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11. Torizo Takahashi and Fumino Yoneda: Syntheses of Heterocyclic Compounds of Nitrogen. CX.[1] Azaphenoxazine Derivatives.

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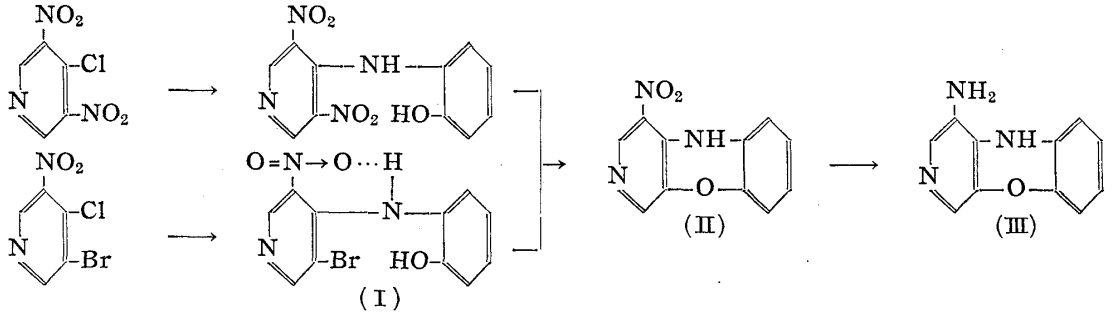
Many papers regarding phenoxazines have appeared since Turpin[2] reported the synthesis of dinitrophenoxazine from picryl chloride and *o*-aminophenol. The literature, however, contains little information about the synthesis of azaphenoxazines, except for the reports published by Petrow[3] and Plażek.[4] The authors prepared several azaphenoxazines with a view to investigating their pharmacological activity and leading them to further pharmacologically active azaphenoxazine derivatives, and the results in this research are herein described.

3-Bromo-4-(*o*-hydroxyphenylamino)-5-nitropyridine (I) was first prepared by the condensation of the potassium salt of *o*-aminophenol with 3-bromo-4-chloro-5-nitropyridine.[5] The reaction of (I) with aqueous potassium hydroxide was effected by heating on a water bath for a while and gave reddish crystals. On heating (I) with piperidine, on the other hand, the same material was also easily obtained in a better yield. This material was confirmed to be 4-nitro-5*H*-benzo[*b*]pyrido[4,3-*e*]-1,4-oxazine (II) by its analytical values, absence of the Beilstein reaction for halogens, and the presence of a nitro group, and also identical with that synthesized by Petrow[3] from 3,5-dinitro-4-chloropyridine and *o*-aminophenol.

From this fact, it may be concluded that because of the formation of a chelate ring between the secondary amino group and the nitro group in (I), a close approach of the hydroxyl group to the bromine atom was brought about so that an intramolecular condensation easily proceeded in alkaline medium to give (II).



The catalytic reduction of (II) with hydrogen in methanol, using $PdCl_2$-charcoal as a catalyst, led it to the hydrochloride of the corresponding amino compound, 4-amino-5*H*-benzo[*b*]pyrido[4,3-*e*]-1,4-oxazine (III), m.p. > 300°, which agreed with that of Petrow's report.[3]

The condensation of the potassium salt of *o*-aminophenol with 2-chloro-3,5-dinitropyridine[6] proceeded on heating in ethanol to provide 2-(*o*-hydroxyphenylamino)-3,5-dinitropyridine (IV). Further attempts were made to prepare a ring-fused azaphenoxazine from (IV) in alkaline medium, but ended in faliure, only recovering the starting

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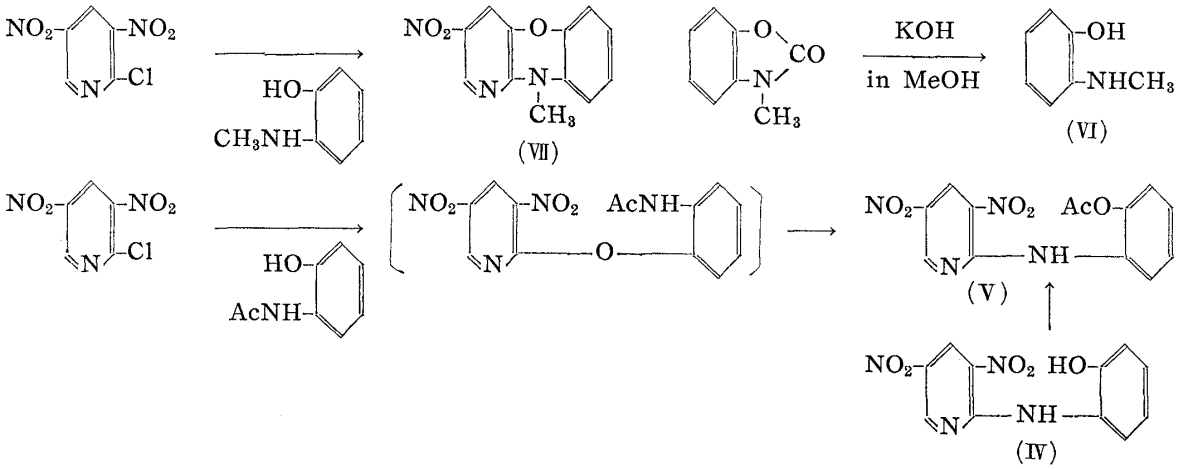
1) Part CIX. Yakugaku Zasshi, **78**, in press (1958).
2) G.S. Turpin: J. Chem. Soc., **59**, 722(1891).
3) V.A. Petrow, E.L. Rewald: *Ibid.*, **1945**, 313.
4) E. Plazek: C.A., **31**, 3918(1937).
5) O. Bremer: Ann. Chem. Liebigs, **529**, 290(1937).
6) E. Plazek: Rec. trav. chim., **72**, 569(1953).

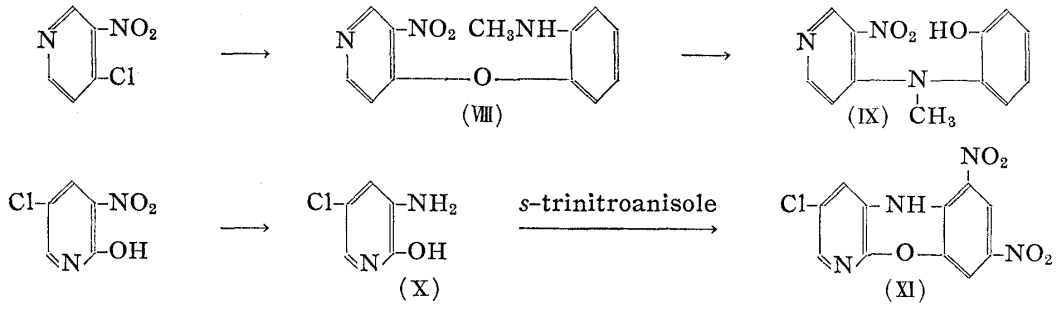
material. On the other hand, when 2-chloro-3,5-dinitropyridine was allowed to react with *o*-methylaminophenol, 3-nitro-10-methylbenzo[*e*]pyrido[3,2-*b*]-1,4-oxazine (VII) was obtained in a good yield. These facts are explainable by the assumption of a chelate ring suggested by Brady.[7] Thus it may be considered that in the former case, because of the formation of a chelate ring between the nitro group at 3-position of the pyridine ring and the secondary amino group, the intramolecular condensation of (IV) did not occur, and that in the latter case, because of the replacement of the hydrogen atom of the secondary amino group with methyl group, chelation did not occur and the condensation took place easily.

Roberts, *et al.*[8] had shown that the condensation of *o*-methylaminophenol with 1-chloro-2,4-dinitrobenzene afforded 2,4-dinitro-2′-methylaminodiphenyl ether and subsequent treatment of the product with alkali gave 4-methylphenoxazine as a result of rearrangement and ring closure. In our case, however, no intermediate was isolated, and only the final product, azaphenoxazine, was formed immediately. 2-Methylaminophenol (VI) used in the above reaction had been prepared by the hydrolysis of 3-methylbenzoxazol-2(3*H*)-one[9] with ethanolic potassium hydroxide.

The reaction of 2-chloro-3,5-dinitropyridine and 2-acetamidophenol was carried out in methanolic potassium hydroxide and furnished 2-(*o*-acetoxyphenylamino)-3,5-dinitropyridine (V), instead of the anticipated azaphenoxazine. Its melting point did not depress on admixture with that derived from the acetylation of (IV) with acetic anhydride in the presence of pyridine. This may be accounted for by the assumption that 2-(*o*-acetamidophenoxy)-3,5-dinitropyridine once formed underwent intramolecular rearrangement to give (V).



The condensation of *o*-methylaminophenol (VI) with 3-nitro-4-chloropyridine was effected by heating in methanolic potassium hydroxide and gave 3-nitro-4-(*o*-methyl-



7) O.L. Brady, C. Waller : J. Chem. Soc., **1930**, 1218.
8) K.C. Roberts, H.B. Clark : *Ibid.*, **1935**, 1312.
9) H. Zinner, H. Herbig : Chem. Ber., 88, 693(1955).

aminophenoxy)pyridine (VIII), and then ring closure was attempted at (VIII) using alkali but (VIII) underwent rearrangement only to form 3-nitro-4-[N-methyl-N-(*o*-hydroxyphenyl)amino]pyridine (IX).

Subsequently, by the catalytic reduction of 3-nitro-5-chloro-2-pyridone with hydrogen in methanol using Pd-black as a catalyst, 3-amino-5-chloro-2-pyridone (X) was obtained. Because of being very labile in the air, (X) without purification was condensed immediately with *s*-trinitroanisole and gave 3-chloro-6,8-dinitro-5*H*-benzo[*b*]-pyrido[3,2-*e*]-1,4-oxazine (XI) in a good yield.

The authors' thanks are due to the members of the microanalytical center of the Institute for the microanalyses.

Experimental[10]

3-Bromo-4-(*o*-hydroxyphenylamino)-5-nitropyridine (I)—3-Bromo-4-chloro-5-nitropyridine (1.2 g.) was added to a solution of *o*-aminophenol (0.6 g.) and KOH (0.3 g.) in EtOH (10 cc.). The reaction mixture was refluxed on a water bath for 30 mins. and the solvent was removed by distillation. Several volumes of water was added, crystals thereby separated were collected by filtration, washed with water, dried, and recrystallized from MeOH. Red prisms, m.p. 191°(decomp.). Yield, 1.5 g. *Anal.* Calcd. for $C_{11}H_8O_3N_3Br$: C, 42.58; H, 2.58. Found : C, 42.74; H, 2.72.

4-Nitro-5*H*-benzo[*b*]pyrido[4,3-*e*]-1,4-oxazine (II)—(I) (1.2 g.) was dissolved in piperidine (4 cc.). The color of the solution immediately became red. Then the solution was heated on a water bath for 1 hr. and allowed to stand at a room temperature. The deposited red crystals, after water was added, were collected by filtration, washed with water, dried, and recrystallized from MeOH to form red needles, m.p. 206°. Yield, 0.7 g. *Anal.* Calcd. for $C_{11}H_7O_3N_3$: C, 57.64; H, 3.08; N, 18.34. Found : C, 57.41; H, 3.37; N, 18.18.

4-Amino-5*H*-benzo[*b*]pyrido[4,3-*e*]-1,4-oxazine (III)—a) (II) (0.2 g.) suspended in MeOH (10 cc.) was catalytically reduced in the presence of $PdCl_2$-charcoal. After absorption of hydrogen ceased, the catalyst was filtered off and MeOH was distilled off from the filtrate. Yellow crystals thereby obtained were collected and recrystallized from MeOH to yellow needles, m.p. >300°.

b) Petrow's method : A suspension of (II) (0.5 g.) in a solution of EtOH (5 cc.) and HCl (5 cc.) containing $SnCl_2 \cdot 2H_2O$ (2.0 g.) was heated on a water bath for 2 hrs. After cool, crystals formed were collected by filtration and recrystallized from water to yellow needles, m.p. >300°. Yield, 0.3 g. *Anal.* Calcd. for $C_{11}H_{10}ON_3Cl$: C, 56.05; H, 4.25. Found : C, 56.21; H, 4.11.

2-(*o*-Hydroxyphenylamino)-3,5-dinitropyridine (IV)—*o*-Aminophenol (1.4 g.) was dissolved in dehyd. EtOH (10 cc.) containing Na (0.23 g.). To this solution, a solution of 2-chloro-3,5-dinitropyridine (1.9 g.) in EtOH (10 cc.) was added gradually under stirring and the mixture was allowed to stand at room temperature for 1 hr. Crystals thereby formed were collected by filtration, washed with water, dried, and recrystallized from EtOH. Red prisms, m.p. 230~232°(decomp.). Yield, 3 g., soluble in aqeous caustic alkali, negative to the diazo test of primary amine. *Anal.* Calcd. for $C_{11}H_8O_5N_4$: C, 47.83; H, 2.92. Found : C, 47.56; H, 2.72.

2-(*o*-Acetoxyphenylamino)-3,5-dinitropyridine (V)—a) *o*-Acetamidophenol (0.75 g.) and KOH (0.28 g.) were added to MeOH (10 cc.). To the mixture was added 2-chloro-3,5-dinitropyridine (1.0 g.) and the reaction mixture was heated on a water bath for 10 mins. The solution was concentrated, water was added to afford red crystals, which were collected by filtration, washed with water, dried, and recrystallized from EtOH. Yellow needles, m.p. 146~147°. Yield, 1.2 g.

b) (IV) (0.5 g.) was dissolved in a mixture of Ac_2O (2 cc.) and pyridine (2 cc.), and the mixture was heated on a water bath for a while. After cool, water was added. Yellow crystals thereby formed were collected by filtration, washed with water, dried, and recrystallized from EtOH. Yellow needles, m.p. 146~147°. *Anal.* Calcd. for $C_{13}H_{10}O_6N_4$: C, 49.06; H, 3.17. Found : C, 48.91; H, 3.32.

***o*-Methylaminophenol (VI)**—A solution of 3-methylbenzoxazol-2(3*H*)-one (1.0 g.) and KOH (2.0 g.) in EtOH (10 cc.) was refluxed for 1 hr. The solvent was distilled off and water was added. The aq. solution was neutralized with 10% AcOH and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and the solvent was distilled off to afford a crystalline residue, which was recrystallized from Et_2O and petr. ether. Colorless tablets, m.p. 93°. Yield, 0.5 g. Its m.p. agreed with that of (VI) obtained by the usual method.

3-Nitro-10-methyl-benzo[*e*]pyrido[3,2-*b*]-1,4-oxazine (VII)—(VI) (0.3 g.) and KOH (0.14 g.) were dissolved in MeOH (5 cc.). To this solution, a solution of 2-chloro-3,5-dinitropyridine (0.42 g.) in MeOH (5 cc.) was added slowly under stirring. The mixture was allowed to stand at room temperature

10) All m.p.s are uncorrected.

for 30 mins. Orange crystals thereby separated out were collected by filtration, washed with water, dried, and recrystallized from MeOH. Orange needles, m.p. 182°. Yield, 0.4 g. *Anal.* Calcd. for $C_{12}H_9O_3N_3$: C, 59.26; H, 3.73; N, 17.28. Found : C, 59.47; H, 3.93; N, 17.19.

3-Amino-5-chloro-2-pyridone (X)—3-Nitro-5-chloro-2-pyridone (0.9 g.) was suspended in MeOH (20 cc.) containing Pd-black (0.1 g.), and catalytic reduction was carried out. After 390 cc. of hydrogen (theoretically 380 cc.) was absorbed, the catalyst was filtered off. The filtrate was used immediately in the next procedure.

3-Chloro-6,8-dinitro-5*H*-benzo[*b*]pyrido[3,2-*e*]-1,4-oxazine (XI)—*s*-Trinitroanisole (1.2 g.) was added to the methanolic solution described above and the mixture was refluxed on a water bath for about 2 hrs. Purple black crystals that separated out were collected by filtration, washed with water, dried, and recrysatllized from pyridine and EtOH. Purple black crystalline powder, m.p. >280°. Yield, 1.0 g. *Anal.* Calcd. for $C_{11}H_5O_5N_4Cl$: C, 42.79; H, 1.62; N, 18.15. Found : C, 42.96; H, 1.91; N, 18.26.

3-Nitro-4-(*o*-methylaminophenoxy)pyridine (VIII)—To a solution of (VI) (0.5 g.) and KOH (0.5 g.) in MeOH (10 cc.), a solution of 3-nitro-4-chloropyridine hydrochloride (1.0 g.) in MeOH (10 cc.) was added under stirring. The mixture was heated on a water bath for 30 mins. and the solvent was distilled off. Water was added to afford crystals, which were collected by filtration, washed with water, dried, and recrystallized from MeOH. Yellow prisms, m.p. 174°(decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52. Found : C, 58.47; H, 4.71.

3-Nitro-4-[N-methyl-N-(*o*-hydroxyphenyl)amino]pyridine (IX)—(VIII) (0.1 g.) was added to a methanolic KOH solution and warmed for a while until (VIII) dissolved completely. Then the reaction mixture was concentrated and neutralized with 10% AcOH. Yellow prisms, m.p. 183°(decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52. Found : C, 58.56; H, 4.84.

Summary

3-Bromo-4-(*o*-hydroxyphenylamino)-5-nitropyridine prepared from the potassium salt of *o*-aminophenol and 3-bromo-4-chloro-5-nitropyridine easily yielded 4-nitro-5*H*-benzo[*b*]pyrido[4,3-*e*]-1,4-oxazine by the intramolecular condensation in the presence of piperidine or potassium hydroxide. Attempts to prepare a ring-fused azaphenoxazine from the potassium salts of *o*-aminophenol and 2-chloro-3,5-dinitropyridine in alkaline medium ended in failure, only giving 2-(*o*-hydroxyphenylamino)-3,5-dinitropyridine. On the other hand, when 2-chloro-3,5-dinitropyridine was allowed to react with *o*-methylaminophenol, 3-nitro-10-methylbenzo[*e*]pyrido[3,2-*b*]-1,4-oxazine was obtained. These facts are well explainable from the hypothesis of a chelate ring formation forwarded by Brady. 3-Amino-5-chloro-2-pyridone was condensed with *s*-trinitroanisole giving 3-chloro-6,8-dinitro-5*H*-benzo[*b*]pyrido[3,2-*e*]-1,4-oxazine.

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