Synthesis and antimicrobial activity of new 1-n-butyl-3-acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylindole derivatives

G S Gadaginamath*, R R Kavali & S R Pujar
P G Department of Studies in Chemistry, Karnataka University, Dharwad-580 003, India
Received 7 May 1999; accepted (revised) 9 September 1999

5-Hydroxyindole 1a is reacted with bromine in acetic acid to yield 6-bromo-5-hydroxyindole 1b. Compounds 1a-b are condensed with chloroacetonitrile in refluxing acetone in the presence of K$_2$CO$_3$ to obtain 3-acetyl-1-n-butyl-2-methylindol-5-yloxyacetonitriles 2a-b which are then reacted with dicyanodiamide in the presence of KOH in methanol and isopropanol to obtain the required 1-n-butyl-3-acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylindoles 3a-b. All these new compounds have been screened for their antibacterial and antifungal activities.

Symmetrical and unsymmetrical triazines are known for their diverse biological activities such as antimalarial$^{1,2}$, anticonvulsant$^3$ and herbicidal$^4$. They are also used, against rhinoviruses$^{5-8}$, and to protect skin and hair against UV radiation$^9$. In the light of above observations and also in continuation of our interest in indole derivatives$^{10}$, it was thought to be of considerable interest to undertake the synthesis of hitherto unknown indole derivatives carrying the above biodynamic 1,3,5-triazine moiety at position-5 through a methoxy linkage.

The convenient starting material for the synthesis of the title compounds, 5-hydroxyindole 1a was prepared by the Nenitzescu method$^{11}$. 1a was brominated to obtain 3-acetyl-6-bromo-5-hydroxy-1-n-butyl-2-methylindole 1b. Further 1a-b were condensed with chloroacetonitrile in the presence of K$_2$CO$_3$ in refluxing dry acetone to afford 3-acetyl-1-n-butyl-2-methylindol-5-yloxyacetonitriles 2a-b in quantitative yields, which were reacted in turn with dicyanodiamide in the presence of KOH in refluxing methanol and isopropyl alcohol to produce the desired 3-acetyl-1-n-butyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methyl-indoles 3a-b in good yields (Scheme 1). The structures of all these new derivatives were established on the basis of their spectral data and elemental analysis.

Antimicrobial activity

All the compounds were screened, for their antibacterial activity against Escherichia coli and Bacillus cirroflagellosus using norfloxacin as a standard and, for antifungal activity against Aspergillus niger and Candida albicans using griseofulvin as standard. Cup-plate method$^{12,13}$ was employed using nutrient agar as culture medium. Test solution was prepared by dissolving 1 mg of the compound in 1 mL of DMF and 0.1 mL of this solution was used for testing. The zones of inhibition were measured in mm (12-16 mm, 17-21 mm and 21-30 mm for weak, moderate and highly active zones respectively). Norfloxacin showed a zone of inhibition of 28 mm against Escherichia coli and 25 mm against Bacillus cirroflagellosus. Griseofulvin exhibited a zone of inhibition of 25 mm against the fungi Aspergillus niger and Candida albicans.

The preliminary screening results revealed that all the compounds have shown weak activity against the bacteria Escherichia coli and Bacillus cirroflagellosus except compound 1b containing bromine which exhibited moderate activity (17-21 mm zone) against the fungi Aspergillus niger and Candida albicans, and 3b which exhibited moderate activity against Candida albicans.

Experimental Section

Melting points are uncorrected. IR spectra ($\nu_{max}$ in cm$^{-1}$) were recorded on a Nicolet Impact 410 FT-IR spectrometer, $^1$H NMR spectra on a Bruker AMX-400, 400 MHz spectrometer using TMS as internal standard and mass spectra on FR VER 1 ON UIC 002002 instrument. Elemental analyses were carried out on a Heraus CHN rapid analyser, and are within satisfactory limits.

3-Acetyl-6-bromo-1-n-butyl-5-hydroxy-2-methylindole 1b. To well stirred solution of 3-acetyl-5-hydroxyindole derivative 1a (0.2 mole) in glacial acetic acid (400 mL) was added dropwise bromine (33 g, 0.2 mole) over a period of 20 min. The reaction mixture was stirred further at room temperature for 2 hr. and then poured into ice cold water (1 L). The separated solid was filtered, washed with water, dried and crystallised from dioxane as colourless needles,
yield 65 %, m.p. 219-20 °C; IR (KBr) : 3135 (OH), 1602 (C=O) and 551 (C-Br). Anal. Found : C, 55.75; H, 5.72; N, 4.18; Calc. for C_{11}H_{10}NO_{2}Br : C, 55.57; H, 5.59; N, 4.32 %.

3-Acetyl-1-n-butyl-2-methylindol-5-yloxyacetonitrile 2a. To 1a (0.005 mole), anhyd. K_{2}CO_{3} (3 g, 0.022 mole) and KI (0.1 g, 0.0006 mole) in dry acetone (100 mL) was added chloroacetonitrile (0.0055 mole). The reaction mixture was refluxed for 50 hr. and filtered hot. The solvent was removed under reduced pressure and the residue was crystallised from ethanol as colourless needles, yield 74 %, m.p. 123-24 °C; IR (KBr) : 1637 (C=O); 'H NMR (CDCl_{3}) : 8 0.91 (t, J = 7 Hz, 3H, N-CH_{3}), 1.35-1.75 (m, 4H, N-CH_{2}-CH_{2}CH_{3}), 2.50 (s, 3H, COCH_{3}), 2.70 (s, 3H, CH_{3}), 4.05 (t, J = 7 Hz, 2H, N-CH_{2}-CH_{2}-CH_{3}), 4.90 (s, 2H, -CH_{2}-), 6.91 (dd, J = 8.5 Hz & 2.5 Hz, 1H, C_{6}-H), 7.23 (d, J = 8.5 Hz, 1H, C_{7}-H) and 7.65 (d, J = 2.5 Hz, 1H, C_{4}-H).

Anal. Found : C, 71.64; H, 7.22; N, 9.67. Calc. for C_{17}H_{19}N_{2}O_{2} : C, 71.81; H, 7.09; N, 9.85 %.

Compound 2b was prepared similarly and crystallised from ethanol as colourless needles, yield 79%, m.p. 150-51°C. Anal. Found : C, 56.32; H, 5.43; N, 7.90; Calc. for C_{17}H_{19}N_{2}O_{2}Br : C, 56.21; H, 5.27; N, 7.71 %.

3-Acetyl-1-n-butyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylindoles 3a. A mixture of 2a (0.001 mole), dicyanodiamide (0.00125 mole) and KOH (0.022 mole) in methanol (6 mL) and isopropanol (50 mL) was refluxed for 8 hr. The reaction mixture was cooled and filtered. The separated solid was washed with water and crystallised from ethanol-dioxane as colourless needles, yield 49 %, m.p. 242-43°C; IR (KBr) : 3397, 3200 (-NH_{2}) and 1634 (C=O); 'H NMR (DMSO-d_{6}) : 6 0.86 (t, J = 7 Hz, 3H, N-CH_{2}-CH_{2}-CH_{2}-CH_{3}), 1.23-1.53 (m, 4H, N-CH_{2}-CH_{2}-CH_{2}-CH_{3}), 2.53 (s, 3H, -
COCH₃), 2.70 (s, 3H, -CH₃), 4.06 (t, J = 7 Hz, 2H, N-CH₂-CH₂-CH₂-NH₂), 4.69 (s, 2H, -CH₂-), 5.77 (br, 4H, -NH₂, disappeared on D₂O exchange), 6.85 (dd, J = 8.5 Hz & 2.5 Hz, 1H, C₆-H) and 7.46 (d, J = 2.5 Hz, 1H, C₄-H), MS (m/z, relative intensity); M⁺ 368 (90), 353 (35), 325 (20), 283 (7), 244 (100), 216 (18), 202 (30), 171 (15), 159 (18), 125 (10) and 43 (35). Anal. Found : C, 61.80; H, 6.72; N, 22.71; Calc. for C₁₉H₂₄N₆O₂ : C, 61.95; H, 6.52; N, 22.82 %.

Compound 3b was prepared similarly and crystallised from ethanol-dioxane as colourless shiny flakes, yield 79 %, m.p. 150-51°C. Anal. Found: C, 50.83; H, 5.40; N, 18.68. Calc. for C₁₉H₂₃N₆O₂Br : C, 51.00; H, 5.14; N, 18.79 %.

Acknowledgement

One of the authors (R R K) wishes to thank the Karnatak University, Dharwad, for the award of a research studentship and also CSIR, New Delhi, for SRF. The authors also thank, RSIC, IISc Bangalore and Dr. L R Subramanian, University of Tubingen, Germany for providing spectral data.

References
