methoxy-1,8-naphthalic anhydride, 17190-36-2; 2-methyl-1,8-naphthalic anhydride, 17190-37-3; 5-methylacenaphthene, 17057-80-6; 4-methyl-1,8-naphthalic anhydride, 17190-39-5; 4-bromoacenaphthalene, 4657-98-1; 5-bromo-2,1,3-*peri*-naphthopyran, 17190-41-9; 5-cyano-2,1,3-*peri*-naphthopyran, 17190-42-0; 2,1,3-*peri*-naphthopyran-5-carboxylic acid, 17190-43-1; 4-methyl-2,1,3-*peri*-naphthopyran, 17190-44-2; 3-methyl-1,8-naphthalic anhydride, 17190-45-3; 4-ethylacenaphthene, 17190-46-4.

Hydrogen and Oxygen Exchange in Δ²-Dihydropyran over Hot Alumina[1]

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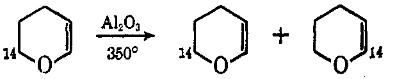
Δ²-Dihydropyran in contact with hot alumina exchanges its oxygen atom, as well as the hydrogen atoms at the 3 and 5 positions. Doubly labeled dihydropyran, needed for one part of the work, was prepared as follows. Pyrolysis of paraformaldehyde-^{18}O gave formaldehyde-^{18}O, which yielded, when combined with 4-pentenylmagnesium bromide, 5-hexenol-^{18}O. A mixture of this with 5-hexenol-6-^{14}C was ozonized, and the resulting 2-hydroxytetrahydropyran-1-^{18}O-6-^{14}C was dehydrated to give Δ²-dihydropyran-^{18}O-6-^{14}C. Exposing the doubly labeled material to alumina at 350° moved carbon-14 from the 6 to the 2 position and at the same time decreased the oxygen-18 content markedly. Allowing dihydropyran in the presence of tritiated water to flow over hot alumina introduced tritium into the organic substrate. By appropriate reactions, at least 75% of the tritium was located at the dihydropyran 3 and 5 positions. Alumina is necessary for these processes; neither carbon scrambling nor tritium insertions occur when glass wool is substituted for alumina. Interconversion with tetrahydropyran cannot be involved in any important way in the carbon scrambling nor presumably in the oxygen and hydrogen exchange. Thus, conditions that produced almost complete scrambling in the dihydropyran of a mixture of Δ²-dihydropyran-6-^{14}C plus unlabeled tetrahydropyran were established. The same conditions transferred none of the radioactivity from tetrahydropyran to dihydropyran when the starting mixture was unlabeled dihydropyran plus tetrahydropyran-2-^{14}C. Mechanisms that accommodate the available facts are proposed.

Passing Δ²-dihydropyran (1) labeled at the 6 position with carbon-14 over alumina at 350° distributes the label between the 2 and 6 positions.[2] We have found that two other processes occur as well, namely, exchange of the dihydropyran oxygen and exchange of certain of the dihydropyran hydrogens. The present paper discusses these reactions as well as other related properties of dihydropyran.[3]



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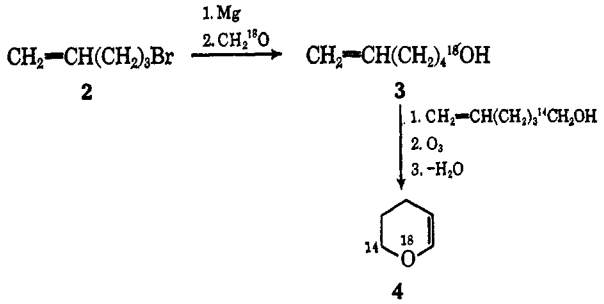
Dihydropyran-^{18}O, used in the oxygen-exchange study, was synthesized as follows. Paraformaldehyde-^{18}O was obtained by dissolving paraformaldehyde in oxygen-18 labeled water and recovering the polymer from solution.[4] The paraformaldehyde-^{18}O served as a source of formaldehyde-^{18}O, which, on combination with the Grignard reagent from 5-bromopropene (2),[2,5] gave 5-hexenol-^{18}O (3). A small quantity of 5-hexenol-1-^{14}C[2] was added at this stage, so that in effect the subsequent steps of ozonolysis to 5-hydroxypentanal (*i.e.*, 2-hydroxytetrahydropyran) followed by dehydration afforded doubly labeled Δ²-dihydropyran-^{18}O-6-^{14}C (4). This material was passed over hot alumina.



The extent of scrambling between the 2 and 6 positions was determined by ozonizing the emergent dihydropyran and counting the cleavage fragments, one in the form of zinc formate (containing the dihydropyran 2 position) and the other in the form of the 2,4-dinitrophenylhydrazone of 4-hydroxybutanal (containing the dihydropyran 6 position). As Table I shows, the radioactivity in the dihydropyran, after contact with alumina, was almost equally divided between the 2 and 6 positions. At the same time, this emergent dihydropyran had lost about half its original content of oxygen-18 (Table I). Clearly, conditions that produce carbon scrambling also lead to oxygen exchange.

To make sure that alumina is necessary for the distribution of radioactivity between the 2 and 6 positions, Δ²-dihydropyran-6-^{14}C was passed over glass wool at 350°. No scrambling was noted, the treated dihydropyran still retaining 100% of its activity at the 6 position.

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[1] This work has been supported in part by National Science Foundation under Research Grant G-19142 and in part by Research Corporation under a Frederick Gardner Cottrell Grant-in-Aid. We are grateful to both organizations for their help.

[2] W. J. Gensler, J. E. Stouffer, and R. G. McInnis, *J. Org. Chem.*, **32**, 200 (1967). Our use of "distributes" or "scrambles" does not imply that the terminal carbon atoms of the Δ²-dihydropyran five-carbon chain have actually changed places.

[3] Part of this work has appeared as a preliminary report; *cf.* W. J. Gensler, G. L. McLeod, J. E. Stouffer, P. T. Manos, and R. G. McInnis, *Chem. Ind.* (London), 1658 (1963).

[4] The nature of paraformaldehyde in water is discussed by J. F. Walker in "Formaldehyde," American Chemical Society Monograph Series No. 120, 2nd ed, Reinhold Publishing Corp., New York, N. Y., 1953. R. N. Renaud and L. C. Leitch [*Can. J. Chem.*, **39**, 261 (1961)] have described a related but much less convenient way to prepare paraformaldehyde-^{18}O.

[5] P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937).

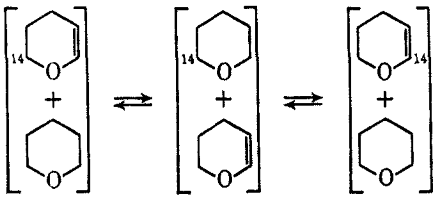
TABLE I

Δ^2-DIHYDROPYRAN-^{18}O-^{14}C OVER HOT ALUMINA[a]

		Before exposure to alumina	After exposure to alumina
^{14}C activity[b]	total	0.50	0.40[f]
	position 2	[0%]	0.19 or 48%
	position 6	[100%]	0.21 or 52%
^{18}O abundance	atom %	0.75[d]	0.43
	excess atom %[c]	0.55 (0.44[e])	0.22

[a] The radioactivity measures have standard deviations no greater than 1%; the oxygen-18 measures have standard deviations estimated to be no more than 5%. [b] Relative molar activity. [c] Normal oxygen-18 abundance taken as 0.204 [A. O. Nier, *Phys. Rev.*, **77**, 789 (1950)]. [d] Average of a single determination on the dihydropyran and two determinations on the precursor 5-hexenol-^{18}O (**3**). [e] Corrected for dilution by unlabeled dihydropyran with the help of the radioactivity measures; *i.e.*, 0.55 × 0.40/0.50 = 0.44. [f] The decrease in total activity is the result of flushing the reaction tube with unlabeled dihydropyran.

The intervention of trace amounts of tetrahydropyran in a carbon-scrambling mechanism involving intermolecular oxidation–reduction as in **5** $\rightleftarrows$ **6** was considered, but could be rejected by experiment. First, conditions were established producing close to complete scrambling (89%) when Δ^2-dihydropyran-6-^{14}C mixed with a small amount of unlabeled tetrahydrofuran was passed over hot alumina. Then, a mixture of dihydropyran at a low molar activity with tetrahydropyran at a high level of activity was exposed to the very same conditions. Little change in molar activity in either the dihydropyran or the tetrahydropyran was found (Table II). On this basis, the possibility that tetrahydropyran participates in the scrambling process in any important way could be dismissed.



5 **6**

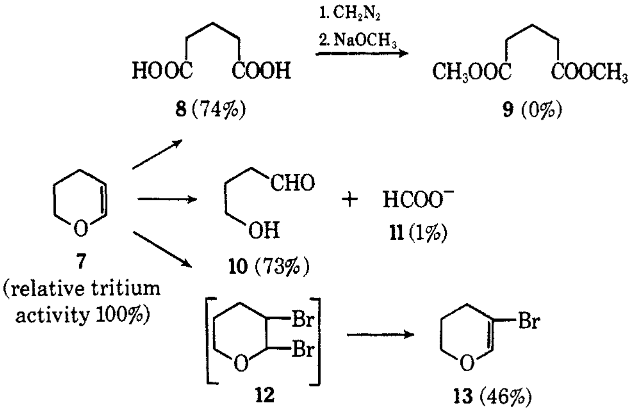
TABLE II

MIXED DIHYDROPYRAN AND TETRAHYDROPYRAN BEFORE AND AFTER EXPOSURE TO HOT ALUMINA

		Activity[b] after exposure		
Component of the mixture[a]	Activity[b] before exposure	Calcd[e] for **5** $\rightleftarrows$ **6** interconversion	Calcd for no **5** $\rightleftarrows$ **6** interconversion	Obsd
Dihydropyran	27[c]	120	21[f]	20[c]
Tetrahydropyran	1800[d]	150	1800	1700[d]

[a] The starting mixture was 93 parts dihydropyran and 7 parts tetrahydropyran. [b] Microcurie per mole. [c] Direct measure by means of a solid derivative. [d] Difference between measured activity of the mixture of dihydro- and tetrahydropyran and measured activity of dihydropyran. [e] Calculated on the basis of 89% scrambling and by taking into account dilution with unlabeled sweep dihydropyran. [f] Original dihydropyran activity corrected for dilution with unlabeled sweep dihydropyran.

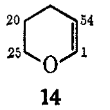
When a mixture of unlabeled dihydropyran and water-^{3}H was passed over hot alumina, the emergent dihydropyran (**7**) contained tritium. The alumina packing was necessary; no tritium was introduced when the alumina was replaced with glass wool. Degradation showed that most, if not all, of the activity resided at the dihydropyran 3 and 5 positions. Thus, oxidation of the tritiated material **7** gave radioactive glutaric acid (**8**) which, in the form of its methyl ester **9**, could be washed free of activity by base-catalyzed hydrogen exchange.[6] Since there is no reason to expect base-catalyzed exchange at the glutaric β position, the site of activity is restricted to the α positions. Accordingly, at least three-quarters of the tritium in the treated dihydropyran (**7**) must be at the 3 and 5 positions and none of the tritium can be at the 4 position. This result is consistent with the radioactivity of the ozonolysis product, 4-hydroxybutanal (**10**), which retained 73% of the activity of the precursor dihydropyran (**7**). The ozonolysis procedure also isolated the lone hydrogen originally at the dihydropyran 2 position in the form of the hydrogen in formate ion (**11**). The minor activity in the formate suggests only a minor incorporation of tritium in the dihydropyran 2 position. Finally, when the hydrogen on the dihydropyran 3 position was removed entirely by adding bromine to form 2,3-dibromotetrahydropyran (**12**) and then dehydrobrominating with N,N-diethylaniline to form 3-bromo-Δ^2-dihydropyran (**13**),[7] more than half the radioactivity was lost, a result that as discussed below is still consistent with the other findings.



Discussion

Before proposing a pathway for the isotope migrations, an acceptable tritium distribution must be arrived at.

Qualitatively, the experiments show that most of the tritium exchange occurs at the dihydropyran 3 and 5 positions. Quantitatively, however, more than one tritium distribution—for example, **14**, **15**, or **16**—can accommodate the data. On the basis of the following arguments, we prefer distribution **16**. If the distribution is that shown in **14**, two conditions must hold. First, no loss of tritium from the 3 and 5 positions of dihydropyran **7** can be tolerated at any stage in its con-



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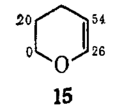

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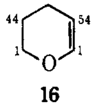

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[6] *Cf.* W. G. Brown and K. Eberly, *J. Amer. Chem. Soc.*, **62**, 113 (1940); J. G. Atkinson, J. J. Csakvary, G. T. Herbert, and R. S. Stuart, *ibid.*, **90**, 498 (1968).

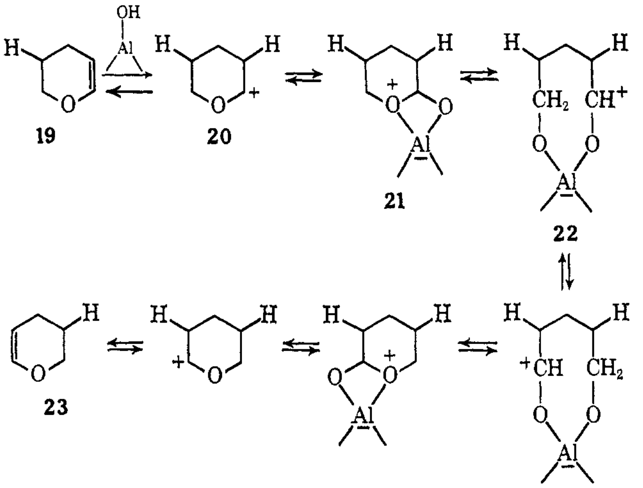
[7] R. Paul, *Bull. Soc. Chim. Fr.*, [5] **1**, 1397 (1934).

version into glutaric acid **8**. In this connection, there is no firm *a priori* basis under the conditions employed on which to predict exchange or the lack of it from these positions. Either result would be both possible and acceptable. Second, much tritium has to be removed from the aldehydic hydrogen position of the ozonolysis product, 4-hydroxybutanal (**10**). Although exchange of tritium at the aldehydic position is not expected, it could occur during formation of the thiosemicarbazone, the derivative in which form the 4-hydroxybutanal was actually counted. Operation of the azo-hydrazone tautomerism **17** $\rightleftarrows$ **18** could provide

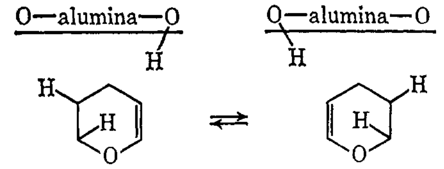
$$\underset{\textbf{17}}{RCH{=}NNHCSNH_2} \rightleftarrows \underset{\textbf{18}}{RCH_2N{=}NCSNH_2}$$

the avenue for exchange.[8] Accordingly, both conditions for **14** could be satisfied. Nevertheless, we can suggest no straightforward way of inserting tritium at the 6 position of **14**, and on this basis alone we do not favor this distribution. If **15** is correct, tritium must be lost from what was the dihydropyran 2 position either during the ozonolysis to formate ion **11** or in the processing leading to its isolation as zinc formate. Since this kind of loss has no analogy[9] and since the appearance of tritium at positions 2, 3, and 5 but *not* at position 6 is hard to explain, we also tend not to favor **15**. If the distribution is given by **16**, tritium must be lost not only from 4-hydroxybutanal (*cf.* **17** and **18**) but also during formation of the glutaric acid **8**. As indicated above, this latter loss could not be anticipated; yet, if it does occur, it can be accounted for plausibly by involving methylene groups next to the carbonyl function at intermediate aldehydic, lactonic, or anhydride stages on the way to glutaric acid. Accordingly, we have provisionally accepted distribution **16** for the tritiated dihydropyran **7**.

A sequence of events may now be written to account for the isotope results. Adsorbed dihydropyran **19** accepts a proton from alumina at the 3 position. This, as the β carbon of a vinyl ether, would be the favored site for electrophilic attack.[10] Bonding can now occur between the charged carbon in **20** and oxygen from alumina. The four-membered aluminum heterocycle shown in **21** is a convenient way to account for the next stage, which cleaves the original dihydropyran 1–2 bond and places a positive charge at the 2 position, as in **22**. This kind of intermediate is familiar in connection with Meerwein–Ponndorf–Verley (MPV) equilibrations.[11] An MPV intramolecular transannular hydride shift[12] now places the positive charge on the other side of the ring. Reversal of the entire process would eventually regenerate dihydropyran **23**. However, this dihydropyran would have the radioactive carbon, originally at position 6, now at position 2, would have a different oxygen atom at position 1, and would have hydrogen from the alumina at its position 5 but not at position 2, 4, or 6. Repetition of the sequence starting with **23** would insert hydrogen from the alumina on both the 3 and 5 positions.



Thus, this scheme accounts for the several isotopic changes. A completely analogous process may also be written to explain the behavior observed with alkyl- and aryl-substituted dihydropyrans.[13] However, it may not be the whole story, since the results of further work with dihydropyran indicates that carbon scrambling occurs at least in part by a mechanism that does not exchange oxygen.[14] The involvement of tetrahydropyran (*cf.* **5** $\rightleftarrows$ **6**), which would provide such a pathway, has already been excluded. Formulation **24**



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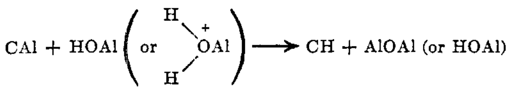
[8] Related processes may be seen in the azo–hydrazone conversions reported by A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 3528 (1965), and earlier references therein, H. C. Yao, *J. Org. Chem.*, **29**, 2959 (1964), H. C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, **84**, 3514 (1962), and T. W. Milligan and B. C. Minor, *J. Org. Chem.*, **27**, 4663 (1962), as well as in the Wolff–Kishner reduction mechanism studied by H. H. Szmant, H. F. Harnsberger, T. J. Butler, and W. P. Barie, *J. Amer. Chem. Soc.*, **74**, 2724 (1952), and D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *ibid.*, **84**, 1734 (1962). Although all evidence points to the hydrazone as the thermodynamically stable form, this does not mean that the reaction from left to right is negligibly show.

[9] J. C. Powers, R. Seidner, T. G. Parsons, and H. J. Berwin, *J. Org. Chem.*, **31**, 2623 (1966), have unsuccessfully sought evidence for formation of carbanion ROOC$^-$ from formate esters exposed to proton extractors such as sodium methoxide and sodium hydride. If, as is likely, a formate ester is formed in the ozonolysis, the aqueous, mildly alkaline conditions would probably saponify the formate before removing its hydrogen. Formate anion appears to resist exchange; thus F. K. Münzberg and W. Oberst, *Chem. Abstr.*, **30**, 2549 (1936) [*Z. Physik. Chem.* (Leipzig), **B31**, 18 (1935)], have to use 0.1 *N* sodium hydroxide solution at 100° to effect some exchange. No exchange occurs in neutral solution.

[10] Attack at the dihydropyran 3 position by surface alumina acting as a Lewis acid so that a C–Al bond forms is also admissable. If this kind of organometallic bond is involved, it would have to be cleaved at some stage by a process the essence of which can be written as



$$CAl + HOAl \left(\text{or } H_2\overset{+}{O}Al \right) \longrightarrow CH + AlOAl \text{ (or HOAl)}$$

Although the Lewis acid nature of alumina may be preferred, we have no evidence from the present work bearing on this point. At least for the time being, we will stick to the simpler Brønsted acid formulation. The surface groups of alumina as well as its action as a catalyst has been discussed recently by H. P. Boehm and by H. Pines and J. Manassen [*Advan. Catal.*, **16**, 52, 254 (1966)].

[11] *Cf.* W. N. Moulton, R. E. Van Atta, and R. R. Ruch, *J. Org. Chem.*, **26**, 290 (1961), where pertinent references are given. Also note V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963).

[12] Transannular hydride shifts across an eight-membered ring are known; *cf.* A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.*, **20**, 119 (1966). V. Prelog and W. King [*Helv. Chim. Acta*, **39**, 1394 (1956)] also have observed 1,6-hydride shifts in cyclodecanes.

[13] (a) W. J. Gensler, I. Ruks, and S. Marburg, *Chem. Commun.*, 782 (1966); (b) G. Descotes, B. Giroud-Abel, and J.-C. Martin, *Bull. Soc. Chim. Fr.*, 2472 (1967); G. Descotes and A. Laily, *ibid.*, 2989 (1967).

[14] *Cf.* S. H. Stein, Doctoral Dissertation, Boston University, 1967. The material is this dissertation is being prepared for publication and will be submitted shortly.

and **25**, showing intramolecular hydride transfer across the intact six-membered ring,[15] is suggested as a possibility for the supplementary pathway.[14]

Experimental Section

General.—Melting points were taken in open capillaries with an apparatus calibrated against standard compounds. Boiling points are uncorrected. Gas-liquid partition chromatography made use of ionization detection with argon as the carrier gas. The 6-ft column operating at 50° was packed with 10% silicone rubber on 60–80 mesh diatomaceous earth (10% SE-30 on Chromosorb). Tritium radioactivity was determined by New England Nuclear Corp., Boston, Mass., as well as in our own laboratories by scintillation counting. Carbon-14 activity reported as "relative molar activity" was determined according to the procedure of Schwebel, Isbell, and Moyer;[16] carbon-14 activity reported in curies was determined by scintillation counting. Oxygen-18 abundance was determined at the Technology Center, Illinois Institute of Technology, Chicago, Ill., by a procedure calling for preliminary conversion of organic oxygen to carbon dioxide in a heat treatment with mercuric chloride.[17] We are indebted to Professor M. L. Bender for his kindness in arranging for these analyses. Those elemental analyses reported to the tenths place were performed by Carol K. Fitz, Needham Heights, Mass. The others were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark, and by Galbraith Laboratories, Inc., Knoxville, Tenn. Uncertainties are expressed throughout as standard deviations.

Alumina Characteristics.—The same lot of Alcoa activated alumina (Grade F-1, 8–14 mesh) was used here as in the earlier work.[2,3] This alumina, with a BET surface of about 220 m^2/g,[18] shows the following characteristics.

When 1.0 g of the Alcoa alumina is swirled with 10 ml of water for 5 min, the mixture becomes slightly basic (pH 9.2). For comparison, Fisher Scientific Co. alumina treated the same way brought the pH to 8.0, and Matheson Coleman and Bell alumina brought the pH to 9.9. Classified according to the Brockmann scheme,[19] Alcoa alumina falls into grade III (retains 1-phenylazo-2-hydroxynaphthalene and 1-[*p*-(phenylazo)phenylazo]-2-hydroxynaphthalene but not 4-methoxyazobenzene), whereas the Fisher and the MCB aluminas fall into grade II (retain 4-methoxyazobenzene and 1-phenylazo-2-hydroxynaphthalene but not azobenzene).

The Alcoa alumina loses weight on heating. Thus when 8.0 g of alumina was heated for 3 hr at 350° in a slow current of nitrogen, the weight decreased by 8.0%. The carbon and hydrogen content also decreased (*Anal.* Found for alumina before heating: C, 0.22; H, 1.60. Found for alumina after heating: C, 0.12; H, 0.84). If carbon is lost as carbon dioxide and hydrogen as water, the weight loss may be calculated to be 0.4% for carbon dioxide and 7.2% for water.

Exposure to dihydropyran changes hot alumina from dull white to dark gray. The same change was noted when 2-methyl- or 6-methyldihydropyran is taken instead of dihydropyran.[13a] Measurements with the methylated compounds showed that the alumina catalyst always retained material from the organic substrate, with weight increases ranging from 10 to 15%. In one run, the alumina was analyzed (*Anal.* Found: C, 7.5; H, 1.43). Thus, decomposition products are formed that are retained at temperatures as high as 350°. The same behavior is almost certainly true of the unsubstituted dihydropyran.

Paraformaldehyde-^{18}O.—A mixture of 6.0 g of paraformaldehyde (equivalent to 0.20 mol of formaldehyde) and 36 g of water containing 1.86 atom % of oxygen-18 was boiled under a reflux condenser for 3 hr. An atmosphere of pure nitrogen was maintained over the boiling mixture and, as far as possible, thereafter. The mixture at 15° was filtered through a fine sintered-glass disk, and volatile material was removed by distilling the filtrate at 18–22° (5 mm). The white compact residue was held under vacuum for 1 hr after distillation had stopped and then, over a period of 1 day, was dried to constant weight in a vacuum desiccator over phosphorus pentoxide. The yield of paraformaldehyde-^{18}O was 5.3 g (88%); the recovery of water, containing traces of formaldehyde, was 34.5 g (96%).

If the paraformaldehyde solution is distilled at 100° under atmospheric pressure, all of the organic material passes over with the distillate. Use of paraformaldehyde that beforehand has been dissolved in and recovered from ordinary water offers some advantage, in that the time required for solution in the labeled water is shorter and the exchange of oxygen closer to completion.[20] Evidently, the preliminary treatment provides paraformaldehyde of a shorter mean molecular weight, which material depolymerizes more readily to the monomeric exchanging form.

5-Hexenol-^{18}O (3).—5-Bromo-1-pentene (**2**) was prepared by allowing 4-pentenol to react with phosphorus tribromide in pyridine.[2,5] Adding an equal volume of dry ether permitted easier stirring of the reaction mixture. The crude product can be isolated by distillation directly from the reaction mixture. However, caution is necessary since, when white fumes are seen in the condenser especially at the end of the distillation, any escaping vapors ignite spontaneously. Redistilled 5-bromo-1-pentene, bp 126–128°, n^{25}D 1.4600, was obtained by this method in 1-mol runs in 73% yield.

The published directions[21] calling for excess formaldehyde in the synthesis of 5-hexenol had to be modified. A solution of 5-bromo-1-pentene (30 g, 0.20 mol) in 200 ml of dry ether was dropped onto stirred magnesium turnings (4.9 g, 0.20 g-atom) at a rate such that a gentle reflux was maintained. Pure nitrogen blanketted the reaction mixture. After the addition, the Grignard solution was boiled for an extra 0.5 hr. The nitrogen flow was interrupted, and dry labeled paraformaldehyde (5.0 g, 0.17 mol) was depolymerized by heating at 160–170° in an apparatus that allowed the gaseous monomer to be discharged into the reaction flask just above the surface of the stirred mixture. To prevent repolymerization, the monomer gas was kept heated (160–170°) until almost to the point at which it entered the ether. The addition required 1 hr, after which time the mixture was boiled for 0.5 hr.

The reaction mixture was carefully added to a stirred mixture of ice (*ca.* 250 g) and 7.5 ml of concentrated sulfuric acid. The lower aqueous layer was extracted twice with ether. The combined ether solutions were dried with magnesium sulfate and concentrated, and the residual oil was distilled through a short column. 5-Hexenol-^{18}O (**3**), bp 156–158°, n^{25}D 1.4322, was obtained in 78% yield (13 g) based on paraformaldehyde. In two runs, the oxygen-18 content was shown to be 0.702 and 0.770 atom %, respectively.

Δ^2-Dihydropyran-^{18}O-6-^{14}C (4).—A mixture of 5-hexenol-^{18}O (12.9 g) and 5-hexenol-1-^{14}C[2] (*ca.* 0.35 g) was distilled through a short column. The fraction (12.3 g), boiling at 156.5–158° with n^{25}D 1.4322, was dissolved in 70 ml of purified methylene chloride and ozonized essentially as described before.[2] Effective collection of the ozonolysis product, 2-hydroxytetrahydropyran, from the aqueous mixture required at least 2 days of continuous extraction. Ozonolysis yields are estimated at 60–70%; the dehydration step gave product in an estimated yield of 60%. Redistilled,

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(15) *Cf.* J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **76**, 4501 (1954); W. F. Erman, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 49Q; J. A. Berson and P. W. Grubb, *ibid.*, **87**, 4016 (1965); N. L. Wendler, R. P. Graber, and F. W. Bollinger, *Chem. Ind.* (London), 1312 (1965). Other references to intramolecular 1,3-hydride shifts are given by B. Capon and C. W. Rees, *Ann. Rept.*, **59**, 216 (1962), as well as by W. A. Ayer and K. Piers, *Chem. Commun.*, 541 (1965), and H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965). Interestingly, the atisine–isoatisine interconversion involves a related six-membered, N-heterocyclic oxidation–reduction and could proceed by intramolecular transannular hydride shift instead of by intermolecular prototropy [*cf.* S. W. Pelletier, *Experientia*, **20**, 1 (1964); S. W. Pelletier, K. Kawazu, and K. W. Gopinath, *J. Amer. Chem. Soc.*, **87**, 5229 (1965)]. We do not believe that the deuterium-exchange studies of N. J. Leonard, K. Conrow, and R. R. Sauers [*ibid.*, **80**, 5185 (1958)] establish the prototropic nature of this kind of rearrangement.

(16) A. Schwebel, H. S. Isbell, and J. D. Moyer, *J. Res. Natl. Bur. Std.*, **53**, 221 (1954); also *cf.* ref 2 as well as W. J. Gensler and W. R. Koehler, *J. Org. Chem.*, **27**, 2754 (1962).

(17) D. Rittenberg and L. Ponticorvo, *Intern. J. Appl. Radiation Isotopes*, **1**, 208 (1956).

(18) A. S. Russell and C. N. Cochran, *Ind. Eng. Chem.*, **42**, 1332 (1950).

(19) C. H. Giles in "Chromatography," E. Heftmann, Ed., Reinhold Publishing Corp., New York, N. Y., 1961, p 34; H. Brockmann and H. Schodder, *Chem. Ber.*, **74**, 73 (1941).

(20) S. H. Walinou, Department of Chemistry, Boston University, unpublished results.

(21) A. Juwala, *Chem. Ber.*, **63**, 1993 (1930); R. E. Lyle, E. J. DeWitt, and I. C. Pattison, *J. Org. Chem.*, **21**, 61 (1956).

doubly labeled dihydropyran 4 (bp 84–85°; $n^{25}\mathrm{D}$ 1.4378) was obtained in this way in 44% yield from 5-hexenol.[22]

Anal. Calcd for C_5H_8O: C, 71.39; H, 9.58. Found: C, 71.2; H, 9.7; ^{18}O, 0.775 atom %.

A thiosemicarbazone was prepared from the hydrolyzed dihydropyran (0.2 ml in aqueous sulfuric acid) essentially according to published directions.[23] Two crystallizations of the crude product (0.34 g; mp 123–126°) from aqueous alcohol (1:1) and one crystallization from methanol–ethyl acetate (1:5) afforded 0.29 g of white aggregates of 5-hydroxypentanal thiosemicarbazone. The melting point, 128.5–129.5°, did not change on further crystallizations.

Anal. Calcd for $C_6H_{13}N_3OS$: C, 41.10; H, 7.48; N, 23.98. Found: C, 41.0; H, 7.4; N, 23.8; relative molar activity,[2,16] 0.504, 0.506.

After an additional recrystallization this derivative showed relative molar activity of 0.503, 0.504 (average, 0.504 ± 0.001).

Attempts made to measure the oxygen-18 content of the solid derivative by an alternative procedure[24] failed. The carbon dioxide that had been equilibrated with the thiosemicarbazone oxygen according to the published directions gave a mass 46 peak that was unreasonably high.[25]

Δ^2-Dihydropyran-^{18}O-6-^{14}C (4) over Hot Alumina.—The procedure was essentially the same as described before,[2,26] use being made of the same apparatus ($^3/_8$-in. reaction tube) with essentially the same alumina pretreatment. The receivers were cooled with liquid nitrogen. The temperature of the catalyst, with the exception of the end zones (*ca.* 335°), was 345–357°.

Freshly distilled, doubly labeled dihydropyran 4 (3.6 g) was added dropwise to the reaction tube over a period of 11 min. A very slow stream of nitrogen aided the passage. As soon as all of the labeled material had been added, 0.92 g of unlabeled dihydropyran was put through as a chaser. The one-phase green liquid in the first trap (no condensate in the second trap) was dried for 2 hr with a small amount of calcium hydride and then with a few granules of lithium aluminum hydride. Two distillations of the product from lithium aluminum hydride through a short column furnished 2.85 g (63% recovery) of dihydropyran: bp 83–85°; $n^{25}\mathrm{D}$ 1.4379.

Anal. Calcd for C_5H_8O: C, 71.39; H, 9.58. Found: C, 71.2; H, 9.2; ^{18}O, 0.439, 0.415 atom %.

The derived thiosemicarbazone, mp 128.5–129.5°, showed relative molar activity of 0.405, 0.402. Recrystallization and reassay gave relative molar activity of 0.405, 0.403 (average, 0.404 ± 0.001).

Degradation of Alumina-Treated Dihydropyran-^{18}O-^{14}C.—Ozonolysis of the doubly labeled dihydropyran was performed practically the same way as described before.[2,26] The derived 4-hydroxybutanal was converted into its 2,4-dinitrophenylhydrazone, which after two crystallizations from 50% aqueous methanol gave tiny needles, mp 115.5–116.5°. Another crystallization did not change the melting point. The measured relative molar activity at this point was 0.206. Crystallization from anhydrous methanol gave shiny yellow plates, with relative molar activity of 0.202, 0.207 (average, 0.205 ± 0.002).

Zinc formate from the ozonolysis was recrystallized three times.

Anal. Calcd for $Zn(CHOO)_2 \cdot 2H_2O$: C, 12.55; H, 3.16; Zn, 34.15. Found: C, 12.6; H, 3.2; Zn, 34.1; $^1/_2$(relative molar activity), 0.191.

A further crystallization afforded zinc formate with $^1/_2$(relative molar activity), 0.195, 0.187. The average was 0.191 ± 0.001.

Tetrahydropyran-2-^{14}C.—The starting point was a sample of 5-hexenol-1-^{14}C diluted with the unlabeled alcohol. The mixture gave a single spot on a thin layer chromatogram consisting of a 0.1-mm layer of silica gel bound with polyvinyl alcohol and developed with ethyl acetate. The labeled alcohol (1.5 g) was ozonized essentially as before.[2] Subjecting the aqueous solution to continuous ether extraction for 60 hr ensured removal of all the desired 2-hydroxytetrahydropyran. The dihydropyran-6-^{14}C, obtained by dehydrating this material, was put through an extra distillation step. On gas–liquid partition chromatography, the water-white product showed one peak at 3.70 min; a slight perturbation of the base line at 4.33 min could correspond to the presence of some tetrahydropyran. The infrared spectrum, taken with neat liquid, was identical with that of authentic dihydropyran.

Δ^2-Dihydropyran-6-^{14}C (0.20 ml with *ca.* 8 mCi/mol) diluted with unlabeled dihydropyran (0.60 ml) and 50 ml of ether was shaken under 50 psi of hydrogen for 0.5 hr in the presence of a one-half teaspoonful of W-5 Raney nickel.[27] The catalyst and ether were removed. Some peroxide-free unlabeled tetrahydropyran used for rinsing to minimize manipulation losses was combined with the hydrogenation product, and the liquid was purified by a bulb-to-bulb transfer at 0.2 mm. The clear colorless distillate (*ca.* 0.20 ml; estimated activity, 0.5 mCi/mol) gave a single gas–liquid partition chromatographic peak at 4.33 min, indistinguishable from that of tetrahydropyran. This labeled tetrahydropyran, as shown below, must be contaminated with some residual labeled dihydropyran. However the upper limit by gas–liquid partition chromatography may be estimated at less than 5% and by calculations based on radioactivity results at less than 1%. In a practice experiment on a slightly larger scale, dihydropyran was converted into tetrahydropyran, bp 87–88° and $n^{25}\mathrm{D}$ 1.4198, with an infrared absorption spectrum devoid of double-bond absorption at 1650 cm^{-1} and identical with the spectrum of authentic tetrahydropyran.

Δ^2-Dihydropyran-6-^{14}C- plus Unlabeled Tetrahydropyran over Hot Alumina.—Tetrahydropyran was freed of peroxide according to the method of Vogel,[28] and a mixture of this material (0.75 ml), radioactive dihydropyran (0.30 ml), and unlabeled dihydropyran (9.70 ml) was prepared. The catalyst tube was packed with 12 g of alumina to a length of 19 in. The tube used here had a smaller inner diameter (6 mm) than the one used before ($^3/_8$ in.). The tube was mounted in a 56-cm furnace tilted about 15° from the horizontal. Slow, steady injection of material at the elevated end of the tube was accomplished with the help of a syringe fitted with a motor-driven plunger.[14] After a preheating period at 280°, 2.95 g of a mixture made up of 3.00 ml of dihydropyran plus 0.23 ml of peroxide-free tetrahydropyran, both unlabeled, was passed through the tube at 335–340°. The emergent material was discarded. Nitrogen was used as a carrier gas during this pretreatment and thereafter. After sweeping for 10 min with nitrogen, 3.03 g of the above radioactive mixture was injected into the tube at 341–345° at a rate of 0.4 g/min. Five minutes after completion of the addition, the collected material was brought to room temperature and reinjected; this process was repeated for a total of four times. Finally, the tube was flushed with 0.46 g of unlabeled dihydropyran, which was collected with the emergent mixture from the last pass. The green, foul-smelling condensate was purified by a bulb-to-bulb distillation at 0.75 mm to give a faintly yellow liquid (2.55 g) overlying a colorless droplet. The droplet was removed with a capillary pipet and the remainder of the product swirled with a small amount of sodium sulfate. Gas–liquid partition chromatography showed a peak at 3.70 min, corresponding to dihydropyran, and a smaller peak at 4.33 min, corresponding to tetrahydropyran.

Thiosemicarbazones were prepared from the dihydropyran in the mixture of dihydropyran and tetrahydropyran both before and after its passage over alumina.

The derivative from the material before contact with alumina was recrystallized twice from aqueous ethanol (1:1), twice from aqueous methanol (1:1), and twice from methanol–ethyl acetate (1:5) to give white 5-hydroxypentanal thiosemicarbazone, mp 128–129°. The radioactivity was measured at 0.26 and 0.25 mCi/mol before, and 0.24 and 0.24 mCi/mol after, an additional crystallization from methanol–ethyl acetate. The average

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[22] In an alternate method, 5-hexenol was cleaved by treating 13.4 g (0.134 mol) of the alcohol in 300 ml of ether plus 300 ml of water with 60.5 g (0.28 mol) of sodium metaperiodate ($NaIO_4$) in the presence of 0.14 g of osmium tetroxide [*cf.* F. F. Caserio, Jr., and J. D. Roberts, *J. Amer. Chem. Soc.*, **80**, 5837 (1958); R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956)]. Dehydration of the resulting 2-hydroxytetrahydropyran afforded redistilled Δ^2-dihydropyran in 45% over-all yield.

[23] *Cf.* N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p 393.

[24] H. Dahn, H. Moll, and R. Menassé, *Helv. Chim. Acta*, **42**, 1225 (1959).

[25] The contribution of CH_2S or SN fragments could be the complicating factor here. We are greatly indebted to Professor K. Biemann, Massachusetts Institute of Technology, for determining the mass spectra of these carbon dioxide samples.

[26] W. J. Gensler and G. L. McLeod, *J. Org. Chem.*, **28**, 3194 (1963).

[27] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, **70**, 695 (1948); D. W. Andrus and J. R. Johnson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 794.

[28] A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1954.

activity of the dihydropyran before contact with hot alumina was, therefore, 0.25 ± 0.01 mCi/mol.

The same derivative from the mixture after contact with alumina showed a radioactivity of 0.21 and 0.21 mCi/mol before, and 0.21 and 0.21 mCi/mol after, a final crystallization. The average activity of the dihydropyran after contact with hot alumina was, therefore, 0.21 ± 0.01 mCi/mol.

Control experiments showed that conditions that produced the thiosemicarbazone of 5-hydroxypentanal either from pure dihydropyran or from a mixture of dihydropyran and tetrahydropyran gave no derivative with tetrahydropyran alone.

Ozonolysis of the dihydropyran–tetrahydropyran mixture that had been passed over hot alumina was performed as before.[2,26] However, instead of continuous extraction of the 4-hydroxybutanal, it was extracted with six 100-ml portions of methylene chloride followed by two 100-ml portions of ether. The derived thiosemicarbazone was recrystallized twice from aqueous ethanol (1:1), once from aqueous methanol (1:1), and twice from methanol–ethyl acetate (1:5). Assay of the white crystals showed a radioactivity of 0.11 and 0.12 mCi/mol before, and 0.11 and 0.12 mCi/mol after, an additional crystallization. The average activity of the 4-hydroxybutanal thiosemicarbazone was, therefore, 0.12 ± 0.01 mCi/mol.

From these figures, 44.5% of the activity in the dihydropyran after treatment resided at its 2 position, or in other words scrambling had occurred to an extent of 89% of the equilibrium value.

Dihydropyran plus Tetrahydropyran-2-^{14}C over Hot Alumina.—Radioactive tetrahydropyran, diluted with a little unlabeled material (total tetrahydropyran, 0.225 ml), was mixed with pure unlabeled dihydropyran (3.00 ml). Duplicate radioactivity determinations indicated the presence of 0.15 ± 0.01 mCi/mol of mixture. A small sample of the mixture was hydrated and converted into 5-hydroxypentanal thiosemicarbazone, which was recrystallized seven times (mp 128–129°). After counting, this material was recrystallized and recounted, and then was recrystallized and counted once more. The three sets of duplicate assays gave the following results: 0.027, 0.027; 0.027, 0.027; 0.026, 0.027 mCi/mol (average, 0.027 ± 0.001 mCi/mol). From this result, the radioactive tetrahydropyran used here must have been slightly contaminated with radioactive dihydropyran.

The above mixture (2.30 g) of tetrahydropyran and dihydropyran was passed over hot alumina in a manner practically the same as that described directly above. The material injected for the fourth pass weighed 1.65 g. Some unlabeled dihydropyran (0.46 g) used at this point to flush the tube was collected with the final mixture, which weighed 2.00 g. Bulb-to-bulb distillation at 0.075 mm afforded 1.90 g of an almost colorless liquid, which was treated as before. Gas–liquid partition chromatography showed only the two expected peaks at 3.70 (dihydropyran) and 4.33 min (tetrahydropyran). This mixture, according to duplicate determinations, was radioactive to an extent of 0.11 ± 0.01 mCi/mol. The pure thiosemicarbazone of 5-hydroxypentanal derived from the dihydropyran in this mixture was counted three times, with recrystallization between each count. The duplicate results are as follows: 0.020, 0.020; 0.020, 0.021; 0.020, 0.020 mCi/mol. The emergent dihydropyran, therefore, had an activity of 0.020 ± 0.001 mCi/mol.

The measured tetrahydropyran activities in the mixtures (see Table II) were found by making use of the following expression.

$$
\begin{aligned}
&[\text{measured molar activity of mixture}] = \\
&\quad [\text{mol fraction of dihydropyran}] \times \\
&\quad [\text{measured activity of dihydropyran}] + \\
&\quad [\text{mol fraction of tetrahydropyran}] \times \\
&\quad [\text{activity of tetrahydropyran}]
\end{aligned}
$$

The calculated values for the molar activities of dihydropyran and tetrahydropyran given in Table II for involvement of tetrahydropyran according to **5** ⇄ **6** assumes a uniform distribution of activity between the dihydropyran and the tetrahydropyran molecules. This is reasonable, since with a 93:7 dihydropyran–tetrahydropyran ratio in the mixture and with scrambling observed to an extent of 89%, the tetrahydropyran molecules must have turned over with dihydropyran an average of 10–11 times at least. If activity is evenly distributed, the following expressions hold.

$$
\begin{aligned}
&[\text{calculated molar activity of treated dihydropyran}] = \\
&\quad \{[1 - 0.93(7/93)][\text{original activity of dihydropyran}] + \\
&\quad [0.93(7/93)][\text{original activity of tetrahydropyran}]\} \times \\
&\quad [\text{dihydropyran dilution factor}]
\end{aligned}
$$

$$
\begin{aligned}
&[\text{calculated molar activity of treated tetrahydropyran}] = \\
&\quad (0.93)[\text{original activity of dihydropyran}] + \\
&\quad (1 - 0.93)[\text{original activity of tetrahydropyran}]
\end{aligned}
$$

These calculations also assume that the ratio of tetrahydropyran to dihydropyran remains the same before and after the alumina treatment. To check this point, gas–liquid partition chromatography was applied in a practice experiment. Based on symmetrical peak heights, the ratio before exposure to alumina was 0.104 ± 0.004 and after exposure was 0.105 ± 0.004. Accordingly, there is no preferential destruction of either component over hot alumina, and the assumption is justified.

Tritiation and Carbon Scrambling of Δ^2-Dihydropyran over Hot Glass Wool.—The tritiation experiment made use of a $^3/_8$-in. reaction tube in the apparatus described before.[2,26] Pyrex glass wool was soaked for 6 hr in 20% aqueous acetic acid, then washed for 3 hr with running tap water, and finally rinsed several times with distilled water. The glass wool packed in the reaction tube was dried for 12 hr at 110° and then for 12 hr at 350° in a slow current of nitrogen. Pure dihydropyran (12.6 g, 0.15 mol) and tritiated water (13.5 ml; 1.53 mCi/ml) were added slowly and simultaneously to the 350° glass wool. The addition required about an hour. A slow stream of nitrogen was maintained during and for 10 min after the addition. The organic layer in the emergent mixture was washed with five 15-ml portions of cold water and then dried over calcium hydride. Two distillations over lithium aluminum hydride furnished 7.6 g of recovered dihydropyran (n^{25}D 1.4382) that showed no counts above background.

For the carbon-scrambling experiment, a mixture of Δ^2-dihydropyran-6-^{14}C (93%) and unlabeled tetrahydropyran (7%) was prepared. A small portion was reserved for conversion to 5-hydroxypentanal thiosemicarbazone. The remainder (2.12 g) was injected into the reaction tube (6-mm i.d.) from a motor driven syringe at a rate of 0.38 g/min. The tube, maintained at 338–347°, was packed with glass wool to a length of 30 cm and was swept as usual with a slow stream of nitrogen (1 bubble/sec). The emergent material was recycled until a total of five passes had been completed. The final product (1.63 g or 77% recovery) was homogeneous, though slightly yellow.

The product (1.58 g) in solution with 70 ml of methylene chloride, freshly distilled from calcium hydride, was ozonized and treated as described before for isolation of 4-hydroxybutanal and conversion to its thiosemicarbazone. Several crystallizations gave the derivative in the form of white, shining crystals, melting constantly at 116–117.5°. The derivative showed a radioactivity of 0.36 and 0.38 mCi/mol; after an additional recrystallization from methanol–ethyl acetate (1:5), the values were 0.35 and 0.38 mCi/mol. The average was 0.37 ± 0.01 mCi/mol.

The thiosemicarbazone of 5-hydroxypentanal derived from the Δ^2-dihydropyran-6-^{14}C in the starting mixture melted at 128–129.5° after several recrystallizations. Assay showed a radioactivity of 0.36 and 0.35 mCi/mol and, after an additional crystallization, of 0.36 and 0.36 mCi/mol; the average was 0.36 ± 0.01 mCi/mol.

Dihydropyran and Tritiated Water over Alumina.—A slow current of nitrogen was passed through a fresh charge of alumina (38 g) at 350° that had been pretreated as usual. At the same time 6.5 ml of water containing about 35 mCi of tritium was added at a rate of 1 drop every 6 sec. After all the water had been added and the hot tube had been swept with nitrogen for 15 min, dihydropyran (10 g, 0.12 mol) and water (3.5 g, 0.19 mol) containing *ca.* 18 mCi of tritium were added simultaneously at an approximate drop ratio of 3:1. After the addition (*ca.* 0.5 hr), the hot tube was swept with nitrogen for 20 min. The upper organic layer in the receiver was shaken with two 5-ml portions of ice–water and then dried over calcium hydride. Two distillations over a few granules of lithium aluminum hydride yielded 6.7 g of recovered dihydropyran, n^{25}D 1.4381. Scintillation counting indicated an activity of 0.745 and a duplicate of 0.730 mCi/ml.

The tritiated dihydropyran (6.35 g), mixed with 34.71 g of pure unlabeled dihydropyran, was washed three times with small portions of ice–water, dried over calcium hydride, and distilled from lithium aluminum hydride. The main fraction, bp 85–86°, n^{25}D 1.4380, weighed 34 g and showed an activity of 0.116 mCi/ml. This value taken with the values calculated (0.115, 0.113) with the help of the appropriate dilution factor gave an average activity of 0.115 mCi/ml or 10.6 mCi/mol.

The procedure for preparing a thiosemicarbazone derivative was similar to that given before with the oxygen-18 labeled material except that the reaction was carried out as fast as possible and without heating. After hydrating 0.40 ml (0.0044 mol) of tritiated dihydropyran **7** in 2 ml of water containing 2 drops of concentrated hydrochloric acid, 0.46 g (0.0046 mol) of thiosemicarbazide was added followed immediately by 10 ml of 10% aqueous sodium acetate. The resulting thiosemicarbazone, after four crystallizations from aqueous ethanol (1:1) and one crystallization from methanol–ethyl acetate (1:5) weighed 0.52 g (67%) and showed mp 128.5–129.5°.

Anal. Calcd for $C_6H_{13}N_3OS$: C, 41.0; H, 7.48. Found: C, C, 41.2; H, 7.4; radioactivity, 7.21 and 7.15 mCi/mol.

After another crystallization from aqueous ethanol (1:1), the radioactivity was 7.16 and 7.10 mCi/mol; the average value is 7.16 ± 0.03 mCi/mol.

Ozonolysis of Tritiated Dihydropyran 7.—Tritiated dihydropyran (3.15 g, 0.0375 mol) was cleaved as before. The extracted colorless 4-hydroxybutanal (**10**) was converted into the thiosemicarbazone (mp 111–114°), which, after two crystallizations from aqueous alcohol (1:1) followed by three crystallizations from aqueous methanol (1:1), weighed 1.8 g and melted at 115.5–117°. Another crystallization from methanol–ethyl acetate (1:5) gave glistening white flakes of 4-hydroxybutanal thiosemicarbazone with the same melting point.

Anal. Calcd for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06; S, 19.88. Found: C, 37.1; H, 6.9; N, 25.9; S, 19.9.

This material showed a tritium activity of 0.0481 and 0.0475 mCi/g. After an additional crystallization from aqueous methanol (1:1), the activity was 0.0483 and 0.0480 mCi/g. The average molar activity was 7.73 ± 0.02 mCi/mol.

The zinc formate dihydrate isolated from this ozonolysis weighed 3.3 g (92%).

Anal. Calcd for $C_2H_6O_6Zn$: C, 12.55; H, 3.16. Found: C, 12.7; H, 3.2.

Duplicate activity analysis showed 1.72×10^{-3} and 1.82×10^{-3} mCi/g, or 0.17 mCi/mol of formate ion.

To wash out radioactivity from the water of crystallization, 2 g of this zinc formate was dissolved in 150 ml of water and, after 2 hr, the water was removed at temperatures below 35°. The solution and evaporation process was applied two more times, after which the isolated zinc formate showed an activity of 1.43×10^{-3} mCi/g. Exposure to another cycle of solution and evaporation gave zinc formate with 1.47×10^{-3} mCi/g. Thus the zinc formate contained activity (0.14 ± 0.002 mCi/mol of formate) that did not wash out with water.[29]

Tritiated Glutaric Acid 8 from Tritiated Dihydropyran 7.—Tritiated dihydropyran **7** (2 g) was converted into glutaric acid essentially by following the directions given before.[26] One crystallization from ether–benzene, one from benzene, and two from ethanol–benzene (1:1) gave 2.0 g (60%) of glutaric acid, mp 96–97°.

Anal. Calcd for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.4; H, 6.0; radioactivity 0.0595 and 0.0593 mCi/g.

After an additional crystallization from ethanol–benzene (1:1), the glutaric acid contained 0.0588 and 0.0592 mCi/g. Averaging the four values led to an activity figure of 7.82 ± 0.02 mCi/mol.

Removal of Tritium from Glutaric Acid 8.—A solution of the glutaric acid (0.66 g) in 20 ml of 5 *M* sodium hydroxide solution was boiled for 3 days. After acidification, the glutaric acid was collected and crystallized to mp 96–97°. Most of the activity was retained as indicated by the 7.07-mCi/mol assay value. Accordingly, the following procedure was adopted.

Tritiated glutaric acid **8** (2.64 g, 0.020 mol) in 20 ml of cold ether was treated with excess cold ethereal diazomethane. After the yellow color was removed by a short distillation, the solution was allowed to stand in contact with magnesium sulfate and decolorizing carbon. Removal of all solvent from the dried, decolorized solution left colorless dimethyl glutarate (3.2 g; 98%). A solution of the ester (2.8 g) in 20 ml of anhydrous methanol containing a small quantity of sodium was boiled for 24 hr.[6] All solvent was removed by distillation at room temperature under reduced pressure. Another 20-ml portion of methanol was added, and the entire process was repeated six times. Finally, the ester was saponified with hot 20% aqueous sodium hydroxide containing methanol. The mixture, acidified to pH 2 with 10% sulfuric acid, was extracted with ether. The glutaric acid obtained in this way was recrystallized once from benzene and once from benzene containing a little absolute alcohol to give shiny colorless needles, mp 96.5–97°, weighing 2.1 g (90%), and containing 0.062 mCi/mol. Reesterification and repetition of the above treatment afforded glutaric acid **9** (85% recovery) the activity of which was essentially the same as background.

Similar results were obtained when the exchange was carried out at room temperature, although the time required was longer.

3-Bromo-Δ²-dihydropyran (13) from Tritiated Dihydropyran.[7]—Bromine (9.6 g, 0.060 mol) was added by drops over a period of 20 min to a solution of 5 g of tritiated dihydropyran **7** (0.06 mol) in 7 ml of sodium-dried ether. The mixture, held in an ice–salt bath, was shaken occasionally and was protected from moisture. N,N-Diethylaniline (10 g) was added and, after 0.5 hr at room temperature, the mixture was warmed to remove ether. Reducing the pressure and gradually increasing the bath temperature to 80–90° caused the desired 3-bromo-Δ²-dihydropyran to distil [bp 60–63° (23 mm)] from the now solid mixture. After drying the distillate with calcium sulfate, two redistillations afforded constant-boiling product: bp 56–57° (20 mm); n^{25}D. 15060; d^{25} 1.528.

Anal. Calcd for C_5H_7BrO: C, 36.84; H, 4.32; Br, 49.03. Found: C, 37.0; H, 4.3; Br, 48.9; radioactivity, 0.0465 mCi/ml.

This 3-bromo-Δ²-dihydropyran (**13**) was distilled again to give product with bp 62–63° (22 mm) and n^{25}D 1.5060, and showing radioactivity of 0.0455 and 0.0458 mCi/ml. The average of the three determinations was 4.90 ± 0.03 mCi/mol.

Registry No.—Δ²-Dihydropyran, 110-87-2; **3**, 17035-47-1; **4**, 17035-48-2; 5-hydroxypentanal thiosemicarbazone, 17037-83-1; 4-hydroxybutanal 2,4-dinitrophenylhydrazone, 17037-84-2; tetrahydropyran-2-^{14}C, 17035-49-3; tritiated glutaric acid **8**, 17037-85-3; **10** thiosemicarbazone, 17037-86-4; **13**, 17037-87-5; alumina, 1344-28-1; **16**, 17132-13-7.

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[29] A good activity balance can be struck as follows. If the starting dihydropyran had 10.6 mCi/mol, and the recovered activity in the form of 4-hydroxybutanal thiosemicarbazone plus washed zinc formate dihydrate is 7.9 mCi/mol, then 2.7 mCi/mol of the original dihydropyran activity is missing. As 0.0375 mol of the dihydropyran was used, this means that 0.1 mCi of tritium activity is unaccounted for. The tritium activity in the hydration water of the isolated zinc formate before the washing process is 0.3×10^{-3} mCi/g of salt (*i.e.*, 1.77×10^{-3} minus 1.47×10^{-3}) or 1.6×10^{-3} mCi/g of water. On the assumption that this activity is the same as that in the water (60 g) in which the zinc formate was dissolved prior to its precipitation, the total activity in the water is 0.1 mCi. Thus, all the missing activity can be accounted for.