Xenon Trioxide Oxidation of Certain Alcohols

By HAROLD J. RHODES and MARTIN I. BLAKE

A series of alcohols, aliphatic and aromatic, was oxidized with xenon trioxide. Oxidation to carbon dioxide and water was effected by adding a known excess of xenon trioxide to the reaction mixture. The excess reagent was determined iodometrically. Of the alcohols tested only triphenylcarbinol resisted oxidation. Essentially quantitative recoveries were obtained for ethanol, normal, secondary, and tertiary butyl alcohols, benzyl alcohol, benzohydrol, and cinnamyl alcohol.

THE PREPARATION and oxidizing properties of xenon trioxide in aqueous solution have been described by Williamson and Koch (1) and Appelman and Malm (2). Jaselskis and his associates have studied the xenon trioxide oxidation of a variety of organic structures including vic-diols, certain primary and secondary aliphatic alcohols, and a number and variety of acids. Quantitative analytical procedures sensitive in the microgram range were developed for these compounds. Those studies have been referred to in an earlier paper (3) which described the xenon trioxide oxidation of benzyl alcohol and benzaldehyde.

The present investigation concerns the determination and stoichiometry involved in the oxidation of certain aliphatic and aromatic alcohols. These include ethanol, normal, secondary, and tertiary butyl alcohols, benzyl alcohol, benzohydrol, triphenylcarbinol, and cinnamyl alcohol. This selection of alcohols permitted a correlation of chemical structure and oxidation capacity.

EXPERIMENTAL

Solutions and Reagents—Xenon trioxide solution (0.0199 *M* to 0.0493 *M*) was prepared by diluting a concentrate (0.2 *M*) with water. The preparation of the concentrated xenon trioxide solution by hydrolysis of xenon hexafluoride has been described by Appelman and Malm (2).

The following stock solutions of the different alcohols were prepared: 0.157 *M* ethanol, 0.253 *M* *n*-butyl alcohol, 0.101 *M* *sec*-butyl alcohol, 0.0915 *M* *tert*-butyl alcohol, 0.0100 *M* and 0.0020 *M* benzyl alcohol, 0.0020 *M* benzohydrol, 0.0020 *M* cinnamyl alcohol, and a suspension of triphenylcarbinol in water (50.0×10^{-3} mmoles in 10 ml. of water).

Sulfuric acid, 10% w/v, and starch test solution. All chemicals and solvents were reagent grade.

Procedure—Aliquots of the alcohol stock solution containing between 0.5×10^{-3} and 20×10^{-3} mmole of the alcohol were added by micropipet to a series of 50-ml. glass-stoppered conical flasks. Ten milliliters of distilled water was added to each flask. Xenon trioxide solution in known excess was added to each solution. The flasks were stoppered and swirled gently to assure homogeneous distribution of the reactants. The reaction mixtures containing the aliphatic alcohols were allowed to stand at room temperature for at least 17 hr. The oxidation of the aromatic alcohols was permitted to continue for longer periods of time; 5 days for cinnamyl alcohol, 6 days for benzyl alcohol, 8 days for benzohydrol, and 30 days for triphenylcarbinol. In each series one flask contained no alcohol and served as a blank. At the end of the reaction period 5.0 ml. of 10% sulfuric acid solution and 1.0 Gm. of potassium iodide were added to each flask. The liberated triiodide was titrated with standard sodium thiosulfate solution using a 10-ml. microburet. As the end point was approached 3 drops of starch solution was added and the titration was continued until the solution turned colorless. The number of millimoles of xenon trioxide consumed in the oxidation was determined from the normality of the thiosulfate solution and the difference in the volumes consumed by the blank and the sample. The millimoles of xenon trioxide consumed in the oxidation was plotted against the millimoles of alcohol added. The slope and *y*-intercept were determined from the data by the least squares method.

In preliminary studies reaction mixtures were prepared of all alcohols and xenon trioxide in minimum excess. The rate of oxidation was followed by analyzing for xenon trioxide consumed after varying periods of time.

Because of the low solubility of triphenylcarbinol in water, 50.0×10^{-3} mmole of the alcohol was dispersed in 10 ml. of water. An excess (493.0×10^{-3} mmole) of xenon trioxide solution was added and the solution was stirred with a magnetic stirrer for 30 days at room temperature. After varying periods of time, an aliquot of the supernatant was analyzed for unspent xenon trioxide.

Gas-liquid chromatography (GLC) and thin-layer chromatography (TLC) were employed to detect whether reaction products other than carbon dioxide and water were formed under the reaction conditions employed. The details of these procedures were described in the previous paper (3); however, pertinent GLC and TLC data are included here.

RESULTS AND DISCUSSION

A series of alcohols of varying structure were oxidized with xenon trioxide. Oxidation of the aliphatic alcohols proceeded rapidly forming carbon dioxide and water as the only reaction products. Although preliminary studies indicated that for the aliphatic alcohols reaction was complete in less than 4 hr., a 17-hr. reaction period was selected for these compounds. The pH of all reaction mixtures was about 4. Analysis of the reaction mixtures by GLC and TLC indicated that oxidation was complete; neither starting alcohol nor intermediate oxidation products were detected. With the water-soluble aromatic alcohols, benzyl alcohol, benzohydrol, and cinnamyl alcohol, a 17-hr. reaction period gave incomplete oxidation, as evidenced by the detection of

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TABLE I—RESULTS OF VAPOR PHASE AND THIN-LAYER CHROMATOGRAPHIC ANALYSIS OF REACTION MIXTURES OF BENZOHYDROL, CINNAMYL ALCOHOL, AND TRIPHENYLCARBINOL

Compd.	Vapor Phase Chromatography Col. Temp., °C.	Vapor Phase Chromatography Retention Time, sec.	Thin-Layer Chromatography[a] $R_f \times 100$
Benzohydrol	190	154	60
Benzophenone	190	92	86
Cinnamyl alcohol	200	308	22
Cinnamaldehyde	200	180	52
Cinnamic acid	200	1440	16
Triphenylcarbinol	190	206	71

[a] Silica Gel HF_{254}; two ascending developments with chloroform for 67 min. each; detection by scanning with ultraviolet light.

oxidation products and unreacted alcohol employing GLC and TLC methods of analysis. The benzyl alcohol reaction was found to contain benzaldehyde, benzoic acid, and unreacted benzyl alcohol. Complete oxidation was noted, however, after 6 days. Benzophenone, benzoic acid, and unreacted benzohydrol were detected in the benzohydrol reaction mixture. However, after 8 days no detectable quantities of organic compounds were observed. The cinnamyl alcohol reaction mixture showed the presence of the corresponding aldehyde and acid along with the unreacted alcohol. After 5 days oxidation was complete. TLC and GLC data characterizing benzyl alcohol, benzaldehyde, and benzoic acid were reported in the previous paper (3). The results for the other alcohols and their corresponding oxidation products are shown in Table I.

Because of poor solubility, a heterogeneous system was used for studying the oxidation of triphenylcarbinol. The xenon trioxide content of the reaction mixture remained unchanged even after a 30-day reaction period. The reaction mixture was extracted with ether and the ether extract was examined by GLC and TLC. Triphenylcarbinol was the only compound identified in the extract. This alcohol appears to be resistant to xenon trioxide oxidation. GLC and TLC data for triphenylcarbinol are shown in Table I.

The results of the oxidation studies are shown in Table II. The concentrations of the alcohol and xenon trioxide before reaction, the amount of xenon trioxide actually consumed in the reaction, and the ratio of xenon trioxide to alcohol involved in the reaction are recorded in the table. A plot of alcohol concentration *versus* xenon trioxide concentration consumed in the oxidation gives a straight line which intersects the ordinate above the origin. The y-intercept and slope, obtained by least square treatment of the data shown in Table II, and the theoretical slope are recorded in Table III. A similar approach was used by Jaselskis and Warriner (4) for the oxidation of methanol, ethanol, and 2-propanol. They attributed the nonstoichiometric nature of the reaction to secondary processes which occur in the oxidation. Theoretically, the curve should pass through the origin ($c = 0$) and the slope of the line should correspond to the ratio of xenon trioxide to alcohol, assuming complete oxidation to CO_2 and H_2O. Such a plot is useful as a calibration curve for determining

TABLE III—RESULTS OF LEAST SQUARE TREATMENT OF DATA FOR EACH ALCOHOL

Alcohol	y-Intercept, mmoles $\times 10^3$	Slope, m	Theoretical Slope,[a] m'
Ethanol	1.29	2.02	2.00
n-Butyl alcohol	2.82	3.75	4.00
sec-Butyl alcohol	1.38	3.76	4.00
tert-Butyl alcohol	2.88	3.76	4.00
Benzyl alcohol	0.27	5.75	5.67
Benzohydrol	2.83	8.84	10.33
Cinnamyl alcohol	2.41	6.84	7.33

[a] Based on alcohol being completely oxidized to carbon dioxide and water.

TABLE II—RESULTS OBTAINED FROM XENON TRIOXIDE OXIDATION OF ALCOHOLS

Alcohol	Alcohol Taken, mmoles $\times 10^3$	Alcohol[a] Found, mmoles $\times 10^3$	Xenon Trioxide Taken, mmoles $\times 10^3$	Xenon Trioxide Consumed, mmoles $\times 10^3$	Xenon Trioxide to Alcohol Ratio
Ethanol	15.70	15.56	57.60	34.90	2.22
	7.85	8.18	57.60	18.90	2.42
	1.57	1.44	57.60	11.90	2.74
n-Butyl alcohol	12.60	12.58	58.00	50.00	3.97
	5.10	5.17	58.00	20.50	4.05
	2.50	2.45	58.00	11.89	4.66
sec-Butyl alcohol	10.10	10.08	40.00	39.30	3.89
	5.10	5.14	40.00	20.71	4.10
	2.00	1.94	40.00	8.66	4.28
tert-Butyl alcohol	9.50	9.47	40.00	38.50	4.04
	4.76	4.86	40.00	21.15	4.44
	1.90	1.84	40.00	9.79	5.60
Benzyl alcohol	2.32	2.29	20.00	16.04	6.90
	1.55	1.61	20.00	12.13	7.83
	0.77	0.74	20.00	7.13	9.20
Benzohydrol	1.50	1.49	20.00	15.99	10.66
	1.00	1.02	20.00	11.83	11.83
	0.50	0.49	20.00	7.20	14.40
Cinnamyl alcohol	1.53	1.51	20.00	12.77	8.35
	1.02	1.05	20.00	9.58	9.40
	0.51	0.50	20.00	5.80	11.38

[a] Calculated from the equation: $y = c + mx$, from data for each alcohol, where y is mmoles of xenon trioxide consumed, c is the y-intercept, m is the slope, and x is mmoles of alcohol.

the alcohol content in a sample for analysis as suggested by Jaselskis and Warriner, or the equation:

$$y = c + mx$$

may be solved; where c is the y-intercept, m is the slope, y is the millimoles of xenon trioxide, and x is the millimoles of alcohol in the sample. This technique was applied to the alcohol samples listed in the first column of Table II. The alcohol concentrations found by substituting in the above equation are listed in the second column. Per cent recovery was better than 97% in most cases.

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Synthesis of Ketoximino Esters as Antihistaminics

By S. L. LEE, B. B. WILLIAMS, and M. M. KOCHHAR*

In a search for new antihistamines, a series of oximino esters of 2-, 3-, and 4-benzoylpyridine oxime and 2-benzoylthiophene oxime was prepared. The respective ketones were oximinated in pyridine with hydroxylamine hydrochloride. The esterification was conducted in benzene with equimolar quantities of acetyl chloride, oxime, and a basic reagent. Twelve new oximino esters were synthesized and evaluated for their antihistaminic activity. All synthesized compounds exhibited antihistaminic activity with almost no anticholinergic action. The propionyl analogs showed the most significant antihistaminic effectiveness.

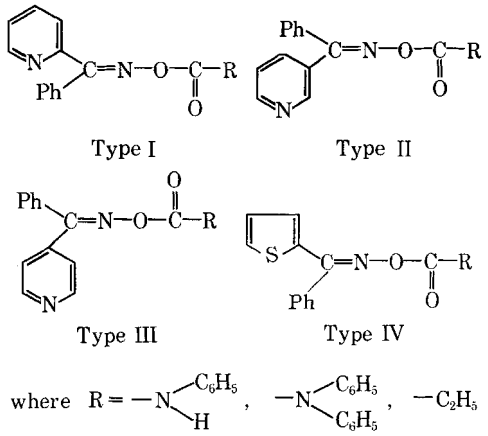
BOVET (1) issued preliminary reports concerning the first effective synthetic antihistaminic drugs. Since that time, a multitude of compounds have been prepared and tested for antihistaminic activity. The chemical structures of these antihistaminic drugs vary, yet the prominent compounds exert similar pharmacological and therapeutic action. Several review articles (2–5) have appeared in the literature. Some of the many useful antihistaminic agents differ sufficiently to hold out hope of attaining drugs which would be more specific for a given allergic manifestation.

Most commonly used drugs can be classified as derivatives of ethanolamine, ethylenediamine, aminopropane, phenothiazine, or piperazine (6). Almost all of these compounds contain a terminal tertiary nitrogen, generally having dimethyl substitution or part of the heterocyclic structure. In the ethanolamine series, the most effective group attached to the oxygen atom has been found to be the benzhydryl radical (7); whereas in the ethylenediamine series, several different radicals on the second nitrogen of the chain have led to active compounds. Several physical properties of antihistaminics have been studied in an effort to relate them to activity of the various drugs (8), but no direct relationship can be made between physical properties and antihistaminic activity.

These observations prompted the investigations reported in this paper. The object of the present work was to prepare and examine some of the oximino esters of benzoylpyridines and benzoylthiophene and to determine whether they possessed significant antihistaminic action.

DISCUSSION

The compounds which were selected for synthesis are the oximino esters of benzoylpyridines and benzoylthiophenes (types I, II, III, and IV).



The preparation of 12 new esters of type I, II, III, or IV, starting with respective benzoylpyridines and 2-benzoylthiophene, was accomplished by modifying the methods described in the literature (9, 10).

The oximes selected in this study included representatives of both syn- (types I and III) and anti- (types II and IV) configuration. The esters were not geometrically confirmed since it was assumed that esterification did not alter configuration. The purpose of including compounds of both configurations was to allow some comparison of antihistaminic effect of the isomers. Pharmacological screening provided no evidence of effect of geometric configuration on intensity of antihistaminic action.

The basic unit for all effective agents contains the ethylamine skeleton in one form or another. It is interesting that the ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole ring. With this in mind the authors attempted replacement of the

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