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Note

A facile synthesis and characterization of 2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepanes

I Antony Danish & K J Rajendra Prasad*
Department of Chemistry, Bharathiar University,
Coimbatore 641 046, India
Email prasad_125@yahoo.com

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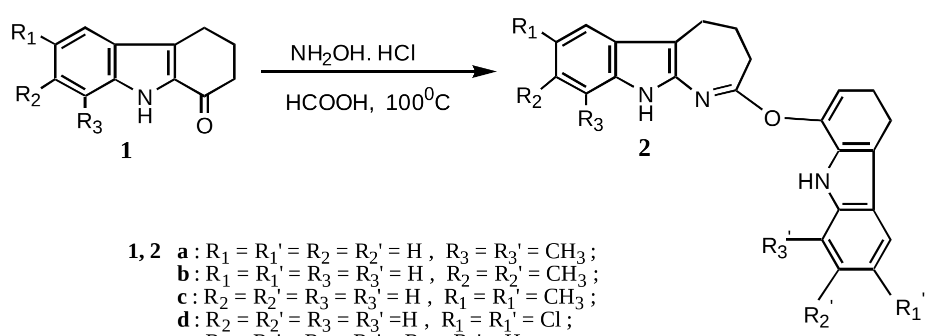
1-Oxo-1,2,3,4-tetrahydrocarbazoles **1** upon reaction with hydroxylamine hydrochloride in the presence of formic acid yield hitherto unknown 2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepanes **2** in good yield in a single step and is characterized by IR, NMR and mass spectra and elemental analysis.

Keywords: 1-Oxo-1,2,3,4-tetrahydrocarbazoles, hydroxylamine hydrochloride, formic acid, tetrahydroindolo[2,3-*b*]azepanes

IPC: **Int.Cl.**[7] **C 07 D**

Over the past decades the isolation of many biologically active carbazole alkaloids such as ellipticine and olivacine has drawn much attention to derive newer strategies towards the synthesis of carbazole derivatives[1,2]. The structural diversity and the association with a wide spectrum of pharmacological potentialities of carbazoles have been documented extensively[3-9]. In particular, pyridocarbazoles were found to elicit anticancer[10] and anti-HIV properties[11]. The indolo[2,3-*a*]carbazole framework is found in the antitumor active alkaloids such as staurosporine, K-252a and rebeccamycin[12]. Moreover, the indole moiety fused with furo-, pyrano- and pyrido-heterocycles has been found to exhibit antineoplastic activity[13]. Due to the wide range of pharmacological profile of carbazole and its related compounds, we felt worthwhile to derive newer intermediate to synthesize important carbazole derivatives. Earlier, the synthesis of 1-hydroxyimino-1,2,3,4-tetrahydrocarabzole from the reaction of 1-oxo-1,2,3,4-tetrahydrocarbazole **1** with hydroxylamine hydrochloride in the presence of pyridine has been reported and it was utilized to synthesize useful heterocyclo-fused carbazoles[14,15]. The combination of hydroxylamine hydrochloride and formic acid was found to convert aldehydes into nitriles in a single step in excellent yields[16]. To know the interesting outcome of the reaction with 1-oxo-1,2,3,4-tetrahydrocarbazole[7] **1** (**Scheme I**), we reacted **1** with hydroxylamine hydrochloride in formic acid, which resulted in the formation of hitherto unknown compound, 2-(3′,4′-dihydro-carbazol-1′-yl)-2, 3, 4, 5-tetrahydroindolo[2,3-*b*]azepane **2** in a single step (**Scheme II**).

In this regard, 8-methyl-1-oxo-1,2,3,4-tetrahyro-carbazole **1a** was treated with hydroxylamine hydrochloride in formic acid for 11 hr, the product formed was separated by column chromatography over silica gel. The white crystalline product obtained from the solvent mixture of petroleum ether-ethyl acetate (95:5) melted at 118°C and its IR spectrum showed the absorptions of broad band at 3460 and 3321 cm^{-1} due to two NH stretching. An intense band at 1560 cm^{-1} was due to the C=N stretching vibrations. A sharp band at 1230 cm^{-1} was due to the presence of C-O-C group. Its ^{1}H NMR spectrum in $CDCl_3$ exhibited the following



1 **2**

1, 2 **a** : $R_1 = R_1' = R_2 = R_2' = H$, $R_3 = R_3' = CH_3$;
b : $R_1 = R_1' = R_3 = R_3' = H$, $R_2 = R_2' = CH_3$;
c : $R_2 = R_2' = R_3 = R_3' = H$, $R_1 = R_1' = CH_3$;
d : $R_2 = R_2' = R_3 = R_3' = H$, $R_1 = R_1' = Cl$;
e : $R_1 = R_1' = R_2 = R_2' = R_3 = R_3' = H$

Scheme I

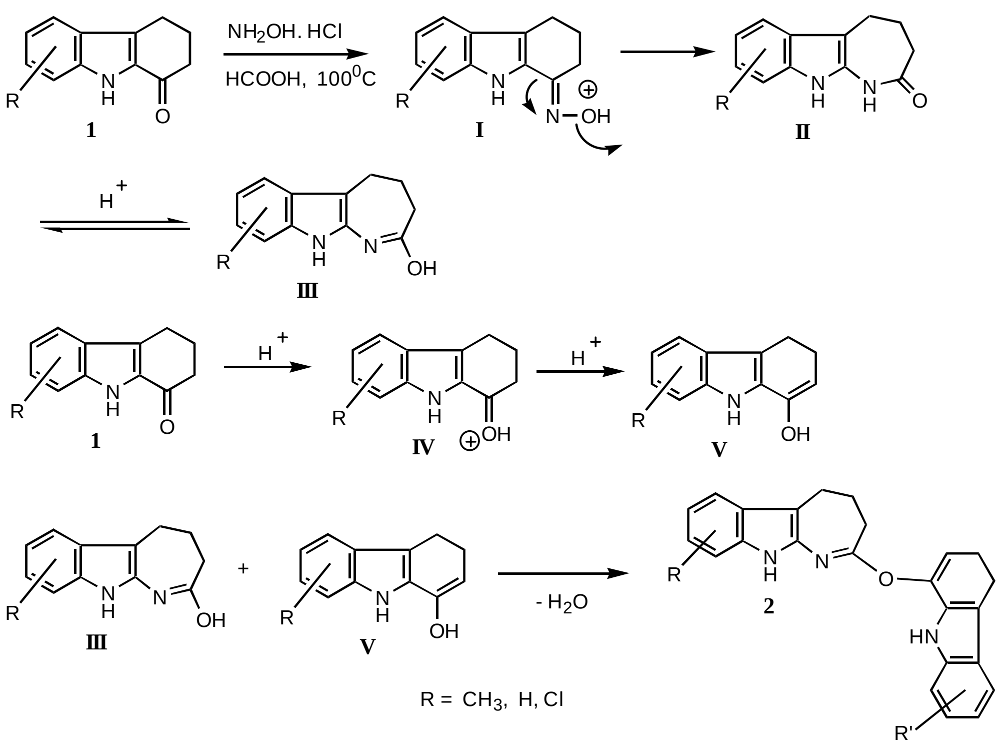
resonances. A multiplet of four-proton intensity appeared at δ 2.04-2.08 for the C_3'-2H and C_4'-2H. The C_2'-H resonated as a multiplet between δ 2.10-2.27. Two singlets of three protons intensity each for two methyl protons of C_9 and C_8' appeared at δ 2.44 and δ 2.51, respectively. The methylene protons at C_3, C_4 and C_5 appeared as an unresolved multiplet of six-proton intensity between δ 2.65-3.03. The aromatic protons of C_6' and C_7 resonated at δ 7.03-7.23. Another multiplet of four-proton intensity at δ 7.29-7.63 was due the protons at C_6, C_8, C_5' and C_7'. A broad singlet at δ 8.56 was due to the N_{10}H proton of the indole moiety. A broad singlet at δ 9.64 was due to the carbazole-N_9'H proton. The mass spectrum of **2a** (**Scheme III**) showed the molecular ion peak at m/z 395 with 3% intensity, the appearance of the fragment ion peak at m/z 391 ($M^{+\cdot}$-4, 30%) further strengthens the proposed molecular formula, $C_{26}H_{25}N_3O$. The results of the mass spectrum and elemental analysis of the product further augmented the presence of the carbazole framework in the compound. These details attest the structure for the product as 9,8′-dimethyl-2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane **2a**. A similar series of products were realized from **1b**, **1c**, **1d** and **1e** as **2b**, **2c**, **2d** and **2e**, respectively (**Scheme I**).

Mechanism

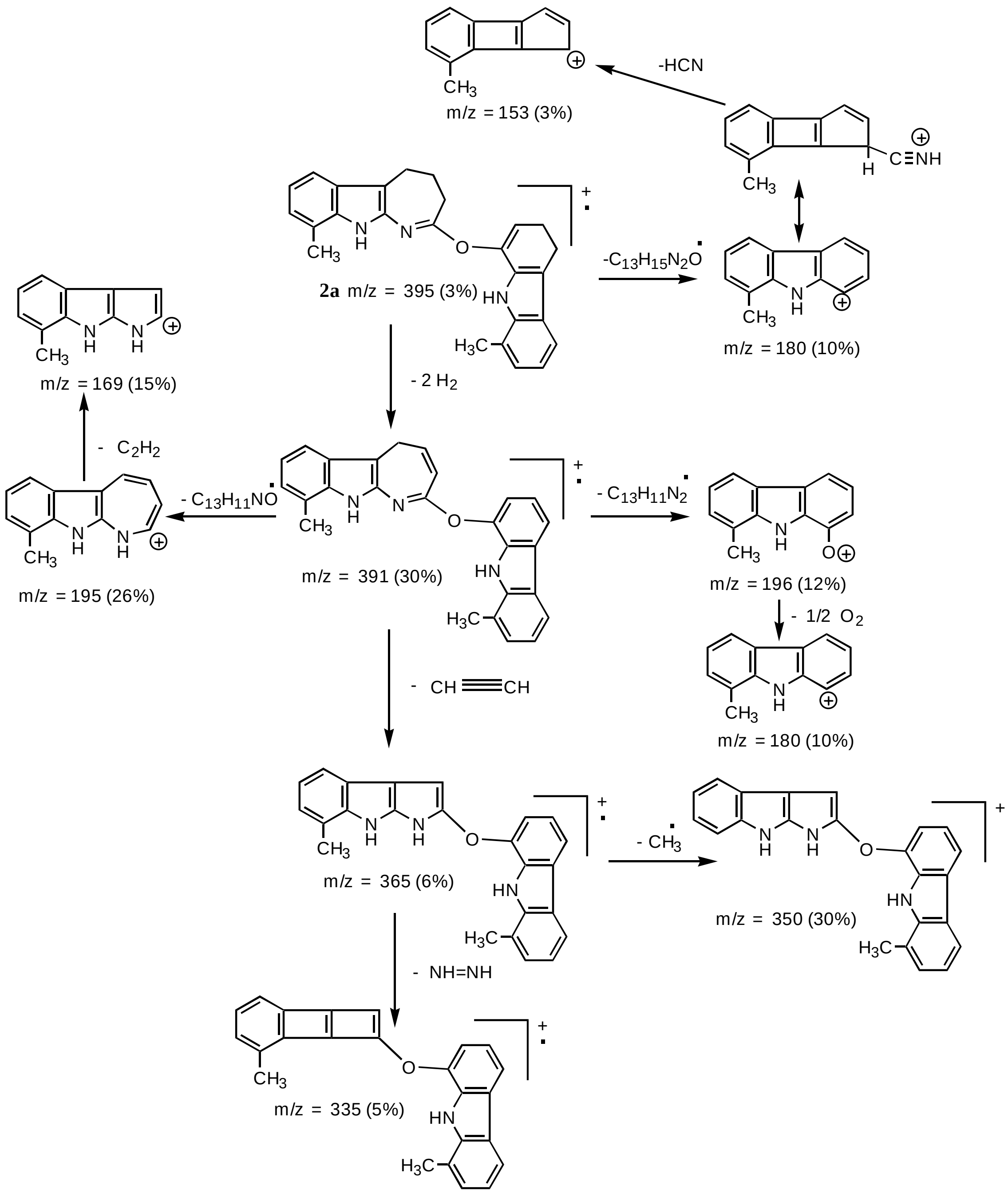
The plausible mechanism (**Scheme II**) for the formation of the product has been proposed as follows. The hydroxylamine hydrochloride reaction of 1-oxo-1,2,3,4-tetrahydrocarbazole **1** can be mechanically viewed as proceeding through the formation of ketoxime **I** followed by the Beckmann rearrangement to give the ring enlarged amide **II** which tautomerises to give **III**. The hydroxy intermediate **IV** formed directly *in situ* from 1-oxo-1,2,3,4-tetrahydrocarbazole **1** in the presence of formic acid reacts with the intermediate **IV**, which results in the removal of a water molecule to give the product **2**.

Experimental Section

Melting points were determined with a Mettler FP 51 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8201 PC infrared spectrophotometer; ^{1}H NMR and ^{13}C NMR spectra on a Varian AMX 400 FT-NMR spectrometer using TMS as internal reference in $CDCl_3$ (chemical shifts in δ, ppm); and mass spectra on a Jeol-JMS-D-300 mass spectrometer. Satisfactory microanalyses were obtained on a Perkin-Elmer Model 240 CHN analyzer. The purity of the products was checked by TLC on silica gel plate. All solvents were purified by distillation or were of HPLC grade.



Scheme II



Scheme III - Mass spectral fragmentation pattern of **2a**

Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles with hydroxylamine hydrochloride in the presence of formic acid. General procedure. The respective 1-oxo-1,2,3,4-tetrahydrocarbazole (**1**, 0.001 mole) was taken in 11 mL formic acid and hydroxylamine hydrochloride (0.002 mole) was added to the above mixture at room temperature. The reaction mixture was then heated on a water-bath and the reaction was monitored by TLC. After 11 hr the reaction mixture was poured into ice water, neutralized with 10% NaOH and extracted with ethyl acetate (3 × 50 mL). The extract was thoroughly washed with water and dried over anhydrous sodium sulphate. The removal of the solvent gave a crude product which was purified by column chromatography packed over silica gel using petroleum ether-ethyl acetate mixture (95:5) as eluant.

9,8′-Dimethyl-2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane 2a: White crystalline prisms from pet. ether-ethyl acetate mixture, m.p. 118ºC; yield 68%; IR (KBr): 3460, 3321, 1637, 1560, 1508, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.04-2.08 (m, 4H, C_3′-2H, C_4′-2H), 2.10-2.27 (m, 1H, C_2′-H), 2.44 (s, 3H, C_9-CH_3), 2.51 (s, 3H, C_8′-CH_3), 2.65-3.03 (m, 6H, C_3-2H, C_4-2H, C_5-2H), 7.03-7.23 (m, 2H, C_6′-H, C_7-H), 7.29-7.63 (m, 4H, C_6-H, C_8-H, C_5′-H and C_7′-H), 8.56 (b s, 1H, indole-N_{10}H), 9.64 (b s, 1H, carbazole-N_9′H); ^{13}C NMR ($CDCl_3$): 16.61 (C_9-CH_3), 20.94 (C_8′-CH_3), 21.80 (C_4), 22.81 (C_3′, C_4′), 23.95 (C_3), 29.63 (C_5) 111.70 (C_4′$_a$, C_{5a}), 117.00 (C_4′$_b$, C_{5b}), 117.51 (C_5′, C_6), 119.72 (C_2′), 119.87 (C_1′), 120.04 (C_7′, C_8), 120.45 (C_9′$_a$), 120.89 (C_6′, C_7), 121.64 (C_9), 124.71 (C_{9a}), 125.01 (C_8′), 125.67 (C_8′$_a$), 136.39 (C_{10a}), 148.92 (C_2); MS (70 eV) m/z (%): 395 (M^+, 3), 391 (30), 365 (6), 350 (30), 335 (5), 214 (100), 196 (12), 195 (26), 180 (10), 169 (15), 153 (3); Anal. Found: C, 78.95; H, 6.38; N, 10.59. Calcd for $C_{26}H_{25}N_3O$: C, 79.00; H, 6.32; N, 10.63%.

8,7′-Dimethyl-2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane 2b: White crystalline prisms from pet. ether-ethyl acetate mixture; m.p. 145ºC; yield 65%; IR (KBr): 3452, 3295, 1624, 1560, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.01-2.11 (m, 4H, C_3′-2H, C_4′-2H), 2.47 (s, 3H, C_8-CH_3), 2.60-2.66 (m, 1H, C_2′-H), 2.69 (s, 3H, $C_{7'}$-CH_3), 2.80-3.19 (m, 4H, C_3-2H, C_5-2H), 3.09-3.19 (m, 2H, C_4-2H), 6.82-7.50 (m, 6H, C_6-H, C_7-H, C_9-H, C_5′-H, C_6′-H, and C_8′-H), 9.61 (b s, 1H, indole-N_{10}H), 9.79 (b s, 1H, carbazole-N_9′H); MS (70 eV) m/z (%): 395 (M^+, 5), 391 (25), 365 (8), 350 (33), 335 (4), 214 (100), 196 (15), 195 (30), 180 (12), 169 (10), 153 (5); Anal. Found: C, 78.97; H, 6.35; N, 10.59. Calcd for $C_{26}H_{25}N_3O$: C, 79.00; H, 6.32; N, 10.63%.

7,6′-Dimethyl-2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane 2c: White crystalline prisms from pet. ether-ethyl acetate mixture; m.p. 159ºC; yield 62%; IR (KBr): 3427, 3350, 1637, 1540, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.99-2.13 (m, 4H, C_3′-2H, C_4′-2H), 2.44 (s, 3H, C_7-CH_3), 2.46 (s, 3H, C_6′-CH_3), 2.65-2.68 (m, 1H, $C_{2'}$-H), 2.80-2.91 (m, 6H, C_3-2H, C_4-2H, C_5-2H), 7.04-7.38 (m, 6H, C_6-H, C_8-H, C_9-H, C_5′-H, C_7′-H, and C_8′-H), 9.25 (b s, 1H, indole-N_{10}H), 9.67 (b s, 1H, carbazole-N_9′H); MS (70 eV) m/z (%): 395 (M^+, 6), 391 (35), 365 (10), 350 (25), 335 (8), 214 (100), 196 (10), 195 (30), 180 (15), 169 (10), 153 (2); Anal. Found: C, 79.02; H, 6.27; N, 10.61. Calcd for $C_{26}H_{25}N_3O$: C, 79.00; H, 6.32; N, 10.63%.

7,6′-Dichloro-2-(3′,4′-dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane 2d: White crystalline prisms from pet. ether-ethyl acetate mixture; m.p. 162ºC; yield 60%; IR (KBr): 3423, 3380, 1636, 1534, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.99-2.12 (m, 4H, C_3′-2H, C_4′-2H), 2.66-2.70 (m, 1H, C_2′-H), 2.76-2.88 (m, 6H, C_3-2H, C_4-2H, C_5-2H), 7.16-7.56 (m, 6H, C_6-H, C_8-H, C_9-H, C_5′-H, C_7′-H, and C_8′-H), 9.35 (b s, 1H, indole-N_{10}H), 9.79 (b s, 2H, carbazole-$N_{9'}$H); MS (70 eV) m/z (%): 439 (M+2, 2), 438 (M+1, 1), 437 (M^+, 7), 433 (20), 407 (10), 377 (7), 372 (32), 239 (100), 217 (10), 216 (20), 202 (7), 201 (5), 191 (15), 175 (5); Anal. Found: C, 66.11; H, 4.32; N, 9.66. Calcd for $C_{24}H_{19}N_3OCl_2$: C, 66.09; H, 4.36; N, 9.63%.

2-(3′,4′-Dihydrocarbazol-1′-yl)-2,3,4,5-tetrahydroindolo[2,3-*b*]azepane 2e: White crystalline prisms from pet. ether-ethyl acetate mixture; m.p. 116ºC; yield 65%; IR (KBr): 3427, 3290, 1630, 1534, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.02-2.18 (m, 4H, C_3′-2H, C_4′-2H), 2.66-2.76 (m, 1H, C_2′-H), 2.84-2.94 (m, 6H, C_3-2H, C_4-2H, C_5-2H), 7.08-7.63 (m, 8H, C_6-H, C_7-H, C_8-H, C_9-H, C_5′-H, C_6′-H, C_7′-H and C_8′-H), 8.93 (b s, 1H, indole-N_{10}H), 9.76 (b s, 2H, and carbazole-N_9′H); MS (70 eV) m/z (%): 367 (M^+, 5), 363 (25), 337 (8), 307 (10), 200 (100), 182 (15), 181 (20), 166 (15), 161 (15), 139 (4); Anal. Found: C, 78.45; H, 5.70; N, 11.40. Calcd for $C_{24}H_{21}N_3O$: C, 78.49; H, 5.72; N, 11.44%.

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