Reduction of 1-Hydroxyimino-1,2,3,4-tetrahydrocarbazoles by Metal and Baker's Yeast – Syntheses of Aminocarbazole Derivatives

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1-Hydroxyimino-1,2,3,4-tetrahydrocarbazoles (**1**) were reduced with zinc in acetic acid and acetic anhydride and with bakers' yeast in an aim to synthesize 1-aminocarbazoles, but interestingly the reaction gave hitherto unknown compounds, 2-acetoxy-1-(acetylamino)carbazoles (**2**) and 6-[acetoxy(hydroxy)methyl]-1-hydroxylaminocarbazoles (**3**), respectively. A plausible mechanism for the formation of compounds **2** and **3** is proposed. All new compounds were characterised by IR, NMR, mass spectral methods and elemental analysis.

Key words: Aminocarbazoles, 1-Hydroxyimino-1,2,3,4-tetrahydrocarbazoles, Metal Reduction, Baker's Yeast

The carbazole ring system and its hydrogenated analogues form the core of a wide range of alkaloids, and several strategies exist for their construction, since many of their derivatives exhibit a broad range of potential pharmacological activities [1, 2]. Aminocarbazoles derivatives have gained much attraction due to their prominent pharmacological activities [3 – 5]. The amino carbazole derivative has the potential of being active against Alzheimer's disease since the presence of an amino group at the indole nucleus has shown much promising results as a rehabilitative medicine [6]. Aminocarbazoles have been an important synthon to construct pyridocarbazoles [7], which are well known for their antitumor properties [8,9]. Also, aminocarbazoles have been utilized to prepare pyrimido[5,4-*b*]carbazole derivatives [10]. Though many reports [11 – 14] are available towards the syntheses of aminocarbazoles, most of the procedures suffer from some limitations such as complicated procedures, low yields or difficulty in accessing the starting materials. These demerits prohibit adoption to larger scale manufacturing of aminocarbazoles in acceptable quantity needed for the pharmaceutical applications. Having felt the lack of reports towards a simple route to prepare aminocarbazoles, an attempt was made to synthesize it from the easily accessible 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles **1** [15].

In recent years the advantages of using enzymes as catalysts in preparative organic chemistry have become apparent, as observed in comprehensive review articles [16, 17]. Most of the reactions were realized with the aid of common baker's yeast (*Saccharomyces cerevisiae*), a microorganism that is easily accessible and can catalyze highly enantioselective reduction [18]. The reason to select baker's yeast is that hydrolytic enzymes do not require cofactor regeneration and are easy to use. Baker's yeast is inexpensive, versatile and its growth does not require the assistance of a microbiologist. But the most common argument is that the reactions are not often reproducible [17].

To our knowledge, there is only one report on the usage of bakers' yeast to reduce simple oximes [19]. Based on the above-mentioned facts and due to the importance of aminocarbazoles, an attempt was made to derive them from easily accessible 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles (**1**) by reduction with either zinc in a mixture of acetic acid/acetic anhydride or with baker's yeast. The reactions afforded hitherto unknown compounds, 2-acetoxy-1-(acetylamino)carbazoles (**2**), and 6-[acetoxy(hydroxy)methyl]-1-hydroxylaminocarbazoles (**3**), respectively.

In order to obtain 1-aminocarbazole, 8-methyl-1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (**1a**) was reduced using zinc metal in acetic acid and acetic anhydride at 95 °C. The reaction mixture afforded a product which melts at 176 °C. The IR spectrum of the product showed bands at 3577 cm^{-1} and 3320 cm^{-1} which were attributed to the two NH stretching vibrations. The presence of two in-

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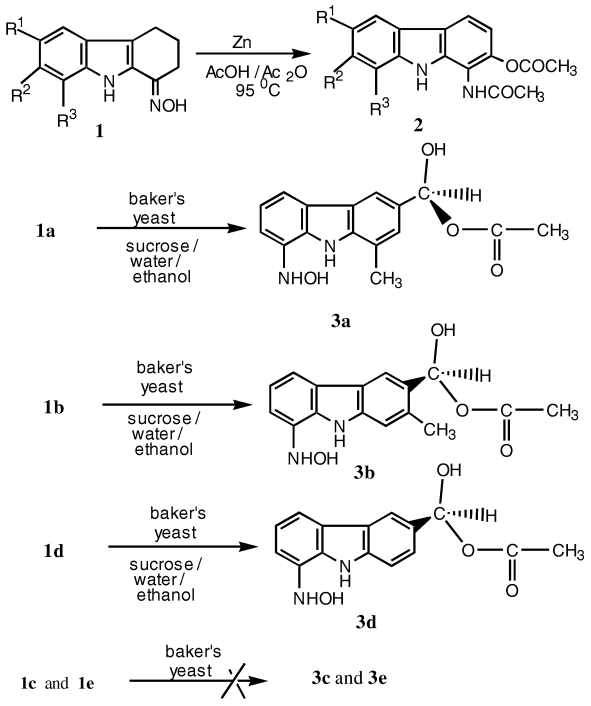
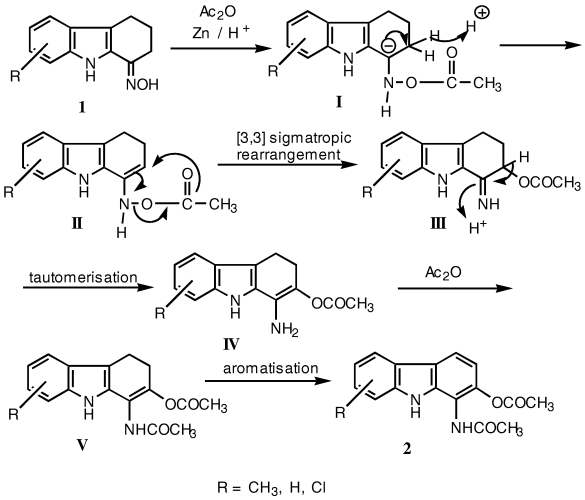


1, **2** **a**: $R^1 = R^2 = H$, $R^3 = CH_3$; **b**: $R^1 = R^3 = H$, $R^2 = CH_3$; **c**: $R^1 = CH_3$, $R^2 = R^3 = H$, **d**: $R^1 = R^2 = R^3 = H$; **e**: $R^1 = Cl$, $R^2 = R^3 = H$

Scheme 1. Reduction of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles by Zn in AcOH / Ac_2O and by baker's yeast.

tense bands at 1738 and 1666 cm^{-1} was due to the two carbonyl groups. The C=C stretching was inferred from the band at 1591 cm^{-1}. The ^1H NMR spectrum displayed three singlets of three proton intensity at $\delta = 2.31$, 2.35 and 2.51 corresponding to N-acetyl protons, 8-*Me* and 2-CO*Me*, respectively. The carbazole NH proton appeared as a broad singlet at $\delta = 9.18$. The NH proton at C-1 appeared as a broad singlet at the downfield region of $\delta = 9.37$. The mass spectrum of the compound showed the molecular ion peak at $m/z = 296$ and the elemental analysis was in good agreement with the molecular formula $C_{17}H_{16}N_2O_3$. Based on the spectral and analytical data the product was identified to be 2-acetoxy-(1-acetylamino)-8-methylcarbazole (**2a**). In an analogous manner 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles, **1b**, **1c**, **1d** and **1e** gave the respective **2b**, **2c**, **2d** and **2e** (Scheme 1).

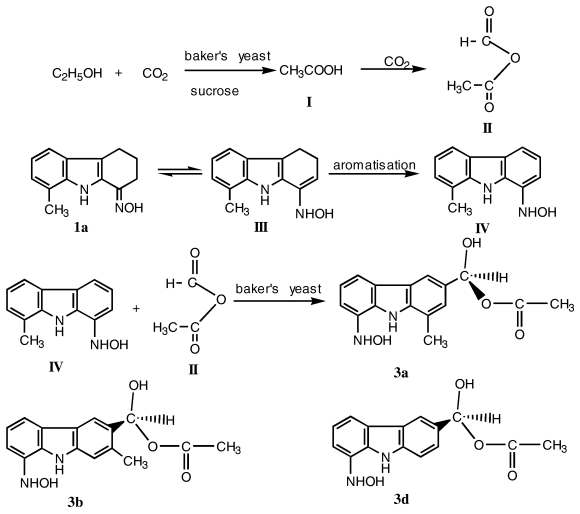
Since the reaction didn't proceed in the absence of zinc, the formation of **2** could be explained as follows (Scheme 2). 1-Hydroxyimino-1,2,3,4-tetrahydrocarbazole (**1**) reacts with acetic anhyride



Scheme 2. Mechanism for the formation of **2**.

catalysed by zinc in acetic acid to form the N-oxyacylated intermediate **I**. Then the intermediate **I**, under acidic conditions looses the C-α hydride ion (α to carbanion), in order to form the more stable intermediate acetoxy enamine (**II**). The intermediate **II** undergoes [3,3]-sigmatropic rearrangement with successive tautomerisation, N-acetylation with excess of acetic anhydride and aromatization to yield the product **2**.

With an aim to obtain 1-aminocarbazole, **1a** was reduced using baker's yeast in the presence of fermented sucrose. The product in its IR spectrum showed prominent absorptions at 3510 (OH), 3475 and 3200 cm^{-1} (two NH groups). The strong band at 1638 cm^{-1} was due to the C=O group. The C-O-C stretching vibration was assigned to a strong band at 1226 cm^{-1}. The ^1H NMR spectrum displayed the following signals, a singlet with six-proton intensity appeared at $\delta = 2.44$ due to the 8-*Me* and 1'-CO*Me* respectively. Two broad singlets appeared at $\delta = 8.78$ and 9.11, which were due to the carbazole-NH and the 1-NH protons, respectively. A singlet appeared at $\delta = 11.50$ due the OH proton of the hydroxylamine group. The ^{13}C NMR spectrum showed a sharp singlet at $\delta = 190.14$ corresponding to the carbonyl group at C-3'. Moreover, the molecular ion peak was found at $m/z = 300$, and elemental analysis was in accordance with the molecular formula $C_{16}H_{16}N_2O_4$. From the above-mentioned spectral and analytical data, it is evident that the product formed was 6-[acetoxy(hydroxy)methyl]-1-hydroxylamino-8-methylcarbazole (**3a**). The reaction was extended to **1b**–**e** but only the products **3b** and **3d** were obtained (Scheme 1). The specific rotation



Scheme 3. Mechanism for the formation of **3**.

$[\alpha]_{\lambda}^{30\ °C}$ of **3a** was found as $-97.5°$. Based on the specific rotation measurements, the configuration of **3a** was assigned as (-)-6-[acetoxy(hydroxy)methyl]-1-hydroxylamino-8-methylcarbazole. The configuration of the other two compounds were found to be (+)-6-[acetoxy(hydroxy)methyl]-1-hydroxylamino-7-methylcarbazole (**3b**) and 6-[acetoxy-(hydroxy)methyl]-1-hydroxylaminocarbazole (**3d**) with a specific rotation, $[\alpha]_{\lambda}^{30\ °C}$, of +142.5° and +77.5°, respectively.

The formation of **3** may be explained as follows (Scheme 3). In the presence of baker's yeast **1a** tautomerises to give **III** followed by aromatisation to yield the more stable 1-hydroxylamino-8-methylcarbazole (**IV**). The stable compound **IV** undergoes acylation with mixed anhydride generated from the reaction of acetic acid (**I**) and CO_2 [21] evolved during the fermentation of sucrose, under the reaction conditions to give the diketone derivative **II**. After the electrophilic substitution reaction of **II** with **IV**, among the two carbonyl groups selectively, the aroyl carbonyl group gets reduced to afford **3a**.

The formation of the 6-[acetoxy(hydroxy)methyl] group could be attributed to the formation of acetic acid during the enzymatic reaction and followed by the generation of the mixed anhydride in the presence of carbon dioxide and bakers' yeast. The electrophilic substitution reaction of this anhydride with carbazole yields the final product. The earlier report [20] from our laboratory suggests that the C-6 position is more susceptible towards the electrophilic substitution reaction and this might be the reason for the absence of products from **3c** and **3e**.

Conclusion

In an effort to prepare 1-aminocarbazoles, 1-hydroxyimino–1,2,3,4–tetrahydrocarbazoles were reduced using Zn in acetic acid and acetic anhydride to furnish 2-acetoxy-1-acetylaminocarbazoles, while baker's yeast afforded hitherto unknown 6-[acetoxy(hydroxy)methyl]-1-hydroxylaminocarbazole derivatives in good yields. The metal reduction was applicable to all the derivatives tested whereas baker's yeast was selective in reducing the starting compounds.

Experimental Section

General: Thin layer chromatography was used to check the purity of the products. Melting points were determined by using a Mettler FP 51 melting point apparatus and are uncorrected. IR spectra were recorded using KBr discs on a Shimadzu FTIR-8201 PC Infrared Spectrophotometer and ^{1}H NMR on a Varian AMX 400 FT-NMR spectrometer using TMS as internal reference [D_6]-DMSO. The chemical shifts are quoted in ppm. Mass spectra were recorded on a Joel JMS-D 300 mass spectrometer. Microanalyses were obtained with a Perkin Elmer Model 240 CHN analyzer. Optical rotation was measured using an ERMA 1775 polarimeter in dry methanol as solvent.

*Reduction of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles (**1**) with zinc in acetic acid and acetic anhydride; general procedure*

The respective 1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (**3**, 0.001 mol) was dissolved in acetic acid (5 ml) and then acetic anhydride (5 ml) was added. The reaction mixture was stirred at room temperature for 10 minutes and 0.410 g of zinc powder was added with stirring. The reaction mixture was further stirred for 5 h. After vigorous stirring, the reaction mixture was heated on a water bath for 12 h. Then the reaction mixture was poured into ice cold water and neutralized with 10% sodium bicarbonate solution. The reaction mixture was extracted with ethyl acetate (3×50 ml) and thoroughly washed with water. The combined organic layers were dried over anhydrous sodium sulfate. After removal of solvent, the crude product obtained was further purified by column chromatography over silica gel using petroleum ether-ethyl acetate (80:20) as eluent.

*2-Acetoxy-(1-acetylamino)-8-methylcarbazole (**2a**)*

M. p.: 176 °C; yield: 48%. – IR (KBr): $\nu = 3577$ (NH), 3320 (NH), 1738 (C=O), 1666 (C=O), 1639, 1591, 1533, 1506, 1431, 1369, 1325, 1217, 1170, 1041 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]-DMSO: $\delta = 2.31$ (s, 3 H, 1-CO*Me*), 2.35 (s, 3 H, 8-*Me*), 2.51 (s, 3 H, 2-CO*Me*), 6.95 (d, 1 H, 3-H,

$J = 7.8$ Hz), 7.11 – 7.16 (m, 1 H, 6-H), 7.20 (d, 1 H, 4-H, $J = 7.8$ Hz), 7.76 (d, 1 H, 5-H, $J = 7.9$ Hz), 7.96 (d, 1 H, 7-H, $J = 8.0$ Hz), 9.18 (b s, 1 H, carbazole-N*H*), 9.37 (s, 1 H, 1-N*H*OMe). – MS (EI, 70 eV): *m/z* (%) = 296 (41) [M^+]. – $C_{17}H_{16}N_2O_3$ (296.17): calcd. C 68.94, H 5.40, N 9.45; found C 68.99, H 5.34, N 9.41.

*2-Acetoxy-(1-acetylamino)-7-methylcarbazole (***2b***)*

M. p. 184 °C; -yield: 45%. – IR (KBr): $\nu = 3510$ (NH), 3325 (NH), 1757 (C=O), 1654 (C=O), 1591, 1535, 1506, 1433, 1365, 1321, 1205, 1171, 1038 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.29$ (s, 3 H, 1-CO*Me*), 2.47 (s, 3 H, 2-CO*Me*), 2.78 (s, 3 H, 7-*Me*), 6.98 (d, 1 H, 3-H, $J = 8.4$ Hz), 7.27 (d, 1 H, 4-H, $J = 8.4$ Hz), 7.52 (s, 1 H, 8-H), 7.91 (d, 1 H, 6-H, $J = 8.2$ Hz), 7.95 (d, 1 H, 5-H, $J = 8.2$ Hz), 9.61 (b s, 1 H, carbazole-N*H*), 10.73 (s, 1 H, 1-N*H*OMe). – MS (EI, 70 eV): *m/z* (%) = 296 (41) [M^+]. – $C_{17}H_{16}N_2O_3$ (296.17): calcd. C 68.94, H 5.40, N 9.45; found C 68.90, H 5.42, N 9.41.

*2-Acetoxy-(1-acetylamino)-6-methylcarbazole (***2c***)*

M. p. 166 °C; -yield: 50%. – IR (KBr): $\nu = 3455$ (NH), 3295 (NH), 1741 (C=O), 1658 (C=O), 1637, 1610, 1590, 1527, 1425, 1364, 1338, 1215, 1197, 1038 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.16$ (s, 3 H, 1-CO*Me*), 2.30 (s, 3 H, 6-*Me*), 2.48 (s, 3 H, 2-CO*Me*), 6.92 (d, 1 H, 3-H, $J = 8.2$ Hz), 7.42 (d, 1 H, 7-H, $J = 8.2$ Hz), 7.94 (d, 1 H, 4-H, $J = 8.2$ Hz), 7.89 (s, 1 H, 5-H), 8.10 (d, 1 H, 8-H, $J = 8.2$ Hz), 9.57 (b s, 1 H, carbazole-N*H*), 10.69 (s, 1 H, N*H*COMe). – MS (EI, 70 eV): *m/z* (%) = 296 (41) [M^+]. – $C_{17}H_{16}N_2O_3$ (296.17): calcd. C 68.94, H 5.40, N 9.45; found C 68.91, H 5.45, N 9.39.

*2-Acetoxy-(1-acetylamino)carbazole (***2d***)*

M. p. 200 °C; -yield: 48%. – IR (KBr): $\nu = 3550$ (NH), 3317 (NH), 1737 (C=O), 1655 (C=O), 1639, 1612, 1591, 1533, 1460, 1365, 1325, 1213, 1167, 1035 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.30$ (s, 3 H, 1-CO*Me*), 2.52 (s, 3 H, 2-CO*Me*), 7.16 – 7.43 (m, 2 H, 6-H, 7-H), 7.45 (d, 1 H, 3-H, $J = 8.0$ Hz), 7.54 (d, 1 H, 4-H, $J = 8.0$ Hz), 7.99 (d, 1 H, 5-H, $J = 8.3$ Hz), 8.10 (d, 1 H, 8-H, $J = 7.6$ Hz), 9.60 (b s, 1 H, carbazole-N*H*), 10.84 (s, 1 H, N*H*COMe). – MS (EI, 70 eV): *m/z* (%) = 282 (51) [M^+]. – $C_{16}H_{14}N_2O_3$ (282.16): calcd. C 68.10, H 4.96, N 9.92; found C 68.06, H 4.99, N 9.97.

*2-Acetoxy-(1-acetylamino)-6-chlorocarbazole (***2e***)*

M. p. 204 °C; -yield: 42%. – IR (KBr): $\nu = 3496$ (NH), 3300 (NH), 1751 (C=O), 1655 (C=O), 1637, 1541, 1535, 1458, 1367, 1339, 1203, 1167 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.16$ (s, 3 H, 1-CO*Me*), 2.31 (s, 3 H, 2-CO*Me*), 6.97 (d, 1 H, 3-H, $J = 8.3$ Hz), 7.45 (d, 1 H, 4-H, $J = 8.3$ Hz), 7.55 (d, 1 H, 7-H, $J = 8.4$ Hz), 8.05 (d, 1 H, 8-H, $J = 8.4$ Hz), 8.22 (s, 1 H, 5-H), 9.65 (b s, 1 H, carbazole-N*H*), 11.00 (s, 1 H, N*H*COMe). – MS (EI, 70 eV): *m/z* (%) = 316 (50) [M^+]. – $C_{16}H_{13}N_2O_3Cl$ (316.16): calcd. C 60.69, H 4.11, N 8.84; found C 60.74, H 4.04, N 8.88.

*Reduction of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (***1***) using baker's yeast; general procedure*

About 2 g of sucrose was dissolved in 10 ml of water, 1 g of bakers' yeast was added and the mixture was stirred well for 30 minutes until the fermentation of the sucrose was complete. Then **1** (0.001 mol) was added to the medium and 5 ml of alcohol was added and stirring was continued for 48 h. Then, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and was dried over anhydrous sodium sulfate. On removal of solvent a yellow crude powder was obtained which was purified by column chromatography using petroleum ether/ethyl acetate (75:25) as eluent to yield a yellow crystalline powder.

*(-)-6-[Acetoxy(hydroxy)methyl]-1-hydroxylamino-8-methylcarbazole (***3a***)*

M. p. 234 °C (dec.);. yield: 80%. – IR (KBr): $\nu = 3510$ (OH), 3475 (NH), 3200 (NH), 2980, 2870, 1638, 1608, 1541, 1431, 1369, 1325, 1226, 1170, 1041 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.44$ (s, 6 H, 8-*Me*, 1'-CO*Me*), 7.17 – 7.24 (m, 2 H, 2-H, 3'-H), 7.37 – 7.73 (m, 3 H, 3-H, 4-H, 3'-O*H*), 8.22 (s, 1 H, 5-H), 8.27 (s, 1 H, 7-H), 8.78 (b s, 1 H, carbazole-N*H*), 9.11 (s, 1 H, 1-N*H*OH) 11.50 (s, 1 H, 1-NHO*H*). – $^{13}C\{^1H\}$ NMR (300 MHz, [D_6]-DMSO): $\delta =$ 17.02 (8-*Me*), 37.56 (1'-O*Me*), 38.44 (C-3'), 103.61 (C-2), 109.13 (C-4), 1118.01 (C-3), 119.20 (C-9a), 121.45 (C-4a), 123.14 (C-7), 134.33 (C-8a), 138.58 (C-4b), 142.35 (C-5), 148.96 (C-8), 158.94 (C-6), 163.28 (C-1), 190.14 (C=O). – MS (EI, 70 eV): *m/z* (%) = 300 (23) [M^+]. – $C_{16}H_{16}N_2O_4$ (300.16): calcd. C 64.02, H 5.33, N 9.33; found C 63.98, H 5.39, N 9.31.

*(+)-6-[Acetoxy(hydroxy)methyl]-1-hydroxylamino-7-methylcarbazole (***3b***)*

M. p. 254 °C; yield: 85%. – IR (KBr): $\nu = 3540$ (OH), 3485 (NH), 3414 (NH), 3168, 3041, 2923, 2853, 1669, 1613, 1564, 1480, 1453, 1347, 1251, 1223, 1121 cm^{-1}. – ^1H NMR (400 MHz, [D_6]-DMSO): $\delta = 2.43$ (s, 3 H, 7-*Me*), 2.45 (s, 3 H, 1'-CO*Me*), 7.17 – 7.23 (m, 2 H, 2-H, 3'-H), 7.50 – 7.62 (m, 3 H, 3-H, 4-H, 3'-O*H*), 7.76 (s, 1 H, 5-H), 7.80 (s, 1 H, 8-H), 8.50 (b s, 1 H, carbazole-N*H*), 8.78 (s, 1 H, N*H*OH), 10.26 (s, 1 H, 1-NHO*H*). – $^{13}C\{^1H\}$ NMR (300 MHz, [D_6]-DMSO): $\delta = 16.95$ (7-*Me*), 38.96 (1'-O*Me*), 39.52 (C-3'), 105.58 (C-2), 108.83 (C-4), 117.74 (C-3), 118.21 (C-9a), 122.50 (C-4a), 124.25 (C-8), 134.94 (C-8a), 139.48 (C-

4b), 142.85 (C-5), 149.96 (C-7), 159.04 (C-6), 161.68 (C-1), 189.54 (C=O). - MS (EI, 70 eV): *m/z* (%) = 300 (23) [M^+]. – $C_{16}H_{16}N_2O_4$ (300.16): calcd. C 64.02, H 5.33, N 9.33; found C 64.07, H 5.30, N 9.36.

*(+)-6-[Acetoxy(hydroxy)methyl]-1-hydroxylaminocarbazole (**3d**)*

M. p. 242 °C; yield: 82%. – IR (KBr): ν = 3540 (OH), 3485 (NH), 3414 (NH), 3200, 2970, 2853, 1661, 1618, 1566, 1497, 1427, 1304, 1259, 1121 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 2.49 (s, 3 H, 1'-CO*Me*), 7.17 – 7.22 (m, 2 H, 2-H, 3'-H), 7.29 – 7.54 (m, 3 H, 3-H, 4-H, 3'-O*H*), 7.72 (d, 1 H, 7-H, J = 7.5 Hz), 7.77 (d, 1 H, 8-H, J = 7.5 Hz), 8.20 (s, 1 H, 5-H), 8.27 (b s, 1 H, carbazole-N*H*), 9.12 (s, 1 H, 1-N*H*OH), 11.49 (s, 1 H, 1-NHO*H*). – MS (EI, 70 eV): *m/z* (%) = 286 (30) [M^+]. – $C_{15}H_{14}N_2O_4$ (286.14): calcd. C 62.96, H 4.89, N 9.79; found C 62.90, H 4.92, N 9.76.

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