A New Synthesis of 2,3-Dihydrofuro[2,3-*b*], [2,3-*c*] and [3,2-*c*]quinolines

A. Godard, J. M. Jacquelin and G. Queguiner*

Institut National des Sciences, Appliquées de Rouen, Place Emile Blondel -B.P. n° 8,
76130 Mont St Aignan, France

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A new synthesis of three isomeric dihydrofuroquinolines is described. This route *via* ortholithiation of *O*-quinolyl carbamates is considerably more effective than that which proceeds *via* lithiation of alkoxyquinolines.

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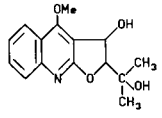
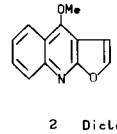
Furoquinolines have been extensively studied because of their interest as natural products [1]. Alkaloids of the linear furo[2,3-*b*]quinoline group are the best known. Myrtopsine **1** [2] and Dictamnine **2** are two examples.

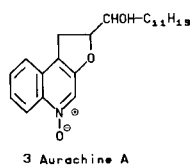


1 Myrtopsine

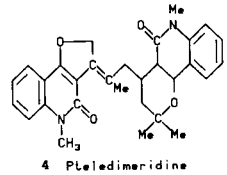


2 Dictamnine

Natural products were also isolated in the angular series. For example Aurachine A **3** in the furo[2,3-*c*]quinoline group [3] and pteledimeridine **4** in the furo[3,2-*c*]-quinoline group [4].



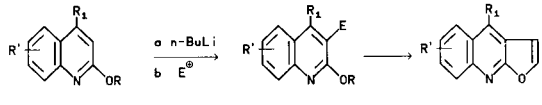
3 Aurachine A



4 Pteledimeridine

Most routes available for the synthesis of linear furoquinolines **1** involve a common feature. The carbon chain at the 3-position required for the formation of the furan ring is incorporated as the quinoline ring is built [5].

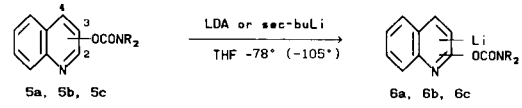
A different approach was described by Narasimhan [6-8] who introduced the necessary side chain at C3 on a preformed quinoline ring, and subsequently modified it into a furan ring.



This interesting method which affords good results with 2,4-dialkoxyquinolines, is restricted by the low yields (4%-7%) obtained in the metalation of quinoline substituted only by an alkoxy group at C2 [6] [9].

We wish to report here a new versatile method providing three isomeric dihydrofuroquinolines using *O*-quinolyl carbamates as starting materials.

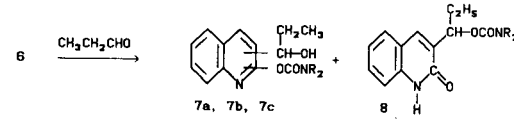
We showed earlier that the *N,N*-dialkyl-*O*-quinolyl carbamates substituted on the pyridine ring **5a, 5b** and **5c** could be lithiated at -78° (or -105°) by using lithium diisopropylamide or *sec*-butyllithium as the reagent [10].



5a, 5b, 5c — 6a, 6b, 6c

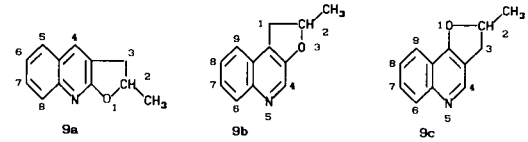
The lithiated species **6a, 6b** and **6c** react with different electrophiles to afford *ortho-O*-quinolyl carbamates.

The reaction of propanal with the lithiated species **6** gave the corresponding alcohols **7** or a mixture of the alcohol **7a** and the rearranged carbamate **8** (obtained in the course of the reaction of **5a**).



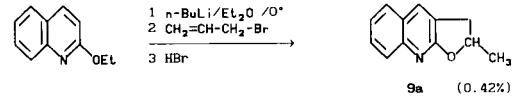
7a, 7b, 7c — 8

Simple heating up to 150-200° did not give the expected furoquinolines. However on heating at 90° in sulfuric acid for 2 hours a mixture of **7a** and **8** or **7b** or **7c** led to the 2-methyl-2,3-dihydrofuroquinolines **9a** (70%), **9b** (81%) and **9c** (30%) respectively.



9a — 9b — 9c

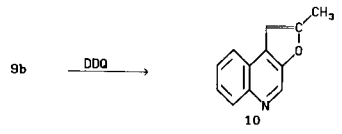
The overall yield of the synthesis of **9a** starting from *N,N*-diethyl-*O*-(2-quinolyl) carbamate is of 35%. This result is to be compared with those (0.42%) obtained from the 2-ethoxyquinoline by Narasimhan [6-7].



9a (0.42%)

Aromatization of the dihydrofuroquinolines is difficult. The use of potassium permanganate in acetone or

chloranyl failed. However DDQ which was used by Piozzi [11] to oxidize the 4-methoxy-2,3-dihydrofuro[2,3-*c*]quinoline to the corresponding aromatized heterocycle allowed the oxidation of **9b** to the aromatic 2-methylfuro[2,3-*c*]-quinoline **10**.



The method described for the synthesis of the furoquinoline synthons is thus very attractive. It provides three isomers starting from the *O*-quinolyl carbamate unsubstituted on the pyridine ring.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ^1H nmr spectra were recorded in deuteriochloroform at 60 MHz on a Varian EM-360L instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus.

N,N-Dialkyl-*O*-[1-(1-hydroxypropyl)quinolyl] carbamates were synthesized as described in a preceding paper [10]. Lithiation of the corresponding *N,N*-dialkyl-*O*-quinolyl carbamates was carried out using LDA or *sec*-butyllithium as the reagent at -78° or -105°. Reaction of the intermediate lithiated species with propanal afforded the alcohols or the rearranged carbamate.

2-Methyl-2,3-dihydrofuroquinolines. General Procedure.

A mixture of 0.45 mmole of *N,N*-dialkyl-*O*-[1-(1-hydroxyethyl)quinolyl] carbamate and 10 ml of concentrated sulfuric acid was heated for 8 hours at 95°. The cooled reaction mixture was then diluted with 100 ml of water. A solution of diluted soda (10%) was added up to *p*H 7 and the resulting solution extracted with methylene chloride (3 x 100 ml). After evaporation and liquid chromatography (silica/ethyl acetate) pure 2-methyl-2,3-dihydrofuroquinolines were recovered.

2-Methyl-2,3-dihydrofuro[2,3-*b*]quinoline (**9a**). (Note: The starting material was a mixture of alcohol **7a** and the rearranged carbamate **8**.)

This compound was obtained as a white deep liquid, yield = 70%; nmr (deuteriochloroform): δ ppm/TMS, 1.5 (d, 3H, CH_3), 2.5-3.6 (m, 2H, CH_2), 4.95 (m, 1H, CH), 7.05-7.95 (m, 5H, H^4-H^8), $J_{CH_3\text{-}CH}$ = 6 Hz.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.35; H, 6.05; N, 7.35.

2-Methyl-2,3-dihydrofuro[2,3-*c*]quinoline (**9b**).

This compound was obtained as a white deep liquid, yield = 81%; nmr (deuteriochloroform): δ ppm/TMS, 1.57 (d, 3H, CH_3), 2.9-3.9 (m, 2H, CH_2), 5.20 (m, 1H, CH), 7.6 (m, 3H, H^6-H^8), 8.1 (m, 1H, H^9), 8.7 (s, 1H, H^4), $J_{CH_3\text{-}CH}$ = 6 Hz.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.50; H, 6.20; N, 7.45.

2-Methyl-2,3-dihydrofuro[3,2-*c*]quinoline (**9c**).

This compound was obtained as a white deep liquid, yield = 30%; nmr (deuteriochloroform): δ ppm/TMS, 1.55 (d, 3H, CH_3), 2.7-3.75 (m, 2H, CH_2), 5.15 (m, 1H, CH), 7.15-8.1 (m, 4H, H^6, H^7 and H^6, H^9), $J_{CH_3\text{-}CH}$ = 6 Hz.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.35; H, 6.30; N, 7.15.

2-Methylfuro[3,2-*c*]quinoline **10**.

A solution of 0.2 g of 2-methyl-2,3-dihydrofuro[2,3-*c*]quinoline (1.08 mmoles) and of 0.28 g of DDQ (1.2 mmoles) in 50 ml of dioxane was refluxed for 2 hours. The resulting mixture was evaporated to dryness. The crude product was extracted with methylene chloride and washed with diluted sodium carbonate solution. Pure **10** (0.135 g) was obtained by liquid chromatography, yield = 66%, mp, 180°; nmr (deuteriochloroform): δ ppm/TMS, 2.5 (s, 3H, CH_3), 6.7 (s, 1H, H^1), 7.2-7.85 (m, 2H, H^7, H^8), 7.85-8.33 (m, 2H, H^6, H^9), 9.0 (s, 1H, H^4).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.68; H, 4.91; N, 7.65. Found: C, 78.39; H, 5.10; N, 7.70.

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