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# SYNTHESIS OF 2,2'-BIINDOLYLS; POTENTIAL INTERMEDIATES FOR INDOLOCARBAZOLE ALKALOIDS

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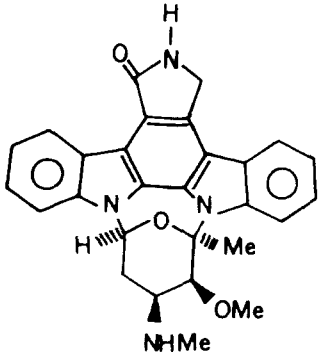
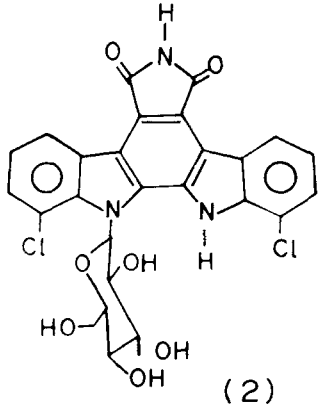
**Abstract:** The synthesis of 2,2'-biindolyls oxygenated in the benzenoid ring is reported. Wittig-Horner reaction of the phosphonate esters of 1-benzenesulfonyl-2-bromomethyl-3-substituted indoles with o-nitrobenzaldehydes followed by deoxygenation with triethyl phosphite gave 2,2'-biindolyls.

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



(1)



(2)

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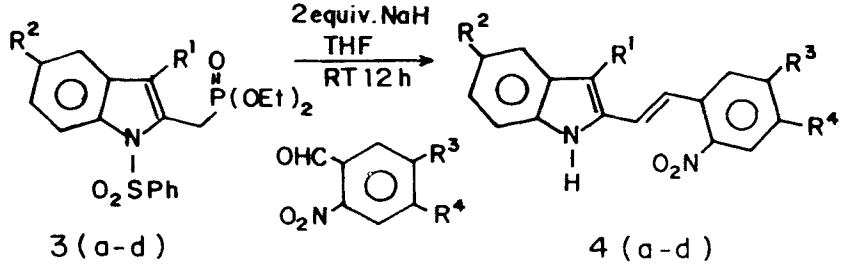
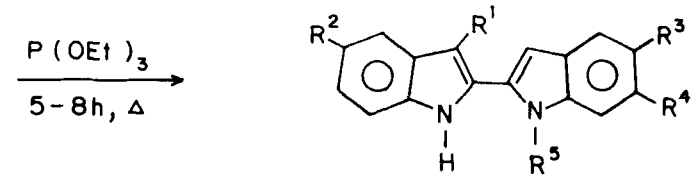
rebaccamycin (2), arcyriaflavins etc. These are known to show antifungal, antimicrobial, antibiotic and antitumor activities[2].

We envisaged that a 2,2'-biindolyl with vacant 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 both the indole portions. Here we report a facile synthesis of the title compounds. Wittig-Horner reaction of the indole phosphonate esters 3 with substituted o-nitrobenzaldehydes in NaH/THF gave the N-free 2-vinyl indoles 4. Compounds 4 were then heated at 170° with excess triethyl phosphite for 5-8 h to give biindolyls 5. It is interesting to note that 4d on deoxygenation with triethyl phosphite gave the N-ethyl derivative exclusively as shown by $^1$H-NMR and mass spectra. Obtention of N-alkylindoles from the corresponding trialkyl phosphites and o-nitrostyrene derivatives has been reported.[3]




3(a-d) 4(a-d)

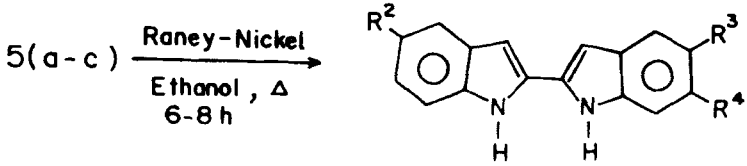



5(a-d)

TABLE

| 4-6 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| a | SPh | H | OMe | OMe | H |
| b | SPh | H | O-$CH_2$-O | | H |
| c | SPh | OMe | O-$CH_2$-O | | H |
| d | COOEt | OMe | OMe | OMe | Et |

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




6(a-c)

**Experimental**

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

390 NMR spectrometer. $^{13}C$-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 procedure[4].

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 o-nitrobenzaldehyde (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 $CaCl_2$ and crystallised from ethyl acetate (yield: 85-93%).

Compound 4a:

mp: 178 - 82°C. IR: 3340 $cm^{-1}$ (NH stretching). $^1H$-NMR ($CDCl_3$/TMS) $\delta$ 3.9 (S, 3H, $OCH_3$), 4.0 (s, 3H, $OCH_3$), 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 ($CDCl_3$/TMS): $\delta$ 5.9 (s, 2H, $CH_2$), 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 ($CDCl_3$/TMS) δ 3.9 (S, 3H, $OCH_3$), 5.9 (S, 2H, $CH_2$), 6.85 - 8.2 (m, 12H, aromatic and vinyl protons), 9.3 (S, 1H, NH).

Compound 4 d:

mp: 206 - 10°C.IR: 3340 (NH stretching) 1670$cm^{-1}$, (C=O stretching). $^1H$-NMR ($CDCl_3$/TMS) δ 1.3 (t, 3H, $CH_3$), 3.83 - 3.9 (3S, 9H, 3 $OCH_3$), 4.2 (q, 2H, $OCH_2$), 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 170° 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°C.IR: 3380, 3300 $cm^{-1}$ (NH stretching).$^1H$-NMR ($CDCl_3$/TMS) δ 3.91 (S, 3H, $OCH_3$), 4.15 (S, 3H, $OCH_3$), 6.85 - 7.9 (m, 12H, aromatics), 9.1 (S, 1H, NH), 10.9 (S, 1H, NH).

Compound 5b:

mp: 218 - 20°C. IR: 3380, 3360 $cm^{-1}$ (NH stretching). $^1H$-NMR ($CDCl_3$/DMSO-$d_6$/TMS) $\delta$ 5.8 (d, 2H, $CH_2$), 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, 3310$cm^{-1}$ (NH stretching). $^1H$-NMR ($CDCl_3$/DMSO - $d_6$/TMS) $\delta$ 3.9 (S, 3H, $OCH_3$), 5.9 (d, 2H, $CH_2$), 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=O stretching). $^1H$-NMR ($CDCl_3$/TMS) $\delta$ 1.4 (t, 3H, $CH_3$), 1.55 (t, 3H, $CH_3$), 4.4 (m, 4H, $2CH_2$), 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°C. IR: 3390, 3370cm$^{-1}$ (NH stretching). $^{1}$H-NMR ($CDCl_3$/DMSO - $d_6$/TMS) $\delta$ 3.9 (2S, 6H, 2 $OCH_3$), 6.75 - 7.4 (m, 8H, aromatics), 10.6 (S, 1H, NH), 10.75 (S, 1H, NH). $^{13}$C - NMR ($CDCl_3$/DMSO - $d_6$/ TMS) $\delta$ 56.07 ($OCH_3$), 56.13 ($OCH_3$), 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: 3420cm$^{-1}$ (NH stretching). $^{1}$H-NMR ($CDCl_3$/DMSO - $d_6$/TMS) $\delta$ 5.95 (S, 2H, CH2), 6.8 - 7.6 (m, 8H, aromatics), 10.65 (S, 2H, 2NH). $^{13}$C - NMR ($CDCl_3$/DMSO - $d_6$/ TMS) $\delta$ 77.71 ($CH_2$), 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°C. IR: 3430cm$^{-1}$ (NH stretching). $^{1}$H-NMR ($CDCl_3$/ DMSO - $d_6$/TMS) $\delta$ 3.9 (S, 3H, $OCH_3$), 5.9 (S, 2H, $CH_2$), 6.8 - 7.5 (m, 7H, aromatics), 10.7 (S, 2H, 2NH).

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