SYNTHESIS OF KEY CARBAZOLES - INTERMEDIATES FOR POLYMETHOXYELLIPTICINES AND OLIVACINES

Robin J. Hall,[a] Anthony H. Jackson,[a]* Ana M.F. Oliveira-Campos,[b] Maria-Joao R.P. Queiroz[b], and Patrick V.R. Shannon[a]*

a School of Chemistry and Applied Chemistry, University of Wales College of Cardiff, Cardiff CF1 3TB, Wales

b Centro de Quimica Pura e Aplicada, Universidade do Minho, Avenida Joao XXI, 4700 Braga, Portugal

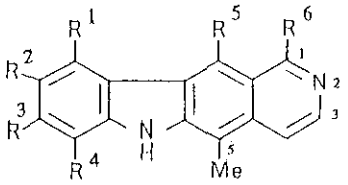
Abstract - The synthesis of three polymethoxycarbazoles, key intermediates for the synthesis of new 6H-pyrido[4,3-b]carbazoles, is described. The required 3-formyl function, or its precursor, is introduced through three different strategies. The validity of these carbazoles for the synthesis of ellipticines and olivacines is demonstrated by the efficient synthesis of the new 7,8,9-trimethoxyellipticine.

In 1981, we reported[1] the synthesis of 8,9,10-trimethoxyellipticine (**1a**) using a method based on a "type D" route,[2] in which the D ring is last to be formed from a suitably substituted carbazole. In our case this was the 3-formyl derivative and isoquinoline annulation was achieved by our modified Pomeranz-Fritsch procedure.[3] Many diverse syntheses of 6H-pyrido[4,3-b]carbazoles, such as ellipticine (**1b**) and olivacine (**1c**) are now known[2,4] including a small number for 9-methoxyellipticine (**1d**) and 9-methoxyolivacine (**1e**)[5] but none of these alternative routes has proved applicable to any di- or trimethoxylated derivatives. Such compounds are, however, now of particular interest because of the known therapeutic use of 2-methyl-9-hydroxyellipticinium acetate (**2**) and the hypothesis that the ring A quinone imine part-structure (**3**) is a significant factor in its anti-tumour action.[6]

We now report that the type D synthesis, based on the Cranwell and Saxton route,[7] is capable of wider development. Thus we have obtained the three 3-substituted carbazoles (**4b**), (**4h**) and (**9**), key intermediates in the synthesis of novel polymethoxy-6H-pyrido[4,3-b]carbazoles (**1f**), (**1g**) and (**1h**). This work significantly extends the small range of polymethoxy substituted ellipticines (and olivacines) accessible to date;[1,8] either 3-aldehydes or 3-nitriles can act as

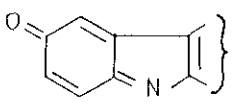
precursors of the pyrido ring. We have converted the carbazolealdehyde (**4b**), via the intermediates shown, into the novel trimethoxyellipticine (**1f**).

5,6,7-Trimethoxyindole[9] condensed[cf.1] with hexane-2,5-dione to give the carbazole (**4a**) mp 177-178°C (52%), Vilsmeier formylation of which gave the 3-formyl-6,7,8-trimethoxycarbazole (**4b**), mp 202-203°C (95%) without the need for chromatography. The aldehyde (**4b**) with aminoacetaldehyde diethyl acetal gave the unstable Schiff's base (**4c**) which was directly hydrogenated to the amine (**4d**) without isolation. This was immediately converted to the stable sulphonamide (**5**), mp 162-165°C [58% from the formylcarbazole (**4b**)]. Treatment of the latter with dilute hydrochloric acid in refluxing dioxan gave, after mild alkaline work-up, the virtually pure 8,9,10-trimethoxyellipticinium toluene-p-sulphinate in 67% yield.

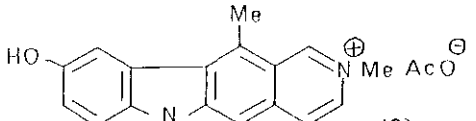


(1)

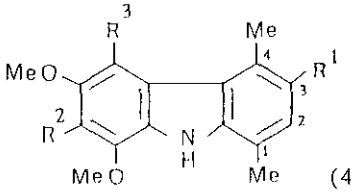
(a) $R^1=R^2=R^3=OMe$; $R^4=R^6=H$, $R^5=Me$
(b) $R^1=R^2=R^3=R^4=R^6=H$; $R^5=Me$
(c) $R^1=R^2=R^3=R^4=R^5=H$, $R^6=Me$
(d) $R^1=R^3=R^4=R^6=H$, $R^2=OMe$, $R^5=Me$
(e) $R^1=R^3=R^4=R^5=H$; $R^2=OMe$; $R^6=Me$
(f) $R^1=R^6=H$; $R^2=R^3=R^4=OMe$; $R^5=Me$
(g) $R^1=R^3=R^6=H$; $R^2=R^4=OMe$; $R^5=Me$
(h) $R^2=R^4=R^5=H$; $R^1=R^3=OMe$; $R^6=Me$



(3)



(2)



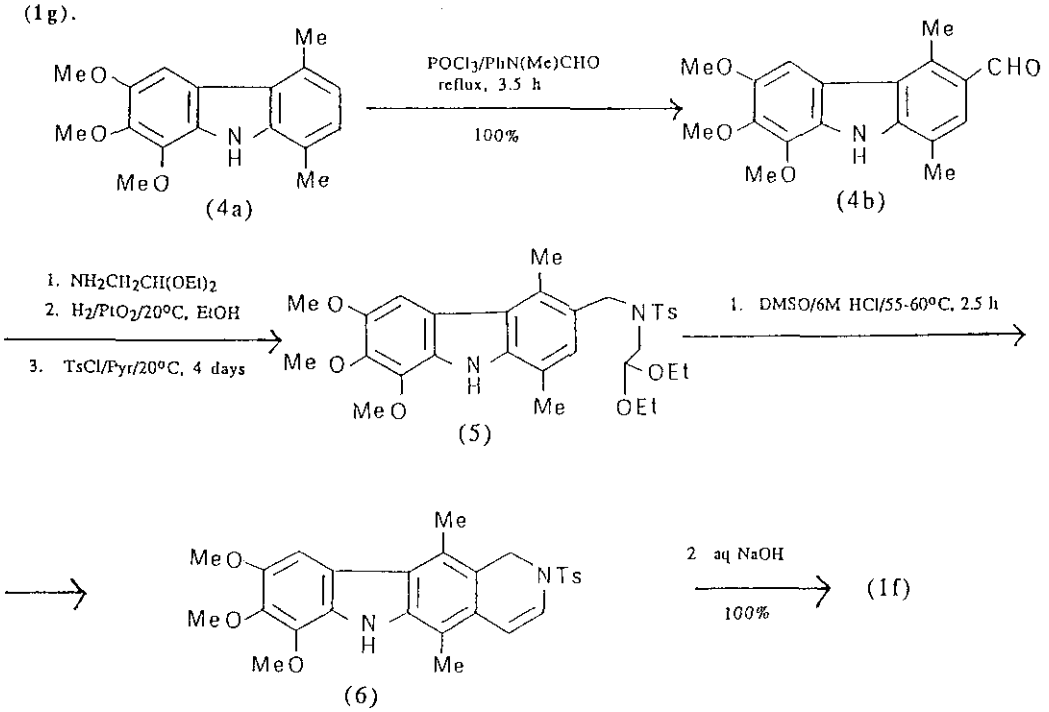
(4)

(a) $R^1=R^3=H$; $R^2=OMe$
(b) $R^1=CHO$; $R^2=OMe$; $R^3=H$
(c) $R^1=CH=NCH_2CH(OEt)_2$; $R^2=OMe$; $R^3=H$
(d) $R^1=CH_2NHCH_2CH(OEt)_2$; $R^2=OMe$; $R^3=H$
(e) $R^1=R^2=R^3=H$
(f) $R^1=R^2=H$; $R^3=CHO$
(g) $R^2=R^3=H$; $R^1=Br$
(h) $R^1=CN$; $R^2=R^3=H$

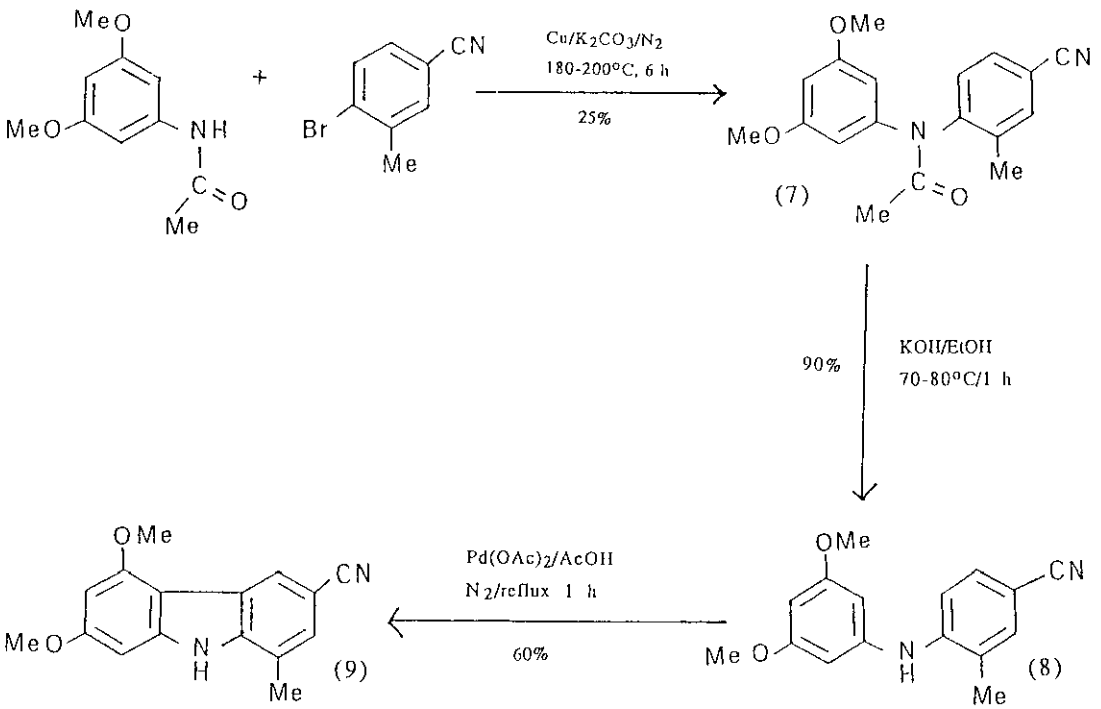
Evidence for the intermediate (**6**) was obtained when the cyclisation of (**5**) was carried out in dimethyl sulphoxide in an nmr tube at temperatures increasing from 20° to 75°C over 4 hours.

The intermediate N-tosyl-1,2-dihydroellipticine (**6**) was formed, (maximally ca. 80% of compounds present) as shown by proton nmr spectroscopy. Alkaline treatment of this solution gave the ellipticine (**1f**) in virtually quantitative yield. An analytical sample was isolated by chromatography as a yellow microcrystalline solid mp 240°C (dec.), $^{m}/_{z}$ 336 (M^{+}). Like its isomer (**1a**), (**1f**) rapidly turned brown in light; both ellipticines showed comparable weak cytotoxic activity; it is noteworthy that isomer (**1a**) had been stored in the dark for almost ten years.

The 6,8-dimethoxycarbazole (**4e**), mp 186-186.5°C (synthesised in 62% yield from 5,7-dimethoxyindole[10] and hexane-2,5-dione) on formylation with N-methylformanilide and phosphoryl chloride, gave mainly the 5-formyl derivative (**4f**), mp 198-200°C. The reactivity of ring A to formylation, as in the case of 1,4-dimethyl-7-methoxycarbazole,[11] precludes subsequent conversion of (**4f**) to the pyridocarbazole (**1g**). Bromination of (**4e**), however, with pyridinium bromide perbromide, reversed the regioselectivity giving the 3-bromocarbazole (**4g**), mp 172-173°C, as the main product. This enabled access[12] to the corresponding nitrile (**4h**) and potentially to further intermediates to 7,9-dimethoxyellipticine (**1g**).



A third novel substitution pattern of the pyridocarbazole system is the 8,10-dimethoxy series but the approach to 1,4-dimethyl-5,7-dimethoxycarbazole from 4,6-dimethoxyindole with hexane-2,5-dione was not successful, only traces of carbazole being formed. Goldberg[13] coupling of 3,5-dimethoxyacetanilide with 4-bromo-3-methylbenzonitrile,[14] however, gave the cyanodimethoxydiphenylamide (7) which was quantitatively hydrolysed to the amine (8). Treatment of this with palladium (II) acetate in refluxing acetic acid afforded the cyanocarbazole (9), a key intermediate in the synthesis of 8,10-dimethoxyolivacine (1h).



ACKNOWLEDGEMENTS

We thank SERC and the Wellcome Research Laboratories, Beckenham, Kent for a CASE award (RJH), to INIC, Portugal for support of M.J.Q., and to Dr. K. Franzmann (Wellcome Laboratories) for discussions.

REFERENCES

1 M. J. E. Hewlins, A. H. Jackson, A. -M. Oliveira-Campos, and P. V. R. Shannon, J. Chem. Soc., Perkin Trans. I, 1981, 2906

2 M. J. E. Hewlins, A. -M. Oliveira-Campos, and P. V. R. Shannon, Synthesis, 1984, 289.

3 a) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, J. Chem. Soc., Perkin Trans. I, 1974, 2185.

b) A. H. Jackson, P. R. Jenkins, and P. V. R. Shannon, J. Chem. Soc., Perkin Trans. I., 1977, 1698.

4 a) M. Sainsbury, Synthesis, 1977, 437.

b) G. W. Gribble and M. G. Saulnier, Heterocycles, 1985, 23, 1277.

5 e.g. a) M. Sainsbury and D. K. Weerasinghe, J. Chem. Soc., Chem. Commun., 1981, 630.

b) M. Sainsbury, D. K. Weerasinghe, and D. Dolman, J. Chem. Soc., Perkin Trans. I, 1982, 587.

c) R. Besselievre and H. -P. Husson, Tetrahedron, 1981, Supp. 1, No. 1, 37, 241.

6 C. Auclair, Arch. Biochem. Biophys., 1987, 259, 1.

7 P. A. Cranwell and J. E. Saxton, J. Chem. Soc., 1962, 3842.

8 R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, and R. W. Kierstead, J. Med. Chem., 1975, 18, 755.

9 R. D. Morin, F. Benington, and L. C. Clark, J. Org. Chem., 1957, 22, 331.

10 P. J. Mulligan and S. LaBerge, J. Med. Chem., 1970, 31, 1248.

11 L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, Aust. J. Chem., 1967, 20, 2715.

12 L. Friedman and H. Shechter, J. Org. Chem., 1961, 26, 2522.

13 I. Goldberg, Ber., 1907, 40, 4541.

14 T. Tanouchi, M. Kawamura, I. Ohyama, I. Kajiwara, Y. Iguchi, T. Okada, T. Miyamoto, K. Taniguchi, M. Hayashi, K. Iizuka, and M. Nakazawa, J. Med. Chem., 1981, 24, 1149.

Received, 19th October, 1989