1,2,3,4-Tetrahydroquinolines and 1,2-Dihydroquinolines from 2-Aminobenzophenes

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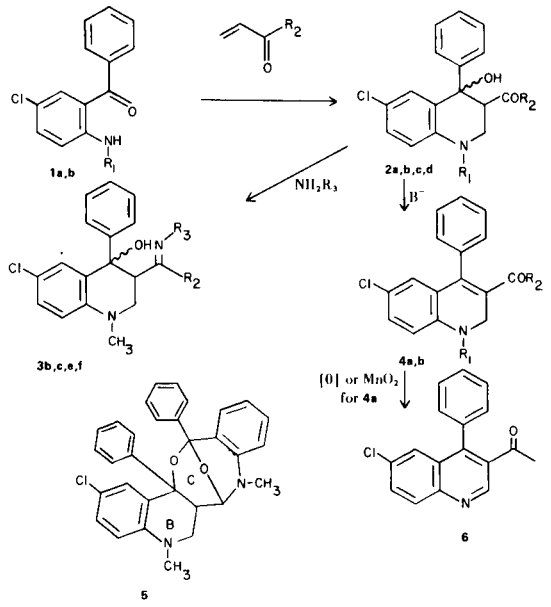
2-Aminobenzophenones (1) have been used as the starting material for the synthesis of many heterocycles. In a previous publication (2) we have reported on the synthesis of 3-acyl-4-phenylquinoline derivatives by condensation of 2-aminobenzophenones with 1,3-dicarbonyl compounds (**3a,b**). We have now found similar quinolines to be accessible by reaction of the 2-aminobenzophenones **1** with α,β-unsaturated carbonyl compounds. Initial conjugate addition of the amino group followed by cyclization resulted in the formation of the 4-hydroxy-4-phenyl-1,2-3,4-tetrahydroquinolines of formula **2**. The zinc chloride catalyzed addition of methyl vinyl ketone to the 2-aminobenzophenone **1a** gave a mixture of the tetrahydroquinolines **2a** and **2d**. The reaction of the same ketone with the methylated 2-aminobenzophenone **1b** was cleaner and gave a single product in good yield. Infrared dilution studies with compound **2b** showed strong intramolecular hydrogen bonding of the hydroxy group to the carbonyl function indicating a *cis* arrangement of these functionalities.

Surprisingly, the analogous reaction of **1b** with acrolein yielded the hydroxyaldehyde **2c** which did not exhibit comparable intramolecular hydrogen-bonding. It appears that in this case the isomer with the hydroxy group *trans* to the carbonyl group was formed. The condensation of **1b** with acrolein gave small amounts of a high melting 2:1 adduct to which we have assigned structure **5** on the basis of analytical and spectral data. The same compound was obtained when the hydroxyaldehyde **2c** was treated with methylaminobenzophenone and zinc chloride. In the nmr spectrum, the absence of any large coupling between the four aliphatic protons of compound **5** suggests that there is no axial/axial interaction of any two protons. Since such conditions are feasible both for *cis*- or *trans*-fused B- and C-rings, depending on the conformation of these rings, we cannot assign the stereochemistry. We also cannot be certain that compound **5** has retained the configuration of the hydroxaldehyde **2c** and the nmr data of **5** therefore do not help to corroborate the *trans* arrangement of the hydroxy groups and the carbonyl function in **2c**.

The 3-acyl-4-hydroxy-tetrahydroquinoline derivatives **2** were quite stable under neutral and weakly acidic conditions. The carbonyl group could be derivatized without disturbing the rest of the molecule. The oximes **3b** and **3c**, the hydrazone **3c** and the semicarbazone **3f** were prepared by standard methods. Dehydration of compounds **2** to the 1,2-dihydroquinolines **4** was readily effected by base. These orange to red colored dihydroquinolines are, as expected, susceptible to oxidation and decolorize on prolonged exposure to air. They may be useful as antioxidants or as hydrogen donors for reductions. Compound **4a** was readily oxidized to the quinoline **6** by short treatment with activated manganese dioxide.



a: R_1 = H, R_2 = CH_3
b: R_1 = CH_3, R_2 = CH_3, R_3 = OH
c: R_1 = CH_3, R_2 = H, R_3 = OH
d: R_1 = CH_2-CH_2COCH_3, R_2 = CH_3
e: R_2 = CH_3, R_3 = NH_2
f: R_2 = H, R_3 = $NHCONH_2$

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

3-Acetyl-6-chloro-4-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinoline (**2a**) and 3-Acetyl-6-chloro-4-hydroxy-1-(3-oxobutyl)-4-phenyl-1,2,3,4-tetrahydroquinoline (**2d**).

A mixture of 230 g. (1 mole) of 2-amino-5-chlorobenzophenone (**1a**) 1 l. of methylene chloride, 90 ml. (1.1 moles) of methyl vinyl ketone and 20 g. (0.15 mole) of zinc chloride was stirred at room temperature for 1½ hours. The exothermic reaction brought the methylene chloride to boiling for a short time. The reaction mixture was washed with water, dried and evaporated. The residue was crystallized from ether to yield 150 g. (50%) of **2a** with m.p. 156-160°. The analytical sample was recrystallized from benzene after treatment with charcoal, m.p. 160-163° dec., uv: λ max 255 mμ (ε, 12,300) 318 (2,930); ir (chloroform): 3450 cm^{-1} (OH, NH) 1700 (CO); nmr (deuteriochloroform): δ 1.97 ppm (s, 3, CH_3) 3.2-4 (m, 3, $-CH_2CH-$) 4.2 (broad s, 2, OH, NH) 6.53 (d, 1, J = 8.5 Hz, C_8-H) 6.85 (d, 1, J = 2.5 Hz, C_5-H) 7.06 (q, 2, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.35 (s, 5, C_6H_5).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.5; Cl, 11.8. Found: C, 67.6; H, 5.2; N, 4.5; Cl, 11.9.

The mother liquor was evaporated and the residue was crystallized from ether/hexane to yield 64.7 g. (17%) of crude **2d** with m.p. 102-104°. For analysis it was twice recrystallized from methylene chloride/hexane, m.p. 120-123°; uv: λ max 265 mμ (ε, 16,400) 322 (3,320); ir (chloroform): 3450 cm^{-1} (OH) 1730 (CO); nmr (deuteriochloroform): δ 1.93 ppm (s, 3, $COCH_3$) 2.15 (s, 3, $COCH_3$) 2.73 (t, 2, CH_2CO) 3.1-4.0 (m, 5, $-N-CH_2$ and $-CH_2-CH-$) 4.42 (s, 1, OH) 6.5 (d, 1, J = 8.5 Hz, C_8-H) 6.8 (d, 1, J = 2.5 Hz, C_5-H) 7.04 (q, 1, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.31 (s, 5, C_6H_5).

Anal. Calcd. for $C_{21}H_{22}ClNO_3$: C, 67.8; H, 6.0; N, 3.8. Found: C, 67.9; H, 6.0; N, 3.6.

3-Acetyl-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**2b**).

Zinc chloride, 2 g. (0.015 mole) was added to a mixture of 24.5 g. (0.1 mole) of 2-benzoyl-4-chloro-*N*-methylaniline (**1b**), 100 ml. of methylene chloride and 9 ml. (0.11 mole) of methyl vinyl ketone. After stirring for 1 hour at room temperature the reaction mixture was washed with water. The aqueous phase was extracted with methylene chloride and the organic layer was again washed with water, dried and evaporated. Crystallization of the residue from ether/hexane yielded 23.3 g. (74%) of yellowish needles with m.p. 96-99°. The analytical sample was recrystallized from ether/hexane, off white needles, m.p. 98-100°; uv: λ max 260 mμ (ε, 14,800) 319 (2,950); ir (chloroform): 3450 cm^{-1} (OH) 1700 (CO); nmr (deuteriochloroform): δ 1.93 ppm (s, 3, $COCH_3$) 2.96 (s, 3, NCH_3) 3.05-3.9 (m, 3, $-CH_2-CH-$) 4.43 (broad s, 1, OH) 6.63 (d, 1, J = 8.5 Hz, C_8-H) 6.86 (d, 1, J = 2.5 Hz, C_5-H) 7.15 (q, 1, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.35 (s, 5, C_6H_5).

Anal. Calcd. for $C_{18}H_{18}ClN_2O$: C, 68.5; H, 5.7; N, 4.4; Cl, 11.2. Found: C, 68.6; H, 5.7; N, 4.5; Cl, 11.5.

6-Chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxaldehyde (**2c**) and 2,11-Dichloro-5,6,6a,7,13,14a-hexahydro-5,8-dimethyl-13,14a-diphenyl-7,13-epoxyquino[4,3-*c*][2,6]benzoxazocine, (**5**).

A mixture of 24.5 g. (0.1 mole) of **1b**, 200 ml. of methylene chloride, 8 ml. (0.122 mole) of acrolein and 2 g. of zinc chloride was stirred at room temperature for 1 hour. The dark solution was washed with water, dried and evaporated. The residue was passed over a funnel containing 100 g. of silica gel with methylene chloride. The fractions rich in product were evaporated and crystallized from ether/hexane to yield 12.6 g. (41.5%) of yellowish crystals with m.p. 94-96°. The analytical sample was recrystallized from methylene chloride/petroleum ether, m.p. 95-97°; uv: λ max 262 mμ (ε, 16,250) 321 (2,900); ir (chloroform): 3700 cm^{-1}, 3500, (OH) 1710 (CO); nmr (deuteriochloroform): δ 2.97 ppm (s, 3, $N-CH_3$) 2.9-3.6 (m, 3, $-CH_2-CH-$) 6.65 (d, 1, J = 8.5 Hz, C_8-H) 6.95 (d, 1, J = 2.5 Hz, C_5-H) 7.2 (q, 1, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.35 (s, 5, C_6H_5) OH appears very broad at about 3 ppm, in DMSO as a singlet at 6.32 ppm.

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.6. Found: C, 67.9; H, 5.3; N, 4.5.

From the combined least polar fractions was obtained 1.13 g. (4.5%) of compound **5** with m.p. 301-302°, crystallized from ether. The analytical sample was recrystallized from methylene chloride/ethyl acetate; uv: λ max 259 mμ (ε, 23,550), 317 (4,900); ir (chloroform): no OH or NH and no carbonyl; nmr (deuteriochloroform:deuteriodimethylsulfoxide, 1:1): δ 2.13 ppm (m, with no coupling greater than 5.5 Hz, 1, -CH-) 2.98 (s, 3, $N-CH_3$) 3.1 (s with fine structure, 2, $-N-CH_2-$) 3.18 (s, 3, $N-CH_3$) 5.15 (d, 1, J = 5.4 Hz, $-CH<^{N}_{O}$) 6.6-7.8 (m, 16, aromatic H); MS: m/e 528 (M^+).

Anal. Calcd. for $C_{31}H_{26}Cl_2N_2O_2$: C, 70.3; H, 4.9; N, 5.3. Found: C, 70.5; H, 5.0; N, 5.3.

6-Chloro-4-hydroxy-3-[1-(hydroxyimino)ethyl]-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**3b**).

A mixture of 31.6 g. (0.1 mole) of **2b**, 21 g. (0.3 mole) of hydroxylamine hydrochloride, 24 g. (0.29 mole) of sodium acetate and 300 ml. of ethanol was heated to reflux for 30 minutes. The product was crystallized by addition of water and collected, washed with water and recrystallized from ethanol/water to yield 25 g. (75%) of colorless crystals with m.p. 185-190°; uv: λ max 266 mμ (ε, 15,200) 322 (3,000); ir (chloroform): 3575 cm^{-1}, 3350 (OH); nmr (deuteriochloroform): δ 1.57 ppm (s, 3, CH_3) 2.94 (s, 3, $N-CH_3$) 3-4 (m, 3, CH_2-CH) 5.1 (broad s, 1, OH) 6.52 (d, 1, J = 8.5 Hz, C_8-H) 6.64 (d, 1, J = 2.5 Hz, C_5-H) 7.03 (q, 1, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.28 (s, 5, C_6H_5) 8.22 (broad s, 1, =NOH).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$: C, 65.4; H, 5.8; N, 8.5. Found: C, 65.6; H, 5.8; N, 8.6.

6-Chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxaldoxime (**3c**).

A mixture of 80 g. (0.27 mole) of **2c**, 19 g. (0.27 mole) of hydroxylamine hydrochloride, 23 g. (0.28 mole) of sodium acetate and 1.5 l. of ethanol was stirred at room temperature for 2 hours. The bulk of the solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ether/petroleum ether yielded 76.7 g. (89%) of cream colored material with m.p. 135-141°. The analytical sample was recrystallized from methylene chloride/petroleum ether and from aqueous methanol, m.p. 144-147°; nmr (deuteriochloroform): δ 2.95 ppm (s, 3, $N-CH_3$) 2.6-4.0 (m, 4, CH_2-CH and OH) 6.55 (d, 1, J = 8.5 Hz, C_8-H) 6.65 (d, 1, J = 2.5 Hz, C_5-H) 7-7.5 (m, C_6H_5, C_7-H, CH=N) 8.0 (broad s, 1, NOH).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.5; H, 5.4; N, 8.8.

3-Acetyl-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline Hydrazone (**3e**).

A mixture of 6.32 g. (0.02 mole) of **2b**, 3 ml. of hydrazine hydrate, 3 ml. of acetic acid and 100 ml. of ethanol was heated to reflux for 2 hours. The product was crystallized by dilution with water, was collected and recrystallized from benzene/methanol to yield 5.3 g. (80%) of off white crystals which were again recrystal-

lized from the same solvents for analysis, m.p. 188-192°; uv: λ max 256 mμ (ε, 15,400) 320 (3,000); nmr (deuteriochloroform): δ 2.47 ppm (s, 3, CH_3) 2.93 (s, 3, N-CH_3) 3-4 (m, 3, CH_2-CH) 4.92 (broad s) and 5.75 (broad s) 3, OH and NH_2) 6.55 (d, 1, J = 8.5 Hz, C_8-H) 6.64 (d, 1, J = 2.5 Hz, C_5-H) 7.02 (q, 1, J_{AB} = 8.5 Hz, J_{AX} = 2.5 Hz, C_7-H) 7.3 (m, 5, C_6H_5).

Anal. Calcd. for $C_{18}H_{20}ClN_3O$: C, 65.6; H, 6.1; N, 12.7. Found: C, 65.6; H, 6.1; N, 12.8.

6-Chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxaldehyde Semicarbazone (**3f**).

A mixture of 12 g. (0.04 mole) of **2c**, 4.45 g. (0.04 mole) of semicarbazide hydrochloride, 3,3 g. (0.04 mole) of sodium acetate, 100 ml. of ethanol and 100 ml. of water was warmed on the steam bath for 5 minutes until solution was complete. After cooling in ice/water the precipitated crystals were collected and recrystallized from aqueous methanol to yield 10.7 g. (75%) with m.p. 198-201° dec.

Anal. Calcd. for $C_{18}H_{19}ClN_4O_2$: C, 60.2; H, 5.3; N, 15.6. Found: C, 60.2; H, 5.6; N, 15.8.

3-Acetyl-6-chloro-1,2-dihydro-4-phenylquinoline (**4a**).

Compound **2a**, 100 g. (0.33 mole) was added to a solution of 1 g. (0.043 mole) of sodium in 1 l. of ethanol. The mixture was heated to reflux for 1 hour under an atmosphere of nitrogen. The product was crystallized by cooling to 0° with stirring. The red crystals were collected, washed with ethanol and dried to yield 86.5 g. (92%) with m.p. 135-138°; uv: λ max 250 mμ (ε, 29,800) sh 305 (4,500) max 425 (3080); ir (chloroform): 3425 cm^{-1} (NH) 1640 (CO); nmr (deuteriochloroform): δ 1.64 ppm (s, 3, $COCH_3$) 4.18 (broad s, 1, NH) 4.32 (s, 2, -CH_2-) 6.49 (d, 1, J = 8 Hz, C_8-H) 6.54 (d, 1, J = 2.5 Hz, C_5-H) 6.9-7.7 (m, 6, C_6H_5 and C_7-H).

Anal. Calcd. for $C_{17}H_{14}ClNO$: C, 71.9; H, 5.0; N, 4.9. Found: C, 71.6; H, 4.8; N, 4.8.

3-Acetyl-6-chloro-1,2-dihydro-1-methyl-4-phenylquinoline (**4b**).

Potassium *t*-butoxide, 0.3 g. (2.6 mmoles) was added to a solution of 3.16 g. (0.01 mole) of **2b** in 30 ml. of methanol. The mixture was heated to reflux under an atmosphere of nitrogen for 15 minutes. The red solution was cooled and the product was crystallized by addition of water. The orange crystals were collected and recrystallized from methanol/water, to yield 2.0 g. (67%) with m.p. 82-85°; uv: λ max 262 mμ (ε, 32,500) sh 303 (4,200) max 341 (2,990); ir (chloroform): 1640 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.63 ppm (s, 3, $COCH_3$) 2.85 (s, 3, NCH_3) 4.14 (s, 2, -CH_2-) 6.52 (d, 1, J = 8 Hz, C_8-H) 6.58 (d, 1, J = 2.5 Hz, C_5-H) 7-7.7 (m, 6, C_6H_5 and C_7-H).

Anal. Calcd. for $C_{18}H_{16}ClNO$: C, 72.6; H, 5.4; N, 4.7. Found: C, 72.3; H, 5.4; N, 4.5.

2,11-Dichloro-5,6,6a,7,13,14a-hexahydro-5,8-dimethyl-13,14a-diphenyl-7,13-epoxyquino[4,3-*c*][2,6]benzoxazocine (**5**).

A mixture of 3 g. of **2c**, 2.45 g. of **1b**, 30 ml. of methylene chloride and 1.5 g. of zinc chloride was stirred at room temperature for 24 hours. After washing with water, the solution was dried and evaporated and the residue was chromatographed over 150 g. of silica gel using methylene chloride/hexane 3:2 (v/v). The fastest moving component was crystallized from ether and recrystallized from ethyl acetate to yield 0.135 g. (2.5%) of product with m.p. 301-302° which was identical in every respect with the material obtained by condensation of acrolein with **1b**.

3-Acetyl-6-chloro-4-phenylquinoline (**6**).

A mixture of 28.4 g. (0.1 mole) of **3a**, 500 ml. of methylene chloride and 140 g. of activated manganese dioxide was stirred at room temperature for 2 hours. The manganese oxide was filtered off and the filtrate was evaporated. Crystallization of the residue from methylene chloride/hexane yielded 25.6 g. (94%) of light yellow product with m.p. 129-131°. The analytical sample was recrystallized from methanol; uv: λ max 243 mμ (ε, 48,100) 285 (6,900) 325 (2,700); ir (chloroform): 1680 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.98 ppm (s, 3, $COCH_3$) 7.2-7.8 (m, 7, C_6H_5, C_5-H, C_7-H) 8.1 (d, 1, J = 9 Hz, C_8-H) 9.12 (s, 1, C_2-H).

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.5; H, 4.3; N, 5.0. Found: C, 72.2; H, 4.1; N, 4.9.

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REFERENCES

(1) L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach and A. Atempel, *J. Org. Chem.*, **27**, 3781 (1962).

(2) A. Walser, T. Flynn and R. Ian Fryer, *J. Heterocyclic Chem.*, 12, 737 (1975).

(3a) E. A. Fehnel, *J. Heterocyclic Chem.*, **4**, 565 (1967); (b) E. A. Fehnel, *J. Org. Chem.*, **31**, 2899 (1966).