A Convenient Synthesis of 5-Substituted-2,5-dihydro-2-furoic Acids

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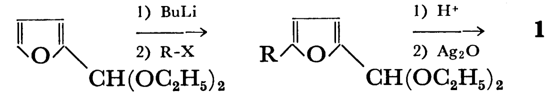
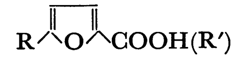
Nine 5-alkyl- and 5-aryl-2-furoic acids were reduced under controlled Birch conditions and then esterified with acidic methanol. 2-Furoic acids with 5-alkyl groups gave good yields of methyl 5-alkyl-2,5-dihydro-2-furoates, which were obtained as mixtures of *cis*- and *trans*-diastereoisomers. These 2,5-dihydrofuroates revealed interesting spectroscopic properties; (1) large long-range coupling constants, 5—7 and 3—4 Hz, between protons at C_2 and C_5 were observed in the NMR spectra of *cis*- and *trans*-diastereoisomers, respectively, and (2) two high absorption maxima due to the ester carbonyl group of each furoate appeared near 1750 and 1730 cm^{-1} in the IR spectrum. On the other hand, the furoic acids with 5-aryl substituents afforded 5-arylpentanoate or 5-arylpent-3-enoate as main products. These esters would be produced as a result of reductive cleavage at C_5 of 5-aryl-2,5-dihydrofuroates formed as intermediates.

In connection with a study aimed at the total synthesis of laurencin[1] with a tetrahydrooxocin skeleton, we have been in search of a facile method for preparation of the titled furoic acids, because an elegant synthesis[2] of the skeleton involved a 3-oxagranatanine derivative[3] as a key intermediate, which had been prepared by the Robinson-Schöpf condensation starting from 3-oxaglutaraldehyde. Only a few papers have been reported of syntheses of 2,5-dihydrofurans.[4] The reduction of furans with dissolving metals seems to be highly dependent on the reaction conditions and gives many products.[5] However, it has been reported recently that 2-furoic acid is reduced efficiently to the 2,5-dihydro derivative under the controlled Birch conditions.[6] We have developed the method for 5-alkyl- and 5-aryl-furoic acids. The present paper describes the reduction result and the spectroscopic properties of resulting 5-alkyl-2,5-dihydro-2-furoic acids. In view of the occurrence of natural products containing this moiety, such as carotenoids,[7] sesquiterpenoids[8] and antibiotics,[9] this result would be useful for synthesis of some of these compounds.

Nine 5-substituted furoic acids (**1a**—**1i**) were used as starting materials. All these compounds are known but were not always obtained under the reported processes or conditions. The first three acids **1a**, **1b** and **1c** (R=CH_3, C_2H_5 and *n*-C_3H_7) were prepared more readily and/or in better yields according to a modified process (Scheme 1). This method, however, was not available for preparation of two other alkyl acids **1d** and **1e** (R=*i*-C_3H_7 and *t*-C_4H_9) with 5-branched alkyl substituents. These two acids and two 5-benzylfuroic acids **1f** and **1g** (R=$C_6H_5CH_2$ and *p*-$CH_3OC_6H_4CH_2$) were synthesized by Friedel-Crafts alkylation of methyl furoate followed by hydrolysis. Two 5-phenylfuroic acids **1h** and **1i** (R=C_6H_5 and *p*-$CH_3OC_6H_4$) were not prepared by the reported methods;[10,11] after careful examination of the reaction process and conditions, the latter **1i**, mp 186—187 °C, was obtained by the Meerwein reaction of *p*-anisidine and 2-furoic acid under the limited conditions, and the former **1h**, mp 150—150.5 °C, by the Vilsmeyer reaction of 2-phenylfuran followed by oxidation



Scheme 1.



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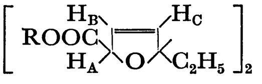
The reductions of 2-furoic acids (**1**) to the 2,5-dihydro derivatives (**2**) were searched under various Birch reductions, using 5-ethyl-2-furoic acid (**1b**). (1) Reduction of **1b** in liquid ammonia with sodium (3 mol) and subsequent addition of methanol afforded, as a main product, a nicely crystalline acid (**3**, R=H) mp 229—230 °C, which was converted into the methyl ester (**3**, R=CH_3), mp 88—89 °C, having a molecular formula of $C_{16}H_{22}O_6$ corresponding to a dihydro dimeric compound; Mass, m/e 310 (M^+) and IR, ν_{max} 1760 and 1740 cm^{-1}. The (planar) formula was assigned on the basis of the NMR spectrum; each of two protons (H_A), on the carbon flanked by a double bond, an oxygen atom and a carbomethoxy group, appeared at low field, δ 5.20, as a double doublet with coupling constants of 2.6 (J_{AB}) and 1.5 Hz (J_{AC}) with olefinic protons (H_B and H_C). On the other hand, (2) treatment of **1b** in both liquid ammonia and methanol with sodium or lithium (3 mol) followed by esterification produced good yields of a 1 : 1 mixture of diastereoisomeric methyl 5-ethyl-2,5-dihydro-2-furoates (**2b**), bp 88—89 °C/13 mmHg. Thus, the reductions of all other furoic acids (**1**) were carried out under these conditions. The products were separated and purified by distillation, gas (glc), thin layer (tlc) and/or column chromatographies, and identified on the spectral data. The results are summarized in Table 1.



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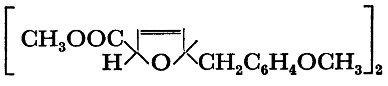

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One example of the structure elucidations of the 2,5-dihydro products (**2**) will be illustrated by the 5-ethyl derivative (**2b**). This compound **2b** proved to be obtained as a 1 : 1 mixture of diastereoisomers by glc, though isolation of each isomer (*cis* and *trans*) was not attempted. The elemental analysis and the Mass [m/e 156 (M^+), 127 (M^+–C_2H_5) and 97 (M^+–$COOCH_3$)] and IR spectra (ν_{max} 1768 and 1743 cm^{-1}) confirmed the molecular formula $C_8H_{12}O_3$, and indicated **2b** to be a dihydro methyl ester of **1b**. In accordance

TABLE 1. THE BIRCH REDUCTION OF 5-SUBSTITUTED 2-FUROIC ACIDS

Compound ($R'=H$)	Substituent	Metal	Yield[a)]	
			Product[b)]	1 ($R'=CH_3$)[c)]
1a	CH_3	Na	**2a** (1:1); 70 (80)	(10)
		Li	83 (90)	(5)
1b	C_2H_5	Na	**2b** (1:1); 65 (85)	(5)
		Li	85 (93)	(3)
1c	C_3H_7	Na	**2c** (1:1); 64 (80)	(13)
		Li	75 (93)	(5)
1d	i-C_3H_7	Na	**2d** (1:1); 69 (81)	(10)
		Li	70 (85)	(8)
1e	t-C_4H_9	Na	**2e** (1:1); 70 (80)	(13)
		Li	71 (87)	(10)
1f	$C_6H_5CH_2$	Na	**2f** (3:2); 40 (55)	(20)
		Li	40 (55)	(20)
1g	p-$CH_3OC_6H_4CH_2$	Na	**2g** (3:2); 40 (50) **4**; (8)	(35)
1h	C_6H_5	Na	**5h**; (40) : **6h**; (5)	(40)
1i	p-$CH_3OC_6H_4$	Na	**5i**; (9) : **6i**; (40)	(40)

a) The figures in parentheses denote yields estimated by glc. b) The figures in parentheses following **2a** to **2g** denote ratios of *cis*- and *trans*-diastereoisomers estimated by glc. c) Recovered acid methyl esters.

with this assigned structure, the NMR spectrum exhibited two triplets (total 3H, $J=7$ Hz) at δ 0.88 and 0.91, a multiplet (2H) centered at 1.57, two singlets (3H) at 3.64 and 3.66, a multiplet (2H) centered at 4.90, and a double quartet (2H) centered at 5.88, which were attributed to ethyl CH_3, ethyl CH_2, and $COOCH_3$ protons, two protons at C_2 and C_5 (H_A and H_B), and two olefinic protons at C_3 and C_4. Irradiation at both δ 1.57 and 5.88 collapsed a H_A and H_B multiplet into two simple AB-type quartets, indicating that H_A and H_B protons in one of the diastereoisomers absorbed at δ 4.91 and 4.62, respectively, with coupling constant of 3—4 Hz, and these protons in the other at δ 4.96 and 4.77 with coupling constant of 5—6 Hz. The latter isomer would be oriented *cis* and the former *trans*, as discussed later. These large, long-range coupling constants and also the two absorption maxima due to a carbomethoxy group in each of compounds **2** are listed in Table 2.

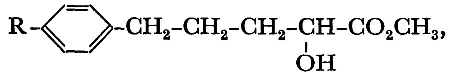
As shown in Table 1, all alkylfuroic acids (**1a**—**1e**) produced the corresponding dihydro methyl esters (**2a**—**2e**) in good yields, only about 10% of the starting acid methyl esters being identified by glc. However, two benzylfuroic acids (**1f** and **1g**) gave only moderate yields (ca. 50%) of the expected dihydro esters (**2f** and **2g**) and most of the remaining esters consisted of the unreacted acid esters and, in case of **1g**, a small amount of the dimer (**4**), mp 210—211 °C. The structure of **4** was determined in the same manner as that of **3**. The lower yields of **2f** and **2g** would be explained well if some sodium metal would be consumed for partial reduction of the phenyl ring followed by dehydrogenation during work-up.

TABLE 2. THE IR AND NMR SPECTRA OF METHYL 5-ALKYL-2,5-DIHYDRO-2-FUROATES

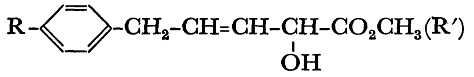
Compound	Absorption maximum[a)] (cm^{-1})	Coupling constant[b)] (Hz)	
		cis	*trans*
2a	1768, 1743	5—6	3—4
2b	1768, 1743	5—6	3—4
2c	1755, 1725	5—6	3
2d	1755, 1725	6	3—4
2e	1755, 1725	7	4
2f	1756, 1735	5—6	3—4
2g	1745, 1735	5—6	3—4

a) Absorption due to the ester carbonyl group in chloroform. b) Coupling constant between protons at C_2 and C_5 in deuterochloroform.

The reductions of 5-phenylfuroic acids (**1h** and **1i**) proceeded in different way. Two products, methyl 2-hydroxy-5-phenylpentanoate (**5**) and the corresponding *cis*-pent-3-enoate (**6**), were identified along with the unreduced methyl esters, the main product from **1h** being pentanoate **5h** and that from **1i** pentenoate **6i**. These compounds would be resulted from facile reductive cleavage at C_5, the carbon atom adjacent to both phenyl and vinyl groups, of the 2,5-dihydro derivative, which would be formed in the same manner as other alkyl- and benzyl-furoic acids. The structure determination of **6i** will be discussed as a representative of these esters. Compound **6i**, oil, was hydrolyzed to give the acid (**6i**, R'=H), mp 101—102 °C, in good yield. The Mass [m/e 222 (M^+) and 121 (base peak, M^+–$C_6H_5CH_2$)] and IR spectra (ν_{max} 3648 and 1738 cm^{-1}) suggested this formula, which was confirmed by the NMR spectrum; a doublet (2H) at δ 3.52, a doublet (1H) at 5.12, a triplet (1H) at 5.52 and a double triplet (1H) at 5.92 were assigned to protons at C_5, C_2, C_3, and C_4, respectively. A broad peak centered at δ 6.42 disappeared on addition of D_2O. The signal at δ 5.92 was simplified to a doublet ($J=11$ Hz) by irradiation at δ 3.52, and that at 5.52 to a doublet ($J=11$ Hz) by irradiation at δ 5.12. These double resonance experiments were consistent with the assigned



5h R=H
5i R=OCH_3



6h R=H
6i R=OCH_3

structure.

In summary, the present result indicates that the relevant Birch reductions under controlled conditions are generally available for the synthesis of methyl 5-alkyl-2,5-dihydro-2-furoates, which will be derived into 2,5-unsymmetrically substituted 2,5-dihydrofurans not readily accessible. The spectroscopic properties of these 2,5-dihydrofuroates deserve some comments. (1) Extremely large long-range coupling constants were demonstrated between two protons (H_A and H_B) at C_2 and C_5 of the dihydrofurans, irrespective of their configurations, *cis* and *trans*. Usually, homoallylic coupling constants fall in a range of 1—3 Hz.[12)] On the other hand, large coupling constants as shown by these compounds have also been observed between protons across five single bonds.[13)] In general, these large values have been interpreted as a result of the transmission through the double "zig-zag" paths of the bonds between the two protons.[14)] 2,5-Dihydrofuroates with *cis*-configuration would readily take this "zig-zag" type of conformation,[9)] whereas those with *trans*-configuration would not be able to adopt such conformations. However, in view of the variety of the coupling constants in question in other 2,5-dihydrofurans,[15)] no definite configurational assignment could not be made to each of the diastereoisomers **2**. Now we only tentatively assign the larger constants (5—7 Hz) to the *cis*-isomers and the smaller (3—4 Hz) to the *trans*-isomers, and point out that both the intervending double bond and oxygen atom would probably play a significant role for this noteworthy finding. (2) Two high absorption maxima due to the ester carbonyl groups were observed near 1750 and 1730 cm^{-1} in the IR spectra. It would not be reasonable to ascribe these two absorptions to the existence of two diastereoisomers, because such two bands have appeared in the spectra of methyl 2,5-dihydro-2-furoate[6)] and ethyl tetrahydro-2-furoate and 2,3-dimethyl-2,3-epoxybutanoate.[16)] This would result from the presence of two conformers caused by rotation of the carbomethoxy group around the bond between the epoxy carbon and carbonyl carbon. Further investigations concerning these bands by the CMR are now in progress.

Experimental

All the mps and bps were uncorrected. The homogenity of each compound was always checked by tlc over silica gel (Wakogel B-5) and/or by glc (Hitachi K-53) over 10% SE-30. Column chromatographies were carried out over silicic acid (Merck, Kieselgel 60 or Mallinckrodt, silicic acid 100 mesh). The IR spectra were taken in chloroform, unless otherwise stated. The NMR spectra were obtained in deuterochloroform, unless otherwise stated, at 100 MHz, and the chemical shifts were given in δ-values, TMS being used as an internal reference. The abbreviations "s, d, t, q, m, and br" in the NMR spectra denote "singlet, doublet, triplet, quartet, multiplet, and broad", respectively.

*5-Methyl-2-furoic Acid (**1a**).* 2-Furfural diethyl acetal was prepared by a modified method;[17)] a solution of furfural (96 g) and triethyl orthoformate (165 ml) in ethanol (150 ml) containing ammonium chloride (1.5 g) was refluxed for 3 hr and then distilled fractionally to give the acetal (134 g), bp 77—79 °C/20 mmHg.

To a suspended mixture of lithium (3.0 g), finely cut, in dry tetrahydrofuran (THF, 90 ml) cooled at −25 °C with Dry Ice-ethanol, was added dropwise *n*-butyl chloride (18.5 g) in THF (90 ml) under stirring and under a stream of nitrogen. When the reaction had started as indicated by the appearance of cloudiness after addition of a small volume of the chloride solution, the remaining solution was further added at −30 °C to −35 °C during 45 min to the mixture, which was then stirred at −25 °C (bath temp) for 4 hr. To this mixture was added dropwise the afore-mentioned acetal (18 g) at this temperature, and the whole mixture was again stirred at −15 °C (bath temp) for 4 hr, forming the 5-furyllithium derivative.[18)] A solution of methyl iodide (28.4 g) in THF (equal weight, 28.4 g) was added to the mixture, which was further stirred at −15 °C (bath temp) for 1 hr and allowed to stand overnight at room temperature. The reaction mixture was poured into cracked ice and water, forming two layers. After separation of the THF layer, the aqueous solution was extracted with ether (3×150 ml). The THF and ether solutions were combined, dried over sodium sulfate and evaporated to leave resinous oil, which was distilled fractionally under reduced pressure to give 5-methyl-2-furfural diethyl acetal (10.3 g), bp 84—85 °C/9 mmHg; NMR (CCl_4), δ 1.15 (6H, t, J=7 Hz, acetal C$\underline{H}_3$), 2.23 (3H, s, 5-C$\underline{H}_3$), (4H, q, J=7 Hz, acetal C$\underline{H}_2$), 5.34 (1H, s, acetal C$\underline{H}$), 5.80 and 6.12 (each 1H, ABq, J=3.5 Hz, 3- and 4-$\underline{H}$).

To the acetal (10.25 g) was added 2 M hydrochloric acid (6 ml), and the mixture was stirred at room temperature for 25 min. After addition of water (10 ml) the mixture was extracted with ether (5×10 ml), and the ether solution was washed with 5% sodium hydrogen carbonate solution (2×10 ml) and water (2×10 ml), dried and distilled to give 5-methyl-2-furfural[19)] (3.1 g), bp 75—76 °C/15 mmHg (lit,[19)] 72—73 °C/11 mmHg).

To a semisolid mixture prepared from silver nitrate (12.75 g) in water (30 ml) and sodium hydroxide (5.0 g) in water (30 ml), was added dropwise 5-methyl-2-furfural (3.1 g) under cooling with ice. The mixture was stirred at room temperature for 12 hr and then filtered to remove silver oxide. The separated precipitate was washed with hot water repeatedly, and these washings and the filtrate were combined, acidified to pH 3 with concd hydrochloric acid, and extracted with ethyl acetate (3×20 ml). The acetate solution afforded crude acid (3.0 g), which was recrystallized from ethyl acetate to give **1a**[19)] (2.14 g), mp 107—108 °C (lit,[19)] 107—108 °C); NMR, δ 2.42 (3H, s, 5-CH_3), 6.21 and 7.28 (each 1H, ABq, J=3 Hz, 3- and 4-H), and 12.68 (1H, s, COOH).

*5-Ethyl-2-furoic Acid (**1b**).* A mixture of 2-diethoxylmethyl-5-furyllithium, prepared from 2-furfural diethyl acetal (13.6 g), lithium (3.0 g), and *n*-butyl chloride (18.5 g) in THF (180 ml), was treated with ethyl bromide (21.8 g) in THF (21.8 g) in the same manner as with methyl iodide and gave 5-ethyl-2-furfural diethyl acetal (9.7 g), bp 103—106 °C/15 mmHg. The acetal (9.5 g) was hydrolyzed with acid (2M HCl, 4 ml) for 30 min and gave the aldehyde[19)] (4.32 g), bp 88—89 °C/14 mmHg (lit,[19] 82—83 °C/11 mmHg); NMR (CCl_4), δ 1.24 (3H, t, J=7.5 Hz, ethyl $\mathrm{C\underline{H}_3}$), 2.68 (2H, q, J=7.5 Hz, ethyl $\mathrm{C\underline{H}_2}$), 6.14 and 7.06 (each 1H, ABq, J=3.5 Hz, 3- and 4-H), and 9.42 (1H, s, $\mathrm{C\underline{H}O}$). This aldehyde (7.15 g), when oxidized with silver oxide, prepared from silver nitrate (24.3 g) and sodium hydroxide (11.4 g) in water (86 ml), afforded crude acid (6.3 g), mp 89—90 °C, which was recrystallized from ethyl acetate to give **1b**[19] (5.1 g), mp 91—92 °C (lit,[19] 93.5—94.5 °C).

*5-Propyl-2-furoic Acid (**1c**).* A mixture of 2-diethoxymethyl-5-furyllithium, prepared from 2-furfural diethyl acetal (13.6 g), lithium (3.0 g), and *n*-butyl chloride (18.5 g) in THF (180 ml), was treated with propyl bromide (24.4 g) in THF (24.4 g) in the same manner as with methyl iodide and gave 5-propyl-2-furfural diethyl acetal (4.76 g), bp 104—106 °C/15 mmHg. Found: C, 67.63; H, 9.70%. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%.

The acetal (4.65 g) was hydrolyzed with acid (2M HCl, 4 ml) for 15 min to the aldehyde[20] (3.0 g), which was oxidized immediately with silver oxide, prepared from silver nitrate (9.35 g) and sodium hydroxide (4.4 g) in water (22 ml), and gave crude acid (2.97 g), mp 57—58 °C, which was recrystallized from ethyl acetate to give **1c**[20] (2.3 g), mp 63—64 °C (lit.,[20] 63—63.5 °C).

*5-Isopropyl-2-furoic Acid (**1d**), 5-*tert*-Butyl-2-furoic Acid (**1e**), and 5-Benzyl-2-furoic Acid (**1f**).* These acids were prepared according to the reported procedures.[21,22] Methyl 2-furoate was converted by the Friedel-Crafts reactions into methyl 5-isopropyl-2-furoate, bp 103—106 °C/14 mmHg (lit.,[21] 110—112 °C/20 mmHg), and methyl 5-*tert*-butyl-2-furoate, bp 95—97 °C/14 mmHg (lit,[21] 110—114 °C/15 mmHg), and methyl 5-benzyl-2-furoate, mp 41—41.5 °C and bp 187—189 °C/7 mmHg (lit,[22] 41—42 °C and 157—160 °C/3 mmHg). These esters were hydrolyzed to the corresponding acids **1d**, mp 65—65.5 °C (lit,[21] 65—66 °C), and **1e**, mp 104—105 °C (lit,[21] 104—105 °C), and **1f**, mp 106—107 °C (lit,[22] 105—105.5 °C).

*5-*p*-Methoxybenzyl-2-furoic Acid (**1g**).* To a mixture of methyl 2-furoate (17 g) in carbon disulfide (26 ml) containing anhydrous zinc chloride (1.45 g) was added dropwise *p*-methoxybenzyl chloride[23] in carbon disulfide (26 ml) under stirring at 0 °C. The mixture was kept for 30 min at 0 °C and further for 45 min at room temperature. It was poured onto crushed ice and the resulting two layers were separated. The aqueous phase was extracted with ether (50 ml). The carbon disulfide and ether layers were combined, washed with 5% sodium carbonate solution (2×50 ml) and water (50 ml), dried and distilled to give methyl *p*-methoxybenzyl-2-furoate (4.0 g), bp 166—167 °C/5 mmHg; IR, ν_{max} 1720, 1595, and 1030 cm^{-1}; NMR, δ 3.76 (3H, s, OCH_3), 3.84 (3H, s, $\mathrm{COOC\underline{H}_3}$), 3.96 (2H, s, $\mathrm{C\underline{H}_2}$), 6.08 and 7.14 (each 1H, ABq, J=3 Hz, 3- and 4-$\underline{H}$), 6.88 and 7.22 (each 2H, ABq, J=7.5 Hz, $\mathrm{CH_3OC_6\underline{H}_4CH_2}$).

A mixture of the ester (4.0 g) and 10% sodium hydroxide solution (40 ml) was boiled under reflux for 1 hr, when it became homogeneous. The solution was poured onto ice and water, acidified to pH 1 with concd hydrochloric acid, and extracted with ethyl acetate (3×50 ml). The acetate solution, after being washed with water, dried and evaporated, gave crude acid (3.1 g), mp 116—120 °C, which on recrystallization afforded **1g**[22] (2.6 g), mp 124—124.5 °C (lit,[22] 123—124 °C). Found: C, 66.82; H, 5.25%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

*5-Phenyl-2-furoic Acid (**1h**).* 2-Phenylfuran was prepared according to the procedure by Johnson;[24] a fraction boiling at 107—109 °C/15 mmHg (lit.,[24] 92—95 °C/10 mmHg) was further separated by column chromatography (Merck, benzene) into 3-phenylfuran,[25] mp 53—54 °C, and 2-phenylfuran, bp 107—109 °C/15 mmHg; NMR, δ 6.38 (1H, double d, J=3.5 and 1.7 Hz, 4-$\underline{H}$), 6.60 (1H, d, J=3.5 Hz, 3-$\underline{H}$), 7.36 (5H, m, $\mathrm{C_6\underline{H}_5}$), and 7.61 (1H, d, J=1.7 Hz, 5-$\underline{H}$).

To a mixture of dry dimethylformamide (1.9 g) and phosphorus oxychloride (3.96 g), which had been kept at 0 °C for 20 min, was added freshly distilled 2-phenylfuran (2.4 g) under stirring below 20 °C.[19] The whole mixture was kept at 0—5 °C for 1 hr and then at room temperature for 1.5 hr, and poured into ice water. The resulting mixture was neutralized with 5% sodium carbonate solution and allowed to stand for 16 hr, forming two layers. The organic layer was separated and the aqueous was extracted with ether (3×60 ml). The organic and the ether solutions were combined, dried and evaporated to leave crude 5-phenyl-2-furfural, (2.86 g), ν_{max} 1660 and 1593 cm^{-1}, which was used for the next oxidation without further purification.

The aldehyde (2.56 g) was added into a semisolid mixture, prepared from silver nitrate (5.03 g) and sodium hydroxide (2.37 g) in water (20 ml) cooled with a ice bath, under vigorous stirring. The whole mixture was stirred at room temperature overnight and worked up as usual to give crude acid (2.20 g), mp 126—130 °C, which was recrystallized from chloroform to give **1h** (1.6 g), mp 150—150.5 °C (lit,[10] no mp, bp 120—122 °C/30 mmHg); IR, ν_{max} 3400, 1695, and 1195 cm^{-1}; NMR, δ 6.76 and 7.80 (each 1H, ABq, J=3.5 Hz, 3- and 4-$\underline{H}$), 7.40 (5H, m, $\mathrm{C_6\underline{H}_5}$), and 10.20 (1H, br s, $\mathrm{COO\underline{H}}$). Found: C, 70.00; H, 4.16%. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29%.

*5-*p*-Methoxyphenyl-2-furoic Acid (**1i**).* This compound was not prepared by the reported method.[10] *p*-Anisidine (12.0 g) was dissolved in boiling 25% hydrochloric acid (40 ml) and cooled, when the hydrochloric acid salt precipitated. To the mixture were added crushed ice (30 g) and then rapidly sodium nitrite (8.0 g) in water (30 ml) under stirring, when the mixture became homogeneous. A saturated sodium acetate solution was added to the solution, until the pH value became 1.0, during which the temperature was kept at 0—10 °C. The solution was added dropwise under cooling to a mixture of 2-furoic acid (11.2 g) in water (100 ml) containing sodium acetate (32.0 g), which had been homogeneous on warming. The resulting mixture was mixed with an aqueous solution (10 ml) containing cupric chloride (4.0 g as $CuCl_2 \cdot 2H_2O$), and the whole mixture was stirred below 15 °C for 5 hr and then at room temperature for 60 hr. After removal of resinous material by filtration and evaporation of volatile substance by steam distillation, the solution became heterogeneous and, after being cooled, was filtered. The precipitate was treated with saturated sodium hydrogen carbonate solutions (3×100 ml). The carbonate extracts and the filtrate were combined, acidified with concd hydrochloric acid, and extracted with ethyl acetate (3×100 ml). The acetate solution was washed with water (100 ml) and a saturated sodium chloride solution (100 ml), dried and evaporated to leave crude acid (4.5 g), mp 166—167 °C. This was recrystallized from 20% ethanol to give **1i** (2.9 g), mp 187—188 °C; IR (Nujol), ν_{max} 1670, 1265, and 1028 cm^{-1}; NMR, δ 3.80 (3 H, s, $\mathrm{OC\underline{H}_3}$), 6.62 and 7.38 (each 1 H, ABq, J=3.5 Hz, 3- and 4-H), 6.94 and 7.74 (each 2 H, ABq, J=8 Hz, $\mathrm{CH_3OC_6\underline{H}_4}$), and 8.84 (1 H, br s, $\mathrm{COO\underline{H}}$). Found: C, 66.03; H, 4.64%. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62%.

*2,2′-Diethyl-2,2′,5,5′-tetrahydro[2,2′-bifuran]-5,5′-dicarboxylic Acid (**3**).* To a mixture of 5-ethyl-2-furoic acid (**1b**) (0.3 g, 0.045 mol) in refluxing ammonia (300 ml) was added sodium (3.1 g, 0.145 mol), when the blue color appeared.

The mixture was stirred for 20 min and, when methanol (4.64 g, 0.145 mol) was added, became colorless and was further stirred for 3 hr. After removal of ammonia, the residue was diluted with water (20 ml), acidified with 2M hydrochloric acid, and extracted with ether (3×20 ml). The ether solution, on being dried and evaporated, gave crude acid (2.85 g), mp 210—215 °C, which was recrystallized from benzene to yield **3** (2.1 g), mp 229—230 °C; IR (Nujol), ν_{max} 1728, 1708, 1108, and 1060 cm^{-1}; NMR (C_6D_5N), δ 0.92 (6 H, t, J=6.5 Hz, $2C\underline{H}_3$), 2.20 (4 H, m, $2C\underline{H}_2$), 5.54 (2 H, double d, J=2.6 and 1.5 Hz, 5- and 5′-$\underline{H}$), 6.03 (2H, double d, J=4.6 and 1.5 Hz, 3- and 3′-$\underline{H}$), 6.60 (2H, double d, J=4.6 and 2.6 Hz, 4- and 4′-H), and 13.62 (2H, s, $COO\underline{H}$).

Compound **3** (243 mg) in ether was converted with diazomethane to the methyl ester (268 mg), which was recrystallized from ethanol to give **3** ($R=CH_3$) (215 mg), mp 88—89 °C; Mass, *m/e* 310 (M^+) and 155 (base); IR, ν_{max} 1760, 1740, 1278, and 1105 cm^{-1}; NMR (the text). Found: C, 62.22; H, 7.12%. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15%.

*Methyl 5-Ethyl-2,5-dihydro-2-furoates (**2b**).* To a refluxing ammonia (49 ml) containing 5-ethyl-2-furoic acid (**1b**, 3.5 g, 0.025 mol) dissolved in dry methanol (12 ml, 0.38 mole) was added lithium (0.53 g, 0.075 mol) during 15 min. The mixture was stirred under reflux for 30 min and, after removal of the ammonia, was mixed with dry methanol (35 ml). Into the solution was passed hydrogen chloride gas, until the pH value became 1 (universal test paper), when salts precipitated and were removed off by filtration. The mother liquors were refluxed for 4 hr, evaporated to remove methanol, diluted with water (30 ml), and then extracted with ether (3×20 ml). The ether solution was dried and evaporated to leave oily substance, which proved to contain a small amount of the unreacted acid methyl ester (**1b**, $R'=CH_3$) by glc, as shown in Table 1. The oil was distilled fractionally and a fraction (3.3 g), boiling 88—89 °C/13 mmHg, was collected. This was identified as a 1 : 1 mixture of diastereoisomers **2b**; Mass (the text); IR, ν_{max} 1768, 1743, 1270, and 1125 cm^{-1}; NMR (the text). Found: C, 61.47; H, 7.97%. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75%.

*Methyl 5-Methyl-, 5-Propyl-, 5-Isopropyl-, 5-*tert*-Butyl-, and 5-Benzyl-2,5-dihydro-2-furoates (**2a**, **2c**, **2d**, **2e**, and **2f**).* These compounds were produced from the corresponding furoic acids essentially in the same manner as the 5-ethyl derivatives (**2b**) and their physical constants are described in the following.

Compounds **2a**, bp 74—75 °C/15 mmHg; Mass, *m/e* 142 (M^+) and 83 (base, $M^+-COOCH_3$); NMR, δ 1.28 and 1.32 (total 3H, two d J=6 Hz, $C\underline{H}_3$), 3.68 (3H, s, $COOC\underline{H}_3$), 5.16 (2H, br m, 2- and 5-$\underline{H}$), and 5.90 (2H, m, 3- and 4-$\underline{H}$). Found: C, 58.81; H, 7.36%. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09%.

Compounds **2c**, bp 80—82 °C/13 mmHg; Mass, *m/e* 170 (M^+), 127 ($M^+-C_3H_7$) and 111 (base, $M^+-COOCH_3$); NMR, δ 0.90 (3H, br t, $CH_2CH_2C\underline{H}_3$), 1.48 (4H, br m, $C\underline{H}_2C\underline{H}_2CH_3$), 3.64 (3H, s, $COOC\underline{H}_3$), 5.15 (2H, m, 2- and 5-$\underline{H}$), and 5.89 (2H, m, 3- and 4-$\underline{H}$). Found: C, 63.19; H, 8.11%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Compounds **2d**, bp 90—91 °C/15 mmHg; Mass, *m/e* 170 (M^+), 127 ($M^+-C_3H_7$) and 111 ($M^+-COOCH_3$); NMR, δ 0.90 (6H, m, isopropyl $C\underline{H}_3$), 1.74 (1H, septet, J=7.5 Hz, isopropyl $C\underline{H}$), 3.63 (3H, s, $COOC\underline{H}_3$), 4.60 (0.5 H, m, 5-$\underline{H}$ of *trans*-**2d**), 4.84 (0.5H, s, 5-$\underline{H}$ of *cis*-**2d**), 5.16 (1H, m, 2-$\underline{H}$), and 5.88 (2H, br s, 3- and 4-$\underline{H}$). Found: C, 63.35; H, 8.48%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Compounds **2e**, bp 102—103 °C/15 mmHg; Mass, *m/e* 184 (M^+), 127 ($M^+-C_4H_9$), 125 ($M^+-COOCH_3$), and 57 (base, $C_4H_9^+$); NMR, δ 0.84 and 0.86 (total 9H, each s, $3C\underline{H}_3$), 3.65 (3H, s, $COOC\underline{H}_3$), 4.54 (0.5H, br d, J=4 Hz, 5-$\underline{H}$ of *trans*-**2e**), 4.72 (0.5H, br d, J=7 Hz, 5-$\underline{H}$ of *cis*-**2e**), 5.22 (1H, m, 2-$\underline{H}$), and 5.92 (2H, br s, 3- and 4-$\underline{H}$). Found: C, 65.02; H, 8.71%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

Compounds **2f**, oil, were separated from the unreacted acid methyl ester (**1f**, $R=CH_3$) and purified by repeated column chromatographies (Merck, benzene); Mass, *m/e* 218 (M^+) and 91 ($C_7H_7^+$); NMR, δ 2.86 and 3.04 (1.2 and 0.8H, each d, J=7 Hz, $C_6H_5C\underline{H}_2$), 3.64 and 3.66 (total 3H, each s, $COOC\underline{H}_3$), 5.12 (2H, m, 2- and 5-$\underline{H}$), 5.90 (2H, br s, 3- and 4-$\underline{H}$), and 7.25 (5H, m, $C_6\underline{H}_5CH_2$). Found: C, 71.50; H, 6.59%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

*Methyl 5-*p*-Methoxybenzyl-2,5-dihydro-2-furoates (**2g**) and Dimethyl 2,2′-*p*-Methoxybenzyl-2,2′,5,5′-tetrahydro[2,2′-bifuran]-5,5′-dicarboxylate (**4**).* 5-*p*-Methoxybenzyl-2-furoic acid (**1g**, 1.1 g) in ammonia (15 ml) and methanol (6 ml) was treated with sodium (0.33 g) in the same manner as **1b** and worked up as usual to give oily product (1.05 g), which on standing crystallized partially. The whole components were checked by glc (Table 1) and separated by column chromatography (Merck a 2 : 1 mixture of benzene and chloroform). Fractions with high R_f afforded oil (0.4 g), which was identified as the unreacted acid methyl ester (**1g**, $R'=CH_3$). Middle fractions gave **2g** (0.45 g), oil, Mass, *m/e* 248 (M^+) and 121 ($CH_3OC_7H_6^+$); NMR, δ 2.88 (2H, m, $CH_3OC_6H_4C\underline{H}_2$), 3.70 (3H, s, $C\underline{H}_3OC_6H_4CH_2$), 3.76 (3H, s, $COOC\underline{H}_3$), 5.12 (2H, m, 2- and 5-$\underline{H}$), 5.84 (2H, m, 3- and 4-$\underline{H}$), 6.81 and 7.10 (4H, br d, J=8 Hz, $CH_3OC_6\underline{H}_4CH_2$). Found: C, 66.75; H, 6.79%. Calcd for $C_{14}H_{16}O_4$: C, 66.73; H, 6.50%.

Fractions with low R_f gave crystalline material **4** (50 mg), mp 120—121 °C, which was recrystallized from chloroform for analysis; Mass, *m/e* 494 (M^+) and 247 (base); IR ν_{max} 1748, 1738, 1280, and 1215 cm^{-1}; NMR, δ 3.26 (4H, m, $2C\underline{H}_2$), 3.68 (6H, s, $2C\underline{H}_3O$), 3.76 (6H, s, $2COOC\underline{H}_3$), 4.56 (2H, m, 2×5-$\underline{H}$), 5.40 and 5.56 (each 1H, m, 2×4-$\underline{H}$), 5.96 and 6.04 (each 1H, m, 2×3-$\underline{H}$), 6.74 and 7.12 (each 4H, ABq, J=8 Hz, $2\times C_6\underline{H}_4$). Found: C, 68.21; H, 6.08%. Calcd for $C_{28}H_{30}O_8$: C, 68.00; H, 6.12%.

*Methyl 2-Hydroxy-5-phenylpentanoate (**5h**).* 5-Phenyl-2-furoic acid (**1h**, 1.08 g) in ammonia (15 ml) and methanol (3 ml) was treated with sodium (0.41 g) in the same manner as **1b** and worked up as usual to give oily product (0.99 g), which consisted of two main components (by glc) and was separated by column chromatography (Merck, a 7 : 2 mixture of benzene and chloroform). Fractions eluted early afforded crystalline material (270 mg), which was recrystallized from ethanol to yield an unreacted acid methyl ester (**1h**, $R'=CH_3$) (245 mg), mp 90—91 °C; IR, ν_{max} 1730 (shoulder), 1715, 1591 (shoulder), 1575, 1273, and 1075 cm^{-1}. The remaining fractions (580 mg) were combined and separated by chromatography under the same conditions, giving small amounts of crude **1h** ($R'=CH_3$) (50 mg) and an unidentified oil (60 mg). After removal of these materials, the residual fraction (390 mg) was again submitted to column chromatography (a 3 : 1 mixture of benzene and hexane) to yield a colorless main product (200 mg), showing a single spot on tlc, along with an oily mixture (75 mg). The latter was presumed to consist mainly of methyl 2-hydroxy-5-phenylpent-3-enoate (**6h**) on the NMR spectrum but was not further purified. A part of the main product was purified by preparative tlc (benzene) for analysis to give **5h** in pure state; Mass, *m/e* 208 (M^+), 131 ($M^+-C_6H_5$), 117 ($M^+-C_6H_5CH_2$), 91 (base, $C_6H_5CH_2^+$), 77 ($C_6H_5^+$), and 59 ($COOCH_3^+$); IR, ν_{max} 3600, 1743, 1608, 1258, 1093, and 1070 cm^{-1} (shoulder); NMR δ 1.74 (4H, m, 3- and 4-$\underline{H}$), 2.68 (3H, m, O$\underline{H}$ and 5-$\underline{H}$), 3.76 (3H, s, CO-OC$\underline{H}_3$), 4.20 (1H, t J=7 Hz, 2-$\underline{H}$), and 7.16 (5H, s, $C_6\underline{H}_5$). Found: C, 68.96; H, 7.68%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

*Methyl 2-hydroxy-5-*p*-methoxyphenylpent-3-enoate* (**6i**). 5-*p*-Methoxyphenyl-2-furoic acid (**1i**, 2.50 g) in ammonia (20 ml) and methanol (6 ml) was treated with sodium (0.80 g) in the same manner as **1b** and gave an oily product (2.56 g), which proved to consist of two main components by glc and tlc. This reaction product was separated by column chromatography (Merck, a 1 : 1 mixture of chloroform and hexane) into 3 parts. The most mobile fractions gave colorless oil (870 mg), which was further purified by column chromatography (a 2 : 1 mixture of benzene and ethyl acetate) to yield crystalline substance (560 mg), which on recrystallization from ethanol afforded the unreacted acid methyl ester (**1i**, R′=CH_3) (500 mg), mp 83—83.5 °C; Mass, *m/e* 232 (M^+), 201 (M^+-CH_3O) and 145 (base); IR, ν_{max} 1738 (shoulder), 1723, 1610, 1253, and 1073 cm^{-1}.

The middle fractions consisted mainly of the main product (**6i**), but resisted further purification. A part (100 mg) of these fractions was hydrolyzed with 5% potassium hydroxide in boiling methanol for 30 min to give crystalline acid (70 mg), mp 90—94 °C, which was recrystallized from chloroform to yield **6i** (R′=H), mp 101—102 °C; Mass (the text); IR (Nujol), ν_{max} 3468, 3030, 1738, 1611, and 1098 cm^{-1}; NMR (the text). Found: C, 64.57; H, 6.28%. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%.

The least mobile fractions gave oily substance (206 mg), which was further purified by chromatography (a 10 : 1 mixture of benzene and ethyl acetate) to give colorless oil (110 mg), identified as methyl 2-hydroxy-5-*p*-methoxypentanoate (**5i**); Mass, *m/e* 238 (M^+) and 121 (base, $CH_3OC_6H_4$-CH_2^+); IR, ν_{max} 3368, 1743, 1723 (shoulder), 1608, and 1248 cm^{-1}; NMR, δ 1.73 (4H, m, 3- and 4-$\underline{H}$), 2.57 (2H, m, 5-$\underline{H}$), 2.84 (1H, br, s, O$\underline{H}$), 3.75 (3H, s, $C\underline{H}_3O$), 3.77 (3H, s, CO-OC$\underline{H}_3$), 4.17 (1H, br t, J=6 Hz, 2-$\underline{H}$), 6.80 and 7.08 (each 2H, ABq, J=8.5 Hz, $C_6\underline{H}_4$). Found: C, 65.70; H, 7.79%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%.

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