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Novel Pathway for the Synthesis of 20-Deethyltubifolidine

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Abstract*. A new and well planned approach has been accomplished for the total synthesis of 20-Deethyltubifolidine, which is effective for biological properties and fascinating molecules. This product embodies the ABCDE-ring system associated with the indole alkaloids. The synthesis was accomplished in six steps and produced a 38% yield.*

Keywords*: azocino[4,3-b]indole, 20-deethyltubifolidine, tetrchloro-1,4-benzoquinone, multi-step synthesis*

1.Introduction

20-Deethyltubifolidine and tubifolidine, which are parts of the five-membered 1,5-methano-azocino[4,3-*b*]indole form, are privileged structures that can be found in natural products endowed with important biological activities, such as anticancer [1,2], anti-malarial [3], and anti- HIV [4]. Permission is given to advanced research of their potential bioactivities. The compound of biological features and charming molecular structures have made chemists' attempts concentrate on the improvement of process for synthesizing such compounds. Accordingly, there have been numerous strategies for the construction of these compounds [5-8]. Even so, uncharted synthetic closings to this frame could very little ensure a precious origin for these kinds of the framework. The existence of the 1,5-methanoazocino[4,3-*b*]indole structure in another type of alkaloids has also led further progress of paths to this frame, which could be an advantageous exemplary for the access to key infrastructure and analogues of *Strychnos* alkaloids (Figure 1) [9,10]. These alkaloids constitute a key subgroup of the *Strychnos* alkaloids [11-20] and belong to moneterpenoid indole alkaloids, which are represented by the existence of the 1,5-methanoazocino[4,3-*b*] indole, including the tetracyclic ring system. Our aim to synthesize deethyltubifolidine is predicated on the structure of a 1,5-methanoazocino[4,3-*b*] indole skeleton, the basic component of deethyltubifolidine and other type alkaloids, by recognizing tetrahydrocarbazole analogues transporting a monoalkyl nitrile side chain (**1**) with tetrachloro-1,4-benzoquinone (TCB) [21-26]. Accordingly, we determined to look for a briefer and more effective direction to tetrahydrocarbazole with a monoalkyl nitrile side chain at the C-2 position; this reaction was mediated by tetrachloro-1,4-benzoquinone (TCB). This synthetic methodology will ensure inherent virtues with the accomplishment of our new cyclization reaction such a higher atom economy and shorter synthetic routes.

This kind of method has never been implemented in the synthesis of *Strychnos* alkaloids The complex structures of such *Strychnos* alkaloids generated a challenge thus the research on the total syntheses of these compounds has been in a constant attempt in the synthetic organic chemistry community [27, 28].

We previously reported the synthesis of the tetracyclic 1,5-methanoazocino[4,3-*b*] indole derivatives via the cyclization-mediated 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [29,30], the acid-catalyzed [31], and the intramolecular aldol reaction [32]. Accordingly, numerous strategies have been reported for the construction of this type of alkaloid [33-36]. We demonstrate an alternative synthetic entry to the tetracyclic indole alkaloids from the 20-Deethyltubifolidine group for the purpose of this study. [37,38]. We describe a valuable way to the syntheses of deethyltubifolidine. The effective structure of the cyclization substrates is critical for the achievement of our synthetic plan.

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For this purpose, this protocol could be a beneficial primer to the divergent synthesis of *Strychnos*-type alkaloids. Besides, it is remarkable that we can prepare tetracyclic 1,5-methanoazocino[4,3-*b*] indole **3** to produce an 85% overall yield. In the way that shown in Scheme 1, our plan for coalescing of this pentacyclic scheme depends on the closing of the amine by cyclization with TCB and an effective route to the synthesis of deethyltubifolidine. This kind of method has never been implemented in the synthesis of 20-Deethyltubifolidine.

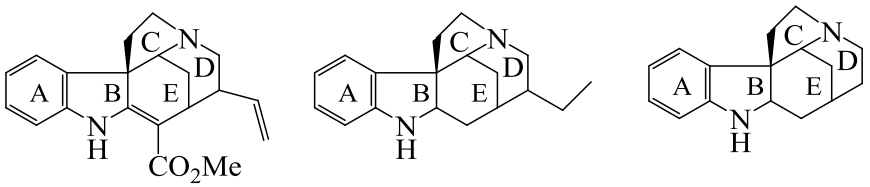


Figure 1. Selected *Strychnos* alkaloids containing 1,5-methanoazocino[4,3-*b*]indole core

2. Materials and methods

Bruker DPX-400 MHz High Performance Digital FT-NMR Spectrometer was used to record in $CDCl_3$ the NMR spectra at the region of 400 MHz (^1H) and in 100 MHz (^{13}C) relative to tetra-methylsilane (TMS) at 25°C. Parts per million (δ) is used to define chemical shifts and Hz is used to describe the coupling constants. Mattson 1000 FT-IR spectrometer was used to record the IR spectra by using KBr pellets. The melting points of the samples were detected by using the Capillary tubes on a Gallenkamp apparatus and were left faulty. Thin-Layer chromatography (silica gel 60 F254) was used to the monitoring of all reactions. Reagents were supplied from Sigma-Aldrich and used as received without further purification. The elemental analyses of all samples were implemented by A Costech ECS 4010 analyzer.

2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl) ethaneamine (2)

1.8 mL (19.0 mmol) of 1M borane was added into a solution mixture of nitrile (**1)** (4.0 g, 19.0 mmol), in anhydrous THF (100 mL). THF with the help of a syringe under a nitrogen atmosphere at rt, and the reaction mixture was processed as being heated at reflux for 6 h, cooled and treated with methanol (10 mL). The temperature was lowered to 25 ^{0}C, and the solvent was vaporized *in vacuo* and the remainder was processed with heating at reflux with 10% HCl (20 mL) for 4 h, filtrated and the filtration was performed by alkaline (*p*H = 12.0) with 10% aqueous NaOH. Ethyl acetate (3 X 100 mL) was used to help extract the mixture and the compounded organic extracts were segregated and dried over anhydrous $MgSO_4$ and concentrated to give oil. The residue content was enriched by using column chromatography furnished 3.6 g of amine (**3**) as a yellow oil, TLC: R_f 0.6 (dichloromethane), yield: 88%. IR (KBr): 2997, 3.28, 2922, 2841, 2251, 1478, 1451, 1267, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.31 (d, 1H, *J* = 8.4 Hz),7.21 (d, 1H, *J* = 8.4 Hz), 6.93- 6.87 (m, 2H), 2.86- 2.69 (m, 4H), 2.60- 2.51 (m, 1H), 2.46-2.31 (m, 1H), 2.11-1.93 (m, 2H), 1.50-1.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 137.6, 135.9, 127.5, 121.8, 118.7, 119.2, 112.5, 108.3, 42.6, 42.1, 33.5, 31.6, 30.1, 23.2; Anal. of $C_{14}H_{18}N_2$, calc: C 78.46%, H 8.47%, N 13.07%, found C 78.35%, H 8.67%, N 13.21%.

1,2,3,4,5,6,7-Hexahydro-1,5-methanoazocino[4,3-b] indole (3)

5.7 g (23.25 mmol) of TCB in one portion at rt was added into a solution mixture of amine (2) (2.0 g, 9.3 mmol), in anhydrous THF (50 mL), and this content was mixed at rt for 10 h. Before the mixture was extracted (2 x50 mL), the reaction mixture was poured into NaOH solution (10%, 50 mL). The compounded organic layers were dried on $MgSO_4$ (anhydrous). After the solvent was got away, the

remainder of the content was purified by silica gel chromatography by eluting with dichloro-methane-triethylamine (5:1) to give 1.9 g of a pale-yellow foam (**3**), TLC: R_f 0.76 (EtOAc), yield: 96%. IR (KBr): 3387, 3214, 3021, 2936, 1613, 1532, 1449, 1413, 1358, 1301, 1266, 1238, 1191, 1058, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.44 (d, 1H, *J* = 7.8 Hz), 7.34 (d, 1H, *J* = 8.1 Hz), 7.05 (t, 1H, *J* = 7.3 Hz),6.95 (t, 1H, *J* = 7.3 Hz), 4.38-4.24 (m, 1H), 3.22 (dd, 1H, *J* = 16.8, 6.3 Hz), 2.71 (d, 1H, *J* = 16.8 Hz), 2.63-2.51 (m, 2H), 2.42-2.36 (m, 1H), 2.22 (dt, 1H, *J* = 12.3, 3.1 Hz), 1.94-1.87 (m, 2H), 1.61-1.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 137.1, 136.8, 125.3, 122.3, 119.3, 118.8, 110.7, 109.2, 44.3, 38.9, 33.5, 33.0, 29.3, 27.5; Anal. of $C_{14}H_{16}N_2$, calc: C 79.21%, H 7.60%, N 13.20%, found C 78.87%, H 7.66%, N 13.11%.

2,2,2-trichloro-1-(1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b] indol-2-yl)ethan-1-one (4)

Triethylamine (1.4 g, 14.0 mmol) and trichloroacetyl chloride (2.5 g, 14.0 mmol) were added into a solution mixture of azocino[4,3-*b*] indol (**3**) (1.5 g, 7.0 mmol) in chloroform at 0 ^0C. The reaction was permitted to rt and mixed for an extra 9 h. Upon extraction with 10% sodium hydroxide (3 X 30 mL), the content was dried on anhydrous $MgSO_4$, treated in concentration process *in vacuo*, then subjected to purification by column chromatography to give 2.3 gr of **4** as a white solid, TLC: R_f 0.81 (EtOAc), yield: 91%, m.p.: 218-220 ^0C. IR (KBr): 3271, 2957, 1658, 1452, 1211, 811, 649, 618, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.51 (s, 1H), 7.77 (d, 1H, , *J* = 8.1 Hz), 7.48 (dt, 1H, *J* = 8.3 Hz), 7.41 (d, 1H, *J* = 7.8 Hz), 7.21 (d, 1H, *J* = 8.1 Hz), 4.68 (t, 1H, *J* = 5.2 Hz), 3.19 (dd, 1H, *J* = 17.2, 6.3 Hz), 2.65 (d, 1H, *J* = 17.2 Hz), 2.62- 2.56 (m, 2H), 2.38-2.24 (m, 1H), 2.12 (dt, 1H, *J* = 12.2, 3.3 Hz), 2.02-1.91 (m, 2H), 1.69 – 1.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 159.6, 137.6, 134.1, 126.7, 123.7, 123.2, 121.8, 121.3, 112.5, 93.2, 44.8, 38.1, 33.7, 33.1, 28.7, 27.2;

Anal. of $C_{16}H_{15}Cl_3N_2O$, calc: C 55.73%, H 4.23%, N 7.83%, found C 55.58%, H 4.35%, N 7.71%.

(11bS)-1,1-dichloro-3a,4,5,6-tetrahydro-3,5-ethanopyrrolo[2,3-d]carbazole-2(1H)-one (5)

Copper(I)chloride (1.0 g, 10. 5 mmol) and TBTA (5.6 g, 10.5 mmol) under a nitrogen atmosphere were added into a solution mixture of trichloroacetamide (**4**) (1.5 g, 4.2 mmol) in acetonitrile (50 mL).

The mixture was mixed for 30 min at rt after that, the resulting suspension was processed with heating up to 55^0C and mixed for 2 h. TLC (EtOAc) was used to monitor how the progress of the reaction was. The reaction was permitted to warm to rt, filtered by means of a sintered funnel and concentrated *in vacuo*. The residue content was dried, filtred and purified by using silica gel chromatography (*n*-hexane: ethyl acetate, 1:7) to give 1.1 gr of **5** as an oil. TLC: R_f 0.88 (*n*-hexane), yield: 81%. IR (KBr): 2951, 2853, 1657, 1452, 1377, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, 1H, *J* = 7.7 Hz), 7.34 (d, 1H, *J* = 7.4 Hz), 7.34-7.29 (m, 2H), 4.63 (dd, 1H, *J* = 11.2, 5.6 Hz), 3.41 (dd, 1H, *J* = 5.2 Hz), 3.30-3.19 (m, 1H), 3.08-2.83 (m, 2H), 2.47-2.33 (m, 1H), 2.11-1-95 (m, 2H), 1.58-1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 189.4, 164.8, 151.3, 130.9, 130.2, 127.4, 126.3, 122.1, 82.6, 75.2, 55.8, 45.5, 31.3, 30.5, 28.7, 26.3; Anal. of $C_{16}H_{14}Cl_2N_2O$, calc: C 59.83%, H 4.39%, N 8.72%, found C 59.76%, H 4.46%, N 8.87%.

(11bS)-3a,4,5,6,6a,7-hexahydro-3,5-ethanopyrrolo[2,3-d] carbazol-2(1H)-one (6)

Zinc powder (2.0 g, 31.0 mmol) and acetic acid (1.8 mL, 31.0 mmol) were added into a solution mixture of dichloroacetamide (**5**) (1.0 g, 3.1 mmol) in CH_3CN (50 mL) in methanol (30 mL).

The reaction was permitted to warm to 85^0C and mixed for 24 h. In order to discharge the existing H_2 gas in reaction, it was vent-holed every 2-6 h. TLC (dichloromethane) was used to monitor how the progress of the reaction was. The mixture was cooled and diluted with EtOAc (50 mL) and then filtrated by means of a sintered funnel. The organic residue was dried, treated in concentration process *in vacuo*, and the remainder was subjected to purification by using silica gel chromatography (EtOAc) to give 662 mg of amide (**6)** as a White solid, TLC: R_f 0.63(*n*-hexane), yield: 84 %, m.p.: 244-246 ^0C. IR (KBr): 3197, 2922, 1687, 1605, 1484, 1461, 1357, 1310, 1283 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.44 (m, 1H), 7.37-7.28 (m, 1H), 7.21-7.13 (m, 2H), 4.37 (dd, 1H, *J* = 10.5, 6.1 Hz),

3.77 (t, 1H, *J* = 8.0 Hz), 3.19 (d, 1H, *J* = 14.1 Hz),3.1-2.93 (m, 1H), 2.88-2.47 (m, 1H), 2.86-2.73 (m, 1H), 2.52-2.47 (m, 1H), 2.44 (dt, 1H, *J* = 15.5, 8.0Hz), 1.93 (dd, 1H, *J* = 14.3, 6.1 Hz), 1.93-1.87 (m, 2H), 1.67-1.51 (m , 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 172.4, 148.4, 133.5, 127.3, 122.6, 119.3, 109.7, 61.2, 54.6, 52.4, 43.8, 42.3, 37.4, 29.3, 26.5, 23.3; Anal. of $C_{16}H_{18}N_2O$, calc: C 75.56%, H 7.13%,11.01 N %, found C 75.46%, H 7.19%, N 11.13%.

20-Deethyltubifolidine (7)

$LiAlH_4$ (360 mg, 9.5 mmol was added into a solution mixture of **6** (500 mg, 1.9 mmol) in dry THF (30 mL). The mixture was mixed at ambient temperature for 0.5 h, afterward provided with heat under reflux for 8 h. The reaction was permitted to warm to rt and was monitored by TLS. Upon extraction with 10% NaOH (3X30 mL), the extract content was dried, treated in concentration process *in vacuo*, then subjected to purification by column chromatography on silica gel (*n*-hexane/EtOAc/ Et_3N, 9:3:1) to 333 mg of **7** as a pale-yellow oil, TLC: R_f 0.88 (ethyl acetate), yield: 73%. IR (KBr): 3265, 2927, 1605, 1480, 1467, 1351, 1315, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09- 7.01 (m, 2H), 6.88-6.76 (m, 1H),6.68-6.54 (m, 1H), 3.71 (dd, 1H, *J* = 9.4, 7.5 Hz), 3.66 (s, 1H), 3.34 (s, 1H), 3.11-3.02 (m, 2H), 2.83 (ddd, 1H, *J* = 12.4, 8.7, 4.1 Hz), 2.53 td, 1H, *J* = 11.6, 5.2 Hz), 2.43 (dt, 1H, *J* = 13.1, 7.7 Hz), 1.97-1.80 (m, 5H, 1.73-1.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) δ: 154.7, 131.3, 127.0, 122.9, 118.7, 109.2, 66.1, 61.5, 54.2, 53.1, 47.5, 42.8, 37.1, 28.8, 27.2, 23.1; Anal. of $C_{16}H_{20}N_2$, calc: C 79.96%, H 8.39%, N 11.66%, found C 79.81%, H8.46%, N 11.49%.

3. Results and discussions

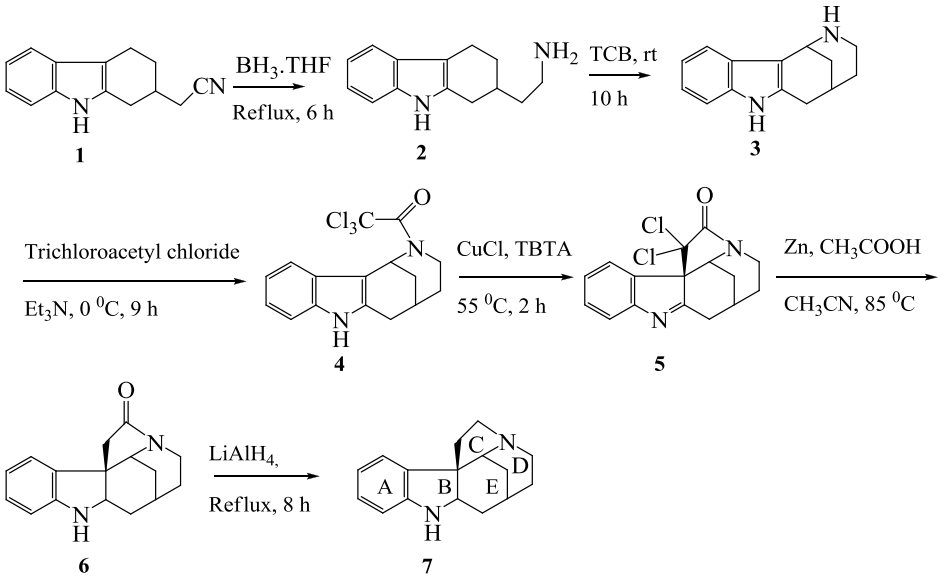
We start to study with synthesizing of the compound (**3**). For this aim, we used 2-(2,3,4,9-tetrahydro-1*H*-carbazol-2-yl) acetonitrile (**1**) as a starting material, which was synthesized according to the literature via the Fischer-indol method [39,40], succeeding the synthetic sequence represented in Scheme 1. In this way, the reduction of **1** with BH_3.THF to compound **2** (88% yield) was pursued by treatment of TCB, leading to the procreation of the structure **3** [41]. At this point, the efficient construction of the cyclization substrates was essential to reach to our synthetic plan successfully. For this purpose, the amine group could be presented with high efficiency with the treatment using TCB for the closure of the amine at room temperature in THF, leading to an escalation in whole of the yield to 96% in one step from compound **2**. At our previous study [42], we formed appropriate tetrahydro-carbazole amide derivatives into azocino[4,3-*b*] indole with $NaBH_4$ and trifluoroacetic acid in a thereafter step. We preferred a one-pot step treatment of amine **2** with TCB. Moreover, we also indicated the effectiveness of new reaction technique in the synthesis of 20-Deethyltubifolidine.

Our strategy provided a scalable approach (1), and we present an alternative procedure for the formation of the tetracyclic ring system. This structure is important as a key structure for the **ABCDE** ring system, which was afterwards turned into azocino[4,3-*b*] indole unit in two steps and five steps for 20-Deethyltubifolidine. The most typical sign for this kind of compounds in ^{1}H-NMR spectrum is a doublet-doublet of methine proton on the C-1 placement at δ 3.71 ppm. It was analogous to the data which was monitored formerly for analogues methanoazocinoindole structure [21]. Besides, ^{1}H-NMR spectrum of compound **7** give the multiplet peaks the aromatic protons in the range of 7.09- 6.54 ppm. In past, the ^{1}H-NMR shifts of the analog compounds were reported as multiplet peaks in 7.34- 6.95 ppm and predicted in 7.56-7.31 ppm [43]. In another work, the same shifts were observed in 7.15-6.97 ppm and computed in 7.32-7.62 ppm by HF [44].

Addition, the FT-IR spectrum of the final product **(7)** implies that the peak observed in 3265 cm^{-1} can be assigned as N-H bond vibration. Also, the observed peak in 2927 cm^{-1} is approximately predicted as C-H bond stretching (νC-H). In recent study, the observed νC-H mode in 2917 cm^{-1} was assigned in 2906 cm^{-1} (91% PED) [43]. In the past, (νN=C) vibration of the analog molecule were observed in 1461 and 1379 cm^{-1} [44], and assigned by PED in the range 1443, 1363 (34%), 1139, 1097 and 911 cm^{-1} contributed by the ring stretching and bending vibrations. Here, the recorded signals in 1467 and 1351 cm^{-1} are approximately determined as the (νN=C) mode. Addition, the peaks recorded

in 1605 cm^{-1} can be C=C stretching (νC=C) vibration according to the past report [44]. Also, the recorded signals in 1480, 1315 and 1278 cm^{-1} can be probably assigned as the bending modes accompanied with the C-H stretching modes based on the previous reports [43-45].

All synthetic steps have high yields while utilizing conventional reagents with a reliable route to the cyclization step. Azocino **3** was treated with **2**, the equivalent of trichloroacetyl chloride in the presence of Et_3N at 0°C, and the mixture was lowered rt, leading to trichloroacetamide (**4**) with a 91% yield [46]. Then compound **4** reacted with copper (I)chloride and TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl) methyl] amine) in the presence of acetononitrile, giving the pentacyclic imine (**5**) substructure of *Strychnos* alkaloids. With a success route to the pentacyclic structure established, we endeavored to complete the *Strychnos* core structure. The imine (**5**) was treated with zinc dust in methanol in the presence of acetic acid as a supplement, presenting exceptional proceeds of amide (**6**), and by using a one-pot, two-step reductant method compound **6** was succeeded. Finally, compound **6** was reduced with $LiALH_4$ in refluxing THF-furnished 20-Deethyltubifolidine [21, 36, 38, 40, 47].



Scheme 1. Synthesis of 20-Deeethyltubifoldine

4. Conclusions

Conclusively, we present here a novel approach for the total synthesis of 20-deeethyltubifoldine. Beginning with nitrile **1**, we obtain the target natural product in a whole yield of 38% which pursues a 6-steps procedure. We developed a strategy herein which is well adapted to the total synthesis of other kinds of alkaloids. Future studies on the synthesis of other strychnos alkaloids are continually progressing and will be announced in due course of time.

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