

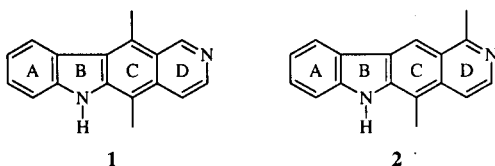
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Ethyl 1,2-dihydro-4-methylcarbazole-3-carboxylate and 11-methyl-6*H*-pyrido[4,3-*b*]carbazole (5-demethylellipticine) have been synthesized by different routes.

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Many chemists have paid great attention to the synthesis of ellipticine (**1**) and olivacine (**2**) which are pyridocarbazole type alkaloids after the discovery of the antitumor activities of these compounds. The synthesis of this type of alkaloids have been successfully accomplished by applying different types of strategies [1,2].

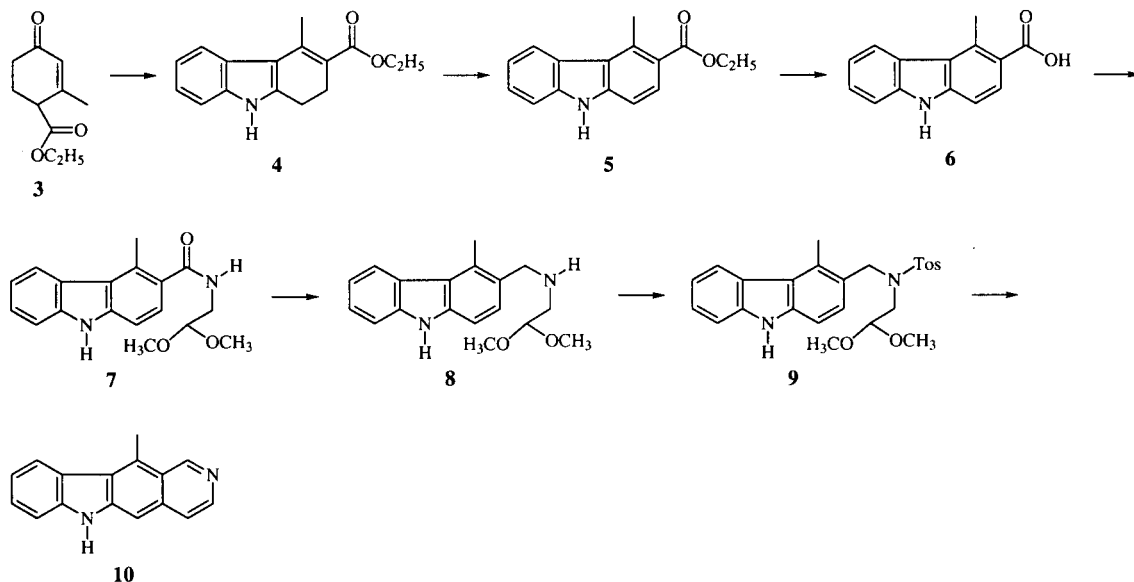


In this study 5-demethylellipticine has been synthesized by **D** ring formation which has been synthesized previously by different routes [3,4]. This study is important for two reasons. First, compound **4** which synthetically is important as a starting material for the synthesis of many carbazole derivatives and indole alkaloids has been successfully synthesized in a higher yield (52%). The first synthesis of the compound **4** and its derivatives was accomplished by Sakan *et al.* by reaction of the tosylate derivatives and ethyl acetoacetate with sodium ethoxide in ethanol [5]. Later Bergman and Pelcman repeated the

same reaction to obtain compound **4** but they were unsuccessful [6]. Then they tried a new method by reaction of Hagemann's ester **3** with phenylhydrazine in acetic acid and obtained **4** in 13% yield [7]. We now report in this study a synthesis of compound **4** in a higher yield of 52% by the reaction of Hagemann's ester **3** with phenylhydrazine hydrochloride in absolute ethanol. Second, in this study our synthetic plan proceeds through amide **7** which forms by the condensation reaction of carbazole acid **6** and an amine. On the other hand the previous studies covers the synthesis of the **D** ring by the condensation reaction of a carbazole derivatives (aldehyde or ketone) with an amine and the subsequent reaction of the imine product formed [8-13]. Compound **5** was synthesized by the same method in the literature [14].

EXPERIMENTAL

All melting points were measured in sealed tubes using an electrothermal digital melting point apparatus (Gallenkamp) and are uncorrected. Infrared spectra were recorded on Hitachi 270-30 infrared spectrometer. The ¹H-nmr spectra were obtained on a high resolution fourier transform Bruker WH-400 and Bruker WH-270 NMR spectrometers with tetramethylsilane as an internal standard. Mass spectra were recorded on a Micromass



UK Platform II LC-MS spectrometer. Analytical and preparative thin layer chromatography (tlc) was performed on silica gel 60 HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 min, Merck).

Ethyl 1,2-Dihydro-4-methylcarbazole-3-carboxylate (4).

A stirred mixture of 9.1 g (50 mmoles) of **3** and 7.23 g (50 mmoles) of phenylhydrazine hydrochloride in 25 ml of absolute ethanol was refluxed under nitrogen for 5 hours. After cooling to room temperature and removed of the solvent, the residue was dissolved in chloroform and washed with 50 ml of 10% hydrochloric acid and 50 ml of 10% potassium carbonate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Recrystallization of the residue from methanol yielded 6.62 g (52%) of **4** as yellow crystals, mp 164-166°; rf. 0.75 (ethyl acetate); ir (potassium bromide): ν 3280 (NH), 1665 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.34 (3H, t, $J = 7.11$ Hz, CH_2CH_3), 2.78 (3H, s, CH_3), 2.80 (4H, s, CH_2CH_2), 4.21-4.29 (2H, q, $J = 7.11$ Hz, CH_2CH_3), 7.10-7.19 (2H, in, aromatic protons), 7.22-7.32 (1H, m aromatic proton), 7.77-7.86 (1H, m, aromatic proton), 8.41 (1H, s, NH); ms: m/z 255 (94), 226 (6), 210 (25), 196 (4), 182 (100), 183 (41), 180 (68), 167 (75), 152 (10), 139 (7), 115 (5), 90 (32).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.06; H, 6.65; N, 5.56.

4-Methyl-9H-carbazole-3-carboxylic Acid (6).

A solution of 2 g (8 mmoles) of **5** in 20 ml of 20% potassium hydroxide (methanol-water) was refluxed for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with water and acidified with 10 ml of 10% hydrochloric acid. The solution was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was recrystallized from dichloromethane-cyclohexane yielded 1.77 g (99%) of **6**, mp 227-228°; rf. 0.42 (ethyl acetate); ir (potassium bromide): ν 3420 (NH), 1715 (C=O) cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 3.22 (3H, s, ArCH_3), 7.20-7.50 (4H, in, aromatic protons), 8.04-8.08 (1H, d, $J = 8.59$ Hz, aromatic proton), 8.25-8.28 (1H, d, $J = 8.59$ Hz, aromatic proton), 10.14 (1H, s, NH), 13.3, (1H, s, OH); ms: m/z 208 (20), 207 (16), 196 (3), 180 (40), 179 (30), 178 (15), 167 (7), 127 (5), 104 (19), 89 (29), 76 (22).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.56; H, 4.87; N, 6.08.

3-[N-(2,2-Dimethoxyethyl)]-4-methyl-9H-carbazole-3-carboxamide (7).

To a solution of 1.09 g (10 mmoles) of ethyl chloroformate in 5 ml of tetrahydrofuran at 0° was added a solution of 2.25 g (10 mmoles) of acid **6**. The mixture was stirred for 2 hours at 0° and 1.10 g (11 mmoles) of 2-aminoacetaldehyde dimethylacetal was added. After 12 hours at 25°, the mixture diluted with 50 ml of ethyl acetate and washed with 50 ml of 10% hydrochloric acid and 50 ml of 10% potassium carbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate and recrystallized from diethyl ether to yielded 1.2 g (37%) of **7**, mp 148°; rf. 0.69 (ethyl acetate); ir (potassium bromide): ν 3320 (NH), 1675 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.84 (3H, s, ArCH_3), 3.38 (6H, s, 2 x OCH_3), 3.58-

3.62 (2H, dd, CHCH_2NH), 4.49-4.52 (1H, dd, $\text{CH}(\text{OCH}_3)_2$), 6.5 (1H, t, NH), 7.20-7.44 (4H, m, aromatic protons), 7.96-8.12 (1H, m, aromatic proton), 8.22-8.28 (1H, d, aromatic proton), 8.57 (1H, s, NH); ms: m/z 312 (4), 224 (81), 223 (41), 208 (100), 180 (55), 167 (18), 157 (17), 127 (8), 90 (8).

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.23; H, 6.41; N, 8.94.

3-[N-(2,2-Dimethoxyethyl)aminomethyl]-4-methylcarbazole (8).

A solution of 1.56 g (5 mmoles) of **7** in 15 ml of anhydrous tetrahydrofuran was added to a stirred solution of 380 mg (10 mmoles) lithium aluminium hydride in 15 ml of tetrahydrofuran at room temperature. The mixture was refluxed under nitrogen for 6 hours and then cooled to 0° and the excess lithium aluminium hydride destroyed with 15 ml of water. The reaction mixture was extracted with ethyl acetate and organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from diethyl ether to yielded 1.40 g (94%) of **8**, mp 164°; rf. 0.56 (ethyl acetate); ir (potassium bromide): ν 3300 (NH), 3200 (amine NH) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.00 (3H, s, ArCH_3), 3.48 (8H, s, 2 x OCH_3 and ArCH_2), 3.67-3.70 (2H, dd, CHCH_2NH), 4.57-4.62 (1H, dd, $\text{CH}(\text{OCH}_3)_2$), 6.05 (1H, t, NH), 7.20-7.52 (5H, in, aromatic protons), 8.25-8.28 (1H, d, aromatic proton), 8.35 (1H, s, NH); ms: m/z 298 (5), 297 (4), 296 (5), 293 (11), 292 (56), 277 (12), 210 (84), 208 (100), 207 (41), 180 (55), 168 (17), 157 (56), 127 (8), 90 (8).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.39; H, 7.52; N, 9.34.

3-[N-(2,2-Dimethoxyethyl)-N-tosylaminomethyl]-4-methylcarbazole (9).

A solution of 2 g (6.7 mmoles) of the reduced compound **8** in 20 ml of chloroform was added to a stirred mixture of 10 ml of triethylamine and freshly crystallized 1.5 g of *p*-toluenesulphonyl chloride and the mixture was stirred at room temperature 2 days. The precipitated triethylamine hydrochloride was filtered and washed with chloroform. The filtrate was washed with dilute 20 ml of 5% hydrochloric acid and water. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate and recrystallized from dichloromethane-hexane yielded 2.8 g (95%) of **9** as prisms, mp 169-170°; rf. 0.65 (ethyl acetate); ir (potassium bromide): ν 3350 (NH), 1345 and 1170 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.40 (3H, s, tosyl- CH_3), 2.95 (3H, s, ArCH_3), 3.10-3.15 (6H, s, 2 x OCH_3), 3.18-3.20 (2H, d, CHCH_2NTos), 4.15-4.20 (1H, dd, $\text{CH}(\text{OCH}_3)_2$), 4.65 (2H, s, ArCH_2NTos), 7.15-7.50 (7H, in, aromatic protons), 7.75-7.80 (2H, in, aromatic protons) 8.10-8.18 (1H, bs, NH), 8.20-8.23 (1H, m, aromatic proton); ms: m/z 452 (5), 420 (20), 388 (70), 378 (20), 369 (26), 349 (12), 339 (11), 303 (32 278 (100), 262 (35), 248 (61), 232 (5), 184 (25), 155 (45), 91 (100).

Anal. Calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{SO}_4$: C, 66.35; H, 6.18; N, 6.22. Found: 66.39; H, 6.12; N, 6.19.

11-Methyl-6H-pyrido[4,3-*b*]carbazole (5-Demethyl Ellipticine) (10).

A solution of 1 g (2.2 mmoles) of tosylate **9** in 20 ml of the dry dioxane containing 2 ml of 6M hydrochloric acid was refluxed under nitrogen. After 12 hours, the reaction mixture was poured into 50 ml of 5% sodium carbonate and extracted with chloroform.

The organic layer was washed with saturated aqueous sodium chloride and dried with anhydrous magnesium sulfate. The solvent was evaporated under the reduced pressure and the resulting residue was chromatographed on neutralized aluminium oxide using ethanol to give 240 mg (47%) of **10** as a yellow solid which was recrystallized from methanol-water to afford yellow needles, mp 278-281°; rf. 0.3 (ethanol); ir (potassium bromide): ν 3400 (NH) cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 3.27 (3H, s, ArCH_3), 7.25-7.29 (1H, t, aromatic proton), 7.35-7.48 (3H, m, aromatic protons), 7.60-7.65 (1H, d, aromatic proton), 7.95-8.10 (1H, bs, aromatic proton), 8.28-8.32 (1H, d, aromatic proton), 8.40-8.45 (1H, d, aromatic proton), 9.60 (1H, s, NH); ms: m/z 233 (19), 232 (100), 231 (42), 215 (10), 116 (14), 102 (14), 88 (12).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.76; H, 5.23; N, 12.01.

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