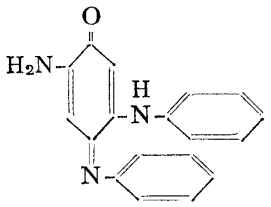
UDC 542.943.6 : 546.157-33 : 547.828

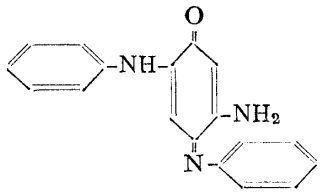
127. Hiroya Tanabe: Studies on the Periodic Acid Oxidation of N-Glycosides. XII.[1] Studies on the Periodic Acid Oxidation of Anilines. (5).

(*National Hygienic Laboratory**)

Previously, it was shown[2,3] that the oxidation products of aniline with periodic acid at its higher concentration contained 15% of amino-anilino-N-phenyl-*p*-benzoquinone-imine (I) of m.p. 127°. This compound had been found by R. Majima[4] for the first time in the oxidation products of aniline with bromic acid, and its structure was concluded by him as either (Ia) or (Ib) from its molecular formula as well as its reaction with aniline. However, there has been no conclusive evidence about which of the two formulae is right.**



(Ia)



(Ib)

In 1935, Saunders, *et al.*[5] gave the structure (Ib) for (I), obtained by oxidation of aniline with hydrogen peroxide and ferrous sulfate, without any experimental evidence.

In studying the oxidation mechanism of aniline with periodic acid, it became neccessary to know the correct structure of (I). Therefore, the present series of experiments were carried out for this purpose and (I) was successfully prepared by a decisive method, concluding the structure of (I) to be (Ia) and not (Ib).

According to theoretical considerations about the oxidation mechanism of aniline with periodic acid, (Ia) and (Ib) would be produced in the manner presented in Chart 1.

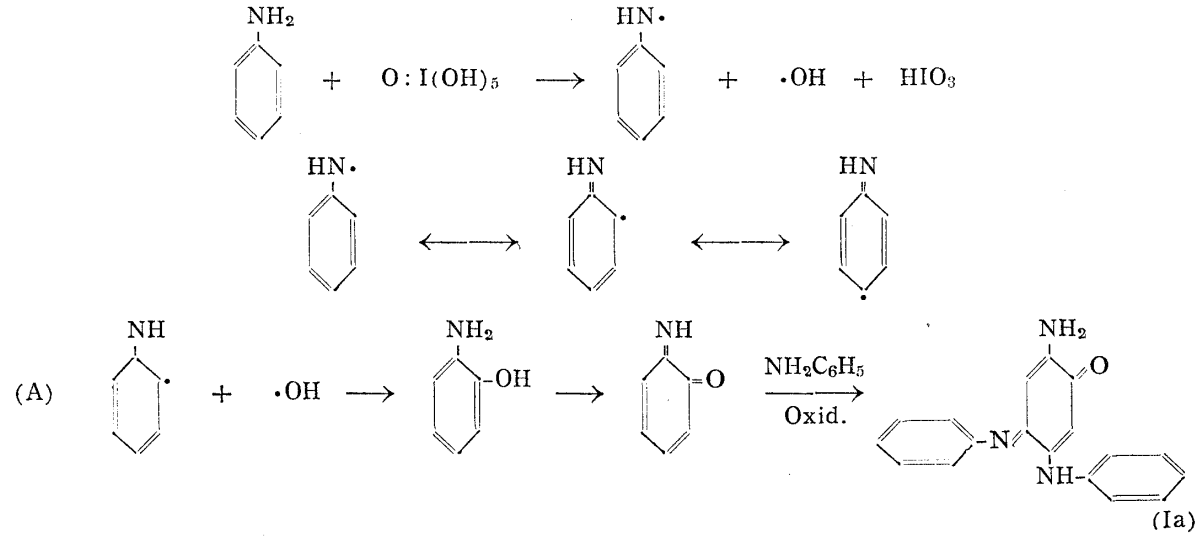


Chart 1.

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** After our contribution of this paper, we received the Tetrahedron, Vol. 2, No. 3/4, in which (p. 289) G. Engesma, *et al.* had proved the structure of (I) as (Ia) by the same method in main point as is described in this paper.

1) Part XI: H. Tanabe: Yakugaku Zasshi, **78**, 410 (1958).
2) H. Tanabe: *Ibid.*, **77**, 161 (1957).
3) T. Tanabe: *Ibid.*, **77**, 867 (1957).
4) R. Majima: Ber., **44**, 229 (1911).
5) B. C. Saunders, P. J. G. Mann: Proc. Roy. Soc. (London), **B 119**, 47 (1935).

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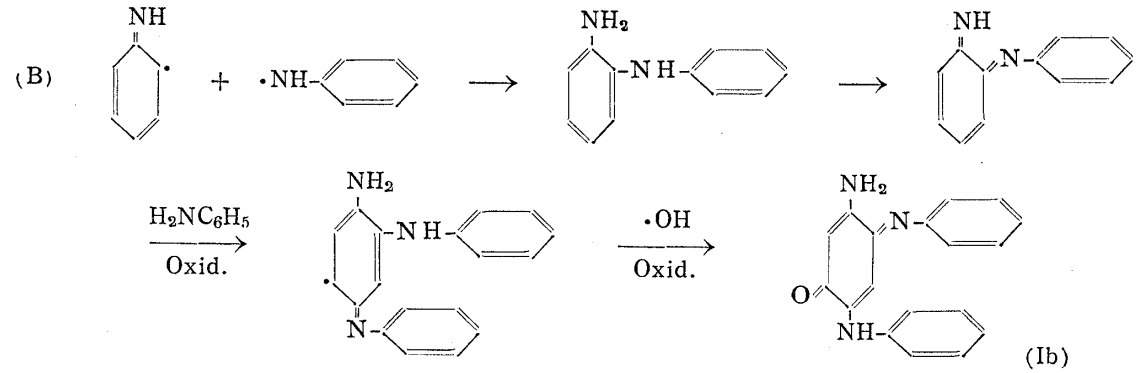
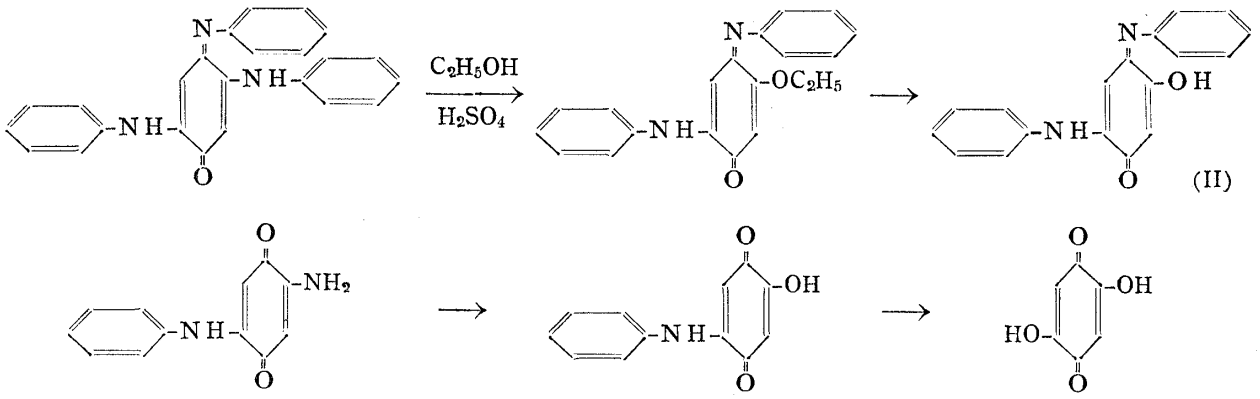
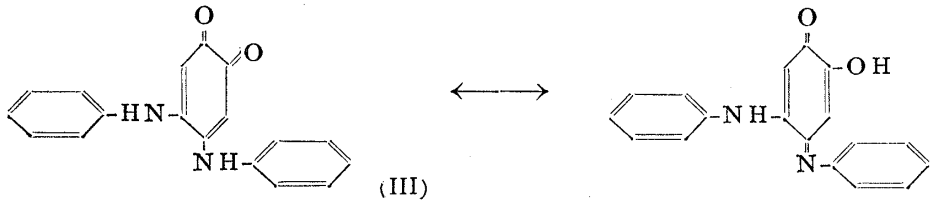


From these reactions it is reasonable to suppose that (Ia) will be produced more easily than (Ib) and if this consideration is right, (I) should be (Ia).

Zincke[6] reported that 2,5-dianilino-N-phenyl-*p*-benzoquinone-imine was hydrolyzed with sulfuric acid in ethanol to 2-alkoxy-5-anilino-N-phenyl-*p*-benzoquinone-imine which was further decomposed by the action of diluted alkali to 2-hydroxy derivative (II). Kehrmann[7] reported that 2-amino-5-anilino-*p*-benzoquinone was hydrolyzed to 2-hydroxy-5-anilino-*p*-benzoquinone and finally to 2,5-dihydroxy derivative by diluted alkali.



These reports suggest that (Ib) should also produce (II) by the action of hydrolyzing agents mentioned above. However, when a suspension of (I) in 1% NaOH solution was heated for 5 hours, (II) was not produced, and a trace of sublimable, alkali-soluble, red crystals were obtained. From its melting point of ca. 190° the structure of this product was assumed to be 4,5-dianilino-*o*-benzoquinone (III). Therefore, (I) seemed more likely to be (Ia) rather than (Ib).



From these theoretical considerations and experimental results, it seemed certain that (I) is (Ia) and attempt was made to synthesize (I) according to the reaction mechanism involved in (A), in order to have a direct structural evidence and, further, to provide experimental proof for studying the oxidation mechanism of aniline with periodic acid.

6) T. Zincke: Ber., **18**, 788 (1885).
7) F. Kehrmann, G. Bahatorian: Ber., **31**, 2401 (1898).

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No report on the synthesis of *o*-benzoquinone-imine is found in literature, but Willstätter[8] synthesized *p*-benzoquinone-imine from *p*-aminophenol by its treatment with silver oxide, and Kehrmann[9] obtained (III) from a reaction mixture of pyrocatechol and aniline with silver oxide in glacial acetic acid. Moreover, Ungnade[10] reported that a solution of *o*-benzoquinone-imine derivative was obtained when 2-phenoxy-4-methyl-6-aminophenol hydrochloride was oxidized with silver oxide in ether. Therefore, a mixed solution of *o*-aminophenol and aniline in glacial acetic acid was oxidized with silver oxide according to Kehrmann's method and a product melting at 125° was obtained in 20% yield, which showed no depression on mixed fusion with (I) synthesized by the method reported by R. Majima. Neither *o*-aminophenol nor aniline alone produced (I) by the action of silver oxide. Therefore, (I) must be produced according to the reaction mechanism involved in (A).

Thus Majima's compound (I) is (Ia) and the reaction (A) seems to be a part of the process in producing (I) from aniline with periodic acid.

Further gradual consumption of periodic acid was observed only in (I) among the products obtained by the oxidation reaction of aniline with periodic acid. This gave the answer to the continuous consumption of periodic acid over the critical point of the same oxidation reaction reported in part IX[2] of this series.

The writer expresses his gratitude to Prof. S. Akiya of the Tokyo Medico-Dental College for his kind guidance and encouragement, to Dr. T. Kariyone, Director of this Laboratory, for giving him facilities for the present study, and to Dr. I. Kawashiro for his kind encouragement.

Experimental

Hydrolysis of (I)[2] with Dilute Alkali—A suspension of (I) in 1% NaOH was heated in a boiling water bath for 5 hrs. After cool, the reaction mixture was filtered, the filtrate was acidified with HCl, and the red precipitate produced was filtered, washed, and dried. It began to sublime at 160° and gave yellowish red needles which melted at 185~190° (microscopic determination).

Ag_2O-Oxidation of a Mixture of *o*-Aminophenol and Aniline—To a suspension of 6.4 g. of fresh Ag_2O in 100 cc. of glacial AcOH, a mixture of 2 g. of *o*-aminophenol and 5 cc. of aniline in 100 cc. of glacial AcOH was added and shaken for 15 mins. at room temperature. The mixture was filtered, the filtrate was diluted with 4 vols. of water, and then filtered. The precipitate was extracted with boiling ligroine, the extract was concentrated, and stood over night to give fine needles which were recrystallized from ligroine, m.p. 125°. On mixed fusion with (I) prepared by Majima's method it showed no depression. Yield, about 1 g.

Periodic Acid Oxidation of HIO_4-Oxidation Product of Aniline—To about 10 mg. of (I), 2,5-dianilino-N-phenyl-*p*-benzoquinone-diimine (II'),[2,3] -imine (III'),[2,3] 2,5-dianilino-*p*-benzoquinone-imine (IV'),[2,3] 2,5-dianilino-N,N'-diphenyl-*p*-benzoquinone-diimine (V)[3], or 2,5-dianilino-*p*-benzoquinone (VI),[3] or to 20 mg. of the total oxidation products of aniline at critical point with periodic acid, other than (I) and (II), extracted completely with ligroine, or (VII), 1.5 cc. of 0.305*M* solution of $NaIO_4$ was added, diluted to 50 cc., and the mixture was left to stand with occasional shaking. Amount of IO_4^- in 5 cc. of reaction mixture was estimated with borate-boric acid buffer, KI-starch, and 0.1*N* As_2O_3 standard solution.

Period (hrs.)	0.1*N* As_2O_3 uptake (cc.)		
	0	20	70
(I)	0.92	0.82	0.77
(II')	〃	0.90	0.89
(III')	〃	〃	〃
(IV)	〃	0.91	0.90
(V)	〃	〃	0.91
(VI)	〃	〃	0.89
(VII)	〃	〃	0.90

8) R. Willstätter, A. Pfannenstiel: Ber., **37**, 4606 (1904).
9) F. Kehrmann, M. Cordon: Ber., **46**, 3011 (1913).
10) H.E. Ungnade, K.T. Zilch: J. Org. Chem., **15**, 1108 (1950).

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Summary

Majima's amino-anilino-N-phenyl-*p*-benzoquinone-imine was prepared by treatment of a mixture of *o*-aminophenol and aniline with silver oxide and it was found that the structure of this quinone-imine is 2-anilino-5-amino-N-phenyl-*p*-benzoquinone-imine. It was found that the reduction of periodic acid after the critical time in periodic acid oxidation of aniline was caused by this compound.

UDC 547.565.2.07

128. Koichi Tomino: Reduction of Substituted Resorcinols. IV. Synthesis of 2-Carbamoyl-4-dimethylaminocyclohexane-1,3-dione and Related Compounds.

(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.**)

Tetracyclines possess remarkable antibacterial activities and, under the assumption that the group responsible for this antibacterial activity might be the A-ring characteristic to tetracyclines, it was considered of interest to synthesize this A-ring and related compounds, and to examine relationship between chemical structure and antibacterial activity in these compounds. For this purpose, compounds possessing partial structure of the A-ring in tetracycline were synthesized and these were reported in Parts I to III of this series.[1~3] The compounds synthesized were the fundamental skeleton of the A-ring, i.e. cyclohexane-1,3-dione, with a stable amino group in its 4-position, 4-benzamidocyclohexane-1,3-dione,[1] and another more closely resembling the structure of the A-ring, 4-dimethylaminocyclohexane-1,3-dione.[2] From a different point of view, the fundamental skeleton having a carbamoyl in 2-position, 2-carbamoylcyclohexane-1,3-dione, and its derivative, 2-methylcarbamoylclohexane-1,3-dione, were also prepared. These compounds were obtained by alkaline catalytic reduction at atmospheric pressure of the corresponding resorcinol derivative, using Raney nickel or palladium-carbon as a catalyst.

In the present series of work, the A-ring of tetracyclines, 2-carbamoyl-4-dimethylaminocyclohexane-1,3-dione, and its derivatives were prepared. Starting with 2,6-dihydroxybenzamide (I), whose synthesis was described in Part III of this series,[3] it was submitted to diazo-coupling with benzenediazonium chloride to form 3-phenylazo-2,6-dihydroxybenzamide (II) (Chart 1). (II) came as orange needles, m.p. 234° (decomp.), and its analytical values agreed with $C_{13}H_{11}O_3N_3$. The position of the phenylazo group was presumed from the fact that the diazo-coupling of 2,6-dihydroxybenzoic acid, as reported by Gore and others,[4] had taken place in 4-position.

(II) was reduced in glacial acetic acid with palladium-carbon as a catalyst and it absorbed 2 moles of hydrogen. Evaporation of the solvent under a reduced pressure afforded white silky crystals, m.p. 151° (decomp.), of 3-amino-2,6-dihydroxybenzamide acetate (III). Acetylation of (III) with acetic anhydride gave white needle crystals which effervesced at about 135°, solidified, and melted at 207°. This substance is insoluble in dil. hydrochloric

* Honjo-Kawasaki-cho, Ohyodo-ku, Osaka (富野耕一).

1) Part I. K. Tomino: Yakugaku Zasshi, **78**, 1419(1958).
2) Part II. *Idem.*: *Ibid.*, **78**, 1423(1958).
3) Part III. *Idem.*: *Ibid.*, **78**, 1425(1958).
4) T.S. Gore, T.B. Pause: Proc. Indian Acad. Sci., **29A**, 289(1949) (C.A., **44**, 3980(1950)).

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