## 'Synopsis'

The objective of the present research was to develop new synthetic methodologies and use them fruitfully for the synthesis of biologically active molecules and compounds of pharmacological importance. In the present thesis, a number of heterocyclic-steroids containing nitrogen (and also a few condensed thiophene ring derivatives) have been synthesised with a view to screening them subsequently for biological activity. Literature reveals that such molecules may act as endocrine agent with a novel spectrum of physiological properties. The thesis consists of six chapters, each containing theoretical and experimental parts and its own bibliography. The content of each chapter is briefly summarised below.

In Chapter 1, the different methods for the synthesis of N-containing heterocyclic steroids (azasteroids) have been reviewed giving particular stress on the more recent developments in the field.

In Chapter 2, a total synthesis of $(\pm)$-3-methoxy-6,15-diazaestra-1,3,5,7,9,14-hexaene (V) has been described. This is the first report of the synthesis of a 6,15-diazaequilenin derivative which incorporates quinoline and indole system in a single molecule. The synthesis which is shown in Scheme 1 starts from a simple cyclohexanedione (I), the nitrogen atom being

introduced in the final step by a modified Curtius reaction[1].
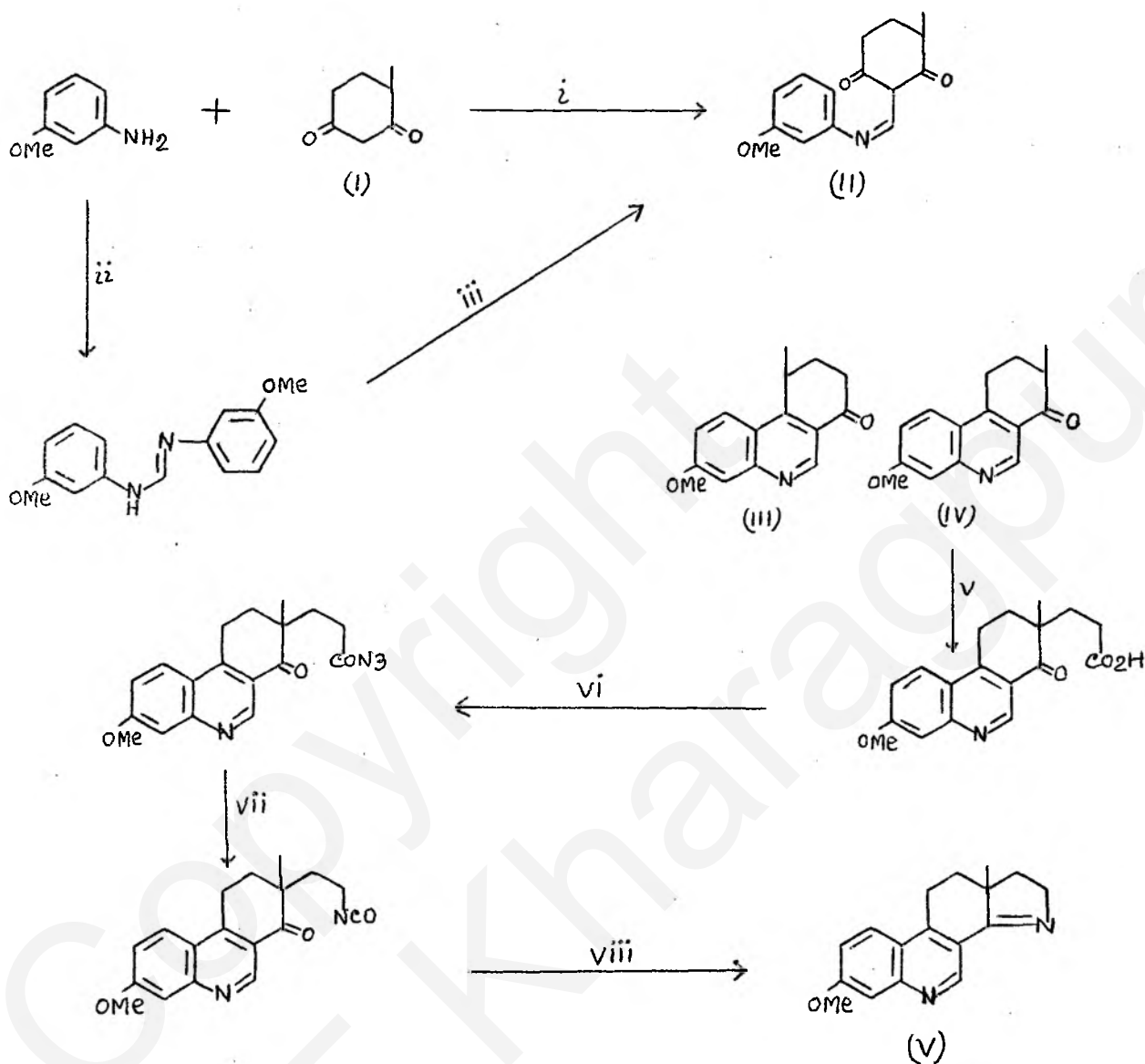
Scheme 1. Reagents : i, $(EtO)_3CH$, 120-130°; ii, $(EtO)_3CH$,EtOH,
reflux; iii,1,130-135°; iv, Polyphosphoric acid ;
v, CH_2CHCO_2Et, OH^-; vi, $ClCO_2Et$, Et_3N,NaN_3 ;
vii, heating in toluene; viii, HCl-AcOH, reflux.

1. J.G. Morgan, K.D. Berlin, N.N. Durham, and R.W. Chesnut,
   J.Org.Chem., 1971, 36, 1599.

One interesting observation was made in this connection. During the cyclisation of the dione (II), the major product was the unwanted quinoline derivative (III), although its formation apparently involved a more crowded transition state. The two products (III) and (IV) could, however, be separated easily through formylation of the mixture. Each was characterised by n.m.r. spectra.

In Chapter 3, a total synthesis of ($\pm$)-11-Aza-8-hydroxy-3-methoxy-18-norestra-1,3,5,9 (11)-tetraen-17-one (X) is described. The intermediate is ($\pm$)-9-17-dioxo-3-methoxy-18-nor-9,11-seco-estra-1,3,5(10)-trien-11-oic acid (VII) which is prepared as shown in Scheme 2.
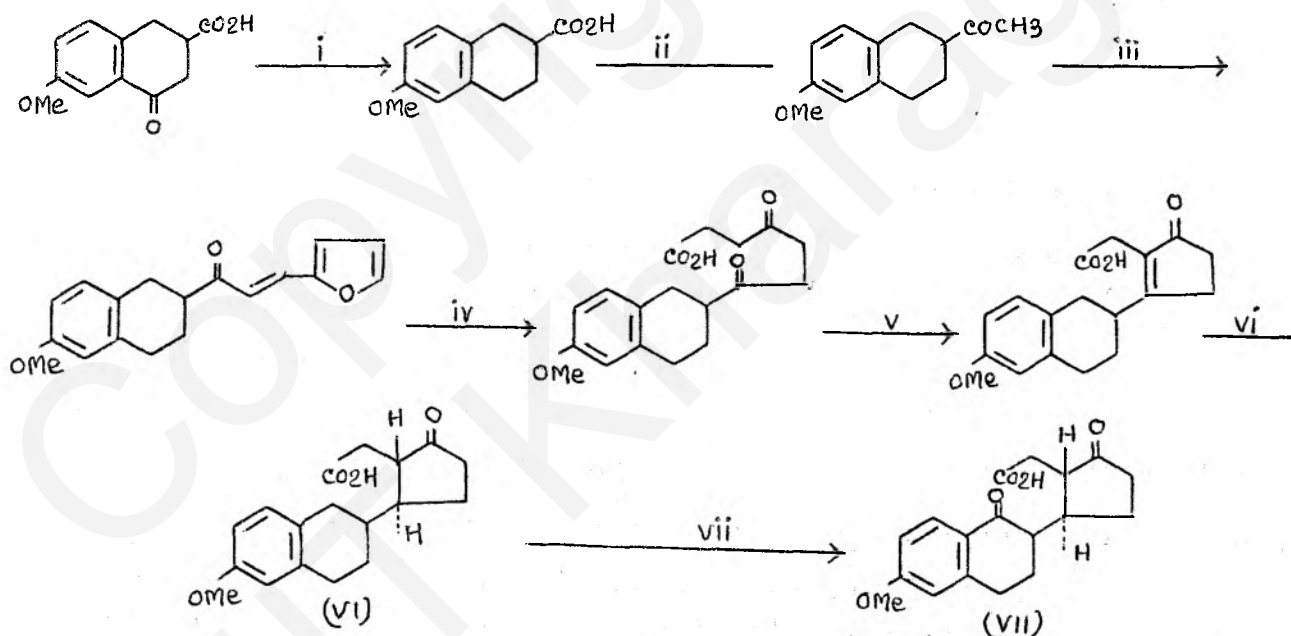
Scheme 2. Reagents : i, H_2NNH_2, KOH, ethylene glycol or 10% Pd-C in acetic acid and few drops of conc.HCl; ii, $SOCL_2$, ethoxymagnesiomalonate, dil.H_2SO_4, reflux with CH_3COOH-H_2SO_4-H_2O; iii, 2-furaldehyde, CH_3ONa; iv, conc.HCl-CH_3COOH-H_2O, reflux; v, 2% KOH; vi, CH_3OH-HCl; Pd-C, H_2; alc.KOH, reflux; vii, CrO_3 oxidation.

The final oxidation of the tetralin (VI) to the tetralone (VII) was carried out with chromic acid in acetic acid, the reaction being monitored by using model systems as shown (VIII $\longrightarrow$ IX) :
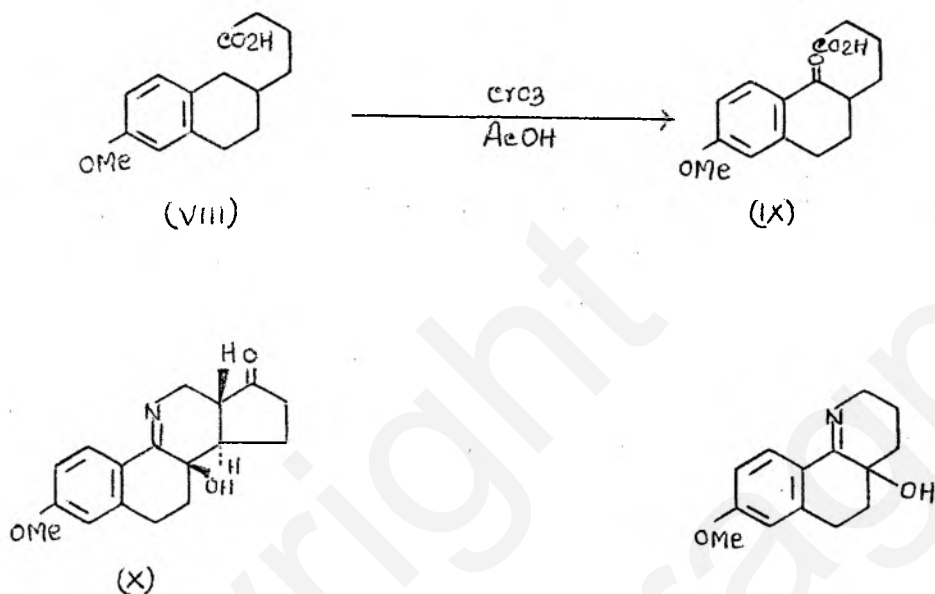
Both the ketoacids (VII) and (IX) were submitted to a modified Curtius reaction described before[2]. ($\pm$)-11-Aza-8-hydroxy-3-methoxy-18-norestra-1,3,5,9(11)-tetraen-17-one (X) and 2,3,4,4a,5,6-hexahydro-4a-hydroxy-8-methoxybenzo[h]quinoline were obtained in 36 and 50% yield respectively. The insertion of the hydroxyl group in the molecules is not surprising because many of the imines are sensitive to oxidation and are converted into hydroperoxides on exposure to air[3]. The latter ordinarily decompose to give secondary products including the β-hydroxy-imines (for further details, see Chapter 5).

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2. D. Nasipuri and S.K. Ghosh, J.C.S. Perkin 1, 1974, 2720.

3. B. Witkop, J.Amer.Chem.Soc., 1950, 72, 1428; B. Witkop and J.B. Patrick, ibid., 1951, 73, 713.

The structure of the azasteroid (X) was confirmed by n.m.r. spectra and from the study of the fragmentation pattern in the mass spectra. The configuration of the hydroxyl group (syn to 13-H) in the azasteroid molecule was determined by experiments to be discussed in Chapter 4.

The method described above is capable of giving a direct entry to 11-azaestrogens[4] from easily accessible materials and provides useful synthetic intermediates for 9,11-secosteroids a number of which have been synthesised lately[5] in view of their modified biological activity.

In Chapter 4, partial synthesis of two 11-azasteroids (XI) and (XII) have been described starting from estrone methyl ether (Scheme 3). Estrone methyl ether was oxidised with chromic acid using a modification of a known procedure[6] and the resultant ketoacid was converted into 11-aza-3-methoxyestra-1,3,5,9(11)-tetraen-17-one (XI) by Curtius reaction. Unlike the case described in Chapter 3, these compounds (XI and XII) do not undergo any oxidation in presence of air. This indirectly proves that the oxygen molecule attacks the imine system from an axial direction syn to C-13 methyl. Some of the experiments overlapped

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4. For a review, See R.I. Blickenstaff, A.C. Ghosh, and G.C. Wolf, 'Total synthesis of steroids', Academic Press, New York, 1974.

5. J.H. Dygos and L.J. Chinn, J.Org.Chem., 1973, 38, 4319; 1975, 40, 685; L.J. Chinn, J.H. Dygos, S.E. Mares, and R.L. Aspinall, R.E. Ranney, J.Med.Chem., 1974, 17, 351; N.S. Crossley and R. Dowell, J.Chem.Soc. (C), 1971, 2496.

6. R.C. Cambie and T.D.R. Manning, J.Chem.Soc. (C), 1968, 2603.

with a work reported earlier by Russian scientists[7] and had to be repeated since the details of the Russian work was not available to us.
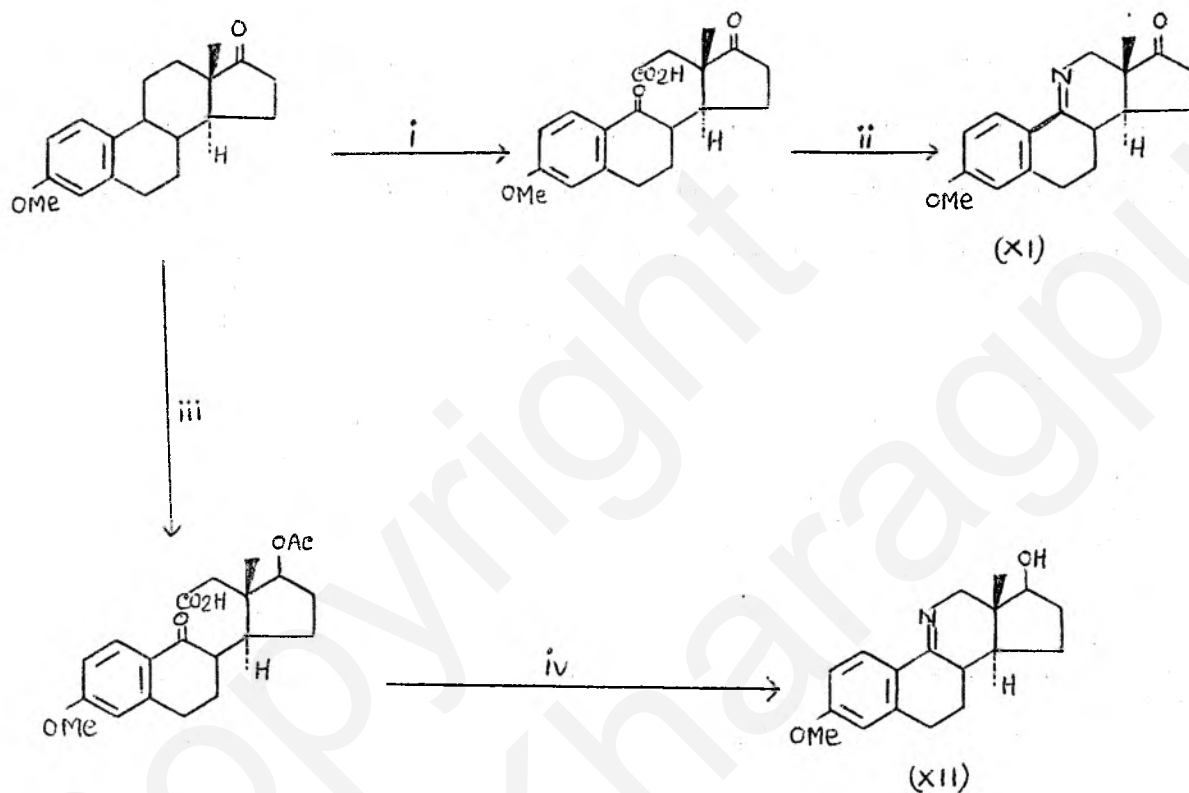
Scheme 3. Reagent: i, CrO_3-CH_3CO_2H, Oxidation; ii, Et_3N, $ClCO_2Et$, NaN_3; heat with toluene at 100°, CH_3CO_2H-HCl-H_2O, reflux; iii, $NaBH_4$, $AcCl$, Ac_2O, Py; CrO_3-CH_3CO_2H, Oxidation; iv, Et_3N, $ClCO_2Et$, NaN_3, heat with toluene at 100°, CH_3CO_2H-HCl-H_2O-reflux.

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7. K.K. Pivnitsky, Yu P. Badanova, and T.I. Ivanenko, Abstracts, III Soviet-Indian Symposium on the Chemistry of Natural Products, Tashkent, Abstracts, 1973, P.124.

In Chapter 5, some benzoquinoline and benzoindole derivatives have been synthesised using the modified Curtius reaction on easily accessible tetralone-butyric and tetralone-propionic acids. The different syntheses are shown schematically below :
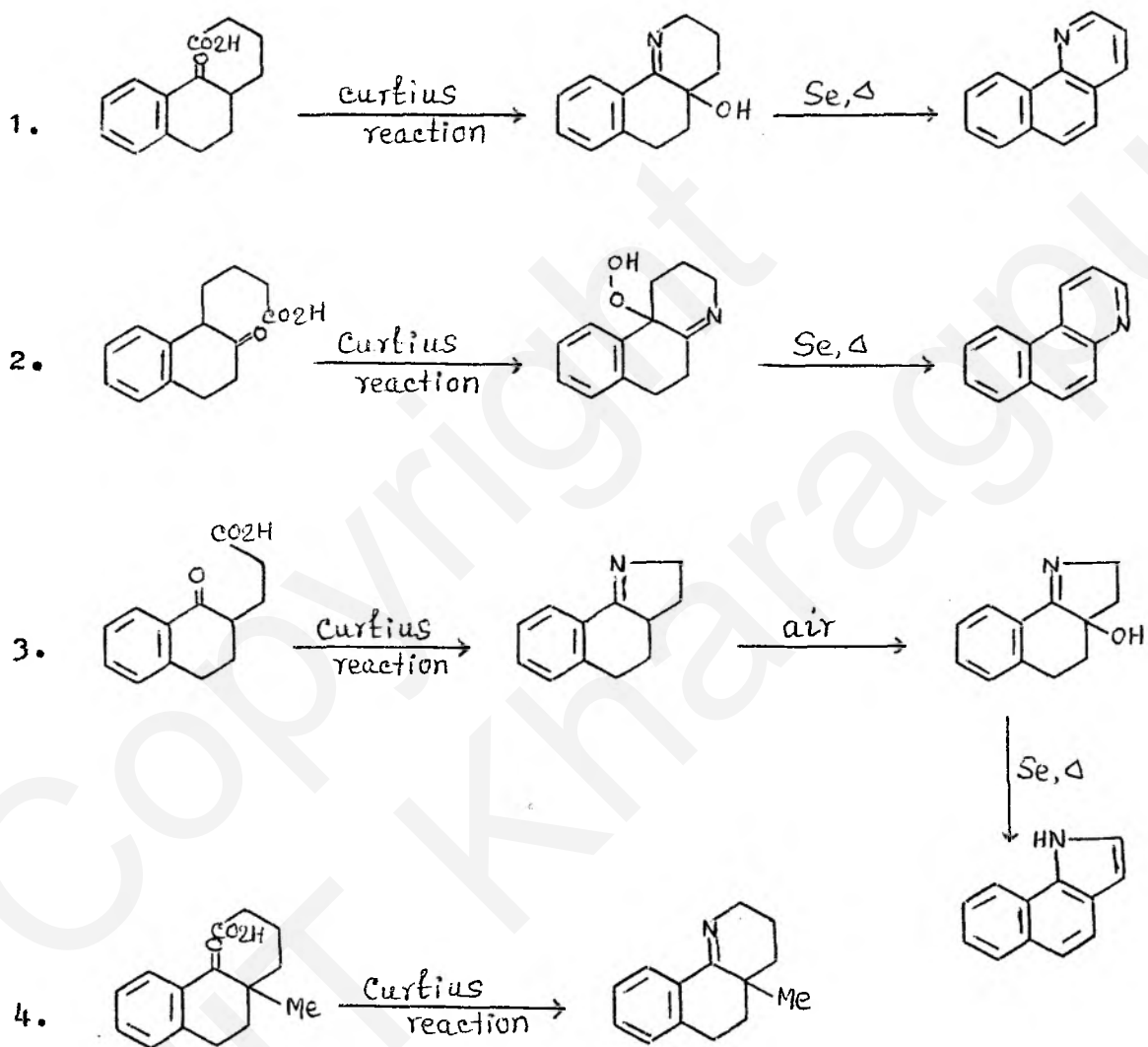

Scheme 4.

In addition to the synthetic utility of the reactions, several valuable informations were available from the above study. Thus in reactions 1-3, the intermediate imines resulting from Curtius rearrangement underwent spontaneous aeroxidation either to β-hydroxy- or β-hydroperoxy-imines. In case of five membered ring imine (reaction 3), however, it was sufficiently stable to allow determination of n.m.r. and mass spectra. Apparently, the five-membered ring imines are slow to oxidise. The formation of the hydroperoxy-imine in reaction 2 indicates that probably in all cases, the imines undergo aeroxidation first by addition of an oxygen molecule and subsequently by giving up an oxygen atom (probably to solvent molecule or to another imine) to give the hydroxyimines. The oxidation does not take place if no allylic hydrogen is present (reaction 4), or if there is sufficient steric hindrance to the approach of oxygen molecule (as in XI and XII). Benzoquinolines and benzoindoles were obtained from the imines or the oxidation products thereof by heating with selenium, in approximately 30-50% yield.

In Chapter 6, a new one-pot synthesis of a number of dibenzothiophenes and benzo[b]naphtho[2,1-d]thiophenes has been described. The method consists in heating 3-arylcyclohex-2-en-1-ones with sulphur either alone or with a catalytic amount of iodine. Interestingly, the products in the two cases (with and without iodine) are different with respect to the position of the phenolic group. Thus when 3-β-naphthylcyclohex-2-en-1-one (XIII) was heated with sulphur alone at 250° (Scheme 5),

some 20% of 10-hydroxybenzo[b]naphtho[2,1-d]thiophene (XIV) was
obtained along with 3-β-naphthylphenol (XV).   On the other hand,
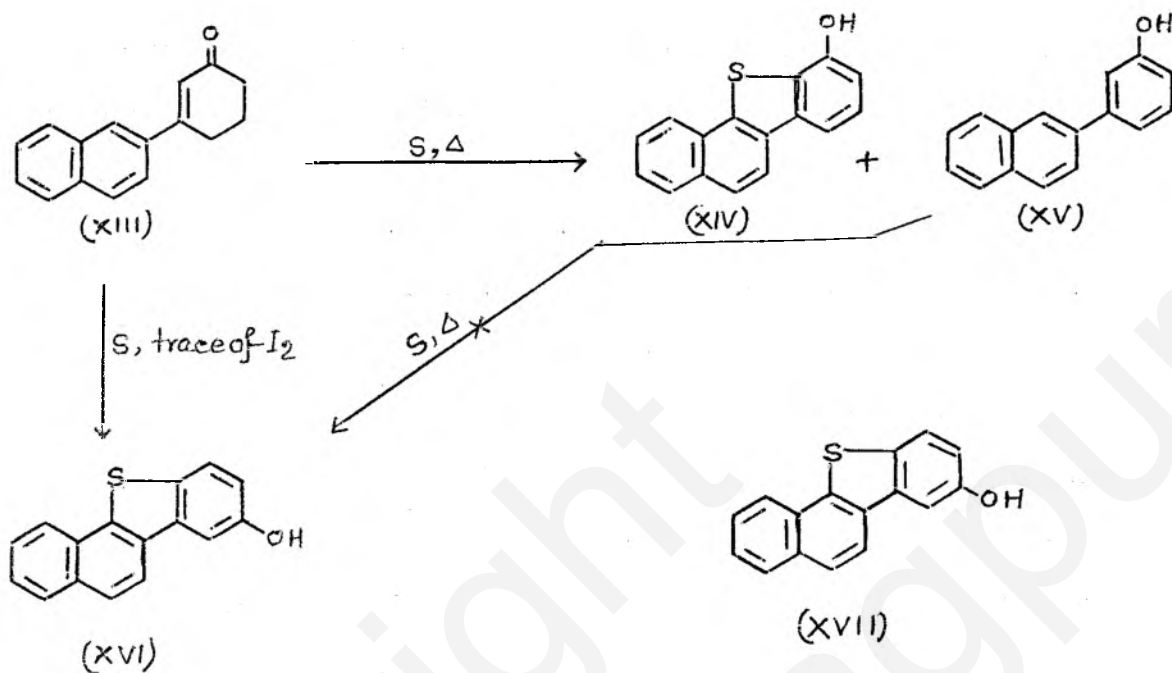
when the same ketone was heated with sulphur in presence of a
trace of iodine, 8-hydroxybenzo[b]naphtho[2,1-d] thiophene (XVI)
was formed in nearly 30% yield.   The compound (XVII) and two
benzo[b]naphtho[2,1-d]thiophenes were prepared in a similar
fashion.   Recently, interest in condensed thiophene ring deriva-
tives has been revived mostly because of certain important
physiological properties such as antitumour activity shown by
some of them[8,9].   The present method of synthesis could be
conveniently used for synthesis of such compounds from easily
accessible compounds.

8.   A.N. Fujiwara, E.M. Acton, and L. Goodmay, J.Heterocyclic
     Chem., 1968, 5, 853.

9.   E. Campaigne, L. Hewitt, and J. Ashby, Chem. Commun., 1969,
     598.