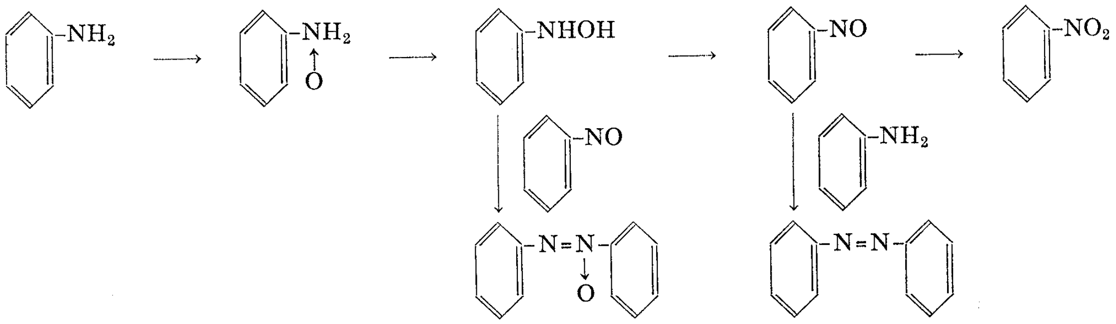
UDC 547.551 : 542.943.6 : 546.157

35. **Hiroya Tanabe** : Studies on the Periodic Acid Oxidation of N-Glycosides. XIII.[1] Studies on the Periodic Acid Oxidation of Anilines. (6).

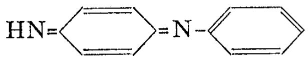
(*National Hygienic Laboratory**)

In Parts IX to XI[2] of this series, detailed investigations were reported on the products obtained on oxidation of aniline with periodic acid. Mechanisms involved in the formation of these compounds was examined and, in order to explain those of some of these compounds, it became necessary to suggest some new, modified mechanisms. In this paper, discussions are made on details of the mechanism of formation of oxidation products, (I) to (VI) reported in Part X[2b] of this series.

During 1898 to 1902, oxidation mechanism was first studied by Bamberger,[3] and the main points of oxidation mechanism with oxidizing agents of the first class[4] were reported by him as follows :



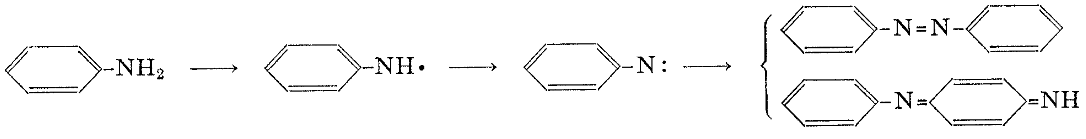
He also studied oxidation mechanisms with oxidizing agents of the second class[4] and found that N-phenyl-*p*-benzoquinone diimine (VII) was the basic intermediate. He



(VII)

supposed that (VII) is also formed from phenylhydroxylamine and this view was accepted for a long time. Saunders, *et al.*[5] tried to explain the mechanism of aniline oxidation with peroxidase-H_2O_2 on this hypothesis. This view, however, does not explain the absence of formation of several kinds of oxidation products from phenylhydroxylamine.

In 1922, Goldschmidt, *et al.*[6] demonstrated that the oxidation of aniline with lead dioxide proceeded with formation of anil radical, and concluded the scheme for the first stage of the oxidation to be as follows :



Thereafter, Horner, *et al.*[7] and Edward[8] studied the production mechanism of anil radical and its mesomerism on the basis of electron theory and developed the

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1) Part XII. H. Tanabe : This Bulletin, **6**, 645(1958).

2) H. Tanabe : a) Part IX : Yakugaku Zasshi, **77**, 161(1957); b) Part X : *Ibid.*, **77**, 867(1957); c) Part XI : *Ibid.*, **78**, 410(1958).

3) E. Bamberger, *et al.* : Ber., **31**, 1522(1898); **32**, 342, 1675, 1882(1899); Ann., **311**, 78(1900).

4) N. Sigdwick : "Organic Chemistry of Nitrogen," 51.

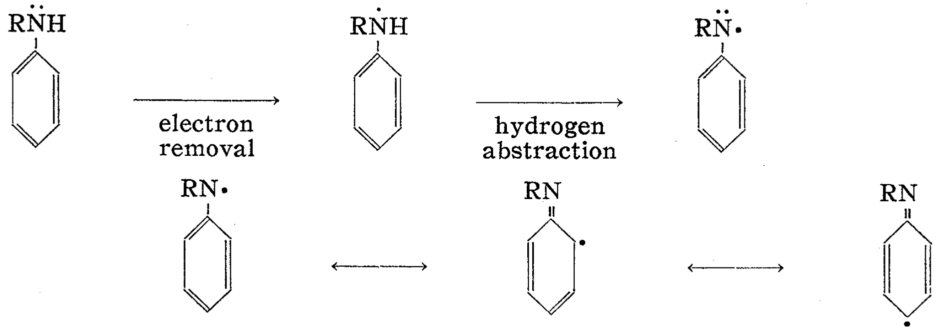
5) B.C. Saunders, *et al.* : Proc. Roy. Soc. (London), **B 119**, 47(1935).

6) S. Goldshmidt, *et al.* : Ber., **55**, 2216(1922).

7) L. Horner, *et al.* : Ann., **566**, 69(1950); **573**, 35(1951); **579**, 175(1953).

8) J.T. Edward : J. Chem. Soc., **1951**, 1464.

theory on mechanism of aniline oxidation with oxidizing agents of second class as follows :



Saunder, *et al.*, Pausacker, *et al.*, and many other chemists explained the aniline oxidation mechanisms with various oxidizing agents of the second class along these theories.

It seems appropriate to assume that periodic acid also belongs to the second class, in spite of the absence of experimental proof, because of the following four reasons :

1) If phenylhydroxylamine is produced at the first step of aniline oxidation with periodic acid the same as in the oxidation by the oxidizing agents of the first class, nitrosobenzene should be produced in quantitative amount as reported in Part VIII[9] in this series, since no azoxybenzene and only a trace amount of azobenzene is obtained which should be derived from this compound. This is experimentally not the case.

2) The oxidation products consist of many kinds of components and these can be obtained in almost same kinds from the reaction mixtures of both pH 4.2 and 9.4.

3) These components are in accord with those produced by the autoxidation of aniline under light irradiation[10] which is believed to cause typical radical reactions.

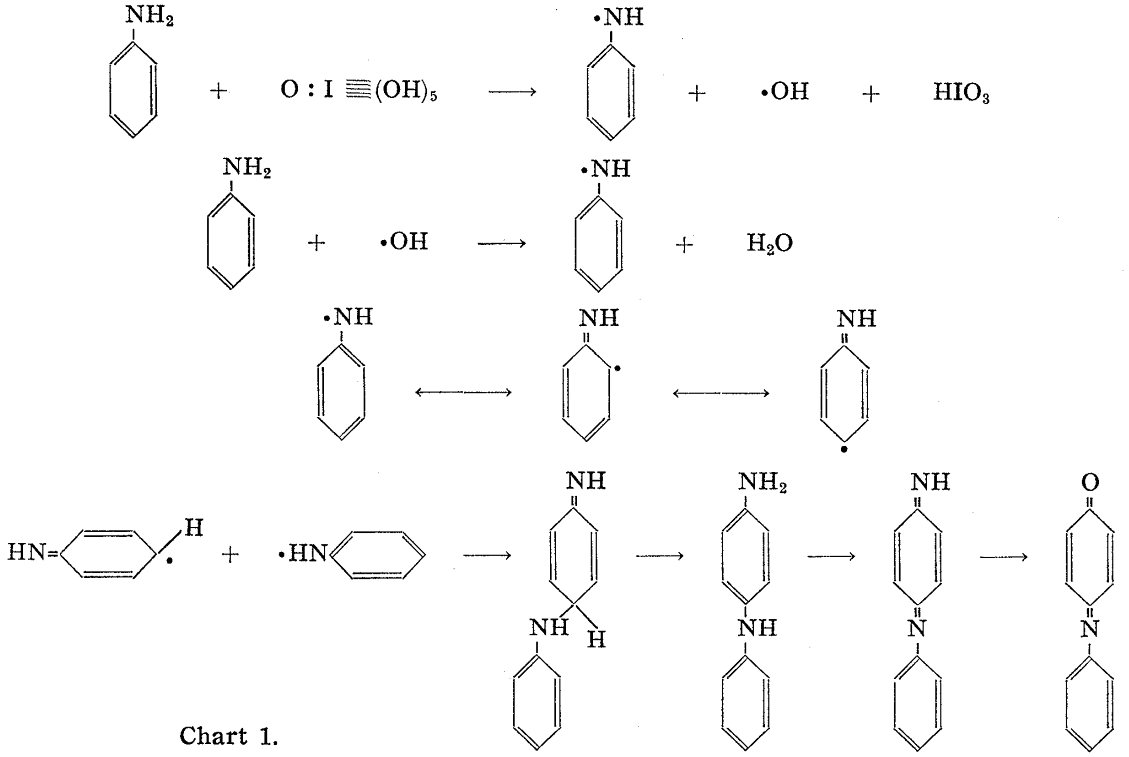


Chart 1.

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[9] H. Tanabe : Yakugaku Zasshi, **76**, 1023(1956).
[10] H. D. Gibbs : J. Am. Chem. Soc., **34**, 1203(1912).

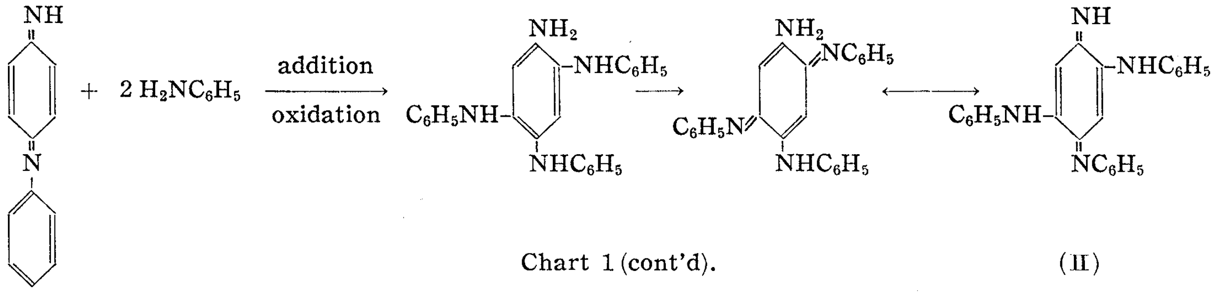
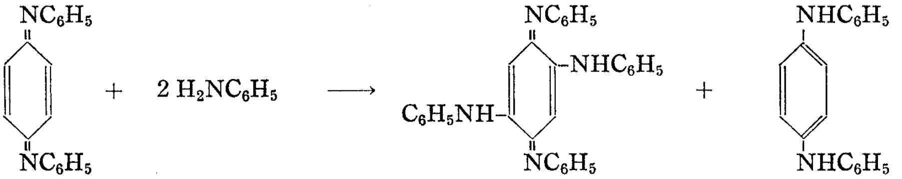


Chart 1 (cont'd). (II)

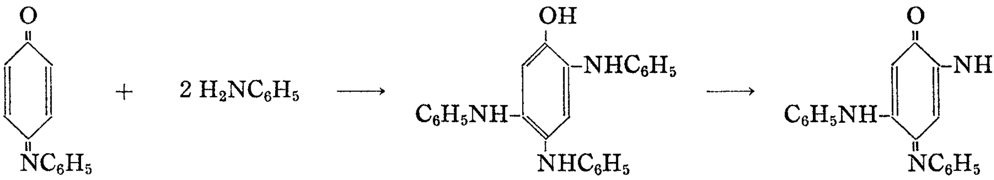
4) The periodic acid oxidation of aniline proceeds in many kinds of hydrous organic solvents having different dielectric constants.

For these reasons, the mechanism of periodic acid oxidation of aniline may be represented as shown in Chart 1.

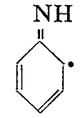
These reactions are generally assumed to involve 1,4-addition and oxidation is perhaps effected not only with periodic acid but also with N-phenyl-*p*-benzoquinone diimine (VII) itself, just as Bandrowsky[11] demonstrated with N,N′-diphenyl-*p*-benzoquinone diimine:

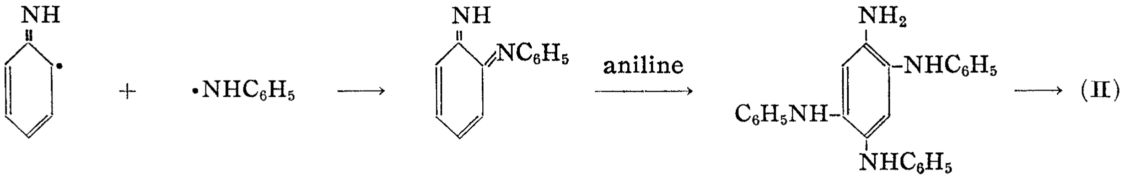


2,5-Dianilino-N-phenyl-*p*-benzoquinone imine (III) is assumed to be produced as follows :



(III)

These reactions with  result in the same products, for example :



The reaction mechanisms mentioned above are the same as those reported by Saunders, *et al.*[12] and by Pausaker, *et al.*,[13] but in the periodic acid oxidation reaction carried out in this Laboratory,[2] 2,5-dianilino-*p*-benzoquinone imine (IV), 2-amino-5-anilino-N-phenyl-*p*-benzoquinone imine (I) and 2,5-dianilino-*p*-benzoquinone (VI) are produced in larger quantities than (II) and (III). For the production of these compounds, the mechanisms mentioned above is not enough and it became necessary to assume that the $>C=N-\phi$ group may be hydrolysed to $>C=O$. However, (VII) was not hydrolysed further than to N-phenyl-*p*-benzoquinone imine under the mild condition of the periodic acid oxidation reaction.[14] Thus, the following, new modified oxidation mechanism is

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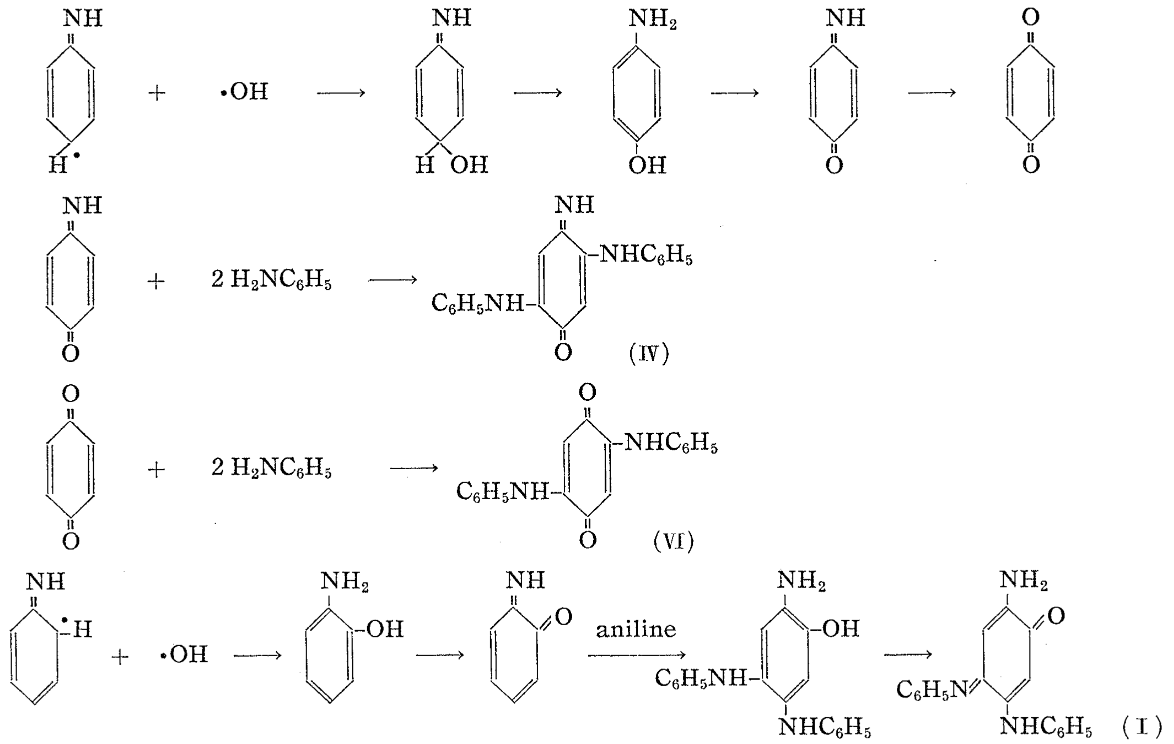
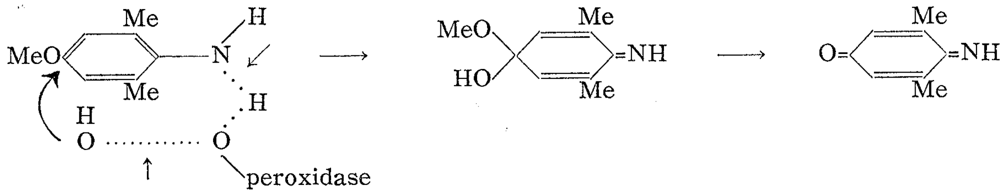
11) E. V. Bandrowsky : Monatsh., 8, 475(1887); **9**, 414(1888).
12) B. C. Saunder, *et al.* : J. Chem. Soc., **1954**, 4630.
13) K. H. Pausaker : *Ibid.*, **1954**, 4502.
14) E. Fischer, *et al.* : Ber., **40**, 2665(1907).

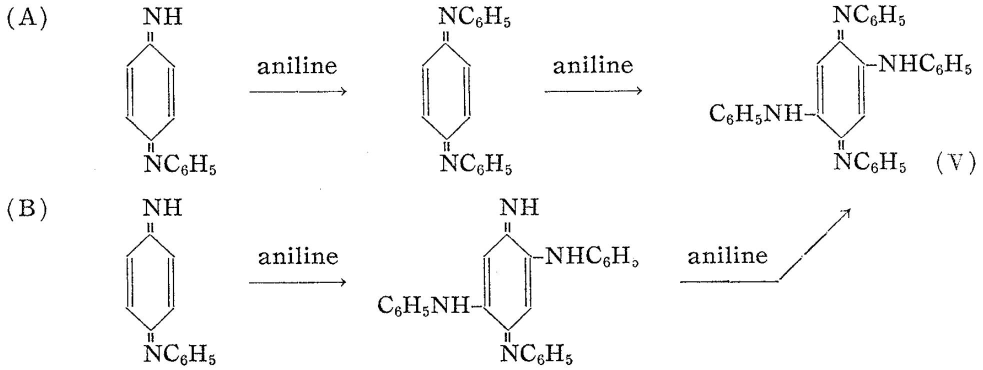
proposed in which aminophenol might be formed as an intermediate due to the reaction between hydroxyl and anil radicals.


(IV)
(VI)
(I)

A part of the last reaction mechanism was proved experimentally as reported in the preceding paper.[1] Saunders, *et al.*[15] assumed somewhat similar mechanism in their studies on peroxidase–H_2O_2 oxidation of 4–methoxy–2,6–dimethylaniline and anisidine.



On the production mechanism of azophenine (V), the following reactions are generally believed.


(A)
(B)
(V)

Reaction (A) was reported by Pausacker, *et al.*[13] on *p*–alkoxyanilines, but this scheme does not seem to be applicable to the present reactions, since (VII) has been

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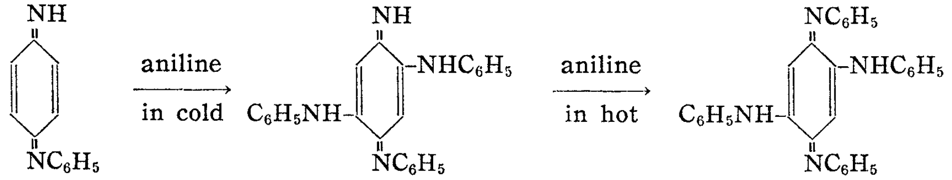
15) B. C. Saunder, *et al.* : a) J. Chem. Soc., **1951**, 2112; b) Biochem. J., **46**, 629(1950).
16) S. Goldschmidt, *et al.* : Ber., **55**, 3220(1922).

shown to react with aniline in water as follows[16] :

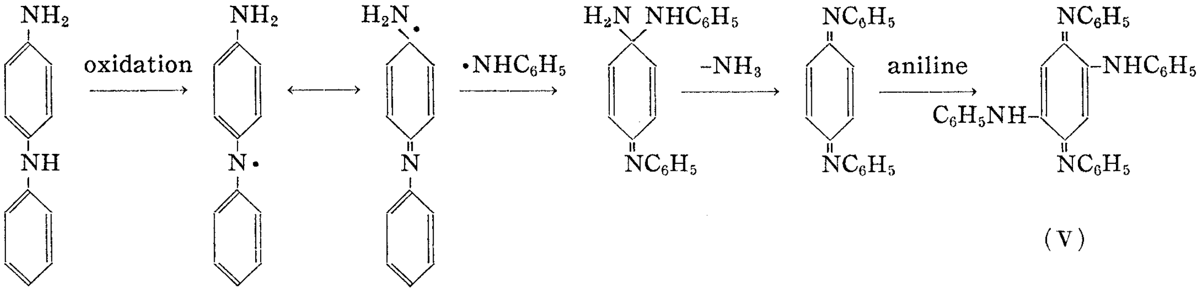


In the paper on studies on the peroxidase-H_2O_2 oxidation of aniline and *p*-haloanilines, Saunders, *et al.*[5,12] without experimental proof, stated that azophenines are produced from N-substituted *p*-benzoquinone diimines and anilines through a seriese of established addition and oxidation reactions on the basis of the reaction (B).

However, 2,5-dianilino-N-phenyl-*p*-benzoquinone diimine (II) does not dissolve in water at all and the azophenine production was not observed when (II) was suspended in water of pH 4.0, half saturated with aniline, and allowed to stand for 5 hours at room temperature with occasional shaking, in spite of the fact that about 1/10 the quantity of azophenine as (II) was produced in the periodic acid oxidation of aniline for 3 hours, and that azophenine was produced very slowly from (II) and aniline in ethanol solution.

Further, there are the experiments of Bandrowsky[17] without discussing the reaction mechanism, in which the oxidation of diphenylamine and aniline with potassium permanganate gave N,N′-diphenyl-*p*-benzoquinone diimine.

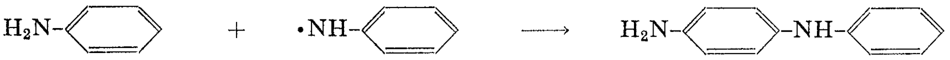
From these facts, it is assumed that there is the following reaction besides the reaction (B) :



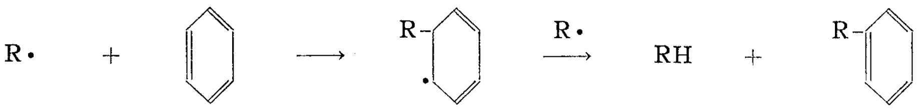
(V)

This view seems to be supported also by the fact that a secondary amino group is more easily attacked by oxidizing agents or radicals than a primary amino group in a compound of similar structure, as known for example, in the case of inhibitor efficiencies of aniline and diphenylamine, and in oxidation-reduction potential of benzidine ($E_0^{25}=921$) and *p*-aminodiphenylamine ($E_0^{25}=751$).[15]

The reaction mechanism for production of (I) to (VI) has only been explained by means of radicals combining with each other, but it is known that the substituted benzene is somewhat reactive with radicals, and at the initial step of the oxidation reaction, initially produced anil radicals are surrounded by unchanged aniline molecules, so that, at this time, an anil radical has more opportunity of coming into contact with an unchanged aniline molecule than with another anil radical. Thus, the following reaction is hypothetically presumable :



At present, the substitution of a radical into benzene ring is considered to be as follows : [18]



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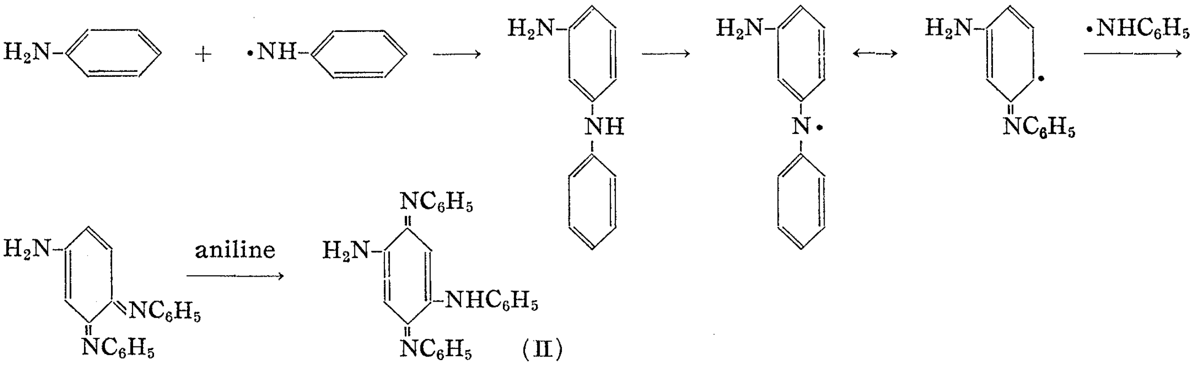
[17] E. V. Bandrowsky : Monatsh., **7**, 382(1886).

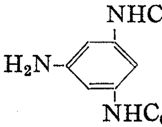
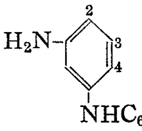
[18] C. Walling : "Free Radicals in Solution," 483(1957).

The first step of this reaction is not hydrogen release and it is, therefore, theoretically reasonable to assume that positions on the benzene ring other than amino group are attacked by a radical at first.

According to this view, it is natural that a position *meta* to the amino group can also be replaced,[19] although this replacement is more difficult than that at *ortho* or *para*.



(II)

Saunders, *et al.*[12] discarded this view because of not obtaining the derivative,  but this does not seem possible because it is presumable that aniline would react with radicals preferably at *ortho* or *para* to the substituent (amino group), which is true in the case of chloro-, bromo-, methyl-, and nitrobenzenes.[19] Thus it seems that 2- and 4-positions in  are too reactive to produce a detectable amount of 3-derivative and that the steric effect of previously combined anil groups at 2- and 4- positions will inhibit the attack of 3-position by an anil radical. In this mechanism it is not clear whether the anil radical and aniline molecule possess sufficient energy to do this.

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

Experimental

Periodic Acid Oxidation of Aniline in Hydrous Organic Solvents—To 5 cc. (v/v) aniline solution in 60% hydr. EtOH, 60% hydr. acetone, and 60% hydr. dioxane, 5 cc. of saturated aqueous solution of $NaIO_4$ was added. In the course of several hrs., the reaction mixture became brown in color and excess of $NaIO_4$ deposited as silky crystals. Paper chromatogram of the reaction mixture gave a spot of (I) at Rf 0.40 (ligroine) coloring pale pink—pale green by HCl gas, and of (III) at Rf 0.70 (ligroine), pale yellow—pale orange by HCl gas.

On using HIO_4, crystals of aniline salt appeared at first, which slowly disappeared, and after standing overnight, a black tarry substance was formed, which probably consists of aniline black.

Reaction between (II) and Aniline—i) Fine powder of (II) was suspended in water, half saturated with aniline and pH of its solution adjusted to 4.0 with HCl. The mixture was left for 5 hrs. at room temperature with occasional shaking. After filtration, the paper chromatogram of the precipitate was examined, and there was no spot of azophenine (V) but only that on (II).

ii) To 10 cc. of saturated EtOH solution of (II), 0.2 cc. of aniline and 2 drops of glacial AcOH were added and the mixture was left to stand at room temperature. After standing overnight, a trace of crystals appeared and this was proved to be azophenine (V) by its m.p. of 232° and paper chromatogram (Rf 0.30, MeOH saturated with CS_2; pale yellow—reddish violet). (II) and aniline seem

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[19] D. H. Hey, *et al.*: J. Chem. Soc., **1951**, 2892; **1952**, 2094.

to react very slowly in EtOH at room temperature, since azophenine (V) scarcely dissolved even in hot EtOH containing aniline and glacial AcOH in the ratio mentioned above.

Summary

The mechanisms of formation of products obtained by oxidation of aniline with periodic acid, (I) to (VI) reported in Part X of this series, are discussed. Mechanism for the production of (I), (IV), and (VI) is considered to involve the action of hydroxyl radical. In the formation of (V) from N-phenyl-*p*-benzoquinone diimine, a radical reaction is assumed to play a part.

(Received August 29, 1958)

UDC 547.466.4.07

36. **Seishi Takagi and Kyozo Hayashi**: Studies on the Synthesis of Amino Acids by the Schmidt Reaction. III.* Synthesis of DL-Homolysine.

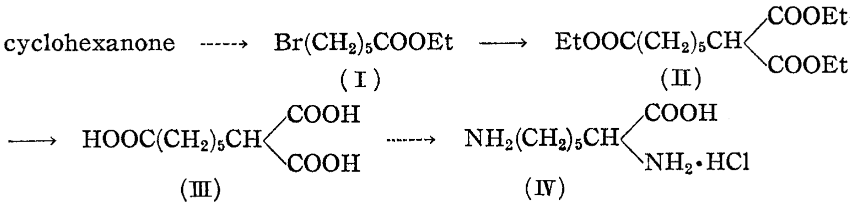
(*Pharmaceutical Institute, Medical Faculty, University of Kyoto***)

Harris, *et al.*¹⁾ has reported that they synthesized DL-homolysine by acetamidomalonate method and obtained crystalline monohydrochloride monohydrate of (IV) melting at 176°. The authors obtained a different result from that of Harris, *et al.* in the synthesis of DL-homolysine by the following several methods and obtained it as a monohydrochloride melting at 263°.

In the first method, 1,1,6-hexanetricarboxylic acid was reacted with more than 2 moles of hydrazoic acid, in the presence of conc. sulfuric acid as the catalyst. In the second method, 7-aminoheptanoic acid was obtained from 1,8-octanedioic acid by the procedure previously described²⁾ and DL-2-amino-7-benzamidoheptanoic acid formed was hydrolyzed. In the third method, ethyl 2-acetamido-2-cyano-7-benzamidoheptanoate, obtained by the condensation of ethyl acetamidocyanoacetate with 1-chloro-5-benzamidopentane, was hydrolyzed.

By these methods, the objective was successfully obtained as white needles melting at 263°, instead of the substance melting at 176° reported by Harris, *et al.*

The first method was carried out by the route shown in Chart 1.



$$\text{cyclohexanone} \dashrightarrow \underset{(\text{I})}{Br(CH_2)_5COOEt} \longrightarrow \underset{(\text{II})}{EtOOC(CH_2)_5CH(COOEt)_2} \longrightarrow \underset{(\text{III})}{HOOC(CH_2)_5CH(COOH)_2} \dashrightarrow \underset{(\text{IV})}{NH_2(CH_2)_5CH(COOH)(NH_2 \cdot HCl)}$$

Chart 1.

Ethyl 5-bromocaproate was synthesized from cyclohexanone by the method of Brown, *et al.*³⁾ and condensed with diethyl malonate to give triethyl 1,1,6-hexanetricarboxylate (II). This was hydrolyzed by the general method and 1,1,6-hexanetricarboxylic acid (III) so formed was reacted with a slight excess of 2 moles of hydrazoic acid to form (IV). From the reaction mixture, (IV) was isolated and purified as previously reported.²⁾ (IV) was adsorbed on Amberlite IR-120, eluted with 0.5~0.6N ammonia

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* Part II: This Bulletin, **7**, 99(1959).

** Sakyo-ku, Kyoto (高木誠司, 林 恭三).

1) J. I. Harris, T. S. Work: Biochem. J., **46**, 190(1950).

2) S. Takagi, K. Hayashi: This Bulletin, **7**, 96(1959).

3) G. B. Brown, C. W. H. Partridge: J. Am. Chem. Soc., **66**, 839(1944).