Synthesis of Pyridazo[4,5-*b*]carbazoles

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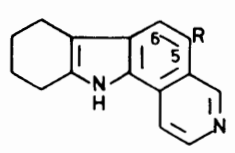
Summary A novel ring-opening–ring-closure sequence is described which allows the synthesis of pyridazo[4,5-*b*]-carbazoles from 5-acylpyrido[4,3-*a*]carbazoles.

THE pyrido[4,3-*b*]carbazole nucleus is present in the alkaloids ellipticine, olivacine, and 9-methoxyellipticine which together with several other derivatives of this nucleus have been shown to have anticancer and anti-leukaemic activity.[1] This biological activity has led to considerable chemical efforts which have resulted in many successful syntheses of the ring system.[2] We report here the first synthesis of aza-analogues.

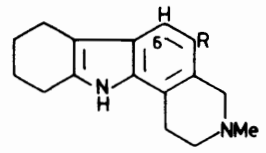
7,8,9,10-Tetrahydro-11*H*-pyrido[4,3-*a*]carbazole (**1a**) was prepared from 8-hydrazinoisoquinoline dihydrochloride in a modification of the published method[3] by treatment with cyclohexanone in refluxing ethanol. Reaction of (**1a**) with $MeCOCl–AlCl_3–PhNO_2$ at 55 °C gave the 5-acetyl-derivative (**1b**) (40%, m.p. 278—80 °C). The position of substitution was confirmed by quaternisation with MeI–MeOH followed by reduction with $NaBH_4$ to give the indole (**2b**). The chemical shift (τ 2·72) of the remaining aromatic proton was very close to that (τ 2·94) for the C-6 proton in (**2a**) obtained by an analogous sequence from (**1a**) and considerably different to that (τ 3·43) for the C-5 proton in (**2a**) [the relative assignments for (**2a**) were made by comparison with spectra[4] of model indoles].

Attempts were made to reduce the ketonic function of (**1b**) under standard[5] Wolff–Kischner conditions. An entirely unexpected product was obtained to which we assign the structure (**3**), 5-ethyl-7,8,9,10-tetrahydro-1-methylpyridazo[4,5-*b*]carbazole [62%, m.p. 313—314 °C; ν_{max}($CHCl_3$) 3460 cm^{-1}; λ_{max} (EtOH) 220, 241sh, 280, 324, and 390 nm (log ϵ 3·94, 3·92, 4·33, 3·24, and 3·29, respectively); τ {$(CD_3)_2SO$} −1·34 (1H, s, NH), 0·42 (1H, s, C-4-H), 2·03 (1H, s, C-11-H), 6·75 (2H, q, *J* 8 Hz, CH_2Me), 7·13 (3H, s, Ar-*Me*), and 8·76 (3H, t, *J* 8 Hz, $MeCH_2$); *m/e* 265 (M^+, 100%), 250 (44), 237 (56), and 222 (44)].† Dehydrogenation of the tetrahydropyridazocarbazole (**3**) with Pd–C in decalin at reflux gave 5-ethyl-1-methylpyridazo[4,5-*b*]carbazole (**4**) [m.p. 328—331 °C (decomp.); ν_{max} ($CHCl_3$) 3460m cm^{-1}; λ_{max} (EtOH) 232, 248sh, 289, 312sh, 327sh and 405 nm (log ϵ 4·16, 4·04, 4·52, 3·74, 3·53, and 3·9, respectively); τ {$(CD_3)_2SO$} −1·84 (1H, s, NH), 0·23 (1H, s, C-4-H), 1·03 (1H, s, C-11-H), 1·51 (1H, d, *J* 8 Hz, C-10-H), 2·4 (2H, m, C-7-H and C-9-H), 2·7 (1H, t, *J* 8 Hz, C-8-H), 6·51 (2H, q, *J* 7 Hz, CH_2Me), 6·98 (3H, s, Ar-*Me*), and 8·68 (3H, t, *J* 7 Hz, $MeCH_2$); *m/e* 261 (M^+, 100%) and 246 (52)]; (**4**) could also be obtained by application of the same $N_2H_4–O(CH_2CH_2OH)_2–KOH$–reflux conditions to the fully aromatic ketone (**5**) which in turn was obtained by dehydrogenation of (**1b**).



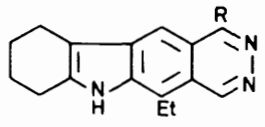
(1)

a; R = H
b; R = COMe
c; R = COEt
d; R = COPh



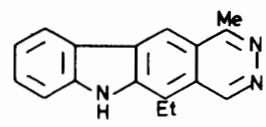
(2)

a; R = H
b; R = CH(OH)Me

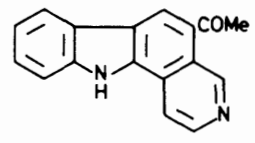


(3)

a; R = Me
b; R = Et
c; R = Ph

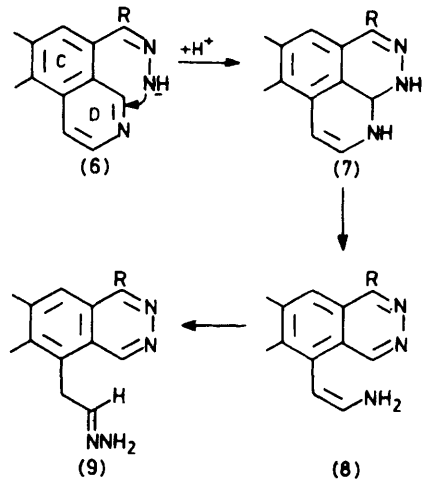


(4)



(5)

† All new compounds gave appropriate elemental analyses.



We have begun the examination of the generality of this novel sequence and have similarly prepared the ethyl ketone (**1c**) (34%, m.p. 250—251 °C) and the phenyl ketone (**1d**) (10%, m.p. 189—193 °C) and transformed them into tetrahydropyridazocarbazoles (**3b**) (51%, m.p. 290—291 °C) and (**3c**) (6%, m.p. 212—215 °C).

We envisage the formation of these pyridazines as involving a sequence, apparently without precedent,[6] involving a series of equilibria in which the key steps would be intramolecular hydrazone anion addition to the pyridine ring [(**6**) → (**7**)] then ring opening and exchange of ammonia for hydrazine in the enamine (**8**) thus produced [(**7**) → (**8**) → (**9**)]. The sequence would be completed by the operation of the irreversible final stages of a Wolff–Kischner reduction on the aldehyde hydrazone (**9**).

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