Synthesis of 2*H*-Pyrano[2,3-*b*]quinolines. Part II. Preparation and ^{1}H-nmr Investigations of 4-Hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines

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Diastereoisomers of 4-hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines **8** and **9** were synthesized starting from the appropriate 2-chloroquinoline-3-carboxaldehydes **1**. The relative configuration of the 1,3-diol intermediates **4** and **5** was determined on the basis of the ^{13}C-nmr spectra of their acetonides. The relative stereochemistry of title compounds was confirmed by using homonuclear NOE and selective decoupling experiments, as well as by analysis of the coupling patterns observed in their ^{1}H-nmr spectra.

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Recently we have demonstrated [1] that 3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines could be readily prepared by acidic treatment of 2-chloro-3-(3-chloro)propylquinolines. These pyranoquinolines proved to be versatile intermediates for the synthesis of the analogues of Cromakalim, a novel antihypertensive agent [2,3]. In continuing our work in this field, we herein describe our endeavours to synthesize new 2-methyl-substituted derivatives of 3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines which would serve as starting materials for the synthesis of new Cromakalim analogues.

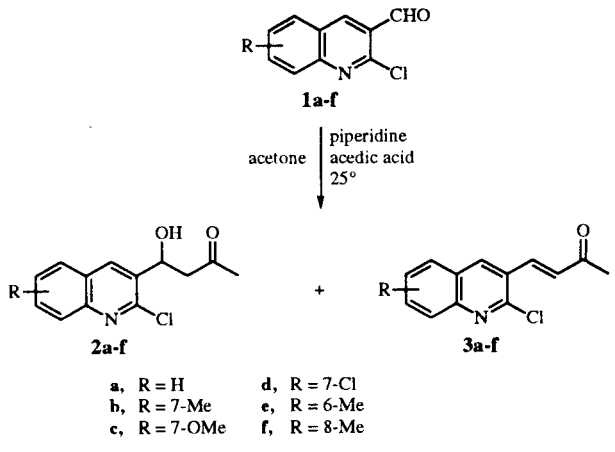
Although a few reports of work have been accomplished earlier on the synthesis of 2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines [4-6], these synthetic methods were only suitable for the preparation of 5-substituted derivatives. For this reason we elaborated a new, convenient synthesis of 4-hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines **8** and **9** which proved to be versatile intermediates for the preparation of further new 2-methyl-2*H*-pyrano[2,3-*b*]quinoline derivatives.

Our synthesis started from 2-chloroquinoline-3-carboxaldehydes **1a-f** [7]. Reaction of these compounds with acetone in the presence of piperidine and acetic acid [8,9] gave 3-(1-hydroxy-3-oxo)butyl-2-chloroquinolines **2a-f** accompanied with a small amount of the dehydrated products **3a-f** (Scheme 1).

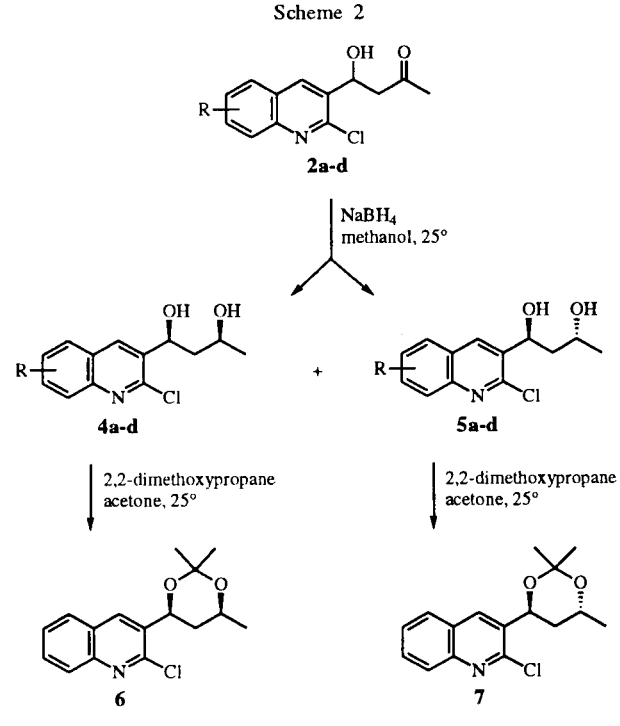
Purification of alcohols **2a-f** can easily be carried out by crystallization of the crude products from ethyl acetate. The yield of the crystallized products **2a-f** was 43-70%. The α,β-unsaturated ketones **3a-f** were isolated from the mother liquors by column chromatography and they proved to be *trans* isomers on the basis of the ^{1}H-^{1}H coupling constant of the -CH=CH- unit (16 Hz). Reduction of the β-keto alcohols **2a-d** with sodium borohydride yielded the diastereoisomer 1,3-diols **4a-d** and **5a-d** which were separated by column chromatography (silica gel, chloroform-acetone, 9:1 v/v) (Scheme 2).

The overall yield of the 1,3-diols **4a-d** and **5a-d** was 64-92%. The stereochemistry of the diastereoisomer diols **4a** and **5a** was determined on the basis of the ^{13}C-nmr

Scheme 1



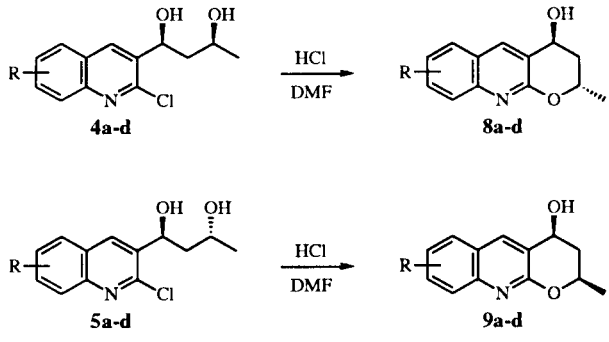
Scheme 2



spectra of their acetonides **6** and **7** using the method elaborated by Rychnovsky and his co-workers [10,11]. They have found that the *syn*-1,3-diol acetonides have ^{13}C acetal methyl shifts at 19 and 30 ppm, while the *anti*-1,3-diol acetonides have ^{13}C acetal methyl shifts at 25 ppm. This method was successfully applied for the structural determination of compounds **6** and **7**. Methyl shifts of the acetonide **6** - prepared from one of the two 1,3-diol - were at 20.5 and 30.5 ppm, thus the corresponding 1,3-diol was assigned as *syn*-1,3-diol **4a**. Methyl shifts of the acetonide **7** - prepared from the other 1,3-diol - were at 25.5 ppm, thus the corresponding 1,3-diol was assigned as *anti*-diol **5a**. Since there were significant differences in the ^1H-nmr spectra of the diastereoisomer pairs **4** and **5** (see Experimental), the identification of the other 1,3-diols **4b-d** and **5b-d** was accomplished on the basis of their ^1H-nmr spectra.

The intramolecular cyclization of the 1,3-diols **4a-d** and **5a-d** was performed in *N,N*-dimethylformamide containing hydrochloric acid (Scheme 3).

Scheme 3



The relative configuration of pyranoquinolines **8a** and **9a** was confirmed by homonuclear NOE difference spectroscopy. Saturating the H-2 proton in **9a**, a strong NOE was observed on H-4, besides the NOEs on H-3_{eq} and 2-CH_3, indicating that these protons situate on the same side of the pyran ring. In case of **8a**, there was no possibility for selective excitation of the same proton (H-2) because its chemical shift is very close to H-4 proton. In this case, irradiation of the 4-OH proton resulted NOEs on H-4 and H-2 protons, according to their different position compared to the other isomer. On the basis of these experiments it can be stated that the relative configuration at C-2 and C-4 positions did not change during the cyclization.

The ^1H-nmr spectra of compounds **8** and **9** showed such characteristic coupling patterns, besides some chemical shift differences, which allowed us to establish the most probable conformation of compounds investigated as they are shown in Figure 1.

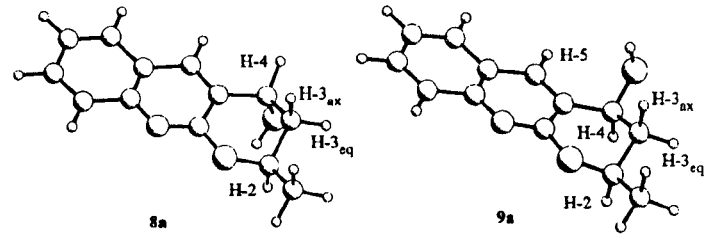


Figure 1. Stereoview of compounds **8a** and **9a**.

Namely, H-3_{ax} proton in compound **9a** showed the same relatively large couplings with H-2 and H-4 protons ($^3J_{H\text{-}3ax,H\text{-}2} = {}^3J_{H\text{-}3ax,H4} = 11.3$ Hz), besides its geminal coupling with H-3_{eq} ($^2J_{H\text{-}3ax,H\text{-}3eq} = -13.2$ Hz), reflecting their *trans* orientation. Similar *trans* position of H-3_{ax} and H-2 protons is indicated by their large vicinal coupling observed in case of compounds **8a**, however the coupling of H-3_{ax} with H-4 is much smaller ($^3J_{H\text{-}3ax,H\text{-}2} = 2.8$ Hz). In this case the coupling of H-4 with H-3_{eq} is also smaller compared to the same coupling in **9a**, as it can be seen in Figure 2.

In accordance with the Karplus equation [12], these couplings indicate the *gauche* position of H-4 proton compared to H-3_{ax} and H-3_{eq}. It's worth noting, that we managed to prove allylic coupling between H-4 and H-5 protons in **9a** ($^4J_{H\text{-}4,H\text{-}5} = -1.5$ Hz) by selective homonuclear decoupling experiments, whereas the same type of coupling was not observed in case of the other isomer. These observations also gave valuable information about the conformation. On the basis of NOE experiments and considering the above detailed coupling patterns which are valid for all of the isomers prepared, it could be stated a quasi-1,3-diaxial orientation of H-2 and H-4 protons in compounds **9a-d**, whereas in **8a-d** isomers their position is quasi-axial-equatorial.

The yields of the crystallized products **8a-d** and **9a-d** were 49-56% and 56-84%, respectively.

EXPERIMENTAL

Melting points were determined in open capillary tubes on an Electrothermal apparatus and are uncorrected. The ^1H (200 MHz) and ^{13}C (50 MHz) nmr spectra were recorded on a Varian Gemini-200 instrument. The ^1H-nmr spectra are referenced to trimethylsilane and ^{13}C-nmr spectra to deuteriochloroform (77.0 ppm). Chemical shifts are expressed in ppm. Mass spectra were scanned on a VG Trio-2 spectrometer in EI mode at 70 eV.

3-(1-Hydroxy-3-oxo)butyl-2-chloroquinoline (**2a**).

2-Chloroquinoline-3-carboxaldehyde **1a** (9.6 g, 50 mmoles) was suspended in acetone (50 ml). Piperidine (0.4 ml) and acetic acid (0.4 ml) were added to the suspension and the reaction mixture was stirred for 24 hours at 25°. The solution was evaporated

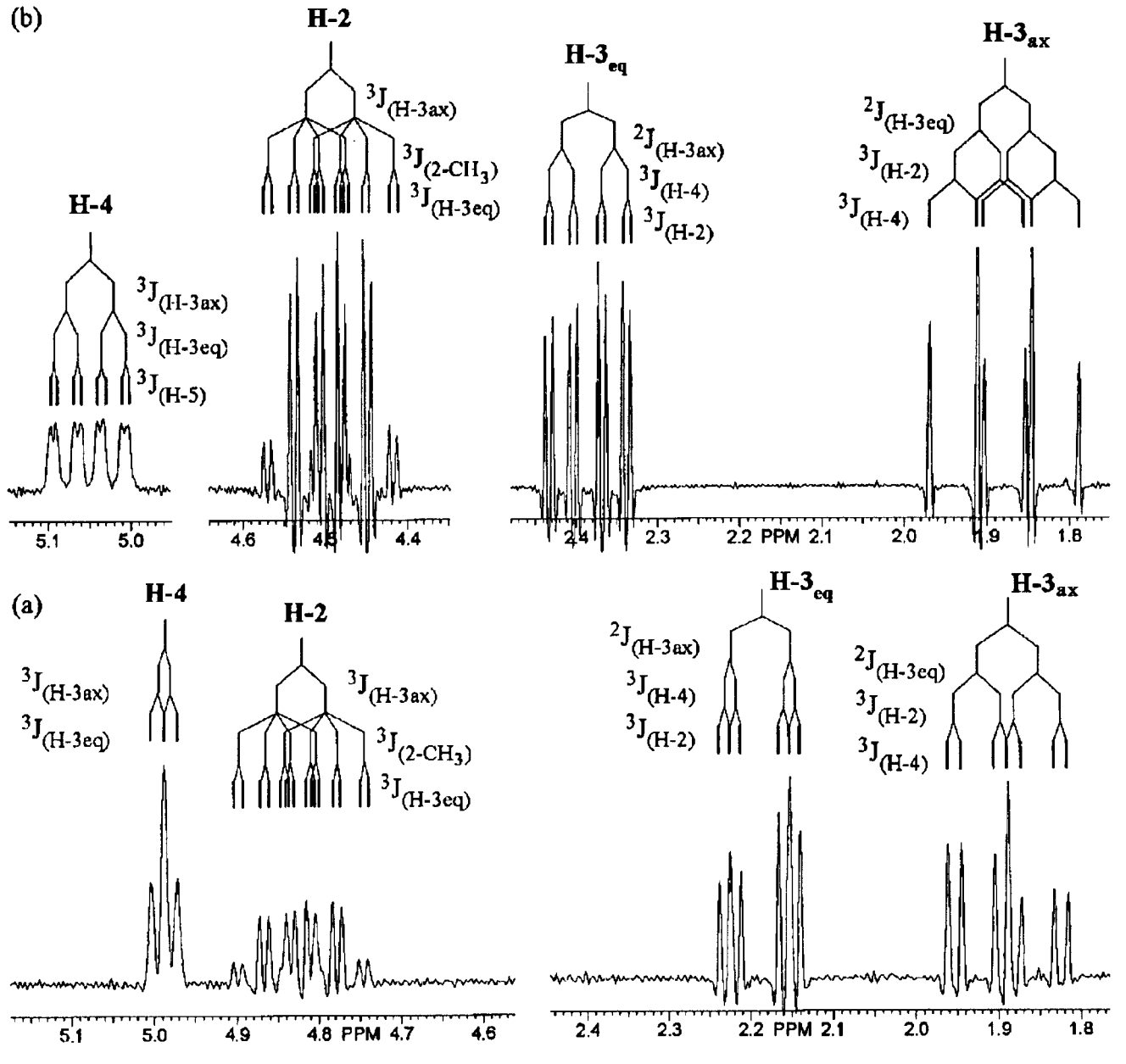


Figure 2. Selected aliphatic region of ^{1}H-nmr spectra of compounds **8a** (a) and **9a** (b).

in vacuum and the residue was crystallized from ethyl acetate to give **2a**, yield 8.7 g (70%), mp 110-112°; ^{1}H-nmr (DMSO-d_6): δ 2.23 (s, 3H), 2.77 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.93 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 5.48 (m, 1H), 5.92 (d, J = 4.5 Hz, 1H), 7.67 (m, 1H), 7.81 (m, 1H), 7.99 (m, 1H), 8.12 (m, 1H), 8.58 (s, 1H); ms: m/z 249 (M^+, 24), 231 (13), 192 (100), 156 (92), 128 (95).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.66; H, 4.90; N, 5.47.

3-(1-Hydroxy-3-oxo)butyl-2-chloro-7-methylquinoline (**2b**).

This compound was produced from **1b** (10.3 g, 50 mmoles) just as **2a** was produced from **1a**, yield 8.9 g (68%), mp 144-146° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 2.18 (s, 3H), 2.51 (s, 3H), 2.72 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.89 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 5.42 (m, 1H), 5.81 (d, J = 4.5 Hz, 1H), 7.49 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 8.50 (s, 1H); ms: m/z 263 (M^+, 18), 245 (7), 206 (100), 170 (89), 142 (68).

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.72; H, 5.44; N, 5.26.

3-(1-Hydroxy-3-oxo)butyl-2-chloro-7-methoxyquinoline (**2c**).

Compound **1c** (11.1 g, 50 mmoles) was subjected to the same procedure as described above for the preparation of **2a**, yield 7.2 g (52%), mp 100-102° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ

2.19 (s, 3H), 2.72 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.87 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 3.91 (s, 3H), 5.38 (m, 1H), 5.78 (d, J = 4.5 Hz, 1H), 7.29 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 1H), 7.36 (d, J = 2.5 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 8.46 (s, 1H); ms: m/z 279 (M^+, 8), 221 (100), 192 (30), 176 (21), 157 (31).

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 59.98; H, 5.00; N, 5.10.

3-(1-Hydroxy-3-oxo)butyl-2,7-dichloroquinoline (**2d**).

Compound **1d** (11.3 g, 50 mmoles) was treated in a manner similar to that described above for the preparation of **2a**, yield 7.3 g (51%), mp 123-125° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 2.20 (s, 3H), 2.72 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.89 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 5.40 (m, 1H), 5.90 (d, J = 4.5 Hz, 1H), 7.70 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 8.04 (d, J = 2 Hz, 1H), 8.17 (d, J = 9 Hz, 1H), 8.62 (s, 1H); ms: m/z 283 (M^+, 5), 225 (65), 189 (39), 161 (80), 58 (100).

Anal. Calcd. for $C_{13}H_{11}Cl_2NO_2$: C, 54.95; H, 3.90; N, 4.93. Found: C, 54.81; H, 3.84; N, 4.96.

3-(1-Hydroxy-3-oxo)butyl-2-chloro-6-methylquinoline (**2e**).

Using the same treatment described in the foregoing preparation of **2a, 1e** (10.3 g, 50 mmoles) gave **2e**, yield 5.7 g (43%), mp 141-143° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 2.20 (s, 3H), 2.50 (s, 3H), 2.67 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.89 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 5.40 (m, 1H), 5.82 (d, J = 4.5 Hz, 1H), 7.62 (dd, J_1 = 8.5 Hz, J_2 = 1 Hz, 1H), 7.82 (d, J = 1 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.45 (s, 1H); ms: m/z 263 (M^+, 25), 228 (11), 206 (89), 170 (100), 142 (76).

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.86; H, 5.32; N, 5.24.

3-(1-Hydroxy-3-oxo)butyl-2-chloro-8-methylquinoline (**2f**).

Compound **1f** (10.3 g, 50 mmoles), treated in the same way described above for the preparation of **2a**, afforded **2f**, yield 7.5 g (57%), mp 106-108° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 2.21 (s, 3H), 2.63 (s, 3H), 2.71 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.87 (dd, J_1 = 16 Hz, J_2 = 3 Hz, 1H), 5.44 (m, 1H), 5.86 (d, J = 4.5 Hz, 1H), 7.54 (m, 1H), 7.63 (m, 1H), 7.90 (m, 1H), 8.52 (s, 1H); ms: m/z 263 (M^+, 26), 245 (8), 205 (100), 170 (74), 141 (48).

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.88; H, 5.27; N, 5.34.

2-Chloro-3-(3-oxo-1-butenyl)quinoline (**3a**).

The mother liquor remained after crystallization of compound **2a** was evaporated and the residue was subjected to column chromatography using silica gel (eluent: chloroform-acetone, 95:5 v/v) to yield 1.2 g of **3a**, (10%), mp 132-134°; ^{1}H-nmr (DMSO-d_6): δ 2.44 (s, 3H), 7.04 (d, J = 16 Hz, 1H), 7.70 (m, 1H), 7.78 (d, J = 16 Hz, 1H), 7.82 (m, 1H), 7.96 (m, 1H), 8.04 (m, 1H), 8.97 (s, 1H); ms: m/z 231 (M^+, 5), 216 (13), 196 (100), 152 (66).

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05. Found: C, 67.36; H, 4.44; N, 6.00.

2-Chloro-7-methyl-3-(3-oxo-1-butenyl)quinoline (**3b**).

This compound was isolated from the mother liquor of the compound **2b** by column chromatography on silica gel (eluent: chloroform-acetone, 95:5 v/v), yield 1.2 g (10%), mp 147-149°; ^{1}H-nmr (DMSO-d_6): δ 2.43 (s, 3H), 2.62 (s, 3H), 7.01 (d, J = 16 Hz, 1H), 7.59 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 16 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 8.90 (s, 1H); ms: m/z 245 (M^+, 7), 230 (13), 210 (100), 166 (35), 140 (18).

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.35; H, 4.99; N, 5.81.

2-Chloro-7-methoxy-3-(3-oxo-1-butenyl)quinoline (**3c**).

Column chromatography of the evaporated mother liquor of the compound **2c** on silica gel (eluent: chloroform-acetone, 95:5 v/v), gave **3c**, yield 2.0 g (15%), mp 193-195° dec; ^{1}H-nmr (DMSO-d_6): δ 2.40 (s, 3H), 3.93 (s, 3H), 7.00 (d, J = 16 Hz, 1H), 7.33 (dd, J_1 = 8.5 Hz, J_2 = 2 Hz, 1H), 7.36 (d, J = 2 Hz, 1H), 7.82 (d, J = 16 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 8.87 (s, 1H); ms: m/z 261 (M^+, 5), 246 (10), 226 (100), 182 (32), 139 (7).

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.39; H, 4.53; N, 5.40.

2,7-Dichloro-3-(3-oxo-1-butenyl)quinoline (**3d**).

The evaporated mother liquor of the compound **2d** was subjected to column chromatography on silica gel (eluent: chloroform-acetone, 95:5 v/v), yield 1.6 g (12%), mp 164-166°; ^{1}H-nmr (DMSO-d_6): δ 2.43 (s, 3H), 7.02 (d, J = 16 Hz, 1H), 7.69 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 7.77 (d, J = 16 Hz, 1H), 8.00 (d, J = 2 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 8.97 (s, 1H); ms: m/z 265 (M^+, 5), 250 (12), 230 (100), 186 (39), 151 (13).

Anal. Calcd. for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; N, 5.26. Found: C, 58.77; H, 3.35; N, 5.17.

2-Chloro-6-methyl-3-(3-oxo-1-butenyl)quinoline (**3e**).

This compound was isolated from the mother liquor of the compound **2e** by column chromatography on silica gel (eluent: chloroform-acetone, 95:5 v/v), yield 1.5 g (12%), mp 142-144°; ^{1}H-nmr (DMSO-d_6): δ 2.41 (s, 3H), 2.50 (s, 3H), 7.02 (d, J = 16 Hz, 1H), 7.68 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.80 (d, J = 16 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 8.82 (s, 1H); ms: m/z 245 (M^+, 5), 230 (8), 210 (60), 166 (18), 43 (100).

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.49; H, 4.88; N, 5.70.

2-Chloro-8-methyl-3-(3-oxo-1-butenyl)quinoline (**3f**).

Column chromatography of the mother liquor of the compound **2f** on silica gel (eluent: chloroform-acetone, 95:5 v/v) gave **3f**, yield 1.4 g (11%), mp 136-138°; ^{1}H-nmr (DMSO-d_6): δ 2.44 (s, 3H), 2.63 (s, 3H), 7.01 (d, J = 16 Hz, 1H), 7.55 (m, 1H), 7.67 (m, 1H), 7.73 (d, J = 16 Hz, 1H), 7.87 (m, 1H), 8.88 (s, 1H); ms: m/z 245 (M^+, 16), 230 (13), 210 (100), 166 (55), 139 (19).

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.50; H, 4.93; N, 5.66.

syn-3-(1,3-Dihydroxy)butyl-2-chloroquinoline (**4a**) and *anti*-3-(1,3-dihydroxy)butyl-2-chloroquinoline (**5a**).

Quinoline derivative **2a** (6.2 g, 25 mmoles) was dissolved in methanol (50 ml). The stirred reaction mixture was cooled to 10° and sodium borohydride (0.95 g, 25 mmoles) was added in portions. The solution was stirred at 25° for 1 hour. The reaction mixture was poured into water (50 ml) and extracted 3 times with chloroform (50 ml). The organic layer was dried with sodium sulfate, evaporated in vacuum and the diastereoisomers **4a** and **5a** were separated by column chromatography on silica gel (eluent: chloroform-acetone, 9:1 v/v), yields 2.8 g (44%) and 2.5 g (39%), respectively.

Compound **4a** had mp 154-155° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.22 (d, J = 6.5 Hz, 3H), 1.79 (m, 2H), 3.95 (m,

1H), 4.50-4.75 (broad, 1H), 5.05 (m, 1H), 5.72 (s, 1H), 7.66 (m, 1H), 7.80 (m, 1H), 7.97 (m, 1H), 8.11 (m, 1H), 8.57 (s, 1H); ms: m/z 251 (M^+, 12), 233 (15), 191 (86), 128 (100).

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.01; H, 5.71; N, 5.62.

Compound **5a** had mp 160-161° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.12 (d, J = 6.5 Hz, 3H), 1.54 (m, 1H), 1.78 (m, 1H), 4.00 (m, 1H), 4.45-4.70 (broad, 1H), 5.22 (m, 1H), 5.61 (s, 1H), 7.64 (m, 1H), 7.79 (m, 1H), 7.97 (m, 1H), 8.09 (m, 1H), 8.55 (s, 1H); ms: m/z 251 (M^+, 3), 233 (5), 191 (25), 156 (14), 128 (100).

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.11; H, 5.61; N, 5.45.

syn-3-(1,3-Dihydroxy)butyl-2-chloro-7-methylquinoline (**4b**) and *anti*-3(1,3-dihydroxy)butyl-2-chloro-7-methylquinoline (**5b**).

Using the same treatment describe in the foregoing preparation of **4a** and **5a**, **2b** (6.6 g, 25 mmoles) gave, after silica gel column chromatography (eluent: chloroform-acetone, 9:1 v/v), 2.3 g of compound **4b** (35%) and 1.9 g of compound **5b** (29%).

Compound **4b** had mp 166-167° (ethanol-acetone); ^{1}H-nmr (DMSO-d_6): δ 1.20 (d, J = 6.5 Hz, 3H), 1.78 (m, 2H), 2.52 (s, 3H), 3.92 (m, 1H), 4.62 (d, J = 4.5 Hz, 1H), 5.02 (m, 1H), 5.67 (d, J = 4.5 Hz, 1H), 7.48 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 8.49 (s, 1H); ms: m/z 265 (M^+, 13), 247 (9), 206 (100), 170 (82), 142 (74).

Anal. Calcd. for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.21; H, 6.10; N, 5.21.

Compound **5b** had mp 132-133° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.11 (d, J = 6.5 Hz, 3H), 1.53 (m, 1H), 1.74 (m, 1H), 2.51 (s, 3H), 3.98 (m, 1H), 4.57 (d, J = 4.5 Hz, 1H), 5.17 (m, 1H), 5.53 (d, J = 4.5 Hz, 1H), 7.49 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.72 (d, J = 1.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 8.48 (s, 1H); ms: m/z 265 (M^+, 16), 247 (10), 206 (100), 170 (90), 142 (83).

Anal. Calcd. for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.42; H, 6.01; N, 5.20.

syn-3-(1,3-Dihydroxy)butyl-2-chloro-7-methoxyquinoline (**4c**) and *anti*-(1,3-Dihydroxy)butyl-2-chloro-7-methoxyquinoline (**5c**).

These compounds were prepared from **2c** (7.0 g, 25 mmoles) just as **4a** and **5a** were prepared from **2a**, yield of **4c**, 4.1 g (58%), yield of **5c**, 2.4 g (34%), after column chromatography on silica gel (eluent: chloroform-acetone, 9:1 v/v).

Compound **4c** had mp 96-98° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.19 (d, J = 6.5 Hz, 3H), 1.75 (m, 2H), 3.88 (m, 1H), 3.92 (s, 3H), 4.55-4.70 (broad, 1H), 4.99 (m, 1H), 5.61 (s, 1H), 7.29 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.35 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.43 (s, 1H); ms: m/z 281 (M^+, 17), 222 (100), 186 (48), 158 (52).

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.68; H, 5.79; N, 4.98.

Compound **5c** had mp 153-154° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.11 (d, J = 6.5 Hz, 3H), 1.53 (m, 1H), 1.72 (m, 1H), 3.90 (s, 3H), 3.95 (m, 1H), 4.45-4.60 (broad, 1H), 5.16 (m, 1H), 5.48 (s, 1H), 7.27 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 8.43 (s, 1H); ms: m/z 281 (M^+, 16), 262 (5), 222 (100), 186 (54), 158 (57).

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.60; H, 5.75; N, 5.04.

syn-3-(1,3-Dihydroxy)butyl-2,7-dichloroquinoline (**4d**) and *anti*-3-(1,3-Dihydroxy)butyl-2,7-dichloroquinoline (**5d**).

Compound **2d** (7.1 g, 25 mmoles), treated in the same way described above for the preparation of **4a** and **5a**, afforded - after column chromatogaphy on silica gel (eluent: chloroform-acetone, 9:1 v/v) - **4d**, yield 2.9 g (40%) and **5d**, yield 2.6 g (36%).

Compound **4d** had mp 175-176° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.20 (d, J = 6.5 Hz, 3H), 1.77 (m, 2H), 3.92 (m, 1H), 4.60 (d, J = 4.5 Hz, 1H), 5.02 (m, 1H), 5.72 (d, J = 4.5 Hz, 1H), 7.69 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 8.03 (d, J = 2 Hz, 1H), 8.17 (d, J = 9 Hz, 1H), 8.60 (s, 1H); ms: m/z 285 (M^+, 13), 267 (17), 226 (100), 190 (72), 162 (81).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_2$: C, 54.57; H, 4.58; N, 4.89. Found: C, 54.44; H, 4.66; N, 4.80.

Compound **5d** had mp 127-128° (acetone-hexane); ^{1}H-nmr (DMSO-d_6): δ 1.12 (d, J = 6.5 Hz, 3H), 1.53 (m, 1H), 1.73 (m, 1H), 3.98 (m, 1H), 4.59 (d, J = 4.5 Hz, 1H), 5.19 (m, 1H), 5.62 (d, J = 4.5 Hz, 1H), 7.69 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 8.02 (d, J = 2 Hz, 1H), 8.16 (d, J = 9 Hz, 1H), 8.59 (s, 1H); ms: m/z 285 (M^+, 10), 267 (18), 226 (100), 190 (66), 162 (81).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_2$: C, 54.57; H, 4.58; N, 4.89. Found: C, 54.55; H, 4.66; N, 4.94.

syn-3-(1,3-Dihydroxy)butyl-2-chloroquinoline acetonide (**6**).

Compound **4a** (0.5 g, 2 mmoles) and 2,2-dimethoxypropane (1.2 ml, 10 mmoles) were stirred in THF (15 ml) in the presence of 0.1 g *p*-toluenesulfonic acid at 25° for 12 hours. The reaction mixture was evaporated in vacuum and the residue was purified by column chromatography on silica gel (eluent: chloroform-acetone, 9:1 v/v), yield 0.30 g (52%), mp 136-138° (acetone-hexane); ^{1}H-nmr (deuteriochloroform): δ 1.23 (d, J = 6.5 Hz, 3H), 1.28 (m, 1H), 1.59 (s, 3H), 1.63 (s, 3H), 2.14 (m, 1H), 4.23 (m, 1H), 5.33 (m, 1H), 7.53 (m, 1H), 7.70 (m, 1H), 7.85 (m, 1H), 8.00 (m, 1H), 8.37 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 20.5; 22.4; 30.5; 40.3; 66.1; 68.5; 98.8.

Anal. Calcd. for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.94; H, 6.17; N, 4.82.

anti-3-(1,3-Dihydroxy)butyl-2-chloroquinoline acetonide (**7**).

This compound was prepared from **5a** (0.5 g, 2 mmoles) just as **6** was prepared from **4a**, yield 0.33 g (56%), mp 147-149° (acetone-hexane); ^{1}H-nmr (deuteriochloroform): δ 1.29 (d, J = 6.5 Hz, 3H), 1.51 (s, 3H), 1.56 (s, 3H), 1.82 (m, 1H), 2.25 (m, 1H), 4.14 (m, 1H), 5.28 (m, 1H), 7.56 (m, 1H), 7.70 (m, 1H), 7.86 (m, 1H), 8.01 (m, 1H), 8.37 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 21.5; 25.5; 40.0; 62.6; 65.3; 100.6.

Anal. Calcd. for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.81; H, 6.26; N, 4.89.

trans-4-Hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**8a**).

The *syn*-1,3-diol **4a** (1.25 g, 5 mmoles) was stirred in DMF containing hydrochloric acid (15 ml, 5 *M*/l) at 25° for 3 hours. The solvent was removed in vacuum, the residue was suspended in water (15 ml) and the *p*H was adjusted to 7 with concentrated ammonia solution. The product was filtered off, washed with water, dried and crystallized from ethanol to give **8a**, yield 0.53 g (49%), mp 174-175° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.52 (d, J = 6.2 Hz, 3H), 1.89 (ddd, J_1 14.4 Hz, J_2 = 11.4 Hz, J_3 = 2.8 Hz, 1H), 2.19 (ddd, J_1 = 14.4 Hz, J_2 = 2.6 Hz, J_3 = 2.6 Hz, 1H), 3.30-3.40 (broad, 1H), 4.82 (dqd, J_1 = 11.4 Hz, J_2 = 6.2 Hz, J_3 = 2.6 Hz, 1H), 4.98 (dd, J_1 = 2.8 Hz, J_2 = 2.6 Hz, 1H),

7.30 (m, 1H), 7.53 (m, 1H), 7.59 (m, 1H), 7.79 (m, 1H), 7.96 (s, 1H); ms: m/z 215 (M^+, 100), 200 (32), 174 (41), 145 (77).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.53; H, 6.19; N, 6.40.

For the compounds of **8b, c** and **d**, the same coupling constants were measured (within the precision of the measurements) in the aliphatic region than in the case of compound **8a**.

cis-4-Hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**9a**).

This compound was produced from **5a** (1.25 g, 5 mmoles) just as **8a** was produced from **4a**, yield 0.91 g (84%), mp 143-145° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.47 (d, J = 6.5 Hz, 3H), 1.89 (ddd, J_1 = 13.2 Hz, J_2 = 11.3 Hz, J_3 = 11.3 Hz, 1H), 2.38 (ddd, J_1 = 13.2 Hz, J_2 = 5.9 Hz, J_3 = 1.9 Hz, 1H), 3.40-3.70 (broad, 1H), 4.49 (dqd, J_1 = 11.3 Hz, J_2 = 6.2 Hz, J_3 = 1.9 Hz, 1H), 5.05 (ddd, J_1 = 11.3 Hz, J_2 = 5.9 Hz, J_3 = 1.5 Hz, 1H), 7.31 (m, 1H), 7.58 (m, 2H), 7.80 (m, 1H), 8.19 (s, 1H); ms: m/z 215 (M^+, 100), 200 (27), 174 (53), 145 (80).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.70; H, 6.05; N, 6.54.

For the compounds of **9b**, **c** and **d**, the same coupling constants were measured (within the precision of the measurements) in the aliphatic region than in the case of compound **9a**.

trans-2,8-Dimethyl-4-hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]-quinoline (**8b**).

Compound **4b** (1.33 g, 5 mmoles) was subjected to the same procedure as described above for the preparation of **8a**, yield 0.61 g (53%), mp 201-203° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.55 (d, J = 6.5 Hz, 3H), 1.78 (m, 1H), 2.17 (m, 1H), 2.20-2.55 (broad, 1H), 2.49 (s, 3H), 4.78 (m, 1H), 4.98 (m, 1H), 7.17 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.98 (s, 1H); ms: m/z 229 (M^+, 100), 214 (25), 196 (58), 159 (91), 142 (23).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.25; H, 6.59; N, 6.18.

cis-2,8-Dimethyl-4-hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]-quinoline (**9b**).

Compound **5b** (1.33 g, 5 mmoles) was treated in a manner similar to that described above for the preparation of **8a**, yield 0.64 g (56%), mp 209-211° dec (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.50 (d, J = 6.5 Hz, 3H), 1.84 (m, 1H), 2.37 (m, 1H), 2.49 (s, 3H), 2.55-2.85 (broad, 1H), 4.46 (m, 1H), 5.03 (m, 1H), 7.18 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 8.18 (s, 1H); ms: m/z 229 (M^+, 100), 214 (32), 196 (35), 159 (96), 142 (26).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.31; H, 6.66; N, 6.10.

trans-4-Hydroxy-8-methoxy-2-methyl-3,4-dihydro-2*H*-pyrano-[2,3-*b*]quinoline (**8c**).

Using the same treatment described in the foregoing preparation of **8a**, **4c** (1.41 g, 5 mmoles) gave **8c**, yield 0.62 g (51%), mp 152-153° (ethyl acetate-cyclohexane); ^{1}H-nmr (deuteriochloroform): δ 1.53 (d, J = 6.5 Hz, 3H), 1.87 (m, 1H), 2.17 (m, 1H), 2.55-2.80 (broad, 1H), 3.88 (s, 3H), 4.78 (m, 1H), 4.96 (m, 1H), 6.98 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 7.13 (d, J = 2 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 7.91 (s, 1H); ms: m/z 245 (M^+, 61), 227 (27), 212 (100), 175 (38), 149 (18).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.56; H, 6.10; N, 5.77.

cis-4-Hydroxy-8-methoxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]-quinoline (**9c**).

Compound **5c** (1.41 g, 5 mmoles), treated in the same way described above for the preparation of **8a**, afforded **9c**, yield 0.76 g (62%), mp 190-192° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.49 (d, J = 6.5 Hz, 3H), 1.84 (m, 1H), 2.45 (m, 1H), 3.05-3.35 (broad, 1H), 3.88 (s, 3H), 4.44 (m, 1H), 5.01 (m, 1H), 6.98 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 7.14 (d, J = 2 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 8.11 (s, 1H); ms: m/z 245 (M^+, 100), 228 (16), 212 (31), 175 (56), 158 (17).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.69; H, 6.07; N, 5.80.

trans-8-Chloro-4-hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano-[2,3-*b*]quinoline (**8d**).

This compound was prepared from **4d** (1.43 g, 5 mmoles) just as **8a** was prepared from **4a**, yield 0.70 g (56%), mp 200-202° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 1.54 (d, J = 6.5 Hz, 3H), 1.88 (m, 1H), 2.19 (m, 1H), 3.05-3.30 (broad, 1H), 4.81 (m, 1H), 4.98 (m, 1H), 7.24 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.98 (s, 1H); ms: m/z 249 (M^+, 96), 216 (63), 179 (100), 162 (51), 151 (61).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.56; H, 5.01; N, 5.55.

cis-8-Chloro-4-hydroxy-2-methyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]-quinoline (**9d**).

Compound **5d** (1.43 g, 5 mmoles) was treated in a manner similar to that described above for the preparation of **8a**, yield 0.99 g (79%), mp 190-192° (ethanol-hexane); ^{1}H-nmr (deuteriochloroform): δ 1.52 (d, J = 6.5 Hz, 3H), 1.88 (m, 1H), 2.40 (m, 1H), 3.15-3.35 (broad, 1H), 4.50 (m, 1H), 5.03 (m, 1H), 7.29 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 8.23 (s, 1H); ms: m/z 249 (M^+, 100), 214 (46), 179 (91), 162 (28), 151 (40).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.47; H, 4.81; N, 5.64.

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