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A Convenient Preparation of N-Acyl-1,2-dihydroquinoline

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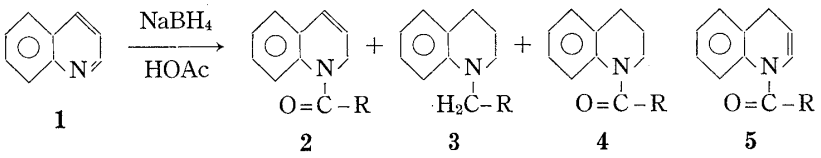
N-Acetyl- and N-formyl-1,2-dihydroquinoline were conveniently prepared by reductive acylation of quinoline without isolating the labile 1,2-dihydroquinoline. This method was also applied to isoquinoline to prepare N-acetyl-1,2-dihydroisoquinoline.

Keywords——sodium borohydride in acetic acid; reductive acylation; N-acetyl-1,2-dihydroquinoline; N-formyl-1,2-dihydroquinoline; N-acetyl-1,2-dihydroisoquinoline

Reduction with sodium borohydride in acidic media is now a widely used procedure.[2] Gribble *et al.*[3] have reported efficient reductive alkylations of indole, quinoline and isoquinoline with sodium borohydride in carboxylic acids. We report here that the reduction of quinoline with sodium borohydride in acetic acid in the presence of acid anhydride provides a convenient method for the preparation of N-acyl-1,2-dihydroquinoline without isolating the labile 1,2-dihydroquinoline.[4] We have prepared N-acetyl- and N-formyl-1,2-dihydroquinoline; our method is simple and gives practically pure N-acyl-1,2-dihydroquinoline either by extraction or by column chromatography.



1 **2** **3** **4** **5**

Additive		Yield [% isolated]		
—	**a**: R=CH_3	48%	39%	—
Ac_2O	**a**: R=CH_3	72%	12%	—
AcOCHO	**b**: R=H	35%	30%	10%

Chart 1

Although Gribble *et al.*[3b] did not isolate N-acetyl-1,2-dihydroquinoline **2a**, the reduction of quinoline **1** with sodium borohydride in anhydrous acetic acid gave N-acetyl-1,2-dihydroquinoline **2a** [48% yield] and N-ethyl-1,2,3,4-tetrahydroqiunoline **3a** [39% yield]. When acetic anhydride was present, the yield of **2a** increased to 72% and that of **3a** decreased to 12%. N-Acetyl-1,2,3,4-tetrahydroquinoline **4a** and N-acetyl-1,4-dihydroquinoline **5a**[5] were not detected in the reduction products.

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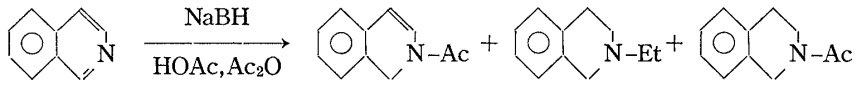
5) We are grateful to Prof. M. Natsume, Itsuu Institute, for providing the nuclear magnetic resonance (NMR) spectrum of N-acetyl-1,2- and N-acetyl-1,4-dihydroquinoline, **2a** and **5a**, respectively.

Addition of acetic-formic anhydride instead of acetic anhydride led to the formation of N-formyl-1,2-dihydroquinoline **2b** [35%], N-methyl-1,2,3,4-tetrahydroquinoline (kairoline) **3b** [30%] and N-formyl-1,2,3,4-tetrahydroquinoline **4b** [10% yield]. N-Acetyl-1,2,3,4-tetrahydroquinoline **4a** remained intact in the reduction but N-formyl-1,2,3,4-tetrahydroquinoline **4b** was partly converted into kairoline **3b** [17% on GLC]. 1,2,3,4-Tetrahydroquinoline was converted into **3a** and **4a** [2/1] by treatment with sodium borohydride in acetic acid. These observations suggest that N-acyl-1,2-dihydroquinoline and N-alkyl-1,2,3,4-tetrahydroquinoline were derived from the initial reduction product, 1,2-dihydro-quinoline.



6	**7**	**8**	**9**
[isolation yield]	80%	6%	9%

Chart 2

Reduction of isoquinoline **6** in the presence of acetic anhydride proceeded in a similar manner to give N-acetyl-1,2-dihydroisoquinoline **7** [80%], N-ethyl-1,2,3,4-tetrahydro-isoquinoline **8** [6%] and N-acetyl-1,2,3,4-tetrahydroisoquinoline **9** [9% yield]. Reduction products were characterized and identified by physical and chemical methods, by comparison with authentic specimens (see "Experimental").

Experimental

Melting and boiling points are uncorrected. Organic extracts were dried over magnesium sulfate for the neutral fraction, and sodium sulfate for the basic fraction. Acetic acid was distilled with phosphorus pentoxide and stored over 4A molecular sieves. Infrared (IR) spectra were measured with a Hitachi 215 grating infrared spectrometer as films unless otherwise noted. NMR spectra were measured with a JEOL JNM-PMX 60 in $CDCl_3$ with tetramethylsilane as an internal standard. GLC was done with a Hitachi 163 machine with FID detection, using a 10% SE-52 column (glass, 3 mm × 2 m) at 190° and a 15% QF-1 column (glass, 3 mm × 2 m) at 230° with nitrogen at a flow rate of 20—30 ml/min.

Reduction of Quinoline 1——a) In the Presence of Acetic Anhydride: Sodium borohydride (0.2 mol) was gradually added to a mixture of quinoline (0.05 mol), acetic acid (75 ml) and acetic anhydride (25 ml) over a period of 1.5 hr under water-cooling, and the mixture was then warmed at 60° for 2 hr. The reduction mixture was concentrated *in vacuo*, diluted with water (300 ml), basified with sodium carbonate and extracted with ether four times. Ethereal extracts were shaken with 0.5 N HCl three times, washed with brine and dried to give N-acetyl-1,2-dihydroquinoline **2a**[4b] [72% yield], bp 125—127°/3 mmHg. mp 41.5—43° (pentane). IR ν_{max} cm^{-1}: 1622. NMR δ: 2.22 (3H, s, COMe), 4.47 (2H, m, C-2-H), 6.09 (1H, t of d, J= 4.5, 10 Hz, C-3-H), 6.50 (1H, t of d, J=1.5, 10 Hz, C-4-H), 7.1—7.4 (4H, m, Ar–H). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.40; N, 8.03. Acidic aqueous extracts were basified with sodium carbonate and extracted with ether to give N-ethyl-1,2,3,4-tetrahydroquinoline **3a**[3b] [12% yield], bp 135—137°/16 mmHg. IR ν_{max} cm^{-1}: 1601, 1575. NMR δ: 1.12 (3H, t, J=7 Hz, N–CH_2–Me), 1.93 (2H, quintet, J=6 Hz, C-3-H), 2.75 (2H, t, J=6.5 Hz, C-4-H), 3.25 (2H, t, J=5.5 Hz, C-2-H), 3.33 (2H, q, J=7 Hz, N–C<u>H</u>$_2$–Me), 6.3—7.2 (4H, m, Ar–H).

b) In the Presence of Formic-acetic Anhydride: Similar reduction was carried out in a mixture of acetic acid (75 ml) and formic-acetic anhydride (25 ml) to give neutral (5.8 g) and basic (1.15 g) fractions of products Column chromatography on silica gel with dichloromethane afforded N-formyl-1,2-dihydroquinoline **2b**, mp 39.5—41° (pentane). IR ν_{max} cm^{-1}: 1703, 1677. NMR δ: 4.49 (2H, m, C-2-H), 6.00 (1H, t of d, J=6, 10 Hz, C-3-H), 6.49 (1H, t of d, J=3.2, 10 Hz, C-4-H), 7.1—7.4 (4H, m, Ar–H), 8.60 (1H, s, N–CHO). *Anal.* Calcd for $C_{10}H_9NO$: C, 75.49; H, 5.66; N, 8.80. Found: C, 75.49; H, 5.61; N, 8.55., kairoline **3b**,[3b] bp 137.5°/30 mmHg. IR ν_{max} cm^{-1}: 1602, 1510. NMR δ: 1.97 (2H, m, C-3-H), 2.77 (2H, t, J=6 Hz, C-4-H), 2.83 (3H, s, NMe), 3.20 (2H, t, J=5.5 Hz, C-2-H), 6.4—6.7 (2H, m, Ar–H), 6.8—7.2 (2H, m, Ar–H)., and N-formyl-1,2,3,4-tetrahydroquinoline **4b**, IR ν_{max} cm^{-1}: 1665. NMR δ: 1.93 (2H, quintet, J=6 Hz, C-3-H), 2.82 (2H, t, J=6 Hz, C-4-H), 3.82 (2H, t, J=6 Hz, C-2-H), 7.17 (4H, s, Ar–H), 8.77 (1H, s, N–CHO). Compounds 3b and 4b were identical with appropriate authentic specimens prepared from 1,2,3,4-tetrahydroquinoline by methylation and formylation.

Reduction of N-Formyl-1,2,3,4-tetrahydroquinoline 4b——The title amide **4b** (0.4 g, 2.5 mmol) was reduced with sodium borohydride (0.38 g, 10 mmol) in acetic acid (10 ml) to give a crude product which was identified as a mixture of kairoline **3b** [17%] and the starting amide **4b** [82%] by GLC and TLC.

Treatment of 1,2,3,4-Tetrahydroquinoline with Sodium Borohydride in Acetic Acid——Tetrahydroquinoline (5 mmol) was treated as described for **4b** to give a mixture of **3a** [40%] and **4a** [60%] on GLC. This mixture was separated by acid extraction into neutral (0.4 g) and basic (0.3 g) fractions. The neutral product was **4a**, IR ν_{max} cm^{-1}: 1655. NMR δ: 1.95 (2H, quintet, $J=6.5$ Hz, C-3-H), 2.23 (3H, s, NCOMe), 2.72 (2H, t, $J=6$ Hz, C-4-H), 3.78 (2H, t, $J=6$ Hz, C-2-H), 7.0—7.3 (4H, m, Ar–H). The basic fraction was purified on an alumina column with dichloromethane to give 0.2 g of **3a**.[3b] Compounds **3a** and **4a** were identical with appropriate authentic specimens prepared from 1,2,3,4-tetrahydroquinoline by alkylation and acylation.

Reduction of Isoquinoline 6——Isoquinoline **6** was reduced as described for quinoline in the presence of acetic anhydride. The product was chromatographed on an alumina column with dichloromethane to give N-acetyl-1,2-dihydroisoquinoline **7**[4a] [80% yield], IR ν_{max} cm^{-1}: 1663, 1627. NMR δ: a mixture of two rotational isomers of the amide bond in a ratio of 88: 12. 2.22 (3H, s, NCOMe), 4.95 and 4.83 (2H, each s, C-1-H), 5.85 and 5.86 (1H, each d, $J=8$ Hz, C-3-H), 6.66 (1H, d, $J=8$ Hz, C-4-H), 6.9—7.4 (4H, m, Ar–H), N-acetyl-1,2,3,4-tetrahydroisoquinoline **9** [9% yield], IR ν_{max} cm^{-1}: 1638. NMR δ: a mixture of two rotational isomers of the amide bond in a ratio of 64: 36. 2.17 (3H, s, N–COMe), 2.90 (2H, m, C-4-H), 3.67 and 3.82 (2H, each t, $J=5$ Hz, C-3-H), 4.73 and 4.62 (2H, each s, C-1-H), 7.17 (4H, s, Ar–H), and N-ethyl-1,2,3,4-tetrahydroisoquinoline **8**[3b] [6% yield], IR ν_{max} cm^{-1}: 1601, 1572. NMR δ: 1.16 (3H, t, $J=7$ Hz, N–CH_2–Me), 2.55 (2H, q, $J=7$ Hz, N–$C\underline{H}_2$–Me), 2.88 (4H, m, C-3-H+C-4-H), 3.60 (2H, s, C-1-H), 7.05 (4H, s, Ar–H). Compounds **8** and **9** were identical with appropriate authentic specimens prepared from 1,2,3,4-tetrahydroisoquinoline by alkylation and acylation.

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Studies on the Antioxidants. XII.[1] Combination Effects of Antioxidants on the Reduction of Ferric Ions

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The reduction of ferric ions by phenolic antioxidants was investigated by the Emmerie–Engel method. Diphenolic and triphenolic compounds reduced 2—2.5 and 5 molar equivalents of ferric ions, respectively. Monophenolic compounds reduced different amounts of ferric ions: BHT, 0.6; tocopherol, 2; BHA, 3 and sesamol, 4 molar equivalents. When two compounds were used in combination, the reducing potency was enhanced or decreased depending on the antioxidants used. The combination of BHA and BHT produced 1.5 times more ferrous ions than the calculated amount, and the combination of BHA and PG produced only 0.75 times the calculated amount of ferrous ions. In the combined use of BHA and BHT, BHT was more rapidly lost than it was in the reaction of BHT alone, probably due to some interaction of the two compounds.

Keywords——Emmerie–Engel reagent; phenols; antioxidants; butylated hydroxyanisole (BHA); butylated hydroxytoluene (BHT)

It has been demonstrated by Bolland[3] that the peroxidation of lipids involves the free radical-forming propagation reactions, in which various peroxy free radicals are formed. Phenolic antioxidants, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), tocopherol and nordihydroguaiaretic acid (NDGA), are used as inhibitors of lipid peroxidation, and several theories have been proposed regarding the mech-

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