SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND SULPHUR

A THESIS
SUBMITTED TO THE
UNIVERSITY OF BOMBAY
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(in the faculty of technology)

BY
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C O N T E N T S

STATEMENT REQUIRED TO BE SUBMITTED UNDER RULE 0.413
OF THE UNIVERSITY OF BOMBAY

No part of this work has been submitted for a degree or diploma or other academic award. The literature concerning the problem investigated has been surveyed, and all the necessary references are given. The experimental work has been carried out entirely by me. In accordance with the usual practice, due acknowledgement has been made whenever the work presented is based on the results of other workers.

K.A.R. Sastry

Poona,

K.A.R. Sastry
Candidate

B.D. Tilak

Professor B.D. Tilak,
Research Guide

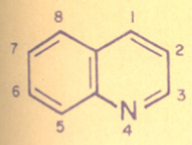
N O T E S

1. Melting points are uncorrected.
2. The liquid compounds were distilled in a bulb tube and the boiling points reported presently correspond to bath temperature.
3. The PMR spectra were recorded on a Varian A-60 and T-60 spectrometer in DMSO, CF_3COOH and/or $CDCl_3$ solutions taking TMS as internal standard. The chemical shifts (δ) values are reported in ppm and J values in Hz.
4. The IR spectra were recorded on a Perkin-Elmer model 221 spectrophotometer using a sodium chloride grating interchange in nujol or HCB mull and in CCl_4 solutions. The instrument was calibrated with water vapour and carbon dioxide bands, calibration being checked from time to time with polystyrene film. Some of the IR spectra were taken in nujol mull or as a liquid film, using Perkin-Elmer Infracord 137 spectrometer. The IR values are recorded in cm^{-1}.
5. Mass spectra were recorded on GEC 21-110B double focussing spectrometer using direct inlet system.
6. UV and visible spectra were recorded on a Beckman ratio recording spectrometer and values reported as λ_{max} in

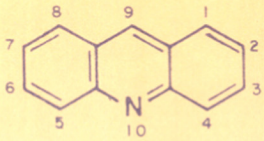
mμ and log ε values in parenthesis. The spectra of the perchlorates reported were taken in acetic acid containing 1% perchloric acid and other compounds were taken in ethanol.

7. The nomenclature and numbering system used by chemical abstracts and Ring index[1] has been adopted in the present work. Chart 1 indicates the names and numbering of some of the typical compounds. Since many workers name the compounds in more than one way (eg, benzo[1,6]naphthyridines are also termed as 1,6-phenanthrolines) the naming and numbering of these compounds suggested by earlier workers have been modified according to the present numbering adopted by chemical abstracts.

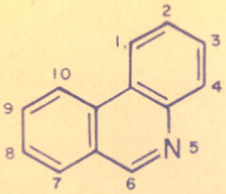
8. Spectral charts, wherever necessary, have been reduced to standard size and attached at the end of the discussion. The actual values are given in the discussion.



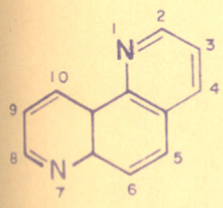
QUINOLINE



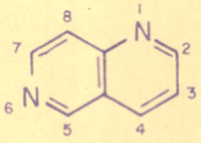
ACRIDINE



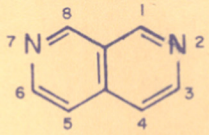
PHENANTHRIDINE



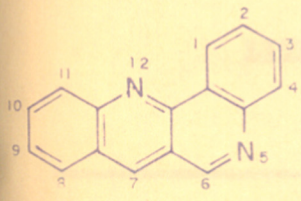
1,7-PHENANTHROLINE



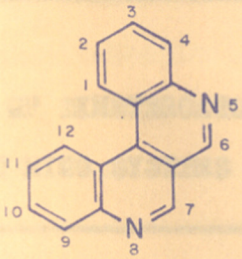
1,6 - NAPHTHYRIDINE



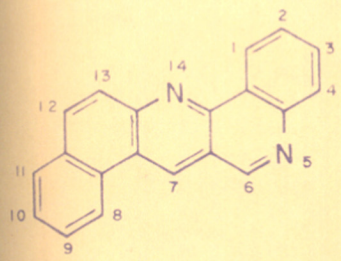
2,7-NAPHTHYRIDINE



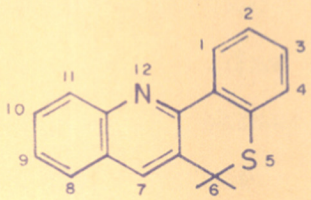
DIBENZO [b,h] [1,6] NAPHTHYRIDINE



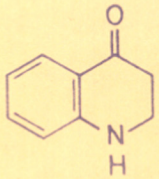
DIBENZO [c,f] [2,7] NAPHTHY-
RIDINE



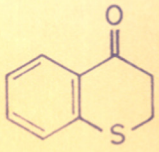
BENZO [h] NAPHTHO [2,1-b] [1,6]
NAPHTHYRIDINE



6H-[1] BENZOTHIOPYRANO-
[4,3-b] QUINOLINE



1,2,3,4 - TETRAHYDROQUINOLIN-4-ONE



THIOCHROMAN-4-ONE

CHART — 1.

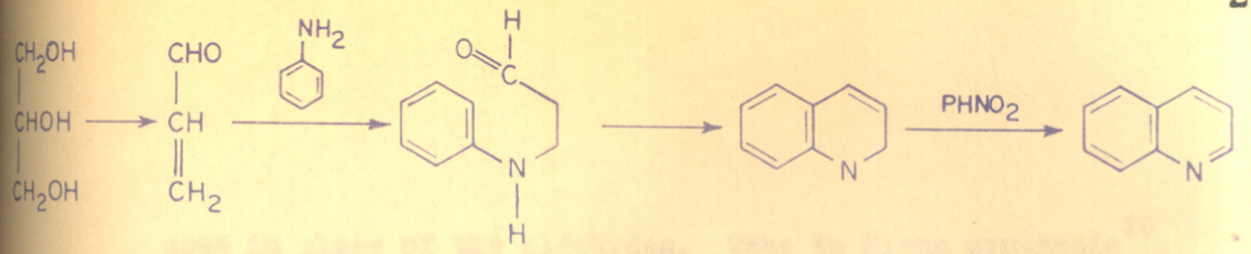
CHAPTER I

LITERATURE SURVEY ON THE SYNTHESIS OF DIHETEROATOMIC TETRACYCLIC AND PENTACYCLIC RING SYSTEMS

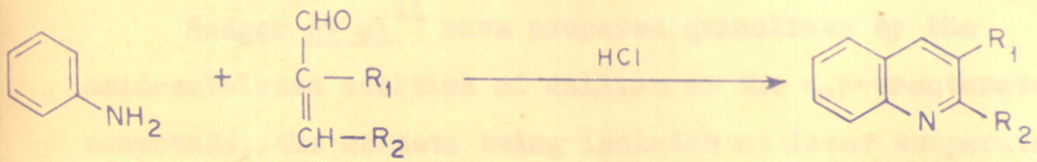
INTRODUCTION

Nitrogen and sulphur heterocycles form an important class of compounds. Many of these are widely used in industry, e.g. as dyes and photographic chemicals[2], and as chemotherapeutic agents possessing antibacterial, antimalarial and trypanocidal activity. The synthesis, properties and uses of the acridines[3], phenanthridines[4], phenanthrolines[5] and naphthyridines[6,7] have been studied in detail. The present work deals with the synthesis of tetracyclic and pentacyclic ring systems containing both nitrogen and sulphur. Literature survey relevant to the synthesis and present work carried out in our laboratory will be discussed in the following pages.

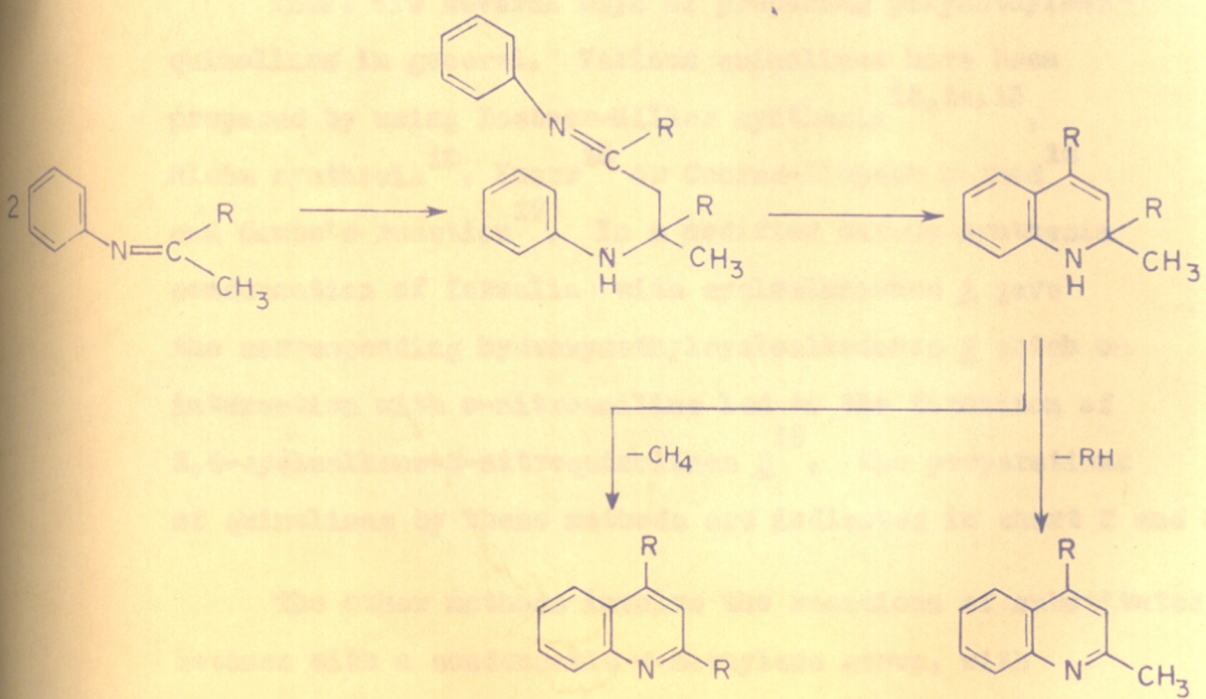
Quinoline was synthesised by Skraup[8,9] in 1880 by heating a mixture of aniline, nitrobenzene, glycerine and concentrated sulphuric acid. First step in the Skraup synthesis, is the dehydration of glycerol to acrolein which then adds to the aromatic amine and subsequently undergoes cyclodehydrogenation under acidic conditions in the presence of oxidising agents to give quinoline. The Skraup synthesis is applicable to any α,β-unsaturated aldehydes. Subsequently α,β-unsaturated ketones have been



SKRAUP SYNTHESIS



DOEBNER - MILLER SYNTHESIS



RIEHM SYNTHESIS

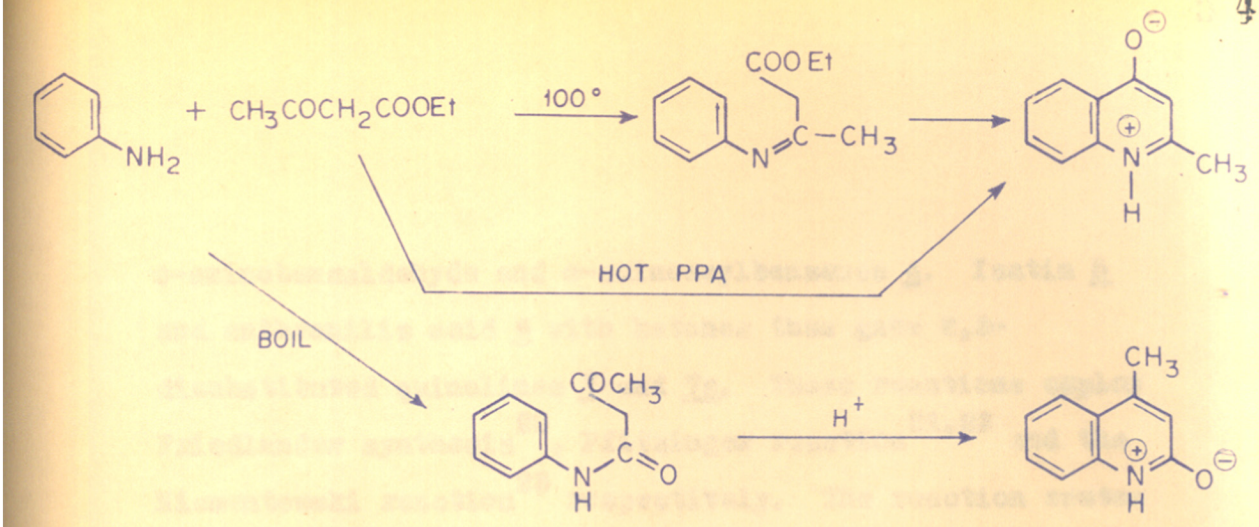
CHART — 2

used in place of the aldehydes. Thus in Riehm synthesis[10], aniline and two molecules of acetone gave 2,4-dimethyl quinoline. Many of the latter methods involve acid catalysed reactions of primary amines and ∝,β-unsaturated carbonyl compounds.

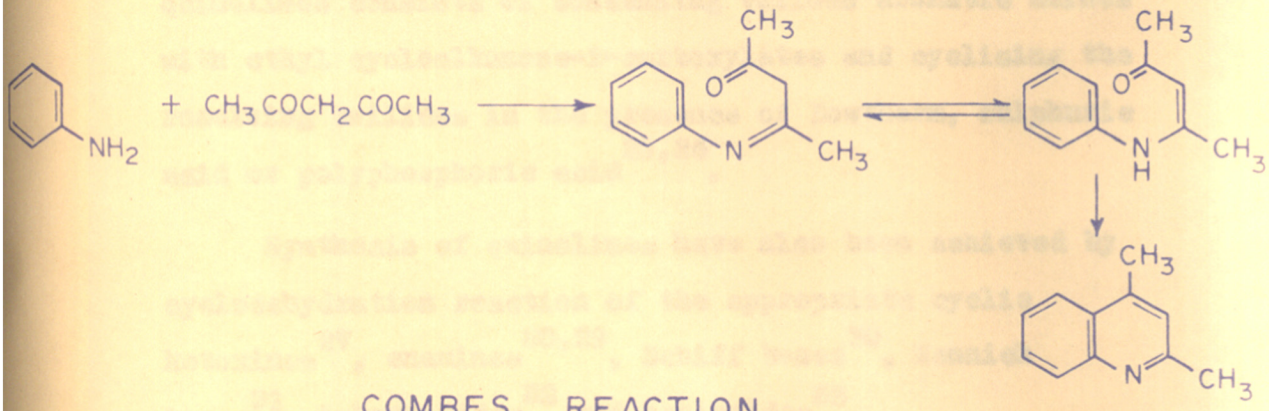
Badger et al[11] have prepared quinolines by the acid-catalysed addition of aniline to the ∝,β-unsaturated compounds, the adducts being isolated at lower temperatures. Badger et al[12] have also prepared the adducts by Mannich reaction and have cyclised it under acidic conditions to yield quinolines.

There are several ways of preparing polymethylene-quinolines in general. Various quinolines have been prepared by using Doebner-Miller synthesis[13,14,15], Riehm synthesis[10], Knorr[18] or Conrad-Limpach method[16] and Combe's reaction[17]. In a modified Skraup synthesis condensation of formalin with cycloalkanones 1 gave the corresponding hydroxymethylcycloalkanones 2 which on interaction with o-nitroaniline led to the formation of 3,4-cycloalkeno-8-nitroquinolines 3[19]. The preparations of quinolines by these methods are indicated in chart 2 and 3.

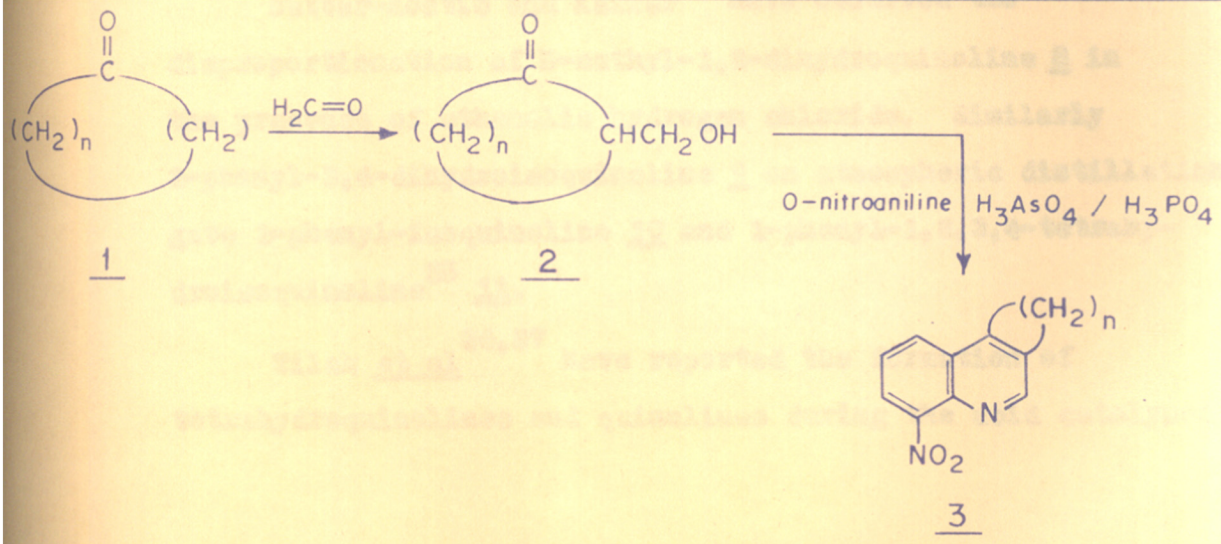
The other methods involve the reactions of substituted ketones with a condensable ∝-methylene group, with



KNORR OR CONRAD-LIMPACH METHOD



COMBES REACTION



1 2 3

MODIFIED SKRAUP SYNTHESIS

CHART – 3

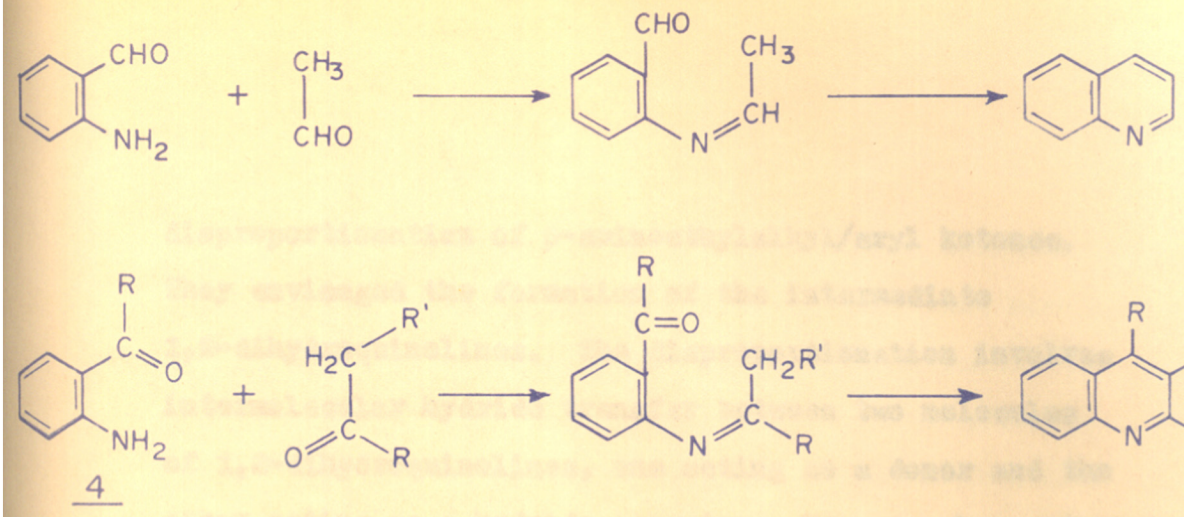
o-aminobenzaldehyde and o-aminoacylbenzenes 4. Isatin 5 and anthranilic acid 6 with ketones thus gave 2,3-disubstituted quinolines 7 and 7a. These reactions employ Friedlander synthesis[20], Pfitzinger reaction[21,22] and the Niementowski reaction[23] respectively. The reaction routes are indicated in chart 4.

Yet another method of preparation of the polymethylene-quinolines consists of condensing various aromatic amines with ethyl cycloalkanone-2-carboxylates and cyclising the resulting anilides in the presence of Dowtherm, sulphuric acid or polyphosphoric acid[25,26].

Synthesis of quinolines have also been achieved by cyclodehydration reaction of the appropriate cyclic ketoximes[27], enamines[28,29], Schiff bases[30], Mannich bases[31], β-ketoamides[32] and arylamides[33].

Sutter-Kostic and Karrer[34] have observed the disproportionation of N-methyl-1,2-dihydroquinoline 8 in the presence of ethanolic hydrogen chloride. Similarly 1-phenyl-3,4-dihydroisoquinoline 9 on atmospheric distillation gave 1-phenyl-isoquinoline 10 and 1-phenyl-1,2,3,4-tetrahydroisoquinoline[35] 11.

Tilak et al[36,37] have reported the formation of tetrahydroquinolines and quinolines during the acid catalysed



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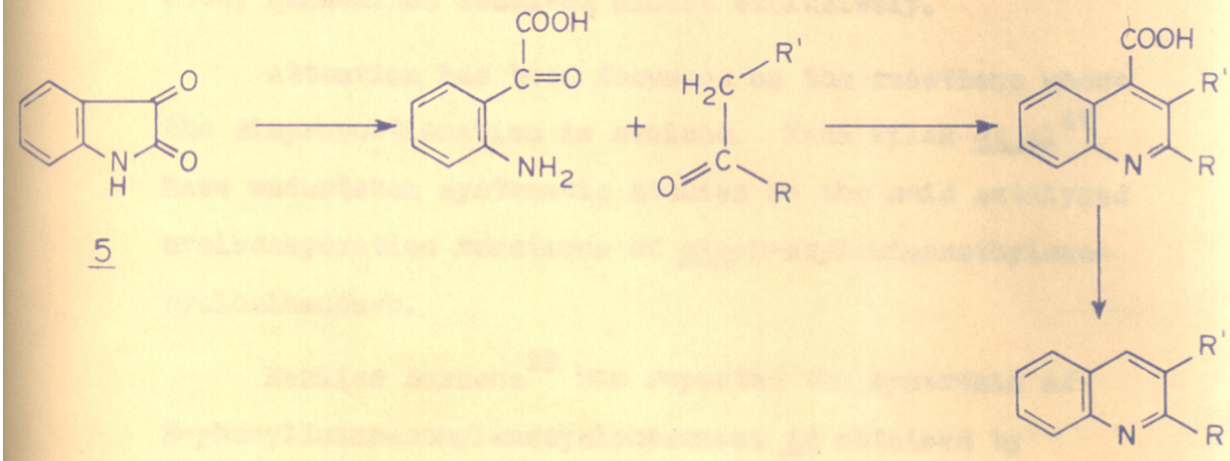
FRIEDLÄNDER SYNTHESIS



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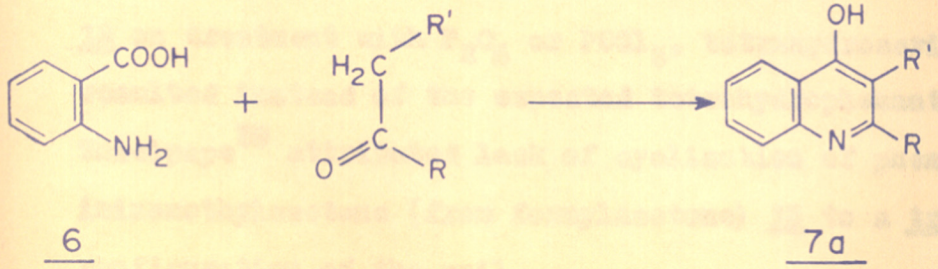
PFITZINGER REACTION



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7a

NIEMENTOWSKI REACTION

CHART – 4

disproportionation of β-aminoethylalkyl/aryl ketones. They envisaged the formation of the intermediate 1,2-dihydroquinolines. The disproportionation involves intermolecular hydride transfer between two molecules of 1,2-dihydroquinolines, one acting as a donor and the other acting as a hydride acceptor. However when external hydride abstractor such as triphenylmethyl chloride was used, quinolines resulted almost exclusively.

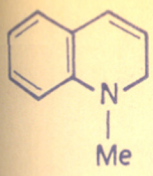
Attention has been focussed on the reactions where the disproportionation is avoided. Thus Tilak et al[47] have undertaken systematic studies on the acid catalysed cyclodehydration reactions of cis-2-arylaminomethylene-cycloalkanones.

Earlier Borsche[38] has reported the synthesis of 2-phenyliminomethylenecyclohexanone 12 obtained by condensing formylcyclohexanone with aniline. However, when 12 was treated with zinc chloride in isoamyl alcohol at reflux, no reaction took place. On the other hand, 12 on treatment with P_2O_5 or $POCl_3$, tetrahydroacridine 13 resulted instead of the expected tetrahydrophenanthridine 14. Thielpape[39] attributed lack of cyclisation of phenyl-iminomethylacetone (from formylacetone) 15 to a trans-configuration of the anil.

Petrow[45] contends that by analogy with salicylidene-aniline 16 to which trans-configuration has been assigned on the basis of the absorption spectra measurements[40], dipole moments[41] and the formation of chelate metallic salts[42], it may be inferred that the anils derived from β-ketoaldehydes are similarly oriented and their direct cyclisation therefore is improbable on stereochemical grounds.

According to Hollingsworth and Petrow[44] compounds such as 2-phenyliminomethylenecyclohexanone 12 have trans-configuration and consequently they resist direct cyclisation. Cyclisation of compound 12 was achieved by heating with formic acid to 7,8,9,10-tetrahydrophenanthridine 14. It was argued that favourable stereochemistry is achieved by the selective reduction of the azomethine linkage to give 2-phenylaminomethylcyclohexanone 17 and then to phenanthridine 14. However, it was shown later by Tilak et al[47] that the anil 12 is in fact the cis isomer only and the cyclisation to 7,8,9,10-tetrahydrophenanthridine 14 could also be achieved with polyphosphoric acid.

Kenner et al[43] have reported the preparation of 7,8,9,10-tetrahydrophenanthridine 14 in moderate yield by the condensation of hydroxymethylenecyclohexanone with aniline and anilinehydrochloride in the presence of



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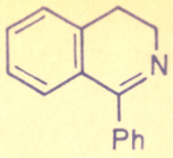

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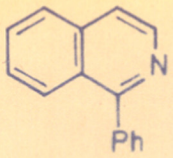

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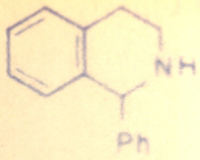

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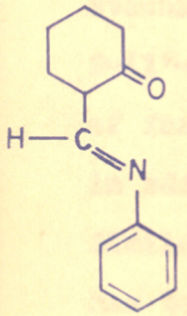

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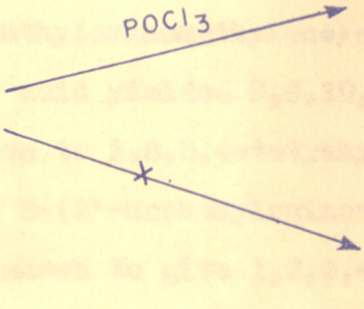

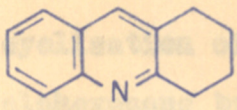

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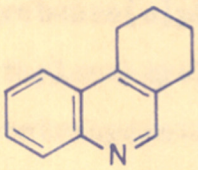

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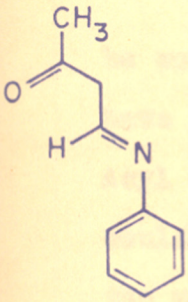

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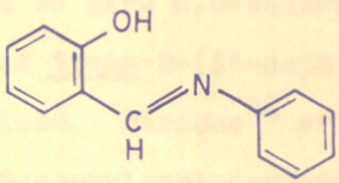

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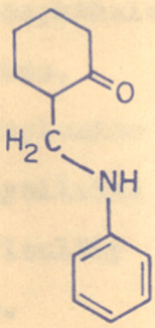

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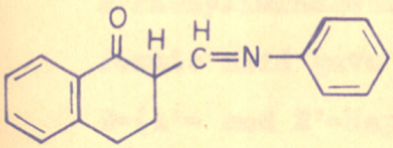

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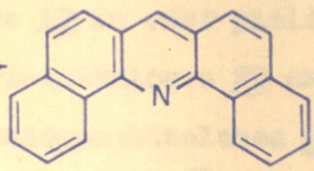

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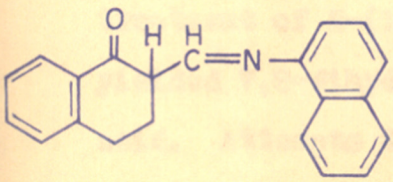

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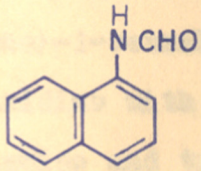

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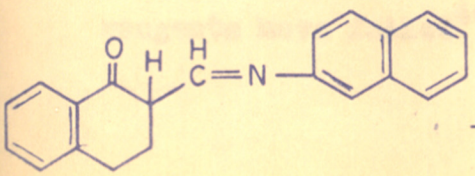

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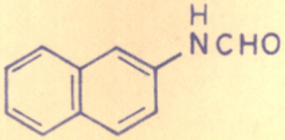


23

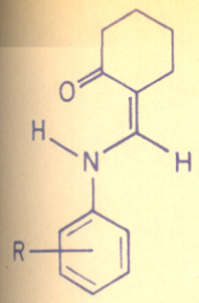
stannic chloride hydrate. The cyclisation of 2-(1'-naphthylaminomethylene) cyclohexanone by means of formic acid yielded 8,9,10,11-tetrahydrobenz[c]acridine in addition to 1,2,3,4-tetrahydrobenzo[c]phenanthridine[45a]. Similarly 2-(2'-naphthylaminomethylene) cyclohexanone has been shown to give 1,2,3,4-tetrahydrobenzo[a]-phenanthridine and 8,9,10,11-tetrahydrobenz[a]acridine[45a].

Among the other miscellaneous reactions, it may be worth mentioning here that 1-O-acylaminoarylanaphthalenes[46] have been cyclised to give 5,6-benzophenanthridines. Acyl derivatives of trans-2-(1'-naphthyl) cyclohexylamine could not be cyclised. Borsche[38] succeeded in cyclising the mono anil of 2-acetylcyclohexanone to a difficultly separable mixture of acridine and phenanthridine. 2-Phenyliminomethyl-1-tetralone 18 when treated with formic acid gave dibenz[c,h]acridine 19 in poor yields. 2-(1'- and 2'-Naphthyliminomethyl)-1-tetralones 20 and 21 gave small yields of 1- and 2-formamidonaphthalenes 22 and 23 respectively. However it was reported[45a] that treatment of 2-(1'-naphthylaminomethylene)-1-tetralone yielded 7,8-dihydrodibenzo[c,k]phenanthridine with formic acid. Attempts to cyclise trans-1-acetamido and trans-1-benzamido-2-α-naphthylcyclohexane with a number of reagents have failed[46].

The cyclising agents used in these reactions are ethanolic hydrogen chloride, polyphosphoric acid (PPA), sulphuric acid, formic acid, lactic acid, monochloroacetic acid, Dowtherm and finally zinc chloride along with amine hydrochloride. Barring a few exceptions it can be said that the cyclodehydration reactions of cis-2-arylaminomethylene-cycloalkanones with lactic acid or anhydrous zinc chloride and the corresponding arylamine hydrochloride in boiling ethanol yield the linear quinolines (acridines). Monochloroacetic acid cyclisations also yield the linear quinolines[48].

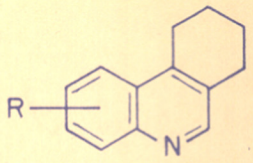
Cyclodehydration of cis-2-(3'-methoxy)anilinomethylene-cyclohexanone 24d by treatment with PPA yielded 8-methoxy-1,2,3,4-tetrahydrophenanthridine 25a in good yield, (96%)[47]. Cyclodehydration of 24d by treatment with aniline hydrochloride/anhydrous zinc chloride in boiling ethanol gave 6-methoxy-1,2,3,4-tetrahydroacridine 26d in 57% yield.

Tilak et al[47] cyclodehydrated cis-2-arylaminomethylene-cyclohexanones with different primary arylamine hydrochlorides in boiling ethanol in the presence of anhydrous zinc chloride to obtain tetrahydroacridines, where the aryl moiety was retained or substituted by interacting arylamine (used as hydrochloride). In the above reactions the amines used were substituted aniline and α- and β-naphthylamines.



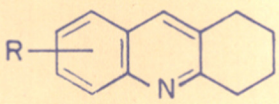
24

a, R = H
b, R = 2'-OCH_3
c, R = 3'-CH_3
d, R = 3'-OCH_3
e, R = 3'-Cl
f, R = 4'-CH_3
g, R = 4'-OCH_3



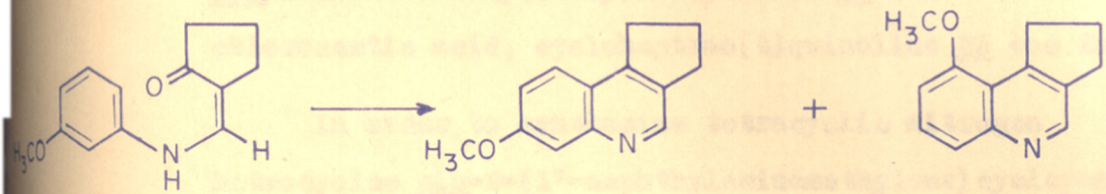
25

a, R = 8-OCH_3
b, R = 7-Cl
c, R = 8-CH_3
d, R = 9-OCH_3

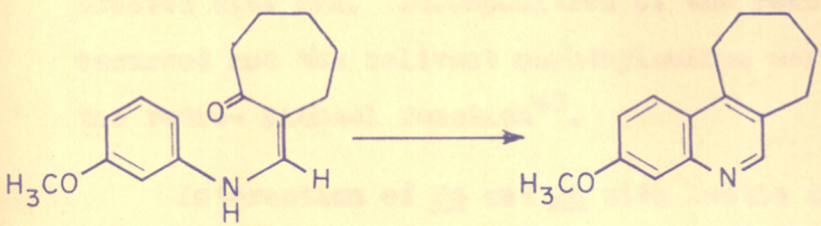


26

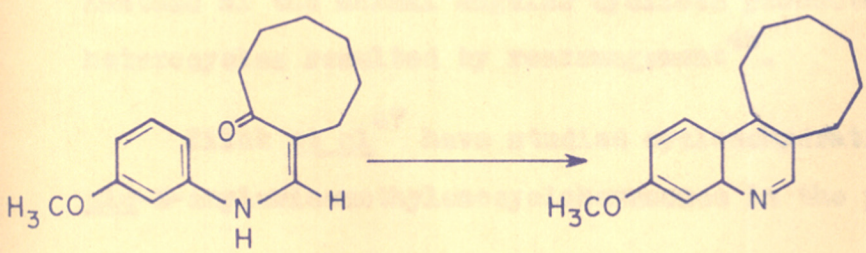
a, R = H
b, R = 5-OCH_3
c, R = 6-CH_3
d, R = 6-OCH_3
e, R = 6-Cl
f, R = 7-CH_3
g, R = 7-OCH_3



27 28 29



30 31



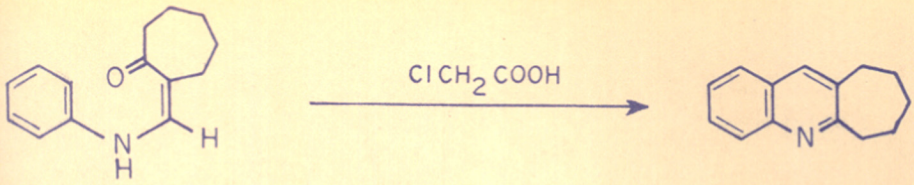
32 33

Cyclodehydration of cis-2-(3'-methoxy)anilinomethylene-cyclopentanone 27 by interaction with PPA gave 3,4-cyclopenteno-7-methoxyquinoline 28 and 3,4-cyclopenteno-5-methoxyquinoline 29 in 61% and 8% yields respectively[48]. Similarly cis-2-(3'-methoxy)anilinomethylenecycloheptanone 30 and cis-2-(3'-methoxy)anilinomethylenecyclooctanone 32 when reacted with PPA gave 3-methoxycycloheptenoquinoline 31 and 3-methoxycyclooctanoquinoline 33 respectively. When cis-2-anilinomethylenecycloheptanone 34 was treated with chloroacetic acid, cyclohepteno[b]quinoline 35 was formed[48].

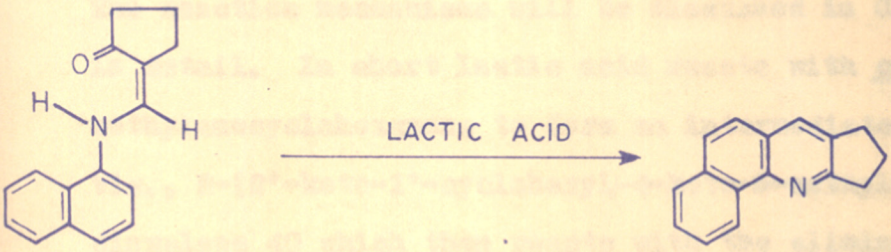
In order to synthesise tetracyclic nitrogen hetrocycles cis-2-(1'-naphthylaminomethylene) cyclopentanone 36 and cis-2-(2'-naphthylaminomethylene) cyclopentanone 38 were treated with PPA. Decomposition of the reaction products occurred and the relevant naphthylamines were formed by the retro- Michael reaction[48].

Interaction of 36 and 38 with lactic acid yielded 4-aza-cyclopenteno[b]phenanthrene 37 and 1-aza-cyclopenteno[b]-phenanthrene 39 respectively. It may be noted that here instead of the normal angular cyclised products, linear heterocycles resulted by rearrangement[48].

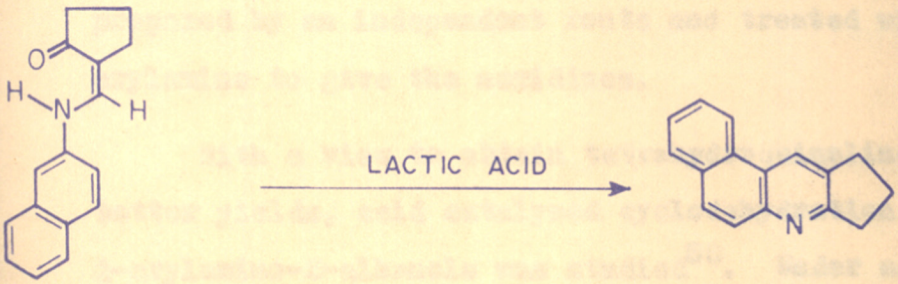
Tilak et al[47] have studied cyclodehydration of cis-2-arylaminomethylenecyclohexanones in the presence of



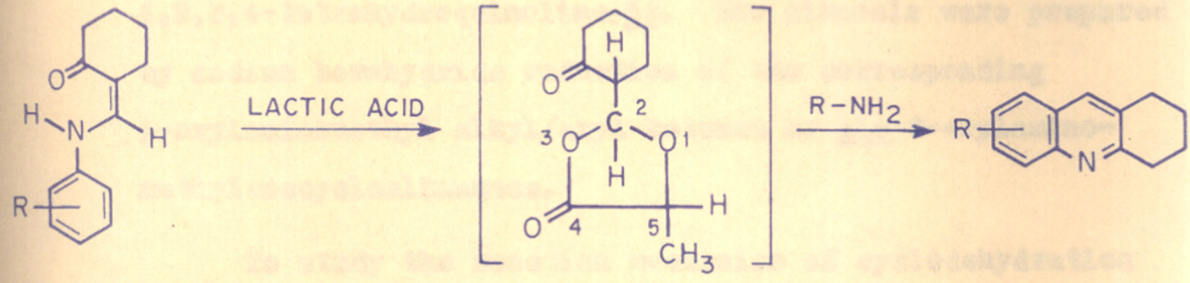
34 35



36 37



38 39



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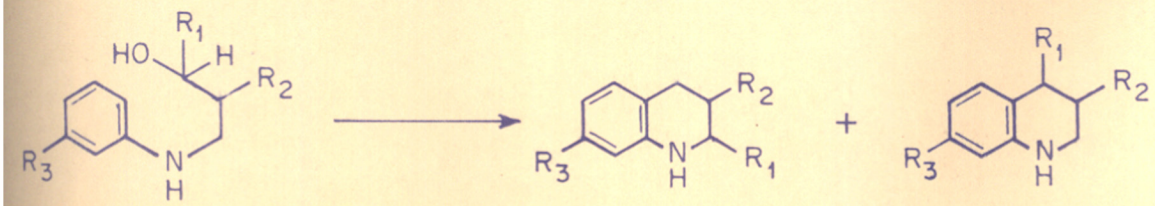


51 52 53

lactic acid. This reaction yielded a mixture of acridines. The reaction mechanisms will be discussed in Chapter III in detail. In short lactic acid reacts with cis-2-arylaminomethylenecyclohexanone to form an intermediate product viz., 2-(2'-keto-1'-cyclohexyl)-4-keto-5-methyl-1,3-dioxalane 40 which then reacts with the eliminated arylamine leading finally to an acridine via the arylimine intermediate. Although the dioxalane 40 could not be isolated, it was prepared by an independent route and treated with the arylamine to give the acridines.

With a view to obtain tetrahydroquinolines in better yields, acid catalysed cyclodehydration of 1-arylamino-3-alkanols was studied[50]. Under acidic conditions, these alkanols 51 yielded 2,3-disubstituted 1,2,3,4-tetrahydroquinolines 52 along with 3,4-disubstituted 1,2,3,4-tetrahydroquinolines 53. The alkanols were prepared by sodium borohydride reduction of the corresponding β-arylaminomethyl alkyl/aryl ketones or cis-2-arylaminomethylenecycloalkanones.

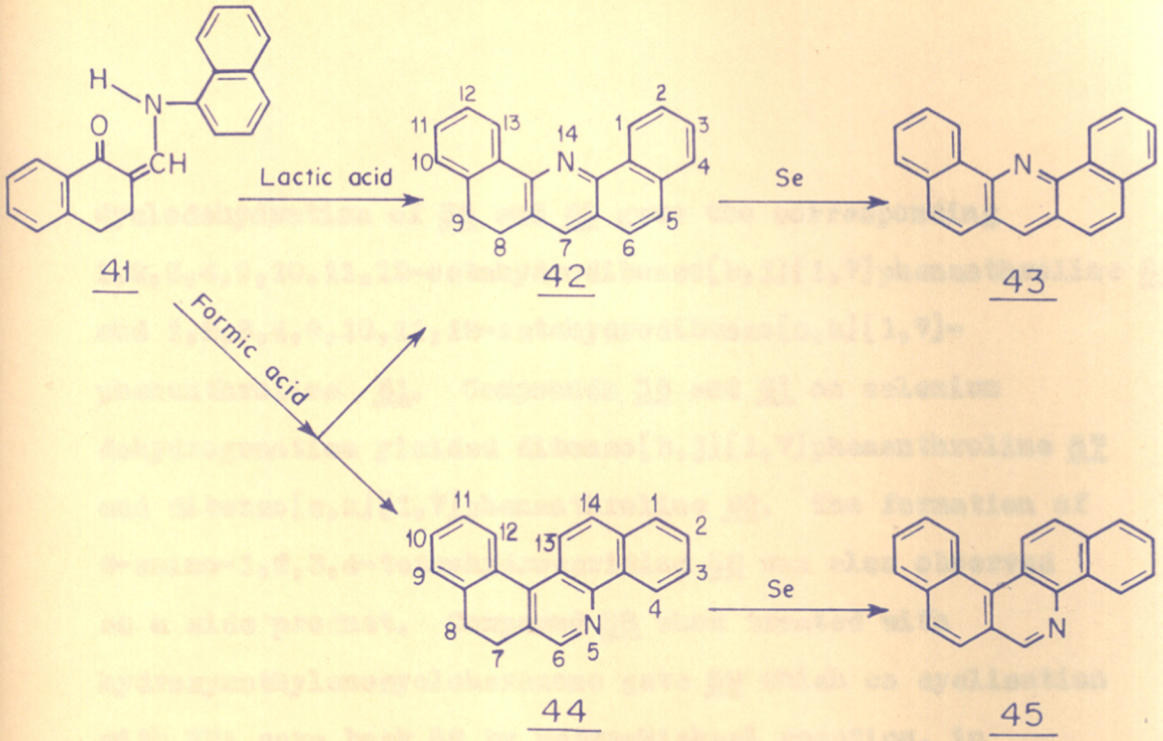
To study the reaction mechanism of cyclodehydration reactions, attempts were made[51] to prepare N-arylazetidines and rearrange them to acridines under acidic conditions.

The work has now been extended by Mullick[49] to synthesise pentacyclic compounds containing one or two nitrogen atoms. 8,9-Dihydrobenz[c,h]acridine 42 and 7,8-dihydrodibenzo[c,k]phenanthridine 44 have been synthesised by the cyclodehydration of 2-(1'-naphthylaminomethylene)-1-tetralone 41. Similarly cyclodehydration of 2-(2'-naphthylaminomethylene)-1-tetralone 46 lead to the formation of 5,6-dihydrodibenz[a,h]acridine 47 and 5,6-dihydrodibenzo[a,k]-phenanthridine 49. Lactic and formic acids have been used for effecting these cyclisations.

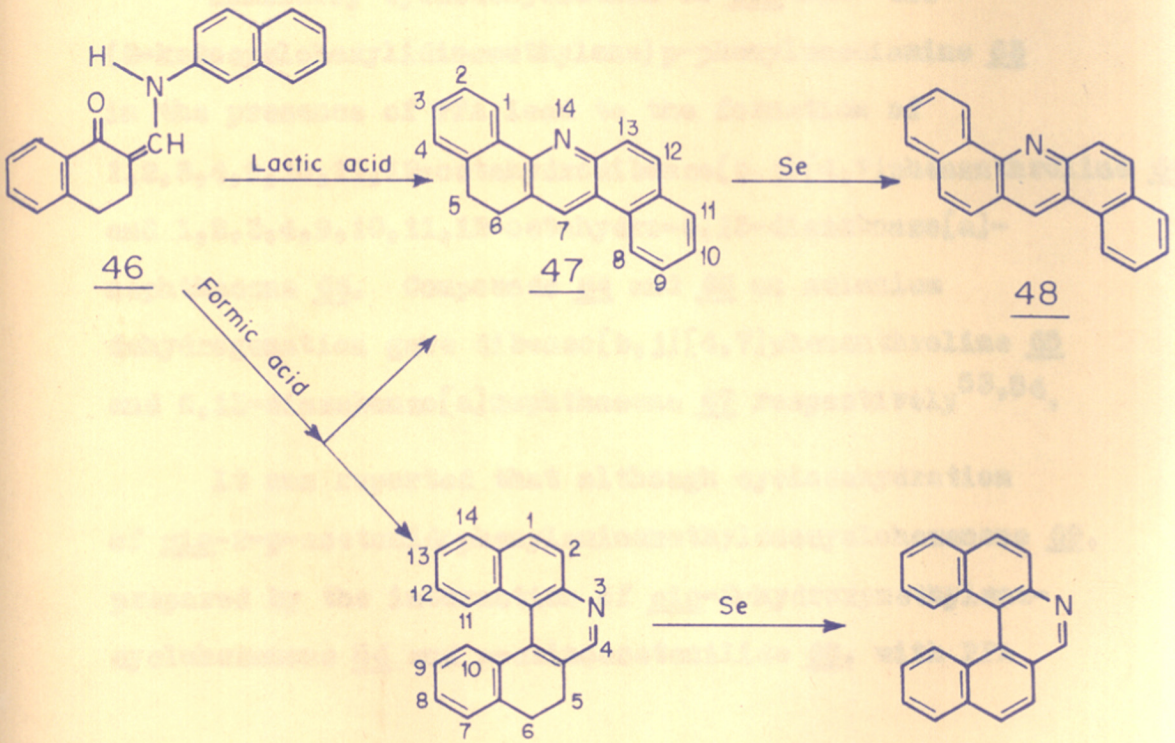
The dihydro compounds on dehydrogenation in presence of selenium at elevated temperatures gave the corresponding dibenzacridines 43, 48 and the corresponding dibenzo-phenanthridines 45, 50.

Structural analysis was based on the PMR studies of the dehydrogenated products. It may be interesting to note that formic acid cyclisation gave both the angular and linear products.

Apropos the work done by Berde[52] to obtain diheteroatomic pentacyclic ring systems, interaction of cis-2-hydroxymethylenecyclohexanone 54 with m-phenylene-diamine gave either a mono- (55) or a dicondensation product (60) depending upon the molar ratios of the reactants[53].



41 42 43 44 45

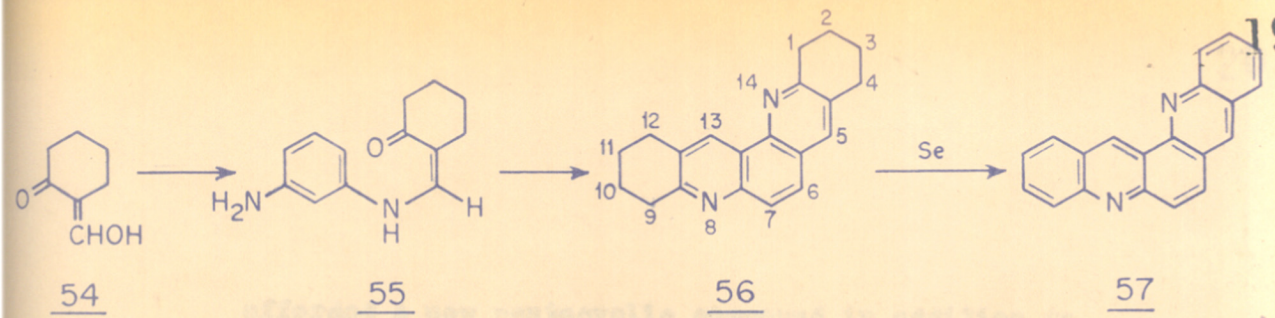


46 47 48 49 50

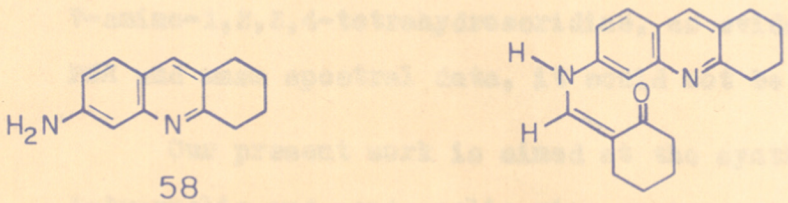
Cyclodehydration of 55 and 60 gave the corresponding 1,2,3,4,9,10,11,12-octahydrodibenzo[b,j][1,7]phenanthroline 56 and 1,2,3,4,9,10,11,12-octahydrodibenzo[c,k][1,7]-phenanthroline 61. Compounds 56 and 61 on selenium dehydrogenation yielded dibenzo[b,j][1,7]phenanthroline 57 and dibenzo[c,k][1,7]phenanthroline 62. The formation of 6-amino-1,2,3,4-tetrahydroacridine 58 was also observed as a side product. Compound 58 when treated with hydroxymethylenecyclohexanone gave 59 which on cyclisation with PPA gave back 58 by retro-Michael reaction, in addition to 56.

Similarly cyclodehydration of cis-N,N'-bis-(2-ketocyclohexylidinomethylene)p-phenylenediamine 63 in the presence of PPA lead to the formation of 1,2,3,4,9,10,11,12-octahydrodibenzo[b,j][4,7]phenanthroline 64 and 1,2,3,4,9,10,11,12-octahydro-6,13-diazabenzo[a]-naphthacene 66. Compounds 64 and 66 on selenium dehydrogenation gave dibenzo[b,j][4,7]phenanthroline 65 and 6,13-diazabenzo[a]naphthacene 67 respectively[53,54].

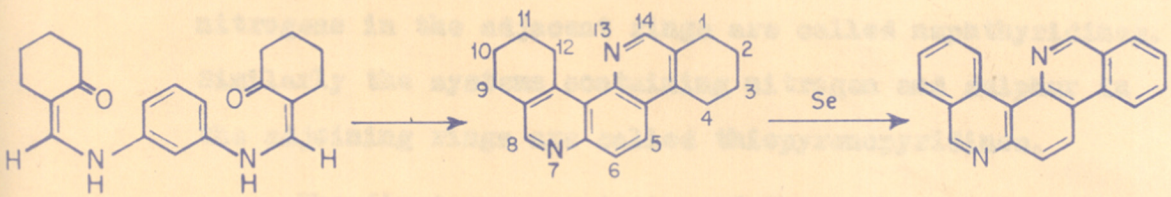
It was reported that although cyclodehydration of cis-2-p-acetamidophenylaminomethylenecyclohexanone 69, prepared by the interaction of cis-2-hydroxymethylene-cyclohexanone 54 and p-aminoacetanilide 68, with PPA



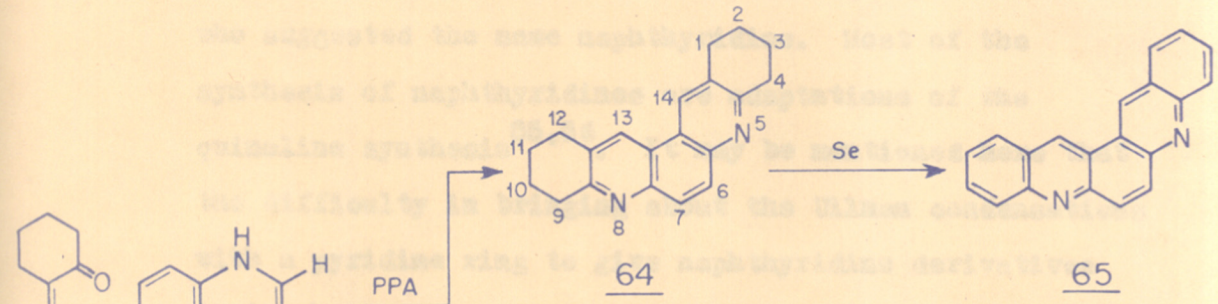
54 55 56 57



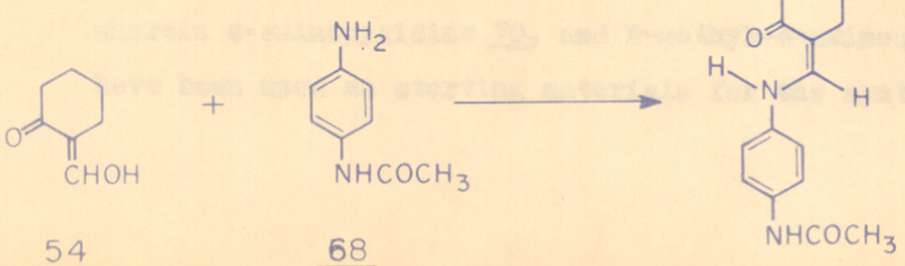
58 59



60 61 62



63 64 65 66 67



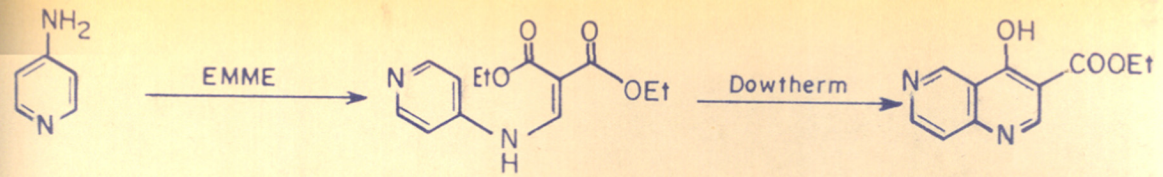
54 68 69

afforded a new pentacyclic compound in addition to 7-amino-1,2,3,4-tetrahydroacridine, as evident by the PMR and mass spectral data, it could not be isolated.

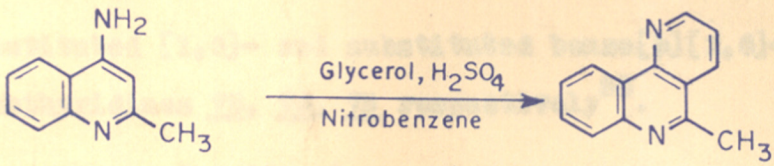
Our present work is aimed at the synthesis of tetracyclic and pentacyclic ring systems containing nitrogen and sulphur. The systems containing two nitrogens in the adjacent rings are called naphthyridines. Similarly the systems containing nitrogen and sulphur in the adjoining rings are called thiopyranopyridines.

The first representative of the naphthyridine system was synthesised about 80 years ago by Reissert who suggested the name naphthyridine. Most of the synthesis of naphthyridines are adaptations of the quinoline synthesis[55,56]. It may be mentioned here that the difficulty in bringing about the Ullman condensations with a pyridine ring to give naphthyridine derivatives is in sharp contrast, the case with which such condensations occur with the benzene ring to yield phenanthridines. It is thus difficult to prepare 1,6-naphthyridine compared to other compounds of the naphthyridine series.

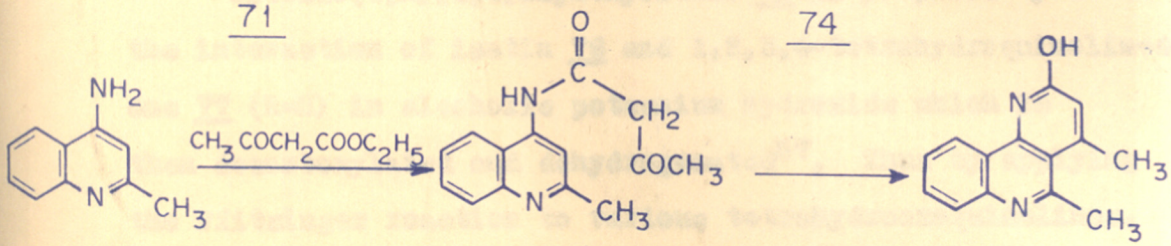
Some of the reactions are described in chart 5 wherein 4-aminopyridine 70, and 2-methyl-4-aminoquinoline 71 have been used as starting materials for the synthesis of



70 73

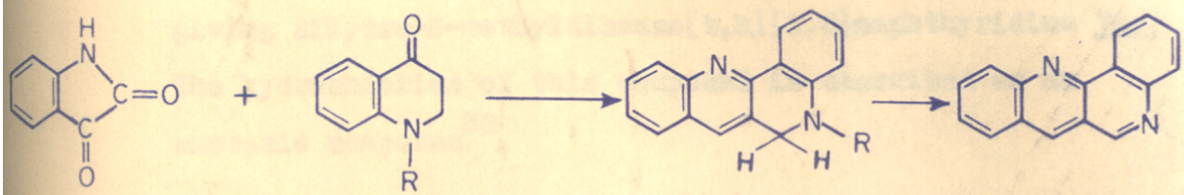


71 74

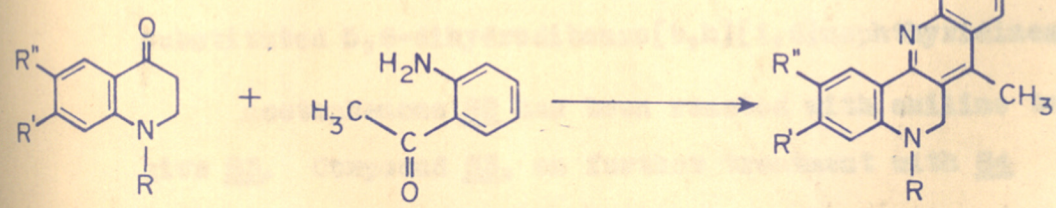


71 75

CHART – 5



76 77 78a 78



79 80 81

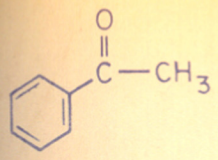
substituted [1,6]- and substituted benzo[b][1,6]-naphthyridines 73, 74, 75 respectively[55].

Dibenzo[b,h][1,6]naphthyridine 78 is prepared by the interaction of isatin 76 and 1,2,3,4-tetrahydroquinolin-4-one 77 (R=H) in alcoholic potassium hydroxide which is then decarboxylated and dehydrogenated[57]. Thus by applying the Pfitzinger reaction to various tetrahydrooxoquinolines, Buu-Hoi and coworkers[57a], prepared a number of substituted dibenzo[b,h][1,6]naphthyridines.

N-methyl-1,2,3,4-tetrahydroquinolin-4-one 77 ($R=CH_3$) reacts with o-aminobenzaldehyde at room temperature giving dihydro-N-methyldibenzo[b,h][1,6]naphthyridine 78a. The hydrochloride of this compound is described as an unstable compound[58].

A number of benzonaphthyridines have been prepared by applying the Friedlander reaction to various tetrahydrooxoquinolines. Thus condensation of o-aminoacetophenone 80 with substituted N-methyl-1,2,3,4-tetrahydroquinolin-4-one 79 resulted in the formation of substituted 5,6-dihydrodibenzo[b,h][1,6]naphthyridines 81[59].

Acetophenone 82 has been reacted with aniline to give 83. Compound 83, on further treatment with 84



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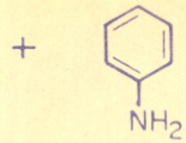

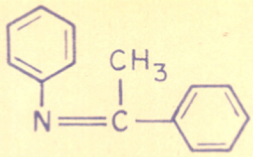

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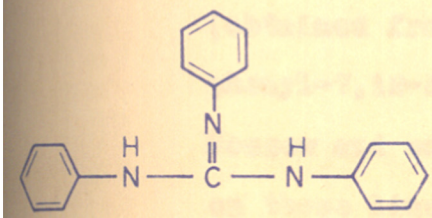

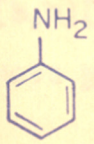

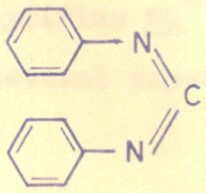

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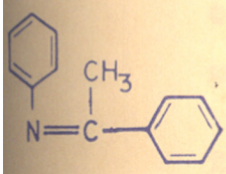

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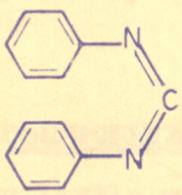

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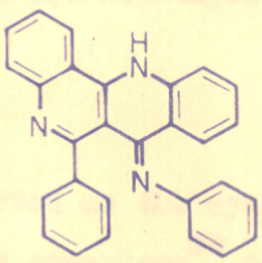

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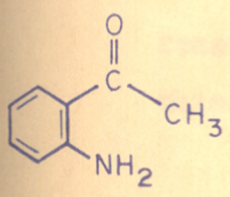

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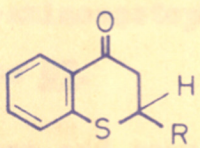

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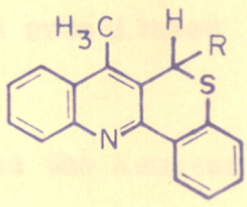
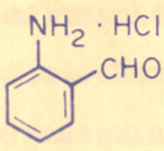


R = H

88



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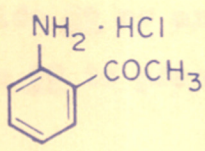

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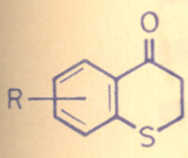

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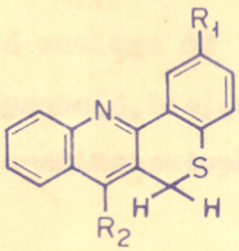
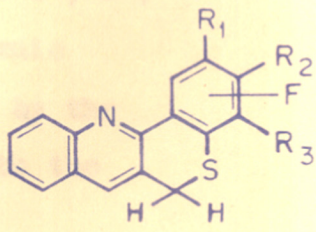


X = O or S

R_1 = H, CH_3 or Cl

R_2 = H, CH_3

91



93

(obtained from triphenylguainidine), gave 7-phenylimino-6-phenyl-7,12-dihydrodibenzo[b,h][1,6]naphthyridine 85[60]. Moszew and coworkers[61,62] have published several papers on these lines.

Little work has been reported on the synthesis of pentacyclic systems containing the 1,6-naphthyridine moiety.

THIOPYRANOQUINOLINES

Very little work has been reported on the synthesis of thiopyranoquinolines. Kempter and coworkers[59] prepared 7-methyl-6H[1]benzothiopyrano[4,3-b]quinolines 88 by the reaction of o-aminoacetophenone 86 with substituted thiochromanones 87.

Jacquignon and coworkers[63,64] used the Kempter modification of the Friedlander reaction starting with o-aminobenzaldehyde hydrochloride 89 or ortho-aminoacetophenone hydrochloride 90 to prepare thiopyranoquinolines 91.

They have also prepared recently the 2-, 3-, and 4-fluorinated analogs of the carcinogenic 6H-[1]benzothiopyrano[4,3-b]quinolines 93 by the condensation of o-aminoacetophenone 86 with the

corresponding thiochromanones 92. They confirmed the structures by PMR studies.

No work has been reported by us so far on the synthesis of naphthyridines and thiopyranoquinolines.

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CHAPTER II

PART A: STUDIES IN CYCLODEHYDRATION REACTIONS USING PERCHLORIC ACID

As will be clear from the latter part of Chapter I, little work has been reported on the synthesis of naphthyridines and thiopyranoquinolines.

The earlier workers prepared the naphthyridine ring systems by applying Friedlander and Pfitzinger reactions[1,2,11] to the various 1,2,3,4-tetrahydroquinolin-4-ones. The thiopyranoquinoline ring systems were prepared by the Kempter modification of the Friedlander reaction[3,4] as discussed in the previous chapter.

The aim of the present work was to extend the studies and scope of the cyclodehydration reactions of arylaminomethylenecycloalkanones to:-

(a) polycyclic systems containing two hetero atoms,

(b) to prepare dicationoid systems, and

(c) to use these compounds for a study of carcinogenesis by such nitrogen and sulphur heterocyclic analogues of polycyclic carcinogenic hydrocarbons.

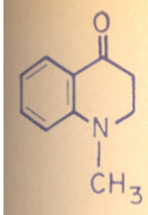
The diheteroatomic polycyclic systems, as will be seen in the earlier chapter, were prepared by starting from aryl diamines[5,6]. An alternative approach would be to start with cycloalkanones containing one hetero-atom and subsequently incorporate another hetero-atom (nitrogen) carried by an arylamine. The condensation products from the above reaction

on subsequent cyclodehydration should lead to diheteroatomic polycyclic ring systems. It is left to be seen whether the above diheteroatomic polycyclics can be converted to the monocationoid or dicationoid systems, which are likely to be coloured compounds.

We have chosen for our study two such cyclic ketones viz., N-methyl-1,2,3,4-tetrahydroquinolin-4-one 1 and thiochroman-4-one 2. These ketones are quite prone to side reactions. It may be worth mentioning some literature data regarding these cyclic ketones.

N-Methyl-1,2,3,4-tetrahydroquinolin-4-one 1 reacts with p-(dimethylamino) benzaldehyde and p-(nitroso)-dimethylaniline to give bright red crystals of 3-(p-dimethylamino) benzylidine derivative 3 and analogous 3-(p-dimethylaminophenylimino) derivative 4. It was stated that under milder conditions the imino derivative 4 isomerised to 3-(p-dimethylaminoanilino)-1-N-methyl-1,4-dihydroquinolin-4-one 5. The substituted quinolones thus can be readily dehydrogenated to give substituted 1:4-dihydro derivatives 6.

The Mannich base of N-methyl-1,2,3,4-tetrahydroquinoin-4-one 7 on boiling gave a pale yellow 1:4-dihydro-3-methyl-N-methylquinolin-4-one 8. It was presumed that the



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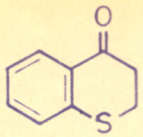

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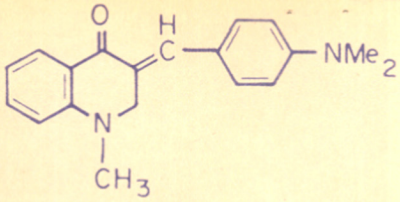

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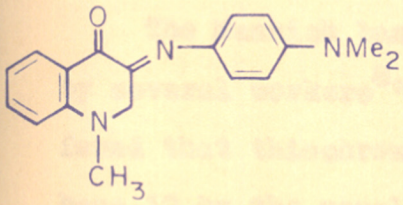

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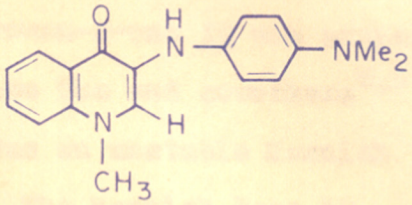

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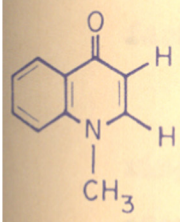

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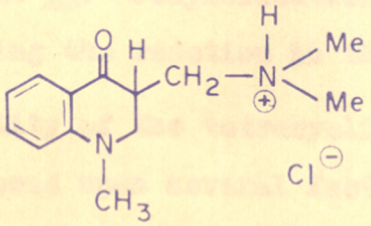

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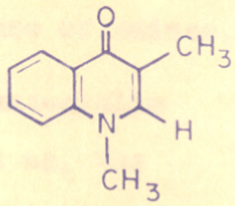

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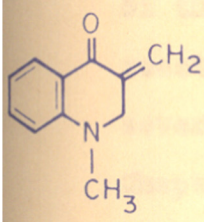

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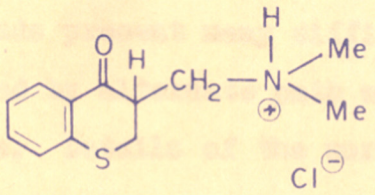

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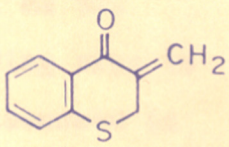

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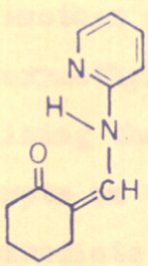

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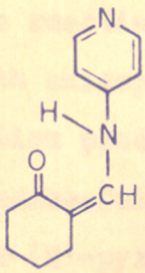


14

the intermediate product is the 3-methylene derivative 9.

The Mannich base of thiochroman-4-one 10 was prepared by several workers[8,9,10]. Sae-Lee Chu and coworkers[8,9] found that thiochroman-4-one gives an unstable Mannich base 10 by the usual procedure. The Mannich base 10 gives rise to a dimer via the intermediate 3-methylene-thiochroman-4-one 11. Polymerisation of 11 was also facilitated during the reaction in the presence of amines.

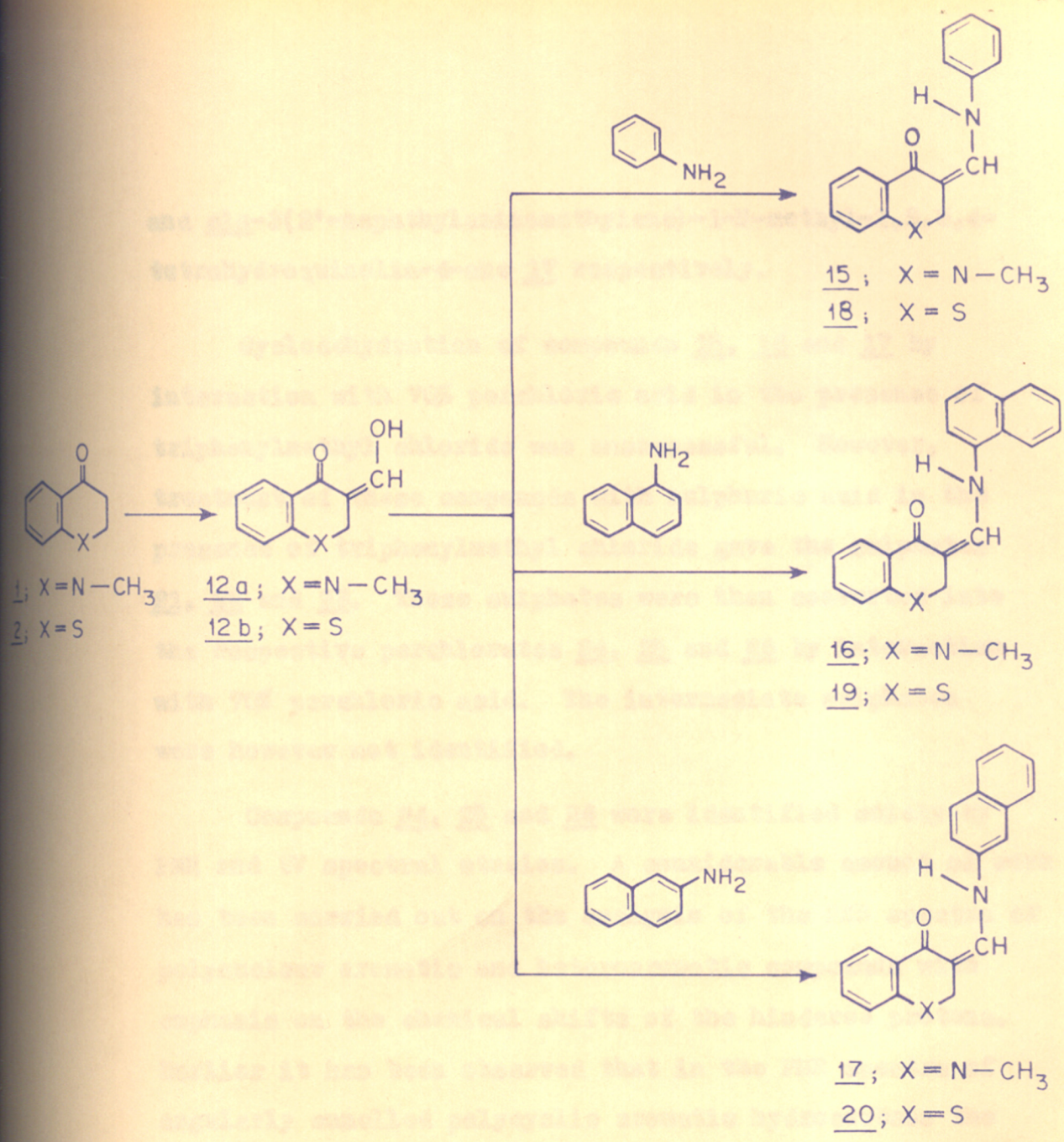
The stability of the tetracyclic and pentacyclic ring systems depend upon several factors such as, the stereochemistry of the molecule, the reactivity of the heteroatoms present in the molecule and formation and stability of the intermediate products. The synthesis of these compounds present many difficulties, as the reactions proceed by alternate path ways, giving rise to several products. Details of the work are discussed in Chapter IV.

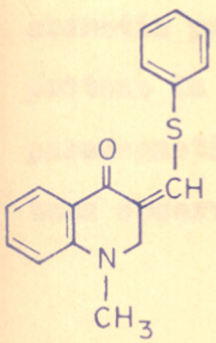
The synthesis of the diheteroatomic polycyclics by yet another route consists in the reaction of hydroxymethylenecyclohexanone with aminopyridines and cyclising the resulting condensation products. However attempts on these lines were unsuccessful although the intermediate products viz., cis-2-(2'-pyridylaminomethylene)-

cyclohexanone 13 and cis-2-(4'-pyridylaminomethylene)-cyclohexanone 14 were readily obtained and characterized from a study of their spectral data.

Cyclodehydration of cis-2-phenylmercaptomethylene-1-tetralone using 70% perchloric acid resulted in the formation of the rearranged 5,6-dihydro-12-thiabenz[a]anthracenium perchlorate instead of 5,6-dihydro-8-thiabenz[a]phenanthrenium perchlorate[12a]. This rearrangement was similar to the one which we had reported earlier in the cyclodehydration of cis-2-arylaminomethylenecycloalkanones[12a-e]. The present work is an extension of these studies in which cyclodehydration of cis-3-arylaminomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 15-17 and cis-3-arylaminomethylene thiochroman-4-ones 18-20 was studied. The experimental details and analysis of the final products are described in the following pages.

3-Hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 12a was prepared by the interaction of ethyl formate with N-methyl-1,2,3,4-tetrahydroquinolin-4-one 1 in the presence of sodium methoxide. Condensation of 12a with aniline, α-naphthylamine and β-naphthylamine led to the formation of cis-3-anilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 15, cis-3-(1'-naphthylamino methylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 16


NH2
15 ; X = N − CH3
18 ; X = S
NH2
16 ; X = N − CH3
19 ; X = S
NH2
17 ; X = N − CH3
20 ; X = S
1 ; X = N − CH3
2 ; X = S
12 a ; X = N − CH3
12 b ; X = S



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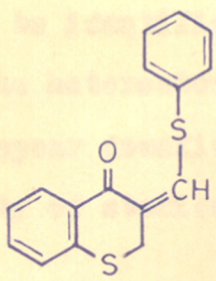

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and cis-3(2'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 17 respectively.

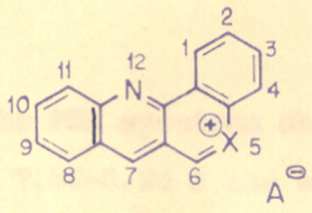
Cyclodehydration of compounds 15, 16 and 17 by interaction with 70% perchloric acid in the presence of triphenylmethyl chloride was unsuccessful. However, treatment of these compounds with sulphuric acid in the presence of triphenylmethyl chloride gave the sulphates 21, 22 and 23. These sulphates were then converted into the respective perchlorates 24, 25 and 26 by interaction with 70% perchloric acid. The intermediate sulphates were however not identified.

Compounds 24, 25 and 26 were identified solely by PMR and UV spectral studies. A considerable amount of work has been carried out on the analysis of the PMR spectra of polynuclear aromatic and heteroaromatic compounds with emphasis on the chemical shifts of the hindered protons. Earlier it has been observed that in the PMR spectra of angularly annelled polycyclic aromatic hydrocarbons the hindered protons appear at a lower field than the other aromatic protons and thus can be identified. Also the protons in the proximity of the heteroatom have a paramagnetic shift and also appear downfield. It has also been observed that the property of sterically hindered

protons in exhibiting downfield shift is also dependent on the planarity of the molecule. The steric interaction between protons in certain complex polycyclic hydrocarbons disturbs the planarity of the molecule and consequently the protons appear to be shielded[13].

These principles were made use of in determining the structures of our compounds. Gogte et al[6] have used these general observations in assigning the structures of various tetracyclic and pentacyclic heterocyclic ring systems. This method proved quite handy in establishing the structure of the products wherein as many as eight different possible structures were assignable to the product.

Compound 15 on cyclodehydration could lead to two possible derivatives, the angular 5-N-methyl-dibenzo[c,f][2,7]naphthyridinium perchlorate 30 or the linear 5-N-methyl-dibenzo[b,h][1,6]naphthyridinium perchlorate 24. In the PMR spectrum, the angular structure 30 should show two multiplets for C-1 and C-12 and two singlets of one proton intensity each for C-6 and C-7 in the low field region. On the other hand the linear compound 5-N-methyldibenzo[b,h][1,6]naphthyridinium perchlorate 24 should show a multiplet of one proton intensity for C-1 and a singlet of one proton intensity



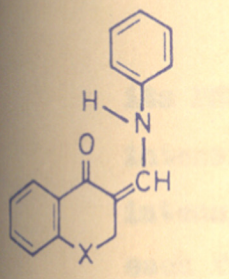
C-1 Multiplet
C-6 Singlet

21; X = N−CH$_3$
A = HSO$_4$

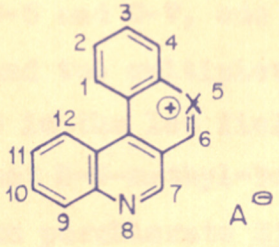
24; X = N−CH$_3$
A = ClO$_4$

27; X = S
A = ClO$_4$

5-N-methyl-dibenzo [b,h] [1,6] naphthyridinium 24
[1] Benzothiopyrano [4,3-b] quinolinium 27



15; X = N−CH$_3$
18; X = S



C-6 and C-7 Singlets
C-1 and C-12 Multiplets

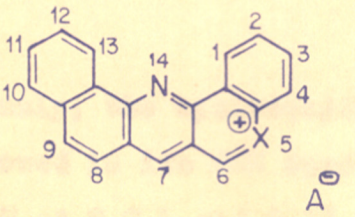
30; X = N−CH$_3$
A = ClO$_4$

33; X = S
A = ClO$_4$

5-N-methyl-dibenzo [c,f] [2,7] naphthyridinium 30
[1] Benzothiopyrano [3,4-c] quinolinium 33

for C-6. In fact the PMR spectrum showed a multiplet for C-1 spread over 7.86-8.24 δ and a singlet for C-6 at 8.00 δ both together integrating for 2 protons. Thus the possibility of the formation of the angular product was ruled out and the linear structure 5-N-methyl-dibenzo-[b,h][1,6]-naphthyridinium perchlorate 24 was assigned.

The cyclodehydration product of compound 16, in its PMR spectrum should show two singlets of one proton intensity each for C-6 and C-7, one doublet of one proton intensity for C-14 and two multiplets of one proton intensity each for C-1 and C-9 in the low field region if it were to be the angular product 5-N-methyl-benzo[f]-naphthol[1,2-c]-[2,7]-naphthyridinium perchlorate 31. In case of linear structure 5-N-methyl-benzo[h]naphtho[1,2-b][1,6]naphthyridinium perchlorate, 25 there should be two multiplets of one proton intensity each for C-1 and C-13 and two singlets of one proton intensity each for C-6 and C-7. The product has shown one singlet for C-6 at 8.26 δ and two contiguous multiplets for C-1 and C-13 spread over 8.4 - 9.0 δ, the singlet for C-7 proton being masked by the other aromatic protons. The low field multiplet expected for C-9 of the angular product 31 is absent. Hence the linear structure was assigned.



22; X = N−CH$_3$, A = HSO$_4$

25; X = N−CH$_3$, A = ClO$_4$

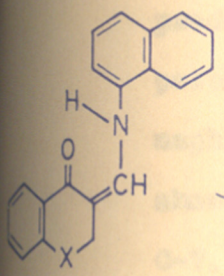
28; X = S, A = ClO$_4$

C-6 and C-7 Singlets

C-1 and C-13 Multipletes

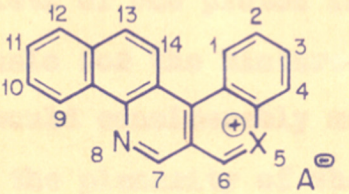
5-N-methyl— benzo[h]naphtho[1,2-b][1,6]naphthyridinium 25

[1] Benzothiopyrano[4,3-b] benzo [h] quinolinium 28



16; X = N − CH$_3$

19; X = S



31; X = N−CH$_3$, A = ClO$_4$

34; X = S, A = ClO$_4$

C-1 and C-9 Multipletes

C-14 Doublet

C-6 and C-7 Singlets

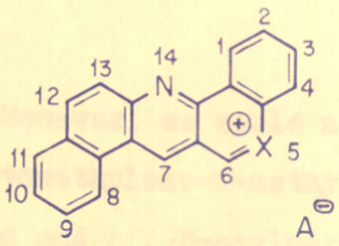
5-N-methyl- benzo[f]naphtho[1,2-c][2,7]naphthyridinium 31

[1] Benzothiopyrano[3,4-c] benzo [h]quinolinium 34

Analogously, the cyclodehydration product of compound 17 showed in its PMR spectrum two close singlets for C-6 and C-7 at 8.2 δ and 8.13 δ respectively and a multiplet of two proton intensity for C-1 and C-8 spread over 8.66 - 9.00 δ.

This product was assumed to be the linear rearranged product 5-N-methyl-benzo[h]naphtho[2,1-b][1,6]naphthyridinium perchlorate 26 for the angular product 5-N-methyl-benzo[f]-naphtho[2,1-c][2,7]naphthyridinium perchlorate 32 should show two singlets of one proton intensity each for C-6 and C-7. The signals for the hindered protons in this case at C-1 and C-14 would considerably move upfield because of the distortion in the planarity of the molecule. But such high field proton signals are not observed.

3-Hydroxymethylenethiochroman-4-one 12b was prepared by the interaction of thiochroman-4-one 2 with ethyl formate in the presence of sodium methoxide. The resulting compound 12b on condensation with aniline, α-naphthylamine and β-naphthylamine gave the cis-3-anilinomethylene-thiochroman-4-one 18, cis-3-(1'-naphthylaminomethylene)-thiochroman-4-one 19 and cis-3-(2'-naphthylaminomethylene)-thiochroman-4-one 20 respectively. Compounds 18, 19 and 20 were identified by their elemental analysis and their



23; X = N−CH$_3$
A = HSO_4

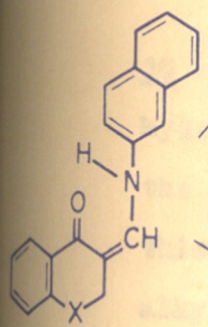
26; X = N−CH$_3$
A = ClO_4

29; X = S
A = ClO_4

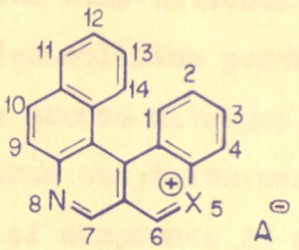
C-1 and C-8 Multiplets
C-6 and C-7 Singlets

5-N-methyl-benzo [h] naphtho [2,1-b] [1,6] naphthyridinium 26

[1] Benzothiopyrano [4,3-b] benzo [f] quinolinium 29



17; X = N−CH$_3$
20; X = S



32; X = N−CH$_3$
A = ClO_4

35; X = S
A = ClO_4

C-1 and C-14 Multiplets (upfield)
C-6 and C-7 Singlets

5-N-methyl-benzo [f] naphtho [2,1-c] [2,7] naphthyridinium 32

[1] Benzothiopyrano [3,4-c] benzo [f] quinolinium 35

spectral data. However, we could not isolate 3-arylmercaptomethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 36 and 3-arylmercaptomethylenethiochroman-4-one 37 by the reaction of 12a and 12b with thiophenol respectively.

Interaction of cis-3-anilinomethylenethiochroman-4-one 18 with 70% perchloric acid in the presence of an external hydride abstractor such as triphenylmethyl chloride afforded the orange coloured mono-cationoid compound [1]benzothiopyrano[4,3-b]quinolinium perchlorate 27. Further alkylation of the second nitrogen atom to form a dicationoid compound was tried unsuccessfully. Similarly, cyclodehydration of compounds 19 and 20 furnished [1]benzothiopyrano[4,3-b]benzo[h]quinolinium perchlorate 28 and [1]benzothiopyrano[4,3-b]benzo[f]quinolinium perchlorate 29, rearrangement to linear structures having occurred during cyclodehydration. The same arguments as in the nitrogen analogs, can be put forward for the elucidation of the structures of benzothiopyranoquinolinium perchlorates.

The PMR spectrum of the cyclodehydration product of compound 18 should show two multiplets of one proton intensity each for C-1 and C-12 and two singlets of one

proton intensity each for C-6 and C-7 in the low field region if it were to be the angular product viz., [1]benzothiopyrano[3,4-c]quinolinium perchlorate 33. The PMR spectrum has shown a multiplet of one proton intensity for C-1 spread over 8.33 - 8.66 δ and a singlet of one proton intensity at 9.13 δ for C-6 in the lower field, a pattern more consistant with the linear product [1]benzothiopyrano[4,3-b]quinolinium perchlorate 27.

Similarly the cyclodehydration product of compound 19 should show two singlets of one proton intensity each for C-6 and C-7, a doublet of one proton intensity for C-14 and two multiples of one proton intensity each for C-1 and C-9 in the low field region in its PMR spectrum in case if the normal compound [1]benzothiopyrano[3,4-c]benzo[h]-quinolinium perchlorate 34 was formed.

In the event of the formation of 28, on the other hand, only two singlets for protons C-6 and C-7 should have appeared in the low field region along with the two protons at C-1 and C-13 as multiplets. The PMR spectrum of 28 in DMSO showed two singlets for C-6 and C-7 at 10.33 δ and 9.16 δ and the multiplets for C-1 and C-13 near the aromatic signals. The low field multiplet for C-9 expected in the alternate angular structure 34 is absent, thus confirming the formation of the linear

structure [1]benzothiopyrano[4,3-b]benzo[h]quinolinium perchlorate 28.

In the same manner the cyclodehydration product of compound 20 should show two multiplets of one proton intensity each for C-1 and C-14 in the upfield region because of the distortion in the planarity of the molecule, and two singlets of one proton intensity each for C-6 and C-7 if it were to be the normal angular product [1]benzothiopyrano[3,4-c]benzo[f]quinolinium perchlorate 35. If the rearrangement has occured then the compound should show two singlets of one proton intensity each for C-6 and C-7 and one multiplet of two proton intensity for C-1 and C-8 protons.

The compound has in fact shown two singlets of one proton intensity for C-6 and C-7 at 9.6 δ and 9.16 δ and one multiplet of two proton intensity for C-1 and C-8 spread over 8.03 - 8.33 δ, thus confirming the linear structure [1]benzothiopyrano[4,3-b]benzo[f]quinolinium perchlorate 29.

In all the above cyclodehydration reactions rearrangement has occurred and the linear products have been formed.

It was also found that the PMR spectra in the diaza systems had more distinct features and thus the choice between the alternative linear and angular structures was easier than in case of sulphur. It seems likely that the lone pair of oxygen in DMSO, the solvent used for PMR spectrum gets accomodated in the d-shell of the sulphur atom in the molecule. Presumably sulphur assumes a neutral covalent character. The chemical shift of $-\overset{+}{S}=CH-$ moves up field in DMSO solvent. This reasoning gets additional support by the fact that in diaza systems, where the distinctive features in the PMR spectra are not lost because of the difficulty of nitrogen to expand its valance shell to accomodate the lone pair of oxygen in DMSO.

Analysis of the UV spectra of the naphthyridinium and thiopyranoquinolinium perchlorates 24 - 26 and 27 - 29

UV spectra have been extensively used for the assignments of structures of tetracyclic and pentacyclic ring systems with or without the heteroatoms[14-20]. While interpreting the results present, the following points have to be taken into consideration:-

(a) The aza substitution in a polycyclic hydrocarbon system results in a bathochromic shift in the UV absorption maxima of group II and III bands.

(b) There is considerable loss of fine structure in replacing a methine group by an annular nitrogen atom and more so in diaza systems where the nitrogen atoms are placed in the adjoining rings.

(c) Finally the absorption maxima of the salts are much broader compared to their parent structures, which give well defined peaks.

We, in our work, have studied the ultraviolet and visible spectra of these compounds in acetic acid containing 1% perchloric acid, and also in dimethyl sulphoxide, as the perchlorates are soluble in these solvents only. In the absence of any available information on the UV and visible spectra of tetracyclic and pentacyclic naphthyridinium and thiopyranoquinolinium salts only vague conclusions could be made from their patterns compared with those of similar compounds.

Compound 27 showed broad absorption maxima around 330 mμ and the pattern is similar to the tetracyclic diheteroatomic ring systems containing nitrogen which showed two broad peaks centred around 300 and 410 mμ as mentioned in the literature[18]. In case of the nitrogen analog 24, a bathochromic shift has occurred.

Pentacyclic ring systems such as dibenz[a,h]acridinium ion and dibenz[c,h]acridinium ion have two broad peaks around 310 mμ and 420 mμ as salient features in their ultraviolet absorption spectra as mentioned in the literature[14,15]. Ultraviolet spectra of compounds 28 and 29 which are similar to the above compounds have also showed absorption maxima peaks around 320 - 350 mμ and a broad hump around 390 - 400 mμ. In case of the nitrogen containing compounds, 25 and 26 a bathochromic shift has occurred.

Far reaching conclusions could not be made as regards to the UV and visible spectra of these compounds. The results are tabulated in Table No.4.

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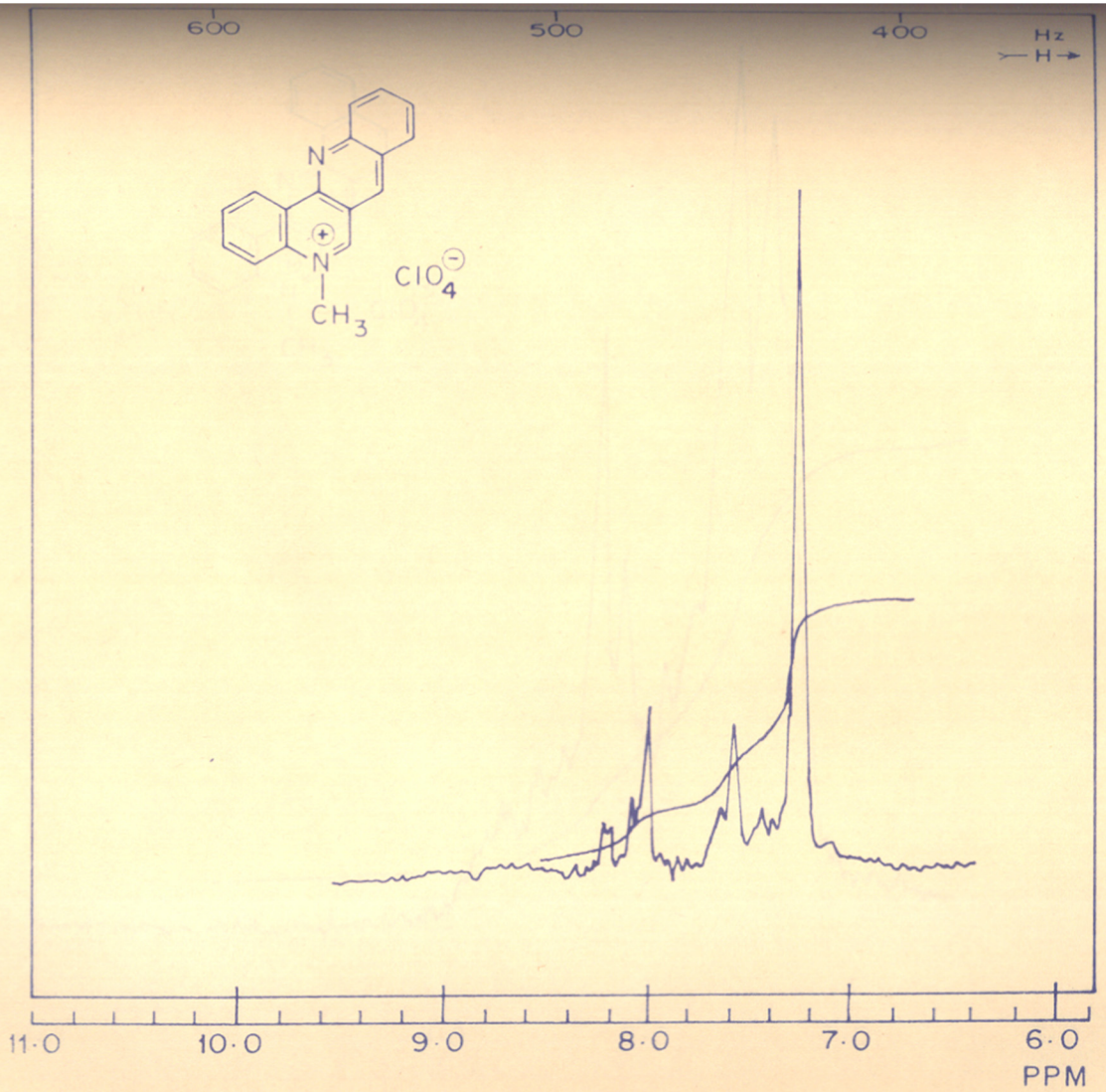
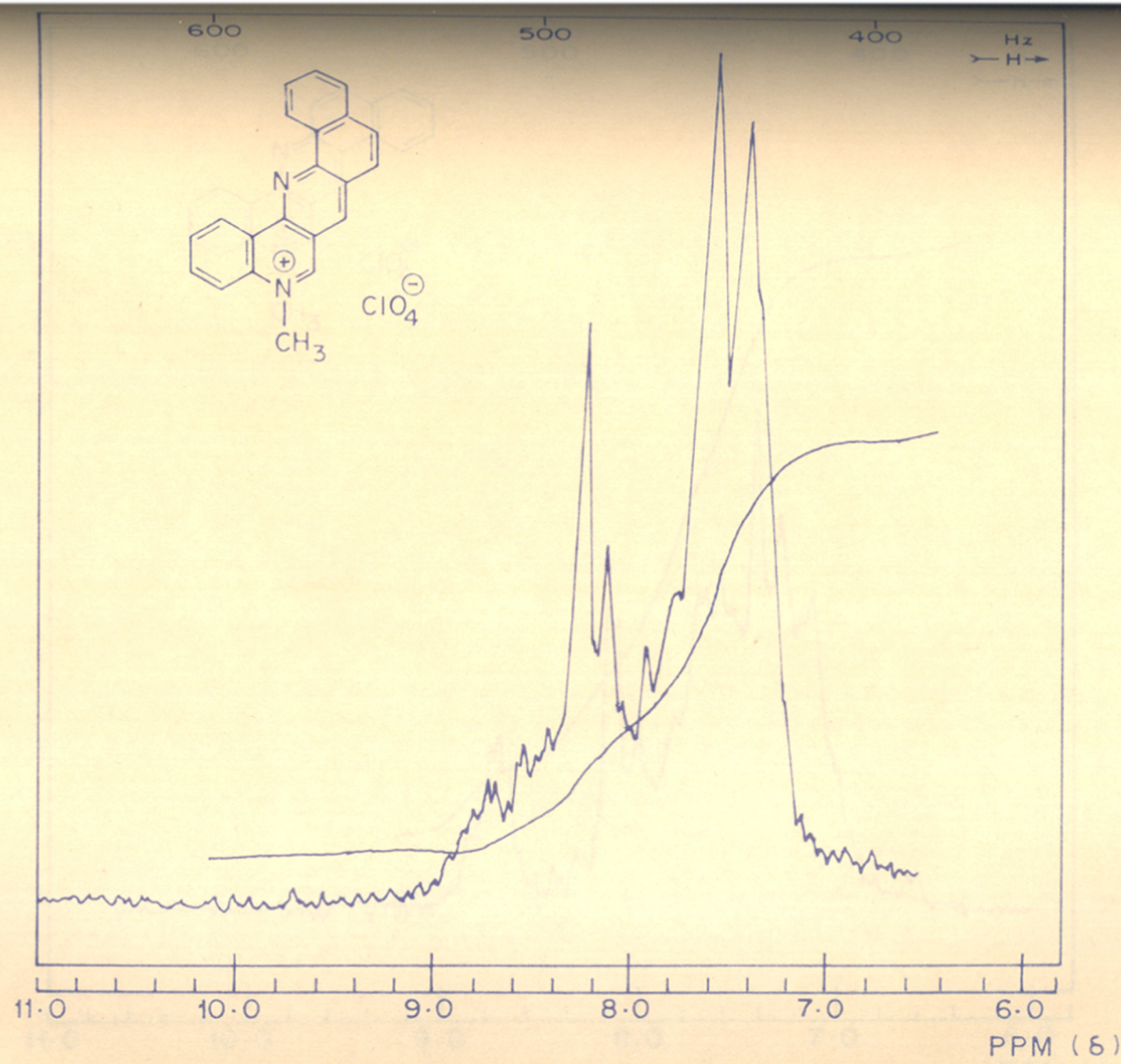
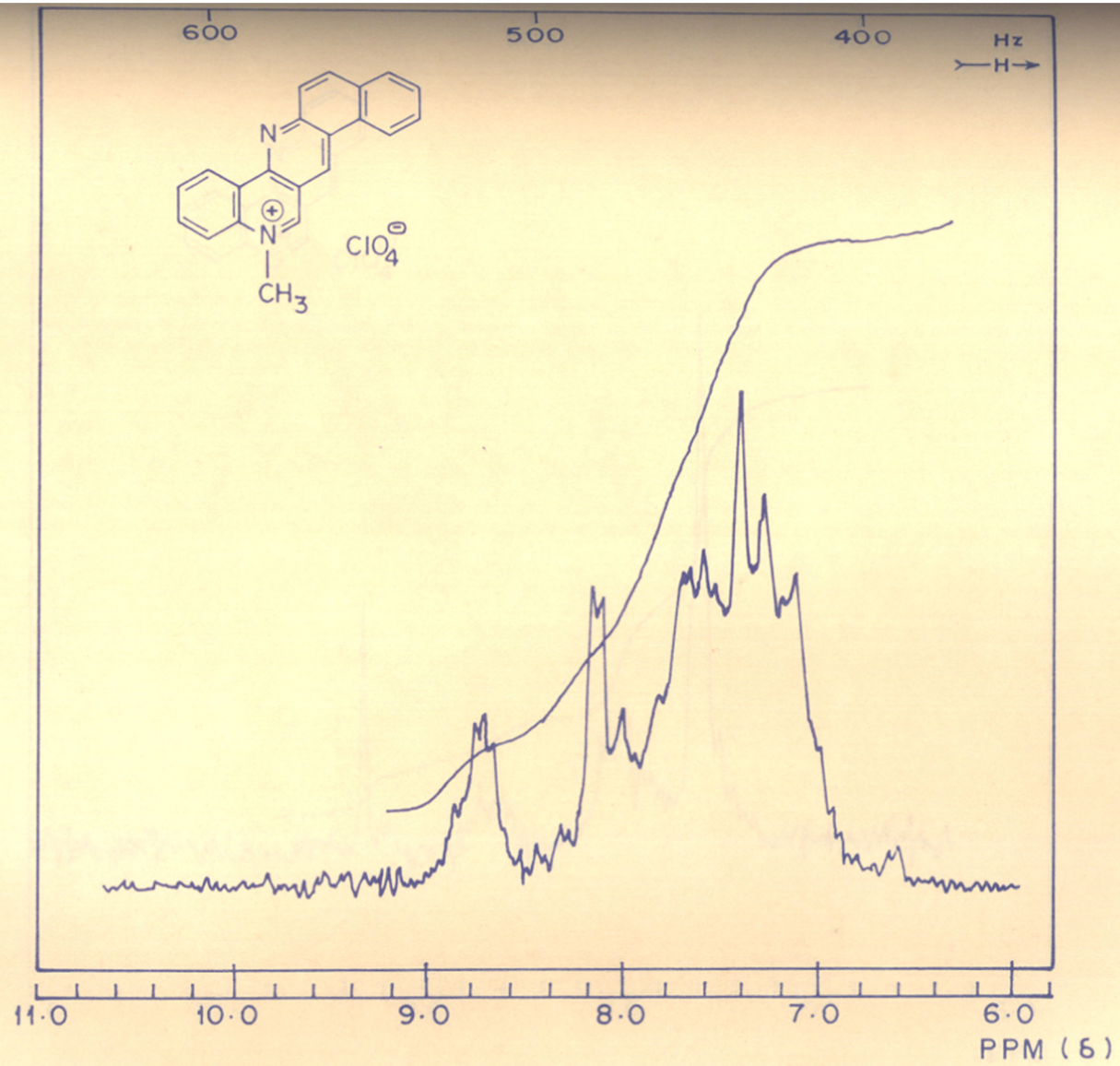


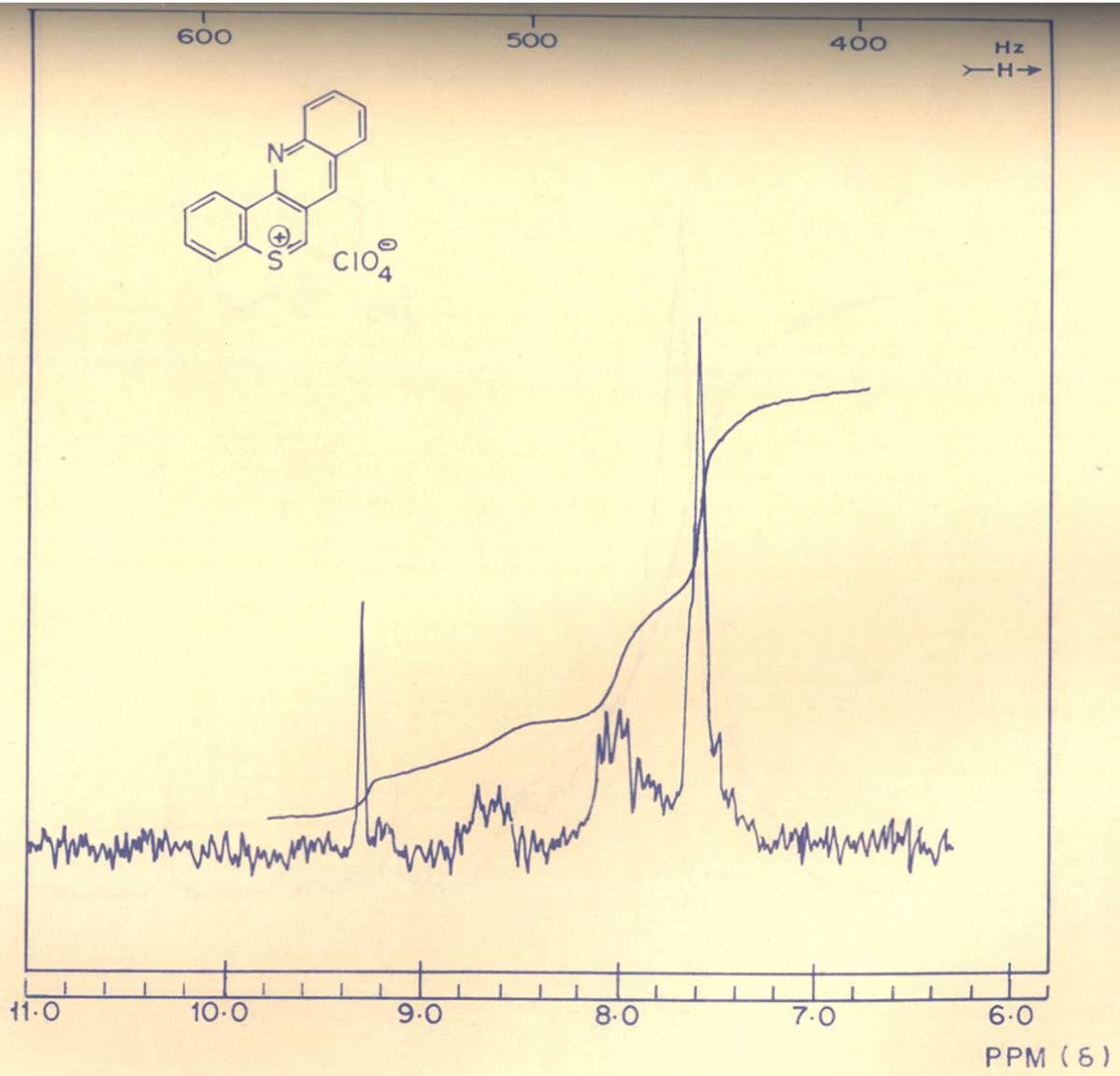
PMR SPECTRUM OF 24 IN DMSO



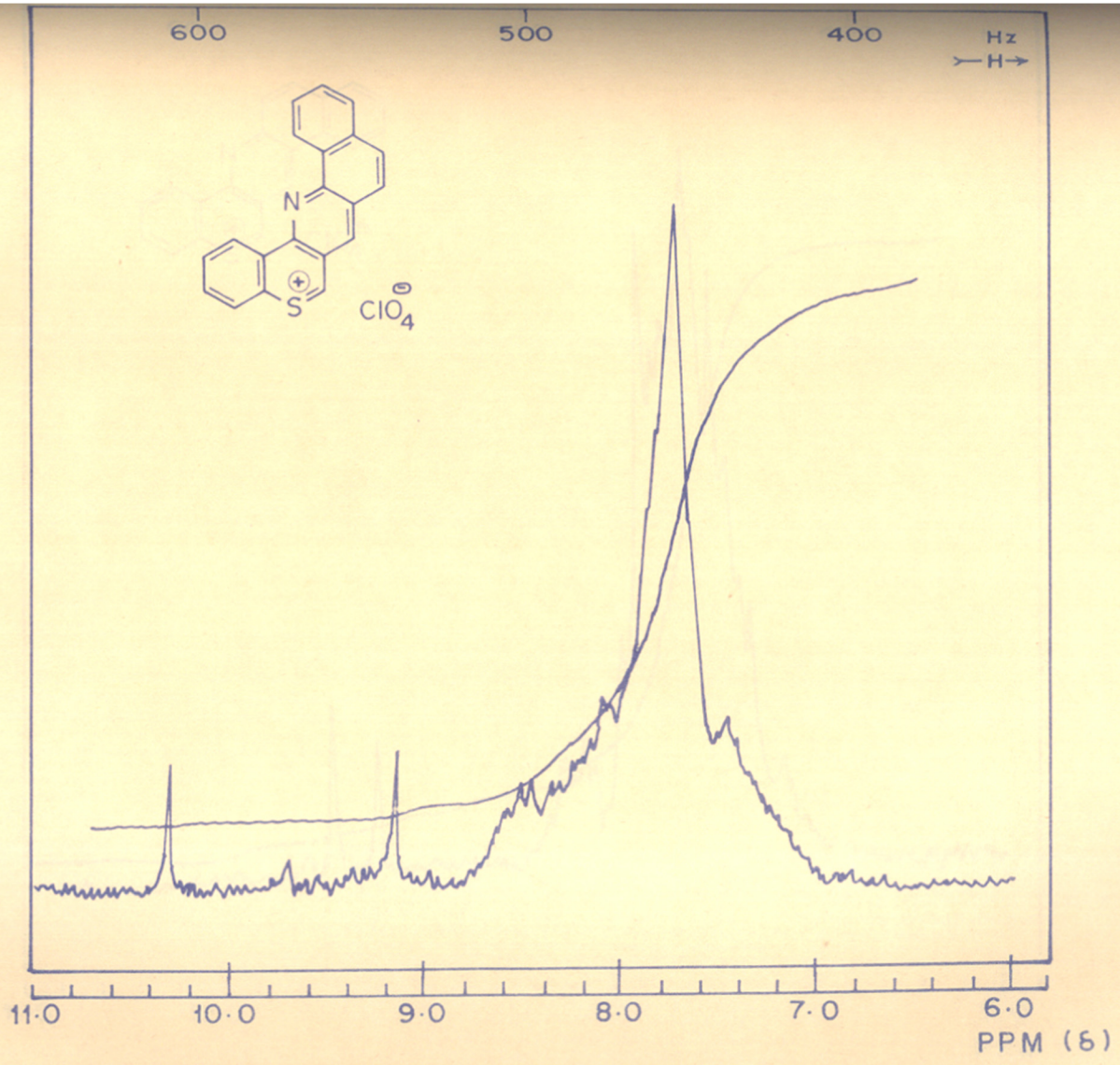
PMR SPECTRUM OF 25 IN DMSO



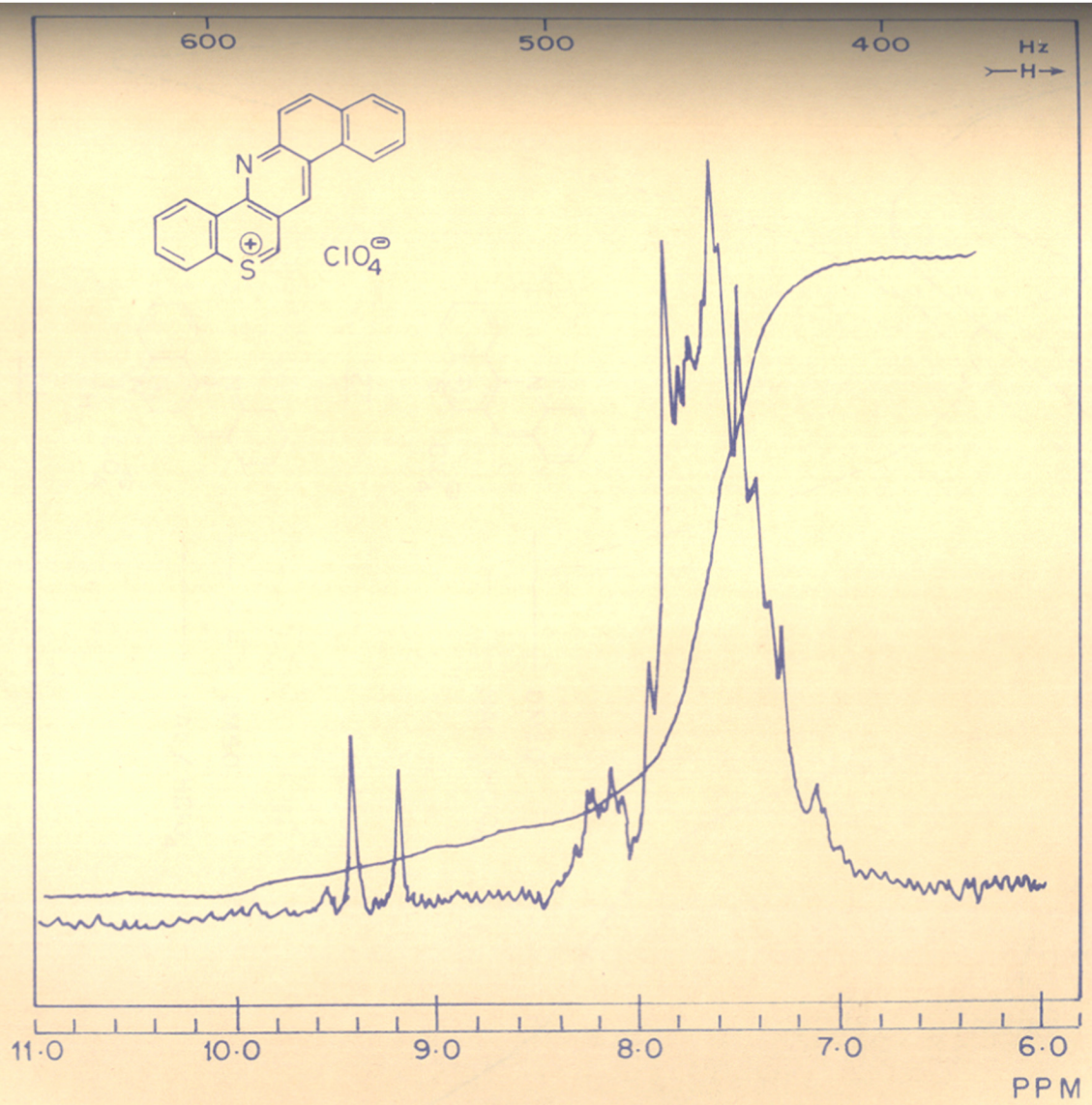
PMR SPECTRUM OF 26 IN DMSO



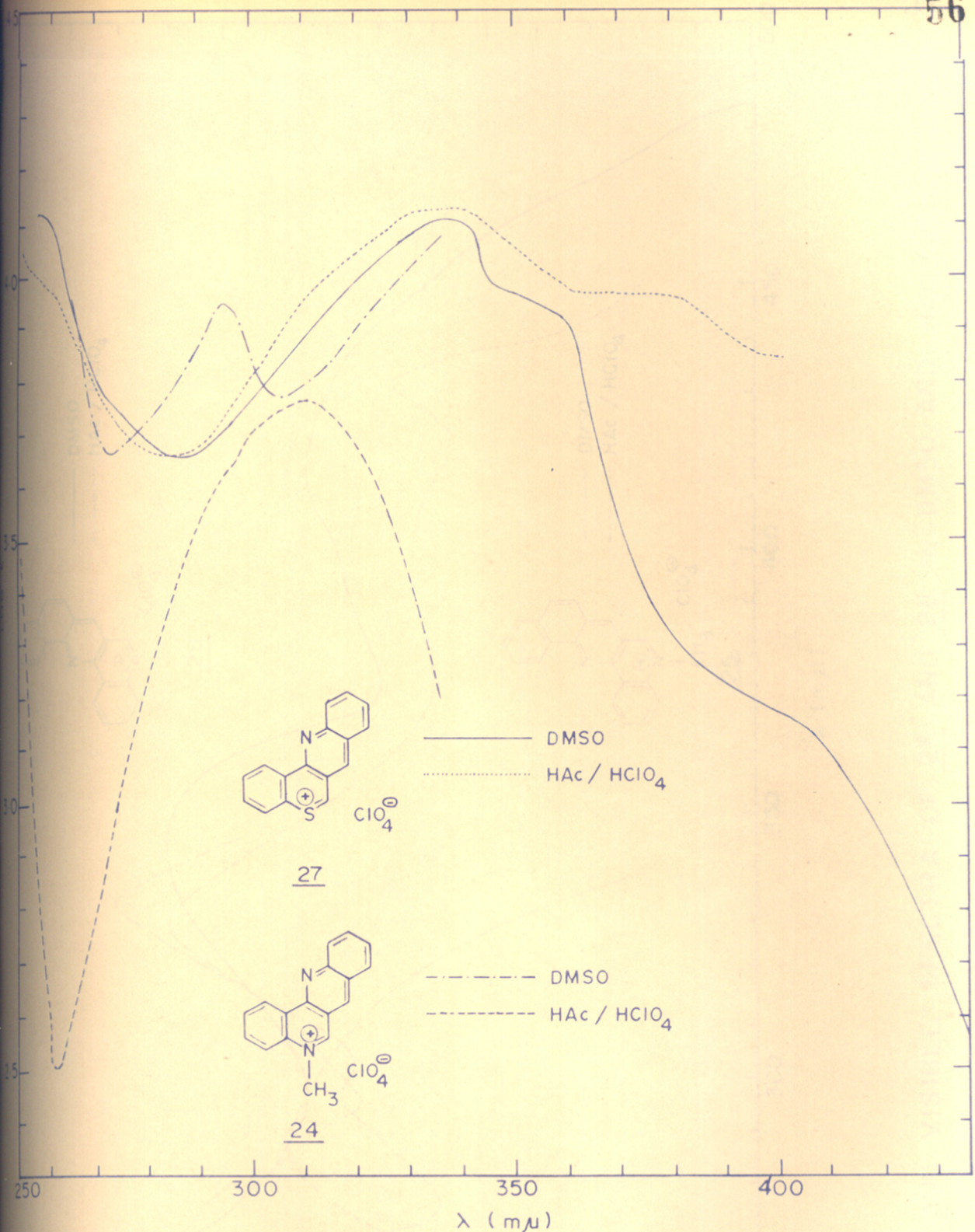
PMR SPECTRUM OF 27 IN DMSO



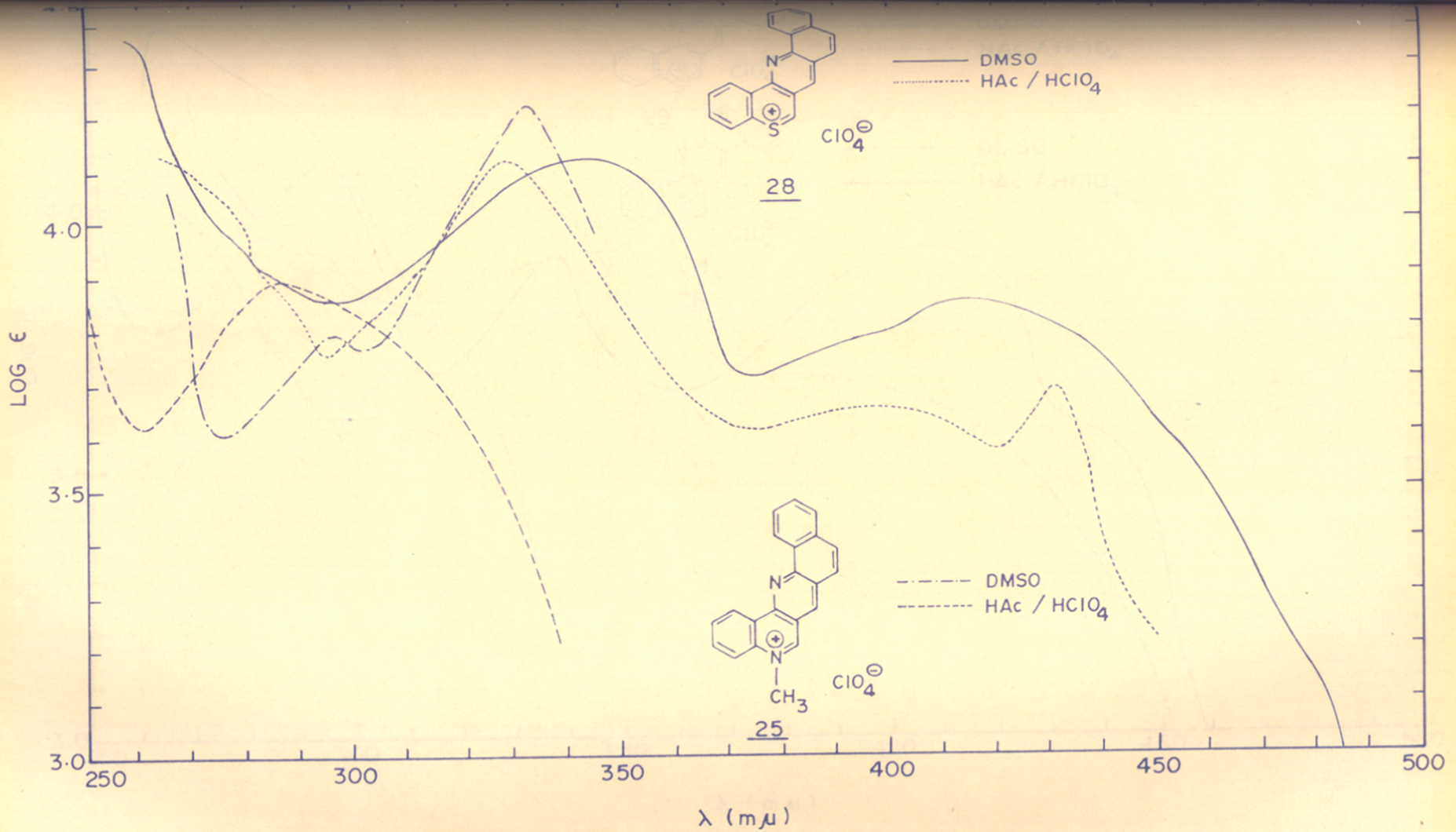
PMR SPECTRUM OF 28 IN DMSO



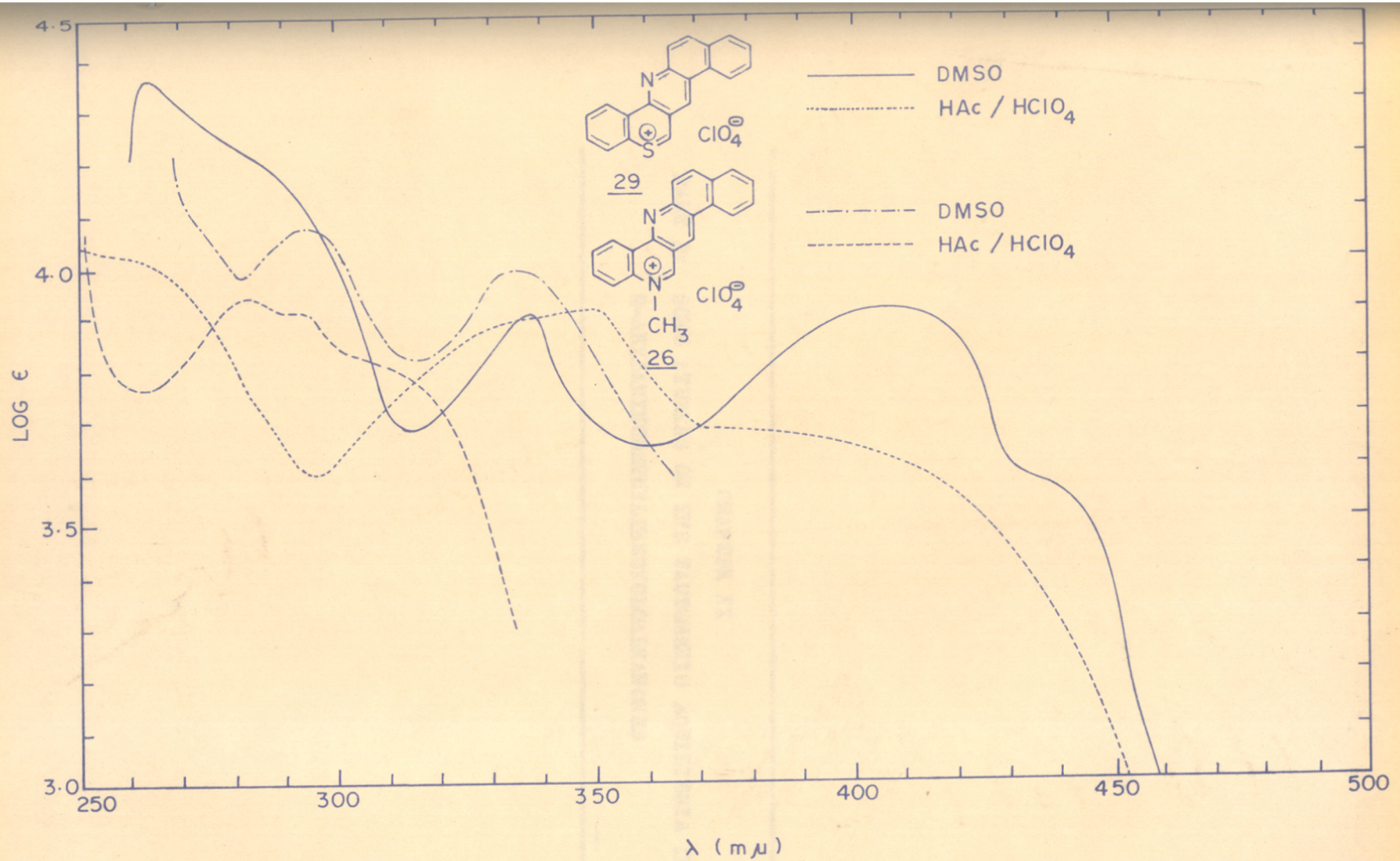
PMR SPECTRUM OF 29 IN DMSO



AND VISIBLE SPECTRA OF 24 AND 27 IN DMSO AND HAc / $HClO_4$



UV AND VISIBLE SPECTRA OF 25 AND 28 IN DMSO AND HAC / $HClO_4$



UV AND VISIBLE SPECTRA OF 26 AND 29 IN DMSO AND HAC/$HClO_4$

CHAPTER II

PART B: SOME STUDIES ON THE TAUTOMERIC EQUILIBRIA IN 2-ARYLAMINOMETHYLENECYCLOALKANONES

Some studies on the tautomeric equilibria in 2-arylaminomethylenecycloalkanones

When two or more tautomeric structures differ in the position of the hydrogen atom or the distribution of valance bonds, the phenomenon is described as prototropy[21]. The acidic proton involved in hydrogen bonding, readily shifts in the conjugated molecule resulting in the reversible equilibrium isomerisation[22]. Tautomeric equilibria have been studied by NMR[23], IR[24] and UV[25] spectroscopy. The detection of tautomer becomes difficult when its concentration in the mixture is less than 5%. With regards to tautomeric equilibria, we have studied the IR and PMR spectra of the cis-2-arylaminomethylene-cyclohexanones[29] and 3-(α-arylaminoethylidino) tetrahydro-furan-2-ones[32]. We have now studied the IR and PMR spectra of cis-3-(arylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 44a-c and cis-3-arylamino-methylenethiochroman-4-ones 43a-c.

Carbonyl compounds exist exclusively in the ketoform unless enol form is stabilised due to hydrogen bonding.

The strength of hydrogen bonding can be studied by the vibrational stretching frequencies of the C=O and OH groups in the infrared and the chemical shifts of the enol proton in the PMR spectra.

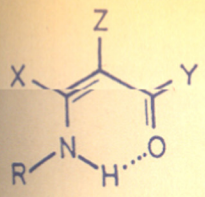
Hydroxymethylene keto-aldo-enol equilibrium has been extensively studied[26]. The nature of the Schiff's bases have been investigated in recent years. The possible tautomeric forms of Schiff base are shown in the chart 1. The keto-enamine (A) enolimine (B) and keto-imine (C) are obtainable by simple prototropy. Interconversion from cis-ketoenamine (A) to trans-ketoenamine (D) is possible through bond rotation. Solvent, concentration, temperature and stereochemical factors affect the tautomeric equilibria. The concentration of the trans isomer increases when bulky groups produce steric interaction.

The role of solvents such as dimethylsulphoxide was not discussed in detail till now, as far as 2-arylaminomethylenecycloalkanones are concerned. Solvent effects on chemical shifts have now been studied in detail[27]. Although DMSO offers excellent solvent properties, it has the disadvantage of entering into hydrogen bonding[28] or dipole-dipole association in the solution.

Berde[29] condensed various arylamines with 2-hydroxymethylenecyclohexanone to give cis-2-arylamino-methylenecyclohexanones. The exclusive formation of the cis isomer has been explained through addition elimination mechanism.

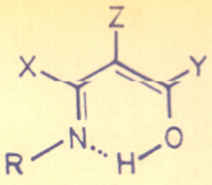
Considering the basic structures as indicated 38, 39, 40 and 41 the ketone 38 did not show many of the ketonic properties. It was proposed by Allison et al[30] that the ionic aromatic form 39 makes the major contribution to the resonance structure. The bright yellow colour of the N-methyl-1,2,3,4-tetrahydroquinolin-4-one 40 is probably due to a considerable contribution by the form 41 in which the charge separation entails the o-quinonoid structure[30]. The condensation products prepared from the above compound also showed special characteristics. It was reported[31] that quinolin-4-ones showed a characteristic absorption band between 1618-1647 (C=O). Also solvent shift studies indicated that a band Ca. 1590 is also partly carbonyl in character.

Compounds 43a, 43b and 43c exist in chloroform solutions as cis-ketoenamine tautomer (A) as revealed by the IR and PMR spectra shown in Table 5. These compounds showed typical bands at 1635 cm^{-1} (C=O) and 3050 cm^{-1}



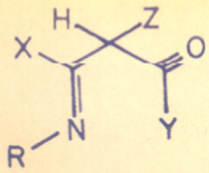
(A)

cis - ketoenamine



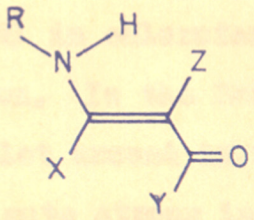
(B)

cis - enolimine



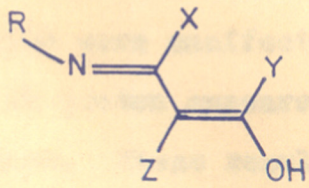
(C)

Ketoimine



(D)

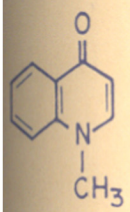
trans - ketoenamine



(E)

trans - enolimine

CHART - 1.



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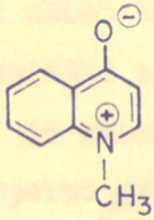

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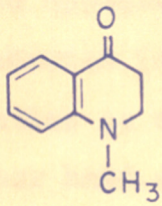

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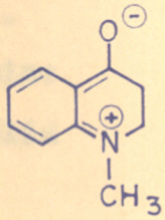

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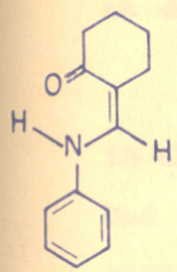

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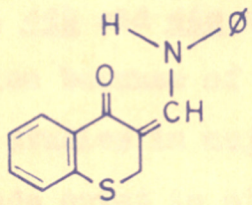
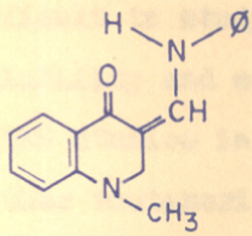


a = Ø = Phenyl -
b = Ø = α-naphthyl -
c = Ø = β-naphthyl -

43



a = Ø = Phenyl -
b = Ø = α-naphthyl -
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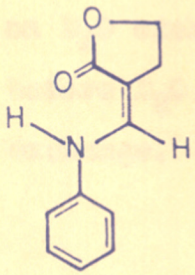
44



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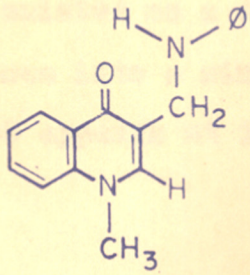

a = Ø = Phenyl -
b = Ø = α-naphthyl -
c = Ø = β-naphthyl -

46

(bonded NH) in chloroform solution which were unaffected by dilution. In the PMR spectra the NH proton appeared as a doublet around 12.0 δ in chloroform. These results thus indicate strong intramolecular hydrogen bonding possible in cis-ketoenamine tautomer (A). Unlike the earlier recorded examples, there is very little isomerisation to trans-ketoenamine tautomer of these compounds in dimethyl sulphoxide in which the NH proton appeared at 12-13 δ. Compound 45 existed as cis-ketoenamine (A) and enolimine tautomers (B) in chloroform solution as well as in solid state[32]. Compound 42 on the other hand existed as cis-ketoenamine tautomer (A) in solid state as well as in chloroform solution[29].

Compounds 44a, 44b and 44c were difficult to study in chloroform solution because of poor solubility and we had to carry out IR studies in nujol and PMR studies in DMSO. These compounds exist in still another tautomeric form 46a, 46b and 46c in DMSO as well as in solid state. This was characterised by the appearance of a triplet (J = 6 cps) typical of NH at about 6 δ which collapses on D_2O exchange. The $-CH_2$ existed as a doublet (J = 6 cps) before D_2O exchange, collapses into a singlet after D_2O exchange. In the IR the C=O appears at 1622 cm^{-1} in nujol

and the NH at 3330 cm^{-1}. The apparently low value of the C=O stretching frequency of the compound 44 is the characteristic of N-methyl-1,2,3,4-tetrahydroquinolin-4-one. This form was not detected by us in any of our earlier compounds. In DMSO, compounds 42 and 45[32] existed as trans-ketoenamine form as against the cis- form in chloroform, the compound 43 showed very little isomerisation to trans form in DMSO. The IR and PMR spectral data is given in Table 5.

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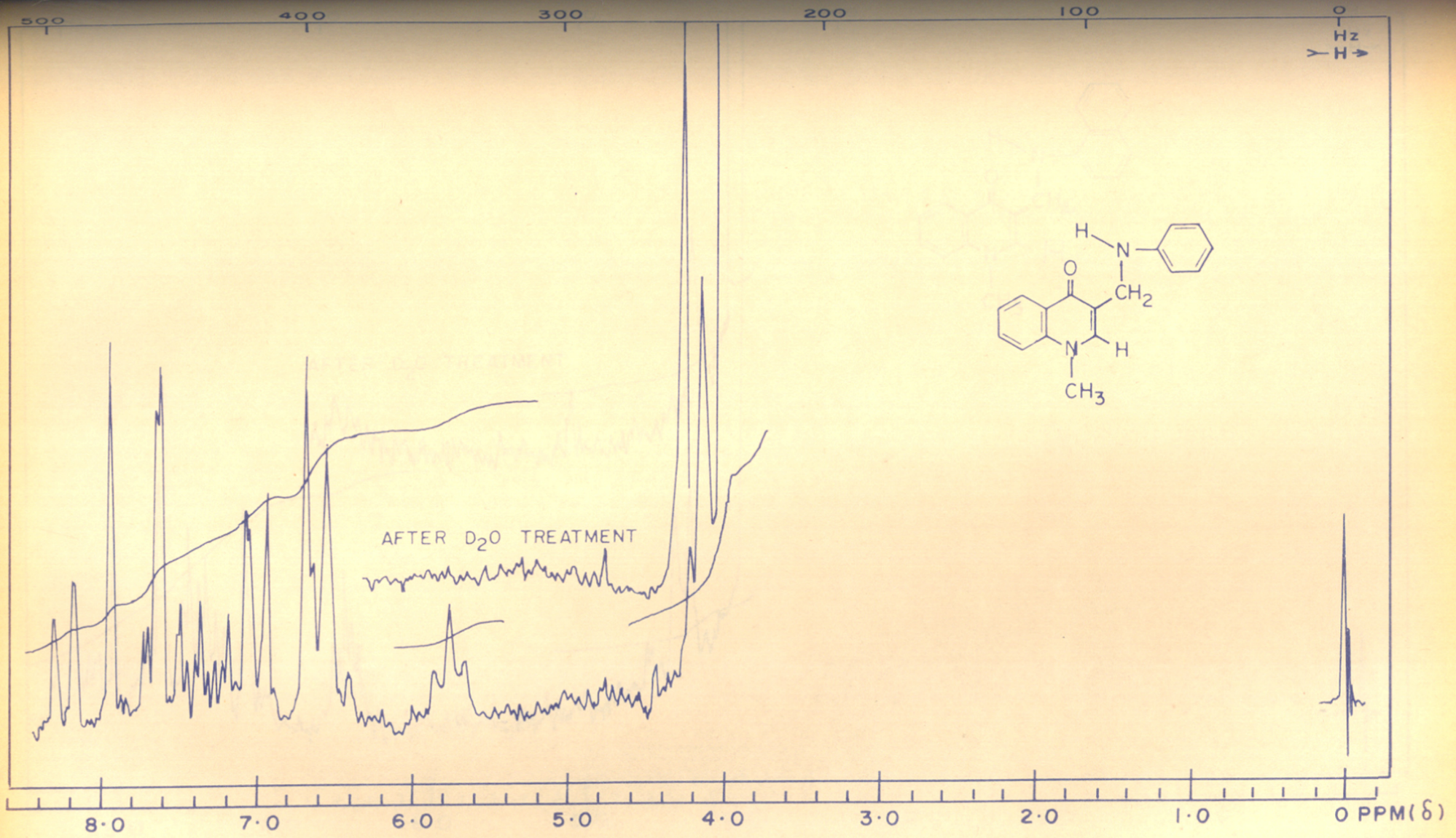
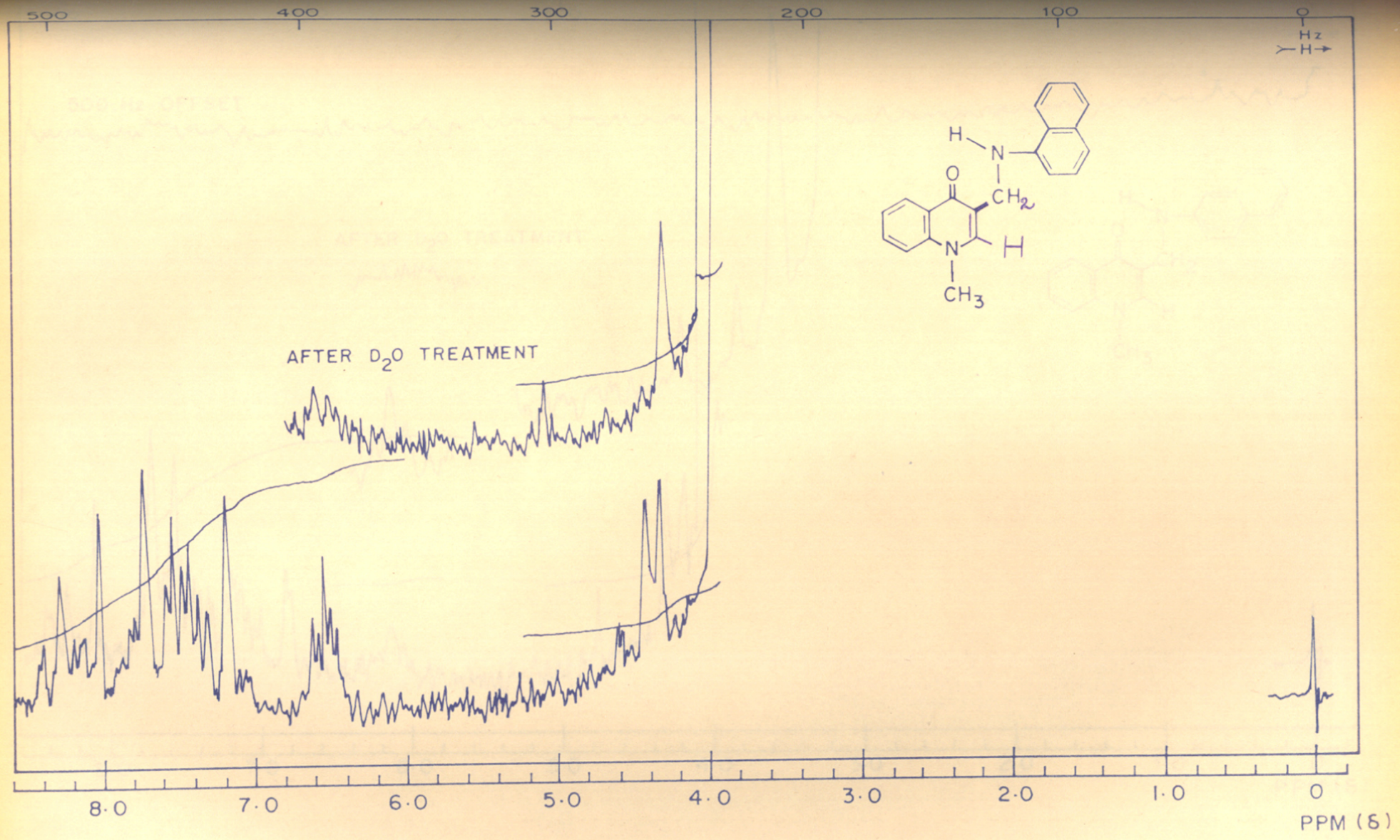
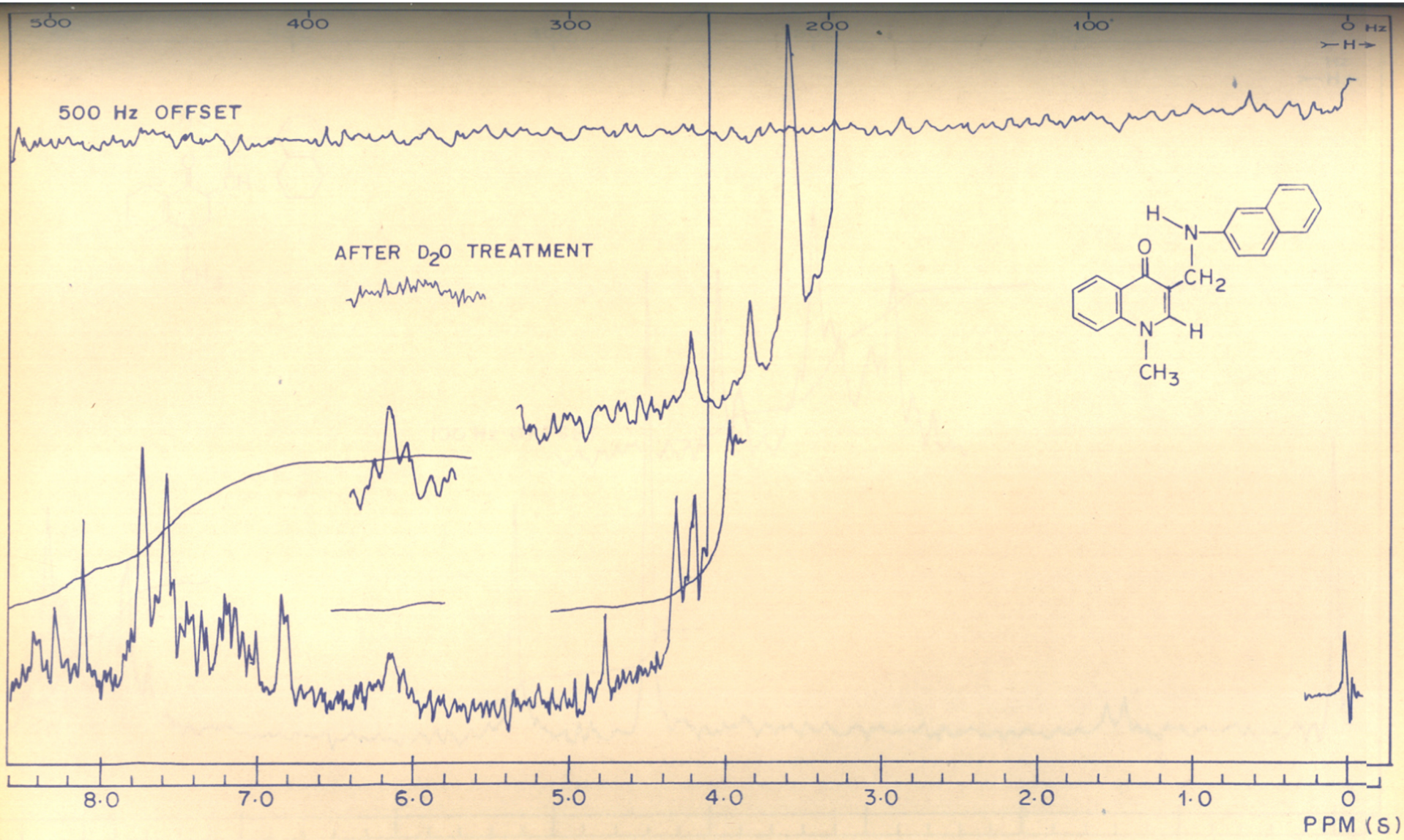


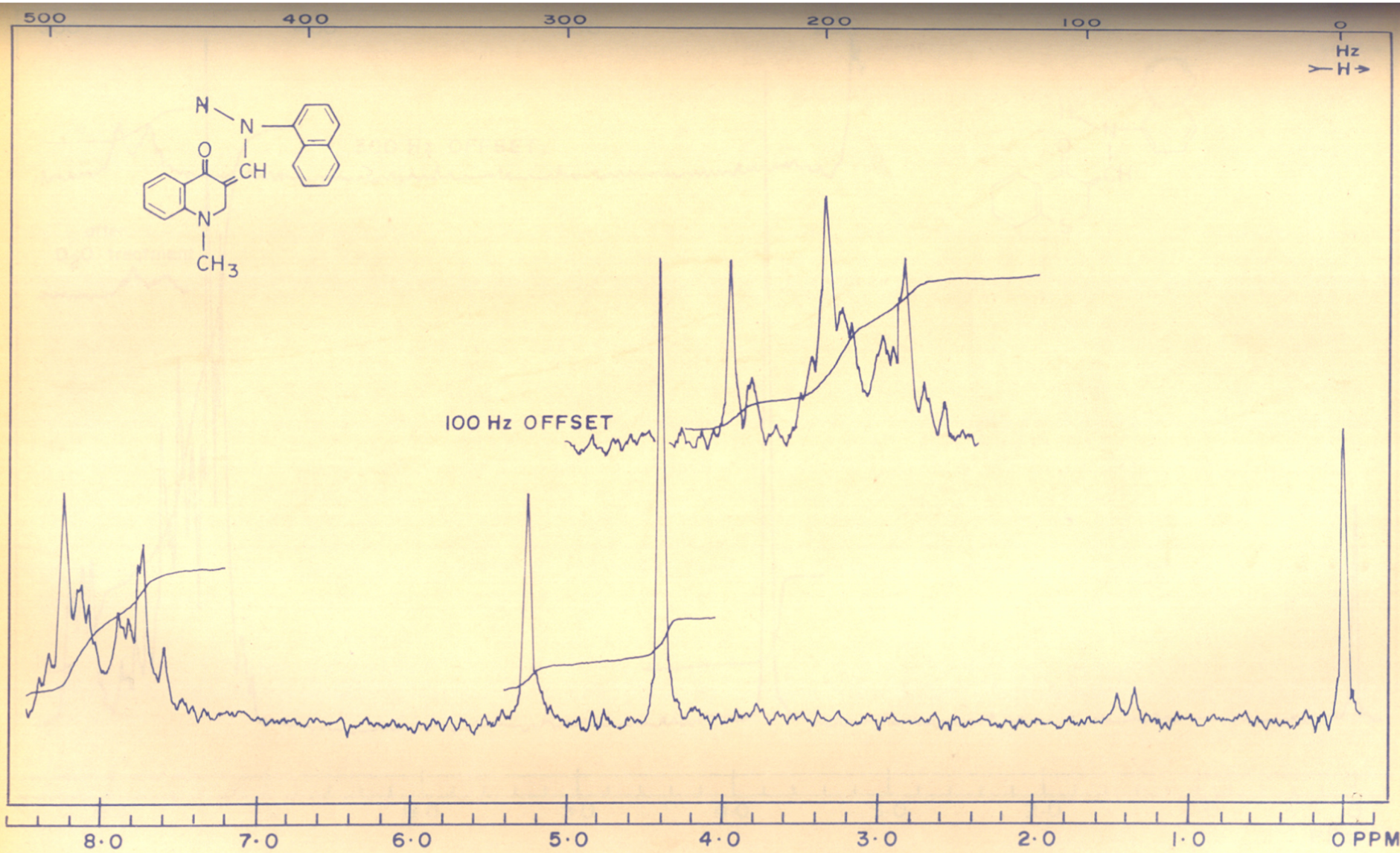
PMR SPECTRUM OF 46 a IN DMSO



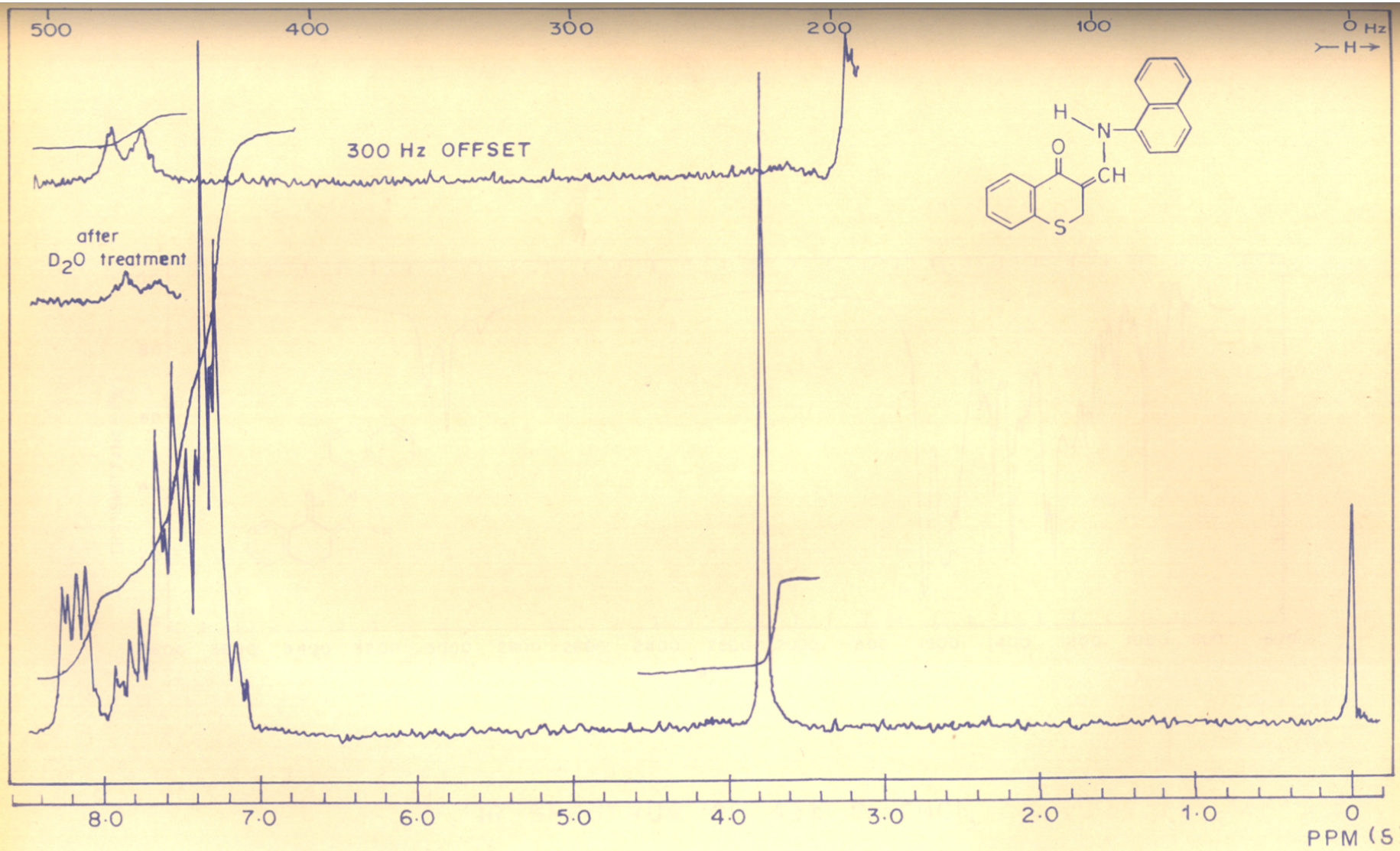
PMR SPECTRUM OF 46 b IN DMSO



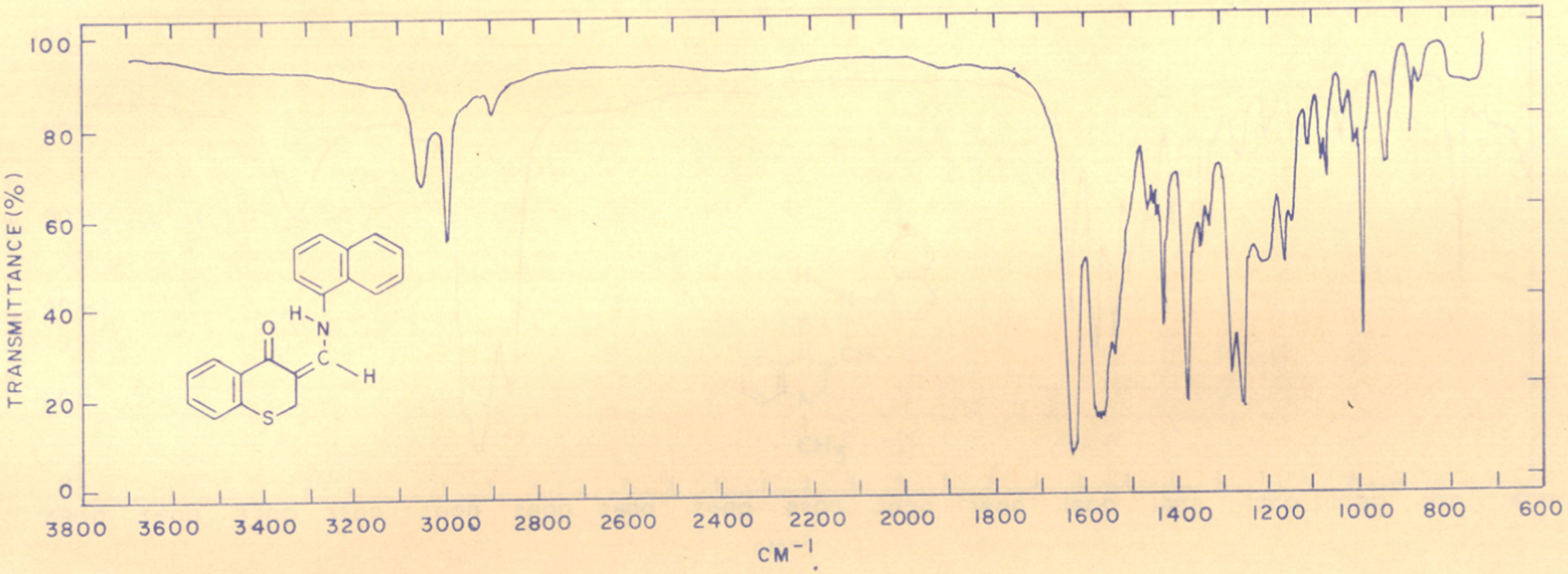
PMR SPECTRUM OF 46c IN DMSO



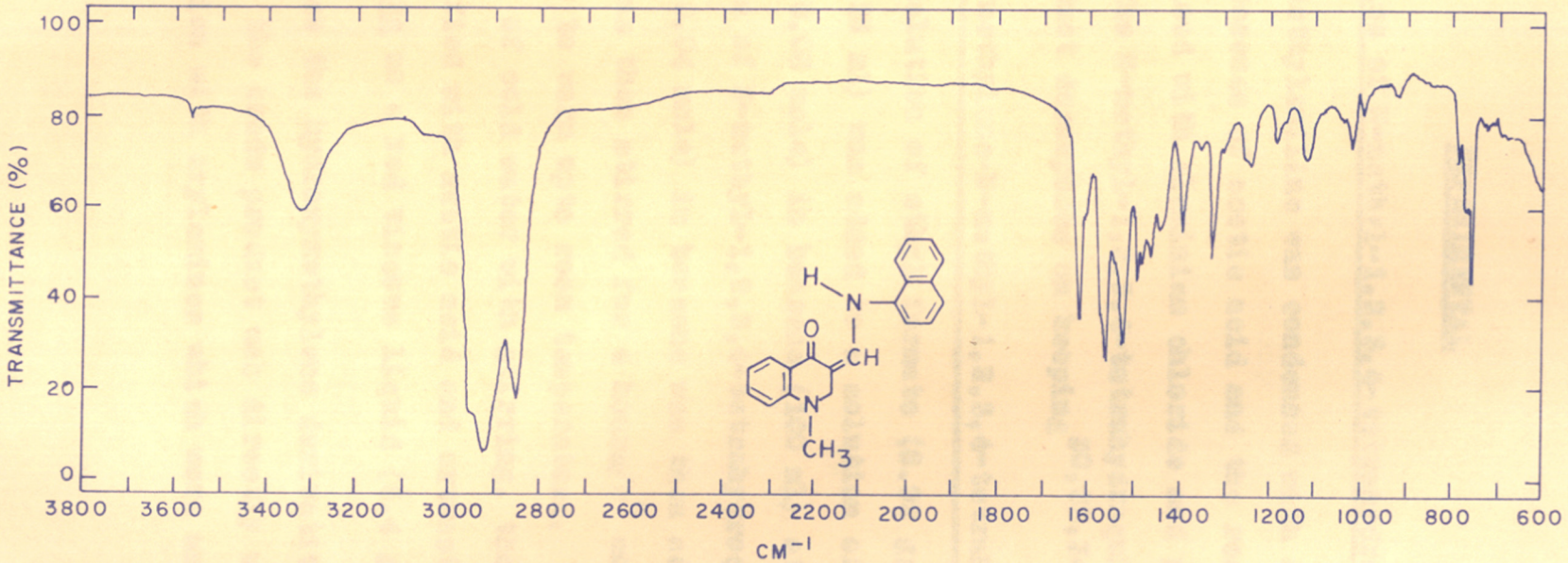
PMR SPECTRUM OF 44 b IN CF_3COOH



PMR SPECTRUM OF 43b IN $CDCl_3$



IR SPECTRUM OF 43b IN $CHCl_3$



IR SPECTRUM OF 44b IN NUJOL

EXPERIMENTAL

Preparation of N-methyl-1,2,3,4-tetrahydroquinolin-4-one 1

N-Methylaniline was condensed with acrylonitrile in the presence of acetic acid and the resulting product was cyclised with aluminium chloride and potassium chloride to give the N-methyl-1,2,3,4-tetrahydroquinolin-4-one 1. This product decomposes on keeping[30,33,34].

3-Hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 12a

A solution of ethyl formate (5.92 g;0.08 mole) in benzene (25 ml) was added to a solution of sodium methoxide (4.32 g; 0.08 mole) in benzene (100 ml) at 0° with stirring. A solution of N-methyl-1,2,3,4-tetrahydroquinolin-4-one 1 (6.44 g; 0.04 mole) in benzene was then added slowly. The mixture was then stirred for 4 hours/0° and was left overnight to warm upto room temperature. After addition of Ca 100 ml of cold water with stirring, the aqueous layer was acidified with acetic acid and extracted with ether to give 12a as a red viscous liquid (6.4 g; yield 85%).

Since the hydroxymethylene derivative is somewhat unstable, the crude product was directly used for condensation with arylamines which were used in excess.

Thiochroman-4-one 2

Condensation of thiophenol with β-propiolactone gave the carboxylic acid, which was then cyclised with sulphuric acid at room temperature to give the thiochroman-4-one 2 [35].

3-Hydroxymethylenethiochroman-4-one 12b

Sodium methoxide (4.32 g; 0.08 mole) in dry benzene (100 ml) was cooled to 0° under stirring. To this suspension was added, ethyl formate (5.92 g; 0.08 mole) in dry benzene (25 ml). After 1 hour, thiochroman-4-one 2 (6.56 g; 0.04 mole) in dry benzene (25 ml) was added to the above suspension. The mixture which turned red was stirred for 1 hour/0° and then left overnight to warm upto room temperature. After dilution with water, the aqueous layer was acidified with glacial acetic acid and then extracted with ether. Removal of ether gave 12b as a red coloured liquid (5.37 g; yield 70%) which was directly used for condensation with arylamines.

General method for the preparation of cis-3-arylamino methylene-1-H-methyl-1,2,3,4-tetrahydroquinolin-4-ones 15-17 and cis-3-arylaminomethylenethiochroman-4-ones 18-20

The hydroxymethylene derivative (1 mole) and arylamines (aniline, α-naphthylamine and β-naphthylamine) (1.1 mole) were mixed in ether at room temperature and

then kept at 0° for 24 hours. In most of the cases a yellow solid separated out which was filtered and washed with ether to remove unreacted arylamines. In case of sulphur compounds which are coloured, a little ether wash was sufficient to prepare the condensed products in pure form. In the case of nitrogen analogs, purification by crystallisation and charcoal treatment was necessary to give the pure products. By concentrating the mother liquor, diluting with benzene and petroleum ether mixture and cooling, a second crop of the condensed compound could be isolated. The concentrates from mother liquors were then subjected to column chromatography over neutral alumina, using petroleum ether, benzene, ethylacetate and methanol as eluents successively, to isolate the remaining portions in pure form.

The condensation products were recrystallised from appropriate solvents and then used for further spectral studies. The experimental details, properties and elemental analysis are tabulated in tables 1 and 2.

General method for the cyclodehydration of cis-3-arylaminomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 15-17.

The respective anilino, (α-naphthylamino)- and

(β-naphthylamino) methylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones (1 mole) were treated with concentrated sulphuric acid (15 ml) and triphenylmethyl chloride (1 mole) at 5° for 3 hours. The resulting mixture was then diluted with cold dry ether and filtered. The solids were washed free of acid by dry ether and dried over P_2O_5 for a long time (48 hours). The cyclodehydrated products 21, 22 and 23 (as sulphates) were then treated with 70% perchloric acid (10 ml) and the mixtures were kept at 60° for 4 hours under stirring. The mixture after trituration with cold ether (250 ml) and keeping at 0° for 24 hours gave the corresponding perchlorates 24, 25 and 26 as yellowish hygroscopic compounds, by filtration, washing with ether and drying over P_2O_5.

General method for the cyclodehydration of cis-3-arylaminomethylenethiochroman-4-ones 18-20

The arylaminomethylenethiochroman-4-one (1 mole) was disolved in glacial acetic acid (10 ml) and cooled to 5° under stirring. Triphenylmethyl chloride (1 mole) was then added followed by 70% perchloric acid (10 ml). This mixture was stirred in the cold at 0° for 1 hour and then at room temperature for 3 hours.

The mixture was then triturated with 500 ml of cold ether and then kept at 0^{0} for 24 hours. The crystalline perchlorates 27-29 which separated out, were filtered, washed with excess of dry ether (250 ml) and dried over P_2O_5 in vacuum. Compounds 27 and 29 are orange coloured compounds, whereas 28 was a yellow crystalline compound. These have marked difference in colour, compared to the nitrogen analogs.

The experimental data, relevant spectral characteristics and the elemental analysis are tabulated in tables 3 and 4.

Table 1 - Preparation of cis-3-arylaminomethyleneketones

Hydroxymethylene ketone No.	g	Arylamine	g	Condensation product No.	g/yield %	Properties, solvent m.p.
12a	3.21	Aniline	1.74	15	1.5 (34)	White needles, ethanol, 185-190°
12a	3.21	α-Naphthylamine	2.67	16	3.2 (48)	White needles, methanol, 234°
12a	3.21	β-Naphthylamine	2.67	17	3.55 (67)	White needles, methanol, 214°.
12b	3.91	Aniline	2.08	18	2.96 (54)	Lemon yellow needles, benzene, 98°
12b	3.91	α-Naphthylamine	3.2	19	3.94 (61)	Orange needles, benzene, 110°
12b	3.91	β-Naphthylamine	3.2	20	4.97 (77)	Orange needles, benzene, 120°

Table 2 - Analytical and mass spectral data of compounds 15-17 and 18-20

Compound No.	Found %			Required %			(M^+)
	C	H	N	C	H	N	
15	77.4	10.7	6.7	77.2	10.6	6.7	264
16	79.9	5.4	9.0	80.2	5.7	8.9	314
17	79.8	5.4	9.1	80.2	5.7	8.9	314
18	72.0	5.1	5.5	71.9	4.9	5.2	267
19	75.3	4.6	4.7	75.7	4.7	4.4	317
20	76.0	4.3	4.4	75.7	4.7	4.4	317

* IR and PMR spectral data was given seperately in the later part of this thesis.

Table 3 - Preparation of the cyclodehydrated products 24-26 and 27-29 (as perchlorates)

Starting ketone No and weight (g)		Perchlorate No and weight (g)		Yield %	m.p.°	Analysis (chlorine) Found	Required
15	(0.5)	24	(0.260)	40	162°	9.7	10.3
16	(1.0)	25	(0.618)	49	190° (d)	8.5	8.9
17	(1.0)	26	(0.565)	45	210° (d)	9.0	8.9
18	(1.0)	27	(0.370)	28	210°	9.5	10.2
19	(1.0)	28	(0.460)	37	216°	9.0	8.9
20	(1.0)	29	(0.5)	40	224-26°	8.2	8.9

Table 4 – UV and visible absorption spectral data of nitrogen and sulphur heterocyclics (as perchlorates)

Compound No.	λ_{max} (log ε) in	
	DMSO	$AcOH/HClO_4$
24	294 (3.94)	310 (3.76)
25	296 (2.795), 330 (4.22)	285 (3.89)
26	295 (4.07), 325 (3.99)	282 (3.94), 294 (3.915) S 315 (3.775)
27	258 (4.12), 340 (4.1) S355(3.95), 400(3.175)	335 (4.12), 375 (3.96)
28	340 (4.125), 415 (3.95)	328 (4.1), 395 (3.65) 430 (3.69)
29	263 (4.37), S292 (4.135) 338 (3.91), 408 (3.92) S 441 (3.55)	261 (4.02), 350 (3.92) 385 (3.68)

Table 5 - IR and PMR spectral data of compounds 43a-c and 44a-c

	PMR (NH) δ	IR C = O cm^{-1}	IR NH cm^{-1}
43a -	11.1 ($CDCl_3$)	1637 ($CHCl_3$)	3050 ($CHCl_3$)
	12.3 (DMSO)	1635 (Nujol)	-
43b -	12.8 ($CDCl_3$)	1640 ($CHCl_3$)	3050 ($CHCl_3$)
	13.0 (DMSO)	1635 (Nujol)	-
43c -	11.8 ($CDCl_3$)	1639 ($CHCl_3$)	3050 ($CHCl_3$)
	12.6 (DMSO)	1638 (Nujol)	-
44a -	5.7 (DMSO)	1626 (Nujol)	3325 (Nujol)
44b -	6.5 (DMSO)	1622 (Nujol)	3330 (Nujol)
44c -	6.1 (DMSO)	1622 (Nujol)	3330 (Nujol)

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CHAPTER III

STUDIES IN CYCLODEHYDRATION REACTIONS USING ZINC CHLORIDE/ARYLAMINE HYDROCHLORIDE

It was mentioned in Chapter I that cyclodehydration of various cis-2-arylaminomethylenecycloalkanones with various cyclising agents like sulphuric acid, formic acid, dl-lactic acid, monochloroacetic acid, polyphosphoric acid, ethanolic hydrogenchloride, acetic and propionic acids and anhydrous zinc chloride along with the appropriate arylamine hydrochloride leads to either the linear or the angular derivatives depending upon the conditions and reagents used. Cyclisation reactions with sulpho-mix[1] and Dowtherm[2,3,4] have also been reported yielding excellent results. The failure of cyclodehydration reactions has been attributed to the reasons like, stereochemical hindrances, poor reactivity of the molecules when the heteroatoms are present and the geometry of the molecular structure i.e. the trans congiruation.

Some of the reagents give exclusively the linear rearranged products while some other reagents gives exclusively the angular products.

Earlier Borsche and coworkers[5] had reported the concomitant formation of both the linear and angular products during the cyclodehydration reactions. Recent studies also indicate similar formation of mixture of products in many cases[6,7].

The reaction mechanism whereby linear rearranged products are obtained is different from the mechanism which leads the (normal) angular derivatives.

The reactive intermediates postulated by various workers have been rarely isolated. In the present work, two such intermediates have now been isolated. The reaction mechanisms postulated by various workers are reviewed below with the view to account for the products described in this chapter.

(a) The formation of the normal angular products, with particular reference to tetrahydrophenanthridines 2 by the acid catalysed cyclodehydration of 1 can be explained by the usual cyclodehydration mechanism as shown in chart 1. The cyclodehydrating agents used are PPA, formic acid and monochloroacetic acid.

(b) Petrow[8] cyclised the anils of β-keto-aldehydes 3 to acridine derivatives 4 by treatment with the same arylamine hydrochloride in boiling ethanolic hydrogenchloride with an optional addition of zinc chloride. He has postulated the formation of an intermediate 'dianil' which then cyclises to tetrahydroacridine as shown in the chart 2. The failure of cyclisations was attributed to the trans-stereochemistry

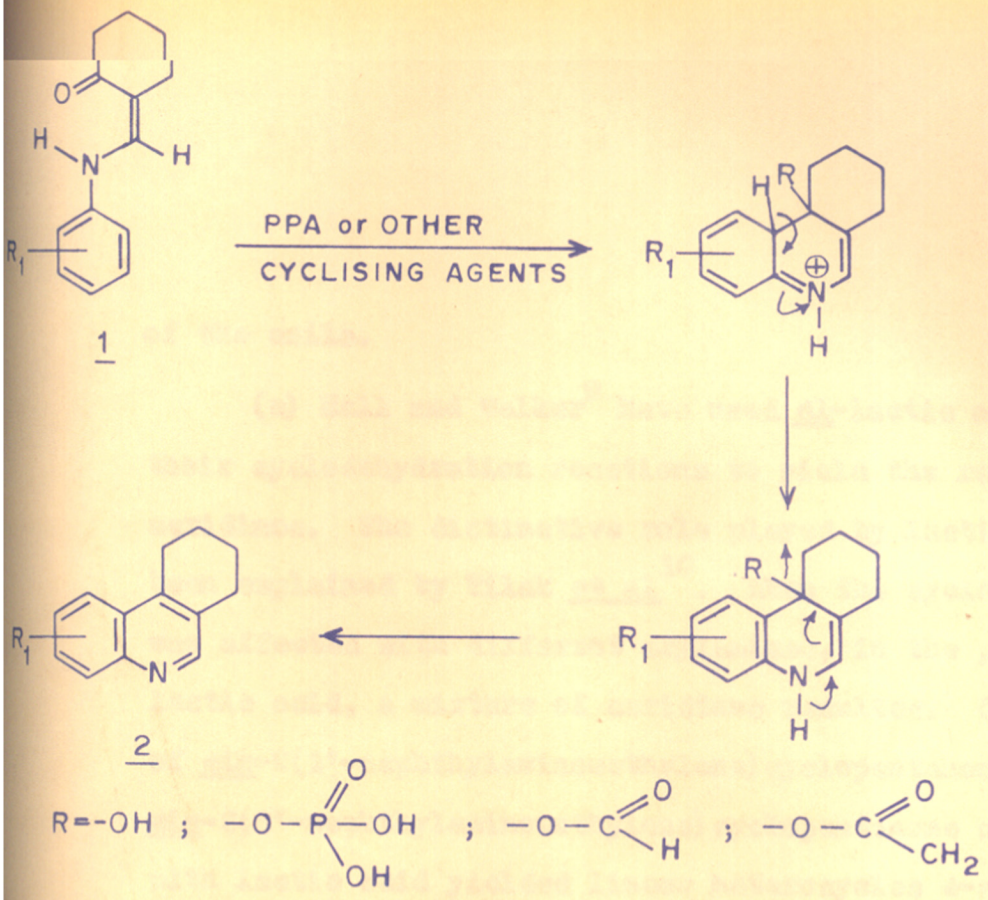


CHART 1

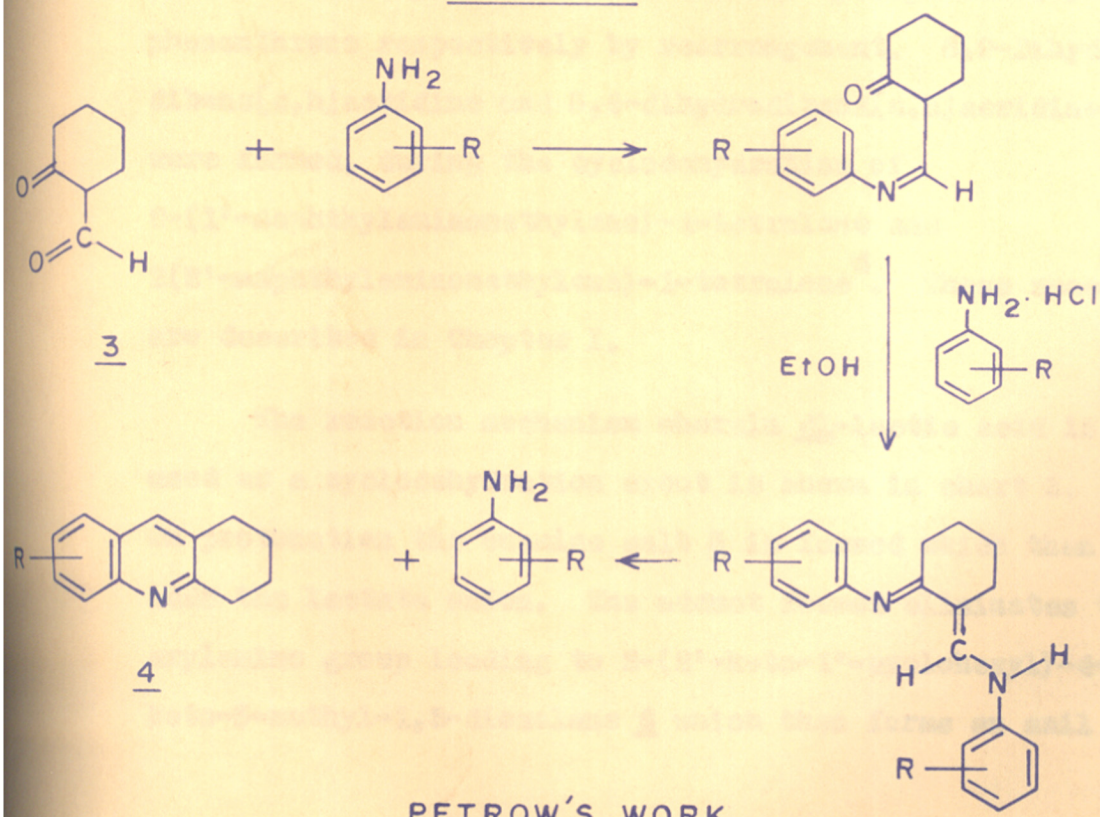


CHART 2

of the anils.

(c) Hall and Walker[9] have used dl-lactic acid for their cyclodehydration reactions to yield the rearranged acridines. The distinctive role played by lactic acid has been explained by Tilak et al[10]. When the cyclodehydration was affected with different arylamines, in the presence of lactic acid, a mixture of acridines resulted. Cyclodehydration of cis-2(1'-naphthylaminomethylene) cyclopentanone and cis-2(2'-naphthylaminomethylene) cyclopentanone on treatment with lactic acid yielded linear heterocycles 4-aza-cyclopenteno[b]phenanthrene and 1-aza-cyclopenteno[b]-phenanthrene respectively by rearrangement. 8,9-Dihydro-dibenz[c,h]acridine and 5,6-dihydrodibenz[a,h]acridine were formed, during the cyclodehydration of 2-(1'-naphthylaminomethylene)-1-tetralone and 2(2'-naphthylaminomethylene)-1-tetralone[6]. These reactions are described in Chapter I.

The reaction mechanism wherein dl-lactic acid is used as a cyclodehydration agent is shown in chart 3. On protonation the enamine salt 5 is formed which then adds the lactate anion. The adduct formed eliminates the arylamino group leading to 2-(2'-keto-1'-cyclohexyl)-4-keto-5-methyl-1,3-dioxolane 6 which then forms an anil

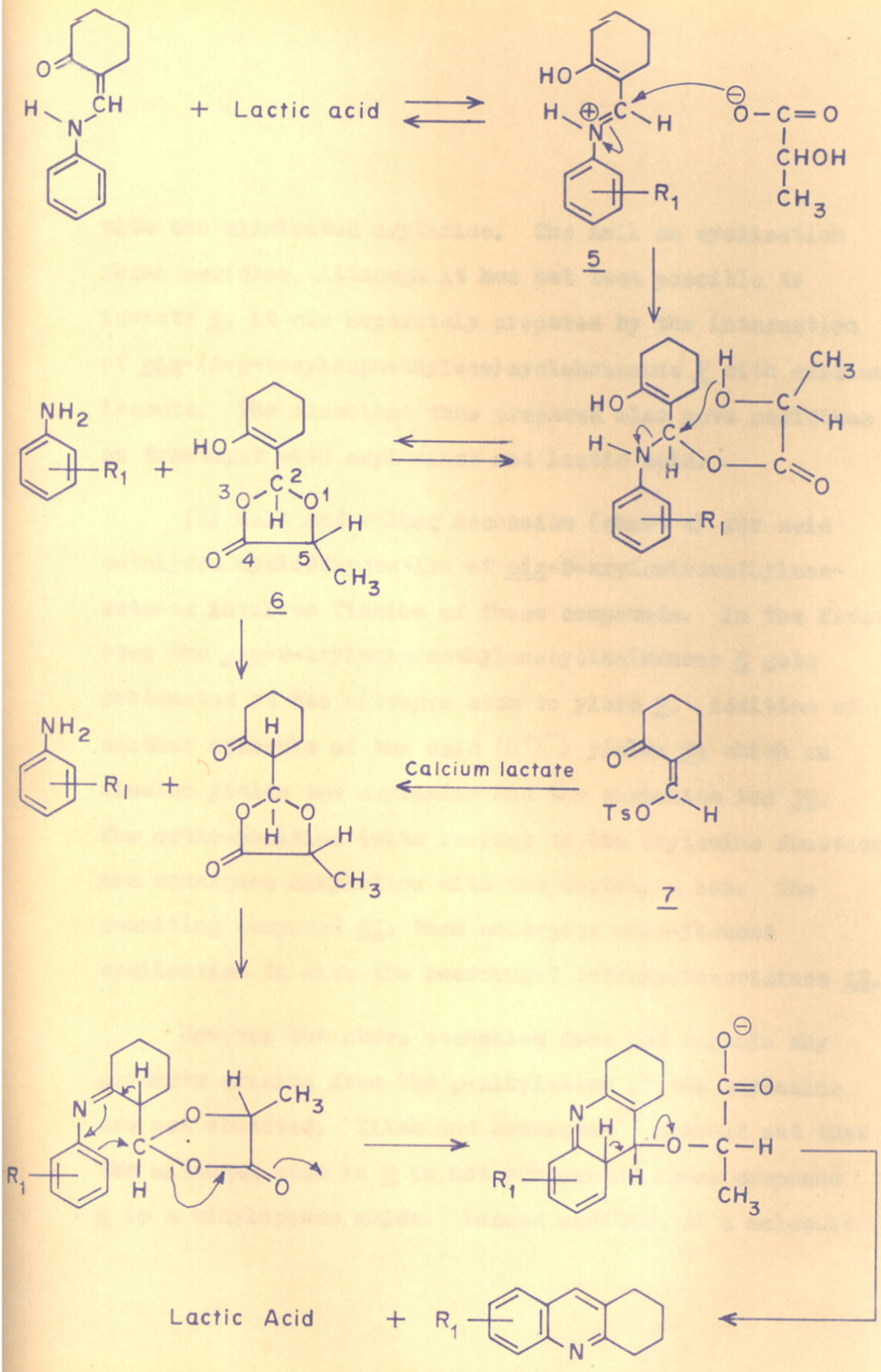
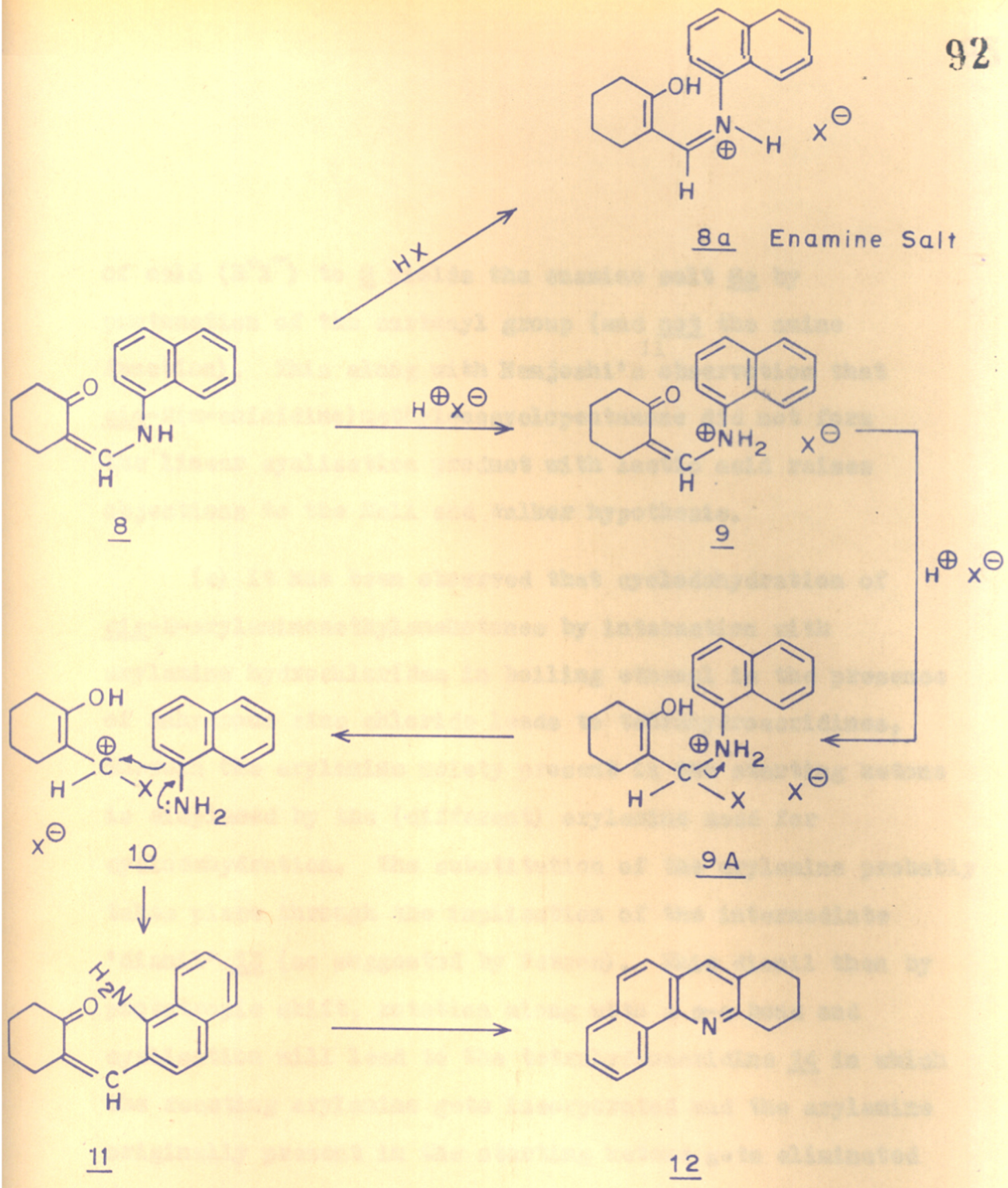


CHART 3

with the eliminated arylamine. The anil on cyclisation forms acridine. Although it has not been possible to isolate 6, it was separately prepared by the interaction of cis-(2-p-tosyloxymethylene) cyclohexanone 7 with calcium lactate. The dioxolone thus prepared also gave acridines on treatment with arylamines and lactic acid.

(d) Hall and Walker mechanism (chart 4) for acid catalysed cyclodehydration of cis-2-arylaminomethylene-ketones involves fission of these compounds. In the first step the cis-2-arylaminomethylenecycloalkanone 8 gets protonated at the nitrogen atom to yield 9. Addition of another molecule of the acid (H^+X^-) yields 9A which on fission yields the arylamine and the carbonium ion 10. The ortho-position (with respect to the arylamine function) now undergoes alkylation with the carbonium ion. The resulting compound 11, then undergoes acid-induced cyclisation to give the rearranged tetrahydroacridines 12.

However the above mechanism does not explain why products arising from the p-alkylation of the arylamine are not observed. Tilak and coworkers[10] pointed out that the nitrogen atom in 8 is not protonated since compound 8 is a vinylogoues amide. Indeed addition of a molecule



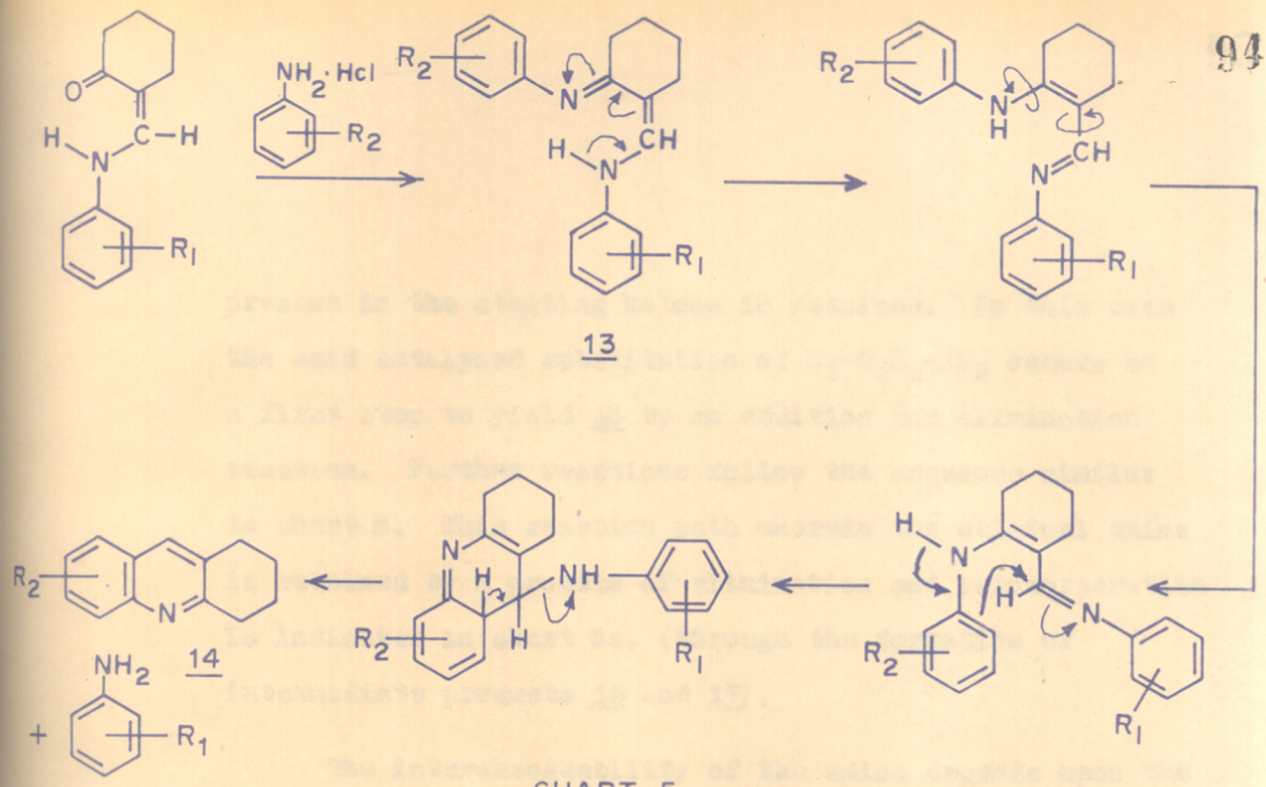
HALL AND WALKER MECHANISM

CHART 4

of acid (H^+X^-) to 8 yields the enamine salt 8a by protonation of the carbonyl group (and not the amine function). This along with Namjoshi's[11] observation that cis-2(m-anisidino)methylenecyclopentanone did not form the linear cyclisation product with lactic acid raises objections to the Hall and Walker hypothesis.

(e) It has been observed that cyclodehydration of cis-2-arylaminomethyleneketones by interaction with arylamine hydrochlorides in boiling ethanol in the presence of anhydrous zinc chloride leads to tetrahydroacridines, wherein the arylamine moiety present in the starting ketone is displaced by the (different) arylamine used for cyclodehydration. The substitution of the arylamine probably takes place through the implication of the intermediate 'dianil' 13 (as suggested by Petrow). This dianil then by prototropic shift, rotation along with a c-c bond and cyclisation will lead to the tetrahydroacridine 14 in which the reacting arylamine gets incorporated and the arylamine originally present in the starting ketone gets eliminated (chart 5).

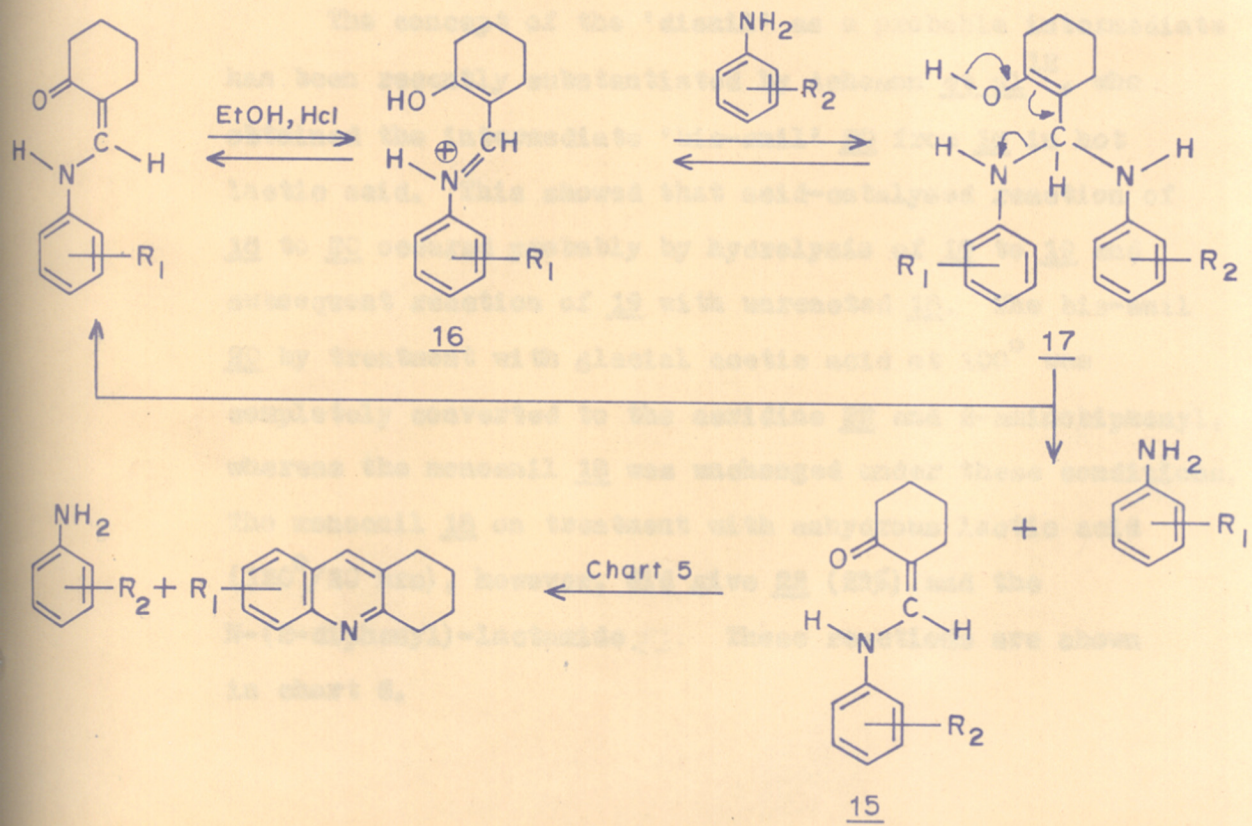
In the above cyclodehydration reactions tetrahydro - acridines are also formed where the arylamine originally



13

14

CHART 5



16

17

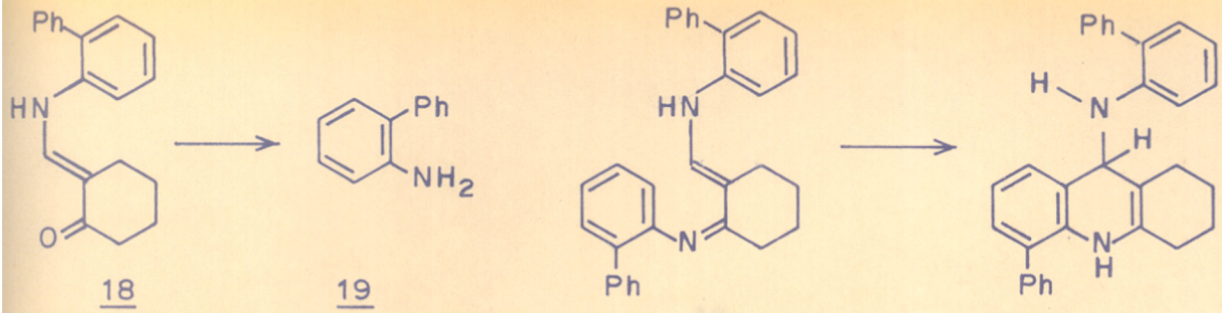
15

CHART 5a

present in the starting ketone is retained. In this case the acid catalysed substitution of R_1-C_6H_4-NH_2 occurs as a first step to yield 15 by an addition and elimination reaction. Further reactions follow the sequence similar to chart 5. This reaction path wherein the original amine is retained by a process of elimination and reincorporation is indicated in chart 5a, (through the formation of intermediate products 16 and 17).

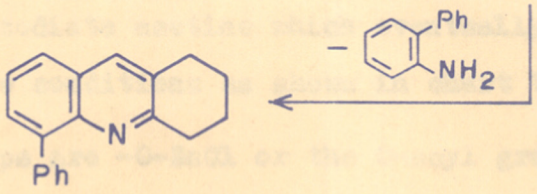
The interchangeability of the amine depends upon the comparative basicities of the two amines.

The concept of the 'dianil' as a probable intermediate has been recently substantiated by Acheson et al[12], who obtained the intermediate 'bis-anil' 20 from 18 in hot lactic acid. This showed that acid-catalysed reaction of 18 to 20 occured probably by hydrolysis of 18 to 19 and subsequent reaction of 19 with unreacted 18. The bis-anil 20 by treatment with glacial acetic acid at 100° was completely converted to the acridine 22 and 2-aminobiphenyl, whereas the monoanil 18 was unchanged under these conditions. The monoanil 18 on treatment with anhydrous lactic acid (130°/20 hrs), however, did give 22 (25%) and the N-(2-diphenyl)-lactamide. These reactions are shown in chart 6.

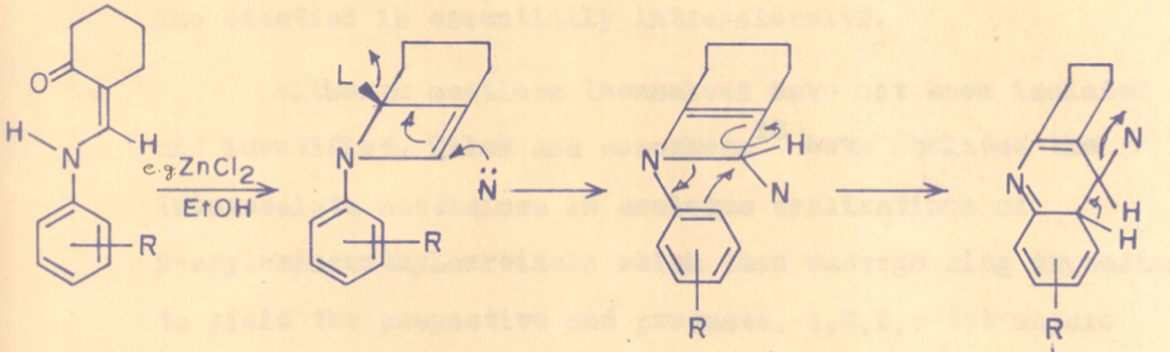


18 19 20 21

ACHESON'S WORK
CHART 6



22



N = Nucleophile (Cl^-, OH^-)

L = Leaving group (-OZnCl, $-O-\overset{O}{\overset{\|}{P}}(OH)(OH)$, $-O-CO-CH_2Cl$, -NH-Aryl, $-O-\overset{O}{\overset{\|}{C}}-H$, -O-Lactyl

AZETINE MECHANISM
CHART 7

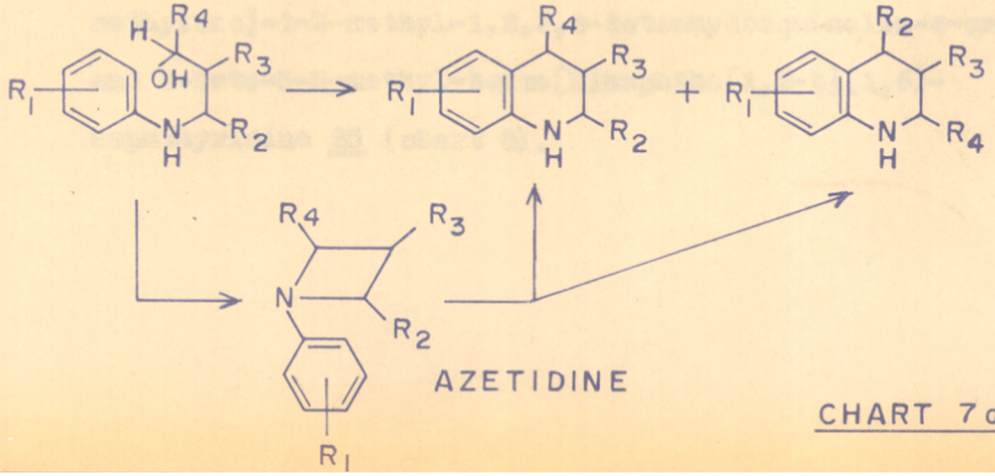


CHART 7a

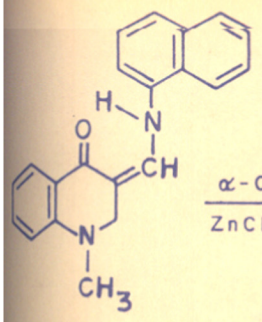
(f) Tilak and coworkers[13] have postulated the formation of the intermediate azetine which eventually rearranges under acidic conditions as shown in chart 7.

The leaving groups are -O-ZnCl or the O-acyl groups (e.g., lactate, formate, propionate, acetate and chloroacetate) depending upon the reagents (acidic) used for cyclisation. The reaction is essentially intramolecular.

Although azetines themselves have not been isolated and identified, Tilak and coworkers[13] have isolated the intermediate azetidines in analogus cyclizations of β-arylaminomethylcarbinols which then undergo ring expansion to yield the respective end products, 1,2,3,4-tetrahydro quinolines (under acidic conditions)[19] (See chart 7a).

Present work

Cyclodehydration of cis-3-(1'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 23 on heating with α-naphthylamine hydrochloride and fused zinc chloride in boiling ethanol gave trans-3-[(1'-amino-2'-naphthyl)-methylene]-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 24 and 6-keto-5-N-methyl-benzo[h]naphtho[1,2-b][1,6]-naphthyridine 25 (chart 8).



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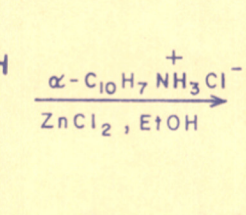

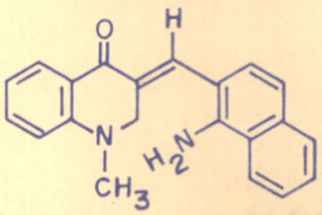

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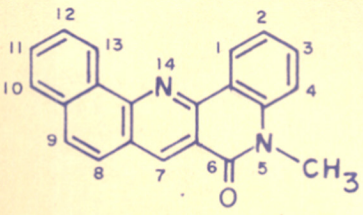

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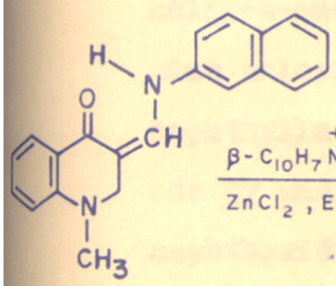

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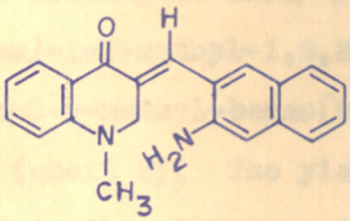

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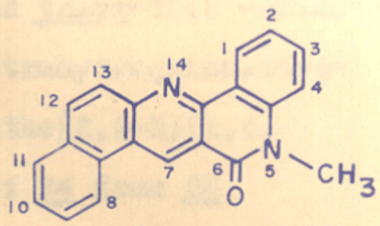

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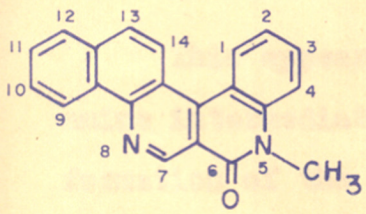

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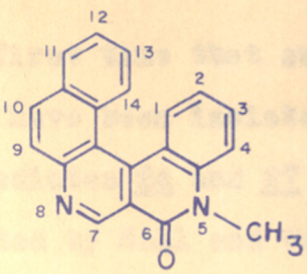

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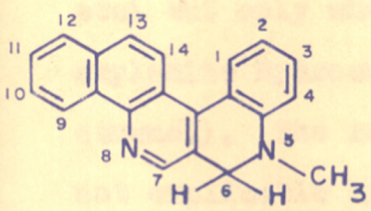

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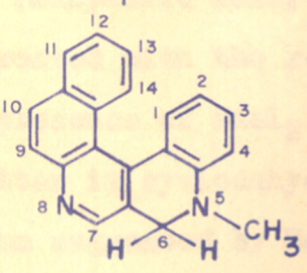


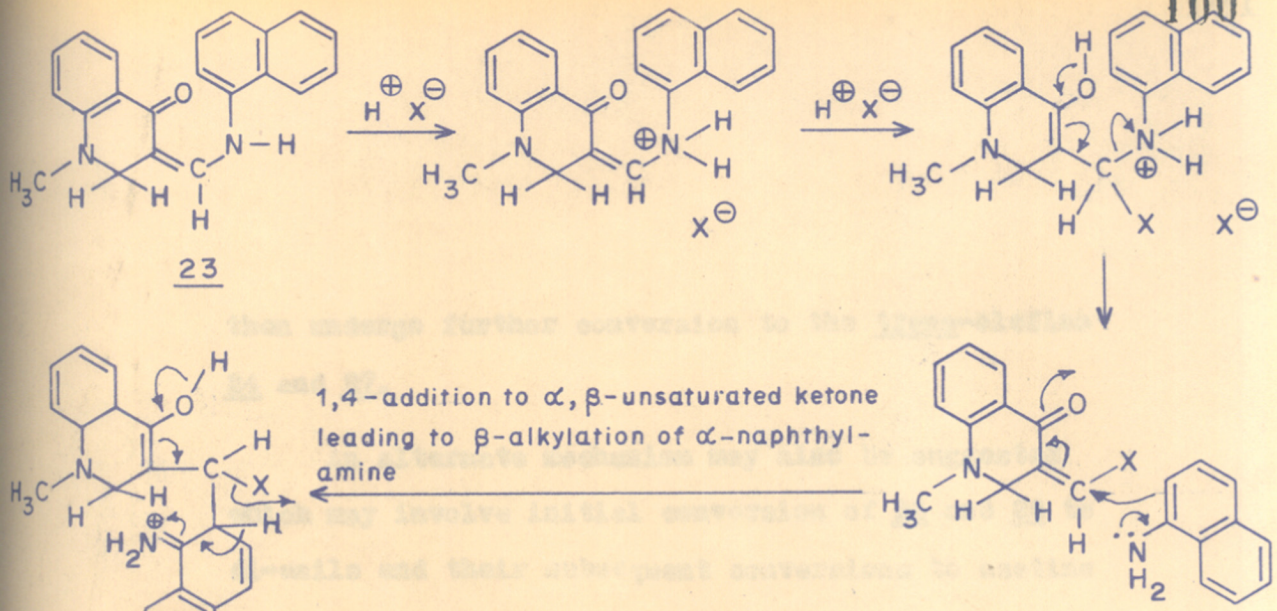
28 a

CHART 8

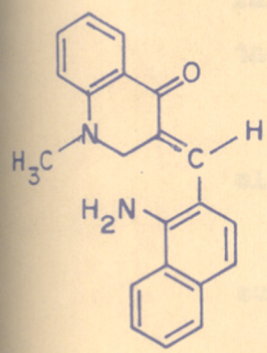
In a similar manner cyclodehydration of cis-3-(2'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 26 (by treatment with β-naphthylamine hydrochloride, zinc chloride and boiling ethanol) yielded trans-3[(2'-amino-1-'naphthyl)methylene]-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 27 and 6-keto-5-N-methyl-benzo[h]naphtho[2,1-b][1,6]-naphthyridine 28 (chart 8). The yields of 24 from 23 and of 27 from 26 in the above reactions were low (< 25%). The yield of the lactams 25 from 23 and 28 from 26 were even still lower (< 5%).

This appears to be the first time that such trans-amine intermediates 24 and 27 have been isolated. The formation of the amine intermediates 24 and 27 may follow the reaction mechanism suggested by Hall and Walker[9] (chart 10).

However the above cis-3-arylaminomethylene ketones 23 and 26 do not yield the trans-olefins 24 and 27 under the usual cyclodehydration agents (sulphuric acid, perchloric acid, etc) but only when they are treated with the respective arylamine hydrochlorides (in presence of $ZnCl_2$ and boiling ethanol). The role of the latter in cyclodehydration is not explicable by the mechanism suggested by Hall and Walker. Hence it seems likely that 23 and 26 are probably converted to di-anils (as proposed by Petrow, c.f. chart 5) which



HALL AND WALKER MECHANISM WHICH MAY BE EXPECTED TO YIELD TRANS-OLEFIN 24



Similarly

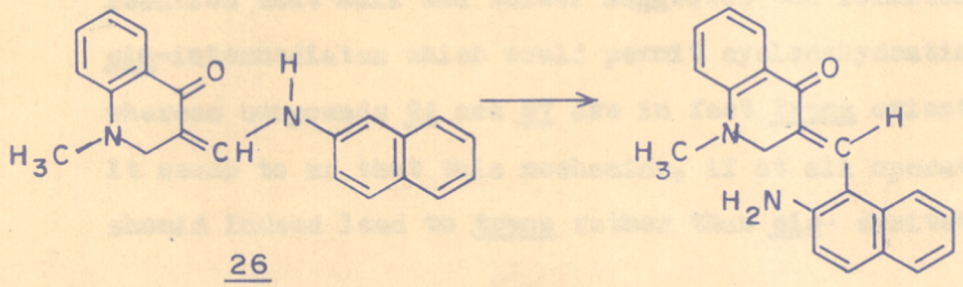


CHART 10

then undergo further conversion to the trans-olefins 24 and 27.

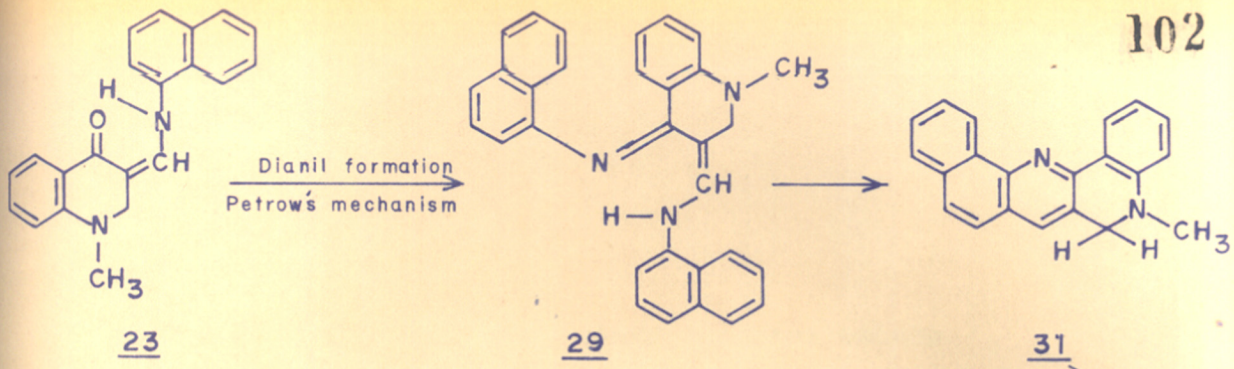
An alternate mechanism may also be suggested which may involve initial conversion of 23 and 26 to di-anils and their subsequent conversions to azetine intermediates as shown in chart 11.

The formation of the keto-naphthyridines can be explained if one assumes di-anil formation as indicated in chart 10a. The sequence of reactions are similar to those shown in chart 5 (Petrow mechanism).

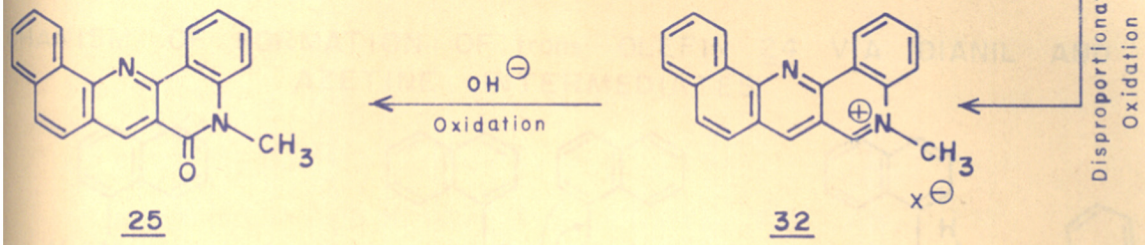
The Hall and Walker mechanism leading to the trans - olefins 24 and 27 does not explain:

(a) why such compounds are not formed in all other such cyclodehydrations and

(b) the role played by the arylamine hydrochloride used in the cyclodehydration since using other reagents the trans-products 24 and 27 were not formed. It may be recalled that Hall and Walker suggested the formation of cis-intermediates which would permit cyclodehydration, whereas compounds 24 and 27 are in fact trans oriented. It seems to us that this mechanism, if at all operative should indeed lead to trans rather than cis- derivatives

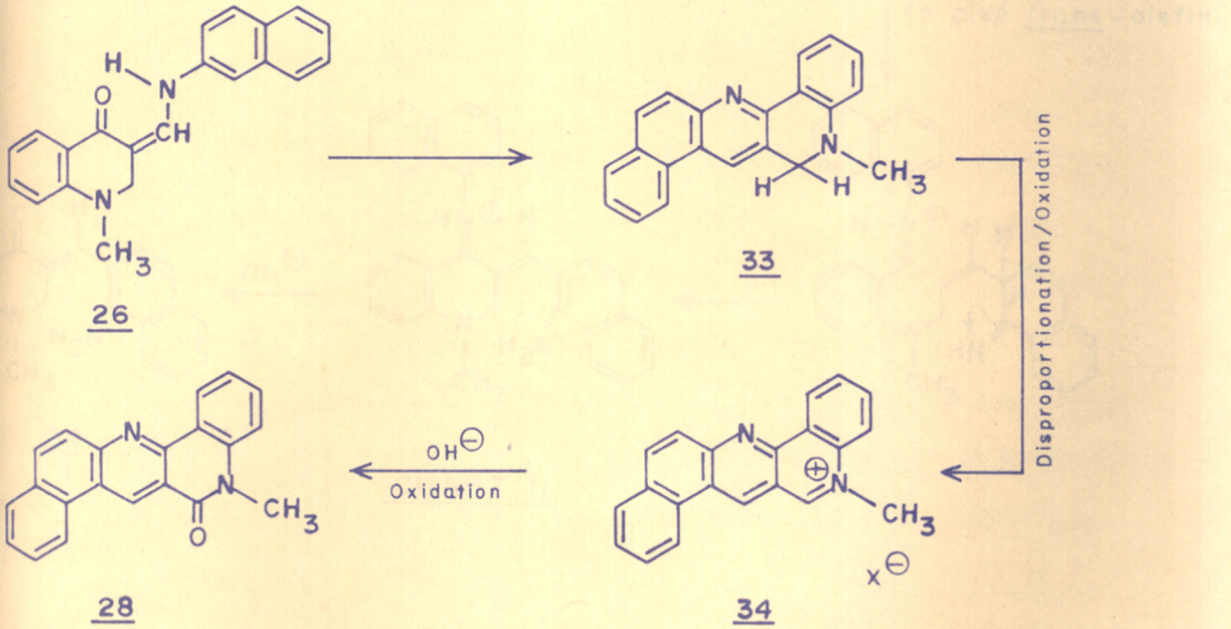


23 29 31



25 32

Similarly

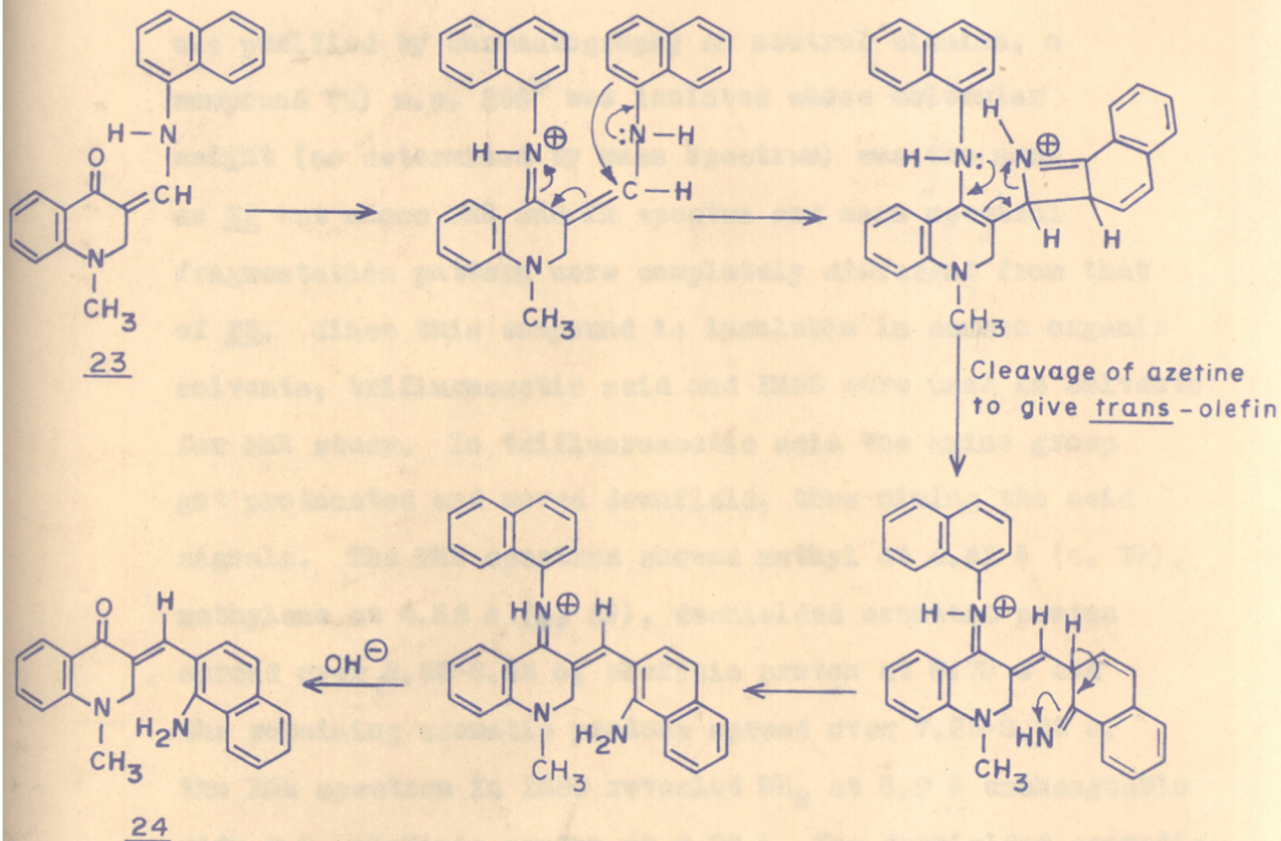


26 33 34 28

MECHANISM OF FORMATION OF KETONAPHTHYRIDINES 25 and 28

CHART 10a

MECHANISM OF FORMATION OF trans-OLEFIN 24 VIA DIANIL AND AZETINE INTERMEDIATES



23

24

CHART II

for reasons which will be obvious from the scheme shown in chart 10.

When 23 was heated with α-naphthylamine hydrochloride and fused zinc chloride in boiling ethanol and the mixture was purified by chromatography on neutral alumina, a compound (A) m.p. 266° was isolated whose molecular weight (as determined by mass spectrum) was the same as 23 but whose PMR and IR spectra and mass spectral fragmentation pattern were completely different from that of 23. Since this compound is insoluble in common organic solvents, trifluroacetic acid and DMSO were used as solvents for PMR study. In trifluoroacetic acid the amine group got protonated and moved downfield, thus mixing the acid signals. The PMR spectrum showed methyl at 4.41 δ (s, 3P), methylene at 4.56 δ (s, 2P), deshielded aromatic proton spread over 8.63-8.33 δ, olefinic proton at 8.75 δ and the remaining aromatic protons spread over 7.23-8.23 δ. The PMR spectrum in DMSO revealed NH_2 at 5.9 δ exchangeable with D_2O, olefinic proton at 8.08 δ, the deshielded aromatic proton spread over 7.95-8.41 δ and the remaining aromatic protons spread over 6.93-7.73 δ.

This compound in IR is characterised by NH_2 bands between 3300 and 3450 and (C=O) absorption near 1625 cm^{-1} both in nujol and chloroform solutions. UV : λ_{max}^{EtOH} mμ (log ε) : 225 (4.21), 238 (4.13), 265 (3.27), 281 (3.44) and no absorption in the visible region.

Compound A was recovered unchanged even after treating with stronger acids like sulphuric acid and also with ethanolic hydrogen chloride. The spectral properties of A are explicable if A is represented by trans-3-[(1'-amino-2'-naphthyl)methylene]-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 24. The other products of the reaction were α-naphthylamine, an intractable gum and a lactam which was identified as 25, on the basis of its properties, PMR and IR spectra and mass spectral degradation pattern. The PMR spectrum of compound 25 in CF_3COOH showed methyl signal at 4.11 δ (s, 3P), proton at C-7 at 10.25 δ (s, 1P), protons at C-1 and C-13 spread over 8.83-9.3 δ (m, 2P) and the other aromatic protons spread over 7.76 - 8.41 δ (m, 9P). IR spectrum showed no absorption bands in the region 3300-3500 indicating the absence of any OH, NH or NH_2 groups. It only showed absorption band at 1655 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 253 (4.407),

292 (4.60), 362 (3.43). Mass spectrum indicated the molecular ion peak at m/e 310.

Similarly when 26 was heated with β-naphthylamine hydrochloride, fused zinc chloride in boiling ethanol, trans-3-[(2'-amino-1'-naphthyl)methylene]-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 27 and 6-keto-5-N-methyl benzo[h]naphtho[2,1-b][1,6]naphthyridine 28 were obtained. Here also the amine peak in compound 27 was observed only in DMSO and not in trifluoroacetic acid. Compound 27 was recovered unchanged even after treating with stronger acids and also with ethanolic hydrogen chloride.

PMR spectrum of compound 27 in trifluoroacetic acid showed methyl at 4.25 δ (s, 3P), methylene at 4.96 δ (s, 2P), deshielded aromatic proton spread over 8.66 to 8.78 δ (m, 1P), the olefinic proton and the other aromatic protons spread over 7.58 - 8.3 δ (m, 9P). The amine got protonated, mixed with the acid signals and thus could not be located. In DMSO compound 27 showed methyl at 4.11 δ (s, 3P), D_2O exchangeable NH_2 centred at 5.63 δ (s, 2P), deshielded aromatic proton spread over 8.2 - 8.45 δ (m, 1P), the olefinic proton and the remaining aromatic protons spread over 6.93-8.03 δ (m, 11P).

Compound 27 was characterised by its IR which showed NH_2 bands between 3200 cm^{-1} and 3400 cm^{-1} and carbonyl near 1660 cm^{-1}. The high value of NH_2 bands in both the compounds 24 and 27 suggests that it is not involved inhydrogen bonding ruling out a cis configuration involving an intramolecular hydrogen bonding between the C=O and NH_2.

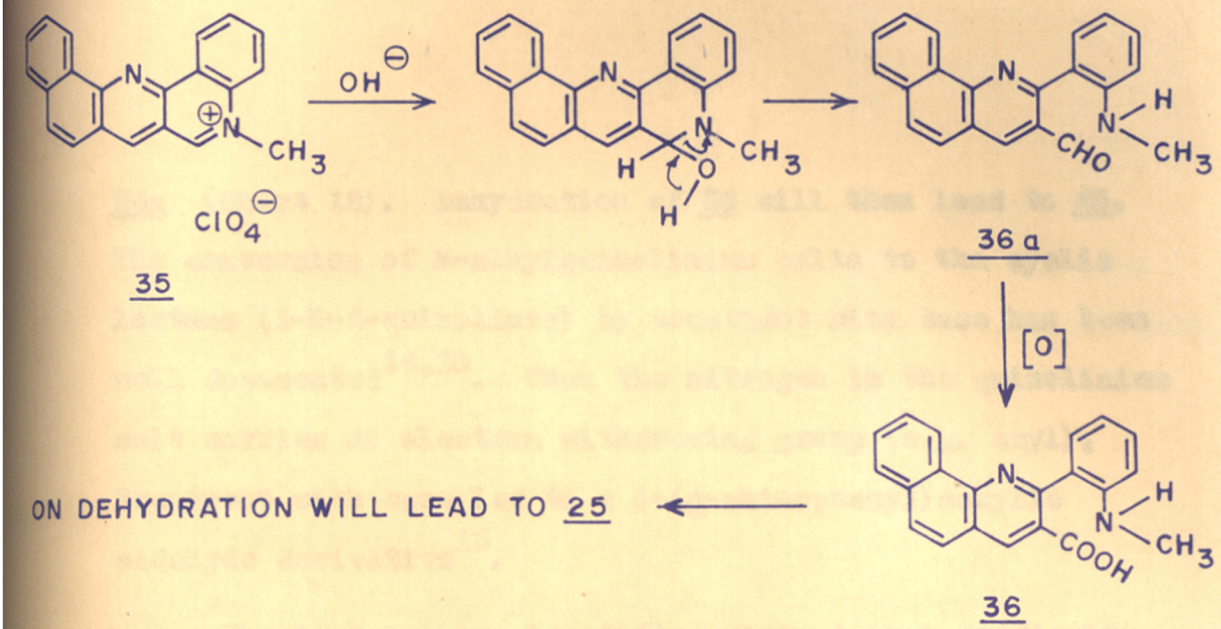
UV of 27 λ_{max}^{EtOH} : 247 (4.83), 280 (4.022) and 290 (4.01) and no absorption in the visible region. Apart from 27 the reaction mixture gave β-naphthylamine, in intractable gum and the lactam 28. The lactam was assigned structure 28 on the basis of its properties, analysis and spectral evidence. Compound 28 in $CDCl_3$ showed methyl at 3.76 δ (s, 3P), proton at C_7 at 9.86 δ (s, 1P) proton at C_1 spread over 8.93-9.26 (m, 1P), proton at C_8 spread over 7.16-8.16 δ (m, 1P) and other aromatic protons spread over 7.16-8.16 δ (m, 8P).

Compound 28 in IR spectrum showed an absorption band at 1655 (C=O), and no absorption in the region 3300-3500 cm^{-1}.
UV : λ_{max}^{EtOH} 227 (4.72), 290 (4.93), 320 (4.35).
Mass spectrum showed a molecular ion peak at m/e 310.

During the above cyclodehydrations using zinc chloride/ arylamine hydrochloride rearrangement has occurred and the

linear products 25 and 28 are formed. In case if the normal cyclisation has occurred, then 5,6-dihydro-5-N-methyl-benzo[f]naphtho[1,2-c][2,7]naphthyridine 25a and 5,6-dihydro-5-N-methyl-benzo[f]naphtho[2,1-c][2,7]-naphthyridine 28a should have been formed. Under the conditions of the reaction, compounds 25a and 28a may suffer disproportionation leading to N-methylquinolium salt which may eventually lead to compounds 25b and 28b on treatment with base during work up [Chart 8]. If 25b and 28b had formed, then the mass spectral fragmentation pattern should have indicated a loss of HCN from the 2,7-naphthyridine moiety. Since there was no such indication in the fragmentation pattern, it may be concluded that the angular products 25b and 28b have not been formed.

The formation of the lactams is explicable if one assumes involvement of intermediates 31, 32, 33 and 34 (Chart IDa). The lactams 25 and 28 were unaffected by strong alkali even at higher temperatures. In order to prepare 25 by an unambiguous route, 5-N-methyl-benzo[h]-naphtho[1,2-b][1,6]naphthyridinium perchlorate 35 (described in Chapter II) was treated with dilute alkali. However this lead to cleavage of 35 yielding the amino acid 36 (probably through the intermediate amino aldehyde

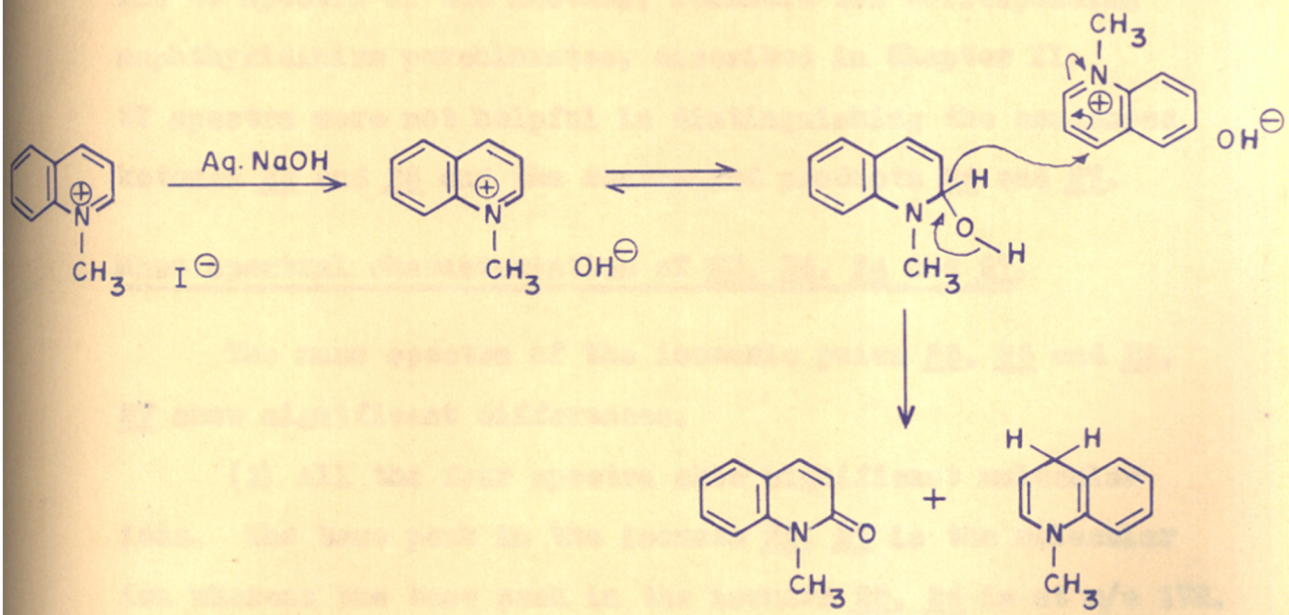


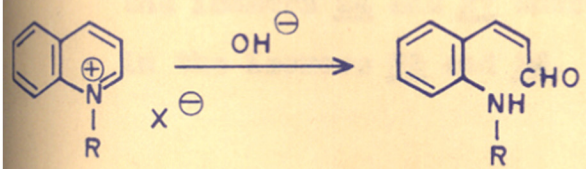
35 36 a

[O]

36

ON DEHYDRATION WILL LEAD TO 25





R = ELECTRON WITHDRAWING GROUP,
eg. $-COCH_3$

CHART 12

36a (Chart 12). Dehydration of 36 will then lead to 25. The conversion of N-alkylquinolinium salts to the cyclic lactams (1-N-2-quinolines) by treatment with base has been well documented[14,15]. When the nitrogen in the quinolinium salt carries an electron withdrawing group (e.g. acyl), treatment with base led to a β-(o-aminophenyl) acrylic aldehyde derivative[16].

The lactams were identified without much difficulty. The UV spectra of the lactams, resemble the corresponding naphthyridinium perchlorates, described in Chapter II. UV spectra were not helpful in distinguishing the condensed ketones 23 and 26 and the rearranged products 24 and 27.

Mass spectral characteristics of 23, 26, 24 and 27.

The mass spectra of the isomeric pairs 23, 26 and 24, 27 show significant differences.

(1) All the four spectra show significant molecular ions. The base peak in the isomers 24, 27 is the molecular ion whereas the base peak in the isomers 23, 26 is at m/e 172.

(2) The peak at m/e 297 (M-OH) is more significant in the isomers 24 and 27 whereas it is relatively less intense in the isomers 23 and 26.

The base peak in the spectra of 23 and 26 is at m/e 172. It's genesis from the molecular ion by the loss of naphthylamine radical is supported by the metastable peak.

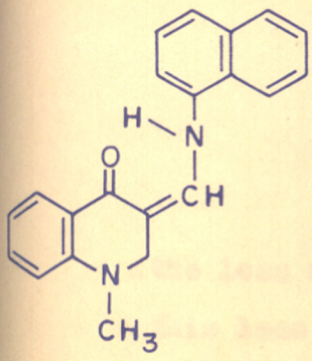
$$M^{+\cdot}_{314} \longrightarrow (172)^{+} + 142 \; ; \; \frac{172^2}{314} = m^{*} \quad (94.21)$$

This fragmentation mode is not favoured in the spectra of 24 and 27. One of the reasons may be the stabilization of the molecular ions of 24 and 27 by conjugation in these compounds as compared to 23 and 26. Also the more favourable heterolytic cleavage of C-N bond in 23 and 26 as compared to the homolytic cleavage of C-C bond in 24 and 27 might be the driving force for this fragmentation in the former pair.

The peak at m/e 297 (M-17), shown in high resolution, may be attributed to the loss of OH and not NH_3.

		Expected	Observed
314	$C_{21}H_{18}N_2O$	314.1419	314.1380
297	$C_{21}H_{17}N_2(-OH)$	297.13917	297.14707
297	$C_{21}H_{15}NO$ $(-NH_3)$	297.1153	

In the absence of deuterium labelling, it is difficult to propose definite fragmentation mechanism for



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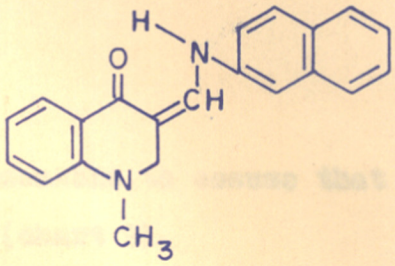

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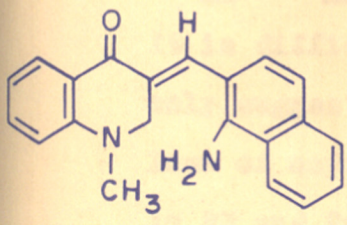

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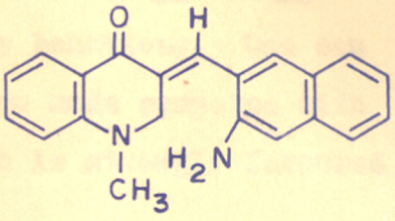

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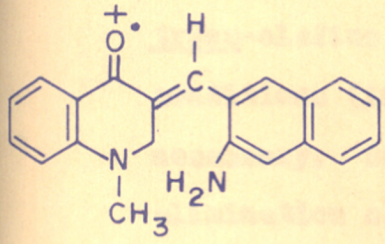
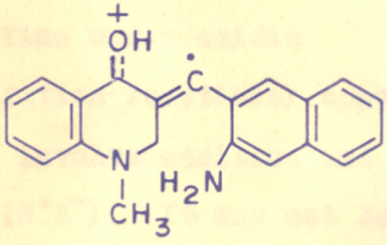
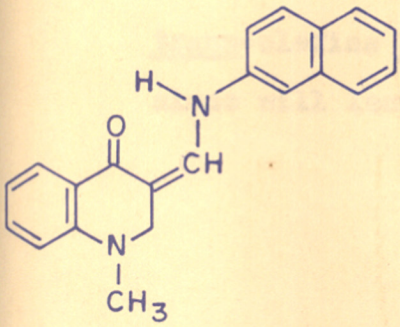






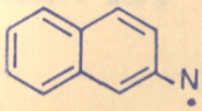
$-C_{10}H_8N$ → m/e 172 [Loss of ]

CHART 9

the loss of OH radical. It is reasonable to assume that this loss occurs by 1,5 mechanism (chart 9).

The loss of OH is more significant in the spectra of 24 and 27 as compared to the spectra of 23 and 26. It is difficult to rationalise this behaviour. One can only suggest that this fragmentation mode competes with loss of naphthylamine radical which is strongly favoured in 23 and 26.

Further work:

Further work on the possible isomerization of the trans-olefins 24 and 27 to cis-olefins under acidic conditions (involved in cyclodehydration reactions) appears necessary. Such a conversion will involve addition and elimination of the acidic reagent (H^+X^-). It may not be surprising, however, if such attempts are unsuccessful since trans-elimination of the added acidic moiety (HX) is likely to be preferred leading to regeneration of the trans-olefins 24 and 27 rather than cis-elimination which alone will lead to cis-isomers 24a and 27a (chart 13).

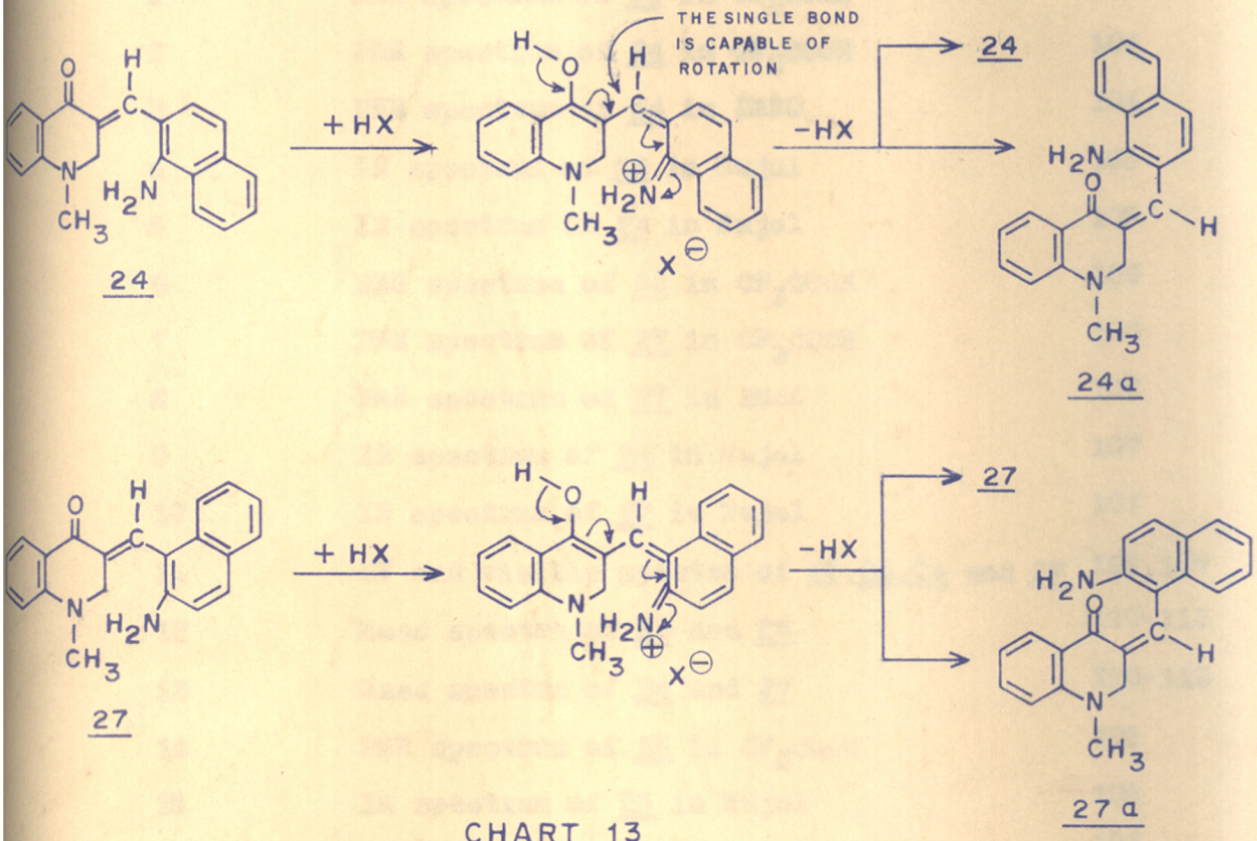
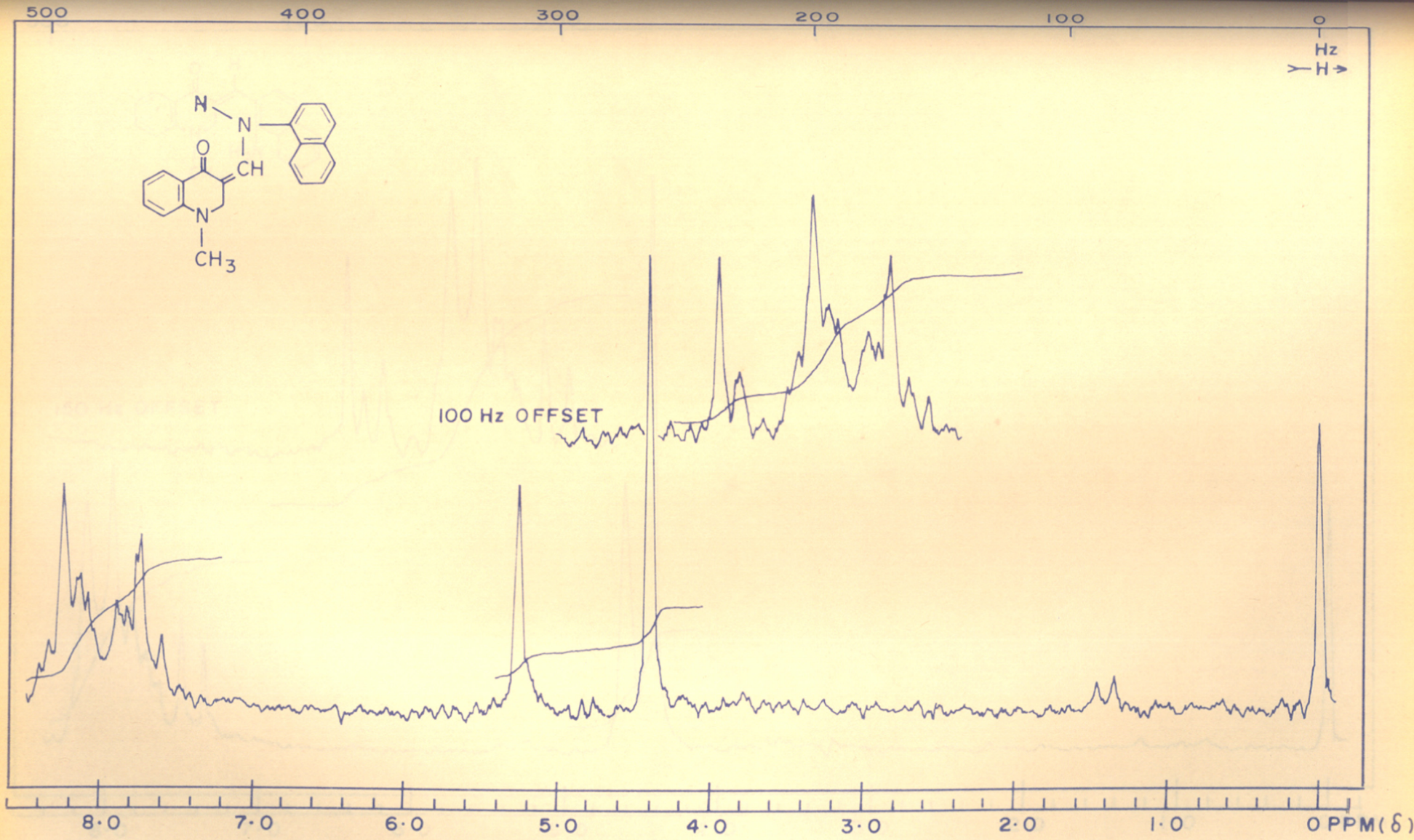
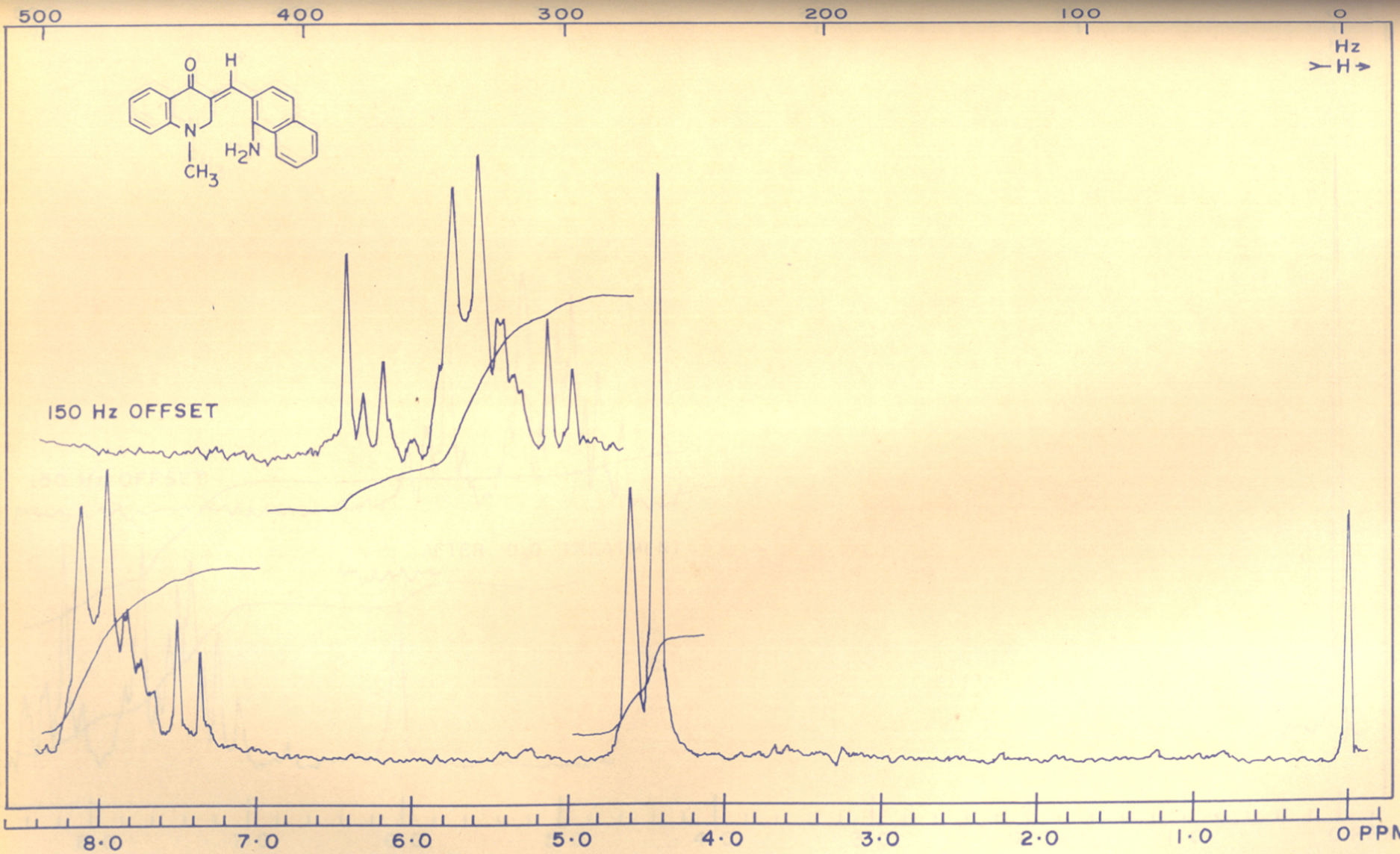


CHART 13

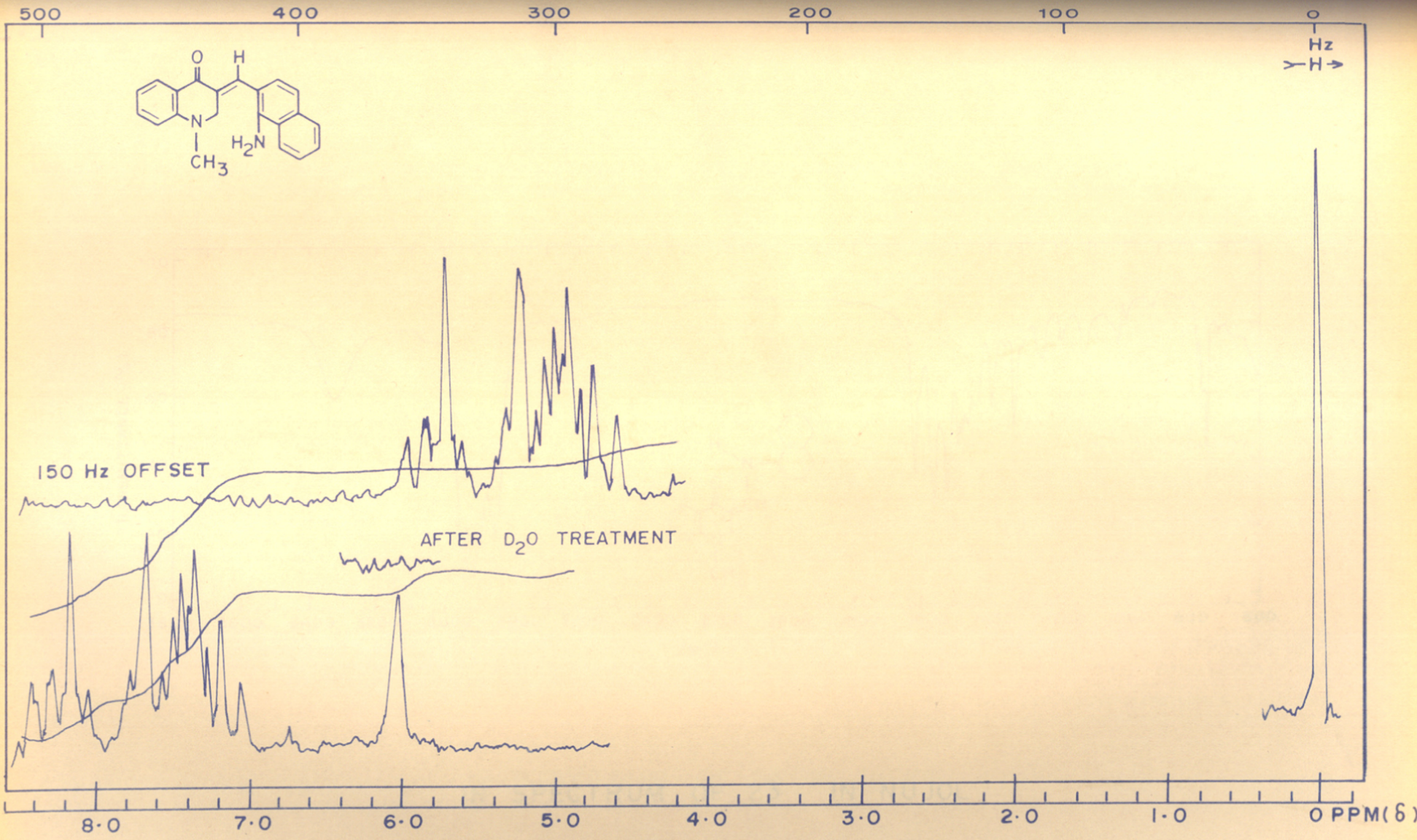
INDEX TO SPECTRAL CHARTS



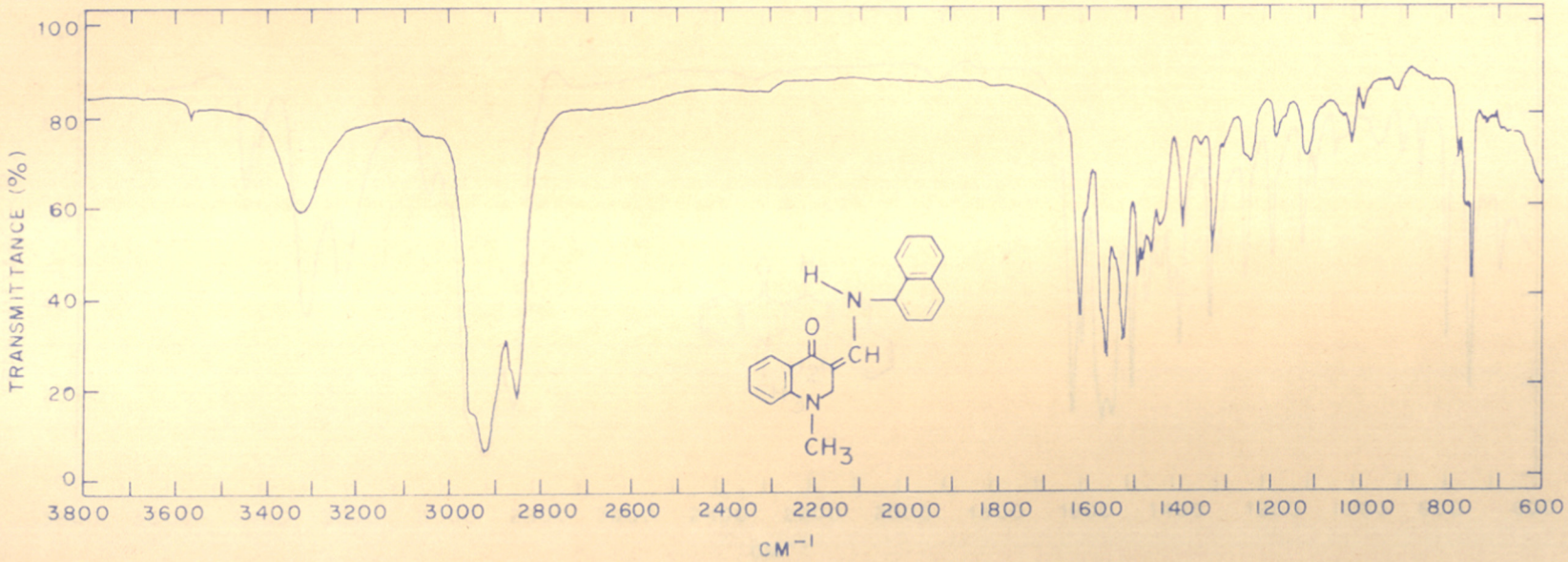
PMR SPECTRUM OF 23 IN CF_3COOH



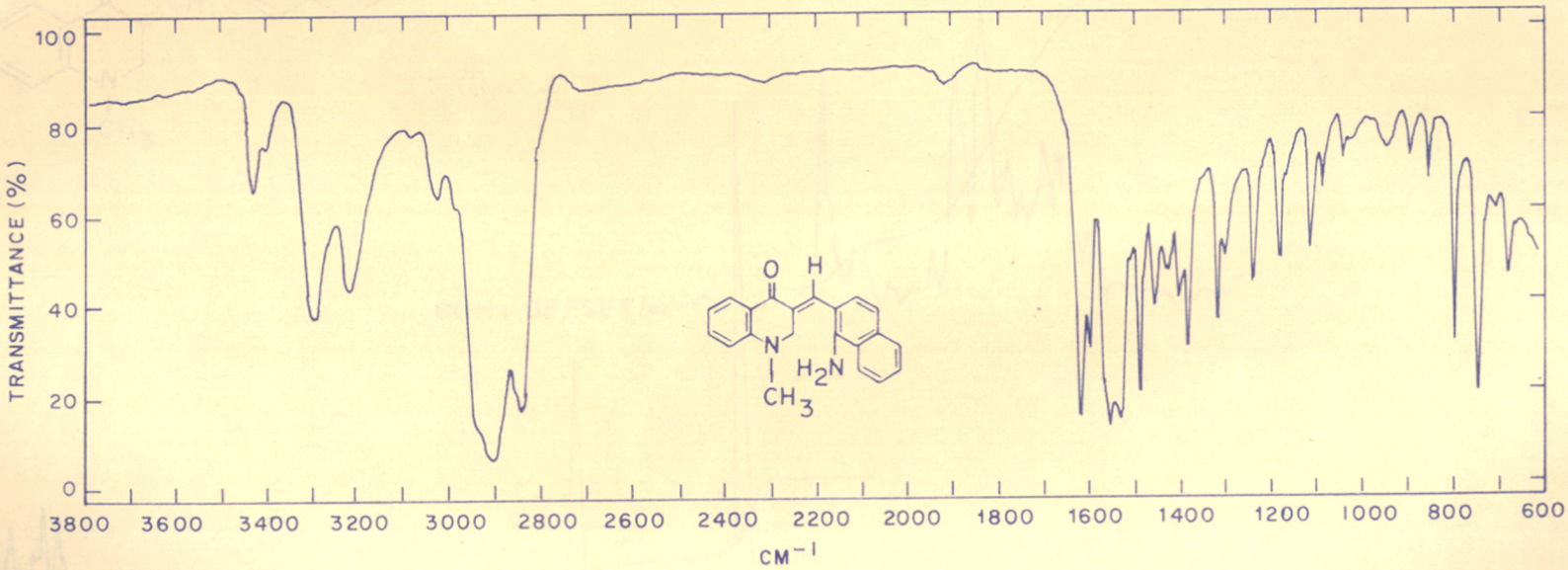
PMR SPECTRUM OF 24 IN CF_3COOH



PMR SPECTRUM OF 24 IN DMSO



IR SPECTRUM OF 23 IN NUJOL



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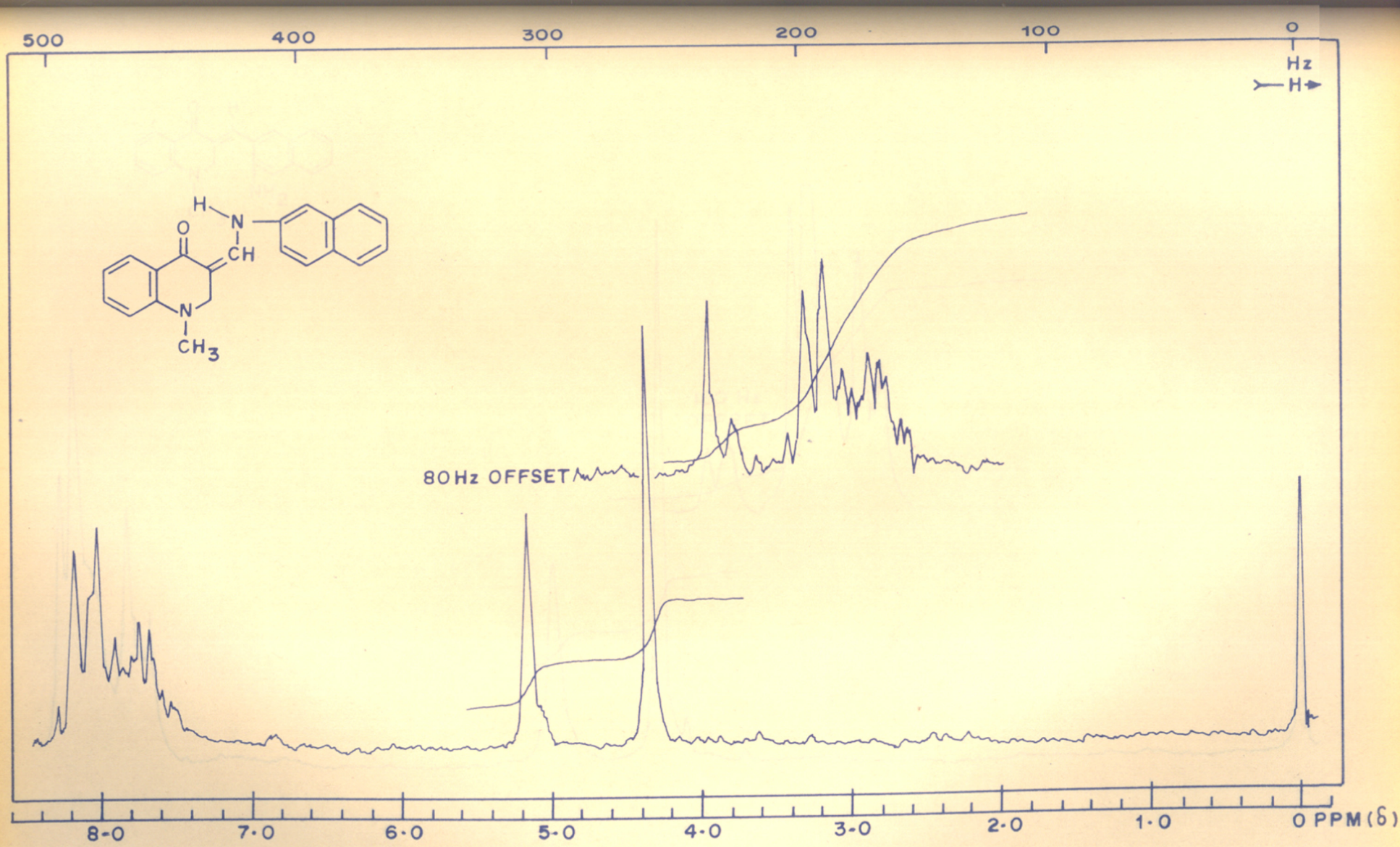
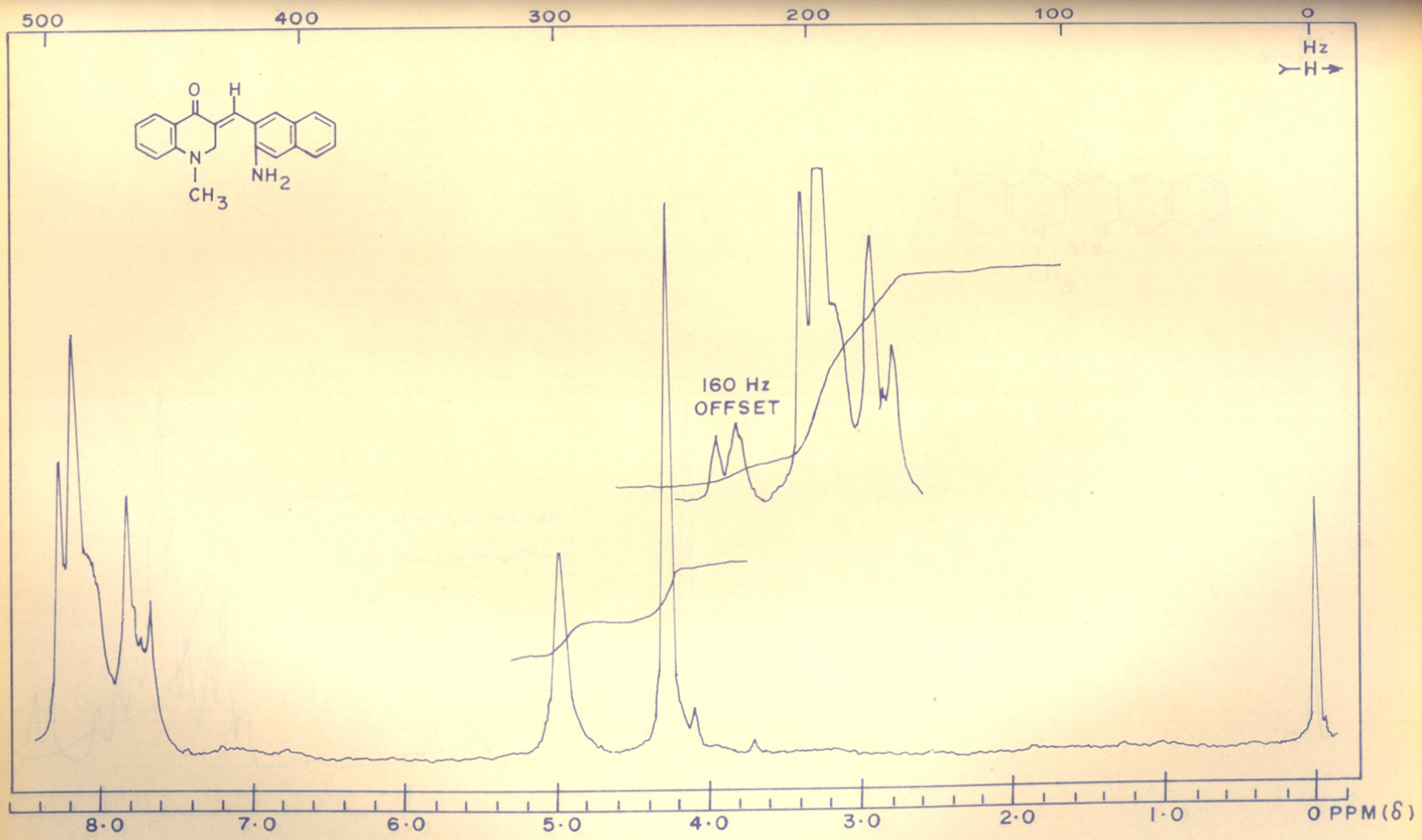
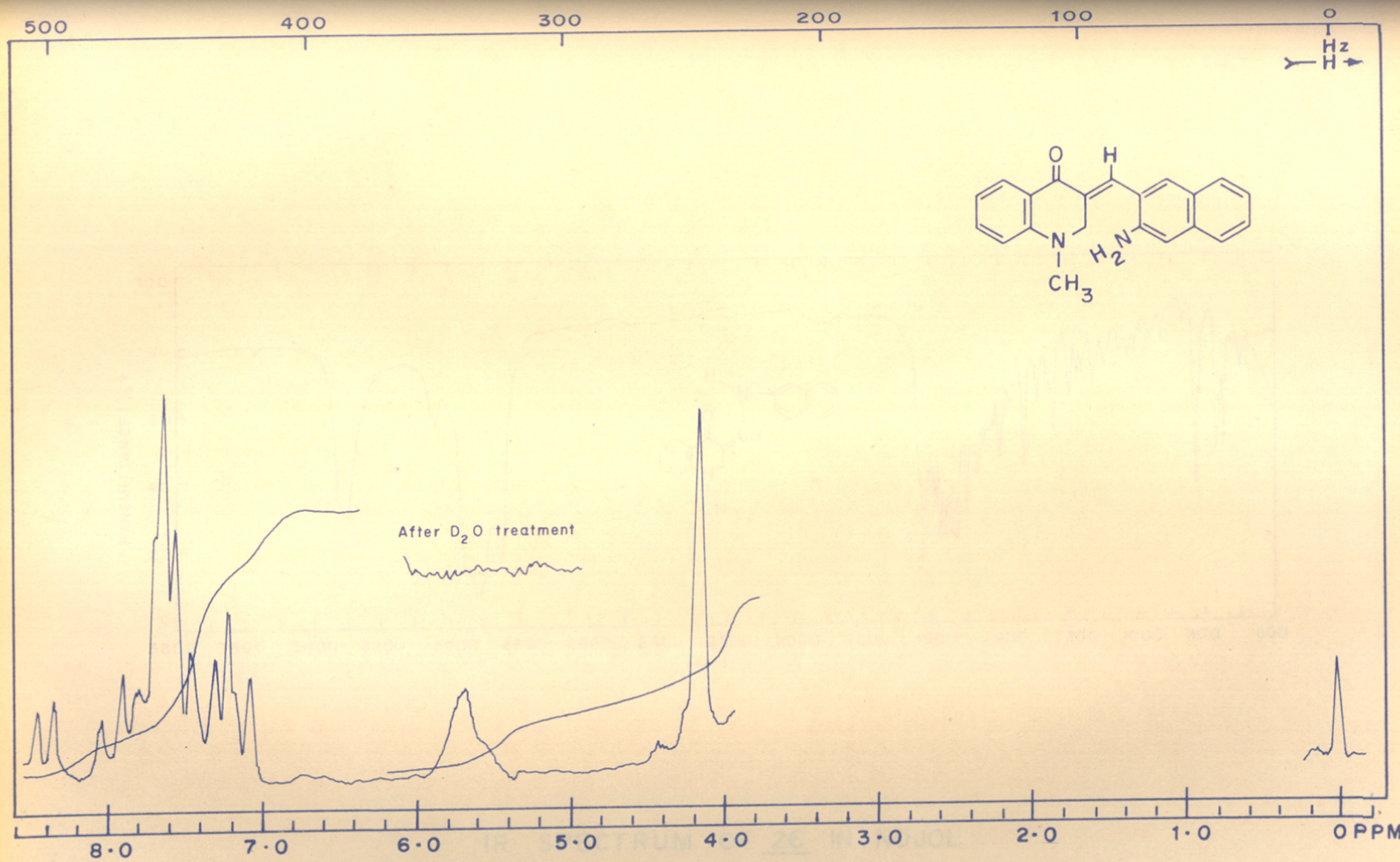


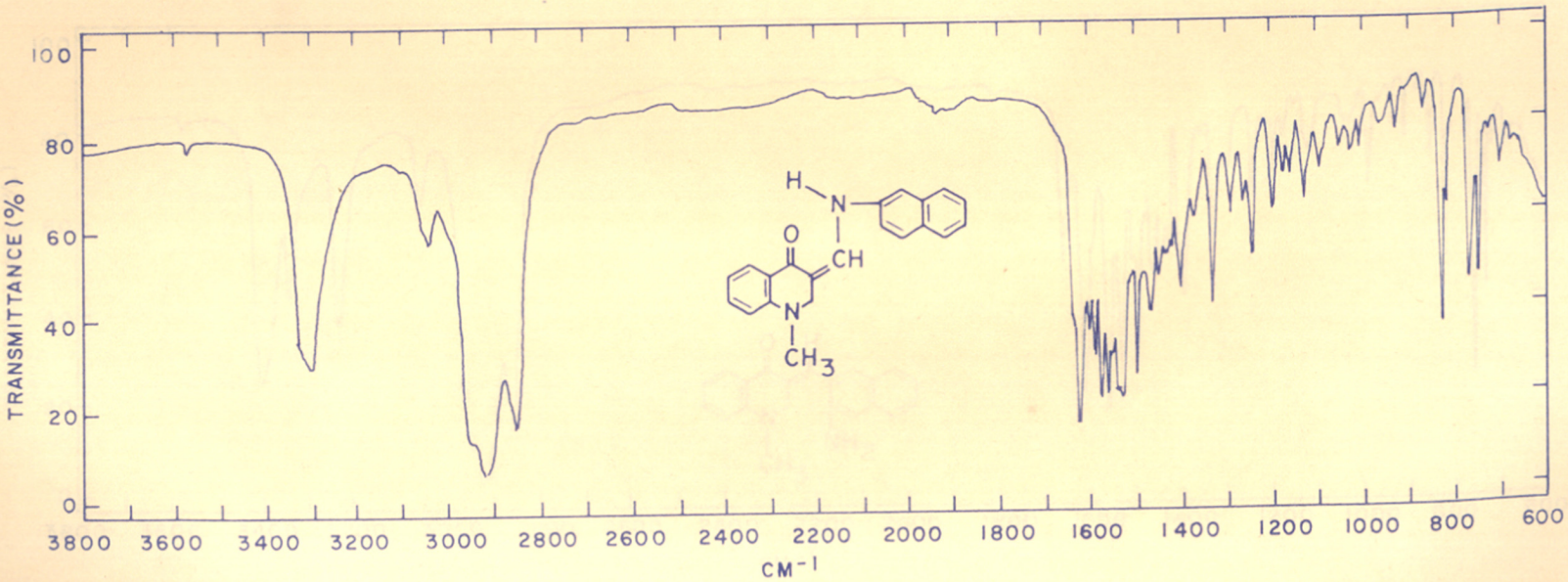
PMR SPECTRUM OF 26 IN CF_3COOH



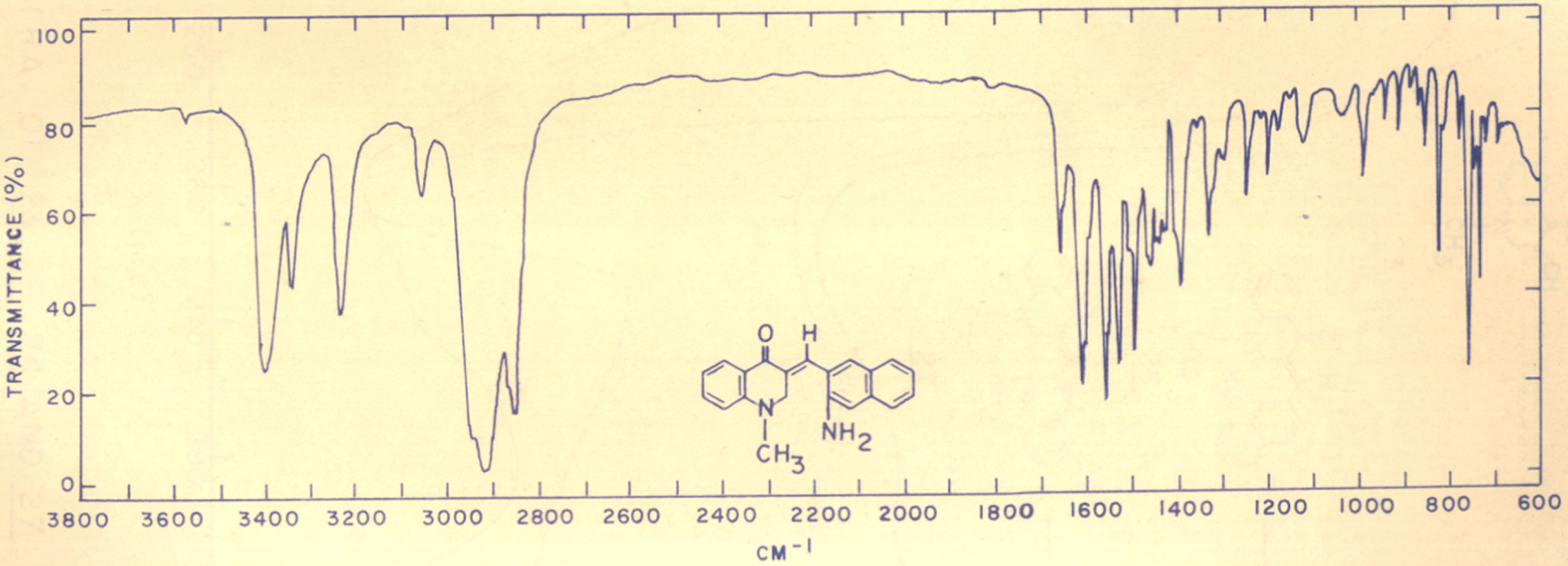
PMR SPECTRUM OF 27 IN CF_3COOH



PMR SPECTRUM OF 27 IN DMSO



IR SPECTRUM OF 26 IN NUJOL



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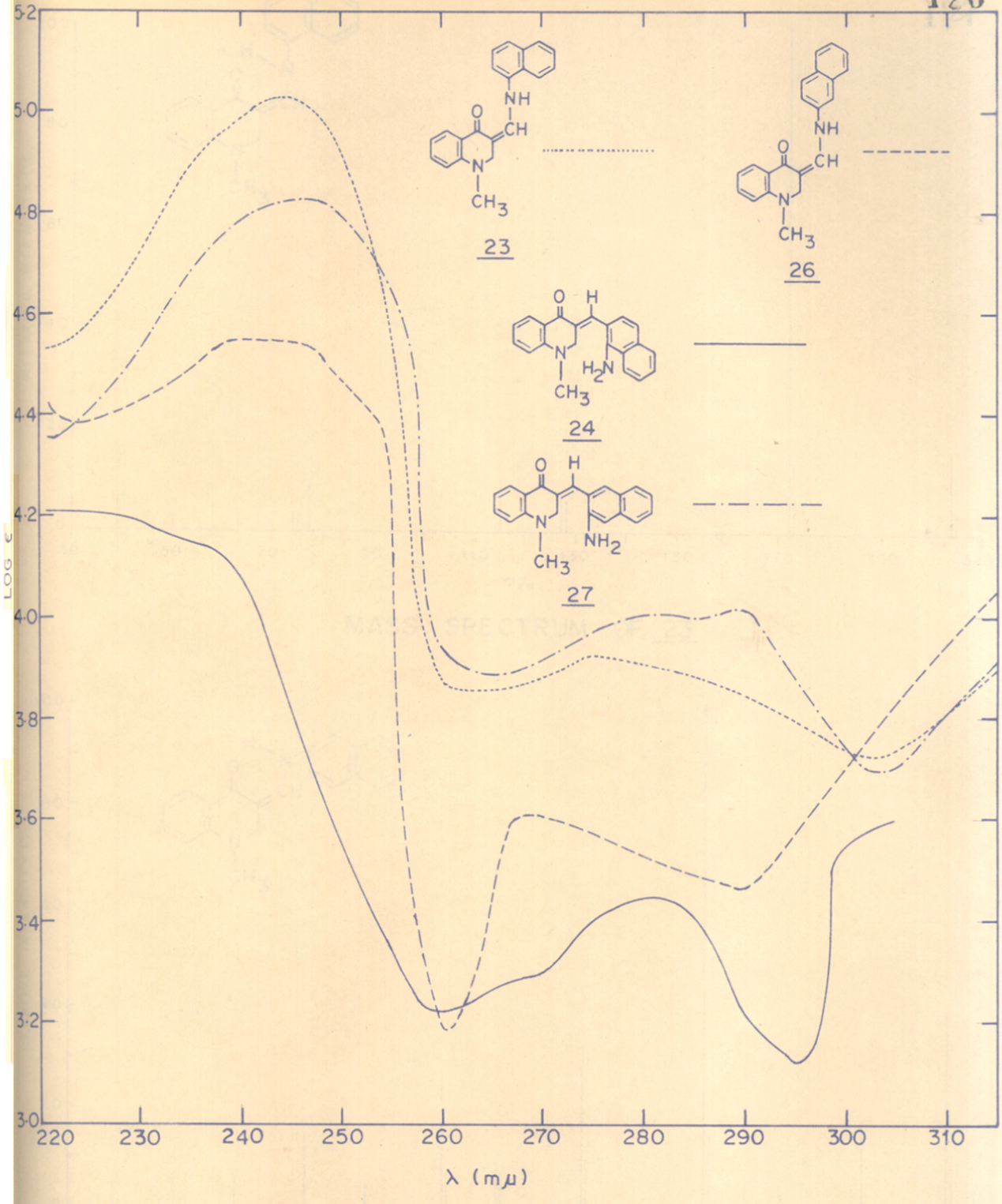
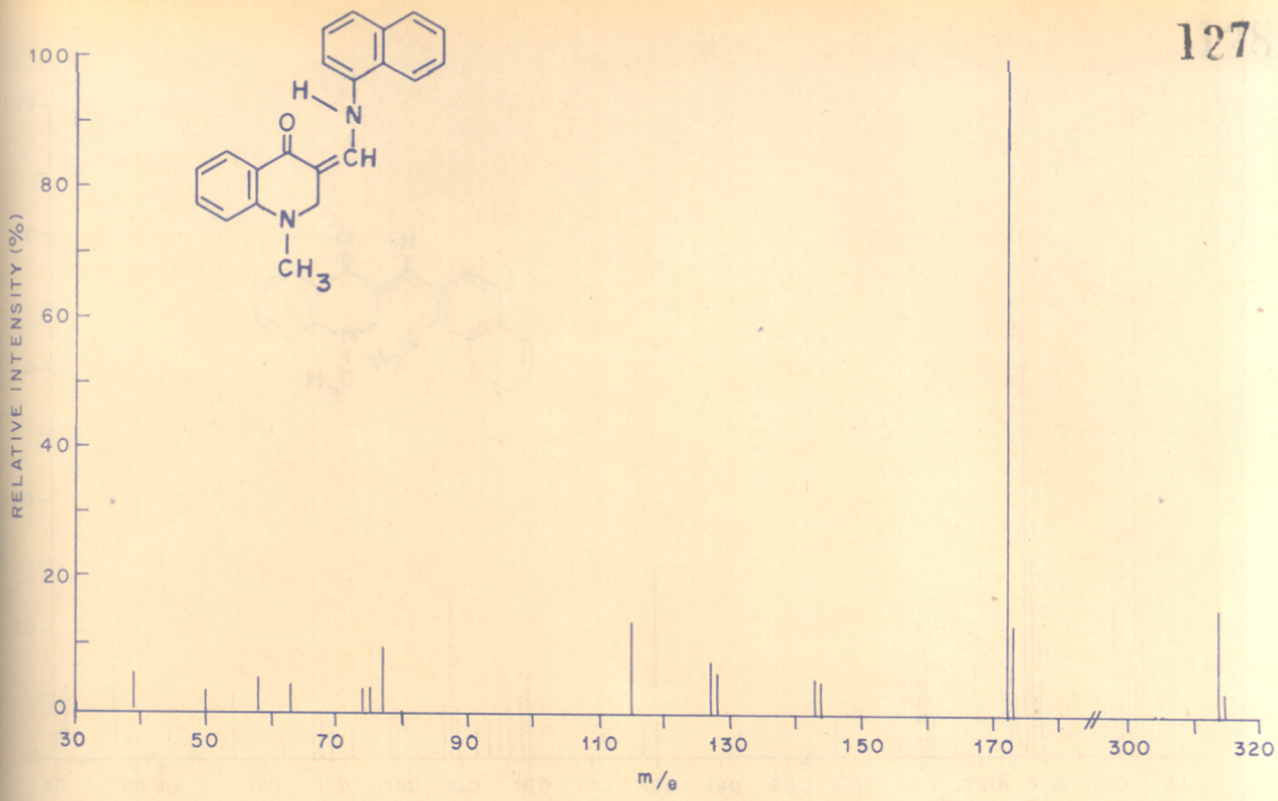
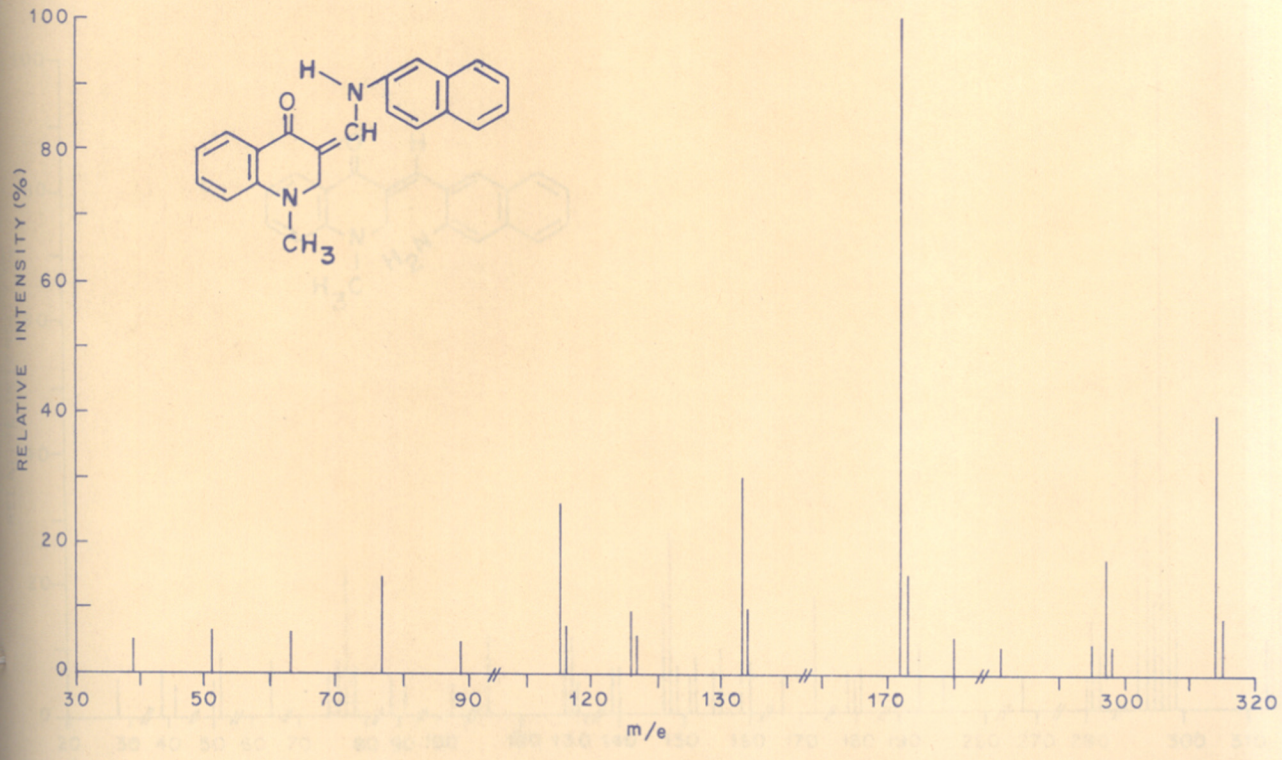


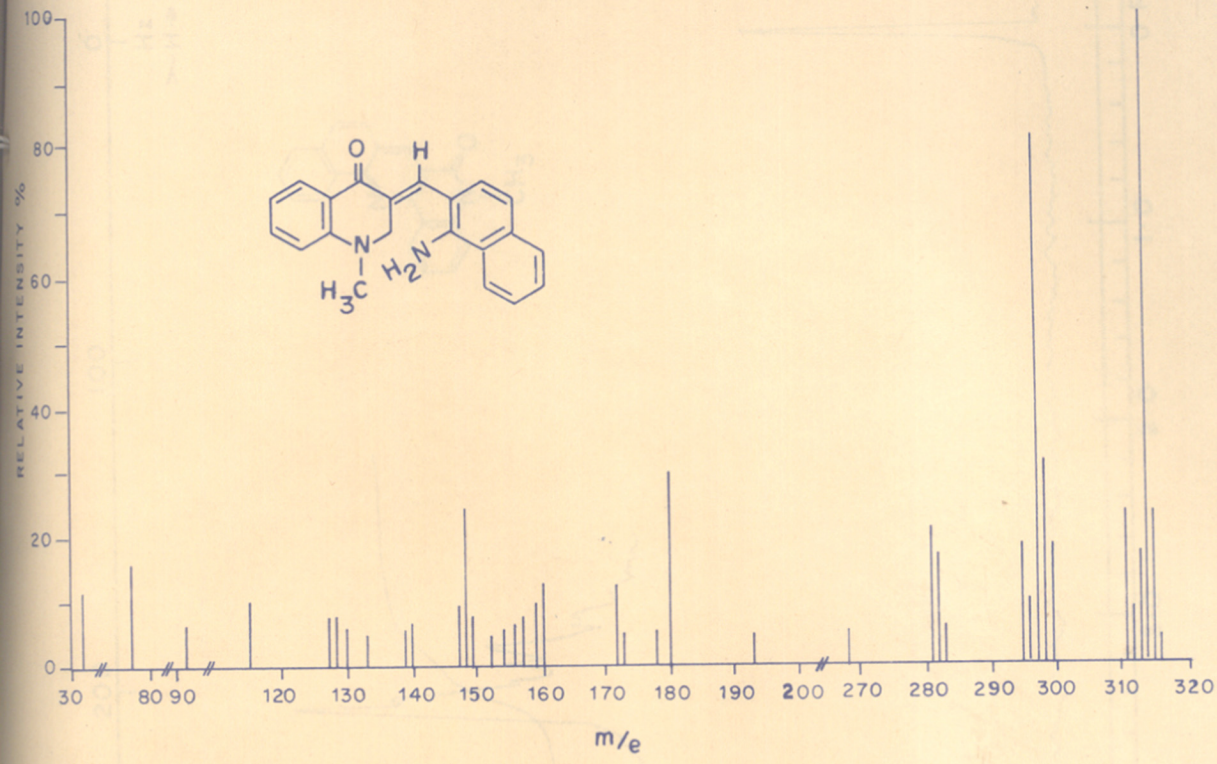
UV SPECTRA OF 23, 26, 24 AND 27 IN ETHANOL



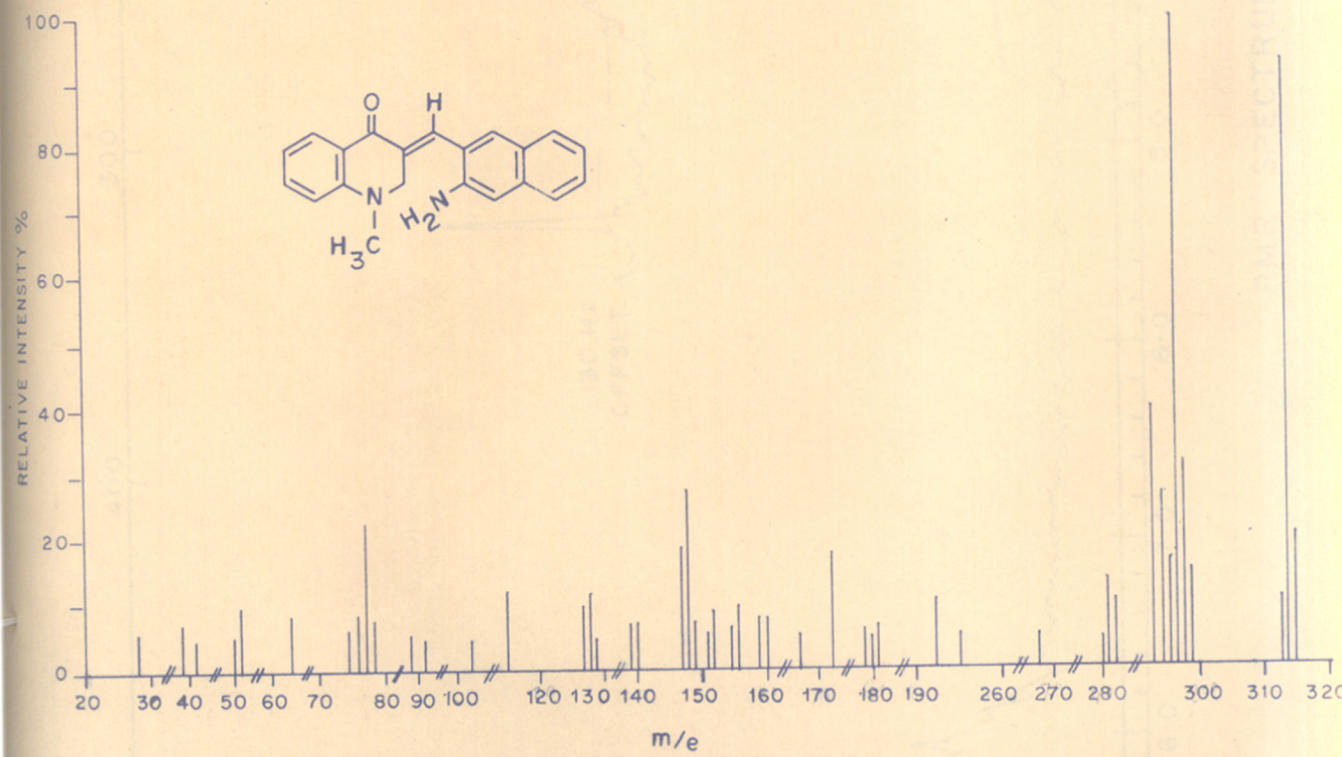
MASS SPECTRUM OF 23



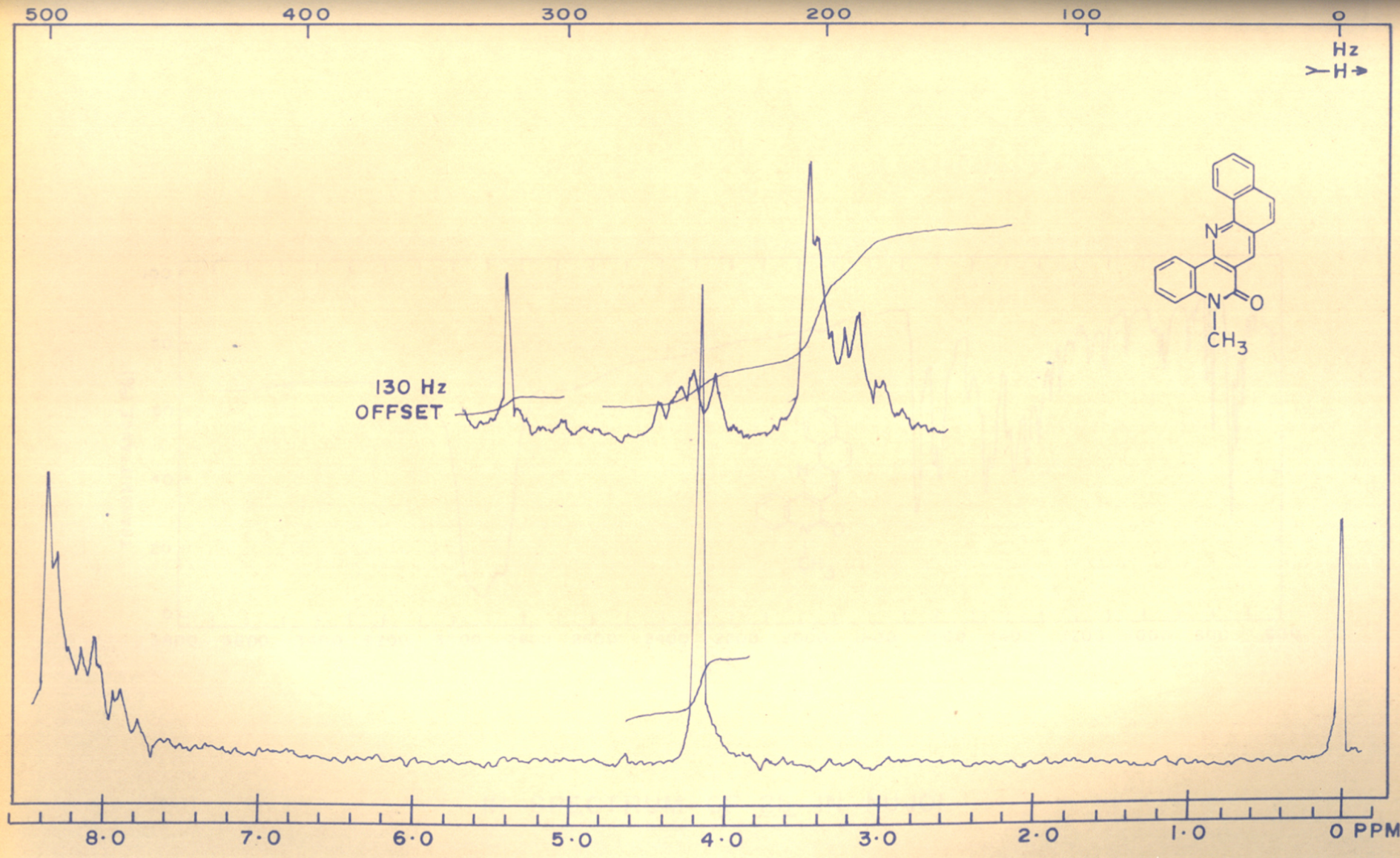
MASS SPECTRUM OF 26



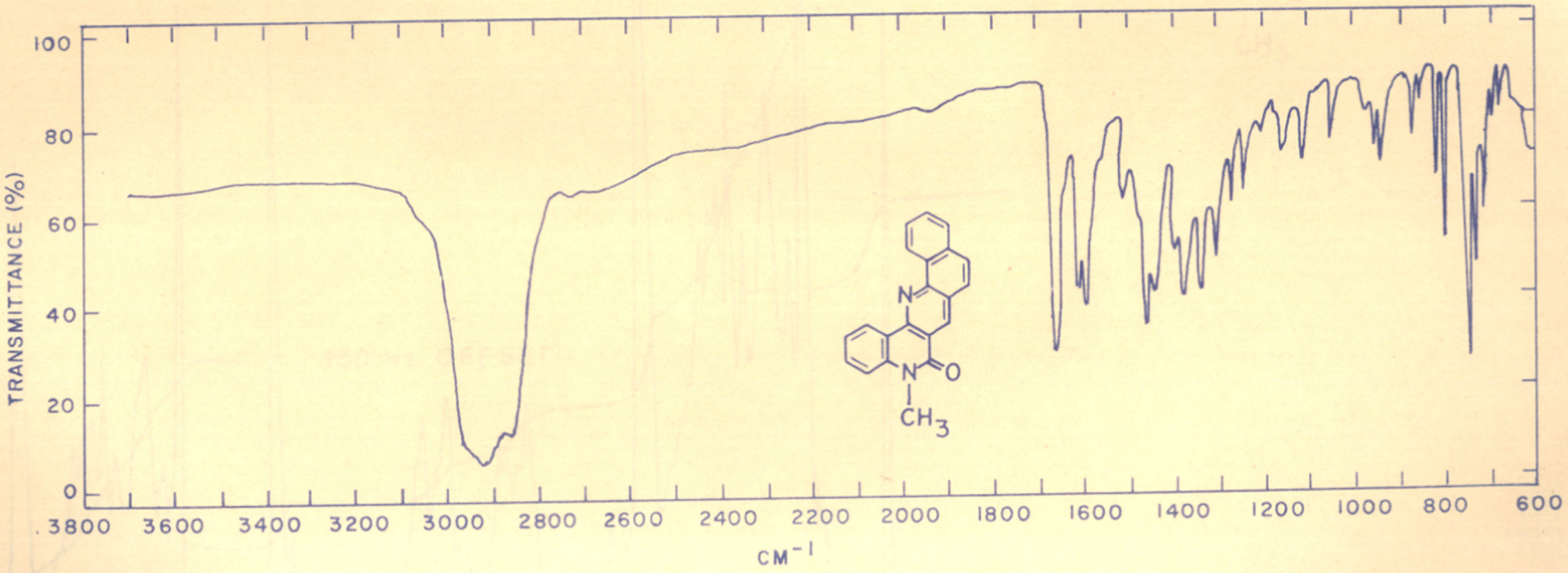
MASS SPECTRUM OF 24



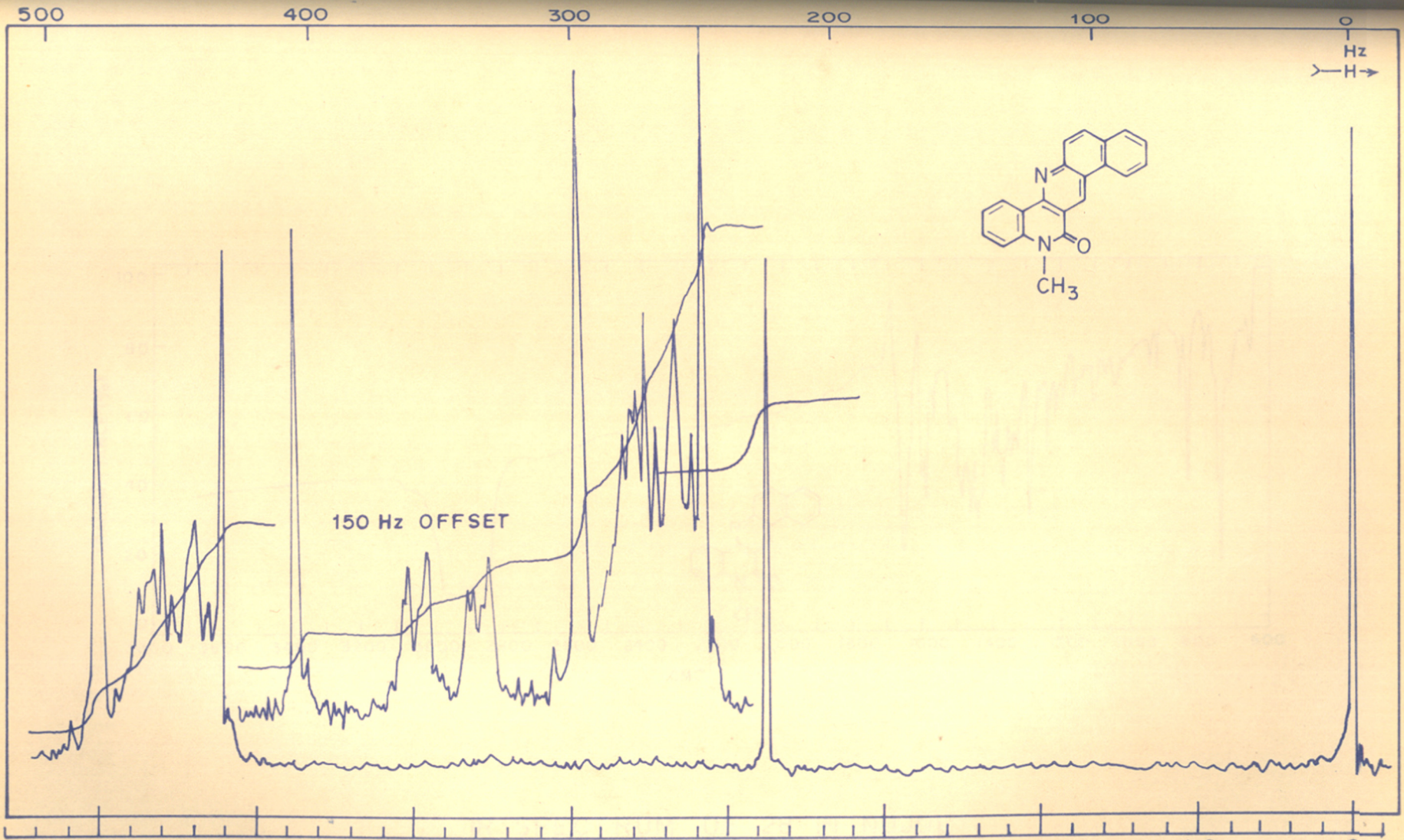
MASS SPECTRUM OF 27



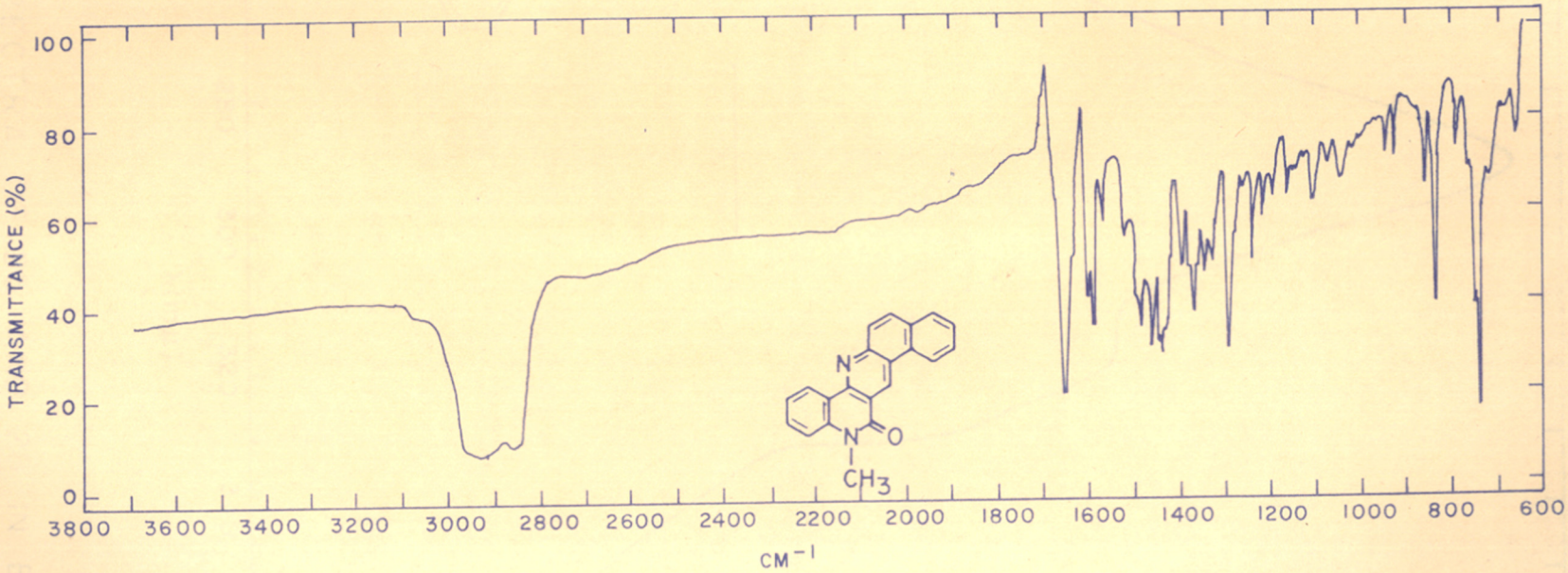
PMR SPECTRUM OF 25 IN CF_3COOH



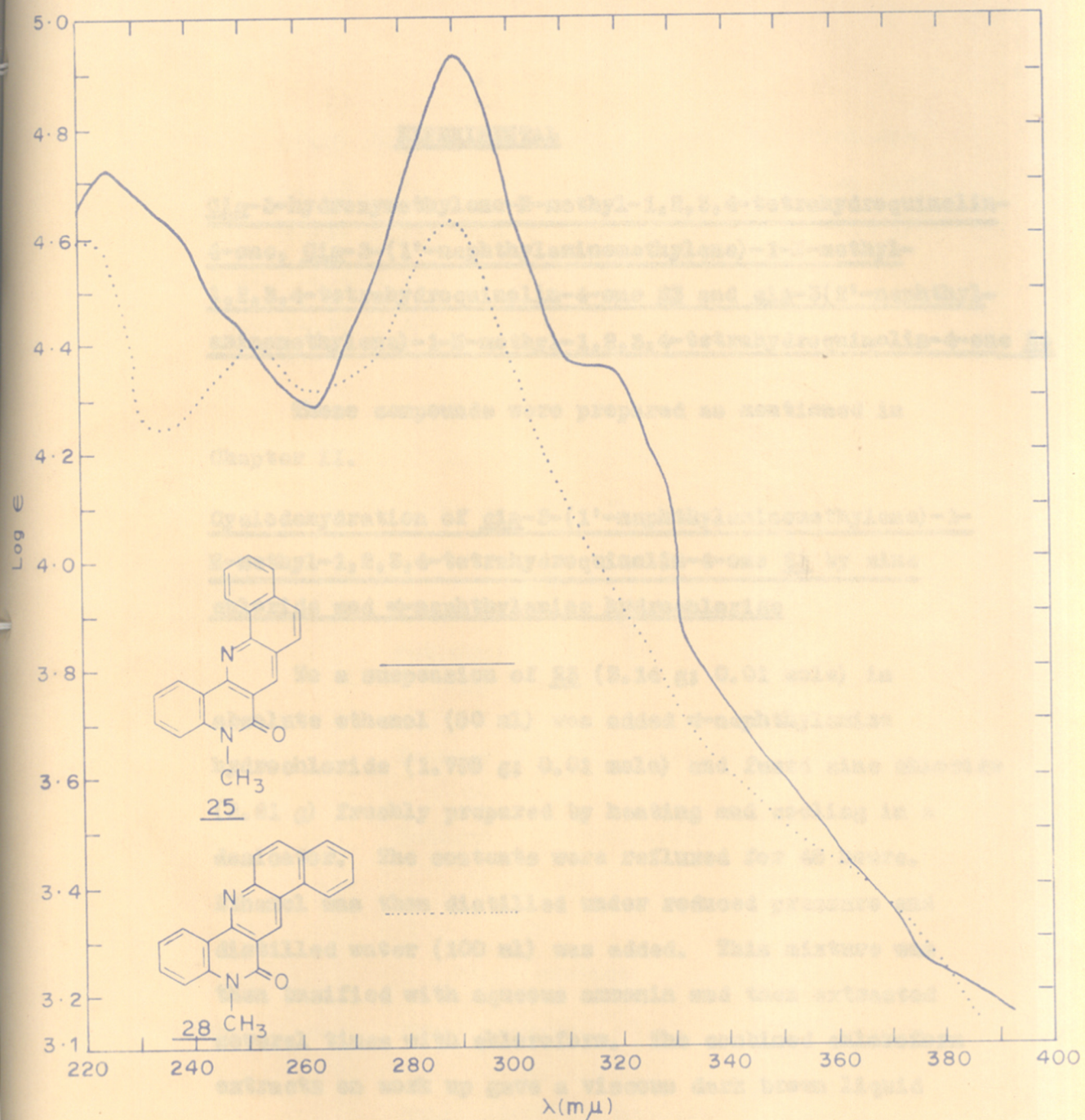
IR SPECTRUM OF 25 IN NUJOL



PMR SPECTRUM OF 28 IN $CDCl_3$



IR SPECTRUM OF 28 IN NUJOL



UV SPECTRA OF 25 AND 28 IN ETHANOL

EXPERIMENTAL

Cis-3-hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one, Cis-3-(1'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 23 and cis-3(2'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 26

These compounds were prepared as mentioned in Chapter II.

Cyclodehydration of cis-3-(1'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 23 by zinc chloride and α-naphthylamine hydrochloride

To a suspension of 23 (3.14 g; 0.01 mole) in absolute ethanol (50 ml) was added α-naphthylamine hydrochloride (1.795 g; 0.01 mole) and fused zinc chloride (2.61 g) freshly prepared by heating and cooling in a desicator. The contents were refluxed for 48 hours. Ethanol was then distilled under reduced pressure and distilled water (100 ml) was added. This mixture was then basified with aqueous ammonia and then extracted several times with chloroform. The combined chloroform extracts on work up gave a viscous dark brown liquid with green fluorescence. This was mixed with chloroform: methanol (80:20) and was kept overnight at 0°, when a

white solid (0.270 g; fraction A) seperated which was filtered out. The mother liquor on concentration gave a thick brown liquid with a green fluorescence (4.19 g) which was then chromatographed. The details of chromatography are given below:

Chromatogram I

Total Compound charged = 4.19 g

Alumina (neutral) = 100 g (grade II)

Fraction (50 ml)	Compound No.	Eluent	Remarks	Weight (g)
1-6	B	Pet.ether : Benzene 50 : 50 To Benzene : Ethyl acetate 90 : 10	Black liquid from which α-naphthylamine crystallised out.	1.404
7-16	C	Benzene : Ethyl acetate 75 : 25 To Ethyl acetate	Starting material, lactam and the rearranged product as shown by TLC	1.444
17-26	D	Ethyl acetate To Ethyl acetate : Methanol 75 : 25	Black tarry liquid	0.940

Total recovery of the compound = 3.788 g

The fraction C containing all the three products was subjected to a second chromatography. This was necessary to separate the starting condensed amine, the lactam and the rearranged product which have very close R_f values.

Chromatogram II

Total compound charged = 1.444 g (C)

Alumina (neutral) = 50 g (grade II)

Fraction (25 ml)	Compound No	Eluent	Remarks	Weight (g)
1-2	C_1	Benzene To Benzene : Ethyl acetate 90 : 10	White solid mp 257°	0.085 g
2-7	C_2	Benzene : Ethyl acetate 90 : 10 To Benzene : Ethyl acetate 75 : 25	White solid mp 170-190°	0.465 g
8-10	C_3	Benzene : Ethyl acetate 75 : 25 To Ethyl acetate	White solid mp 200-240°	0.670 g

Total recovery = 1.220 g

Fraction C_1 - was crystallised from methanol as white flakes (0.075 g; yield 2.4%).
m.p. 260°, confirmed as the lactam 25.

Fraction C_2 - mixture of the condensed ketone and a little of the rearranged amine.

Fraction C_3 - Contains a little of the condensed ketone 23 and the rearranged product 24. crystallised 10 times, from chloroform: methanol and methanol as solvents till a constant melting point is reached to remove 23 (yield 450 mg).

Fraction A (obtained from the reaction mixture directly, 0.270 g) was identical in all respects with the crystalline compound obtained in fraction C_3 after crystallisations. Total yield of Compound 24 = 0.720 g (23.6%), m.p. 266°.

Cyclodehydration of cis-3-(2'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 26.

Cyclodehydration of 26 was carried out on similar lines to the one described above with the same weight of the reactants.

During the final work up, the combined chloroform extracts on evaporation to dryness gave a brown viscous liquid which was directly chromatographed. No solid could be isolated from the viscous liquid before chromatography, as was the case in the previous experiment.

The compound was chromatographed twice and crystallised several times in order to get pure compounds. The purification details are described below:

Chromatogram I

Total compound charged = 3.8 g

Alumina (neutral) - 100 g (Grade II)

Fraction (50 ml)	Compound No.	Eluent	Remarks	Weight (g)
1-4	A	Pet ether : Benzene 50 : 50	Yellow liquid from which yellowish white needles separated out.	0.256
5-7	B	Benzene	Dark reddish brown liquid	0.870
8-19	C	Benzene : Ethyl acetate 90 : 10 To Benzene : Ethyl acetate 25 : 75	Reddish brown liquid from which white solid separated out	1.50
20-28	D	Benzene : Ethyl acetate 25 : 75 To Ethyl acetate : methanol 75 : 25	Dark viscous black liquid	1.057

Total recovery = 3.68 g

Fraction A - The solid separated was crystallised from chloroform (yield, 0.15 g; 4.8%) mp 255°. Identified as the lactam 28.

Fraction B - Comprised mostly of naphthylamine and also a little of the condensed ketone 26.

Fraction C - The solids from this fraction containing the condensed ketone 26 and the rearranged amine 27 (showing close R_f values) were rechromatographed.

Fraction D - Intractable gums resulted

Chromatogram II

Total compound charged = 1.5 g [C]

Alumina (neutral) - 50 g (grade II)

Fraction No. (25 ml)	Compound No.	Eluent	Remarks	Weight (g)
1-3	C_1	Benzene To Benzene : Ethyl acetate 90 : 10	Reddish brown solution yielding brown crystalline solids	0.263
3-9	C_2	Benzene : Ethyl acetate 90 : 10 To Benzene : Ethyl acetate 50 : 50	White solids separated	0.654

Total recovery = 0.917 g

Fraction C_1 - showed the presence of condensed ketone 26 with a little rearranged product 27.

Fraction C_2 - contains mainly the rearranged compound 27 with a little condensed ketone. Crystallised from chloroform : methanol (20:80), several times, till a constant m.p. was obtained, to give 27 (0.575 g; yield 17%), m.p. 235°.

Elementary analyses and physical data of the above compounds are given in table 1.

TABLE 1

Compound No.	g/yield %	Properties, solvent, m.p.	Found			Required		
			C	H	N	C	H	N
23	-	White needles, methanol, 235°	79.9	5.4	9.0	80.2	5.7	8.9
24	0.72/23.6	White crystals, methanol, 266°	80.67	5.27	8.64	80.2	5.7	8.9
25	0.075/2.4	White flakes, methanol, 260°	80.72	4.71	8.64	81.3	4.5	9.0
26	-	White needles, methanol, 214°	79.8	5.4	9.1	80.2	5.7	8.9
27	0.575/17	White needles with brown tint, methanol, 235°	80.7	5.31	8.71	80.2	5.7	8.9
28	0.15/4.8	Yellowish white needles, chloroform, 255°	81.44	4.39	8.73	81.3	4.5	9.0

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CHAPTER IV

MISCELLANEOUS CYCLODEHYDRATIONS

In the previous chapters the synthesis of tetracyclic and pentacyclic ring systems containing nitrogen and sulphur has been described. The aim of this work was to prepare systems like dibenzonaphthyridines, thiopyranoquinolines and thiopyranothiopyrans which are shown in chart 1 and 2.

We were also interested in preparing some of the angular cyclised products 5, 6, 7 and 8. Our earlier work indicated that a good method for the preparation of angular (normal) cyclization products would be by cyclodehydration of 3-arylaminomethyl-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 1, 3-arylmercaptomethyl-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 2, 3-arylaminomethylthiochroman-4-ones 3 and 3-arylmercaptomethylthiochroman-4-ones 4 by treatment with PPA (in presence or absence of a hydride acceptor). Cyclodehydration of cis-3-arylaminomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 9, 3-arylmercaptomethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones 10, cis-3-arylaminomethylenethiochroman-4-ones 11 and 3-arylmercaptomethylenethiochroman-4-ones 12 by interaction with lactic acid or formic acid, on the other hand, may be expected to lead to linear products 13, 14, 15 and 16 respectively.

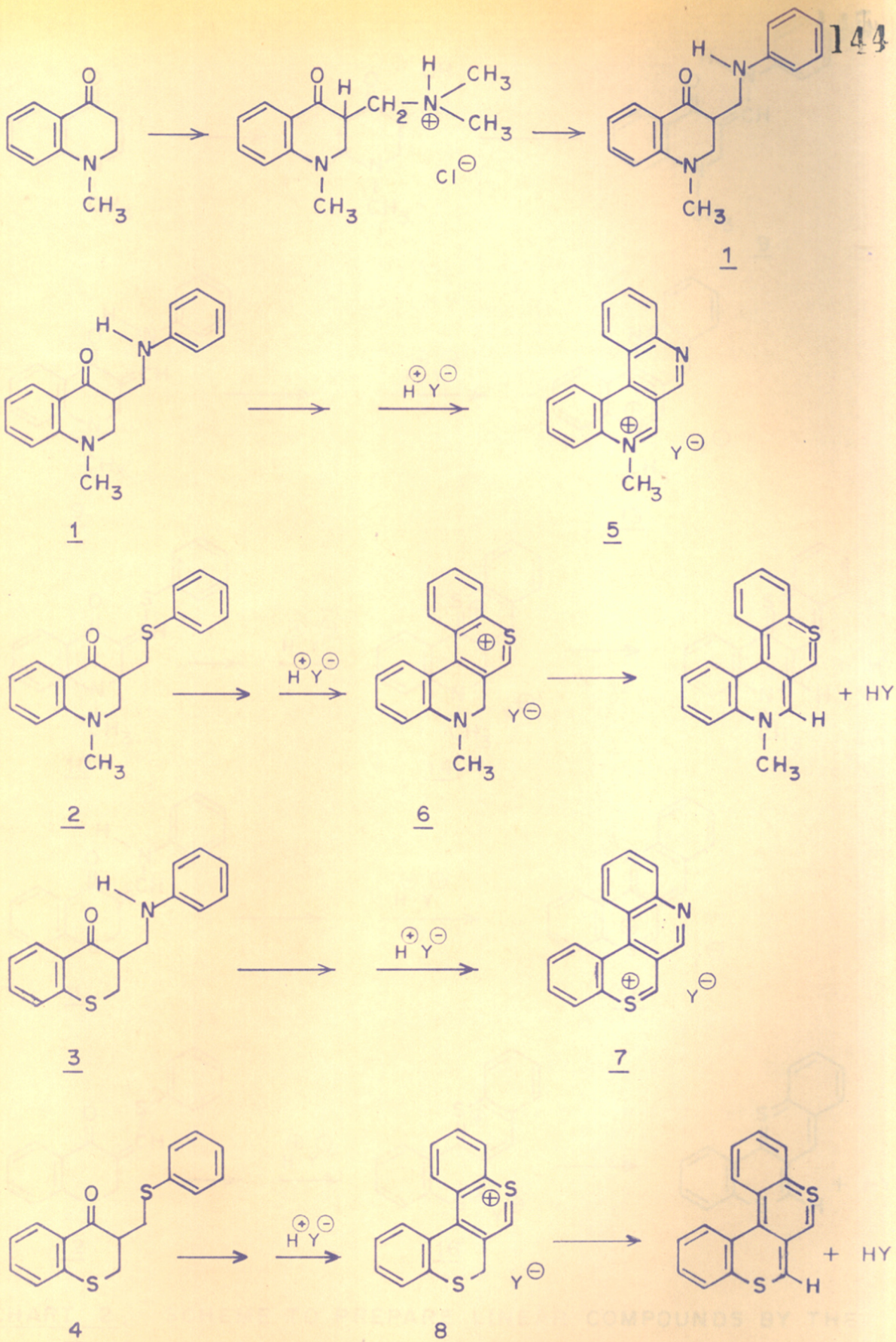


CHART 1. SCHEME TO PREPARE SOME OF THE ANGULAR COMPOUNDS BY THE CYCLODEHYDRATION OF 3-ARYLAMINOMETHYLKETONES.

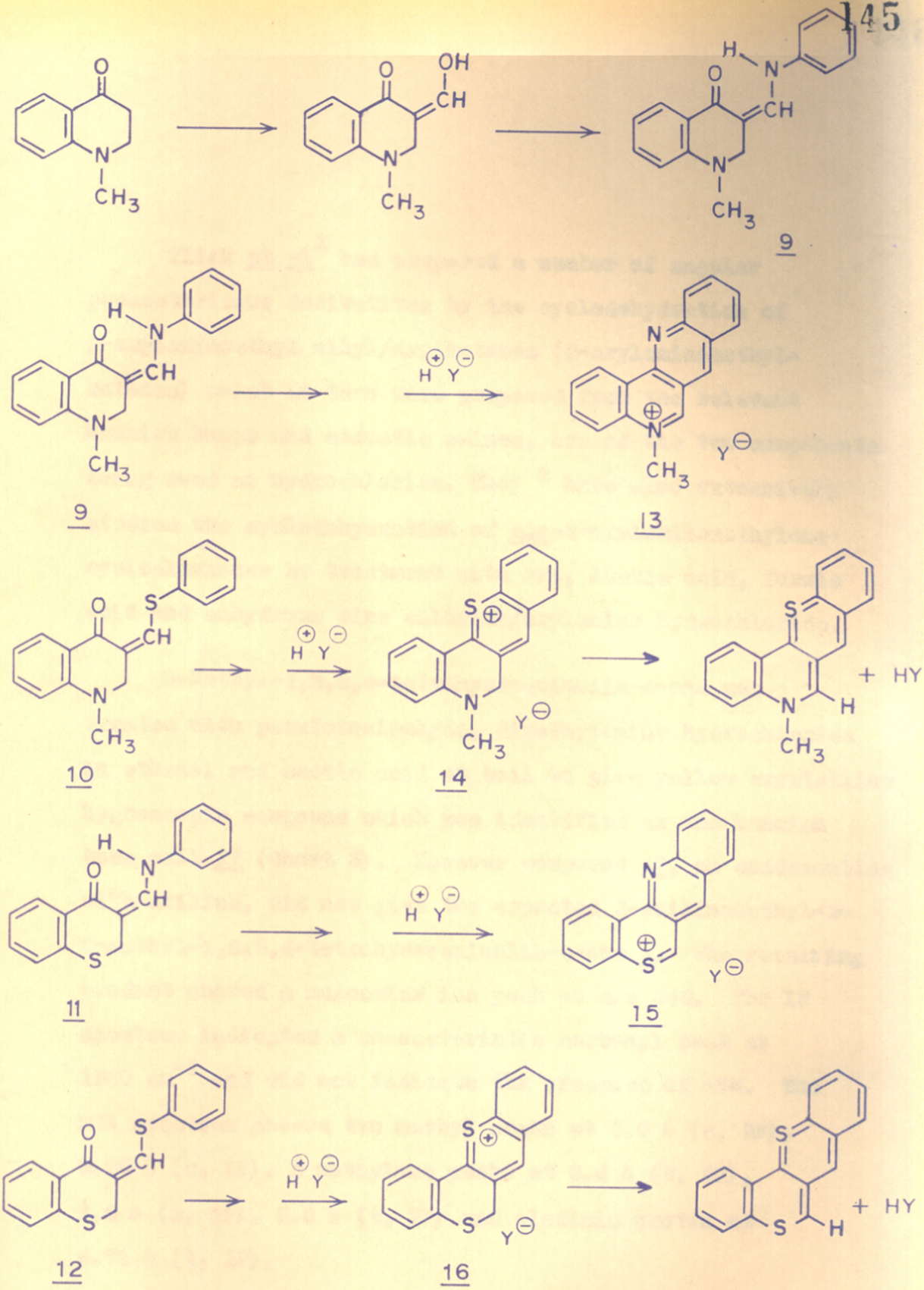


CHART 2. SCHEME TO PREPARE LINEAR COMPOUNDS BY THE CYCLODEHYDRATION OF Cis-3-ARYLAMINOMETHYLENE-KETONES

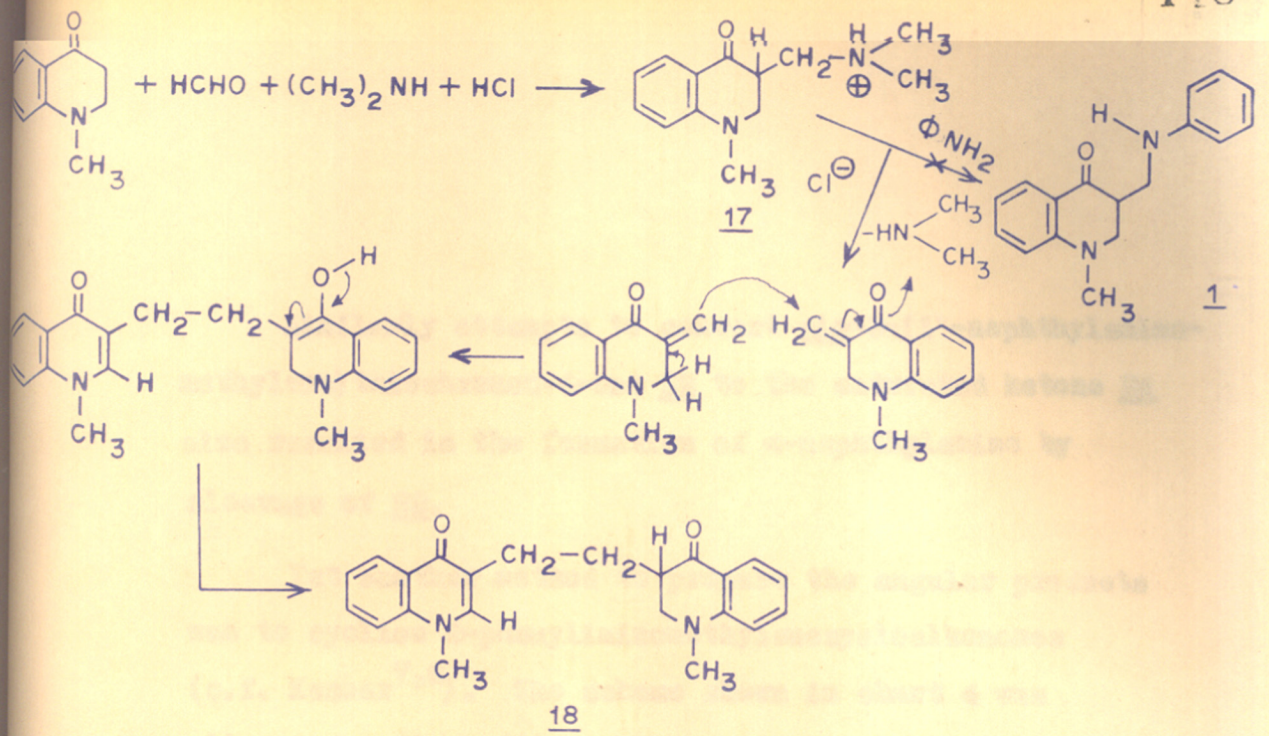
Tilak *et al*[1] had prepared a number of angular phenanthridine derivatives by the cyclodehydration of β-arylaminoethyl alkyl/arylketones (2-arylaminomethyl-ketones) which in turn were prepared from the relevant Mannich bases and aromatic amines, one of the two components being used as hydrochloride. They[2] have also extensively studied the cyclodehydration of *cis*-2-arylaminomethylene-cycloalkanones by treatment with PPA, lactic acid, formic acid and anhydrous zinc chloride/arylamine hydrochloride.

N-Methyl-1,2,3,4-tetrahydroquinolin-4-one was treated with paraformaldehyde, dimethylamine hydrochloride in ethanol and acetic acid at boil to give yellow crystalline hygroscopic compound which was identified as the Mannich base salt **17** (Chart 3). However compound **17**, on condensation with aniline, did not give the expected 3-anilinomethyl-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one **1**. The resulting product showed a molecular ion peak at m/e 346. The IR spectrum indicated a characteristic carbonyl peak at 1660 cm^{-1} and did not indicate the presence of -NH. The PMR spectrum showed two methyl peaks at 3.0 δ (s, 3P), 3.76 δ (s, 3P), 3 methylene peaks at 3.4 δ (t, 2P), 2.6 δ (m, 2P), 2.0 δ (t, 2P) and olefinic proton at 6.71 δ (t, 1P).

The above product, therefore, appears to be constituted as 18. The probable sequence of the reactions which lead to 18 are shown in the chart 3.

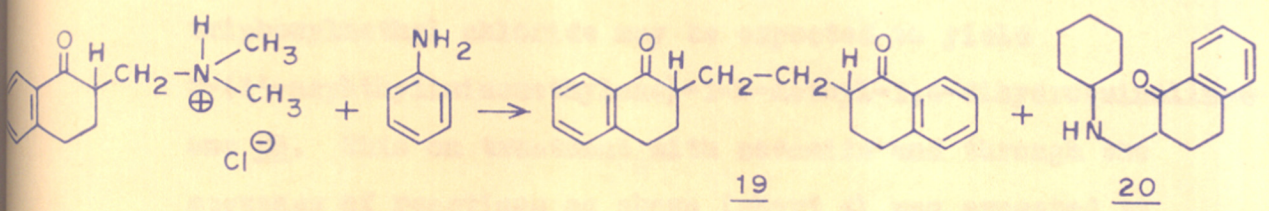
Subbaswami[1] has reported that when the Mannich base derived from α-tetralone was reacted with aniline in aqueous ethanol, in addition to 3-anilinomethyl-α-tetralone 20, a non-nitrogenous, colourless crystalline substance was also obtained, which was identified as α,β-bis-(1-keto-1,2,3,4-tetrahydro-2-naphthyl) ethane 19. Similar dimers such as, bis-2-keto-2-cyclopentanylmethane have also been reported[3,4]. Dimers[5,6] from the Mannich base of thiochroman-4-one also have been reported.

Another possible method for the synthesis of intermediates required for the cyclodehydration reactions leading angular products was to reduce the cis-2-arylaminomethylenecycloalkanones to the saturated ketones (e.g. 23 and 24). Cis-3-(1'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 21 on hydrogenation using 10% Pd/carbon catalyst, however, resulted in the formation of α-naphthylamine as one of the products. Thus the cleavage of 21 took place under these conditions.

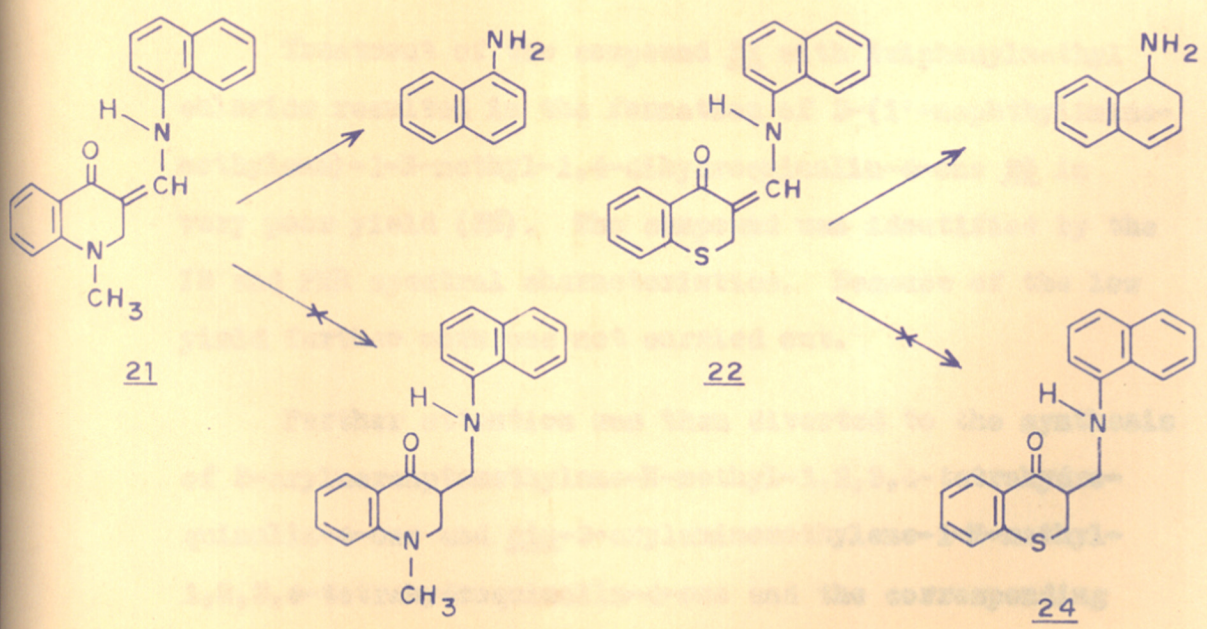


17 1 18

CHART 3



19 20



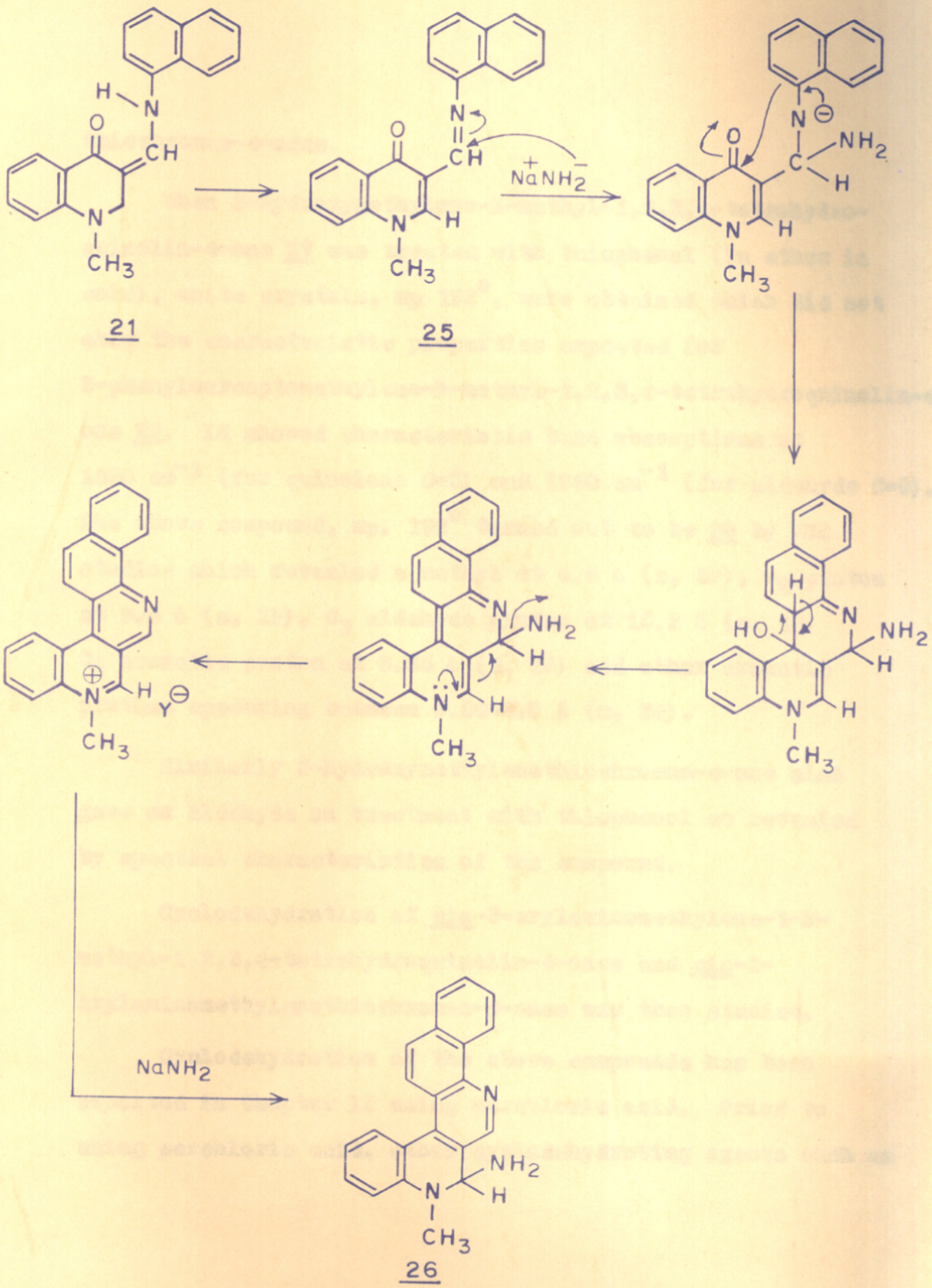
21 22 23 24

Similarly attempts to convert cis-3-(1'-naphthylamino-methylene) thiochroman-4-one 22 to the saturated ketone 24 also resulted in the formation of α-naphthylamine by cleavage of 22.

Yet another method to prepare the angular products was to cyclise 2-phenyliminomethylenecycloalkanones (c.f. Kessar[7,8]). The scheme shown in chart 4 was attempted. Cis-3-(1'-Naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 21 on treatment with triphenylmethyl chloride may be expected to yield 3-(1'-naphthyliminomethylene)-1-N-methyl-1,4-dihydroquinolin-4-one 25. This on treatment with sodamide and through the sequence of reactions as shown (chart 4) was expected to yield the angular 2,7-naphthyridine 26.

Treatment of the compound 21 with triphenylmethyl chloride resulted in the formation of 3-(1'-naphthylimino-methylene)-1-N-methyl-1,4-dihydroquinolin-4-one 25 in very poor yield (3%). The compound was identified by the IR and PMR spectral characteristics. Because of the low yield further work was not carried out.

Further attention was then diverted to the synthesis of 3-arylmercaptomethylene-N-methyl-1,2,3,4-tetrahydro-quinolin-4-one and cis-3-arylaminomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one and the corresponding



21 25 26

CHART 4

thiochroman-4-ones.

When 3-hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 27 was treated with thiophenol (in ether in cold), white crystals, mp 192°, were obtained which did not show the characteristic properties expected for 3-phenylmercaptomethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 29. IR showed characteristic band absorptions at 1630 cm^{-1} (for quinolone C=O) and 1660 cm^{-1} (for aldehyde C=O). The above compound, mp. 192° turned out to be 28 by PMR studies which revealed a methyl at 4.6 δ (s, 3P), C_2 proton at 9.4 δ (s, 1P), C_3 aldehyde proton at 10.2 δ (s, 1P) C_5 aromatic proton at 8.86 δ (d, 1P) and other aromatic protons appearing between 8.08-8.5 δ (m, 3P).

Similarly 3-hydroxymethylenethiochroman-4-one also gave an aldehyde on treatment with thiophenol as revealed by spectral characteristics of the compound.

Cyclodehydration of cis-3-arylaminomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones and cis-3-arylaminomethylenethiochroman-4-ones was then studied.

Cyclodehydration of the above compounds has been reported in Chapter II using perchloric acid. Prior to using perchloric acid, other cyclodehydrating agents such as

PPA, formic acid, lactic acid and zinc chloride with the appropriate arylamine hydrochloride were also tried. The perchloric acid cyclisations are described in Chapter II, whereas zinc chloride cyclisations were described in Chapter III. Following are the results with other cyclising agents:-

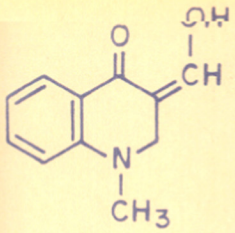
PPA cyclisation of cis-3-anilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 9 resulted in formation of tarry products which could not be identified. Further work was not carried out with the other amines.

Compound 9 on heating with formic acid could have cyclised to yield both angular and linear products (in analogy with earlier work)[9,10]. TLC showed the presence of a new compound in addition to the starting material. The former isolated in 80% yield, proved to be 3-N'-formylanilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 30. IR indicated characteristic band absorptions at 1630 cm^{-1} (for quinolone C=O) and 1690 cm^{-1} (for N'-formyl C=O) and no bands for NH. PMR studies revealed methyl at 4.41 δ, (s, 3P) methylene at 4.36 δ (s, 2P), olefinic proton at 8.2 δ (s), aldehyde proton at 8.6 δ (s) and other aromatic protons spread over 7.08-9.08 δ (m, 9P). Thus the N'-formyl structure 30 has been confirmed (chart 5).

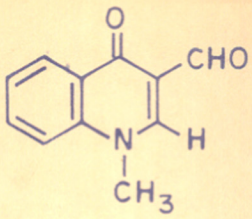
The compound 2 on treatment with lactic acid at 140°/8 hrs and work up gave in addition to the starting material, a white crystalline compound (mp 212°). PMR spectrum indicated the following:- methyl at 1.73 δ (d, 3P) methylene at 4.33 δ (s, 2P), N-methyl at 4.43 δ (s, 3P), methine of CHOH centred at 4.6-5.05 δ (q, 1P) and all other protons spread over 7.21-8.33 δ (m, 11P). IR indicated characteristic band absorptions at 1630 cm^{-1} (for quinolone C=O) and 1680 cm^{-1} (for N'-lactyl C=O), and OH spreading between 3200-3300 cm^{-1}. Thus the above compound is the N'-lactate 31 (chart 5).

Finally cyclodehydration of the relevant arylaminomethyleneketones to naphthyridines and thiopyrano-quinolines was successfully achieved by using perchloric acid and triphenylmethyl chloride (as the hydride abstractor).

To prepare tricyclic diheteroatomic systems shown in chart 5, 3-hydroxymethylenecyclohexanone 32 was condensed with 2- and 4-aminopyridines in boiling ethanol with piperdine as a catalyst whereby cis-2-(2'-pyridylamino)-methylenecyclohexanone 33 and cis-2-(4'-pyridylamino)-methylenecyclohexanone 34 were obtained. The PMR spectrum of the compounds 33 and 34 in DMSO indicated the existence of cis- and trans-tautomers.



27



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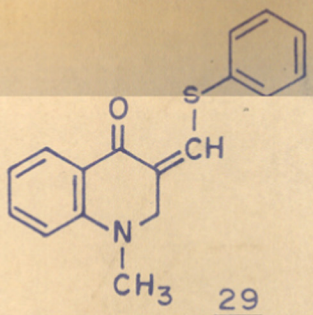

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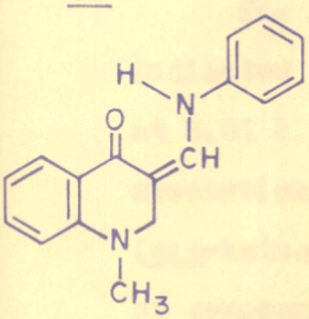
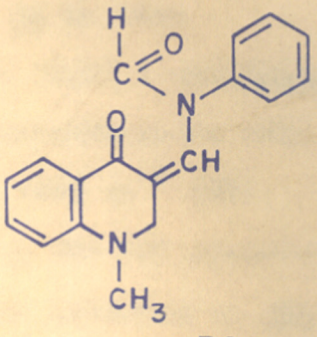


9

HCOOH



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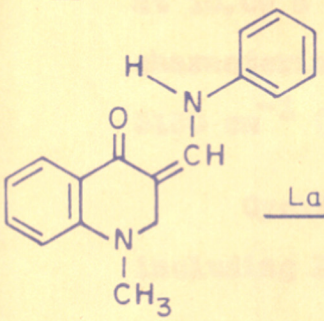
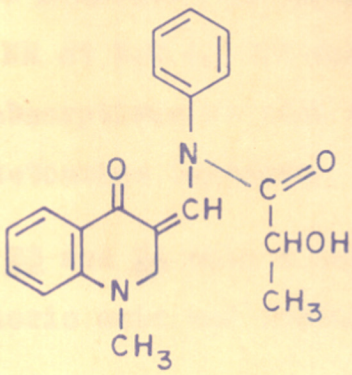


9

Lactic acid



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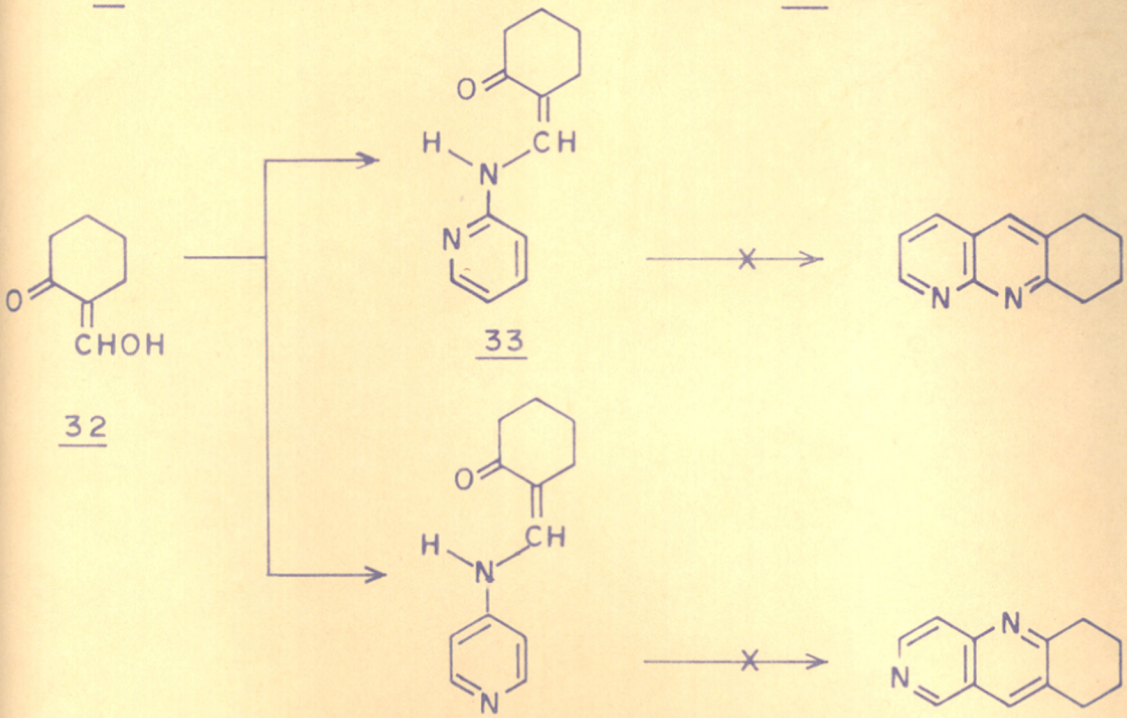


32

33

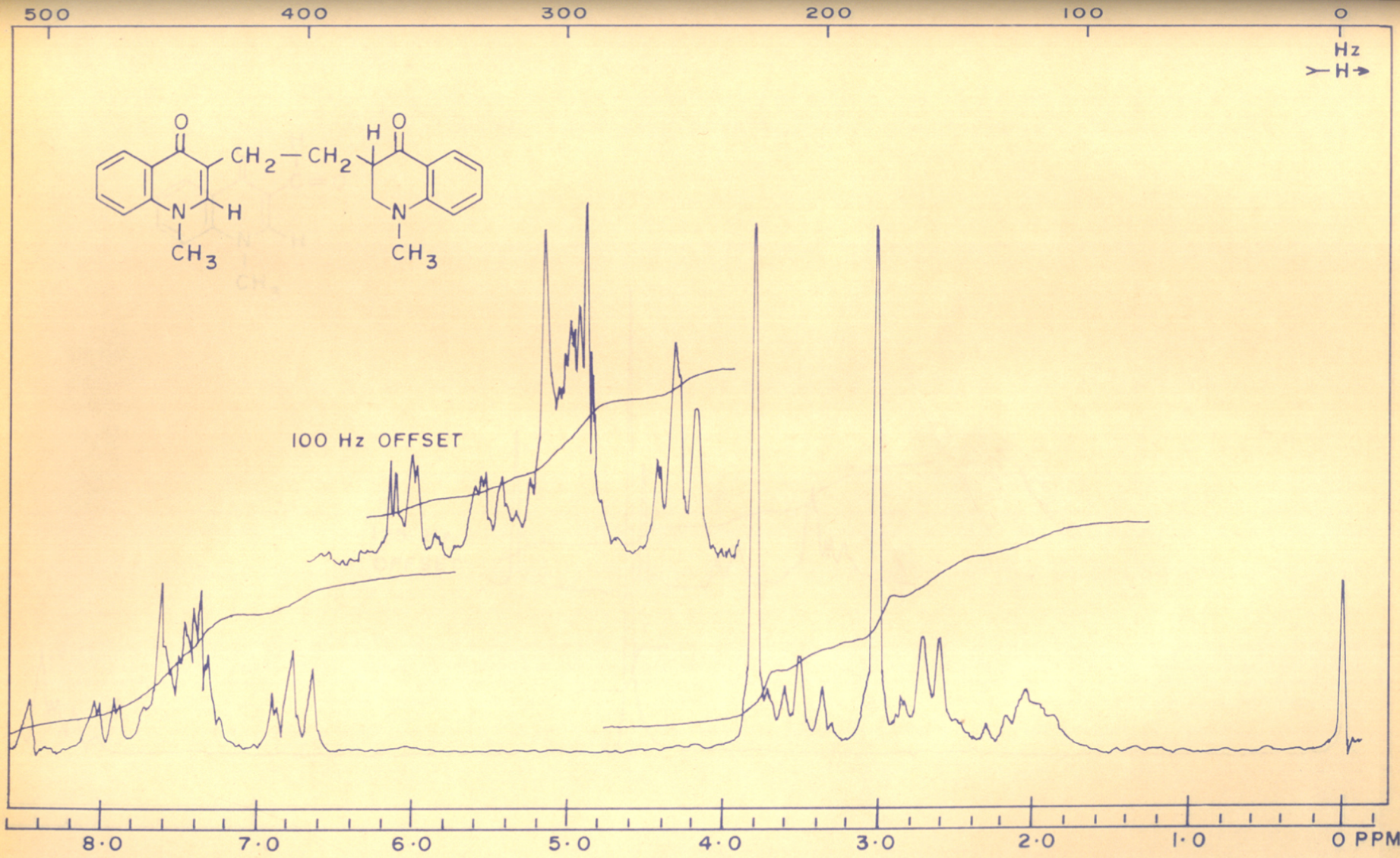
34

CHART 5

The PMR spectrum of compound 33 in DMSO indicated the presence of cis NH at 10.51 δ and trans NH at 8.01 δ. IR (nujol) indicated characteristic band absorptions at 1660 cm^{-1} (C=O) and 3200 cm^{-1} (NH) (cis-ketoamine tautomer). Similarly the PMR spectrum of compound 34 in DMSO indicated the presence of cis NH at 10.09 δ and trans NH at 9.0 δ. IR (nujol) indicated characteristic band absorptions at 1660 cm^{-1} (C=O) and 3180 cm^{-1} (NH) (cis-ketoamine tautomer).

Cyclisation of 33 and 34 with a number of reagents including PPA, perchloric acid and Dowtherm have failed.

INDEX TO SPECTRAL CHARTS



PMR SPECTRUM OF 18 IN $CDCl_3$

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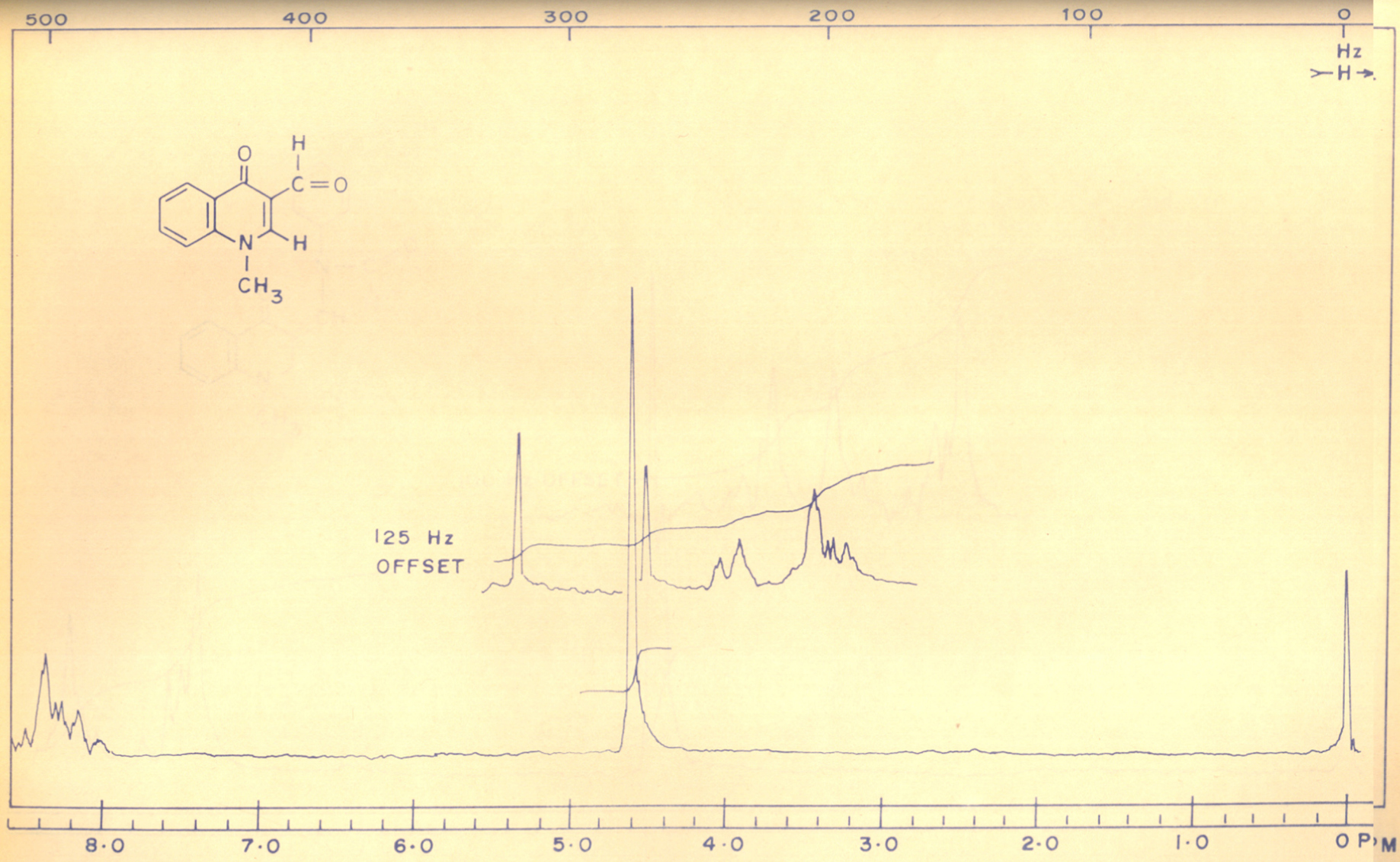
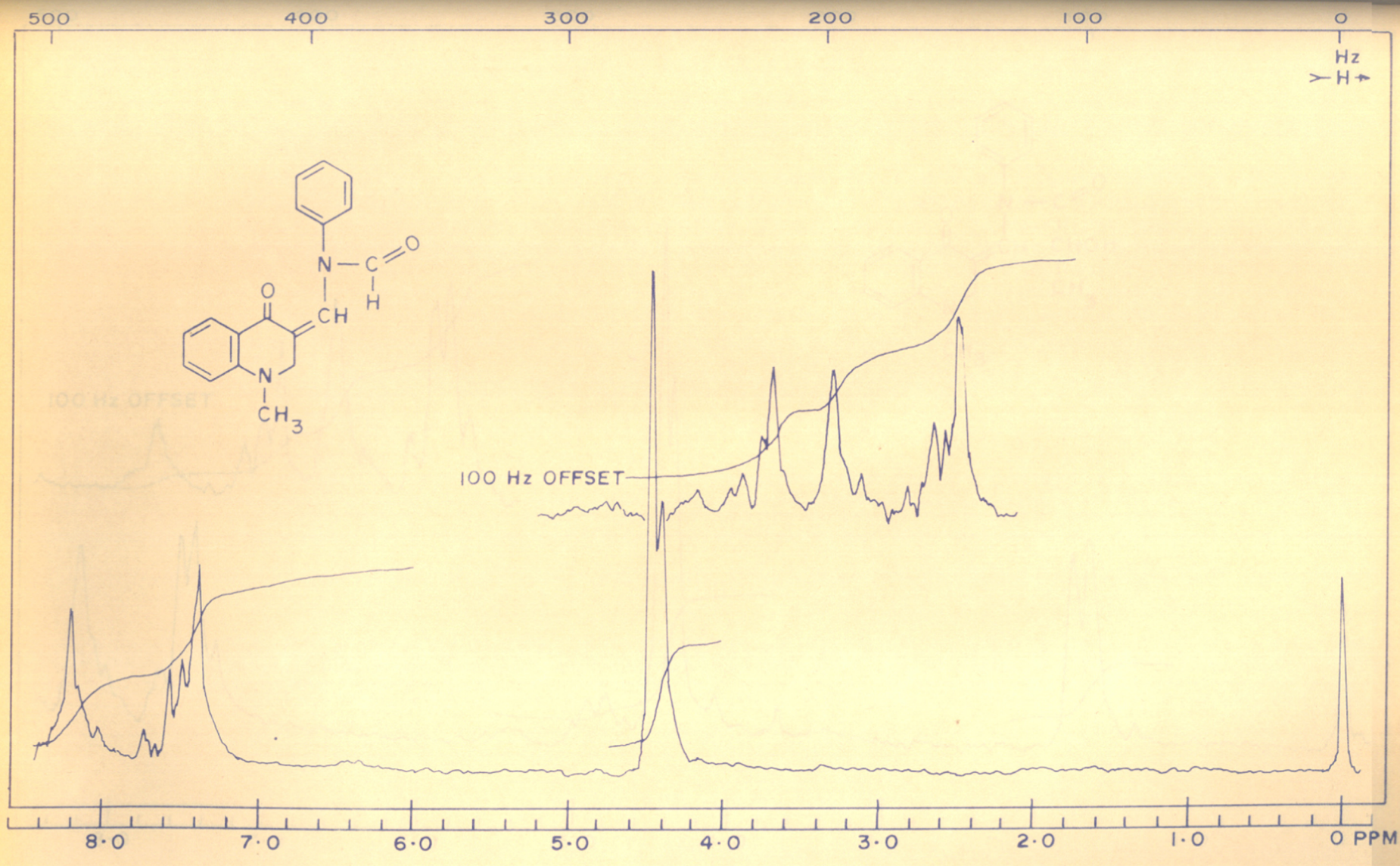
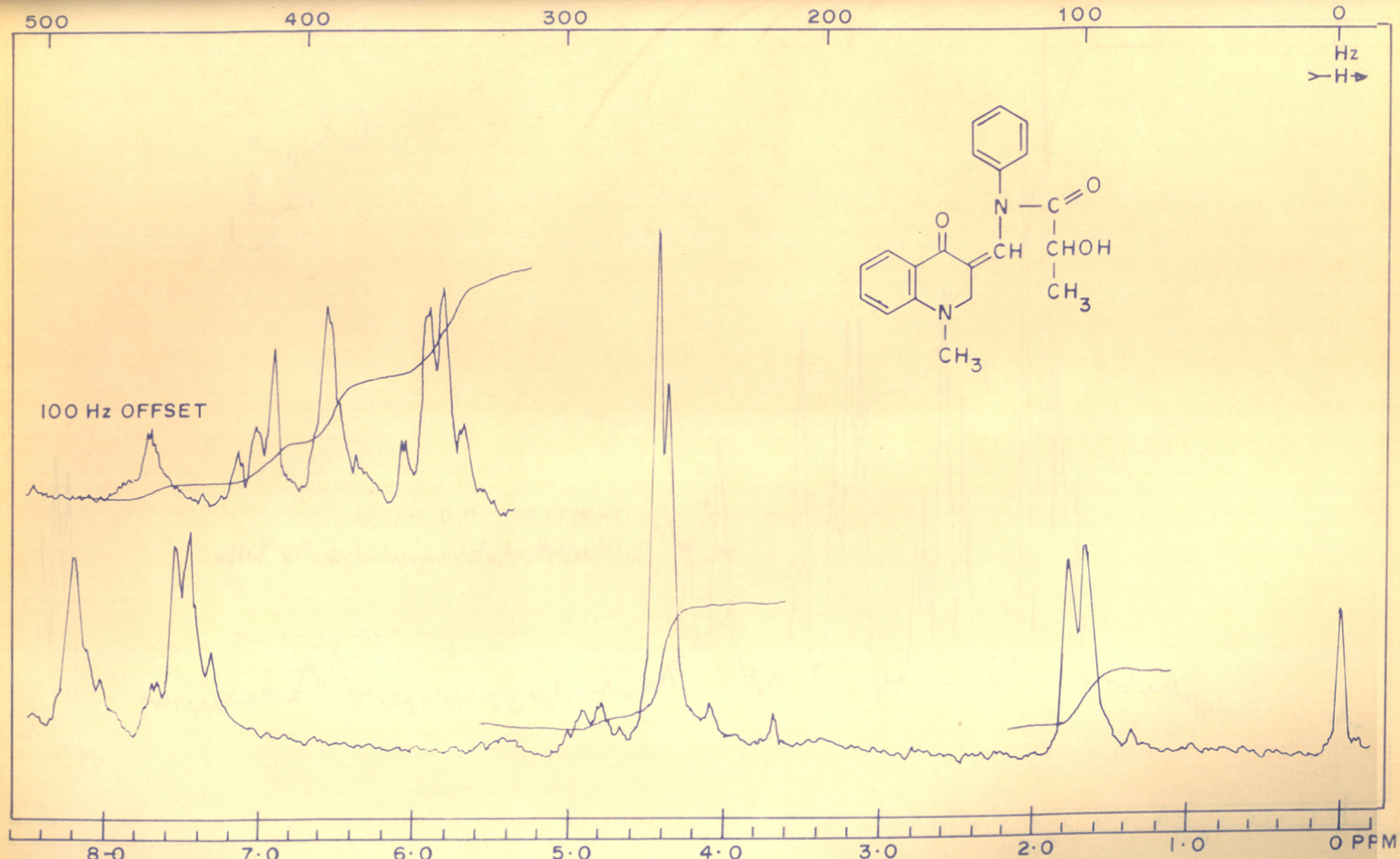


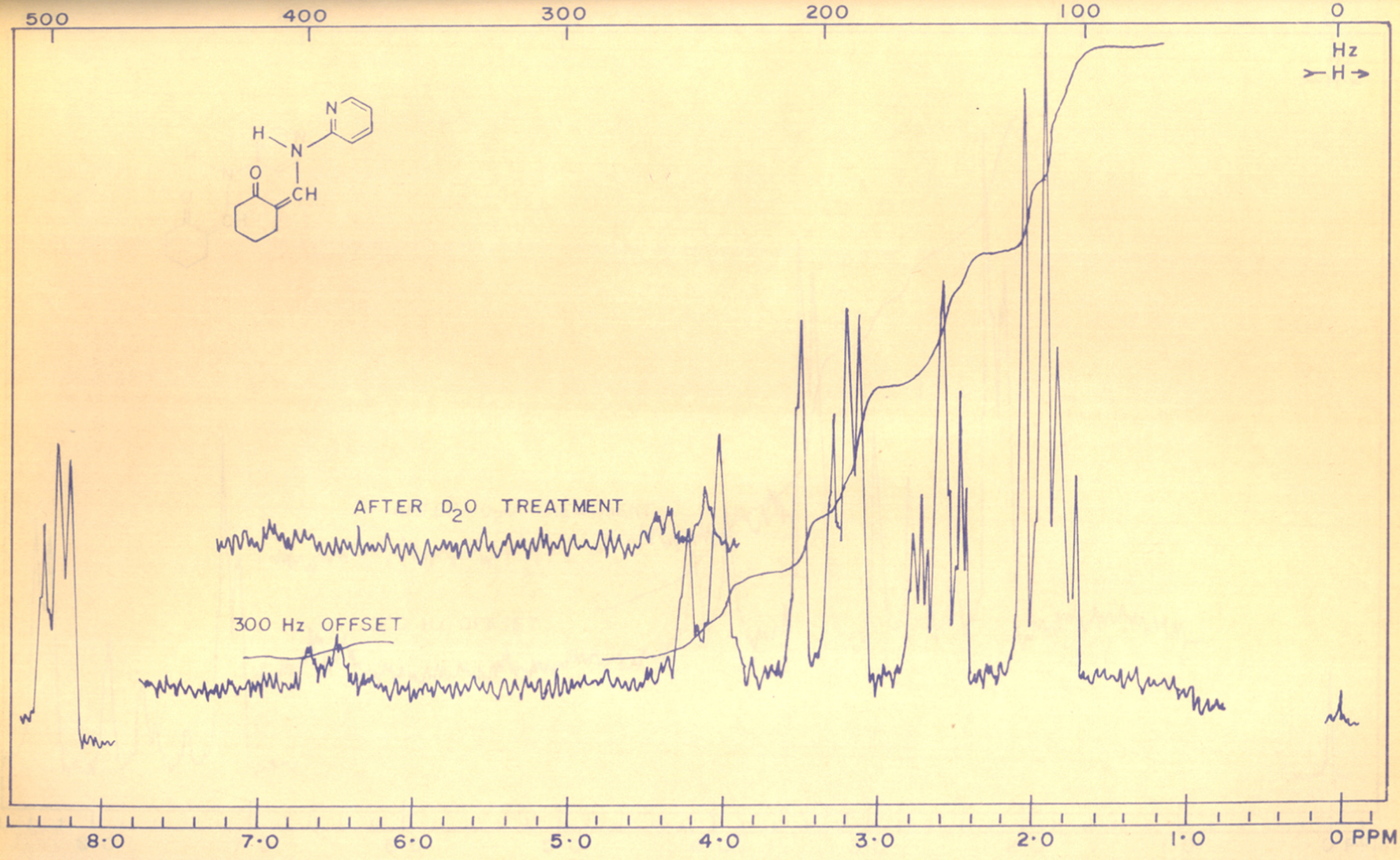
PMR SPECTRUM OF 28 IN CF_3COOH



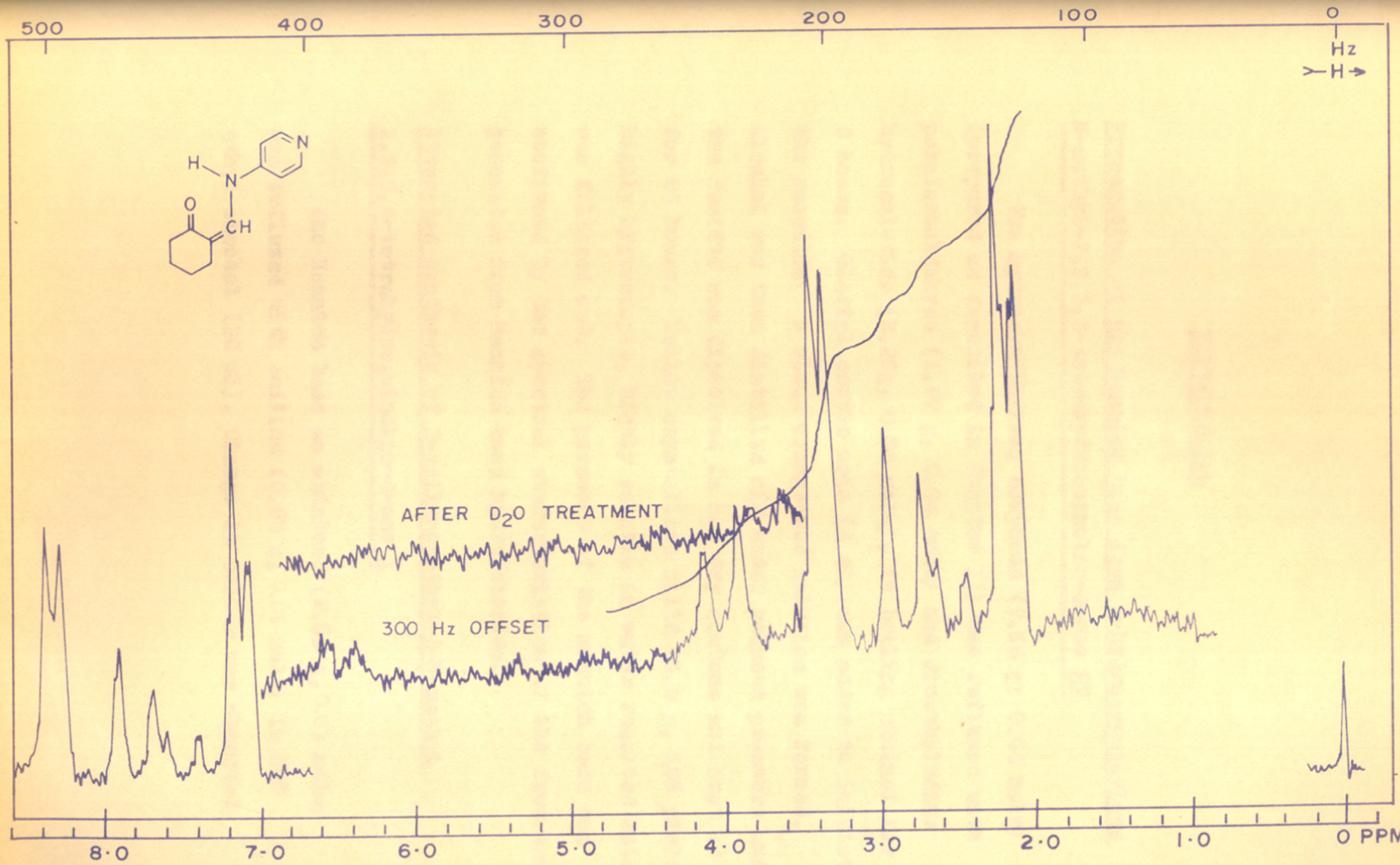
PMR SPECTRUM OF 30 IN CF_3COOH



PMR SPECTRUM OF 31 IN CF_3COOH



PMR SPECTRUM OF 33 IN DMSO



PMR SPECTRUM OF 34 IN DMSO

EXPERIMENTAL

Preparation of the Mannich base from 3-hydroxymethylene N-methyl-1,2,3,4-tetrahydroquinolin-4-one 27

The hydroxymethylene compound (7.56 g; 0.04 mole) (prepared as described in Chapter II) was refluxed with paraformaldehyde (1.20 g, 0.04 mole) and dimethylamine hydrochloride (3.28g, 0.04 mole), in boiling ethanol for 6 hours. Glacial acetic acid (4 ml) was added to initiate the reaction. A clear orange-red solution was formed. Alcohol was then distilled off under reduced pressure and the residue was dissolved in hot dry acetone and kept at 0° for 24 hours. Yellow crystalline solid (5.0 g, 50% yield), highly hygroscopic, highly soluble in water resulted which was filtered out. The presence of the mannich base was confirmed by the spectral characteristics of the free base generated from Mannich base hydrochloride.

Attempted synthesis of 3-anilinomethyl-1-N-methyl 1,2,3,4-tetrahydroquinolin-4-one 1

The Mannich base so obtained (2.53 g, 0.01 mole) was refluxed with aniline (0.93 g, 0.01 mole) in 50% ethyl alcohol (20 ml). Change in colour was observed.

Alcohol was then removed and the aqueous phase was extracted with chloroform. Chloroform was removed by distillation and ether (50 ml) was added whereby a crystalline compound resulted as yellow needles (2.55 g, 75% yield), mp. 210°. The elemental analysis and spectral characteristics of this compound was found to be that of 18. Elemental analysis of the compound gave C, 76.43; H, 6.74; N, 8.14. Required for $C_{22}H_{22}O_2N_2$. C, 76.3; H, 6.3; N, 8.3. The compound has a molecular ion peak at m/e 346 as shown by the mass spectroscopy.

Attempted synthesis to prepare 3-arylmercaptomethylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 29

The hydroxymethylene compound (3.78 g, 0.02 mole) was treated with thiophenol (4.4 g, 0.02 mole) under nitrogen atmosphere with stirring at room temperature for 5 hours. Work up of the reaction product yielded in addition to the starting material a compound which was identified as 28 on the basis of the spectral characteristics. No formation of 29 was observed. Elemental analysis gave C, 70.03; H, 4.77; N, 6.93. $C_{11}H_9O_2N$ requires C, 70.58; H, 4.8; N, 7.4. The molecular ion peak at m/e was found to be 187.

Preparation of 3-N'-formylanilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 30

Cis-3-anilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one (1.31 g,.01 mole) was refluxed with formic acid (15 ml) (99%) for 8 hours. The reaction mixture was cooled and dumped on ice and basified with aqueous ammonia and extracted with chloroform. After work up 1.5 g of the crude material resulted. This was crystallised from benzene (yield, 0.46 g). The mother liquor, when subjected to chromatography on silica gel column, using benzene:ethyl acetate (75:25) as eluent gave a further amount (0.52 g) of the formylated compound (mp 236°). Total yield of the crystallised product is 0.98 g, 62%. Identification was based on elemental analysis and other spectral characteristics.

Elemental analysis was found to be C, 75.98; H, 5.33 and N, 9.05. $C_{18}H_{16}N_2O_2$ requires C, 76.3; H, 5.5 and N, 9.5. The molecular weight was found to be 262 by mass spectroscopy.

Preparation of 3-N'-lactylanilinomethylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 31

Cis-3-anilinomethylene-1-N-methyl-1,2,3,4-tetrahydro

quinolin-4-one (1.3 g, 0.01 mole) on treatment with dl-lactic acid (15 ml) at 140° for 8 hours and on usual work up and purification gave 31 (0.9 g, 56% yield) as yellowish white needle (mp, 212°). Elemental analysis: C, 71.52; H, 5.93; N, 7.9. $C_{20}H_{20}N_2O_3$ requires C, 71.4; H, 6.0; N, 8.3. The molecular weight was found to be 336 by mass spectroscopy.

Hydrogenation of cis-3(1'-naphthylaminomethylene)-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one 21

The ketone was hydrogenated using 10% pd/c. After the stochiometric intake of H_2, the reaction mixture was filtered and the filtrate on work up gave α-naphthylamine in addition to the starting material showing only hydrogenolysis of C-N bond.

Preparation of cis-2 (2'-pyridylaminomethylene)- and cis-2-(4'-pyridylaminomethylene) cyclohexanones 33 and 34

2-Hydroxymethylenecyclohexanone was prepared by the method described by earlier workers[2]. 2-Hydroxymethylene-cyclohexanone (12.6 g, 0.01 mole) was reacted with 2- and 4-aminopyridines in boiling ethanol (100 ml) with piperidine (0.5 ml) as a catalyst. After the conventional work up and chromatography cis-2(2'-pyridylaminomethylene)-

cyclohexanone was obtained as white crystals from methanol mp 161° (3.4 g, 30% yield) and cis-2(4'-pyridylaminomethylene)-cyclohexanone, also as white crystals from methanol mp 163°. (5.0 g, 45% yield). The 2-pyridyl derivative gave an elemental analysis C, 70.81; H, 6.86; N, 13.9. $C_{12}H_{14}N_2O$ requires C, 71.2; H, 6.93; N, 13.8. The 4-pyridyl derivative gave an elemental analysis C, 70.7; H, 6.44; N, 13.5. $C_{12}H_{14}N_2O$ requires C, 71.2; H, 6.93; N, 13.8. Both these compounds gave a molecular ion peak at m/e 202 by mass spectroscopy.

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SUMMARY

Chapter I

The Chapter includes back ground information regarding the present work and a summary of earlier work carried out in this Laboratory.

Chapter II

Arylaminomethylenecycloalkanone derivatives obtained from thiochroman-4-ones, on cyclodehydration with 70% perchloric acid in the presence of an external hydride abstractor, like triphenylmethyl chloride, afforded corresponding quinolinium perchlorates, rearrangement having occurred during cyclodehydration. Similarly arylaminomethylenecycloalkanone derivatives derived from N-methyl-1,2,3,4-tetrahydroquinolin-4-one on cyclodehydration gave the corresponding perchlorates which have been assigned the linear configurations on the basis of spectral evidence.

Some aspects of the tautomeric equilibria of the condensed ketones is also discuss ed in this chapter.

Chapter III

Cyclodehydration of *cis*-3-(1'-naphthylamino)-methylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one

by heating with α-naphthylamine hydrochloride and fused zinc chloride in ethanol led to trans -3-[(1'-amino-2'-naphthyl)methylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one and 6-keto-5-N-methyl-benzo[h]naphtho[1,2-b][1,6]-naphthyridine. In a similar manner cyclodehydration of cis-3-(2'-naphthylamino)methylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one yielded trans-3-[(2'-amino-1'-naphthyl]methylene-N-methyl-1,2,3,4-tetrahydroquinolin-4-one and 6-keto-5-N-methyl-benzo[h]naphtho[2,1-b][1,6]-naphthyridine. The formation of the above keto-naphthyridines may follow the reaction mechanism suggested by Petrow.

Chapter IV

As in our earlier work, various reagents like formic acid, lactic acid and PPA were used to effect cyclodehydration of cis-3-(anilino)methylene-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-one. However instead of the expected rearranged cyclodehydration products, formate and lactate derivatives of the condensed ketone were isolated. Various attempts to synthesise arylaminomethyl-1-N-methyl-1,2,3,4-tetrahydroquinolin-4-ones, through different routes are also discussed in this Chapter.

ACKNOWLEDGMENTS

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(K.A.R. Sastry)