

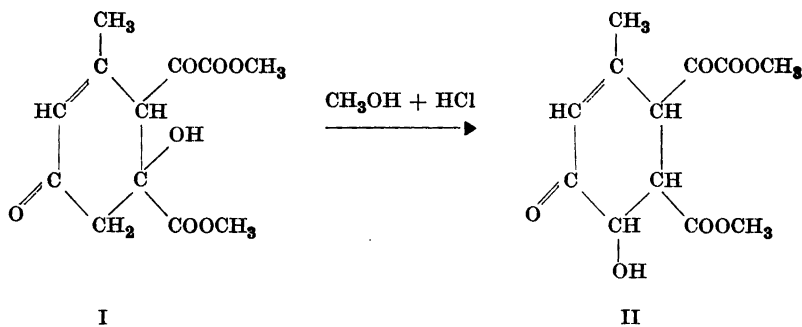
Cyclic Compounds from Acetylpyruvic Esters. II

ERLING BERNATEK

Universitetets Kjemiske Institutt, Blindern — Oslo, Norway

HYDROGENATION AND SUBSEQUENT DEGRADATION OF THE HCl-PRODUCT

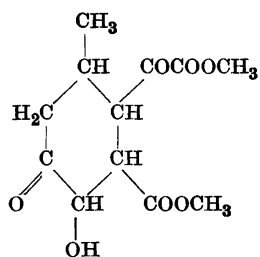
In part I of this series Berner and Laland¹ described an interesting intermolecular rearrangement obviously involving the migration of a hydroxyl group in a hydroaromatic ring under the influence of methanolic hydrogen chloride. The reaction was assumed to proceed in the following way:



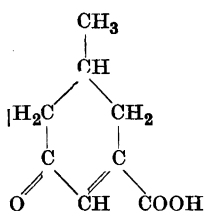
The resulting product II (designated as HCl-product) could be titrated as a monobasic acid while the original dimethyl ester (I) was found to be neutral. The acidity was assumed to be due to a free hydroxyl group in ortho position to a carbonyl group.

When the HCl-product was hydrogenated with PtO_2 as a catalyst in 98 to 99 per cent methanol under a pressure of about 1200 mm it took up one mole of hydrogen. The reaction product could, however, only be obtained as a highly viscous syrupy oil, from light to deep yellow in colour. It did not crystallise on standing for several weeks in a refrigerator but hardened into a glassy mass when kept above phosphorus pentoxide in a desiccator. Obviously it contained free carboxyl groups because of its acidic properties and low methoxyl content.

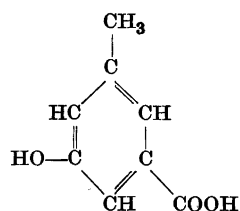
When the hydrogenation was undertaken in anhydrous methanol also one mole of hydrogen was taken up, but the product consisted then of about 65 per cent crystalline material besides the above-mentioned oil. The crystalline product had the composition $C_{12}H_{16}O_7$ and was evidently the normal hydrogenated HCl-product III.



III



IV

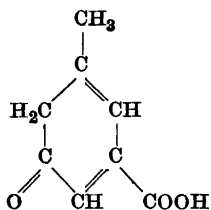


V

It should be mentioned that this compound was very easily hydrolysed. If not absolutely pure it deliquesced in moist air giving a syrupy liquid which could not be brought to crystallisation again and whose methoxyl content was very low. A similar syrupy liquid was obtained if recrystallisation was attempted in methanol that contained from 1 to 2 per cent of water.

On heating with aqueous barium hydroxide the compound III was decomposed into oxalic acid and a substance $C_8H_{10}O_3$ which was assumed to have the formula IV. The same compound could also be obtained from the above-mentioned syrupy hydrogenation product by heating it with aqueous barium hydroxide.

The hydroaromatic compound IV could be dehydrogenated in one operation with N-bromosuccinimide giving an acid $C_8H_8O_3$ which was identified as 3-methyl-5-hydroxybenzoic acid (V). Ziegler² writes that the presence of free

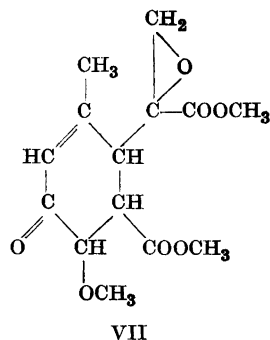


VI

carboxyl groups interferes with the bromination by means of N-bromosuccinimide. The low yield of our dehydrogenation (about 5 per cent) may be in accordance with this fact. Consistent with the same fact the yield was increased to about 30 per cent when the methyl ester of IV was dehydrogenated. According to Ziegler³ conjugated dienes such as 1,3-cyclohexadiene are very resistant to N-bromosuccinimide. In our case the bromination most likely will take place with the keto form of IV giving the compound VI which then enolises into the aromatic acid V.

INTERACTION BETWEEN THE HCl-PRODUCT AND DIAZOMETHANE

When treated with diazomethane the HCl-product $C_{12}H_{14}O_7$ gave a compound $C_{14}H_{18}O_7$ to which Berner and Laland¹ assigned the formula VII assuming that a ketomethylation had taken place. It was now found that such a compound was not formed directly and that a nitrogen-containing intermediate could first be isolated. On heating this intermediate easily split off one mole of nitrogen giving the compound $C_{14}H_{18}O_7$. The pronounced thermolability makes it probable that the intermediate is a pyrazoline derivative. From the works of Buchner⁴, von Pechmann⁵ and others pyrazolines are known to be formed by the action of diazomethane (or ethyl diazoacetate) on unsaturated carbon-carbon double bonds. The author has found no case of ketomethylation described in the literature in which any nitrogen-containing intermediate was isolated.



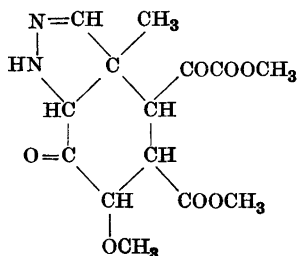
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On attempting a catalytic hydrogenation of $C_{14}H_{18}O_7$ no hydrogen was taken up and a carbon-carbon double bond is therefore hardly present in the molecule.

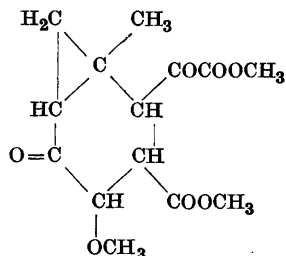
When heated with aqueous barium hydroxide $C_{14}H_{18}O_7$ split off oxalic acid to an extent of 33 per cent based on the assumption that one mole of oxalic acid has been split off from each mole of $C_{14}H_{18}O_7$. This reaction indicates the presence of an α -keto acid in the side chain. It ought to be added that the precipitate obtained on heating with barium hydroxide besides oxalate also contained barium carbonate. Thus a semi-quantitative experiment performed in a nitrogen atmosphere gave a precipitate containing about 30 per cent barium carbonate. The degradation of $C_{14}H_{18}O_7$ must therefore at least have followed two different courses. From the reaction mixture an acid $C_{10}H_{10}O_4$ could be isolated which reduced Tollens reagent, easily gave a precipitate with dinitrophenylhydrazine and contained no methoxyl groups. The elucidation of its structure will, however, make further investigations necessary.

Based upon the above facts the structure VIII is proposed for the nitrogen-containing intermediate $C_{14}H_{18}N_2O_7$.

As the splitting off of nitrogen from a compound containing a pyrazoline ring is known to result in the formation of a cyclo-propane derivative the new formula IX is proposed for the final product from the action of diazomethane on the HCl-product.



VIII



IX

One fact remains still to be explained, namely that $C_{14}H_{18}O_7$ only gives a mono-dinitrophenylhydrazone. This has also been observed by Berner and Laland¹ and is in accordance with their formula (VII). The author hopes later on to be able to give a satisfactory explanation of this apparent discrepancy.

EXPERIMENTAL PART

Hydrogenation of HCl-product

a) In 98–99 per cent methanol:

A solution and dispersion of HCl-product (10 g) in "AnalaR" methanol (150 ml) to which platinum oxide (0.3 g) had been added took up 565 ml hydrogen (1 200 mm Hg) in 110 minutes; calc. for one mole hydrogen 554 ml. After filtering the methanol was evaporated above calcium chloride in a vacuum desiccator.

The syrupy residue was placed in a refrigerator for five weeks with occasional scratching but did not crystallise. Placed in a vacuum desiccator above phosphorus pentoxide for one week it became hard and brittle but weakened again after being exposed to the air for a couple of days.

The product evolved carbon dioxide from a solution of sodium carbonate (2N) and evolved hydrogen chloride and sulfur dioxide from thionyl chloride.

Methoxyl determinations after Zeisel-Fanto:

OCH_3	4.21,	4.22
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Other preparations showed different but still low methoxyl contents.

b) In anhydrous methanol:

The commercial methanol (AnalaR) was dehydrated with magnesium methoxide. A solution and dispersion of HCl-product (5.0 g) in methanol (150 ml) to which platinum oxide (0.1 g) had been added took up 290 ml hydrogen (1 200 mm Hg) in one hour; calculated for one mole hydrogen 277 ml. After filtering the methanol was evaporated as before.

The residue crystallised into a hard cake which was broken up and washed thoroughly with dry ether giving a completely white and dry crystalline powder (3.3 g).

The raw product was exposed to moist air for four days and was then completely deliquesced. The oil was placed in a desiccator above phosphorus pentoxide but did not crystallise again. It evolved carbon dioxide from a solution of sodium carbonate (2N).

Methoxyl content 6.91

Another part of the raw product was dissolved in anhydrous methanol (50 ml) and then water (one ml) was added. The solution was placed as usual in a vacuum desiccator above calcium chloride. The residue consisted of a small part of crystalline material besides an oil with strong acidic properties.

The raw product from the hydrogenation was recrystallised twice from acetone-petrol ether. M. p. 126–129°. With alkali the substance gave only a faint yellow colour.

$C_{12}H_{16}O_7$	Calc.	C	52.94	H	5.93	OCH_3	22.81
	Found	»	53.11	»	5.99	»	22.70, 22.95

Degradation of hydrogenated product

a) Crystalline product:

The hydrogenated product (20.0 g) was heated with barium hydroxide (40 g) and water (200 ml) for fifty minutes on a water-bath. During the reaction a salt separated which was found to be barium oxalate. It was dissolved in dilute hydrochloric acid and again precipitated by adding ammonia until pH about 6. The dry salt weighed 16.03 g which is 96.8 per cent of the amount (16.56 g) calculated on the assumption that one mole of oxalic acid had been split off each mole of the hydrogenated product. The oxalic acid was isolated by extracting the solution of the salt in hydrochloric acid several times with ether. A crystalline substance was obtained which had m. p. 101° and gave a crystalline precipitate with calcium ions.

The filtrate from the barium oxalate was acidified with hydrochloric acid and extracted four times with 150 ml ether. Evaporation of the combined and dried extracts gave 3.7 g of a crystalline substance which on recrystallising twice from benzene-carbon tetrachloride gave colourless tables with m. p. 95–96°.

	0.1179 g subst. required 7.58 ml 0.1013 N NaOH						
$C_8H_{10}O_3$	Calc.	C	62.33	H	6.52	M	154.2
	Found	»	62.33	»	6.56	»	153.4

b) Oily product:

The hydrogenated product (7.7 g) was heated with barium hydroxide (10 g) and water (75 ml) for forty-five minutes on a water-bath. A salt precipitated immediately and was treated and identified as barium oxalate as in the preceding paragraph. 5.36 g which is 84 per cent of the theoretical amount (6.37 g).

The filtrate from the barium oxalate was acidified with hydrochloric acid and extracted four times with 75 ml ether. Evaporation of the combined and dried extracts gave an oily residue which did not crystallise on scratching, inoculation or after having been kept in a refrigerator for two days. It was therefore dissolved in 96 per cent alcohol and boiled with some charcoal for a few minutes. After evaporation of the alcohol the residue

crystallised partially on scratching giving 0.6 g of a substance which when recrystallised twice from benzene-carbon tetrachloride had m. p. 95–96° and showed no depression in mixed melting point with the substance $C_8H_{10}O_3$ from the preceding paragraph.

Dehydrogenation of $C_8H_{10}O_3$

$C_8H_{10}O_3$ (1.0 g), N-bromosuccinimide (2.5 g) benzoyl peroxide (ca 5 mg) and carbon tetrachloride (25 ml) was refluxed for six hours with occasional stirring. During the reaction the solution became yellowish brown. After cooling the carbon tetrachloride layer was decanted and the residue extracted with ether. The ether was evaporated very slowly to a small volume and then decanted into another evaporating dish, the separated crystals of succinimide sticking to the first dish. The ethereal solution was then evaporated to dryness and the residue extracted again with a small volume of ether. Again the ether was evaporated and the residue was sublimed in a vacuum giving a white substance with m. p. 206–208° (50 mg). Mixed melting point with 3-methyl-5-hydroxybenzoic acid from another source showed no depression.

Dehydrogenation of methyl ester of $C_8H_{10}O_3$

The ester was prepared by aid of diazomethane. To an ethereal suspension of $C_8H_{10}O_3$ (2 g) was added the calculated amount of ethereal diazomethane (CH_2N_2 -content determined by the benzoic acid method). The ester was obtained as an oil which could not be brought to crystallisation.

Methyl ester (2 g), N-bromosuccinimide (5 g), benzoyl peroxide (ca 5 mg) and carbon tetrachloride (25 ml) was refluxed for six hours with occasional stirring. During the reaction hydrogen bromide was evolved. After cooling the carbon tetrachloride layer was decanted and the residue extracted several times with the same solvent. The combined extracts were shaken with some sodium thiosulphate solution and dried over sodium sulphate. The carbon tetrachloride was evaporated on a steam bath whereby more hydrogen bromide was evolved. The brownish, oily residue was distilled at ordinary pressure. At about 200° a clear liquid passed over and crystallised in the receiver. The crystalline product (0.58 g) was recrystallised from dilute alcohol. M. p. 96–97°. Mixed melting point with an authentic sample of methyl 3-methyl-5-hydroxybenzoate showed no depression.

HCl-product and diazomethane

Diazomethane was prepared from nitrosomethylurea (5 g). The clear ethereal solution was cooled in ice and HCl-product (4 g) was added slowly. After the brisk evolution of nitrogen had ceased the solution was kept at room temperature for 17 hours. The separated crystals was filtered and washed with dry ether. Yield 3.0 g.

Thermolabile nitrogen:

$C_{14}H_{18}O_7N_2$	Calc.	8.58
	Found	8.34, 9.02

The nitrogen-containing compound (3.0 g) was recrystallised from methanol. During the recrystallisation nitrogen was evolved. On cooling and scratching colourless crystals

separated. Washed with 1 N sodium carbonate in order to remove unchanged HCl-product and recrystallised again from methanol they had m. p. 135–137° (yield 2.5 g). Berner and Laland¹ found the same m. p.

Attempted hydrogenation of $C_{14}H_{18}O_7$

A solution of $C_{14}H_{18}O_7$ (1.0 g) in methanol (30 ml) to which platinum oxide (0.1 g) had been added was exposed to hydrogen of a pressure of 1 200 mm Hg at 20° for 3 hours, but no uptake of hydrogen could be observed. After filtering and evaporation of the methanol $C_{14}H_{18}O_7$ could be recovered unchanged.

Degradation of $C_{14}H_{18}O_7$

$C_{14}H_{18}O_7$ (2.0 g) was heated with barium hydroxide (4 g) and water (50 ml) for 135 min. During the heating a white precipitate was formed and the solution became gradually red-orange. The precipitate was dissolved in hot dilute hydrochloric acid. During the dissolution a violent evolution of carbon dioxide was observed. The dissolved salt was precipitated again by adding ammonia until pH about 6. The dry salt weighed 0.50 g which is 33 per cent of theory. Oxalic acid was isolated by extracting the solution of the salt in hydrochloric acid several times with ether. A crystalline substance was obtained which under the microscope underwent some change at about 100° and melted at 188–189°; with calcium ions it gave a crystalline precipitate in dilute acetic acid.

The red-orange filtrate from the barium oxalate was acidified with hydrochloric acid. After a couple of hours a crystalline dirty-red substance precipitated. The substance (50 mg) was recrystallised twice from acetone-petrol ether and was still faintly brownish red. M. p. 156° dec.

$C_{10}H_{10}O_4$	Calc.	C	61.80	H	5.20	
	Found	»	62.00	»	5.12	no OCH_3

It evolved carbon dioxide from a solution of sodium carbonate and gave easily a precipitate with dinitrophenylhydrazine in 1 N hydrochloric acid.

A similar experiment with 1.0 g $C_{14}H_{18}O_7$ and 2 g barium hydroxide was performed with a stream of nitrogen bubbling through the reaction mixture. When dissolved in hot dilute hydrochloric acid the precipitate (0.38 g) briskly evolved carbon dioxide. After reprecipitation as before it weighed 0.25 g.

$C_{14}H_{18}O_7$ and dinitrophenylhydrazine

a) Dinitrophenylhydrazine (0.6 g) was dissolved in 2 N hydrochloric acid (50 ml) by heating. The solution was filtered and cooled to 30–40° and $C_{14}H_{18}O_7$ (0.3 g) dissolved in methanol (25 ml) was added. Next day the precipitate was collected and recrystallised from chloroform-gasoline. M. p. 178–179°.

$C_{22}H_{22}O_{10}N_4$	Calc.	N	11.71	Found	N	11.66
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b) Dinitrophenylhydrazine (0.3 g) was dissolved in alcohol (200 ml) to which glacial acetic acid (3 drops) had been added. To the filtered solution $C_{14}H_{18}O_7$ (0.19 g) dissolved in alcohol (10 ml) was added. The solution was heated for one hour on a steam-bath and

left by room temperature for 36 hours. Then about 100 ml of the ethyl alcohol was distilled off, the rest being diluted with some water and left in an evaporating dish. The first fraction of crystals which consisted of dark red and light orange ones was discarded. The next fraction in which the light orange crystals were preponderant was recrystallised from chloroform-gazoline. M. p. 177°. Mixed melting point with the prepurate from a): 178°.

SUMMARY

Hydrogenation and subsequent degradation of the hydroaromatic so-called HCl-product gave a cyclohexene derivative, which could be transformed into an aromatic compound by means of N-bromosuccinimide.

The reaction between the HCl-product and diazomethane is investigated and a new formula for the resulting product is proposed.

The author wishes to express his gratitude to professor Dr. E. Berner for his kind interest in the work and for many valuable discussions.

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