Synthesis of Simple Quinoline Alkaloids. A Novel Quinazoline Synthesis

Ib Thomsen and Kurt B. G. Torssell*

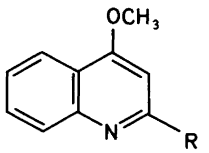
Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Århus C, Denmark

Thomsen, I. and Torssell, K. B. G., 1988. Synthesis of Simple Quinoline Alkaloids. A Novel Quinazoline Synthesis. – Acta Chem. Scand., Ser. B 42: 309–313.

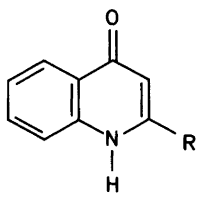
2-Alkyl (aryl), 4-amino-substituted quinolines are prepared in two steps by cycloaddition of 2-nitrobenzaldoximes with acetylenes and subsequent reductive cleavage of the intermediate isoxazole in acetic acid. Diazotization of the 4-aminoquinolines gives the corresponding 4-hydroxyquinolines, some of which occur naturally in *Lunasia* spp. Selective reduction of the nitro group in the intermediate isoxazole, acylation of the amino function, reductive cleavage of the isoxazole ring and acid- or base-catalyzed cyclization constitute a novel route to various quinazolines.

In continuation of our studies[1] on the use of nitrile oxides and the intermediate isoxazole heterocycles in organic synthesis, we present a quinoline synthesis with a substitution pattern contained in some simple quinoline alkaloids.[§] 4-Methoxy-2-phenylquinoline[3] (**1a**) and 4-methoxy-2-pentylquinoline[4] (**1b**) have been isolated from *Lunasia amara* and *Galipea officinalis*, and have also been synthesized earlier by simple procedures. Hydrolysis of the methoxy group gives the corresponding quinolones (**2a,b**), which by treatment with diazomethane reform the alkaloids (**1a,b**). The 4-quinolones are structurally (but not biosynthetically) closely related to the flavones. Replacement of the ring-oxygen in the flavones with nitrogen gives the corresponding quinolones. In an earlier paper,[1] a synthesis of flavones via the isoxazole route was presented. Thus, by analogy it should be possible to prepare the quinolones **2a,b** by starting from *ortho*-nitrobenzaldoxime and an acetylene (or an enamine) according to Scheme 1.

The cycloaddition to **3a,b** proceeded satisfactorily.[5] **3a,b** were reduced rapidly (within 1 h) to **4a,b** by catalytic reduction over Raney-Ni. Complete reductive cleavage (ca. 20 h) under various conditions gave only **8a,b**. The desired **2a,b** could not be observed. Apparently, cyclization proceeds faster than hydrolysis of the enamino function. Therefore we decided to selectively reduce the nitro group in **3a,b**, protect the amine by acetylation and then reductively cleave the N-O bond to **5a,b**. However, acid treatment of **5a,b** gave the quinazolines **6a,b**, which on treatment with base formed 2,4-dimethylquinazoline (**7**). Benzoic and hexanoic acid were eliminated in a retro-Claisen reaction. Reaction of **5a** or **5b** with base gave quinazoline **7** directly (Scheme 1). Various substituents can be introduced at C-2 by changing the acyl group. According to IR_1 ^1H and



1a,b



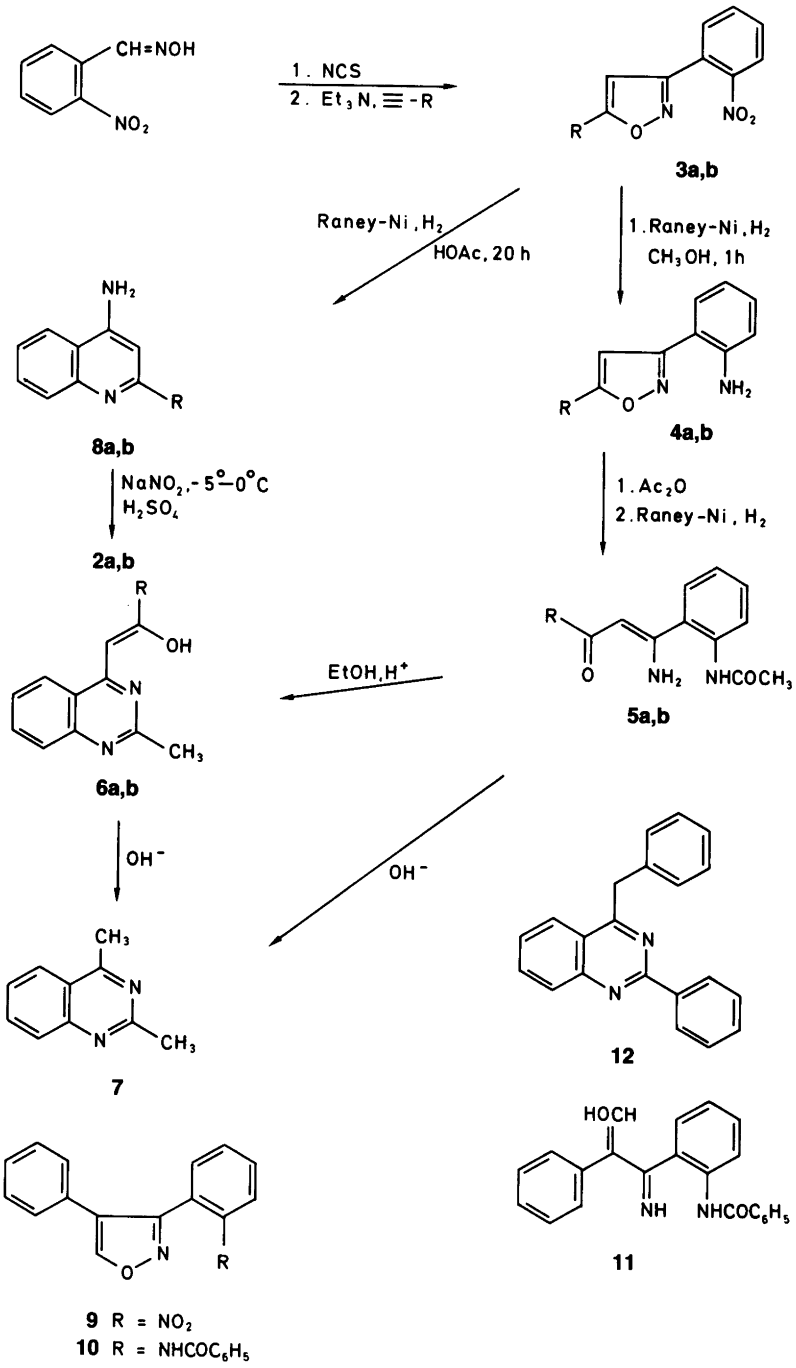
2a,b

a: R = C_6H_5

b: R = C_5H_{11}

*To whom correspondence should be addressed.

§For reviews on quinoline alkaloids, see. e.g. Ref. 2.


CH=NOH
NO2
1. NCS
2. Et3N, ≡-R
R
N
O
NO2
3a,b
Raney-Ni, H2
HOAc, 20 h
1. Raney-Ni, H2
CH3OH, 1h
NH2
R
N
O
NH2
4a,b
8a,b
NaNO2, -5°–0°C
H2SO4
2a,b
1. Ac2O
2. Raney-Ni, H2
R
OH
N
N
CH3
6a,b
EtOH, H+
R
O
NH2
NHCOCH3
5a,b
OH-
OH-
CH3
N
N
CH3
7
N
N
12
HOCH
NH
NHCOC6H5
11
R
9 R = NO2
10 R = NHCOC6H5

Scheme 1.

^{13}C NMR spectroscopic data the side chain carbonyl group of **6a,b** occurs in its enol form.

3-(2-Nitrophenyl)-4-phenylisoxazole (**9**) was prepared from the morpholine enamine of phenylacetaldehyde and 2-nitrobenzaldoxime (cf. Ref. 1). Selective reduction of the nitro group and benzoylation gave **10**, which on reductive cleavage and acid- or base-catalyzed cyclization formed the quinazoline **12** via compound **11**. This sequence of reactions thus unintentionally led to a novel quinazoline synthesis.

Our primary goal of synthesizing the naturally occurring 4-hydroxyquinoline derivatives **2a,b** was finally reached by diazotization of **8a,b** in sulfuric acid.

Experimental

3-(2-Nitrophenyl)-5-phenylisoxazole (**3a**). *O*-Nitrobenzaldoxime was chlorinated with NCS in chloroform under reflux for ca. 20 min in the presence of a few drops of pyridine.[6] Phenylacetylene was added and then, dropwise, a chloroform solution of triethylamine. The solution was heated under reflux for 1/2 h, washed with water, evaporated and the residue recrystallized from methanol/water. The yield of **3a** was 56 %; m.p. 86–94 °C (lit.[5] 84 %, m.p. 92 °C). ^1H NMR ($CDCl_3$): δ 6.61 (C^4-H, s).

3-Nitrophenyl-5-pentylisoxazole (**3b**), an oil, was prepared similarly in a yield of 32 %. An excess of 1-heptyne (100 %) was used. The crude product was purified by column chromatography (SiO_2, hexane, diethyl ether 20 %). ^1H NMR ($CDCl_3$): δ 1.92 (3H, t, *J* 7 Hz), 1.2–2.0 (6H, m), 2.79 (2H, t, *J* 7 Hz), 6.08 (1H, s), 7.3–8.2 (4H, m).

3-(2-Aminophenyl)-5-phenylisoxazole, 3-(2-aminophenyl)-5-pentylisoxazole. **4a,b** *and their acetamides.* **3a,b** were reduced catalytically over Raney-Ni in methanol. The reduction was stopped after ca. 45 min, when 3 equiv. of H_2 were absorbed. Filtration, evaporation of the solvent and purification by preparative TLC (SiO_2, CH_2Cl_2, 2–10 % CH_3OH) gave the amines in a yield of 60–70 %. The melting point for **4a** is 106 °C (lit.[5] 98–100 °C). MS: 237, 236 (M^+), 235. The acetyl derivative obtained by acylation of the crude product with acetyl chloride and triethylamine in chloroform melted unsharply at ca. 120 °C (lit.[5] 128 °C). ^1H NMR ($CDCl_3$): δ 2.23 (3H, s), 6.82 (1H, s), 7.0–7.9 (8H, m), 8.62 (1H, dd, *J* 8 and 2 Hz). MS: 278 (M^+). *3-(2-Aminophenyl)-5-pentylisoxazole* (**4b**) is an oil. ^1H NMR ($CDCl_3$): δ 0.89 (3H, t, *J* 7 Hz), 1.0–2.0 (6H, m), 2.72 (2H, t, *J* 7 Hz), 5.3 (2H, br.s), 6.23 (1H, s), 6.4–7.5 (4H, m); *the acetamide,* m.p. 59–61 °C. ^1H NMR ($CDCl_3$): δ 0.91 (3H, t, *J* 7 Hz), 1.0–2.0 (6H, m), 2.23 (3H, s), 2.77 (2H, t, *J* 7 Hz), 6.29 (1H, s), 6.9–7.6 (3H, m), 8.61 (1H, dd, *J* 8 and 1.5 Hz).

The reduction of acetylated **4a** *to* **5a** was carried out in methanol/water (5:1) with Raney-Ni as catalyst in the presence of 3 equiv. of boric acid. The solution was filtered through a thin layer of celite and evaporated to dryness *in vacuo*. Chromatographic purification on the TLC plate (SiO_2, $CHCl_3$, 10 % CH_3OH) and recrystallization from benzene gave **5a** (78 %); m.p. 164–166 °C. ^1H NMR ($CDCl_3$): δ 2.05 (3H, s), 5.85 (1H, s), 6.9–8.3 (10H, m). MS: 263, 262 (M^+-18). **5b**, m.p. 129–131 °C (methanol), was prepared analogously. ^1H NMR ($CDCl_3$): δ 0.85 (3H, t, *J* 7 Hz), 1.0–2.0 (6H, m), 2.06 (3H, s), 2.30 (2H, t, *J* 7 Hz), 5.16 (1H, s), 6.9–7.6 (3H, m), 8.12 (1H, d, *J* 9 Hz).

The quinazolines **6a,b** are formed by heating **5a,b** (0.10 g) under reflux in ethanol (1 ml) containing 1 drop of conc. hydrochloric acid for 30 min. Evaporation of the solvent *in vacuo*, dissolution of the residue in chloroform, washing with aqueous sodium bicarbonate, evaporation and recrystallization gave the quinazolines. **6a**: m.p. 126–127 °C (ether); ^1H NMR ($CDCl_3$): δ 2.49 (3H, s), 6.63 (1H, s), 7.1–8.1 (9H, m). ^{13}C NMR ($CDCl_3$): δ 22.45 (CH_3),

$$\left(CH = C\begin{matrix}OH\\ C_6H_5\end{matrix}\right), \quad 85{,}51$$

$$\left(CH = C\begin{matrix}OH\\ C_6H_5\end{matrix}\right), \quad 189.06$$

6b: m.p. 42–43 °C (hexane); ^1H NMR ($CDCl_3$): δ 0.91 (3H, t, *J* 7 Hz), 1.0–2.0 (6H, m), 2.43 (3H, s), 2.43 (2H, t, *J* 7 Hz), 5.90 (1H, s), 7.1–7.9 (4H, m). The yields are in the range of 70–80 %.

2,4-Dimethylquinazoline (**7**). **5a** (50 mg) was heated under reflux in methanol (0.6 ml) contain-

ing 20 mg of sodium methoxide for 1 h. Evaporation of methanol *in vacuo,* dissolution of the residue in $CHCl_3$ and washing with water gave **7** quantitatively upon evaporation of $CHCl_3$; m.p. 72 °C from ether (lit.[7] 72 °C, dihydrate). The ^1H NMR spectrum was identical to that of an authentic specimen. MS: 159, 158 (M^+). Benzoic acid was isolated following acidification of the aqueous phase. **5b** gave **7** in 86 % yield using the same method. Hexanoic acid was isolated from the aqueous phase by acidification and extraction with methylene chloride. **6a,b** were also transformed practically quantitatively into **7** on treatment with base.

Synthesis of 2-phenyl-4-aminoquinoline (**8a**) *and 2-pentyl-4-aminoquinoline* (**8b**). **3a** or **3b** was reduced catalytically over Raney-Ni in acetic acid (ca. 20 h). The solution was filtered through a bed of celite, evaporated to small volume, and the residue was dissolved in chloroform and extracted twice with water. **8a,b** were precipitated from the aqueous solution together with Ni salts by addition of sodium bicarbonate to give pH ca. 9. The precipitate was filtered off from the cooled solution and extracted with boiling ethanol. Evaporation of the ethanol and recrystallization of the residue from benzene gave **8a**, m.p. 160–162 °C) (lit.[5] 164 °C), and **8b**, m.p. 103–105 °C; ^1H NMR ($CDCl_3$): δ 0.80 (3H, t, *J* 7 Hz), 1.0–2.0 (6H, m), 2.81 (2H, t, *J* 8 Hz), 5.3 (2H, br.s), 6.32 (1H, s), 7.0–8.0 (4H, m).

3-(2-Nitrophenyl)-4-phenylisoxazole (**9**) was prepared from 2-nitrophenylbenzaldoxime and the morpholine enamine of phenylacetaldehyde according to the procedure described for the corresponding 2-hydroxyphenyl derivative (compound **17**) in Ref. 1. The yield of recrystallized product (ethanol), m.p. 88–89 °C, was 59 %. ^1H NMR ($CDCl_3$): δ 6.8–8.2 (9H, m), 8.57 (1H, s).

3-(2-Benzoylamidophenyl)-4-phenylisoxazole (**10**) was partially reduced in methanol over Raney-Ni as described for **4a,b**. The crude amine from the work-up was benzoylated directly with benzoyl chloride and triethylamine in chloroform. **10** was purified by preparative TLC (SiO_2, $CHCl_3$, 1 % CH_3OH). The yield was 83 %; m.p. 155 °C from ethanol. ^1H NMR ($CDCl_3$): δ 6.6–7.6 (11H, m), 7.6–8.0 (2H, m), 8.43 (1H, s), 8.53 (1H, d, *J* 10 Hz), 10.2 (1H, br.s).

Compound **11** was obtained by catalytic reduction of **10** over Raney-Ni in acetic acid. Filtration, evaporation of the solvent *in vacuo,* and partition of the product between chloroform and water (HCO_3^-) lead to the quantitative isolation of crude **11** upon evaporation of the chloroform phase. It was recrystallized from acetonitrile; m.p. 174 °C.

2-Phenyl-4-benzylquinazoline (**12**) was formed on heating **11** under reflux in ethanol containing catalytic amounts of either conc. hydrochloric acid or sodium ethoxide for 1 h. Evaporation of the solvent followed by partition of the product between chloroform and aqueous sodium bicarbonate gave **12**; m.p. 56–59 °C (from hexane). The yield was 49 % ^1H NMR ($CDCl_3$): δ 4.59 (2H, m), 6.9–8.2 (12H, m), 8.2–8.8 (2H, m).

2-Phenyl-4-hydroxyquinoline (**2a**) was prepared by diazotization of **8a** (100 mg) dissolved in water (2 ml) and conc. sulfuric acid (3 ml) with sodium nitrite (60 mg in 0.5 ml H_2O) at ca. 0–5 °C for 40 min. The solution turned red on addition of the first drop of aqueous sodium nitrite. Water (15 ml) was added and a yellow precipitate was formed with evolution of N_2. It was filtered off and recrystallized from ethanol. The yield was 60 mg. The compound melted unsharply at 170–180 °C. Purification by preparative TLC (SiO_2, CH_2Cl_2, CH_3OH 10 %) and recrystallization from ethanol raised the m.p. to 245–264 °C. There was no melting point depression on mixing with an authentic specimen. According to the literature,[3] **2a** melts at 256–258 °C and has crystal transformations at 215 °C and 247–251 °C. An absolute MS determination verified the expected molecular composition $C_{15}H_{11}NO$.

2-Pentyl-4-hydroxyquinoline (**2b**) was prepared analogously, starting from **8b**. The yellow precipitate which was obtained by addition of water (cf. **2a**) was filtered off, dried and purified by preparative TLC (SiO_2, $CHCl_3$, 10 % CH_3OH). **2b** was obtained as an oil which solidified on stirring with dilute hydrochloric acid. The yield was ca. 70 %. Reprecipitation from boiling water gave white needles; m.p. 142–145 °C (lit.[4] 144 °C). ^1H NMR (CD_3CN + CD_3OD + $CDCl_3$): δ 0.90 (3H, br.t, *J* 7 Hz), 1.1–2.1 (6H, m), 3.06 (2H, t, *J* 8 Hz), 7.15 (1H, s), 7.3–8.3 (4H, m). MS: 215 (M^+), 172, 159. When the compound was recrys-

tallized from acetonitrile, it melted at 175–185 °C with crystal transformation at ca. 80 °C.

References

1. Thomsen, I. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B 42* (1988) 303; Torssell, K. B. G. *Use of Nitrile Oxides, Nitrones and Silyl Nitronates in Organic Synthesis. Novel Strategies in Synthesis,* Verlag Chemie, New York 1988.
2. Boit, H. G. *Ergebnisse der Alkaloidchemie bis 1960,* Akademie-Verlag, Berlin 1961; Openshaw, H. T. In: Manske, R. H. F., Ed., *Alkaloids 9* (1967) 223.
3. Goodwin, S., Smith, A. F. and Horning, E. C. *J. Am. Chem. Soc. 79* (1957) 2239.
4. Späth, E. and Pikl, J. *Chem. Ber. 62* (1929) 2244.
5. Casnati, G., Quilico, A., Ricca, A. and Vita Finzi, P. *Gazz. Chim. Ital. 96* (1966) 1073.
6. Larsen, K. E. and Torssell, K. B. G. *Tetrahedron 40* (1984) 2985.
7. Bischler, A. and Buckart, E. *Chem. Ber. 26* (1893) 1349.

Received February 19, 1988.