Acknowledgment. The authors are indebted to Dr. J. B. Dickey of the Tennessee Eastman Co. for samples of Ibanitrile and to the National Science Foundation for a grant in partial support of this research.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE 8, KY.

Synthesis and Properties of *N*-Acetoxytrimethylammonium Bromide[1]

WALTON B. GEIGER

Received July 12, 1957

N-Acetoxytrimethylammonium bromide, which is the initial member of a homologous series of parasympathomimetic substances including acetyl-*nor*-choline[2] (acetoxymethyltrimethylammonium bromide), acetylcholine, and acetyl-*homo*-choline[3] (3-acetoxy-*n*-propyltrimethylammonium bromide), seems not to have been previously described. This substance may be considered to be an acetylated derivative of trimethylamine-*N*-oxide, or as a quaternary hydroxylammonium salt. It has been found possible to prepare the substance by the reaction of acetyl peroxide with trimethylamine:

$$Ac_2O_2 + Me_3N \longrightarrow (Me_3NOAc)^+ + OAc^-$$

Attempts to make the compound by other routes, such as the reaction of trimethylamine with lead tetraacetate, acetylation of trimethylamine-*N*-oxide with acetyl bromide, and methylation of the *O*-acetyl-*N*-dimethylhydroxylamine with methyl iodide seem to have led to poor yields of highly impure material, since biological assay of the crude products showed only low levels of parasympathomimetic activity.

The assigned structure is supported both by the analytical data, and by the properties of the substance. The presence of a trimethylamino group was indicated by the formation of trimethylamine on both acid and alkaline hydrolysis. Reaction with Hestrin's[4] reagent solutions (alkaline hydroxylamine followed by acidified ferric chloride), which indicates the presence of an ester-like linkage, proceeded somewhat more slowly than with acetylchlorine, 15 minutes being required at 25°. The product had the same molar extinction coefficient at 540 mμ as acetylcholine.

N-Acetoxytrimethylammonium bromide shows parasympathomimetic properties. The substance causes the contraction of guinea pig ileum at $1.7 \times 10^{-6}M$, an action which is prevented by atropine, $4.8 \times 10^{-5}M$. The substance also stimulates eserinized leech dorsal muscle at $1.7 \times 10^{-5}M$, and eserinized frog *rectus abdominis* muscle at $4.3 \times 10^{-6}M$.

N-Acetoxytrimethylammonium bromide is not hydrolyzed by the acetylcholinesterase of guinea pig brain, but is hydrolyzed by horse serum cholinesterase about one-tenth as rapidly as acetylcholine. *N*-Acetoxytrimethylammonium bromide, $1.8 \times 10^{-3}M$, does not inhibit the action of horse serum cholinesterase on acetylcholine.

EXPERIMENTAL

N-Acetoxytrimethylammonium bromide. To 118 g. of a 25% solution of acetyl peroxide (0.25 mole) in dimethyl phthalate,[5] cooled to −5°, was added over 2 hr. 7.4 g. of trimethylamine (0.125 mole) in 25 ml. of sodium-dried ether. (Insufficient cooling has led to explosions.) The reaction mixture was kept at −5° for 48 hr., and was then shaken with 100 ml. of water and 60 ml. of ether. The *p*H of the aqueous layer, originally about 4.6, was adjusted to 3.6 by adding about 12 ml. of concentrated hydrobromic acid, and was reextracted with about ten 50-ml. portions of ether until a test for peroxides with starch-iodide paper was negative. The *p*H was continuously readjusted to 3.6 during this process. The aqueous solution was concentrated under reduced pressure to a crystalline mass, which was dried *in vacuo* over phosphorus pentoxide. The dried solid was refluxed with several 100-ml. portions of dry chloroform, and the extracts were chilled overnight at −5°. The crystals that appeared were filtered off, washed with cold chloroform, and dried *in vacuo* over phosphorus pentoxide. The yield was usually about 3.5 g. The substance (noticeably hygroscopic) melted at 148° with gas evolution.

Anal. Calcd. for $C_5H_{12}O_2NBr$: C, 30.32; H, 6.11; N, 7.07; Br, 40.35. Found:[6] C, 29.65; H, 6.78; N, 6.67; Br, 39.34.

The data indicate the presence of about 2% of water. The chloroplatinate melted at 242°, the chloroaurate at 145°, and the reineckate at 159°. All melting points have been corrected.

Hydrolysis of N-acetoxytrimethylammonium bromide. The substance (0.1 g.) was refluxed with 5.0 ml. of 0.1*M* hydrobromic acid for 1 hr. The hydrolyzate was evaporated to dryness *in vacuo*, and the residue crystallized from alcohol and ether. The product melted at 245°. A mixed melting point with an authentic sample of trimethylamine hydrobromide (melting point, 245°) showed no depression. Treatment of the substance with alkali, and aeration of the gaseous product into dilute hydrobromic acid, yielded the same product.

Anal. Calcd. for $C_3H_{10}NBr$: C, 25.79; H, 7.20; N, 10.00. Found:[6] C, 25.84; H, 7.33; N, 9.94.

Enzyme and pharmacological tests. The tests for susceptibility to acetylcholinesterase and cholinesterase were made manometrically, as described by Augustinsson.[7] The assays with guinea-pig ileum, leech dorsal muscle, and frog *rectus*

(1) Supported by grants from the National Heart Institute (H-2321), and the National Science Foundation (G-2500).

(2) R. R. Renshaw and J. C. Ware, *J. Am. Chem. Soc.*, **47**, 2990 (1925).

(3) D. Glick, *J. Biol. Chem.*, **125**, 729 (1938).

(4) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

(5) From Becco Chemical Division, Food Machinery and Chemical Corp., Buffalo 7, N. Y.

(6) By Joseph F. Alicino, Box 267, Metuchen, N. J.

(7) K. B. Augustinsson, *Acta Physiol. Scand.*, **15**, Suppl. 52, 37 (1948).

abdominis muscle were made as described by MacIntosh and Perry.[8]

SEMMES CHEMISTRY LABORATORY, TRINITY UNIVERSITY, AND SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION
SAN ANTONIO 12, TEX.

(8) F. C. MacIntosh and W. L. M. Perry in *Methods in Medical Research*, Vol. III, 78, Year Book Publishers, New York, 1950.

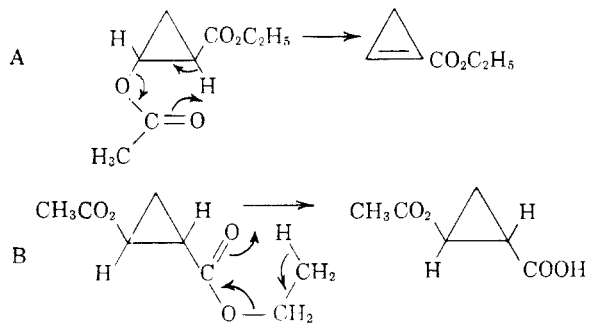
Cyclopropene. II. The Pyrolysis of *trans*-2-Acetoxycyclopropanecarboxylates[1]

KENNETH B. WIBERG AND ROBERT K. BARNES

Received June 17, 1957

The results obtained in the attempted dehydrobromination of ethyl 2-bromocyclopropanecarboxylate[2] indicate that ethyl cyclopropenecarboxylate is particularly reactive towards Michael addition of nucleophilic agents. It would then be desirable to try to prepare this compound using a reaction which may be effected in the absence of any nucleophilic agents. A particularly attractive reaction is the thermal elimination of acetic acid from an acetate ester.

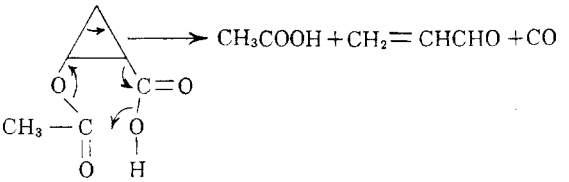
D'yakonov[3] found that the reaction of ethyl diazoacetate with vinyl acetate gave an ethyl 2-acetoxycyclopropanecarboxylate (I). This probably has the *trans*-configuration in analogy with other compounds prepared by this method.[4] The pyrolysis of acetates probably proceeds *via* a cyclic activated complex[5] giving *cis*-elimination. Ethyl 2-acetoxycyclopropanecarboxylate thus has the proper stereochemistry for this type of elimination, and



should give a cyclopropenecarboxylic ester as the product of the pyrolysis if the ease of introducing a double bond into the cyclopropane ring is greater than that of introducing a double bond into the ethyl group. It is known that the pyrolysis of 2° acetates proceeds much faster than that of 1° acetates and this one factor will favor the desired course.

The pyrolysis was first effected at 500°C.[6] using a short contact time, giving starting material, acrolein, acetic acid, ethylene and a small amount of acetic anhydride as the main products. There was also obtained a small amount of a solid acid with an empirical formula $C_6H_8O_4$, which had carbonyl bands in its infrared spectrum at 5.69 μ and 5.87 μ, and also had a broad absorption at 8.12–8.19 μ. The 5.69 μ and 8.12–8.19 μ bands probably correspond to an acetoxy group, and the 5.87 μ band probably corresponds to the carboxylic acid function. The small amount of material available precluded a more thorough investigation, but the available data, and the method of preparation suggest that it is 2-acetoxycyclopropanecarboxylic acid formed by path B.

The other products could arise from this acid as follows:



A *cis*-configuration would appear desirable for this reaction. It is possible that at the reaction temperature the *trans*-compound may be converted to *cis*, or under these conditions, a direct reaction of the *trans*-compound may be possible.

Since the difficulty with this reaction might have been a consequence of initial elimination of ethylene from the ester, followed by decomposition of the acid, the methyl ester which could not lead to the acid was prepared. The pyrolysis of the methyl ester led to the same mixture of products as did the ethyl ester, except that instead of ethylene and acetic acid, methyl acetate was obtained. Thus, this mode of ring cleavage is possible even with an ester.

In connection with other experiments, the methyl ester was subjected to acid catalyzed cleavage. The expected product, methyl β-formylpropionate was formed.

EXPERIMENTAL

Ethyl 2-acetoxycyclopropanecarboxylate. The procedure of D'yakonov[3] was used. A mixture of 290 ml. of freshly dis-

(1) Taken from part of a thesis submitted by R. K. Barnes to the University of Washington in partial fulfillment of the requirements for the Ph.D. degree, 1955. Shell Oil Co. fellow 1953–5.

(2) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4994 (1957).

(3) I. A. D'yakonov, *Zhur. Obshchei Khim.*, **20**, 2289 (1950).

(4) Ethyl acrylate, vinyl bromide, and *t*-butyl vinyl ether all give predominantly the trans isomer on reaction with ethyl diazoacetate (*cf.* ref. 2).

(5) C. D. Hurd and F. H. Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

(6) At lower temperatures, considerable starting material was recovered and the course of the reaction was unchanged. It should be noted that the observed products could not be formed by a route involving the formation of the cyclopropenecarboxylic ester followed by the decomposition of the latter.