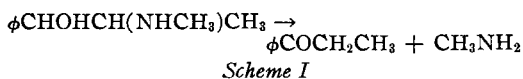


Chemistry of the Ephedrine Spot Test Based on Its Pyrolytic Oxidation to Acetaldehyde by Sodium Bismuthate

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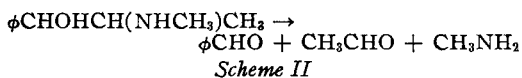
The presence of acetaldehyde in the pyrolysis products resulting from heating ephedrine with sodium bismuthate can be explained by a hydramine fission reaction or a periodate-type α -aminoalcohol mechanism. Model experiments using gas chromatographic analysis indicate that the reaction is analogous to a periodate oxidation.

FEIGL AND SILVA (1) described a sensitive and selective spot test for ephedrine based on the detection of acetaldehyde produced by heating the alkaloid or its salts with sodium bismuthate. They rationalized the reaction as a hydramine fission of the phenethanolamine to methylamine and propiophenone catalyzed by the alkalinity of the bismuthate reagent (Scheme I) followed by oxida-



tion of the latter to acetaldehyde by excess bismuthate. The authors have found that propiophenone responds to the ephedrine spot test with a detection limit of less than 3 mcg., which lends credence to their explanation of the reaction route; however, an alternative explanation is possible.

Rigby (2) described the use of sodium bismuthate in acid solution for the facile cleavage of 1,2-glycols to aldehydes and ketones and for related reactions analogous to those effected by lead tetraacetate and periodic acid. The periodate oxidation of ephedrine was first reported by Wickström (3), who identified the products as benzaldehyde, acetaldehyde, and methylamine (Scheme II). He showed that the oxidation was highly dependent on pH,



proceeding quantitatively in minutes at room temperature at pH 7.5, but at an immeasurably slow rate at pH 6 or lower. Chafetz (4) indicated that periodate oxidation of phenethanolamines appears to require the availability of an unshared electron pair on the amine nitrogen. Assuming that the bismuthate and periodate reactions proceed by analogous mechanisms, one would not expect the acidic reagent described by Rigby to react with ephedrine; however, the spot test is performed with dry sodium bismuthate, an aqueous suspension of which gives a strongly alkaline reaction.

The problem of discriminating between the alternative reaction routes resolves itself to a matter of determining whether benzaldehyde or propiophenone is produced by the reaction of ephedrine with bismuthate. The experiments described here were designed to provide elucidation.

EXPERIMENTAL

Equipment and Supplies—Ephedrine HCl N.F., sodium bismuthate, propiophenone, benzaldehyde,

isooctane, methylene chloride, and 2,4-dinitrophenylhydrazine were the best available laboratory grades used without further purification. A Beckman DK-2 recording spectrophotometer was used with 1-cm. silica cells for U.V. measurements. A Perkin-Elmer model 801 gas chromatograph was employed using the following experimental parameters.

Column: a 2 M. glass helix of 0.25 in. o.d. packed with 3% HI-EFF 8 BP on 100/120 mesh Gas Chrom Q (Applied Science Laboratories, Inc., State College, Pa.); injector temperature: 200°; helium flow: 40 ml./min.; hydrogen flow: 30 ml./min.; column temperature: 80°, programmed immediately after injection at 10°/min. to a final temperature of 150°; sample collection: a Perkin-Elmer 008-0525 sample collector chilled in a Dewar flask of dry ice-acetone was used with a collection ratio of 4 parts effluent to the collector and 1 part to the flame ionization detector.

Reaction of Ephedrine with Aqueous Bismuthate

—A solution of 2.0 mg. of ephedrine HCl in 5.0 ml. of water was mixed with a suspension of 330 mg. of sodium bismuthate in 1 ml. of water and 20.0 ml. of isooctane in a 50-ml. glass-stoppered centrifuge tube. The stoppered mixture was heated 30 min. in a boiling water bath and cooled at the tap. The isooctane layer was filtered through Whatman No. 1 paper, and its ultraviolet spectrum was scanned from 300 to 205 μ versus solvent. The extent of conversion of ephedrine to benzaldehyde was calculated from the ratio of the molar absorptivity obtained in this experiment to the molar absorptivity of benzaldehyde in isooctane determined concomitantly.

A mixture of 2 Gm. of ephedrine HCl and 3.5 Gm. of sodium bismuthate was heated at reflux with 5 ml. of water in a round-bottom flask for 15 min. The cooled mixture was extracted with ether twice, and the ether was allowed to evaporate. The residue was taken up in 20 ml. of alcohol and treated with 10.0 ml. of 2,4-dinitrophenylhydrazine reagent prepared by dissolving 800 mg. of 2,4-dinitrophenylhydrazine in 4 ml. of concentrated sulfuric acid to which 6 ml. of water and 10 ml. of alcohol are added after cooling. The resulting 2,4-dinitrophenylhydrazone was recrystallized from alcohol. Its melting point was determined by the capillary method in a Thomas-Hoover apparatus and compared with that of authentic benzaldehyde 2,4-dinitrophenylhydrazone.

Pyrolysis and Gas Chromatography Experiments—Pyrolysis was effected in a test tube fitted with a sidearm. The vapors were collected through a pipet secured with rubber tubing in 1 ml. of methylene chloride in a second test tube. The pyrolysis tube was heated with a free flame until the vapors were observed to have been driven into

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the collection tube (no more than 5 min.). The following mixtures were pyrolyzed: 500 mg. of ephedrine HCl and 1.65 Gm. sodium bismuthate, 200 mg. propiophenone and 800 mg. sodium bismuthate, 500 mg. ephedrine HCl and 1.5 Gm. sodium hydroxide pellets, 0.5 ml. acetaldehyde and 1.5 Gm. sodium bismuthate, 0.5 ml. acetaldehyde and 1.5 Gm. sodium hydroxide pellets.

The methylene chloride solutions obtained were injected into the gas chromatograph, using 5- μ l. volumes. Peaks with retention times corresponding to benzaldehyde and propiophenone were collected, and the trapped fractions were washed into 1-cm. cells with methanol and scanned in the ultraviolet range with the recording spectrophotometer.

RESULTS AND DISCUSSION

Ephedrine Reaction with Aqueous Bismuthate—

A conversion of 2% of the ephedrine to benzaldehyde was obtained under the conditions used. The low yield is not unexpected, for the bismuthate is both insoluble and unstable in aqueous medium. The ultraviolet spectra of benzaldehyde and propiophenone are closely similar, and for this reason the identity of the product was checked by derivative formation. The 2,4-dinitrophenylhydrazone obtained in the second experiment melted at 236°. Authentic benzaldehyde 2,4-dinitrophenylhydrazone melted at 236°, and the mixed melting point was not depressed. The literature (5) melting point for benzaldehyde 2,4-dinitrophenylhydrazone is 237°, while the propiophenone derivative melts at 191°. The reaction in aqueous medium appears analogous to periodate oxidation, and it might be expected to proceed by a similar mechanism.

Pyrolysis Experiments—Dry-heating ephedrine with sodium bismuthate led to six major peaks. The peak with the retention time of benzaldehyde (4.0 min.) constituted 13.8% of the total detector response as determined by the internal normalization technique. The methanol solution of the isolated peak showed an absorption maximum at 244 m μ , and its spectrum corresponded with that of benzaldehyde in methanol. Other peaks were found with retention times of 2.4, 2.8, 6.0, 7.5, 8.4, 12.4, 14.4, and 16.0 min. The major peak, which amounted to nearly 75% of the total response, had a retention time of 12.4 min. It was not identified. The peak which eluted at 7.5 min. amounted to 2.5% of the total and eluted at about the same time as

propiophenone. However, its ultraviolet spectrum after elution did not correspond with propiophenone; it had an absorption maximum at 270 m μ . Sodium bismuthate is a very alkaline material, and complex aldol and Cannizzaro products might well be expected. Heating ephedrine with sodium hydroxide led to a typical pyrolysis chromatogram with a large number of peaks and no major components. Pyrolysis of propiophenone with sodium bismuthate leads to a positive test for acetaldehyde under the Feigl and Silva conditions; however, the gas chromatogram showed no peak corresponding to benzaldehyde. This indicates that propiophenone is not an intermediate in the formation of benzaldehyde from ephedrine. Heating acetaldehyde with either sodium hydroxide or sodium bismuthate led to only minor amounts of products.

SUMMARY AND CONCLUSIONS

The Feigl and Silva rationalization of the spot test they described for ephedrine (1), detection of acetaldehyde after pyrolysis of the alkaloid with sodium bismuthate, was hydramine fission to propiophenone and methylamine followed by oxidation of propiophenone to acetaldehyde and other products. No propiophenone was detected in the reaction of ephedrine with bismuthate either during heating in aqueous medium or under pyrolytic conditions, which militates against acceptance of the hydramine fission explanation for the reaction. An alternative rationalization is presented: periodate-type cleavage of the ethanolamine side chain of ephedrine to benzaldehyde, acetaldehyde, and methylamine. Evidence supporting the alternative explanation includes the analogous behavior of bismuthate with periodate on glycols, identification of benzaldehyde as a product of oxidation of ephedrine by bismuthate under both aqueous and pyrolysis conditions, and the absence of benzaldehyde as a pyrolysis product of propiophenone with bismuthate. Gas chromatographic analysis of the ephedrine pyrolyzate showed it to be a complex mixture of products, of which benzaldehyde amounted to 14% and a major component accounted for nearly 75% of the total detector response.

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