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A Reinvestigation of Stillwell's Synthesis of 6*H*-Pyrido[4,3-*b*]-carbazoles

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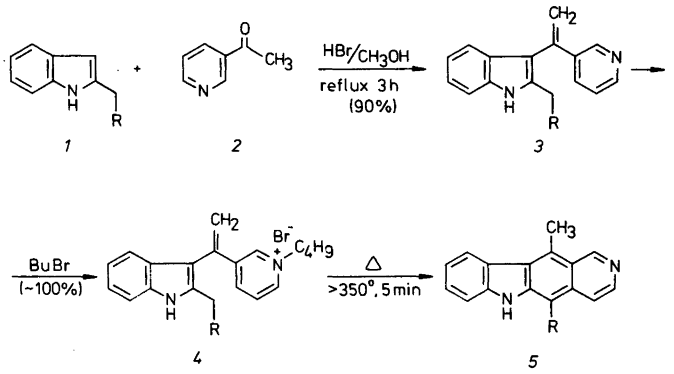
11-Methyl-6*H*-pyrido[4,3-*b*]carbazole (5-norellipticine) has been synthesized using a new method for the construction of the central carbocyclic ring. 5-Norellipticine synthesized by this route is identical with a product earlier reported.

To test the generality of the synthesis of the antitumor indole alkaloid ellipticine[1] (*5a*) outlined in Scheme 1, some analogues (like *5b*) have been synthesized.[2] In this connection it was found that the properties (m.p. 277–280 °C, very stable) of 5-norellipticine (*5b*) prepared according to Scheme 1 differed considerably from those reported by Stillwell[3] (m.p. 208 °C, dec.). We have therefore repeated this interesting approach (Scheme 2), which later has been used by Rastogi *et al.*[4] for the synthesis of 9-fluoroellipticine (using *N*-benzoyl-1,3,4,7,8,8a-octahydro-6[2H]isoquinolone as starting material).

Compound *9* was obtained in good yield by catalytic hydrogenation of *8*. Stillwell obtained compound *9* as a partially undesired product in the reductive methylation of *8* yielding octahydro-2,5,8-trimethyl-6[2*H*]isoquinolone as the main product. Fischer cyclization of *9* yielded *10* which could be efficiently dehydrogenated to *5b* identical in every respect with a sample obtained using the route in Scheme 1.

The possibility of the formation of isomers in the Fischer cyclization step as implied in Scheme 2 was discussed by Stillwell and the formation of the angular isomer was ruled out from spectroscopic evidence. This conclusion seems to be correct as we have now synthesized the dehydrogenated angular isomer (*14*) of *5b* and shown that *14* is not co-formed with *5b* in the dehydrogenation step. The exclusive formation of the linear isomer is in agreement with the report[5] that Fischer indolization of *cis*- as well as *trans*-9-methyl-3-decalone yielded linear products only.

In conclusion it is obvious that both routes (Scheme 1 and 2) yield the same products. The



Scheme 1. *a*, R = CH_3; *b*, R = H.

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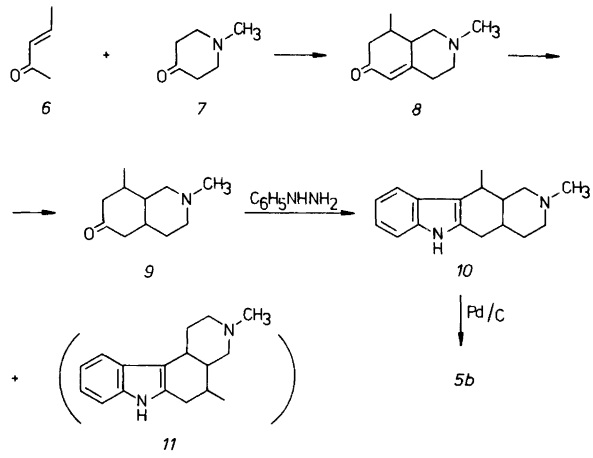


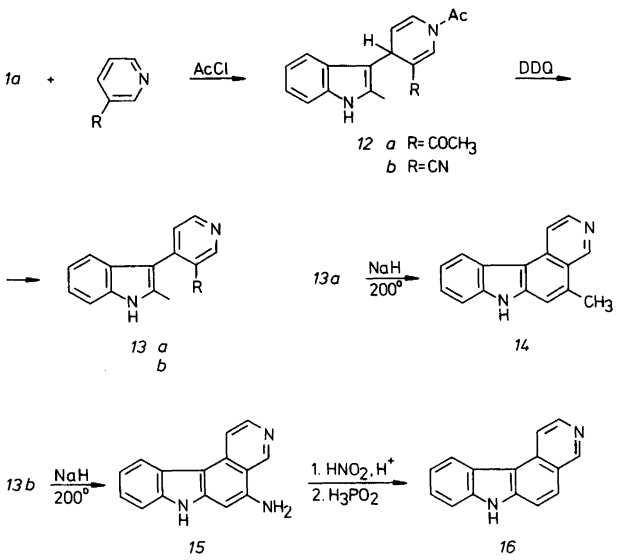
Scheme 2.

difference in properties between ours and Stillwell's product might be attributed to the presence of acids in the dehydrogenation step which might induce transmethylations (indicated by mass spectroscopy in a testing experiment) or simply due to the difficulties involved in the purification of the limited amount of material (9 mg).

In connection with the synthesis of *14* (Scheme 3) using an NaH-induced cyclization in the crucial final step, it was found that the known[6] parent compound of *14*, 7*H*-pyrido[3,4-*c*]-carbazole (*16*) could be similarly and conveniently prepared. These results also further establish the generality of this NaH-induced cyclization method.[2] Details of the DDQ dehydrogenation step have already been published.[7]

EXPERIMENTAL

Melting points were determined on a Leitz melting point apparatus and are uncorrected. IR



Scheme 3.

spectra were recorded using a Perkin-Elmer 257 spectrophotometer. ^{1}H NMR spectra were obtained by using a Varian EM-360 spectrometer (60 MHz) or a Bruker WP 200 spectrometer (200 MHz). Mass spectra were obtained on an LKB 9000 instrument (1P 70 ev).

Hexahydro-2,8-dimethyl-6[2H]-isoquinolone (8). *N*-Methyl-4-piperidone (22.6 g, 0.2 M) was added to a suspension of NaH (4.8 g, 0.2 M) in dry ether under N_2 and stirred for 1 h. The mixture was chilled with ice and 2-penten-4-one (16.8 g, 0.2 M) was added dropwise, whereupon the mixture was kept for 18 h at 0–5 °C. After acidification with 0.2 M HCl, the non-basic material was removed with CH_2Cl_2. The residue of this extract was distilled (132 °C/3 mm Hg) to give the isoquinolone as a light yellow oil (13.5 g) with a green fluorescence. The oil crystallized slowly when stored under N_2 at −15 °C. The crystals were washed with cold light petroleum yielding 10.2 g of *8*. The analytical sample was recrystallized from light petroleum to give pale yellow crystals, m.p. 48–49 °C (lit.[3] 52.5–53 °C). IR (KBr): 2960, 2795, 1665 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.8 (1H,s), 3.4–1.3 (13H,m), 1.05 (3H,d,CH_3). MS: *m/e* (% rel. int.) 180 (100, M^+), 164 (68), 136(22), 44(66).

Octahydro-2,8-dimethyl-6[2H]-isoquinolone (9). Hexahydro-2,8-dimethyl-6[2*H*]-isoquinolone (10.8 g, 0.06 M) was dissolved in ethanol (100 ml) and hydrogenated using 10 % Pd/C catalyst (1 g) for 48 h. Concentration after removal of the catalyst yielded crude material which was purified by sublimation (90 °C/10 mm Hg) to give white crystals (8.2 g) m.p. 53–56 °C (lit.[3] 65–72 °C). IR (KBr): 2780, 1715 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.1 (1H, d), 2.9 (1H, d), 2.50–1.25 (14 H, m), 1.01 (3H, d, CH_3).

2-Methyloctahydro-5-norellipticine (10). Phenylhydrazine (4.32 g, 0.04 M) in methanol (30 ml) was added to octahydro-2,8-dimethyl-6[2*H*]-isoquinolone (*9*) (7.20 g, 0.04 M) in methanol (40 ml) under N_2. 4 drops of conc. H_2SO_4 were then added and the mixture was allowed to stand at room temperature overnight. Added 4 ml of conc. H_2SO_4 in methanol and the mixture was heated (50–55 °C, 10 h). The precipitate (hydrogen sulfate of *10*) formed was collected after final cooling (+5 °C, 10 h). The free base was liberated by dissolution in hot water and adjustment of pH to 10. The base was collected and crystallized in ethanol to give white crystals of 2-methyloctahydro-5-norellipticine.C_2H_5OH (m.p. 98–100 °C, 6.25g). Sublimation (360 °C/1mm Hg) afforded crystals of 2-methyloctahydro-5-norellipticine free of crystal-C_2H_5OH, m.p. 178–181 °C (lit.[3] 165–182 °C). IR (KBr): 3400, 2920, 2900, 2850, 2820, 2795, 2780, 1620, 1460, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.04 (1H,s,NH), 7.61–7.56 (1H, m, ar), 7.25–7.21 (1H, m,ar), 7.14–7.04 (2H,m,ar), 3.29 (1H,d), 2.94 (1H,d), 2.63 (1H,d), 2.45–1.42 (13H,m). MS *m/e* (% rel. int.): 255 (22, M^+1), 254 (11, M^+), 253 (13), 239 (36), 194 (29), 182 (11), 180 (11), 167 (19), 166 (18), 156 (23), 127 (17), 124 (11), 110 (11), 109 (15) 96 (100), 92 (15), 58 (45), 43 (22), 42 (16), 41 (14), 28 (29).

5-Norellipticine (5b). 2-Methyloctahydro-5-norellipticine (200 mg) was mixed with 10 % Pd/C (100 mg) and heated in a salt bath at 220 °C for 4 h in an evacuated tube (1 mm Hg). The reaction mixture was then extracted with hot acetic acid, neutralized with K_2CO_3 and reextracted with CH_2Cl_2 and dried. The crude 5-norellipticine so obtained was sublimed (360 °C/1 mm Hg) to give yellow crystals. Yield 80 mg (40 %) m.p. 277–280 °C. IR (KBr): 3400, 3140, 3020, 2980, 2940, 2830, 2760, 2720, 2670, 1630, 1600 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.50–7.19 (9H,m,ar), 3.27 (3H,s,CH_3). MS *m/e* (% rel. int.): 233 (M^++1, 17), 232 (M^+, 100), 231 (40), 230 (11), 216 (10), 116 (14), 102 (13), 88 (10).

3-(1,3-Diacetyl-1,4-dihydro-4-pyridyl)-2-methylindole (12a). Acetyl chloride (16 g, 0.2 M) was added to 3-acetylpyridine (24.2 g, 0.2 M) in dry dioxane (250 ml). The mixture was stirred for 4 h at 30 °C. 2-Methylindole (26.2 g, 0.2 M) was added and the mixture was stirred at 30 °C for 30 min and then at 58 °C for 90 min. The reaction mixture was then transferred to water (950 ml) and the oil separated was collected and washed well with water. Trituration with acetonitrile yielded bright yellow crystals of *12a*. Yield 12.9 g (22 %), m.p. 216–218 °C. IR (KBr): 3320 (NH), 1710, 1670, 1650, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.84 (1H,s,ar), 7.32–7.08 (6H,m,ar), 4.82 (1H,d), 2.45 (6H,s,CH_3), 2.20 (3H,s,CH_3). MS *m/e* (% rel. int.): 295 (12, M^++1), 294 (54, M^+), 252 (10), 251(28), 250 (13), 173 (19), 163 (24), 132 (10), 131 (100), 122 (13), 121 (17), 106 (26), 42 (10).

3-(3-Acetyl-4-pyridyl)-2-methylindole (13a). DDQ (5.68 g, 25 mM) in dioxane (25 ml) was added to 3-(1,3-diacetyl-1,4-dihydro-4-pyridyl)-2-methylindole (7.35 g, 25 mM) in dioxane (150 ml) and the mixture stirred for 10 h. It was then poured into water (360 ml) containing KOH (6 g). The product separated partially on standing. The mother liquor was extracted with $CHCl_3$, dried and evaporated and the combined crude product was crystallized from acetonitrile (2.6 g) m.p. 184–185 °C. IR (KBr): 3210, 3170, 3050, 1680, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.86–8.73 (3H,m,ar), 7.45–7.39 (3H, m,ar), 7.36–7.17 (2H,m,ar), 2.34 (3H,s,CH_3), 2.01 (3H,s,CH_3). MS *m/e* (% rel. int.): 250 (M^+, 96), 236 (17), 235 (100), 233 (16), 232(18), 206 (14), 178 (14), 130 (20), 103 (18), 43 (18), 28 (71), 18 (96), 17 (22).

5-Methyl-7H-pyrido[3,4-c]carbazole (14). 3(3-Acetyl-4-pyridyl)-2-methylindole (500 mg) and NaH (200 mg) were added to diphenyl ether (25 ml) and heated (200 °C, 48 h) under N_2. Extraction with conc. HCl, neutralization and reextraction with CH_2Cl_2

yielded after drying and sublimation (360 °C/1 mm Hg) yellow crystals (80 mg, 17 %) m.p. 291 – 293 °C. IR (KBr): 3470, 3375, 3120, 3020, 1615 (broad) 1580 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.46 (1H,s,NH), 8.69 – 8.54 (3H,m,ar), 7.7 – 7.6 (2H,d,ar), 7.48 – 7.30 (3H,m,ar), 2.89 (3H,s,CH_3). MS *m/e* (% rel. int): 233 (M^+1,100), 232 (M^+,39), 112 (16), 103 (14), 89 (12), 28(30), 19 (42).

3-(N-Acetyl-3-cyano-1,4-dihydro-4-pyridyl)-2-methylindole (12b). Acetyl chloride (7.9 g, 0.1 M) was added to 3-cyanopyridine (10.4 g, 0.1 M) in dry dioxane (100 ml). The mixture was stirred for 4 h at 30 °C. 2-Methylindole (13.1 g, 0.1M) was added and the temperature was maintained at 30 °C for 30 min and then at 58 °C for 90 min. The reaction mixture was then transferred to water (950 ml) and the oil separated was collected, washed well with water. Trituration with acetonitrile yielded white crystals 3.8 g, (14 %) m.p. 209 – 211 °C. IR (KBr): 3350 (NH), 2220 (CN), 1705, 1680, 1615 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.7 (1H,s,NH), 7.8 (1H,s,ar), 7.5 – 6.8 (4H,m), 5.2 – 4.9 (1H,m), 4.7 – 4.5 (1H,m). MS *m/e* (% rel.int.): 278 ($M^+ + 1$, 11), 277 (M^+, 53), 235 (37), 234 (100), 233 (22), 232 (13), 220 (45), 219 (10), 158 (11), 149 (15), 143 (13), 131 (24), 130 (41), 105 (17), 104 (16), 103 (15), 77 (15).

3-(3-Cyano-4-pyridyl)-2-methylindole (13b). 3-(*N*-Acetyl-3-cyano-1,4-dihydro-4-pyridyl)-2-methylindole (0.93 g, 4 mM) was transferred into dioxane (25 ml). A suspension of DDQ (0.908 g, 4 mM) in dioxane (5 ml) was added and stirred overnight. The mixture was then poured into water (360 ml) containing KOH (6 g). An oil separated out which crystallized on standing (0.61 g) m.p. 197 – 199 °C. ^1H NMR ($CDCl_3$): δ 8.99 (1H,s,NH), 8.79 (1H,m,ar), 8.40 (1H,s,ar) 7.59 – 7.17 (5H,m,ar), 2.51 (3H,s,CH_3).

5-Amino-7H-pyrido[3,4-c]carbazole (15). Compound *13b* (500 mg) was cyclized as described for *14* using NaH (200 mg). Yield 250 mg, yellow crystals m.p. 234 – 236 °C. IR (KBr): 3450, 3390, 3325, 3200, 1645, 1625, 1580 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.08 (1H,s,NH), 8.85 – 8.82 (1H,d,ar), 7.68 – 7.65 (1H,d, ar), 7.45 – 7.41 (3H,m,ar), 7.21 – 7.04 (3H,m,ar), 2.46 (2H,s). MS *m/e* (% rel. int.): 234 ($M^+ + 1$, 18), 233 (M^+, 100), 232 (20), 106 (16), 102 (10), 27 (21), 18 (43).

7H-Pyrido[3,4-c]carbazole (16). 5-Amino-7*H*-pyrido[3,4-*c*]carbazole (*15*) (233 mg) was dissolved in conc. HCl (15 ml) at 30 °C. Water (3 ml) was added and the solution was cooled to 0 – 5 °C, whereupon sodium nitrite (75 mg) in water was added to the stirred solution. After further 2 h at 10 °C the solution was poured into H_3PO_2 (90 ml, aq. 30 %). The resulting solution was kept at 25 °C for 16 h, whereupon the base was liberated by addition of KOH (aq. 20 %), 160 mg (73 %), m.p. 254 – 255 °C (lit.[6] 254 – 255 °C).

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