Periodic Acid Oxidation on N-Arylamino Alcohols

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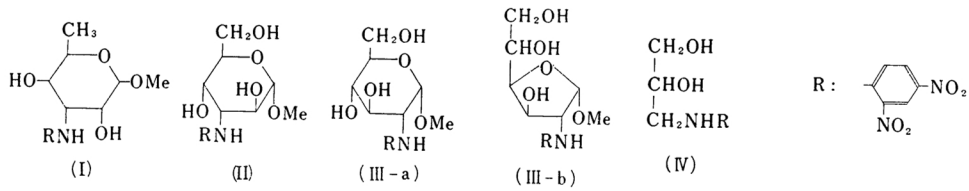
It has been known that the primary and secondary α-amino alcohols[1] are cleft by periodic acid like the vicinal glycols, whereas the tertiary α-amino alcohols are not, excepting a few examples[2]. Upon the periodic acid oxidation, the side reactions take place depending on the quantity of oxidant, temperature, pH, and even light. Some examples of such reactions have also been reported with phenols[3] and aromaitc amines[4] not containing the α-glycol or α-amino alcohol group.

The preparation of the *N*-2, 4-dinitrophenyl derivative of amine is widely used for the purpose of the isolation of amine from its mixture. We have also obtained an amino sugar in the form of *N*-2, 4-dinitrophenyl derivative from the antibiotic trichomycin. Investigations showed that this dinitrophenylamino sugar was not attacked by periodic acid[5] and was identical with the *N*-2, 4-dinitrophenyl derivative of mycosamine methyl glycoside obtained from pimaricin[6].

The cleavage reaction of the *N*-alkylamino alcohol group by periodic acid is well known[7], but that of the *N*-arylamino alcohol group is hardly known. In order to check the unreactivity of the above mentioned *N*-2, 4-dinitrophenyl derivative of mycosamine methyl glycoside (I), other *N*-2, 4-dinitrophenyl derivatives of amino alcohols have been examined.

Since it has been known that the *trans*-glycol group is difficultly attacked by periodic acid, methyl *N*-2, 4-dinitrophenyl-3-amino-3-deoxy-altroside (I) containing both cis and trans amino alcohol groups was studied. This compound was not attacked and the same applies for the *N*-2, 4-dinitrophenyl derivatives of D, L-serine and ethanolamine. These results indicated that the unreactivity of these compounds do not depend on the difference of the configuration of the amino and hydroxyl groups. Therefore, it can be said that the substitution of the *N*-2, 4-dinitrophenyl group on an amino alcohol almost protects the compound from the periodate oxidation. In general, the presence of an hydrogen atom on the amino nitrogen atom is important for the cleavage reaction of an amino alcohol by periodic acid, and in the case of the *N*-acetylated amino alcohol the reactivity is also reduced and no reaction occurs. Therefore, it might be inferred that one reason for the unreactivity of the *N*-2, 4-dinitrophenyl derivative is very similar to that

1) B. E. Nicolet and L. A. Shinn, *J. Am. Chem. Soc.*, **61**, 1615 (1939).
2) E. H. Flynn, M. V. Sigal, Jr, B. F. Wiley and K. Gerzon, ibid., **76**, 3121 (1954).
3) J. P. Feifer, M. A. Smith and B. R. Willeford, *J. Org. Chem.*, **24**, 90 (1959).
4) H. Tanabe, *J. Pharm. Soc. Japan (Yakugaku Zasshi)*, **76**, 1023 (1956); **78**, 410 (1958).
5) H. Nakano, *J. Antibiotics, Ser. A*, **12**, 72 (1961).
6) J. B. Patrick, R. B. Williams and J. S. Webb, *J. Am. Chem. Soc.*, **80**, 6689 (1958).
7) P. Fleury, J. Courtois and M. Grandchamp, *Bull. soc. chim. France*, **1949** 88.



of the *N*-acyl substituent and lies in the strongly electron attracting property of the nitro group.

Jeanloz and Forchielli[8] reported that about six and two mole equivalents of periodic acid were consumed by one mole each of *N*-acetyl glucosamine and methyl *N*-acetyl glucosamide, respectively at 25°C. Similarly, as shown in Fig. 1, we observed that *N*-2, 4-dinitrophenyl-

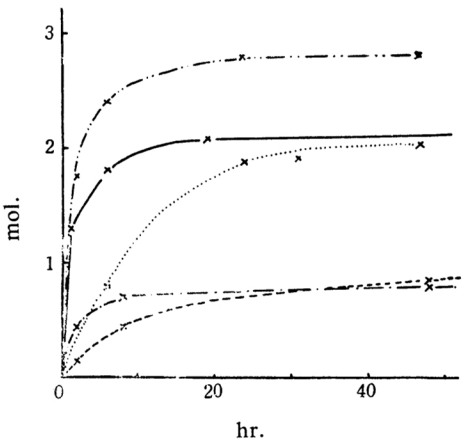


Fig. 1. Periodate consumption curves.
—··— *N*-2, 4-Dinitrophenyl glucosamine
------ (III-a) mole ratio, 1 : 2
..... (III-a) mole ratio, 1 : 5
·—·— (III-b) mole ratio, 1 : 5
——— (IV)

D-α-methyl-glucopyranosamide (III-a) consumed one mole equivalent of the oxidant at 4°C, when the mole ratio of the reagent and sample was two. But anomalously when the mole ratio was increased to five, another one mole was consumed.

Another unusual example has been reported by Neuberger[9]; namely, *N*-benzoyl glucosamine was observed to be overoxidized by lead tetra-acetate. Since we had assumed the *N*-2, 4-dinitrophenyl substitution of α-amino alcohols had a masking effect towards periodic acid oxidation, the reactivity of compound III-a consuming two moles of the oxidant was unexpected. Further, the above-mentioned examples appeared to be very analogous, too. Besides, it was shown that 2, 4-dinitroanilino-1-propane-2, 3-diol (IV) consumed two mole equivalents of periodic acid, and that formaldeyde and formic acid were detected as the reaction products. The formation of formaldehyde was due to the normal cleavage of the α-glycol group. In order to avoid the side reaction, all experiments were run under the selected condition[10] in which the oxidation from aldehyde to acid did not occur. Therefore, the additional one mole consumption of periodic acid was caused by the cleavage reaction of the newly produced α-amino aldehyde group. With methyl *N*-2, 4-dinitrophenyl glucofuranosamide (III-b) having no possibility to produce the α-amino aldehyde group, the consumption of periodic acid was only one mole. From these results it might be said that the *N*-2, 4-dinitrophenyl derivative of the α-amino aldehyde group can be attacked by periodic acid, but that of the α-amino alcohol group can not be cleft under this condition even when the quantity of the oxidant is increased.

The unreactivity of the *N*-2, 4-dinitrophenyl-α-amino alcohol group towards periodate oxidation might suggest that the electron density of the amino nitrogen atom which is reduced by the nitro substitution has an important role in this reaction. In order to examine this effect of the nitro group, two mono-substituted aryl-amino alcohols were investigated as shown in Fig. 2. Since *N*-*p*-nitrophenylethanolamine consumed one mole equivalent of the oxidant, while *N*-*o*-nitrophenylethanolamine consumed only a small amount, it was presumed that the ortho substituted phenyl group might have a much greater masking effect against the attack

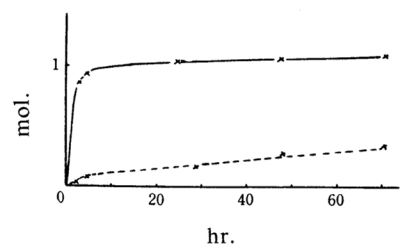


Fig. 2. Periodate consumption curves of *N*-*p*-nitrophenylethanolamine (——) and *N*-*o*-nitrophenylethanolamine (----).

8) R. W. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **188**, 361 (1951).
9) A. Neuberger, *J. Chem. Soc.*, **1941**, 47.
10) C. F. Huebner, S. R. Ames and E. C. Bubl, *J. Am. Chem. Soc.*, **68**, 1621 (1946); L. Hough, T. J. Taylor, C. H. S. Thomas and B. M. Woods, *J. Chem. Soc.*, **1958**, 1212.

of periodic acid than the para substituted isomer. Accordingly, the influence of various ortho substituents were investigated.

As shown in Fig. 3, all substituents excepting the nitro group showed no masking effect and gave the abnormally high consumption value

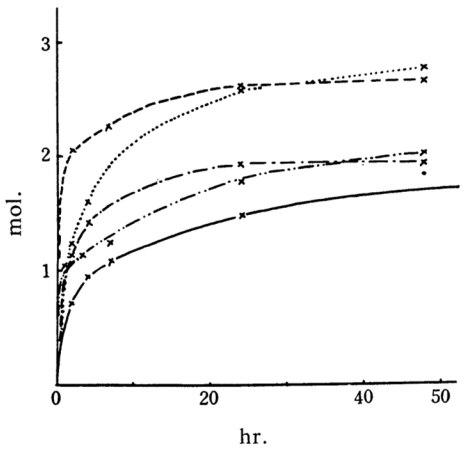
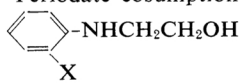
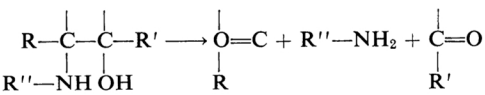


Fig. 3. Periodate cosumption curves.



X; OMe ·····, NH_2 ------,
Cl —·—, CH_3 ·—·—
H ———

of the oxidant. This tendency to afford the high consumption value was more apparent for the introduction of an amino or a methoxy group. As the pH of the reaction medium had some influence on the reaction curve as shown in Fig. 4, these measurements were all carried out in a constant buffer solution of pH 4.5. One of the factors giving such abnormally high consumption values might be considered to be the difference in electron negativity of the amino nitrogen atom, but other factors should be also considered, since the order of consumption and electron negativity was not parallelled, and the order was reversed for *N*-phenylethanolamine and *N*-*o*-chlorophenylethanolamine. The p*K* value of each amines was as follows; *N*-phenylethanolamine (3.8), *N*-*o*-nitrophenylethanolamine and *N*-*p*-nitrophenylethanolamine (below 2.5), *N*-*o*-methoxyphenylethanolamine (4.8), *N*-*o*-aminophenylethanolamine (4.6), *N*-*o*-chlorophenylethanolamine(2.6) in aqueous methanol (33%).



From the reaction scheme of α-amino alcohol[11] the abnormal consumption of periodic acid upon the *N*-arylamino alcohols might be caused by the oxidation of the newly produced aromatic amines. Tanabe has already investigated the periodate oxidation of aromatic amines in detail[4]. Thus we have examined the periodate oxidation of the aromatic amines which were expected to be produced by the oxidation of the *N*-arylamino alcohols, and straightforward results were obtained. An example shown in Fig. 5 indicated that the difference in the oxidation curves of *N*-*o*-chlorophenylethanolamine and *o*-chloroaniline gave the normal consumption value. The normal consumption curve of *N*-*o*-nitrophenylethanolamine was probably due to the property of *o*-nitroaniline which was not oxidized by periodic acid. Thus it was proved that the over-oxidation of *N*-arylaminoalcohols by periodic acid is due to the oxidation of the newly produced aromatic amine.

We are also investigating the masking property of other substituents including steric requirements, and will report on this subsequently.

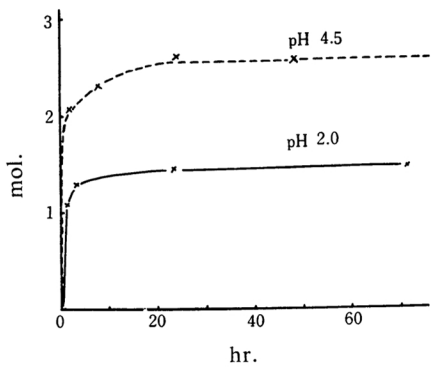


Fig. 4 Periodate consumption curves of *N*-*o*-aminophenylethanolamine at different pH.

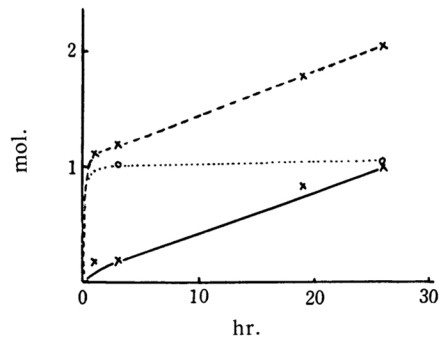


Fig. 5. Periodate consumption curves of *N*-*o*-chlorophenylethanolamine (----) and *o*-chloraniline (——); difference (·····).

11) L. A. Shinn, B. H. Nicolet, *J. Biol. Chem.*, **139**, 687 (1941).

Experimental

Preparation of Amino alcohols. — *N-2, 4-Dinitrophenyl Derivatives.*—Those were prepared by the usual condensation method of a primary amine and 2, 4-dinitrofluorobenzene in an alkaline medium. *N*-2, 4-Dinitrophenyl-D, L-serine[12], pale yellow crystals from aqueous ethanol, m. p. 198~201°C : *N*-2,4-dinitrophenylethanolamine[13], yellow crystals from ether-methanol, m. p. 89~91°C : *N*-2,4-dinitrophenyl glucosamine[14], pale yellow needle from benzene-methanol, m. p. 194~197°C : methyl *N*-2,4-dinitrophenyl glucopyranosamide[14], yellow needle from acetone-ether, m. p. 212~214°C : methyl *N*-2,4-dinitrophenyl glucofuranosamide[14], pale yellow needle from aqueous ethanol, m. p. 164~166°C : methyl *N*-2, 4-dinitrophenyl-3-amino-3-deoxy-D-altroside, yellow needle from aqueous methanol, m. p. 176~179°C : *N*-2,4-dinitrophenyl-1-aminopropane-2,3-diol, yellow crystals from aqueous ethanol, m. p. 82~83°C.

Found : N, 16.21. Calcd. for $C_9H_{11}N_3O_6$: N, 16.34%.

N-Phenylethanolamine.—This was prepared from aniline and ethylene chlorohydrin by the method of Knorr[15]. Pale yellowish viscid liquid of b. p. 151~156°C (16 mmHg). Benzoyl derivative, m. p. 90~92°C.

N-Nitrophenylethanolamine.—This was prepared from nitrochlorobenzene and ethanolamine as described by Kremer[16]. *N-o*-Nitrophenylethanolamine; deep orange needle from ethanol, m. p. 74~76°C.

Found : N, 15.44. Calcd. for $C_8H_{10}N_2O_3$: N, 15.38%.

N-p-Nitrophenylethanolamine ; golden yellow plate from ethyl acetate, m. p. 109~111°C.

Found : N, 15.51. Calcd. for $C_8H_{10}N_2O_3$: N, 15.38%.

N-o-Aminophenylethanolamine : By reduction of *o*-nitrophenylethanolamine with zinc and dilute acetic acid at 40°C, colorless plate crystals were obtained from benzene extraction and were recrystallized from benzene-ethanol, m. p. 105~107°C[17]. By the method of reductive acetylation, this compound was converted into *N,N'*-diacetyl-*o*-aminophenylethanolamine ; colorless needle, m. p. 128~130°C.

Found : C, 60.98 ; H, 6.71 ; N, 11.92. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00 ; H, 6.83 ; N, 11.86%.

Further acetylation of this derivative changed to be *N,N',O*-triacetyl derivative ; colorless needle, m. p. 137~138°C.

Found : C, 60.23 ; H, 6.67 ; N, 10.28. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42 ; H, 6.52 ; N, 10.02%.

N-o-Methoxyphenylethanolamine.—This was prepared by the method of Knorr[15] as pale yellowish liquid of b. p. 210~225°C (18 mmHg). This hydrochloride ; colorless crystals from ethanol, m. p. 149~153°C.

Found : N, 7.11. Calcd. for $C_9H_{13}O_2N \cdot HCl$: N, 6.91%.

N-o-Chlorophenylethanolamine.—This was prepared by the method of Dashen[18]. A fraction of b. p. 180~190°C (18 mmHg) was collected and converted into its hydrochloride ; colorless crystals from ethanol, m. p. 116~117°C.

Found : C, 45.99 ; H, 5.32 ; N, 6.88. Calcd. for $C_8H_{10}NOCl \cdot HCl$: C, 46.15 ; H, 5.33 ; N, 6.77%.

N-o-Tolylethanolamine.—After heating of a mixture of *o*-toluidine and ethylene chlorohydrin at 120°C for 6 hr., the fraction of b. p. 140~170°C (17 mmHg) was collected and dissolved in ethanol.

The insoluble fraction was *N,N'*-bistolylpiperazine ; sublimate at 166~168°C.

Found : C, 81.43 ; H, 8.49 ; N, 10.20. Calcd. for $C_{18}H_{22}N_2$: C, 81.16 ; H, 8.33 ; N, 10.52%.

The ethanol soluble fraction gave colorless crystals by treating with hydrochloric acid and ether. This was *N-o*-tolylethanolamine hydrochloride, recrystallized from ethanol, m. p. 134~135°C.

Found : C, 57.63 ; H, 7.46 ; N, 7.57. Calcd. for $C_9H_{13}NO \cdot HCl$: C, 57.59 ; H, 7.51 ; N, 7.46%.

Benzoyl derivative, m. p. 141~142°C.

Oxydation by Periodic Acid.—A quantity (about 0.02~0.03 mmol.) sample was dissolved in 2 cc. of methanol and added with about 3 equiv. of periodic acid, then the volume made up to 10 cc. with addition of pH 4.5 acetate buffer. The oxidation was carried out in a dark place at 4°C. A blank test was carried out similarly with the same concentration of periodic acid and no sample, and titration was practiced every times during the course of the oxidation. For the measurement of periodate consumption, 1 cc. of aliquot was pipetted into 3 cc. of saturated aqueous sodium bicarbonate solution, added with 2 cc. of N/100 arsenious acid solution and 1 cc. of potassium iodide (10%), and titrated with N/100 iodine solution.

N-2,4-Dinitrophenyl derivatives of serine, ethanolamine, methylamine and methyl 3-amino-3-deoxy-altroside did not consume periodic acid after 72 hr., whenever the reaction temperature changed to 9°C or room temperature (about 20°C), and the quantity of oxidant changed to about six mole equivalents.

Production of formaldehyde was identified by making its 2,4-dinitrophenylhydrazone and dimedone derivatives, and paper chromatographic analysis and mercuric chloride method[19] was applied for the detection of formic acid.

Sample	Mol. equiv. of periodate consumption, hr.
N-DNP-glucosamine	1.77(2), 2.41(6), 2.83(24), 2.83(31), 2.83(47)
N-DNP-glucosamide (III-a) mole ratio (1 : 5),	0.78 (6), 1.79(24), 1.80(31), 2.02(47)
(1 : 2),	0.16 (2), 0.37 (8), 0.79(48), 0.77(72)

12) F. C. Green and L. M. Key, *Anal. Chem.*, **24**, 727 (1952).
13) K. F. Wadkoetter, *Rec. trav. chim.*, **57**, 1294 (1938); *Chem. Abstr.*, **33**, 1286 (1939).
14) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 120 (1960).
15) L. Knorr, *Ber.*, **22**. 2092 (1889).
16) C. B. Kremer, *J. Am. Chem. Soc.*, **59**, 1681 (1937).
17) G. R. Ramage and G. Trappe, *J. Chem. Soc.*, **1952**, 4406.
18) L. Dashen and R. Q. Brewster, *Trans. Kansas Acad. Sci.*, **40**, 103 (1937) ; *Chem. Abstr.*, **33**, 5395 (1939).
19) J. R. Dyer, "Methods of Biochemical Analysis", (1954), p. 131.

N-DNP-glucosamide (III-b)
mole ratio (1 : 5), 0.49 (2), 0.73 (8), 0.70(48), 0.93(72)

N-DNP-1-aminopropane-2,3-diol (IV)
1.33 (1), 1.86 (6), 2.13(19), 2.38(73)

N-Arylethanolamine derivatives

p-Nitrophenyl	0.86(2), 0.94(4), 1.07(24), 1.09(48), 1.10(72)
o-Nitrophenyl	0.03(2), 0.10(4), 0.19(24), 0.27(48), 0.34(72)
Phenyl	0.73(1), 0.96(4), 1.10(7), 1.49(24), 1.83(72)
o-Tolyl	1.19(2), 1.41(4), 1.94(24), 1.95(48)
o-Methoxyphenyl	1.32(2), 1.66(4), 2.55(24), 2.75(48)
o-Chlorophenyl	1.09(1), 1.20(3), 1.37(7), 1.79(25), 2.03(48)
o-Aminophenyl	2.09(2), 2.30(7), 2.64(24), 2.59(48), 2.61(96)
(pH 2.0)	1.12(1), 1.31(3), 1.45(24), 1.46(72)

For Fig. 5

o-Chloroaniline	0.19(1), 0.18(3), 0.82(19), 0.99(26)
N-*o*-Chlorophenylethanolamine	1.13(1), 1.19(3), 1.77(19), 2.03(26)

Summary

The authors have examined the cleavage reaction with periodic acid of the *N*-aryl-α-amino alcohols. It has been seen that the α-amino alcohols do not react with the oxidant when substituted by the *N*-2, 4-dinitrophenyl or *o*-nitrophenyl group. When *N*-aryl-α-amino aldehyde groups were produced during the course of oxidation, the normal cleavage reaction took place even if the substituent was a *N*-2, 4-dinitrophenyl group. An over-oxidation was observed in the periodate oxidation of other *N*-aryl-α-amino alcohols, and it was proved that the cause of such high consumption of periodic acid was due to the oxidation of the aromatic amine that was produced by the normal cleavage of the *N*-aryl-α-amino alcohol group.

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