[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

# Some Reactions of Ketals[1]

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## Introduction

Very little work is reported in the literature concerning the chemical behavior of the higher ketone acetals (ketals). Prior to their preparation from alkyl acetylenes by Hennion, Killian and Nieuwland,[2] these compounds were prepared by the condensation of ketones with alkyl orthoformates in the presence of appropriate alcohols.[3–5]

Killian, Hennion and Nieuwland[6] report a reaction of ketals involving an interchange of alkoxy groups to yield a ketal of higher molecular weight. This is effected by heating the ketal with an alcohol of higher boiling point than that used in the preparation of the ketal. A trace of strong acid is necessary to catalyze this reaction. Hoch[7] reports a similar reaction between ketals and primary amines to yield N-substituted imines of aliphatic ketones. In each of these reactions an intermediate step is undoubtedly the addition of a compound having a labile hydrogen atom to the vinyl ether formed by desaturation of the ketal.

While investigating the properties of the ketals prepared in this Laboratory, the work of Post[8] attracted our attention. He investigated the reaction of benzoyl chloride with certain ortho esters and acetals. They were found to react according to the equations

$$HC(OR)_3 + C_6H_5COCl \longrightarrow RCl + HCOOR + C_6H_5COOR$$

$$CH_3CH(OR)_2 + C_6H_5COCl \longrightarrow C_6H_5COOR + CH_3CHClOR$$

These reactions previously had been investigated by Blaise.[9]

It might be expected that ketals would react very much as acetals do with benzoyl chloride to yield, in this case, an alkyl benzoate and a chlorinated secondary ether. We have found, however, that the reaction proceeds differently. Post reports that no hydrogen chloride is evolved in the reaction of benzoyl chloride with an acetal. In the case of the ketals appreciable quantities are formed. This indicates that the primary reaction is one of desaturation of the ketal to form an alcohol and a vinyl ether.

$$R—C(OCH_3)_2CH_3 \longrightarrow R—C(OCH_3)=CH_2 + CH_3OH$$

The alcohol thus formed reacts with the benzoyl chloride to yield methyl benzoate and hydrogen chloride. It is our belief that the hydrogen chloride adds to the vinyl ether to give a compound of the type $R—C(OCH_3)(Cl)—CH_3$, which, being unstable, breaks down to form a ketone and methyl chloride. This view has been confirmed by the isolation and identification of both the ketone and the methyl chloride, and also by the reaction of hydrogen bromide with a vinyl ether, which yielded methyl bromide and a ketone. The reaction of ketals with acetyl chloride proceeds similarly, the ester produced being in this case methyl acetate.

The reaction of ketals with acid anhydrides has been investigated and found to proceed much more simply. In this case the alcohol formed by the desaturation of the ketal reacts with the acid anhydride to form an ester and an organic acid. In the absence of catalysts, the weak organic acid will not add to the vinyl ether. The reaction is therefore one of desaturation.

$$R—C(OCH_3)_2—CH_3 + (CH_3CO)_2O \longrightarrow R—C(OCH_3)=CH_2 + CH_3COOCH_3 + CH_3COOH$$

The tendency of ketals to lose alcohol under the influence of heat and an acid catalyst is one characteristic in which they differ markedly from acetals, closely related as they are structurally. In view of this tendency, we may predict that many reactions undertaken with ketals under acid conditions and at temperatures much above 100° could as well be carried out using the vinyl ether.

With the intention of repeating the above experiments with di-*t*-butoxy ketals, attempts were made to prepare these from 2,2-dimethoxyalkanes and *t*-butyl alcohol.[6] The reaction proceeded anomalously, yielding primarily methyl *t*-butyl ether, methyl alcohol, and methyl alkyl ketone. We believe the reactions proceed as follows

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(1) Paper XXIII on the chemistry of the alkylacetylenes and their addition products; previous paper, THIS JOURNAL, **59**, 1310 (1937).

(2) Hennion, Killian and Nieuwland, *ibid.*, **56**, 1130 (1934); **56**, 1384 (1934); **58**, 80 (1936).

(3) Hess, German Patent 197,804 (1908); *cf. Frdl.*, **9**, 1004 (1908–10).

(4) Claisen, *Ber.*, **31**, 1012 (1898).

(5) Evlampiev, *J. Russ. Phys.-Chem. Soc.*, **54**, 462 (1923).

(6) Killian, Hennion and Nieuwland, THIS JOURNAL, **57**, 544 (1935).

(7) Hoch, *Compt. rend.*, **199**, 1428 (1934).

(8) Post, *J. Org. Chem.*, **1**, 231 (1936).

(9) Blaise, *Compt. rend.*, **139**, 1211 (1904); **140**, 661 (1905).

$$R{-}C(OCH_3)_2{-}CH_3 \longrightarrow R{-}C(OCH_3){=}CH_2 + CH_3OH \tag{1}$$

$$t\text{-}C_4H_9OH \longrightarrow (CH_3)_2C{=}CH_2 + HOH \tag{2}$$

$$R{-}C(OCH_3){=}CH_2 + HOH \longrightarrow R{-}CO{-}CH_3 + CH_3OH \tag{3}$$

$$(CH_3)_2C{=}CH_2 + CH_3OH \longrightarrow (CH_3)_3C{-}O{-}CH_3 \tag{4}$$

## Experimental

**Reaction of 2,2-Dimethoxyhexane with Benzoyl Chloride.**—The ketal was prepared by the method of Hennion and Killian[2] and the benzoyl chloride was redistilled before use. The reagents (one mole of each) were heated on an oil-bath, in an all-glass reflux apparatus, for five hours at 100°, and then for a few hours longer at 140°. Early during the reaction period there was a fairly rapid evolution of a gas having the odor of hydrogen chloride.

The reaction mixture was then fractionally distilled. The methyl benzoate fraction was heated with a sodium bicarbonate solution to remove any remaining benzoyl chloride. This fraction yielded 90 g. (66% yield) of methyl benzoate. The bicarbonate layer yielded only 4.7 g. of benzoic acid.

The only other identifiable product isolated was 28.3 g. (28.3% yield) of methyl *n*-butyl ketone. The ketone had the following properties: b. p. 125°; $n^{25}_{D}$ 1.4000; $d^{25}_{4}$ 0.8061. Values reported in the literature[2,10] are: b. p. 126–128°; $n^{20}_{D}$ 1.4010; $d^{20}_{20}$ 0.818.

**Reaction of 2,2-Dimethoxyhexane with Acetyl Chloride.**—The formation of ketone in the above experiment suggested the possibility of methyl chloride being formed according to the equation

$$RC(OR'){=}CH_2 + HCl \longrightarrow RCOCH_3 + R'Cl$$

An experiment was performed to test this possibility.

The apparatus consisted of a flask attached by a ground glass joint to a reflux condenser. From the top of the condenser a tube led to a calcium chloride drying tube, and then to a trap consisting of a distilling flask immersed in a carbice-bath. The side-arm of the distilling flask was connected to two gas bottle traps, one of which contained a standardized solution of sodium hydroxide.

Acetyl chloride and 2,2-dimethoxyhexane were used. The acetyl chloride was Merck Reagent and was redistilled shortly before use. The reagents (one-third mole of each) were heated on a water-bath for three and one-half hours.

The liquid which condensed in the carbice-bath fumed and had the odor of hydrogen chloride, so the bath was removed and the liquid allowed to evaporate. The vapor, after passing through the caustic trap, was caught in a weighed bottle containing ether as a solvent. In this way 5.5 g. (32.7% yield) of methyl chloride was obtained. The methyl chloride was identified by fractionation from the ether and by a determination of its vapor density. This gave a molecular weight of 52.8 (actual 50.5).

Back titration of the contents of the caustic trap indicated that 0.241 mole of hydrogen chloride had been evolved, a yield of 72.4% based on the assumption that every molecule of ketal furnishes one of methyl alcohol and subsequently one of hydrogen chloride.

**Reaction of 2-Methoxy-1-hexene with Benzoyl Chloride.**—To elucidate the mechanism of these reactions the action of benzoyl chloride on vinyl ethers was investigated. In this reaction one-third mole of 2-methoxy-1-hexene, prepared by the method of Killian, Hennion and Nieuwland,[6] was treated with one-third mole of benzoyl chloride. The reagents were heated (low free flame) in the apparatus described above, using a caustic trap to absorb any hydrogen chloride evolved.

There was no evidence of reaction during thirty minutes of heating. Back titration of the contents of the trap showed that no hydrogen chloride had been evolved. A small amount of *p*-toluenesulfonic acid (Eastman c. p. grade) was then added as a catalyst. This caused the mixture to become warm and to darken in color.

The flask and contents were then heated (free flame) for thirty minutes, during which time hydrogen chloride was given off. Back titration indicated that only 0.057 mole of hydrogen chloride had been evolved. Almost all of the benzoyl chloride was recovered (33 g. out of 47). A considerable amount of polymer, boiling over a wide range of temperature, was obtained also. Apparently the main reaction was polymerization of the vinyl ether.

**Reaction of 2-Methoxy-1-hexene with Hydrogen Bromide.**—As a final check on these reactions, hydrogen bromide was added to a vinyl ether. One-quarter mole (28.5 g.) of 2-methoxy-1-hexene was used. The reaction was carried out in a 200-cc., three-necked flask fitted with a mercury-sealed, motor-driven stirrer and a reflux condenser. A tube led from the top of the condenser to a trap consisting of a distilling flask immersed in liquid ammonia. The outlet of this flask was connected to a trap filled with water.

The reaction flask was heated on a water-bath for two hours, during which time the hydrogen bromide was bubbled slowly through the reaction mixture. At the end of the two hours the gas began to come through the water trap.

The methyl bromide, condensed in the liquid ammonia trap, was distilled into a Dumas bulb and weighed. The yield was 5.7 g. (24% yield). A vapor density measurement indicated a molecular weight of 93.3 (actual 94.9). From the reaction mixture was isolated a small amount (1.8 g.) of methyl *n*-butyl ketone, identified by its semicarbazone (m. p. 118.5–119.5°).

A small amount of an unidentified compound was obtained from this reaction, with the following properties: b. p. 127–128° at 27 mm.; $n^{25}_{D}$ 1.4508; $d^{25}_{4}$ 0.8649; molecular weight (cryoscopic determination in benzene), 183.9. Sodium fusion gave a negative test for halogen. The compound decolorizes a solution of bromine in carbon tetrachloride. A semicarbazone or a dinitrophenylhydrazone of the compound could not be obtained.

**Reaction of 2,2-Dimethoxyhexane with Acetic Anhydride.**—One-third mole each of 2,2-dimethoxyhexane and acetic anhydride were placed in an all-glass reflux apparatus. The acetic anhydride was Mallinckrodt Analytical Reagent. The reagents were heated on an oil-bath for four hours at 150°. Vigorous refluxing began almost at once, indicating an early reaction.

Fractional distillation of the reaction mixture yielded 20.7 g. (83.8% yield) of methyl acetate, boiling at 56–

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(10) Doolittle, *Ind. Eng. Chem.*, **27**, 1172 (1935).

56.5°. Practically all of the liquid remaining came over in the range of acetic acid and the vinyl ether of the ketal used. Attempts to separate the acetic acid and the vinyl ether were unsuccessful. For this reason the experiment was repeated using 2,2-dimethoxyheptane.

**Reaction of 2,2-Dimethoxyheptane with Acetic Anhydride.**—The reaction was carried out as above, using one-third mole each of 2,2-dimethoxyheptane and acetic anhydride. The yield of methyl acetate was approximately the same as in the preceding experiment (85.5% yield). Little difficulty was experienced in isolating the acetic acid. The final yield of acetic acid was 69% of the theoretical. It boiled at 115–118° and melted at 15.5°.

Another fraction boiled over a range of several degrees (139–150°) and apparently consisted of the vinyl ether and methyl *n*-amyl ketone, these components having boiling points quite close together (142–143° for the vinyl ether and 148–150° for the ketone). The index of refraction of the sample indicated, however, that it was mostly the vinyl ether: $n^{26}\text{D}$ (sample) 1.4186, $n^{24}\text{D}$ (vinyl ether)[6] 1.4198, $n^{24}\text{D}$ (ketone)[2] 1.4080. The total weight of this fraction was 24.8 g., indicating a yield of not over 59% for the vinyl ether.

**Reaction of 2,2-Dimethoxyhexane with *t*-Butyl Alcohol.**—An attempt was made to prepare a *t*-butoxy ketal after the manner described by Killian, Hennion and Nieuwland.[6] In this experiment 90 g. of 2,2-dimethoxyhexane was heated with 45.6 g. of *t*-butyl alcohol and a trace of *p*-toluenesulfonic acid. The alcohol was obtained from Eastman Kodak Co. and was purified by freezing before use. The flask in which the reagents were heated was attached to a fractionating column consisting of a jacketed, 7-mm. Pyrex tube, 130 cm. long, containing a single monel wire spiral.

During the heating period 55 cc. of liquid was removed through the column. This was redistilled through a small column packed with wire helices. There was obtained 27 cc. of liquid boiling at 47–51°, and 11 cc. boiling at 64–65°. More *t*-butyl alcohol was added to the reaction flask and about 20 cc. more was taken off below 80°. Again *t*-butyl alcohol was added to the reaction flask, but this time no fraction could be distilled below 80°.

The low boiling fraction was identified as methyl *t*-butyl ether. Its constants were: b. p. 54–56°, $n^{27}\text{D}$ 1.3680, $d^{27}_4$ 0.733. Those reported[11] are: b. p. 55.2°, $n^{20}\text{D}$ 1.3689, $d^{25}_4$ 0.7352. Some of this ether was lost in handling, but its yield was estimated at about 44% of the theoretical.

Fractional distillation of the mixture remaining in the reaction flask gave some *t*-butyl alcohol and 52.6 g. (85.4% yield) of methyl *n*-butyl ketone, b. p. 125.5–126°, $n^{20}\text{D}$ 1.4010.

**Reaction of 2,2-Dimethoxyheptane with *t*-Butyl Alcohol.**—The above experiment was repeated using 2,2-dimethoxyheptane. The reagents, 40 g. (one-quarter mole) of 2,2-dimethoxyheptane and 37 g. (one-half mole) of *t*-butyl alcohol, with a little *p*-toluenesulfonic acid, were heated in a flask, using the same fractionating column as in the preceding experiment.

The fraction boiling below 70° was caught in a receiver immersed in ice-cooled water. The outlet of the receiver was connected to a trap immersed in a salt-ice mixture. This trap caught most of the isobutylene formed in the reaction

$$t\text{-}C_4H_9OH \longrightarrow (CH_3)_2C{=}CH_2 + HOH$$

The liquids in the receiver and in the trap were combined and fractionally distilled. The non-condensed vapors were caught in a trap filled with a solution of bromine in chloroform. A fraction boiling at 50–51° was obtained which weighed 10.5 g. This was believed to be the azeotropic mixture of methyl *t*-butyl ether and methyl alcohol which boils at 51.6°. Treatment of this mixture with solid calcium chloride gave the pure ether, $n^{27}\text{D}$ 1.3647 and $n^{21}\text{D}$ 1.3680. The yield of ether was 40.5% of the theoretical.

From the trap was isolated 10.5 g. of isobutylene dibromide, boiling at 145–147°. This corresponds to 2.7 g. of isobutylene, which is only about 10% of that which could have been formed had all of the *t*-butyl alcohol been dehydrated.

The mixture in the reaction flask separated into two layers on cooling. The lower layer, believed to be water, had a volume of 3.5 cc., was miscible with water, and readily dissolved about 1 g. of sodium chloride. The upper layer yielded 24.1 g. of methyl *n*-amyl ketone, boiling at 148–150°. Upon redistillation 22.8 g. (80% yield) of the ketone was obtained. The ketone was identified by its index of refraction ($n^{25}\text{D}$ 1.4070), and by its semicarbazone (m. p. 121–122°).

**Reaction of 2-Methoxy-1-hexene with *t*-Butyl Alcohol.**—To ascertain the mechanism of these reactions an attempt was made to add *t*-butyl alcohol to a vinyl ether. In a weighed graduated cylinder was placed 19 g. (one-sixth mole) of 2-methoxy-1-hexene and 12.3 g. (one-sixth mole) of *t*-butyl alcohol. The container and contents were cooled to 5° and the volume of the mixture noted. A few crystals of *p*-toluenesulfonic acid were then added. There was no apparent temperature or volume change on addition of the catalyst.

The temperature of the mixture was allowed to rise to 25°. The index of refraction of the mixture was taken at intervals for a period of four hours, during which it changed very little, indicating that no reaction was taking place.

The mixture was then fractionated, under reduced pressure, on a water-bath (to avoid heating above 100°). Almost all of the *t*-butyl alcohol was recovered (10.6 g. out of 12.3). It was very evident that below 100° *t*-butyl alcohol does not react with 2-methoxy-1-hexene.

This reaction was repeated, however, using 22 g. of 2-methoxy-1-heptene and 18.5 g. of *t*-butyl alcohol. The reagents were heated, with a little *p*-toluenesulfonic acid, over an open flame in a flask attached to the fractionating column used in the preceding experiments on the preparation of methyl *t*-butyl ether.

In this case only 6 cc. of liquid was distilled up to 64°. A gas, probably isobutylene, also was liberated. The distillate was treated with a saturated solution of calcium chloride. On redistillation 0.8 g. (5.3% yield) of methyl *t*-butyl ether was isolated ($n^{24}\text{D}$ 1.3670).

## Summary

The reaction of ketals with acyl halides has been studied and found to yield an ester, ke-

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[11] Evans and Edlund, *Ind. Eng. Chem.*, **28**, 1188 (1936).

tone, alkyl halide and a hydrogen halide.

Ketals react with acid anhydrides to yield mainly an ester, acid and vinyl ether.

The reaction of a ketal with *t*-butyl alcohol has been investigated and found to result in an unexpected product, methyl *t*-butyl ether. These studies are being continued.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY AND THE RESEARCH LABORATORY OF THE ATLAS POWDER COMPANY]

# Crystalline Lactositol

BY M. L. WOLFROM, W. J. BURKE, K. R. BROWN AND ROBERT S. ROSE, JR.

Glycosides of many different types of alcohols and phenols have long been known, but to our knowledge no glycoside of a sugar alcohol containing more than three carbon atoms has so far been obtained by coupling reactions. The reduction of a disaccharide offers a method for obtaining such derivatives and crystalline cellobiositol has been reported by Levene and Kuna.[1]

Various attempts to reduce lactose to the alcohol stage have been reported in the literature. Bourchadat,[2] using sodium amalgam, made the first attempt to reduce lactose. He isolated dulcitol, isopropyl alcohol and hexyl alcohol. Neuberg and Marx,[3] using calcium amalgam, reported a crystalline reduction product of lactose which they called lactobiotol. They reported that it did not melt even at 280°. No rotation was recorded.

An aqueous solution of lactose was subjected to hydrogen at seventy-four atmospheres pressure at 130° in the presence of a nickel catalyst by Ipatieff.[4] Under these conditions, dulcitol and a sirup were obtained. Karrer and Büchi[5] hydrogenated lactose with a Raney nickel catalyst under thirty atmospheres pressure and a temperature of 70°, to obtain an amorphous, hygroscopic solid exhibiting a specific rotation of +14.8° in water.[5a]

In 1920 Senderens[6] repeated the work of Ipatieff and decreased the amount of dulcitol formed. Senderens reported a crystalline monohydrate of lactositol and recorded the constants: m. p. 78°; spec. rot. +12.2° (water).

In the work herein reported, lactose was reduced with hydrogen and nickel at high pressure under acid conditions in the Research Laboratory of the Atlas Powder Company and the resultant sirup was obtained crystalline in the Chemical Laboratory of The Ohio State University. Our crystalline lactositol showed the constants: m. p. 146°; spec. rot. (23°) +14° in water. The crystalline material was anhydrous and a crystalline hydrate was not obtained. Sorbitol and galactose were identified as its hydrolytic products. A crystalline tritrityl lactositol hexaacetate was obtained. This crystalline sugar derivative is of interest because of its high molecular weight of 1323.

Our main interest in lactositol consisted in having in hand a crystalline glycoside of a sugar alcohol (4-*d*-sorbitol-β-*d*-galactopyranoside). Considerable data have been accumulated pertaining to the hydrolysis of glycosides. It is known that the nature of the aglucone portion can exert a considerable influence on the rate of glycosidic hydrolysis. It was then of interest to determine the rate of hydrolysis of a glycoside wherein the aglucone portion was a hexitol and accordingly the rate of hydrolysis of lactositol (0.05 molar) in 1 *N* hydrochloric acid was determined at three temperatures. The reactions followed the monomolecular law and from the determined velocity constants, the energy of activation for the hydrolysis was calculated. Moelwyn-Hughes[7] considers that the energy of activation is more significant for comparative purposes than the velocity constants.

The data obtained are tabulated in Table I and are therein compared with those for substances of related structure. It is seen that the velocity of hydrolysis of lactositol is of the same order of magnitude as that of the common py-

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(1) P. A. Levene and M. Kuna, *Science*, **85**, 550 (1937).

(2) G. Bourchadat, *Bull. soc. chim.*, **16**, 38 (1871).

(3) C. Neuberg and F. Marx, *Biochem. Z.*, **3**, 543 (1907).

(4) V. Ipatieff, *Ber.*, **45**, 3218 (1912).

(5) P. Karrer and J. Büchi, *Helv. Chim. Acta*, **20**, 86 (1937).

(5a) All specific rotations are herein recorded to the D-line of sodium light.

(6) J. B. Senderens, *Compt. rend.*, **170**, 47 (1920).

(7) E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, **24**, 309 (1928); *ibid.*, **25**, 81, 503 (1929).