Neutron Irradiation of Acetoxime and Acetaldoxime

By Enzo TACHIKAWA and Gen-ichi TSUCHIHASHI

(Received September 12, 1961)

Previously, the present authors irradiated propionamide[1] with thermal neutrons and found that the yields of methylation products from propionamide, ^{14}C-isobutyramide and ^{14}C-butyramide were proportional to the number of hydrogen atoms which are available for substitution. These results served to indicate that "synthesis"[2] products were mainly formed by the methylation reaction.

In order to understand the mechanism more completely, however, further studies were required. The present authors carried out the neutron irradiation of acetoxime and acetaldoxime and so separated a few "synthesis" products and "re-entry"[2] products.

Particular attention was paid to the relationship between the yields of these products. The Beckmann rearrangement product of acetoxime was also examined. Carbon-14 distributions in the product molecules from acetoxime were determined by a stepwise degradation method.

On the basis of these results, the relationship between "re-entry" and "synthesis" reactions is discussed.

Experimental

Materials. — Acetoxime was synthesized from hydroxylamine hydrochloride and acetone[3]. Acetaldoxime, ethylmethylketoxime and propionaldoxime were synthesized by a method analogous to that for acetoxime. *N*-Methylacetamide was obtained from acetic anhydride and methylamine hydrochloride. These compounds were purfied in a Podbielniak high-temperature distillation apparatus (with a 60-plates heli-grid packing column).

Neutron Irradiation. — About 15 g. of acetoxime was sealed in a polyethylene tube, which was then packed in a polyethylene capsule. Also, 15 g. of pure acetaldoxime was sealed in a quartz tube under a pressure of 10^{-4} mmHg, and then the ampoule was packed in an aluminum capsule. These assemblies were irradiated for 120 hr. in the No. 13 experimental hole of the J. R. R.-1, with an approximate flux of 10^{11} n./cm^2·sec. Samples were cooled for about two weeks after irradiation in order to eliminate short-living activities stemming from impurities in the polyethylene capsule or the aluminum capsule.

Processing of Irradiated Acetoxime.—In order to determine the reaction products, the isotope-dilution method was used. After the irradiated sample was divided into four portions, each portion was distilled in order to remove polymeric substances produced. Before beginning the distillation, known amounts of corresponding carriers were first added to the distillation vessel separately. Gas liquid partition chromatography was employed for the final purification of the desired compounds.

For chromatography, a 6 ft. column, 1/2 inch i. d., packed with 30~80 mesh fire brick coated with polyethylene glycol-600, was used. The column was operated at 100°C, and the flow rate of helium carrier gas was kept about 150 ml./min.

Degradation of ^{14}C-Acetoxime.—After 3 g. of the irradiated sample had been distilled in the usual way, the portion of acetoxime was purified by gas chromatography. ^{14}C-acetoxime purified was divided into two portions. By the usual iodoform reaction[4], one portion of ^{14}C-acetoxime was converted to iodoform, which was then recrystallized until it showed a constant specific activity. The remaining ^{14}C-acetoxime was converted into *N*-methylacetamide by the Beckmann rearrangement and was then hydrolyzed to acetic acid. The acetic acid was treated with benzoyl chloride and ammonia, and the resulting acetamide was recrystallized from methanol-ether.

Degradation of ^{14}C-Ethyl Methyl Ketoxime.—After 4 g. of ethyl methyl ketoxime had been added to 3.99 g. of the irradiated sample as a carrier, the mixture was distilled and the ^{14}C-ethyl methyl ketoxime collected was purified further by gas chromatography. Purified ^{14}C-ethyl methyl ketoxime was also divided into two portions. The first portion was hydrolyzed to ethyl methyl ketone, which was then converted to iodoform by the iodoform reaction. The rest of the ^{14}C-ethyl methyl ketoxime was converted to propionic acid by the bromoform reaction[5]. The propionic acid thus obtained was decarboxylated to ethylamine by Schmidt's method in order to locate the distribution of carbon-14 according to the suggestions of Phares[6]. The ethylamine produced was converted to acetic acid by the method of Phares and was further degraded to methylamine. The methylamine produced was oxidized to carbon dioxide by the same method.

Degradation of ^{14}C-*N*-Methylacetamide. — *N*-Methylacetamide (3.02 g.) was added to the

1) E. Tachikawa and G. Tsuchihashi, This Bulletin, **34**, 770 (1961).
2) A. P. Wolf, *Angew. Chem.*, **71**, 237 (1959).
3) N. D. Cherronis, "Technique of Organic Chemistry, Vol. VI. Micro and Semimicro Method", Interscience Publishers, Inc., New York (1954), p.337.
4) N. D. Cherronis, "Technique of Organic Chemistry, Vol. VI. Micro and Semimicro Method", Interscience Publishers, Inc., New York (1954), p. 284.
5) "Organic Syntheses", Coll. Vol. I (1948), p. 526.
6) E. F. Phares, *Arch. Biochem. Biophys.*, 33, 173 (1951).

irradiated sample (3.00 g.) as a carrier. The ^{14}C-*N*-methylacetamide separated from the mixture by the same procedure was hydrolyzed by refluxing it for two hours with potassium hydroxide. The acetic acid obtained was fractionated by gas-liquid chromatography, using 50% D. C. 710 silicone plus 10% stearic acid as the liquid phase. The methylamine was oxidized to carbon dioxide.

Processing of Irradiated Acetaldoxime. — The irradiated sample was distilled in order to remove polymeric substances after the sample had been divided into several portions. The acetoxime and propionaldoxime formed by the neutron irradiation of acetaldoxime were identified separately by gas chromatography after suitable amounts of acetoxime or propionaldoxime had been added as a carrier. The separated oximes were further purified by gas chromatography until they showed constant specific activity.

Measurement of Activity. — The purified compounds were converted to carbon dioxide by the Van Slyke-Folch method[7]. The resulting carbon dioxide was converted to barium carbonate by the same method as in the previous paper[1]. About 150 mg. of the barium carbonate suspended in ethyl alcohol was poured into a particular type of counting dishes (0.8 cm.ϕ). Using an infrared lamp, ethyl alcohol was evaporated and barium carbonate was dried up. This barium carbonate was mounted in the dishes in infinite thickness. The specific activity of barium carbonate was measured with an Aloka low-back ground counter (model: BD-1). Barium carbonate of 22.4 d.p.s./mg. was used as a standard sample. These measurements are reproducible to about 3% for samples of the same material and to about 3~4% samples of different compound containing the same labelled group. The absolute accuracy of the assays is probably good to about 7%.

Results and Discussion

The Distribution of Carbon-14 in Neutron Irradiation Products. — As is well known, an ^{14}N(n, p)^{14}C reaction occurs on the nitrogen atom of oxime during neutron irradiation. Because ^{14}C recoil atoms have high energy, they are supposed to undergo various reactions. Among them, "re-entry" and "synthesis" products have been considered in the present study, together with the Beckmann rearrangement product. In the neutron irradiation of acetoxime, the ^{14}C-acetoxime, ^{14}C-ethyl methyl ketoxime and ^{14}C-*N*-methylacetamide produced are here called "re-entry", "synthesis" and rearrangement products respectively. Table I shows the distribution of carbon-14 in each compound.

Analogously, neutron irradiation of acetaldoxime will bring about reactions similar to those for acetoxime. In this reaction, ^{14}C-acetaldoxime is a "re-entry" product. Both ^{14}C-acetoxime and ^{14}C-propionaldoxime are referred to as "synthesis" products.

The comparative yields of these compounds are shown in Table II. Table II shows that the ratio of the yields of ^{14}C-acetoxime and ^{14}C-propionaldoxime is about 1 : 3, which agrees with the ratio of the number of hydrogen atoms available for the substitution in acetaldoxime to give acetoxime or propionaldoxime. This result is in accord with that for the neutron irradiation of propionamide[1].

Carbon-14 Distribution on Molecules. — Recently, many researchers have carried out stepwise degradations of "synthesis" and "re-entry" products[8]. These results have shown that the differences betwen theoretical and experimental values for the distribution of carbon-14 are not so large in "re-entry" products, while the differences become remarkable in "synthesis" product. Especially in the latter case, one finds a considerable number of carbon-14 atoms at positions where carbon-14 could not be found theoretically. In the present study, degradations of ^{14}C-acetoxime,

TABLE I. YIELDS OF RADIOACTIVE SPECIES FROM THE NEUTRON IRRADIATION OF ACETOXIME

Product	Total activity, assay of compd. $\times 10^{-1}$ μc./mol.	Activity relative to total activity in irradiated crude sample, %	Relative ratio
Acetoxime	4.4	2.1	1.0
Ethyl methyl ketoxime	9.9	3.9	1.9
N-Methylacetamide	2.9	1.3	—

TABLE II. YIELDS OF RADIOACTIVE SPECIES FROM THE NEUTRON IRRADIATION OF ACETALDOXIME

Product	Total activity, assay of compd. $\times 10^{-1}$ μc./mol.	Activity relative to total activity in irradiated crude sample, %	Relative ratio
Acetaldoxime	3.0	3.0	1.0
Acetoxime	1.7	1.3	0.4
Propionaldoxime	4.6	3.6	1.2

7) D. D. Van Slyke and H. Folch, *J. Biol. Chem.*, **139**, 509 (1940).

8) R. C. Extermann, "Radioisotopes in Scientific Research", Vol. 2, Pergamon Press, London (1958), p. 114.

Table III. Carbon-14 distribution in "re-entry" product from the neutron irradiation of acetoxime

	Product		
	CH_3	C(NOH)	CH_3
Theoretical	33	33	33
Found	36	28	36

Table IV. Carbon-14 distribution in "synthesis" product from the neutron irradiation of acetoxime

	Product			
	4 CH_3	3 CH_2	2 C(NOH)	1 CH_3
Theoretical	100	0	0	0
Found	69	9	9	13

^{14}C-ethyl methyl ketoxime and ^{14}C-*N*-methylacetamide were carried out in order to discover the distributions of carbon-14 atoms in these molecules. Degradation of ^{14}C-acetoxime showed that 72% of the carbon-14 activity was present in methyl groups. Similar studies on the ^{14}C-ethyl methyl ketoxime showed that 70% of the activity was in the 4-position. Tables III and IV illustrate the observed values together with the theoretical values.

The results in Table III seem to indicate that ^{14}C-acetoxime has resulted from a "knock on" reaction between carbon-14 and carbon-12 in acetoxime. The methyl group is tagged with about 8 per cent more carbon-14 than the central carbon atom. This is perhaps caused by the steric effects of neighboring CH_3 groups that hinder the attack of carbon-14 on the central carbon atom.

As Table IV shows, the 1-, 2- and 3-positions in ethyl methyl ketoxime are all labelled with carbon-14. This result coincides well with those of others[8]. In this compound, the amount of compound, the amount of carbon-14 in the 1-position exceeds that in the 2- or 3-position. This is also caused by the steric effects similar to that in the case of acetoxime.

When an organic molecule reacts with a carbon-14 hot atom, the kinetic energy given to the organic molecule is so high that isomerizations or some other reactions could easily take place. The distribution of carbon-14 in *N*-methylacetamide, the Beckmann rearrangement product of acetoxime, is shown in Table V.

Table V. Carbon-14 distribution in ^{14}C-*N*-methylacetamide produced from the neutron irradiation of acetoxime

	Product		
	CH_3	CONH	CH_3
Theoretical	33	33	33
Found	50		50

From Table V, one finds a higher C-14 distribution in the migrating methyl group than in the other positions. Possibly the mechanism for the formation of ^{14}C-*N*-methylacetamide differs from that of the acid-catalyzed Beckmann rearrangement. In this case, the rearrangement probably takes place for the following reason. When a methyl group in acetoxime is labelled with carbon-14, a high kinetic energy is given to it. An excited acetoxime isomerizes rather easily into *N*-methylacetamide by the migration of the labelled methyl group before the kinetic energy in this methyl group completely diffuses over the molecule.

The Relation between the Yields of "Re-entry" and "Synthesis" Products.—Acetoxime contains three carbon atoms, each of which could be tagged with carbon-14, forming ^{14}C-acetoxime. Also, it contains six hydrogen atoms which are available for methylation, resulting in ^{14}C-ethyl methyl ketoxime. Also, acetaldoxime contains two carbon atoms, three hydrogen atoms attached to carbon atom 2, and one hydrogen atom attached to carbon atom 1, all of which are available for giving ^{14}C-acetaldoxime, ^{14}C-propionaldoxime and ^{14}C-acetoxime respectively. Similarly, propionamide has three carbon atoms, two hydrogen atoms attached to carbon atom 2, and three hydrogen atoms attached to carbon atom 3.

These carbon or hydrogen atoms are capable of being used for the formation of "re-entry" or "synthesis" product. The preceeding paper[1] gave the results of the neutron irradiation of propionamide, results shown in Table VI.

The above results seem to show that some relationship exists between the yields of "re-entry" or "synthesis" products and the number of carbon or hydrogen atoms in the mother compounds. Table VII shows the number of atoms which are available for the formation of "re-entry" or "synthesis" products, together with the ratio of the yields of "synthesis" products to that of "re-entry" products.

Previously, Wolf et al.[9] examined the neutron irradiation of benzene, toluene, aniline, pentane, methanol, acetamide and alanine. Except for pentane and methanol, similar results were observed. In pentane and methanol, hydrogen replacement was found to be favored twofold over carbon replacement.

In Fig. 1, the relative values of activity found in "synthesis" product, divided by that in "re-entry" products, are plotted as a function of the ratio of the number of hydrogen atoms which are available to form "synthesis"

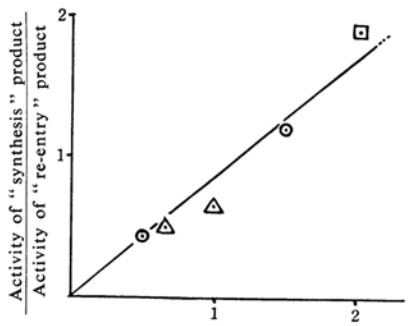
9) A. P. Wolf, BNL, 4891 (1960).

Table VI. Results of neutron irradiation of propionamide

Product	Total activity, assay of compd. $\times 10^{-1}$ μc./mol.	Activity relative to total activity in irradiated crude sample, %	Relative ratio
Propionamide	6.6	3.3	1.0
Isobutyramide	4.1	1.7	0.5
Butyramide	5.2	2.1	0.6

Table VII. From the neutron irradiation acetoxime (CH_3-C($=NOH$)-CH_3)

Product	No. of atoms available for the substitution	Yield of "synthesis" or "re-entry" products
Acetoxime	3 carbon	—
Ethylmethylketoxime	6 hydrogen	1.88
From the neutron irradiation of acetaldoxime (CH_3-CHNOH)		
Acetaldoxime	2 carbon	—
Acetoxime	1 hydrogen	0.43
Propionaldoxime	3 hydrogen	1.20
From the neutron irradiation propionamide (CH_3-CH_2-$CONH_2$)		
Propionamide	3 carbon	—
Isobutyramide	2 hydrogen	0.50
Butyramide	3 hydrogen	0.64

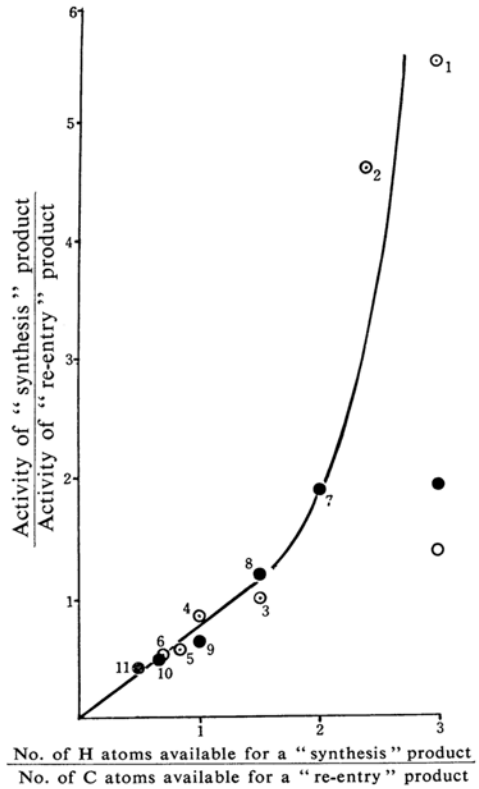


⊡: From neutron irradiation of acetoxime
⊙: From neutron irradiation of acetaldoxime
△: From neutron irradiation of propionamide

Fig. 1.

products to the number of carbon atoms available for the formation of "re-entry" products. This figure is based on the present authors' results, together with results obtained by Wolf et al.

This figure shows that a linearity exists over nearly the range from zero to two of the horizontal values; beyond this range the yields of "synthesis" products increase rapidly.



⊙ Results obtained by Wolf et al.
1: Ethanol/methanol
2: *n*-Hexane+2Me-pentane+3Me-pentane/pentane
3: Propionamide/acetamide
4: Toluene/benzene
5: Toluidines/aniline
6: Xylenes/toluene
● Our results
7: Ethyl methyl ketoxime/acetoxime
8: Propionaldoxime/acetaldoxime
9: Butyramide/propionamide
10: Isobutyramide/propionamide
11: Acetoxime/acetaldoxime

Fig. 2.

In the range where the ratios of the number of hydrogen atoms to that of carbon atoms are less than two, it seems that the amount of "synthesis" and of "re-entry" products are proportional to the number of hydrogen and carbon atoms available for the product formation.

Since in the present results, nearly 70% of the activity in the "synthesis" product exists in the methyl group attached to the mother skeleton, the major reaction undoubtedly being the methylation.

The distribution of the activity in ^{14}C-acetoxime is nearly uniform, and the yields of "re-entry" products are proportional to the carbon atoms. These results seem to suggest that the "knock on" and methylation reactions are the main paths for the formation of "re-entry" and "synthesis" products respectively when the two reactions occur simultaneously in a constant ratio as shown in Fig. 1. However, as the ratio of hydrogen to carbon atoms increases, the methylation reaction gradually predominates, as in pentane and methanol.

Summary

The neutron irradiation of acetoxime and acetaldoxime was studied. Degradation of the products obtained from the neutron irradiation of acetoxime shows that the distribution of carbon-14 activity deviates a little from the statistical behavior on account of steric and other effects.

However, the yields of "synthesis" product are found to be proportional to the number of hydrogen atoms available for their formation. Also there seems to be a linear relationship between the yields of "re-entry" or "synthesis" products and the number of atoms available for formation. The present results suggest that the main process forming the "synthesis" products is simple methylation by ^{14}C-methyl or ^{14}C-methylene radicals, while that giving the "re-entry" products is a "knock on" reaction of carbon-12 by carbon-14.

The authors wish to express their thanks to Professor K. Kimura, Dr. A. Danno and Dr. T. Ishimori for their kind encouragement and helpful discussions throughout the present work.

Division of Radiation Applications
Japan Atomic Energy Research Institute
Tokai, Ibaraki-ken