The Thermal Decarboxylation of 2-Furoic Acids

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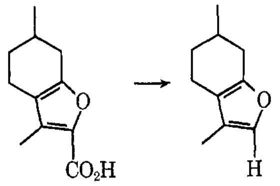
Received November 15, 1971

One solution to the problem of introducing a deuterium into a specific position on a furan ring[1] would be by thermal decarboxylation of a furoic acid subjected to prior exchange of the carboxyl hydrogen with deuterium oxide.

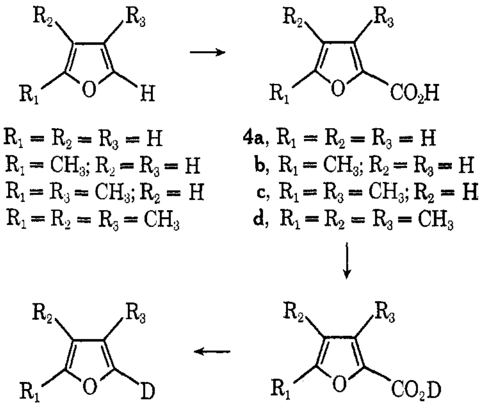
Little is known about the thermal decarboxylation of furoic acids. Eastman and Wither[2] reported the decarboxylation of menthofuroic acid (**1**) to menthofuran (**2**) under "illuminating gas" at 230°. The only other report of a thermal decarboxylation[3] does not discuss isolation of the product furan.



1 **2**

The general synthetic route used is shown in Scheme I. Conversion of a furan (**3**) to a 2-furoic acid (**4**) was effected in low yields[4] by lithiation[5] with phenyllithium or, a better choice in all instances,[4] *n*-butyllithium followed by carbonation,[5] or *via* the anilide by the method of Eastman and Wither[2] in better yields.[6] After purification of the 2-furoic acids by sublimation,[7] exchange of the carboxyl hydrogen with deuterium oxide was performed neat or in various solvents,[6] and the decarboxylation proceeded with good efficiency at reasonably accessible temperatures. Of the five 2-furoic acids (**4a–d**, **1**) subjected to an exchange–decarboxylation procedure, only 2-furoic acid (**4a**) failed to decarboxylate. The product from each reaction mixture was purified by distillation and/or preparative vapor phase chromatography.

SCHEME I



3a, $R_1 = R_2 = R_3 = H$
b, $R_1 = CH_3; R_2 = R_3 = H$
c, $R_1 = R_3 = CH_3; R_2 = H$
d, $R_1 = R_2 = R_3 = CH_3$

4a, $R_1 = R_2 = R_3 = H$
b, $R_1 = CH_3; R_2 = R_3 = H$
c, $R_1 = R_3 = CH_3; R_2 = H$
d, $R_1 = R_2 = R_3 = CH_3$

3-5-*d* **4**-d_1

The furans were analyzed for deuterium incorporation by mass spectrometry[6,8] and, in each instance, the presence of dideuterated and trideuterated furans was indicated[6] (Table I). A combination of proton magnetic resonance spectroscopy and mass spectrometry was used to evaluate the distribution of the deuterium. In each instance, deuterium incorporation at the α position in each furan was found to equal the sum of all of the monodeuterated product, one deuterium from all the dideuterated product, and one deuterium from all of the trideuterated product (Table II). Most of the remaining deuterium in the polydeuterated species was located in the methyl group occupying the other α position. Thermal decarboxylation is therefore not a reasonable method for the introduction of a deuterium into a specific position on a furan ring.

TABLE I

DEUTERIUM CONTENT BY MASS SPECTROMETRY[a]

Compd	% d_1	% d_2	% d_3
2-Methylfuran	62	11	2
2,4-Dimethylfuran	49	13	3
2,3,4-Trimethylfuran	57	19	5.5
2,3,4-Trimethylfuran[b]	50	23	9
Menthofuran	41	16	3.6

[a] All deuterium percentages are corrected for natural isotopic abundances. [b] This sample was inefficiently dried in order to evaluate the possible influence of traces of deuterium oxide.

TABLE II

DEUTERIUM DISTRIBUTION BY PROTON MAGNETIC RESONANCE SPECTROSCOPY

Compd	% at α[a]	% in C-2 methyl[b]	% in C-4 methyl
2-Methylfuran	(75)	(15)	
2,4-Dimethylfuran	75 (65)	26 (19)	
2,3,4-Trimethylfuran	79 (81)	30 (30)	
2,3,4-Trimethylfuran[c]	82 (82)	42 (41)	7
Menthofuran	60 (60)		

[a] Number in parentheses is per cent deuterium predicted from mass spectrometry from ($d_1 + d_2 + d_3$). [b] Number in parentheses is per cent deuterium predicted from mass spectrometry from ($d_2 + 2d_3$). [c] This sample was inefficiently dried in order to evaluate the possible influence of traces of deuterium oxide.

Several alternatives must be considered to account for the formation of polydeuterated products and to evaluate the mechanism in such thermal decarboxylations. As a control experiment, menthofuran (**2**) was subjected to the conditions of the exchange–decarboxylation sequence and no deuterium was incorporated. Hence, for the decarboxylation reaction, intro-

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(1) For straightforward systems, see D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968); B. Bak, L. Hansen, and J. Rastrey-Anderson, *Discuss. Faraday Soc.*, **19**, 30 (1955).

(2) R. H. Eastman and R. P. Wither, *J. Amer. Chem. Soc.*, **75**, 1492 (1953); R. P. Wither, Dissertation, Stanford University, 1955.

(3) K. Kato, *Agr. Biol. Chem.* (*Tokyo*), **31**, 657 (1967).

(4) The choice of organolithium and exact reaction conditions resulted in wide fluctuations in yields and extensive amounts of ketonic materials.[5] For analogous results with aryllithiums, see D. S. Sethi, M. R. Smith, Jr., and H. Gilman, *J. Organometal. Chem.*, **24**, C41 (1970).

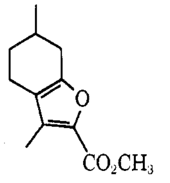
(5) P. H. Boyle, W. Cocker, J. B. H. McMurry, and A. C. Pratt, *J. Chem. Soc. C*, 1993 (1967).

(6) J. A. Hirsch, Dissertation, Stanford University, 1966.

(7) The parent 2-furoic acid (**4a**) was obtained from Matheson Coleman and Bell.

(8) D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968); K. Heyns, R. Stute, and H. Scharmann, *Tetrahedron*, **22**, 2223 (1966); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 23; K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 106.

duction of deuterium must occur prior to product formation. This does not rule out the possibility that furoic acid-*O-d* reacts with the furan by some mechanism to give exchanged product.[9] Another possibility—deuterium incorporation prior to decarboxylation—was eliminated from consideration in two ways. Methyl menthofuroate (**5**), prepared from menthofuroic acid (**1**) by treatment with diazomethane[6] or boron trifluoride–methanol complex, was subjected to the exchange–decarboxylation sequence without deuterium uptake. Subsequent to this experiment, Zoltewicz and Jacobson[10] reported that 2-furoic acid (**3a**) could be converted to 2-furoic-*5-d* acid (**3a**-*5-d*) and 2-furoic-*3,5-d*$_2$ acid (**6**) by heating the carboxylic acid in a deuterium oxide–carbonate buffer at 165° in a bomb or by heating the *O*-deuterated carboxylic acid in a bomb at 250°. We have repeated their work under the latter reaction conditions using O-deuterated 2-furoic acid (**4a**-d_1) as the substrate with similar results. However, placing the same furoic acid or 5-methyl-2-furoic acid (**4b**-d_1) in our apparatus at 240° for 1–2 hr, cooling the flask to room temperature, and back-exchanging the carboxyl deuterium, produced furoic acid containing only 2–3% deuterium. These experiments demonstrate that very little deuterium is being introduced at any furan carbon atom prior to decarboxylation by our procedure.



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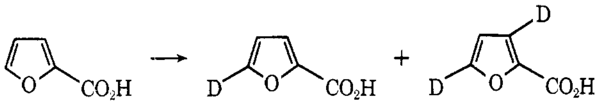
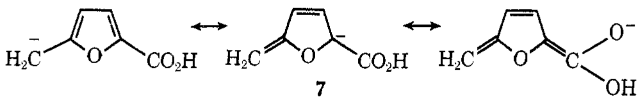


3a **3a**-*5-d* **6**

The only remaining alternative is deuterium incorporation during decarboxylation. As shown by decarboxylation of O-deuterated 3,4,5-trimethylfuroic acid (**4d**-d_1) in an incompletely dried medium (Tables I and II), the presence of an external base increases the amount of polydeuteration, thereby reinforcing the intermolecular character of the process leading to polydeuteration. The lack of decarboxylation with 2-furoic acid (**4a**) and the primary incorporation of the second and third deuterium atoms of the polydeuterated species in the α-methyl groups both suggest the involvement of an anion formed by proton abstraction from an α-methyl group (**7**), an enol (**8**), or an intermediate formed by a type of electrophilic substitution[9] (**9**).



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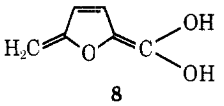

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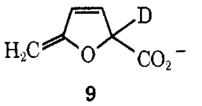

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Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using approximately 10% solutions in deuteriochloroform unless otherwise indicated and are reported in parts per million downfield from tetramethylsilane as an internal standard. Only distinct absorptions will be reported herein. Infrared spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. Mass spectral analyses were performed by Morgan Schaeffer Corporation, Montreal, Canada, and were obtained at 70 eV. Lower voltages were not useful, as desired minimization of M − 1 species was accompanied by sufficient broadening of molecular ion peaks to introduce new errors.

Preparation of 2-Furoic Acids.—A solution containing an equal volume of Na_2SO_4-dried hexane and the appropriate furan was added dropwise to an equivalent amount of 2.2 *M* *n*-butyllithium in hexane (Alfa Inorganics) under a nitrogen stream. The reaction mixture was mechanically stirred until the color changed to a dark blood-red. If this color change did not occur within 15 min, the temperature was raised by 10° intervals with a temperature-controlled oil bath until the color change began. The contents were returned to room temperature and poured over Dry Ice. The residue was dissolved in 10% NaOH, while the solution was extracted with ether to remove unreacted furan and ketonic material. The basic solution from the residue was acidified with cold dilute HCl until the 2-furoic acid no longer precipitated. The solid material was dissolved in ether and dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in boiling water, filtered hot, and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent was removed. The product was then sublimed at reduced pressures.

2-Furoic acid (**4a**) was purchased from Matheson Coleman and Bell.

5-Methyl-2-furoic Acid (4b).—This acid was prepared by the above procedure from 2-methylfuran (**3b**) (Aldrich) in 6.6% yield: mp 108–110° (lit.[11] mp 108–109°); nmr (CCl_4) δ 2.3 (s, 3), 6.0 (d, 1, J = 3 Hz), 7.1 (d, 1, J = 3 Hz), 12.3 (s, 1, COOH).

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.18; H, 4.62.

3,5-Dimethyl-2-furoic Acid (4c).—This acid was prepared by the above procedure in 11.7% yield from 2,4-dimethylfuran (**3c**) prepared by the method of Morel and Verkade:[12] mp 140–145° (lit.[13] mp 146–147°); nmr δ 6.05 (broad s, 1), 2,3 (broad s, 6), 10.7 (broad s, 1, COOH).

Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.89; H, 5.83.

3,4,5-Trimethyl-2-furoic Acid (4d).—This acid was prepared by the above procedure in 9.6% yield from 2,3,4-trimethylfuran (**3d**) prepared by the method of Hirsch:[6] mp 188° dec (lit.[14] mp 185° dec); nmr δ 1.9 (s, 3), 2.3 (broad s, 6), 11.6 (broad s, 1, COOH).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.51; H, 6.69.

Menthofuroic Acid (1).—This acid was prepared from menthofuran (**2**) by the above procedure in 8.4% yield and by the method of Wither and Eastman[2] in 46.5% yield: mp 178–182° dec (lit.[2] mp 179–180° dec); ir (KBr) 1660, 1595, 3000–2500 cm^{-1} uv λ_{max}^{EtOH} 270 mμ (log ϵ 4.12) (as reported);[2] nmr δ 1.0 (d, 3, J = 5 Hz), 2.2 (s, 3), 11.5 (broad s, 1, COOH).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.07; H, 7.04.

Exchange and Decarboxylation of 2-Furoic Acids.—An ethereal solution of 0.5 g of a 2-furoic acid was magnetically stirred in a stoppered flask with 2 ml of deuterium oxide (Bio-Rad Laboratories, 99.8%). The deuterium oxide was removed with a pipette, and the exchange was performed two more times. The ether was removed by distillation under nitrogen. Dried benzene was added in sufficient amount for azeotropic removal of

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[9] We are indebted to a reviewer for pointing out this possibility.

[10] J. A. Zoltewicz and H. L. Jacobson, *J. Heterocycl. Chem.*, **8**, 331 (1971).

[11] Hill and Sawyer, *J. Amer. Chem. Soc.*, **20**, 171 (1898).

[12] J. Morel and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas*, **70**, 35 (1951).

[13] T. Reichstein, H. Zschokke, and A. Georg, *Helv. Chim. Acta*, **14**, 1277 (1931).

[14] T. Reichstein, H. Zschokke, and W. Syz, *ibid.*, **15**, 1117 (1932).

any remaining deuterium oxide. Nitrogen was passed over the acid for 10 min, and then the flask was heated to 220–250° for a few hours in a flask fitted with an acetone–Dry Ice condenser. The flask was then cooled to room temperature, and the furan was removed by molecular distillation and collected in a Dry Ice trap. The furan was then purified by preparative gas chromatography if impurities were present.

2-Furoic Acid (4a).—Decarboxylation did not occur under these reaction conditions. Decarboxylation by method B of Zoltewicz and Jacobson[10] in a bomb produced 32% of 5-deuterio-2-furoic acid (**3a**-5-*d*) and 4% of 3,5-dideuterio-2-furoic acid (**6**).

5-Methyl-2-furoic Acid (4b).—Decarboxylation proceeded smoothly to 2-methylfuran (**3b**): mass spectrum, molecular ion *m/e* 82, base peak *m/e* 83.

When decarboxylation was stopped prior to completion, unreacted starting material was recovered, back-exchanged with water, dried, and sublimed. Less than 2% deuterium was evident in the resulting acid.

3,4-Dimethyl-2-furoic Acid (4c).—Decarboxylation to 2,4-dimethylfuran (**3c**) proceeded smoothly: mass spectrum, molecular ion and base peak *m/e* 96; nmr δ 1.9 (s, 3), 2.2 (s, 2.22), 5.6 (s, 1), 6.9 (s, 0.25).

3,4,5-Trimethyl-2-furoic Acid (4d).—Decarboxylation by the above procedure produced 2,3,4-trimethylfuran (**3d**): mass spectrum, molecular ion *m/e* 110, base peak *m/e* 111; nmr δ 1.8 (s, 3), 1.9 (d, 3), 2.1 (s, 2.1), 6.9 (s, 0.21).

The exchange and decarboxylation procedure was performed with the omission of the azeotropic distillation. The resulting 2,3,4-trimethylfuran (**3d**) exhibited nmr δ 1.8 (s, 3), 1.9 (d, 2.79), 2.1 (s, 1.74), 6.9 (3, 0.18).

Menthofuroic Acid (1).—Decarboxylation of menthofuroic acid (**1**) using the general exchange–decarboxylation sequence mentioned above or a variety of other exchange techniques[6] produced menthofuran (**2**) of roughly the same isotopic composition. Submission of menthofuran (**2**) to the exchange–decarboxylation procedure did not lead to deuterium incorporation.

Registry No.—**1**, 34289-48-0; **2**-*2-d*, 34289-49-1; **3a**-*5-d*, 6142-86-5; **3b**-*5-d*, 23451-00-5; **3c**-5-*d*, 34289-51-5; **3d**-5-*d*, 34289-52-6; **4a**, 88-14-2; **4b**, 1917-15-3; **4c**, 34297-68-2; **4d**, 34289-53-7.

Acknowledgment.—We wish to thank Dr. R. H. Eastman for helpful comments during the early phases of this work.