One of us is indebted to the Graduate School of the University of Minnesota for a grant from its research funds in support of a part of this work.

Summary

Diethylmagnesium and dimethylmagnesium, prepared from solutions of ethyl- and methylmagnesium bromides by the method of Schlenk, react with cyclohexene oxide without rearrangement to give, respectively, *trans*-2-ethyl- and *trans*-2-methylcyclohexanol. This is in contrast to the behavior of ethylmagnesium bromide, which undergoes a different mode of addition to the oxide ring, leading to ethylcyclopentylcarbinol.

MINNEAPOLIS, MINN. RECEIVED AUGUST 15, 1934

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE BONEFF MANUFACTURING COMPANY, GABROVO, BULGARIA]

Synthesis and Reactions of 1,4-Hydroxy Ketones. Derivatives of 5-Hydroxyhexanone-2 and 2,5-Dimethyl-4,5-dihydrofuran

BY GEORGI POJARLIEFF

In effecting the synthesis of 5,6-dihydroxyhexanone-2 (IIa) from epichlorohydrin and ethyl acetoacetate, Traube and Lehmann[1] obtained the lactone (Ib) as an intermediate product. (IIa) is prepared by boiling the lactone with half a mole of potassium carbonate. To obtain (IIb) from the same lactone, the ring must be broken. In aqueous suspension this reaction can be brought about by the use of mineral acid, in which (IIb) is unstable. A better yield and a purer product can be obtained in the following way. In a methyl alcohol solution with a small quantity of hydrogen chloride gas at ordinary temperature the lactone (Ib) gives, in the first place, the lactolide (VIIb). On distillation, especially if acids are present, methyl alcohol is eliminated with the formation of the ester of dihydrofurancarboxylic acid (VIIIb). The latter can be saponified with one mole of sodium hydroxide to give (IXb), which in a free state can easily be purified by recrystallization from water. When heated, the acidified aqueous solution of the free acid liberates carbonic acid and (IIb) is formed.

This method of synthesis of (IIb) seems to be generally applicable. In quite an analogous way (IIc) was obtained from epimethyline and ethyl acetoacetate.

5-Hydroxy-6-chlorohexanone-2 shows a great tendency to undergo internal condensation. This occurs with the elimination of water, as in the internal condensation of (IIa), which was first observed by Hibbert and Timm.[2] The methoxyl analog (IIc) is more stable. When heated with a trace of concd. sulfuric acid (1:1000) for four minutes at 150° about 50% is condensed and the mixture of unaltered ketone and its anhydride (Vc) can be distilled in high vacuum. On the other hand, (IIb) and (IIc) are resinified by similar treatment.

Levene and Walti[3] have shown that in all probability with the internal condensation of (IIa) an intermediate product—furan (Va) or pyran (VI)—was formed and the condensation was caused by the presence of the double bond. They believe the sensitivity of the glucals (which are closely related to the desoxy sugars) toward acids is likewise due to the presence of a double bond in the 2,3-position. However, the esters of dihydrofurancarboxylic acid (VIIIb and VIIIc) are very stable, which seems to indicate that a double bond in the 2,3-position is not alone sufficient to cause polymerization. Bergmann and Pojarlieff[4] expressed the opinion that the sensitivity of the glucals and of the intermediate product formed in the internal condensation of (IIa) toward acid was the result of the presence of both a double bond and of hydroxyl groups.

When heated with a trace of concentrated sulfuric acid, the methyl lactolide[3] of (IIa) likewise undergoes internal condensation with the elimination of methyl alcohol. I have found that this lactolide consists chiefly of the tetrahydrofuran (IVa). This suggests that the dihydrofuran (Va), which is probably the intermediate product of the condensation, also possesses a tendency to polymerize. A comparison with the dihydro-

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[1] W. Traube and E. Lehmann, *Ber.*, **34**, 1971 (1901).

[2] H. Hibbert and J. A. Timm, THIS JOURNAL, **45**, 2433 (1923).

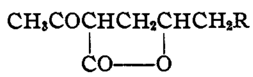
[3] P. A. Levene and A. Walti, *J. Biol. Chem.*, **88**, 771 (1930).

[4] M. Bergmann and G. Pojarlieff, *Naturwiss.*, **18**, 1114 (1930); *Collegium*, 244, 1931.

furan (Vb), the intermediate product of the internal condensation of (IIb), shows that by substituting a chlorine atom for the likewise electronegative hydroxyl group, the tendency to polymerize is retained.

The furan structure of the methyl lactolide of (IIa) was proved in the following way. (IVc) was oxidized with chromic acid and a diketone was obtained which was identified by its dinitrophenylhydrazone. The same diketone (III) was obtained by oxidizing (IIc), which was identified by the same dinitrophenylhydrazone.

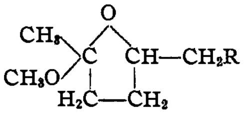
I



$$\begin{array}{l} CH_3COCHCH_2CHCH_2R \\ \qquad\quad CO\text{——}O \end{array}$$

II $CH_3COCH_2CH_2CHOHCH_2R$

III $CH_3COCH_2CH_2COCH_2OCH_3$



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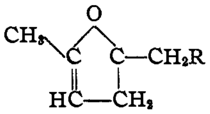

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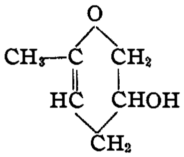

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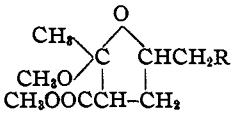
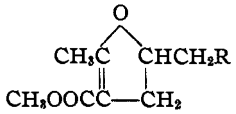
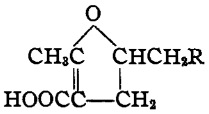


VII



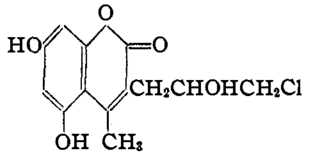
VIII

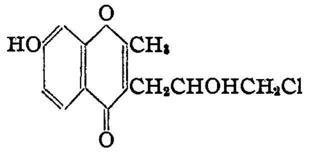


IX

R in the above formulas may be any of the following radicals: a = —OH; b = —Cl; c = —OCH_3.

The esters of (VIII), which are easily obtainable, can be used for the synthesis of substances with a benzopyran ring. Thus, for example, (VIIIb) when heated with phloroglucinol and hydrochloric acid gave a crystalline product which is either a cumarin (X) or a chromone (XI).





This reaction is similar to Pechmann's synthesis of cumarins from phenols and esters of β-keto acids.

Experimental

2-Methyl-3-carbomethoxy-5-chloromethyl-4,5-dihydrofuran (VIIIb).—Fifty grams of (Ib) was allowed to stand for forty hours at room temperature in 400 g. of dry methyl alcohol containing 0.5% of hydrogen chloride gas. The hydrogen chloride was removed with silver carbonate. After evaporation of the solvent an oil distilled at 98° (1.3 mm.); yield 50 g. This slightly impure oil was the lactolide (VIIb). For the preparation of (VIIIb) hydrogen chloride gas was passed into the oil, the mixture heated for half an hour at 120–130° and distilled: b. p. 127° (14 mm.), $n_D^{21.5}$ 1.4968, yield 42 g.

Anal. Calcd. for $C_8H_{11}O_3Cl$ (190.6): C, 50.35; H, 5.82. Found: C, 50.38; H, 6.00.

When heated with hydrogen chloride gas the methyl alcohol solution of (VIIIb) remains colorless, while under the same conditions (IVa) gives an intense violet color.

Three grams of the dihydrofuran (VIIIb) was refluxed for two hours with 30 cc. of methyl alcohol. After evaporation of the solvent the oil distilled at 97° (1 mm.), n_D^{24} 1.4701.

Anal. Calcd. for $C_9H_{15}O_4Cl$ (226): C, 48.52; H, 6.79. Found: C, 48.93; H, 6.59.

The dihydrofuran had added methyl alcohol on the double bond, with the regeneration of the lactolide (VIIb).

2-Methyl-5-chloromethyl-4,5-dihydrofurancarbonic Acid-3 (IXb).—Thirty grams of (VIIIb) was boiled for two hours with 190 cc. of normal aqueous sodium hydroxide. After acidifying an oil separated and soon crystallized. The yield was 26 g. (90% of the theoretical). After recrystallization from water, needles were obtained, m. p. 110° (corr.).

Anal. Calcd. for $C_7H_9O_3Cl$ (176.5): C, 47.59; H, 5.14. Found: C, 47.83; H, 5.38.

6-Chloro-5-hydroxyhexanone-2 (IIb).—Fifty grams of (IXb) was boiled for an hour with 50 cc. of 0.2 *N* sulfuric acid. The oil which was obtained from the neutralized aqueous solution through extraction with ether, could not be isolated in a pure state, because, even with repeated distillation, it split off water and was partly polymerized. The greater part of it distilled at 95° (3 mm.).

Its methyllactolide (IVb) is more stable. It was best obtained by allowing the crude undistilled (IIb) to stand in a methyl alcohol solution of hydrogen chloride gas. The yield was 70% of the theoretical: b. p. 73.5° (13 mm.), n_D^{25} 1.4435.

Anal. Calcd. for $C_7H_{13}O_2Cl$ (164.6): C, 51.03; H, 7.96. Found: C, 51.30; H, 8.26.

Four and one-half grams of crude (IIb) was acetylated with 6 cc. of pyridine and 6 cc. of acetic anhydride: b. p. 117° (5 mm.), yield 3.5 g. (60% of the theoretical), $n_D^{19.6}$ 1.4505.

Anal. Calcd. for $C_8H_{13}O_3Cl$ (192.6): C, 49.84; H, 6.80. Found: C, 49.42; H, 6.97.

With semicarbazide the acetate yielded a semicarbazone at once. The prisms obtained by recrystallization from water melted at 131° (corr.).

Anal. Calcd. for $C_{10}H_{19}O_4N_3$ (245.2): N, 17.14. Found: N, 17.00.

Condensation Product of Dihydrofurancarbonic Acid Ester (VIIIb) and Phloroglucinol.—Two grams of the ester and 1.2 g. of phloroglucinol were boiled for ten minutes with 10 cc. of 0.2 *N* hydrochloric acid. The solution became yellow and needles separated; yield, 2.6 g. After recrystallization from a mixture of alcohol and water the melting point was 250° (corr.).

Anal. Calcd. for $C_{13}H_{13}O_5Cl$ (284.55): C, 54.8; H, 4.61. Found: C, 54.9; H, 4.63.

α-Acetyl-δ-methoxy-γ-valerolactone (Ic).—Thirteen and one-half grams of sodium was dissolved in 150 cc. of absolute alcohol. To this solution 74 g. of ethyl acetoacetate and 50 g. of epimethyline (3-methoxy-1,2-epoxypropane) were added. The mixture was heated for eight hours at 60–70° and finally boiled for one hour. To the residue after evaporation of the alcohol 130 cc. of ice cold 5 *N* sulfuric acid was added and the solution extracted with ether: yield 40 g. (50% of the theoretical), b. p. 134° (4 mm.), n^{19}_{D} 1.4612.

Anal. Calcd. for $C_8H_{12}O_4$ (176.1): C, 55.78; H, 7.03. Found: C, 55.94; H, 7.11.

Blanchard's method[5] of obtaining epimethyline was altered in the following way: a solution of 160 g. of potassium hydroxide in 140 cc. of water was cooled with ice and salt and in the course of one and one-half hours 270 g. of α-chloro-β-hydroxy-γ-methoxypropane was added, the mixture being stirred continually. After one hour the solution was extracted with ether. The yield was 46% of the theoretical.

2-Methoxy-3-carbomethoxy-5-methoxymethyl-4,5-dihydrofuran (VIIIc).—This was obtained in a way analogous to (VIIIb). The yield from 40 g. of the lactone (Ic) was 32 g. (75% of the theoretical); b. p. 126° (15 mm.), n^{20}_{D} 1.4782.

Anal. Calcd. for $C_9H_{14}O_4$ (186.1): C, 58.0; H, 7.5. Found: C, 58.0; H, 7.58.

2-Methyl-5-methoxymethyl-4,5-dihydrofurancarbonic Acid-3 (IXc).—This was obtained similarly to (IXb). From 30 g. of the ester the yield was 24 g. of the acid (85% of the theoretical). The prisms melted at 82°.

Anal. Calcd. for $C_8H_{12}O_4$ (172.1): C, 55.78; H, 7.03. Found: C, 55.75; H, 7.25.

2-Methyl-2-methoxy-5-methoxymethyl-tetrahydrofuran (IVc).—This was obtained similarly to (IVb). From 7 g. of the ester 3 g. of the tetrahydrofuran was obtained: b. p. 72° (14 mm.), n^{25}_{D} 1.4252.

Anal. Calcd. for $C_8H_{16}O_3$ (160): C, 60.00; H, 10.00. Found: C, 60.11; H, 9.98.

5-Hydroxy-6-methoxyhexanone-2 (IIc) and 2-Methyl-5-methoxymethyl-4,5-dihydrofuran (Vc).—An aqueous solution of (IIc) was obtained by heating the acid (IXc) with dilute sulfuric acid. When heated at atmospheric pressure the oil lost water. On fractionation, 0.7 g. of the anhydride (Vc) was obtained from 5 g. of crude (IIc) (20% of the theoretical): b. p. 47–48° (11 mm.), $n^{20.5}_{D}$ 1.4442.

Anal. Calcd. for $C_7H_{12}O_2$ (128.1): C, 65.6; H, 9.4 Found: C, 65.24; H, 9.50.

Oxidation of 2-Methyl-5,6-dimethoxytetrahydrofuran (IVc) with Chromic Acid.—A solution of 8.5 g. of potassium dichromate in 16 g. of concd. sulfuric acid and 45 cc. of water was cooled to 0°, and 5 g. of (IVc) prepared by the method of Levene and Walti[3] was added drop by drop. The solution was allowed to stand at ordinary temperature for one hour, boiled for half an hour under a reflux and afterward extracted with ether. The ether extract was fractionated: I, fraction 68–70° at 0.6 mm., 1 g.; II, fraction 70–75° at 0.6 mm., 1.5 g.; III, fraction 105–115° at 0.6 mm., 0.9 g.

Fraction I was α-methoxyacetonylacetone (III). The oil gave with *p*-nitrophenylhydrazine a di-α-nitrophenylhydrazone. The impure product was recrystallized from aqueous pyridine. The yellow plates melted at 175° (corr.). The yield was 80% of the theoretical.

Anal. Calcd. for $C_{19}H_{22}O_5N_6$ (414.2): N, 20.29. Found: N, 20.31.

Fraction II probably consisted chiefly of unoxidized 5-hydroxy-6-methoxyhexanone-2 (IIc).

Fraction III was levulinic acid identified as a crystalline silver salt.

Anal. Calcd. for $C_5H_7O_3Ag$ (222.9): C, 26.92; H, 3.17; Ag, 48.40. Found: C, 26.9; H, 3.33; Ag, 48.3.

Neither fraction gave a red color with fuchsin reagent.

The dinitrophenylhydrazone obtained in the same way from the methyllactolide of (IIc) had the same properties.

Anal. Calcd. for $C_{19}H_{22}O_5N_6$ (414.2): N, 20.29. Found: N, 20.40.

The melting point of the mixture of the two bidinitrophenylhydrazones obtained in different ways did not show any depression.

Summary

1. A new method is given for the synthesis of 1,4-hydroxy ketones and some reactions are studied.

2. The relations which exist between the constitutional properties and the tendency of internal condensation of some closely related hydroxy ketones and dihydrofurans, are discussed.

3. It was found that from the 5,6-dihydroxyhexanone-2 a methyllactolide with a furan ring was formed more easily than a methyllactolide with a pyran ring.

GABROVO, BULGARIA RECEIVED AUGUST 15, 1934

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(5) L. Blanchard, *Bull. soc. chim.*, **41**, 826 (1927).