Synthesis of 3-Aryl-6-methyl-7-phenyl-8-oxo-2*H*,8*H*-pyrano[3,2-*g*][1,4]benzoxazines as Potent Antimicrobial Agents

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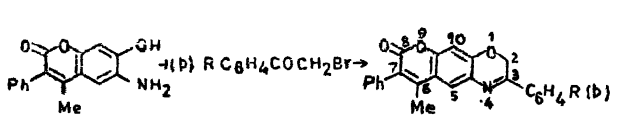
IT is established that angular coumarin-oxazine derivatives[1] exhibit antifungal activity, with a view to evaluating and comparing their biological activity with angular analogues, we have undertaken the synthesis of linear coumarinoxazine derivatives.

The condensation of 6-amino-7-hydroxy-4-methyl-3-phenylcoumarin[2] (**1**) with various ω-bromoacetophenones[3] (**2**) in the presence of anhydrous potassium carbonate-acetone, yielded respective 3-aryl-6-methyl-7-phenyl-8-oxo-2*H*,8*H*-pyrano[3,2-*g*][1,4]benzoxazine-(**3a–e**) which were characterised by their analytical and spectral data.



1 **2** **3a–e**

a; R=H
b; R=Br
c; R=Cl
d; R=NO_2
e; R=OMe

The ir bands of **3a–e** appeared at 1 620–1 590 (C=N) and 1 330–1 160 and 1 100–1 070 cm^{-1} of symmetric and asymmetric stretching of the aliphatic and aromatic ether system respectively[4], which are totally absent in the spectrum of its precursor (**1**) and confirms the cyclisation to **3a–e**. All compounds revealed the absorption bands as expected, along with a band at 1 730–1 700 cm^{-1} for the lactone carbonyl group[5].

The pmr spectrum of **3e** contained a neat three-proton singlet at δ 2.3 due to C-6 methyl group. Another three-proton singlet which appeared at δ 4.00 is due to methoxy group of 3-phenyl ring attached to oxazine nucleus. The C-2 methylene group of oxazine nucleus appeared as a singlet at δ 5.05. A complex multiplet appeared around δ 6.8–8.0 integrating for eleven aromatic protons.

The mass spectra of **3a–e** exhibited a general fragmentation pattern. In almost all the spectra, it is observed that loss of aryl acetylene or phenyl or CO group converting it into the corresponding fragments is the predominant pattern.

Biological activity: Compounds **3a–e** were screened for their antibacterial activity by the filter paper disc diffussion plate method[6] and for their antifungal activity by the food poisoning technique[7].

The antibacterial activity was carried out against the microorganisms *Bacillus megaterium* and *Proteus vulgaris*. All the compounds were found less toxic towards the bacteria tested. The relatively high toxicity of compound **3d** may be attributed to *p*-nitrophenyl moiety.

The antifungal activity was tested against *Fusarium solani* and *Dreschelera specifera*. All the compounds were found toxic whereas **3a** and **3c** less toxic. The compounds showed maximum inhibition at 800 μg ml^{-1}. Compounds **3d** and **3e** showed 100% inhibition in both the fungi at 800 μg ml^{-1}. In general, the linear coumarinoxazoles exhibited less antibacterial and antifungal activities than those of their angular analogues[1].

Experimental

The purity of the compounds was checked by tlc. Melting points are uncorrected. Ir spectra (KBr/nujol) were recorded on a Perkin-Elmer 283 spectrophotometer, pmr spectra ($CDCl_3$) on a EM-390 (90 MHz) spectrometer using TMS as an internal standard and mass spectra on a Jeol JMS-D-300 spectrometer at 70 eV.

*3-Aryl-6-methyl-7-phenyl-8-oxo-2*H,*8*H-*pyrano[3,2-g][1,4]benzoxazines* (**3a–e**). *General procedure:* A mixture of **1** (0.01 mol) and anhydrous potassium carbonate (2.07 g, 0.01 mol) in dry acetone (250 ml) was stirred for 3 h at room temperature. The ω-bromoacetophenones (0.01 mol) were then added and the mixture was refluxed for 24 h. The excess of acetone was distilled off and the residue washed with ice-cold water (150 ml), filtered and the solid recrystallised from suitable solvents: **3a** (60%), m.p. 170°, *m/z*

367 ($M^{+\cdot}$, 100), 366 (22.77), 352 (6.25), 339 (62.5), 290 (3.68), 265 (17.18), 236 (60), 103 (90.6) and 77 (62), δ 6.9–8.0 (m, ArH), 5.6 (s, 2-H), 2.3 (s, 6-CH_3) ; **3b** (58%), m.p. 166°, δ 7.0–8.2 (m, ArH), 5.6 (s, 2-H), 2.3 (s, 6-CH_3) ; **3c** (55%), m.p. 215°, δ 7.0–8.0 (m, ArH), 5.5 (s, 2-H), 2.3 (s, 6-CH_3) ; **3d** (55%), m.p. 160°, δ 7.1–8.3 (m, ArH), 5.6 (s, 2-H), 2.3 (s, 6-CH_3) ; **3e** (53%), m.p. 190°, δ 6.8–8.0 (m, ArH), 5.5 (s, 2-H), 2.3 (s, 6-CH_3), 4.0 (s, OCH_3).

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