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3-HYDROQUINOLYLQUINOLINES AND BISQUINOLYL-ANNELATED OXEPIN AS UNEXPECTED PRODUCTS FROM THE REACTION OF *p*-BENZOQUINONE AND *N*-ACETYL-1,4-DIHYDROQUINOLINES

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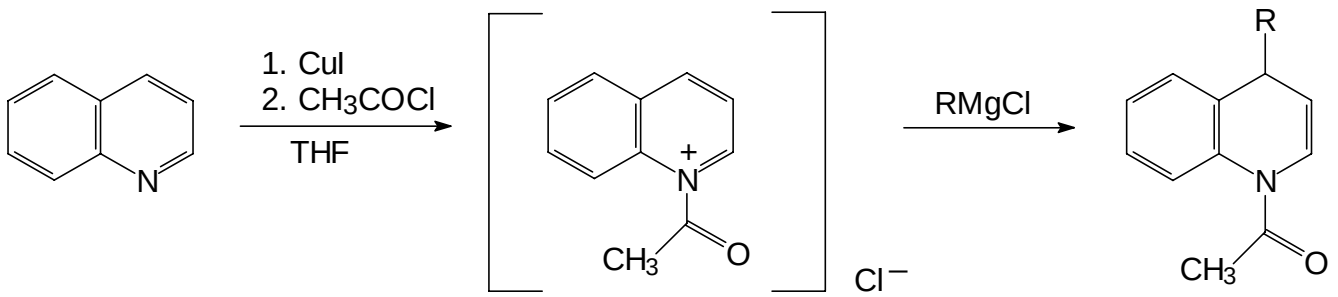
Abstract - 4-Substituted *N*-acyl-1,4-dihydroquinolines (**1a**, **b**) have been yielded by regioselective 4-arylation/alkylation *via* quinolinium intermediates. Acid-catalysed reaction of **1a**, **b** with *p*-benzoquinone leads to unexpected 3-hydroquinolylquinolines (**5a**, **b**). The structure of compounds (**5a**, **b**) has been confirmed by spectroscopical data and additionally by formation of both *O*-acetyl derivatives (**7a**, **b**). Bisquinolyl-annelated oxepin (**9a**) was found as side product. Formation and stereochemistry of the spectroscopically characterized compound (**9a**) are discussed.

We recently reported the regioselective formation of 3-acyl- and 4-substituted 1,4-dihydropyridine compounds.[1] Tetrahydro-1-aza-9-oxafluorenes have been characterized as given reaction products with *p*-benzoquinone, whereas pyridine oxidation products were not found. 1-Aza-9-oxafluorenes as resulting oxidation products from the tetrahydro derivatives were biologically demonstrated as novel class of small-sized cytostatics in in vitro screens.[2] Designed as DNA-intercalators with a planar aromatic system they were reported not to act as intercalators by an ethidium bromide displacement assay.[3] Their inability to intercalate was discussed to be caused by a non-planarity of the 4-aryl substituent with the tricyclic 1-aza-9-oxafluorene scaffold that was demonstrated to correlate with a twisting of the 3-carbonyl substituent out of the molecular plane.[4] We now selected quinolines instead of 3-acyl substituted pyridines as starting structures for synthesis of analogs benzo-anelated 1-aza-9-oxafluorenes. Comparing to those 3-acyl substituted 1-aza-9-oxafluorenes with the non co-planar 4-phenyl ring the 4-phenyl ring in the benzo-annelated 1-aza-9-oxafluorenes may probably show planarity with the heterocyclic scaffold thus promising

DNA-intercalating properties. The following synthetic procedure is described and unexpected reaction products are characterized. Mechanisms of product formation are discussed und stereochemistry is supported by spectroscopic data.

Results and Discussion

Starting materials, *N*-acyl-1,4-dihydroquinolines (**1a**, **b**) have been prepared from quinoline by regioselective 4-arylation and -alkylation, respectively, of the non-isolated *N*-acylquinolinium salt intermediates in dry THF using equimolar amounts of corresponding Grignard reagents and catalytic amounts of copper(I) iodide.[5]



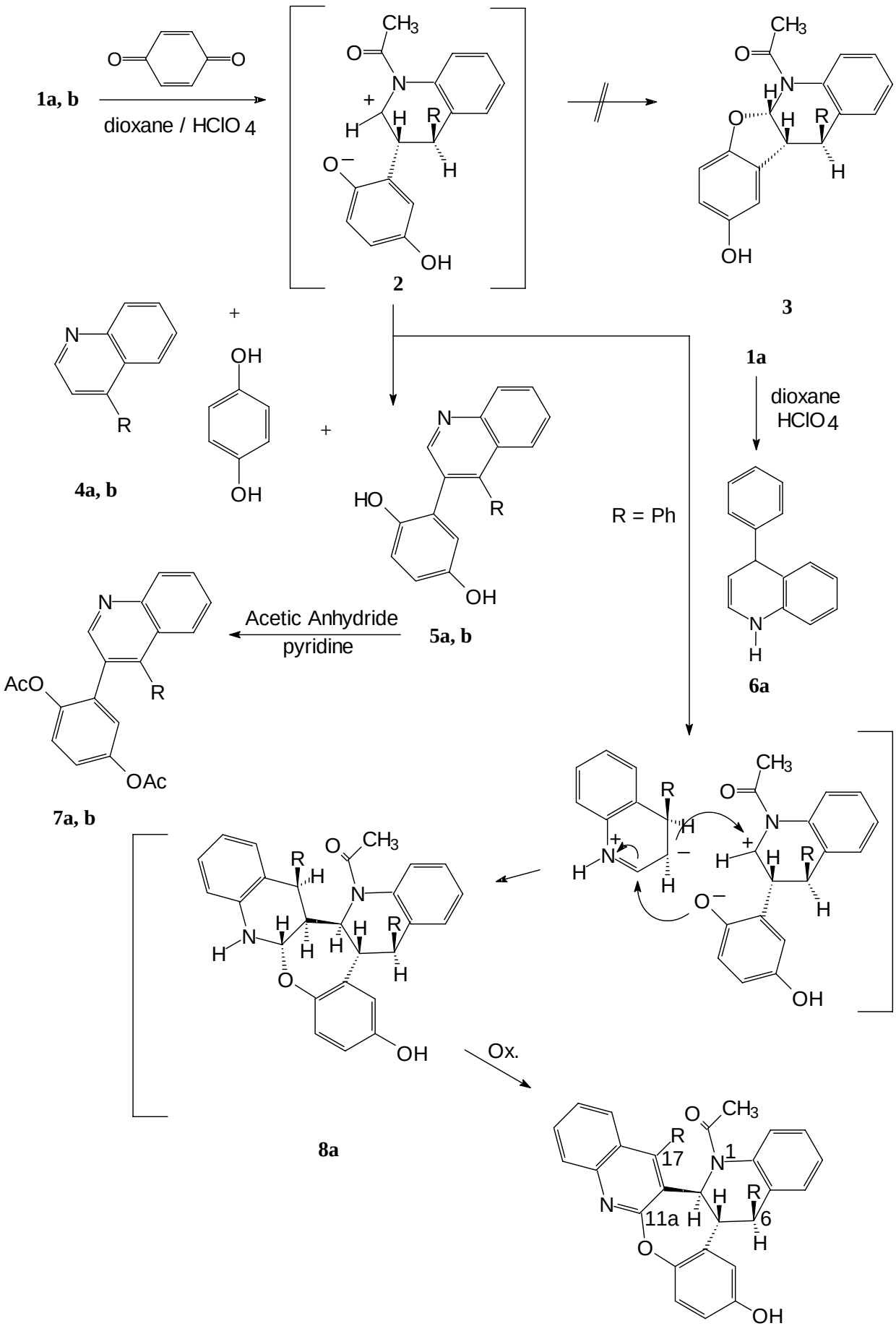
1a, R = Ph
b, R = CH_3

Scheme 1

In comparison to related 3-acyl- or ethoxycarbonyl substituted 1,4-dihydropyridines with *N*-acyl substitution 1,4-dihydroquinolines (**1a**, **b**) do not exist as rotamers as is evident from one set of proton signals for *N*-acyl neighboring protons 2-H and 8-H, respectively, while a double set for *N*-acyl neighboring protons 2-H and 6-H has been found in corresponding 1,4-dihydropyridines.[1]

First, an almost equimolar mixture of *p*-benzoquinone and *N*-acyl-1,4-dihydroquinoline (**1**) was stirred at room temperature in dioxane containing 5% of perchloric acid with first products being detectable by TLC. Stirring was continued after the addition of nearly a twofold excess of the oxidizing agent and finalized product formation with two main products and one side-product in the case of the 4-phenyl starting compound (**1a**).

Work up of the reaction mixtures and spectroscopical characterization of the isolated main products proved them as unexpected 3-hydroquinolylquinolines (**5a**, **b**) beside quinoline oxidation products (**4a**, **b**)[6,7] (Scheme 2). The formation of formal addition products (**5a**, **b**) might have followed the primary Michael addition as an initial step to the described tetrahydro-1-aza-9-oxafluorene synthesis.[1,8] However, before a ring closure reaction to a tetrahydro-1-aza-9-oxafluorene addition product (**3**), oxidation of the Michael


1a, b
dioxane / HClO 4
2
3
1a
dioxane
HClO4
6a
R = Ph
4a, b
5a, b
Acetic Anhydride
pyridine
7a, b
8a
Ox.
9a

Scheme 2

adduct (**2**) itself must have taken place by remaining *p*-benzoquinone consequently leading to 3-hydroquinolylquinolines (**5a**, **b**). Structure of compounds (**5a**, **b**) is spectroscopically characterized by the occurance of low-field proton resonances for 2-H of the quinoline at 8.83 (**5a**) and 8.66 ppm (**5b**). Due to different chemical surroundings exchangable hydroxy protons result in different resonances (see **EXPERIMENTAL**). The observed high-field shift of the 5-H to 7.59 ppm in the phenyl derivative (**5a**) compared to its resonance at 8.03 ppm in the methyl derivative (**5b**) may be caused by a shielding effect of the neighboring phenyl substituent which consequently does not within the molecular plane as was reported for 1-aza-9-oxafluorene compounds.[2] The structures (**5a**, **b**) were furthermore confirmed by formation of *O*-acetyl derivatives (**7a**, **b**) with characteristic IR carbonyl ester bonds between 1720 and 1765 cm^{-1}.

Comparing to reaction behavior of 3-acyl substituted 1,4-dihydropyridines and their Michael adducts which are stable intermediates so that tetrahydro-1-aza-9-oxafluorenes are yielded, the 1,4-dihydroquinolines proved to be less stable towards oxidation process by the formation of considerable amounts of quinoline oxidation products (**4a**, **b**) as well as the formation of intermediate oxidation products (**5a**, **b**). However, these differences in reactivity are plausible with respect to the discussed oxidation stability of the 3-carbonyl substituted dihydropyridines.[1] In those compounds the enhanced conjugation possibilities of the *N*-acyl substituent with the 3-acyl substituent resulted in described rotamers. Corresponding rotamers were not found for the dihydroquinolines so that such oxidation stability due to the reported enhanced conjugation possibilities of the dihydropyridines cannot be stated for the dihydroquinolines.

The isolated side-product (**9a**) was characterized to have two quinoline moieties, one as quinoline and the other as *N*-acetyl tetrahydro-compound both which anelated to a benzoxepin, so that the stoichiometric relation between quinolines and *p*-benzoquinone is just two to one. The formation is suggested to follow the primary Michael reaction to the addition product (**2**). Then an attack of C-3 in a 4-phenyl-1,4-dihydroquinoline (**6a**) may have competed with that of the less nucleophilic oxygen leading to octahydro intermediate (**8a**), though it was merely characterized by MS spectrometry (EI-MS: *m/z*: 564 (M^+)) due to solvent instability for further characterization. Such 4-phenyl-1,4-dihydropyridine product (**6a**) was demonstrated to easily form from acid treatment of the *N*-acetyl starting compound (**1a**). This intermediate (**8a**) undergoes oxidation to bisquinonly-anelated oxepin compound (**9a**) by *p*-benzoquinone employed here.

The ring junction of the tetrahydroquinoline to the oxepine proved to be *trans* by a small coupling constant (< 1 Hz) between 6a-H and 17b-H compared to *cis* coupling in tetrahydro 1-aza-9-oxafluorenes with constants of about 10 Hz.[1] With a similar *trans* coupling between 6-H and 6a-H of 1.2 Hz the attack of the *p*-benzoquinone might have taken place from the rear side of the 1,4-dihydroquinoline, e. g. the side that does not face the pseudoaxially orientated phenyl ring, corresponding to previous reports,[1,9] while the following front attack of C-3 in the 1,4-dihydroquinoline consequently leads to the *trans* ring junction.

An absence of further oxidation of tetrahydro-partial structure of the oxepine (**9a**) by an excess of *p*-benzoquinone confirms the *trans* ring junction, because a *trans* ring junction may cause steric hindrance for a *p*-benzoquinone approach as oxidizing agent from the front side. In the case of a *cis* ring junction a *p*-benzoquinone approach from the front side might have taken place without steric hindrance because in the reported tetrahydro-1-aza-9-oxafluorenes with *cis* ring junction oxidation to 1-aza-9-oxafluorene by *p*-benzoquinone took place.[2]

In summary, 4-substituted *N*-acyl-1,4-dihydroquinolines show different reaction properties towards *p*-benzoquinone than corresponding 3-acyl-1,4-dihydropyridines with resulting quinoline oxidation products as well as 3-hydroquinolylquinolines. So they show the reduced oxidation stability compared to 1,4-dihydropyridines as could also be derived from the absence of rotamers of the *N*-acyl starting structures. Such presence of reported rotamers turned out as a proven feature of their oxidation stability by enhanced conjugation possibilities.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Varian Gemini-400 and Varian Gemini-500 with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale (ppm). MS spectra were taken with a AMD 402 spectrometer. IR spectra were recorded on a Bruker IFS-28 spectrophotometer. Preparative TLC was carried out with silica gel plates 60_{F254} with a layer thickness of 1 mm.

General Procedure for the Preparation of 1-Acetyldihydroquinolines

1.0 g (7.74 mmol) of freshly distilled quinoline was solved in 50 mL of anhydrous THF. After addition of copper(I) iodide 0.07 g (0.39 mmol) the solution was cooled down to -8 °C. Then 0.61 g (7.74 mmol) of acetyl chloride were added dropwise to the solution. The reaction mixture was stirred for 15 min at -8 °C. Then 7.7 mL (7.7 mmol) of a 1 M solution of phenylmagnesium chloride and methylmagnesium chloride, respectively, was added. Stirring was continued for 15 min and for additional 30 min at rt. Then 42 mL of an aqueous solution of ammonium chloride (20%, 8.4 g, 157 mmol) was added, followed by the extraction with ether (3 x 150 mL). The ether phase was then washed with 42 mL of a 20% solution mixture (1/1) of ammonia/ammonium chloride (4.2 g, 78.5 mmol), 42 mL of water, 42 mL of 10% hydrochloride acid (2 x), 42 mL of water and 42 mL of a saturated solution of sodium chloride. The ether phase was dried over sodium sulfate. After filtration the ether was removed under vacuum leaving white-yellow crystals of compound (**1a**) and a yellow oil of compound (**1b**).

1-Acetyl-1,4-dihydro-4-phenylquinoline (1a)

Yellow needles from ether, mp 126-129 °C (1.35 g, 70%). IR (KBr): 1659 (*N*$COCH_3$) cm^{-1}. MS *m/z*: 249 (M^+). ^{1}H NMR ($CDCl_3$): 7.94 (d, ^3J = 8.2 Hz, 1 H, 2-H), 7.33-6.96 (m, 9 H, aromat. H), 5.57 (dd, ^3J = 8.2 Hz and 4.7 Hz, 1 H, 3-H), 4.58 (d, ^3J = 4.7 Hz, 1 H, 4-H), 2.39 (s, 3 H, *N*$COCH_3$). *Anal.* Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N 5.62. Found: C, 81.73; H 6.18; N 5.57.

1-Acetyl-1,4-dihydro-4-methylquinoline (1b)

Yellow oil (1.12 g, 80%). IR ($CDCl_3$): 1668 ($NCOCH_3$) cm^{-1}. ESI-MS *m/z*: 188 ($M + H^+$). ^1H NMR ($CDCl_3$): 7.84 (d, ^3J = 7.4 Hz, 1 H, 2-H), 7.23-7.13 (m, 3 H, 6-, 7-, 8-H), 6.83 (d, ^3J = 7.0 Hz, 1 H, 5-H), 5.45 (dd, ^3J = 7.4 Hz and 5.3 Hz, 1 H, 3-H), 3.38 (dq, ^3J = 7.0 Hz and 5.3 Hz, 1 H, 4-H), 2.36 (s, 3 H, $NCOCH_3$), 1.28 (d, ^3J = 7.0 Hz, 1 H, 4-CH_3). For elemental analysis of the quinoline picrate (**4b**) see below.

General Procedure for the Preparation of Quinolines (4a, b), 3-Hydroquinolylquinolines (5a, b) and Bisquinolylbenzoxepin (9a)

A mixture of 1 g (4 mmol) of **1a** or 0.75 g (4 mmol) of **1b** with 0.5 g (4.8 mmol) of *p*-benzoquinone was solved in a minimum volume of dioxane/$HClO_4$ (5%). The mixture was stirred at rt and the reaction was monitored by TLC. With decreasing amounts of oxidizing agent additional *p*-benzoquinone was added in portions (each 0.16 g, 1.8 mmol) up to a twofold excess until the product formation was completed. Then the mixture was poured into ice-water and the pH was adjusted to pH = 7 using 1 M ammonuim hydroxide solution. The separating hydroquinone was filtered off and the water phase extracted with ether (3 x 150 mL). The organic phase was dried over sodium sulfate. After filtration ether was removed in vaccum leaving brownish oils. Preparative TLC of the oil in chloroform/ethyl acetate/methanol (85/15/2) led to quinolines (**4a, b**), 3-hydroquinolylquinoline compounds (**5a, b**) and side-product (**9a**).

4-Phenylquinoline (4a)

Yellow oil (0.64 g, 40%); mp (picrate) 215-218 °C (ethanol, ref. 6 : 226 °C).

4-Methylquinoline (4b)

Yellow oil (0.33 g, 30%), mp (picrate) 210-215 °C (ethanol, ref. 7: 219-220 °C).

3-(2,5-Dihydroxyphenyl)-4-phenylquinoline (5a)

Greenish powder from ether, mp 269-276 °C (0.73 g, 30%). IR (KBr): 3330 (OH) cm^{-1}. MS *m/z*: 313 (M^+). ^1H NMR (acetone-D_6): 8.83 (s, 1 H, 2-H), 8.11 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1 H, 8-H), 7.74 (dt, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1 H, 7-H), 7.62 (br s, 1 H, 2´-OH, exchangable), 7.59 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1 H, 5-H), 7.53 (dt, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1 H, 6-H), 7.30-7.35 (m, 6 H, Ph-H, 5´-OH, exchangable), 6.68 (d, ^3J = 8.8 Hz, 1 H, 3´-H), 6.57 (dd, ^3J = 8.8 Hz, ^4J = 2.9 Hz, 1 H, 4´-H), 6.48 (d, ^4J = 2.9 Hz, 1 H, 6´-H). *Anal.* Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N 4.47. Found: C, 80.09; H 4.67; N 4.35.

3-(2,5-Dihydroxyphenyl)-4-methylquinoline (5b)

Brownish powder from ether, mp > 350 °C (sublimation) (0.97 g, 50%). IR (KBr): 3361 (OH) cm^{-1}. ESI-MS *m/z*: 252 ($M + H^+$). ^1H NMR (acetone-D_6): 8.66 (s, 1 H, 2-H), 8.16 (d, ^3J = 7.8 Hz, 1 H, 8-H), 8.03 (d, ^3J = 9.0, 1 H, 5-H), 7.91 (s, 1 H, 2´-OH, exchangable), 7.72 (t, ^3J = 7.8 Hz, 1 H, 7-H), 7.67 (s, 1 H, 5´-OH, exchangable), 7.62 (dd, ^3J = 9.0 Hz and 7.8 Hz, 1 H, 6-H), 6.88 (d, ^3J = 8.6 Hz, 1 H, 3´-H), 6.80 (dd, ^3J = 8.6 Hz, ^4J = 2.9 Hz, 1 H, 4´-H), 6.72 (d, ^4J = 2.9 Hz, 1 H, 6´-H), 2.57 (s, 3 H, 4-CH_3). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N 5.57. Found: C, 76.23; H 4.86; N 5.32.

Preparation of 1,4-Dihydro-4-phenylquinoline (6a)

1 g (4 mmol) of **1a** was dissolved in 50 mL of dioxane/$HClO_4$ (5%). The solution was stirred at rt for 24 h and then poured into ice-water. The pH was adjusted to pH = 7 using 1 M ammonium hydroxide solution and then the water phase was extracted with ether (3 x 150 mL). The organic phase was dried over sodium sulfate. After filtration ether was removed in vaccum leaving a brownish oil. Preparative TLC of the oil in chloroform/ethyl acetate/methanol (85/15/2) led to 1,4-dihydroquinoline (**6a**).

1,4-Dihydro-4-phenylquinoline (6a)

Yellow oil (0.54 g, 65%). IR ($CDCl_3$): 3317 (*N*H) cm^{-1}. MS *m/z*: 207 (M^+). ^1H NMR ($CDCl_3$): 7.22-7.00 (m, 9 H, aromat. H), 6.50 (t, ^3J = 4.6 Hz, 1 H, 2-H), 5.96 (br "s", 1 H, *N*H), 5.52 (t, ^3J = 4.6 Hz, 1 H, 3-H), 3.71 (br "s", 1 H, 4-H). For elemental analysis of the quinoline picrate (**4a**) see above.

Preparation of the *O*-Acetyl-1,4-dihydroquinolines (7a, b)

1 g (3.2 mmol) of **5a** and 0.8 g (3.2 mmol) of **5b** were dissolved in a minimum volume of acetic anhydride and 10 drops of dried pyridine were added. Stirring at rt was carried out for 24 h and then the solvent was removed in vacuum under addition of portions of dried ethanol. The remaining yellow oil was separated by TLC using a mixture of toluol/methanol (85/15). After washing of the silica gel with acetone and removal of the solvent yellow oils of compounds (**7a, b**) remained.

3-(2,5-Diacetoxyphenyl)-4-phenylquinoline (7a)

Yellow oil (0.64 g, 40%). IR ($CDCl_3$): 1765, 1725 (CO) cm^{-1}. MS *m/z*: 397 (M^+). ^1H NMR (acetone-D_6): 8.78 (s, 1 H, 2-H), 8.90 (dd, ^3J = 8.5 Hz, ^4J = 1.1 Hz, 1 H, 8-H), 7.79 (dt, ^3J = 8.5, ^4J = 1.1 Hz, 1 H, 7-H), 7.50-7.62 (m, 7H, Ph-H, 6-H, 5-H), 7.12 (d, ^3J = 8.9 Hz, 1 H, 3´-H), 7.07 (dd, ^3J = 8.9 Hz, ^4J = 2.8 Hz, 1 H, 4´-H), 6.95 (d, ^4J = 2.8 Hz, 1 H, 6´-H), 2.17 (s, 3 H, C2´-$OCOCH_3$), 2.57 (s, 3 H, C4´-$OCOCH_3$). *Anal.* Calcd for $C_{31}H_{22}N_4O_{11}$ (picrate): C, 59.43; H, 3.54; N 8.94. Found: C, 59.20; H 3.32; N 8.62.

3-(2,5-Diacetoxyphenyl)-4-methylquinoline (7b)

Yellow oil (0.4 g, 30%). IR ($CDCl_3$): 1763, 1720 (sh) (CO) cm^{-1}. ESI-MS *m/z*: 336 (M + H^+). ^1H NMR (acetone-D_6): 8.60 (s, 1 H, 2-H), 8.35 (dd, ^3J = 7.1 Hz, ^4J = 1.3 Hz, 1 H, 8-H), 8.06 (dd, ^3J = 7.1, ^4J = 1.5 Hz, 1 H, 5-H), 7.77 (ddd, ^3J = 7.1 Hz and 6.9 Hz, ^4J = 1.5 Hz, 1 H, 7-H), 7.66 (ddd, ^3J = 7.1 Hz and 6.9 Hz, ^4J = 1.3 Hz, 1 H, 6-H), 7.34 (d, ^3J = 8.7 Hz, 1 H, 3´-H), 7.29 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1 H, 4´-H), 7.22 (d, ^4J = 2.5 Hz, 1 H, 6´-H), 2.55 (s, 3 H, C4-CH_3), 2.28 (s, 3 H, C2´-$OCOCH_3$), 1.85 (s, 3 H, C4´-$OCOCH_3$). *Anal.* Calcd for $C_{26}H_{20}N_4O_{11}$ (picrate): C, 55.33; H, 3.57; N 9.93. Found: C, 54.96; H 3.18; N 9.57.

6(*RS*),6a(*SR*),17b(*SR*)-1-Acetyl-1,6,6a,17b-tetrahydro-8-hydroxy-6,17-diphenylquino[2´,3´:4,5]benz-[6,7]oxepino[2,3-*b*]quinoline (9a)

Yellow crystals from ether, mp 275-278 °C (0.22 g, 10%). IR (KBr): 3425 (OH), 1674 (*N*$COCH_3$) cm^{-1}. MS *m/z*: 560 (M^+). ^1H NMR (acetone-D_6): 8.08 (dd, ^3J = 8.5 Hz, ^4J = 1.2 Hz, 1 H, 13-H), 7.78 (dt, ^3J = 8.5 Hz, ^4J = 1.5 Hz, 1 H, 14-H), 7.77 (d, ^3J = 7.0 Hz, 1 H, C17-Ph-2-H), 7.73-7.68 (m, 4 H, C17-Ph-3-H, -4-H, -5-H, 16-H), 7.67 (s, 1 H, OH, exchangable), 7.54 (d, ^3J = 7.3 Hz, 1 H, C17-Ph-6-H), 7.51 (d, ^4J = 1.2

Hz, 1 H, 7-H), 7.50 (dt, ^{3}J = 8.5 Hz, ^{4}J = 1.2 Hz, 1 H, 15-H), 7.37 (d, ^{3}J = 8.5 Hz, 1 H, 10-H), 7.32-7.16 (m, 8 H, C6-Ph-H, C17-Ph-3-H, -4-H, 5-H), 7.10 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.2 Hz, 1 H, 9-H), 6.11 ("s", 1 H, 17b-H), 5,10 (spl. d, ^{3}J = 1.2 Hz, 1 H, 6-H), 4.87 ("d", ^{3}J = 1.2 Hz, 1 H, 6a-H), 2.08 (s, 3 H, *N*COCH$_3$). *Anal.* Calcd for $C_{38}H_{28}N_2O_3$: C, 81.41; H, 5.03; N 5.00. Found: C, 81.05; H 4.82; N 4.75.

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