A Novel Synthetic Approach for the Synthesis of Pyridocarbazole Alkaloids

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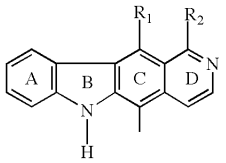
Received July 24, 2003

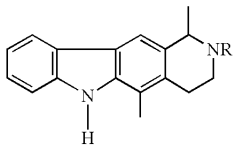
The synthesis of 11-methyl-6*H*-pyrido[4,3-*b*]carbazole-1(2*H*)-one (5), which can be important for the synthesis of other pyridocarbazole alkaloids and especially 1-substituted ellipticines, is described. Construction of the tetracyclic structure was achieved by a new route and two important precursor compounds (4a and 4b) for the synthesis of pyridocarbazole alkaloids and also many new tetrahydrocarbazole derivatives (7, 8, 9, 10, 11, 12, 13) were synthesized.

J. Heterocyclic Chem., **40**, 1005 (2003).

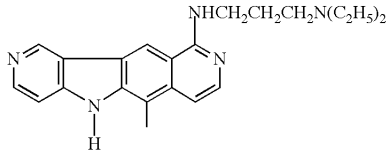
The 6*H*-pyrido[4,3-*b*]carbazole alkaloids, ellipticine (**1a**), olivacine (**1b**) and their derivatives such as janetine (**2a**) and guatambuine (**2b**), occur in the genera *Ochrasia*, *Aspidosperma*, *Tabernaemontana* which are members of the family *Apocynnaceae* [1]. These alkaloids display pronounced antitumor activity in several animal and human tumor systems [2-4]. Especially 1-substituted ellipticines with dialkylamino-alkylamino side chain such as compound **3** have higher antitumor activity on L1210 leukaemia in mice with lower cardiovascular effect compared with the parent ellipticines [5-7]. Therefore, many chemists have paid great attention to the synthesis of 6*H*-pyrido[4,3-*b*]carbazole alkaloids [8-12]. The 6*H*-pyrido[4,3-*b*]carbazole alkaloids are tetracyclic. The synthetic strategies for the preparation of the tetracyclic 6*H*-pyrido[4,3-*b*]carbazole alkaloids are classified in four main groups, such as B type, C type, B+C type and D type, based upon the last ring to be constructed [13,14].



1a R_1= CH_3 R_2= H
1b R_1= H R_2= CH_3



2a R= H
2b R= CH_3

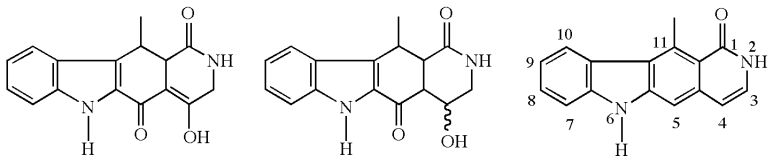


3

The B type synthesis includes Goldberg's coupling of substituted nitro anilines with a bromo isoquinoline derivative. The B ring is constructed with the subsequent reactions [15]. In the C type of synthesis, Diels-Alder reaction plays a role between pyrano[3,4-*b*]indol-3-one and arynes [16]. The B+C type of synthesis covers an intramolecular Diels-Alder cycloaddition of an acetylenic vinylketeneimine as a key step in constructing the B+C ring of the ellipticine or its derivatives simultaneously [17]. In the D type of synthesis, ellipticine and its derivatives are synthesized by the intramolecular aromatic electrophilic substitution reaction with suitable carbazole derivatives [18,19].

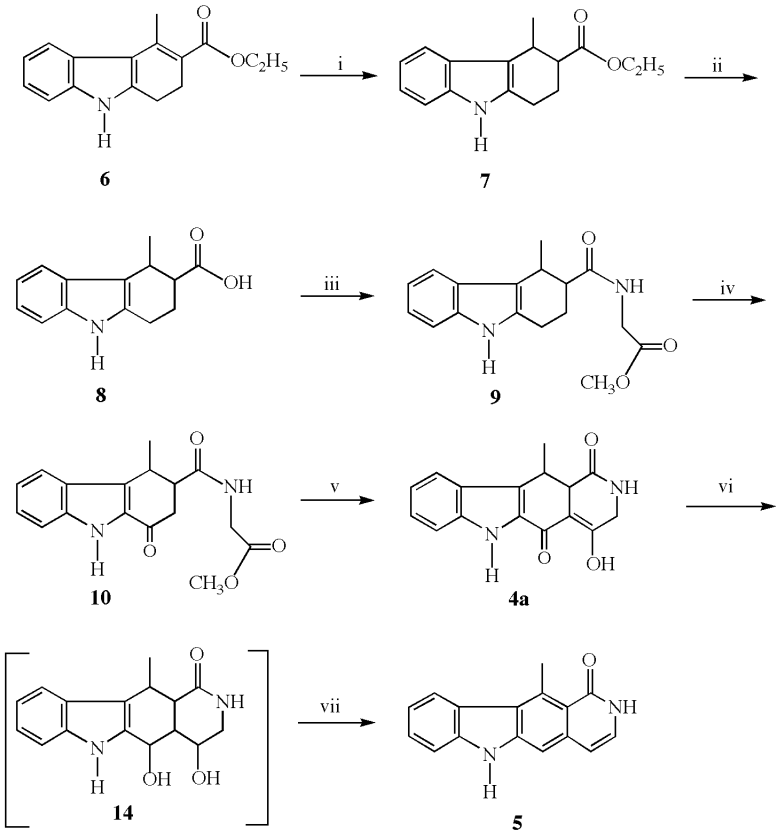
In this work, we used a D type of synthetic strategy and developed a novel approach. All of the previous studies on D type of synthesis construct the D ring in the final step using the intramolecular aromatic electrophilic substitution reaction. In the present work we first achieved the construction of the D ring both with an intramolecular condensation reaction between an ester and a ketone group on the tetrahydrocarbazole derivative (Scheme 1) and with intramolecular aldol condensation reaction between an aldehyde and ketone group on the tetrahydrocarbazole derivative (Scheme 2). Thus we synthesized two new precursor compounds **4a** and **4b** which can be a useful key intermediate for the synthesis of 6*H*-pyrido[4,3-*b*]carbazole alkaloids using a new synthetic approach. Finally we accomplished the synthesis of 11-methyl-6*H*-pyrido[4,3-*b*]carbazole-1(2*H*)-one (**5**) which can be important for the synthesis of other pyridocarbazoles and especially 1-substituted ellipticines from these closely related compounds **4a** and **4b** with a novel synthetic approach. Previously some 6*H*-pyrido[4,3-*b*]carbazole-1(2*H*)-ones similar to compound **5** were synthesized and used efficiently for the synthesis of 1-substituted ellipticines [20-25].

In our study we selected a 1,2-dihydrocarbazole **6** as the starting material (Scheme1) [26]. Compound **6** was hydrogenated with Pd/C (10 %) in tetrahydrofuran to give tetrahydrocarbazole **7** [27]. Tetrahydrocarbazole ester **7** was then refluxed with sodium hydroxide solution (30 %) in methanol-water (1:1) yielding tetrahydrocarbazole carboxylic acid **8** [28]. Compound **8** was then converted to amide **9** using ethyl chloroformate, triethyl amine and



4a **4b** **5**

Scheme 1



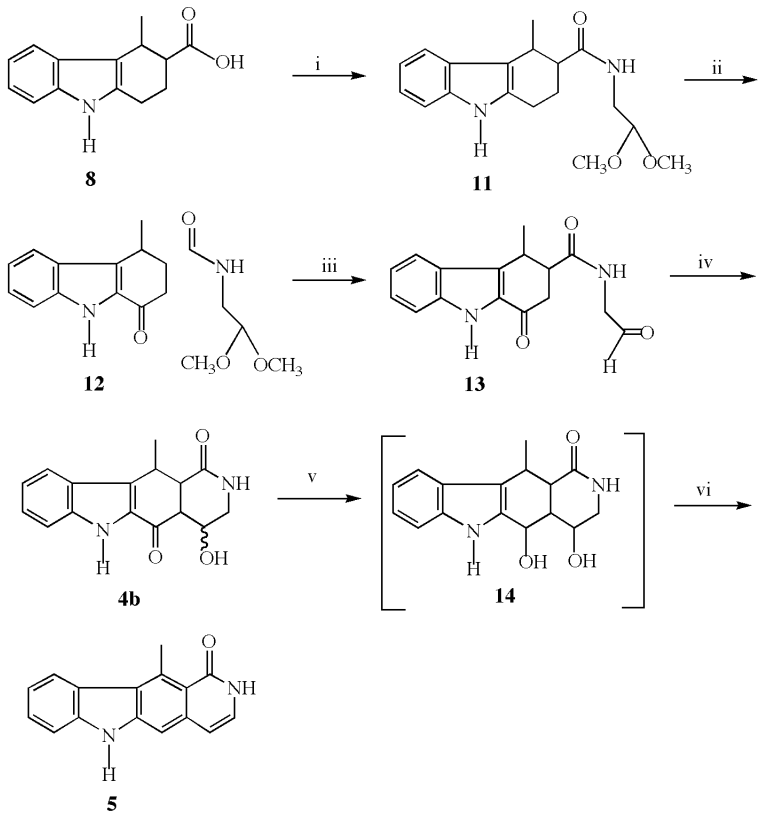
Reagents and conditions: i) Pd/C (10%), H_2, THF, 24h, 92%; ii) NaOH (30%), metanol-water (1:1), reflux, 2h, 96%; iii) $ClCO_2C_2H_5$, $(C_2H_5)_3N$, CH_2Cl_2, stirred, 2h, 0°C, then methyl glycinate hydrochloride, stirred, 12h, 75%; iv) periodic acid, 0°C, 2h, 67%; v) NaH, THF, reflux, 5h, 62%; vi) $NaBH_4$, MeOH-THF, 0°, 3h; vii) p-TsOH, Pd/C (10%), decalin, Δ, 6h, 34%.

methyl glycinate hydrochloride [29]. Oxidation of the amide **9** at position 1 with periodic acid yielded the 1-oxo-tetrahydrocarbazole derivative **10** [30]. Then we treated compound **10** with sodium hydride in anhydrous tetrahydrofuran under nitrogen atmosphere and obtained the tetracyclic intermediate **4a** with a condensation reaction which as a new precursor compound with potential biological activity for the synthesis of the pyridocarbazole alkaloids [31].

Alternatively we constructed the D ring *via* intramolecular aldol condensation. First compound **8** was converted to tetrahydrocarbazole amide **11** with ethyl chloroformate, triethyl amine and aminoacetaldehyde dimethylacetal [32]. Oxidation of the tetrahydrocarbazole amide **11** at position 1 with periodic acid in methanol-water (1:1) yielded compound **12** [33]. Compound **12** was treated with boron tribromide in dichloromethane at -78° in order to convert the acetal group to aldehyde to afford the compound **13** [34]. Then we treated compound **13** with sodium hydride in anhydrous tetrahydrofuran under nitrogen atmosphere and obtained the tetracyclic compound **4b** as a mixture of the epimeric alcohols with intramolecular aldol condensation reaction which as a new precursor compound with potential biological activity for the synthesis of the pyridocarbazole alkaloids.

Finally the reduction of these similar compounds **4a** and **4b** at 5 position in order to change ketone to alcohol with

Scheme 2



Reagent and conditions: i) $ClCO_2C_2H_5$, $(C_2H_5)_3N$, 0°C, stirred, 2h, then aminoacetaldehyde dimethylacetal, stirred, 12h, 68%; ii) periodic acid, MeOH-H_2O, stirred, 6h, 45%; iii) BBr_3, CH_2Cl_2, -78°C, stirred, 2h, 63%; iv) NaH, THF, stirred, 5h, 57%; v) $NaBH_4$, MeOH-THF, 0°, 3h; vi) p-TsOH, Pd/C (10%), decalin, Δ, 6h, 34%.

sodium borohydride yielded intermediate **14** [35,36]. Compound **14** treated with *p*-toluene sulfonic acid and palladium-charcoal (10 %) in decalin without isolation afforded 11-methyl-6*H*-pyrido[4,3-*b*]carbazole-1(2*H*)-one (**5**) [37,38].

We used two different routes to synthesize compound **5** shown in Scheme 1 and Scheme 2. Compound **8** is a common compound in two synthetic paths. If we compared two synthetic plan, it is seen that the reaction steps in Scheme 1 is one step less than in Scheme 2 and also the yield in first route (Scheme 1) is higher than the second route (Scheme 2).

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 an Hitachi 270-30 infrared spectrometer. ^{1}H NMR spectra were obtained on a high resolution fourier transform Bruker WH-400 NMR spectrometer with tetramethylsilane as an internal stantard. Mass spectra were recorded on a Micromass UK Platform II LC-MS spectrometer. Column chromatography was carried out using 70-230 mesh silica gel (0.063-0.2 mm, Merck).

Ethyl 4-Methyl-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxylate (**7**).

A mixture of 5 g (19.6 mmoles) of ethyl 4-methyl-1,2-dihydrocarbazole-3-carboxylate, 250 mg of palladium-charcoal (10%) and 5 ml of acetic acid in 100 ml of tetrahydrofuran was hydrogenated at atmospheric pressure. After the cessation of hydrogen uptake the mixture was filtered and the filtrate evaporated. The crude product was filtered through a short silica gel column with ethyl acetate. After evaporation of the solvent, the residue was crystallized from methanol to yield 4.64 g (92 %) of **7**; mp: 105-106°; ir (potassium bromide): ν 3350 (NH), 2945 (CH), 1710 (C=O, ester) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (3H, d, J=6.92 Hz, CHC*H*$_3$), 1.37 (3H, t, J=7.30 Hz, OCH$_2$C*H*$_3$), 2.14-2.19 (2H, m, CH$_2$), 2.77-2.82 (2H, m, CH$_2$), 2.89-2.94 (1H, m, CH), 3.61-3.66 (1H, m, CH), 4.28 (2H, q, J=7.21 Hz, OC*H*$_2$CH$_3$), 7.05-7.15 (2H, m, aromatic protons), 7.30 (1H, d, J=7.44 Hz, aromatic proton), 7.52 (1H, d, J=7.43 Hz, aromatic proton), 7.71 (1H, s, NH); ms: m/z 257 (100) [M]$^+$, 212 (11.30) [M-C_2H_5O]$^+$, 184 (14.62) [M-$C_3H_5O_2$]$^+$, 169 (17.12) [M-$C_4H_8O_2$]$^+$.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C 74.71; H 7.39; N 5.45. Found: C 74.76; H 7.30; N 5.49.

4-Methyl-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxylic acid (**8**).

A solution of 2.5 g (9.70 mmoles) of **7** and 20 ml of 30 % sodium hydroxide solution in methanol-water was refluxed for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with water and acidified with hydrochloric acid. The solution was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was crystallized from dichloromethane-cyclohexane yielding 2.13 g (96 %) of **8**; mp: 173.5-174.2°; ir (potassium bromide): ν 3410 (NH), 2935 (CH), 1715 (C=O, acid) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 1.15 (3H, d, J=6.84 Hz, CHC*H*$_3$), 1.90-2.10 (2H, m, CH_2), 2.62-2.75 (3H, m, CH and CH_2), 3.40-3.45 (1H, m, CH), 6.90-7.05 (2H, m, aromatic protons), 7.20 (1H, d, J=7.78 Hz, aromatic proton), 7.22 (1H, d, J=7.58 Hz, aromatic proton), 10.12 (1H, s, NH), 11.95 (1H, s, CO_2H); ms: m/z 229 (100) $[M]^+$, 184 (8.10) $[M-CH_2O]^+$, 169 (14.83) $[M-C_2H_4O_2]^+$, 167 (19.20) $[M-C_2H_6O_2]^+$.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C 73.36; H 6.55; N 6.11. Found: C 73.30; H 6.52; N 6.15.

3-(*N*-Methoxycarbonylmethyl)-4-methyl-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxamide (**9**).

To a solution of 1.09 g (10 mmoles) of ethyl chloroformate in 25 ml of dichloromethane at 0° was added dropwise a solution of 2.29 g (10 mmoles) of **8** followed by 3.10 g (30.69 mmoles) of triethyl amine in 25 ml of dichloromethane. The solution was stirred for 2 hours at 0° and 1.26 g (10 mmoles) of methylglycinate hydrochloride was added. After 12 hours at room temperature, the mixture was diluted with ethyl acetate and washed first with 50 ml of 10 % hydrochloric acid and then with 50 ml of 10 % sodium carbonate solutions. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate and crystallized from diethyl ether yielding 2.25 g (75 %) of the amide **9**; mp: 149.5-150.5°; ir (potassium bromide): ν 3400 (NH), 3350 (NH), 2940 (CH), 1755 (C=O, ester), 1634 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (3H, d, J=6.92 Hz, CHC*H*$_3$), 2.07-2.25 (2H, m, CH_2), 2.70-2.85 (3H, m, CH and CH_2), 3.42-3.52 (1H, m, CH), 3.80 (3H, s, OCH_3), 4.10 (1H, dd, J=5.21 and 18.25 Hz, HN*H*CHCO$_2$CH$_3$), 4.17 (1H, dd, J=5.38 and 18.22 Hz, HNHC*H*CO$_2$CH$_3$), 6.17 (1H, t, J=4.84 Hz, NH), 7.07-7.14 (2H, m, aromatic protons), 7.29 (1H, d, J=7.49 Hz, aromatic proton), 7.51 (1H,d, J=7.42 Hz, aromatic proton), 7.86 (1H, s, NH); ms: m/z 300 (48.14) $[M]^+$, 285 (4.65) $[M-CH_3]^+$, 269 (2.41) $[M-CH_3O]^+$, 212 (5.59) $[M-C_3H_6NO_2]^+$, 184 (11.30) $[M-C_4H_6NO_3]^+$, 167 (34.31) $[M-C_5H_{11}NO_3]^+$.

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C 68.00; H 6.67; N 9.33. Found: C 68.07; H 6.62; N 9.38.

3-(*N*-Methoxycarbonylmethyl)-4-methyl-1-oxo-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxamide (**10**).

To a solution of 5.7 g (25 mmoles) of periodic acid in 100 ml of methanol-water (1:1) was added dropwise 3.75 g (12.5 mmoles) of **9** in 25 ml of methanol at 0°. The reaction mixture was stirred for 1 hour at 0°, then stirring was continued for one more hour at room temperature. The solvent was evaporated, then the residue was dissolved in chloroform and washed first with 50 ml of 10 % sodium carbonate and then with 50 ml of 10 % sodium bisulfide solutions. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was chromotographed on silica gel using ethyl acetate and crystallized from methanol, yielded 2.63 g (67 %) of **10**; mp: 182-183°; ir (potassium bromide): ν 3450 (NH), 3380 (NH), 2945 (CH), 1735 (C=O, ester), 1670 (C=O, ketone), 1635 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.58 (3H, d, J=6.98 Hz, CHC*H*$_3$), 2.90 (1H, dd, J=3.61 and 17.21 Hz, CO*H*CHCH), 3.40 (1H, dd, J=13.36 and 17.21 Hz, COHC*H*CH), 3.50-3.60 (1H, m, CH), 3.83-3.97 (1H, m, CH), 4.06 (3H, s, OCH_3), 4.35 (1H, dd, J=5.35 and 18.31 Hz, HN*H*CHCO$_2$CH$_3$), 4.46 (1H, dd, J=5.44 and 18.31 Hz, HNHC*H*CO$_2$CH$_3$), 6.55 (1H, s, NH), 7.41 (1H, t, J=7.55 Hz, aromatic proton), 7.62 (1H, t, J=7.74 Hz, aromatic proton), 7.68 (1H, d, J=8.31 Hz, aromatic proton), 7.85 (1H, d, J=8.10 Hz, aromatic proton), 9.36 (1H, s, NH); ms: m/z 314 (38.40) $[M]^+$, 198 (65.30) $[M-C_4H_6NO_3]^+$, 183 (33.40) $[M-C_5H_9NO_3]^+$, 167 (26.40) $[M-C_5H_9NO_4]^+$, 154 (100) $[M-C_6H_{10}NO_4]^+$, 115 (57.40) $[M-C_9H_{13}NO_4]^+$.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C 64.97; H 5.73; N 8.92. Found: C 64.89; H 5.77; N 8.90.

4-Hydroxy-11-methyl-1,2,3,5,11,11a-hexahydro-6*H*-pyrido[4,3-*b*]carbazole-1,5-dione (**4a**).

A solution of 1.5 g (4.78 mmoles) of **10** and 0.63 g (15.75 mmoles) sodium hydride (60 % dispersion in oil) in anhydrous tetrahydrofuran was refluxed under nitrogen atmosphere for 5 hours. Then the mixture was cooled in an ice bath and 20 ml of 10 % hydrochloric acid was added. After extraction with chloroform, the organic layer was washed with 10 ml of 10% sodium carbonate solution, dried with anhydrous magnesium sulfate and the solvent was evaporated. After purification of the residue by column chromatography using silica gel and ethyl acetate-methanol (1:1) and crystallized from diethyl ether, yielded 0.84 g (62 %) of the tetracyclic compound **4a**; mp: 249-251°; ir (potassium bromide): ν 3445 (NH), 3350 (NH), 2942 (CH), 1675 (C=O, ketone), 1637 (C=O, amide) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 1.23 (3H, d, J=6.94 Hz, CHC*H*$_3$), 3.15-3.20 (1H, m, CH), 3.35 (1H, d, J=5.35 Hz, CH), 3.70 (1H, dd, J=5.70 and 17.42 Hz, HN*H*CH), 3.85 (1H, dd, J=5.86 and 17.44 Hz, HNHC*H*), 7.10 (1H, t, J=7.49 Hz, aromatic proton), 7.31 (1H, t, J=7.30 Hz, aromatic proton), 7.41 (1H, d, J=8.26 Hz, aromatic proton), 7.70 (1H, d, J=7.99 Hz, aromatic proton), 8.35 (1H, t, J=5.42 Hz, NH, amide), 11.59 (1H, s, NH), 12.48 (1H, bs, OH, enol); ms: m/z 282 (4.31) $[M]^+$, 254 (2.76) $[M-CO]^+$, 225 (10.81) $[M-C_2H_3NO]^+$, 199 (7.10) $[M-C_3HNO_2]^+$, 198 (80.35) $[M-C_3H_2NO_2]^+$, 197 (10.37) $[M-C_3H_3NO_2]^+$, 184 (33.62) $[M-C_4H_4NO_2]^+$, 183 (24.89) $[M-C_4H_5NO_2]^+$, 167 (22.71) $[M-C_4H_5NO_3]^+$, 115 (17.65) $[M-C_8H_9NO_3]^+$.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C 68.08; H 4.96; N 9.93. Found: C 68.13; H 4.98; N 9.89.

[*N*-(2,2-Dimethoxyethyl)]-4-methyl-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxamide (**11**).

To a solution of 1.09 g (10 mmoles) of ethyl chloroformate in 15 ml of dichloromethane at 0° was added dropwise a solution of 2.29 g (10 mmoles) of **8** followed by 3.10 g (30.69 mmoles) of triethyl amine in 25 ml of dichloromethane. The solution was stirred for 2 hours at 0° and 1.05 g (10 mmoles) of aminoacetaldehyde dimethylacetal was added. After 12 hours at room temperature, the mixture was diluted with ethyl acetate and washed first with 50 ml of 10 % hydrochloric acid and then with 50 ml of 10 % sodium carbonate solutions. The organic layer was dried with anhydrous magnesium sulfate and the solvent was

evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate and crystallized from diethyl ether to yield 2.15 g (68 %) of amide **11**; mp: 145-146°; ir (potassium bromide): ν 3425 (NH), 3285(NH), 2934 (CH), 1665(C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (3H, d, J=6.93 Hz, CHC*H*$_3$), 2.06-2.11 (1H, m, CH), 2.13-2.19 (1H, m, CH), 2.62-2.69 (1H, m, CH), 2.73-2.84 (3H, m, CH and CH_2), 3.44 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.52 (2H, t, J=5.56 Hz, NHC*H*$_2$CH(OCH_3)$_2$), 4.45 (1H, t, J=5.26 Hz, C*H*(OCH_3)$_2$), 5.84 (1H, t, J=5.48 Hz, NH), 7.08-7.16 (2H, m, aromatic protons), 7.30 (1H, d, J=7.49 Hz, aromatic proton), 7.51 (1H, d, J=7.50 Hz, aromatic proton), 7.84 (1H, s, NH); ms: m/z 317 (18.08) $[M+1]^+$, 316 (100) $[M]^+$, 285 (36.16) $[M-CH_3O]^+$, 253 (3.04) $[M-C_2H_7O_2]^+$, 212 (7.53) $[M-C_4H_{10}NO_2]^+$,184 (29.28) $[M-C_5H_{10}NO_3]^+$, 168 (40.11) $[M-C_6H_{14}NO_3]^+$.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.85; H, 7.70; N, 8.45.

[*N*-(2,2-Dimethoxyethyl)]-4-methyl-1-oxo-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxamide (**12**).

To a solution of 3.60 g (16.55 mmoles) of periodic acid in 100 ml of methanol-water (1:1) was added dropwise 2.5 g (7.91 mmoles) of **11** in 25 ml of methanol at 0°. The reaction mixture was stirred for 1 hour at 0°, then stirring was continued for one more hour at room temperature. The solvent was evaporated then the residue was dissolved in chloroform and washed first with 50 ml of 10 % sodium carbonate and then with 50 ml of 10 % sodium bisulfide solutions. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was chromotographed on silica gel using ethyl acetate and crystallized from methanol to yield 1.18 g (45 %) of compound **12**; mp: 189-189°; ir (potassium bromide): ν 3380 (NH), 3250 (NH), 2950 (CH), 1660 (C=O), 1640 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (3H, d, J=7.03 Hz, CHC*H*$_3$), 2.64 (1H, dd, J=16.92 and 3.44 Hz, CH), 3.14 (1H, dd, J= 16.95 and 13.48 Hz, CH), 3.23-3.29 (1H, m, CH), 3.45 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.51 (2H, t, J=5.62 Hz, NHC*H*$_2$CH(OCH_3)$_2$), 3.63-3.68 (1H, m, CH), 4.47 (1H, t, J=5.40 Hz, C*H*(OCH_3)$_2$), 5.95 (1H, t, J=5.35 Hz, amide-NH), 7.18 (t, 1H, J=7.05 Hz, aromatic proton), 7.40-7.45 (2H, m, aromatic protons), 7.64 (1H, d, J=8.06 Hz, aromatic proton), 9.15 (1H, s, NH); ms: m/z 331 (1.82) $[M+1]^+$, 330 (6.19) $[M]^+$, 298 (10.59) $[M-CH_4O]^+$, 267 (1.91) $[M-C_2H_7O_2]^+$, 197 (100) $[M-C_5H_{11}NO_3]^+$.

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.45; H, 6.67; N, 8.48. Found: C, 64.85; H, 6.37; N, 8.57.

N-Formylmethyl-4-methyl-1-oxo-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxamide (**13**).

To a stirred solution of 1.57 g (4.75 mmoles) of **12** in 25 ml of chloroform under nitrogen at -78° was added *via* syringe 3.57 g (14.25 mmoles) of boron tribromide in chloroform. After 1 hour at -78°, the reaction mixture was allowed to warm to room temperature over 2 hours. Then the reaction mixture was poured into ice-water mixture slowly and extracted with chloroform. The organic phase was washed with 25 ml of 10 % sodium carbonate and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel using ethyl acetate and crystallized from ether to yield 0.85 g (63 %) of **13**; mp: 131-132°; ir (potassium bromide): ν 3320 (NH), 3250 (NH), 2948 (CH), 1680 (C=O), 1660 (C=O), 1640 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (3H, d, J=7.11 Hz, CHC*H*$_3$), 2.61 (1H, dd, J=16.30 and 3.78 Hz, CH), 2.83 (1H, dd, J=16.35 and 13.85 Hz, CH), 3.15-3.25 (1H, m, CH), 3.30-3.40 (1H, m, CH), 3.54-3.62 (2H, m, NHC*H*$_2$CHO), 7.11 (1H, t, J=7.70 Hz, aromatic proton), 7.24 (1H, t, J=7.90 Hz, aromatic proton), 7.37 (1H, d, J=8.20 Hz, aromatic proton), 7.52 (1H, d, J=8.10 Hz, aromatic proton), 7.75 (1H, t, J=5.65 Hz, N*H*CH$_2$CHO), 11.10 (1H, s, NH), 11.90 (1H, sb, C*H*O); ms: m/z 284(8.43) $[M]^+$, 255 (22.56) $[M-CHO]^+$, 242 (48.20) $[M-C_2H_2O]^+$, 198(100) $[M-C_3H_4NO_2]^+$, 183 (100) $[M-C_4H_7NO_2]^+$, 167 (19.52) $[M-C_4H_7NO_3]^+$, 115 (52.37) $[M-C_8H_{11}NO_3]^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63; N, 9.86. Found: C, 68.08; H, 5.70; N, 10.18.

4-Hydroxy-11-methyl-1,2,3,4,4a,5,11,11a-octahydro-6*H*-pyrido-[4,3-*b*]carbazole-1,5-dione (**4b**).

Compound **13** (2 g, 7.40 mmoles) of was treated with 0.89 g (22.2 mmoles; 60% dispersion in oil) of sodium hydride in 25 ml of anhydrous tetrahydrofuran and the mixture was stirred under nitrogen atmosphere for 5 hours at 50°. Then the mixture was cooled in an ice bath and hydrochloric acid was added slowly. After extraction with chloroform, the organic layer was washed with 10 ml of 5 % sodium carbonate, dried with anhydrous magnesium sulfate and the solvent was evaporated. After purification of residue by column chromatography using silica gel and ethyl acetate-methanol (1:1) and crystallization from ether 1.2 g (57 % yield) of compound **4b** was obtained as a mixture of epimeric alcohols; mp: 223-224°; ir (potassium bromide): ν 3500 (OH), 3375 (NH), 3260 (NH), 2945 (CH), 1665 (C=O), 1630 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.05 (3H, d, J=7.02 Hz, CHC*H*$_3$), 2.22-2.28 (1H, m, CH), 2.35-2.45 (1H, m, CH), 2.54-2.63 (1H, m, CH), 3.05 (1H, bs, OH), 3.10-3.17 (1H, m, CH), 3.59 (2H, t, J=5.30 Hz, NHC*H*$_2$CH), 6.05 (1H, bs, amide-NH), 6.85-7.05 (2H, m, aromatic protons), 7.18 (1H, d, J=7.72 Hz, aromatic proton), 7.33 (1H, d, J=7.51 Hz, aromatic proton), 9.87 (1H, s, NH); ms: m/z 284 (12.43) $[M]^+$, 266 (23.42) $[M-H_2O]^+$, 197 (24.17) $[M-C_3H_5NO_2]^+$, 183 (100) $[M-C_4H_7NO_2]^+$, 167 (71.18) $[M-C_4H_7NO_3]^+$, 115 (52.14) $[M-C_8H_{11}NO_3]^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63; N, 9.86. Found: C, 67.96; H, 5.32; N, 9.68.

11-Methyl-6*H*-pyrido[4,3-*b*]carbazole-1(2*H*)-one (**5**).

A solution of 1 g (3.5 mmoles) of **4a** (**4b**) in 15 ml of tetrahydrofuran-methanol (1:1) was cooled 0° and treated with 400 mg (10.67 mmoles) of sodium borohydride and the reaction mixture stirred for 3 hours at room temperature. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated to yield 0.72 g of the crude product **14**. After that, a solution of 0.72 g (2.5 mmoles) of **14**, 250 mg of palladium-charcoal (10 %) and 100 mg of *p*-toluene sulfonic acid in 15 ml of decalin was refluxed under nitrogen atmosphere for 6 hours. The catalyst was separated and the solvent was removed under reduced pressure. The crude product was dissolved in chloroform and extracted with 20 ml of 5 % sodium bicarbonate solution. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated. The crude product was chromatographed with silica gel and ethyl acetate. The solvent was removed under reduced pressure and the product was crystallized from diethyl ether to yield 300 mg (34 %) of **5** as a yellow solids, mp: 236-237°; ir (potassium bromide): ν 3350 (NH), 3275 (NH),

1670 (C=O, amide) cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.80 (3H, s, CH_3), 6.09 (1H, dd, J=10.02 and 4.09 Hz, 3-CH), 6.26 (1H, d, J=10.05 Hz, 4-CH), 7.18 (1H, t, J=7.94 Hz, aromatic proton), 7.37 (1H, t, J=7.10 Hz, aromatic proton), 7.44-7.50 (2H, m, aromatic protons), 7.68 (1H, d, J=8.25 Hz, aromatic proton), 8.31 (1H, d, J=4.15 Hz, amide-NH), 10.90 (1H, s, NH); ms: m/z 248 (8.41) $[M]^+$, 220 (13.42) $[M-CO]^+$, 179 (60.35) $[M-C_3H_3NO]^+$, 165 (40.37) $[M-C_4H_5NO]^+$, 115 (100) $[M-C_8H_7NO]^+$.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.19; H, 4.97; N, 11.41.

Acknowledgement.

The authors wish to express their gratitute to The Scientific and Technical Research Council of Turkey (TUBITAK Grant No:2024) for financial support.

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