SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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

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C O N T E N T S

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 DMSO and/or $CDCl_3$ or CCl_4 solutions taking TMS as internal standard. The chemical shifts (δ) values are reported in ppm and J values in Hz.

4 The IR spectra were recorded on a Perkin-Elmer model 221 Spectrophotometer using a sodium chloride-grating interchange in nujol or HCB mull and in DMSO, $CHCl_3$ and CCl_4 solutions. 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 polyester and SE-30 columns on Hewlett-Packard-700.

6 Mass spectra were recorded on CEC 21-110 B double focussing spectrometer, using direct inlet system.

7 UV spectra were recorded in ethanol on a Perkin-Elmer model 350 spectrophotometer and the values are quoted as λ_{max} in $m\mu$ and log ϵ in parenthesis.

CHAPTER I - SPECTROSCOPIC INVESTIGATION OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

INTRODUCTION

The term tautomerism is defined as the structural isomerism with a low barrier to interconversion between the isomers[1a]. Tautomerism fades into ordinary isomerism for high barriers and into resonance for a zero barrier[2]. Intramolecular proton transfer gives rise to tautomerism[3]. When two or more tautomeric structures differ in the position of hydrogen atom and in the distribution of valence bonds the phenomenon is described as prototropy[4]. The acidic proton involved in hydrogen bonding readily shifts in the conjugated molecule resulting into the reversible equilibrium isomerisation[5].

The isomers, which are in equilibrium, can be identified by chemical means of study but spectral analysis is convenient, sensitive, conclusive and quantitative. Tautomerism is a time-dependent phenomenon. Processes of this type are so fast that the resulting isomers cannot be separated at room temperature[6]. The activation energy associated is relatively small and the rate of intramolecular reaction is such that spectroscopy becomes the only means of detecting such processes. NMR spectroscopy detects intramolecular movements with activation energy of 5-25 KCal/mole[7,8,9]. The species having life time of the order of 10^{-2} to 10^{-4} sec can be detected by NMR whereas IR detects the functional group changes in the species with life time even upto 10^{-12} sec. Tautomeric equilibria have

been studied by NMR[10], IR[11] and UV[12] spectra.

The limitation to the study of tautomeric equilibria by NMR spectroscopy is that the detection of a minor tautomer is difficult when it is present as less than 5% of the mixture. Equilibria fast on NMR time scale cannot be studied. But tautomeric interconversion can be slowed down by solvent and temperature to obtain the NMR spectrum of the mixture. The careful examination and correlation of NMR, IR and UV spectra of a tautomeric system and its derivatives under various conditions of temperature, concentration and solvent many times overcome the limitations.

A very large number of publications have appeared in literature on the phenomenon of tautomerism which are now widely discussed in various text books[1,4,13]. Pople et al.[14] have summarised the work in this area with references upto 1958. Murthy and Rao[15] gave an excellent account on the study of hydrogen bond by spectroscopic methods covering the period from 1958 to 1967. Extensive use of NMR to analyse related stereochemical problems is outlined with illustrations[16,17]. Tautomerism in phenols[18], purines[19], heteroaromatic compounds[20] and aromatic azo compounds[21] has been reviewed. Two fairly recent reviews by Russian authors describe the contribution of NMR to the study of keto-enol equilibria[22] and other types of prototropic tautomerism[23].

The present work deals with the investigation on

2-arylaminomethylenecycloalkanones which are the starting materials in the synthesis of tri- and tetracyclic nitrogen heterocyclics. This system is potentially tautomeric and involve hydrogen bonding. Hence to study the system in detail, we were interested in looking up the literature on tautomeric systems which involved hydrogen bonding. Following examples are cited to illustrate the use of spectroscopy in structural assignments and the solvent effects on equilibria.

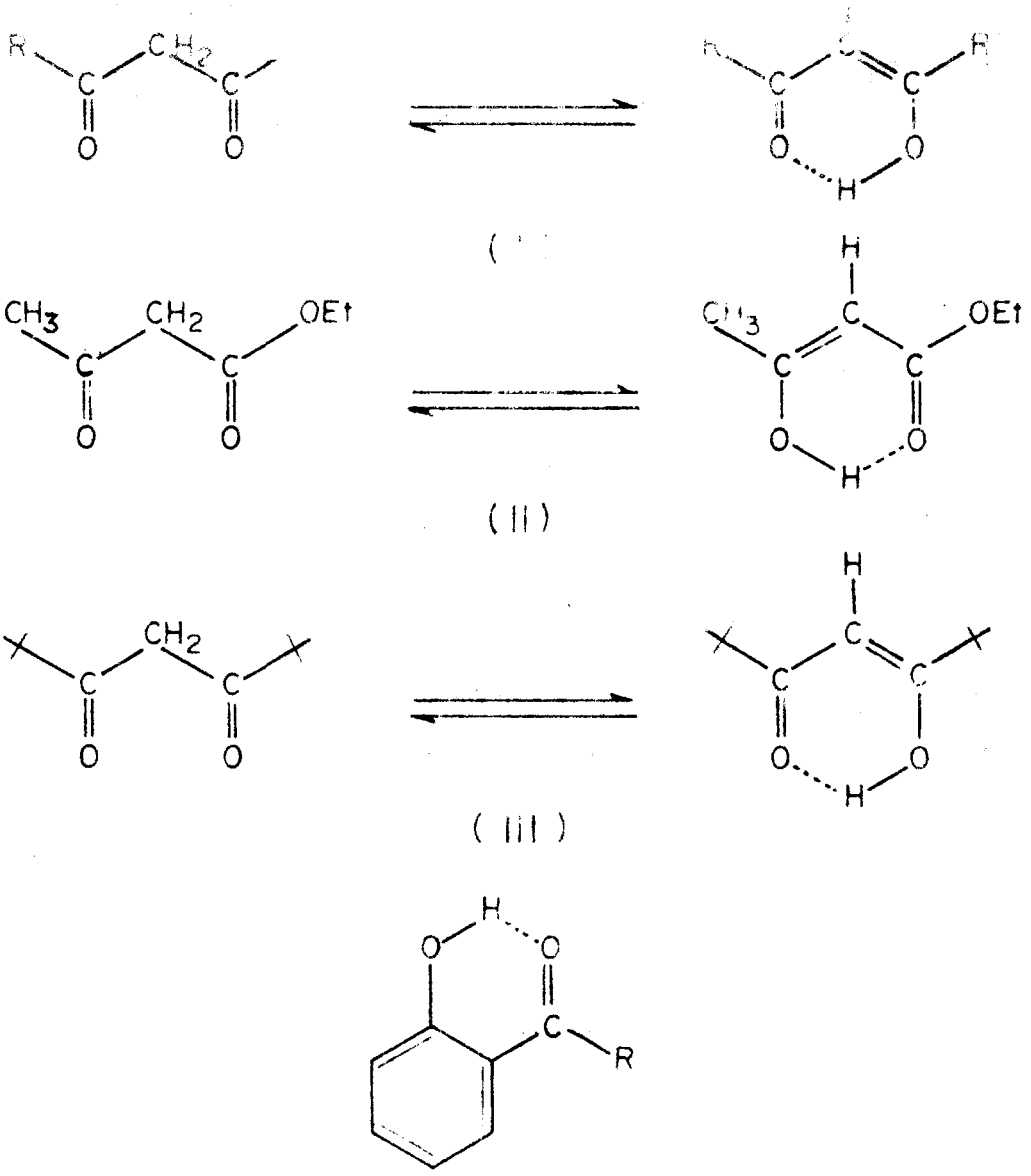
Carbonyl compounds exist exclusively in the keto form unless enol form is stabilized due to hydrogen bonding and steric hindrance[18]. Enol content of acyclic ketones or cycloalkanones is negligibly small[24] whereas ethylacetoacetate (II) (Fig.1) is a keto-enol equilibrium mixture owing to the reactive methylene group. In the enol form of ethylacetoacetate, the hydrogen bonding is stabilized by six-membered cyclic geometry. The accurate analytical method for determining the equilibrium point is based on the fact that the enol form reacts exceedingly rapidly with bromine while keto form does not[25]. NMR[1], on the other hand, provides a very precise measure of direct determination of the proportions of the keto and enol tautomers, by integration of intensities of peaks associated with each form.

The enol forms of o-hydroxyaldehydes and ketones, β-keto-esters and β-diketones (I) (Fig.1) form strong intramolecular hydrogen bonded chelate rings[26]. The strength of hydrogen bond can be studied by IR absorptions of the CO

and OH groups and the chemical shifts of the enolic form in the NMR spectra. The sterically hindered β-diketones (III) (Fig.1) show high degree of enolization[27]. Reeves and Schneider[28] have investigated the effects of solvents on the equilibrium in acetylacetone wherein the di- and triethylamine cause the equilibrium to shift entirely in favour of enol form.

Hydroxymethylene keto-aldo-enol equilibrium (Fig.2) has been extensively studied[29]. Forsen et al.[30] have reported NMR and IR investigations on hydrogen bonding and tautomerism in cyclopentane enols. Garbisch[31] has shown, in the case of β-keto-aldehydes, that the percentage of hydroxy-methylene component in the equilibrium mixture of the two possible enol tautomers is proportional to the coupling constant between the OH and CH protons of the hydroxymethylene group. The equilibrium of 3-formyl-bornan-2-one will be discussed separately. The factors influencing the relative directions of enolization of α-formyl cyclic ketones[32] (Fig.2) are the torsional and angle bending strains associated with the fragment $>$C - C$<$ and $>$C=C$<$. The specific strains, cumulatively considered as I-strain, affect chemical reactivities and equilibria in cyclic structures where molecular geometry takes on various forms of constraint.

The nature of Schiff's bases has been investigated in recent years[33-58]. The possible tautomeric forms of Schiff bases are shown in Fig.3. The keto-enamine (A), enol-imine (B) and keto-imine (C) forms are obtainable by



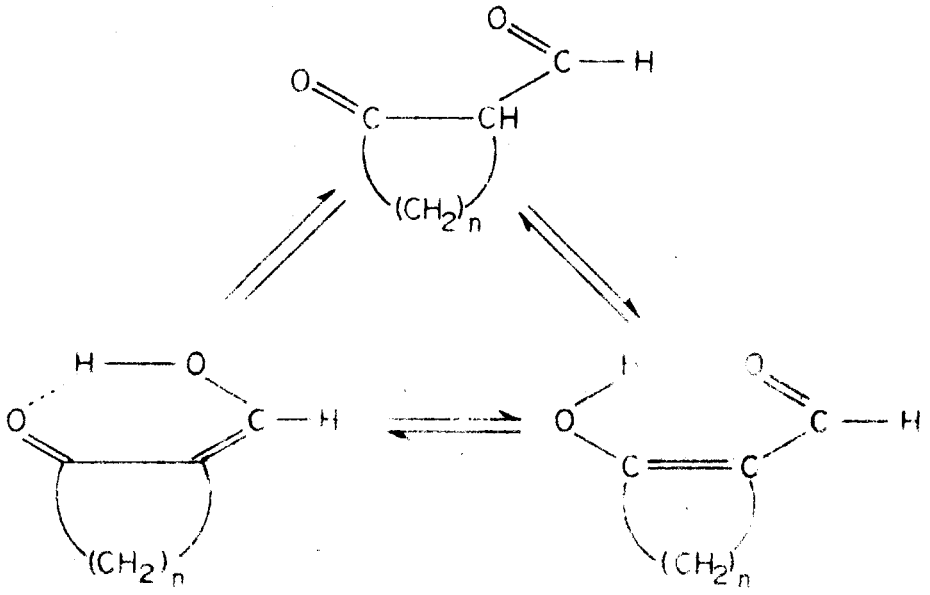
(I)

(II)

(III)

(IV)

FIG. 1.



simple prototropy. The cis-ketoamine (A) and trans-ketoamine (D) interconversion is possible through bond rotation process. The compounds, in principle, may exist as a single tautomer or a mixture. Compounds may show tautomeric equilibrium which would be affected by concentration, temperature and solvent changes and by the stereoelectronic factors constituting the structure. Schiff bases have been studied on these aspects as follows.

Martell and coworkers[33,34] have examined the infrared and ultraviolet spectra of bisacetylacetoneethylenediimine. Cromwell and coworkers[35,36] studied the IR spectra of β-alkylamino-α,β-unsaturated ketones and concluded that these compounds behave like vinylogous amides rather than like ketone or vinyl amines. IR spectra of these compounds as well as those reported by Weinstein and Wyman[37], Holtzclaw and coworkers[38] and Witkop[39] strongly support ketoamine (A) structure for the condensation products of a variety of β-diketones and various amines. However, this data do not unequivocally eliminate enol-imine (B) structure. Edwards and Petrov[40] from IR study of chloranils of acetylacetone favour enol-imine structure; so do Martin and coworkers[41] from the study of the acid dissociation constants of the compounds.

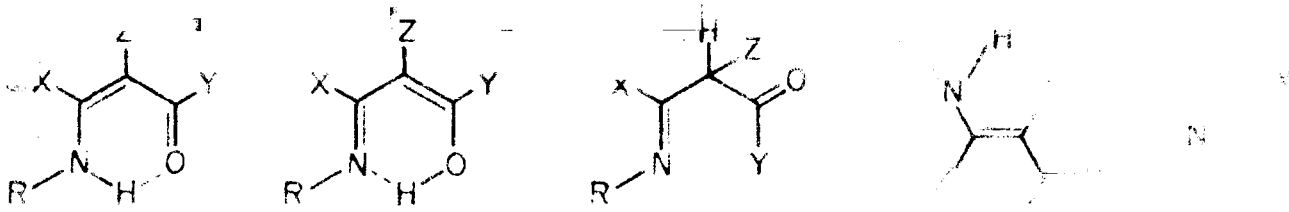
Dudek and Holm[42,43] have studied the nature of 1:2 and 1:1 condensation products between acetylacetone and aliphatic amines on the basis of NMR spectra. The suggestion, based on the ultraviolet spectra[44], that the enol-imine tautomer (B)

and(E) exist is refuted by PMR data[45,46]. Schiff bases usually exist in the stable cis-keto-enamine chelate form (A) rather than enol-imine (B) or keto-imine (C) form has been proved by PMR by observing low-field signals due to chelated protons which are split with the α-protons. The broadening effect of the ^{14}N quadrupole moment was eliminated by nitrogen labelling[47] and the large ^{15}N-H coupling constant (J = 88-95 Hz) permitted ready detection of tautomeric interconversion and exchange process.

The keto-amine form predominates in a variety of compounds like (IV)[48], (V)[49] and (VI)[50] (Fig.4). Brown and Nonhebel[51] could identify by NMR, only the ketoamine form in the Schiff bases of aromatic amines with β-diketones. A good correlation between the position of lowfield signals and Hammett constant (σ) was also obtained.

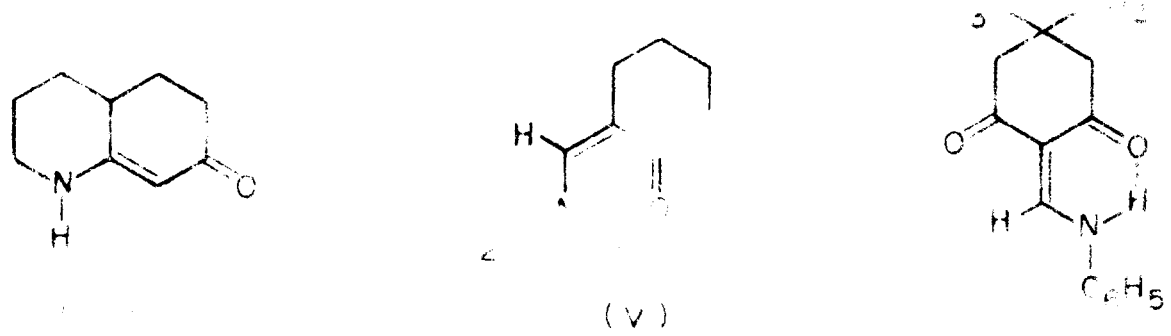
In order to explain marked stability of cis-ketoamine over the enolimine and ketoimine forms, the heats of combustion with various fragments (Fig.5) are obtained (gaseous, 25°, 1 atm.), showing marginal difference between ketoamine and enolimine fragments[43]. The preferential existence of keto-amine form must be due to greater extent of stabilization through resonance and hydrogen bonding of similar nature. Resonance in ketoamine form is intrinsically more stabilizing than that in the enolimine form in which negative charge cannot be delocalised on oxygen (Fig.6).

The trans-isomers of the ketoamine tautomer have been

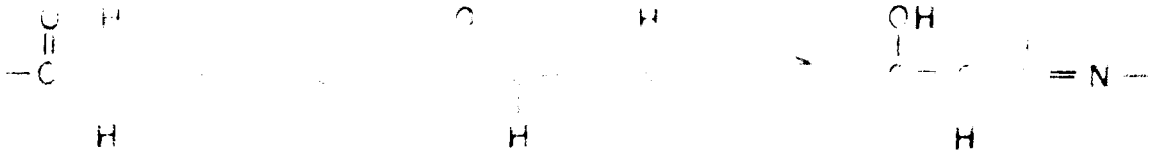


(A) ketoamine (B) cis-enolimine ketoimine trans-ketoamine

FIG 3 TAUTOMERISM IN SCHIFF BASES

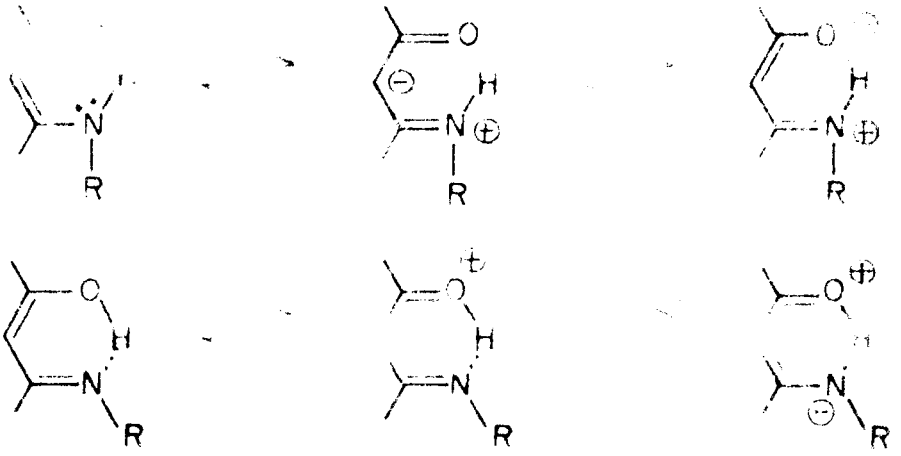


(V)



280 294 295 K cal

HEATS COMBUSTION OF FRAGMENTS



FIG·6 RESONANCE IN KETOAMINE & ENOLIMINE FO

detected for a number of amino derivatives of β-aldoketones[45] and acetoacetic ester[52]. Different chemical shifts of NH and the spin-spin coupling constant of the vinyl protons, in different forms, were observed. The J value of amine proton remains unchanged for the cis and trans isomers. The concentration of trans isomer increases when the bulky groups R, Y, Z (Fig.3) produce steric interactions. The cis-trans equilibrium varies with the various solvents due to the ability of solvent to solvate the nitrogen. Dilution in inert solvent decreases the proportion of the trans isomer. The trans isomers were not detected in the Schiff bases of acyclic β-diketones[47,51]. Isomeric Schiff bases such as ethyl-β-benzylaminocrotonate have been isolated[53,54] as well as studied[45] spectroscopically.

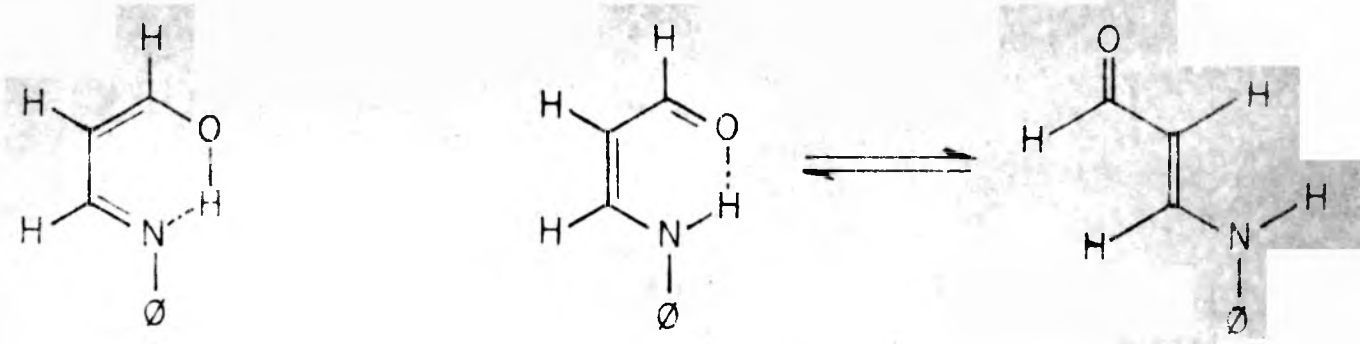
The reaction product (VII) (Fig.7) of 2-propynal with aniline was suggested enolimine (B) structure[55] based on infrared spectral analysis of product, its inability to dehydrate and its failure to give a precipitate with ammoniacal silver nitrate. The NMR evidence showed error in structure and established the cis-enaminoaldehyde (A) structure which exists in equilibrium with trans (D) form. The equilibrium was affected by the polarity of the solvent, the more polar solvent favouring the more polar trans. Thus percentage trans was 100, 92, 80 in DMSO-d_6, $(CD_3)_2CO$ and CD_3CN respectively.

Domnin and Yakimovich[56] found the presence of three tautomeric forms, cis-ketoamine (A), ketoimine (C) and

trans-ketoamine (D) in the monocondensation product (VIII) (Fig.8) of β-diketone with dimethylhydrazine (z = alkyl). Only chelate ketoamine form was noticed (when Z = H).

Schiff bases as derivatives of phenol[57] and naphthalene[58] form a condensed system containing chelate and aromatic rings, conjugation has a significant influence on the amine-imine equilibrium like (X) in (Fig.9). The amine form is possible only when the aromatic character of the ring is destroyed which requires expenditure of large quantities of energy (10 KCal/mole)[58]. The NMR spectrum of N-benzyl-salicylaldehydimine[51] (IX), shows a sharp singlet for methylene indicating that the hydrogen bonded proton is not bonded to nitrogen and thus exclusively enolimine form is present. Nevertheless, the existence of considerable quantities of the amine form has been demonstrated in others. Schiff bases (X) derived from aromatic amines and 2-hydroxy-1-napthaldehyde[51] exist as an equilibrium mixture of ketoenamine (A) and enolimine (B) forms. The existence of greater percentage of ketoamine form, even though the enolimine form in this case would have a significant degree of extra resonance stabilization, suggests that the NH....O hydrogen bond is appreciably stronger than the O-H....N hydrogen bond. The increase in the polarity of the medium in the order CCl_4, $CHCl_3$ and CH_3OH, increases the concentration of ketoamine form considerably.

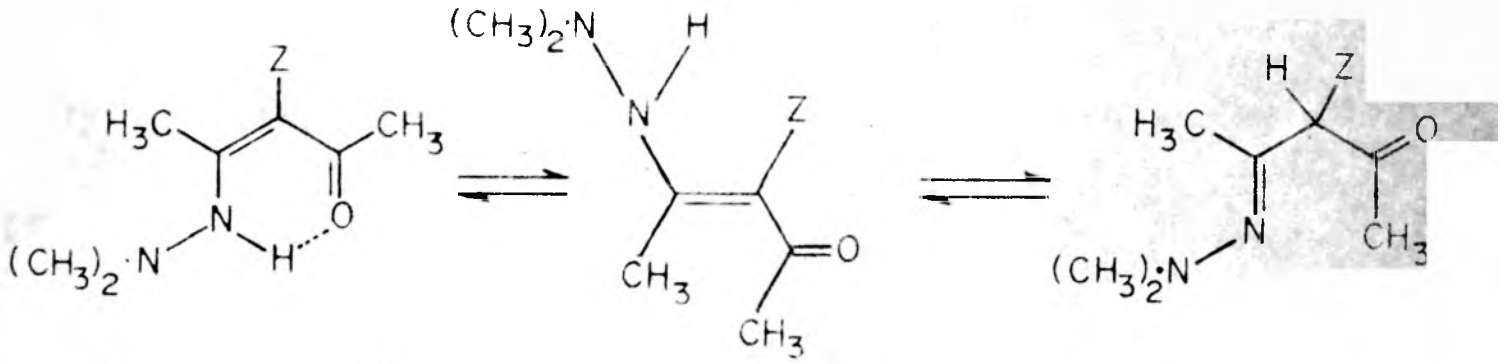
Tautomerism in β-ketoamides and β,β-diketoamides[52],



(B) (A) (D)

(VII)

FIG. 7.



(VIII)

FIG. 8.

pyridone derivative[59], picolyl ketones[60], anilides[61] and enaminoketones[4,62,63] has been studied. Configurational isomerism[64,65] occurring due to bond rotation process also fall in the class of tautomeric equilibria. Examples of these are amide[66], lactam[67], thioacetamide[68], formanilide[69], syn and anti-mixtures of oximes, semicarbazones[70] and 2:4-dinitrophenylhydrazones[71], cis and trans forms of enamines[45] and the two forms of protonated formic acid[72].

Solvent effects on chemical shifts have been studied in detail[73]. Commonly used solvents are chloroform and benzene. Less attention has been paid to the solvent effects of dimethyl sulfoxide (DMSO) as such[74]. The literature on DMSO particularly attracted our attention as the tautomeric equilibrium of 2-arylaminomethylenecycloalkanones was affected by this peculiar solvent.

The dipolar aprotic solvent dimethyl sulfoxide (DMSO), a liquid over a wide range of temperature, is a strong electron donor and has a high polarity[75]. Dipolar aprotic solvents are highly polar but no more than very weak hydrogen bond donors[76]. Parker[77,78] has discussed the use of dipolar aprotic solvents in organic reactions. Among common dipolar aprotic solvents like dimethylformamide (DMF), dimethylacetamide (DMAC), acetone, acetonitrile, etc., dimethyl sulfoxide has become increasingly important in recent years[75]. DMSO is best formulated as a resonance hybrid of the canonical structures having a polarised S-O bond and that having a (p → d) π S-O double bond[79]. Physical

and chemical properties of DMSO have been described[79-81]. As a solvent for spectroscopic studies, DMSO frequently offers decisive advantages in addition to its excellent solvent properties. It serves perfectly well in PMR when lowfield signals such as due to aromatic and vinylic signals need to be recorded. Deuterated solvent (DMSO-d_6) is useful in aliphatic region also.

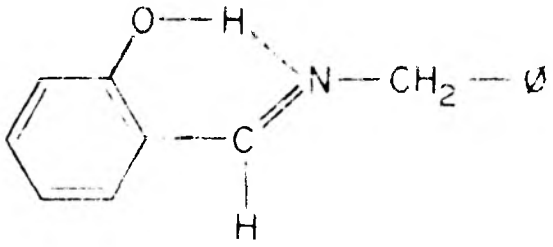
Nature of interactions will be important in the interpretation of solvent effects on structure reactivity correlations. For the purpose of assigning configurations or establishing conformations of molecules and in the study of rates of proton transfer reactions, the solvent effects of interest are the specific solute-solvent interactions[82]. Four types are possible in solute-solvent interactions[83]: electrostatic (ion-dipole or dipole-dipole), hydrogen bonding, dispersion forces and structure making and breaking. Dimethyl sulfoxide is known to enter hydrogen bonding[84] or dipole-dipole association[75]. Possible use of DMSO in structural investigations has been demonstrated with examples and the results are accounted for in terms of collision complexes stabilized by hydrogen bonding[74].

When an alcohol is examined in DMSO the OH signal has a markedly lowfield position due to strong hydrogen bonding between OH and solvent and its position is much less sensitive to temperature and concentration changes[85]. It reduces the proton exchange rate so that primary, secondary

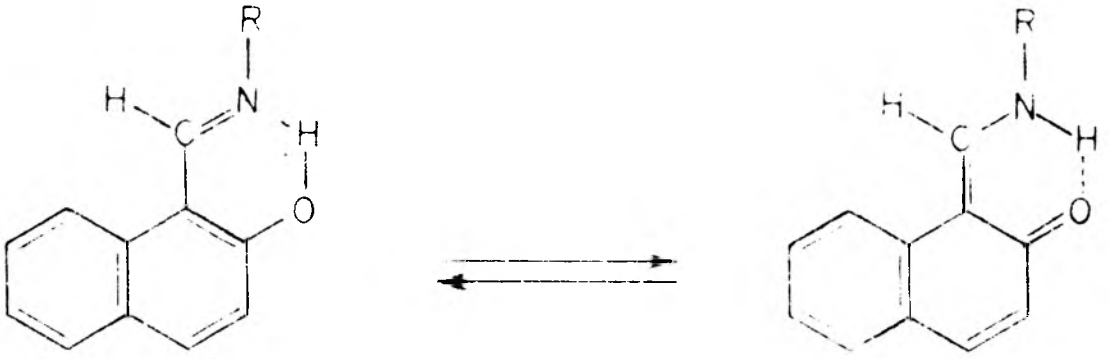
and tertiary alcohols gave clearly resolved triplets, doublets and singlets. Hydroxyl signal in DMSO provides stereochemical information on partially acylated sugars[86] and carbohydrates[87]. In the NMR spectra of epimeric cyclohexanols[88] (XI) (Fig.10) the axial hydroxyl appears at high field than its equatorial counterpart, since the latter forms strong hydrogen bonds due to steric accessibility.

Like OH, the NH function in DMSO also forms hydrogen bonds. This is shown by spectral studies of mixtures of DMSO with various amides[89], succinimide[90] and pyrrole[91] (XII) (Fig.10). Proton exchange in compounds such as, RNHOH was investigated by NMR and the results revealed that the OH group participates to a greater extent in H-bonding than the NH group[92]. In contrast to OH association, very few investigations have been carried out on NH complex formation in DMSO[75].

Nitriles and ketones form dipole-dipole complexes with DMSO, as is shown in the position and intensity of the carbonyl and nitrile absorption in the IR spectrum[93-95]. In nitrile-DMSO complex (XIII) (Fig.10), the DMSO was so oriented that its dipole was aligned opposite to that of the nitrile group. The complex is one in which the bulk of the solvent need not approach closely to the bulk of the solute species. The dipole dipole complexes of the dipolar aprotic solvent with the polar groups of the solute affect reactivity and conformation of the solute. The complex is more sensitive to steric effects and therefore more selective than the hydrogen



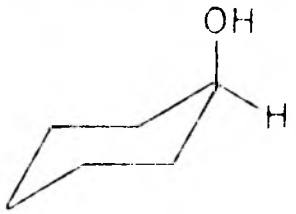
(IX)

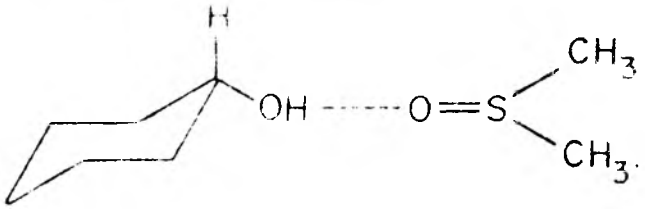


(B) (A)

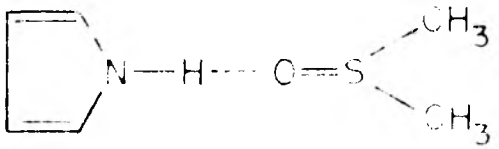
(X)

FIG. 9.

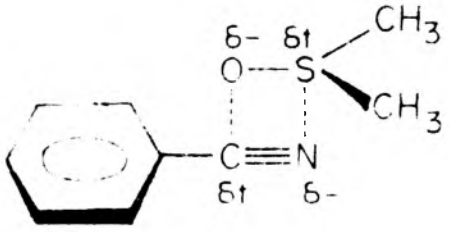




(XI)



(XII)



(XIII)

FIG. 10.

bonded complex formation. Similar complex is also postulated in case of study on cyclohexanol[96] with DMSO.

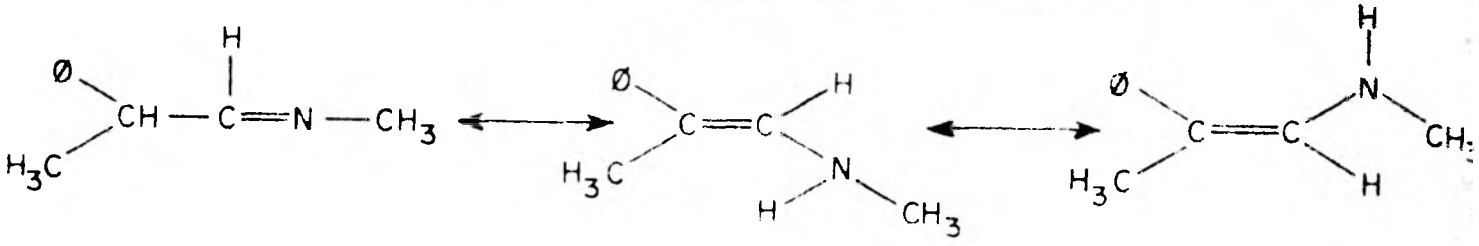
Tautomeric equilibria have been affected by the solvent dimethyl sulfoxide. In a few cases, the role of DMSO in altering the equilibrium has been discussed. Following are some examples:

The condensation product (XIV) (Fig.11) between α-phenyl-propionaldehyde and methylamine, gradually establishes an equilibrium between imine (B) and enamine (A) forms[97]. At 50°, the equilibrium mixture contains 72% of imine in chloroform and 32% in DMSO. The amine tautomer consists of a mixture of cis (A) and trans (D) isomers. The cis-trans isomerisation takes place in the tautomeric changes.

3-Hydroxyisothiazole (XV) has two rapidly interconvertible tautomeric forms[98]. The lactim form (B) predominates in $CDCl_3$ (100%) and in DMSO (75%), the remainder being the lactam form (A).

In the aldo-enol tautomerism of 2-hydroxymethylene-ketones such as 3-formylcamphor (XVI), it is shown that the trans-enolic (D) form exists in various solvents in slow equilibrium with the aldo (F and G) form and cis-enol (A) form[31,99,100]. The addition of DMSO to the PMR sample in CCl_4 sharply increases the content of trans enolic form. Baker and Bartley[101] conceived this as probably due to competition between intramolecular hydrogen bonding in solute and intermolecular hydrogen bonding between solute and solvent. However

FIG. 11. TAUTOMERIC EQUILIBRIA

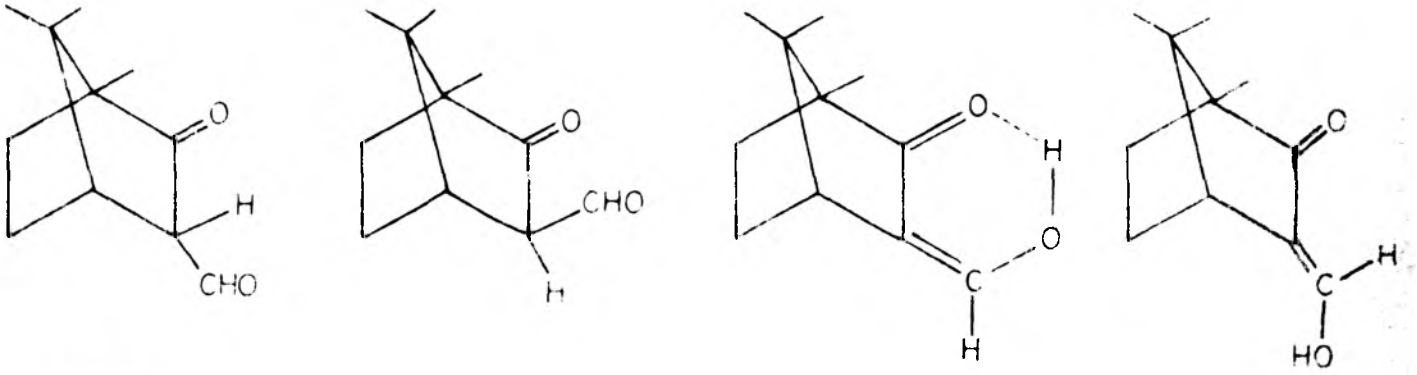


(B) (A) (D)

(XIV)

(A) (B)

(XV)



(F) (G) (A) (D)

(XVI)

(A) (B)

(XVII)

proof for intermolecular hydrogen bonding is not given.

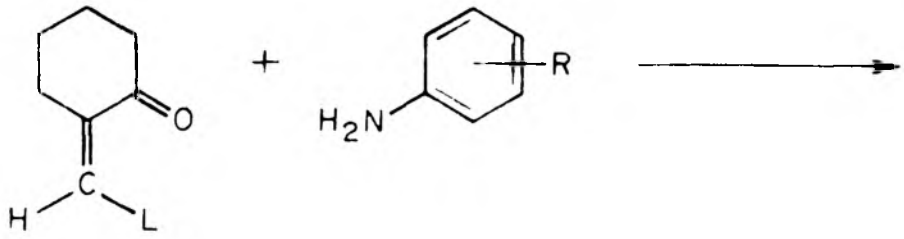
Substituted pyrazoline (XVII) exists entirely as the hydrazone form (A) in $CDCl_3$[102,103] while in DMSO or pyridine the presence of a broad signal of the labile proton, even at the low temperature, suggests interconversion at moderate rate between the hydrazone (A) and enol-azo (B) forms[104].

PREVIOUS WORK

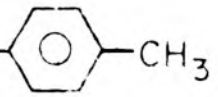
Compounds of the type (XVIII) (Fig.12) were prepared by Borsche[105] in 1910 and Petrow[106] in 1942 by the condensation of arylamines with 2-formylcyclohexanone and were described as 2-aryliminomethylcyclohexanones without any convincing proof. The compounds may also exist in tautomeric forms like 2-aryliminomethylcyclohex-1-ene-1-ol (XVIII) (B) and 2-arylimino-methylenecyclohexanone (XVIII) (C). Mehta *et al.*[107] have reported that the above reaction leads to vinylogous anilide of 2-formylcyclohexanone. Grob and Wilkens[48] in 1967 condensed aniline with 2-hydroxymethylenecyclohexanone. Hall and Walker[108] synthesised 2-(1-napthylaminomethylene)-cyclohexanone. Forsen *et al.*[30] prepared anilinomethylenecyclopentanone. Tilak *et al.*[109] prepared 3-α-(arylamino)-ethylidinotetrahydrofuran-2-one (XXI) for spectral studies.

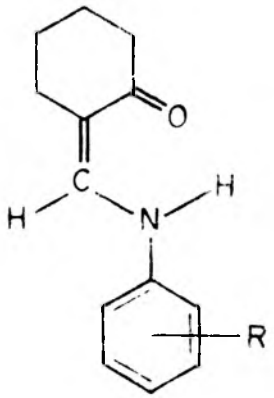
Berde[110], condensed various arylamines with 2-hydroxy-methylenecyclohexanone (XIX) to give 2-arylaminomethylenecyclo-hexanone (XVIII) (A) (Fig.12). The reaction involves a nucleo-philic substitution on sp^2 hybridised carbon. The mechanistic

FIG. 12

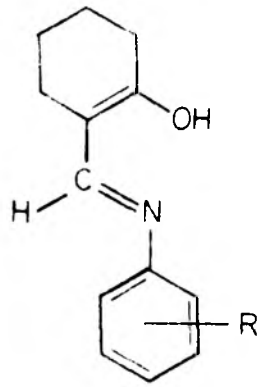


(XIX) L = OH

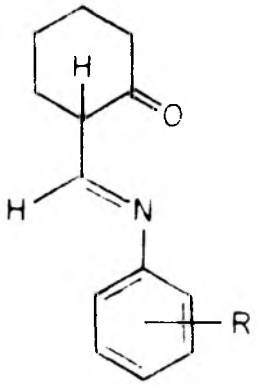
(XX) L = O—SO_2—  —CH_3



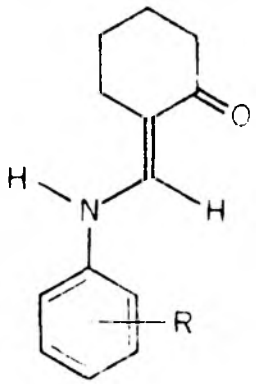
(XVIII A)



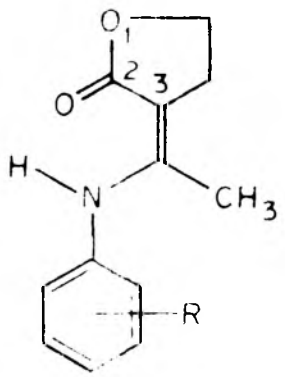
(XVIII B)



(XVIII C)



(XVIII D)



(XXI)

implication in the exclusive formation of the cis isomer of the reaction product has been explained through addition-elimination mechanism. The retention of cis configuration as in the starting material is in accordance with the literature on similar reactions. Miller and Yonan[111] have indicated that such reactions mostly proceed with retention of configuration. Other workers[112-114] in this laboratory have also observed that nucleophilic substitution in (XIX) and (XX) by phenoxide or phenylmercaptide anions takes place with retention of configuration.

The structures of cis-2-arylaminomethylenecyclohexanones (XVIII) (A)[110] and cis-3-(α-arylamino)-ethylidinotetrahydrofuran-2-ones (XXI)[109] have been studied spectroscopically. Whereas in non-polar solvents the former compound existed largely as cis-ketoamine the latter existed as a mixture of the keto-amine and enolimine tautomers. It was also shown that in solvents like dimethyl sulfoxide, compound (XVIII) (A) partially isomerised to trans-ketoamine (XVIII) (D) species. By comparing NH chemical shift in NMR, it was assessed that the substituents in -m and -p positions in the arylamine residue have apparently little effect on the strength of hydrogen bond. In the compounds with ortho substitution in the phenyl group (XVIII) (A) (Fig.12), the trans isomerisation was not appreciable and it was attributed to the steric restraints imposed by the substituents.

PRESENT WORK

In order to find out the relation between the lowfield NH proton and the Hammett constant (σ), we re-examined the spectra of cis-2-arylaminomethylenecyclohexanones with m- and p- substituents as-OCH_3, -CH_3 and -Cl in the arylamine moiety. NMR spectra of these compounds in $CDCl_3$ shows the lowfield doublet for NH proton due to coupling with the α-proton. The spin coupling of two protons leads to the 'AB case' giving symmetrical AB-quartet. In DMSO solution compounds give two separate quartets assignable to cis and trans isomers. The spectra thus have characteristic pattern although the broadening effect is seen due to quadrupole relaxation. The exact chemical shifts of four lines of two quartets downfield from TMS are separately calculated, following the first order approximation[1b]. The data is summerised in Table 1. The straight line graph of δ NH (cis) against Hammett's constant (σ)[115] for m- and p- substituents indicates the correlation (Fig.13).

Since hydrogen bonding seems to be affected by deactivating substituents in arylamine part, it will be interesting to analyse the reflection of this effect in the cis- trans- equilibrium ratio.

Although the structure of 2-arylaminomethylenecyclohexanones has been proved by their IR and NMR spectral data, the low solubilities of these compounds in organic solvents greatly restricted the scope of these studies[110]. The NMR spectra of most of the compounds could only be recorded in

TABLE 1 - NMR DATA OF 2-ARYLAMINOMETHYLENECYCLOHEXANONES (XVIII)[110] (Fig.12)

Compounds in DMSO solution showed 'AB-quartet' for 'HC-NH' protons. Chemical shifts are expressed in Hz.

(XVIII) R	Isomer	Chemical shift of methine proton		Chemical shift of NH proton		Exact chemical shift of proton A.	Exact chemical shift of proton B.	J_{AB}	Hammet constant (σ)
		1st band	2nd band	3rd band	4th band	ν_A	ν_B		
p-OCH_3	cis	437	450	708	721	444	714	13	-0.268
	trans	460.5	474.5	511	525	468.49	517.01	14	
p-CH_3	cis	439	451	701	713	445.15	706.85	12	-0.170
	trans	463	475	510	522	469.78	515.22	12	
p-Cl	cis	440	452	696	708	446.15	701.85	12	+0.227
	trans	458	471	517	530	465.23	522.77	13	
m-OCH_3	cis	462	474	718	730	468.2	723.85	12	+0.115
	trans	485	498	535	548	492.4	540.6	13	
m-CH_3	cis	442	454	698	710	448.15	703.85	12	-0.069
	trans	465	478	512	525	472.42	517.58	13	
m-Cl	cis	442	454	692	704	448.15	697.85	12	+0.373
	trans	460	473	521	534	467.2	526.8	13	

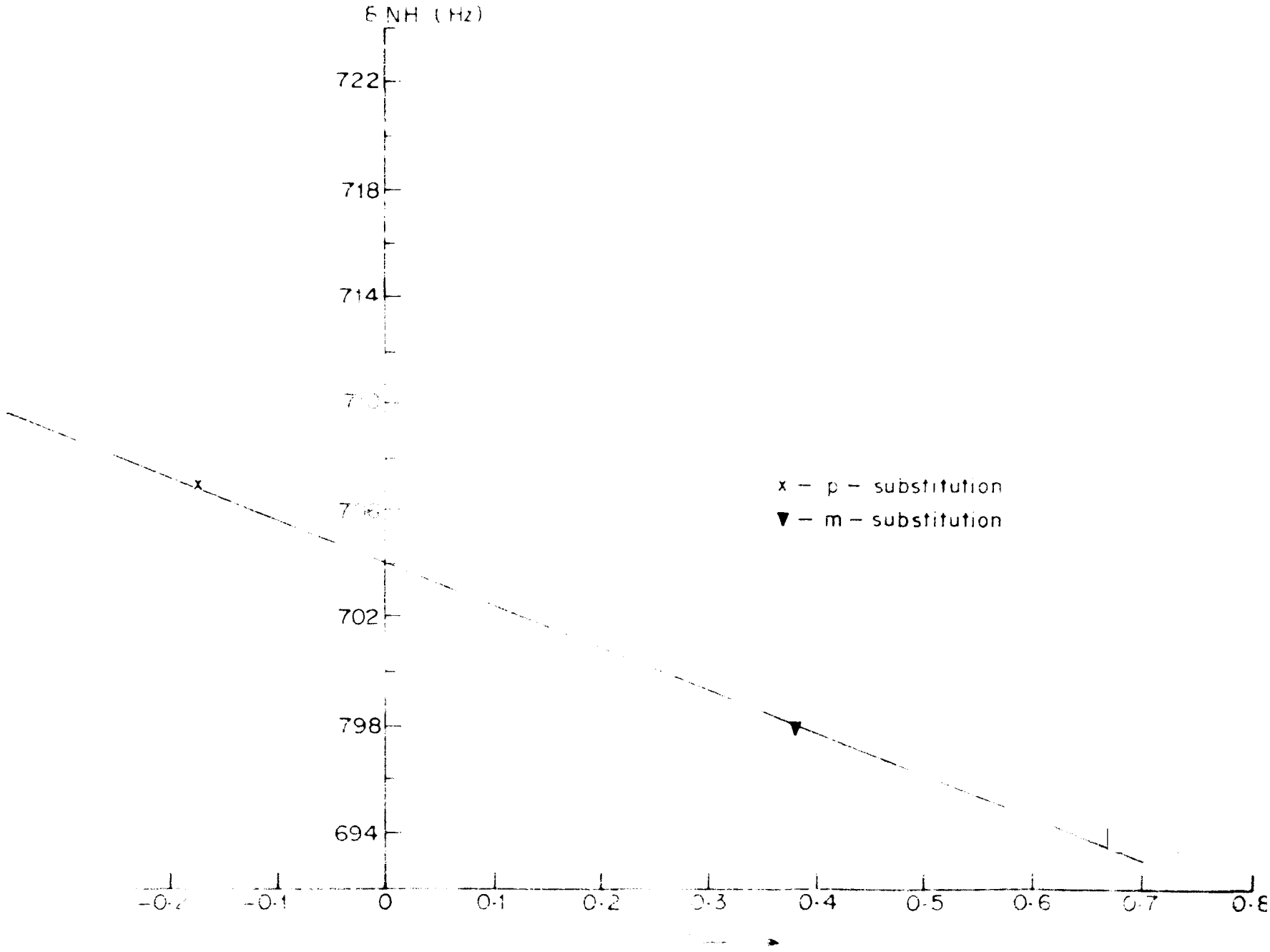
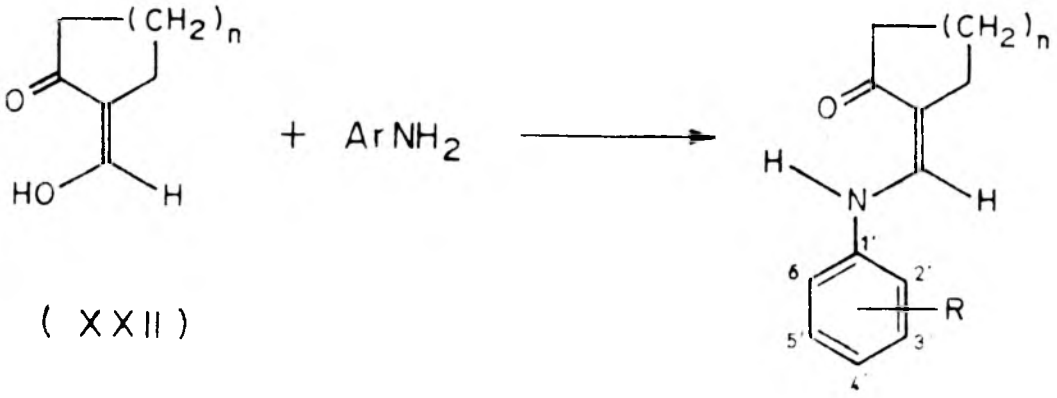


FIG. 1 GRAPH OF CHEMICAL SHIFT δ N α HAMMETT CONSTANT (σ

DMSO. To overcome this difficulty a comparative study was thought of.

It was further interesting to elaborate on the steric and electronic factors which govern the strength of hydrogen bonding between (C=O and NH in form (A) and/or C=N and OH in form (B)), the effect of the solvent on the tautomeric equilibria in 2-arylaminomethylenecycloalkanones and to investigate the specific role of DMSO in effecting the isomerisations. In 2-arylaminomethylenecyclohexanones (XVIII) (A) (Fig.12), the tautomeric equilibria were largely in favour of cis-ketoamine tautomer. This may be due to the fact that cyclohexane ring is strain-free. In its higher and lower homologues (n = 1,3,4) (Fig.14), there would be ring strain and other steric considerations[32,116] which might alter the strength of H-bonding, the tautomeric equilibria and the extent of isomerisation. The former would be reflected in the form of a substantial change in the chemical shift of the NH proton and the stretching vibrations of the NH and CO groups. Hence a detailed IR and PMR spectral study of various 2-arylaminomethylenecycloalkanones was undertaken.

A set of different compounds was prepared by changing the ring size and the substituents in the arylamine part (Fig.14). Derivatives of 2-arylaminomethylenecyclohexanones have been already reported. Remaining derivatives were prepared as shown in (Fig.15). The products were characterised by their NMR, IR, UV and Mass spectra.



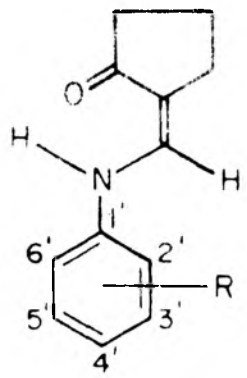
(XXII)

n = 1, 2, 3, 4

R = 4'–OCH_3 , a
3'–OCH_3 , b
2'–OCH_3 , c
4'–CH_3 , d
3'–CH_3 , e
4'–NO_2 , f
3'–NO_2 , g
4'–Cl , h
3'–Cl , i

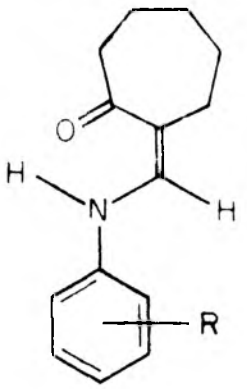
R = 2', 3'– benzo , j
3', 4'– benzo , k
4' – tBu , l
2', 6' – dichloro, m
H , n

FIG. 14.



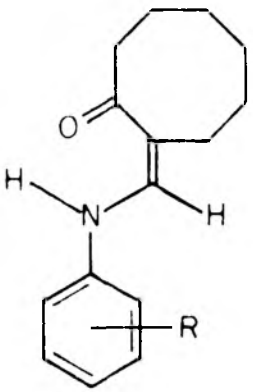
(XXIII)

R = 4'—OCH_3 , a
3'—OCH_3 , b
4'—CH_3 , d
4'—NO_2 , f
2',3'—benzo, j
3',4'—benzo, k
2',6'—dichloro, m
H , n



(XXIV)

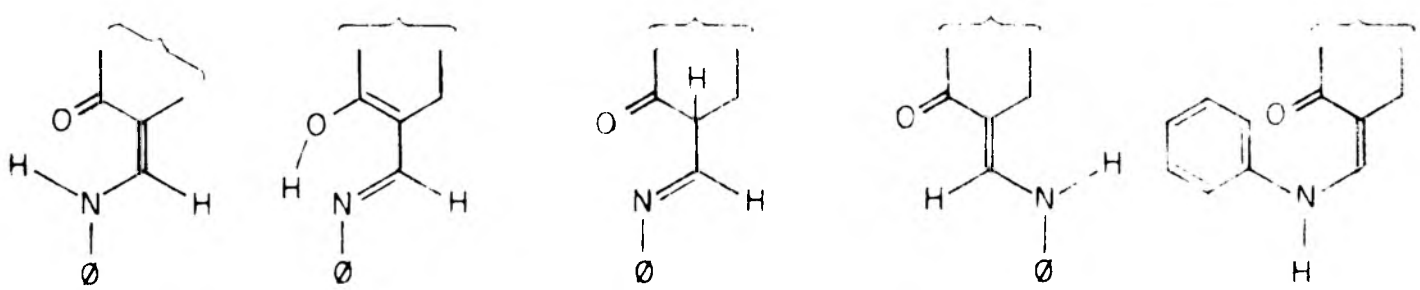
R = 4'—OCH_3 , a
3'—OCH_3 , b
4'—CH_3 , d
4'—NO_2 , f
2',6'—dichloro, m
H , n



(XXV)

R = 4'—OCH_3 , a
3'—OCH_3 , b
H , n

FIG 15.



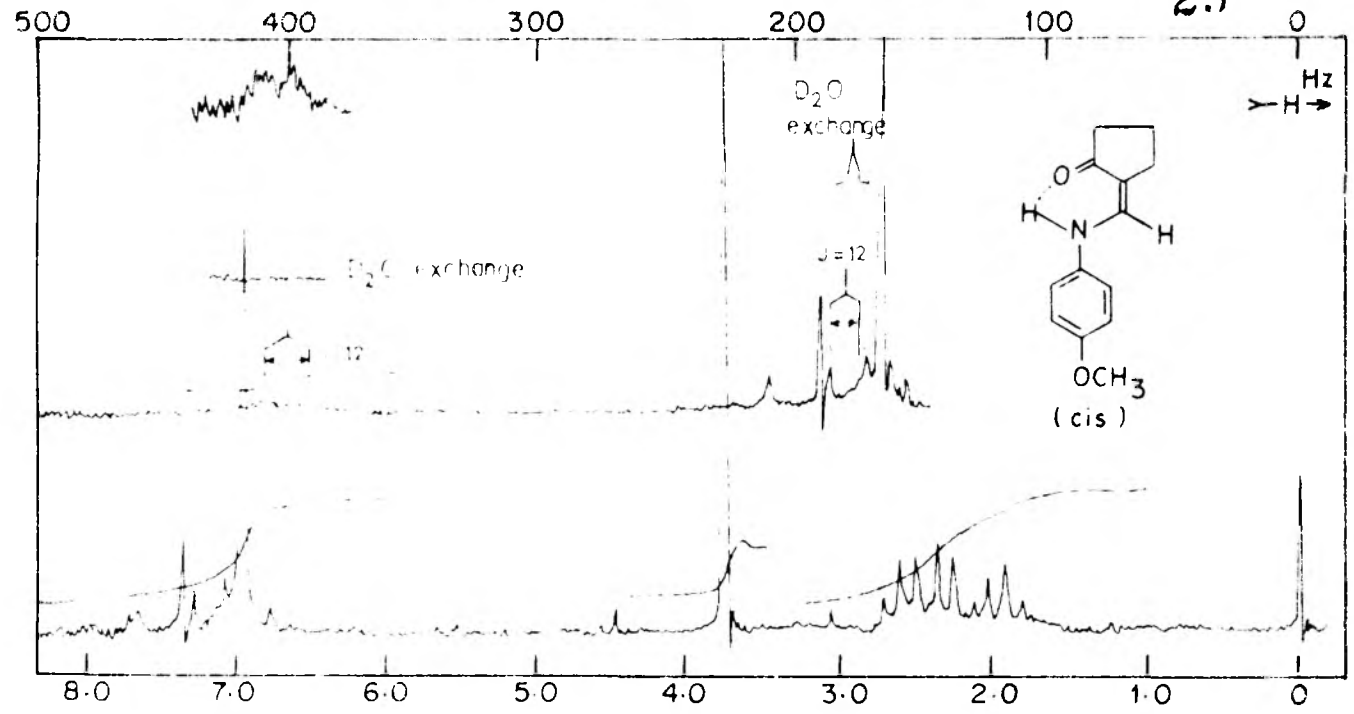
(A) (B) (C) (D) (H)

The various possible tautomeric forms of Schiff bases as derivatives of 2-arylaminomethylenecycloalkanones are: the cis-ketoamine (A), enol-imine (B), keto-imine (C) and the trans-ketoamine (D) (Fig.16). The actual structures were established by spectroscopy.

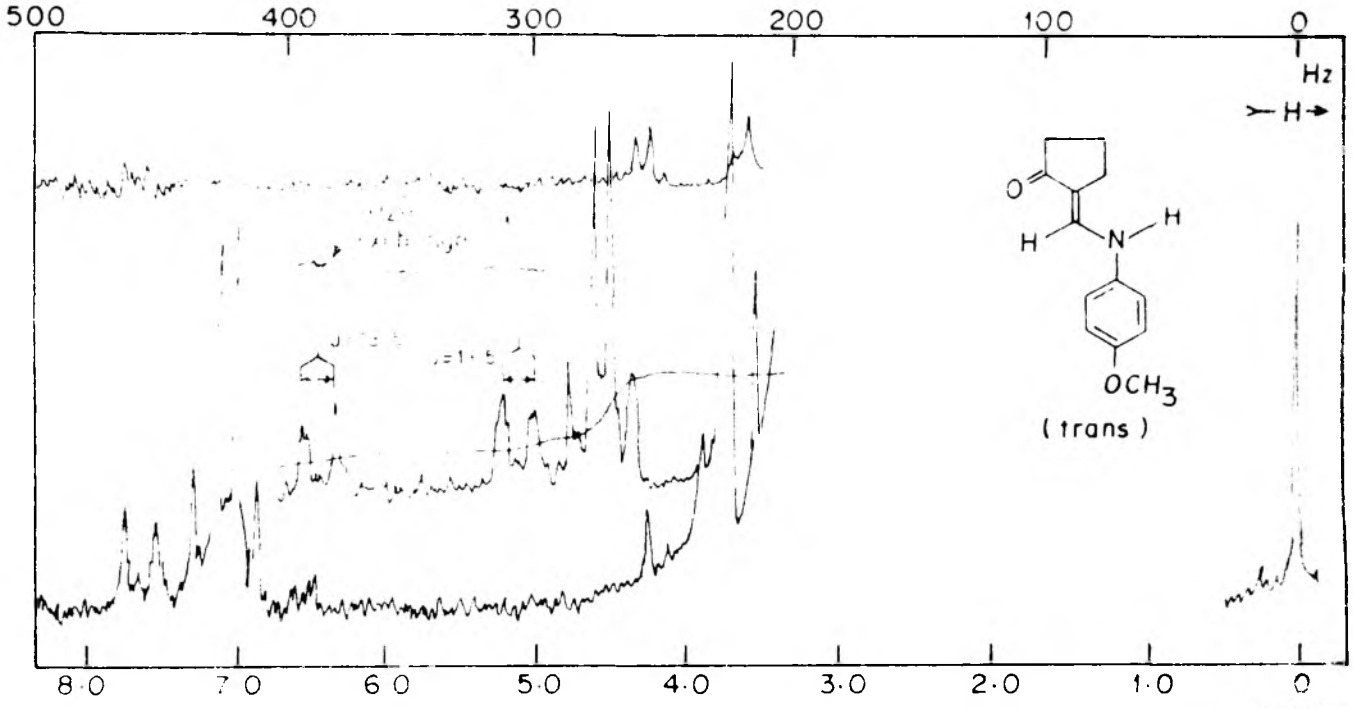
Methods and Results

The salient features of the NMR spectra are recorded in Table 2. The typical spectra of (XXIII) and (XXIV) in $CDCl_3$ and DMSO are given in (Fig.17) and (Fig.18) respectively. These spectra in $CDCl_3$ and other solvents except DMSO showed two sets of broad doublets with identical coupling constant $J = 12$. On deuterium exchange the lowfield doublet disappears while highfield doublet reduces to a singlet. It suggested that the two doublets form a typical AB quartet occurring due to the spin coupling of protons. The lowfield doublet around 11.75 ppm can be assigned to a strongly hydrogen bonded NH proton as in cis-ketoamine (A) tautomer. The highfield doublet is due to the α-proton to nitrogen. The AB-quartet rules out the enolimine (B) structure since in that case the pattern would be of two singlets for OH and CH. The lowfield singlet would then have only disappeared on D_2O exchange. The ketoimine (C) structure is discarded as there is no chelated proton present in this form. On the other hand appearance of AB-quartet establishes that only cis-ketoamine (A) form must be present.

Dudek and Holm[43] have shown that the most shielded proton signal in the NMR spectra of Schiff bases of β-diketones arose



(a) in $CDCl_3$ soln.



(b) in DMSO soln.

FIG 17. PMR SPECTRUM OF (XXIII-a) IN $CDCl_3$ & DMSO

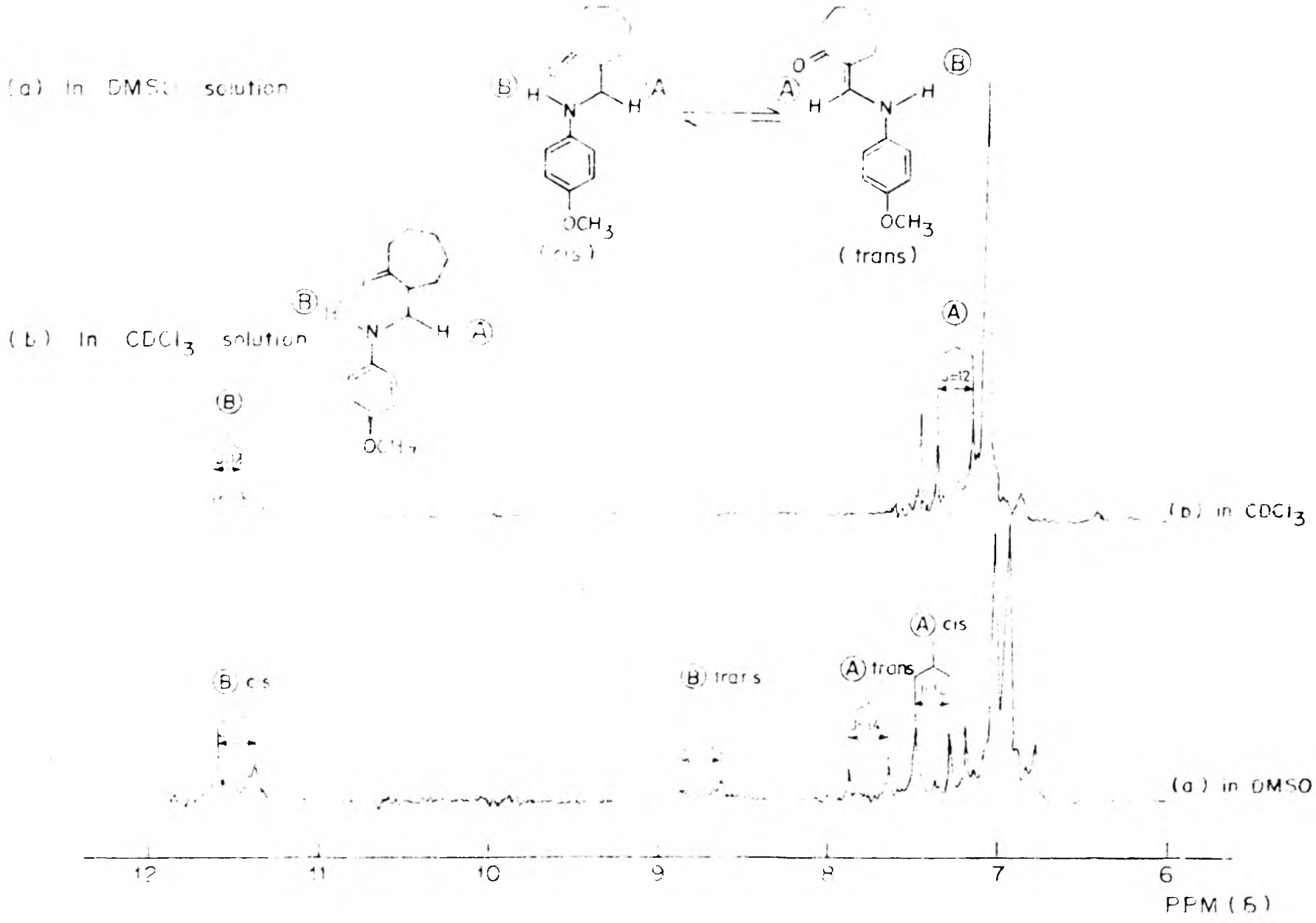
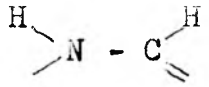


FIG. 18. PMR SPECTRAL REGION BETWEEN 6-12 δ PPM OF (XXIV-a)

from the chelated proton attached to the nitrogen atom.

Dudek and Volpp[45] have also observed the coupling constant between  as 12.8 Hz. The spin spin coupling constants of the amine proton with the α-proton were the same for the cis- and trans. isomers. Forsen and Nilsson[50] similarly showed that the coupling constant of NH proton for 3-anilinomethylenepentan-2,4-dione was 12.5 Hz suggesting the ketoenamine form.

To find out whether the hydrogen bonding is intramolecular or intermolecular, the NMR spectra of 1:1 condensation products of various arylamines and 2-hydroxymethylenecycloalkanones were recorded in $CDCl_3$ and other solvents (Table 2). The change in solvent and concentration does not alter the position of the signals for the NH proton suggesting fairly strong intramolecular H-bonding in solute.

Similar to 2-arylaminomethylenecyclohexanones, all the derivatives of 2-arylaminomethylenecycloalkanones exist exclusively as chelated cis-ketoamine (A) structure. The reaction of cis-hydroxymethylenecycloalkanones with various arylamines gives the product with cis orientation. In the cis-ketoamine structure the carbonyl group comes within the bond forming distance of the proton on nitrogen by forming a six-membered cyclic geometry resulting in strong intramolecular hydrogen bonding. From the Dreiding models it is seen that the distance between the carbonyl oxygen to nitrogen atom is between 2-3 A°, as required for hydrogen bond formation.

TABLE 2 - NMR SPECTRA OF 2-ARYLAMINOMETHYLENECYCLOALKANONES DESCRIBING 'AB QUARTET' FOR 'HC-NH' PROTONS

d = doublet, s = singlet, E = exchanged with D_2O * = Ref.110

Compd.	Solvent	δ NH cis/trans	δ CH cis/trans	J cis/trans	% isomers cis/trans
XXIII-a	$CDCl_3$	11.11(d)	7.1(d)	12	95/5
	$CDCl_3 + D_2O$	E	7.1(s)	-	do
	DMSO	nil/8.5(d)	nil/7.5(d)	nil/13	10/90
	DMSO + D_2O	E	nil/7.6(d)	-	do
	CH_2Cl_2	11.0 (d)	7.1(d)	12	95/5
	Pyridine	11.0 (d)	masked	-	masked
XVIII-A R=4'-OCH_3 (Fig.12)	$CDCl_3$	Insoluble			
	DMSO*	11.9(d)/ 8.61 (d)	7.4(d)/ 7.8(d)	13/14	40/60
	DMSO + D_2O	E	7.4(s)/ 7.83(s)	-	do
XXIV-a	$CDCl_3$	11.5(d)	7.07(d)	12	95/5
	$CDCl_3 + D_2O$	E	7.06(s)	-	do
	DMSO	11.5(d)/ 8.75(d)	7.4(d)/ 7.71(d)	12/14	65/35
	DMSO + D_2O	E	7.36(s)/ 7.8 (s)	-	do
	CH_3CN	11.5(d)	7.3(d)	12	95/5
	Acetone	11.7(d)	7.36(d)	12	do
	Dioxan	11.66(d)	7.2(d)	12	do
	Sulfolane	11.5(d)	7.33(d)	12	90/10
	Hexachloro-acetone	11.5(d)	7.07(d)	12	95/5
	CS_2	11.51(d)	7.0(d)	12	do
	CCl_4	11.5(d)	7.0(d)	12	do
	DMF	11.5(d)	masked	12	masked
	PBr_3	..No signals...		-	-

...contd.

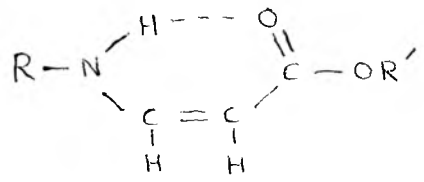
Compd.	Solvent	δNH cis/trans	δCH cis/trans	J cis/trans	% isomers cis/trans
XXV-a	$CDCl_3$	11.9(d)	7.06(d)	12	95/5
	$CDCl_3$ + D_2O	E	7.06(s)	-	do
	DMSO	11.85(d)/ 8.96(d)	7.6(d)/ 8.0(d)	12/13	55/45
	DMSO+D_2O	E	7.58(s)/ 8.1(s)	-	do
XXIII-m	$CDCl_3$	11.1(d)	-	12	95/5
	DMSO	11.2(d)	-	12	95/5
XXIV-m	$CDCl_3$	11.88(d)	7.43(d)	12	95/5
	DMSO	11.9(d)	7.76(d)	12	95/5
XXIII-b	$CDCl_3$	10.76(d)	7.1(d)	12	95/5
	$CDCl_3$+D_2O	E	7.1(s)	-	do
	DMSO	nil/8.91(d)	nil/7.58(d)	13	5/95
	DMSO+D_2O	E	nil/7.6(s)	-	do
XXIV-b	$CDCl_3$	11.5(d)	7.11(d)	12	95/5
	DMSO	11.5(d)/ 8.75(d)	7.43(d)/ 7.73(d)	12/13.5	65/35
XXV-b	$CDCl_3$	11.83(d)	7.5(d)	12	95/5
	DMSO	11.83(d)/ 8.9(d)	7.06(d)/ 7.9(d)	12/14	55/45
XXIII-d	$CDCl_3$	10.83(d)	7.66(d)	12	95/5
	CH_2Cl_2	10.83(d)	7.66(d)	12	95/5
XXIII-n	$CDCl_3$	10.71(d)	7.71(d)	12	95/5
XXIV-d	$CDCl_3$	11.56(d)	7.66(d)	12	95/5
XXV-n	$CDCl_3$	11.83(d)	7.75(d)	12	95/5

In dimethyl sulfoxide solution these spectra showed in all four doublets. The lowermost doublet around 11-12 ppm with J = 12-13 Hz and the next higher around 8-9 ppm with J = 13-14 Hz. The lowerfield doublet is assigned to the chelated proton in cis-ketoamine structure and the next higher is assigned to the non-bonded NH proton as in trans-ketoamine (D) form. The large coupling constant (J = 14 Hz) by which the signal is split rules out the possibility of its being due to the OH group as in enolimine (B) structure.

The two doublets assigned to NH proton in two different forms disappear on D_2O exchange whereas the other two doublets reduce to singlets. The doublet for methine proton in the cis-ketoamine structure should come upfield compared to the methine proton in trans-isomer, since the latter is deshielded due to the anisotropy of the neighbouring carbonyl group. The deshielding effect caused by the carbonyl group[117] can be used to assign the stereochemistry of olefinic compounds, particularly when the C=O is directly attached to the C=C. The spin spin coupling constants in case of cis and trans isomers vary just by 1-2 Hz, however the assignments on the methine doublets can readily be confirmed by critical examination of J value in comparison with those of NH. The analysis of pattern evidently suggests that there are two AB-quartets. The additional quartet which appeared in DMSO but which was absent in $CDCl_3$ solution, has now been assigned to the trans-ketoamine (D) structure. It can thus be inferred

that in DMSO solution the species exist as an equilibrium mixture of cis and trans isomers. These observations are comparable with the earlier results[110] obtained in this laboratory.

A related case of interest is that of the syn and anti isomers of 3-aminoacrylic esters (XXVI)[118,119]. A relatively large coupling exists between the NH proton and that of the adjacent methine proton and values are generally higher and less variable (12-15 Hz) for the cis-esters than for the trans isomers (7.5 - 14 Hz). In the cis compound intramolecular

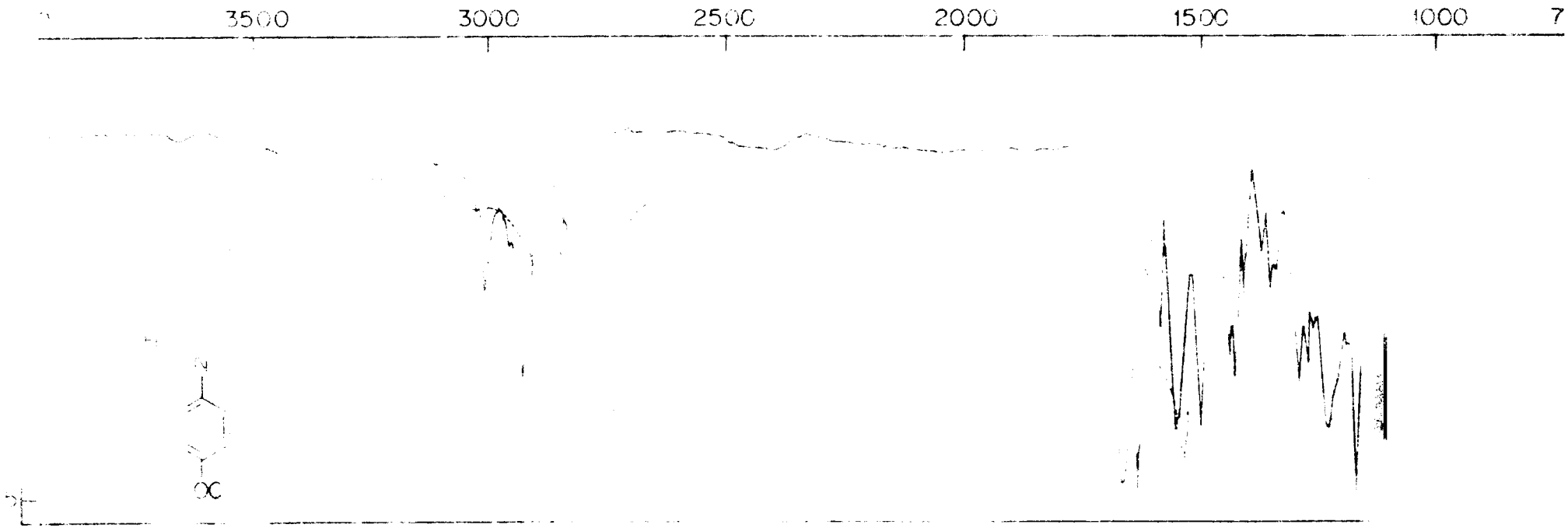


(XXVI)

hydrogen bonding favour anti configuration with the result that strong NH-CH coupling is observed.

The structure as well as the tautomeric equilibrium of these compounds (Fig.15) were also investigated by infrared spectroscopy in various solvents or as a nujol mull. The spectrum of a typical compound (XXIV) is shown in (Fig.19). The absorption bands in the NH stretching and C=O stretching region of compounds in nujol and in various solvents are given in Table 3 and Table 4 respectively.

Infrared spectra of these compounds in solid state showed absorptions at 1660 cm^{-1} (s) and 3250 cm^{-1} (m. broad)



FR ... SPECTRA OF (XXIV-a) IN $CHCl_3$ & NUJOL

TABLE 3 - IR SPECTRA OF 2-ARYLAMINOMETHYLENECYCLOALKANONES IN NUJOL

PE Infracord 137 Spectrometer.

Assignments	2-arylaminomethylenecyclopentanone (XXIII)							
	a	b	d	f	j	k	m	n
ν NH	3410(w) 3240(m) 3210(w)	3410(w) 3250(m) 3200(w)	3410(w) 3220(s) 3180(w)	3410(w) 3200(s) 3120(w)	3410(vw) - 3020(m)	3410(w) 3250(s) 3110(w)	3410(vw) -	3410(w) 3250(m) 3210(m)
ν c=o	1685(s) 1660(w)	1690(s) 1660(w)	1690(s) 1660(w)	1690(s) 1665(w)	1660(s) 1640(w)	1690(s) 1640(m)	- 1660(s)	1690(s) 1660(w)
ν c=c	1560(vs) 1570(s)	1600(s) 1560(m)	1590(s) 1560(vs)	1610(s) 1570(vs)	1590(s) 1570(vs)	1590(s) 1560(s)	1610(s) 1590(vs)	1580(s) 1560(vs)
δ NH	1540(w)	1540(w)	1520(s)	1540(m)	1520(w)	1540(s)	1560(m)	1520(w)

.....Contd.

TABLE 3 (Contd.)

Assignments	2-arylaminomethylenecycloheptanone (XXIV)						2-arylaminomethylenecyclooctanone (XXV)		
	a	b	d	f	m	n	a	b	n
ν NH	3250(w) 3180(w)	3250(m) 3200(w)	3250(w) 3180(m)	3200(w) 3100(w)	3200(w) 3100(w)	3250(s) 3150(w)	3200(m) -	3250(w) 3200(m)	3250(s) 3150(w)
ν c=o	1640(s)	1650(s)	1650(s)	1650(s)	1650(s)	1660(s) 1640(s)	1640(s)	1640(s)	1650(s)
ν c=c	1580(s) 1560(vs)	1580(s) 1560(vs)	1580(vs) 1560(s)	1610(vs) 1580(s)	1590(vs) 1560(s)	1590(vs) 1560(s)	1590(s) 1570(vs)	1610(vs) 1570(s)	1590(s) 1550(vs)
δ NH	1520(s)	1520(w)	1520(m)	1510(s)	1510(w)	1540(s)	1520(s)	1540(s)	1540(s)

TABLE 4 - IR SPECTRA OF 2-ARYLAMINOMETHYLENECYCLOALKANONES IN SOLUTION

PE 221, Path length = 0.1 mm Conc. 5 mg/0.1 ml

Compd.	Solvent	ν NH	ν c=o	ν c=c
XXIII-a	$CHCl_3$	3410(m), 3250(vw)	1665(s), 1690(w)	1605(vs), 1575(s)
	DMSO	-, 3250(m), 3170(w)	1660(w), 1690(s)	1605(s), 1575(vs)
	CH_3CN	3160(vw)	1690(w), 1660(m)	1605(vs), 1570(m)
XVIII	$CHCl_3$ (Ref. 110)	3420(w), 3275(w), 3223(w), 3160(w)	1650(m), 1640(s)	1592(m)
R=4'-OCH_3 (Fig. 12)	DMSO	-, 3270(w), 3240(m)	1660(s), 1640(m)	1592(m)
XXIV-a	$CHCl_3$	3260(w)	1640(s)	1590(m), 1560(s)
	DMSO		1660(m), 1640(s)	1590(m), 1560(vs)
	CH_3CN	3230(m), 3180(w)	1640(s)	1590(m), 1560(s)
	Dioxan	3180(m)	1640(s)	1590(m), 1560(s)
XXV-a	$CHCl_3$	3270(w), 3220(w), 3165(w)	1640(s)	1590(m), 1550(vs)
	DMSO	3270(w), 3240(w)	1660(m), 1640(s)	1590(m), 1560(s)
XXIII-m	$CHCl_3$	3410(m), 3240(w), 3170(w)	1675(s)	1610(vs), 1590(vs)
	DMSO	-, 3240(m), 3170(w)	1675(s)	1610(vs), 1590(vs)
XXIV-m	$CHCl_3$	3200(m-b)	1645(s)	1585(vs), 1550(m)
	DMSO	3200(w-b)	1640(s)	1585(vs), 1550(m)
XXIV-f	$CHCl_3$	3240(w), 3200(m), 3170(w)	1645(s)	1595(s), 1570(vs)
XXIII-b	$CHCl_3$	3410(m), 3250(w)	1665(s), 1685(w)	1595(s), 1575(vs)
XXIV-b	CCl_4	3190(m)	1640(s)	1595(s), 1565(vs)
XXV-b	$CHCl_3$	3220(w), 3190(m)	1640(s)	1590(s), 1550(vs)
XXIII-n	$CHCl_3$	3410(m), 3250(w)	1665(s), 1685(w)	1595(vs), 1570(vs).

ascribable to bonded C=O and NH stretching modes of the intramolecularly H-bonded cis-ketoamine species. In chloroform solution, additional weak bands at 1690 cm^{-1} and 3410 cm^{-1} having 5-10% intensity of the stronger band, are ascribable to free C=O and NH stretching modes of the trans isomer. The band at 3410 cm^{-1} can also be ascribed to the non-bonded gauche form (H) (Fig.16) since it is very close to the value of free NH stretching absorption. The amount of trans isomer (D) was very small (< 10 per cent) and not observed in the PMR spectra.

A set of p-anisidinomethylenecycloalkanones (Fig.15, R= p-OCH_3) was chosen for detailed PMR and IR studies. We were interested only in aromatic and onward region of the PMR spectra. The reason behind selecting the above set is that theoretically the p-anisidino part will form a separate quartet and thus the aromatic signals can be distinguished from the NH-CH quartets.

In DMSO solution, the NMR spectra of above compounds, as seen earlier, showed two types of AB quartets which could be assigned to cis-ketoamine (A) and trans-ketoamine (D) isomers. The percentages of the individual isomers and hence the extent of isomerisation can be calculated by comparing the relative intensities of peak heights of the doublets for NH proton in the two forms. Whereas the extent of isomerisation to trans-ketoamine varied from $\sim$15 to 40% in compounds (XXIV, XXV), it was found to be as high as 90% in compound (XXIII). Taking the

chemical shift of the NH proton as a pointer, it was seen that the H-bonding was the strongest in case of 2-arylamino-methylenecyclohexanone (XVIII) and weakest in 2-arylamino-methylenecyclopentanone (XXIII). From this it can be inferred that the extent of isomerisation was a function of the strength of hydrogen bonding between the carbonyl and the NH groups.

Support for this inference was obtained from the IR studies of the carbonyl stretching bands. The frequencies of C=O region of 2-arylaminomethylenecyclopenta (XXIII-a), -hexa (XVIII-a),-hepta (XXIV-a) and -octanone (XXV-a) derivatives, in chloroform and DMSO solutions are given in (Fig.20). The compounds in DMSO solution showed the absorption peaks characteristic of non-bonded C=O stretching mode whose intensity determined the amount of trans-ketoamine species present. The percentages of cis/trans isomers, thus obtained are comparable with those obtained from PMR data.

The IR spectra of (XXIII-a), (XXIV-a) and (XXV-a) in DMSO showed two carbonyl stretching frequencies each at 1690(s), 1665(m); 1660(s), 1640(m) and 1660(m) and 1640(s) cm^{-1}. These were ascribed to non-bonded and bonded species respectively in comparison with their spectra in chloroform. In chloroform solution, (XXIII-a) gives two carbonyl bands at 1690(m) and 1665(s) cm^{-1} indicating that non-bonded species was absent or very small. Thus spectra of (XXIII-a) in chloroform and dimethylsulfoxide solution showed a reversal of the C=O and C=C absorption intensities due to bonded

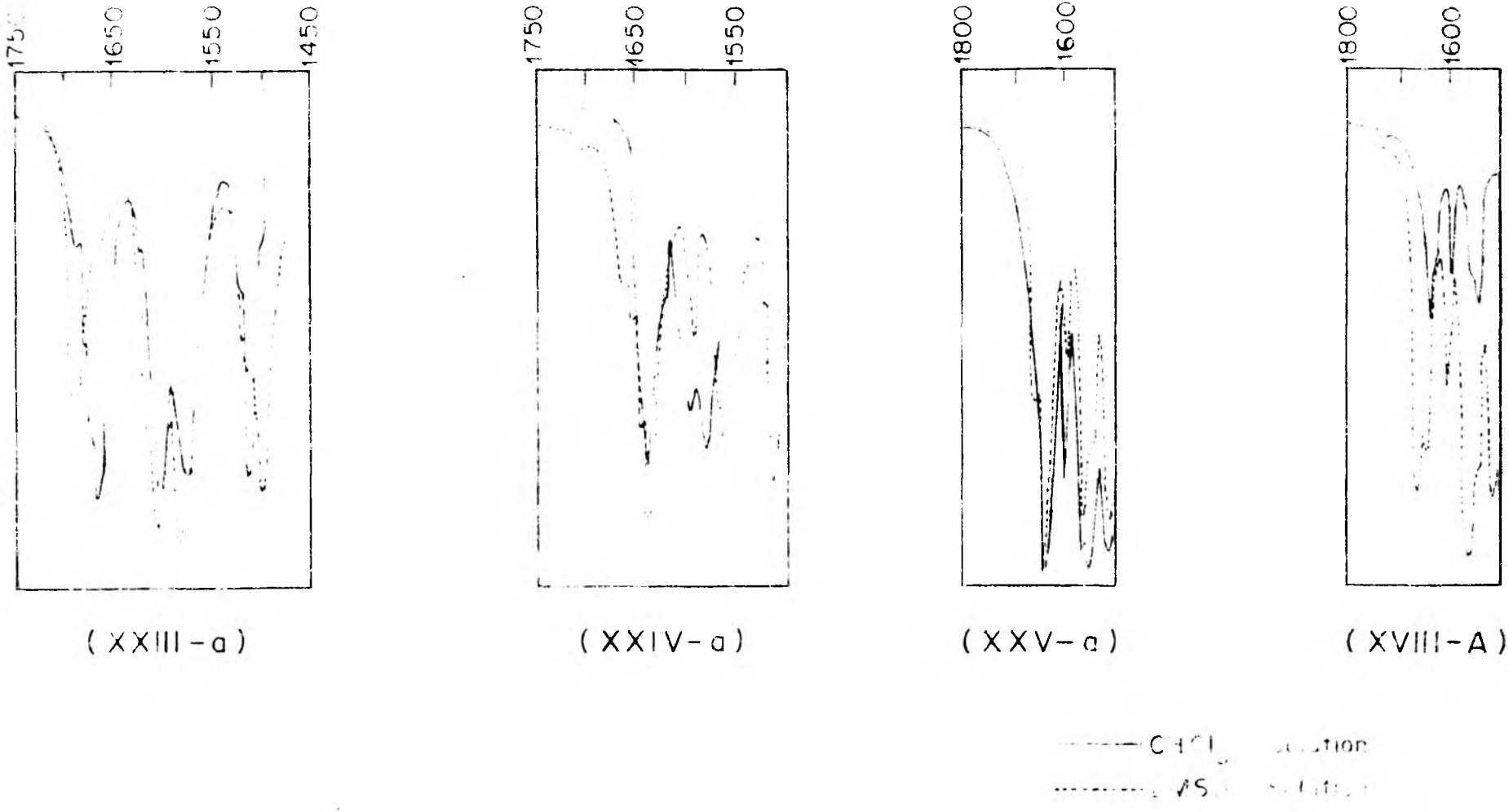


FIG. 20. INFRARED CARBONYL FREQUENCIES OF (XXIII-a – XXVa) AND (XVIII-A)

cis-ketoamine and non-bonded trans-ketoamine species (Fig.20). Similarly (XXIV-a) in chloroform showed single peak for the C=O stretching frequency, however in DMSO, additional band in the carbonyl region at 1660 cm^{-1} showed the presence of trans isomer to the extent of ~ 30 per cent.

The NH-stretching region in IR spectra of above compounds in DMSO solution shows a complex pattern. The three bands near 3200-3300 cm^{-1} do not change their relative intensity on dilution indicating that intermolecular hydrogen bonding is absent. It was not possible, even with careful experiments, to assess the band at 3450 cm^{-1}, whether coming from moisture in DMSO or a genuine peak. The band at 3410 cm^{-1} observed in nujol mull of (XXIII-a) and (XVIII-a) vanished in DMSO, suggests that it might not be due to trans-species but may be due to the gauche form (H) (Fig.16).

In order to find out whether other polar and dipolar aprotic solvents are able to bring about isomerisation, we investigated the PMR and IR spectra of p-anisidinomethylene-cycloheptanone (XXIV-a) in the following solvents:- acetonitrile, acetone, dimethylformamide (DMF), dioxan, carbon disulfide, sulfolane, hexachloroacetone and pyridine. In PMR, no evidence for trans isomer was found in any of these solvents. The C=O and NH absorptions in IR were similar to those found in $CHCl_3$, indicating that the trans-species was present only to a small extent (< 5%). However, similar studies on (XXIII-a) could not satisfactorily be carried out due to solubility difficulties.

It may be recalled at this stage that a very small extent of trans isomerisation was observed[110] in case of O-anisidinomethylenecyclohexanone (XVIII-C) and it was attributed to the steric crowding. In order to elaborate on this aspect, the PMR and IR spectra of 2-(2',6'-dichloro-anilino)methylenecyclopentanone (XXIII-m) and -heptanone (XXIV-m) were recorded in DMSO. No isomerisation was found and the compounds remained as cis-ketoamine tautomer in contrast to -m and -p substituted compounds wherein varying amounts of the trans-ketoamine isomer was found. This suggests that in isomerisation process, the solvent DMSO should be interacting with NH and not with the carbonyl group. In (XXIII-m) the approach of DMSO is sterically hindered by the neighbouring bulky chloro-substituents. The interactions appear to be selective since these are quite sensitive to steric effects.

In order to investigate the extent of isomerisation in mixture of DMSO with a non-polar solvent CCl_4, the PMR spectra of (XXIV) were taken in a large number of mixtures. Starting from pure CCl_4, till DMSO concentration was 50% by volume, the trans species could not be detected by PMR. However, with further addition of DMSO, the trans form began to appear which reached a maximum of 30% in pure DMSO. In all the mixtures the chemical shift of the NH proton either in cis or trans forms was found to be independent of the concentration of the compounds and composition of the mixtures. This showed

that the self association between the solute as well as intermolecular association between NH and solvent molecules were not present. It was also observed that temperatures upto 120° had a little or no effect on the cis/trans isomerisation in DMSO. Both the dilution and temperature studies do not support solute-DMSO complex formation, like 1:1 complex formation of amines in DMSO as concluded by Fung[120]. The above studies on 2-arylaminomethylenecycloalkanones suggest that an isomeric equilibrium phenomenon is set up when these compounds are dissolved in DMSO.

DISCUSSION

The predominance of the cis-ketoamine form is due to its high stability achieved through extensive delocalisation in the conjugated part of the molecule and the energy gained in the formation of an intramolecular H-bond. The absence of enolimine form can be accounted in terms of unfavoured resonance as lone pair on nitrogen is not available for delocalisation in this structure, although intramolecular H-bonding is possible. The ketoimine form does not have chelated proton and it is energetically least favoured.

Cis isomer (A) is more stabilized due to intramolecular hydrogen bonding than trans isomer (D). Hence any solvent, by interaction or by solvation energy, if initially overcomes the energy gained in H-bonding will bring about cis/trans isomerisation.

The equilibrium found in DMSO solution has the cis and trans forms showing large and similar spin spin coupling constants between the amine proton and α-proton. From the coupling constant data (J = 12-14 Hz), the rate of rotation around central C-C double bond can be readily calculated using equation[14],

$K = n\,2\pi r$ $\qquad$ $r = 1$

$= 88\ sec^{-1}$ $\qquad$ $n = J = 14$

Hence, Average life

$$\tau = \frac{1}{K}$$

$$= \frac{1}{88}$$

$$= 0.026$$

$$= 2.6 \times 10^{-2}\ sec.$$

The rate of rotation and average life of species suggest that the equilibrium is not fast on NMR time scale and the process can be studied by spectroscopy.

The process of isomerisation which is sensitive to 'ortho blocking' suggests that the site of interactions of DMSO with solute molecules must only be in the vicinity of NH group. Hence any mechanism involving interactions through carbonyl group or central double bond would be unlikely since it will not explain the steric effect (Fig.21). Further the trans-conversion is seen only when massive molar excess of DMSO is used in relation to the solute. This would also discount a mechanism involving 'chemical interactions' as shown in Fig.21.

The protonation studies[121] on cis-2-arylaminomethylene-cyclohexanone (XVIII) indicate that the electron drift, in resonance, is towards oxygen. Therefore, hydrogen bonding type interactions of DMSO with OH group of solute in enolimine form might occur. However, no enolimine structure is noticed by IR and PMR spectra. Evidently these interactions are dropped out.

The other interactions of DMSO with solute could be as follows (Fig.21):-

i) Hydrogen bonding type interactions with NH donor.

ii) Lone pair on heteroatom of solute interacts with DMSO.

iii) Dipolar interactions.

Following are the factors which will govern these interactions:-

i) Dimethylsulfoxide being basic, may associate through the electronegative oxygen atom with the proton donor molecule e.g. with NH in cis-ketoamine form (Fig.21). Hence intramolecular H-bonding would be weakened. Enolisation would be favoured giving single bond character to the central C=C double bond. Isomerisation would occur by rotation and the trans form be stabilized by intermolecular H-bonding with solvent. However, the chemical shift of non-bonded NH in trans-ketoamine form is not much different from that of the secondary amides in non-polar solvents. The slight lowfield shift in the present case may be due to vinylogous nature of these compounds and the solvent effect of DMSO. In the event of a complex formation

through hydrogen, the amine proton would have shifted still downfield. The value of NH at 12 ppm indicates strong intramolecular hydrogen bonding and cis species is also present in DMSO solution. Free NH of 3-aminoacrylic ester[119] in DMSO appears near 7 ppm where intermolecular hydrogen bonding is also present. The cis amine proton appearing at 12 ppm in present compounds, in comparison with the above, suggests that the intramolecular hydrogen bonding in cis-2-arylaminomethylenecycloalkanones is stronger than intermolecular hydrogen bonding between NH and DMSO. However, the dilution and temperature studies do not favour intermolecular hydrogen bonding interactions. Secondly, the cis-2-p-anisidinomethylenecyclopentanone (XXIII-a) in DMSO does not show cis-amine proton whereas it is definitely shown in more basic pyridine medium. It is hence inferred that DMSO does not act as a general base catalyst in effecting cis/trans isomerisation.

ii) In the absence of hydrogen-bonding type interactions and any interactions through carbonyl or hydroxyl group, one can consider nitrogen lone pair interactions with electropositive sulfur atom of DMSO (Fig.21). Such interactions have been suggested by Kivelson[122] to interpret the results on the negative heats of mixing of water and methanol with DMSO, which could not be explained entirely on hydrogen bonding between OH and S=O group. The unique role of DMSO can be explained as the nitrogen lone pair can be accommodated in the vacant sulfur d-orbitals. This mechanism, although explains steric effect, has a drawback that the lone pair

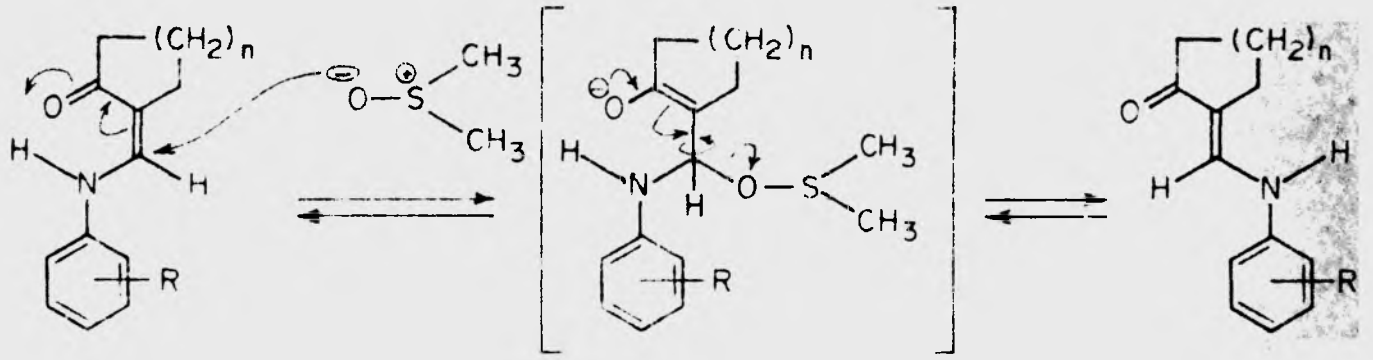
on nitrogen being in vinylogous conjugation with carbonyl group may not be available as indicated by protonation studies[121].

iii) The dipolar interactions of solvent and solute, leading to 'collision complex' (Fig.21) may best explain the experimental results.

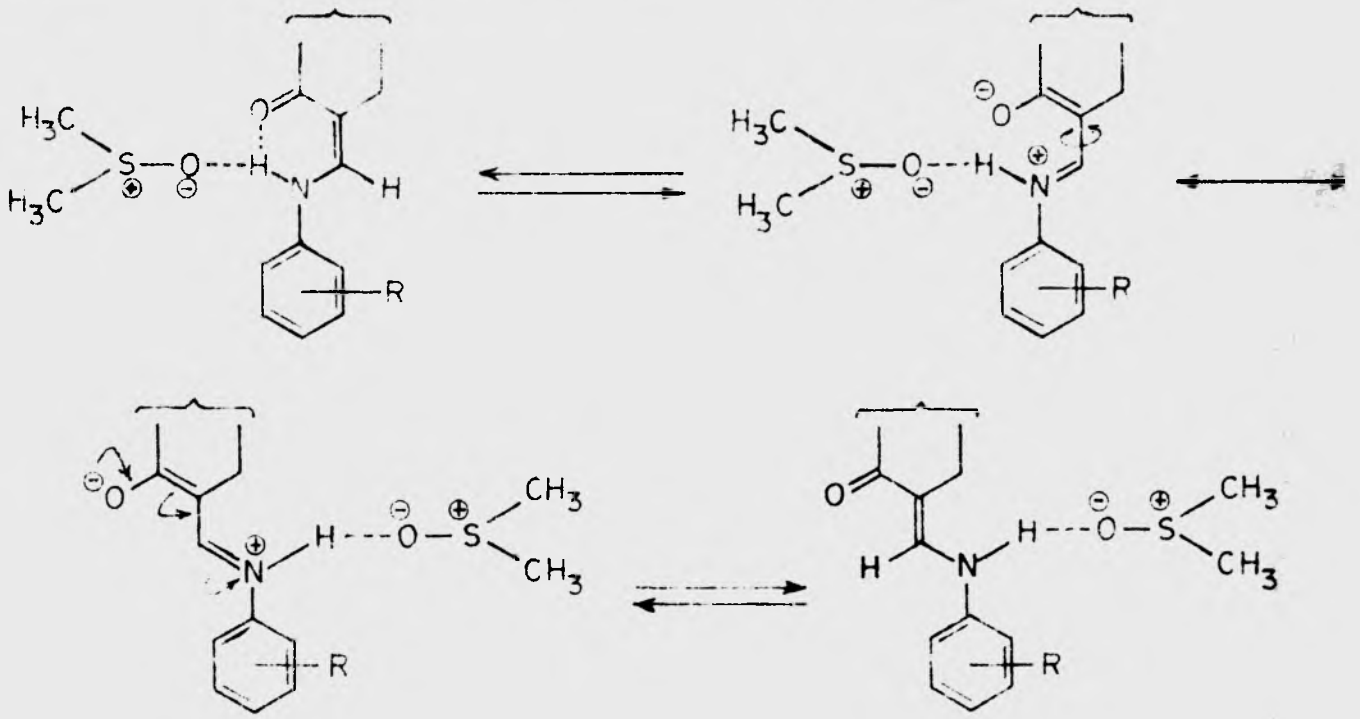
A large charge separation with oxygen at the negative end and nitrogen at the positive end leads to a strong dipolar character in the solutes (XXIII-XXV). The conjugation of the lone pair on nitrogen with the α,β-unsaturated ketone will induce a partial double bond character in the -N-C= single bond and a partial single bond character to central C-C double bond. There would be hindered rotation around N-C bond as in amides. On the contrary the formal C-C double bond will have easy rotation so that <u>cis</u> and <u>trans</u> isomers are possible.

The dipolar interactions would be as follows:- The $S^{\delta+} - O^{\delta-}$ dipole in DMSO aligns with the dipole of $N^{-\delta} - H^{+\delta}$ in solute, which would further induce and stabilize the dipolar transition state. The solvation <u>via</u> dipolar interactions would significantly lower the barrier to rotation around central C-C double bond in solute, resulting into the equilibrium. On the other hand, dimethyl sulfoxide being a strong positive ion solvator, may solvate the uniformly distributed positive pole in the solute and stabilize the dipolar transition state (Fig.21). However, the creation of a dipole at NH in solute, which would in turn reduce the

CHEMICAL INTERACTIONS :



(i) INTERMOLECULAR H-BONDING INTERACTIONS :



(ii) LONE PAIR INTERACTIONS :

(iii) DIPOLAR INTERACTIONS :

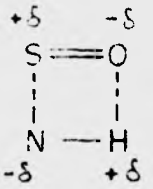


FIG. 21 .

C=C rotational barrier by mesomeric effect is considered rational, since such dipolar interactions would be more selective and sensitive to steric effects.

The difference between the energies involved in intermolecular interactions between DMSO and solute and the intramolecular hydrogen bonding would decide the extent of isomerisation in the various 2-arylaminomethylenecycloalkanones. Further support was sought from the substituent effect in the aryl residue of cis-2-arylaminomethylenecyclohexanones (XVIII). The strength of hydrogen bonding was affected by electron withdrawing substituents in the arylamine part and accordingly the extent of trans isomerisation varied[110].

The fact that the trans-ketoamine isomer cannot be isolated suggests that a low barrier to interconversion exists between the isomers. It is impossible to isolate the conformers having free energy of activation ($\Delta G^{\ddagger}$)[6] below 23 KCal/mole. Thus, the cis and trans isomers described here as configurational isomers are really very stable conformers. The low activation energy for bond rotation process also demonstrates easy polarisation.

Examples of isomerisation around double bond have been described in case of fulvene[65], fulvalene, diphenoquinone[6], 3-aminoacrylic ester[119] and β-thioketoester[123]. In case of cis-2-arylaminomethylenecycloalkanones, the dipolar nature of solute molecule and the dipolar interactions of DMSO leading to solvation and thereby reducing the barrier to rotation are the potential causes of cis-trans equilibrium.

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

Preparation of spectra-grade solvents

Commercial solvents were purified by the usual procedures, (a) chloroform was washed with water to remove ethanol, dried over calcium chloride, distilled, passed over neutral alumina and filtered. Freshly treated chloroform was used. (b) Spectrophotometric grade DMSO from Crown Zellerbach Corporation, Camas Washington was available. Solvent was kept in a dry-box over calcium hydride and dryness checked from time to time by adding calcium hydride. Drying of a separate sample over molecular sieves was also done.

Preparation of 2-hydroxymethylenecyclopentanone (XXII, n=1) (Fig.14):

The method of Johnson and coworkers[124] was modified.

A 500 ml three-necked flask equipped with a mercury sealed half moon stirrer, stopper and a 100 ml pressure-equalising dropping funnel with a guard tube was cooled in an ice-bath. Into the flask was placed dry powdered sodium methoxide (22 g) in dry benzene (100 ml). To this ethyl formate (30 ml) in dry benzene (30 ml) was added dropwise over a period of 45 minutes. Cyclopentanone (16.8 g) in dry benzene (10 ml) was then added in lots in three minutes, when the yellow cake of sodium salt of hydroxymethylene-cyclopentanone separated out obstructing stirring. Additional dry benzene (30 ml) may be added to achieve stirring for 2 hr at room temperature. The yellow cake turns brown on

keeping. Cake was dissolved in water (80 ml) and benzene layer removed. Aqueous layer again washed with benzene (20 ml). Combined benzene layer was washed with water (15 ml) and water was mixed with aqueous layer. The aqueous layer was cooled (< 10°) and acidified with 10N HCl (21-24 ml) at pH 4 when clear yellow solution appeared turbid and solid particles of product (XXII, n=1) began to float. Sodium chloride (15 g) was dissolved in it and the mixture was extracted with ether (100 ml + 2 x 25 ml). Ether extract after washing with brine (25 ml) was dried over anhydrous sodium sulfate. Solvent was removed at 40°/20 mm to give crude orange liquid (23 g) which was susceptible to air-oxidation. Distillation between 60-70°/4 mm gave colorless solid (17 g, yield 75%), colorless needles (pet.ether), m.p. 77°, lit.[124] m.p. 76-77°.

Nitrogen flush did not avoid polymerisation. The reaction mixture was also kept for 18 hrs at room temperature for completion of reaction but the yellow cake turned brown and work up gave red liquid as final product.

Preparation of cis-2-arylaminomethylenecycloalkanones (XXIII, XXIV, XXV) (Fig.15)

(a) General method: Equimolecular amounts of the arylamine and 2-hydroxymethylenecycloalkanone were dissolved in ether and the solution kept at 0°. Within 10 minutes to 24 hrs, a yellow crystalline product began to separate out. To subside the

initial exothermic reaction and avoid polymerisation the reaction mixture was kept at low temperature and under nitrogen. In some cases scratching or seedling was necessary for separation of the reaction product. The yellow crystalline condensation product was filtered, washed with a small quantity of ether to remove unreacted starting materials and dried. The products were purified by column chromatography over neutral alumina, using benzene as eluent. The purified products were then crystallised usually first from benzene-pet. ether and finally from ethanol or chloroform-pet. ether. Experimental details of these preparations are given in Table 5. The elemental analyses and molecular weights as molecular ion peaks from mass spectra are given in Table 6. The NMR and IR data are given in Table 2 and Tables 3 and 4 respectively.

(b) Preparation of compounds (XXIV-m), (XXIV-f) and (XXIII-k).

When arylamine did not dissolve in ether then following procedure was used. Equimolecular quantities of arylamine and 2-hydroxymethylenecycloalkanone were mixed at room temperature in the presence of absolute ethanol as solvent. The mixture was refluxed on boiling waterbath for 1 hr and then cooled to room temperature, when condensation product separated out. The product was filtered, washed with a small quantity of absolute ethanol and dried. The products were purified by column chromatography and then crystallised from ethanol. Products were characterised by NMR, IR, Mass spectra and

TABLE 5 - PREPARATION OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

Arylamine	Wt/g	2-hydroxy-methylene cycloalka-none.	Wt/g	2-arylaminomethylenecycloalkanones				
				Compd.	Yield g.	Yield %	Crystalline shape (solvent)	m.p. °C
p-OCH_3-$C_6H_4NH_2$	6.15	-penta-none	5.6	XXIII-a	8.7	80	Yellow plates ($CHCl_3$-Pet.eth)	159°
m-OCH_3-$C_6H_4NH_2$	6.1	"	5.6	XXIII-b	5.0	45	Colourless transparent rectangular plates ($CHCl_3$-Pet.eth)	154°
p-CH_3-$C_6H_4NH_2$	5.3	"	5.6	XXIII-d	6.4	64	Light yellow flakes (Benzene-Pet. ether)	174°
p-NO_2-$C_6H_4NH_2$	6.9	"	5.6	XXIII-f	4.8	41	Golden yellow shining plates (EtOH)	230° (dec)
α-$C_{10}H_7NH_2$	8.3	"	5.6	XXIII-j	8.3	70	Yellow plates ($CHCl_3$-Pet.eth)	132-134°
β-$C_{10}H_7NH_2$	8.3	"	5.6	XXIII-k	9.5	80	Yellow thin plates (EtOH)	232-234°
O,O'-$Cl_2C_6H_3NH_2$	8.0	"	5.6	XXIII-m	7.2	57	Lemon yellow needles(Pet.eth)	105°
$C_6H_5NH_2$	4.6	"	5.6	XXIII-n	6.7	72	Colorless needles($CHCl_3$-Pet.eth)	176° (lit.[30] 176)
p-OCH_3-$C_6H_4NH_2$	4.4	-heptanone	5.0	XXIV-a	7.0	80	Yellowish needles (Pet.eth)	79°
m-OCH_3-$C_6H_4NH_2$	2.6	"	3.5	XXIV-b	5.8	96	Colorless rectangular plates (Pet.eth)	93°
p-CH_3-$C_6H_4NH_2$	3.7	"	5.0	XXIV-d	8.0	98	Colorless flakes (Benzene)	111°
p-NO_2-$C_6H_4NH_2$	6.9	"	7.0	XXIV-f	11.1	85	Golden yellow silky needles(EtOH)	183°
O,O'-Cl_2-$C_6H_3NH_2$	6.0	"	5.2	XXIV-m	9.5	90	Shining yellow bars (EtOH)	130°
$C_6H_5NH_2$	2.3	"	3.5	XXIV-n	5.0	92	Colorless plates (Pet.eth)	118-20°
p-OCH_3-$C_6H_4NH_2$	3.7	-octanone	4.6	XXV-a	6.0	91	Lemon yellow needles (Pet.eth)	96°
m-OCH_3-$C_6H_4NH_2$	6.6	"	7.7	XXV-b	12.5	97	Colorless plates (Pet.eth)	77°
$C_6H_5NH_2$	4.6	"	7.7	XXV-n	11.2	98	Colorless plates (Pet.eth)	129°

TABLE 6 - ANALYTICAL DATA AND MOLECULAR ION PEAKS OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

Compd. No.	Molecular formula	Molecular ion peak M^+ at m/e	Analysis					
			Found			Required		
			C	H	N	C	H	N
XXIII a	$C_{13}H_{15}NO_2$	217	71.6	6.9	6.7	71.9	6.9	6.5
XXIII b	$C_{13}H_{15}NO_2$	217	71.6	7.2	6.8	71.9	6.9	6.5
XXIII d	$C_{13}H_{15}NO$	201	77.5	7.8	7.3	77.6	7.5	7.0
XXIII f	$C_{12}H_{12}N_2O_3$	232	62.4	5.5	11.8	62.1	5.2	12.1
XXIII j	$C_{16}H_{15}NO$	237	81.0	6.6	6.2	81.0	6.3	5.9
XXIII k	$C_{16}H_{15}NO$	237	81.0	6.4	6.2	81.0	6.3	5.9
XXIII m	$C_{12}H_{11}NOCl_2$	255	56.5	4.4	5.8	56.3	4.3	5.5
XXIII n	$C_{12}H_{13}NO$	187	*					
XXIV a	$C_{15}H_{19}NO_2$	245	73.8	7.9	5.7	73.5	7.8	5.7
XXIV b	$C_{15}H_{19}NO_2$	245	73.4	7.8	5.8	73.5	7.8	5.7
XXIV d	$C_{15}H_{19}NO$	229	79.0	8.6	6.1	78.6	8.3	6.1
XXIV f	$C_{14}H_{16}N_2O_3$	260	64.5	5.9	9.5	64.6	6.1	9.3
XXIV m	$C_{14}H_{15}NOCl_2$	283	59.2	5.6	4.9	59.3	5.3	4.9
XXIV n	$C_{14}H_{17}NO$	215	78.3	8.2	6.7	78.1	7.9	6.6
XXV a	$C_{16}H_{21}NO_2$	259	74.5	8.4	5.6	74.1	8.1	5.5
XXV b	$C_{16}H_{21}NO_2$	259	74.5	7.8	5.2	74.1	8.1	5.5
XXV n	$C_{15}H_{19}NO$	229	78.4	8.1	6.4	78.6	8.3	6.1

*Known (Ref.30).
Halogen analysis for,
(XXIII-m), Cl = 28.1 required Cl = 27.8
(XXIV-m), Cl = 25.4 " Cl = 25.1

elemental analysis (Tables 2,3 and 4,5 and 6 as above).

Deuteration studies: Deuteration of cis-2-p-anisidinomethylenecyclopentanone (XXIII-a) (10 mg) was carried out by refluxing the compound in excess of D_2O (10 ml) over heating mantle for 1 hr. The mixture was concentrated by distillation under reduced pressure and final traces removed over water bath. The infrared spectrum of deuterated sample was recorded. Band at 3250 cm^{-1} (bonded NH) on deuteration shifted to 2390 cm^{-1} (N-D).

Ultraviolet spectra: Quantitative UV absorption spectra of (XXIII-a), (XVIII-A), (XXIV-a) and (XXV-a) were recorded in 95% ethanol and dimethyl sulfoxide. All the compounds showed identical absorptions, λ max in $m\mu$ at 238, 310, 359 with different optical densities.

PMR spectra of p-anisidinomethylenecycloheptanone (XXIV-a):

a) Dilution study: PMR spectra of (XXIV-a) in 5-8% solutions of various solvents were recorded. No change was found in the chemical shift of NH proton (Table 2). Spectra immediately taken after making solution and after 18 hr standing were unchanged.

b) Temperature study: PMR spectra of (XXIV-a) (0.049 g in 0.5 ml DMSO) at temperatures 40°, 60°, 80°, 120° showed no change either in the intensity or chemical shift of various protons.

c) Mixture of solvents: PMR spectra of (XXIV-a) (0.049 g) were recorded after dissolving separately in following mixtures: (i) pure CCl_4 (0.5 ml) (ii) CCl_4 (0.2 ml) + DMSO (0.3 ml), (iii) CCl_4 (0.25 ml) + DMSO (0.25 ml) (iv) CCl_4 (0.3 ml) +

DMSO (0.2 ml) (v) CCl_4 (0.1 ml) + DMSO (0.4 ml) (vi) pure DMSO (0.5 ml).

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CHAPTER II - SYNTHESIS OF TRICYCLIC AND TETRACYCLIC NITROGEN HETEROCYCLICS

INTRODUCTION

In the field of nitrogen heterocyclics polymethylene-quinolines, phenanthridines and acridine derivatives[1] have found commercial applications as chemotherapeutic agents, dyestuffs and photographic chemicals. Compounds like 5-amino-1,2,3,4-tetrahydroacridines (4-amino-2,3-tetramethylenequinoline) were originally synthesised in order to examine antibacterial, antimalarial and trypanocidal activity but later were shown to possess a wide spectrum of pharmacological actions which include anticholinesterase, antagonism to psychotomimetics, morphine antagonist, analepic and decurarising actions[2]. Acridines have provided a series of orange-yellow basic dyestuffs, red-purple vat dyestuffs and red-violet pigments. Cyanine dyes derived from acridines have found uses as photosensitisers[3]. Some other uses include industrial disinfection, preservation, corrosion inhibition and as biochemical, microscopic reagents and antioxidants[4].

The versatile uses of these compounds has aroused much technical and scientific interest. Systematic reviews on the synthesis, properties and uses of acridines[4] and phenanthridines[5] are also available.

Except for two old reports, not much was known about the pharmacology of polymethylenequinolines[2] until 1965. It seems interesting to study the chemistry of polymethylenequinolines. The chemistry of polymethylene-quinolines does not appear to have been reviewed so far.

The present work deals with the synthesis of tri- and tetra-cyclic nitrogen heterocyclics by cyclodehydration of cis-2-arylaminomethylenecycloalkanones. The synthesis of various linear polymethylenequinolines involves a rearrangement described earlier in the case of the synthesis of acridines by acid catalysed cyclodehydration of cis-2-arylaminomethylenecyclohexanones. Discussion on the mechanism involved in these reactions will be treated separately. Literature survey relevant to the synthesis of polymethylenequinolines is described in the following pages.

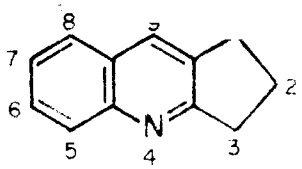
The nomenclature and numbering system used by Chemical Abstract, Ring Index[6] and Chemical Society has been adopted in the present work. Fig.(1) indicates the name and numbering. Literature pertaining to C_5N-C_6-C_5, C_5N-C_6-C_7 and C_5N-C_6-C_8 systems has been reviewed.

General Methods for the Synthesis of polymethylenequinolines

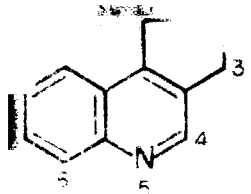
The methods developed for the synthesis of quinolines are usually extended to synthesise higher membered ring systems. Substituted quinolines are found in coal tar but most quinolines are obtained by synthetic methods. The common skeletons from which the heterocyclic ring is built up are Types:- A, B, C and D (Fig.2).

Synthesis: Type A (Skraup, Doebner von Miller, Combe's reaction etc.).

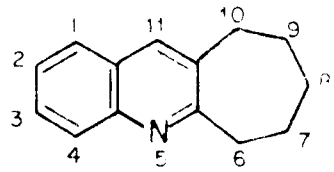
The most commonly employed synthesis is through



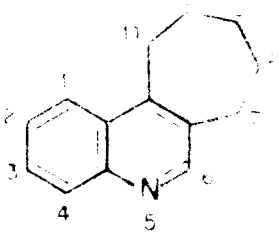
2,3 dihydro-1H-cyclopenta [b] quinoline, β-quinindane



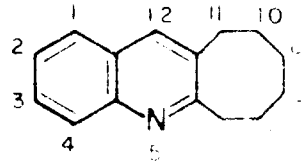
hydro-1H-cyclopenta [b] quinoline, α-quinindane



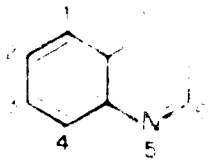
Cyclohepteno[b] quinoline



Cyclohepten noline

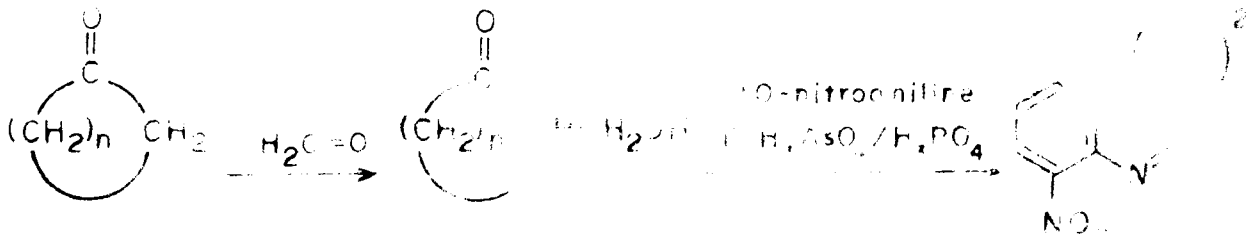


Cyclooctено [b] quin



Types: (A) B) (C)

FIG. 2



type (A) and the most important reaction of this class is the Skraup reaction. Starting with a suitable amine and a carbonyl compound, various substituted quinolines[1] have been prepared by using Doebner von Miller synthesis, Riehm's synthesis, Knorr or Conrad-Limpach method and Combe's reaction.

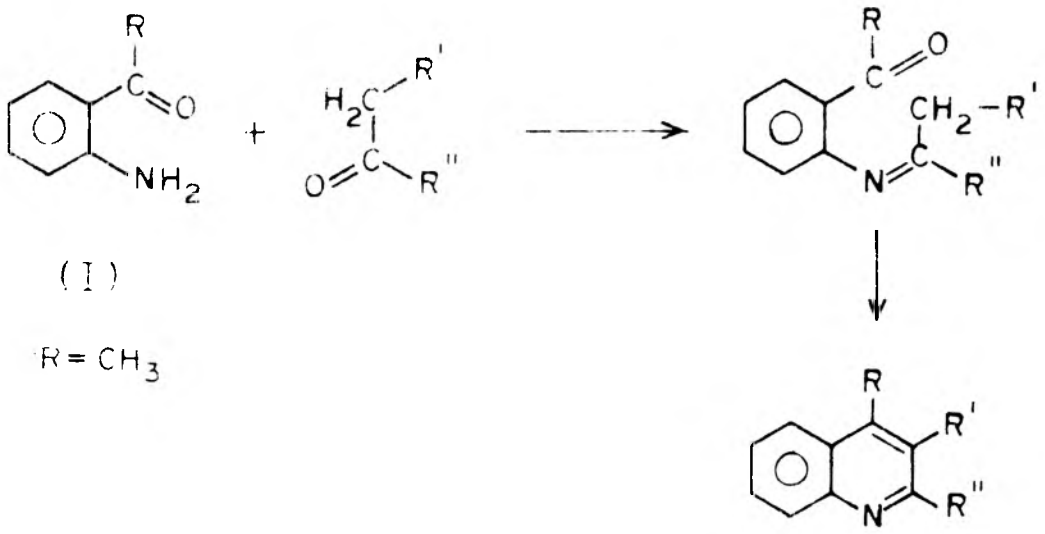
Condensation of formalin with cyclopentanone, cycloheptanone and cyclooctanone yields the corresponding hydroxymethylenecycloalkanones which on interaction with o-nitroaniline in a modified Skraup reaction lead to the respective 3,4-cycloalkeno-8-nitroquinolines[7] (Fig.3).

Synthesis: Type B (Friedländer, Pfitzinger, Niementowski reaction).

The reactions of type (B) are, Friedländer cyclisation, Pfitzinger synthesis and Niementowski reaction (Fig.4). In these reactions substituted ketones with a condensable α-methylene group are reacted with o-aminobenzaldehyde, isatin and anthranilic acid respectively to produce 2,3- and 3,4-disubstituted quinolines. Hence selecting R_1 and R_2 as $-(CH_2)_n-$, the required polymethylenequinolines can be synthesised by following the above synthetic routes. However, in the Friedländer reaction, substitutions in the aryl moiety of polymethylenequinolines cannot be accomplished since substituted o-aminobenzaldehydes are difficult to prepare. Important features of above reactions are well-known[8], however their use to synthesise polymethylenequinolines is outlined below.

FIG·4

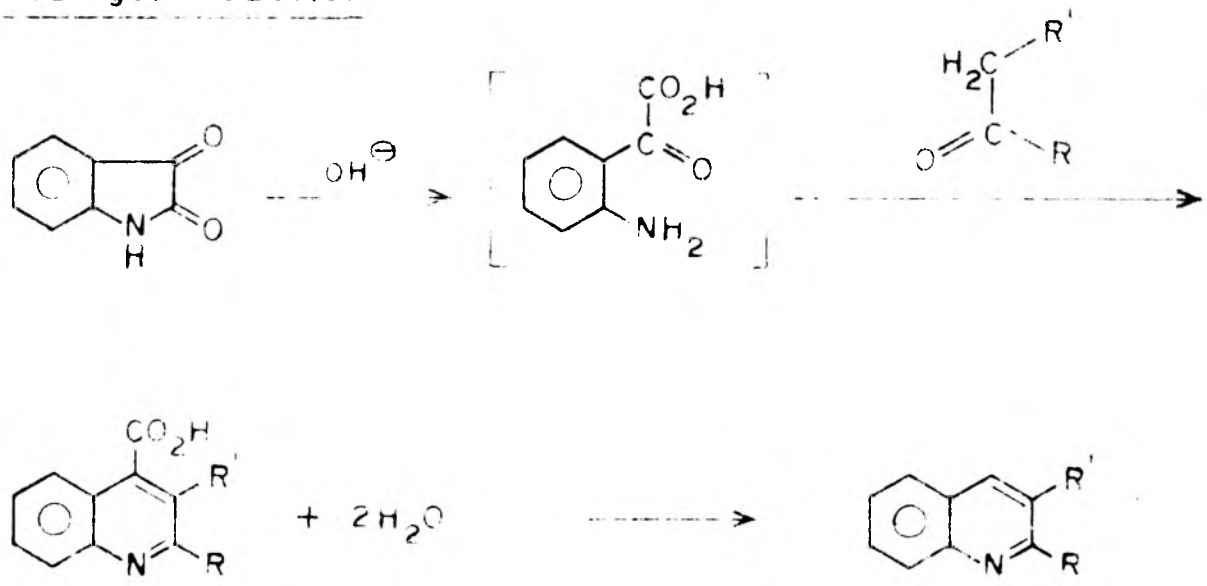
Friedländer reaction



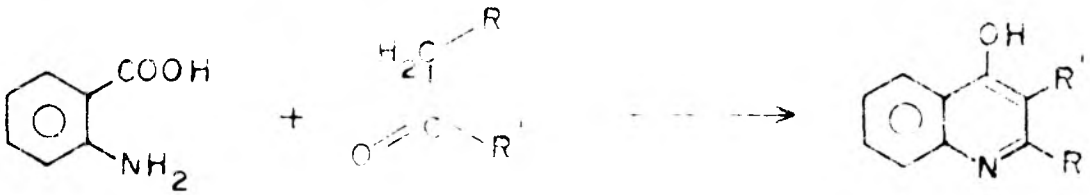
(I)

R = CH_3

Pfitzinger reaction



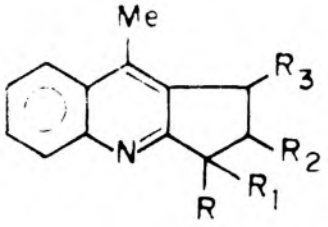
Niementowski reaction



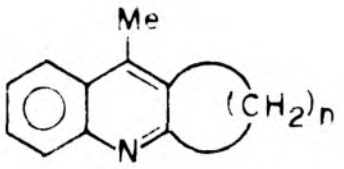
Polymethylenequinoline derivatives have been obtained by improved Friedländer reaction in which o-aminoacetophenone was used in place of o-aminobenzaldehyde. Cycloalkane-1,2-diones were condensed[9,10] with o-aminoacetophenone (I) at 100° to give the intermediates which on dehydration lead to keto-polymethylenequinolines. Cyclic ketones were also condensed with o-aminoacetophenone hydrochloride and then heated gradually to the desired reaction temperature 110-80° with removal of water to afford the precipitated hydrochloride salt of substituted lepidine in 60-90% yield[11]. Thus lepidines (II), (III), (IV) and (V) were prepared[12] (Fig.5). Acid catalysed condensation of o-aminobenzophenone with a variety of alicyclic ketones produce polymethylenequinolines[13]. In a variation, o-aminophenylglyoxaldimethylacetal (VI) has been condensed[14] with several cyclic ketones in refluxing Na/EtOH to yield polymethylenequinoline-4-aldehyde (VII) (Fig.6). Friedländer reaction has been applied to prepare steroidal heterocycles in which the quinoline moiety was fused to the D-ring in steroids[15].

Borsche[16] successfully applied Pfitzinger reaction to synthesise polymethylenequinolines in high yield. Cyclic ketones were condensed with isatin under alkaline conditions to give the corresponding cinchoninic acids which readily decarboxylated by heating them above their melting points and vacuum distillation of residue yielded the corresponding quinolines[17]. Buu-Hoï et al.[18] have extensively investigated

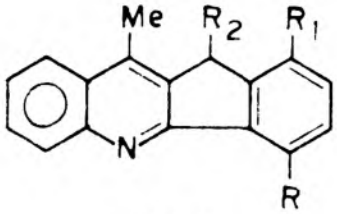
FIG. 5



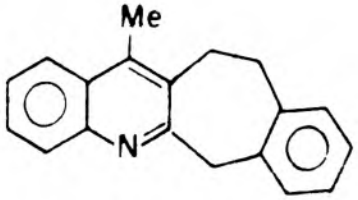
(II)



(III) n = 4,5,6

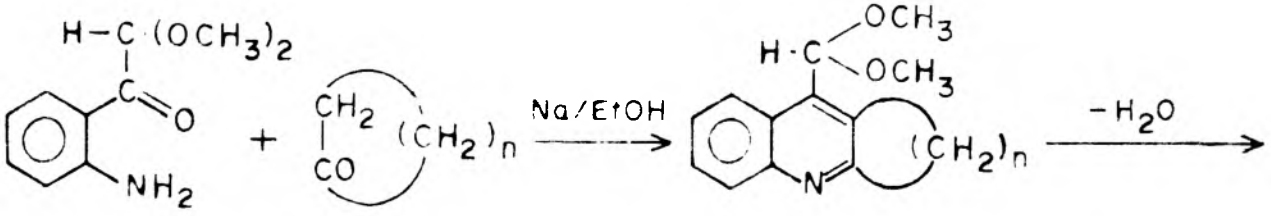


(IV)



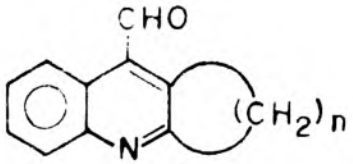
(V)

FIG. 6



(VI)

n = 4,5,6



(VII)

the Pfitzinger reaction as a method of preparation of a number of substituted quinoline derivatives. Recently Kholodov et al.[19] studied this reaction in detail while preparing β-quinindanes.

Tiedtke's method[20] and Niementowski quinoline cyclisation are modifications where anthranilic acid is interacted with a carbonyl compound possessing a condensable α-methylene group. These methods have been used to prepare tri-, tetra-, penta- and hexamethylene-4-quinolones[21,22].

A general synthetic route[23-31] (Fig.7) leading to polymethylenequinolines consists of condensing various aromatic amines with ethyl cycloalkanone-2-carboxylate (VIII) at room temperature or at elevated temperature between 140-190°. The resulting anilide (X) or the vinylogous amide (IX) were cyclised in boiling liquid paraffin or by refluxing in dowtherm. The ring closure has also been effected by treating compounds (IX) and (X) either with concentrated sulfuric acid or with polyphosphoric acid. When 2-diazo-cyclohexane-1,3-dione was thermolysed in aniline afforded carboxanilide (X) which cyclised on acid treatment[32]. This route has been made use of in the synthesis of azasteroids[33].

Synthesis of polymethylenequinolines has been achieved by cyclodehydration reactions of appropriate cyclic ketoximes[34], enamines[35,36], Schiff bases[37], Mannich bases[38], aryl amides[39] and β-ketoamides[40]. A convenient procedure[41] to

prepare 2,3-cycloalkenoquinolines is by treating β-chlorovinylaldehydes with arylamines in refluxing acetic acid.

Other miscellaneous methods include application of Bruckner method by Govindachari et al.[42] to prepare 3,4-dihydro-1-phenylcyclopenta[C]quinoline. A novel method[43] involves treatment of anthranil with cyclic ketones to give cyclohepta- and cyclooöcta[b]quinolines. Hydroperoxide of the carbazole derivative (XI)[44] when decomposed with alkali afforded cyclopenteno quinoline (XII) (Fig.8). Cyclization of o-cycloalkylanilides (XIII) with PPA yields the polymethylene-quinolines (XIV)[45] (Fig.9).

Some Properties and Uses of polymethylenequinolines

Stereoisomerism in hexahydroquinindenes has been analysed[46,47]. The reactivity of quinindane at C_3 position is shown by electrophilic substitution[48] yielding various 3-substituted derivatives[49,50]. On IR and UV spectral evidence it has been shown that the protonation of 3-acyl-1,2-dihydro-4H-β-quinindenes occurs at the C_3 atom[51]. Tautomerism in 3-acyl-β-quinindanes has been studied[52,53]. Comparative spectroscopic study[54] of polymethylenequinolines regarding cycloalkane ring size and effect of substituents[55] has been carried out.

Cyanine dyes from 2,3-dihydro-β-quinindene have been prepared[56]. Recently papers[57-61] and patents[62-65] have appeared on the pharmacological studies of the above compounds.

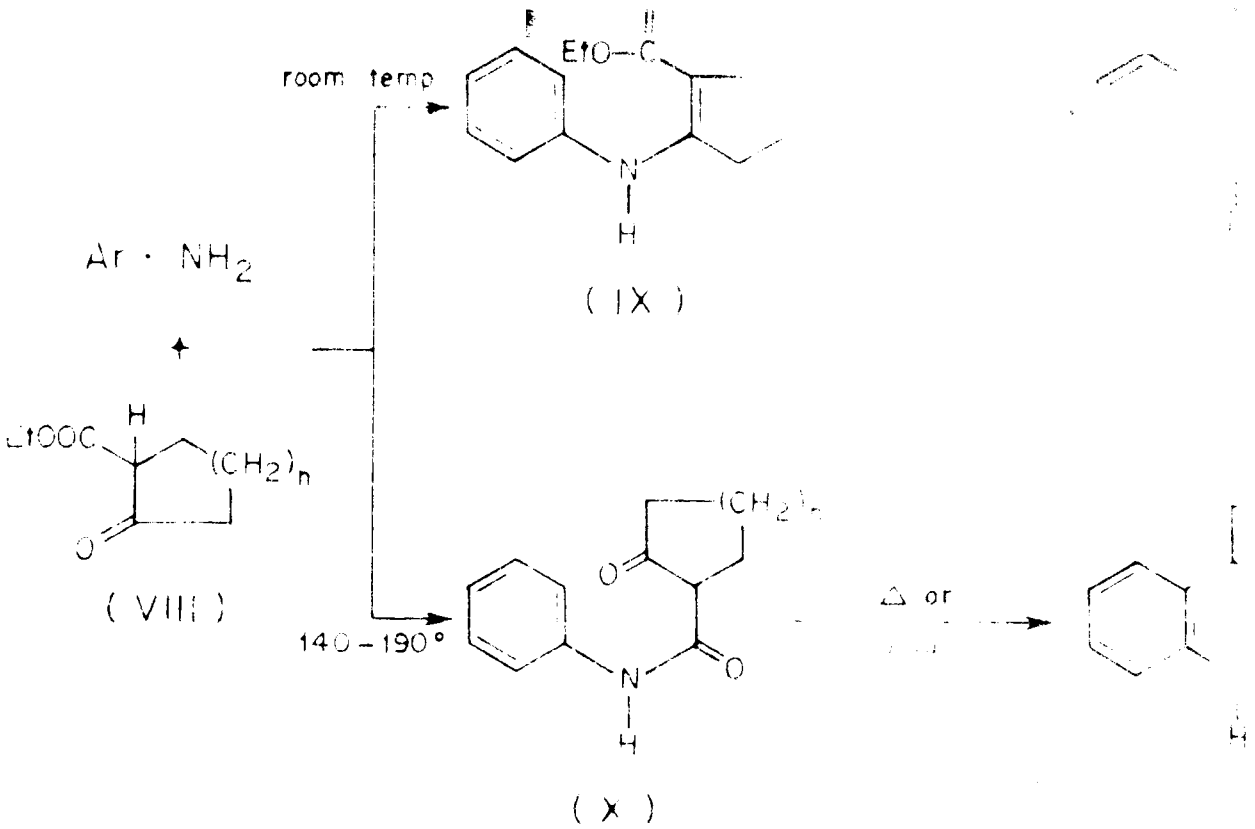


FIG. 7

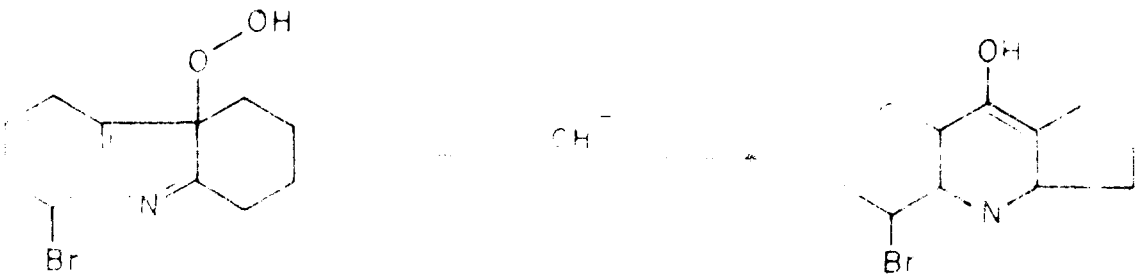
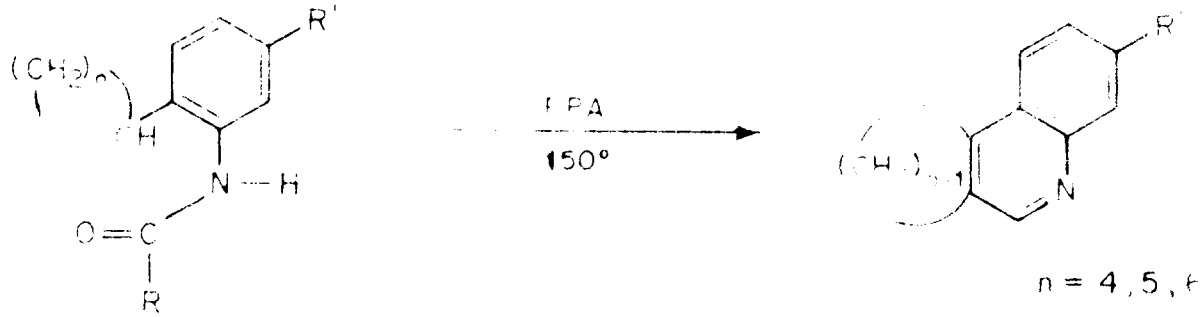


FIG. 8



(XII) (XIII)

Polymethylenequinoline derivatives are potential anti-hypertensive, antidepressant or tranquilising agents.

PRESENT WORK

The syntheses of polymethylenequinolines described in the introductory part generally give low yields of condensed quinolines. In the present work, the synthesis of tri- and tetracyclic quinolines was undertaken. Major interests in the present work have been to develop useful preparative methods for the synthesis of tri- and tetracyclic quinolines and in subsequent work to use these compounds to build up biologically active systems. Earlier work carried out in this laboratory on the synthesis of quinoline derivatives is reviewed in the following pages.

Tilak et al.[66] have reported that in the cyclodehydration of 2-arylaminomethylalkanones (XV), the intermediate 1,2-dihydroquinoline (XVI) undergoes disproportionation to yield quinoline (XVII) and tetrahydroquinoline (XVIII) (Fig.10). The reaction involved intermolecular hydride transfer and the yield of either of these products was less than 50%. However, when an external hydride abstractor like trityl chloride was used, disproportionation was suppressed and the quinolines were obtained almost exclusively.

A brief survey of cyclodehydration reactions leading to hydrophenanthridines is available[5b]. Mention may be made of Borsche[16], Hollingsworth and Petrov[67] and Hall and Walker[68]

for their major contributions. Cyclodehydrations of 'anil' of the type (XIX) (Fig.11) with sulfuric acid, polyphosphoric acid and hot formic acid yielded phenanthridines whereas treatment with arylamine hydrochloride/ zinc chloride or lactic acid yielded acridines. Although these cyclodehydrations were reported earlier, the reaction mechanism for these cyclodehydration reactions leading to phenanthridines (angular-normal cyclodehydration products and to acridines (linear-rearranged cyclodehydration products) was not elucidated by earlier authors.

In our laboratory, cyclodehydrations of cis-2-arylaminomethylenecyclohexanones (XIX) under acidic conditions leading to (angularly cyclised) tetrahydrophenanthridines or by a rearrangement to (linearly cyclised) tetrahydroacridines have been carried out and critically studied[69] (Fig.11). Plausible mechanisms to account for these rearrangements have been proposed[70].

The above methods appear of general application and could be extended further to synthesise polymethylenequinolines by acid catalysed cyclodehydrations of appropriate cis-2-arylaminomethylenecycloalkanones. The preparation of the relevant precursors has been discussed in the first Chapter and these were used for further reactions.

Polyphosphoric acid (PPA) is a facile cyclodehydrating agent yielding in most cases the normally expected angularly

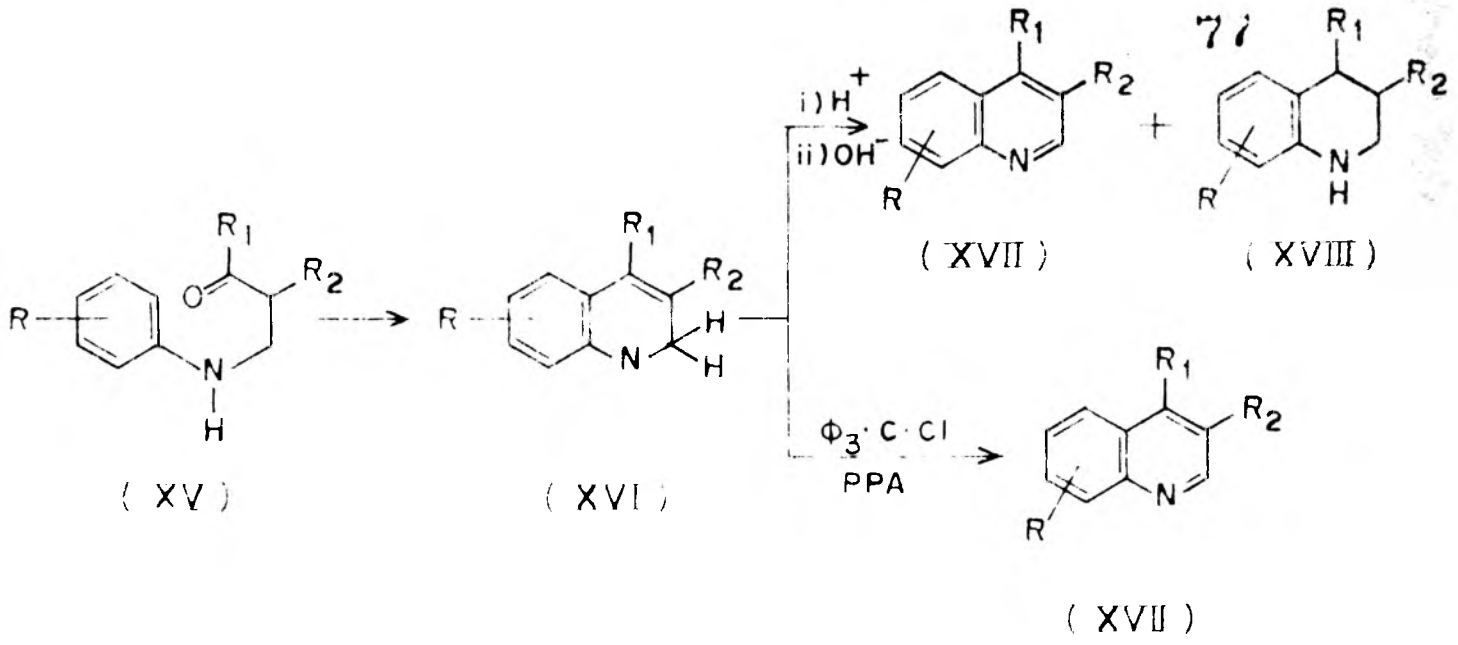

R1
R2
R
O
N
H
i) H+
ii) OH-
Φ3 · C · Cl
PPA
(XV)
(XVI)
(XVII)
(XVIII)
(XVII)

FIG · 10

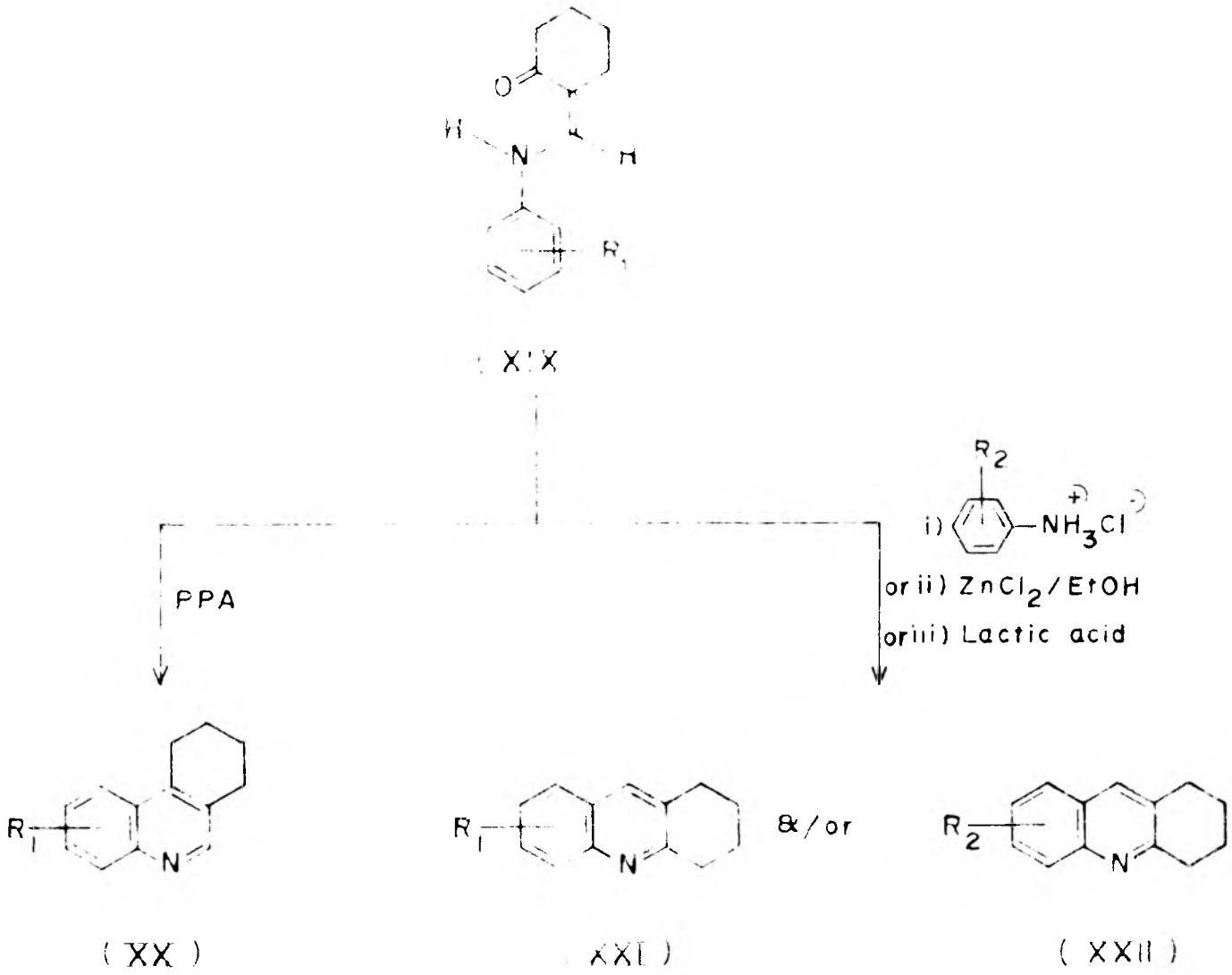

O
H
N
R1
(XIX)
R2
i) NH3Cl
or ii) ZnCl2 / EtOH
or iii) Lactic acid
PPA
R1
N
(XX)
R1
N
&/or
(XXI)
R2
N
(XXII)

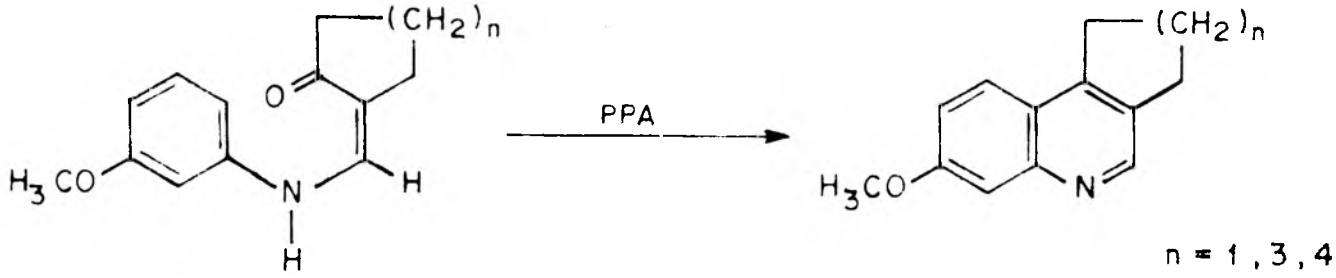
FIG · 11

cyclised products. Cyclodehydration of cis-2-arylamino-methylenecycloalkanones (XXIII) by means of PPA thus afforded cycloalkeno[c]quinolines (XXIV) in good yield (a portion of this work has been published recently[70]). The reactions were optimised as regards the quantity of PPA used, temperature and time of heating. Various angular polymethylenequinolines were thus synthesised as indicated in Fig.12. The acid catalysed cyclodehydrations of (XXIII) may be explained by the mechanism shown in Fig.13.

Cyclodehydration of 2-(3'-methoxy)anilinomethylene-cyclopentanone (XXIII, n = 1) by interaction with PPA gave 3,4-cyclopenteno-7-methoxyquinoline (XXV) and 3,4-cyclo-penteno-5-methoxyquinoline (XXVI) in 61% and 8% yield (Fig.12).

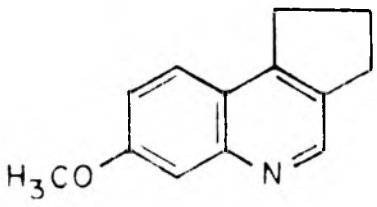
It has been reported[23] that attempts to cyclodehydrate 2-anilinomethylenecyclopentanone were unsuccessful. The present facile cyclodehydration of (XXIII) suggeats that the methoxy group activates the phenyl ring sufficiently to promote cyclodehydration reaction. The $-OCH_3$ group also served as a standard signal which proved useful in interpreting the PMR spectra of the cyclization products.

The PMR spectrum of (XXV) and (XXVI) shows a deshielded singlet at 8.53 ppm for the C_4 proton (Table 1). The identification of (XXVI) was based on spectral analysis. The aromatic region in (XXVI) shows an ABC pattern rather than ABX pattern. Secondly unlike in (XXV), the allylic

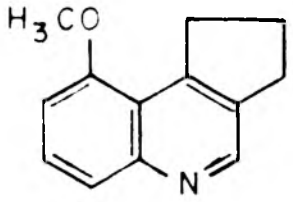


(XXIII)

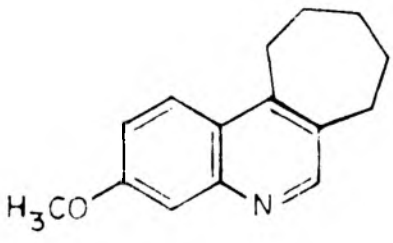
(XXIV)



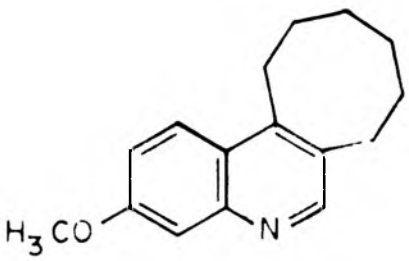
(XXV)



(XXVI)

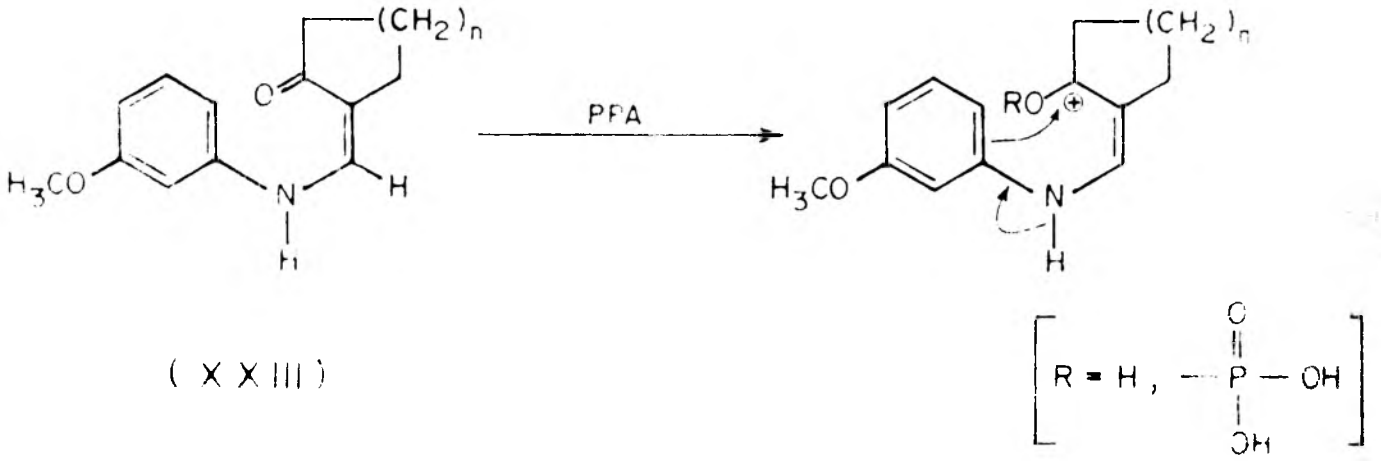


(XXVII)



(XXVIII)

FIG. - 12



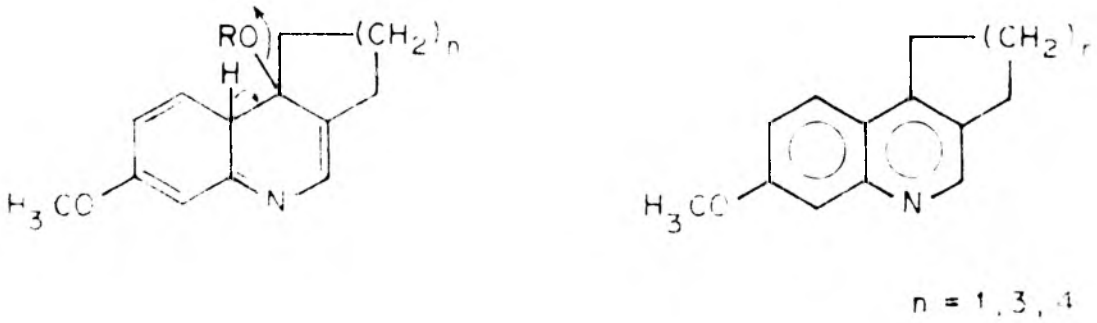


FIG 13 PPA CYCLIZATION OF ARYLAMINO — METHYLENECYCLOALKANONES.

TABLE 1 : NMR DATA OF CYCLODEHYDRATED PRODUCTS AND METHIODIDES

Solvent for (XLIII-XLV) CF_3CO_2H and for others $CDCl_3$

Description: Shift (pattern, intensity, assignment).

s: singlet
t: triplet
q: quintet
m: multiplet

Compd. No.	Methyl	Methylene	Aromatic	Deshielded aromatic proton
XXV	3.9(s,3p,-OCH_3)	3.06(m,4p,C_1 and C_3), 2.15(t, 2p, C_2)	7.0 - 7.7 (m,3p,C_6C_8 and C_9)	8.66 (s,1p,C_4)
XXVI	3.9(s,3p,-OCH_3)	2.1(q,2p,C_2),3.0(t,2p,C_3), 3.5(t,2p,c_1)	6.6 - 7.0 (m,3p, C_6C_7 and C_9)	8.66 (s,1p,C_4)
XXVII	3.9(s,3p,-OCH_3)	1.78(m,6p,C_8C_9 and C_{10}), 3.0 (m,4p, C_7 and C_{11})	6.85 (m, 3p, C_1C_2 and C_4)	8.38 (s,1p,C_6)
XVIII	3.9(s,3p,-OCH_3)	1.23-2.0(m,8p,$C_8C_9C_{10}$ C_{11}), 2.71-3.31 (m,4p,C_7 and C_{12})	7.03-7.95 (m, 3p, C_1C_2 and C_4)	8.55 (s,1p,C_6)
XXX	-	1.8(m,6p,C_7C_8 and C_9), 2.8-3.23 (m, 4p, C_6 and C_{10})	7.35-8.05 (m, 5p, C_1-C_4 and C_{11})	-
XXXVIII	-	2.0-3.23 (m, 6p, $C_{11}C_{12}$ and C_{13})	7.28-7.63 (m, 6p, C_6-C_{10} and C_1). 9.1-9.33 (m, 1p, C_5)	-
XXXIX	-	2.0-3.31 (m, 6p, $C_{11}C_{12}$ and C_{13})	7.3-8.3 (m, 7p, C_5-C_{10} and C_4)	-
XLIII	4.16(s,3p,-OCH_3) 4.55(s,3p,-NCH_3)	3.33 (m,4p,C_1 and C_3), 2.5 (t, 2p, C_2)	7.33-8.25 (m, 3p, C_6-C_9)	8.75 (s,1p,C_4)
XLII	-	1.66(m,4p,C_6 and C_{11}), 2.75-3.28 (m, 8p, C_7-C_{10})	7.18-8.05 (m, 5p, C_1-C_4 and C_{12})	-
XLIV	4.16(s,3p,-OCH_3) 4.55(s,3p,-NCH_3)	2.0 (m,6p,C_7C_8 and C_9), 3.1-3.65 (m, 4p, C_7 and C_{11})	7.45-8.5 (m, 3p, C_1C_2 and C_4)	8.7 (s,1p,C_6)
XLV	4.2(s,3p,-OCH_3) 4.56(s,3p,-NCH_3)	1.56-2.1 (m,8p,C_8-C_{11}), 3.2 (t,2p,C_7); 3.6 (t,2p,C_{12})	7.46-8.5 (m, 3p, C_1C_2 and C_4)	8.66 (s,1p,C_6)

methylene protons in (XXVI) appear as two triplets due to steric proximity of the methoxy group which makes them non-equivalent.

Compound (XXV) has also been obtained earlier in our laboratory by cyclodehydration of 2-m-anisidinomethylcyclopentanone [XV, R= m-OCH_3, R_1R_2 = $-(CH_2)-_3$] (Fig.10) by PPA in presence of triphenylmethyl chloride used as external hydride abstractor[71]. The obvious advantage in cyclodehydration of 2-(3'-methoxy)anilinomethylenecyclopentanone (XXIII, n = 1) is that no such hydride abstractor is necessary.

2-(3'-Methoxy)anilinomethylenecycloheptanone (XXIII, n=3) and 2-(3'-methoxy)anilinomethylenecyclooctanone (XXIII, n=4) when interacted with PPA gave 3-methoxy-cycloheptenо[c]quinoline (XXVII) and 3-methoxy-cyclooctenо[c] quinoline (XXVIII) respectively. Unlike in (XXIII, n=1), the cyclodehydrations of (XXIII, n=3) and (XXIII, n=4) afforded exclusively single cyclised products (exclusive p-cyclisation with respect to -OCH_3 group). In all these reactions excess PPA and low temperature were found to improve the yield of cyclodehydration products. PMR spectra of (XXVII) and (XXVIII) also showed the deshielded singlets around 8.4 - 8.5 ppm for C_6 proton which is characteristic for angularly cyclised products.

It has been reported that cyclodehydrations of cis-2-arylaminomethylenecyclohexanones by treatment with

/hydrochloride in boiling ethanol yields the linear lactic acid or anhydrous zinc chloride and the arylamine/ quinolines (acridines)[69], a rearrangement having taken place during cyclodehydration. Monochloroacetic acid when used as a cyclodehydrating agent for cis-2-arylaminomethylene-cycloalkanones also yields the rearranged linear polymethylene-quinolines. When cis-2-anilinomethylenecycloheptanone (XXIX) was heated with chloroacetic acid, cyclohepteno[b]quinoline (XXX) was obtained (Fig.14).

The structure assignment for (XXX) was based on the comparison of its PMR spectrum with that of (XXVII) (Fig.15). In (XXVII) the proton at C_6 appears as a singlet at 8.38 ppm whereas in (XXX), the proton at C_{11} merges with other aromatic protons.

The structure given to the product (XXX) was confirmed by preparing the authentic sample by Pfitzinger reaction[16] in which the cycloheptanone and isatin were condensed in alkali medium and the resulting cinchoninic acid was then decarboxylated (Fig.14). Mixed melting point and spectral data are in agreement with the assigned structure.

The mechanism of formation of linear-polymethylene-quinolines by cyclodehydration of the cis-2-arylaminomethylene-cycloalkanones is suggested in Fig.16. The scheme envisages the intermediate formation of the azetine (E) which eventually rearranges under acidic conditions to finally yield polymethylenequinolines. An alternative opening of the azetine intermediate (E) is also indicated. The reaction

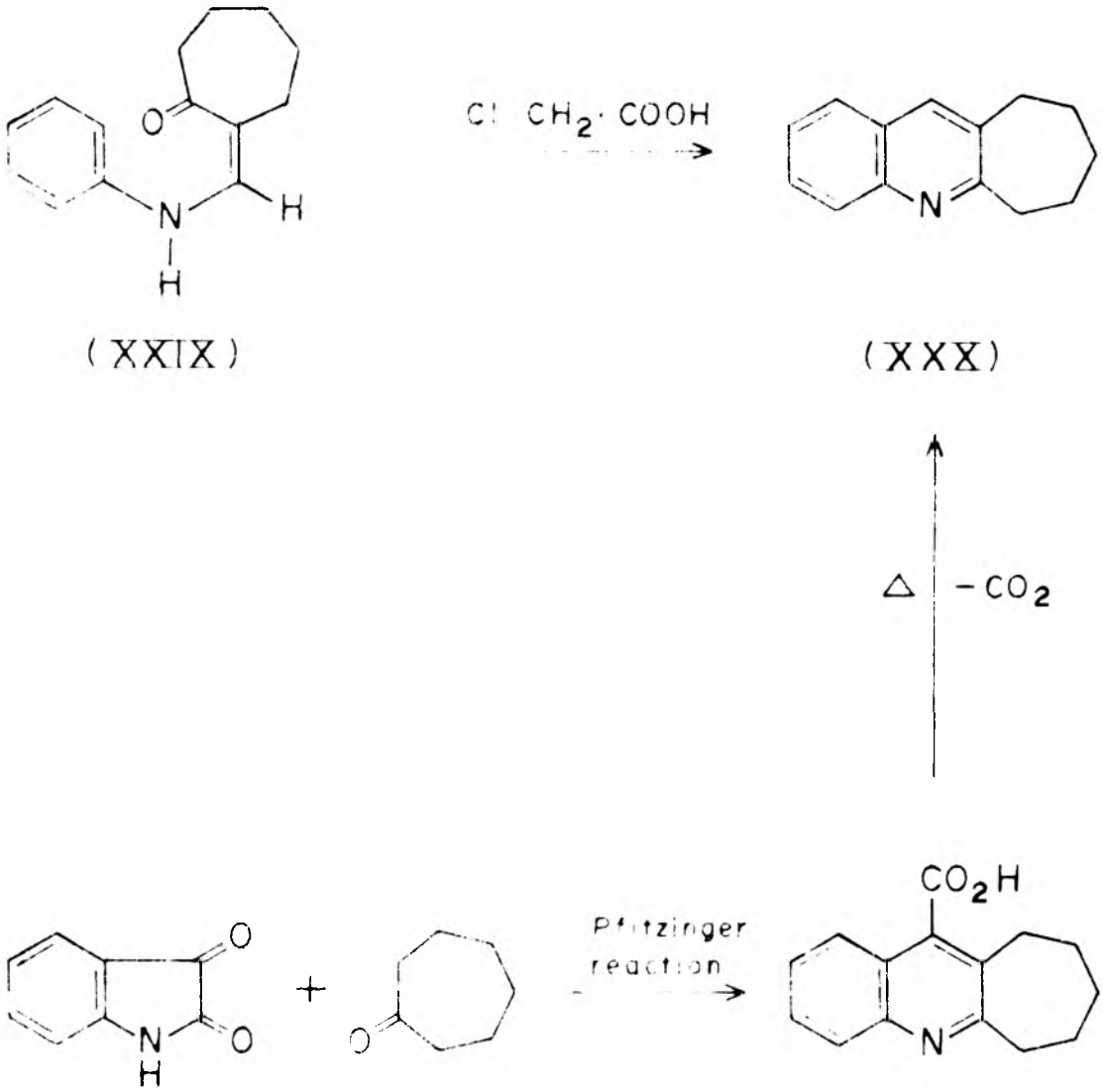
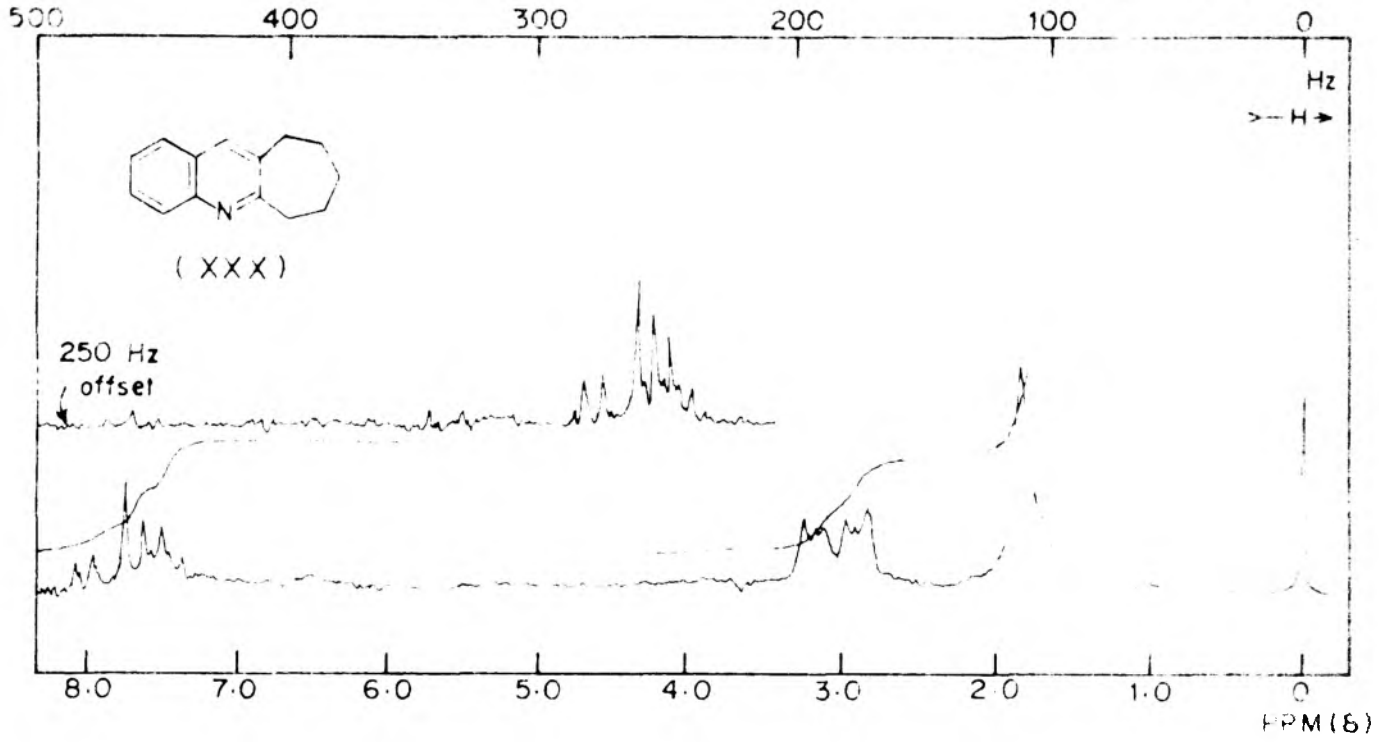
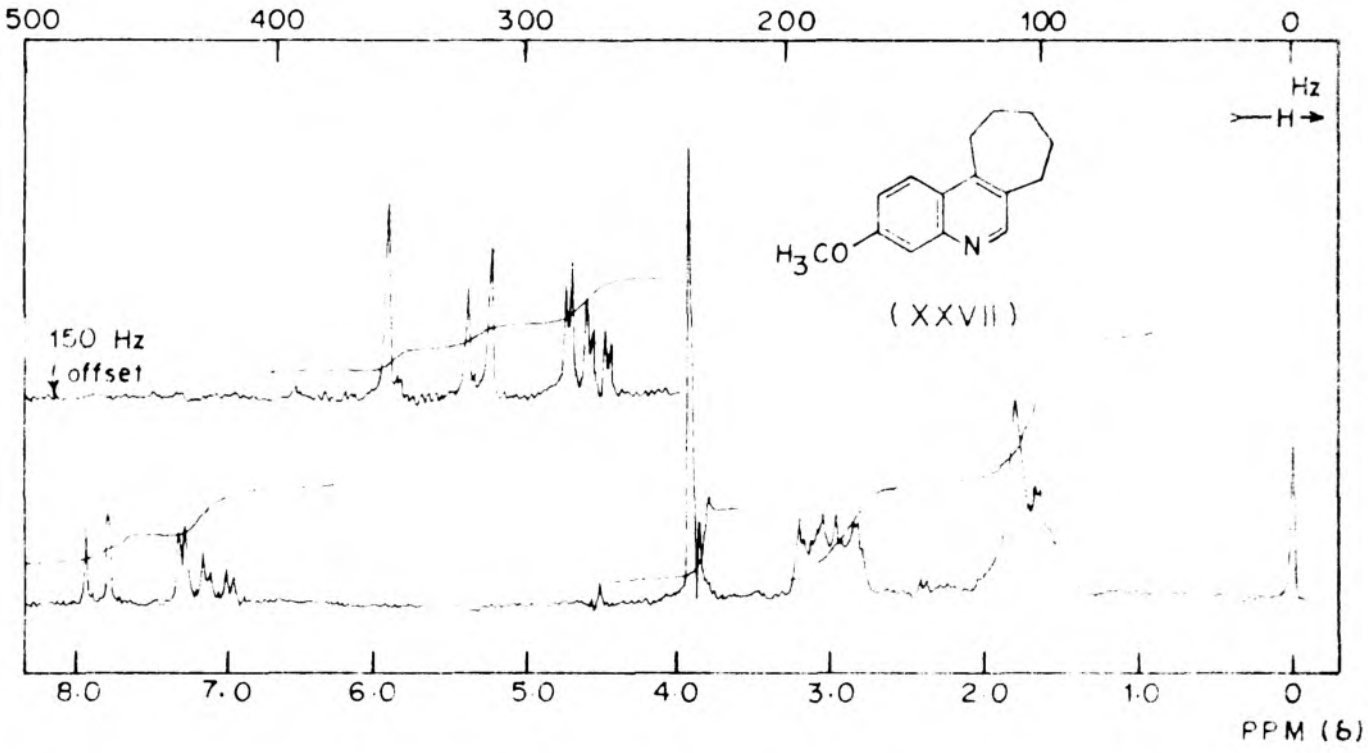

O
N
H
H
(XXIX)
Cl CH2·COOH
N
(XXX)
Δ −CO2
O
O
N
H
+
O
Pfitzinger reaction
CO2H
N

FIG 14



(XXX)



(XXVII)

FIG. 15. PMR SPECTRA OF (XXX) & (XXVII) IN CARBON TETRACHLORIDE SOLUTION

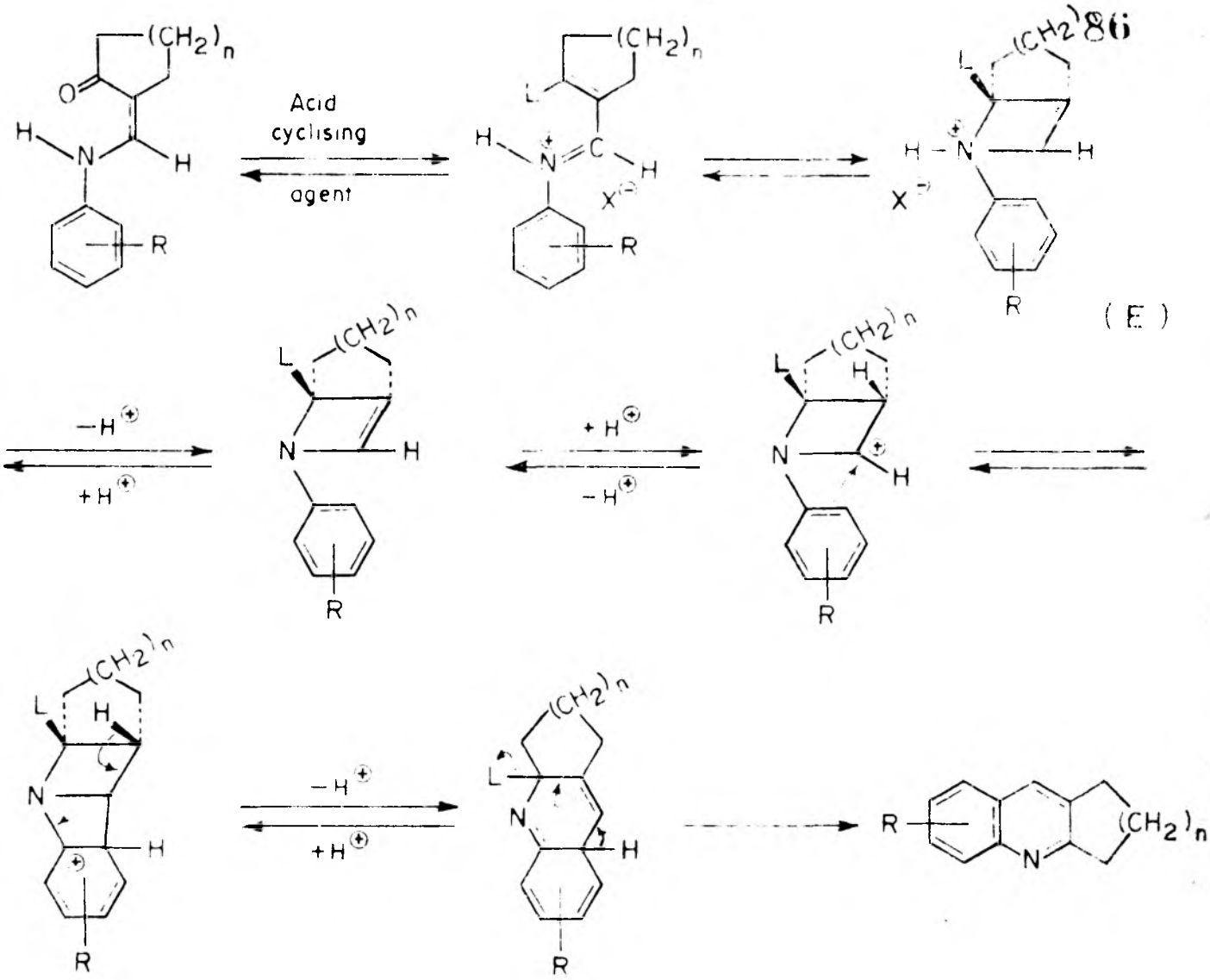


FIG. 16. AZETINE MECHANISM FOR CYCLODEHYDRATION OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

is essentially intramolecular and the feasibility of existence of azetine has been indicated by extended HMO calculations[69]. Various cyclising agents like zinc chloride/ethanol, formic acid, propionic acid, chloroacetic acid yield linearly cyclised products and they follow azetine mechanism. In this event the leaving group in azetine (E) will be an arylamino or O-acyl group (e.g. -O-ZnCl, formate, propionate, chloroacetate) depending on the acid used in effecting cyclodehydration.

Recently Tilak and coworkers[72,73] have carried out the synthesis of N-arylazetidines (XXXII) by cyclodehydration of arylaminomethylalkanols (XXXI) (Fig.17). It has been shown that (XXXII) rearrange to tetrahydroquinolines (XXXIII) by means of H^+, photolysis and pyrolysis. On this ground the 'azetine mechanism' appears attractive, however, an independent synthesis of azetine and its rearrangement under acidic or thermal conditions has yet to be achieved. Seshadri et al.[74] have postulated similar four membered intermediate for the cyclisation of 3-chloro-2-dimethylaminomethylene-1,4 benzothiazine with aniline.

All attempts to prepare cyclopenteno[b]quinoline (Fig.1) by cyclodehydration of 2-(3'-methoxy)anilinomethylenecyclopentanone (XXIII, n=1) and anilinomethylenecyclopentanone by means of $ZnCl_2$/EtOH, HCl/EtOH, $POCl_3/ZnCl_2$, $ZnCl_2/Ar.NH_2.HCl$/EtOH, chloroacetic acid proved unsuccessful. In all the above reactions starting material was recovered along with the polymeric

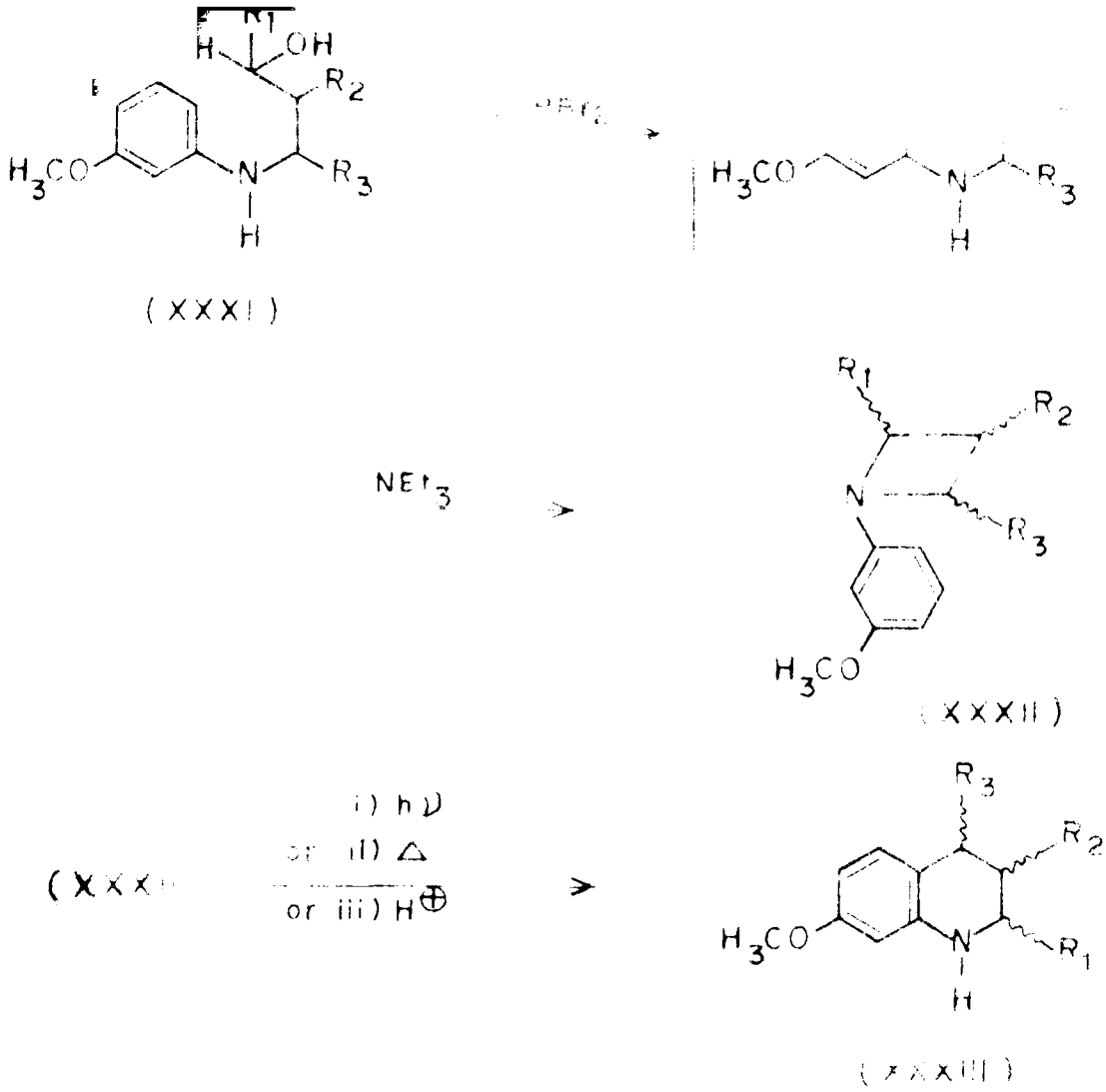


FIG 17 REARRANGEMENT OF AZETIDINES

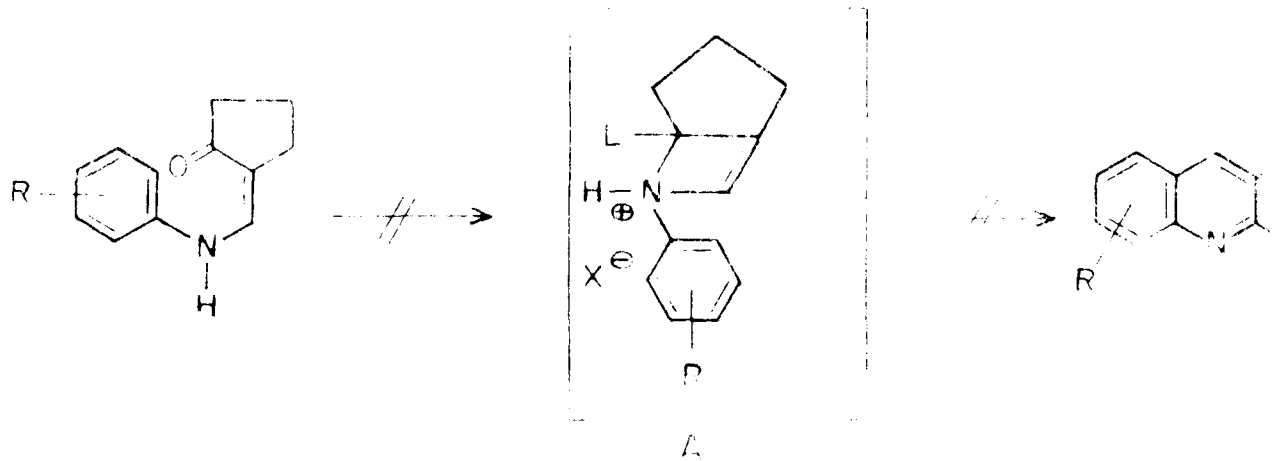


FIG 18

side products. Failure to get a linear cyclodehydration product may be attributed to the high steric strain involved in the formation of the intermediate azetine (A) (Fig.18) having a fused four-membered unsaturated N-heterocyclic ring and a five-membered ring.

An alternative mechanism to account for the formation of linear (rearranged) cyclodehydration products has been proposed by Hall and Walker[68]. This mechanism (scheme B) (Fig.19) involves fission of the cis-2-arylaminomethylene-cycloalkanones and recombination of the fragments (inter-molecular condensation) to yield the end products. The azetine mechanism (Fig.16) on the other hand, involves an intramolecular reaction. Whereas conclusive proof for the choice of either of these mechanisms has not been adduced so far, the fact that cis-2(3'-methoxy)anilinomethylene cyclopentanone does not yield the linear cyclodehydration product 6-methoxy-cyclopenteno[b]quinoline (Fig.18) seems to support the azetine mechanism. There is no reason why the linearly cyclodehydrated product of cis-2(m-anisidino-methylene)cyclopentanone should not be formed if the reaction was intermolecular as proposed by Hall and Walker[68].

In order to synthesise tetracyclic nitrogen hetero-cyclics, cis-2-(1'-napthylaminomethylene)cyclopentanone (XXXIV) and cis-2-(2'-napthylaminomethylene)cyclopentanone (XXXV) were cyclodehydrated (Fig.20). Surprisingly cyclodehydration of (XXXIV) and (XXXV) by means of PPA failed to yield (XXXVI)

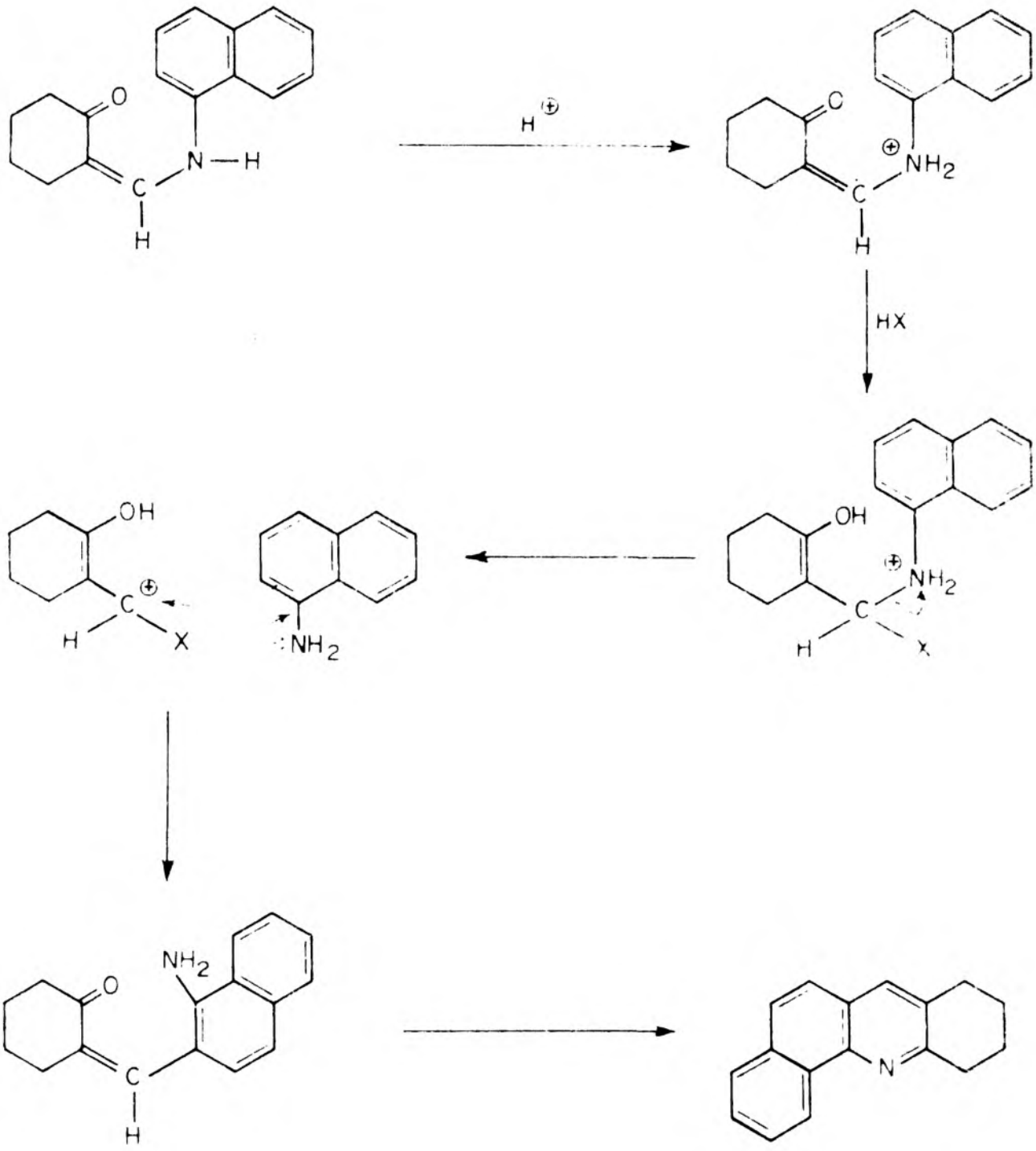


FIG. 19. (Scheme B)

INTERMOLECULAR MECHANISM FOR CYCLODEHYDRATION

(cf Hall and Walker[68])

and (XXXVII) respectively. In both the cases the relevant napthylamines were formed by decomposition of (XXXIV) and (XXXV) probably via retro-Michael reaction.

However interaction of (XXXIV) and (XXXV) with lactic acid yielded 4-aza-cyclopenteno[b]phenanthrene (XXXVIII) and 1-aza-cyclopenteno[b]phenanthrene (XXXIX) respectively. In the cyclodehydration of (XXXV), (XXXIX) and β-napthylamine lactate (XL) were formed in nearly equivalent quantities. It may be noted that cyclodehydration of both (XXXIV) and (XXXV) leads to linear heterocycles (XXXVIII) and (XXXIX) by rearrangement instead of the normal angular cyclodehydration products (XXXVI) and (XXXVII).

The structure assignment (XXXVIII) and (XXXIX) for the cyclodehydration products follows from a study of the PMR spectra (Table 1). Thus in (XXXVIII), a multiplet of one proton intensity appears at 9.1 - 9.33 ppm and all other aromatic protons appear between 7.2 and 5.7 ppm. If the compound had the alternative structure (XXXVI), one would have seen a singlet at 8.53 ppm for the C_3 proton, as in the case of other phenanthridine derivatives. In (XXXIX), a multiplet spread between 8.12 and 8.45 ppm and a singlet at 8.33 ppm is found in the low-field region. If this compound has the angular structure (XXXVII), the proton at C_2 again should have appeared at 8.5 ppm.

The distinctive role played by lactic acid in cyclodehydration of cis-2-arylaminomethylenecyclohexanones has been

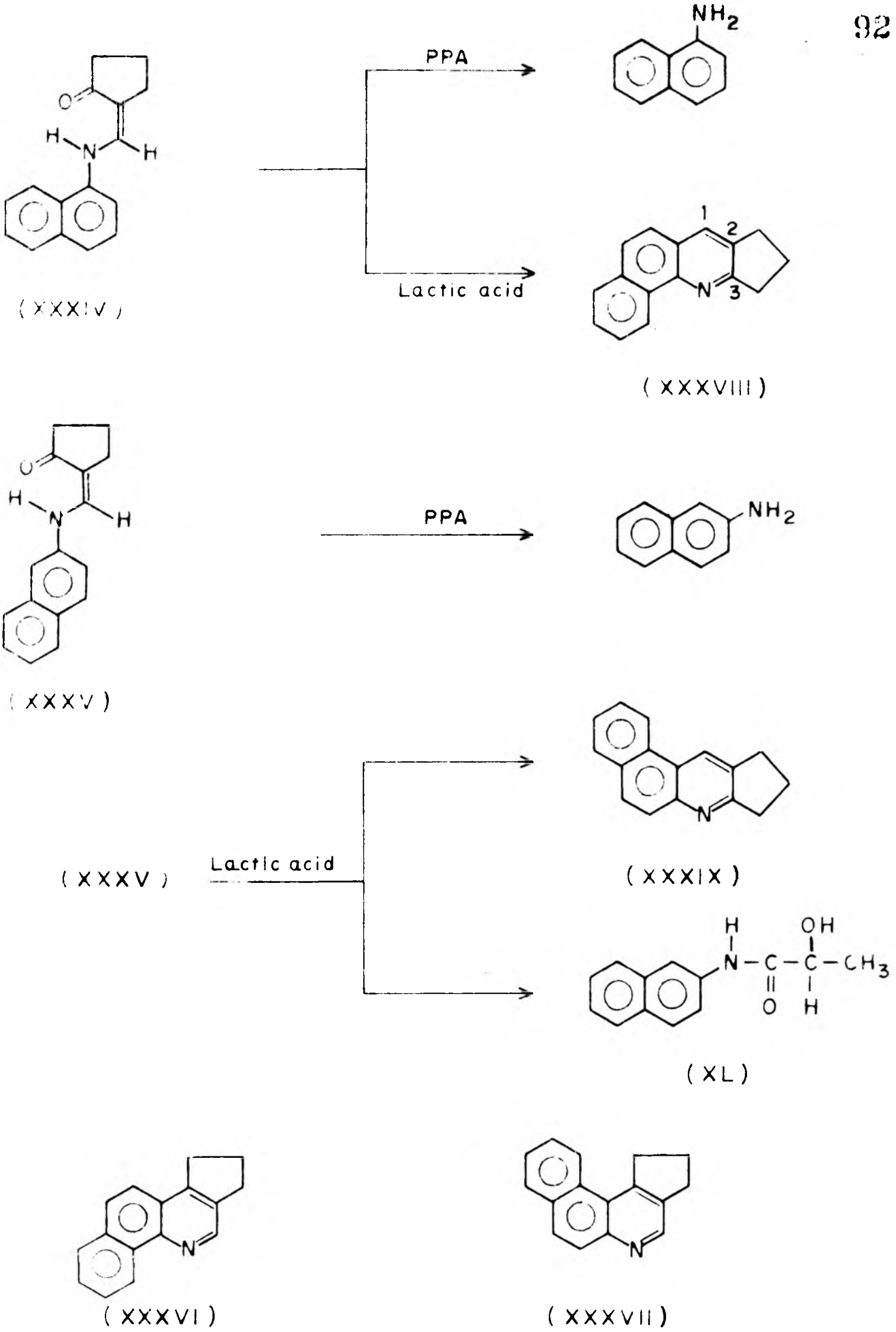

NH2
PPA
Lactic acid
1
2
N
3
(XXXIV)
(XXXVIII)
PPA
NH2
(XXXV)
Lactic acid
(XXXV)
(XXXIX)
H
OH
N
C
C
CH3
O
H
(XL)
N
N
(XXXVI)
(XXXVII)

FIG. - 20.

reported by Tilak et al.[69] earlier. The cyclodehydration of (XXXIV) and (XXV) using lactic acid may follow the similar sequence of reactions shown in Fig.21. On acid treatment enolimine structure is formed and further elimination of arylamino group leads to 2-(2'-keto-1'-cycloalkyl)-4-keto-5-methyl-1,3-dioxolane (F), which then reacts with the eliminated arylamine, leading finally to linear heterocyclics. The eliminated arylamine may also react with lactic acid to give the lactate. Formation of β-napthylamine lactate (XL) and the rearranged product (XXXIX) in the cyclodehydration of (XXXV) support the above mechanism.

Cyclodehydration of cis-2-anilinomethylenecyclo-octanone (XLI) (Fig.22) by interaction with chloroacetic acid or lactic acid was unsuccessful as decomposition products were formed. However cyclooöcteno[b]quinoline (XLII) was obtained by treating (XLI), with fused zinc chloride and aniline hydrochloride in boiling ethanol. The product (XLII) was characterised by its PMR and Mass spectral data and by its unambiguous synthesis by employing the Pfitzinger reaction.

Cyclodehydration of several cis-2-arylaminomethylene-cyclohexanones (XIX) (Fig.11) by means of different primary arylamine hydrochlorides in boiling ethanol in the presence of anhydrous zinc chloride gave rearranged tetrahydroacridines (XXI, XXII) wherein the arylamine moiety present originally

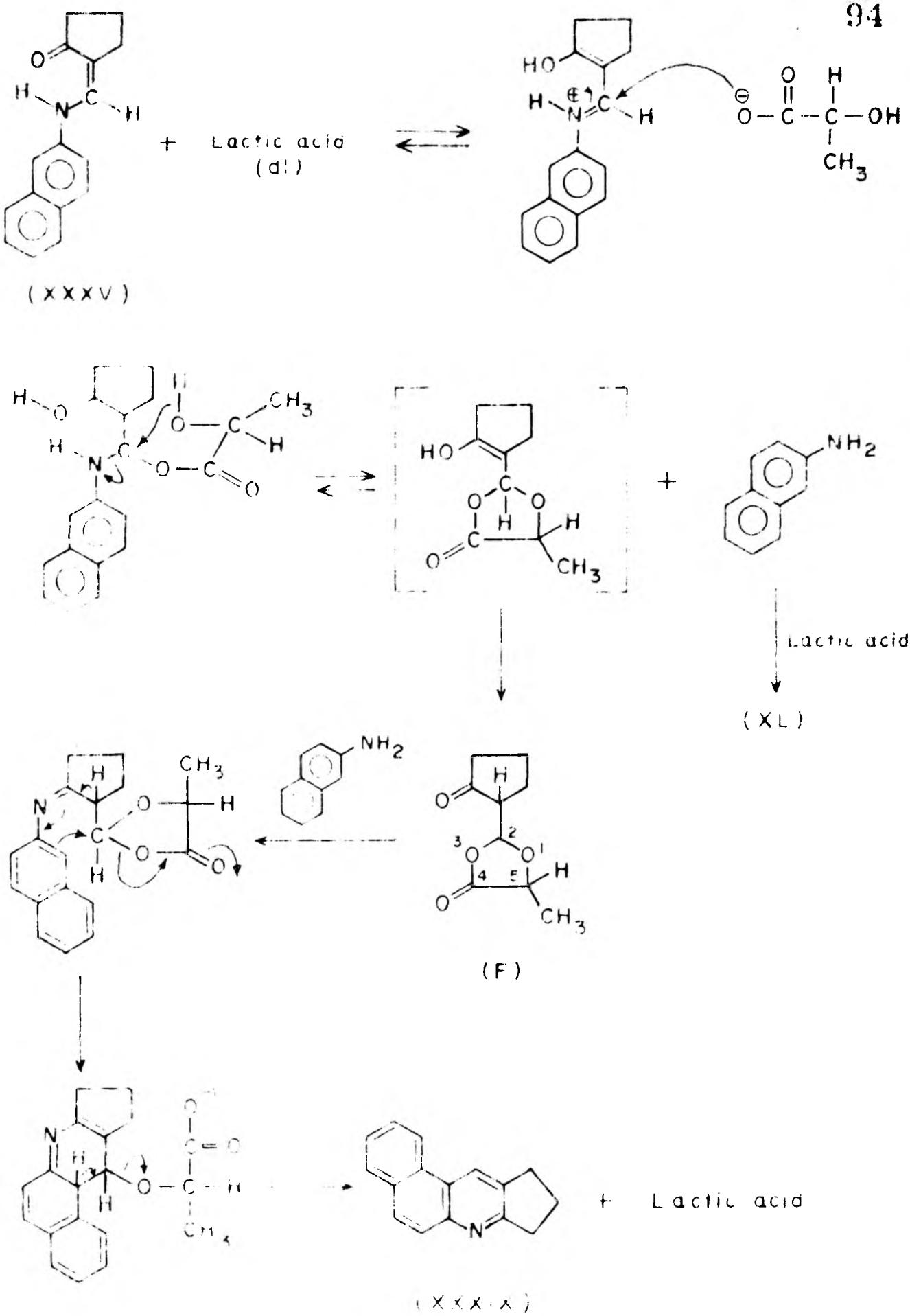


FIG. 17. SEQUENCE OF REACTIONS OCCURRING DURING CYCLO-
ISATION OF (XXXV) USING LACTIC ACID

in (XIX) was retained or substituted by the interacting arylamine (used as hydrochloride)[75].

Substitution in the arylamine R_1-C_6H_4-NH_2 in (XIX) by the arylamine R_2-C_6H_4-NH_2 used in the cyclodehydration probably takes place through the implication of the intermediate dianil (G) as shown in the scheme-H given in Fig.23. This dianil by prototropic shift followed by rotation along with a C-C bond and then cyclisation gives the linearly cyclised product (XXII) in which the reacting arylamine gets incorporated and the original arylamine gets liberated[69,75].

Acheson et al.[76] have recently isolated the intermediate 'bis-anil' while cyclodehydrating N-2(2-biphenyl amino)methylene cyclohexanone using lactic acid and water. The bis-anil has been shown to rearrange further to tetrahydroacridine by extrusion of biphenyl amine.

Formation of tetrahydroacridines (XXI) was also observed in which the original arylamine was retained[75]. This can be explained if one assumes that the reactions follow an alternate path as shown in scheme-J (Fig.24). In this case, acid-catalysed substitution of R_1-C_6H_4-NH_2 present in (XIX) by R_2-C_6H_4-NH_2 occurs as a first step to yield (K) by an addition-elimination mechanism. Then further reactions follow a sequence similar to the scheme-H given in (Fig.23) whereby rearranged linearly cyclised products (XXI) finally result, in which the arylamine moiety present

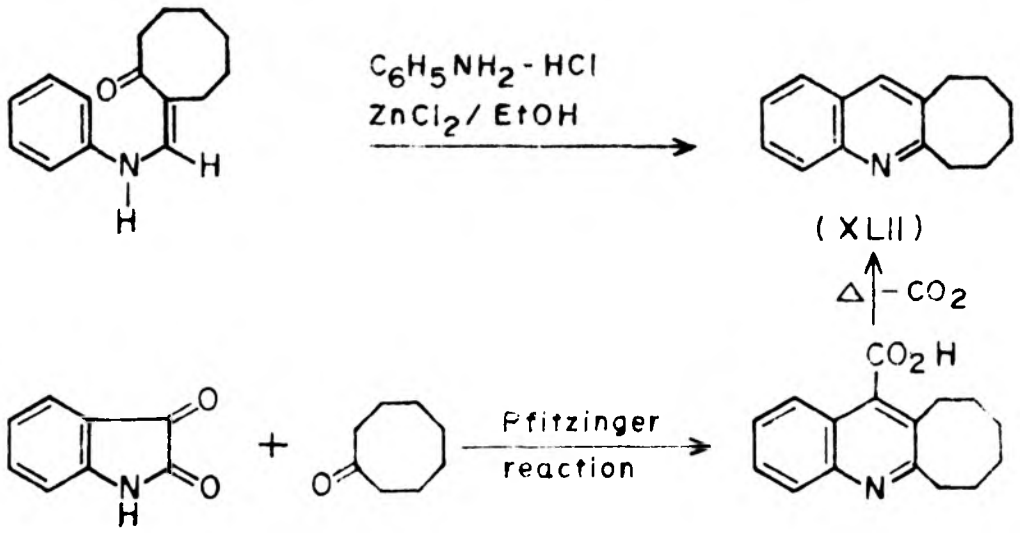


FIG. 22

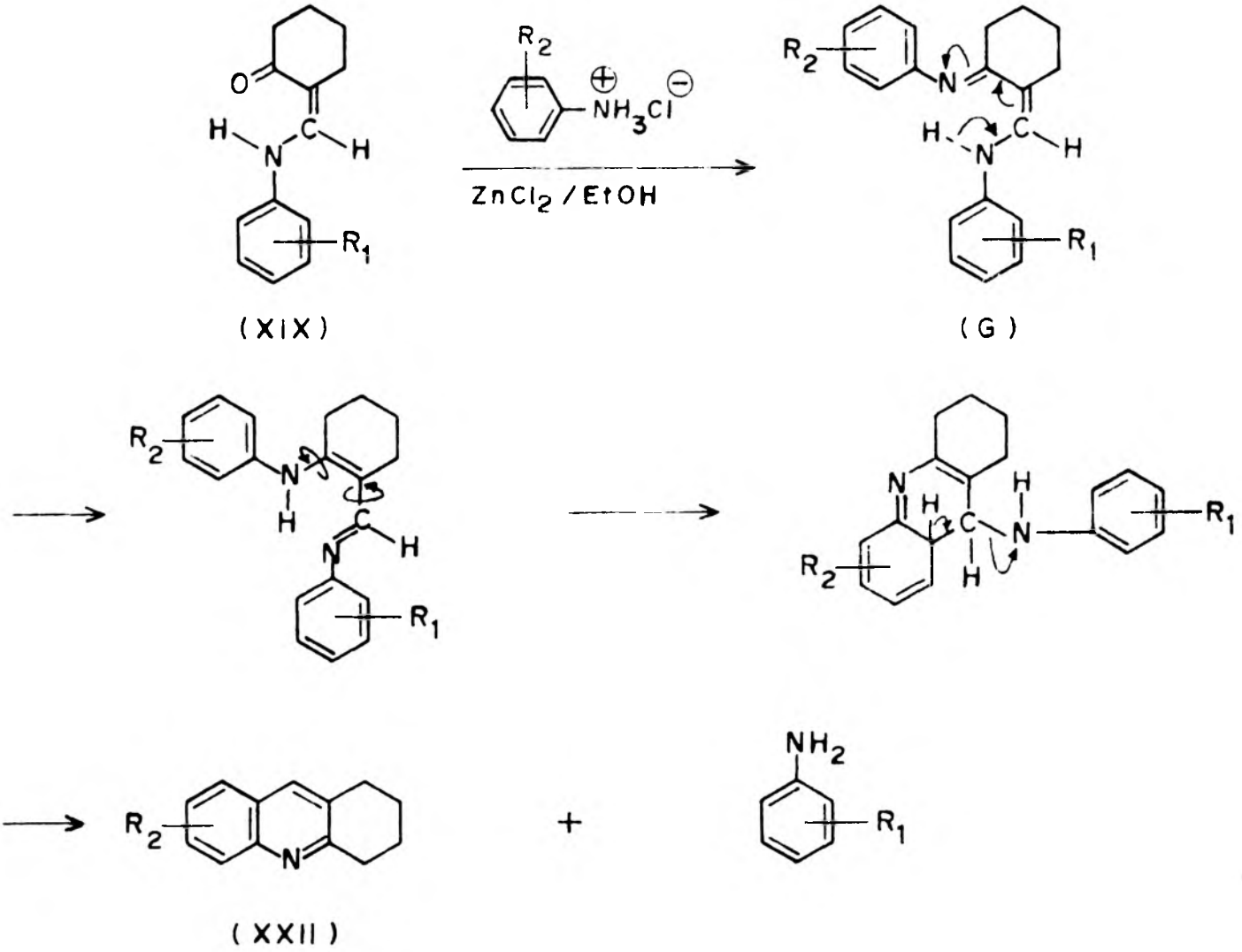


FIG. 23 (SCHEME H) MECHANISM OF CYCLODEHYDRATION OF (XIX) BY Ar·NH$_2$·HCl WHERE REACTING Ar·NH$_2$ GETS INCORPORATED

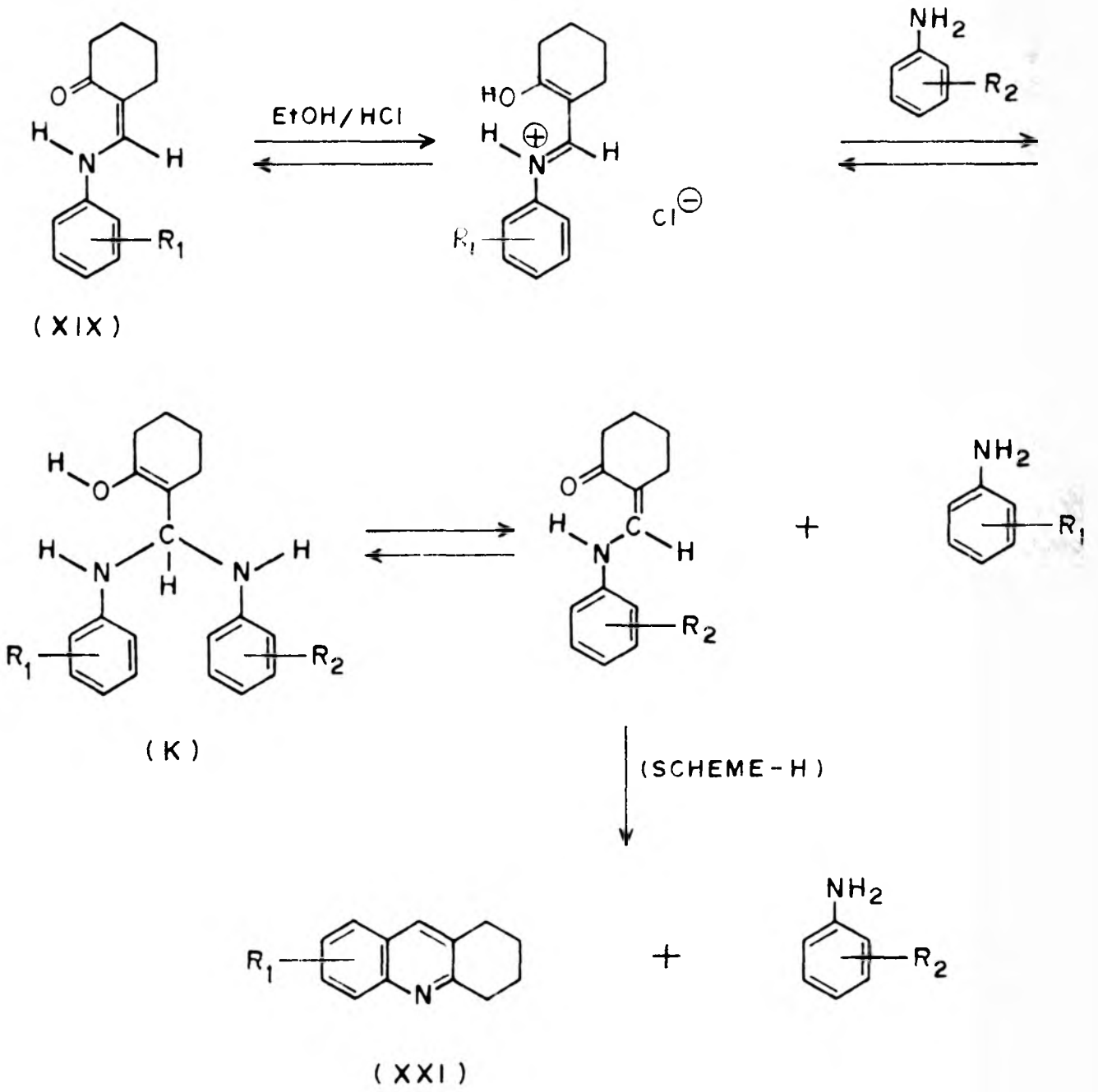


FIG. 24 (SCHEME J) MECHANISM OF CYCLODEHYDRATION OF (XIX) BY Ar·NH_2·HCl WHERE ORIGINAL Ar·NH_2 IS RETAINED

in (XIX) is retained by a process of elimination and reincorporation.

Cyclodehydration of cis-2-anilinomethylenecyclo-
öctanone (XL) giving cyclooöcteno[b]quinoline (XLII) is another
se for the above mechanism.

.odehydrations involving rearrangement, the
s 2-anilinomethylenecycloalkanones (no
ıe arylamine part) (XXIX, XLI) were so
final products (XXX, XLII) could also be
ternative route employing the Pfitzinger

s be concluded that a simple route to
polymethylenequinolines is the acid catalysed
of 2-arylaminomethylenecycloalkanones.
:id is the best cyclodehydrating agent
;ular polymethylenequinolines (normal
:eas chloroacetic acid, lactic acid, anhydrous
ylamine hydrochloride in ethanol lead to
the rearrangement products viz. the linear polymethylene-
quinolines. Synthesis of tri- and tetra-cyclic nitrogen
heterocyclics support the rearrangement mechanisms suggested
earlier.

The infrared spectra of all the cyclised products showed hydrocarbon pattern with a band at 1620 cm^{-1} assignable to either C=N or C=C stretching frequency. An interesting

observation is that the 1620 cm^{-1} band was strong in case of angularly cyclised products (XXV - XXVIII) and characteristically weak in case of linearly cyclised products (XXX, XXXVIII, XXXIX and XLII).

Derivatives of polymethylenequinolines were prepared by treating them with methyl iodide to give methiodides (XLIII - XLVI) (Table 4). The derivatives are being examined for their biological activity.

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

Synthesis of 2-arylaminomethylenecycloalkanones (XXIII; n=1,3,4), (XXIX), (XXXIV), (XXXV) and (XLI) is described in Chapter I.

Cyclodehydration of 2-arylaminomethylenecycloalkanones

(a) In the presence of PPA

General Method: A mixture of ketone (XXIII) (1 g) and PPA [prepared from P_2O_5 (40 g) and H_3PO_4 (25 ml)] was stirred at 90-180° for 2-4 hr, following the reaction by TLC. The mixture was left overnight. After warming, it was poured on crushed ice, neutralised with aqueous sodium hydroxide (50%), cooled to room temperature and then extracted with ether. Removal of ether gave crude product which was purified by column chromatography on a silica gel column using benzene and benzene-ethyl acetate as eluents. Unreacted ketone was removed in the benzene fraction whereas the fraction eluted between 2-20% ethyl acetate-benzene contained the cyclodehydrated product. The reaction products were purified by crystallisation from petroleum ether (40-60°) or further by vacuum distillation. The experimental details, elemental analyses and molecular ion peaks from mass spectra are given in Table 2. Products were identified by their characteristic spectra and preparing methiodide derivatives. PMR spectral data is given in Table 1.

(b) Interaction with chloroacetic acid

A mixture of anilinomethylenecycloheptanone (XXIX)

TABLE 2 : PPA CYCLISATION OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

Ketone	Wt. (g)	Reaction temp.°C/ time hr.	Reaction product[a] Compd. No.	Wt. (g)	Yield %	m.p.°C b.p.°C/ mm	M^+ at m/e	Analysis Found C	H	N	Required C	H	N
XXIII (n=1)	2.0	98/3.5	XXV[c]	1.1	61	104	199	78.3	6.8	7.0	78.4	6.5	7.0
			XXVI	0.15	8	61	199	78.2	6.3	7.0	78.4	6.5	7.0
XXIII (n=3)	2.0	90/3.5	XXVII	1.2	70	87 (140/0.0034)	227	79.2	7.7	6.1	79.3	7.5	6.2
XXIII (n=4)	3.0	97/6	XXVIII	2.2	78	56	241	79.4	7.6	5.6	79.7	7.9	5.8
XXXIV[d]	4.0	100/22											
	1.0	180/2											
XXXV[d]	2.0	97/8											

(a) Products (XXV - XXVIII) were crystallised from pet. ether, (XXVII) white shining needles and (XXV, XXVI, XXVIII) colourless needles.

(b) Lit.[71] m.p. 98°

(c) UV: λ_{max}^{EtOH} mμ (log ε): 232 (3.13), 322 (3.32), 335 (3.32).

(d) Ketones decomposed to α- and β-napthyl amines.

(3 g) and chloroacetic acid (6 g) was heated at 140° for 15 hr. After cooling, the reaction mixture was poured on ice, basified with aqueous sodium hydroxide (10%) and then extracted with ether. Removal of ether gave a residue (1.9 g) which was dissolved in benzene and the solution chromatographed on a silica gel column using benzene and benzene-ethyl acetate as eluents. Work up of the major fraction eluted between 5-20% ethyl acetate-benzene gave cyclohepteno[b]quinoline (XXX) (1.4 g, yield 58%) m.p. 92°. On recrystallisation from pet. ether it gave shining needles m.p. 94° (Lit.[16] m.p. 93.5°) (Found: C, 85.4; H, 7.6; N, 7.1. Calc. for $C_{14}H_{15}N$: C, 85.1; H, 7.6; N, 7.1%), M^+ at m/e 197. Structure (XXX) for the reaction product was confirmed by its PMR spectrum given in Table 1.

The same product obtained by following the procedure given by Borsche[16] was identical by TLC, mixed m.p. and spectral characteristics to the assigned structure of (XXX).

(c) Interaction with lactic acid

General Method: A mixture of the ketone and dl-lactic acid was heated at 130-140° for 7-24 hr, following the reaction by TLC at different time intervals. The cooled red-coloured syrup was poured on crushed ice, basified with 10% aq. ammonia and then extracted with benzene. Removal of solvent by distillation gave a mixture of products which was separated by chromatography on a silica gel column using first benzene and then benzene-ethyl acetate as eluents.

TABLE 3 : LACTIC ACID CYCLISATION OF 2-ARYLAMINOMETHYLENECYCLOALKANONES

Ketone	Wt (g)	Lactic acid ml	Reaction temp.°C/ time hr.	Reaction product[a] Compd. No.	Wt. (g)	Yield %	m.p.°C b.p.°C/ mm	M^+ at m/e	Analysis Found C	H	N	Required C	H	N
(XXXIV)	0.5	10	140/24	XXXVIII	0.08	32	114-116	219	87.4	6.2	6.5	87.7	5.9	6.4
(XXXV)	0.5	10	140/20	XXXIX	0.08	35	118-120 160/ 0.0034	219	87.7	6.2	6.6	87.7	5.9	6.4
(XXIII)[c] (n=1)	0.5	10	130/15	(XL)[b]	0.10	38	141	215	73.0	6.1	6.8	72.6	6.0	6.5
(XXIII)[c] (n=4)	1.0	20	130/31											

(a) (XXXVIII) and (XXXIX) colorless needles (pet. ether)
(XL) white plates ($CHCl_3$/Pet. ether).

(b) NMR:($CDCl_3$), 1.5 (d,3p,-CH_3), 3.65 (s, 1p, OH), 4.36 (q, 1p, -CH), 7.3-8.16 (m, 7p, aromatic), 8.8 (s, 1p, NH).

IR: cm^{-1}: 1660(s), 3200-3320 (m, broad)

(c) Unreacted ketone and polymeric mass obtained. No cyclodehydrated product formed.

The reaction products were then crystallised from pet. ether or purified further by vacuum distillation. The structures of the cyclised products were confirmed by their PMR and mass spectral data. The experimental details, elemental analyses and molecular ion peaks (M^+) are given in Table 3. PMR data is summarised in Table 1.

(d) Interaction with arylamine hydrochloride, fused zinc chloride and absolute ethanol

Equimolecular quantities of 2-anilinomethylene-cyclooctanone (XLI) (2.29 g), aniline hydrochloride (1.3 g) and fuzed zinc chloride (1.5 g) were heated under reflux in absolute ethanol (150 ml) for 21 hr. After removal of ethanol under vacuum, the residue was diluted with water (100 ml), neutralised with aqueous ammonia and then extracted with ether (200 ml). Work up of ether extract gave an oil which showed three spots on TLC (10% ethyl acetate-benzene as solvent front, iodine exposure): unreacted ketone (XLI) (Rf 0.68), aniline (Rf 0.5) and reaction product (Rf 0.4). The reaction product was separated from the mixture by chromatography on silica gel column using successively pet. ether-benzene and benzene-ethyl acetate as eluents. Fractions from pet. ether onward upto 80% benzene pet. ether contained ketone and aniline. Reaction product was collected from the fractions between benzene and 2% ethyl acetate-benzene. Compound (XLII) crystallised from pet.ether in fern shaped needles (1.1 g, 52%) m.p. 56° (Found: C, 85.0; H, 8.1; N, 6.8. Calculated for $C_{15}H_{17}N$: C, 85.3; H, 8.1; N,6.6%),

M^+ at m/e 211. The structure of the reaction product was characterised from its PMR spectrum (Table 1) and comparing it with an authentic sample obtained through Pfitzinger reaction.

Preparation of Methiodides of polymethylenequinolines

General Method: Cycloalkenoquinoline was either directly or after dissolving in dry benzene was mixed with excess methyl iodide. The solution left at room temperature for 2-24 hr, until quinolinium iodide separated out in high yield. The solid methiodide was filtered, washed with dry benzene and dried. Recrystallisation from methanol afforded yellow needles or flakes. The experimental details and elemental analyses are given in Table 4. PMR spectra of methiodides displayed typical pattern analogous to corresponding cycloalkenoquinolines and the details of spectra are given in Table 1. No mass spectra could be obtained as the methiodides were non-volatile or decomposed at high temperature.

Attempted cyclodehydration reactions

(a) 2-(1'-napthylaminomethylene)cyclopentanone (XXXIV) and 2-(2'-napthylaminomethylene)cyclopentanone (XXXV) failed to cyclise with polyphosphoric acid but yielded α- and β-napthyl amines (TLC, NMR, Mass) respectively (Table 2).

(b) Following the standard procedures[69], 2-(3'-methoxy) anilinomethylenecyclopentanone (XXIII, n=1) and 2-anilino-methylenecyclopentanone were interacted with zinc chloride

TABLE 4 : PREPARATION OF METHIODIDES

Cyclo-alkeno-quinoline	Wt. (g)	Meth-iodide	Wt.(g)/ Yield (%)	Crystal shape/ solvent	m.p.°C	Analysis Found C	H	N	I	Required C	H	N	I
XXV	1.0	XLIII	1.2/70	Yellow needles/ CH_3OH	190	Known[a,b]							
XXVII	0.5	XLIV	0.6/75	Yellow flakes/ CH_3OH	230	52.0	5.5	3.5	34.1	52.0	5.4	3.8	34.4
XXVIII	0.24	XLV	0.24/63	Yellow flakes/ CH_3OH	216 (dec)	52.8	5.6	3.9	33.3	53.2	5.7	3.7	33.2
XXX	0.2	XLVI	0.26/80	Yellow needles/ CH_3OH	196[c]	52.8	5.0	3.9	37.2	53.1	5.3	4.1	37.5

(a) Ref.71

(b) UV: λ_{max}^{EtOH} mμ (log ε): 240 (4.06), 305 (3.44), 347 (3.65)

(c) Ref.16.

in absolute ethanol; hydrochloric acid in refluxing ethanol; $POCl_3/ZnCl_2$; zinc chloride, arylamine hydrochloride in ethanol and chloroacetic acid. In all the experiments unreacted ketone, decomposition products or polymeric masses were obtained.

(c) Interaction of 2-anilinomethylenecyclooctanone (XLI) (2.0 g) with chloroacetic acid (3.0 g) at 140° for 24 hr lead to decomposition of ketone yielding free amine which in turn reacted with solvent to produce 2-chloro-acetanilide m.p. 135° (NMR, Mass).

(d) Interaction of (XXIII, n=4) with lactic acid produced polymeric side products (Table 3).

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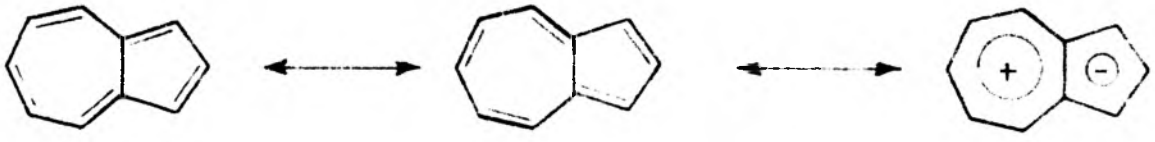
CHAPTER III - SYNTHESIS OF QUININDINE DERIVATIVES : ISOELECTRONIC ANALOGUES OF BENZAZULENE

INTRODUCTION

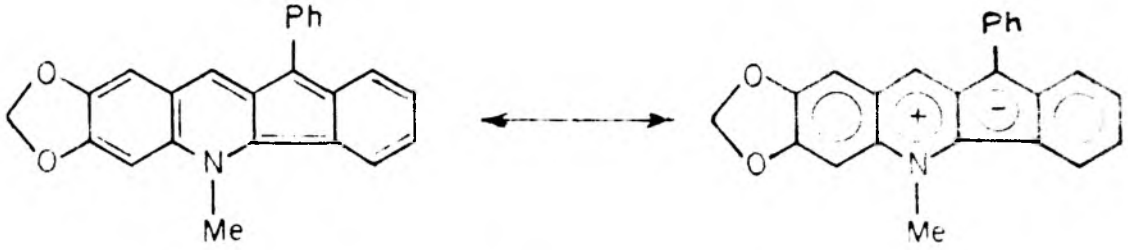
Pseudoazulenes belong to a novel class of cyclic conjugated, non-benzenoid, heteroaromatic compounds. The heterocyclic analogs of azulene are non-alternant, iso-π-electronic systems containing the element of cross conjugation. Pseudoazulenes are hence expected to resemble azulene (I) (Fig.1).

Robinson[1] in 1925 explicitly stated his concept of 'aromatic sextet' as a criteria for 'aromatic character'. In order to show that aromatic character may be associated with a five membered ring, Armit and Robinson[2] synthesised anhydro bases like indenoquinolines (II) where a cationic N-alkylpyridinium ring is fused to a ring bearing anionic cyclopentadienyl character. This is similar to azulene structure (I) in which the dipolar form contributes to the classical covalent forms in the resonance hybrid.

It has been often pointed out[3] that (isoelectronic) replacement of the group (-CH=CH-) in an aromatic ring by -O-, -S- or -NR- providing an electron pair, results in a molecule which retains the aromatic character of the parent. Two adjacent carbons in the seven membered ring of azulene if replaced by a heteroatom will form molecules which would be related to azulene as pyrrole, thiophene and furan are related to benzene. In the dipolar form of azulene (I), replacement of cationic carbocycle moiety by a heterocyclic ring would lead to pseudoazulenes (III - IX) (Fig.2). These

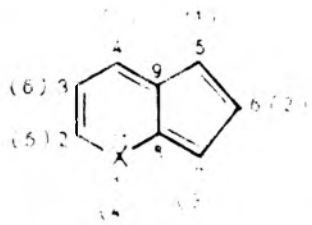


(I)



(II)

FIG. 1.



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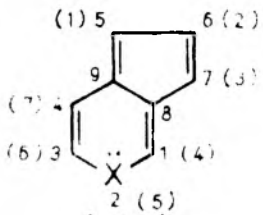

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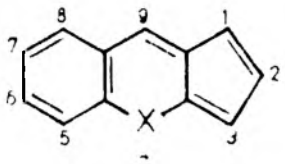

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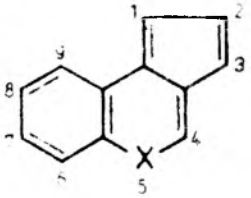

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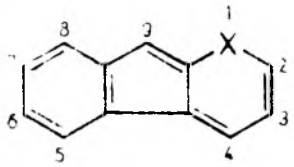

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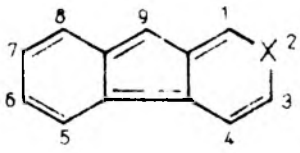

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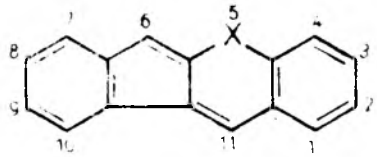

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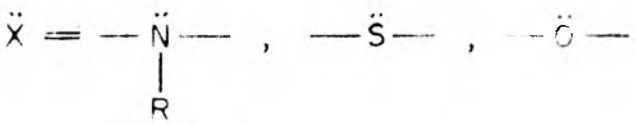


FIG. 2.

compounds have more π-electrons than ring atoms and have been called as π-excessive. The lone pair of electrons on the heteroatom can delocalise in the molecule. Pseudoazulenes of this type are reviewed in following pages.

Pseudoazulenes can also be obtained when one or more (-C=) atoms in azulene are substituted by the heteroatom (-X=), the hetero atom being in the five or seven-membered ring of azulene. Compounds have the same number of π-electrons as ring atoms and have been described as π-equivalent. Lone pair on hetero atom which is not involved in conjugation is free. Some examples of this type are Aza-azulenes[4,5], 2H-cyclopenta[d]pyridazine[6] and indolizine[7] (pyrrocoline). These systems bear the same relationship to azulene as pyridine and pyrimidine to benzene. Pseudoazulenes of this type, however, are not considered in this review.

The term 'pseudoazulene' was first quoted by Mayer[8] in 1957 claiming the synthesis of cyclopenta[b]thiapyran and cyclopenta[b][1]benzothiapyran (Fig.3). Boyd[9] in the same year prepared a derivative of cyclopenta[b]pyran. Los, Saxena and Stafford[10] reported, the derivatives of ε-quinindene which are nitrogen isosters of benzazulene (Fig.3).

The literature from 1957 to 1973 on pseudoazulenes discloses a growing interest in this field. Attempts to synthesise parent compounds and their valuable derivatives

have been reported by Boyd, Stafford, Mayer, Robinson, Treibs, Anderson, Reese, Kholodov, Tilak, Eisch and a few others. Modern developments serve to emphasise the importance of 'aromatic sextet' in five-, six- and seven-membered carbocyclic and heterocyclic rings.

The text book information on pseudoazulenes is limited and scattered. Pyrindines and quinindenes have been reported[11], but the text only deals with the preparation of precursors, pyrindanes and quinindanes. Yates[12] while reviewing fulvenes has quoted the preparation of a hetero-cyclic analog of azulene. Hafner et al.[13] have similarly described pseudoazulenes. UV spectral data[14] of pyrindines and synthesis of cyclopenta[b]pyrilium salts[15] have been discussed. Badger[16] in his book on aromaticity has only mentioned the nitrogen and sulfur isoster of azulene.

Indeed, the subject of pseudoazulenes appears to be a "hot" topic of research. A review of the subject appears therefore to be worthwhile.

Nomenclature

In German papers, nitrogen, sulfur and oxygen, isosters (III, X = NR, S, O) of azulene (Fig.2) have been termed as 'azalene', 'thialene' and 'oxalene' respectively. Compounds (IV) have been treated as isomers; (V - VIII) as benzologs and (IX) as a dibenzo analog.

The nomenclature followed by Chemical Abstracts is given below. Alternative numberings are given in parantheses (Fig.2).

Structure	X	Nomenclature
III	-NR-	1H-1-Pyrindine 1-H-Cyclopenta[b]pyridine
	-S-	Cyclopenta[b]thiapyran
	-O-	Cyclopenta[b]pyran
IV	-NR-	2H-2-Pyrindine 2H-Cyclopenta[c]pyridine
	-S-	Cyclopenta[c]thiapyran
	-O-	Cyclopenta[C]pyran
V	-NR-	4H-cyclopenta[b]quinoline β-quinindene
		Benzo[b][1]pyrindine
	-S-	Cyclopenta[b][1]benzothiapyran
	-O-	Cyclopenta[b][1]benzopyran Benzo[b]cyclopenta[e]pyran
VI	-NR-	5H-Cyclopenta[c]quinoline α-quinindene Benzo[c][1]pyrindine
	-S-	Cyclopenta[c][1]benzothiapyran
	-O-	Cyclopenta[c][1]benzopyran
VII	-NR-	Indeno[2,1-b]pyridine
	-S-	Indeno[2,1-b]thiapyran
	-O-	Indeno[2,1-b]pyran
VIII	-NR-	Indeno[2,1-c]pyridine
	-S-	Indeno[2,1-c]thiapyran
	-O-	Indeno[2,1-c]pyran
IX	-NR-	Indeno[2,1-b]quinoline
	-S-	Benz[b]indeno[2,1-e]thiapyran
	-O-	Benz[b]indeno[2,1-e]pyran.

Theoretical considerations

Pseudoazulene is a conjugated bicyclic system containing 10 π-electrons and the benzo and dibenzo analogues contain 14 π- and 18 π-electrons. Molecules not only satisfy Robinson's 'aromatic sextet' rule but also Hückel's 4n + 2 aromaticity rule[17].

Hückel molecular orbital (HMO) method is useful to calculate the π-electron energy levels, bond orders and charge densities of a molecule. The theoretical values provide a useful basis for study of the observed chemical and physical properties of known substances. The calculations can be used for ground state properties like dipole moments, interpretation of electronic spectra and predicting stability and chemical reactivity of unknown compounds.

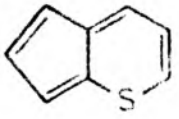
Theoretical considerations on pseudoazulenes are of interest because of its association with the problem of 'aromaticity' and further to predict about 'heteroaromatic reactivity'. As pseudoazulenes would resemble azulene, a comparison of the properties of these molecules with those of azulene would provide data useful in the theoretical interpretation of the role of the hetero atom in heteroaromatic compounds in general.

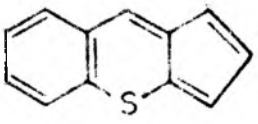
Aromaticity of pseudoazulenes on theoretical grounds has been studied by Borsdorf[18]. By using LCAO-MO (HMO) method, calculations have been made of the electron distribution, reactivity, basicity and light absorption of oxalene and

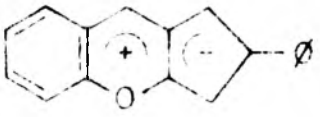
benzoxalene. The results suggested similarity between oxalene and azulene. Polarisability of pseudoazulenes, as a consequence of their fully aromatic nature has been shown through a study of infrared, visible and dipole moment data on dibenzoxalene and dibenzazalene.

Boyd[19] applied HMO method on pseudoazulenes (III and IV) and calculated charges on atoms, bond orders, delocalisation energy, charge separation between the rings and energy of $\pi \rightarrow \pi^*$ transition. For each molecule five bonding molecular orbitals have been obtained which are filled with 10-π-electrons. It has been shown that stability and aromatic character decreases in the order Azulene > (III) > (IV).

Borsdorf[20] by using LCAO-MO theory, calculated bond lengths and the electron density at each atom for compounds (III-V, VII, IX where X = N-Me) and compared with the data of azulene and oxalene. The azalenes showed an azulene like electron excess in the 5-membered ring and deficiency in the pseudo 7-membered ring. The molecular diagrams of azulene and oxalene have been shown in Fig.4. All C atoms have a greater electron density than do those in oxalene. It has also been shown that for compound (III) the lowest cation localisation energy and greatest reactivity for electrophilic substitution occur in positions 3 and 1; for nucleophilic substitution at carbon atoms 6 and 4; and for radical substitution C atom 6 is most reactive. Electrophilic substitution reactivity has been expected to increase in the order azulene <







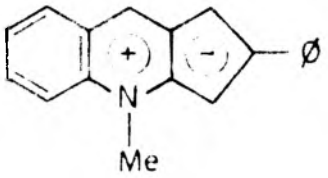
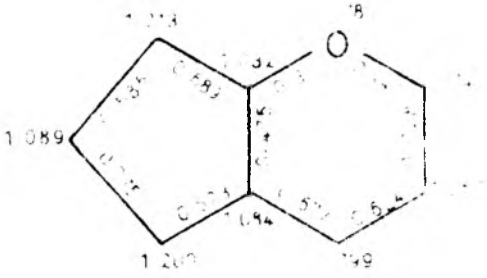
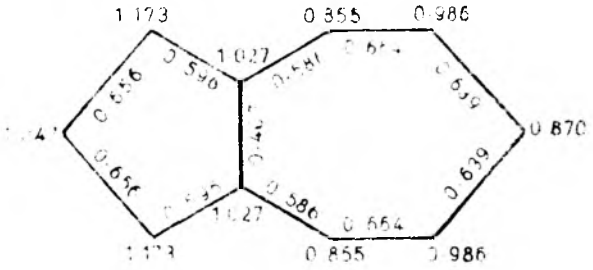
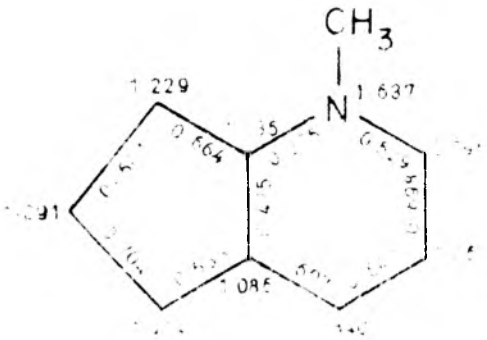
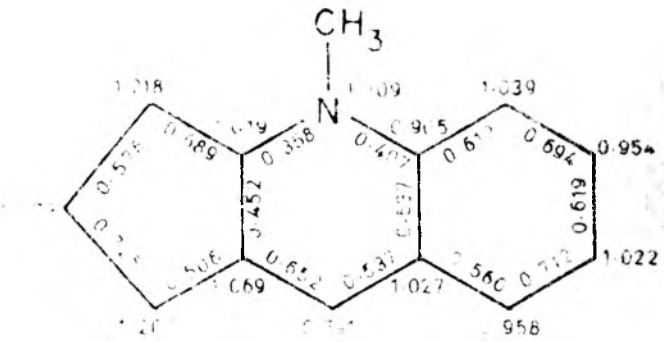


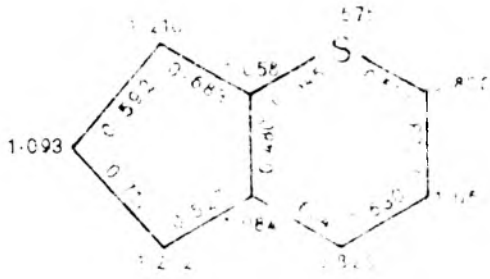
FIG. 3.











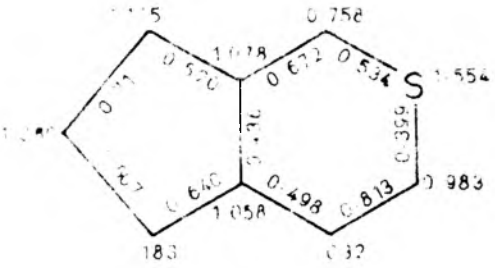


FIG. 4. MOLECULAR DIAGRAMS OF AZULENE AND PSEUDOAZULENES SHOWING π-ELECTRON DENSITY AND BOND ORDERS

oxalene < azalene. Azalenes showed the same long wavelength absorption of light as do azulene and oxalene.

Evleth et al.[21] by theoretical calculations with initial bond alteration, have provided dipole moment data for 1-methyl-1-pyrindine (III; X = NMe) and 2-methyl-2-pyrindine (IV; X = NMe) as 4.9 and 5.6 D (azulene 1.0 D). Data confirms the contributions from resonance structures having a separation of charges. The electronic absorption spectra of 1- and 2- pyrindines have been rationalised using semiempirical SCF-CI calculations[22].

Zahradnik et al.[23,24] have extensively studied thialene, iso-thialene and benzologs of thialene with molecular diagrams. Simple LCAO-MO calculations have been carried out for both; a model in which **S** atom d-orbitals are considered to participate in conjugation and a model in which their participation is neglected. The π-electron densities, free valences and bond orders are in accordance with experiments. The relation between the excitation energy of the first intense band and the theoretical $N \rightarrow V_1$ energies have been discussed. In general both the models interpret electronic spectra and predict chemical reactivity.

The molecular diagrams of thialene (III, X=S) and isothialene (IV, X=S) where d orbital participation is neglected have been shown in Fig.4. As seen, maximum electron density lies at positions 1 and 3. As the difference in the q values is small it can be expected that substitutions

would occur at both these positions. The minimum π-electron density and maximum free valence is associated with 4 and 6 positions. Hence in (III) nucleophilic reactivity will primarily be at 4 position and further, the sterically less hindered 6 position. In isothialene also the 1- and 3-positions would be the centres of electrophilic reactivity.

The semiempirical method introduced by Pariser, Parr and Pople (P-P-P method) has been applied in sulfur series of pseudoazulenes which offered a satisfactory interpretation of the singlet-singlet absorptions of pseudoazulenes in the UV and visible spectral regions[25,26].

SYNTHESIS

The syntheses of pseudoazulenes have been divided in following parts: (i) preparation of precursors (ii) dehydrogenation (iii) chemical introduction of unsaturation and (iv) condensation type reactions.

Synthetic routes to pseudoazulenes mostly involve perhydro compounds as precursors. Pyrindine and quinindene have been obtained from pyrindane and quinindane. Starting materials for oxygen and sulfur analogs of azulene are the cyclopenteno- pyrone, -pyran and cyclopenteno-thiapyrone, -thiapyran respectively.

The methods for the synthesis of pyrindane and quinindane have been discussed[11]. Methods of preparation of quinindanes which are in turn applicable for pyrindanes have

been discussed in Chapter II. Some schemes leading to pseudoazulenes which contain the preparation of precursors will be outlined later. Remaining methods are given below.

Isolation of 2,3-cyclopentenopyridine (X) (Fig.5) has been effected from California petroleum distillates[27] and coal tar bases[28]. Identical compounds have been synthesised according to a new method given in Fig.5.

The reaction of magnesium in tetrahydrofuran with γ-(3-pyridyl)propylchloride afforded pyrindane in low yield[29].

Syntheses of 2,3-cycloalkenopyridines have been conveniently achieved[30] by condensing 3-aminoacrolein with the cycloalkanone in the presence of triethyl amine (Fig.6). Similarly 2-(aminomethylene)cycloalkanone when reacted with 1,3-dicarbonyl compounds gave cycloalkeno[b]pyridine[31].

Cycloalkenopyrylium salts have been obtained by condensing hydroxymethylenecyclohexanone with cyclic ketones[32]. Polyphosphoric ester cyclisation of 2-phenacyl-5-methyl cyclopentanone-4-carboxylic acid gave derivative of cyclopenta[c]pyran[33]. Condensation of thiophenol and β-ketoacid ester in PPA yielded the corresponding thiachromones[34]. Boyd *et al.*[35] have prepared 2,3-cycloalkenochromones and thiachromones. Cyclic sulfides have been synthesised involving cyclisation of related open chain compounds[36,37].

Kessar *et. al.*[38] converted the lactone (XI) by thermolysis in ammonia to lactam (XII) which on LAH reduction

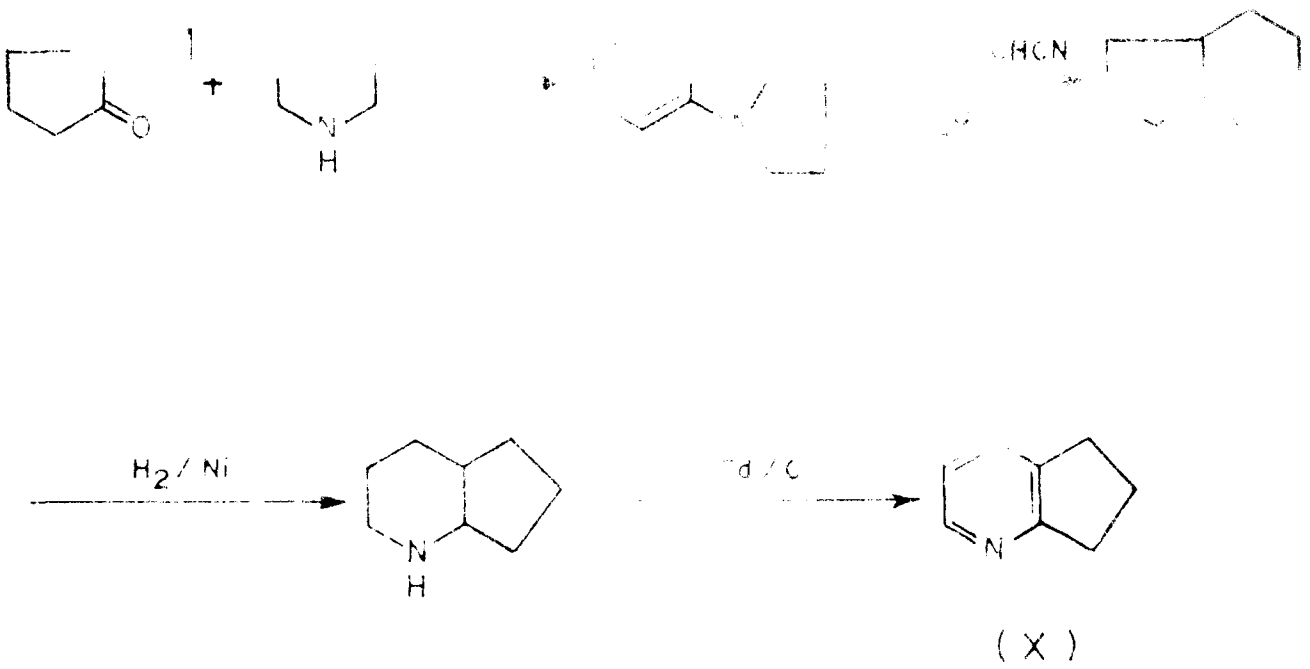
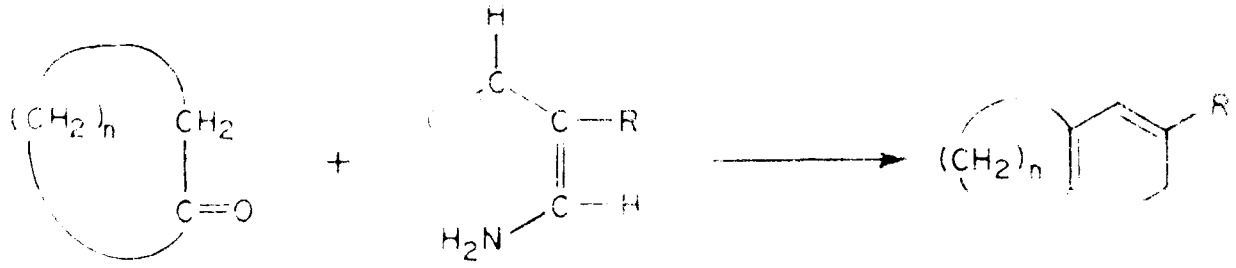


FIG. 5.



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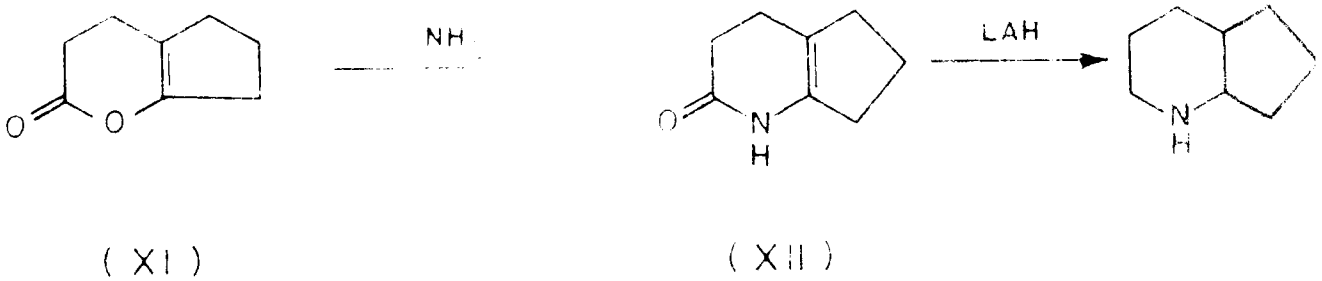


afforded perhydropyrindine (Fig.7).

Catalytic dehydrogenation of pyrindane has been attempted by Prelog and Szpilfogel[39]. Dehydrogenation could not be effected with Pd/c at 350° or with selenium at 400°, in both cases the starting material was recovered. Similarly the liquid phase dehydrogenation of perhydropyrindine with $PdO/BaSO_4$ under nitrogen gave only cyclopenteno[b]pyridine[28] (Fig.5).

The first successful attempt of catalytic dehydrogenation was made by Treibs and Kempter[40]. The scheme given in Fig.8 envisages the formation of the methosulfate of cyclopenteno[b]quinoline. The latter on treatment with alkali gave an unstable intermediate which on dehydrogenation with Pd/C in xylene yielded the substituted 8-quinindene.

Anderson et al.[41,42] have reported the synthesis of unsubstituted 2-phenyl-2-pyrindine (IV, X = NC_6H_5 and cyclopenta[c]thiapyran (IV, X=S) according to the scheme as shown in Fig.9. Dehydrogenation with S at 200° or with chloranil at 80° failed. A vapour phase process with Cu-Cr-C catalyst at 300° gave trace materials. However vapour phase dehydrogenation with Pd/C catalyst at 300° afforded (IV, X=S) as red plates and (IV, X = NC_6H_5) as orange prisms.

Mayer et al.[43] have also carried out vapour phase dehydrogenation of cyclopenteno[b]thiapyran using Pd-C to give thialene as an unstable blue violet oil. Another route to thialene (Fig.10) involved interaction of enamine and H_2S

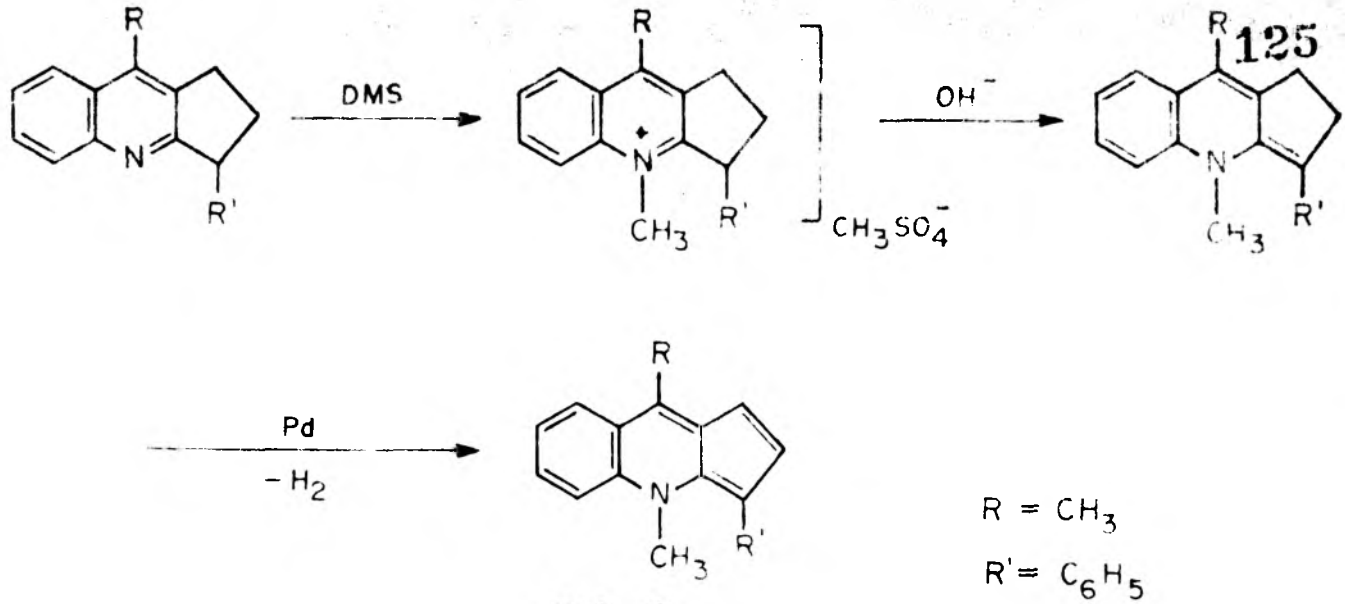
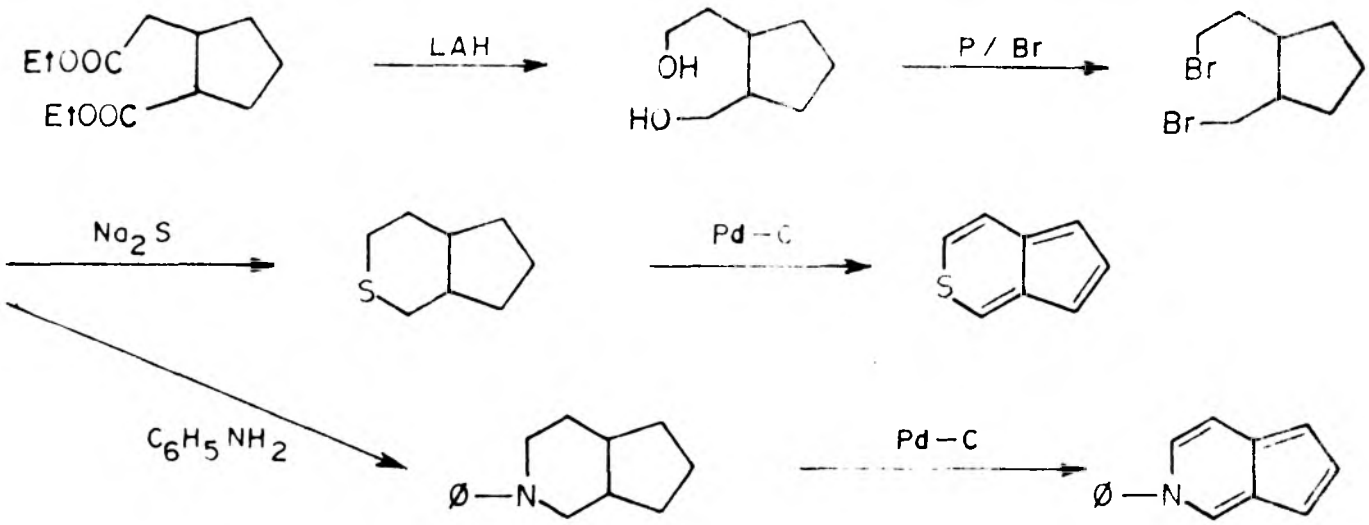


FIG. 8.



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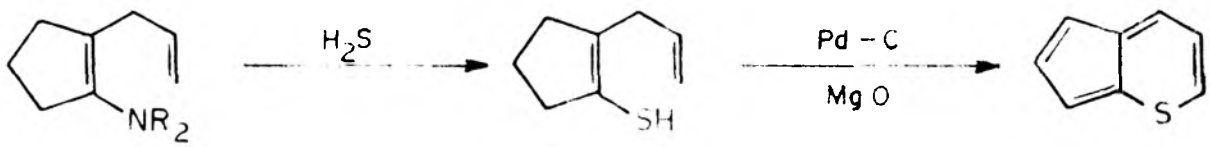


FIG. 10.

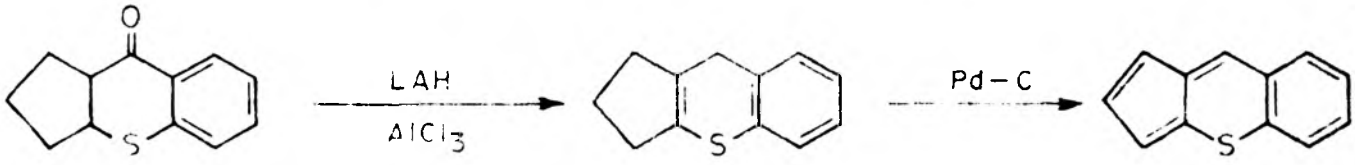


FIG. 11

to give 2-allyl-1-mercapto-1-cyclopentene which was further cyclodehydrogenated (on Pd-C-MgO under nitrogen at 20.5 mm and 320-50°). The synthetic route[44] to 5,6-benzothialene is shown in Fig.11. The appropriate thiapyrone was reduced with LAH to thiapyran which on catalytic dehydrogenation in vapour phase yielded 5,6-benzothialene as dark violet leaflets with metallic luster. Similarly indeno[2,1-b]thiapyran has been prepared.

Phenol was condensed with 2-carbethoxycyclopentanone to give a chromone which was reduced and dehydrogenated with chloranil to 2,3-benzooxalene[45] (Fig.12). The thia-analog has also been prepared by a similar method.

A dihydro analog of substituted indeno[b]pyran has been dehydrogenated by interaction with sulphur in decalin.

Apart from the catalytic dehydrogenation method, an alternative approach was to introduce a functional group in the five-membered ring whose subsequent elimination would result in unsaturation.

Robinson[47] converted pyrindane to N-oxide, followed by acylation. Subsequent deacetolysis with concentrated sulfuric acid at 125° afforded the pyrindine (Fig.13). The ester was also saponified and then dehydrated with sulfuric acid. Dehydration was effected by polyphosphoric acid by other workers[48]. Same sequence of reactions was extended to synthesise dehydroquinindenes[49,50]. In a variation, 3-acetoxy-2,3-dihydro-1H-cyclopenta[b]quinoline (XIV)

was quaternised to the methosulfate which on treatment with sulfuric acid at 120° and basification yielded 4-methyl-4H-cyclopenta[b]quinoline[51,52] (Fig.14).

An interesting route[53] (Fig.15) in arriving at unsaturation in pyrindane (XIII) consisted of the quaternisation of nitrogen and basification of the aqueous solution of the quaternary salt with sodium carbonate at 0° under an inert atmosphere and with simultaneous extraction in organic phase. From solvent 1-methyl-1H-1-pyrindine was isolated as a deep red oil which was stable at -70° under nitrogen but unstable at higher temperatures and quite unstable in the presence of oxygen. Dimeric products also resulted in above scheme due to substitution reactions[54].

Synthesis of aza-fluorene has been reported[55]. Treibs et al.[56] have converted aza-fluorene (XV) to tricyclic isoazalene (XVI) by following the method of quaternisation and basification (Fig.16). Similarly pseudoazulene from indanone was obtained[57]. When picric acid was added to stabilize the tricyclic azalene picryl derivatives were formed[58].

Recently introduction of hydroxyl group in cyclopenteno[b]quinoline has been achieved[49] by bromination to give bromo derivative and its hydrolysis to the hydroxy derivative or by metalation with phenyl lithium and oxidation to give the hydroxy derivative. Dehydration under well defined conditions produced benzo[b][1]pyrindine which

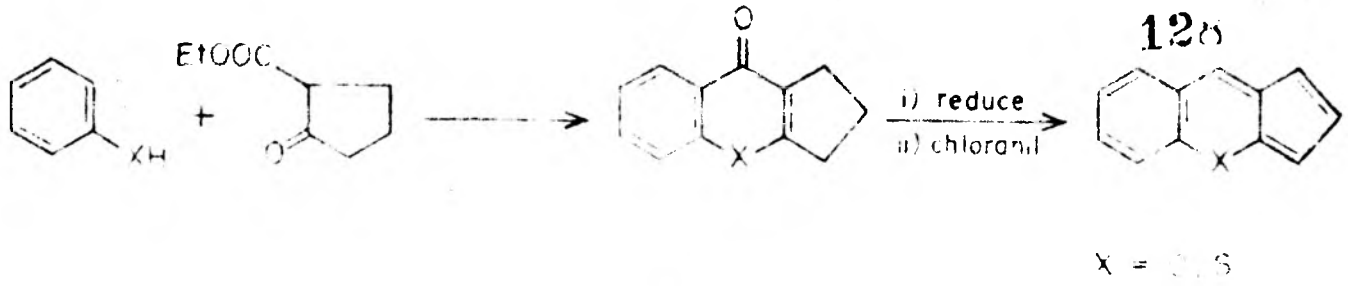
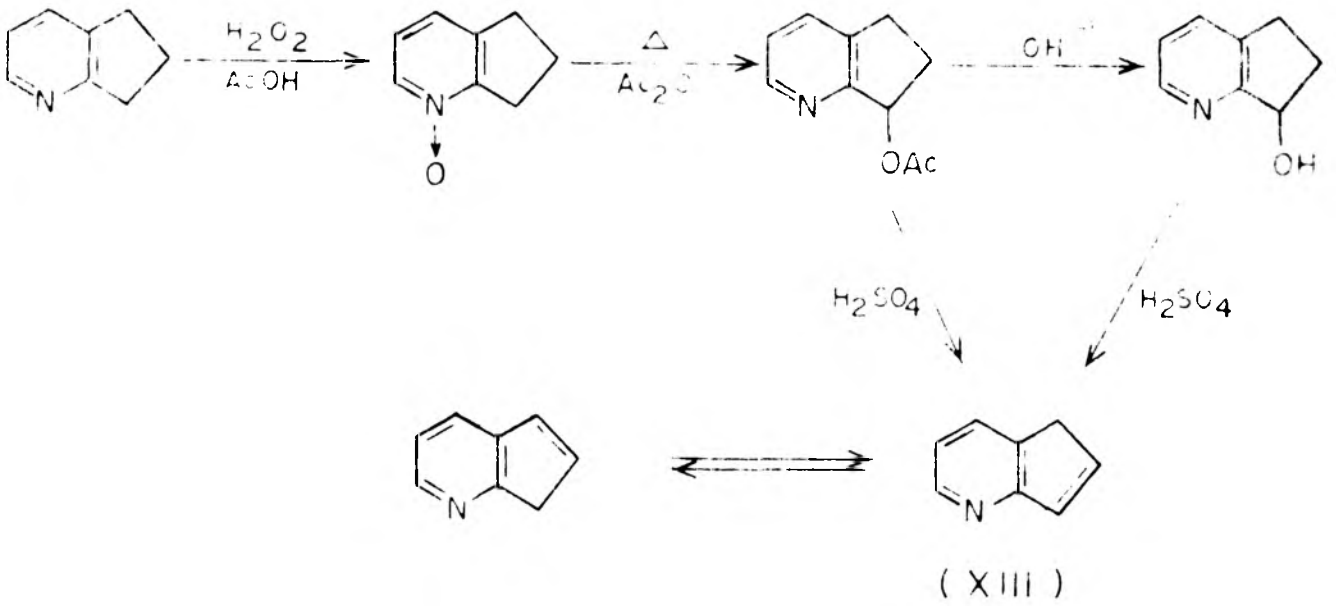
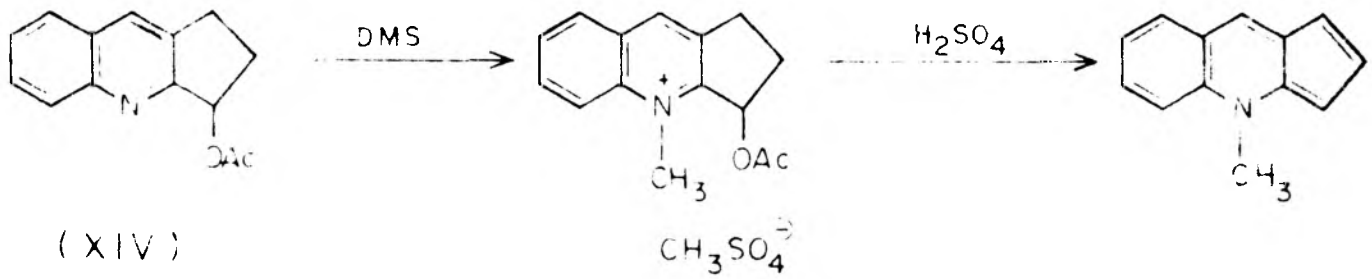


FIG. -12



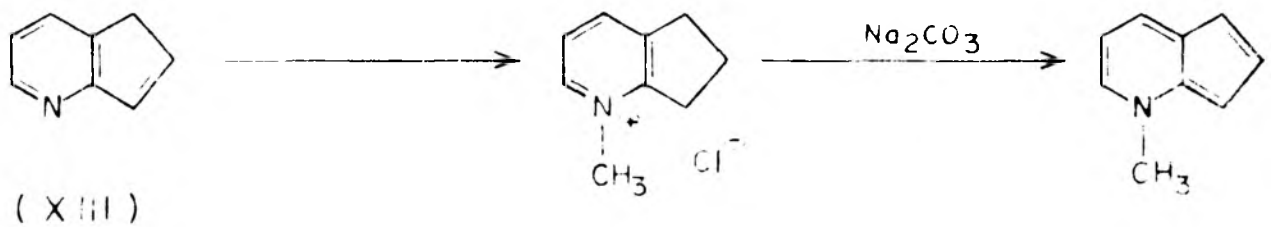
(XIII)

FIG. -13



(XIV)

FIG. -14



(XII)

FIG. -15

was stored below 0° under nitrogen.

The synthesis of the fully conjugated heterocycles involves a second stage of unsaturation e.g. dehydropyrindine to pyrindine (Fig.15). For this purpose the method of quaternisation and basification has been applied. Los et al.[59] and Anderson et al.[54] treated the quaternary salt with dilute sodium carbonate solution or diazomethane to yield the final anhydronium base.

Eisch et al.[49,52] treated dehydro-8-quinindene with molar equivalent of phenyl lithium at 0° and obtained the lithium salt of 8-quinindene (Fig.17). However treatment of dehydro-8-quinindene or its lithium salt with benzoyl chloride, benzophenone, 9-fluorenone, methyl lithium, methyl iodide, DMS, picric acid or trityl fluoroborate yielded substituted products instead of fully conjugated pseudoazulene.

Dehydrogenation using DDQ or chloranil has been attempted. Kholodov et al.[60,61] found that dehydrogenation accompanies substitution to give disubstituted products. Eisch et al.[62] have dehydrogenated the substituted dehydroquinindene with DDQ. However, in case of unsubstituted dehydroquinindene dehydrogenation with DDQ and triphenyl fluoroborate were found unsuccessful[52].

Catalytic dehydrogenation or chemical means of introducing unsaturation gives rise to the side reactions and the yield of the desired product is usually low. The

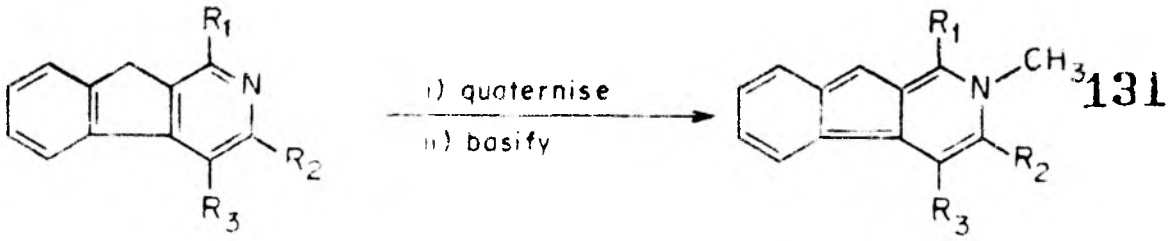
inherent instability and high reactivity of pseudoazulenes make their preparation difficult. However, the condensation type reactions leading to pseudoazulenes are relatively easy but give rise to substituted derivatives.

Los et al.[59] elaborated Borsche's synthesis of cyclopenteno[b]quinoline. Thus interaction of isatin and 3-phenylcyclopent-2-enone in ethanolic potassium hydroxide gave the 8-quinindene acid (XVII) (Fig.18).

Condensation of indan-2-one with salicylaldehyde and o-mercaptobenzaldehyde in presence of piperidine acetate has been exploited[63-66] to produce indenopyran and indeno-thiapyran respectively (Fig.19). Similarly 3-phenyl-cyclopent-2-enone with o-mercaptobenzaldehyde apparently gave a purple thiapyran. When 5-salicylidene-3-phenyl-cyclopent-2-enone (XVIII) was heated with acetic acid-hydrochloric acid a benzopyrylium chloride was obtained which on dissolution in water gave the purple coloured 2-phenylbenzo[b]cyclopent[e]pyran (Fig.20). The reaction of pyrilium perchlorate with aniline or methylamine yielded pyrindinium perchlorate.

Interaction of hydroxyfulvenealdehyde (XIX) and ethyl ester of sarcosine gave the intermediate (XX) which under basic conditions underwent intramolecular condensation to give the pseudoazulene (XXI)[13] (Fig.21).

Other miscellaneous methods are as follows. The product obtained by condensing cyclopentadienyl sodium and N-methylthiazolium bromide, when further pyrolysed, gave



(XV) (XVI)

FIG.- 16

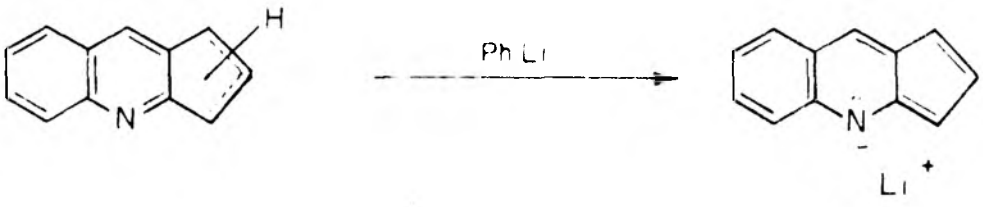
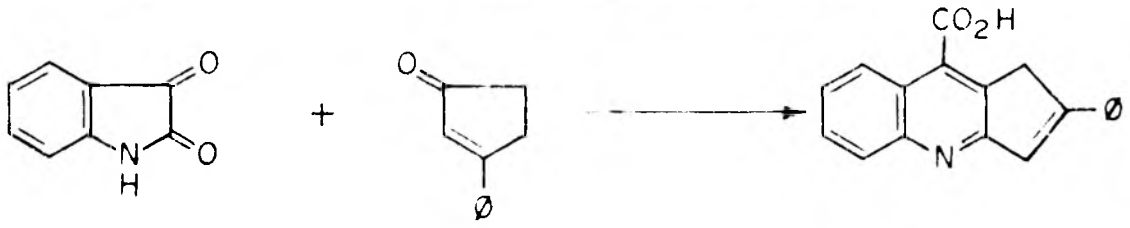
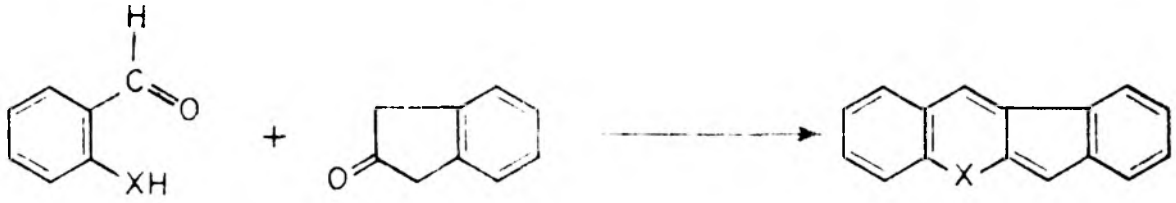


FIG.- 17.



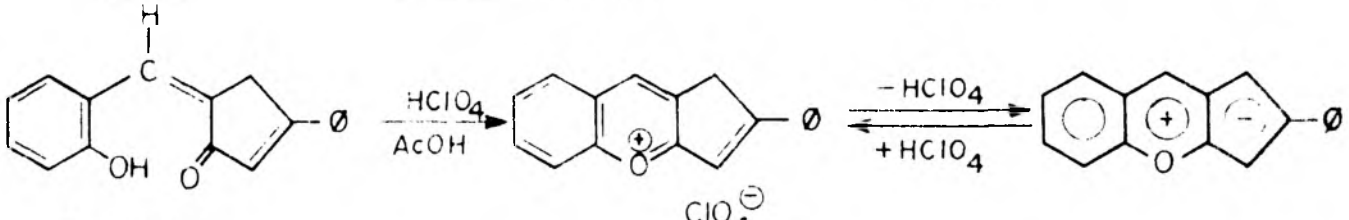
(XVII)

FIG.- 18.



X = O, S

FIG.- 19.



(XVIII)

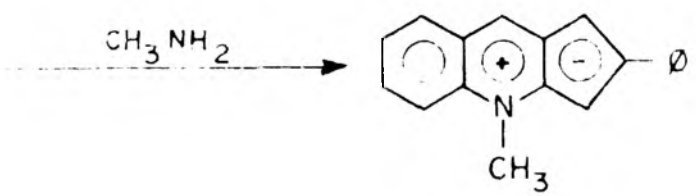


FIG.- 20.

cyclopenta[c]thiapyran[67].

Cycloaddition reaction of 2,6-dimethylphenylisonitrile with dimethyl acetylenedicarboxylate afforded substituted pyrindine derivative[68].

Condensation of acetylacetone with cyanoacetic acid ester[69] or with malononitrile[70] gave cyclopenta[b]pyran and substituted pyrindine derivative respectively.

Properties

Pseudoazulenes were stable, deeply coloured, basic compounds showing resemblance to the azulenes[65]. In the oxygen series the compounds were purple or red and they formed orange-yellow salts. The sulfur and nitrogen analogues were blue-violet or green anhydronium bases which on treatment with sulfuric acid or phosphoric acid formed yellow salts possessing an intense blue fluorescence in solution[59].

The basic character of pseudoazulenes has been shown by their solubility in sulfuric acid and the change in absorption spectra in sulfuric acid[41]. Compounds were stable to alcoholic alkali but degraded slowly by concentrated sulfuric acid or glacial acetic acid.

The solutions of compounds were susceptible to atmospheric oxidation as indicated by the fading of colour. Pseudoazulenes were unstable to chromatography on floracil, neutral alumina and silica gel[71]. Most of the compounds formed stable, crystalline complexes with 1,3,5-trinitrobenzene. Compounds in the nitrogen series have been purified

and analysed as TNB complexes.

Aromatic character of pseudoazulenes has been interpreted in terms of theoretical calculations, thermal stability, similarity of electronic spectra with azulene and the electrophilic substitution reactions.

In some cases the complexity in the structures of pseudoazulenes prevented their comparison with azulene. Unlike the isomerisation of azulene to napthalene on heating, the cyclopenta[b]thiapyran did not isomerise to thionapthene or isothionapthene neither could it be desulfurised to pentalene[44]. Electronic spectra of substituted azulenes have different bathochromic shifts than the corresponding substituted azulenes, probably due to the non-coplanarity of pseudoazulenic ring caused by molecular overcrowding[65].

The ultraviolet and visible spectra of pseudoazulenes have been shown to resemble those of azulenes. Azulenes and pseudoazulenes showed broad absorption in the visible and two bands in the UV region of the spectrum. Visible part of the spectrum showed regular displacements with substitution[59]. Cyclopenta-pyrans[65], -thiapyrans[42,43] and pyrindine derivatives[42] have resembled azulene whereas β-quinindenes[59], cyclopenta-benzopyrans[65] and -thiapyrans[44] have resembled benzazulene. The nature of pseudoazulene[66] has a marked effect on the visible absorption with the order of λ_{max} as NMe > S > O. Theoretical calculations have been used to investigate electronic spectra of pyrindines[72]. The effect of solvent

polarity on the absorption maxima of cyclopenta[c]thiapyran indicated the contribution of dipolar character in the ground state[42].

Recently NMR data has been used to evaluate the structures of pseudoazulenes. NMR spectra of cyclopenta[c]-thiapyran[73,74], cyclopenta benzopyran[75], 2-phenyl-2-pyrindine[71], 1-methyl-1H-1-pyrindine[53] and 4-methyl-4H-cyclopenta[b]quinoline[52] have been discussed.

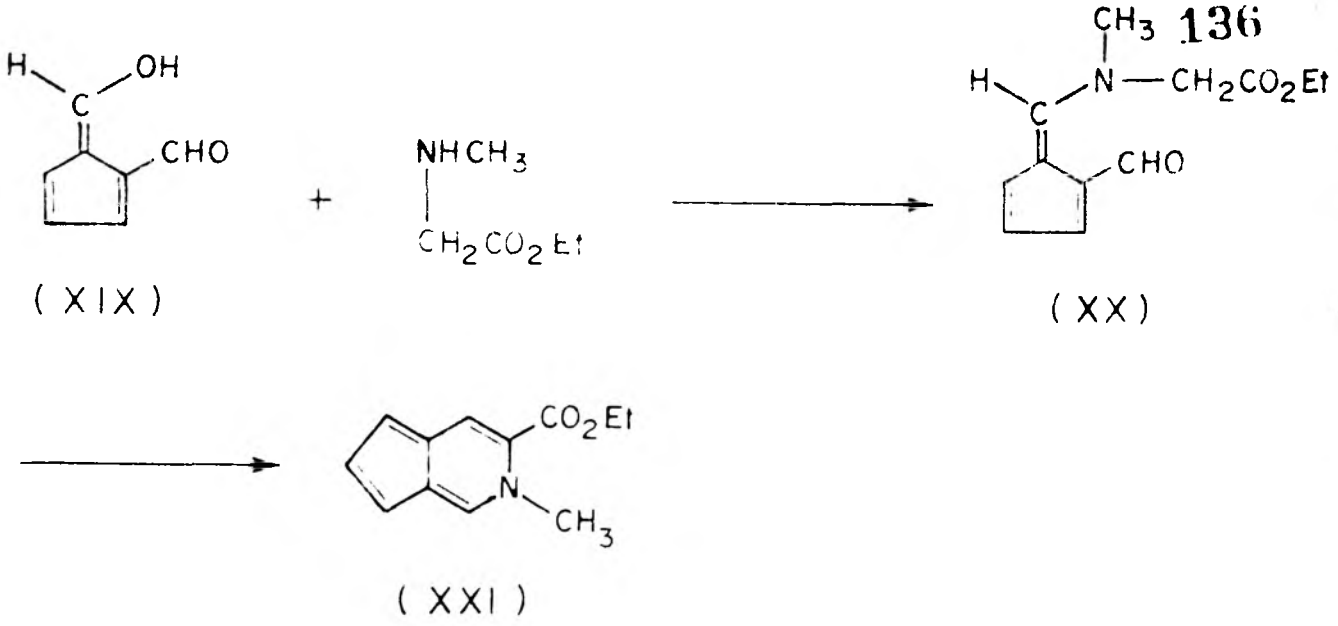
Tautomerism in pyrindine has been analysed by electronic spectra, NMR, pKa measurements and M.O. calculations. Dehydropyrindine (XIII) (Fig.22) has 1H-(XIII-a), 3H-(XIII-b) and 4H-(XIII-c) tautomeric forms. Robinson[47] prepared 1H-1-pyrindine and noted that the freshly distilled liquid has an orange colour which was discharged on dilution with organic solvents. Anderson *etal*[41] suggested that the colour was due to the presence of the 4H-tautomer (XIII-c). Reese[76] has confirmed this hypothesis by comparing the UV spectrum of 1-methyl-1H-1-pyrindine with that of the compound prepared by Robinson. Anderson *et al*.[53,54] also synthesised 1-methyl-1H-1-pyrindine and by using NMR and infrared spectra determined the percentages of the tautomers. Tautomerism in pyrindine has been discussed in terms of the calculated and observed electron excitation energies[77]. Proportion of tautomers in s-quinindene[49] has been directly found out by measuring the intensity of methylene peaks in the NMR spectrum. It has been shown that the 4H-tautomer was less

than 1% and 1H-tautomer was more stable than the 3H-tautomer.

Protonation of pseudoazulenes provided the simplest case of electrophilic attack. Azulene has been reversibly protonated in the five membered ring to yield the tropylium ion (Fig.23). Pseudoazulenes also produced analogous cations but because of their lower symmetry, two tautomeric forms have been generated. The site of protonation in cyclopenta[b]-pyran[75], cyclopenta[c]thiapyran and 2-phenyl-2-pyrindine[71] has been shown to be corresponding to the C_1 and C_3 atoms of azulene.

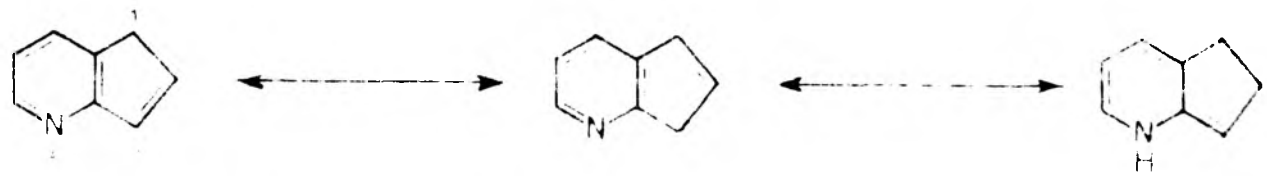
Ready polarisation in pseudoazulenes resulted in easier accessibility to electrophilic reagents and substitutions occurred in the five membered ring. Reactivity indices of various heteroazulenes suggested that C_1 and C_3 positions would be the most reactive to electrophilic attack[78]. Disubstitution has been frequently observed[79]. The orientation in the monosubstitution products has been determined by spectral analysis[62].

Positions of electrophilic, nucleophilic and radical substitution reactions in thialene and isothialene[80] have been shown in Fig.24. Cyclopenta[c]thiapyran[71,73] underwent smooth reactions with N-chloro- or N-bromosuccinimide, thiocyanogen and acetic anhydride to give 1,3-disubstituted derivatives. Thialene[43] and benzothialene[44] also produced 1,3-dihalogenated products. Halogenation, nitration, formylation, azo-coupling and Friedel-Craft's reaction of



(XIX) (XX) (XXI)

FIG. -- 21.



(XIII-a) (XIII-b) (XIII-c)

FIG. - 22.

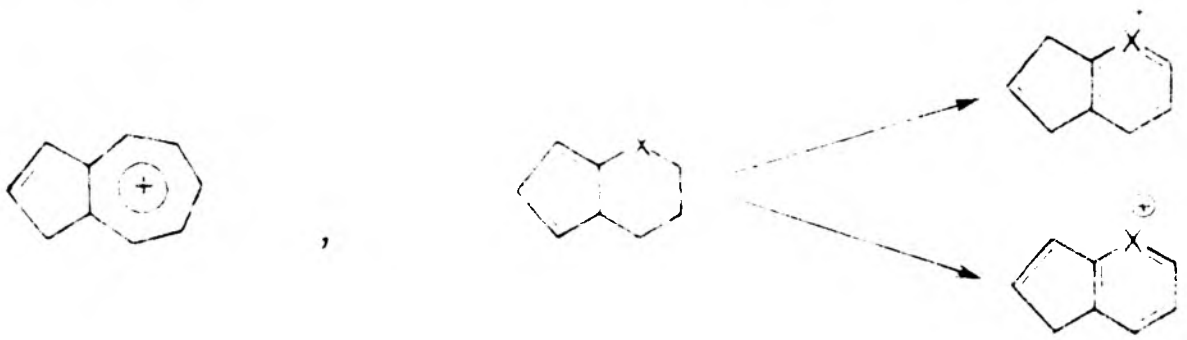


FIG - 23

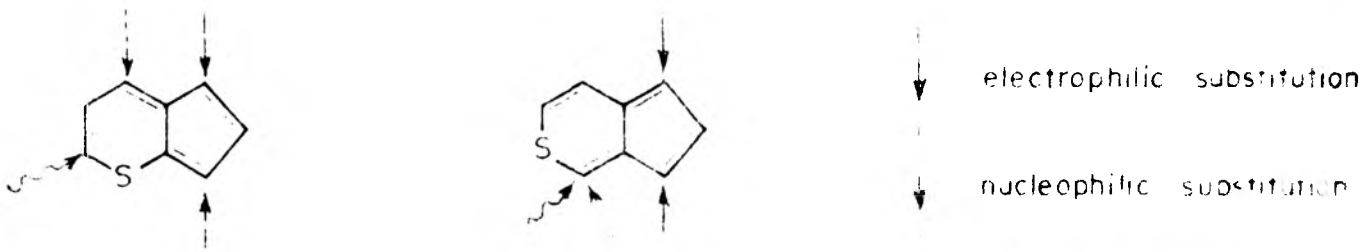


FIG - 24

tetraarylcyclopenta[b]pyran[79] took place at the C_3 position. Mono- and disubstituted derivatives of β-quinindenes have been obtained[61,62]. All these reactions emphasised the similarity to azulene.

PRESENT WORK

It can be readily seen from the review on pseudo-azulenes that the research work on quinindenes has been reported fairly recently. When we undertook the work on quinindenes, no report in the literature was available on the synthesis of α-quinindenes. Some reports[40,58,59] have described the synthesis of derivatives of β-quinindene and a few papers were published on the related pyrindine[42,47,53,54] and indenoquinoline[2,65,66] systems.

The sulfur and oxygen hetero azulenes have been found thermally stable[66]. On the contrary, compounds in the nitrogen series were extremely unstable and decomposed rapidly in the presence of oxygen, high temperature and sunlight[54,59]. The unstable and sensitive nature of nitrogen isosteres of azulene greatly hampered their synthesis although the precursors[81] were known for a long time.

Suitable starting materials for the synthesis of α- and β-quinindenes were 7-methoxycyclopenteno[c]quinoline (XXII) and cyclopenteno[b]quinoline (XXIII) respectively (Fig.25). Cyclodehydration of 2-m-anisidinomethylenecyclopentanone afforded 7-methoxycyclopenteno[c]quinoline (Chapter II). However, no rearrangement occurred in the above

cyclodehydration by various acids, which would have otherwise also offered cyclopenteno[b]quinoline. Hence cyclopenteno[b]quinoline (XXIII) was prepared using the Pfitzinger reaction[82] by interaction of isatin and cyclopentanone in alkali medium and subsequent thermal decarboxylation of the resulting 2,3-dihydro-1H-cyclopenta[b] quinoline-9-carboxylic acid.

7-Methoxy-α-quinindane (XXII) and the β-quinindane (XXIII) may be regarded as the dihydro derivatives of the respective quinindene ring systems (XXIV-a) and (XXV-a). It was expected that the prototropic shift in dehydroquinindenes (XXIV-a and XXV-a) obtained by dehydrogenation of (XXII and XXIII) would lead to the ring systems (XXIV-c and XXV-c).

Dehydrogenation of (XXII) and (XXIII) was interesting on the following grounds. Dehydrogenation involved introduction of a double bond in the five-membered ring whereby a stable 4n + 2 π-electron system (XXII) would be converted to 4n π-electron system (XXIV). Further if a base induced prototropic shift could have been achieved then it would lead to a system containing (4n + 2)π-electrons but it would be unstable because of the presence of a trans conjugated double bond. Thus dehydrogenation involved transformation of a stable aromatic system to an unstable aromatic one.

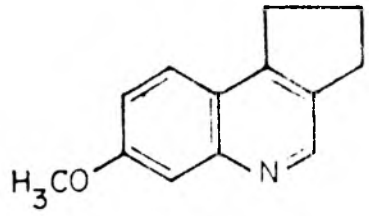
In order to introduce a double bond in the cyclopenteno residue of (XXII), the method of dehydrohalogenation was attempted (Fig.26). Bromination of (XXII) with N-bromosuccinimide in carbon tetrachloride afforded a labile

monobromo derivative (XXVI). As (XXVI) was too unstable, it was immediately subjected for dehydrohalogenation with various bases like triethyl amine, DMF/collidine, DMF/$LiCO_3$ and NaOMe. However, these reactions lead only to decomposition products.

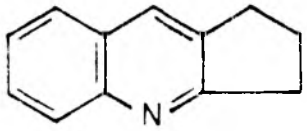
Catalytic dehydrogenation of (XXII) (Fig.26) with Pd/C in boiling p-cymene was also unsuccessful since only the starting material was obtained.

We then selected 2:3-dichloro-5:6-dicyanobenzoquinone (DDQ) and chloranil as dehydrogenating agents as these have high oxidation potentials. Treatment of (XXII) with equimolecular amount of DDQ in dry benzene afforded a maroon coloured substance (XXVII) (Fig.27), UV: λ_{max}^{EtOH} $m\mu$ (log ϵ): 475 (3.22), 335 (3.41), 323 (3.38), 284 (3.56), 254 (3.74), IR: γ cm^{-1} 1650 (quinone). NMR spectrum of (XXVII) displayed the methylene peaks identical to the cyclopenteno ring of the starting material (XXII) (Table 1). When (XXVII) was treated with dilute alkali and then extracted with ether it gave back the starting material. From this data, it was inferred that compound (XXVII) was a charge transfer complex and the complex was not that derived from the dehydrogenated product but simply the donor nitrogen atom of (XXII) complexed with the acceptor quinone.

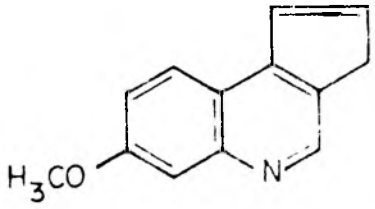
The donor-acceptor interactions between (XXII) and DDQ suggested that the lone pair on nitrogen atom prevents chloranil and DDQ to act as dehydrogenating agents (hydride



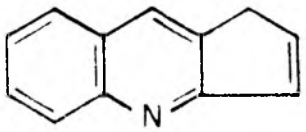
(XXII)



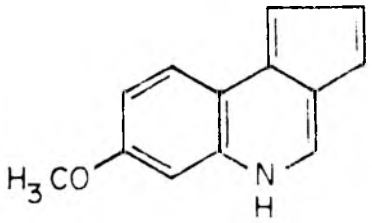
(XXIII)



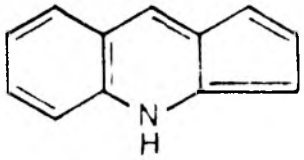
(XXIV – a)



(XXV – a)



(XXIV – c)



(XXV – c)

FIG. 25.

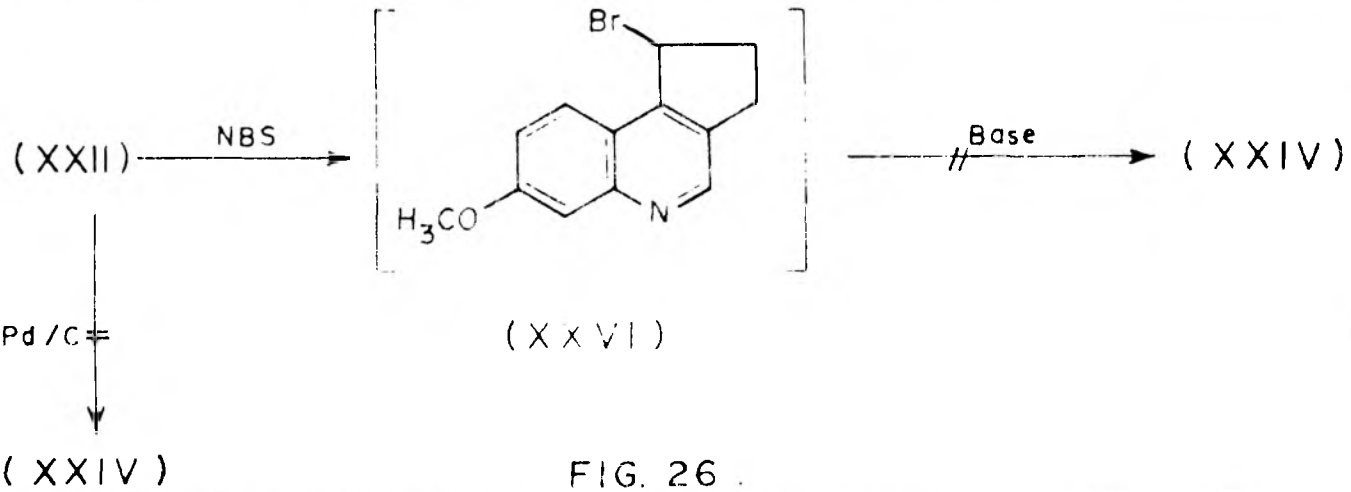


FIG. 26.

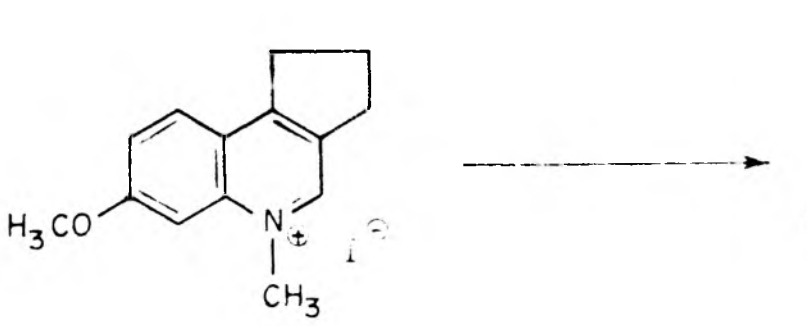
Charge – transfer complex

FIG. 27.

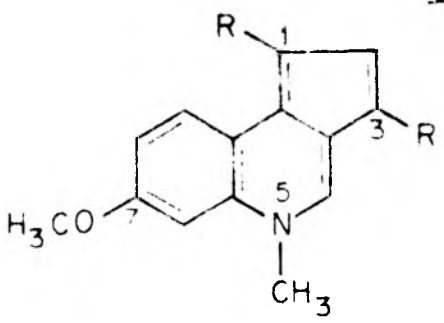
acceptors). To get over this difficulty 7-methoxy-5-methyl-cyclopenteno[c]quinolinium iodide[83] (XXVIII) and 4-methyl-cyclopenteno[b]quinolinium iodide (XXIX) (Fig.28) were prepared by interaction of (XXII) and (XXIII) with methyl iodide. In converting the quinoline (XXII) to methiodide (XXVIII), the lone pair on nitrogen has been removed. The quaternary nitrogen also served as an electron sink whereby the C_1-methylene protons were activated permitting their facile removal.

When (XXVIII) (Fig.28) was treated with two molar equivalents of chloranil in methylene chloride a fast (oxidation) reaction occurred and the mixture turned to deep green. The resulting mixture when chromatographed on neutral alumina afforded a faint pink colored fraction containing tetrachlorohydroquinone (XXXIV), m.p. 227°. PMR spectrum displayed a single deuterium exchangeable hydroxyl peak. IR: γ cm^{-1} 3350 (-OH). Isolation of (XXXIV) clearly indicated that dehydrogenation must have occurred. Next major chromatographic fraction gave a stable green coloured compound which was found to be 1,3-bis(3',5',6'-trichloro-1',4'-benzoquinonil-2')-7-methoxy-5-methyl-5H-cyclopenta[c]quinoline (XXX). The structure assignment of (XXX) was based on analytical data and spectral characteristics.

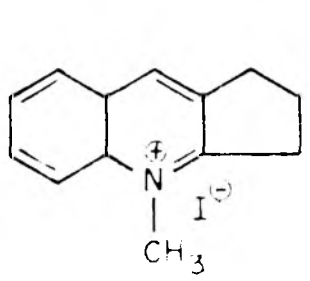
PMR spectrum of (XXX) (Table 1) is outlined in Fig.29. Absence of methylene protons indicated the formation of a dehydrogenated species. Singlets at 4.31 and 4.75 ppm were assigned to O-CH_3 and N-CH_3 protons. A multiplet of five



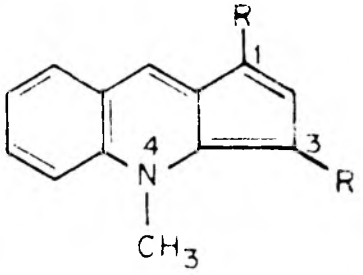
(XXVIII)



(XXX) , (XXXI)

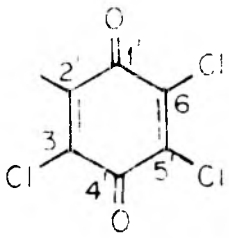


(XXIX)

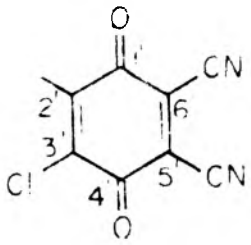


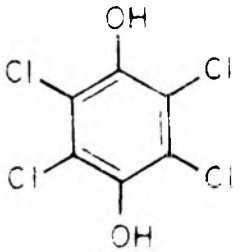
(XXXII) , (XXXIII)

(XXX) , (XXXII) R =

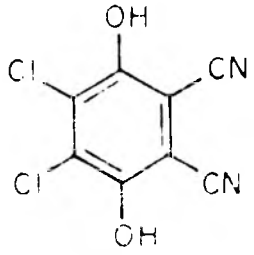


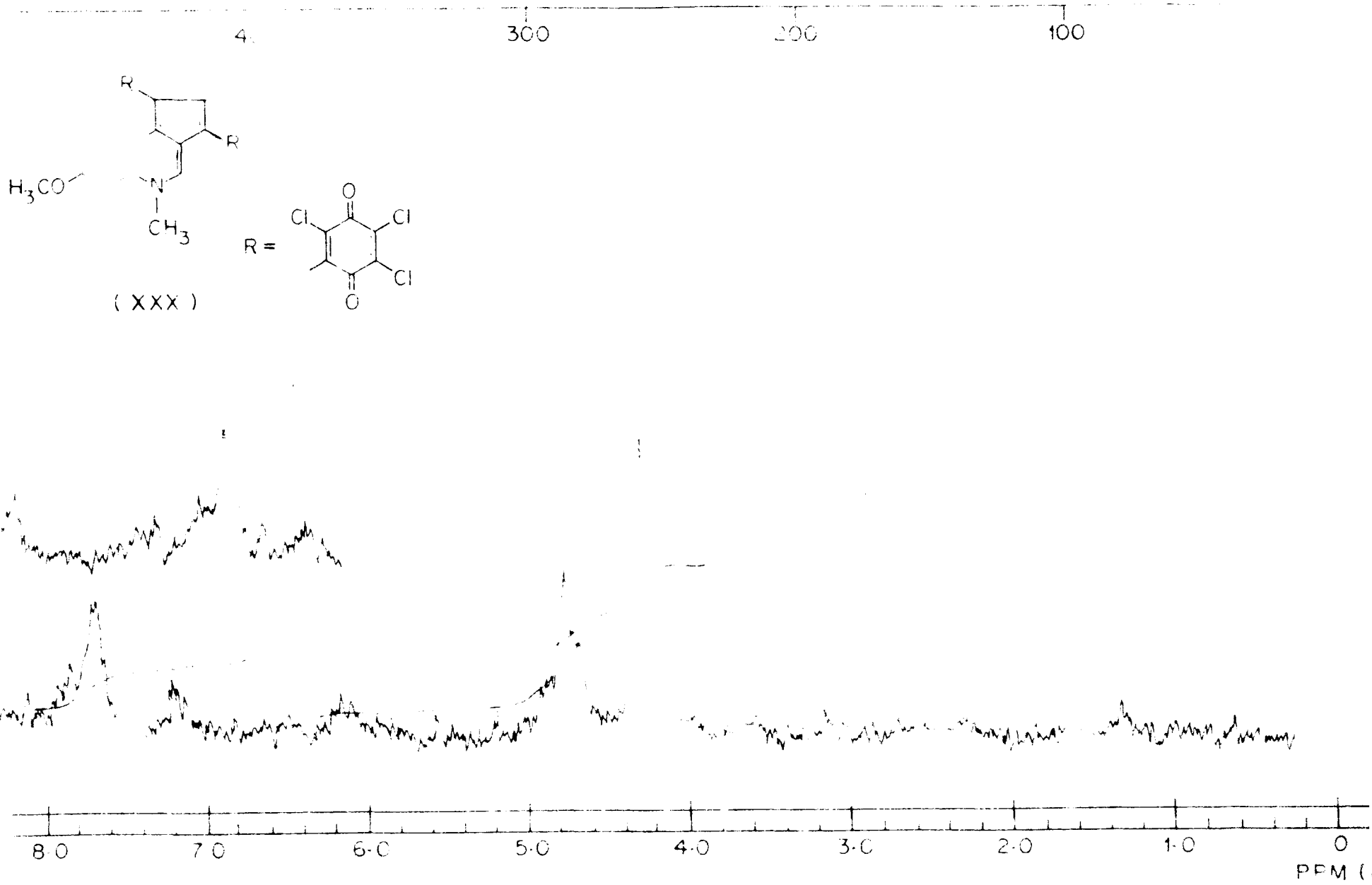
(XXXI) , (XXXIII) R =





(XXXIV)





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F 29. PMR SPECTRUM OF (XXX) IN CF_3COOH

TABLE 1 - PMR SPECTRAL DATA OF VARIOUS COMPOUNDS

Description: Chemical shift in δ ppm (pattern, proton intensity, assignment)

s: singlet
d: doublet
t: triplet
m: multiplet

Compd. No.	Solvent	Regions			
		Methyl	Methylene	Aromatic	Other typical signals
XXIII	CCl_4	-	2.05(t,2p,C_2),3.0 (m,4p, C_1C_3)	7.23-8.0 (m,5p,C_5-C_9)	-
XXIX	CF_3CO_2H	4.5 (s,3p, N-CH_3)	2.5(t,2p,C_2), 3.5 (q,4p, C_1C_3)	8.15(m, 4p, C_5-C_8)	8.66 (s, 1p, C_9)
XXX	$CDCl_3$	4.3 (s,3p, O-CH_3), 4.75 (s,3p, N-CH_3)	-	7.0-8.0 (m, 3p, $C_6C_7C_8$)	7.65 (s, 1p, C_2), 9.0 (s, 1p, C_4)
XXXI	DMSO-d_6	4.16 (s,3p, O-CH_3) 4.58 (s,3p, N-CH_3)	-	7.6-8.1 (m, 3p, $C_6C_8C_9$)	7.65 (s, 1p, C_2), 9.3 (s, 1p, C_4).
XXXII	$CDCl_3$	4.0 (s,3p, N-CH_3)	-	7.26 (m, 4p, C_5-C_8)	7.76 (s, 1p, C_2), 8.21 (s, 1p, C_9)
XXXIII	$CDCl_3$	4.1 (s,3p, N-CH_3)	-	7.2 (m, 4p, C_5-C_8)	7.76 (s, 1p, C_2), 8.2 (s, 1p, C_9).
XXXIV	DMSO-d_6	-	-	-	3.41 (broad s, D_2O exchangeable, -OH)
XXXV	DMSO-d_6	-	-	-	6.5 (broad s, D_2O exchanged -OH)
XXXIX	$CDCl_3$	3.73-4.0 (broad s, 6p, OCH_3 and NCH_3)	-	7.13 (broad s, 10p, -S C_6H_5), 7.4 (m, 3p, $C_6C_8C_9$).	8.1 (s, 1p, C_2), 9.35 (broad s, 1p, C_4).

.....Contd.

TABLE 1 (Contd.)

Compd. No.	Solvent	Regions			Other typical signals
		Methyl	Methylene	Aromatic	
XXXIX	CF_3CO_2H	4.13 (s, 3p, OCH_3) 4.5 (d, 3p, NCH_3)	-	6.95-7.5 (m, 13p, $C_2C_6C_8C_9$ and [s C_6H_5]$_2$)	8.91 (broad s, 1p, C_4).
XL	CF_3CO_2D	4.06 (s,3p, OCH_3), 4.23 (s,3p, OCH_3) 4.46 (broad s, 3p NCH_3).	2.46 (m,2p), 3.48 (m, 2p)	7.23 - 7.93 (m, 12p)	-
XLI	$CDCl_3$	4.68 (s, 3p, N-CH_3)	-	7.1 (s, 10p, -SC_6H_5), 7.26 (m, 4p, C_5-C_8)	7.73 (s, 1p, C_2), 8.5 (s, 1p, C_9).
XLIII	CCl_4	-	1.6-2.8 (m, 8p, [CH_2]$_4$), 3.38 (d, 1p, -CH)	7.0 - 7.36 (m, 5p, -C_6H_5)	-
XLIV	CCl_4	-	2.58 (t,2p,C_2), 3.78 (m,6p,C_1C_3 and C_4)	8.21 - 8.81 (m, 4p, C_6-C_9)	-
XLV	CCl_4	-	-	7.0-7.58 (m, 15p, C_6-C_9, C_2, mercaptophenyl).	8.65 (broad s, 1p, C_4).

PMR spectrum of (XXVII) was similar to (XXII). Spectrum of (XXII) is given on page 81 .

proton intensity spreaded between 6.9 - 9.0 ppm was assigned to aromatic protons from which a deshielded singlet at 9.0 ppm for C_4-H could be distinguished whereas C_2-H at 7.65 ppm was merged with other aromatic protons. Infrared spectrum of (XXX) is given in Fig.30. IR: γ cm^{-1} 1680(s) indicated presence of a quinone moiety and the fingerprint region was characteristic to 1:3-disubstituted azulene[84] (Table 2). Visible spectrum λ_{max}^{DMSO} mμ (log ϵ): 710 (3.58), 435 (3.84) (Table 3). Spectral data thus supported the assigned structure.

Interaction of two molar equivalents of DDQ with (XXVIII) in boiling acetonitrile gave dichlorodicyanohydroquinone (XXXV) m.p. 265°(dec.) and a greenish compound (XXXI) containing two DDQ residues. Compound (XXXI) was found to be 1,3-bis(3'-chloro-5',6'-dicyano-1',4'-benzoquinonil-2')-7-methoxy-5-methyl-5H-cyclopenta[c]quinoline. The structure assignment was based on PMR (Table 1), IR (Table 2), visible spectrum (Table 3) and analytical data.

Cyclopenteno[b]quinolinium iodide (XXIX) (Fig.28) on treatment with chloranil and DDQ as above also gave the corresponding 1,3-disubstituted linear quinindene derivatives (XXXII) and (XXXIII). Structures (XXXII) and (XXXIII) have been supported by PMR (Table 1), Infrared (Table 2) and visible spectra (Table 3). Interaction of (XXIX) and chloranil gave, in addition to (XXXII), a blue coloured compound in low yield. Structure of the blue coloured compound was not established but it is likely to be the mono-substitution product.

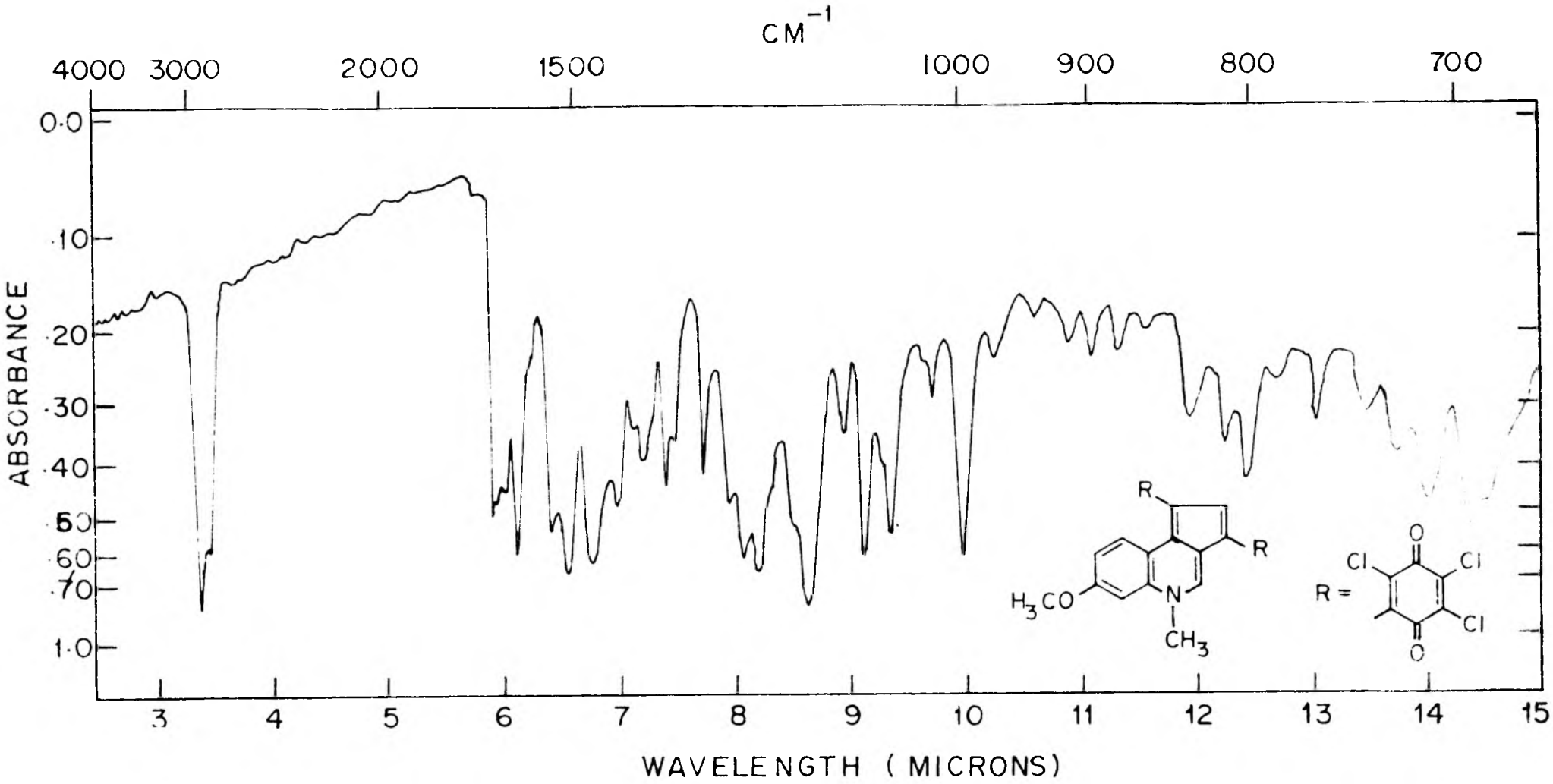


FIG. 30. INFRARED SPECTRUM OF (XXX) IN NUJOL

TABLE 2 - INFRARED SPECTRAL DATA OF VARIOUS COMPOUNDS

Nujol mull

Compound No.	(Frequency)$_{(Intensity)}$(Assignment)
(XXVIII)	$2230_{(m)}$(-CN); $1690_{(s)}$(quinone), $1650_{(s)}$(quinone)
(XXX)	$1680_{(s)}$(quinone); $1000_{(s)}$, $1160_{(s)}$, $1220_{(s)}$, $1350_{(m)}$ (bands characteristic to 1:3 disubstituted azulene[84]); $695_{(s)}$.
(XXXII)	$1680_{(s)}$(quinone); $1050_{(s)}$, $1175_{(s)}$, $1240_{(s)}$, $1370_{(s)}$, $695_{(s)}$.
(XXXI)	$2220_{(w)}$(-CN), $1640_{(s)}$(quinone); $1020_{(m)}$, $1210_{(s)}$, $1250_{(s)}$, $1370_{(s)}$.
(XXXIII)	$2220_{(w)}$(-CN), $1640_{(s)}$(quinone), $1020_{(w)}$, $1210_{(w)}$, $1370_{(s)}$.
(XXXIV)	$3350_{(s)}$(-OH), $1190_{(m)}$, $1310_{(s)}$, $1410_{(s)}$; $720_{(s)}$.
(XXXV)	$3200_{(s)}$(-OH); $2220_{(s)}$(-CN); $1190_{(s)}$, $780_{(m)}$.
(XXXIX)	$1570_{(m)}$, $1220_{(s)}$, $1060_{(s)}$ (sulfur stretching), $866_{(m)}$, $740_{(m)}$ (Hydrocarbon pattern).
(XL)	$1520_{(w)}$, $1220_{(s)}$, $1100_{(w)}$, $1060_{(m)}$, $840_{(m)}$, $740_{(m)}$ (Hydrocarbon pattern).
(XLI)	$1580_{(s)}$, $1560_{(s)}$, $1060_{(s)}$.

For (XXVII), refer page 139 .

TABLE 3 - ULTRAVIOLET AND VISIBLE SPECTRAL DATA OF VARIOUS COMPOUNDS

Compound No.	Solvent	λ_{max} mμ (log ε)
XXVIII	EtOH	254(3.74), 284 (3.56), 323 (3.38), 335 (3.42)
XXX	DMSO	435(3.84), 710 (3.58)
XXXI	DMSO	660 (3.6)
XXXII	DMSO	710 (3.77)
XXXIII	DMSO	640 (3.79)
XXXIX	EtOH	246(3.82), 290 (3.54), 354 (3.45), 445 (3.42)
XL	EtOH	231(4.08), 335 (3.27), 475 (3.46)
XLI	EtOH	234(3.4), 237 (3.40), 305 (3.11), 312 (2.93), 318(2.83), 505 (2.96)
XLV	EtOH	251(3.33), 356 (3.53), 374 (3.51), 465 (3.30)

For (XXVII), refer page 139 .

Buckley and Henbest[85] investigated the reaction between triethylamine and chloranil (Fig.31). The products contained triethylamine hydrochloride, tetrachlorohydroquinone and a blue coloured compound which was found to be diethylaminovinyl quinone. Formation of the blue quinone has been shown to proceed by dehydrogenation of the tertiary amine to vinyl diethylamine, followed by the reaction of the latter as a nucleophile with a second molecule of chloranil. The overall reaction took place readily at room temperature in benzene solution even when light and oxygen were excluded.

Interaction of methiodides (XXVIII) and (XXIX) with chloranil and DDQ giving 1,3-disubstituted quinindene derivatives (XXX - XXXIII) also followed the dehydrogenation coupled substitution reactions.

The plausible mechanism of formation of (XXX) or (XXXI) by the reaction of (XVIII) with chloranil or DDQ is outlined in Fig.32. The oxidation process comprising of successive proton removal and hydride transfer from methiodide (XVIII), leads to the fully dehydrogenated aromatic substrate. The latter being highly unstable and reactive undergoes electrophilic substitution with a second molecule of chloranil. The overall reaction probably being synchronous finally leads to the stable 1,3-disubstituted β-quinindene derivatives.

The synthesis of (XXXII) and (XXXIII) by interaction of (XXIX) with chloranil and DDQ would also follow a reaction path analogous to the above scheme.

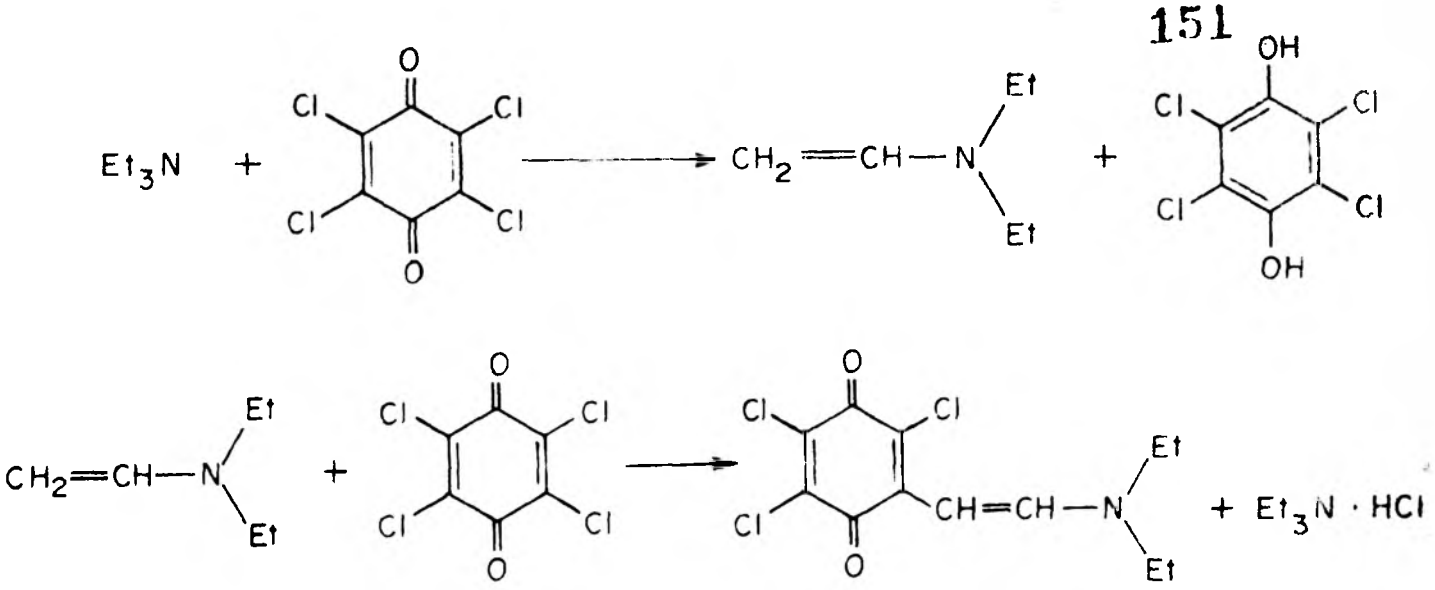
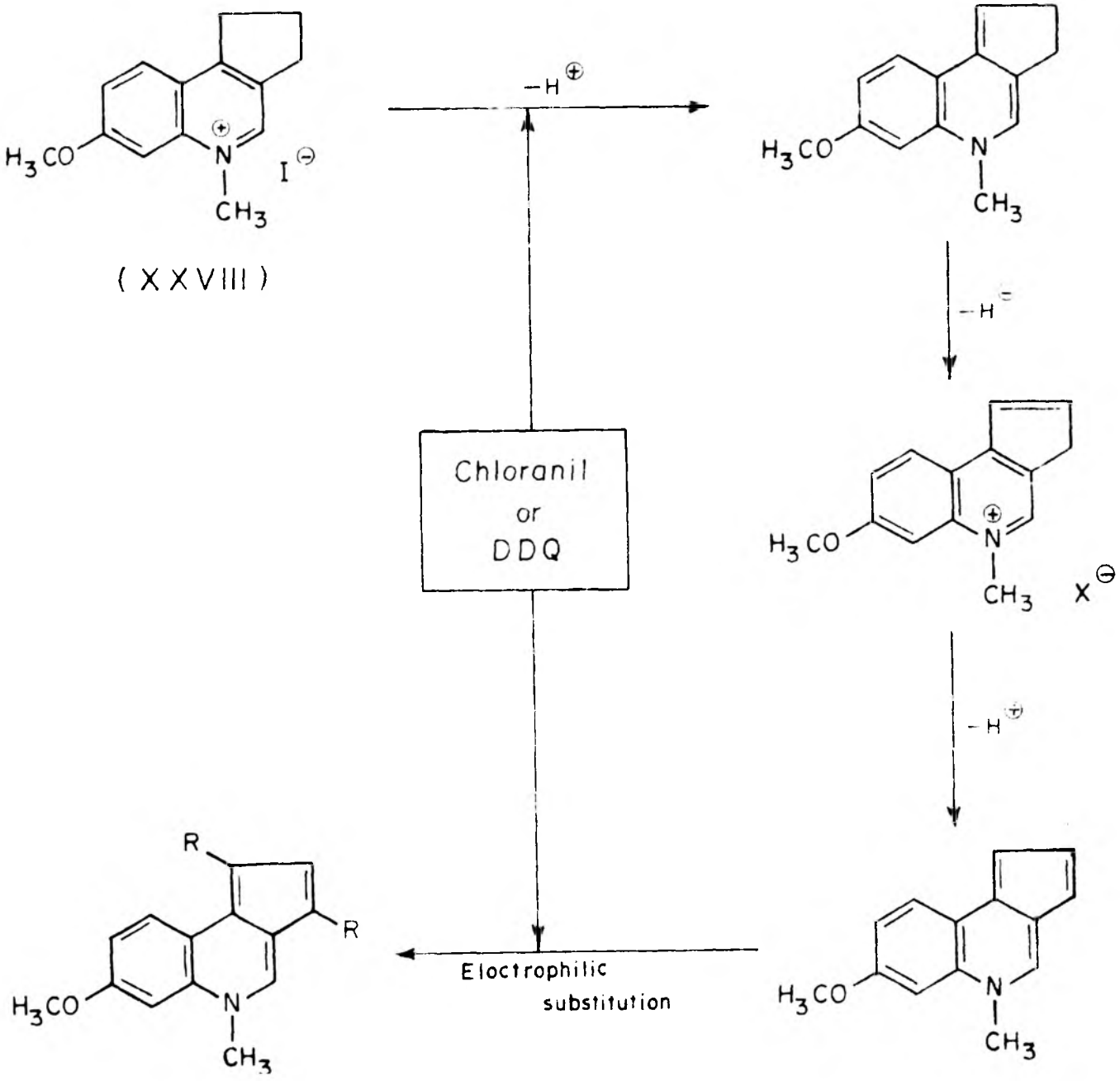

Et3N
CH2=CH—N
Et
Et
OH
Cl
O
CH=CH—N
+ Et3N · HCl

FIG. 31.


H3CO
I⊖
CH3
(XXVIII)
−H⊕
−H⊖
−H⊕
X⊖
Chloranil
or
DDQ
Electrophilic
substitution
R

It is interesting to note that hydroaromatic heterocyclic quaternary salts have been dehydrogenated with chloranil or DDQ. The stable cationoid heterocyclic ring systems (XXVIII and XXIX) have been converted by the above procedure to the non-alternant 14 π-electron systems (XXX - XXXIII), wherein the highly reactive aromatic substrate formed by dehydrogenation undergoes electrophilic substitution. The positions of electrophilic substitution C_1 and C_3 conform to the reactivity predicted by HMO calculations of 14 π^{20} - and 10 π^{78}-electron systems.

Tilak et al.[86] have reported the hydride transfer reactions by using diphenyl disulphide as a mild dehydrogenating agent for the dehydrogenation of hydroaromatic heterocyclic compounds. An indirect route (Fig.33) for the aromatisation of polycyclic hydroaromatic (tetrahydro) thiapyrylium salts involved their reduction to the dihydro derivatives followed by dehydrogenation by interaction with diphenyl disulphide to give dihydrothiaphenanthrene and quaternisation of the latter by trityl chloride.

Aromatisation of cationoid heterocyclic ring systems such as (XVIII) and (XXIX) was difficult due to the lack of driving force for removal of hydrogen atoms as hydride ions by usual dehydrogenating agents like diphenyl disulphide. Hence the methiodide (XXVIII) was reduced[83] with sodium borohydride to give isomeric dihydro derivatives (XXXVI-a and XXVI-b) (Fig.34). Since the dihydro derivatives were highly sensitive towards heat and light they were immediately treated without

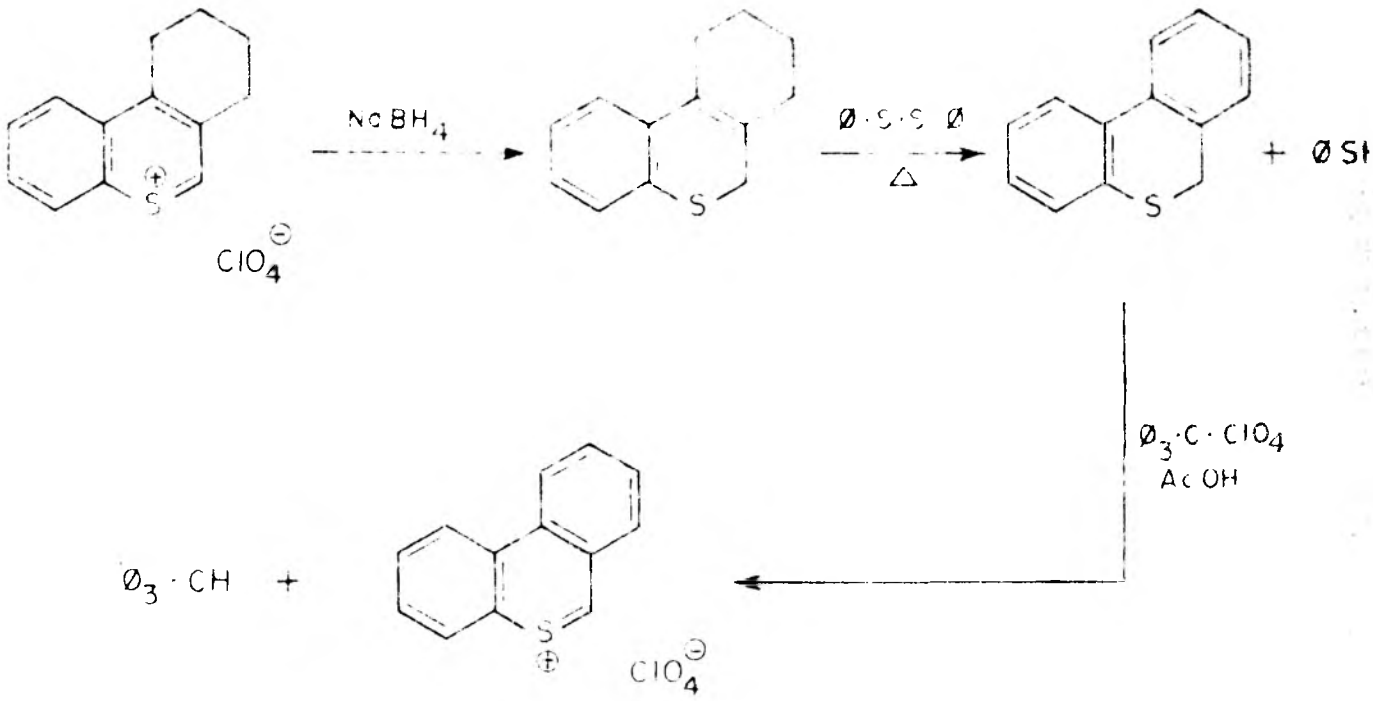
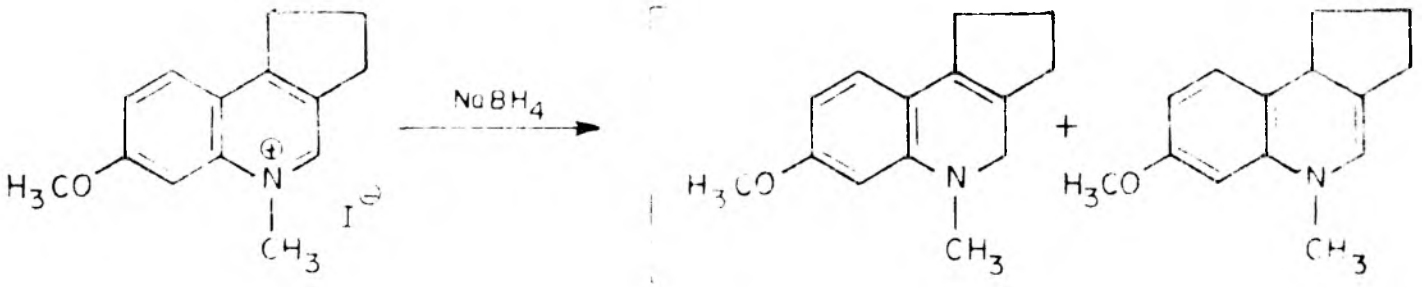
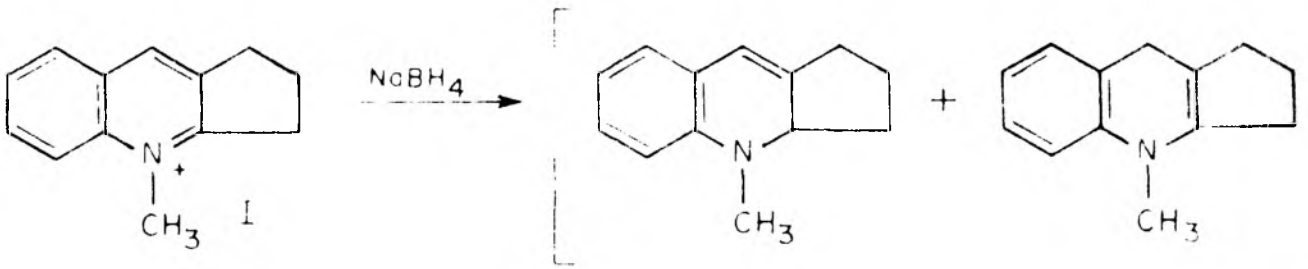


FIG. 33.



(XXVIII) (XXXVI-a) (XXXVI-b)



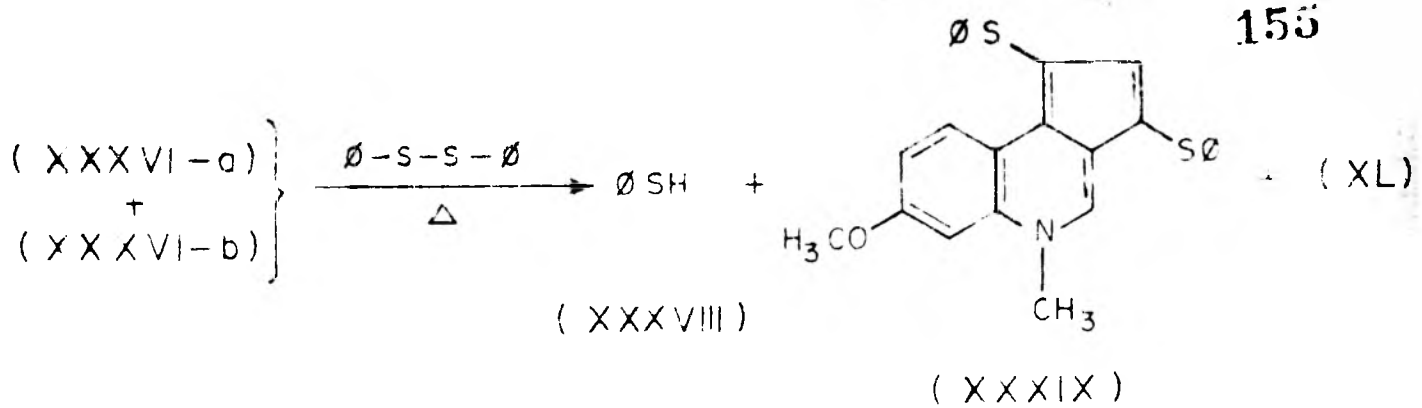
(XXIX) (XXXVII-a) (XXXVII-b)

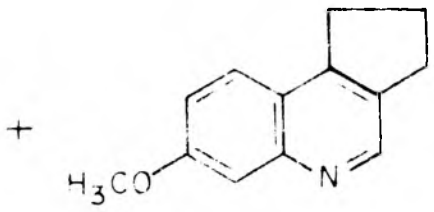
FIG. 34.

separation with excess diphenyl disulphide. Heating the mixture at 170-190° gave thiophenol (XXXVIII) which distilled over and the residue after ether-extraction was chromatographed on a silica gel column for separation of the reaction products.

The red coloured chromatographic fraction gave 1,3-bis(phenyl mercapto)-7-methoxy-5-methyl-5H-α-quinindene (XXXIX) (Fig.35) as golden yellow needles. PMR spectrum of (XXXIX) (Fig.36) indicated broad singlet around 3.73 - 4.0 ppm was assigned to both $O\text{-}CH_3$ and $N\text{-}CH_3$ protons and a multiplet between 7.13 - 9.35 ppm was corresponding to aromatic protons from which a sharp singlet of 10 proton intensity at 7.13 ppm was assigned to the mercaptophenyl protons. PMR spectrum of (XXXIX) in trifluoroacetic acid showed clearly separated $O\text{-}CH_3$ and $N\text{-}CH_3$ signals (Table 1). Infrared spectrum of (XXXIX) (Fig.37) showed a typical hydrocarbon pattern with a sulfur stretching band at 1060 cm^{-1} (Table 2). Electronic spectrum (Fig.38) comprised of a broad band at λ_{max} 445 mμ (log ε 3.42) in the visible region and three bands at 354 (3.45), 290 (3.54) and 246 (2.82) in the UV region. The spectrum was comparable with benzazulene and 1,3-disubstituted azulene. Mass spectral and analytical data supported the structure assignment.

In addition to (XXXIX), an orange crystalline substance (XL) was isolated. The substance (XL) from its mass spectrum (m/e 516) appeared to contain two nitrogen atoms and hence probably was dimeric in nature. PMR spectrum of (XL) (Table 1) displayed two OCH_3 singlets at 4.06 and 4.23 ppm and a singlet





(XXII)

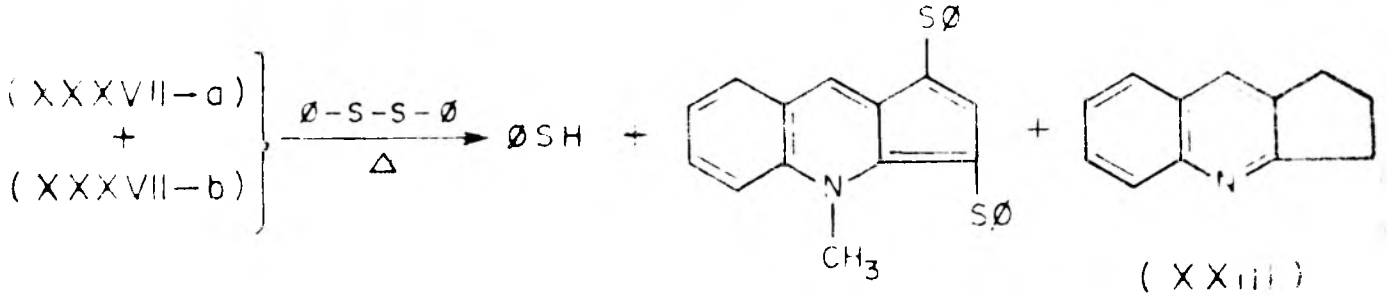
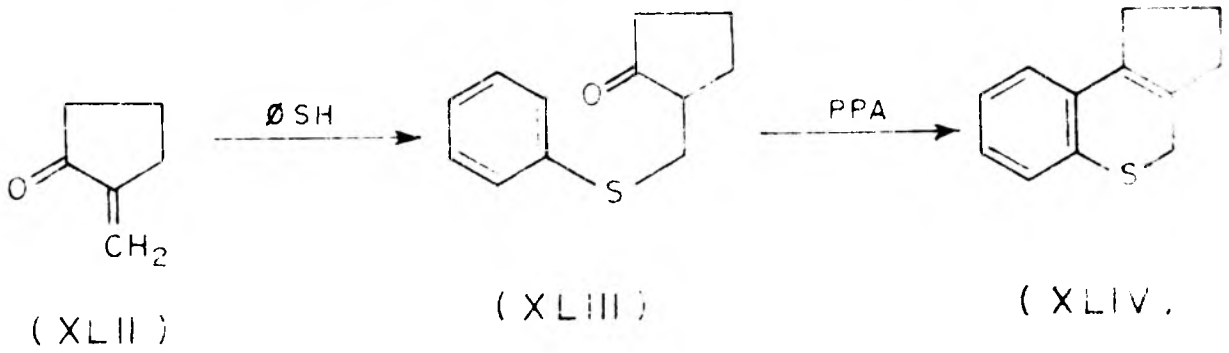


FIG. 35



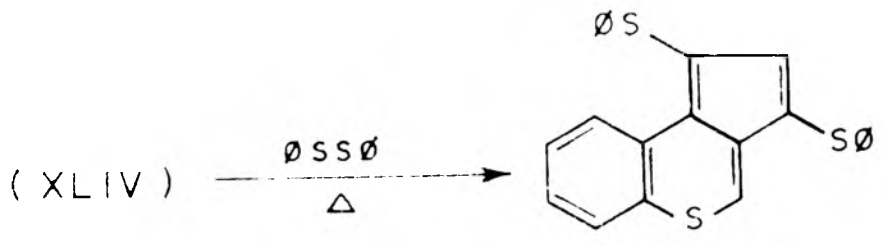


FIG. 39

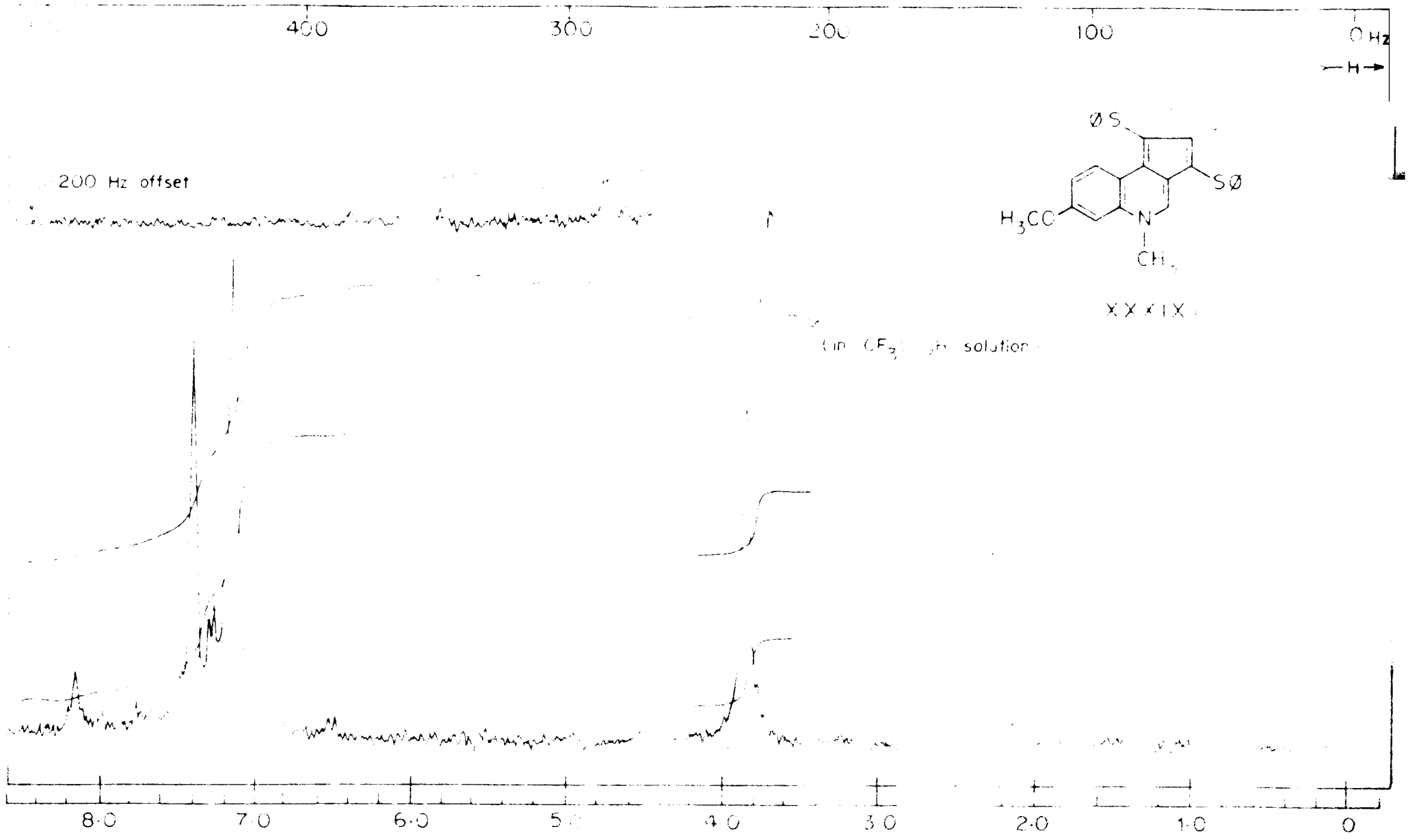


FIG. 36. PMR SPECTRUM OF (XXXI) IN $CDCl_3$

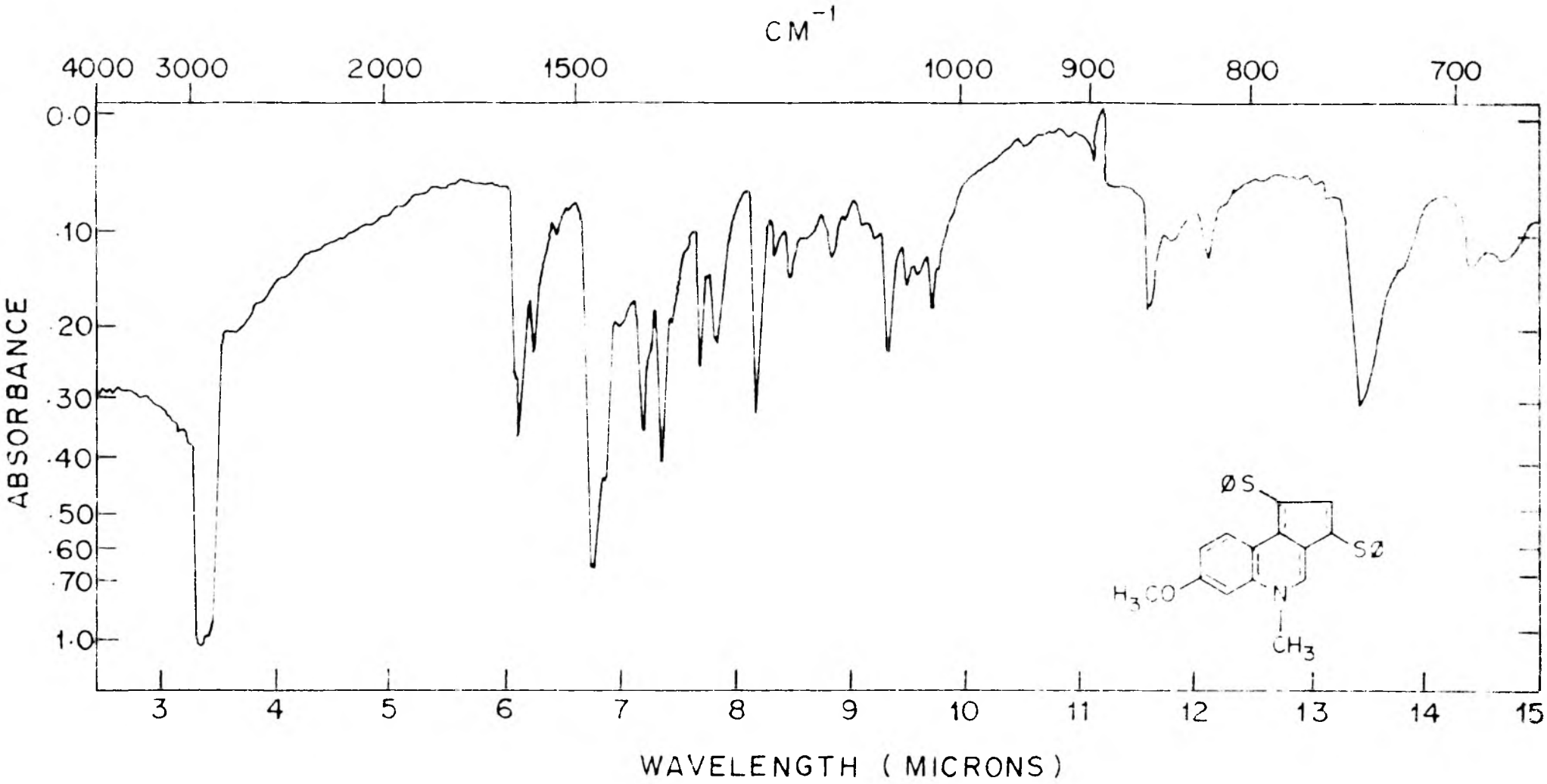
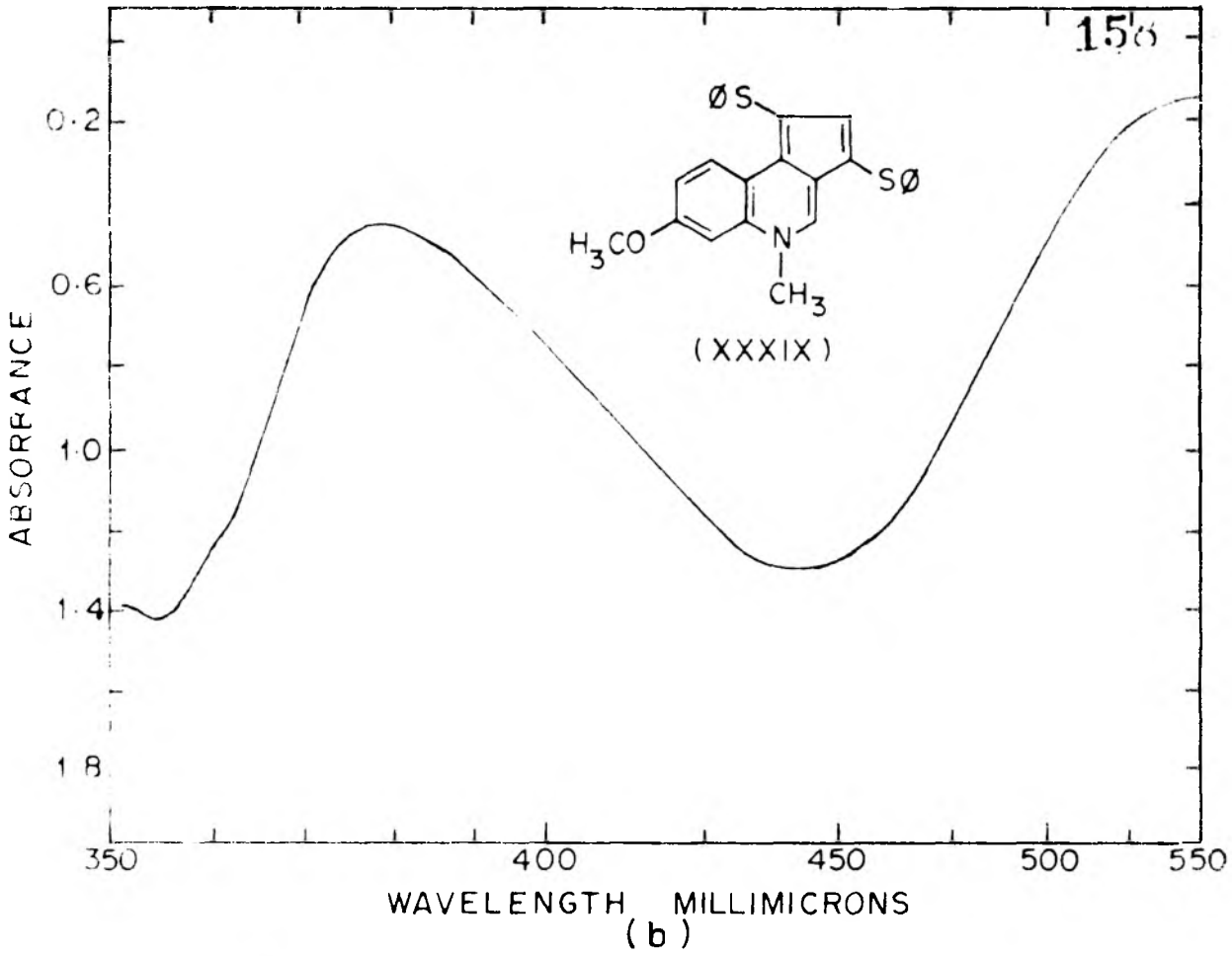


FIG. 37 INFRARED SPECTRUM OF (XXXIX) IN NUJOL



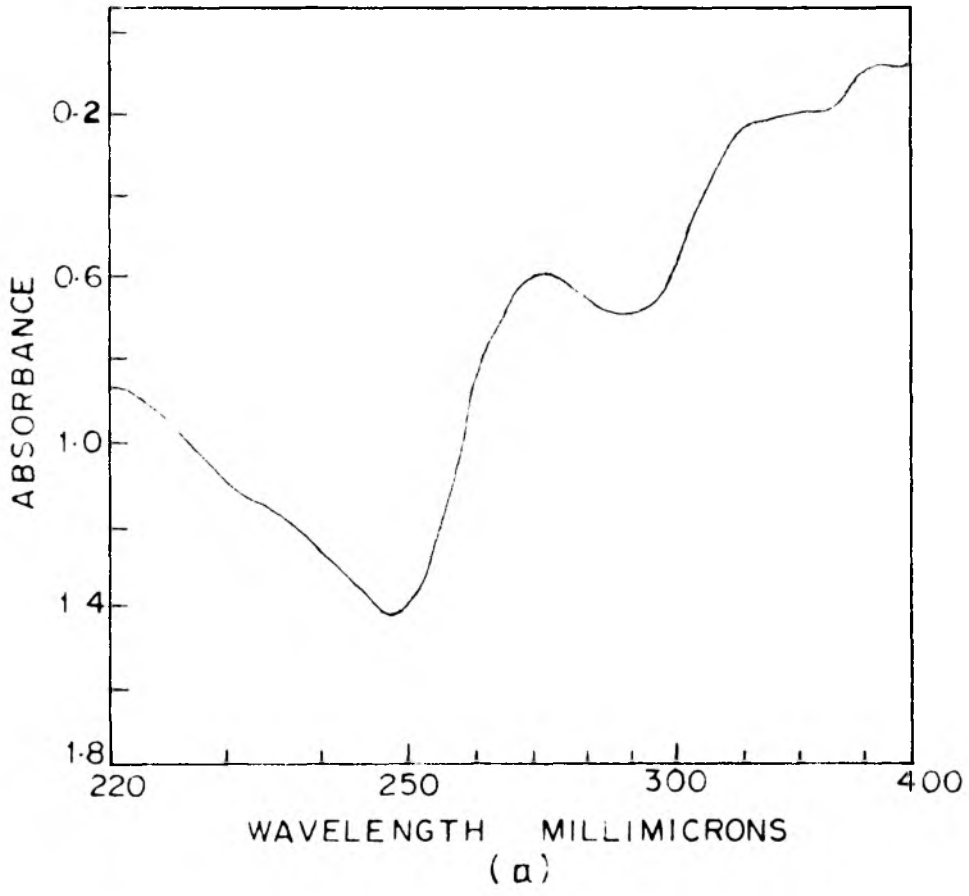


FIG. 38. (a) ULTRAVIOLET AND (b) VISIBLE SPECTRUM OF (XXXIX) IN ETHANOL

at 4.46 ppm was assigned to N-CH_3 protons. Multiplets in methylene and aromatic regions were also observed. Infrared spectrum of (XL) (Table 2) also showed the hydrocarbon pattern nearly identical to that of (XXXIX). UV: λ_{max}^{EtOH} mμ (log ε): 475 (3.46), 335 (3.27), 231 (4.08). Although the nature of the dimeric product (XL) has not been established, the postulated structure would have similarity with the dimeric product obtained by Anderson et al.[54] while treating the pyrindinium methiodide by alkali.

Dehydrogenation of (XXXVI-a + XXXVI-b) by diphenyl disulphide also led to the formation of 7-methoxycyclopenteno[c]-quinoline (XXII) m.p. 103° in low yield. Formation of (XXII) from (XXXVI) occurred due to loss of methane from the dihydro compound (XXXVI).

Cyclopenteno[b]quinolinium iodide (XXIX) on similar reduction with sodium borohydride gave a mixture of isomeric dihydro derivatives (XXXVII-a and XXXVII-b) (Fig.34) which on treatment with diphenyl disulphide as above and further work up yielded 1,3-bis-(phenylmercapto)-4-methyl-4H-cyclopenta [b]quinoline (XLI) (Fig.35). The structure assignment was based on PMR (Table 1), IR (Table 2) and UV (Table 3) spectra and further supported by analytical and mass spectral data. In the above reaction also cyclopenteno[b]quinoline (XXIII) m.p. 59° was formed by the loss of methane from the corresponding dihydro derivative (XXXVII). Dehydrogenation of (XXXVII) with diphenyl disulfide led to polymerisation products although the

reaction was carried out under nitrogen.

Dehydrogenation using diphenyl disulphide was then extended to the cyclopenta[c][1]benzothiapyran system (XLIV).

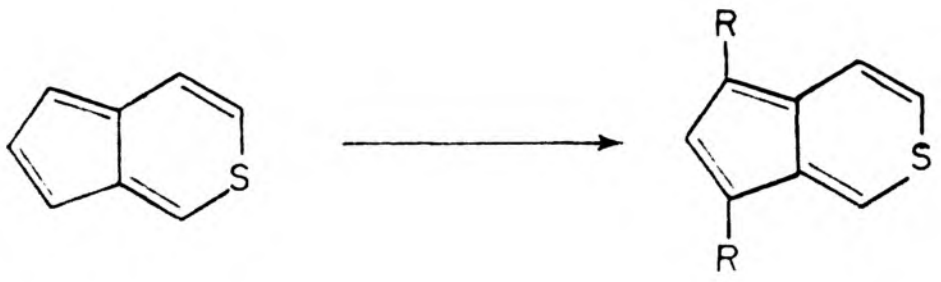
2-Methylenecyclopentanone (XLII)[87] (Fig.39) on condensation with thiophenol gave 2-phenylmercaptomethylcyclopentanone (XLIII) in good yield. Polyphosphoric acid cyclodehydration of (XLIII) furnished cyclopenteno-4H-[c][1]-benzothiopyran (XLIV).

Dehydrogenation of (XLIV) was beset with difficulties. Compound (XLIV) was found stable to catalytic dehydrogenation. Irradiation of (XLIV) in presence of excess diphenyl disulphide was unsuccessful as the reaction led to intractable polymeric products and a red gum. Treatment of (XLIV) with DDQ produced a charge transfer complex from which the starting material (XLIV) was recovered by chromatographic separation on neutral alumina. Compound (XLIV) was however successfully dehydrogenated by heating the mixture of (XLIV) and excess diphenyl disulphide at 170-190^{o} till most of the thiophenol formed distilled over. The residue was further heated at 240^{o}. On work up 1,3-bis(mercapto phenyl)cyclopenta[c][1]benzothiapyran (XLV) was isolated in poor yield. Structure (XLV) was based on PMR (Table 1) and visible (Table 3) spectra. Analytical and mass spectral data also supported the assigned structure.

The positions of electrophilic substitution in (XLV) were identical to the derivatives of cyclopenta[c]thiapyran[71] (Fig.40). Electrophilic substitution reactions on azulene[88],

indene[89], indolizine[90], cyclopenta[d]pyridazine[91] and cyclopenta[b]pyran[79] have been shown to take place at C_1 and C_3 positions corresponding to azulene. It has been recently reported that acylation of 2H-cyclopenta[d]pyridazine[91] with an excess of trifluoroacetic acid at room temperature gave 5,7-bis-trifluoroacetyl derivative (Fig.41). The 1,3-disubstituted derivatives of quinindene and cyclopenta[c][1] benzothiopyran systems obtained above thus conform to earlier observations as regards the sites of electrophilic substitution in these ring systems.

It may be recalled at this stage that when our studies on α- and β-quinindenes[92] were nearing completion, Kholodov et al.[61] reported 1,3-disubstituted derivatives of β-quinindene. Eisch et al.[49] also reported the abortive and successful attempts on the synthesis of β-quinindene derivatives.



R = Cl , Br

R = SCN

R = $COCH_3$

FIG. 40.

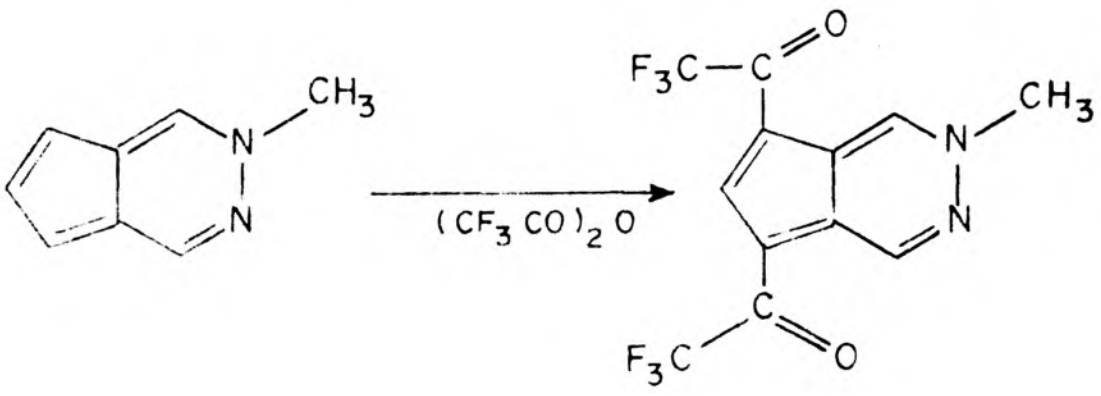


FIG. 41.

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

A. Preparation of precursors

(a) Preparation of 7-methoxy-cyclopenteno[c]quinoline (XXII) and 7-methoxy-5-methyl-cyclopenteno[c]quinolinium iodide (XXVIII) have been described in Chapter II.

(b) Cyclopenteno[b]quinoline (XXIII): Reported procedure[82] for the preparation of (XXIII) was modified as follows:

A mixture of isatin (50 g), cyclopentanone (90 g) aqueous potassium hydroxide (200 ml, 30%) and alcohol (400 ml) was refluxed for 8 hr, followed by vacuum distillation of alcohol. The residue was diluted with water (800 ml) and extracted with methylene chloride (300 ml) to remove impurities. The aqueous layer was treated with activated charcoal, filtered and acidified by excess glacial acetic acid when yellow solid of 2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid separated out. The product was filtered, washed with water and dried (4 hr, 85°, 15 mm). The crude acid (m.p.280°) was directly heated, in a distillation assembly, at a temperature just above its melting point so that the decarboxylated product was simultaneously distilled over. The distillate was further fractionated to give a colorless fraction (b.p. 106°/0.25 mm) which was further dissolved in ether, washed with aqueous sodium carbonate (10%) followed by water and dried over anhydrous sodium sulfate. Removal of ether gave cyclopenteno[b]quinoline (XXIII) (20 g) colorless needles from pet. ether, m.p. 60° (lit.[81] 59-61°). PMR spectrum of

(XXIII) is given in Table 1.

Cyclopenteno[b]quinolinium iodide (XXIX) (m.p. 207°) was prepared as reported[81]. PMR spectrum of (XXIX) is given in Table 1.

B. Dehydrogenation of (XXVIII) and (XXIX) with chloranil

General Method: Methiodide (XXVIII or XXIX) (2 m. mole) and chloranil (4.5 m. mole) were separately dissolved in methylene chloride (total 200 ml). To the methiodide solution was added the filtered solution of chloranil and the mixture kept in freeze (5°) for 48 hr. Removal of the solvent by distillation afforded a residue which was directly adsorbed on neutral alumina (10 g). The reaction products were separated by column chromatography on neutral alumina using benzene, benzene-ethyl acetate and finally ethanol as eluents. Reaction products were then repeatedly crystallised from suitable solvents, filtered and dried. The structures of the products were confirmed by their PMR (Table 1), IR (Table 2) and visible (Table 3) spectral data. Experimental details and elemental analyses are given in Tables 4 and 5 respectively.

C. Dehydrogenation of (XXVIII) and (XXXIX) with DDQ

General Method: Methiodide (XXVIII or XXIX) (2 m. mole) and 2,3-dichloro-5,6-dicyano benzoquinone (4.5 m. mole) were separately dissolved in acetonitrile (total 200 ml). To the filtered solution of DDQ in acetonitrile was added the solution of methiodide. The dark red mixture was refluxed on waterbath for 4-5 hr, when the colour of the solution

TABLE 4 - DEHYDROGENATION OF (XXVIII) AND (XXIX) BY CHLORANIL AND DDQ

Methiodide	Wt/g	Dehydrogenating agent.	Wt/g	Column chromatographic fraction eluted with solvent.	Reaction product	Wt/g	Crystalline shape (solvent)	m.p. °C
(XXVIII)	0.682	Chloranil	1.084	i) Benzene	Chloranil	0.28	Yellow needles (Benzene)	
				ii) Ethyl acetate-benzene (5%)	(XXXIV)	0.09	Pink needles (Ethanol)	227°
				iii) Ethyl acetate-benzene (20-40%)	(XXX)	0.22	Emerald green, rhombic (Methanol-benzene)	>300° (blacken
				iv) Ethanol.	Residue	0.3		
(XXIX)	0.622	Chloranil	1.084	(i),(ii),(iii), (iv) as above.	Chloranil	0.2	Yellow needles (Benzene)	
					(XXXIV)	0.1	Colorless needles (Ethanol)	227° (dec.)
					(XXXII)	0.28	Dark green, rhombic (Benzene-pet.ether)	>340° (dec.)
					Residue	0.2		
(XXVIII)	0.682	DDQ	1.008	i) Ethyl acetate-benzene(40-60%)	DDQ	0.3		
				ii) Ethyl acetate	(XXV)	0.07	Needles (Ethanol)	265° (dec.)
				iii) Methanol-benzene (10-25%)	(XXXI)	0.25	Greenish, rhombic (Acetonitrile-benz.)	290-330° (dec. temp.)
(XXIX)	0.622	DDQ	1.008	(i),(ii),(iii), (iv) as above.	DDQ	0.2		
					(XXV)	0.08	Needles (Ethanol)	263° (dec.)
					(XXXIII)	0.34	Dark green, rhombic (Methanol-benzene)	320° (dec.)

TABLE 5 - ANALYTICAL DATA OF THE PRODUCTS OF DEHYDROGENATION OF (XXVIII) AND (XXIX) BY CHLORANIL AND DDQ

Compd. No.	Molecular formula	Analysis								
		Found				Required				
		C	H	N	Cl	C	H	N	Cl	O
(XXX)	$C_{26}H_{11}NO_5Cl_6$	49.7	2.1	2.1	33.5	49.5	1.8	2.2	33.8	12.7
(XXXI)	$C_{30}H_{11}N_5O_5Cl_2$	60.4	2.1	13.3	11.8	60.8	1.9	13.5	12.0	11.8
(XXXII)	$C_{25}H_9NO_4Cl_6$	49.7	1.8	2.2	35.2	50.0	1.5	2.3	35.5	10.7
(XXXIII)	$C_{29}H_9N_5O_4Cl_2$	61.5	1.9	12.4	12.4	61.9	1.6	12.5	12.7	11.4

changed to yellowish-green. Removal of the solvent by distillation afforded a residue which was directly adsorbed on neutral alumina. Reaction products were separated by column chromatography on neutral alumina using successively benzene, benzene-ethyl acetate and finally benzene-methanol as eluents. The products were repeatedly crystallised from suitable solvents, filtered and dried. The structures of the products were confirmed by PMR (Table 1), IR(Table 2) and visible (Table 3) spectra. Experimental details and elemental analyses are given in Tables 4 and 5 respectively.

D. Dehydrogenation using diphenyl disulphide

Prior to dehydrogenation, the methiodides were reduced by sodium borohydride.

Step (a): Sodium borohydride reduction of methiodides (XXVIII) and (XXIX)

To a solution of methiodide (XXVIII or XXIX) (0.01 mole) in water (400 ml) was added ether (400 ml). With stirring, excess sodium borohydride (5 g) was added in portions over a period of 0.5 hr, till the yellow aqueous layer appeared colourless and the dihydro derivative (XXXVI or XXXVII) was dissolved in ether. The ether layer was removed, washed with water and dried over anhydrous sodium sulfate. As the dihydro derivatives[83] were extremely sensitive towards heat and light, these were immediately subjected for dehydrogenation.

Step (b): Dehydrogenation of (XXXVI or XXXVII) by diphenyl disulphide

To the ethereal solution of the dihydro derivative

TABLE 6 - DEHYDROGENATION OF (XXVIII) AND (XXIX) BY DIPHENYL DISULPHIDE

Starting methiodide	Wt/g	Borohydride reduced product in ether.	Diphenyl disulphide Wt/g	Column chromatographic fraction eluted with solvent.	Reaction product	Wt/g	Crystalline shape (solvent)	m.p./b.p. °C
(XXVIII)	3.41	(XXXVI-a) + (XXXVI-b)	8.72	-	(XXXVIII)	2.25	Yellowish liquid.	170-180° (Distillation temp.)
				Pet. ether	Diphenyl disulphide.	2.5	White needles (pet.ether)	59°
				Benzene	(XXXIX)	0.8	Golden yellow needles (benzene-pet. ether).	206°
				Ethyl acetate-benzene (10%)	(XXII)	0.1	Colorless needles (Pet.ether)	103°
				Ethyl acetate-benzene (20%)	(XL)	0.8	Orange neddles (ethanol)	284°
(XXIX)	3.11	(XXXVII-a) + (XXXVII-b)	8.72	-	(XXXVIII)	2.5	Yellowish liquid.	170-180°
				Pet.ether	Diphenyl disulphide	2.0	White needles (pet.ether)	60°
				Benzene-Pet.ether (30%)	(XLI)	0.5	Orange needles (pet.ether)	142°
				Ethyl acetate-benzene (2%)	(XXIII)	0.12	Colorless needles (pet. ether)	59°
				Ethyl acetate-benzene (30%)	Blue compound	0.01	-	Unknown.

TABLE 7 - ANALYTICAL DATA OF THE PRODUCTS OF DEHYDROGENATION OF (XXVIII) AND (XXIX) BY DIPHENYL DISULPHIDE

Compound No.	Molecular formula	Analysis								
		Found				Required				
		C	H	N	S	C	H	N	S	O
(XXXIX)	$C_{26}H_{21}NOS_2$	73.5	4.6	3.1	15.3	73.1	4.9	3.3	15.0	3.8
(XL)	-	77.0	5.9	3.2	1.5	Structure not established.				
(XLI)	$C_{25}H_{16}NS_2$	76.0	4.4	3.5	15.9	76.1	4.1	3.6	16.2	-

(XXXVI or XXXVII) was added excess diphenyl disulphide (0.04 mole) and the ether was removed by distillation. The reaction mixture was heated in a distillation bulb-tube in an air-bath. Temperature of bath was held between 160-180° for 1-2 hr with mild suction (20 mm) when most of the thiophenol was distilled over. Heating was further continued at 230-240° for 1-2 hr when evolution of thiophenol ceased. The cooled reaction mixture was dissolved in ether and the blood-red ether extract was washed with aqueous sodium hydroxide (10%), followed by water and dried over anhydrous sodium sulfate. Removal of ether gave a residue which was adsorbed on silica gel (10 g). Reaction products were separated by column chromatography on silica gel using pet.ether, pet. ether-benzene and benzene-ethyl acetate as eluents. Products were then crystallised from suitable solvents, filtered and dried. Structures of the products were confirmed by PMR (Table 1), IR (Table 2) and UV (Table 3) spectra. Experimental details and elemental analyses are given in Tables 6 and 7 respectively.

E. Experiments leading to cyclopenta[c][1] benzothiapyran derivative (XLV)

(a) 2-Methylenecyclopentanone (XLII): Reported procedure[87] was followed. Starting from cyclopentanone (69 g), dimethyl amine hydrochloride (86 g) and p-formaldehyde (24 g) was obtained a red liquid (34 g) which when vacuum distilled at 50-70°/15 mm gave (XLII) (18 g, 23%).

(b) 2-(phenylmercapto)methyl cyclopentanone (XLIII)

To the solution of (XLII) (4.8 g, 0.05 mole) and thiophenol (5.5 g, 0.05 mole) in dry benzene (75 ml) was added piperidine (4 drops) as catalyst and the mixture was refluxed on water bath for 14 hr. Removal of benzene by distillation gave a red liquid which was vacuum distilled to remove unreacted thiophenol and diphenyl disulphide at 120°/6 mm. The residue was further distilled under high vacuo and the fraction distilled at 120°/0.1 mm gave (XLIII) (8 g, 78%) (Found: C, 70.2; H, 6.5; S, 15.3. Calcd. for $C_{12}H_{14}SO$: C, 69.9; H, 6.8; S, 15.5%) M^+ at m/e 206. Structure (XLIII) for the reaction product was confirmed by its PMR (Table 1) spectrum.

(c) 4H-Cyclopenteno[c][1]benzothiopyran (XLIV)

A mixture of (XLIII) (4 g) and PPA [prepared from P_2O_5 (32 g) and H_3PO_4 (20 ml)] was stirred at 70° for 5 hr and left overnight. The reaction mixture, after warming, was poured on crushed ice and extracted with chloroform. The chloroform layer was washed with aqueous bicarbonate solution, followed by water and dried over anhydrous calcium chloride. Removal of chloroform by distillation gave a thick red oil which when vacuum distilled gave a fraction between 120-30°/ 0.1 mm containing (XLIV) (2 g, yield 55%) (Found: C, 76.2; H, 6.1; S, 16.8. Calcd. for $C_{12}H_{12}S$: C, 76.6; H, 6.4; S, 17.0%). M^+ at m/e 188. Structure (XLIV) for the reaction product was confirmed by its PMR (Table 1) spectrum.

(d) Dehydrogenation of (XLIV) by diphenyl disulphide

Dehydrogenation of (XLIV) (1.9 g) by excess diphenyl disulphide (8.7 g) was done according to the procedure described earlier for the dehydrogenation of (XXXVI or XXXVII) by diphenyl disulphide. Reaction products were separated by column chromatography and the major fraction eluted by benzene gave (XLV) (0.050 g), red needles from benzene-pet. ether, m.p. 110° (Found: C, 71.6; H, 4.2; S, 23.7. Calcd. for $C_{24}H_{16}S_3$: C, 72.0; H, 4.0; S, 24.0%). M^+ at m/e 400. Structure (XLV) was confirmed by PMR (Table 1) and visible (Table 3) spectra. Low yield is due to decomposition of the reaction mixture. Polymeric products could not be avoided even by using nitrogen flush in the dehydrogenation.

F. Attempts for introduction of unsaturation

(a) Bromination and dehydrobromination of (XXII)

A mixture of (XXII) (0.6 g), colorless pure N-bromosuccinimide (0.54 g) and benzoyl peroxide (0.05 g) in dry carbon tetrachloride (75 ml) was heated in an oil bath at reflux temperature (75°) for 1 hr. After cooling, the mixture was filtered twice to remove succinimide. The filtrate when concentrated by distillation under vacuum gave a residue which was extracted with pet. ether (3 x 50 ml). Combined extracts on evaporation afforded yellow bromo-derivative (XXVI) (0.6 g, 72%) which was found sensitive towards heat and light as it rapidly turned brown. Hence it was immediately subjected for dehydrobromination.

Mono-bromo derivative (XXVI) (0.55 g) was separately added in portions to the mixture of triethylamine (0.2 g) in dry DMF (15 ml), collidine (0.25 g) in DMF (15 ml), $LiCO_3$ (0.3 g) in DMF (20 ml) and sodium methoxide (0.3 g) in methanol (15 ml). The mixtures were left under nitrogen for 24 hr at room temperature and then worked up. However, the resulting oily mass showed three to four spots on TLC and it was impractical to isolate the product by PLC as the polymeric products resulted.

(b) Catalytic dehydrogenation of (XXII) and (XLIV)

A mixture of (XXII) (0.2 g) and 10% Pd-C (0.1 g) in p-cymene (50 ml) was heated in an oil bath under vigorous reflux (b.p. 177°) for 48 hr. After cooling, the catalyst was removed by filtration and washed with ethyl acetate. Removal of solvent from the filtrate gave back the starting material (XXII).

Similarly a mixture of (XLV) (0.2 g) with 10% Pd-C (0.1 g) in p-cymene (50 ml) after reflux for 24 hr and work up afforded starting material.

(c) Charge-transfer complexes of (XXII) and (XLIV) with DDQ

A mixture of (XXII) (0.199 g, 1 m. mole) and 2:3-dichloro-5:6-dicyano-benzoquinone (0.227 g, 1 m. mole) in dry benzene (30 ml) was refluxed on water bath for 1 hr, when the solid was separated out. After cooling, the solid was filtered, washed with benzene and dried. Solid (XXVII) (0.320 g, 80%) m.p. 180-184° (dec.) was characterised by PMR (Table 1), IR (Table 2) and UV (Table 3) data. When (XXVII) was treated with aqueous sodium hydroxide (10%) and subsequent ether

extraction afforded starting material (XXII).

A solution of (XLIV) (0.376 g, 2 m. mole) in methylene chloride (25 ml) was mixed with the solution of DDQ (0.908 g, 4 m. mole) in methylene chloride (150 ml), when the color of the mixture immediately changed to dark green. After keeping the reaction mixture for 24 hr, solvent was removed by distillation. The residue when column chromatographed on neutral alumina gave starting material (XLIV) (0.3 g) as red oil.

(d) Photolysis of (XLIV) in the presence of diphenyl disulphide

A mixture of (XLIV) (1.99 g) and diphenyl disulphide (4.1 g) in thiophene-free dry benzene (400 ml) was kept under nitrogen and with stirring it was cooled in an ice-bath. The reaction mixture was irradiated for 13 hr by the ultra-violet light obtained from a medium pressure mercury vapour lamp. The solvent was removed by distillation and the residue was dissolved in ether. The ether layer was washed with aqueous sodium hydroxide (10%) followed by water and dried over anhydrous calcium chloride. After removing ether by distillation the residue was adsorbed on neutral alumina. Reaction products were separated by column chromatography on neutral alumina using pet. ether and pet. ether-benzene as solvents. However, no desired product of dehydrogenation was obtained, instead only red gummy material and decomposition products were resulted.

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SUMMARY

CHAPTER I SPECTROSCOPIC INVESTIGATION OF 2-ARYLAMINO-METHYLENECYCLOALKANONES

Recent work on the spectroscopic studies of various equilibria involving H-bonding and solvent effect on the tautomeric equilibria with special reference to dimethyl sulfoxide has been discussed in the introductory part.

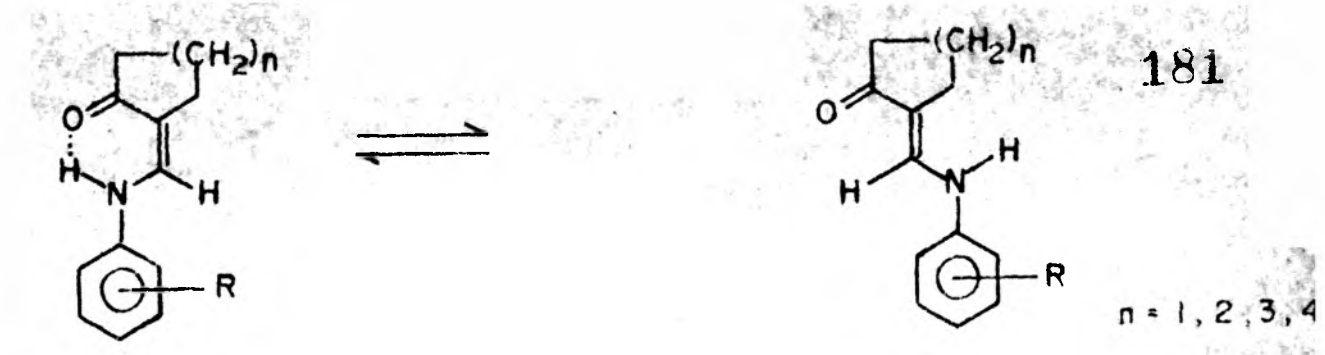
Present work is connected with the study of the tautomeric equilibria in the set of compounds (I) (Fig.1).

The PMR and IR studies of these compounds revealed that they existed mostly as cis-ketoamine tautomers (A) as solids and when dissolved in various solvents. Only in dimethyl sulphoxide, these compounds get converted into the trans-ketoamine isomer (D). Various factors affecting the tautomerism and cis-trans isomerisation in solvents like DMSO have been studied.

CHAPTER II SYNTHESIS OF TRICYCLIC AND TETRACYCLIC NITROGEN HETEROCYCLICS

The introductory part deals with a review on the synthetic methods, properties and uses of polymethylene-quinolines.

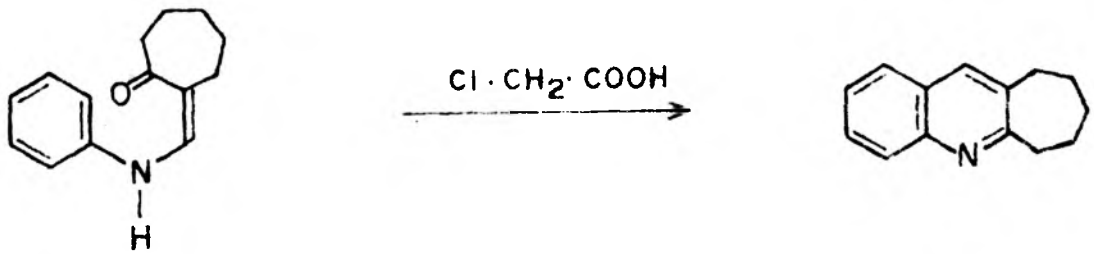
Cyclodehydration of cis-2-arylaminomethylene cycloalkanones (I) (Fig.1) by interaction with arylamine-hydrochloride, fused zinc chloride and absolute ethanol, lactic acid and chloroacetic acid yield the linear tri- and tetra-cyclic nitrogen containing heterocyclic compounds.

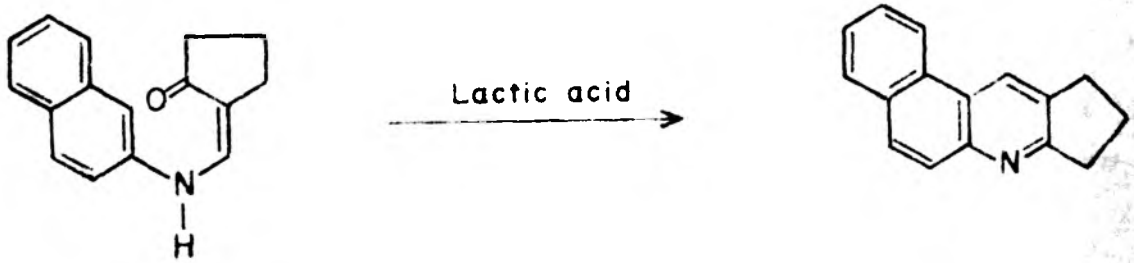

(CH2)n
O
H
N
H
R
n = 1, 2, 3, 4

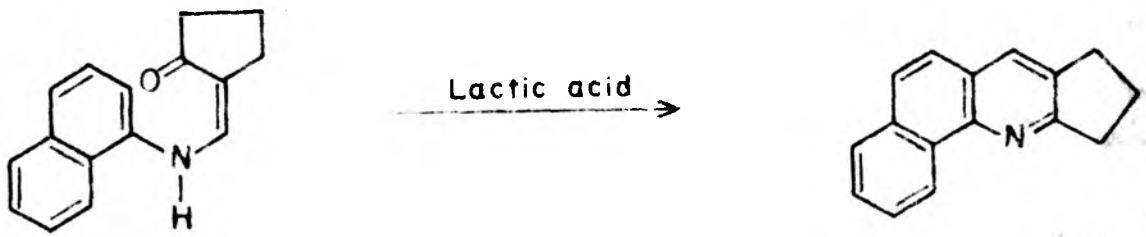
(I) (A) (D)

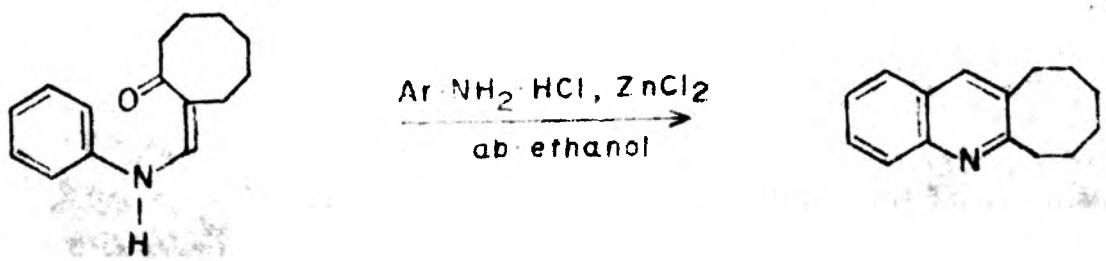
FIG·1


(CH2)n
O
H3CO
N
H
PPA
n = 1,3,4


O
N
H
Cl·CH2·COOH


O
N
H
Lactic acid


O
N
H
Lactic acid


O
N
H
Ar·NH2·HCl, ZnCl2
ab ethanol

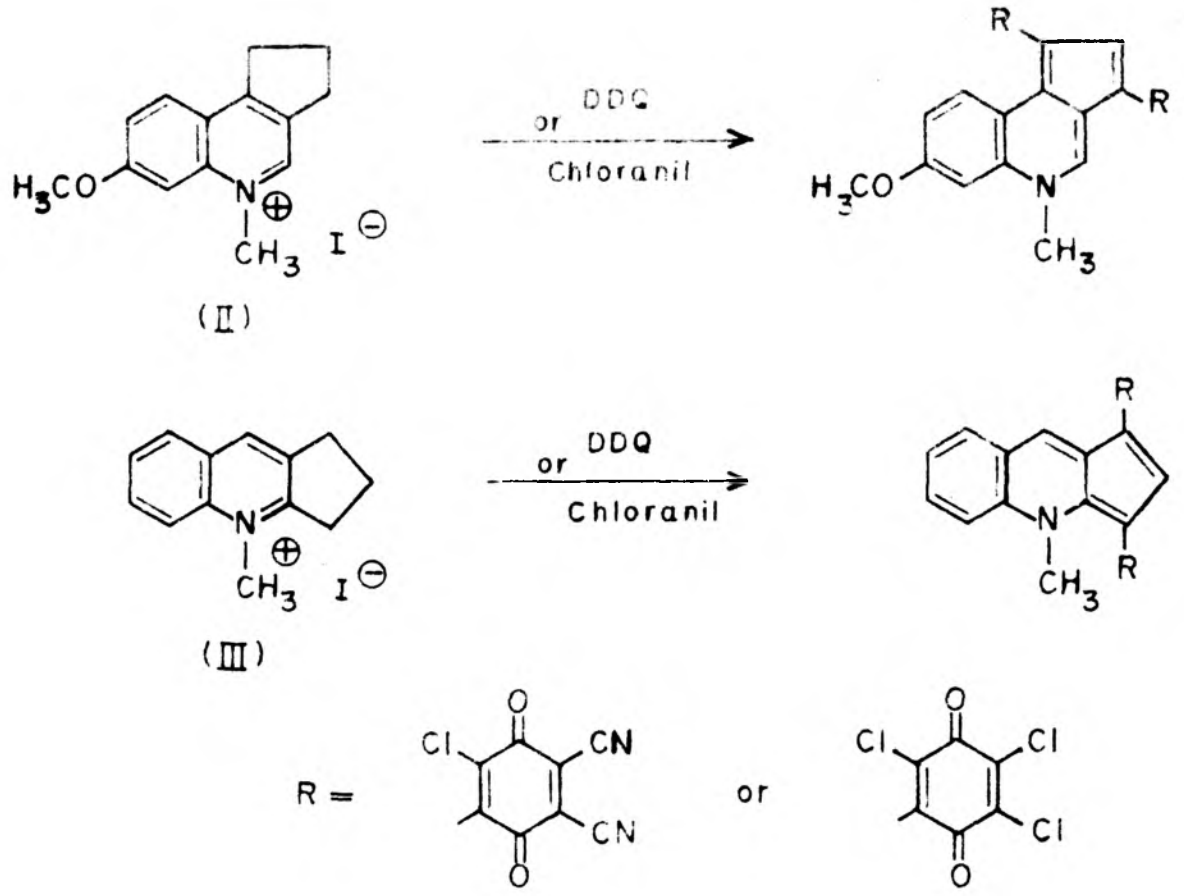
The formation of these compounds involves a rearrangement reaction[1] described earlier by us. When PPA is used for cyclodehydration, no rearrangement occurs and the products are the normally expected angular heterocyclics. This Chapter thus includes the account of the synthesis of quinolines containing fused cyclopenteno, cyclohepteno, and cyclooöcteno rings[2] (Fig.2).

CHAPTER III SYNTHESIS OF QUININDINE DERIVATIVES : ISOELECTRONIC ANALOGUES OF BENZAZULENES[3]

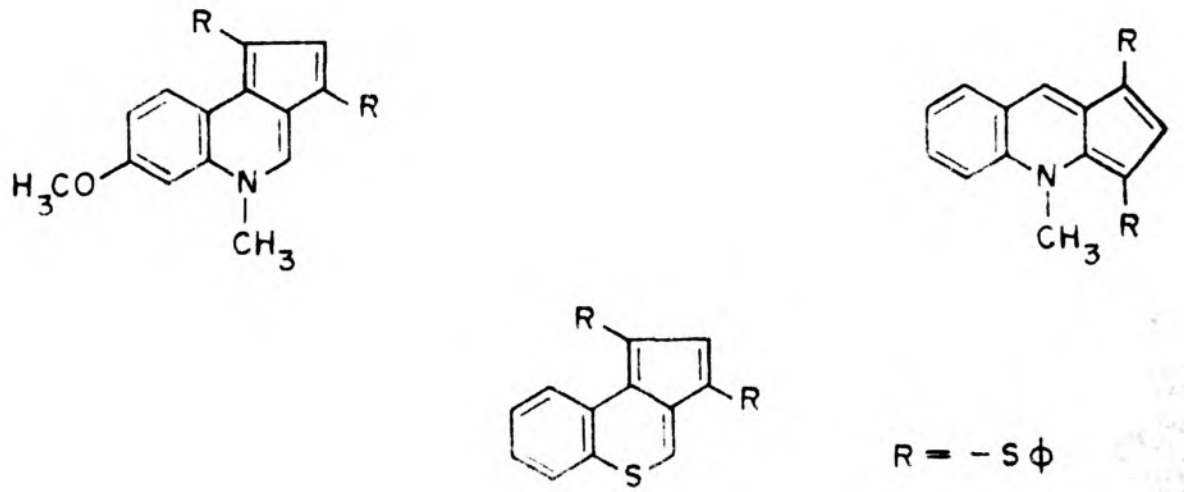
In this chapter a review on the chemistry of Heterocyclic Azulenes (Pseudoazulenes) is presented with an account of the synthetic work on the quinindine derivatives.

5-Methyl-5H-α-quinindine and 4-methyl-4H-δ-quinindine are heterocyclic non-benzenoid aromatic compounds resembling benzazulene. Derivatives of above were prepared by successful dehydrogenation of 7-methoxy cyclopenteno[c] quinolinium methiodide (II) and cyclopenteno[b] quinolinium methiodide (III) using DDQ and chloranil (Fig.3). This results in 1,3-disubstituted quinindine derivatives. This represents unique example of dehydrogenation of a hydroaromatic heterocyclic quaternary salt by chloranil and DDQ. The stable heterocyclic cationoid ring systems have been converted to non-alternant 14-π electron system wherein highly reactive aromatic substrate formed by dehydrogenation undergoes electrophilic substitution.

Another method to obtain the above quinindine derivatives consisted of the prior reduction of the methiodides



FIG·3



FIG·4

to the corresponding dihydro derivatives which were further dehydrogenated by heating with diphenyl disulphide. This also resulted in the formation of 1,3-disubstituted quinindines[4] (Fig.4).

Both these sets of experiments indicate that the parent quinindines are extremely reactive species and are capable of undergoing electrophilic substitution reactions preferably in 1,3 positions. This substitution pattern is well supported by HMO calculations on 14 - π^5 and 10 π^6 electron systems.

The study was then extended to the cyclopenta[c][1] benzothiopyran system to give 1,3-disubstituted derivative (Fig.4).

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