[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Derivatives of γ-Acetopropyl Alcohol[1]

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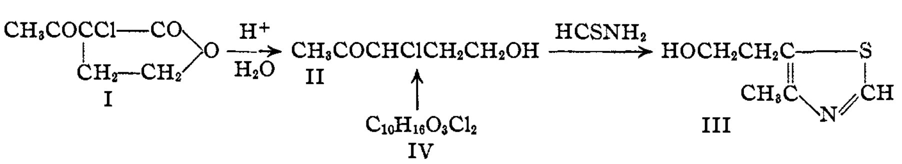
While attempting to prepare pure chloroacetopropyl alcohol (II), following the Buchman[2] synthesis for 4-methyl-5-(β-hydroxyethyl)-thiazole, it was found that the principal product ultimately formed by the decarboxylation of chloroacetobutyrolactone (I) is an ether, $C_{10}H_{16}O_3Cl_2$ (IV), formed from two moles of the expected alcohol by the elimination of one mole of water.



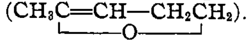
As a result, an investigation was made to determine the structure and properties of this compound, to find out whether this ether formation is possible with γ-acetopropanol and its bromo derivative, and further to prepare chloroacetopropyl alcohol (II) and study its properties.

Discussion

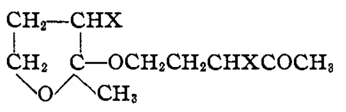
Although the ether is the principal product, chloroacetopropyl alcohol (II) is present in the reaction mixture and can be isolated from it. Chloroacetopropanol is found to be distillable at room temperature (molecular still); on mild heating, it is readily converted to its ether. By warming its *dilute* aqueous solution, the ether in turn is easily hydrolyzed to the alcohol, as demonstrated by the freezing point depression of the aqueous solution and by isolation. The ether with thioformamide hydrate yields 4-methyl-5-(β-hydroxyethyl)-thiazole (III), giving further evidence for the ease of cleavage of its ether linkage.

It is possible to distinguish between γ-chloroacetopropyl alcohol and its ether by means of their solubilities in ligroin; the former is not soluble whereas the latter is miscible. The crude reaction product (organic layer) obtained by decarboxylating chloroacetobutyrolactone (I) is miscible with ligroin, showing that the ether of chloroacetopropyl alcohol is not a secondary product formed during the purification (distillation) procedure.

Similar results are obtained in the preparation of bromoacetopropyl alcohol by bromination of γ-acetopropanol. In this case, the reaction mixture does not separate into two layers, suggesting that the product is chiefly bromoacetopropanol as it exists in the crude reaction mixture. However, when the extract is distilled at room temperature, only the ether $C_{10}H_{16}O_3Br_2$ is obtained. This ether is easily hydrolyzed to a dilute solution of bromoacetopropyl alcohol, but the extract of this solution yields only the ether. Apparently, the bromo alcohol is less stable in its free form than its chloro analog and reconverts spontaneously to its ether. From these facts one would expect the parent γ-acetopropyl alcohol to be the most stable member of this series, as was found to be the case.

γ-Acetopropyl alcohol is known in its free form and can be distilled at atmospheric pressure (b. p. 207–208°, 729 mm.). Lipp[3] observed partial dehydration of this alcohol on prolonged heating and under more severe conditions he was able to prepare an internal anhydride  $(CH_3\underbrace{C=CH-CH_2CH_2}_{O})$. In the course of this investigation, it was found that by slowly distilling γ-acetopropyl alcohol several times at 10 mm. pressure and fractionating the product, an ether between two moles of γ-acetopropanol is obtained. Small quantities of acids catalyze its formation. This substance behaves like an anhydride; it is quickly hydrolyzed with small quantities of water to γ-acetopropyl alcohol. When treated with semicarbazide in methanol, the semicarbazone of acetopropyl alcohol slowly forms.

Apparently these substances have the mixed ether structure (V) between the two recognized tautomeric forms[2] of γ-acetopropyl alcohol, the evidence for which follows



V

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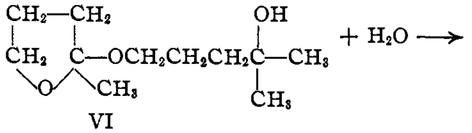
[1] This paper is No. XIX in the R. R. Williams Vitamin B_1 Series (XVIII, Buchman and Richardson, THIS JOURNAL, **61**, 891–893 (1939).

[2] Buchman, *ibid.*, **58**, 1803–1805 (1936).

[3] Lipp, *Ber.*, **22**, 1196 (1889).

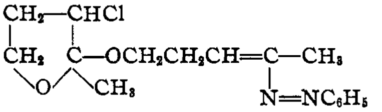
(1) The ether of acetopropyl alcohol shows no active hydrogen and one mole of Grignard reagent is consumed in a modified Zerewitinoff determination. When this reaction is carried out on a laboratory scale the reaction product is found to consist of a mixture of acetopropyl alcohol and 2-methylpentanediol-2,5, indicating the formation of an intermediate ketal (VI) which hydrolyzes



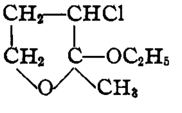
VI

$CH_3COCH_2CH_2CH_2OH + (CH_3)_2COHCH_2CH_2CH_2OH$

(2) The ether of chloroacetopropyl alcohol when treated with an excess of phenylhydrazine in an inert solvent gives a rapid precipitation of phenylhydrazine hydrochloride which stops when one mole has been formed, showing a marked difference between the activity of the two halogen atoms. The mother liquor yields a crystalline substance, $C_{16}H_{21}O_2N_2Cl$, corresponding to one mole each of the reactants, less a mole of water and a mole of hydrogen chloride. α-Bromoacetophenone reacts with phenylhydrazine[4] to give a similar product. By analogy chloroacetopropyl ether, if it contains a single —CO—CHCl— grouping, should yield the product (VII), which is in accordance with the composition of the isolated product.



VII



VIII

The Klingenfuss[5] ether (VIII), prepared by decarboxylating γ-chloroacetobutyrolactone in aqueous alcohol, does not react with phenylhydrazine under similar experimental conditions.

(3) Values obtained for the amount of iodine consumed in the iodoform reaction with the ether of chloroacetopropyl alcohol are about one-half as large as those for samples which have been previously heated in water in order to effect hydrolysis, indicating the presence of one free CH_3CO— group and another easily generated by hydrolysis.

The formation of the Klingenfuss ether may be considered as simple ketal formation from the cyclic tautomer of chloroacetopropanol. The presence of chloroacetopropyl alcohol during the reaction is demonstrated easily by the isolation of its ether as a principal product in the reaction mixture. In the preparation of the Klingenfuss compound (VIII), chloroacetobutyrolactone (I) may be replaced by the ether (IV).

The ether (VIII) is also easily hydrolyzed with water. When dissolved in water, in which it is soluble to a limited extent, the resulting solution gives no iodoform test. However, if the solution is brought to *p*H 3 or heated slightly and then cooled, complete hydrolysis occurs resulting in a solution which gives a strong iodoform reaction. When this solution is extracted with ether and the extract is distilled, the ether of chloroacetopropyl alcohol is obtained. From these results, it is apparent that chloroacetopropyl alcohol is the common intermediate in these reactions.

Experimental

Ether of γ-Chloro-γ-acetylpropanol.—Four hundred and ten grams of α-chloro-α-acetobutyrolactone (b. p. 74–75° at 1.5 mm.) was heated for about seven hours on the steam-bath with 410 cc. of water and 12 cc. of 38% hydrochloric acid until decarboxylation was complete.[6] On cooling, most of the ether separated as an oil, which was repeatedly extracted from the water layer with petroleum ether. After shaking the petroleum ether extracts with solid potassium carbonate, in order to render the product acid-free, the solvent was removed and the remaining oil was distilled. The cut (246 g.), b. p. 68–120° (1 mm.), on fractionation gave a product b. p. 111–112° (1 mm.); yield 200 g. (62%).

Anal. Calcd. for $C_{10}H_{16}O_3Cl_2$: C, 47.04; H, 6.32; Cl, 27.81; mol. wt., 255. Found: C, 47.13; H, 6.13; Cl, 28.07; mol. wt., 259 (dioxane).

This substance is a colorless and almost odorless liquid; it is difficultly soluble in water, easily soluble in organic solvents; d^{25} 1.2175; $n^{25}D$ 1.4748.

The ether (40 g.) when treated with thioformamide hydrate (38.5 g.) in isopropyl alcohol (17 cc.) gave 4-methyl-5-(β-hydroxyethyl)-thiazole (31.5 g.) boiling at 97.3–97.5° at 0.5 mm.; picrate m. p. (cor.) 164.5–165° (Buchnan 163°).

Anal. Calcd. for $C_{12}H_{12}O_8N_4S$: C, 38.69; H, 3.25. Found: C, 38.65; H, 3.10.

3-Chloro-3-acetylpropyl Alcohol.—When the low boiling fraction b. p. 68–75° (1 mm.) in a preparation such as that described above is collected separately and subjected to series of molecular distillations, 3×10^{-3} mm. at 20–24°, a product which is insoluble in ligroin can be isolated from the more volatile portion.

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[4] Bodforss, *Ber.*, **52**, 1762, 1767 (1919); **72**, 468 (1939).

[5] Klingenfuss, U. S. Patent 2,123,653.

[6] In a private communication Dr. Buchman has suggested the use of weaker acid than that given in his original article. We have found these conditions satisfactory. Stronger acid gives more tarry products and a small amount of acetochloropropyl chloride, resulting in a contaminant in the final thiazole derivative. The principal reaction products are the same following both procedures. As judged by boiling point and chlorine analysis, Buchman apparently had fairly pure chloroacetopropyl ether which he reported as chloroacetopropyl alcohol.

Anal. Calcd. for $C_5H_9O_2Cl$: C, 43.95; H, 6.64; Cl, 25.97; mol. wt., 136.5. Found: C, 44.64; H, 6.29; Cl, 26.43; mol. wt., 146 (dioxane).

This substance is readily soluble in water. When it was redistilled at 1 mm., most of it distilled in the ether range up to 120°, with elimination of water, which was observed in a carbon dioxide trap.

Chloroacetopropyl Alcohol from its Ether by Hydrolysis.—The preparation of water solutions of this compound required warming. A minimum warming period at 60° of eighty minutes was found necessary. The solution then showed an inappreciable formation of chloride ion. The average of four determinations gave a freezing point lowering value of 1.57° per gram of added material per 10 cc. The apparent molecular weight is 119. Addition of 9 ($^1/_2$ mole of water) units to this figure, gives 128; mol. wt. chloroacetopropyl alcohol, 136.5.

Five grams of the ether was warmed at 60° for about six hours with 500 cc. of water. After allowing the mixture to stand overnight, all of the oily layer dissolved on shaking. The solution was extracted with ether, the ether solution dried and concentrated at 20°. The residual oil was distilled in a molecular still, at 27° (bath), press. 0.01 mm., d^{25} 1.210; $n^{25}{}_D$ 1.4684.

Anal. Calcd. for $C_5H_9O_2Cl$: C, 43.95; H, 6.64. Found: C, 44.35; H, 6.48.

Ether of Bromoacetopropyl Alcohol.—Thirty-one grams of acetopropyl alcohol (b. p. 81–84° at 7 mm.) was dissolved in 150 cc. of water and 48 g. of bromine slowly added with stirring at 24–30° over a period of one and one-half hours. The aqueous layer was decanted from a small amount of oil, then treated with a little norit–charcoal. The resulting water-clear solution was extracted with ether; the ether extract after drying with sodium sulfate was concentrated at 20° under vacuum. About 55 g. of a colorless oil was obtained, part of which was distilled in a molecular still for analysis: boiling point 40° (bath) at 0.008 mm., d^{25} 1.592; $n^{25}{}_D$ 1.4989.

Anal. Calcd. for $C_{10}H_{16}O_3Br_2$: C, 34.89; H, 4.69; mol. wt., 344. Found: C, 34.84; H, 4.56; mol. wt., 316 (dioxane).

A sample of this substance was dissolved in water and the freezing point was found to be 1.25° per g. of ether per 10 cc. of H_2O. The apparent molecular weight is 149, corrected for $^1/_2$ mole of water gives 158 as compared to 181 calculated for bromoacetopropanol. The test for Br^- ion was positive and the *p*H of the solution was 2.58. The hydrogen bromide concentration indicated by the *p*H gives rise to a 2% error in the determination.

Ether of γ-Acetopropyl Alcohol.—One hundred cc. of γ-acetopropyl alcohol, b. p. 81–84° (7 mm.), $n^{20}{}_D$ 1.4372, containing one drop of concd. hydrochloric acid, was distilled several times. In each case the fraction of b. p. 105–115° (10 mm.) was collected. These combined cuts were fractionated and gave a product of b. p. 110–112° (10 mm.), d^{25} 0.9968; $n^{20}{}_D$ 1.4435.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.59; H, 9.75; mol. wt., 186. Found: C, 64.28; H, 9.79; mol. wt., 182 (dioxane).

This substance dissolves readily in cold water; freezing point depression 1.98° per gram per 10 cc.; apparent molecular weight corrected for $^1/_2$ mole of water (+9) is 103; calculated for acetopropyl alcohol 102.

Two millimoles of semicarbazide hydrochloride was dissolved in 0.5 cc. of cold methanol, 2 millimoles of potassium acetate added and the potassium chloride centrifuged off. To the filtrate was added 1 millimole of ether of acetopropyl alcohol and the mixture allowed to stand at room temperature. The crystals that separated after a few hours had m. p. 157°. A mixed m. p. with the semicarbazone of γ-acetopropanol gave no depression.

2 - Methyl - 2 - ethoxy - 3 - chlorotetrahydrofuran.—One hundred grams of chloroacetobutyrolactone, 120 g. of 80% ethyl alcohol and 36 g. of concd. sulfuric acid were stirred together and maintained at 40–50° until the evolution of carbon dioxide had ceased, which required about seven hours. After cooling, water and ether were added and the aqueous layer extracted several times with ether. The combined ether extracts were washed with a little cold water, neutralized with sodium carbonate solution and dried over calcium chloride. The ethereal solution was then distilled. The lower cuts, 50–70° at 13 mm., yielded on further fractionation about 30 g. of 2-methyl-2-ethoxy-3-chlorotetrahydrofuran (30%).

Anal. Calcd. for $C_7H_{13}O_2Cl$: C, 51.04; H, 7.97. Found: C, 51.22; H, 7.91.

The higher boiling cuts (70–120° at 1 mm.) gave about 28 g. of the pure ether of chloroacetopropyl alcohol.

Anal. Calcd. for $C_{10}H_{16}O_3Cl_2$: C, 47.04; H, 6.32. Found: C, 47.01; H, 6.12.

2-Methyl-2-ethoxy-3-chlorotetrahydrofuran from Ether of Chloroacetopropyl Alcohol.—To a cold mixture of 18 g. of sulfuric acid and 80 g. of 80% ethyl alcohol was slowly added 50 g. of chloroacetopropyl ether with cooling; the mixture was warmed at 40–50° for about seven hours and worked up as described above; yield 33 g.

Anal. Calcd. for $C_7H_{13}O_2Cl$: C, 51.04; H, 7.97. Found: C, 50.87; H, 7.77.

Ether of Chloroacetopropyl Alcohol from 2-Methyl-2-ethoxy-3-chlorotetrahydrofuran.—Twelve and one-half grams of 2-methyl-2-ethoxy-3-chlorotetrahydrofuran was shaken at room temperature with 100 cc. of water which was previously acidified with hydrochloric acid to a *p*H of 3. After a few minutes of shaking, all the oil had dissolved, and after thirty minutes the characteristic camphor-like odor of the compound had disappeared completely. At the end of one hour the solution was extracted several times with ether, etc.; the extracts yielded 5.4 g. of product, b. p. 111–112°.

Anal. Calcd. for $C_{10}H_{16}O_3Cl_2$: C, 47.04; H, 6.32. Found: C, 46.41; H, 6.36.

Reaction of Methylmagnesium Iodide on the Ether of γ-Acetopropanol.—A modified Zerewitinoff[7] analysis showed 0.24 equivalent of active hydrogen and 1.16 equivalents of reagent consumed.

Forty-three grams of the ether of γ-acetopropyl alcohol was treated with the Grignard reagent made from 66 g. of methyl iodide in the usual manner. After decomposition the aqueous layer was extracted exhaustively with ether.

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(7) We are indebted to Dr. Richard Cramer of Harvard University for this determination.

The oil (39 g.) was found to be a mixture. A portion on treatment with semicarbazide gave the γ-acetopropyl alcohol semicarbazone, m. p. 157°, mixed m. p. no depression. This crude oil contained another substance in about equal amounts which was separated by extracting all of the acetopropyl alcohol with ligroin and distilling the residue; b. p. 77.5° (0.1 mm.), atmospheric pressure 218–219°. The recorded[8] boiling point of 2-methyl-2,5-dihydroxypentane is 218–219°. When heated with 10% sulfuric acid the characteristic camphor odor of 2,2-dimethyltetrahydrofuran[9] was observed.

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.96; H, 11.95. Found: C, 61.07; H, 11.89.

Ether of Chloroacetopropanol and Phenylhydrazine.—A solution of 2.55 g. (0.01 mole) of the freshly distilled ether of chloroacetopropyl alcohol in about 80 cc. of absolute ethyl ether was chilled in ice; a cold solution of 2.16 g. (0.02 mole) of freshly distilled phenylhydrazine in about 20 cc. of absolute ether was added with shaking. After a few minutes the mixture became yellow and phenylhydrazine hydrochloride began to separate. After a few hours, all the phenylhydrazine hydrochloride had separated. This was filtered off, washed with ether and dried; yield 1.420 g. (0.98 mole) of phenylhydrazine hydrochloride, m. p. 240°; calcd. for 1 mole, 1.445 g. The reddish ether solution was washed with cold water until no chloride could be detected in the wash water; it was dried with calcium chloride and the ether was evaporated at room temperature, using high vacuum at the end of the concentration, in order to remove traces of ether. The remaining red viscous oil (about 3 g.) was dissolved in a minimum amount of isopropyl alcohol, and the solution chilled in a freezing mixture. The oil which separated soon crystallized. After centrifuging there remained a half oily, half crystalline mass which was recrystallized several times from warm isopropyl alcohol. The light yellow crystals thus obtained were dried in a high vacuum at room temperature; m. p. 85° (unsharp due to decomposition).

Anal. Calcd. for $C_{16}H_{21}O_2N_2Cl$: C, 62.21; H, 6.86; N, 9.07. Found: C, 62.20; H, 7.02; N, 9.19.

Titration Results with Iodine (Iodoform).—The samples for titration were dissolved in cold water (about 100 mg./100 cc.) with shaking. About 30 cc. of *N* potassium hydroxide was added, followed immediately with 70 cc. of 0.2 *N* iodine solution. The mixture was allowed to stand for fifteen minutes at room temperature. It was acidified with 40 cc. of 2.5 *N* hydrochloric acid and the free iodine titrated.

A. **Ether of 3-Chloro-3-acetopropanol.**—(1). Freshly prepared solution: iodine consumed 6.04 atoms; (2) after twelve hours, 7.7 atoms; (3) when the aqueous solution is heated for thirty-five minutes on a steam-bath, cooled, and treated with iodine, etc., 9.9 atoms were consumed.

The amount of iodoform which can be isolated from these mixtures is less than that calculated from the iodine consumed; apparently some of the iodination occurs on the 3 carbon atoms, complicating the reaction. The relative values are considered significant.

B. **2-Ethoxy-2-methyl-3-chlorotetrahydrofuran.**—The cold aqueous solution shows no iodine consumed and no iodoform reaction. When it is heated at 100° for thirty-five minutes, cooled and assayed, 4.8 atoms of iodine are consumed. When the solution is kept at *p*H 3 for thirty minutes, neutralized and assayed, 5.3 atoms are consumed. A blank containing an equivalent of ethanol gave a negative result in this determination.

Acknowledgment.—The authors are grateful to Dr. Randolph T. Major, Dr. R. R. Williams, and Dr. E. R. Buchman for their many helpful suggestions. Mr. E. M. Chamberlin, Mr. M. Freiman and Mr. T. Perrine assisted with the experimental work. The physical measurements were made by Mr. W. A. Bastedo and the microanalyses by Mr. D. Hayman and Mr. W. Reiss.

Summary

γ-Acetopropanol is shown to be converted readily into its ether by repeated distillation. The ether readily is hydrolyzed back to the alcohol.

γ-Chloro and γ-bromoacetopropanols and their corresponding ethers are spontaneously interconvertible in water solution.

All three ethers contain one tetrahydrofuran ring, the other molecule of the propanol being in straight chain form.

2-Alkoxy-2-methyl-3-chlorotetrahydrofuran is similarly labile, being converted by mild hydrolysis to chloroacetopropanol and in turn to its ether. The reverse action proceeds in aqueous alcohol.

RAHWAY, N. J. RECEIVED NOVEMBER 4, 1939

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[8] Franke and Kohn, *Monatsh.*, **28**, 1006 (1907).

[9] Henry, *Compt. rend.*, **143**, 1221 (1906); Franke and Kohn, *Monatsh.*, **28**, 1006 (1907).