The Isotopic Substitutions of 4-Pyrone

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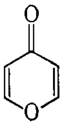
The treatment of 4-pyrone with deuterium oxide at 98° for 26 hr. leads to 4-pyrone-3,5-d_2 as the major volatile product. Upon corresponding treatment with oxygen-18 enriched water, 4-pyrone incorporates oxygen-18 into both the carbonyl group and the heterocyclic ring. These substitutions in conjunction with the observation that 4-pyrone is not formed from formic acid and acetone under conditions similar to those which yield the isotopic substitution products indicate that the intermediates in these reactions may be ring opened but not completely cleaved. Other pyrones fail to give incorporations under the same conditions. The infrared spectrum of 4-pyrone-3,5-d_2 establishes that a Fermi resonance is responsible for the splitting observed in the 1667-cm.$^{-1}$ absorption of 4-pyrone. The synthesis of 3,5-dimethyl-4-pyrone is a variant of an earlier synthesis which should make compounds of this type readily available.

The report that 4-pyrone (**1**) reacts with deuterium oxide to give 4-pyrone-2,6-d_2[1] (**2**) cannot be rationalized by orthodox mechanistic pathways. In an attempt to gain information about this process we have repeated the reaction and found that the major volatile product is actually 4-pyrone-3,5-d_2 (**3**). The evidence for this structural assignment and the nature of the intermediates involved in the formation of **3** are the subject of the present paper.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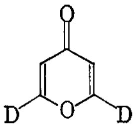

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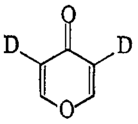

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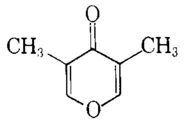
Results and Discussion

The treatment of 4-pyrone with 99.7% deuterium oxide (pD 6.4) at 98° for 26 hr. gave a product in 73% yield which had a vapor phase chromatographic retention time identical with 4-pyrone and was shown by mass spectral analysis to be 62 ± 2% $C_5H_2D_2O_2$, 16 ± 2% C_5H_3DO, and 23 ± 2% $C_5H_4O_2$. This agreed with a nuclear magnetic resonance (n.m.r.) analysis which indicated an incorporation of 80 ± 10% for one type of hydrogen. Infrared and ultraviolet spectral data gave qualitative indication that the functional groups and chromophore of 4-pyrone were intact in the product. The major volatile component, $C_5H_2D_2O_2$, may be assigned the structure 4-pyrone-3,5-d_2 (**3**) on the basis of a comparison of its n.m.r. spectrum with that of 4-pyrone (**1**), 3,5-dimethyl-4-pyrone (**4**), and 2,6-dimethyl-4-pyrone (**5**).



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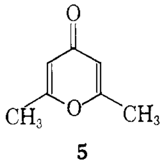

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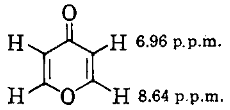
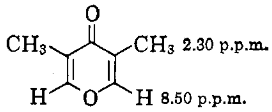
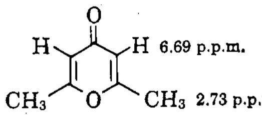
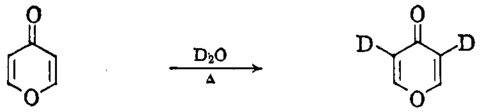
Although the n.m.r. spectrum of 4-pyrone is of the AA'BB' type, it can be treated approximately as an A_2X_2 system.[2] The spectrum in deuterium oxide solution consists of two multiplets of equal area centered at δ = 8.64 and 6.96 p.p.m.[3] These resonances may be assigned to the protons bonded to the 2- and 6-carbon atoms (H-2 and H-6) and the protons bonded to the 3 and 5 carbon atoms (H-3 and H-5), respectively, on the basis of chemical shifts of δ = 8.50 p.p.m. observed for the ring protons (H-2 and H-6) of 3,5-dimethyl-4-pyrone (**4**) and of δ = 6.69 p.p.m. observed for the ring protons (H-3 and H-5) of 2,6-dimethyl-4-pyrone (**5**). The redetermination of the n.m.r. spectrum of an 11% solution of 4-pyrone in deuterium oxide after heating for 26 hr. at 98° showed that the upfield multiplet (δ = 6.96 p.p.m.) has been reduced in area to about 20% of the downfield peak and that the latter has largely collapsed to a broad singlet.[4] Moreover, a third peak due to the protium of the water produced by the exchange also appears in the spectrum. In accordance with the chemical shift assignments, the spectrum indicates that protons on C-3 and C-5 of 4-pyrone have been exchanged with the medium.









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[1] R. C. Lord and W. D. Phillips, *J. Am. Chem. Soc.*, **74**, 2429 (1952).

(1b) NOTE ADDED IN PROOF.—After acceptance of the present work for publication Professor R. C. Lord brought to our attention the fact that the structural proposal of **2** was modified to **3** in a paper presented at the 1954 Pittsburgh Conference on Applied Spectroscopy. A brief abstract of this work has appeared [R. C. Lord, D. W. Mayo, and W. D. Phillips, *Anal. Chem.*, **26**, 429 (1954)], but the report was not abstracted in *Chemical Abstracts* or *Chemisches Zentralblatt*. We are grateful to Professor Lord for this information and for making a manuscript [D. W. Mayo, P. J. Sapienza, R. C. Lord, and W. D. Phillips, *J. Org. Chem.*, **29**, 2682 (1964)] available to us prior to publication.

[2] The n.m.r. spectrum of 4-pyrone in deuteriochloroform has been analyzed independently by Dr. J. Jonas using this approximation. The parameters J_A = 2.88 c.p.s., J_B = 1.21 c.p.s., J = 6.33 c.p.s., J' = 0.38 c.p.s., and $\delta\nu_{AB}$ = 94.51 c.p.s. give a fit of the calculated and observed spectrum which is within experimental error. The nomenclature used is that of J. A. Pople, W. G. Schneider, and H. J. Bernstein ("High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 138–142). We are grateful to Dr. Jonas for this information.

[3] The spectra referred to in the discussion were obtained in deuterium oxide and have been extrapolated to infinite dilution relative to external tetramethylsilane.

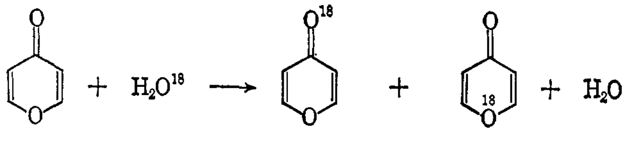
[4] H. S. Gutowsky "Techniques of Organic Chemistry," Vol. I, part IV, A. Weissberger, Ed., Interscience Publishing Co., New York, N. Y., 1960, p. 2772.

In a subsequent experiment it was established that treatment of 4-pyrone with an acidified solution (pD 2.75) of deuterium oxide for 26 hr. at 98° led to a 93% gross incorporation of deuterium into the 3- and 5-positions of 4-pyrone. It was also observed that **3** was produced when 4-pyrone was treated with more acidic solutions of deuterium oxide (pD 0.7 and −0.3), but not when the pyrone was treated with a catalytic amount of base. Heating deuterium oxide solutions of 3,5-dimethyl-4-pyrone (**4**) and 2,6-dimethyl-4-pyrone (**5**) at 98° for 26 hr. followed by redetermination of the n.m.r. spectra, isolation, and mass spectral analyses showed that these compounds have incorporated no more than 1% deuterium under these conditions. Similarly, 2-pyrone and 4,6-dimethyl-2-pyrone incorporated less than 5% deuterium, determined by n.m.r. analyses, under the same conditions.

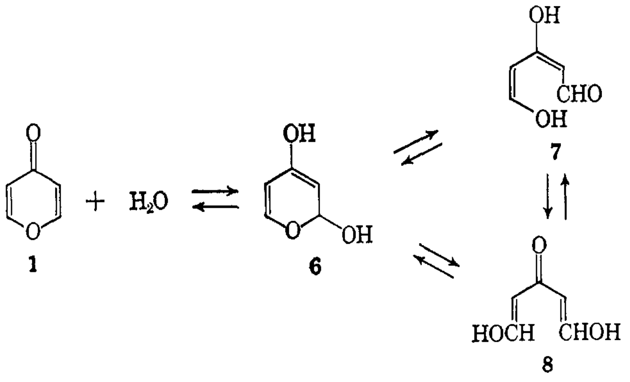
In a preparative experiment, 4-pyrone was treated successively with two portions of deuterium oxide; the deuterated product was isolated in 32% yield. Mass spectral analysis showed this to be 83 ± 1% $C_5H_2D_2O_2$, 12 ± 1% $C_5H_3DO_2$, and 5 ± 1% $C_5H_4O_2$, consistent with an n.m.r. analysis which indicated 93 ± 5% deuterium incorporation. This sample, predominately 3,5-d_2-4-pyrone (**3**), was used for the subsequent infrared measurements.

A study of the incorporation of oxygen-18 into 4-pyrone from oxygen-18 enriched water provides information about the possible intermediates in the deuterium incorporation. The specific point in question was whether one or both oxygen atoms of the pyrone would be available for exchange with the medium. Assuming that the equilibrium distribution of the oxygen-18 in the water and 4-pyrone will be statistical,[5] an exchange of one oxygen atom of 4-pyrone with the medium would lead to an equilibrium oxygen-18 enrichment in the pyrone slightly less[6] than the original enrichment in the water; whereas, if both oxygen atoms of 4-pyrone are available for exchange with the medium, the oxygen-18 enrichment in the pyrone at equilibrium will be slightly less than twice the original enrichment in the water.

Heating a 19% solution of 4-pyrone in 6.55 atom % oxygen-18 enriched water (pH 2.75) for 26 hr. at 98° yielded an organic product in 65% yield which was identified as 4-pyrone and shown by mass spectral analysis to have incorporated 12.9 ± 1% oxygen-18. Since the calculated excess, taking dilution into account and presuming an equilibrium and statistical distribution of the label into both oxygen atoms of the pyrone, is 12.2%[7] this result indicates that both oxygen atoms of 4-pyrone are available for equilibration with the medium. Treatment of 3,5-dimethyl-4-pyrone (**4**) and 2,6-dimethyl-4-pyrone (**5**) with 6.55 atom % oxygen-18 enriched water under the same reaction conditions led to less than 2% oxygen-18 incorporation into these pyrones.



The observed isotopic incorporations at pH or pD 2.75 may be accommodated economically by conventional intermediates. The nucleophilic 1,4 addition of water to 4-pyrone may be envisioned to give **6** which can undergo ring opening to give the tautomers **7** and **8**. Deuteration could occur by the usual keto–enol equilibria of any of the intermediates **6**, **7**, or **8**. Oxygen-18 incorporation by a hydration–dehydration sequence could involve **1**, **7**, or **8** for incorporation into the carbonyl group of 4-pyrone, while the incorporation of oxygen-18 into the heterocyclic ring implies the intermediacy of **7** or **8**. In the proposed scheme the roles assigned to **1**, **6**, **7**, and **8** could equally be fulfilled by tautomers or protonated intermediates derived from them. The possibility that a major pathway for the isotopic substitution of 4-pyrone may be ascribed to the complete dissociation of 4-pyrone, *via* the reaction of intermediates **7** or **8** with water, into acetone and formic acid with these molecules incorporating isotope and then recondensing to form the labeled pyrone was tested by attempting to prepare 4-pyrone by refluxing acetone and formic acid in aqueous solution (pH 1.5) for 26 hr. at 98°. Since less than 1% of 4-pyrone was formed under these conditions, it follows that, insofar as the conditions of this experiment may be assumed to represent those of the isotope incorporation experiments, a pathway of incorporation involving cleavage of 4-pyrone to formic acid and acetone is not of major importance. The failure of the other pyrones, which might reasonably be expected to incorporate the label, to do so is presumably simply a reflection of the lower reactivities of these compounds under the reaction conditions.



The proposed intermediates and the observed products are consistent with previous knowledge of the chemistry of 4-pyrones and of processes of isotopic substitutions. The opening of the 4-pyrone ring by nucleophilic attack by hydroxide, methoxide, and ethanol at the 2- and 6-positions under basic and acidic conditions was reported by Willstater and Pummerer[8] in 1905. The well-known conversion of 4-pyrones into

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[5] Essentially the assumption is that isotopic fractionation which would incorporate oxygen-18 selectively into the 4-pyrone will be small. Single-stage isotopic fractionations involving oxygen-18 generally are considered to be a few per cent of the available label. (a) H. C. Urey and L. J. Grief, *J. Am. Chem. Soc.*, **57**, 321 (1935); (b) H. C. Urey, *J. Chem. Soc.*, 562 (1947); (c) M. Dole, *Chem. Rev.*, **51**, 263 (1952); (d) M. Cohn and H. C. Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).

[6] Owing to the dilution of the label by the oxygens from the 4-pyrone.

[7] Owing to the absence of quantitative information about the isotopic fractionation in this system, the close agreement of the calculated and observed values may not be taken as evidence that the equilibrium has been fully attained.

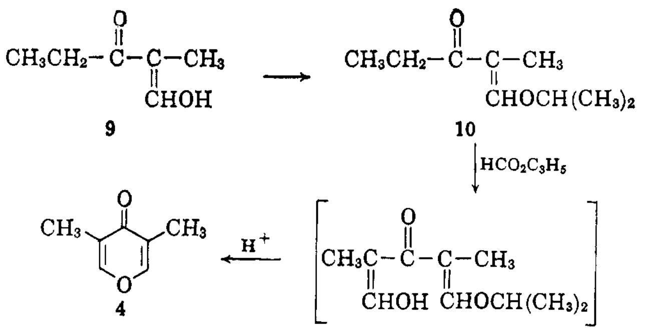
[8] R. Willstater and R. Pummerer, *Ber.*, **38**, 1461 (1905).

4-pyridones[9] illustrates a similar nucleophilic addition followed by ring opening and ring closure. The incorporation of deuterium into the α-position of an α,β-unsaturated carbonyl system by an addition–elimination process has been observed under acidic[10] and basic[11] conditions. The isotopic exchange of carbonyl oxygen atoms with oxygen-18 has been known for some time[5a,5d,12] and the substitution of oxygen-18 for oxygen-16 located at the β-position of an α,β-unsaturated carbonyl system has also been previously reported.[13]

The infrared spectrum of 4-pyrone-3,5-d_2 (**3**) provides definitive information about the nature of the splitting of the 1667-cm.$^{-1}$ absorption observed in the infrared spectrum of 4-pyrone (**1**). In 1959, Jones, Angell, Ito, and Smith[14] postulated that this was due to a slightly anharmonic Fermi resonance involving the out-of-plane deformation mode ascribed to H-3 and H-5 which appears at 851 cm.$^{-1}$. The spectrum of 4-pyrone-3,5-d_2 confirms this assignment since the spectrum has no appreciable absorptions in the 800–900-cm.$^{-1}$ region and does have an unsplit absorption at 1648 cm.$^{-1}$.[15] This evidence is similar to that presented in 1958 by Yates and Williams[11a] for the presence of Fermi resonance in some cyclopentenones.

The syntheses of 3,5-dimethyl-4-pyrone is a variant of an older procedure[16] which should allow the preparation of a wide variety of 3,5-disubstituted 4-pyrones. Two approaches have been used in previous preparations of this type of compound. In 1928 Benary and Bitter[16] reported the preparation of 3,5-diphenyl-4-pyrone from the condensation of dibenzyl ketone and ethyl formate followed by acid-catalyzed cyclization. More recently Leonard and Choudhury[17] have investigated the preparation of substituted 3,5-dibenzyl-4-pyrones by the palladium-on-charcoal promoted isomerizations of 3,5-dibenzylidenetetrahydro-4-pyrones as part of a larger study of heterocyclic aromatizations.

In our hands, a number of attempts to prepare 3,5-dimethyl-4-pyrone by the direct condensation of diethyl ketone with 2 moles of ethyl formate failed. Presumably the enolate produced by the condensation of 1 mole of ethyl formate with diethyl ketone lacked the necessary reactivity for a second condensation under these conditions. To circumvent this difficulty the isopropyl derivative (**10**) of the monocondensation product[18] (**9**) was prepared, condensed with ethyl formate, and cyclized under acid conditions to give 3,5-dimethyl-4-pyrone in 25% yield based on **10**. The yield is probably not optimal.



Experimental

The infrared spectra were determined on a Perkin-Elmer 521 infrared spectrophotometer using chloroform solutions. The ultraviolet spectra were determined on a Perkin-Elmer 202 ultraviolet visible spectrophotometer using 95% ethanol solutions. The molecular weight mass spectral analysis were carried out on an Atlas CH 4 mass spectrometer with the source at 250°, using a variable temperature stainless steel inlet system and 12 e.v. as the ionizing potential. The proton magnetic resonance spectra were determined on a Varian A-60 spectrometer at a sweep width of 500 c.p.s. using 10% deuteriochloroform solutions containing tetramethylsilane as an internal standard unless otherwise noted. The melting points were determined on a Büchi-Tottoli oil bath apparatus. The vapor phase chromatography was carried out on a Aerograph A-90-P using a 5-ft. column of 0.25-in. diameter containing 20% Carbowax 20M supported on base-washed fire brick at 180°. The pH and pD readings were taken on a Polrad automatic recording titrator Model AT-2A using a calomel and a glass electrode. The microanalyses was performed by Mr. Joseph Nemeth and associates.

4-Pyrone (**1**) was prepared by the decarboxylation of cheledonic acid according to the method of Willstater and Pummerer.[19] The crude product was purified by vapor phase chromatography. The product had m.p. 33–35° (lit.[19] m.p. 32.5°) and was characterized by the expected infrared[14] and n.m.r. spectrum. The latter consisted of two multiplets centered at δ = 6.40 p.p.m. (relative area 1.0) assigned to H-3 and H-5 and at δ = 7.76 p.p.m. (relative area 1.0) assigned to H-2 and H-6.[20]

2-Pyrone was prepared by the decarboxylation of 6-carboxy-2-pyrone according to the method of Fried and Elderfield.[21] The crude product was purified by vapor phase chromatography, $n^{24}\text{D}$ 1.5285 (lit.[21] 1.5272). The infrared[14] and spectral data were consistent with the established structure. The latter consisted of two complex multiplets located at δ = 7.25–7.70 and 6.16–6.50 p.p.m.[20]

2,6-Dimethyl-4-pyrone (**5**) was prepared by the method of Collie and Tickle,[22a] m.p. 132–134° (lit.[22b] m.p. 132°). The established structural assignment was confirmed by the compound's infrared[15] and nuclear magnetic resonance spectrum. The latter consisted of a singlet at δ = 2.25 p.p.m. (relative area 3.1) assigned to the methyl group and a singlet at 6.07 p.p.m. (relative over area 1.0) assigned to H-3 and H-5.

4,6-Dimethyl-2-pyrone was prepared by the method of Smith and Wiley,[23] m.p. 50–52° (lit.[23] m.p. 50–51°). The infrared[24] and n.m.r. spectrum were consistent with the established structure. The latter consisted of two singlets at δ = 2.12 (relative

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[9] This area has been reviewed by (a) H. Meislich in "Pyridine and Its Derivatives," part III, E. Klingsberg, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 552–560; (b) L. F. Cavalierei, *Chem. Rev.*, **41**, 550 (1947). Other examples of formally similar reactions have been reported by (c) P. Yates, M. J. Jorgenson, and S. K. Roy, *Can. J. Chem.*, **40**, 2146 (1962); (d) R. B. Woodward, cited by F. D. Bergman, D. Ginsberg, and R. Pappo, *Org. Reactions*, **10**, 219 (1959). For recent work in a closely related area see (e) S. Garratt, *J. Org. Chem.*, **28**, 1886 (1963); (f) S. Iguchi and A. Inue, *Chem. Pharm. Bull.* (Tokyo), **11**, 390 (1963); (g) D. Cook, *Can. J. Chem.*, **41**, 1435 (1963); (h) R. N. Schut, W. G. Strycker, and T. M. H. Liu, *J. Org. Chem.*, **28**, 3046 (1963).

[10] D. S. Noyce, P. A. King, F. B. Kirby, and W. L. Reed, *J. Am. Chem. Soc.*, **83**, 1632 (1962).

[11] (a) P. Yates and L. L. Williams, *ibid.*, **80**, 5896 (1958); (b) B. W. Rockett, T. M. Harris, and C. R. Hauser, *ibid.*, **85**, 3491 (1963); (c) R. H. Shapiro, J. M. Wilson, and C. Djerassi, *Steroids*, **1**, 1 (1963).

[12] (a) A. Murry and D. L. Williams, "Organic Synthesis with Isotopes," Interscience Publishing Co., New York, N. Y., 1958, p. 1844; (b) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 237–239.

[13] (a) K. B. Wiberg and K. A. Sagebarth, *J. Org. Chem.*, **25**, 832 (1960); (b) R. A. Kloss and C. Wiener, *ibid.*, **28**, 1671 (1963).

[14] R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959).

[15] This absorption has recently been assigned a largely carbonyl character by A. R. Katritzky and R. A. Jones, *Spectrochim. Acta*, **17**, 64 (1961).

[16] E. Benary and G. A. Bitter, *Ber.*, **61**, 1057 (1928).

[17] N. J. Leonard and D. Choudhury, *J. Am. Chem. Soc.*, **79**, 156 (1957).

[18] L. Claisen and L. Meyerowitz, *Ber.*, **22**, 3273 (1889).

[19] R. Willstater and R. Pummerer, *ibid.*, **37**, 3745 (1904).

[20] The n.m.r. spectra of 2-pyrone, 4-pyrone, and 2,6-dimethyl-4-pyrone in chloroform–carbon tetrachloride solution have been reported by A. Terahara, M. Ohashi, K. Nakanishi, I. Yamaguchi and N. Hayakawa [*Bull. Chem. Soc. Japan*, **33**, 1310 (1960)].

[21] J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

[22] (a) J. N. Collie and T. Tickle, *J. Chem. Soc.*, **75**, 710 (1899); (b) J. N. Collie, *ibid.*, **59**, 617 (1891).

[23] N. R. Smith and R. H. Wiley, *Org. Syn.*, **32**, 57 (1952).

[24] R. H. Wiley and J. G. Esterle, *J. Org. Chem.*, **22**, 1257 (1957).

area 3.0) and 2.20 p.p.m. (relative area 3.0) assigned to the methyl groups and a broad singlet at δ = 5.92 p.p.m. (relative area 1.1) assigned to H-3 and H-5.

3,5-Dimethyl-4-pyrone (4).—To 7.6 g. of 2-methyl-1-penten-1-ol-3-one[18] (**9**) in 100 ml. of acetone was added 18.0 ml. of isopropyl bromide and 15.5 g. of anhydrous potassium carbonate.[25] The mixture was refluxed for 34 hr. and then cooled and poured into 100 ml. of water. The aqueous solution was extracted twice with ether and the etheral extract was washed with dilute potassium carbonate and water and dried over anhydrous magnesium sulfate. Evaporation of the ether under reduced pressure followed by distillation of the residue gave 3.36 g. (30.6%) of 1-isopropoxy-1-ene-3-pentanone (**10**), b.p. 80–86° (3.0 mm.), as a slightly yellow liquid. Vapor phase chromatography of this material gave two peaks with the major one (retention time 11.5 min.) accounting for approximately 98% of the material. The infrared, ultraviolet, and nuclear magnetic resonance spectra of the material were consistent with the assigned structure **10**. The compound appeared to be quite sensitive to air and an analytical sample could not be obtained. Accordingly, the material was used without further purification in the subsequent reaction.

To an ice-cooled solution of 3.18 g. of **10** and 5.0 ml. of ethyl formate in 25 ml. of dry benzene was added 0.518 g. of 52% sodium hydride in mineral oil.[26] The resulting red solution was allowed to stand overnight. After the addition of 5 ml. of methanol, the mixture was poured into 100 ml. of a 1:1 mixture of hydrochloric acid and water. The acidic solution was extracted with three 50-ml. portions of ether, and the ether was dried over anhydrous magnesium sulfate. Evaporation of the ether under reduced pressure followed by distillation of the residue gave 1.62 g. of yellow liquid, b.p. 57–110° (1.0 mm.). Chromatography of this oil on 30 g. of neutral alumina gave 0.568 g. (25% based on 10) of 3,5-dimethyl-4-pyrone (**4**), m.p. 73–76°. Two recrystallizations from petroleum ether (b.p. 65–67°) yielded white needles (0.323 g.), m.p. 76–77°.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.58.

The infrared spectrum showed strong absorptions at 1653 and 1610 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 259 mμ (ϵ 10,200) and end absorption at 210 mμ. The n.m.r. spectrum showed a singlet at δ = 1.97 (relative area 3.0) assigned to the methyl groups and a singlet at 7.71 p.p.m. (relative area 1.0) assigned to H-2 and H-6.

4-Pyrone-3,5-d_2 (3).—A solution of 55 mg. of 4-pyrone in 0.45 ml. of 99.7% deuterium oxide (pD 6.40)[27] was heated at 98 ± 2° for 26 hr. An n.m.r. spectrum of the solution (which contained a small amount of solid material) showed that the upfield peak (*vide supra*) had about 20% the area of the downfield peak. Moreover, an additional sharp singlet assigned to the protium of water had appeared in the spectrum. The solution was dried under ether and over magnesium sulfate and the ether was removed by distillation to give 41 mg. of a low-melting solid. This material had a vapor phase chromatographic retention time identical with that of 4-pyrone. Infrared and ultraviolet spectral analysis qualitatively indicated that the functional groups and chromophore of 4-pyrone were intact. Mass spectral analysis showed that the material was 62 ± 2% $C_5H_2D_2O_2$, 16 ± 2% $C_5H_6DO_2$, and 23 ± 2% $C_5H_4O_2$. Comparison of the n.m.r. spectrum of the product with that of 4-pyrone, 3,5-dimethyl-4-pyrone, and 2,6-dimethyl-4-pyrone indicated that it was predominately 4-pyrone-3,5-d_2 (**3**) (*vide supra*).

A solution with pD 2.75[27] was prepared from *ca.* 0.001 ml. of 12 *N* hydrochloric acid and 10.0 g. of 99.7% deuterium oxide. The n.m.r. spectrum of 38 mg. of 4-pyrone in 0.4 ml. of this solution showed two multiplets centered at δ = 8.54 and 6.92 p.p.m. A redetermination of the n.m.r. spectrum after the solution had been heated at 98 ± 2° for 26 hr. showed that the upfield multiplet had decreased to about 7% the area of the downfield peak which was now largely a broad singlet. In accordance with the previous experiments, the product was assigned structure **3**.

In further experiments it was shown that **3** was obtained with solutions of deuterium chloride[28] in deuterium oxide with pD 0.7 and −0.3, but not when a small amount of sodium hydroxide was added to a solution of 4-pyrone in deuterium oxide. In the latter case, the extensive formation of a precipitate occurred, as previously reported,[1] and a determination of the n.m.r. spectrum of the supernatent solution showed that the 4-pyrone remaining in solution was not appreciably deuterated.

In a preparative experiment a solution of 2.35 g. of 99.7% deuterium oxide (pD 6.40)[27] and 0.400 g. of 4-pyrone was heated for 36 hr. at 95 ± 2°. The solution was dried under ether and over excess sodium sulfate. The residue obtained after distillation of the ether was dissolved in 1.41 g. of deuterium oxide and heated for 20 hr. at 95°. After a similar work-up 0.130 g. of product was obtained by microdistillation. The n.m.r. spectrum of the product indicated 93% deuterium incorporation in the 3- and 5-positions. The vapor phase chromatographic retention time was identical with that of 4-pyrone. A mass spectral analysis indicated that the product was 83 ± 2% $C_5H_2D_2O_2$, 12 ± 1% $C_5H_3DO_2$, and 5 ± 1% $C_5H_4O_2$. The strong absorptions in the infrared spectrum of this mixture were considered to be due to the major component **3** and were found at 1648, 1599, 1408, and 923 cm.$^{-1}$.

Oxygen-18 Incorporation into 4-Pyrone.—A solution of 2.80 g. of 6.55 atom % oxygen-18 enriched water[29] (pH 2.75) and 0.654 g. of 4-pyrone was heated for 26 hr. at 98 ± 2°. Work-up essentially identical with that in the preparative deuteration gave 0.426 g. of product. Vapor phase chromatography and the infrared spectrum of this material indicated that it was predominately 4-pyrone. Mass spectral analysis gave $C_5H_4O_2^{16}$, 86.6%; $C_5H_4O^{16}O^{18}$, 12.9%. The error is ±1.0%. The calculated incorporation assuming complete exchange of both oxygen atoms of 4-pyrone, taking dilution into account and ignoring isotopic fractionation,[5,7] is 12.2%.

Attempted Isotopic Incorporation into 3,5-Dimethyl-4-pyrone (4), 2,6-Dimethyl-4-pyrone (5), 2-Pyrone, and 4,6-Dimethyl-2-pyrone.—Treatment of deuterium oxide solutions of the 4-pyrones **4** and **5** at 98° for 26 hr. followed by isolation and mass spectral analysis showed that less than 1% deuterium was incorporated into these pyrones. Similar treatment of 2-pyrone and 4,6-dimethyl-2-pyrone and n.m.r. analysis showed that less than 5% deuterium was incorporated into these compounds. Heating solutions of the 4-pyrones **4** and **5** with 6.55 atom % oxygen-18 enriched water followed by isolation and mass spectral analysis showed less than 2% oxygen-18 incorporation under these conditions.

Attempted Synthesis of 4-Pyrone from Acetone and Formic Acid.—A solution of 0.300 g. of formic acid and 0.188 g. of acetone in 2 ml. of water (pH 1.5) was refluxed for 26 hr. Work-up as in the case of the preparative deuteration followed by vapor phase chromatographic analysis showed that less than 1% 4-pyrone was formed under these conditions.

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