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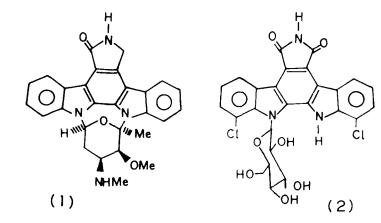
SYNTHESIS OF 2,2'-BIINDOLYLS; POTENTIAL INTERMEDIATES

FOR INDOLOCARBAZOLE ALKALOIDS

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Abstract: The synthesis of 2,2'-biindolyls oxygenated in the benzenoid ring is reported. Wittig-Horner reaction of of 1-benzenesulfony1-2the phosphonate esters bromomethy1-3-substituted indoles with odeoxygenation with nitrobenzaldehydes followed by triethyl phosphite gave 2,2'-biindolyls.

The indolocarbazole alkaloids are structurally rare and biologically interesting¹. The important members of this family are staurosporin (1),



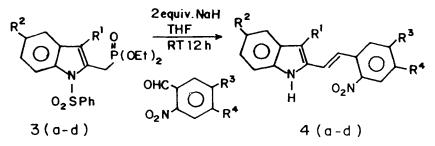
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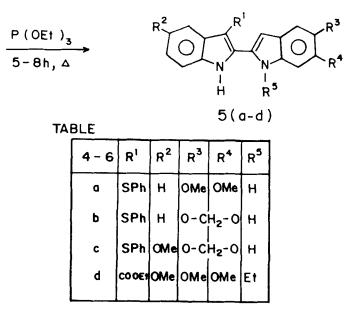
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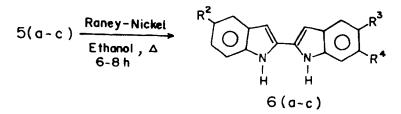
rebaccamycin (2), arcyriaflavins etc. These are known to show antifungal, antimicrobial, antibiotic and antitumor activities².

envisaged that a 2,2'-biindolyl with vacant We 3-positions would be an ideal intermediate for the synthesis of analogs of these alkaloids. A survey of the literature showed that there is no general synthesis for such class of compounds with substituents in either or the indole portions. Here we report a both facile synthesis of the title compounds. Wittig-Horner reaction of the indole phosphonate esters 3 with substituted onitrobenzaldehydes in NaH/THF gave the N-free 2-vinyl 170° with indoles 4. Compounds 4 were then heated at excess triethyl phosphite for 5-8 h to give biindolyls It is interesting to note that 4d on deoxygenation 5. with triethyl phosphite gave the N-ethyl derivative exclusively as shown by ¹H-NMR and mass spectra. Obtention of N-alkylindoles from the corresponding trialkyl phosphites and o-nitrostyrene derivatives has been reported.³





Raney-Nickel treatment of biindolyls 5(a-c) in boiling ethanol gave the title compounds 6.



Experimental

All melting points reported are uncorrected. IR spectra were taken on a Perkin Elmer model 598 spectrophotometer. ¹H-NMR spectra were taken at 400 MHz a Jeol GSX 400 NMR spectrometer or at 300 MHz on on а Gemini - 300 spectrometer or at 90 MHz on a varian EM-

390 NMR spectrometer. ¹³C-NMR spectra were taken at 75 MHz on a Gemini 300 spectrometer.

Preparation of phosphonate esters 3 (a-d)

Compounds 3 (a-d) were prepared according to the published procedure⁴.

Synthesis of compounds 4: General Procedure

Phosphonate ester (5.8 mmol) was added to a suspension of sodium hydride (11.6 mmol) in THF (60 mL) under nitrogen atmosphere followed by the substituted onitrobenzaldehyde (5.8 mmol) and the mixture stirred at room temperature for 12h. The solvent was then removed under vacuum and the residue was treated with ice. The solid was filtered, washed with water, dried on CaCl₂ and crystallised from ethyl acetate (yield: 85-93%).

Compound 4a:

mp: $178 - 82^{\circ}$ C. IR: 3340 cm^{-1} (NH stretching). ¹H-NMR (CDCl₃/TMS) δ 3.9 (S, 3H, OCH₃), 4.0 (S, 3H, OCH₃), 6.85-8.3 (m,13H, aromatic & vinyl protons), 9.1 (S,1H,NH).

Compounds 4b:

mp: 232 - 4° C. IR: 3360 cm⁻¹ (NH stretching). ¹H-NMR (CDCl₃/TMS): δ 5.9 (s, 2H, CH₂), 6.9-8.1 (m, 13H, aromatic & vinyl protons), 9.2 (S, 1H, NH). Compound 4 C:

mp: 220 - 4° C. IR: 3350 cm⁻¹ (NH stretching) ¹H - NMR (CDCl₃/TMS) & 3.9 (S, 3H, OCH₃), 5.9 (S, 2H, CH₂), 6.85 - 8.2 (m, 12H, aromatic and vinyl protons), 9.3 (S, 1H, NH).

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Compound 4 d:
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mp: 206 - 10° C.IR: 3340 (NH stretching) 1670 cm⁻¹, (C=0 stretching). ¹H-NMR (CDCl₃/TMS) δ 1.3 (t, 3H, CH₃), 3.83 - 3.9 (3S, 9H, 3 OCH₃), 4.2 (q, 2H, OCH₂), 6.9 - 8.2 (m, 7H, aromatic & vinyl protons), 9.75 (S,1H, NH).

Synthesis of compounds 5 : General Procedure

2-Vinyl compound 4 (1.5 mmol) was taken in triethyl phosphite (7.5 mmol) and heated at 170⁰ under nitrogen atmosphere for 5-8h. The mixture was then poured over ice and acidified with Con HCl. The precipitated solid was filtered, washed with water, dried and crystallised from ethyl acetate - petrol. (Yield: 90 - 95%).

Compound 5a:

mp: $152-4^{\circ}C.IR$: 3380, 3300 cm⁻¹ (NH stretching).¹H-NMR (CDCl₃/TMS) & 3.91 (S, 3H, OCH₃), 4.15 (S, 3H, OCH₃), 6.85 - 7.9 (m, 12H, aromatics), 9.1 (S, 1H, NH), 10.9 (S, 1H, NH). Compound 5b:

mp: 218 - 20^oC. IR: 3380, 3360 cm⁻¹ (NH stretching).¹H-NMR (CDCl₃/DMSO-d₆/TMS) δ 5.8 (d, 2H, CH₂), 6.3 (S, 1H, indole 3H), 6.8 - 7.3 (m, 12H, aromatics), 10.7 (S, 1H, NH), 11.05 (S, 1H, NH).

Compound 5c:

mp: 202 - 4° C. IR: 3380, 3310cm⁻¹ (NH stretching). ¹H-NMR (CDCl₃/DMSO - d₆/TMS) & 3.9 (S, 3H, OCH₃), 5.9 (d, 2H, CH₂), 6.3 (S, 1H, Indole 3H), 6.8-7.5 (m, 11H, aromatics), 10.1 (S, 1H, NH), 10.9 (S, 1H, NH).

Compound 5d:

mp: 220 - 4° C. IR: 3280 (NH stretching), 1670 cm⁻¹ (C=0 stretching). ¹H-NMR (CDCl₃/TMS) & 1.4 (t, 3H, CH₃), 1.55 (t, 3H, CH₃), 4.4 (m, 4H, 2CH₂), 6.7 (S, 1H, Indole 3H), 6.95 - 7.7 (m, 5H, aromatics), 11.2 (S, 1H, NH). MS: m/e 422 (M⁺ base peak).

Synthesis of Compounds 6: General Procedure

Phenylthiobiindolyls 5 a-c (5.4 mmol) were mixed with Raney-Nickel (5g) in absolute ethanol. The mixture was refluxed for 6 - 8 h. Raney - Nickel was filtered and washed with hot ethanol. The ethanol was removed under vacuum to give 6. Recrystallisation from acetone gave biindolyls as crystalline solid in 49-52% yield.

Compound 6a:

mp: $274 - 6^{\circ}$ C. IR: 3390, 3370 cm⁻¹ (NH stretching). ¹H-NMR (CDCl₃/DMSO - d₆/TMS) & 3.9 (2S, 6H, 2 OCH₃), 6.75 -7.4 (m, 8H, aromatics), 10.6 (S, 1H, NH), 10.75 (S, 1H, NH). ¹³C - NMR (CDCl₃/DMSO - d₆/TMS) & 56.07 (OCH₃), 56.13 (OCH₃), 94.45, 97.75, 98.8, 101.8, 110.7, 119.5,119.76, 121.3, 121.6, 128.9, 130.0, 131.25, 131.9, 136.6, 144.9, 146.82 (aromatics).

MS: m/e 292 (M^+ base peak).

Compound 6b:

mp: 298 - 300°C. IR: 3420 cm^{-1} (NH stretching). ¹H-NMR (CDCl₃/DMSO - d₆/TMS) & 5.95 (S, 2H, CH2), 6.8 - 7.6 (m, 8H, aromatics), 10.65 (S, 2H, 2NH). ¹³C - NMR (CDCl₃/DMSO - d₆/TMS) & 77.71 (CH₂), 91.8, 97.7, 98.4, 99.2, 100.2, 110.7, 119.5, 119.8, 121.3, 122.6, 128.8, 130.14, 131.7, 136.6, 142.7, 144.6 (aromatics). MS: m/e 276 (M⁺)

Compound 6c:

mp: 290 - 2^oC. IR: 3430cm⁻¹ (NH stretching). ¹H-NMR (CDCl₃/ DMSO - d_6 /TMS) & 3.9 (S, 3H, OCH₃), 5.9 (S, 2H, CH₂), 6.8 - 7.5 (m, 7H, aromatics), 10.7 (S, 2H, 2NH).

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