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The Birch Reduction of Heterocyclic Carboxylic Acids. I.
The Birch Reduction of 3-Furoic Acid

Takamasa Kinoshita, Kouichi Miyano, and Toshio Miwa
Faculty of Science, Osaka City University, Sumiyoshiku, Osaka 558

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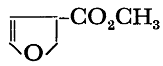
The reduction of 3-furoic acid with sodium and 2-propanol in liquid ammonia gave 2,3-dihydro-3-furoic acid, which was isolated as a methyl ester (**1**) in 85% yield. The acid-catalyzed addition of methanol, ethanol, or 2-propanol to the ester **1** yielded 5-alkoxytetrahydro-3-furoate ester, **2**, **3**, or **4**, respectively, in a quantitative yield. When methanol or ethanol was used as a proton source in the reduction, work-up of the reaction mixture gave 5-alkoxytetrahydro-3-furoic acid, which was isolated as the methyl ester, **2** or **3**, in 87 or 92% yield, respectively. A mechanism for the Birch reduction of aromatic carboxylic acids is proposed.

The Birch reduction of the aromatic molecules has been extensively studied and widely applied to synthetic reactions.[1] Nevertheless, only few papers concerned with the Birch reduction of furan derivatives. Furan and its alkyl derivatives resist the Birch reduction.[2] Recently, Bedenbaugh *et al.* reduced simple furans with lithium in methylamine.[3] 2-Furoic acid has been reduced under the condition of the Birch reduction,[4] as expected from a facile reduction of benzoic acid.[5] The Birch reduction of 3-furoic acid into 2,3-dihydro-3-furoic acid and its application to a one-step synthesis of 5-alkoxytetrahydro-3-furoic acids will be described in this paper. The Birch reduction of 3-furoic acid provides a useful entry into the total synthesis of the branched-chain sugars.[6]

Results and Discussions

The Birch Reduction of 3-Furoic Acid. The reduction of 3-furoic acid with sodium and 2-propanol in liquid ammonia gave an acid, which, after esterification with diazomethane, was isolated as a methyl ester in 85% yield. The molecular formula, $C_6H_8O_3$, was determined by the elemental analysis and mass spectrometry ($M^+=128$). The IR spectrum of the ester showed the presence of a saturated ester function (1735 cm^{-1}) and an enol ether (3120 and 1620 cm^{-1}),[7] suggesting the product to be methyl 2,3-dihydro-3-furoate (**1**). The NMR spectrum of this compound shows a pattern characteristic of 3-substituted 2,3-dihydrofurans[8] as indicated in the experimental part.



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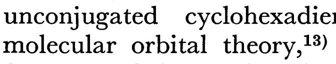
Syntheses of Methyl 5-Alkoxytetrahydro-3-furoates. Treatment of the ester **1** in methanol with acid catalyst gave methyl tetrahydro-5-methoxy-3-furoate (**2**) in a quantitative yield. The fact that the acid-catalyzed addition of alcohols to the α,β-unsaturated ether is a well-established reaction[9] may suffice to assign the structure **2** to the ether. Disappearance of the C=C stretching band due to enol ether function of **1** in its IR spectrum supports the structure.

Although the methyl peaks of **2** show sharp singlets in the NMR spectrum, the signal for H-5 is rather complex, inferring that the product is a mixture of stereoisomers. Actually, the gas chromatography of **2** gave two peaks in a ratio of 2 : 1. The major fraction was assumed to have a *trans* configuration from a stereochemical consideration of the addition of methanol. This was further confirmed by the downfield shift of the proton H-3 (δ 3.16) deshielded by the 5-methoxy group compared to that of the *cis* isomer (δ 3.04).[10]

Treatment of the ester **1** with ethanol or 2-propanol in the presence of acid gave an ethyl ether **3** or an isopropyl ether **4** corresponding to **2**, respectively, in a quantitative yield. They also were mixtures of stereoisomers, showing a signal for H-5 similar to that of the methyl ether **2**; however, no attempts were made to separate the isomers.

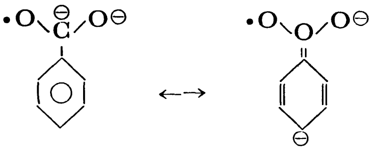
The reduction of 3-furoic acid with sodium and methanol or ethanol in liquid ammonia produced the methyl ether **2** or the ethyl ether **3** in 87 or 92% yield, respectively, after the methylation with diazomethane. Apparently, these ethers, **2** and **3**, were formed by the addition of alcohols to 2,3-dihydro-3-furoic acid in the course of work-up of the reaction mixture.[11]



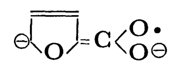
2: $R=CH_3$
3: $R=C_2H_5$
4: $R=CH(CH_3)_2$

Reaction Mechanism for the Birch Reduction of Aromatic Carboxylic Acids. The Birch reduction is initiated with the addition of an electron to the substrate molecule to form a radical anion, followed by the rapid protonation at the position with the highest electron density. The addition of another electron produces an anion, which is kinetically protonated to give an unconjugated cyclohexadiene.[12] According to the molecular orbital theory,[13] the extra electron in the first step of the Birch reduction will be introduced to the lowest unoccupied molecular orbital of symmetric or anti-symmetric character depending upon whether the substituent is electron-withdrawing or electron-releasing. Protonation at the highest electron density will occur at the 1- or 4-position in the former case and at the *o*- or *m*-position in the latter. The Birch reduction of benzoic acid gave 1,4-dihydrobenzoic acid,[14] indicating the carboxylate group is sufficiently electron-withdrawing in the Birch reduction. The highest spin density at the para position of the radical dianion derived from benzoate anion was also verified by the ESR study.[15] Apart from the MO argument, the products of the Birch reduction of the aromatic carboxylic acids may be rationalized as follows. All the aromatic carbonyl compounds, including benzoate anion, are assumed to add the electron not to the aromatic nucleus but to the carbonyl group.[16] In the case of benzoate anion, the negative charge of the carboxylate anion will repel the charge of the resulting radical dianion **5a** as far as possible, favoring the contributing structure **5b** with the highest electron density at the carbon-4. As a corollary, benzamides may be well reduced on their aromatic nucleus only when the amide proton can be removed by a base to form amide anion. Thus, more acid benzamide substituted by methoxy groups at the meta positions can be reduced in good yield.[14]

The same argument may be valid for the Birch reduction of furoic acids. The addition of an electron to 2-furoate anion will produce a radical dianion with the highest electron density at the carbon-5 in its most favorite contributing structure **6**, followed by protonation at the position. The kinetic protonation of the dianion formed by the addition of another electron should occur at the carbon-2, forming the unconjugated acid, 2,5-dihydro-2-furoic acid. On the other hand, the radical dianion formed by the addition of an electron to 3-furoate anion will have the highest electron density at the carbon-2 in the most important contributing structure **7**; thus, the product of the Birch reduction of 3-furoic acid is 2,3-dihydro-3-furoic acid.



5a **5b**



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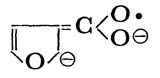

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Experimental

General. IR spectra were taken neat on a JASCO Model IR-E IR spectrometer and were calibrated against the 1600 cm^{-1} band of polystyrene. NMR spectra were recorded in deuteriochloroform solution at 100 MHz with a JEOL Co PS-100 spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded with a Hitachi RMU-6 mass spectrometer.

The Birch Reduction of 3-Furoic Acid. All the Birch reductions were carried out as follows: To a mixture of 3-furoic acid and *ca.* 8 molar equivalents of alcohol in liquid ammonia (*ca.* 10 ml per mole of acid) was added 3 equivalent atoms of sodium little by little with constant stirring under reflux. The mixture was stirred for an additional hour and excess of ammonium chloride was added. After evaporation of liquid ammonia at room temperature, the residue was dissolved in water. The aqueous solution was washed with several portions of ether to remove alcohol, acidified and immediately extracted continuously with ether for 24—48 h. The ether extract was esterified with excess of diazomethane and, after evaporation of the solvent, the residue distilled under reduced pressure.

With 2-Propanol: Methyl 2,3-dihydro-3-furoate (**1**), bp 83—84 °C/30 mmHg, was obtained in 85% yield. MS: (80 eV) *m/e* (rel intensity) 128 (20), 69 (100), 41 (26), 39 (16). NMR: δ 3.72 (s, 3, ester CH$_3$), 3.75 (m, 1, H-3), 4.44 (q, 1, $J_{2,3}=11$, $J_{2,2'}=-9.5$ Hz, H-2), 4.69 (q, 1, $J_{2',3}=7$ Hz, H-2′), 5.03 (t, 1, $J_{3,4}=3$, $J_{4,5}=3$ Hz, H-4), 6.42 ppm (t, 1, $J_{3,5}=2$ Hz, H-5).

Found: C, 56.08; H, 6.41%. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29%.

With Methanol: Methyl tetrahydro-5-methoxy-3-furoate (**2**), bp 90—92 °C/10 mmHg, n_D^{25} 1.4325, was isolated in 87% yield. IR: 1735 cm^{-1}. MS: (80 eV) *m/e* (rel intensity) M$^+$ absent[17], 159 (1.3), 145 (1.8), 129 (55), 115 (12), 100 (29), 99 (28), 87 (14), 71 (18), 69 (100), 59 (25), 58 (35), 55 (14), 45 (15), 41 (41), 39 (12). NMR: δ 2.00—2.45 (m, 2, H-4), 3.00—3.25 (m, 1, H-3), 3.27 (s, 3, ether CH$_3$), 3.65 (s, 3, ester CH$_3$), 4.05 (d, 2, H-2), 5.0 ppm (m, 1, H-5).

Found: C, 52.31; H, 7.44%. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55%.

Preparative gas chromatography of **2** was performed on a Varian Aerograph Model 90-P instrument equipped with a 4 mm × 2 m column of 20% Carbowax 20M at 150 °C with a flow rate of 40 ml/min. Two peaks of retention times of 9.1 and 10.8 min appeared in a ratio of 2 : 1. The faster-moving fraction showed the following NMR spectrum: δ 2.0—2.45 (m, 2, H-4), 3.16 (quintet, 1, H-3), 3.27 (s, 3, ether CH$_3$), 3.65 (s, 3, ester CH$_3$), 4.05 (d, 2, H-2), 5.02 ppm (q, 1, H-5). The slower-moving fraction showed the following NMR spectrum: δ 2.20—2.35 (m, 2, H-2), 3.04 (quintet, 1, H-3), 3.27 (s, 3, ether CH$_3$), 3.65 (ester CH$_3$), 4.05 (d, 2, H-2), 5.00 ppm (t, 1, H-5).

With Ethanol: Methyl 5-ethoxytetrahydro-3-furoate (**3**), bp 106—110 °C/15 mmHg, was obtained in 92% yield.[18] IR: 1735 cm^{-1}. MS: (80 eV) *m/e* (rel intensity) M$^+$ absent, 173 (0.7), 159 (2.7), 143 (12), 129 (47), 115 (10), 100 (24), 99 (13), 87 (15), 85 (17), 72 (19), 69 (100), 59 (17), 57 (12), 55 (15), 45 (11), 41 (28), 32 (22). NMR: δ 1.16 (t, 3, C–CH$_3$), 1.95—2.45 (m, 2, H-4), 2.90—3.40 (m, 1, H-3), 3.49 (q, 2, OCH$_2$), 3.64 (s, 3, OCH$_3$), 4.08 (d, 2, H-2), 5.18 ppm (m, 1, H-5).

Found: C, 55.05; H, 8.10%. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10%.

*Acid-catalyzed Addition of Alcohols to Ester **1**.* A solution of the ester **1** in appropriate amount of alcohol containing Dowex 50 (W-X8, H$^+$) ion-exchange resin (200—400 mesh) was stirred at room temperature overnight. After filtration of the resin followed by evaporation of the solvent, the residue was distilled under reduced pressure. The yields were quantitative. The esters, **2** and **3**, obtained by the Birch reduction were identified with the compounds produced by the acid-catalyzed addition of methanol and ethanol, respectively, by NMR spectrometry. The addition of 2-propanol gave methyl tetrahydro-5-isopropyloxy-3-furoate (**4**), bp 120—121 °C/30 mmHg. IR: 1735 cm^{-1}. MS: (80 eV) *m/e* (rel intensity) M$^+$ absent, 189[19] (0.6), 187 (0.4), 173 (3.1), 145 (13), 129 (89), 128 (11), 115 (16), 100 (40), 87 (37), 85 (10), 69 (100), 59 (13), 55 (11), 45 (10), 43 (22), 41 (26), 39 (13). NMR: δ 1.16 (d, 3, C–CH$_3$), 1.18 (d, 3, C–CH$_3$), 1.95—2.45 (m, 2, H-4), 2.90—3.45 (m, 1, H-3), 3.65 (s, 3, OCH$_3$), 3.84 (m, 1, O–CH), 4.00—4.15 (m, 2, H-2), 5.3 ppm (m, 1, H-5).

Found: C, 57.03; H, 8.46%. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.

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