Tetrahedron Letters,Vol.29,No.49,pp 6505-6508,1988 0040-4039/88 $3.00 +
Printed in Great Britain Pergamon Press plc

AN EFFICIENT SYNTHESIS OF 3-ACYLCARBAZOLES AND OBSERVATIONS ON THE FURTHER ELABORATION OF THESE COMPOUNDS TO 6H-PYRIDOCARBAZOLES

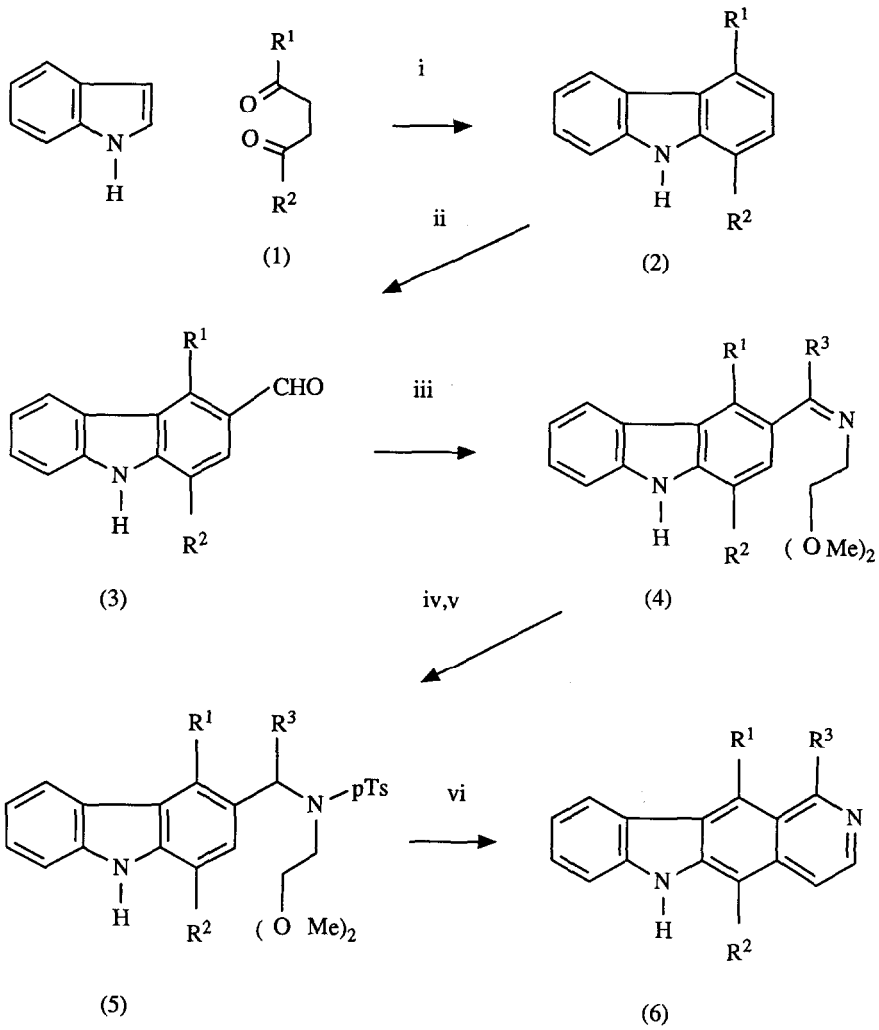
Iain Hogan, Paul Jenkins, and Malcolm Sainsbury*,
School of Chemistry, University of Bath, Claverton Down,
Bath BA2 7AY, UK.

Summary: A new procedure for the synthesis of 3-acylcarbazoles useful for the construction of 6H-pyrido[4,3-b]carbazoles is described starting from readily available gramines, or indoles. This methodology is exemplified by a synthesis of the anticancer alkaloid olivacine. Some discrepancies are noted between our results and those of other authors.

One of the most effective routes to the pyrido[4,3-*b*]carbazole (6) ring system is that devised by Cranwell and Saxton and modified by Birch *et al.*[1] Here a pyridine ring is built on to a preformed carbazole (5) by means of a Pomeranz-Fritsch reaction. The approach depends on the regioselective acylation of carbazoles (2) which are obtained from indoles through condensations with symmetrical 1,4-dicarbonyl compounds (1). The steps involved are summarised in the scheme .

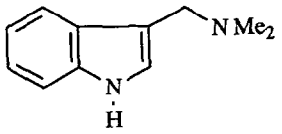
Clearly unsymmetrical 1,4-dicarbonyl compounds may lead to mixed products and our aim was to develop a versatile route to suitably functionalised carbazoles which avoids all structural ambiguities. Thus gramine (7) when reacted with 2-cyano-4-oxopentanonitrile (8, R^1=R^2=CN) in the presence of dimethylacetylene dicarboxylate affords the dinitrile (9, R^1=R^2=CN) (70%), which on treatment with hot 50% acetic acid cyclises in almost quantitative yield to the exocyclic methylene compound (10, R^1=R^2=CN). Similarly the cyanoethoxycarbonyl analogue (10, R^1=CN;R^2=CO_2Et) is obtained in 99% yield from gramine and ethyl 2-cyano-4-oxopentanoate (8, R^1=CN;R^2=CO_2Et), followed by reaction of the intermediate product with acetic acid . The appropriate endo cyclic tautomers (11) are not observed, although in a similar set of reactions involving ethyl 2-acetyl-4-oxopentanoate (8,R^1=COMe;R^2=CO_2Et) and gramine both the exo- and endo-cyclic isomers (10, R^1=COMe; R^2=CO_2Et) and (11, R^1=COMe;R^2=CO_2Et) are formed in approximately equal amounts. It is also noteworthy that the cyclisations to the tricyclic systems proceed with complete regioselectivity in all cases, so that if 3,3-spirocyclic-indolenium intermediates are involved in the reactions only one rearrangement pathway is favoured[2]. Treatment of the mixed isomers (10, R^1=COMe;R^2=CO_2Et) and (11, R^1=COMe;R^2=CO_2Et) with lithium chloride in aqueous DMSO gave both 3-acetyl-1-methylcarbazole (12, R=COMe) (15%), and 3-ethoxycarbonyl-1-methylcarbazole (12,R =CO_2Et)(20%). This result is disappointing since similar treatment of the cyanoester (10, R^1=CO_2Et; R^2=CN) affords only the dihydrocarbazole (10, R^1=H: R^2=CN) in 84% yield. Reaction of the last product with DDQ gives the fully aromatic carbazole (12, R=CN) in 72 % yield. The same compound is formed in 55% yield when the dinitrile (10, R^1=R^2=CN) is absorbed on to silica gel and heated at ~250^0 C
The acetylcarbazole (12, R=COMe), required for the synthesis of the anticancer alkaloid olivacine

(6,R^1=H;R^2=R^3=Me), may be obtained either by reacting the cyanocarbazole (12, R=CN) with methyl lithium (98% yield), or by treating the ester (12,R=CO_2Et) first with dimsyl sodium and treatment of the intermediate ketosulphoxide with aluminium amalgam (72% yield).



Scheme Reagents: i H^+; ii $POCl_3$\$HCONMe_2$; iii $NH_2CH_2CH(OMe)_2$; iv $NaBH_4$; v p-TsCl; vi HCl\Dioxane

Narasimhan and Gokhale[3] state that they were able to convert the acetyl compound (12,R=COMe) into olivacine (6, R^1=H;R^2=R^3=Me), albeit in poor yield, by implementation of the Cranwell-Saxton procedure; however, in our hands we are unable to obtain the imine (4, R^1=H;R^2=R^3=Me) by reacting the same acetyl compound with aminoacetaldehyde dimethylacetal. On the otherhand, the formyl compound (12,R=CHO), obtained from the nitrile (12, R=CN) in 94% yield by reduction with DIBAL reacts smoothly to give the imine (4, R^1=R^3=H;R^2=Me) in 96 % yield. This product may then be converted into the sulphonamide (5, R^1=H;R^2=R^3=Me) by treatment with methyllithium, and reaction with 4-toluenesulphonyl chloride (65% yield, overall).



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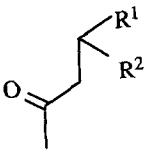

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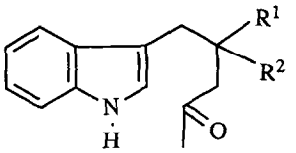

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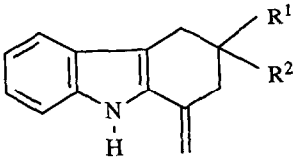

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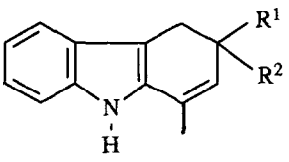

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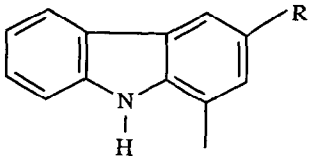

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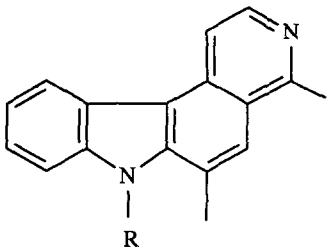
Whereas the cyclisation of the sulphonamide (5,R^1=R^2=Me;R^3=H) by heating it with hydrochloric acid in dioxane can only lead to ellipticine (6, R^1=R^2=Me;R^3=H), a similar cyclisation of the isomer analogue (5, R^1=H;R^2=R^3=Me) may in theory afford both olivacine (6, R^1=H;R^2=R^3=Me) and its angular isomer (13,R=H). However, Narasimhan and Gokhale failed to detect the latter product when cyclising the sulphonamide (5, R^1=H;R^2=R^3=Me). This result contrasts with the report by Murakami and his colleagues[4] that under the same conditions the N-benzyl derivative (15) affords both (13,R=Bn) and 6-benzylolivacine (14) in about equal amounts.



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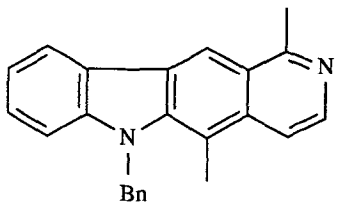

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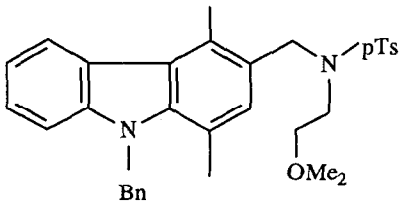

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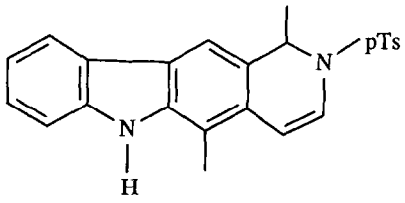

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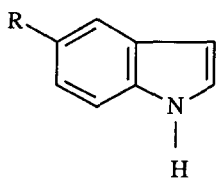
Our findings are that under the conditions described by Narasimhan and Gokhale the sulphonamide (5, R^1=H;R^2=R^3=Me) affords mainly the *dihydrocarbazole* (16), with only a trace of olivacine and none of the angular isomer(13,R=H). Dihydrocarbazoles have been noted previously during the cyclisation of acetals of this type[2], but these products then eliminate 4-toluenesulphinic acid to give the corresponding

pyridocarbazole if the period of the reaction is extended. The dihydrocarbazole (16) is, however, remarkably stable and shows little tendency to aromatise when heated with acid for up to 48h. Interestingly the formation of the dihydrocarbazole is implicit in Murakami *et al.*'s work, although not stated, since in order to obtain the mixed pyridocarbazoles (13,R=H) and olivacine the product from the cyclisation of the aminoacetal (15) was treated first with sodium in liquid ammonia and then heated with palladium-carbon. When our dihydrocarbazole (16) is treated with sodium in liquid ammonia olivacine is produced in 85 % yield.

For pyrido[4,3-*b*]carbazoles bearing an alkyl group at C-11, we have alkylated the indole (17,R=OBn) directly with α,β-unsaturated α-cyanoesters (18) in the presence of acetic anhydride and acetic acid at 90^0 C for 16h[5], and converted the products (19) into the ketones (20) by further alkylation with bromoacetone. In this way a precursor of the antitumour drug 9-hydroxyellipticine (21), the ketone (20,R=Me), has been synthesised from 5-benzyloxyindole and methyl α-cyanoprop-2-enoate in an overall yield of 68%.

Since gramines and indoles are readily available, and the other starting materials are all easily homologated or derivatised the route here described offers a direct and versatile approach to a wide variety of pyrido[4,3-*b*]carbazoles.



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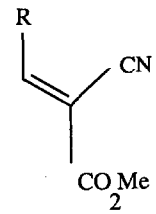

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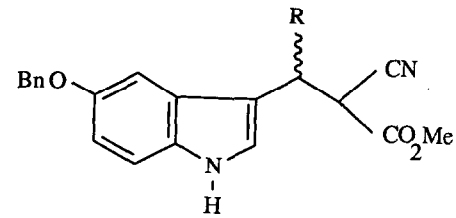

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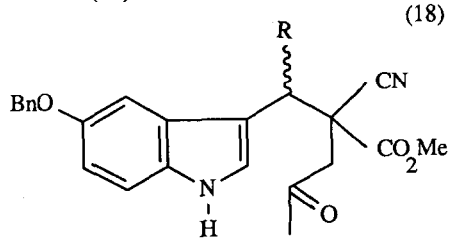

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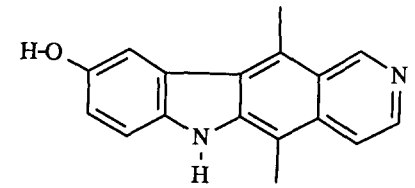

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5. Alkylations catalysed by clays [Z.Iqbal,A.H.Jackson, and K.R.Nagaraja Rao, *Tetrahedron Letters,* **29**, 2577(1988)] were less satisfactory.

Acknowledgements

I.H. was sponsored by a studentship from the Cancer Research Campaign; P.J. holds an SERC CASE award in collaboration with Glaxo Group Research Ltd., We thank Professor Murakami for samples and spectra of olivacine and its angular isomer.

(Received in UK 12 October 1988)