the same property whereas 5,8-FH_2 and 7,8-FH_2, with symmetry at the C6-position, would not. From the data of Table II it can be seen that synthetic FH_2 shows greater than 50% enzymic activity, indicating that either the 5,8- or 7,8-configuration represents the enzymatically active form.

Inhibition experiments on FH_2-reductase were performed with aminopterin, *p*-chloromercuribenzoate and *o*-iodosobenzoate. Inhibition by aminopterin was found to be essentially the same as reported by Osborn, *et al.*,[7] while no inhibition by sulfhydryl reagents could be observed.

Experimental

Apparatus and Materials.—A Beckman model DU spectrophotometer and 1 cm. Corex cuvettes were used for the determination of nucleotide oxidation. A Beckman model B spectrophotometer was used for the estimation of diazotizable amine production. A Beckman model G *p*H meter was used for *p*H determinations.

FH_2 was prepared by the method of Futterman[5] and was estimated by its extinction coefficient in 0.01 *N* NaOH (E_{283} = 21,000). FH_2 could be stored as a suspension in 0.005 *N* HCl at 0° for periods up to two weeks. Nucleotides were products of the Sigma Chemical Company, St. Louis, Mo.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF ENGELHARD INDUSTRIES, INC.]

Use of Ruthenium Tetroxide as a Multi-purpose Oxidant

BY LEWIS M. BERKOWITZ AND PAUL N. RYLANDER

RECEIVED AUGUST 19, 1958

Ruthenium tetroxide is a powerful oxidizing agent and readily attacks a variety of functional groups and aromatic systems. Aldehydes are oxidized to acids, alcohols to aldehydes or ketones, olefins to aldehydes, amides to imides and ethers to esters.

Osmium tetroxide has been used frequently for the oxidation of organic compounds, especially the hydroxylation of olefins,[1] but ruthenium tetroxide has been used practically not at all. *A priori* the two compounds might be expected to behave very similarly since ruthenium appears directly above osmium in the periodic table. Ruthenium would appear to offer several practical advantages in that it is less volatile, less toxic, less expensive, and more readily available than osmium. Further examination of the reaction of ruthenium tetroxide seemed worthwhile especially in regard to delimiting the scope of its usefulness.

Only two prior references to the reactions of ruthenium tetroxide have been made. Djerassi and Engle[2] oxidized several sulfides to sulfoxides and sulfones and oxidized phenanthrene to 9,10-phenanthrenequinone. They also reported that ether, benzene and pyridine, the solvents usually found useful for osmium tetroxide oxidations, reacted violently and instantaneously with ruthenium tetroxide. The only other reference to reactions of ruthenium tetroxide is to an unsuccessful oxidation of a very hindered olefin.[3]

Ruthenium tetroxide is so much more powerful an oxidizing agent than osmium tetroxide that it cannot be used without a solvent. Carbon tetrachloride and alcohol-free chloroform are satisfactory solvents for most reactions.[2] Paraffins, ketones, esters and water may also be used, although the tetroxide reacts slowly with the oxygenated compounds. A solution of the tetroxide in carbon tetrachloride is reported[2] to have remained unchanged for a year. In the present work, the tetroxide was made as needed by a simple procedure and either collected on a condenser or distilled directly into a solvent.

Ruthenium tetroxide at 0° oxidizes secondary alcohols very rapidly to ketones, and primary alcohols to aldehydes or acids. *t*-Butyl alcohol reacts very slowly, possibly through dehydration. Cyclohexanol, menthol and 3β-cholestanol were all cleanly oxidized to their respective ketones. Benzyl alcohol gave benzaldehyde without difficulty. This is especially interesting since benzene is reported to explode on contact with ruthenium tetroxide[2] and even in dilute carbon tetrachloride solution benzene is oxidized with reasonable rapidity, although qualitatively more slowly than alcohols. It was not found possible to convert aliphatic alcohols to aldehydes. *n*-Hexyl alcohol gave only caproic acid even when an excess of the alcohol was used. Infrared analysis of the crude reaction mixture revealed no aldehyde at all.

The reaction of *trans*-1,2-cyclohexanediol with ruthenium tetroxide was accomplished using water as a solvent. The product, whose infrared spectrum showed a carbonyl band at 5.78 μ, gave a 2,4-dinitrophenylhydrazone identical with that of 1,2-cyclohexanedione. The product was either 1,2-cyclohexanedione or 2-hydroxycyclohexanone, both of which give the same 2,4-dinitrophenylhydrazone.[4]

Aldehydes are oxidized rapidly by ruthenium tetroxide to acids. *n*-Heptaldehyde gave heptanoic acid and benzaldehyde gave benzoic acid. The latter case provides another example of a functional group being oxidized preferentially to the aromatic nucleus.

Ruthenium tetroxide reacts very rapidly with olefins in a manner quite unlike osmium tetroxide. Osmium tetroxide gives hydroxylation of the

---

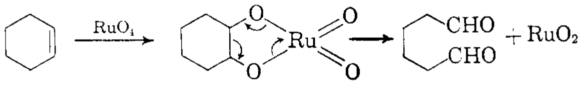
(1) H. Gilman, "Organic Chemistry, an Advances Treatise," Vol IV, J. Wiley & Sons, Inc., New York, N. Y., 1953, p. 1180.

(2) C. Djerassi and R. R. Engle, THIS JOURNAL, **75**, 3838 (1953).

(3) P. D. Bartlett and M. Stiles, *ibid.*, **77**, 2806 (1958).

(4) J. C. Sheehan, R. C. O'Neill and M. A. White, *ibid.*, **72**, 3376 (1950).

double bond; ruthenium tetroxide causes carbon–carbon bond cleavage. Cyclohexene was converted to adipaldehyde, and 1-octene to heptaldehyde and presumably formaldehyde. A possible course for the reaction is



These reactions contrast with the reaction of ruthenium tetroxide with the semi-olefinic double bond of phenanthrene which gave 9,10-phenanthrenequinone, formed possibly by the further oxidation of an intermediate diol.[2]

The reaction of ruthenium tetroxide with olefins was so rapid and vigorous that it seemed of interest to try the oxidation with a cyclopropane ring as substrate. The physical and chemical similarity of cyclopropane to olefin has been frequently noted.[5] Accordingly methyl cyclopropyl ketone was mixed with ruthenium tetroxide in carbon tetrachloride. Only a very slow, unidentified reaction occurred which may have been with the enol rather than the cyclopropyl ring; most of the ketone was recovered after several hours in solution with the tetroxide.

An interesting reaction of ruthenium tetroxide that seems to be unique with this reagent, is the oxidation of ethers to esters. Tetrahydrofuran was oxidized smoothly to γ-butyrolactone in nearly quantitative yield. Whatever activating effect the oxygen of the ether linkage exerts on the adjacent methylene is absent in the ester. Butyrolactone is stable toward further oxidation and attempts to carry the oxidation to succinic anhydride failed. Tetrahydrofurfuryl alcohol reacted similarly to give a compound tentatively identified as an aldehyde lactone, by analogy to the oxidation of tetrahydrofuran, by its infrared spectrum, (5.60, 5.75 μ) and by formation of a 2,4-dinitrophenylhydrazone.

This novel and gentle oxidation of ethers to esters appeared to offer a route by oxidation of an ethylene oxide to a hitherto unknown class of compound, an α-lactone. Isolation of an α-lactone would be of considerable theoretical interest. These compounds have been proposed as intermediates to account for certain stereochemical results in displacement reactions of α-substituted acids,[6] but the same results have been alternatively interpreted as involving a dipolar ion.[7] Accordingly, ethylene oxide was oxidized at 0° in carbon tetrachloride with ruthenium tetroxide in the hope of obtaining evidence for even a transitory existence of an α-lactone. The oxidation was much slower than that of tetrahydrofuran, and as it proceeded the flask became filled with a thick, very sticky, precipitate resembling polyglycolide.[8] The cold solvent was decanted and examined by infrared. No trace of an absorption band in the expected 5.2–5.4 μ region was found[9]; all absorption was due to unreacted oxide. Perhaps the decomposition and polymerization of the α-lactone was catalyzed by either ruthenium tetroxide or ruthenium dioxide in much the same way that propiolactone is polymerized to a polyester with extreme rapidity when mixed with certain Friedel–Crafts catalysts.[10]

Benzene and pyridine react immediately with ruthenium tetroxide, but the products could not be identified. The lability of the aromatic nucleus to ruthenium tetroxide suggested that this might be a novel reagent for destroying the aromatic nucleus of an alkyl benzene at the same time leaving the side-chain intact. Accordingly, an attempt was made to oxidize 2-phenylbutane with excess ruthenium tetroxide. A product was obtained whose infrared spectrum showed a carbonyl band at 5.88 μ, and which gave a 2,4-dinitrophenylhydrazone, but it could not be purified. Possibly the benzene ring was oxidized randomly to a mixture of carbonyl compounds. Benzene itself gave a carbonyl compound not further identified. Other aromatics examined were dibenzyl, triphenylmethane, tetralin, α-nitronaphthalene, azobenzene, phenylacetylene and tolan. Reaction was immediate in all cases, but no oxidation products could be isolated.

Amines are not oxidized as smoothly as alcohols or ethers. Ruthenium tetroxide was treated with triamylamine, diethylamine and piperidine, but all gave intractable products. In each case the infrared spectrum of the reaction mixture was compatible with that of an amide, but pure products could not be obtained. *n*-Hexylamine gave a product whose infrared spectrum indicated the presence of an aldehyde (5.83 μ) and a nitrile (4.44 and 7.00 μ). There were no absorption bands in the amide region.

Although esters are stable to ruthenium tetroxide, amides are not. Amides are oxidized to imides. Butyrolactam was converted in good yield to succinimide. *n*-Hexylamine was acylated with heptoyl chloride and the resultant amide oxidized. The amide reacted readily yielding an imide, identified by its infrared spectrum[11] (3.1, 5.74, 5.92 μ) and analysis. This oxidation of amides provides a new degradative tool in nitrogen chemistry.

Experimental

Preparation of Ruthenium Tetroxide.—The following procedure for the preparation of ruthenium tetroxide from acid solution was found convenient. The generator was composed of the following pieces of standard equipment: a 200-cc. round-bottom flask, a three-way 75° connecting tube with 10/30 thermometer opening, a 10/30 plug, a two-way 105° connecting tube with a suction tube, and a long test-tube used as an ice-cooled condenser. All connections were unlubricated, ground-glass joints. The suction tube was connected by means of a short length of Tygon tubing to a gas-washing bottle containing some carbon tetrachloride. A solution of 4.37 g. of ruthenium trichloride (containing 18% water) in 80 ml. of a 0.5 *N* hydrochloric acid was placed in the flask and heated to boiling. A 1 *N* sodium bromate solution was added, a few cc. at a time, to the mixture through the 10/30 opening. The mixture was boiled gently while ruthenium tetroxide and water distilled into the ice-cooled condenser. More sodium bromate solution was added until further addition failed to generate any

---

[5] A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

[6] W. A. Cowdery, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1254 (1937).

[7] E. Grunwald and S. Winstein, THIS JOURNAL, **70**, 841 (1948).

[8] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IB, p. 790, Elsevier Press, New York, N. Y., 1952.

[9] β-Butyrolactone absorbs at 5.50 μ, γ-valerolactone at 5.65 μ and δ-valerolactone at 5.75 μ.

[10] T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **70**, 998 (1948).

[11] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1954, p. 190.

Starting matl.	Product	Yield, %	Derivative	M.p., °C.	
				Obsd.	Lit.
l-Menthol	*l*-Menthone	96	Semicarbazone	194–196	193[a]
3β-Cholestanol	3-Cholestanone	49	2,4-DNPH	227–228	228–230[b]
Benzyl alcohol	Benzaldehyde	90	2,4-DNPH	238–240	237[c]
n-Hexyl alcohol	Caproic acid	10	*p*-Br-phenacyl ester	71–72	72[c]
trans-1,2-Cyclohexanediol	1,2-Cyclohexanedione	15	2,4-DNPH	217–218	218–219[d]
Benzaldehyde	Benzoic acid	33	. . .	122–123	121[c]
n-Heptaldehyde	Heptanoic acid	30	*p*-Br-phenacyl ester	68–70	72[c]
Cyclohexene	Adipaldehyde	10	2,4-DNPH	240–242	241–242[e]
1-Octene	Heptaldehyde	12	2,4-DNPH	107–108	108[c]
Tetrahydrofuran	γ-Butyrolactone	100	Phenylhydrazide	88–89	. . .
n-Hexylheptamide	Heptoylhexoylamine	58	. . .[f]	89–90	. . .

[a] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 11B, Elsevier Press, New York, N. Y., 1953, p. 515. [b] C. Djerassi, THIS JOURNAL, **71**, 1003 (1949). [c] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, N. Y. 1948. [d] H. Adkins and A. G. Rossow, THIS JOURNAL, **71**, 3836 (1949). [e] W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956). [f] *Anal.* Calcd. for $C_{13}H_{25}NO_2$: C, 68.72; H, 11.01. Found: C, 69.29; H, 11.00.

more ruthenium tetroxide. The supernatant water in the condenser was removed by a capillary dropper and the residue of ruthenium tetroxide, 1.5 g., was dissolved in 10 ml. of carbon tetrachloride to give a deep red solution. The yield of ruthenium tetroxide in a number of preparations averaged 55%.

Reaction of Ruthenium Tetroxide with Cyclohexanol.—The above ruthenium tetroxide solution was added dropwise with stirring to a solution of 1.50 g. (0.015 mole) of cyclohexanol in 10 ml. of carbon tetrachloride, cooled in ice, at a rate slow enough to maintain a temperature of 10–15°. Reaction was very fast and a black precipitate formed immediately. The reaction mixture was allowed to stand overnight at room temperature. The precipitated ruthenium dioxide (2.18 g.) was filtered off and washed with carbon tetrachloride. Continuous chloroform extraction of the ruthenium dioxide yielded 87 mg. of organic residue. This was combined with the residue of 1.09 g. found in the carbon tetrachloride filtrate and washings. Removal of the solvents left a residue containing 72% cyclohexanone by infrared analysis. Assay of the ruthenium dioxide precipitate (42.6% ruthenium) showed a 93% yield of cyclohexanone based on ruthenium tetroxide. The semicarbazone was prepared, m.p. 165–166°, m.m.p. 165–166°.

Reaction of Ruthenium Tetroxide with *n*-Butyl Ether.—In the same manner, 2.55 g. (0.02 mole) of *n*-butyl ether was treated with 1.91 g. of ruthenium tetroxide. Formation of ruthenium dioxide after the first addition of ruthenium tetroxide did not occur until after a few minutes. However, after this "induction period" reaction proceeded at a good rate as evidenced by the rise in temperature. The filtrate and washings of the ruthenium dioxide were washed with sodium bicarbonate solution to remove a very small amount of butyric acid. Infrared analysis of the reaction product showed an essentially quantitative yield of *n*-butyl *n*-butyrate.

Reaction of Ruthenium Tetroxide with γ-Butyrolactam.—In the same manner, 1.33 g. (0.015) of γ-butyrolactam was treated with 1.69 g. of ruthenium tetroxide. The filtrate and washings of the ruthenium dioxide were evaporated to leave 0.5 g. of solid material (49%). After one recrystallization from acetone, the m.p. was 124–126°. The m.m.p. with an authentic sample of succinimide was 125–6°.

Reaction of Ruthenium Tetroxide with Other Compounds.—In the same manner, the following compounds were oxidized by ruthenium tetroxide. Yields in many cases are probably not optimum. The low yield of aldehyde from the oxidation of olefins is attributed to difficulty in removing aldehyde absorbed on the precipitated ruthenium dioxide. No other products were found in the reaction mixture. Identification was made by infrared spectra and by the derivatives listed. All melting points are uncorrected. Infrared spectra were determined by Mr. O. Wolsky on a Perkin-Elmer double beam spectrophotometer, model 21. Microanalyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, N. Y.

Acknowledgment.—The procedure of oxidizing ruthenium trichloride to the tetroxide was worked out by Mr. Frank A. Meier.

NEWARK 2, N. J.