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Synthesis of Quinolono[4,3-b] and [3,4-b]Carbazoles Potential DNA Binders

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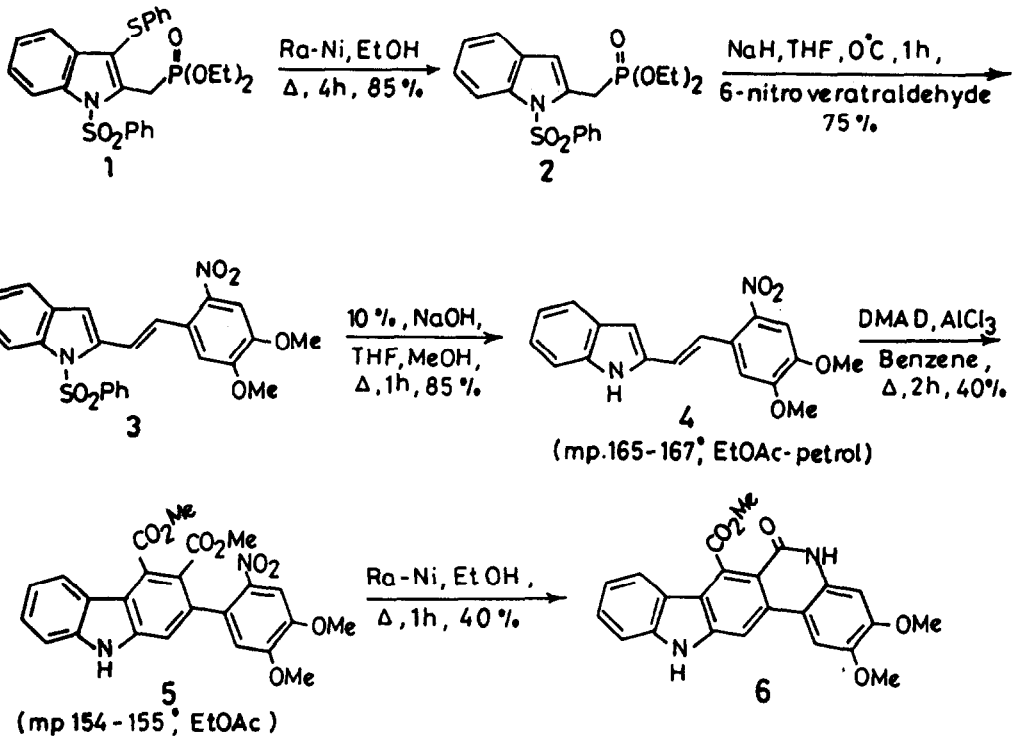
Abstract : 2-and 3-β-[arylvinyl]indoles, obtained by Wittig-Horner reaction of the corresponding N-benzenesulfonylbromomethylindoles with o-nitrobenzaldehydes, gave 2- and 3-arylcarbazoles respectively upon Diels-Alder reaction with DMAD. On reductive cyclisation, these carbazoles gave the title compounds.

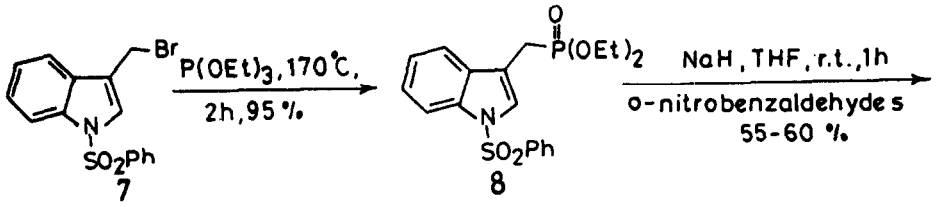
The molecular basis of the biological activity of many medicinally important compounds has been the binding or more specifically intercalation of the molecules with DNA of the host cell. All these molecules are planar with 3 or 4 rings fused in a linear manner carrying substituents like OH, OMe or $(CH_2)_nNR_2$ at judicious positions. Examples[1,2] of this class range from the classical antibacterial proflavine, antimalarial chloroquine upto anticancer antibiotic daunomycin etc. The other well known DNA intercalators[1,3] are hycanthone - an antischistosomaiasis drug, ethidium bromide - a trypanocidal and antibacterial drug, actinomycin-an antitumour antibiotic. Recently some synthetic indoloquinoxolines[4] (antiviral) and 2-amino-3-nitro-α-carbolines[5] have been shown to be DNA binders. Intercalation with DNA has been implicated[6] as the basis for antitumour activity of ellipticine and 9-methoxyellipticine also.

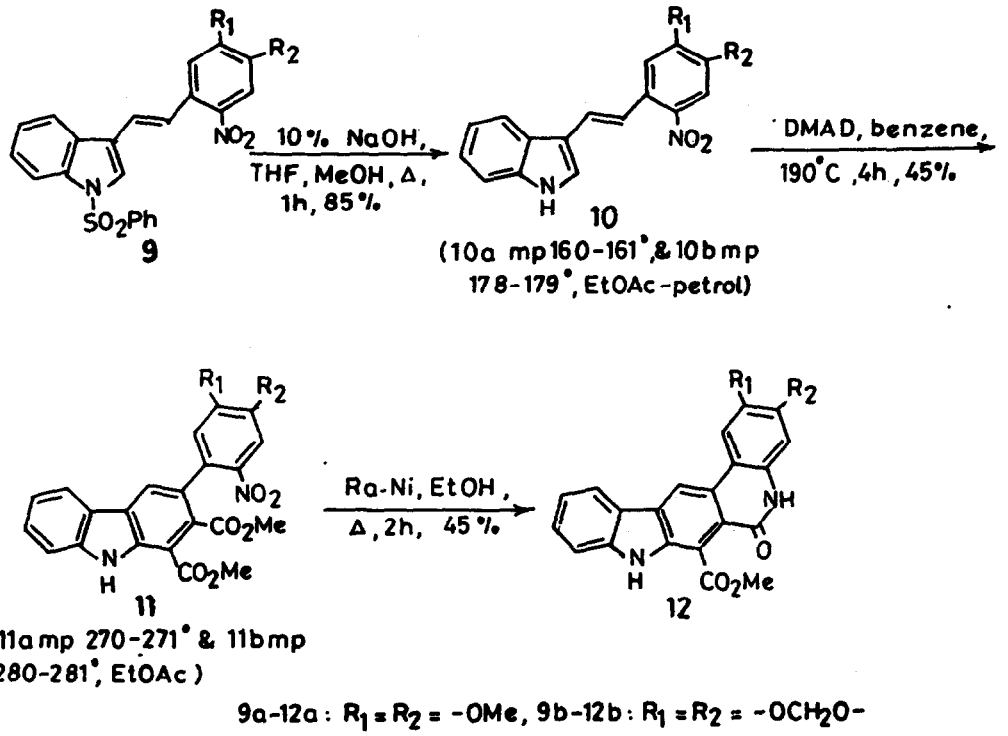
In continuation of our interest[7] with 2-and 3-vinylindoles and also prompted by recent reports[8], we report here the synthesis of quinolonocarbazoles which have a benzene ring fused to the D-ring of pyridocarbazole system. The synthesis of such ring systems has not been reported so far, but unsuccessful attempts have been made to synthesize benzoellipticine in which the benzene ring was fused to A-ring[9]. The thiophenyl group in **1**[10] was selectively deblocked by Ra-Ni in boiling ethanol and the resulting N-protected phosphonate ester **2** (mp 84°, benzene-petrol) upon Wittig-Horner reaction with 6-nitroveratraldehyde at 0°C gave **3** (mp 200°, EtOAc). The latter was desulfonylated to give **4** which on Diels-Alder reaction with DMAD, followed by Ra-Ni treatment in ethanol gave **6** (mp 174°, EtOH).



Scheme 1

Arbuzov reaction of bromo compound 7[11] with triethyl phosphite (at 170°C for 2h) gave 8 (mp 120°, benzene-petrol). Wittig-Horner reaction of 8 with o-nitrobenzaldehydes gave the vinylindoles 9. (9a mp 244-246° and 9b mp 240-242°, EtOAc).





Scheme 2

The latter were converted into **12** (**12a** and **12b** mp > 320°, ethanol) by a similar sequence of reactions as in the previous case. All compounds gave satisfactory spectral data[12]. Further work is in progress to elaborate **6** and **12**, and to synthesize pyrido[4,3-b]carbazoles from **2** using the same strategy.

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12. ^{1}H-nmr and ir data for selected compounds:
6 : ir(KBr) (cm^{-1}) 3280(broad), 1720, 1650, 1620.
^{1}H-nmr (400 MHz, DMSO-d_6) δ 3.9(3H,s), 4(3H,s), 4.1(3H,s), 7-8.3 (7H,m), 11.2 (1H,s), 11.6(1H,s).
12a : ir(KBr)(cm^{-1}) 3300 (broad), 1720, 1650, 1620.
^{1}H-nmr (90 MHz, DMSO-d_6) δ 3.6 (3H,s), 3.8(6H,s), 6.7-8.9(7H,m), 10.8(1H,s), 11(1H,s).
12b : ir(KBr)(cm^{-1}) 3300, 3200, 1700, 1650, 1620.
^{1}H-nmr (400 MHz, DMSO-d_6) δ 4 (3H,s), 6.1(2H,dd), 6.9-9.4(7H,m), 11.6(2H,s)

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