SUMMARY.

Synthesis of Phenanthroindolizidines and Nitrogen Mustards as Anticancer Agents:

Govindachari et al. (J. Chem. Soc., 1954, 2801) isolated tylophorine and tylophorine from Tylophora asthematica, the structures of which have been proved by degradative and synthetic methods. Gellert, Govindachari and et al. (J. Chem. Soc., 1962, 1008) isolated Tylocrebrine from Tylophora Crebriflora and assigned its structure by degradative and synthetic methods. Gellert and Rudzats (J. Med. Chem., 2, 361, 1964) reported that tylocrebrine shows high activity against lymphoid leukaemia L 1210 in mice, the best results being obtained at a dose level of 10 mg./kg.

It was, therefore, thought of interest to synthesise phenanthroindolizidines, having different substituents in the phenanthrene ring system of the molecule to study the structure and anticancer activity relationship.

In Chapter I, different methoxy substituted phenanthrene-9-carboxylic acids are prepared by modification of Pschorr synthesis from trans-o-aminophenyl cinnamic acid derivatives which in turn were synthesised from trans-o-nitrophenyl cinnamic acid, prepared by
condensation of o-nitrobenzaldehyde and phenylacetic acid derivatives in the presence of acetic anhydride and triethylamine. Phenanthrene-9-carboxylic acid and its derivatives were reduced by either diborane or sodium dihydro-bis(2-methoxy-ethoxy)aluminate to the corresponding 9-hydroxymethyl-phenanthrene derivatives in about 60-90% yield. They were converted to the corresponding 9-chloromethylphenanthrene derivatives by the action of thionyl chloride. Different methoxy substituted 9-chloromethylphenanthrene were prepared by this procedure. 9-Chloromethylphenanthrene and 9-chloromethyl-6-methoxyphenanthrene were used as starting material for a synthesis of phenanthroindolizidine and 6-methoxyphenanthroindolizidine respectively.

9-Chloromethylphenanthrene was condensed with (-)-benzyl-L-prolinate in the presence of anhydrous potassium carbonate. During the reaction, transesterification occurred and instead of benzyl-L-phenanthr-9-ylmethyl-L-prolinate, the corresponding methyl ester was obtained. This methyl ester was also prepared by condensing proline methylester hydrochloride with 9-chloromethylphenanthrene in dimethylformamide. The benzyl ester could also be isolated when dimethylformamide was used as a solvent for N-alkylation. The proline methyl ester derivative was hydrolysed to the acid hydrochloride with conc. hydrochloric acid, which when heated with polyphosphoric
acid gave phenanthroindolizidone, the structure of which was confirmed by I.R. and Mass spectra. The phenanthroindolizidone, on reduction with sodium dihydro-bis(2-methoxyethoxy)aluminate in dry benzene gave phenanthroindolizidine in 70\% yield. The structure of this compound was confirmed by U.V., N.M.R. and Mass spectra.

By using the above procedure, 6-methoxyphenanthroindolizidone and naphthoindolizidone have been synthesised from 9-chloromethyl-6-methoxyphenanthrene and 1-chloromethylnaphthalene respectively. The structures of intermediates and final compounds were confirmed by U.V., I.R., N.M.R. and Mass spectra. Attempts to reduce 6-methoxyphenanthroindolizidone and naphthoindolizidone to the corresponding indolizidine derivatives with different reducing agents met with failure.

Chapter II, Section I deals with the condensation of different 9-chloromethylphenanthrene derivatives with diethanolamine which gave N,N-bis(β-hydroxyethyl)-9-aminomethylphenanthrene derivatives which were converted into the corresponding N,N-bis(β-chloroethyl)-9-aminomethylphenanthrene derivatives by reacting with thionyl chloride. 9-Phenanthroyl chloride, on condensation with N,N-bis(2-chloroethyl)-amine hydrochloride in dry benzene gave phenanthrene-9- \([N,N-bis(2-chloroethyl)]\) carboxamide which rearranged to phenanthrene-9- \([N,N-bis(2-chloroethyl)\text{anion}]\) carbo-
xamide ion during crystallisation in aqueous alcohol. The structure of which confirmed by I.R. spectrum. Similarly phenanthrene-9-\([N,N\text{-}\text{bis}(2\text{-chloroethyl} \text{aminon})]^{2-}\) \(2,3,6\)-trimethoxy-carboxamide ion was prepared from \(2,3,6\)-trimethoxy-9-phenanthroyl chloride and \(N,N\text{-}\text{bis}(2\text{-chloroethyl})\) amine hydrochloride.

Most of the nitrogen mustards of phenanthrene derivatives were screened against Walker 256 Carcinosarcoma and P 388 tumour system, some of them have shown good activity against both the above mentioned tumour systems.

Chapter II - Section II, deals with the bromination of methylcoumarin derivatives with \(N\text{-bromo-succinimide}\) to form bromomethylcoumarin derivatives. These halogenomethylcoumarin derivatives on condensation with diethanolamine furnished \([N,N\text{-}\text{bis}(\beta\text{-hydroxyethyl})\text{-aminomethyl}]\) coumarin hydrochloride or hydrobromide derivatives, which in turn were converted to the corresponding nitrogen mustards by the treatment with thionyl chloride. 6-Bromomethylcoumarin was directly treated with \(N,N\text{-}\text{bis}(2\text{-chloroethyl})\) amine hydrochloride in dry benzene to give 6-\([N,N\text{-}\text{bis}(2\text{-chloroethyl})\text{aminomethyl}]\) coumarin.

Most of the above coumarin nitrogen mustards were screened against Walker 256 Carcinosarcoma, P 388 tumour system and L 1210, some of them have shown encouraging results.
In recent years considerable interest has been displayed in the so-called antimalarial mustards as possible chemotherapeutic agents in the management of neoplastic diseases. 2-Hydroxy-4-\(\text{N},\text{N}-\text{bis(3-hydroxyethyl) aminomethyl}\) quinoline hydrochloride, 2-hydroxy-4-\(\text{N},\text{N}-\text{bis(3-hydroxyethyl)aminomethyl}\) 6-methylquinoline hydrochloride and 2-hydroxy-4-\(\text{N},\text{N}-\text{bis(3-hydroxyethyl)aminomethyl}\) 8-methylquinoline hydrochloride were prepared from their corresponding 4-bromomethylcarbostyril derivatives, which were converted to the corresponding nitrogen mustards on treatment with thionyl chloride.

In Chapter II - Section IV, the reactivity of 9-chloromethylphenanthrene derivatives and halogenomethylcoumarin derivatives has been studied. Various Mannich bases were prepared by condensing primary amines and the secondary amines with 9-chloromethylphenanthrene derivatives and halogenomethylcoumarin derivatives. 9-Chloromethylphenanthrene derivatives and halogenomethylcoumarin derivatives on condensation with piperidine, morpholine and dimethylamine, afforded the corresponding piperidinomethyl, morpholinomethyl, dimethylaminomethyl derivatives. The Mannich reaction on 5-methyl-7-hydroxycoumarin with diethanolamine and paraformaldehyde in absolute alcohol gave the Mannich base in poor yield, which in turn was converted into the corresponding nitrogen mustard.
In Chapter III, the reactivity of 1-chloromethylnaphthalene, 9-chloromethylphenanthrene, halogenomethylcoumarin and halogenomethylquinoline derivatives with diethylsodicacetamidomalonate has been studied.

It was thought of interest to synthesise phenanthroindolizidine and naphthoindolizidine by different routes, for which \( \beta-(9\text{-phenanthryl})\)-alanine and \( \beta-1\text{-naphthyl}\)-alanine required in large quantity.

Condensation of 9-chloromethylphenanthrene with diethylacetamidomalonate in the presence of pulverised sodium and absolute alcohol gave only 40% yield of diethyl(9-phenanthrylmethyl)acetamidomalonate, but yield of this diester was increased to about 80% by using sodium hydride and dimethyl sulphoxide as a solvent. The structure of diester was confirmed by I.R. and N.M.R. spectra. Diester on hydrolysis with 48% of hydrobromic acid and then on careful neutralisation of the hydrobromide with dilute ammonium hydroxide with cooling afforded \( \beta-(9\text{-phenanthryl})\)-alanine in good yield. This alanine derivative was cyclised with formalin and conc. hydrochloric acid using the Pictet-Spengler reaction to the corresponding 1,2,3,4-tetrahydribenzo \([f,h]\) isoquinoline-3-carboxylic acid. The structure of which was confirmed by Mass spectrum. This on esterification with dry methanol and thionyl chloride gave methyl-1,2,3,4-tetrahydribenzo \([f,h]\)
isoquinoline-3-carboxylate hydrochloride. The structure of this was confirmed by I.R. spectrum. No further work could be carried out because of poor yield at this stage.

In the case of naphthalene, coumarin and quinoline derivatives also, further work was not possible because of low yield of isoquinoline-3-carboxylic acid derivative. In case of naphthalene, while the Pictet-Spengler reaction failed in case of coumarin and quinoline derivatives.