

Cyclohepta[*b*][1,4]benzoxazines 3.¹⁾ The Reaction of 6-Bromocyclohepta-*b*[1,4]benzoxazine with *o*-Aminophenol²⁾

Tetsuo NOZOE,* Harue OKAI, Hidetsugu WAKABAYASHI,*[†] and Sumio ISHIKAWA[†]

Tokyo Research Laboratories, Kao Corporation, Bunka-2, Sumida-ku, Tokyo 131

[†]Department of Chemistry, Faculty of Science, Josai University, Sakado-shi, Saitama-ken 350-02

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The reaction of 6-bromocyclohepta[*b*][1,4]benzoxazine (**19**) and *o*-aminophenol (**3**) was studied and compared with that of 3-bromo-2-methoxytropone (**2**) with **3**. 14H-[1,4]Benzoxazino[3',2':3,4]cyclohepta[1,2-*b*]-[1,4]benzoxazine, 10-(*o*-hydroxyanilino)cyclohepta[*b*][1,4]benzoxazine (**D**), 1- and 4-formylphenoxazines and their Schiff bases (**C** and **X**) were obtained in very good yields by modifying the conditions of the reaction of **19** with **3**. Structures of **D**, **C**, and their isomers were determined and the possible reaction pathways for the formation of various products are discussed.

We have reported that the reaction of 2-bromo-7-methoxytropone (**1**) and 3-bromo-2-methoxytropone (**2**) with *o*-aminophenol (**3**) in refluxing acetic acid gave quite different results: while **1** afforded mainly 2-bromo-7-(*o*-hydroxyanilino)tropone (**4**) besides small amounts of two by-products (compounds **A** and **B**, vide infra),³⁾ the reaction of **2** turned out to be very

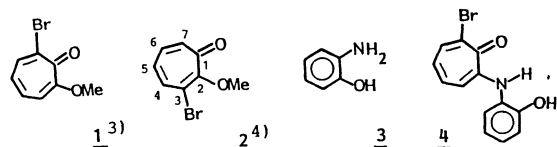
(**7**) on heating in methanol.⁴⁾ However, since **C** and **D** were not isolated as pure materials, we could not determine their exact structures at that time.

Meanwhile, we were able to resolve the chiral acetal **9** (**F**) and its derivatives into their optical antipodes and to determine their absolute configurations by an X-ray method⁵⁾ and by theoretical calculations of their CD spectral data.⁶⁾

It has generally been recognized that the course of various reactions of troponoids are often extremely sensitive towards a slight structural difference of both substrates and reagents, as well as the reaction conditions employed (solvent and concentration, temperature, and with or without catalyst, etc.).^{2,5)} However, the considerable difference between the reactions of two isomers (**1** and **2**) with **3** under the same conditions was far beyond our expectation.

At that time, we considered that the methoxyl group at C-2 of **2** would be very inactive to the nucleophilic replacement due to steric interferences (between carbonyl and bromine atom), and we believed that 1:1 condensation products (**J** and **G**) had been produced via **11** (normal substitution at C-3) and **12** (cine substitution at C-7). On the other hand, compounds **D**, **A** (**10**), **C**, and **B** (**7**) were thought to be formed through a common intermediate, **15**, via 2,3-disubstituted product **13** followed by an oxidative ring closure to **10**, and a rearrangement to **18** and **7** via spirooxazole **17**. The possible pathways proposed then are summarized in Scheme 1; however, we did not have any positive proof of the intermediates for each products.

Takase and his coworkers found⁸⁾ that the treatment of **2** and morpholine or pyrrolidine first afforded two monosubstitution products (normal and cine at C-3 and C-7, respectively), and then the 2,3- and 2,7-disubstituted products. However, differing from the above-mentioned case, the most preferable site of substitution of **2** with arylamine has recently been found by us to be the C-2 and then C-7 positions.⁹⁾ We have also found that the bromine atoms on a cyclohepta[*b*][1,4]benzoxazine ring are easily saponified by warm acetic acid to give cyclohepta[*b*][1,4]-



complex, giving various colorful products, which were easily separated by preparative silica-gel TLC and conveniently named compounds **A—L** according to their decreasing *R_F*-values.⁴⁾ The structures of most of these compounds (**A**, **B**, **F**, **G**, **J**, and **L**) were determined by spectroscopy, as shown in Chart 1. Among them, compounds **5** (**G**) and **6** (**J**) were 1:1 condensation products, whereas compounds **10** (**A**), **7** (**B**), **C**, **D**, **9** (**F**), and **8** (**L**) were 1:2 condensation products; compound **B** was a secondary product from compound **C** (see below). Compound **D** (**15**, Scheme 1) changed to compound **A** (**10**) by autoxidation, while compound **C** (**18**, Scheme 1) gradually decomposed to compound **B**

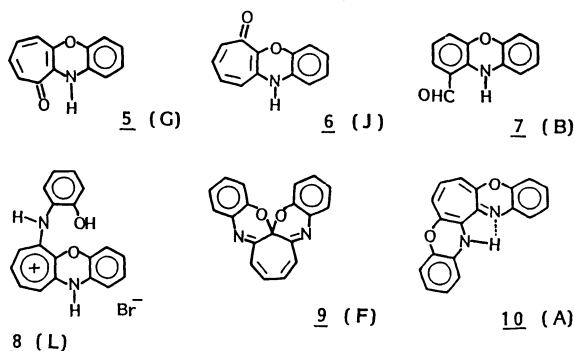
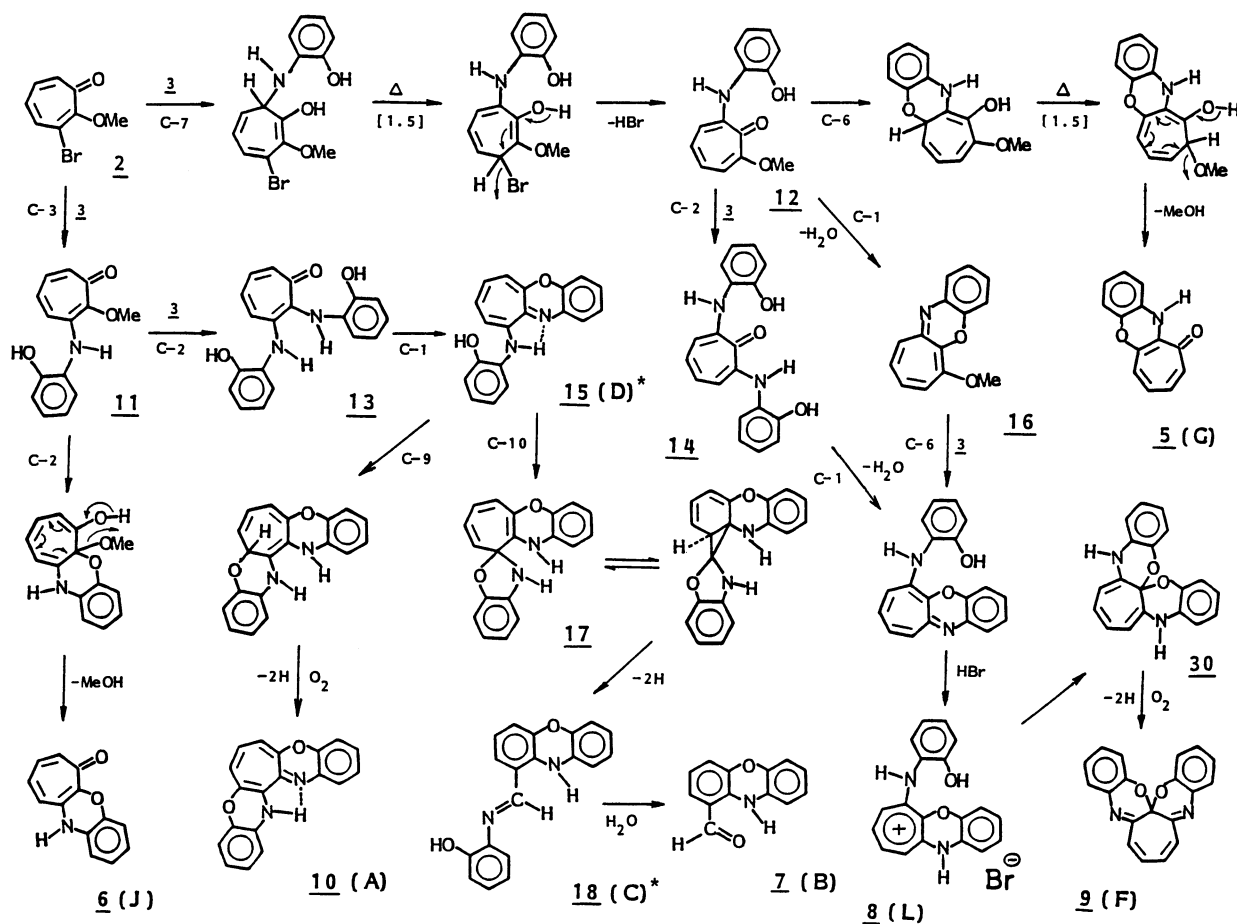
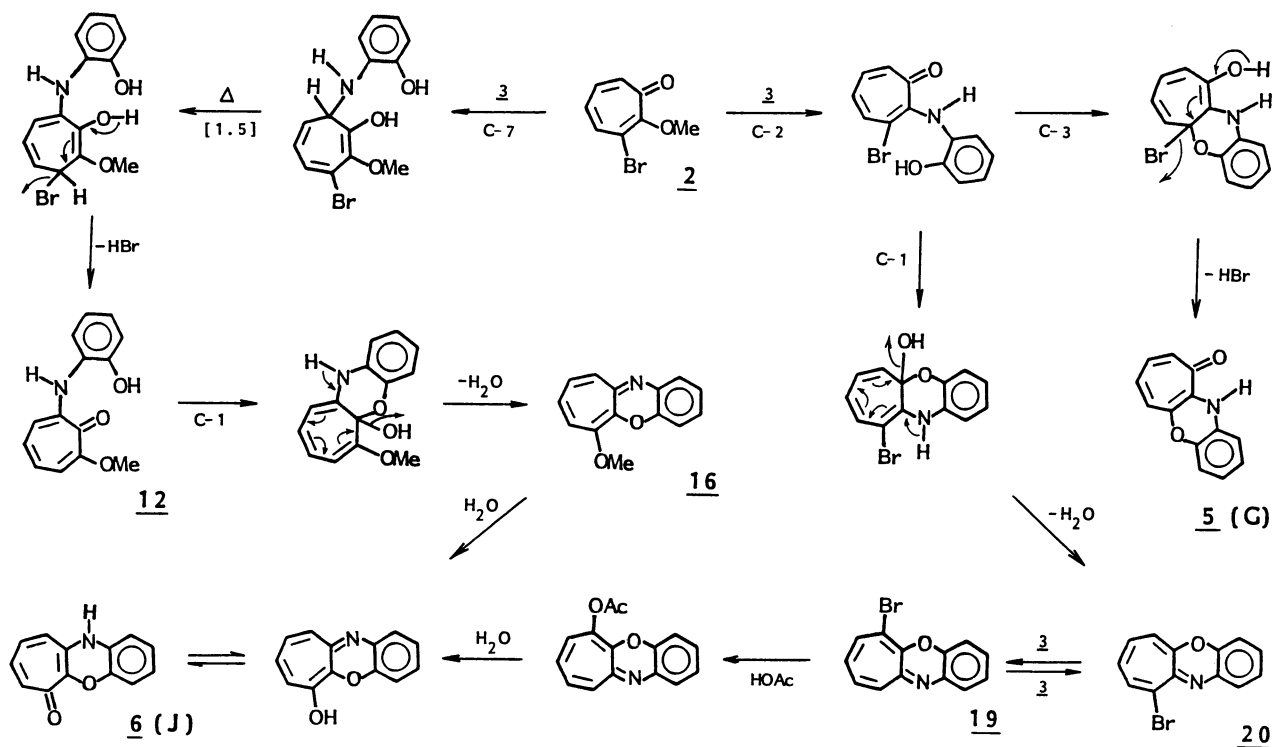


Chart 1.

Scheme 1.⁴⁾ * Structure of these compounds were determined in this paper.

Scheme 2.

benzoxazines.¹⁰ Therefore, the formation of 1:1 condensation products should now be formulated, as in Scheme 2.

In this paper, we would like to describe the reaction of 6-bromocyclohepta [*b*][1,4]benzoxazine (**19**) with **3** and *p*-anisidine along with a reexamination of the reactions of **2** with **3**, to obtain useful information about these very complex reactions of the special heterocyclic tropylium system.

Results and Discussion

Reaction of 2 with 3. To obtain useful information about the formation sequence of various products from **2** and **3** and to confirm the structures of intermediates for these compounds, we first reexamined the reaction in refluxing acetic acid by periodically checking the reactant with the reversed-phase high-pressure liquid chromatography (HPLC) equipped with a stopped-flow UV-spectrometer. An example of the chromatograph of the reaction mixture heated at 120 °C for 30 min is shown in Fig. 1a. Each peak was characterized by the stopped-flow UV-visible spectra as well as MS after separation and the assignment of the main peaks was made as follows: peaks 1 (**L**), 3(**3**), 5(**J**), 8 (**2** and **H**¹), and 10 (**G**). When the heating was continued for several hours, peaks 11–16 began to appear at a retention time (RT) of 20–50 min, as seen in their amplified figures in Fig. 1b. Peaks 12, 13, and 14 were identified by TLC and UV to be compounds **C**, **D**, and **B** (**7**), respectively.

After heating **2** and **3** in acetic acid for 60 min, the reaction mixture was separated by HPLC (Fig. 1b) and we obtained small amounts of compounds **C** and **D**. Compound **D** ($C_{19}H_{14}N_2O_2$, reddish-brown needles, mp 135–138 °C decomp) was quantitatively converted into **10** (**A**, $C_{19}H_{12}N_2O_2$) by silica-gel TLC eluted with benzene. Orange-colored compound **C** (mp 158–

160 °C, $C_{19}H_{14}N_2O_2$), which gradually degraded to **7** (**B**) on heating or standing in methanol, was therefore thought to be a Schiff base (**18**) of **7**. Upon the addition of a trace of dil sulfuric acid the methanolic solution of **C** instantly became deep purple red and then discolored after 10–20 seconds, giving HPLC peaks due to **7** and oxidative dimer **H**¹ (**22**),⁷ but only a trace amount of **3**; we found that **22** was, however, not produced when the experiment was conducted under nitrogen.

Since the quantity of pure compounds **C** and **D** were not sufficient for their structural studies, we then studied the reaction of **3** with **19** as an analogue of the possible reaction intermediates, **16** and **20**, under various conditions.

Reaction of 19 and 3. Under Acidic Conditions. On heating **19** with **3** in acetic acid at 120 °C for 1.5 h and after careful separation of the reaction mixture, compounds **L** (**8**, 55%), **D** (25%), the rearranged product **B** (**7**, ca. 10%), and a trace amount of compound **A** were isolated. Compound **D** was assigned to have the structure of 10-(*o*-hydroxyanilino)-cyclohepta[*b*][1,4]benzoxazine (**15**), based on the evidence of the spectral data; the AA'BB' singlet pattern of the four protons on the seven-membered ring in the ¹H NMR spectrum should be noted (see Experimental part). Pure **15** is stable as crystals, but its methanolic solution was autoxidized rapidly in the presence of a weak base or an acid to give a quantitative yield of **10** (**A**, Scheme 3). Hydroperoxyl radical (HOO·), which is expected to be liberated when **15** (**D**) is autoxidized to **10** (**A**) [and **8** (**L**) to **9** (**F**)], would induce oxidation of **3** to the dehydro dimer **22**. As a consequence, **22** always accompanies, as one of the products, in the reaction of this series. **10** exists as a symmetrical and almost planar hydrogen bonded form, as shown by X-ray crystallography,¹¹ and does not open its benzoxazine ring, even upon heating with methanolic

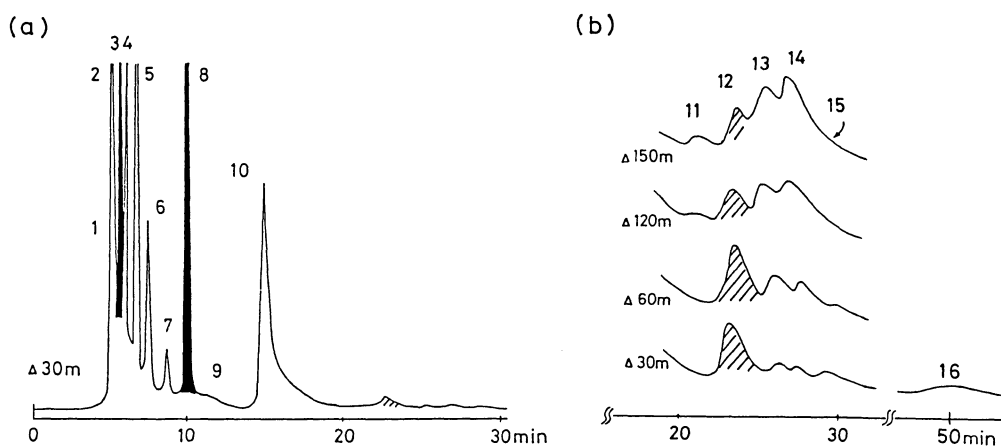
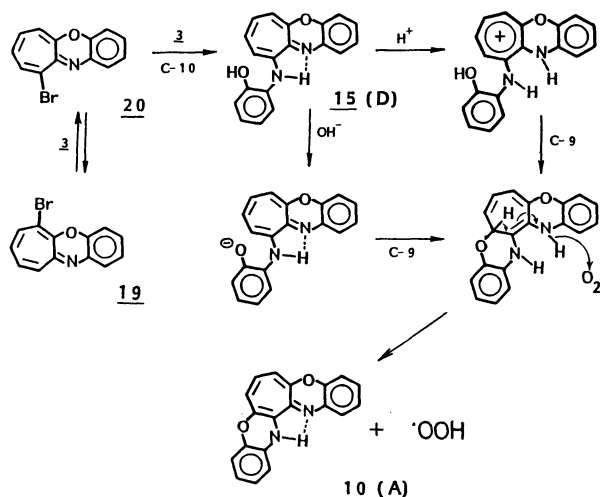
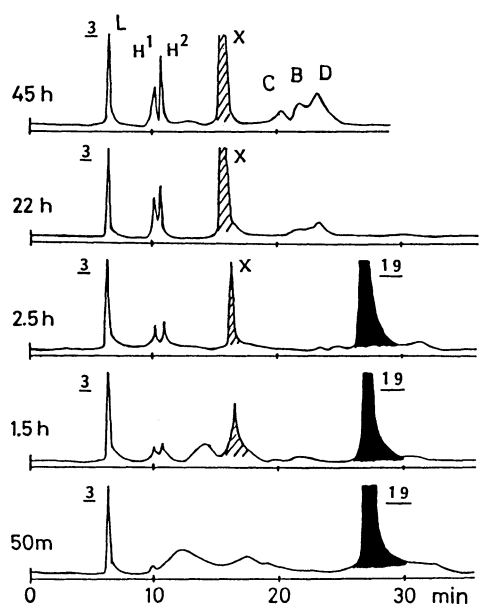


Fig. 1. Time-dependent HPLC chromatograms of the reaction of **2** and **3** in AcOH at 120 °C for 30 minutes.

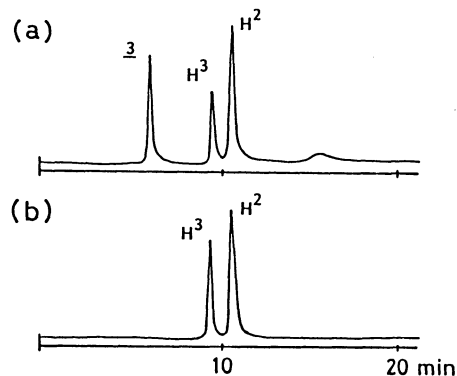


Scheme 3.

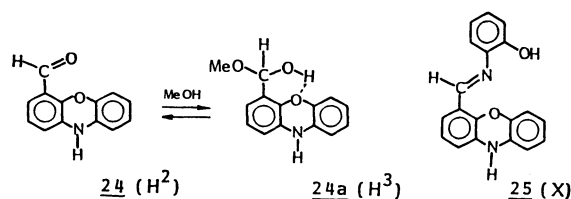
Fig. 2. Time-dependent HPLC chromatograms of the reaction of **19** and **3** in MeOH at room temp in the presence of DABCO.

alkali. We could not obtain its *N*-methyl or *N*-acetyl derivative by ordinary method, presumably because of the strong intramolecular hydrogen bonding.

Under Basic Conditions. Since compound **C** was extremely unstable in dil mineral acid, we then examined the reaction of **19** with **3** at room temperature in methanol containing an equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO) in order to neutralize HBr produced during the reaction; the time-dependent HPLC chromatograms are shown in Fig. 2. Many initially observed peaks became simplified after a few hours. Then, peaks of **3** (RT, 6 min), **22** (**H**¹, RT, 10.5 min), **H**² (RT, 11 min), and **X** (RT, 16 min) as well as weak peaks of **8** (**L**), **C**, **7** (**B**), and **15** (**D**)

Fig. 3. (a) HPLC chromatograms of compound **X** in MeOH containing a trace amount of dil sulfuric acid. (b) HPLC chromatograms of compound **H**² in MeOH containing a trace amount of dil sulfuric acid.

remained unchanged; unknown peak **X** corresponding to the main peak gradually crystallized out. Compound **X** (yellow needles, mp 210–211 °C) showed IR absorbance maxima at 3350 and 1618 cm⁻¹ due to NH and C=N, respectively, exhibited ¹H NMR (DMSO-*d*₆) signals at δ 8.85, 8.75, and 8.27 due to OH, NH, and HC=N, respectively, and was identified to be an isomer of compound **C** by MS. The addition of a small amount of dil sulfuric acid to compound **X** dissolved in methanol, resulting in the production of a deep purple color, quickly followed by a complete bleaching of the solution. This solution was found to consist of three components: **3**, **H**² (RT, 11 min), and **H**³ (RT, 9.8 min) by HPLC (Fig. 3a). Compound **H**² (yellow needles, mp 186–187 °C) isolated by TLC, showed IR absorbance maxima at 3250 (NH) and at 2840, 2780, and 1675 cm⁻¹ (CHO), and exhibited ¹H NMR (acetone-*d*₆) signals at δ 10.36 (CHO), 7.61 (NH), and 7.02 (1 benzene ring proton adjacent to CHO). These data and the results of the X-ray analysis^{12b} indicate that compound **H**² is 4-formylphenoxazine (**24**), an isomer of **7** (**B**). Compound **H**³ [UV λ_{max} (MeOH) 236 and 318 nm] was partly produced from **24** [UV λ_{max} (MeOH) 228, 276, 313, and 416 nm, (MeOH+6 M HCl) 236 and 318 nm] in MeOH by the addition of a small amount of dil sulfuric acid (Fig. 3b). The compound isolated from peak **H**³ showed the same HPLC retention time (11 min) and MS of **24**, suggesting that **H**³ would be the hemiacetal **24a**, which is stabilized somewhat by hydrogen bonding with the *O*-atom of heterocyclic ring.



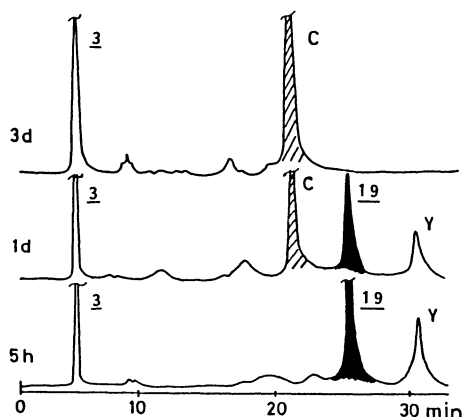
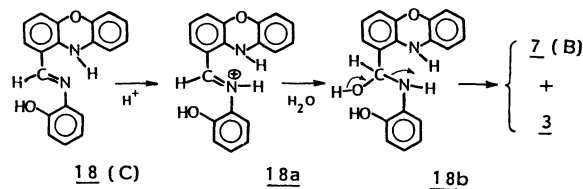


Fig. 4. Time-dependent HPLC chromatograms of the reaction of **19** and **3** in MeOH at 5°C.

Under Neutral Conditions. Since we unexpectedly obtained the Schiff base **25** instead of the Schiff base of **7(B)** in the presence of DABCO, reactions of **19** and **3** in MeOH at 5°C were performed without the base and were periodically monitored by HPLC. As shown in Fig. 4, a peak of compound **Y** (see later) appears first, and compound **C** increased as **Y** and **19** decreased among the reaction mixture. Almost no other products [e.g. **7(B)**, **10(A)**, **15(D)**] were observed in this case, even upon standing for 3 days. The product corresponding to the main peak of compound **C** gradually crystallized out in high yield. The IR spectrum of compound **C** showed OH and NH absorptions at 3470 and 3200 cm^{-1} , respectively. The ^1H NMR spectrum consisted of a proton signal of the benzene ring adjacent to the C=N group (δ 6.88, dd, $J=8$ and 2 Hz) and the signals at δ 9.78, 8.50, and 6.05 due to OH, HC=N, and NH groups, respectively. Taken together with the results of high-resolution MS, compound **C** was unambiguously identified as being the Schiff base **18** of 1-formylphenoxazine (**7**). A complete assignment for the ^1H NMR signals was made by using a decoupling technique; the result is described in the Experimental section.

When this reaction of **19** with **3** is studied using greater amounts for preparative purposes, we obtained about 70% yield of **18(C)**, besides a 20% yield of **15(D)** and a trace amount of the ring-opened product **4**.³⁾ It is noted that the yields of **15** and **18** highly depend on the reaction conditions employed; for example, at 50°C a 30% yield of **18** and 50% of **15** were produced along with 10% of **4**. The temporary deep-violet color observed when trace acid was added to the solution of **18** is considered to be due to the formation of a cyanine dye-type iminium salt of the Schiff base **18**, (or its 4-isomer in the case of **24**). This was followed by facile hydrolysis to produce **7** (or **24**) and **3** (Scheme 4). As for **Y**, we later identified it¹³⁾ to be a 10-bromo compound **20** produced by an unprecedented inter-

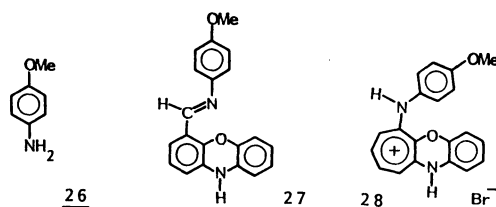


Scheme 4.

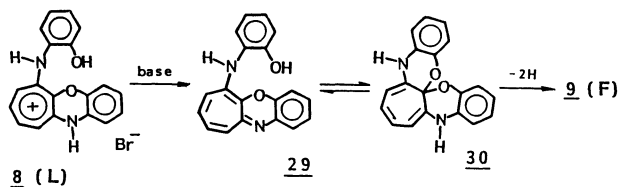
molecular heterocyclic exchange reaction between **19** and **3**. Isomers **19** and **20** are shown in the presence of **3** to exist in solution at equilibrium, as shown in Scheme 2.

From its structure, we first considered²⁾ that **15** was formed from 6-bromo compound **19** by cine substitution at C-10 followed by [1,5]hydrogen-shift. However, this assumption became doubtful because **15** was produced from **19** and **3**, even at low temperature (described before). Indeed, a recent study of the reaction of 10-bromo compound **20** with arylamine has confirmed that **15** is the normal substitution product of **20** with **3** (Scheme 3).¹⁴⁾

To clarify the reason why two different Schiff bases, **18** and **25**, are produced from **19** and **3**, in the absence or presence of base (DABCO), we examined the reaction of **19** with the *p*-anisidine (**26**) having no OH group at the *o*-position. Upon standing a methanolic



solution of **19** and **26**, we obtained, besides some ring-opened compound **4**, mainly rearranged 4-formylphenoxazine (**24**, 65%) which was produced by the hydrolysis of Schiff base **27**. Upon heating at 50°C, a 57% yield of 6-substituted cations **28**, 38% of **24** and some anilintropone **4** were obtained. The addition of DABCO or acetic acid to the methanolic solution of **19** and **26** did not change the result, and no C-10 substituted compound (D-type) and 1-formylphenoxazine (**7**) were formed. However, an almost quantitative yield of **28** was obtained upon refluxing **19** and **26** in acetic acid. Compound **28** (reddish-brown needles, mp >300°C), which exhibited a UV spectrum very similar to that of **8(L)**, was assigned to have a structure of 6-(*p*-methoxyanilino)cyclohepta[*b*][1,4]benzoxazine hydrobromide on the basis of spectral data (see Experimental part). From this evidence, and also from the structure of **9(F)**, **8(L)** is obviously the normal substitution product derived from **3** and **19** and stabilized as the HBr salt. 6-(*o*-Hydroxyanilino)cyclohepta[*b*][1,4]benzoxazine (**29**) was obtained as a yellowish-

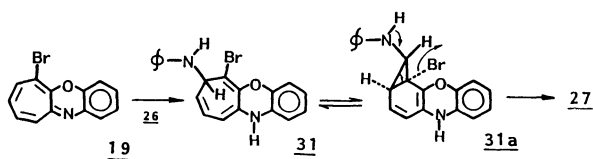


Scheme 5.

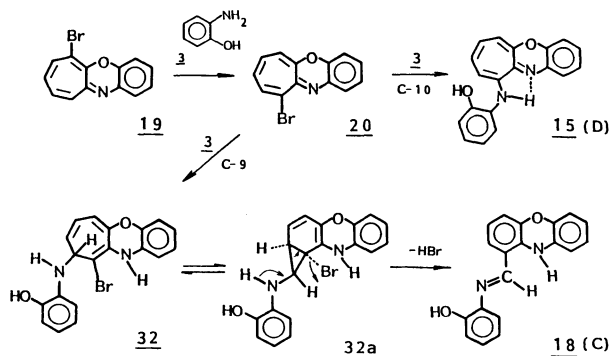
brown solid by neutralizing the salt **8**. However, it was very unstable in open air and was easily dehydrogenated to give stable dehydro acetal **9 (F)** via acetal **30** (Scheme 5).

These results indicate that the presence of an OH group at ortho to the anilino nitrogen is essential to produce **7**, **10**, **15**, and **18**. Since the rearranged product **18** was produced by the reaction of **19** and **3** in neutral or even weakly acidic conditions, and also from its structure, we first speculated⁴⁾ that the spiroxazole intermediate **17** produced from **15** by ring closure at C-10 rearranged to Schiff base **18** via norcaradiene form (in Scheme 1).

However, we later confirmed that **15 (D)** did not yield the rearranged product under various conditions. Therefore, the formation of Schiff base **27 (X-type)** from **19** and *p*-anisidine (**26**) must have proceeded by the attack of the arylamine at C-7 (to give **31**), followed by rearrangement via norcaradiene **31a** shown in Scheme 6. The production of **25** (and **24**) from **19** and **3** in the presence of a base can be similarly interpreted, since the heterocycle exchange reaction¹³⁾ of **19** to **20** is significantly retarded by a base. These pieces of evidence indicate that **15 (D)** and **18 (C)** are not derived directly from 6-bromo compound **19** by a cine



Scheme 6.



Scheme 7.

substitution at C-10, but instead, are produced from the exchanged 10-bromo compound **20** by normal substitution at C-10 (for **15**) and by an attack at C-9 (for **18**), as illustrated in Scheme 7.

Thus, the unusually complex nature of the reaction of **19** and **3** was finally unveiled by the discovery of the novel and facile heterocycle-exchange reaction between the substrate and the reagent,¹³⁾ details of which will be reported elsewhere.

Experimental

Melting points were determined with a Yanagimoto MP-3S and are uncorrected. The IR and electronic spectra were measured by using a Shimadzu IR-450 and a Shimadzu UV-202 spectrometer, respectively; the UV spectra in acid or alkali solutions were taken after adding a few drops of 6 M HCl or 6 M NaOH (1 M = 1 mol dm⁻³) to the sample solution. The ¹H NMR spectra were measured in CDCl₃ (unless otherwise specified) with a JEOL JNM-PS/PFT (100 MHz) or a JEOL JNM-GX270 (270 MHz) spectrometer using TMS as the internal standard. The assignments of all signals were made by employing a first-order analysis with the aid of a decoupling technique. The mass spectra were taken on a JEOL JMS-DX300 mass spectrometer and a Shimadzu LKB 9000 GC-mass spectrometer at 70 eV. The HPLC was carried out with Hitachi gel #3011 with MeOH-hexane (9:1) as the solvent. The centrifugal chromatography was performed with a Hitachi CLC-5 instrument in a Fuji silica gel layer (KT-2151, 3 mm thickness) using benzene as an eluent. TLC analyses were carried out with Merck Kieselgel 60F-254 plate.

Reaction of 3-Bromo-2-methoxytropone (2) with o-Aminophenol (3). a) **At 120 °C:** A solution of 167 mg (0.78 mmol) of **2** and 127 mg (1.17 mmol) of **3** in 5 cm³ of acetic acid was heated at 120 °C for 1 h and then evaporated in vacuo. The residue was preliminarily separated into four fractions by means of silica-gel column with benzene-MeOH (20:1) as the eluent. Each fraction was carefully separated by preparative HPLC with Hitachi gel #3019 using MeOH-hexane (9:1) or TLC with silica gel 60F-254 (0.25 mm, Merck) using benzene-MeOH (10:1) as the eluent, giving compounds **A**⁴⁾ (10 mg, 4% yield), **B**⁴⁾ (7 mg, 4% yield), **C** (see below, 3 mg, 1% yield), **D** (see below, 2 mg, 1% yield), **G**⁴⁾ (35 mg, 21% yield), **J**⁴⁾ (16 mg, 10% yield), and **L**⁴⁾ (82 mg, 28% yield), besides the recovered **2** (30 mg, 20%).

b) **At 60 °C:** A solution of 30 mg (0.14 mol) of **2** and 30 mg (0.28 mmol) of **3** in 3 cm³ of methanol was heated at 60 °C for 5 h, followed by the same work-up procedures mentioned above, giving 2 mg (5%) of **G**, besides the recovered **2** (25 mg, 85%).

c) **At 80 °C:** Procedures similar to the those at 60 °C were employed. Thus, a solution of 20 mg (0.1 mol) of **2** and 20 mg (0.2 mmol) of **3** was heated in 2 cm³ of 1-butanol at 80 °C for 3 h, giving 4 mg (20%) of **G** and a small amount of **J**, besides the recovered **2** (15 mg, 75%).

Reaction of 6-Bromocyclohepta[*b*][1,4]benzoxazine (19) and o-Aminophenol (3). A. **Under Acidic Conditions:** A solution of 50 mg (0.2 mmol) of **19** and 30 mg (0.3 mmol) of **3** in 2 cm³ of acetic acid was heated at 120 °C for 1 h. The solvent was evaporated in vacuo and the residue was chromatographed in a column of silica gel with benzene,

giving 40 mg (55%) of compounds **L**, 15 mg (25%) of **D**, 4 mg (10%) of **B**, and a trace amount of **A**.

B. Under Basic Conditions: A solution of 20 mg (0.07 mmol) of **19**, 12 mg (0.11 mmol) of **3**, and 14 mg (0.11 mmol) of DABCO in 2 cm³ of methanol was allowed to stand for 1 d at room temp. After cooling, the ppt was filtered off and recrystallized from methanol to give 14 mg (64%) of compound **X** (see below). The above filtrate was a mixture of compounds **A**, **B**, **C**, **D**, **H**¹, **H**² (see below), **4**³ and **L** (by TLC, HPLC, and UV).

C. Under Neutral Conditions: a) Similar procedures for acidic conditions were followed. Thus, 30 mg (0.11 mmol) of **19** with 22 mg (0.22 mmol) of **3** in 2 cm³ of methanol was heated at 50 °C for 3 h, giving 18 mg (50%) of compounds **D**, 10 mg (30%) of **C**, and 3 mg (10%) of **4**.

b) Similar procedures for basic conditions were followed. Thus, a solution of 22 mg (0.08 mmol) of **19** and 13 mg (0.12 mmol) of **3** in 1 cm³ of methanol was kept at 5 °C (refrigerator) for 3 d, giving 17 mg (70%) of **C**, 4 mg (15%) of **D**, and a small amount of **4**.

Compound C, Schiff Base of 1-Formylphenoxazine (18): Orange needles; mp 158—160 °C (from benzene); UV $\lambda_{\max}$ (MeOH) 227 (log ϵ 4.56), 279 (4.07), 327 (4.03), 344^{sh} (3.98), 363^{sh} (3.82), and 430 nm (3.88), (MeOH+6 M NaOH) 226 (log ϵ 4.63), 275 (4.17), 315 (3.84), and 407 nm (4.00); IR (KBr) 3470 (NH) and 1615 cm⁻¹ (C=N); ¹H NMR (270 MHz) δ =9.78 (1H, br, OH), 8.50 (1H, s, HC=N), 7.20 (1H, td, *J*=8.0 and 1.7 Hz, H-4'), 7.07 (1H, dd, *J*=8.0 and 1.7 Hz, H-6'), 7.03 (1H, dd, *J*=8.0 and 1.7 Hz, H-3'), 6.95 (1H, td, *J*=8.0 and 1.7 Hz, H-5'), 6.88 (1H, dd, *J*=7.5 and 2.1 Hz, H-2), 6.72 (1H, td, *J*=7.5 and 2.0 Hz, H-8), 6.64 (4H, m, H-3,4,7,9), 6.40 (1H, dd, *J*=7.5 and 2.0 Hz, H-6), and 6.05 (1H, br, NH); ¹³C NMR (67.8 MHz) δ (off resonance)=162.7 (d, HC=N), 150.1 (s), 144.1 (s), 143.8 (s), 137.4 (s), 134.5 (s), 130.0 (s), 128.2 (d), 127.9 (d), 123.9 (d), 122.4 (d), 120.9 (d), 119.5 (d), 117.6 (d), 117.2 (d), 117.1 (s), 115.6 (d), 115.2 (d), and 114.3 (d).

Found: *m/z* 302.1090. Calcd for C₁₉H₁₄N₂O₂: M, 302.1054.

Hydrolysis of C: To a solution of **C** (20 mg, 0.07 mmol) in methanol (2 cm³) was added a trace of dil sulfuric acid. Then, the mixture, which instantly became deep purple red and then discolored after 10—20 seconds, was evaporated in vacuo. The residue was neutralized with aq NaHCO₃ and extracted with benzene.

The extracts were combined, dried (Na₂SO₄) and evaporated in vacuo. The residue was chromatographed on silica gel thin-layer plates with benzene as the eluent, followed by recrystallization from benzene, giving **B** and **3** in almost quantitative yields.

Compound D, 10-(*o*-Hydroxyanilino)cyclohepta[*b*][1,4]-benzoxazine (15): Reddish brown needles (from MeOH); mp 135—138 °C (decomp); UV $\lambda_{\max}$ (MeOH) 233 (log ϵ 4.30), 265 (4.34), 311^{sh} (3.99), and 467 nm (4.08), (MeOH+6 M HCl) 220 (log ϵ 4.34), 265 (4.35), 273 (4.36), 303 (4.08), 451^{sh} (3.91), and 499 nm (3.91); IR (KBr) 3350 (OH), 3250 (NH), and 1600 cm⁻¹ (C=N); ¹H NMR (270 MHz) δ =9.86 (1H, br, OH), 8.58 (1H, br, NH), 7.24 (1H, dd, *J*=7.5 and 1.6 Hz, H-6'), 7.06 (1H, td, *J*=8 and 2 Hz, H-3'), 6.86 (1H, td, *J*=8 and 2 Hz, H-5'), 6.79 (3H, m, H-1,2,3), 6.53 (1H, m, *J*=8 and 2 Hz, H-4), 6.34 (2H, m, H-6,9), and 6.14 (2H, m, H-7,8).

Found: *m/z* 302.1080. Calcd for C₁₉H₁₄N₂O₂: M, 302.1054.

Conversion of D into A: a) A solution of 2 mg of **D** in 2 cm³ of methanol was allowed to stand for 2 d at room temp.

After removing the solvent in vacuo, the residue was recrystallized from hexane, giving **A** in an almost quantitative yield.

b) A solution of 1 mg of **D** in 2 cm³ of methanol containing a drop of 6 M NaOH was allowed to stand for 3 h at room temp. After removal of the solvent in vacuo, the residue was chromatographed in a column of silica gel with benzene as the eluent, giving **A**.

Compound H², 4-Formylphenoxazine (24): Yellow needles (from MeOH); mp 186—187 °C (decomp); UV $\lambda_{\max}$ (MeOH) 228 (log ϵ 4.53), 236^{sh} (4.44), 276 (3.90), 313 (3.81), and 416 nm (3.43), (MeOH+6 M HCl) 236 (log ϵ 4.57), and 318 nm (3.94); IR (KBr) 3260 (NH), 2840, 2780, and 1675 cm⁻¹ (CHO); ¹H NMR (270 MHz, acetone-*d*₆) δ =10.36 (1H, s, CHO), 7.61 (1H, br, NH), 7.02 (1H, dd, *J*=8 and 2 Hz, H-3), 6.81 (1H, t, *J*=8 Hz, H-2), 6.76 (2H, m, H-7,9), 6.71 (1H, dd, *J*=8 and 2 Hz, H-1), 6.27 (1H, td, *J*=8 and 2 Hz, H-8), and 6.54 (1H, dd, *J*=8 and 2 Hz, H-6); ¹³C NMR (67.8 MHz, acetone-*d*₆) δ (off resonance)=188.2 (d, CHO), 147.6 (s), 143.3 (s), 134.3 (s), 132.7 (s), 125.4 (d), 124.3 (d), 121.9 (d), 118.8 (d), 118.7 (d), 116.4 (d), and 114.5 (d).

Found: *m/z* 211.0658. Calcd for C₁₃H₉NO₂: M, 211.0633.

Compound H³, 4-Formylphenoxazine Hemiacetal (24a): To a solution of compound **X** (1 mg) in methanol (0.5 cm³) was added a trace of dil sulfuric acid. After 10 min at room temp, the solution was found to be a mixture of **3** (RT, 6 min), **H**² (RT, 11 min), and **H**³ (RT, 9.8 min) by means of reversed-phase HPLC and UV absorptions. The compound isolated from peak **H**³ showed the same RT (11 min by repeated HPLC) and MS (*M*⁺, 211) as those of **24**.

Compound X, Schiff Base of 4-Formylphenoxazine (25): Yellow needles; mp 210—211 °C decomp (from MeOH); UV $\lambda_{\max}$ (MeOH) 230 (log ϵ 4.73), 285 (4.14), 324 (4.11), 353^{sh} (4.05), and 425 nm (3.44), (MeOH+6 M NaOH) 230 (log ϵ 4.76), 271 (4.23), 315^{sh} (3.98), and 399 nm (3.88); IR (KBr) 3350 (NH) and 1618 cm⁻¹ (C=N); ¹H NMR (270 MHz) δ =9.05 (1H, s, HC=N), 7.48 (1H, dd, *J*=8 and 2 Hz, H-3), 7.34 (1H, dd, *J*=8 and 2 Hz, H-6'), 7.21 (1H, td, *J*=8 and 2 Hz, H-4'), 7.01 (1H, dd, *J*=8 and 2 Hz, H-3'), 6.93 (1H, td, *J*=8 and 2 Hz, H-5'), 6.82 (1H, t, *J*=8 Hz, H-2), 6.74—6.82 (2H, m, H-7,9), 6.71 (1H, td, *J*=8 and 2 Hz, H-8), 6.48 (1H, dd, *J*=8 and 2 Hz, H-1), 6.43 (1H, dd, *J*=8 and 2 Hz, H-6), and 5.26 (1H, br, NH); (100 MHz, DMSO-*d*₆) δ =8.85, 8.75, and 8.27 (3H, s, NH, OH, and HC=N, respectively), 7.37 (1H, dd, *J*=8.0 and 2.0 Hz, H-3), 6.4—7.4 (10H, m, others).

Found: *m/z* 302.1041. Calcd for C₁₉H₁₄N₂O₂: M, 302.1054.

Hydrolysis of X: Similar procedures for compound **C** were followed. Thus, 50 mg (0.17 mmol) of compound **X** in 5 cm³ of methanol gave **3** and 33 mg (94%) of **H**².

Reaction of 19 with *p*-Anisidine (26). a) **At Room Temperature:** A solution of 50 mg (0.18 mmol) of **19** and 30 mg (0.28 mmol) of **26** in 2 cm³ of methanol was stirred for 1 d at room temp. After removal of the solvent, the residue was chromatographed in a column of silica gel with benzene-methanol (50:1) as the eluent, giving 11 mg (20%) of **28** and 25 mg (65%) of **H**², along with a small amount of ring-opened compound **4**.

b) **At 50 °C:** A solution of 42 mg (0.15 mmol) of **19** and 28 mg (0.23 mmol) of **26** in 2 cm³ of methanol was heated at 50 °C for 3 h, followed by the same work-up procedures as above, giving 35 mg (57%) of **28**, 12 mg (38%) of **H**², and a small amount of **4**.

c) At 120 °C: The procedures similar to those at 50 °C were employed. Thus, 30 mg (0.11 mmol) of **19** and 20 mg (0.18 mmol) of **26** were heated in 2 cm³ of methanol at 120 °C for 1 h, giving 26 mg (75%) of **28**, 4 mg (15%) of **H²**, and a small amount of **4**.

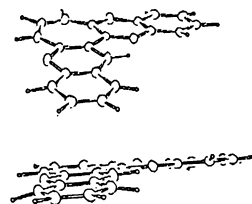
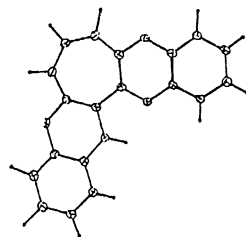
6-(p-Methoxyanilino)cyclohepta[b][1,4]benzoxazine (28): Reddish brown needles (from methanol); mp >300 °C (decomp); UV λ_{max} (MeOH) 234, 268, 300, and 428 nm, (MeOH+6 M NaOH) 238, 304, 451, 480^{sh}, and 630 nm; ¹H NMR (270 MHz, CD₃OD) δ =7.23 (2H, m, H-2',6'), 7.08 (2H, m, H-3', 5'), 6.98—7.20 (3H, m, H-8,9,10), 6.85—6.95 (3H, m, H-1,2,3), 6.38 (1H, m, H-7), 6.61 (1H, m, H-4), and 3.85 (3H, s, OCH₃).

Found: m/z 316.1217. Calcd for C₂₀H₁₆N₂O₂: M, 316.1211.

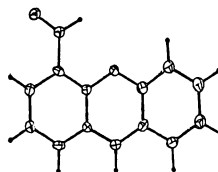
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