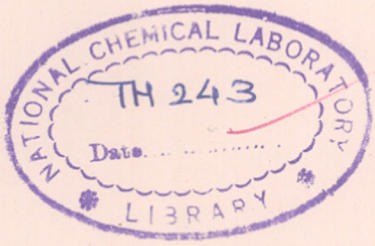
SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)



BY
S. B. KULKARNI
M. Sc.

NATIONAL CHEMICAL LABORATORY
POONA - 411 008 (India)
NOVEMBER 1974

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C O N T E N T S

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NOTES

1. Melting points are uncorrected.
2. The liquid compounds were distilled in a bulb-tube and the boiling points reported presently correspond to bath temperatures.
3. The NMR spectra were recorded on a Varian A-60 and T-60 spectrometer in CCl_4 solution taking TMS as internal standard. The chemical shifts (δ) values are reported in ppm and J values in Hz.
4. The IR spectra were recorded on a Perkin-Elmer model 221 Spectrophotometer using a sodium chloride grating interchange in nujol or HCB mull and in CCl_4 solution. The instrument was calibrated with water vapour and carbon dioxide bands, the calibration being checked from time to time with polystyrene film. Some of the IR spectra were taken in nujol mull or as a liquid film, using Perkin-Elmer Infracord 137 spectrometer. The IR values are recorded in cm^{-1}.
5. GLC analysis was carried out on SE-30 column on Hewlett-Packard-700.
6. Mass spectra were recorded on CEC 21-110B double focussing spectrometer, using direct inlet system.

CHAPTER I - INTRODUCTION

INTRODUCTION

Sutter-Kostic and Karrer[1] were the first to observe the disproportionation of N-methyl-1,2-dihydroquinoline 1 in the presence of ethanolic hydrogen chloride. 1-Phenylisoquinoline 2 and 1-phenyl-1,2,3,4-tetrahydroisoquinoline 3 have been obtained by distillation of 1-phenyl-3,4-dihydroisoquinoline 4 [2]. 4-(β-Phenylethylamino)-1,2,3,4-tetrahydroquinoline 5 and the corresponding quinoline are formed by the interaction of β-phenylethylamine and 4-keto-1,2,3,4-tetrahydroquinoline 6 with ammonium chloride and zinc chloride[3]. This reaction probably involves intermediate formation of 4-(β-phenylethylamino)-1,2-dihydroquinoline 7. The synthesis of lepidine and its derivatives, starting from β-arylaminoethyl ketones, in the presence of oxidising agents and acids has been reported[4].

The acid-catalysed cyclodehydration of alkyl/aryl β-aminoethyl ketones and disproportionation of the intermediate 1,2-dihydroquinolines leading to formation of tetrahydroquinolines and quinolines has been studied by Tilak et al. in greater detail[5,6]. The mechanism of the formation of quinolines and tetrahydroquinolines from 1,2-dihydroquinoline and its precursors such as alkyl/aryl β-aminoethyl ketones is analogous to the acid-catalysed disproportionation of Δ^3-thiachromens[7,8] and Δ^3-chromenes[9]. The disproportionatio

involves an intermolecular hydride transfer between one molecule of dihydroquinoline acting as hydride donor and another molecule of the same in its protonated form as a hydride acceptor.

The above cyclodehydration reaction yields exclusively quinolines when triphenylmethylchloride is used as an external hydride abstractor[6]. For example, methyl β-(phenylaminoethyl) ketone 8 on treatment with polyphosphoric acid gave a mixture of 4-methylquinoline 9 and 4-methyl-1,2,3,4-tetrahydroquinoline 10 along with traces of 4-methyl-1,2-dihydroquinoline. Methyl 2-(β-naphthylamino)-ethyl ketone 11 prepared by[10] condensation of β-naphthylamine 12 and 1-diethylamino-3-butanone hydrochloride 13 gave on cyclisation with ethanolic HCl a mixture of 4-methylbenzo[f]quinoline 14 [11] and 4-methyl-1,2,3,4-tetrahydrobenzo[f]quinoline 15. 2-(Dimethylamino-ethyl)-cyclohexanone hydrochloride 16 was condensed with m-anisidine 17, β-naphthylamine 12 and α-naphthylamine 18 to give the β-arylaminomethylcyclohexanones 19, 21 and 27 respectively. Compound 19 on cyclisation with PPA in the presence of triphenylmethyl chloride gave 8-methoxy-1,2,3,4-tetrahydrobenzo[C]quinoline 20. Compound 21 on treatment with PPA alone gave a mixture of 1,2,3,4,4a,5,6,12c-octa-hydrobenzo[a]phenanthridine 22 and 1,2,3,4-tetrahydro-benzo[a]phenanthridine 23[12]. However, when 21 was reacted with PPA in the presence of triphenylmethylchloride a

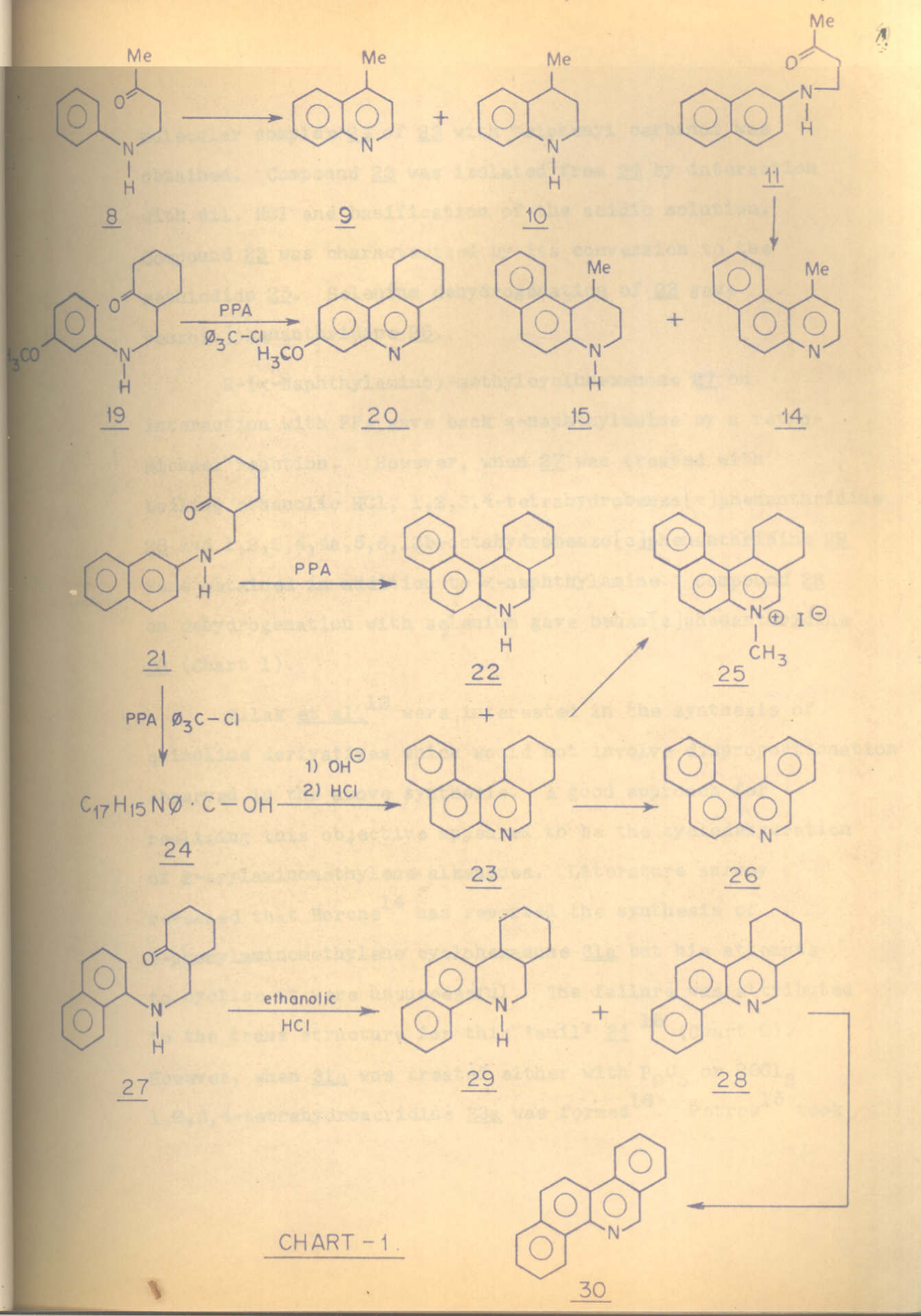
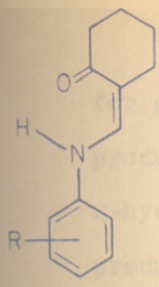

Me
O
N
H
8
9
10
11
PPA
Ø3C-Cl
H3CO
19
20
15
14
21
22
25
I⊖
CH3
PPA
Ø3C-Cl
1) OH⊖
2) HCl
C17H15NØ·C-OH
24
23
26
ethanolic
HCl
27
29
28
30

CHART - 1

molecular complex 24 of 23 with triphenyl carbinol was obtained. Compound 23 was isolated from 24 by interaction with dil. HCl and basification of the acidic solution. Compound 23 was characterised by its conversion to the methiodide 25. Selenium dehydrogenation of 23 gave benzo[a]phenanthridine 26.

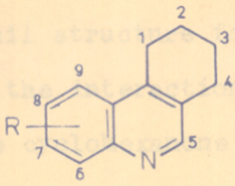
2-(α-Naphthylamino)-methylcyclohexanone 27 on interaction with PPA gave back α-naphthylamine by a retro-Michael reaction. However, when 27 was treated with boiling ethanolic HCl, 1,2,3,4-tetrahydrobenzo[c]phenanthridine 28 and 1,2,3,4,4a,5,6,12b-octahydrobenzo[c]phenanthridine 29 were obtained in addition to α-naphthylamine. Compound 28 on dehydrogenation with selenium gave benzo[c]phenanthridine 30 (Chart 1).

Tilak et al.[13] were interested in the synthesis of quinoline derivatives which would not involve disproportionation observed in the above synthesis. A good approach for realizing this objective appeared to be the cyclodehydration of 2-arylaminomethylene alkanones. Literature survey revealed that Borche[14] has reported the synthesis of 2-phenylaminomethylene cyclohexanone 31a but his attempts to cyclise it were unsuccessful. The failure was attributed to the trans structure for this 'anil' 34 [15] (Chart 2). However, when 31a was treated either with P_2O_5 or $POCl_3$ 1,2,3,4-tetrahydroacridine 33a was formed[16]. Petrow[15] took



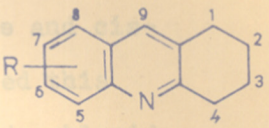
31

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



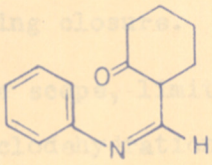
32

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

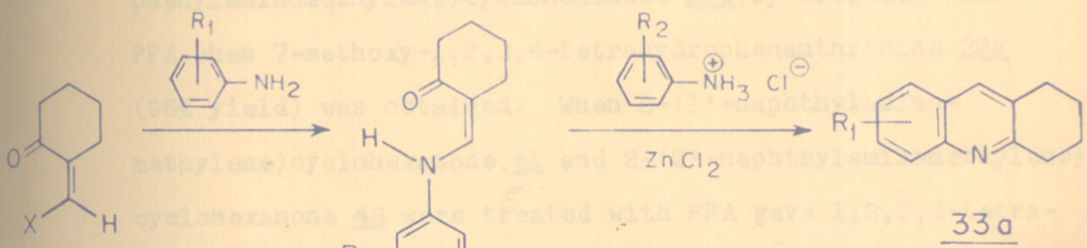


33

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

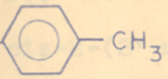


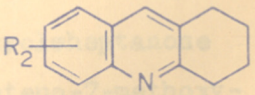
34



31

35 X = OH

36 X = O$-SO_2$-  $-CH_3$



33 b

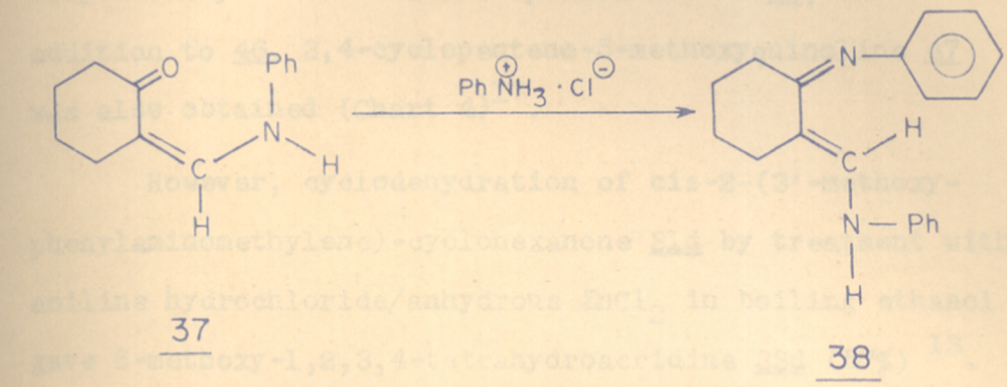
R_1 and

R_2 = H , CH_3 , $-OCH_3$, Cl

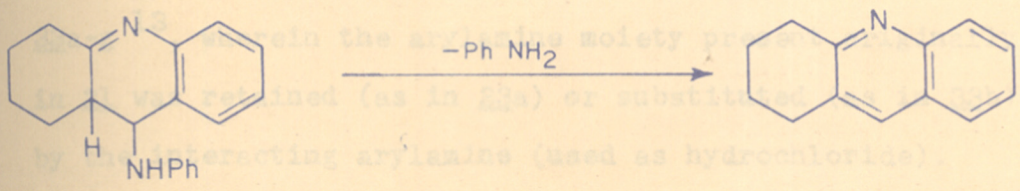
CHART – 2

for granted the anil structure for the reaction product formed by the interaction of aniline and cis-2-hydroxymethylene cyclohexanone and cyclised this product to 33a by treatment with aniline hydrochloride as such or in ethanolic solution with an optional addition of zinc chloride. In terms of Petrow's mechanism (Chart 3) ring closure of the arylaminomethylene ketone 37 in the presence of amine hydrochloride occurs through reaction of the second molecule of amine with the remaining carbonyl group in the starting material with final extrusion of the amine residue originally present after the ring closure.

To define the scope, limitations and to elucidate the mechanism of cyclodehydration of arylaminomethylene alkanones, Tilak et al.[13] cyclodehydrated cis-2(3'-methoxyphenylaminomethylene)cyclohexanone 31d by treatment with PPA when 7-methoxy-1,2,3,4-tetrahydrophenanthridine 32a (96% yield) was obtained. When 2-(1'-naphthylaminomethylene)cyclohexanone 41 and 2-(2'-naphthylaminomethylene)-cyclohexanone 43 were treated with PPA gave 1,2,3,4-tetrahydrobenzo[c]phenanthridine 42 and 1,2,3,4-tetrahydrobenzo[a]phenanthridine 44. Cyclodehydration of cis-2(3'-methoxyphenylaminomethylene)-cyclopentanone 45 and cis-2-(3'-methoxyphenylaminomethylene)-cycloheptanone 48 by interaction with PPA gave 3,4-cyclopenteno-7-methoxyquinoline 46 and 3,4-cyclohepteno-7-methoxyquinoline 49



37 38



39 40

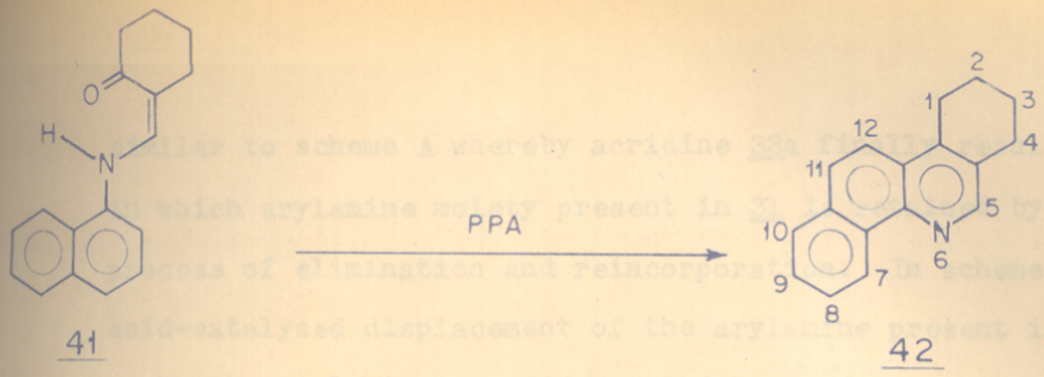
CHART — 3.

respectively. In the above cyclisation of 45, in addition to 46, 3,4-cyclopenteno-5-methoxyquinoline 47 was also obtained (Chart 4)[17].

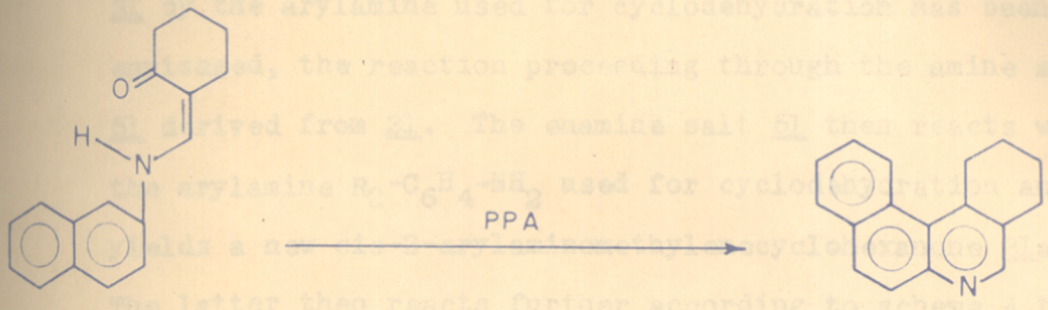
However, cyclodehydration of cis-2-(3'-methoxy-phenylaminomethylene)-cyclohexanone 31d by treatment with aniline hydrochloride/anhydrous $ZnCl_2$ in boiling ethanol gave 6-methoxy-1,2,3,4-tetrahydroacridine 33d (57%) [13].

Several cis-2-arylaminomethylenecyclohexanones 31a-g were cyclodehydrated with different primary arylamine hydrochlorides in boiling ethanol in the presence of anhydrous zinc chloride to obtain tetrahydroacridines 33a-g [13], wherein the arylamine moiety present originally in 31 was retained (as in 33a) or substituted (as in 33b) by the interacting arylamine (used as hydrochloride).

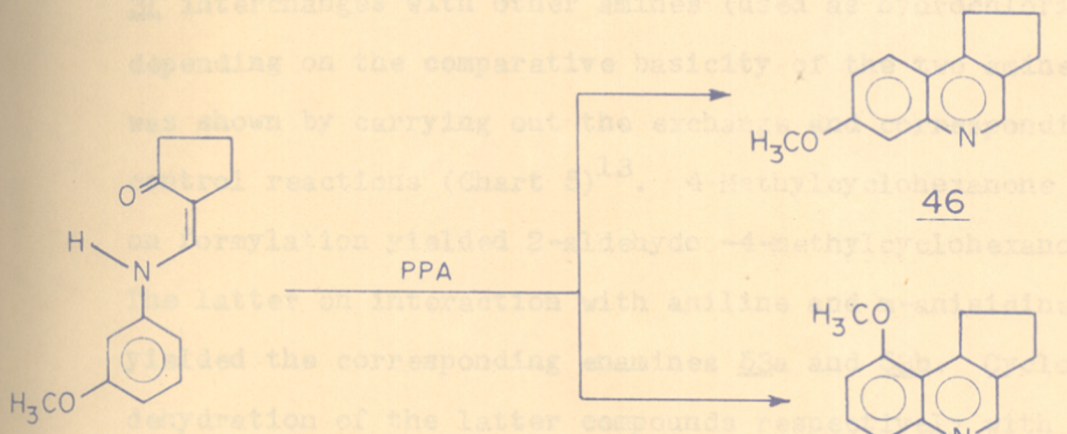
The mechanism suggested by Tilak et al.[13] postulates that the substitution of the arylamine R_1-C_6H_4-NH_2 used in cyclodehydration probably takes place through the implication of the intermediate 'dianil' 50 (Chart 5) (reaction following scheme A). The retention of original arylamine present in 31 in the final tetrahydro-acridine 33a was explained on the assumption that the reaction follows an alternate path (scheme B, Chart 5). In latter case acid-catalysed substitution of R_1-C_6H_4-NH_2 present in 31 by R_2-C_6H_4-NH_2 occurs as a first step to yield 31a and then further reactions follow a sequence



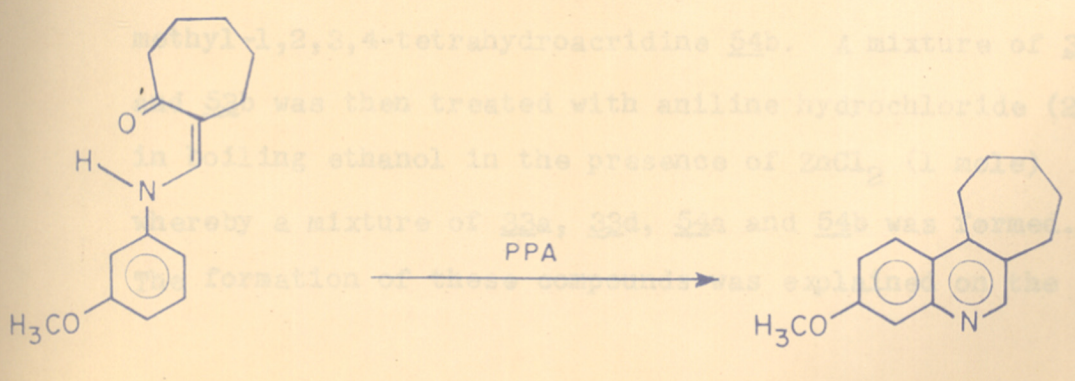
41 42



43 44



45 46 47



48 49

CHART - 4

similar to scheme A whereby acridine 33a finally results in which arylamine moiety present in 31 is retained by a process of elimination and reincorporation. In scheme B acid-catalysed displacement of the arylamine present in 31 by the arylamine used for cyclodehydration has been envisaged, the reaction proceeding through the amine salt 51 derived from 31. The enamine salt 51 then reacts with the arylamine R_2-C_6H_4-NH_2 used for cyclodehydration and yields a new cis-2-arylaminomethylenecyclohexanone 31a. The latter then reacts further according to scheme A to finally yield 33a. The fact that the amine present in 31 interchanges with other amines (used as hydrochlorides), depending on the comparative basicity of the two amines was shown by carrying out the exchange and corresponding control reactions (Chart 5)[13]. 4-Methylcyclohexanone (D) on formylation yielded 2-aldehydo -4-methylcyclohexanone 52. The latter on interaction with aniline and m-anisidine yielded the corresponding enamines 53a and 53b. Cyclodehydration of the latter compounds respectively with aniline hydrochloride and m-anisidine hydrochloride gave 2-methyl-1,2,3,4-tetrahydroacridine 54a and 6-methoxy-2-methyl-1,2,3,4-tetrahydroacridine 54b. A mixture of 31a and 53b was then treated with aniline hydrochloride (2 moles) in boiling ethanol in the presence of $ZnCl_2$ (1 mole) whereby a mixture of 33a, 33d, 54a and 54b was formed. The formation of these compounds was explained on the basis

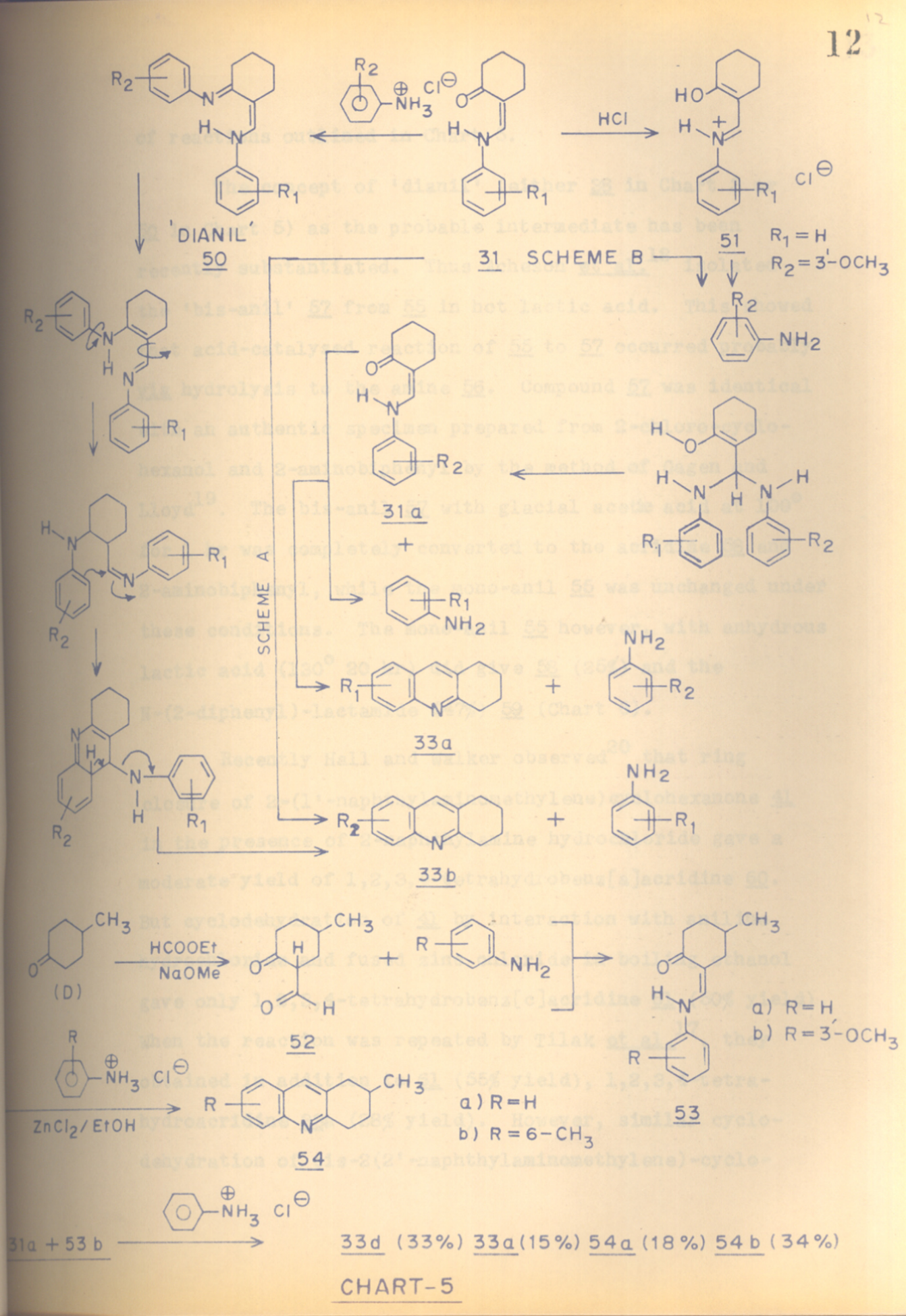
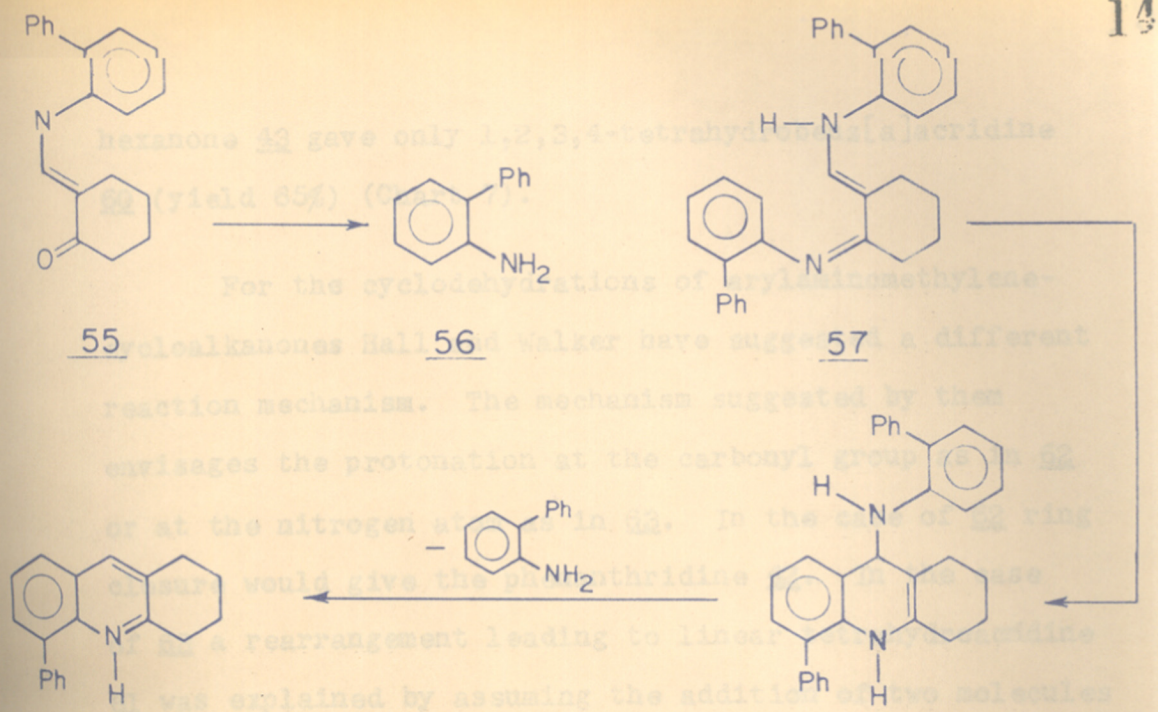

'DIANIL'
50
31
SCHEME B
HCl
51
R1 = H
R2 = 3'-OCH3
SCHEME A
31a
+
33a
33b
(D)
HCOOEt
NaOMe
52
a) R = H
b) R = 3'-OCH3
53
ZnCl2/EtOH
54
a) R = H
b) R = 6-CH3
31a + 53b
33d (33%) 33a (15%) 54a (18%) 54b (34%)

CHART-5

of reactions outlined in Chart 5.

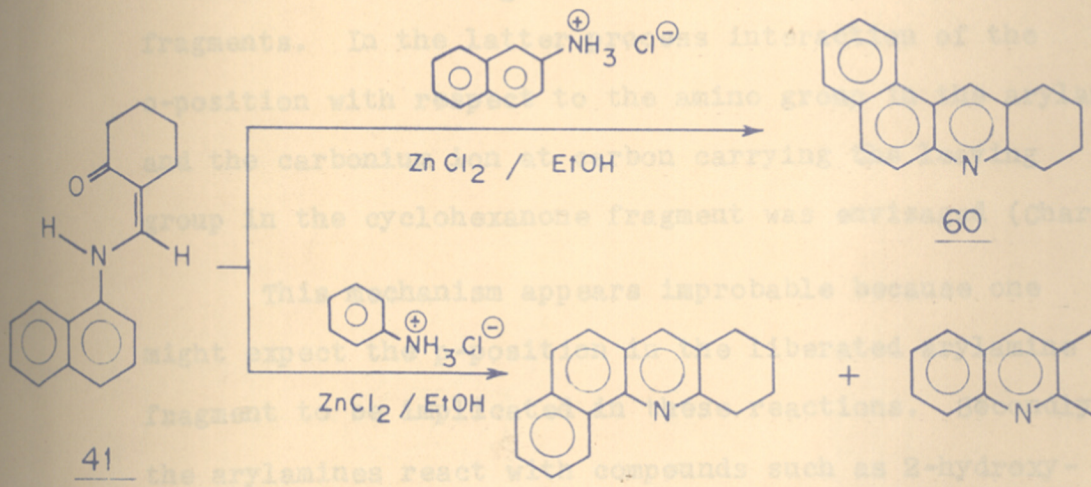
The concept of 'dianil' (either 38 in Chart 3 or 50 in Chart 5) as the probable intermediate has been recently substantiated. Thus Acheson et al.[18] isolated the 'bis-anil' 57 from 55 in hot lactic acid. This showed that acid-catalysed reaction of 55 to 57 occurred probably via hydrolysis to the amine 56. Compound 57 was identical with an authentic specimen prepared from 2-chloro-cyclohexanol and 2-aminobiphenyl by the method of Gagen and Lloyd[19]. The bis-anil 57 with glacial acetic acid at 100° for 1 hr was completely converted to the acridine 58 and 2-aminobiphenyl, while the mono-anil 55 was unchanged under these conditions. The mono-anil 55 however, with anhydrous lactic acid (130° 20 hr) did give 58 (25%) and the N-(2-diphenyl)-lactamide (47%) 59 (Chart 6).

Recently Hall and Walker observed[20] that ring closure of 2-(1'-naphthylaminomethylene)cyclohexanone 41 in the presence of 2-naphthylamine hydrochloride gave a moderate yield of 1,2,3,4-tetrahydrobenz[a]acridine 60. But cyclodehydration of 41 by interaction with aniline hydrochloride and fused zinc chloride in boiling ethanol gave only 1,2,3,4-tetrahydrobenz[c]acridine 61 (50% yield). When the reaction was repeated by Tilak et al.[17], they obtained in addition to 61 (55% yield), 1,2,3,4-tetrahydroacridine 33a (28% yield). However, similar cyclodehydration of cis-2(2'-naphthylaminomethylene)-cyclo-

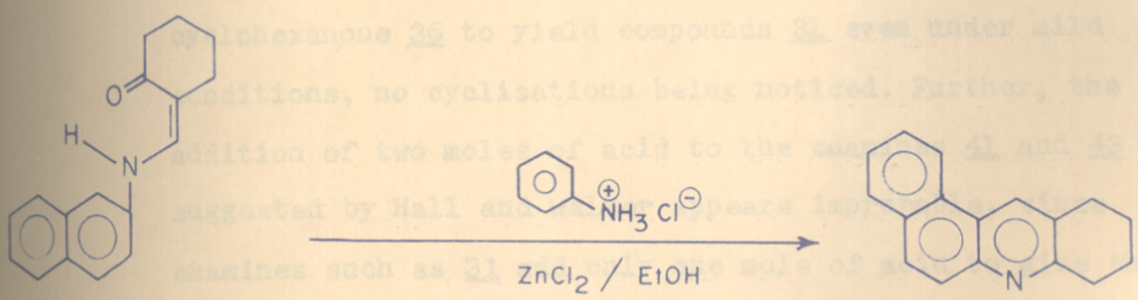


55 56 57 58

CHART – 6.



41 61 33 a



43 60

CHART – 7.

hexanone 43 gave only 1,2,3,4-tetrahydrobenz[a]acridine 60 (yield 65%) (Chart 7).

For the cyclodehydrations of arylaminomethylene-cycloalkanones Hall and Walker have suggested a different reaction mechanism. The mechanism suggested by them envisages the protonation at the carbonyl group as in 62 or at the nitrogen atom as in 63. In the case of 62 ring closure would give the phenanthridine 42. In the case of 63 a rearrangement leading to linear tetrahydroacridine 61 was explained by assuming the addition of two molecules of the acid to the starting enamines 41, followed by cleavage of the $-C-\overset{+}{N}H_2$ bond and recombination of the fragments. In the latter process interaction of the o-position with respect to the amino group in the arylamine and the carbonium ion at carbon carrying the leaving group in the cyclohexanone fragment was envisaged (Chart 8).

This mechanism appears improbable because one might expect the p-position in the liberated arylamine fragment to be implicated in these reactions. Secondly, the arylamines react with compounds such as 2-hydroxy-methylenecyclohexanone 35 and cis-2-(4'-tosyloxymethylene)-cyclohexanone 36 to yield compounds 31 even under mild conditions, no cyclisations being noticed. Further, the addition of two moles of acid to the enamines 41 and 43 suggested by Hall and Walker appears improbable, since enamines such as 31 add only one mole of acid to give the

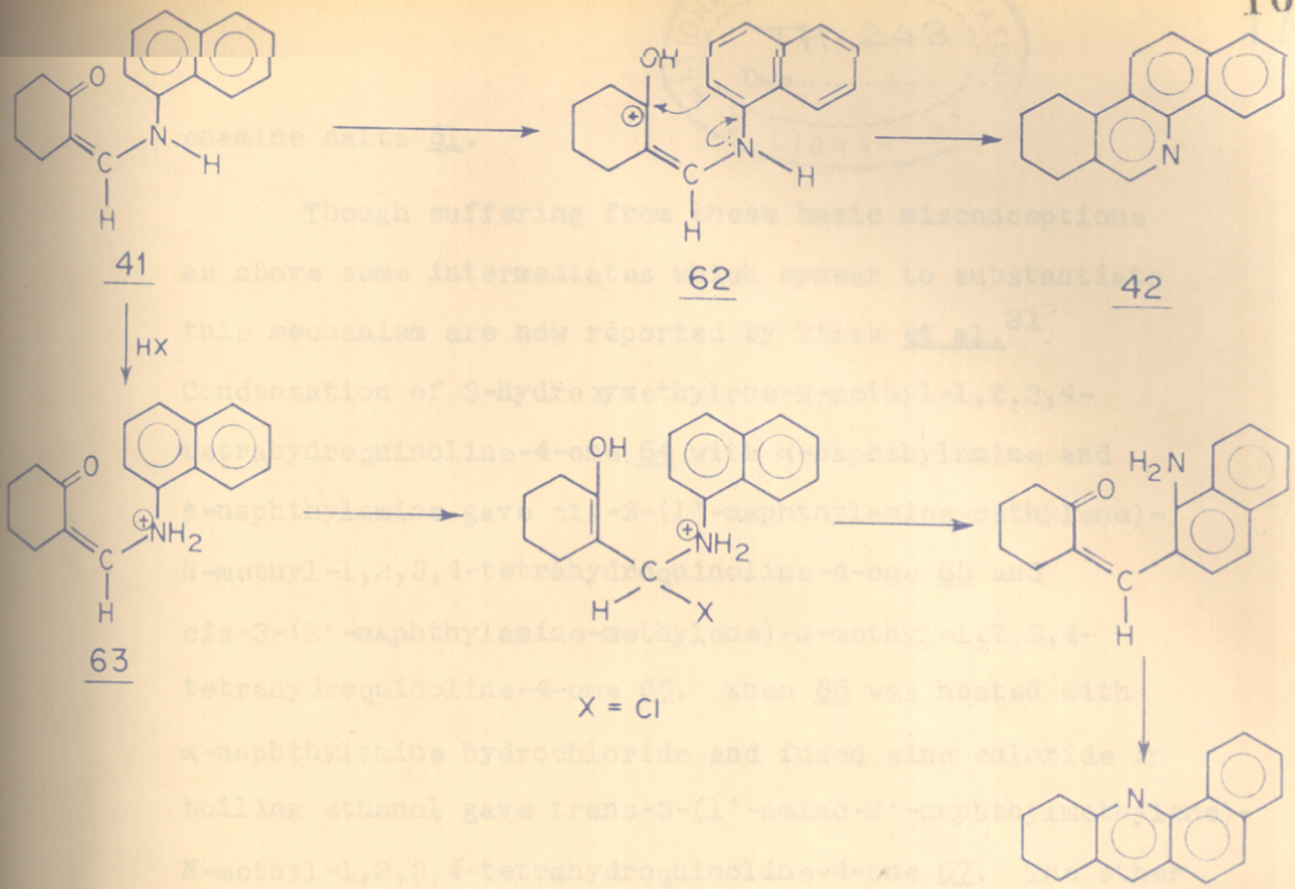
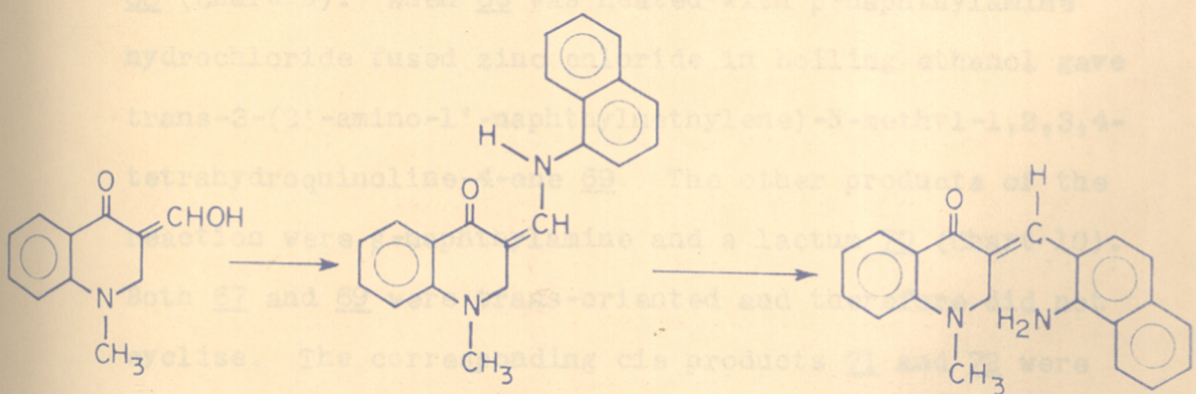


CHART – 8.



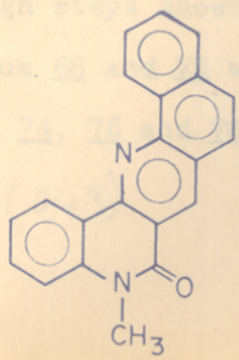
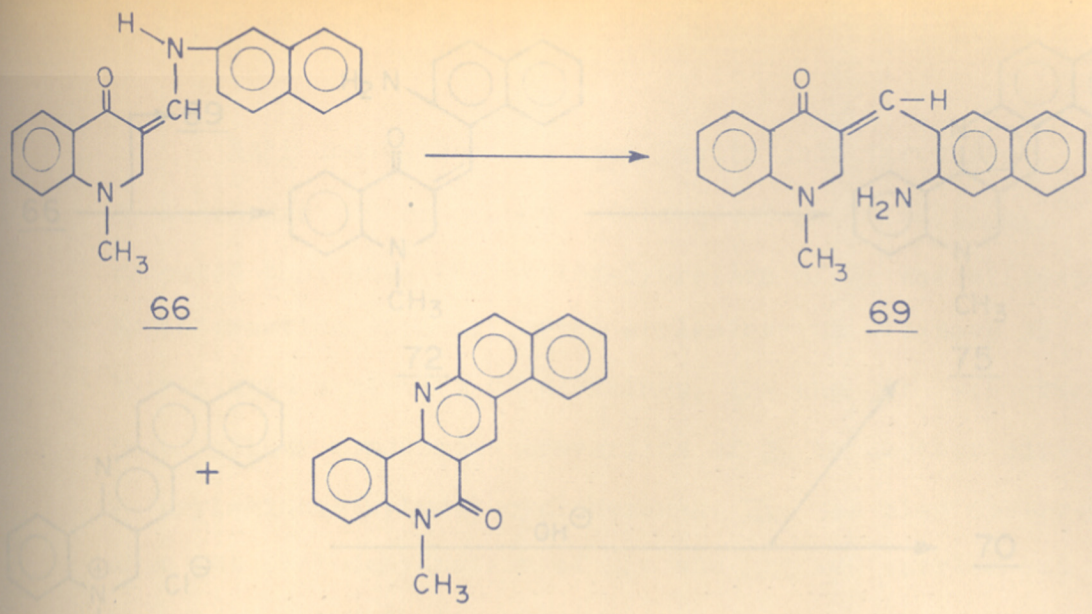


CHART – 9.

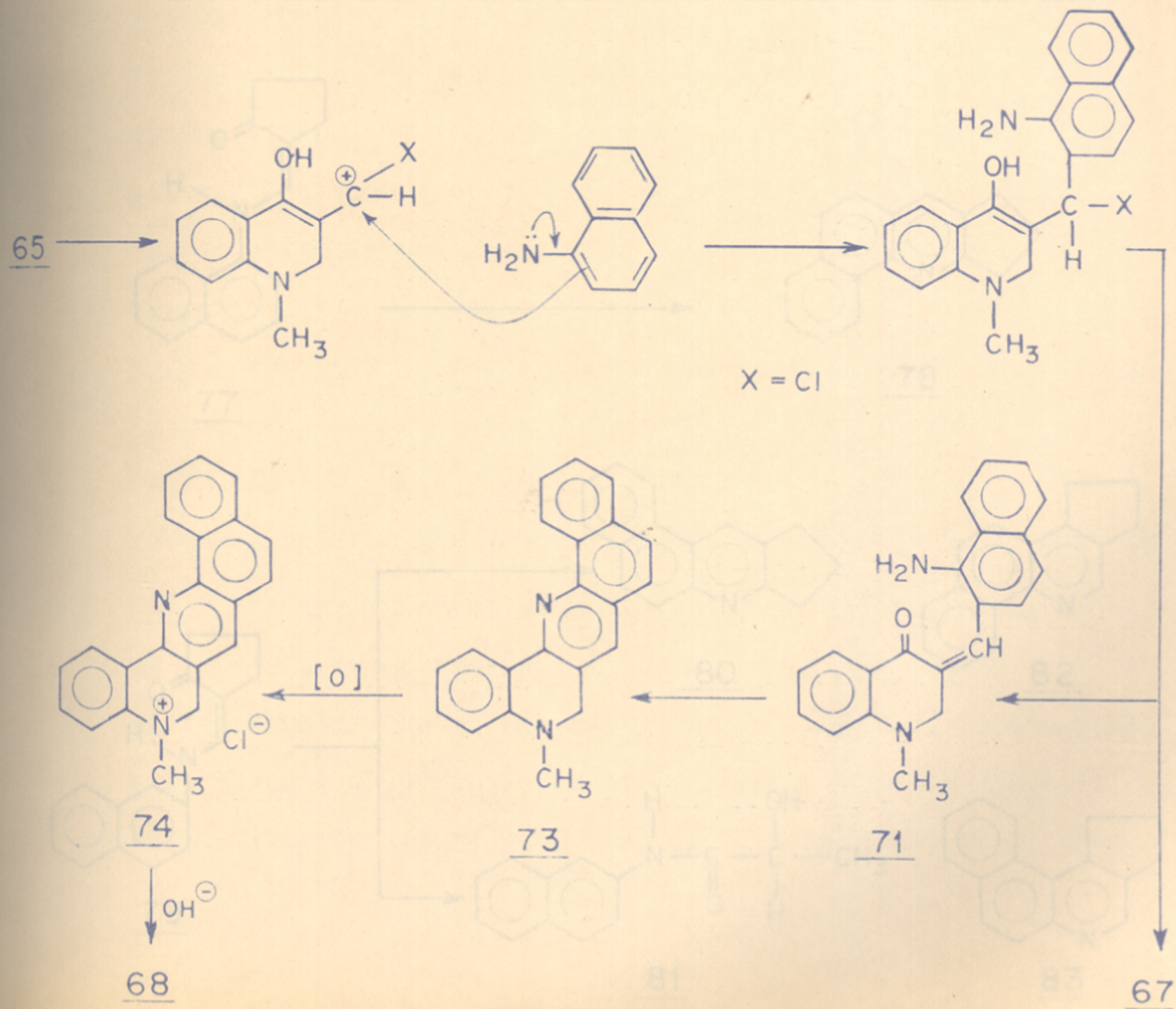
enamine salts 51.

Though suffering from these basic misconceptions as above some intermediates which appear to substantiate this mechanism are now reported by Tilak et al.[21]. Condensation of 3-hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 64 with α-naphthylamine and β-naphthylamine gave cis-3-(1'-naphthylamine-methylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 65 and cis-3-(2'-naphthylamine-methylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 66. When 65 was heated with α-naphthylamine hydrochloride and fused zinc chloride in boiling ethanol gave trans-3-(1'-amino-2'-naphthylmethylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 67. The other products of the reaction were α-naphthylamine and a lactum 68 (Chart 9). When 66 was heated with β-naphthylamine hydrochloride fused zinc chloride in boiling ethanol gave trans-3-(2'-amino-1'-naphthylmethylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 69. The other products of the reaction were β-naphthylamine and a lactum 70 (Chart 10). Both 67 and 69 were trans-oriented and therefore did not cyclise. The corresponding cis products 71 and 72 were also formed but they undergo spontaneous cyclisation leading eventually to 68 and 70, through steps shown in Charts 11 and 12. The formation of lactum 68 and 70 was explained on the basis of intermediates 73, 74, 75 and 76.



66 69 70

CHART – 10.



X = Cl

65 71 73 74 68 67

CHART – 11.

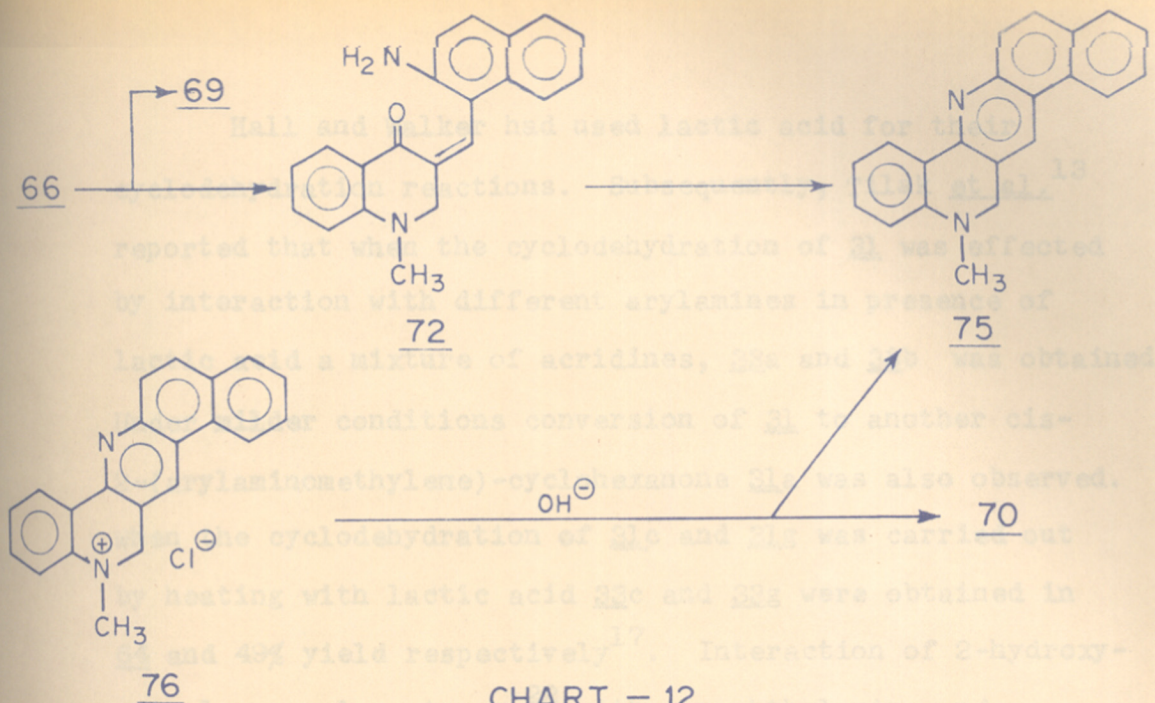
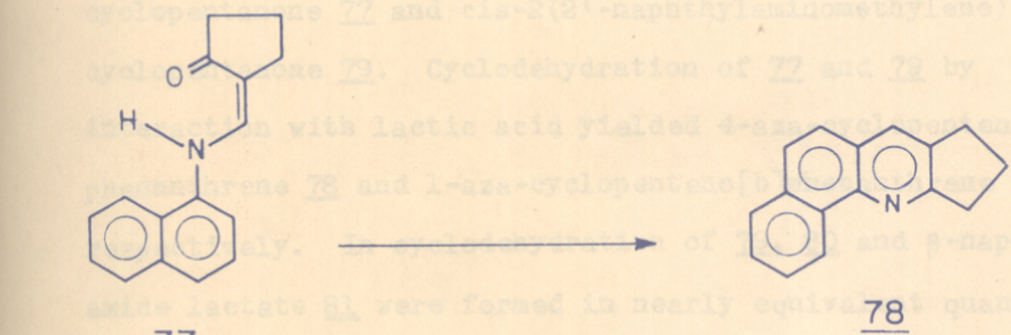


CHART – 12 .



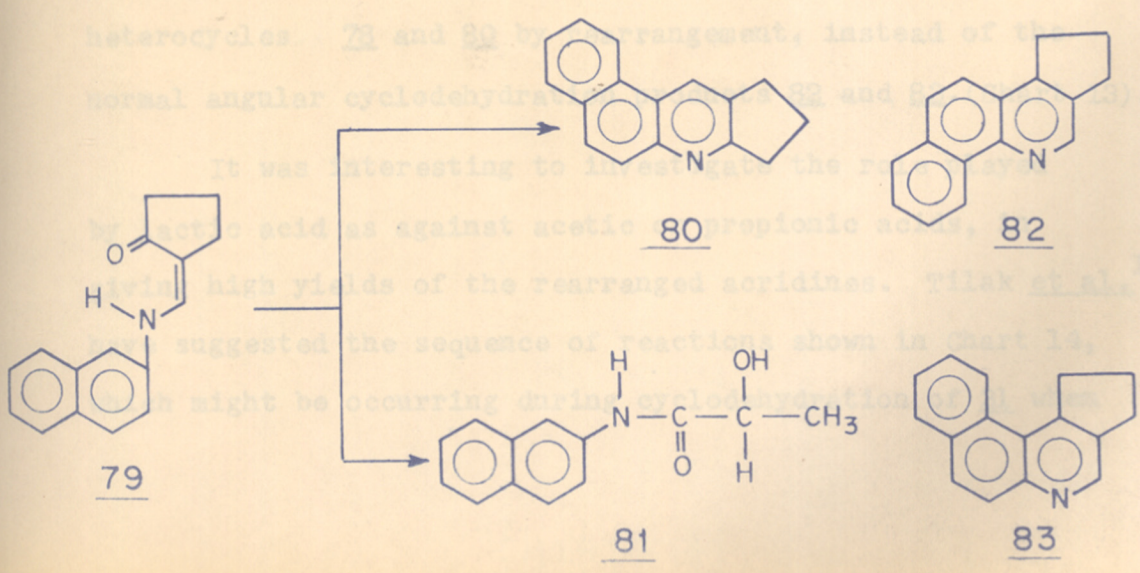


CHART – 13 .

Hall and Walker had used lactic acid for their cyclodehydration reactions. Subsequently, Tilak et al.[13] reported that when the cyclodehydration of 31 was effected by interaction with different arylamines in presence of lactic acid a mixture of acridines, 33a and 33b was obtained. Under milder conditions conversion of 31 to another cis-2-(arylaminomethylene)-cyclohexanone 31a was also observed. When the cyclodehydration of 31c and 31g was carried out by heating with lactic acid 33c and 33g were obtained in 64 and 49% yield respectively[17]. Interaction of 2-hydroxy-methylene-cyclopentanone[22] with α-naphthylamine and β-naphthylamine gave cis-2-(1'-naphthylaminomethylene)-cyclopentanone 77 and cis-2(2'-naphthylaminomethylene)-cyclopentanone 79. Cyclodehydration of 77 and 79 by interaction with lactic acid yielded 4-aza-cyclopenteno[b]-phenanthrene 78 and 1-aza-cyclopenteno[b]phenanthrene 80 respectively. In cyclodehydration of 79, 80 and β-naphthyl-amine lactate 81 were formed in nearly equivalent quantities. Cyclodehydration of both 77 and 79 leads to linear heterocycles 78 and 80 by rearrangement, instead of the normal angular cyclodehydration products 82 and 83.(Chart 13).

It was interesting to investigate the role played by lactic acid as against acetic or propionic acids, in giving high yields of the rearranged acridines. Tilak et al.[13] have suggested the sequence of reactions shown in Chart 14, which might be occurring during cyclodehydration of 31 when

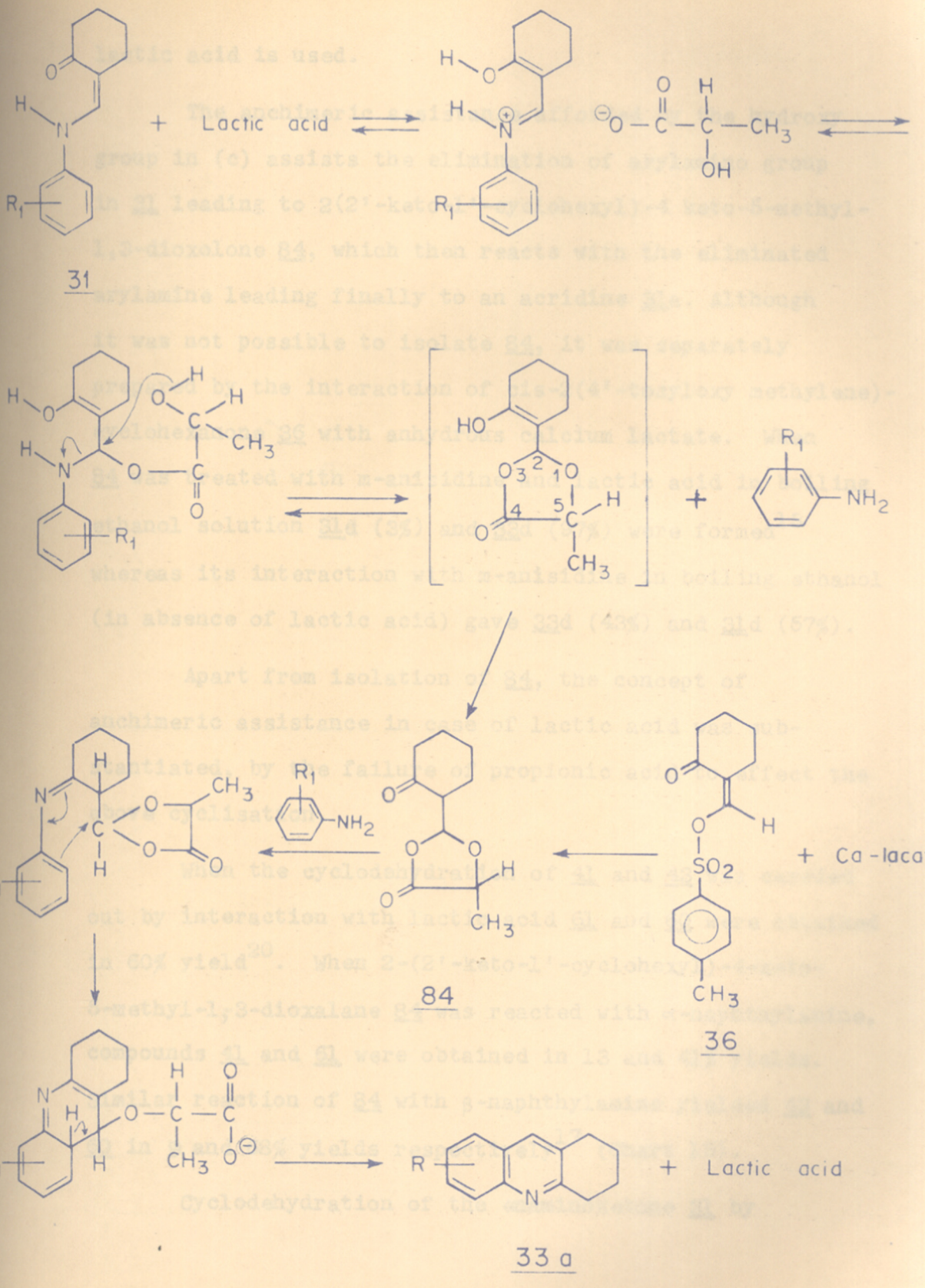


CHART – 14.

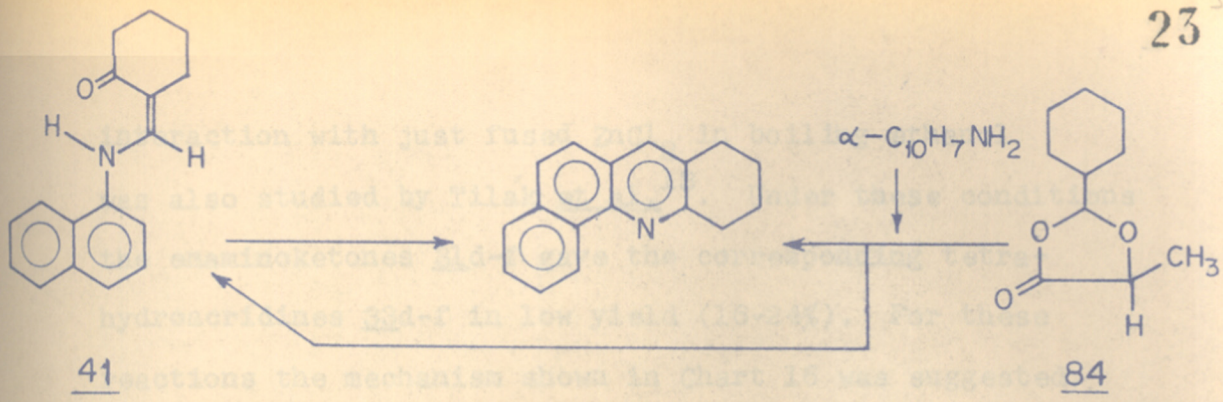
lactic acid is used.

The anchimeric assistance afforded by the hydroxy group in (c) assists the elimination of arylamino group in 31 leading to 2(2'-keto-1'-cyclohexyl)-4 keto-5-methyl-1,3-dioxolone 84, which then reacts with the eliminated arylamine leading finally to an acridine 31a. Although it was not possible to isolate 84, it was separately prepared by the interaction of cis-2(4'-tosyloxy methylene)-cyclohexanone 36 with anhydrous calcium lactate. When 84 was treated with m-anisidine and lactic acid in boiling ethanol solution 31d (3%) and 33d (97%) were formed[13] whereas its interaction with m-anisidine in boiling ethanol (in absence of lactic acid) gave 33d (43%) and 31d (57%).

Apart from isolation of 84, the concept of anchimeric assistance in case of lactic acid was substantiated, by the failure of propionic acid to effect the above cyclisation.

When the cyclodehydration of 41 and 43 was carried out by interaction with lactic acid 61 and 60 were obtained in 60% yield[20]. When 2-(2'-keto-1'-cyclohexyl)-4-keto-5-methyl-1,3-dioxalane 84 was reacted with α-naphthylamine, compounds 41 and 61 were obtained in 13 and 41% yields. Similar reaction of 84 with β-naphthylamine yielded 43 and 60 in 9 and 68% yields respectively[17] (Chart 15).

Cyclodehydration of the enaminoketone 31 by



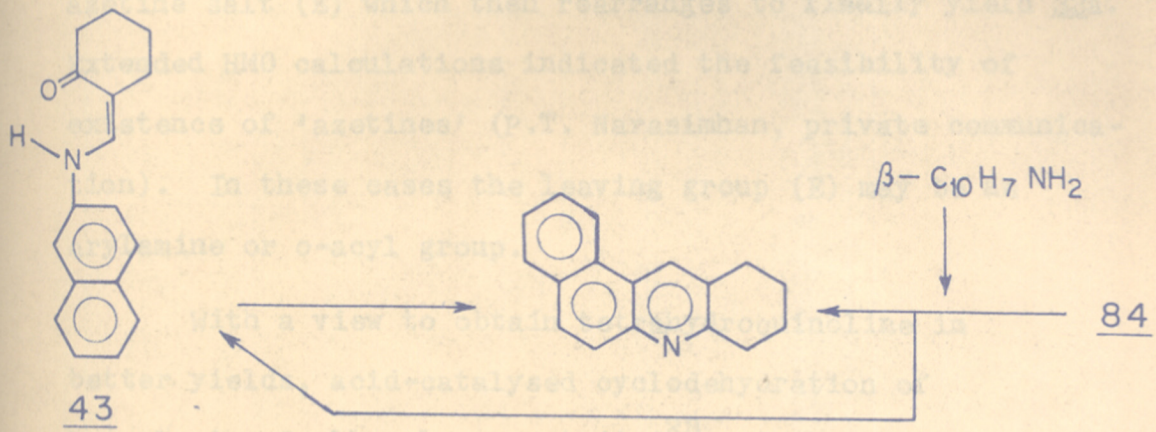
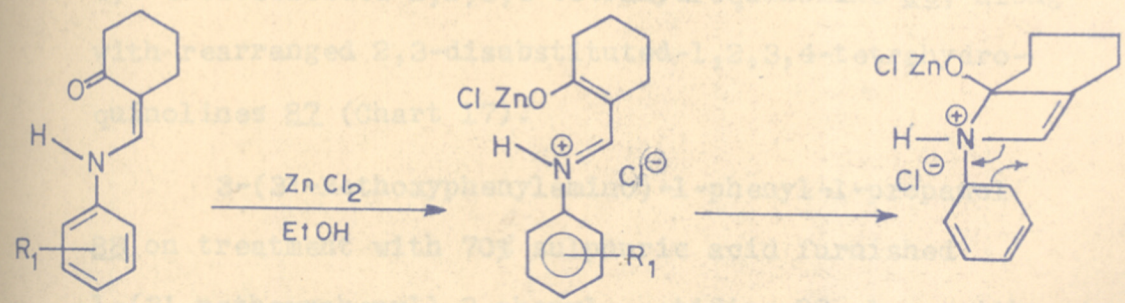


CHART – 15.



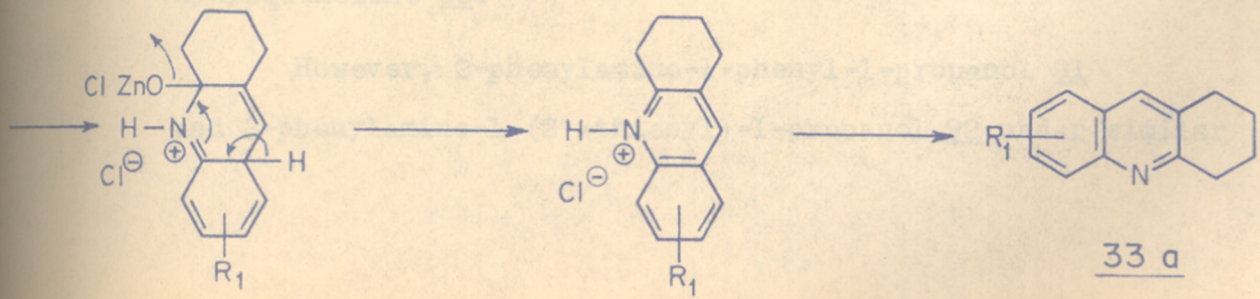


CHART – 16.

interaction with just fused $ZnCl_2$ in boiling ethanol was also studied by Tilak et al.[13]. Under these conditions the enaminoketones 31d-f gave the corresponding tetrahydroacridines 33d-f in low yield (16-24%). For these reactions the mechanism shown in Chart 16 was suggested. The above scheme envisages the intermediate formation of the azetine salt (E) which then rearranges to finally yield 33a. Extended HMO calculations indicated the feasibility of existence of 'azetines' (P.T. Narasimhan, private communication). In these cases the leaving group (E) may be an arylamine or o-acyl group.

With a view to obtain tetrahydroquinoline in better yields, acid-catalysed cyclodehydration of 1-arylamino-3-alkanols was studied[23]. Cyclodehydration of the alkanols 85, under acid conditions, yielded 3,4-disubstituted-1,2,3,4-tetrahydroquinoline 86, along with rearranged 2,3-disubstituted-1,2,3,4-tetrahydroquinolines 87 (Chart 17).

3-(3'-Methoxyphenylamino)-1-phenyl-1-propanol 88 on treatment with 70% sulphuric acid furnished 1-(3'-methoxyphenyl)-2-phenyl-azetidine 89 along with the rearranged product 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 90.

However, 3-phenylamino-1-phenyl-1-propanol 91 and 3-phenylamino-1-(2'-thienyl)-1-propanol 92 under similar

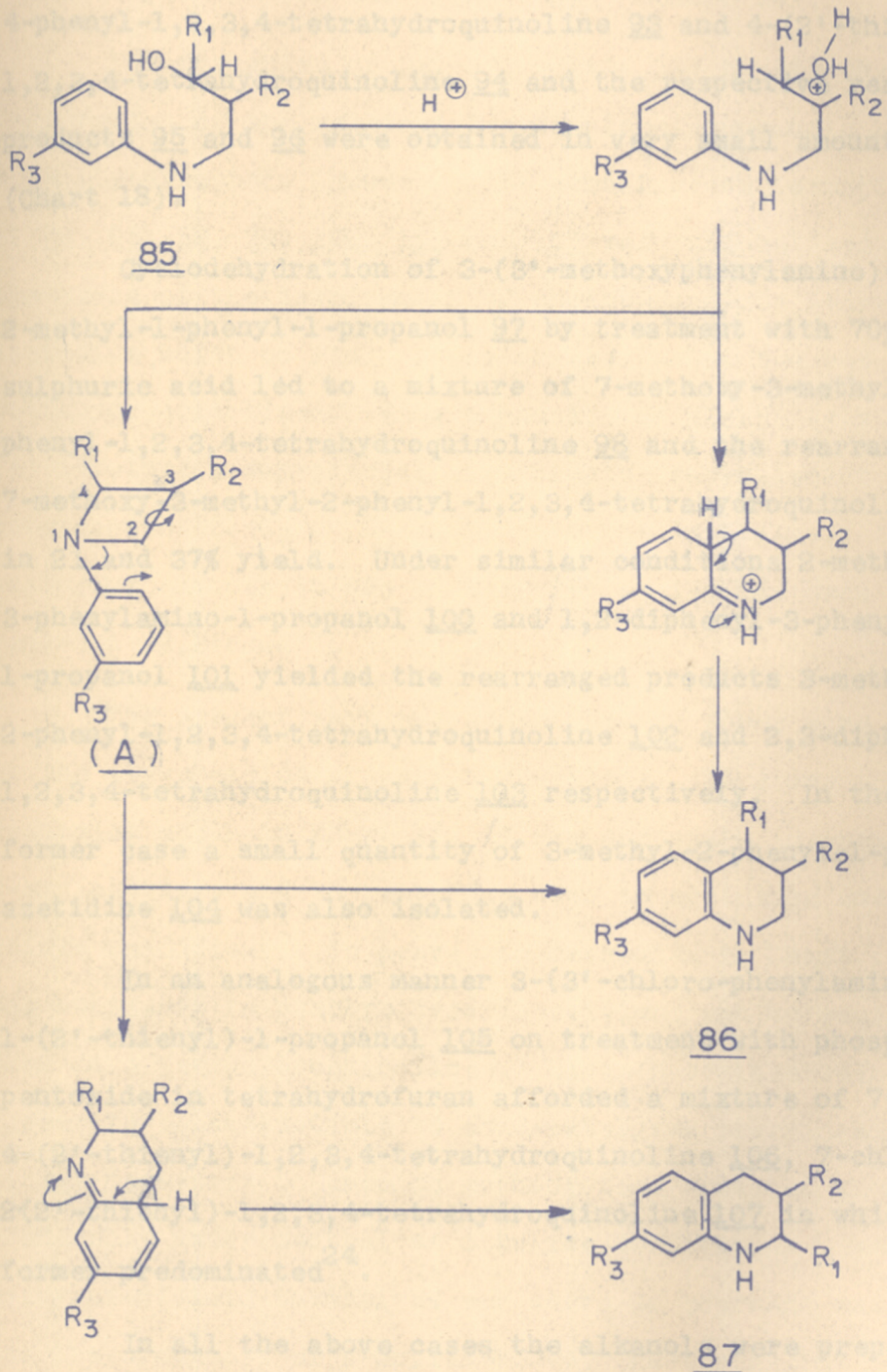


CHART – 17 .

conditions yielded essentially the normal products, 4-phenyl-1,2,3,4-tetrahydroquinoline 93 and 4-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 94 and the respective rearranged products 95 and 96 were obtained in very small amounts (Chart 18).

Cyclodehydration of 3-(3'-methoxyphenylamino)-2-methyl-1-phenyl-1-propanol 97 by treatment with 70% sulphuric acid led to a mixture of 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 98 and the rearranged 7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 99 in 21 and 37% yield. Under similar conditions 2-methyl-3-phenylamino-1-propanol 100 and 1,2-diphenyl-3-phenylamino-1-propanol 101 yielded the rearranged products 3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 102 and 2,3-diphenyl-1,2,3,4-tetrahydroquinoline 103 respectively. In the former case a small quantity of 3-methyl-2-phenyl-1-phenyl-azetidine 104 was also isolated.

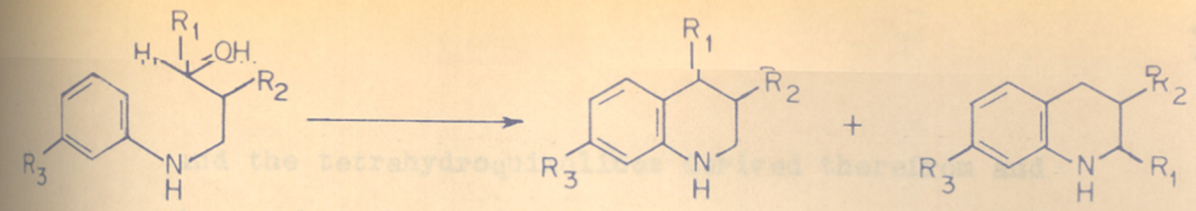
In an analogous manner 3-(3'-chloro-phenylamino)-1-(2'-thienyl)-1-propanol 105 on treatment with phosphorous pentoxide in tetrahydrofuran afforded a mixture of 7-chloro-4-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 106, 7-chloro-2-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 107 in which the former predominated[24].

In all the above cases the alkanols were prepared by the sodium borohydride reduction of either the corresponding

β-arylaminoethyl, alkyl/aryl ketones or cis-2-aryl-aminomethylene alkanones (108 to 114) (Chart 18).

The formation of 93, 94, 98 and 106 by the cyclodehydration of the relevant 3-arylamino-1-propanols was normally expected. However, the simultaneous formation of 90, 95, 96, 99, 102, 103 and 107 was rationalised on the basis of the involvement of an intermediate 1-aryl-azetidine which on ring expansion led to the two possible tetrahydroquinolines. Ring expansion of N-aryl azetidines (A) involves a suprafacial sigmatropic rearrangement with inversion at C_3-C_4 or C_2-C_3 bond in the azetidine. An analogous example in the carbocyclic series has been reported by Berson[25].

The present work was undertaken to throw more light on the above cyclodehydration reactions. To prove the mechanism shown in Chart 16, it was necessary to prepare N-arylazetines and to rearrange them to acridines under acidic conditions. To prove the mechanism in Chart 17 it was necessary to prepare N-arylazetidines and to rearrange them into tetrahydroquinolines. Since N-arylazetidines appear to be susceptible to acid-catalysed rearrangement, it was necessary to develop methods to synthesise them preferably under neutral or alkaline conditions. Secondly, N-arylazetidines themselves may serve as starting materials for the synthesis of N-arylazetines. Lastly it was of great interest to study the stereochemistry of N-arylazetidines



88 : $R_1 = \emptyset$; $R_2 = H$; $R_3 = OCH_3$

90 : $R_1 = \emptyset$, $R_2 = H$; $R_3 = OCH_3$

91 ; $R_1 = \emptyset$; $R_2 = R_3 = H$

93 : $R_1 = \emptyset$; $R_2 = R_3 = H$

95 : $R_1 = \emptyset$; $R_2 = R_3 = H$

92 : R_1 = 2'-thienyl ; $R_2 = R_3 = H$

94 : R_1 = 2'-thienyl ; $R_2 = R_3 = H$

96 : R_1 = 2'-thienyl ; $R_2 = R_3 = H$

97 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = OCH_3$

98 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = OCH_3$

99 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = OCH_3$

100 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = H$

101 $R_1 = R_2 = \emptyset$; $R_3 = H$

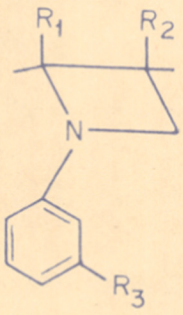
102 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = H$

103 : $R_1 = R_2 = \emptyset$; $R_3 = H$

105 : R_1 = 2'-thienyl ; $R_2 = H$; $R_3 = Cl$

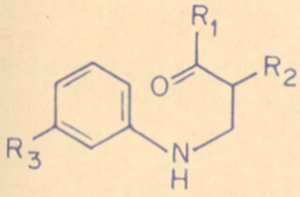
106 : R_1 = 2'-thienyl ; $R_2 = H$; $R_3 = Cl$

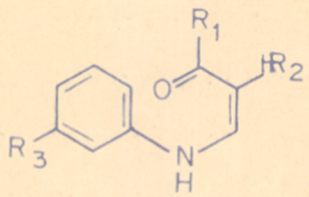
107 : R_1 = 2'-thienyl ; $R_2 = H$; $R_3 = Cl$



89 : $R_1 = \emptyset$; $R_2 = H$; $R_3 = OCH_3$

104 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = H$





108 : $R_1 = \emptyset$; $R_2 = H$; $R_3 = OCH_3$

111 : $R_1 = \emptyset$; $R_2 = CH_3$; $R_3 = OCH_3$

109 : $R_1 = \emptyset$; $R_2 = H$; $R_3 = H$

112 : $R_1 = O$; $R_2 = CH_3$; $R_3 = H$

110 : R_1 = 2'-thienyl ; $R_2 = R_3 = H$

113 : $R_1 = R_2 = \emptyset$; $R_3 = H$

114 : R_1 = 2'-thienyl ; $R_2 = H$; $R_3 = Cl$

CHART – 18

and the tetrahydroquinolines derived therefrom and to see how the products fit in with Woodward and Hoffmann hypotheses of orbital symmetry.

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Synthesis of Heterocyclic Compounds : X Part XIX

CHAPTER II-A - CYCLODEHYDRATION OF 1-ARYLAMINO-3-ALKANOLS

Synthesis of 2,4-Disubstituted 1,2,3,4-Tetrahydroquinolines

V. N. Gogte, S. B. Kulkarni and
R. D. Tilak
N. C. L., Poona 411008.

CYCLODEHYDRATION OF 1-ARYLAMINO-3-ALKANOLS

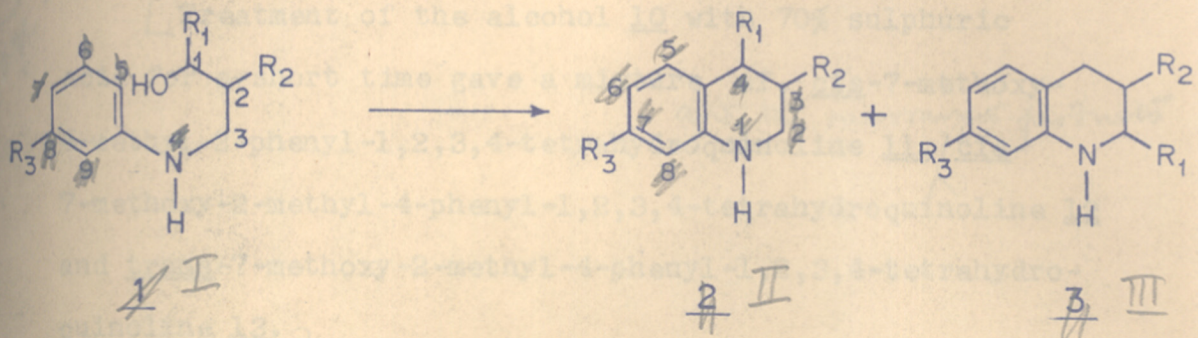
Cyclodehydration of 3-arylamino-propane-1-ol 1 by means of 70% sulphuric acid gave 3,4-disubstituted-1,2,3,4-tetrahydroquinoline 2 and/or rearranged 2,3-disubstituted-1,2,3,4-tetrahydroquinoline 3[1]. To study this rearrangement further cyclodehydration of 3-arylaminobutane-1-ols and 1-arylaminobutane-3-ols (R_1 and R_2 being CH_3, Ø, etc.) by means of 70% sulphuric acid was investigated. This reaction would lead to 2,4-disubstituted-1,2,3,4-tetrahydroquinolines 5 and/or 6 (Chart 1).

Condensation of m-anisidine 7 with benzoyl acetone 8 gave a mixture of β-(3'-methoxyphenylamino)crotonophenone 14 and ∝-(3'-methoxyphenylamino)styryl methyl ketone 9 in 43 and 57% proportion. Benzoyl acetone, a 1:3 diketone, occurs in two enolate forms A and B in 43 and 57% proportion[2].

The mixture of products 9 and 14 was separated on a spinning band column and each reduced by treatment with $NaBH_4$. Compounds 9 and 14 thus gave 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 10 and 3-(3'-methoxyphenylamino)1-phenylbutane-1-ol 15 respectively.

Condensation of m-anisidine 7 with benzal acetone 17 gave β-(3'-methoxyphenylamino)-β-phenethyl methyl ketone 18. Similarly interaction of m-anisidine 7 with crotonophenone 20 gave β-(3'-methoxyphenylamino)propyl phenyl ketone 21.

continued (Δ) on page 34



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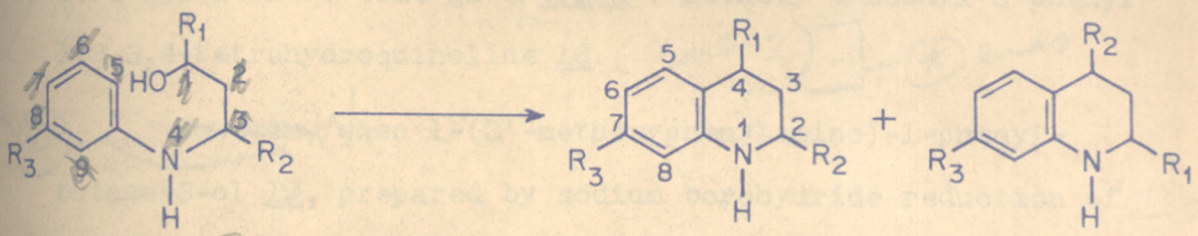

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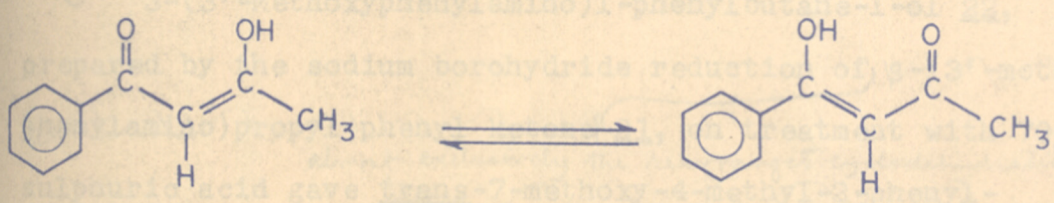


CHART – 1.

Treatment of the alcohol 10 with 70% sulphuric acid for a short time gave a mixture of, cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 11, cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 12 and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 13.

Treatment of the alcohol 15 with 70% sulphuric acid for a short time gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 16.

However, when 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 19, prepared by sodium borohydride reduction of β-(3'-methoxyphenylamino)-β-phenethyl methyl ketone 18, was treated with 70% sulphuric acid, it gave cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 11, but not 12 + 13 as

3-(3'-Methoxyphenylamino)1-phenylbutane-1-ol 22, prepared by the sodium borohydride reduction of β-(3'-methoxyphenylamino)propyl phenyl ketone 21, on treatment with 70% sulphuric acid gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 16 (Chart 3).

Identification of the tetrahydroquinolines 11, 12, 13 and 16 was based on interpretation of their PMR spectra and their correlation with authentic samples (synthesis of these compounds is discussed in Chapter II-B). The GLC analysis of 11, 12, 13 and 16 was also carried out and given in Table 1, which showed that they are all different.

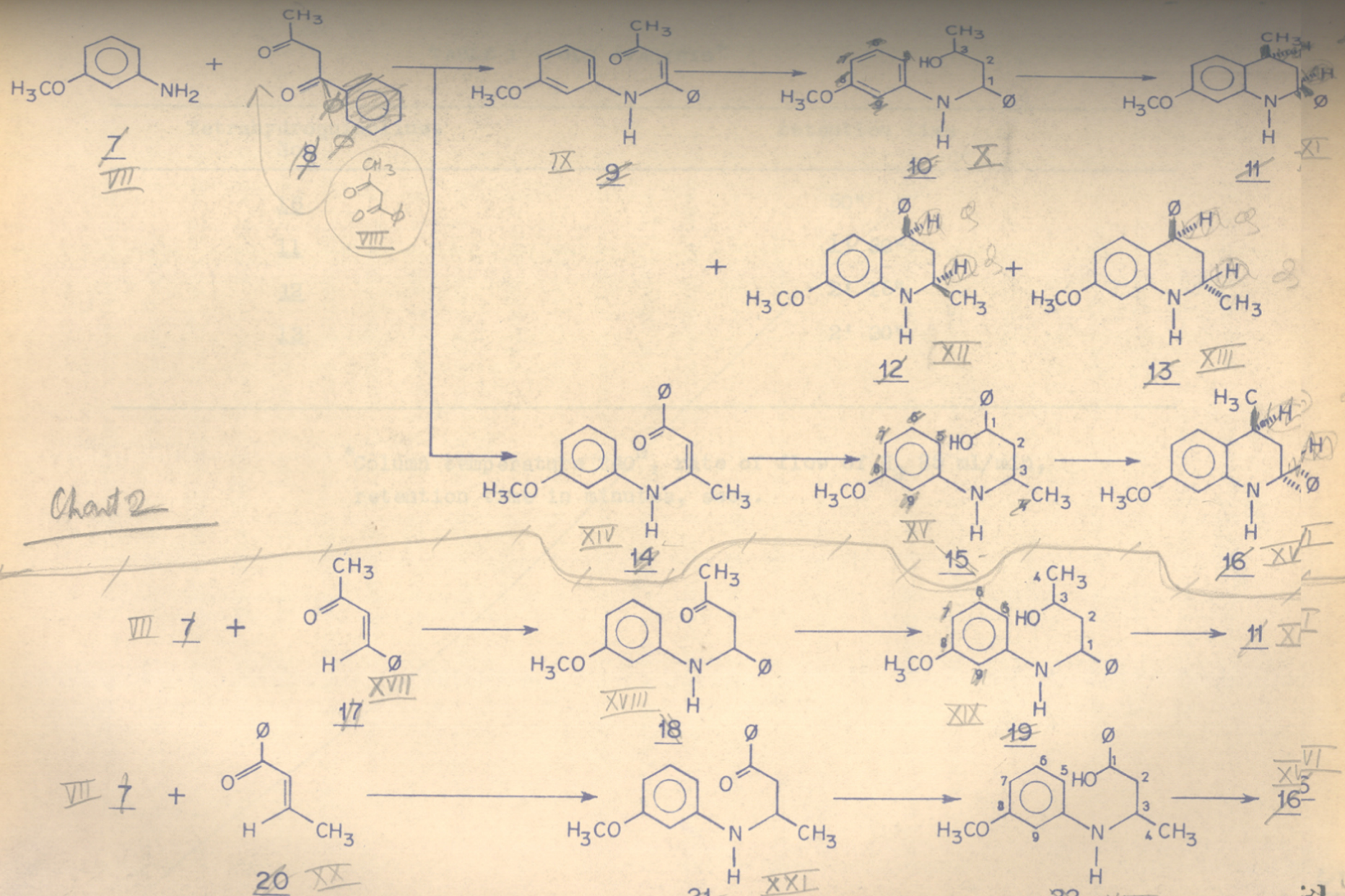


Chart 2
7
VII
8
VIII
IX
9
10
X
11
XI
12
XII
13
XIII
14
XIV
15
XV
16
XVI
17
XVII
18
XVIII
19
XIX
20
XX
21
XXI
22
XXII

CHART – 2.3.

TABLE 1 - GLC ANALYSIS*

Tetrahydroquinolines No.	retention time
16	50"
11	1' 30"
12	2' 15"
13	2' 30"

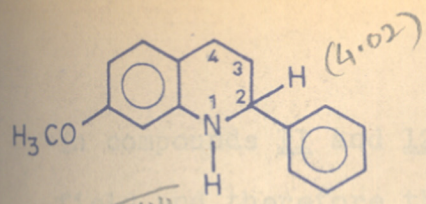
*Column temperature 240°, rate of flow of H_2 85 ml/min, retention time in minutes, secs.

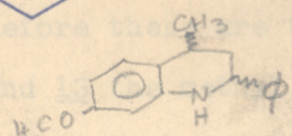
It was observed by Tilak et al.[8] that in 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 23 and 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 24 the methine proton adjacent to nitrogen (C_2-CH) appears as a triplet at a lower field (4.02)* as compared to the C_4-proton adjacent to the phenyl ring (3.96) (C_4-CH). (Chart 3).

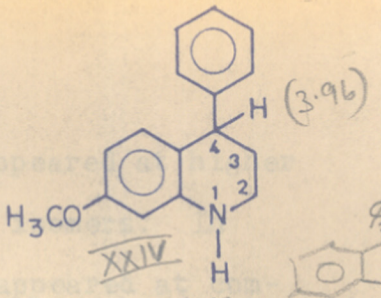
The observation that the methine proton adjacent to methyl group would always appear as a multiplet as against a triplet in case of the methine proton adjacent to phenyl group was used in sorting out the stereoisomers of 7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 26, and 7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 25 (Chart 3). In the case of compound 26 methine proton adjacent to nitrogen (C_2-CH) will appear as a triplet and C_4-CH as a multiplet, and in the case of compound 25 methine proton adjacent to nitrogen C_2-CH will appear as a multiplet and C_4-CH as a triplet in PMR spectra.

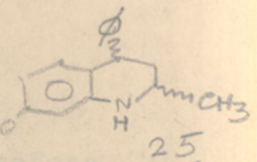
In cis derivatives the methyl group will, in general, appear at higher field than in trans compounds. Dreiding models of these compounds clearly showed that in case of cis compounds the methyl group being above or below the plane of phenyl ring will be shielded and should therefore appear at higher field than in the trans compound (Chart 3). In compounds 16 and 11 the methyl group appeared at 1.03 - 1.15 and 0.90 - 1.03 respectively. In compounds 12 and 13 methyl group appeared at 1.1 - 1.21 and 1.11 - 1.23 respectively.

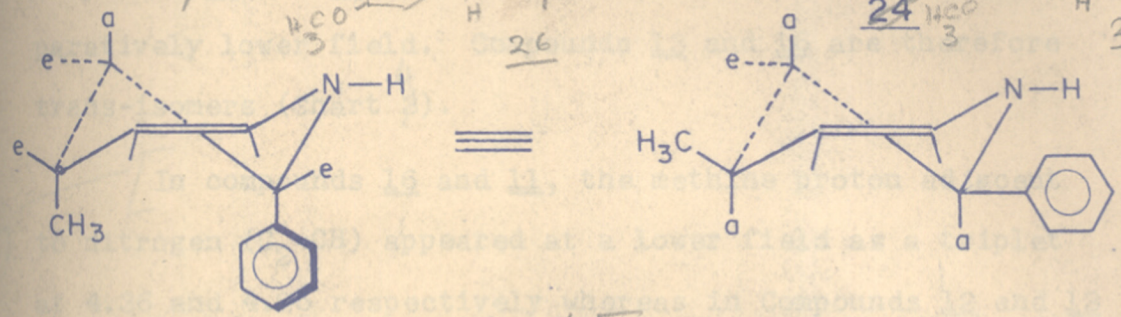
* PMR : 60 MHz, Solvent, TMS, values given in δ ppm.



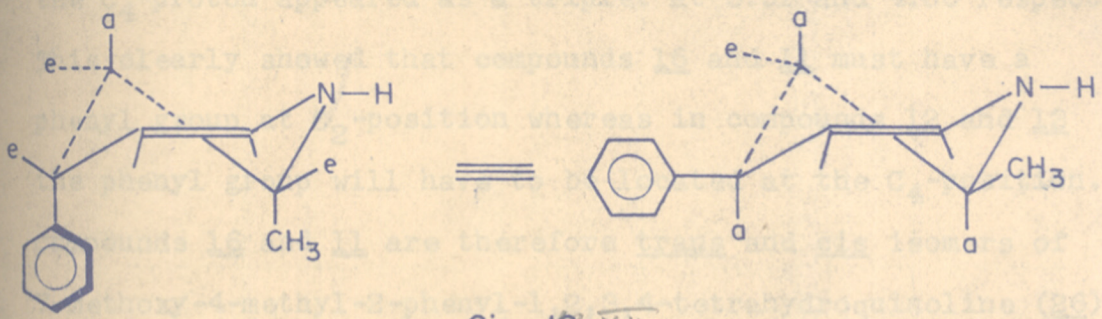




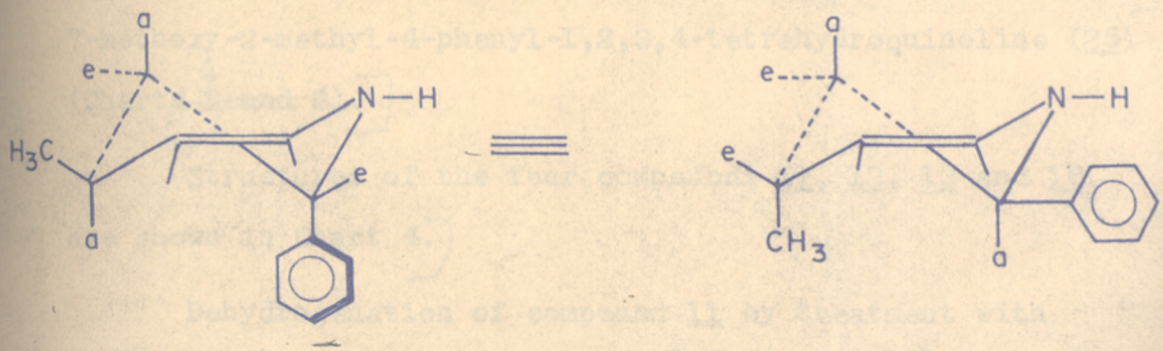




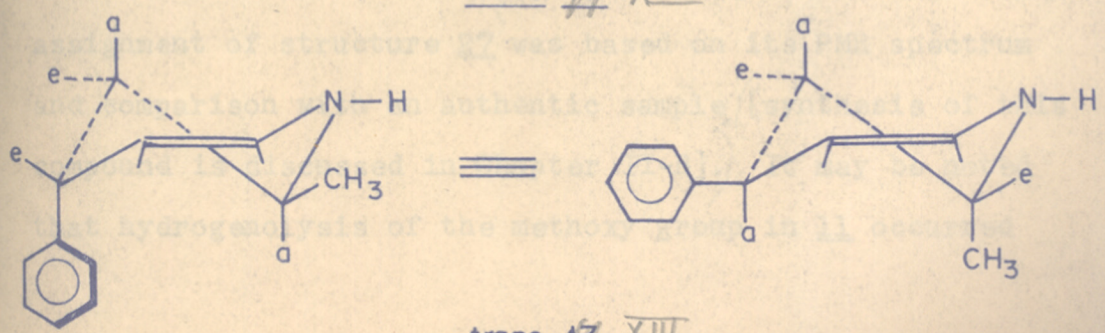
Cis 11 XI



Cis 12 XII



trans 16 XVI



trans 13 XIII

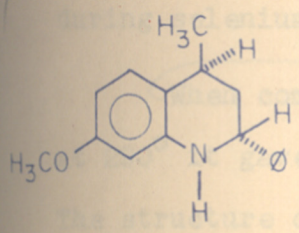
CHART – 3.

In compounds 11 and 12 methyl group appeared at higher field and therefore these are the cis isomers. In compounds 16 and 13 the methyl group appeared at comparatively lower field. Compounds 13 and 16 are therefore trans-isomers (Chart 3).

In compounds 16 and 11, the methine proton adjacent to nitrogen (C_2-CH) appeared at a lower field as a triplet at 4.36 and 4.25 respectively whereas in Compounds 12 and 13 the C_4 proton appeared as a triplet at 3.91 and 4.06 respectively. This clearly showed that compounds 16 and 11 must have a phenyl group at C_2-position whereas in compounds 12 and 13 the phenyl group will have to be located at the C_4-position. Compounds 16 and 11 are therefore trans and cis isomers of 7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (26) and Compounds 12 and 13 are cis and trans isomers of 7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (25) (Charts 2 and 3).

Structures of the four compounds 11, 12, 13 and 16 are shown in Chart 4.

Dehydrogenation of compound 11 by treatment with selenium at 290° gave 4-methyl-2-phenylquinoline 27. The assignment of structure 27 was based on its PMR spectrum and comparison with an authentic sample [synthesis of this compound is discussed in Chapter II-B]. It may be noted that hydrogenolysis of the methoxy group in 11 occurred



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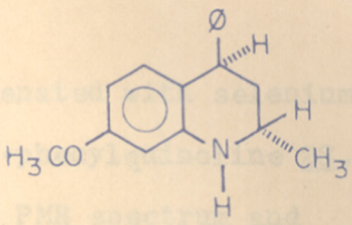

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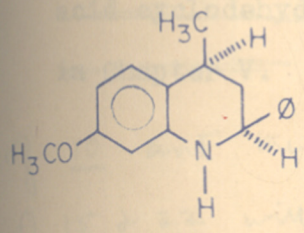

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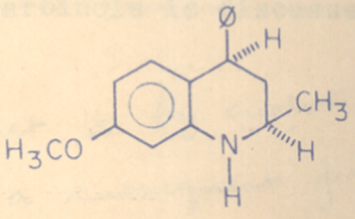
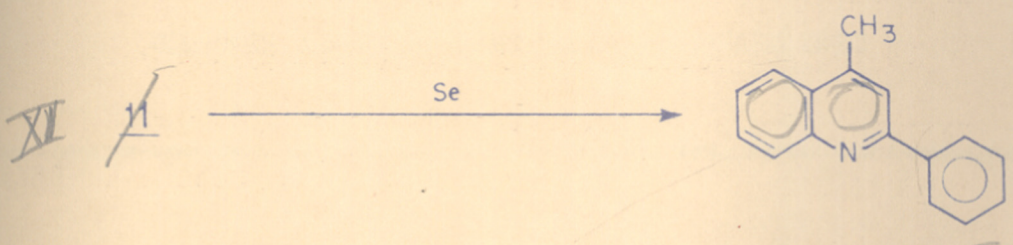


12

CHART – 4.



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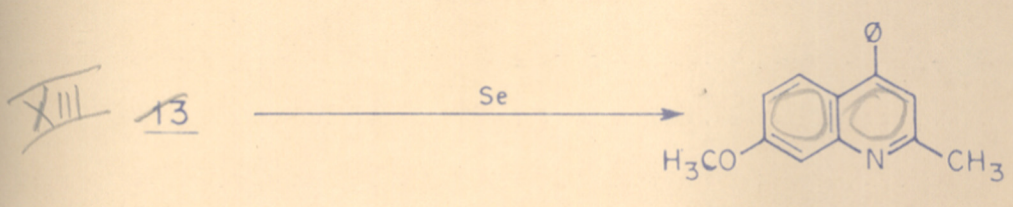


28

CHART – 5.

during selenium dehydrogenation.

When compound 13 was dehydrogenated with selenium at 290° it gave 7-methoxy-2-methyl-4-phenylquinoline 28. The structure of 28 follows from its PMR spectrum and comparison with an authentic sample (Chart 5).

The reaction mechanisms involved in the sulphuric acid cyclodehydration of the above carbinols is discussed in Chapter V.

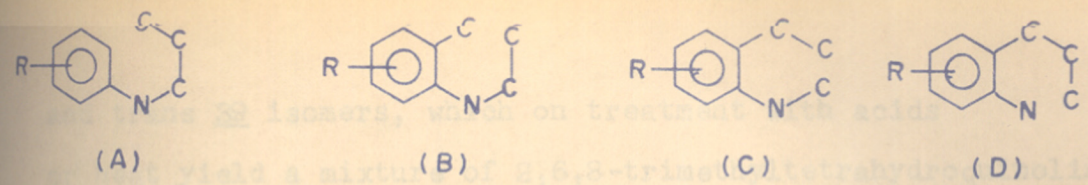
CHAPTER II-B - SYNTHESIS OF QUINOLINES

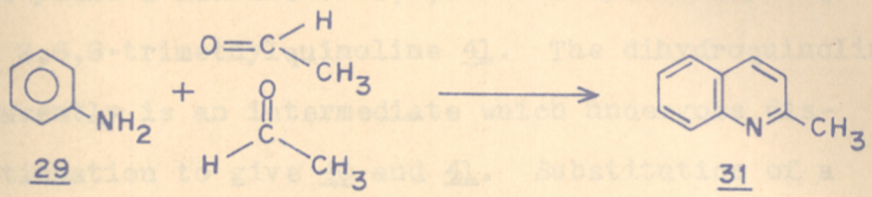
SYNTHESIS OF QUINOLINES

Substituted quinolines are found in coal tar but most quinolines are obtained by synthetic methods. The common skeleton from which the heterocyclic ring is built up are types A, B, C, D (Chart 6).

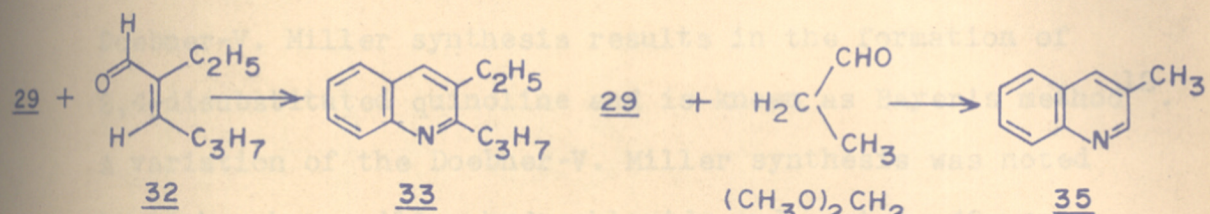
The Doebner-V. Miller synthesis is the most general of the type (A) quinoline synthesis. The Skraup synthesis which antedates the Doebner-V. Miller synthesis may be regarded as a special case of the latter method.

In 1881 Doebner and V. Miller substituted ethylene glycol for glycerine in Skraup reaction and obtained quinaldine. When aniline 29 is heated with paraldehyde 30 and sulphuric acid, quinaldine 31 is obtained[4]. When α,β-unsaturated aldehydes such as crotonic[5], tiglic[6] or cinnamic aldehyde[7] are used in this general reaction, 2,3-disubstituted quinolines are obtained. From aniline 29 and the substituted butyraldehyde 32, 2-propyl-3-ethyl-quinoline 33 is formed[8]. 3-Substituted quinolines arise from condensation of an arylamine with an aldehyde and methylal 34 as shown by the preparation of 3-methylquinoline 35 [9]. The mechanism of the Doebner - V. Miller reaction has been satisfactorily explained by Jones and his coworkers. Thus Jones, Evans and Edwards[10], Garrod and Jones[11] showed that the so-called aldol bases formed from m-xylidine 36 and crotonaldehyde 37 in the presence of iodine are cis 38

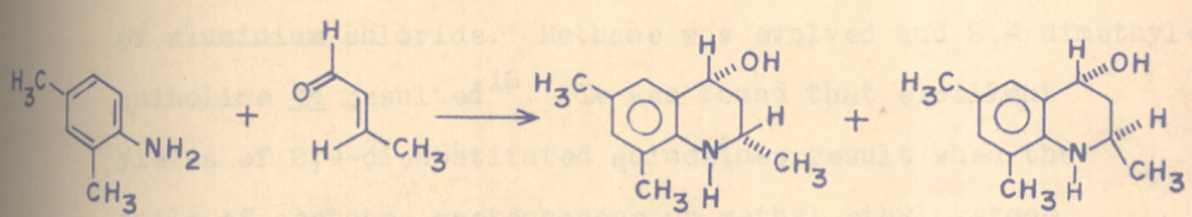




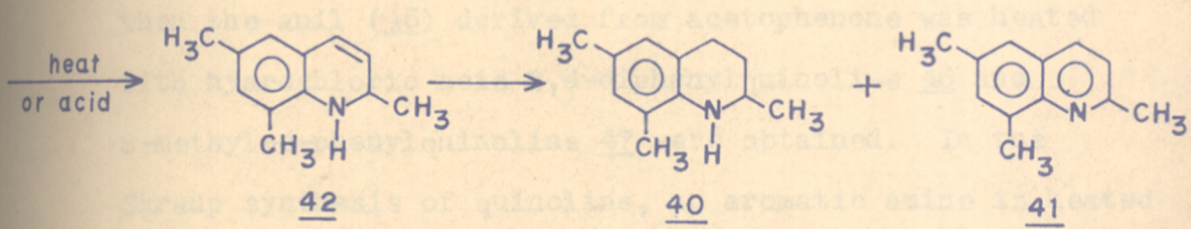
29 30 31



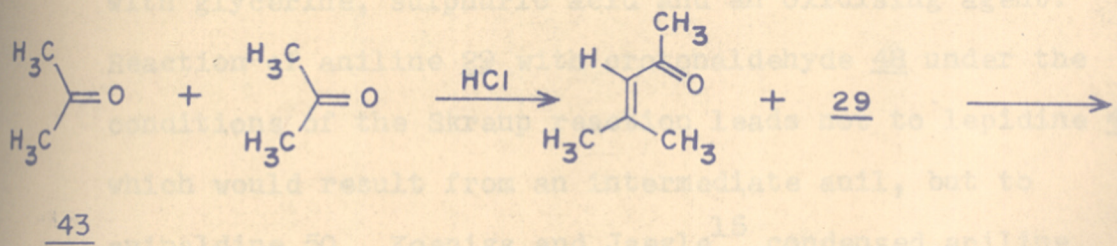
32 33 34 35



36 37 38 39



42 40 41



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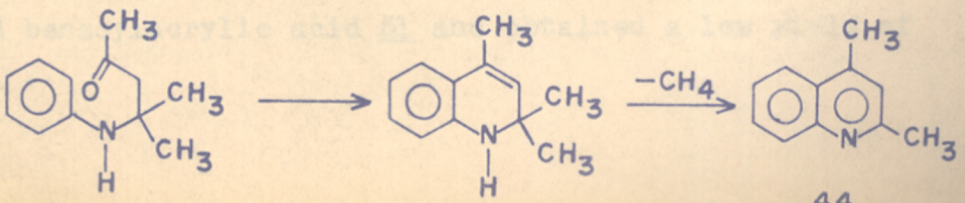


44

CHART-6

and trans 39 isomers, which on treatment with acids or heat yield a mixture of 2,6,8-trimethyltetrahydroquinoline 40 and 2,6,8-trimethylquinoline 41. The dihydroquinoline 42 apparently is an intermediate which undergoes disproportionation to give 40 and 41. Substitution of a methyl ketone for the second molecule of aldehyde in the Doebner-V. Miller synthesis results in the formation of 2,4-disubstituted quinoline and is known as Bayer's method[12]. A variation of the Doebner-V. Miller synthesis was noted by Riehm when aniline hydrochloride and acetone 43 were heated together for 3 days with phosphorus pentachloride or aluminium chloride. Methane was evolved and 2,4-dimethylquinoline 44 resulted[13]. It was found that excellent yields of 2,4-disubstituted quinolines result when the anils of acetone, acetophenone or methyl ethyl ketone are heated with hydrochloric acid at 180-200° [14]. Thus, when the anil (45) derived from acetophenone was heated with hydrochloric acid 2,4-diphenylquinoline 46 and 2-methyl-4-phenylquinoline 47 were obtained. In the Skraup synthesis of quinoline, an aromatic amine is heated with glycerine, sulphuric acid and an oxidising agent. Reaction of aniline 29 with crotonaldehyde 48 under the conditions of the Skraup reaction leads not to lepidine 49, which would result from an intermediate anil, but to quinaldine 50. Koenigs and Jaegle[15] condensed aniline 29 and benzoylacrylic acid 51 and obtained a low yield of

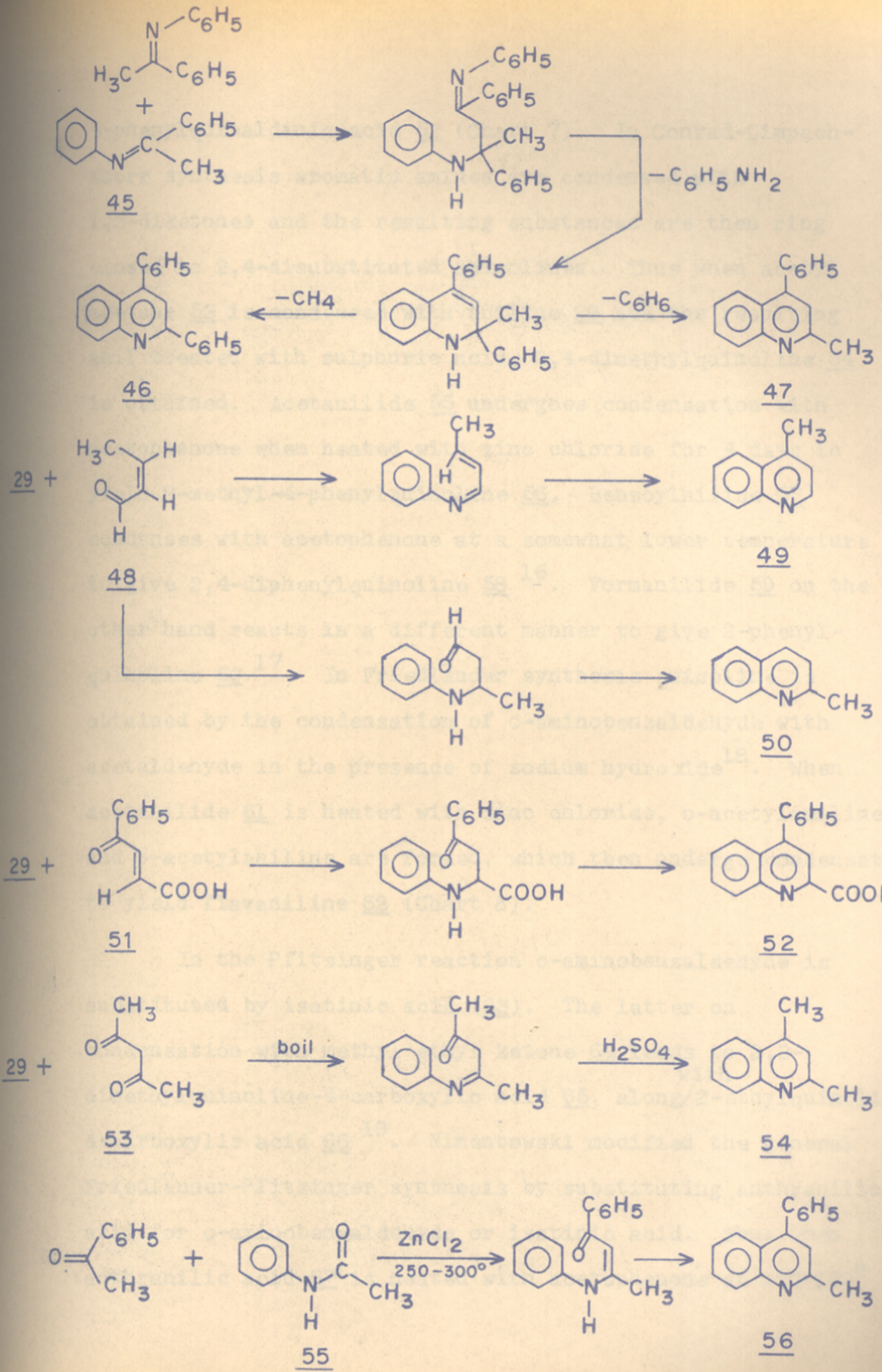
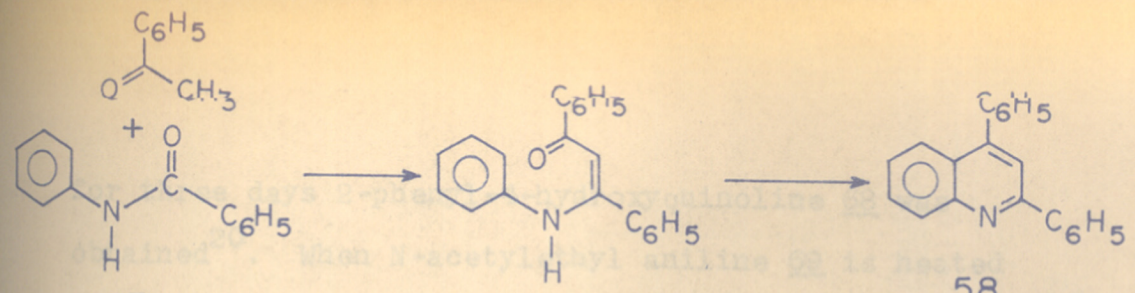

45
−C6H5NH2
−CH4
−C6H6
46
47
29 +
48
49
50
51
52
boil
H2SO4
53
54
ZnCl2
250-300°
55
56

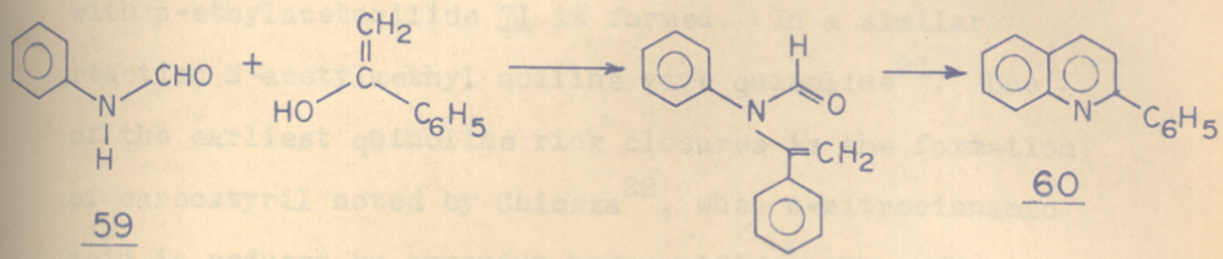
CHART-7

4-phenylquinaldinic acid 52 (Chart 7). In Conrad-Limpach-Knorr synthesis aromatic amines are condensed with 1,3-diketones and the resulting substances are then ring closed to 2,4-disubstituted quinolines. Thus when acetyl acetone 53 is condensed with aniline 29 and the resulting anil treated with sulphuric acid, 2,4-dimethylquinoline 54 is obtained. Acetanilide 55 undergoes condensation with acetophenone when heated with zinc chloride for 4 days to yield 2-methyl-4-phenylquinoline 56. Benzoylnilide 57 condenses with acetophenone at a somewhat lower temperature to give 2,4-diphenylquinoline 58 [16]. Formanilide 59 on the other hand reacts in a different manner to give 2-phenyl-quinoline 60 [17]. In Friedländer synthesis quinoline is obtained by the condensation of o-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide[18]. When acetanilide 61 is heated with zinc chloride, o-acetylaniline and p-acetylaniline are formed, which then undergo condensation to yield flavaniline 62 (Chart 8).

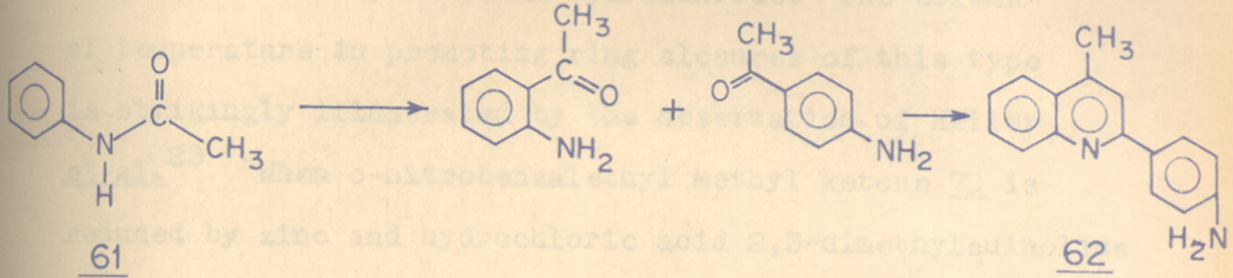
In the Pfitzinger reaction o-aminobenzaldehyde is substituted by isatinic acid (63). The latter on condensation with methyl ethyl ketone 64 leads to 2,3-dimethylquinoline-4-carboxylic acid 65, along with 2-ethylquinoline-4-carboxylic acid 66 [19]. Nimentowski modified the general Friedländer-Pfitzinger synthesis by substituting anthranilic acid for o-aminobenzaldehyde or isatinic acid. Thus when anthranilic acid 67 is heated with acetophenone at 120-130°



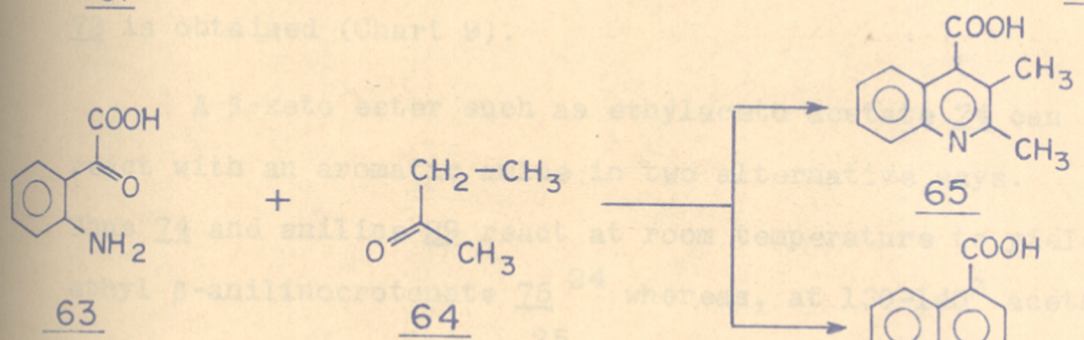
57 58



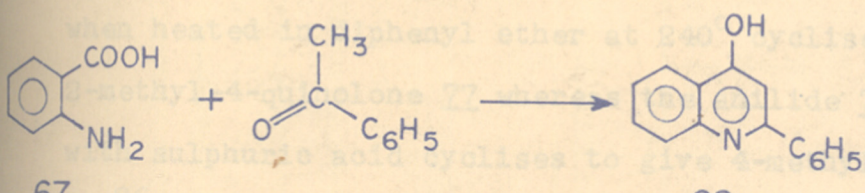
59 60



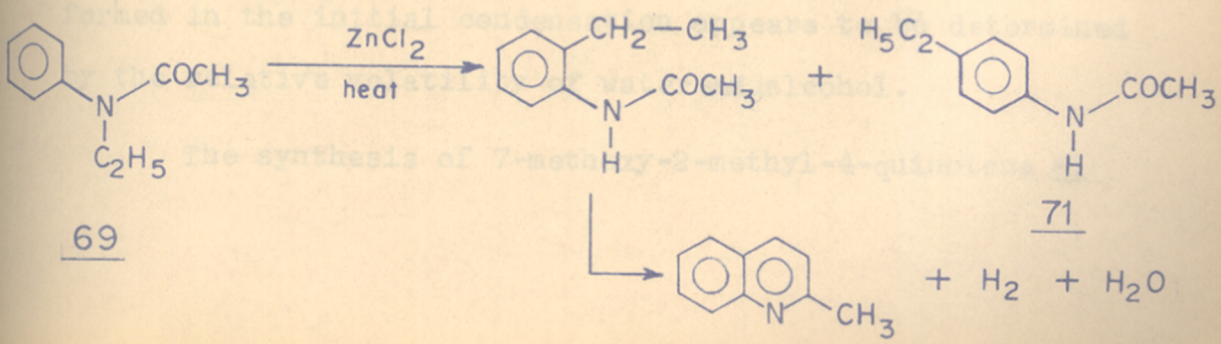
61 62



63 64 65 66



67 68



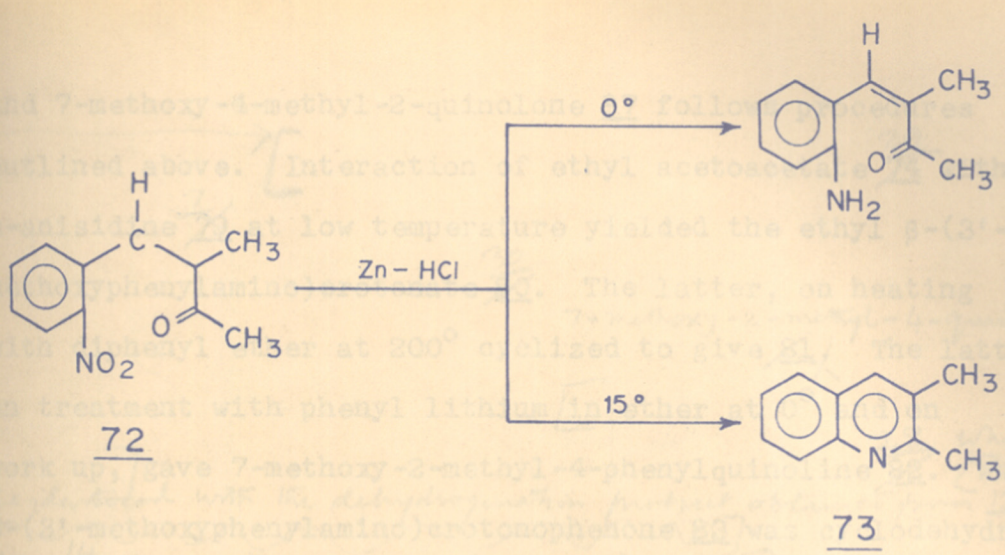
69 70 71

CHART – 8

for three days 2-phenyl-4-hydroxyquinoline 68 was obtained[20]. When N-acetylethyl aniline 69 is heated with zinc chloride a small amount of quinaldine 70 along with p-ethylacetanilide 71 is formed. In a similar reaction N-acetylmethyl aniline gave quinoline[21]. One of the earliest quinoline ring closures is the formation of carbostyril noted by Chiozza[22], when o-nitrocinnamic acid is reduced by ammonium hydrosulfide. The effect of temperature in promoting ring closures of this type is strikingly illustrated by the observation of Heller et al.[23]. When o-nitrobenzalethyl methyl ketone 72 is reduced by zinc and hydrochloric acid 2,3-dimethylquinoline 73 is obtained (Chart 9).

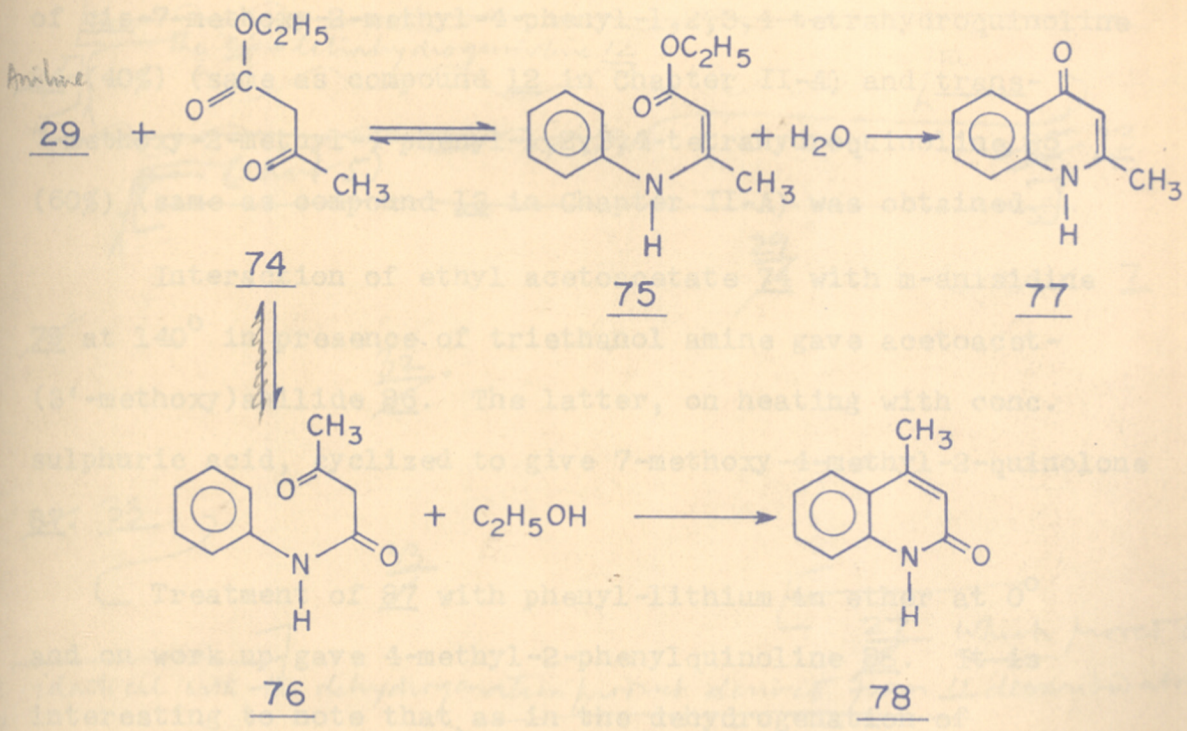
A β-keto ester such as ethylaceto acetate 74 can react with an aromatic amine in two alternative ways. Thus 74 and aniline 29 react at room temperature to yield ethyl β-anilinocrotonate 75 [24] whereas, at 130-140° aceto-acetanilide 76 is produced[25]. Ethyl β-anilinocrotonate 75 when heated in diphenyl ether at 240° cyclises to yield 2-methyl-4-quinolone 77 whereas the anilide 76 on treatment with sulphuric acid cyclises to give 4-methyl-2-quinolone 78 [26] (Chart 10). Whether the anilide or crotonate is formed in the initial condensation appears to be determined by the relative volatility of water and alcohol.

The synthesis of 7-methoxy-2-methyl-4-quinolone 81



72 73

CHART – 9.



29 74 75 77 76 78

CHART – 10.

and 7-methoxy-4-methyl-2-quinolone 87 follows procedures outlined above. Interaction of ethyl acetoacetate 74 with m-anisidine 79 at low temperature yielded the ethyl β-(3'-methoxyphenylamino)crotonate 80. The latter, on heating with diphenyl ether at 200° cyclized to give 81. The latter, on treatment with phenyl lithium in ether at 0° and on work up, gave 7-methoxy-2-methyl-4-phenylquinoline 82. When 3-(3'-methoxyphenylamino)crotonophenone 83 was cyclodehydrated by polyphosphoric acid (PPA) 82 was formed. When 82 was reduced by sodium and alcohol a mixture of cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 84 (40%) (same as compound 12 in Chapter II-A) and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 85 (60%) (same as compound 13 in Chapter II-A) was obtained.

Interaction of ethyl acetoacetate 74 with m-anisidine 79 at 140° in presence of triethanol amine gave acetoacet-(3'-methoxy)anilide 86. The latter, on heating with conc. sulphuric acid, cyclized to give 7-methoxy-4-methyl-2-quinolone 87.

Treatment of 87 with phenyl-lithium in ether at 0° and on work up gave 4-methyl-2-phenylquinoline 88. It is interesting to note that as in the dehydrogenation of cis-7-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (compound 11 in Chart 6 of Chapter II-A), interaction of 85 with phenyl-lithium also leadsto the hydrogenolysis of the

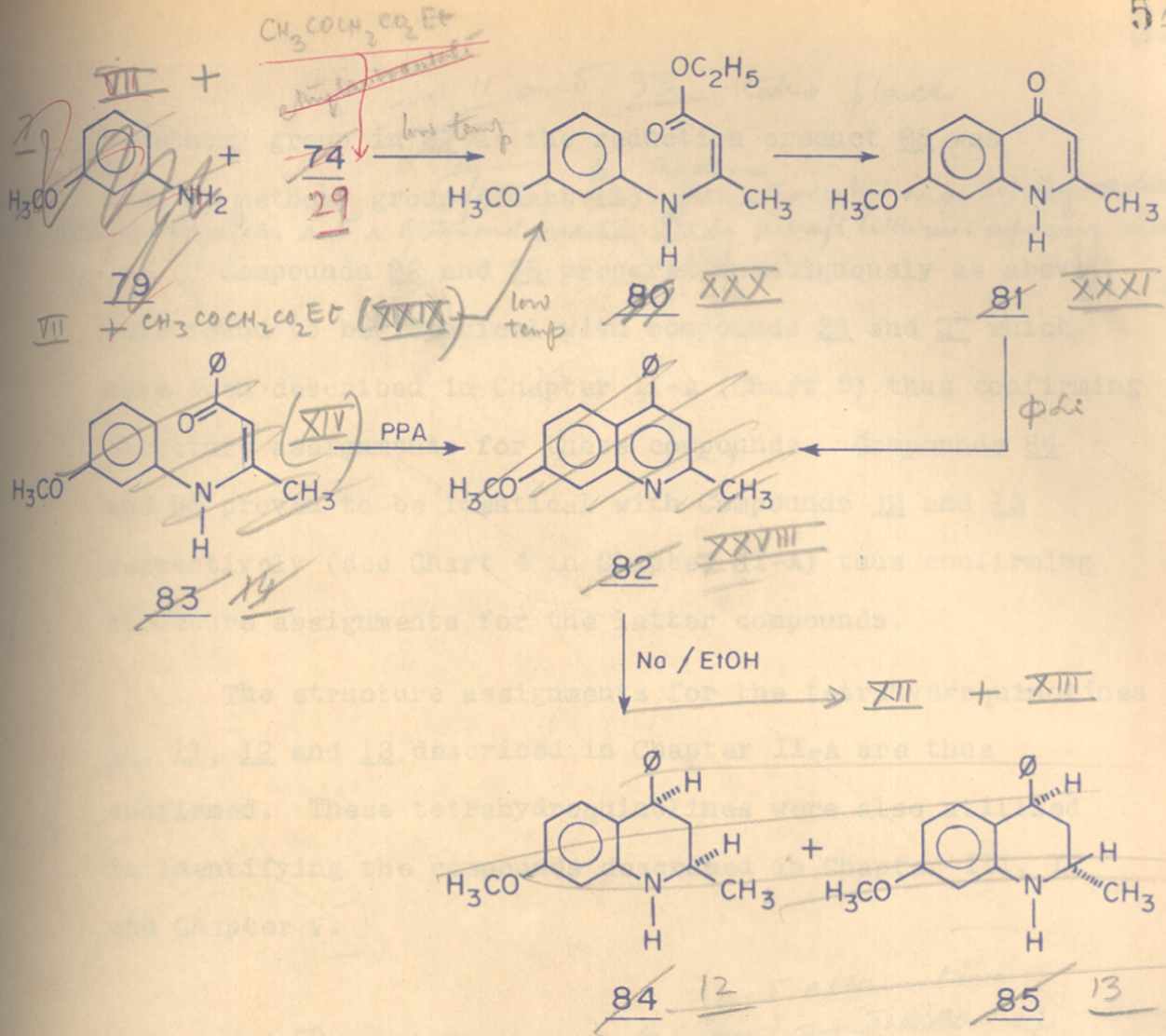


Chart 6

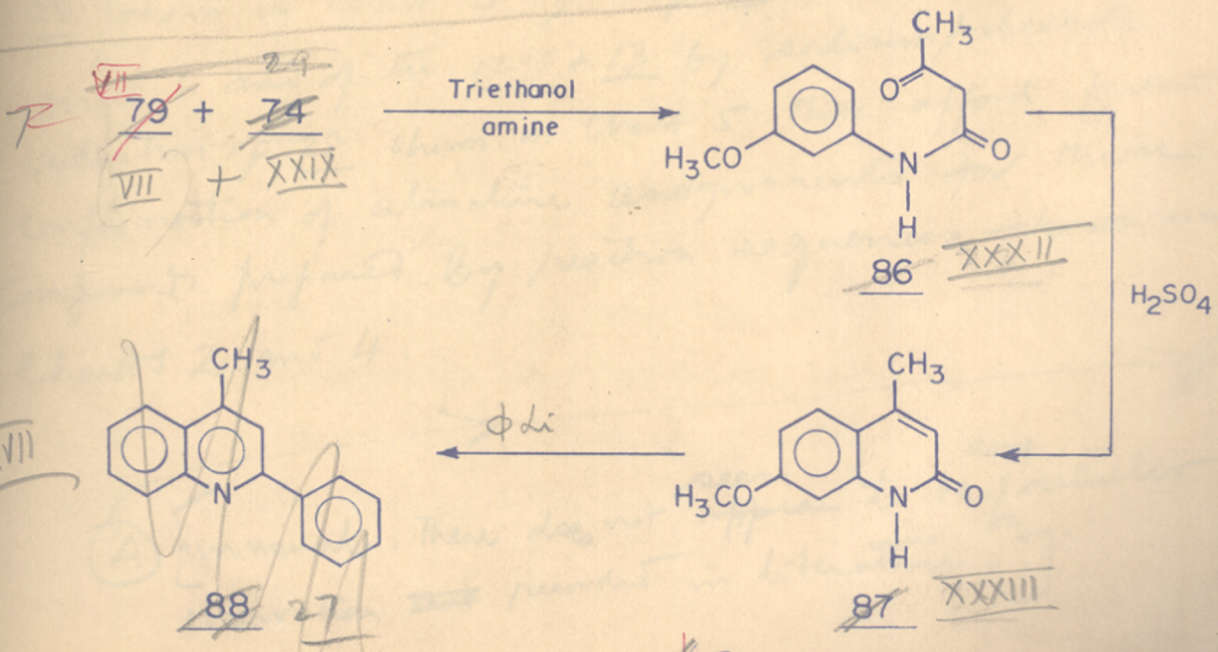


CHART – 11

7-methoxy group in 87 as the reduction product 88 was free of methoxy group (Chart 11). Compounds 82 and 88 prepared unambiguously as above, were found to be identical with compounds 28 and 27 which have been described in Chapter II-A (Chart 5) thus confirming structure assignments for these compounds. Compounds 84 and 85 proved to be identical with Compounds 12 and 13 respectively (see Chart 4 in Chapter II-A) thus confirming structure assignments for the latter compounds.

The structure assignments for the tetrahydroquinolines 16, 11, 12 and 13 described in Chapter II-A are thus confirmed. These tetrahydroquinolines were also utilised in identifying the compounds described in Chapter III, IV and Chapter V.

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

Note :- Insert C from page 2

β-(3'-Methoxyphenylamino)crotonophenone 14 and α-(3'-methoxyphenylamino)styryl methyl ketone 9:

A mixture of benzoylacetone 8 (8.1 g) and m-anisidine 7 (6.1 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave pale yellow oil. This was separated on spinning band column to give 14 pale yellow oil, b.p. 100°/0.1 mm (5.7 g; yield 43%), (Found: C, 76.3; H, 6.5; N, 5.3. $C_{17}H_{17}NO_2$ requires: C, 76.4; H, 6.4; N, 5.2%) and 9 as a solid which crystallised from methanol as pale yellow crystalline needles, m.p. 62° (7.6 g; yield 57%), (Found: C, 76.4; H, 6.3; N, 5.3). $C_{17}H_{17}NO_2$ requires: C, 76.4; H, 6.4; N, 5.2%).

The compounds 9 and 14 were characterised by their PMR spectra. The PMR spectrum of 14 shows the following characteristics:

Compound 14: D_2O exchangeable NH proton 10.58, broad, s; C_2, 5.78, s, 1P; C_3, 2.0, d, 3P; $C_{5,6,7,9}$ and C_1-phenyl, 6.03 - 7.93, m, 9P; C_8, 3.56, s, 3P.

The PMR spectrum of 9 shows the following characteristics:

Compound 9: D_2O exchangeable NH proton 10.93, broad, s; C_2, 5.78, s, 1P; C_1, 2.01, s, 3P; $C_{5,6,7,9}$ and C_3-phenyl; 6.63 - 8.03, m, 9P; C_8, 3.73, s, 3P.

β-(3'-Methoxyphenylamino)-β-phenethyl methyl ketone 18:

A mixture of benzalacetone 17 (7.3 g) and m-anisidine 7 (6.1 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 18 as pale yellow oil, b.p. 110°/0.1 mm (9.4 g; yield 70%) (Found: C, 75.8; H, 7.1; N, 5.2). $C_{17}H_{19}NO_2$ requires: C, 75.8; H, 7.1; N, 5.2%).

The compound 18 was characterised by its PMR spectrum which shows the following characteristics:

D_2O exchangeable NH proton 4.03, broad, s; C_1, 1.73, s, 3P; C_2, 2.73, d, 2P; C_3, 5.03, t, 1P; $C_{5,6,7,9}$ and C_3-phenyl, 5.93 - 7.40, m, 9P; C_8, 3.50, s, 3P.

β-(3'-Methylphenylamino)propyl phenyl ketone 21:

A mixture of crotonophenone 20 (7.3 g) and m-anisidine 7 (6.1 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 21 as pale yellow oil, b.p. 115°/0.1 mm (10.0 g; yield 75%) (Found: C, 75.7; H, 7.1; N, 5.1). $C_{17}H_{19}NO_2$ requires: C, 75.8; H, 7.1; N, 5.2%).

The compound 21 was characterised by its PMR spectrum which shows the following characteristics:

D_2O exchangeable NH proton 4.02 broad, s; C_2 and C_3, 2.21 - 2.60, m, 3P; C_3, 1.02, s, 3P; $C_{5,6,7,9}$ and C_1-phenyl, 5.98 - 7.03, m, 9P; C_8, 3.52, s, 3P.

General method for reduction of the above ketones with sodium borohydride:

A mixture of the ketones and sodium borohydride and ethanol 50 ml was kept at room temperature for 20 minutes. The mixture was warmed on boiling water bath for further twenty minutes. After dilution with water (200 ml), the mixture was extracted with ether. The ether extract was washed twice with water, dried over anhydrous sodium sulphate and ether removed. The carbinol thus obtained was then distilled under vacuum. Details of these experiments are given in Table 1. PMR spectra of alcohols are given in Table 2.

Cyclodehydration of 3-(3'-methoxyphenylamino)1-phenyl-butane-1-ol 15 by sulphuric acid:

The alcohol 15 was characterised by its IR and PMR spectra.

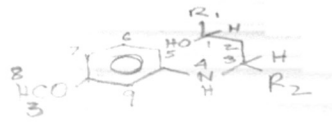
To a mixture of alcohol 15 (2 g) and crushed ice (10 g), 70% sulphuric acid (20 ml) was added gradually with shaking. This mixture was warmed on boiling water bath for thirty minutes. The mixture was kept at room temperature for 48 hr. and then neutralised with aq. sodium hydroxide and then extracted with ether. The ether extract on work up gave an oil (1.7 g), which was chromatographed using silica gel and benzene as eluent. The fraction eluted gave brownish oil which on distillation gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 16 as colourless oil, b.p.

TABLE I - Arylaminobutanols
REDUCTION OF KETONES

Starting ketone No.	Starting ketone Wt.g	$NaBH_4$ used Wt.g	Carbinol No.	Yield Wt.g	Yield %	Colour	M.p. or B.p. °C	Analysis *Found % C	Analysis *Found % H	Analysis *Found % N
14	2.0	0.3	15	1.8	90	Pale yellow oil.	125°/9.56 x 10^{-3} mm	75.4	7.3	5.5
9	1.5	0.4	10	1.2	80	Pale yellow oil.	115°/9.56 x 10^{-3} mm	75.6	7.2	5.1
18	3.0	0.8	19	2.7	90	Colourless oil.	160°/9.56 x 10^{-3} mm	75.3	7.5	5.2
21	3.0	0.6	22	2.5	83	Yellowish oil.	140°/9.56 x 10^{-3} mm	75.4	7.6	5.1

*Compounds 15, 10, 19 and 22 ($C_{17}H_{21}NO_2$) require: C, 75.3; H, 7.7; N, 5.1%.

TABLE 2 - PMR SPECTRA OF 3-ARYLAMINOALKANOLS

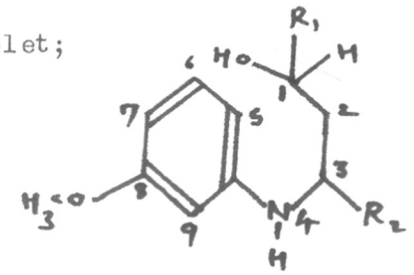


Assignments and intensities

Carbinol No.	C_1	C_2	C_3	R_1	R_2	C_8	$C_{5,6,7,9}$	NH and OH
15 R_1 = Ø R_2 = CH_3	4.35(t) 1P	1.70-2.01(m) 3P		7.25(m) 5P	1.05(d) 3P	3.66(s) 3P	6.06-7.25 (m) 4P	3.16 (s) 2P
10 R_1 = CH_3 R_2 = Ø	1.66-1.93(m) 3P		4.51 (t) 1P	1.1(d) 3P	7.23(m) 5P	3.53(s) 3P	5.90-7.23(m) 4P	2.81 (s) 2P
22 R_1 = Ø R_2 = CH_3	4.30(t) 1P	1.65-2.01 (m) 3P		7.10(m) 5P	1.10(d) 3P	3.55(s) 3P	6.0-7.05(m) 4P	3.1 (s) 2P
19 R_1 = CH_3 R_2 = Ø	1.60-1.90 (m) 3P		4.45 (t) 1P	1.05(d) 3P	7.30(m) 5P	3.60(s) 3P	5.95-7.25(m) 4P	3.05(s) 2P

s = singlet; d = doublet; t = triplet; m = multiplet;

values in ppm. P = proton/s.



$100^{\circ}/9.56 \times 10^{-3}$ mm (1.6 g yield;91.2%) (Found: C, 80.9; H, 7.2; N, 6.0. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

The PMR spectrum of 16 shows the following characteristics: D_2O exchangeable NH proton, 3.16, broad, s, 1P; C_4, 1.15, d, 3P; C_4 and C_3, 1.7 - 2.1, m, 3P; C_2, 4.36, t, 1P; $C_{5,6,8}$, C_2-phenyl, 6.0 - 7.23, m, 8P; C_7, 3.61, s, 3P.

Cyclodehydration of 1-(3'-methoxyphenylamino)1-phenyl-butane-3-ol 10 by sulphuric acid:

The alcohol 10 was characterised by its IR and PMR spectra.

Compound 10 (2 g) was treated with 70% sulphuric acid (20 ml) as above. Work up gave a brownish oil (1.6 g) which was chromatographed on silica gel using benzene as eluent. The first fraction gave cis 7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 11 which crystallised from methanol in colourless needles, m.p. 92° (0.47 g; yield 29%) (Found: C, 80.9; H, 7.0; N, 5.8. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%). The second fraction on distillation gave cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 12 as colourless liquid,b.p. $150^{\circ}/9.56 \times 10^{-3}$ mm (0.59 g; yield, 37%) (Found: C, 80.8; H, 7.1; N, 5.7. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%). The third fraction gave trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 13 which crystallised from methanol in colourless needles, m.p. 91° (0.54 g; yield 34%) (Found: C, 81.1; H, 6.9; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8;

N, 5.6%).

Compound 11 was characterised by its PMR spectrum :— and also by its mass spectrum (m/e 253). The PMR spectrum (Fig.2) shows the following characteristics:

D_2O exchangeable NH proton 3.6, s, 1P; C_4, 1.09, d, 3P; C_4 and C_3, 1.7 - 1.93, m, 3P; C_2, 4.25, t, 1P; $C_{5,6,8}$ and C_2-phenyl 6.0 - 7.05, m, 8P; C_7, 3.6, s, 3P.

Compound 12 was characterised by its PMR spectrum and also by its mass spectrum (m/e 253). The PMR spectrum :— (Fig.3) shows the following characteristics:

D_2O exchangeable NH proton 3.53 broad, s, 1P; C_2, 0.97, d, 3P; C_2 and C_3, 1.73 - 1.93, m, 3P; C_4, 3.91, t, 1P; $C_{5,6,8}$ and C_4-phenyl, 5.90 - 6.95, m, 8P; C_7, 3.66, s, 3P.

Compound 13 was characterised by its PMR spectrum and also by its mass spectrum (m/e 253). The PMR spectrum (Fig.4) shows the following characteristics:

D_2O exchangeable NH proton 3.53 broad, s, 1P; C_2, 1.16, d, 3P; C_3 and C_2, 1.6 - 2.13, m, 3P; C_4, 4.05, t, 1P; $C_{5,6,8}$ and C_4-phenyl, 5.90 - 7.16, m, 8P; C_7, 3.66, s, 3P.

Cyclodehydration of 1-(3'-methoxyphenylamino)1-phenyl-butane-3-ol 19 by sulphuric acid:

The alcohol 19 was characterised by its IR and PMR spectra.

Compound 19 (2 g) was treated with 70% sulphuric acid (20 ml) as above. Work up gave a brownish coloured oil

(1.5 g) which was chromatographed on silica gel using benzene as eluent. The eluted fraction gave cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 11 which crystallised from methanol in colourless needles, m.p. 92° (1.45 g; yield 80%) (Found: C, 80.9; H, 6.9; N, 5.3. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

Cyclodehydration of 3-(3'-methoxyphenylamino)-1-phenylbutane-1-ol 22 by sulphuric acid:

The alcohol 22 was characterised by its IR and PMR spectra.

Compound 22 (2 g) was treated with 70% sulphuric acid (20 ml) as above. Work up gave a brownish coloured oil, (1.8 g) which was chromatographed on silica gel using benzene as eluent. The eluted fraction gave brownish oil which on distillation gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 16 as colourless liquid, b.p. 100°/ 9.56×10^{-3} mm (1.75 g; yield 83%) (Found: C, 81.3; H, 6.9; N, 5.4. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

Dehydrogenation of cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 11:

Compound 11 (0.1 g) was mixed with selenium (0.04 g) and heated to 290° for 2 hr., reaction product was extracted with chloroform and the extract was then chromatographed on silica gel using benzene as eluent. The eluted fraction gave 4-methyl-2-phenylquinoline 27 as colourless plates from methanol, m.p. 67° (0.055 g; yield 55%) (Found: C, ~~81.5~~ 87.5;

H, 5.5; N, 5.8. $C_{16}H_{13}NO$ requires: C, 81.6; H, 5.5; N, 5.9%).

The compound 27 was characterised by its PMR spectrum which shows the following characteristics:

C_4, 1.3, s, 3P; $C_{3,5,6,7,8}$ and C_2-phenyl, 6.63 - 7.26, m, 10P.

Dehydrogenation of trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 13:

Compound 13 (0.1 g) was mixed with selenium (0.04 g) and heated to 290° for 2 hr., reaction product was extracted with chloroform and the extract was then chromatographed on silica gel using benzene as eluent. The eluted fraction gave 7-methoxy-2-methyl-4-phenylquinoline 28 as colourless plates from ethanol, m.p. 110° (0.05 g; yield 50%) (Found: C, 82.4; H, 5.4; N, 5.6. $C_{17}H_{15}NO$ requires: C, 82.5; H, 5.3; N, 5.6%).

The compound 28 was characterised by its PMR spectrum which shows the following characteristics:

C_2, 2.66, s, 3P; C_7, 3.93, s, 3P; $C_{3,5,6,8}$ and C_4-phenyl, 7.0 - 7.43, m, 9P.

Preparation of Ethyl-β-(3'-methoxyphenylamino)crotonate 80:

A mixture of ethylacetoacetate 74 (13 g), m-anisidine 79 (12.3 g) and glacial acetic acid (1 cc) in benzene (100 ml) was heated on boiling water bath for 3 hr. and water was removed azeotropically. When the theoretical quantity of water (2 ml) was collected, the solvent was evaporated and reaction product was distilled under vacuum which gave ethyl-β-(3'-methoxyphenyl-amino)-crotonate 80 as a pale yellow oil, b.p. 170°/12 mm (20 g,

yield 80%) (Found: C, 66.3; H, 7.1; N, 5.9. $C_{13}H_{17}NO_3$ requires: C, 66.3; H, 7.2; N, 5.9%).

Compound 80 was characterised by its IR spectrum which shows typical ketone 1700 and -NH 3390 cm^{-1}.

Preparation of 7-Methoxy-2-methyl-4-quinolone 81:

A mixture of compound 80 (5.1 g) and diphenyl ether (25 ml) was heated at 200° for 0.5 hr., the reaction mixture was cooled and to it pet. ether was added and mixture stirred, when white solid was obtained which crystallised from methanol to give 7-methoxy-2-methyl-4-quinolone 81 as colourless prisms, m.p. 232° (3.1 g; yield 60%) (Found: C, 69.7; H, 5.6; N, 7.4. $C_{11}H_{11}NO_2$ requires: C, 69.8; H, 5.8; N, 7.4%).

Compound 81 was characterised by its mass spectrum (m/e 189) and IR spectrum which shows the typical ketone 1660 and NH 3390 cm^{-1}.

Preparation of 7-Methoxy-2-methyl-4-phenyl quinoline 82:

To a mixture of compound 81 (1.0 g) and sodium dried ether (60 ml), small pieces of lithium metal (0.4 g) were added slowly. To this solution ethereal bromobenzene (5 g) solution was added slowly and then reaction mixture was refluxed for 2 hr. Ether was evaporated and reaction mixture after cooling was poured over crushed ice and treated with dil. sulphuric acid (10 ml). Then neutralised with aqueous sodium hydroxide. Extraction with ether and work up gave crude solid (0.7 g) which was chromatographed on silica gel

with benzene as eluent. The eluted fraction gave 7-methoxy-2-methyl-4-phenyl quinoline 82 as colourless plates from methanol, m.p. 110° (0.68 g; yield 50%) (Found: C, 82.4; H, 5.3; N, 5.5. $C_{17}H_{13}NO$ requires: C, 82.5; H, 5.3; N, 5.6%).

Preparation of 7-methoxy-2-methyl-4-phenyl-quinoline 82 with PPA:

A mixture of 3-(3'-methoxyphenylamino)crotonophenone 83 (1.0 g) and PPA (5 g) [prepared from o-phosphoric acid 75% 4 ml and phosphorus pentoxide (2 g)] was heated on a boiling water bath for 3 hr. with occasional shaking. The dark red reaction mixture was diluted with cold water (100 ml) and then neutralised with aqueous sodium hydroxide and finally extracted with ether, which on evaporation gave a crude solid (0.65 g) which was chromatographed on silica gel using benzene as eluent. The eluted fraction gave 7-methoxy-2-methyl-4-phenyl-quinoline 82 as colourless plates from methanol, m.p. 110° (0.6 g; yield 60%) (Found: C, 82.4; H, 5.2; N, 5.7. $C_{17}H_{13}NO$ requires: C, 82.5; H, 5.3; N, 5.6%).

Conversion of 28 to 12 & 13

Compound 82 (0.5 g) thus obtained was dissolved in absolute ethanol (50 ml) and the solution treated with sodium (0.4 g) which was added in small quantities. The mixture was heated under reflux on boiling water bath for 1 hr. Work up gave an oil which was chromatographed on silica gel and using benzene as eluent. The eluted fraction gave a mixture of cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 84 and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 85 as colourless oil, b.p. 150°/9.56 x 10^{-3} mm (0.36 g;

yield 72%) (Found: C, 81.1; H, 6.9; N, 3.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

VPC of the oil showed that it was a mixture of 12 & 13 present in a ratio of 40:60.

This mixture consisted of 84 and 85 in 40:60 ratio as indicated by its Vapour Phase Chromatography.

Preparation of Acetoacet-(3'-methoxy)anilide 86:

A mixture of ethylacetoacetate (13 g) 74, m-anisidine 79 (12.3 g) and triethanol amine (0.24 g) in dry xylene (100 ml) was refluxed in oil bath at 140° for 0.5 hr. The solvent xylene was evaporated along with ethanol formed in the reaction, the reaction product was distilled under vacuum, which gave 86 as pale yellow oil, b.p. 185°/12 mm (17.5 g; yield 76%) (Found: C, 63.7; H, 6.4; N, 6.82. $C_{11}H_{13}NO$ requires: C, 63.7; H, 6.3; N, 6.7%).

30 mts. Xylene was continuously distilled out. Work up gave 32 which on distillation gave a

32 showed peaks at 1700 & 3390 cm^{-1} for the CO & NH groups.

Compound 86 was characterised by its IR spectrum which shows typical ketone 1700 and -NH 3390 cm^{-1}.

Cyclodehydration of Acetoacet-(3'-methoxy)anilide 86: 7-Methoxy-4-methyl-2-quinolone, 33

To a mixture of 86 (3 g), and crushed ice (10 g), and 70% sulphuric acid (25 ml) was added gradually with shaking. The mixture was warmed on water bath for thirty minutes and kept at room temperature for 48 hr. The mixture was then neutralised with aqueous sodium hydroxide and extracted with ether. The ether extract on work up gave 7-methoxy-4-methyl-2-quinolone 87 as colourless plates from methanol, m.p. 200° (1.5 g; yield 50%) (Found: C, 70.0; H, 5.8; N, 7.6. $C_{11}H_{11}NO_2$ requires: C, 69.8; H, 5.8; N, 7.4%).

as gradually heated in a boiling water bath for 30 mts & the

Compound 87 was characterised by its mass spectrum (m/e 189) and IR spectrum which shows typical ketone 1660 and NH 3390 cm^{-1}.

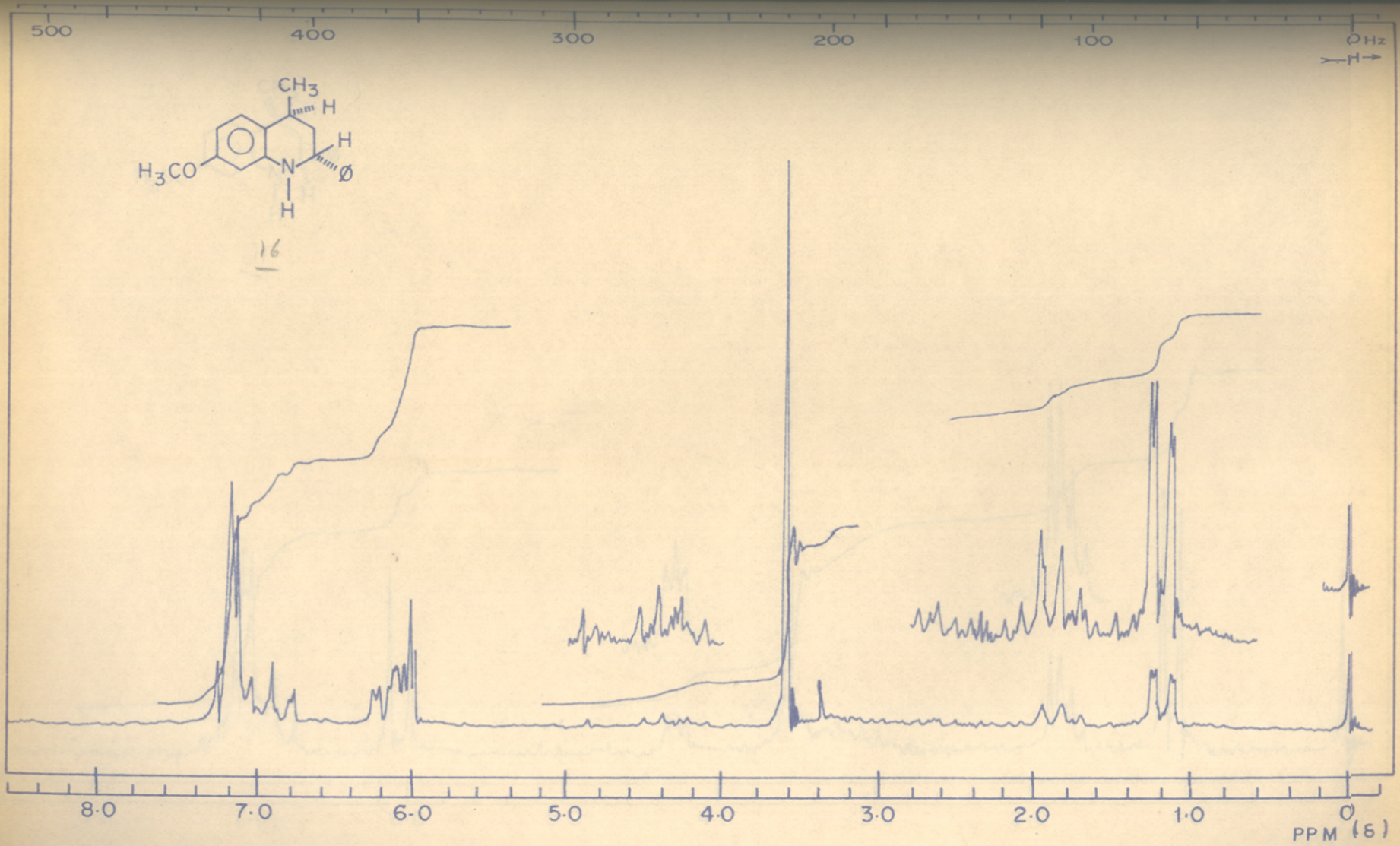
Preparation of 4-Methyl-2-phenylquinoline 88:

To a mixture of compound 87 (1.0 g) and sodium dried ether (60 ml), small pieces of lithium metal (0.4 g) were added slowly. To this solution ethereal bromobenzene (5 g) solution was added slowly and reaction mixture was refluxed for 2 hr. Ether was evaporated and reaction mixture after cooling was poured over crushed ice and treated with dilute sulphuric acid (10 ml). Then neutralised with aqueous sodium hydroxide. Extraction with ether and work up gave crude solid (0.4 g) which was chromatographed on silica gel and benzene as eluent. The eluted fraction gave 4-methyl-2-phenylquinoline 88 as colourless plates from methanol, m.p. 67° (0.38 g; yield 38%) (Found: C, 81.6; H, 5.5; N, 5.9. $C_{16}H_{13}NO$ requires: C, 81.6; H, 5.5; N, 5.9%).

Compound 88 was characterised by its PMR spectrum which shows the following characteristics:

C_4, 1.3, s, 3P; $C_{3,5,6,7,8}$ and C_2-phenyl, 6.63 - 7.26, m, 10P.

ILLUSTRATIONS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400
300
200
100
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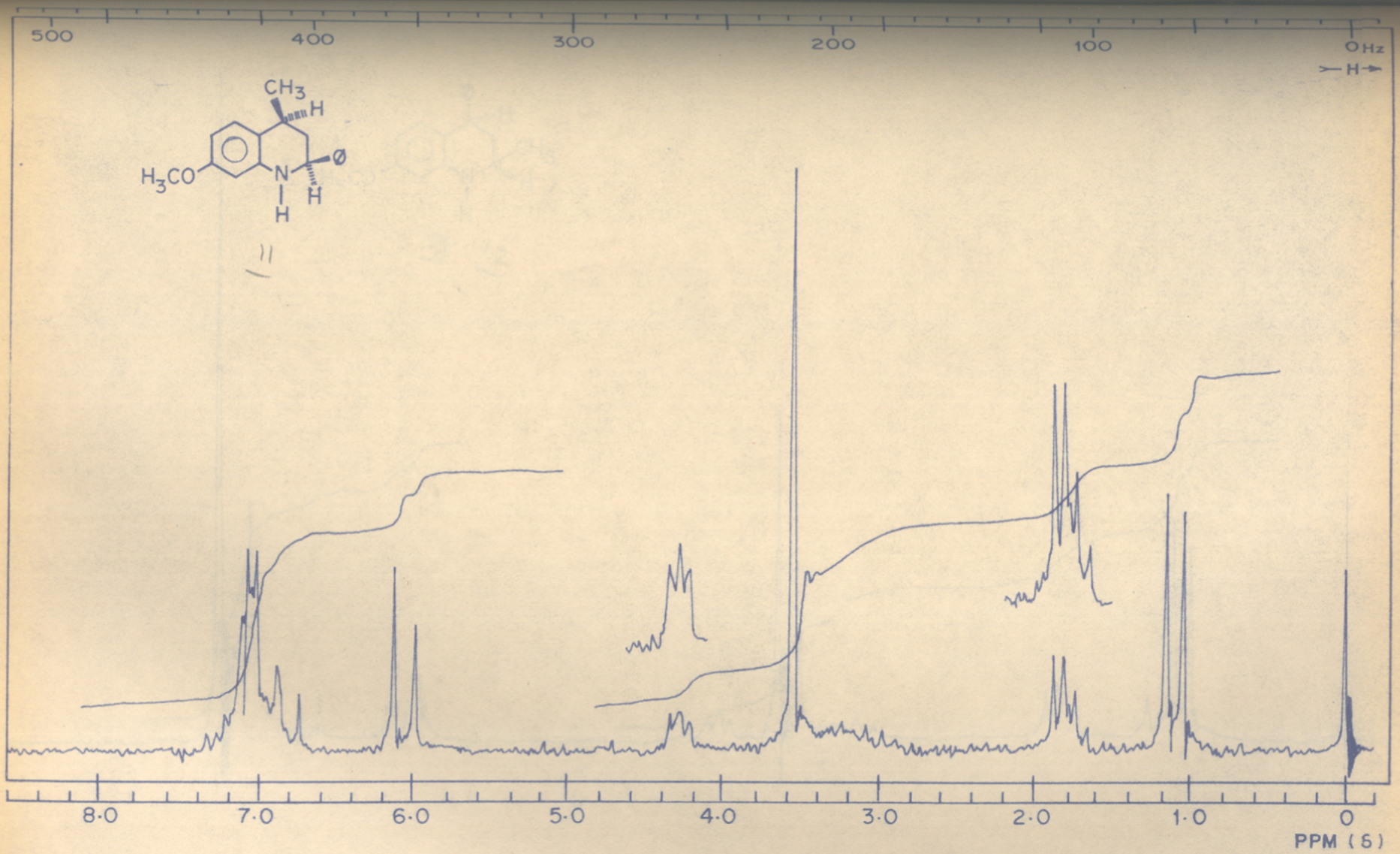
CH3
H
H
H3CO
N
Ø
H
16
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG .– 1 .


500
400
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H
CH3
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H3CO
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H
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H
8·0
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4·0
3·0
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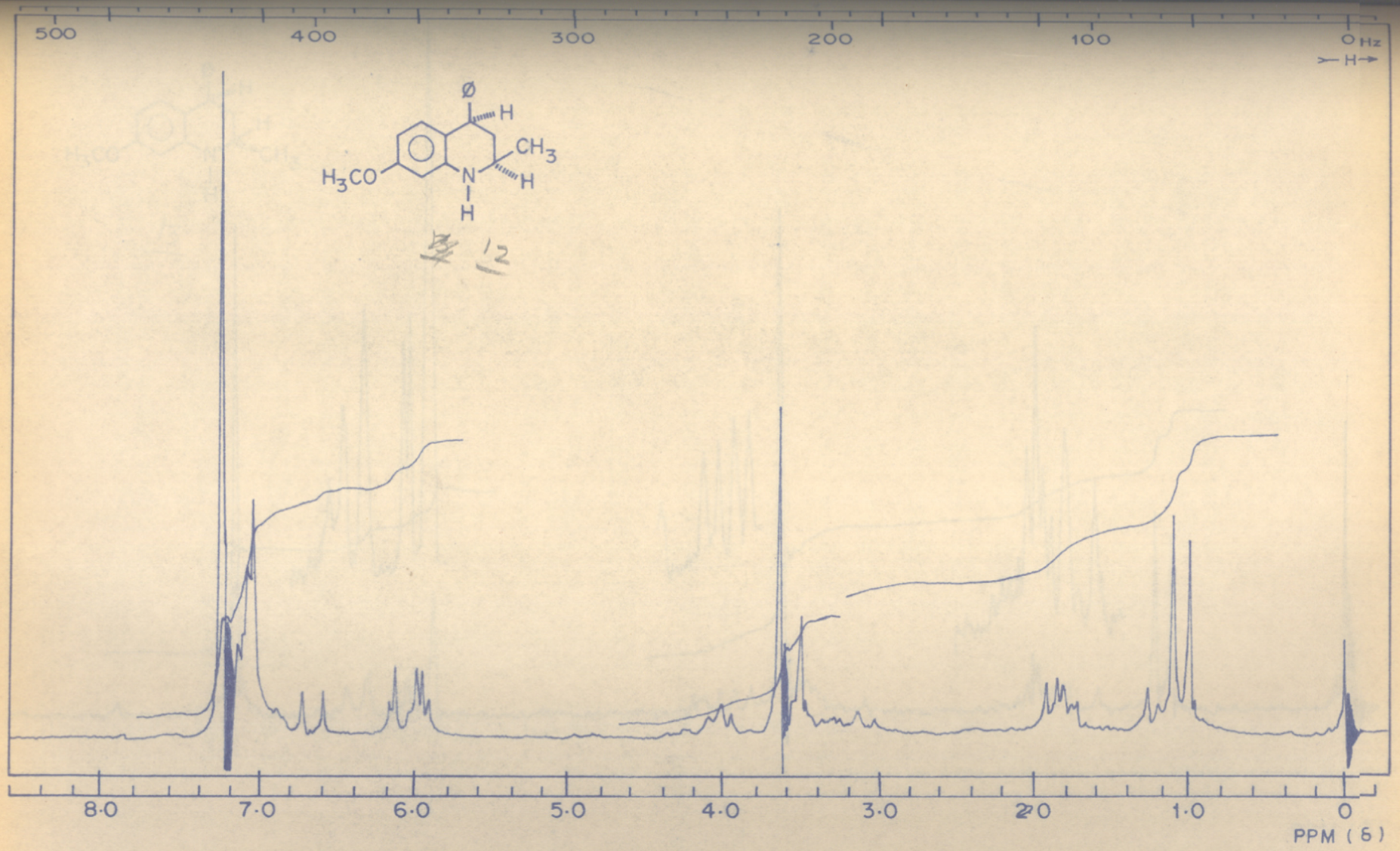
1·0
0
PPM (δ)

FIG. - 2.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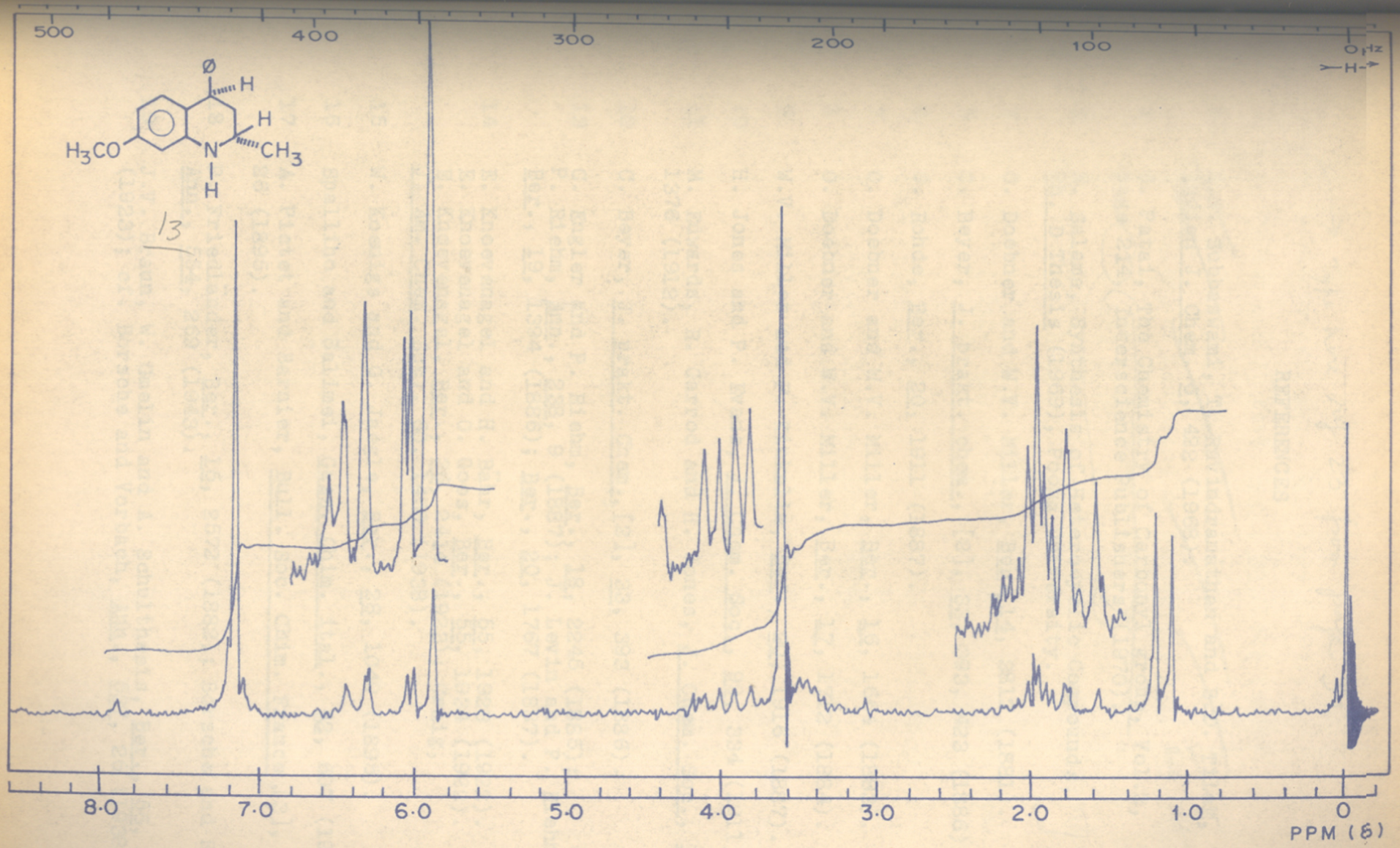
Ø
H
CH3
H3CO
N
H
12
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. 3.


500
400
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200
100
0 Hz
H
Ø
H
H
H_3CO
N
CH_3
H
13
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. – 4.

69

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CHAPTER III - SYNTHESIS OF N-ARYLAZETIDINES

SYNTHESIS OF N-ARYLAZETIDINES

Literature survey revealed that an early claim to the preparation of N-phenylazetidine had been discounted[1]. Scholtz[2] in 1899 had claimed to have prepared 1-phenylazetidine 1 by the reaction of 1,3-dibromopropane 2 with aniline 3. Fisher et al.[3] in 1960 repeated Scholtz's preparation in which the diamine 4 was distilled whereby a low boiling fraction could be separated into aniline and a material answering to Scholtz's description of the azetidine 1. However, it was found that the compound was in fact 1,2,3,4-tetrahydroquinoline 5 (Chart 1).

Later Deady et al.[4] tried two possible synthesis of N-arylazetidines. The first involved the cyclisation of intermediates of the type 6. Deady et al. mentioned that when N-(3-bromopropyl)aniline 6 (prepared from the corresponding alcohol) was treated with hot sodium hydroxide solution, 1,2,3,4-tetrahydroquinoline 5 and other product named julolidine 8 were obtained. If ethanolic sodium hydroxide was used, the major product N-(3-ethoxypropyl)aniline 9 and a small amount (7-8%) of N-phenylazetidine 1 together with some N-(3-propylene)aniline 10 was also formed (Chart 2).

The second approach which Deady et al.[4] tried involved nucleophilic substitution of parent azetidine by a suitably substituted benzene derivative. Azetidine was reacted with several substituted mono and dibromo aromatic

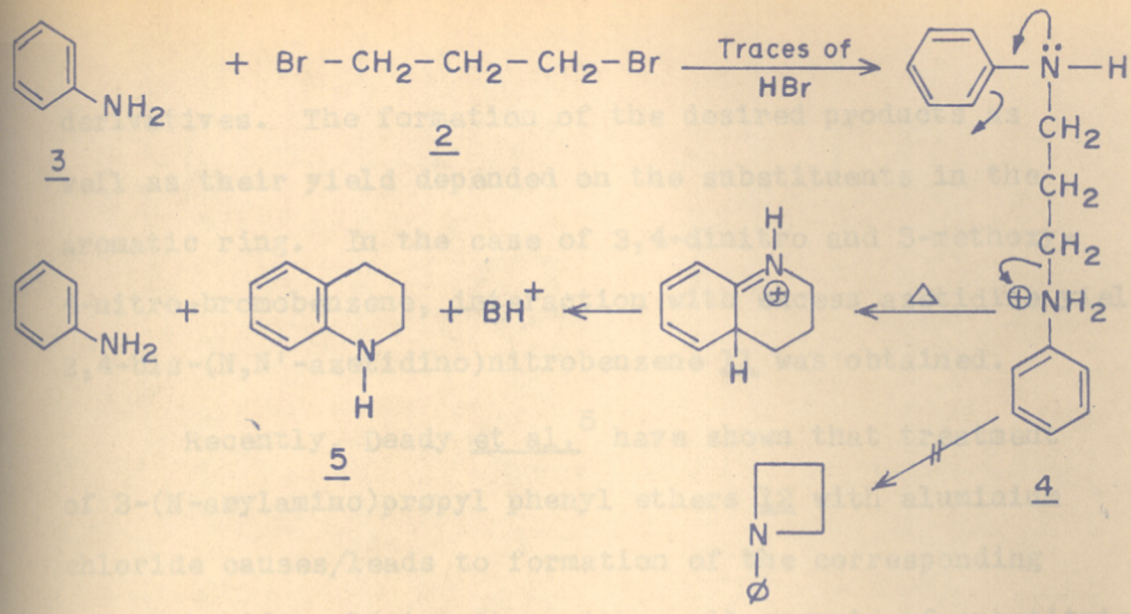


CHART-1

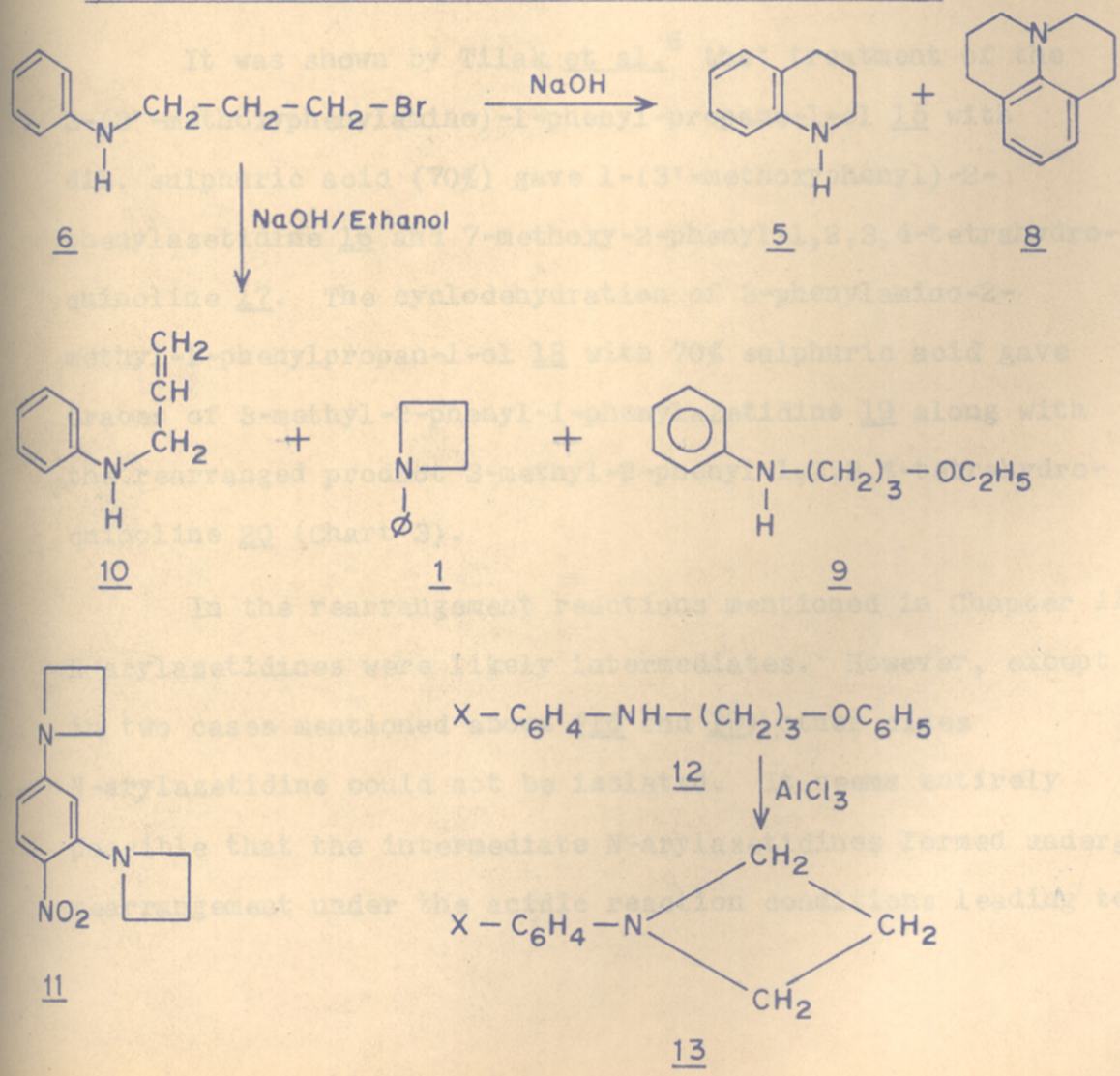


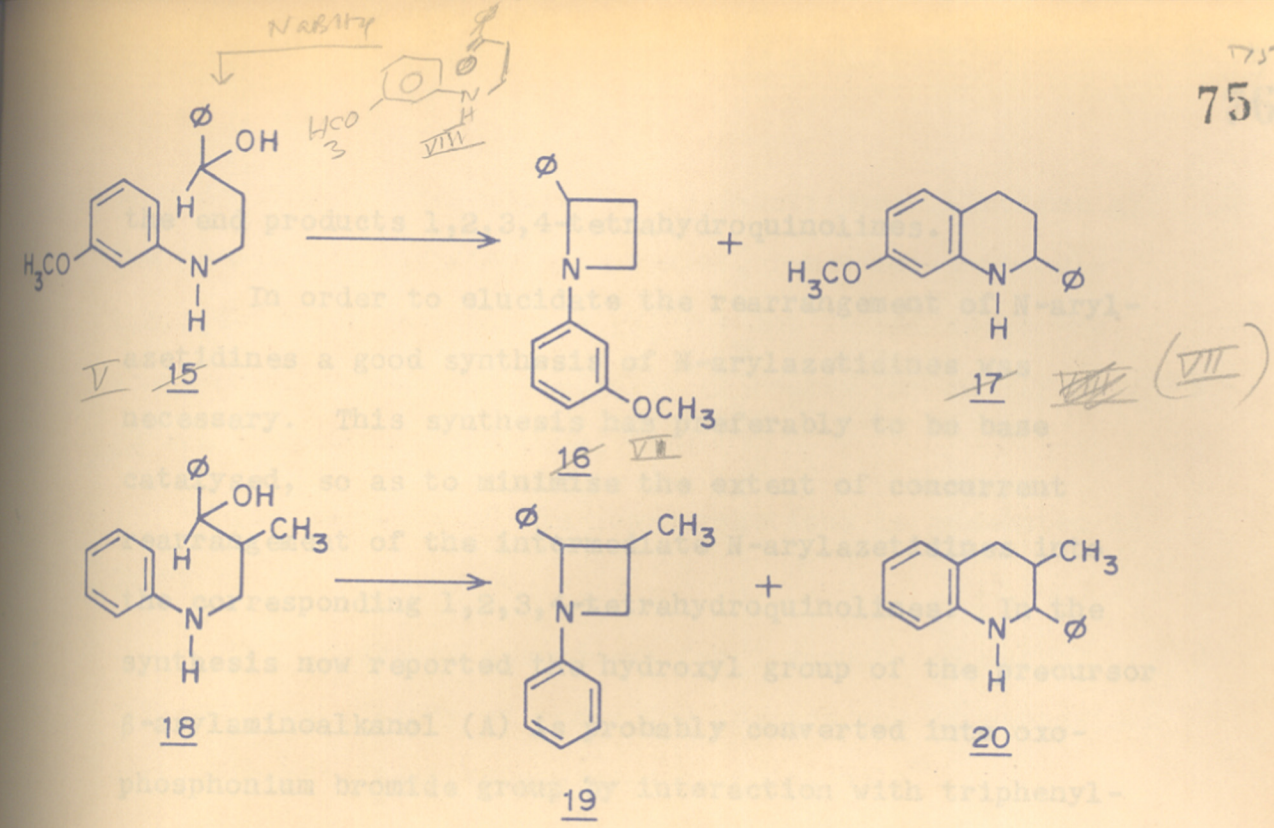
CHART-2

derivatives. The formation of the desired products as well as their yield depended on the substituents in the aromatic ring. In the case of 3,4-dinitro and 3-methoxy-4-nitro-bromobenzene, interaction with excess azetidine yielded 2,4-bis-(N,N'-azetidino)nitrobenzene 11 was obtained.

Recently, Deady et al.[5] have shown that treatment of 3-(N-arylamino)propyl phenyl ethers 12 with aluminium chloride causes/leads to formation of the corresponding N-arylazetidine 13 together with small amounts of substituted tetrahydroquinolines and 3-chloropropylanilines 14.

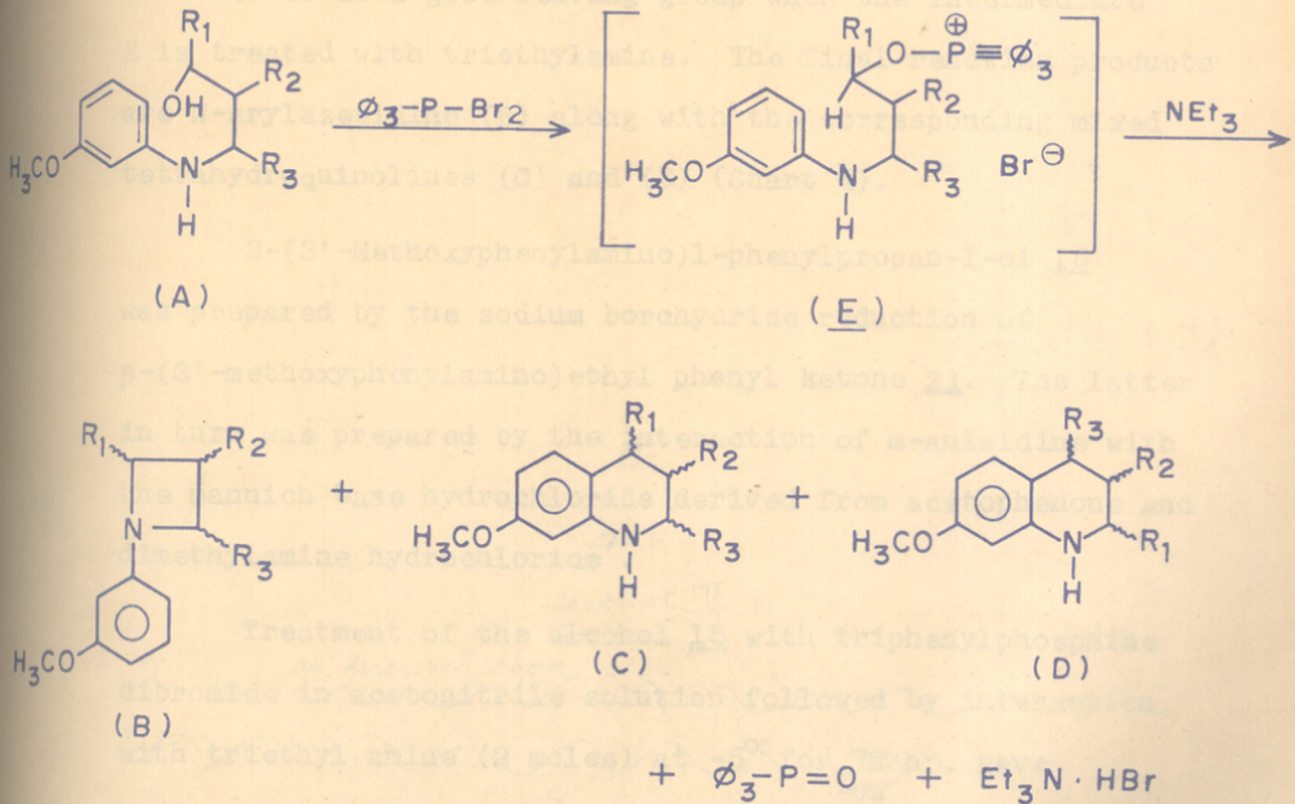
It was shown by Tilak et al.[6] that treatment of the 3-(3'-methoxyphenylamino)-1-phenyl-propane-1-ol 15 with dil. sulphuric acid (70%) gave 1-(3'-methoxyphenyl)-2-phenylazetidine 16 and 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 17. The cyclodehydration of 3-phenylamino-2-methyl-1-phenylpropan-1-ol 18 with 70% sulphuric acid gave traces of 3-methyl-2-phenyl-1-phenylazetidine 19 along with the rearranged product 3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 20 (Chart 3).

In the rearrangement reactions mentioned in Chapter II-A, N-arylazetidines were likely intermediates. However, except in two cases mentioned above (16 and 19) other cases N-arylazetidine could not be isolated. It seems entirely possible that the intermediate N-arylazetidines formed undergo rearrangement under the acidic reaction conditions leading to



15 16 17 18 19 20

CHART-3



(A) (E) (B) (C) (D)

CHART-4

the end products 1,2,3,4-tetrahydroquinolines.

In order to elucidate the rearrangement of N-aryl-azetidines a good synthesis of N-arylazetidines was necessary. This synthesis has preferably to be base catalysed, so as to minimise the extent of concurrent rearrangement of the intermediate N-arylazetidines into the corresponding 1,2,3,4-tetrahydroquinolines. In the synthesis now reported the hydroxyl group of the precursor β-arylaminoalkanol (A) is probably converted into oxo-phosphonium bromide group by interaction with triphenyl-phosphine dibromide. The triphenyl oxophosphonium moiety then serves as a good leaving group when the intermediate E is treated with triethylamine. The final reaction products are N-arylazetidine (B) along with the corresponding mixed tetrahydroquinolines (C) and (D) (Chart 4).

3-(3'-Methoxyphenylamino)1-phenylpropan-1-ol 15 was prepared by the sodium borohydride reduction of β-(3'-methoxyphenylamino)ethyl phenyl ketone 21. The latter in turn was prepared by the interaction of m-anisidine with the mannich base hydrochloride derived from acetophenone and dimethylamine hydrochloride[7].

Treatment of the alcohol 15 with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethyl amine (2 moles) at -5° for 72 hr. gave 1-(3'-methoxyphenyl)-2-phenylazetidine 16 and the rearranged

product, 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 17. The normal cyclodehydration product, 7-methoxy-4-phenyl-1,2,3,4-tetrahydroquinoline 17A was not formed under the above conditions. The azetidine 16 rearranges slowly to 17 even at room temperature.

The sequence of the above reactions is presented in Chart 5.

The structure assignment for Compounds 16 and 17 follows from a study of their PMR spectra and by comparison with authentic samples prepared unambiguously.[8]

3-(3'-Methoxyphenylamino)-2-propyl phenyl ketone 22 on reduction with sodium borohydride yielded 3-(3'-methoxy-phenylamino)-2-methyl-1-phenyl-propan-1-ol 23. Compound 22 was prepared by the interaction of m-anisidine with mannich base hydrochloride derived from propiophenone and dimethylamine hydrochloride[7].

The alcohol 23 on treatment with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethylamine (2 moles) at -5° for 72 hr. gave 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 24, 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 25 and the rearranged product 7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 26.

Compounds 25 and 26 have already been reported by Tilak et al.[9,6] who obtained them by acid catalysed

cyclodehydration of 22 and 23 (Charts 6 and 7).

The structure assignment for Compounds 25 and 26 follows from a study of their PMR spectra and by comparison with authentic samples prepared by unambiguous methods.[9,6]

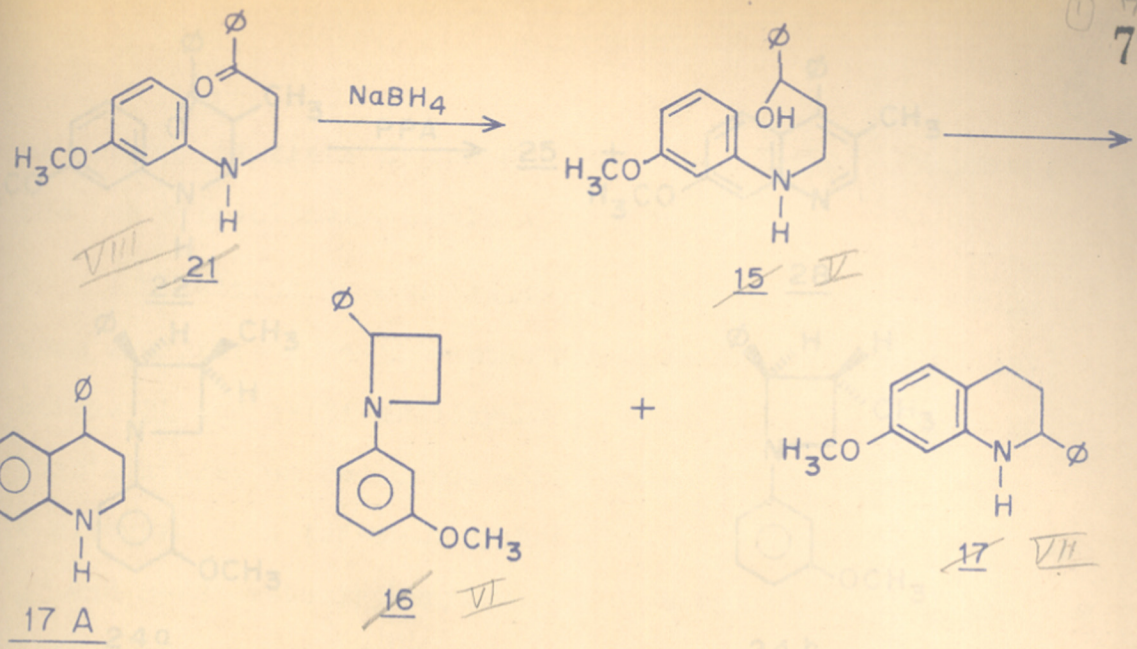
In the case of 24 a mixture of two stereoisomeric azetidines 24A and 24B (Chart 7) was obtained as revealed by two types of methyl doublets in the PMR spectrum (Fig.1). These two stereoisomers could not be separated by conventional methods.

2-(3'-Methoxyphenylamino)-pent-2-en-4-one 29 on reduction with sodium borohydride yielded 2-(3'-methoxyphenylamino)pentan-4-ol 30. The ketone 29 in turn was prepared by the interaction of m-anisidine with acetylacetone.

The alcohol 30 on treatment with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethylamine (2 moles) at -5° for 72 hr. gave 1-(3'-methoxyphenyl)-2,4-dimethylazetidine 31 along with 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 32.

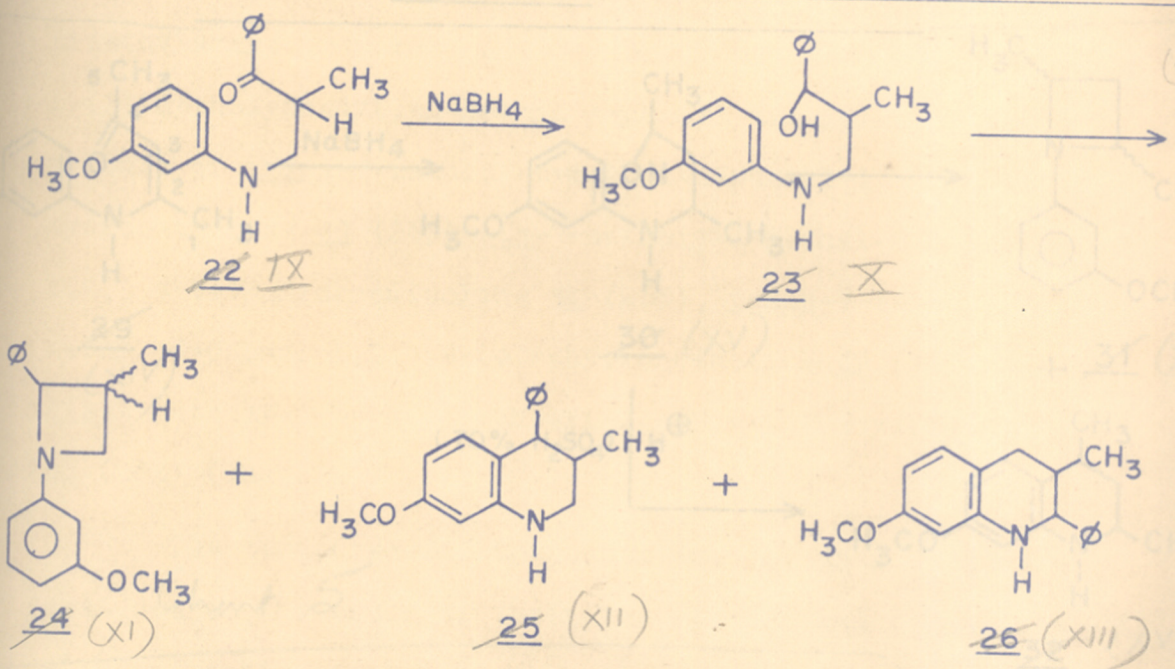
Compound 30 on treatment with 70% sulphuric acid gave 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 32 (Chart 8) (PMR spectrum of 32 given in Fig.2, is discussed in the Experimental part).

Compound 31 was found to be a mixture of two stereoisomeric azetidines 31A and 31B since it revealed two types

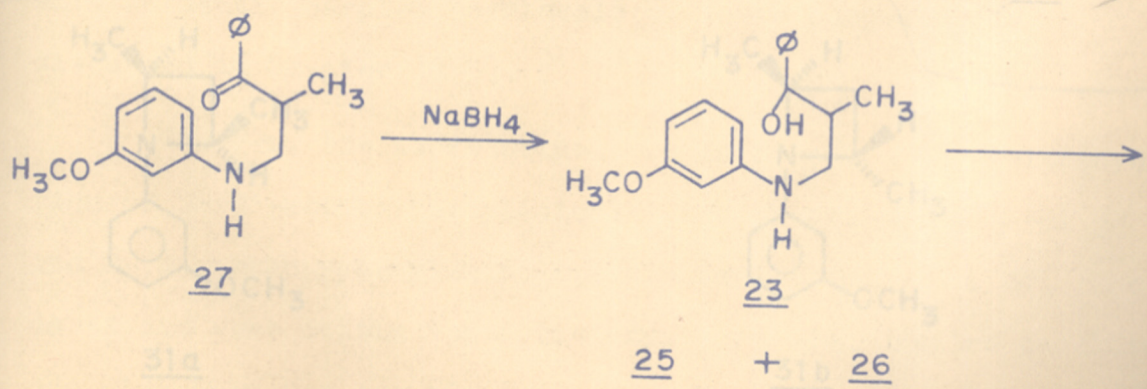


21 (VIII) 15 (IV) 17 A 16 (VI) 17 (VII)

CHART-5.

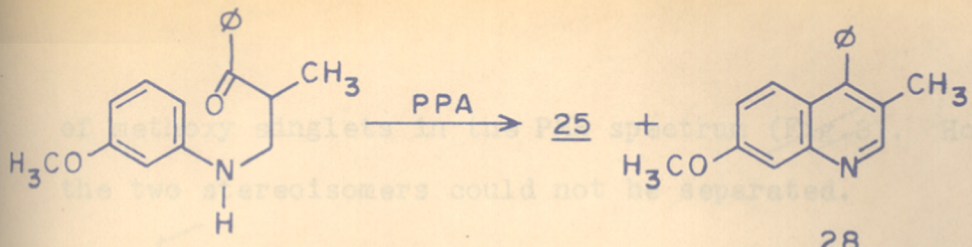


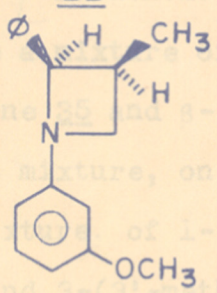
22 (IX) 23 (X) 24 (XI) 25 (XII) 26 (XIII)



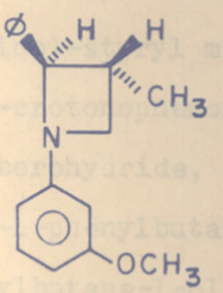
27 23 25 + 26

CHART-6.



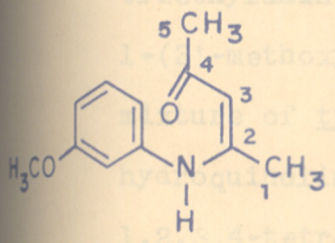


24a

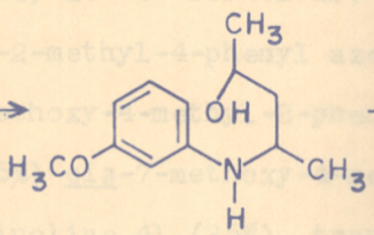


24b

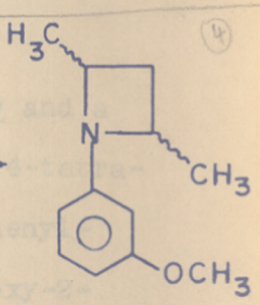
CHART-7



29 (XIV)

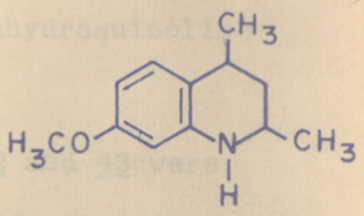


30 (XV)



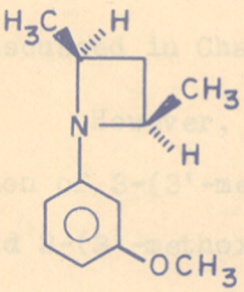
+ 31 (XVI)

(70% H_2SO_4) $H^{\oplus}$

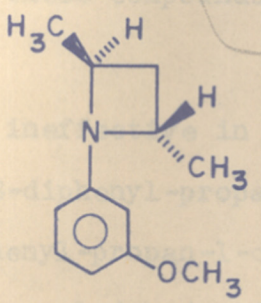


32 (XVII)

Chart 5



31a



31b

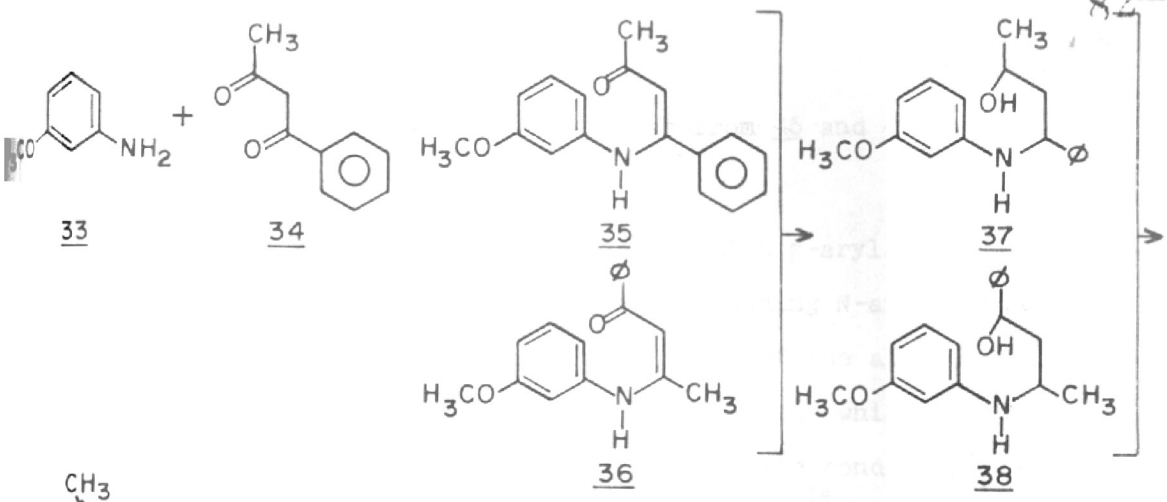
CHART-8

of methoxy singlets in the PMR spectrum (Fig.3). However, the two stereoisomers could not be separated.

Treatment of m-anisidine 33 with benzoylacetone 34 gave a mixture of β-(3'-methoxyphenylamino)-styryl methyl ketone 35 and β-(3'-methoxyphenylamino)-crotonophenone 36. This mixture, on reduction with sodium borohydride, gave a mixture of 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 37 and 3-(3'-methoxyphenylamino)-1-phenylbutane-1-ol 38. The latter mixture on treatment with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethylamine (2 moles) at -5° for 72 hr. gave 1-(3'-methoxyphenyl)-2-methyl-4-phenyl azetidine 39 and a mixture of trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 40 (25%) cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 41 (25%), trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 42 (30%) and cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 43 (20%) (Chart 9).

The strucures for Compounds 40, 41, 42 and 43 were assigned on the basis of their PMR spectra and comparison with authentic samples [synthesis of these compounds is discussed in Chapter II-B].

However, the above method was ineffective in cyclodehydration of 3-(3'-methoxyphenylamino)-1,3-diphenyl-propan-1-ol 45 and 3-(3'-methoxyphenylamino)1,2-diphenyl-propan-1-ol 47. The carbinols were stable under the usual cyclodehydration conditions and also when the reaction was carried out at room temperature


CH3
NH2
33
34
35
36
37
38
OH
Ø
H3CO
N
H

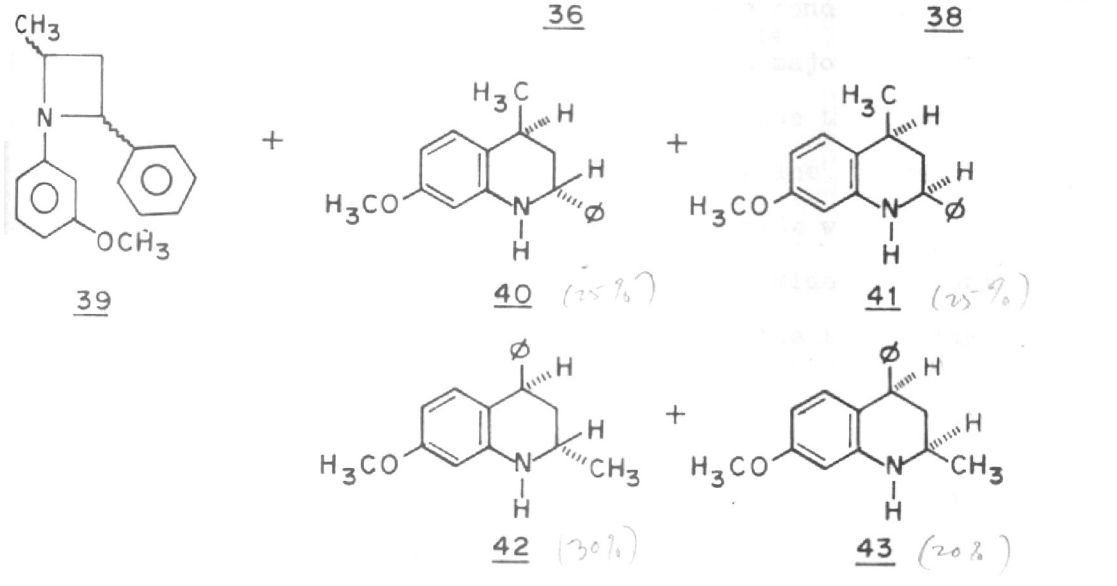
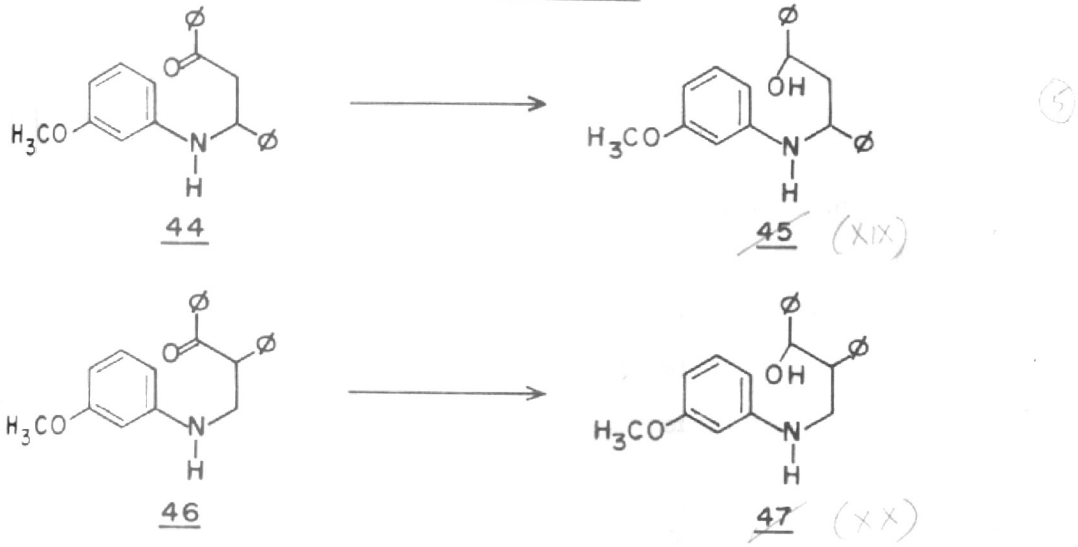

CH3
N
OCH3
39
H3C
H
H3CO
Ø
40 (25%)
41 (25%)
42 (30%)
43 (20%)

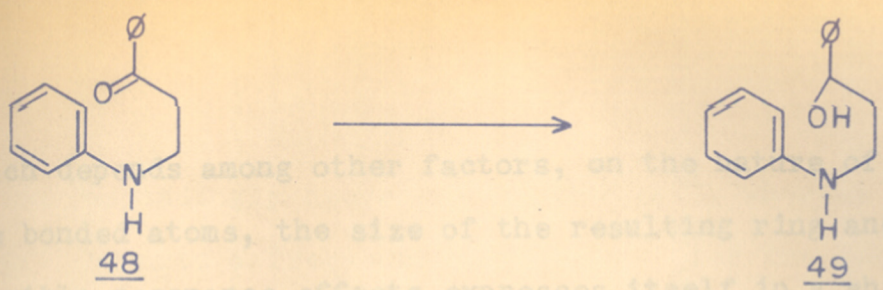
CHART-9


Ø
OH
H3CO
N
H
44
45 (XIX)
46
47 (XX)

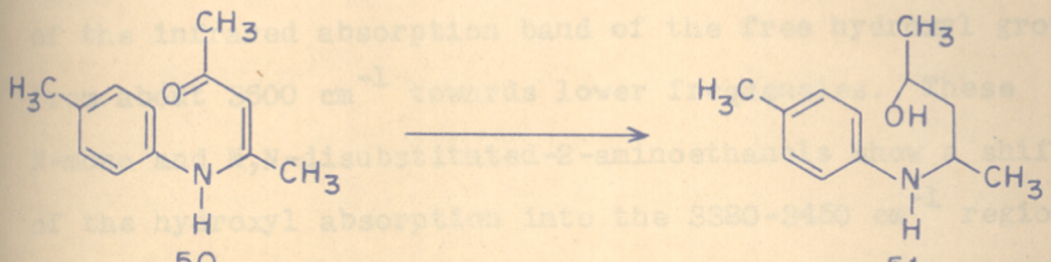
(~27-29°). The relevant azetidines from 45 and 47 were thus not obtained (Chart 10).

In the series of reactions in which β-arylamino-alkanols are converted into the corresponding N-arylazetidines, we had envisaged that the hydroxyl group of the alkanol would get converted into triphenylphosphonium group which would prove to be a good leaving group under basic conditions leading to N-arylazetidine and triphenylphosphine oxide as major products (see Chart 4). However, in all these reactions triphenyl-phosphine was also isolated. Triphenylphosphine arises from hydrolysis of triphenylphosphine dibromide with triethylamine. Some triphenylphosphine dibromide therefore remains unreacted. One possible reason for the latter may be the non-availability of the OH group for conversion into oxotriphenylphosphonium group due to the inter and intramolecular bonding of the OH group with NH. To study this aspect further infrared spectra of the carbinols were studied critically. An examination of the infrared spectra of the 3-arylaminoalkanols revealed that in all these compounds inter and intramolecular hydrogen bonding between NH and OH groups was present to a variable extent.

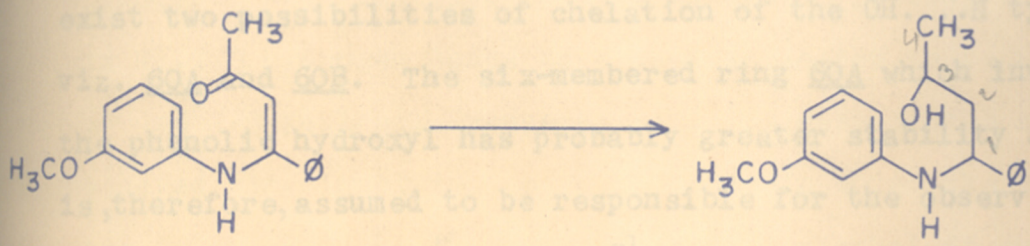
Literature survey revealed that Bergmann, Gil-Av and Pinchas[10] first reported a downward shift of the OH stretching frequency on intramolecular OH...N hydrogen bond formation in N-mono and N,N-disubstituted 2-aminoethanols in dilute CCl_4 solution. The strength of internal hydrogen bonding



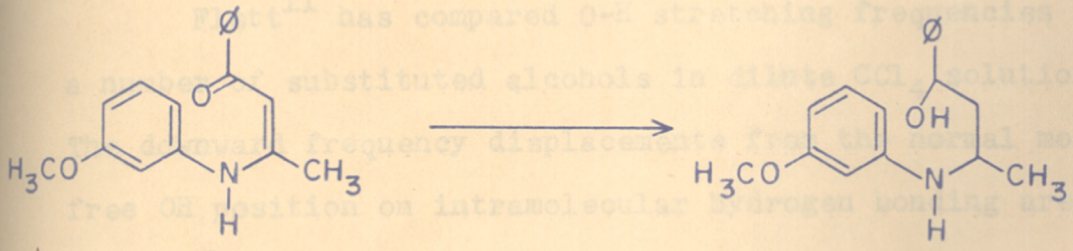
48 49



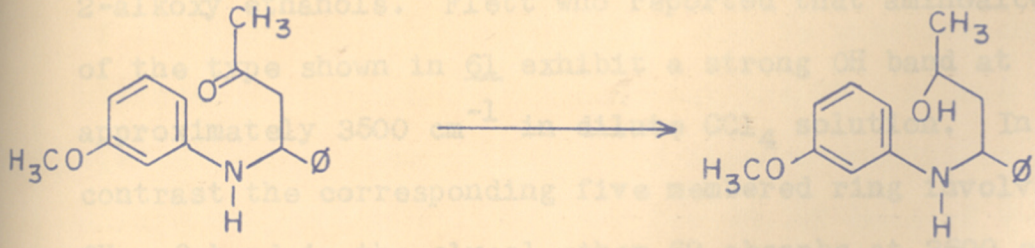
50 51



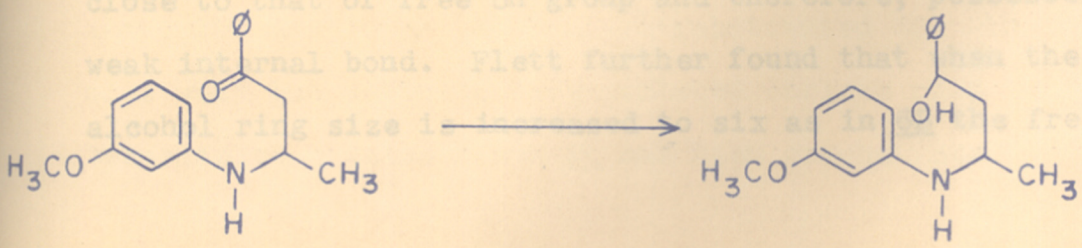
52 53



54 55



56 57



58 59

CHART-10

which depends among other factors, on the nature of the bonded atoms, the size of the resulting ring and possible resonance effects expresses itself in a shift of the infrared absorption band of the free hydroxyl group from about 3600 cm^{-1} towards lower frequencies. These N-mono and N,N-disubstituted-2-aminoethanols show a shift of the hydroxyl absorption into the 3380-3450 cm^{-1} region. In case of N-(O-hydroxybenzylidene)aminoethanol 60 there exist two possibilities of chelation of the OH....N type viz. 60A and 60B. The six-membered ring 60A which involves the phenolic hydroxyl has probably greater stability and is,therefore,assumed to be responsible for the observed hydroxyl absorption at 3420 cm^{-1}.

Flett[11] has compared O-H stretching frequencies in a number of substituted alcohols in dilute CCl_4 solution. The downward frequency displacements from the normal monomeric free OH position on intramolecular hydrogen bonding are much greater in N,N-dialkyl-2-amino ethanols, than in 2-alkoxy ethanols. Flett who reported that aminoalcohols of the type shown in 61 exhibit a strong OH band at approximately 3500 cm^{-1} in dilute CCl_4 solution. In contrast the corresponding five membered ring involving an OH...O bond in the glycol ether 62 absorbs at 3600 cm^{-1} close to that of free OH group and therefore, possesses a weak internal bond. Flett further found that when the amino alcohol ring size is increased to six as in 63 the frequency

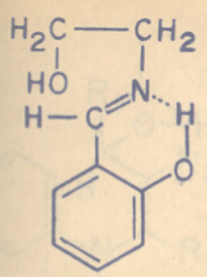
is correspondingly decreased to 3295 cm^{-1}, whereas Kuhn[12] reports a frequency of 3448 cm^{-1} for the intramolecular OH...O bond of trimethylene glycol 64.

Freedman[13] reviewed the frequency shift data pertaining to inter and intramolecular OH...O and OH...N hydrogen bonds concluding that in simple compounds containing similar OH...O and OH...N hydrogen bonds, the latter are stronger. Mean energies of intermolecular OH...N, OH...O and NH...O hydrogen bonds have been estimated to be about 7,6 and 2-3 Kcal/mole respectively. In case of the six membered ring involving an OH...O bond in which the donor atom is phenolic as in O-hydroxy benzyl alcohol 65 only a small frequency lowering is realized as compared to its straight chain counterpart 64. The presence of intramolecular bonding in 65 has been reported by Freedman who assigns the band at 3436 cm^{-1} to the OH...O bonded hydroxyl and a weaker band at 3597 cm^{-1} to unbonded OH. The expected frequency increase in accordance with the decreased strength of the H-bond is observed when phenyl is substituted on nitrogen. Freedman also finds that the OH...N bond of α,α'-ethylene-diamino-o-cresol 66 appears at 3125 cm^{-1} in dilute CCl_4 solution. Whereas the OH...N bond of N-2-hydroxybenzylaniline 67 absorbs at 3250 cm^{-1} an increase of about 100 cm^{-1} over the N-alkyl-substituted 66. The presence of a weak but definite five-membered chelate ring in benzylidine o-aminophenol 68 has been demonstrated by two

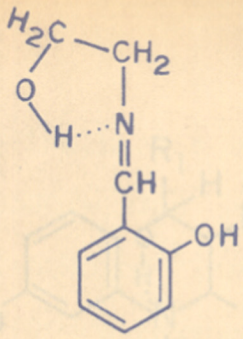
investigators[14,15]. Its OH absorption is found at 3443 cm^{-1} lower than its non-hydrogen bonded p-amino-isomer[14].

Krueger and Mettee[16] have reported the spectra of N,N-dimethylethanolamine and 2-methoxyethylamine which are simply interpreted in terms of an equilibrium between free and bonded OH and NH_2 groups respectively arising from trans and gauche conformers. In N,N-dimethylethanol-amine 69 the γ OH shift on intramolecular OH...N hydrogen bond formation is 132 cm^{-1}. For 2-methoxyethylamine 70 where weaker intramolecular NH...O hydrogen bonds are formed, free and bonded NH groups exhibit the antisymmetric vibrational mode at 3398 and 3387 cm^{-1} respectively (γ NH shift = 10 cm^{-1}) (Chart 11).

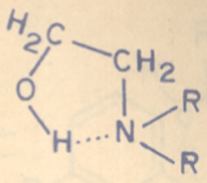
The spectra of 3-arylaminoalkanols in very dilute CCl_4 solution are similarly composed of 'free' OH and NH bands as well as the characteristically broad OH..N and the bonded NH bands which have undergone only a small dis-placement. There are four possible tautomers in 3-arylamino-alkanols 71A, 71B, 71C and 71D (Chart 12). In the tautomer 71A both the OH and NH groups are not bonded and are free. In tautomers 71B and 71C NH and OH groups are bonded to each other and should give bonded and free NH and OH absorptions in the infrared spectrum. In tautomer 71D intramolecular hydrogen bonding results in a four-membered ring where both OH and NH groups are bonded.



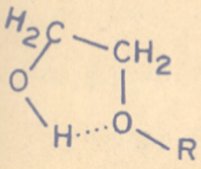
60a



60b



61



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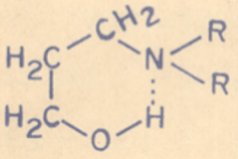

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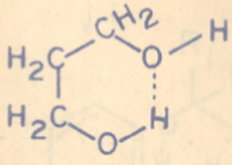

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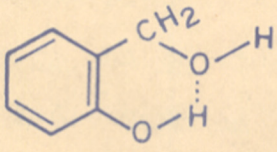

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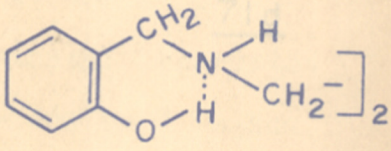
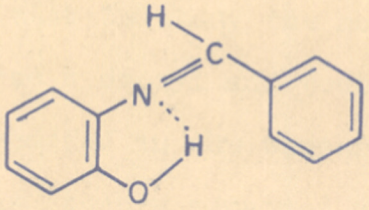


66

67



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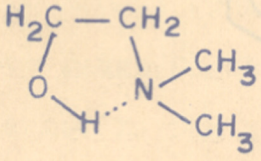

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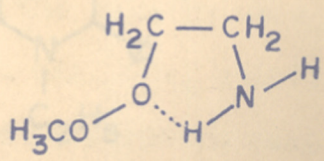
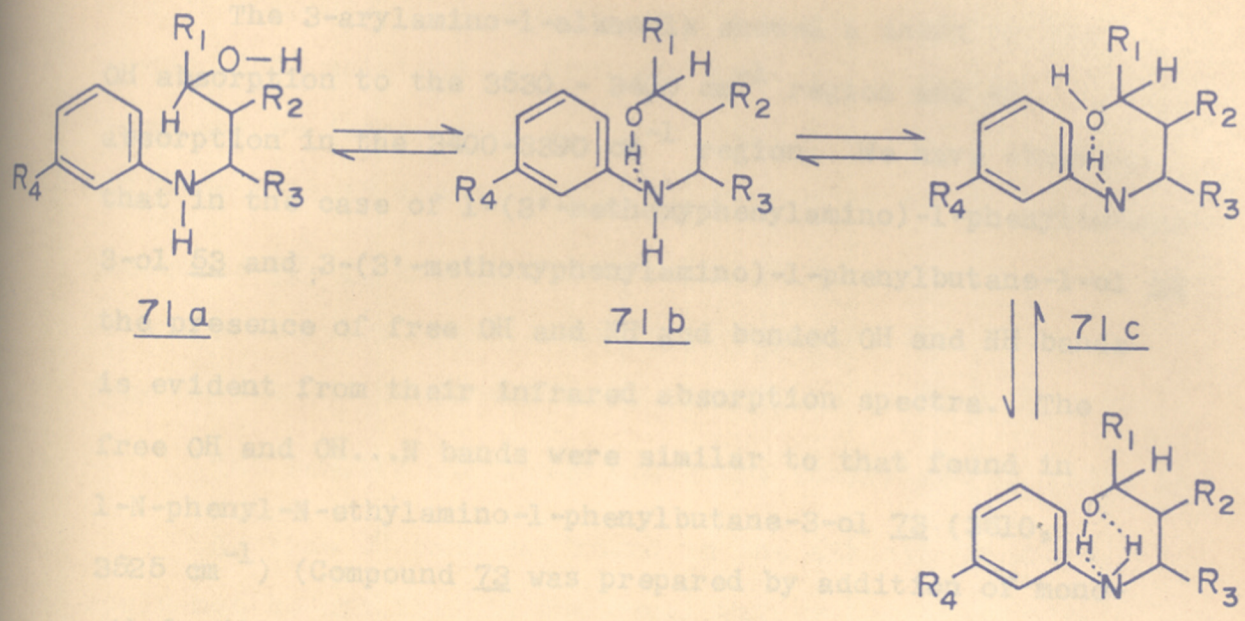


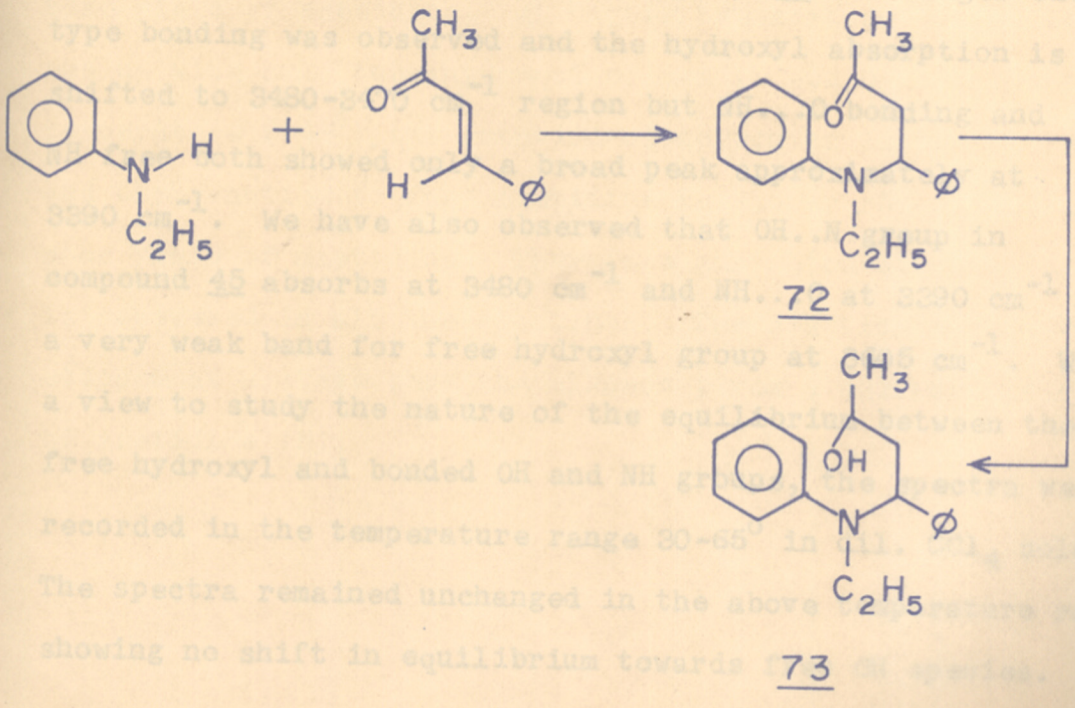
70

CHART-11.



71a 71b 71c 71d

CHART-12



72 73

CHART-13

The 3-arylamino-1-alkanols showed a shift of the OH absorption to the 3530 - 3400 cm^{-1} region and NH absorption in the 3400-3390 cm^{-1} region. We have observed that in the case of 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 53 and 3-(3'-methoxyphenylamino)-1-phenylbutane-1-ol 55 the presence of free OH and NH and bonded OH and NH bands is evident from their infrared absorption spectra. The free OH and OH...N bands were similar to that found in 1-N-phenyl-N-ethylamino-1-phenylbutane-3-ol 73 (3610, 3525 cm^{-1}) (Compound 73 was prepared by addition of mono-ethylaniline to benzalacetone and reduction of the resulting condensation product with sodium borohydride, Chart 13). Alkanols 53 and 55 showed a shift of the hydroxyl absorption to the 3525 - 3530 cm^{-1} region and NH to the 3390-3400 cm^{-1} region. In the case of compounds 59, 15, 23 and 49 a stronger OH..N type bonding was observed and the hydroxyl absorption is shifted to 3480-3470 cm^{-1} region but NH...O bonding and NH free both showed only a broad peak approximately at 3390 cm^{-1}. We have also observed that OH..N group in compound 45 absorbs at 3480 cm^{-1} and NH...O at 3390 cm^{-1} with a very weak band for free hydroxyl group at 3605 cm^{-1}. With a view to study the nature of the equilibrium between the free hydroxyl and bonded OH and NH groups, the spectra were recorded in the temperature range 30-65° in dil. CCl_4 solution. The spectra remained unchanged in the above temperature range showing no shift in equilibrium towards free OH species. In

case of compound 47 bonded OH and NH bands are obtained in dil. CCl_4 solution at 3480 and 3390 cm^{-1} respectively. These may be interpreted as due to OH...N and NH free (71B) or both NH and OH bonded to each other as in 71D. Compounds 57, 30 and 51 showed only two bands the latter of which was very broad comprising of OH..N, NH...O and free NH bands, the former being attributed to free OH group.

The results mentioned above are summarised in Table 1.

No free OH band was found in the alkanol 47 which could not be cyclized in the usual way by reacting with triphenylphosphine dibromide. To convert these molecules into oxophosphonium bromide group one has to break OH...N hydrogen bonding by supplying more energy to the molecule. But this reaction is preferably carried out at -5^{o} to get more yield of azetidine. At higher temperature one would end up with only tetrahydroquinolines (C and D). At lower temperature (-40^{o}) the rotation of molecules is restricted and the reaction to form azetidine is slower resulting in very poor yield of azetidine. Therefore unreacted alkanol (A) is recovered in all the reactions. The reaction should be stopped at a stage when the alkanol gives a maximum yield of azetidine (B).

TABLE 1

STRETCHING OH and NH/FREQUENCIES IN 3-ARYLAMINOALKANOLS (TEMPERATURE 25° DILUTE CCl_4 SOLUTION)

Alkanol	Free OH	OH....N		Frequency cm^{-1} Free NH/NH....O
53	3610(m)	3530(b)	3485(b)	3395(m)
55	3610(m)	3525(b)	3480(b)	3395(m)
49	3610(m)	3480(b)		3400(b)
59	3610(m)	3480(b)		3395(m)
15	3605(s)	3470(b)		3390(m)
23	3610(m)	3480(m)		3395(m)
45	3610(w)	3480(m)		3400(s)
57	3620(m)	3415(b)		*
30	3610(m)	3410(b)		*
51	3620(m)	3400(vb)		*
47		3480(m)		3390(m)

*NH bands overlapped by OH...N band.

m = medium; w = weak; s = strong; vb = very broad; b = broad.

Path length 0.01 cm; conc. $\sim 10^{-4}$ M.

EXPERIMENTAL

General method for the preparation of β-arylaminoethylaryl ketones:

Equimolar proportions of Mannich base hydrochlorides (derived from the relevant ketones and dimethylamine and formaldehyde) and the primary arylamine were refluxed in 1:1 aq. ethanol for 1 hr. When the resultant product was solid, the reaction mixture was filtered, the residue washed thrice with aq. ethanol and crystallised from ethanol. When the ketone settled down as an oil, it was extracted with ether. The oily product obtained on work up was further purified by distillation[7,8].

2-(3'-Methoxyphenylamino)pent-3-en-4-one 29:

A mixture of acetylacetone (5 g) and m-anisidine (6.15 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 2-(3'-methoxyphenylamino)pent-3-en-4-one 29 as pale yellow oil, b.p. 115°/0.1 mm (7.8 g; yield 75%). (Found: C, 68.4; H, 7.8; N, 7.3. $C_{11}H_{15}NO_2$ requires: C, 68.3; H, 7.8; N, 7.2%).

Compound 29 was characterised by its IR spectrum which shows the typical ketone absorption at 1660 and NH 3390 cm^{-1}.

2-(4'-Methylphenylamino)pent-3-en-4-one 50:

A mixture of acetylacetone (5 g) and p-toludine (5.4 g)

was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 2-(4'-methylphenylamino)-pent-3-en-4-one 50 as pale yellow oil, b.p. 125°/0.1 mm (8.5 g; yield 81%) (Found: C, 75.4; H, 8.6; N, 7.8. $C_{11}H_{15}NO$ requires: C, 75.5; H, 8.5; N, 7.9%).

Compound 50 was characterised by its IR spectrum which shows the typical ketone absorption at 1665 and NH 3390 cm^{-1}.

1-(3'-Methoxyphenylamino)propyl-1,3-diphenyl ketone 44:

A mixture of benzalacetophenone (10.4 g) and m-anisidine (6.15 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 1-(3'-methoxyphenylamino)propyl-1,3-diphenyl ketone 44 as yellowish oil, b.p. 132-135°/0.1 mm (12.5 g; yield 76%) (Found: C, 79.8; H, 6.4; N, 4.2. $C_{22}H_{21}NO_2$ requires: C, 79.7; H, 6.3; N, 4.2%).

Compound 44 was characterised by its IR spectrum which shows the typical ketone absorption at 1700 and NH 3390 cm^{-1}.

(N-phenyl-N-ethylamino)-β-phenethyl methyl ketone 72:

A mixture of benzalacetone (7.2 g) and monoethylaniline (6.0 g) was heated on boiling water bath for 3 hr. till the mixture became clear. On cooling brownish oil was obtained which on distillation under vacuum gave 72 as pale yellow oil,

b.p. 120°/0.1 mm (10.0 g; yield 77%) (Found: C, 81.0; H, 7.9; N, 5.1. $C_{18}H_{21}ON$ requires: C, 80.9; H, 7.9; N, 5.2%).

Compound 72 was characterised by its IR spectrum which shows the typical ketone absorption at 1700 cm^{-1}.

General method for reduction of the above ketones with sodium borohydride:

A mixture of the ketone and sodium borohydride and ethanol (50 ml) was kept at room temperature for twenty minutes. The mixture was warmed on boiling water bath for further twenty minutes. After dilution with water (200 ml), the mixture was extracted with ether. The ether extract was washed twice with water, dried over anhydrous sodium sulfate and ether removed. The carbinol thus obtained was then crystallised or distilled under vacuum. Details of these experiments are given in Table 1 and analytical data in Table 2. PMR spectra of alcohols are given in Table 3.

Compound 73 was characterised by its PMR and mass spectra (m/e 269). The PMR spectrum of 73 shows the following characteristics:

D_2O exchangeable OH proton at 4.06, broad, s, 1P; C_1, 1.21, d, 3P; C_2, 1.70 - 2.05, m, 2P; C_1, C_3, N_4 (CH_2), 4.1 - 4.53 (m), 4P; N_4 (CH_3), 1.26, t, 3P; $C_{5,6,7,8,9}$ and C_3-phenyl, 7.06, s, 10P.

Cyclisation of 3-(3'-methoxyphenylamino)1-phenylpropane-1-ol 15:

Treatment of the alcohol 15 (5 g) with triphenyl

TABLE 1 - REDUCTION OF KETONES

Starting ketone No.	Starting ketone Wt.g	$NaBH_4$ used Wt.g	Carbinol No.	Yield Wt.g	Yield %	Shape and colour	M.p. or B.p. °C
21	2.0	0.3	15	1.8	90	Colourless oil	$145\text{-}65^{\circ}/3.4 \times 10^{-3}$ mm
22	3.0	0.8	23	2.8	93	Colourless oil	$140\text{-}50^{\circ}/3.4 \times 10^{-3}$ mm
48	1.0	0.2	49	0.8	80	Pale yellow oil	$140^{\circ}/8.5 \times 10^{-4}$ mm
44	2.0	0.35	45	1.7	85	Colourless oil	$150\text{-}55^{\circ}/9.56 \times 10^{-3}$ mm
46	3.0	0.8	47	2.6	86	Colourless oil	$145^{\circ}/9.56 \times 10^{-3}$ mm
50	2.5	0.6	51	2.2	88	Pale yellow oil	$135\text{-}40^{\circ}/9.56 \times 10^{-3}$ mm
29	2.0	0.4	30	1.75	87	Pale yellow oil	$145\text{-}50^{\circ}/9.56 \times 10^{-3}$ mm
72	2.0	0.4	73	1.7	85	Colourless oil	$130^{\circ}/9.56 \times 10^{-3}$ mm

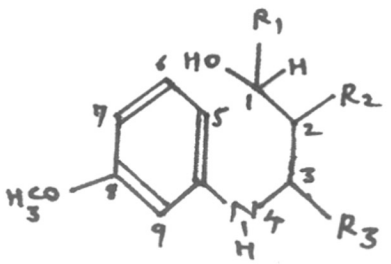
TABLE 2

Carbinol No.	- Analysis - Found %			Required %		
	C	H	N	C	H	N
15	74.4	7.5	5.2	74.7	7.4	5.4
23	75.4	7.6	5.1	75.2	7.8	5.2
49	79.6	7.4	6.7	79.3	7.5	6.2
45	78.9	6.8	4.1	79.3	6.9	4.2
47	79.2	6.8	4.2	79.3	6.9	4.2
51	74.4	9.9	7.4	74.6	9.9	7.3
30	68.7	9.1	6.7	68.8	9.2	6.7
73	80.2	8.5	5.1	80.2	8.6	5.2

TABLE 3 - PMR SPECTRA OF 3-ARYLAMINO ALKANOLS

Assignments and intensities

Carbinol No.	C_1	C_2	C_3	R_1	R_2	R_3	C_8	$C_{5,6,7,9}$	NH and OH
15 R_1 = Ø R_2 = R_3=H	4.60(t) 1P	1.83(q) 2P	3.08(t) 2P	7.24 (m) 5P			3.65(s) 3P	5.8 - 7.2 (m) 4P	3.58 (s) 2P
23 R_1 = Ø R_2 = CH_3 R_3 = H	4.38(d) 1P	1.4- 1.27 (m) 3P		7.18 (m) 5P	0.73 (d) 3P		3.66(s) 3P	5.96 - 7.1(m) 4P	3.43 (s) 2P
30 R_1 = CH_3 R_2 = H R_3 = CH_3	1.31- 1.85 (m) 3P		3.55 (m) 1P			1.05 (d) 6P	3.61(s) 3P	6.01 - 7.05(m) 4P	3.46 (s) 2P



phosphine dibromide, prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution at 0°. When the pale yellow precipitate of triphenylphosphine dibromide is dissolved and solution becomes clear, triethylamine (5.2 g) in 20 ml acetonitrile solution was added and mixture was stirred at -5° for 72 hr. The precipitated triethylamine hydrobromide (5.73 g) was filtered off. The filtrate was concentrated by rotary evaporation. The residue was extracted several times with pet. ether ($60-80^{\circ}$), and extract was concentrated by rotary evaporation to give brownish oil, (7.5 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 15 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet.ether	Colourless plates m.p. 80°.	Triphenylphosphine	0.52
2	95% pet.ether + 5% benzene	Colourless oil.		1.0
3	25% pet.ether + 75% benzene	Colourless needles.		0.99
4	Benzene	Yellowish oil.	Recovered 15	0.59
5	50% benzene + 50% ethyl acetate.	Colourless prisms m.p. 49°.	Triphenylphosphine oxide.	4.19

i) Alcohol converted in the reaction 88%.

ii) Total yield .. 46%.

iii) Fraction 2. The yellowish oil obtained was distilled under vacuum and identified as 1-(3'-methoxyphenyl)-2-phenylazetidine 16 as colourless oil, b.p. 140-45°/8.5 x 10^{-4} mm (yield 24%) (Found: C, 80.5; H, 7.3; N, 6.0. $C_{16}H_{17}NO$ requires: C, 80.3; H, 7.3; N, 5.9%).

The PMR spectrum of 16 shows the following characteristics: C_2, 4.02, t, 1P; C_3, 6.9, m, 2P; C_4, 3.2, t, 2P; $C_{6,7,8,10}$ and C_2-phenyl 5.8 - 7.3, m, 9P; C_9, 3.7, s, 3P.

Fraction 3. The colourless solid obtained was crystallised from methanol to give 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 17 as colourless needles, m.p. 143-145° (lit.[8] m.p. 145°) (yield 22%) (Found: C, 80.1; H, 7.3; N, 5.6. $C_{16}H_{17}NO$ requires: C, 80.3; H, 7.2; N, 5.9%).

The PMR spectrum of 17 shows the following characteristics: A D_2O exchangeable NH proton at 3.68, broad, s, 1P; C_2, 4.26, t, 1P; C_3, 1.95, t, 2P; C_4, 3.95, t, 2P; $C_{5,6,8}$ and C_2-phenyl, 5.8 - 7.3, m, 8P; C_7, 3.7, s, 3P.

Cyclisation of 3-(3'-methoxyphenylamino)-2-methyl-1-phenylpropane-1-ol 23:

Treatment of the alcohol 23 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution was stirred at -5° for 72 hr. The work up as above gave brownish oil, (7.9 g) which was

chromatographed on silica gel.

CHROMATOGRAM

Alcohol 23 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet. ether	Colourless plates.	Triphenyl-phosphine	1.3
2	95% pet.ether + 5% benzene	Colourless plates.		0.43
3	25% pet.ether + 75% benzene	Brownish oil		0.9
4	25% pet.ether + 75% benzene	Colourless oil.		0.5
5	Benzene	Yellowish oil	Recovered 23	0.29
6	50% benzene + 50% ethyl acetate.	Colourless prisms.	Triphenyl-phosphine oxide.	4.12

i) Alcohol converted in the reaction 90%.

ii) Total yield.. 40%.

iii) Fraction 2. The colourless solid obtained was crystallised from methanol to give 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine 24 as colourless plates, m.p. 94° (yield 9%) (Found: C, 80.8; H, 6.7; N, 5.7. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

The PMR spectrum of 24 shows the following characteristics: C_2, 4.16, d, 1P; C_3, 0.9, d, 3P; C_3 and C_4, 1.35 - 1.88, m, 3P; C_9, 3.6, s, 3P; $C_{6,7,8,10}$ and C_2-phenyl, 5.95 - 7.25, m, 9P.

Fraction 3. The brownish oil obtained was distilled under

vacuum to give 7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 26 as colourless plates, (crystallised from methanol) m.p. 97° (lit.[8] m.p. 97°) (yield 20%) (Found: C, 80.7; H, 6.8; N, 5.7. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

The PMR spectrum of 26 shows the following characteristics: D_2O exchangeable NH proton at 3.65, broad, s, 1P; C_2, 3.75, d, 1P; C_3, 1.04, d, 3P; C_3 and C_4, 1.80-3.20, m, 3P; $C_{5,6,8}$ and C_2-phenyl, 6.0 - 7.95, m, 8P; C_7, 3.45, broad, s, 1P.

Fraction 4. The colourless oil obtained was distilled under vacuum to give 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 25 as colourless oil, b.p. 150°/7.6 x 10^{-3} mm (lit.[8] b.p. 150°/7.6 x 10^{-3} mm) (yield 11%) (Found: C, 80.8; H, 6.7; N, 5.2. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

The PMR spectrum of 25 shows the following characteristics: D_2O exchangeable NH proton at 3.70, broad, s, 1P; C_3, 0.72, d, 3P; C_3 and C_2, 1.95 - 3.02, m, 3P; C_4, 3.4, d, 1P; $C_{5,6,8}$, C_4-phenyl, 5.85-7.35, m, 8P; C_7, 3.55, s, 3P.

Cyclisation of 2-(3'-methoxyphenylamino)pentan-4-ol 30:

Treatment of the alcohol 30 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml

acetonitrile solution was stirred at -5° for 72 hr. The work up as above gave brownish oil, (7.1 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 30 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet. ether	Colourless plates.	Triphenyl-phosphine	0.51
2	95% pet. ether + 5% benzene	Yellowish oil.		0.84
3	25% pet.ether + 75% benzene	Yellowish oil.		0.55
4	Benzene	Yellowish oil.	Recovered 30	0.42
5	50% benzene + 50% ethyl acetate.	Colourless prisms.	Triphenyl-phosphine oxide.	4.52

i) Alcohol converted in the reaction 92%.

ii) Total yield .. 30.5%.

iii) Fraction 2. The yellowish oil obtained was distilled under vacuum to give 1-(3'-methoxyphenyl)2,4-dimethylazetidine 31 as yellow oil, b.p. $100^{\circ}/2.13 \times 10^{-2}$ mm (yield 16%) (Found: C, 75.2; H, 8.8; N, 7.2. $C_{12}H_{17}NO$ requires: C, 75.3; H, 8.9; N, 7.3%).

The PMR spectrum of 31 shows the following characteristics: C_2 and C_4, 1.09, d, 6P; C_3, 1.86 - 2.83, m, 2P;

C_2 and C_4, 3.96 - 4.43, m, 2P; $C_{5,6,7,9}$, 5.7 - 7.23, m, 4P; C_8, 3.65, s, 3P.

Fraction 3. The yellowish oil obtained was distilled under vacuum to give 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 32 as yellowish oil, b.p. $150^{\circ}/2.13 \times 10^{-2}$ mm (yield 14.5%) (Found: C, 75.4; H, 8.9; N, 7.4. $C_{12}H_{17}NO$ requires: C, 75.3; H, 8.9; N, 7.3%).

The PMR spectrum of 32 shows the following characteristics: D_2O exchangeable NH proton at 3.36, broad, s, 1P; C_2 and C_4, 1.08, d, 6P; C_3, 1.3 - 1.53, m, 2P; C_2, 3.01, m, 1P; $C_{5,6,8}$, 5.7 - 7.26, m, 3P; C_7, 3.63, s, 3P; C_4, 2.96, m, 1P.

Cyclisation of 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 37 and 3-(3'-methoxyphenylamino)1-phenylbutane-1-ol 38:

Treatment of the mixture of alcohols 37 and 38 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution, followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution was stirred at -5° for 72 hr. The work up as above gave brownish oil (7.8 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohols 37 and 38 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt.g
1	Pet. ether	Colourless plates.	Triphenyl-phosphine	0.50
2	95% pet.ether + 5% benzene	Colourless plates.		0.46
3	25% pet.ether + 75% benzene	Yellowish oil.		1.21
4	Benzene	Yellowish oil.	Recovered 37 and 38	0.45
5	50% benzene + 50% ethyl acetate	Colourless prisms	Triphenyl-phosphine oxide.	5.10

i) Alcohol converted in the reaction 90%.

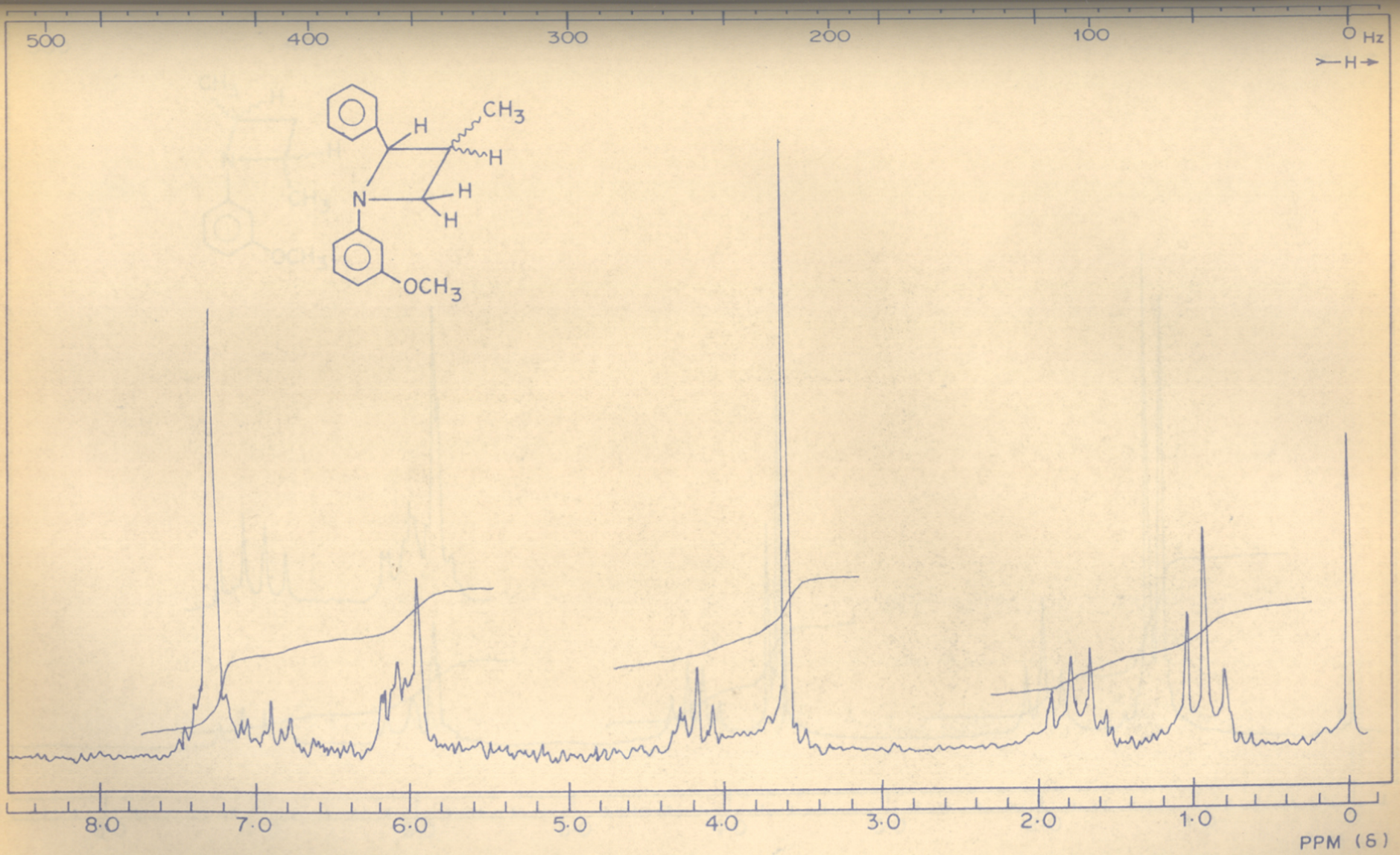
ii) Total yield..35.5%.

iii) Fraction 2. The colourless solid obtained was crystallised from methanol to give 1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 39 as colourless plates, m.p. 89° (yield 12.5%) (Found: C, 80.7; H, 6.7; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

Fraction 3. The yellowish oil obtained was distilled under vacuum to give pale yellow oil, b.p. 140°/9.56 x 10^{-3} mm (yield 23%) (Found: C, 81.4; H, 6.9; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 40, cis-7-methoxy-4-methyl-2-phenyl-

1,2,3,4-tetrahydroquinoline 41, trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 42 and cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 43. The VPC analysis also showed it to be a mixture of 40, 41, 42 and 43 in 25: 25: 30: 20 ratio respectively.

ILLUSTRATIONS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300
200
100
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H
CH3
H
H
H
N
H
OCH3
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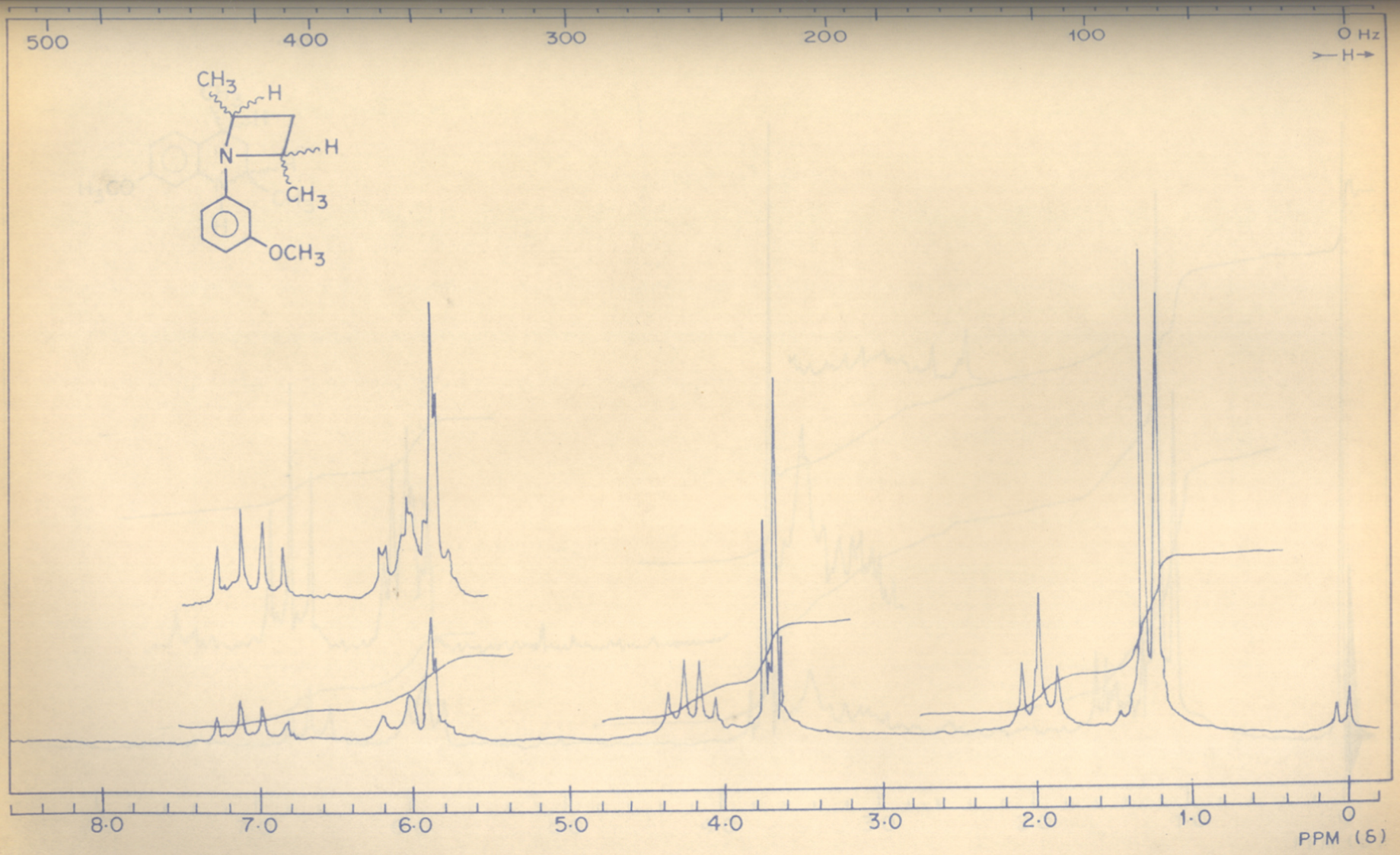
3·0
2·0
1·0
0
PPM (δ)

FIG. – 1.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N
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CH3
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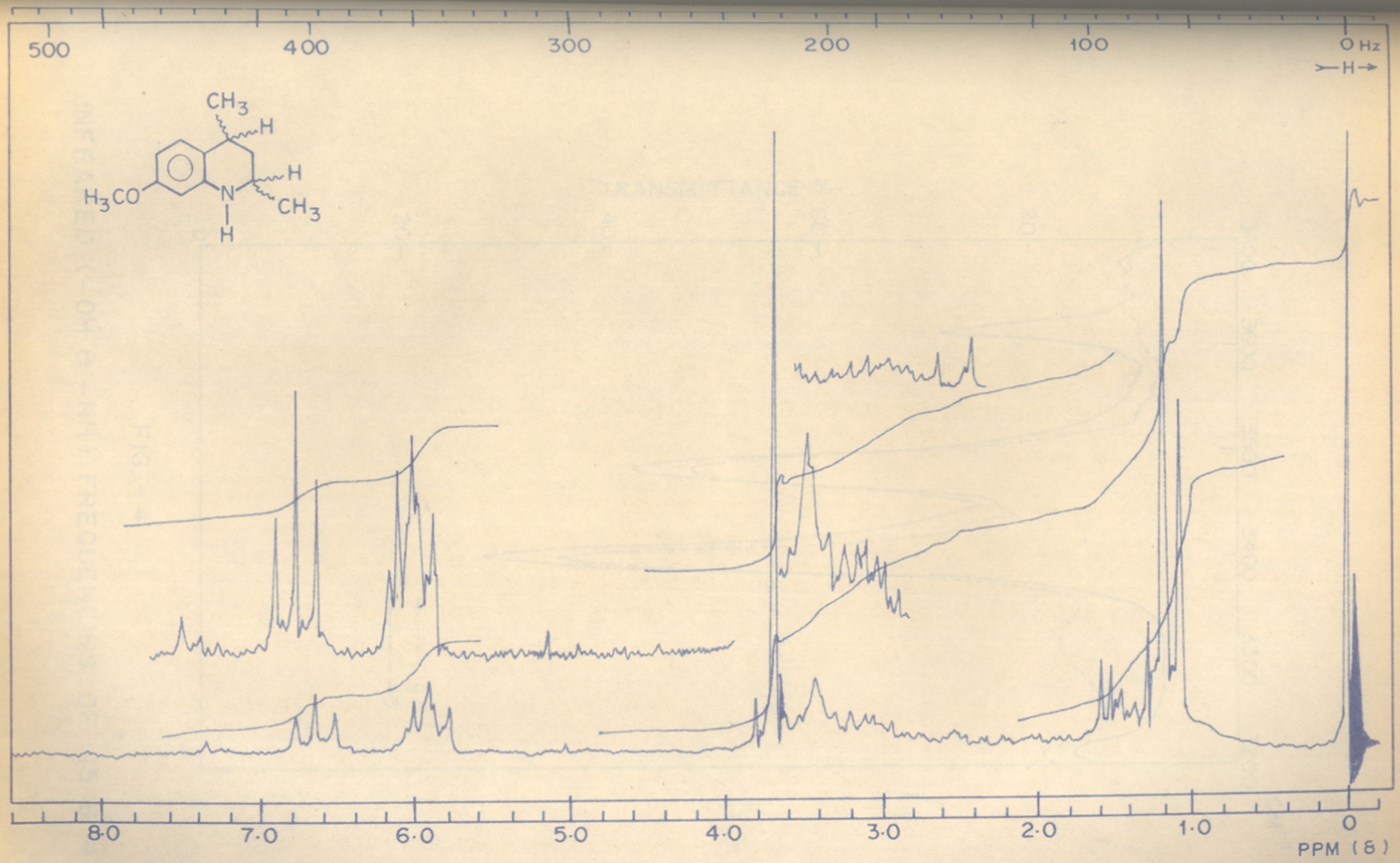
PPM (δ)

FIG. 2.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CH3
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0
PPM (δ)

FIG. 3.

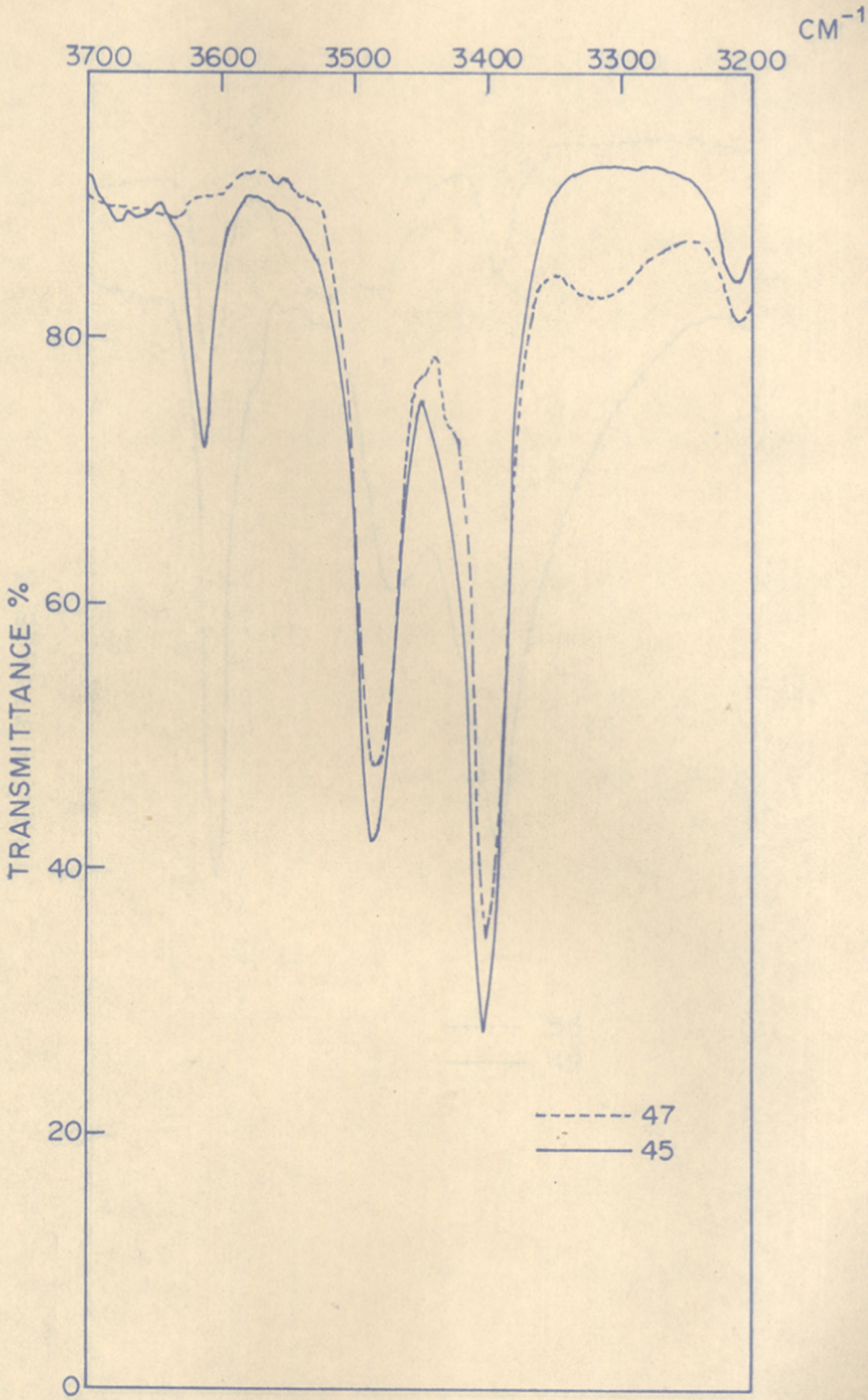

FIG. - 4

INFRARED (-OH & -NH) FREQUENCIES OF 45 & 47

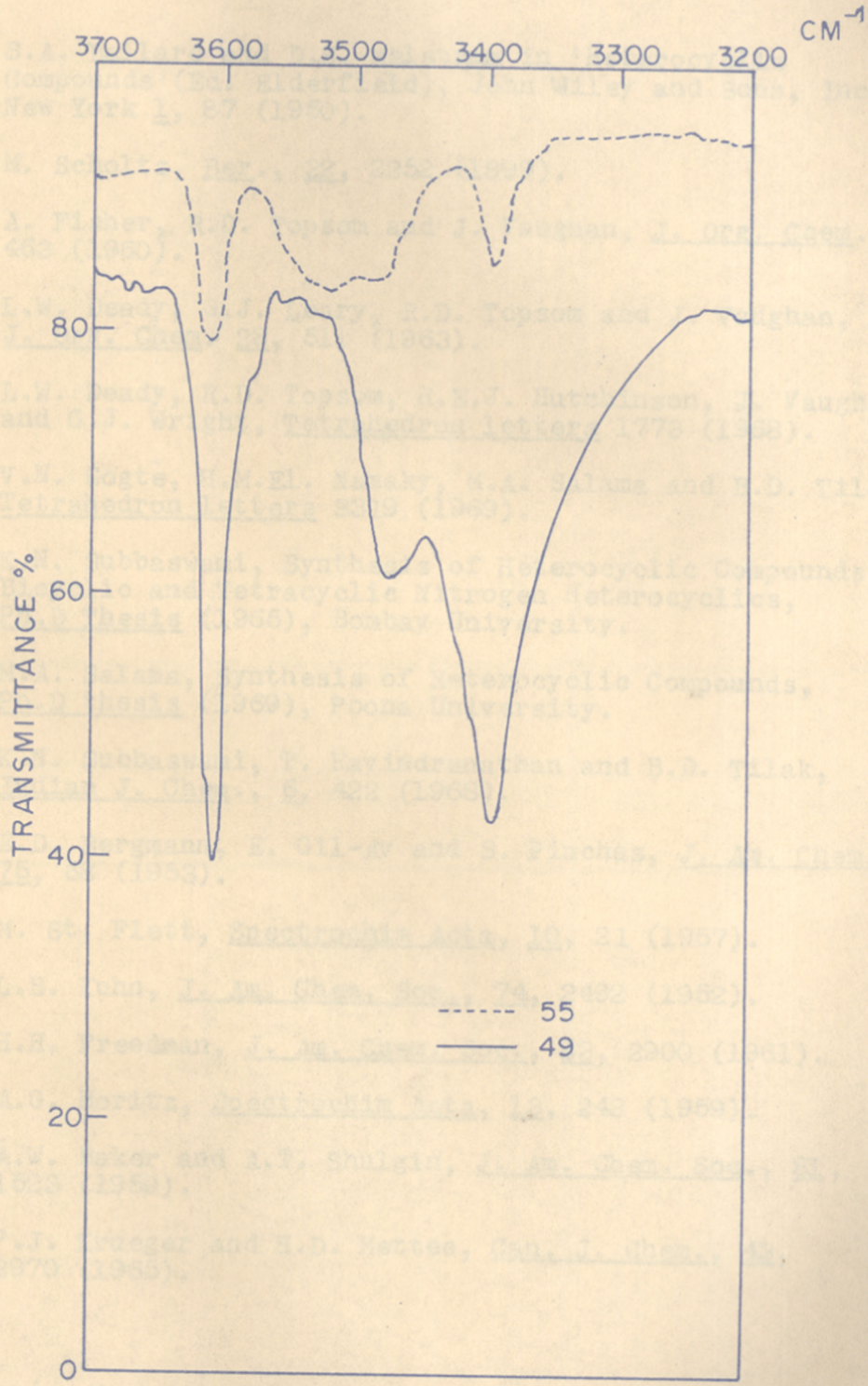

FIG. - 5

INFRARED (-OH & -NH) FREQUENCIES OF 49 & 55

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CHAPTER IV - STEREOSELECTIVE SYNTHESIS OF 2,4-DISUBSTITUTED N-ARYLAZETIDINES

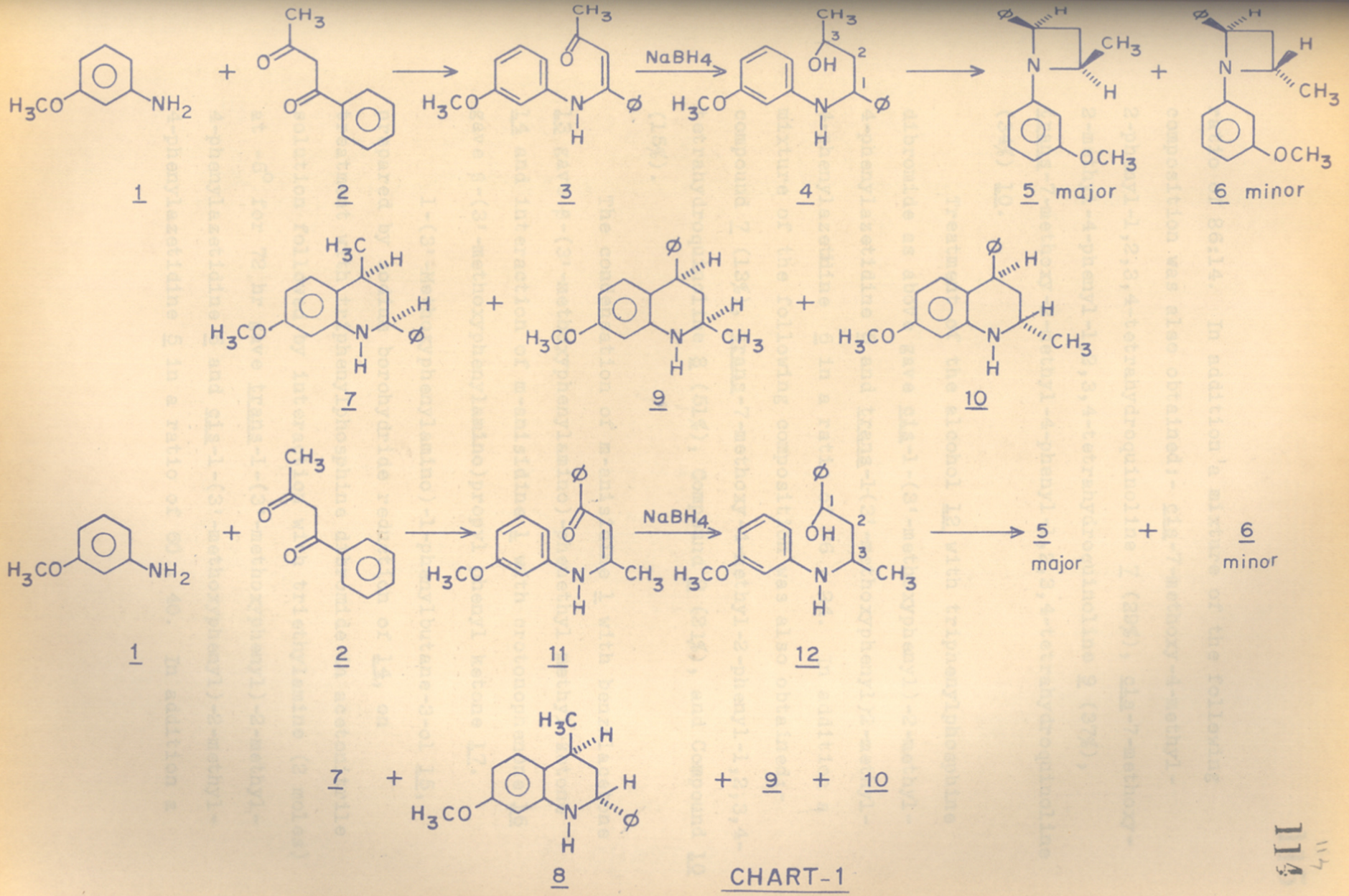
STEREOSELECTIVE SYNTHESIS OF 2,4-DISUBSTITUTED N-ARYLAZETIDINES

To study the stereoselectivity in the rearrangement of N-arylazetidines resulting into 1,2,3,4-tetrahydroquinoline, a stereoselective synthesis of 2,4-disubstituted N-aryl-azetidine was necessary. Excepting one example[1] by Cromwell et al. stereospecific syntheses of azetidines have not been reported.

Condensation of m-anisidine 1 with benzoylacetone 2 gave as expected a mixture of β-(3'-methoxyphenylamino)-crotonophenone 11 and α-(3'-methoxyphenylamino)styryl methyl ketone 3 in 43 and 57% yield respectively. Benzoylacetone is known to occur as two different enolates A and B in a ratio of 43 to 57 [2] (see page 33, Chapter II).

The mixture of 3 and 11 was separated on a spinning band column and the separated compounds were reduced by treatment with sodium borohydride. Compounds 3 and 11 thus gave 1-(3'-methoxyphenylamino)1-phenylbutane-3-ol 4 and 3-(3'-methoxyphenylamino)1-phenylbutane-1-ol 12 respectively.

Treatment of the alcohol 4 with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethylamine (2 moles) at -5° for 72 hr. gave cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 and trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6 in a


NaBH4
NaBH4
1
2
3
4
5 major
6 minor
7
9
10
11
12
8
CHART-1

ratio of 86:14. In addition a mixture of the following composition was also obtained:- cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 7 (29%), cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 9 (37%), trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (34%) 10.

Treatment of the alcohol 12 with triphenylphosphine dibromide as above gave cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 and trans-1-(3'-methoxyphenyl)2-methyl-4-phenylazetidine 6 in a ratio of 76 : 24. In addition a mixture of the following composition was also obtained:- compound 7 (13%), trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 8 (51%), Compound 9 (21%), and Compound 10 (15%).

The condensation of m-anisidine 1 with benzalacetone 13 gave β-(3'-methoxyphenylamino)-phenethyl methyl ketone 14 and interaction of m-anisidine 1 with crotonophenone 16 gave β-(3'-methoxyphenylamino)propyl phenyl ketone 17.

1-(3'-Methoxyphenylamino)-1-phenylbutane-3-ol 15, prepared by sodium borohydride reduction of 14, on treatment with triphenylphosphine dibromide in acetonitrile solution followed by interaction with triethylamine (2 moles) at -5° for 72 hr gave trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6 and cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 in a ratio of 60 : 40. In addition a

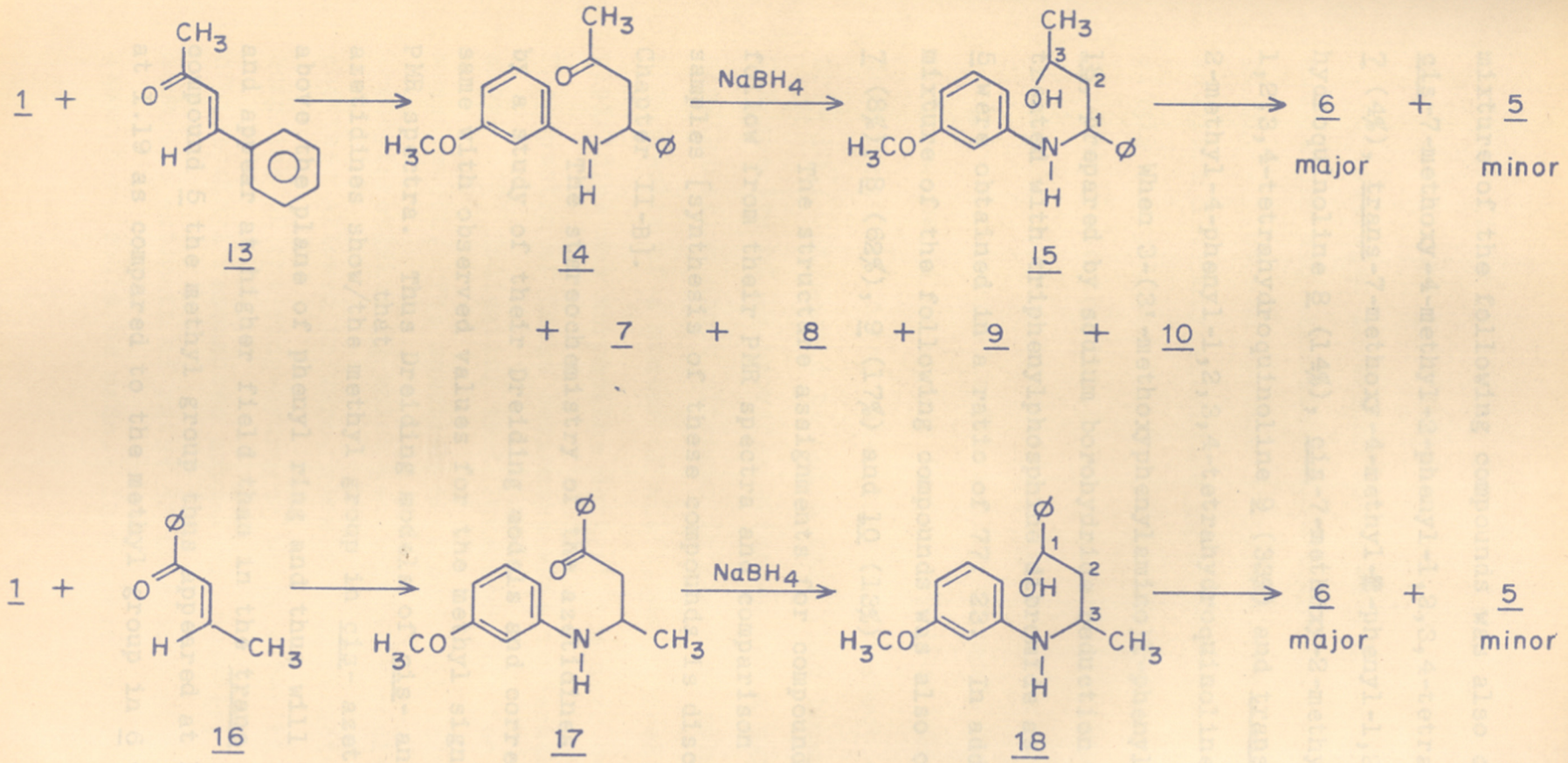

1 +
NaBH4
13
14
15
6
major
+
5
minor
+ 7 + 8 + 9 + 10
1 +
NaBH4
16
17
18
6
major
+
5
minor
+ 7 + 8 + 9 + 10

CHART-2.

mixture of the following compounds was also obtained:- cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 7 (4%), trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 8 (14%), cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 9 (33%) and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 10 (49%).

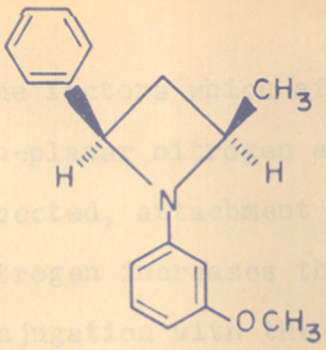
When 3-(3'-methoxyphenylamino)1-phenylbutane-1-ol, 18, prepared by sodium borohydride reduction of 17, was treated with triphenylphosphine dibromide as above, 6 and 5 were obtained in a ratio of 77: 23. In addition a mixture of the following compounds was also obtained:- 7 (8%), 8 (62%), 9 (17%) and 10 (13%).

The structure assignments for compounds 7, 8, 9, 10 follow from their PMR spectra and comparison with authentic samples [synthesis of these compounds is discussed in Chapter II-B].

The stereochemistry of the azetidines was elucidated by a study of their Dreiding models and correlating the same with observed values for the methyl signals in their PMR spectra. Thus Dreiding models of cis- and trans-azetidines show that the methyl group in cis- azetidine comes above the plane of phenyl ring and thus will be shielded and appear at higher field than in the trans azetidine. In compound 5 the methyl group thus appeared at higher field at 1.19 as compared to the methyl group in 6 which appeared

at lower field at 1.25. The azetidine 5 is thus the cis- isomer and 6 is trans (Chart 3).

Nitrogen inversion rates of N-substituted azetidines and aziridines have been studied by Bottini et al.[3]. The NMR spectra of pure 1-phenylaziridine 19 and pure 1-t-butylaziridine 20 at -77° possess only single sharp lines for the ring-hydrogens indicating that inversion was too rapid for measurement. In 0.01N methanolic sodium hydroxide solution, the inversion rate of 19 was decreased sufficiently to cause two ring-hydrogen bands to appear in the spectrum and permit determination of the rate constant as about 40 sec^{-1} at 60 ± 10°. It should be noted that this behaviour of the NMR spectra of 19 provides evidence for a pyramidal configuration about nitrogen in aromatic amines. The NMR spectra of a number of azetidine, pyrrolidine, pipiridine and morpholine derivatives have been examined. The spectra of these compounds were temperature independent above -77° indicating that inversion was too rapid for measurement. The spectrum of a methanol solution of 1-ethylazetidine 21 which was initially cooled to -196° and then allowed to warm, showed fine structure for spin spin coupling of the ring-hydrogen bands after the fine structure of the ethyl resonances appeared. However, no reasonably accurate estimate of rates of inversion at the nitrogen atom could be made. It has been possible to evaluate



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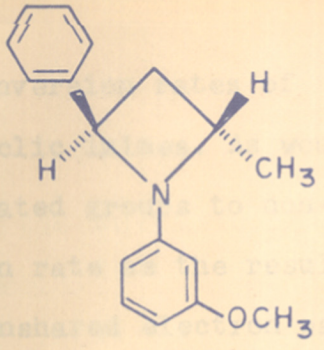

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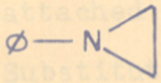
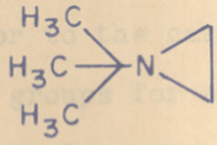


19



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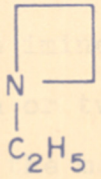
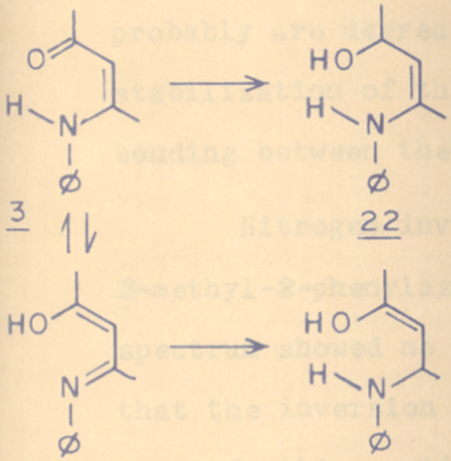
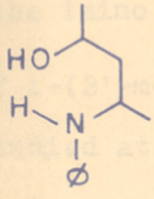


21

CHART-3

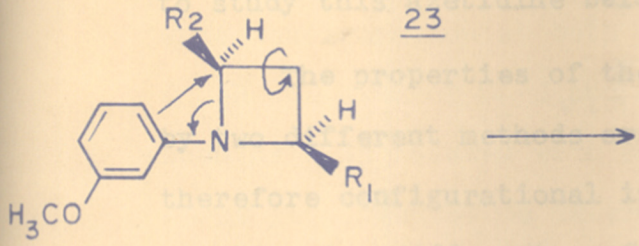


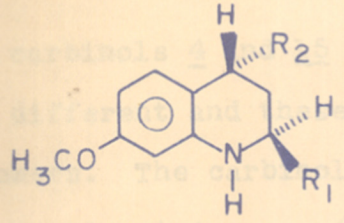
3 22 23

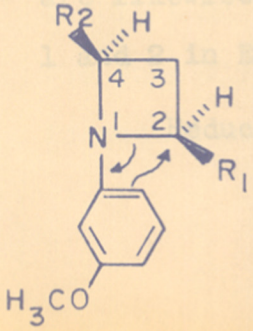


4

CHART-4







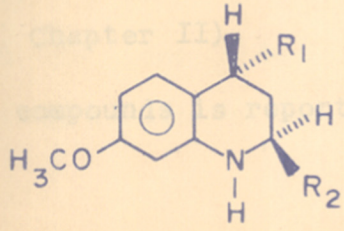


CHART-5

some factors which affect the inversion rates of non-planar nitrogen atoms in cyclic imines. As would be expected, attachment of unsaturated groups to non-planar nitrogen increases the inversion rate as the result of conjugation with the nitrogen unshared electron pairs. The rates are also increased by bulky groups whether attached to nitrogen or to the carbons of the imine ring. Substitution of alkyl groups for one hydrogen or two cis hydrogens attached to carbon appears to make the molecules assume preferred configurations with the N-substituent trans to the ring substituent. The inversion rates most probably are decreased in hydroxylic solvents because of stabilization of the separate configurations by hydrogen bonding between the solvent and the imino nitrogen.

Nitrogen inversion rate of 1-(3'-methoxyphenyl)-3-methyl-2-phenylazetidine was studied at -40° but NMR spectrum showed no change at this temperature indicating that the inversion was too rapid for measurement. Attempts to study this azetidine below -77° are underway.

The properties of the carbinols 4 and 15 prepared by two different methods are different and these are therefore configurational isomers. The carbinols 12 and 18 are likewise different configurational isomers (see Table 1 and 2 in Experimental part Chapter II).

Reduction of carbonyl compounds is reported to

proceed as follows[4,5,6,7]:-

$$4\ R_1\ R_2CO + M\ BH_4 \rightarrow MB\ (O\ CHR_1R_2)_4$$

Subsequent hydrolysis of the insoluble complex then gives primary or secondary alcohols.

$$MB\ (OCH\ R_1R_2)_4 + 2NaOH + H_2O \rightarrow Na_2BO_3 + 4R_1R_2CHOH$$

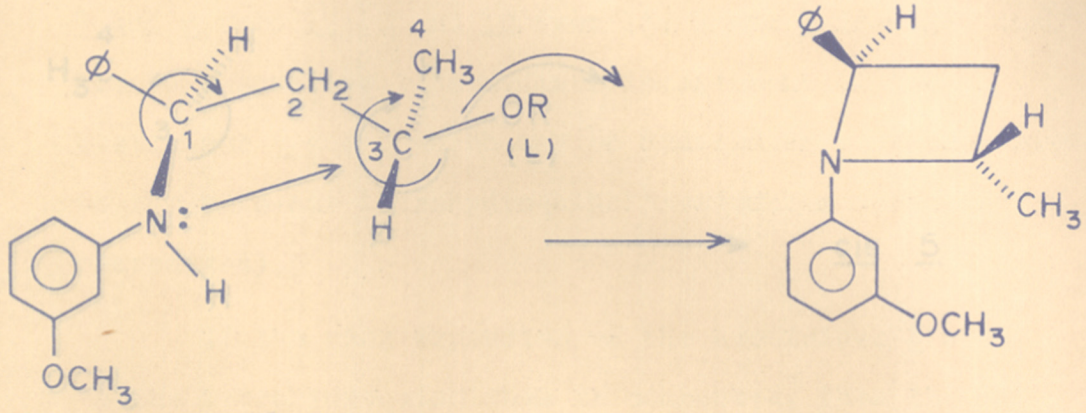
By potentiometric titration of a sodium borohydride solution with formaldehyde solution, Jensen[8] showed that all four hydrogen atoms participate in reduction in the same manner. Detailed study of the kinetics of the reaction of sodium borohydride with acetone, acetophenone, benzophenone and benzaldehyde has been done by Brown et al.[6]. From the study of the reduction of acetone in isopropanol and in diglyme Brown et al.[9,10] believe that the solvent participates in the reaction. β-Aminoketones when reduced with sodium borohydride gives β-amino-alcohols in such a way that the reduced alcohol will have preferentially the same configuration at the β-carbon atom. Incoming hydride is directed in such a way that reduced alcohol will have the same configuration at both the carbon atoms, C_1 and C_3 (C_1-R and C_3-R or C_1-S and C_3-S). However, when an enamino ketone such as 3 is reduced with sodium borohydride, the ketone first gets reduced to intermediate 22 or 23 and then the double bond gets reduced to give β-amino alcohol 4 (Chart 4). The enol first formed directs the incoming hydride ion in such a way that the resulting β-amino alcohol will have

different configurations at C_1 and C_3 atoms (C_1-R and C_3-S, or C_1-S and C_3-R). If in enamino ketone the double bond had got reduced first and then the saturated ketone, it would have led to a β-amino-alcohol where the configurations at C_1 and C_3 assymetric carbon atoms would have been identical. It has however been noted earlier that the β-amino-alcohol obtained from enamino ketone 3 gives preferentially cis-azetidine 5 whereas the β-amino-alcohol obtained from β-amino ketone 14 gives preferentially the trans azetidine 6. The dissimilar configurations would be favoured in carbinols 4 and 15 and in case of 15 and 18 similar configurations at both the carbon atoms would be favoured.

The stereoselective formation of cis and trans-azetidines can then be rationalized by assuming that during cyclisation the electron pair from N-H group eliminates the leaving group by an attack from the hinder side (Charts 6 and 7).

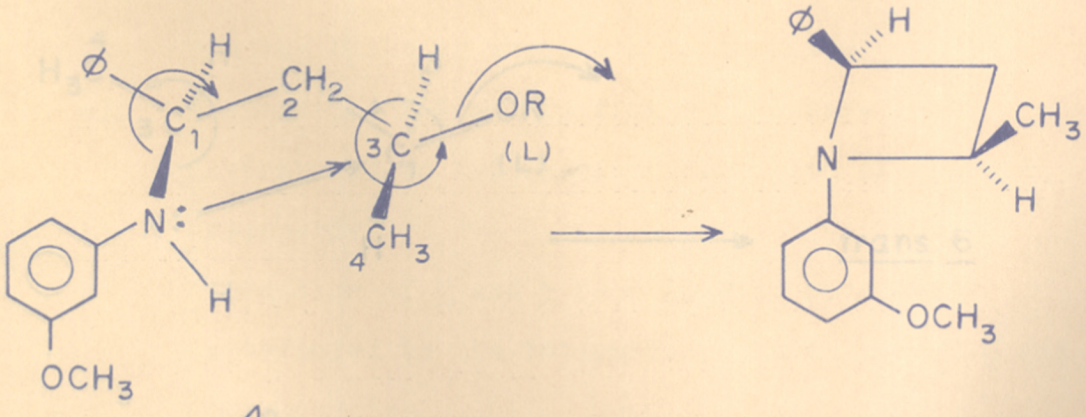
Stereochemistry and rationale of formation of tetrahydroquinolines from the carbinols 4, 12, 15 and 18 (Charts 1 and 2).

Base-catalysed conversion (cyclodehydration) of the carbinols 4, 12, 15 and 18 in presence of triphenylphosphine dibromide to the tetrahydroquinolines may be proceeding directly to give the normally expected tetrahydroquinolines



15 trans 6

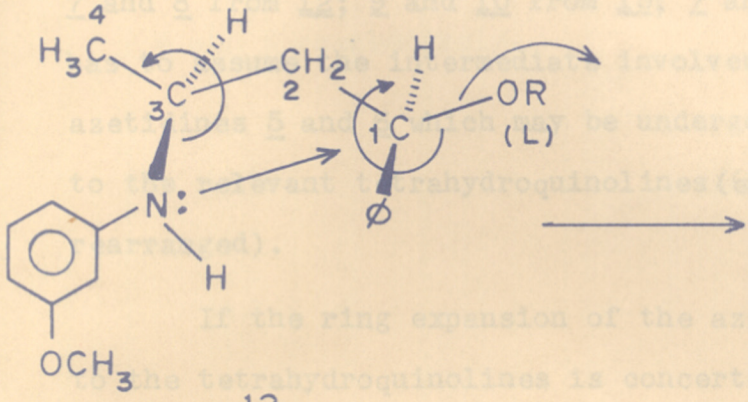
CONFIGURATION AT C_1 – R
C_3 – R



4 cis 5

CONFIGURATION AT C_1 – R
C_3 – S

CHART–6

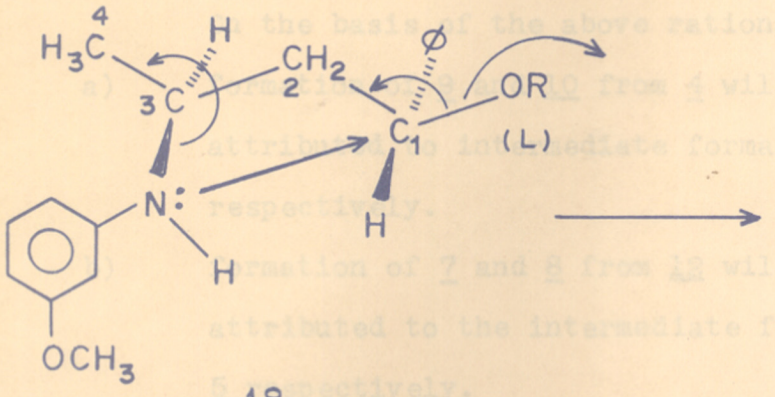


cis 5

12

CONFIGURATION AT C_1 –R

C_3 –S



trans 6

18

CONFIGURATION AT C_1 –S

C_3 –S

CHART – 7

(e.g. 7 from 4; 9 and 10 from 12; 7 and 8 from 15; 9 and 10 from 18). On the other hand for the formation of rearranged tetrahydroquinolines (9 and 10 from 4; 7 and 8 from 12; 9 and 10 from 15; 7 and 8 from 18) one has to assume the intermediate involvement of the azetidines 5 and 6 which may be undergoing ring expansion to the relevant tetrahydroquinolines (either normal or rearranged).

If the ring expansion of the azetidines 5 and 6 to the tetrahydroquinolines is concerted, then the sterdochemistry of the C_1 and C_4 substituents in the tetrahydroquinolines will have to be the reverse of that of the C_2 and C_4 substituents in the parent azetidines from which the tetrahydroquinolines are derived. This expectation follows from the suprafacial sigmatropic nature of the rearrangement which necessitates an inversion at the carbon atom involved in the rearrangement (Chart 5).

On the basis of the above rationale -

a) formation of 9 and 10 from 4 will have to be attributed to intermediate formation of 6 and 5 respectively.

b) formation of 7 and 8 from 12 will have to be attributed to the intermediate formation of 6 and 5 respectively.

c) formation of 9 and 10 from 15 will have to be attributed to the intermediate formation of 6 and 5

respectively.

d) formation of 7 and 8 from 18 will have to be attributed to the intermediate formation of 6 and 5 respectively.

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

Cyclisation of 1-(3'-methoxyphenylamino)-1-phenylbutane-3-ol 4:

Treatment of the alcohol 4 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution was stirred at -5° for 72 hr. and work up as described in the experimental section of Chapter III gave brownish oil, (9.2 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 4 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet. ether	Colourless plates	Triphenyl-phosphine	1.03
2	95% pet.ether + 5% benzene	Yellowish oil		0.07
3	95% pet.ether + 5% benzene	Colourless plates.		0.46
4	25% pet. ether+ 75% benzene	Yellowish oil		0.98
5	Benzene	Pale yellow oil.	Recovered 4	1.10
6	50% benzene + 50% Ethyl acetate.	Colourless prisms.	Triphenyl-phosphine oxide.	5.22

i) Alcohol converted in the reaction 78%.

ii) Total yield 38%.

iii) Fraction 2. The yellowish oil obtained was distilled under vacuum to give trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6 as yellow oil, b.p. $85^{o}/9.56 \times 10^{-3}$ mm, (yield 4.1%), (Found: C, 81.1; H, 6.7; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

The PMR spectrum of 6 shows the following characteristics: C_2, 1.25, d, 3P; C_2, 4.0, m, 1P; C_3, 1.66 - 2.33, m, 2P; C_4, 4.16, t, 1P; $C_{5,6,7,9}$ and C_4-phenyl, 5.96 - 7.23, m, 9P; C_8, 3.66, s, 3P.

Fraction 3. The colourless solid obtained was crystallised from methanol to give cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 as colourless plates, m.p. 89^{o}, (yield 11.4%), (Found: C, 80.8; H, 6.7; N, 5.4. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.7; N, 5.6%).

Fraction 4. The yellow oil obtained was distilled under vacuum to give pale yellow oil, b.p. $145^{o}/9.56 \times 10^{-3}$ mm (yield, 22.5%) and was found to be a mixture of cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 7, cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 9 and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 10 in 29:37:34 ratio by VPC analysis. (Found: C, 81.3; H, 6.4; N, 5.2. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

Cyclisation of 3-(3'-methoxyphenylamino)1-phenylbutane-1-ol 12:

Treatment of the alcohol 12 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution was stirred at -5° for 72 hr. The work up as above gave brownish oil (8.5 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 12 (5 g) Silica gel 300 g Grade II

Frac.No.	Eluent	Remark		Wt. g
1	Pet.ether	Colourless plates	Triphenyl-phosphine	0.85
2	95% pet.ether + 5% benzene	Yellowish oil		0.22
3	95% pet.ether + 5% benzene	Colourless plates.		0.7
4	25% pet.ether + 75% benzene	Yellowish oil.		0.59
5	Benzene	Pale yellow oil.	Recovered 12	0.85
6	50% benzene + 50% ethyl acetate.	Colourless prisms.	Triphenyl-phosphine oxide.	4.92

i) Alcohol converted in the reaction 82%.

ii) Total yield 37.5%.

iii) Fraction 2. The yellowish oil obtained was distilled

under vacuum to give a yellow oil, b.p. $85^{\circ}/9.56 \times 10^{-3}$ mm (yield, 4.5%) which was identified as trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6. The spectral analysis and TLC was identical with authentic sample.

Fraction 3. The colourless solid obtained was crystallised from methanol to give cis-1-(3'-methoxyphenyl)2-methyl-4-phenylazetidine 5 as colourless plates, (m.p. 89°), (yield 15%), which was identified by TLC, spectral analysis and also identical with authentic sample.

Fraction 4. The yellowish oil, b.p. $140^{\circ}/9.56 \times 10^{-3}$ mm was proved to be a mixture of cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 7, trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 8, cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 9 and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 10 in 51:13:21:15 ratio as characterised by VPC analysis, (yield 18%), (Found: C, 81.4; H, 6.6; N, 5.3. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%).

Cyclisation of 1-(3'-methoxyphenylamino)-1-phenyl-butane-3-ol 15:

Treatment of the alcohol 15 (5 g) with triphenylphosphine dibromide, (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution was stirred at -5° for 72 hr. The work up as above gave brownish oil, (8.5 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 15 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet.ether	Colourless plates.	Triphenyl-phosphine	0.52
2	95% pet.ether + 5% benzene	Yellowish oil		1.40
3	95% pet.ether + 5% benzene	Colourless plates.		0.91
4	25% pet.ether + 75% benzene	Yellowish oil.		0.58
5	Benzene	Yellow oil	Recovered 15	1.03
6	50% benzene + 50% ethyl acetate.	Colourless prisms.	Triphenyl-phosphine oxide.	4.01

i) Alcohol converted in the reaction 80%.

ii) Total yield 75%.

iii) Fraction 2. The yellowish oil obtained was distilled under vacuum to give a yellow oil, (b.p. $85^{\circ}/2.13 \times 10^{-3}$ mm, yield 35%) which was identified as trans-1-(3'-methoxy-phenyl)-2-methyl-4-phenylazetidine 6. The spectral analysis and TLC was identical with the authentic sample.

Fraction 3. The colourless solid obtained was crystallised from methanol to give cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 as colourless plates, m.p. 89°, (yield 22.7%), which was identified by TLC, spectral analysis and identical with authentic sample.

Fraction 4. The yellowish oil, b.p. 140-45°/9.56 x 10^{-3} mm was proved to be a mixture (yield, 17.3%). (Found: C, 81.4; H, 7.1; N, 5.9. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%) of 7, 8, 9 and 10 in 4: 14: 33: 49 ratio respectively as characterised by VPC analysis.

Cyclisation of 3-(3'-methoxyphenylamino)-1-phenylbutane-1-ol 18:

Treatment of the alcohol 18 (5 g) with triphenylphosphine dibromide (prepared from 6.8 g of triphenylphosphine and 1.2 g of bromine in 60 ml acetonitrile solution), followed by interaction with triethylamine (5.2 g) in 20 ml acetonitrile solution, was stirred at -5° for 72 hr. The work up as above gave brownish oil, (9.5 g) which was chromatographed on silica gel.

CHROMATOGRAM

Alcohol 18 (5 g) Silica gel 300 g Grade II

Fr.No.	Eluent	Remark		Wt. g
1	Pet. ether	Colourless plates.	Triphenyl-phosphine	0.73
2	95% pet.ether + 5% benzene	Yellowish oil		1.54
3	95% pet.ether + 5% benzene	Colourless plates.		0.34
4	25% pet.ether + 75% benzene	Yellowish oil		0.72
5	Benzene	Yellow oil	Recovered 18	0.93
6	50% benzene + 50% ethyl acetate	Colourless prisms.	Triphenyl-phosphine oxide.	5.21

i) Alcohol converted in the reaction 81%.

ii) Total yield 65%.

iii) Fraction 2. The yellowish oil obtained was distilled under vacuum to give a yellow oil, b.p. $85^{o}/9.56 \times 10^{-3}$ mm, (yield, 38.5%), which was identified as trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6. The spectral analysis and TLC was identical with authentic sample.

Fraction 3. The colourless solid obtained was crystallised from methanol to give cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5 as colourless plates, m.p. 89^{o}, (yield 8.5%). The spectral analysis and TLC was identical with authentic sample.

Fraction 4. The yellow oil b.p. $140^{o}/9.56 \times 10^{-3}$ mm, (yield 18%), (Found: C, 81.3; H, 6.5; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of 7, 8, 9 and 10 in 8: 62: 17: 13 ratio as characterised by VPC analysis.

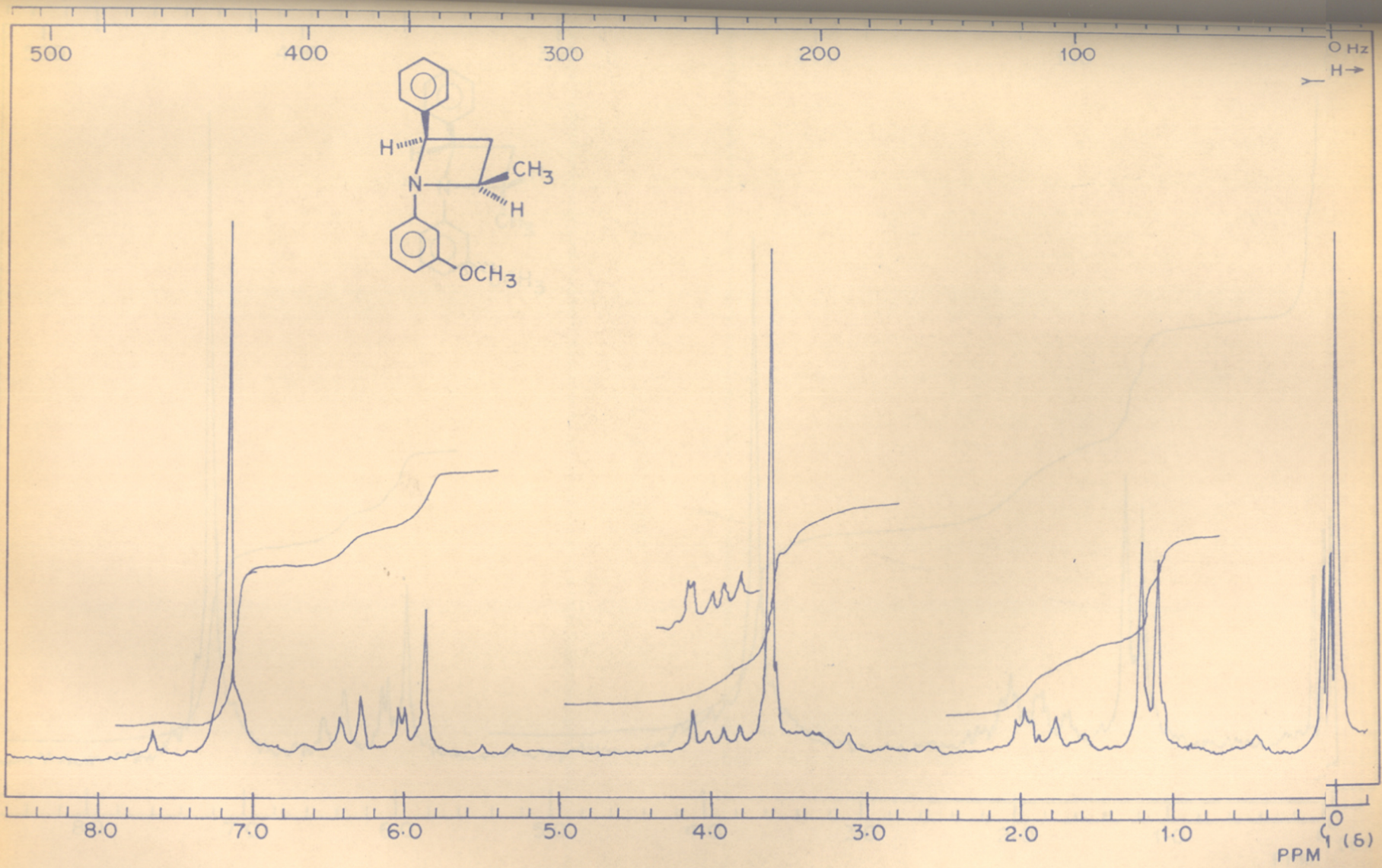

500
400
300
200
100
0 Hz
H
H
N
CH3
H
OCH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM
τ (δ)

FIG. – 1.

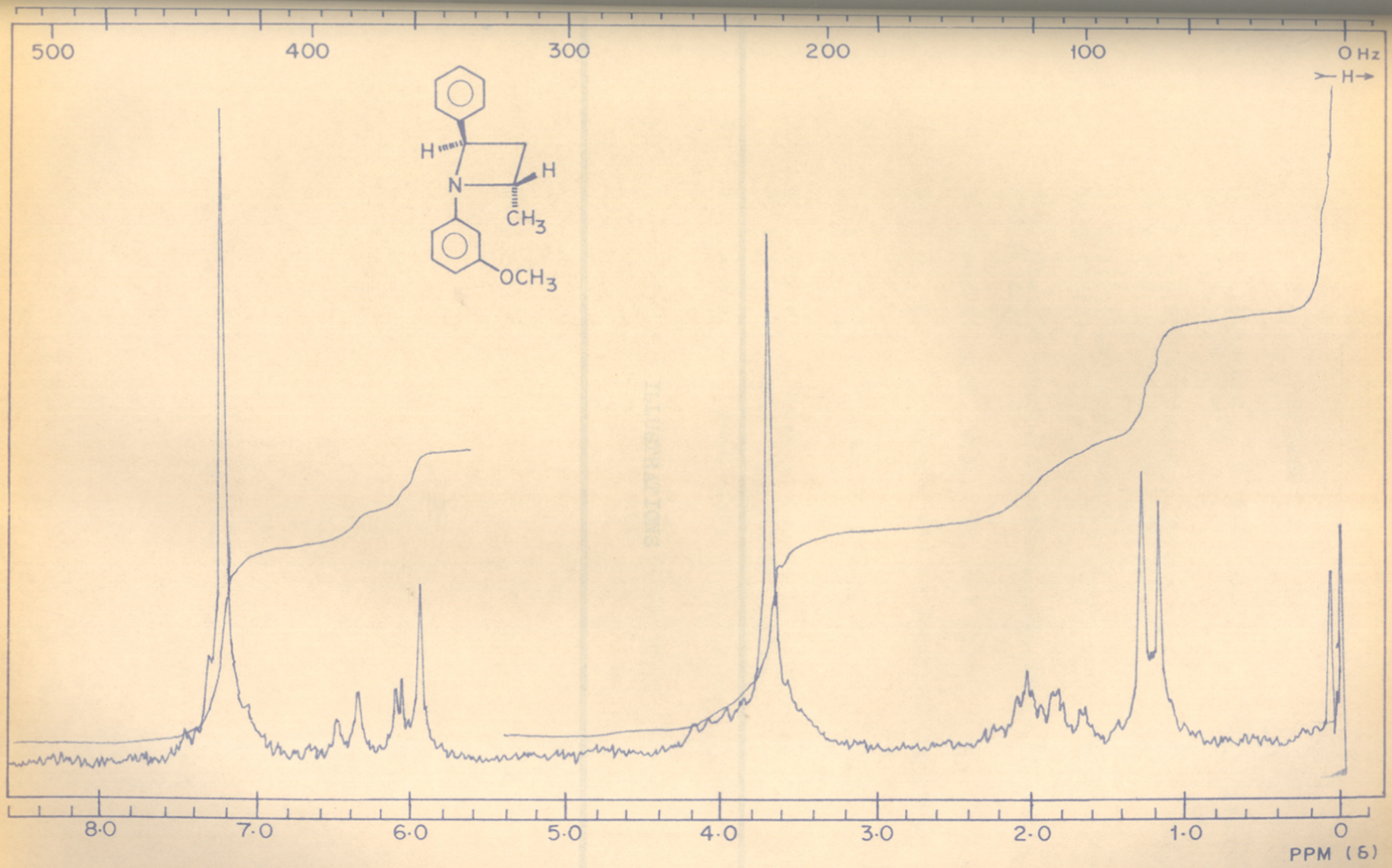

500
400
300
200
100
0 Hz
H
H
N
H
CH3
OCH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. – 2.

ILLUSTRATIONS

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CHAPTER V - SOME REARRANGEMENTS OF N-ARYLAZETIDINES

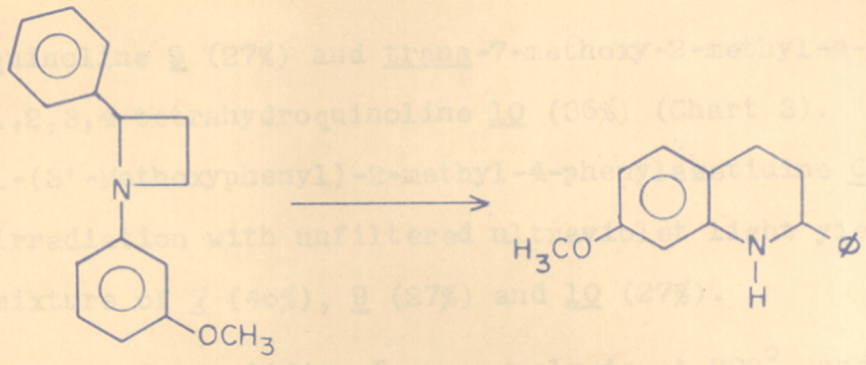
SOME REARRANGEMENTS OF N-ARYLAZETIDINES

It was reported by Tilak et al.[1] that 1-(3'-methoxyphenyl)-2-phenylazetidine 1 appeared to be quite stable but it rearranged partially to 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 2 when its solution in n-hexane was exposed to sunlight. 1-(3'-Methoxyphenyl)-2-phenylazetidine 1 also changes to 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 2 on prolonged heating (Chart 1).

1-(3'-Methoxyphenyl)-2,4-dimethylazetidine 3 on irradiation with unfiltered ultraviolet light emitted by 125 Watt mercury vapour lamp yielded 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 4. On pyrolysis at 290° under nitrogen and by treatment with 70% sulphuric acid, 3 also gave 4 (This work was recently published[2]) (Chart 2).

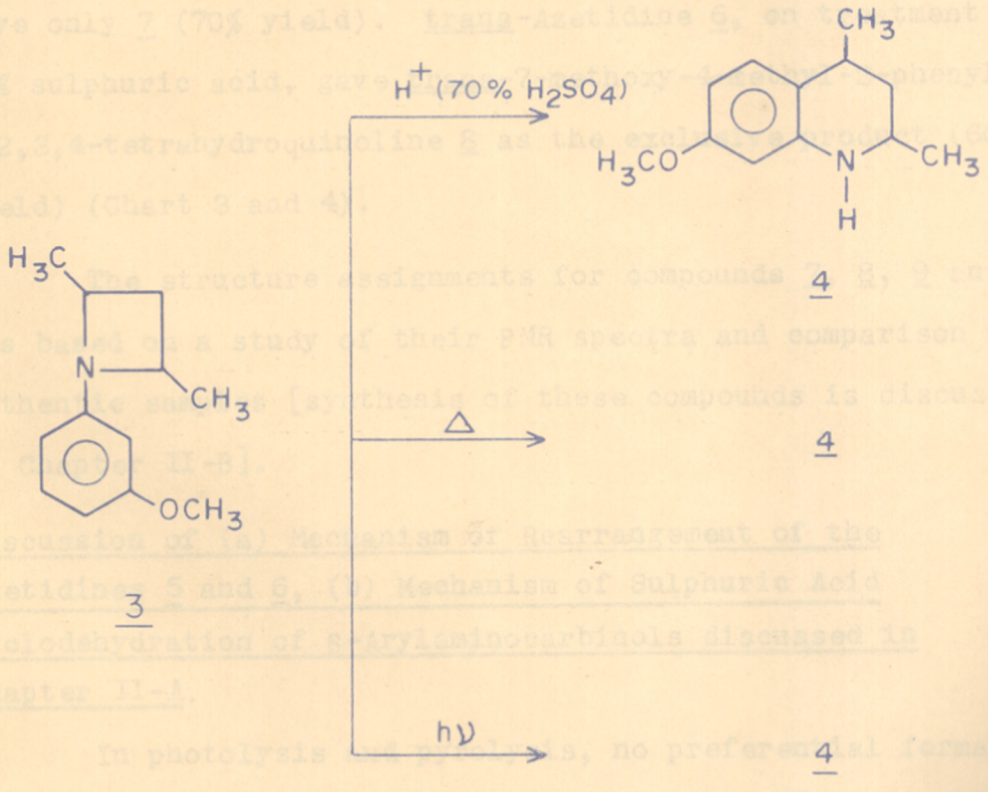
In Chapter IV we have described a stereoselective synthesis of cis-1-(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 5 and trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6. These compounds on exposure to ultraviolet light, or treatment with 70% sulphuric acid or pyrolysis at 290° gave 2,4-disubstituted-1,2,3,4-tetrahydroquinolines.

cis-1-(3'-Methoxyphenyl)-2-methyl-4-phenylazetidine 5 on irradiation with unfiltered ultraviolet light emitted by 125 Watt mercury vapour lamp yielded a mixture of cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 7 (36%), cis-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydro-



1 2

CHART-1



3 4 4 4

CHART-2

quinoline 9 (27%) and trans-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 10 (36%) (Chart 3). trans-1-(3'-Methoxyphenyl)-2-methyl-4-phenylazetidine 6, on irradiation with unfiltered ultraviolet light yielded a mixture of 7 (46%), 9 (27%) and 10 (27%).

cis-Azetidine 5, on pyrolysis at 290°, under nitrogen atmosphere, gave a mixture of 7 (37%), 9 (25%) and 10 (37%). trans-Azetidine 6, on pyrolysis as above gave a mixture of 7 (40%), 9 (40%) and 10 (20%).

cisAzetidine 5, on treatment with 70% sulphuric acid, gave only 7 (70% yield). trans-Azetidine 6, on treatment with 70% sulphuric acid, gave trans-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 8 as the exclusive product (60% yield) (Chart 3 and 4).

The structure assignments for compounds 7, 8, 9 and 10 was based on a study of their PMR spectra and comparison with authentic samples [synthesis of these compounds is discussed in Chapter II-B].

Discussion of (a) Mechanism of Rearrangement of the Azetidines 5 and 6, (b) Mechanism of Sulphuric Acid Cyclodehydration of β-Arylaminocarbinols discussed in Chapter II-A.

In photolysis and pyrolysis, no preferential formation of products was observed. However, the products 9 and 10 in which N-C-(Ø) bond in azetidines 5 and 6 is broken, are formed

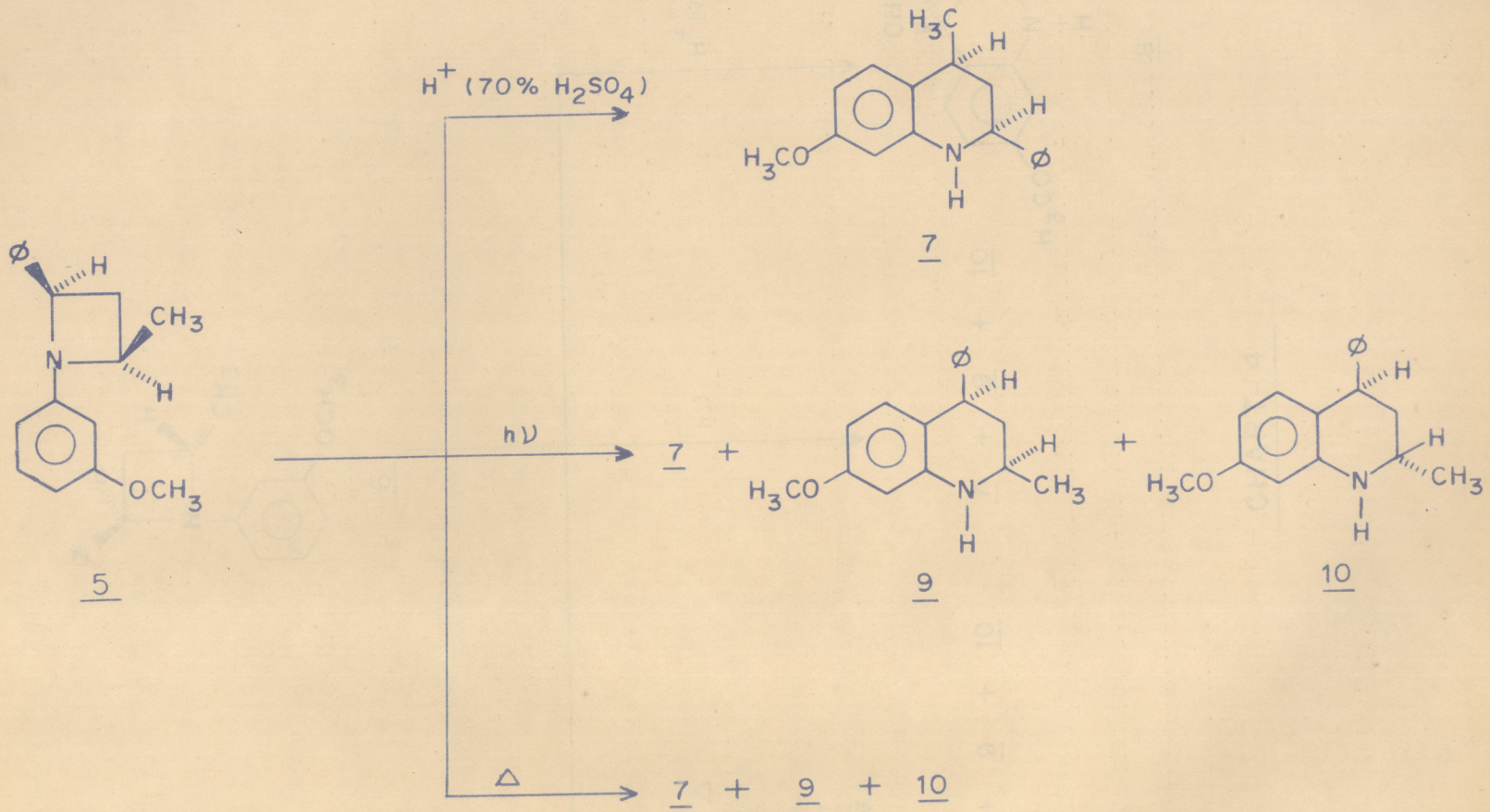
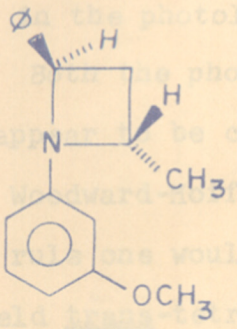
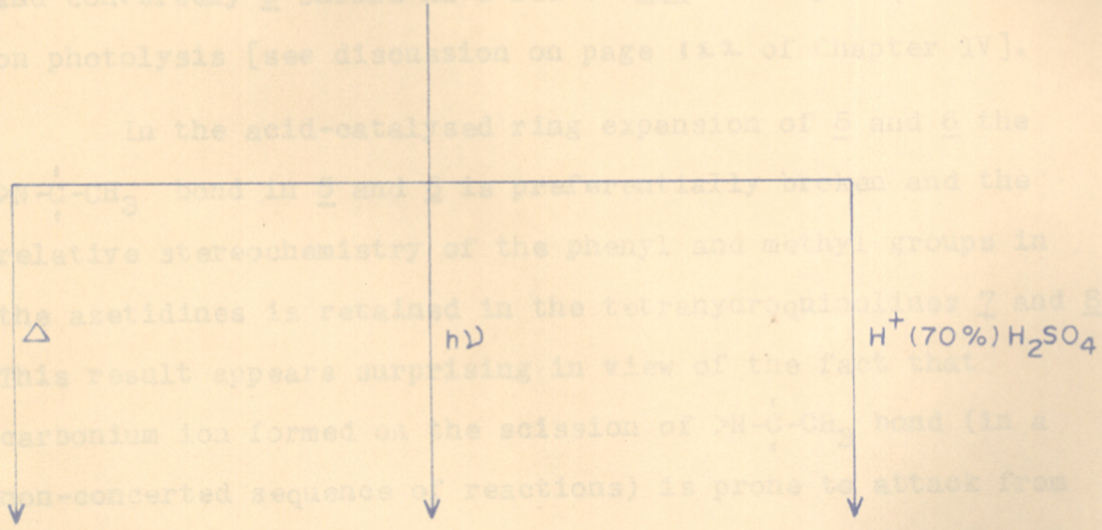


CHART-3

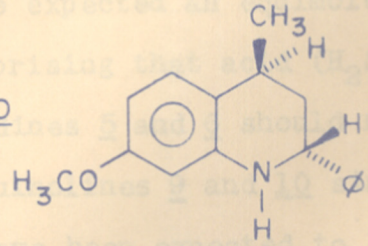


6



7 + 9 + 10

7 + 9 + 10



8

CHART-4

in greater proportion. One would have expected a greater stereospecificity in the photolysis of 5 and 6, but this was not observed. Both the photolysis and pyrolysis reactions therefore do not appear to be concerted as the end products do not confirm to Woodward-Hoffmann rule.[3] Thus according to Woodward-Hoffmann rule one would have expected the cis-azetidine 5 to yield trans-tetrahydroquinolines on pyrolysis and conversely 5 should have led to cis-tetrahydroquinolines on photolysis [see discussion on page 122 of Chapter IV].

In the acid-catalysed ring expansion of 5 and 6 the $>N-\overset{|}{C}-CH_3$ bond in 5 and 6 is preferentially broken and the relative stereochemistry of the phenyl and methyl groups in the azetidines is retained in the tetrahydroquinolines 7 and 8. This result appears surprising in view of the fact that carbonium ion formed on the scission of $>N-\overset{|}{C}-CH_3$ bond (in a non-concerted sequence of reactions) is prone to attack from both the surfaces and one would have expected an equimolecular mixture of 7 and 8. It is also surprising that acid (H_2SO_4) induced ring expansion of the azetidines 5 and 6 should not have yielded any of the tetrahydroquinolines 9 and 10 since a benzylic carbonium ion (A), may have been expected to be formed to a larger extent than the carbonium ion on a secondary carbon atom (B) (Chart 5). The exclusive formation of 7 from 5 and 8 from 6 on sulphuric acid treatment is however interesting in view of the fact that it has been observed earlier in Chapter II-A that cyclodehydration of the carbinols 12 and 14

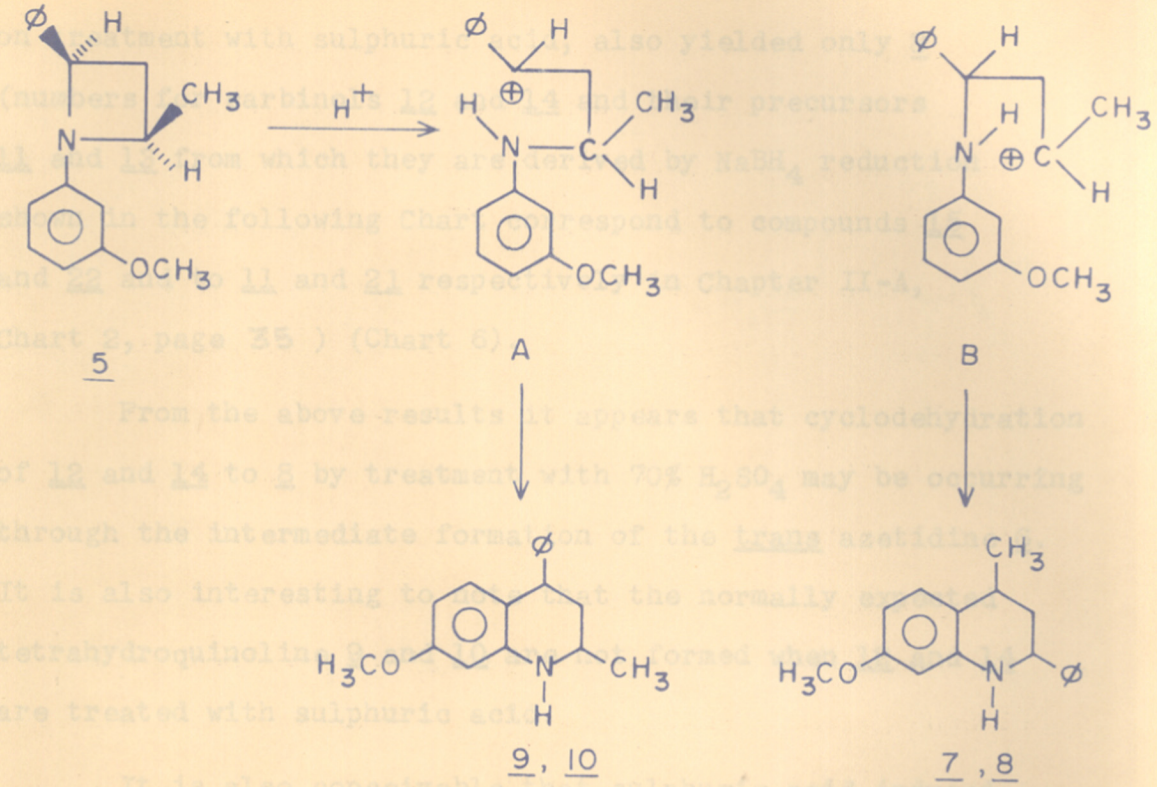
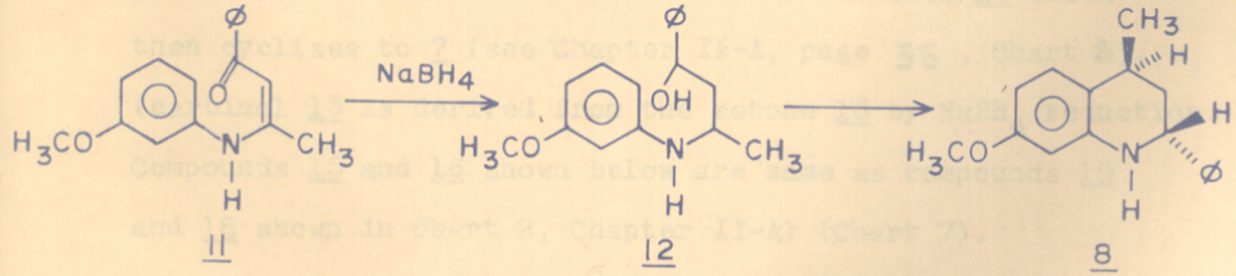


CHART-5



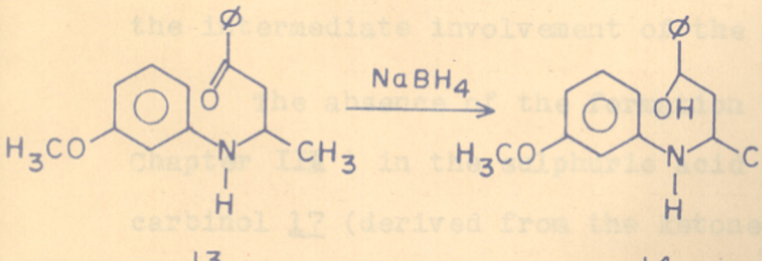


CHART-6

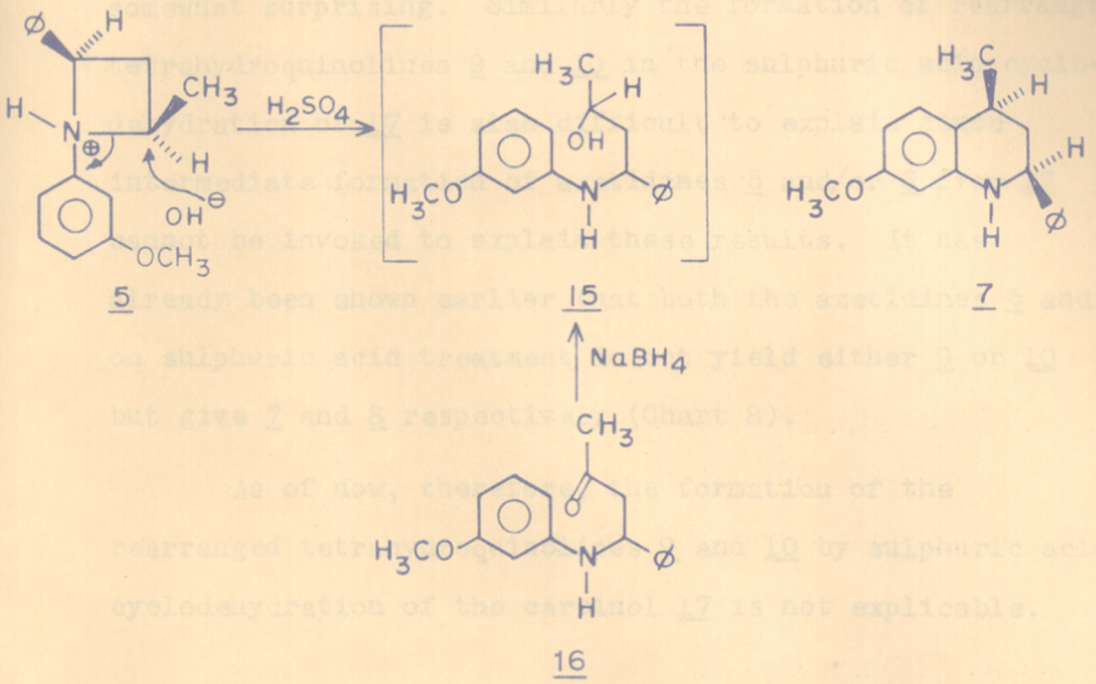
on treatment with sulphuric acid, also yielded only 8 (numbers for carbinols 12 and 14 and their precursors 11 and 13 from which they are derived by $NaBH_4$ reduction shown in the following Chart correspond to compounds 15 and 22 and to 11 and 21 respectively in Chapter II-A, Chart 2, page 35) (Chart 6).

From the above results it appears that cyclodehydration of 12 and 14 to 8 by treatment with 70% H_2SO_4 may be occurring through the intermediate formation of the trans azetidine 6. It is also interesting to note that the normally expected tetrahydroquinoline 9 and 10 are not formed when 12 and 14 are treated with sulphuric acid.

It is also conceivable that sulphuric acid induced conversion of the cis-azetidine 5 to 7 may be also taking place by intermediate formation of the carbinol 15 which then cyclizes to 7 (see Chapter II-A, page 35 , Chart 2), (carbinol 15 is derived from the ketone 16 by $NaBH_4$ reduction. Compounds 15 and 16 shown below are same as compounds 19 and 18 shown in Chart 2, Chapter II-A) (Chart 7).

Conversely 15 may be getting converted to 7 through the intermediate involvement of the cis-azetidine 5.

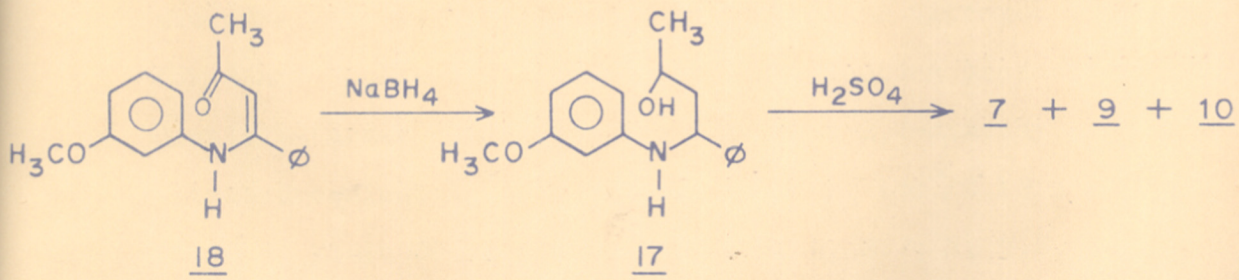
The absence of the formation of 8 (compound 16 in Chapter III) in the sulphuric acid cyclodehydration of the carbinol 17 (derived from the ketone 18 by $NaBH_4$ reduction), (compounds 17 and 18 correspond to compounds 10 and 9 in



5 15 7

16

CHART-7



18 17 7 + 9 + 10

CHART-8

Chart 2, Chapter II-A) and the carbinol 15 appears somewhat surprising. Similarly the formation of rearranged tetrahydroquinolines 9 and 10 in the sulphuric acid cyclodehydration of 17 is also difficult to explain since intermediate formation of azetidines 5 and/or 6 from 17 cannot be invoked to explain these results. It has already been shown earlier that both the azetidines 5 and 6 on sulphuric acid treatment do not yield either 9 or 10 but give 7 and 8 respectively (Chart 8).

As of now, therefore, the formation of the rearranged tetrahydroquinolines 9 and 10 by sulphuric acid cyclodehydration of the carbinol 17 is not explicable.

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

Photolysis of 1-(3'-methoxyphenyl)-2,4-dimethylazetidine 3:

Azetidine 3 (0.5 g) was dissolved in cyclohexane (500 ml) and irradiated with unfiltered ultraviolet light emitted by 125 Watt mercury vapour lamp for 3 hr. Solvent was evaporated and reaction product was distilled under vacuum to give 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 4 as yellow oil, b.p. $150^{\circ}/2.13 \times 10^{-2}$ mm (0.31 g, yield 62%). (Found: C, 75.5; H, 8.9; N, 7.4 . $C_{12}H_{17}NO$ requires: C, 75.3; H, 8.9; N, 7.3%).

The compound 4 was characterised by its spectral analysis and identification with authentic sample.

Pyrolysis of 1-(3'-methoxyphenyl)-2,4-dimethylazetidine 3:

Azetidine 3 (0.5 g) was dissolved in decalin (500 ml) and pyrolysis was carried out at 290° under nitrogen atmosphere for 3 hr. Solvent was evaporated and reaction product was distilled under vacuum to give 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 4 as yellow oil, b.p. $150^{\circ}/2.13 \times 10^{-2}$ mm, (0.25 g, yield 50%), (Found: C, 75.5; H, 8.7; N, 7.5. $C_{12}H_{17}NO$ requires: C, 75.3; H, 8.9; N, 7.3%).

Compound 4 was characterised by its spectral analysis and identification with authentic sample.

Acid-catalysed rearrangement of 1-(3'-methoxyphenyl)-2,4-dimethylazetidine 3:

To a mixture of azetidine 3 (0.5 g) and crushed ice (5 g),

70% sulphuric acid (5 ml) was added gradually with shaking. This mixture was warmed on boiling water bath for thirty minutes. The mixture was kept at room temperature for 48 hr., neutralised with aqueous sodium hydroxide and then extracted with ether. The ether extract on work up gave an oil, which was distilled under vacuum to give 7-methoxy-2,4-dimethyl-1,2,3,4-tetrahydroquinoline 4 as yellow oil, b.p. $150^{\circ}/2.13 \times 10^{-2}$ mm (0.29 g, yield 58%), (Found: C, 75.0; H, 8.8; N, 7.4. $C_{12}H_{17}NO$ requires: C, 75.3; H, 8.9; N, 7.3%).

Compound 4 was characterised by spectral analysis and identification with authentic sample.

Photolysis of cis-1-(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 5:

Azetidine 5 (0.5 g) was dissolved in cyclohexane (500 ml) and irradiated with unfiltered ultraviolet light emitted by 125 Watt mercury vapour lamp for 3 hr. The work up as above gave pale yellow oil, b.p. $145^{\circ}/9.56 \times 10^{-3}$ mm (0.25 g, yield 50%), (Found: C, 81.3; H, 6.4; N, 5.6. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of 7, 9 and 10 in 36:27:36 ratio respectively as characterised by VPC analysis.

Photolysis of trans-1-(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 6:

Azetidine 6 (0.5 g) was dissolved in cyclohexane (500 ml)

and irradiated with unfiltered ultraviolet light emitted by 125 Watt mercury vapour lamp for 3 hr. Solvent was evaporated and work up as above gave pale yellow oil, b.p. 140-45°/9.56 x 10^{-3} mm (0.21 g, yield 42%), (Found: C, 81.5; H, 6.5;N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of 7, 9 and 10 in 46:27:27 ratio respectively as characterised by VPC analysis.

Pyrolysis of cis-1(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 5:

Azetidine 5 (0.5 g) was dissolved in decalin (500 ml) and pyrolysed at 290° under nitrogen atmosphere for 3 hr. Solvent was evaporated and work up as above gave pale yellow oil, b.p. 140°/9.56 x 10^{-3} mm (0.23 g, yield 46%), (Found: C, 81.5; H, 7.0; N, 5.8. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of 7, 9, 10 in 37:26:37 ratio respectively as characterised by VPC analysis.

Pyrolysis of trans-1-(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 6:

Azetidine 6 (0.5 g) was dissolved in decalin (500 ml) and pyrolysis was carried out at 290° under nitrogen atmosphere for 3 hr. The solvent was evaporated and work up as above gave pale yellow oil, b.p. 145°/9.56 x 10^{-3} mm (0.25 g, yield 50%), (Found: C, 81.5; H, 6.7; N, 5.4. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%), which was proved to be a mixture of 7, 9, 10 in 40:40:20 ratio respectively as characterised by VPC analysis.

Acid-catalysed rearrangement of cis-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 5:

To a mixture of azetidine 5 (0.5 g) and crushed ice (5 g), 70% sulphuric acid (5 ml) was added gradually and on work up as above gave 7 as colourless needles crystallised from methanol, m.p. 92° (0.35 g, yield 70%), (Found: C, 81.5; H, 7.1; N, 5.5, $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%) which was characterised by its spectral analysis and comparison with authentic sample.

Acid-catalysed rearrangement of trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 6:

To a mixture of azetidine 6 (0.5 g) and crushed ice (5 g), 70% sulphuric acid (5 ml) was added gradually and on work up as above gave 8 as colourless oil, b.p. $100°/9.56 \times 10^{-3}$ mm (0.30 g), (yield 60%), (Found: C, 81.4; H, 7.1; N, 6.0. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%) which was characterised by its spectral analysis and comparison with authentic sample.

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SUMMARY OF THE PRESENT WORK

SUMMARY

CHAPTER I

In this Chapter previous work carried out in this laboratory which led to the present investigation is discussed. The acid-catalysed cyclodehydration of alkyl/aryl β-aminoethylketones and disproportionation of the intermediate 1,2-dihydroquinolines and quinolines has been studied by Tilak *et al.*[1,2]. The mechanism of the formation of quinolines and tetrahydroquinolines from 1,2-dihydroquinoline and its precursors such as alkyl/aryl β-aminoethyl ketones is analogous to the acid-catalysed disproportionation of Δ^3-thiachromens[3,4] and Δ^3-chromenes[5]. This disproportionation involves an intermolcular hydride transfer between one molecule of dihydroquinoline acting as hydride donor and another molecule of the same as in its protonated form as a hydride acceptor. Tilak *et al.*[6] were interested in the synthesis of quinoline derivatives which would not involve disproportionation observed in the above synthesis. When *cis*-2-(3'-methoxyphenylaminomethylene)cyclohexanone was treated with PPA 7-methoxy-1,2,3,4-tetrahydrophenanthridine was obtained whereas treatment with aniline hydrochloride/anhydrous $ZnCl_2$ in boiling ethanol gave 6-methoxy-1,2,3,4-tetrahydroacridine. *Cis*-(3'-methoxyphenylaminomethylene)-cycloalkanones were also cyclodehydrated by formic acid, lactic acid and other acidic reagents. Acid-catalysed

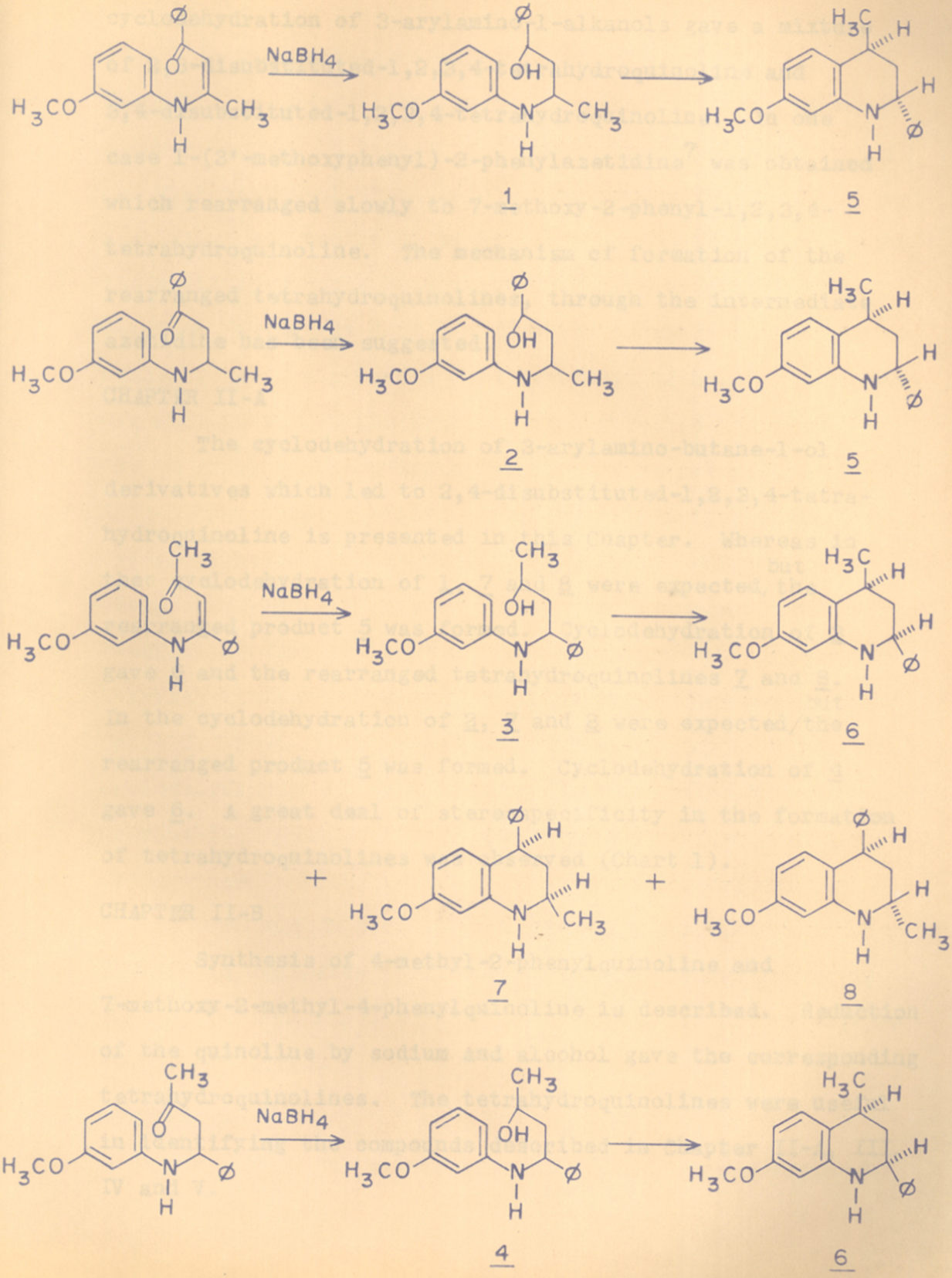


CHART-1

cyclodehydration of 3-arylamino-1-alkanols gave a mixture of 2,3-disubstituted-1,2,3,4-tetrahydroquinoline and 3,4-disubstituted-1,2,3,4-tetrahydroquinoline. In one case 1-(3'-methoxyphenyl)-2-phenylazetidine[7] was obtained which rearranged slowly to 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline. The mechanism of formation of the rearranged tetrahydroquinolines, through the intermediate azetidine has been suggested.

CHAPTER II-A

The cyclodehydration of 3-arylamino-butane-1-ol derivatives which led to 2,4-disubstituted-1,2,3,4-tetrahydroquinoline is presented in this Chapter. Whereas in the cyclodehydration of 1, 7 and 8 were expected, but the rearranged product 5 was formed. Cyclodehydration of 3 gave 6 and the rearranged tetrahydroquinolines 7 and 8. In the cyclodehydration of 2, 7 and 8 were expected, but the rearranged product 5 was formed. Cyclodehydration of 4 gave 6. A great deal of stereospecificity in the formation of tetrahydroquinolines was observed (Chart 1).

CHAPTER II-B

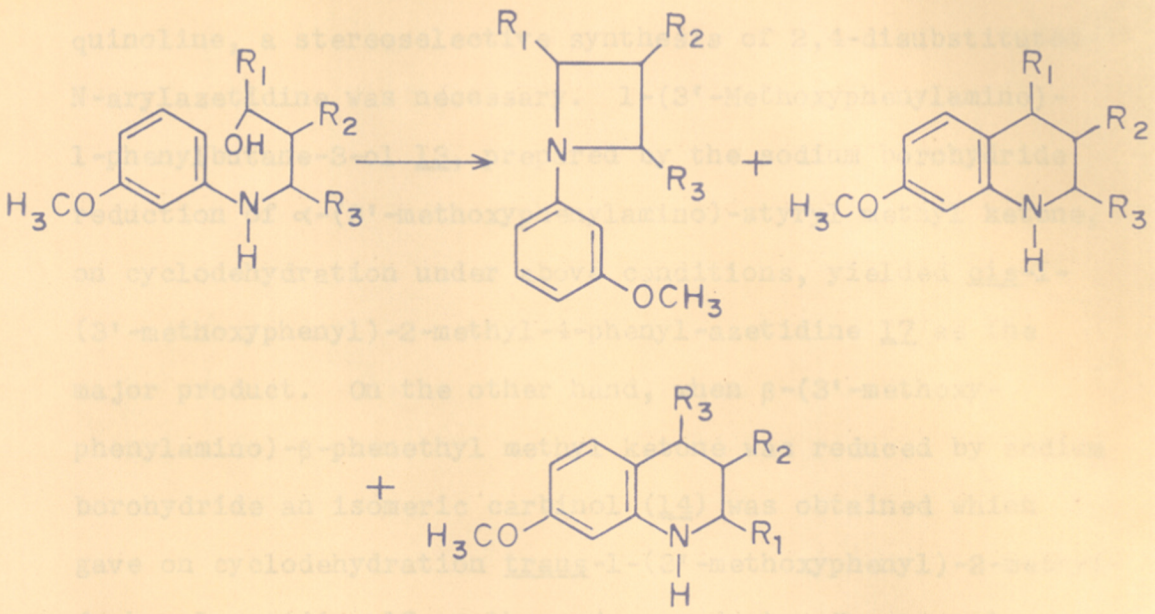
Synthesis of 4-methyl-2-phenylquinoline and 7-methoxy-2-methyl-4-phenylquinoline is described. Reduction of the quinoline by sodium and alcohol gave the corresponding tetrahydroquinolines. The tetrahydroquinolines were useful in identifying the compounds described in Chapter II-A, III, IV and V.

CHAPTER III

In the rearrangement reactions mentioned in Chapter II-A, N-arylazetidines were likely intermediates. However, except in case of 3-(3'-methoxyphenylamino)-1-phenylpropane-1-ol where 1-(3'-methoxyphenyl)-2-phenyl-azetidine[7] was isolated, in none of the β-arylaminocarbinols the azetidines could be isolated in the cyclodehydration reaction (using 70% H_2SO_4). In order to elucidate the above rearrangement reactions a good synthesis of N-arylazetidines was necessary. In the synthesis described in this Chapter, the OH group of the β-arylamino alkanol is probably converted into oxophosphonium bromide group by interaction with triphenylphosphine dibromide. The oxophosphonium bromide group then probably acts as a good leaving group when the reaction product is treated with triethylamine. Some of the N-arylazetidines synthesised by this method are given in Chart 2. However, this method could not be applied for the cyclodehydration of 3-(3'-methoxyphenylamino)-1,3-diphenyl-propane-1-ol and 3-(3'-methoxyphenylamino)-1,2-diphenyl-propane-1-ol. Probable explanation for this failure may be that the NH and OH groups are bonded intramolecularly and no free OH is available for conversion into the leaving group. This suggestion finds support from a study of the IR spectra of the carbinols.

CHAPTER IV

To study the stereoselectivity in the rearrangement



9 $R_1 = \phi$; $R_2 = R_3 = H$

10 $R_1 = \phi$; $R_2 = CH_3$; $R_3 = H$

11 $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3$

12 $R_1 = \phi$; $R_2 = H$; $R_3 = CH_3$

CHART-2

of N-arylazetidines resulting into 1,2,3,4-tetrahydroquinoline, a stereoselective synthesis of 2,4-disubstituted-N-arylazetidine was necessary. 1-(3'-Methoxyphenylamino)-1-phenylbutane-3-ol 13, prepared by the sodium borohydride reduction of α-(3'-methoxyphenylamino)-styryl methyl ketone, on cyclodehydration under above conditions, yielded cis-1-(3'-methoxyphenyl)-2-methyl-4-phenyl-azetidine 17 as the major product. On the other hand, when β-(3'-methoxyphenylamino)-β-phenethyl methyl ketone was reduced by sodium borohydride an isomeric carbinol (14) was obtained which gave on cyclodehydration trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidine 18 as the major product. In an analogous manner, cyclodehydration of 3-(3'-methoxyphenylamino)-1-phenylbutane-1-ol 15, prepared by the sodium borohydride reduction of β-(3'-methoxyphenylamino)-crotonophenone, gave 17. Finally the carbinol 16, obtained by $NaBH_4$ reduction of β-(3'-methoxyphenylamino)-propyl phenyl ketone, on cyclodehydration gave 18 as the major product. The sequence of the reaction is presented in Chart 3.

CHAPTER V

Rearrangement (ring expansion) of cis- and trans-1-(3'-methoxyphenyl)-2-methyl-4-phenylazetidines 17 and 18 to give tetrahydroquinolines by (1) pyrolysis at 290°, under nitrogen atmosphere, (2) by exposure to ultraviolet light from a medium pressure mercury vapour lamp and (3) by

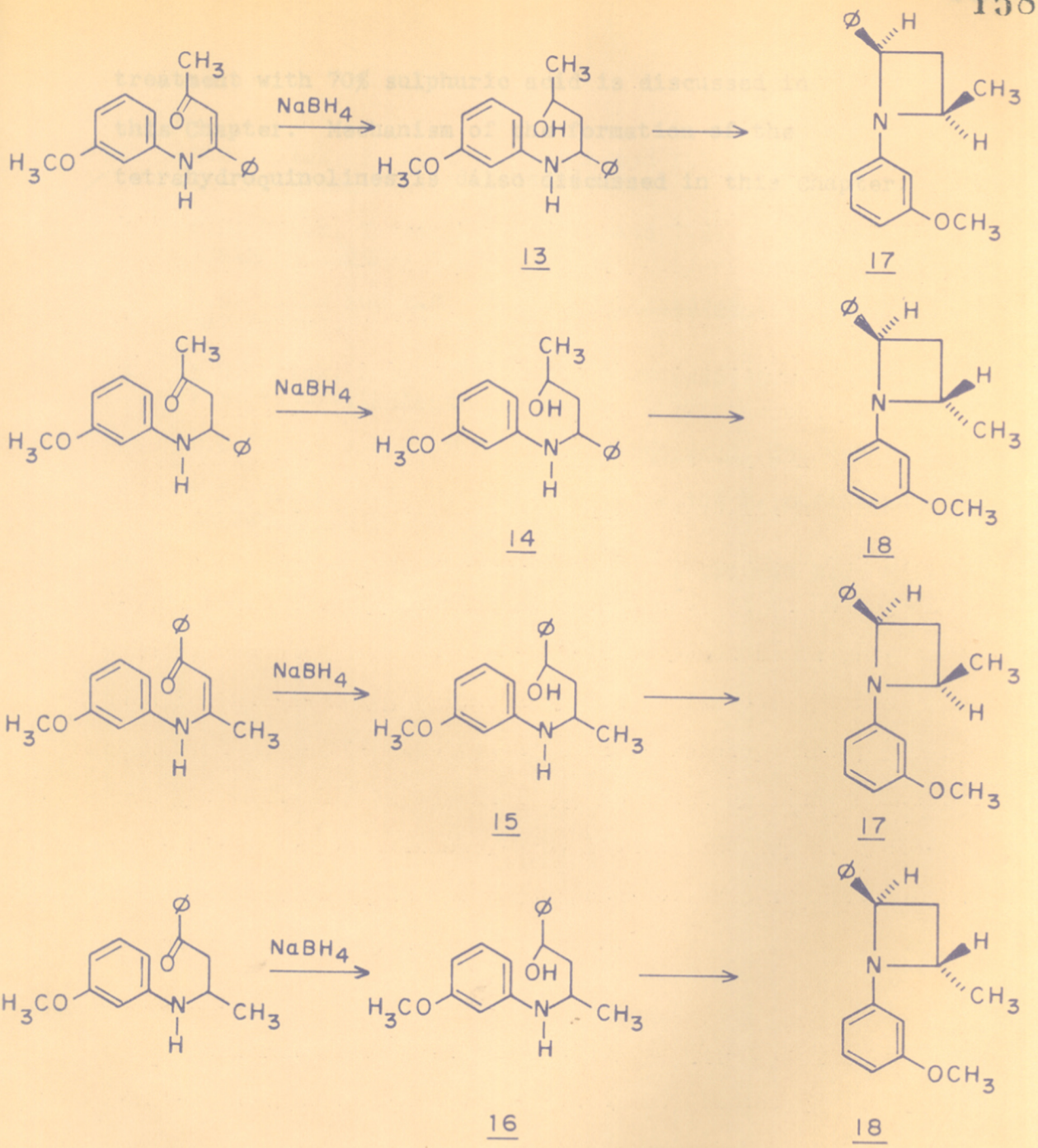


CHART-3

treatment with 70% sulphuric acid is discussed in this Chapter. Mechanism of the formation of the tetrahydroquinolines is also discussed in this Chapter.

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S. B. Kulkarni

(S. B. KULKARNI)

NCL, Poona 8
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