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Study of Synthesis of Some Pyrroloquinolines, Pyrroloisoquinolines, Pyridocarbazoles and Their Derivatives

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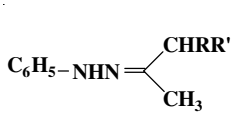
The new isomers of pyrroloquinolines, pyrroloisoquinolines and pyridocarbazoles have been synthesized from the hydrazone of methylisopropylketone, 2-methylcyclohexanone, 5 and 8-quinolylhydrazine and 5-isoquinolylhydrazine by ring closure in AcOH at reflux in excellent yields. The methiodide of pyrroloisoquinoline and pyridocarbazole were reduced with $NaBH_4$ at room temperature to produce corresponding hexahydropyrroloisoquinoline and decahydropyridoisoquinoline in good yields.

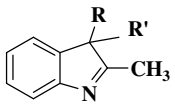
Key Words: Pyrroloquinoline, Pyrroloisoquinoline, Pyridocarbazole, 5- and 8-quinolylhydrazine, 5 and 8-Isoquinolylhydrazine.

INTRODUCTION

2-Methyl-3*H*-indoles (**II**, R and R' = alkyl) can be synthesized by known methods[1-4]. The indolization of ketone phenylhydrazones of the (I, R and R' = alkyl), gives exclusively (**II**) in acetic acid.

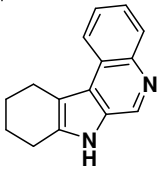


(**I**)

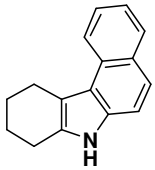


(**II**)

However in (**I**) indolization occurs in both possible directions and leads to a mixture of the corresponding indole and 3*H*-indole in hydrochloric acid[5]. Indolization of cyclohexane 3-quinolylhydrazone and 2-naphthylhydrazone gives exclusively (**III**)[6] and (**IV**)[7] respectively.



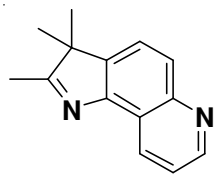
(III)



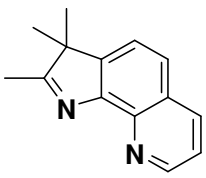
(IV)

The fusion of the quinoline and isoquinoline ring to the 2,3-position of indolenine or the fusion of a pyrido ring to carbazolenine may result in six isomeric pyrido-indolenines and pyridocarbazolenines namely 2,3,3-trimethyl-3*H*-pyrrolo[2,3-f]quinoline (**V**), 2,3,3-trimethyl-3*H*-pyrrolo[3,2-h]quinoline (**VI**), 2,3,3-trimethyl-3*H*-pyrrolo[2,3-f] isoquinoline (**VII**), 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[3-2-a]carbazole (**VIII**), 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[2,3-a]carbazole (**IX**), 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[4,3-a]carbazole (**X**).

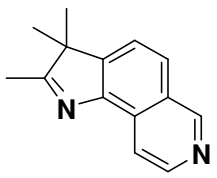
The general method adapted was the fischer indole ring closure of the hydrazone of methyl isopropyl ketone and 5-and 8- quinolylhydrazine[8], 5-isoquinolyl-hydrazone[9]. The resulted hydrazones were treated with acetic acid by refluxing underwent ring closure almost quantitavely to give (**V**), (**VI**), (**VII**).



(**V**)

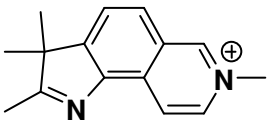


(**VI**)

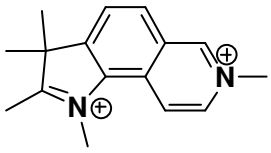


(**VII**)

The reaction of pyridoindolenine (**VII**) with methyl iodide at reflux for 3 h. gave only mono N-methylated product (**VI**) and dimethylation was achived with excess of methyl iodide at reflux for 24 h to give N,N-dimethyl-2,3,3-trimethyl-3*H*-pyrrolo[2,3-f]-isoquinolinium iodide (**XII**) in excellent yield.

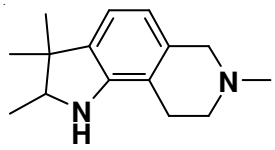


(**XI**)

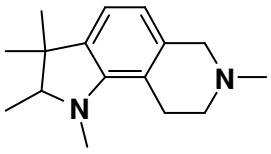


(**XII**)

Reduction of resulted methiodides with $NaBH_4$ gave 2,3,3,7-tetramethyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-f]isoquinoline (**XIII**) and 1,2,3,3,7-pentamethyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-f]isoquinoline (**XIV**) respectively.



(**XII**)



(**XIV**)

EXPERIMENTAL

General procedure: Isoquinoline, quinoline and solvents were purchased from commercial sources and were used without further purification. The products were characterized by a comparison with authentic samples (melting points) and their ^{1}H NMR or IR spectra. Organic layers were dried with anhydrous sodium sulphate before concentration in vacuum. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 GF_{254} aluminum sheet plates. The products were purified by a column chromatography packed with silica gel or preparative thin layer chromatography. All compounds were named as IUPAC by chemdraw 8.0 computer program. Infrared spectra were recorded on thermonicolet (Nexus 670) FT-IR instrument. All melting points (m.p.) were determined on Philip Harris C4954718 melting point apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR measurement were determined on Bruker instrument. Tetramethyl silane was used as an internal standard. The following abbreviations are used: s = singlet, d = doublet, m = multiplet, bs = broad singlet, bd = broad doublet; dd = doublet of doublet, td = triplet of doublet.

Synthesis of 5-hydrazinoisoquinoline: In a round-bottomed flask, is placed concentrated hydrochloric acid (300 mL) and was cooled with mixture of ice and salt and when the contents were at 0 °C, 5-amino isoquinoline (3 g, 21 mmol) was added in during 0.5 h and was stirred for 1 h. The cold solution of sodium nitrite (2 g, 28.5 mmol) in water (5 mL) was added dropwise to reaction mixture and then the cold solution of stannous choride (21 g) in hydrochloric acid (630 mL) was added dropwise. The reaction mixture was kept at 8 °C for 24 h. The solvent was evaporated and the residue was dissolved in water (300 mL) and was saturated with hydrogen sufide. The reaction mixture was filtered and the filtrate was nutralized with sodium hydroxide (40 %) and was extracted with dichloromethane. The organic layer was dried and was evaporated to give 5-hydrazinoisoquinoline as brown crystals in 36 % yield, m.p. 165-169 °C (lit. 166-167 °C). FT-IR ν_{max} (KBr disk): 3281, 3169, 1586, 1387,814, 739 cm^{-1}.

Synthesis of 2,3,3-trimethyl-3*H*-pyrrolo[2,3-f]isoquinoline (VII): 5-Hydrazinoisoquinoline (0.1 g, 0.6 mmol) was refluxed with isopropyl methyl ketone (0.052 g, 0.6 mmol) in glacial acetic acid (2 mL) for 1.5 h. The reaction mixture was diluted with water (5mL) and then was extracted with ethyl acetate. Hydrochloric acid (10 %, 10 mL) was added to organic layer and the resulted acidic solution was neutralized with sodium carbonate and then was extracted with ethyl acetate. The organic layer was dried and the solvent was evaporated affording a crude product which was purified by chromatography (pet. ethyl acetate:toluene 1:1) on silica to gave compound (**VII**) as light brown crystals in 67 % yield, m.p. 87-90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.36 (s, 6H, $2CH_3$), 2.39 (s, 3H, CH_3), 7.55 (d, J = 8.2 Hz, 1H, Ar), 7.84 (d, J = 8.2 Hz, 1H, Ar), 8.27 (d, J = 5.8 Hz, 1H, Ar), 8.57 (d,

J = 5.8 Hz, 1H, Ar), 9.27(s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.61, 21.33, 28.63, 54.0, 115.10, 119.78, 124.21, 127.82, 127.99, 141.99, 145.50, 146.80, 151.3. FT-IR ν_{max} (KBr disk): 2967, 2925, 1630, 1581, 1370 cm^{-1}.

Synthesis of N,N-dimethyl-2,3,3-trimethyl-3*H*-pyrrolo[2,3-f]isoquinolinium iodide (XII): Indolenine (**VII**) (2 g, 9.5 mmol) was refluxed with an excess of methyl iodide in acetone (5mL) for 24 h. The solvent was evaporated affording a crude product which was recrystallized from ethanol to give the compound (**XII**) as golden crystals in 85 % yield, m.p. 185 °C (dec.). ^{1}H NMR (DMSO) δ (ppm): 1.4 (s, 6H, $2CH_3$), 2.41 (s, 3H, CH_3), 3.34(s, 3H, N^+CH_3), 4.50 (s, 3H, N^+CH_3), 8.26 (d, *J* = 8.1, 1H, Ar), 8.36 (d, *J* = 8.1, 1H, Ar), 8.66 (dd, J_1 = 0.9 Hz, J_2 = 6 Hz, 1H, Ar), 8.75 (d, *J* = 6.9 Hz, 1H, Ar), 10.06 (s, 1H, Ar). ^{13}C NMR (DMSO) δ (ppm): 16.15, 21.72, 48.41, 56.54, 121.16, 126.0, 127.38, 128.22, 129.07, 136.40, 148.26, 151.42, 153.96, 193.07. FT-IR ν_{max} (KBr disk): 3434, 3009, 1650, 1581, 1378, 1195, 694 cm^{-1}.

Synthesis of 1,2,3,3,7-pentamethyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-f]isoquinoline (XIV): The methiodide (**XII**) (0.2 g, 0.68 mmol) was reduced with an excess of sodium borohydride in ethanol (5 mL). After stirring for 2 h, the solution was diluted with water (5 mL) and extracted with ethyl acetate. The organic layer was dried and the solvent was evaporated affording a crude product which was purified by chromatography (ethyl acetate:ethanol 2:3) on silica to gave the compound (**XIV**) as light brown crystals in 82 % yield, m.p. 59-61 ºC. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.04 (s, 3H, CH_3), 1.21-1.34 (m, 8H), 2.49 (s, 3H, NCH_3), 2.56-2.74 (m, 4H), 3.1-3.4 (m, 1H), 3.54 (s, 3H, NCH_3), 6.49 (d, *J* = 7.5 Hz, 1H, Ar), 6.85 (d, *J* = 7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.24, 22.39, 24.55, 26.37, 29.69, 43.44, 46.00, 52.57, 58.07, 65.44, 115.39, 116.97, 119.46, 133.55, 136.23, 147.21. FT-IR ν_{max} (KBr disk): 2958, 2783, 1593, 1458, 1380 cm^{-1}.

Synthesis of 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[4,3-a]carbazole (X): Using the procedure to synthesis of the compound (**VII**) 5-hydrazinoisoquinoline was reacted with 2-methyl cyclohexanone affording a crude product which was purified by chromatography (ethyl acetate: toluene 1:1) on silica to gave the compound (**X**) as cream crystals in 75 % yield, m.p. 151-154 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.1-1.3 (m, 1H), 1.39-1.60 (m, 4H), 1.78-1.85 (m, 2H), 2.20-2.50 (m, 2H), 2.60-2.80 (m, 1H), 3.01-3.20 (m, 1H), 7.59 (d, *J* = 9, 1H, Ar), 7.85 (d, *J* = 9, 1H, Ar), 8.33(d, *J* = 6.7, 1H, Ar), 8.6 (d, *J* = 6.7, 1H, Ar), 9.30 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.13, 21.15, 29.23, 29.93, 38.43, 55.24, 116.18, 120.83, 124.93, 128.88, 129.38, 143.12, 147.73, 148.60, 152.51, 191.60. FT-IR ν_{max} (KBr disk): 2933, 2858, 1628, 1581, 1441, 1367, 834, 712 cm^{-1}.

Synthesis of 3,6b-dimethyl-7,8,9,10-tetrahydro-6b*H*-pyrido[4,3-a] carbazolium iodide (XV): Using the procedure to synthesis of the compound (**XII**) carbazole (**X**) gave the compound (**XV**) as light brown crystals in 87 % yield, m.p. 188-190 °C (d). ^{1}H NMR(DMSO) δ (ppm): 0.9-1.1 (m, 1H), 1.13-1.40 (m, 4H), 1.66-1.70 (m, 1H), 1.82-1.91 (m, 1H), 2.01-2.07 (m, 1H), 2.15-2.3 (m, 1H), 2.74-

2.91 (m, 2H), 4.37 (s, 3H, N^+CH_3), 8.22 (d, J = 8.1 Hz, 1H, Ar), 8.34 (d, J = 8.1 Hz, 1H, Ar), 8.69 (d, J = 6.9 Hz, 1H, Ar), 8.80 (d, J = 6.9 Hz, 1H, Ar), 10.02 (s, 1H, Ar). FT-IR ν_{max} (KBr disk): 2933, 1644, 1580, 1375 cm^{-1}.

Synthesis of 3,6b-dimethyl-2,3,4,6b,7,8,9,10,10a,11-decahydro-1*H*-pyrido.3.3[4,3-a] carbazole (XVI): Using the procedure to synthesis of the compound (**XIV**) gave the compound (**XVI**) as light brown crystals in 84 %, m.p. 90-93 ºC. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3 (s, CH_3, 3H), 1.39-1.48 (m, 4H), 1.61-1.69 (m, 4H), 2.46 (s, 3H, NCH_3), 2.63-2.76 (m, 5H, 1H removed by addition of D_2O), 3.40-3.43 (m, 1H), 3.56 (s, 2H, CH_2NMe), 6.48 (d, J = 7.5 Hz, 1H, Ar), 6.83(d, J = 7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.25, 21.54, 24.12, 24.58, 28.99, 34.93, 42.85, 46.02, 52.61, 58.14, 66.19, 115.94, 116.74, 118.82, 133.33, 136.31, 147.49. FT- IR ν_{max} (KBr disk): 3439, 2927, 1853, 2783, 1595 and 1449 cm^{-1}.

5 and 8-Hydrazinoquinoline: Using the procedure to synthesis of the hydrazino isoquinoline, 5 and 8-aminoquinolines gave 5 and 8-hydrazinoquinoline as brown crystals with 38 and 40 % yields, m.p. 223-226 °C (lit.[10] 225 °C) and 203-205 °C (lit.[11] 225 °C), respectively.

Synthesis of 2,3,3-trimethyl-3*H*-pyrrolo[2,3-f]quinoline (V): Using the procedure to synthesis of compound (**VII**) 5-hydrazinoquinoline affording a crude product which was purified by chromatography (ethyl acetate:toluene 4:1) on silica to gave compound (**V**) as light brown oil in 67 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.32 (s, 6H, $2CH_3$), 2.35 (s, 3H, CH_3), 7.42 (dd, $J_1 = J_2$ = 4.2, 1H, Ar), 7.62 (d, J = 8.4 Hz, 1H, Ar), 7.97 (d, J = 9 Hz, 1H, Ar), 8.82-8.88 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.57, 22.50, 54.77, 121.11, 121.87, 122.54, 126.47, 131.80, 142.28, 148.21, 148.67, 149.9, 189.72. FT-IR ν_{max} ($CHCl_3$): 2964, 2928, 1561, 1366 cm^{-1}.

Synthesis of 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[3,2-a]carbazole (VIII): Using the procedure to synthesis of the compound (**V**) 5-hydrazinoiso-quinoline was reacted with 2-methyl cyclohexanone affording a crude product which was purified by chromatography (ethyl acetate: toluene 4:1) on silica to gave the compound (**VIII**) as brown oil in 75 % yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.16-1.47 (m, 2H), 1.37 (s, 3H, CH_3), 1.75-1.81 (m, 2H), 2.20-2.40 (m, 2H), 2.62-2.71 (m, 1H), 2.9-3.03 (m, 1H), 7.47 (dd, $J_1 = J_2$ = 4.5, 1H, Ar), 7.67(d, J = 8.4, 1H, Ar), 7.99 (d, J = 8.4, 1H, Ar), 8.89-8.93 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.27, 21.19, 29.24, 29.96, 38.63, 55.00, 121.02, 122.21, 122.65, 126.22, 131.91, 143.93, 148.21, 149.49, 149.89 and 191.88. FT-IR ν_{max} ($CHCl_3$): 2934, 2861, 1583, 1368, 754 cm^{-1}.

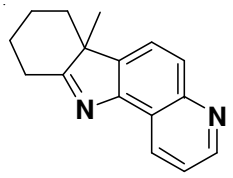
Synthesis of 2,3,3-trimethyl-3*H*-pyrrolo[3,2-h]quinoline (VI): Using the procedure to synthesis of compound (**V**) 8-hydrazinoquinoline affording a crude product which was purified by chromatography (ethyl acetate:toluene 4:1) on silica to gave compound (**VI**) as light brown oil in 63 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.39 (s, 6H, $2CH_3$), 2.42 (s, 3H, CH_3), 7.42-7.44 (m, 1H, Ar), 7.53 (d, J = 7.5 Hz, 1H, Ar), 7.72 (d, J = 6.3 Hz, 1H, Ar), 8.21 (d, J = 7.5 Hz, 1H, Ar),

9.02-9.03 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.58, 22.43, 55.45, 120.37, 120.97, 125.37, 128.36, 136.59, 140.40, 146.03, 148.64, 150.58, 189.87. FT-IR ν_{max} ($CHCl_3$): 2966, 1686, 1515, 1359 cm^{-1}.

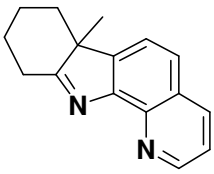
Synthesis of 6b-methyl-7,8,9,10-tetrahydro-6b*H*-pyrido[2,3-a]carbazole (IX): Using the procedure to synthesis of the compound (**VIII**) 8-hydrazinoisoquinoline was affording a crude product which was purified by chromatography (ethyl acetate:toluene 4:1) on silica to gave the compound (**VIII**) as brown oil in 68 % yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.1-1.4 (m, 2H), 1.72-1.93 (m, 2H), 2.24-2.42 (m, 2H), 2.62-3.17 (m, 2H), 1.31 (s, 3H), 7.45 (dd, $J_1 = J_2 = 4.2$, 1H, Ar), 7.56 (d, $J = 8.4$, 1H, Ar), 7.77 (d, $J = 8.1$, 1H, Ar), 8.28 (d, $J = 8.4$, 1H, Ar), 9.05-9.06 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.10, 21.25, 29.14, 29.87, 38.63, 55.46, 120.39, 120.81, 122.10, 125.02, 128.36, 136.56, 140.80, 147.50, 150.43, 191.72. FT-IR ν_{max} ($CHCl_3$): 2934, 2861, 1579, 1358, 752 cm^{-1}.

RESULTS AND DISCUSSION

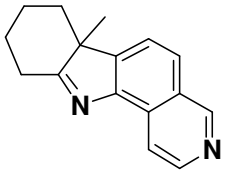
When 5 and 8-quinolylhydrazine and 5-isoquinolylhydrazine reacted with 2-methyl cyclohexanone in acetic acid at reflux. The new pyrido carbazolenines (**VIII**), (**IX**) and (**X**) were produced in excellent yields.



(**VIII**)

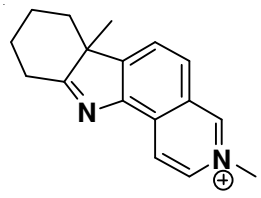


(**IX**)

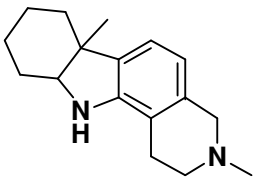


(**X**)

The mono methylation of (**VIII**) was accured with methyl iodide at reflux to give methiodide (**XV**) as a yellow crystals. The salt was reduced with $NaBH_4$ in ethanol at room temperature to produce 3,6b-dimethyl-2,3,4,6b,7,8,9,10,10a,11-decahydro-1*H*-pyrido[4,3-a]carbazole (**XVI**) in excellent yield.



(**XV**)



(**XVI**)

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