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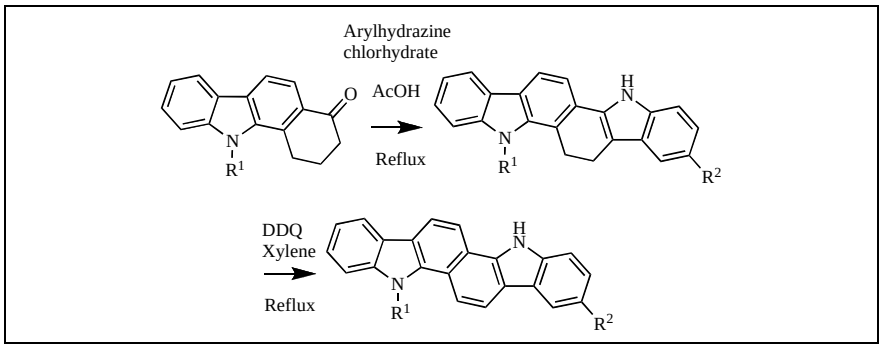
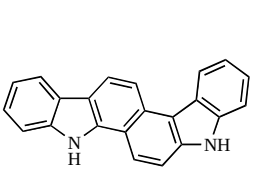


A series of new carbazolo[2,1-*a*]carbazoles was synthesized from 4-oxo-1,2,3,4-tetrahydrobenzo[*a*]-carbazole derivatives.

J. Heterocyclic Chem., **45**, 161 (2008).

INTRODUCTION

Chemistry of carbazolocarbazoles is not well documented in the literature. Known carbazolo[3,4-*a*]-carbazole **1**, symmetrical carbazolo[3,4-*c*]carbazole **2** and carbazolo-[2,1-*a*]carbazole **3a** were synthesized by Bucherer carbazole synthesis [1,2,3] .



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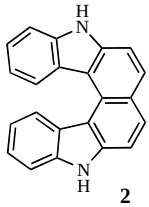

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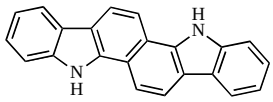

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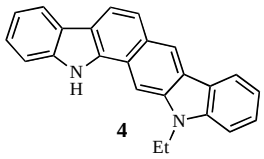

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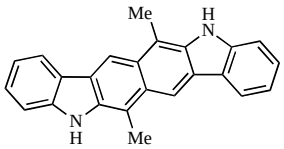

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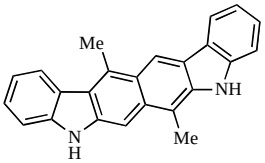

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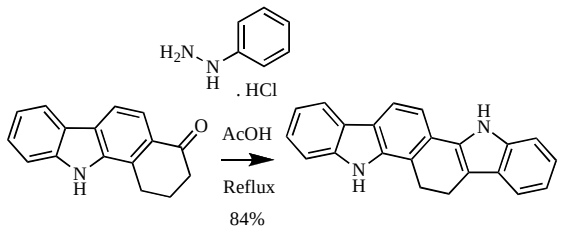
Carbazolo[2,3-*a*]carbazole **4** and some methyl derivatives were prepared through a Fischer indole synthesis and subsequent aromatisation [4]. More recently, Haider *et al.* obtained carbazolo[3,2-*b*]carbazole **5** and carbazolo[2,3-*b*]carbazole **6** as by-products [5]. Few substituted analogues of these structures have been prepared, and to our knowledge not any for **3a** have been prepared.

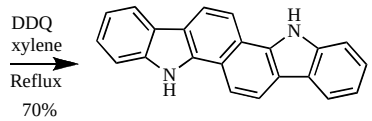
RESULTS AND DISCUSSION

In the course of the synthesis of modified ellipticines, we described previously the new ketonannulated carbazole 4-oxo-1,2,3,4-tetrahydrobenzo[*a*]carbazole **7** [6] obtained by a regioselective 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation. **7** was used in a Fischer indole synthesis to get 6,7-dihydrocarbazolo[2,1-*a*]carbazole **8a**. Aromatisation with DDQ in boiling xylene gave carbazolo[2,1-*a*]carbazole **3a** in 70% yield (Scheme I).

Scheme I



7 **8a**

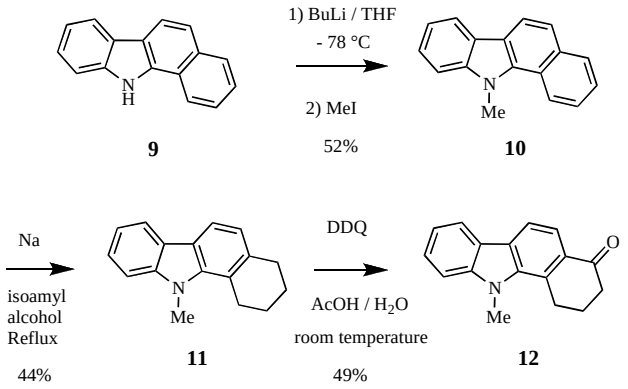


3a

The yield reported in the literature is only 0.1% from 1,5-dihydroxynaphthalene and phenylhydrazine [3] without structural proof, so that our synthesis represents a noteworthy improvement.

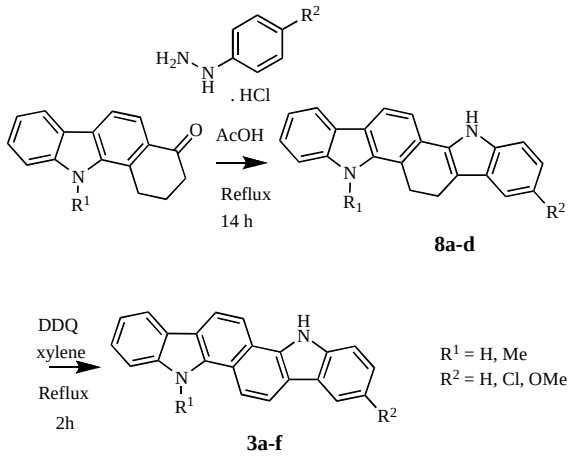
As shown in Scheme II, methylated analogue of **7**, *N*-methyl-4-oxo-1,2,3,4-tetrahydrobenzo[*a*]carbazole **12** was obtained in 3 steps from benzo[*a*]carbazole **9**. Fischer indole synthesis starting from **7** or **12** allows the preparation of different substituted carbazole[2,1-*a*]-carbazoles **3** *via* the dihydro intermediate **8** (Scheme III).

Scheme II



The preparation we present here shows an unequivocal pathway to **3**. Several 4-substitued phenylhydrazine hydrochlorides were treated with **7** or **12** in refluxing acetic acid to undergo a Fischer indole synthesis with good yields (Table I). In the case of the 4-methoxy substituent partial aromatization occurred spontaneously, so that the dihydro product was not isolated, but used without purification for oxidation with DDQ. Aromatization was first tried on **8b** with 5% palladium on charcoal in boiling xylene for 12 h, and was not quantitative. Therefore, one equivalent of DDQ in boiling xylene (or dioxane for **8d**) was used and the reactions were effective after 2 h reflux.

Scheme III



Our synthesis allowed us to prepare a series of new carbazolo[2,1-*a*]carbazoles in a controlled manner. Some biological tests about possible intercalation between DNA bases will be run later.

EXPERIMENTAL

Arylhydrazine hydrochlorides are commercial products used as received. The ^{1}H NMR spectra were recorded on an ACS250 Bruker (250 MHz) apparatus. Melting points were determined on a Stuart Scientific SMP 3 capillary apparatus (< 300°C), higher melting points were obtained by DSC analysis with a TA Instruments 2920 DSC device, with a heating ramp of 10 °C/min (see Table I and II). Exact masses were confirmed by Laser Desorption/Ionization Time-Of-Flight Mass spectrometry, using the fourth harmonic of a Nd:YAG laser (λ = 266 nm, Minilite I, Continuum Inc., Santa Clara, USA) coupled to a Reflex IV MALDI-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany). Molecular ions were obtained with mass errors from 0.3 to 7 ppm. (see Table I and II).

Table I

Physical and Analytical Data of 6,7-Dihydrocarbazolo[2,1-*a*]carbazoles **8**.

Compound	R^1	R^2	Yield (%)	Mp (°C)	Appearance (solid)	Molecular Formula	Calculated m / z	TOF mass analyzer values m / z
8a	H	H	84	475-476	Pale yellow	$C_{22}H_{16}N_2$	308.130	308.128
8b	Me	H	77	353-354	Pale yellow	$C_{23}H_{18}N_2$	322.146	322.148
8c	H	Cl	79	506-507	Pale yellow	$C_{22}H_{15}N_2Cl$	342.092	342.094
8d	Me	Cl	73	349-350	Pale yellow	$C_{23}H_{17}N_2Cl$	356.107	356.106

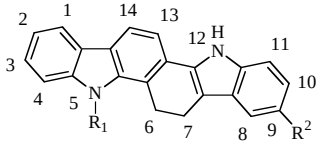


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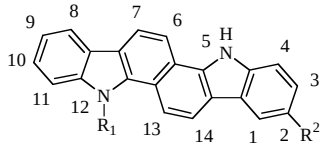
Table II

Physical and Analytical Data of Carbazolo[2,1-*a*]carbazoles **3**.

Compound	R^1	R^2	Yield (%)	Mp (°C)	Appearance (solid)	Molecular Formula	Calculated m / z	TOF mass analyzer values m / z
3a	H	H	70	483-484, lit: 489-490 [3]	Brown	$C_{22}H_{14}N_2$	306.115	306.116
3b	Me	H	75	383-384	Brown	$C_{23}H_{16}N_2$	320.131	320.130
3c	H	Cl	75	510-511	Brown	$C_{22}H_{13}N_2Cl$	340.076	340.077
3d	Me	Cl	74	472-473	Brown	$C_{23}H_{15}N_2Cl$	354.092	354.091
3e	H	OMe	48 (2 steps)	469-470	Brown	$C_{23}H_{16}N_2O$	336.126	336.128
3f	Me	OMe	46 (2 steps)	432-433	Brown	$C_{24}H_{18}N_2O$	350.141	350.142



3

N-methylbenzo[*a*]carbazole (10). 21.7 g of benzo[*a*]carbazole [6] (0.1 mol) dissolved in 100 ml of THF was cooled to -78°C. 38.5 mL of a 2.6 *M* solution of *n*-butyllithium in toluene was added dropwise. The mixture was allowed to warm to room temperature and stirred 1 h at this temperature. The reaction was cooled to -78°C and 6.9 mL of methyl iodide (0.11 mol) was added dropwise. The mixture was allowed to warm to room temperature, stirred 1 h and poured onto 300 mL of ice water. The product was extracted three times with ethyl acetate. The organic layer was washed with 100 mL of water, dried on magnesium sulfate, and evaporated to yield colorless solid, crystallized from petroleum ether, 12 g (52%), mp 170-172 °C, ^{1}H NMR (deuteriochloroform): δ 4.40 (s, 3H), 7.30 (m, 1H), 7.45-7.70 (m, 5H), 8.05 (d, 1H), 8.20 (m, 2H), 8.70 (d, 1H)

***N*-Methyl-1,2,3,4-tetrahydrobenzo[*a*]carbazole (11)**. To a solution of 12 g (0.052 mol) of *N*-methylbenzo[*a*]carbazole **(10)** in 300 mL of boiling isoamyl alcohol, was added carefully 12 g of sodium (10 eq.), portion by portion, in the course of 1 hour. After the addition, stirring and heating were continued until total dissolution of sodium. The hot solution was poured onto 500 mL of ice water. The solid was collected by filtration, washed several times with water, and crystallized from ethanol, 5.4 g (44%), mp 140-142 °C, ^{1}H NMR (deuteriochloroform): δ 1.80-2.00 (m, 4H), 3.00 (t, 2H), 3.40 (t, 2H), 4.10 (s, 3H), 7.00 (d, 1H), 7.20-7.50 (m, 3H), 7.80 (d, 1H), 8.00 (d, 1H)

***N*-Methyl-4-oxo-1,2,3,4-tetrahydrobenzo[*a*]carbazole (12)**. To a suspension of 4.4 g (0.0187 mol) of *N*-methyl-1,2,3,4-tetrahydrobenzo[*a*]carbazole **(11)** in a mixture of 300 mL of acetic acid and 100 mL of water, was added 14 g (3.3 eq.) of DDQ in one portion, the mixture was stirred 14 h at room temperature, poured slowly onto a cold solution of 500 g of sodium hydroxide in 1 L of water, and extracted three times with ethyl acetate. The organic layer was washed with brine, dried on magnesium sulfate and evaporated. The brown crude product was recrystallized in toluene giving a pale rose solid, 2.3 g (49%), mp 158-160 °C, ^{1}H NMR (deuteriochloroform): δ 2.30 (q, 2H), 2.75 (t, 2H), 3.65 (t, 2H), 4.20 (s, 3H), 7.30 (m, 1H), 7.45 (d, 1H), 7.55 (t, 1H), 8.00-8.15 (m, 3H)

General Procedure for Fischer indole reaction affording 6,7-dihydrocarbazolo[2,1-*a*]carbazoles (8). 1 mmol of ketone **7** or **12** and 1 mmol of arylhydrazine hydrochloride in 10 mL of acetic acid were heated at reflux for 14 h. The reaction mixture was poured onto 40 mL of cold water, the solid was collected by filtration, washed with water, and dried at 60°C. Crystallization from methanol gave products **8a**, **8b**, **8c**, and **8d**.

^{1}H NMR values (acetone-d_6): **8a:** δ 3.10 (t, 2H), 3.35 (t, 2H), 7.00-7.20 (m, 3H), 7.30-7.60 (m, 5H), 8.00-8.10 (m, 2H), 10.30 (br, 1H), 10.60 (br, 1H), **8b**: δ 3.10 (t, 2H), 3.75 (t, 2H), 4.20 (s, 3H), 7.00-7.20 (m, 3H), 7.35-7.60 (m, 5H), 8.00-8.10 (m, 2H), 10.60 (br, 1H), **8c**: δ 3.10 (t, 2H), 3.40 (t, 2H), 7.05-7.20 (m, 2H), 7.35-7.60 (m, 5H), 8.00-8.10 (m, 2H), 10.40 (br, 1H), 10.80 (br, 1H), **8d**: δ 3.10 (t, 2H), 3.75 (t, 2H), 4.20 (s, 3H), 7.00-7.20 (m, 2H), 7.30-7.60 (m, 5H), 8.00-8.10 (m, 2H), 10.80 (br, 1H).

General Procedure for aromatization affording carbazolo-[2,1-*a*]carbazoles (3). Compound **8** and 1 eq. of DDQ in xylene (or dioxane for **8d**) were heated at reflux for 2 h. The mixture was cooled to 0 °C, filtered. Crystallization from methanol gave products **3**.

^{1}H NMR values (acetone-d6): **3a**: 7.25 (t, 2H), 7.40 (t, 2H), 7.65 (d, 2H), 8.15-8.40 (m, 6H), 11.30 (br, 2H), **3b**: δ 4.55 (s, 3H), 7.20-7.80 (m, 6H), 8.20-8.40 (m, 5H), 8.70 (d, 1H), 11.30 (br, 1H), **3c** : δ 7.25 (t, 1H), 7.40 (m, 2H), 7.65 (m, 2H), 8.20-8.40 (m, 6H), 11.30 (br, 1H), 11.45 (br, 1H), **3d**: δ 4.55 (s, 3H), 7.25-7.80 (m, 5H), 8.20-8.45 (m, 5H), 8.70 (d, 1H), 11.45 (br, 1H), **3e**: δ 3.90 (s, 3H), 7.05 (dd, 1H), 7.25 (td, 1H), 7.40 (td, 1H), 7.55 (d, 1H), 7.65 (dd, 1H), 7.75 (d, 1H), 8.15-8.35 (m, 5H), 11.10 (br, 1H), 11.30 (br, 1H), **3f**: δ 3.95 (s, 3H), 4.55 (s, 3H), 7.10 (d, 1H), 7.30 (t, 1H), 7.45-7.80 (m, 4H), 8.20-8.40 (m, 4H), 8.65 (d, 1H), 11.10 (br, 1H).

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