PART III

PRESENT WORK ON THE REGIOSELECTIVE SYNTHESIS OF 
PYRROLO[3,2-f][1]BENZOPYRAN-7-ONES

DISCUSSION
Coumarin$^{140}$ and its derivatives$^{141-142}$ are interesting due to their physiological activity$^{140}$. The biological activity$^{143-145}$ of 4-alkyl and 3-alkyl coumarins has made their synthesis$^{146-147}$ important. In this context we have reported the regioselective synthesis of 3,4-fused pyrano- and furocoumarins$^{90-91,93,112,114,148}$ from propynylidene and allylic ethers of coumarin. Our continued interest in this area prompted us to undertake a programme for the synthesis of pyrrolocoumarins. Here we report the results of our investigation.

The starting materials 6-N(4-aryloxybut-2-ynyl), N-methylaminocoumarins (251a-h) were synthesised in good yields by refluxing 6-N-methylaminocoumarin (250) and 1-aryloxy-4-chlorobut-2-ynes (80a-h) in acetone in presence of anhydrous potassium carbonate (Scheme 14). Compound 250 in turn was prepared from 6-aminocoumarin$^{149}$ through a sequence of reactions viz., (i) tosylation with 4-toluenesulphonyl chloride in pyridine, (ii) methylation with methyl iodide in acetone-potassium carbonate, (iii) detosylation with a mixture of glacial acetic acid and conc. sulphuric acid (Scheme 13).
As our aim was to synthesize pyrrolocoumarins from the substrates (251) at first the substrate 251a was subjected to thermal rearrangement under different conditions viz., heating of the substrate 251a in N,N-dibutylaniline at 260° and also in quinoline, (240°) resulted in the recovery of the starting material, neat heating under nitrogen on a woods metal bath upto 210° showed no sign of change and on heating at 240°C for 2h., decomposition of the substrate (251a) took place and only 6-N-methylaminocoumarin (250) was isolated from the reaction mixture. Having failed to achieve the synthesis of the pyrrolocoumarin from substrates (251) by thermal rearrangement we became interested in the methodology of Thyagarajan and coworkers for the construction of the five-membered heterocyclic ring in benzo(b)thiophenes and indoles. This was shown to be an excellent high yield one-step process and the nitrogen heterocycles are obtained in almost quantitative yields by simply stirring a solution of the arylpropynylamine in dichloromethane at r.t. with one equivalent of m-chloroperoxybenzoic acid. We, therefore, decided to investigate whether the five-membered pyrrole ring in coumarin with the 3,4-double bond could be constructed via the aforesaid Amine Oxide Rearrangement. Consequently the tertiary amine 251a
was treated with one equivalent of m-chloroperoxybenzoic acid in dichlo-
romethane at ambient temperature. A white crystalline solid is obtained
which has been characterised as pyrrolocoumarin derivative 252a with the
help of elemental analysis and spectral data. Only the angularly fused
pyrrolocoumarin derivative as evidenced from the p.m.r. spectra has been
obtained, no trace of linearly fused pyrrolocoumarin derivative could be
detected in the reaction mixture. Encouraged by the initial success, all
the remaining substrates 251b-h have also been subjected to Amine Oxide
Rearrangement to furnish pyrrolocoumarin derivatives 252b-h.

The formation of the pyrrolocoumarin derivatives 252 from 251 may
easily be explained\textsuperscript{59ab,156-158} by the formation of the N-oxide (253) followed
by a [2,3]sigmatropic rearrangement to give the intermediate 254 which
in turn undergoes a [3,3]sigmatropic rearrangement and internal Michael
addition to give the Ketol 256. Acid-catalysed allylic rearrangement of 256
leads to the product 252 (Scheme 15).
The benzoate group of the pyrrolocoumarin derivatives 252(a-h) is easily displaced by a methoxy group when the compounds 252(a-h) are refluxed in absolute methanol to furnish a series of methoxy derivatives 253(a-h).

![Scheme 16]

Although we had obtained only a single product from the rearrangement of each of the substrates studied and in some cases we were able to conclude from the $^1$H-NMR, the formation of the expected angularly fused product but in some cases it became quite difficult to firmly conclude as the aromatic protons were not well separated. All the substrates studied so far contained aryloxybutynyl group and consequently the final product after methanolysis also carried the aryloxy-aromatic protons. So we have attempted to synthesise pyrrolocoumarin devoid of the aryloxy group. We first prepared 6-N-propynyl,N-methylaminocoumarin 257 and subjected this to amine oxide rearrangement and attempted to get the pyrroloquinoline derivative by the addition of cyanide nucleophile. No tractable product could be isolated. We next prepared 6-N(4-hydroxybut-2-ynyl), N-methylaminocoumarin 258 from 6-N-methylaminocoumarin 250 and 4-chlorobut-2-ynyl-1-ol. This compound 258 was then treated with one equivalent of $m$-chloroperoxybenzoic acid in dichloromethane for 12 h. In this case too no pure product could be isolated after usual work up. This compound was converted to its acetate 259 and the acetate was subjected to amine oxide rearrangement to give the
pyrrolocoumarin derivative 260. Compound 260 was then treated with methanol to give the methoxy derivative 261.

The $^1$H-NMR of compound 261 showed two well-separated ortho-coupled aromatic protons centred at $\delta$ 7.30 (d, 1H, $J=9$Hz) and at 7.55 (1H, d, $J=9$Hz) besides two protons at $\delta$ 6.50 (d,1H, $J=10$Hz) and at 8.48 (1H, d, $J=10$Hz) due to protons at coumarin $\pi$-bond. The presence of this two ortho-coupled protons conclusively shows this product to be the angularly fused pyrrolocoumarin.

This is an extremely facile and mild synthesis for pyrrolocoumarin derivatives. The generality of the method has been tested by the successful conversion of eight substrates 251a-h to pyrrolocoumarin derivatives 252a-h in very good yields and in each case the regioselectivity has been achieved. It is interesting to note that the 3,4-double bond of coumarin is totally unaffected by the peracid. This is also the first example of the application of the Amine Oxide Rearrangement in heterocyclic substrates to give polyheterocycles.