A SIMPLE ROUTE TO 3-AMINO-1,4-DIMETHYL-6-HYDROXY- (OR METHOXY-)CARBAZOLES

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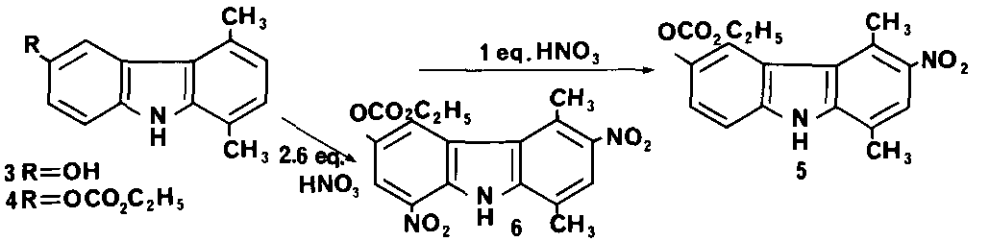
Abstract - A convenient synthesis of 3-amino-1,4-dimethyl-6-hydroxy- (or methoxy-) carbazoles was described starting from 1,4-dimethyl-6-hydroxycarbazole. Structures were confirmed by unequivocal synthesis.

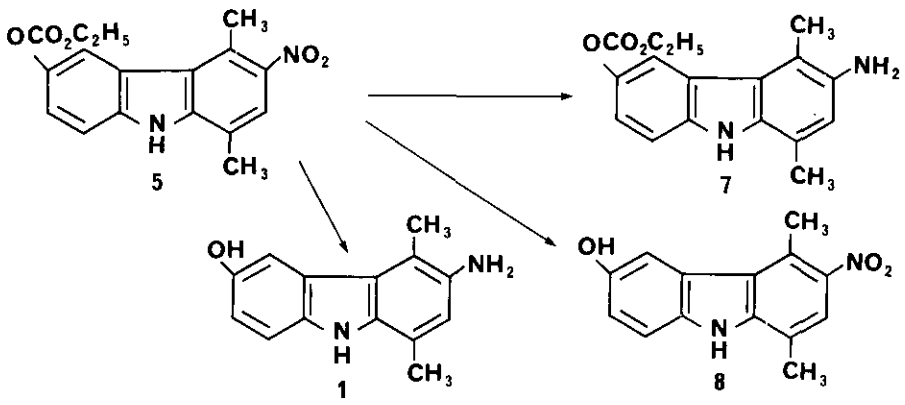
In relation with antineoplastic activity of ellipticine, considerable interest has been focused on the synthesis of dimethylcarbazole derivatives[1] ; however, no synthesis of 3-amino-1,4-dimethyl-6-hydroxy- (or methoxy-)carbazoles has been yet published. As part of our work on the synthesis of potential DNA intercalating carbazoles,[2-3] we wish to describe herein a facile route to the versatile title compounds.

3-Amino-1,4-dimethyl-6-hydroxycarbazole 1

Numerous attempts of direct nitration of 6-hydroxycarbazole[4] 3 in various conditions have always led to mixtures of starting material and mono or dinitro compounds. Their failures prompted us to investigate this reaction starting with 6-ethoxycarbonyloxy derivative 4. Thus, when this reaction was conducted in acetic anhydride with one equivalent of nitric acid (d:1.52) at room temperature the 3-nitro derivative 5 was selectively obtained in a moderate yield (72 %). In a similar manner, with 2.6 equivalents of nitric acid 3,8-dinitro derivative 6 was isolated (91%).

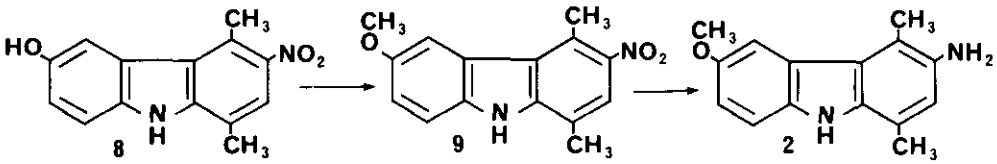


Our study of the reduction of the nitro group[2] has shown that, when this reaction was run with palladium charcoal under hydrogen pressure (50 kg/cm^2 at 80°C) it afforded the O-protected amine 7. When sodium borohydride (1 eq.) was used in refluxed methanol only hydrolysis of the O-protecting group occured to give the nitrophenol 8, but when an excess of sodium borohydride (5 eq.) was employed, the reaction produced in one step the expected amino phenol 1. (The reactivity of the sodium borohydride in this reduction is surprising). The same result could be obtained using stannous chloride in a mixture of dimethylformamide, hydrochloric acid and acetic anhydride but, in this case, the isolation of the product from the reaction mixture was very difficult.

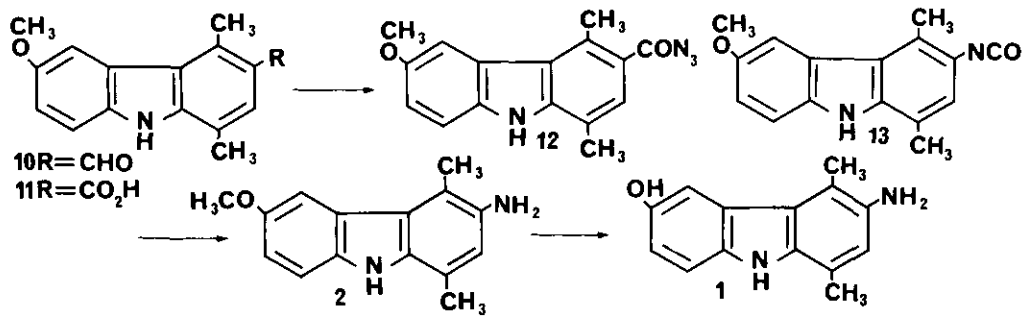


3-Amino-1,4-dimethyl-6-methoxycarbazole 2

The latter sequence was turned to account to synthesize the methoxy derivative 2. Reaction of diazomethane with nitro phenol 8 gave the methoxy compound 9 which was then reduced with stannous chloride in a mixture of dimethylformamide, hydrochloric acid and acetic anhydride. It must be pointed out that sodium borohydride was ineffective to reduce the methoxy compound 8.



These two amines 1 and 2 could be obtained by a less effective route confirming the proposed structures. Starting with 1,4-dimethyl-6-methoxy-3-formylcarbazole[5] 10, oxidation with potassium permanganate in acetone gave in poor yield the carboxylic acid 11 which then provided the amine 2 via a Curtius rearrangement. Thus treatment of the carboxylic acid 11 with ethyl chloroformate in the presence of triethylamine in acetone at 0°C, followed by sodium azide reaction led to the unstable azide 12 which was rearranged spontaneously at room temperature. In fact, this reaction gave a mixture (50/50) of azide 12 and isocyanate 13. Treatment of the latter in boiling hydrochloric acid followed by sodium hydroxide reaction furnished the free methoxy amine 2. Demethylation of the latter was then conducted with hydrobromic acid to give in poor yield (15 %) the aminophenol 1. Samples of 1 or 2 thus obtained by the two routes are identical. These results are currently being applied to the synthesis and biological evaluation of new pyridocarbazoles.



Ir AND Nmr PARAMETERS

No	ir(KBr) (ν cm^{-1})	nmr/TMS (ppm)	Solvent
1	3380 (OH) 3360 (NH_2) 3270 (NH)	10.36 (s,NH) ; 8.60 (s,OH) ; 4.13 (s,NH_2) ; 7.40 (d,H5) ; 7.13 (d,H8 ; 6.60 (dd,H7) ; (s,CH_3(4)).	DMSO-d_6
2	3390, 3320 (NH_2) 1605 (NH_2) 3160 (NH)	10.33 (s,NH) ; 4.26 (s,NH_2) ; 7.56 (d,H5) ; 7.30 (d,H8) ; 6.93 (dd, H7) ; 6.60 (s,H2) ; 3.80 (s,OCH_3) ; 2.46 (s,CH_3(1)) ; 3.26 (s,CH_3(4)).	DMSO-d_6
4	3400 (NH) 1745 (CO)	11.09 (s,NH) ; 7.83 (d,H5) ; 7.43 (d,H8) ; 7.16 (dd,H7) ; 7.00 and 6.73 (dd,H2,H3) ; 4.16 (q,CH_2) ; 1.26 (t,CH_3) ; 2.66 and 2.43 (s,CH_3(1) or s,CH_3(4)).	DMSO-d_6
5	3340 (NH) 1760 (CO) 1320 (NO_2)	11.76 (s,NH) ; 7.96 (d,H5) ; 7.76 (s,H2) ; 7.53 (d,H8) ; 7.26 (dd,7H) ; 4.26 (q,CH_2) ; 1.30 (t,CH_3) ; 2.90 (s,CH_3(4)) ; 2.50 (s,CH_3(1)).	DMSO-d_6
6	3400 (NH) 1760 (CO)	11.43 (s,NH) ; 8.43 (d,H5) ; 8.23 (d,H7) ; 7.80 (s,H2) ; 4.33 (q,CH_2) ; 1.36 (t,CH_3) ; 2.80 (s,CH_3(4)) ; 2.66 (s,CH_3(1)).	DMSO-d_6
7	3360 (NH_2) 3280 (NH_2) 3180 (NH) 1730 (C=O)	10.83 (s,NH) ; 8.00 (d,H5) ; 7.53 (d,H8) ; 7.20 (dd,H7) ; 6.80 (s,H2) ; 4.33 (q,CH_2) ; 1.43 (t,CH_3) ; 4.10 (s,NH_2) ; 2.63 (s,CH_3(1)) ; 2.50 (s,CH_3(4)).	DMSO-d_6
8	3440 (OH) 3320 (NH) 1280 (NO_2)	11.33 (s,NH) ; 9.00 (s,OH) ; 7.63 (s,H2) ; 7.46 (d,H5) ; 7.30 (d,H8) ; 7.20 (dd,H7) ; 2.86 (s,CH_3(4)) ; 2.50 (s,CH_3(1)).	DMSO-d_6
9	3300 (NH) 1280 (NO_2)	9.06 (s,NH) ; 7.70 (s,H2) ; 7.53 (d,H5) ; 7.36 (d,H8) ; 6.93 (dd,H7) ; 3.83 (s,OCH_3) ; 2.96 (s,CH_3(4)) ; 2.50 (s,CH_3(1)).	DMSO-d_6
11	3300 (NH) 1670 (CO)	7.75 (s,H2,H5) ; 7.50 (d,H8) ; 7.10 (dd,H7) ; 12.55 (s,OH) ; 11.35 (s,NH) ; 3.80 (s,OCH_3) ; 3.06(s,CH_3(4) ; 2.50 (s,CH_3(1)).	DMSO-d_6

J(H_3) H_5/H_7 = 2.10 ; H_7/H_8 = 8.40 ; CH_2/CH_3 = 7.20

EXPERIMENTAL

3-Amino-1,4-dimethyl-6-hydroxy-9H-carbazole (1)

a) Method a

A solution of nitro compound 5 (5 g, 0.015 mol) and sodium borohydride (2.85 g, 0.075 mol) in methanol (100 ml) is heated at reflux temperature for 2.5 h and then evaporated to dryness under reduced pressure. The residue is triturated with water (50 ml) and then extracted with ether (100 ml). The etheral layer is decanted, washed with water (50 ml), dried over magnesium sulfate, and the solvent is removed under reduced pressure ; yield : 2.76 g (81 %) ; mp : 250°C (from acetonitrile).

Anal. Calcd $C_{14}H_{14}N_2O$ (226.27) : C, 74.31 ; H, 6.24 ; N, 12.38. Found : C, 74.40 ; H, 6.23 ; N, 12.45.

b) Method b

A solution of methoxy compound 2 (1 g, 0.004 mol) in hydrobromic acid 33 % solution in acetic acid (20 ml) is heated at reflux temperature for 48 h and then evaporated to dryness under reduced pressure. The solid residue is triturated with a saturated sodium hydrogenocarbonate solution (50 ml), and collected by filtration and dried ; yield : 0.15 g (15 %) (from acetonitrile).

3-Amino-1,4-dimethyl-6-methoxy-9H-carbazole (2)

a) Method a

To a solution of nitro compound 9 (2 g, 0.007 mol) in dimethylformamide (15 ml) is added with stirring at room temperature a solution of stannous chloride (4.92 g, 0.026 mol) in a mixture of 12N hydrochloric acid (20 ml) and acetic acid (15 ml). Stirring is continuated for 2 h and the resulting mixture is poured on to 10N sodium hydroxide solution (200 ml). The precipitate is collected by suction, washed with water, dried and recrystallized ; yield : 1.2 g (68 %) ; mp : 200°C (from acetonitrile).

Anal. Calcd $C_{15}H_{16}N_2O$ (240.29) : C, 74.97 ; H, 6.71 ; N, 11.66. Found : C, 74.92 ; H, 6.80 ; N, 11.72.

b) Method b

A solution of mixture of azide 13 and isocyanate 14 (1/1, 6 g) in acetone (200 ml) and 12N hydrochloric acid (20 ml) is heated at reflux temperature for 2 h and then evaporated to dryness under reduced pressure. The residue is triturated with 3N aqueous sodium hydroxide (100 ml) and then extracted with ether (50 ml x 3). The etheral layers are washed with water (100 ml), dried over magnesium sulfate, and the solvent is removed under reduced pressure ; yield : 0.8 g (15 %) (from acetonitrile).

1,4-Dimethyl-6-ethoxycarbonyloxy-9H-carbazole (4)

A solution of hydroxy compound 3 (5 g, 0.024 mol) ethyl chloroformate (3.4 g, 0.031 mol) and triethylamine (3.04 g, 0.031 mol) in toluene (250 ml) is heated at reflux temperature for 2.5 h. After cooling the reaction mixture is washed with water (100 ml x 2), the organic layer is dried over calcium chloride and the toluene is removed under reduced pressure. The solid residue is recristallized ; yield : 3.75 g (55 %) ; mp : 138°C (from ether).

1,4-Dimethyl-6-ethoxycarbonyloxy-3-nitro-9H-carbazole (5)

To a solution of ethoxycarbonyloxy compound 4 (5 g, 0.018 mol) in acetic anhydride (60 ml) is added with stirring at room temperature nitric acid (d 1.52, 0.75 ml, 0.018 mol) and after 3 h the solid precipitate is isolated by suction, washed with ether and recrystallized ; yield : 4.2 g (72 %) ; mp : 226°C (from acetonitrile).

Anal. Calcd $C_{17}H_{16}N_2O_5$ (328,32) : C, 62.19 ; H, 4,91 ; N, 8.53. Found : C, 62.22 ; H, 4.96 ; N, 8.61.

1,4-Dimethyl-3,8-dinitro-6-ethoxycarbonyloxy-9H-carbazole (6)

A solution of ethoxycarbonyloxy compound 4 (3 g, 0.01 mol) in acetic anhydride (60 ml) is treated as above with nitric acid (d 1.52, 1.1 ml, 0.026 mol) ; yield : 3.4 g (91 %) ; mp : 270°C (from acetonitrile).

Anal. Calcd $C_{17}H_{15}N_3O_7$ (373.31) : C, 54.69 ; H, 4.05 ; N, 11.26. Found : C, 54.72 ; H, 4.07 ; N, 11.31.

3-Amino-1,4-dimethyl-6-ethoxycarbonyloxy-9H-carbazole (7)

A solution of nitro compound 5 (10 g, 0.03 mol) in ethanol (600 ml) is hydrogenated under pressure (H_2, 50 atm) at 80°C over palladium charcoal (5 g, 10 %) for 2 h in a steel bomb. After cooling palladium charcoal is filtered off and ethanol was evaporated under reduced pressure. The solid residue is recrystallized ; yield : 4.5 g (50 %) ; mp : 185°C (from acetonitrile).

Anal. Calcd $C_{17}H_{18}N_2O_3$ (298.33) : C, 68.44 ; H, 6.08 ; N, 9.39. Found : C, 68.52 ; H, 6.12 ; N, 9.41.

1,4-Dimethyl-6-hydroxy-3-nitro-9H-carbazole (8)

A solution of nitro compound 5 (5 g, 0.015 mol) and sodium borohydride (0.56 g, 0.015 mol) in methanol (100 ml) is heated at reflux temperature for 2 h and then evaporated to dryness under reduced pressure. The residue is triturated with water (100 ml) and extracted with ether (100 ml). The etheral layer is decanted, dried over magnesium sulfate and evaporated. The solid residue is recrystallized ; yield : 2.3 g (60 %) ; mp : 258°C (from acetonitrile).

Anal. Calcd $C_{14}H_{12}O_3N_2$ (256.25) : C, 65.52 ; H, 4.72 ; N, 10.93. Found : C, 65.46 ; H, 4.79 ; N, 10.86.

1,4-Dimethyl-6-methoxy-3-nitro-9H-carbazole (9)

A solution of nitro compound 8 (2 g, 0.008 mol) in methanol (50 ml) is slowly added at 0°C to saturated solution of diazomethane in ether (100 ml) and after 2 h the solvents are removed under reduced pressure. The solid residue is recrystallized ; yield : 1.9 g (88 %) ; mp : 260°C (from acetonitrile).

Anal. Calcd $C_{15}HO_{14}O_3N_2$ (270.28) : C, 66.65 ; H, 5.22 ; N, 10.37. Found : C, 66.72 ; H, 5.18 ; N, 10.46.

3-(1,4-Dimethyl-6-methoxy-9H-carbazolyl)carboxylic acid (11)

Potassium permanganate (44 g, 0.28 mol) is added to a solution of compound 10 (30 g, 0.12 mol) in acetone (1500 ml) and then the mixture is stirred at room temperature for 3 h. The resulting precipitate is filtered, washed with boiling acetonitrile (2 x 100 ml), dried and then triturated in a saturated aqueous sodium hydrogenocarbonate solution (700 ml). The aqueous solution is filtered and the filtrate is cooled to 5°C in an ice bath and slowly acidified with 6N hydrochloric acid. The precipitate is filtered, washed with water, dried and recrystallized ; yield : 30 g (93 %) ; mp : 172°C (from ethanol).

Anal. Calcd $C_{16}H_{15}NO_3$ (269.29) : C, 71.36 ; H, 5.61 ; N, 5.20. Found : C, 71.40 ; H, 5.63 ; N, 5.25.

Mixture of 3-azido- and 3-isocyanato-1,4-dimethyl-6-methoxy-9H-carbazole (12) and (13) (a/a)

Triethylamine (5.4 ml, 0.039 mol) is added at 0°C to a solution of acid 11 (8.4 g, 0.031 mol) in acetone(120 ml), after 30min ethyl chloroformate (3.72 ml 0.039 mol) is slowly added at such rate that the temperature of reaction mixture is kept between 0 and 5°C, and then after 30 min solution of sodium azide (2.64 g, 0.041 mol) in water (15 ml) is slowly added. The reaction mixture is stirred for 2 h and poured on water (180 ml). The resulting precipitate is collected by succion and dried ; yield : 6 g ; mp : 130°C (dec) (from ether).

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