazophos marketed by Hoechst is useful as insecticide, miticide and nematicide. It is used as a cholinesterase inhibitor. Azacyclatin, a Bayer A.G. product is a long acting acaricide with contact action against all stages of spider mites.

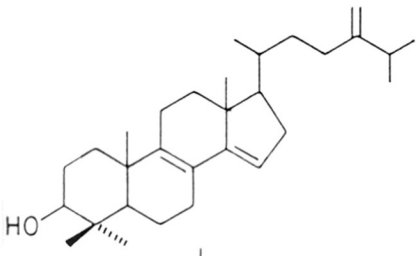
3-Amino-1,2,4-triazole, Amitrole (20) patented in 1954 had been widely used as a herbicide and plant growth regulator. It was proposed that this pesticide could induce thyroid tumors in rats, hence its all registered uses on food crops were cancelled in 1971. The Boots Company Ltd., have found that advantgeous and valuable herbicidal properties are associated with a relatively narrow group of 1,2,4-triazoles which is 1-N,N-disubstituted carbamoyl-1,2,4-triazoles with alkylsulfonyl functionality at C-3 (21).

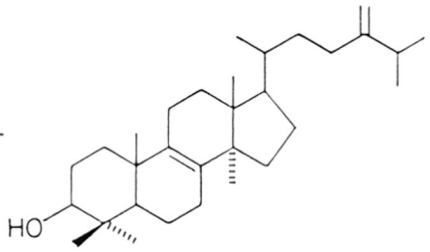
Ribavarin (22) is the most widely used broad spectrum antiviral drug[8]. It is active against both DNA and RNA viruses in vitro

SCHEME - II

INHIBITION OF C-14 DEMETHYLATION IN ERGOSTEROL BIOSYNTHESIS

ACETATE → MEVALONATE → SQUALENE → LANOSTEROL



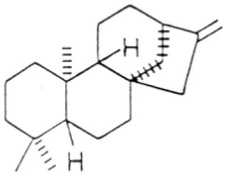


24-METHYLENE DIHYDROLANOSTEROL

ERGOSTEROL

SCHEME III

INHIBITION IN BIOSYNTHESIS OF GIBBERELLINS WITH PACLOBUTRAZOLE 9.



→ ENT - KAURENOL → ENT - KAURENAL

ENT - KAURENE

→ ENT - KAURENOIC ACID →→→ GIBBERELLINS

and in vivo.

Trapymin (**23**), a triazolo [1,5-a] pyramidine derivative synthesised by Tenor and Ludwig is used clincally as a coronary dialator[9].

A hypnotic antianxiety drug Alprazolam (**24**) is a bicyclic triazolo [4,3-a] [1,4] benzodiazepine derivative.

Pharmacological properties such as platelet agreegation inhibitor, antidepressant, antiinflamatory, antihypertensive, gastric antisectretory are also observed in triazole derivatives. Hence there is a great promise in the synthesis of new 1,2,4-triazole derivatives.

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CHAPTER I

Section B

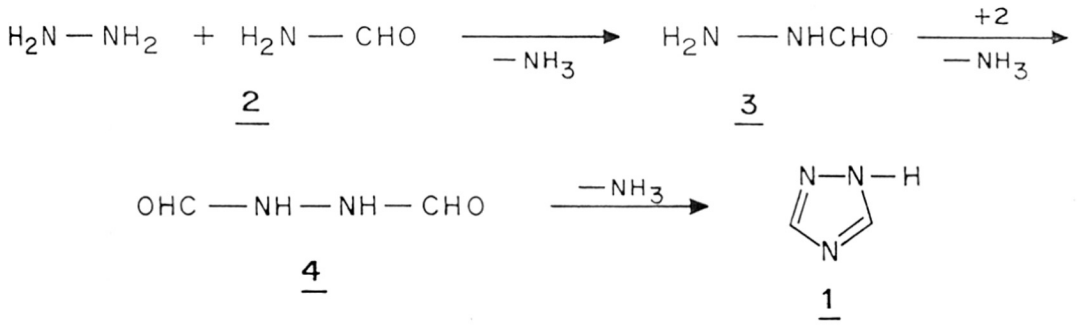
Properties and methods of syntehsis of 1,2,4-triazoles

Considering the abundant selection opportunities for biological and medicinal activities available in 1,2,4-triazole derivatives, we decided to synthesise some new triazole derivatives. This necessitated a study of the chemistry of 1,2,4-triazole nucleus.

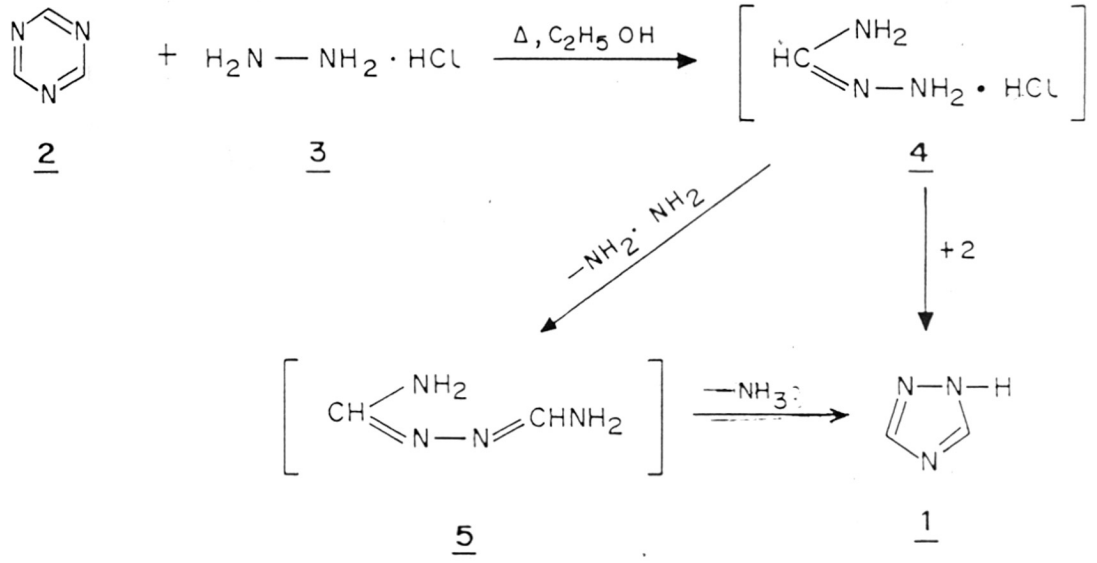
The history of 1,2,4-triazole is about a century old and starts with the work of Bladin[1], who synthesised the first representative of this class and coined the name for it. Soon thereafter Pellizzari obtained the parent ring system from the reaction of formyl hydrazine with formamide[2]. Ainsworth and Jones observed that a large quantity of ammonia is evolved in the reaction of hydrazine with formamide and to prevent the loss of ammonia, the intermediate N,N'-diformyl hydrazine was reacted with excess ammonia in a pressure vessel to give 70 to 80% yield of S-triazole (**1**, scheme I)[3]. Grundmann and Ratz obtained it in 95% yield by interaction of S-triazine with hydrazine hydrochloride[4]. Apparently the intermediate amidrazone (**4**, scheme II) was initially formed, which was postulated to react with another molecule of S-triazine to give 1,2,4-triazole (**1**, scheme II). However, 1,2,4-triazole might have been formed by acid-catalysed self condensation of amidrazone via the intermediate (**5**, scheme II).

Allen and Bell prepared 4-amino-1,2,4-triazole [**5**, scheme III] by reaction of ethyl formate and 85% hydrazine hydrate. The intermediate formylhydrazine on heating at 150°-200° for 3 hours gives 4-amino-1,2,4-triazole in 70% yield[5a]. This can be then deaminated with nitrous acid to give 1,2,4-triazole (**1**, scheme III)[5b]. Currently this synthesis is achieved industrially by introducing hydrazine hydrate (90%) below the surface of formamide at 170°, at a rate of 2-3 moles/hr with distilling

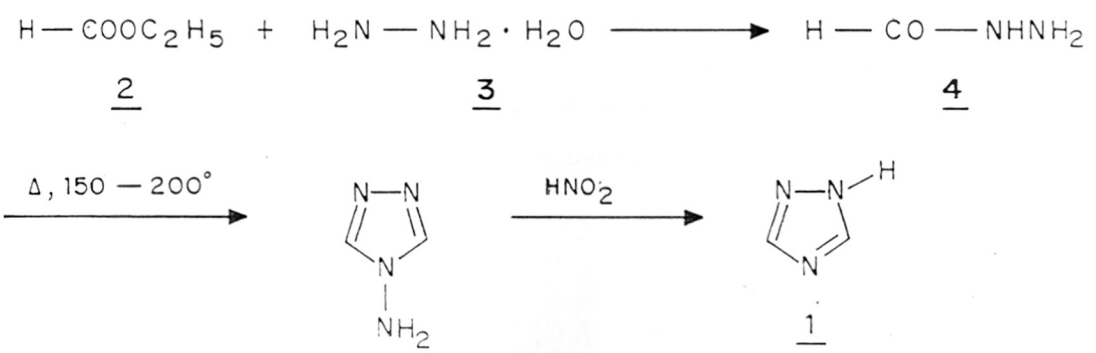
SCHEME I



SCHEME II



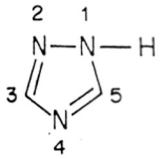
SCHEME III



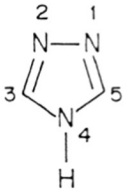
out the byproducts of the reaction and then heating further at 170° for 3 hours[6] 1,2,4-Triazole is obtained in 95-98% yield by this method.

The heteroaromatic triazole ring system is composed of five atoms, two carbons and three nitrogens which can be arranged to give 1,2,3-triazole (ʊ-triazole) or 1,2,4-triazole (S-triazole). Three possible structures for 1,2,4-triazole are represented in scheme IV. The theorectically unlikley isotriazole [**3**, scheme IV] is best understood as the acid [**4**, scheme IV] consisting of a proton balanced by mesomeric triazolate anion[7]. The prefixes 1H and 4H are used to distinguish between [**1**, scheme IV] and [2, scheme IV]. The tautomnerism of 1,2,4-triazole may involve following possibilities, annular prototropy, prototropy involving both ring and substituent and tautomerism restricted to the substituent only. In N-unsubstituted triazoles prototropy between nuclear nitrogen centres may occur i.e. (**1**) and (**2**) may be linked by intermolecular bridges between "pyrrole" NH and "pyridine" type -N= [scheme IV]. But in substituted 1,2,4-triazole when R^3 and R^5 are different the equilibrium in (**1**) and (**2**) of scheme V is not only of theoretical importance but may affect alkylation, acylation, prototropy between ring and substituents, ligand properties and so on. Most experimental and theoretical considerations favour 1H (**1**, scheme V) or 2H (**2**, scheme V) as the predominant tautomers; the 4H (**3**, scheme V) tautomer sometimes plays a comparable role. But an unanimous decision for or against a certain tautomer cannot be made as the tautomeric status of a given triazole need not be same in solution, melt, solid or gas phase. Variation of substituents, solvent and temperature can also change its form. Studies in the complexity of tautomeric problems of 1,2,4-triazole is

SCHEME IV



1



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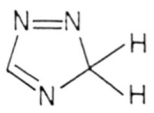

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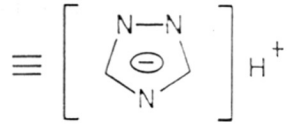
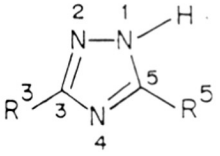
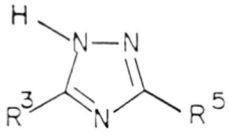


4

SCHEME V



1



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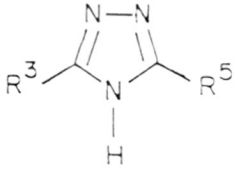

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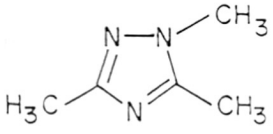
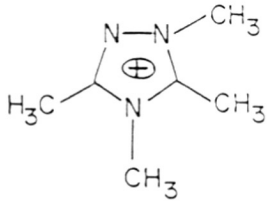
SCHEME VI





$CH_3NH_2 + CH_3NH\,NH_2$

one of the enduring charms of the chemistry of 1,2,4-triazole. Prototropy in triazole becomes still complex when substituents such as -OH, -SH and -NHR are available to donate protons to annular nitrogen[8].

Reactions of 1,2,4-triazole

1,2,4-Triazoles are amphoteric in nature, forming salts with acids and bases. They are such weak bases that the salts with mineral acids are usually completely dissociated in aqueous solution. Alkali metal salts formed by replacement of the imino hydrogen atom are unstable in aqueous solution.

The characteristic feature of 1,2,4-triazole is the stability of the nucleus, an inherent property of its aromatic nature. It can form quaternary salt with methyl iodide which on treatment with alkali provides a way of breaking the 1,2,4-triazole ring [scheme VI][10]. This method was used in structure determination of 1,2,4-triazole derivatives. C-Methyl substituent of these quaternary salts is active, which condenses with heterocyclic dye salt to give cyanine dyes. These dyes have excellent photographic sensitizing properties[9].

The majority of reactions of 1,2,4-triazoles are the reactions of the substituent groups and these are fully diversified as those found in benzene chemistry.

1,2,4-Triazole ring remains unaffected at high temperatures although substituents and their location on the ring may undergo changes on heating it is insensitive to photolysis and also survives during oxidative destruction of aromatic substituents. The nucleus is inert to lithium aluminium hydride[11], sodium and liquid ammonia[12] and oxidizing agents in general.

Because of the aromatic character electrophilic reactions occur in 1,2,4-triazole compounds. Alkylation of triazole either by diazomethane or by sources of carbonium ion reactants introduce substituents on N-1 rather than N-4 in agreement with statistical considerations. N-4 alkylation, though rare, is also observed[13]. In a substituted triazole, both N-1 and N-2 alkylated products are formed, product ratio being dependent upon the nature of substituent, alkylating agent and reaction conditions[14]. Triazoline thiones are preferentially alkylated on sulfur in general but N-alkylation takes place in some cases[15]. Alkylation of 3-amino-1,2,4-triazole gives rise to all possible four mono-alkylated products.

Acylations are mostly performed by anhydride or acyl halides in an inert solvent. N-Acyl bond in these compounds is very labile and extremely moisture sensitive. This property has made us available the reagent N,N'-dicarbonyl-1,2,4-triazole which has excellent practical utility in organic synthetic preparations.

Halogenation of 1,2,4-triazoles initially gives N-halo derivatives and then C-halogenation takes place. Halogen on nitrogen rearranges to carbon on heating[17]. Both 1,2,4-triazole and its 1-benzyl derivative undergo hydroxymethylation at carbon by a mannich reaction[18].

Nucleophilic reactions take place by exchange of anionic substituents like halo, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, amino or cyano by generation of a trasient carbonium ion. An unusual feature of triazole chemistry is the ready exchange of nitro group of nitro, dinitrotriazole and nitrotriazolinones. The reaction of 1-methyl-3,5-dinitrotriazole with hydrazine affords 5-hydrazino derivative with simultaneous formation of 5-amino compound formed by reduction[19]. Arylation of triazole by Gomberg-Bachmann method has been described[20].

Reactivity of substituents

C-Alkyl substituted triazoles are readily oxidised to the carboxylic acids by oxidising agents such as alkaline potassium permangnate[21,22]. The carboxylic acid is readily decarboxylated by heating above its melting point. However, oxidation with potassium poermangnate under acidic conditions is very effective in removing N-aryl substitutent while C-alkyl group is oxidised to a very little extent.[2] C-Amino compounds behave as aromatic amines. Halides undergo nucleophilic displacement reactions. Esters, amides and hydrazides react in a normal fashion. Triazolinones are reduced with phosphorus sulfide to give triazoles[23].

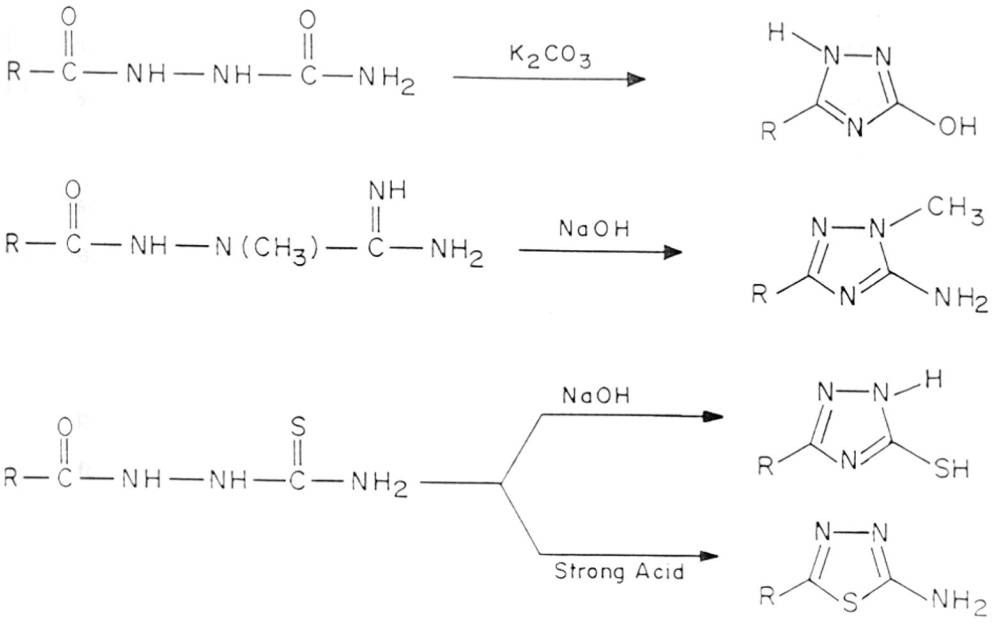
The simplest sulfur containing derivatives of triazole are thiones by structure but behave as thiols in their most important reactions. Alkylation has already been considered. Triazol-3-yl sulfonamides are obtained from triazoline thiones on oxidative chlorination to sulfonyl chlorides followed by reaction with liquid ammonia[24]. Oxidative desulfurisation is achieved with nitric acid, Raney-nickel or hydrogen peroxide[25]. Permagnate oxidation of thiones affords sulfonic acids. Unlike benzenesulfonic acid, triazole sulfonic acids are resistant to boiling with hydrobromic acid or heating with alkali. Treatment with hydrazine however eliminates the sulfonic acid function.

Synthesis

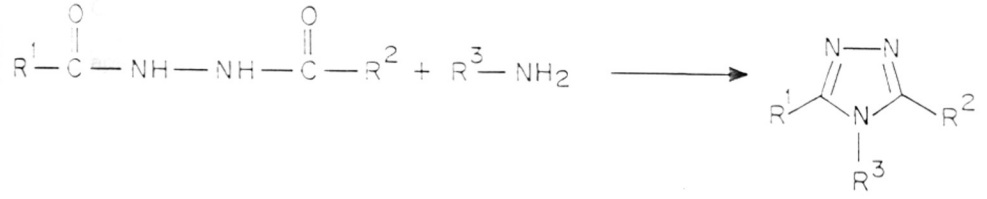
Major methods of synthesis include (i) formation of the 3,4-bond (ii)formation of 3,4- and 4,5-bonds (iii) formation of 2,3- and 3,4-bonds (iv) formation of 1,5- and 2,3- bonds (v) formation of 1,5- and 3,4-bonds

Ring closure of acyl derivatives of semicarbazides, thiosemicarbazides or aminoguanidines in alkaline medium is the most widely applied

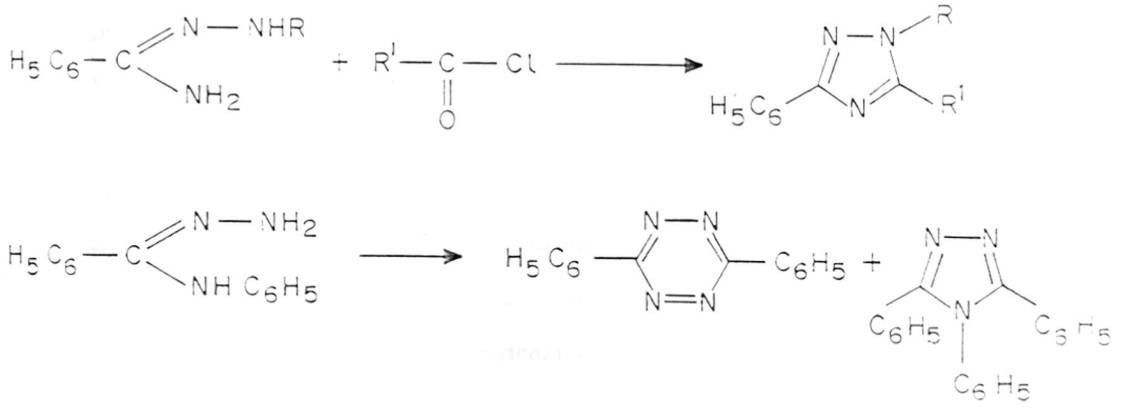
SCHEME VII



SCHEME VIII



SCHEME IX



method for the preparation of 1,2,4-triazole compounds (scheme VII). Starting materials are obtained on acylation of semicarbazides, thiosemicarbazides, aminoguanidines or their derivatives. The required acyl semicarbazides are also available from the combination of acyl hydrazines or thiocarbohydrazides and potassium cyanate or thiocyanate[26,27]. Formation of alternative heterocycles is the main side reaction with semicarbazides and thiosemicarbazides. In strongly acidic condition protonation of N-4 accompanied by loss of nucleophilicity results in the formation of thiadiazole ring (scheme VII), while in basic medium nucleophilicity of N-4 is enhanced giving cyclisation to 1,2,4-triazole nucleus[28]. Aminoguanidines also can give rise to isomeric triazoles on condensation. Sometimes the cyclisation is also achieved by heating (scheme VII)[29].

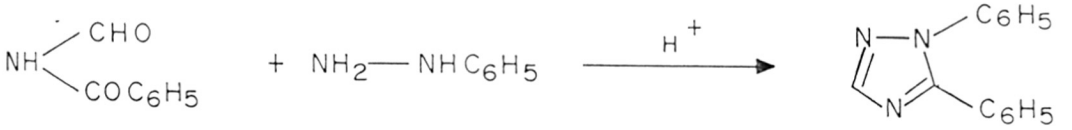
Synthesis of 4-substituted 1,2,4-triazoles is achieved by forming 3,4- and 4,5-bonds in the reaction of diacyl hydrazines with amines[30]. Cyclisation can also be achieved thermally or in presence of dehydrating agents. Diformyl hydrazine with an excess of ammonia in autoclave at 200° for 24 hours gives 1,2,4-triazole in good yield (scheme VIII).

Reaction of amidrazones or hydrazidines with carbonyl compounds such as acid chlorides or anhydrides is illustrated in method 3 (scheme IX)[31]. Phenyl benzamidrazone self condenses to form a mixture of diphenyltetrazine and 3,4,5-triphenyl-1,2,4-triazole[32]. Synthesis starting from amidrazone is the most versatile preparation of 1,2,4-triazole derivatives. Synthetic methods using starting materials other than amidrazone or acylamidrazones can be best explained by intermediate amidrazone formation in the rate determining step of the reaction (scheme IX).

Method IV, i.e. formation of 1,5- and 2,3-bonds is a typical Einhorn-Brunner reaction of hydrazines with diacylamines in mildly acidic

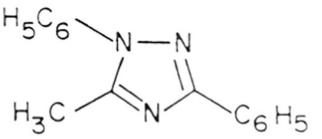
SCHEME X

EINHORN — BRUNNER REACTION

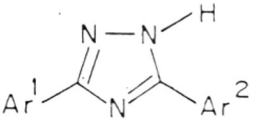


SCHEME XI

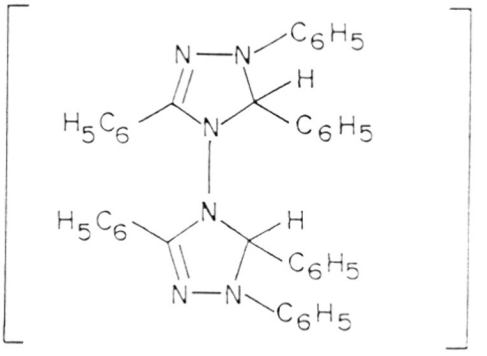
a) $CH_3CONH_2 + C_6H_5NH-NHCOC_2H_5 \xrightarrow{< 210^\circ}$

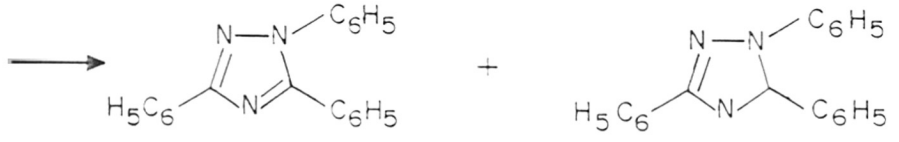


b) $Ar^1CN + Ar^2CONH-\overset{+}{N}H_3 \cdot C_6H_5SO_3^- \longrightarrow$

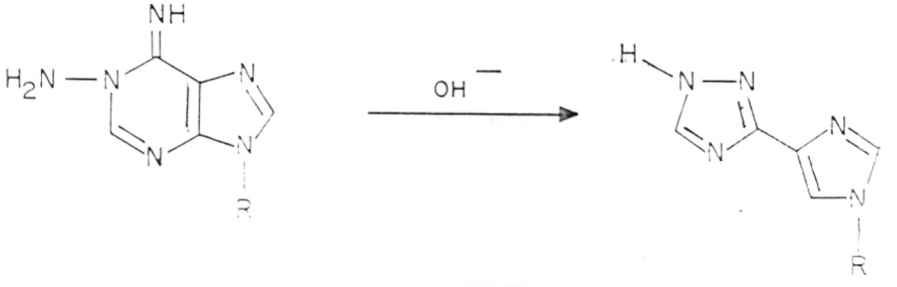


c) $C_6H_5C\equiv\overset{+}{N}-\overset{-}{N}-C_6H_5 \longrightarrow$





SCHEME XII



condition: giving rise to triazole compounds[33]. Advantage of the method is that it is very general and does not produce mixture of isomeric triazoles when unsymmetrical diacyl amines are used[34]. More electrophilic carbonyl group reacts first. This method can be safely extended to the corresponding thioacyl or imino compounds (scheme X).

Pellizzari reaction of heating hydrazides and amides at high temperatures in absence of solvent produces 1,2,4-triazoles, forming 1,5- and 3,4-bonds[2]. The method gives low yields due to complications such as concurrent dehydration of amide, aryl interchange between amide and hydrazide resulting in formation of many byproducts (Scheme XI,a).

Pott's procedure for the preparation of 3,5-diaryltriazoles by heating an arenenitrile with the arenesulfonate of an aryl hydrazine can be classified under method (V)[35]. The method can be extended to the reactions of arenenitriles with alkyl hydrazide benzenesulfonates (scheme XI, b).

Nitrilimines formed by dehydrohalogenation of C-halobenzylidene phenyl hydrazones, react with $>C=C<$, $>C=N-$ to afford triazoles and triazolines in 50 to 75% yields (scheme XI, c)[36].

Synthetic schemes described above use derivatives of hydrazines as starting materials because of difficulties encountered in the formation of N-N bonds while C-N and C=N bonds are formed easily.

Acylhydrazines, amidrazones, acylamidrazones, semicarbazides, thiosemicarbazides, aminoguanidines, all these compounds can be derived starting from hydrazine as reactant.

Synthesis of triazole ring can also be achieved by transformation of other heterocyclic rings which involves (1) destruction of rings leaving an intact triazole core behind, (2) cleavage of the ring to an open acyclic intermediate which then recyclises with or without rearrangement.

1-Amino-adenosine is converted to imidiazolyl-triazole by the first type (scheme XII)[37], 3,4-oxadiazoles and thiadiazoles rearrange to 1,2,4-triazoles via an acyclic intermediate[38]. Excellent reviews on 1,2,4-triazole chemistry are available by Potts[7], Temple[39] and Polya[40].

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CHAPTER II

Regiochemistry of alkylation in substituted 1,2,4-triazoles

SUMMARY

Study of regiochemical outcome of phenacylation reaction in substituted 1,2,4-triazoles was carried out.

Substituted 1,2,4-triazoles visibly ethyl 1,2,4-triazole-3-carboxylate (**6**), 3-methyl-5-methylthio-1,2,4-triazole (**7**), 3-methyl-5-methylsulfonyl-1,2,4-triazole (**8**) and 3-bromo-5-methyl-1,2,4-triazole (**9**) were prepared. Each one of these was phenacylated with phenacyl bromide to give compounds (**10**), (**17**), (**34**) and (**33**) respectively. The structure of (**10**) was confirmed as ethyl 1-phenacyl-1,2,4-triazole-3-carboxylate by X-ray analysis. Compound (**10**) was converted to 3-methyl-1-(2-phenylethyl)-1,2,4-triazole (**16**) by a sequence of reactions. Similarly 5-methyl-3-methylthio-1-phenacyl-1,2,4-triazole (**17a**) was converted to 5-methyl-1-(2-phenylethyl)-1,2,4-triazole (**21**). Authentic 3-methyl-4-(2-phenylethyl)-1,2,4-triazole (**28**) was preparead by an unambiguous route. Comparison of spectroscopic data of (**21**) with that of (**16**) and (**28**) confirm the correctness of the regiostructure assigned to the compound (**21**).

Further phenacylated compound (**33**) was hydrogenated with 5% palladised charcoal to give 1-[(2-hydroxy-2-phenyl)ethyl]-5-methyl-1,2,4-triazole (**23**). Compound (**17**) also gave (**23**) after desulfurisation and sodium borohydride reduction. This ensures the location of phenacyl group in compound (**33**).

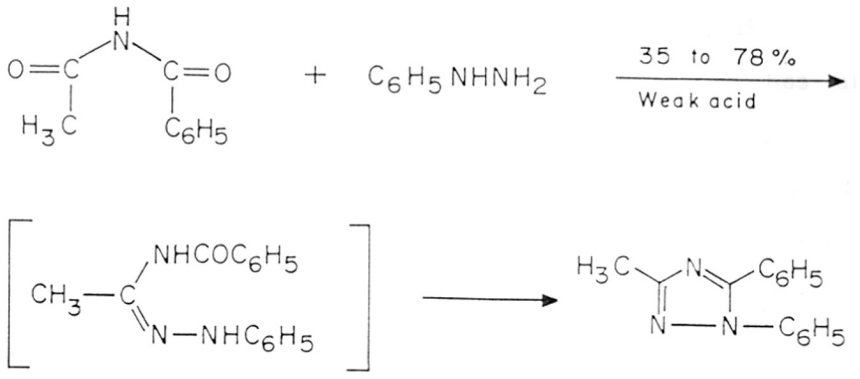
Similarly compound (**34**) obtained by phenacylation of 3-methyl-5-methylsulfonyl-1,2,4-triazole (**8**) was identical with the product of potassium permangnate oxidation on 5-methyl-3-methylthio-1-phenacyl-1,2,4-triazole (**17a**)

This shows that in phenacylation reaction of these substituted 1,2,4-triazoles steric factor plays comparable role along with electronic factor.

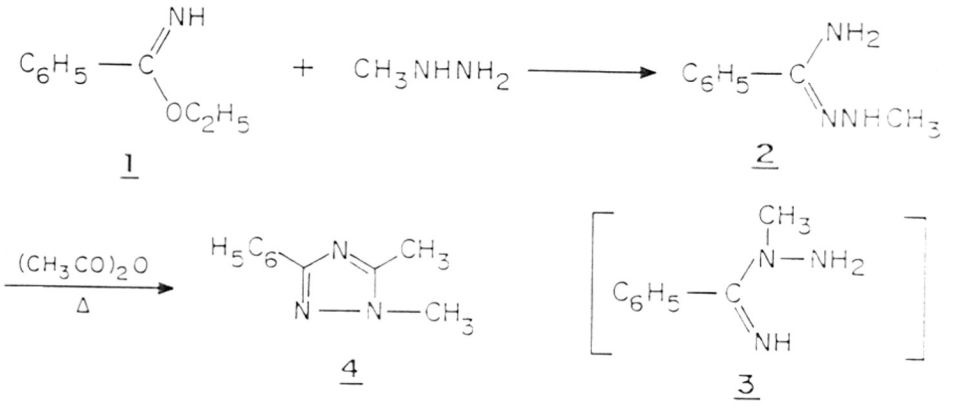
In view of the vast array of biological activities associated with 1,2,4-triazole derivatives, we planned to synthesise some novel fused bicyclic or tricyclic heterocycles, containing the 1,2,4-triazole moiety. This can be achieved in two ways, (i) a triazole ring can be built on a preformed heterocyclic nucleus or (ii) a substituted 1,2,4-triazole can be cyclised to a bicyclic system. We decided to adopt the second route. This necessitates the synthesis of appropriately functionalised substituted 1,2,4-triazole derivatives which can later be cyclised to the bicyclic fused systems. Exercise of adequate regio control during introduction of the substituent is crucial in this synthetic strategy. Synthetic methodologies available in literature for preparation of such derivatives invariably give mixtures. Some of these are briefly reviewed below:

The Einhorn-Brunner reaction of diacylamines with hydrazines provides a direct route for 1,5-disubstituted and 1,3,5-trisubstituted 1,2,4-triazoles (scheme I).[1] Reaction of the imino ether (1) with methylhydrazine provides 1-methylamidrazone (2) rather than 2-methylamidrazone (3). Cyclisation of (2) with acetic anhydride gives the 1,5-dimethyl-1,2,4-triazole derivative (scheme II).[2] Alkylation of C-monosubstituted 1,2,4-triazoles also gives a mixture of 1,3, 1,5 and 3,4 disubstituted triazoles. 1,5-Disubstituted Δ^4-1,2,4-triazolin-3-ones are also the potential intermediates for 1,5-disubstituted triazoles. These can be prepared by dehydration of 4-acyl-1-alkyl (aryl) semicarbazides. Treatment with dilute base[3] or polyphosphoric acid[4] both are effective for elimination of water molecule. The oxo function can be removed with P_4S_{10} (scheme III).[5] Similarly there are many other methods for preparation of substituted 1,2,4-triazoles. Survey of literature reveals that the majority

SCHEME - I



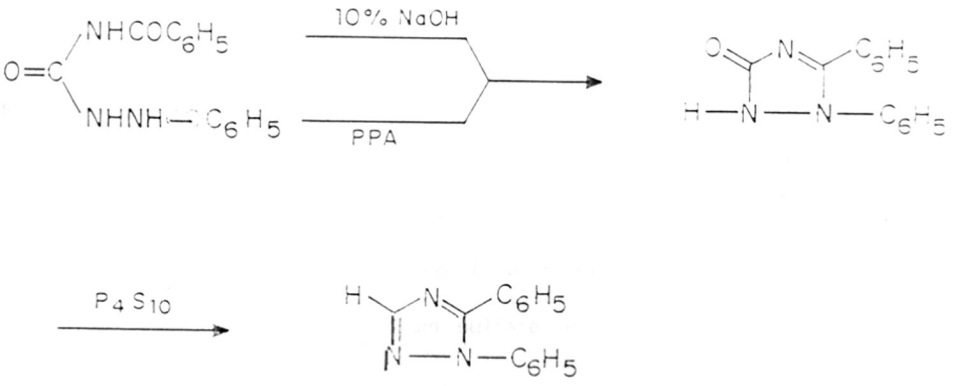
SCHEME - II



1 2

4 3

SCHEME - III



of the studies concerning regiochemistry of alkylation are limited to methylation reactions. Regiochemistry of ribosilylation has also been studied by Witkowski et al. which is described later.

In 1,2,4-triazole with three nitrogens available for electrophilic substitution reaction, N-1, N-2 and N-4 substituted products can be formed (scheme IV). N-1 or N-2 substitution is preferred to N-4. This is due to the α-diaza effect[6,7]. This is observed in compounds having an atom with an unshared pair of electrons in the α-position to the nucleophilic centre. Because of electron-electron repulsion, higher nucleophilicity and hence enhancead reactivity is observed at the nucleophilic centre. This explains the preferential substitution on vicinal nitrogens rather than at N-4 in 1,2,4-triazole nucleus.

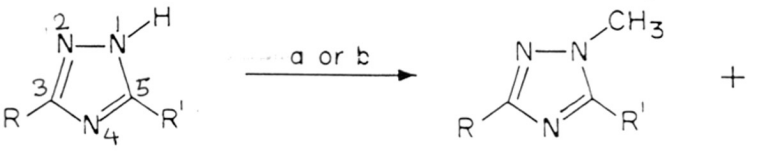
Tautomerism of substituted 1,2,4-triazole derivatives has been investigated by M. Uda and S. Kubota[8a]. It is inferred from the studies that electron withdrawing substituent at C-3 makes 1-H tautomer predominant while electron donating substitutuents like $-OCH_3$ or $-NH_2$ make the 2-H tautomeric form predominant.

Methylations by diazomethane and methyl iodide in 3,5-unsymmetrically disubstituted 1,2,4-triazoles has been carried out[8b]. General procedure for the methylation adopted by M. Uda et al. is as follows:

Methylation with methyl iodide

An appropriate 1,2,4-triazole (0.2 mmol) was weighed into a small glass tube and 1N aqueous sodium hydroxide (1 ml) was added. To this solution was added methyl iodide (0.22 mmol) in ethanol and the glass tube was stoppered tightly and shaken at room temperature for 3 days. The reaction mixture was extracted five times with chloroform. Chloroform extract on drying over sodium sulfate and evaporation gave methylated

SCHEME-IV



1-METHYL ISOMER

2-METHYL ISOMER

4-METHYL ISOMER

a = CH_3I , b = CH_2N_2

product.

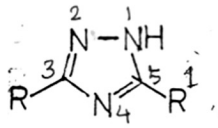
Methylation with Diazomethane

Etherial diazomethane (0.6 mmol) was added to an appropriate 1,2,4-triazole (0.2 mmol) in methanol (5 ml) and mixture was kept at room temperature for 3 days. Evaporation of the solvent gave methylated product.

In reaction with diazomethane the first step is the formation of the diazomethyl cation by abstraction of a proton from a triazole compound while in methylation with methyl iodide SN^2 type displacement reaction involving triazole anion takes place. N-1 or N-2 substitution products are the major regioisomers formed. N-4 substitution products are either not formed or obtained in very low yields. The ratio of N-1 substitution to N-2 substitution product varies in the two types of methylation reactions. Results are tabulated in Table 1. One can visualise how the alkylating agent as well as nature of substituents affect the regiochemical outcome of the alkylation reaction. Atkinson and Polya[1a] also reported N-1 and N-2 alkylated product in 2:1 ratio in methyl iodide methylation of 3-phenyl-1,2,4-triazole. The sodio derivative of 3-phenyl-1,2,4-triazole in methanol was reacted with methyl iodide at 20°. Reaction mixture was then heated at 100° for 12 hrs. Product was isolated by usual work up procedures. The ratio becomes reverse i.e. 1:2 when diazomethane is the alkylating agent. Ainsworth and Jones[9] obtained N-1 and N-2 methylated products in ratio 1:2 on alkylating 3-phthalmidoethyl-1,2,4-triazole with methyl iodide (Table 1).

Table 1

Product ratios on methylation of 3,5-disubstituted 1,2,4-triazoles



M. Uda et al.

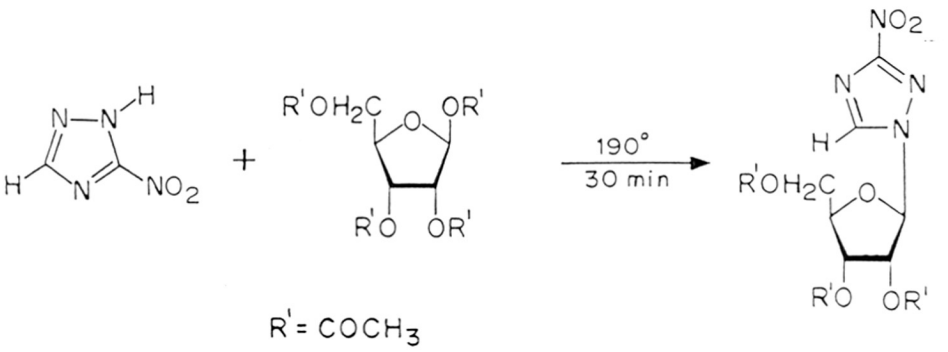
Substituents		Reagent	Yields	Product Ratio		
R	R'	(A or B)	%	1-methyl	2-methyl	4-methyl
S-CH_3	CH_3	A	100	55	34	11
		B	100	42	52	6
Ph	CH_3	A	90	64	32	4
		B	84	58	39	3
-Py	CH_3	A	92	76	21	3
		B	88	62	36	2
-Py	CH_3	A	100	47	43	10
		B	94	12	75	13
-Py	Ph	A	90	20	75	5
		B	85	14	83	3
Alkinson and Polya						
Ph	H	A		66	33	
		B		38	62	
Ph	Me	A		100		
		B		21	79	
Ainsworth						
		A		33	66	

A = methyl iodide B = diazomethane

Extensive work has been carried out by Witkowski et al.[10a-d] Two types of reaction conditions were adopted for ribosilylation. One is the fusion procedure of a substituted triazole and blocked sugar moiety in presence or absence of an acidic catalyst, Bis (p-nitrophenyl) phosphate[11]. In the second method, trimethylsilyl derivative of a substituted 1,2,4-triazole is reacted with O-protected ribofuranosyl bromide. It has been observed that ribosilylation of 3-nitro-1,2,4-triazole gives only N-1 substituted product[10a] (scheme Va) while that of 3-cyano-1,2,4-triazole gives N-1 and N-2 substituted products in the ratio 94:6 by both methods[10b]. In the case of 5-substituted-1,2,4-triazole-3-carboxylic acid esters, N-1 and N-2 substituted products are formed in variable ratios (Table 2)[10c]. Treatment of the trimethylsilyl derivative of methyl 1,2,4-triazole-3 carboxylate with an acyl-blocked ribofuranosyl bromide in acetonitrile at room temperature provides a 1:1 mixture of the two nucleosides (**5**) and (**6**) in greater than 90% yield (scheme Vb). Alternatively acid-catalysed fusion procedure with methyl 1,2,4-triazole-3-carboxylate and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose provided an 85% yield of the same nucleosides (**5**) and (**6**) in 10:1 ratio (scheme Vb). One can visualise from Table 2 that variation of the substituents changes N-1 to N-2 product ratio to a greater extent. Acid catalysed fusion procedure is generally adopted with substituents having electron withdrawing effect suggesting the alkylation of a triazole anion, while the same effect makes direct glycosilylation difficult owing to the decrease in electron density at the pyrimidine type nitrogen atom. These observations clearly indicate that neither steric nor electronic factor of the substituents can alone

SCHEME-V

a.


NO2
H
N
N
H
NO2
R'OH2C
O
OR'
R'O
OR'
190°
30 min
R'= COCH3

b.

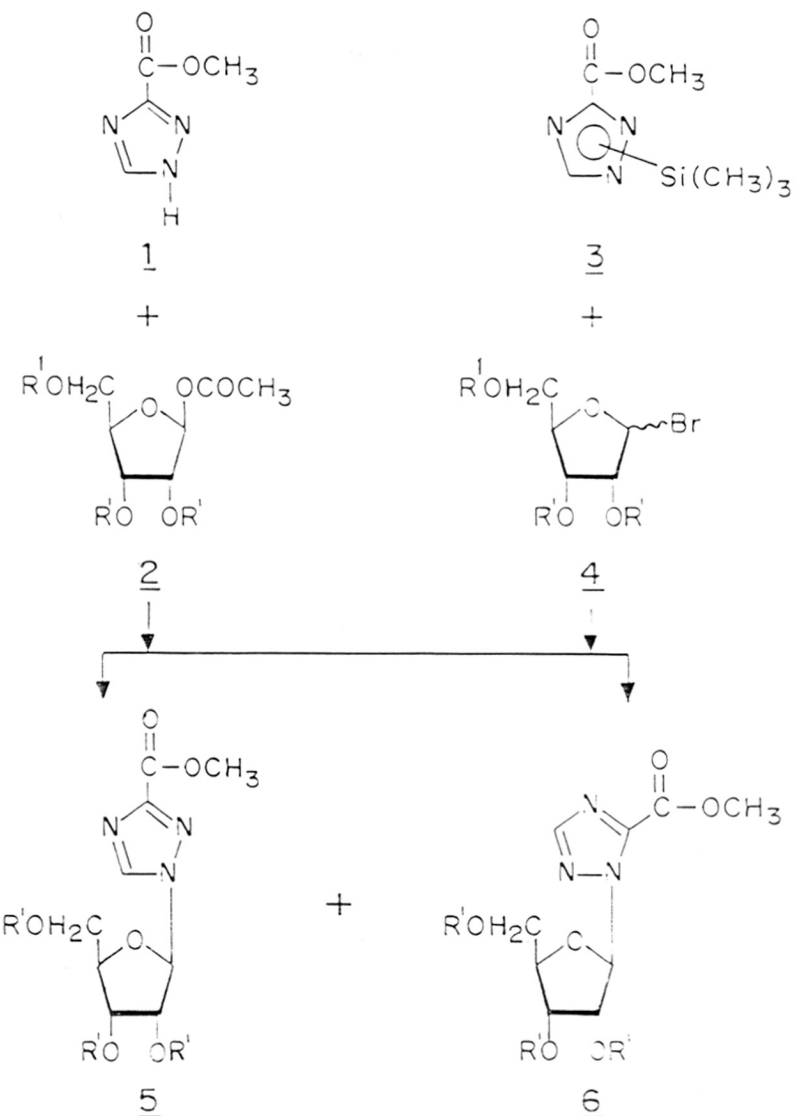
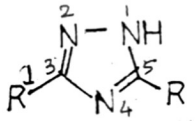

O
C–OCH3
N
N
H
1
Si(CH3)3
3
R'OH2C
OCOCH3
R'O
OR'
2
Br
4
5
6
R' = –C(=O)CH3 , –C(=O)C6H5

Table 2

Product ratio in ribosilylation of substituted 1,2,4-triazole derivative



Substituents R	Substituents R'	Method A or B	Yield in %	Product ratio 1-ribosyl	Product ratio 2-ribosyl
H	$-NO_2$	B		100	
H	CN	A & B		94	6
H	$-\overset{\overset{O}{\|}}{C}-OCH_3$	A		50	50
		B		90	10
Cl	$-\overset{\overset{O}{\|}}{C}-OCH_3$	B	86	36	50
$-NO_2$	$-\overset{\overset{O}{\|}}{C}-OCH_3$	B	77	0	100
CH_3	$-\overset{\overset{O}{\|}}{C}-OCH_3$	B			
NH_2	$-\overset{\overset{O}{\|}}{C}-OCH_3$	A	65	0	100

A = Ribosilylation from trimethylsilyl derivative

B = Fusion procedure

be decisive for or against the formation of a particular regioisomer. Reaction conditions and nature of alkylating agent also greatly affect the regioselectivity of alkylation.

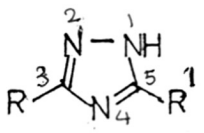
In alkylation of 3-halo substituted 1,2,4-triazoles, formation of all 3 isomers, regardless of nature of alkylating agent has been observed[12]. The yield, however of each isomer was dependent upon the nature of alkylating agent as can be seen from Table 3. Synthesis of N-alkyl-1,2,4-triazoles has also been achieved by phase transfer catalysis[13].

Olofson and Kendall[60] achieved the synthesis of 4-alkyl-1,2,4-triazoles in two steps namely acylation followed by alkylation with powerful oxonium or carboxinium ions as alkylating agents. In the acylation step more nucleophilic N-1 nitrogen gets acylated resulting in alkylation at N-4 nitrogen (scheme VI).

Methods are also available in which the possibility of formation of N-4 substituted product is completely eliminated (scheme VI)[14]. Regiospecific synthesis of 1-alkyl-1,2,4-triazole was successfully effected by Kotone et al.[14a] and Astleford et al.[14b] with 4-amino-1,2,4-triazole as the substrate. Alkylation of 4-amino-1,2,4-triazole results in the formation of triazolium salt which is further deaminated with nitrous acid to give 1-alkyl-1,2,4-triazole (scheme VI).

The above mentioned two synthetic methodologies cannot be applied to substituted 1,2,4-triazoles, since the location of acyl group in the previous method and alkyl group in the later case will again be dependent on the nature of substituents and alkylating agents. Thus one sees that

Table 3

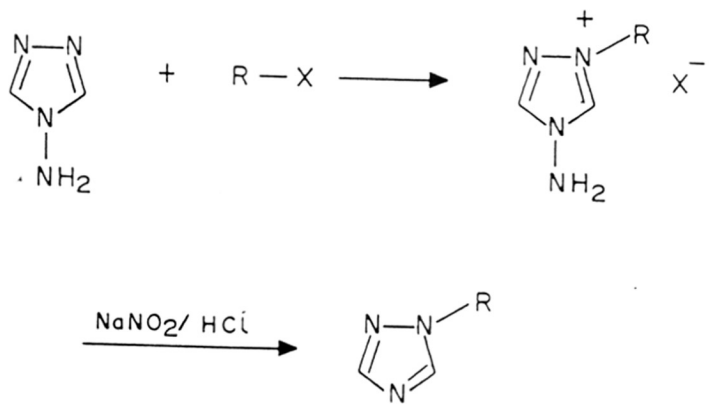


Substituents		Reagents	Yield	Product ratio		
R	R'		%	N-1	N-2	N-4
Br	H	CH_3I	60	56	34	10
		CH_2N_2	70	50	45	5
		$(CH_3)_2SO_4$	70	5	10	85
Br	CH_3	CH_3I	75	55	35	10
		CH_2N_2	70	60	60	10
		$(CH_3)_2SO_4$		8	8	84

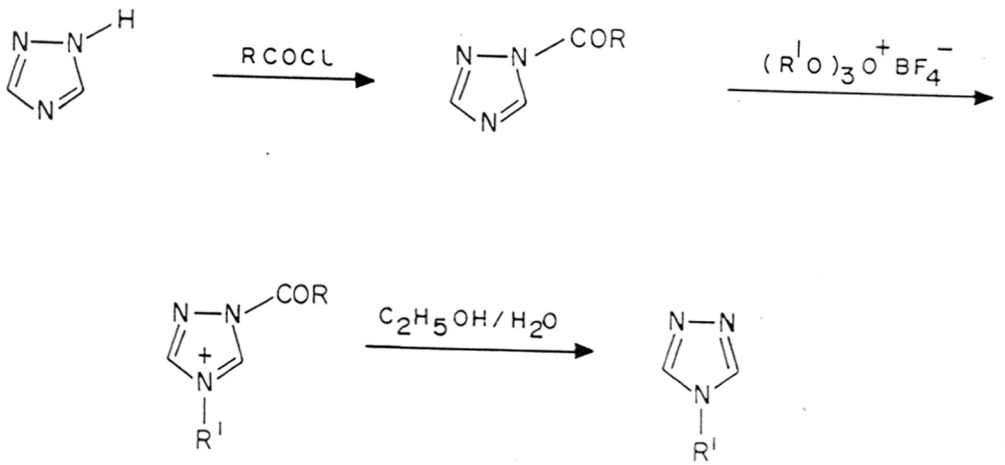
not a single strategy is developed for getting only the particular regio-isomer in alkylation of 1,2,4-triazole derivative with given substituents and alkylating agents.

SCHEME VI

a.



b.



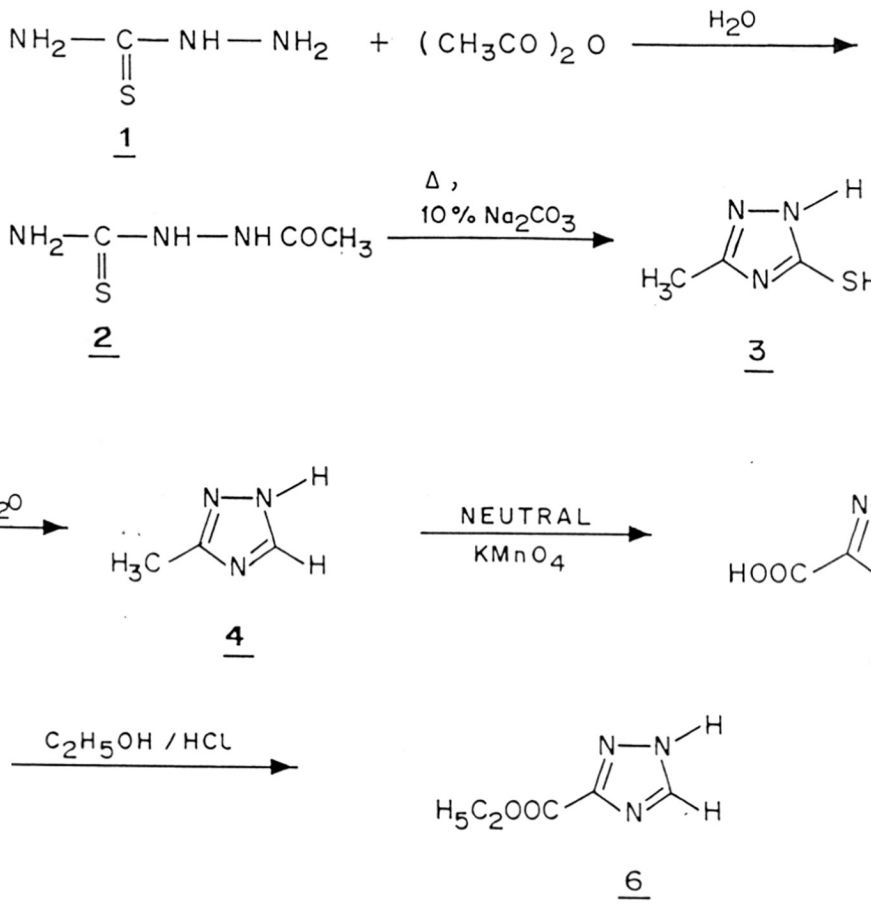
PRESENT WORK

Since our strategy for synthesising the fused bicyclic triazolo systems necessitated as a first step the introduction of appropriate substituents with adequate regio-control, it was decided to first study the regiochemistry of phenacylation of various substituted 1,2,4-triazoles.

The model triazoles chosen were ethyl 1,2,4-triazole-3-carboxylate (**6**), 3-methyl-5-methylthio-1,2,4-triazole (**7**), 3-methyl-5-methylsulfonyl-1,2,4-triazole (**8**) and 3-bromo-5-methyl-1,2,4-triazole (**9**). Thus both electron withdrawing and electron donating groups were considered as well as an electronegative large atom bromine. Another important factor dictating the choice of these models was their ease of convertibility by a sequence of standard straightforward reactions into common derivatives, the structure of which would help in the unambiguous determination of the site of phenacylation. For example, the ester group of (**6**) could later be reduced to methyl and the alkylation product compared with that of 3-methyl-1,2,4-triazole. Similarly, the methylthio group of (7) could be removed by Raney nickel desulfurisation and again the product compared with that of 3-methyl-1,2,4-triazole.

The substituted triazoles were prepared from easily available thiosemicarbazide as starting material. Thus thiosemicarbazide (1) was acylated with acetic anhydride using Wojahn's procedure to give 1-acetyl-thiosemicarbazide (**2**)[15]. Ring closure to 3-methyl-1,2,4-triazoline-5-thione (**3**) was accomplished by heating (**2**) in aqueous alkali[8c]. The mercapto group of (**3**) was removed by nitric acid oxidation to give 3-methyl-1,2,4-triazole (**4**)[16]. Further oxidation with neutral potassium

SCHEME VII


NH2—C(=S)—NH—NH2 + (CH3CO)2O
H2O
1
NH2—C(=S)—NH—NH COCH3
Δ ,
10 % Na2CO3
2
3
HNO3/ H2O
NaNO2
4
NEUTRAL
KMnO4
5
C2H5OH / HCl
6

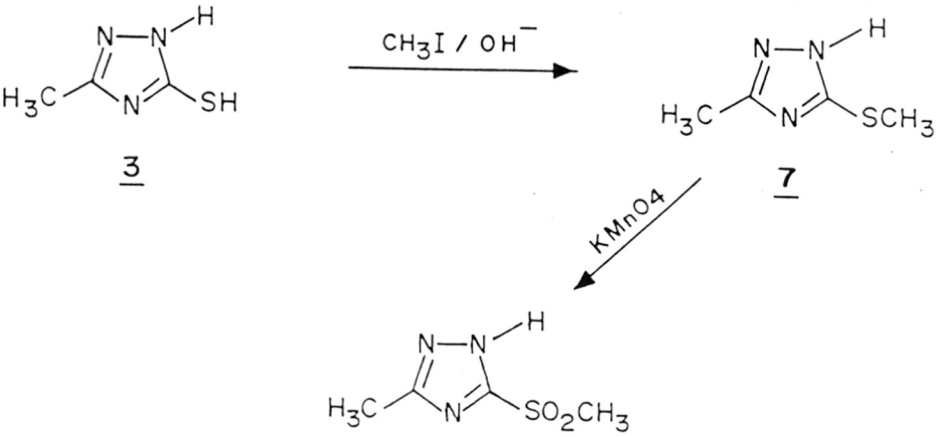
permanganate provided 1,2,4-triazole-3-carboxylic acid (**5**). A suspension of 6.8 g of carboxylic acid (**5**) in ethanol (100 ml) was saturated with hydrogen chloride at 0° and it was stirred for 3 days at room temperature. Ethanol was removed under reduced pressure and residue was treated with saturated aqueous sodium bicarbonate solution when solid ester (**6**) separated out in 50% yield (scheme VII)[17]

3-Methyl-1,2,4-triazoline-5-thione (**3**) was further methylated with methyl iodide in alkaline medium to give the methylthio derivative (**7**)[8b] which on further oxidation with potassium permangnate in acidic medium gave the corresponding sulfone (**8**)[18].

Electrophilic substitution of N-unsubstituted triazole derivatives either with chlorine or bromine gives N-halo derivatives which are halogenating agents. Halogen bonded to nitrogen rearranges itself thermally to carbon. This property is used in the preparation of 3-bromo-5-methyl-1,2,4-triazole (**9**)[19]. Thus bromination of 3-methyl-1,2,4-triazole (**4**) with one molar equivalent of bromine and one molar equivalent of alkali in aqueous solution at 80°C and further heating at 80°C gave (**9**) in 99% yield. Another common method for the preparation of halotriazoles includes diazotisation of 3-amino-1,2,4-triazole to give 3-diazotriazole which on further treatment with a halogen acid gives a halotriazole[20]. Chlorodehydroxylation of triazoline-5-ones with phosphorus oxychloride also yields chlorotriazoles[21].

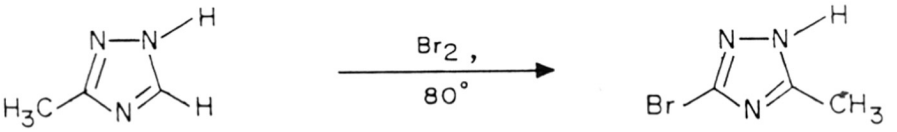
Phenyacylation with phenacyl bromide[28] was carried out in these substituted triazoles and location of the phenacyl group was fixed by correlation of these compounds with each other and performing a few chemical transformations on these phenacylated products.

SCHEME VIII



3 → 7 → 8

SCHEME IX

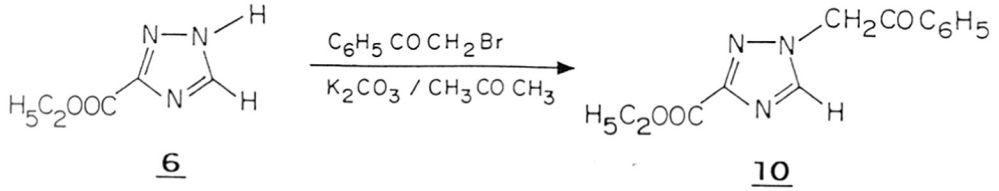


3 → 9

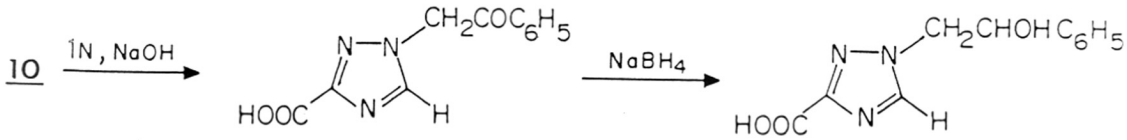
The general procedure adopted for phenacylation was to treat the triazole compound with equimolar quantities of potassium carbonate at 0 to 10° with equimolar quantity of phenacyl bromide and stirring the reaction mixture for 4 to 5 hours. Thus ethyl 1,2,4-triazole-3-carboxylate (**6**) was phenacylated, which after workup gave a crude product (90% yield), was essentially a single compound as seen by its PMR spectrum. The crude product was crystallised from carbon tetrachloride : chloroform (50:50) to give a sharp melting white crystalline solid (m.p.116°) PMR ($CDCl_3$, δ): 1.23 (t, 3H, J=8 Hz), 4.33 (q, 2H, J=8 Hz), 5.73 (s, 2H), 7.56 (m, 3H), 8.00 (dd, 2H, J=6, 2 Hz), 8.3 (s, 1H). As it was difficult to assign the correct structure to the phenacylated product (**10**) just by its PMR, it was hydrolysed in aqueous sodium hydroxide solution to the keto acid (**11**) and then further reduced with sodium borohydride to the hydroxy acid (**12**). Attempts to cyclise this hydroxy acid (**12**) by reactions with (i) p-toluenesulfonic acid and (ii) polyphosphoric acid met with failure, suggesting a 1,3-substitution pattern for phenacyl and ester groups in compound (**10**) (scheme X). Finally an X-ray analysis of compound (**10**) proved it's 1,3-substitution pattern[30].

Taking into consideration the nature of substituted triazoles which we had prepared, we decided to transform phenacylated compounds into C-methyl, N-phenethyl triazoles allowing us to fix the regiochemistry of phenacylation.

SCHEME - X

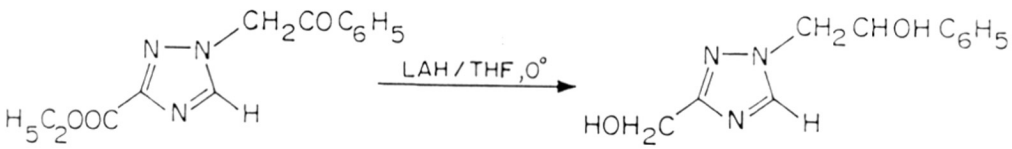


6 10



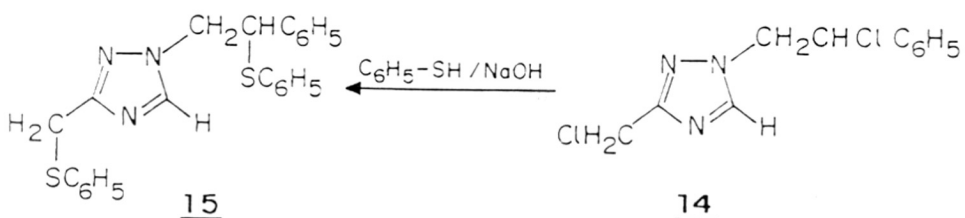
11 12

SCHEME - XI

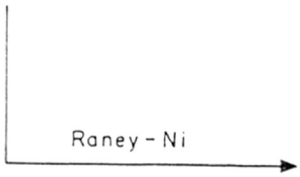


10 13

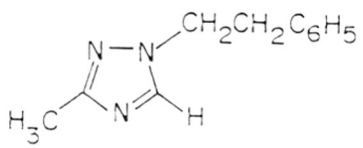
SO_2Cl_2



15 14



Raney - Ni



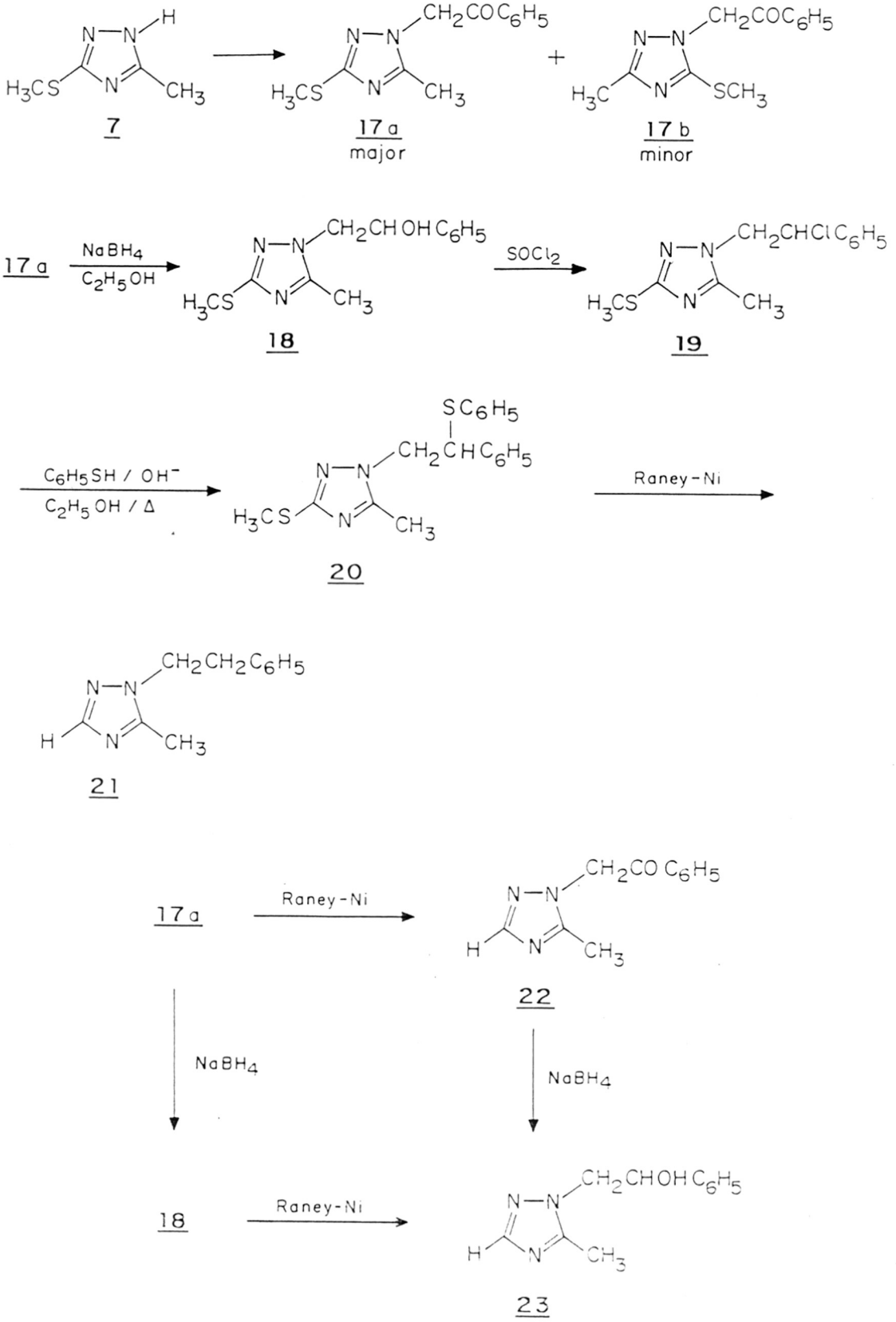
16

Thus compound (**10**) was reduced with lithium aluminium hydride in tetrahydrofuran at 0° to give diol (**13**) in 85% yield (m.p.118°). Treatment of (**13**) in chloroform with thionyl chloride afforded the dichloro analogue as a white crystalline solid (76%, m.p.82-83°) (**14**). Reaction of the dichloro compound with freshly prepared tributyl-tin hydride in persence of azobisisobutyronitrile as a radical initiator gave 3-methyl-1-(2-phenylethyl)-1,2-4 triazole as can be seen by its PMR but the product could not be purified from the traces of tributyl tin moiety accompaying it. Reaction of compound (**14**) with sodium thiophenate in refluxing ethanol for 4 hours gave the di(phenylthio) derivative (**15**) as a thick oil (62%). Desulfurisation was carried out with W-2-Raney nickel as a catalyst on compound (**15**) to give the required 3-methyl-1-(2-phenylethyl)-1,2-4-triazole (**16**) as a colorless oil (86%)[22]. PMR ($CDCl_3$, δ): 2.41 (s, 3H), 3.13 (t, 2H), 4.28 (t, 2H), 7.15 (m, 5H), 7.63 (s, 1H, heteroaromatic proton) (scheme XI)

Later 3-methyl-5-methylthio-1,2,4-triazole (**7**) was phenacylated in a similar way in acetone and potassium carbonate with phenacyl bromide. The crude product (90%) could be visualised as a 80:20 mixture of isomers from the intensity of the methylthio protons in its PMR. Two singlets are seen at 2.56 (80%) and 2.66 (20%) δ.

Crystallisation from benzene-pet.ether (50:50) gave a sharp melting (102°) crystalline compound which was the major isomer. product. PMR ($CDCl_3$, δ): 2.36 (s, 3H), 2.56 (s, 3H), 5.6 (s, 2H), 7.53 (m, 3H), 7.9 (dd, 2H, J=6, 2 Hz). The keto function of compound (**17a**) was reduced with sodium borohydride to give (**18**) in 91% yield as a white solid m.p.123-124°. Reaction of (**18**) with thionyl chloride

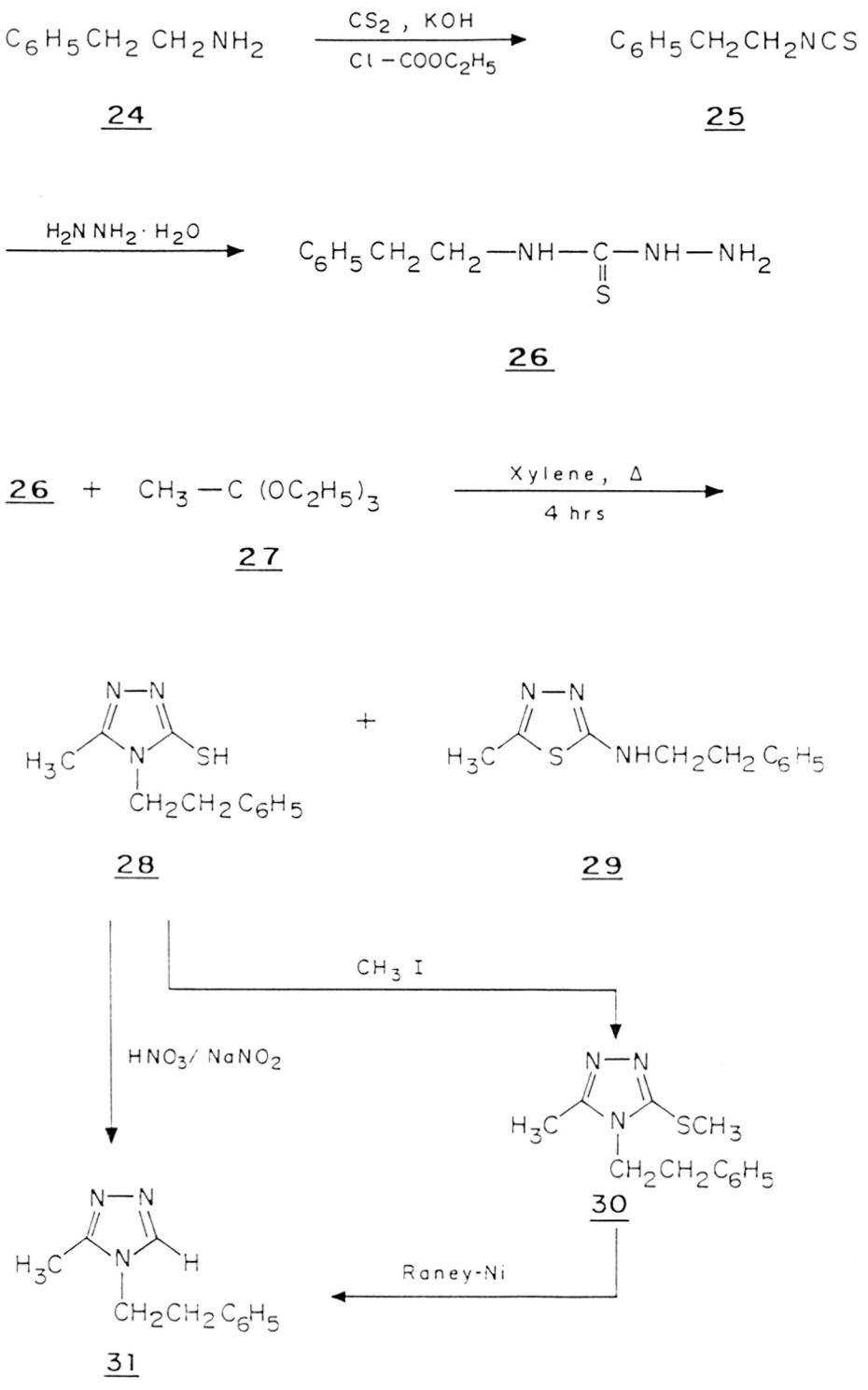
SCHEME - XII


7
17 a
major
17 b
minor
17 a
NaBH4
C2H5OH
18
SOCl2
19
C6H5SH / OH⁻
C2H5OH / Δ
20
Raney-Ni
21
17 a
Raney-Ni
22
NaBH4
NaBH4
18
Raney-Ni
23

gave (19) (95%) as a thick liquid b.p.192° at 2.5 mm. The chloro group was displaced by thiophenyl moiety by reacting (19) with sodium thiophenate in ethanol and refluxing the reaction mixture for 5 hours, (20) was obtained as thick liquid (82%), b.p.200° at 1 mm. Desulfurisation with Raney nickel gave compound (21) as C-methyl-N-phenethyl-1,2,4-triazole by knocking off both methylthio and phenylthio groups. PMR ($CDCl_3$, δ): 1.96 (s, 3H), 3.11 (t, 2H, J=8 Hz), 4.26 (t, 2H, J=8 Hz), 7.15 (m, 5H), 7.82 (s, 1H). Difference observed for methyl and triazole protons in compounds (16) and (21), indicated that most likely the 1,5 substitution pattern or less probable 3,4-substitution pattern for (21), as in alkylation reactions vicinal nitrogens get alkylated in preference to N-4 nitrogen. This also suggested that phenacyl group has entered at the nitrogen which was away from the methylthio group. A remote possibility of N-4 nitrogen getting alkylated was ruled out by synthesising 3-methyl-4-(2-phenylethyl)-1,2,4-triazole (31) by an unambiguous route (scheme XII). Thus compound (21) is 5-methyl-1-(2-phenylethyl)-1,2,4-triazole.

β-Phenethylamine was reacted with carbon disulfide in aqueous alkali to give βphenethyl isothiocyanate (25)[23] which with hydrazine hydrate in ethanol gave 4-phenethyl-3-thisemicarbazide (26)[24]. (26) was cyclised to the triazoline thione (28) by reaction with ethylorthoacetate in refluxing xylene for 5 hrs.[25] 3-methyl-4-(2-phenylethyl)-1,2,4-triazoline-5-thione (28) was methylated with methyl iodide to give methylthio derivative (30) which was then desulfurised with Raney nickel to give 3-methyl-4-phenethyl-1,2,4-triazole (31). Oxidation of (28) with nitric acid also gave (31) (50% yield). 2-Amino (phene-

SCHEME-XIII



24 25 26 27 28 29 30 31

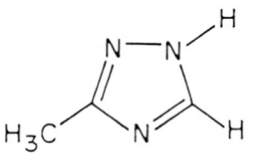
ethyl)-5-methyl-1,3,4-thiadiazole is the side product formed in cyclisation reaction with ethylortho acetate (scheme XIII).

PMR of (**31**) ($CDCl_3$, δ): 2.11 (s, 3H), 2.95 (t, 2H, J=6 Hz), 4.17 (t, 2H, J=6 Hz), 7.24 (m, 5H), 7.88 (s, 1H). This confirms the correct structure assignment to the compound (**21**) as 5-methyl-1-(2-phenylethyl)-1,2,4-triazole.

Further 3-methyl-1,2,4-triazole was phenacylated with phenacyl bromide under identical reaction conditions. Total crude product (90%) obtained as a semisolid was a 60:40 mixture of N-1 and N-2 phenacylated methyl-triazoles. PMR ($CDCl_3$, δ): 2.41, 2.43 (s, 3H), 5.6 (s, 2H), 7.6 (m, 3H), 7.86 (s, 0.4H), 8.0 (dd, 2H, J=6, 2 Hz), 8.13 (s, 0.6H). These regioisomers could not be separated either by crystallisation or by extensive column chromatography hence the total crude phenacylated products were converted to C-methyl-N-phenethyl-1,2,4-triazoles following a similar reaction sequence as adopted for compound (**17a**) (scheme XIV). Separation of regioisomers was not feasible at any of the stages. Total crude product as C-methyl-N-phenethyl-1,2,4-triazole was a mixture of (**21**) and (**16**) in the ratio 40:60. This clearly shows that only vicinal nitrogens were phenacylated and percentage of the compound in which phenacyl group is located away from the methyl group is more than the compound (**22**) in which phenacyl group is at the nitrogen adjacent to the 3-methyl group (scheme XIV).

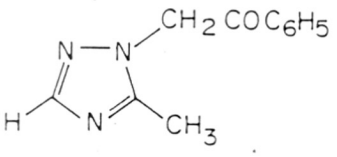
The crude product obtained on phenacylation of (**7**) was desulfurised with Raney nickel to give a mixture of compounds(**22**) and (**32**). The PMR spectsrum was identical with the PMR spectrum of phenacylated 3-methyl-1,2,4-triazole except the intensities of signals for methyl protons

SCHEME - XIV



4

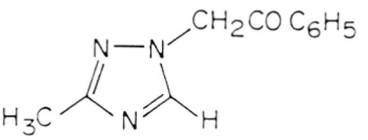
$C_6H_5COCH_2Br$ / K_2CO_3 / CH_3COCH_3



22

40%

+



32

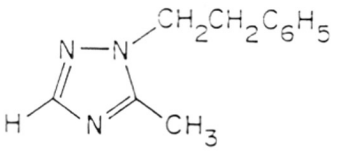
60%

a

b

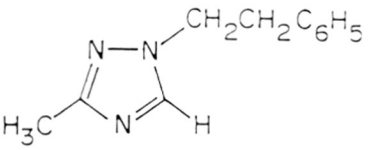
c

d



21

+



16

a = $NaBH_4$

b = $SOCl_2$

c = C_6H_5SH / NaCH / C_2H_5OH

d = W_2 Raney - Ni

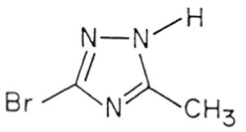
This was much clearer in the PMR spectrum of the sodium borohydride reduction product as the aromatic protons in this compound appear as a singlet. This showed that the minor product formed in phenacylation of (7) was 1-phenacyl-3-methyl-5-methylthio-1,2,4-triazole. Hence in phenacylation only N-1 and N-2 nitrogens are alkylated. The compound (17a) was also desulfurised to give (22) in 80% yield. PMR ($CDCl_3$, δ): 2.46 (s, 3H), 5.56 (s, 2H), 7.53 (m, 3H), 7.73 (s, 1H); 7.8 (dd, 2H). Further, (22) was reduced with sodium borohydride in ethanol to give the hydroxy compound (23) which showed PMR ($CDCl_3$, δ), 2.23 (s, 3H), 4.22 (m, 2H), 5.17 (m, 1H), 7.33 (s, 5H), 7.76 (s, 1H, hetero aromatic proton).

Phenacylation of 3-bromo-5-methyl-1,2,4-triazole (9) gave a single product (33) (90%) m.p.115-117°. In order to determine the structure of (33) it was subjected to hydrogenolysis with 5% palladised charcoal at 50 psi for 18 hours. . Both dehalogenation and reduction took place to give the alcohol (23) (scheme XV).

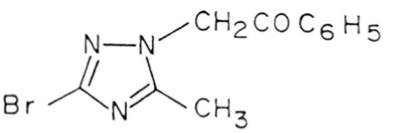
Phenacylation of 3-methyl-5-methylsulfonyl-1,2,4-triazole (8) also gave a single compound (34). Potassium permanganate oxidsation of the phenacylated methylmercapto compound (17a) gave compound (34). Identification of the compound (34) formed by both reactions was done on the basis of mixed melting points and comparison of PMR spectra.

Simple 1,2,4-triazole was also phenacylated to give a single compound 1-phenacyl-1,2,4-triazole (36) (scheme XVI). PMR ($CDCl_3$, δ): 5.7 (s, 2H, N-CH_2), 7.6 (m, 3H), 8.0 (m, a singlet merged inside at 8.0 3H), 8.26 (s, 1H, heteroaromatic proton).

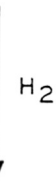
SCHEME XV

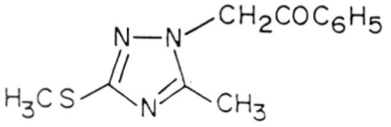


9

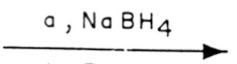


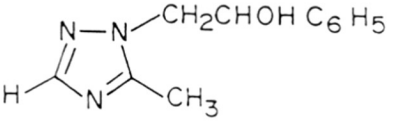
33



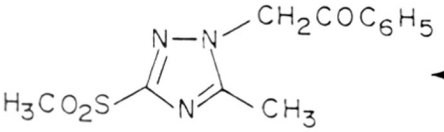


17a

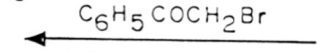


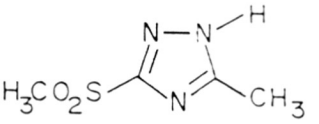


23



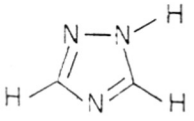
34



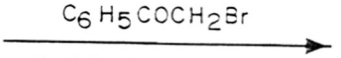


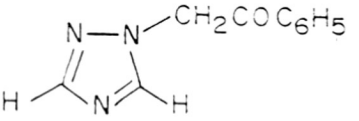
8

SCHEME XVI



35





36

It had been observed that in PMR proton at C-5 appears downfield compared to proton at C-3.[26] Witkowsky and co-workers had assigned the site of ribosilylation in 3-nitro-1,2,4-triazole on the basis of this assignment made for heteroaromatic proton at C-5 as the donwifled proton. Results obtained by us are tabulated in Table 4. One sees that expected deshielding of heteroaromatic proton due to phenacyl group is not observed even in compound (**36**). Heteroaromatic protons at C-3 and C-5 are observed at 8.0δ and 8.26δ while in simple 1,2,4-triazole these protons are located at 8.3δ. For 3-methyl-1,2,4-triazole (**4**) C-5 proton appears at 8.09δ while in compound (**22**) which is a 3-methyl − 1-phenacyl-1,2,4-triazole, C-5 proton is observed at 7.86δ Same effect of sheilding is observed in compound (**10**).

The C-5 proton in compound (**16**)is observed at 7.63δ upfield as compared to C-3 proton at 7.82 in compound (**21**) where the substituent on nitrogen is 2-phenyl ethyl. Thus in these compounds it was not possible to assign the position of N-substitution on the basis of shift of heteroaromatic proton in the PMR spectrum.

C O N C L U S I O N

In phenacylation of substituted 1,2,4-triazoles, occurrence of N-4 substitution was not observed. Phenacylation of compound (**7**) has given N-1 to N-2 substituted products in the ratio 80:20 which M. Uda and co-workers had obtained on methylation of compound (**7**), N-1, N-2, N-4 substituted products in the ratio 55:34:11. Even in compound (**4**) i.e. 3-methyl-1,2,4-triazole where the bulk of the substituent is small both vicinal nitrogens are phenacylated and in the product

Table 4

No.	Compound	No.	PMR, in δ value C-3 proton	C-5 proton	Methyl protons
1.	1,2,4-triazole	35	8.3		
2	1-phenacyl-1,2,4-triazole	36	8.0	8.26	
3	3-methyl-1,2,4-triazole	4		8.09	
4	3-methyl-1-phenacyl-1,2,4-triazole + 5-methyl-1-phenacyl-1,2,4-triazole		7.86	8.13	2.43 ; 2.41
5	3-methyl-5-methylthio-1,2,4-triazole	7			2.43 2.53
6	3-methyl-5-methylthio-1-phenacyl-1,2,4-triazole	17			2.36(-Me) 2.56 (-SMe)
7	5-Methyl-1-phenacyl-1,2,4-triazole	22	7.86		2.43
8	ethyl-1,2,4- (DMSO) 3-carboxylate	6		9.9	
9	ethyl 1-phenacyl-1,2,4-triazole-3-carboxylate	10		8.36	
10.	3-methyl-1-(2-phenylethyl)-1,2,4-triazole	16		7.63	2.41
11	5-methyl-1-(2-phenylethyl)-1,2,4-triazole	21	7.82		1.96
12	3-methyl-4-(2-phenylethyl)-1,2,4-triazole	31		7.88	2.11

that compound in which phenacyl group is located away from the C-methyl substituent is formed to a greater extent. In compounds (**6**), (**8**) and (**9**) where the substituents are bulkier and electron withdrawing, substitution takes place on the nitrogen remote from the substituent. Hence one can conclude that steric factors play comparable role to electronic factor of the substituent in phenacylation reactions of these substituted 1,2,4-triazoles. This also suggests that probably the mechanism of phenacylation reaction under the conditions employed by us involves SN_2 type displacement reaction by a triazole anion. Here in the rate determining step the transition state will favour a minimum steric hindrance giving substitution on nitrogen which is away from the bulkier substituent.

E X P E R I M E N T A L

1-Acetylthiosemicarbazide (2)[15]

Thiosemicarbazide (13.65 g, 0.15 m) was dissolved in hot water (250 ml). To this solution acetic anhydride (15 ml, 0.16 m) was added in small portions with occasional stirring. Reaction was exothermic and was cooled with water intermitantly. The solution was kept overnight at room temperature and then water was completely removed to give a white solid 1-acetylthiosemicarbazide (18 g, 90%), m.p.158°.

IR (Nujol): 3700, 3500, 1700, 1235, 1100 cm^{-1}.

PMR (D_2O, δ): 1.9 (s)

3-Methyl-1,2,4-triazoline-5-thione (3)[8c]

1-Aceatylthiosemicarbazide (18 g, 0.135 m) was taken in 10% aqueous sodium carbonate solution (90 ml) and heated on waterbath for 4 hours. Acidification with concentrated hydrochloric acid on cooling the reaction mixture gave 3-methyl-1,2,4-triazoline-5-thione (13 g, 84%), m.p.281° (lit. m.p.282-283°)[17].

IR (Nujol): 3000, 1600, 1050 cm^{-1}.

PMR (D_2O, δ): 2.3 (s)

3-Methyl-1,2,4-triazole (4)[16]

To sodium nitrite (65 mg) and concentrated nitric acid (6.5 ml) in water (13 ml), 3-methyl-1,2,4-triazoline-5-thione (2.6 g, 0.023m) was added in small quantities with stirring and maintaining the temperature below 40°. Reaction mixture was stirred for half an hour more and was neutralised with solid sodium carbonate. Water was removed completely

under reduced pressure and residue was extracted with ethyl acetate (5 x 30 ml) and the combined extracts evaporated to give 3-methyl-1,2,4-triazole (900 mg, 47%), m.p.95°.

IR (Nujol): 3000 (b), 1190, 1055 cm^{-1}.

PMR (DMSO, δ): 8.35 (s)

1,2,4-Triazole-3-carboxylic acid (5)[17]

A solution of 3-methyl-1,2,4-triazole (8.3 g, 0.1 m) and potassium permangnate (31.6 g, 0.2 m) in water (300 ml) was heated on steam bath for 8 hours. The manganese dioxide formed was removed by filtration and filtrate was concentrated to about 15 ml by heating under reduced pressure. It was then cooled and acidified to pH 1 with concentrated hydrochloric acid; separated solid was filtered, washed with water and dried. The yield of acid was 60% and it melted at 135-7°.

IR (Nujol): 3200, 3000 (b), 1720 cm^{-1}.

Ethyl 1,2,4-triazole-3-carboxylate (6)[17]

A mixture of acid (6.8 g) and ethanol (100 ml) was saturated with hydrogen chloride at 0° and was stirred at room temperature for 3 days. Ethanol was removed and residue was treated with saturated aqueous sodium bicarbonate solution and the solid ester separated was filtered (3.6 g, 50%), m.p.178°.

IR (Nujol): 3000, 1725, 1520, 1260, 1200 cm^{-1}.

PMR (DMSO, δ): 1.5 (t, 3H), 4.56 (q, 2H), 9.9 (s, 1H).

3-Methyl-5-methylthio-1,2,4-triazole (7)[8b]

To the solution of 3-methyl-1,2,4-triazoline-5-thione (2.3 g, 0.02 m) in aqueous 10% sodium hydroxide (0.8 g, 0.02 m) and methanol

(10 ml) was added methyl iodide (2.86 g, 0.02 m) slowly. The solution was stirred overnight. Methanol was removed and aqueous layer was extracted with ethyl acetate after neutralisation with dilute hydrochloric acid, if necessary. Organic extract was then washed with water, brine and dried over sodium sulfate. Solvent was removed to give methylthio derivative in almost quantitative yield. Crystallisation from benzene-pet.ether furnished 3-methyl 5-methylthio-1,2,4-triazole m.p.112° (lit. 113°)[27].

PMR (CCl_4, δ): 2.43 (s, 3H, C-$\underline{CH_3}$), 2.63 (s, 3H, S-CH_3).

3-Methyl-5-methyl sulfonyl-1,2,4-triazole (8)[18]

To the solution of compound (7) (645 mg, 5 mmol) in acetic acid (15 ml) was added a solution of potassium permangnate (1.6 g, 10 mmol) in water (15 ml) during half an hour with occasional cooling. Decolorisation could be observed instantaneously in the beginning. After stirring for 5 hours reaction mixture was filtered and most of the water and acetic acid from filtrate was removed under vacuum. Residue was neutralised with saturated aqueous sodium carbonate solution, then treated with ammonium sulfate and extracted with ethyl acetate (3 x 30 ml). Concentration of the solvent yielded sulfone (360 mg, 45%), m.p.172°.

IR (Nujol): 1600, 1333, 1160, 1140, 1065, 960, 780, 705 cm^{-1}.

PMR (D_2O, δ): 2.4 (s, 3H, -C-$\underline{CH_3}$), 3.3 (s, 3H, -SO_2-$\underline{CH_3}$).

M/e 161, 146, 97, 79, 64.

Analysis: Calcd. for $C_4H_7N_3O_2S$: C, 29.82; H, 4.38; N, 26.08

observed C, 29.49; H, 4.58; N, 25.57%.

3-Bromo-5-methyl-1,2,4-triazole (9)[19]

To the solution of 3-methyl-1,2,4-triazole (1.66 g, 20 mmol) and potassium hydroxide (1.28 g, 20 mmol) in water (20 ml) at 75-80°, bromine-water (10 ml) containing potassium bromide (2.38 g, 20 mmol) and bromine (1.2 ml, 20 mmol) was added slowly with stirring during 20 minutes. Reaction mixture was refluxed further for 2 to 3 hours till bromine color disappeared. On cooling the reaction mixture 3-bromo-5-methyl-1,2,4-triazole separated as a solid (2.99 g, 99%), m.p.167-8°. (lit. 168°)[19].

Preparation of phenacyl bromide[28]

To acetophenone (20 g, 0.13 m) in glacial acetic acid (100 ml) bromine (9 ml, 0·13 m) was added dropwise with constant shaking. After 20 minutes the solution suddenly lightened in colour. It was immediately poured into a large quantity of ice water containing a little sodium carbonate, and kept overnight. The white crystals which separated were recrystallised from 95% alcohol. Yield 80%, m.p.50°.

General procedure for N-phenacylation

Ethyl 1-phenacyl-1,2,4-triazole-3-carboxylate (10)

To ethyl 1,2,4-triazole-3-carboxylate (705 mg, 5 mmol) and potassium carbonate (660 mg, 5 mmol) in acetone (40 ml) at 0 to 10° was added phenacyl bromide (1 g, 5 mmol) during 1 hour. Reaction mixture was stirred further for 4 hours for completion of the reaction. It was then filtered and filtrate evaporated to dryness. Residue was extracted with ethyl acetate, washed with water, brine and

dried over anhydrous sodium sulfate. Evaporation gave crude product (90%) which was essentially a single compound as seen by its p.m.r. spectrum. Crystallisation from CCl_4-$CHCl_3$ gave a sharp melting (m.p.116°) white crystalline compound .

IR (Nujol): 1725, 1698, 1600, 1450, 1335, 1250, 1220, 1050, 1020, 960, 750 cm^{-1}.

PMR ($CDCl_3$, δ): 1.23 (t, 3H, J=8 Hz), 4.33 (q, 2H, J=8 Hz), 5.73 (s, 2H, N-$\underline{CH}_2$), 7.56 (m, 3H), 8.0(dd, 2H, J=6, 2 Hz), 8.36 (s, 1H, heteroaromatic proton).

M/e: 259 (M^+), 231 ($M^+ - C_2H_4$), 214 ($M^+ - OEt$), 105 ($C_6H_5\overset{+}{C}O$), 77.

Analysis: Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05
observed C, 59.99; H, 4.95%.

1-Phenacyl-1,2,4-triazole-3-carboxylic acid (11)

Phenacylated ester (**10**) (251 mg, 1 mmol) was dissolved in methanol (15 ml). To this solution was added aqueous 10% sodium hydroxide solution (0.5 ml, 1.25 mmol) dropwise and reaction mixture was stirred overnight at room temperature. Methanol was removed under reduced pressure and aqueous layer was acidified. Precipitated solid (185 mg, 84%) was filtered, m.p.197°.

IR (Nujol): 3600, 1700, 1460, 1240, 1170, 1150, 1030, 980.

PMR (TFA, δ): 6.3 (s, 2H), 7.8 (m, 3H), 8.13 (dd, 2H), 9.6 (s, 1H).

1-[(2-Hydroxy-2-phenyl)ethyl]-1,2,4-triazole-3-carboxylic acid (12)

To keto acid (**11**) (223 mg, 1 mmol) dissolved in ethanol (60ml) was added sodium borohydride (170 mg, excess) in small portions at 10 to 15°. Reaction mixture was stirred overnight, ethanol was removed on rotary evaporator. Residue was acidified with concentrated hydrochloric acid giving hydroxy acid (**12**) (110 mg, 49%) melting at 192°.

IR (Nujol): 3600, 3150, 1720, 1080, 1050, 920, 880, 840, 730 cm^{-1}.

PMR (DMSO, δ): 5.03 (t, 1H), 7.36 (s, 5H), 8.4 (s, 1H).

3-Hydroxymethyl-1-[(2-hydroxy-2-phenyl)ethyl]-1,2,4-triazole (13)

To lithium aluminium hydride (360 mg, excess) in tetrahydrofuran (25 ml) at 10-15°C, compound **10** (520 mg, 2 mmol) was added during thirty to forty minutes. After stirring for 2 hours excess lithium aluminium hydride was decomposed with small pieces of ice and reaction mixture was filtered. Filtrate was saturated with ammonium sulfate and separated tetrahydrofuran layer was evaporated to dryness to give the dihydroxy compound in 85% yield. Crystallisation from chloroform gave white solid (m.p.118°).

IR (Nujol): 3400-3200 (broad), 1530, 1200, 1060, 1020 cm^{-1}.

PMR (acetone): 3.9 (d, 2H, J=6 Hz), 4.16 (s, 2H), 4.73 (t, 1H, J=6 Hz), 6.9 (s, 5H), 7.7 (s, 1H) δ.

M/e: 219 (M^+), 176, 113, 91, 77, 28.

Analysis: Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98

observed C, 59.99; H, 5.90%.

General procedure for converting hydroxy compound into chloro compound with thionyl chloride

3-Chloromethyl-1-[(2-chloro-2-phenyl)ethyl]-1,2,4-triazole (14)

Diol (**13**) (278 mg, 1.3 mmol) was taken in dry chloroform (25ml) and to this was added thionyl chloride (1 ml, excess) at 10-15° with stirring. As the reaction proceeds a clear solution is slowly formed. After stirring for 4 hours at room temperature, chloroform and excess thionyl chloride were removed. Residue was extracted with chloroform, washed with water till neutral, then with brine. Chloroform extract after drying over sodium sulfate was evaporated to give the dichloro derivative (**14**) (76%, m.p.83°).

IR (Nujol): 1510, 1455, 1445, 1340, 1260, 1210, 1150, 1035, 770, 750, 700, 640 cm^{-1}.

PMR ($CDCl_3$, δ) 4.53 (d, 2H, J=6 Hz), 4.60 (s, 2H), 5.26 (t, 1H, J=6 Hz), 7.3 (s, 5H), 7.8 (s, 1H).

M/e: 255, 220, 193, 138, 125(B), 105, 89, 77.

Analysis: Calcd. for $C_{11}H_{11}Cl_2N_3$: C, 51.56; H, 4.297; Cl, 27.74

observed: C, 51.75; H, 4.38; Cl, 27.34%.

General procedure for the preparation of phenylthio derivative from the chloro compound.

1-[(2-Phenyl-2-(phenylthio)ethyl]-3-(phenylthio)methyl -1,2,4-triazole(15)

Dichloro compound (**14**) (180 mg, 0.7 mmol) and thiophenol (170 mg, 1.54 mmol) and aqueous concentrated solution of sodium hydroxide (65 mg, 1.62 mmol) in ethanol (20 ml) were refluxed together for 9 hours under nitrogen atmosphere. Ethanol was removed and residual

portion was extracted with ethyl acetate. Extract was washed with water till neutral, then with brine and dried over sodium sulfate. The solvent was removed to get a thick oil (269 mg) in 95% yield. It was purified by silica gel column chromatography using benzene–pet.ether (4:1) as eluent to give pure compound (175 mg) in 62% yield.

IR (liquid film): 1665, 1585, 1515, 1480, 1440, 1330, 1200, 1030, 950, 740, 690 cm^{-1}.

PMR (CCl_4, δ): 4.03 (d, 4H), 4.3 (m, 1H), 7.0 (m, 15H), 7.8 (s, 1H).

M/e: 403 (M^+), 212, 194, 183, 117.

Analysis: Calcd. for $C_{23}H_{21}N_3S_2$: C, 68.47; H, 5.25; S, 13.4
observed C, 68.03; H, 5.58; S, 12.97%

General procedure for desulfurisation of phenylthio derivative with Raney nickel catalyst

3-Methyl-1-(2-phenyl ethyl)-1,2,4-triazole (16)

The di(phenylthio) derivative (15) (140 mg, 0.35 mmol) was taken in acetone:alcohol (9:1) mixture (40 ml) and W-2 Raney nickel catalyst (1.8 g) was added to it in portions. It was stirred for 12 hours then filtered. Filtrate was evaporated to give 3-methyl-1-(2-phenylethyl)-1,2,4-triazole (56 mg, 86%) as a thick oil. Purification on silica gel column using benzene–pet.ether as eluent afforded pure compound, b.p. 169-70°/3.5 mm (bath temp.).

IR (liquid film):1520, 1450, 1435, 1310, 1190, 1030, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.41 (s, 3H), 3.13 (t, 2H, J=8 Hz), 4.28 (t, 2H, J=8 Hz), 7.15 (m, 5H), 7.63 (s,1H, heteroaromatic proton).

M/e: 187 (M^+), 155, 118, 105, 104, 91, 77, 69.

Analysis: Calcd. for: $C_{11}H_{13}N_3$: C, 70.56; H, 7.00

observed: C, 70.60; H, 6.95 %.

5-Methyl-3-methylthio-1-phenacyl-1,2,4-triazole (17a)

5-Methyl-3-methylthio-1,2,4-triazole (**7**) was phenacylated with phenacyl bromide as per the procedure adopted for preparation of compound (**10**). Total crude product (90%) showed a major isomer (80%) in its PMR spectrum. Crystallisation from benzene, pet.ether (1:1) gave a sharp melting (102°) crystalline compound.

IR (Nujol): 1695, 1600, 1520, 1490, 1430, 1350, 1225, 1000, 840, 780, 755, 720.

PMR ($CDCl_3$, δ): 2.36 (s, 3H), 2.56 (s, 3H, S-$\underline{CH_3}$), 5.6 (s, 2H), 7.53 (m, 3H), 7.9 (dd, 2H, J=6, 2 Hz).

M/e: 246 (M^+ -1), 219, 105 ($C_6H_5\overset{+}{C}O$), 77, 51, 28.

Analysis: Calcd. for: $C_{12}H_{13}N_3OS$: C, 58.29; H, 5.30

observed C, 58.39; H, 5.60%.

General procedure for sodium borohydride reduction of phenacylated compounds

1-[(2-Hydroxy-2-phenyl)ethyl]-5-methyl-3-methylthio-1,2,4-triazole (18)

To 5-methyl-3-methylthio-1-phenacyl-1,2,4-triazole (17a) (500 mg, 2 mmol) in ethanol (15 ml) was added sodium borohydride (76 mg, 2 mmol) in about an hour with stirring. Reaction mixture was stirred for 4 to 5 hours and ethanol was distilled off. Residue was extracted with ethyl acetate. Organic layer was washed thoroughly with water, brine and dried over sodium sulfate. The solvent

was evaporated to give hydroxy compound (**18**) almost quantitatively. Crystallisation from benzene– pet.ether (1:1) gave white crystalline needles (m.p.122°).

IR (Nujol): 3250, 1460, 1375, 1290, 1050, 910, 880, 740, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.2 (s, 3H), 2.5 (s, 3H), 4.2 (d, 2H, J=6 Hz), 5.2 (t, 1H, J=6 Hz), 7.3 (s, 5H).

M/e: 249 (M^+), 205, 144, 77, 55, 28.

Analysis: Calcd for $C_{12}H_{15}N_3OS$: C, 57.82; H, 6.07; S, 12.86 observed C, 57.68; H, 6.34; S, 12.94%.

1-[(2-Chloro-2-phenyl)ethyl]-5-methyl-3-methyl thio-1,2,4-triazole (19)

Compound (**19**) was prepared from compound (**18**) by reaction of thionyl chloride as described in the general procedure adopted from compound (**14**). It was obtained in 98% yield as an oil, b.p.192°/2.5 mm (bath temp.).

IR (liquid film): 1660, 1510, 1440, 1280, 1260, 750, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 2.26 (s, 3H), 2.66 (s, 3H), 4.42 (dd, 2H, J=6, 4 Hz), 5.36 (t, 3H, J=6 Hz), 7.42 (s, 5H).

M/e: 266 (M^+), 232, 205, 142, 129, 117, 105, 101, 83, 74.

5-Methyl-3-methylthio-1-(2-(phenylthio) ethyl)-1,2,4-triazole (20)

Compound (**20**) was prepared from compound (**19**) by reacting it with sodium thiophenate in refluxing ethanol as per general procedure given for compound (**15**). The yield was 86% as an oil, b.p.200°/1mm (bath temp.).

IR (liquid film): 1660, 1580, 1480, 1440, 1260, 1050, 1020, 740, 690 cm^{-1}.

PMR (CCl_4, δ): 2.6 (s, 3H), 2.7 (s, 3H), 4.3 (m, 2H), 4.7 (m, 1H), 7.23 (s, 10H).

M/e: 231 ($M^+ - C_6H_5SH$), 117, 97, 77.

Analysis: Calcd. for $C_{18}H_{19}N_3S_2$: C, 63.33; H, 5.61
observed: C, 63.10; H, 5.75%.

5-Methyl-1-(2-phenyl ethyl)-1,2,4-triazole (21)

Raney nickel desulfurisation of compound (**20**) as given for compound (**16**) afforded 5-methyl-1-(2-phenylethyl)-1,2,4-triazole (**21**) in 80% yield b.p.153-154°/3.5 mm (bath temp.).

IR (liquid film): 1520, 1450, 1400, 1275, 1180, 750, 700, 685 cm^{-1}.

PMR ($CDCl_3$, δ): 1.96 (s, 3H), 3.11 (t, 2H), 4.26 (t, 2H), 7.15 (m, 5H), 7.82 (s, 1H, hetero aromatic proton).

M/e: 187 (M^+), 104, 91, 77, 51, 28.

Analysis Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00;
observed C, 70.43; H, 6.97%.

5-Methyl-1-phenacyl-1,2,4-triazole (22)

5-Methyl-3-methylthio-1-phenacyl-1,2,4-triazole (**17**) (247 mg, 1 mmol) and W-2 Raney nickel catalyst (1.8 g) were stirred in a mixture of acetone, ethanol (10 ml, 9:1) at room temperature for 16 hours. Reaction mixture was then filtered and residue washed with acetone. Filtrate on evaporation gave 5-methyl-1-phenacyl-1,2,4-triazole in 80% yield (m.p.121°).

IR (Nujol): 1695, 1620, 1540, 1220, 1190, 1000, 760 cm^{-1}.

PMR ($CDCl_3$, δ): 2.46 (s, 3H), 5.56 (s, 2H), 7.8 (m, 5H), 7.73 (s, 1H).

M/e: 201, 173, 106, 105(B), 77.

Analysis: Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51
observed C, 65.2; H, 5.7%.

1-[(2-Hydroxy-2-phenyl)ethyl]-5-methyl-1,2,4-triazole (23)

Compound (**23**) was prepared by sodium borohydride reaction on compound (**22**) using general procedure adopted for preparation of compound (**18**). Compound (**23**) is obtained in quantitative yield. Crystallisation from benzene-pet.ether (1:1) gave shining white crystalline needles (m.p. 102°).

IR (Nujol): 3350, 1540, 1180, 1060, 860, 770, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.23 (s, 3H), 4.22 (m, 2H), 5.17 (m, 1H), 7.33 (s, 5H), 7.76 (s, 1H, heteroaromatic proton).

M/e: 203 (M^+), 185 ($M^+ - H_2O$), 106, 77.

Analysis: Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45
observed C, 65.14; H, 6.76%.

3-Methyl-1-phenacyl-1,2,4-triazole and 5-methyl-1-phenacyl-1,2,4-triazole[29]

3-Methyl-1,2,4-triazole (**4**) was phenacylated with phenacyl bromide according to general procedure given for compound (**10**). Total crude product was obtained as a semisolid (90%). PMR spectrum shows that it contains 40% of compound (**22**).

PMR ($CDCl_3$, δ): 2.41, 2.43 (two s, 3H), 5.6 (s, 2H), 7.6 (m, 3H), 7.86 (s, 0.4H), 8.0 (dd, 2H, J=6, 2Hz), 8.13 (s, 0.6H).

3-Methyl-1-(2-phenylethyl)-1,2,4-triazole (16) and 5-methyl-1-(2-phenylethyl)-1,2,4-triazole (21)

The mixture of 3-methyl-1-phenacyl-1,2,4-triazole (60%) and 5-methyl-1-phenacyl-1,2,4-triazole (**22**) (40%) was converted into the mixture of 3-methyl-1-(2-phenylethyl)-1,2,4-triazole (**16**) (60%) and 5-methyl-1-(2-phenyethyl)-1,2,4-triazole (**21**) (40%) as shown in scheme XIII by general procedures adopted for (a) sodium borohydride reduction (b) thionyl chloride reaction (c) reaction with sodium thiophenate and desulfurisation with Raney nickel catalyst. Identification is based on comparison of the PMR spectra.

3-Bromo-5-methyl-1-phenacyl-1,2,4-triazole (33)[29]

To 3-bromo-5-methyl-1,2,4-triazole (**9**) (700 mg, 4.3 mmol) and potassium carbonate (600 mg, 4.4 mmol) in acetone (60 ml) was added phenacyl bromide (890 mg, 4.4 mmol) at 10-15° during 1 hour. After stirring for 4 hours reaction was worked up as described previously to give phenacylated product (**33**) (1.04 g, 90%), m.p.115-7°.

IR (Nujol): 1690, 1280, 1225, 1000, 750, 680, 620 cm^{-1}.

PMR ($CDCl_3$, δ): 2.36 (s, 3H), 5.5 (s, 2H), 7.53 (m, 3H), 7.9 (dd, 2H, J=6, 2 Hz).

M/e: 279 (M^+), 251, 172, 105, 77.

Analysis Calcd. for $C_{11}H_{10}BrN_3O$: C, 35.87; H, 3.58 .
observed: C, 35.71; H, 3.35%.

1-[(2-Hydroxy-2-phenyl)ethyl]-3-methyl-1,2,4-triazole (23)

3-Bromo-5-methyl-1-phenacyl-1,2,4-triazole (**33**) (200 mg, 0.7 mmol) in ethanol:water (15 ml, 2:1) and sodium acetate (100 mg, 1.22 mmol) were shaken with 15% palladium on carbon (100 mg) on a Parr hydrogenation apparatus at 50 psi for 12 hours at room temperature. Reaction mixture was filtered and filtrate evaporated to dryness. Residue was extracted with ethyl acetate. Organic extract washed with water followed by brine and dried over anhydrous sodium sulfate. The solvent was evaporated to give compound (**23**) (87 mg, 62%) m.p.102°.

IR (Nujol): 3350, 1540, 1180, 1060, 860, 770, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.23 (s, 3H), 4.22 (m, 2H), 5.17 (m, 1H), 7.33 (s, 5H), 7.76 (s, 1H, heteroaromatic proton).

5-Methyl-3-methylsulfonyl-1-phenacyl-1,2,4-triazole (34)

3-Methyl-5-methylsulfonyl-1,2,4-triazole (**8**) (240 mg, 1.5 mm) was phenacylated with phenacyl bromide using general procedure to give compound (**34**) in 99.2% yield (411 mg) crystallisation from benzene gave sharp melting solid m.p.120°.

IR (Nujol): 1695, 1600, 1515, 1465, 1315, 1220, 1140, 985, 950, 835, 820, 760 cm^{-1}.

PMR ($CDCl_3$, δ): 2.43 (s, 3H), 3.2 (s, 3H, $-SO_2\underline{CH}_3$), 5.7 (s, 2H), 7.56 (m, 3H), 8.0 (dd, 2H, J=6, 2 Hz).

Analysis Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.69

observed C, 51.33; H, 4.61%.

5-Methyl-3-methylsulfonyl-1-phenacyl-1,2,4-triazole (34)

5-Methyl-3-methylthio-1-phenacyl-1,2,4-triazole (**17**) (500 mg, 2.02 mmol) was dissolved in acetic acid (3 ml). To this was added solution of potassium permangnate (646 mg, 4.10 mm) in water (6 ml) slowly and reaction mixture was stirred for 3 hours. Excess potassium permangnate was decomposed with sodiumbisulfite. Reaction mixture was filtered. Filtrate concentrated under reduced pressure and then extracted with ethyl acetate. After washing with water, brine, it was dried over sodium sulfate. Concentration of the organic extract gave compound (**34**) (510 mg, 88%). Crystallisation from benzene gave crystalline solid m.p.120°.

2-(Phenyl) ethyl isothiocyanate (25)[23].

2-(Phenyl) ethylamine (21.78 g, 0.18 m) was added with stirring to a mixture of carbon disulfide (11 ml, 0.18 m) and sodium hydroxide (7.2 g, 0.18 m) in water (16 ml) below 10-15° during half an hour. The mixture was warmed gently on steam bath for 2 hours to ensure complete reaction. The bright orange red coloured solution was then cooled to room temperature and ethyl chloroformate (17.5 ml, 0.18 m) was added to it during 1 hour. After stirring for 30 minutes more, the organic layer was separated, dried over sodium sulfate and distilled at 95°/0.5 mm to give 2-phenylethyl isothiocyanate (25 g) in 85% yield.

IR (liquid film): 2190, 2100, 1350, 1350, 750, 700 cm^{-1}.

4-[(2-Phenyl)ethyl]-3-thiosemicarbazide (26)[24]

To hydrazine hydrate (80%) (1.7 ml) in ethanol (10 ml) at 10-15° was added, 2-(phenyl)ethyl isothiocyanate (4.21 g, 25 mmol) in ethanol (10 ml) slowly with stirring. Solid thiosemicarbazide precipitated out just within 10 to 15 minutes. Stirring was continued further for half an hour and the solid was then filtered (3.5 g, 75%). Crystallisation from ethanol gave shining white needles m.p.114°.

IR (Nujol): 3300, 3200, 1670, 1545, 1260, 1195, 1000, 745, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.86 (t, 3H), 3.73 (t, 3H), 7.16 (s, 5H)

3-Methyl-4-(2-phenyl ethyl)-1,2,4-triazoline-5-thione (28)

Thiosemicarbazide (**26**) (3.5 g, 0.018 m) and ethyl orthoacetate (**27**) (2.9 g, 0.018 m) in xylene (40 ml) were refluxed for 4 hours. Xylene was removed by distillation. Residue was taken in 10% aqueous sodium hydroxide solution and alkaline layer was separated. It was then cooled and acidified with dilute hydrochloric acid. Precipitated solid was filtered (2.1 g, 53%). Crystallisation from benzene: pet.ether (1:1) gave thione (**28**) m.p.157°.

IR (Nujol): 1580, 1510, 1420, 1380, 1360, 1245, 1180, 740, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 1.8 (s, 3H), 3.03 (t, 2H, J=6 Hz), 4.1 (t, 2H, J=6 Hz), 7.13 (m, 5H).

M/e: 219 (M^+), 104, 91, 77, 28, 186.

Analysis: Calcd. for $C_{11}H_{13}N_3S$: C, 60.26; H, 5.98; N, 19.15

observed C, 59.64; H, 6.31; N, 18.85 %.

3-Methyl-5-methylthio-4-(2-phenyl ethyl)-1,2,4-triazole (30)

Thione (**28**) (1.1 g, 5 mmol) was dissolved in sodium hydroxide (200 mg, 5 mmol) aqueous solution. Methyl iodide (0.35 ml, 5.6 mmol) in methanol (10 ml) was added to it. The solution was kept overnight. Methanol was removed and residue was extracted with ethyl acetate. It was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed to give oil (1.126 g, 96%) b.p.208°/0.5 mm.

IR (liquid film): 1570, 1525, 1180, 760, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 2.0 (s, 3H), 2.66 (s, 3H), 3.0 (t, 3H, J=6Hz), 4.03 (t, 3H, J=6 Hz), 7.1 (m, 5H).

3-Methyl-4-(2-phenyl ethyl)-1,2,4-triazole (31)

(a) 3-Methyl-5-methylthio-4-(2-phenyl ethyl)-1,2,4-triazole (**30**) (1.7 g, 7.3 mmol) in acetone, ethanol (30 ml, 9:1) was hydrogenated with Raney nickel catalyst (5.4 g). After stirring for 16 hours reaction mixture was filtered and filtrate evaporated to give 3-methyl-4-(2-phenylethyl)-1,2,4-triazole (**31**) (1 g, 75%) as an oil, b.p.265°/1mm.

PMR($CDCl_3$, δ): 2.11 (s, 3H), 2.99 (t, 2H, J=6 Hz), 4.17 (t, 3H, J=6 Hz), 7.24 (m, 5H), 7.88 (s, 1H, hetero-aromatic proton).

M/e: 187 (M^+), 92, 85, 77, 28.

Analysis Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00

observed C, 70.39; H, 6.91%.

(b) 3-Methyl-4-(2-phenylethyl)-1,2,4-triazoline-5-thione (**28**) (788mg, 3.6 mmol) was added to the stirred solution of nitric acid (1 ml), sodium nitrite (10 mg) and water (2 ml) below 40°. The thione was dissolved with evolution of nitric oxide. After stirring for two hours reaction mixture was neutralised with sodium carbonate and was extracted with ethyl acetate. Ethyl acetate layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated to give compound (**31**) (300 mg, 45%).

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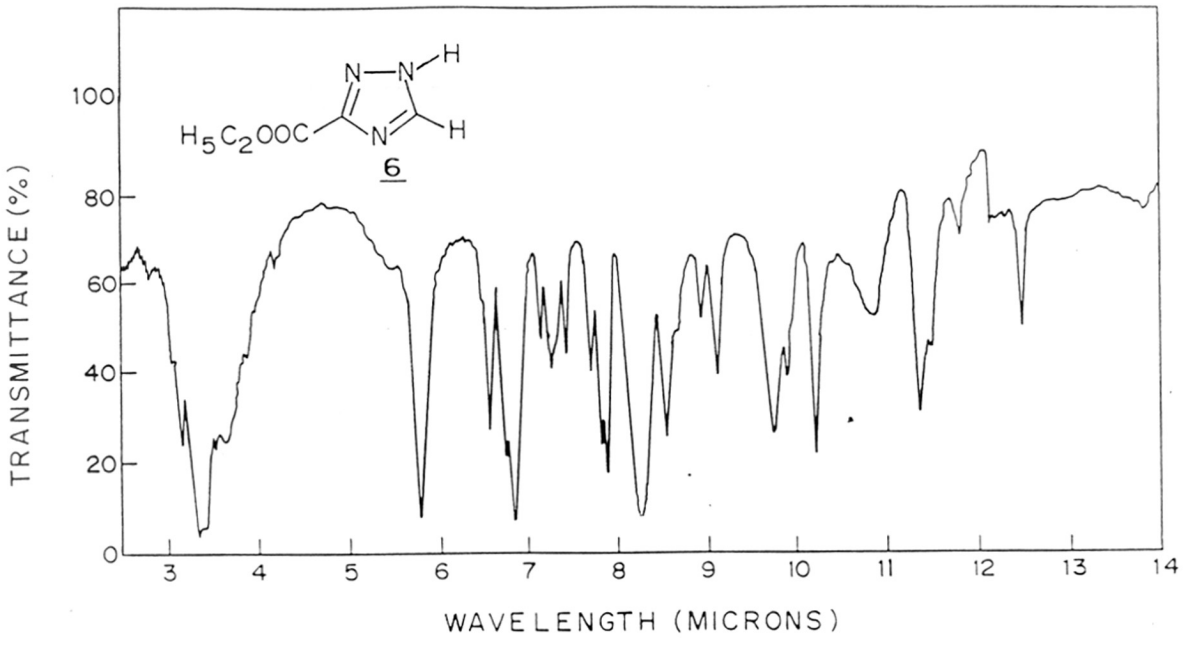
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40
20
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3
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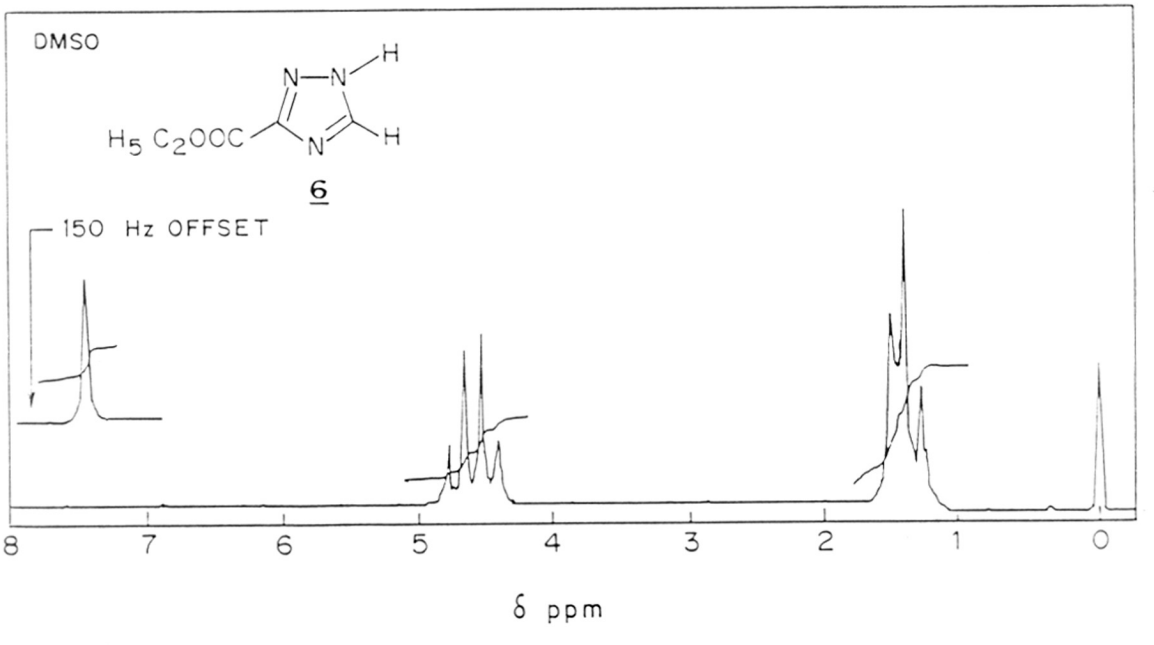
7
8
9
10
11
12
13
14
WAVELENGTH (MICRONS)
H5C2OOC
6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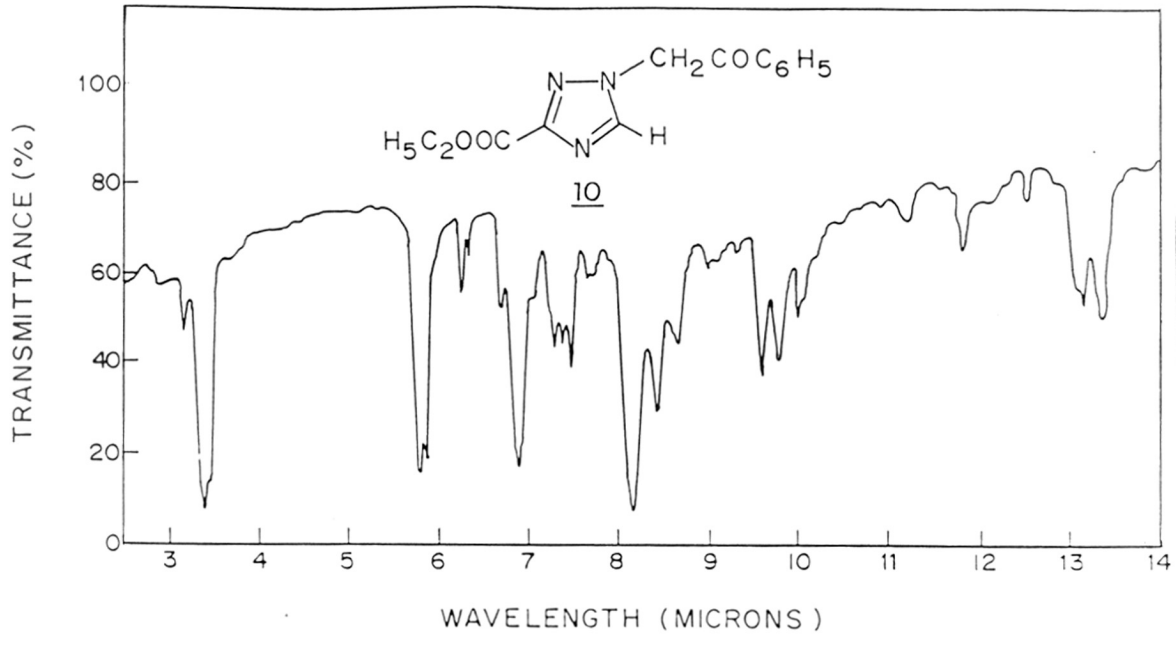
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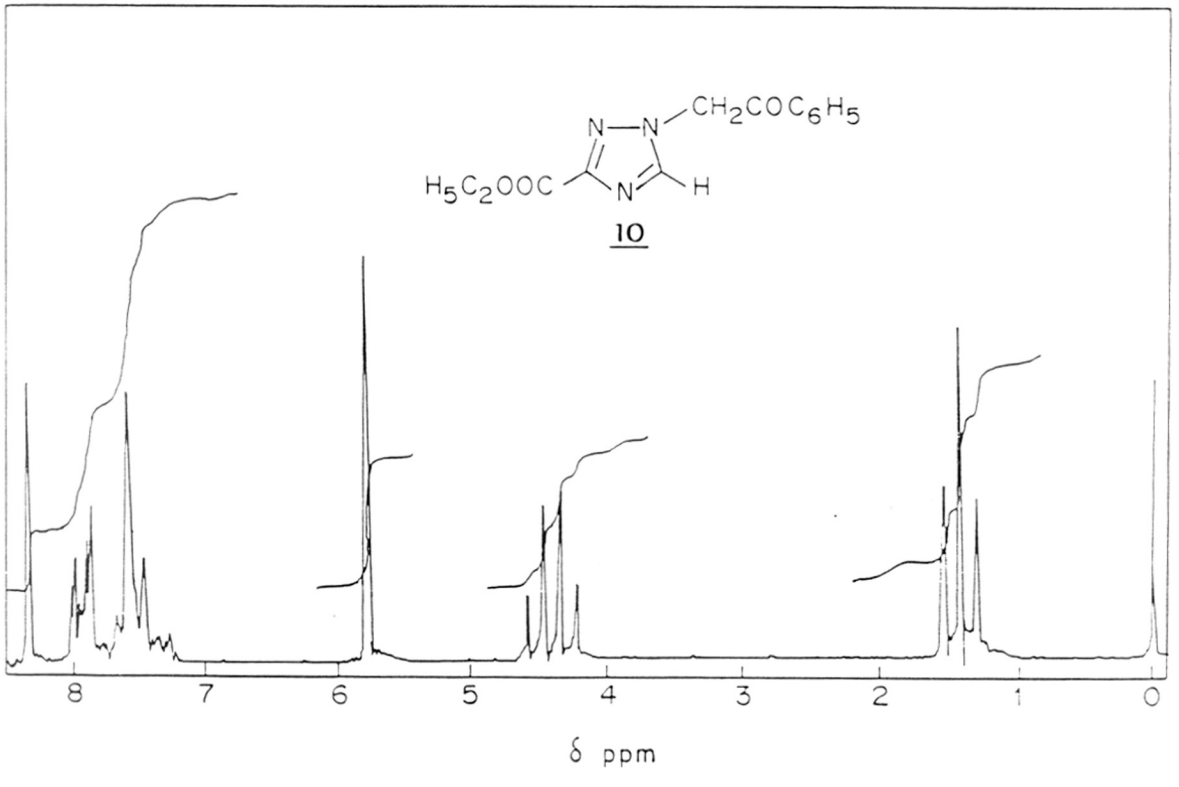
CH2COC6H5
H5C2OOC
N
H

10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N
H
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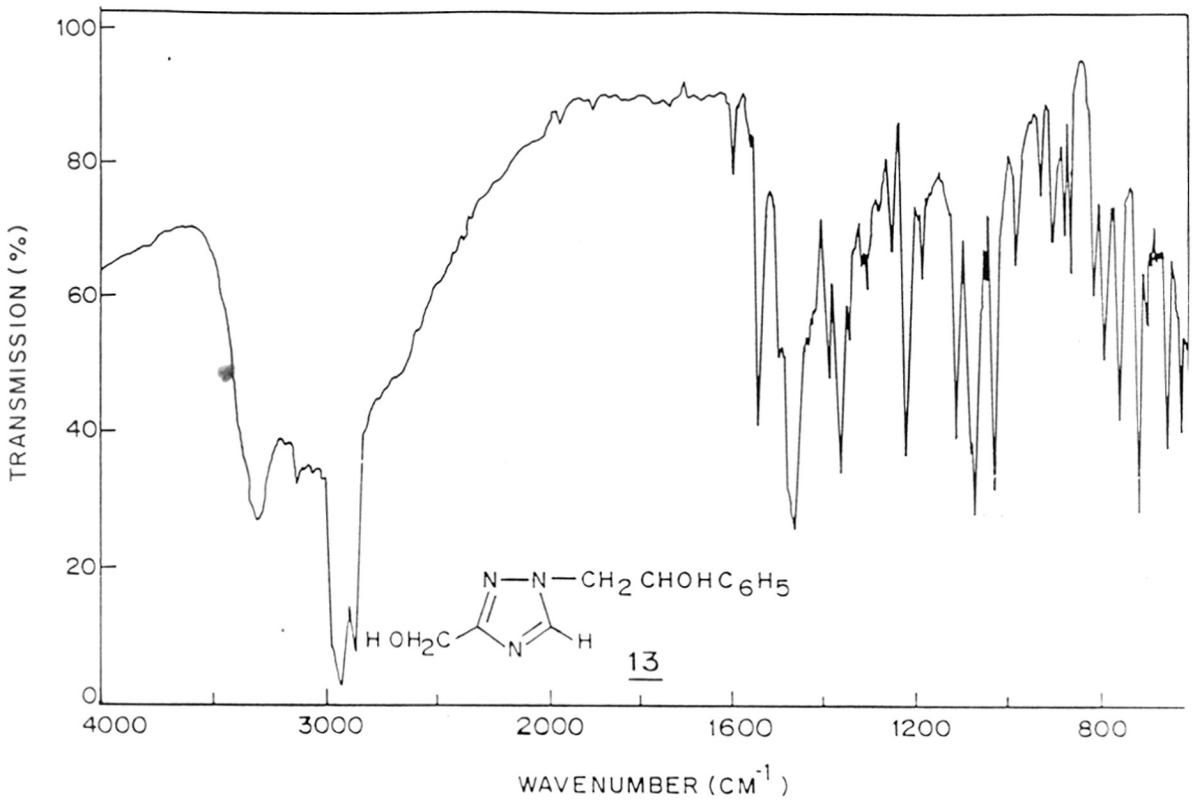
7
6
5
4
3
2
1
0
δ ppm

10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60
40
20
0
TRANSMISSION (%)
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2000
1600
1200
800
WAVENUMBER (CM-1)
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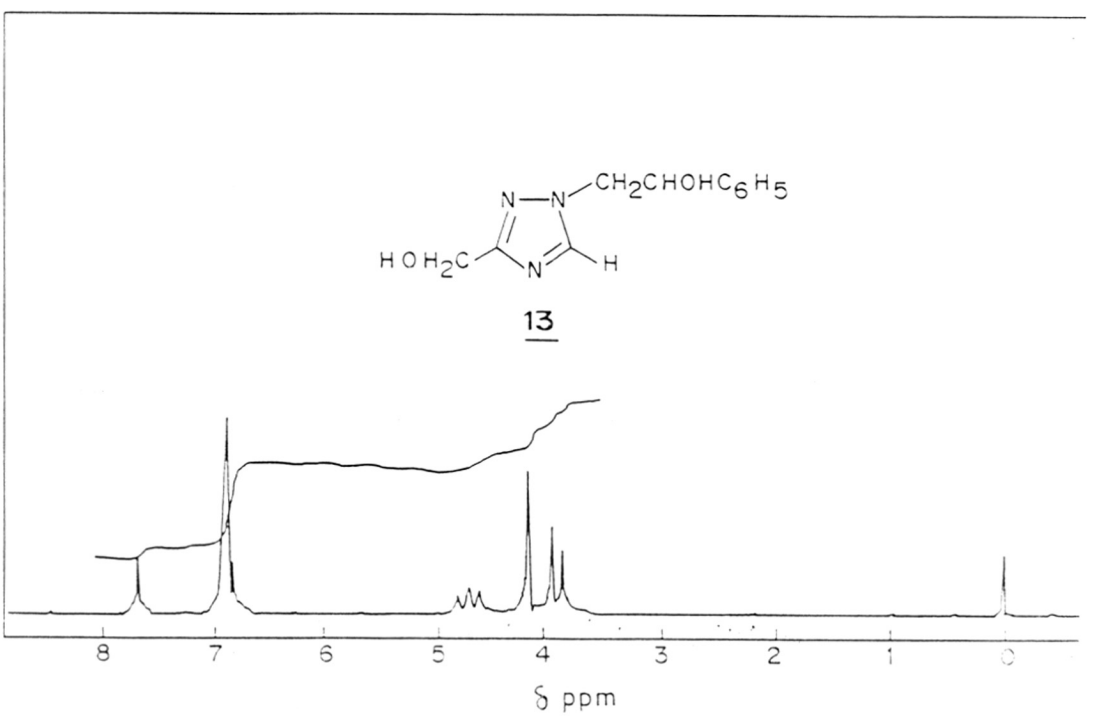
H OH2C
N
H
13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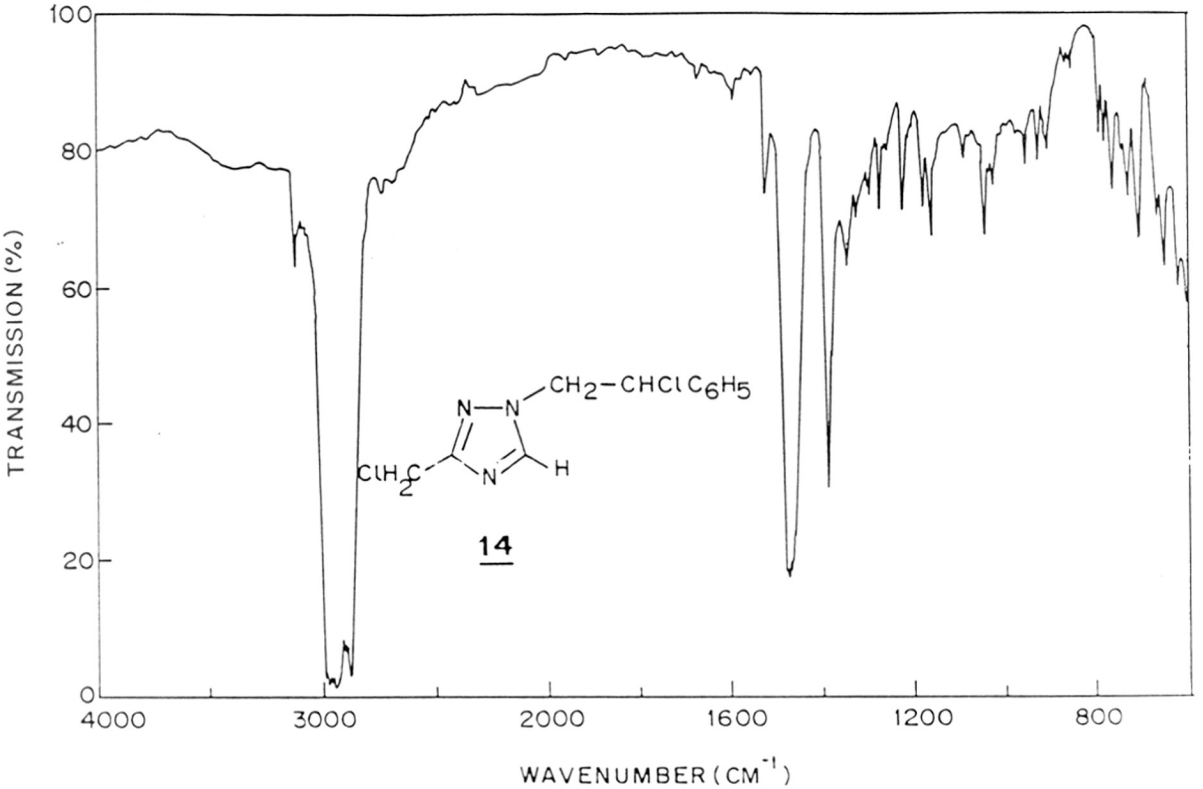
H OH2C
N
H
13
8
7
6
5
4
3
2
1
0
δ ppm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60
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20
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TRANSMISSION (%)
4000
3000
2000
1600
1200
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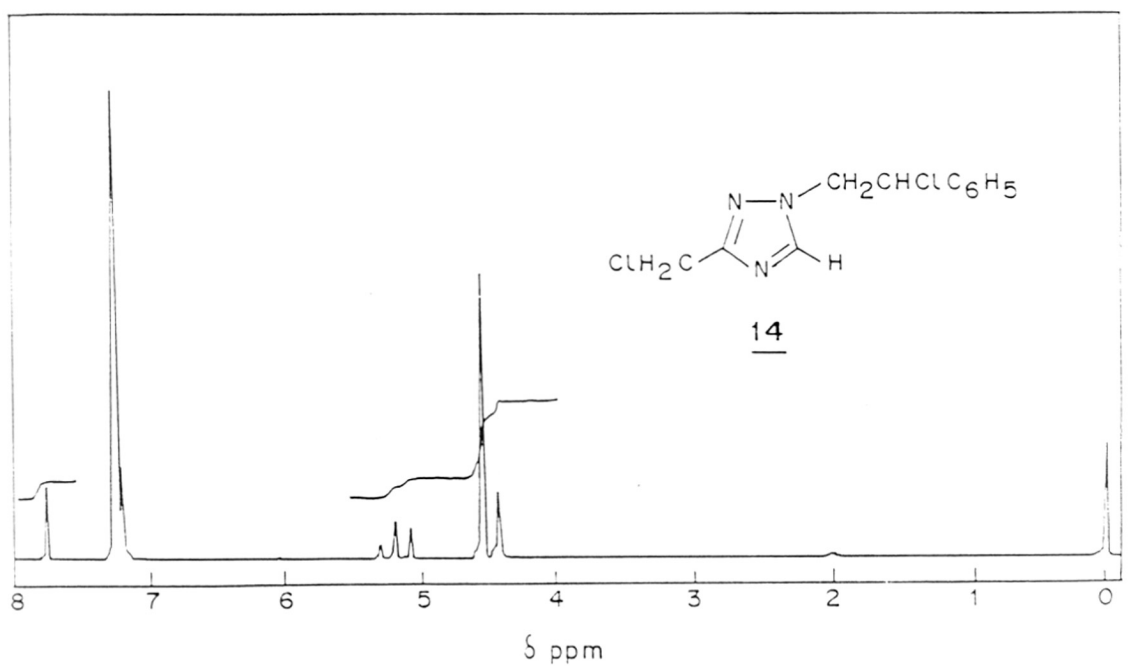
CH2—CHClC6H5
ClH2C
N
H

14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2
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0
δ ppm
N—N
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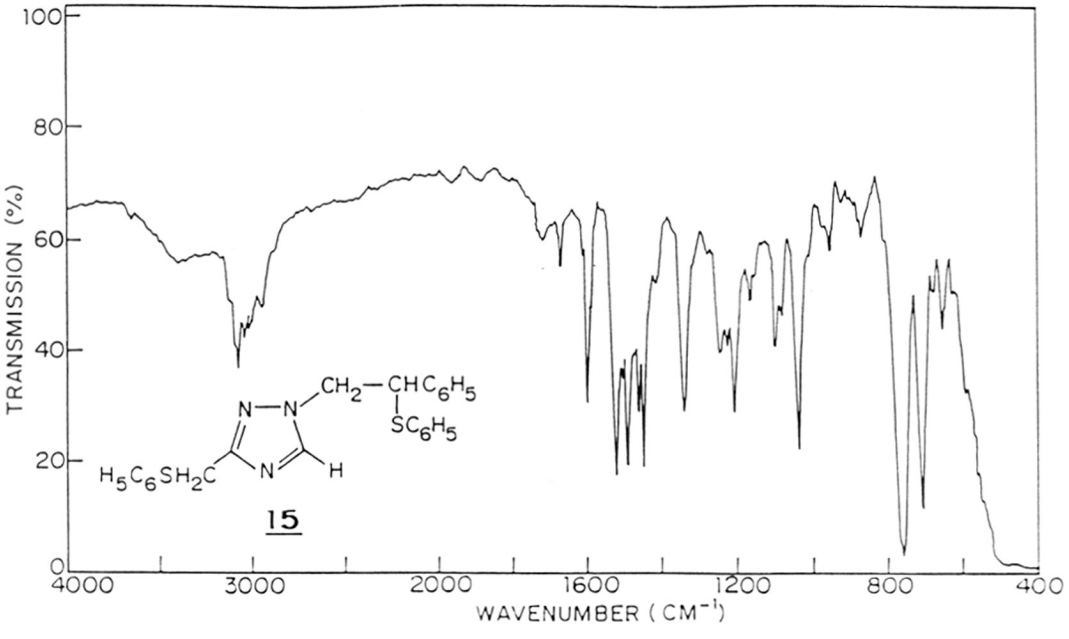
ClH2C
N
H

14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TRANSMISSION (%)
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2000
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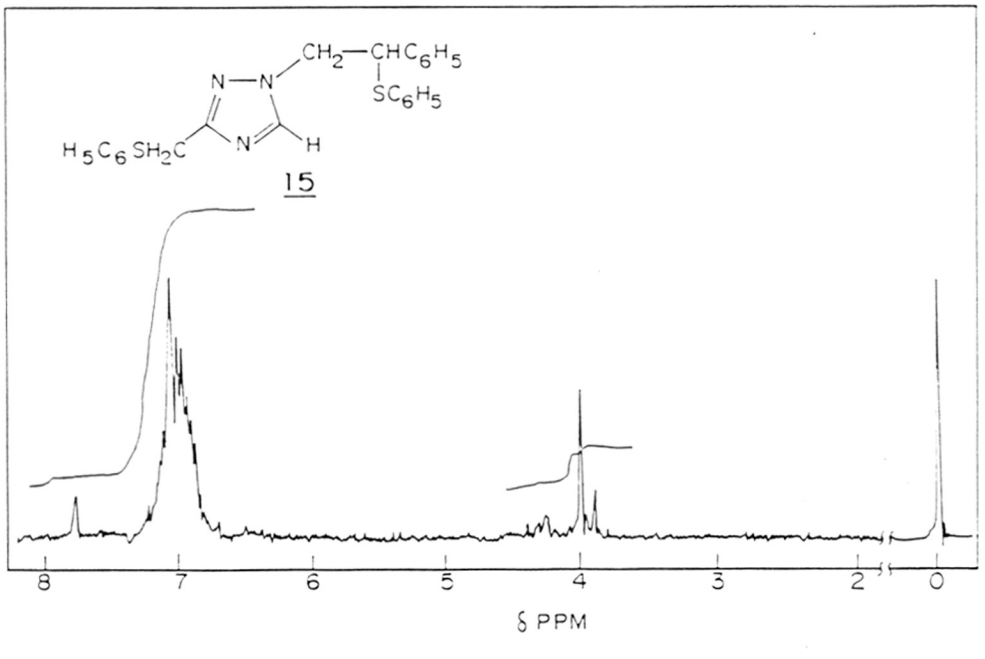
SC6H5
N—N
H5C6SH2C
N
H
15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H
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2
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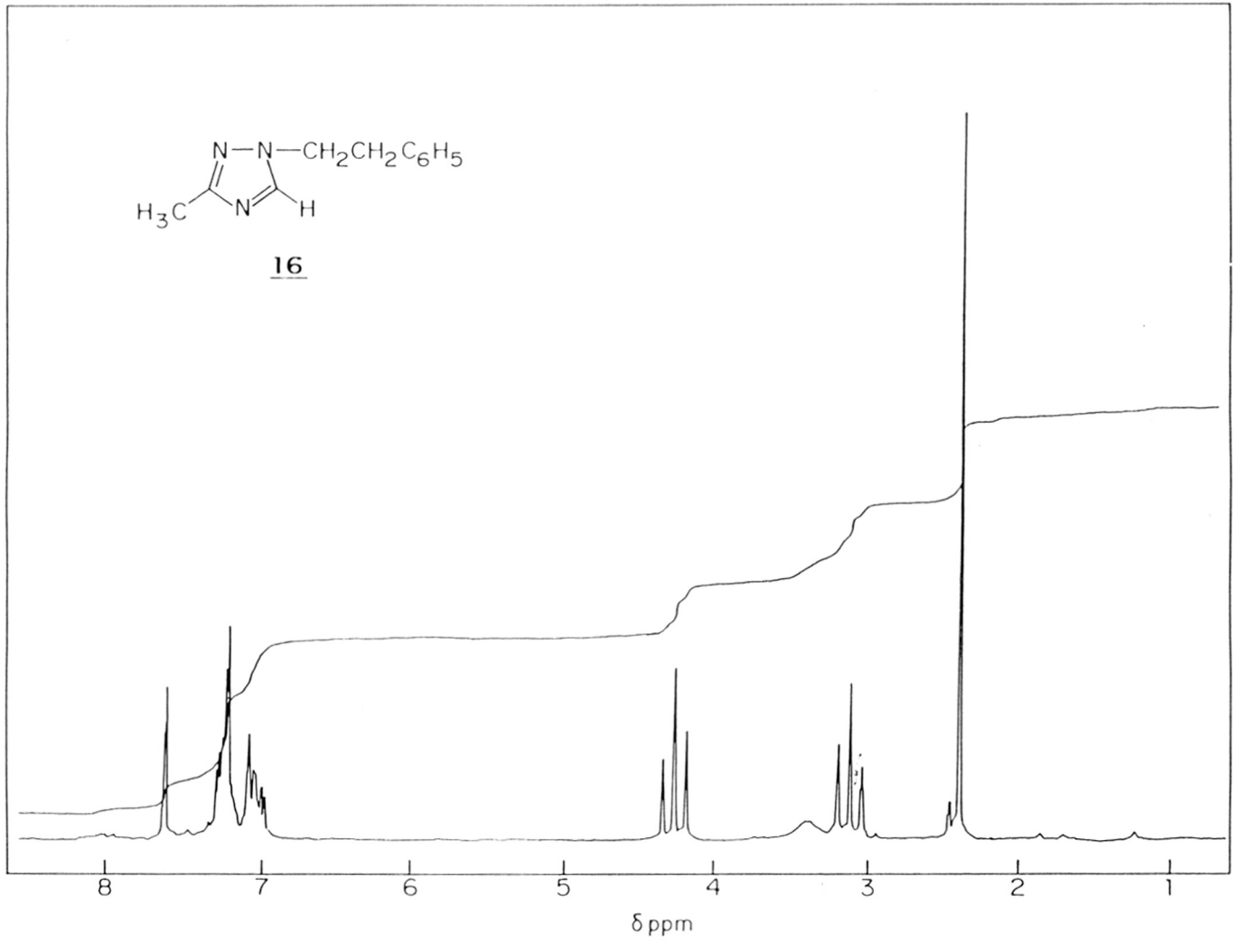
δ PPM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N
H
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7
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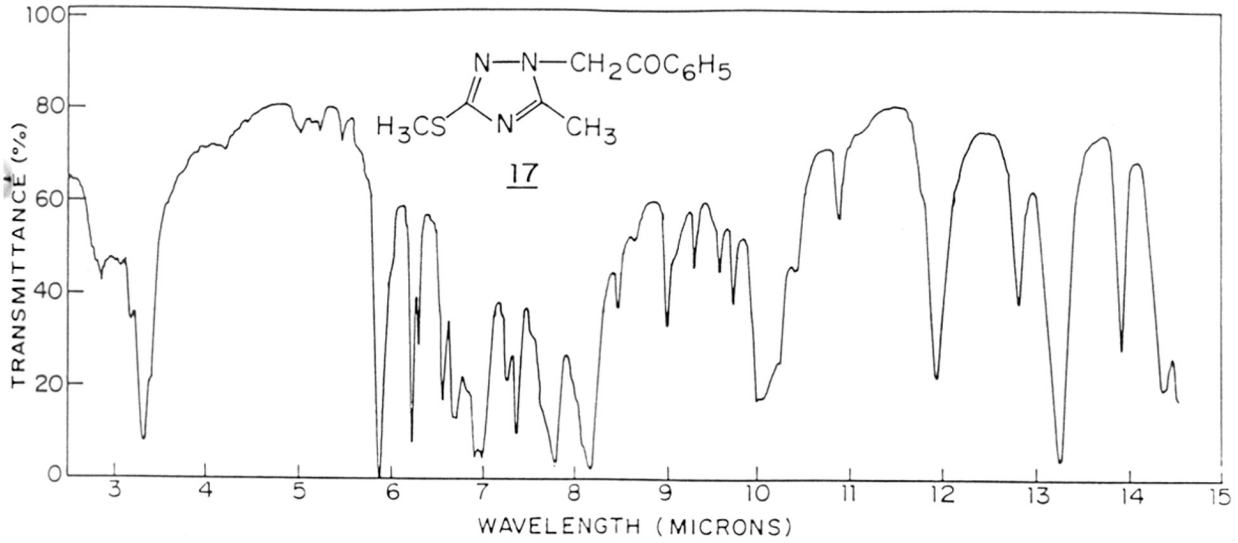
3
2
1
δ ppm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6
7
8
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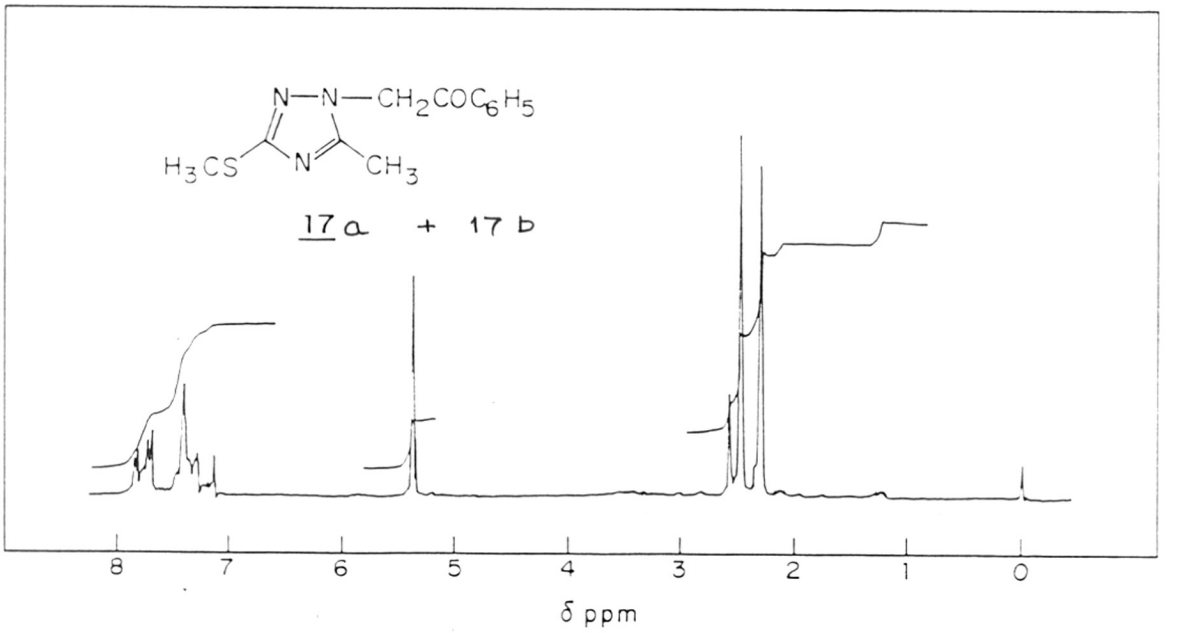
12
13
14
15
WAVELENGTH (MICRONS)
N—N—CH2COC6H5
H3CS
N
CH3

17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H3CS
N
CH3
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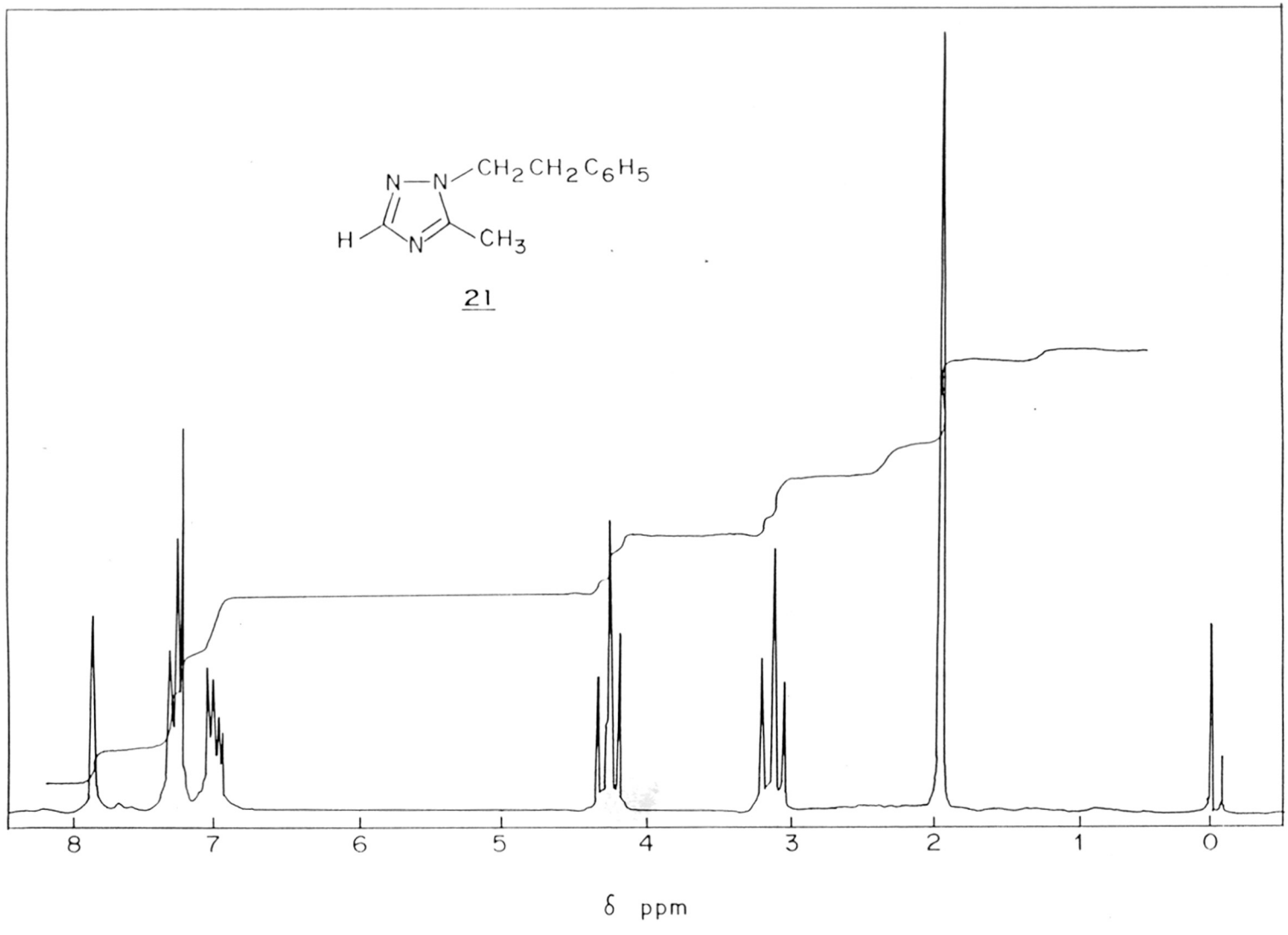
7
6
5
4
3
2
1
0
δ ppm

17a + 17b



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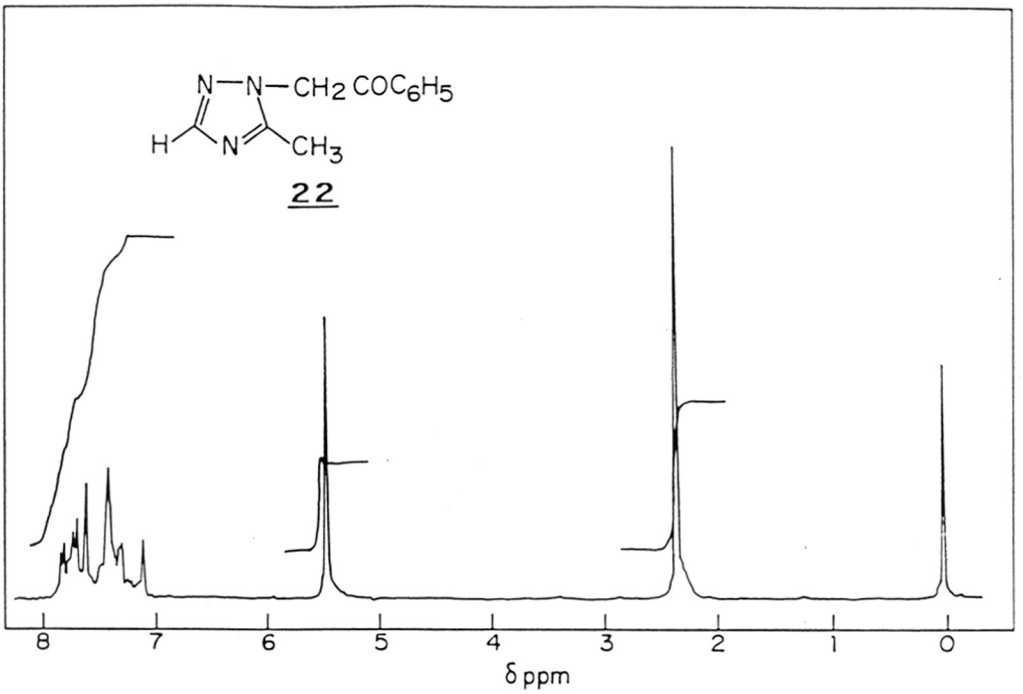
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H
N
CH3
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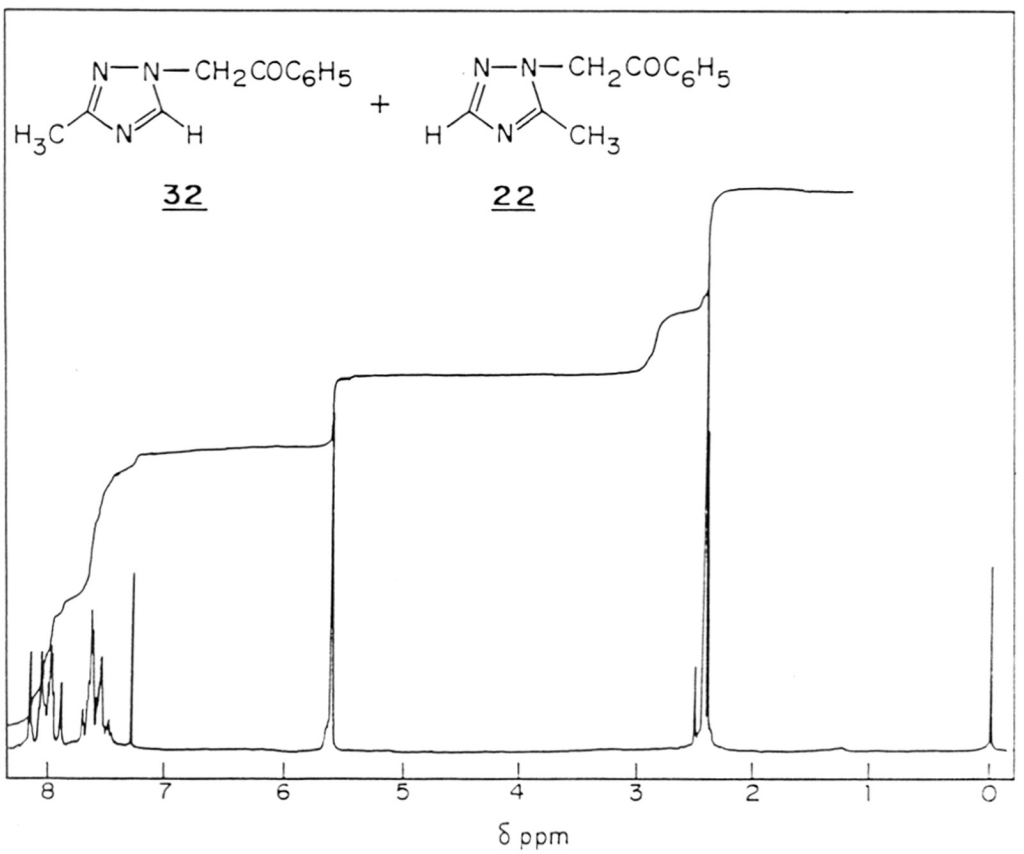
8
7
6
5
4
3
2
1
0
δ ppm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H3C
N
H
32
+
N—N—CH2COC6H5
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N
CH3
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6
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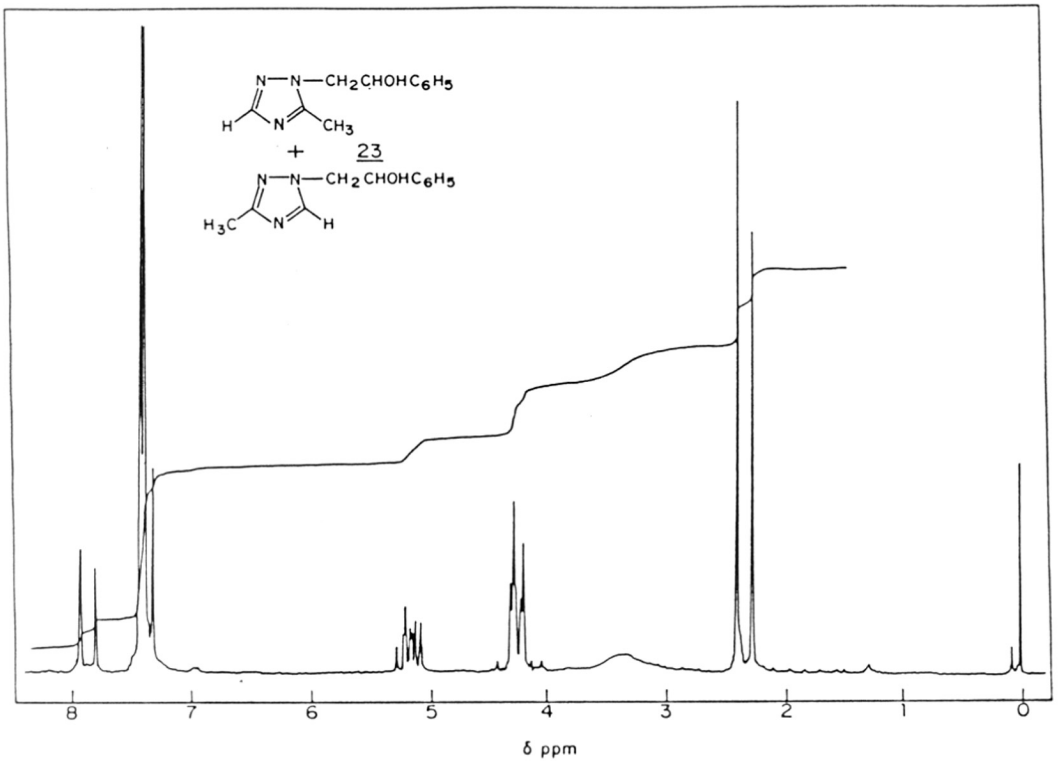
4
3
2
1
0
δ ppm


+
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8
7
6
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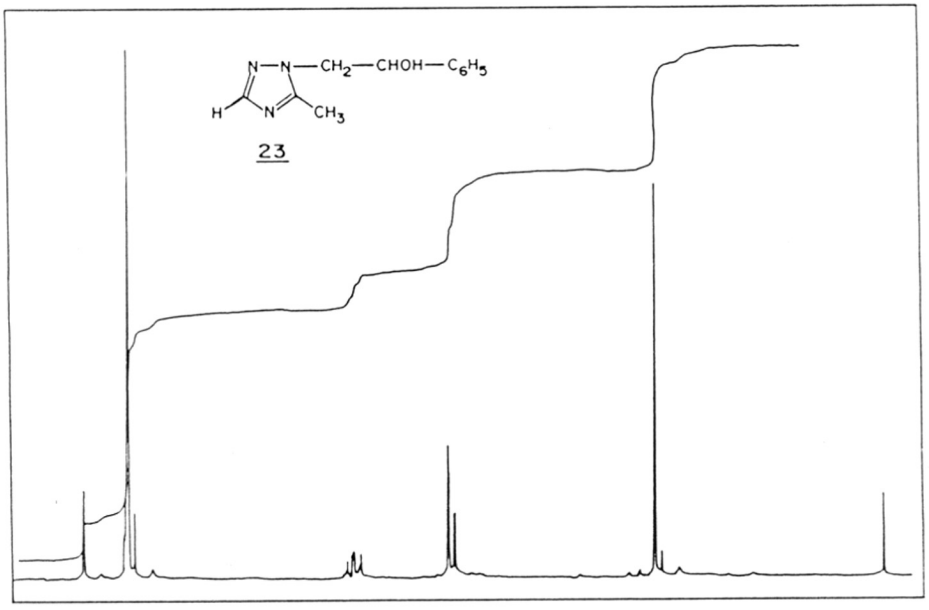
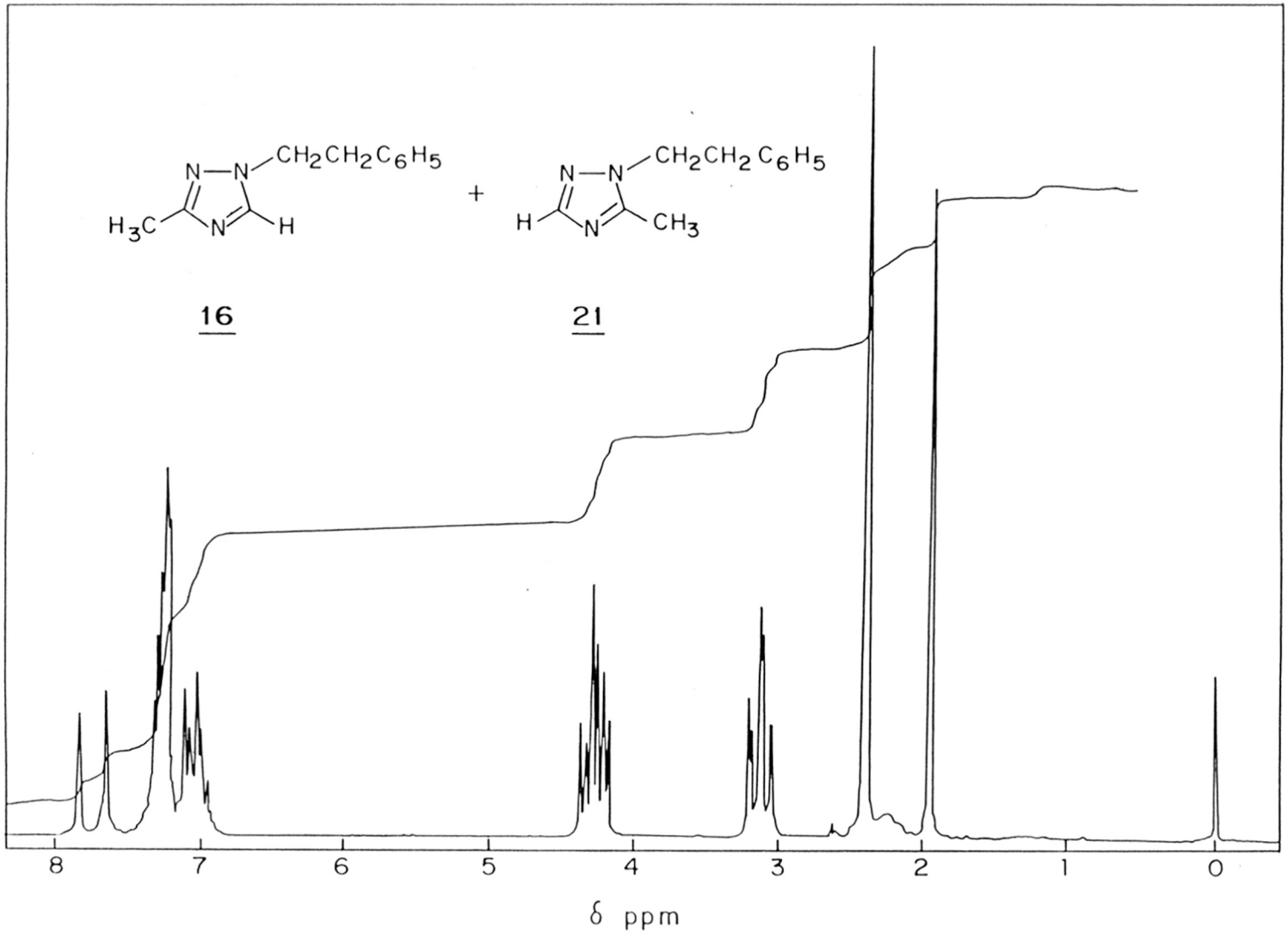
2
1
0
δ ppm


23
δ ppm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CH3
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3
2
1
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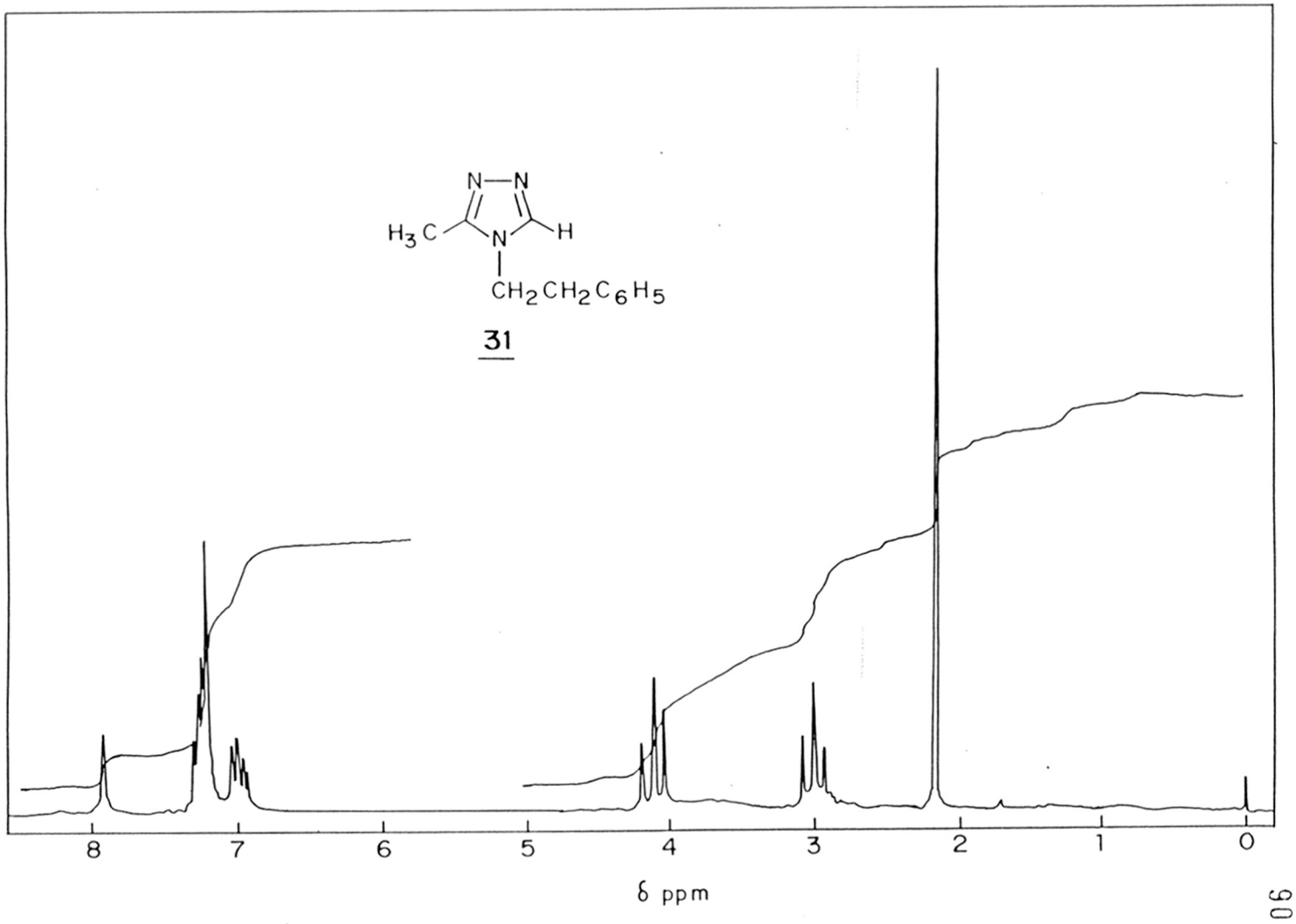
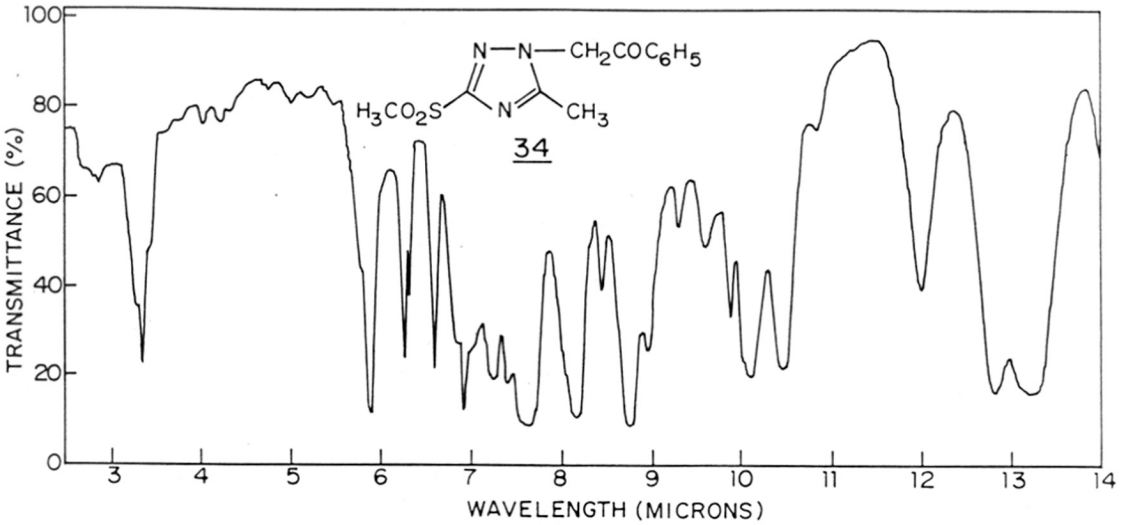
δ ppm



31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20
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TRANSMITTANCE (%)
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5
6
7
8
9
10
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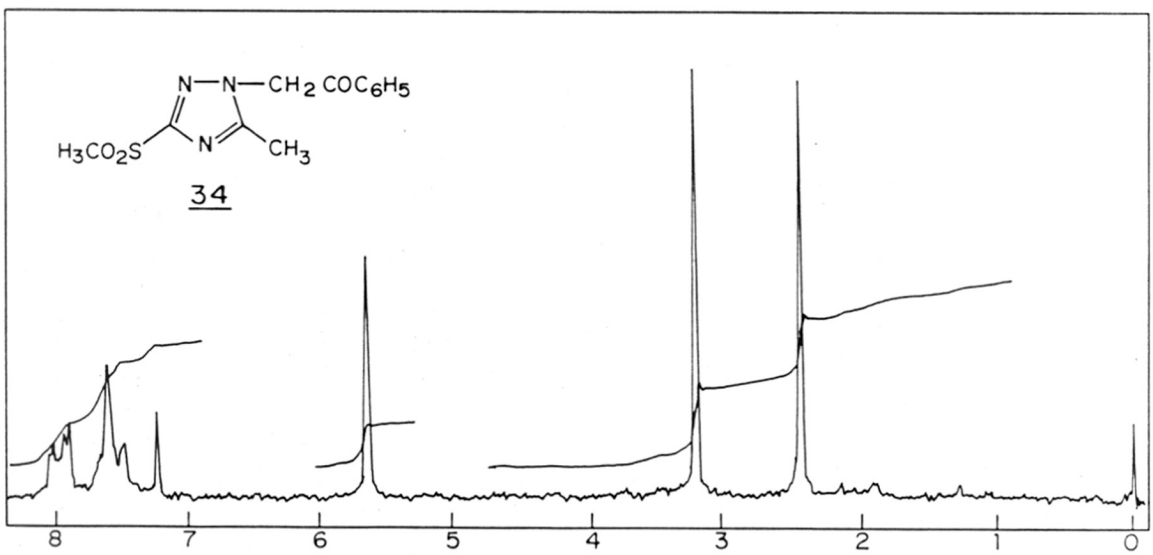
12
13
14
WAVELENGTH (MICRONS)
N—N—CH2COC6H5
H3CO2S
N
CH3
34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H3CO2S
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CH3
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7
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2
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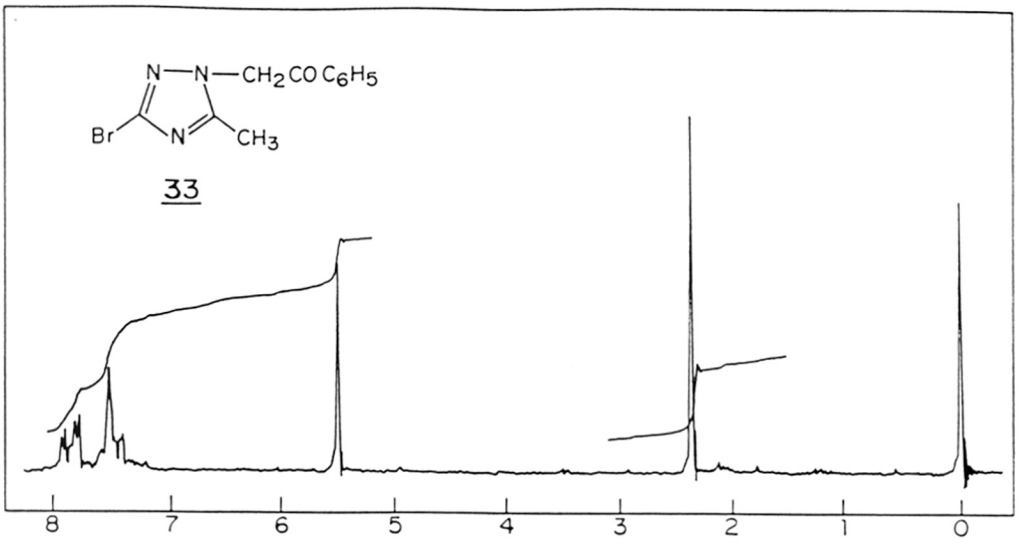
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Br
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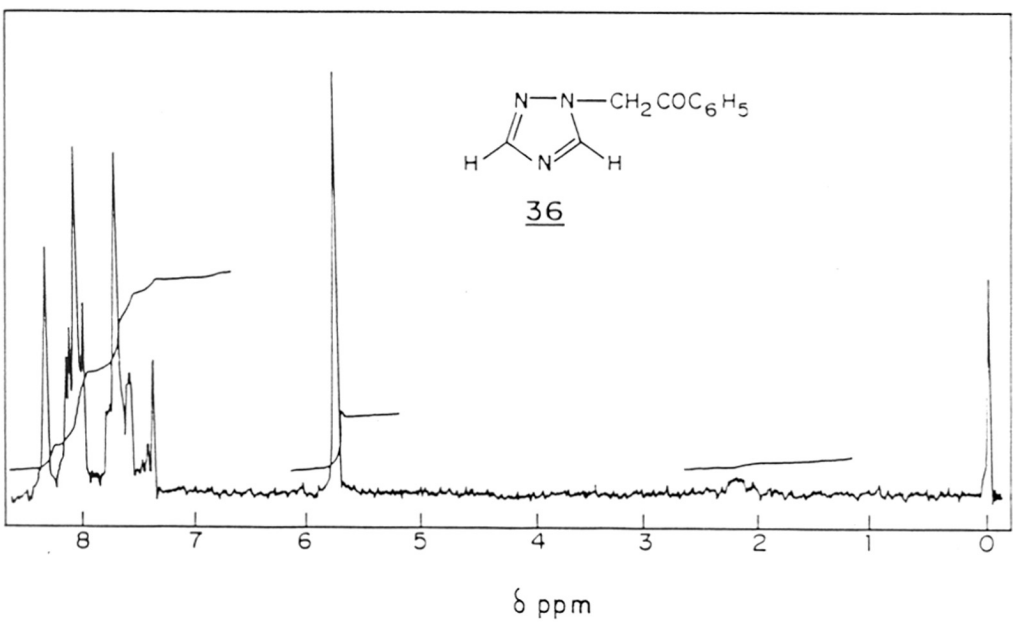
CH3
33
8
7
6
5
4
3
2
1
0
δ ppm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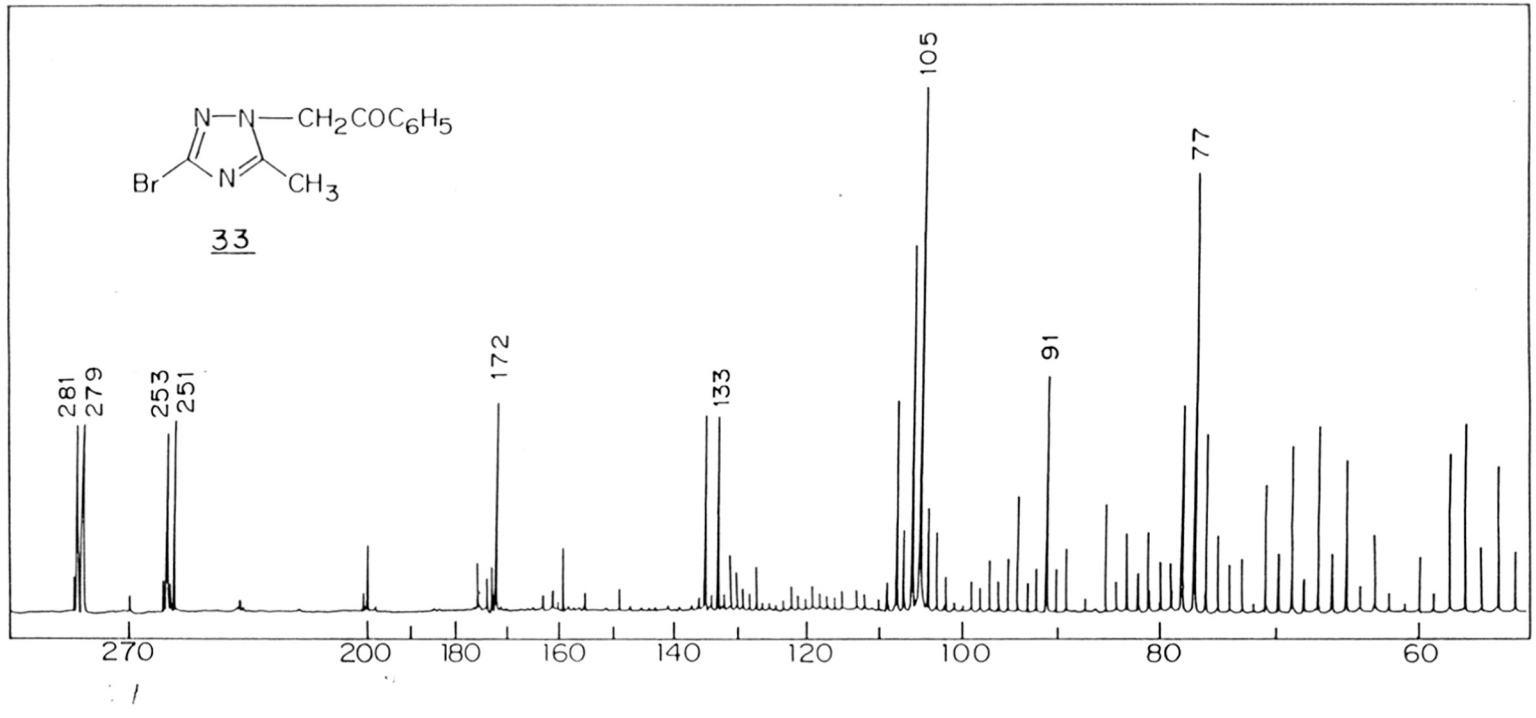
H
N
H
36
8
7
6
5
4
3
2
1
0
δ ppm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Br
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CH3
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281
279
253
251
172
133
105
91
77
270
200
180
160
140
120
100
80
60

CHAPATER III

Synthesis of 1,2,4-triazolo fused bicyclic and tetracyclic systems

SUMMARY

Synthesis of novel 1,2,4-triazolo fused heterocycles was achieved.

3-Hydroxymethyl-5-phenyl-1,2,4-triazole (**4**) was phenacylated with phenacylbromide to give the phenacylated compound (**5a**). Reaction of (**5a**) with thionyl chloride gave chloro compound (**6a**) which was cyclo-condensed to 2,6-diphenyl-8H-1,2,4-triazolo [5,1-c] [1,4] oxazine (**7a**) with sodium hydride. Lawesson reagent converted (**6a**) to 2,6-diphenyl-8H-1,2,4-triazolo [5-1-c] [1,4]thiazine (**9a**). Dihydro derivative of 1,2,4-triazolo [3,4-c] [1,4] oxazine (**17**) was prepared by an unambiguous route. Compound (**7a**) was hydrogenated to give compound (**8**) which was different from compound (**17**). This shows that initial phenacylation of (**5a**) had taken place at nitrogen N-1 which is vicinal to hydroxymethyl group.

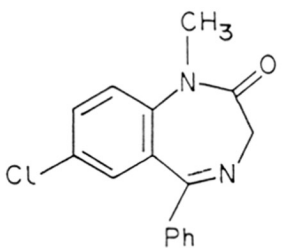
Adopting similar strategy novel 1,2,4-triazolo fused tetracyclic system was syntehsised from 3-hydroxymethyl-5-phenyl-1,2,4-triazole (**4**) and 2-bromo-α-tetralone.

Azoles and azines such as pyrazoles, thiadiazoles, triazoles, triazines, pyrazines, pyridazines and thiadiazines are well known for diverse biological activities in isolated as well as fused states. Some times the fusion of heterocyclic nuclei enhances the pharmacological activities manyfold more than the parent nucleus. The therapeutic importance of 1,4-benzodiazepine Diazepam[1] (scheme 1) has driven considerable attention to the synthesis of tricyclic benzodiazepines. Triazolobenzodiazepines show similar pharmacological profiles to the benzodiazepines from which they are derived but which are in order of magnitude more potent. Alprazolam is one such example , [1,2,4] triazolo [3,4-a] isoquinolines are valuable pharmaceuticals especially as cardiovascular and antiinflamatory agents[2]. [1,2,4] Triazolo [4,3-a] pyrazines are also associated with broncodilator activity, when R_1 and R_2 are small alkyl groups[3]. Fused triazolo pyridines and pyrimidines are also useful in photography. The variety of applications available with 1,2,4-triazole compounds led us towards the synthesis of novel triazolo fused heterocyclic nuclei. Two approaches possible for such fused ring systems are (a) building a triazole ring on a preformed heterocycle and (b) to build a heterocycle on a triazole moiety. Because of the complications arising due to structural isomerism in 1,2,4-triazoles, the second route has been rarely adopted. Abundant methods following route (a) are available in literature and are described further.

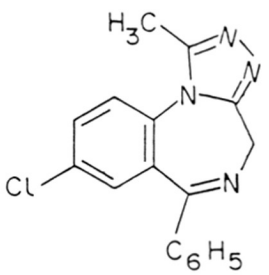
The annulation of the 1,2,4-triazole ring to various heterocycles through α-hydrazino derivatives is one of the most widely used transformations.

The reaction of α-heterylhydrazines with aliphatic carboxylic

SCHEME I



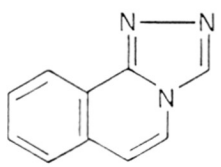
DIAZEPAM



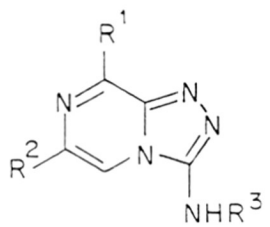
ALPRAZOLAM

[1,2,4] TRIAZOLO [4,3—a] [1,4]

BENZODIAZEPINE

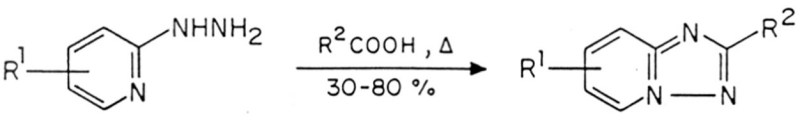


[1,2,4] TRIAZOLO [3,4—a] ISOQUINOLINE



[1,2,4] TRIAZOLO [4,3—a] PYRAZINE

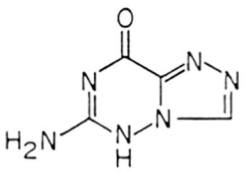
SCHEME - II



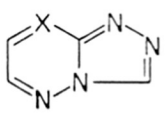
[1,2,4] TRIAZOLO [1,5-a] PYRIDINE

$R^1 = H, NH_2, NO_2$

$R^2 = H, CH_3, C_6H_5$



[1,2,4] TRIAZOLO [3,4-f] [1,2,4] TRIAZIN-8-ONE

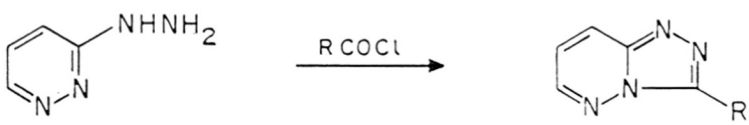


X = CH , N

[1,2,4] TRIAZOLO [4,3-b] PYRIDAZINE

[1,2,4] TRIAZOLO [4,3-b] [1,2,4] TRIAZINE

SCHEME - III



[1,2,4] TRIAZOLO [4,3-b] PYRIDAZINE

acids is the most widely used method in a preparative respect (scheme II)[4,5]. Essentially the cyclisation takes place during refluxing of the heterylhydrazine with a large excess of carboxylic acid and proceeds through intermediate N-heteryl-N'-acylhydrazine. This intermediate is the main product of the reaction if R^2 contains more than two carbon atoms. Further cyclisation of this acylhydrazine can be achieved by heating in phosphorus oxychloride or phenol.

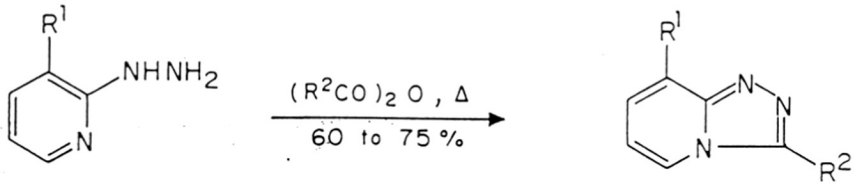
α-Heterylhydrazines when treated with the chloride of substituted benzoic or heteryl carboxylic acids in the presence of bases (pyridine and triethylamine) give condensed 1,2,4-triazoles (scheme III)[6].

Acetic anhydride has successfully condensed 2-hydrazino pyridine to [1,2,4] triazolo-[4,3-a] pyridine in 60 to 76% yield (scheme IV)[7].

In all these cases ring closure takes place by the nucleophilic attack of ring nitrogen on the intermediate carbocation of the hydrazide side chain.

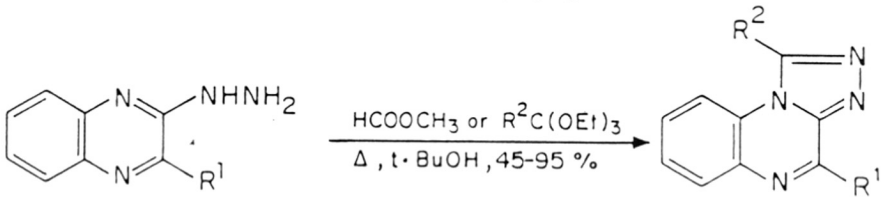
Dimroth type of rearrangement is observed in some of the fused systems (scheme VII), for example [1,2,4] triazolo [1,5-a] pyridine is formed via the isomerisation of [1,2,4] triazolo [4,3-a] pyridine. Electron withdrawing substituents at C-5 facilitate the isomerisation to a greater extent than electron donating substituents. The extreme ease of rearrangement in triazolo-pyrimidines and triazolo [1,2,4] triazines can be attributed to the increase in electron deficiency at the C-5 centre as a result of additional nitrogen atoms present in the system[11]. The rearrangement takes place both in acidic and basic media or under the influence of heat.

SCHEME – IV



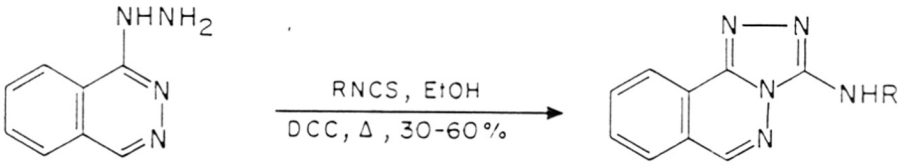
[1,2,4] TRIAZOLO [4,3-a] PYRIDINE

R^1 = pyrrol-1-yl
R^2 = Alkyl, C_6H_5



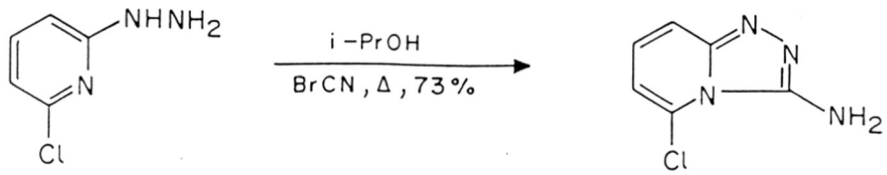
[1,2,4] TRIAZOLO [4,3-a] QUINOXALINE

SCHEME – V

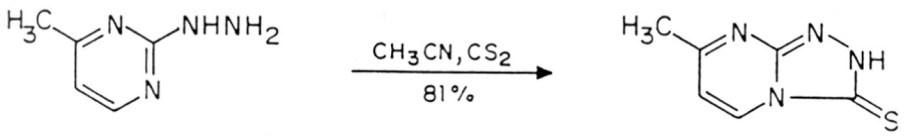


[1,2,4] TRIAZOLO [3,4-a] PHTHALAZINE

SCHEME-VI



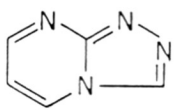
[1,2,4] TRIAZOLO [4,3-a] PYRIDINE



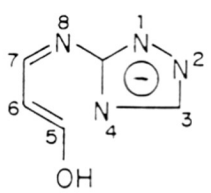
[1,2,4] TRIAZOLO [4,3-a] PYRIMIDIN-3-THIONE

SCHEME-VII

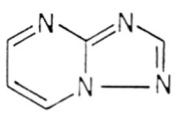
DIMROTH TYPE REARRANGEMENT



[1,2,4] TRIAZOLO [4,3-a] PYRIMIDINE



INTERMEDIATE



[1,2,4] TRIAZOLO [1,5-a] PYRIMIDINE

The best way to avoid this Dimroth arrangement is to use ortho esters in condensation of α-heterylhydrazine[5,8]. [1,2,4]triazolo(4,3-a) pyrazine ring system is best prepared by this method. Analogously cyclisation of 2-hydrazino derivatives of the pyridazine, pyrimidine and quinoxaline ring systems led to the corresponding fused 1,2,4-triazole derivatives. (scheme IV).

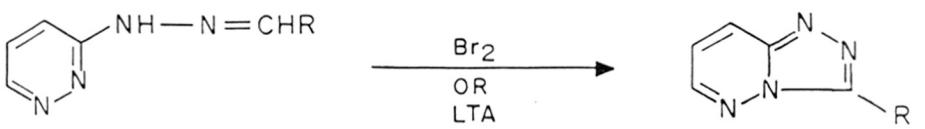
1-Hydrazinophthalazine with alkyl isothiocyanate in refluxing ethanol in presence of DCC cyclises to [1,2,4] triazolo [3,4-a] phthalazine[9]. Replacing isothiocyanate by 5-methylisothiourea, the same product can be obtained. (scheme V).

A general method for the preparation of condensed 1,2,4-triazoles with an amino group in the triazole ring is by reaction of α-heteryl-hydrazines with cyanogen bromide in alcohol or aqueous alcoholic solution[10]. Cyclisation can give rise to both types of fused triazolo ring systems depending upon the reaction conditions. (scheme VI).

Among the reagents which are used to convert α-hydrazino-N-heterocycle into the fused triazolone, are ethyl chloroformate[12], urea and phosgene. The fused 1,2,4-triazolin-thiones are prepared in high yield by using carbon disulfide or thiocarbonyldi-imidazole (scheme VI)[13]. Many such systems have been synthesised[14].

Methods described earlier present a way of building the 1,2,4-triazole ring by C-N bond formation. The same can also be achieved by forming a nitrogen nitrogen bond. Oxidative cyclisation of N-(2-pyridyl)alkyl- or aryl amidines has been accomplished using lead tetra-acetate in refluxing benzene (scheme IX)[16]. Reaction of N'-N'-dimethyl-formamidine derivative of 1-aminoisoquinoline with hydroxylamine O-sulfonic acid followed by ring closure gives [1,2,4] triazolo [5,1-a]

SCHEME VIII

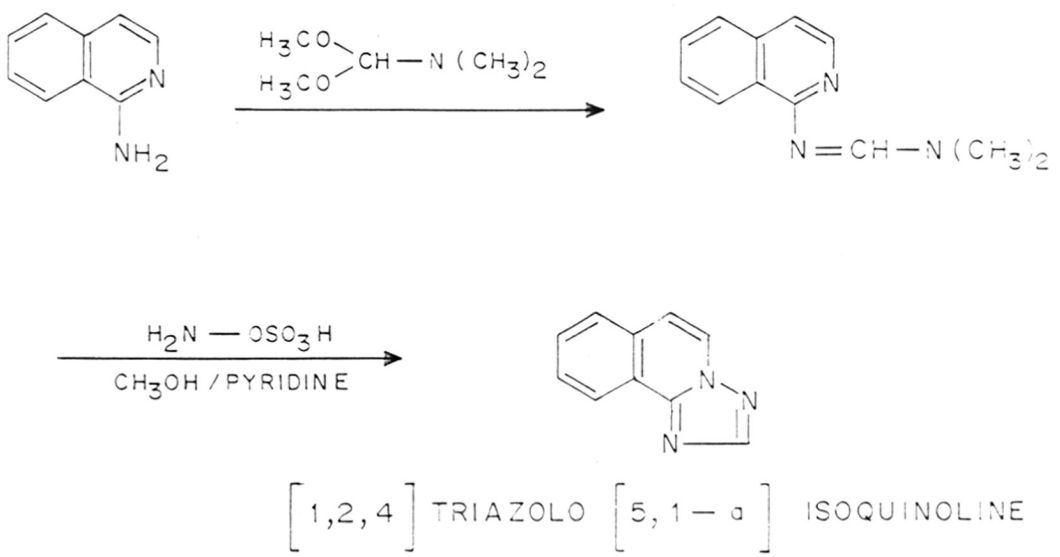


[1,2,4] TRIAZOLO [4,3—b] PYRIDAZINE

SCHEME IX

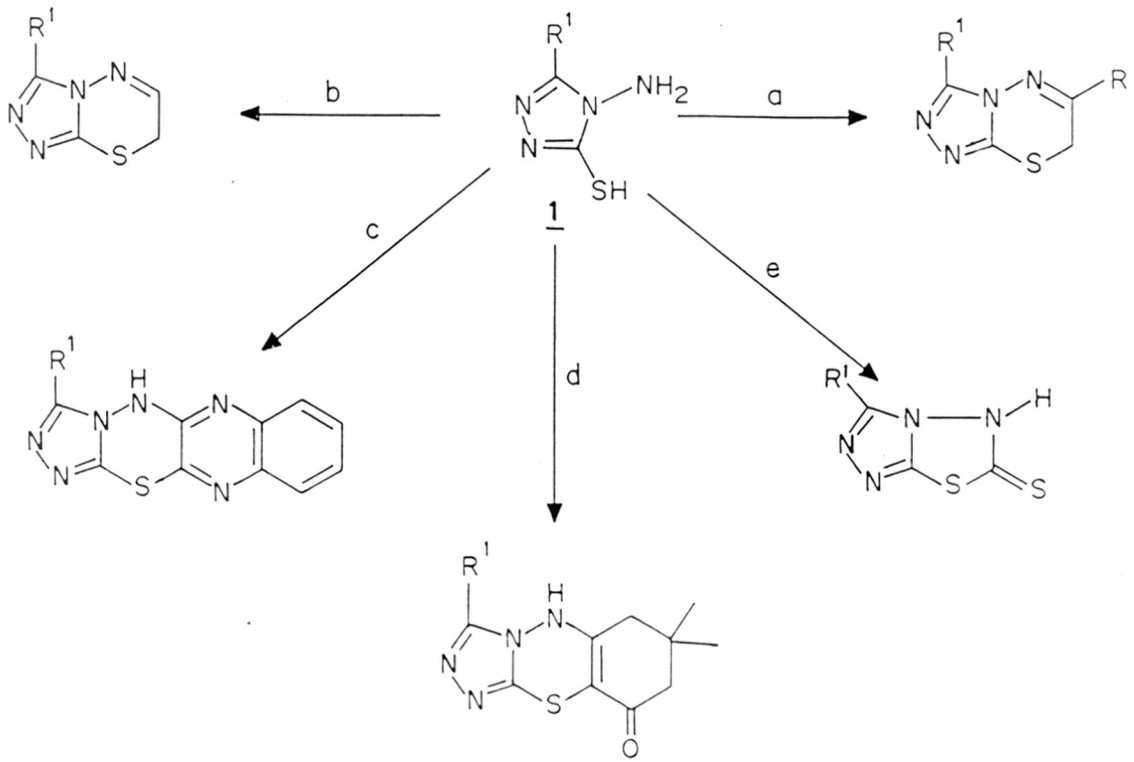
[1,2,4] TRIAZOLO [1,5—a] PYRIDINE

SCHEME X



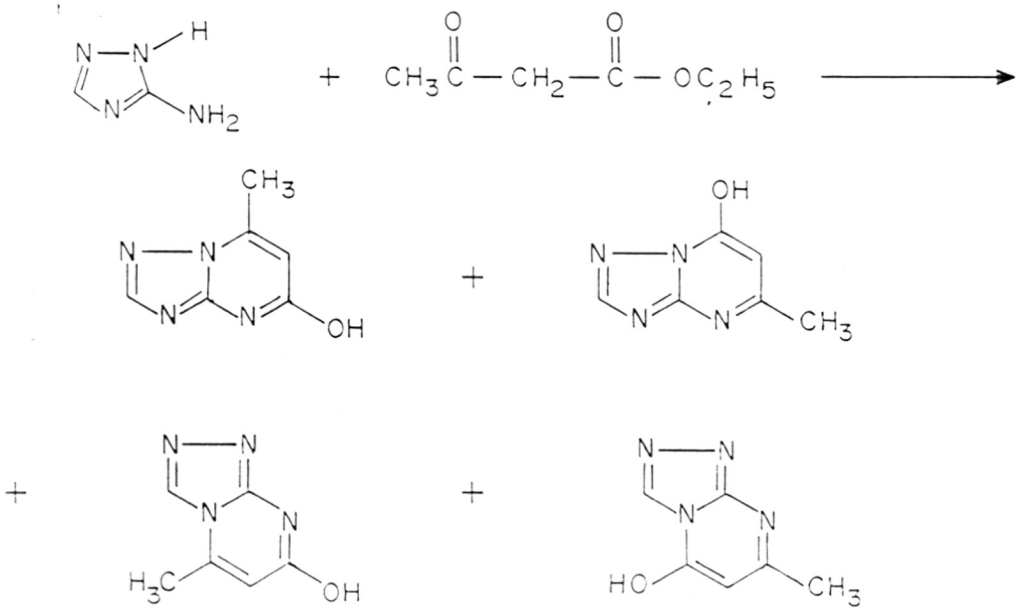
[1,2,4] TRIAZOLO [5,1—a] ISOQUINOLINE

SCHEME XI

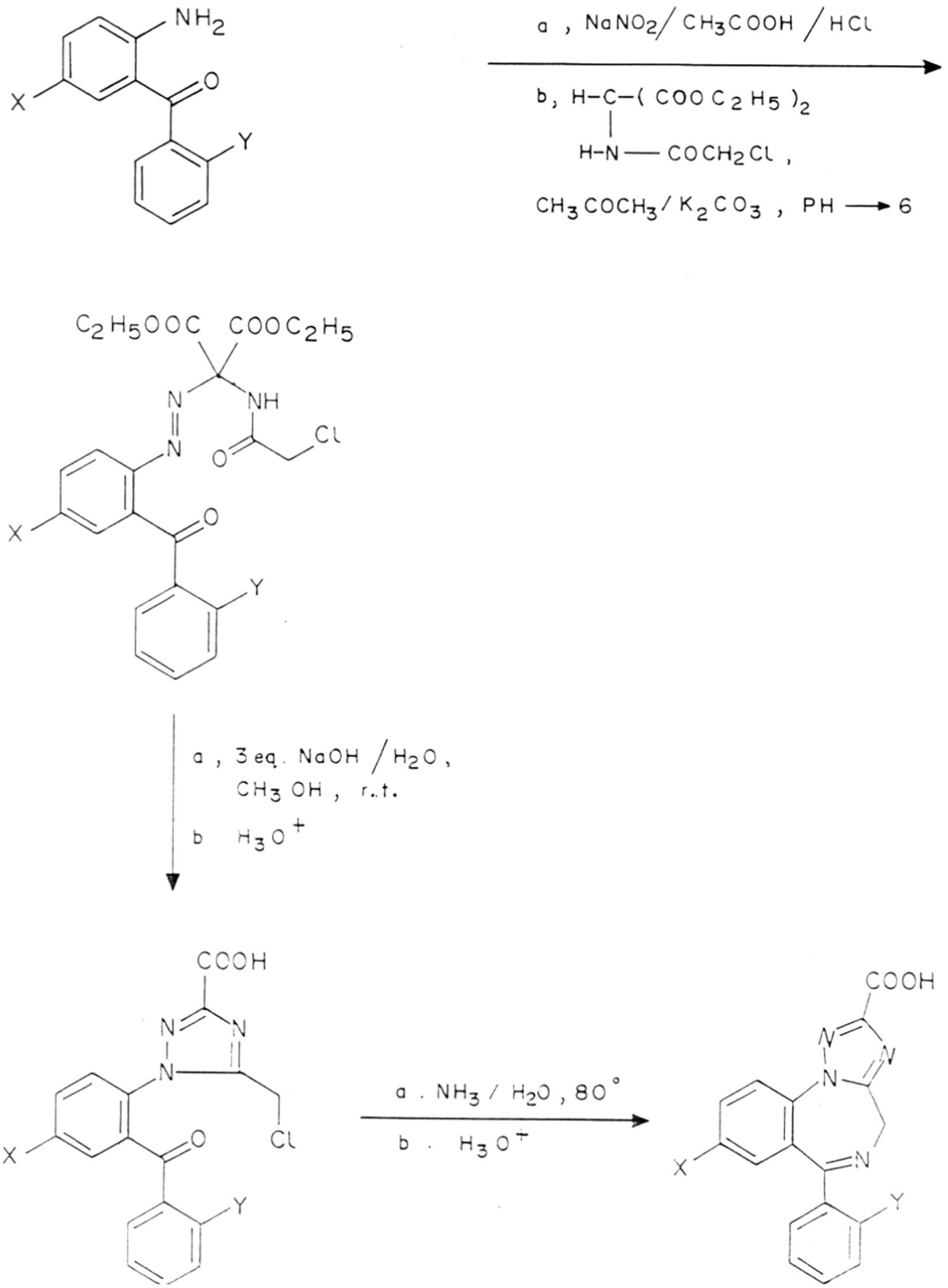


a, $RCOCH_2X$, b, $ClCH_2CH(OEt)_2$, C, 2,3 – DICHLOROQUINOXALINE
d, DIMEDONE e, CS_2 – PYRIDINE .

SCHEME XII



SCHEME XIII


NH2
X
O
Y
a , NaNO2/ CH3COOH / HCl
b, H–C–(COO C2 H5)2
H–N — COCH2Cl ,
CH3COCH3/ K2CO3 , PH ⟶ 6
C2H5OOC COOC2H5
N
NH
N
O
Cl
a , 3eq. NaOH / H2O ,
CH3 OH , r.t.
b H3O+
COOH
a . NH3 / H2O , 80°
b . H3O+

isoquinoline (scheme X)[17].

Synthetic methods for fused triazole systems starting with 1,2,4-triazole derivatives are discussesd further.

4-Amino-1,2,4-triazole-5-thiones when reacted with α-halogeno ketones, alkyl halides, dimedone, benzoin, carbon disulfide, chloro-acetaldehyde and many other substrates containing two electrophilic centres have produced number of fused 1,2,4-triazole heterocycles (scheme XI)[18]. Reaction of 3-amino-1,2,4-triazole with a compound having two reactive groups in the β-positions such as keto, aldehyde, cyano or ester groups produces triazolopyrimidine system. As mentioned earlier in cyclisation with ethyl acetoacetate all possible four isomers are formed (scheme XII)[19]. Various polyaza-heterocycles have been synthesised by Ciba-Geigy Ltd. by the malonic ester variation of the Japp-Klingemann reaction.[20] Arylazomalonates formed by coupling malonate with diazonium salts are extensively used as versatile intermediates. Malonates having suitable electrophilic centres in the side chain can then further cyclise under basic conditions to give the desired heterocycle. An important feature of this synthesis is the fact that all the heterocycles created are substituted by an ester group or a carboxy group which serves as an efficient functional handle for a medicinal chemist. Several triazolo fused heterocycles are prepared adopting this methodology (scheme XIII).

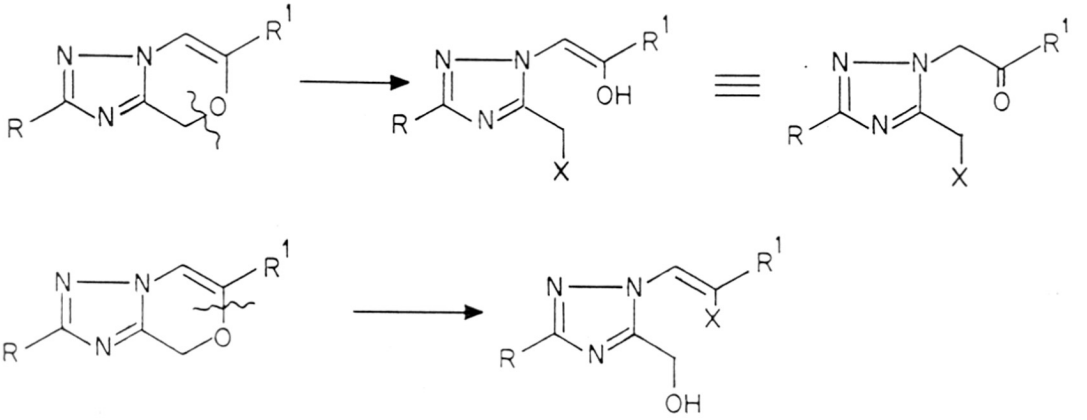
PRESENT WORK

A survey of the literature revealed that [1,2,4] triazolo [5,1-c] [1,4] oxazines and the corresponding thiazines had not been synthesised so far. 8-Oxo analogues of 1,2,4-triazolo [5,1-c] [1,4] oxazine system were reported by Japanese workers[21] simultaneously when our work was also published[22]. Retro synthetic analysis as in scheme (XIV) shows that one can synthesise such fused ring systems starting from a substituted 1,2,4-triazole with a hydroxymethyl function at C-5 and suitably functionalised substituent at N-1 of the 1,2,4-triazole nucleus. On the basis of our regiochemical study in alkylation of substituted 1,2,4-triazoles[23], it was anticipated to have an alkylation reaction occurring at the N-1 position in C-5 hydroxymethyl substituted triazoles with an electron withdrawing or a bulky substituent at C-3. Keeping this in mind, 3-hydroxymethyl-5-phenyl-1,2,4-triazole was chosen as a substrate for the alkylation reaction.

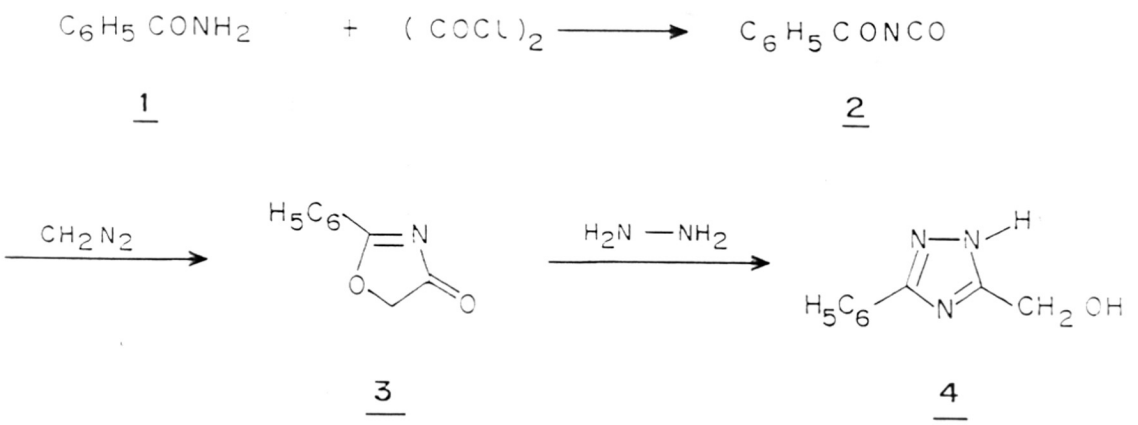
Benzoyl isocyanate (2) was prepared by reaction of oxalyl chloride and benzamide[24]. Further reaction of(2)with diazomethane gave 2-phenyl-4-oxazolone (3)[25]. This freshly prepared oxazolone was rearranged with 60% hydrazine hydrate to 3-hydroxymethyl-5-phenyl-1,2,4-triazole (4) (scheme XV)[26]. The compound can also be prepared from methyl benzimidoate and hydroxy acetohydrazide[26]. We prepared it by the earlier method.

3-Hydroxymethyl-5-phenyl-1,2,4-triazole (4) was reacted with equimolar quantities of phenacyl bromide in acetone potassium carbonate in cold conditions to give an alkylated product in 94% yield. The

SCHEME XIV



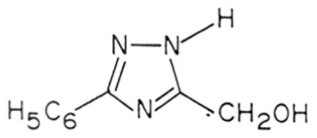
SCHEME XV



crude product melted in the range 175-193°, crystallisation from pet.ether-ethyl acetate reduced the range to 187-192°. Extensive column chromatographic separation did not yield a sharper melting compound. However, the crude product showed a clean PMR pattern, PMR ($CDCl_3$, δ): 4.9 (s, 2H, -$C\underline{H}_2$OH), 5.8 (s, 2H, N-$C\underline{H}_2$-CO-), 7.5 (m, 6H, Ar$\underline{H}$), 8.0 (m, 4H Ar$\underline{H}$). The range in melting point is attributed to small quantities of regioisomers present which are difficult to remove in the purification steps. Structure (**5a**) was assigned to the major product of phenacylation reaction; the valadity of which was borne out by subsequent transformations carried out on it. Compound (**5a**) was converted to its chloromethyl analogue by reacting it with thionyl chloride in cold conditions in quantitative yields. The product was crystallised from methanol to give a sharp melting crystalline solid m.p.143°. Treatment of (**6a**) with sodium hydride in tetrahydrofuron effected the desired base catalysed cyclocondensation. Abstraction of a proton by the hyride ion to give the enolate followed by displacement of the chlorine with the enolate anion gave 2,6-diphenyl-8H-[1,2,4] triazolo [5,1-c] [1,4] oxazine (**7a** scheme XVI). The crude product of the reaction was purified over silica gel column using benzene-ethyl acetate (95:5) as an eluent. Compound (7 a) was obtained in 55% yield, m.p.154°. PMR ($CDCl_3$, δ): 5.5 (s, 2H, -$C\underline{H}_2$-0-), 7.3 (s, 1H, -N-C$\underline{H}$=C-0-), 7.4 (m, 8H, Ar$\underline{H}$), 8.1 (dd, 2H, J=6 2 Hz, Ar$\underline{H}$). UV spectrum of the compound in methanol gave λ_{max} at 310 nm and 205 nm.

In order to achieve the desired triazolothiazine system, the best way would be to convert an oxo function into thioko function, Hence compound (**6a**) was reacted with phosphorus pentasulfide. The product

SCHEME XVI



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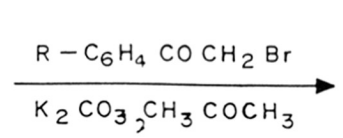

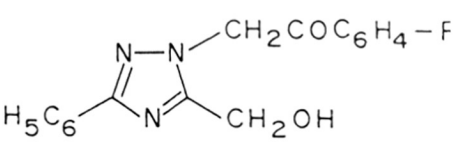

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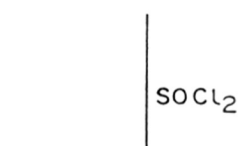

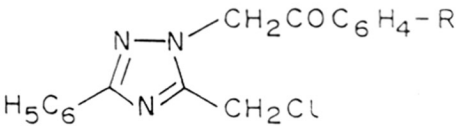

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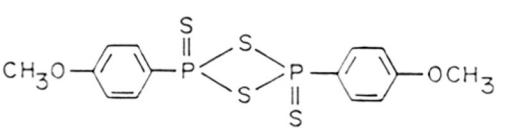
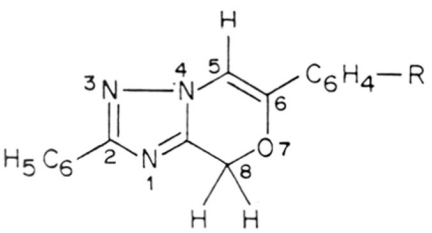


L.R.



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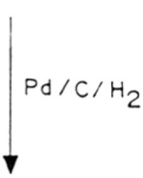
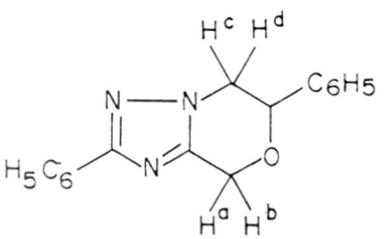
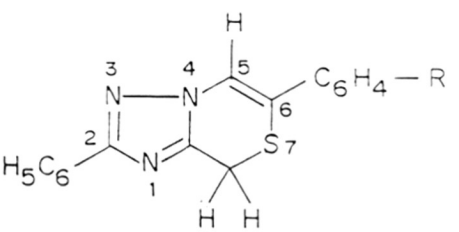
2,6-Diphenyl-8H-[1,2,4] triazolo [5,1-c][1,4] oxazine.





8



9

a, R = C6H5

b, R = C6H4-4-Chloro

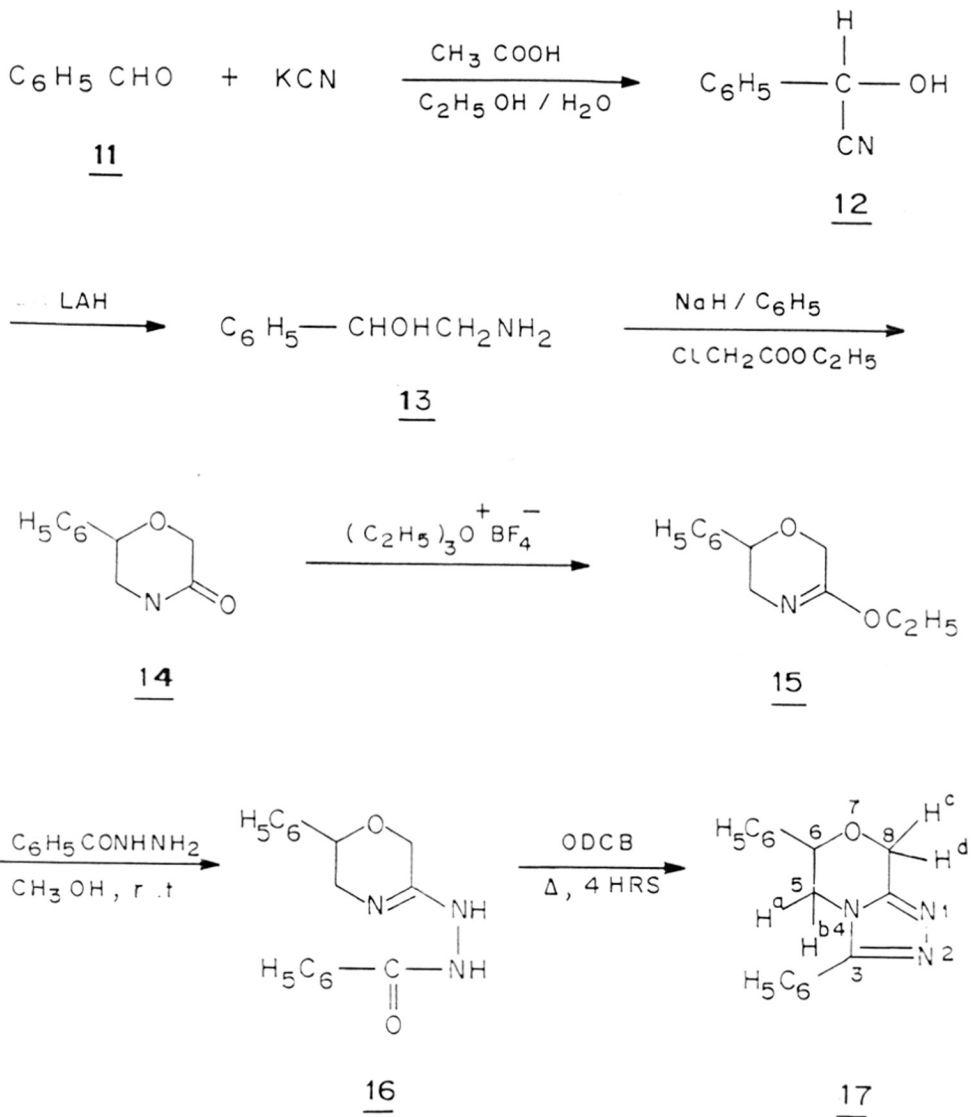
2,6-Diephenyl-8H-[1,2,4] triazolo [5,1-c][1,4] Thiazine.

of the reaction was a cyclised triazolothiazine compound. Most probably the thioketone formed must have been cyclised immediately under the reaction conditions. As the yield in this reaction was only about 15% we changed the thiating reagent from phosphorus pentasulfide to Lawesson reagent[27]. Compound (**6a**) on reaction with Lawesson reagent in refluxing toluene for three hours afforded cyclised product in 50% yield, after purification of the product over silica gel column using benzene-ethyl-acetate (95:5) as eluent. Compound (**9a**), 2,6-diphenyl-8H-[1,2,4] triazolo [5,1-c[[1,4] thiazine was crystallised from benzene-pet.ether to give crystalline solid m.p.148-9°. PMR ($CDCl_3$, δ): 4.3 (s, 2H, $-CH_2-S$), 7.3 (m,8H, ArH), 7.5 (s, 1H, N-CH=C-S), 8.0 (dd, 2H, J=6, 2 Hz, ArH).

On comparison of the PMR spectra of the two compounds (**7a**) and (**9a**) i.e. triazolo oxazine and triazolothiazine, one finds that the methylene protons singlet has appeared upfield in (**9a**) as compared to in (**7a**) but vinylic proton is seen at 7.5 δ in (**9a**) whereas it appears at 7.3 δ in the oxygen analogue (**7a**). This may be due to anisotropic effect of sulfur in compound (**9a**).

The assignment of the structures to the compounds (**5**), (**6**), (**7**) and (**9**) is on the assumption that the initial phenacylation has taken place at N-1 nitrogen and the basis for it is the established predominant alkylation observed at vicinal nitrogens rather than at N-4 as discussed in chapter II. Remote possibility of occurence of phenacylation at N-4 position, leading to compound (**10**) was ruled out by synthesising (**17**) in an unambiguous way, as per the procedure adopted by Shridhar et al.[28] (**17**) is the dihydro derivative of (**10**).

SCHEME XVII

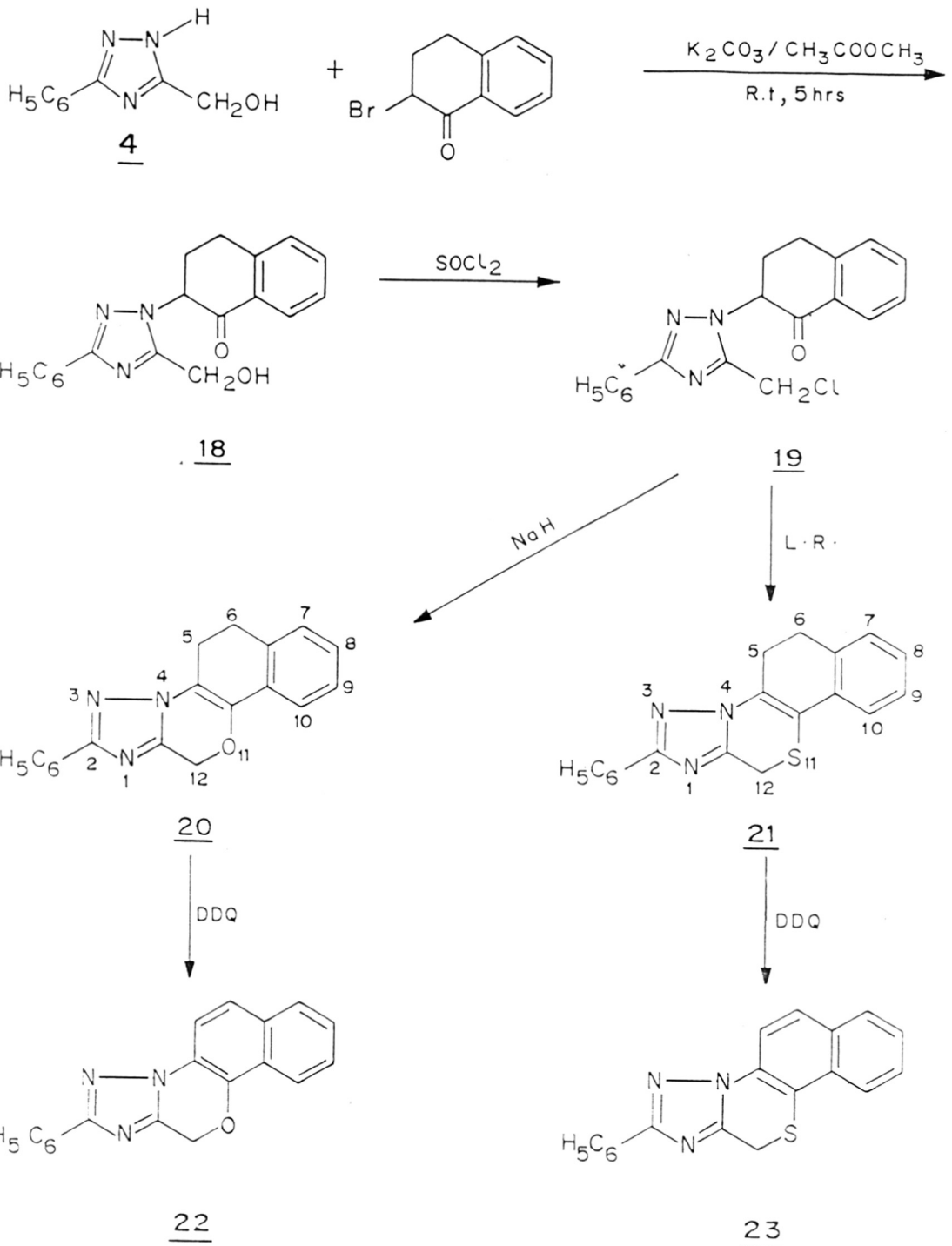

C6H5 CHO + KCN
CH3 COOH
C2H5 OH / H2O
11
12
LAH
C6 H5— CHOHCH2NH2
13
NaH / C6H5
ClCH2COOC2H5
14
(C2H5)3O+ BF4−
15
C6H5CONHNH2
CH3OH, r.t
16
ODCB
Δ, 4 HRS
17

Benzaldehyde (**11**) was converted to its cyanohydrin derivative (**12**) using potassium cyanide in ethanol, acetic acid and water as solvent. The cyanohydrin was further reduced with lithium aluminium hydride in ether to 2-amino-1-phenylethanol (**13**)[29]. Compound (**13**) was refluxed with sodium hydride in benzene and the sodio derivative was treated with ethyl chloroacetate to give 6-phenyl-3-morpholinone (**14**)[30]. It was further alkylated using triethyloxoniumfluoroborate as alkylating agent to the corresponding lactim ether (**15**)[31]. Alkylation with diethyl sulfate has been reported to be failed. Reaction of the lactim ether with benzoyl hydrazide in methanol at room temperature gave the hydrazine (**16**) which when further refluxed in o-dichlorobenzene for 4 hours furnished 3,6-diphenyl-5,6 dihydro [1,2,4] triazolo [3,4-c] [1,4] oxazine (**17**) m.p.164°. (**17**) is the dihydro derivative of compound (**10**). For comparison, we found it suitable to convert compound (**7a**) into the dihydro derivative (**8**) which was obtained by hydrogenation of (**7a**) over palladised charcoal m.p.111-2°. PMR ($CDCl_3$, δ) of (**8**): 4.2 (dd, 1H. J=12, 4 Hz, $\underline{H}^c$), 4.5 (dd, 1H, J=12, 11 Hz, $\underline{H}^d$), 5.0 (dd, 1H, J=11, 4Hz, -C$\underline{H}$Ph), 5.0 (d, 1H, J=16 Hz, $\underline{H}^a$), 5.3 (d, 1H, J=16 Hz, $\underline{H}^b$), 7.4 (s, 8H), 8.1 (dd, 2H, J=6, 2 Hz).

PMR ($CDCl_3$, δ) of (**17**): 4.1 (m, 2H, $\underline{H}^a$, $\underline{H}^b$), 4.8 (dd, 1H, J=9, 4Hz, -C$\underline{H}$Ph), 5.1 (d, 1H, J=16 Hz, $\underline{H}^c$), 5.4 (d, 1H, J=16 Hz, $\underline{H}^D$), 7.4 (m, 8H), 7.7 (dd, 2H, J=6, 2 Hz).

Comparison of the spectroscopic data, melting points and tlc analysis reveals that compounds (**8**) and (**17**) are two different compounds, so the structures assigned to the compounds (**5**), (**6**), (**7**), (**8**) and (**9**) are correct.

SCHEME XVIII



After achieving the synthesis of triazolo fused bicycle we tried to prepare a fused tricyclic system. For this 3-hydroxymethyl-5-phenyl-1,2,4-triazole was reacted with 2-bromo cyclohexanone under our usual alkylation conditions but reaction did not take place. Varying the parameters of the reaction such as temperature, solvent, change of base did not succeed in getting the alkylated product. Hence synthesis of a tetracyclic system was attempted. The alcohol (**4**) was reacted with 2-bromo-α-tetralone in acetone/potassium carbonate at room temperature to give alkylated product in 50% yield, a sharp melting solid 181°. The product was obtained after column chromatography over silica gel using ethyl acetate as an eluent. With thionyl chloride compound (**18**) was converted to the chloro compound (**19**) which was further cyclised with sodium hydride in tetrahydrofuran to 2-phenyl-12H-5,6-dihydronaphtho [1,2-b][1,2,4] triazolo [1,5-d] [1,4] oxazine (**20**) in 71% yield m.p.182°. Similarly cyclisation of (**19**) with Lawesson reagent gave 2-phenyl-12H-5,6-dihydronaphtho [1,2-b] [1,2,4] triazolo [1,5-d] [1,4] thiazine (**21**) in 40% yield, m.p.192°. PMR ($CDCl_3$, δ) of (**20**): 3.1 (s, 4H), 5.5 (s, 2H), 7.3 (m, 7H), 8.0 (dd, 2H, J=6, 2 Hz). PMR ($CDCl_3$, δ) of (**21**): 3.1 (m, 4H), 4.2 (s, 2H), 7.4 (m, 7H), 8.0 (dd, 2H, J=6, 2 Hz). Methylene protons adjacent to hetero atoms are appearing very much at the same δ value as in their bicyclic analogues. Both compounds (**20**) and (**21**) were further oxidised with 2,3-dichloro 5,6-dicyanoquinone to (**22**) and (**23**).

Structure assignment to the tetrayclic compounds is based on the expectation that the alkylation with bulkier 2-bromo-α-tetralone must have taken place at N-1 nitrogen of the 1,2,4-triazole ring. This was based on the analogy of alkylation with phenacyl bromide has taken placae at N-1 nitrogen as proved earlier.

EXPERIMENTAL

Benzoyl isocyanate (2)[24]

To a stirred mixture of benzamide (12.1 g, 0.1 m) and ethylene dichloride (60 ml), oxalyl chloride (15.6 g, 0.125 m) was added rapidly. The mixture was refluxed for 16 hrs. The ethylene dichloride was distilled under vacuo and benzoyl isocyanate was isolated by distillation at 92° at 12 mm pressure in 75% yield.

IR (liquid): 2225 cm^{-1} (for -N=C=O)

2-Phenyl-4-oxazolone (3)[25]

Dilute ethereal solution of diazomethane (120 ml) was prepared by reaction of nitrosomethyl urea (11 g) with 50% aqueous solution of potassium hydroxide (30 ml). This was carefully added to benzoyl isocyanate (4.77 g, 32 mmol) in dry ether (20 ml). The reaction was instantaneous with simultaneous deposition of colorless crystalline oxazolone. The reaction mixture was allowed to stand at room temperature for one hour and then overnight at 0°. It was then filtered to give 4.0 g of oxazolone (68%, m.p.154°).

3-Hydroxymethyl-5-phenyl-1,2,4-triazole (4)[26]

Freshly prepared 2-phenyl-4-oxazolone (3.2 g, 20 mmol) was added to cooled 60% hydrazine hydrate (1.5 ml) with stirring. Reaction was exothermic and solid hydroxymethyl triazole separated. Water (10 ml) was added and the alcohol was filtered. The yield was 77% (2.7g) m.p.160-161°.

IR (Nujol): 3150-2500 (b) 1580, 1500, 1300, 1240, 1180, 1080, 1030, 690, 640, 630 cm^{-1}.

PMR (DMSO, δ): 4.67 (s, 2H), 7.4 (m, 3H), 8.16 (m, 2H).

M/e : 175 (M^+, B) , . 159, 146, 129, 118, 104, 91, 77.

Analysis Calcd for $C_9H_9N_3O$: C, 61.72; H, 5.142

observed C, 61.42; H, 5.32%

3-Hydroxymethyl-1-phenacyl-5-phenyl-1,2,4-triazole (5a)

To alcohol (**4**) (515 mg, 3 mmol) and potassium carbonate (408mg, 3 mmol) in acetone (25 ml) was added phenacyl bromide (660 mg, 3.3 mmol) over a period of 1 hour at 0 to 10°. Further stirring for 4 hours at room temperature completed the reaction. Reaction mixture was then filtered and filtrate was evaporated. Residue was washed with water and extracted with ethyl acetate. Organic layer was then washed with brine, dried over sodium sulfate and evaporated to give compound (**5a**) in quantitative yield. The white solid obtained melted in the range 175-192°. The crude product showed a clear PMR ($CDCl_3$, δ): 4.9 (s , 2H, $-CH_2OH$), 5.8 (s, 2H, $N-CH_2-CO-$), 7.5 (m, 6H, ArH), 8.0 (m, 4H ArH). Crystallisation from ethyl acetate reduced the range in melting point to 187-192°. Extensive column chromatography using pet.ether-ethyl acetate (mixtures) as eluent did not yield sharp melting solid, so further reaction were carried out on the crude product.

IR (Nujol): 3150 (b), 1700, 1600, 1440, 1340, 1220, 1050, 760, 720, 690 cm^{-1}.

M/e: 293 (M^+), 186, 174, 131, 105, 91, 77.

Analysis: Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12

observed: C, 69.33; H, 4.96%.

3-Hydroxymethyl-1-(4-chlorophenacyl)-5-phenyl-1,2,4-triazole (5b)

Prepared the same way as (**5a**)in quantitative yield, m.p.199-203° for the crude compound. Crystallisation from methanol yielded solid, m.p.203°.

IR (Nujol): 3250(b), 1720, 1600, 1500, 1420, 1230, 1100, 1050, 830, 795, 780, 730 cm^{-1}.

PMR ($CDCl_3$, δ): 4.85 (s, 2H), 5.8 (s, 2H), 7.5 (m, 5H), 8.0 (m, 4H).

M/e: 327 (M^+), 141, 139(B), 131, 111, 104, 77.

Analysis: Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.38; H, 4.28; Cl, 10.70.
observed C, 62.07; H, 4.11; Cl, 10.26%

3-Chloromethyl-1-phenacyl-5-phenyl-1,2,4-triazole (6a)

To the stirred suspension of phenacylated alcohol (**5a**) (1 g) in dry chloroform (25 ml) at 0-10° was added thionyl chloride (1.5 ml). As the reaction proceeds a clear solution is formed. After stirring overnight, excess thionyl chloride and chloroform were removed under reduced pressure. Residue was thoroughly washed with water and extracted with ethyl acetate. Ethyl acetate layer was then washed with brine and dried over sodium sulfate. Evaporation of the solvent gave chloro compound in quantitative yield. Crystallisation from methanol yielded sharp melting (143°) crystalline solid.

IR (Nujol): 1700, 1600, 1440, 1340, 1220, 720 cm^{-1}.

PMR ($CDCl_3$, δ): 4.73 (s, 2H, $-C\underline{H}_2Cl$), 5.76 (s, 2H, $N-C\underline{H}_2-C-$), 7.43 (m, 6H, Ar$\underline{H}$), 8.0 (m, 4H, Ar$\underline{H}$).

M/e: 311 (M^+), 276, 193, 131, 106, 105, 91, 77, 51.

Analysis: Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.59;H, 4.50;Cl,11.26

observed C, 65.87; H, 4.74; Cl, 11.28%.

3-Chloromethyl-1-(4-chlorophenacyl)-5-phenyl-1,2,4-triazole (6b)

Prepared the same way as (**6a**).

Yield: 99.1%, m.p. 170°.

IR (Nujol): 1700, 1600, 1400, 1220, 1100, 1000, 820, 790, 720, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 4.77 (s, 2H), 5.82 (s, 2H), 7.4 (m, 5H), 7.95 (m, 4H).

M/e: 345 (M^+), 139, 131.

Analysis: Calcd. for $C_{17}H_{13}Cl_2N_3O$: C, 59.13; H, 3.79

observed: C, 58.87; H, 4.02%

2,6-Diphenyl-8H-[1,2,4] triazolo [5,1-c] [1,4] oxazine (7a)

50% dispersion of sodium hydride (72 mg, 1.5 mmol) was washed with dry petroleum ether. It was suspended in tetrahydrofuran and cooled to 15°. To this stirred suspension chlorocompound (**6a**) (311 mg, 1 mmol) was added in small quantities. Reaction was slightly exothermic. Addition was complete in fifteen minutes. After stirring for another two hours, solvent was removed and residue was extracted with ethyl acetate. Extract was washed with water till neutral, then with brine and dried over sodium sulfate. Evaporation of the solvent gave crude product (235 mg). Purification by silica gel column chromatography using benzene-ethyl acetate (95:5) as an eluent yielded triazolo oxazine (**7a**) in 55% yield melting at 154°.

IR (Nujol): 1480, 1460, 1360, 1285, 1060, 840, 820, 785 cm^{-1}.

PMR ($CDCl_3$, δ): 5.5 (s, 2H $-\underline{CH}_2-O$), 7.3 (s, 1H, N $-\underline{CH}=C(Ph)O-$), 7.4 (m, 8H, Ar$\underline{H}$), 8.1 (dd, 2H, J=6, 2 Hz).

M/e: 275 (M^+), 246, 137.5 (M^{++}), 105, 104, 77.

UV (MeOH): 310 nm and 205 nm.

Analysis: Calcd. for $C_{17}H_{13}N_3O$: C, 73.91; H, 4.99.

observed C, 74.2; H, 4.727%.

2-Phenyl-6-(4-chlorophenyl)-8H-[1,2,4] triazolo [5,1-c] [1,4] oxazine (7b)

Prepared the same way as (**7a**)

Yield: 95%, m.p.187-8°.

IR (Nujol): 1610, 1490, 1460, 1420, 1390, 1365, 1100, 1280, 1020, 840, 730, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 5.5 (s, 2H), 7.4 (m, 8H), 8.06 (dd, 2H, J=6, 2 Hz).

M/e: 309, 139, 111, 103, 75.

Analysis: Calcd. for $C_{17}H_{12}ClN_3O$: 66.02; H, 3.87; Cl, 11.32.

observed: C, 66.44; H, 4.13; Cl, 11.16%.

Preparation of Lawesson's reagent[27]

Freshly distilled anisole (10.8 g) and phosphorus pentasulfide (4.4 g) in the mole ratio 10:1 were heated at 155° for 6 hrs. Moisture was strictly forbidden. After cooling, precipitated yellow coloured crystalline solid was filtered. It was washed with chloroform and ether (m.p. 229°, 50%).

2,6-Diphenyl-8H-[1,2,4]triazolo [5,1-c] [1,4) thiazine (9a)

Chloro compound (**6a**) (311 mg, 1 mmol) and Lawesson reagent (202 mg, 0.5 mmol) were refluxed in toluene (30 ml) for 3 hours. Completion of the reaction was determined by tlc analysis using benzene-ethyl acetate (95:5) as a solvent system. Toluene was removed under reduced pressure and residue was chromatographed on a silica gel column using benzene-ethyl acetate (98:2) as an eluent. Triazolothiazine (**9a**) was obtained in 50% yield (161 mg), m.p.148-9°.

IR (Nujol): 1465, 1350, 1270, 1100, 760, 750, 720, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 4.3 (s, 2H), 7.3 (m, 8H, ArH), 7.5 (s, 1H, -N-CH=C(Ph)S-), 8.0 (dd, 2H, J=6, 2 Hz).

M/e: 291 (M^+), 145.5 (M^{++}), 121 ($C_6H_5CS^+$), 105, 77.

Analysis: Calcd. for $C_{17}H_{13}N_3S$: C, 70.1; H, 4.57; S, 11.0.

observed C, 69.91; H, 4.60; S, 10.63%.

UV (MeOH): 325, 250.5 and 205 nm.

2-Phenyl-6-(4 -chlorophenyl)-8H-[1,2,4] triazolo [5,1-c] [1,4] thiazine(9b)

Prepared the same way as (**9a**) in 50% yield, m.p.205°.

IR (Nujol): 1610, 1570, 1470, 1090, 1010, 820, 720, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 4.3 (s, 2H), 7.53 (m, 6H), 8.2 (dd, 4H, J=6, 2 Hz).

M/e: 325 (M^+), 155 ($4\text{-}Cl\text{-}C_6H_4CS^+$)

Analysis: Calcd. for $C_{17}H_{12}ClN_3S$: C, 62.76; H, 3.692;

observed: C, 62.53; H, 3.42%.

2,6-Diphenyl-8H-5,6-dihydro [1,2,4] triazolo [5,1-c][1,4] oxazine (8)

Compound (**7a**) (270 mg, 0.98 mmol) with 10% palladised charcoal (140 mg) in ethyl acetate (20 ml) was hydrogenated with hydrogen gas at room temperature at 50 psi pressure till no more hydrogen was absorbed. Reaction mixture was then filtered and filtrate evaporated to give 265mg (95%) of white solid. Crystallisation from pet.ether-ethyl acetate (40:60) yielded compound (**8a**) melting at 112°.

IR (Nujol): 1500, 1460, 1370, 1260, 1080, 1020, 750, 730, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 4.2 (dd, 1H, J=12, 4 Hz, -$\underline{H}^e$), 4.5 (dd, 1H, J=12, 11 Hz, -$\underline{H}^d$), 5.0 (dd, 1H, J=11, 4 Hz, -C$\underline{H}$Ph), 5.0 (d, 1H, J=16 Hz, -$\underline{H}^a$), 5.3 (d, 1H, J=16 Hz, -$\underline{H}^b$), 7.4 (s, 8H), 8.1 (dd, 2H, J=6, 2 Hz).

M/e: 277 (M^+), 171 ($M^+ - C_6H_5CHO$), 131, 104, 91, 77.

Analysis: Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.425;
observed: C, 73.93; H, 5.58%

Cyanohydrin of benzaldehyde (12)

To an ice cooled solution of benzaldehyde (10.6 g, 0.1 m) in acetic acid (40 ml), ethanol (40 ml) and water (50 ml), was added potassium cyanide (32.5 g, 0.5 m) in small quantities with stirring for 30 minutes. Reaction mixture was stirred at 0° for 2 hours and then brought to room temperature. It was diluted with some more water and extracted with ether (500 ml). Ethereal layer was washed with water several times, then with brine solution and dried

over sodium sulfate. Solvent was stripped off to give cyanohydrin derivative in 86% yield (11.4 g).

IR (Nujol): 3400 (b), 1600, 1500, 1450, 1200, 1020, 740, 700 cm^{-1}.

PMR (CCl_4, δ): 4.43 (bs, exchanges with D_2O, 1H), 5.4 (s, 1H), 7.36 (s, 5H).

2-Amino-1-phenyl ethanol (13)

To lithium aluminium hydride (5 g, 0.131 m) in dry ether (75ml) at 0° was added cyanohydrin (**12**) (6.3 g, 47 mmol) in ether (75 ml). Reaction mixture was stirred at room temperature for 1 hour and then refluxed for 10 hours. It was then cooled to 0° and water (15 ml) was added cautiously. Further, 20% sodium hydroxide solution (7 ml) was added and the separated solid was filtered and washed with hot ether several times. Organic layer was dried over sodium sulfate and evaporated to give 2-amino-1-phenyl ethanol (2 g, 31%). It was distilled at 140° at 5 mm pressure.

IR (liquid): 3350-320 (b), 1600, 1500, 1460, 1020, 740 cm^{-1}.

PMR ($CDCl_3$, δ): 2.6 (d, 2H, J=6 Hz), 3.0 (s, 3H, exchangable with D_2O), 4.3 (m, 1H), 7.06 (s, 5H).

6-Phenyl-morpholin-3-one (14)

2-Amino-1-phenyl ethanol (**13**) (2.215 g, 16 mmol) was refluxed with sodium hydride (0.415 g, 17 mmol) in benzene (25 ml) for one hour. Reaction mixture was cooled and methyl chloroacetate (1.79 g, 19 mmol) was added during fifteen minutes period. The suspension was stirred for 1 more hour and then treated with enough water to dissolve the solid. It was acidified with 5% aqueous hydrochloric acid and

aqueous layer was extracted with ether. Ether and benzene extracts were dried together and concentrated to give 6-phenyl-morpholin-3-one as white solid (.945 g, 34%) m.p.112-4°.

IR (Nujol): 3190, 1700, 1100 cm^{-1}.

PMR ($CDCl_3$, δ): 3.36 (bd, 2H), 4.23 (s, 2H), 4.4 (t, 1H, J=6 Hz), 7.2 (s, 5H), 7.93 (bs, 1H).

3-Ethoxy-6-phenyl-3,4-dehydromorpholine (15)

Compound (**14**) (380 mg, 2.15 mmol) in chloroform (20 ml) was added to a stirred suspension of triethyloxoniumfluoroborate (400 mg, 2.2 mmol) in chloroform (15 ml) at 10° and the mixture was stirred for 5 hours. It was then cooled to -3° and stirred vigorously when a complex separated. Then 50% potash solution was added at 5° dropwise till pH 8, to separate potassium fluoroborate as precipitate. It was filtered through a cloth filter and organic layer was separated. Aqueous layer was extracted with chloroform, bulk extracts were dried over sodium sulfate and evaporated to give lactim ether (330 mg, 75%).

IR (Nujol): 1695, 1260, 1120, 760, 700 cm^{-1}.

PMR (CCl_4, δ): 1.2 (t, 3H, J=7 Hz), 3.3 (m, 2H), 4.16 (m, 5H), 7.06 (s, 5H).

1-Benzoyl-2-(2H,5,6-dihydro[1,4] oxazin-3-yl) hydrazine (16)

To the lactim ether (**15**) (1.1 g, 5.3 mmol) in ethanol (10 ml) was added benzoyl hydrazide (750 mg, 5.5 mmol) and solution was stirred for 2 hours and kept overnight at room temperature. White solid separated (900 mg, 57%) was filtered, m.p.199°.

IR (Nujol): 3280, 1660, 1610, 1550, 730, 690 cm^{-1}.

PMR (TFA, δ): 4.4 (s, 4H), 4.75 (m, 1H), 7.4 (m, 8H), 7.8 (dd, 2H).

M/e: 295 (M^+), 105 ($C_6H_5\overset{+}{C}O$), 104, 77.

Analysis: Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 6.09

observed C, 68.70; H, 6.09%

3,6-Diphenyl-8H-5,6-dihydro [1,2,4] triazolo [3,4-c][1,4] oxazine (17)

Compound (**16**) (590 mg, 2 mm) was refluxed in o-dichlorobenzene (25 ml) for 4 hours. On cooling separated starting hydrazide was filtered and filtrate was concentrated to about 10 ml and then pet.ether was added to get 300 mg of condensed product (**17**) (56%), m.p. 164°.

IR (Nujol): 1500, 1440, 1240, 1030, 890 cm^{-1}.

PMR ($CDCl_3$, δ): 4.1 (m, 2H, $-\underline{H}^a-\underline{H}^b$), 4.8 (dd, J = 9,4 Hz, -CHPh), 5.1 (d, 1H, J=16 Hz, $-H^c$), 5.4 (d, 1H, J=16 Hz, $-H^d$), 7.4 (m, 8H), 7.7 (dd, 2H, J=6, 2 Hz).

M/e: 277 (M^+), 171 ($M^+ - C_6H_5CHO$).

Analysis: Calcd. for $C_{17}H_{15}N_3O$: C, 73.64; H, 5.41.

observed C, 73.32; H, 5.23%

Preparation of 2-bromo-α-tetralone[32]

To a suspension of α-tetralone (14.6 g, 0.1 m) in anhydrous ether (100 ml), bromine (16 g, 0.1 m) was added dropwise. Reaction was exothermic and bromine color decolorised very fast hence the solution was cooled to 10° and bromine addition was carried out slowly. Reaction mixture was stirred for 1 hour after complete addition and then poured on ice water. Ether layer was separated, washed with dilute aqueous

sodium bicarbonate solution water and dried over sodium sulfate. Evaporation of the solvent gave 2-bromo-α-tetralone, 15.6 g(70%) (lit. m.p.37-38°).

3-Hydroxymethyl-1-[1-oxo-3,4-dihydronaphth-2-yl]-5-phenyl-1,2,4-triazole (18)

To the stirred suspension of 3-hydroxymethyl-5-phenyl-1,2,4-triazole (**4**) (875 mg, 5 mmol) and potassium carbonate (680 mg, 5.5 mmol) in acetone (60 ml) was added 2-bromo-α-tetralone (1.125g, 5 mmol) during 1 hour. Reaction mixture was stirred for 20 hours. Solvent was removed. Residue was washed thoroughly with water, dried and then chromatographed on a silica gel column using ethyl acetate as an eluent to afford alkylated product (800 mg) in 50% yield. Starting unreacted alcohol was also recovered from the column. Crystallisation from methanol afforded sharp melting crystalline solid m.p.180-1°.

IR (Nujol): 3200-3100(b), 1700, 1610, 1440, 1230, 1020 cm^{-1}.

PMR ($CDCl_3$, δ): 2.8 (m, 4H), 4.8 (s, 2H, $-CH_2OH$), 5.28 (dd, 1H, J=6, 2 Hz), 7.24 (m, 6H), 8.04 (m, 3H).

M/e: 319 (M^+), 176 (B)

Analysis: Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.33

observed: C, 71.18; H, 5.15%

3-Chloromethyl-1-[1-oxo-3,4-dihydronaphth-2-yl]-5-phenyl-1,2,4-triazole(19)

To the stirred suspension of compound(**18**)(638 mg, 2 mmol) in chloroform(20 ml)was added thionyl chloride(2 ml, excess) under ice cold condition. It was further stirred for 5 hrs., solvent and excees thionyl chloride were then removed under reduced pressure.

Residue was washed with water and extracted with ethyl acetate. Organic extract was washed with brine and dried over sodium sulfate. Evaporation of the solvent gave chloro compound (**19**) (660 mg) in 99% yield. Crystallisation from methanol gave sharp melting crystalline solid 183-4°.

IR (Nujol): 1700, 1610, 1280 cm^{-1}.

PMR ($CDCl_3$, δ): 2.88 (m, 4H), 4.84 (q, 2H, J=5.28 (m, 1H), 7.40 (m, 6H), 8.0 (m, 3H),

M/e: 337 (M^+), 301, 144.

Analysis: Calcd. for $C_{19}H_{16}ClN_3O$: C, 67.65; H, 4.747

observed C, 67.82; H, 4.64%

2-Phenyl-12H-5,6-dihydronaphtho[1,2-b][1,2,4]triazolo [1,5-d] [1,4] oxazine (20)

To sodium hydride (180 mg, 3.75 mmol) in suspension with tetrahydrofuran (20 ml) was added chloro compound (**19**) (422 mg, 1.25 mmol) with stirring. Evolution of hydrogen gas could be observed. After stirring for 2 hours, it was poured on ice cold water and extracted with ethyl acetate. Ethyl aceatate layer was washed with water, brine, dried over sodium sulfate and solvent was removed to give cyclised product (298 mg) in 71% yield. Crystallisation from pet. ether-ethyl acetate (50:50) gave solid m.p.182°.

IR (Nujol): 1680, 1480, 1400, 790, 765, 720 cm^{-1}.

PMR ($CDCl_3$, δ): 3.1 (s, 4H), 5.5 (s, 2H), 7.3 (m, 7H), 8.0 (dd, 2H, J=6, 2 Hz).

M/e: 301 (M^+), 158, 103, 77.

Analysis: Calc. for $C_{19}H_{15}N_3O$: C, 75.74; H, 4.98

observed C, 75.43; H, 4.81%

2-Phenyl-12H-5,6-=dihydronaphtho [1,2-b] [1,2,4] triazolo [1,5-d] [1,4] thiazine (21)

Chloro compound (**19**) (740 mg, 2.2 mmol) and Lawesson reagent (444 mg, 2.2 mmol) in toluene (25 ml) were refluxed together for 4 hours. Toluene was removed and residue was chromatographed over silica gel column (30 g) using pet.ether-chloroform (60:40) as eluting solvent to yield (**21**) in 46% yield (320 mg). Crystallization from pet. ether-ethyl acetate (70:30) gave crystalline solid m.p.192°.

IR (Nujol): 1610, 1550, 1510, 1120, 760, 720, 680 cm^{-1}.

PMR ($CDCl_3$, δ): 3.1 (m, 4H), 4.2 (s, 2H), 7.4 (m, 7H), 8.0 (dd, 2H, J=6, 2 Hz)

M/e: 317 (M^+).

Analysis: Calcd. for $C_{19}H_{15}N_3S$: C, 71.92; H, 4.73

observed: C, 71.52; H, 5.09%

2-Phenyl-12H-naphtho[1,2-b][1,2,4]triazolo[1,5-d] [1,4] Oxazine (22)

Dihydro compound (**20**) (602 mg, 2 mmol) and DDQ (500 mg, 2.2 mmol) were refluxed together in dry benzene (25 ml) under nitrogen atmosphere for 5 hours. Solvent was removed and residue was chromatographed over neutral alumina using chloroform-pet.ether (50:50) as eluting solvent. Compound (**22**) was obtained in 53% yield. Crystallisation from pet.ether-ethyl acetate (30:70) aforded solid melting at 210°.

IR (Nujol): 1630, 1600, 1490, 1440, 1180, 1000, 810, 710, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 5.65 (s, 2H), 7.8 (m, 11H).

M/e: 299 (M^+), 156, 128, 101, 77.

Analysis: Calcd. for $C_{19}H_{13}N_3O$: C, 76.25; H, 4.34.

observed C, 76.35; H, 4.34%.

2-Phenyl-12H-naphtho [1,2-b] [1,2,4] triazolo [1,5-d] [1,4] thiazine(23)

Dihydro compound (**21**) (380 mg, 1.2 mmol) and DDQ (590 mg, 2.6 mmol) in dry benzene (60 ml) were refluxed under nitrogen atmosphere for 5 hours. Solvent was removed and residue chromatographed over alumina column using chloroform-pet.ether (40:60) as eluting solvent to obtain a light green colored solid melting at 205°.

IR (Nujol): 1620, 1550, 1380, 770, 730, 700 cm^{-1}.

PMR ($CDCl_3$, δ): 4.33 (s, 2H), 7.8 (m, 11H).

M/e: 229, 228, 202, 200, 183.

Analysis: Calcd. for $C_{19}H_{13}N_3S$: C, 72.38; H, 4.13; N, 13.33.

observed C, 71.96; H, 3.87; N, 13.12%

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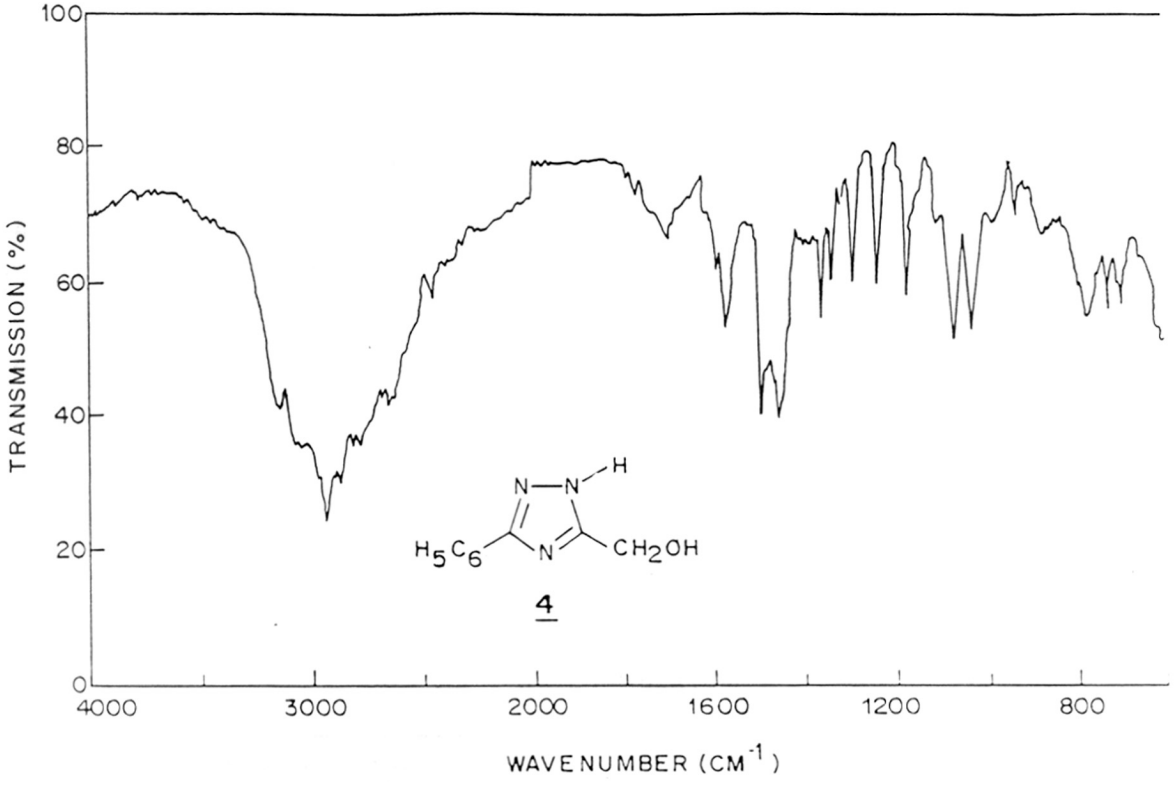
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20
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1600
1200
800
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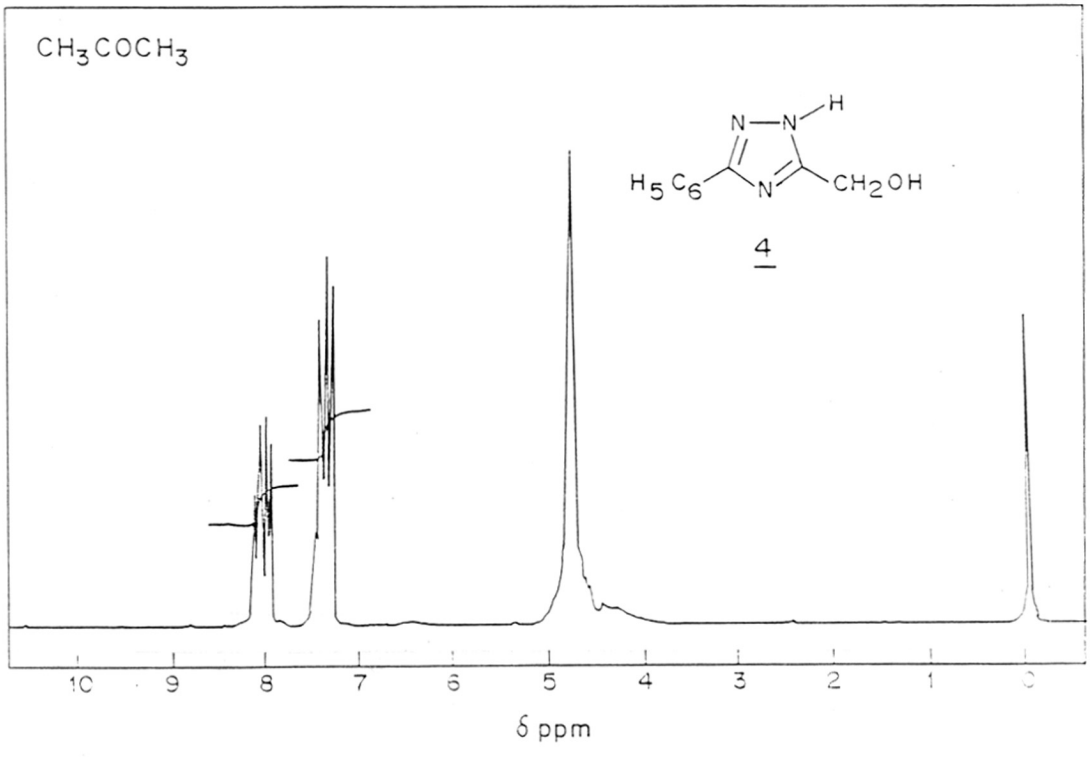
CH2OH

4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N—N—H
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7
6
5
4
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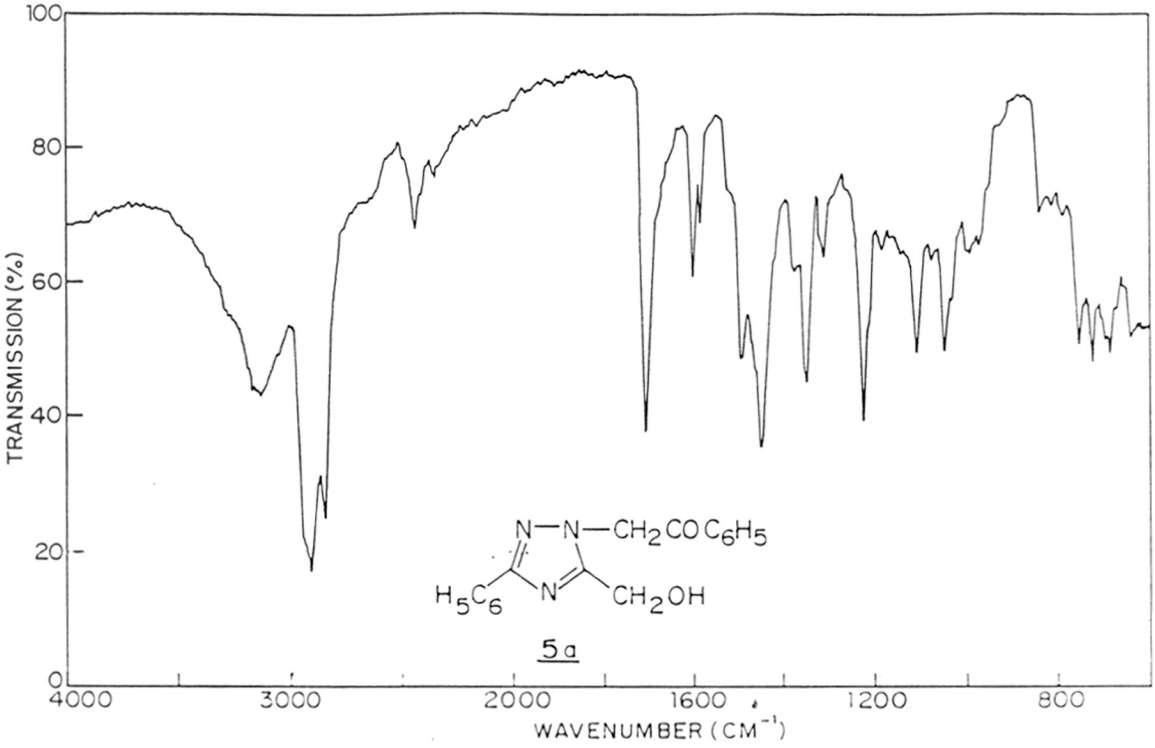
2
1
0
δ ppm

4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TRANSMISSION (%)
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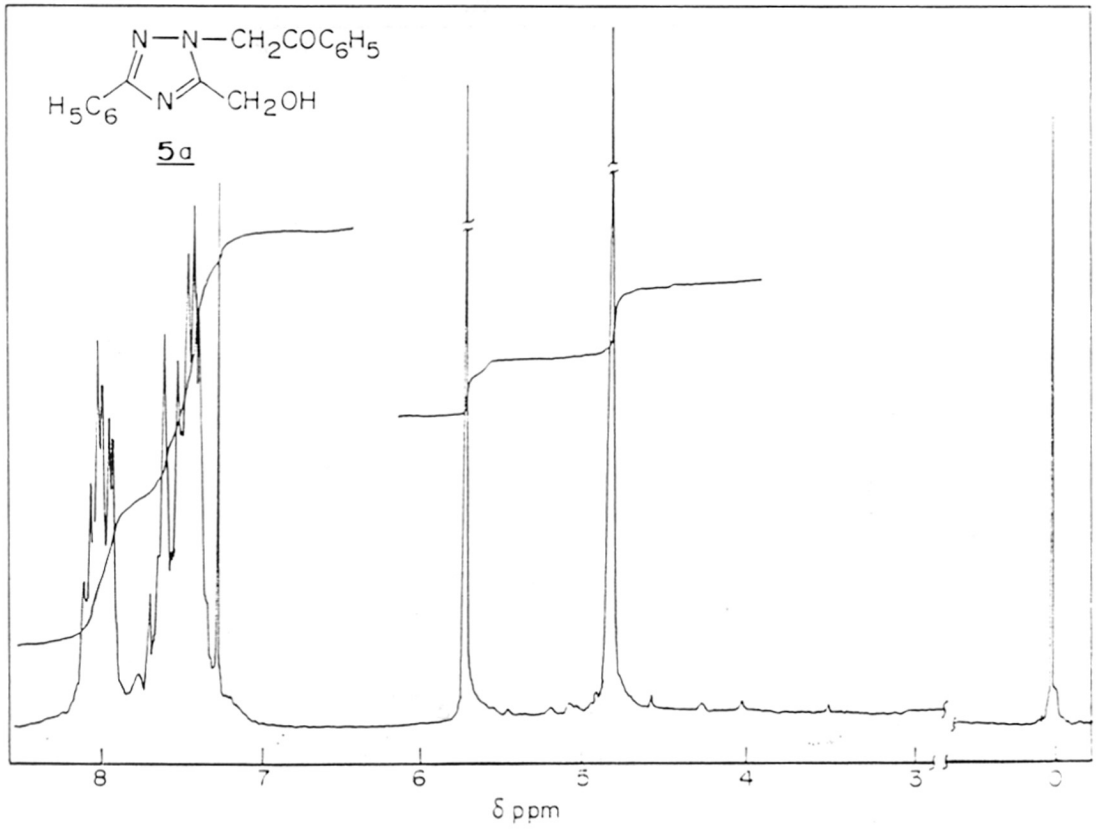
H5C6
N
CH2OH

5a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H5C6
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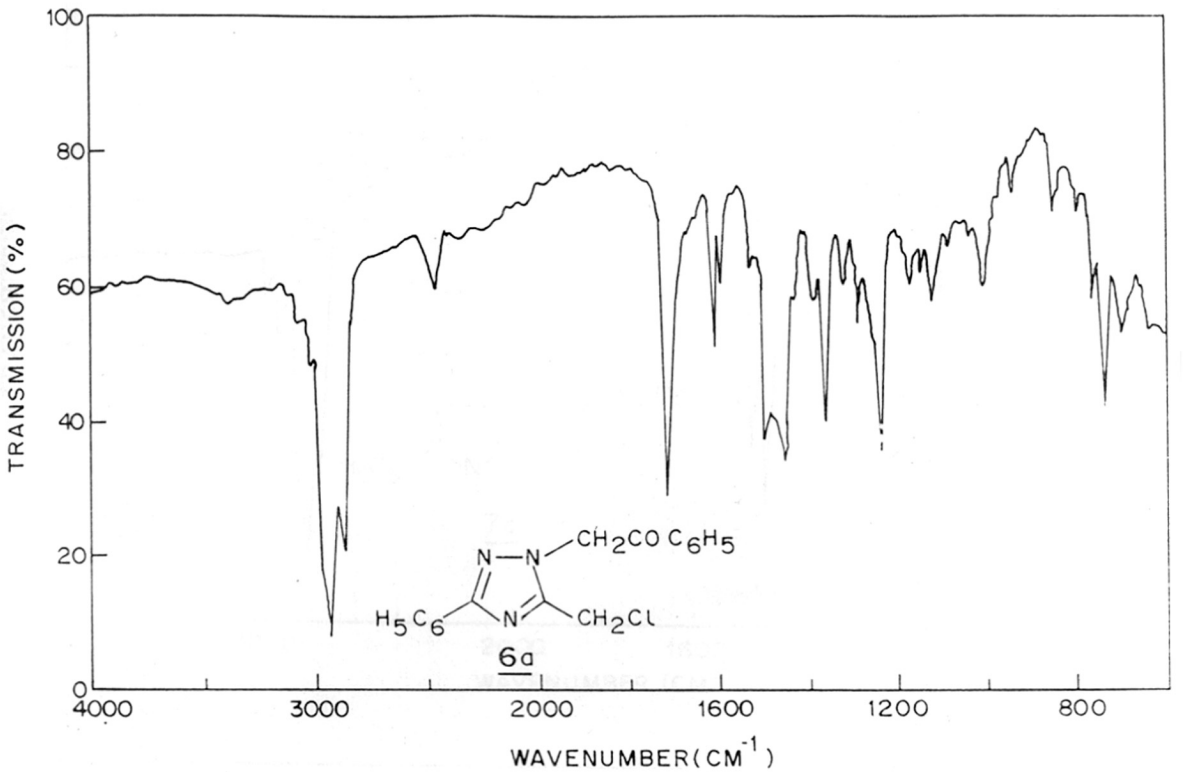
CH2OH
8
7
6
5
4
3
δ ppm

5a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TRANSMISSION (%)
4000
3000
2000
1600
1200
800
WAVENUMBER(CM^{-1})
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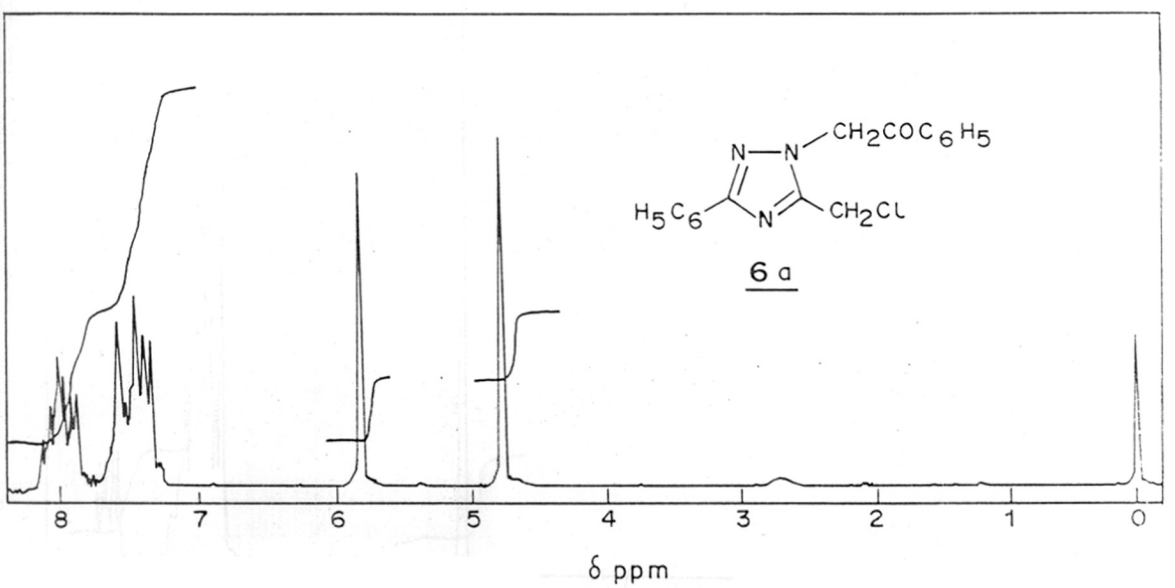
CH$_2$CO C$_6$H$_5$
H$_5$C$_6$
N
CH$_2$Cl
6a


N—N
CH$_2$COC$_6$H$_5$
H$_5$C$_6$
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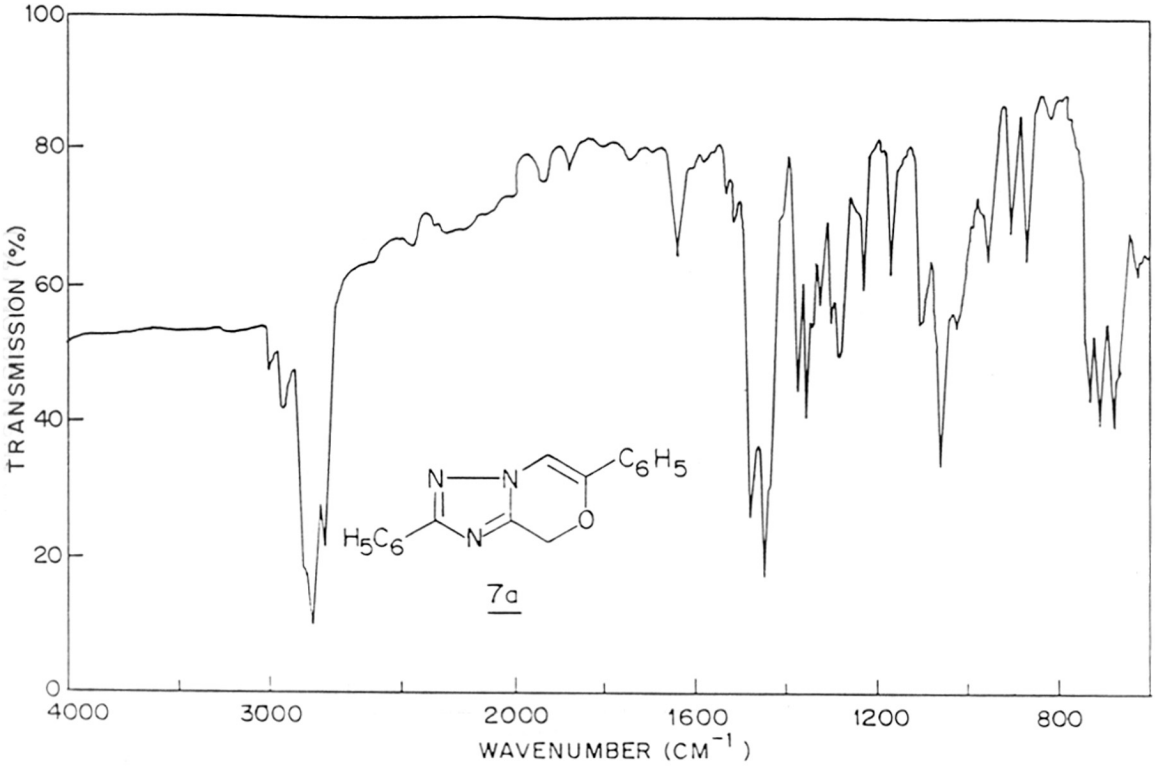
CH$_2$Cl
6 a
8
7
6
5
4
3
2
1
0
δ ppm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20
0
TRANSMISSION (%)
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2000
1600
1200
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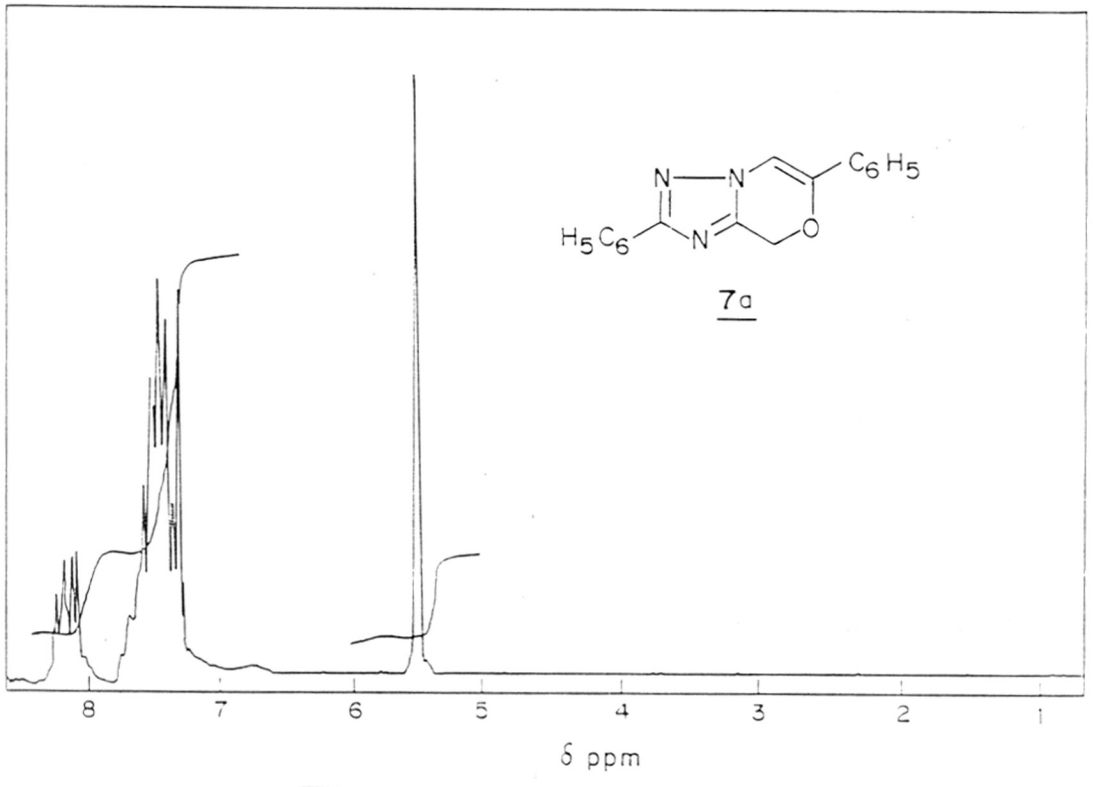
H_5C_6
N
O

7a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C_6H_5
H_5C_6
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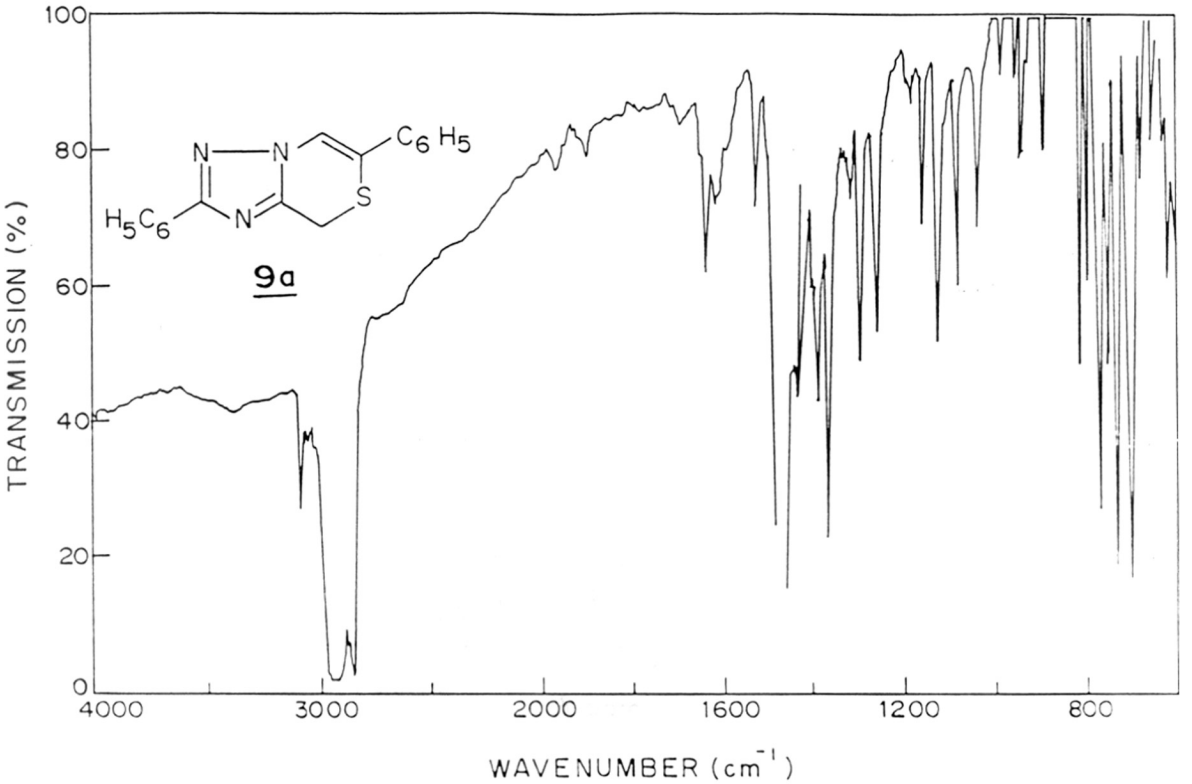
O
8
7
6
5
4
3
2
1
δ ppm

7a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20
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1200
800
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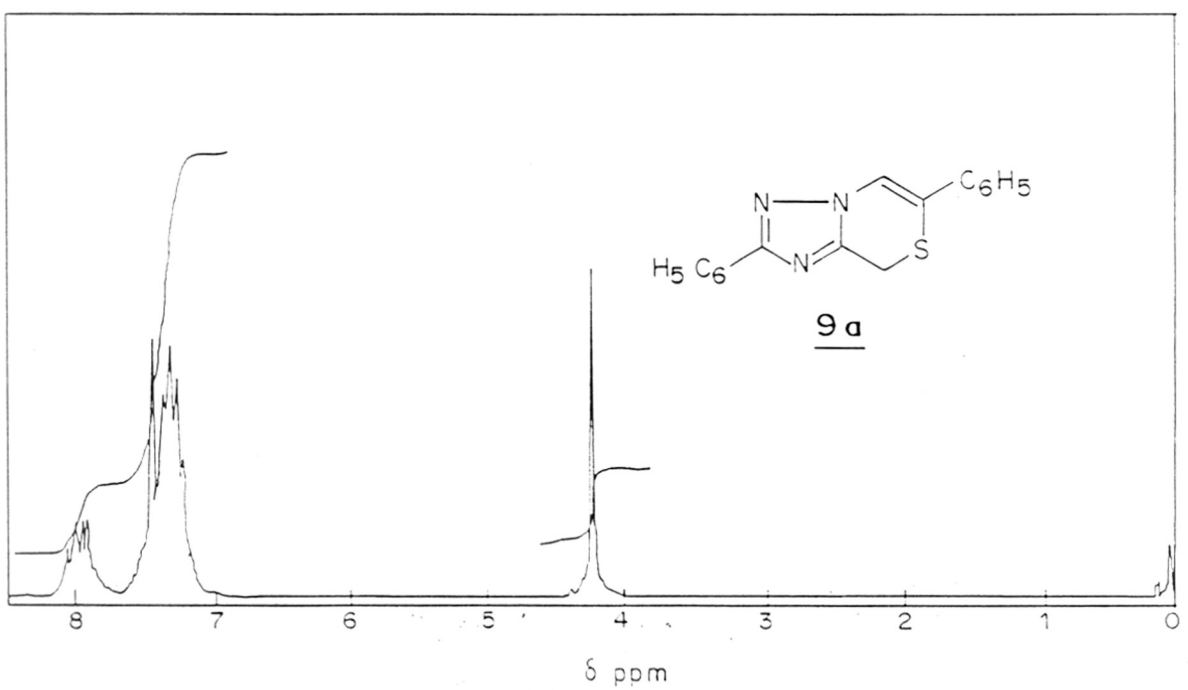
N
C6 H5
S
H5C6
N
9a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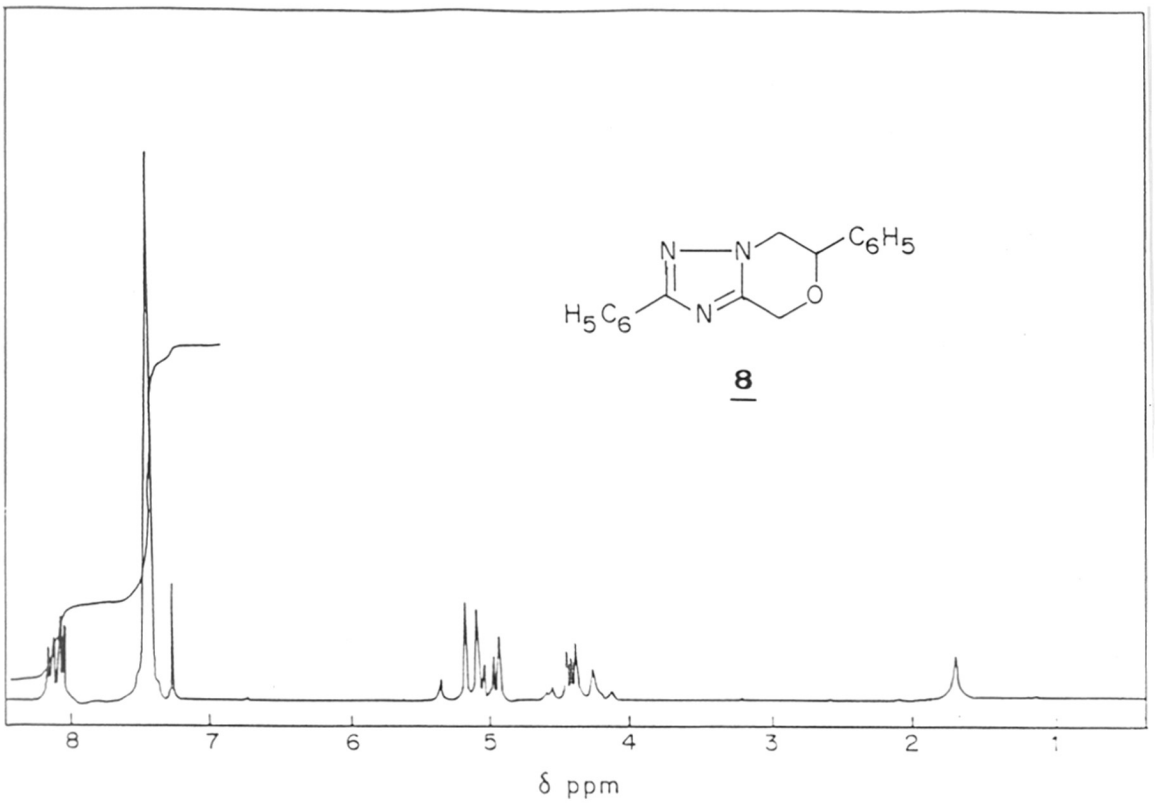
7
6
5
4
3
2
1
0
δ ppm
N
N
C6H5
S
H5 C6
N
9a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C_6H_5
H_5C_6
N
O
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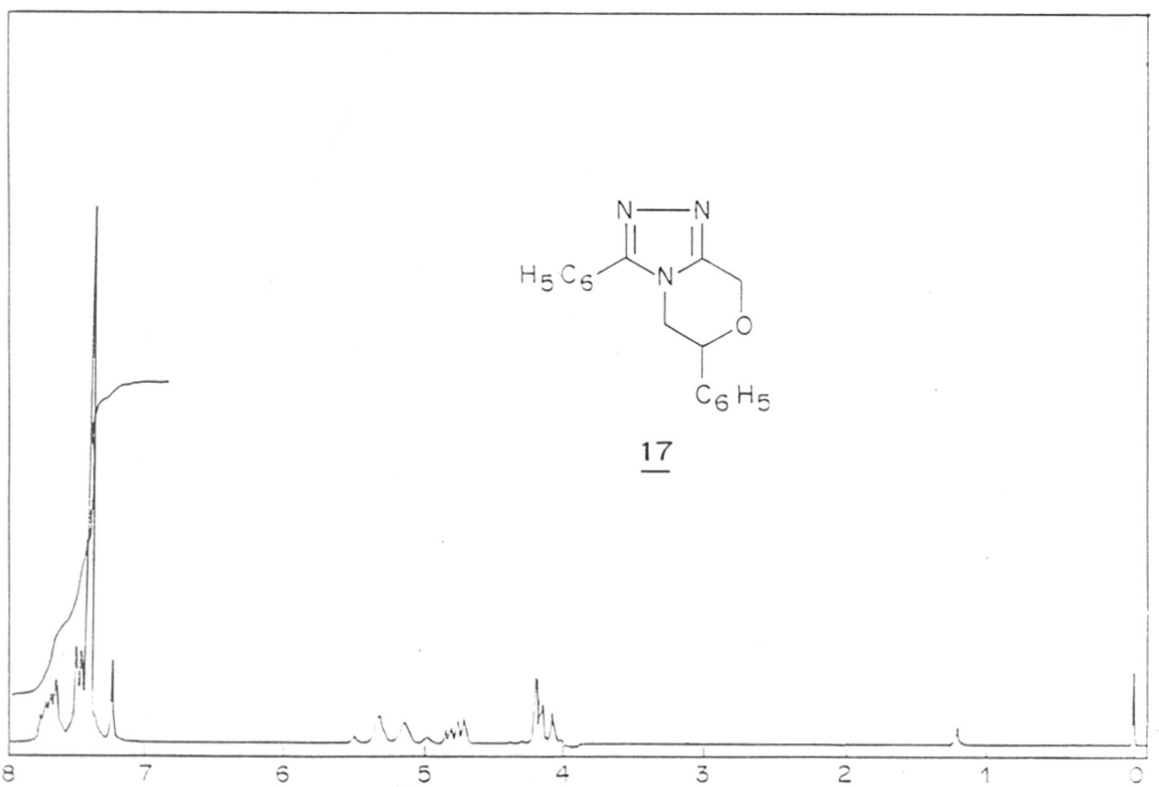
7
6
5
4
3
2
1
δ ppm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H_5C_6
N
O
C_6H_5
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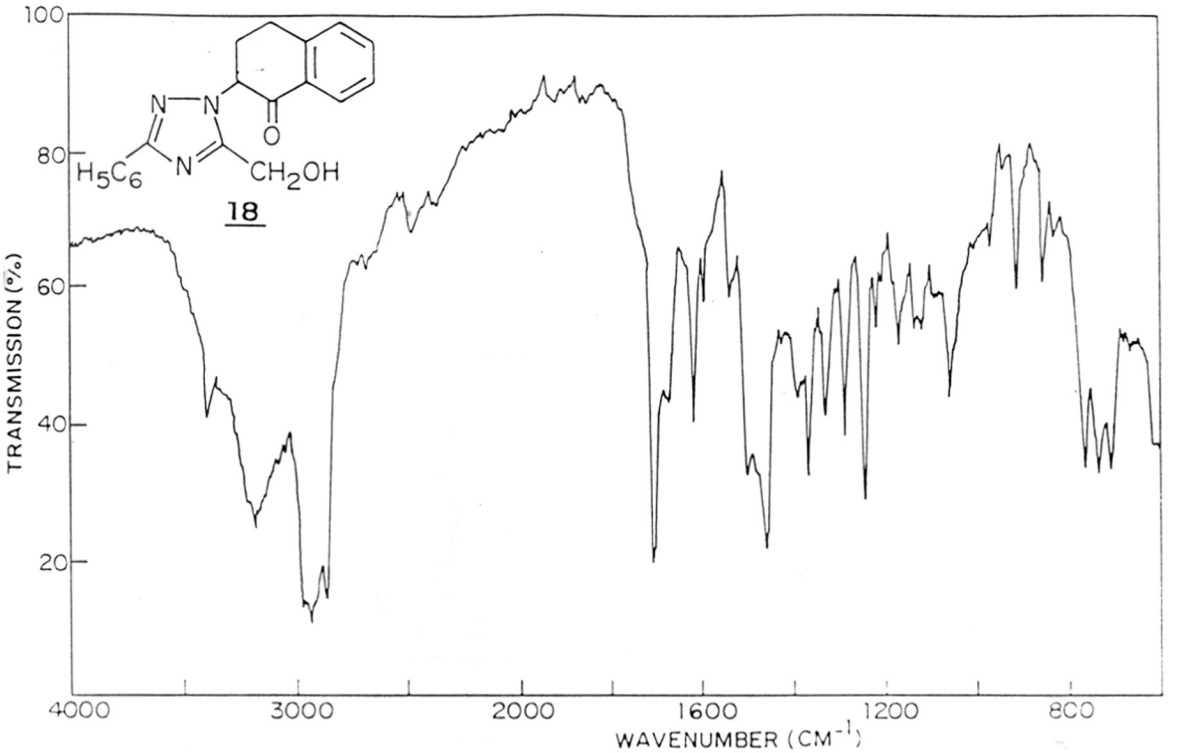
6
5
4
3
2
1
0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H5C6
N
CH2OH
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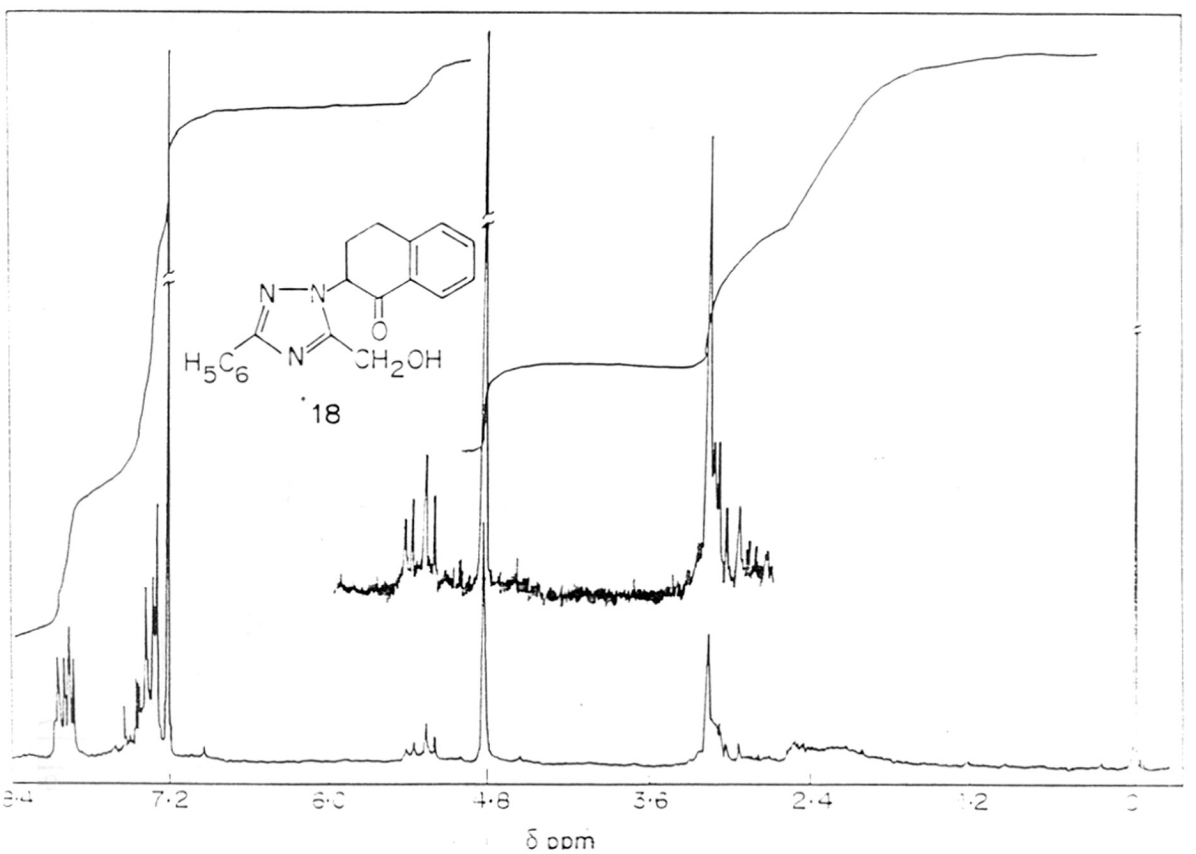
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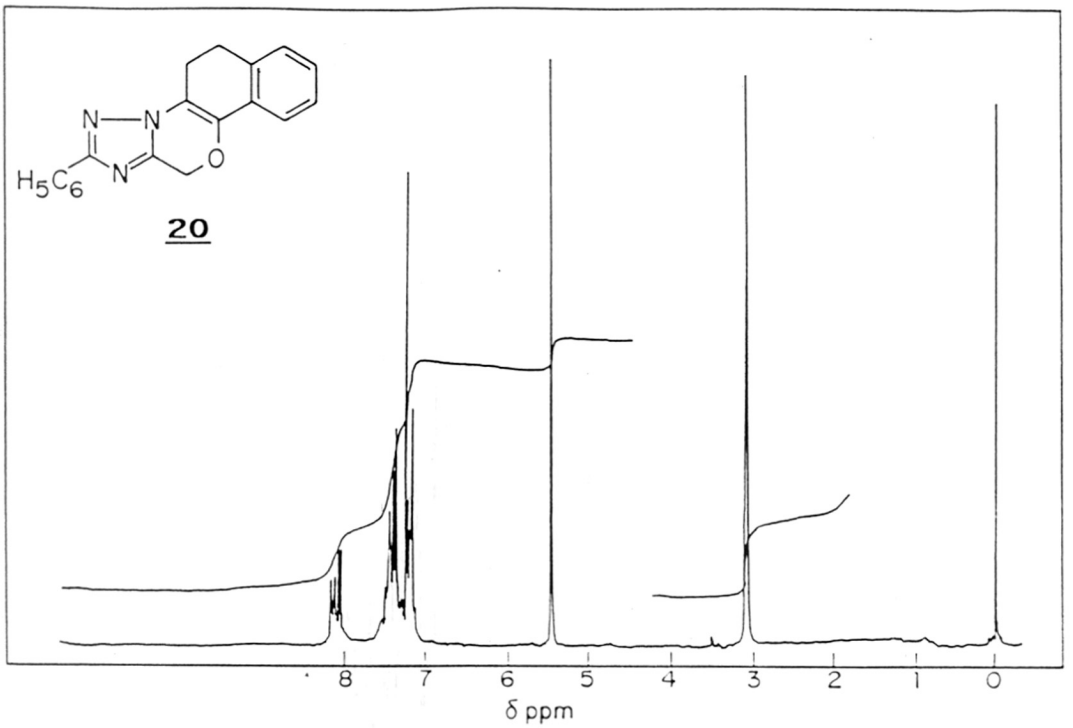
O
H5C6
N
CH2OH
18
7·2
6·0
4·8
3·6
2·4
δ ppm



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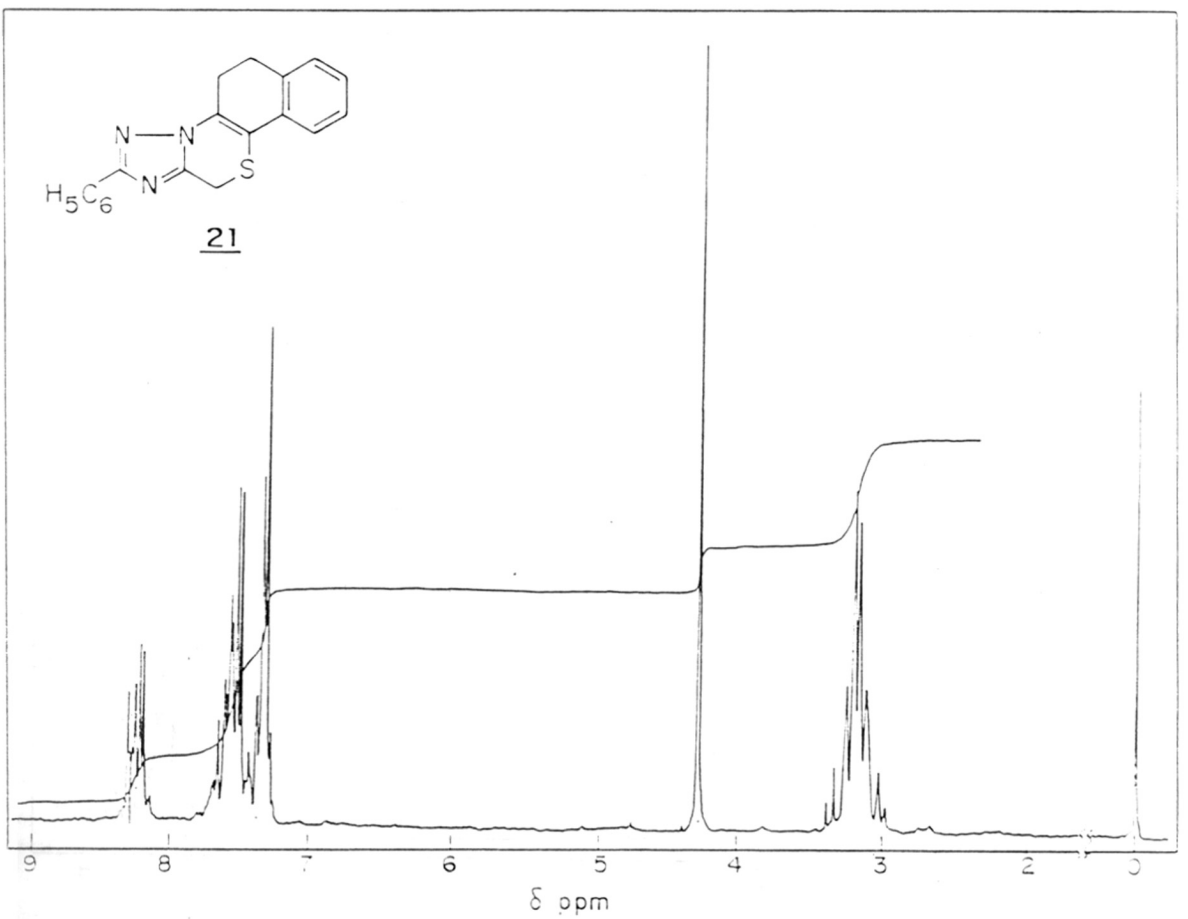

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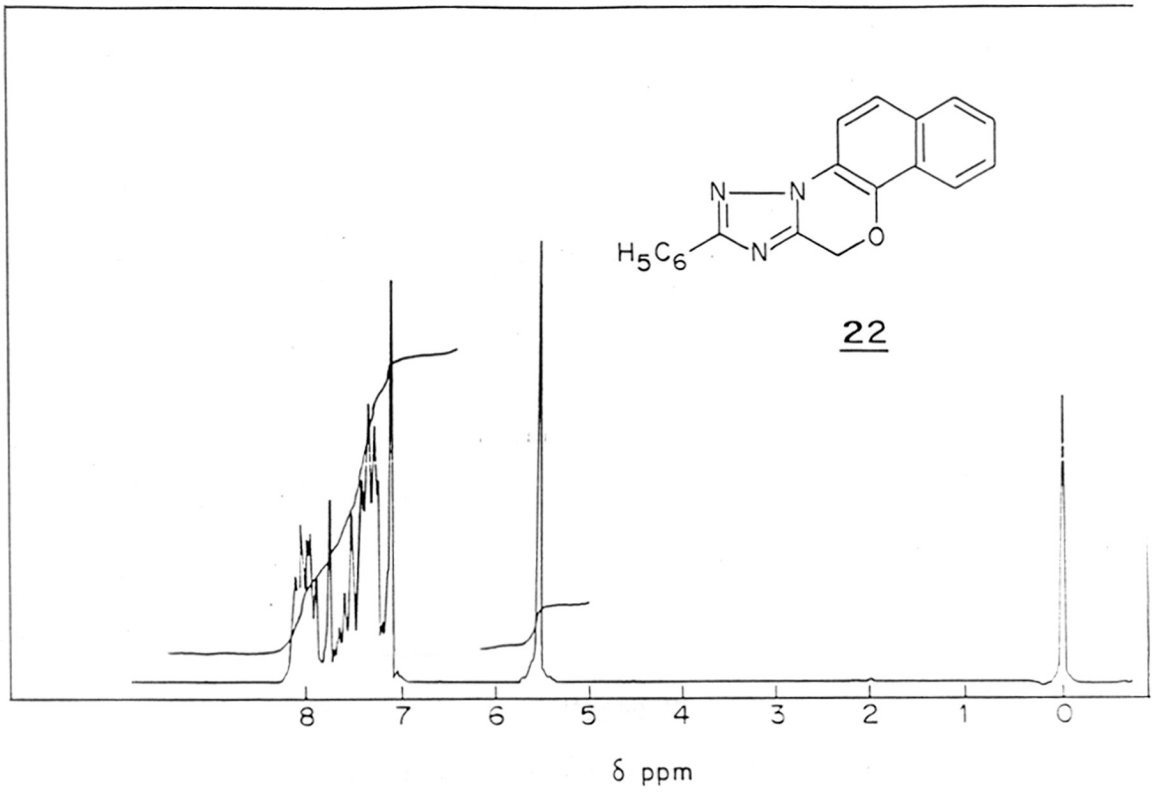

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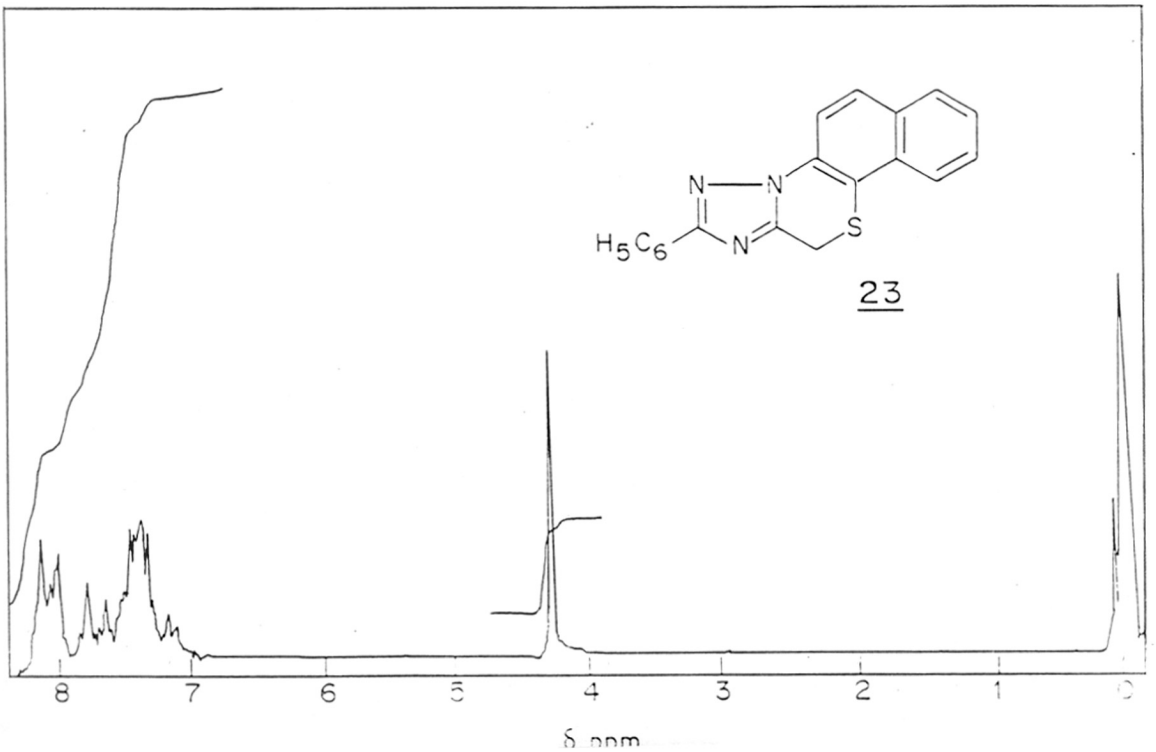


23

CHAPTER IV

Synthesis of thiophene derivatives from enamine-isothiocyanate adduct

SUMMARY

A versatile route has been developed by Rajappa et al.[1] for thiophene synthesis starting from enamine-isothiocyanate adduct. Effect of strong electron attracting groups like carbethoxy and sulfonyl on the isothiocyanate residue was studied by reacting N-carbethoxy and N-sulfonyl isothiocyanates with an enamine in this synthesis.

Ethoxycarbonyl isothiocyanate (**3**) and enamine (**2**) form the adduct (**4**) which was alkylated with substituted phenacyl bromides and further cyclised to thiophenecarbamates (**5**).

Arylsulfonyl isothiocyanates (**8**) when reacted with the enamine (**2**) did not give the expected adduct. Structural assignment to the main product of this reaction needs X-ray diffraction analysis.

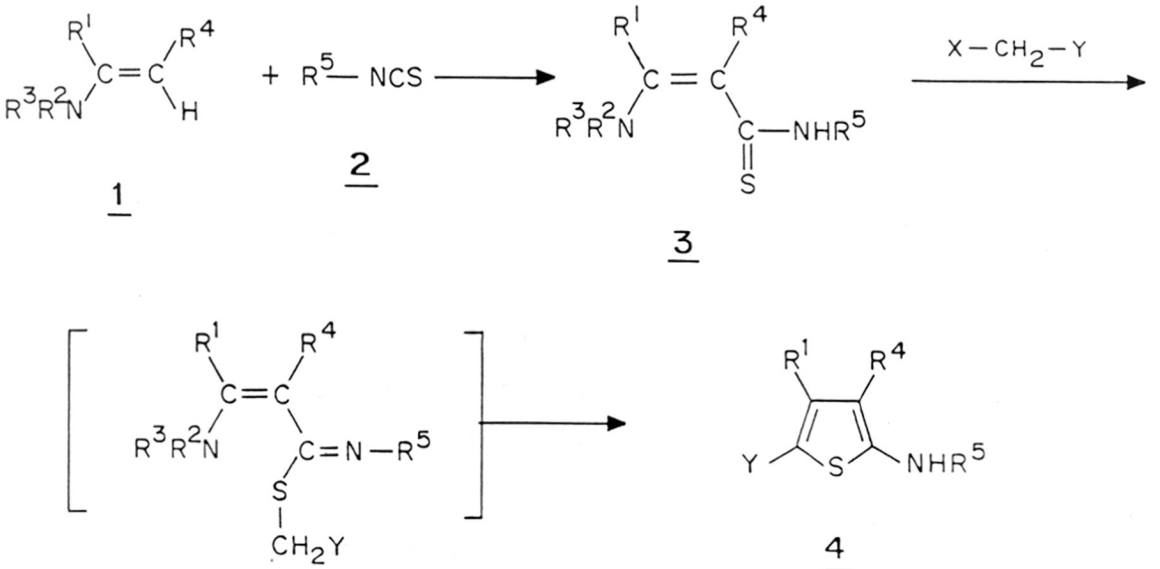
INTRODUCTION

A useful and flexible synthetic route to thiophenes via the adduct formed from enamines and isothiocyanates was reported by Rajappa[1]. The scope of the reaction was later fully explored by Rajappa and co-workers[2], systematically varying all the constituents. The strategy followed was the S-alkylation of the enamine-isothiocyanate adduct with an alkylating agent bearing an active methylene group which could subsequently further cyclise to the thiophene (Scheme I).

In the present work described in this chapter, it was thought worthwhile and interesting to study the reactivity of isothiocyanates bearing strong electron withdrawing groups like N-carbethoxy or N-sulfonyl in adduct formation with enamines, S-alkylation of the adduct and subsequent cyclisation to the heterocycle. For example, N-sulfonyl isothiocyanates are known to be highly reactive in addition reactions of a variety of nucleophilic reagents.

Enamines are versatile starting materials for the synthesis of a wide variety of heterocycles[3]. Especially useful intermediates result from the union of enamines and isothiocyanates leading to a vast array of heterocyclic systems. The most useful preparative methodology for enamines involves the condensation of aldehydes and ketones with secondary amines. Mannich and Davidsen[4] prepared the enamines by reaction of secondary amine with aldehydes in the presence of potassium carbonate at 0°. Ketones and disubstituted aldehydes form enamines by removing water azeotropically in the condensation reaction[5]. Drying agents like calcium carbide, calcium chloride or molecular sieves can

SCHEME-I



1 2 3 4

$R^1 = CH_3$

$R^2\ R^3 = H$

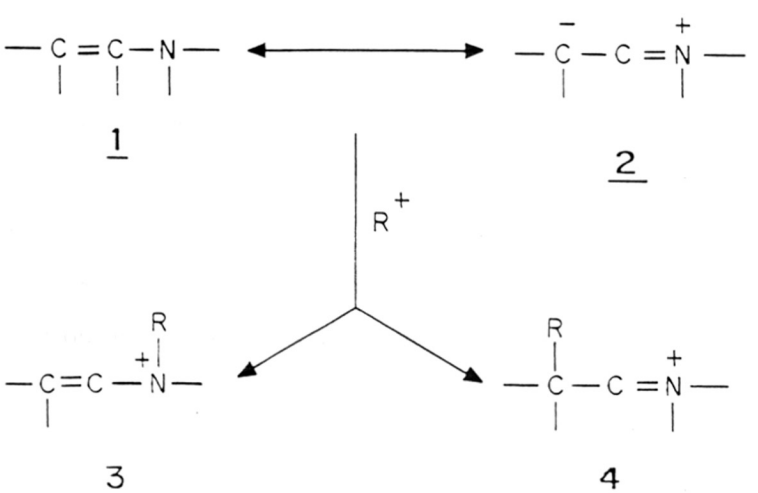
$R^4 = CN, -COOC_2H_5, COCH_3$

$R^5 = Alkyl, Aryl, Acyl$

$X = Br, Cl$

$Y = COC_6H_5, NO_2$

SCHEME-II



1 2 3 4

be employed for removal of water.

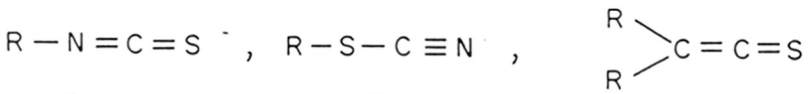
The term "enamine" was introduced by Wittig and Blumenthal[6] as the nitrogen analogue of term "enol". It exists in two mesomeric forms (1 and 2) (scheme II). The electrophilic attack can occur at the nitrogen atom of the enamine to give an enammonium cation (3) or at the - carbon atom of the enamine to give an iminium cation (4) (scheme II). This type of mesomerism is much more important in the enamines possessing a tertiary nitrogen atom than in those possessing a secondary nitrogen atom since the latter exists largely in the tautomeric form (2).

As per our strategy it was needed to synthesize carbethoxy and sulfonyl isothiocyanates.

Isothiocyanates (1) (scheme III) can be regarded as the esters of isothiocyanic acid, a very strong acid. They are isomeric with thiocyanates (2) and isoelectronic with thioketens (3). A number of of isothiocyanates are found in volatile oils from plants. The only one of importance is the allyl compound, the chief constituent of mustard oil. Hence all isothiocyanate esters aryl, alkyl and alkenyl are called as mustard oils. Simple isothiocyanates are stable, colorless liquids with characteristic odour. They are characterised by a strong, often disperse and split band at 2100-2000 cm^{-1} assigned to the -N=C= S stretching vibration in their i.r. spectra. Bifunctional nature of these systems provides an easy access to the variety of 4-, 5- and 6-membered heterocycles. Carbon atom in these compounds is highly reactive and reacts with various types of nitrogen, oxygen, sulfur and carbon nucleophiles. A few examples are cited in scheme IIIb. Heterocyclic compounds are often produced in reactions between isothiocyanates and nucleophilic

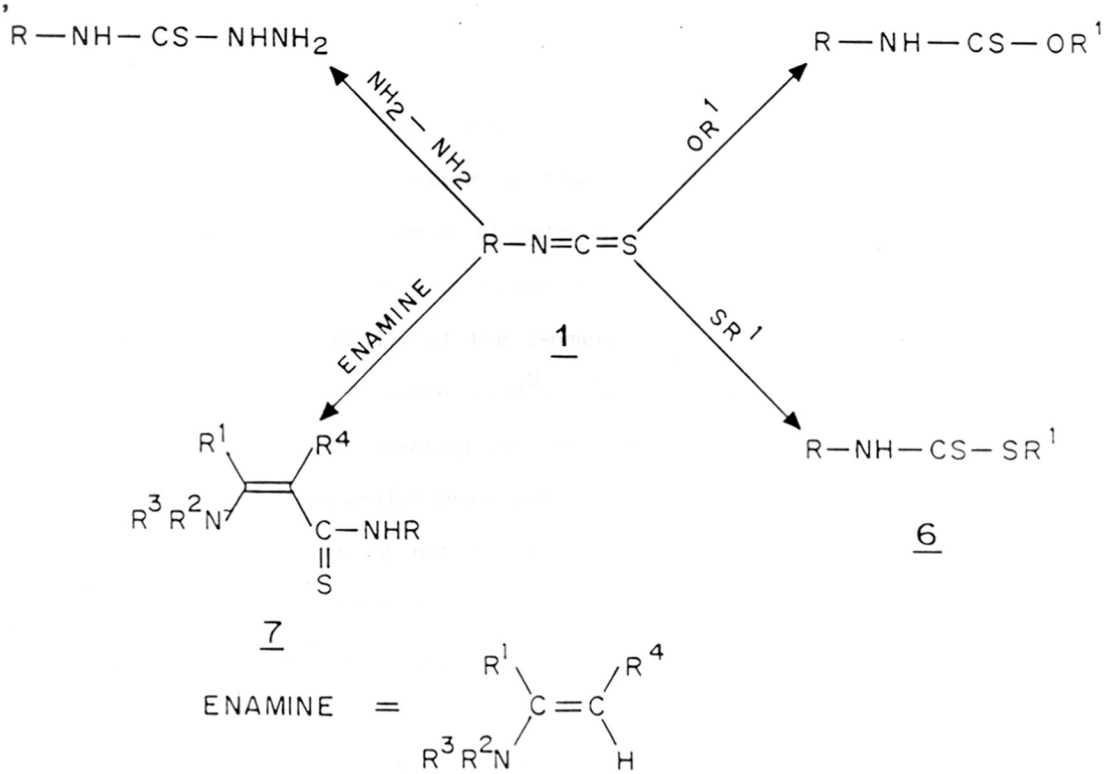
SCHEME III

a,

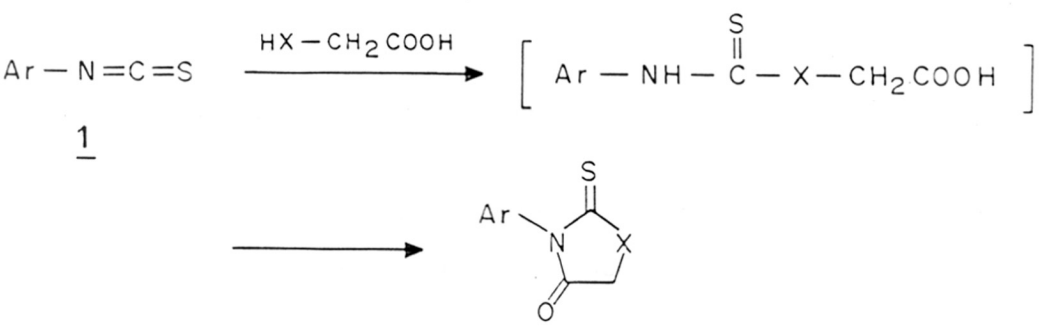


1 2 3

b,



c,



8 , X = S

9 , X = NH

reaction partners, either spontaneously or by additional external influence, if either or both of the reactants possess a further reactive functional group. Thus aryl isothiocyanates react with α-mercapto acids and α-amino acids to form spontaneously the heterocycles (**8**) and (**9**) (scheme IIIc).[7]

Various functional derivatives of the parent isothiocyanic acid ester can be easily prepared, thus widening the scope of their utility in building a large number of heterocyclic moieties.

One of the earliest known methods of synthesising isothiocyanate depends on the ability of the isomeric thiocyanate to rearrange thermally into the former (scheme IVa)[8]. In common practice this synthesis is carried out by heating an alkyl halide together with a thiocyanate salt. Most frequently ammonium, lead and alkali metal salts are used. In many cases it is not possible to isolate the initially formed thiocyanate. The method applies as well to the synthesis of alkoxycarbonyl isothiocyanates[9] and apparently is the general method of preparing acyl isothiocyanates[10]. Thioacyl isothiocyantes have been obtained analogously by reaction of appropriate thioacyl halides with sodium thiocyanate and subsequent thermal rearrangement[11].

Trimethylsilyl isothiocyanate easily obtainable from trimethylsilyl chloride and an alkali metal thiocyanate may undergo substitution at the nitrogen atom on treatment with alkyl or aryl chloroformate yielding conveniently alkoxy or aryloxycarbonyl isothiocayanate (scheme IVb)[12].

Most of the routes to isothiocyanates involve the participation of amines or amine derivatives as starting materials. Primary amines

SCHEME-IV

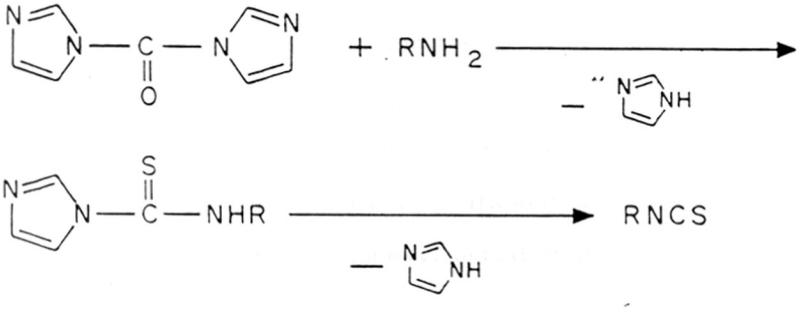
a. $R-X + \bar{S}cN \longrightarrow [R-S-C\equiv N] \xrightarrow{\Delta} R-N=C=S$

b. $(SiMe)_3-N=C=S + X-\underset{\underset{O}{\|}}{C}-OY \longrightarrow$

$YO-\underset{\underset{O}{\|}}{C}-N=C=S + Me_3SiCl$

Y=R, Ar

c. $R-NH_2 + CSCl_2 \longrightarrow R-N=C=S + 2\,HCl$

d. 

e. $R-NH_2 + CS_2 \xrightarrow{B} RNH-\underset{\underset{S}{\|}}{C}-\bar{S} + \overset{+}{B}H$

$R-NH-\underset{\underset{S}{\|}}{C}-\bar{S}$ → $COCl_2$, $-Cl^-$, HCl, $-COS$ → RNCS

$R-NH-\underset{\underset{S}{\|}}{C}-\bar{S}$ → $Cl-COOC_2H_5$, $-Cl^-$, $-C_2H_5OH$, $-COS$ → RNCS

$R-NH-\underset{\underset{S}{\|}}{C}-\bar{S}$ → $Pb(NO_3)_2$, $-PbS$, $-HNO_3$, $-NO_3^-$ → RNCS

f. $R-NH_2 + CS_2 \xrightarrow{DCC} RNCS$.

g. $R-SO_2-N=C(\bar{S}K^+)_2 + COCl_2 \longrightarrow R-SO_2-NCS + 2KCl + COS$

react with equimolar quantity of thiophosgene to produce isothiocyanate (scheme IVc)[8]. With excess thiophosgene thioureas are formed.

Reaction of primary amine with N,N'-thiocarboyldiimidazole presents an elegant route to isothiocyanate (scheme IVd)[13]. N,N'-disubstituted thioureas decompose into isothiocyanates on treatment with strong acids at high temperatures.

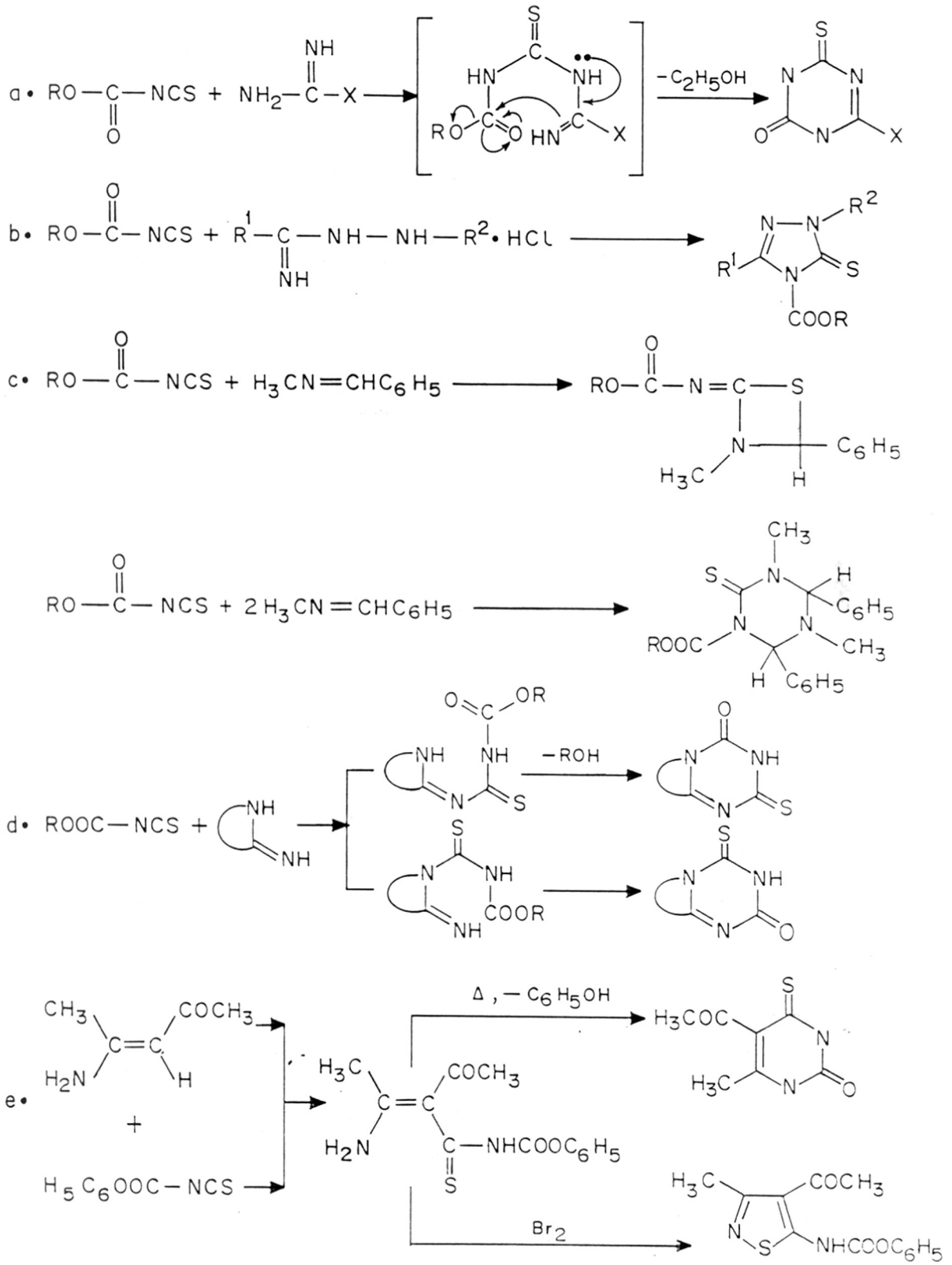
Easily generated N-monosubstituted dithiocarbamate anions formed by reaction of alkyl amines and carbon disulfide in basic condition decompose into isothiocyanates with various reagents as illustrated in scheme IVe[14].

Both aliphatic and aromatic isothiocyanates may be formed when the appropriate amines are allowed to react with carbon disulfide in the presence of dicyclohexylcarbodiimide (scheme IVf)[15].

The unstable sulfonyl isothiocyanates are conveniently prepared by reaction of dipotassium salts of sulfonyliminodithiocarbamic acids with phosgene or alternatively with either ethyl chloroformate, phosphorus pentachloride, thionyl chloride or sulfuryl chloride as described in scheme IVg[16].

As stated earlier we were mainly interested in alkoxycarbonyl isothiocyanates and arylsulfonyl isothiocyanates.

Alk-(or aryl)oxycarbonyl isothiocyanates are highly reactive multifunctional compounds which undergo a wide range of condensation, cyclisation and cycloaddition reactions[9]. The strong electron withdrawing power of the ethoxycarbonyl group enhances the reactivity of the adjacent isothiocyanate function so that the usual nucleophilic addition to this moiety is promoted.



Alkoxy carbonyl isothiocyanates react exothermally with excess alcohols to produce N-alkoxy thiocarbamic acid esters almost quantitatively[17]. In reaction with primary and secondary amines expected di- and trisubstituted ureas are formed in excellent yield[18]. Reaction of ethoxycarbonyl isothiocyanates with amidines and guanidines involves addition-elimination process with loss of ethanol to form cyclic six membered heterocyclic systems (scheme Va)[19].

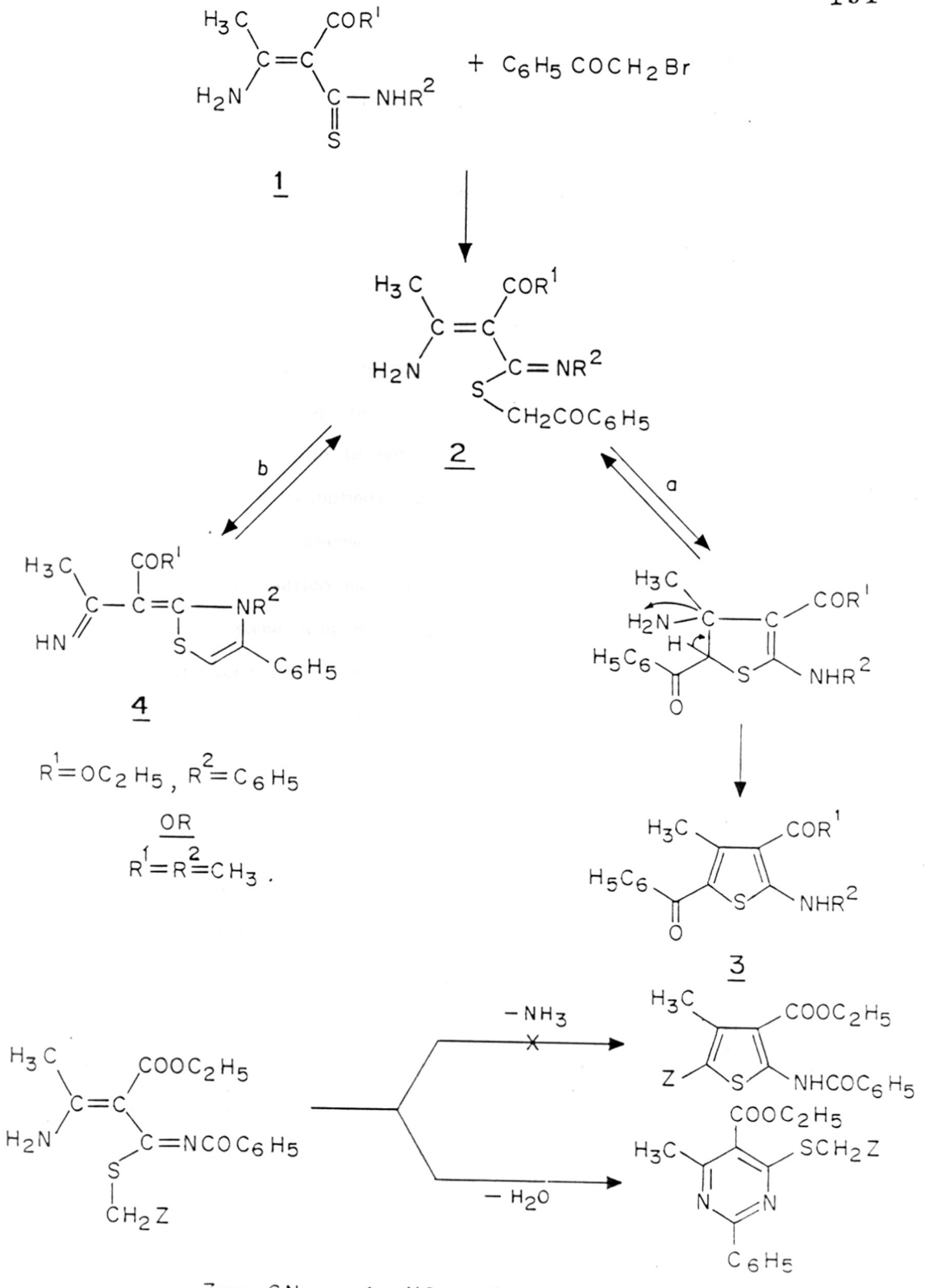
Amidrazone hydrochlorides react in absence of solvent at $\sim$ 100° with loss of ammonia to yield 1,2,4-triazoline-5-thiones (scheme Vb)[20].

The cycloaddition of oxycarbonyl isothiocyanates to Schiff's bases produces substituted thiazetidines or S-triazines[21]. The steric effects of the constituent parts of the Schiff's bases may be responsible for the control of preferential formation of the 4- or 6-membered heterocycles (scheme Vc).

Alkoxycarbonyl isothiocyanates have assumed particular importance as synthetic reagents in opening a versatile route to condensed poly-hetero-systems incorporating an S-triazine nucelus. The method consists essentially of the addition of the isothiocyanate to an aminoazole and simultaneous or subsequent cyclisation, with loss of ethanol, of the resulting intermediate N-ethoxycarbonyl-N'-heterythiourea (scheme Vd)[9].

The addition of alkoxycarbonyl isothiocyanate to β-amino ketones and β-imino nitriles occurs at the activated methylene, rather than the imino group[22]. Enaminoisothiocyanate adducts are very useful starting intermediates for the synthesis of various substituted thiophenes[1] and isothiazoles[23]. Alternatively adducts cyclise spontaneously or preferentially under the influence of heat or basic catalysts to produce 4-

SCHEME VI


+ C6H5COCH2Br
1
2
b
a
4
R1=OC2H5, R2=C6H5
OR
R1=R2=CH3.
3
-NH3
-H2O
Z=-CN, -4-NO2-C6H4

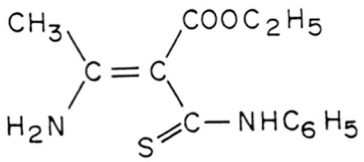
thiouracil derivatives (scheme Ve)[23]. This is one of the best methods of preparing isothiazole derivatives with various functional groups attached to it.

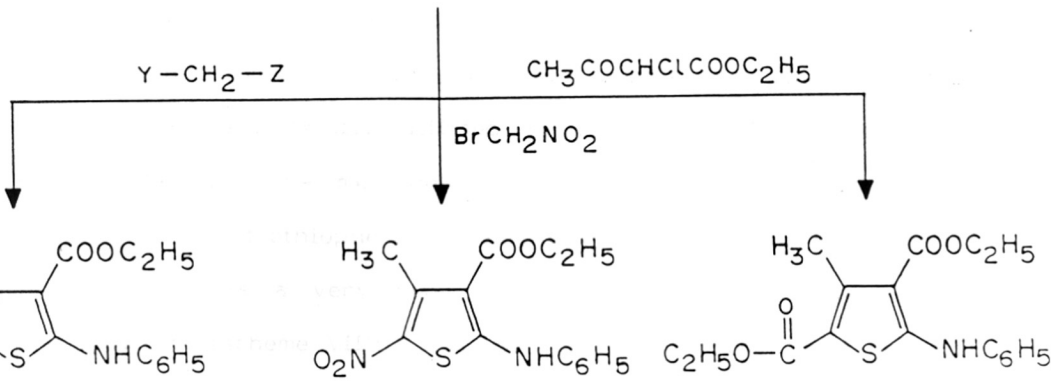
So far we have seen the general methods of preparation of enamines and isothiocyanates and reactivity of alkoxy-(aryloxy)carbonyl isothiocyanates towards varied substrates. With regard our interest it is necessary to make a brief outline of the previous work for the thiophene synthesis by the route developed by Rajappa.

In the beginning the enamine isothiocyanate adduct (1) was reac ed with phenacyl bromide in refluxing isopropanol. The fate of the reaction can be either a thiophene (3) (pathway a, scheme VI) or a thiazole (4) (pathway b, scheme VI). It was anticipated that the driving force for aromatisation may lead to the thiophene (3) instead of thiazole (4) and the same was observed[2,24]. However, when alkylating agents like p-nitrobenzyl bromide or chloroacetonitrile were reacted with enamine-acyl isothiocyanate adduct (5), cyclisation gave pyrimidine derivative (6) instead of a thiophene (scheme VI)[25]. Enamine isothiocyanate adduct of type (1) with p-nitrobenzyl bromide and chloro-acetonitrile did not give cyclised thiophene, only the S-alkylated product is obtained[26]. This suggests that in these alkylating agents methylene group is not active enough for further cyclisation.

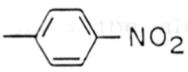
With ethyl α-chloroacetoacetate as an alkylating agent thiophene-2,4-dicarboxylate is obtained in 50% yield (scheme VII)[26]. 2-Nitro-thiophenes are obtained if bromonitromethane is used as an alkylating agent. However, yields are low because of competing isothiazole formation. Higher yields of thiophenes can be obtained by using a tertiary

SCHEME-VII

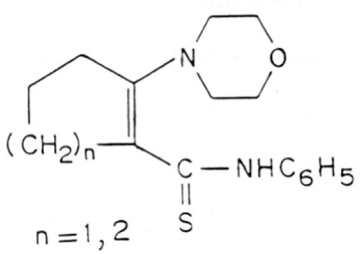




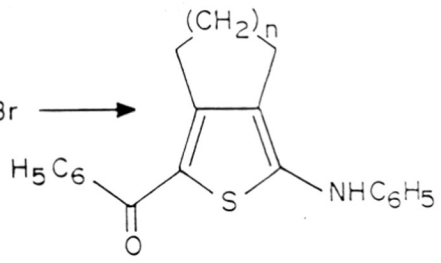
Y = Halide

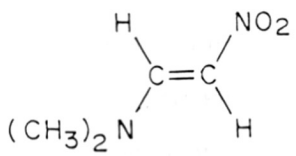
Z = −CN, 

SCHEME-VIII

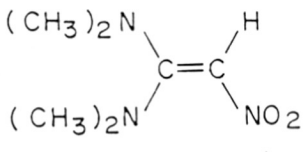
a. 

n = 1, 2

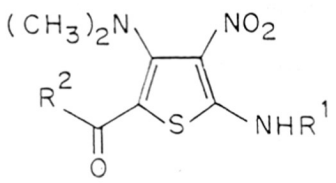
+ $C_6H_5COCH_2Br$ ⟶ 

b. 

1



2

2 ⟶ (1) R^1NCS, (2) R^2COCH_2Br ⟶ 

$R^1, R^2 = C_6H_5$

enamine in the enamine isothiocyanate adduct[27].

There is also a scope for varying the third component, the enamine As discussed earlier enamines which are conjugated to an ester, a ketone or a nitrile form good reactive partners. Simple unconjugated enamines also have been successfully utilised to produce condensed thiophenes (scheme VIIIa)[26]. The methodology was successfully adopted for the preparation of 3-nitrothiophenes. Simple nitroenamine of the type (1) (scheme VIIIb) was a very poor enamine but when nitroketene aminal of the type (2) (scheme VIIIb) was used 3-nitrothiophene could be easily obtained[28].

The simple process developed by Smutney[29] for thiophene synthesis involves the alkylation of thioamide having an enamine function. Ring closure of the resulting product is believed to proceed through ylide (2) (scheme IX).

2-Aminothiophene-3-carboxylic acids can be readily prepared by Gewalds[30] simple reaction. Easily available starting materials like aldehyde or a ketone with a α-methylene group, a compound of the type $X\text{-}CH_2CN$ (X = COOH, CN), and sulfur are needed. Reactants are heated together in ethanol or dimethylformamide in the presence of an organic base. Enamines can replace both aldehyde and ketone in this synthesis. Krutak and Maleski[31] have prepared a few derivatives of 2-thiophene carbamates utilising Rajappa's method.

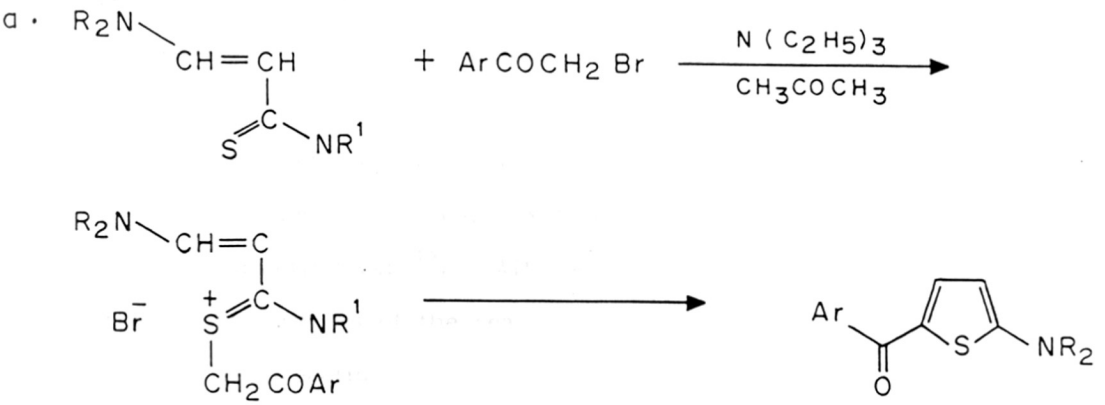
Other synthetic methodologies and chemistry of thiophene is excellently reviewed in Gronowitz's 3 volumes[32].

We were also interested in using sulfonyl isothiocyantes in our reaction sequence. Preparative methods for these have already been

SCHEME-IX

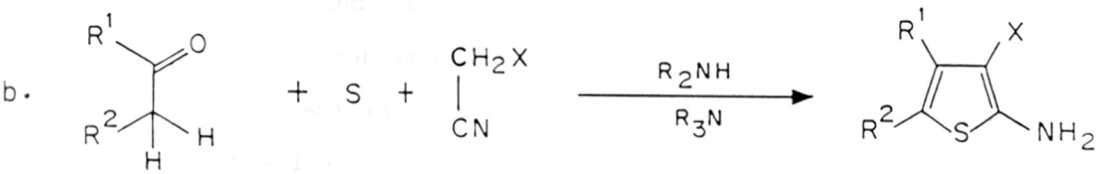
SMUTNEY'S METHOD

a.

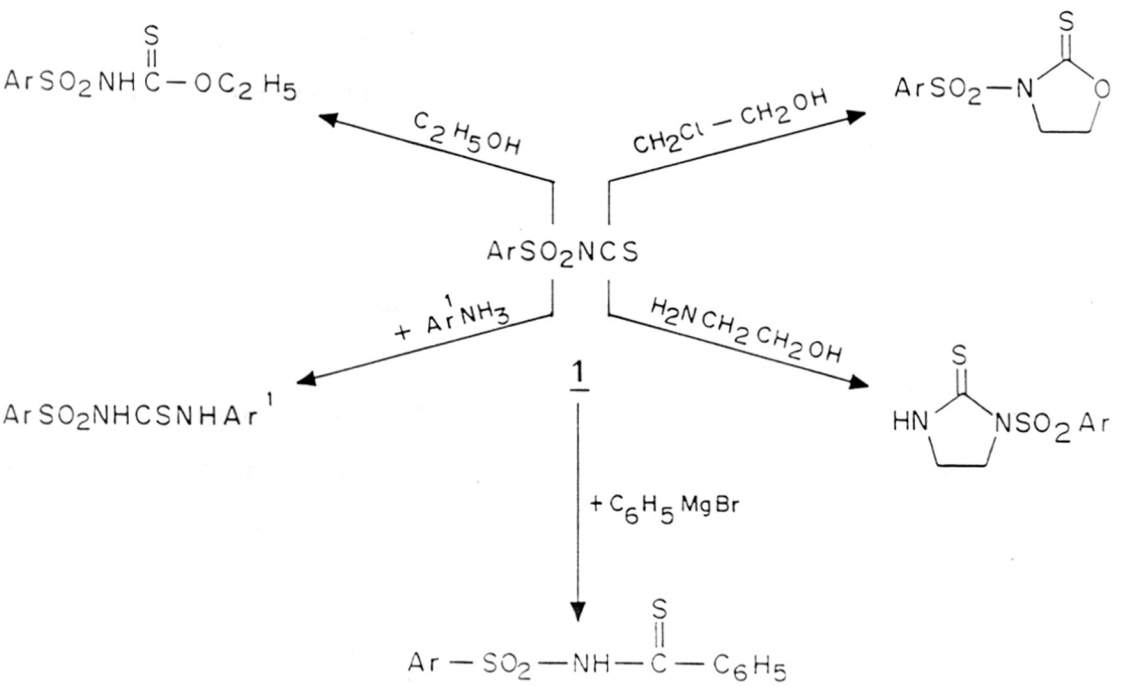


GEWALD'S METHOD

b.



SCHEME-X



mentioned[16]. These reactive isothiocyanates are unstable and dimerise on keeping. In their reactions with nucleophiles they undergo many cycloaddition reactions.

Reaction of isothiocyanates with alcohols is a slow process while sulfonyl isothiocyanates react exothermally with alcohols giving sulfonyl urethanes quantitatively[33]. With anilines sulfonyl thioureas are formed if equimolar amounts of the reactants are used.

In its reaction with Grignard reagent, trisubstituted product is formed at room temperature. At 0° monosubstituted product can be isolated (scheme X)[33].

Mcfarland and coworkers[34] have reacted sulfonyl isothiocyantes with 2-chloroethanol and 2-amino ethanol. Initially formed urethanes and thioureas are cyclised to oxazolidine-2-thiones and imidazolidine-2-thiones respectively.

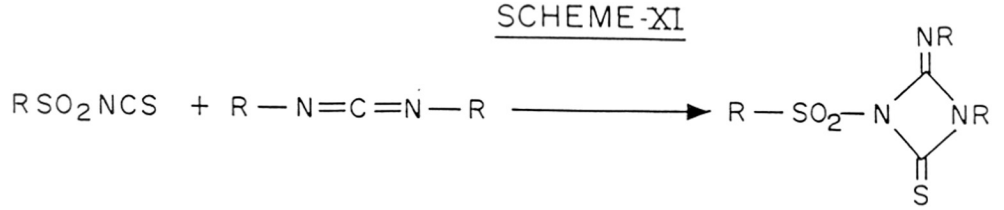
Herbicidal sulfonyl thioureas result from sulfonyl isothiocyanates and aminopyrimidines or amino triazines[35].

Ulrich and coworkers[36] observed the quantitative formation of 2-imino-1,3-diazetidin-4-thione in the reaction between sulfonyl isothiocyanates with carbodiimide in a 1,2-dipolar cycloaddition reaction (scheme XI).

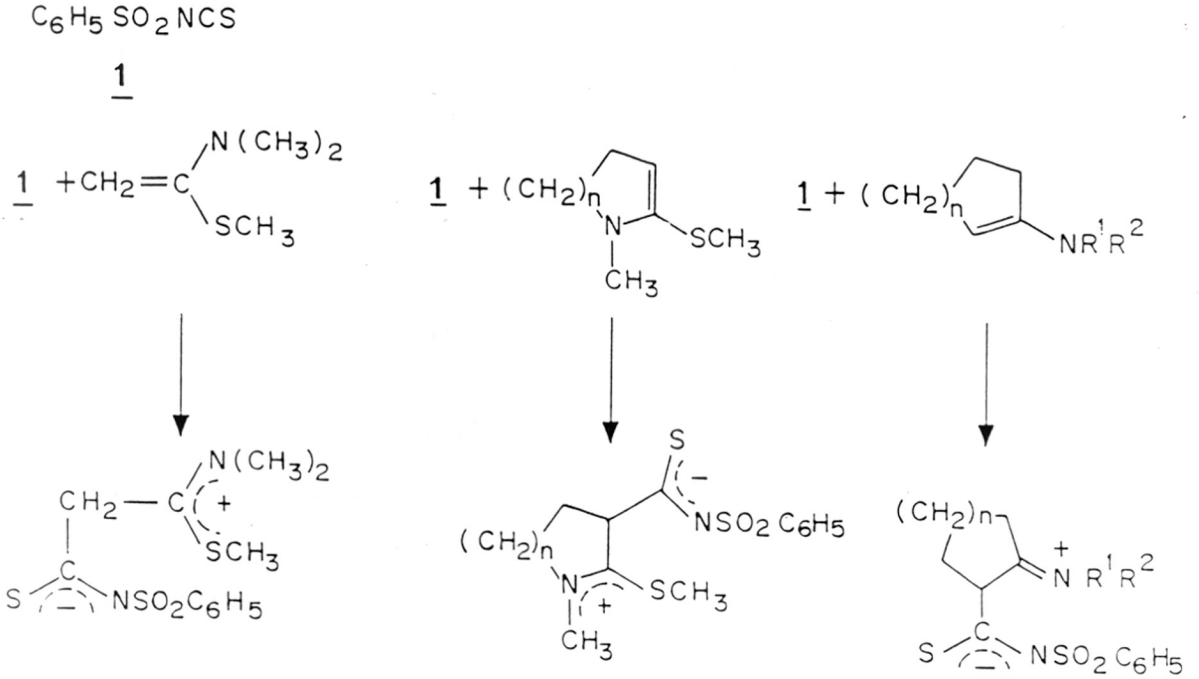
Gomper and Wetzel[37] recognised the 1,4 dipolar product formation in the reaction between sulfonyl isothiocyanates and electron rich olefins (scheme XII).

Further Schaumann[38] obtained crystalline adducts of β,β-disubstituted enamines and sulfonyl isothiocyanate. Characteristic $>C=\overset{+}{N}<$ frequency at 1630-1690 cm^{-1} and 1400 cm^{-1} for $-SO_2NCS^-$ were observed

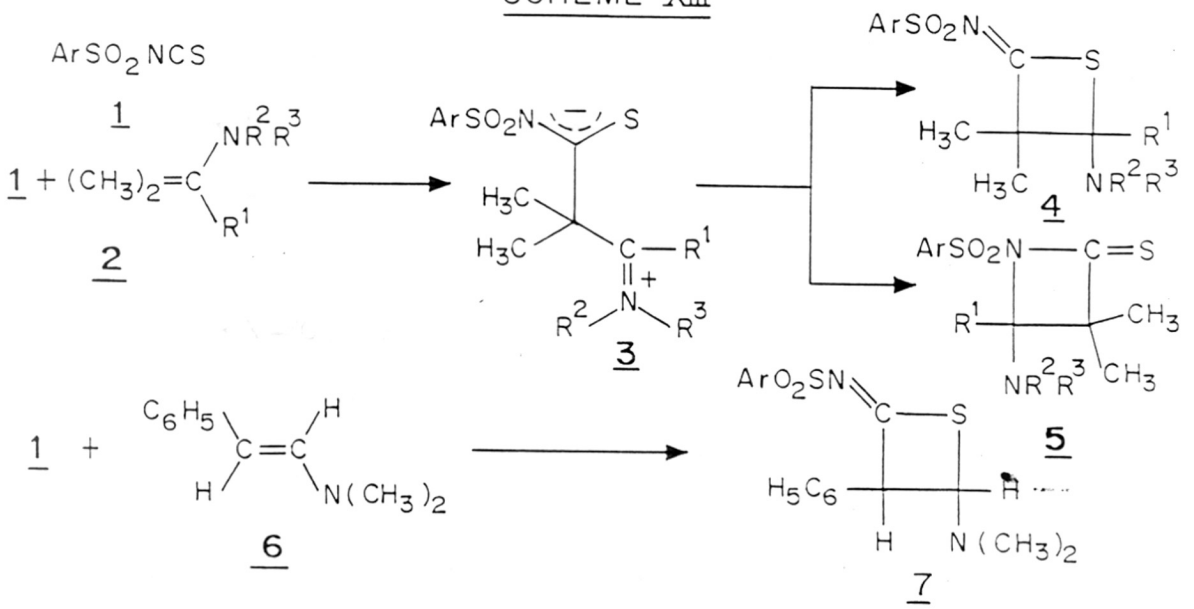
SCHEME-XI



SCHEME-XII



SCHEME-XIII

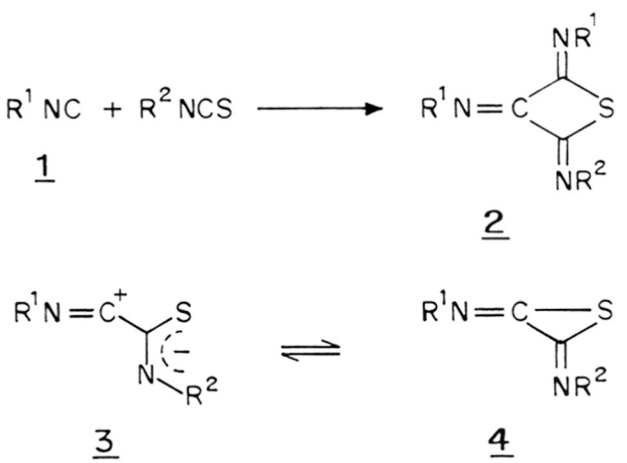


in i.r. spectrum of the product assigning it a dipolar structure (3) (scheme XIII). The alternative imidothietane (4) and β -thiolactame (5) structures can be ruled out since they would not show a band in the region 1630-1690 cm^{-1}. When p-tosylisothiocyanate was reacted with diastereomeric enamine (6) the crystalline cycloadduct was formed. The product can be identified by a strong i.r. absorption at 1590 cm^{-1} which can be assigned to the exocyclic N-sulfonyl C=N double bond. It is likely that bulkier phenyl group might have forced intermediate dipole to ring close.

Tris (imino) thietan's (2) result by treating arene sulfonyl isothiocyanates with t-butyl isonitrile probably through intermediate (3) (scheme XIV)[39].

Cycloaddition reactions of sufonyl isothiocyantes with vinyl ethers, ketene acetals, imidocarbonates, isoureas, vinylidenediamines, S,N acetals, heterocyclic compounds epoxides, ethers and many others are also reported in the last two decades.

SCHEME-XIV



$R^1 = C(CH_3)_3$, $R^2 = -SO_2-C_6H_5$

PRESENT WORK

As already stated we were interested in synthesising N-carbethoxy and N-sulfonyl derivatives of 2-amino-thiophene-3-carboxylates using enamines and the relevant isothiocyanates as the reactants.

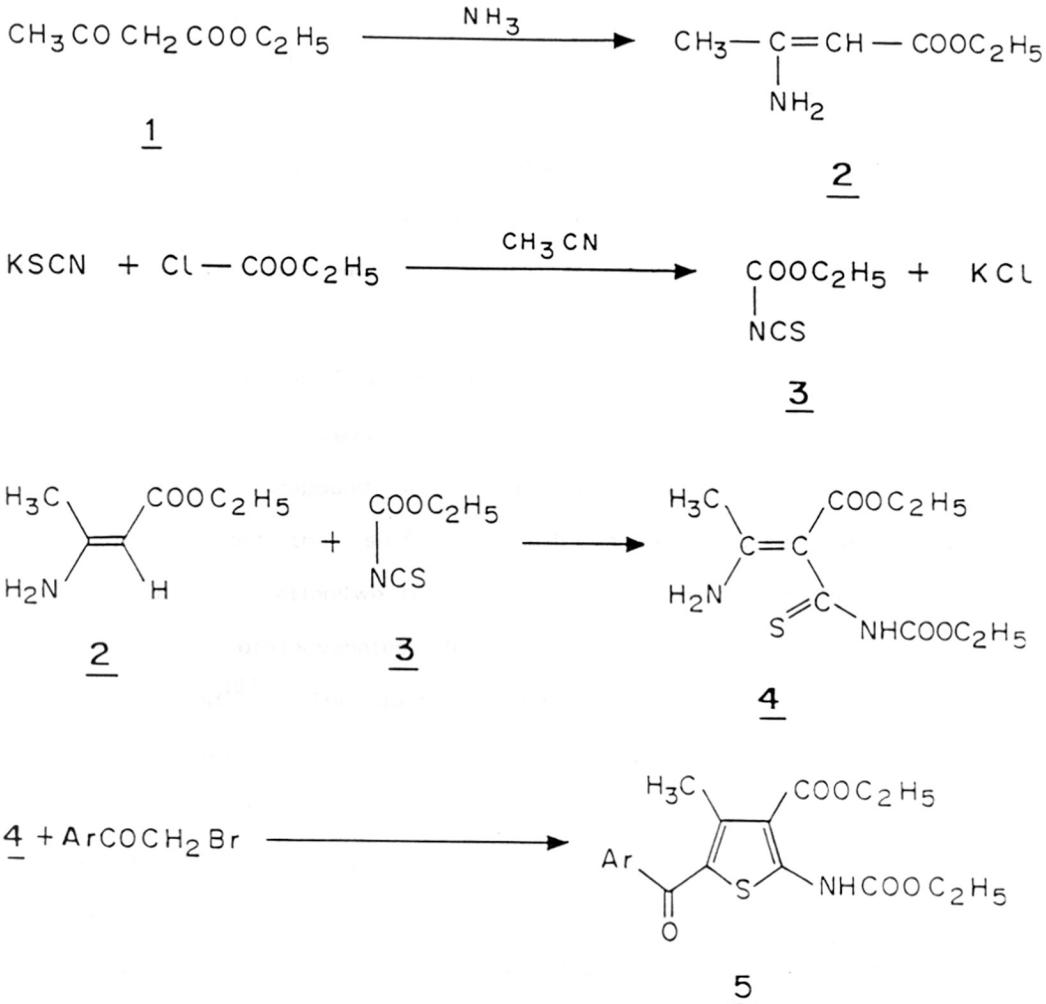
Enamine of ethyl acetoacetate was prepared as follows[40]. Ethyl acetoacetate (1) was taken in double the volume of solvent, ether or dichloromethane and was cooled to 0-10°. A stream of ammonia was passed for 3 to 4 hrs. Solid ethyl β-aminocrotonate ester was separated. After completion of the reaction, water layer formed was removed and residue was concentrated and further distilled to give pure β-amino-crotonate ester (2) (scheme XV). Another method[41] reported in the literature describes the preparation of (2) by passing dry ammonia in ethyl aceatoacetate till temperature rises to 80° and comes back to room temeprature.

Ethoxycarbonyl isothiocyanate (3) was prepared by adding ethyl chloroformate to freshly fused potassium thiocyanate in acaetonitrile. Exothermic reaction sets in and solid potassium chloride separates. It was then filtered and residue on removing solvent was distilled to give pure isothiocyanate in 60% yield. IR shows 1950 cm^{-1} and 1740 cm^{-1} frequencies for -N=C=S and ester groupings.

Enamine-isothiocyanate adduct (4) was prepared by adding the two reactants (2) and (3) in equimolar proportions to each other in dichloromethane as solvent. Exothermic reaction sets in separating the bright orange yellow coloured solid the required product in 75% yield[23].

Later this adduct was alkylated with substituted phenacyl bromides by taking both the reactants in equimolar quantities and refluxing in isopropanol. Decolorisation of the reaction mixture with smultaneous separation of

SCHEME-XV



a , Ar = C_6H_5

b , Ar = $-C_6H_4-4-$ Chloro

c , Ar $-C_6H_4-4-$ Nitro

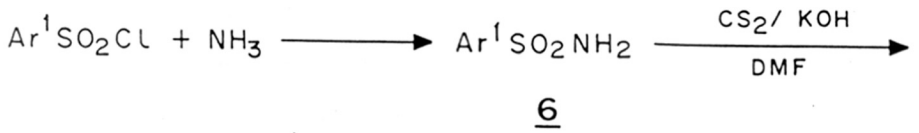
white solid (NH_4Br) took place. Thiophenes (**5**) were purified further by column chromatography and crystallisation. PMR ($CDCl_3$, δ): 1.35 (q, two triplets merged, 6H, J=8 Hz), 2.6 (s, 2H), 4.33 (m, 4H), 7.23 (d, 2H, J=8 Hz), 7.7 (d, 2H, J=8 Hz), 10.8 (s, 1H) of (**5b**) is in agreement with the expected product. Mass, i.r. and analytical data further confirmed the structure (**5**) for the product. The 2-thiophene-carbamates described here have not yet been reported although Krutak et al.[31] have prepared a few thiophene carbamates by a similar route.

N-Sulfonyl 2-thiophene carbamates can also be prepared by treating 2-aminothiophene compound with the arene sulfonyl chloride. Being aware of the fact that sulfonyl isothiocyanates undergo various types of cycloaddition reactions we tried its reaction with the enamine (**2**).

Sulfonyl isothiocyanates (**8**) (scheme XVI) were prepared as per Hartke's method[16b] The starting sulfonamides were obtained by treatment of an arene sulfonyl chloride with excess of an aqueous ammonia solution. The sulfonamidess were then reacted with carbon disulfide in dimethyl-formamide under the influence of powdered potassium hydroxide. Ethyl acetate was added to the deep red colored solution formed, when di-potassium salts of sulfonyliminodithiocarbamic acid (**7**)were precipitated. These salts react with thionyl chloride to form sulfonyl isothiocyanates, which were purified by distillation, characteristic i.r. absorption at 1900 cm^{-1} was observed for $-SO_2-NCS$ group.

Further the two sulfonyl isothiocyanates prepared were reacted with equimolar enamine (**2**) in dichloromethane at 10°. White solid (**9a** and **9b**) separated after about an hour.Reaction mixture was stirred

SCHEME-XVI



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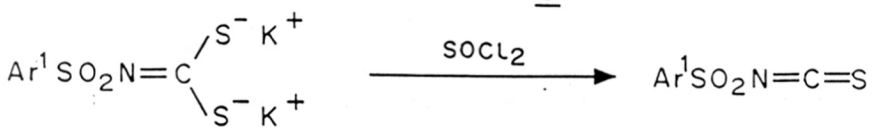

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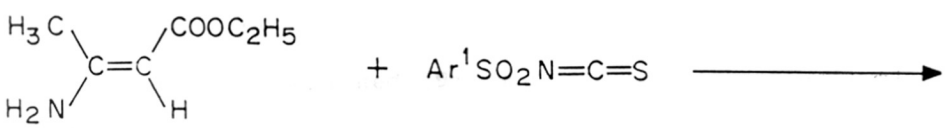
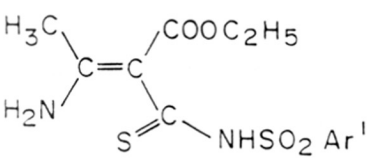


2 8

9

a , $Ar^1 = C_6H_5$

b , $Ar^1 = C_6H_4-4-CH_3$



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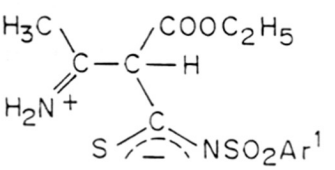

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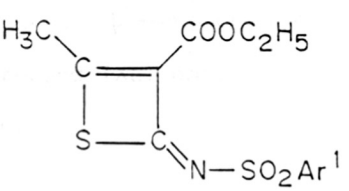

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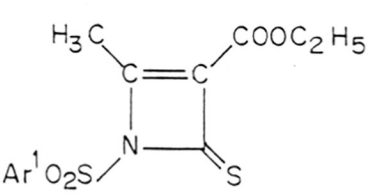

13

for 3 hrs then filtered. Filtrate was evaporated and residue was chromatographed on silica gel column using pet.ether– ethyl acetate (1:1) as an eluent. The less polar components turned out to be a mixture of ethyl β-aminocrotonate and ethyl acetoacetate (15%). Probably the unreacted β-aminocrotonate has been transformed into ethyl acetoacetate on silica gel column.

The second compound eluted from column (compound X) is obtained in about50% yield.

The solids separated (**9a**) and (**9b**) were characterised as follows (20%).

9a, m.p.138-9° has molecular formula $C_7H_8N_2O_2S_2$, gave analysis for C, 39.21; H, 3.92; N, 12.60, S, 29.78%

IR (Nujol): 3520, 3400, 3300, 3190, 1600 (v.strong) cm^{-1}

No absorption for $-\overset{\overset{O}{\|}}{C}-$ frequency

PMR (TFA, δ): 5.8 (s, 2H), 6.6 (s, 1H), 7.5 (m, 5H).

(DMSO, d_6, δ): 7.6 (m, ArH).

M/e: 216 (M^+, v.weak), 199 ($C_6H_5SO_2NCS$),

157 ($C_6H_5SO_2NH_2$), 141 ($C_6H_5SONH_2$), 110 (C_6H_5SH), 77.

9a was identified as 1-benzene sulfonyl-2-thiourea (Lit.m.p.138°)[42].

Analogously, **9b** was characterised as 1-p-tolylsulfonyl-2-thiourea from it's elemental analysis and spectral data (Lit.m.p.128°)[42].

The sulfonyl thiourea can be formed if ammonia is evolved during the reaction course, this prediction might be correct as we get back unreacted β-aminocronate from the reaction mixture. The more polar compound (Xa) obtained from column gave following analytical and spectral data.

m.p. 143°.

IR: absence of -NH frequency, 1700 (-C-) cm^{-1}
‖
O

PMR ($CDCl_3$, δ): 1.2 (t, 3H), 2.5 (s, 3H), 4.3 (q, 2H), 7.6 (m, 5H).

M/e: 343 (M^+), 298 ($M^+ - OC_2H_5$), 265 ($M^+ - 78$), 206, 157 ($C_6H_5SO_2NH_2$), 141 ($C_6H_5SO_2$), 125 (C_6H_5SO), 77.

Analysis: Calcd. for $C_{13}H_{13}NO_4S_3$: C, 45.48; H, 3.79; N, 4.06; S, 27.98

observed C, 44.95; H, 3.64; N, 4.44; S, 27.70%

We expected that compound (X) can have 4 possible structures (**10**, **11**, **12** and **13**) (Scheme XVI).

The structures (**10**) and (**11**) can be ruled out since both are expected to come out of the reaction mixture as per their nature and no absorption for -NH frequency in the i.r. spectrum.

The structure (**12**) is also expected to have strong absorption for exocyclic $SO_2N{=}C$ bond in the i.r. spectrum. Absence of this absorption leaves behind the probable structure (**13**), an azetidinethione derivative. Comparison of methyl, methylene and aromatic protons in the p.m.r. spectrum shows that the compound is formed by 1:1 equivalent of enamine and isothiocyanate while mass spectrum and elemental analysis appear to indicate the presence of an extra sulfur atom in the structure of the compound. Thus it cannot have structure (**13**). Similarly, enamine (**2**) and isothiocyanate (**8b**) gave a novel but as yet unidentified compound (Xb) having the molecular formula $C_{14}H_{15}NO_4S_3$ as indicated by M^+ at 357 in its mass spectrum and elemental analysis which showed 3 S-atoms.

Attempts are being made to identify the structure (X) by X-ray diffraction.

EXPERIMENTAL

Ethyl 3-aminocrotonic acid ester or ethyl β-amino crotonate (2)

Ethyl acetoacetate (10 g) in dichloromethane (20 ml) was cooled to 0 to 10° and a stream of ammonia was passed. Formation of solid was seen after about an hour. Ammonia was passed for almost 3 to 4 hours and separated water layer was removed. Residue was concentrated and distilled under reduced pressure (15 mm) at 105° to yield β- amino-crotonate (**2**)

IR (Neat): 3430, 3320, 1680, 1650, 1570, 1300, 1170, 1040, 790 cm^{-1}.

PMR ($CDCl_3$, δ): 1.23 (t, 3H), 1.9 (s, 3H), 3.63 (q, 2H), 4.03 (s, 1H).

Ethoxycarbonyl Isothiocyanate (3)[9]

Freshly fused and finely ground potassium thiocyanate (19.4g, 0.2 m) was suspended in dry acetonitrile (70 ml) and warmed on a steam bath. It was treated in portions with ethyl chloroformate (21.7g, 0.2 m) when an exothermic reaction sets in. The reaction mixture turns yellow and thickens. Heating was stopped and reaction was allowed to run its course. After cooling to room temperature it was further chilled and filtered to remove potassium chloride. Filtrate was concentrated and distilled at 51-55° at 13 mm pressure to give a colourless liquid (16g, 60%).

IR (Neat): 1950 (-N=C=S), 1750 ($-\overset{\overset{O}{\|}}{C}-OC_2H_5$) cm^{-1}.

Enamine-isothiocyanate adduct (4)

To β-aminocrotonate ester (**2**) (1.95 g, 15 mmol) in dichloromethane (10 ml) was added ethoxycarbonyl isothiocyanate (**3**) (1.96 g, 15 mmol) with stirring. Exothermic reaction took place giving dark red colour to the reaction mixture slowly separating the crystalline bright orange coloured solid. The solid was filtered to give adduct (2.7 g, 70%), m.p.130° (Lit.m.p.130)[23].

IR (Nujol): 3410, 3190, 1730, 1680, 1620, 1510, 1250, 1190, 1040 cm^{-1}.

M/e: 260 (M^+), 231, 187, 159, 141(B), 127, 109.

Ethyl 5-benzoyl-3-carbethoxy-4-methylthiophene-2-carbamate (5a)

The adduct (**4**) (1.3 g, 5 mmol) and phenacyl bromide (1 g, 5 mmol) were refluxed together in isopropanol (15 ml). Lightening of the dark yellow colour with simultaneous deposition of white solid is observed. Reaction mixture was cooled and separated ammonium bromide was filtered. Filtrate was evaporated and residue was chromatographed over silica gel column using pet.ether-ethyl acetate (85:15) as an eluent to give 1.6 g of cyclised thiophene (**5a**) in 60% yield. Crystallisation yielded sharp melting compound (m.p.96-97°).

IR (Nujol): 3260 (-NH), 1730 ($-\underset{\underset{O}{\|}}{C}-$), 1680, 1650 cm^{-1}.

PMR ($CDCl_3$, δ): 1.4 (q, 6H, J=8 Hz), 2.56 (s, 3H), 4.33 (m, 4H), 7.5 (m, 5H), 10.8 (s, 1H, -NH).

M/e: 361 (M^+), 314, 285, 268, 242 (B), 105 ($C_6H_5\overset{+}{C}O$), 77.

Analysis: Calcd. for $C_{18}H_{19}NO_5S$: C, 59.83; H, 5.263; N, 3.88.

observed: C, 59.47; H, 4.96; N, 3.62%

Ethyl 3-carbethoxy-5-(4-chlorobenzoyl)-4-methylthiophene-2-carbamate(5b)

(**5b**) was prepared, as per the procesdure adopted for (**5a**). It was eluted with pet.ether-ethyl acetate (85:15) and was obtained in 52% yield.

m.p.106°.

IR (Nujol): 3240, 1720, 1670, 1640, 1550, 1500, 1370, 1300, 1240, 1200, 1130, 1020, 870, 830, 770, 660, 610 cm^{-1}.

PMR ($CDCl_3$, δ): 1.355 (q, two triplets merged, 6H, J=8 Hz), 2.6 (s, 3H), 4.33 (m, 4H), 7.23 (d, 2H, J=8 Hz), 7.7 (d, 2H, J=8 Hz), 10.8 (s, 1H, NH).

M/e: 395 (M^+), 349 (M^+-HCl), 276 (B), 242, 139, 111.

Analysis: Calcd. for $C_{18}H_{18}ClNO_5S$: C, 54.68; H, 4.55; S, 8.10.
observed: C, 54.32; H, 4.13; S, 7.63%.

Ethyl 3-carbethoxy-4-methyl-5-(4-nitrobenzoyl)-2-thiophenecarbamate(5c)

(**5c**) was prepared by the procedure described for (**5a**). It was eluted from column with pet.ether-ethyl acetate (80:20) in 50% yield. m.p.108°.

IR (Nujol): 3220, 1730, 1670, 1630, 1460, 1370, 1300, 1250, 1200, 1060, 1020, 350, 340, 710, 680 cm^{-1}.

PMR ($CDCl_3$, δ): 1.4 (q, 6H, J=8 Hz), 2.6 (s, 3H), 4.3 (m, 4H), 7.85 (d, 2H, J=9 Hz), 8.26 (d, 2H, J=9 Hz), 10.82 (s, 1H, NH).

M/e: 406 (M^+), 360 ($M^+ - C_2H_5OH$), 343, 315, 297, 287, 271, 241(B), 213, 150 ($4\text{-}NO_2\text{-}C_6H_4\text{-}CO^+$), 104.

Analysis: Calcd. for $C_{18}H_{18}N_2O_7S$: C, 53.20; H, 4.43; N, 6.89.
observed C, 52.87; H, 4.08; N, 6.53%.

Benzene sulfonamide (6a)

Benzene sulfonyl chloride (40 ml) was added to ice cooled 25% aqueous ammonia solution(200 ml)slowly during 30 minutes.White solid which separated was filtered and washed with cold water. It was obtained in quantitative yield, m.p.156°.

p-Toluene sulfonamide or 4-methylphenyl sulfonamide (6b)

It was prepared analogously, m.p.137°.

Dipotassium salt of benzenesulfonyliminodithiocarbamic acid (7a)

To the solution of benzene sulfonamide (15.7 g, 0.1 mmol) in dimethylformamide (75 ml) was added carbon disulfide (7.6 g, 0.1 m) and powdered potassium hydroxide (5.6 g, 0.1 m) alternatively in small portions. Temperature was maintained below 25° by occassional cooling. A deep red colored solution is formed. One more equivalent of potassium hydroxide was then added and reaction mixture was stirred for 2 hours when all potassium hydroxide had dissolved. Dry ethyl acetate (150ml) was then added dropwise when dipotassium salt was separated. It was filtered, washed with ethyl acetate and evacuated at 65°C.

IR(Nujol): 1620, 1450, 1380, 1260, 1140, 1080, 750, 720, 680 cm^{-1}.

Dipotassium salt of p-toluenesulfonyl iminodithiocarbamic acid (7b)

(7b) was prepared in the same way as (7a).

Benzenesulfonyl isothiocyanate (8a)

Finely crushed dipotassium salt of benzenesulfonyliminodithiocarbamic acid (6.2, 20 mmol) was suspended in methylene chloride (20 ml). along with potassium chloride (0.2 g). It was cooled to 0° and thionyl chloride (2.62 g, 22 mmol) was added at the same temperature during

1 hour. Reaction mixture was stirred overnight, separated potassium chloride was filtered and filtrate was evaporated, then distilled at 0.3 mm at 120-125° to yield benzenesulfonyl isothiocyanate.

IR (Neat): 1900 cm^{-1} (broad disperse).

4-(Methyl phenyl) sulfonyl isothiocyanate (8b)

The isothiocyanate was prepared as described in the preceeding method.

B.p. 0.05 mm/100-110°.

IR (Neat): 1900 cm^{-1} (broad)

Reaction between enamine (2)and benzenesulfonyl isothiocyanate (8a)

Freshly distilled benzenesufonyl isothiocyanate (**8a**) (4.0 g, 20 mmol) was dissolved in dry dichloromethane (20 ml) and was cooled to 10° β-aminocrotonate (2.6 g, 20 mmol) in dichloromethane (15 ml) was added during 30 minutes. While solid starts separating after about an hour. The stirring was continued further for two hours. Reaction mixture was filtered to give solid (**9a**) (1.3 g, 20%), m.p.138°.

IR (Nujol): 3520, 3400, 3300, 3190, 1600 (strong) cm^{-1}.

PMR ($DMSOd_6$, δ): 7.6 (m, ArH)

M/e: 216 (M^+, v.weak), 199 ($C_6H_5SO_2NCS$), 157 ($C_6H_5SO_2NH_2$), 141 ($C_6H_5SO_2NH_2$), 110 (C_6H_5SH), 77.

Analysis: Calculated for $C_7H_8N_2O_2S_2$: C, 38.88; H, 3.70; N, 12.96,S,29.62.
observed C, 39.21;H, 3.92;N, 12.60;S,29.78%.

Filtrate was evacuated and residue was chromatographed over silica gel column. Compounds eluted with pet.ether-ethyl acetate (80:20) turns out to be a mixture of ethyl acetoacetate (1) and ethyl 3-

aminocrotonic acid ester (**2**) and was obtained back in 1 g (15%) quantity. PMR ($CDCl_3$, δ) confirms the starting esters.

Pet.ether-ethyl acetate (50:50) eluted the compound (Xa) 3.3 g i.e. 50% of the expected yield. It was crystallisesd from pet.ether-ethyl acetate (20:80) to give a crystalline solid, m.p.143°.

IR(Nujol): 1700, 1480, 1360, 1300, 1220, 1140, 850, 800, 710 cm^{-1}.

PMR ($CDCl_3$, δ): 1.2 (t, 3H), 2.53 (s, 3H), 4.3 (q, 2H), 7.6 (m, 5H).

M/e: 343 (M^+), 298 ($M^+ - OC_2H_5$), 265 (M^+ -78) 157 ($C_6H_5SO_2NH_2$), 141, 125 (C_6H_5SO), 77.

Analysis: Calcd. for $C_{13}H_{13}NO_4S_3$: C, 45.48; H, 3.79; N, 4.06;S,27.98.
observed: C, 44.95; H, 3.64; N, 4.44;S,27.70%

Reaction between enamine (2) and 4-methylphenyl isothiocyanate (8b)

The reaction was carried out in a similar way as with benzenesulfonyl isothiocyanate (**8a**) and enamine (**2**). Solid preceipitated from the reaction mixture (**9b**) was characterised as N-(4-methylphenyl)sulfonyl-2-thiourea, m.p.130° (Lit. 128°)[42].

IR (Nujol): 3450, 3320, 3200, 1620 (strong) cm^{-1}.

PMR(DMSO d_6, δ): 2.4 (s, 3H), 7.25 (d, 2H), 7.65(d,2H).

M/e: 213 (v.w.), 171, 166, 155 ($ArSO_2$), 124, 107, 91, 65.

Analysis: Calcd. for $C_8H_{10}N_2O_2S_2$:C, 41.55;H, 4.32; N,12.12; S,27.70
observed C, 41.07; H, 4.61; N, 12.0;
S, 27.5%.

The more polar compound (Xb) obtained from column gave the following data:

m.p. 138°.

IR (Nujol): 1730, 1600, 1470. 1380, 1340, 1290, 1200, 880, 730, 680 cm^{-1}.

PMR ($CDCl_3$, δ): 1.23 (t, 3H), 2.36 (s, 3H), 2.5 (s, 3H), 4.33 (q, 2H), 7.26 (d, 2H), 7.87 (d, 2H).

M/e: 357 (M^+), 312 ($M^+ - OC_2H_5$), 265, 155, 139, 91.

Analysis: Calcd. for $C_{14}H_{15}NO_4S_3$: C, 47.05; H, 4.20; N, 3.92; S, 26.87

observed C, 47.56; H, 4.50; N, 4.45; S, 27.2%

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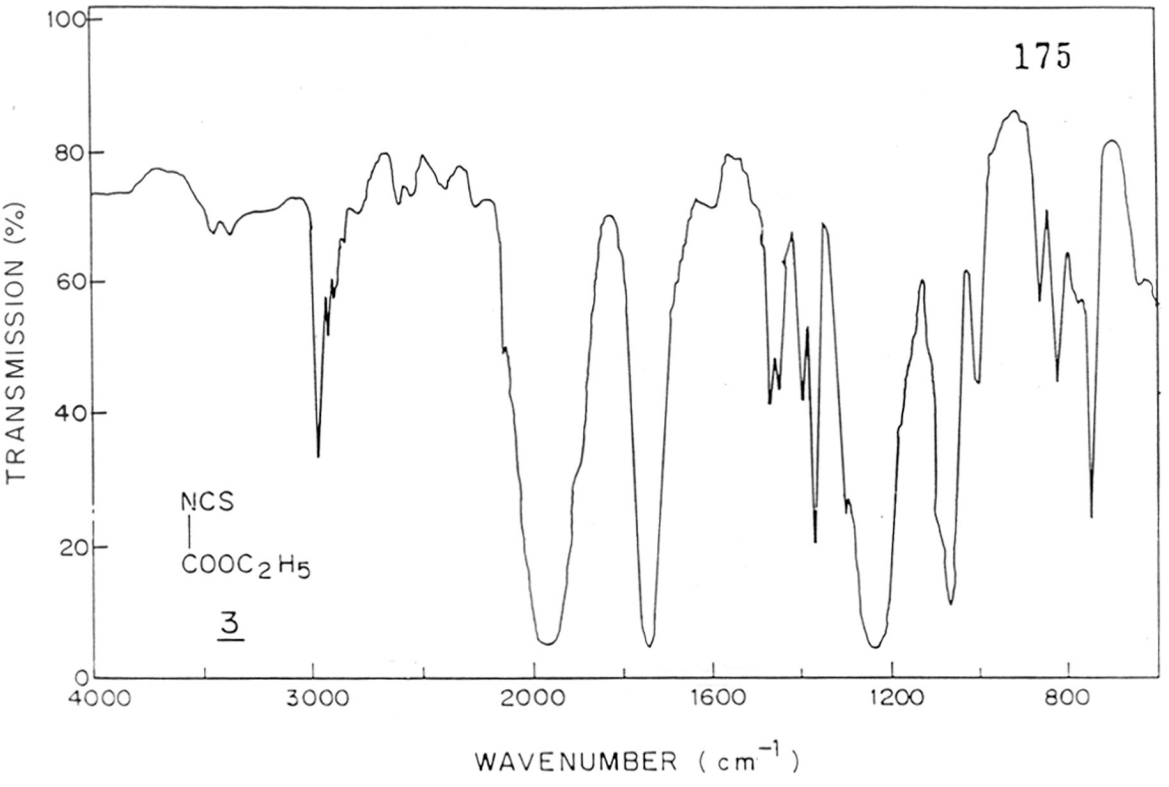
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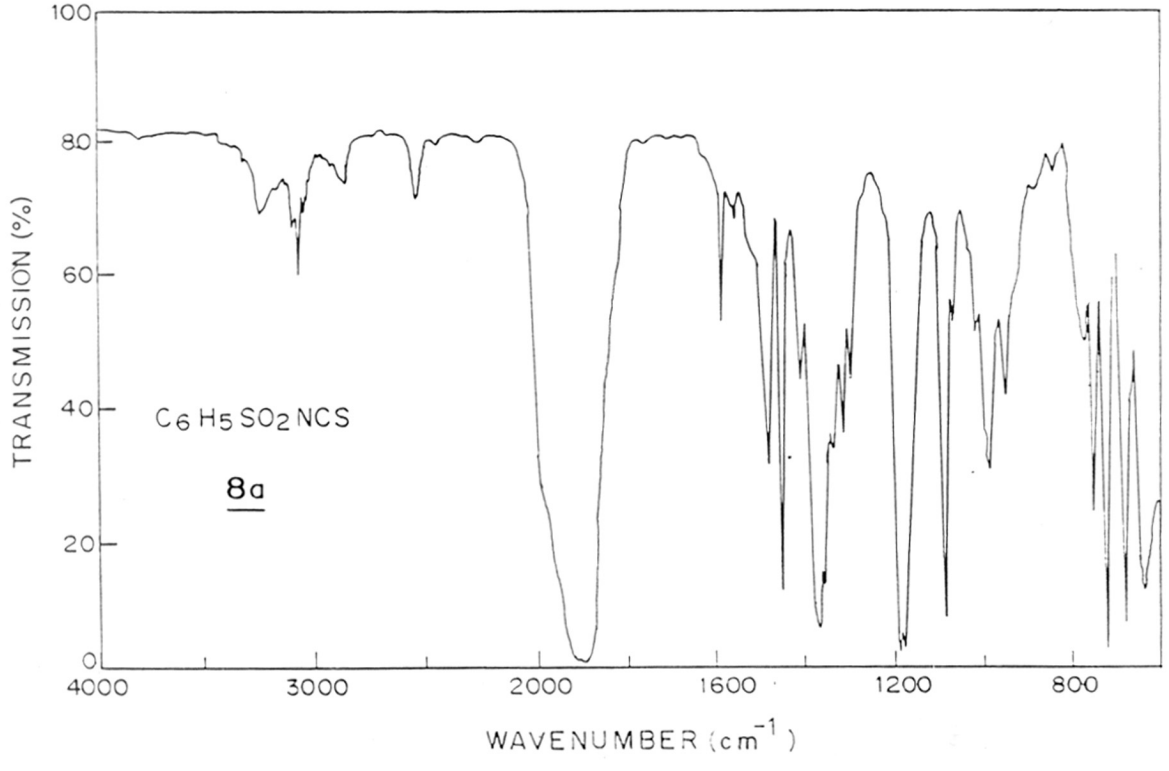
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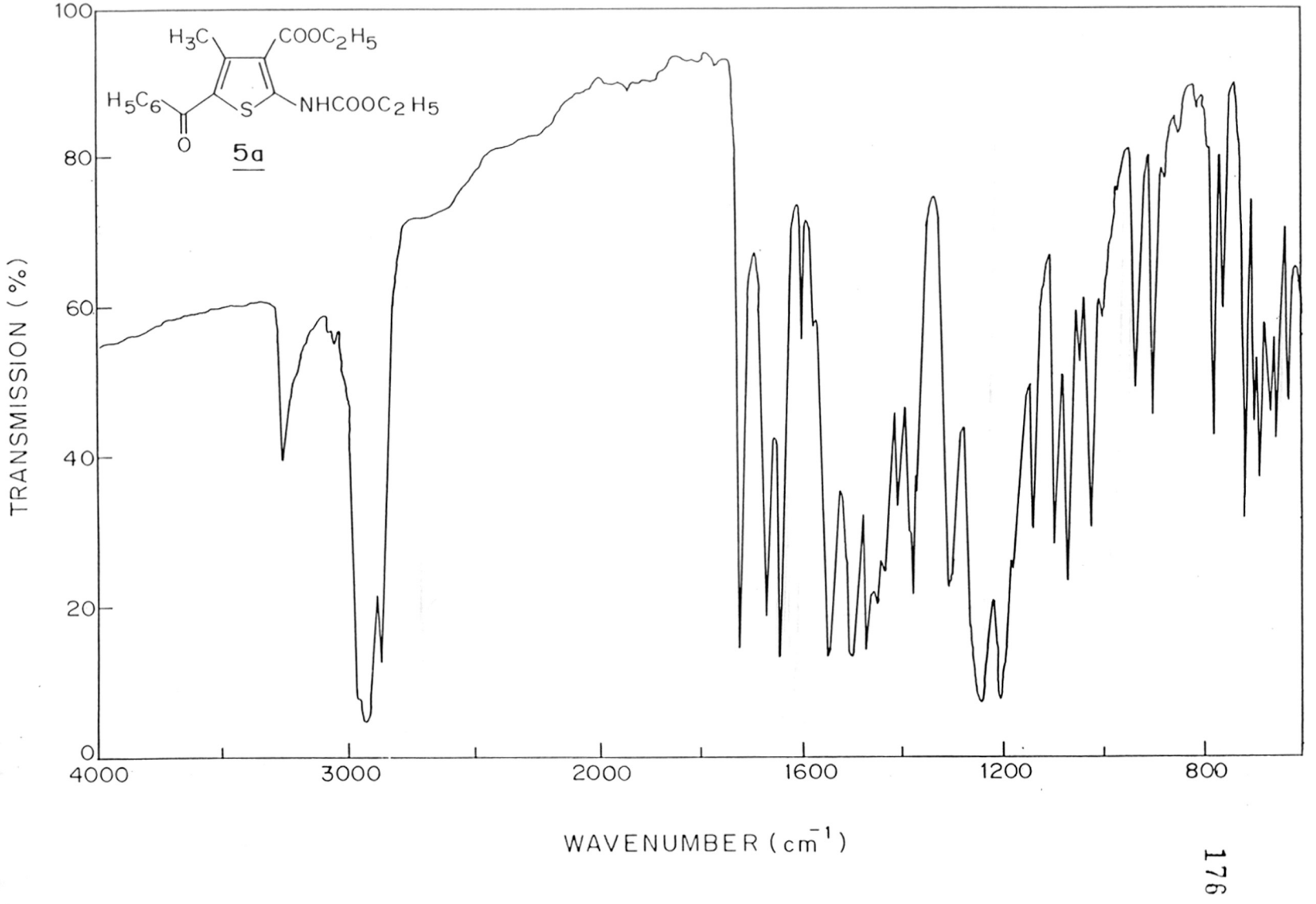
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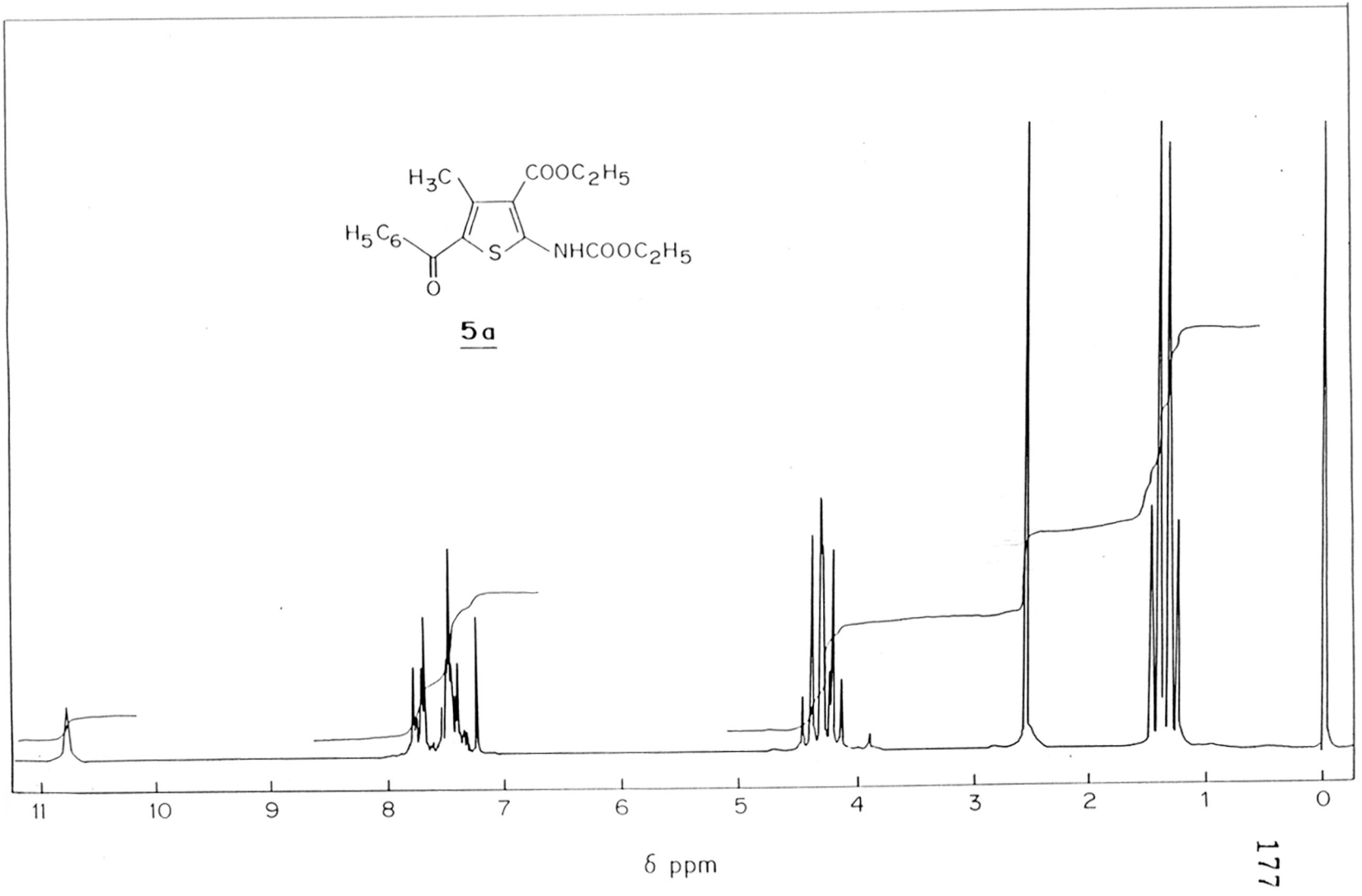

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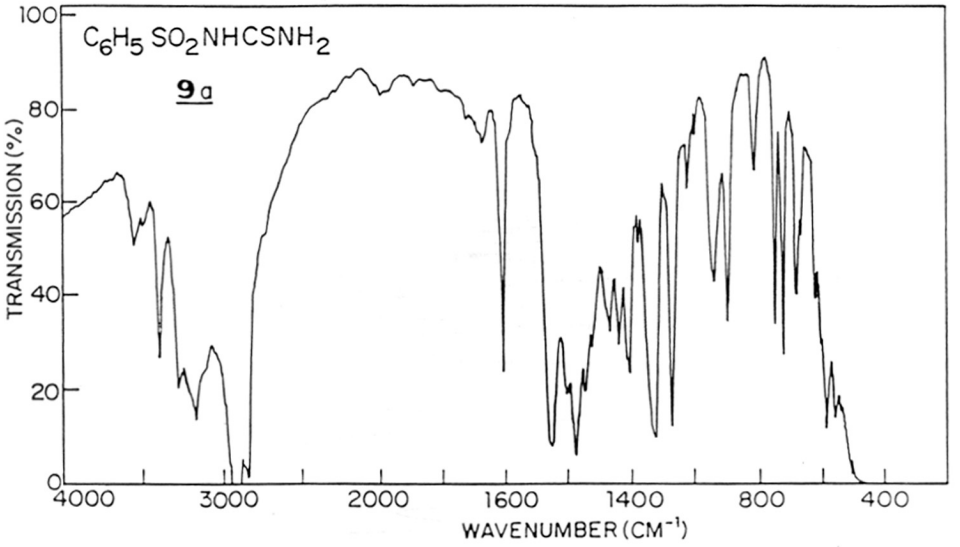
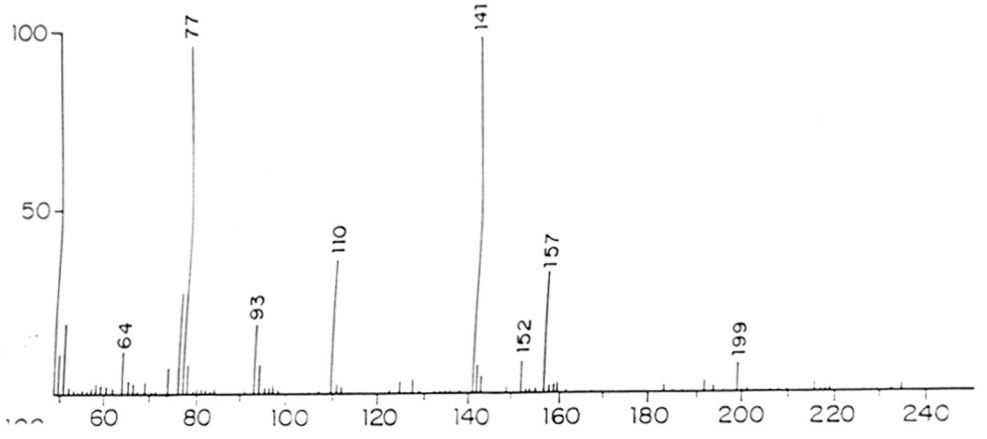
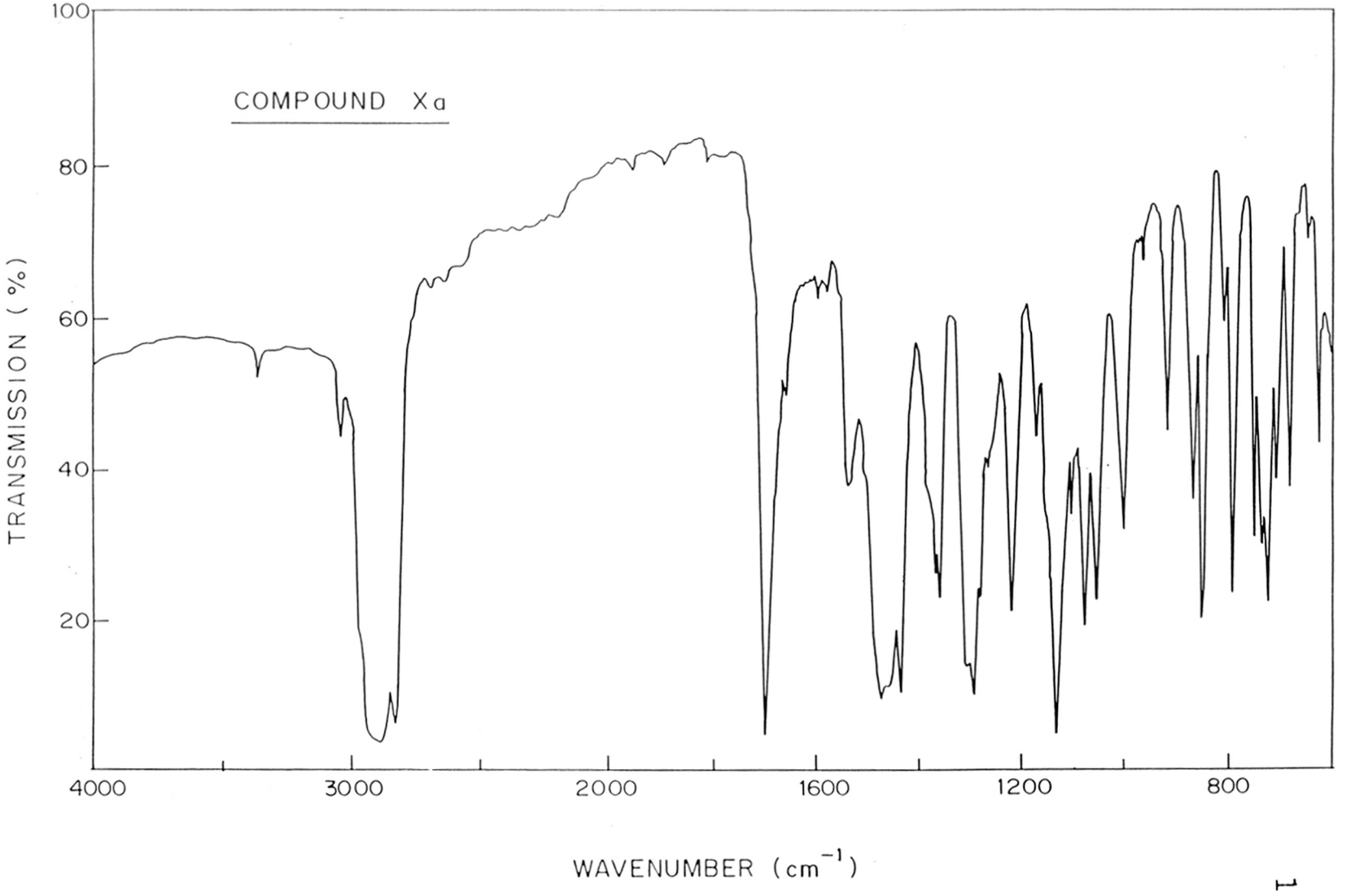




$C_6H_5SO_2NHCSNH_2$

9a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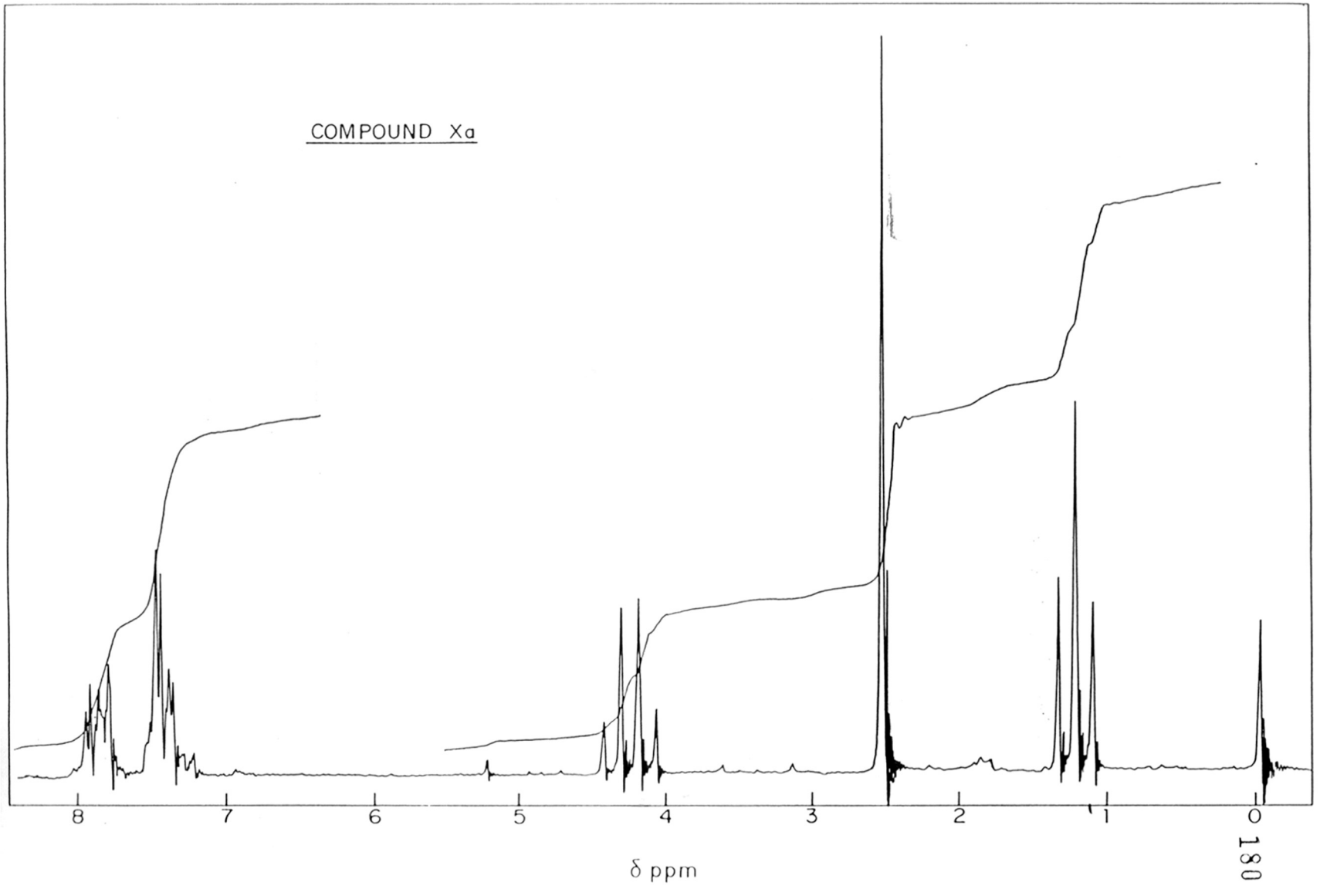
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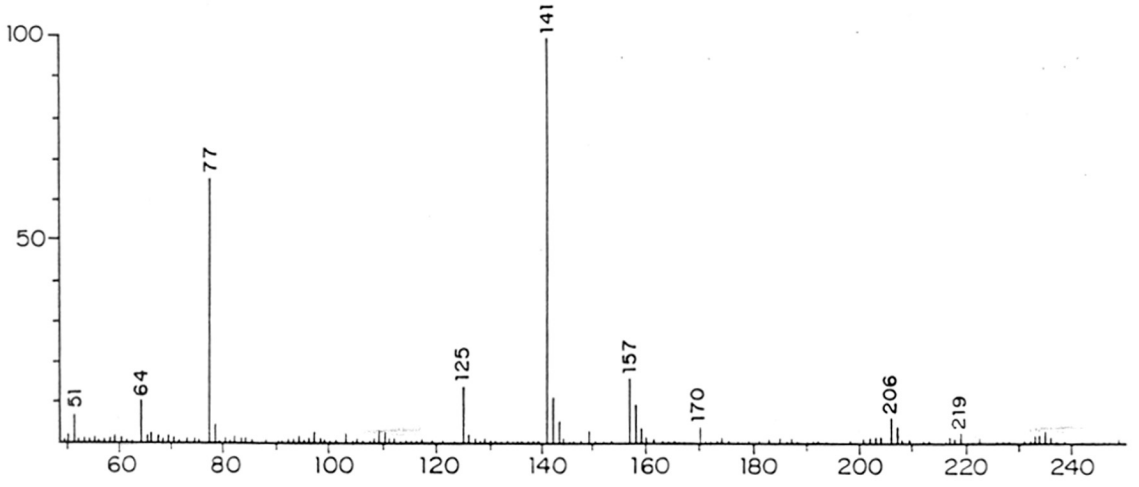
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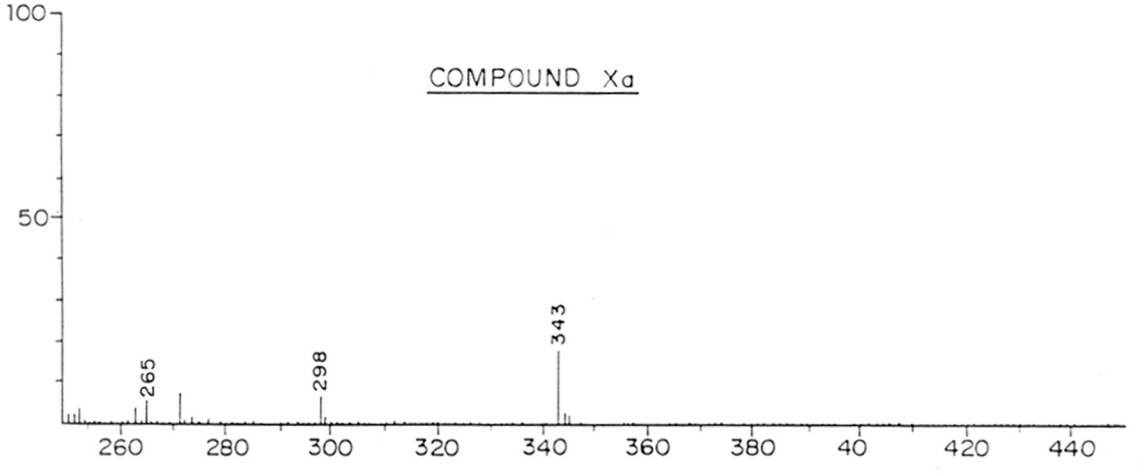
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PUBLICATIONS

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Regiochemistry of Alkylation in Substituted 1,2,4-Triazoles[a,b]

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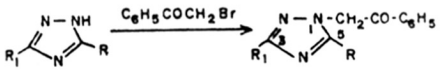
The regiochemistry of N-alkylation of substituted 1, 2, 4-triazoles has been studied and the results indicate that steric factors play a significant role in determining the site of N-alkylation in these compounds.

Derivatives of 1, 2, 4-triazole are of intense current interest in view of the wide ranging biological activity exhibited by these compounds as drugs[1], fungicides[2] and plant growth regulators[2]. As a part of our programme in preparing some novel fused systems containing the 1, 2, 4-triazole unit, it became necessary to assign unambiguous structures to the major products obtained on phenacylation of substituted 1,2,4-triazoles (**1-4**)[3].

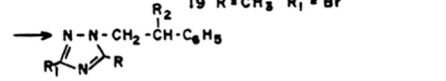
A perusal of literature showed that not much attention has been paid to the study of regiochemistry of N-alkylation in substituted triazoles, although it has been established[4,5] that alkylation takes place preferentially at the N_1 or N_2 position; the N_4 derivatives are either not formed at all or obtained in very low yields[6].

We have assigned structures to our phenacylated products in the following manner: Triazole (**1**) was reacted with phenacyl bromide in acetone and potassium carbonate at 0-10°. PMR[c] of the crude product (90%) showed essentially a single major compound which was crystallised from CCl_4-$CHCl_3$ to give a sharp melting (m.p. 116°) compound which was assigned structure (**5**)[d] by X-ray crystallography: PMR: 1.23 (3H, *t*, J = 8Hz), 4.33 (2H, *q*, J = 8Hz), 5.73 (2H, *s*), 7.56 (3H, *m*), 8.0 (2H, *dd*, J = 6, 2Hz), 8.36 (1H, *s*). Compound (**5**) was reduced with LAH in THF to give the diol (**6**), m.p. 118° (85%), which on treatment with thionyl chloride in chloroform in the cold gave the dichloro compound (**7**) as a crystalline solid, m.p. 82-83° (76%). The dithiophenyl derivative (**8**) was obtained as a thick oil (65%) by refluxing **7** with sodium thiophenate in ethanol for 4 hr. Desulphurisation of **8** with Raney nickel, in acetone-ethanol (9:1) at room temperature for 12 hr resulted in the formation of the phenethyl derivative (**9**) as a colourless oil (86%); PMR: 2.41 (3H, *s*), 3.13 (2H, *t*), 4.28 (2H, *t*), 7.15 (5H, *m*), 7.63 (1H, *s*).

Triazole (**2**) was treated with phenacyl bromide as above. PMR of the crude product (90%) showed a major isomer (80%) which was crystallised from benzene-pet. ether to give a sharp melting (102°) crystalline compound: PMR: 2.36 (3H, *s*), 2.56 (3H, *s*), 5.6 (2H, *s*), 7.53 (3H, *m*), 7.9 (2H, *dd*, J = 6, 2Hz). This compound was identified as **10** in the following way. Sodium borohydride reduction of **10** gave the alcohol (**11**) as a crystalline compound, m.p. 122° (90%), which was converted into the chloro compound (**12**) (oil, 98%), **13** (oil, 86%) and finally to the phenethyl derivative (**14**) have the following PMR: 1.96 (3H, *s*), 3.11 (2H, *t*), 4.26 (2H, *t*), 7.15 (5H, *m*), 7.82 (1H, *s*). Because of the difference in chemical shifts of methyl and heteroaromatic protons in **9** and **14**, compound (**14**) can have the structure indicated or it can be the less



1 R = H, R_1 = $COOC_2H_5$ **5** R = H, R_1 = $COOC_2H_5$
2 R = CH_3, R_1 = SCH_3 **10** R = CH_3, R_1 = SCH_3
3 R = H, R_1 = CH_3 **15a** R = CH_3, R_1 = H
4 R = CH_3 R_1 = Br **15b** R = H R_1 = CH_3
19 R = CH_3 R_1 = Br



6 R = H, R_1 = CH_2OH, R_2 = OH
7 R = H, R_1 = CH_2Cl, R_2 = Cl
8 R = H, R_1 = CH_2SPh, R_2 = SPh
9 R = H, R_1 = CH_3, R_2 = H
11 R = CH_3, R_1 = SCH_3, R_2 = OH
12 R = CH_3 R_1 = SCH_3 R_2 = Cl
13 R = CH_3, R_1 = SCH_3, R_2 = SPh
14 R = CH_3, R_1 = H, R_2 = H
16a R = CH_3, R_1 = H, R_2 = OH
16b R = H, R_1 = CH_3, R_2 = OH
17a R = CH_3, R_1 = H, R_2 = Cl
17b R = H, R_1 = CH_3, R_2 = Cl
18a R = CH_3, R_1 = H, R_2 = SPh
18b R = H, R_1 = CH_3, R_2 = SPh

(a) Presented at National Symposium on Heterocyclic Chemistry, Jaipur, 5-8 Feb., 1985.

(b) NCL Communication No. 3553.

(c) PMR spectra were recorded in $CDCl_3$ on WH-90 FT Spectrometer. Chemical shifts are given in δ values. Where not described all compounds gave satisfactory NMR spectra.

(d) All new compounds gave satisfactory mass spectra and or elemental analyses.

likely N_4-substituted isomer. The possibility of its being the N_4-isomer was ruled out by preparing authentic 3-methyl-4-phenethyl-1, 2, 4-triazole by an unambiguous route[7] as follows: Reaction of 4-phenethyl-3-thiosemicarbazide with ethyl *ortho* acetate resulted in 4-phenethyl-3-methyl-5-mercepto-1, 2, 4-triazole which was desulphurised after conversion to the $-s$-CH_3 derivative to give 3-methyl-4-phenethyl-1, 2, 4-triazole[3]. The N_4-isomer could be distinguished from **9** and **14** by its PMR [2.11 (3H, *s*), 2.95 (2H, *t*), 4.17 (2H, *t*), 7.24 (5H, *m*), 7.88 (1H, *s*)], thus confirming the structure (**14**) as indicated.

The total crude product (90%) obtained as a semisolid by reacting **3** with phenacyl bromide displayed PMR signals at 2.41, 2.43 (3H, *s*), 5.6 (2H, *s*), 7.6 (3H, *m*), 7.86 (0.4H, *s*), 8.0 (2H, *dd*, $J = 6$, 2Hz), 8.13 (0.6H, *s*). Comparison of the methyl and heteroaromatic proton signals showed it to be an approximately 40:60 mixture of **15a** and **15b** which was further confirmed by the conversion described above. Compound (**15**) was converted into a mixture of alcohols (**16a**) and (**16b**) (98%), chloro compounds (**17a**) and (**17b**) (95%) and phenylthio compounds (**18a**) and (**18b**) (97%), and finally to a 40:60 mixture of phenethyl compounds (**14**) and (**9**) as indicated by its PMR when compared with that of the PMR of pure **9** and **14** obtained above.

Lastly triazole (**4**) was phenacylated to give a crystalline solid, m.p. 115-17° (90%); PMR: 2.36 (3H, *s*), 5.5 (2H, *s*), 7.53 (3H, *m*), 7.9 (2H, *dd*, $J = 6$, 2Hz). Structure (**19**) was assigned to this compound on the following ground: Hydrogenation over 5% Pd/C in ethanol at 50 psi in the presence of sodium acetate resulted in the formation of a compound identical in all respects with **16a**, m.p. 102° [PMR: 2.23 (3H, *s*), 4.22 (2H, *m*), 5.17 (1H, *m*), 7.33 (5H, *s*), 7.76 (1H, *s*)], obtained by the desulphurisation of **11**. These PMR signals could also be assigned to **16a** in the 40:60 mixture of **16a** and **16b** obtained above.

We have thus prepared several derivatives of 1, 2, 4-triazole of unambiguous structures. It appears from the above work that steric factors play a significant role in directing the entry of the phenacyl group in substituted 1, 2, 4-triazoles. Further work on these lines is in progress.

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SYNTHESIS OF 1,2,4-TRIAZOLO FUSED HETEROCYCLES

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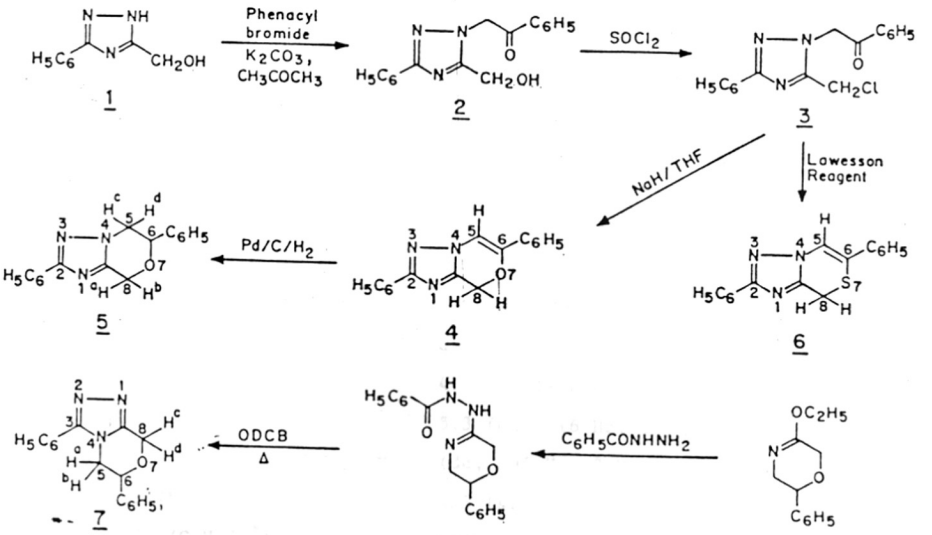
Abstract - Synthesis of bicyclic and tetracyclic ring systems containing 1,2,4-triazole unit has been achieved by alkylation of substituted 1,2,4-triazoles followed by base catalysed cyclocondensation.

The broad spectrum of activity[1,2,3] associated with substituted 1,2,4-triazoles prompted us to carry out the synthesis of novel fused ring systems containing the 1,2,4-triazole unit. Only recently the 8-oxo analogue of the 1,2,4-triazolo[5,1-c][1,4]oxazine system has been reported[4].

Herein, we describe a synthesis of triazolo fused bicyclic and tetracyclic systems by base catalysed cyclocondensation of the substituted 1,2,4-triazole derivatives.

On the basis of our earlier study[5] in the regiochemistry of alkylation in substituted 1,2,4-triazoles, it is now possible to predict the major regioisomer formed on alkylation. 3-Hydroxymethyl-5-phenyl-1,2,4-triazole 1[6] was phenacylated with phenacyl bromide and anhydrous potassium carbonate in acetone to give 2 (94%, mp 175-193°C)[7]. Structure 2 was assigned to the major product, the validity of which was verified by subsequent transformations. Compound 2 on treatment with thionyl chloride in chloroform yielded 3 (99%, mp 143°C). Reaction of 3 with sodium hydride in tetrahydrofuran gave a crude product which on column chromatographic separation over silica gel furnished 2,6-diphenyl-8H-[1,2,4]triazolo[5,1-c][1,4]oxazine 4 (55%, mp 154°C) (Scheme I). The structure of 4 was confirmed by pmr (Table 1), mass spectrum and elemental analysis. Further, 4 on catalytic hydrogenation over palladised charcoal gave 5 (94%, mp 111-112°C). Pmr (Table 1), mass spectrum and elemental analysis confirmed the structure of 5. In the uv, 4 showed maxima at 310 nm and 205 nm whereas 5 gave peaks at 240 nm and 200 nm.

It is well established in the literature[8,9,10], that alkylation in substituted 1,2,4-triazoles occurs mainly at vicinal nitrogens rather than at N_4 because of their enhanced nucleophilicities and N_4 derivatives are either nor formed at all



SCHEME - I

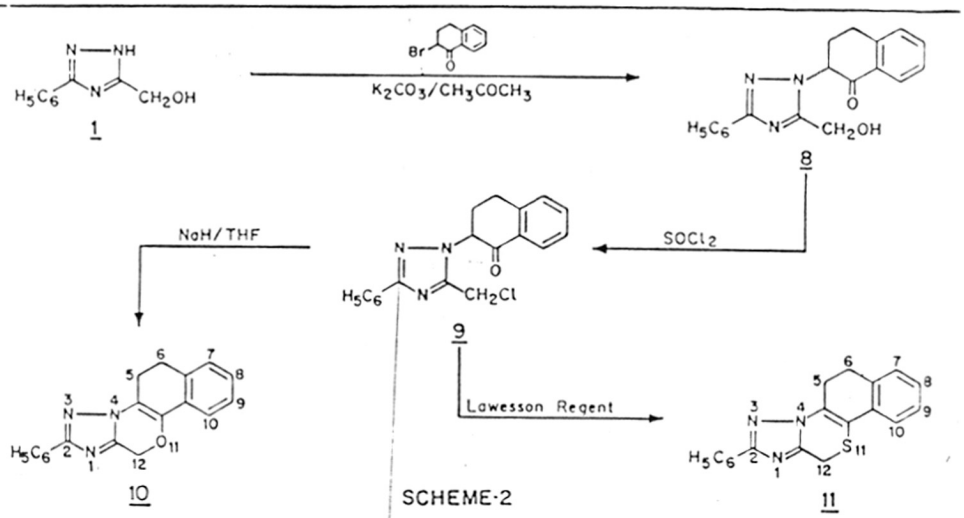
or obtained in very low yields. To rule out the remote possibility of the initial phenacylation having occurred at N_4 to give the isomeric bicyclic compound 3,6-diphenyl-8H-5,6-dihydro[1,2,4]triazolo[3,4-c][1,4]oxazine 7, the latter was synthesised (56%, mp 164°C) unambiguously starting from 3-ethoxy-6-phenyl-3,4-dehydromorpholine[11] (Scheme I). Comparison of spectroscopic data, melting points and tlc behaviour of compounds 5 and 7 showed that they are two different compounds. This confirmed the correct structure assignment to the compounds 2 to 5.

In order to get the thione analogue of 3, it was reacted with Lawesson reagent[12] in refluxing toluene. Instead of the required thione, the cyclized product 2,6-diphenyl-8H-[1,2,4]triazolo[5,1-c][1,4]thiazine 6 (50%, mp 148-149°C) was obtained.

To prepare a tetracyclic derivative containing 1,2,4-triazole, 1 was alkylated with 2-bromo-1-tetralone to give compound 8 (50%, mp 181°C), which was converted to its chloromethyl derivative 9 (99%, mp 183-184°C) with thionyl chloride (Scheme II). Compound 9 on reaction with sodium hydride in tetrahydrofuran gave 2-phenyl-12H-5, 6-dihydronaphtho[1,2-b][1,2,4]triazolo[1,5-d]-[1,4]oxazine 10 (71%, mp 182°C). Similarly, 9 with Lawesson reagent gave 2-phenyl-12H-5,6-dihydronaphtho[1,2-b][1,2,4]triazolo[1,5-d]thiazine 11 (46%, mp 192°C).

TABLE 1

Compound	Mass (m/z)	Pmr ($CDCl_3$) δ ppm
4	275 (M^+), 137.5 (M^{++})	5.5 (s, 2H), 7.3 (s, 1H), 7.4 (m, 8H),
	105 ($C_6H_5CO^+$)	8.1 (dd, J=6 Hz, 2 Hz, 2H).
5	277 (M^+), 171(M^+-C_6H_5CHO)	4.2 (dd, J=12 Hz, 4 Hz, 1H)-H^c, 4.5 (dd, J=12 Hz, 11 Hz, 1H)- H^d, 5.0 (dd, J=11 Hz, 4 Hz, 1H)-CHPh, 5.0 (d, J=16 Hz, 1H)-H^a, 5.3 (d, J=16 Hz, 1H)-H^b, 7.4 (s, 8H), 8.1 (dd, J=6 Hz, 2 Hz, 2H).
6	291(M^+), 145.5 (M^{++}),	4.3 (s. 2H), 7.3 (m, 8H), 7.5 (s, 1H), 8.0
	121 ($C_6H_5CS^+$)	(dd, J=6 Hz, 2 Hz, 2H).
7	277(M^+), 171(M^+-C_6H_5CHO)	4.1 (m, 2H)-H^a,-H^b, 4.8 (dd, J=9 Hz, 4 Hz, 1H)-CHPh, 5.1 (d, J=16 Hz, 1H)-H^c, 5.4(d, J=16 Hz, 1H)-H^d, 7.4 (m, 8H), 7.7 (dd, J=6 Hz, 2 Hz, 2H).
10	301(M^+)	3.1 (s, 4H), 5.5 (s, 2H), 7.3 (m, 7H),
		8.0 (dd, J=6 Hz, 2 Hz, 2H).
11	317 (M^+)	3.1 (m, 4H), 4.2 (s, 2H), 7.4 (m, 7H),
		8.0 (dd, J=6 Hz, 2 Hz, 2H).



SCHEME-2

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