# Cyclohepta[*b*][1,4]benzoxazines 3.[1] The Reaction of 6-Bromocyclohepta[*b*][1,4]benzoxazine with *o*-Aminophenol[2]

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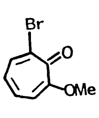
The reaction of 6-bromocyclohepta[*b*][1,4]benzoxazine (**19**) and *o*-aminophenol (**3**) was studied and compared with that of 3-bromo-2-methoxytropone (**2**) with **3**. 14H-[1,4]Benzoxazino[3′,2′:3,4]cyclohepta[1,2-*b*]-[1,4]benzoxazine, 10-(*o*-hydroxyanilino)cyclohepta[*b*][1,4]benzoxazine (**D**), 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 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** (**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.



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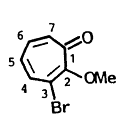

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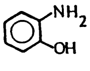

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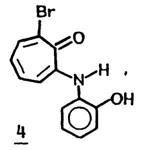

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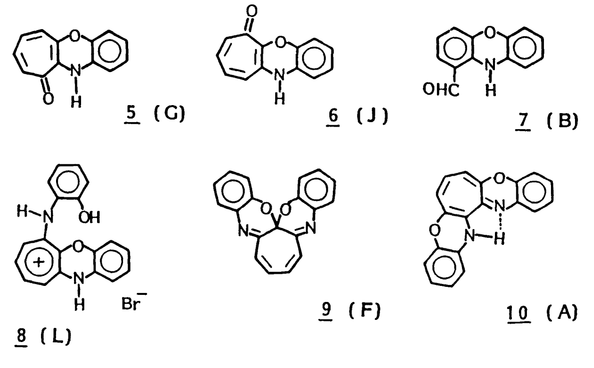


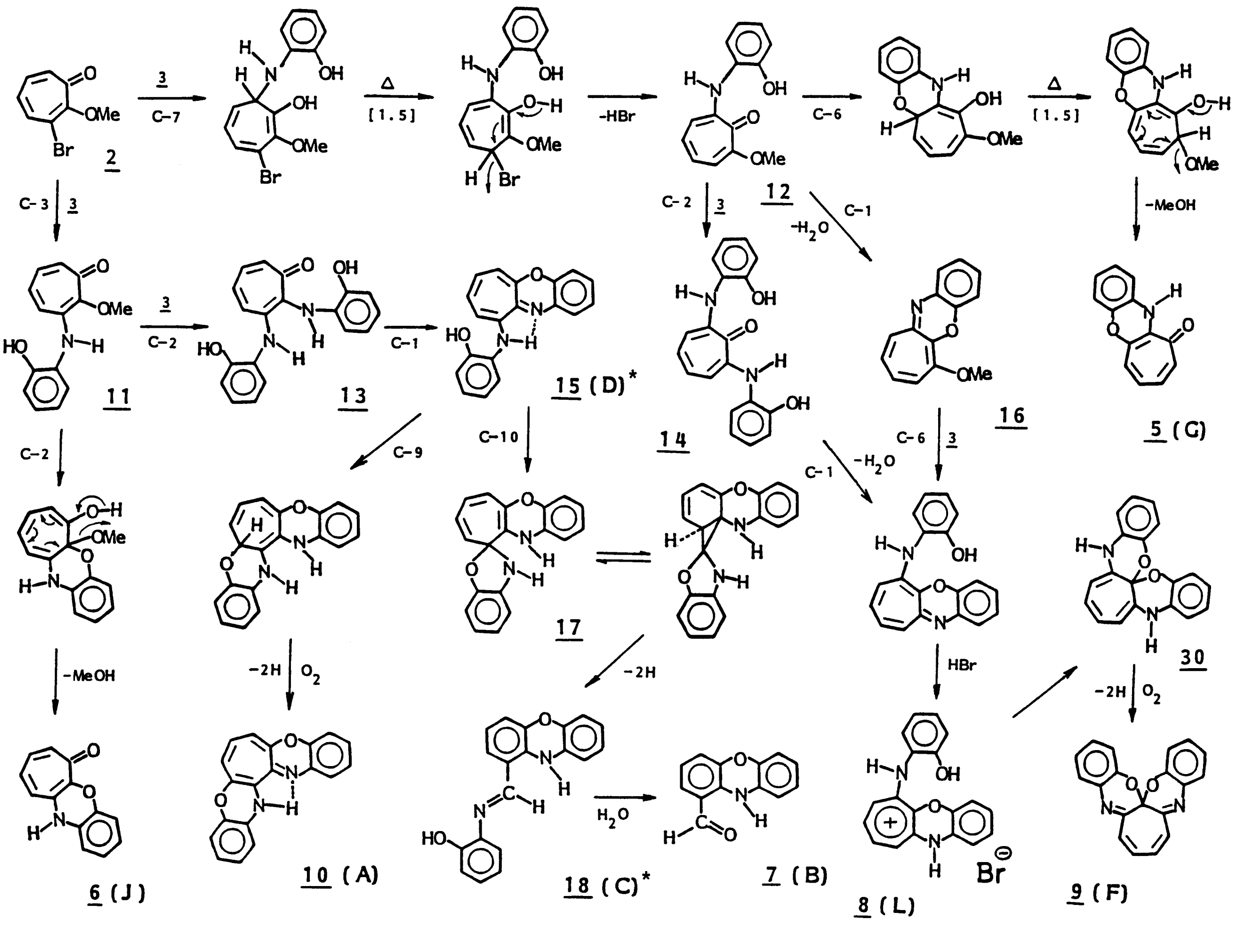
Chart 1.

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 method[5] and by theoretical calculations of their CD spectral data.[6]

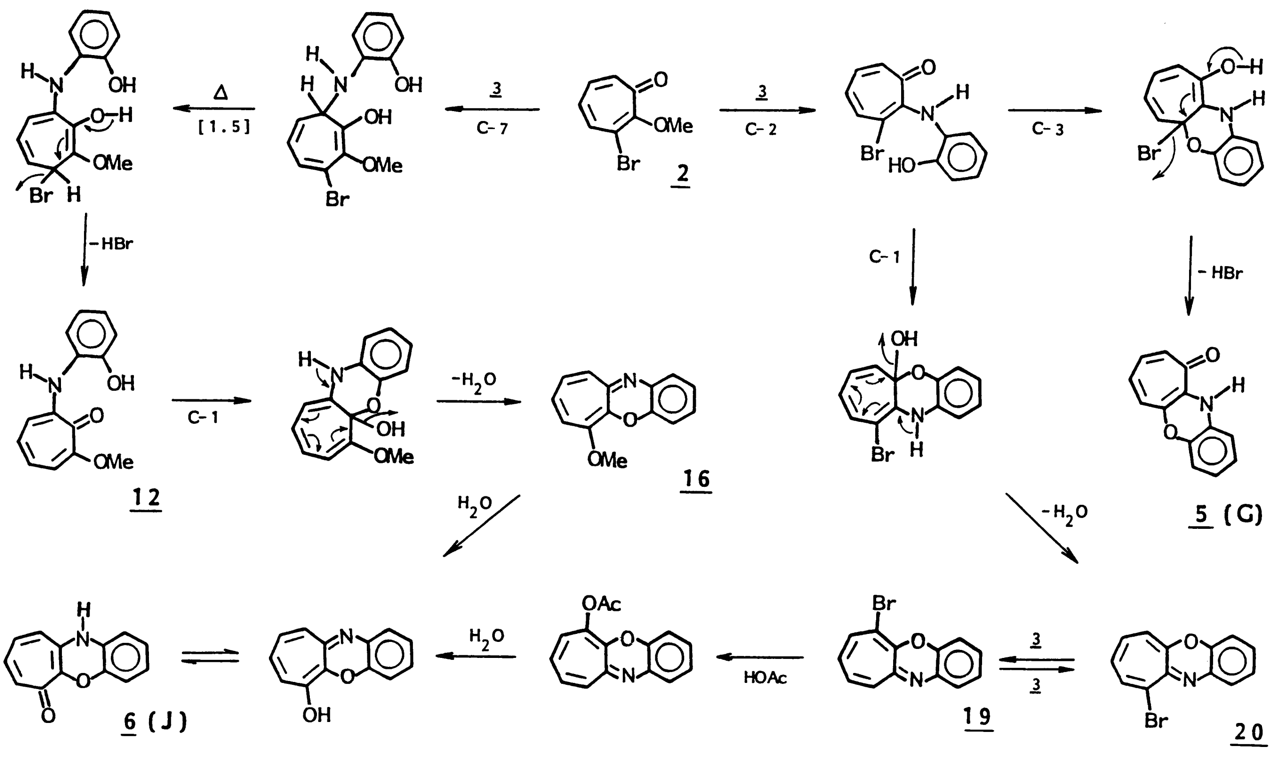
It has generally been recognized that the course of various reactions of troponoids are often extremely sensitive towards a slight structural difference of both substrates and reagents, as well as the reaction conditions employed (solvent and concentration, temperature, and with or without catalyst, 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 found[8] 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]-



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-pressured 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 thougth 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′ singal pattern of the four protons on the seven-membered ring in the $^1$H 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

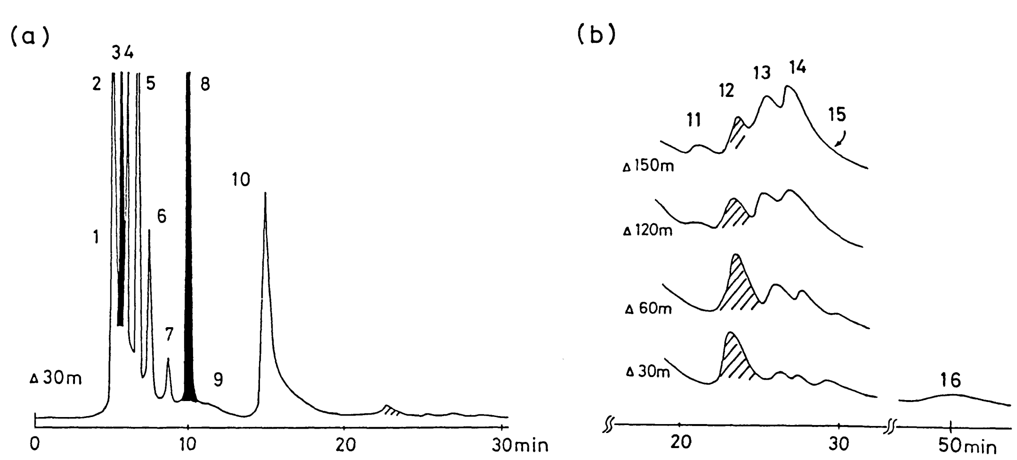
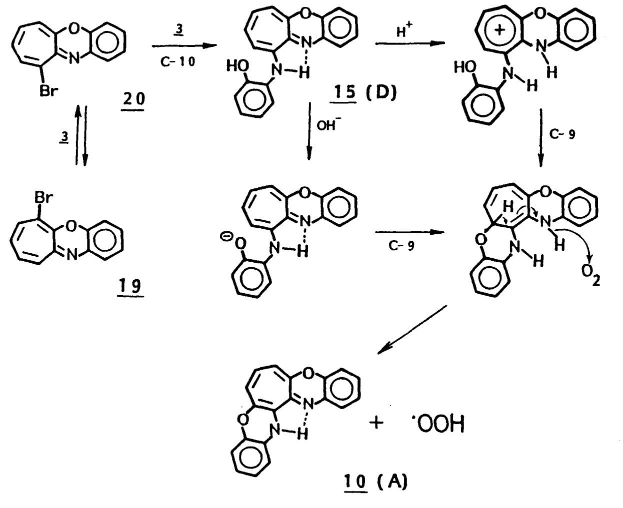


Fig. 1. Time-dependent HPLC chromatograms of the reaction of **2** and **3** in AcOH at 120°C for 30 minutes.



Scheme 3.

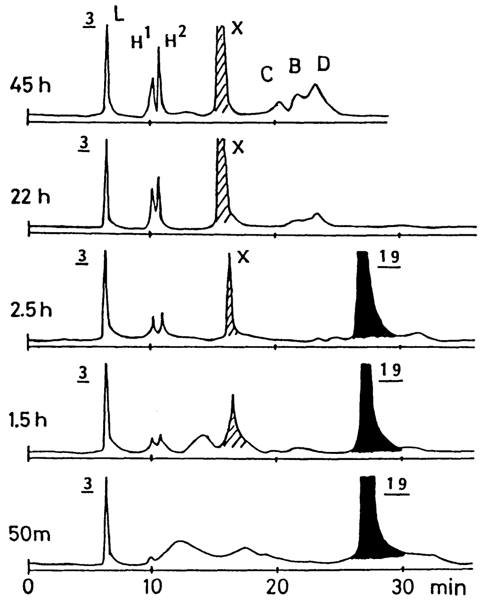


Fig. 2. Time-dependent HPLC chromatograms of the reaction of **19** and **3** in MeOH at room temp in the presence of DABCO.

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**) 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 $^1$H NMR (DMSO-$d_6$) signals at $\delta$ 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 $^1$H NMR (acetone-$d_6$) signals at $\delta$ 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$^{12)}$ indicate that compound **H**$^2$ is 4-formylphenoxazine (**24**), an isomer of **7** (**B**). Compound **H**$^3$ [UV $\lambda_{\max}$ (MeOH) 236 and 318 nm] was partly produced from **24** [UV $\lambda_{\max}$ (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 aicd (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.

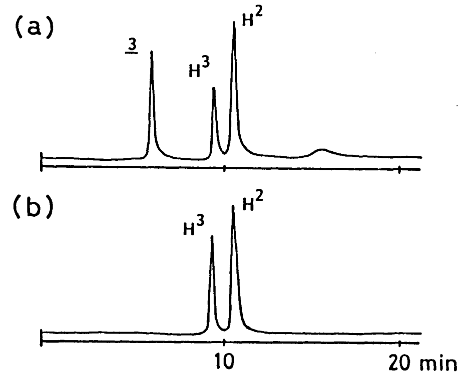
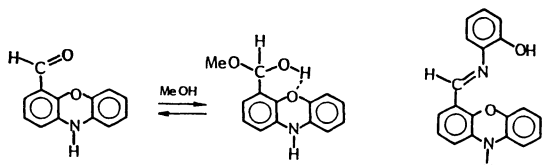


Fig. 3. (a) HPLC chromatograms of compound **X** in MeOH containing a trace amount of dil sulfuric acid. (b) HPLC chromatograms of compound **H**$^2$ in MeOH containing a trace amount of dil sulfuric acid.



24 (H$^2$) 24a (H$^3$) 25 (X)

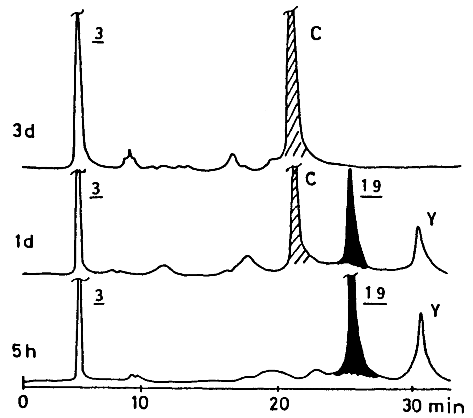
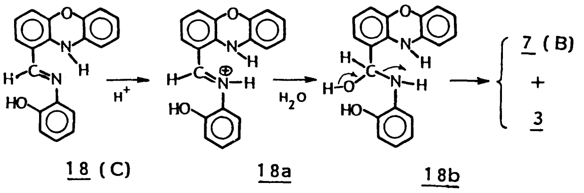


Fig. 4. Time-dependent HPLC chromatograms of the reaction of **19** and **3** in MeOH at 5 °C.

**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 $^{1}$H NMR spectrum consisted of a proton signal of the benzene ring adjacent to the C=N group ($\delta$ 6.88, dd, $J$=8 and 2 Hz) and the signals at $\delta$ 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 $^{1}$H NMR signals was made by using a decoupling technique; the result is described in the Experimental section.

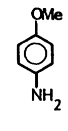
When this reaction of **19** with **3** is studied using greater amounts for preparative purposes, we obtained about 70% yield of **18** (**C**), besides a 20% yield of **15** (**D**) and a trace amount of the ring-opened product **4**.[3] It is noted that the yields of **15** and **18** highyl depend 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 soltion 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 it[13] to be a 10-bromo compound **20** produced by an unpercedented intermolecular 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.



Scheme 4.

From its structure, we first considered[2] 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% fo **24** and some anilinotropone **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-



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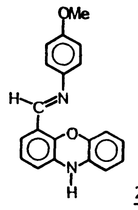

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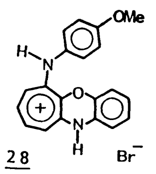

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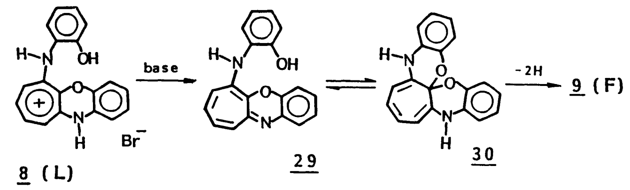
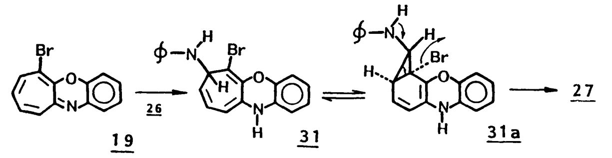


Scheme 5.

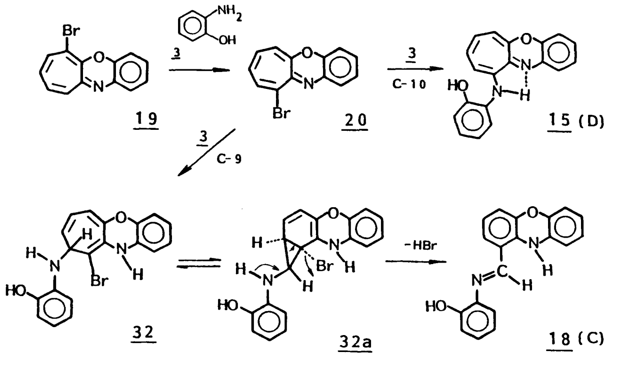
brown solid by neutralizing the salt **8**. However, it was very unstable in open air and was easily dehydrogenated to give stable dehydro acetal **9** (**F**) via acetal **30** (Scheme 5).

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 speculated[4)] that the spiroxazole intermediate **17** produced from **15** by ring closue 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 reaction[13)] 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 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.



Scheme 6.



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 $^1$H NMR spectra were measured in $CDCl_3$ (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 empoloying 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 cm$^3$ 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 cm$^3$ 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 cm$^3$ 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 cm$^3$ 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 cm$^3$ 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 cm$^3$ 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 soluion of 22 mg (0.08 mmol) of **19** and 13 mg (0.12 mmol) of **3** in 1 cm$^3$ 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 $\varepsilon$ 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 $\varepsilon$ 4.63), 275 (4.17), 315 (3.84), and 407 nm (4.00); IR (KBr) 3470 (NH) and 1615 cm$^{-1}$ (C=N); $^1$H NMR (270 MHz) $\delta$=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); $^{13}$C NMR (67.8 MHz) $\delta$ (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 $C_{19}H_{14}N_2O_2$: M, 302.1054.

**Hydrolysis of C:** To a solution of **C** (20 mg, 0.07 mmol) in methanol (2 cm$^3$) 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 $NaHCO_3$ and extrated with benzene.

The extracts were combined, dried ($Na_2SO_4$) and evaporated in vacuo. The residue was chromatogrphed 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)cyclohepata[*b*][1,4]-benzoxazine (15):** Reddish brown needles (from MeOH); mp 135—138 °C (decomp); UV$\lambda_{max}$ (MeOH) 233 (log $\varepsilon$ 4.30), 265 (4.34), $311^{sh}$ (3.99), and 467 nm (4.08), (MeOH+6 M HCl) 220 (log $\varepsilon$ 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); $^1$H NMR (270 MHz) $\delta$=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 $C_{19}H_{14}N_2O_2$: M, 302.1054.

**Conversion of D into A:** a) A solution of 2 mg of **D** in 2 cm$^3$ 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 cm$^3$ 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 H$^2$, 4-Formylphenoxazine (24):** Yellow needles (from MeOH); mp 186—187 °C (decomp); UV $\lambda_{max}$ (MeOH) 228 (log $\varepsilon$ 4.53), $236^{sh}$ (4.44), 276 (3.90), 313 (3.81), and 416 nm (3.43), (MeOH+6 M HCl) 236 (log $\varepsilon$ 4.57), and 318 nm (3.94); IR (KBr) 3260 (NH), 2840, 2780, and 1675 cm$^{-1}$ (CHO); $^1$H NMR (270 MHz, acetone-$d_6$) $\delta$=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); $^{13}$C NMR (67.8 MHz, acetone-$d_6$) $\delta$ (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 $C_{13}H_9NO_2$: M, 211.0633.

**Compound H$^3$, 4-Formylphenoxazine Hemiacetal (24a):** To a solution of compound **X** (1 mg) in methanol (0.5 cm$^3$) 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 $\varepsilon$ 4.73), 285 (4.14), 324 (4.11), $353^{sh}$ (4.05), and 425 nm (3.44), (MeOH+6 M NaOH) 230 (log $\varepsilon$ 4.76), 271 (4.23), $315^{sh}$ (3.98), and 399 nm (3.88); IR (KBr) 3350 (NH) and 1618 cm$^{-1}$ (C=N); $^1$H NMR (270 MHz) $\delta$=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-$d_6$) $\delta$=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 $C_{19}H_{14}N_2O_2$: M, 302.1054.

**Hydrolysis of X:** Similar procedures for compound **C** were followed. Thus, 50 mg (0.17 mmol) of compound **X** in 5 cm$^3$ 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 cm$^3$ 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 cm$^3$ 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 cm$^3$ of methanol at 120 °C for 1 h, giving 26 mg (75%) of **28**, 4 mg (15%) of $\mathbf{H}^2$, 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 $\lambda_{max}$(MeOH) 234, 268, 300, and 428 nm, (MeOH+6 M NaOH) 238, 304, 451, 480$^{sh}$, and 630 nm; $^1$H NMR (270 MHz, $CD_3OD$) $\delta$=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, $OCH_3$).

Found: *m/z* 316.1217. Calcd for $C_{20}H_{16}N_2O_2$: M, 316.1211.

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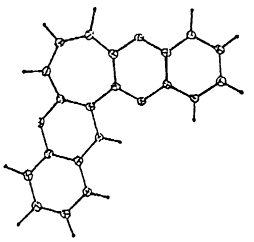
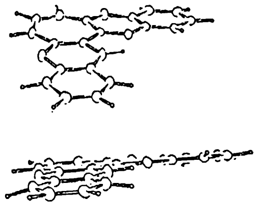
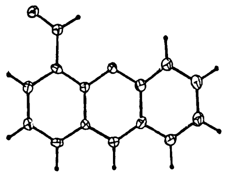
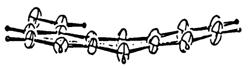
11) Recently, structure **10** for Comound **A** was confirmed by X-ray crystallographic analysis and the results will be reported elsewhere by Prof. Y. Iitaka and Mrs. H. Nakamura, Department of Pharmaceutical Sciences, Tokyo University.





12) The X-ray crystallographic analysis of Compound **24** by Prof. Y. Iitaka and Mrs. H. Nakamura (to be published):





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