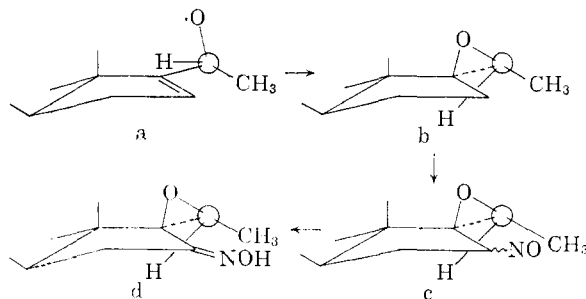
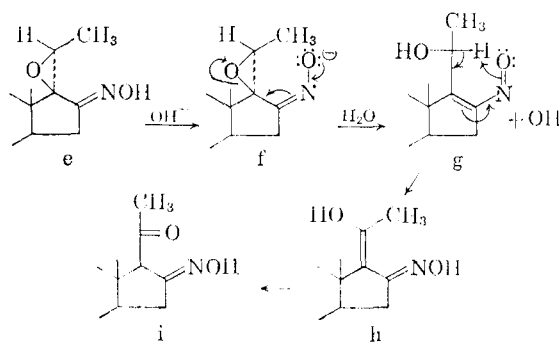


A corresponding bis-ketal (VII) already had been described⁶ and we proceeded to synthesize it by a combination of the methods of Julian⁷ and Bernstein.^{8,9} When this material was subjected to a mild acetic acid ketal cleavage, a spectrum of six paper spots appeared which also could be observed in an identical control experiment with VI. A preparative deketalization of VII then resulted in the actual isolation of VI by absorption chromatography.

We rationalize the photolysis as depicted in (a) to (d): an alkoxide free radical would be expected to have the same conformation during its short life-time as its nitrite precursor. The close proximity of the single electron to the π system of the double bond would make the reaction described probable, and the other π electron would then undergo chain termination with NO.



The alkaline rearrangement of V to VI can be considered to involve the conjugate base (f) of the oxime, which experiences an electron shift involving oxide opening, and cyclic collapse as shown in (g)



On the basis of these considerations, the irradiation product has been assigned structure and stereochemistry as in V. It would be difficult to explain its formation without resorting to an intermediate alkoxide free radical.⁹

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(9) We wish to thank Dr. P. Kabasakalian and his staff for the analytical data.

NEW REAGENT FOR LABELING ORGANIC COMPOUNDS WITH TRITIUM¹

Sir:

Though numerous forms of acid catalysis are known² for promoting hydrogen isotope exchange labeling, evaluation of the powerful acid complex $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$ for this purpose has revealed significant advantages. Its proficiency for very rapid exchange without side reactions makes it useful both for labeling and fundamental studies of reactivity of various forms of bound hydrogen. $\text{H}_3\text{PO}_4\cdot\text{BF}_3$ has been used for some time strictly as a catalyst,³ especially for alkylating aromatics. However, there is apparently no previous description of its utility as a hydrogen isotope exchange reagent when its hydrogen is partially replaced with tritium or deuterium. Because of easier detection, the radioactive tritium was preferred over stable deuterium.

Like the Wiltzsch method^{4,5,6} of radiation induced self-labeling with tritium, this method also can be applied where radio-chemical synthesis is not possible.

The tritiating reagent is $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$ nominally, *i.e.*, the tritium-hydrogen ratio is arbitrary. This complex is made very easily by stoichiometric admixture of tritiated water and P_2O_5 and saturation with BF_3 gas. It is a dense liquid that should be stored only in polyethylene containers, though glassware can be used for experiments of less than twenty hours.

Labeling of many organics is effected by simply contacting them with the reagent in a stirred flask at ambient temperature. The exchange mechanism very likely is initiated by transfer of a triton from the acid to the organic molecule. The resultant cation undergoes loss of a proton, yielding the tagged molecule. Hydrocarbons are insoluble in the reagent and are recovered by decantation of liquids or filtering of solids. Organic compounds containing oxygen dissolve but are separated out after tagging by addition of a small amount of water. The exchange reaction is quite rapid and equilibrium distribution of the tritium is effected readily in many cases. It is easy to show, if the tritium atoms are statistically distributed among all exchangeable hydrogen positions including the three of the phosphoric acid complex, that equation 1 applies

$$S_x = \frac{S_r}{3/166 \cdot M/N_H + W_x/W_r} \quad (1)$$

where S_x is the ultimate specific activity of the tracer, M its molecular weight, and N_H the number of exchangeable hydrogen positions in it. S_r is the original specific activity of the reagent. W_x/W_r is the weight ratio of tracer to reagent. Thus,

(1) This work was supported in part by the Division of Isotopes Development, U. S. Atomic Energy Commission under Contract No. AT (30-1)-2350.

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(6) K. E. Wiltzsch, "Tritium Gas Exposure Labeling," *Atomlight*, No. 15, December 1960 (Issued by New England Nuclear Corp.).

if very high specific activity tracers are desired, high activity tritiated water is used to make the reagent. The weight ratio also can be adjusted to favor high tagging.

Some initial labeling results are shown in Table I. These compounds were all mixed with half their weight of $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$ which had a specific activity of 1400 $\mu\text{c./g.}$, except for anisole where the reagent had a specific activity of 380 $\mu\text{c./g.}$ The naphthalene was tagged in cyclohexane solution (10%) to facilitate contact with the reagent. The degree of tagging shown was accomplished in about six hours. The aromatic compounds tag very rapidly as demonstrated by the first five listed. The non-aromatics that contain a hydrogen on tertiary carbon, namely, methylcyclohexane and decalin, also tag but at a lesser degree. The non-branched aliphatics as exemplified by cyclohexane and *n*-octane appear not to tag at all. In fact, preparative chromatography eliminates the tritium activity from these. Thus there is selectivity in this method of labeling, with preferential labeling of aromatic hydrogen positions, considerably less for hydrogen on tertiary carbon atoms and essentially none for non-tertiary alkane hydrogen. Future studies will determine the degree of labeling of other forms of hydrogen as those on carbon atoms adjacent to carbonyl groups.

TABLE I

TRITIUM TRACERS PRODUCED WITH $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$ AT 23°

Labeled compound	Specific activity before purification, $\mu\text{c./g.}$	Specific activity, purified tracer, $\mu\text{c./g.}$
Benzene	106.6	108.2
Toluene	550.0	554.0
Tetralin	536.0	531.0
Naphthalene	1422.0	1440.0
Anisole	146.0	146.0
Methylcyclohexane	9.25	9.36
Decalin	32.2	31.4
Cyclohexane (99.6%)	0.96	0
<i>n</i> -Octane (98.6%)	16.3	0

The radio-chemical purity of the tracers produced with $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$ is demonstrated by comparison of the last two columns. The purification tests were applied in three stages, first treatment with sodium to eliminate any labile tritium, then fractional distillation and finally vapor phase preparative chromatography with discriminative collection of the single elutriating peak identified as the original compound. The agreement between the last two columns indicates that essentially all the tritium radioactivity is in the radio-chemically pure tracer. The small tagging observed in the last two compounds—the non-branched aliphatics—is attributable to chemical impurities originally present before tagging. Indications are that in most hydrocarbons, if one starts with an absolutely pure compound, after-purification of the tracer

is unnecessary and the only reaction that occurs is tagging by exchange of tritium for hydrogen.

Preliminary kinetic studies of tagging rate reveal that the specific activities of tetralin and toluene exponentially approach, in 6 hours (saturation tagging), the limits predicted by Equation (1). The limits were calculated assuming that only the aromatic hydrogens exchanged. Agreement between calculated and observed tagging limits confirmed this assumption and no labeling occurs at the aliphatic hydrogen positions in these two compounds. Similarly, anisole also was observed to label at the aromatic hydrogen positions only. Anisole reaches equilibrium labeling in 2 hours, benzene in 80 hours. Increasing exchange rate in the series benzene, toluene, anisole is expected because of the electron directional influence of the ring substituted groups, CH_3 and OCH_3 , that enhance the chemical activity of aromatic hydrogen in this order.

To compare this reagent's proficiency for isotopic exchange against tritiated 80% H_2SO_4 as reported by Olssen,⁷ first order rate constants were calculated for exchange to benzene at 25°. The rate constant is about 200 times greater for the $\text{TH}_2\text{PO}_4\cdot\text{BF}_3$.

The effect of temperature on exchange rate is very pronounced. Equilibrium or maximum labeling of benzene is completed in 2 hours at 65° as compared to 80 hours at 21°.

Further detailed studies of exchange rates are expected to lead to use of this tritiating reagent as a fundamental tool to delineate the various forms of hydrogen in complex or unknown organic structures, such as ratios of aromatic to aliphatic hydrogen. Preliminary work with toluene already indicates that ortho and para hydrogen may be resolved from meta hydrogen by the difference in exchange rates.

Summarily, the advantages of this new labeling method are: radiochemically pure tracers often are produced immediately, obviating drastic post-labeling purification that may be required for some acids and is always required after the Wilzbach method of labeling.^{6,8,9} Labeling is very rapid, sometimes requiring only a few hours to complete. It is simple, requiring no special equipment as for gas handling or high temperatures. Very high specific activity tracers can be produced where desired by starting with highly tritiated water.

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