(decomp.), which were identical to S-butoxycarbonylthiamine (Ⅷb) and X respectively by IR spectra were obtained. Yield, Ⅷb, 0.26 g., X, 0.35.

Reaction of VII with Dialkyl Ethoxycarbonylphosphite (III)——To a suspension of dry Ⅶ in dry benzene, 2 mol. equivalent of Ⅲa, b, c or d was added and heated for 2 hr. with stirring. The reaction mixture was extracted with N HCl and HCl was washed with Et_2O, and extracted with $CHCl_3$. The residue from the $CHCl_3$ layer was dissolved in N HCl and again extracted with $CHCl_3$ after decoloring. From the $CHCl_3$ layer dried over anhyd. Na_2SO_4, O,S-bis(ethoxycarbonyl)thiamine hydrochloride (Ⅸa), m.p. 120~121° (decomp.) was obtained. Yield, 0.5~2.0%. The HCl extract was neutralized by K_2CO_3 and extracted with $CHCl_3$. From this $CHCl_3$ layer, S-alkylthiamine (Ⅺa, b, c or d) corresponding to dialkyl ethoxycarbonylphosphite and X were obtained. These crystals were proved to be identical by IR spectra with authentic samples : S-ethylthiamine, S-methylthiamine, S-propylthiamine or S-isopropylthiamine, respectively.

Reaction of VII with Diphenyl Ethoxycarbonylphosphite (IIIe)——On the treatment of Ⅶ with Ⅲe by a similar method, X was given, but no further product was isolated.

Summary

On the reaction of potassium O-ethyl thiocarbonate (I) or potassium O-ethyl dithiocarbonate (Ⅳ) with phosphorus trichloride, tris(ethoxycarbonyl) phosphorotrithioite (Ⅱa) or tris(ethoxythiocarbonyl) phosphorotrithioite (Ⅴ) were synthesized, respectively. From the treatment of Ⅱa or Ⅴ with ethyl chloroformate, the same product, diethyl ethoxycarbonylphosphite (Ⅲa), accompanied by carbonyl sulfide and ethyl chloride from Ⅱa, and carbon disulfide and ethyl chloride from Ⅴ, were given in high yield.

When tris(alkoxycarbonyl) phosphorotrithioite (Ⅱ) and thiamine sodium salt (Ⅶ) were reacted together, O,S-bis(alkoxycarbonyl)thiamine (Ⅸ) was produced. On the other hand, from the reaction of dialkyl ethoxycarbonylphosphite with Ⅶ, O,S-bis(ethoxycarbonyl)thiamine (Ⅸa) was also obtained, but in this cases S-alkylthiamines were main products.

(Received October 25, 1963)

[Chem. Pharm. Bull. 12 (4) 403 ~ 407]

UDC 547.943.6 : 547.457

58. **Kunio Nakagawa, Ken-ichi Igano, and Jitsuo Sugita** : Oxidation with Nickel Peroxide. III.[*1] Oxidative Cleavage of α-Glycols, α-Hydroxy Acids, α-Keto Alcohols, and α-Keto Acids.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.*[*2])

In previous papers,[*1] it was shown that polyene alcohols, allylic alcohols, benzyl alcohols, and secondary aromatic alcohols were oxidized by nickel peroxide, readily obtainable by the treatment of nickel salts with sodium hypochlorite in alkaline solution, to give the corresponding carbonyl compounds in satisfactory yields. It seemed desirable to extend the investigation to other kinds of alcohols.

This paper reports the oxidative cleavage of α-glycols, α-hydroxy acids, α-keto alcohols, and α-keto acids by means of nickel peroxide. α-Hydroxy acids have analogous structure with glycols, namely, both of these compounds contains two hydroxyl groups attached to two neighbouring carbon atoms, and keto compounds might be able

---

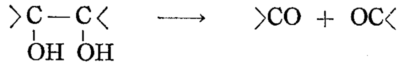
[*1] Part Ⅰ : J. Org. Chem., **27**, 1597 (1962); Part Ⅱ : This Bulletin, **11**, 296 (1963).

[*2] Fukushima-ku, Osaka (中川国夫, 伊賀野憲一, 杉田実男).

to form the necessary hydroxyls by addition of water to the keto group on the way of reaction.

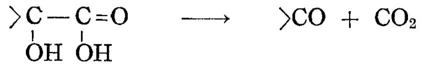
In 1931 Criegee¹⁾ reported the possibility of splitting glycols into aldehydes or ketones by oxidation with lead tetraacetate in absolutely unhydrous solvents. The application of this technique for the other kinds of compounds, whose structure would permit the formation of adjacent hydroxyl groups in the presence of water or alcohols was developed by Baer.²⁾

i) α-Glycol



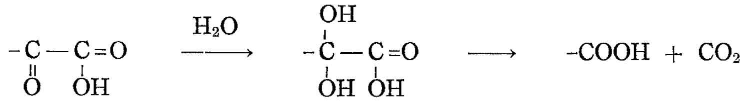
$$>\underset{OH}{C}-\underset{OH}{C}< \longrightarrow >CO + OC<$$

ii) α-Hydroxy acid



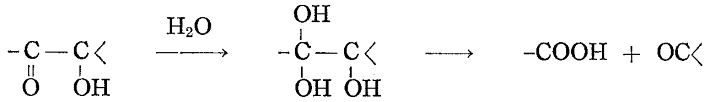
$$>\underset{OH}{C}-\underset{OH}{C}=O \longrightarrow >CO + CO_2$$

iii) α-Keto acid



$$-\underset{O}{\overset{\|}{C}}-\underset{OH}{C}=O \xrightarrow{H_2O} -\underset{OH}{\overset{OH}{C}}-\underset{OH}{C}=O \longrightarrow -COOH + CO_2$$

iv) α-Keto alcohol



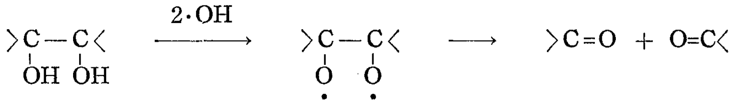
$$-\underset{O}{\overset{\|}{C}}-\underset{OH}{C}< \xrightarrow{H_2O} -\underset{OH}{\overset{OH}{C}}-\underset{OH}{C}< \longrightarrow -COOH + OC<$$

We have treated nickel peroxide with a wide variety of α-glycols, α-hydroxy acids, α-keto alcohols, and α-keto acids in organic solvents or water in the presence or absence of caustic alkali. The results given in the Table show clearly that the nickel peroxide can be regarded as an interesting oxidizing agent for glycol splitting.

Oxidation in Organic Solvents

Hydrobenzoin and phenylethylene glycol which have benzene nucleus in a position to conjugate with the carbonyl group formed in the course of reaction underwent rapid oxidative cleavage by this reagent in benzene or ether, while alkyl ethylene glycols such as pinacol or 2,3-butanediol were cleaved slowly to two molecules of their corresponding carbonyl compounds. These reactions were well explained by the behavior of the nickel peroxide similar to that we previously reported on the oxidation of some amines.¹⁾

Therefore, one atom of the active oxygen of nickel peroxide would be consumed for this cleavage reaction as shown in the following scheme.



$$>\underset{OH}{C}-\underset{OH}{C}< \xrightarrow{2\cdot OH} >\underset{\dot{O}}{C}-\underset{\dot{O}}{C}< \longrightarrow >C=O + O=C<$$

Assuming that the same type of oxidation occurs in the case of α-hydroxy acids just as in glycols, the formation of carbonyl compounds and carbon dioxide were expected.

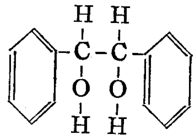
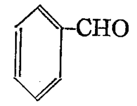
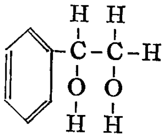
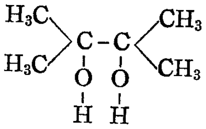
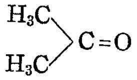
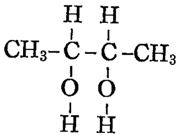
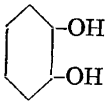
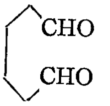
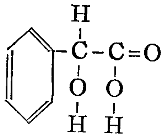
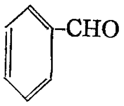
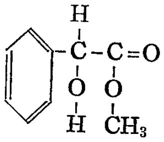
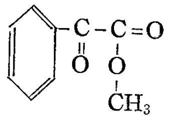
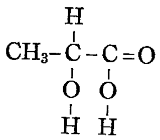
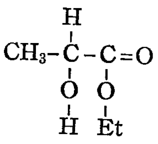
The authors tried the oxidation of mandelic acid and its ester in benzene solution.

As expected, benzaldehyde was easily obtained from mandelic acid in good yield but the oxidation of methyl mandelate was proceeded without cleavage of carbon bond to yield α-keto ester. However, the reaction rate of oxidation for lactic acid was very slow and a portion of acetaldehyde formed was oxidized to carbon dioxide, so the yield of acetaldehyde was very poor.

---

1) R. Criegee : Ber., **64**, 260 (1931).
2) E. Baer : J. Am. Chem. Soc., **62**, 1597 (1940).

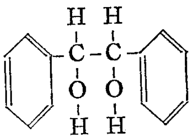
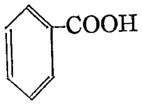
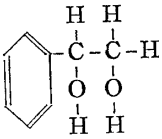
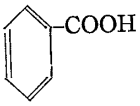
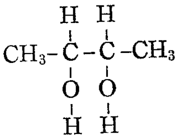
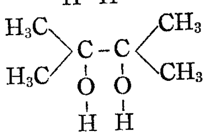
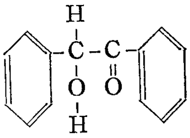
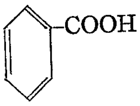
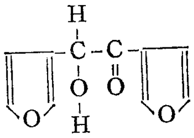
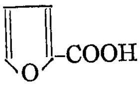
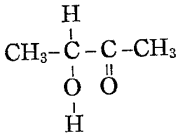
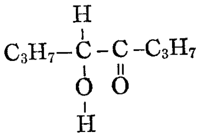
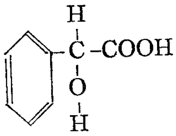
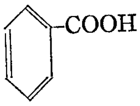
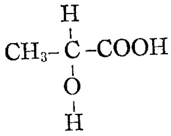
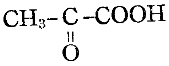
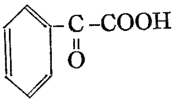
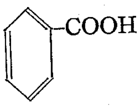
Table I. Oxidation in Organic Solvents

Reactant	Solvent[a]	NiO_2[b] 0*	Temp. (°C)	Time (hr.)	Product	Yield[c] (%)
	B	1.1×0*	50	1.0		85.0
〃	〃	2.0×0*	50	5.0	〃	81.0
〃	E	1.1×0*	35[d]	0.5	〃	90.0
	B	3.3×0*	50	2.0	〃	90.0
 $(H_3C)_2C(OH)-C(OH)(CH_3)_2$	〃	1.1×0*	70[d]	3.0	 $(H_3C)_2C=O$	61.0[e]
〃	〃	2.2×0*	30	81.0	〃	70.0
 $CH_3-CH(OH)-CH(OH)-CH_3$	〃	1.1×0*	50	5.0	CH_3CHO[f]	30.0
 cis	〃	1.1×0*	50	5.0		17.0
	〃	1.2×0*	50	1.5		78.0
〃	W	1.1×0*	10	7.0	〃	51.0
	B	1.1×0*	50	11.0		63.0
 $CH_3-CH(OH)-C(=O)-OH$	W	1.1×0*	50	7.0	CH_3CHO[f]	12.6
〃	〃	1.1×0*	10	7.0	〃	2.0
 $CH_3-CH(OH)-C(=O)-OEt$	B	1.2×0*	60	6.0	NO	

---

[a] B: benzene; E: Et_2O; W: H_2O.
[b] The number in the column indicate the ratio of NiO_2 to reactant based on the available oxygen atom (0*).
[c] Yields were calculated from the weight of 2,4-dinitrophenylhydrazone.
[d] Reactions were carried out under reflux condenser.
[e] The yield is considerably low due to further-oxidation into CO_2.
[f] Product was absorbed into 2,4-dinitrophenylhydrazine·HCl solution from the reaction mixture by passing N_2 gas.

Table II. Oxidation in Alkaline Aqueous Solution

Reactant	NiO_2 0*	Temp. (°C)	Time (hr.)	Product	Yield (%)
	3.3×0*	50	8.0		97.0
	4.4×0*	50	5.0	 CO_2	92.0
 $CH_3-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-CH_3$	3.3×0*	50	7.0	CH_3COOH a)	90.0
	1.1×0*	30	24.0	Me_2CO CO_2	10.0
	2.4×0*	50	5.0		99.0
〃 b)	2.4×0*	80	8.0	〃	95.0
	2.4×0*	30	5.0		91.0
 $CH_3-\overset{H}{\underset{OH}{C}}-\underset{O}{\overset{\Vert}{C}}-CH_3$	2.2×0*	50	5.0	CH_3COOH a)	66.7
 $C_3H_7-\overset{H}{\underset{OH}{C}}-\underset{O}{\overset{\Vert}{C}}-C_3H_7$	2.2×0*	50	5.0	C_3H_7COOH a)	67.7
	2.4×0*	50	5.0		90.0
 $CH_3-\overset{H}{\underset{OH}{C}}-COOH$	2.4×0*	50	7.0	CH_3COOH a)	92.0
 $CH_3-\underset{O}{\overset{\Vert}{C}}-COOH$	2.2×0*	50	10.0	〃 a)	75.0
	1.1×0*	50	3.0		98.0

All oxidations were done in alkaline solution containing the equivalent amount of NaOH.

a) Product was steam-distilled and titrated with 0.1*N* NaOH.

b) H_2O was used in the absence of NaOH.

Oxidation in Neutral or Alkaline Aqueous Solution

With nickel peroxide in alkaline solution, both aromatic and aliphatic glycols were effectively cleaved oxidatively to two molecules of their corresponding carboxylic acids by consuming three active oxygen atoms of the oxidant. However, pinacol was ultimately oxidized to carbon dioxide and gave acetone in poor yield. The same reaction of α-keto alcohols gave two molecules of corresponding carboxylic acids in good yields consuming about two active oxygen atoms of nickel peroxide.

α-Hydroxy acids and α-keto acids were also oxidized to give corresponding carboxylic acids and carbon dioxide in alkaline aqueous solution. The oxidation of α-hydroxy acids and α-keto acids by various kinds of oxidizing agents usually yields carboxylic acids losing a carbon atom from the parent compound. Nickel peroxide behaves in a similar manner, but the procedure is much simple and convenient for use in synthesis, because the work-up is only the filtration of inorganic oxide and acidification of the filtrate.

Experimental

Preparation of Nickel Peroxide and Determination of its Available Oxygen——NiO_2 was prepared from $NiSO_4$ and its available O_2-content was determined by the iodimetry as reported in the previous papers.*[1]

Determination of Carbonyl Compounds——Carbonyl compounds were determined by precipitation of an aliquot of the reaction filtrate with saturated 2,4-dinitrophenylhydrazine in $2N$ HCl solution.

Oxidation of Hydrobenzoin(*meso*) in Benzene——The oxidation of hydrobenzoin with NiO_2 in benzene is a typical procedure employed for glycol cleavage. To a solution of 0.01 mole of hydrobenzoin in 100 ml. of benzene was added 3.29 g. (10% excess) of NiO_2. The mixture was stirred for 1 hr. at 50° in N_2 atmosphere. The reaction mixture was filtered to remove the oxidant and washed with benzene. Then a 1/10 amount of the filtrate was weighed out and added into 100 ml. of 2,4-dinitrophenylhydrazine reagent. After shaking vigorously for 10 min., the mixture was heated on a water bath to evaporate the benzene and allowed to stand overnight. Benzaldehyde was precipitated as 2,4-dinitrophenylhydrazone, m.p. 232~234° (reported 235°).

Oxidation of Mandelic Acid in Alkaline Solution——To a solution of 3.05 g. (0.02 mole) of mandelic acid and 1.7 g. (0.04 mole × 1.2) of NaOH in 100 ml. of H_2O was added 13.5 g. of NiO_2 (0.0035 g.-atom of active oxygen/g.) under stirring on a magnetic stirrer, and the heterogeneous mixture was allowed to react at 50° for 5 hr. The reaction mixture was filtered through a glass filter and oxidant was washed with H_2O. The combined filtrate was extracted with Et_2O to remove by-products and the solution was acidified with dil. H_2SO_4. By extracting the solution with Et_2O, 2.2 g. of the pure BzOH was obtained, m.p. 122.5°.

Summary

Solid nickel peroxide, readily obtainable by the treatment of nickel salts with sodium hypochlorite in alkaline solution, has been proved to be an useful reagent for the oxidative cleavage of α-glycols and α-hydroxy acids in aprotic solvents. Some kinds of aldehydes or ketones were obtained in moderately good yield as glycol cleavage products. With nickel peroxide in an aqueous alkaline solution, α-keto alcohols and α-keto acids were transformed into carboxylic acids by the oxidative cleavage.

(Received October 14, 1963)