agreement than was formerly found for the molecular constants of these proteins.

UPSALA, SWEDEN

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE HYDROGENATION OF ACETOACETIC ESTER AND CERTAIN OF ITS DERIVATIVES OVER NICKEL

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The hydrogenation of acetoacetic ester in the liquid phase with a nickel catalyst has apparently not previously been investigated although Sabatier and Mailhe[1] obtained ethyl butyrate, acetone, isopropyl alcohol, propionic and dehydroacetic acids in a vapor phase reduction over nickel. The methods used in the present investigation were essentially the same as those previously described.[2]

Acetoacetic ester absorbed one mole equivalent of hydrogen when reduced over a nickel catalyst. There were produced small quantities of alcohol and dehydroacetic acid, two parts of ethyl β-hydroxybutyrate and one part of a derivative of this ester, ethyl β-(β′-hydroxybutyryloxy)-butyrate, $CH_3CHOHCH_2CO_2CH(CH_3)CH_2COOC_2H_5$. The ratio of the mono-ester (I) to the di-ester (II) when the reduction was carried out in various solvents is as indicated: no solvent 67% I, 33% II; in ethanol 100% I; in diethyl ether 68% I, 32% II; in methylcyclohexane 68% I, 32% II; in ethyl β-hydroxybutyrate 69% I, 31% II; in *tert.*-butyl alcohol 83% I, 17% II; in *n*-butanol 66% I and 34% *n*-butyl β-hydroxybutyrate, b. p. 96–97 (13 mm.). Ethyl α-methylacetoacetate upon reduction gave a mono- and di-ester (ethyl α-methyl-β-(α′-methyl-β′-hydroxybutyryloxy)-butyrate), in the ratio of approximately two parts by weight of the latter to five parts of ethyl α-methyl-β-hydroxybutyrate. However, the dialkyl substituted derivatives of acetoacetic ester, ethyl α,α-dimethylacetoacetate and ethyl α-methyl-α-ethylacetoacetate, gave quantitative reduction to the corresponding α,α-dialkyl-β-hydroxybutyric ester. The formation of the di-esters may be avoided by the use of ethanol, for a quantitative yield of ethyl α-methyl-β-hydroxybutyrate was obtained by reducing ethyl α-methylacetoacetate in that solvent.

The salient facts seem to be: (1) the two beta ketonic esters capable of enolization upon hydrogenation in the absence of a solvent or in the presence of the ethyl-β-hydroxybutyrate or of ether or methylcyclohexane gave large amounts of di-esters along with the simple hydroxy ester.

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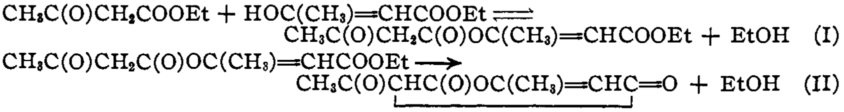
[1] Sabatier and Mailhe, *Bull. soc. chim.*, [4] **3**, 232 (1908).

[2] Adkins and Cramer, THIS JOURNAL, **52**, 4349 (1930).

(2) The amount of the di-ester was less if tertiary butyl alcohol was used as a solvent and was negligible in the product from the hydrogenations carried on in ethyl or *n*-butyl alcohols. (3) The two keto esters incapable of enolization were hydrogenated quantitatively even without a solvent to the corresponding simple hydroxy esters.

The effect of the alcohols in decreasing the yield of di-ester was not due to the alcoholysis of the di-ester after it was formed, for the alcoholysis of the di-ester was very difficult and did not occur under the conditions in which the alcohols were effective. For example, ethyl β-(β′-hydroxybutyryloxy)-butyrate did not undergo alcoholysis with ethanol upon being heated for three hours at 150° in the reduction apparatus. Only 40% of it was converted to ethyl β-hydroxybutyrate after six and one-half hours at 190°. The resistance of this ester to alcoholysis is further shown by the fact that there was no alcoholysis of the di-ester after it had been refluxed with an ethanol solution of sodium ethoxide for two and one-half hours.

The effectiveness of the alcohols in inhibiting the formation of the di-ester is understandable upon the hypothesis of Arndt and Nachtwey[3] with regard to the formation of dehydroacetic acid from acetoacetic ester. They suggested that two reactions are involved. The first of these was supposed to be reversible since removal of ethyl alcohol permitted the formation of dehydroacetic acid, while the second was supposed to be an irreversible reaction, since boiling alcohol did not convert dehydroacetic acid into acetoacetic ester. (It will be shown later that the latter is also a reversible reaction.) These authors suggest that the mechanism of the formation of dehydroacetic acid may be as shown in Reactions I and II



$$CH_3C(O)CH_2COOEt + HOC(CH_3){=}CHCOOEt \rightleftharpoons CH_3C(O)CH_2C(O)OC(CH_3){=}CHCOOEt + EtOH \quad \text{(I)}$$

$$CH_3C(O)CH_2C(O)OC(CH_3){=}CHCOOEt \longrightarrow CH_3C(O)\underbrace{CHC(O)OC(CH_3){=}CHC}{=}O + EtOH \quad \text{(II)}$$

The formation of ethyl β-(β′-hydroxybutyryloxy)-butyrate in the reduction of acetoacetic ester substantiates the mechanism postulated by Arndt and Nachtwey, since it is the reduction product of the intermediate indicated in the formation of dehydroacetic acid from acetoacetic ester. The presence of ethanol would shift the first reaction to the right and thus greatly decrease the amount of $CH_3C(O)CH_2C(O)OC(CH_3){=}CHCOOEt$ and consequently of the di-ester formed from it by hydrogenation. *n*-Butanol would behave similarly since there is little difference among the primary alcohols in the concentration at equilibrium in similar reactions such as ester and acetal formation. Tertiary butyl alcohol would be expected to be much less effective in shifting the equilibrium toward the left since it is so little active in ester and acetal formation.

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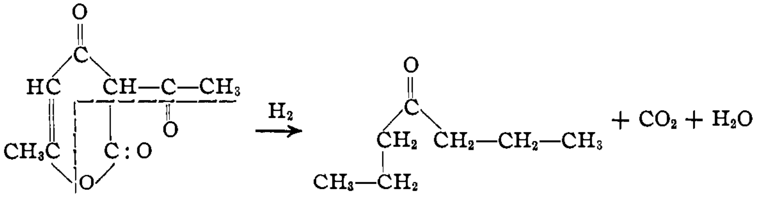
[3] Arndt and Nachtwey, *Ber.*, **57B**, 1489 (1924).

The rate of reduction of acetoacetic ester in methylcyclohexane or ether was three times as great as in the absence of a solvent; in fact pure acetoacetic ester reduced much more slowly at 150° than it did in the presence of these solvents at 125°. The rate of reduction of an alcoholic solution of the ester was intermediate between that of the pure ester and that in a methylclohexane solution.

The formation of 1 or 2% of dehydroacetic acid in the reduction of acetoacetic ester and the possible relationship of the di-ester obtained to an intermediate in the formation of dehydroacetic acid led to an investigation of the hydrogenation of the latter compound. Dehydroacetic acid was not readily reduced, as from two to five applications of catalyst were necessary in each run before the maximum absorption of hydrogen was obtained. The temperature of reduction was 185–190° and the pressures were from 108 to 325 atmospheres, the reduction going approximately four times as rapidly at the highest as at the lowest pressure.[4] At pressures of about 130 atmospheres three moles of hydrogen per mole of dehydroacetic acid were absorbed, but at a pressure of about 325 atmospheres, five moles of hydrogen were taken up. Methylcyclohexane was used as a solvent for the reduction. It was found that when ethanol was used as a solvent, no reduction occurred, but heating with or without nickel at 190° for two hours gave 70% conversion of dehydroacetic acid to ethyl acetoacetate, the remainder of the acid being recovered unchanged.

The chief product obtained in the hydrogenation of dehydroacetic acid was heptanone-4, the yield being 40 to 45% under the optimum conditions. The formation of this ketone must involve the removal of oxygen and decarboxylation as well as hydrogenation, *e. g.*



The water formed in the removal of the oxygen would hydrolyze dehydroacetic acid[5] and the products under reducing conditions would presumably give acetone, acetic acid and isopropyl and ethyl alcohols. These alcohols would in turn bring about the formation of acetoacetic ester through the alcoholysis of dehydroacetic acid. These compounds except acetic acid were all found among the reduction products of dehydroacetic acid.

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[4] Adkins, Cramer and Connor, unpublished work.

[5] Collie, *J. Chem. Soc.*, 59, 179 (1891).

It is noteworthy that in the hydrogenation of dehydroacetic acid in methylcyclohexane and in the attempted hydrogenation in ethanol, there were formed compounds (acetone, heptanone-4 and acetoacetic ester) which are readily hydrogenated under the conditions of temperature and pressure at which they were formed. This is not due to the action of dehydroacetic acid, for acetoacetic ester in a mixture of it with dehydroacetic acid was readily hydrogenated but the acetoacetic ester produced by the dehydrogenation of the dehydroacetic acid was not reduced. This was indicated by the hydrogen absorption and by the evidence for acetoacetic ester in the reaction product.

Experimental Part

A summary of typical results obtained in the reduction of acetoacetic ester and some of its derivatives is given below. There is given in

TABLE I

REDUCTION OF VARIOUS DERIVATIVES OF ACETOACETIC ESTER

No.	Compound	Moles	Moles H_2	Catalyst G.	Catalyst No. (portions)
1	Acetoacetic ester	0.39	0.39	2	1RAC
2	Acetoacetic ester	.39	.40	2	1RAC
3	Acetoacetic ester	.39	.43	2	1RAC
4	α-Methylacetoacetic ester	.35	.37	2	4RAC
5	α-Methylacetoacetic ester	1.04	1.06	4	5RAC
6	α-Methyl-α-ethylacetoacetic ester	0.28	0.32	2	3KF
7	α,α-Dimethylacetoacetic ester	.62	.64	3	4KF
8	Dehydroacetic acid	.30	..	20	1RAC (5)
9	Dehydroacetic acid	3.0	.90	11	1RAC (3)
10	Dehydroacetic acid	.30	1.48	11	5RAC (3)
11	Dehydroacetic acid	.12	0	None or 3g1RAC	
12	Dehydroacetic acid	.21	1.0	4	5RAC

No.	Ml.	Solvent	Temp., °C.	Press., Atm.	Time, Hours	Yield, %
1		None	125	94±11	4.5	B67 mono-ester B33 di-ester
2	50	EtOH	125	89±15	2.5	B100 mono-ester
3	50	C_7H_{14}	125	103±14	1.5	B68 mono-ester B32 di-ester
4	50	EtOH	150	110±7	0.75	A85, B100 mono-ester
5		None	175	160±24	9	A52, B70 mono-ester A19, B26 di-ester
6		None	175	150±10	3	B100 mono-ester
7		None	185	150±10	2	B100 mono-ester
8	100	C_7H_{14}	185	132±16	21	See exptl. part
9	100	C_7H_{14}	185	174±18	10.5	See exptl. part
10	100	C_7H_{14}	185–190	332±41	8.5	See exptl. part
11	50	EtOH	190	165	2	C70 acetoacetic acid C30 dehydroacetic acid
12	0.42 moles of acetoacetic ester		190	132±28	3	See exptl. part

order, the name and amount in moles of the compound reduced, the moles of hydrogen absorbed, the weight and number of the catalyst according to our records, the volume and name of solvent when one was used, the temperature, pressure and time for reduction after reaching the designated temperature, the name and yield of product(s). The yields marked "A" are those actually obtained while in those marked "B" allowance is made for the mechanical losses in handling the materials during reduction and filtration, and in "C" for mechanical losses and for the amount of the starting material recovered unchanged.

The product from 50 g. of acetoacetic ester after separation of the nickel catalyst in a typical experiment weighed 45 g. It gave no coloration with a ferric chloride solution and upon fractionation through a 20-cm. Widmer column gave two main fractions: 28 g. 77–79° (15 mm.) and 13 g. 154–156° (15 mm.). The remainder (4 g.) distilled below, between and above these fractions. The part distilling below the two main fractions was identified as ethanol through the formation of its 3,5-dinitrobenzoate. The part distilling above the two main fractions contained dehydroacetic acid, m. p. 110°. The fraction boiling at 77–79° (15 mm.) was ethyl β-hydroxyethylbutyrate. The fraction boiling at 154–156° (15 mm.) was identified as ethyl β-(β'-hydroxybutyryloxy)-butyrate on the basis of the following experimental findings. Upon saponification ethanol, identified as the 3,5-dinitrobenzoate, was formed. The acid so produced was a white rancid-smelling solid melting at 72° and boiling at 184° (740 mm.). It rapidly reduced cold alkaline permanganate solution, showed a neutral equivalent of 87, and gave a dibromide melting at 85–86.5°. Crotonic acid melts at 72°, has a neutral equivalent of 86 and its dibromide melts at 87°. The ester showed a saponification number of 109.5 and 110.3, d^{25}_{25} 1.0678, n^{25}_{D} 1.4360, and a molecular refraction of 53.36 (MR'$_{\mathrm{D}}$). The calculated saponification number for the di-ester is 109 and the MR'$_{\mathrm{D}}$ 53.39.

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.05; H, 8.25. Found: C, 54.97; 54.70; H, 8.30, 8.33.

The ester showed no alcoholysis when 15 g. was boiled for two and one-half hours in 50 ml. of ethanol containing 6.8 g. of sodium ethoxide, nor when it was heated with ethanol alone for three hours at 150° under a pressure of 130 atmospheres of hydrogen. However, 40% of it was converted to ethyl β-hydroxybutyrate in six hours at 190°. Butyl β-hydroxybutyrate was identified on the basis of the facts that it showed a saponification value of 157 and 160 (theoretical 160) and gave *n*-butanol, identified as the dinitrobenzoate, upon saponification.

The fractionation of the products from the reduction of ethyl α-methylacetoacetate showed 1.4% ethanol, 70.5% ethyl α-methyl-β-hydroxybutyrate, b. p. 85–87° (22 mm.), 26% ethyl α-methyl-β-(α'-methyl-β'-hydroxybutyryloxy)-butyrate, b. p. 155–158° (17 mm.), and 1.4% residue. The ethyl α-methyl-β-(α'-methyl-β'-hydroxybutyryloxy)-butyrate was characterized by a saponification number of 124.4 and 124.1 (calcd. 123), d^{25}_{25} 1.0332, n^{25}_{D} 1.4393, MR'$_{\mathrm{D}}$ 62.65 (calcd. 62.59).

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.53; H, 8.94. Found: C, 58.29, 58.49; H, 8.94, 8.81. The acid corresponding to this ester has been prepared previously.[6]

Dehydroacetic Acid.—In the runs made at 130 atmospheres three main fractions, besides the solvent, were obtained upon distilling the reduction product of dehydroacetic acid. The first of these comprised 23% of the recovered material and contained ethyl

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[6] Wislicenus, *Ber.*, **8**, 1036 (1875); Rohrbeck, *Ann.*, **188**, 229 (1877); *cf.* Skau and Saxton, THIS JOURNAL, **52**, 335 (1930).

alcohol, acetone and water. The second was heptanone-4, b. p. 144–146° (735 mm.), and comprised 17.3% of the material recovered, while the third fraction was acetoacetic ester, b. p. 178° (735 mm.), and amounted to 29.8%. When the latter fraction was collected over a four degree range, 174–178° (735 mm.), enough butyric acid was present after hydrolysis to obtain as derivatives, the anilide and the *p*-bromo-anilide. The 30% of the material not included here represents the transition material between fractions, and about 7.6% of unreduced material.

The fractionation of the products from the hydrogenation of dehydroacetic acid at 325 atmospheres gave amounts of compound boiling below 140° similar to those obtained in the hydrogenation at lower pressures but there was approximately two and one-half times as much heptanone-4 as under those conditions. There was less than half as much material boiling above the range of heptanone-4 with no evidence of the presence of acetoacetic ester. Unquestionably ethyl β-hydroxybutyrate and probably ethyl β-(β'-hydroxybutyryloxy)-butyrate were present in the high fractions but the total amount (3 g.) was too small and impure to obtain crystalline derivatives.

The presence of ethanol and of acetone among the reduction products of dehydroacetic acid was demonstrated through the formation of the 3,5-dinitrobenzoate of the former and the dibenzal derivative of the latter. Heptanone-4 was characterized by its boiling point 145–146° and the melting point of its semicarbazone (133–134°) and the melting point (133–134°) of a mixture of this semicarbazone with some known semicarbazone of this ketone. It was further characterized by reduction over nickel at 175° and 160 atmospheres to heptanol-4, b. p. 152–154 (740 mm.), which gave a 3,5-dinitrobenzoate melting at 64° and an α-naphthylurethan melting at 79–80°.

Anal. Calcd. for $C_{18}H_{32}NO_2$: C, 75.52; H, 8.39. Found: C, 75.68, 75.58; H, 8.34, 8.25.

The fraction, b. p. 170–174° (740 mm.), was characterized as acetoacetic ester by its boiling range and its coloration with ferric chloride solution, by the formation of acetone and ethanol through alkaline hydrolysis. The fraction gave a vigorous reaction with phenylhydrazine but the reaction product was an oil which could not be purified.

Dehydroacetic acid was prepared as by Arndt and Nachtwey.[7] Three hundred grams of acetoacetic ester in a 500-ml. flask was heated so that the vapors reaching the top of a 60-cm. Vigreux column had a temperature of 78–85°. After 40 g. of ethanol had distilled, 34.4 g. of dehydroacetic acid separated out on cooling the contents of the reaction flask. Fifteen grams of ethanol was then distilled out and 29.5 g. of dehydroacetic acid obtained; further heating gave successively 8.3 g. of ethanol, 14.5 g. of the acid and 10 g. of ethanol and 17.5 g. of the acid. The total yield from 300 g. of the ester was 96 g. or 50% of the theoretical yield. Much lower yields were obtained when attempts were made to distil out all the ethanol without the removal of the dehydroacetic acid from time to time as indicated. The product had a melting point of 98–103°, and 109–110° after recrystallization from ethanol and water. The product used for reduction was not so purified.

Summary

Ethyl acetoacetate readily took up one molecular equivalent of hydrogen over a nickel catalyst at temperatures from 100 to 150°. If the hydrogenation was carried out in an ethanol solution, ethyl β-hydroxybutyrate was formed practically quantitatively. In the absence of a solvent or in ether or methylcyclohexane, there was formed along with two parts of ethyl β-hydroxybutyrate, one part of a derivative of it,

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[7] Arndt and Nachtwey, *Ber.*, **57B**, 1487 (1924).

ethyl β-(β′-hydroxybutyryloxy)-butyrate. This ester despite the fact that it is the ester of a secondary alcohol did not undergo alcoholysis at the temperature used for the reduction of acetoacetic ester or in a boiling alcoholic solution of sodium ethoxide. It did undergo alcoholysis at 190° in the presence of a nickel catalyst. This complex ester appears to be formed through the reduction of two molecules of acetoacetic ester with the elimination of one molecule of ethanol. This condensation product was postulated by Arndt and Nachtwey as an intermediate in the formation of dehydroacetic acid from acetoacetic acid, so that the results here reported support their hypothesis. The methyl derivative of acetoacetic ester on reduction behaved similarly to the unsubstituted ester. The α,α-dimethyl and the α-methyl-α-ethylacetoacetic ester reduced smoothly to the corresponding simple hydroxy ester either with or without a solvent since there is no possibility of the formation of a complex ester analogous to that formed from the β-ketonic esters capable of enolization.

Dehydroacetic acid appears to give heptanone-4 as the chief product in hydrogenation over nickel. The use of hydrogen pressure in excess of 300 atmospheres appears not only very greatly to accelerate the rate of hydrogenation but to favor the formation of heptanone-4 with a decrease in the products formed through the hydrolysis and alcoholysis of the dehydroacetic acid. Dehydroacetic acid has been found to undergo a smooth alcoholysis to acetoacetic ester at 190°.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

THE STRUCTURE OF PARA-DIMETHYLAMINOBENZOIN[1]

BY SANFORD S. JENKINS[2] WITH LUCIUS A. BIGELOW AND JOHANNES S. BUCK

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In the preceding paper, dealing with the reduction of *p*-dimethylaminobenzil,[3] it was found that the corresponding benzoin, on treatment with tin and hydrochloric acid in alcohol solution, yielded *two* isomeric desoxy derivatives, designated as α- and β-forms, the structures of which were established. This fact made it seem possible that the benzoin itself might be a mixture of α- and β-modifications, which, at least theoretically, would be expected to exist.

Accordingly, efforts were made to separate the apparently pure benzoin (m. p. 163–164°) into isomeric components by ordinary methods. For

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[1] This paper is in part constructed from portions of a thesis presented by Sanford S. Jenkins in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Arts and Sciences, Duke University.

[2] Angier B. Duke Memorial Fellow, 1929–1930.

[3] Jenkins, Buck and Bigelow, THIS JOURNAL, 52, 4495 (1930).