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Synthesis of Substituted 1,2,3,4-Tetrahydroquinoline-4-carboxylic Acids

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Abstract—Reduction of some substituted quinoline-4-carboxylic acids was studied. The reduction of 2-alkylquinoline-4-carboxylic acids with Raney nickel in aqueous alkali was stereoselective, and the resulting 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acids were individual *cis* isomers.

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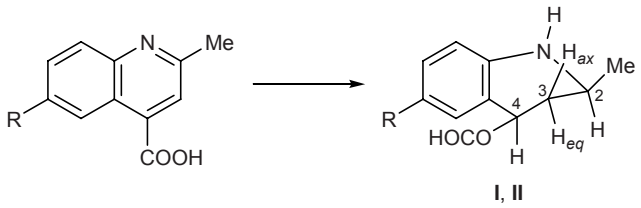
Tetrahydroquinoline derivatives are widespread in nature. They possess unique biological properties and are promising as intermediate products for the synthesis of various compounds [1, 2]. 1,2,3,4-Tetrahydroquinolinecarboxylic acids are widely used as convenient polyfunctional synthons [3]. 1,2,3,4-Tetrahydroquinolinecarboxylic acids are prepared most frequently by direct reduction of quinolinecarboxylic acids. Procedures for catalytic hydrogenation of quinoline-containing compounds with hydrogen in the presence of platinum catalysts [4, 5], as well as for reduction with tin in hydrochloric acid [6], with zinc in formic acid [5], and with a mixture of formic acid and triethylammonium formate [5], have been reported. In the latter case [5], the products were the corresponding *N*-formyl derivatives. The above procedures often require increased pressure and elevated temperature, and the yields of the reduction products are not always good. Gracheva and Tochilkin [7] described the reduction of methyl-substituted quinoline-5-carboxylic acids with Raney nickel in alkaline medium at room temperature.

The present work was aimed at developing convenient preparative procedures for the synthesis of 1,2,3,4-tetrahydroquinoline-4-carboxylic acids. For this purpose, we examined reduction of a series of substituted quinoline-4-carboxylic acids. We found that the reduction should be performed under different conditions, depending on the nature of substituent in position *2* of the quinoline ring and the degree of substitution. In the reduction of 2-alkyl-substituted derivatives, the best results were obtained using Raney nickel in aqueous solution. We thus obtained 2-methyl- and 2,6-dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acids **I** and **II** (Scheme 1). However, we failed to isolate compounds **I** and **II** from the reaction mixtures in good yields by treatment with a solution of hydrogen chloride in alcohol, as described in [7]. The most appropriate procedure for the isolation of acids **I** and **II** was acidification of the reaction mixture with formic acid, followed by extraction with chloroform.

Scheme 1.



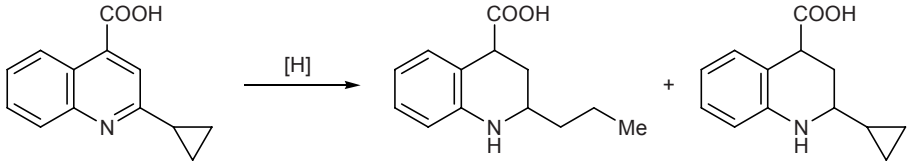
I, **II**

I, R = H; **II**, R = Me.

According to the ^{1}H NMR and GC–MS data, tetrahydroquinolinecarboxylic acids **I** and **II** were pure *cis* isomers. Their configuration was assigned on the basis of the coupling constants for the axial 3-H proton. The existence of large coupling constants (J = 11.0, 12.3 Hz) indicated equatorial orientation of substituents on C^4 and C^2, i.e., *cis* arrangement of the carboxy and methyl groups [8, 9].

2-Cyclopropylquinoline-4-carboxylic acid was reduced with Raney nickel in aqueous alkali. However, the reaction was not selective. As a result, a mixture of 2-propyl- and 2-cyclopropyl-1,2,3,4-tetrahydroquino-

Scheme 2.

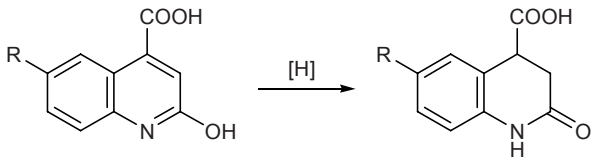


line-4-carboxylic acids at a ratio of 1.7:1 was obtained (Scheme 2). The ratio of the reduction products did not change on raising the amount of Raney nickel and increasing the reaction time. Obviously, the reduction of the cyclopropane fragment is possible only when it is conjugated with quinoline π-electron system, whereas reduction of 2-cyclopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid does not occur under the given conditions.

Introduction of a bulky aromatic substituent, such as phenyl or biphenyl-4-yl, into the 2-position of quinoline-4-carboxylic acid hampers reduction of the pyridine ring. The behavior of such substrates is determined mainly by steric factor, and neither 2-phenylquinoline-4-carboxylic acid nor 2-(biphenyl-4-yl)-quinoline-4-carboxylic acid was reduced with Raney nickel in alkaline solution, zinc in acetic acid, or iron in hydrochloric acid.

2-Oxo- and 2-oxo-6-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acids **III** and **IV** were obtained in 80 and 75% yield, respectively, by reduction of the corresponding substrates with zinc in acetic acid [10] (Scheme 3).

Scheme 3.



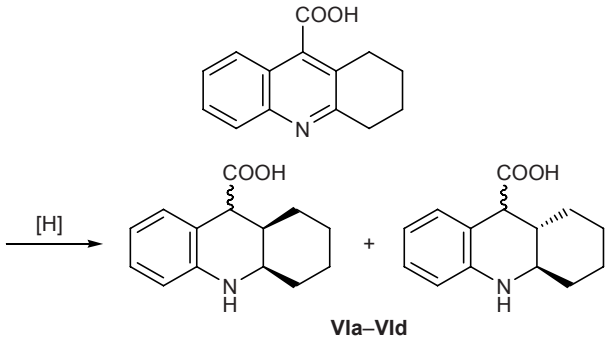
III, **IV**

III, R = H; **IV**, R = Me.

On the other hand, this procedure turned out to be inapplicable to the synthesis of 3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (**V**); the use of Raney nickel in aqueous alkali was also ineffective. Thus the behavior of quinoline-4-carboxylic acids in the reduction processes depends on the substitution pattern in the quinoline ring, which does not contradict published data [11, 12].

The reduction of 1,2,3,4-tetrahydroacridine-9-carboxylic acid with Raney nickel in alkaline medium resulted in the formation of a mixture of four stereoisomers: *cis*- and *trans*-1,2,3,4,4a,9,9a,10-octahydroacridine-9-carboxylic acids **VIa**–**VId** with axial and equatorial orientation of the carboxy group on C^9 at a ratio of 4.6:3.5:1.7:1 (according to the GLC data; Scheme 4). Unfortunately, it was impossible to rigorously identify the stereoisomers.

Scheme 4.



VIa–**VId**

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer from samples prepared as KBr pellets. Gas chromatographic–mass spectrometric analysis was performed on a Finnigan Trance DSQ instrument (electron impact, 80 eV; ZB-5MS column, 30 m×0.32 mm; oven temperature programming from 80 to 340°C at a rate of 15 deg/min; carrier has helium). The ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz using tetramethylsilane as internal reference and $CDCl_3$ as solvent. The elemental compositions were determined on a Euro Vector EA 3000 analyzer.

Initial quinoline-4-carboxylic acids were synthesized according to the procedures described in [13–16].

2-Hydroxy-6-methylquinoline-4-carboxylic acid. A mixture of 208 ml of water and 8.6 ml of 40% aqueous sodium hydroxide was heated under stirring to 108–110°C, 7 g (0.04 mol) of 5-methyl-1-acetyl-2,3-dihydro-1*H*-indole-2,3-dione was added, and the mixture was heated for 45 min. The resulting solution was filtered, and the filtrate was acidified at 70–80°C with

20% hydrochloric acid. The precipitate was filtered off from the hot mixture and washed with hot water. Yield 5.6 g (81%), yellow crystals, mp 340–342°C (from EtOH). IR spectrum, ν, cm^{-1}: 3421 (OH), 1735 (C=O). ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 6.83 s (1H, 3-H), 7.3 d (1H, 8-H), 7.4 d (1H, 7-H), 7.85 s (1H, 5-H). Found, %: C 65.10; H 4.50; N 6.46. $C_{11}H_9NO_3$. Calculated, %: C 65.02; H 4.46; N 6.89.

2-Methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (I). Raney nickel, 2 g, was added in small portions over a period of 1 h under stirring to a solution of 2 g (0.01 mol) of 2-methyl-4-quinolinecarboxylic acid [13] in 10 ml of 10% aqueous sodium hydroxide, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered off and washed with hot water, the filtrate was acidified to pH 3 with formic acid and extracted with chloroform, the extract was dried over anhydrous sodium sulfate and evaporated, and the residue was recrystallized from 50% ethanol. Yield 1.6 g (80%), colorless crystals, mp 131–134°C. IR spectrum, ν, cm^{-1}: 3278 (NH), 2966 (CH_3), 1701 (C=O). ^1H NMR spectrum, δ, ppm: 1.29 d (3H, CH_3, J = 6.11 Hz), 2.01 d.d (1H, 3-H_{ax}, J = 12.21, 10.98 Hz), 2.26 d.d.d (1H, 3-H_{eq}, J = 10.98, 6.11, 2.44 Hz), 3.45 d.d.d (1H, 2-H_{ax}, J = 10.98, 6.11, 2.44 Hz), 4.01 d.d (1H, 4-H_{ax}, J = 12.21, 6.11 Hz), 6.56 d (1H, 8-H, J = 7.33 Hz), 6.71 t (1H, 6-H, J = 7.33 Hz), 7.07 t (1H, 7-H, J = 7.33 Hz), 7.14 d (1H, 5-H, J = 3.33 Hz). Mass spectrum,* m/z (I_{rel}, %): 205 (44) $[M]^+$, 190 (28), 146 (91), 130 (100), 118 (9.5), 103 (4), 77 (19), 65 (8). Found, %: C 69.00; H 6.87; N 7.40. $C_{11}H_{13}NO_2$. Calculated, %: C 69.09; H 6.85; N 7.32. M 191.23.

2,6-Dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (II) was synthesized in a similar way. Yield 85%, mp 136–140°C (from 50% ethanol). IR spectrum, ν, cm^{-1}: 3382 (NH); 2950, 2854 (CH_3); 1716 (C=O). ^1H NMR spectrum, δ, ppm: 1.29 d (3H, CH_3, J = 6.3 Hz), 1.8 d.d (1H, 3-H_{ax}, J = 12.3, 11.1 Hz), 2.11 s (3H, CH_3), 2.2 d.d.d (1H, 3-H_{eq}, J = 11.3, 7.11, 2.6 Hz), 3.35 d.d.d (1H, 2-H_{ax}, J = 11.11, 6.58, 2.4 Hz), 3.85 d.d (1H, 4-H_{ax}, J = 12.5, 6.6 Hz), 6.4 d (1H, 8-H, J = 8.1 Hz), 6.8 d (1H, 7-H, J = 8.33 Hz), 7.4 s (1H, 5-H). Mass spectrum, m/z (I_{rel}, %): 219 (45) $[M]^+$, 204 (25), 160 (78), 144 (100), 143 (9.5), 103 (3), 91 (9.5), 71 (8), 65 (6). Found, %: C 70.10; H 7.30; N 6.85. $C_{12}H_{15}NO_2$. Calculated, %: C 70.22; H 7.37; N 6.82. M 205.26.

* Hereinafter, the mass spectra of the corresponding methyl esters are given.

The reduction of 2-cyclopropylquinoline-4-carboxylic acid [14] was performed according to the procedure described above for the synthesis of compound **I**. Overall yield of acid mixture 0.78 g (78%).

2-Propyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid. ^1H NMR spectrum, δ, ppm: 0.89–1.00 m (3H, CH_3), 1.30–1.55 m (2H, CH_2), 1.69 q (1H, CH_2), 1.89 q (1H, CH_2), 3.70 d.d (1H, 4-H), 6.00 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 233 (10) $[M]^+$, 190 (22), 174 (10), 131 (12), 130 (100), 128 (4), 103 (6), 77 (8).

2-Cyclopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid. ^1H NMR spectrum, δ, ppm: 0.15–0.35 m (2H, CH_2), 0.40–0.65 m (2H, CH_2), 1.15–1.30 m (1H, CH), 2.15 d.d (1H, 3-H_{ax}), 2.45 d.d.d (1H, 3-H_{eq}), 6.00 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 231 (26) $[M]^+$, 216 (14), 203 (8), 190 (14), 173 (6), 172 (48), 170 (16), 157 (12), 144 (18), 130 (100), 128 (10), 103 (9), 102 (4), 77 (17).

2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (III) was synthesized according to the procedure reported in [10]. Yield 0.8 g (80%), mp 218–220°C (from water); published data [11]: mp 218°C. IR spectrum, ν, cm^{-1}: 3384 (NH); 1708 (C=O, acid), 1647 (C=O, lactam). ^1H NMR spectrum, δ, ppm: 2.71 q (2H, CH_2), 4.05 t (1H, 4-H), 6.9 d (1H, 8-H), 6.95 t (1H, 6-H), 7.2 t (1H, 7-H), 7.25 s (1H, 5-H). Mass spectrum, m/z (I_{rel}, %): 205 (36) $[M]^+$, 147 (6), 146 (100), 128 (52), 117 (20), 89 (10), 77 (8), 51 (6). Found, %: C 62.50; H 4.46; N 7.52. $C_{10}H_9NO_3$. Calculated, %: C 62.82; H 4.74; N 7.33. M 191.19.

6-Methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (IV). A solution of 1 g (5 mmol) of 2-hydroxy-6-methylquinoline-4-carboxylic acid in 15 ml of acetic acid was heated to 80°C on a water bath, 4 g (0.06 mol) of zinc dust was added in portions over a period of 1 h under stirring, and the mixture was stirred for 1.5 h. The mixture was then filtered, the filtrate was diluted with 10 ml of water and left overnight, and the colorless needles were filtered off. Yield 0.75 g (75%), mp 223–225°C. IR spectrum, ν, cm^{-1}: 3452 (NH), 1708 (C=O, acid), 1643 (C=O, lactam). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.65 q (2H, CH_2), 3.80 t (1H, 4-H), 6.75 d (1H, 8-H), 7.0 d (1H, 7-H), 7.1 s (1H, 5-H). Mass spectrum, m/z (I_{rel}, %): 219 (24) $[M]^+$, 161 (11), 160 (100), 142 (56), 130 (19), 117 (13), 115 (10), 103 (5), 77 (8), 65 (7). Found, %: C 64.10; H 5.30; N 6.96. $C_{11}H_{11}NO_3$. Calculated, %: C 64.38; H 5.40; N 6.83. M 205.21.

Reduction of 1,2,3,4-tetrahydroacridine-9-carboxylic acid. Raney nickel, 3 g, was added in small

portions over a period of 2 h under stirring to a solution of 1 g (5 mmol) of 1,2,3,4-tetrahydroacridine-9-carboxylic acid [16] in 10 ml of 10% aqueous potassium hydroxide, and the mixture was stirred for 2 h at room temperature. The precipitate was filtered off and washed with hot water, the filtrate was acidified to pH 3 with formic acid and extracted with chloroform, and the extract was dried over anhydrous sodium sulfate and evaporated. The residue was a colorless oily substance which crystallized on storage. Yield 0.75 g (75%), mixture of four stereoisomers **VIa**–**VId**. Mass spectrum, *m/z* (I_{rel}, %), **VIa**: 245 (27) $[M]^+$, 187 (16), 186 (100), 184 (19), 156 (14), 130 (35), 118 (24), 115 (8), 77 (12); **VIb**: 245 (41) $[M]^+$, 213 (98), 185 (100), 184 (57), 170 (23), 157 (17), 144 (11), 115 (21), 91 (24), 77 (21), 65 (11); **VIc**: 245 (26) $[M]^+$, 187 (14), 186 (100), 184 (19), 156 (14), 130 (50), 118 (21), 115 (8), 77 (12); **VId**: 245 (20) $[M]^+$, 187 (14), 186 (100), 184 (12), 156 (12), 130 (36), 118 (14), 115 (8), 77 (11).

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