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Note

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

Dundappa S Donawade[+], A V Raghu & Guru S Gadaginamath*

Post Graduate Department of Chemistry & CEPS, Karnatak University, Dharwad 580 003, India

[+]Cipla Ltd, Bangalore 560 049, India

E-mail: profgmath@yahoo.co.in

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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 C_6-acetyl function over that of C_3-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

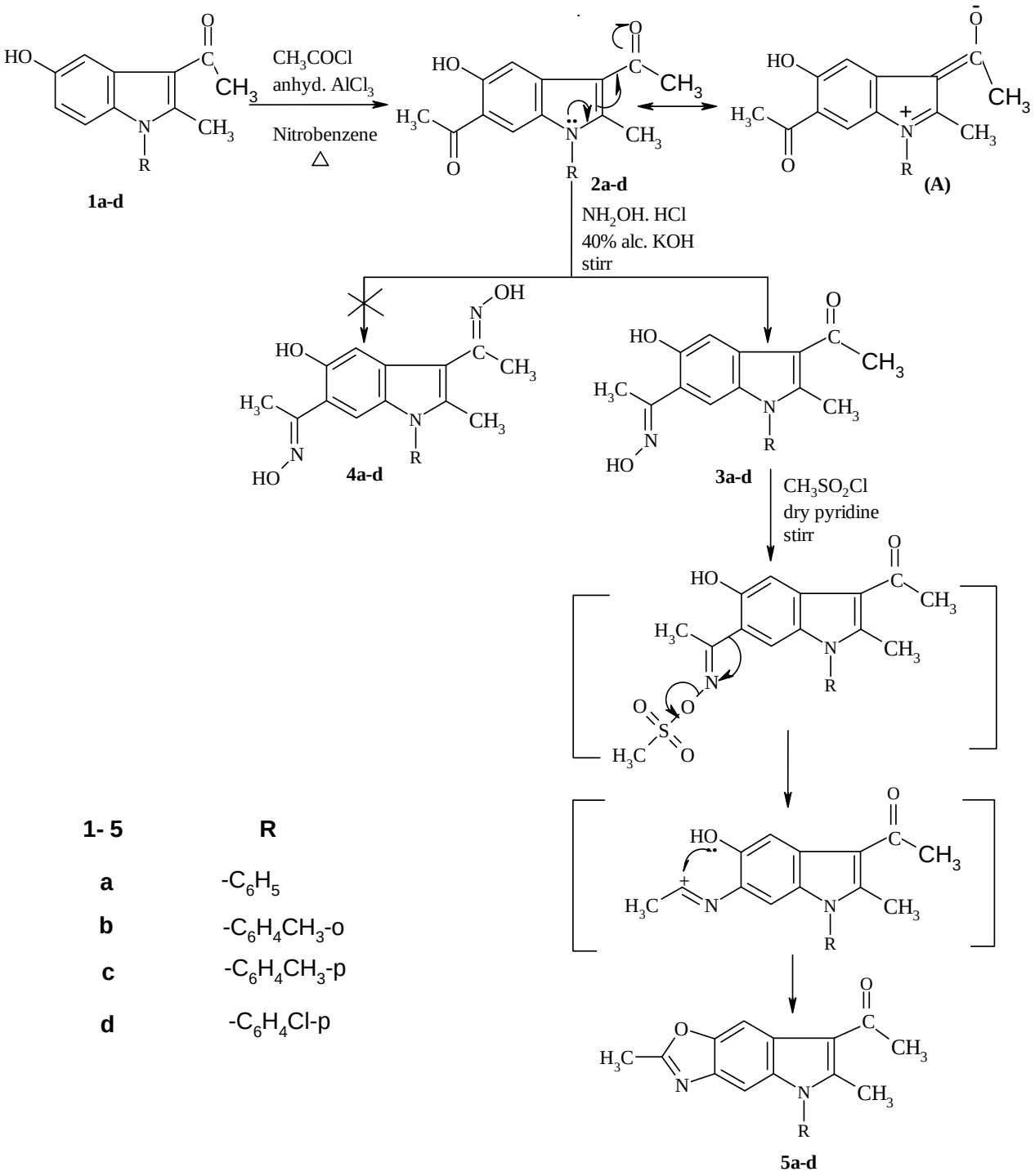
IPC: Int.Cl.[8] C07D

Indole derivatives occupy a prime place in heterocyclic chemistry owing to their valuable properties as therapeutic agents[1], drugs, dyestuffs etc. Oxazoles are reported to possess antiinflammatory[2], antidiabetic[3], hemoregulatory[4], antimicrobial[5], blood platelet aggregation inhibiting property[6] and also the pesticidal properties[7]. 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 reaction[8,9]. The indoles **1a-d** were subjected to regioselective Friedel Crafts acetylation[10,11] using acetyl chloride and $AlCl_3$ in freshly distilled nitrobenzene to produce 3,6-diacetylindoles **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-methylindoles **3a-d** instead of the expected dioximes **4a-d**. This reaction revealed the chemoselectivity of C_6-acetyl over that of C_3-acetyl function towards the nucleophilic attack of hydroxylamine (**Scheme I**). The observed resistance of C_3-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 C_3-acetyl carbonyl as shown in resonating structure **(A)** leading to the reduced double bond character of C_3-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 report[12] on the reaction of 3,6-diacetylindoles towards nucleophnic 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 plate[13] 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



Scheme I

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;

Table I — Characterisation data of the new compounds synthesised

Compd	R	m.p. °C	Yield (%)	Nature	Mol. formula	Found (Calcd)		
						C	H	N
3a	$-C_6H_5$	271-72	84	Colourless tiny needles	$C_{19}H_{18}N_2O_3$	70.61 (70.79	5.78 5.63	8.54 8.69)
3b	$-C_6H_4-CH_3$(*o*)	285-86	78	Colourless granules	$C_{20}H_{20}N_2O_3$	71.56 (71.40	6.12 5.99	8.17 8.33)
3c	$-C_6H_4-CH_3$(*p*)	266-67	82	Colourless silky needles	$C_{20}H_{20}N_2O_3$	71.56 (71.40	6.12 5.99	8.17 8.33)
3d	$-C_6H_4-Cl$(*p*)	296-97	78	Colourless tiny needles	$C_{19}H_{17}N_2O_3Cl$	64.07 (63.95	4.71 4.80	7.78 7.85)
5a	$-C_6H_5$	184-85	67	Colourless long needles	$C_{19}H_{16}N_2O_2$	75.16 (74.98	5.23 5.30	9.12 9.00)
5b	$-C_6H_4-CH_3$(*o*)	191-92	71	Brown needles	$C_{20}H_{18}N_2O_2$	75.39 (75.45	5.83 5.70	8.91 8.83)
5c	$-C_6H_4-CH_3$(*p*)	173-74	60	Brown granules	$C_{20}H_{18}N_2O_2$	75.39 (75.45	5.83 5.70	8.91 8.83)
5d	$-C_6H_4-Cl$(*p*)	186-87	72	Grey powder	$C_{19}H_{15}N_2O_2Cl$	67.52 (67.35	4.48 4.43	8.34 8.27)

^{1}H NMR spectra in $CDCl_3$ or DMSO-d_6 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 repid 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 **3b**: IR(KBr): 1596 (C_3-acetyl C=O, C_6-C=N) and 3229 cm^{-1} (C_5-OH and C_6-oxime OH); ^{1}H NMR ($CDCl_3$+DMSO-d_6 / TMS): δ 1.92 (s, 3H, *o*-tolyl-CH_3), 2.17 (s, 3H, C_3-acetyl-CH_3), 2.45 (s, 3H, C_6-oxime-CH_3), 2.67 (s, 3H, C_2-CH_3), 6.78-7.56 (m, 6H, 4H of *o*-tolyl ring and 2H of indole ring), 11.00 (br, s, 2H, C_5-OH and C_6-oxime OH, disappeared on D_2O exchange).

5-Substituted-7-acetyl-3,6-dimethyloxazolo[4,5-*f*]indoles 5a-d. Compounds **3a-d** (0.001 mole) were dissolved in 4 mL anhydrous pyridine and methanesulfonyl chloride (0.5 mL) was added dropwise with vigorous stirring. The solution originally colourless, became intensely red and was allowed to stay 1 hr at room temperature. Water was added and extraction with ethyl acetate was followed by washing with 5% HCl, water and dried over anhydrous Na_2SO_4. Evaporation of ethyl acetate gave the solid that was recrystallised from ethanol (**Table I**).

Compound **5b**: IR(KBr): 1628 cm^{-1} (C_7-acetyl C=O); ^{1}H NMR ($CDCI_3$/TMS): δ 1.92 (s, 3H, *o*-tolyl-CH_3), 2.50 (s, 3H, C_7-acetyl-CH_3), 2.54 (s, 3H, C_2-CH_3), 2.75 (s, 3H, C_6-CH_3), 6.89-7.56 (m, 4H, of *o*-tolyl ring and C_4-H of indole ring), 8.23 (s, 1H, C_8-H); ^{13}C NMR ($CDCl_3$/TMS): δ 10.69 (*o*-tolyl-CH_3-carbon), 14.54 (C_2-CH_3-carbon), 17.54 (C_6-CH_3-carbon), 31.94 (C_7-acetyl-CH_3), 100.21 (C_4), 101.27 (C_8), 114.84 (C_7), 119.43 (C_6), 128.10 (C_3-*o*-tolyl), 129.42 (C_4-*o*-tolyl), 130.02 (C[b]), 130.44 (C_5-*o*-tolyl), 132.44 (C_6-*o*-tolyl), 135.22 (C[a]), 135.92 (C_2-*o*-tolyl), 137.46 (C_1-*o*-tolyl), 149.79 (C_4f), 155.33 (C_5f), 160.33 (C_2) 194.47 (C_7-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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