Synthesis and antimicrobial activity of novel linearly fused 5-substituted-7-acetyl-2,6-dimethyloxazolo[4,5-f]indoles

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The exclusive formation of 1-substituted-6-α-oximino-ethylindoles 3a-d from the reaction of 3,6-diacetylindoles with hydroxylamine reveals the chemoselectivity of C6-acetyl function over that of C3-acetyl function towards the nucleophilic attack of hydroxylamine. These monooximes 3a-d are stirred with methanesulphonyl chloride in dry pyridine at room temperature to give the novel 5-substituted-7-acetyl-3,6-dimethyloxazolo[4,5-f]indoles 5a-d in good yields. The structures of all these newly synthesised compounds have been confirmed by their spectral and analytical data and they have been screened for antibacterial and antifungal activities.

Keywords: Indoles, hydroxylamine, mono-oximes, antibacterial activity, antifungal activity

IPC: Int.Cl.8 C07D

Indole derivatives occupy a prime place in heterocyclic chemistry owing to their valuable properties as therapeutic agents1, drugs, dyestuffs etc. Oxazoles are reported to possess antiinflammatory2, antidiabetic3, hemoregulatory4, antimicrobial5, blood platelet aggregation inhibiting property6 and also the pesticidal properties7. The interesting biological activities associated with oxazoles and also practically there are no reports wherein the oxazole moiety is linearly fused to the benzenoid part of the biologically active indole moiety prompted us to report here the synthesis of hitherto unknown novel oxazolo[4,5-f]indoles.

The starting materials used for the synthesis of title compounds are 5-hydroxy- indoles 1a-d prepared by adopting the Nenitzescu reaction8,9. The indoles 1a-d were subjected to regioselective Friedel Crafts acetylation10,11 using acetyl chloride and AlCl3 in freshly distilled nitrobenzene to produce 3,6-diacylindoles 2a-d, which were further reacted with hydroxylamine hydrochloride in 40% KOH in ethyl alcohol to yield exclusively the monooximes, 1-substituted-3-acetyl-6-α-oximinoethyl-5-hydroxy-2-methyindoles 3a-d instead of the expected dioximes 4a-d. This reaction revealed the chemoselectivity of C6-acetyl over that of C3-acetyl function towards the nucleophilic attack of hydroxylamine (Scheme 1). The observed resistance of C3-acetyl group of these diacetylindoles 2a-d towards hydroxylamine could be presumably due to the delocalisation of lone pair of electrons on indole nitrogen to C3-acetyl carbonyl as shown in resonating structure (A) leading to the reduced double bond character of C3-acetyl carbonyl group. An additional support to this fact was adduced by attempting to react 3-acetyl-2-methyl-5-methoxy-1-phenylindole with hydroxylamine under identical conditions which always gave back the starting materials. This observation is in conformity with our earlier report12 on the reaction of 3,6-diacylindoles towards nucleophilic attack of hydrazine hydrate. When the monooximes 3a-d were stirred with methanesulfonyl chloride in dry pyridine at room temperature underwent Beckmann type rearrangement followed by cyclisation to produce the desired novel 5-substituted-7-acetyl-3,6-dimethyloxazolo[4,5-f]indoles 5a-d in good yields. The structures of all these compounds were confirmed by their analytical and spectral data.

Antimicrobial activity

All the newly synthesised compounds were screened for their antimicrobial activity in vitro at doses of 100 μg in 0.1 mL of DMF against the bacteria Escherichia coli and Bacillus cirroflagellosus using Norfloxacin as standard and for their antifungal activity in vitro against the fungi Aspergillus niger and Penicillium using Griseofulvin as standard. DMF was used as solvent control, nutrient agar was used as culture medium and the method employed was cup plate13 method. The zone of inhibition was measured in mm and was compared with standard drugs. Compounds 3a, 3c, 5c and 5d displayed higher activity against E. coli and only compound 3c displayed higher activity towards B. cirroflagellosus. Compounds 5a, 5b showed moderate activity towards E. coli while compounds 3a, 3d, 5a and 5b displayed

Note
moderate activity towards *B. cirroflagellosus*. Rest of the compounds showed weak activity towards both the bacteria. Compounds 3c and 5c were highly active towards *Penicillium* while compound 5a was highly active against *A. niger*. Compounds 3a, 5a, and 5b were moderately active towards *Penicillium* whereas compounds 3c, 5b and 5d were moderately active towards *A. niger*. All other compounds displayed weak activity towards both fungi.

**Experimental Section**

Melting points were determined in open capillary tubes and are uncorrected. IR Spectra (cm⁻¹) were recorded on a Perkin Elmer 881 spectrophotometer;
Evaporation of ethyl acetate gave the solid that was recrystallised from ethanol (Ev). The separated solid was filtered, washed with water and dried over anhydrous Na₂SO₄. Water was added and extraction with ethyl acetate was followed by washing with 5% HCl, water and dried over anhydrous Na₂SO₄. The separated solid was filtered, washed with water and recrystallised from ethanol (Ev).

Table I — Characterisation data of the new compounds synthesised

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Nature</th>
<th>Mol. formula</th>
<th>Found (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>-C₆H₅</td>
<td>271-72</td>
<td>84</td>
<td>Colourless tiny needles</td>
<td>C₁₉H₁₈N₂O₃</td>
<td>70.61 (70.79, 5.78, 5.63, 8.54, 8.69)</td>
</tr>
<tr>
<td>3b</td>
<td>-C₆H₅-CH₃(o)</td>
<td>285-86</td>
<td>78</td>
<td>Colourless granules</td>
<td>C₂₀H₂₀N₂O₃</td>
<td>71.56 (71.40, 6.12, 5.99, 8.17, 8.33)</td>
</tr>
<tr>
<td>3c</td>
<td>-C₆H₅-CH₃(p)</td>
<td>266-67</td>
<td>82</td>
<td>Colourless silky needles</td>
<td>C₂₀H₂₀N₂O₃</td>
<td>71.56 (71.40, 6.12, 5.99, 8.17, 8.33)</td>
</tr>
<tr>
<td>3d</td>
<td>-C₆H₃Cl(p)</td>
<td>296-97</td>
<td>78</td>
<td>Colourless tiny needles</td>
<td>C₁₉H₁₈N₂O₅Cl</td>
<td>64.07 (63.95, 4.71, 4.80, 7.78, 8.85)</td>
</tr>
<tr>
<td>5a</td>
<td>-C₆H₅</td>
<td>184-85</td>
<td>67</td>
<td>Colourless long needles</td>
<td>C₁₉H₁₈N₂O₂</td>
<td>75.16 (74.98, 5.23, 5.30, 9.12, 9.00)</td>
</tr>
<tr>
<td>5b</td>
<td>-C₆H₃Cl(o)</td>
<td>191-92</td>
<td>71</td>
<td>Brown needles</td>
<td>C₁₉H₁₈N₂O₂</td>
<td>75.39 (74.55, 5.83, 5.70, 8.91, 8.83)</td>
</tr>
<tr>
<td>5c</td>
<td>-C₆H₅Cl(p)</td>
<td>173-74</td>
<td>60</td>
<td>Brown granules</td>
<td>C₁₉H₁₈N₂O₃</td>
<td>75.39 (75.45, 5.83, 5.70, 8.91, 8.83)</td>
</tr>
<tr>
<td>5d</td>
<td>-C₆H₅Cl(p)</td>
<td>186-87</td>
<td>72</td>
<td>Grey powder</td>
<td>C₁₉H₁₈N₂O₃Cl</td>
<td>67.52 (67.35, 4.48, 4.43, 7.78, 7.85)</td>
</tr>
</tbody>
</table>

1H NMR spectra in CDCl₃ or DMSO-d₆ on a Bruker’s 300 MHz NMR spectrophotometer (chemical shifts in δ, ppm); and mass spectra on a Autospec EI mass spectrometer. Elemental analysis was carried out on Heraeus CHN rapid analyser.

1-Substituted-3-acetyl-6-α-oximinoethyl-5-hydroxy-2-methylindoles 3a-d. 3,6-Diacetylindoles 10,11

2a-d (0.002 mole) were stirred with 15 mL of 40% KOH in a little ethanol (5 mL). The solid dissolved and an orange yellow potassium derivative was separated. The reaction mixture was then cooled and stirred while hydroxylamine hydrochloride (0.005 mole) was added over a period of 15 min. When no more heat was evolved, the flask was stoppered and stirred for 4 hr and left to stand overnight. The resulting clear yellow solution was poured onto crushed ice (25g) and acidified with dil. HCl (10%). The separated solid was filtered, washed with water and recrystallised from ethanol (Table I).

Compound 5b: IR(KBr): 1628 cm⁻¹ (C₇-acetyl C=O); 1H NMR (CDCl₃/TMS): δ 1.92 (s, 3H, o-tolyl-CH₃), 2.50 (s, 3H, C₆-acetyl-CH₃), 2.54 (s, 3H, C₂-tolyl), 2.75 (s, 3H, C₆-CH₃), 5.89-7.56 (m, 4H, of o-tolyl ring and C₄-H of indole ring), 8.23 (s, 1H, C₈-H); 13C NMR (CDCl₃/TMS): δ 10.69 (o-tolyl-CH₃-carbon), 14.54 (C₂-CH₃-carbon), 17.54 (C₆-CH₃-carbon), 31.94 (C₇-acetyl-CH₃), 100.21 (C₄), 101.27 (C₈), 114.84 (C₅), 119.43 (C₆), 128.10 (C₃-o-tolyl), 129.42 (C₄-o-tolyl), 130.02 (C[β]), 130.44 (C₇-o-tolyl), 132.44 (C₅-o-tolyl), 135.22 (C[α]), 135.92 (C₂-o-tolyl), 137.46 (C₁-o-tolyl), 149.79 (C₄f), 155.33 (C₃f), 160.33 (C₂) 194.47 (C₇-acetyl-C=O); MS (m/z, relative intensity): 318 (M⁺, 37.9), 303 (100), 260 (6.8), 234 (3.4), 204 (6.9), 91 (8.3).

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Reference

4 Bhatnagar P & Heerding D, PCT Int Appl, WO 9604261; Chem Abstr, 125(3), 1996, 33626m.