SYNTHESES, SUBSTITUTION AND CYCLIZATION REACTIONS OF 7a,8,9,10,11a-HEXAHYDRO-PYRIDO[3,2,1-*jk*]CARBAZOLES WITH A STRYCHNOS ALKALOIDS PARTIAL STRUCTURE [1]

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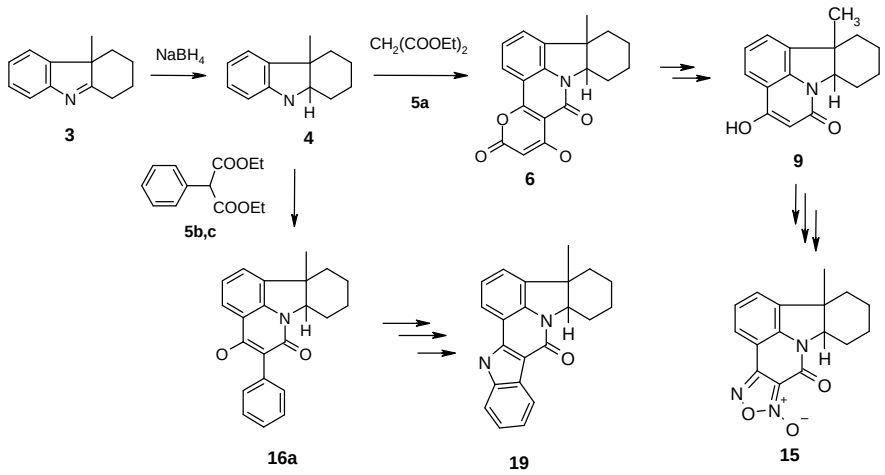
Abstract

4a-Methyl-2,3,3,4a-tetrahydro-1*H*-carbazole (**3**)**,** obtained from phenylhydrazinium chloride and 2-methylcyclohexanone, was regioselectively reduced with sodium borohydride to 4a-methyl-2,3,4,4a,9a-hexahydro-1*H*-carbazole (**4**). Cyclocondensation of **4** with 2 molecules of diethyl malonate **5a** gives 7-hydroxy-13a-methyl-9a,10,11,12,13,13a-hexahydro-5*H*,8*H*-pyrano[2',3':4,5] pyrido[3,2,1-*jk*]carbazole-5,8-dione (**6**), which affords in a 2-step degradation 5-unsubstituted 4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**9**). Nitration forms the 5-nitro compound, which cyclized after chlorination and azidation at position 4 on thermolysis to the furoxane **15**. Cyclocondensation of **4** with phenylmalonate **5b** forms 4-hydroxy-11a-methyl-5-phenyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**16a**), which cyclized after chlorination and azidation at position 4 on thermolysis to the indole derivative **19**.

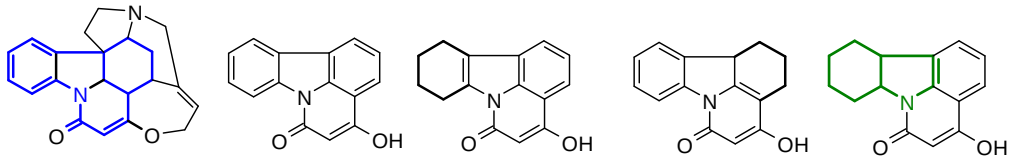


Introduction

Hexahydropyrido[3,2,1-*jk*]carbazol-6-one (blue structure part in **A)** is part of the heterocyclic skeleton of many natural products (e. g. Strychnos alkaloids **A** such as strychninolones and derivatives [2, 3a]). It possesses the biological interesting combination of the well-known indole structure [4] and

the 4-hydroxy-2-pyridone structure, which can be found in many natural products (e.g. Flavipucin [5] with antibiotic activity).

Scheme 1



A **B** **C** **D** **E**

Recently we published the synthesis and reactions of a series of pyrido[3,2,1-*jk*]carbazol-6-ones **B** with two aromatic benzo rings in the carbazole moiety [6], and of tetrahydropyrido[3,2,1-*jk*]carbazol-6-ones with one hydrogenated benzo ring (bold drawn) of type **C** [7], having the pyridone part fused to the aromatic ring. Cyclization of 2,3,4,5-tetrahydrocarbazoles ("indolenines") resulted in the formation of tetrahydro-pyrido[3,2,1-*jk*]carbazoles of type **D** [8] which comprise already four rings as found in Strychnos alkaloids [2].

A further possible isomer of pyrido[3,2,1-*jk*]carbazol-6-one is the hexahydro-pyrido[3,2,1-*jk*] carbazol-6-one of type **E** (with the green hydrogenated partial structure) which is investigated in this paper (Scheme 1).

Results and Discussion

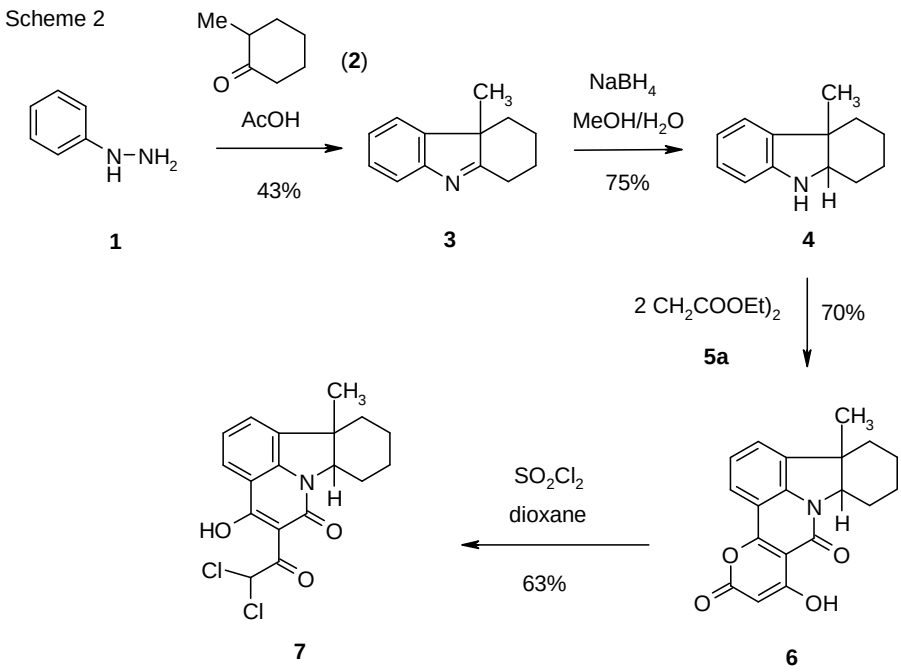
1. Synthesis of Hexahydrocarbazole 3 and Cyclocondensation with Malonate 5a to Hexahydropyrano[2',3':4,5]pyrido[3,2,1-*jk*]carbazolone 6.

Our synthetic approach to the hexahydropyridocarbazole system **E** started with the synthesis of 2,3,4,4a-tetrahydro-1*H*-carbazole (**3**) obtained from phenylhydrazine hydrochloride (**1**) and 2-methylcyclohexanone (**2**), which are brought to reaction directly in glacial acetic acid as soft acid and as solvent without releasing the free phenylhydrazine bases. The work-up includes the extraction of **3** with diethyl ether from the alkaline isomer mixture to isolate the crude so-called "basic product" as oil [9-15], which crystallizes on addition of hexane (Scheme 2). In the ^{1}H nmr spectra of **3** the 4a-methyl group shows a signal at 1.30 ppm.

The regioselective reduction of the enamine double bond in tetrahydrocarbazole **3** can be achieved with sodium borohydride to give 4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**4**) as a mixture of two diastereomeric compounds [16]. The spectral data show that in the isolated product mainly the *cis* isomer is present, and in less than 3% the *trans* isomer. This mixture was used for further reactions without separation.

Syntheses, Substitution and Cyclization Reactions of 7a,8,9,10,11,11a-Hexahydro-pyrido[3,2,1-jk]carbazoles With a Strychnos Alkaloids Partial Structure

Scheme 2



Hexahydrocarbazole **4** behaves in the following cyclocondensation reactions with malonates **5** like a N-substituted aniline [17]. Cyclocondensation of **4** with excess diethyl malonate **5a** in boiling diphenyl ether as solvent is directed after primary N-acylation in the first step to the aromatic ring. The thermally produced intermediate ketene derivative attacks the adjacent aromatic ring position. In the second step a further malonate molecule produces primarily with the intermediate 4-hydroxy-pyrido-carbazolone an ester, and then the second thermal induced cyclization takes place directed to the enolized carbon of the 1,3-dicarbonyl moiety in the pyridone ring. This bis-condensation gives in good yields 7-hydroxy-13a-methyl- 9a,10,11,12,13,13a-hexahydro-5*H*,8*H*-pyrano[2',3':4,5]pyrido[3,2,1-*jk*] carbazole-5,8-dione (**6)**. The formed pyridocarbazole ring system of **6** has the correct hydrogenation degree as e.g. visible in strychnos alkaloids (formula **A**, Scheme 1), however the carbazole rings are arranged in the reverse sequence (see formula **E**, Scheme 1).

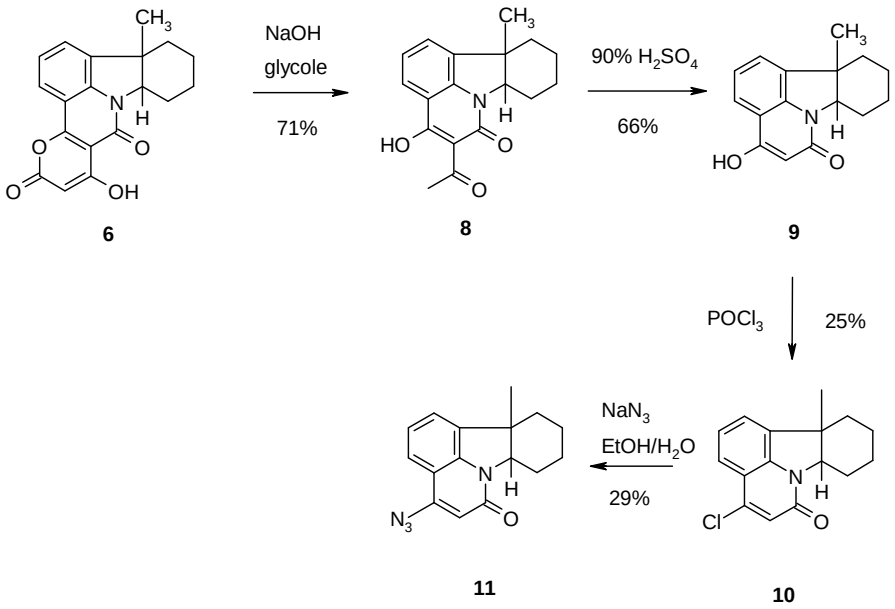
Electrophilic chlorination of hexahydro-pyrano-pyridocarbazoledione **6** with sulfuryl chloride followed by an aqueous work-up leads by bis-chlorination at the carbon of the enolized 1,3-dioxo moiety and subsequent degradation of the pyrono ring to a ring-opened product under loss of carbon dioxide (Scheme 2). In this way 5-(2,2-dichloroacetyl)-4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexa-hydro-6*H*- pyrido[3,2,1-*jk*]carbazol-6-one (**7**) was obtained in good yields. Although excess sulfuryl chloride has to be applied (in a ratio of 4:1), no multiple chlorinated by-products (e.g. at the benzo ring) are observed.

2. Degradation of Hexahydropyrano[2',3':4,5]pyrido[3,2,1-*jk*]carbazole-5,8-dione 6. Substitution and Ring Closure Reactions at the 4- and 5-Positions of Tetrahydropyrido[3,2,1-*jk*]-carbazolone 9

4-Hydroxy-hexahydropyridocarbazolone **9** with an reactive unsubstituted position 5 at the enolized dicarbonyl moiety can serve for the synthetic approach to electrophilic substitutions. Its synthesis includes a 2-step degradation of pyrano-hexahydropyridocarbazoledione **6** and follows a well established route which we have applied in a series of heterocycles containing the structural element of 4-hydroxypyridone [18]. Best results in the ring opening are obtained when **6** is reacted with potassium hydroxide with glycol as the solvent because of a higher reaction temperature and short reaction time. Acidification of the basic reaction mixture with hydrochloric acid results in the formation of an aceto-acetic acid fragment as substituent. This intermediate decarboxylates spontaneously at elevated temperatures already in weak acidic media to give 5-acetyl-4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**8**) in good yields. The 5-acetyl group in **8** is removed in a smooth reaction with 90% sulfuric acid at 140°C by ipso-substitution and results in a good overall yield of highly pure 5-unsubstituted 4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido [3,2,1-*jk*]carbazol-6-one (**9**) after all 3 steps.

A nucleophilic halogen introduction at position 4 was carried out with phosphoryl chloride by exchange of the 4-hydroxy group. 5-Unsubstituted tetrahydropyridocarbazolone **9** is chlorinated in this way and gives 4-chloro-11a-methyl-7a,8,9,10,11,11a-hexahydropyrido[3,2,1-*jk*]carbazol-6-one (**10**) in moderate yield. Azidation of **10** at position 4 can be performed in ethanol/water at reflux temperature without by-products and gives 4-azido-11a-methyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (**11**) in moderate yields (Scheme 3).

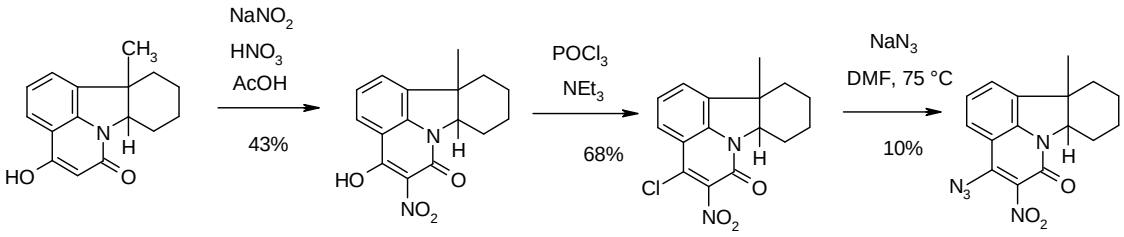
Scheme 3



6 **8** **9** **10** **11**

Nitration of hexahydropyridocarbazole **9** with nitric acid catalyzed by a small amount of sodium nitrite gives pure 4-hydroxy-11a-methyl-5-nitro-7a,8,9,10,11,11a-hexahydropyrido[3,2,1-*jk*] carbazol-6-one (**12**) in moderate yields without side reactions by attack at the benzo part of the molecule (Scheme 4).

Scheme 4

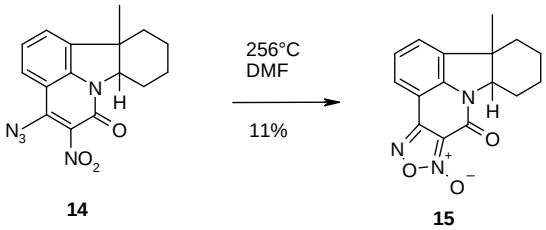


A halogenation reaction of 5-nitro-hexahydropyridocarbazole **12** similar as described for **10** with phosphoryl chloride at position 4 by exchange of the hydroxy group does not work. It was found that the reaction needs first the cleavage of the hydrogen bonding between the hydroxy and the nitro group which hinders the attack of phosphoryl chloride. Addition of triethylamine during the chlorination cleaves the hydrogen bonding and leads in good yields to 4-chloro-5-nitro-hexahydropyrido-carbazolone **13**. The exchange of the chloro against an azido group forms 4-azido-5-nitro compound **14** in moderate yields (Scheme 4).

3. Thermal Ring Closure Reaction of 4-Azido-5-nitro-tetrahydropyrido[3,2,1-*jk*]carbazolone 14 to Hexahydro-oxadiazolo[3',4':4,5]pyrido[3,2,1-*jk*] carbazol-6-oxide 15.

In the last years we investigated a series of cyclization reactions of azides with reactive ortho-substituents [19-22]. The conditions for the thermolysis reaction of 4-azido derivative **14** was investigated by differential scanning calorimetry (DSC) to obtain the information on the cyclization temperature to obtain the planned furoxane **15** and get information for possible further decomposition reactions. The DSC diagram of azide **14** shows a reaction range with 147.9 °C onset and 179.7 °C maximum, which allows to use dimethylformamide at reflux temperature as the suitable cyclization solvent. The introduction of the azido group into chloro derivative **13** to get the azido derivative **14** must be carried out below 75°C, to avoid partial decomposition to furoxane **15** visible in the TLC analysis. In the synthetic experiment, cyclization from **14** to **15** was carried out in boiling dimethylformamide and gives 12a-methyl-7-oxo-8a,9,10,11,12,12a-hexahydro-7*H*-[1,2,5]oxadiazolo[3',4':4,5]pyrido[3,2,1-*jk*] carbazol-6-oxide (**15**) in moderate yields (Scheme 5).

Scheme 5

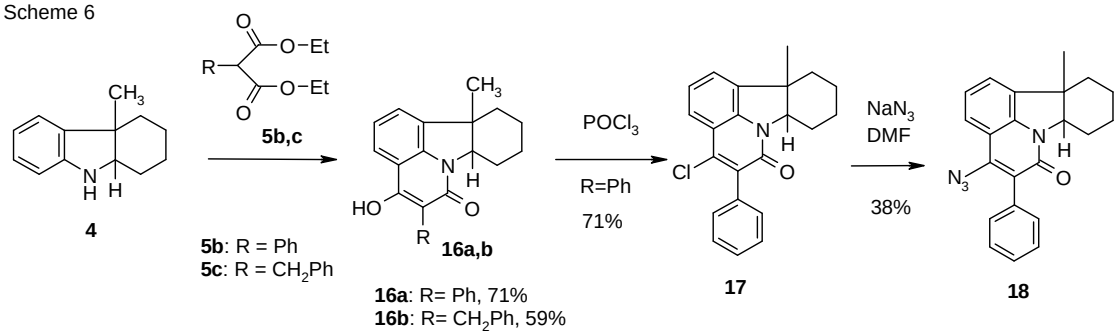


The reaction enthalpy in the formation of **15** is ΔH = -125 J/g, which is a rather high value, and must be taken into consideration when larger batches are thermolyzed. The structure of **15** is supported by IR data, which show that the azide signal of **14** at 2115 cm^{-1} is missing.

4. Cyclocondensation of Hexahydrocarbazole 4 with Substituted Malonates 5b,c to 5-phenylhexahydropyrido[3,2,1-*jk*]carbazolone 16a,b.
Halogenation and Azidation Reaction of 16a to 4-Chloro- and 4-Azido-5-phenylhexahydropyrido[3,2,1-*jk*]carbazolone 17 and 18.

The thermal cyclocondensation of hexahydrocarbazole **4** with diethyl phenylmalonate (**5b**) and diethyl benzylmalonate (**5c**) in boiling diphenylether as the solvent gives via reactive ketene intermediates [17] 4-hydroxy-hexahydropyridocarbazolones **16a,b**. The spectral analyses show that the ring closure was again directed to the aromatic ring, visible by the lack of the fourth aromatic proton from the carbazole part. In this way, 4-hydroxy-5-substituted-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*] carbazol-6-ones **16a,b** have been obtained in good yields (Scheme 6).

Scheme 6



Chlorination of 4-hydroxy-5-phenyl-hexahydropyridocarbazolone **16a** with phosphoryl chloride gives by exchange of the 4-hydroxy group without catalyst in good yields 4-chloro5-phenyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (**17**). Azidation at position 4 is performed in dimethylformamide at 90°C without by-products and gives 4-azido-5-phenyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (**18**) in moderate yields.

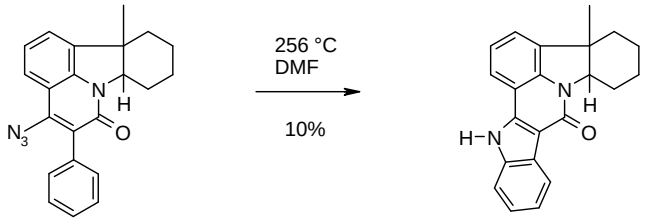
4. Ring Closure Reaction of 4-Azido-5-phenylhexahydropyrido[3,2,1-*jk*]carbazolone 18 to Hexahydroindolo[2',3':4,5]pyrido[3,2,1-*jk*]carbazolone 19.

The conditions of the ring closure reaction of the 4-azido derivative **18** were investigated by differential scanning calorimetry (DSC) to obtain the information on the cyclization temperature from azide **18** to 3b-methyl-3b,4,5,6,7,7a-hexahydroindolo[2',3':4,5]pyrido[3,2,1-*jk*]carbazol-9(14*H*)-one (**19**) and possible further decomposition reactions (Scheme 7).

The DSC diagram of 4-azido-hexahydropyridocarbazolone **18** shows a cyclization range with 241.2°C onset and 241.8°C peak maximum, which allows to use dimethylformamide at reflux temperature as the suitable cyclization solvent. The reaction enthalpy in the formation of **19** is ΔH = -15.1 J/g which is rather low. At 246.3°C a melting point of the azide **18** is observed, which is identical with the melting

point data obtained from the cyclized indolo-pyridocarbazolone **19** (246.3°C). The structure of **19** is supported by IR data, which show that the azide signal of **18** at 2111 cm^{-1} disappeared.

Scheme 7



18 **19**

Conclusion

This investigation shows that the reduction of tetrahydrocarbazole **3** with sodium borohydride leads in good yields to hexahydrocarbazole **4**. Cyclocondensation of **4** with diethyl malonate (**5a**) results in the formation of hexahydropyrano-pyridocarbazoledione **6** which was ring-opened to 5-acetyl derivatives **7** and **8**.

Removal of the acetyl group in **8** produced 5-unsubstituted 4-hydroxy-hexahydropyridocarbazolone **9**, which gave in an electrophilic nitration the 5-nitro derivative **12.** Nucleophilic chlorination of **12** gives 4-chloro derivative **13** and subsequent azidation leads to 4-azido-5-nitro-hexahydropyridocarbazolone **14**, which cyclized under thermal conditions to the furoxane **15**. The thermolytical conditions were investigated by differential scanning calorimetry (DSC).

Cyclocondensation of **4** with aryl- or alkylmalonates (**5b**,**c**) resulted in the formation of 5-alkyl- or aryl-hexahydropyridocarbazolones **16a,b.** Halogenation of **16a** with phosphoryl chloride gave 4-chloro derivative **17** and subsequent azidation leads to 4-azido-5-phenyl-hexahydropyridocarbazolone **18.** Thermal cyclization of the azide **18** was investigated by differential scanning calorimetry (DSC) and allowed the synthesis of hexahydro-indolo-pyridocarbazolone **19** under suitable conditions obtained from DSC data.

Methods and Experimental

General

Melting points were determined using a Stuart SMP3 Melting Point Apparatus (Bibby Scientific Limited, Stone, Staffordshire, UK) in open capillary tubes. Calorimetric data were obtained on a Perkin Elmer Pyris 1 DSC instrument with the Pyris Software for Windows (Pyris Thermal Analysis System) V3.72. The differential scanning calorimetry plots were recorded between 25-600°C, with a heating rate of 2-10°C/min, and 1.5-3 mg compound in sealed aluminium crucibles (11 bar). Infrared spectra were taken on a Bruker Alpha–P instrument (Bruker GmbH, Karlsruhe, Germany), with Attenuated Total Reflectance (ATR) measurement, using a reflexion method. NMR spectra were recorded on a Bruker Avance III instrument (300 MHz ^{1}H). Chemical shifts are

given in ppm (δ) from the internal TMS standard. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria, and are within ±0.4 of the theoretical percentages. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (Agilent Technologies, Santa Clara, CA, USA) with either positive or negative atmospheric pressure chemical ionization (APCI) ion source, 50–200 V, nitrogen. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 µm) column, running in acetonitrile/water gradient (30-100% acetonitrile). Dry column flash chromatography [23] was carried out on silica gel 60 H (5-40 µm) (Merck, Darmstadt, Germany). All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F 254 plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

4a-Methyl-2,3,3,4a-tetrahydro-1*H*-carbazole (3): A suspension of phenylhydrazinium chloride (**1)** (90.0 g, 0.62 mol) in glacial acetic acid (400 mL) was warmed to 50°C. To this suspension, a solution of 2-methylcyclohexanone **2** (70.0 g, 0.62 mol) in glacial acetic acid (110 mL) was added dropwise under stirring which caused boiling because of the strong exotherm reaction. After the addition, the mixture was heated under reflux for further 2 hours and then cooled to room temperature. The solvent was removed under reduced pressure, the residue diluted with water (200 mL) and then 2 *M* aq. sodium hydroxide solution was added to the residue until an alkaline pH was reached. The product was extracted with diethyl ether (200 mL), the organic phase dried with sodium sulfate, filtered and the solvent removed at the rotary evaporator. The residue was distilled under reduced pressure to get a light yellow oil at 154-158°C / 19-20 mm Hg.; lit. bp 158°C/20 mm Hg [15]. On addition of hexane, the oil crystallized. The yield was 49.17 g (43%); colorless prisms, mp 68°C (hexane) lit. mp 69°C [15]. IR: 3042 w, 2931 m, b, 1612 w, 1575 s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20 (m, 1 H, 3-$CH_{2(ax)}$), 1.30 (s, 3 H, Me), 1.40-1.55 (m, 1 H, 3-$CH_{2(eq)}$), 1.65-1.95 (m, 2 H, 2-H), 2.10-2.30 (m, 2 H, 4-CH_2), 2.50-2.70 (m, 1 H, 1-$CH_{2(ax)}$), 2.80-2.95 (m, 1 H, 1-$CH_{2(eq)}$), 7.15-7.35 (m, 3 H, ArH), 7.60 (d, J = 7 Hz, 1 H, ArH). Anal. calcd for $C_{13}H_{15}N$ (185.27): C, 84.28; H, 8.16; N, 7.56. Found: C, 83.81; H, 8.36; N, 7.66.

4a-Methyl-2,3,4,4a,9a-hexahydro-1*H*-carbazole (4): A solution of tetrahydrocarbazole **3** (41.4 g, 0.26 mol) in 80% methanol-water (150 mL) was cooled to 0°C. Then sodium borohydride (5.3 g, 0.14 mol) was added in small portions and the temperature of the mixture was kept between 0-10°C. The reaction mixture was stirred at 5°C for 10 hours, then it was heated under reflux for further 3 hours and then cooled to room temperature. The solvent was removed in the rotary evaporator, the yellow oily residue diluted with water (50 mL) and made alkaline by addition of 2 *M* aq. sodium hydroxide solution. The product was extracted with diethyl ether, dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was distilled to afford a light yellow oil [15]. The yield was 31.45 g (75%) light yellow oil, bp 118°C/19 mm Hg. IR**:** 3362 s, 3030-3050 m, 2920 s,b, 2851 s, 1612 s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 3 H, Me), 1.38-1.82 (m, 8 H, 1-CH_2, 2-CH_2, 3-CH_2, 4-CH_2), 3.45 (t, J = 7.0 Hz, 1 H, 9a-H), 3.70 (s, b, 1 H, NH), 6.65-7.15 (m, 4 H, ArH). Anal. calcd for $C_{13}H_{17}N$ (187.29): C, 83.37; H, 9.15; N, 7.48. Found: C, 83.59; H, 8.97; N, 7.32.

7-Hydroxy-13a-methyl-9a,10,11,12,13,13a-hexahydro-5*H*,8*H*-pyrano[2',3':4,5] pyrido[3,2,1-*jk*]carbazole-5,8-dione (**6):** A mixture of hexahydrocarbazole **4** (15.0 g, 80 mmol), diethyl malonate (**5a**) (38.5 g, 240 mmol) and diphenyl ether (10.0 g) was heated in a 2-necked flask equipped with a distillation bridge and a 20 cm Vigreux column. Liberation of ethanol starts at about 180°C. The temperature was raised to 200°C internal temperature and kept there for 6 hours. Then the temperature was raised to 210°C and kept there until no more ethanol was formed (about 3 hours). The reaction mixture was then cooled to approx. 40°C and triturated with diethyl ether (100 mL). The resulting solid was filtered by suction, washed with diethyl ether and dried under reduced pressure at 40°C. The yield was 18.13 g (70%), yellowish prisms, mp 205°C (1-butanol). IR: 2931 w, 1736 s, 1672 s, 1561 s cm^{-1}. ^1H NMR ($CDCl_3$)**:** δ 1.35 (s, 3 H, Me), 1.40-2.43 (m, 8 H, 10-CH_2, 11-CH_2, 12-CH_2, 13-CH_2), 4.65 (t, J = 7.0 Hz, 1 H, 9a-H), 5.68 (s, 1 H, 6-H) 7.35-7.50 (m, 2 H, 1-H, 2-H), 7.98 (dd, J = 7.0+1.0 Hz, 1 H, 3-H), 13.22 (s, 1 H, OH). Anal. calcd for $C_{19}H_{17}NO_4$ (323.35): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.69; H, 5.20; N, 4.21.

Syntheses, Substitution and Cyclization Reactions of 7a,8,9,10,11,11a-Hexahydro-pyrido[3,2,1-jk]carbazoles With a Strychnos Alkaloids Partial Structure

5-(2,2-Dichloroacetyl)-4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**7**): To a suspension of pyrano-pyridocarbazoledione **6** (4.45 g, 13.8 mmol) in dioxane (30 mL), sulfuryl chloride (7.56 g = 4.5 mL, 56 mmol) was added portionwise under stirring, while the temperature was kept below 50°C. After about 10 minutes the mixture was heated to boil for 5 minutes, then poured onto crushed ice/ water (400 mL). The mixture was stirred for 4 hours, the obtained solid filtered by suction, washed with water until neutral and dried under reduced pressure at room temperature. The yield was 3.15 g (63%), yellowish prisms, mp 97°C (glacial acetic acid). IR: 3032 w, 2943 b, 1641 s, 1615 s, 1551 m cm^{-1} . ^{1}H-NMR($CDCl_3$): δ 1.30 (s, 3 H, Me), 1.35-2.40 (m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.50 (t, J = 7.0 Hz, 1 H, H-7a), 7.18-7.46 (m, 2 H, 1-H, 2-H), 7.85 (dd, J = 7.0+1.0 Hz, 1 H, 3-H), 8.05 (s, 1 H, $CHCl_2$), 15.50 (s, 1 H, OH). Anal. calcd for $C_{18}H_{17}Cl_2NO_3$ (366.25): C, 59.03; H, 4.68; N, 3.82. Found: C, 58.82; H, 4.43; N, 3.72.

5-Acetyl-4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**8**): To a suspension of pyrano-pyridocarbazoledione **6** (6.47 g, 20 mmol) in 1,2-ethanediol (50 mL), sodium hydroxide (4.4 g in 20 mL of water) was added. The reaction mixture was heated under reflux for 1.5 hours, then poured onto ice/water (300 mL), and slowly acidified with concentrated hydrochloric acid**.** The obtained precipitate was filtered by suction, washed with water (100 mL) and dried under reduced pressure at 40°C. The yield was 4.23 g (71%) beige prisms, mp 107°C (glacial acetic acid). IR: 2922 m, 2845 w, 1655 sh, 1645 s, 1611 m, 1551 m cm^{-1} . ^{1}H NMR($CDCl_3$): δ 1.25 (s, 3 H, Me), 1.30-2.40 (m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 2.82 (s, 3 H, COMe), 4.45 (t, J = 7.0 Hz, 1 H, 7a-H), 7.10-7.45 (m, 2 H, 1-H, 2-H), 7.80 (dd, J = 7.0+1.0 Hz, 1 H, 3-H). Anal. calcd for $C_{18}H_{19}NO_3$ (297.36): C, 72.71; H, 6.44; N, 4.71. Found C, 72.54; H, 6.58; N, 4.66.

4-Hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**9**): A solution of 5-acetyl-pyridocarbazolone **8** (3.60 g, 12 mmol) in 90% sulfuric acid (10 mL) was heated for 10 minutes to 135°C. Then the solution was poured onto ice/water (300 mL) and allowed to stand for 12 hours at room temperature. The precipitate was filtered by suction, washed with water (3x 50 mL) and dried under reduced pressure at 40°C. The yield was 2.05 g (66%), colorless prisms, mp 271°C (dimethylformamide). IR: 2960-2920 m,b, 1644 s, 1626 s, 1591 s cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.22 (s, 3 H, Me), 1.30-2.10 (m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.30 (t, J = 7.0 Hz, 1 H, 7a-H), 5.75 (s, 1 H, 5-H), 7.15 (m, 1 H, 1-H), 7.37 (dd, J = 7.0+1.0 Hz, 1 H, 2-H), 7.52 (dd, J = 7.0+1.0 Hz, 1 H, 3-H), 11.27 (s, OH). Anal. calcd for $C_{16}H_{17}NO_2$ (255.32): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.15; H, 6.74; N, 5.55.

4-Chloro-11a-methyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (10): A solution of 4-hydroxy-pyridocarbazolone **9** (1.40 g, 5.5 mmol) in phosphoryl chloride (7 mL) was heated under reflux for 10 hours. After cooling, the reaction mixture was poured onto ice/water (600 mL) and brought to pH = 4-6 with 2 *M* aq. sodium hydroxide solution. The obtained solid was filtered by suction, washed with hexane and dried under reduced pressure at 40 °C. The yield was 0.374 g (25%), grey prisms, mp 268 °C (ethanol). IR: 2930 m, 2863 w, 1735 w, 1611 s, 1601 s, 1543 w cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 3 H, Me), 1.63-1.71 and 2.06-2.33 (2 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.58-4.63 (t, J = 7.0 Hz, 1 H, 7a-H), 5.65 (s, 1 H, 5-H), 7.34-7.44 and 7.67-7.92 (2 m, 2 H, 1-H, 2-H), 8.39 (dd, J = 1.00 + 7.00 Hz, 1 H, 3-H). MS (APCI pos): m/z (%) = 276 (M+3, 30), 274 (M+1, 100). Anal. calcd for $C_{16}H_{16}ClNO$ (273.77): C, 70.20; H, 5.89; Cl, 12.95, N, 5.12. Found: C, 70.51; H, 5.97; Cl, 12.55, N, 4.93.

4-Azido-11a-methyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (11):
To a solution of 4-chloro-pyridocarbazolone **10** (0.100 g, 0.42 mmol) in ethanol (4 mL) and water (0.25 mL), sodium azide (0.17 g, 2.6 mmol) was added and the resulting mixture was heated under reflux for 3.5 hours. The end of the reaction was detected by tlc control. Insoluble inorganic material was removed by hot filtration and the solution poured onto ice/water (70 mL). The mixture was allowed to stand for 12 hours , filtered by suction, washed with water (50 mL) and dried under reduced pressure at 30°C. The yield was 0.030 g (29%), black prisms**,** mp 155°C dec. (ethanol). IR: 2929 m, 2862 w, 2121 m, 1711 w, 1646 s, 1602 s, 1559 sh, 1542 m cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3 H, Me), 1.41-1.64 and 2.07-2.29 (2 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.52-4.60 (m, 1 H, 7a-H), 5.36 (s, 1 H, 5-H), 7.32-7.97 (m, 2 H, 1-H, 2-H), 8.20-8.31 (m, 1 H, 3-H). Anal. calcd for $C_{16}H_{16}N_4O$ (280.33): C, 68.55; H, 5.75; N, 19.99, Found: C, 68.91; H, 5.94; N, 19.67.

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4-Hydroxy-11a-methyl-5-nitro-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*] carbazol-6-one (12): To a solution of 4-hydroxy-pyridocarbazolone **9** (1.50 g, 6 mmol) in glacial acetic acid (50 mL), concentrated nitric acid (4.0 mL, 60 mmol) was slowly added at room temperature. Then sodium nitrite (0.25 g, 3.6 mmol) was added as a catalyst. The mixture was stirred for 2.5 hours at 20°C, then poured onto ice/water (150 mL), the mixture stirred for 2 hours, and the precipitated solid filtered by suction. The product was washed with water (3x 20 mL) until acid-free (pH=6) and dried under reduced pressure at 40 °C. The yield was 0.75 g (43%), mp 137 °C, followed by dec. at 146°C, yellow prisms (ethanol). IR: 2931 m, 2864 w, 1754 m, 1666 s, 1614 s, 1559 s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, 3 H, Me), 1.39-1.46, 1.69-1.78, 1.89-2.05 and 2.13-2.35 (4 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.69 (t, J = 7.0 Hz, 1 H, 7a-H), 7.46-7.61 (m, 2 H, 1-H, 2-H), 7.88-7.97 and 8.02 (dd, J = 1.0 and 7.0 Hz, 1 H, 3-H), 13.87 (s, OH). MS (APCI pos): m/z (%) = 302 (M+2, 25), 301 (M+1, 100), 283 (15). Anal. calcd for $C_{16}H_{16}N_2O_4$ (300.31): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.83; H, 4.99; N, 9.07.

4-Chloro-11a-methyl-5-nitro-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (13): 4-Hydroxy-5-nitro-pyridocarbazolone **12** (0.25 g, 0.8 mmol) was dissolved in phosphoryl chloride (4 mL) and then triethylamine (0.25 mL) was added dropwise. The mixture was heated under reflux for 2 hours, then cooled to room temperature and poured onto ice/water (100 mL). The mixture was brought to pH = 4-6 with 2 *M* aq. sodium hydroxide solution and kept for 12 hours at 20°C. The formed solid was filtered by suction, washed with water and dried under reduced pressure at 40 °C. The yield was 0.18 g (68 %), black prisms, mp 93°C (dec) (ethanol). IR: 2933 m, 2865 w, 1758 m, 1661 s, 1611 m, 1540 s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, 3 H, Me), 1.39-1.49, 1.63-1.69, 1.71-2.08 and 2.10-2.37 (4 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.62 (t, J = 7.0 Hz, 1 H, 7a-H), 7.37-7.60 and 7.75-7.78 (2 m, 2 H, 1-H, 2-H), 7.96 (dd, J = 1.0 and 7.0 Hz, 1 H, 3-H). MS (APCI pos): m/z (%) = 321 (M+3, 32, 319 (M+1, 100), 301 (42), 296 (25), 256 (20). Anal. calcd for $C_{16}H_{15}ClN_2O_3$ (318.76): C, 60.29; H, 4.74; N, 8.79. Found: C, 59.93; H, 4,40; N, 9.08.

4-Azido-11a-methyl-5-nitro-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (14): To a solution of 4-chloro-pyridocarbazolone **13** (0.10 g, 0.30 mmol) in dimethylformamide (4 mL), sodium azide (0.5 g, 7.7 mmol) was added and the mixture heated to 75 °C under stirring for about 10 hours. The end of the reaction was detected by tlc check. The mixture was cooled to room temperature, poured onto ice/water (30 mL) and kept for 12 hours at 20°C. The solid was filtered by suction, washed with water (30 mL) and dried under reduced pressure at 30°C. The yield was 0.010 g (10%), black prisms**,** mp 180°C dec (ethanol). Calorimetric data for the thermolysis: reaction onset 147.9 °C, peak maximum 179.7 °C, ΔH = -125 J/g. IR: 2922 s, 2853 m, 2115 w, 1729 sh, 1642 m, 1603 s cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.23 (s, 3 H, Me), 1.27-1.49, 1.51-1.71, 2.01-2.12 and 2.73-2.89 (4 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.30-4.50 (m, 1 H, 7a-H), 7.17-7.31 and 7.39-7.57 (2 m, 2 H, 1-H, 2-H), 7.70-7.75 and 7.90-8.25 (m, 1 H, 3-H). Anal. calcd for $C_{16}H_{15}N_5O_3$ (325.33): C, 59.07; H, 4.65; N, 21.53. Found: C, 59.34; H, 4.43; N, 21.15.

12a-Methyl-7-oxo-8a,9,10,11,12,12a-hexahydro-7*H*-[1,2,5]oxadiazolo[3',4':4,5]pyrido[3,2,1-*jk*] carbazol-6-oxide (15): A solution of 4-azidopyridocarbazolone **14** (10 mg, 0.034 mmol) in dimethylformamide (2 mL) was heated under reflux for 2 h. After cooling to room temperature, the mixture was poured onto crushed ice/water (20 mL). The formed solid was filtered by suction, washed with water and dried. The yield was 1.0 mg (11%), brown powder, mp 263°C (methanol). Calorimetric data for the thermolysis: mp onset 255.2 °C, peak maximum 262.5 °C, ΔH =3.0 J/g. IR: 2951 m, 1695 s, 1652 m, 1611 s, 1595 s cm^{-1}.

4-Hydroxy-11a-methyl-5-phenyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (16a): A mixture of hexahydrocarbazole **4** (3.75 g, 20 mmol) and diethyl phenylmalonate (**5b**) (4.73 g, 20 mmol) in diphenyl ether (5 mL) was heated in a 2-necked flask with a 20 cm Vigreux column and a distillation bridge to 220°C. The mixture was kept at this temperature for 1 hour, then the temperature was raised for about 20 minutes to 230°C, until no more ethanol was liberated. The mixture was then cooled to room temperature, laced with diethyl ether (100 mL), the formed precipitate filtered by suction and washed with hexane. The yield was 4.71 g (71%), colorless prisms, mp 224°C (1-butanol). IR: 2920 b, m, 2861 w, 1632 s, 1585 b,s cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.30 (s, 3 H, Me), 1.35-2.25 (m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.41 (t, J = 7.0 Hz, 1 H, 7a-H), 7.10-7.50 (m, 2 H, 1-H, 2-H), 7.40 (s, 5 H, Ph), 7.80 (dd, J = 7.0+1.0 Hz, 1 H, 3-H). Anal. calcd for $C_{22}H_{21}NO_2$ (331.42): C, 79.73; H, 6.39; N, 4.23. Found: C, 79.47; H, 6.35; N, 4.05.

5-Benzyl-4-hydroxy-11a-methyl-7a,8,9,10,11,11a-hexahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (**16b**): This compound was obtained from hexahydrocarbazole **4** (4.00 g, 21 mmol) and diethyl benzylmalonate (5.30 g, 21 mmol) using the procedure and work-up described for **16a**. The yield was 4.35 g (59%), colorless prisms, mp 185°C (1-butanol). IR: 2920 b, 2860 w, 1635 m, 1585 s, b cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.27 (s, 3 H, Me), 1.30-2.20 (m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 3.90 (s, 2 H, benzyl-CH_2), 4.35 (t, J = 7.0 Hz, 1 H, H-7a), 7.05-7.40 (m, 7 H, 1-H, 2-H, Ph), 7.75 (dd, J = 7.0+1.0 Hz, 1 H, 3-H). Anal. calcd for $C_{23}H_{23}NO_2$ (345.45): C, 79.97; H, 6.71; N, 4.05. Found: C, 79.87; H, 6.76; N, 3.98.

4-Chloro-11a-methyl-5-phenyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*] carbazol-6-one (17): A mixture of 2-phenyl-pyridocarbazolone **16a** (1.01 g, 3 mmol) and phosphoryl chloride (10 mL) was heated under reflux for 4 hours. The resulting solution was poured onto ice/water (100 mL) and brought to pH = 4–6 with 2 *M* aqueous sodium hydroxide solution. The solid was filtered by suction, washed with water (3x10 mL) and dried under reduced pressure at 40°C. The yield was 0.75 g (71%), colorless prisms, mp 182°C (ethanol). IR: 3058 w, 2826 m, 2850 m, 1640 s, 1603 m, 1553 w cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 3 H, Me), 1.40-1.49, 1.62-1.75, 1,76-1.90, 2.06-2.14, 2.29-2.35 (5 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.59 (t, J = 7.0 Hz, 1 H, H-7a), 7.28-7.36, 7.40-7.52 (2 m, 7 H, 1-H, 2-H, Ph), 7.73-7.76 (dd, J = 7.0+1.5 Hz, 3-H). MS (APCI pos): m/z (%) = 352 (M+3, 28), 350 (M+1, 100), 282 (8), 268 (15). Anal. calcd for $C_{22}H_{20}ClNO$ (349.86): C, 75.53; H, 5.76; N, 4.00. Found: C, 75.86; H, 5.63; N, 3.72.

4-Azido-11a-methyl-5-phenyl-7a,8,9,10,11,11a-hexahydro-pyrido[3,2,1-*jk*]carbazol-6-one (18): To a solution of 4-chloro-5-phenyl-tetrahydropyridocarbazolone **17** (0.52 g, 1.5 mmol) in dimethylformamide (10 mL), sodium azide (0.25 g, 3.8 mmol) was added and the resulting mixture was heated to 90°C for 12 hours. The reaction mixture was then cooled to 20°C, poured onto ice/water (50 mL) and the formed solid filtered by suction. The precipitate was washed with water (3x10 mL) and dried for 12 hours under reduced pressure at 40°C. The yield was 0.20 g (38%), yellow prisms**,** mp. 73°C and dec. at 137°C (ethanol). Calorimetric data for the thermolysis: decomposition at 241.2°C onset, 241.8°C maximum, ΔH = -15.1 J/g; mp at 245.6°C onset, 246.3°C maximum, ΔH = 2.0 J/g. IR: 3056 w, 2927 m, 2860 w, 2111 s, 1640 s, 1604 m, 1553 m cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 3 H, Me), 1.43-1.45, 1.66-1.68, 1.80-1.82, 2.07-2.12, 2.29-2.35, 2.90-2.97 (6 m, 8 H, 8-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 4.57-4.61 (m, 1 H, H-7a), 7.19-7.33 and 7.45-7.48 (2 m, 7 H, 1-H, 2-H, Ph), 7.73-7.76 (dd, J = 7.0+1.5 Hz, 3-H). Anal. calcd for $C_{22}H_{20}N_4O$ (356.43): C, 74.14; H, 5.66; N, 15.72. Found: C, 74.51; H, 5.33; N, 15.35.

3b-Methyl-3b,4,5,6,7,7a-hexahydroindolo[2',3':4,5]pyrido[3,2,1-*jk*]carbazol-9(14*H*)-one (19): A solution of 4-azido-5-phenyl-tetrahydropyridocarbazolone (**18**) (170 mg, 0.5 mmol) in dimethylformamide (10 mL) was heated under reflux for 12 hours, then cooled to room temperature, poured onto ice/water (60 mL) and the mixture extracted with acetic acid. The solvent was concentrated to 5 mL, the product precipitaed with water (50 mL) and centrifuged. The yield was 16 mg (10%), yellow prisms, mp 236°C (dimethylformamide/ methanol). Calorimetric data for the thermolysis: mp at 245.0°C onset, 246.3°C maximum, ΔH = 3.0 J/g. IR: 3149 w, 3055 w, 2948 w, 2921 s, 2852 m, 1638 m, 1592 s, 1577 m cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.35 (s, 3 H, Me), 1.42-1.45, 1.66-1.82, 2.07-2.30 (3 m, 8 H, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 4.52-4.54 (m, 1 H, H-7a), 7.20-7.45 (m, 2 H, ArH), 7.56-7.63 (m, 2 H, ArH), 7.70-7.72 (d, J = 7.00 Hz, 1 H, ArH), 8.06 (s, 1 H, ArH), 8.23-8.26 (d, J = 7.0 Hz, 1 H, ArH), 12.62 (s, 1 H, NH). MS (APCI pos): m/z (%) = 330 (M+2, 6), 329 (M+1, 100). Anal. calcd for $C_{22}H_{20}N_2O$ (328.42): C, 80.46; H, 6.14; N, 8.53. Found: C, 80.79; H, 5.82; N, 8.21.

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