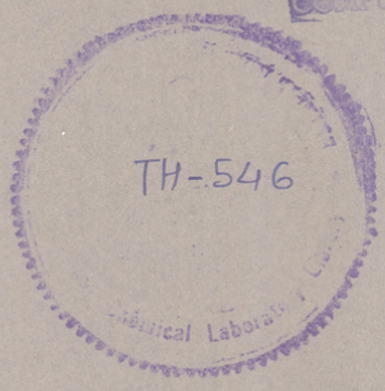


To

Dr V N Gogte

with best regards

H K Ponkshe.

SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A THESIS

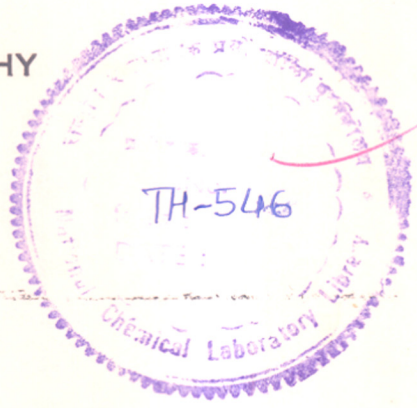
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)



BY

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FEBRUARY 1979

C O N T E N T S

GENERAL REMARKS

Spectral Data

Infrared spectra were recorded as nujol mulls on a Perkin-Elmer Infracord 137 Spectrophotometer. The absorption values are recorded in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on Varian T-60 Spectrometer using tetramethyl silane as the internal standard and the chemical shifts are cited on scale. Mass spectra were obtained with a CEC 21-110B double focussing mass spectrometer operating at 70 eV using a direct inlet system. GLC were recorded on Hewlett-Packard-700 instrument. GLC were carried out using phases like QF1-3%; SE-30- 3%; QF1-OV-17- 3%. GLC/MS were taken with an AEI-MS 3074 mass spectrometer (at 28 eV) connected to a Pye-Unican 104 chromatograph.

Temperature are in ^{o}C. Melting points are uncorrected and have been taken in capillaries. The figures underlined indicate structure numbers and the figures in superscript are literature references.

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.

CHAPTER I : SYNTHESIS AND REARRANGEMENT OF N-ARYLAZETINES

Introduction

Nitrogen heterocycles form an important group of compounds because of their varied uses such as chemotherapeutic agents, dyestuffs, photographic chemicals and various other industrial products. Even though compounds such as quinolines, benzoquinolines, acridines and phenanthridines have long been synthesised, newer synthetic routes and the chemistry of nitrogen heterocycles are still being actively investigated.

Many workers have studied base and acid catalysed cyclodehydrations of relevant carbinols to yield 1,2,3,4-tetrahydroquinolines, 1,2,3,4-tetrahydroacridines and tetrahydrophenanthridines. However adequate attention has not been paid to the reaction mechanisms involved in such cyclisations.

During the last decade Tilak *et al.* have studied extensively, the acid catalysed cyclodehydration reactions of β-arylamino-/, β-mercaptophenyl-/, β-phenoxyalkylethyl-/ cycloalkyl/aryl ketones. These cyclodehydrations lead to a mixture of aromatic compounds such as quinolines or thiapyrillium or pyrillium salts along with their 1,2,3,4-tetrahydroderivatives. These reactions involve an intermolecular hydride transfer. Thus cyclodehydration of β-arylaminoethylalkanone 1,

should yield as a first step 3,4-disubstituted-1,2-dihydroquinoline 4 (Chart 1). Under the acidic reaction conditions, an intermolecular hydride shift occurs between one molecule of dihydroquinoline 4 acting as a hydride donor and another molecule of the same in its protonated form 3 as a hydride abstractor[1,2]. This results in the concomitant formation of quinoline 5 and 1,2,3,4-tetrahydroquinoline 6 derivatives in equimolecular proportion (Chart 1).

If an external hydride abstractor, such as triphenylmethyl chloride, is present during the cyclodehydration, quinoline 5 is mostly formed along with triphenylmethane.

It was of interest to synthesise quinoline derivatives exclusively avoiding disproportionation involved in the above synthesis. A good approach for realizing this objective appeared to be cyclodehydration of 2-arylaminomethylenealkanones/cycloalkanones[2]. Thus cyclodehydration of cis-2-arylaminomethylenecyclohexanone 7 by treatment with polyphosphoric acid (PPA) gave the angularly cyclised 'normal' product viz. 7,8,9,10-tetrahydrophenanthridine 8. However when cyclodehydration was carried out by treatment of 7 with an arylamine hydrochloride in

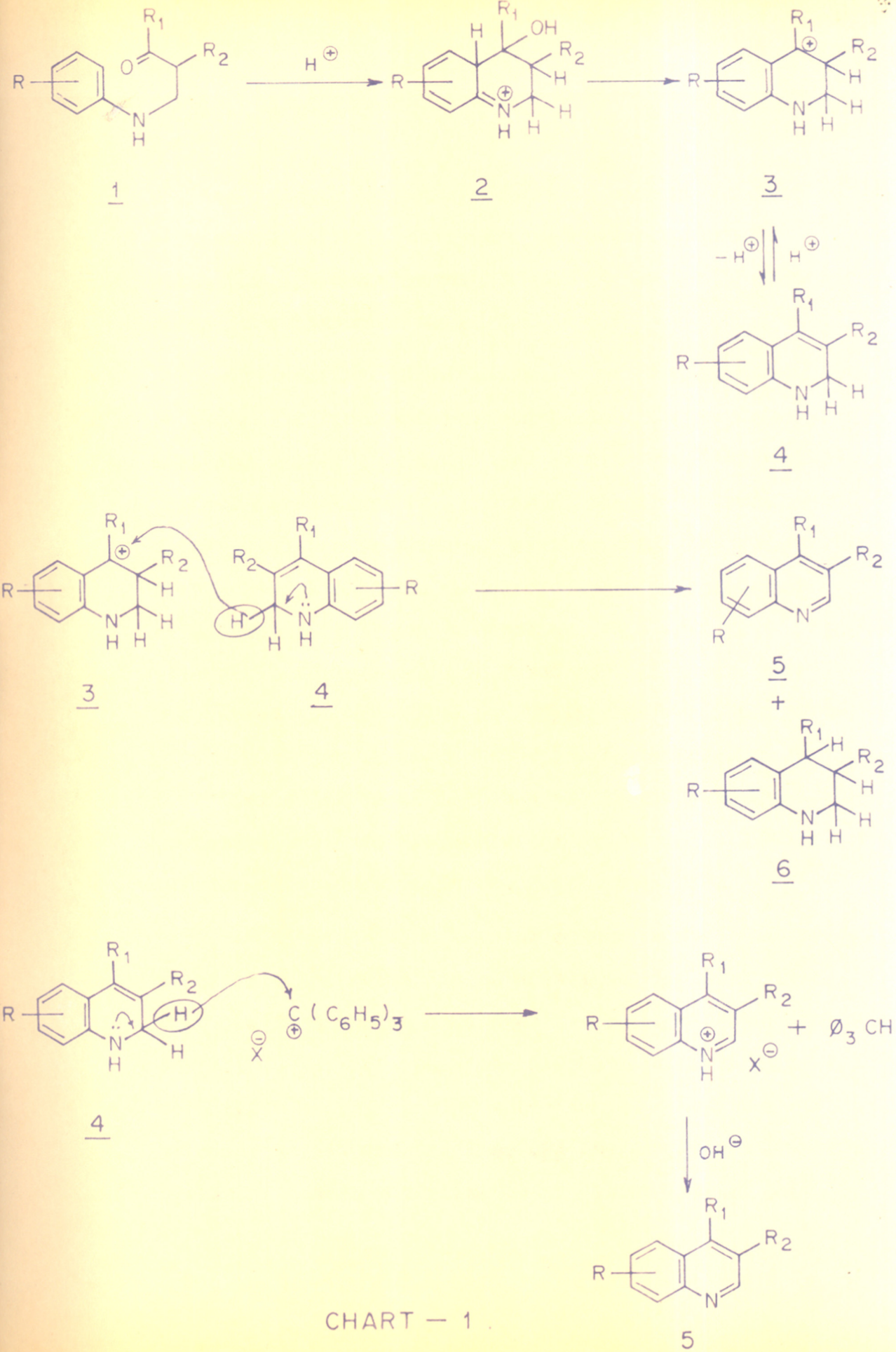
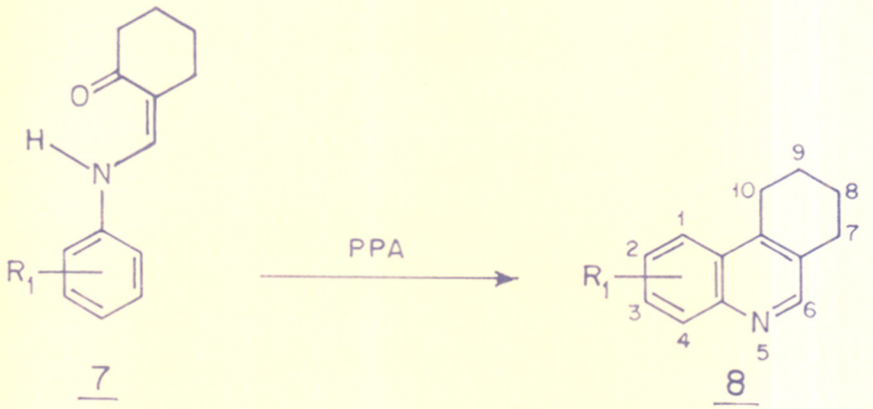


CHART — 1

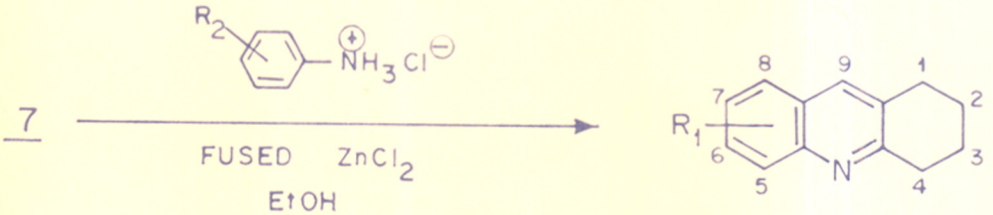
boiling ethanol (in the presence or absence of fused zinc chloride) or lactic acid or monochloroacetic acid; 1,2,3,4-tetrahydroacridines 9A and/or 9B were obtained as shown in Chart 2.

To investigate the mechanism of the formation of phenanthridines and acridines, Borsche[3], Petrow[4], Hall and Walker[5], Acheson[6] and Tilak[7] have synthesised various derivatives and suggested plausible mechanisms. Tilak et al.[7] have observed earlier that cyclodehydration of cis-2-arylaminomethylenecyclohexanone 7 by means of different arylamine hydrochlorides in boiling ethanol in the presence of fused zinc chloride gave rearranged products viz. tetrahydroacridines 9A and/or 9B where the arylamine moiety present originally in 7 is either retained or replaced by the interacting arylamine (used as hydrochloride) probably following the Scheme A and/or B as shown in Chart 3.

An alternative mechanism suggested by Tilak et al.[7] to explain the formation of acridines, is shown in Chart 4. This scheme envisages the intermediate formation of N-aryl azetine (C) which under acidic conditions undergoes ring expansion to yield the relevant tetrahydroacridines (9A and/or 9B). Different cyclising agents give rise to the formation of the

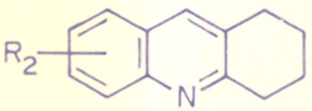


7 8



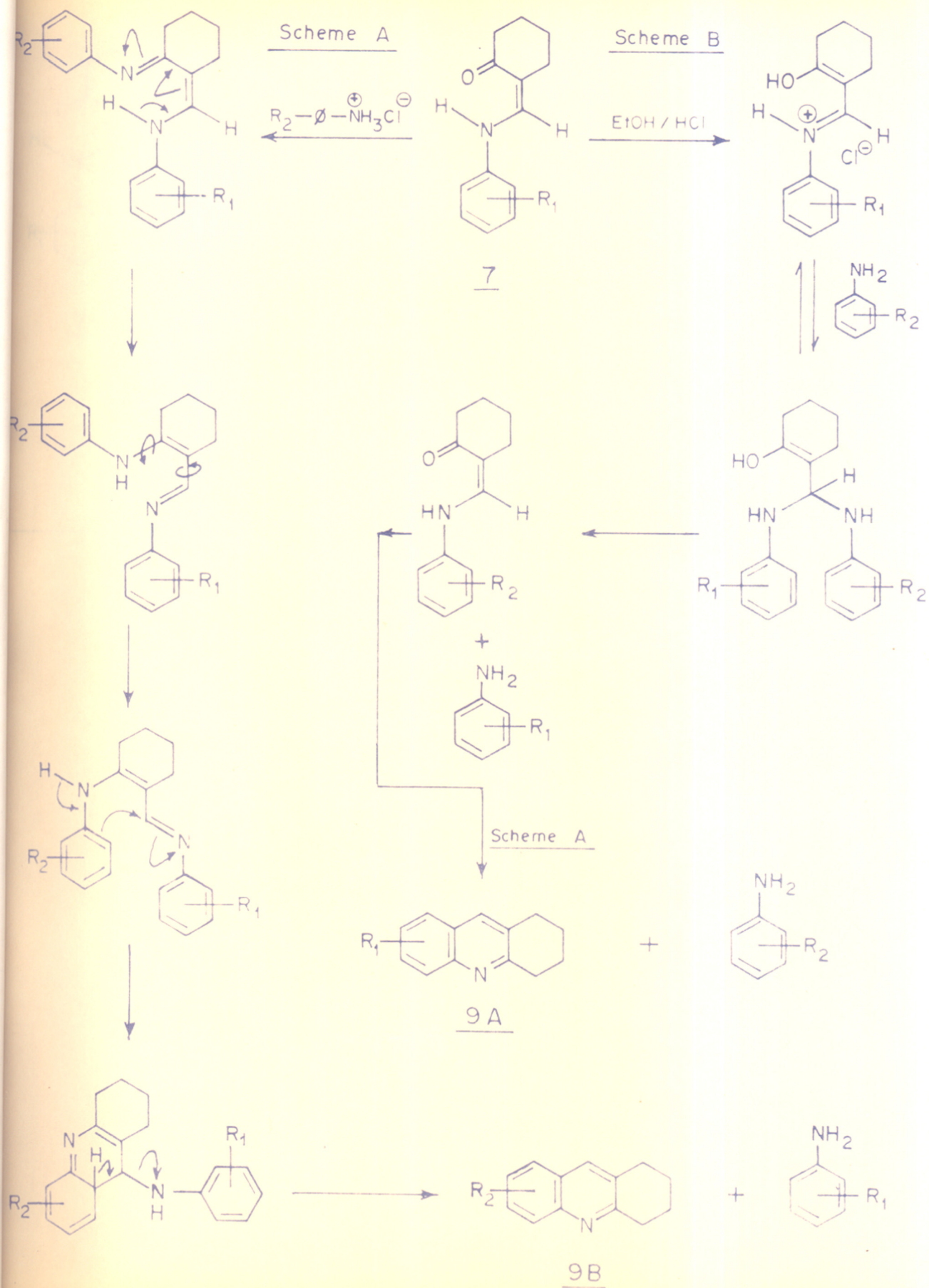
9A

and / or

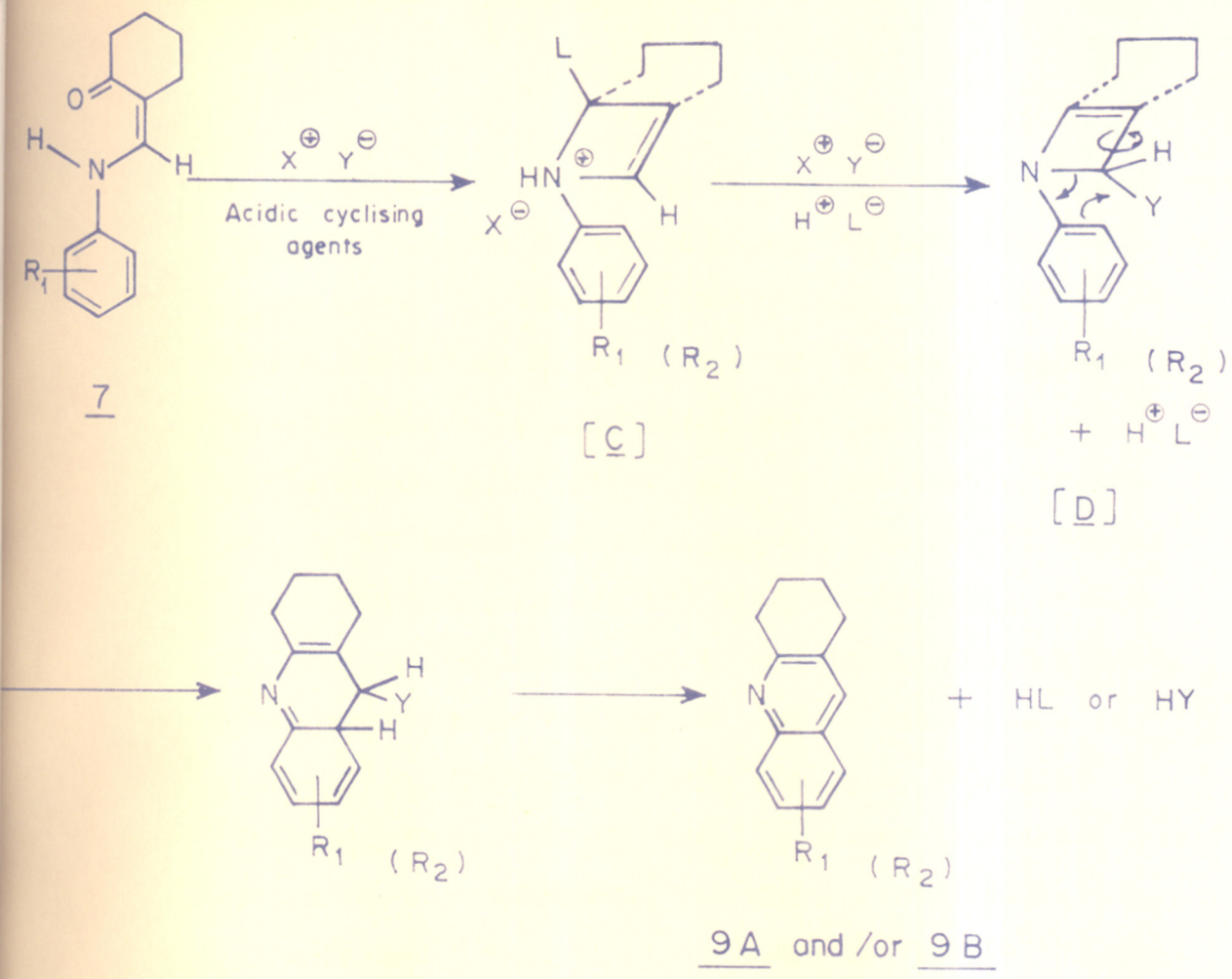


9B

CHART—2 .



CHART—3



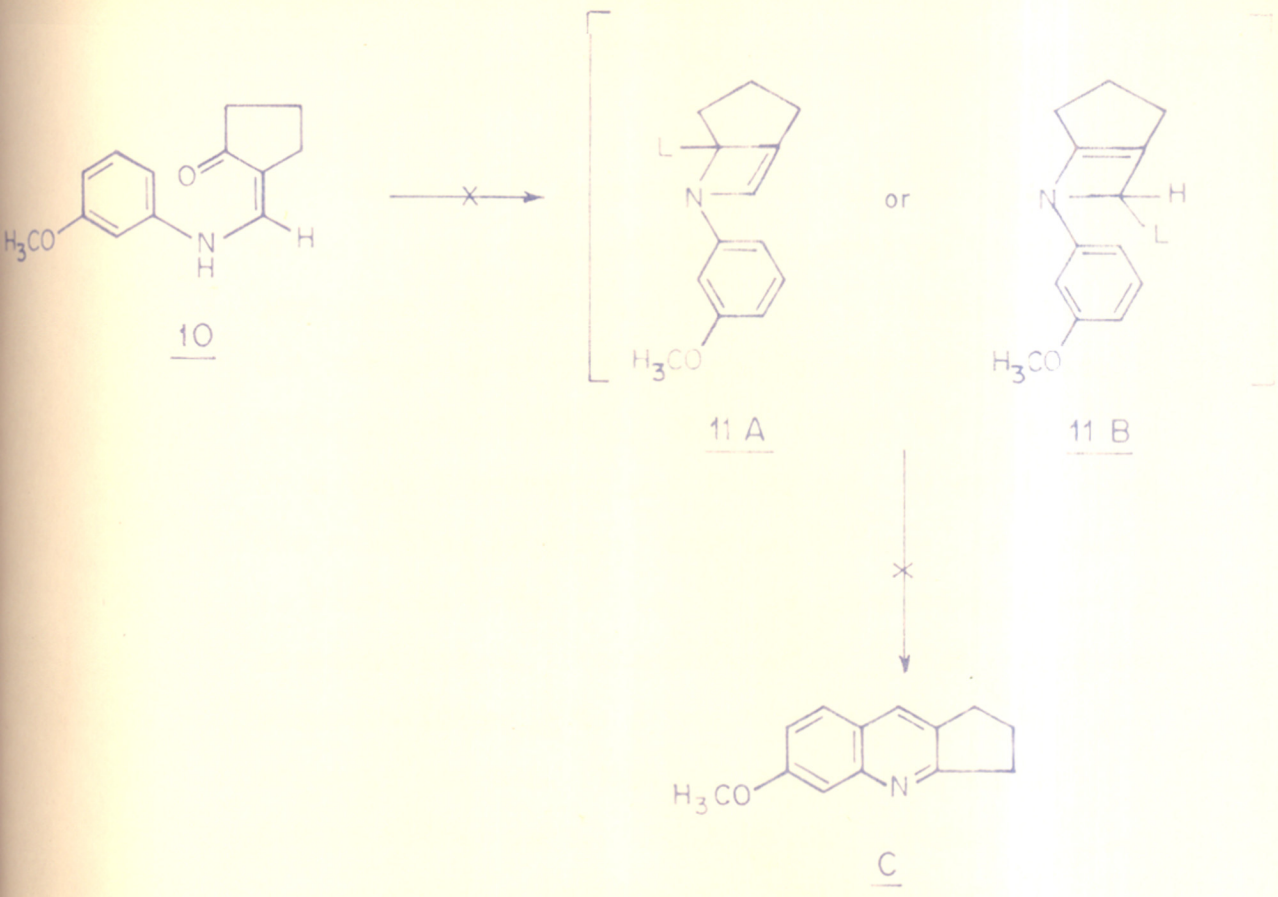
L, Y are leaving groups such as :—

—OH , —O—Zn—Cl , —O—C(=O)—CH_2Cl , —NH—(R_2) , etc.

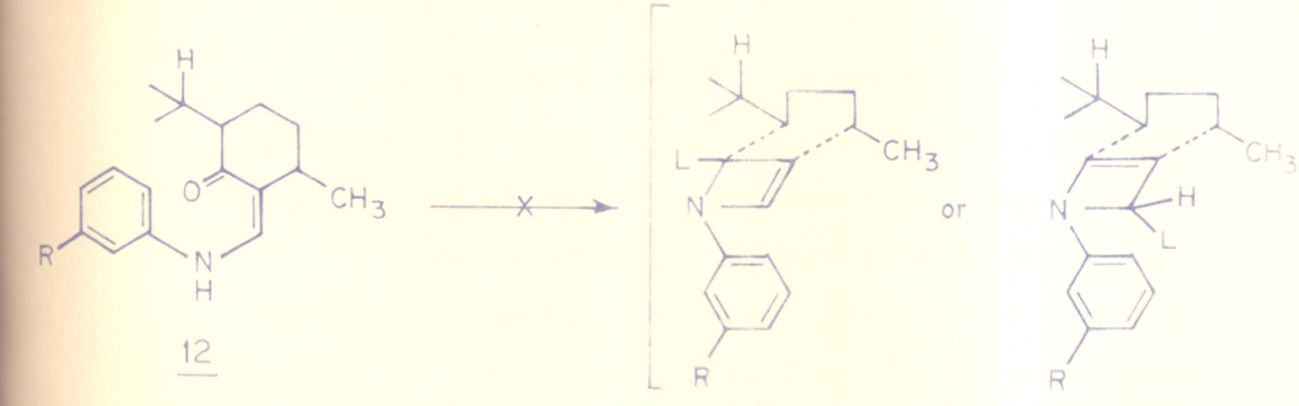
CHART — 4 .

N-arylazetine intermediate (C) or (D) where the leaving groups differ in each case depending upon the cyclising agent used. The observation by Namjoshi[8a] that cyclodehydration of 2-(3'-methoxyanilino)methylene-cyclopentanone 10 does not lead to the linear cyclopentano[b]quinoline (C) (through rearrangement during cyclodehydration of 10) was attributed to the fact that the intermediate N-arylazetine 11A and/or 11B may not be formed due to excessive steric strain. This observation derives support by the finding of Vankar[8b] of this laboratory, that acid catalyzed cyclodehydration of 12A and 12B (using lactic acid, arylamine hydrochloride, monochloroacetic acid, etc.) also failed. This was attributed by Vankar[8b] to the high steric strain imposed by the isopropyl group in the formation of a four membered (azetine) ring 13A and/or 13B (Chart 5).

In view of the rearrangements noted during cyclodehydration of cis-2-arylaminomethylene-cyclohexanone 2, it was of interest to investigate if during cyclodehydration of β-arylaminoethylalkyl/cycloalkyl/aryl ketones such as 14, similar rearrangements also occur. In the case of β-aminoethyl ketone one may expect formation of hexahydroacridine through



10 11 A 11 B C



12 13 A 13 B

A) R = H

B) R = OCH_3

CHART – 5

the intermediate formation of azetidine such as E which on ring expansion and dehydration (or loss of arylamine) should yield a hexahydroacridine 21. The latter on disproportionation through hydride transfer will yield 17 and 18 (Chart 6). More[9] from this laboratory has found this to be the case. The reaction sequences studied by More[9] are shown in Chart 6. More[9] explained the formation of normally expected tetrahydrophenanthridine 15 and octahydrophenanthridine 16 by a reaction sequence (Path A) shown in Chart 6. The azetidine intermediate E (Chart 6) may as well lead to the angular hexahydrophenanthridine 20, Path C (Chart 6), which on disproportionation will yield 15 and 16 (Chart 6). These reactions could also be generalized as shown in Chart 7 (Tilak[10]).

The mechanism proposed envisages the intermediate formation of N-arylazetidine 24 and/or N-arylazetine 25A and/or 25B (Chart 7 and 8 respectively). Formation of N-arylazetidine 24 can be explained in two ways, either in a concerted way which involves protonation of the aminoketone 22 followed by simultaneous attack of nitrogen loan pair to give 24 or by a stepwise process through a carbonium ion 23 under acidic conditions

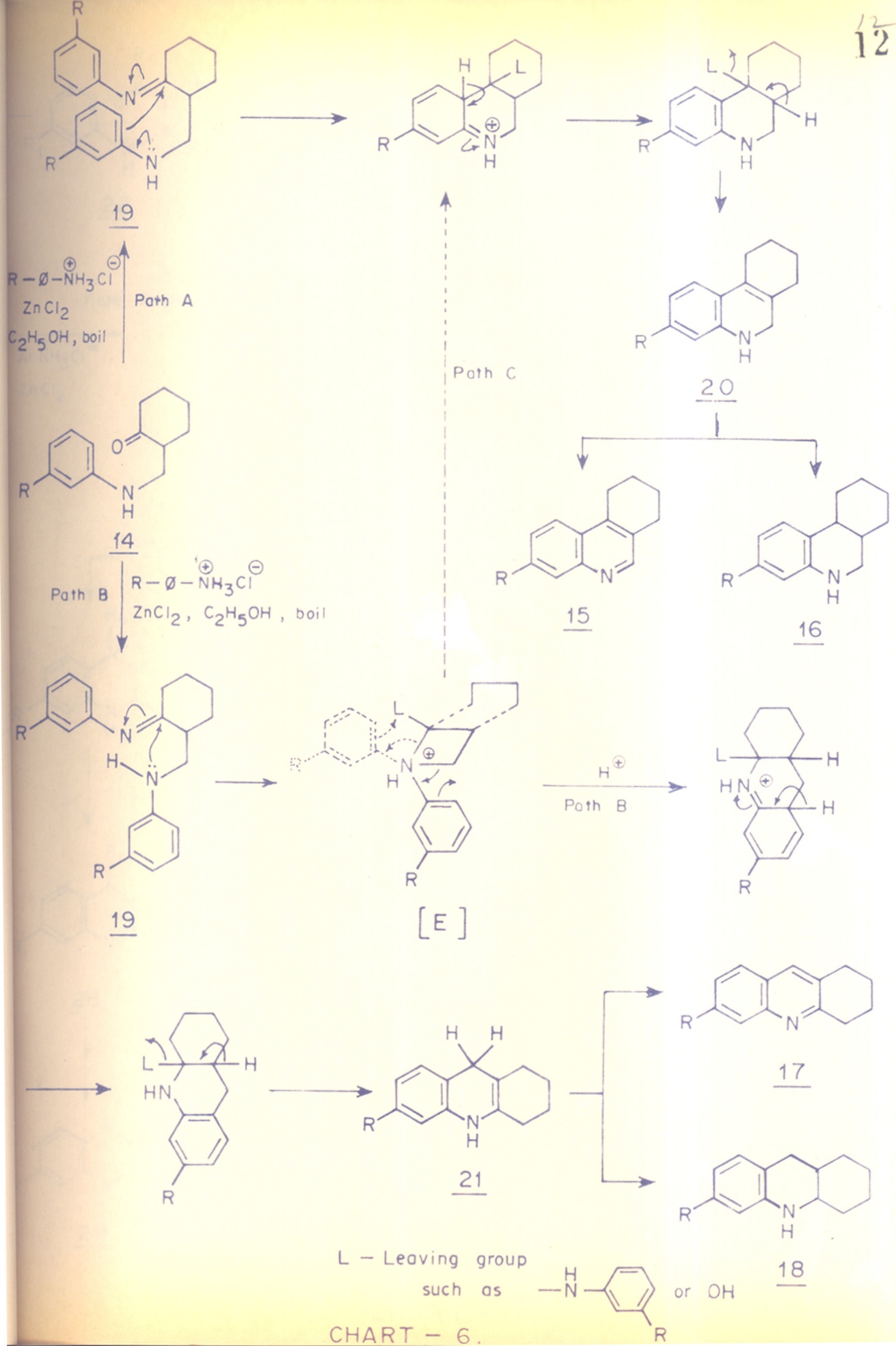

19
R−Ø−NH3Cl
ZnCl2
C2H5OH, boil
Path A
Path C
20
14
Path B
R−Ø−NH3Cl
ZnCl2, C2H5OH, boil
15
16
19
[E]
H⊕
Path B
17
21
18
L − Leaving group
such as
or OH

CHART – 6.

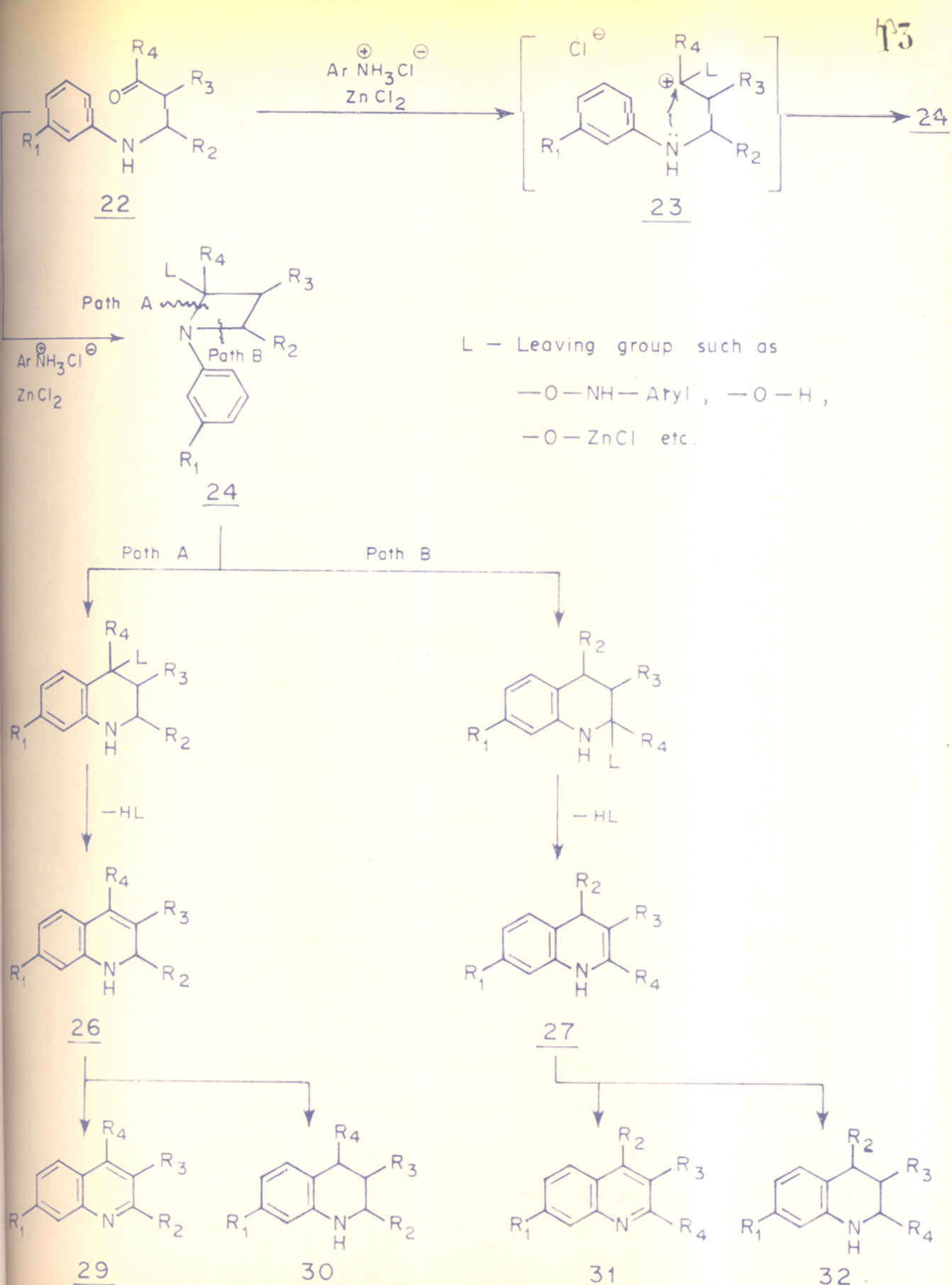

Ar NH3Cl
Zn Cl2
22
23
24
Path A
Path B
L — Leaving group such as
—O—NH—Aryl , —O—H ,
—O—ZnCl etc.
Path A
Path B
—HL
—HL
26
27
29
30
31
32
Normal
Rearranged

CHART — 7

followed by an attack of the nitrogen loan pair electrons. N-arylazetidine 24 further undergoes ring expansion either by breakage of N-C-R_4 bond or breakage of N-C-R_2 bond, followed by the loss of HL moiety, to yield two different dihydroquinolines 26 and 27, which subsequently disproportionate under acidic conditions to give a mixture of cyclodehydration products 29, 30 (normal) and 31, 32 (rearranged) (Chart 7).

Formation of 29, 30 and 31, 32 can also be explained by assuming the involvement of an N-arylazetine 25A species. 25A can result from N-arylazetidine 24 by loss of HL (L being a leaving group) (Chart 8).

Under acidic conditions 25A may further undergo a prototropic shift to form an isomeric azetine 25B. Compounds 25A and 25B will undergo a ring expansion to give two different dihydroquinolines 27 and 28. The latter on disproportionation will yield 29, 30 and 31, 32 (Chart 8). It is difficult to decide if the above reaction proceeds either through N-arylazetidine 24 or through N-arylazetine 25A and/or 25B. It is also difficult to find out whether the formation of azetidine 24 is a concerted process or a stepwise process.

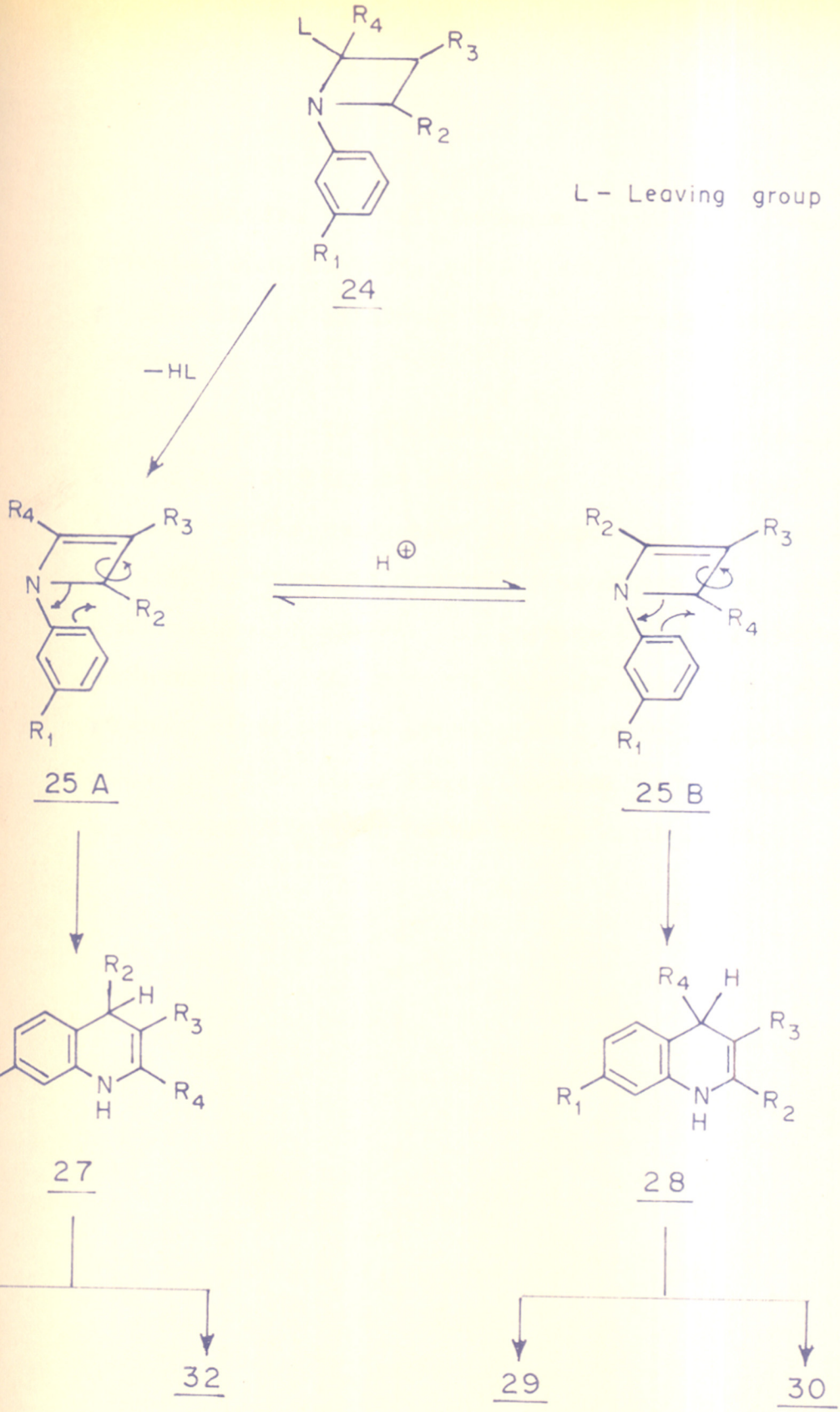

L
R4
R3
N
R2
R1
24
L – Leaving group
–HL
R4
R3
N
R2
R1
25 A
H⊕
R2
R3
N
R4
R1
25 B
R2
H
R3
R1
N
H
R4
27
R4
H
R3
R1
N
H
R2
28
31
32
29
30

CHART – 8.

Extended HMO calculations (Prof. P.T. Narasimhan, private communication, IIT Kanpur) indicated the possibility of existence of stable N-arylazetine systems.

In order to elucidate the above mechanisms, it was of interest to synthesise N-arylazetines and to study their rearrangement under acidic conditions. Several attempts to synthesise azetines were initially unsuccessful. However one azetine has been synthesised successfully. The present Chapter describes these studies aimed at the synthesis of N-arylazetines and a study of their ring expansion to quinolines and tetrahydroquinolines under acidic conditions.

Present Work

Tilak et al.[11] have reported earlier the synthesis of N-arylazetidines by treatment of carbinol 33 with triphenylphosphine dibromide followed by triethylamine. The reaction mixture on work up gave a mixture of N-arylazetidine 34 along with a mixture of tetrahydroquinolines 35 and 36. It was thought worthwhile to partially dehydrogenate the azetidine 34 using a mild hydride abstractor such as trityl fluoroborate as a plausible route to synthesise N-arylazetine 37 or 38 (Chart 9).

1-N-(m-Methoxyphenyl)-2-(p-methoxyphenyl)-azetidine 41 was the choice for this reaction as the p-methoxy group was expected to facilitate the hydride abstraction from C_2 atom. β-(m-Methoxyphenylamino)-ethyl p-methoxyphenyl ketone 39 was prepared by interaction of Mannich base hydrochloride of p-methoxyacetophenone with m-anisidine. Ketone 39, on sodium borohydride reduction, yielded 3-(m-methoxyphenylamino)-1-(p-methoxyphenyl)-propan-1-ol 40. Treatment of this carbinol 40 with triphenylphosphine dibromide followed by triethylamine afforded a mixture of 1-N-(m-methoxyphenyl)-2-(p-methoxyphenyl)azetidine 41 along with 7-methoxy-2-(p-methoxyphenyl)-1,2,3,4-tetrahydroquinoline 42 and 7-methoxy-4-(p-methoxyphenyl)-1,2,3,4-tetrahydroquinoline 43 (Chart 10).

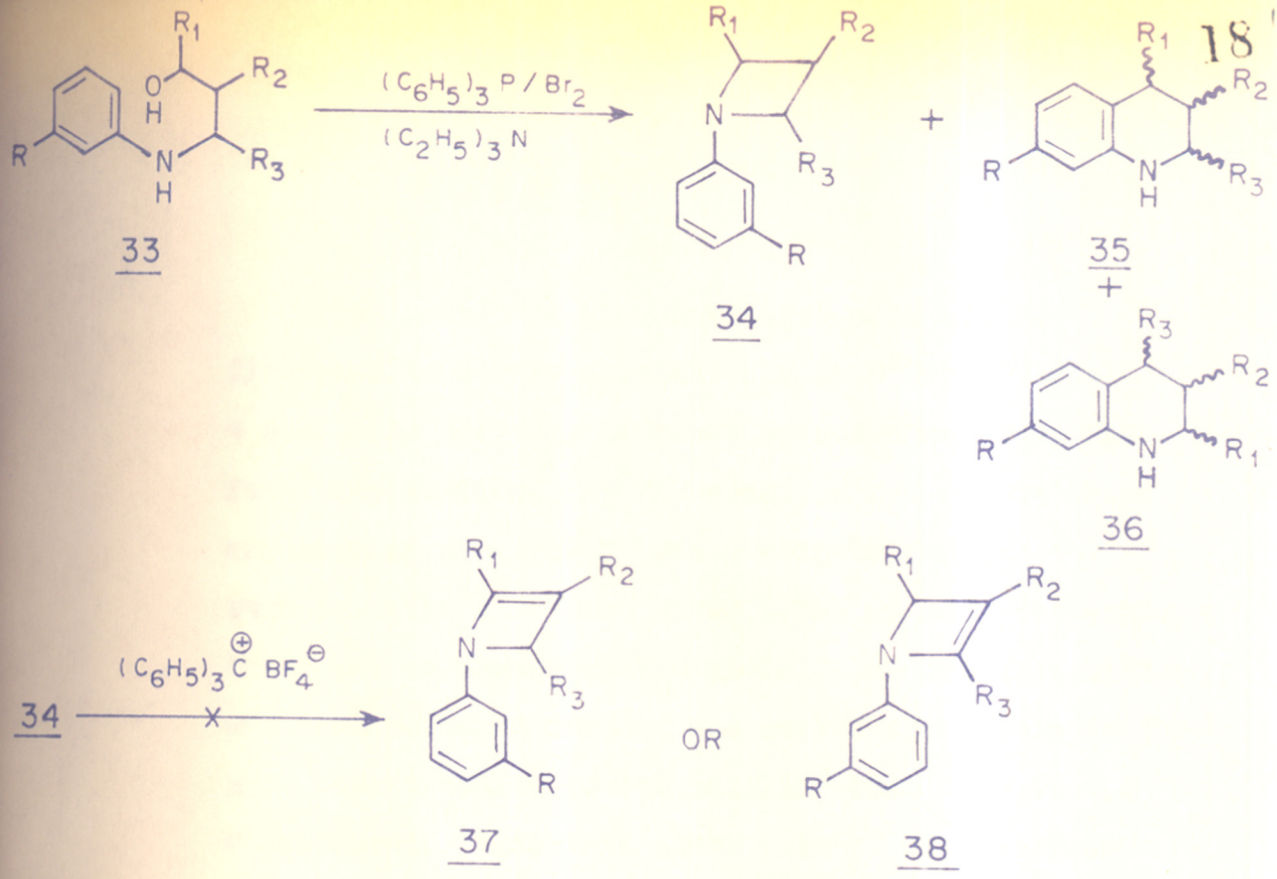


CHART — 9

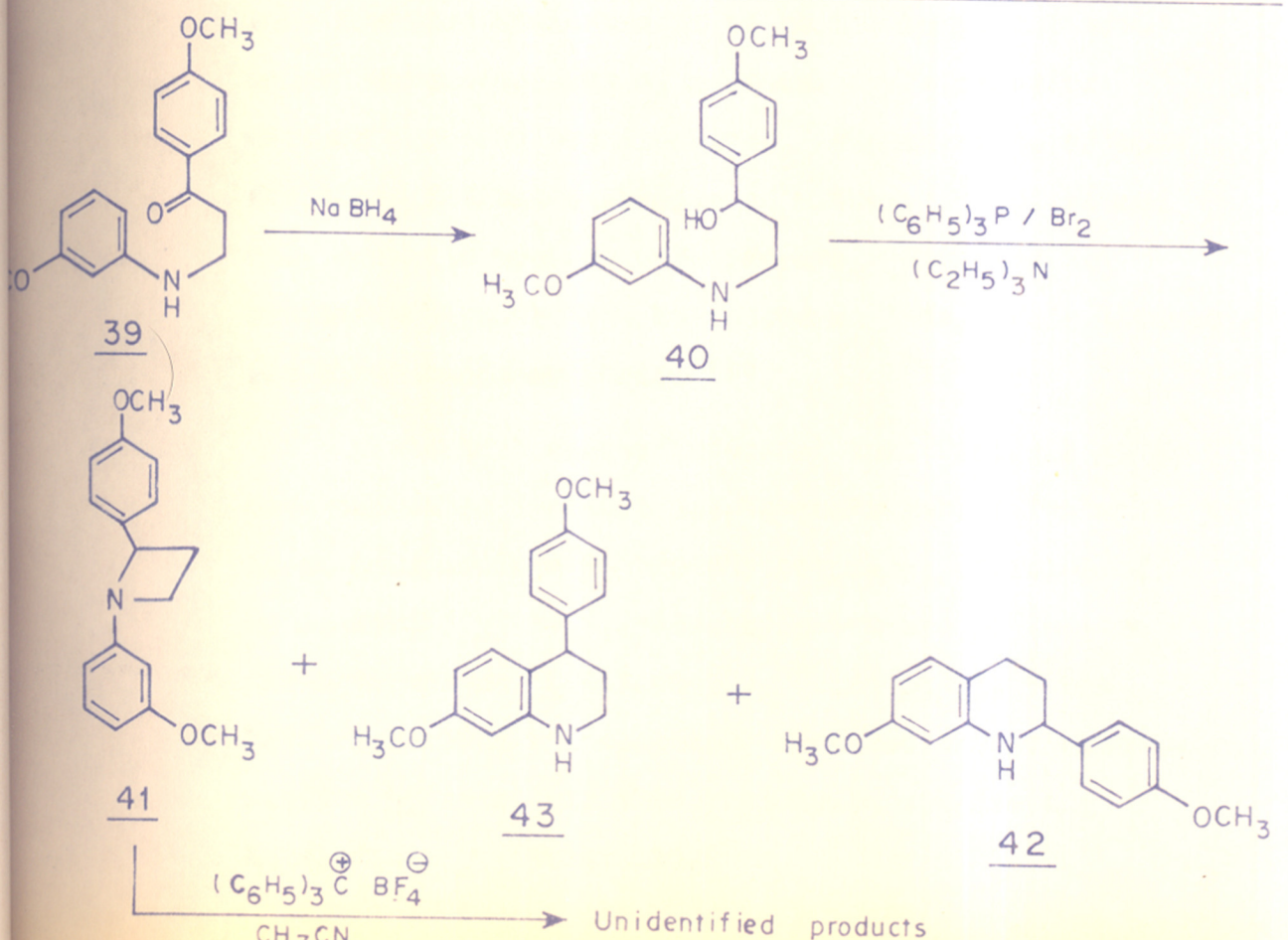


CHART — 10

The azetidine 41 was treated with trityl fluoroborate in dry acetonitrile at 0° to -5° for 4 hrs. The progress of reaction was checked by TLC from time to time. As the reaction did not indicate any sign of progress it was continued further at room temperature. Even after 2 hrs at room temperature, there was no change on TLC plate. The reaction mixture was then refluxed further and worked up as soon as the spot corresponding to the starting azetidine in TLC disappeared. Petroleum ether extract of the crude reaction mixture afforded a solid. NMR spectrum of this fraction indicated it to be triphenyl methane. Column chromatography of residual crude reaction mixture afforded two fractions. NMR spectrum of both fractions indicated absence of methoxy functions and only aromatic protons were present. Starting azetidine 41 could not be recovered back. This attempt was then abandoned (Chart 10).

Literature survey indicated that Cantrell et al.[12] have suggested 2-phenyl-3,3,4,4-tetramethyl-1-azetine 46 as an intermediate in the photochemical addition of benzonitrile 44 to 2,3-dimethylbut-2-ene 45 to give the heterodiene 47 (Chart 11). Yang et al.[13] who have reexamined the reaction, isolated the intermediate azetine 46 which was then photolysed to give the heterodiene 47 (Chart 11).

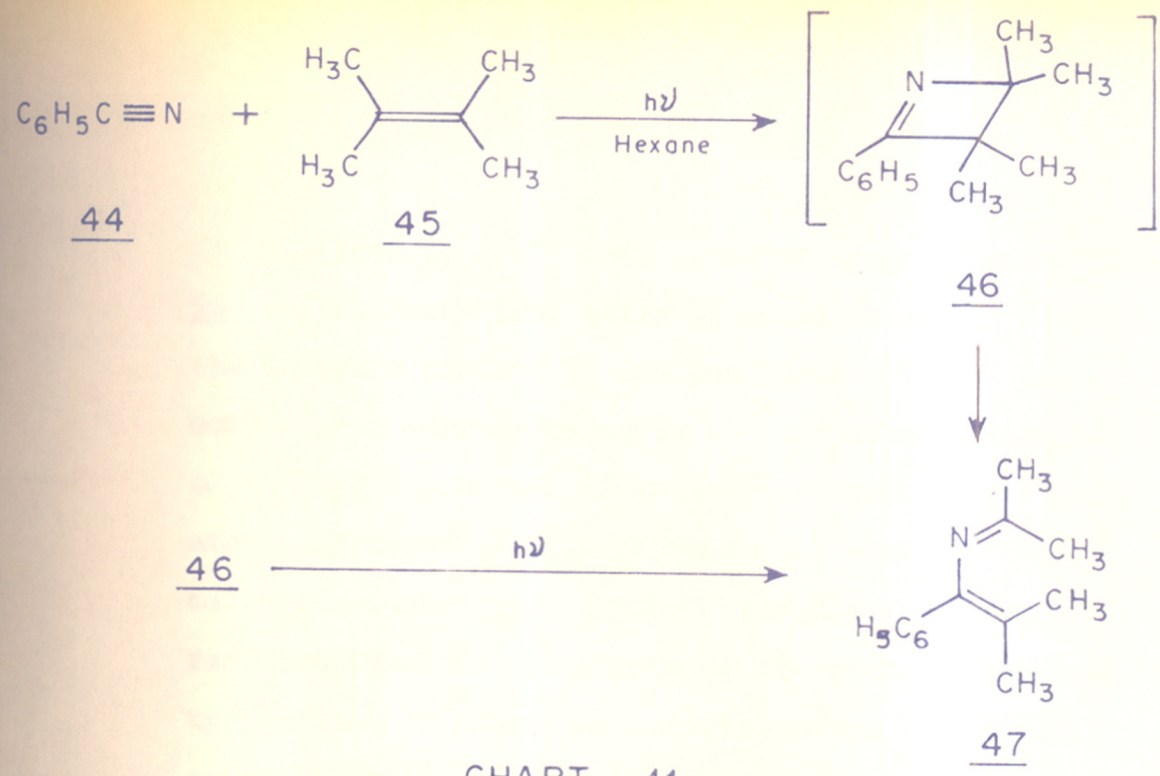


CHART – 11 .

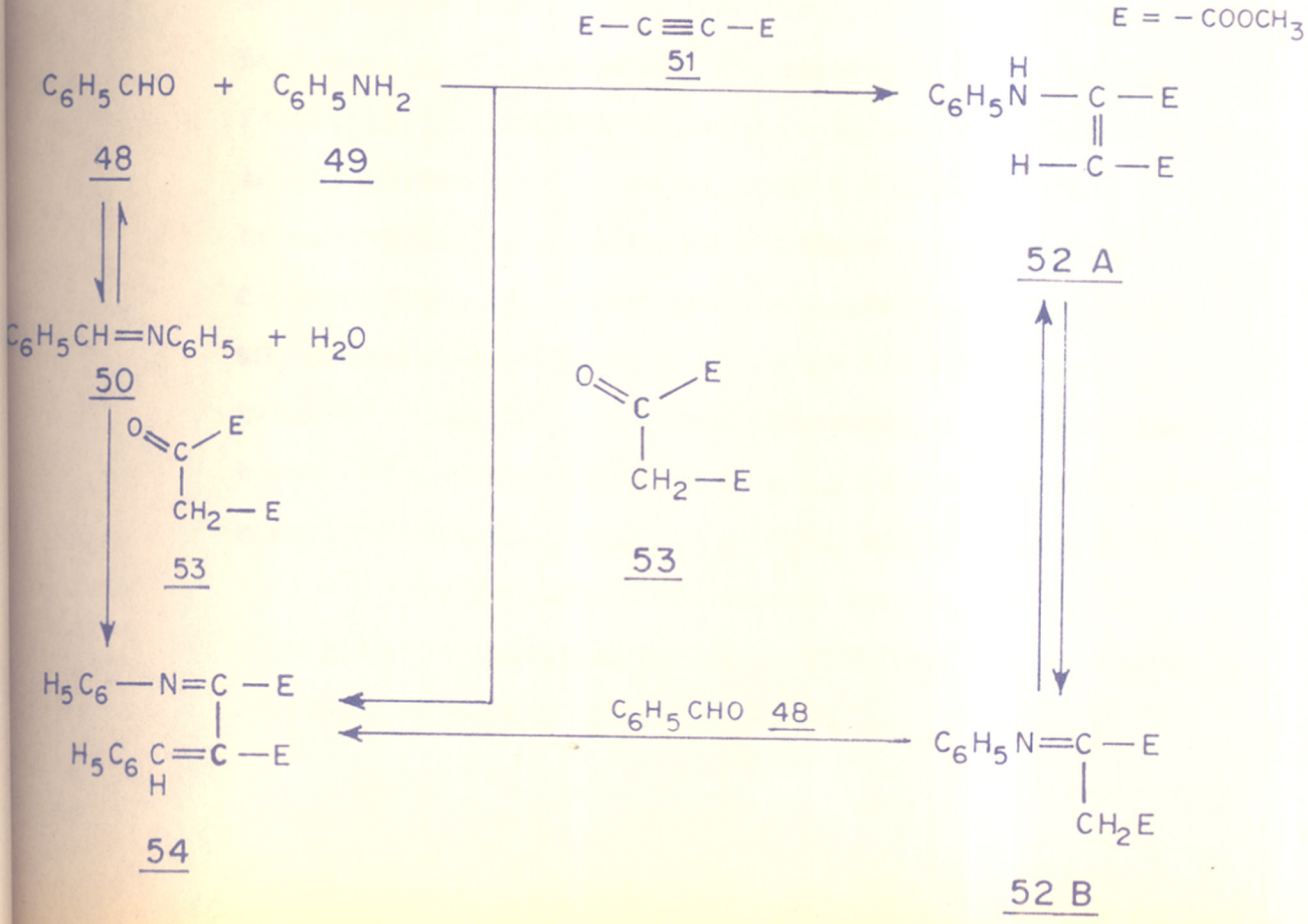
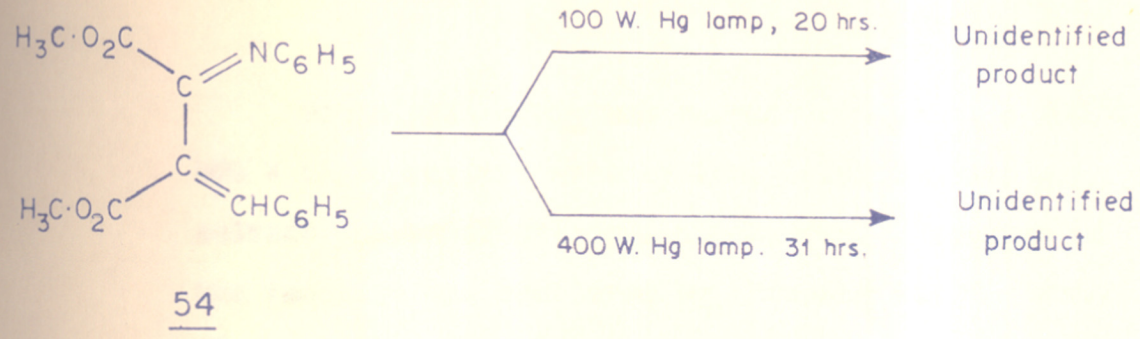
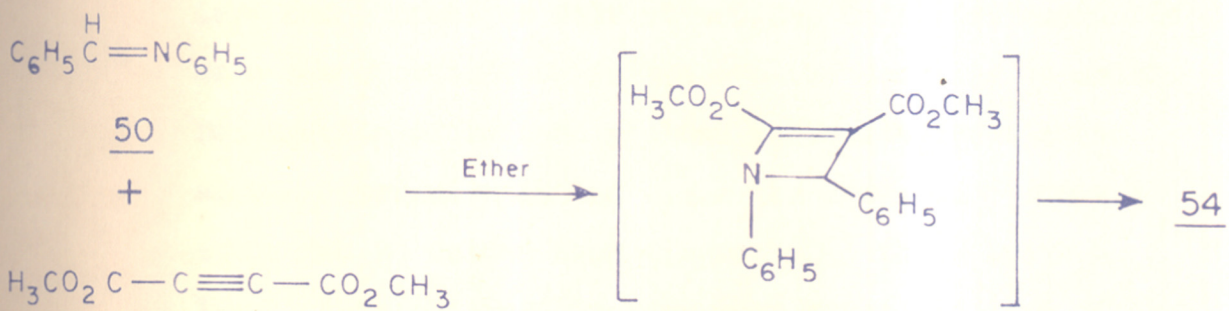


CHART – 12 .

Snyder et al.[14] have reported that benzalaniline 50 and the acetylinic ester 51 react in ether to give the addition product 54 (in low yields) which has a composition corresponding to the addition of one mol of anil 50 to one mol of ester 51. Presence of small amount of water greatly improved the yield of the addition product 54. Snyder[14] suggested that the reaction involves hydrolysis of the anil 50 followed by addition of liberated aniline to the acetylenic ester 51 giving rise to two tautomeric compounds 52A and 52B. Condensation of the latter with benzaldehyde then yields the heterodiene 54 (Chart 12). Snyder et al.[14] confirmed the structure of 54 by its formation from methyloxalacetate 53 and benzalaniline 50 in the presence of trace of water; and also from benzaldehyde 48, aniline 49 and dimethyl acetylene-dicarboxylate 51. Dimethyl acetylenedicarboxylate 51 and benzalaniline 50 were mixed in diethyl ether, trace of water was added and the mixture kept at room temperature for 48 hrs. Work up gave methyl-α-benzal-α'-phenyl iminosuccinate 54 as a white mass. Expecting 54 to be a very reactive heterodiene system, attempts were made to photocyclize it in the hope of preparing N-arylazetine ring system (Chart 13).


H3C·O2C
NC6H5
C
C
H3C·O2C
CHC6H5
100 W. Hg lamp, 20 hrs.
Unidentified product
400 W. Hg lamp. 31 hrs.
Unidentified product

54


C6H5 C H NC6H5
50
+
H3CO2C — C ≡ C — CO2CH3
51
Ether
H3CO2C
CO2CH3
N
C6H5
C6H5
55
54

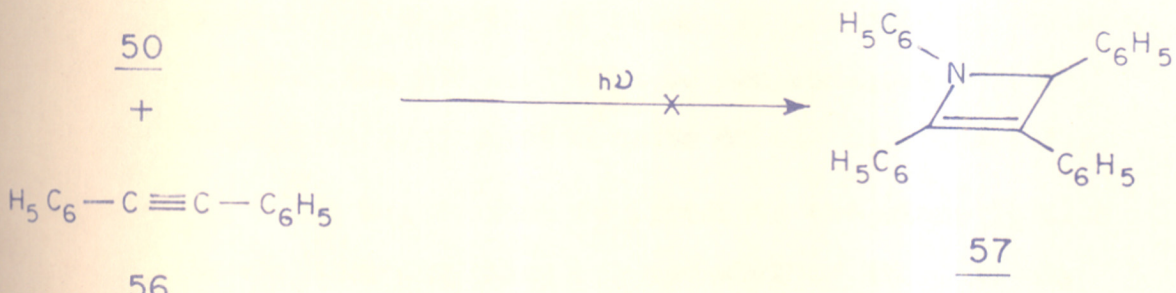

50
+
H5C6 — C ≡ C — C6H5
56
hν
X
H5C6
N
C6H5
H5C6
C6H5
57

CHART — 13.

Photolysis of 54 was carried out using a 100 W, 400 W high pressure mercury lamp using benzene as solvent and under nitrogen atmosphere. Progress of the reaction was monitered by checking its TLC from time to time.

Irradiation of 54 for 20 hrs, using a 100 W lamp and benzene as solvent medium, indicated emergence of a new spot on TLC, just above the starting material. Evaporation of benzene yielded yellowish brown solid with a depression in the m.p. The crude compound was subjected to column chromatography. A thick brown liquid thus obtained in very poor yield and most of the starting material was recovered back. NMR spectrum indicated presence of a ghost peak at 1.2 δ (s), OCH_3 at 3.6 δ (s), methine at 5.6 δ and aromatic protons at 7.02 δ with integration ratio 0.5 : 3 : 1 : 18 respectively. On this basis it was difficult to assign any definite structure to the product isolated. Irradiation for more than 20 hrs resulted in the emergence of some more spots on the TLC (Chart 13).

It was decided to irradiate the diene 54 with a 400 W mercury lamp and see whether there is any change in the reaction product pattern. However, under these conditions of photolysis even for 31 hrs

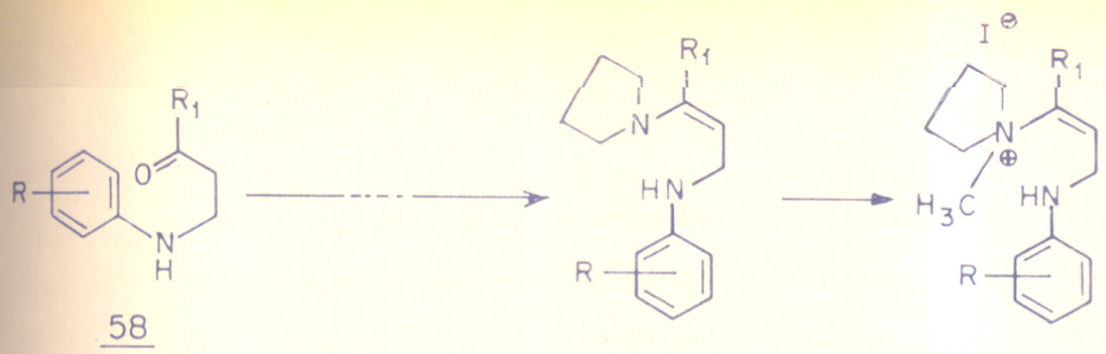
failed to give the desired azetine. A study of the spectral data of various reaction products which were isolated did not lead to any definite conclusions regarding structure.

In accordance to Cantrell[12] and Yang's[13] observations it is likely that N-arylazetine 55 might have been formed during the addition of benzalaniline 50 to dimethyl acetylenedicarboxylate 51, but the azetine formed rapidly undergoes fission to give the stable heterodiene 54 (Chart 13).

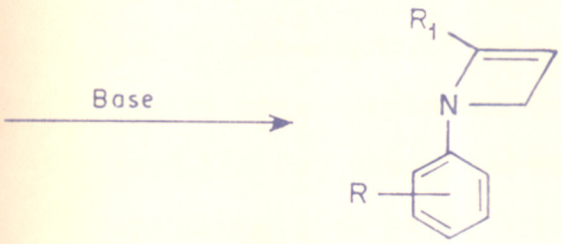
In another attempt a 1 : 1 mixture of diphenylacetylene 56 and benzalaniline 50 was irradiated using benzene, concentrated H_2SO_4, EtOH/HCl/H_2O as different solvent systems. This attempt also failed to yield the desired azetine (Chart 13).

A new approach was thought in which a β-arylaminoketone was to be converted into an enamine and then to the enamine methiodide. Treatment of the latter with base was expected to give the desired N-arylazetine 59 (Chart 14).

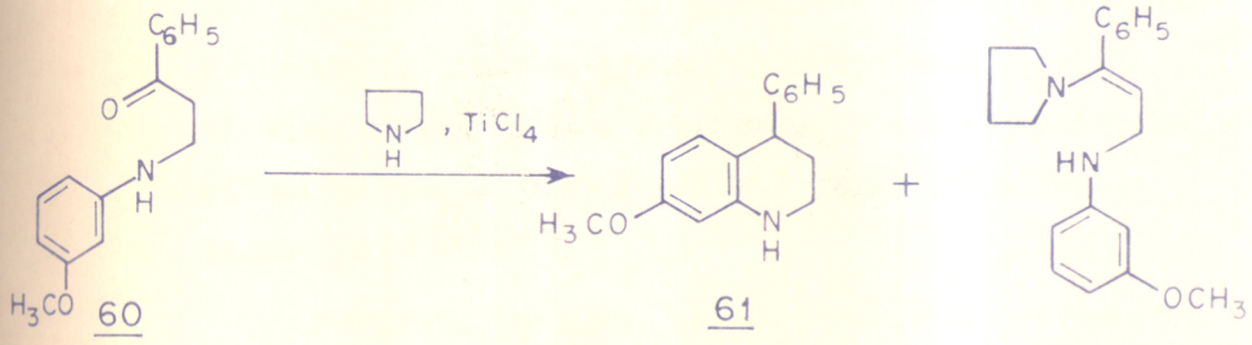
Ketones are reported to be readily converted to enamines[15,16] by condensation of the carbonyl function with a secondary amine such as pyrrolidine, morpholine or piperidine and azeotropic removal of water, with a solvent such as benzene. In some cases,



58



59



60

61 + 63

62 + 63

CHART – 14

acid catalysis with p-toluene sulfonic acid or benzoic acid and refluxing in toluene or benzene is found useful. The ease of formation of the enamine depends on the structure of the secondary amine as well as the structure of the ketone. Thus pyrrolidine reacts faster than morpholine or piperidine. Six membered ring ketones without α-substituent form pyrrolidine enamines, even at room temperature in methanol[17] and morpholine enamines are generated in cold acetic acid[18].

Literature survey revealed more recent methods for synthesis of enamines at low temperatures. White and Weingarten[19] have thus reported a versatile enamine synthesis by allowing a stoichiometric mixture of titanium tetrachloride, a secondary amine and aldehyde/ ketone to react. This leads to a rapid and direct synthesis of enamine.

Following the above method β-(m-methoxyphenylamino)-propiophenone 60[2] was reacted with pyrrolidine in the presence of titanium tetrachloride. On work up, the reaction product showed three new spots on TLC along with the spot corresponding to unreacted starting ketone 60. Column chromatography yielded three fractions in poor yield (Chart 14).

NMR spectrum of first fraction (R_f 6.5, benzene)

indicated it to be a mixture of 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 61 and probably the desired enamine 62 which may be present in very small quantity. NMR spectrum of the second fraction indicated it to be *m*-anisidine which is obviously formed by cleavage of the parent aminoketone 60. NMR spectrum of the third fraction (R_f 2.2, benzene) indicated it to be 7-methoxy-4-phenylquinoline 63. This was further confirmed by preparing its methoiodide and comparing m.p. with an authentic sample.[2]

A little modification was also tried. Aminoketone 60 in cold benzene (5 ~ 10°) was treated with titanium tetrachloride with stirring. In this case work up yielded a brown oil, which on chromatography gave 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 61 along with the quinoline 63.

It is reported[20] that triphenylphosphine and carbon tetrachloride converts primary and secondary alcohols into the corresponding chlorides under mild (essentially) neutral conditions.

If the compound 60 is in equilibrium with its tautomeric (enol) structure 60A even to a small extent (Chart 15), 60 in acetonitrile was treated with triphenyl phosphine and carbon tetrachloride at room temperature with the view to prepare 60B. After 24 hrs, triethylamine was added. The reaction mixture on work up gave a dark brown thick liquid. Chromatography over silica yielded a dichloroolefin 64 which can be formed by a Wittig type reaction (Chart 15).

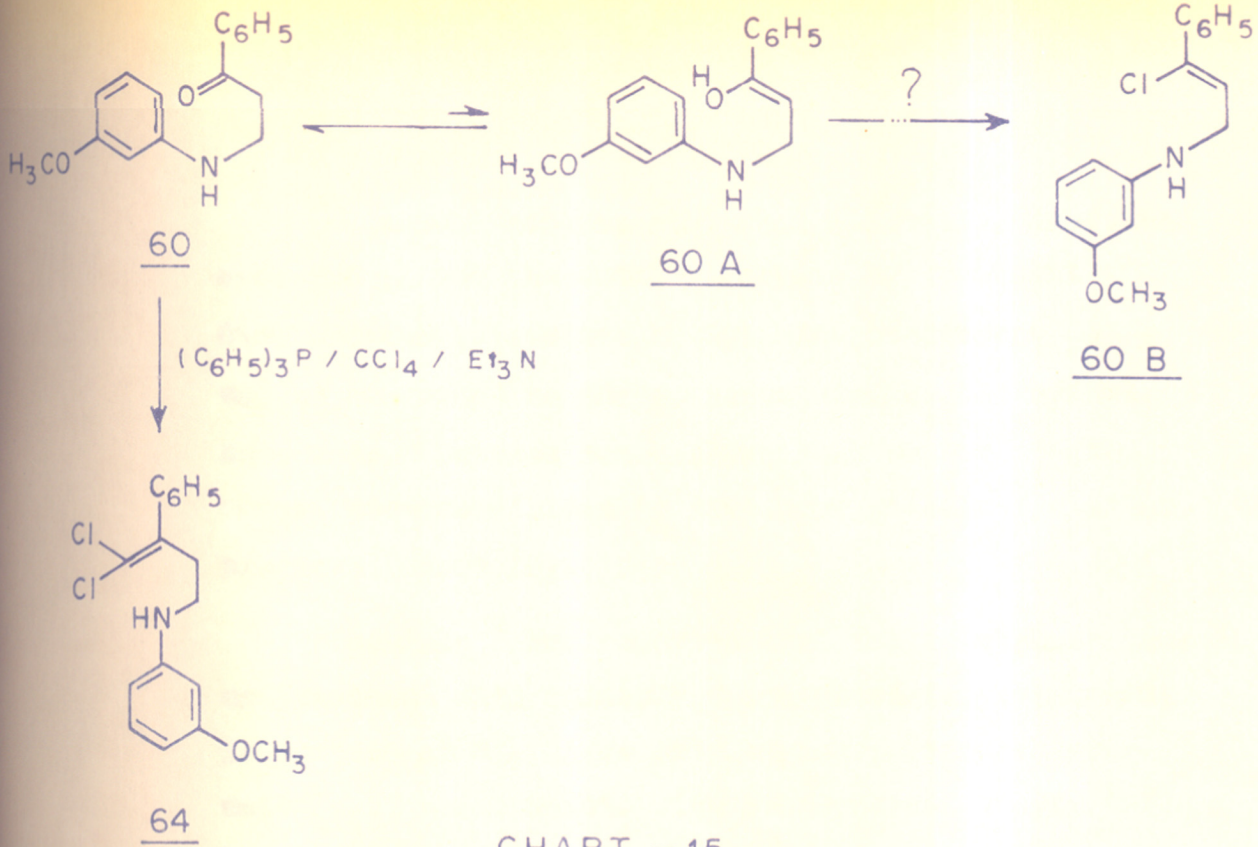


CHART – 15.

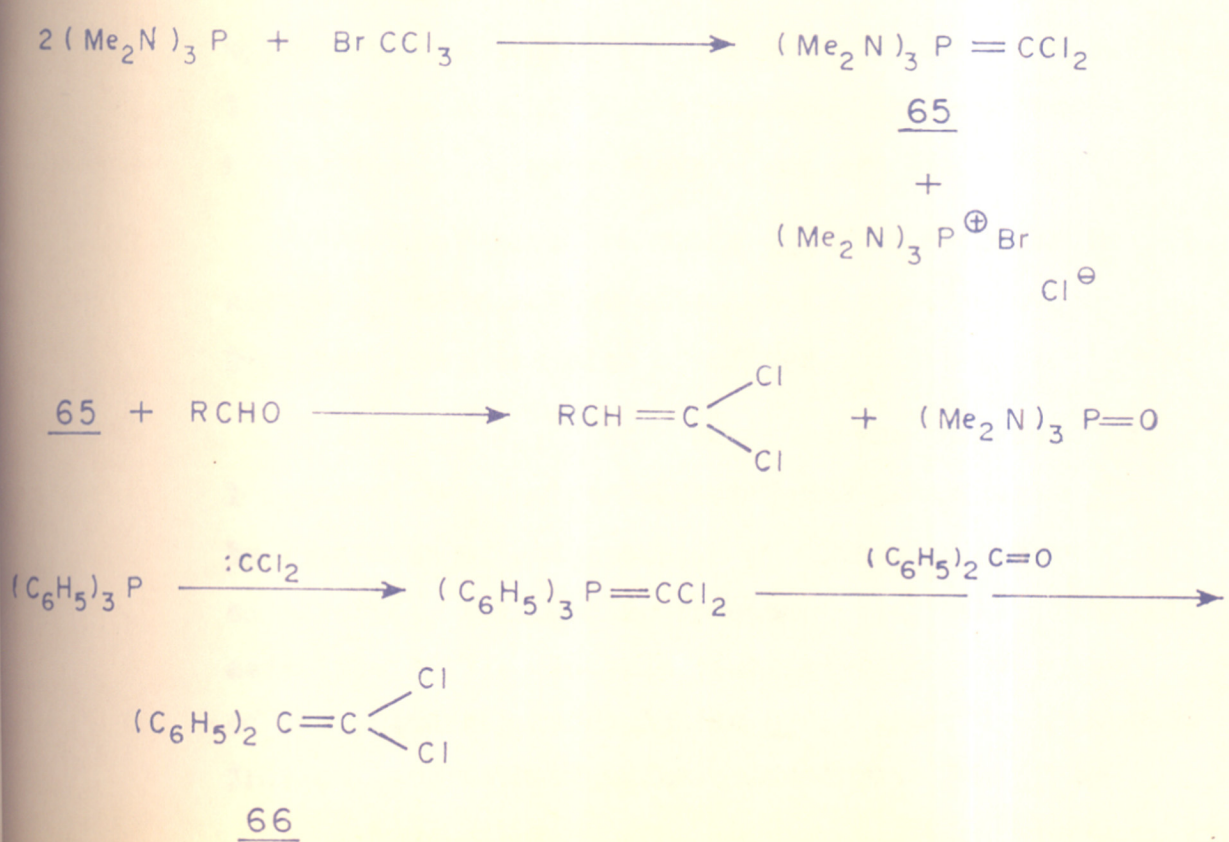


CHART — 16.

Salmond[21] has reported that aliphatic, aromatic, cyclopropyl and steroidal aldehydes by treatment of dichloromethylenetris-dimethylaminophosphorane 65 can be converted to the corresponding dichlorovinyl compounds. Ketones react sluggishly or not at all under these conditions to give poor yields of similar products (Chart 16).

Speziale[22] has reported that triphenylphosphine, on treatment with chloroform and potassium-t-butoxide in pentane at 0°, gives triphenylphosphinodichloromethylene, which reacts with benzophenone to yield 1,1-diphenyl-2,2-dichloroethylene 66 (Chart 16).

NMR spectrum of 64 shows a quintet at 3.00 δ, 4p, methoxy at 3.65 δ(s), 3p, exchangable NH at 3.4 δ, 1p. IR shows absence of >C=O absorption and presence of NH at 3265 cm^{-1}, mass shows M^{+} at m/e 322.

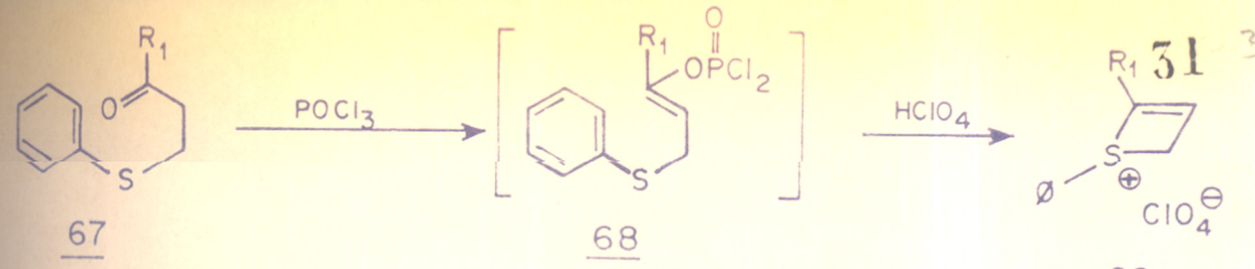
As the desired chloride 60B from β-arylaminoketone 60 could not be obtained this route to N-arylazetines was also abandoned.

Tilak et al.[23] have reported the synthesis of 1-3-phenyl-1-thioniumcyclobut-2-ene perchlorate 69 by treatment of ketosulphide 67 with phosphorous oxychloride, followed by treatment with 70% perchloric acid (Chart 17). In this synthesis the keto group of the precursor ketosulphide 67 is probably converted into an oxophosphoniumdichloride derivative 68 by

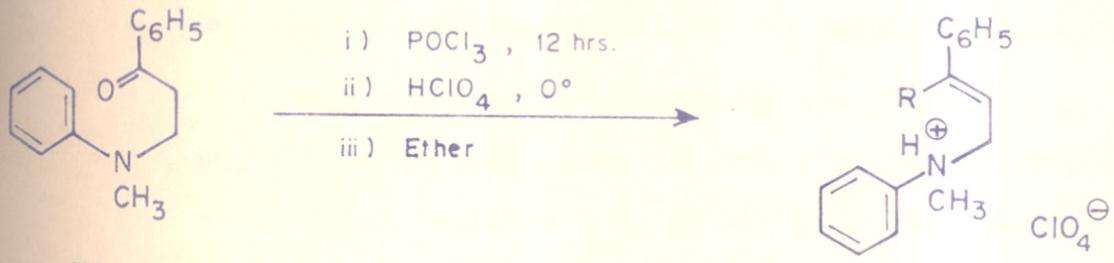
interaction with phosphorous oxychloride. The dichlorooxophosphonium moiety then serves as a good leaving group. When intermediate 68 is treated with 70% perchloric acid resulting in cyclisation, to yield 1-3-phenyl-1-thioniumcyclobut-2-ene perchlorate 69.

On the above lines, it was hoped that β-(N-methylanilino)propiophenone 70[24] could be used as a starting material for a similar synthesis of N-arylazetine. 70[24] was prepared by interaction of N-methylaniline and β-diethylaminoethylphenyl ketone hydrochloride in ethanol. 70 was treated with phosphorous oxychloride for 12 hrs at room temperature and then reacted with perchloric acid. Diethyl ether was added and the mixture was kept at -20°. White solid separated out. NMR spectrum of the solid shows a methyl doublet at 3.65 δ, methylene at 4.2 δ, m and aromatic protons at ~ 7.7 δ, m with integration ratio for aromatic to aliphatic protons as 51:36.

A study of the NMR spectrum indicates that the above product is the perchlorate 71 (Chart 17). With a view to avoid salt formation and also the fact that azetines may not be stable under acidic conditions, it was decided to modify the procedure. Instead of starting with a tertiary aminoketone 70, compound 60



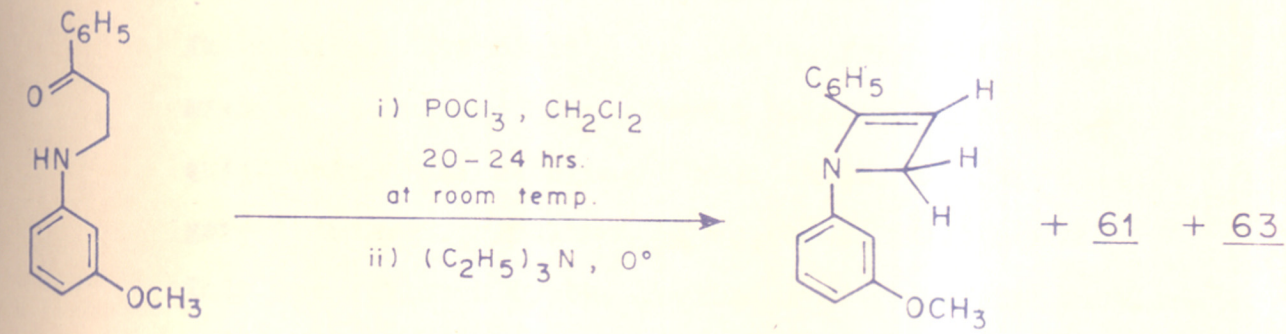
67 68 69



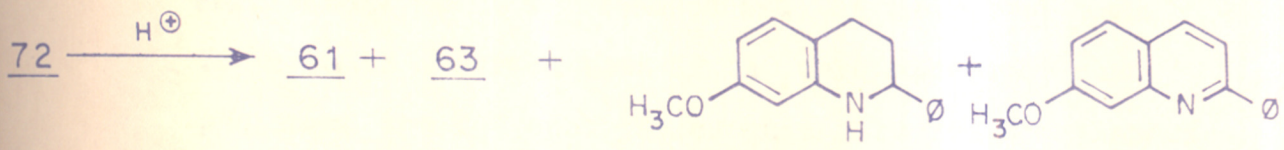
70 71

R = O — PCl_2 (O) or OH

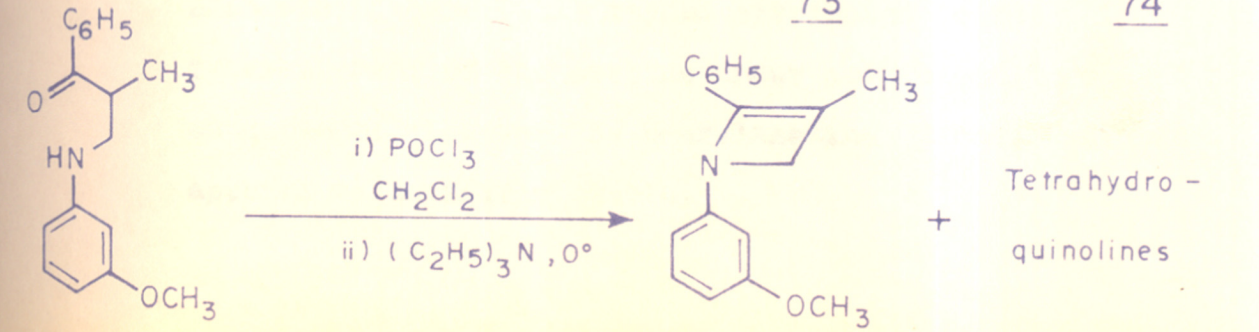
CHART – 17.



60 72



73 74



75 76

CHART – 18

was used and triethylamine was employed instead of perchloric acid to neutralise the reaction mixture.

Under the above conditions the N-arylazetine was indeed formed. Thus treatment of β-(m-methoxyphenylamino)propiophenone 60[2] in methylene chloride with phosphorous oxychloride for 20-24 hrs at room temperature, follwed by treatment with triethylamine gave a dark brown liquid. Evaporation of methylene chloride under reduced pressure and dilution of the reaction mixture with benzene in cold, precipitated triethylamine hydrochloride, which was removed by filtration. Evaporation of benzene from the reaction mixture (solution) gave a brown coloured liquid. A quick column chromatography over silica of the latter gave tetrahydroquinoline 61 as the first fraction. This was followed by the desired 1-N-(m-methoxyphenyl)-2-phenylazetine 72 as a crystalline compound (Chart 18). Under the above reaction conditions some starting aminoketone remains unreacted and was recovered back. It was also observed that if the chromatography was prolonged the TLC spot corresponding to the N-arylazetine also diminishes. This may be attributed to the rearrangement of the azetine under acidic (silica) conditions. However the N-arylazetine 72 once isolated appears to be fairly stable.

NMR spectrum of the azetine 72 shows a methoxy singlet at 3.75 δ ; a set of two quartets, one centred at 4.1 δ and the other at 4.4 δ corresponding to two methylene protons, a multiplet at 5.8 δ corresponding to the proton on double bond and aromatic protons centred at 7.1 δ (Fig.1). IR shows absence of NH absorption. Mass spectrum shows M^+ at m/e 237.

To study the ring expansion of the N-arylazetine 72 under acidic conditions it was treated with 70% sulphuric acid at room temperature. Work up gave a brown liquid, which on GLC analysis was found to be a mixture of 2-phenylquinoline 74 and 4-phenylquinoline 63 and their corresponding tetrahydroquinoline derivatives 73 and 61. The identity of these compounds in the reaction mixture was confirmed by comparing the peaks derived from authentic samples of the respective quinolines and their tetrahydroderivatives. The result of this experiment lends support to the reaction mechanism suggested earlier in Chart 8 to account for the formation of rearranged quinolines and tetrahydroquinolines on acid catalysed cyclodehydration of β-arylaminoethyl ketones.

Another attempt to synthesise N-arylazetine was also successful to a limited extent. Treatment

of α-(m-methoxyphenylamino)methylpropiophenone 25 [25] with phosphorous oxychloride, followed by triethylamine furnished a mixture of tetrahydroquinolines and 1-H-(m-methoxyphenyl)-3-methyl-2-phenylazetine 26. Attempts to purify the azetine 26 by repeated column chromatography proved unsuccessful as 26 was unstable under these conditions (Chart 18).

EXPERIMENTAL

β-(*m*-Methoxyphenylamino)ethyl(*p*-methoxyphenyl)ketone 39

Interaction of *m*-anisidine (12.3 g, 0.1 mol) with Mannich base hydrochloride of *p*-methoxyacetophenone (24.6 g, 0.1 mol) in boiling rectified spirit for 2 hrs and cooling gave 39 as brown solid (17.0 g). Recrystallization of the crude product afforded 39 as white needles (15.2 g, yield 53.3%), m.p. 83°C.
IR: >C=O at 1680 cm^{-1}, NH at 3225 cm^{-1}
NMR: (CCl_4, δ); D_2O exchangable NH at 3.83, s (broad), 1 p; methoxy (-*m*) at 3.6, s, 3p; methoxy (-*p*) at 3.7, s, 3p; methylene centred at 3.27, m, 4p; aromatic centred at 6.5, m, 4p; aromatic centred at 7.4, q, 4p.
Analysis: Found C, 71.2; H, 6.6; N, 4.7. $C_{17}H_{19}NO_3$ requires C, 71.57; H, 6.6; N, 4.9%.
Mass: M^+ 269.

3-(*m*-Methoxyphenylamino)-1-(*p*-methoxyphenyl)-1-propan-1-ol 40.

A solution of ketone 39 (6.1 g) in ethanol was treated with sodium borohydride (0.51 g) and stirred for 1/2 hr at room temperature. Reaction mixture was refluxed for 1 hr, cooled, ethanol evaporated and the contents diluted with water (100 ml). Acidification with dilute acetic acid and extraction with benzene afforded 40 as brownish liquid. Vacuum distillation

of the crude product gave carbinol 40 as colourless liquid (5.3 g, yield 86.3%), b.p. 175°/5 x 10^{-3} mm.
IR: NH, OH; broad 3350 cm^{-1}
NMR: (CCl_4, δ); D_2O exchangable NH and OH (broad) and methoxy at 3.53, 8p; methylenes at 1.73, q, 2p; methylenes at 2.9, t, 2p; benzylic at 4.4, t, 1p; aromatic centred at 6.5, m, 8p.
Analysis: Found C, 70.8; H, 7.2; N, 4.7. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.3; N, 4.8%.

Cyclisation of carbinol 40 using triphenylphosphine dibromide, triethylamine.

Carbinol 40 (5.0 g) was treated with triphenylphosphine dibromide [prepared from triphenylphosphine (6.8 g) and bromine (1.2 ml)] in acetonitrile (60 ml), followed by dropwise addition of triethylamine (5.2 g) in acetonitrile (20 ml) at 0-5°, with stirring. Stirring was continued for 72 hrs. Reaction mixture was filtered and the filtrate evaporated by rotary evaporator. Petroleum ether extraction of the crude product followed by concentration of the extracts gave 6.2 g of thick liquid. Chromatography of the above liquid over silica gave triphenylphosphine as the first fraction (0.760 g); second fraction obtained as yellowish liquid was identified as 1-N-(m-methoxyphenyl)-2-(p-methoxyphenyl)-azetidine 41 (0.082 g, 1.75%).

Further elution gave 7-methoxy-2-(p-methoxyphenyl)-1,2,3,4-tetrahydroquinoline 42 (1.062 g, yield 23.5%) m.p. 67°; followed by 7-methoxy-4-(p-methoxyphenyl)-1,2,3,4-tetrahydroquinoline 43 as liquid, (0.84 g, yield 17.9%), b.p. 115/1 x 10^{-2} mm.

NMR of 41: (CCl_4, δ); methoxy at 3.23, s, 3p; methoxy at 3.66, s, 3p; methylene 1.83, m, 4p; methine 4.4, t, 1p; aromatic 6.8, m, 8p.
Analysis: Found C, 75.6; H, 6.8; N, 5.1. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%.
NMR of 42: (CCl_4, δ); D_2O exchangable NH at 3.65, 1p; methoxy at 3.5, s, 3p; methoxy at 3.7, s, 3p; C_3 methylene 1.9, m, 2p; C_4 methylene 3.0, m, 2p; C_2 methine 4.26, t, 1p; aromatic centred at 6.5, m, 7p.
Analysis: Found C, 76.1; H, 7.1; N, 5.1. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%.

NMR of 43: (CCl_4, δ); D_2O exchangable NH at 3.5, s, broad, 1p; methoxy at 3.6, s, 3p; methoxy at 3.7, s, 3p; C_3 methylene, 2.0, m, 2p; C_2 methylene, 3.13, t, 2p; C_4 methine, 3.9, t, 1p; aromatic centred at 6.4, m, 7p.
Analysis: Found C, 75.8; H, 7.2; N, 5.1. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1 ; N, 5.2%.

Reaction of β-(m-methoxyphenylamino)propiophenone 60[2] with pyrrolidine and titanium tetrachloride.

To a stirred solution of ketone 60 (5.1 g, 0.002 mol) and pyrrolidine (4.26 g, 0.002 mol) in dry benzene at 0-5°, $TiCl_4$ (1.9 g, 0.001 mol) was added over 30 min., while keeping the temp. of reaction mixture below 10°. After $TiCl_4$ addition, reaction mixture stirred at room temperature for 12 hrs, decomposed with water, filtered, extracted with benzene, benzene extracts dried over anhydrous Na_2SO_4. Evaporation of benzene gave crude product (3.1 g).

Chromatography of the crude product gave thick liquid (0.228 g, which was identified as a mixture of 7-methoxy-4-phenyl,1,2,3,4-tetrahydroquinoline 61 and probably the desired enamine 62.

NMR (CCl_4, δ) (Fraction with Rf 6.5, benzene).

Four sets of multiplets at 0.9, 1.3, 2.0 and 2.2 singlet at 3.6 with shoulder aromatic centred at 6.6, m; integration ratio; aliphatic : aromatic

59 52

Second fraction was identified as m-anisidine (0.100 g).

Third fraction was identified as 7-methoxy-4-phenylquinoline 63 (0.184 g), m.p. 69°.

NMR: (CCl_4, δ); (Fraction with Rf 2.2, benzene); methoxy at 3.4, s, 3p; aromatic centred at 7.4, m, 10p. Structure of 63 was confirmed by preparing its methyl iodide salt and comparing m.p. with authentic samples[2]. m.p. of methiodide 214-15°.

NMR: (TFAA, δ); methoxy at 4.2, s, 3p; methoxy at 4.2, s, 3p; NCH_3 at 4.7, s, 3p; aromatic centred at 8.35, m, 10p.

Treatment of 60 with $TiCl_4$

Treatment of 60 (0.255 g, 0.001 mol) in 12 ml benzene with $TiCl_4$ (0.95 g, 0.0005 mol) for 1 hr at ice-water temperature and decomposition of the reaction mixture with cold water and extraction with benzene and work up gave (0.104 g) crude product. Column chromatography of the above product furnished 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 61 (0.042 g, 17.64%) and 7-methoxy-4-phenylquinoline 63 (0.038 g, 16.2%) which were identified by comparing NMR with authentic samples[2].

α-(m-Methoxyphenylamino)ethyl β,β-dichlorostyrene 64

To a stirred solution of triphenylphosphine (2.6 g, 0.01 mol) in dry CH_3CN (10 ml) was added carbon tetrachloride (0.154 g, 0.01 mol) with stirring. 60 (2.55 g,

0.001 mol) was added as soon as the reddish yellow coloured complex formation was observed and stirred for 12 hrs. Further acetonitrile evaporated and the crude product treated with triethylamine or aqueous bicarbonate solution. Benzene extracts on drying over NO_2SO_4 evaporated and column chromatography over silica gel gave 64 as thick yellow liquid (0.358 g, 11.11%), (b.p. 130-5°/3.4 x 10^{-2} mm). Further elution afforded unreacted (0.87 g, 33.7%) 60.

Analysis: Found C, 63.8; H, 5.6; N, 4.5; Cl, 21.9.
$C_{17}H_{17}Cl_2NO$ requires C, 63.34; H, 5.78; N, 4.3; Cl, 22.5%.

Mass : M^+ 322.

β-(N-Methylanilino)propiophenone 70 [24]

Interaction of N-methylaniline (10.7 g, 0.1 mol) with Mannich base hydrochloride of acetophenone viz. (β-dimethylaminoethylphenyl ketone hydrochloride) (22.4 g, 0.1 mol) in boiling ethanol for 2.5 hrs gave on cooling 70 as solid mass. Recrystallisation of the crude product gave 70 as white needles (10.0 g, 42%), m.p. 61°.

NMR: (CCl_4, δ) discussed earlier.

1-N-(*m*-Methoxyphenyl)-3-phenylazetine 72

60[2] (1.25 g, 0.005 mol) in 20 ml dry methylene chloride was treated with phosphorousoxychloride (1.0 g, 0.007 mol) with stirring. Stirring continued for 20 hrs. Reaction mixture cooled with ice salt mixture and treated dropwise with triethylamine (3.1 ml, excess). After 2 hrs, methylene chloride was evaporated under reduced pressure and the contents diluted with dry benzene in cold. Triethylamine hydrochloride separated out, filtered and benzene evaporated under reduced pressure (without heating the reaction mixture above 40°). (Complete evaporation of benzene reduces the yield of 72.) Thick brown liquid obtained, on a quick column chromatography gave 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 61 as the first fraction (0.134 g, 22.5%).

Second fraction was identified as the desired azetine 72 which crystallises on standing, m.p. 104°, (0.228 g, 19.2%). IR, NMR ($CDCl_3$) and Mass discussed earlier.

The third fraction was identified as the unreacted ketone 60 (0.126 g, 10.1%).

The fourth fraction was identified as 7-methoxy-4-phenylquinoline 63 (0.102 g, 17.4%).

61 and 63 were identified by comparing GLC and NMR spectra with those of authentic samples.

1-N-(m-Methoxyphenyl)-3-methyl-2-phenylazetine 76.

Ketone 75 [2,25] (1.1 g) was similarly treated as above, with phosphorous oxychloride (1.1 ml) (24 hrs, room temperature) and triethylamine (3.1 ml) with cooling. Work up and column chromatography of the crude product over silica gave a mixture of 7-methoxy-4-phenyl-3-methyl-1,2,3,4-tetrahydroquinoline and the azetine 76 (0.186 g). Many attempts to purify 76 by repeated column chromatography or PLC proved to be unsuccessful.

NMR (CCl_4, δ) of the above mixture indicated CH_3 at 2.01, s; OCH_3 at 3.8, s, besidies the signals corresponding to tetrahydroquinoline.

ILLUSTRATION

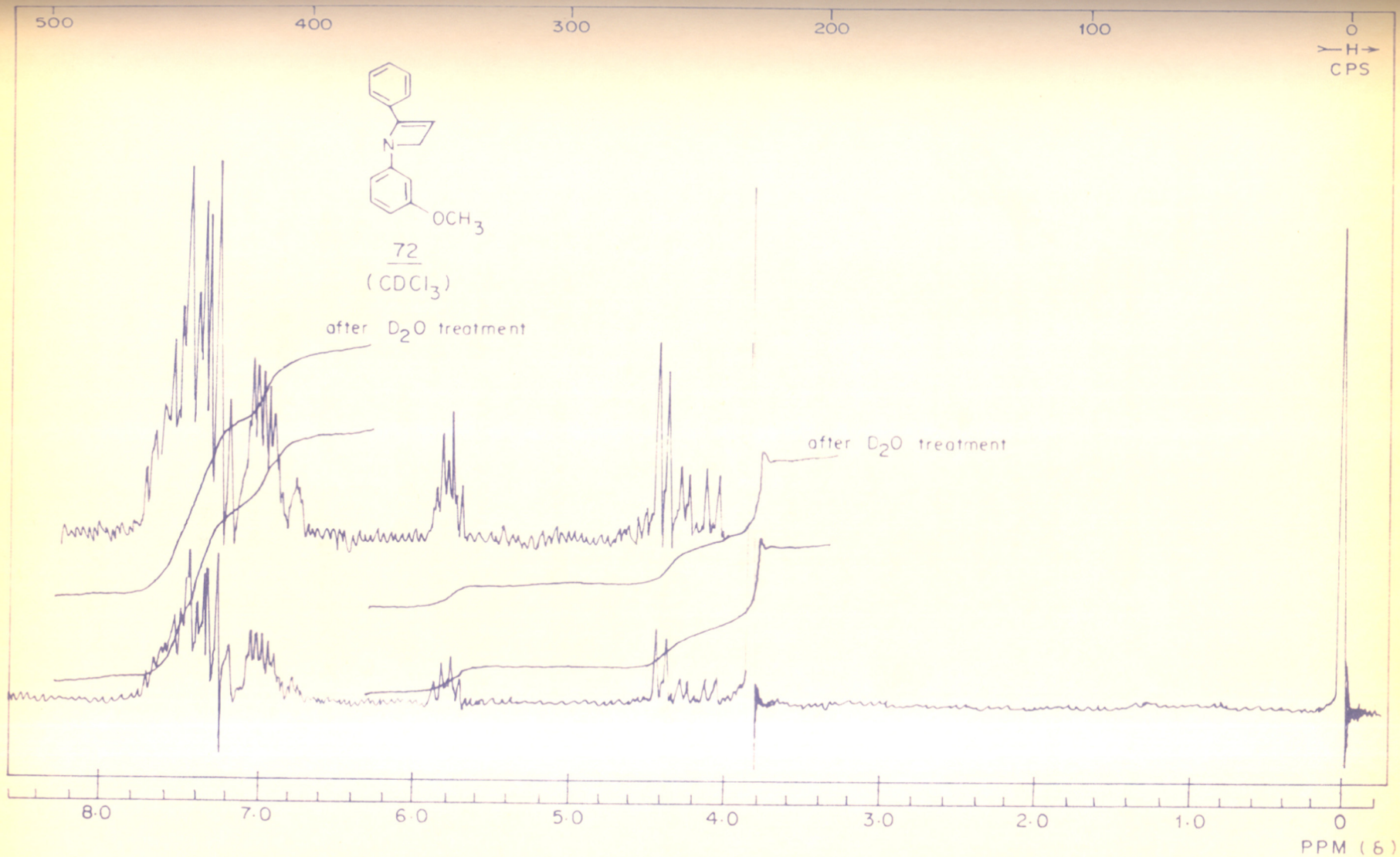

500
400
300
200
100
0
H
CPS
N
OCH3
72
(CDCl3)
after D2O treatment
after D2O treatment
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG.-1

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CHAPTER II : ATTEMPTS TOWARDS STEREOSELECTIVE SYNTHESIS OF 2,3-DISUBSTITUTED N-ARYLAZETIDINES

Introduction

Tilak *et al.*[1] have reported earlier, the cyclodehydration of 3-arylamino-1-propan-1-ol 1 by means of 70% sulphuric acid to give 3,4-disubstituted 1,2,3,4-tetrahydroquinoline 2 and/or rearranged 2,3-disubstituted-1,2,3,4-tetrahydroquinoline 3.

Formation of 2 by the cyclodehydration of 1 was normally expected. However the simultaneous formation of 3 was rationalised on the basis of the involvement of an intermediate N-arylazetidine (A) which on ring expansion led to the two possible tetrahydroquinolines.

To prove the mechanism shown in Chart 1, it was necessary to prepare N-arylazetidines and rearrange them to tetrahydroquinolines under acidic conditions. Soon after a convenient synthesis of N-arylazetidines was achieved by Tilak and co-workers[2].

Kulkarni[3] has studied the cyclodehydration of 3-arylaminobutan-1-ols and 1-arylaminobutan-3-ols 4 (R_1 and R_2 being phenyl and methyl or vice versa) by means of 70% sulphuric acid, which led to 2,4-disubstituted-1,2,3,4-tetrahydroquinolines 5 and/or 6 (Chart 1).

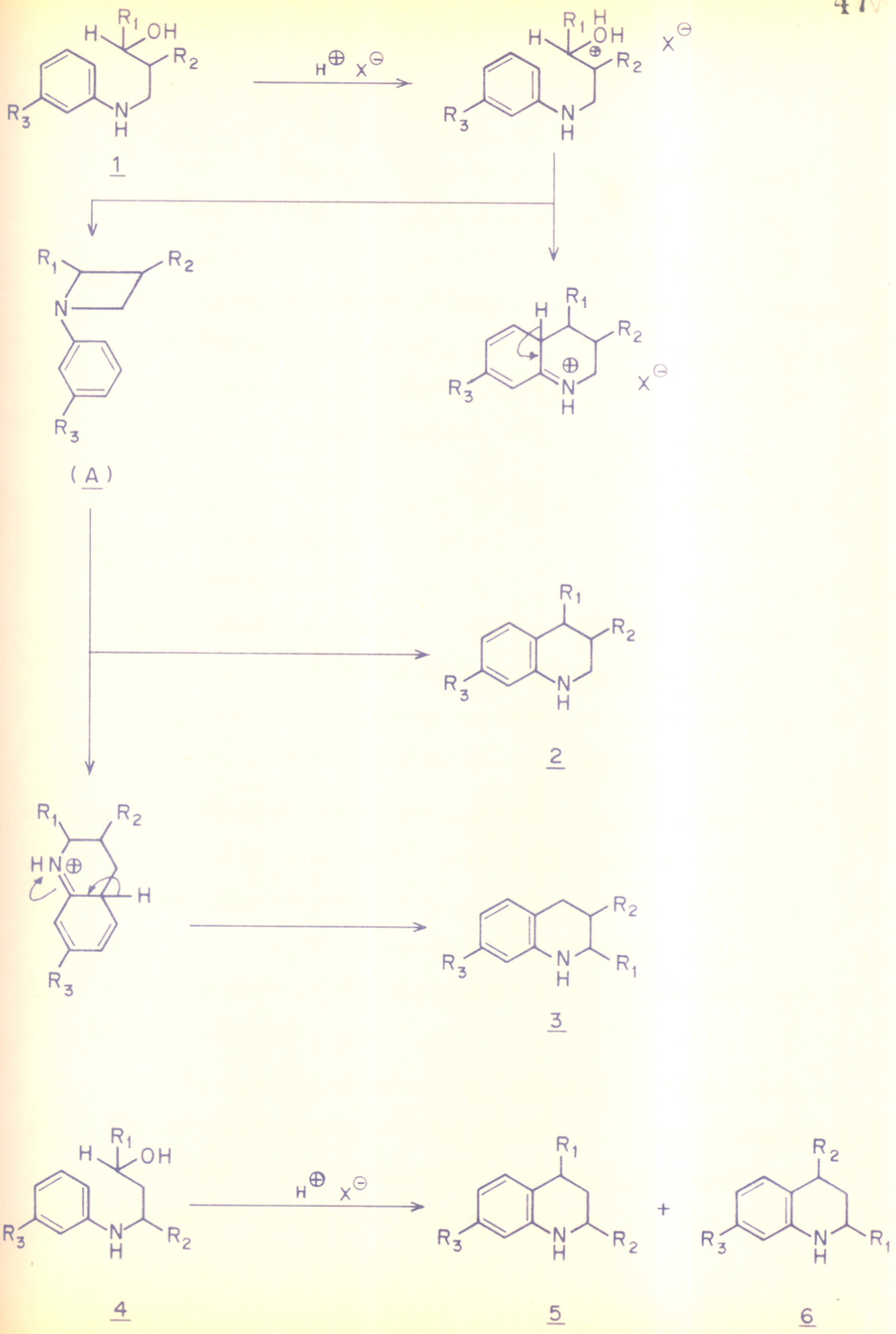


CHART - 1

Interaction of m-anisidine 7 with benzalacetone 8 and crotonophenone 11 led respectively to [β-(3'-methoxyphenylamino)-β-phenyl]ethyl methyl ketone 9 and β-(3'-methoxyphenylamino)propiophenone 12. Sodium borohydride reduction of 9 gave 1-(3'-methoxyphenylamino)-1-phenylbutan-3-ol 10 and that of 12 gave 3-(3'-methoxyphenylamino)-1-phenylbutan-1-ol 13 (Chart 2).

Condensation of m-anisidine 7 with benzoylacetone 14 gave a mixture of phenyl-(3'-methoxyphenylamino)-methyleneacetone 15 and methyl-(3'-methoxyphenylamino)-methyleneacetophenone 16. This mixture was separated on a spinning band column to yield the ketones 15 and 16 which on sodium borohydride reduction gave the carbinols 17 and 18 respectively (Chart 2).

Sulphuric acid (70%) catalysed cyclodehydration of 10 prepared by sodium borohydride reduction of 9 yielded cis-4-methyl-2-phenyl-7-methoxytetrahydroquinoline 19. The product being exclusively cis and no rearrangement was observed during cyclodehydration (Chart 2).

Cyclodehydration of 13, prepared by sodium borohydride reduction of 12 under acidic conditions led exclusively to the rearranged trans-4-methyl-2-phenyl-7-methoxytetrahydroquinoline 20.

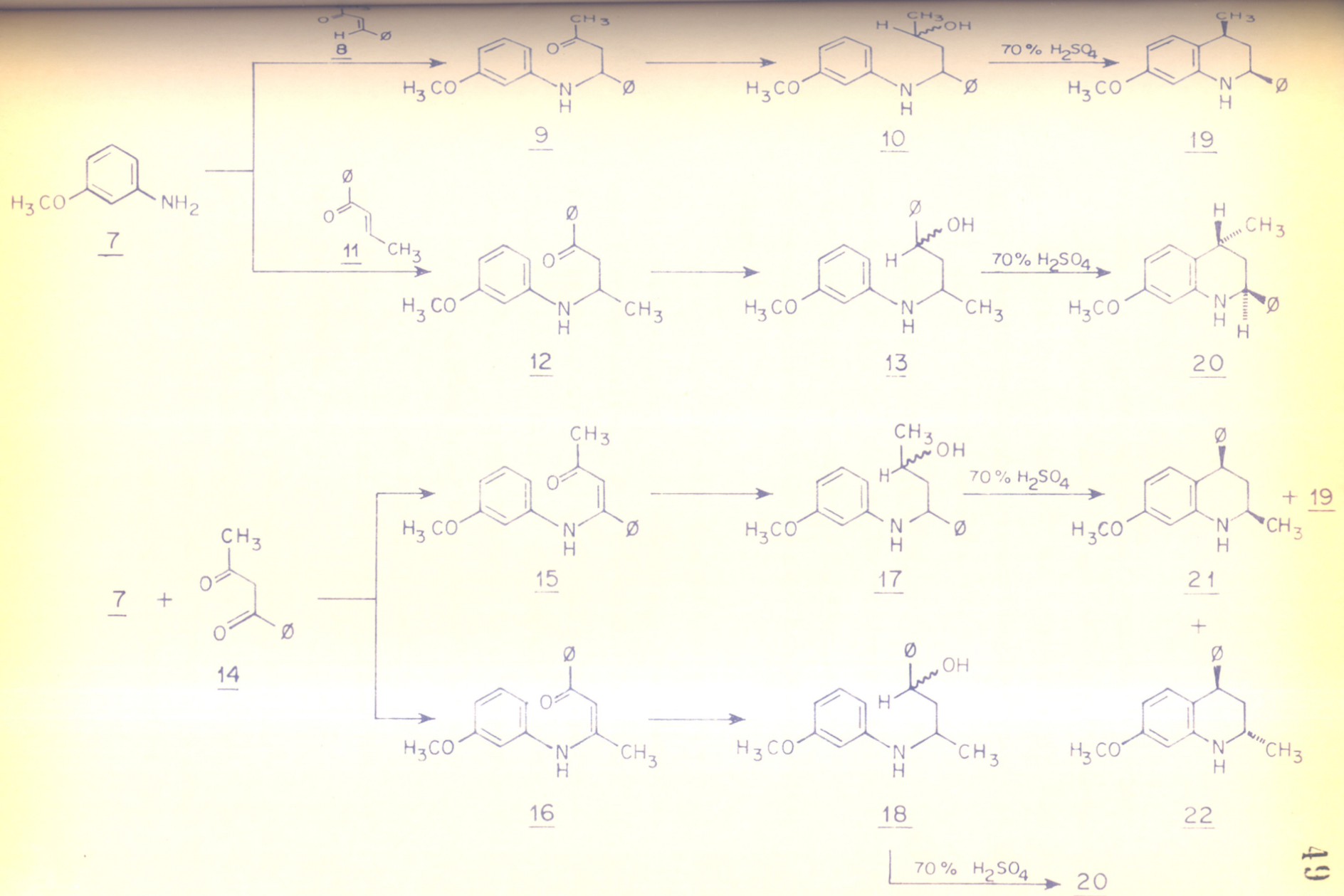

8
9
10
70% H_2SO_4
19
7
11
12
13
70% H_2SO_4
20
7 +
14
15
17
70% H_2SO_4
+ 19
21
+
16
18
22
70% H_2SO_4
20

CHART – 2.

Carbinol 17, prepared by sodium borohydride reduction of 15, however under identical cyclodehydration conditions as above yielded a mixture of the rearranged cis and trans 2-methyl-4-phenyl-7-methoxytetrahydroquinoline 21 and 22 and the normally expected 19.

Carbinol 18 prepared by sodium borohydride reduction of 16, led only to the rearranged trans-4-methyl-2-phenyl-7-methoxytetrahydroquinoline 20, the normal cyclodehydration product not being isolated (Chart 2).

The above set of cyclodehydration reactions indicated that except in one case 17, the reactions were stereoselective. Using the carbinols, which showed stereoselectivity during acid catalysed cyclodehydrations, Kulkarni[4] successfully prepared 2,4-disubstituted N-arylazetidines in a stereoselective manner, and studied their rearrangement reactions.

Excepting one example by Cromwell et al.[5] stereospecific synthesis of N-arylazetidines has not been reported so far.

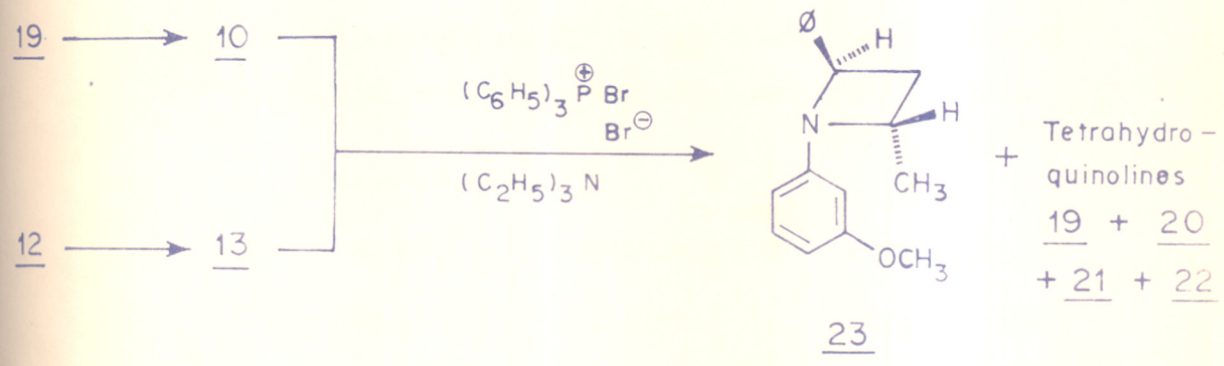
Cyclodehydration of carbinols 10 and 13 by interaction with triphenylphosphine dibromide/triethylamine led to preferential formation of trans-2-methyl-4-phenyl-1-N-(3'-methoxyphenyl)azetidine 23.

Likewise similar cyclodehydration of the carbinols 17 and 18 gave essentially cis-2-methyl-4-phenyl-1-N-(3'-methoxyphenyl)azetidine 24 along with a mixture of cis- and trans-2,4-disubstituted 1,2,3,4-tetrahydroquinolines (Chart 3).

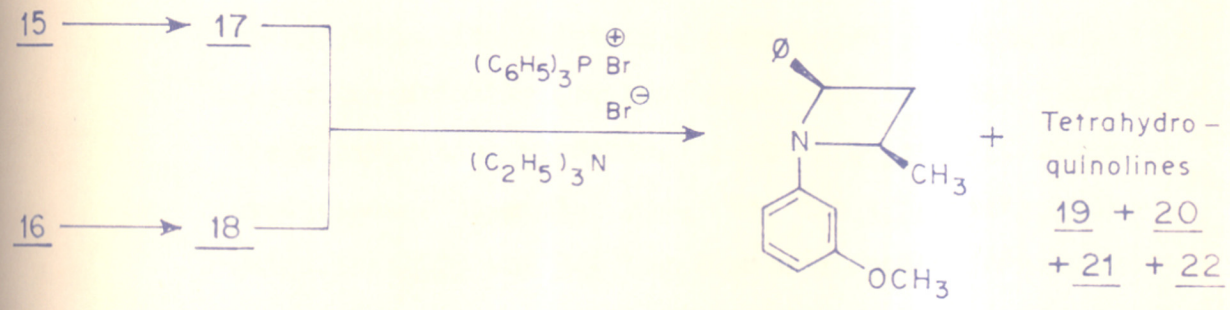
The above results indicated that carbinols 10 and 13 prepared by sodium borohydride reduction of saturated ketones (e.g. 9 and 12) yielded preferentially trans-azetidines, and the carbinols (e.g. 17 and 18) prepared by reduction of corresponding enaminoketones (e.g. 15 and 16) yielded cis-2,4-disubstituted azetidines (Chart 3).

This clearly indicated that carbinols 10, 17 and 13, 18 prepared by two different methods are configurational isomers and that the orientation of substituents in the starting carbinols has a key role to play in these cyclodehydrations.

Salama[1a] has reported earlier that cyclodehydration of carbinol 26 (obtained by sodium borohydride reduction of the enaminoketone 25) by treatment with 70% H_2SO_4, yielded a mixture of 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27 (the normal cyclodehydration product) and 7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28 (the rearranged product) in 21%


19
10
12
13
$(C_6H_5)_3 \overset{\oplus}{P}\ Br$
$Br^{\ominus}$
$(C_2H_5)_3 N$
Ø
H
N
H
CH_3
OCH_3
+
Tetrahydro – quinolines
19 + 20
+ 21 + 22

23


15
17
16
18
$(C_6H_5)_3 \overset{\oplus}{P}\ Br$
$Br^{\ominus}$
$(C_2H_5)_3 N$
Ø
N
CH_3
OCH_3
+
Tetrahydro – quinolines
19 + 20
+ 21 + 22

24

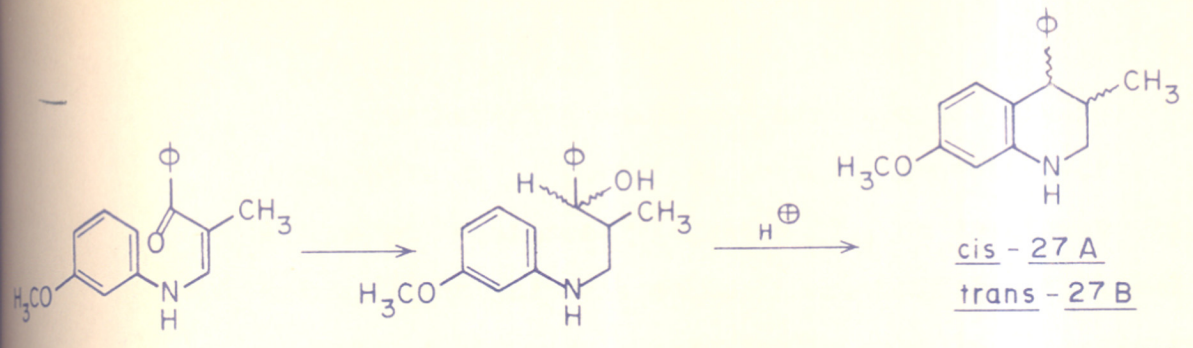
CHART – 3

and 37% yields respectively (Chart 4). By careful examination of NMR spectra and Dreiding models of various isomers of 27 and 28 Salama[10] has assigned the methyl shifts in various isomers as follows:

centred at δ		
0.73	(Normal)	cis- 27A
0.86	(Normal)	trans- 27B
1.04	(Rearranged)	trans- 28B
1.2	(Rearranged)	cis- 28A

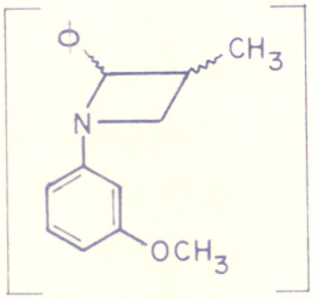
It may thus be inferred that in the above cyclodehydration reactions, rearranged products are formed in slightly greater proportion than the normal cyclodehydration products. Further trans- 28B isomer predominates over cis- 28A. The two trans-tetrahydroquinolines 27B and 28B together are formed in larger amounts than the two cis-tetrahydroquinolines 27A and 28A.

To explain the formation of rearranged tetrahydroquinoline in the above cyclodehydrations, Tilak et al.[1] postulated the intermediate involvement of 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29 (Chart 4). The latter then undergoes ring expansion under acid conditions to furnish either or both of the normal and rearranged tetrahydroquinolines.



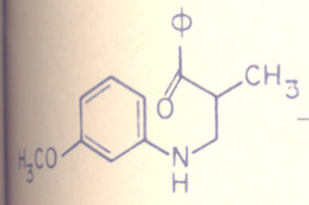
25 → 26 → cis - 27 A, trans - 27 B

cis - 28 A
trans - 28 B

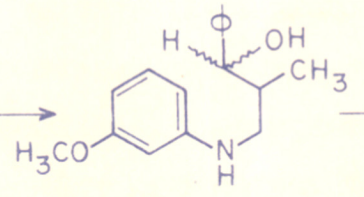


29

cis - 29 A
trans - 29 B



30



31

$(C_6H_5)_3P/Br_2$, $(C_2H_5)_3N$ → 29 A,B + 27 A,B + 28 A,B

CHART 4

Incidentally Kulkarni[3] has reported earlier that carbinol 31 (obtained by $NaBH_4$ reduction of saturated β-aminomethyl ketone 30), on treatment with triphenylphosphinedibromide in acetonitrile followed by interaction with triethylamine gave 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29, cis- and trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (27A and 27B) and the rearranged cis- and trans-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 28A and 28B. This azetidine 29 was found to be a mixture of cis-29A and trans- 29B isomers. Attempts to separate cis-29A and trans-29B were unsuccessful (Chart 4).

Objectives of the present investigation

As very little information regarding synthesis and rearrangements of 2,3-disubstituted N-arylazetidines was available, it was necessary to synthesise them. It was also of interest to study the stereochemistry involved in the acid catalysed cyclodehydration of 3-arylamino-1-propan-1-ols prepared by two different routes.

Present work

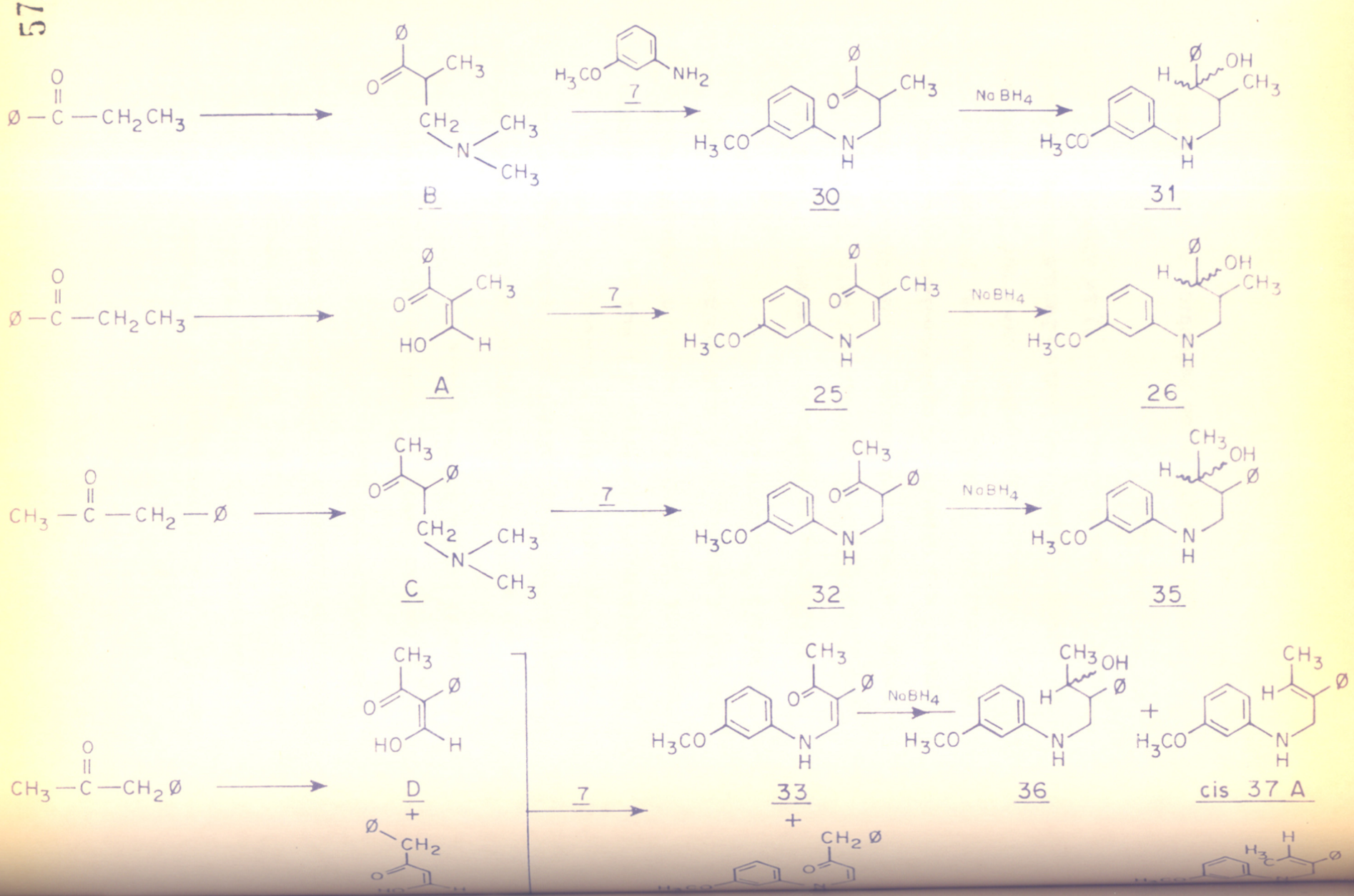
Precursors for this study were 3-(3'-methoxyphenylamino)-2-methyl-1-phenylpropan-1-ols 26, 31 and 4-(3'-methoxyphenylamino)-3-phenyl-butan-2-ols 35, 36. These carbinols were prepared by two alternate methods as shown in Chart 5.

α-(3'-Methoxyphenylamino)methylpropiophenone 30 was prepared by refluxing the Mannich base hydrochloride (B) derived from propiophenone and m-anisidine 7. Yield of compound 30 was low (~ 20%) probably due to α-substitution in the Mannich base. This has also been observed by Craig et al.[6] Yield of the product 30 was improved from 20% to 56% by addition of excess sodium carbonate and refluxing the reaction mixture for 14 hours.

Interaction of cis-2-hydroxymethylenepropiophenone (A)[10] and m-anisidine 7 gave cis-α-(3'-methoxyphenylaminomethylene)-propiophenone 25.

Mannich base hydrochloride of benzyl methyl ketone was prepared according to Wilson et al.[7] House et al.[8] have studied the equilibrium composition of solutions of potassium enolates derived from unsymmetrical ketones, such as benzyl methyl ketone.

Structure of Mannich base hydrochloride of benzyl methyl ketone viz. 4-dimethylamino-3-phenylbutan-2-one


Ø—C(=O)—CH2CH3
B
7
30
NaBH4
31
A
25
26
CH3—C(=O)—CH2—Ø
C
32
35
D
+
33
36
cis 37 A

HCl [c] has also been confirmed by Buchanan et al.[9] Condensation of Mannich base hydrochloride of benzylmethyl ketone and m-anisidine 7 in the presence of sodium carbonate yielded 4-(3'-methoxyphenylamino)-3-phenylbutan-2-one 32.

Many workers[10-14] have studied hydroxymethylation of benzyl methyl ketone (BMK).

In our hands treatment of BMK with ethyl formate using dry ether as solvent and sodium hydride as a condensing agent yielded a mixture of isomeric hydroxymethylene derivative D and E. This mixture on treatment with equimolar amount of m-anisidine 7 yielded a mixture of enaminoketones 33 and 34 in 65:35 proportion (as revealed by GLC).

Attempts to separate the enaminoketones 33 and 34 by column chromatography using silica gel or neutral alumina and various combinations of solvent systems and also fractional distillation proved unsuccessful. Finally the desired product 4-(3'-methoxyphenylamino)-3-phenyl-but-3-ene-2-one 33 was separated by chromatography over basic alumina using petroleum ether as eluent. The ketone 33 is eluted first followed by isomeric 34.

Sodium borohydride reduction of the ketone 30

yielded 3-(3'-methoxyphenylamino)-2-methyl-1-phenyl-propan-1-ol 31[3].

The enaminoketone 25, on sodium borohydride reduction, yielded the carbinol 26 [1a].

Similarly the ketone 32 on sodium borohydride reduction yielded carbinol 35. An isomeric carbinol 36 along with a dehydrated product 37 (37A and 37B) was obtained by sodium borohydride reduction of the corresponding enaminoketone 33 (Chart 5).

Cyclodehydration of carbinol 31 (prepared by sodium borohydride reduction of the saturated β-aminomethyl ketone 36) using 70% sulphuric acid yielded a mixture of cis and trans normal as well as rearranged tetrahydroquinolines 27 and 28. NMR spectrum (Fig 1) of the mixed tetrahydroquinolines revealed it to be a mixture of trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B as the major product (50% as per GLC) along with trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B (20% as per GLC) and cis-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28A (30% as per GLC).

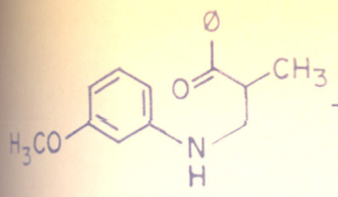
The above mixture when subjected to GLC/MS analysis confirmed the above results. This will be discussed later (see page).

Carbinol 26 on treatment with triphenylphosphine-dibromide in acetonitrile followed by interaction with triethylamine on work up afforded to our surprise, exclusively cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A, together with a mixture of corresponding tetrahydroquinolines (27B) and (28A, 28B). NMR spectrum study of 29A (Chart 6) indicated the presence of a set of doublets centred at 1.26 δ due to methyl group; a multiplet centred at 2.53 δ which can be assigned to Hb as it has three neighbouring protons. Two sets of fine triplets centred at 3.26 δ and 4.08 δ can arise from methylenic protons Hc and Hd depending upon their stereochemistry. If Hc is above the plane of four membered ring it will be under the shielding zone of phenyl ring and will appear upfield (3.26 δ). Hd being below the plane of the four membered ring will be deshielded by m-methoxyphenyl group and will appear at downfield (4.08 δ). A doublet at 4.3 δ can be assigned for Ha as it has got only one neighbour Hb. Methoxy appears at 3.46 δ as singlet. NMR also indicates absence of D_2O exchangable NH proton. IR also supports absence of NH. The other products of the reaction being cis- and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28A and 28B and trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B.

A variation in the above reactions was to use triphenylphosphoniumtrichloromethyl chloride in place of bromotriphenylphosphonium bromide ($\phi_3P^+Br\ Br^-$). This led to reduction in reaction time from 72 hrs to 20 hrs. Triphenylphosphoniumtrichloromethyl chloride was prepared by interaction of triphenylphosphine (1 mole) with carbon tetrachloride (1 mole) in acetonitrile at 0 ~ 5° for 1 hr.

Treatment of the carbinol 31 with triphenylphosphine, carbon tetrachloride and triethylamine and work up yielded cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A. NMR spectrum of azetidine 29A was again showing a methyl doublet centred at 1.26 δ indicating formation of only one isomer. Other products formed are trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B and trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B (Chart 6).

Treatment of carbinol 26 with triphenylphosphine, carbon tetrachloride and triethylamine yielded an isomeric mixture of 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A and 29B together with a mixture of tetrahydroquinolines 27A, 27B and 28B. NMR spectrum (Fig 2) of the first fraction viz. azetidine 29A and 29B indicated presence of two sets of doublets corresponding to CH_3 group, appearing centred at 1.26 δ



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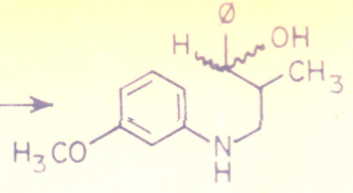
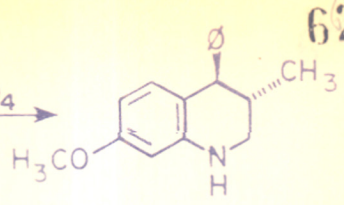


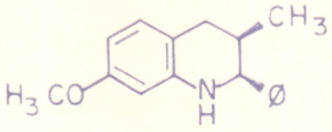
31

70 % H_2SO_4



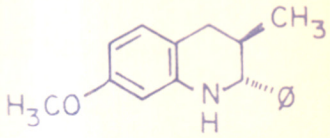
trans 27 B

+

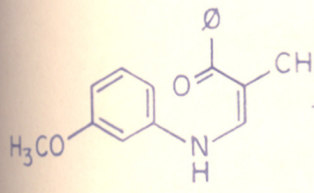


cis 28 A

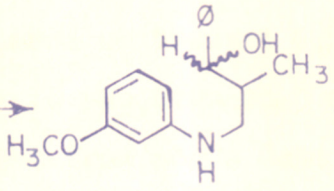
+



trans 28 B



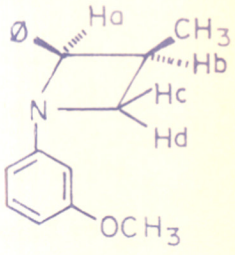
25



26

$(C_6H_5)_3\overset{\oplus}{P}\,Br\ Br^{\ominus}$

$(C_2H_5)_3N$



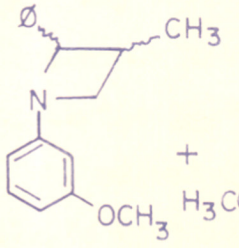
cis 29 A

+

trans 27 B + cis 28 A + trans 28 B

30 → 31 $\xrightarrow[(C_2H_5)_3N]{(C_6H_5)_3\overset{\oplus}{P}\,CCl_3\ Cl^{\ominus}}$ cis 29 A + trans 27 B + trans 28 B

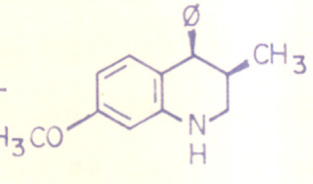
25 → 26 $\xrightarrow[(C_2H_5)_3N]{(C_6H_5)_3\overset{\oplus}{P}\,CCl_3\ Cl^{\ominus}}$



cis 29 A

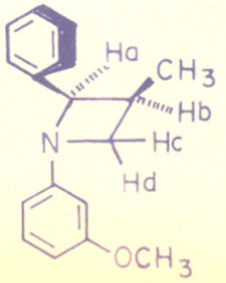
trans 29 B

+

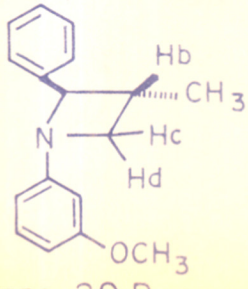


cis 27 A

+ trans 27 B + trans 28 B



cis 29 A



trans 29 B

CHART – 6

and the other at 1.85 δ with 3 proton intensity. The former was much more intense. The NMR spectrum also indicated a multiplet centred at 2.53 δ, a triplet centred at 3.26 δ and 4.08 δ, doublet centred at 4.3 δ and methoxy protons appearing at 3.56 δ. Aromatic protons appeared centred at 6.5 δ. D_2O exchangable NH was absent. IR spectrum also supported the latter fact. It was evident from above data that the methyl doublets at 1.26 δ and 1.85 δ must arise from a cis-azetidine 29A and/or trans-azetidine 29B. To assign the respective values for the methyl shifts in cis- and trans-isomers of azetidine for orientation of the methyl group with respect to the adjacent phenyl group, further consideration is necessary.

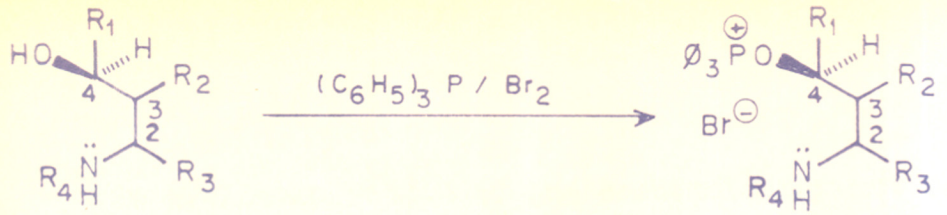
If the C_2 phenyl and C_3 methyl are cis with respect to each other as in 29A then the C_2 phenyl will orient itself in such a way that it will have least interactions with neighbouring methyl group. Obviosuly the ϕ group in cis-azetidine 29A will shield the CH_3 group. Consequently the signal for methyl group in cis-azetidine 29A will be upfield as compared to CH_3 signal in trans-azetidine 29B which will appear comparatively downfield. Thus it may be inferred that the doublet centred at 1.26 δ arises from a cis-azetidine 29A and 1.85 δ form a trans-azetidine 29B.

Treatment of carbinols 26 and/or 31 with triphenylphosphine dibromide probably converts the hydroxy group into oxophosphonium moiety (without any change in the configuration at C_4) (Chart 7). This oxophosphonium bromide derivative on treatment with triethylamine undergoes perhaps an inversion due to backside attack of N-loan pair electrons to yield an N-arylazetidine (with different configuration at the C_4-carbon under consideration) (Chart 7).

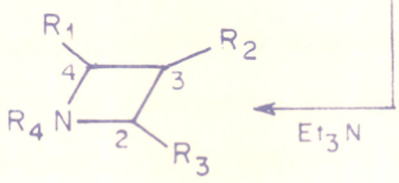
Synder et al.[15] have reported that reaction of carbinols with triphenylphosphine and carbon tetrachloride gives alkyl chlorides with inversion in configuration.

It was anticipated that the treatment of the carbinols 26 and 31 with triphenylphosphine and carbon tetrachloride would furnish the corresponding chloro derivatives with inversion in configuration. The chloro derivatives during ring closure on treatment with triethylamine would undergo one more inversion to yield an azetidine derivative, the net result being retention of stereochemistry of substituents (phenyl and methyl group) attached to the C_4 and C_3 atoms in the parent carbinols 26 and 31.

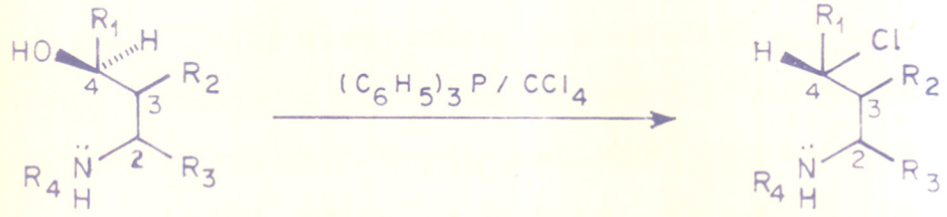
There was, however, little difference in the product pattern between reactions involving the use of $\phi_3P^+Br\ Br^-$ and $\phi_3P^+-CCl_3\ Cl^-$. Hence the leaving group



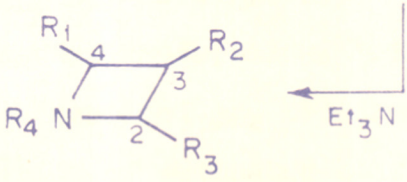
C_4R C_4R



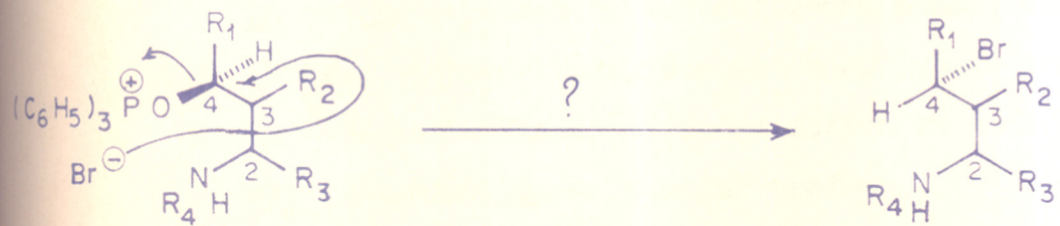
C_4S



C_4R C_4S



C_4R



C_4R C_4S

CHART – 7 .

in cyclodehydration of the carbinols may not be an oxophosphonium bromide but a halide ion (bromide or chloride). These cyclodehydrating agents probably convert the carbinols first into the corresponding halogeno derivatives by inversion at C_4 atom and the halogeno derivatives are subsequently converted to azetidines by another inversion process. These postulates however will need more rigid proof for confirmation.

The observation that carbinol 26 on treatment with triphenylphosphoniumdibromide and triethylamine gave essentially cis-azetidine 29A is in confirmity with our earlier observation, that carbinols obtained by sodium borohydride reduction of corresponding enaminoketones furnish cis-2,4-disubstituted azetidines on treatment with triphenylphosphoniumdibromide, triethylamine in acetonitrile. The carbinol 31, obtained by sodium borohydride reduction of saturated aminomethyl ketone 30, on treatment with $\phi_3P^+CCl_3Cl^-$, NEt_3 in acetonitrile also yielded cis-2,3-disubstituted azetidine 29A as the only product. This indicated that both the carbinols 26 and 31 obtained by two different routes were identical. Further their cyclodehydration under above conditions appears to be fairly stereoselective in that both yield cis-azetidine 29A as a major product.

On the parallel lines it was also of interest to see if stereoselectivity is observed during cyclodehydration of the isomeric carbinols 4-(3'-methoxyphenylamino)-3-phenylbutan-2-ols 35 and 36 which were prepared by two alternate methods as shown in Chart 5.

As discussed earlier the saturated aminomethyl ketone 32 on sodium borohydride reduction yielded the carbinol 35; and an isomeric carbinol 36 was obtained by sodium borohydride reduction of enaminoketone 33. All attempts to cyclodehydrate carbinols 35 and 36 using 70% H_2SO_4 either failed or ended with polymeric product. However, the carbinols on treatment with 70% perchloric acid gave the cyclodehydrated products as discussed below:

Carbinol 35 on treatment with 70% perchloric acid gave a mixture of products which on work up and column chromatography gave a mixture of tetrahydroquinolines, along with some unreacted carbinol and some polymeric material. NMR spectrum (Fig 3) of the tetrahydroquinolines isolated by the above column chromatography, indicated the presence of four sets of methyl doublets centred at 0.84δ, 0.93δ, 1.13δ and 1.26δ. Formation of normal cyclodehydration product viz. the tetrahydroquinoline 38 and the isomeric rearranged tetrahydroquinoline 39 may be rationalized as shown in the Chart 8. The

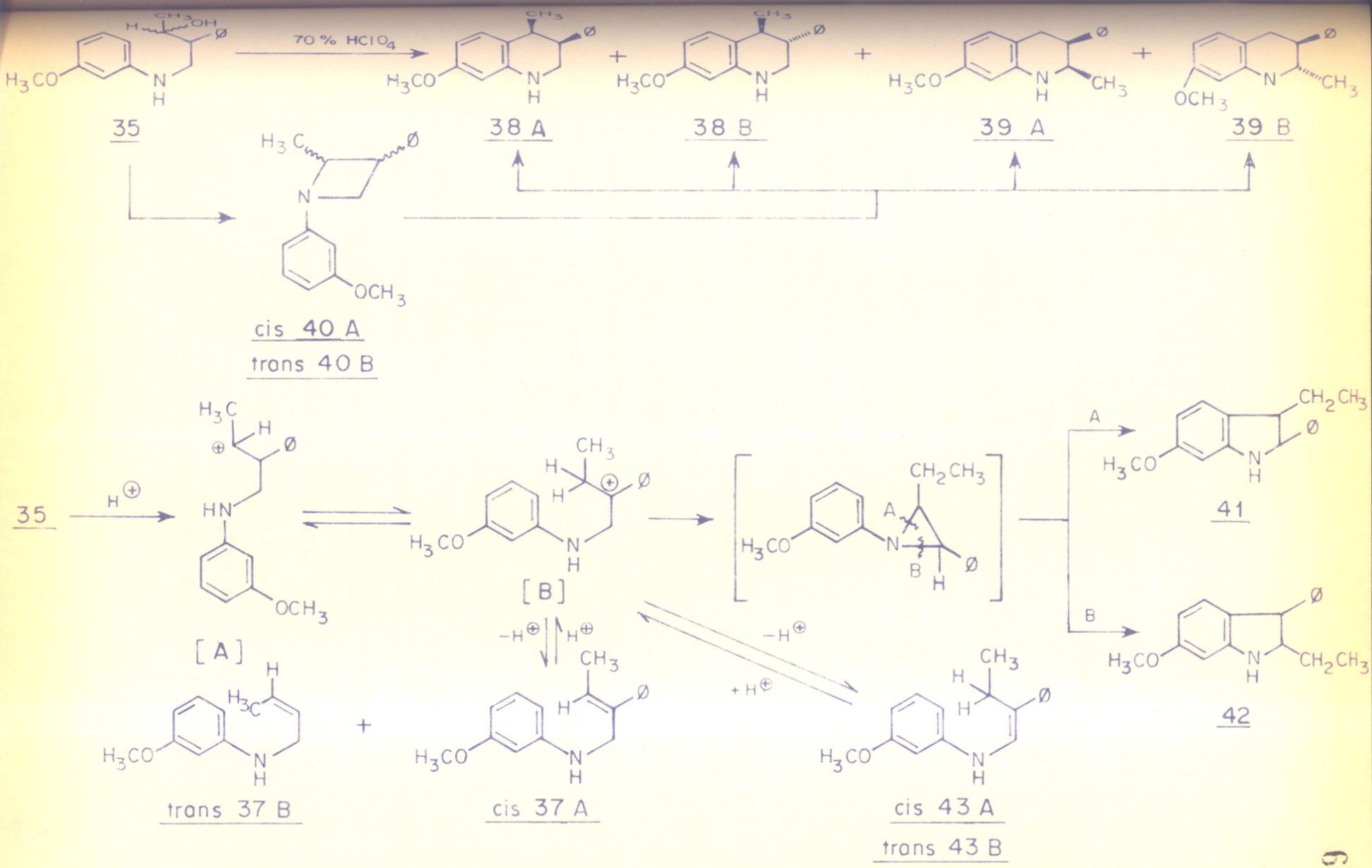

70 % HClO4
35
38 A
38 B
39 A
39 B
cis 40 A
trans 40 B
35
[A]
[B]
41
42
trans 37 B
cis 37 A
cis 43 A
trans 43 B

CHART - 8 .

tetrahydroquinoline 38 may be formed by direct cyclodehydration of 35 whereas the isomeric tetrahydroquinoline 39 is probably formed through intermediate involvement of azetidine 40.

Another possibility which needs to be considered is the likely rearrangement of the carbonium ion[A] to the more stable benzylic carbonium ion [B] which may loose a proton leading to the dehydration product 37A and/or 37B. Alternatively the carbonium ion [B] may yield an aziridine [C] which may subsequently be converted to indoles 41 and 42 through two alternate modes of ring expansion (Chart 8).

However, a study of the NMR spectrum of the reaction products rules out the presence of indoles as there is no signal corresponding to ethyl group which is present in indoles 41, 42 and also in the olefin 43.

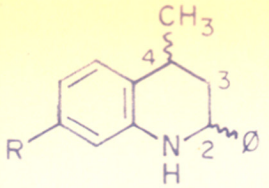
As NMR spectrum revealed the absence of indole derivatives 41, 42; and the olefins 37 and 43, the cyclodehydration products are the tetrahydroquinolines 38 (cis-38A; trans-38B) and 39 (cis-39A and trans-39B).

It has been observed earlier by Kulkarni[3] that in the case of 4-methyl-2-phenyl-1,2,3,4-tetrahydroquinolines 44 and 2-phenyl-4-methyl-1,2,3,4-tetrahydroquinolines 45, the C_4 methyl in 44 appears (as a doublet) comparatively

upfield as compared to the C_2 methyl group in 45 (Chart 9). This is due to the locations of the C_2-methyl group adjacent to the N-atom in 45.

Applying the above analogy to the present case for differentiation between 2,3-disubstituted tetrahydroquinolines (39A and 39B) and 3,4-disubstituted tetrahydroquinolines (38A and 38B), the methyl signal in the NMR spectra of the normal cyclodehydration products 38 should appear slightly upfield as compared to the methyl signal in the rearranged tetrahydroquinoline 39.

Thus doublets appearing centred at 0.84 δ and 0.93 δ may be assigned to cis-38A and trans-38B, whereas the methyl doublet signals centred at 1.13 δ and 1.26 δ may be assigned to cis-39A and trans-39B. Dreiding models of cis-38A and trans-38B were examined. The study revealed that in the preferred configuration of trans-38B [CH_3 (e) and ϕ- (e)] the CH_3 group at C_4 lies below the plane of phenyl ring and does not come under shielding zone of C_3 phenyl at all. Hence in case of cis-38A (preferred configuration being C_4-CH_3 axial and C_3 phenyl equatorial) the CH_3 protons will be slightly more shielded than the CH_3 protons in trans-38B. Careful examination of cis-38A model indicated that in the preferred configuration of the C_4-methyl will not be exactly axial but will be



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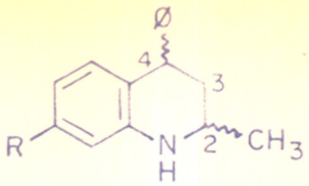

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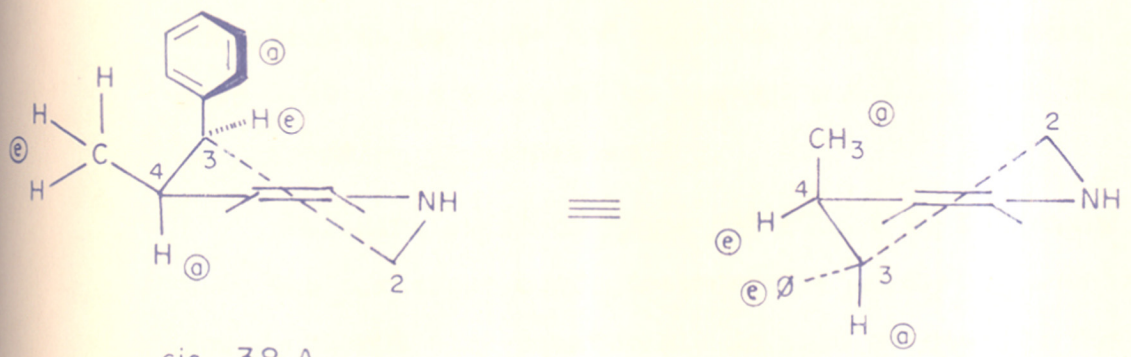
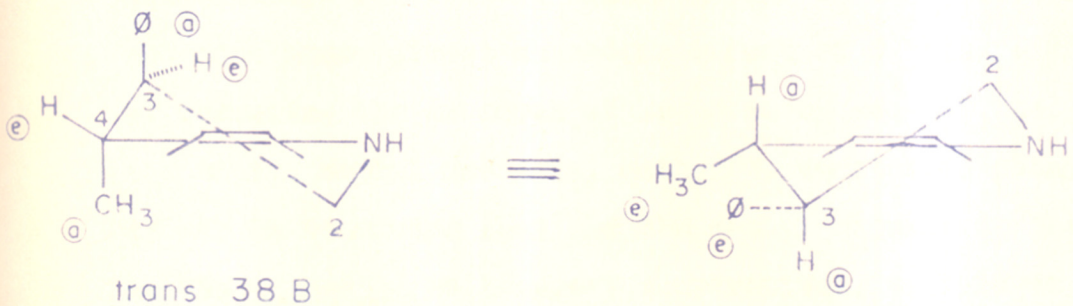
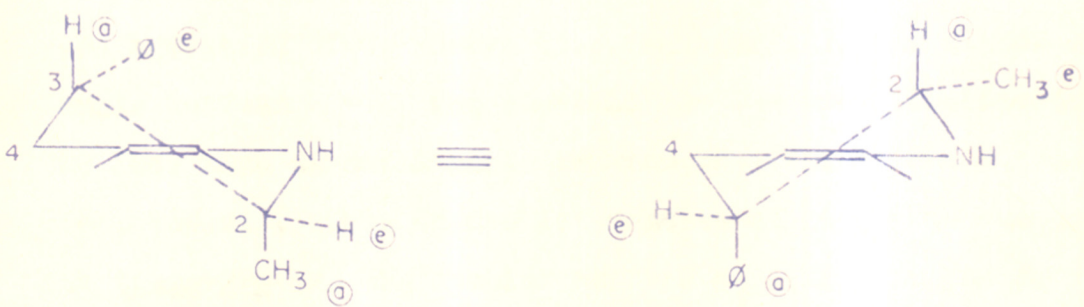


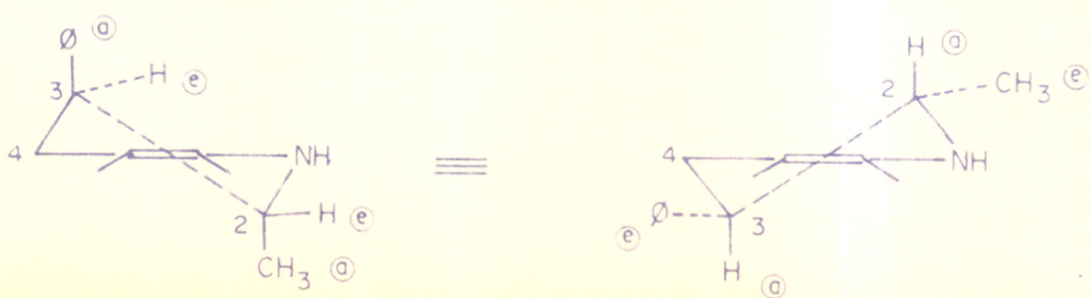
cis 38 A



trans 38 B



cis 39 A



trans 39 B

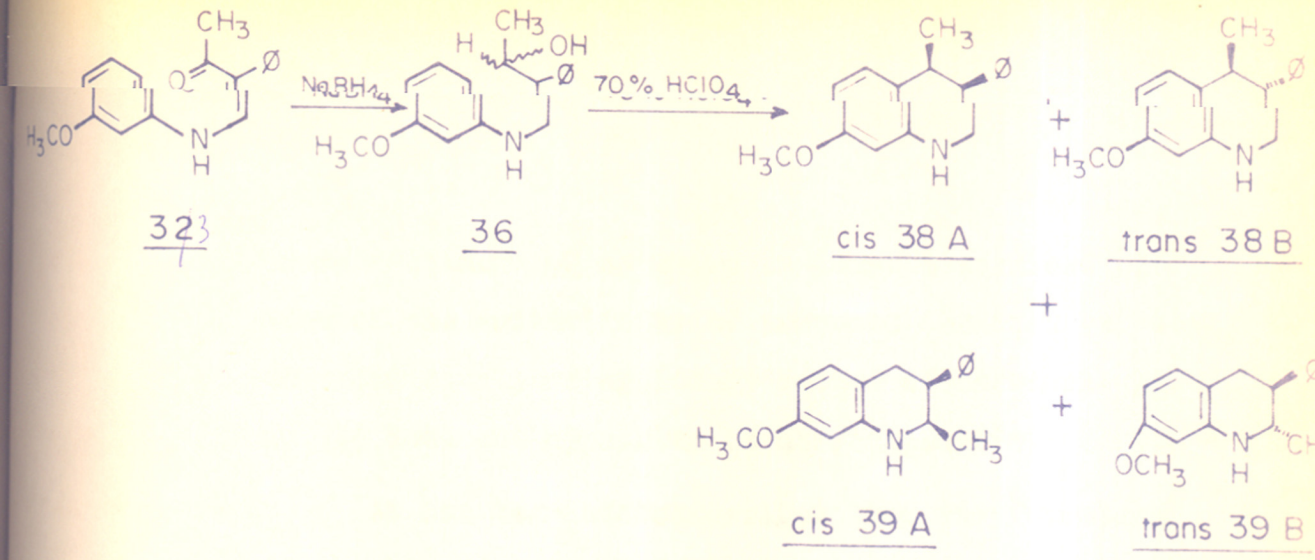
CHART – 9 .

quasi-axial as the tetrahydrohetero ring is slightly deformed due to -C=C- and presence of a hetero atom. Thus 0.84 δ was assigned to cis-38A and 0.93 δ to the corresponding trans-isomer 38B.

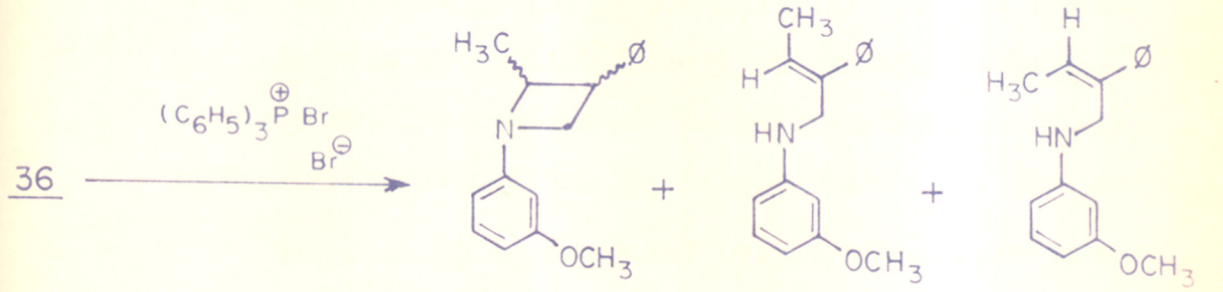
Drieding model of trans-39B (Chart 9) indicated that the preferred configuration will be C_2-CH_3 equatorial and C_3-phenyl also equatorial. In case of cis-39A the preferred configuration will be C_2-CH_3 axial and C_3-phenyl equatorial. Now even if either of the C_2-CH_3 groups do not come under direct shielding effect of C_3 phenyl ring, by comparing the dihedral angles made by each of the equatorial methyl and axial methyl with C_3 equatorial-phenyl, it may be concluded that the NMR methyl signals in case of the trans-39B will appear comparatively upfield as compared to cis-39A. This is because in the preferred configuration of C_3-phenyl (i.e. equatorial), the dihedral angle between C_2-CH_3 (equatorial) and C_3-phenyl (equatorial) is less than dihedral angle between CH_3 (axial) and C_3-phenyl (equatorial). Thus CH_3 doublet centred at 1.13 δ is due to trans-39B and CH_3 doublet centred at 1.26 δ is due to cis-39A. Intensity of peaks are as follows: 0.84 δ about 40% ; 0.93 δ about 25% ; 1.13 δ about 20% and 1.26 δ about 15% (Fig 3).

In an another experiment Carbinol 36 (obtained by sodium borohydride reduction of the enaminoketone 33) (Chart 5) was cyclodehydrated by treatment with 70% perchloric acid. Work up of the reaction mixture followed by column chromatography gave as first fraction a mixture of cis-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38A (70%) [CH_3 doublet (major) centred at 0.84] and cis-7-methoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39A (30%). A CH_3 doublet signal corresponding to trans-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38B was also present. The methylene and C_3 methine protons centred at 3.3 as multiplet. D_2O exchangable NH proton appeared at 3.55 , a methoxy at 3.73 aromatic protons ortho to OCH_3 centred at 6.0 and other at 7.0 as multiplets. NMR spectrum of the second fraction in comumn chromatography gave the following data: A CH_3 doublet centred at 1.13 corresponding to trans-7-methoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39B. Methylene, NH and C_3 methine protons centred at 3.4 as multiplet, methoxy at 3.6 , aromatic protons as a multiplet centred at 6.0 and 7.0 (Chart 10).

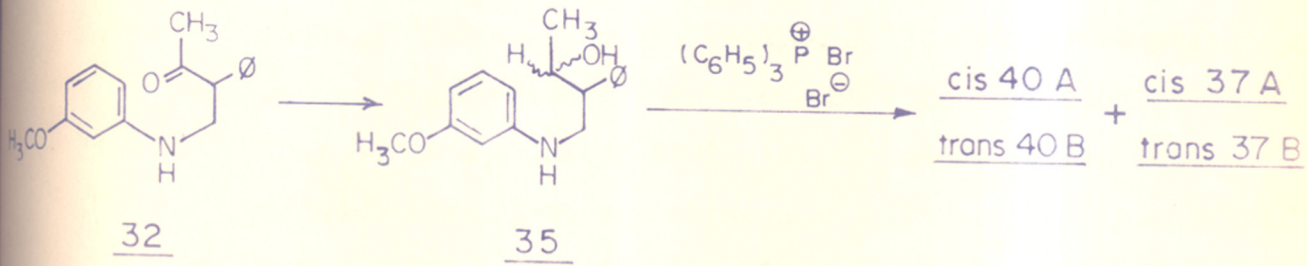
The formation of rearranged tetrahydroquinolines cis-39A and trans-39B in the above reactions is explicable if one assumes the intermediate formation



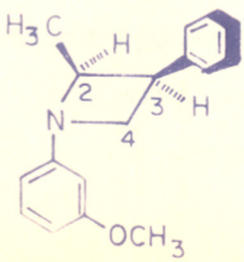
32 → 36 → cis 38 A + trans 38 B + cis 39 A + trans 39 B



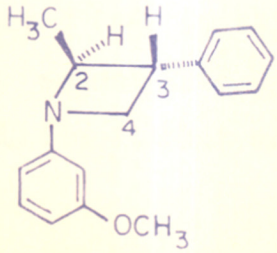
cis 40 A + trans 40 B + cis 37 A + trans 37 B



32 → 35 → cis 40 A + trans 40 B + cis 37 A + trans 37 B



cis 40 A



trans 40 B

CHART – 10

of an azetidine 40 as shown in Chart 8 earlier. In view of the multiplicity of products obtained as above, the acid catalysed cyclodehydration of carbinols 35 and 36 does not appear to be stereospecific.

It has been stated earlier that the formation of rearranged 2,3-disubstituted tetrahydroquinolines cis-39A and trans-39B by acid catalysed cyclo-dehydration of the carbinols 35 and 36 is explicable if one assumes the formation of an azetidine 40 as an intermediate. To prove the involvement of the 1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidine 40, its synthesis was necessary.

Carbinol 36 on treatment with triphenylphosphine dibromide in acetonitrile solution followed by treatment with triethylamine gave a mixture of compounds. Work up followed by column chromatography of the crude reaction mixture afforded triphenyl phosphine as the first fraction followed by the desired 1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidine 40.(Chart 10). NMR spectrum (Fig 4) of the latter indicated presence of two sets of methyl doublets one centred at 1.01 δ (~ 90% intensity) and the other at 1.35 δ (~ 10 % intensity). Methoxy protons appeared at 3.71 δ. A quartet (may be expected to be a multiplet) centred at 4.0 δ arises from C_4 methylenic protons and C_3-H. Another multiplet centred at

4.4 δ arises from a methine proton situated at C_2. Aromatic protons appeared at 6.08 δ and 7.08 δ as multiplets. D_2O exchangable NH was absent, thus ruling out the tetrahydroquinoline structures as well as open chain structures. IR also showed absence of either NH or OH. Product from the next fraction obtained in column chromatography was subjected for NMR study. NMR spectrum (Fig 5) of this fraction indicated again two sets of (methyl) doublets centred at 1.59 δ and the other at 1.89 δ . D_2O exchangable NH proton appeared at 3.5 δ (1 proton intensity), methoxy at 3.66 δ (3 protons intensity), a broad singlet at 3.83 δ and a small singlet at 4.0 δ (2 protons intensity), A fine multiplet at 5.86 δ mixed with aromatic protons, which appeared at 6.0 δ and 7.08 δ (10 protons intensity). As the two methyl doublets (1.59 δ and 1.89 δ) appearing very much downfield do not correspond to any of the cis or trans (normal and rearranged) tetrahydroquinolines 38, 39, these doublets may be attributed to the olefins 37 (cis A or trans B) obtained by dehydration of the carbinol 36. Tetrahydroquinolines 38 or 39 were absent.

It may be recalled (see page) that α-(3'-methoxyphenylamino)methyl-β-methylstyrene 37A/B

was formed during sodium borohydride reduction of the enaminoketone 33 which shows identical NMR (Fig 5) and IR spectrum. It shows M^+ peak at m/e 257.

4-(3'-Methoxyphenylamino)-3-phenyl-butan-2-ol 35 (obtained by sodium borohydride reduction of the saturated β-aminoethyl ketone 32) which is likely to be isomeric with carbinol 36 was also cyclized as above with the view to synthesise the azetidine 40 (cis-A or trans-B).

Carbinol 35 on treatment with triphenylphosphine dibromide (in acetonitrile followed by interaction with triethylamine at 0 to -5°C for 72 hrs) and work up as above yielded again an isomeric mixture of 1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidines 40A and 40B. NMR spectrum again showed a CH_3-doublet centred at 1.01 δ being the major and a CH_3 doublet of very poor intensity centred at 1.35 δ. A product corresponding to cis- and trans- olefin 37A and 37B was also isolated (Chart 10).

Both the carbinols 35 and 36 behaved similarly in cyclodehydration under above conditions. In both cases the yield of azetidines 40 (cis-A and trans-B) was low.

To assign the correct values for the methyl shift, in the isomeric mixture of cis- and trans-azetidine 40, one can visualize a system whereby CH_3 at C_2 and phenyl at C_3 are cis. In the latter case to avoid Vanderwall interactions phenyl at C_3 will remain perpendicular to plane of paper (Chart 10). Thus CH_3 at C_2 will be slightly shielded and will appear upfield as compared to trans-isomer 40B. On the same lines one can differentiate CH_3 doublet values in cis- and trans-olefins 37A and 37B. If the CH_3 and ϕ are cis, methyl group will be slightly shielded and will appear upfield (Fig 5).

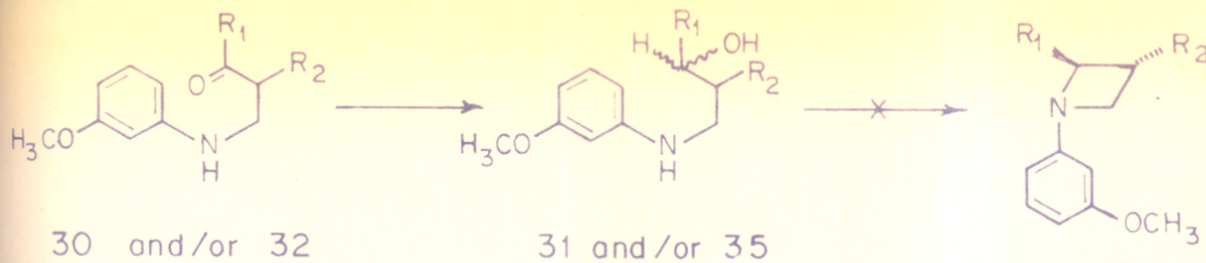
From the above considerations signal at 1.01 δ may be attributed to cis-azetidine 40A (C_2-methyl). The other signal at 1.35 δ may be assigned for the trans-azetidine 40B (C_2-methyl). The cis-azetidine 40A is formed as a major product and trans-azetidine 40B as the minor product in the cyclodehydration of both the carbinols 35 and 36. All atttempts to separate 40A from 40B were unsuccessful.

In the light of earlier work by Kulkarni[3] it was anticipated that the carbinols 31 and 35 prepared by sodium borohyride reduction of saturated β-aminoethyl ketones (30 and 32) would furnish exclusively trans-2,3-disubstituted azetidines (29B and 40B) and the carbinols (26 and 36) derived from enaminoketones (25 and 33)

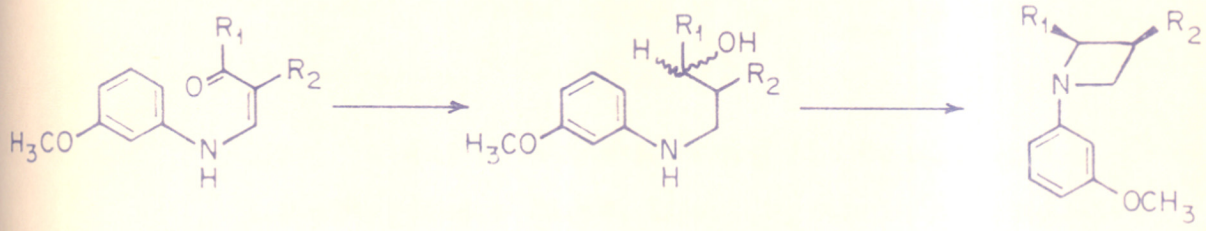
essentially cis-2,3-disubstituted azetidines (29A and 40A).(Chart 11). Actually in both carbinols 31 and 35 the cis-azetidines 29A and 40A were obtained as major products and the trans-azetidines 29B and 40B were formed in much smaller quantity. These observations are at variance with those made earlier by Kulkarni[3].

The above result indicate that the carbinols 26 and 31 are identical and have identical stereochemistry at the C_3, C_4 carbon atoms. Similarly carbinols 35 and 36 also have the same stereochemistry at the asymmetric C_3 and C_4 atoms. Further it does seem that location of the substituents at C_3, C_4 positions as in 25 and 33 as against at C_2 and C_4 atoms in enaminoketones 15 and 16 seems to play a key role in the $NaBH_4$ reduction of these enaminoketones. This reduction may be occuring as follows in two steps (shown in Chart 12).

β-Aminoketones when reduced with sodium borohydride give β-aminoalcohols in such a way that the reduced carbinol will have preferentially the same configuration at the β-carbon atom. However, when an enaminoketone such as 15 and/or 16 is reduced with sodium borohydride, the carbonyl function first gets reduced to intermediate A or B and then the double bond gets reduced to give β-aminoalcohol(carbinol) (Chart 12). Enol first formed directs the hydride in



30 and/or 32 — 31 and/or 35 — trans 29 B, trans 40 B

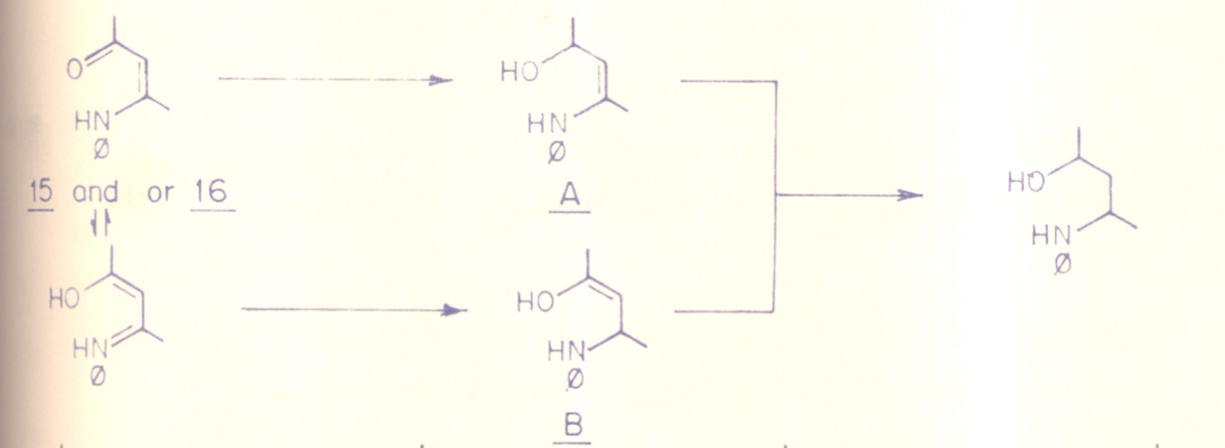


25 and/or 33 — 26 and/or 36 — cis 29 A, cis 40 A

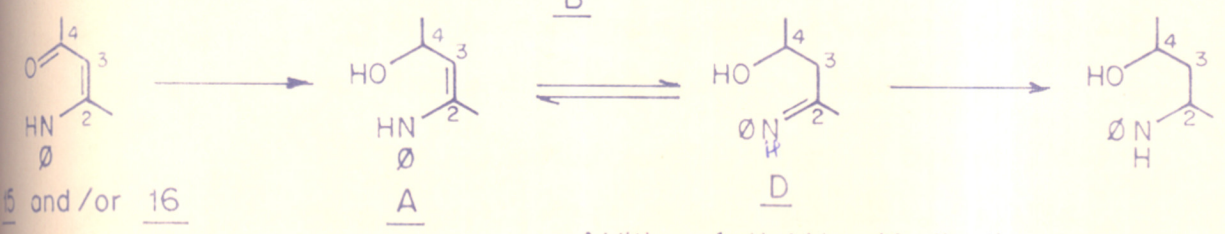
30, 31, 25, 26, 29A/B $R_1 = \emptyset$, $R_2 = CH_3$

32, 35, 33, 36, 40A/B $R_1 = CH_3$, $R_2 = \emptyset$

CHART – 11



15 and or 16 — A, B



16 and/or 16 — A — D

Addition of Hydride with directive effect of C_2 substituent

25 and or 33 — C — E

Addition of Hydride without any directive effect

such a way that the resulting carbinol will have different configurations at C_1 and C_3 atoms (C_1R, C_3S or C_1S, C_3R).

If in the enaminoketone, the double bond had got reduced first, then the resulting saturated ketone would have led to a β-aminoalcohol (carbinol) where the configurations at C_1 and C_3 assymetric carbon atoms would have been identical.

However, carbinols obtained from 2,4-disubstituted saturated aminoketone 9 and 12, and corresponding 2,4-disubstituted enaminoketone 15, 16 were isomeric.

Based on the above rationale Kulkarni[3] came to the conclusion that sodium borohydride reduction of enaminoketone proceeds via intermediate formation of enol A or B.

In the present case viz. sodium borohydride reduction of 3,4-disubstituted aminoethyl ketones 30, 32 and corresponding enaminoketones 25, 33 led to carbinols with identical configurations.

The following modification in the mechanism proposed earlier may explain the above results. Sodium borohydride reduction of enaminoketones 25 and/or 33 probably proceeds as follows:-

i) Carbonyl function of 25 and/or 33 gets reduced to intermediate enol A or C.

ii) Above enol A or C probably get transformed to imine of the type D/E by a prototropic shift.

iii) Further reduction of imine D and/or E to carbinol.

The third step being crucial

If the starting enaminoketone is 2,4-disubstituted, the incoming hydride will have a directive effect of a substituent at C_2 (during the last step viz. reduction of imine) to yield carbinol with specific configuration, whereas if the starting enaminoketone is 3,4-disubstituted incoming hydride may not have any directive effect (during reduction of the imine) as C_2 substituent is absent.

Examination of IR, NMR spectra of the carbinol pairs 26, 31 and 35, 36 obtained by two different routes were nearly identical. Even GLC of the corresponding silyl derivatives also showed no difference. The above evidence indicates that carbinols 26 and 31 are identical and so also carbinols 35 and 36. It may be noted here that Kulkarni[3] had prepared silyl derivatives of the isomeric carbinols whose GLC revealed that the silyl

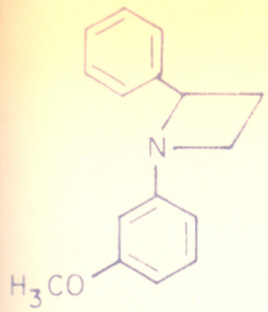
derivatives of carbinols 10 and 17 were different and also those of 13 and 18 were different. This showed that the carbinols 10, 17 and 13, 18 were configurational isomers.

Rearrangement reactions of N-arylazetidines

Tilak et al.[1] have reported earlier that 1-(3'-methoxyphenyl)-2-phenylazetidine 44 rearranged partially to 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 45 when its solution in n-hexane was exposed to sunlight. It was also observed that 44 rearranges to 45, on prolonged heating (Chart 13).

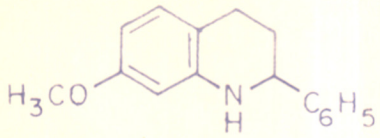
1-(3'-Methoxyphenyl)-2,4-dimethylazetidine 46 on UV irradiation gave 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 47; which was also obtained by pyrolysis of 46 at 290° (under nitrogen atmosphere) and by treatment of 46 with 70% sulphuric acid (Chart 13).

Kulkarni[3] has reported earlier that cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 24 on irradiation with unfiltered light emitted by 125 watt Hg vapour lamp gave a mixture of cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 19 (36%), cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 21 27% and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 22 (36%).



44

Sunlight



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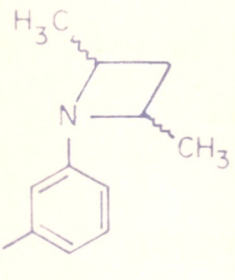
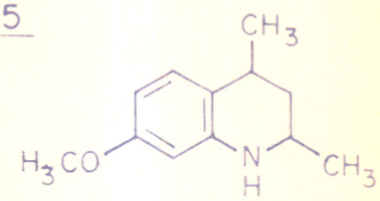


46

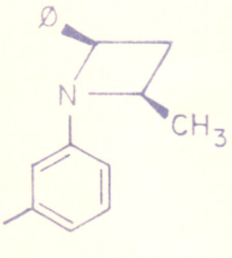
70 % H_2SO_4



47

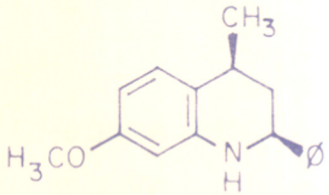
△ → 47

hν → 47

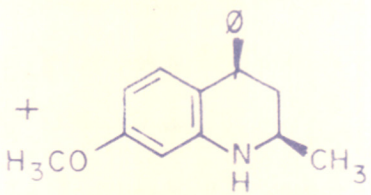
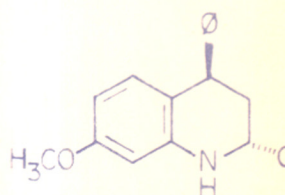


24

70 % H_2SO_4

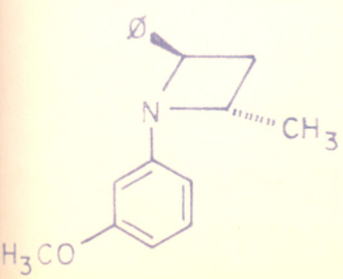


19

hν → 19 (36 %) +  + 

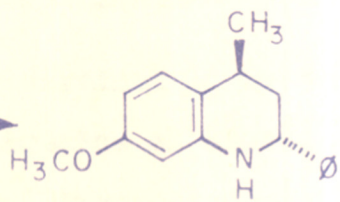
21 (27 %) 22 (36 %)

△ → 19 (37 %) + 21 (25 %) + 22 (37 %)



23

70 % H_2SO_4



20

hν → 19 (46 %) + 21 (27 %) + 22 (27 %)

△ → 19 (40 %) + 21 (40 %) + 22 (20 %)

CHART — 13 .

Trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 23, on irradiation under above conditions yielded a mixture of 19 (46%), 21 (27%) and 22 (27%).

Cis-azetidine 24 on pyrolysis at 290°, under nitrogen atmosphere, gave a mixture of 19 (37%), 21 (35%) and 22 (37%). Trans-azetidine 23, on pyrolysis gave a mixture of 19 (40%), 21 (40%) and 22 (20%).

Cis-azetidine 24 on treatment with 70% sulphuric acid, gave essentially only 19 (70%), whereas trans-azetidine 23 under similar conditions gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 20 (Chart 13).

The above results indicated absence of any preferential product formation during photolysis or pyrolysis of cis- and trans-azetidines 24 and 23.

Ring expansion of Azetidines cis-29A and cis-40A, trans-40B

Cyclodehydration of carbinol 26 by treatment with triphenylphosphinedibromide as stated above yielded exclusively cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A (Chart 6). The latter was subjected to photolysis, pyrolysis and acid catalysed ring expansion.

Similarly cyclodehydration of carbinol 35 using triphenylphosphinedibromide and triethylamine gave an isomeric mixture of 1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidines 40A and 40B (Chart 10). Many attempts to separate cis- and trans-azetidines 40A and 40B were unsuccessful. Consequently mixture of cis- and trans-isomers containing essentially the cis-azetidine 40A was subjected to ring expansion studies.

Ring expansion of 29A/40A,B by UV irradiation proved to be unsuccessful as it yielded demethoxylated and fragmented products. Reaction products were identified by comparing their NMR spectra with those of authentic samples.

Cis-Azetidine 29A on treatment with 70% sulphuric acid gave trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B (normal product) and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B (rearranged product) in equal proportions (Chart 14).

Acid catalyzed ring opening of cis-azetidine 29A may proceed in two ways, one being stepwise and the other concerted (Chart 15).

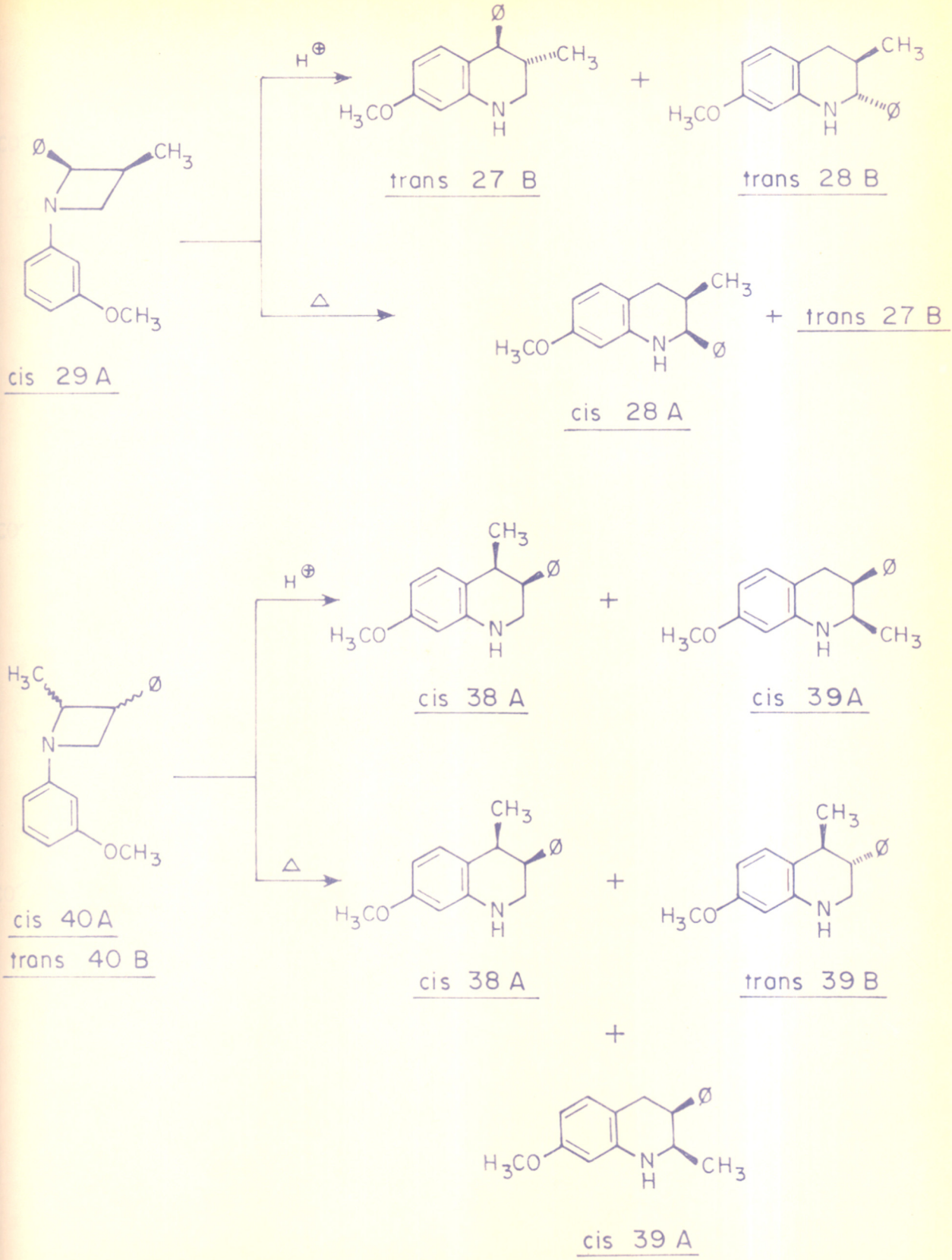
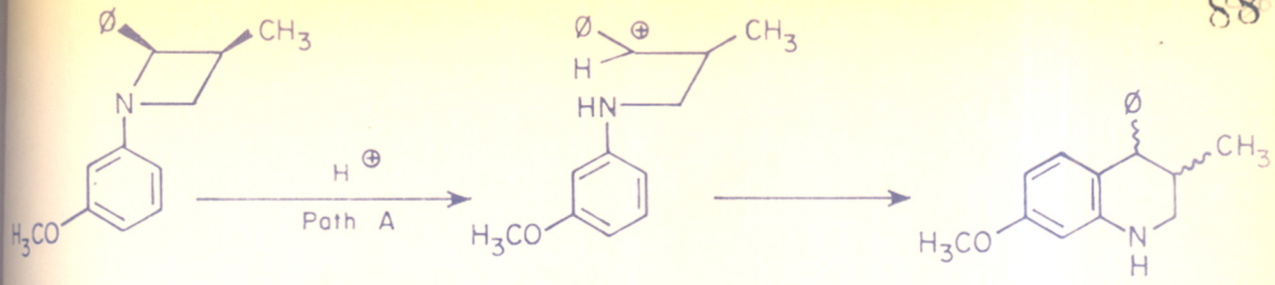

H⊕
Ø
CH3
H3CO
N
H
+
trans 27 B
trans 28 B
cis 29 A
OCH3
Δ
+ trans 27 B
cis 28 A
H3C
cis 38 A
cis 39A
cis 40A
trans 40 B
trans 39 B
cis 39 A

CHART – 14

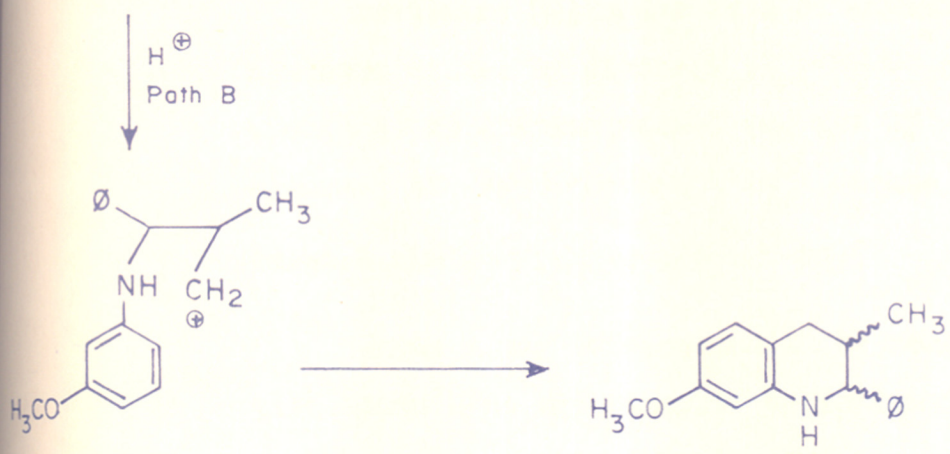


cis 29 A

[A]

cis 27 A

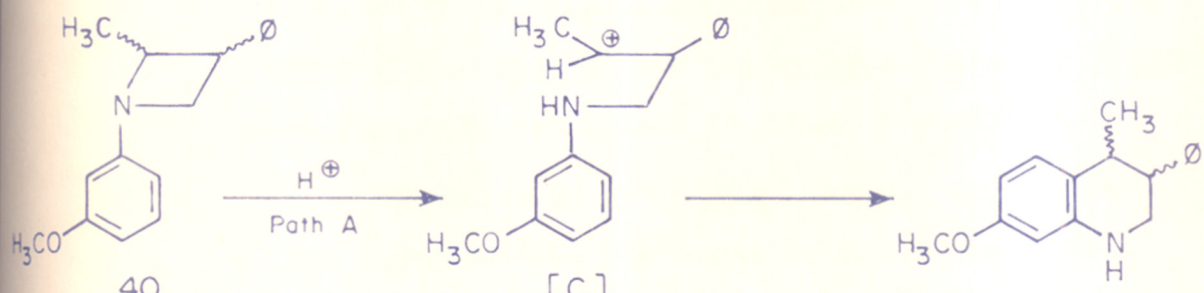
trans 27 B



[B]

cis 28 A

trans 28 B

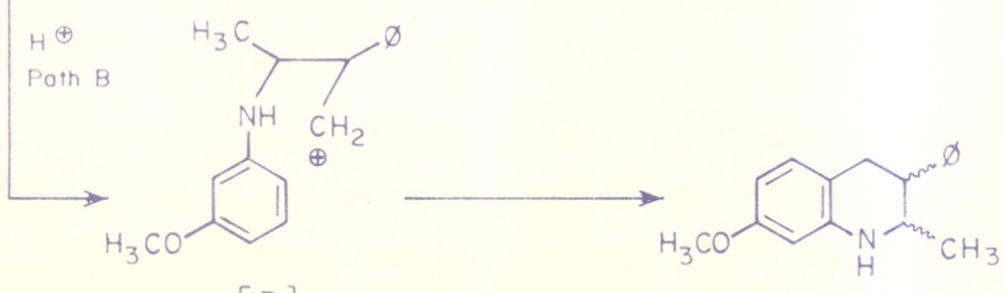


40

[C]

cis 38 A

trans 38 B



[D]

cis 39 A

trans 39 B

CHART — 15 .

1) Stepwise process

Azetidine 29A under acid catalysed conditions can open either by cleavage of -N-C ϕ bond (Route A) to furnish normal product 27 or by cleavage of -N-C-CH-CH_3 bond (Route B) to furnish the rearranged product 28.

Route A may be expected to be more facile than Route B as the benzylic carbonium ion (A) would be more stable than the primary carbonium ion (B).

If the carbonium ion derived from 29A is formed prior to cyclisation it can be attacked from both sides to yield equimolecular mixture of cis-27A and trans-27B or cis-28A and trans-28B. Actually trans-27B and trans-28B are formed in equal proportions.

Formation of trans-28B (rearranged product) from cis-azetidine 29A through the intermediate involvement of the primary carbonium ion (B) is difficult to explain since the carbonium ion (B) may be expected to be much less stable than carbonium ion (A).

Similarly if ring opening of azetidine 29A was to follow Route A, it should have yielded equimolecular mixture of cis-27A and trans-27B. However, only trans-27B is formed.

It appears from above result that the ring expansion of cis-azetidine 29A may not be stepwise process involving discret carbonium ions but a concerted process in which the stereochemistry in the parent azetidine is not retained in the ring expansion products.

It should be noted that during acid catalysed ring expansion of trans-azetidine 23 and cis-azetidine 24, the end products (tetrahydroquinolines) have the same stereochemistry as the parent azetidines.

Azetidine 40 can open in two ways (Chart 15).

Stepwise process

Cleavage of -N-$\overset{3}{\underset{}{}}$C- CH_3 bond will give carbonium ion (C)which will yield equimolecular mixture of cis-38A and trans-38B whereas cleavage of -N-$\overset{3}{\underset{}{}}$C-C$\phi$ bond will give rise to carbonium ion (D) which will lead to an equimolecular mixture of cis-39A and trans-39B.

Carbonium ion (C) may be expected to be more stable than the primary carbonium ion (D). This is reflected in the fact that the ring expansion product 38 is mostly formed and 39 is obtained only in low yield.

It is difficult to explain as to why the stereochemistry of the parent azetidine 40

(essentially cis) is retained in the acid catalysed ring expansion products 38A, and 39A.

Cis-azetidine 29A on pyrolysis gave a mixture of trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B and cis-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28A in equal proportions.

Azetidine 40 (mostly cis-) on pyrolysis gave a mixture of cis-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38A, trans-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38B in 45:45 proportion along with cis-7-methoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39A (20%) (Chart 14).

Above results indicate pyrolysis of azetidines 39A or 40A/B is not stereospecific.

GLC/MS Identification

Even though not much attention has been paid towards the mass spectra of tetrahydroquinolines, mass spectra of many saturated heterocycles including piperidine[16-18], piperidine alkaloids[19] and oxygen heterocycles[20,21] have been studied in detail. In addition, spectra of tetrahydronaphthalenes[22,23] and tetrahydroisoquinolines[24] have been reported.

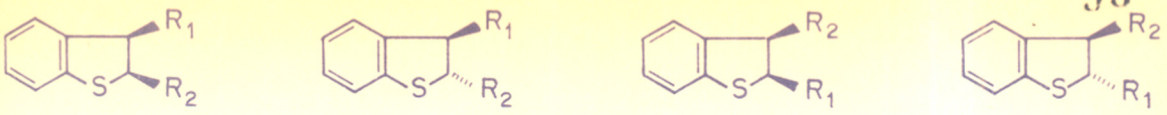
Mass spectra of 2-, 3- and 4-methyl-1,2,3,4-tetrahydroquinolines has been studied by Draper and McClean[25]. They have reported that mass spectra of 2- and 4-methyltetrahydroquinolines are similar, in that they both showed weak M-1 peaks and a base peak at M-15. Substitution of a hydrogen by a methyl group in 2- and 4-position resulted in an intense M-15 peak whereas substitution in the 3-position resulted in m/e at m-29.

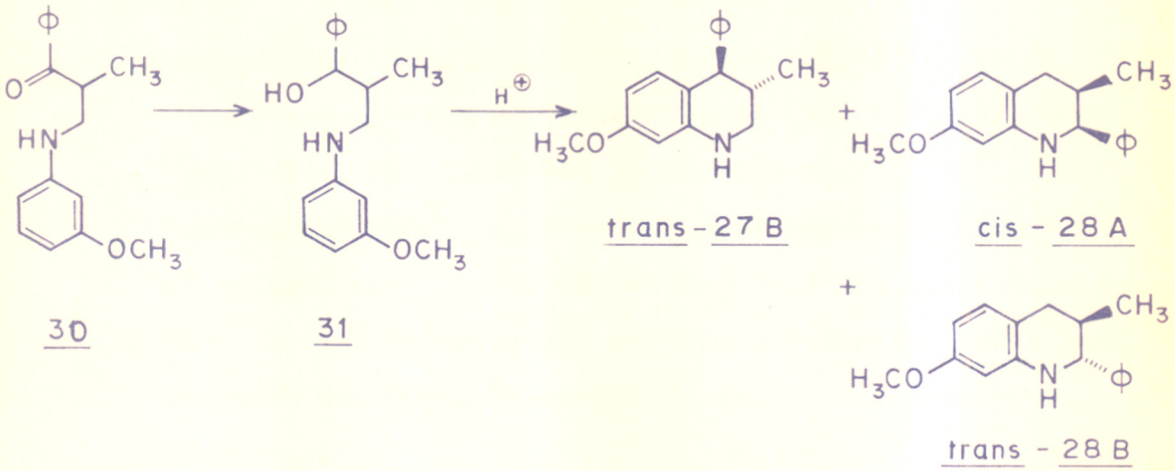
Incidentally Modak[26] from this laboratory has analysed a mixture of 2,3-disubstituted benzo-[b]-thiophenes with the help of GLC/MS technique and has successfully interpreted in the results (Chart 16).

Modak[26] has noted that in cis- and trans-isomers of 2,3-dihydrobenzo-[b]-thiophene, when the substituents R_1 and R_2 were cis with respect to each other loss of $[M- R_1 + R_2]$ was intense.

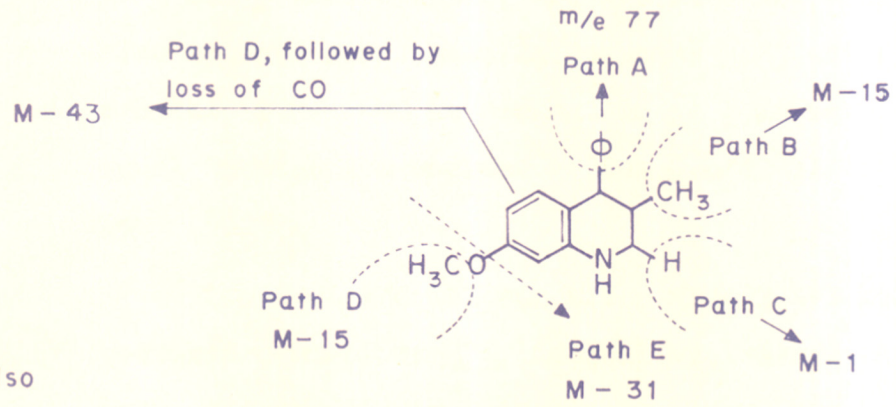
On similar lines study of GLC/MS pattern of 2,3-disubstituted and 3,4-disubstituted tetrahydroquinolines was undertaken.

As discussed earlier cyclodehydration of carbinol 31 using 70% sulphuric acid gave a mixture of 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline





Common Fragmentation pattern expected for 27 A , 28 A and 28 B



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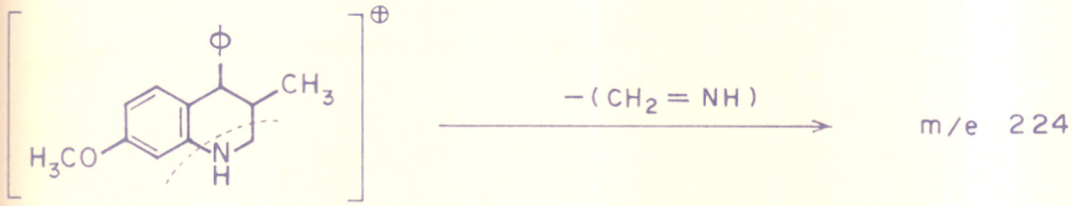


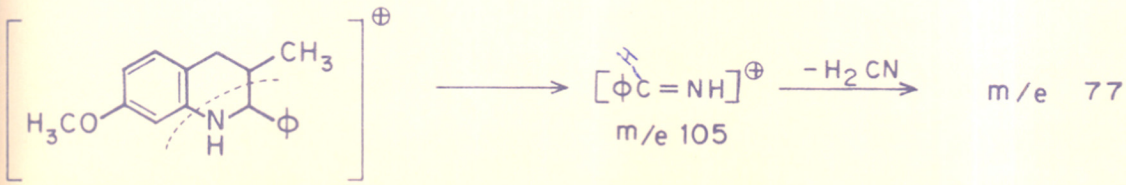


CHART 16

(trans-27B) and cis- and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolines (28A and 28B), page (Chart 6). GLC indicates it to be a mixture of 3 compounds (peaks A, B and C) with retention time as A: 3.85 min, B: 5.0 min, and C: 7.3 min. respectively. Mass spectra recorded for each peak indicates molecular ion peak as 100%. Relevant m/e values are tabulated (Table 1).

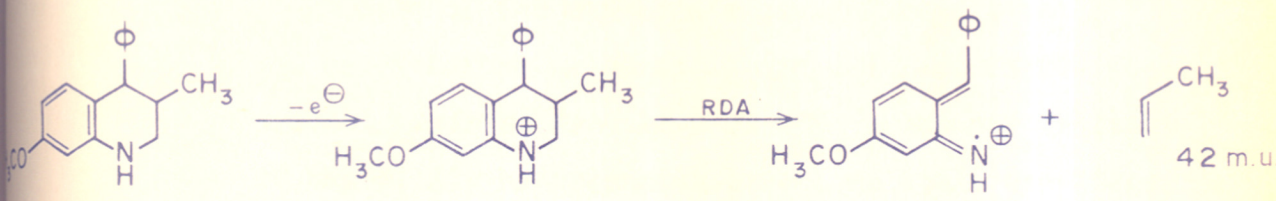
All the mass spectra corresponding to peaks A, B and C show M-1 i.e. m/e 252 intense, M-15 is also intense corresponding to peaks A, B and C m/e 211, i.e. M-42 is present in A, B in more or less equal intensities whereas for C m/e 211 is low ~ 4.3%.

Fragment m/e 211 can arise from 3,4-substituted tetrahydroquinoline 27B, (normal cyclodehydration product from 31) by Retro-Diels Alder type fragmentation (Chart 17).

Table 1

m/e	M-x	A (%)	B (%)	C (%)
253	M^+	100	100	100
252	M-1	21.9	21.1	11.4
238	M-15	28.1	31.6	17.1
224	M-29	40.6	52.6	15.7
211	M-42	10.3	13.7	4.3
210	M-43			
176	M-77	56.0	44.7	50.0
135	M-118	9.1	16.8	< 2
118	M-135	10.0	14.7	< 2
105	M-148	23.1	26.3	6.0
77		10	17	< 2

HARACTERISTIC RETRO-DIELS ALDER FRAGMENTATION OF 3,4 AND 2,3 DISUBSTITUTED TETRAHYDROQUINOLINES



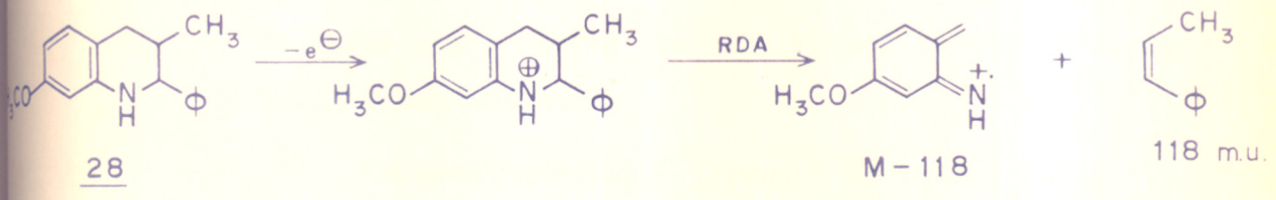
27

M − 42
i.e. m/e 211

ormal cyclodehydration

oduct: 3,4-disubstituted

etrahydroquinoline



28

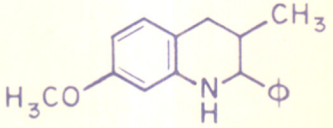
M − 118
i.e. m/e 135

earranged cyclodehydration

oduct 2,3-disubstituted

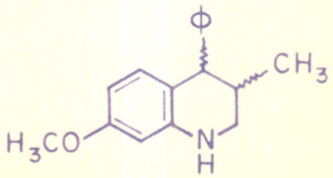
etrahydroquinoline

GLC / Mass spectral study of the mixture revealed that GLC peak A and GLC peak B correspond to cis and trans mixture of



28

Whereas GLC-peak C corresponds to



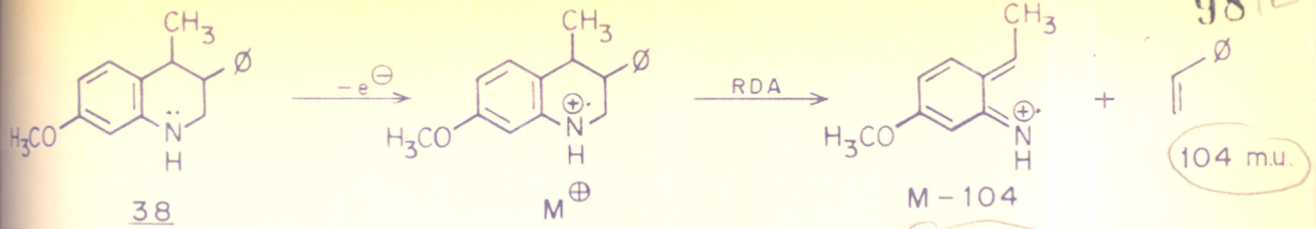
27

CHART - 17

Some of the common m/e peaks for A, B and C can be explained as peaks at m/e 224 i.e. (M-29) probably arising from loss of OCH_3 group and transfer of two of its hydrogens to parent molecule resulting in a cyclohexadiene type structure. It is reported in literature[27] that when a methoxy function is present in a quinoline molecule, m/e at M-29, M-30 and M-31 are intense. Peaks at m/e 210 arises due to loss of 43 m.u. This is ascribed to loss of $[M-CH_3-CO]$ i.e. M-15 -28 (Chart 16). Further loss of 77 i.e. phenyl (ϕ) can take place either from the normal or the rearranged tetrahydroquinolines.

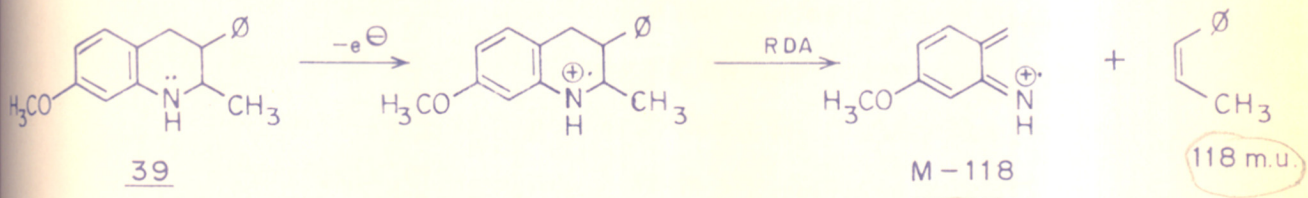
Fragment m/e 135 is present in both A and B with 9.1 and 16.8% intensities, whereas m/e 135 in C is less than 8%. Moreover m/e 135 can arise due to Retro-Diels-Alder type fragmentation in case of rearranged product (Chart 18). As A and B are showing m/e 135 comparatively more intense than m/e 135 in case of C, it may be said that A and B are probably rearranged products.

Further examination of the mass spectra show that m/e 105 to be very intense in the case of A (23.1%) and B (26.3%) as compared to C (6.0%). This can easily be explained if we assume that the phenyl



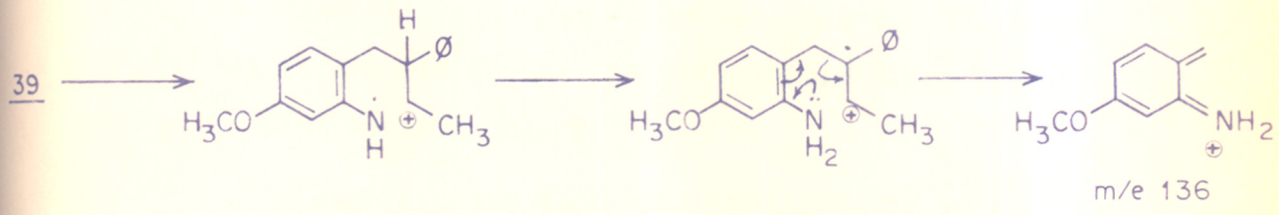
38

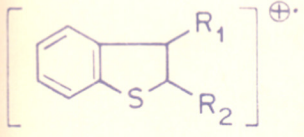
Normal cyclodehydration product (Mixture of cis 38 A, trans 38 B)



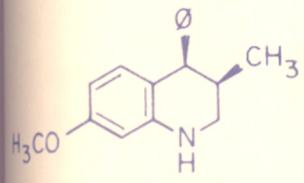
39

Rearranged cyclodehydration product (Mixture of cis 39 A, trans 39 B)

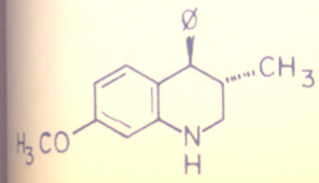




⟶ [M − (R_1 + R_2)] prominant when R_1 and R_2 are cis



cis 27 A ⟶ m/e at 161 , expected to be intense



trans 27 B ⟶ m/e at 175 , expected to be intense

CHART − 18

group is occupying 2-position in A and B (Chart 16). The other possible structures for m/e 105 ($C_7H_5O^+$ and $C_8H_9^+$) can be ruled out since their formation requires rigorous rearrangement. Low abundance of the ion at m/e 105 in C also supports this fact. Moreover the ion at m/e 77 is also very much intense in case of A and B only. This is explicable by the loss of H_2CN (28 m.u.) from the intense ion at m/e 105 from A and B. These arguments are further supported by the fact that the ions at m/e 135 which can be formed only from the rearranged products (C_2-phenyl) are present only in A and B. The other ion at m/e 118 during the Retro-Diels-Alder fragmentation is also present only in A and B.

Based on the above observations, it is concluded that GLC fractions A and B are rearranged 2,3-disubstituted tetrahydroquinolines whereas fraction C is the normal cyclodehydration product 3,4-disubstituted tetrahydroquinoline. These conclusions based on study of mass spectra support the conclusions based on study of NMR spectra which are discussed earlier.

No definite conclusions regarding identification of cis- and trans-isomers among the tetrahydroquinolines could be arrived at since fragments at m/e 161 and

m/e at 175 (corresponding to cis- and trans-isomers (Table 1) were present in all the spectra with almost same intensities. This may be due to non-resolution of GLC peaks. It is likely that high resolution mass spectroscopy may throw more light as regards identification of cis- and trans-isomers.

As stated earlier cyclodehydration of carbinol 35 with 70% perchloric acid yielded a cis- and trans-mixture of normal cyclodehydration products (3,4-disubstituted tetrahydroquinolines cis-38A and trans-38B normal and the rearranged products viz. 2,3-disubstituted tetrahydroquinolines cis-39A and trans-39B. This mixture of four products (as revealed by NMR) was subjected to GLC/MS analysis, the result of which are discussed below:

GLC of the mixture indicated four peaks, A, B, C and D; corresponding to four tetrahydroquinolines viz. 38A, 38B, 39A and 39B.

Mass spectra were recorded for each GLC peak. All compounds except fraction B indicated M^+ 100%. In case of fraction B m/e 136 was 100%. (Table 2 showing m/e, % intensities).

Table 2

m/e	A (%)	B (%)	C (%)	D (%)	
253	100	40	100	100	
252	25.0	11.3	21.67	18.3	M-1
238	100	23	100	83	M-15
224	19.4	11.9	16.6	16.6	M-29
211	11.1	-	6.6	4.6	M-42
210	17.2	-	10.83	10.0	M-43
176	19.1	4.6	14.7	12.0	M-77
175	11.1	7.4	9.3	10.0	~~M-118~~
161	23.6	12.0	26.6	20.0	
149	33.3	12.67	32.5	28.5	
136	28.39	100.0	22.6	18.33	
135	21.1	25.3	20.0	15.3	M-118
105	27.7	16.0	36.6	5.0	M-148
77	19.4	20.0	18.33	15.0	

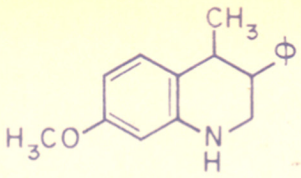
Identification of the normal and rearranged tetrahydroquinoline was again based on Retro-Diels-Alder reaction. Probable fragmentation patterns of normal and rearranged tetrahydroquinolines (cyclodehydration products) revealed that in the case of normal cyclodehydration products (cis-38A and trans-38B) m/e 149 should be intense and in the rearranged cyclodehydration products (cis-39A and trans-39B) m/e 135 should be intense (Chart 18).

Some of the common m/e values for 2,3- and 3,4-disubstituted tetrahydroquinolines 39 and 38 are as follows (Chart 19):

Compounds corresponding to GLC peaks A, C and D show M^+ at m/e 235 as 100% intense, whereas in the case of B m/e 136 is 100% intense.

m/e at 252 i.e. M-1 can be explained by loss of a hydrogen from C_2 position. m/e at 252 is comparatively intense for A and C than B and D. Loss of a CH_3 group i.e. m/e at M-15 is also intense in case of A and C (100%) whereas B shows it to be 23% and D to be 100%. m/e at 224 is intense in A than in B; whereas for C and D it is equal in intensity.

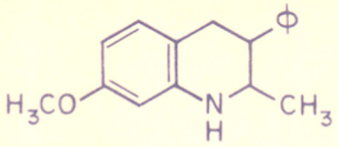
It appears from above results that compounds corresponding to fractions A and C are having similarity



38

cis --- A

trans -- B

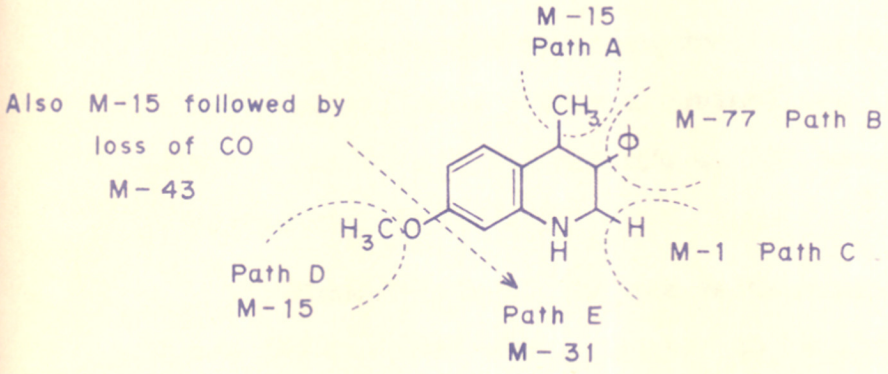


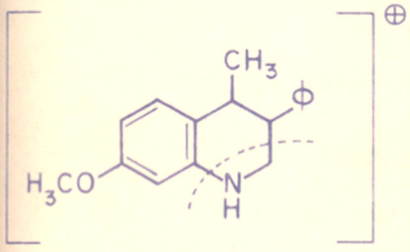
39

cis --- A

trans -- B

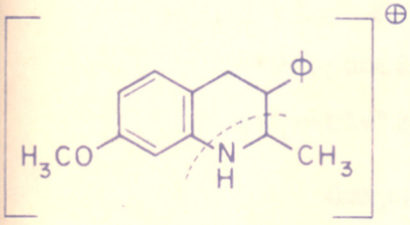
Common Fragmentation pattern expected for tetrahydroquinolines 38 , 39





$-(CH_2 = NH)$ → m/e 224

38



$-(CH_3C = NH)$ → M – 42

39

CHART – 19

in their structure and can form a pair, similarly B and C form another pair.

To identify as to which of the above pair corresponds to normal cyclodehydration products viz. the 3,4-disubstituted tetrahydroquinolines (38A, 38B) and the rearranged cyclodehydration products viz. 2,3-disubstituted tetrahydroquinolines (39A, 39B), the peaks at m/e 149 and m/e at 135 were the main criterion.

Examination of the m/e values indicate that m/e 149 for GLC peak A appears to be intense (33.3%) as compared to m/e 149 for B (12.67%) (Table 2).

Also m/e 135 is slightly more intense (25.3%) than m/e 135 for peak A.

Thus GLC peak A (m/e 149) can be assigned to 4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38 (38A or 38B) and the peak B (m/e 149) as due to rearranged 2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39 (cis-39A or trans-39B) m/e 253 - m/e 149 = 104 units corresponding to loss of styrene from 38A and 38B by Retro-Diels-Alder reaction.

Compounds corresponding to GLC fractions C and D both indicate presence of m/e 135 and m/e 149.

It seems that peaks C and D are not well separated and fraction D is probably contaminated with compound from fraction C.

No definite conclusion regarding cis- or trans- isomers present in 38 and 39 was possible at m/e 161 (corresponding to cis-disubstituted compound) and m/e 175 (corresponding to trans-disubstituted compound) (Chart 18) were present in all the spectra.

Presence of the two sets of tetrahydroquinolines in the cyclodehydration products obtained from the carbinol 35 was thus proven based on NMR and mass spectral studies.

EXPERIMENTAL

α-(3'-Methoxyphenylamino)methylpropiophenone 30

was prepared according to the procedure reported by Kulkarni[3]. A little modification wherein sodium carbonate was employed as condensing agent improved the yield of 30 from 20% to 56%.

A mixture of Mannich base hydrochloride of propiophenone (B) (22.7 g, 0.1 mol), m-anisidine 7 (12.3 g, 0.1 mol) and sodium carbonate (21.2 g, 0.2 mol) was refluxed in aqueous ethanol for 14 hrs. Reaction mixture on usual work up gave 30 (15 g, 56% yield), b.p. 144-50°/6 x 10^{-2} mm.

Cis-1-(3'-methoxyphenylamino)methylenepropiophenone 25.

25 was prepared according to the procedure reported by Salama[1a].

4-(3'-Methoxyphenylamino)-3-phenyl-butan-2-one 32

32 was prepared by refluxing a mixture of Mannich base hydrochloride[7] (C) of benzyl methyl ketone (22.7 g, 0.1 mol), m-anisidine 7 (12.3 g, 0.1 mol) and sodium carbonate (21.2 g, 0.2 mol) in 1:1 aqueous ethanol for 14 hrs. Ethanol evaporated and the reaction mixture was extracted with chloroform. Chloroform layer was washed thoroughly with water, dried over anhydrous Na_2SO_4. On removal of chloroform gave thick brown liquid (16.2 g). Filtration of

the brown liquid through a short column and distillation under reduced pressure gave 32 as thick yellow liquid (11.3 g, 42%), b.p. 135-40°/3.45 x 10^{-2} mm.
IR showed >C=O at 1685 cm^{-1}.
NMR (CCl_4, δ) indicated D_2O exchangable NH proton at 3.78, broad s, 1p; methyl at 1.96, s, 3p; methoxy at 3.66, s, 3p; methylenes centred at 3.3, m, 2p; benzylic and aromatic centred at 6.6, m, 8p.
Analysis: Found C, 76.1; H, 7.2; N, 5.1. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%.
Mass showed M^+ 269

4-(3'-Methoxyphenylamino)-3-phenyl-but-3-ene-2-one 33.

To a stirred suspension of sodium hydride (80% in wax) (9.0 g, 0.3 mol) in dry ether, ethyl formate (22.5 g, 0.3 mol) was added (dropwise) with cooling. The reaction mixture was stirred for 30 min. more after the addition. Benzyl methyl ketone (20.1 g, 0.15 mol) was added slowly. Stirring was continued for 2 hrs further and then the reaction mixture was set aside for 14 hrs. Solid mass which got formed was treated with 150 ml water with cooling. The aqueous layer was separated and acidification with dilute HCl in cold to get a mixture of isomeric hydroxymethylene derivatives viz. 4-hydroxy-3-phenylbuten-2-one (D) and 4-hydroxy-1-phenyl-3-

buten-2-one (E) as thick liquid. (Crude product 20.2 g, 83.12%).

The mixture of isomeric hydroxymethylene derivatives D and E (16.2 g, 0.1 mol) was treated with m-anisidine 2 (12.3 g, 0.1 mol) when an exothermic reaction was set in. Ethanol (150 ml) was added and reaction mixture was refluxed on water bath for 2 hrs. Evaporation of ethanol yielded thick brown liquid. GLC of the condensed product indicated it to be a mixture of isomeric enaminoketones 33 and 34 (65:35) along with unreacted m-anisidine 2. m-Anisidine was removed by vacuum distillation to give a mixture of 33 and 34 (18.7 g, 68.4%). Column chromatography of the above reaction mixture (12.0 g) using basic alumina (480 g) and petroleum ether as the eluent afforded the desired 4-(3'-methoxyphenylamino)-3-phenylbut-3-ene-2-one 33 (6.5 g) (fraction 1) which on distillation, gave 5.8 g of pure 33 as thick yellow liquid (b.p. 115-120°/ 1 x 10^{-3} mm). Further chromatography afforded a mixture of 33 and isomeric enaminoketone 34 (3.8 g) (fraction 2).

IR of 33 showed >C=O at 1665 cm^{-1}.
NMR of 33 (CCl_4, δ) indicated methyl at 2.0, s, 3p; methoxy at 3.66, s, 3p; aromatic and ethylenic

centred at 6.86, m, 10p; NH and/or OH (enolic) at 12.0, broad doublet, 1p.
Analysis: Found C, 76.1; H, 6.2; N, 4.9. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.3; N, 5.2%.
Mass showed M^+ 267.

[Carbinols 26 and 31 were prepared according to Salama[1a] and Kulkarni[3]].

A mixture of β-arylaminoketone 32 (5.5 g, 0.021 mol) and sodium borohydride (0.40 g, 0.012 mol) in ethanol (150 ml) was kept at room temperature for 0.5 hr. Mixture was warmed on water bath for further 0.5 hr. After dilution with water (200 ml), the reaction mixture acidified with acetic acid and extracted with ether. Ether extract was successively washed with water, bicarbonate solution and water ether extract dried over anhydrous Na_2SO_4. Ether was evaporated and the carbinol thus obtained was chromatographed over silica gel and distilled under vacuum, gave 4-(3'-methoxyphenylamino)-3-phenylbutan-2-ol 35 as thick yellow liquid, (5.1 g, 92.7%), b.p. $135\text{-}40^0/2.4 \times 10^{-4}$ mm of Hg.
IR showed a broad band at 3320 cm^{-1} (NH and OH).
NMR indicated D_2O exchangable NH and OH at 3.01, broad, 2p; methyl at 1.01, t, 3p; methoxy at 3.55, s, 3p; methylene and methine at 3.06, m, 3p; benzylic at

3.95, m, 1p; aromatic at 6.0, m, 9p.
Analysis: Found C, 75.1; H, 7.6; N, 4.7. $C_{17}H_{21}NO_2$ requires C, 75.2; H, 7.7; N, 4.6%.
M^+ at 271.

Sodium borohydride reduction of enaminoketone 33.

A mixture of enaminoketone 33 (5.2 g, 0.019 mol) and sodium borohydride (0.8 g, 0.02 mol) in ethanol (150 ml) was set aside at room temperature for 0.5 hr. Mixture was warmed on water bath for further 0.5 hr. Work up as above and chromatography over silica gel gave a mixture of cis/trans-α-(3'-methoxyphenylamino)methyl-β-methylstyrene 37 (37A/37B) as the first fraction (0.7 g, 13.28%) b.p. 115-20°/1.2 x 10^{-2} mm.
NMR of 37 (CCl_4, δ): (Fig 5).
IR: NH at 3220 cm^{-1}
Analysis: Found C, 80.2; H, 7.5; N, 5.3. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.
M^+ at 253.

Further chromatography afforded carbinol 36 (3.7 g, 70.23%) b.p. 135-40°/2.4 x 10^{-4} mm of Hg.
IR, NMR and Mass spectra of carbinol 36 were identical with those of carbinol 35.

Cyclodehydration of 3-(3'-methoxyphenylamino)-2-methyl-1-phenylpropan-1-ol 31.

To a mixture of carbinol 31 (1.0 g) and crushed ice (10.0 g), 70% sulphuric acid (10 ml) was added gradually with shaking. Mixture was warmed on water bath for 30 min and kept aside for 48 hrs. Reaction mixture was neutralised with aqueous NaOH and then extracted with ether. Ether extract, on work up, gave thick liquid (0.81 g, 86.7%) which was then chromatographed over silica gel using benzene as eluent. NMR spectrum of the above cyclodehydration product indicated it to be a mixture of cis- and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28A, 28B and trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B in 30:20:50 proportion. Above result was arrived at by comparing the GLC and NMR spectrum with authentic samples[1a]. To confirm the above interpretation this sample was subjected for GLC/MS analysis (see page).

Cyclisation of 3-(3'-methoxyphenylamino)-2-meth/1-1-phenylpropan-1-ol 26, using triphenylphosphine, bromine, triethylamine.

Treatment of the carbinol 26 (5.0 g) obtained by sodium borohydride reduction of enaminoketone 25

with triphenylphosphine dibromide (prepared from 6.8 g triphenylphosphine and 1.2 ml bromine) in acetonitrile (60 ml) furnished yellow coloured turbid solution. When the precipitate dissolved and solution became clear, triethylamine (5.2 g) in acetonitrile (20 ml) was added and the mixture stirred at 0-5° for 72 hrs. Triethylamine hydrobromide (precipitated) was filtered off. The filtrate was concentrated under reduced pressure. The residue was extracted several times with petroleum ether. Petroleum ether extract on concentration gave brown oil (6.8 g) which was chromatographed over silica gel.

CHROMATOGRAM

Carbinol 26

Fraction No.	Eluent	Remarks	Wt. g
1	Pet.ether	Colourless plates m.p. 80° Triphenylphosphine	0.768
2	Pet.ether + benzene 95 : 5	Colourless thick liquid	0.352
3	Pet.ether + benzene 75 : 25	Thick liquid	0.681
4	Pet.ether + benzene 25 : 75	Thick liquid	0.413
5	Benzene	Recovered carbinol 26	0.460
6	Benzene-ethyl acetate 80 : 20	Triphenyl phosphine oxide white solid	3.9

Fraction 2 colourless liquid obtained was distilled under vacuum to give cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A as colourless liquid b.p. 120-5°/1 x 10^{-3} mm (yield 7.5%).
NMR (CCl_4, δ) is discussed on (page

IR indicated the absence of NH and OH functions.
Analysis: Found C, 80.8; H, 7.2; N, 5.2. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.

Fraction 3: Thick liquid on standing solidified which was recrystallised from methanol (m.p. 97-98°C) to give trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B. NMR was compared with authentic sample[1a].

Fraction 4: Thick liquid obtained was distilled under vacuum to give a mixture of trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B (minor) and cis-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B (major), b.p. 135/0.005 mm.

Cyclisation of carbinols 31 and 26 using triphenylphosphine, carbon tetrachloride and triethylamine.

To a stirred solution of triphenylphosphine (5.2 g, 0.02 mol) in dry acetonitrile (60 ml) was added carbon tetrachloride (3.05 g, 0.02 mol) with

IIA →

cooling. Reaction mixture was stirred for half an hour further and carbinol 31 (3.5 g,) in dry acetonitrile (20 ml) was added dropwise. Stirring continued for half an hour further, followed by dropwise addition of triethylamine (3.5 g, 0.03 mol) in dry acetonitrile (20 ml). Reaction mixture was stirred further for 20 hrs at 0-5°. Triethylamine hydrochloride was filtered and the filtrate was concentrated under reduced pressure gave thick brown liquid. This was extracted with petroleum ether, which on concentration under reduced pressure yielded yellowish liquid (3.8 g). Column chromatography of the yellowish liquid using silica gel and petroleum ether as eluent yielded triphenylphosphine (0.362 g) as the first fraction. Further elution yielded cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A as colourless liquid (0.15 g, 4.7%) which was followed by trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B (0.328 g, 10.1%) and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 27B (0.189 g, 5.5 %) carbinol 31 (0.446 g, 13.6 %) was recovered.

Cyclisation of carbinol 26.

Cyclisation of carbinol 26 (5.2 g) using triphenylphosphine, carbon tetrachloride and triethylamine and on work up gave thick liquid (4.8 g)

as above column chromatography of the above liquid using silica gel and petroleum ether as eluent yielded triphenyl phosphine (1.25 g) as the first fraction. Second fraction of the chromatography was identified as a cis/trans- mixture of 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29 (29A/29B) (0.250 g, 4.9%). Further elution gave trans-7-methoxy-3-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 28B (0.595 g, 11.8%) as the third fraction. The fourth fraction was identified as a mixture of cis/trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27 (27A/27B) (0.383 g, 7.6%). Carbinol 26 (0.725 g, 14.38%) was recovered.

The structures for tetrahydroquinolines 27A, 27B, 28A and 28B were confirmed by comparing the IR, NMR and analytical data with the reported ones[1a].

Cyclodehydration of 4-(3'-methoxyphenylamino)-3-phenylbutan-2-ol 35, 36.

Many attempts to cyclodehydrate carbinols 35, 36 using 70% H_2SO_4 were unsuccessful.

Cyclodehydration of carbinols 35, 36 using 70% perchloric acid.

To a mixture of carbinol (1.0 g) and ice (10.0 g) 70% $HClO_4$ (10 ml) was added slowly with shaking. The reaction mixture allowed to come to room temperature;

then warmed for 6 hrs at 60 ~ 65° and kept aside for 48 hrs. Reaction mixture neutralised with bicarbonate solution and extracted with chloroform. Chloroform layer washed with water and dried over anhydrous Na_2SO_4. Evaporation of the chloroform gave thick brown liquid which was chromatographed over silica gel.

Cyclodehydration of carbinol 35.

Carbinol 35 (1.0 g) on treatment with 70% perchloric acid (10 ml) in cold and usual work up of the reaction mixture afforded thick brown liquid (0.86 g) which on chromatography afforded cyclodehydrated product (0.352 g, 37.7%), and unreacted carbinol 35 (0.216 g, 21.6%). The crude product on vacuum distillation furnished thick yellow liquid (b.p. 135°/3.5 x 10^{-2}) mm.

NMR (CCl_4, δ) of the product [(Fig 3) corresponding to 38A, 38B and 39A, 39B] indicated D_2O exchangable NH at 3.66, mixed with methoxy signal; four sets of doublets corresponding to methyl group at 0.84, (40% intense), 0.93 (25% intense), 1.13 (20% intense) and 1.26 (15% intense). Two methoxy signals one at 3.66 and another at 3.73 and aromatic protons centred at 6.63.

IR : NH at 3230 cm^{-1}

Analysis: Found C, 80.4; H, 7.1; N, 5.3. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.

This sample was subjected for GLC/MS analysis, which has been discussed earlier (page)

Cyclodehydration of carbinol 36.

Cyclodehydration of carbinol 36 (1.0 g) using 70% perchloric acid (10 ml) and work up as above yielded 0.788 g of crude product which on column chromatography gave cyclodehydrated product (0.322 g, 34.2%) and unreacted carbinol 36 (0.195 g, 19.5%). Cyclodehydrated product on further chromatography afforded a mixture of cis-7-methoxy-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 38A (70%) and cis-7-methoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39A (30%) as the first fraction (0.162 g, 17.49%). NMR of this fraction discussed in the present work (page).

IR: NH at 3230 cm^{-1}

Analysis: Found C, 80.9; H, 7.2; N, 5.2. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5.

NMR of the second fraction indicated it to be trans-7-methoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 39B (0.128 g, 13.8%).

NMR was discussed in present work (page)

IR: NH at 3230 cm^{-1}

Analysis: Found C, 80.8; H, 7.3; N, 5.4. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.

Cyclisation of carbinol 35 using triphenylphosphine, bromine and triethylamine.

Treatment of carbinol 35 (5.4 g) with triphenylphosphine dibromide (prepared from 6.8 g triphenyl phosphine and 1.2 ml bromine) in acetonitrile (60 ml), furnished yellow coloured turbid solution. When the precipitate dissolved and solution became clear, triethylamine (5.2 g) in acetonitrile (20 ml) was added and the reaction mixture stirred at 0-5° for 72 hrs. Triethylamine hydrobromide (precipitated) was filtered off. The filtrate was concentrated under reduced pressure. The residue was extracted several times with petroleum ether. Petroleum ether extract on concentration gave brown oil which was chromatographed over silica gel yielded triphenyl phosphine (1.3 g) as the first fraction, m.p. 79-80°. Second fraction of the chromatography was identified as a cis/trans-mixture of 1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidine 40 (0.122 g, 2.4%), (b.p. 125/1 x 10^{-3} mm), (cis-40A, trans-40B).

IR showed absence of NH or OH absorption.
Analysis: Found C, 80.5; H, 7.5; N, 5.2. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.

The third fraction of chromatography was identified as cis/trans-α-(3'-methoxyphenylamino)-methyl-β-methylstyrene 37 (37A/37B) (0.826 g, 16.4%), (b.p. 110°/1 x 10^{-3} mm).
IR showed NH absorption at 3220 cm^{-1}.
Analysis: Found C, 80.2; H, 7.7; N, 5.2. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.
Mass : M^+ 253
Carbinol 35 (1.2 g, 22.2%) was recovered.

VIIP5→

Cyclisation of carbinol 36 using triphenylphosphine, bromine and triethylamine.

Carbinol 36 (4.8 g) was treated with triphenylphosphine dibromide (6.8 g) in acetonitrile (60 ml) and triethylamine (5.2 g) in acetonitrile (20 ml) and work up as above gave brown oil which was chromatographed over silica gel using petroleum ether as eluent. Triphenylphosphine (1.56 g) was recovered as the first fraction. Second fraction of the chromatography was identified as a mixture of cis/trans-1-(3'-methoxyphenyl)-2-methyl-3-phenylazetidine 40 (40A/40B) (0.148 g, 3.3%). The third fraction was identified as a mixture of

cis/trans-α-(3'-methoxyphenylamino)methyl-β-methylstyrene 37 (37A /37B) (0.886 g, 19.7%). Carbinol 36 (0.98 g, 20.4%) was recovered.

Acid catalysed ring expansion of cis-1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 29A.

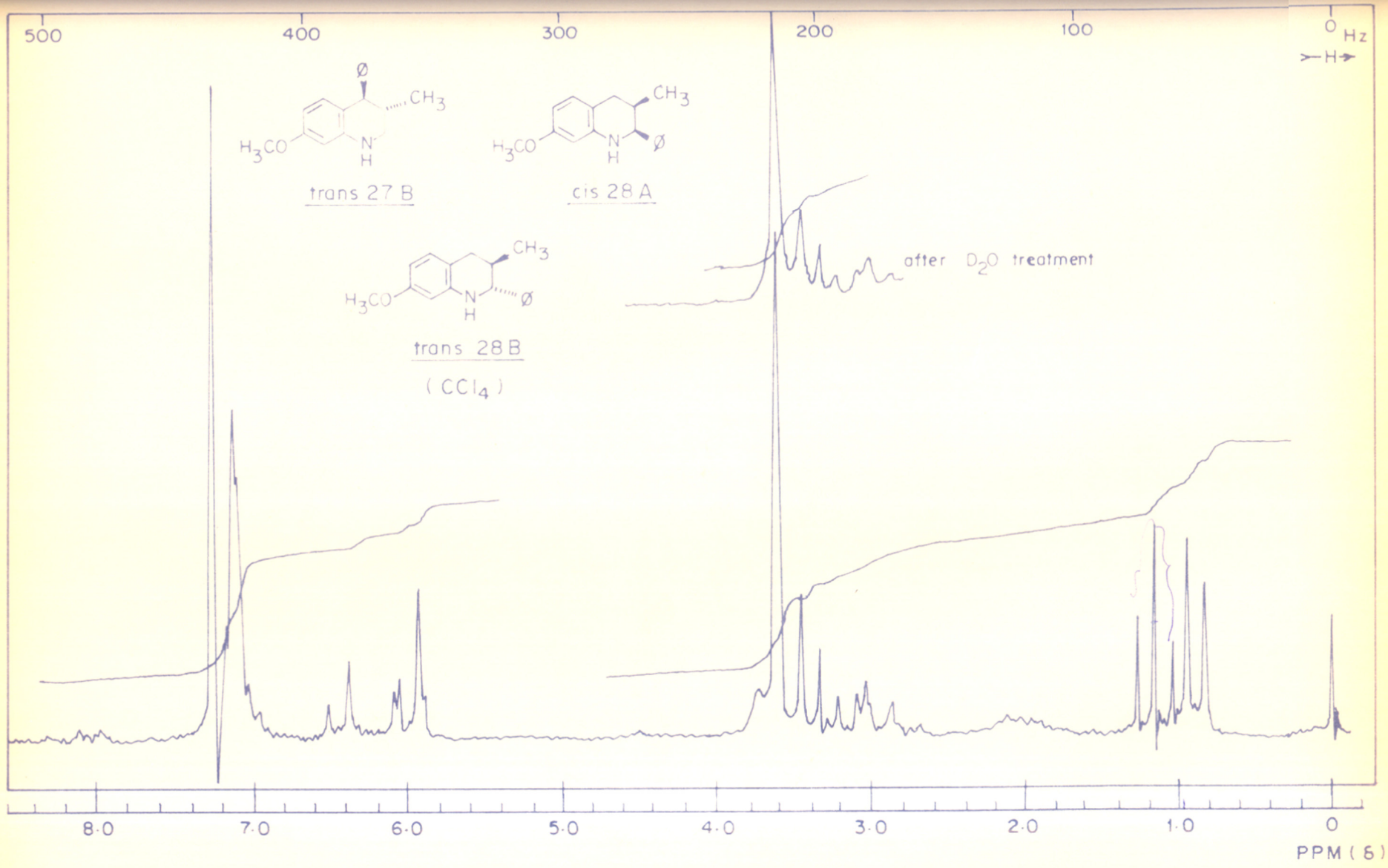
Azetidine 29A (0.120 g) was treated with 70% H_2SO_4 (10 ml) in cold and reaction mixture kept aside for 48 hrs at room temperature. Reaction mixture neutralised with aqueous NaOH and extracted with chloroform. Chloroform layer washed with water, dried over anhydrous Na_2SO_4 and evaporated, gave oily liquid; which on chromatography yielded a mixture of trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B and trans-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28B in equal proportions (as revealed by NMR) (0.087 g, 72.49%).

Pyrolysis of azetidine 29A.

Petroleum ether solution of azetidine 29A (0.1 g) was slowly evaporated using a rotavac in order to obtain a thin film of 29A on the inner surface of a round bottom flask. Rotating flask was dipped into an oil bath kept at 240-50° for 2 hrs. After 2 hrs the flask was cooled and benzene was added, solution filtered through a short column. Benzene evaporated

and the sample (0.087 g, 87%) subjected for NMR study. NMR spectrum indicated it to be a mixture of trans-7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 27B and cis-7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 28A in equal proportions.

ILLUSTRATIONS


500
400
300
200
100
0 Hz
H
trans 27 B
cis 28 A
trans 28 B
(CCl_4)
after D_2O treatment
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7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. — 1 .

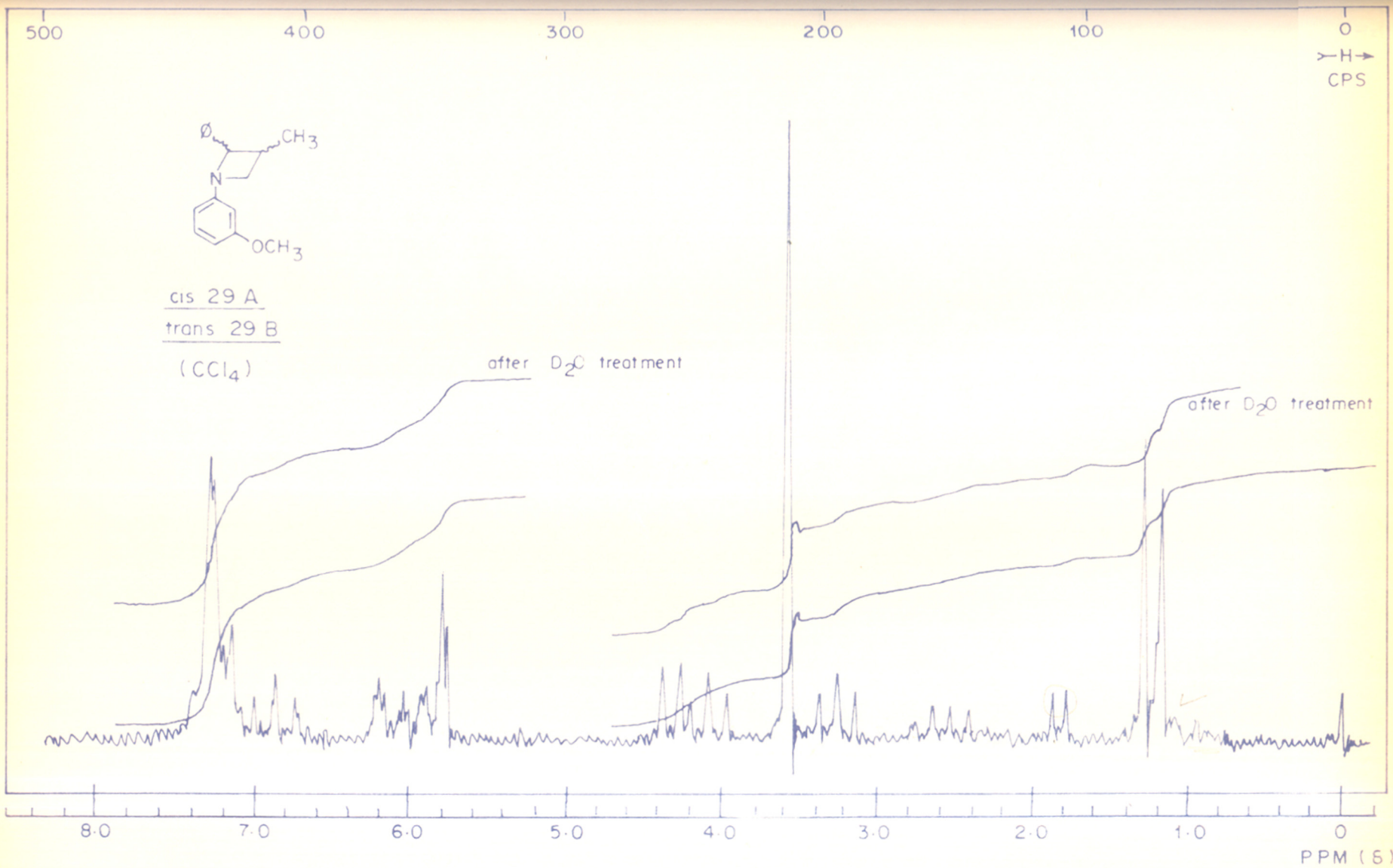
500
400
300
200
100
0
→H→
CPS
Ø
CH3
N
OCH3
cis 29 A
trans 29 B
(CCl4)
after D2O treatment
after D2O treatment
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. – 2.

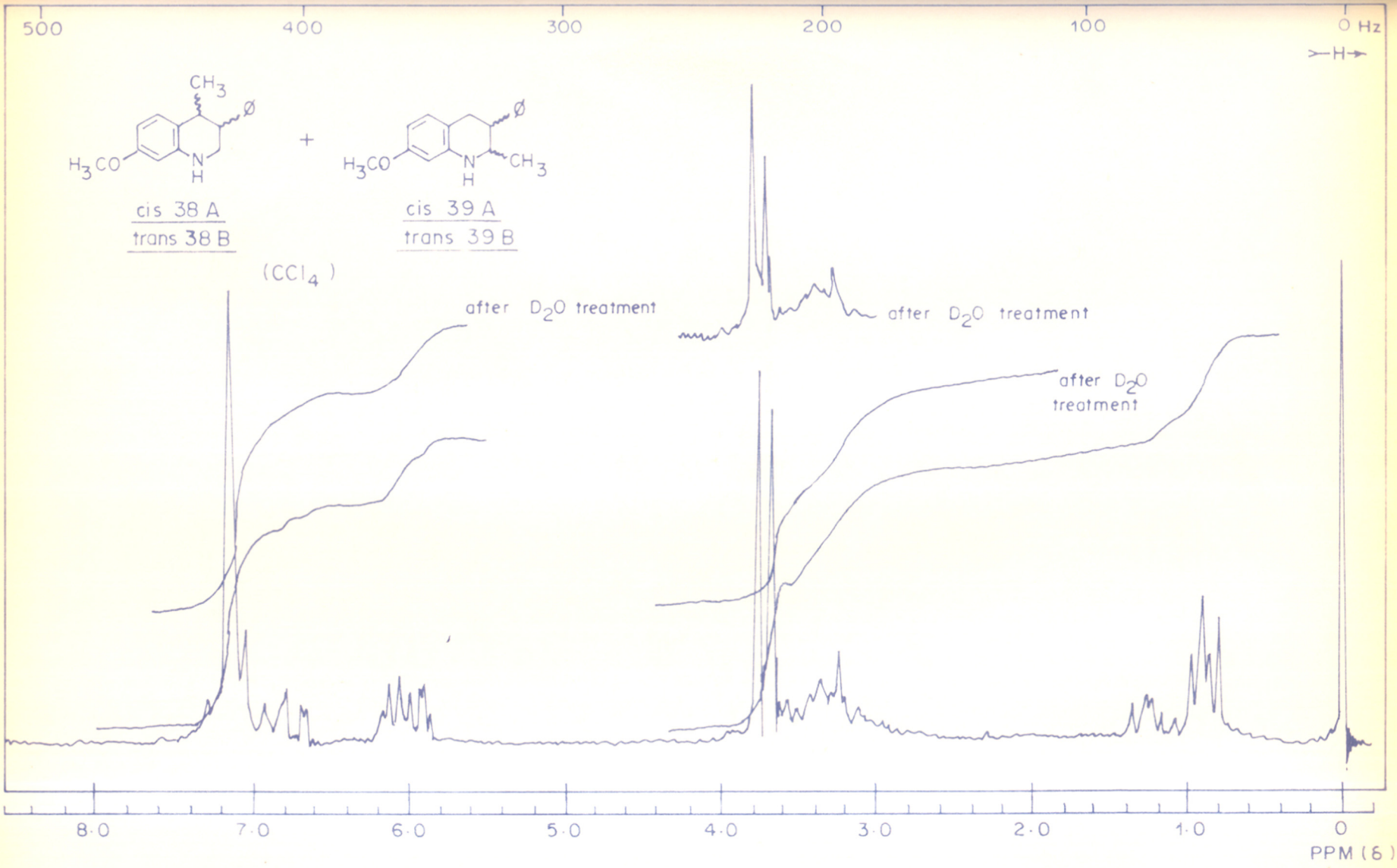
500
400
300
200
100
0 Hz
H
CH3
Ø
H3CO
N
H
+
CH3
cis 38 A
trans 38 B
cis 39 A
trans 39 B
(CCl4)
after D2O treatment
after D2O treatment
after D2O treatment
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. 3.

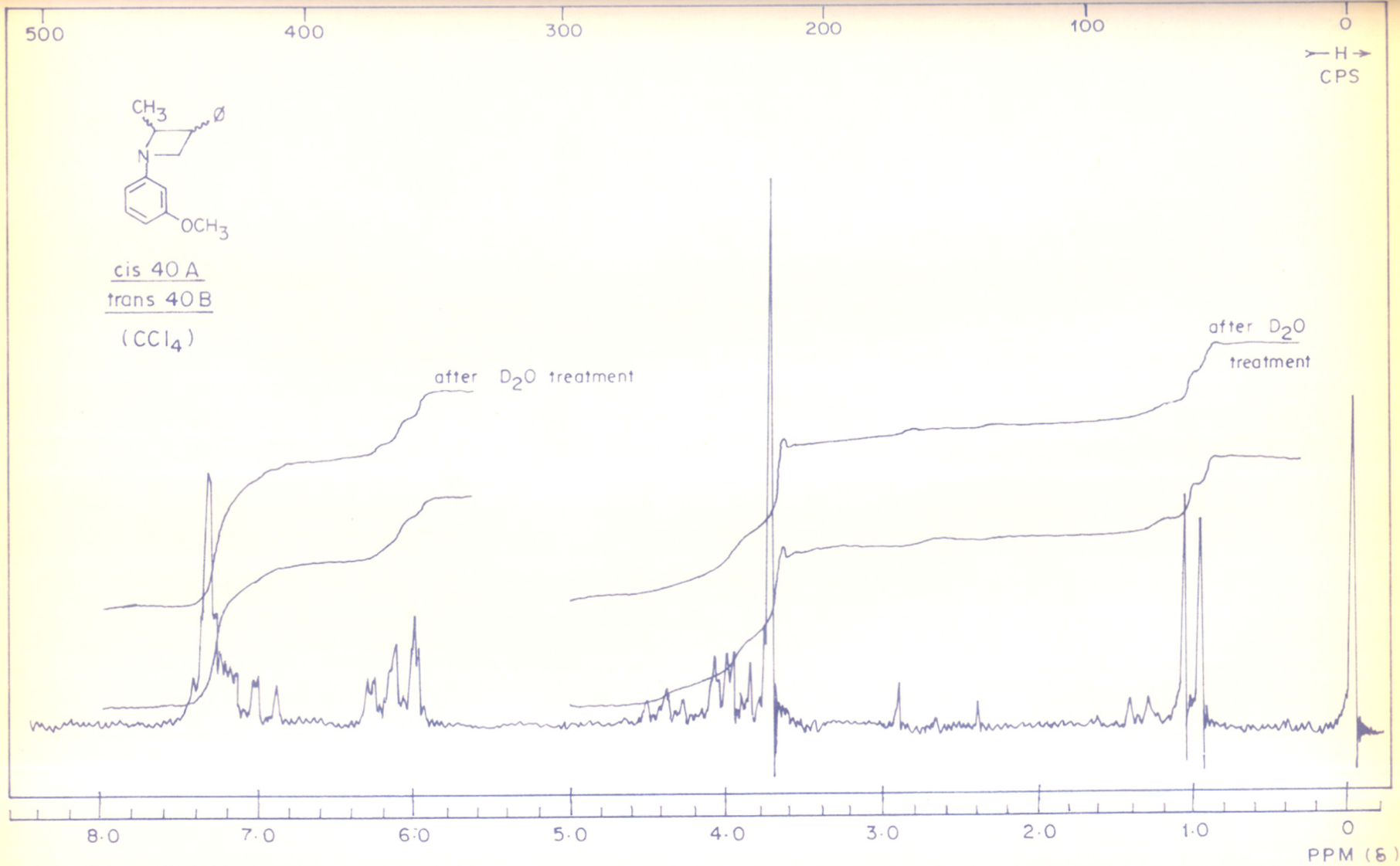
500
400
300
200
100
0
→H→
CPS
CH3
Ø
N
OCH3
cis 40 A
trans 40 B
(CCl4)
after D2O treatment
after D2O
treatment
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. — 4.

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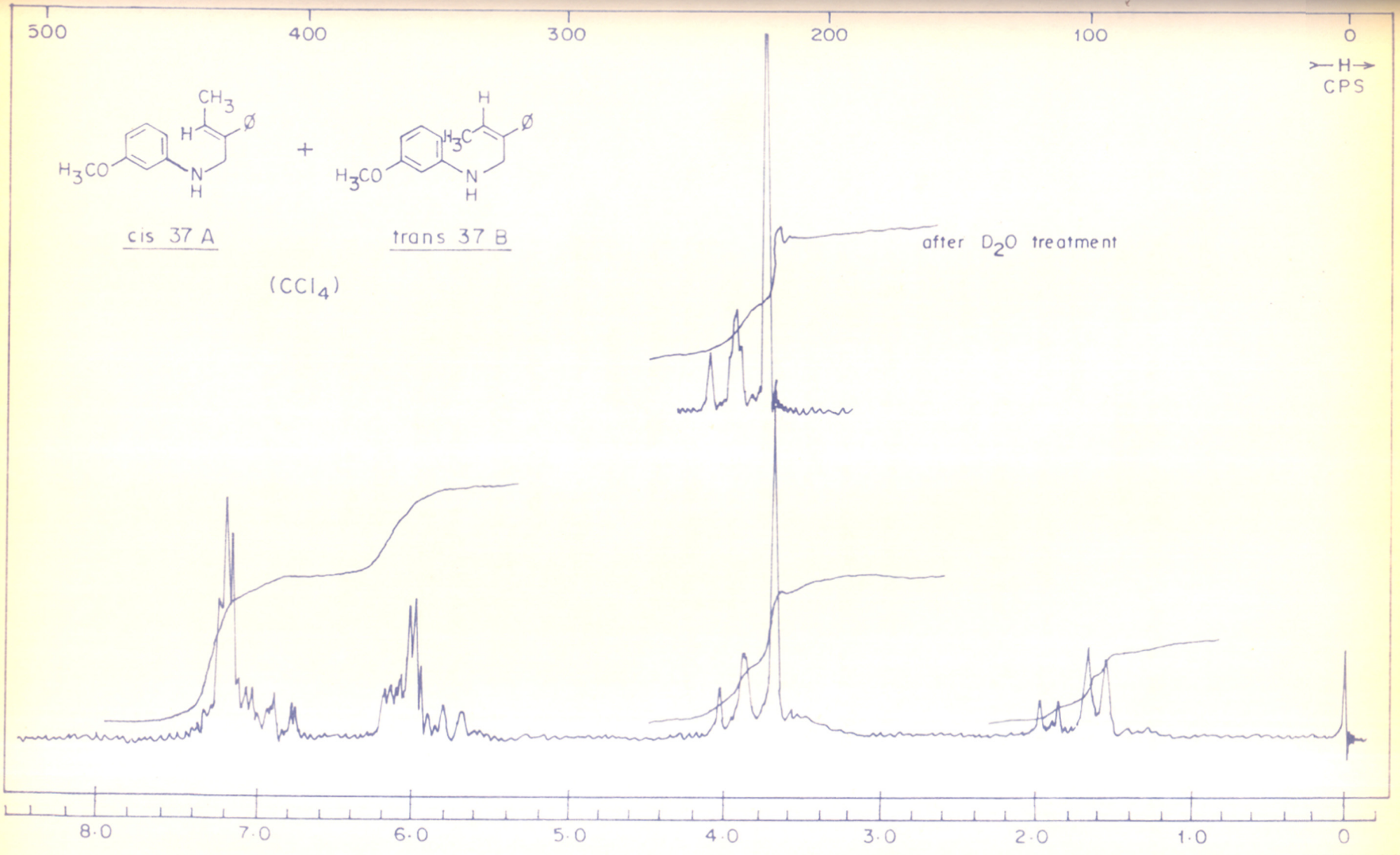
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400
300
200
100
0
H
CPS
CH3
H
Ø
H3CO
N
H
+
H
H3C
Ø
H3CO
N
H
cis 37 A
trans 37 B
(CCl4)
after D2O treatment
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG – 5.

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CHAPTER III : SYNTHESIS AND REARRANGEMENT OF 2,3-DISUBSTITUTED 1-S-PHENYLTHIONIUMCYCLOBUT-2-ENE-PERCHLORATES

Introduction

Tilak and co-workers[1-6] have studied the mechanism of acid catalysed cyclodehydration of β-phenylmercaptoethyl alkyl/cycloalkyl/aryl ketones which lead to the formation of thianaphthalenium salts and thiachromans.

Careful reexamination[7] of the perchloric acid catalysed cyclodehydration products of γ-(β-phenylmercapto)propyl phenyl ketone 1 and β-phenyl-β-phenylmercaptoethyl methyl ketone 2 revealed that in both these reactions a mixture of 2-methyl-4-phenylthianaphthalenium perchlorate 3 and 4-methyl-2-phenylthianaphthalenium perchlorate 4 was obtained along with mixture of cis- and trans-2-methyl-4-phenylthiachroman 5 and 4-methyl-2-phenylthiachroman 6, in varying proportions (Chart 1).

Formation of 3, 5 from 1 and 4, 6 from 2 is normally expected by an acid catalysed cyclodehydration reaction. However, formation of 4, 6 from 1 and 3, 5 from 2 can only be explained through the intermediacy of 1-β-phenyl-1-thioniumcyclobut-2-ene derivatives 7 and 8.

Tilak et al.[8] have reported a novel synthesis of 7 and 8. Treatment of the ketosulphide 1 with phosphorous oxychloride followed by 70% perchloric acid in cold

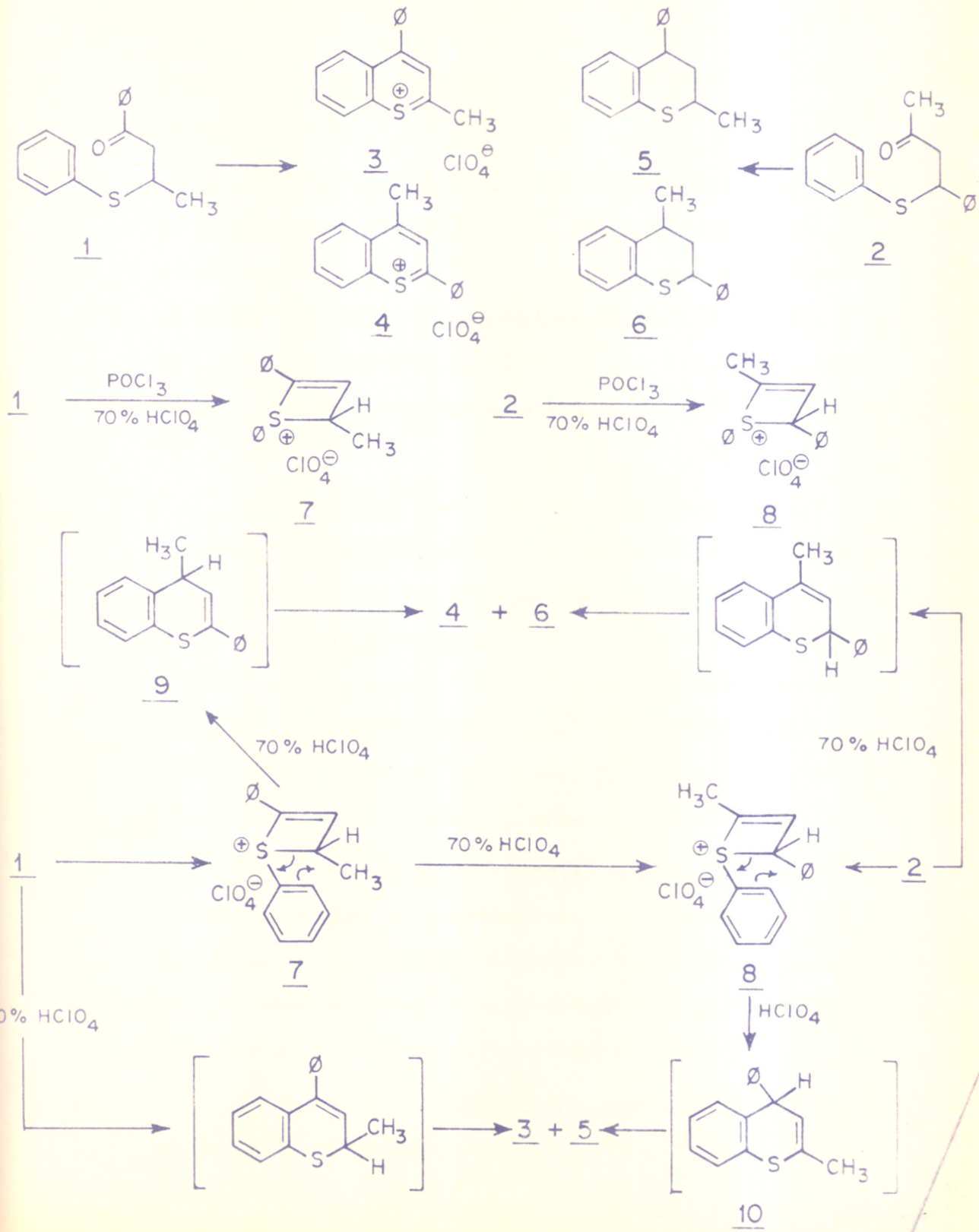


CHART – 1

afforded 7. Similarly 8 was obtained from the ketosulphide 2.

Tilak et al.[8] have also reported that compound 7, on warming with 70% perchloric acid, rearranges to perchlorates 3, 4 and thiachromans 5, 6. Formation of these compounds was explained by bond migration in 7 to give isomeric 8 partially and then these lead to 3, 5 and 4, 6 via intermediate Δ^2-thiachromene 9 and 10 (Chart 1).

Tilak et al.[8] have reported that compounds 7 and 8 on treatment with NaH in THF/Diethyl ether yielded a deep green coloured neutral compound 11 which appears to be a ylide 11A. It may also be formally represented as 3-methyl-4-phenyl-1-S-1-phenylthiacyclobutadiene 12 or as an alternative ylide 12A. Since reprotonation of the green compound gives only 8, it appears that the ylide 12A is dominantly present (Chart 2).

Devadhar[7] has also reported acid catalysed cyclodehydration of 1-mercaptoaryl-3-propanols. The carbinols 1-phenylmercapto-1-phenylbutan-3-ol 13, 14 and 3-phenylmercapto-1-phenylbutan-1-ol 15, 16 were prepared by two alternative methods (Chart 3).

In these cyclodehydration reactions it was observed that carbinols 15 and 16 yield normally

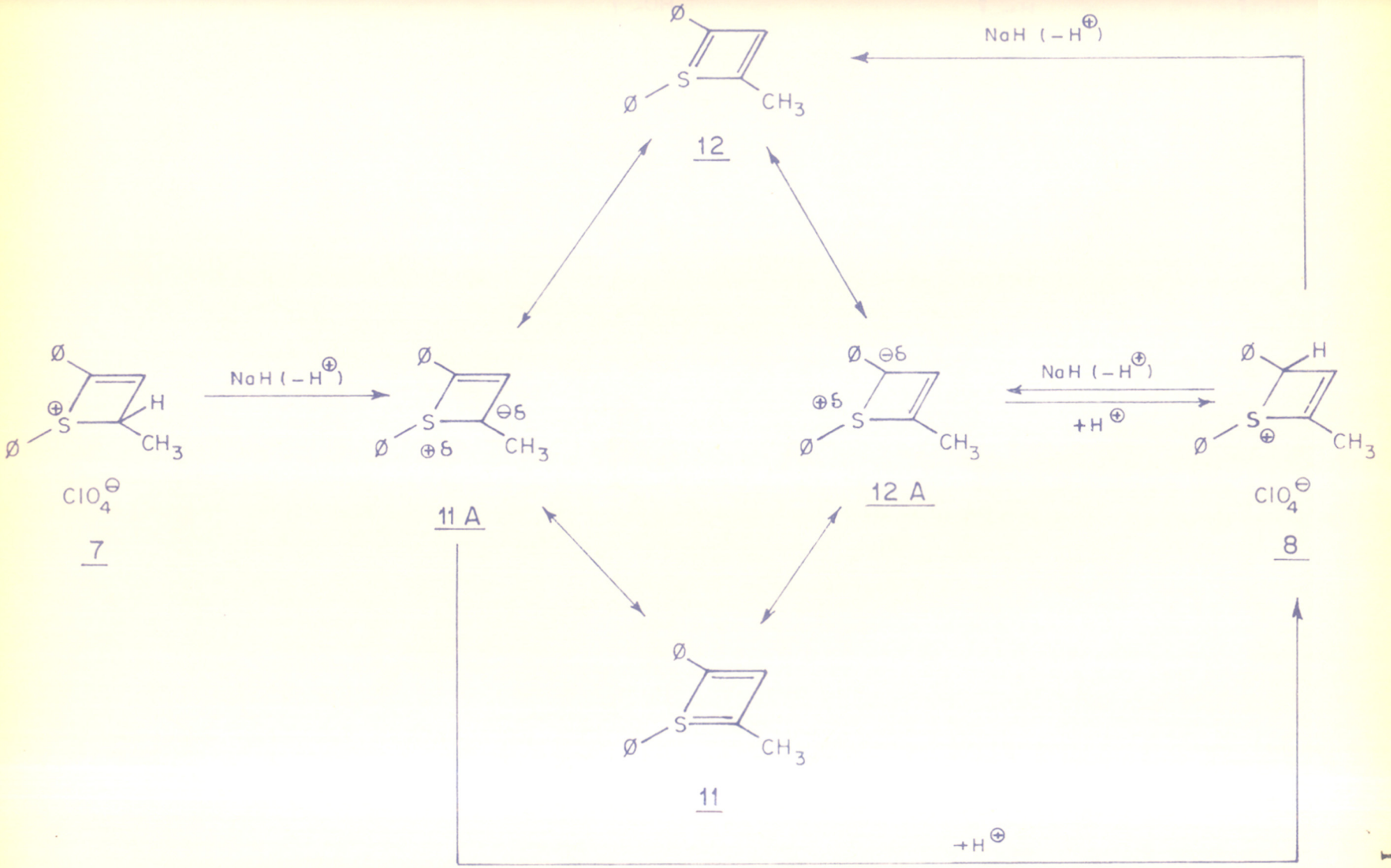


CHART – 2.

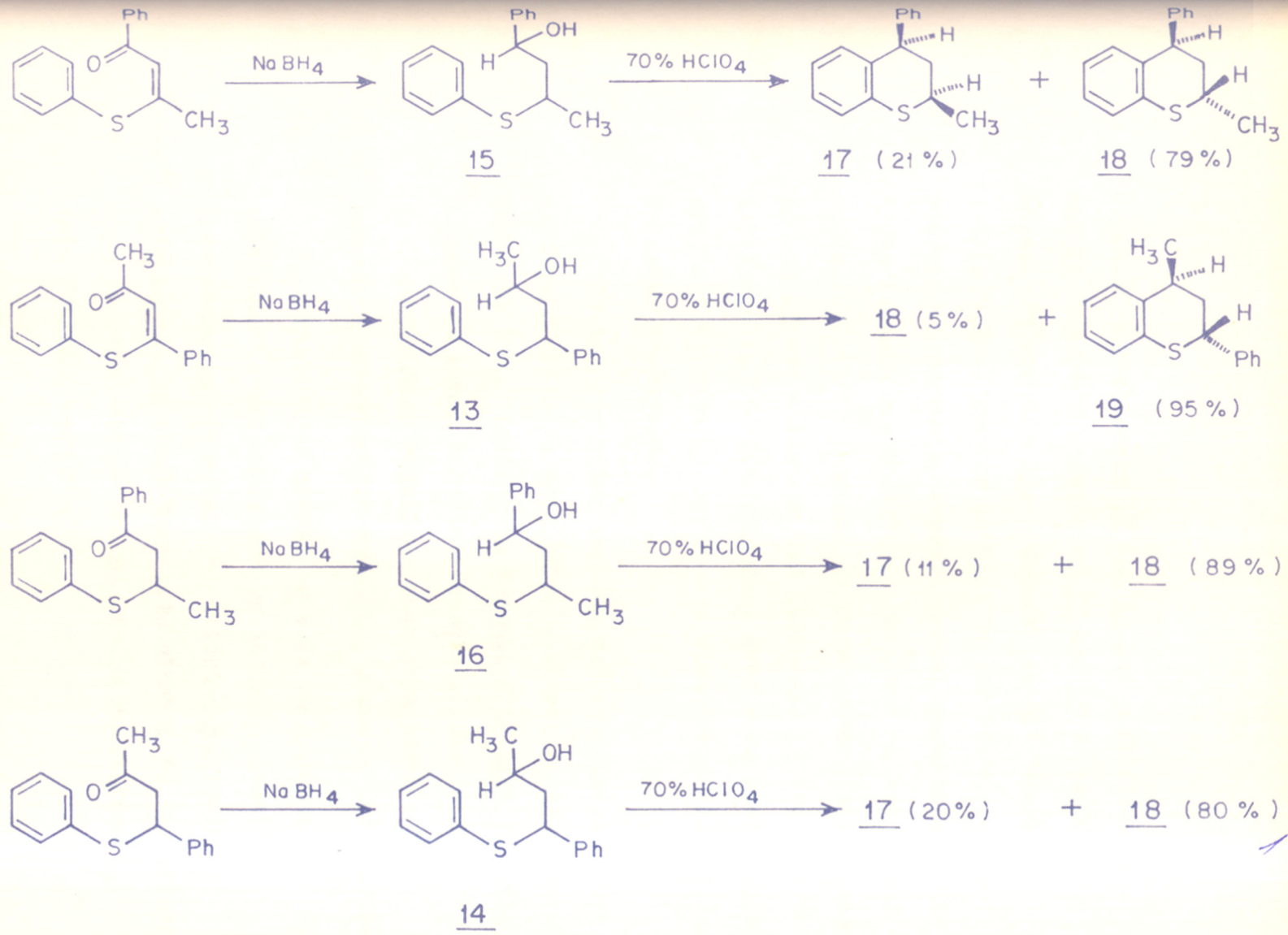


CHART — 3.

expected thiachromans 17 and 18 but carbinols 13 and 14 furnished rearranged 17 and 18 as well as normal thiachroman 19. However, in all these cyclisations, whether leading to the normal or rearranged products, a preferential formation of the trans-isomers was observed. From the nature of the cyclodehydration products it does appear that carbinols 13 and 14 are different but carbinols 15 and 16 are likely to be identical as they gave same cyclodehydration products (17 and 18) which are also formed in similar relative proportion.

If the carbonium ion derived from carbinol 20 is formed prior to cyclisation, it can be attacked from both the sides leading to formation of cis- and trans-isomers in equal amounts (Chart 4). The above cyclodehydration reactions therefore appear to be largely stereospecific involving a concerted process.

Formation of normal as well as rearranged thiachromans was explained by assuming possible involvement of 1-3-phenyl-1-thioniumcyclobutane perchlorate 21 which then gets cleaved in two alternate ways to yield either normal or the rearranged thiachroman (Chart 4).

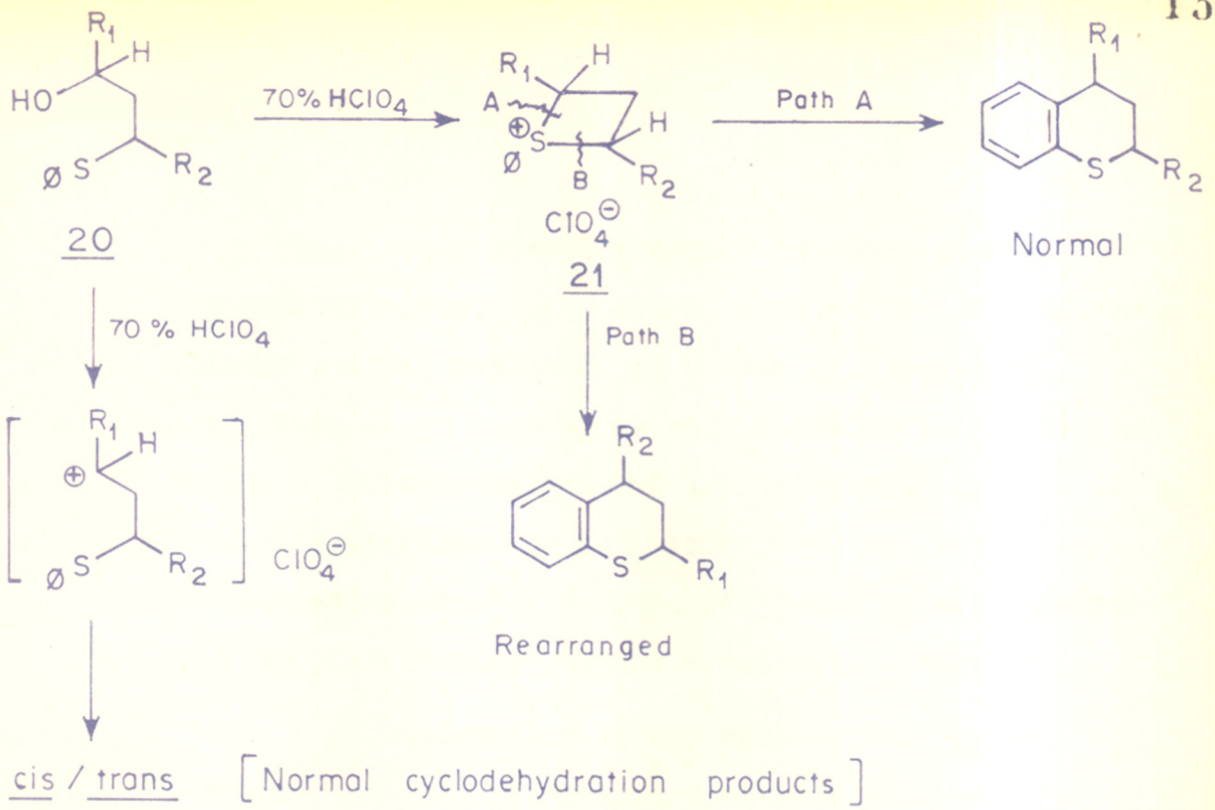


CHART – 4.

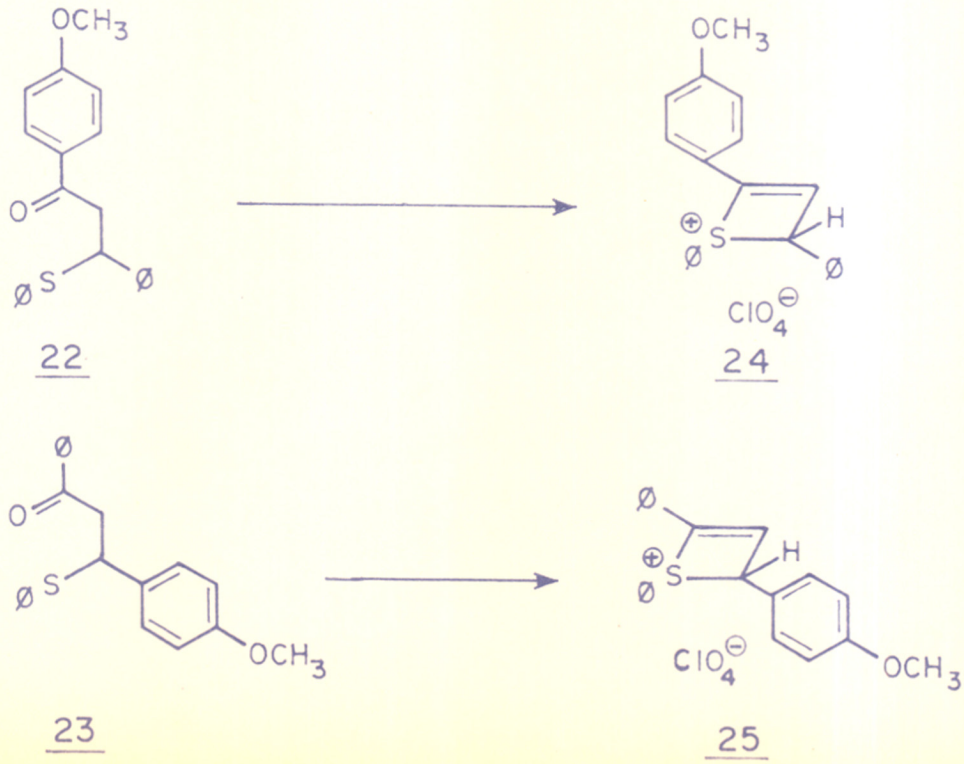


CHART – 5.

Modak[9] from this laboratory has also studied the acid catalysed ring opening of some 2,4-disubstituted thiacyclobutene perchlorates 24 and 25. However, conversion of 24 into 25 or vice versa could not be achieved through the intermediate formation of thiacyclobutadiene (or its ylide form) and its reprotonation since treatment of 24 and 25 with sodium hydride yielded only polymeric products (Chart 5).

As a continuation to our earlier work on the synthesis and ring expansion reactions of 2,4-disubstituted thiacyclobut-2-ene perchlorates, we attempted the synthesis of 2,3-disubstituted thiacyclobut-2-ene perchlorates. These studies are presented in this Chapter.

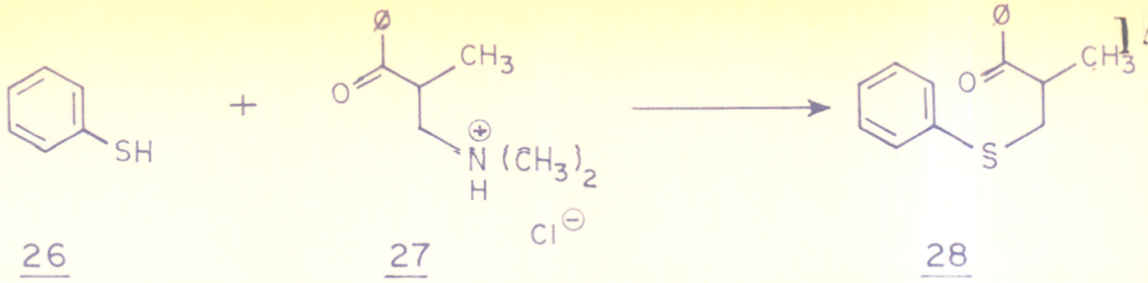
Present work

Cyclodehydration of α-phenylmercaptomethyl-propiophenone 28 by means of 70% perchloric acid gave a mixture of the normal 3,4-disubstituted and the rearranged 2,3-disubstituted thianaphthalenium perchlorates 31 and 33 along with the corresponding normal and rearranged thiachromans 32 and 34 (Chart 6).

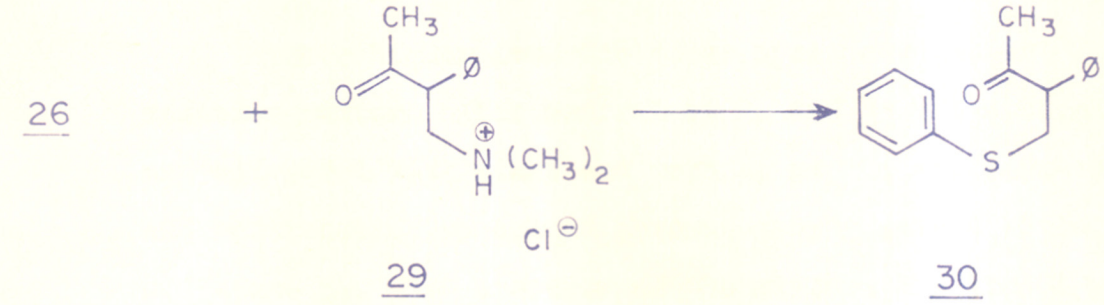
Cyclodehydration of 3-phenyl-4-phenylmercapto-butan-2-one 30 by treatment with 70% perchloric acid yielded both the normal and rearranged thianaphthalenium perchlorates 35 and 37 as well as the normal and rearranged thiachromans 36 and 38.

Ketosulphide 28 was prepared by the interaction of thiophenol 26 with Mannich base hydrochloride of propiophenone 27 in aqueous sodium carbonate-ethanol mixture. Similarly ketosulphide 30 was prepared by interaction of thiophenol 26 and Mannich base-hydrochloride of benzyl methyl ketone 29 (Chart 6).

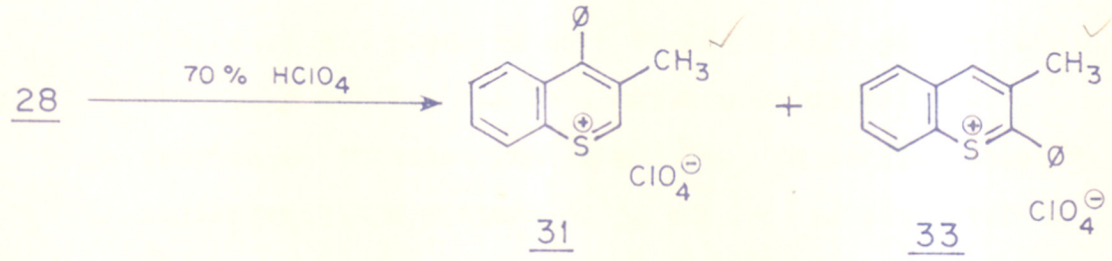
The mixture of thianaphthalenium perchlorates 31 and 33 obtained above could not be separated by fractional crystallization. NMR spectrum (Fig 1) of the mixture, however, indicated the presence of two methyl singlets one at 2.7 δ and the other at 2.9 δ ,



26 27 28

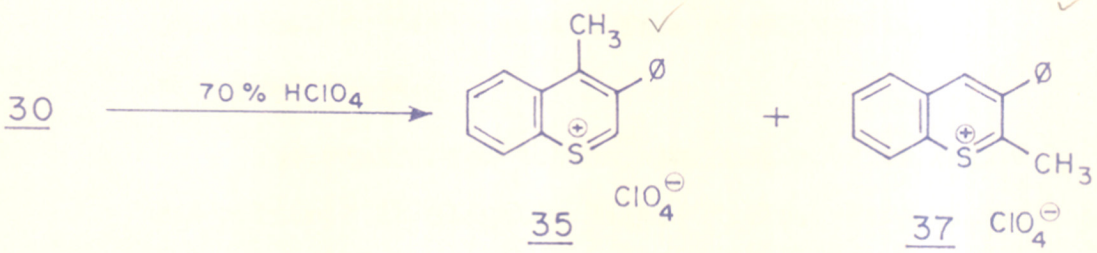


26 29 30

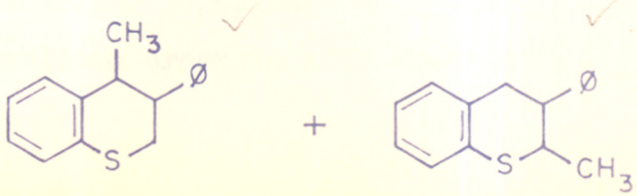


28 31 33

32 34



30 35 37



36 38

CHART – 6

corresponding to the normal and rearranged thianaphthalenium perchlorates 31 and 33.

Mother liquor from the above cyclodehydration reaction mixture after removal of 31 and 33 was neutralized and extracted with ether and work up of the ether extract and purification by column chromatography gave a mixture of 32 and 34. NMR spectrum of the mixture and its GLC/MS analysis was studied. NMR spectrum of the product indicated the presence of a broad doublet centred at 1.18 δ, obviously arising due to a mixture of normal and rearranged thiochromans 32 and 34. To confirm these assignments the mixture of 32 and 34 was subjected to GLC/MS analysis, the results of which are discussed later in this Chapter (see page).

Cyclodehydration of ketosulphide 30 by means of 70% perchloric acid gave a mixture of the thianaphthalenium perchlorates 35 and 37 (Figs 2, 3) along with the thiachromans 36 and 38. The mixture was separated by fractional crystallisation from dichloromethane - petroleum ether.

The rearranged thianaphthalenium perchlorate 37 was obtained in slightly higher yield. Neutralisation of the mother liquor after separation of 35 and 37 and isolation of the cyclized products with ether gave a

mixture of thiachromans 36 and 38. On column chromatography of the mixture a thick brown liquid was obtained. NMR spectrum of the latter showed the presence of two sets of methyl doublets, centred at 0.95 δ and another at 1.15 δ.

Formation of the rearranged cyclodehydration products 33 and 34 by treatment of 28 with 70% perchloric acid may be rationalised by postulating the formation of an intermediate 3-methyl-2-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 39 (Chart 7).

Similarly formation of the rearranged cyclodehydration products 37 and 38 from 30 may be rationalised by postulating the intermediate formation of 2-methyl-3-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 40 (Chart 7).

Tilak et al.[8] have reported the synthesis of 2,4-disubstituted 1-S-phenylthioniumcyclobut-2-ene perchlorates. In this synthesis the keto group of the precursor ketosulphide was probably converted into an enolphosphodichloridate derivative 42 by interaction with phosphorous oxychloride. The oxophosphonium dichloride group probably serves as a good leaving

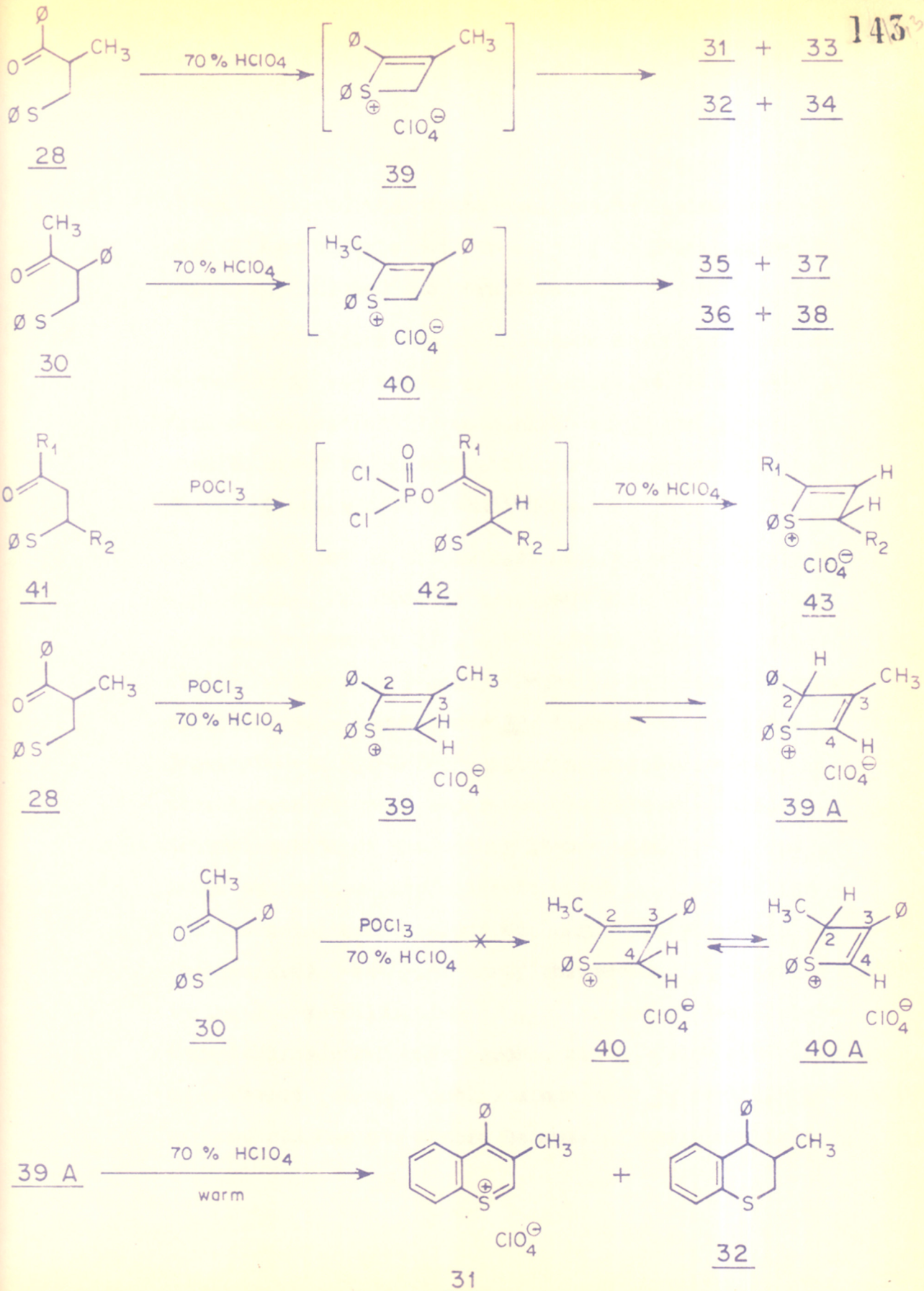

70 % HClO4
31 + 33
32 + 34
28
39
70 % HClO4
35 + 37
36 + 38
30
40
POCl3
70 % HClO4
41
42
70 % HClO4
43
POCl3
70 % HClO4
28
39
39 A
POCl3
70 % HClO4
30
40
40 A
39 A
70 % HClO4
warm
31
32

CHART – 7.

group. Interaction of the enolphosphodichloridate 42 with 70 % perchloric acid then leads to 1-3-phenylthioniumcyclobut-2-ene perchlorate 43 (Chart 7).

For confirmation of the above suggested reaction mechanism it was necessary to synthesise 39 and 40 from the corresponding ketosulphides 28 and 30, and then to study the isomerization and ring expansion of 39 and 40 under acidic conditions.

Treatment of the ketosulphide 28 with phosphorous oxychloride, followed by treatment with 70 % perchloric acid and saturation of the $POCl_3/HClO_4$ solution with diethyl ether gave 3-methyl-2-phenyl-1-3-phenylthioniumcyclobut-3-ene perchlorate 39A instead of the expected 3-methyl-2-phenyl-1-3-phenylthioniumcyclobut-2-ene perchlorate 39 which separated out as a crystalline solid. Neutralization of the mother liquor with $NaHCO_3$ and ether extraction gave a liquid which on distillation and chromatography yielded diphenyl disulphide and the (rearranged) 3-methyl-2-phenylthiachroman 34 (yield < 10%). During recrystallization of 39A, traces of 3-methyl-2-phenylthianaphthalenium perchlorate 33 which must have been also formed (concomitantly) along with 34 probably gets removed and was not traced because of very low yield.

Confirmation of the structure 39A followed from its NMR spectrum (Fig 4). The NMR spectrum indicated absence of methylenic protons at C_4, (Chart 7). This indicated that compound 39 initially formed rapidly isomerized to 39A through double bond migration from C_2-C_3 to C_3-C_4 position. NMR spectrum also indicated presence of a methyl singlet at 2.67 δ corresponding to 3 protons integration. The methine proton (at C_4 in 39A) and/or benzylic proton (at C_2 in 39A) could not be distinguished separately as they were merged with aromatic protons centred at 7.9 δ, integration being equivalent to 12 protons.

The above data clearly shows that the thioniumcyclobutene perchlorate obtained from 28 as described above is 3-methyl-2-phenyl-1-S-phenylthioniumcyclobut-3-ene perchlorate 39A and not the expected perchlorate 39.

Treatment of the ketosulphide 30 with phosphorous oxychloride followed by interaction with 70% perchloric acid yielded a mixture of the normal and rearranged thianaphthalenium perchlorates 35 and 37 instead of the expected 2-methyl-3-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 40 or 40A. Several attempts to isolate the intermediate 40 were unsuccessful (Chart 7).

The 4-membered and 6-membered perchlorates are

distinguishable by the following characteristics:-

1) Thiacyclobuten derivative undergo ring expansion on heating (at 60-70°) with 70% perchloric acid.

2) On proton abstraction (by treatment with NaH) the thiacyclobutenes give thiacyclobutadienes which on reprotonation yield same or different thiocyclobutenes.

Ring expansion of 3-methyl-2-phenyl-1-β-phenylthioniumcyclobut-3-ene perchlorate 39A.

Compound 39A was warmed with 70% perchloric acid. The reaction mixture on saturation with diethyl ether gave 3-methyl-4-phenylthianaphthalenium perchlorate 31 as the only product along with corresponding thiachroman 32. Compounds 33 and 34 were not formed. Obviously 39A does not isomerize to 39 which is the precursor for 33 and 34.

The formation of 31 and 32 by ring expansion of 39A is shown in Chart 8. This Chart also outlines the formation of the rearranged products 33 and 34 by acid catalysed cyclodehydration of the ketosulphide 28.

It seems entirely possible that 28 on cyclodehydration may be initially yielding 39. The latter is then either isomerized rapidly to 39A or it ring expands to give the Δ^2-thiachromene 44.

Disproportionation of 44 through hydride transfer will then lead to 33 and 34, whereas 39A will undergo ring expansion to the Δ^2-thiachromene 45 which subsequently disproportionates to give 31 and 32. It is also likely that the ketosulphide 28 will directly cyclize to give the Δ^3-thiachromene A as may be normally expected. Compound A will then undergo disproportionation through hydride transfer to yield 31 and 32 (Chart 8).

Since ring enlargement of 39A under acidic conditions yielded only 31, 32 it appears that 39A is more stable than the isomeric 3-methyl-2-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 39 from which 39A is formed by bond migration probably through thiacyclobutadiene 46 (or its corresponding dominant resonance ylide form 46A) as shown in Chart 9.

Treatment of the thiacyclobut-3-ene perchlorate 39A with sodium hydride in THF/Diethyl ether gave the unstable neutral intermediate thiacyclobutadiene 46 (resonating with canonical structures such as 46A, 46B and 46C). Reprotonation of the ylide 46A by treatment with perchloric acid gave back exclusively 39A, no trace of 39 being formed. It is therefore obvious that the ylide formed by deprotonation of 39A by treatment with NaH is essentially 46A, a result

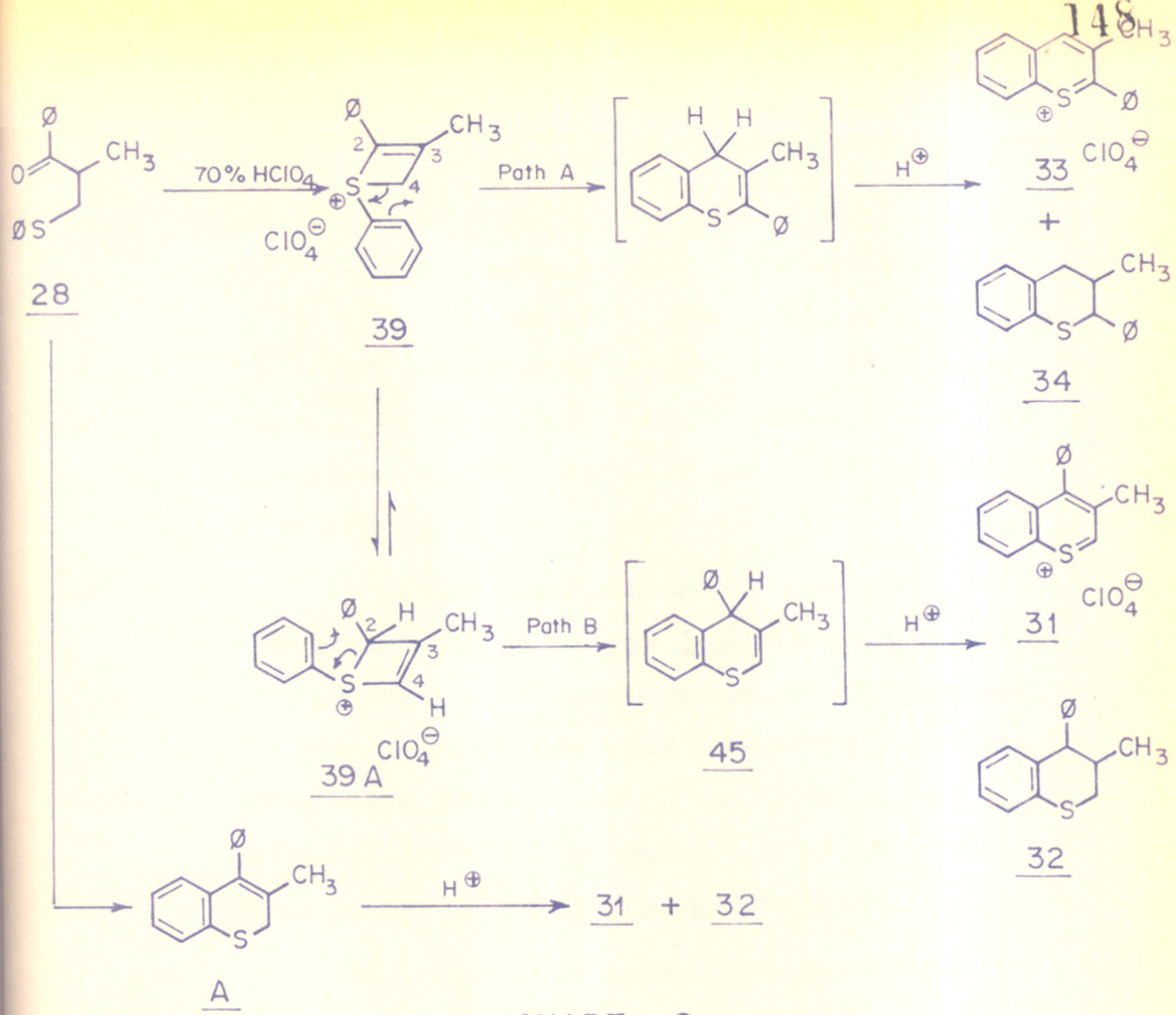


CHART – 8

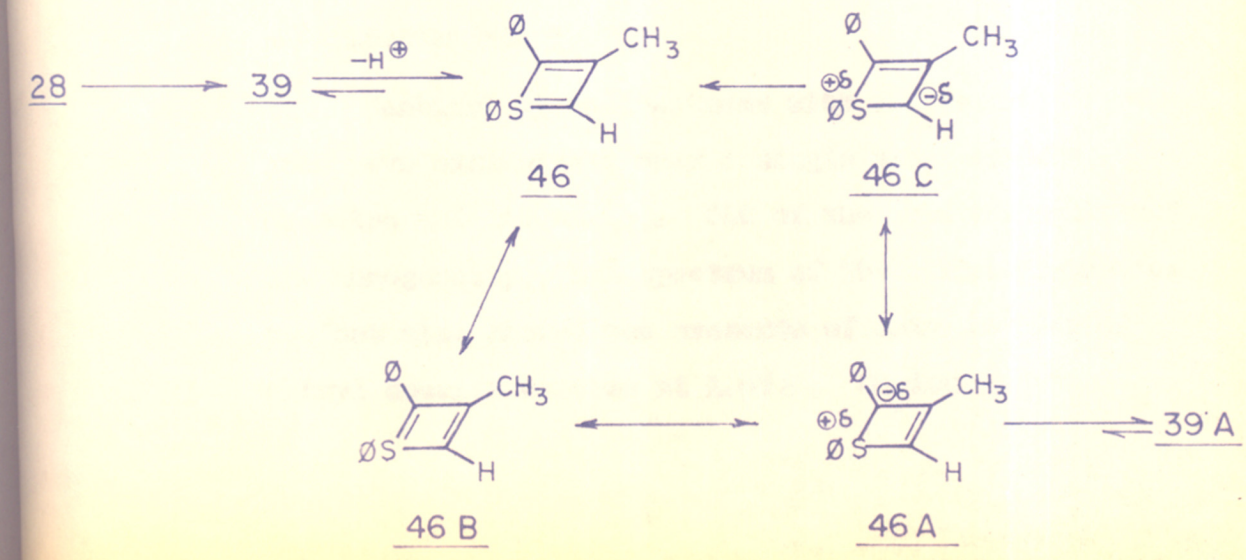


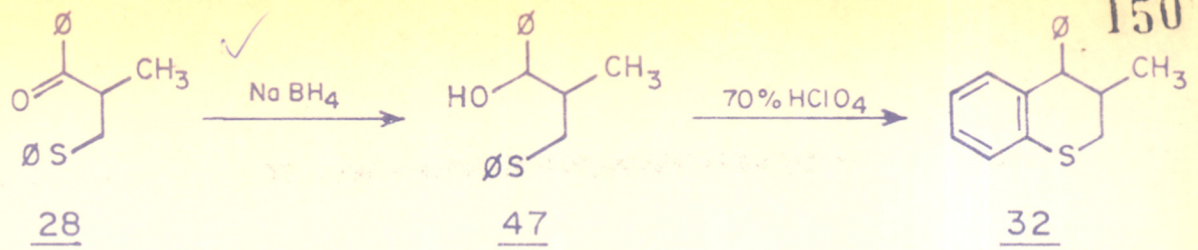
CHART – 9 .

which may be expected in view of the stabilization of the carbonium ion at C_2 atom in 46A which carries the phenyl substituent. A similar observation as regards greater stabilization of the carbanion at a benzylic carbon atom has also been noted earlier by Tilak et al.[8]

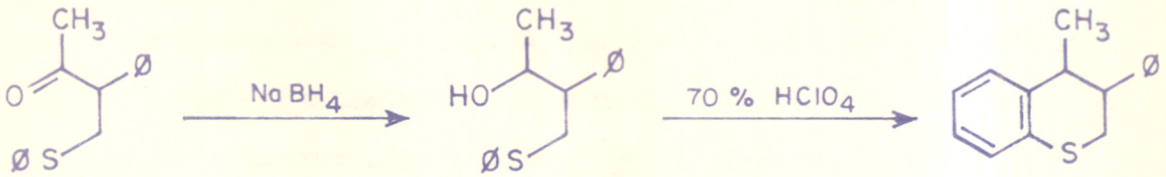
To confirm the structures of the above thiachromans 32, 34 and 36, 38 independent synthesis of respective thiachromans was necessary. Obviously the precursors of choice for thiachromans were the 3-mercaptoaryl-1-alkanols 47 and 48 which on cyclodehydration may be expected to yield the desired thiachromans 32, 34 and 36, 38 (Chart 10).

The ketosulphide 28 on sodium borohydride reduction furnished 3-phenylmercapto-2-methyl-1-phenylpropan-1-ol 47. Similarly the ketosulphide 30 on sodium borohydride reduction gave 4-phenylmercapto-3-phenylbutan-2-ol 48.

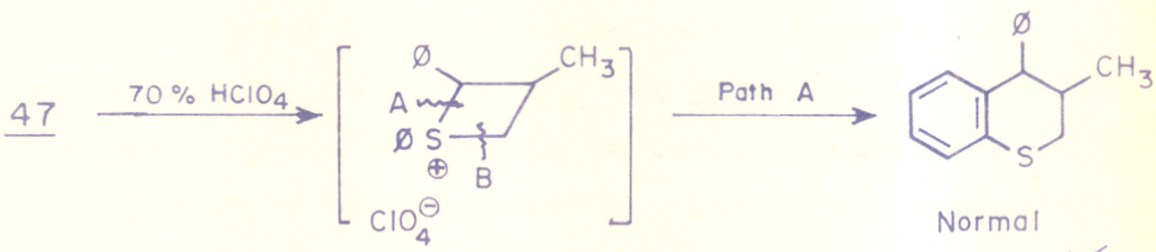
Carbinol 47 on treatment with 70% perchloric acid gave exclusively only a single and normally expected thiachroman 32. GLC of the product indicated its homogeneity. NMR spectrum of the cyclodehydration product also showed the presence of only one set of methyl doublet centred at 1.05 δ. Obviously



28 47 32



30 48 cis 36 A trans 36 B



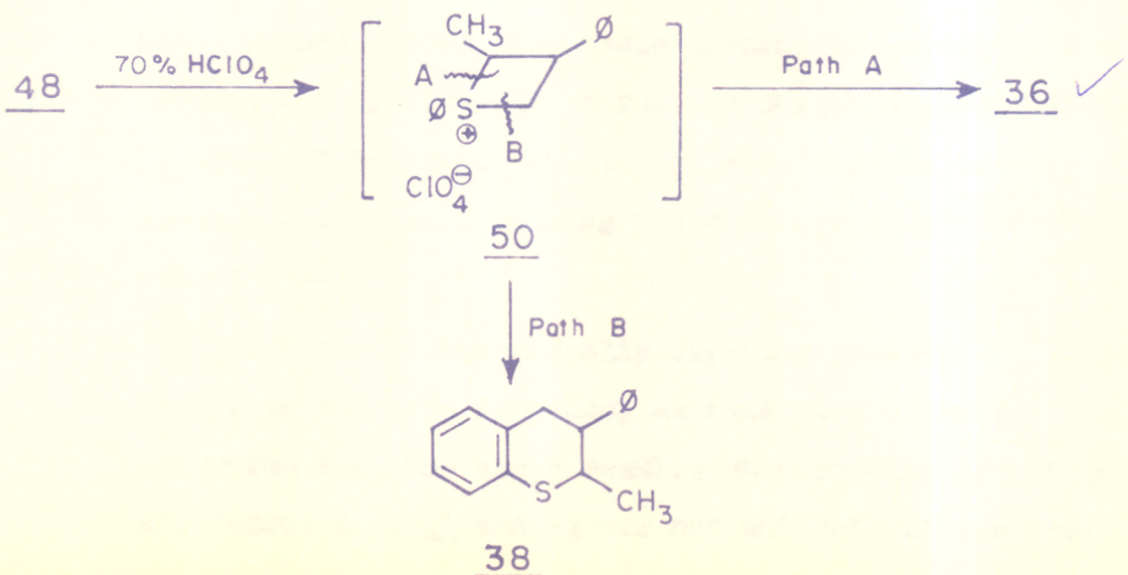


CHART – 10.

cyclodehydration of 47 proceeds directly to the normal thiachroman 32 without the involvement of a 4-membered 3-phenylthioniumcyclobutan perchlorate 49. It may also be entirely possible that 49 if formed, expands only through ring cleavage between -S-C(H)-φ bond as shown (Chart 10).

Carbinol 48 on treatment with 70% perchloric acid, gave a mixture of cis- and trans-thiachromans 36A and 36B. NMR spectrum of the mixture showed the presence of two sets of methyl doublets, one centred at 0.85 δ and the other at 0.95 δ.

GLC of the cyclodehydration product from 48 also showed presence of two peaks corresponding to the two thiachromans, 36A and 36B. As in the case of 47, cyclodehydration of 48 also yields the normally expected thiachroman 36, no rearrangement product 38 being formed. Here also cyclodehydration proceeds without the involvement of the 3-phenylthioniumcyclobutan 50 or if 50 is formed at all, it ring expands only through one route involving the cleavage of φ-S-C-CH_3 (Chart 10).

In view of the normally expected greater stabilization of a secondary as against a primary carbonium ion, the above results whereby only 32 and 36 are formed from 47 and 48 are not entirely unexpected.

The three methyl shifts in the NMR spectrum of cis and/or trans compounds, 32 and 34 appear at 1.05 δ and 1.18 δ. To confirm the structures and stereochemistry of the above thiachromans, GLC/MS study was undertaken. The thiachromans and their precursors are shown in Chart 11.

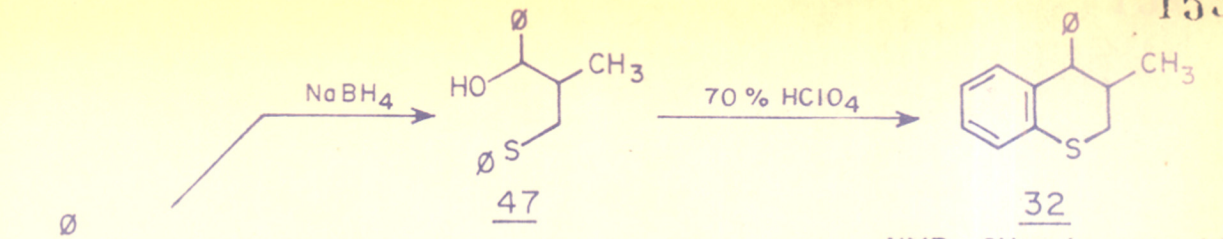
To distinguish between the 3-methyl-4-phenyl-thiachroman 32 and 3-methyl-2-phenylthiachroman 34 two criteria were used viz. the study of their Retro-Diels-Alder type mass spectral fragmentation pattern and to study the m/e at (M-SCH) and (M-SCφ) (Chart 11).

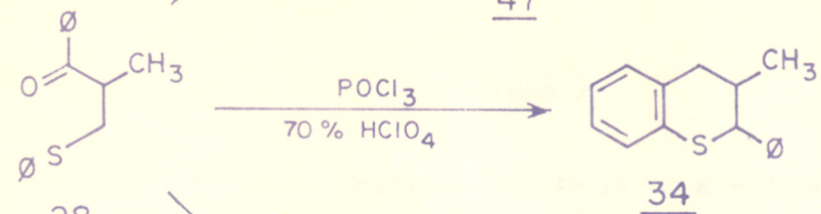
Modak[9] from this laboratory has observed earlier that loss of the adjacent groups is prominent when the groups are cis-located with respect to each other.

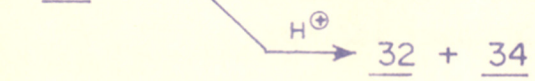
In the present case loss of 92 m.u. was anticipated when φ and CH_3 were cis and loss of φ and H i.e. 77 was anticipated when φ and CH_3 were trans situated with respect to each other.

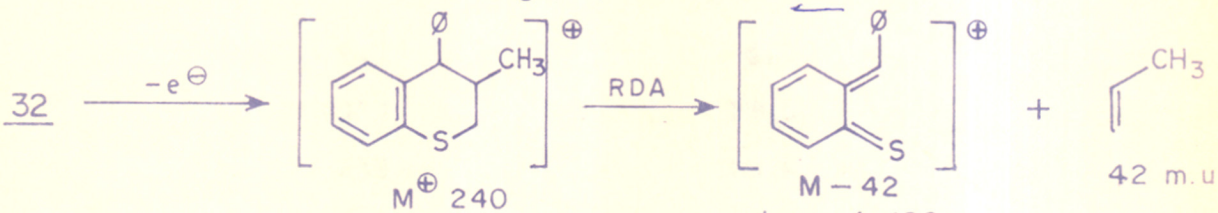
Some mass fragments are tabulated (Tables 1, 2 and 3).

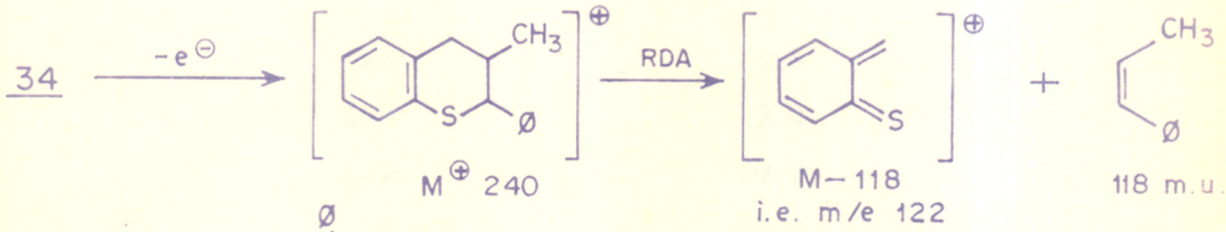
Thiachroman 32 obtained by cyclodehydration of the carbinol 47 indicated M^+ as 240 (6.5% intense), whereas m/e at 238 was 100% intense. This can be explained by loss of two hydrogens from the molecular ion to give a dihydro compound (thiachromene).

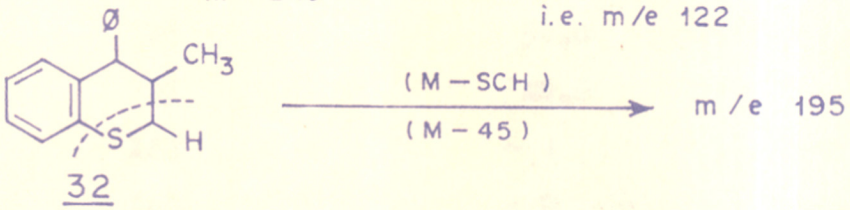

NaBH4
HO
CH3
Ø
S
47
70 % HClO4
CH3
S
32
NMR : CH3 , d , centred at 1·05 δ


O
CH3
Ø
S
28
POCl3
70 % HClO4
CH3
S
Ø
34
From mother liquor of reaction mixture
NMR : CH3 , d , centred at 1·18 δ


H⊕
32 + 34
From mother liquor of the reaction mixture
(NMR : CH3 , d , centred at 1·18 δ)


32
-e⊖
Ø
CH3
S
M⊕ 240
RDA
M − 42
i.e. m/e 198
+
CH3
42 m.u


34
-e⊖
CH3
S
Ø
M⊕ 240
RDA
M − 118
i.e. m/e 122
+
CH3
Ø
118 m.u.


Ø
CH3
S
H
32
(M − SCH)
(M − 45)
m/e 195
CH3
S
Ø
34
(M − SCØ)
(M − 121)
m/e 119

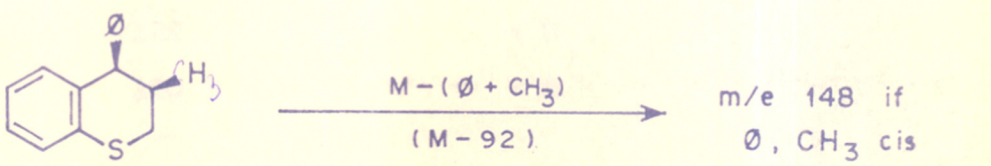

Ø
H
S
cis 32 A
M − (Ø + CH3)
(M − 92)
m/e 148 if Ø , CH3 cis
Ø
H
CH3
S
trans 32 B
M − (Ø + H)
(M − 78)
m/e 162 if Ø , CH3 trans

CHART — 11

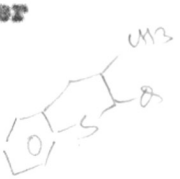
Table 1

Mass spectral fragments corresponding to cyclodehydration product, the thiachroman 32 from the carbinol 47.

m/e	%
240	6.5
239	18.0
238	100.0
225	< 2
223	2.4
198	3.0
197	10.2
196	50.0
195	80.0
163	~ 2
162	< 2
148	< 2
147	< 2
146	< 2
122	< 2
120	< 2

Table 2

Thiachroman 34 obtained from the mother liquor of 28 (ketosulphide) $POCl_3/HClO_4$ reaction after removal of 39A.



m/e	%
240	17.0
238	22.5
232	37.5
218	40.0
198	< 2
162	< 2
148	16
145	37.5
122	100
119	16
109	55

M-78 ↑ compare ↓ M-92 medicals cis

Rearranged 34

cis 34

1.18 — cis 34

Table 3

Thiachromans 32 and 34 obtained from the mother liquor of ketosulphide 28 perchloric acid cyclodehydration.

GLC peak A		GLC peak B	
m/e	%	m/e	%
240	8.33	240	32.5
238	6.67	239	45.0
225	6.67	238	100
223	8.3	225	40.0
198	4.66	224	48.0
197	6.6	223	95.0
162	5.0	198	25.0
161	5.0	197	35.0
151	100	195	15.0
148		162	38.0
132	66.6	161	70.0
122	8.33	148	18.0
121	8.0	147	33.0
		122	15.0
		119	15.0

m/e at 198 was only 3% intense whereas m/e at 122 was 2% in intensity. Thus it was very difficult to say whether the cyclodehydration product was the normally expected 32 or the rearranged thiochroman 34 simply on the basis of these RDA fragments.

m/e at 196 was however 50% intense which can be formed by the following sequence[1]-

$$M^{+} \xrightarrow{-2H} M^{+}-2 \xrightarrow{\text{loss of } 42 \text{ m.u.}} \text{m/e } 196$$

i.e. m/e 238

Also m/e at 195 was 80% intense. Loss of 45 m.u. can be accounted as loss of CHS moiety (Chart 11). Loss of CHS is possible only when the carbon adjacent to sulphur is unsubstituted as in thiachroman 32 but not in thiachroman 34. Further confirmation that the cyclodehydration product from the carbinol 47 is indeed 3,4-disubstituted thiachroman 32 from the fact that m/e at 119 i.e. $(M - SC\phi)^{+}$ (which would arise from the thiachroman 34) was less than 2% (Chart 11).

It was not possible to assign cis or trans stereochemistry for C_4-phenyl and C_3-methyl substituents in 32 since m/e 142 (due to cis structure) and m/e 162 (due to trans structure) both were less than 2% intensity.

Above data indicated that the carbinol 47 on perchloric acid catalysed cyclodehydration gave 3-methyl-4-phenylthiachroman 32 and not 34.

The mixture of products obtained from the mother liquor after rearranged thiacyclobuten 39A showed M^+ i.e. m/e at 240 to be 17.0% intense. M-2 i.e. m/e at 238 was 22.5% intense, m/e at 198 (Retro-Diels-Alder fragment corresponding to normal product) and m/e at 195 (due to M-CHS) both were absent.

m/e at 122 was 100% intense indicating an ion formed by Retro-Diels-Alder type fragmentation arising from the rearranged thiachroman 34. Also m/e at 119 was also 16.0% intense i.e. loss of 121 m.u. (M-SCϕ). This loss can take place only when ϕ group is situated on a carbon atom adjacent to sulphur atom.

m/e at 162 was less than 2.0% as against m/e at 148 (16.0%) indicating the loss of C_7H_8. This can take place only when the groups are cis.

Above data indicated that the thiachroman obtained during the synthesis of 39A from 28 was cis-3-methyl-2-phenylthiachroman 34.

The mixture of thiachromans obtained in the cyclodehydration of the ketosulphide 28 by treatment with 70% perchloric acid was subjected for GLC/MS

analysis. GLC showed two peaks corresponding to the two thiachromans (Table 3). Mass spectra corresponding to the GLC peak A was showing M^+ as 8.33%, m/e at 238 as 6.67%. M-15 was also less intense. m/e at 198 (4.66%) was less intense as compared to m/e at 122 (8.33%) indicating it to be the rearranged thiachroman 34.

GLC peak B however indicated m/e at 240 as 32.5% intense and 238 as 100% intense peak. Loss of CH_3 i.e. M-15 and loss of 17 i.e. M-2, followed by loss of a CH_3 group were also intense. m/e at 198 was 25% as against m/e 122 (15.0%) indicating that the product was the normally expected thiachroman 32. Surprisingly m/e 119 and 195 were 15% (intense) each. m/e at 162 was 38% as against m/e at 148 (18%) indicating again presence of trans (normal) thiachroman, viz. trans-3-methyl-4-phenylthiachroman 32.

Being partially successful in identifying the thiachromans 32 and 34 through mass spectral studies, it was of interest to study the mass spectral analysis of the thiachroman 36 obtained by cyclodehydration of the carbinol 48.

As shown in the Chart 10, carbinol 48 on cyclodehydration using 70% perchloric acid gave a

mixture of cis- and trans-thiachromans 36A and 36B (NMR: CH_3 doublets, one centred at 0.85 δ and the other at 0.95 δ). To confirm the structure, the mixture was subjected for GLC/MS analysis.

GLC of the mixture indicated two peaks A and B corresponding to the two thiachromans. Some of the m/e values are listed in Table 4.

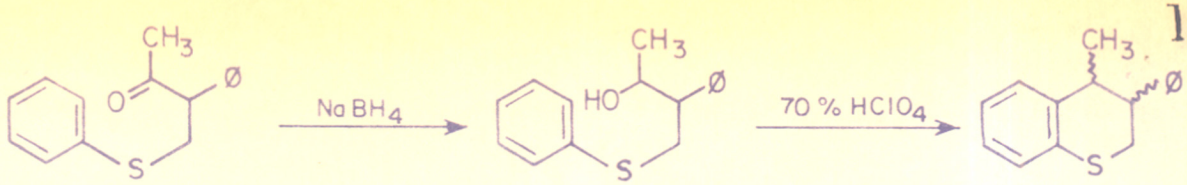
To distinguish the normal cyclodehydration product, the thiachroman 36 from the rearranged thiachroman 38 (may also be formed in cyclodehydration of carbinol 48), the Retro-Diels-Alder fragmentation pattern in mass spectral degradation was used as one of the criteria. Another criterion was to look for the loss of $SCCH_3$ moiety or loss of SCH moiety as shown in Chart 12.

Mass spectra of the GLC peak A (Table 4) indicated M^+ as a 90% intense peak, loss of CH_3 group i.e. m/e at 225 was 8.0%, m/e 136 was 100% intense as compared to m/e at 122 (< 2%) indicating that compound corresponding to peak A was the normal cyclodehydration product the thiachroman 36. Surprisingly 195 and 181 (i.e. M-SCH and M-$SCCH_3$) fragments were less than 2.0%. Thus cis/trans isomers of 36 if present could not be identified. Thus m/e 162 (corresponding to trans-thiachroman 36B) and m/e 148 (corresponding to cis-thiachroman 36A)

Table 4

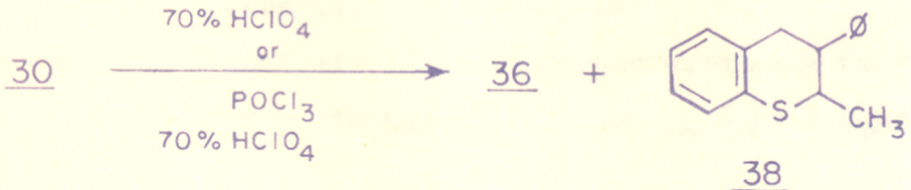
Thiachromans obtained by cyclodehydration of carbinol 48.

GLC peak A		GLC peak B	
m/e	% intensity	m/e	% intensity
240	90	240	34.29
225	8.0	225	5.71
211	3.125	214	6.428
210	< 2	195	< 2
195	< 2	181	< 2
181	< 2	162	4.285
163	4.25	149	8.57
162	1.9	148	8.57
147	2.75	136	68.5
136	100.0	123	15.7
122	< 2	122	-
110	< 2	110	100



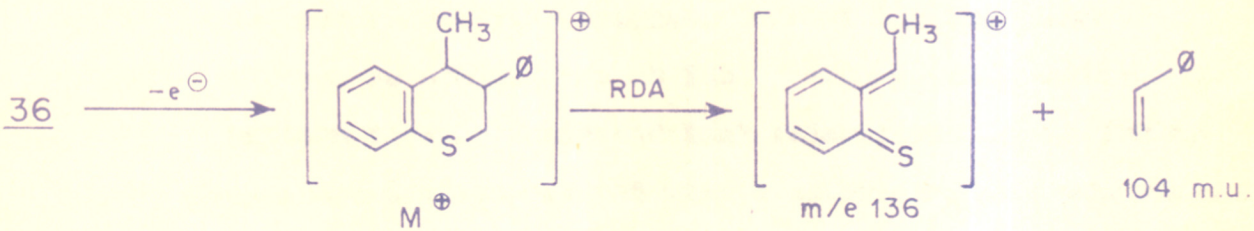
30 48 36

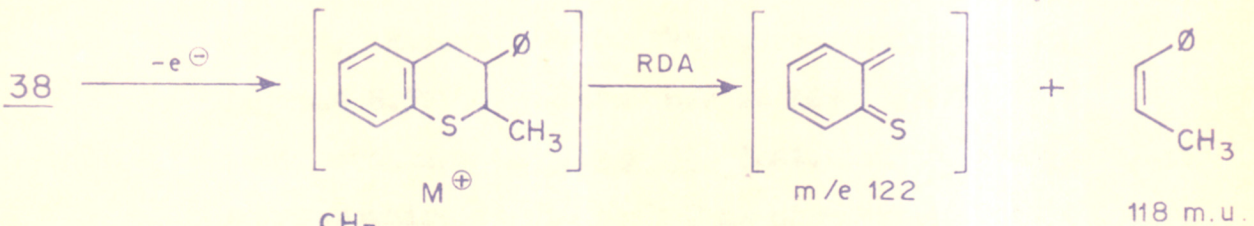
NMR : CH_3, d, centred at 0·85 δ and 0·95 δ

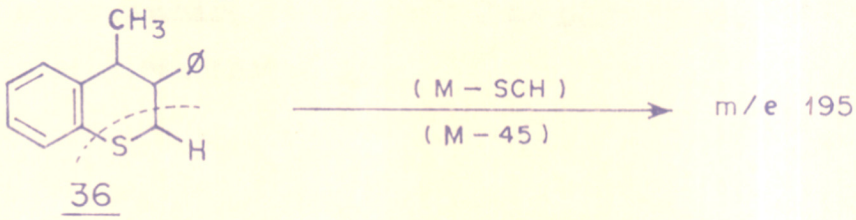


38

NMR : CH_3, d, centred at 0·95 δ and 1·15 δ







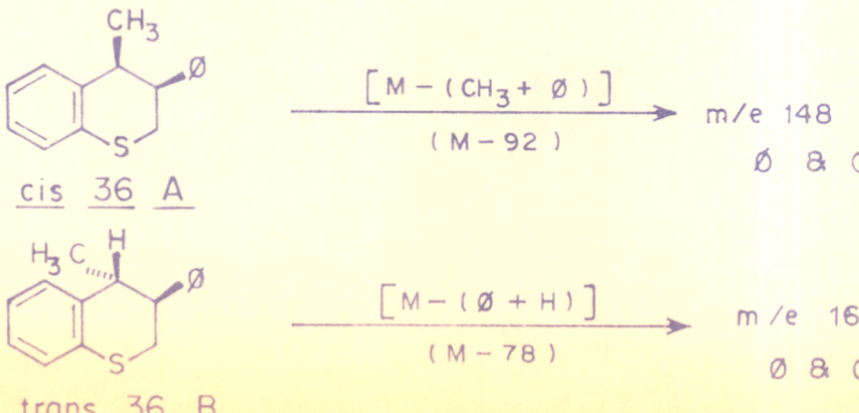


CHART – 13

were both less than 2.0% (Chart 12). The mass spectral analysis of compound corresponding to GLC peak A showed it to be the thiachroman 36 (cis /trans).

Mass spectrum of thiachroman corresponding to GLC peak B showed M^+ (34.29%), m/e at 225 (loss of CH_3 group) was 5.7% intense. m/e at 136 was 68.5% intense as against m/e at 122 (< 2.0%). This degradation pattern clearly indicated that thiachroman is the normal cyclodehydration product viz. 4-methyl-3-phenylthiachroman 36. Further m/e at 195 and m/e at 181 were both absent. However m/e at 148 (corresponding to cis-36A)was 8.57% as against m/e at 162 (4.28%) (corresponding to trans-36B) indicated that the product corresponding to GLC peak B as cis-4-methyl-3-phenylthiachroman 36A.

EXPERIMENTAL

α-Phenylmercaptomethylpropiophenone 28.

Interaction of thiophenol 26 (11.0 g, 0.1 mol) with Mannich base hydrochloride of propiophenone 27 (22.7 g, 0.1 mol) and sodium carbonate (21.2 g, 0.2 mol) in boiling ethanol for 2 hrs gave on work up 28 as brownish oil. Vacuum distillation of the crude product afforded 28 as yellow liquid. b.p. 140-45°/1.7x 10^{-3} mm (18.6 g, yield 72.6%).

IR showed >C=O at 1685 cm^{-1}

NMR: (CCl_4, δ); CH_3 centred at 1.26, d, 3p; methylene and methine centred at 3.28, m, 3p and aromatic centred at 7.3, m, 10p.

Analysis: Found C, 75.2; H, 6.4; S, 12.6. $C_{16}H_{16}OS$ requires C, 75.0; H, 6.3; S, 12.5%.

Mass: M^+ 256.

3-Phenyl-4-phenylmercapto-butan-2-one 30

Interaction of thiophenol 26 (11.0 g, 0.1 mol) with Mannich base hydrochloride of benzyl methyl ketone 29 (22.7 g, 0.1 mol) and sodium carbonate (21.2 g, 0.2 mol) in boiling ethanol for 2 hrs gave on work up 30 as dark brown oil. Vacuum distillation of the crude product afforded 30 as pale yellow liquid. b.p. 135-45°/2 x 10^{-3} mm (13.4 g, yield 52.3%).

IR showed >C=O at 1710 cm^{-1}.

NMR: (CCl_4, δ); CH_3 at 1.96, s, 3p; methylene and benzylic centred at 3.4, m, 3p and aromatic centred at 7.25, m, 10p.
Analysis: Found C, 75.3; H, 6.3; S, 13.1. $C_{16}H_{16}OS$ requires C, 75.0; H, 6.3; S, 12.5%.
Mass showed M^+ 256.

Cyclodehydration of α-phenylmercaptomethylpropiophenone 28 ✓

A mixture of α-phenylmercaptomethylpropiophenone 28 (1.0 g) and 70% perchloric acid (3.0 ml) was stirred for 3 hrs at 70°. Resulting dark brown liquid cooled in ice and saturated with ether, which on cooling gave a mixture of 3-methyl-4-phenylthianaphthalenium perchlorate 31 and 3-methyl-2-phenylthianaphthalenium-perchlorate 33 (0.322 g, 24.6%) m.p. 160°.
NMR: (TFAA, δ); CH_3 at 2.7 and 2.9, s, 3p; aromatic protons centred at 8.16, m, 10p (Fig.1).
Analysis: Found S, 9.6; Cl, 10.2. $C_{16}H_{13}SClO_4$ requires S, 9.5; Cl, 10.4%.

Mother liquor of the above reaction mixture was neutralised with bicarbonate solution extracted with ether and dried over sodium sulphate. Ether evaporation afforded brownish liquid (0.577 g) column chromatography of the crude product gave diphenyl-disulphide as the first fraction (0.062 g). Second

fraction was obtained as a mixture of thiachromans 32 and 34 (0.198 g) along with unreacted ketosulphide 28 as the third fraction (0.187 g).
NMR of thiachromans 32, 34 : (CCl_4, δ); CH_3 at 1.18, broad doublet 3p; methylenes centred at 2.71 and 3.45 m, 4p; aromatic centred at 6.96 m, 9p.
GLC/MS indicated it to be a mixture of trans-3-methyl-4-phenylthiochroman 32 and 3-methyl-2-phenylthiachroman 34 (cis/trans- assignment for 34 was difficult from the mass pattern).

Cyclodehydration of 3-phenyl-4-phenylmercapto-butan-2-one 30.

Cyclodehydration of 3-phenyl-4-phenylmercapto-butan-2-one 30 (1.0 g) using 70% perchloric acid (3.0 ml) and work up as above furnished a mixture of 4-methyl-3-phenylthianaphthalenium perchlorate 35 and 2-methyl-3-phenylthianaphthalenium perchlorate 37 (0.286 g). Fractional crystallisation of the mixture afforded 37 (0.171 g, 13.1%) and 35 (0.101 g, 7.3%).

4-Methyl-3-phenylthianaphthalenium perchlorate 35

m.p. 194°. NMR: (TFAA, δ); CH_3 at 3.1, s, 3p; aromatic protons centred at 8.13 d, m, 10p (Fig 2).
Analysis: Found S, 9.2; Cl, 10.3. $C_{16}H_{13}SClO_4$ requires S, 9.5; Cl, 10.4%.

2-Methyl-3-phenylthianaphthalenium perchlorate 37 ✓

m.p. 162°C. NMR: (TFAA, δ); CH_3 at 3.8, s, 3p; aromatic centred at 8.16, m, 10p (Fig 3).
Analysis: Found S, 9.3; Cl, 10.4. $C_{16}H_{13}SClO_4$ requires S, 9.5; Cl, 10.4%.

Mother liquor of the above reaction on neutralisation with bicarbonate solution and usual work up yielded brown liquid as the crude product (0.411 g). Column chromatography gave diphenyl disulphide as the first fraction (0.079 g). Further elution yielded a mixture of thiachromans 36 and 38 (0.102 g), followed by unreacted ketosulphide 30 (0.186 g).
NMR of thiachromans 36 and 38 : (CCl_4, δ).
Set of CH_3 doublets at 0.95 and 1.15 3p, methylene and benzylic centred at 2.93 and 3.46, m, 4p; aromatic centred at 6.95 m, 9p.
Mass showed M^+ 240.

3-Methyl-2-phenyl-1-S-phenylthioniumcyclobut-3-ene perchlorate 39A

A mixture of α-phenylmercaptomethylpropiophenone 28 (1.2 g) and phosphorous oxychloride (2.5 ml) was stirred for 14 hrs at room temperature, cooled with ice salt mixture and treated with 70% perchloric acid (2 ml). Reaction mixture stirred for 4 hrs.

Further with cooling, saturated with diethyl ether and kept at -20°, gave 39A as yellow solid (0.422 g, 31.9%), m.p. 184°.

NMR: (TFAA, δ); CH_3 at 2.67, s, 3p; aromatic centred at 7.9, m, 12p (Fig 4).

Analysis: Found S, 9.4; Cl, 10.2. $C_{16}H_{15}SClO_4$ requires S, 9.4; Cl, 10.5%.

Attempted synthesis of 2-methyl-3-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 40.

Treatment of ketosulphide 30 (1.0 g) with phosphorous oxychloride (2.5 ml), followed with 70% perchloric acid (2.0 ml) in cold as above and saturation with diethyl ether failed to give 2-methyl-3-phenyl-1-S-phenylthioniumcyclobut-2-ene perchlorate 40. Instead a mixture of thianaphthalenium salts 35 and 37 (0.322 g). Fractional crystallisation afforded perchlorate 35 (0.121 g) and 37 (0.182 g). Compounds 35 and 37 were identified by comparing their m.p. and NMR spectrum with authentic samples.

70% perchloric acid catalysed ring expansion of 3-methyl-2-phenyl-1-S-phenylthioniumcyclobut-3-ene perchlorate 39A.

Thiacyclobutene 39A (0.400 g) was warmed (70°) with 70% perchloric acid (2 ml) for 14 hrs.

Reaction mixture cooled and saturated with diethyl ether, gave 3-methyl-4-phenylthianaphthalenium perchlorate 31 (0.148 g, 22.1%), m.p. 164° and 3-methyl-4-phenylthiachroman 32 (0.96 g, 20%).

Proton abstraction from 39A and reprotonation of the intermediate thiacyclobutadiene

3-Methyl-4-phenyl-1-S-phenylthioniumcyclobut-3-ene perchlorate 39A (0.338 g, 0.001 mol) and dry ether (15 ml) was stirred in cold water bath (5°C), to this solution sodium hydride (0.003 g) was added and stirring continued. Half an hour later tetrahydrofuran (10 ml) was added. The reaction did not turn deep green. After stirring for half an hour, the reaction mixture was filtered under nitrogen atmosphere. Ether and THF were evaporated off on rotavac. Reprotonation of the above mass with 70% perchloric acid and saturation with ether in cold yielded 39A back (0.042 g, 12.4%).

3-Phenylmercapto-2-methyl-1-phenylpropan-1-ol 47. ✓

To α-phenylmercaptomethylpropiophenone 28 (1.2 g) in ethanol (10 ml) was added sodium borohydride (0.05 g) and stirred for 2 hrs. Ethanol evaporated, contents diluted with water (20 ml) and acidified with acetic acid. Extraction with ether, drying over

anhydrous Na_2SO_4, ether evaporation and vacuum distillation yielded 47 as colourless liquid, b.p. 130°/2 x 10^{-3} mm (0.96 g, 79.4%).

NMR: (CCl_4, δ); CH_3 at 0.8, d, 3p; methylenes centred at 2.8, m, 2p; methine and benzylic centred at 1.8, 4.1, m, 2p. D_2O exchangable OH at 4.4, broad s, 1p; aromatic centred at 6.8, m, 10p.

IR: OH at 3510 cm^{-1}.

Analysis: Found C, 75.6; H, 7.2; S, 11.9. $C_{16}H_{18}OS$ requires C, 74.4; H, 7.0; S, 12.4%.

Mass M^+ 258.

3-Phenylmercapto-2-phenylbutan-2-ol 48

Reduction of 3-phenyl-4-phenylmercapto-butan-2-one 30 (1.1 g) with sodium borohydride (0.05 g) in ethanol and work up as above yielded 48 as crude product. Vacuum distillation of the crude carbinol gave 48 as colourless liquid, b.p. 120°/1 x 10^{-3} mm (0.92 g, 83.03%).

NMR: (CCl_4, δ); CH_3 centred at 0.97, d, 3p; D_2O exchangable OH at 1.76, broad s, 1p; methine centred at 2.76, m, 1p. Methylenes centred at 3.28, m, 2p; benzylic centred at 4.13, m, 1p and aromatic centred at 7.18, m, 10p.

IR : OH at 3480 cm^{-1}.

Analysis: Found C, 73.9; H, 7.4; S, 12.3. $C_{16}H_{18}OS$ requires C, 74.4; H, 7.0; S, 12.4%.

Mass M^+ 258.

Cyclodehydration of carbinol 47.

A mixture of carbinol 47 (1.0 g) and (3.0 ml) 70% perchloric acid (3.0 ml), stirred for 2 hrs at 60-70° and on cooling neutralised with bicarbonate solution, extracted with benzene. Benzene extract dried over anhydrous sodium sulphate. Evaporation of benzene gave brown liquid, which on vacuum distillation gave 3-methyl-4-phenylthiachroman 32 (0.68 g, 72.3%) b.p. 135-40°/1.4 x 10^{-2} mm.

NMR: (CCl_4, δ); CH_3 doublet centred at 1.05, 3p; methylenes and methine centred at 2.55, m, 3p; benzylic centred at 3.73, d, 1p; aromatic centred at 6.93, m, 3p. GLC/MS could not indicate cis/trans- stereochemistry definitely.

Analysis: Found C, 79.9; H, 6.8; S, 14.9. $C_{16}H_{16}S$ requires C, 80.1; H, 6.6; S, 13.3%.

Cyclodehydration of carbinol 48.

Cyclodehydration of carbinol 48 (1.0 g) using 70% perchloric acid and work up as above yielded cis/trans-4-methyl-3-phenylthiachroman 36 (0.72 g, 76.5%) b.p. 120° /1.6 x 10^{-2} mm.

NMR: (CCl_4, δ); CH_3 doublets centred at 0.85 and 0.95, 3p; methylenes and benzylic centred at 2.9, m, 3p; methine centred at 3.96, m, 9p.

Analysis: Found C, 80.1; H, 6.4; S, 13.1. $C_{16}H_{16}S$ requires C, 80.1; H, 6.6; S, 13.3%.

GLC/MS also supports above (normal) structure for the cyclodehydration product.

ILLUSTRATIONS

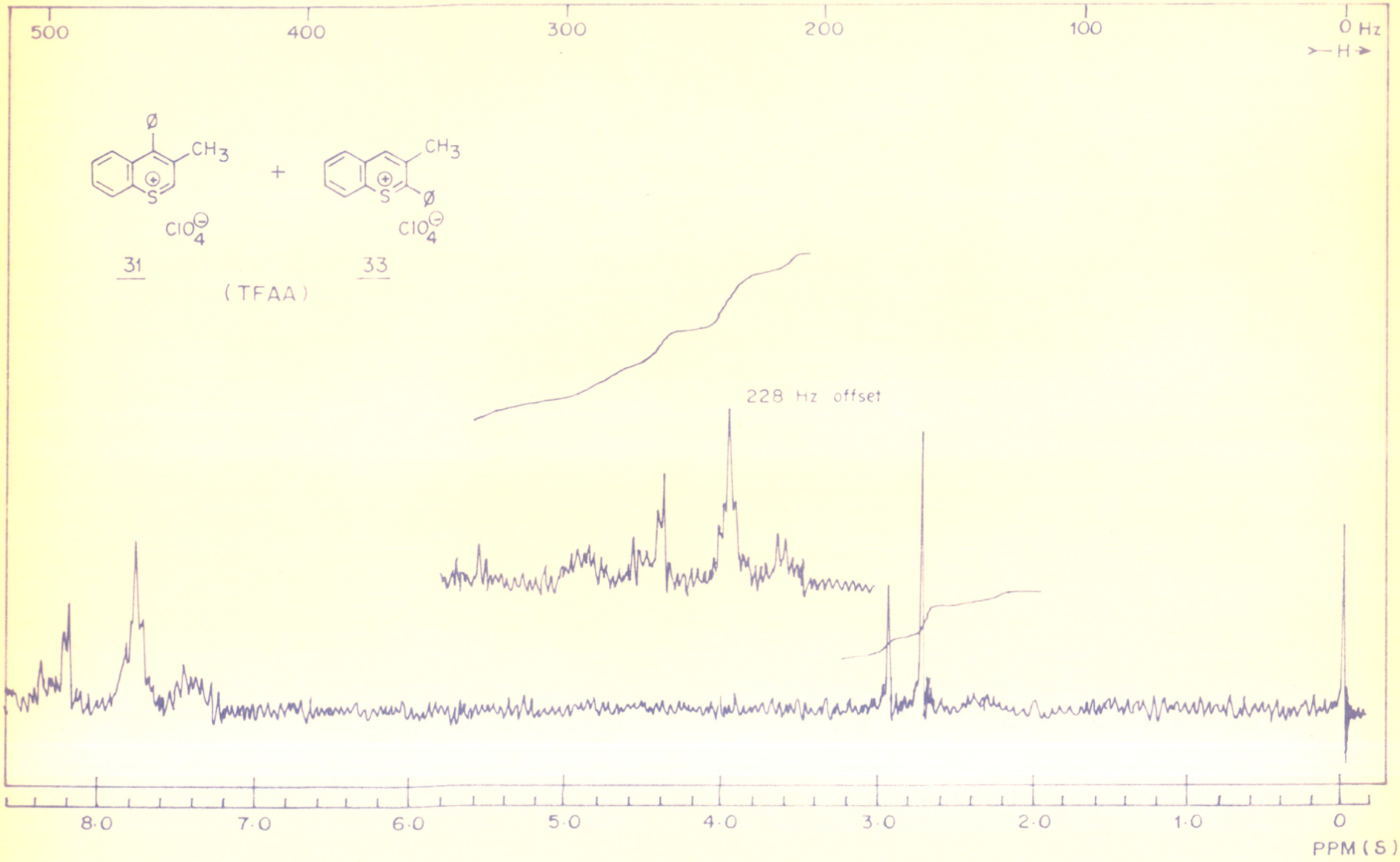
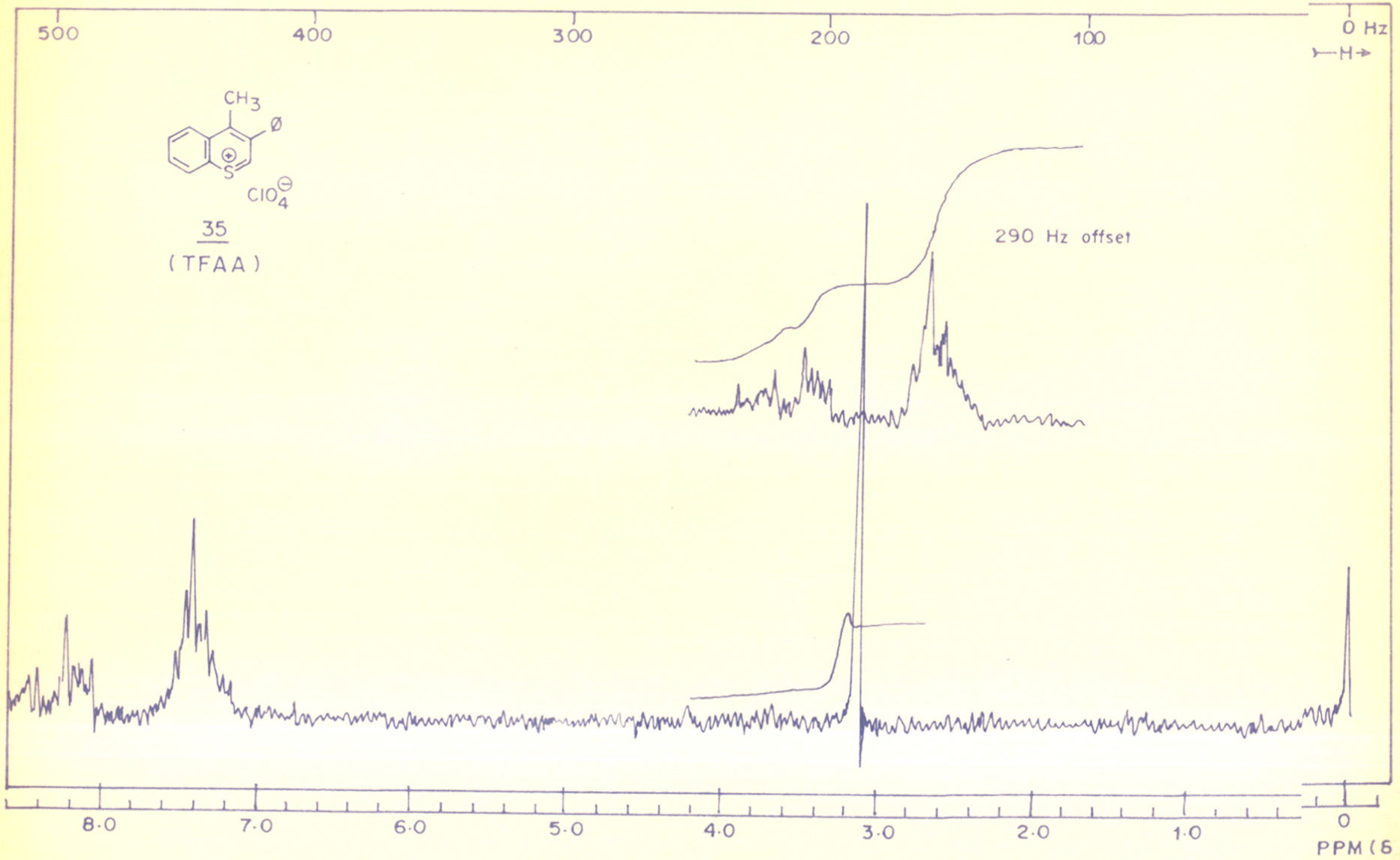

500
400
300
200
100
0 Hz
H
Ø
CH3
S
ClO4
31
+
CH3
Ø
S
ClO4
33
(TFAA)
228 Hz offset
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (S)

FIG – 1


500
400
300
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H
CH3
Ø
S
ClO4⊖
35
(TFAA)
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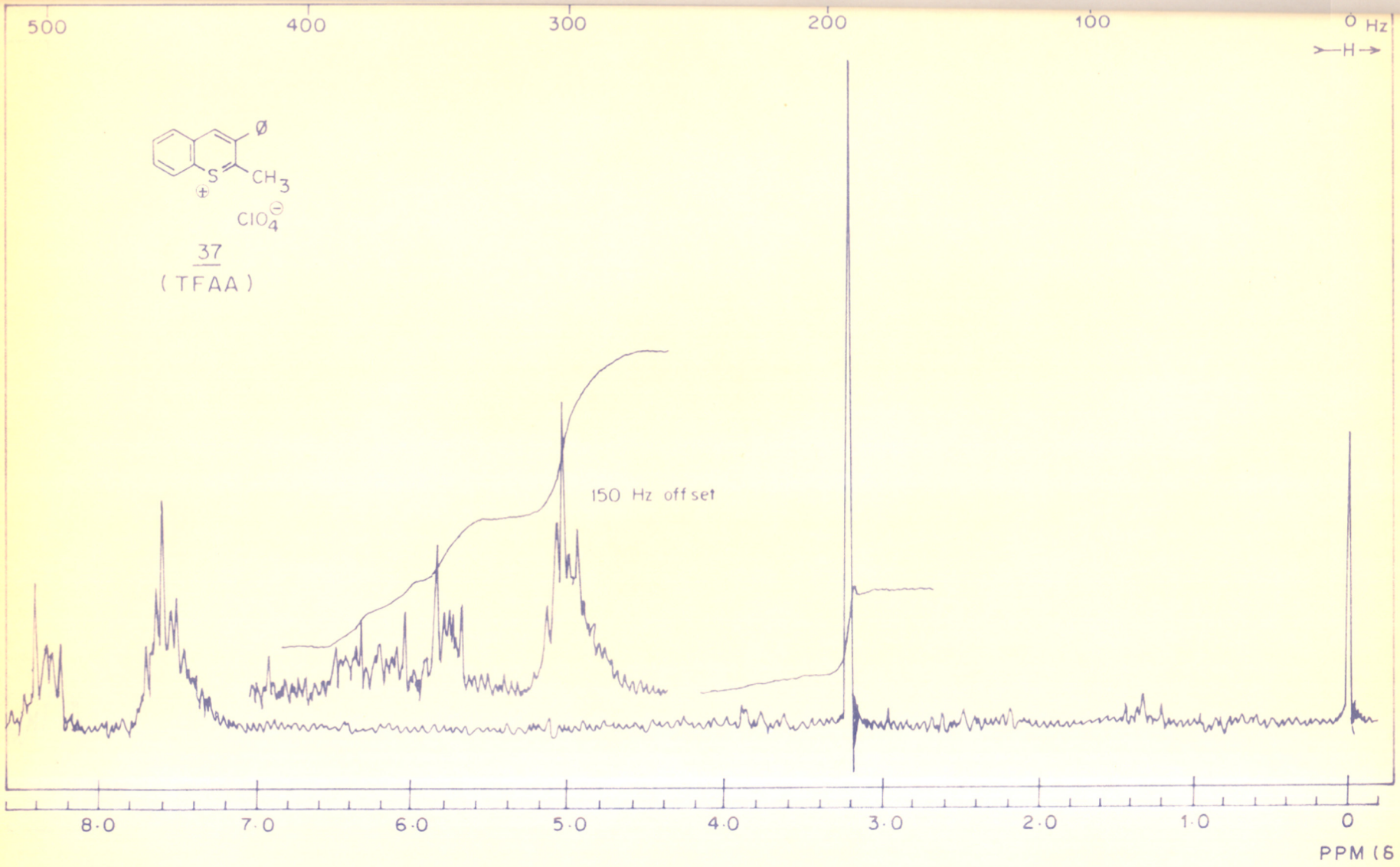
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. – 2 .


500
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H
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37
(TFAA)
150 Hz offset
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3·0
2·0
1·0
0
PPM (δ)

FIG. – 3.

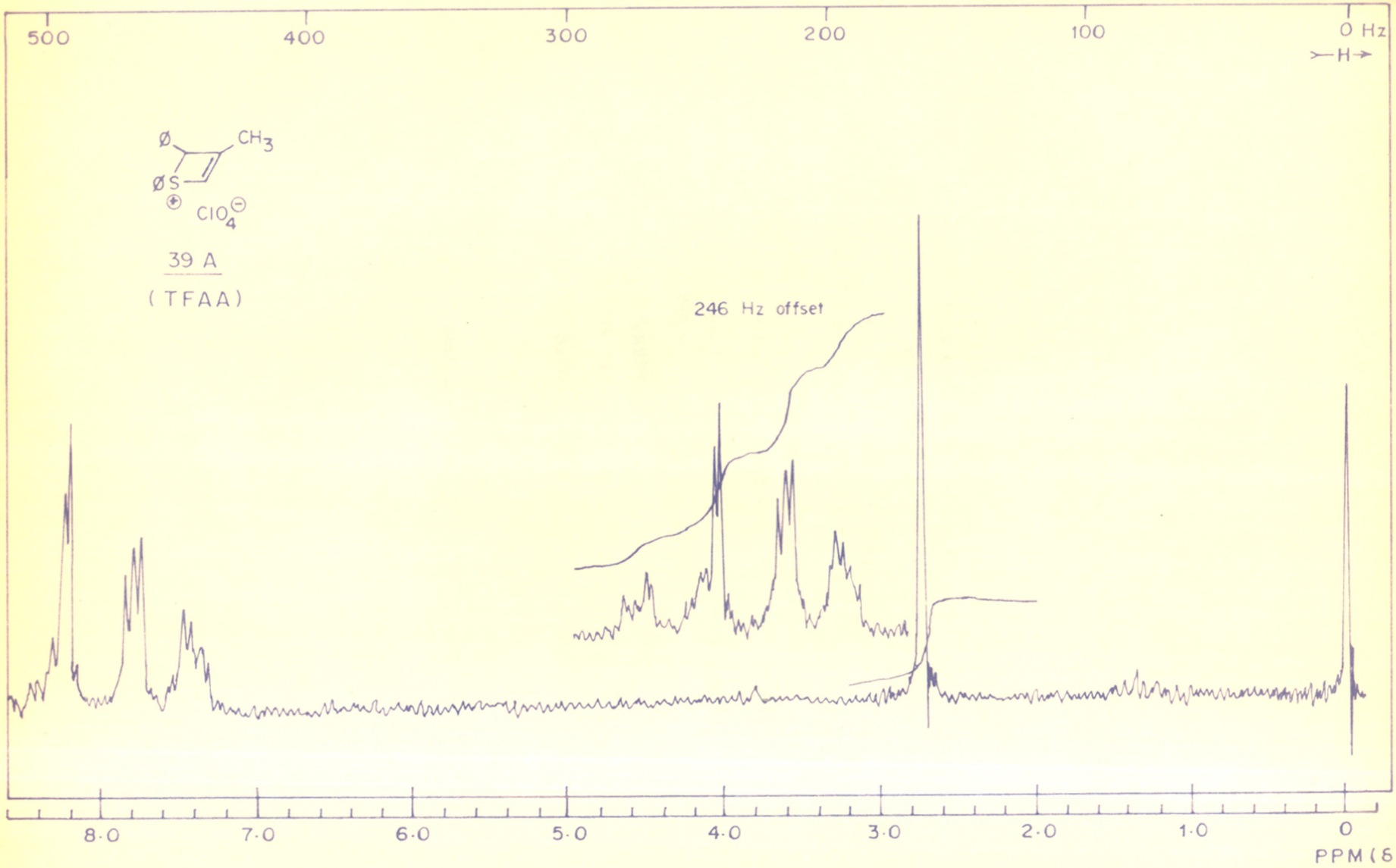
500
400
300
200
100
0 Hz
H
Ø
CH3
ØS
ClO4
39 A
(TFAA)
246 Hz offset
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. — 4.

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SUMMARY

CHAPTER I : SYNTHESIS AND REARRANGEMENT OF N-ARYLAZETINES

Cyclodehydration reaction of cis-2-arylaminomethylene cyclohexanone 7 by means of various arylaminehydrochlorides, fused zinc chloride in boiling ethanol, lactic acid, monochloroacetic acid gave tetrahydroacridines 9A/9B, whereas cyclodehydration by polyphosphoric acid gave tetrahydrophenanthridine 8 as the exclusive product (see Chapter I, Chart 2).

A plausible mechanism[1] for the formation of tetrahydroacridines 9A/9B necessarily involves the intermediate formation of N-arylazetine (C) or (D) (Chapter I, Chart 4).

To support the mechanism suggested in Chart 4, it was necessary to isolate the intermediate azetine and study its rearrangement under acidic conditions.

A number of attempts via different routes to synthesise the desired azetine were initially unsuccessful and finally we synthesized it by the reaction sequence shown in Chart 18 (Chapter I).

Structural identification of the above species was based on IR, NMR and mass spectra. Under acidic conditions it rearranges to a mixture of the relevant quinolines 63, 74 and tetrahydroquinolines 61, 73 (Chapter I, Chart 18).

CHAPTER II: ATTEMPTS TOWARDS STEREOSELECTIVE SYNTHESIS OF 2,3-DISUBSTITUTED N-ARYLAZETIDINES

It was evident from earlier work[2] on the synthesis of 2,4-disubstituted N-arylazetidines that carbinols obtained by $NaBH_4$ reduction of saturated β-arylaminoketones gave essentially trans-azetidines, whereas carbinols arising from enaminoketones gave essentially cis-azetidines. An attempt was made to synthesise 2,3-disubstituted azetidines stereoselectively as an extension of the earlier work. Carbinols 26, 31 and 35, 36 were prepared by the two different routes (Chapter II, Chart 5).

However, stereoselectivity was not observed during cyclodehydration of the carbinols 26, 31 and 35, 36. Ring expansion reactions of the azetidines were studied.

CHAPTER III : SYNTHESIS AND REARRANGEMENT OF 2,3-DISUBSTITUTED 1-S-PHENYLTHIONIUMCYCLOBUT-2-ENE PERCHLORATES

2,3-Disubstituted 1-S-phenylthioniumcyclobut-2-ene perchlorates were prepared by the route shown in Chart 6 (Chapter III) as an extension of earlier work[3]. Rearrangement of the thioniumcyclobutene perchlorates was then studied.

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