2. The naphthoxypropanones have been condensed with 5-methylisatin to produce two substituted quinoline acids.

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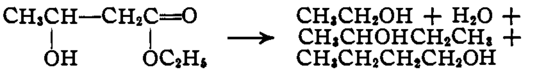
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Hydrogenolysis of β-Oxygenated Esters to Glycols

BY RALPH MOZINGO AND KARL FOLKERS

Under the usual conditions for ester reduction,[1] esters containing negative substituents in the β-position to the carboalkoxy group do not give rise to the corresponding alcohols when submitted to hydrogenolysis[2] over copper–chromium oxide catalyst.[3] Under these conditions cleavage products result. However, it has now been found that with these compounds satisfactory ester hydrogenolysis, without additional cleavage at other points, may be accomplished when modified conditions are used.

When ethyl β-hydroxybutyrate is hydrogenated at 250° over copper–chromium oxide under hydrogen at 150–400 atmospheres, the final products obtained are ethyl alcohol, *n*-butyl alcohol and *s*-butyl alcohol,[4] according to the following scheme in which the bonds undergoing hydrogenolysis are indicated by lines.



$$\underset{OH}{CH_3CH}—\underset{OC_2H_5}{CH_2C{=}O} \longrightarrow CH_3CH_2OH + H_2O + CH_3CHOHCH_2CH_3 + CH_3CH_2CH_2CH_2OH$$

I

It would appear, however, that the reaction may take the course

$$CH_3CHOHCH_2CO_2C_2H_5 \longrightarrow CH_3CHOHCH_2CH_2OH + C_2H_5OH$$
$$CH_3CHOHCH_2CH_2OH \longrightarrow CH_3CHOHCH_2CH_3 \text{ or } CH_3CH_2CH_2CH_2OH + H_2O$$
$$\xrightarrow{\text{or}} 2C_2H_5OH$$

If the reaction does proceed stepwise and the glycol is not isolated because the second reaction is the more rapid under the conditions which have been used and if sufficiently mild conditions can be found for the hydrogenation, it seems reasonable to expect that some of the glycol might be isolated. Such conditions were found and it was possible to isolate the glycol in reasonable yields.

Since, at any pressure above a certain minimum which is characteristic of the compound being hydrogenated, the effect of temperature is probably the greatest factor in controlling the hydrogenation products, lower temperatures of reaction seemed desirable. It had been demonstrated[5] that the hydrogenation of esters of certain sugar acids at 75° gives rise to the corresponding sugar alcohols. Ethyl α-hydroxyisobutyrate is hydrogenated at 200°.[6] Further, it had been shown that ethyl benzilate is hydrogenated rapidly to the corresponding 1,2-glycol at 125°.[7] In the last case this has been postulated to be due to tautomerization, and the same might be the controlling factor in all of these cases, since each ester contains an α-hydroxyl. The β-hydroxy esters cannot undergo such enolization, but must be hydrogenated in the ester form.

The hydrogenation of β-oxygenated esters was found to proceed smoothly at temperatures between 150 and 180° when relatively large amounts of copper–chromium oxide catalyst[3] were used. The hydrogenation of the β-oxygenated esters appears to be more satisfactory at higher hydrogen pressures (250–400 atmospheres) since the reactions are rather slow. The hydrogenolysis was carried out most successfully in methyl alcohol, which is quite contrary to the general practice when temperatures in excess of 220° are used for ester reduction.[8] For example, ethyl β-hydroxybutyrate (I) (or ethyl acetoacetate)[9] was hydrogenated to 1,3-butylene glycol (II) in 30% yield and ethyl β-ethoxypropionate (III) was converted into 3-ethoxy-1-propanol (IV) in 78% yield.

Likewise, α-alkyl and α-alkylidine acetoacetic esters gave rise to the corresponding 1,3-glycols. Ethyl α-isobutylideneacetoacetate (V) and ethyl ethylacetoacetate (VI) were

$$\underset{I}{CH_3CHOHCH_2CO_2C_2H_5} \longrightarrow \underset{II}{CH_3CHOHCH_2CH_2OH} + C_2H_5OH$$

$$\underset{III}{C_2H_5OCH_2CH_2CO_2C_2H_5} \longrightarrow \underset{IV}{C_2H_5OCH_2CH_2CH_2OH} + C_2H_5OH$$

converted under these conditions into 2-isobutyl-1,3-butylene glycol (VII) and 2-ethyl-1,3-butylene glycol (VIII), respectively. Both of the racemic forms of these two glycols were formed in the reduction and were separated through their *p*-nitrobenzoyl derivatives.

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(1) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 97.

(2) Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932).

(3) Connor, Folkers and Adkins, *ibid.*, **53**, 2012 (1931).

(4) Adkins, ref. 1, p. 103.

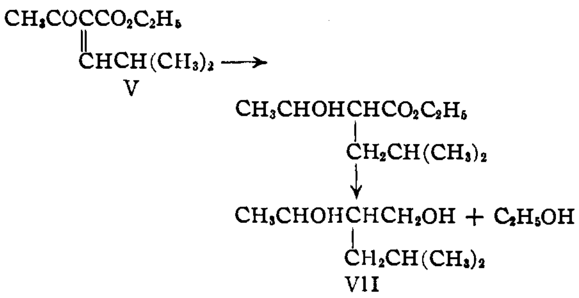
(5) Levene, Meyer and Kuna, *J. Biol. Chem.*, **125**, 703 (1938).

(6) Lazier, U. S. Patent 2,094,611 (October 5, 1937).

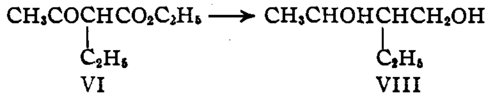
(7) Wojcik, Covert and Adkins, THIS JOURNAL, **55**, 1669 (1933).

(8) Lazier, U. S. Patent 2,079,414 (May 4, 1937.)

(9) Since it has been demonstrated that the β-keto esters are converted rapidly to β-hydroxy esters below the temperature used here, the keto esters may be used (see Connor and Adkins, THIS JOURNAL, **53**, 1091 (1931)).

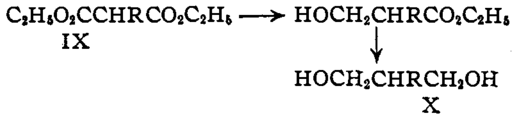


$$\underset{\text{V}}{\overset{\displaystyle CH_3COCCO_2C_2H_5}{\overset{\|}{CHCH(CH_3)_2}}} \longrightarrow \underset{\displaystyle CH_2CH(CH_3)_2}{CH_3CHOH\overset{}{C}HCO_2C_2H_5} \downarrow \underset{\text{VII}}{\underset{\displaystyle CH_2CH(CH_3)_2}{CH_3CHOHCHCH_2OH}} + C_2H_5OH$$



$$\underset{\text{VI}}{\underset{\displaystyle C_2H_5}{CH_3COCHCO_2C_2H_5}} \longrightarrow \underset{\text{VIII}}{\underset{\displaystyle C_2H_5}{CH_3CHOHCHCH_2OH}}$$

The esters of the alkylmalonic acids (IX) were hydrogenated to 2-alkyl-1,3-propanediols (X).



$$\underset{\text{IX}}{C_2H_5O_2CCHRCO_2C_2H_5} \longrightarrow HOCH_2CHRCO_2C_2H_5 \downarrow \underset{\text{X}}{HOCH_2CHRCH_2OH}$$

Ethyl benzylmalonate, ethyl *s*-butylmalonate and ethyl ethylmalonate were converted into the corresponding 1,3-glycols in 26, 24 and 49% yields, respectively.

These results indicate that the β-oxygenated esters, such as acetoacetic esters, malonic esters and the like, may be converted into the corresponding 1,3-glycols (or their esters) as a general convenient preparative method. While many of the yields reported are low, the method offers a convenient way for the preparation of glycols. The yields reported are usually based upon a single run on each of the esters; no attempt has been made to obtain the maximum yield. The present experiments were merely intended to show that such products can be obtained.

Experimental

Copper-Chromium-Barium Oxide Catalyst.—The catalyst was prepared in the usual way.[3] The decomposition of the ammonium salts was done at the minimum temperature. The catalyst contained barium.

Purification of the Esters.—The esters were distilled over Raney nickel catalyst[10] before use.

Ethyl Isobutylideneacetoacetate.—This ester was prepared in 49% yield by a method for the preparation of ethyl butylideneacetoacetate.[11] The ester boiled at 79–80° at 2 mm.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.46; H, 9.21.

Hydrogenation of β-Oxygenated Esters.—The various esters were each hydrogenated in methyl alcohol over copper–chromium oxide under 250–400 atmospheres of hydrogen at about 160–180° in a manganese steel bomb. The exact temperature, amount of reactants, time, etc., are listed for each ester.

The product was isolated in each case by a standard method. The contents of the bomb was washed out with methyl alcohol and filtered. To the filtrate was added 1.5 equivalents of sodium or potassium hydroxide based on the amount of ester submitted to reduction and about 100 ml. of water. The mixture was then refluxed several hours to saponify any unconverted ester. The methyl alcohol was distilled. The aqueous solution was extracted with chloroform in a continuous extractor to remove the glycol. The chloroform solution was concentrated, and the residue was fractionated.

The liquid glycols and alcohols were converted into their *p*-nitrobenzoates for characterization.

Hydrogenation of Ethyl Acetoacetate.—Sixty-five grams of ethyl acetoacetate in 200 ml. of methyl alcohol was reduced to ethyl β-hydroxybutyrate at 125–140° with 30 g. of copper–chromium oxide for fifteen minutes under 100 atmospheres of hydrogen. The bomb was then cooled, and the pressure drop was the expected amount for one mole of hydrogen. The pressure was then increased to 250 atmospheres and the hydrogenation allowed to proceed at 166–170° for nine hours.

The 1,3-butylene glycol, b. p. 115–120° at 21 mm., obtained after saponification, weighed 13.6 g. (30%). The *p*-nitrobenzoate of the 1,3-butylene glycol melted at 101–102°.

Anal. Calcd. for $C_{18}H_{16}O_8N_2$: C, 55.67; H, 4.12; N, 7.21. Found: C, 55.75; H, 4.13; N, 7.18.

Hydrogenation of Ethyl Isobutylideneacetoacetate.—A solution of 43 g. of ethyl isobutylideneacetoacetate in 100 ml. of methyl alcohol was hydrogenated at 160° and 3400–4600 p. s. i. for thirty hours.

The 2-isobutyl-1,3-butylene glycol, b. p. 142–143° at 22 mm., weighed 6 g. (17%).

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.62; H, 12.32.

The di-*p*-nitrobenzoate of this glycol was prepared and found to be a mixture of the two racemic modifications. The product was repeatedly extracted with hot methyl alcohol. The methyl alcohol extracts were concentrated and then cooled. After several recrystallizations from methyl alcohol, this *p*-nitrobenzoate melted at 129–130°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.45; N, 6.30. Found: C, 59.69; H, 5.54; N, 6.49.

The methyl alcohol insoluble residue was recrystallized from acetone to give the second form of the *p*-nitrobenzoate, m. p. 158–159°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.45. Found: C, 59.31; H, 5.62.

From the water solution, there was isolated 23.8 g. of acidic material which was fractionated to give 16.1 g. (43%) of β-hydroxy-α-isobutylbutyric acid which after crystallization melted at 68–70°.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.28; H, 10.30.

In another similar run, 8.4 g. (25%) of the glycol was obtained from 27.6 g. of the ester.

Hydrogenation of Ethyl Ethylacetoacetate.—A solution of 23.7 g. of ethyl ethylacetoacetate in 100 ml. of methyl alcohol was hydrogenated at 160–168° and 5000–5300 p. s. i. over 5 g. of copper–chromium oxide for eleven hours.

Fractionation of the chloroform extract gave 2.6 g. (15%) of 2-ethyl-1,3-butylene glycol, b. p. 110–120° at 21 mm., which was identified by conversion into its di-*p*-nitrobenzoate. The glycol was a mixture of both of the racemic modifications since it gave two *p*-nitrobenzoyl derivatives. These were separated by extraction with methyl alcohol as above. The methyl alcohol soluble fraction melted at 124–125° (from methyl alcohol).

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.60; H, 4.79; N, 6.98.

The second *p*-nitrobenzoate was recrystallized from acetone and melted at 139–140°.

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84; N, 6.73. Found: C, 58.05; H, 5.17; N, 7.05.

Hydrogenation of Ethyl β-Ethoxypropionate.—A solution of 146 g. of ethyl β-ethoxypropionate in 100 ml. of methyl alcohol was hydrogenated over 30 g. of copper-chromium oxide at 168–172° and 4200–6350 p. s. i. for twenty-three hours.

The 3-ethoxy-1-propanol, b. p. 160–161°, obtained as above, weighed 81.2 g. (78%). The usual esters of this

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[10] "Organic Syntheses," 21, 15 (1941).

[11] Cope and Hofmann, THIS JOURNAL, 63, 3456 (1941).

glycol appear to be liquids, but its boiling point agrees with the recorded value.[12]

Hydrogenation of Ethyl Benzylmalonate.—Nineteen grams of the ester in 100 ml. of methyl alcohol was hydrogenated over 8 g. of copper–chromium oxide at 160° and 4900–5600 p. s. i. for six hours. The 2-benzyl-1,3-propanediol was collected by distillation and boiled at 143–145° at 0.5 mm. After standing, the glycol crystallized and was recrystallized from benzene, after which it melted at 68–70°. The yield was 3.3 g. (26%).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 72.26; H, 8.49. Found: C, 72.52; H, 8.44.

The *p*-nitrobenzoate of this glycol melted at 130–131° (from chloroform–ether).

Anal. Calcd. for $C_{24}H_{20}O_8N_2$: C, 62.06; H, 4.35; N, 6.03. Found: C, 61.88; H, 4.27; N, 6.06.

Hydrogenation of Ethyl *s*-Butylmalonate.—A solution of 53.7 g. of ethyl *s*-butylmalonate in 85 ml. of methyl alcohol was hydrogenated over 12.5 g. of copper–chromium oxide catalyst at 157–162° and 4700–6400 p. s. i. for ten hours.

The 2-*s*-butyl-1,3-propanediol, isolated as above, boiled at 92–105° at 0.5 mm. and weighed 7.9 g. The *p*-nitrobenzoate of this glycol melted at 101–102°.

Anal. Calcd. for $C_{21}H_{22}O_8N_2$: C, 58.60; H, 5.15; N, 6.51. Found: C, 58.68; H, 5.03; N, 6.55.

Hydrogenation of Ethyl Ethylmalonate.—A solution of 28.2 g. of ethyl ethylmalonate in 100 ml. of methyl alcohol was reduced at 160–162° for nine hours and then at 180° for fifteen hours at 4100–5500 p. s. i. over 8 g. of copper–chromium oxide. The 2-ethyl-1,3-propanediol, b. p. 86–87° at 0.5 mm., weighed 7.7 g. (49%).

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.66; H, 11.62. Found: C, 57.02; H, 10.99.

The *p*-nitrobenzoate prepared from this glycol was recrystallized from methyl alcohol and melted at 88–89°.

Anal. Calcd, for $C_{19}H_{18}O_8N_2$: C, 56.72; H, 4.51; N, 6.96. Found: C, 56.81; H, 4.44; N, 7.09.

Acknowledgment.—The authors wish to express their appreciation to Mr. William B. Wright for technical assistance and Messrs. R. N. Boos, D. F. Hayman, Wilhelm Reiss, W. K. Humphrey, E. Thornton and Leonard Rosalsky, and Mrs. E. H. Meiss for carrying out the analyses.

Summary

Hydrogenation of β-oxygenated esters has been found to give rise to 1,3-glycols or their ethers by a lower temperature ester reduction method. When the malonic esters, acetoacetic ester, the β-hydroxy esters and β-alkoxy esters are hydrogenated at 160–180° over copper–chromium oxide, the corresponding glycols and their derivatives are produced.

By this method, ethyl acetoacetate, ethyl ethylacetoacetate and ethyl isobutylideneacetoacetate were converted into 1,3-butylene glycol, 2-ethyl-1,3-butylene glycol and 2-isobutyl-1,3-butylene glycol.. Ethyl β-ethoxypropionate gave 3-ethoxy-1-propanol. The ethyl alkylmalonates (ethyl, *s*-butyl and benzyl) give the corresponding 2-alkyl-1,3-propanediols. The yields were 15–78%.

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[12] Bouveault and Blanc, *Bull. soc. chim.*, [3] 31, 1211 (1904).

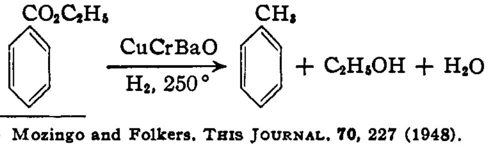
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Hydrogenolysis of Aromatic Esters to Alcohols

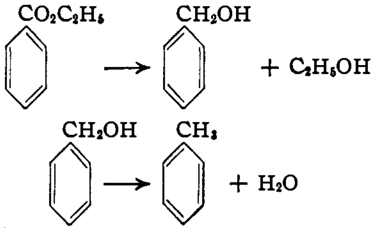
BY RALPH MOZINGO AND KARL FOLKERS

The hydrogenolysis of β-oxygenated esters and their ethers to 1,3-glycols and 1,3-glycol ethers[1] has lead to a reinvestigation of the hydrogenolysis of aromatic esters. While the hydrogenation of aromatic esters under the usual conditions[2] for ester hydrolysis leads to products in which the carboalkoxy group has been converted to a methyl group, it is possible by the low temperature technique previously described[1] to isolate the intermediate alcohol.

When an aromatic ester is hydrogenated at temperatures between 200 and 250° over a copper–chromium oxide catalyst[3] under 200 atmospheres of hydrogen it is converted rapidly into the corresponding methyl derivative. For example, ethyl benzoate gives toluene, ethanol and water.[2]



None of the corresponding alcohol has been obtained under these conditions and it has been suggested that the hydrogenolysis proceeds preferentially to the hydrocarbon.[4] However, it seems equally reasonable that the hydrogenation of an aromatic ester to the hydrocarbon may proceed stepwise.



This has now been found to be the case.

When hydrogenation is carried out between 125 and 175°, the exact temperature depending somewhat upon the ester, hydrogenolysis to the alcohol can be effected. For example, under these conditions ethyl benzoate (I, R = H) and its alkyl derivatives (I, R = CH_3, and II) and its

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[1] Mozingo and Folkers, THIS JOURNAL, 70, 227 (1948).

[2] Adkins, "Reaction of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 97–104.

[3] Connor, Folkers and Adkins, THIS JOURNAL, 53, 2012 (1931).

[4] Lazier, U. S. Patent 2,079,414 (May 4, 1937).