Synthesis of Novel 3-Acetyl-2-hydroxy-1-N,N-diacetylaminocarbazole Derivatives

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1-Hydroxyimino-1,2,3,4-tetrahydrocarbazoles, 3-Acetyl-2-hydroxy-1-N,N-diacetylaminocarbazoles, Aromatization, Thermal Fries Rearrangement, Antimicrobial Activities

The synthesis of hitherto unknown 3-acetyl-2-hydroxy-1-N,N-diacetylaminocarbazole (**3a–f**), is reported. The hydroxyiminocarbazoles (**2a–f**), prepared from 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a–f**) on treatment with acetyl chloride in acetic anhydride yielded the title compounds (**3a–f**).

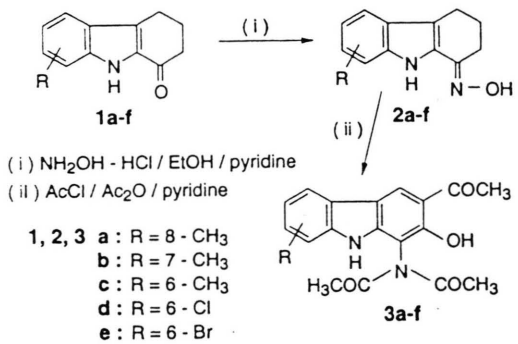
Various carbazole skeletons, such as simple, pyrano, pyrido, pyrazino and carbazolyloxypropanolamines, have recently provided many leads towards the basic models in the design of new drugs [1–7]. In connection with the search for newer physiological active carbazole compounds, we first report the synthesis of novel carbazole derivatives, 3-acetyl-2-hydroxy-1-N,N-diacetylaminocarbazoles (**3a–f**).

1-Oxo-1,2,3,4-tetrahydrocarbazoles **1a–f**, prepared according to our reported procedure [3, 8] on treatment with hydroxylamine hydrochloride in pyridine, afforded the 1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (**2a–f**) (Table I). **2a** was reacted with equimolar acetyl chloride in acetic anhydride and pyridine. It gave, after work up, a single compound, **3a,** m.p. 215–216 °C. Its IR spectrum showed a strong band at 1640 cm^{-1} due to the presence of C=O groups and bands at 3420 and 3260 cm^{-1} due to the presence of –OH and –NH groups, respectively. Its PMR spectrum showed a singlet at δ 1.59, indicating six protons of $N(COCH_3)_2$, singlets at δ 2.36 showed the presence of C_8-methyl protons and a at δ 2.59 the presence of 3 protons in C_3–$COCH_3$. The aromatic region indicated a multiplet at δ 6.99–7.94, assigned to C_2–OH, C_4–H, C_5–H, C_6–H and C_7–H. A broad singlet appeared at δ 9.47, due to the NH proton which is D_2O exchangeable. The molecular ion peak (M^+) at *m/e* 338 in its mass spectrum and elemental analysis are in accord with the molecular

Table I. The physical and IR data of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles (**2a–f**).

Compound	m.p.[a] [°C]	Yield [%]	M.F.[b] (Molecular formula)	IR[c] [ν_{max} · cm^{-1}]
2a	144–145	70	$C_{13}H_{14}N_2O$ (214.26)	3450 3350
2b	143–144	65	$C_{13}H_{14}N_2O$ (214.26)	3450 3200
2c	139–140	75	$C_{13}H_{14}N_2O$ (214.26)	3400 3250
2d	141–142	65	$C_{12}H_{11}N_2OCl$ (234.67)	3420 3260
2e	149–150	55	$C_{12}H_{11}N_2OBr$ (279.12)	3400 3200
2f	142–143°	65	$C_{12}H_{12}N_2O$ (200.23)	3450 3400

[a] Uncorrected, measured using mettler FP_5 apparatus and a Boetius micro heating table; [b] satisfactory micro analysis obtained C±0.25, H±O.11, N±0.13; [c] recorded on Perkin Elmer 597 spectrophotometer.



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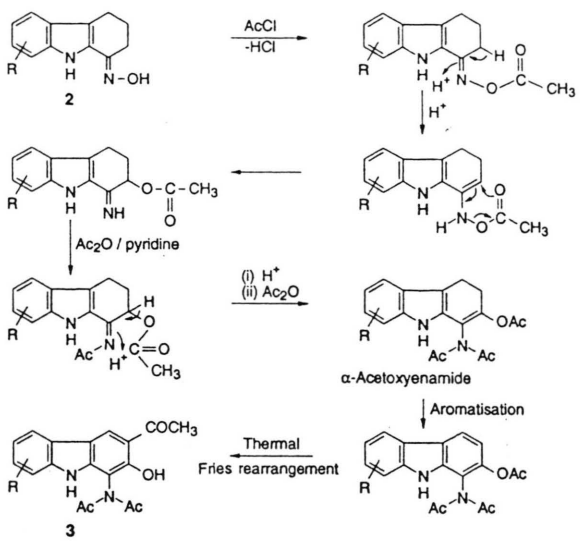
formula $C_{19}H_{18}N_2O_4$. From these data the structure of **3a** was assigned to be 3-acetyl-2-hydroxy-1-N,N-diacetylamino-8-methylcarbazole.

The carbazole derivatives **3b, 3c, 3d, 3e** and **3f** were prepared similarly.

A plausible mechanism for the conversion of 1-hydroxyimino carbazole **2** to 3-acetyl-2-hydroxy-1-N,N-diacetylaminocarbazole derivative **3** is represented in Scheme 1.

Scheme 1.



The ketoxime **2** gets N-oxyacetylated first. Then an intramolecular migration of the acetyloxy group from the nitrogen atom to the β-carbon atom in the presence of acid, liberated *in situ,* results the formation of an α-acetoxyimine as in the transformation of a ketoxime having an α-methylene group [9]. It is successively followed by the diacetylation at the nitrogen atom, aromatization and thermal Fries rearrangement of the O-acetyl to δ-carbon atom to yield the final product (**3**) (Scheme 1).

The compounds **3a–f** were screened for their *in vitro* growth inhibitory action against different strains of pathogenic bacteria, namely Bacillus subtilis (gram positive), *Escherichia coli, Salmonella typhi* and *Pseudomonas aurogenosa* (gram negative). The bacteria were maintained on Mueller-Hinton Agar [10] slants, and testing was carried out by the disk diffusion method [11] using a concentration of 100 μg/ml for the above strains. In this method, compounds were dissolved in acetone, and the growth of the bacteria was observed after 32 h. Among them, halogen derivatives (**3d, 3e**) were found to be highly active against Escherichia coli and Bacillus subtilis.

Experimental

Melting points were determined with a Boetius-microheating table and a Mettler FP5 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 597 spectrometer. ^{1}H NMR spectra were recorded on JEOL GSx 400 MHz FTNMR and WH 270 MHz spectrometers using TMS as an internal standard. Microanalyses were performed on Carlo Erba 1106 and Perkin Elmer model 240 CHN analyzers. Mass spectra were recorded on a Finnigan MAT 8230 GC-MS mass spectrometer. Pyridine was dried over potassium hydroxide pellets. Petroleum ether of boiling range 60–80 °C was used.

General procedure for the preparation of 1-hydroxyiminotetrahydrocarbazoles (**2a–f**)

A mixture of 1-oxo-1,2,3,4-tetrahydrocarbazole derivatives [8] (**1,** 5 mmol), hydroxylamine hydrochloride (3,5 g, 50 mmol) in dry pyridine (5 ml) and absolute ethanol (10 ml) was heated on a water bath under nitrogen atmosphere for 1 h. The residue obtained on evaporation of excess solvent was diluted with water (10 ml) and extracted with chloroform (3×10 ml). The extract was successively washed with dil. HCl and water and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by crystallization of the residue obtained with a pet. ether-benzene mixture yielded **2** as colourless prisms.

Experimental data of the 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles **2a–f** thus produced are collected in Table I.

General procedure for the preparation of 3-acetyl-2-hydroxy-1-N,N-diacetylaminocarbazoles (**3a–f**)

To an ice-cooled solution of carbazoleoxime (**2,** 3 mmol) in acetic anhydride (2 ml) and pyridine (3 ml), acetylchloride (1 ml) was added slowly and heated at 80 °C for 10 h. The reaction mixture was diluted with ice water and extracted with chloroform (3×20 ml). The chloroform extract was washed with dil. HCl and water, dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed over a column of silica gel and eluted with a pet. ether-

ethyl acetate (99:1) mixture to afford **3** as colourless needles.

3a: Yield: 510 mg (50%), m.p. 215–216 °C (pet. ether-ethyl-acetate).

IR(KBr) ν_{max}: 3420 (OH), 3260 (NH), 1640 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 1.59 (s, 6H, C_1−$N(COCH_3)_2$], 2.36 (s, 3H, C_8−CH_3), 2.59 (s, 3H, C_3−$COCH_3$), 6.99–7.94 (m, 5H, C_2−OH, C_4−H, C_5−H, C_6−H and C_7−H) and 9.47 (br s, 1H, NH, D_2O exchangeable) ppm.

Mass *m/e:* 338(M^+), 239, 238, 220, 196, 195, 168, 167, 140, 115, 89, 77, 63.

Analysis for $C_{19}H_{18}N_2O_4$ (338.35)
Calcd C 67.44 H 5.36 N 8.28%,
Found C 67.35 H 5.32 N 8.15%.

3b: Yield: 435 mg (43%), m.p. 210–212 °C (Pet. ether-ethylacetate).

IR(KBr) ν_{max}: 3380 (OH), 3240 (NH), 1690 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 2.29 [s, 6H, C_1−$N(COCH_3)_2$], 2.48 (s, 3H, C_7−CH_3), 2.80 (s, 3H, C_3−$COCH_3$), 7.19–8.00 [m, 6H, C_2−OH, C_4−H, C_5−H, C_6−H, C_8−H and H_9−H].

Mass *m/e:* 338(M^+), 239, 238, 218, 195, 166, 167, 143, 113, 88, 75, 62.

Analysis for $C_{19}H_{18}N_2O_4$ (338.35)
Calcd C 67.44 H 5.36 N 8.28%,
Found C 67.40 H 5.31 N 8.25%.

3c: Yield: 435 mg (43%), m.p. 207–209 °C (Pet. ether-ethylacetate).

IR(KBr) ν_{max}: 3430 (OH), 3240 (NH), 1680 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 2.40 [s, 6H, C_1−$N(COCH_3)_2$], 2.50 [s, 3H, C_6−CH_3], 2.70 [s, 3H, C_3−$COCH_3$], 5.90 (s, 1H, C_2−OH), 7.20–8.10 [m, 4H, C_4−H, C_5−H, C_7−H, C_8−H], 9.45 [br, s, 1H, NH, D_2O exchangeable] ppm.

Mass *m/e:* 338 (M^+), 239, 236, 219, 195, 190, 168, 143, 75, 65.

Analysis for $C_{19}H_{18}N_2O_4$ (338,35)
Calcd C 67.44 H 5.36 N 8.28%,
Found C 67.40 H 5.32 N 8.24%.

3d: Yield: 430 mg (41%), m.p. 98–100 °C (Pet. ether-ethylacetate).

IR(KBr) ν_{max}: 3440 (OH), 3230 (NH), 1680 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 1.87 [s, 6H, C_1−$N(COCH_3)_2$], 2.95 [s, 3H, C_3−$COCH_3$), 7.26–8.11 [m, 6H, C_2−OH, C_4−H, C_5−H, C_7−H, C_8−H and H_9−H].

Mass *m/e:* 358 (M^+), 300, 298, 260, 259, 241, 218, 217, 215, 119, 108, 83, 81.

Analysis for $C_{18}H_{15}N_2O_4Cl$ (358,76)
Calcd C 60.25 H 4.21 N 7.81%,
Found C 60.12 H 4.19 N 7.63%.

3e: Yield: 465 mg (39%), m.p. 157–158 °C (Pet. ether-ethylacetate).

IR(KBr) ν_{max}: 3380 (OH), 3280 (NH), 1640 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 1.59 [s, 6H, C_1−$N(COCH_3)_2$], 2.34 [s, 3H, C_3−$COCH_3$], 6.99–8.15 [m, 5H, C_2−OH; C_4−H, C_5−H, C_7−H and C_8−H] and 9.57 [br, s, 1H, NH, D_2O exchangeable] ppm.

Mass *m/e:* 403 (M^+), 345, 343, 306, 305, 304, 286, 263, 260, 153, 127, 126, 101.

Analysis for $C_{18}H_{15}N_2O_4Br$ (403.21)
Calcd C 53.61 H 3.75 N 6.95%,
Found C 53.58 H 3.63 N 6.89%.

3f: Yield: 660 mg (46%), m.p. 198–199 °C (Pet. ether-ethylacetate).

IR(KBr) ν_{max}: 3450 (OH), 3270 (NH), 1620 (−C−) cm^{-1}
||
O

^1H NMR ($CDCl_3$) δ: 2.27 [s, 6H, C_1−$N(COCH_3)_2$], 2.87 [s, 3H, C_3−$COCH_3$], 7.24–7.48 [m, 6H, C_2−OH, C_4−H, C_5−H, C_6−H, C_7−H and C_8−H] and 8.21 [br, s, 1H, NH, D_2O exchangeable] ppm.

Mass *m/e:* 324 (M^+), 225, 206, 182, 181, 154, 153, 126, 101, 75, 63, 49.

Analysis for $C_{18}H_{16}N_2O_4$ (324.32)
Calcd C 66.65 H 4.97 N 8.63%,
Found C 66.52 H 4.87 N 8.51%.

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