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NOVEL SYNTHESIS OF OXAZINES FROM 4-HYDROXYCOUMARIN AND SCHIFF BASES.

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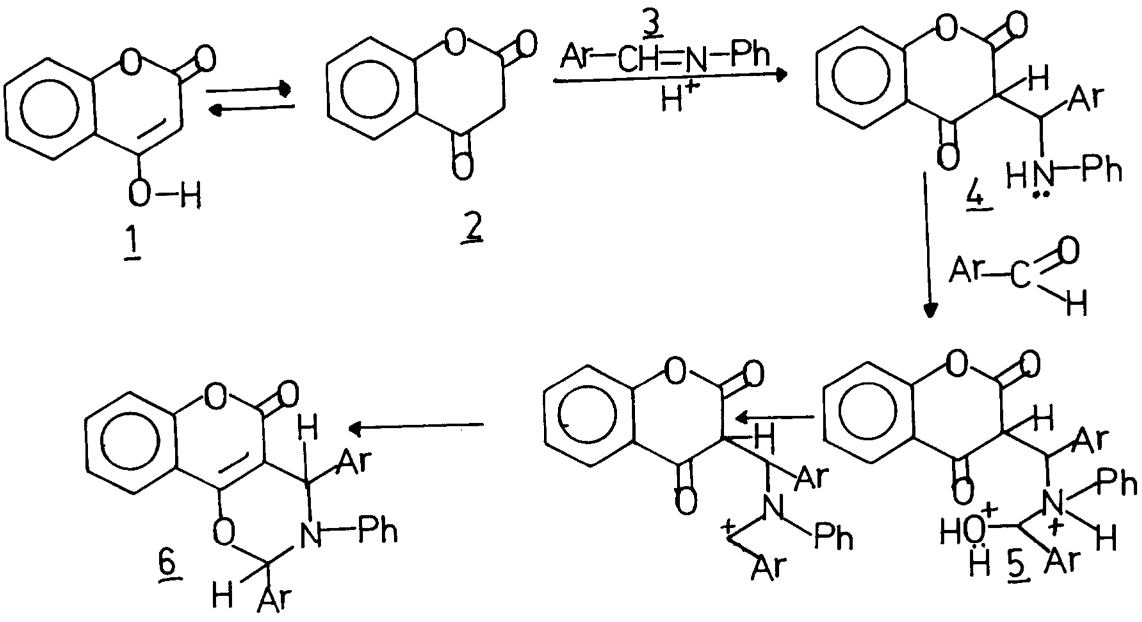
It has long been known that Schiff bases are easily acylated with acid halides or anhydrides[1] and the resulting adducts have been used in the synthesis of heterocyclic compounds such as β-lactams etc.[2] The reaction involves an addition across the -CH=N- bond in the presence of a tertiary amine. Recently, Haimova et al.[3] have reported the reaction of 1,3-isochromandiones (homophthalic anhydrides) with Schiff bases to yield the corresponding isoquinolinones in one step. Also, in connection with the total synthesis of the alkaloid nitidine chloride, Cushman and Cheng[4] reacted Schiff bases with substituted homophthalic anhydrides.

In view of the above interesting reactions we were prompted to study the reaction of 4-hydroxycoumarin 1 with Schiff bases 3a-d in acidic medium as the reaction failed to give any pure product in the presence of a base. 1 was chosen for study since it exists in tautomeric forms and also possesses many interesting pharmacological properties.

A typical experiment involves the condensation of 1 (1 mole) with benzylidene-aniline (2 moles) with vigorous stirring in glacial acetic acid at 30° for 1-3 hrs. to give a crystalline pale yellow compound, m.p. 169-70°. Elemental analysis of the same led to a molecular formula $C_{29}H_{21}O_3N$ which was confirmed by its MS (M^+ 431) taken at 30 eV. However, MS taken at 70 eV did not record the correct molecular weight, but instead gave the highest peak at 250 which suggests that a fragment corresponding to benzylidene aniline had been lost. In the IR (nujol) spectrum of the compound, a band at 1700 cm^{-1} confirmed the retention of the coumarin ring while a band at 1220 cm^{-1} was indicative of an ether linkage. The spectrum also showed the absence of any OH or NH bands. NMR (CF_3CO_2H) showed two singlets, each integrating for one proton at δ 6.25 and δ 8.00 in addition to a multiplet corresponding to 19 protons in all. The above spectral analysis led us to assign the structure benzopyrano-oxazine 6 to the product. The downfield shift of the proton at δ 8.00 was ascribed to the proximity of the carbonyl function. The formation of oxazine could be explained as follows :



Scheme 1 in $\underline{6}$ Ar is : a = Ph, m.p. 169-70° (needles); b = p-OMe C_6H_4, m.p. 248-49° (needles), c = p-Cl-C_6H_4, m.p. 240-42° (prisms); d = Ph = C_5H_5N, m.p. 228-29° (needles).

Schiff bases are known to act as proton acceptors and as parent aldehyde source also. $\underline{1}$ being strongly acidic (solubility in $NaHCO_3$) reacts with the protonated Schiff base $\underline{3}$ readily to give $\underline{4}$ which reacts immediately with benzaldehyde to yield $\underline{6}$ via $\underline{5}$. In order to confirm the role of $\underline{1}$ as a proton donor, as well as to isolate an intermediate $\underline{4}$, the reaction was carried out in methanol as a solvent when the same product $\underline{6}$ was isolated in 50-60% yield. The reaction described above seems to be a general one and has been carried out with other Schiff bases described in the Scheme indicated above.

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