OXIDATION OF SOME α-HYDROXY-ACIDS WITH LEAD TETRA-ACETATE.(1)

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Lead tetra-acetate, the tetravalent lead salt of acetic acid, was introduced by Dimroth as a new oxidising agent. This salt is easily prepared from minium and acetic acid. It was recommended by him as a more convenient oxidising agent than lead peroxide itself in two respects. First, it is soluble in organic solvents such as benzene or glacial acetic acid, and the oxidation can be smoothly carried out as homogeneous reaction in these

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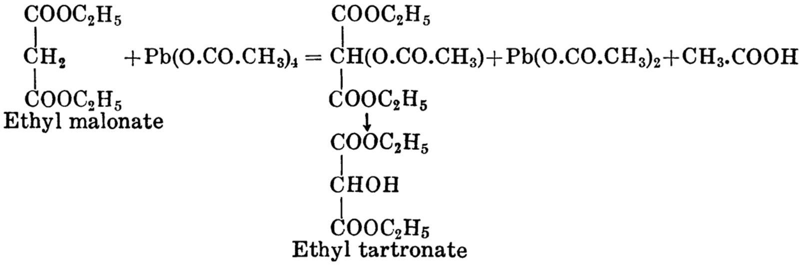
(1) Studies on Hydroxy-acids and their Derivatives. Part I.

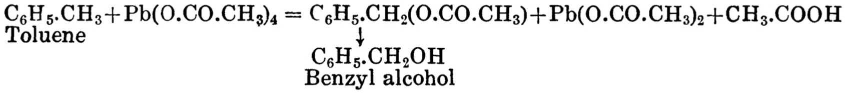
solvents. Secondly, after the oxidising action, it changes to lead acetate, which easily separates out as crystals when ether is added to the solution.

Various oxidation reactions hitherto described by Dimroth, Criegee and others are summarised as follows.

I.(2) The reagent is efficient for the conversion of hydrogen atom into hydroxyl group, especially in the case of substances such as ethyl malonate, ethyl acetoacetate and acetone which contain labile hydrogen atoms ($-CH_2.CO-$). It can also be applied to the homologues of toluene.



$$\begin{array}{l} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} + Pb(O.CO.CH_3)_4 = \begin{array}{l} COOC_2H_5 \\ | \\ CH(O.CO.CH_3) \\ | \\ COOC_2H_5 \\ \downarrow \\ COOC_2H_5 \\ | \\ CHOH \\ | \\ COOC_2H_5 \end{array} + Pb(O.CO.CH_3)_2 + CH_3.COOH$$

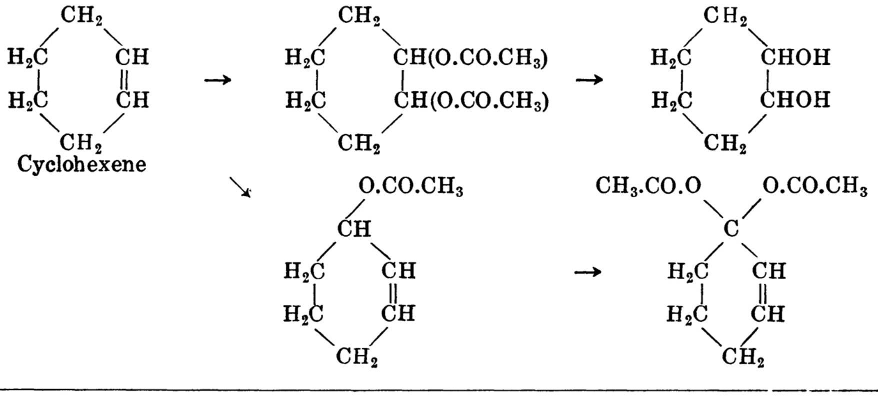


$$C_6H_5.CH_3 + Pb(O.CO.CH_3)_4 = \begin{array}{c} C_6H_5.CH_2(O.CO.CH_3) \\ \downarrow \\ C_6H_5.CH_2OH \end{array} + Pb(O.CO.CH_3)_2 + CH_3.COOH$$

II.(3) Oxidation of unsaturated substances of hydroaromatic type with this reagent occurs in two ways :

(1) addition of two acetoxy-groups to the double linking, and

(2) substitution of the adjascent hydrogen atoms by acetoxy-groups, whilst the double linking is unattacked.



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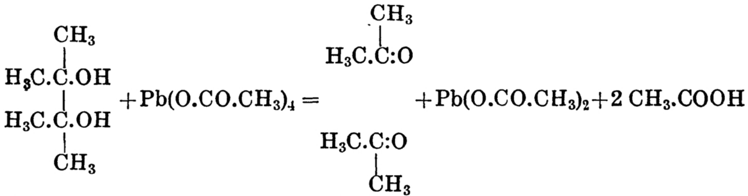
(2) O. Dimroth u. R. Schweizer, *Ber.*, **56** (1923), 1375.

(3) R. Criegee, *Ann.*, **481** (1930), 263.

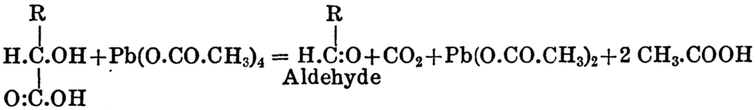
III.(4) Glycols are oxidised by this reagent, yielding two molecules of carbonyl compounds.



$$\begin{array}{c} CH_3 \\ | \\ H_3C.C.OH \\ | \\ H_3C.C.OH \\ | \\ CH_3 \end{array} + Pb(O.CO.CH_3)_4 = \begin{array}{c} CH_3 \\ | \\ H_3C.C{:}O \\ \\ H_3C.C{:}O \\ | \\ CH_3 \end{array} + Pb(O.CO.CH_3)_2 + 2\,CH_3.COOH$$

Pinacone Acetone

Now, α-hydroxy-acids have analogous structure with glycols, namely, both of these compounds contain two hydroxyl groups combined to two neighbouring carbon atoms. Assuming that the oxidation of the same type occurs in the case of α-hydroxy-acids as in the case of glycols, the formation of aldehydes is easily expected.



$$\begin{array}{c} R \\ | \\ H.C.OH \\ | \\ O{:}C.OH \end{array} + Pb(O.CO.CH_3)_4 = \begin{array}{c} R \\ | \\ H.C{:}O \end{array} + CO_2 + Pb(O.CO.CH_3)_2 + 2\,CH_3.COOH$$

Aldehyde

α-Hydroxy-acids

The present author tried the oxidation of some simple α-hydroxy-acids with lead tetra-acetate and confirmed the formation of aldehyde from each of the following five acids.*

$CH_3.CHOH.COOH$ Lactic acid	→	$CH_3.CH{:}O$ Acetaldehyde
$(CH_3)_2CH.CH_2.CHOH.COOH$ Leucic acid	→	$(CH_3)_2CH.CH_2.CH{:}O$ Isovaleraldehyde
$C_6H_5.CHOH.COOH$ Mandelic acid	→	$C_6H_5.CH{:}O$ Benzaldehyde
$C_6H_5.CH_2.CHOH.COOH$ β-Phenyl-lactic acid	→	$C_6H_5.CH_2.CH{:}O$ Phenyl acetaldehyde
$HO.C_6H_4.CH_2.CHOH.COOH$ *p*-Hydroxy-phenyl-lactic acid	→	$HO.C_6H_4.CH_2.CH{:}O$ *p*-Hydroxy-phenyl acetaldehyde

The oxidation of α-hydroxy-acids to aldehydes having an atom of carbon less is a reaction which can be performed with many oxidising agents. But

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(4) R. Criegee, *Ber.*, **64** (1931), 260. H. Raudnitz u. J. Peschel, *Ber.*, **66** (1933), 903. The reagent was utilised for the differentiation between furanose and pyranose forms of sugars, since, on oxidation with this reagent, formaldehyde can result only when CH_2OH is adjacent to a free hydroxyl, namely, from the furanose modification. R. Criegee, *Ann.*, **495** (1932), 211.

* Japanese Patent: 98,241 (Suzuki, Takayama, Ôeda.)

at times the reactions produce not only expected aldehydes but also other oxidation products of further advanced stage. For example, when phenyllactic acid is oxidised with lead peroxide, it yields the mixture of benzaldehyde and phenyl acetaldehyde. In the case with lead tetra-acetate, there is no fear of such extreme oxidation, as this acts only as a dehydrogenating agent.

Experimental Part.

General. Lead tetra-acetate was prepared according to the description of Dimroth. Red lead oxide (minium) (400 gr.) was gradually added to glacial acetic acid (1000 gr.), which was thoroughly stirred and kept at 45–55°C. On cooling, a considerable amount of lead tetra-acetate was precipitated. It was obtained as colourless crystals on warming with a small bulk of warm acetic acid. Lead tetra-acetate is very hygroscopic and is, on exposure to moisture, easily decomposed to lead peroxide and acetic acid.

In each experiment, α-hydroxy-acid (10 gr.) was dissolved in benzene (120–150 c.c.) and an equimolecular amount of lead tetra-acetate was added to it. But, when the sample is not sufficiently soluble in benzene, glacial acetic acid was used as the solvent. Oxidation mixture was vigorously stirred throughout the whole operation.

During the course of the oxidation a small bulk of the solution was pipetted out from time to time and water was added to it. The completion of oxidation was roughly indicated by the termination of separation of lead peroxide.

Oxidation of Lactic Acid. Lactic acid (Merck) was subjected to vacuum distillation, when the main part distilled at 126–133°C. under 16 mm. The distillate (10 gr., 0.11 mol) was dissolved in warm glacial acetic acid (100 c.c.), and the solution was put in a flask having three necks, provided with a mechanical stirrer, an inlet for the oxidising agent and a reflux condenser to which two absorption bottles filled with cooled (–12°C.), dry ether were connected. The flask was kept at 50°C. on the water bath and lead tetra-acetate (44 gr., 0.11 mol) was added little by little. During the oxidation a rapid current of dry carbon dioxide was passed from the inlet tube through the whole apparatus. The aldehyde formed by the oxidation was completely absorbed by the ether.

After the completion of oxidation, dry ammonia was passed through the ether, and acetaldehyde was precipitated as aldehyde-ammonia. It melted at 88°C. and the yield was 3.0 gr. representing 45% of the hydroxy-acid used.

Identification of the Aldehyde. The aldehyde-ammonia was added to an aqueous solution containing roughly the equivalent amount of semicarbazide hydrochloride. On cooling, semicarbazone of acetaldehyde(5) crystallised out, which melted at 160–162°C. after recrystallisation from water.

Anal.: Subst. = 2,249 mg., N = 0.832 c.c. (23.0°C., 762.4 mm.)
Found: N = 42.09%
Calc. for $C_3H_7ON_3$: N = 41.57%

Oxidation of Leucic Acid. *l*-Leucic acid was prepared by the action of nitrous acid upon natural leucine and it was precipitated as zinc salt. The free acid melted at 73°C. after recrystallisation from benzene.

Leucic acid (10 gr., 0.076 mol) was dissolved in benzene (140 c.c.). The solution was kept at 60°C. and lead tetra-acetate (33 gr., 0.76 mol) was added in the course of an hour. During the oxidation lead acetate separated out as a viscous jelly and then gradually changed to a crystalline mass. Benzene was decanted and the residue was well washed with a new bulk of benzene.

The combined benzene solution was shaken with an aqueous solution of sodium bicarbonate to remove acids. After drying, the solvent was removed by distilling on a boiling water-bath, simple still-head being provided. The greater part of benzene was distilled off without considerable loss of the aldehyde, though the complete separation was impossible. The residual oil was subjected to distillation, when the main part (4.9 gr.) distilled at 82–84°C., but it was not free from benzene.

Identification of the Aldehyde. *p*-Nitrophenyl hydrazine dissolved in five times of its weight of 40% aqueous acetic acid was added to the aqueous solution saturated with aldehyde. *p*-Nitro-phenyl hydrazone of isovaleraldehyde(6) separated as flocculent precipitates. It melted at 109°C. after recrystallisation from alcohol.

Anal.: Subst. = 2.780 mg., N = 0.467 c.c. (26.0°C., 766.5 mm.)
Found: N = 19.33%
Calc. for $C_{11}H_{15}O_2N_3$: N = 19.00%

Oxidation of Mandelic Acid. *dl*-Mandelic acid (Merck, m.p. 118°C.) (10 gr., 0.066 mol) was dissolved in benzene (150 c.c.) and lead tetra-acetate (27 gr., 0.066 mol) was added. Further treatments were the same as described above. After removing benzene, the residual oil was distilled in vacuo. The part distilling at 72–73°C. under 21 mm. amounted to 3.7 gr. representing 54%.

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(5) J. Thiele u. J. Bailey, *Ann.*, **303** (1898), 79.

(6) D. Dakin, *J. Biol. Chem.* **4** (1908), 236.

Identification of the Aldehyde. The aldehyde was added to an alcoholic solution of *p*-nitro-phenyl hydrazine. On cooling, *p*-nitro-phenyl hydrazone of benzaldehyde(7) separated out. It melted at 189°C. after recrystallisation from alcohol with an addition of animal charcoal.

Anal.: Subst. = 2.973 mg., N = 0.466 c.c. (30.0°C., 759.4 mm.)
Found: N = 17.64%
Calc. for $C_{13}H_{11}O_2N_3$: N = 17.43%

Oxidation of Phenyl-lactic Acid. *l*-Phenyl-lactic acid was prepared by the action of nitrous acid upon natural phenyl alanine. It melted at 124°C. after recrystallisation from chloroform.

Phenyl-lactic acid (10 gr., 0.060 mol) was added to benzene (150 c.c.). The greater part of the acid can be brought into dissolution when the solution is kept boiling. Lead tetra-acetate (26 gr., 0.060 mol) was then added. Further treatments were the same as in the previous two cases.

After removing benzene, the residual oil was distilled in vacuo. The part distilling at 84–86°C. under 17 mm. amounted to 4.2 gr. representing 58%.

Identification of the Aldehyde. Alcoholic solutions of neutral hydroxylamine and of the aldehyde were mixed and allowed to stand overnight. A large volume of ether was then added and the excess of hydroxylamine was removed by extraction with water. Oxime of phenyl acetaldehyde thus prepared(8) was soluble in hot petroleum ether, from which it can be recrystallised. It melted at 101–102°C.

Anal.: Subst. = 4.202 mg., N = 0.381 c.c. (24.0°C., 751.9 mm.)
Found: N = 10.31%
Calc. for C_8H_9ON : N = 10,36%

Oxidation with Lead Peroxide. Phenyl-lactic acid (5 gr.) was added to a mixture of water (20 c.c.) and phosphoric acid (5 c.c.). The presence of the latter prevented the formation of insoluble lead salt. Lead peroxide (13 gr.) was poured to the solution little by little, interrupting each time the steam which was passed into the flask throughout the reaction to transfer the aldehyde formed into the distillate.

The aldehyde (1.2 gr.) was obtained from the distillate after removing acidic part. About the half of hydroxy-acid was recovered from the residue.

The aldehyde obtained from several oxidations was brought together and subjected to vacuum distillation. It distilled at 65–80°C. under 22 mm.

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(7) H. Biltz u. F. Sieden, *Ann.*, **324** (1902), 321.

(8) C. Harries u. A. de Osa, *Ber.*, **37** (1904), 843.

(lower than that of the oxidation product with lead tetra-acetate). The formation of crystalline oxime from the above sample was not successful. After long standing the colourless crystals were deposited from the distilled aldehyde and it amounted to 0.5 gr. It melted at 122°C. after recrystallisation from water, and showed no depression of melting point when mixed with a pure specimen of benzoic acid. The benzoic acid thus obtained may be regarded as an oxidation product of benzaldehyde in air. This fact shows that the aldehyde obtained was a mixture of benzaldehyde and phenyl acetaldehyde.

Oxidation of *p*-Hydroxy-phenyl-lactic Acid. *l*-*p*-Hydroxy-phenyl-lactic acid was prepared by the action of barium nitrite upon dilute sulphuric acid solution of natural tyrosine. It melted at 166°C. after recrystallisation from water.

p-Hydroxy-phenyl-lactic acid (2 gr., 0.011 mol) was dissolved in glacial acetic acid (60 c.c.) and the solution was kept at 50°C. Lead tetra-acetate (10 gr., 0.011 mol) was then added. The solution gradually assumed reddish tint. After cooling, a large volume of ether was added to precipitate the greater part of lead acetate. After complete separation of lead salt, ether was expelled under reduced pressure, and then the temperature was raised to 60°C. to remove the rest of acetic acid.

Identification of the Aldehyde. *p*-Hydroxy-phenyl acetaldehyde was obtained by Langheld⁽⁹⁾ when he oxidised tyrosine with sodium hypochlorite. No other information on this aldehyde was found in the literature.

To the residue of above distillation, an alcoholic solution of *p*-nitrophenyl hydrazine (1:6) was added. On cooling, flocculent precipitates of reddish brown tint were formed, which were separated and moistened with a few drops of alcohol. It changed to crystalline mass taking one molecule of alcohol as alcohol of crystallisation. After recrystallisation from alcohol, it began to sinter at 165°C.

Anal.: Subst. = 1.806 mg., N = 0.210 c.c. (25.0°C., 761.5 mm.)
Found: N = 13.35%
Calc. for $C_{14}H_{13}O_3N_3+C_2H_5OH$: N = 13.20%

In conclusion, the author wishes to express his gratitude to Professor K. Matsubara for kind inspection of this paper and thanks are also due to Dr. Y. Takayama for the valuable suggestions and constant encouragements during this study.

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(9) K. Langheld, *Ber.*, **42** (1909), 2360.