STUDIES IN HETEROCYCLIC CHEMISTRY

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FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
(CHEMISTRY)

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19 May 1975

C O N T E N T S

N O T E S

1. Melting points are uncorrected.
2. The cyclisation temperatures reported presently correspond to oil bath temperatures.
3. The IR spectra were taken in nujol mull using Perkin-Elmer Infracord 137 spectrometer. The IR values are recorded in cm^{-1}.
4. The PMR spectra were recorded on a Varian T-60 spectrometer in DMSO/CCl_4/$CDCl_3$/Acetone-d_6/Benzene-d_6 solutions taking TMS as internal standard.
5. Mass spectra were recorded on CEC 21-110 B double focussing spectrometer, using direct inlet systems.
6. UV spectra were recorded in ethanol on a Perkin-Elmer model 350 spectrophotometer and the values are quoted as λ_{max} in mμ and log ε in parenthesis.

CHAPTER I

REVIEW OF CARCINOGENESIS BY NITROGEN CONTAINING HYDROCARBONS

Carcinogenesis can be defined as the process whereby normal tissue is transformed into cancer tissue. Willis [1] defined cancer as "A tumour in an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after the cessation of the stimuli which evoked the change".

Polycyclic Aromatic Hydrocarbons as Carcinogens

It was established about forty years ago that certain polycyclic hydrocarbons have the property of inducing cancerous growths, either when painted on the skin or injected into the animal concerned. Since then attempts to accumulate biological data and the study of the reactions and properties of polycyclic aromatic compounds as carcinogens have continued unabated. Various reviews [2-11] in this field have appeared. Hartwell [12] has published a "Survey of Compounds Which Have Been Tested for Carcinogenic Activity".

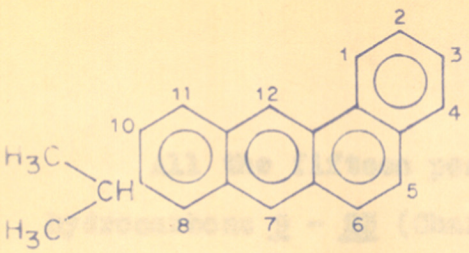
The names and numberings laid down by Chemical Abstracts (also used by the Ring Index) are employed throughout.

Amongst the early synthetic hydrocarbons, dibenz(a,h)anthracene 10 (Chart 2a), 5-methyl derivative of dibenz(a,h)anthracene and 9- isopropylbenz(a)anthracene 1 (Chart 1) were tested by application in benzene solution to the skin of mice. After lengthy latent periods, tumours were produced by all the three compounds [13,14]. A potent cancer producing hydrocarbon benz(a)pyrene 9 was isolated from coal tar [15]. Another potent carcinogenic hydrocarbon, 3-methylcholanthrene 2 was produced by a series of degradations from deoxycholic acid [16].

Since compounds 2, 9, 10 may be considered as derivatives of benz(a)anthracene, the latter ring system has been thoroughly investigated. Other tricyclic, tetracyclic and pentacyclic systems have all also been studied.

Among the unsubstituted hydrocarbons, only a very limited number of the basic structures are carcinogenic. Less complex hydrocarbons with less than four condensed benzene rings (benzene, naphthalene, anthracene and phenanthrene) are inactive.

Of the six possible tetracyclic hydrocarbons 3 - 8 (Chart 1), only benzo(c)phenanthrene 3 has been shown to possess activity. Tumours have been observed [17,18] with benz(a)anthracene 4 and to a very small extent with chrysene 6.



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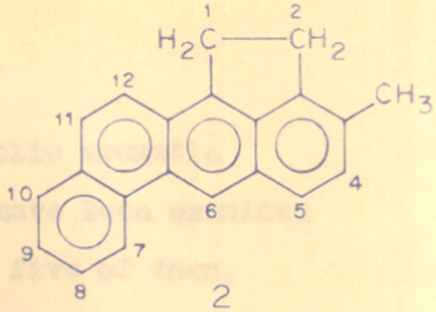

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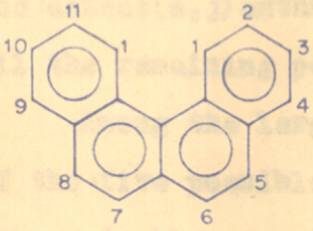

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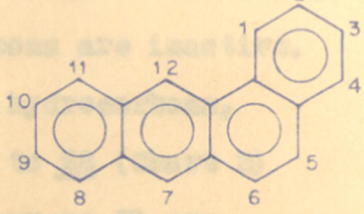

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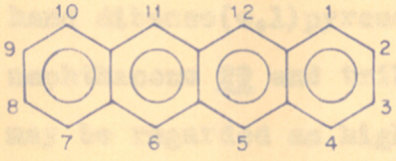

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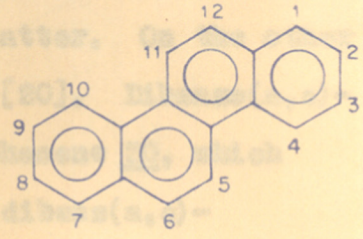

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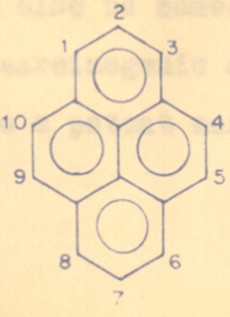

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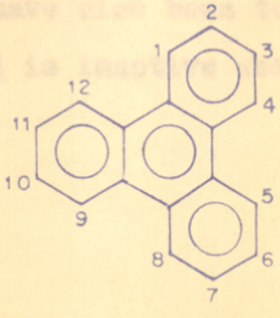

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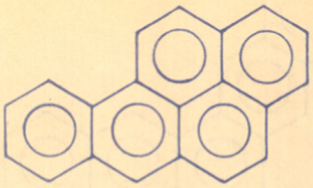
CHART – 1

All the fifteen possible pentacyclic aromatic hydrocarbons 9 - 23 (Chart 2a and 2b) have been examined for their carcinogenic activity. Only five of them, benzo(a)pyrene 9 dibenz(a,h)anthracene 10 (mentioned earlier) dibenzo(a,i)phenanthrene 11, dibenzo(a,c)phenanthrene 12 and dibenz(a,j)anthracene 13 have been found to be active. All the remaining pentacyclic hydrocarbons are inactive.

Among the larger size polycyclic hydrocarbons, of the five possible dibenzopyrenes 24 to 28 (Chart 3) dibenzo(a,h)pyrene 24 and dibenzo(a,i)pyrene 25 are highly potent in inducing subcutaneous tumours. Lacassagne et al. [19] have shown that dibenzo(a,l) - and dibenzo(a,c)pyrene 26, 27 are also potent sarcomatogens, the former being less active than the latter. On the other hand dibenzo(e,l)pyrene 28 is inactive [20]. Dibenzo(a,c)-naphthacene 29 and tribenzo(a,c,j)naphthacene 30, which may be regarded as higher benzologs of dibenz(a,c)-anthracene 18 are not sarcomatogenic in situ, but have produced ovarian tumours and leukemia in mice [20]. Pyranthrene 31 and dibenzo(h,r,s,t)pentaphene 32 [can also be named as tribenzo(a,e,i)pyrene] have also been tested for carcinogenic activity. Compound 31 is inactive whereas 32 is a potent carcinogen [21,22].



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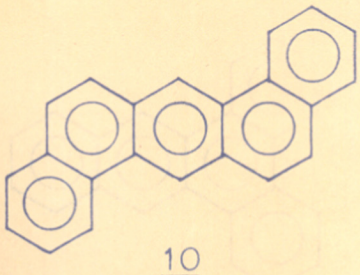

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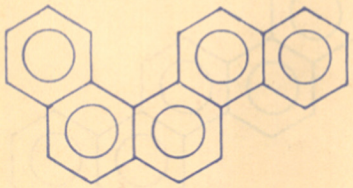

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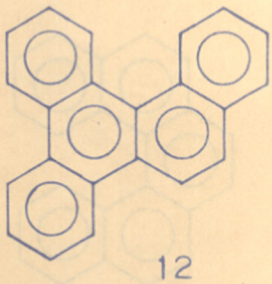

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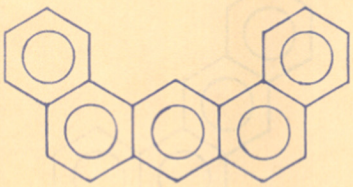

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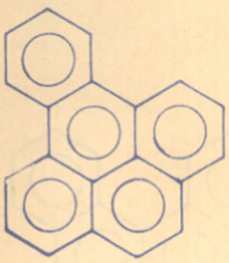

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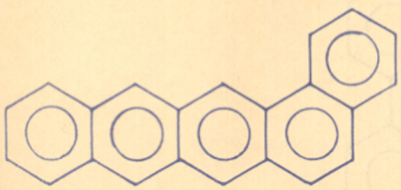

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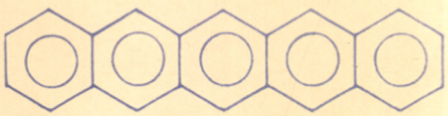

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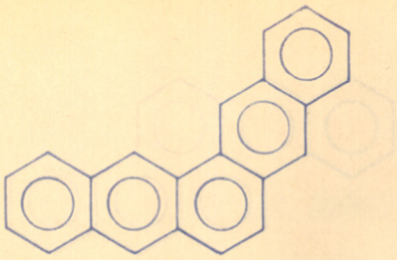
CHART – 2 a



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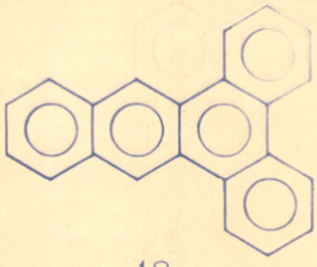

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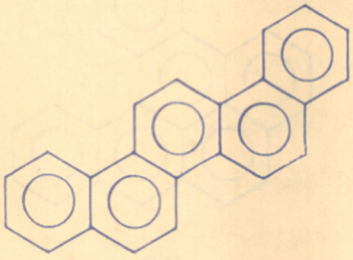

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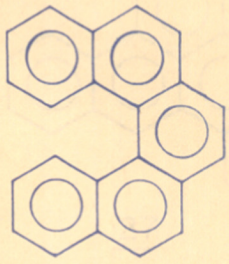

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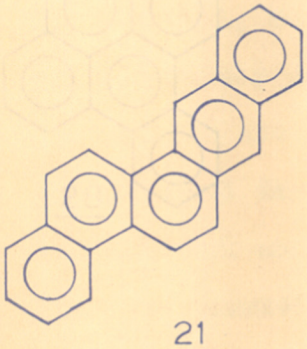

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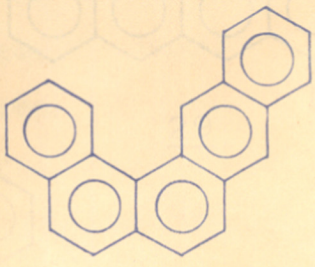

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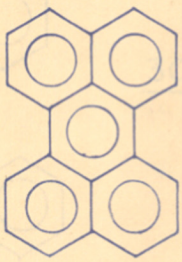

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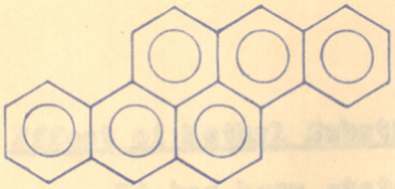
CHART – 2 b.



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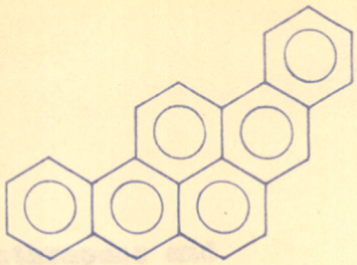

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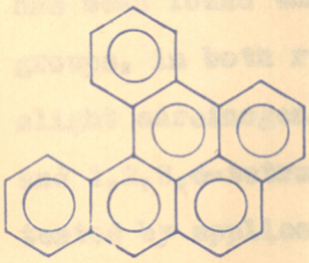

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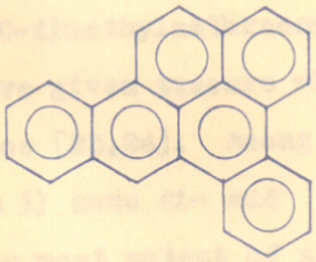

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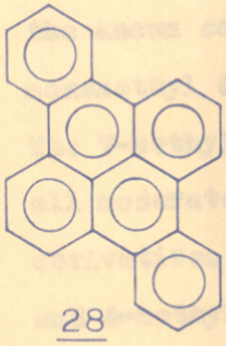

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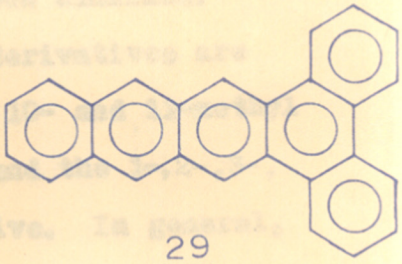

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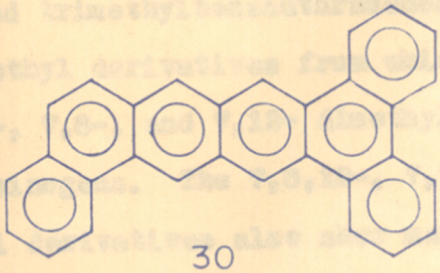

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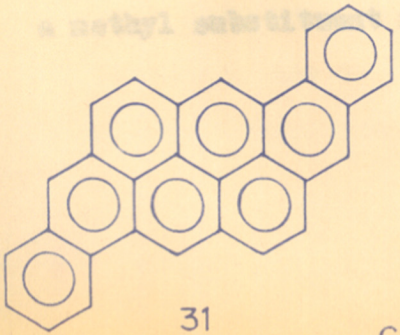

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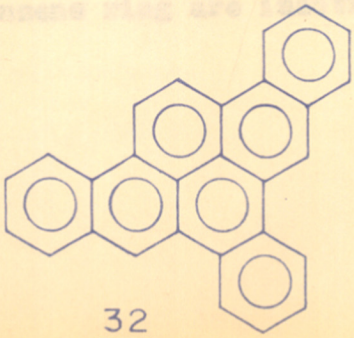

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CHART – 3

Effect of Methyl Substituents

It has been stated earlier that anthracene and phenanthrene have been shown to be inactive. However, it has been found that the introduction of substituent methyl groups, in both ring systems leads to compounds having slight carcinogenic activity. Both 9,10-dimethylanthracene and 1,2,3,4-tetramethyl phenanthrene have given tumours when tested by application to the skin of mice [23,24]. Among the two benzanthracenes, 4 and 5 (Chart 1) some di- and trimethyl derivatives of 4 are among the most potent of all the known carcinogens [11]. There are twelve possible monomethyl derivatives, and all have been examined. The 7-methyl, 8-methyl, and 12-methyl derivatives are all moderately potent; the 5-, 6-, 9-, 10- and 11-methyl derivatives are all weak carcinogens, and the 1-,2-,3-, and 4-methyl derivatives are all inactive. In general, the dimethyl and trimethylbenzanthracenes are more active than the monomethyl derivatives from which they are derived. 8,12-, 7,8-, and 7,12- dimethyl benz(a)anthracene are potent carcinogens. The 7,8,12-, 7,9,12-, and 7,8,9-trimethyl derivatives also show marked carcinogenic activity. However, all the dimethylbenzanthracenes having a methyl substituent in the angular benzene ring are inactive.

All the simple derivatives of 5 that have been tested have failed to induce tumours.

Out of the four benzophenanthrenes, benzo(c)-phenanthrene 3, benzo(a)phenanthrene 6 (chrysene), benzo(d,e,f)phenanthrene 7 (pyrene) and benzo(l)phenanthrene 8 (triphenylene), and the 1-, 2-, 3-, 7-, and 8-methyl derivatives of 3 show carcinogenic activity. The 6-methyl and 5,6-dimethyl derivatives of 6 are moderately active. Derivatives of 7 and 8 have been found to be inactive.

It has been observed that whereas methyl substitution in tetracyclic compounds often enhances activity, the result of similar substitution in pentacyclic compounds are somewhat irregular [25]. Thus 14-methyl dibenz(a,h)anthracene is more active than parent ring system 10, but 7,14-dimethyl derivative is much less so. Heidelberger et al. [26] have, however, demonstrated that this compound is also a strong carcinogen. On the other hand 7,14-dimethyl derivative of dibenz(a,j)anthracene is much more active than the unsubstituted compound 13. Again, although dibenzo(a,c)phenanthrene 12 is an active carcinogen, its 5-methyl, and 6-methyl derivatives appear to be inactive. Several methyl derivatives of benzo(a)-pyrene 9 have been tested. The 8- and 9-methyl derivatives are inactive, the 7- and 5-methyl derivatives appear to be less active than the parent compound, and the

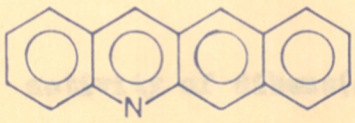
6-methyl and 2-methyl derivatives have been shown to possess approximately the same activity as the parent compound.

Polycyclic Aza-Heterocyclic Compounds as Carcinogens

The heterocyclic nitrogen containing compounds (aza-analogues) which are structurally related to the polycyclic hydrocarbons described above also possess the essential features of aromaticity. The $-\overset{|}{\underset{H}{C}}=$ atoms in these hydrocarbons are isoelectronic with the polycyclic aza- ($-N=C-$) linkage. It appeared therefore likely that aza-analogues of carcinogenic hydrocarbons may also exhibit carcinogenic activity.

Acridine and its homologues appeared to be of no great interest from the point of view of carcinogenic activity [27,28]. However, that was not true of the angular monobenzacridines and dibenzacridines. Amongst the existing three groups of monobenzacridines, the linear benz(b)acridine 33 (Chart 4) and its derivatives have not shown any activity. On the other hand, in the angular benz(a)acridine 34 and particularly the benz(c)acridine 35 series, a considerable number of carcinogenic compounds have been found.

In the dibenzacridine series, 36 - 42 (Chart 4), dibenz(a,h)acridine 36 was found to be less active than that of the homologous hydrocarbon. Conversely the carcinogenic



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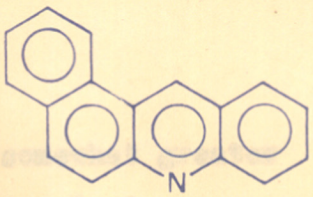

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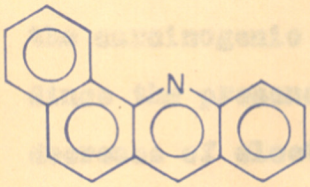

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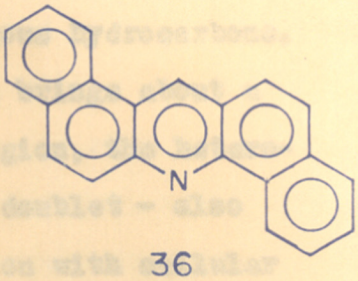

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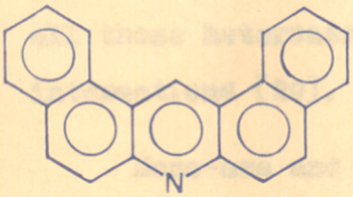

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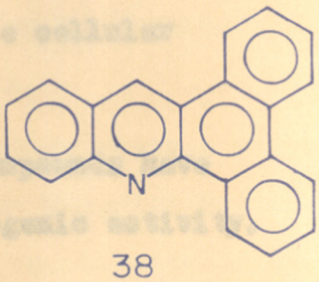

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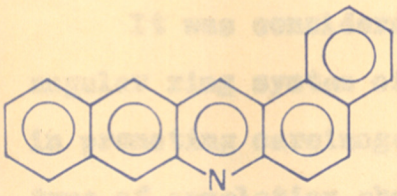

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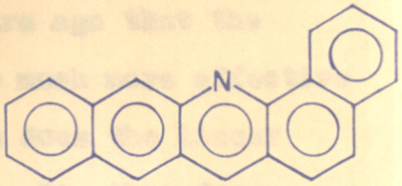

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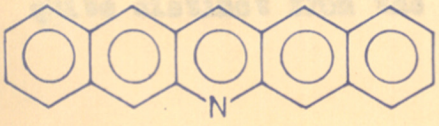

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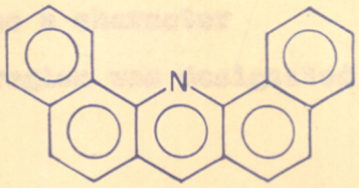

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CHART – 4

activity of dibenz(a,j)acridine 37 was somewhat greater than in the case of dibenz(c,h)acridine 42 [16]. It is evident from a study of the benzacridines that in some instances, the introduction of the hetero-atom increases the carcinogenic activity of the analogous hydrocarbons. Since the presence of the nitrogen atom brings about a decrease of electron charge at the K-region, the hetero-atom itself - by means of its electron doublet - also appears to participate in the interaction with cellular receptor sites. In compounds with two or more nitrogens all these heteroatoms may partake in the cellular interactions [29].

Mono-aza and diaza pentacyclic compounds have not been much studied for their carcinogenic activity.

Carcinogenic Activity - Structural Relationship. K-Region

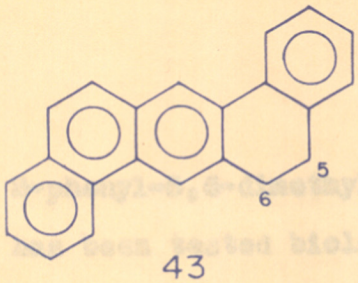
It was considered about forty years ago that the angular ring system of phenanthrene was much more effective in promoting carcinogenic activity than does the linear type of annelation shown in anthracene. It, therefore, became customary to distinguish between the anthracene and phenanthrene type skeletons by saying that in the latter, the 9,10- double bond region has a character quite distinct from the former. This region was designated

as the K-region [30,31]. The electronic distribution at the various double bonds including the K-region was studied. The influence of substitution (particularly by methyl groups) or by the aza group on electronic distribution has also been studied. It has been argued that the K-region, in polycyclic molecules, by virtue of a higher electron density of π electrons in this location, is able to contribute to carcinogenicity. The bond order, net charge, free valence, energy of excitation and resonance energy in above polycyclic hydrocarbons and their heterocyclic analogues have been studied with the view to elucidate the mechanism of chemical carcinogenesis.

Recently a strong defence [32] and an attempt at generalisation [33] has been made of the K-region hypothesis. However, substitution in position 7 in benz(a)anthracene 5 by either electron attracting or electron donating substituents (e.g., $-OCH_3$, $-C{\equiv}N$, $-CHO$, or by $-CH_3$ or $-C_2H_5$) invariably led to compounds which showed carcinogenic activity. In the framework of the theory, electron attracting substituents should decrease carcinogenecity since they may be expected to decrease the reactivity at the K-region. Many compounds have also been found which are carcinogenic although they do not possess free phenanthrenoid bonds [34]. It has been stated by

Mason [35] that the theories of carcinogenic activity in term of electron distribution and associated properties of polycyclic aromatic molecules, which rely on small differences in local electronic distribution to explain considerable variation of physiopathological activity must be open to considerable doubt. Bond orders calculated by simple molecular orbital approximation will give bond lengths which are correct to 0.01Å. More detailed theoretical calculations and a better understanding of donor acceptor phenomenon may be needed before small differences in electronic distribution within the molecules can be accepted as an explanation of variations in biological activity.

It has been argued that shape, size and steric factors of the compounds are all of importance for carcinogenic activity [36]. Carcinogenicity is largely maintained as long as molecular planarity and the presence of resonant diphenylnaphthalene segments are preserved. Lijinsky et al. [37] studied the effect of hydrogenation upon the carcinogenic activity of certain compounds (Chart 5). They have shown that 5,6-dihydrodibenz(a,h)anthracene 43 and 1,2,3,4,12,13-hexahydro-dibenz(a,h)anthracene 45 are both moderately active carcinogens. The hydrogenated derivative 43 has resonance pathways identical to 2-phenylphenanthrene 44 and compound 45 to that of



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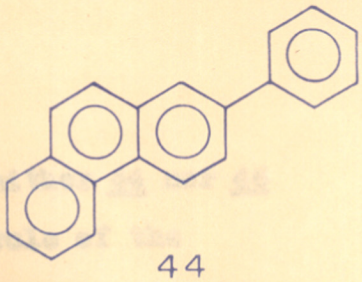

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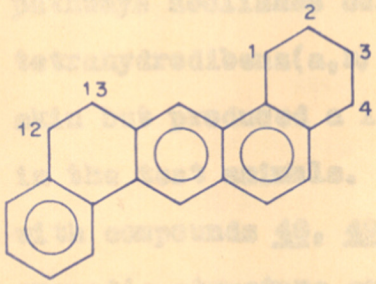

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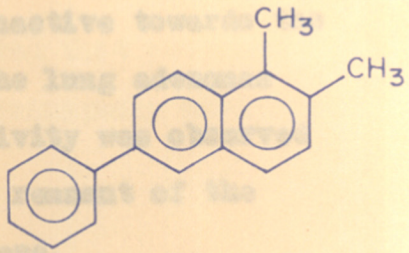

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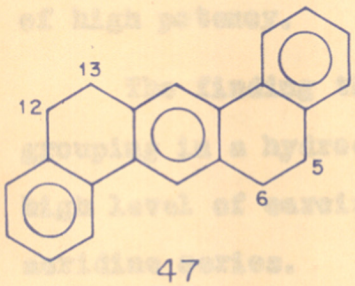

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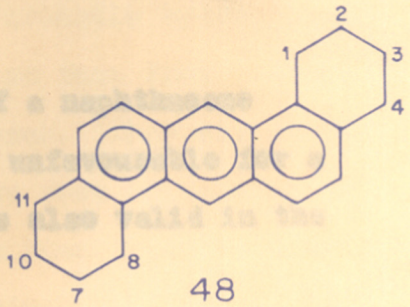

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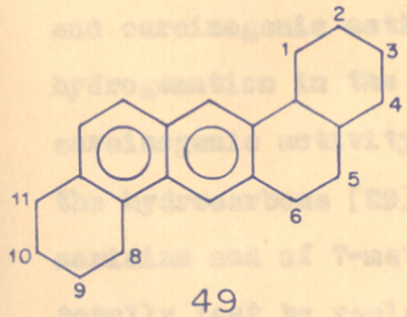

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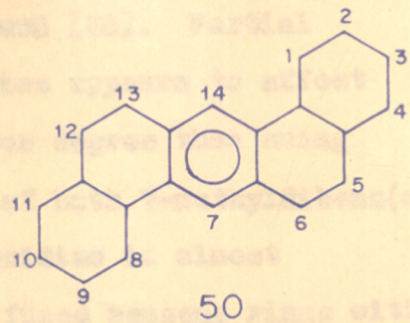

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CHART – 5

2-phenyl-5,6-dimethylnaphthalene 46. Neither 44 nor 46 has been tested biologically; thus the role of the intercyclic $-CH_2-CH_2-$ groups in carcinogenic activity cannot be assessed. Further degradation of the resonance pathways abolishes carcinogenic activity; thus 5,6,12,13-tetrahydrodibenz(a,h)anthracene 47 is inactive towards the skin but produced a large increase in the lung adenomas in the test animals. No biological activity was observed with compounds 48, 49, 50, in which the remnant of the aromatic structure corresponds to an acene.

The aza polycyclics appear more likely to possess carcinogenic activity if they are isosteric with hydrocarbons of high potency.

The finding that the presence of a naphthacene grouping in a hydrocarbon molecule is unfavourable for a high level of carcinogenic activity is also valid in the acridine series.

The activity of benzacridines have been reviewed earlier. No convincing correlation between molecular size and carcinogenic activity has been found [28]. Partial hydrogenation in the benzacridine series appears to affect carcinogenic activity to a much greater degree than among the hydrocarbons [29]. The activity of both 7-methyldibenz(a,h)-acridine and of 7-methyldibenz(a,j)acridine is almost totally lost by replacing one of the fused benzene rings with a hydrogenated ring. Thus 1,2,3,4-tetrahydro-7-methyl

dibenz(a,h)acridine and 1,2,3,4-tetrahydro-7-methyl-dibenz(a,j)acridine are almost totally inactive. Hydrogenation brings about only a small loss of coplanarity, which, thus, cannot account for the considerable loss of biological activity.

From the above, it may be concluded that attempts to correlate chemical structure and carcinogenic activity have by and large been unsuccessful.

Aim of the present work

Among the vast number of compounds which have been found to be carcinogenic, a majority of them have been polycyclic hydrocarbons. Polycyclic aromatic hydrocarbons have several features which distinguish them from many of the more recently discovered carcinogens. They act at the site of the application, the effective dose is minute, of the order of micrograms and they have been found to induce tumours in almost every tissue and animal species in which they have been tested.

Compared to the polycyclic aromatic hydrocarbons, only a few of their nitrogen containing heterocyclic analogs have been tested. Many of these compounds have also not been synthesised so far.

The aim of the present work is to evolve general methods of synthesis for some mono- and diaza-pentacyclic compounds. These compounds could add to the number of available compounds for studying the carcinogenic activity and its relationship with the structure of these compounds.

The work on the mechanism of the cyclodehydration reactions of arylaminomethylenecycloalkanones by various acid reagents, by our laboratory, during the last five years have afforded several convenient methods of synthesis of a very wide variety of polycyclic nitrogen containing hetero-aromatic systems. The present work is an extension of this work wherein synthetic procedures developed earlier have been extensively used.

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CHAPTER II

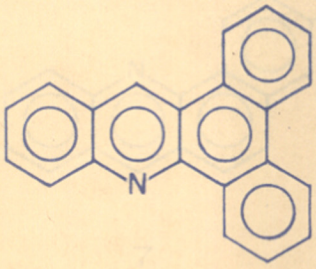
LITERATURE SURVEY OF THE SYNTHETIC METHODS OF MONOAZA AND DIAZA PENTACYCLIC COMPOUNDS

Introduction

A literature survey reveals that little work has been carried out on monoaza and diaza pentacyclic compounds, although a number of substituted derivatives have been made, and tested as carcinogens. The survey given here will be confined mainly to the unsubstituted monoaza pentacyclic compounds, dibenzacridines 1 - 6 (Chart 1a) and 7 - 12 (Chart 1b), dibenzophenanthridines 13 - 18 (Chart 2) and diaza pentacyclic compounds, dibenzophenanthrolines 19 - 23 (Chart 3). The methods of preparation of these compounds are surveyed below.

Dibenzacridines

Dibenz(a,c)acridine 1 has been prepared by heating phenanthraquinone 24, 2-nitrobenzyl chloride 25 and stannous chloride in concentrated hydrochloric acid (Chart 4) [1]. Compound 1 has also been obtained [2] by thermal rearrangement of 6-bromo-5,6-dihydro-5,5-tetramethylenebenz(c)acridine 30 followed by Pd - C dehydrogenation (Chart 5). Compound 30 has in turn been prepared by the condensation of 4,4-tetramethylene-1-tetralone 26 with o-nitrobenzaldehyde in the presence of acetic acid and sulphuric acid providing 2-(o-nitrobenzal)-



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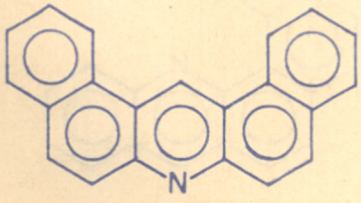

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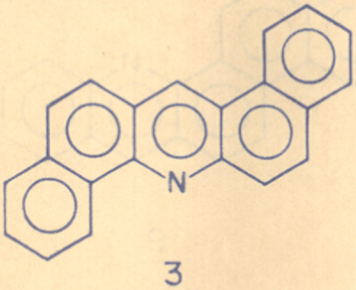

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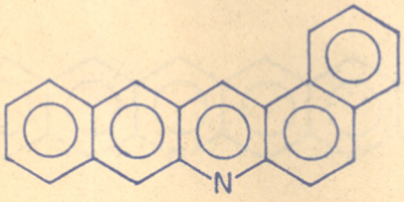

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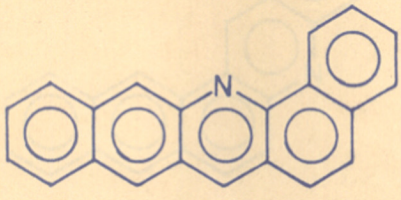

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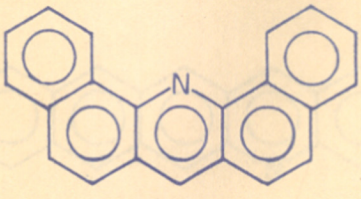

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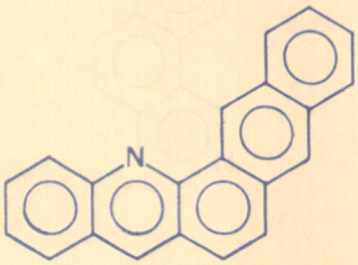
CHART — 1 a.



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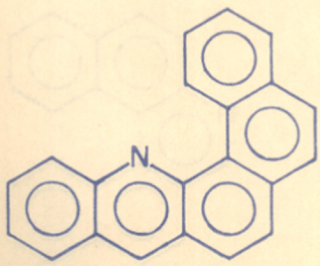

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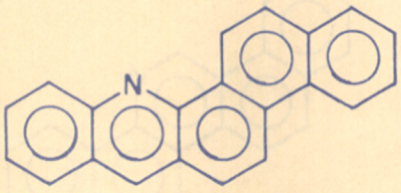

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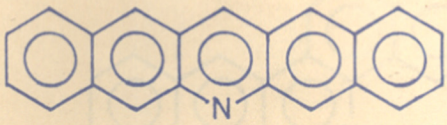

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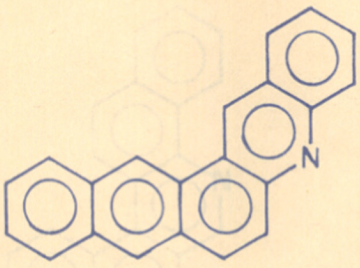

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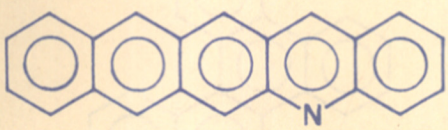

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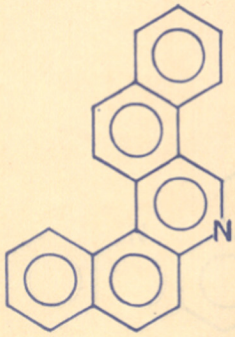
CHART – 1 b.



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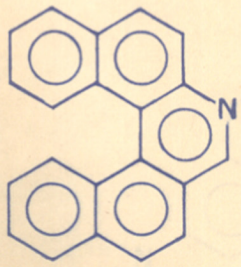

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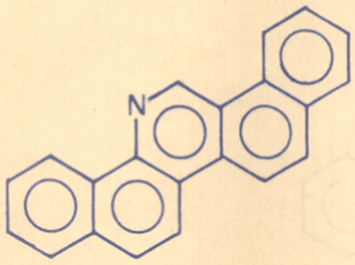

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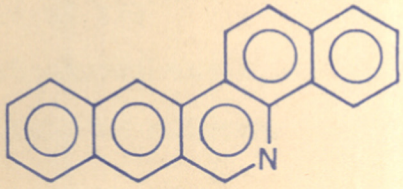

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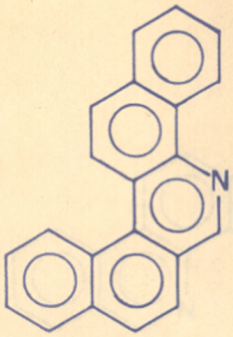

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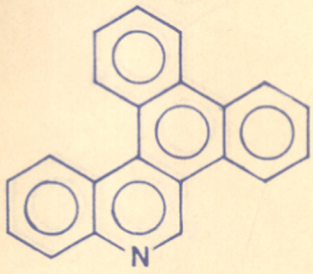

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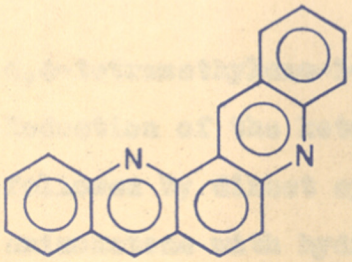
CHART – 2



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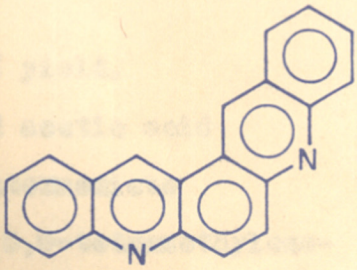

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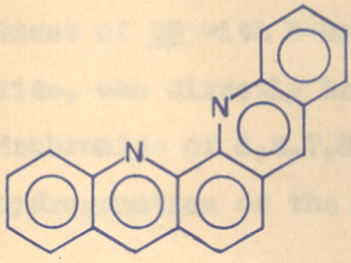

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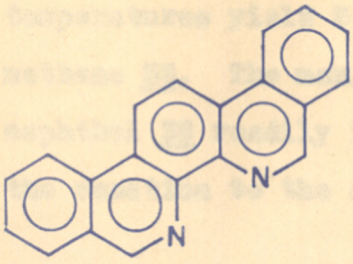

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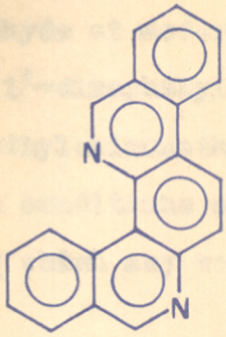

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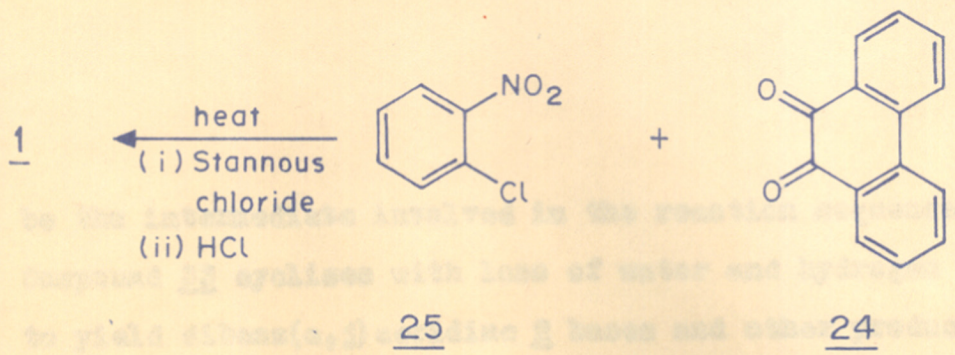
CHART – 3

4,4-tetramethylene-1-tetralone 27 in 84% yield. Reduction of the ketone 27 with iron and acetic acid followed by direct cyclisation of the intermediate aminoketone with hydrochloric acid gave 5,5-tetramethylene-5,6-dihydrobenz(c)acridine 29 in 83% overall yield. Reaction of the tetralone 26 with isatin under basic conditions afforded 7-carboxy-5,5-tetramethylene-5,6-dihydrobenz(c)acridine 28. Thermal decarboxylation of the acid 28 also gave 29. The unstable bromide 30 obtained by treatment of 29 with N-bromosuccinimide in carbon tetrachloride, was directly heated at 170° affording the hydrobromide of 5,6,7,8-tetrahydrobenz(a,c)-acridine 31. Dehydrogenation of the tetrahydro compound 31 gave 1.

Dibenz(a,j)acridine 2 has been prepared [3] by the interaction of β-naphthol, β-naphthylamine and formaldehyde. The reaction sequence is shown in (Chart 6): β-naphthol, β-naphthylamine and formaldehyde at moderate temperatures yield 2-amino-2'-hydroxy-1,1'-dinaphthyl methane 33. The mannich base 1-(2'-naphthylaminomethyl)-2-naphthol 32 readily isomerises under the conditions of the reaction to the dinaphthylmethane 33 which may well



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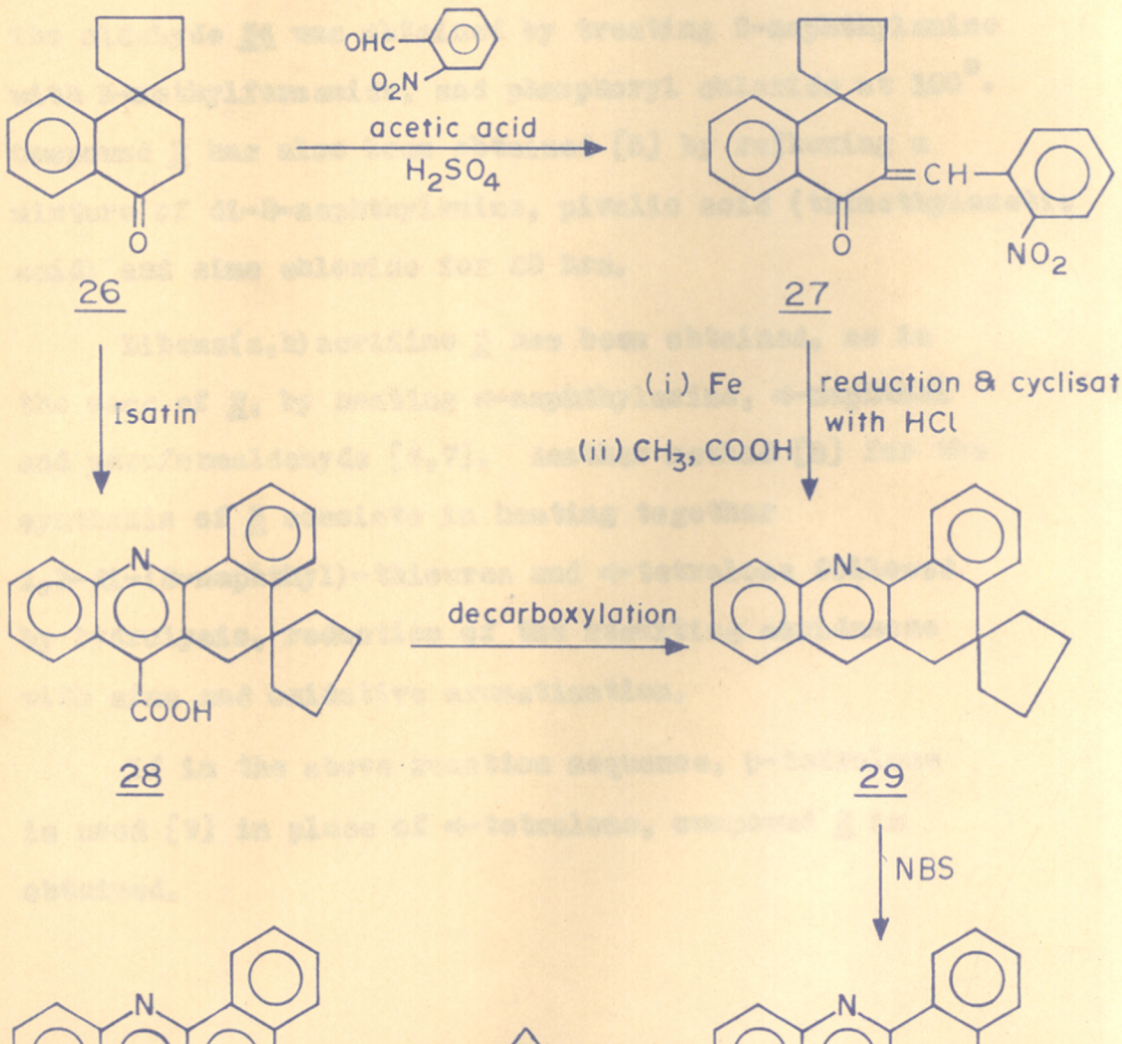


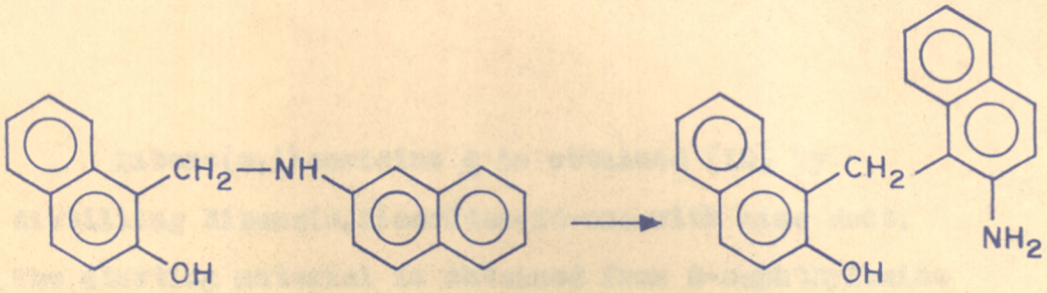
CHART – 5

be the intermediate involved in the reaction sequence. Compound 33 cyclises with loss of water and hydrogen to yield dibenz(a,j)acridine 2 bases and other products. Compound 2 has also been prepared [4] by cyclising 1-formyl-di(2-naphthyl)amine 34 by pyrolysis or better, by heating with sulphuric acid in acetic acid (Chart 7). The aldehyde 34 was obtained by treating 2-naphthylamine with N-methylformamide, and phosphoryl chloride at 100°. Compound 2 has also been obtained [5] by refluxing a mixture of di-2-naphthylamine, pivalic acid (trimethylacetic acid) and zinc chloride for 20 hrs.

Dibenz(a,h)acridine 3 has been obtained, as in the case of 2, by heating α-naphthylamine, α-naphthol and paraformaldehyde [6,7]. Another method [8] for the synthesis of 3 consists in heating together 1,3-di-(2-naphthyl)-thiourea and α-tetralone followed by hydrolysis, reduction of the resulting acridanone with zinc and oxidative aromatisation.

If in the above reaction sequence, β-tetralone is used [9] in place of α-tetralone, compound 2 is obtained.

β-Naphthol + β-naphthylamine + HCHO ⟶



32 33

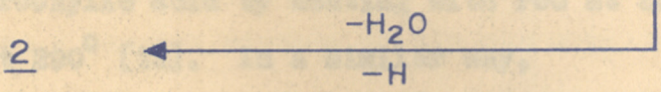


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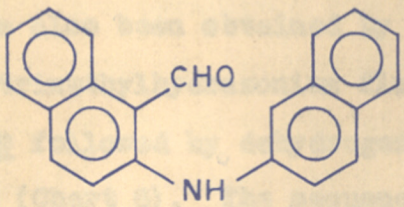
CHART – 6



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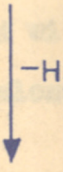


2

CHART – 7

Dibenz(a,i)acridine 4 is obtained [10] by distilling dibenz(a,i)acridan-14-one with zinc dust. The starting material is obtained from 2-naphthylamine and 2-hydroxymethylene-3-carboxylic acid [10,11].

Dibenz(b,h)acridine 5 has been obtained by decarboxylation and dehydrogenation of 5,6-dihydrodibenz(b,h)-acridine-7-carboxylic acid by heating with PbO at 300° or in vacuo at 290° [12]. In a similar way, 5,6-dihydrodibenz(a,i)acridine-14-carboxylic acid gives compound 4 [12,13].

Dibenz(c,h)acridine 6 has been obtained by heating 1-naphthylamine and dichloromethane in a sealed tube at 220-230° [10] or by heating a mixture of 1-naphthylamine, dichloromethane and potassium carbonate at 150-160° [14]. Compound 6 has also been obtained by the pyrolysis [15] of the N,N,N-trimethylhydrazonium fluoborate of 1-tetralone 32 followed by dehydrogenation (Pd-C) at 250° in vacuo (Chart 8). The sequence is that α-tetralone 35 is refluxed with an excess of anhydrous N,N-dimethyl-hydrazine 36 to give α-tetralone N,N-dimethylhydrazone 37. The latter is quaternised with methyl iodide to give the corresponding α-tetralone-N,N,N-trimethylhydrazonium

iodide 38 which, on treatment with a hot aqueous solution of sodium fluoborate, is converted into the corresponding ketone N,N,N-trimethyl hydrazonium fluoborate 39. Compound 39 on pyrolysis gives 5,6,8,9-tetrahydrodibenz(c,h)acridine 40 which on dehydrogenation with Pd-C yields dibenz(c,h)acridine 6.

Naphth(2,3-c)acridine 7 (Chart 1b) has been isolated from a complex mixture of six new compounds which are formed when acridine 41 and 1,3-dihydroisothianaphthene-2,2-dioxide 42 are heated in diethyl phthalate at 300° (Chart 9). Compound 7 isolated in this reaction was found to be identical with an authentic sample prepared by zinc dust distillation of naphth(2,3-c)acridan 5,8,14-trione [16].

Naphth(2,1-c)acridine 8 has been obtained by the decarboxylation and dehydrogenation of the product prepared from isatin and 4-oxo-1,2,3,4-tetrahydrophenanthrene [17]. Naphth(1,2-c)acridine 9 has been obtained [18,19] as in case of 8. Only the derivatives of naphth(2,3-a)acridine 11 [20,21] and naphth(2,3-b)-acridine 12 [21,22,23] are known.

To:

Shri. G.S. Jadhav,
Scientific Officer (R&D)
Hindustan Organic Chemicals Limited
Rasayani - 410 207,
Panvel, ~~Kix~~
District : Colaba.

Subject : Registration as guest worker for Ph.D Degree in N.C.L.

Sir,

With reference to your letter No. nil dated 6-7-1978 on the subject mentioned above I am to inform you that the Director, NCL, has been pleased to grant you the permission to work as a guest worker (external) under the guidance of Dr. G.T. Panse, Scientist, of this Laboratory for completion of your Ph.D work.

It may, however, kindly be noted that you would have to carry out the experimental work at R&D Laboratory of HOC, Rasayani only.

However, you are permitted to visit NCL for consultations with Dr. Panse, Scientist, N.C.L. regarding your research work.

Yours faithfully,

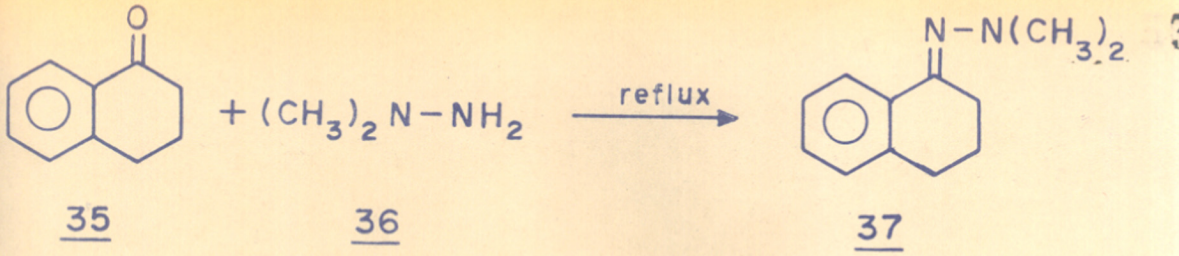
Kripa Shanker

(Kripa Shanker)
Section Officer

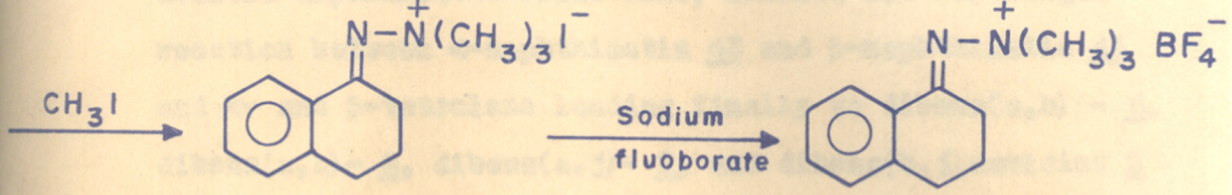
Copy to :-

The Manager Research and Development Division,
Hindustan Organic Chemicals Limited,
Rasayani-410207, Pavel,
District : Colaba.

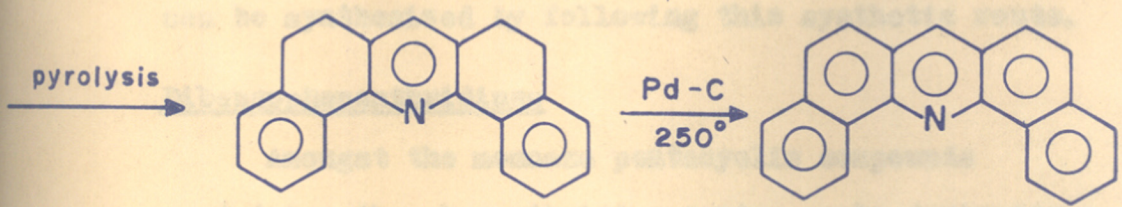
Copy to : Dr. G.T. Panse, Scientist, TRL NCL



35 36 37

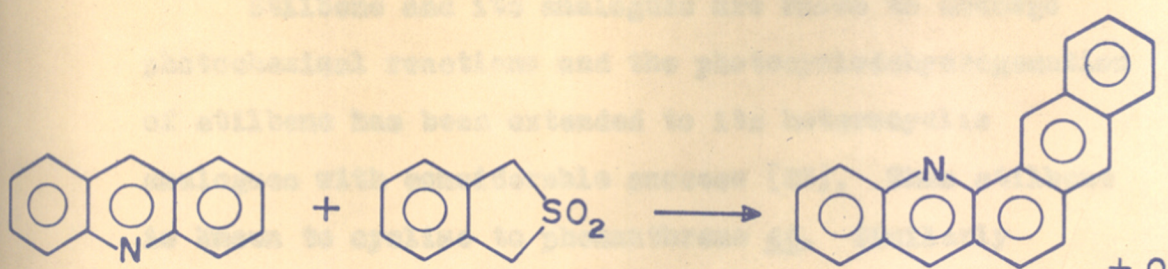


38 39



40 6

CHART 8



41 42 7

CHART 9

Recently, Jacquignon et al.[24] have, by using drastic experimental conditions, carried out Pfitzinger reaction between α-naphthisatin 43 and β-naphthisatin 44 and α- and β-tetralone leading finally to dibenz(c,h) - 6, dibenz(a,h)- 3, dibenz(a,j)- 2, and dibenz(b,j) acridine 5 (Chart 10).

In the Pfitzinger reaction, a substituted ketone with a condensable α-methylene group is reacted with isatin to produce disubstituted quinolines. Hence selecting R_1 and R_2 as $-(CH_2)_n$ the required polymethylenequinolines can be synthesised by following this synthetic route.

Dibenzophenanthridines

Amongst the monoaza pentacyclic compounds containing the phenanthridine system, only derivatives of dibenzo(a,k)phenanthridine 14, dibenzo(c,j)phenanthridine 16 and dibenzo(i,k)phenanthridine 18 have been reported.

Stilbene and its analogues are known to undergo photochemical reactions and the photocyclodehydrogenation of stilbene has been extended to its heterocyclic analogues with considerable success [25]. Thus stilbene is known to cyclise to phenanthrene 46. Similarly 2,-3,- and 4-styryl-pyridines on photochemical

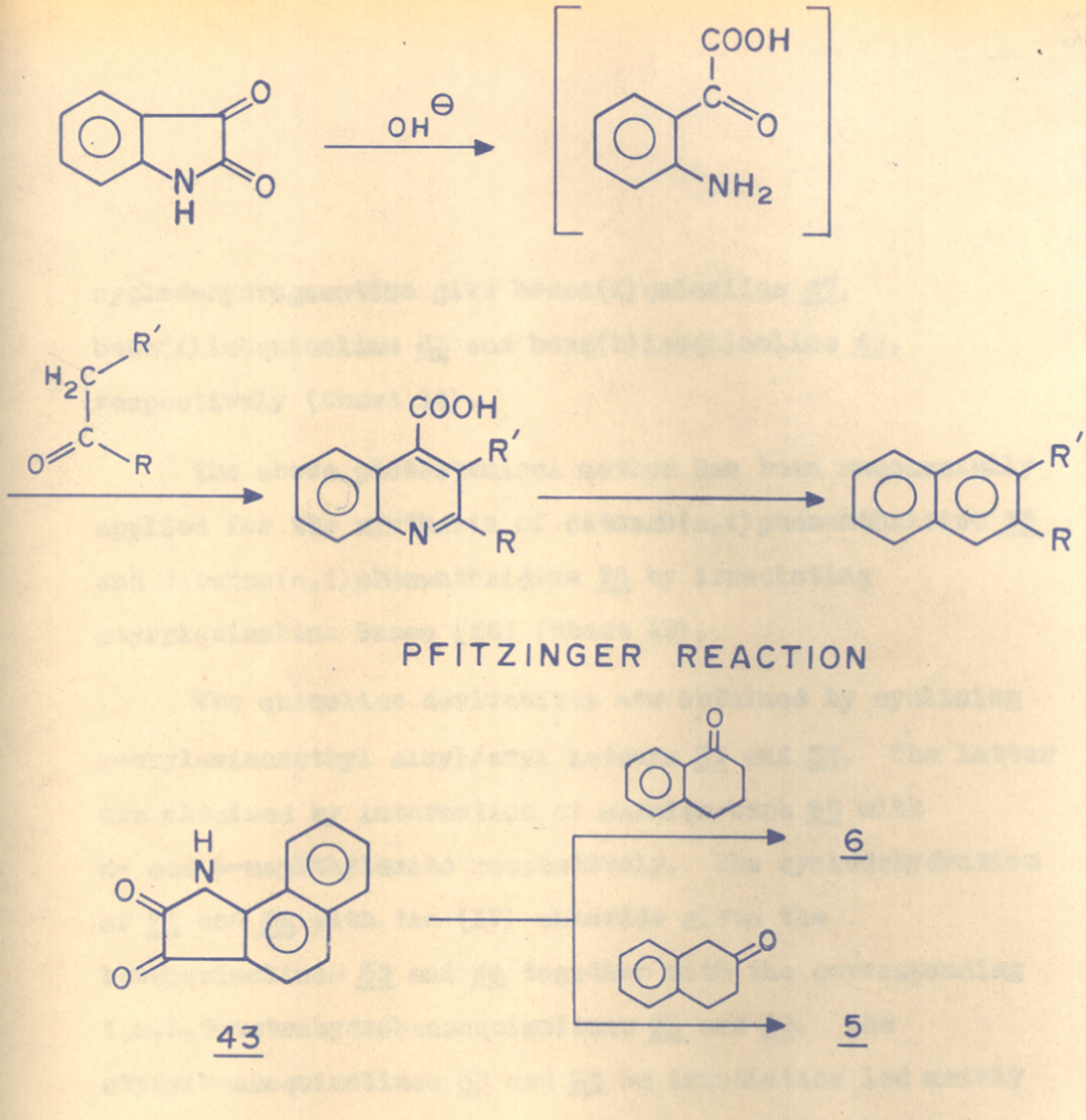


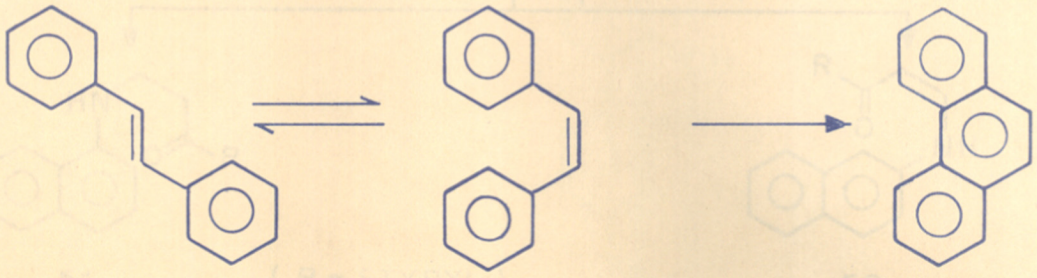
CHART 10

cyclodehydrogenation give benzo(f)quinoline 47, benz(f)isoquinoline 48 and benz(h)isoquinoline 49, respectively (Chart 11).

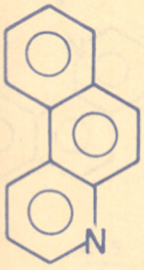
The above photochemical method has been successfully applied for the synthesis of dibenzo(a,i)phenanthridine 13 and dibenzo(c,i)phenanthridine 15 by irradiating styrylquinoline bases [26] (Chart 12).

The quinoline derivatives are obtained by cyclising β-arylaminomethyl alkyl/aryl ketones 51 and 52. The latter are obtained by interaction of mannich base 50 with α- and β-naphthylamine respectively. The cyclodehydration of 51 and 52 with tin (IV) chloride gives the benzoquinolines 53 and 54 together with the corresponding 1,2,3,7-tetrahydrobenzoquinolines 55 and 56. The styrylbenzoquinolines 53 and 54 on irradiation led mainly to trans-cis isomerisation followed by cyclodehydrogenation; thus 53 gives dibenzo(c,i)phenanthridine 15, whereas 54 gives dibenzo(a,i)phenanthridine 13.

Compound 15 has also been obtained by the ultraviolet irradiation [27] of the schiff base 57 (Chart 13). The structure of 15 was confirmed by an independent synthesis. The reaction of dibenzo(a,i)fluorenone with hydroxylamine—



trans 45 cis 46



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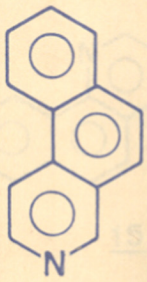

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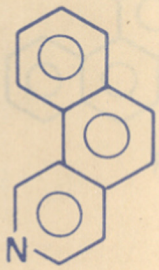

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CHART 11

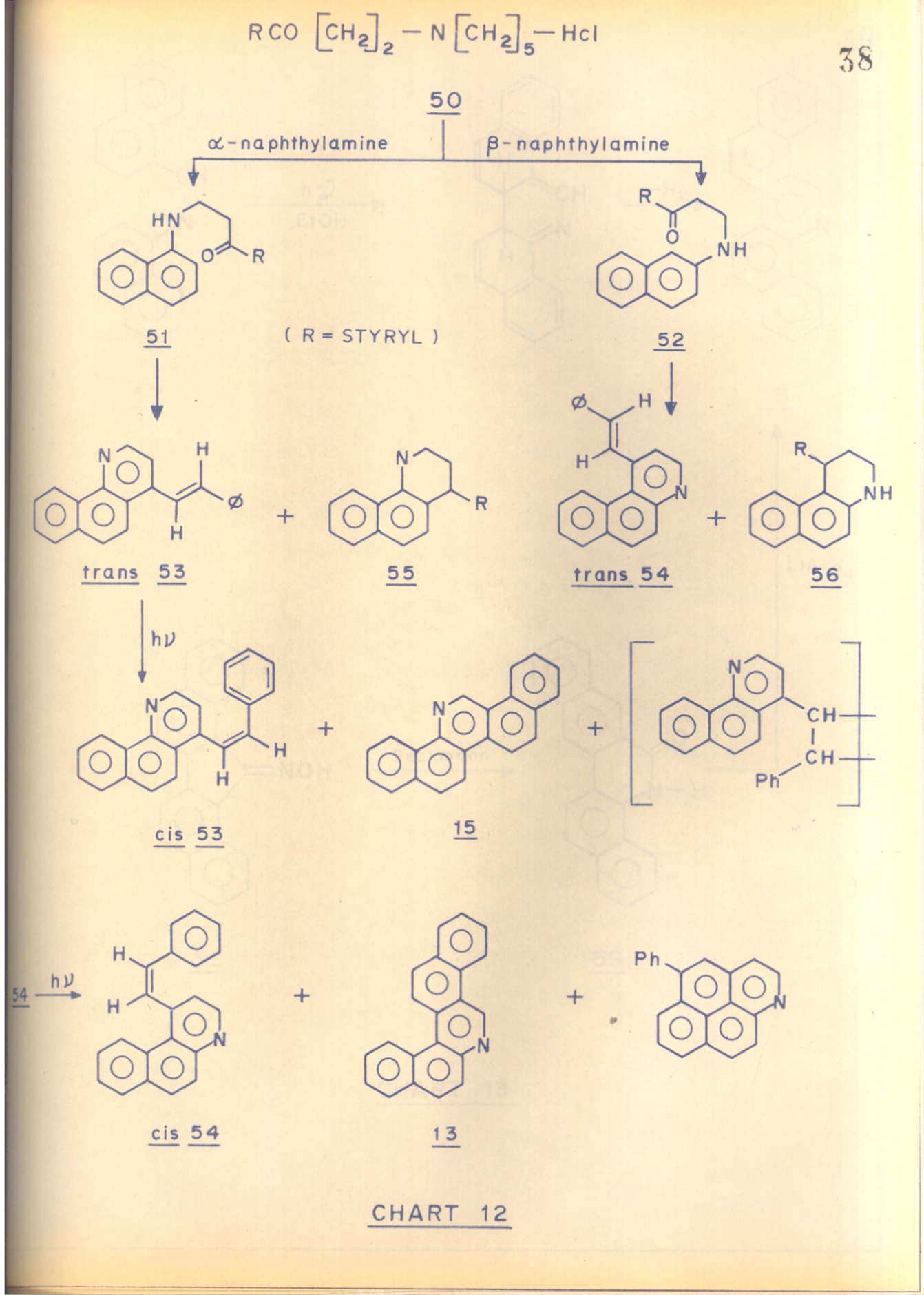

RCO [CH2]2 — N [CH2]5 — Hcl
50
α-naphthylamine
β-naphthylamine
51
(R = STYRYL)
52
trans 53
55
trans 54
56
hν
cis 53
15
54
hν
cis 54
13
Ph

CHART 12

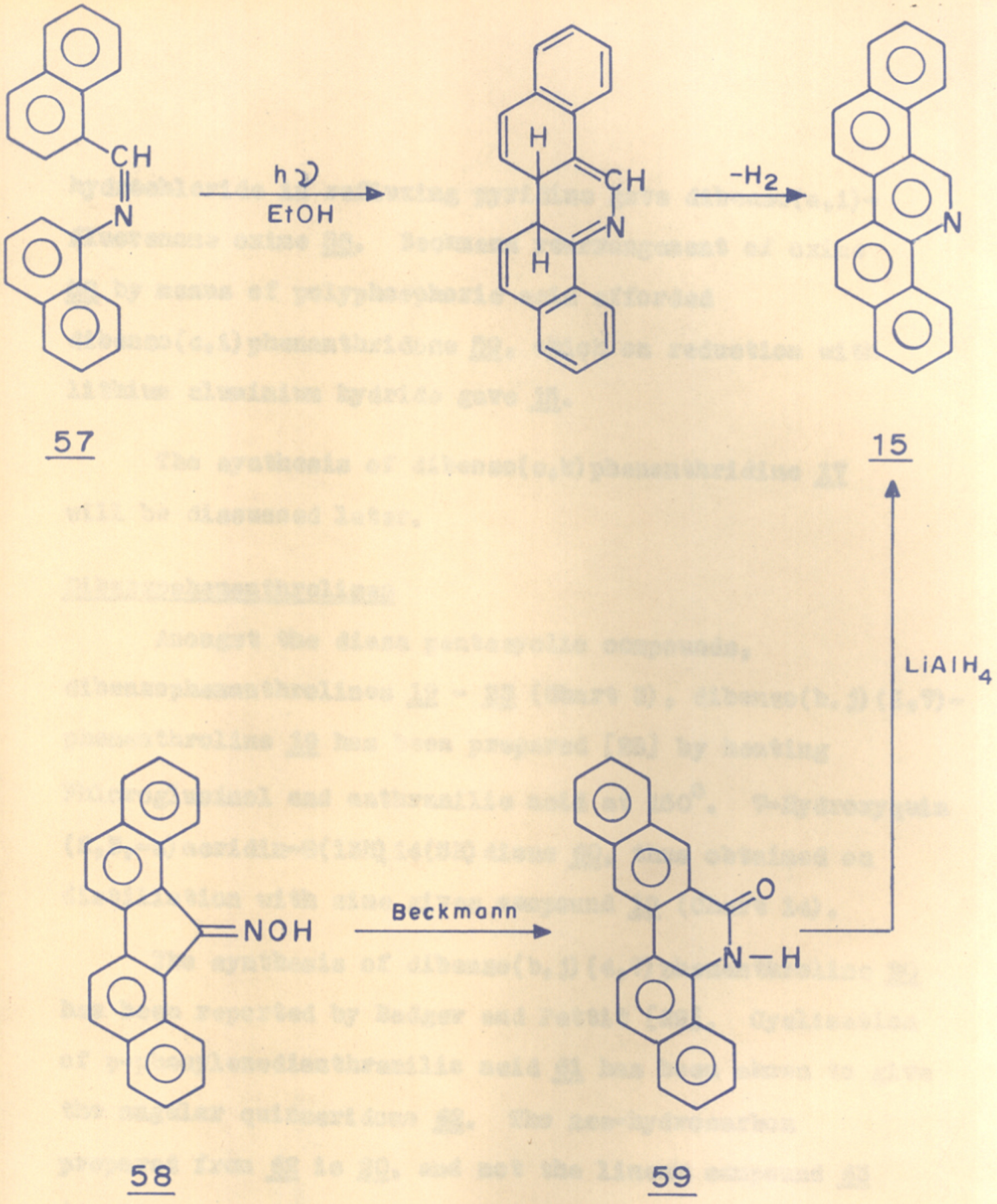


CHART 13

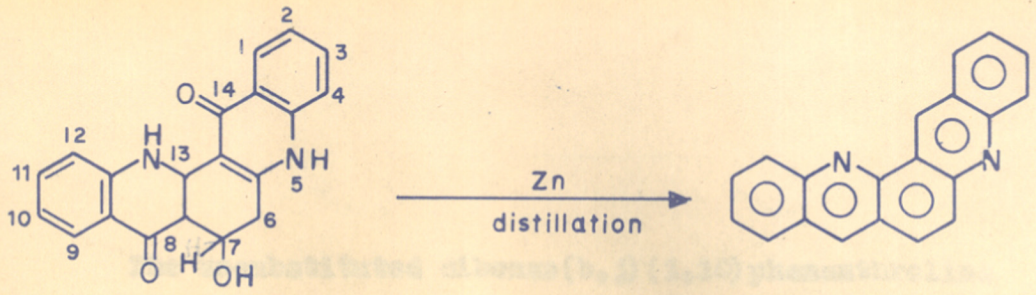
hydrochloride in refluxing pyridine gave dibenzo(a,i)-fluorenone oxime 58. Beckmann rearrangement of oxime 58 by means of polyphosphoric acid afforded dibenzo(c,i)phenanthridone 59, which on reduction with lithium aluminium hydride gave 15.

The synthesis of dibenzo(c,k)phenanthridine 17 will be discussed later.

Dibenzophenanthrolines

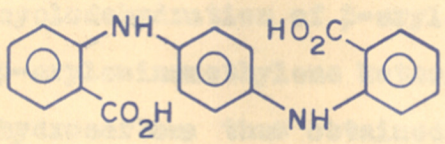
Amongst the diaza pentacyclic compounds, dibenzophenanthrolines 19 - 23 (Chart 3), dibenzo(b,j)(1,7)-phenanthroline 19 has been prepared [28] by heating Phloroglucinol and anthranilic acid at 150°. 7-Hydroxyquin (2,3,-a)acridin-8(13H),14(5H)dione 60, thus obtained on distillation with zinc gives compound 19 (Chart 14).

The synthesis of dibenzo(b,j)(4,7)phenanthroline 20 has been reported by Badger and Pettit [29]. Cyclisation of p-phenylenedianthranilic acid 61 has been shown to give the angular quinacridone 62. The aza-hydrocarbon prepared from 62 is 20, and not the linear compound 63 (derived from 64) as originally supposed by Ullmann and Maag [30] (Chart 15).

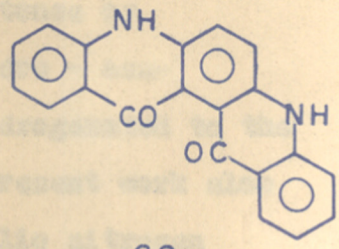


60 19

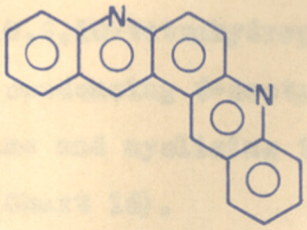
CHART 14



61



62



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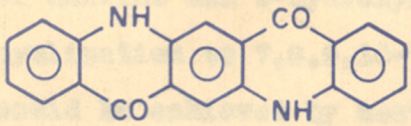

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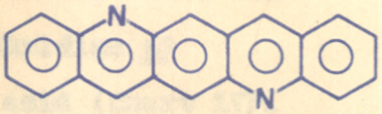


63

CHART 15

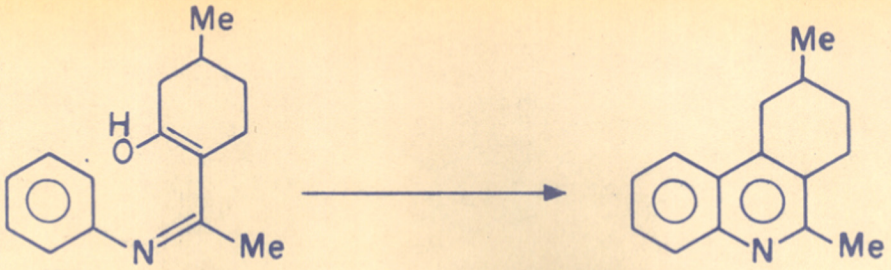
The unsubstituted dibenzo(b,j)(1,10)phenanthroline 21, dibenzo(c,i)(1,10)phenanthroline 22 and dibenzo(c,k)(1,7)-phenanthroline 23 have not been reported so far.

Cyclodehydration Reactions Leading to Hydro Derivatives of Aza-Hydrocarbons

Unsubstituted mono- and di- aza pentacyclic compounds have been prepared by acid catalysed cyclodehydration of β-arylaminomethyl ketones or β-arylaminomethylene ketones. The perhydro - aza-hydrocarbons thus obtained are then dehydrogenated to the parent aza - pentacyclic systems. The present work also employs this route to synthesise polycyclic nitrogen compounds.

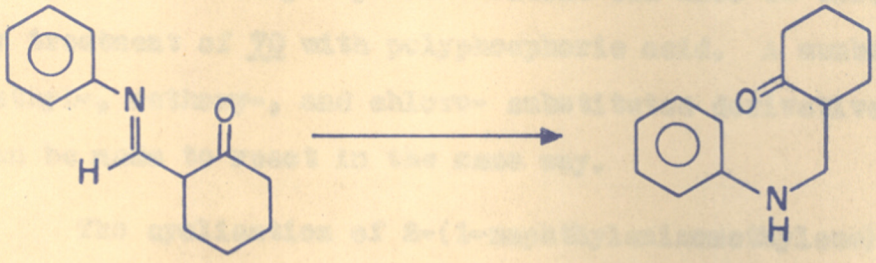
In the first reported example, Borsche [31] obtained 6,9-dimethyl-7,8,9,10-tetrahydrophenanthridine 66 in 15% overall yield by condensing 6-acetyl-3-methyl-cyclohexanone with aniline and cyclising the resultant anil 65 with sulphuric acid (Chart 16).

Hollingsworth and Petrow, who assumed the trans - anil structure 67 for the condensation product of aniline and 2-hydroxymethylenecyclohexanone, found that cyclisation to 7,8,9,10-tetrahydrophenanthridine 69 could be achieved by heating with formic acid (Chart 17).

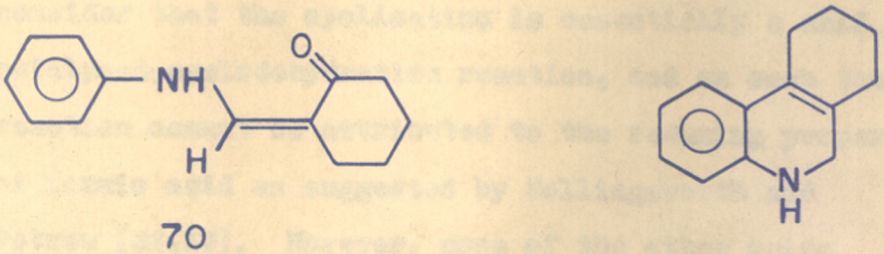


65 66

CHART 16



67 68



70

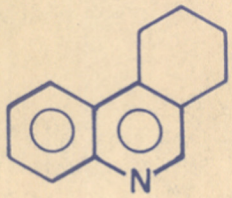
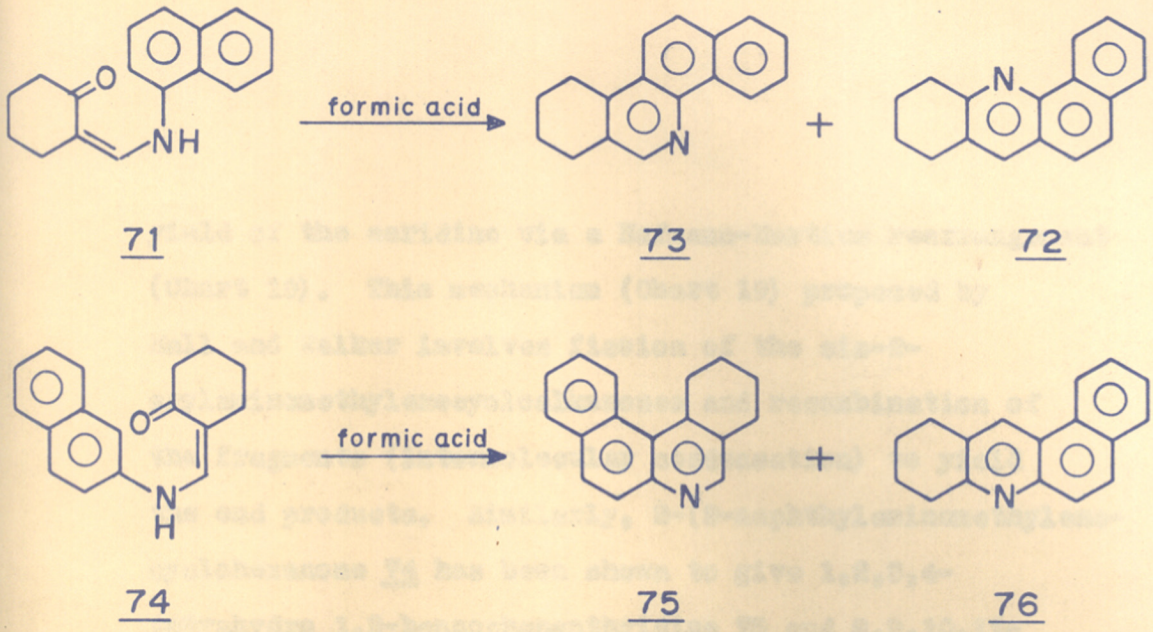


CHART 17 69

Since this reagent reduces azomethine bonds, it was argued that favourable stereochemistry is achieved by reduction [32] and in fact the secondary amine 68 was isolated [33]. However, it has been shown later by Tilak et al [34] (Chart 17) that the anil is in fact cis aminomethylenecyclohexanone 70 and that the cyclisation to 7,8,9,10-tetrahydrophenanthridine can also be effected by treatment of 70 with polyphosphoric acid. A number of methyl-, methoxy-, and chloro- substituted derivatives can be made to react in the same way.

The cyclisation of 2-(1-naphthylaminomethylene)-cyclohexanone 71 by means of formic acid has been shown by Hall and Walker [35] to yield 6,7,8,9-tetrahydro-1,2-benzacridine 72 in addition to 7,8,9,10-tetrahydro-3,4-benzophenanthridine 73 (Chart 18). Hall and Walker consider that the cyclisation is essentially a acid catalysed cyclodehydration reaction, and as such the reaction cannot be attributed to the reducing property of formic acid as suggested by Hollingsworth and Petrow [32,33]. However, none of the other acids examined (except polyphosphoric acid) gave any appreciable yield of the phenanthridine, although most gave good



71 73 72

74 75 76

CHART 18

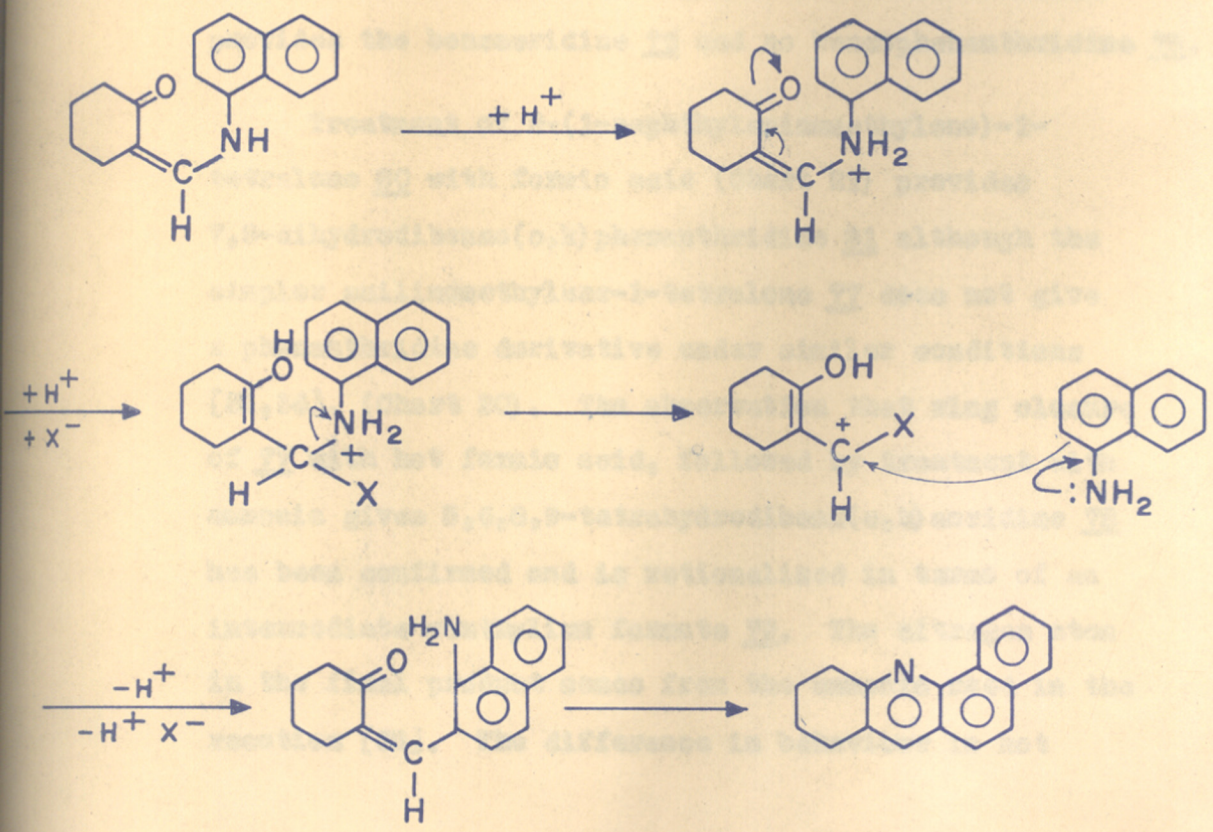
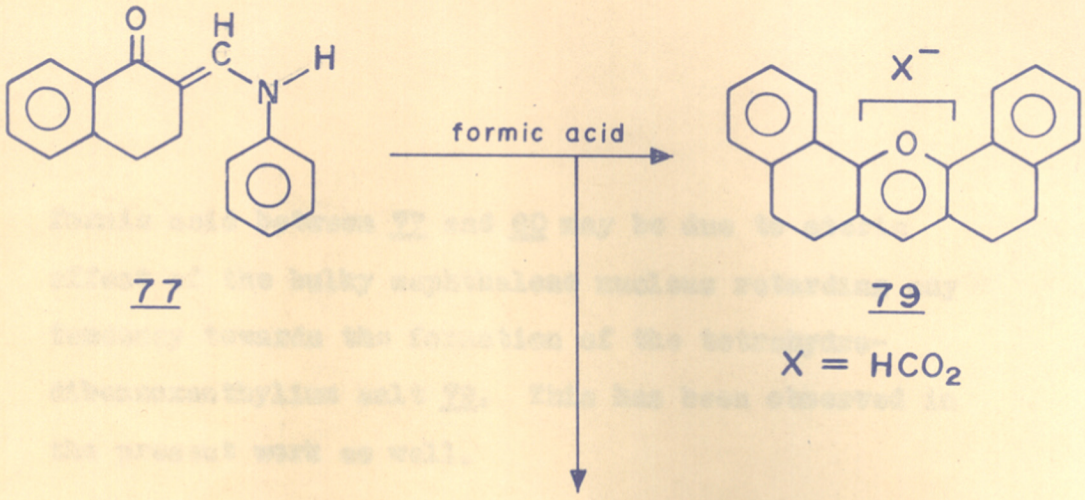


CHART 19

HOFMANN-MARTIUS TYPE MECHANISM

yield of the acridine via a Hofmann-Martius rearrangement (Chart 19). This mechanism (Chart 19) proposed by Hall and Walker involves fission of the cis-2-arylaminomethylenecycloalkanones and recombination of the fragments (intermolecular condensation) to yield the end products. Similarly, 2-(2-naphthylaminomethylene-cyclohexanone 74 has been shown to give 1,2,3,4-tetrahydro 1,2-benzophenanthridine 75 and 8,9,10,11-tetrahydrobenz 1,2-acridine 76 in hot formic acid (Chart 18), whereas treatment with lactic acid at 130° provides the benzacridine 76 and no benzophenanthridine 75.

Treatment of 2-(1-naphthylaminomethylene)-1-tetralone 80 with formic acid (Chart 21) provides 7,8-dihydrodibenzo(c,k)phenanthridine 81 although the simpler anilinomethylene-1-tetralone 77 does not give a phenanthridine derivative under similar conditions [35,36]. (Chart 20). The observation that ring closure of 77 with hot formic acid, followed by treatment with ammonia gives 5,6,8,9-tetrahydrodibenz(c,h)acridine 78 has been confirmed and is rationalised in terms of an intermediate xanthylium formate 79. The nitrogen atom in the final product comes from the ammonia used in the reaction [35]. The difference in behaviour in hot



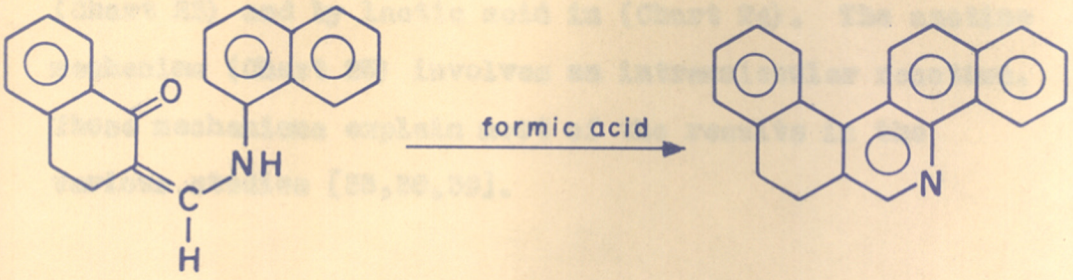
77

79

X = HCO_2

78

CHART 20



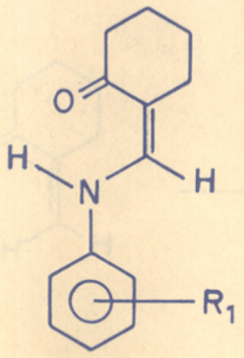
80

81

CHART 21

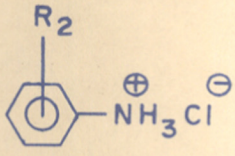
formic acid between 77 and 80 may be due to steric effect of the bulky naphthalene nucleus retarding any tendency towards the formation of the tetrahydrodibenzoxanthylium salt 79. This has been observed in the present work as well.

In our laboratory, cyclodehydration of cis-2-arylaminomethylenecyclohexanones 82 under acidic conditions leading to (angularly cyclised) tetrahydrophenanthridines or by a rearrangement to (linearly cyclised) tetrahydroacridines have been carried out and studied exhaustively [34]. Cyclodehydrations of 'anil' of the type 82 (Chart 22) with sulphuric acid, polyphosphoric acid and hot formic acid yielded phenanthridines whereas treatment with arylamine hydrochloride/zinc chloride or lactic acid yielded acridines. Plausible mechanisms to account for these rearrangement have been proposed [37]. The mechanism of cyclodehydration by polyphosphoric acid is shown in (Chart 23) and by lactic acid in (Chart 24). The azetine mechanism (Chart 25) involves an intramolecular reaction. These mechanisms explain most of the results in the various studies [35,38,39].



82

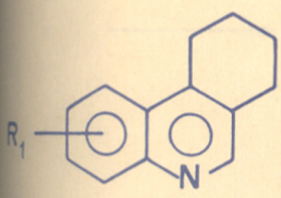
i) PPA
or
ii) formic acid

i) 

or

ii) $ZnCl_2$ / EtOH or

iii) Lactic acid



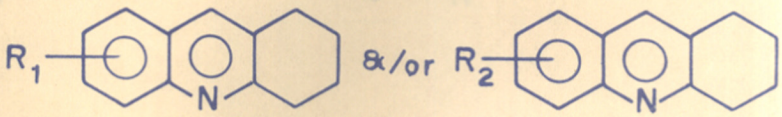


CHART 22

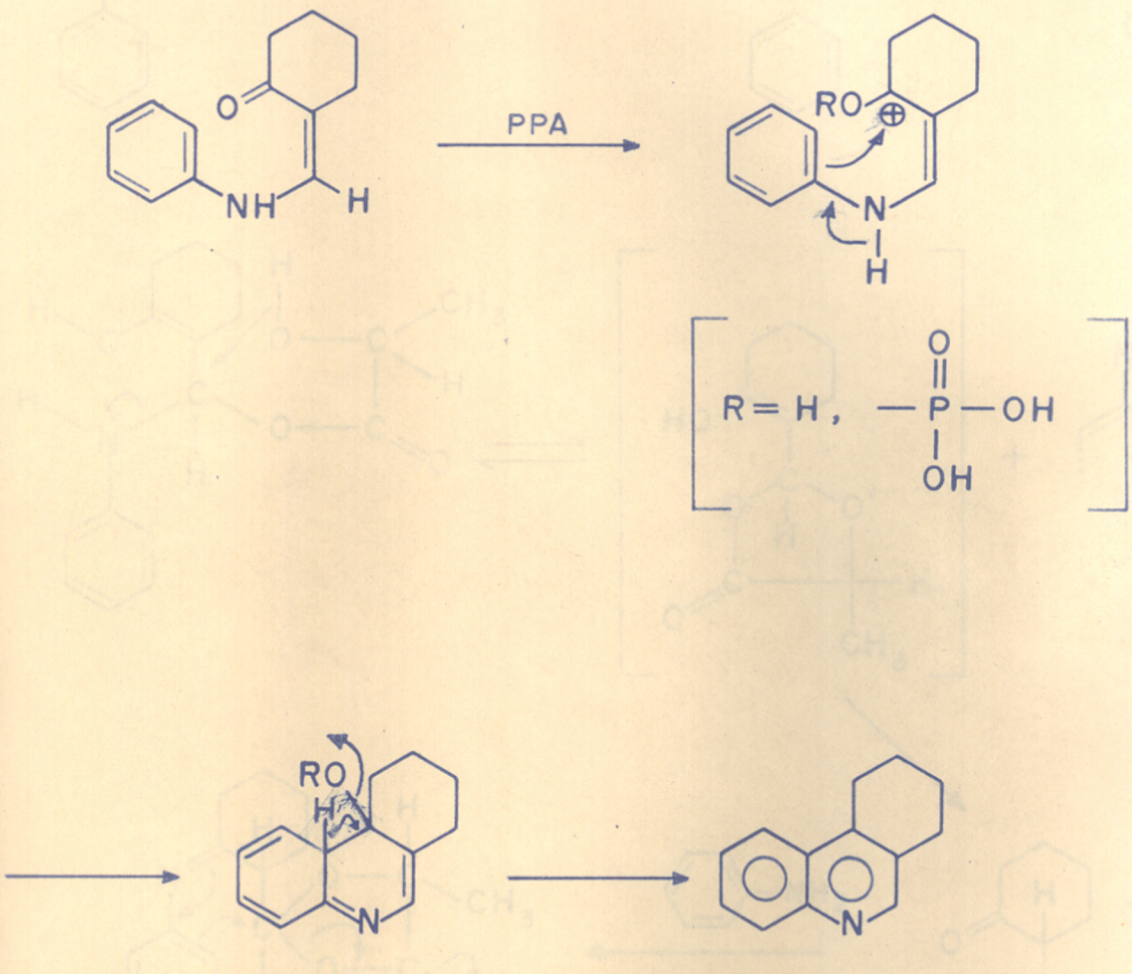


CHART 23

PPA CYCLISATION OF ARYLAMINOMETHYLENECYCLO-ALKANONES

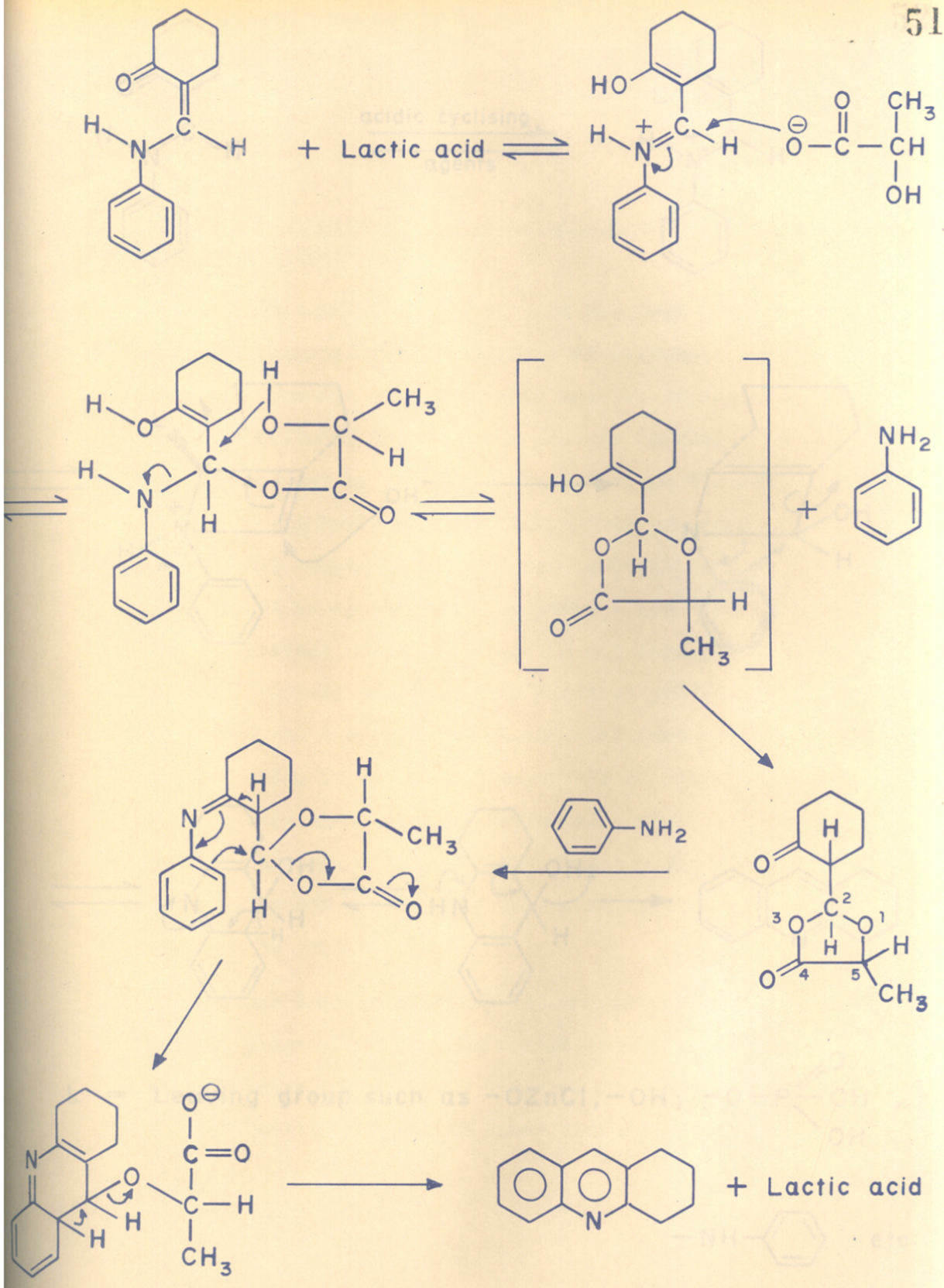


CHART 24

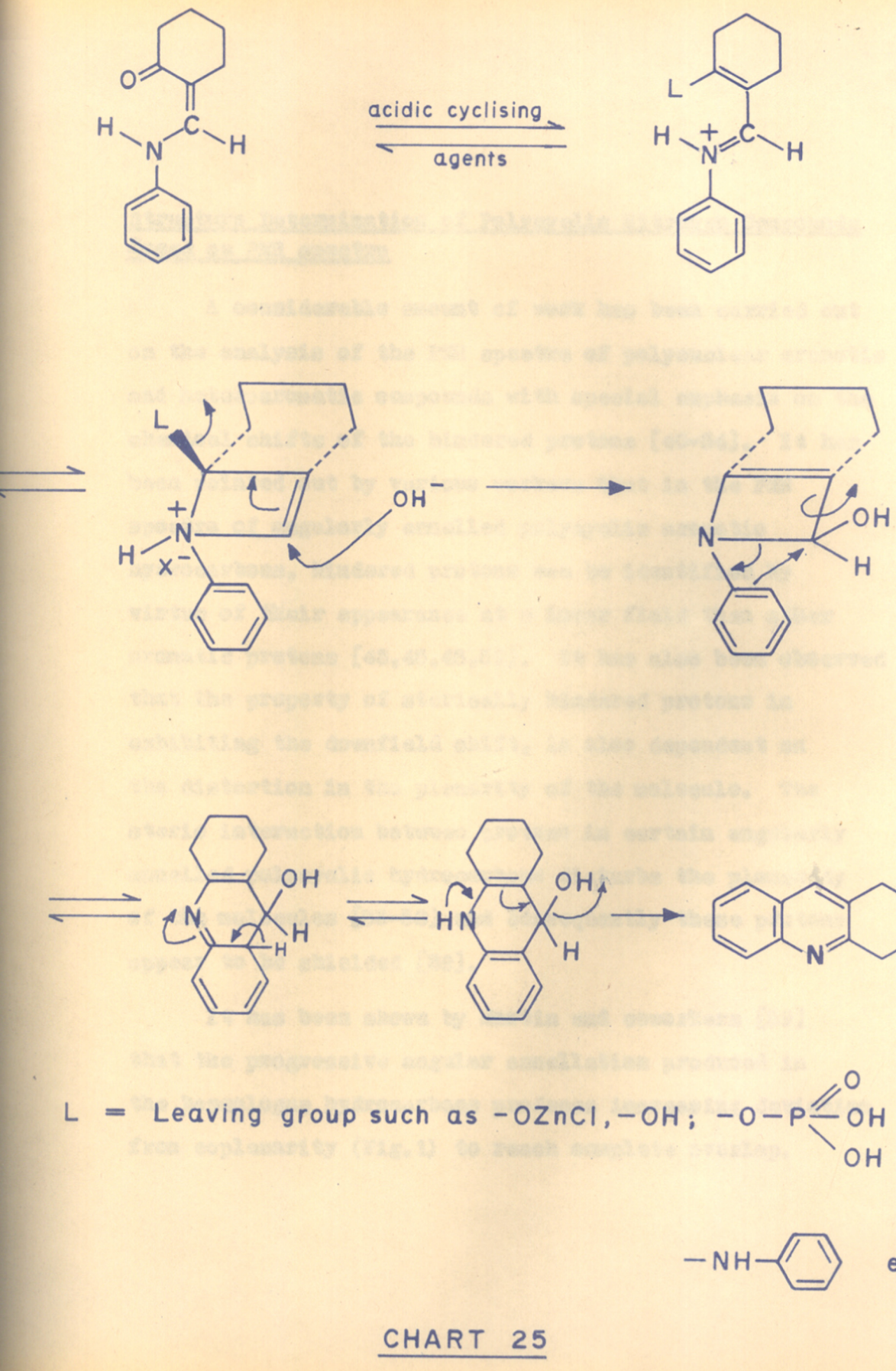
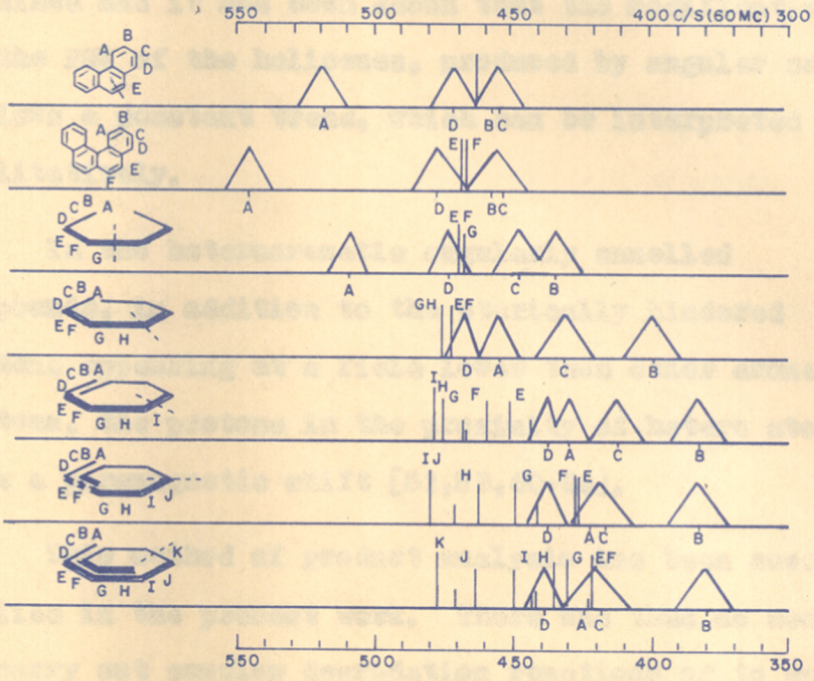

acidic cyclising
agents
L = Leaving group such as -OZnCl, -OH; -O-P(=O)(OH)OH ,
-NH- etc.

CHART 25

Structure Determination of Polycyclic Nitrogen Compounds Based on PMR spectra

A considerable amount of work has been carried out on the analysis of the PMR spectra of polynuclear aromatic and heteroaromatic compounds with special emphasis on the chemical shifts of the hindered protons [40-54]. It has been pointed out by various workers that in the PMR spectra of angularly annelled polycyclic aromatic hydrocarbons, hindered protons can be identified by virtue of their appearance at a lower field than other aromatic protons [43,45,48,59]. It has also been observed that the property of sterically hindered protons in exhibiting the downfield shift, is also dependent on the distortion in the planarity of the molecule. The steric interaction between protons in certain angularly annelled polycyclic hydrocarbons disturbs the planarity of the molecules [55-58] and consequently these protons appear to be shielded [59].

It has been shown by Martin and coworkers [59] that the progressive angular annellation produced in the benzologue hydrocarbons produces increasing deviation from coplanarity (Fig.1) to reach complete overlap.



DIAGRAMMATIC REPRESENTATION OF THE NMR SPECTRA OF HELICINES OF LOWER BENZOLOGUES AS SHOWN BY MARTIN & COWORKERS [59]

FIG. - 1.

The repercussion of these geometrical distortions on the PMR spectra of these hydrocarbons have been examined and it has been shown that the modifications of the PMR of the helicenes, produced by angular annellation, follows a constant trend, which can be interpreted qualitatively.

In the heteroaromatic angularly annelled compounds, in addition to the sterically hindered protons appearing at a field lower than other aromatic protons, the protons in the proximity of hetero atom have a paramagnetic shift [51,53,60-64].

This method of product analysis has been successfully applied in the present work. There was thus no necessity to carry out complex degradation reactions or to carry out unambiguous synthesis of these complex polycyclic compounds. As will be found during the discussions in the subsequent Chapters, this method proved quite versatile in establishing the structures of various reaction products and it was possible to choose the right structure, in some cases, from as many as six to seven possible structures.

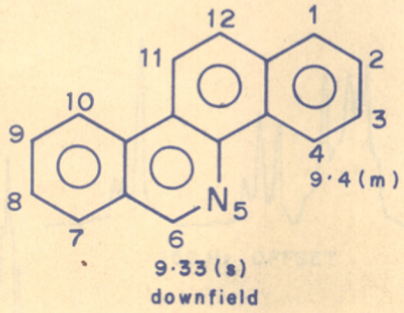
To check whether these principles could be applied in the present work, the spectra of the monoaza tetracyclic

systems benzo(c)phenanthridine 83, benzo(a)phenanthridine 84, benz(c)acridine 85 and benz(a)acridine 86 were compared (Chart 26). Compound 83 in its PMR spectrum is expected to show a multiplet for proton at C-4 and a singlet for proton at C-6. The spectrum did show a singlet at 9.33 δ for proton at C-6 and a downfield multiplet centred at 9.4 δ for proton at C-4 (Fig.2).

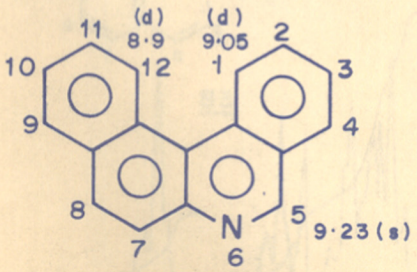
Compound 84 is having one proton at C-5 in proximity of nitrogen and as such should appear as a singlet at downfield. Proton at C-1 and C-12 are hindered and should appear as two doublets. The PMR spectrum showed a singlet at 9.23 δ for proton at C-5 and two doublets centred at 9.05 δ and 8.9 δ ascribable to protons at C-1 and C-12 respectively. (Fig.3).

Similarly PMR spectrum of 85 showed, as expected, a downfield multiplet for proton at C-1 spread between 9.33 - 9.66 δ and another multiplet for proton at C-11 spread between 8.03 - 8.5 δ. A singlet appearing at 8.3 δ could be assigned to proton at C-7. (Fig.4).

Also, PMR spectrum of compound 86 shows, as expected, a singlet at 9.16 δ for proton at C-12 and two multiplets centred at 8.16 δ and 8.6 δ ascribable to protons at C-11 and C-1 respectively. (Fig.5).



83



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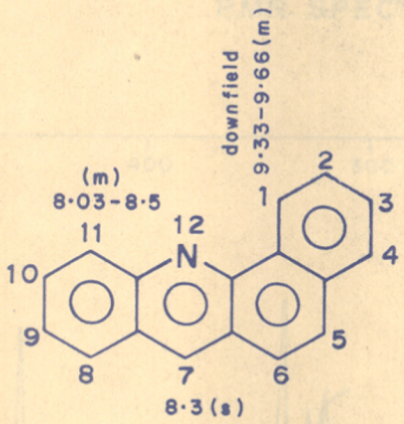
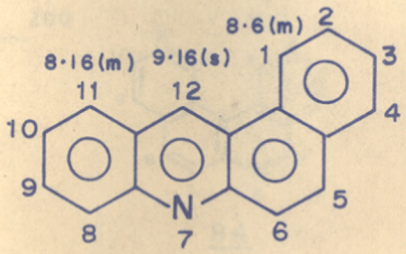
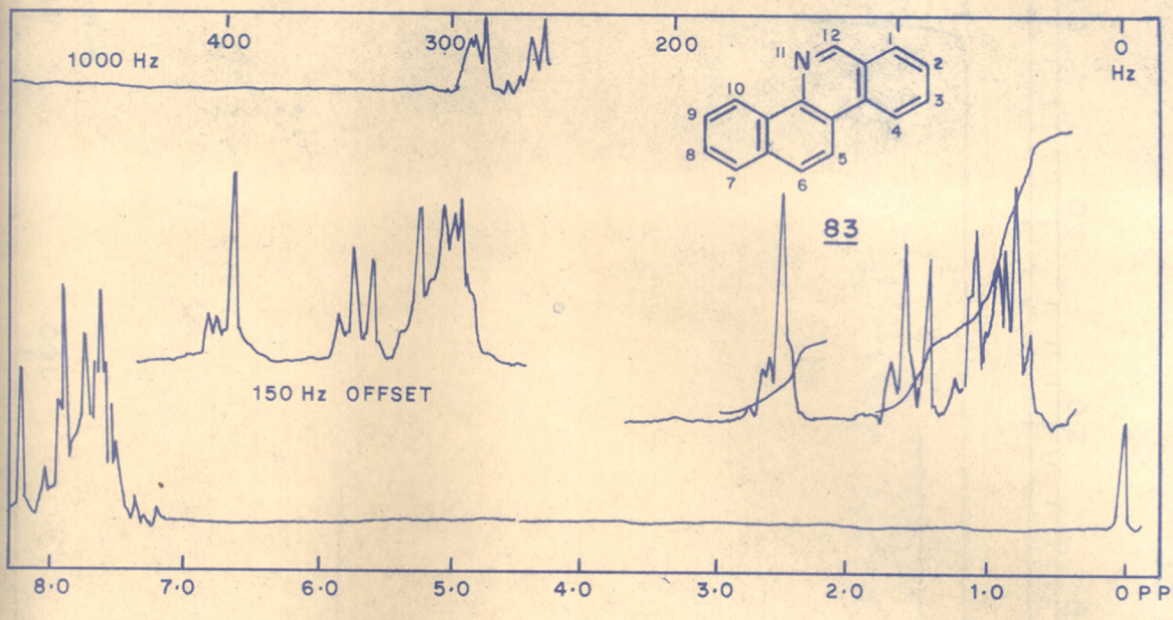


85



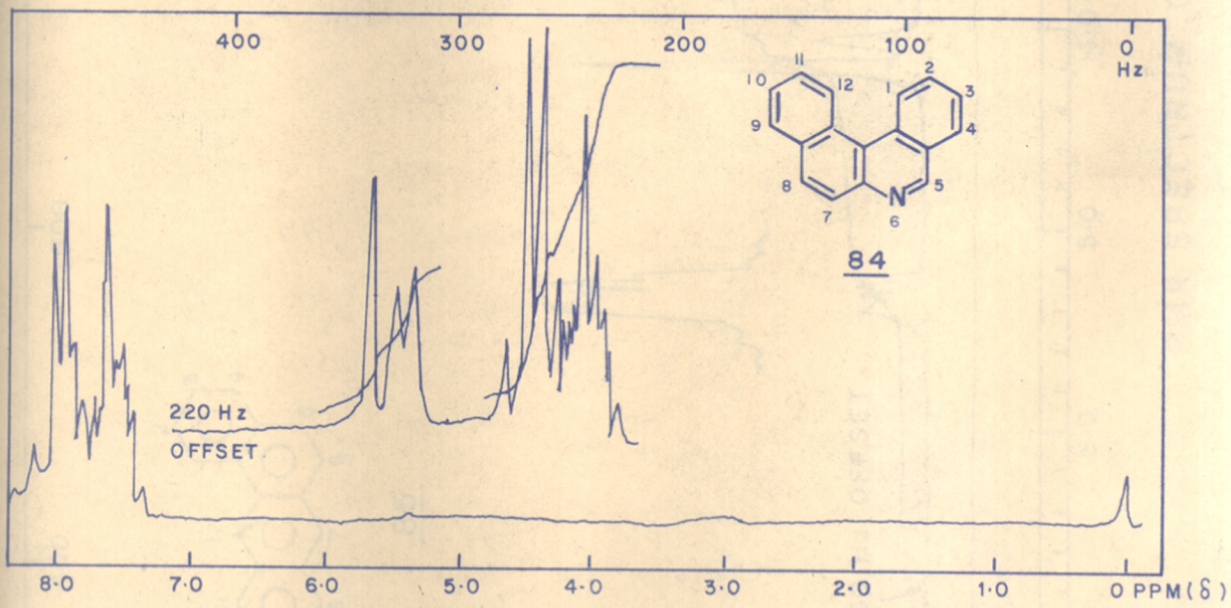
86

CHART 26



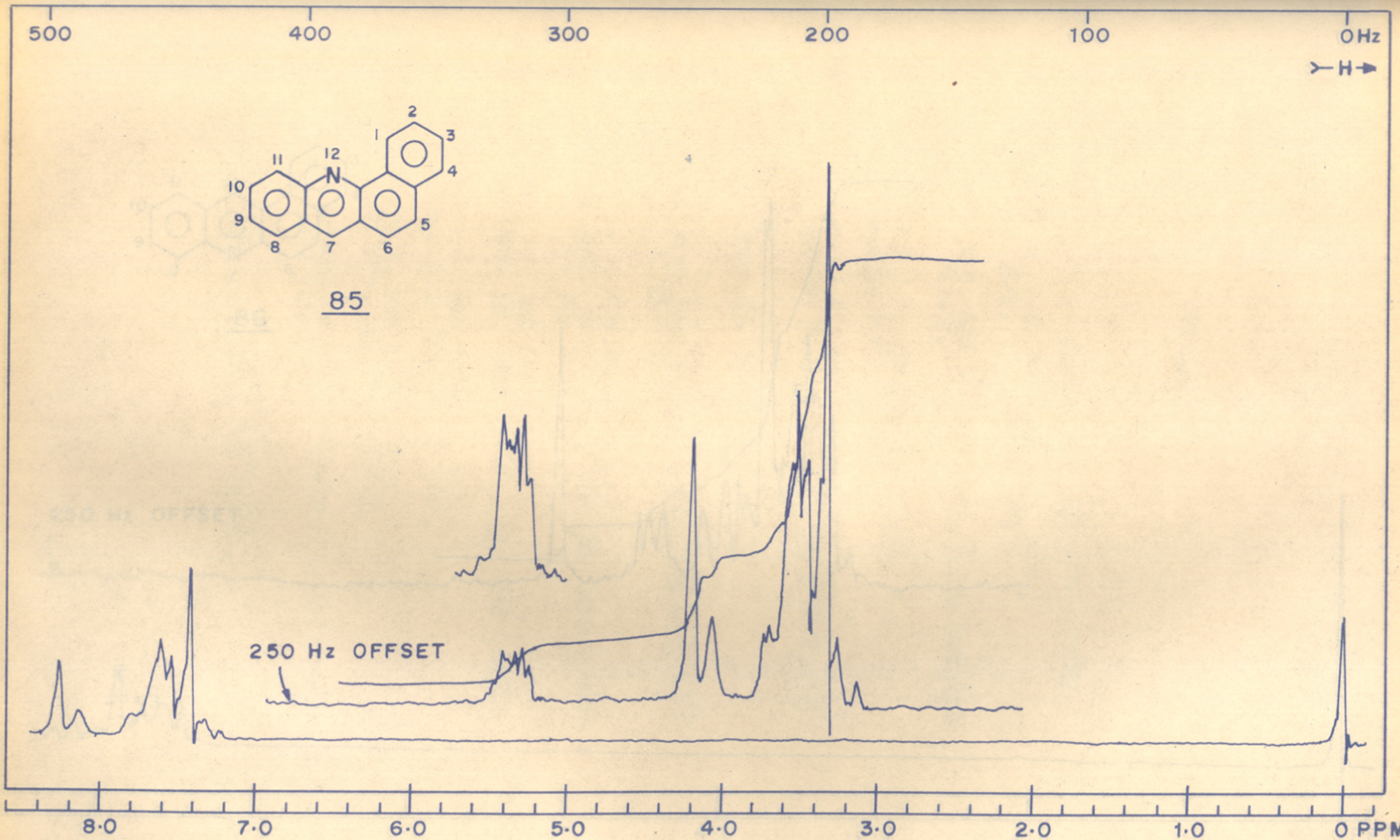
PMR SPECTRUM OF 83 IN CCl_4

FIG·2



PMR SPECTRUM OF 84 IN CCl_4

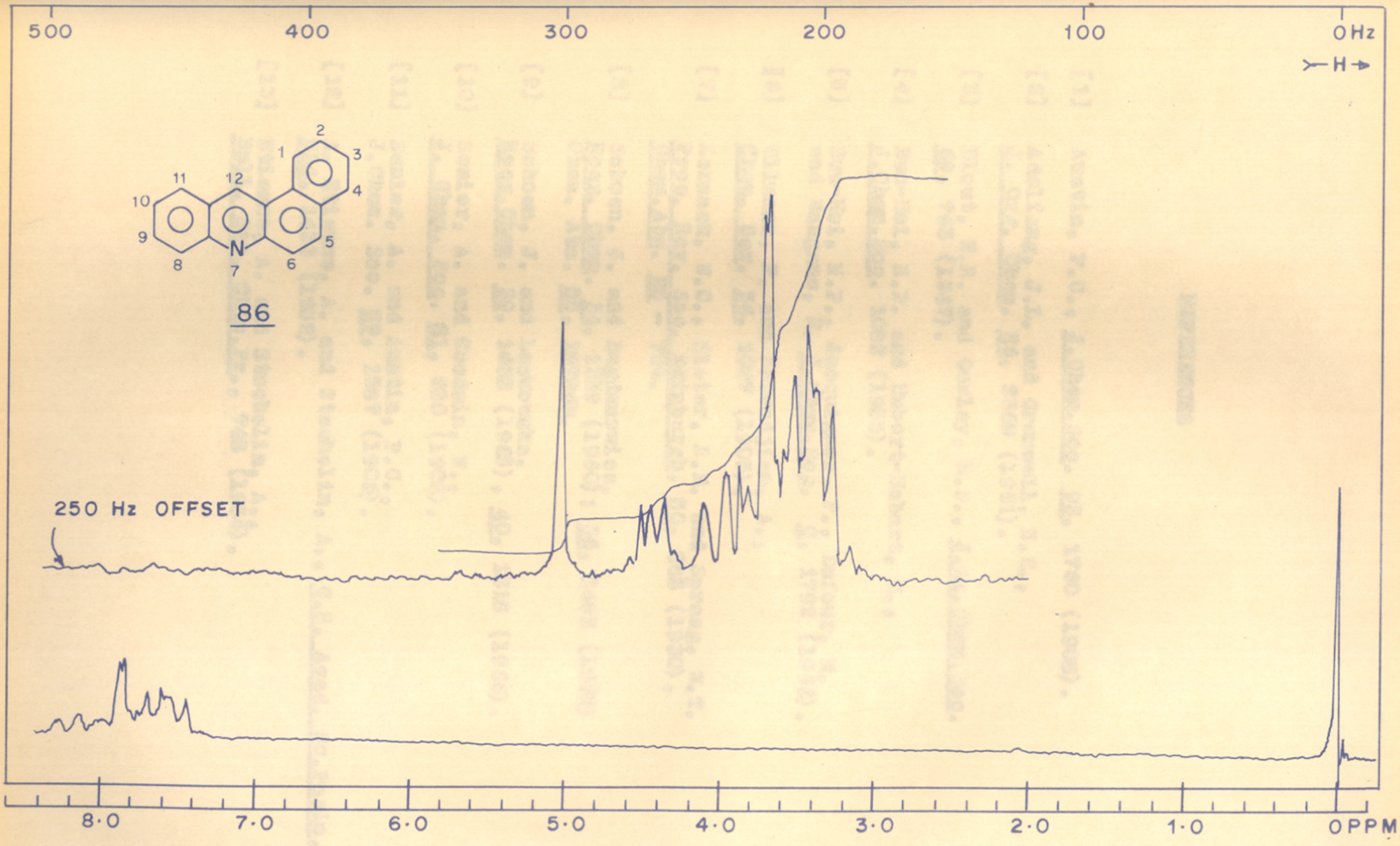
FIG·3



85

PMR SPECTRUM OF 85 IN CCl_4

FIG. 4



PMR SPECTRUM OF 86 IN CCl_4

FIG. 5

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CHAPTER III

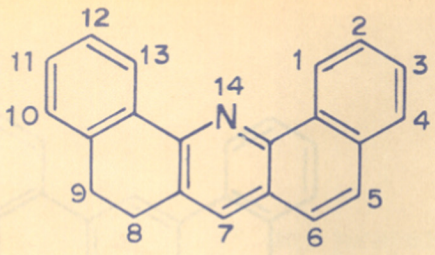
SYNTHESIS OF MONOAZA PENTACYCLIC COMPOUNDS

The synthesis of condensed nitrogen heterocyclics (quinolines and acridines) by acid catalysed cyclodehydration of cis-2-arylaminomethylenecyclohexanones has been described by Tilak et al. [1,2,3]. The present extension of this work describes the synthesis of 8,9-dihydrodibenz(c,h)-acridine 1, 7,8-dihydrodibenzo(c,k)phenanthridine 2, 5,6-dihydrodibenz(a,h)acridine 3 and 5,6-dihydrodibenzo(a,k)-phenanthridine 4. These dihydro compounds were then dehydrogenated to give the parent monoaza pentacyclic compounds viz., dibenz(c,h)acridine 5, dibenzo(c,k)-phenanthridine 6, dibenz(a,h)acridine 7 and dibenzo(a,k)-phenanthridine 8 (Chart 1).

Compounds 5 and 7 which are the aza analogues of the carcinogenic hydrocarbons dibenz(a,j)anthracene 9 and dibenz(a,h)anthracene 10, are reported to show carcinogenic activity [4]. Compounds 6 and 8 are the aza analogues of benzo(c)chrysene 11 and dibenzo(c,g)-phenanthrene 12, respectively (Chart 2).

As in the case of earlier work, the starting point for the above synthesis was the preparation of 2-(1'-naphthylaminomethylene)-1-tetralone 13 and 2-(2'-naphthylaminomethylene)-1-tetralone 14 (Chart 2).

The names and numberings laid down by Chemical Abstracts (also used by the Ring Index) are employed throughout.



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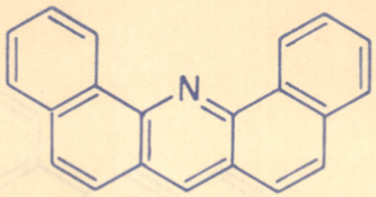

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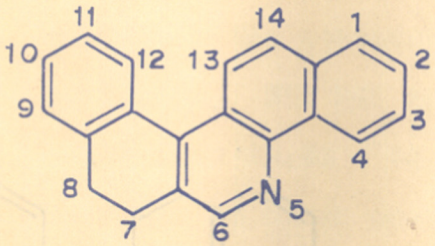

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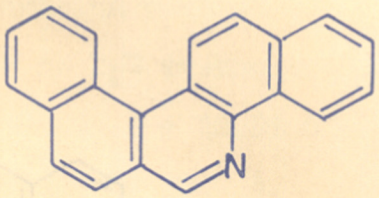

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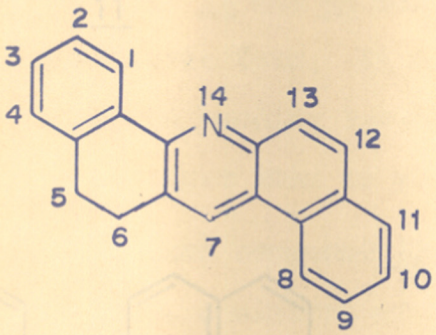

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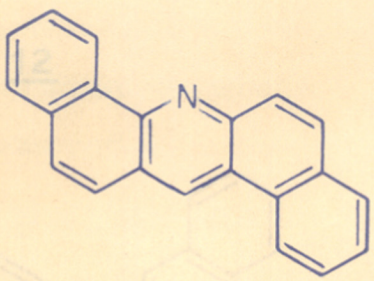

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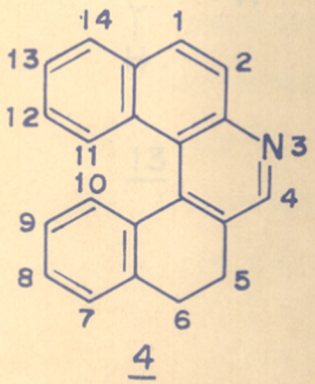

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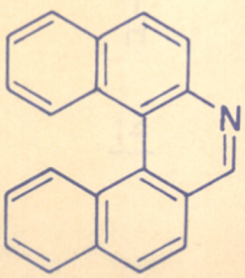

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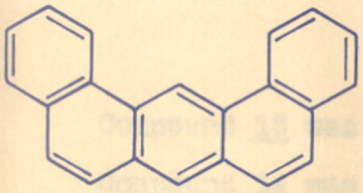
CHART 1



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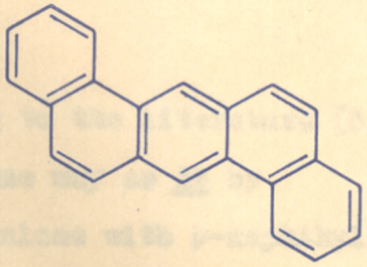

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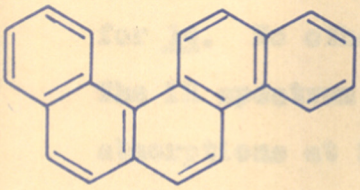

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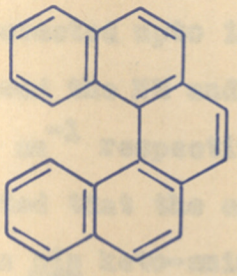

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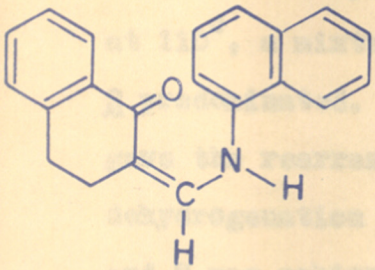

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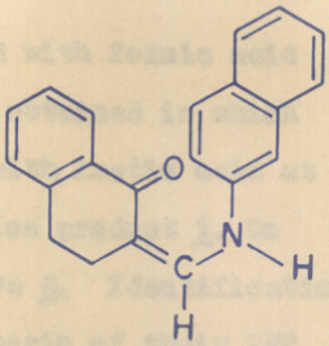


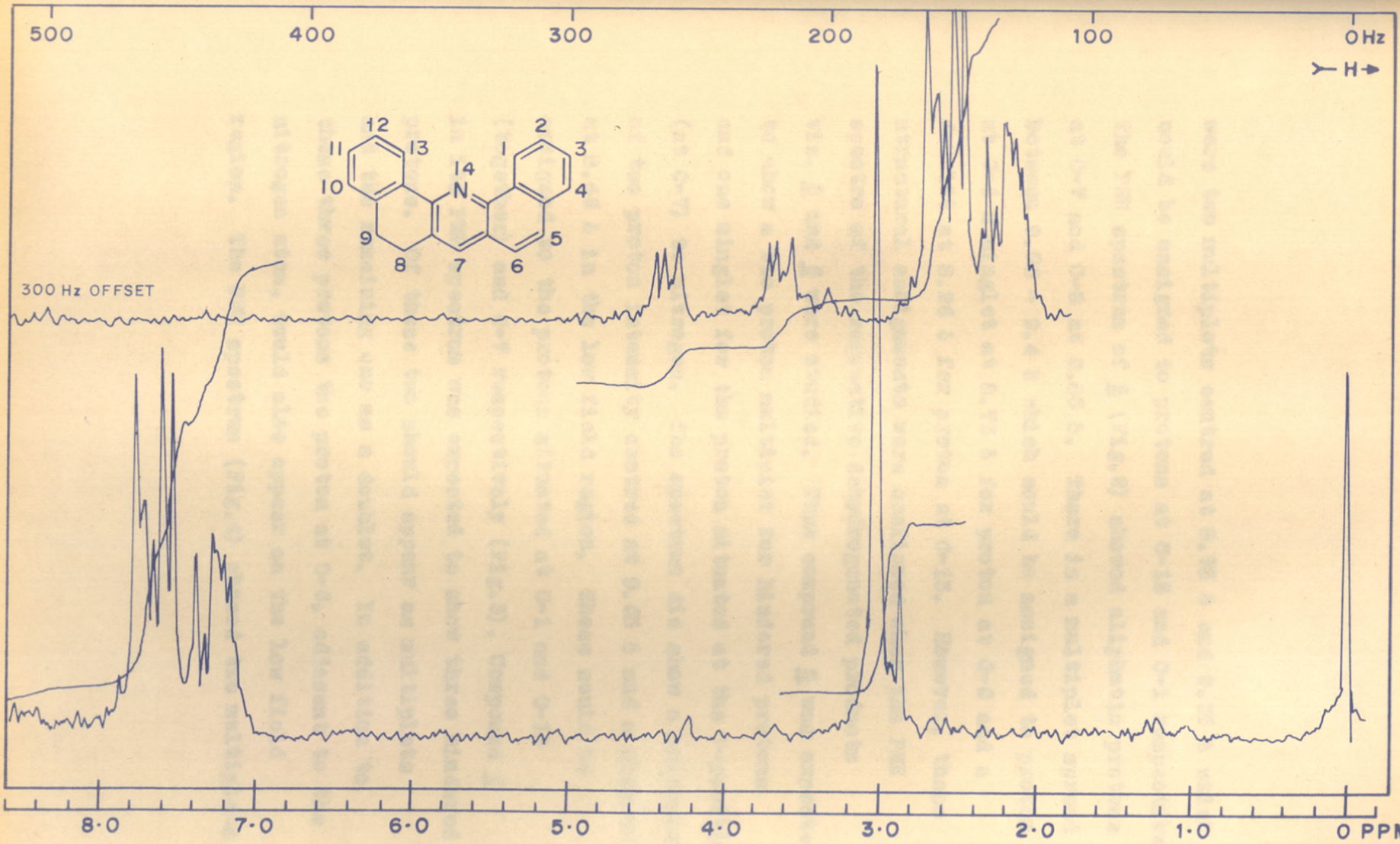
14

CHART 2

Compound 13 was prepared according to the literature [5]. Compound 14 was prepared in the same way as 13 by condensing hydroxymethylene-α-tetralone with β-naphthylamine.

As in earlier cases [6,7,8], it was necessary to ascertain the structures of the condensation products 13 and 14. The PMR spectrum showed NH as D_2O exchangeable doublet at 12.68 - 13.08 δ for 13 and at 12.0 - 12.21 δ for 14. No other peak could be detected upto 15.0 δ. The IR spectrum in chloroform showed the NH and C=O absorptions at 3000 cm^{-1} and 1635 cm^{-1} respectively for both 13 and 14. This data indicated that the condensation products 13 and 14 mostly exist in cis keto-amine tautomeric form. It may be pointed out here that the hydrogen bonding between NH and C=O in these compounds is stronger than in phenylaminomethylenecyclohexanones [6].

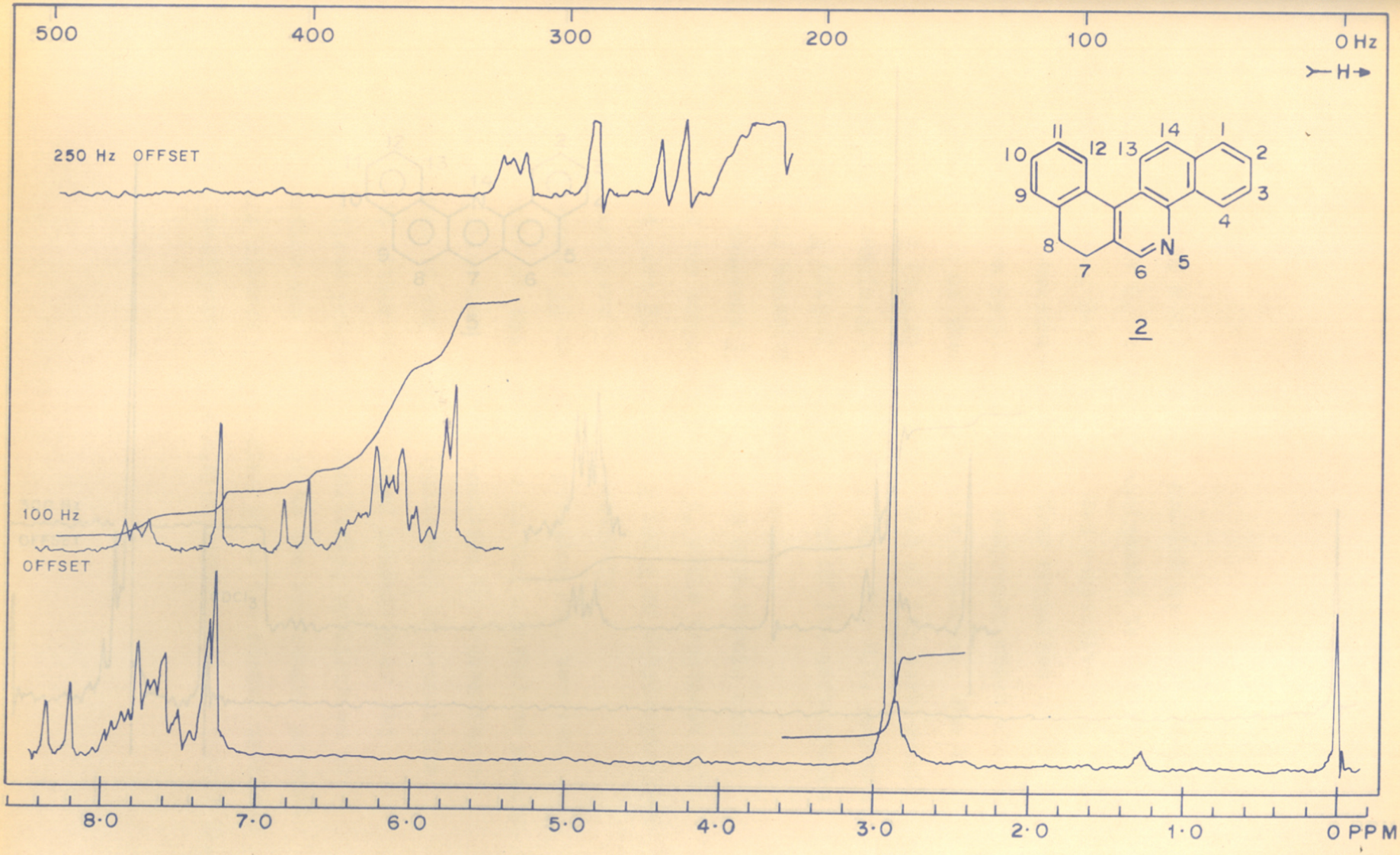
When compound 13 was treated with formic acid at 110°, a mixture of 1 and 2 was obtained in which 2 predominated. Treatment of 13 with lactic acid at 140° gave the rearranged cyclodehydration product 1. On dehydrogenation 1 gave 5 and 2 gave 6. Identification of 1 and 2 was achieved either on the basis of their PMR spectra or the spectra of their dehydrogenated products. The PMR spectrum of 1 (Fig. 1) showed aliphatic protons at C-8 and C-9 at 3.0 δ as four proton singlet. There



PMR SPECTRUM OF 1 IN CCl_4

FIG·1

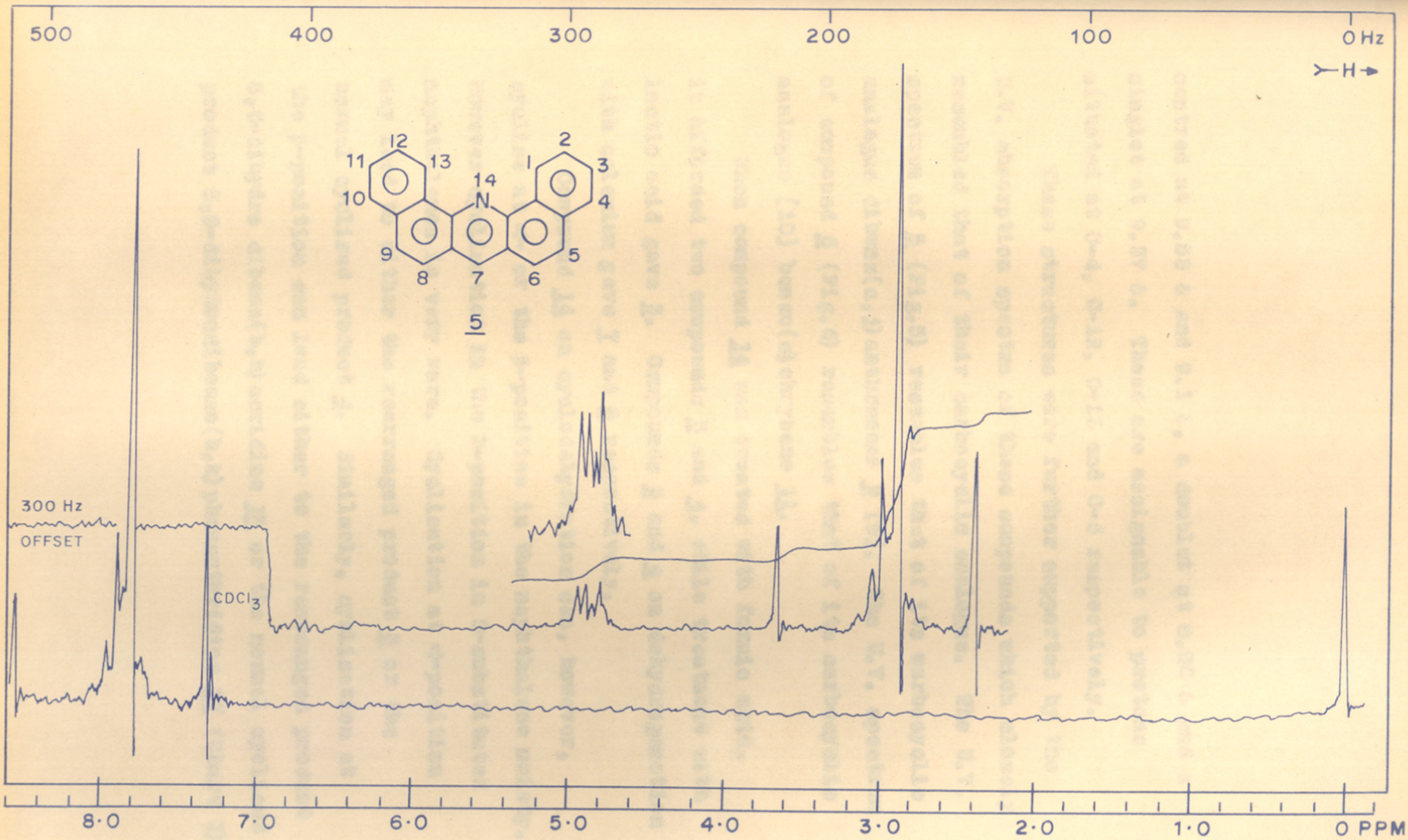
were two multiplets centred at 8.75 δ and 9.33 δ which could be assigned to protons at C-13 and C-1 respectively. The PMR spectrum of 2 (Fig.2) showed aliphatic protons at C-7 and C-8 at 2.83 δ. There is a multiplet spread between 9.06 - 9.4 δ which could be assigned to proton at C-4 a singlet at 8.73 δ for proton at C-6 and a doublet at 8.26 δ for proton at C-13. However, these structural assignments were confirmed when the PMR spectra of the respective dehydrogenated products viz. 5 and 6 were studied. Thus compound 5 was expected to show a two proton multiplet for hindered protons and one singlet for the proton situated at the γ-position (at C-7) to nitrogen. The spectrum did show a multiplet of two proton intensity centred at 9.65 δ and a singlet at 8.46 δ in the low field region. These could be assigned to the protons situated at C-1 and C-13 (together) and C-7 respectively (Fig.3). Compound 6 in its PMR spectrum was expected to show three hindered protons. Of these two should appear as multiplets and the remaining one as a doublet. In addition to these three protons the proton at C-6, adjacent to the nitrogen atom, would also appear on the low field region. The PMR spectrum (Fig.4) showed two multiplets



2

PMR SPECTRUM OF 2 IN CCl_4

FIG. 2



PMR SPECTRUM OF 5 IN $CDCl_3$

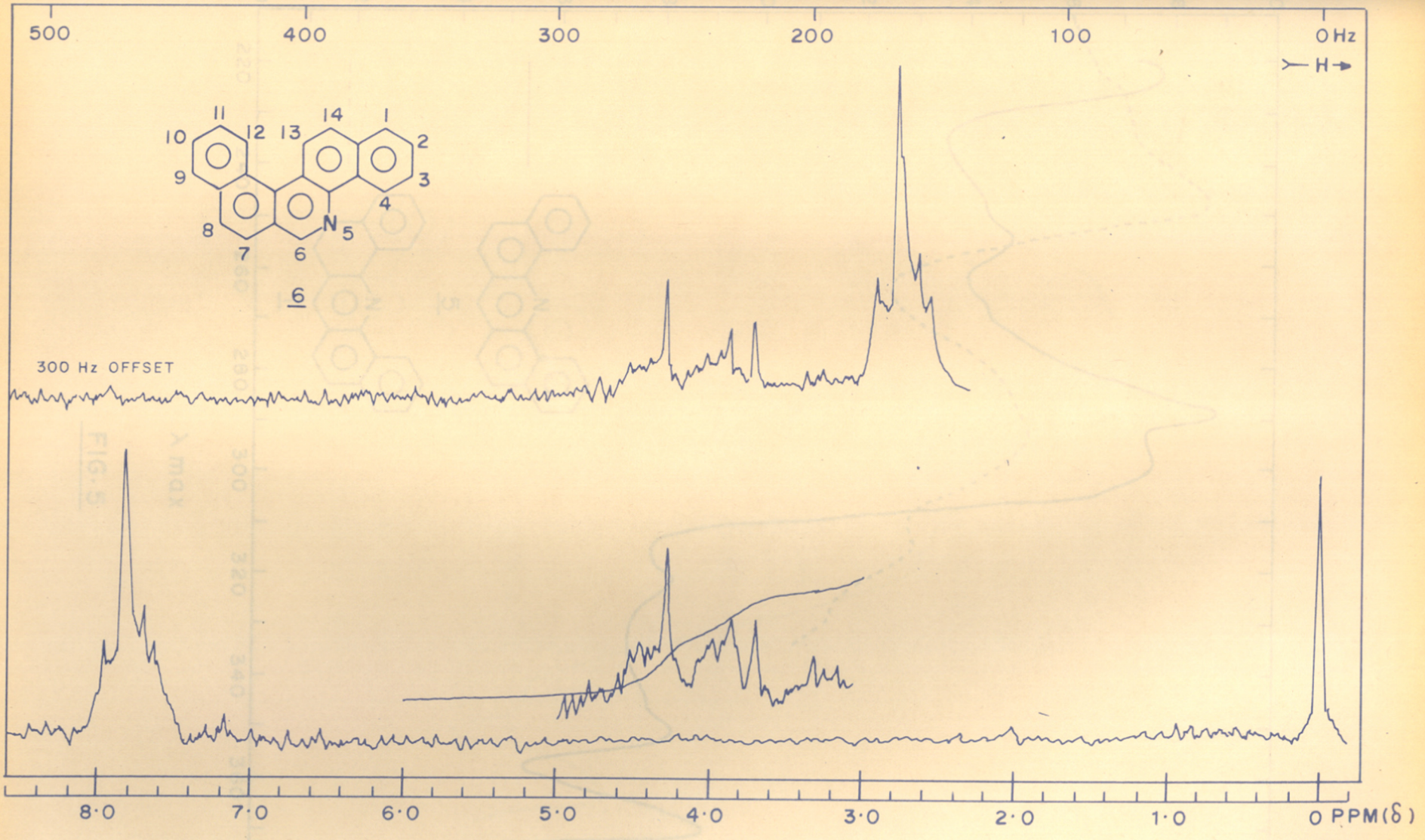
FIG. 3

centred at 9.53 δ and 9.1 δ, a doublet at 8.80 δ and a singlet at 9.37 δ. These are assignable to protons situated at C-4, C-12, C-13 and C-6 respectively.

These structures were further supported by the U.V. absorption spectra of these compounds which closely resembled that of their carbocyclic analogue. The U.V. spectrum of 5 (Fig.5) resembles that of its carbocyclic analogue dibenz(a,j)anthracene 9 [9]. The U.V. spectrum of compound 6 (Fig.6) resembles that of its carbocyclic analogue [10] benzo(c)chrysene 11.

When compound 14 was treated with formic acid, it afforded two compounds 3 and 4, while treatment with lactic acid gave 3. Compounds 3 and 4 on dehydrogenation with selenium gave 7 and 8 respectively.

Compound 14 on cyclodehydration can, however, cyclise at α- or the β-position in the naphthalene moiety. However cyclisation in the 3-position in 2-substituted naphthalenes is very rare. Cyclisation at α-position may lead to either the rearranged product 3 or the normal cyclised product 4. Similarly, cyclisation at the β-position can lead either to the rearranged product 5,6-dihydro dibenz(b,h)acridine 15 or the normal cyclised product 8,9-dihydrodibenzo(b,k)phenanthridine 17 (Chart 3).



PMR SPECTRUM OF 6 IN CCl_4

FIG. 4

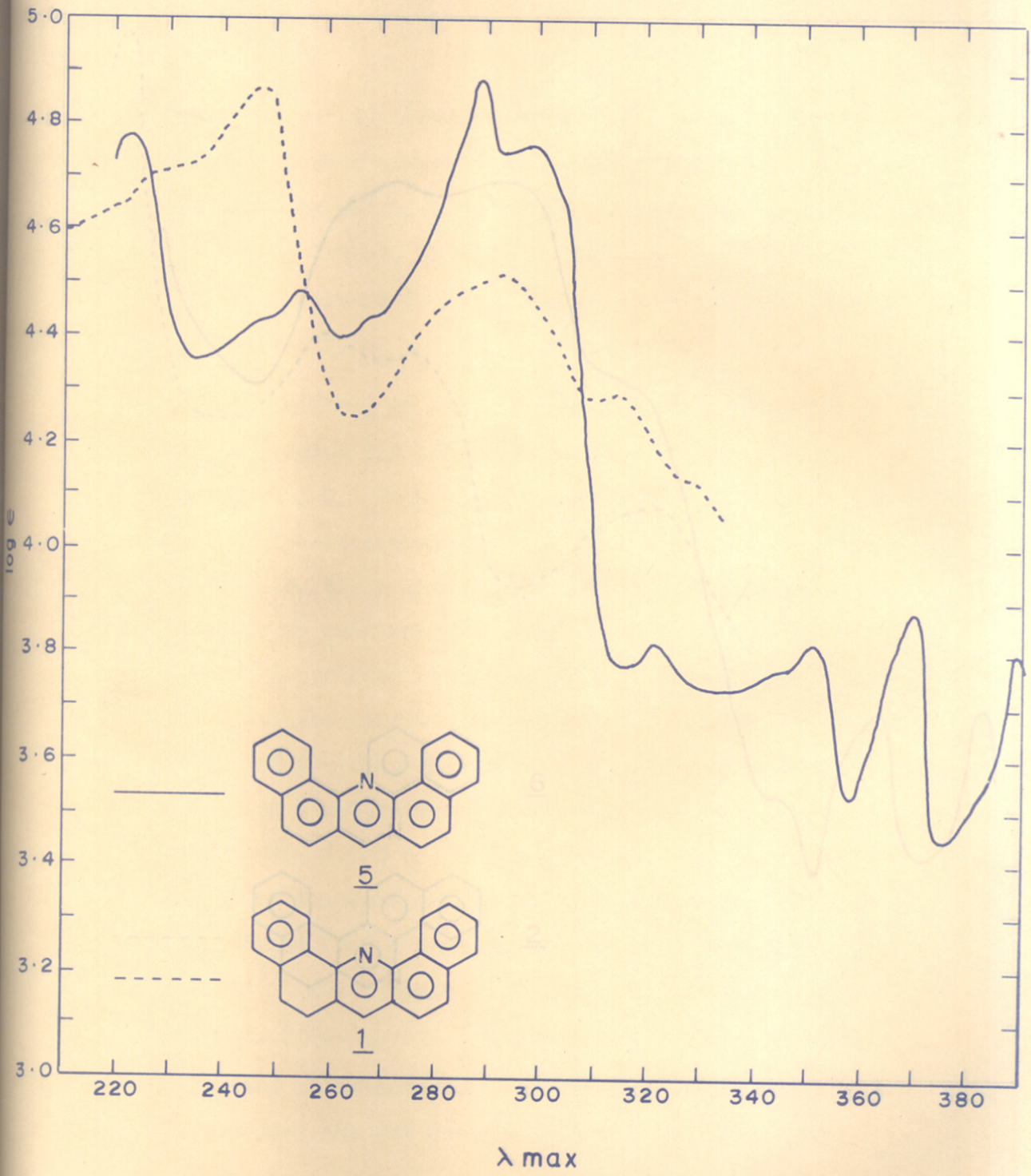
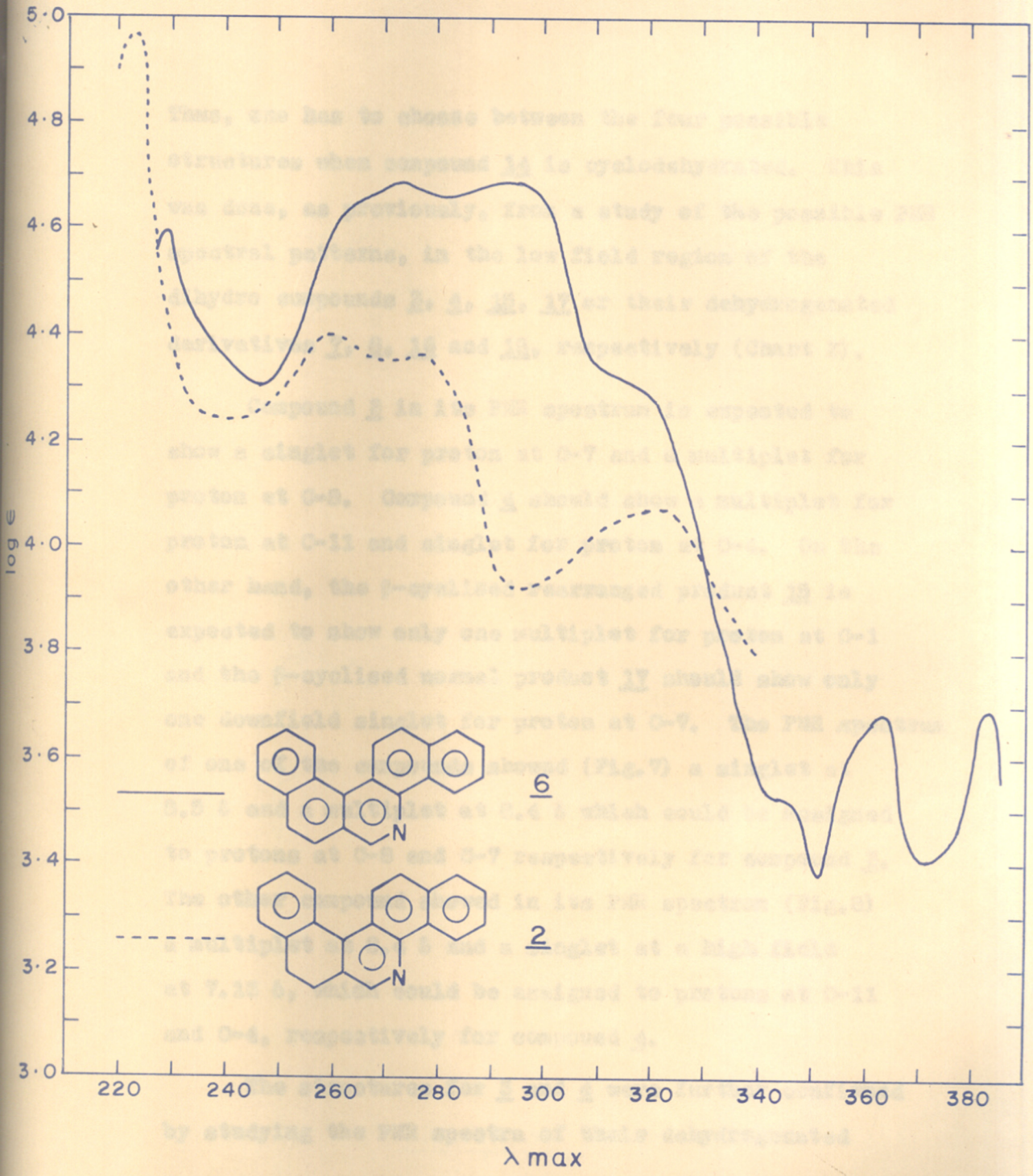

5·0
4·8
4·6
4·4
4·2
4·0
3·8
3·6
3·4
3·2
3·0
log ε
220
240
260
280
300
320
340
360
380
λ max
N
5
N
1

FIG. 5


5·0
4·8
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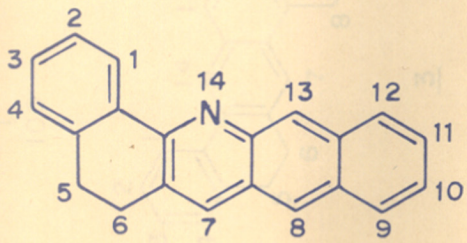
3·6
3·4
3·2
3·0
log ∈
220
240
260
280
300
320
340
360
380
λ max
6
2
N
N

FIG·6

Thus, one has to choose between the four possible structures when compound 14 is cyclodehydrated. This was done, as previously, from a study of the possible PMR spectral patterns, in the low field region of the dihydro compounds 3, 4, 15, 17 or their dehydrogenated derivatives 7, 8, 16 and 18, respectively (Chart 3).

Compound 3 in its PMR spectrum is expected to show a singlet for proton at C-7 and a multiplet for proton at C-8. Compound 4 should show a multiplet for proton at C-11 and singlet for proton at C-4. On the other hand, the β-cyclised rearranged product 15 is expected to show only one multiplet for proton at C-1 and the β-cyclised normal product 17 should show only one downfield singlet for proton at C-7. The PMR spectrum of one of the compounds showed (Fig.7) a singlet at 8.5 δ and a multiplet at 8.4 δ which could be assigned to protons at C-8 and C-7 respectively for compound 3. The other compound showed in its PMR spectrum (Fig.8) a multiplet at 8.4 δ and a singlet at a high field at 7.13 δ, which could be assigned to protons at C-11 and C-4, respectively for compound 4.

The structures for 3 and 4 were further confirmed by studying the PMR spectra of their dehydrogenated



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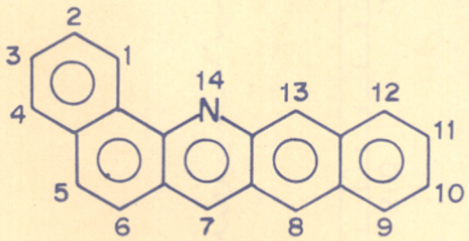

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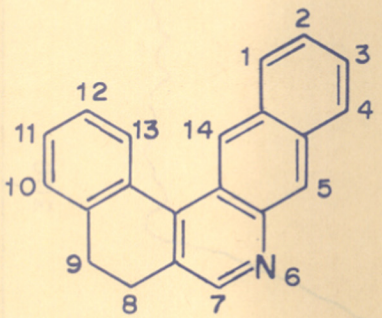

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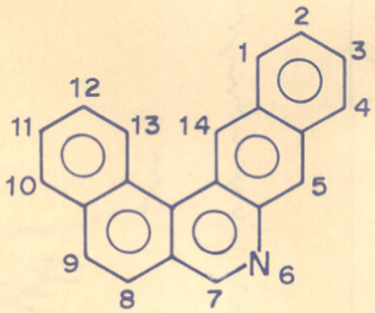

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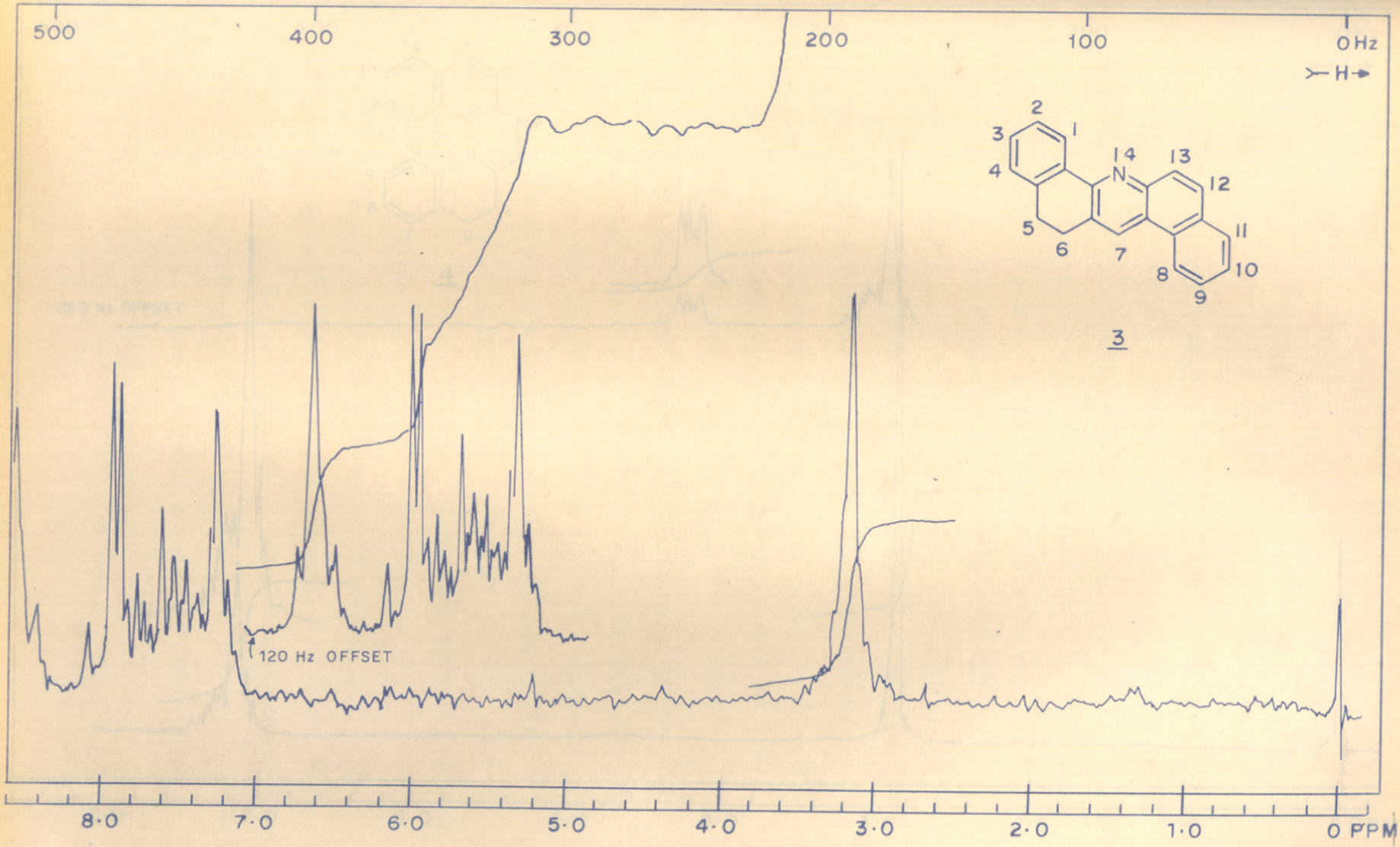
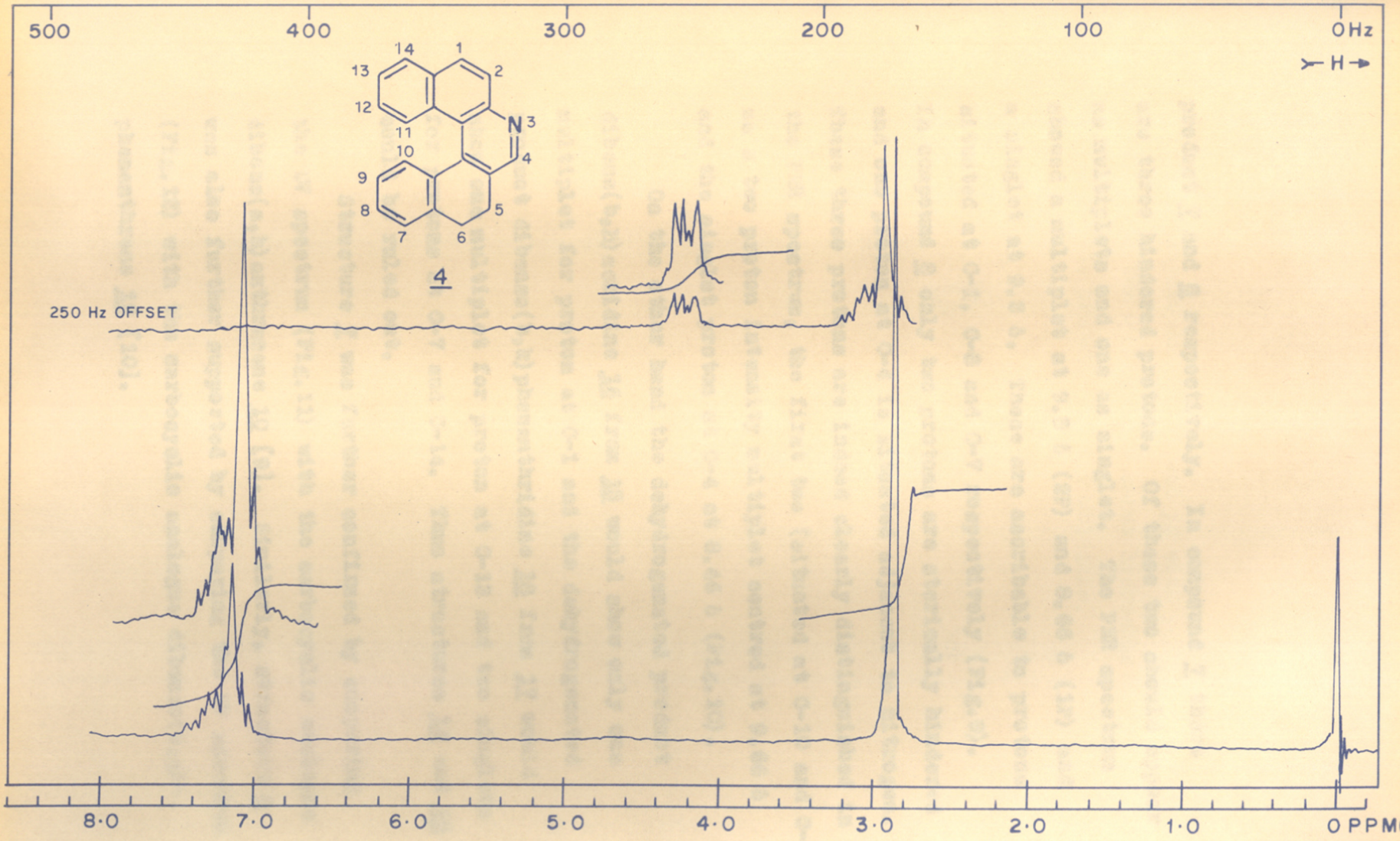
CHART 3



PMR SPECTRUM OF 3 IN CCl_4

FIG·7



PMR SPECTRUM OF 4 IN CCl_4

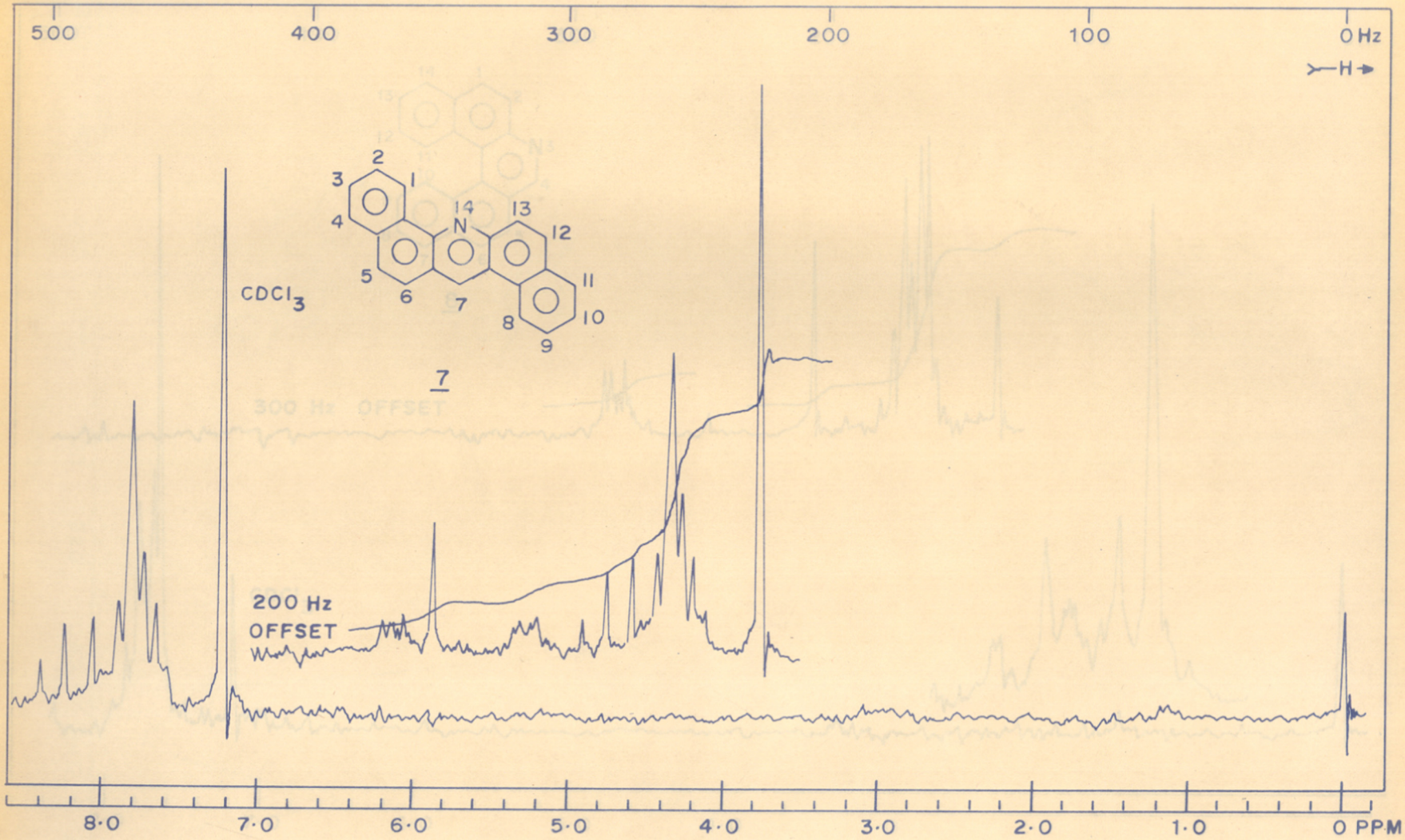
FIG·8

product 7 and 8 respectively. In compound 7 there are three hindered protons. Of these two should appear as multiplets and one as singlet. The PMR spectrum showed a multiplet at 9.5 δ (2P) and 8.66 δ (1P) and a singlet at 9.3 δ. These are ascribable to protons situated at C-1, C-8 and C-7 respectively (Fig.9). In compound 8 only two protons are sterically hindered and one proton at C-4 is situated adjacent to nitrogen. These three protons are indeed clearly distinguished in the PMR spectrum, the first two (situated at C-10 and C-11) as a two proton intensity multiplet centred at 9.66 δ and the singlet proton at C-4 at 8.46 δ (Fig.10).

On the other hand the dehydrogenated product dibenz(b,h)acridine 16 from 15 would show only one multiplet for proton at C-1 and the dehydrogenated product dibenzo(b,k)phenanthridine 18 from 17 would show one multiplet for proton at C-13 and two singlets for protons at C-7 and C-14. Thus structures 16 and 18 could be ruled out.

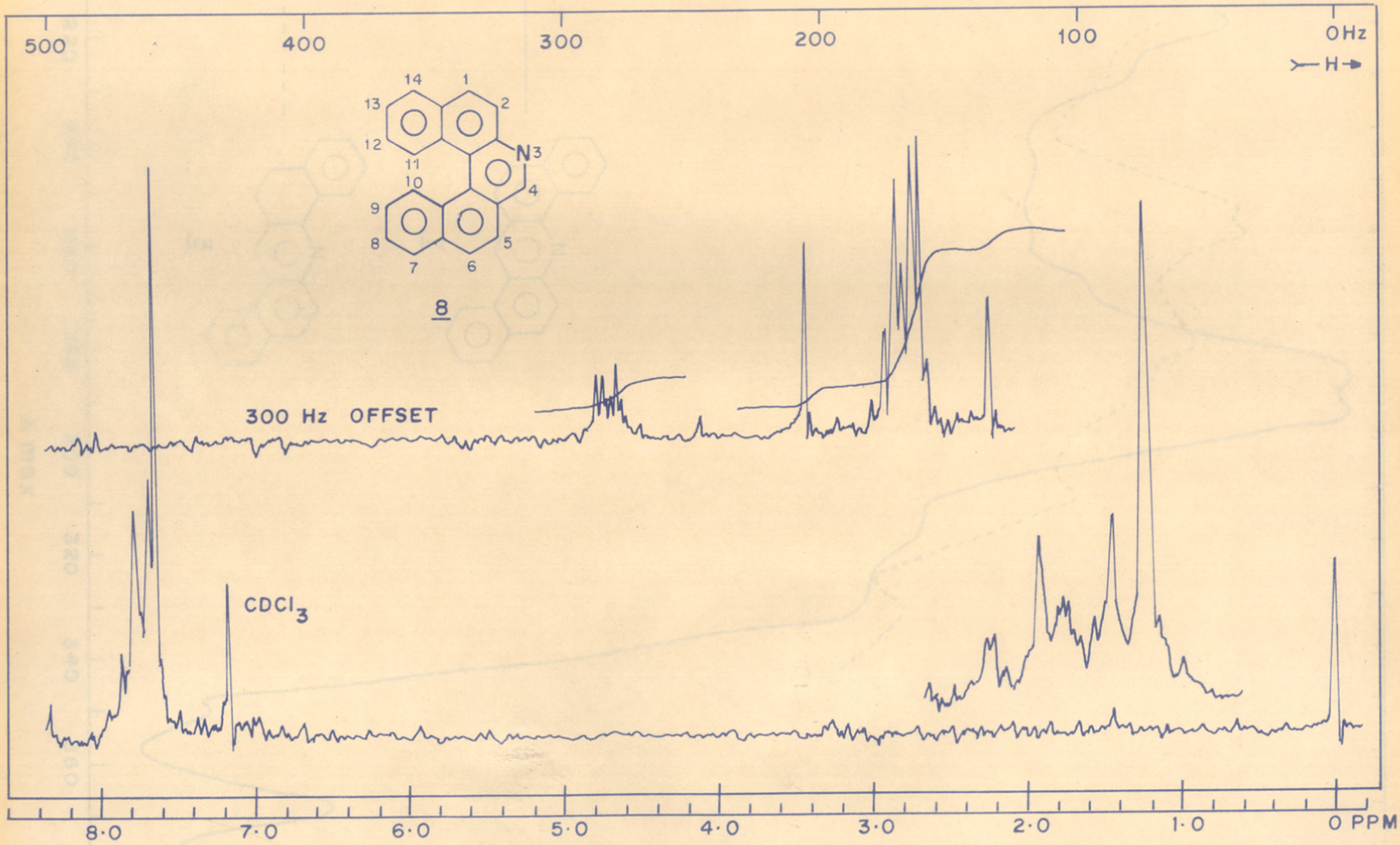
Structure 7 was further confirmed by comparing the UV spectrum (Fig.11) with the carbocyclic analogue dibenz(a,h)anthracene 10 [9]. Similarly, structure 8 was also further supported by comparing the UV spectrum (Fig.12) with the carbocyclic analogue dibenzo(c,g)-phenanthrene 12 [10].

Cyclodehydration of 13 and 14 with polyphosphoric acid and with the appropriate amine hydrochlorides resulted in the breaking of the molecule.



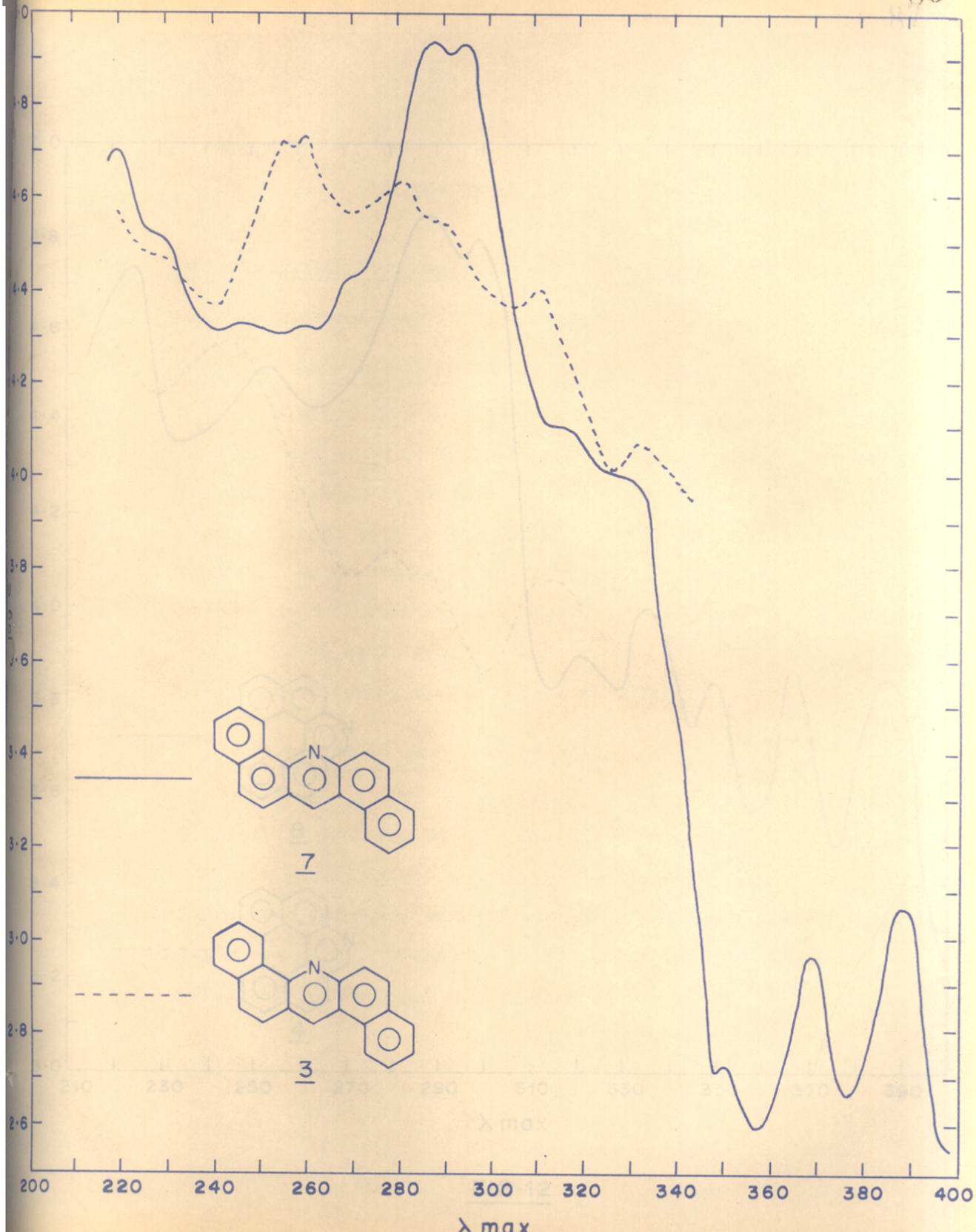
PMR SPECTRUM OF 7 IN $CDCl_3$

FIG. 9

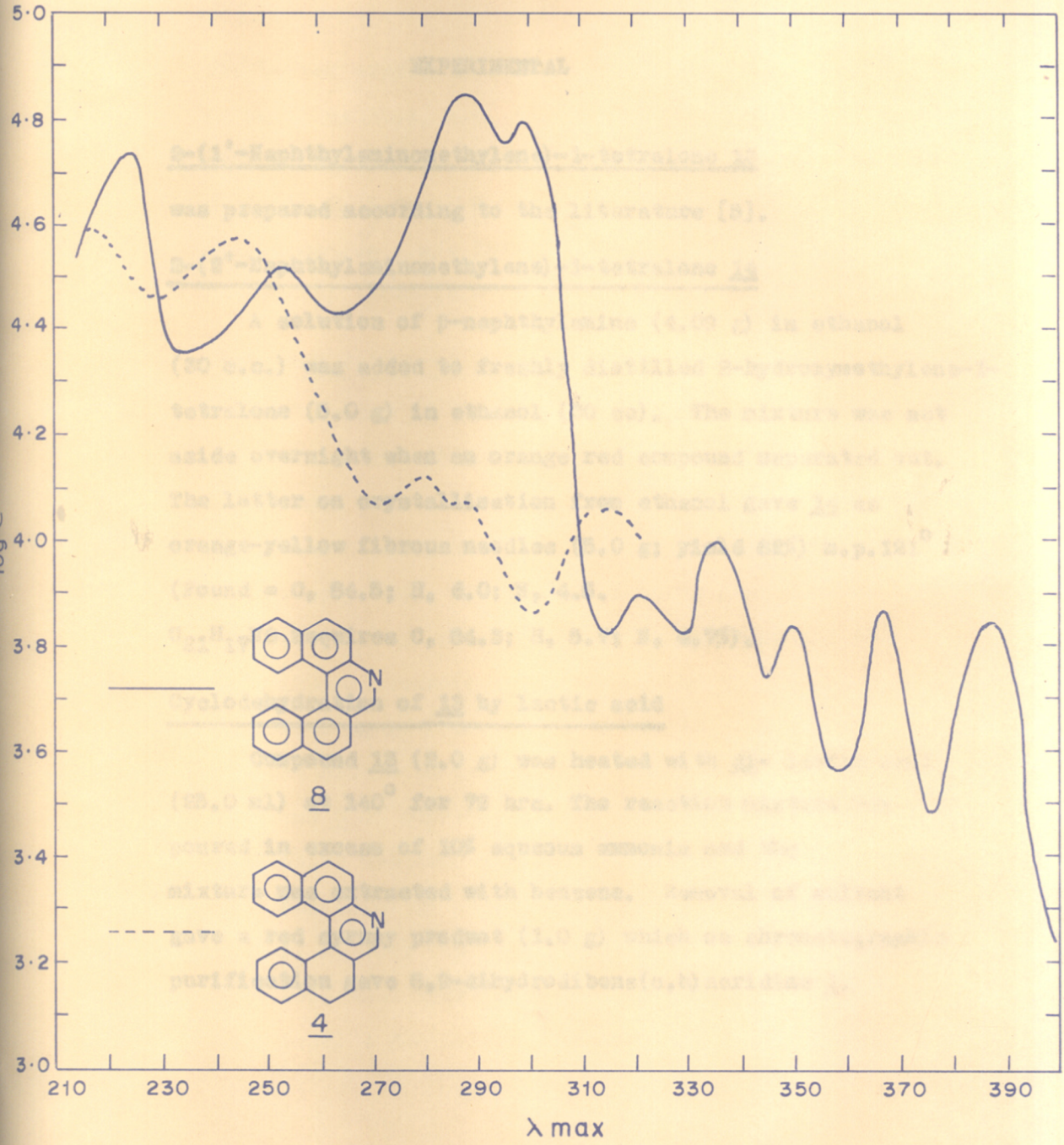


PMR SPECTRUM OF 8 IN $CDCl_3$

FIG·10


4·8
4·6
4·4
4·2
4·0
3·8
3·6
3·4
3·2
3·0
2·8
2·6
200
220
240
260
280
300
320
340
360
380
400
λ max
N
7
N
3

FIG·11


5·0
4·8
4·6
4·4
4·2
4·0
3·8
3·6
3·4
3·2
3·0
log ε
210
230
250
270
290
310
330
350
370
390
λ max
N
8
N
4

FIG·12

EXPERIMENTAL

2-(1'-Naphthylaminomethylene)-1-tetralone 13

was prepared according to the literature [5].

2-(2'-Naphthylaminomethylene)-1-tetralone 14

A solution of β-naphthylamine (4.09 g) in ethanol (30 c.c.) was added to freshly distilled 2-hydroxymethylene-1-tetralone (5.0 g) in ethanol (30 cc). The mixture was set aside overnight when an orange red compound separated out. The latter on crystallisation from ethanol gave 14 as orange-yellow fibrous needles (5.0 g; yield 82%) m.p. 121°
(Found = C, 84.5; H, 6.0; N, 4.5.
$C_{21}H_{17}NO$ requires C, 84.3; H, 5.7; N, 4.7%).

Cyclodehydration of 13 by lactic acid

Compound 13 (2.0 g) was heated with dl- lactic acid (25.0 ml) at 140° for 72 hrs. The reaction mixture was poured in excess of 10% aqueous ammonia and the mixture was extracted with benzene. Removal of solvent gave a red syrupy product (1.0 g) which on chromatographic purification gave 8,9-dihydrodibenz(c,h)acridine 1.

The latter crystallised from pet.ether (b.p. 60-80°) in white needles, m.p. 141° (0.18 g; yield 10%) (Found: C, 89.8; H, 5.7; N, 5.3. $C_{21}H_{15}N$ requires C, 89.7; H, 5.3; N, 5.0).
Mass spectrum : m/e 281 (M^+).
UV (Fig.5) : 246 (4.87); 294 (4.52); 314 (4.30); 330 (4.12).

Cyclodehydration of 13 with formic acid

Compound 13 (2.09 g) was heated under reflux with 98% formic acid (30 cc.) for 18 hrs. The red syrupy liquid was poured in excess of 10% aqueous ammonia and the mixture extracted with benzene. TLC showed the presence of two compounds. Removal of benzene gave a crude product (1.85 g) which on chromatography gave 1 and 7,8-dihydrodibenzo(c,k)phenanthridine 2. Compound 1 was found to be identical with lactic acid cyclisation product mentioned earlier (by PMR and mixed m.p.). Compound 2 on crystallisation from pet. ether (b.p. 60-80°) gave white needles, m.p. 140° (lit. [5] 138-140° from ethanol) (0.28 g; yield 14%). (Found: C, 90.0; H, 5.5; N, 5.2. $C_{21}H_{15}N$ requires C, 89.7; H, 5.3; N, 5.0%). Mass spectrum : m/e 281 (M^+).
UV (Fig.6) : 223(4.96); 260(4.4); 275(4.35); 320(4.07).

Dibenz(c,h)acridine 5

Compound 1 (80 mg) was mixed with selenium powder (150 mg) and heated at 300° for 5 hrs. The product was extracted with benzene which on chromatographic purification and crystallisation from pet. ether (60-80°) and small amount of benzene gave 5 in yellow needles (30 mg; yield 38%) m.p. 191 (lit.[5,11] 189-191°). (Found: C, 90.4; H, 5.0; N, 5.4. $C_{22}H_{13}N$ requires C, 90.3; H, 4.7; N, 5.0%).
Mass spectrum: m/e 279 (M^+).
UV (Fig.5) : 223 (4.78), 254(4.46), 288(4.88), 299(4.76), 324(3.82), 337(3.88), 354(3.83), 373(3.88), 384(3.56), 391(3.81).

Dibenzo(c,k)phenanthridine 6

Compound 2 (120 mg) was heated with selenium powder (200 mg) at 300° for 6 hrs and worked up as in 5. Chromatographic purification and crystallisation with petroleum ether (60-80°) and small amount of benzene gave 6 in light yellow plates (90 mg; yield 76%) m.p. 123° (lit.[5] 122.5-123° in ethanol) (Found: C, 90.6; H, 5.0; N, 4.9. $C_{21}H_{13}N$ requires C, 90.3; H, 4.7; N, 5.0%). Mass spectrum : m/e 279 (M^+).
UV : (Fig.6) 229 (4.58), 273(4.89); 289(4.68), 298(4.68), 318(4.36), 350(3.53), 369(3.70), 388(3.69).

Cyclodehydration of 14 by lactic acid

Compound 14 (2.0 g) was heated with dl- lactic acid (20 cc.) at 140° for 72 hrs and the reaction mixture was worked as in the case of 1. The reaction product on chromatography gave 5,6-dihydrodibenz(a,h)-acridine 3 which crystallised from pet.ether (b.p.60-80°) in white fibrous needles, m.p. 154° (0.235 g, yield 12%). (Found: C, 89.7; H, 5.5; N, 4.7. $C_{21}H_{15}N$ requires C, 89.7; H, 5.3; N, 5.0%). Mass spectrum : m/e 281 (M^+). UV (Fig.11) : 255(4.72); 262(4.73); 280(4.62); 290(4.55); 314(4.39); 332(4.07).

Cyclodehydration of 14 with formic acid

Compound 14 (2.0 g) was refluxed with 98% formic acid (30 cc.) for 18 hrs. The red coloured reaction mixture was worked up as in 1 and 2. The crude product (1.8 g) on chromatography yielded 5,6-dihydrodibenzo(a,k)-phenanthridine 4 and 3. Compound 4 eluted first, crystallised from pet.ether (b.p. 60-80°) in white needles, m.p. 140° (0.22 g; yield 12%). (Found: C, 90.0; H, 5.4; N, 5.0. $C_{21}H_{15}N$ requires C, 89.7; H, 5.3; N, 4.9%). Mass spectrum : m/e 281 (M^+).
UV (Fig.12) : 244 (4.57); 280(4.13); 290(4.03); 332(4.05).
The second fraction in chromatography yielded 3 (0.035 g; yield 2%).

Dibenz(a,h)acridine 7

Compound 3 (50 mg) was heated with selenium (100 mg) at 300° for 6 hrs. The crude product was extracted with benzene which on chromatographic purification over alumina (neutral) column and crystallisation from pet.ether (b.p. 60-80°) and small amounts of benzene gave 7 in yellow fibrous crystals m.p. 221° (lit. [11] 228°) (30 mg; yield 60%). (Found: C, 89.9; H, 4.6; N, 4.8. $C_{21}H_{13}N$ requires: C, 90.3; H, 4.7; N, 5.0%). Mass spectrum : m/e 279 (M^+). UV (Fig.11) : 220(4.70); 228(4.51); 248(4.33); 259(4.31); 268(4.42); 288(4.94); 295(4.94); 316(4.1); 330(3.99); 350(2.73); 368(2.97); 388(3.06).

Dibenzo(a,k)phenanthridine 8

Compound 4 (80 mg) was heated with 150 mg of selenium powder at 300° for 6 hrs. The crude product was worked up, chromatographed and crystallised as in 1 to give yellow fibrous needles m.p. 180° (50 mg; yield 63%). (Found: C, 90.3; H, 5.0; N, 5.4. $C_{21}H_{13}N$ requires: C, 90.3; H, 4.7; N, 5.0%). Mass spectrum : m/e 279 (M^+). UV (Fig.12) : 223(4.74); 254(4.51); 266(4.54); 288(4.87); 299(4.78); 320(3.79); 336(4.00); 350(3.83); 368(3.43); 382(3.59); 388(3.86).

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CHAPTER IV

SYNTHESIS OF DIAZA PENTACYCLIC COMPOUNDS

The synthesis of nitrogen heterocyclics by acid-catalysed cyclodehydration of cis-2-arylaminomethylenecycloalkanones has been reported earlier [1-6]. The synthesis of pentacyclic monoaza systems has been described in the previous chapter. In the present chapter, the synthesis of diaza pentacyclic systems viz. dibenzo(b,k)(4,7)-phenanthroline 7, dibenzo(b,j)(1,7)phenanthroline 21, and dibenzo(c,k)(1,7)phenanthroline 23 is described. Here again, PMR has been used as the main tool for structure assignments.

Cyclodehydration of cis-N,N-bis-(2-ketocyclohexylidinomethylene)-p-phenylenediamine 3 [prepared by the interaction of cis-2-hydroxymethylenecyclohexanone 1 with p-phenylenediamine 2] by interaction with polyphosphoric acid leading to the formation of 1,2,3,4,9,10,11,12-octahydro-6,13-diazabenzo(a)naphthacene 4, and the subsequent dehydrogenation of 4 to 6,13-diazabenzo(a)-naphthacene 5 has been reported earlier from this laboratory [3]. Further examination of this reaction has led to the isolation of another new pentacyclic compound

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The names and numberings laid down by Chemical Abstracts (also used by the Ring Index) are employed throughout .

1,2,3,4,9,10,11,12-octahydrodibenzo(b,j)(4,7)phenanthroline 6. The latter on selenium dehydrogenation gave dibenzo(b,k)-(4,7)phenanthroline 7. (Chart 1).

The choice for the right structure 6 out of the six possible cyclodehydration products 4, 6 (Chart 1), 8 - 11 (Chart 2), was made on the basis of the PMR spectrum of the compound and its dehydrogenation product, 7. The PMR spectrum of 6 (Fig.1) shows two singlets at 8.03 δ and 8.45 δ of two proton intensity each. This showed that the molecule has a plane of symmetry and hence structure 4 and 8, which do not possess plane of symmetry, are ruled out. Moreover, compound 4 would show in its PMR spectrum four non-equivalent protons of one proton intensity each, and compound 8 would show four signals of 1:1:1:1 proton intensity with a quartet. In compound 9 none of the proton would appear below 500 cps and as such this structure is also ruled out. The choice was now between 6, 10 and 11. The final structure assignment was done on the basis of the PMR spectrum of the dehydrogenated product 7 from 6 (Fig.2). This showed a two proton singlet at 9.25 δ and a multiplet for twelve protons spread between 8.61 δ - 10.01 δ. The singlet could be

assigned to the two protons at C-13 and C-14 of compound 7. The dehydrogenation product 12 from 10 would have shown two singlets, each of two proton intensity, one for protons at C-14 and C-7 and another downfield singlet for protons at C-5 and C-12. It would also show a multiplet for protons at C-1 and C-8. On the other hand, the dehydrogenation product 13 from 11 would show one singlet of two proton intensity for protons at C-1 and C-6 and a multiplet for two protons at C-10 and C-11. Thus the structure of the cyclodehydrated product from 5 is 6 and that of the dehydrogenated product from 6 is 7.

The structures 6 and 7 were further confirmed by a study of the UV spectra of the two compounds (Fig.3). The UV spectrum of 6 shows a p-phenanthroline 14 chromophore in its two absorption bands. It is mentioned that the UV spectra of o-, m-, and p-phenanthrolines resemble each other in their two absorption bands [7]. The UV spectrum of 7 is the same as reported by Badger and Pettit [8] and also resembles its carbocyclic analogue pentaphene 15 [8].

Interaction of cis-2-hydroxymethylenecyclohexanone 1 with m-phenylenediamine 16 gave either a mono 17 - or a

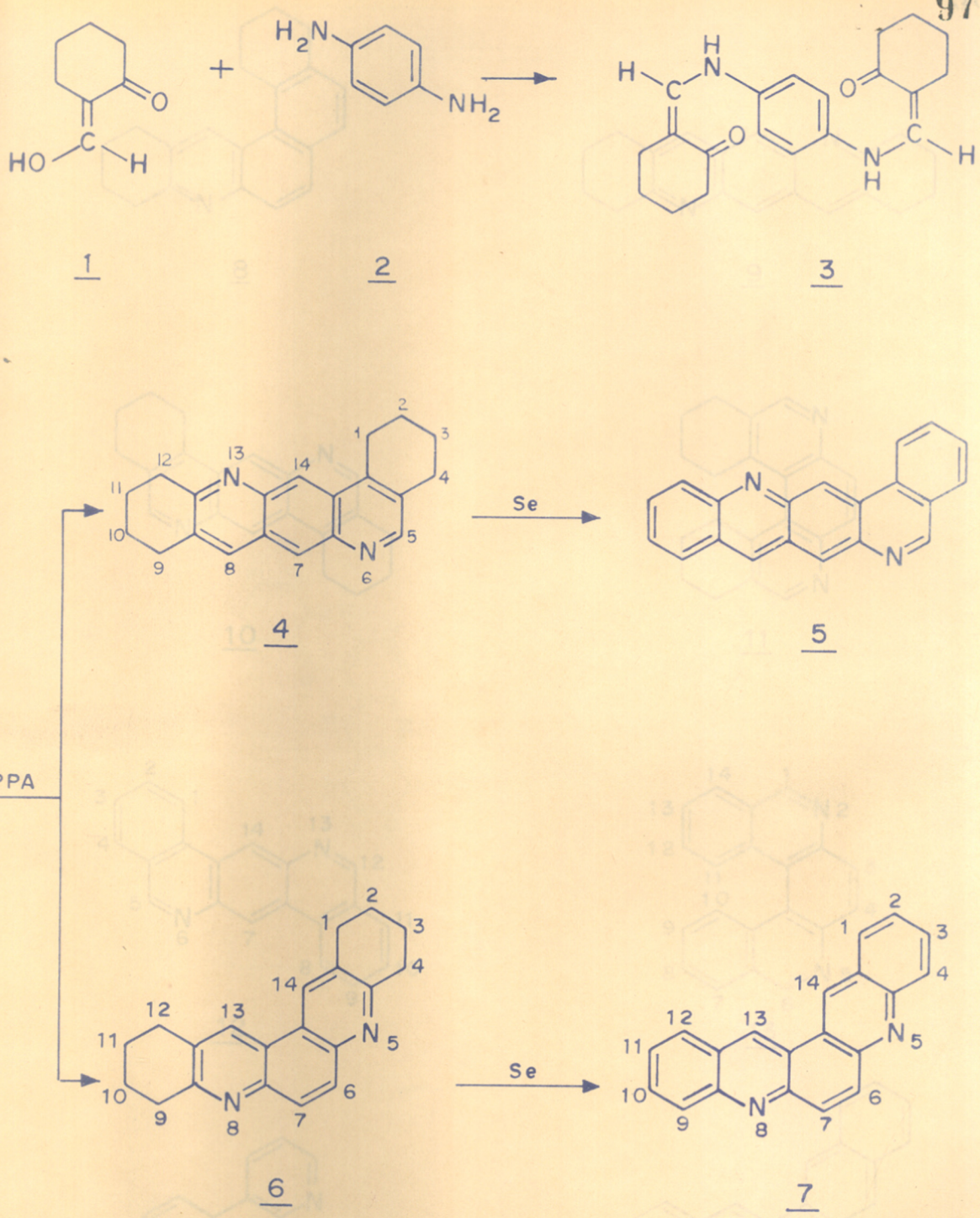
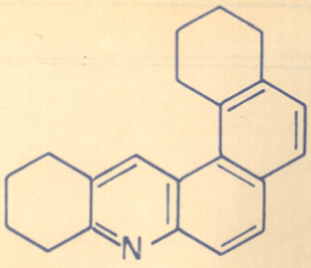


CHART I



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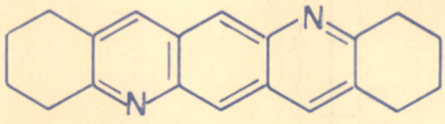

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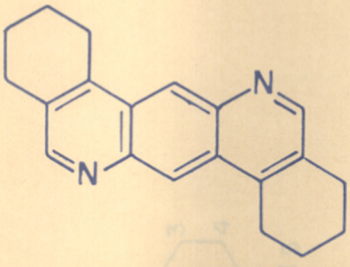

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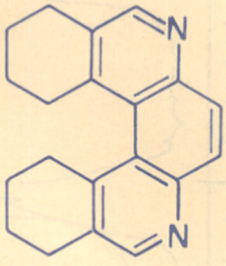

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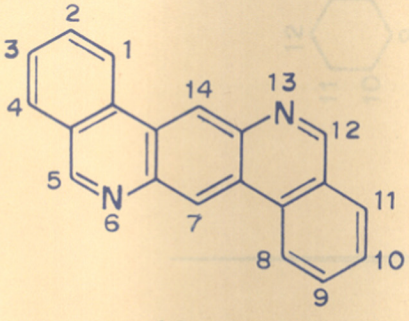

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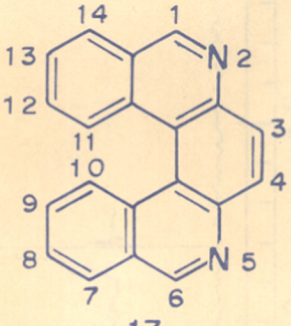

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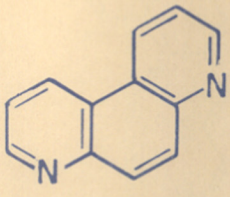

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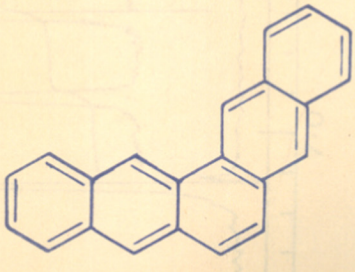

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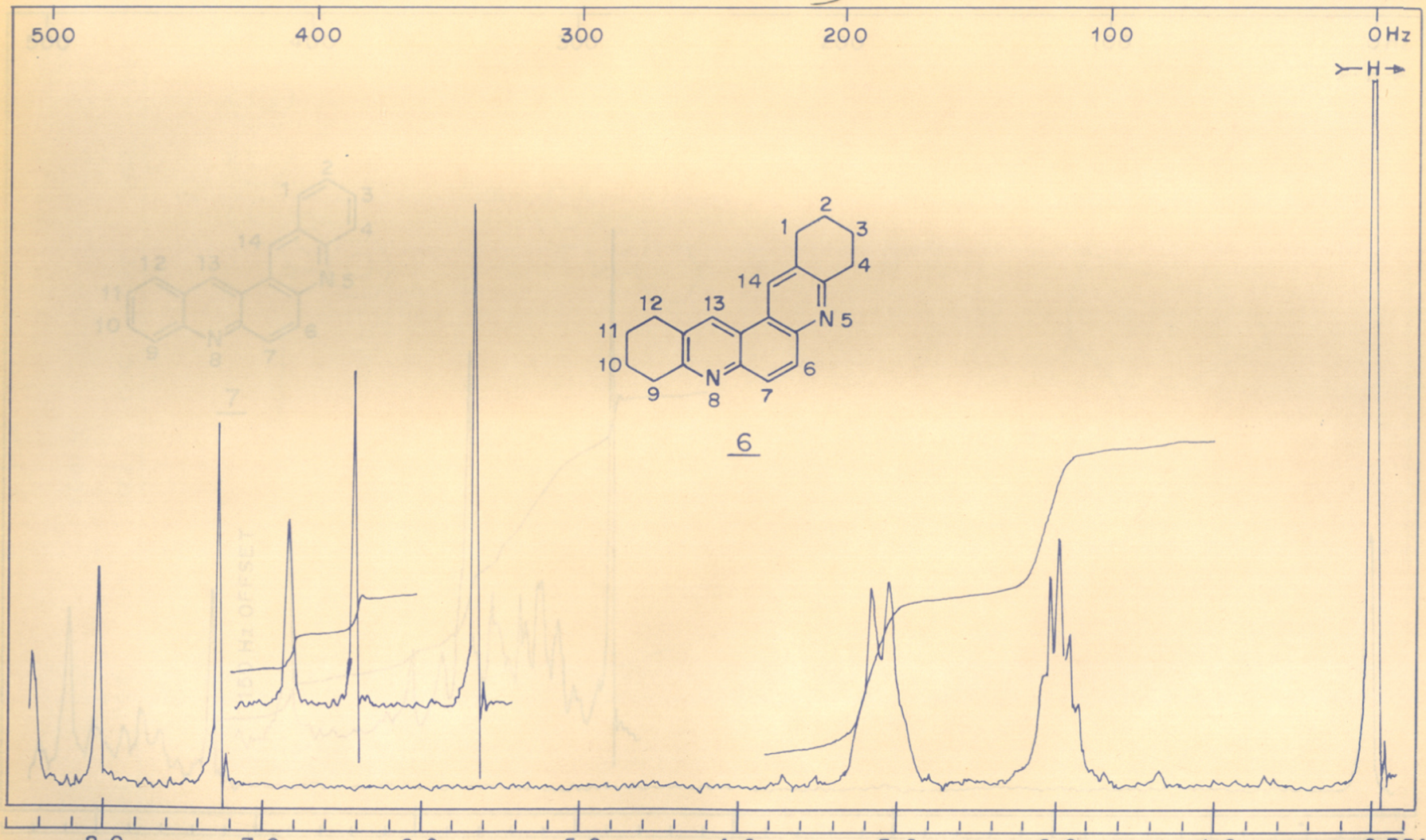
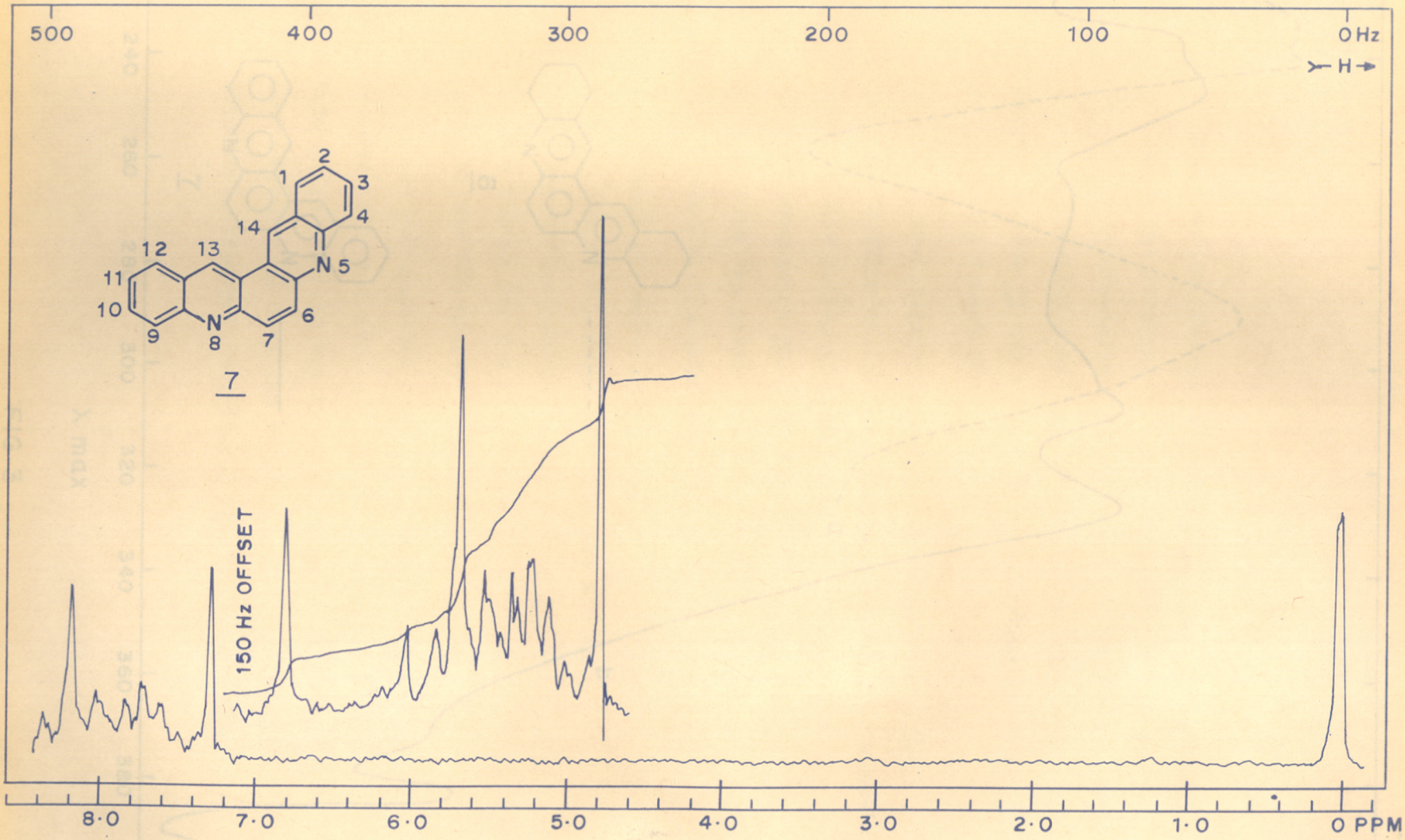
CHART 2



6

PMR SPECTRUM OF 6 IN $CDCl_3$

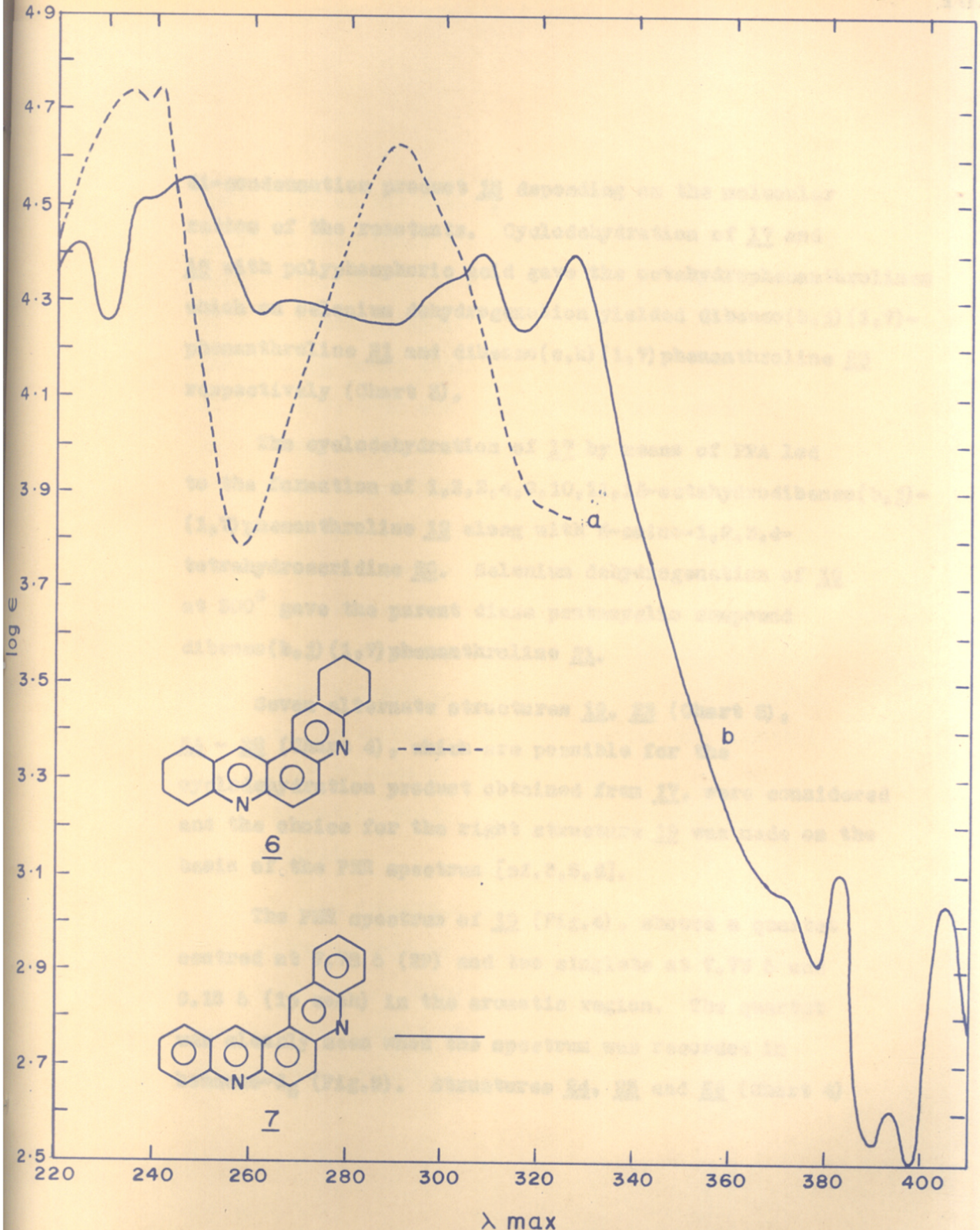
FIG·1



7

PMR SPECTRUM OF 7 IN $CDCl_3$

FIG·2


4·9
4·7
4·5
4·3
4·1
3·9
3·7
3·5
3·3
3·1
2·9
2·7
2·5
log ∈
220
240
260
280
300
320
340
360
380
400
λ max
a
b
N
N
6
N
N
7

FIG·3

di-condensation product 16 depending on the molecular ratios of the reactants. Cyclodehydration of 17 and 18 with polyphosphoric acid gave the octahydrophenanthrolines which on selenium dehydrogenation yielded dibenzo(b,j)(1,7)-phenanthroline 21 and dibenzo(c,k)(1,7)phenanthroline 23 respectively (Chart 3).

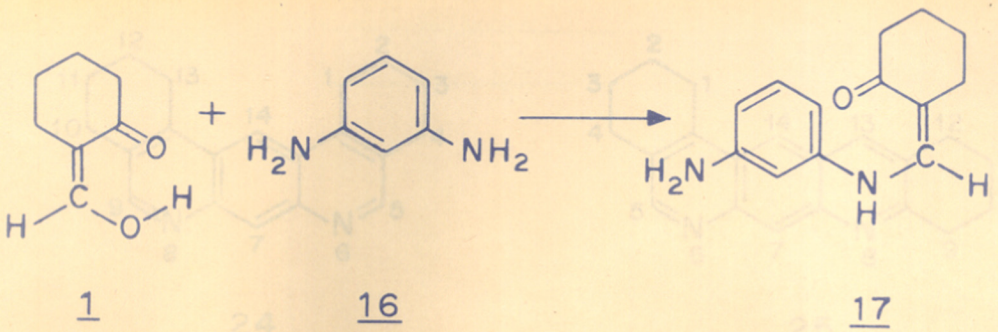
The cyclodehydration of 17 by means of PPA led to the formation of 1,2,3,4,9,10,11,12-octahydrodibenzo(b,j)-(1,7)phenanthroline 19 along with 6-amino-1,2,3,4-tetrahydroacridine 20. Selenium dehydrogenation of 19 at 300° gave the parent diaza pentacyclic compound dibenzo(b,j)(1,7)phenanthroline 21.

Seven alternate structures 19, 22 (Chart 3), 24 - 28 (Chart 4), which are possible for the cyclodehydration product obtained from 17, were considered and the choice for the right structure 19 was made on the basis of the PMR spectrum [cf.3,5,6].

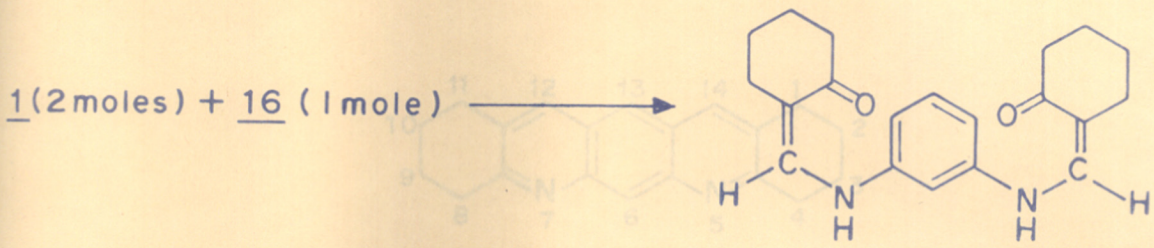
The PMR spectrum of 19 (Fig.4), showed a quartet centred at 7.78 δ (2P) and two singlets at 7.73 δ and 9.15 δ (1p each) in the aromatic region. The quartet was clearly seen when the spectrum was recorded in benzene-d_6 (Fig.5). Structures 24, 25 and 26 (Chart 4)

were ruled on the basis of this splitting pattern as 24 would show three singlets; one for proton at C-14, another for proton at C-7 and a third downfield singlet of two proton intensity for protons at C-5 and C-9. Compound 25 would exhibit four singlets for protons at C-5, C-7, C-13 and C-14, in its PMR spectrum, proton at C-5 appearing downfield. Compound 26 would show four singlets, for protons at C-6, C-12, C-13 and C-14, all appearing upfield. Structure 22 can be ruled out because neither of the proton at C-8 or C-14 is likely to appear at as high a field as 7.73 δ. In structure 27 also, the protons at C-12 and C-14 would not appear at 7.73 δ. The choice between 19 and 28 was difficult to make. However, the choice between the latter two possibilities could only be made on studying the PMR spectrum of the dehydrogenation product derived from the octahydrodibenzo-phenanthroline.

In the dehydrogenation product 30 from 28, only one proton at C-13 is likely to appear at the low field as a multiplet. Except perhaps the proton at C-5 and C-1, other protons would appear as a multiplet without any distinctive features. On the other hand, in the low



1 16 17



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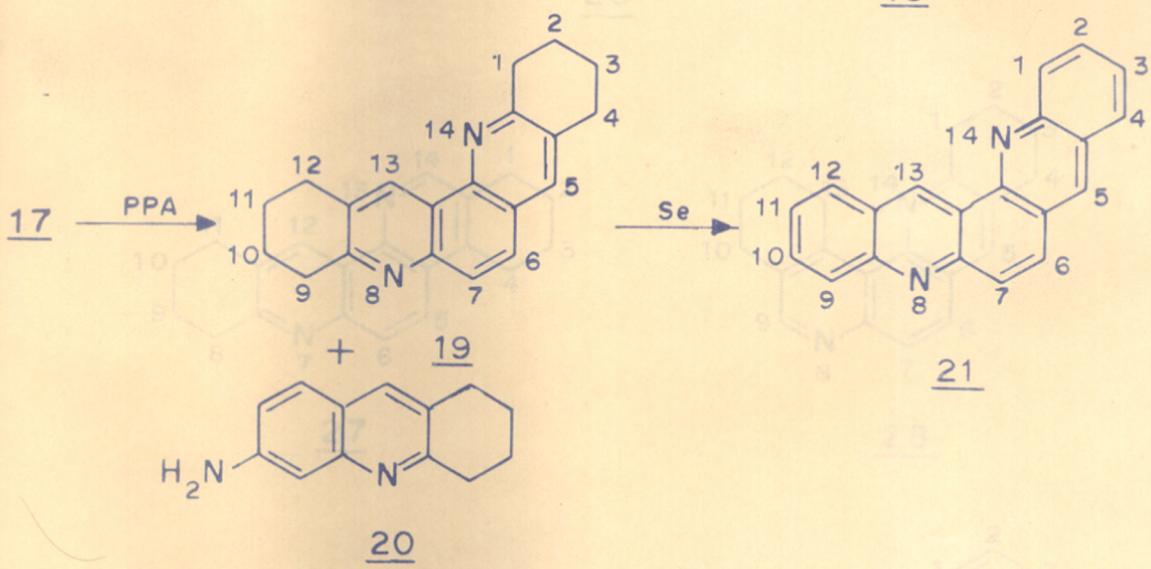

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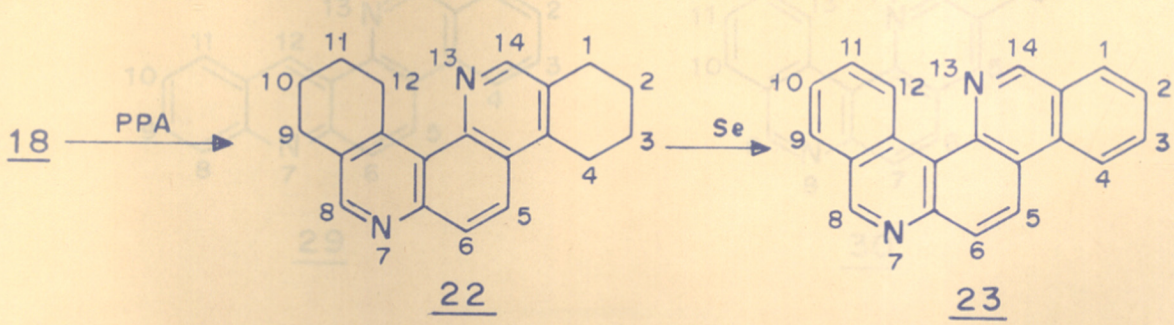
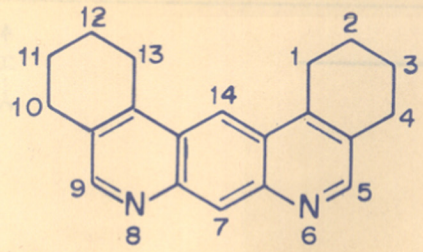


22 23

CHART 3



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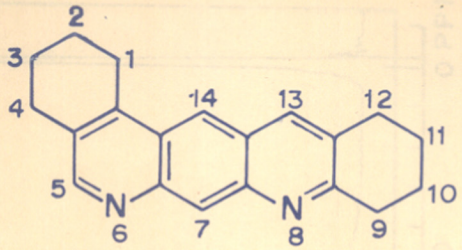

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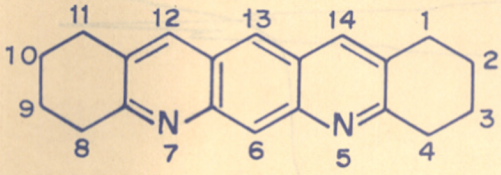

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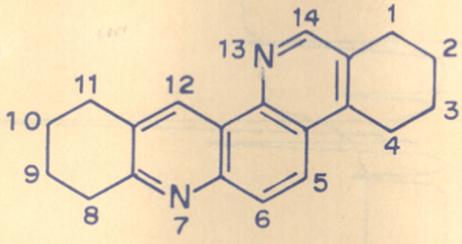

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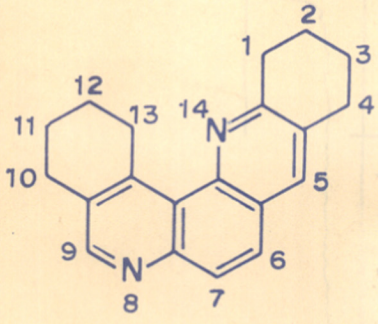

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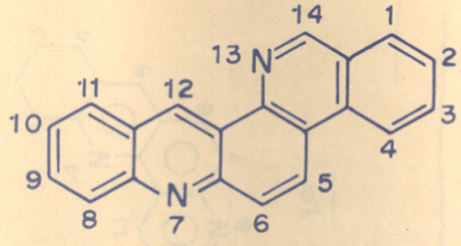

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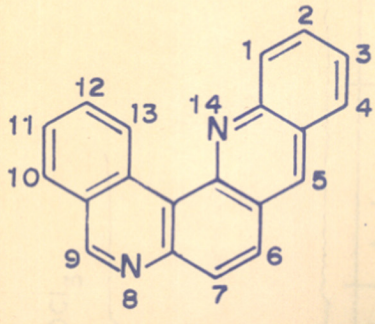

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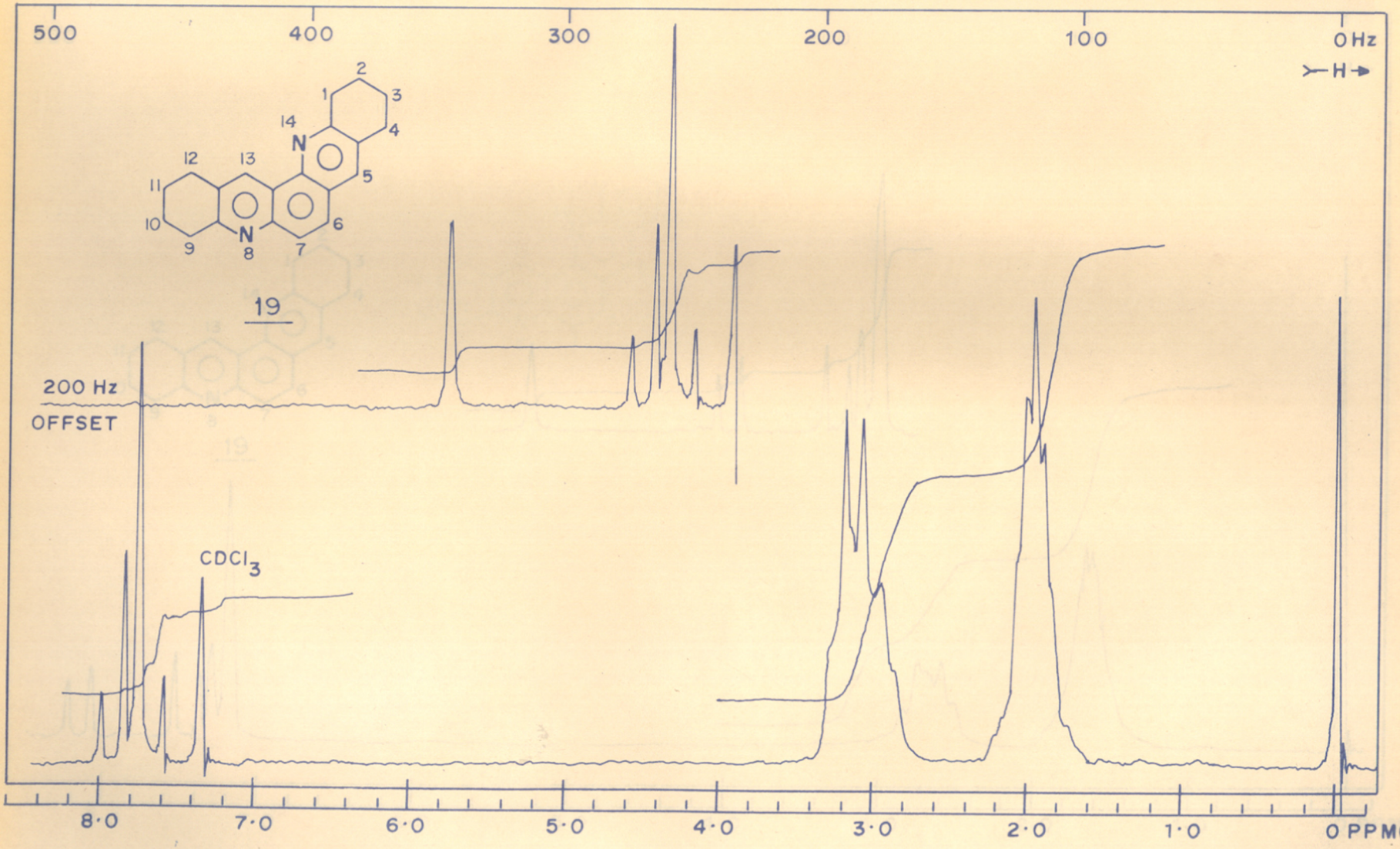
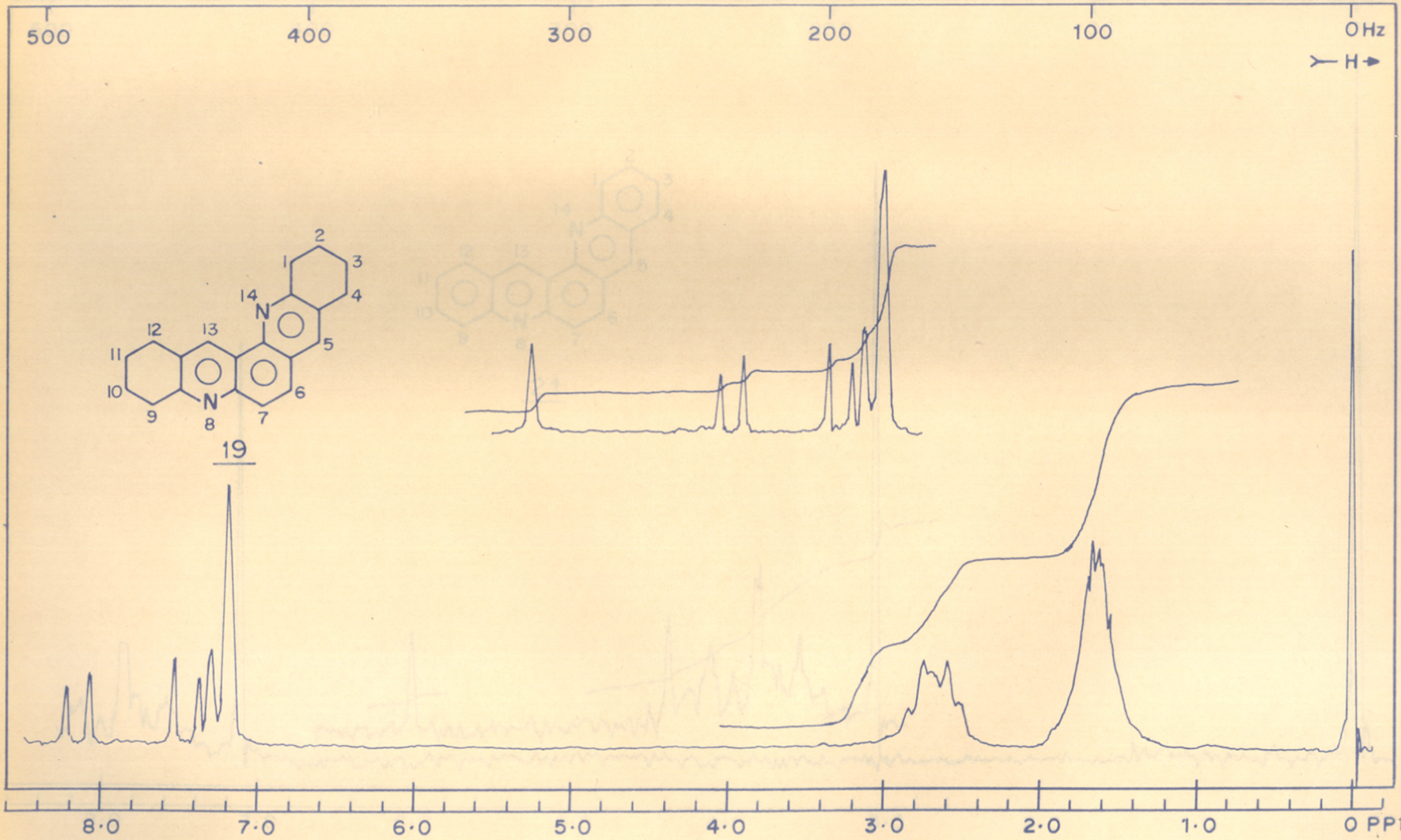
CHART 4



PMR SPECTRUM OF 19 IN $CDCl_3$

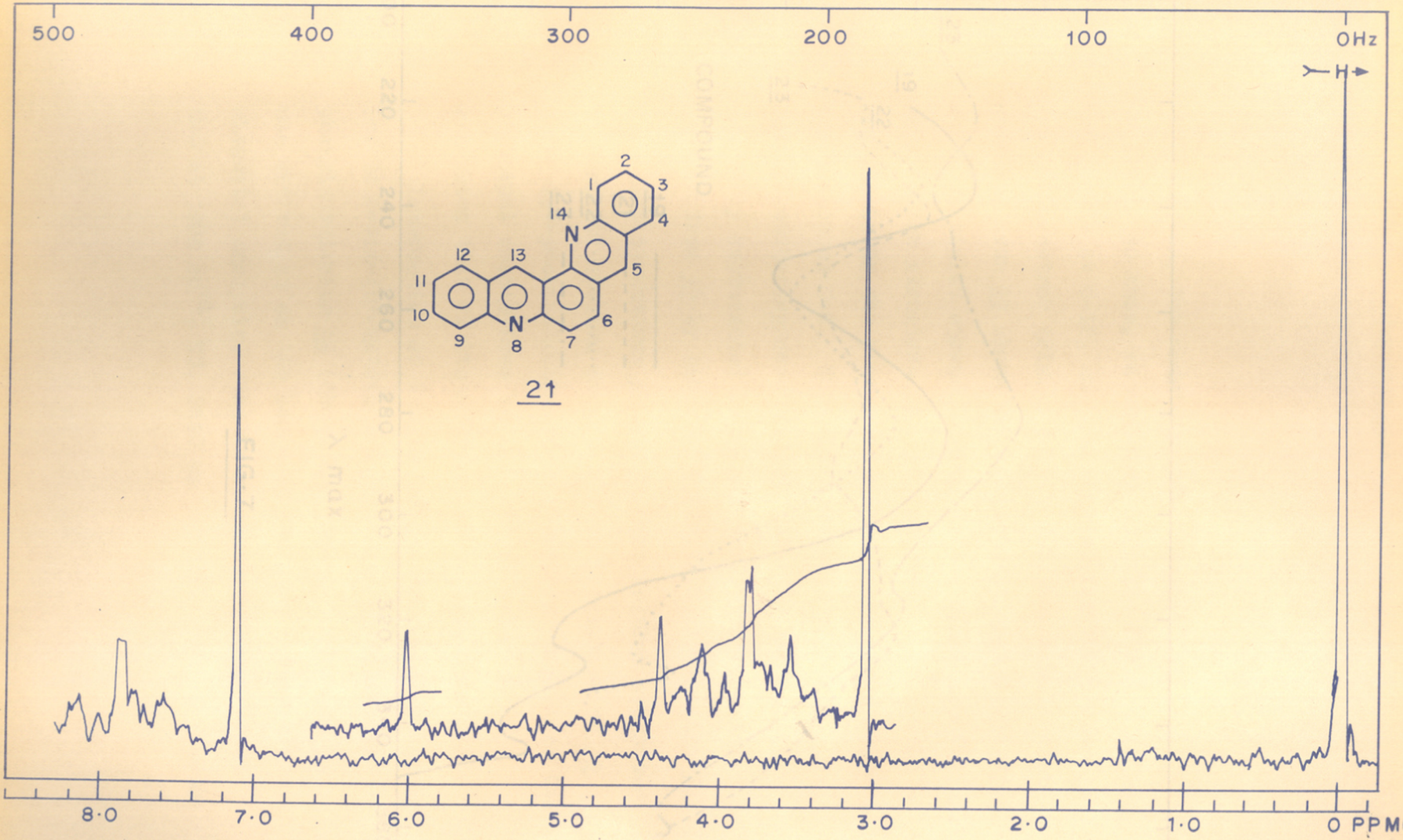
FIG·4



19

PMR SPECTRUM OF 19 IN BENZENE- d_6

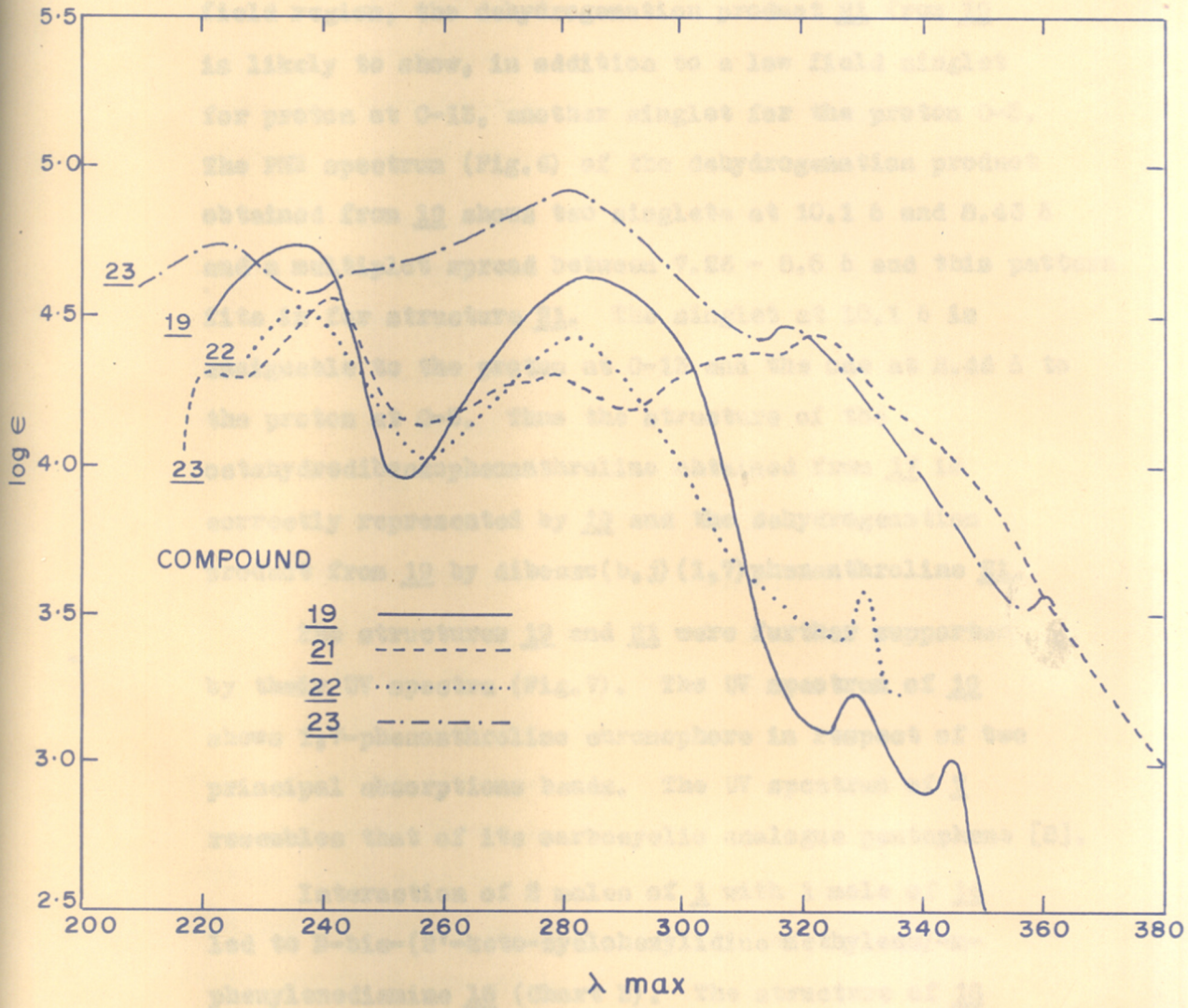
FIG·5



21

PMR SPECTRUM OF 21 IN $CDCl_3$

FIG. 6


5·5
5·0
4·5
4·0
3·5
3·0
2·5
log ∈
200
220
240
260
280
300
320
340
360
380
λ max
23
19
22
23
COMPOUND
19
21
22
23

FIG·7

field region, the dehydrogenation product 21 from 19 is likely to show, in addition to a low field singlet for proton at C-13, another singlet for the proton C-5. The PMR spectrum (Fig.6) of the dehydrogenation product obtained from 19 shows two singlets at 10.1 δ and 8.46 δ and a multiplet spread between 7.26 - 8.5 δ and this pattern fits in for structure 21. The singlet at 10.1 δ is assignable to the proton at C-13 and the one at 8.46 δ to the proton at C-5. Thus the structure of the octahydrodibenzophenanthroline obtained from 17 is correctly represented by 19 and the dehydrogenation product from 19 by dibenzo(b,j)(1,7)phenanthroline 21.

The structures 19 and 21 were further supported by their UV spectra (Fig.7). The UV spectrum of 19 shows 1,7-phenanthroline chromophore in respect of two principal absorptions bands. The UV spectrum of 7 resembles that of its carbocyclic analogue pentaphene [8].

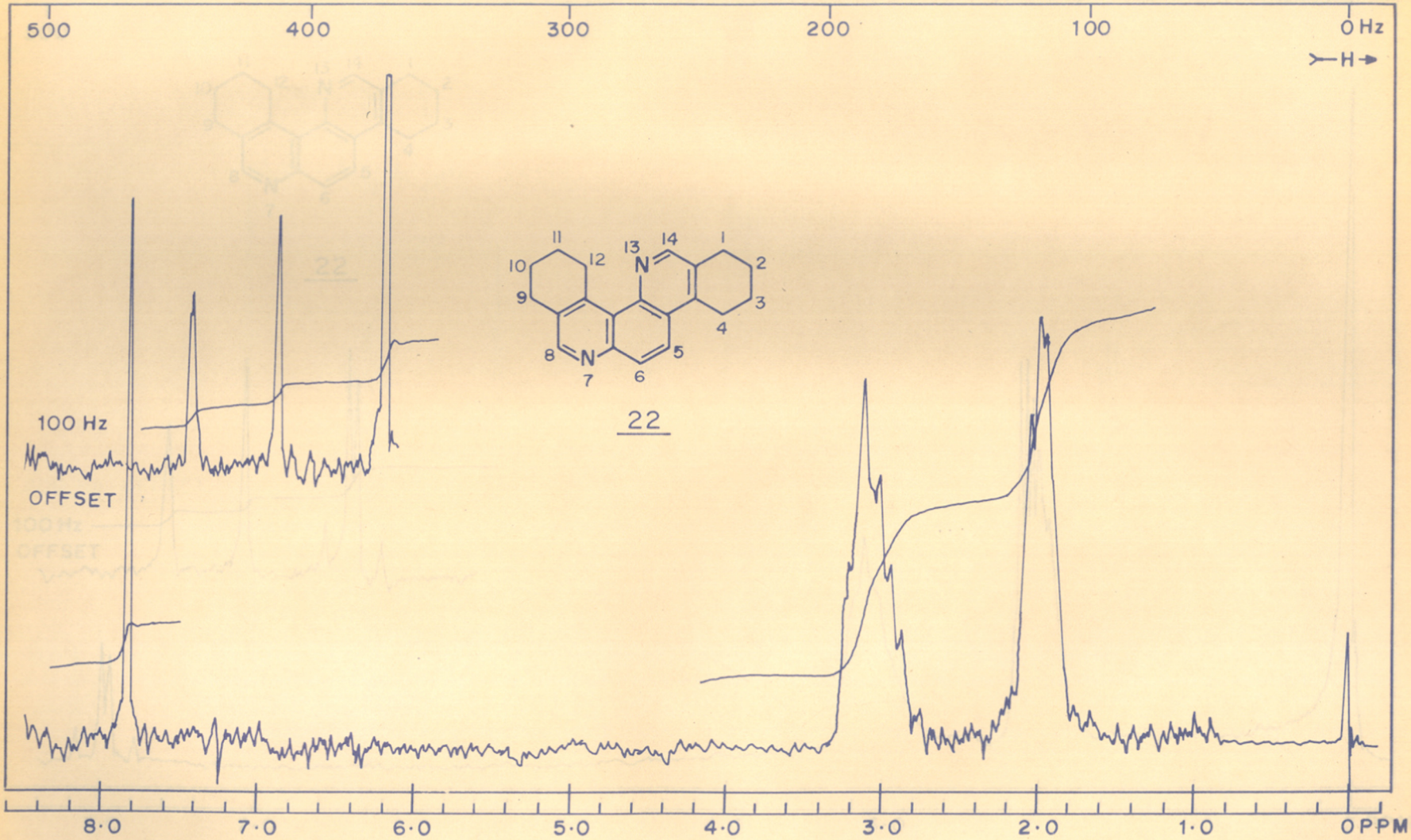
Interaction of 2 moles of 1 with 1 mole of 16 led to N-bis-(2'-keto-cyclohexylidino methylene)-m-phenylenediamine 18 (Chart 3). The structure of 18 was arrived at on the basis of its mass spectrum and elemental analysis. The IR spectrum in nujol showed C=O at 1655 cm^{-1}, NH, 3230 cm^{-1}. Treatment of 4 with

PPA led to the formation of 1,2,3,4,9,10,11,12-octahydrodibenzo(c,k)(1,7)phenanthroline 22 which on selenium dehydrogenation at 300° gave dibenzo(c,k)(1,7)-phenanthroline 23 (Chart 3).

In this case also the choice of the structure for the cyclodehydration product 22 was made on the basis of its PMR spectrum (Fig.8) which showed three singlets at 7.83 δ (2P), 8.51 (1P) and 9.06 δ (1P). This pattern would not fit in for any of the possible seven structures 12, 22, 24 - 28 and it was suspected that the two proton singlet at 7.83 δ may in fact be a quartet. This did show up clearly when the spectrum was recorded in acetone -d_6 (Fig.9) and benzene-d_6 (Fig.10). This again reduced the choice to 27 and 22. The final assignment could however be made on the basis of the PMR spectrum of the dehydrogenation product. Whereas the dehydrogenation product 23 from 22 was likely to show up five low field protons (including the hindered protons and those situated on carbons which are ∝ to nitrogen), the dehydrogenation product 29 from 27 would show only four low field protons. The PMR spectrum (Fig.11) of the dehydrogenation product, was, however, more consistent with 23 than with 29. It showed a multiplet at 11.03 δ

for proton at C-12, two singlets at 9.55 δ and 9.40 δ for protons at C-8 and C-14 respectively, a doublet at 8.81 δ for proton at C-5 and a multiplet centred at 8.65 δ for proton at C-4 in the low field region.

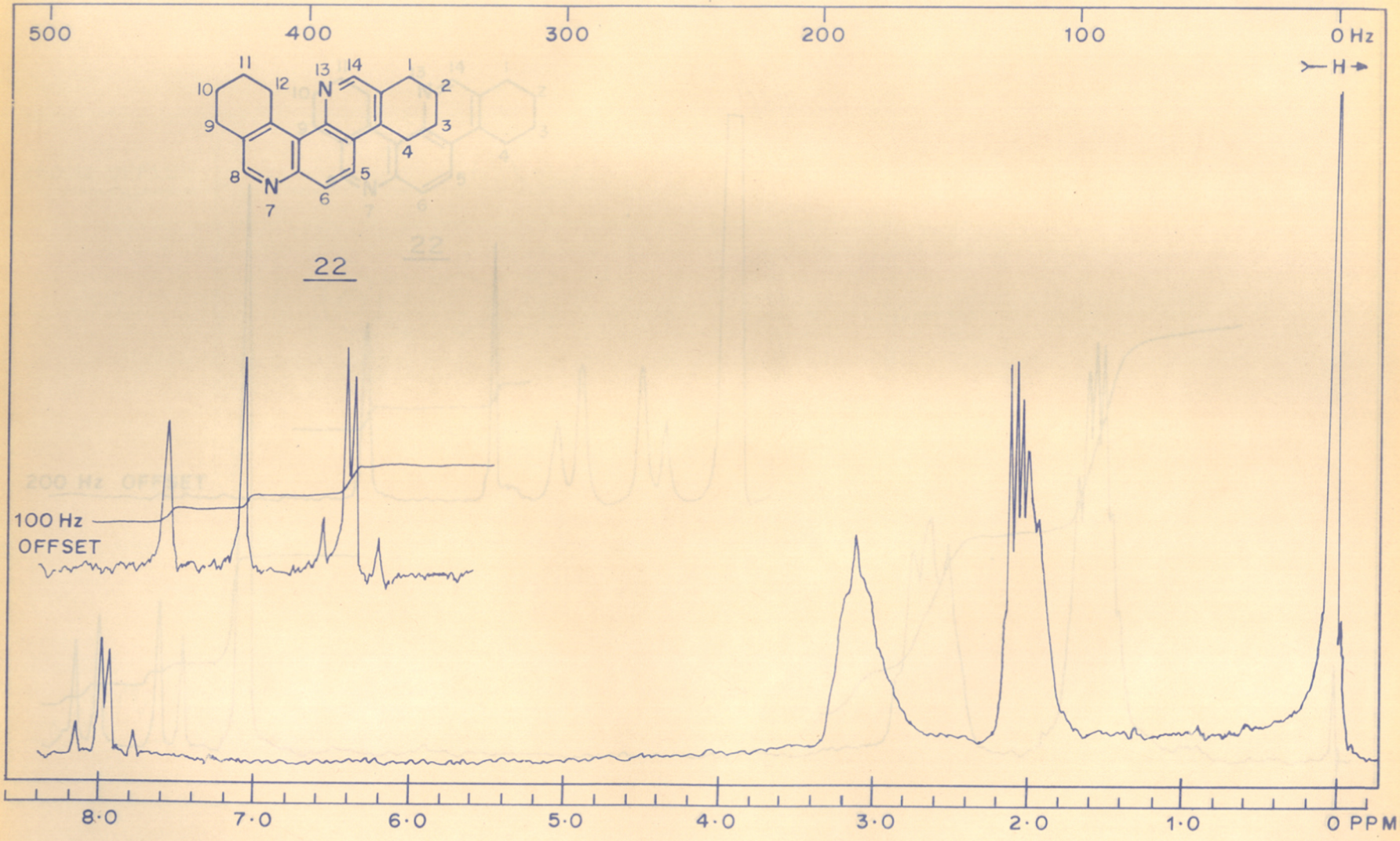
The structures 22 and 23 were further substantiated by their UV spectra (Fig.7). The UV spectrum of 22 showed a m-phenanthroline chromophore in having two principal absorption bands [7]. The UV spectrum of 23 was similar in pattern to its carbocyclic analogue benzo(c)chrysene [9].



22

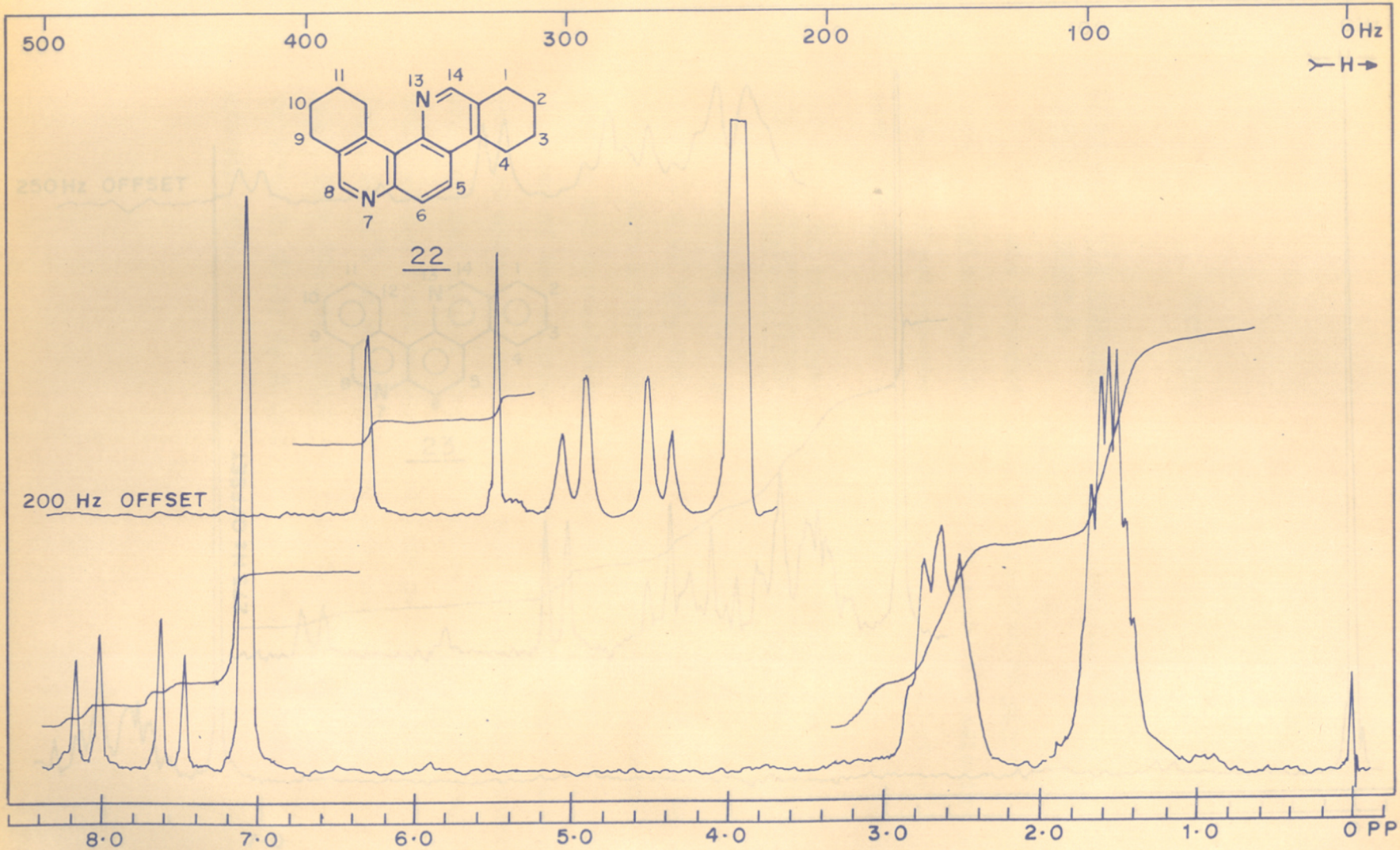
PMR SPECTRUM OF 22 IN $CDCl_3$

FIG·8



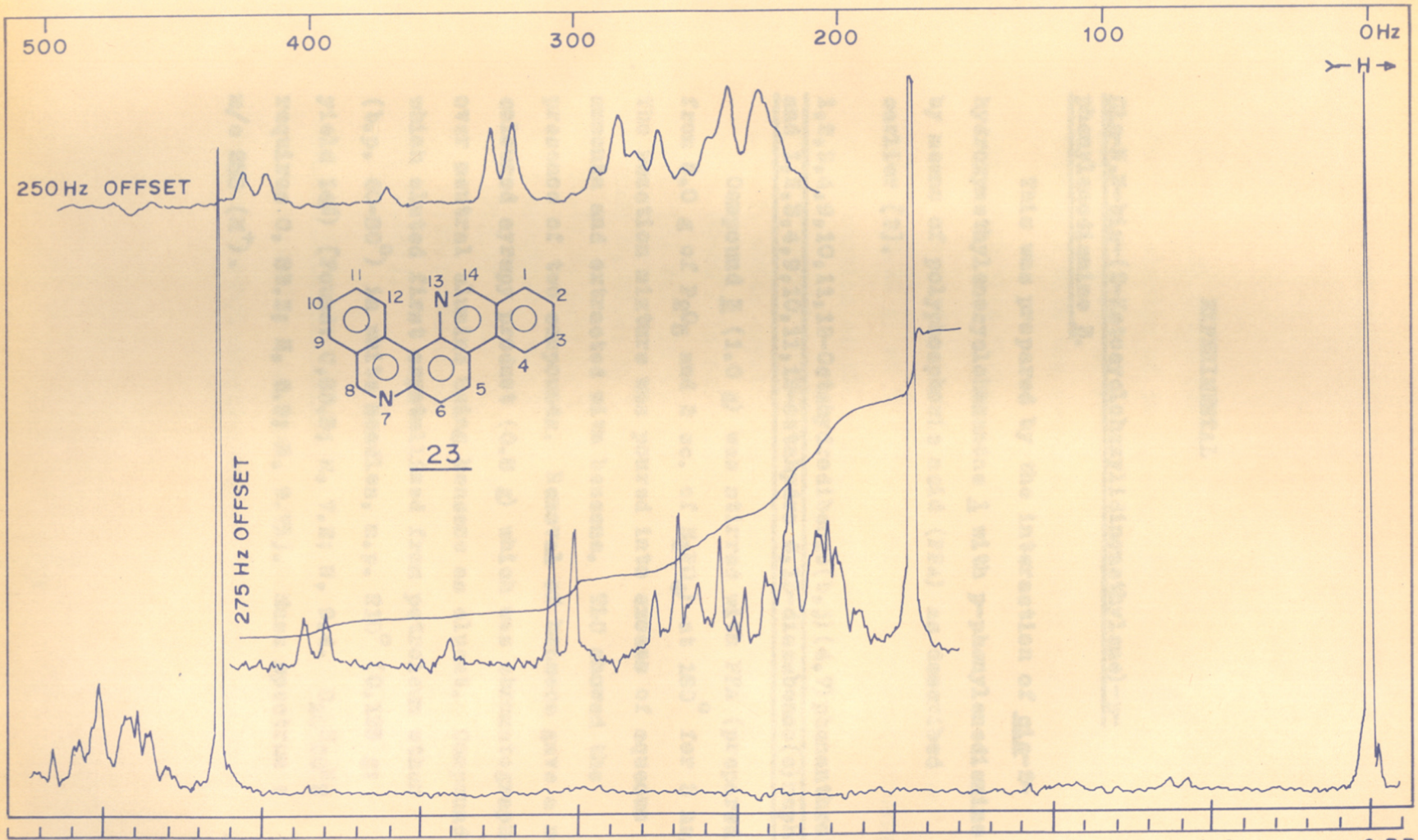
PMR SPECTRUM OF 22 IN ACETONE-d_6

FIG·9



PMR SPECTRUM OF 22 IN BENZENE-d_6

FIG·10



PMR SPECTRUM OF 23 IN $CDCl_3$

FIG· 11

EXPERIMENTAL

Cis-N,N-bis-(2-Ketocyclohexylidinomethylene)-p-phenylenediamine 3.

This was prepared by the interaction of cis-2-hydroxymethylenecyclohexanone 1 with p-phenylenediamine 2 by means of polyphosphoric acid (PPA) as described earlier [3].

1,2,3,4,9,10,11,12-Octahydrodibenzo(b,j)(4,7)phenanthroline 6 and 1,2,3,4,9,10,11,12-octahydro 6,13-diazabenco(a)naphthacene 4

Compound 3 (1.0 g) was stirred with PPA (prepared from 5.0 g of P_2O_5 and 3 cc. of H_3PO_4) at 180° for 3 hr. The reaction mixture was poured into excess of aqueous ammonia and extracted with benzene. TLC showed the presence of two compounds. Removal of benzene gave a red coloured syrupy product (0.8 g) which was chromatographed over neutral alumina using benzene as eluent. Compound 6, which eluted first crystallised from petroleum ether (b.p. 60-80°) in white needles, m.p. 210° (0.125 g; yield 14%) [Found: C,83.5; H, 7.2; N, 9.4. $C_{20}H_{20}N_2$ requires C, 83.3; H, 6.9; N, 9.7%]. Mass spectrum : m/e 288 (M^+).

[UV (Fig.3) : 234 (4.73); 240 (4.74); 290 (4.63)].
Further elution of the column gave compound 4, m.p. 154° (0.45 g; yield 51%) which proved to be identical with the compound described earlier [3].

Dibenzo(b.j)(4,7)phenanthroline 7

Compound 6 (0.06 g) was heated with selenium powder (0.12 g) at 300° for 5 hr. The product obtained by extraction of the mixture with benzene, on chromatographic purification, over neutral alumina, gave 7, which crystallised from petroleum ether (b.p. 60-80°) in white needles, m.p. 240° (lit. [8] 245° in ethanol) (0.022 g; yield 38%) (Found: C, 85.4; H, 5.1; N, 9.8. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.8; N, 10.1%).
Mass spectrum : m/e 280 (M^+).
[UV (Fig.3) : 223 (4.41); 241 (4.51); 246 (4.55); 308 (4.39); 326 (4.40); 382 (3.11); 393 (2.62); 404 (3.05)].

Cis-2-m-Aminophenylaminomethylenecyclohexanone 17

Equimolar quantities of freshly distilled 2-hydroxymethylenecyclohexanone 1 (1.26 g in 10 cc ethanol)

and m-phenylenediamine 16 (1.08 g in 10 cc. ethanol) were mixed at room temperature. After the initial exothermic reaction, the mixture was cooled when a yellow solid separated. Unreacted 1 and 16 were removed by washing the solid with ether and alcohol. The product on crystallisation from ethanol gave 17 as yellow cubes, m.p. 146° (1.4 g; yield 65%) (Found: C, 72.2; H, 7.6; N, 12.7. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.5; N, 12.9%). IR: NH, 3240, NH_2, 3200; C=O, 1650. Mass spectrum : m/e 216 (M^+). PMR (in DMSO) - Bonded NH at 11.72 exchangeable with D_2O and CH at 7.3 as a doublet collapses into a singlet on D_2O treatment, free NH at 8.48 exchangeable with D_2O and CH at 7.78 as a doublet collapses into a singlet on D_2O exchange.

N,N-bis-(2-ketocyclohexylidinomethylene)-m-phenylenediamine 18.

Interaction of 1 (6.3 g; 2 moles) and 16 (2.7 g; 1 mole) as above gave 18 in yellow cubes (from ethanol), m.p. 220° (6.5 g; yield 80%) (Found : C, 74.4; H, 7.3; N, 8.8. $C_{20}H_{24}N_2O_2$ requires C, 74.1; H, 7.4; N, 8.6%). Mass spectrum : m/e 324 (M^+).

1,2,3,4,9,10,11,12-Octahydrodibenzo(b,j)(1,7)-phenanthroline 19 and 6-Amino-1,2,3,4-tetrahydroacridine 20

A mixture of 17 (0.7 g) and PPA (prepared from 2.5 g; P_2O_5 and 1.3 cc. H_3PO_4) was stirred at 160-170° for 2 hr. After cooling, the reaction mixture was poured in excess of aqueous ammonia and the mixture was extracted with benzene. TLC showed the presence of two compounds. Removal of solvent gave a red syrupy product (0.5 g) which on chromatographic separation gave 19 and 20. Compound 19, which eluted first, on crystallisation from petroleum ether (b.p. 60-80°), gave white needles, m.p. 166° (0.186 g; yield 40%) (Found: C, 83.7; H, 7.0; N, 9.5. $C_{20}H_{20}N_2$ requires C, 83.3; H, 6.9; N, 9.7%). Mass spectrum: m/e 288 (M^+). UV (Fig.7) : 236 (4.74); 285 (4.64); 329 (3.23); 346 (3.0). Compound 20 crystallised from petroleum ether (b.p. 60-80°) in yellow fibrous needles, m.p. 152° (0.174 g; yield 27%) (Found: C, 78.8; H, 7.3; N, 14.7. $C_{13}H_{14}N_2$ requires C, 78.8; H, 7.1; N, 14.2%). IR: NH_2 3150, 3350. Mass spectrum : m/e 198 (M^+). PMR (in $CDCl_3$): C_2+C_3 proton at 1.68-2.16, (m),

(4P); C_1+C_4 protons at 2.67-3.17; (m), (4P); NH_2 protons at 4.08, (S),(2P), exchangeable with D_2O; C_7 proton at 6.8 (q; $J_{7,5}$=2.5; $J_{7,8}$=8.5), (1P); C_5 proton at 7.07, (d; $J_{5,7}$=2.5), (1P); C_8 proton at 7.42; (d, $J_{8,7}$=8.5), (1P); and C_9 proton at 7.53 (S), (1P).

1,2,3,4,9,10,11,12-Octahydrodibenzo(c,k)(1,7)-phenanthroline 22

A mixture of 18 (2.0 g) and PPA (prepared from 20.0 g P_2O_5 and 10 cc. H_3PO_4) was stirred at 180° for 6 hr. The reaction product was worked up as in 19. The crude reaction product (1.2 g) on chromatography and crystallisation from petroleum ether (b.p. 60-80°) gave 22 in white needles, m.p. 162° (0.28 g; yield 16%) (Found: C, 83.1; H, 6.8; N, 9.7. $C_{20}H_{20}N_2$ requires C, 83.3; H, 6.9; N, 9.7%). Mass spectrum : m/e 288 (M^+). UV (Fig.7) : 236(4.51); 281(4.42); 329(3.58).

Dibenzo(b,j)(1,7)phenanthroline 21

Compound 19 (0.288 g) was heated with selenium powder (0.4 g) at 300° for 6 hr. The reaction product was extracted with benzene, chromatographed and crystallised

(petroleum ether b.p. 60-80°) to give 21, in white needles, m.p. 219° (Lit.[10]221°) (0.163g; yield 58%) (Found: C, 85.6; H, 4.5; N, 10.0. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.8; N, 10.0%). Mass spectrum: m/e 280 (M^+). UV (Fig.7): 221 (4.32); 241 (4.56); 272 (4.28); 280 (4.32); 310 (4.36); 323 (4.44).

Dibenzo(c,k)(1,7)phenanthroline 23

Compound 22 (0.06 g) was heated with selenium powder (0.120 g) at 300° for 6 hr. The reaction product was treated as in case of 21 to give 23 in white needles (petroleum ether 60-80°), m.p. 181° (0.032 g; yield 55%) (Found: C, 85.8; H, 4.6; N, 9.8. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.8; N, 10.0%). Mass spectrum : m/e 280 (M^+). UV (Fig.7): 226 (4.70); 242 (4.62); 280 (4.93); 316 (4.46); 357 (3.54).

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SUMMARY

CHAPTER I: REVIEW OF CARCINOGENESIS BY NITROGEN CONTAINING HYDROCARBONS

Carcinogenic polycyclic aromatic hydrocarbons and the aza polycyclics showing carcinogenic activity have been reviewed. The effect of methyl substituents, structure (K-region), shape, size and steric factors, on carcinogenesis has been discussed.

CHAPTER II: LITERATURE SURVEY OF THE SYNTHETIC METHODS OF MONOAZA AND DIAZA PENTACYCLIC COMPOUNDS

Literature survey of the various synthetic methods of the unsubstituted dibenzacridines, dibenzophenanthridines and dibenzophenanthrolines has been given. Cyclodehydration reactions leading to hydro derivatives, which have been employed in the present work, are discussed. The various mechanisms proposed in the acid catalysed cyclodehydrations and further substantiated by the present work, have been discussed. The analysis of the PMR spectra of polynuclear aromatic and heteroaromatic compounds with special emphasis on the chemical shifts of the hindered protons, and its scope of application in the product analysis of the monoaza and diaza pentacyclic compounds synthesized in the present work, has been discussed.

CHAPTER III: SYNTHESIS OF MONO-AZA PENTACYCLIC COMPOUNDS
(Chart 1)

The synthesis of 8,9-dihydrodibenz(c,h)acridine 1, 7,8-dihydrodibenzo(c,k)phenanthridine 2, 5,6-dihydrodibenz(a,h)-acridine 3 and 5,6-dihydrodibenz(a,k)phenanthridine 4 and the dehydrogenation of these dihydro compounds to give the parent monoaza pentacyclic compounds viz. dibenz(c,h)acridine 5, dibenzo(c,k)phenanthridine 6, dibenz(a,h)acridine 7 and dibenzo(a,k)phenanthridine 8 has been described. Compound 1 and 2 have been synthesised by the cyclodehydration of 2-(1'-naphthylaminomethylene)-1-tetralone 9, while compound 3 and 4 have been synthesised by the cyclodehydration of 2-(2'-naphthylaminomethylene)-1-tetralone 10. Lactic and formic acid have been used for effecting the cyclodehydration of 9 and 10.

Structure elucidation for these compounds has been done by a study of the PMR spectra.

CHAPTER IV: SYNTHESIS OF DIAZA PENTACYCLIC COMPOUNDS

Cyclodehydration of cis-N,N-bis(2-ketocyclo-hexylidinomethylene)-p-phenylenediamine 13 (prepared by the interaction of cis-2-hydroxymethylene-cyclohexanone 11 with p-phenylenediamine 12) with polyphosphoric acid leading to the formation of

1,2,3,4,9,10,11,12-octahydro-6,13-diazabenzo(a)-naphthacene 14 and 1,2,3,4,9,10,11,12-octahydrodibenzo(b,j)-(4,7)phenanthroline 15, and the subsequent dehydrogenation of 14 and 15 with selenium to give the parent compounds 16 and 17 respectively, has been described (Chart 2).

Interaction of cis-2-hydroxymethylenecyclohexanone 11 with m-phenylenediamine 18 to give the mono- 19 and the di-condensation product 20 has been described (Chart 3). The cyclodehydration of 19 and 20 by means of polyphosphoric acid leading to 1,2,3,4,9,10,11,12-octahydrodibenzo(b,j)(1,7)phenanthroline 21 and 1,2,3,4,9,10,11,12-octahydrodibenzo(c,k)(1,7)phenanthroline 22 respectively, and the subsequent dehydrogenation of 21 and 22 to give the parent diaza pentacyclic compounds dibenzo(b,j)(1,7)phenanthroline 23 from 21, and dibenzo(c,k)(1,7)phenanthroline 24 from 22 has been described.

The choice for the right structures has been made on the basis of the PMR spectra of these compounds.

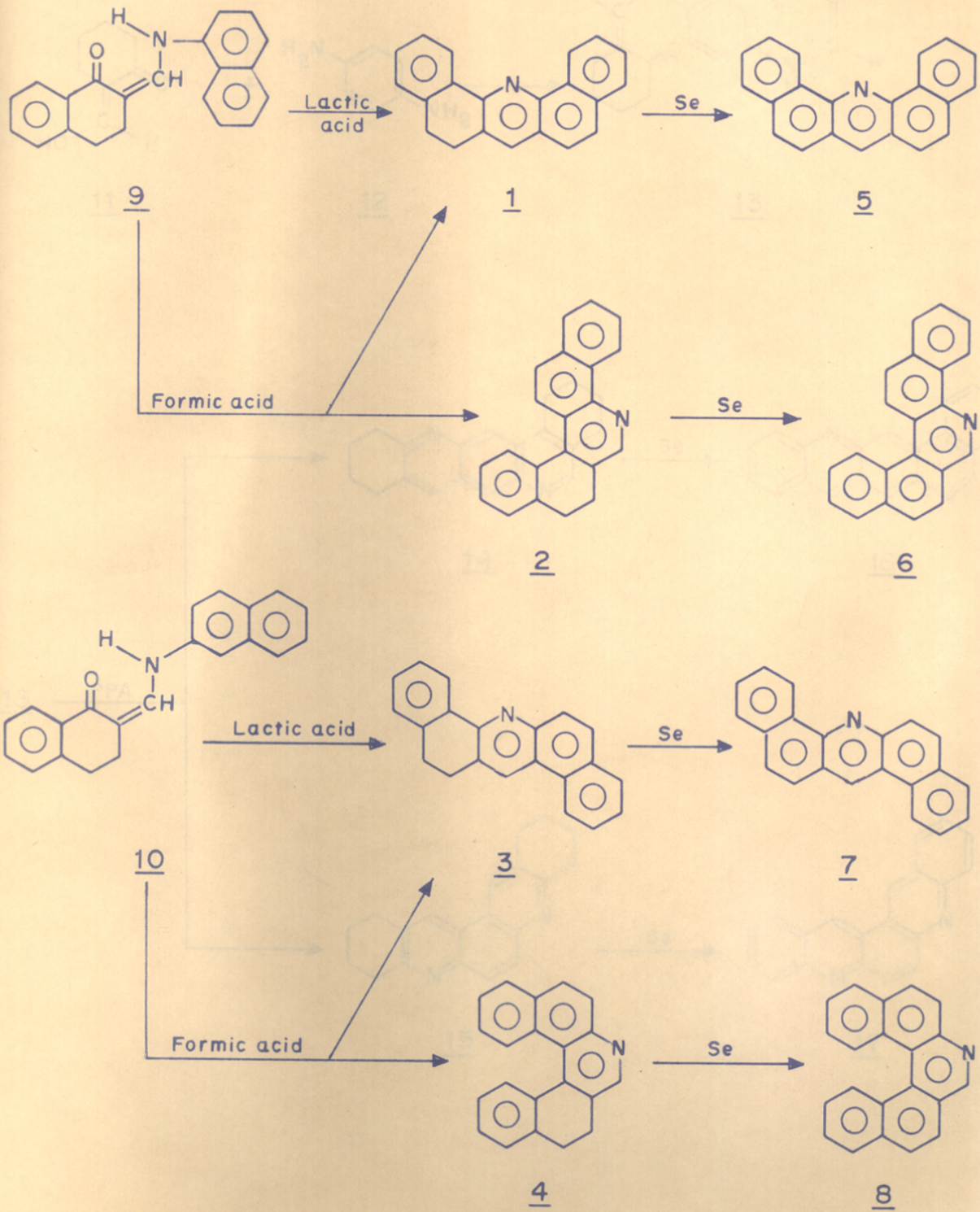
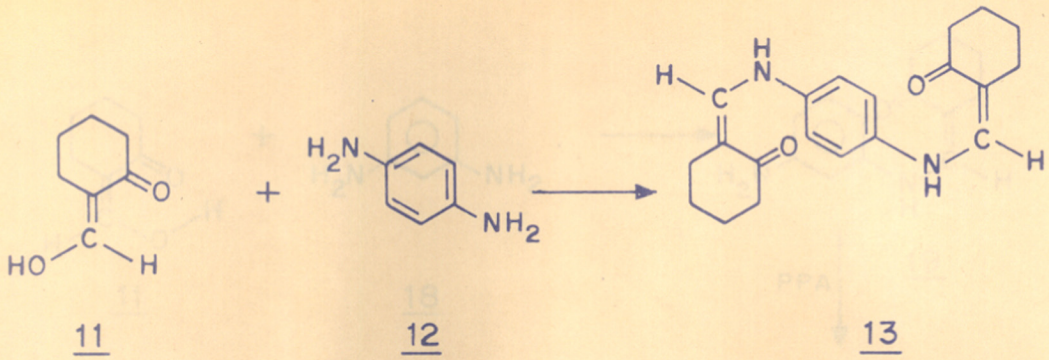
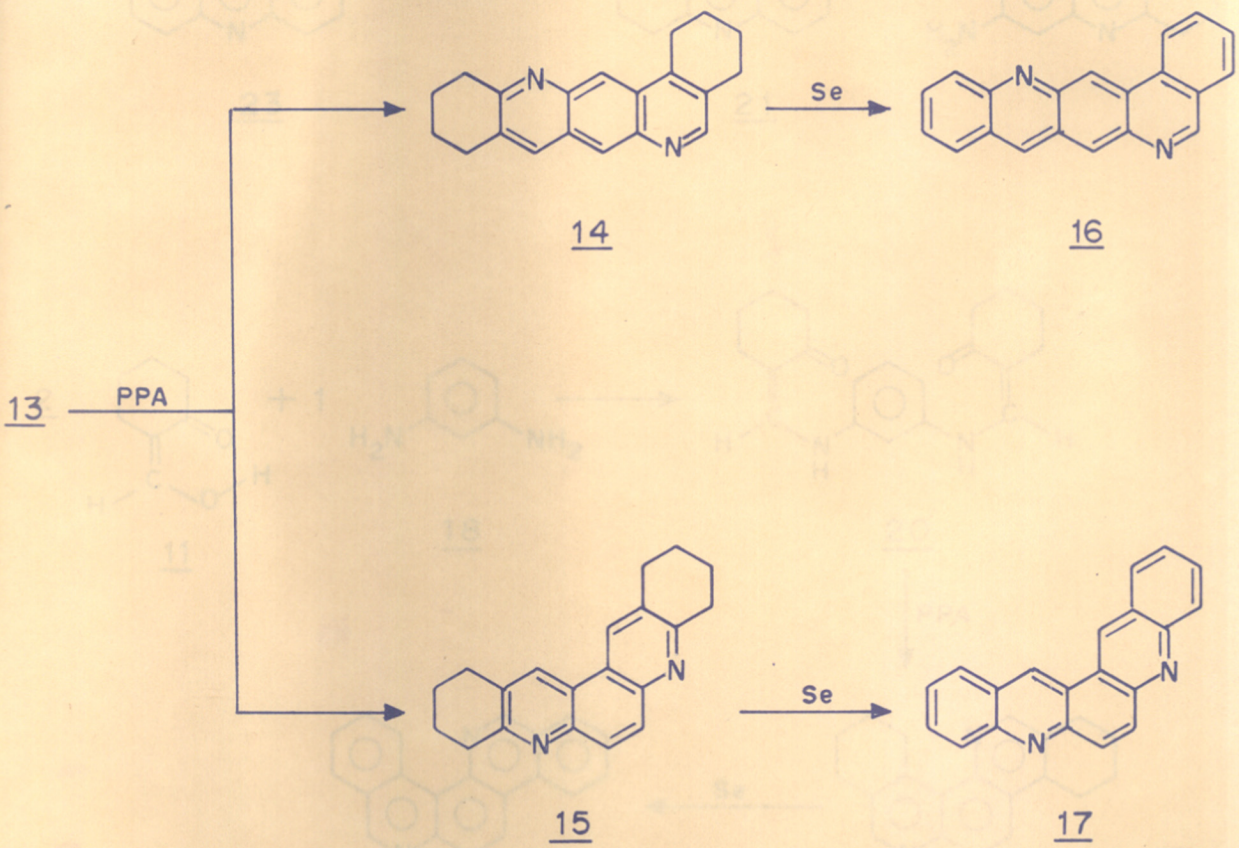


CHART 1



11 12 13



14 16

15 17

CHART 2

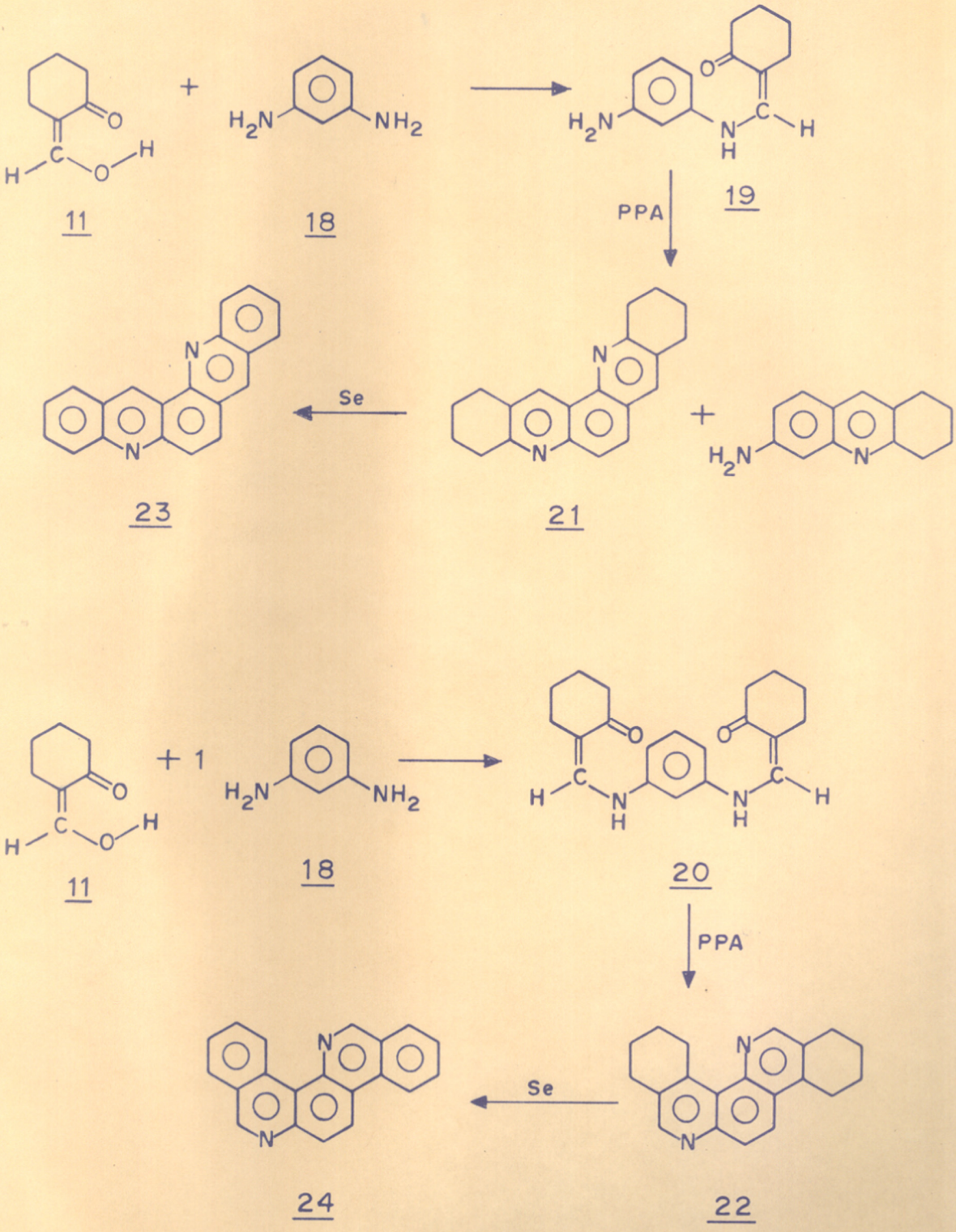


CHART 3