Novel Functionalized 1,4,4a,9a-Tetrahydro-1-aza-9-oxafluorenes by Cycloaddition of 4-(4-Methoxyphenyl)-1,4-dihydropyridines and *p*-Benzoquinone

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An unexpected acid-catalysed cycloaddition reaction between 2,6-unsubstituted 3,5-diacetyl-4-(4-methoxyphenyl)-1,4-dihydropyridines **1** and *p*-benzoquinone yields novel, functionalized 1,4,4a,9a-tetrahydro-1-aza-9-oxafluorenes **3** contrasting the expected redox reaction of corresponding 4-hydrogen-1,4-dihydropyridine and *p*-benzoquinone.

While the structural variety of reduced nicotinamide adenine dinucleotide (NADH) model compounds proceeded from *N*-benzyldihydronicotinamide meanwhile includes substances with different *N*-alkyl- and carboxamide substituents [1,2] and annelated rings like acridones [3] or pyrido[3,2-*c*]azepins [4], recent investigations have been taken into the oxidation mechanism of 4-substituted nicotinamide adenine dinucleotide model compounds [5].

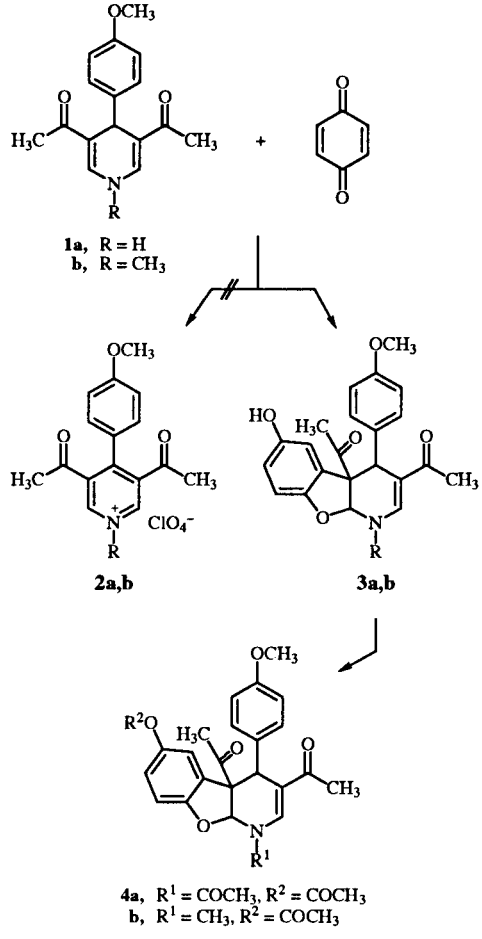
We have been interested in the redox behaviour of 2,6-unsubstituted 3,5-diacetyl-1,4-dihydropyridines as reduced nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide model compounds with *p*-benzoquinone. Contrasting the described reducing reactions of 2,6-dimethyl-4-aryl-1,4-dihydropyridines with various oxidizing agents [6], our results concerning the 4-(4-methoxyphenyl)-derivates **1** with *p*-benzoquinone were completely surprising as **1a,b** exclusively undergoes a novel cycloaddition reaction with *p*-benzoquinone to 1,4,4a,9a-tetrahydro-1-aza-9-oxafluorenes **3a,b** under acid-catalysis without any oxidation to corresponding pyridinium salts. Thus the unexpected formation of **3** opens a novel synthetic route to functionalized 1-aza-9-oxafluorenes which have been reported as interesting pharmacological agents with a broad antiviral activity [7].

3,5-Diacetyl-1,4-dihydropyridine [8] was found to yield 3,5-diacetylpyridine [9] (90%) or corresponding pyridinium perchlorate [10] (95%), respectively, as oxidation products of a redox reaction with equimolar amounts of *p*-benzoquinone in dioxane after 8 hours or in dioxane/perchloric acid (5%) after 6 hours at room temperature [11].

3,5-Diacetyl-4-(4-methoxyphenyl)-1,4-dihydropyridine **1a** was made by cyclocondensation reaction of 4-methoxybenzaldehyde, the sodium salt of hydroxymethylenacetone and ammonium carbonate in ethanol following the method of Kuthan and Paleček [12]. The *N*-methyl-derivative **1b** was achieved by the methylation of **1a** in dimethylpropylenurea.

Surprisingly **1a,b** remained unchanged on treatment with both equimolar and excess amounts of *p*-benzoquinone in dioxane at room temperature and even under heating of the solution mixture. Under acid conditions in dioxane/perchloric acid (5%) novel 1,4,4a,9a-tetrahydro-

Scheme 1



1-aza-9-oxafluorenes **3a,b** were exclusively gained as cycloaddition products between equimolar amounts of **1a,b** and *p*-benzoquinone.

Even the *N*H-derivate **1a** gives no detectable oxidation product **2a** as was proved by tlc in comparison with oxidized **1a** made by reaction with manganese(IV) oxide.

The structure of **3** was completely characterized by spectroscopical methods and additionally confirmed by the acetylation to corresponding *O*- and *N*-actetyl derivatives **4**, respectively. While the *N*-H derivate **3a**, *e. g.*, has two ir-carbonyl bands with ν = 1711 and 1608 cm^{-1}, its *N*-acetyl-derivative **4a** shows additional carbonyl absorptions at ν = 1762 and 1636 cm^{-1}. The ^{1}H-NMR spectrum of **3a** shows characteristic singulets at 4.76 (4-H) and 6.31 (9a-H) ppm. The doublet of 2-H at 7.49 ppm (J = 7 Hz) coupling with the 1-*N*H at 7.87 ppm appears as a singulet after deuterium oxide-exchange. In summary, 3,5-diacetyl-4-hydrogen-1,4-dihydropyridine undergoes expected redox reaction with *p*-benzoquinone, whereas the 4-(4-methoxyphenyl)-derivatives remain stable to *p*-benzoquinone oxidation. Instead their unexpected cycloaddition reaction leads to novel functionalized 1,4,4a,9a-tetrahydro-1-aza-9-oxafluorenes. Investigations concerning reactivity and redox potentials are currently made in order to explain the different behaviour of the 4-hydrogen- and 4-(4-methoxyphenyl)-substituted 3,5-diacetyl-1,4-dihydropyridines.

EXPERIMENTAL

Commercial reagents were used as received without additional purification. The ^{1}H nmr spectra were recorded on a Bruker AC-200 F spectrometer at 200 MHz using tetramethylsilane as an internal standard. Melting points were determined with a Linström-apparatus and are uncorrected. Tlc was performed on silica gel 60 plates F_{254}. The ir spectra were recorded as potassium bromide disks. Mass spectra were recorded on a Finnigan 3500 mass spectrometer.

3,5 Diacetyl-4-(4-methoxyphenyl)-1,4-dihydropyridine (**1a**).

A mixture of 5 g (47 mmoles) of the sodium salt of hydroxymethylenacetone [12], 2.9 g (37 mmoles) of ammonium carbonate in 30 ml of water and 3.3 g (24 mmoles) of 4-methoxybenzaldehyde dissolved in 25 ml of ethanol was stirred at room temperature for 1 hour and then heated at 85° for additional 5 hours. After that the solution was extracted with chloroform (3 x 150 ml), the combined extracts were dried over sodium sulphate and evaporated. The crude reaction product partly dissolved in a mixture of ethyl acetate/ethanol/petroleum ether 40/60/acetone/chloroform. The insoluble residue consisted of pure **1a** as yellow powder, mp 214-216° (2.1 g, 32%); ir: ν 3321 (*N*H), 1628 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.12 (s, 6H, $COCH_3$), 3.66 (s, 3H, OCH_3), 4.89 (s, 1H, 4-H), 6.72-7.03 (m, 4H, aromat H), 7.52 (d, J = 5 Hz, after deuterium oxide-exchange s, 2H, 2-H, 6-H), 9.43 (t, J = 5 Hz, 1H, exchangeable, *N*H); ms: m/z 271 (M^+, 40).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.20. Found: C, 70.90; H, 6.46; N, 4.84.

3,5-Diacetyl-4-(4-methoxyphenyl)-1-methyl-1,4-dihydroypridine (**1b**).

One g (3.7 mmoles) of **1a** dissolved in 3 ml of dimethylpropylenurea was treated with a 1.5-fold excess of sodium hydride suspension in oil (80%). After stirring for 1 hour at room temperature 0.53 g (3.7 mmoles) of methyl iodide was added. Having stirred for additional 2 hour at room temperature the solution was hydrolysed with portions of water. Upon standing overnight the separated, semisolid product was filtered and recrystallized from toluene in yellow crystals, mp 172-174° (0.25 g, 24%); ir: ν 1630 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.15 (s, 6H, $COCH_3$), 3.34 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 5.09 (s, 1H, 4-H), 6.76-7.25 (m, 4H, aromat H), 7.09 (s, 2H, 2-H, 6-H); ms: m/z 285 (M^+, 27).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.90. Found: C, 71.59; H, 6.70; N, 4.91.

3,5-Diacetyl-4-(4-methoxyphenyl)pyridine (**2a**).

Compound **1a** (0.3 g, 1.1 mmoles) was heated with 0.6 g (6.9 mmoles) manganese(IV) oxide in boiling toluene for 10 hours. After that the oxidizing reagent was filtered, the solution dried over sodium sulphate and evaporated. The residual oil was dissolved in petroleum ether 60/80 from which **2a** crystallized in white needles, mp 97-98° (0,12 g, 40%); ir: ν 1685 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.96 (s, 6H, $COCH_3$), 3.88 (s, 3H, OCH_3), 6.98-7.27 (m, 4H, aromat H), 8.74 (s, 2H, 2-H, 6-H); ms: m/z 269 (M^+, 38).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.57; H, 5.66; N, 5.11.

3,4a-Diacetyl-1,4,4a,9a-tetrahydro-6-hydroxy-4-(4-methoxyphenyl)benzo[4,5]dihydrofuro[2,3-*b*]pyridine (**3a**).

Compound **1a** (0.5 g, 1.8 mmoles) and 0.19 g (1.8 mmoles) of *p*-benzoquinone were stirred at room temperature in dioxane/perchloric acid (5%) for 48 hours. After that the solution was evaporated and the residual oil dissolved in isopropyl alcohol from which **3a** crystallized as brownish powder (0.55 g). It was recrystallized from toluene, mp 190-192° (0.5 g, 75%); ir: ν 3374 (OH), 3308 (NH), 1707 (C-4a-$COCH_3$), 1608 (C-3-$COCH_3$) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.90 (s, 3H, C-4a-$COCH_3$), 2.00 (s, 3H, C-3-$COCH_3$) 3.69 (s, 3H, OCH_3), 4.76 (s, 1H, 4-H), 6.31 (s, 1H, 9a-H), 6.58 (dd, J = 9 Hz, J = 2Hz, 1H, 7-H), 6.65 (d, J = 9 Hz, 1H, 8-H), 6.75-6.79 (m, 2H, 3'-H, 5'-H), 6.92 (d, J = 2 Hz, 1H, 5-H), 7.16-7.20 (m, 2H, 2'-H, 6'-H), 7.49 (d, J = 7 Hz, after deuterium oxide exchange s, 1H, 2-H), 7.87 (d, J = 7 Hz, 1H, exchangeable, *N*H), 9.14 (s, 1H, exchangeable, OH); ms: m/z 379 (M^+, 5), 336 (M^+-$COCH_3$, 2).

Anal. Calcd. for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.12; H, 5.17; N, 3.48.

3,4a-Diacetyl-1,4,4a,9a-tetrahydro-6-hydroxy-4-(4-methoxyphenyl)-1-methyl-benzo[4,5]dihydrofuro[2,3-*b*]pyridine (**3b**).

Compound **1b** (0.5 g, 1.8 mmoles) and 0.19 g (1.8 mmoles) of *p*-benzoquinone were stirred at room temperature in dioxane/perchloric acid (5%) for 48 hours. After that the solution was evaporated and the remaining brownish powder (0.7 g) of **3b** was recrystallized from toluene, mp 243-245° (0.56 g, 80%); ir (potassium bromide): ν 3394 (OH), 1708 (C-4a-$COCH_3$), 1607 (C-3-$COCH_3$) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.92 (s, 3H, C-4a-$COCH_3$), 1.99 (s, 3H, C-3-$COCH_3$), 3.17 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 4.77 (s, 1H, 4-H), 6.18 (s, 1H, 9a-H), 6.58 (dd, J =

9 Hz, J = 2 Hz, 1H, 7-H), 6.70 (d, J = 9 Hz, 1H, 8-H), 6.75-6.79 (m, 2H, 3'-H, 5'-H), 6.93 (d, J = 2 Hz, 1H, 5-H), 7.13-7.18 (m, 2H, 2'-H, 6'-H), 7.57 (s, 1H, 2-H), 9.17 (s, 1H, exchangeable, OH); ms: m/z 393 (M^+, 2), 350 (M^+-$COCH_3$, 2).

Anal. Calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.55. Found: C, 70.35; H, 6.15; N, 3.81.

6-Acetoxy-1,3,4a-triacetyl-1,4,4a,9a-tetrahydro-4-(4-methoxyphenyl)-benzo[4,5]dihydrofuro[2,3-*b*]pyridine (**4a**).

Compound **3a** (0.3 g, 0.8 mmoles) was dissolved in 100 ml of acetic anhydride. After addition of 10 drops of pyridine the solution was stirred for 2 hours at room temperature and then evaporated. The residue was taken up in warm cyclohexane from which **4a** crystallized as a white powder, mp 255-256° (0.19 g, 50%); ir: ν 1762 (CH_3COO-C-6), 1711 (CH_3CO-C-4a), 1636 ($NCOCH_3$), 1609 (CH_3CO-C-3) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.13 (s, 3H, CH_3CO-C-4a), 2.18 (s, 3H, CH_3CO-C-3), 2.29 (s, 3H, CH_3COO-C-6), 2.66 (s, br, 3H, $NCOCH_3$), 3.75 (s, 3H, OCH_3), 4.98 (s, 1H, 4-H), 6.75-6.79 (m, 2H, 3'-H, 5'-H), 6.79 (s, 1H, 9a-H), 6.81 (d, J = 9 Hz, 1H, 8-H), 6.95 (dd, J = 9 Hz, J = 2 Hz, 1H, 7-H), 7.05-7.09 (m, 2H, 2'-H, 6'-H), 7.17 (d, J = 2 Hz, 1H, 5-H), 8.21 (s, 1H, 2-H) ; ms: m/z 463 (M^+, 1).

Anal. Calcd. for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.43; N, 3.02. Found: C, 67.03; H, 5.26; N, 2.79.

6-Acetoxy-3,4a-diacetyl-1,4,4a,9a-tetrahydro-4-(4-methoxyphenyl)-1-methyl-benzo[4,5]dihydrofuro[2,3-*b*]pyridine (**4b**).

Compound **3b** (0.24 g, 0.6 mmoles) was dissolved in 20 ml of acetic anhydride. After addition of 10 drops of pyridine the solution was stirred for 2 hours at room temperature and then evaporated. The remaining oil was dissolved in toluene from which **4b** crystallized in white needles, mp 196-198° (0.21 g, 80%); ir: ν 1759 (CH_3COO-C-6), 1706 (CH_3CO-C-4a), 1605 (CH_3CO-C-3) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.01 (s, 3H, CH_3CO-C-4a), 2.06 (s, 3H, CH_3CO-C-3), 2.28 (s, 3H, CH_3COO-C-6), 3.20 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 4.87 (s, 1H, 4-H), 6.36 (s, 1H, 9a-H), 6.73-6.79 (m, 2H, 3'-H, 5'-H), 6.82 (d, J = 9Hz, 1H, 8-H), 6.93 (dd, J = 9 Hz, J = 2Hz, 1H, 7-H), 7.13-7.23 (m, 3H, 5-H, 2'-H, 6'-H), 7.50 (s, 1H, 2-H); ms: m/z 435 (M^+, 2), 392 (M^+-$COCH_3$, 3).

Anal. Calcd. for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.21. Found: C, 69.12; H, 5.88; N, 3.05.

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[9] 3,5-Diacteyl-1,4-dihydropyridine (0.20 g, 1.2 mmoles) was stirred with an equimolar amount of *p*-benzoquinone (0.13 g) in 100 ml of dioxane at room temperature. After 8 hours the solution was evaporated to dryness and the remaining oil was dissolved in toluene from which *p*-hydroquinone crystallized (0,10 g, 0.9 mmoles). The mother liquid was evaporated to dryness again and the residual oil dissolved in petroleum ether 60/80 from which 3,5-diacetyl-pyridine crystallized in white needles (0.18 g, 90%), mp 71-72° (ref [8] 72°).

[10] 3,5-Diacteyl-1,4-dihydropyridine **1** (0.20 g, 1.2 mmoles) was stirred with an equimolar amount of *p*-benzoquinone (0.13 g) in 100 ml dioxane/perchloric acid (5%) for 6 hours at room temperature. The precipitate was filtered off and recrystallized from chloroform/acetone under the dropwise addition of toluene in white needles, mp 108-109° (0.30 g, 95%); ir: ν 1705 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.70 (s, 6 H, $COCH_3$), 7.78 (s, br, exchangeable, 1H, N^+H), 8.66 (t, br, J = 2 Hz, 1H, 4-H), 9.31 ("s", br, 2H, 2-H, 6-H); ms: m/z 163 (M^+ - base, 60), 148 (M^+-CH_3, 100).

Anal. Calcd. for $C_9H_9NO_2 \cdot HClO_4$: C, 41.00; H, 3.82; N, 5.31. Found: C, 40.79; H, 3.77; N 5.21.

[11] Previous attempts to make the *N*-methyl-3,5-diacetyl-1,4-dihydropyridine by methylation of the *N*-unsubstituted derivative in order to analyse its redox behaviour with *p*-benzoquinone failed due to the low stability of the *N*-methyl-derivative.

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