

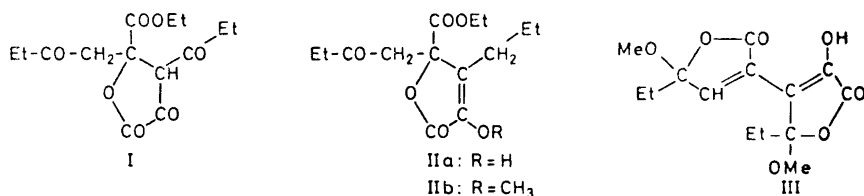
## Selfcondensation of Propionylpyruvic Ethyl Ester

ODD ANTONSEN and ENDRE BERNER

*Kjemisk Institutt, Universitetet i Oslo, Blindern, Oslo 3, Norway*

The condensation of propionylpyruvic ester proceeded analogous to that of acetylpyruvic esters. The condensation product on degradation led to several acids amongst which a  $\beta$ -ketoacid  $C_{14}H_{12}O_6$  on sublimation or by dissolving in conc. sulphuric acid split off one molecule of water. This reaction was found to be due to the occurrence of the lactol-form of the  $\beta$ -ketoacid.

The bimolecular condensation of acetylpyruvic esters was first described by Claisen<sup>1</sup> but only quite recently a satisfactory scheme for the condensation process has been put forward by Berner and Kolsaker.<sup>2</sup> It has now been found that the ethyl ester of propionylpyruvic acid undergoes a similar condensation. The new condensation product (called PPE) is a crystalline substance with m.p. 67–70°C and the composition  $C_{14}H_{18}O_7$ . Contrary to the condensation products from acetylpyruvic esters, it does not contain crystal water. Based upon the results obtained with the acetylpyruvic esters, PPE is assigned the structural formula I.

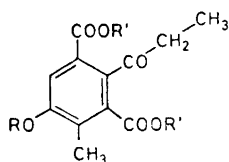


As in the case of the condensation products of acetylpyruvic esters, PPE on catalytic hydrogenation took up 2 mol of hydrogen and split off 1 mol of water giving a crystalline product  $C_{14}H_{20}O_6$  which is given formula IIa. It could be titrated as a monovalent acid and on treatment with diazomethane gave a methoxy derivative (IIb).

Similarly PPE on treatment with methanol containing hydrogen chloride gave a so-called isoester with the same composition as PPE and assigned formula III.

Formula I was verified by the results of a degradation which took place on heating PPE with barium hydroxide. Besides ethanol and water also oxalic and propionic acids were split off, and, although with considerable difficulty, the following three aromatic acids were isolated: *A*,  $C_{12}H_{12}O_6$ , containing all the carbon atoms from the original carbon-skeleton and obviously being 2-propionyl-4-methyl-5-hydroxyisophthalic acid (IVa). *B*,  $C_{10}H_{12}O_3$ , arising when oxalic acid is lost. It is accordingly homologous to the 3-methyl-5-hydroxybenzoic acid obtained from the condensation product of acetopyruvic ester and has the formula 3-ethyl-4-methyl-5-hydroxybenzoic acid. *C*,  $C_9H_8O_5$ , which as a propionyl group has been split off, must be 4-methyl-5-hydroxyisophthalic acid.

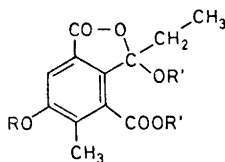
The separation of these acids could not be effected by crystallization alone, but sublimation in a vacuum had alternately to be used. The least volatile of the acids (*A*) was isolated as a rest after a partial sublimation and after recrystallization had the composition  $C_{12}H_{12}O_6$  (IVa). But even this acid could be sublimated by using sufficiently high temperature, resulting, however, in a crystalline substance with the formula  $C_{12}H_{10}O_5$  (VIa). A similar dehydration took place when *A* was dissolved in conc. sulphuric acid. Recently it has been found in this institute<sup>3</sup> that even other  $\beta$ -ketoacids on dissolving in conc. sulphuric acid split off water. The explanation for this must be that  $\beta$ -ketoacids occur at least in part in the lactol-form (*e.g.* Va) in accordance with the fact that the esters of such acids are known both in open and cyclic forms. The dehydration in question proceeds as demonstrated in the formulæ IVa, Va, and VIa, which was verified by means of PMR. (Alternatively, the other carboxylic group could be engaged in the cyclization.)



IVa: R = H, R' = H

IVb R = H, R' = CH<sub>3</sub>

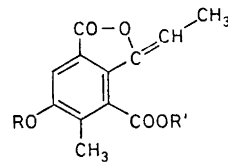
IVc R = CH<sub>3</sub>, R' = CH<sub>3</sub>



Va: R = H, R' = H

Vb: R = H, R' = CH<sub>3</sub>

Vc: R = CH<sub>3</sub>, R' = CH<sub>3</sub>



VIa: R = H, R' = H

VIb: R = CH<sub>3</sub>, R' = CH<sub>3</sub>

It should be added that also the iso-ester (III) was degraded similarly on heating with barium hydroxide, but in this case only the acid  $C_9H_8O_5$  was isolated and identified with the acid obtained directly from PPE.

## EXPERIMENTAL

*Ethyl propionylpyruvate.* The ester was first prepared according to Diels *et al.*<sup>4</sup> and later according to Mumm and Böhme.<sup>5</sup> The last mentioned method gave best results especially when working with small portions.

*Condensation of ethyl propionylpyruvate.* The condensation took place when the ester was shaken at room temperature with an aqueous solution of sodium acetate (equimolecular amounts of acetate and ester). In the course of a few days, the ester had dissolved

and an excess of hydrochloric acid was added. The condensation product separated as an oil which was dried in a vacuum above calcium chloride. All attempts to purify the product at first failed; it was only when the oil after several months spontaneously crystallized that the pure PPE could be isolated. The partly crystallized oil was pressed on a porous plate and the crystals recrystallized from ethyl acetate-ligroin. Yield about 15 %. M.p. 69–70°. \* 53.8 mg req. 1.79 ml 0.1004 N NaOH. (Found: C 56.30; H 6.10; M 299. Calc. for  $C_{14}H_{18}O_7$ : C 56.37; H 6.08; M 298.3.)

*Degradation of PPE.* 20 g PPE, 40 g barium hydroxide (hydrate) and 400 ml water were heated in a water-bath under stirring for 30 min. The barium oxalate which had separated after reprecipitation weighed 3.2 g (oxalic acid, m.p. 101°, isolated and identified), showing that 22.5 % of PPE had split off oxalic acid. (In a separate experiment, the presence of propionic acid in the filtrate was proved using the method of McNair.<sup>6</sup>) The filtrate from the oxalate on adding 55 ml of 5 N HCl became strongly violet, and on standing until the next day, 8.8 g of a crystalline mixture of acids had separated which showed the equiv. weight 116.

The first acid to be isolated was *B*, viz. by sublimating the mixture of acids in a vacuum (12 mmHg) at about 170°. The sublimate after recrystallization from dilute ethanol had m.p. 192°. 51.1 mg req. 2.76 ml 0.101 N NaOH. (Found: C 66.69; H 6.75; M 183. Calc. for  $C_{10}H_{12}O_3$ : C 66.65; H 6.67; M 180.2.) The acid gave no derivative with dinitrophenylhydrazine and no colour with ferric chloride. The methyl ester, prepared by means of diazomethane, had m.p. 106°. (Found: C 68.00; H 7.33. Calc. for  $C_{11}H_{14}O_3$ : C 68.02; H 7.27.)

Rising the temperature during sublimation to about 250° a second fraction was obtained containing mainly the acid *C*. As it was futile to purify by crystallization, the acid was first esterified by boiling a 10 % solution in methanol containing 5 % sulphuric acid. The ester after recrystallization from dilute methanol had m.p. 168°. (Found: C 58.85; H 5.10. Calc. for  $C_{11}H_{12}O_5$ : C 58.92; H 5.40.) PMR showed the following singlets:  $\pi$  7.47 (s,3H), 6.05 (s,6H), 1H at 4.08, 2.31 and 192.

By saponifying the ester, m.p. 168°, the pure acid *C* was obtained. Recrystallized from dilute ethanol, m.p. 310°. 75.6 mg req. 3.84 ml 0.2 N NaOH. (Found: C 55.00; H 4.16; E 98.5. Calc. for  $C_9H_8O_5$ : C 55.05; H 4.11; E 98.1.)

A solution of the ester, m.p. 168°, in ether containing a little methanol gave with diazomethane the fully methylated derivative of *C*, m.p. 82° after crystallization from dilute ethanol. (Found: C 60.19; H 5.85;  $CH_3O$  39.78. Calc. for  $C_{12}H_{14}O_5$ : C 60.50; H 5.92;  $CH_3O$  39.08.) PMR:  $\pi$  7.53 (s,3H), 6.1 (s,9H), 2.41 (s,1H), and 192 (s,1H). By saponifying the ester, m.p. 82°, the 5-methoxy-4-methylisophthalic acid was isolated, m.p. 310°.

The rest after the sublimation of the mixture of the acids contained mostly both *A* and dehydrated *A*. In order to isolate *A* itself, the mixture was esterified by boiling a solution of it (5.7 g) in 80 ml methanol and 2 ml conc. sulphuric acid for 5 h. After removing the sulphuric acid with barium carbonate and evaporating the solvent, the solid residue was recrystallized many times, partly from ethyl acetate and partly from dilute ethanol. The pure cyclic ester (Vb) had m.p. 207°. (Found: C 60.30; H 5.88;  $CH_3O$  22.41. Calc. for  $C_{14}H_{16}O_6$ : C 59.99; H 5.76;  $CH_3O$  22.14.) PMR:  $\pi$  9.24 (t,3H), 7.31 (s,3H), 6.90 (s,3H), 6.06 (s,3H), 3.80 (s,1H) 3.24 (s,1H) and a quartet at 7.65 (2H). Saponification: 0.85 g ester, a little methanol and 8 ml 2 N NaOH heated a short time to 50°. On adding 10 ml 2 N  $H_2SO_4$ , *A* separated immediately and was recrystallized from water, m.p. 325°. 63.0 mg req. 2.43 ml 0.2 N NaOH. (Found: C 57.36; H 4.92; E 130. Calc. for  $C_{12}H_{12}O_6$ : C 57.14; H 4.80; E 126.)

The dehydration of *A* was effected either by sublimation in a vacuum at 250–260° or by dissolving the acid in conc. sulphuric acid, and after 15 min pouring the solution in ice-water. In both cases, crystalline VIa was obtained which after recrystallization from dilute ethanol had m.p. 335°. (Found: C 61.73; H 4.47. Calc. for  $C_{12}H_{10}O_5$ : C 61.54; H 4.30.) PMR in DMSO:  $\pi$  8.05 (d, 3H), 7.51 (s, 3H), a quartet at 3.33 (1H), 2.24 (1H) and besides 2 mobile H. When VIa was treated with diazomethane in the presence of methanol, a crystalline ester (m.p. 187°) was obtained which as expected from the formula contained two methoxyl groups. PMR:  $\pi$  7.98 (d, 3H), 7.36 (s, 3H), 6.03 (s, 6H), 3.28 (q, 1H), and 2.28 (s, 1H).

\* All melting points are in °C.

When *A* (IVa) was treated with diazomethane in the presence of methanol, the methoxy-derivative of the open ester (IVc) was obtained, m.p. 117°. (Found: C 60.92; H 5.98; CH<sub>3</sub>O 31.75. Calc. for C<sub>15</sub>H<sub>18</sub>O<sub>6</sub>: C 61.22; H 6.16; CH<sub>3</sub>O 31.64.) PMR:  $\pi$  8.82 (t, 3H), 7.74 (s, 3H), 6.08–6.14 (s, 9H), 7.26 (q, 2H), and 2.54 (s, 1H).

*Transformation of open into cyclic ester.* A solution of 0.5 g ester, m.p. 117°, in 5 ml methanol containing 0.2 ml conc. sulphuric acid was boiled for 5 h. On dilution with water the ester Vc separated and was recrystallized from dilute ethanol, m.p. 112°. (Found: C 61.08; H 6.15; CH<sub>3</sub>O 32.05. Calc. for C<sub>15</sub>H<sub>18</sub>O<sub>6</sub>: C 61.22; H 6.16; CH<sub>3</sub>O 31.64.) PMR:  $\pi$  9.25 (t, 3H), 7.36 (s, 3H), 6.92 (s, 3H), 6.03 (s, 6H), 7.62 (q, 2H), and 2.32 (s, 1H).

*Hydrogenation of PPE.* 10 g PPE and 0.5 g platinum oxide in 100 ml methanol during 22 h took up 1345 ml hydrogen (0°, 760 mm); calc. for 2 mol 1420 ml. The filtrate from platinum on evaporation gave 8.9 g crystalline product (IIa) which after successive crystallizations from benzene, water, and dilute methanol had m.p. 123°. 54.6 mg required 0.96 ml 0.2 N NaOH. (Found: C 59.47; H 6.83; CH<sub>3</sub>O 16.21; E 285. Calc. for C<sub>14</sub>H<sub>20</sub>O<sub>6</sub>: C 59.14; H 7.09; CH<sub>3</sub>O 15.85; E 284.3.) A methoxy-derivative obtained by treatment with diazomethane had m.p. 55°. PMR is rather complex but obviously supporting formula IIb.

*Preparation of the isoester.* To a solution of 10 g PPE in 50 ml methanol, 2.5 ml conc. HCl were added. After 4 days crystallization started and after 9 days 3.4 g isoester (III) was filtered off. From the mother liquor a little more crystals separated; yield in all, 40 %. Recrystallized from ethyl acetate, m.p. 126°. 41.9 mg req. 1.41 ml 0.102 N NaOH. (Found: C 56.53; H 6.10; CH<sub>3</sub>O 21.0; E 292. Calc. for C<sub>14</sub>H<sub>18</sub>O<sub>7</sub>: C 56.37; H 6.08; CH<sub>3</sub>O 20.80; E 298.3.) Degradation of III with barium hydroxide was carried out as described for PPE, but in this case only the most volatile of the acids was isolated. M.p. 192°, mixed m.p. 192°. (Found: C 66.36; H 6.72. Calc. for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: C 66.65; H 6.67.)

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