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Novel Intermolecular Heterocycle Exchange Reaction of Cyclohepta[b][1,4]benzoxazines with o-Aminophenol Derivatives[1)]

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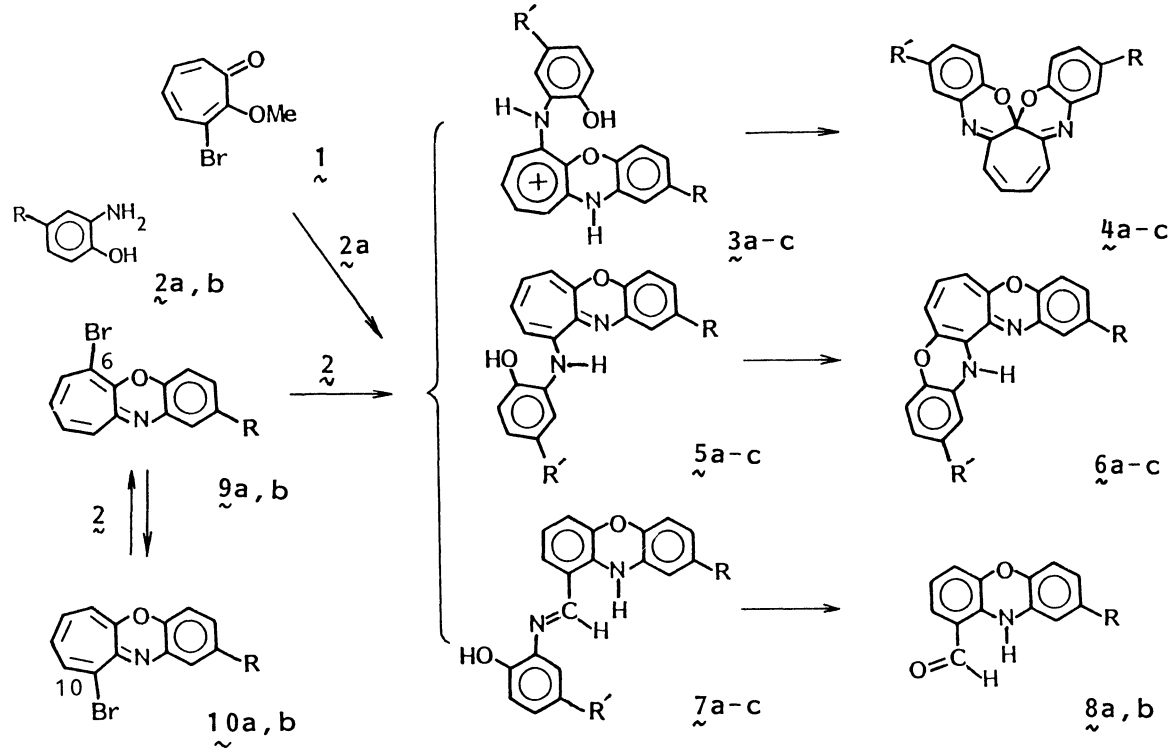
The benzoxazine moiety of 7-, 8-, and 9-isopropyl- as well as 6-bromocyclohepta[b][1,4]benzoxazines was easily exchanged with o-aminophenol and its methyl derivatives in methanol or acetic acid. A possible pathway of this novel intermolecular heterocycle exchange reaction is discussed.

Previously we reported[2)] that 3-bromo-2-methoxytropone (1) and an excess of o-aminophenol (2a) in refluxing acetic acid afforded various 1:2-condensation products: 6-(o-hydroxyanilino)- (3a as HBr salt), 10-(o-hydroxyanilino)cyclohepta-[b][1,4]benzoxazine (5a), their respective dehydrocyclized products 4a and 6a, and the Schiff base 7a of 1-formylphenoxazine (8a)(Scheme 1). We later found[3)] that these compounds can be prepared more easily by the reaction of 2a with 6-bromo-cyclohepta[b][1,4]benzoxazine (9a), which is now known to be in equilibrium with the former in the presence of 2a.

To examine generality of such complex reactions, the condensation of 9a with 2-amino-4-methylphenol (2b) has now been studied by checking with a timedependent, reversed phase HPLC, which showed the formation of as many as 30 products. Surprisingly we found by HPLC and mass spectra that dimethyl derivatives, 3c,[4)] 4c,[3)] 5c,[5)] 6c,[3)] and 7c,[6)] and also their respective parent compounds[2)] without methyl group (3a, 4a, 5a, 6a, and 7a) were produced besides the expected monomethyl derivatives (3b, 4b, 5b, 6b, and 7b). This experimental evidence strongly

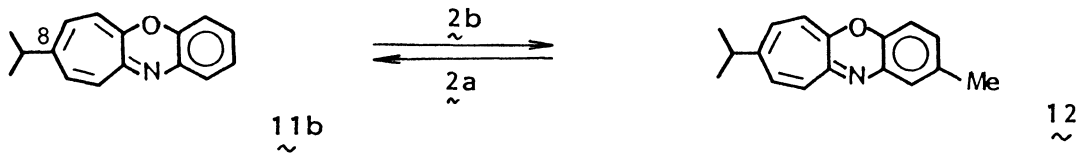
suggested that a certain kind of interconversion between the substrate and the reagent must have been taking place to form isomeric 10-bromo compounds 10 as an intermediate (Scheme 1).



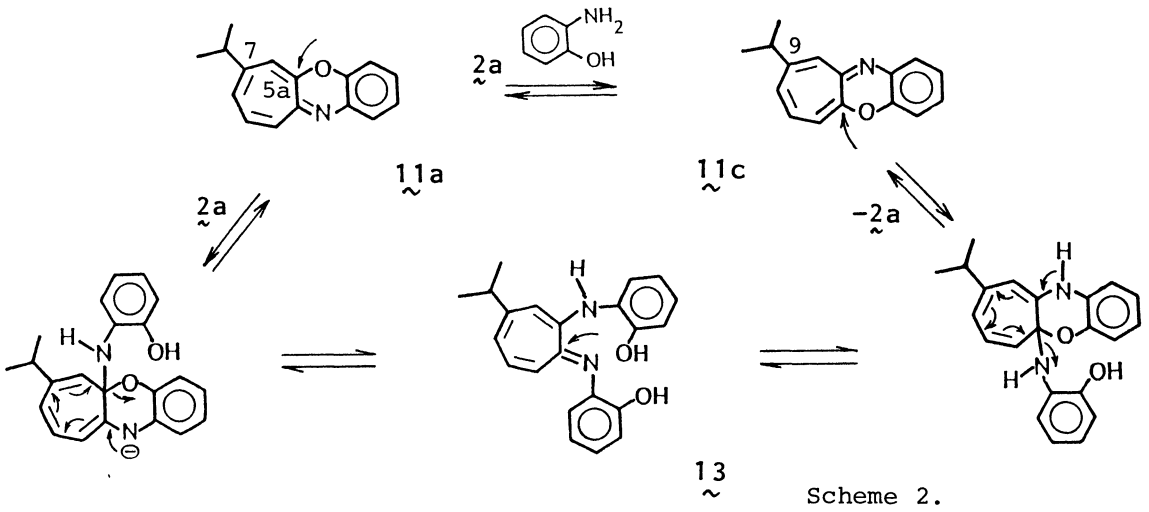
a: R=R'=H, b: R=Me, R'=H and R=H, R'=Me, c: R=R'=Me

Scheme 1.

To elucidate the reaction pathway, we first examined the reaction of 7-, 8-, and 9-isopropyl derivatives 11a-c[7] with 2a and 2b. When a methanolic solution of 8-isopropyl compound 11b and 2b was allowed to stand at room temperature, an additional peak due to the methyl-containing product 12 (by MS) began to appear in the HPLC chromatogram and an equilibrium reached within a few hours.



The unsymmetrically substituted 11a and 11c gave a mixture of an equal proportion of both compounds even if either of 11a and 11c was used as the starting material. This can be explained in terms of the cyclic equilibrium, involving the ring-opened 2-aminotroponeimine intermediate 13 formed by the nucleophilic attack of the amino group of 2a at the most reactive C-5a[8] position



Scheme 2.

of 11a or 11c (Scheme 2).

We then found that the heterocycle exchange reaction of 6-bromo compound 9a with 2a in methanol proceeded much faster than the bromine substitution, and the isomerized 10-bromo compound 10a was isolated in a pure crystalline form.[9] From the evidence that the reaction of 9a and 10a with p-toluidine (or p-anisidine) gave only the crresponding, nomal subustitution products, we concluded that 5 and 6 were the normal substitution products of 10 with 2, and not cine substitution products of 9, as had been presumed earlier.[2] It was also proved that the Schiff base 7 was produced by the nucleophilic attack of 2 at position 9 of 10a, while the Schiff base of 4-formylphenoxazine (14)[10] was predominantly isolated in the presence of DABCO. This is apparently because the heterocyclic exchange reaction is suppressed by the base to a considerable extent.

References

1) Part of the results has been presented: T. Nozoe, H. Okai, H. Wakabayashi, K. Shindo, and S. Ishikawa, 14th Japanese Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, Okayama, October 1981, Abstr. 1X11; 15th Symposium, Kyoto, 1982, Abstr. 4I07; 47th National Meeting of the Chemical Society of Japan, Kyoto, April 1983, Abstr. 1C17; 5th International Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, St Andrews, U.K., September 1985.

2) T. Someya, H. Okai, H. Wakabayashi, and T. Nozoe, Bull. Chem. Soc. Jpn., 56, 2756 (1983).

3) T. Nozoe, H. Okai, H. Wakabayashi, and S. Ishikawa, Chem. Lett., 1984, 1145.

4) 3c: Brown needles (from MeOH); mp >300 °C; UV λmax (MeOH) 228, 268, 277, 311, 335,sh and 438 nm (log ε 4.22, 4.20, 4.21, 3.97, 3.86, and 3.92); (MeOH + 3 M NaOH) 282, 306, 466, and 497sh nm (log ε 4.22, 3.99, 4.00, and 3.90); IR(KBr) 3375 cm^{-1}(OH); ^1H NMR(270 MHz, CD_3OD) δ =7.09 (1H, dd, J=8 and 2 Hz, H-4'), 7.01 (1H, d, J=2 Hz, H-6'), 6.87 (1H, d, J=8 Hz, H-3'), 6.78 (1H, d, J=8 Hz, H-4),

6.8-7.2 (4H, m, H-7,8,9,10), 6.65 (1H, dd, J=8 and 2 Hz, H-3), 6.43 (1H, d, J=2 Hz, H-1), 2.29 (3H, s, Me), and 2.17 (3H, s, Me); Found: M^+, 330.1361. Calcd for $C_{21}H_{18}N_2O_2$: M, 330.1367.

5) 5c: Red brown needles (from MeOH); mp 206-208 °C (decomp.); UV λ max (MeOH) 237, 272, 310, and 474 nm (log ε 4.40, 4.40, 4.09, and 4.12); (MeOH + 3 M HCl) 272, 280, 306, 450, and 505 nm (log ε 4.43, 4.46, 4.12, 3.95, and 3.93); IR(KBr) 3400 cm^{-1}(OH); ^1H NMR(270 MHz, $CDCl_3$) δ =7.01 (1H, dd, J=8 and 2 Hz, H-4'), 6.93 (1H, d, J=8 Hz, H-3'), 6.90 (1H, d, J=2 Hz, H-6'), 6.61 (1H, d, J=2 Hz, H-1), 6.55 (1H, dd, J=8 and 2 Hz, H-3), 6.33 (1H, d, J=8 Hz, H-4), 5.85-6.10 (4H, m, H-6,7,8,9), 2.29 (3H, s, Me), and 2.14 (3H, s, Me); Found: M^+, 330.1366. Calcd for $C_{21}H_{18}N_2O_2$: M, 330.1367.

6) 7c: Orange needles (from benzene); mp 166-167 °C (decomp.); UV λ max (MeOH) 230, 283, 330, 352, 372, and 437 nm (log ε 4.57, 4.03, 3.95, 3.91, 3.80, and 3.84); (MeOH + 3 M NaOH) 230, 282, 316, and 417 nm (log ε 4.61, 4.11, 3.80, and 3.97); IR(KBr) 3470 (OH), 3220 (NH), and 1658 cm^{-1}(C=N); ^1H NMR(270 MHz, $CDCl_3$) δ =9.78 (1H, br, OH), 8.49 (1H, s, HC=N), 7.00 (1H, dd, J=8 and 2 Hz, H-7), 6.91 (1H, d, J=8 Hz, H-6), 6.89 (1H, d, J=2 Hz, H-9), 6.87 (1H, dd, J=8 and 2 Hz, H-2), 6.64 (1H, dd, J=8 and 2 Hz, H-4), 6.61 (1H, t, J=8 Hz, H-3), 6.51(1H, d, J=8 Hz, H-3'), 6.45 (1H, dd, J=8 and 2 Hz, H-4'), 6.23 (1H, d, J=2 Hz, H-6'), 5.92 (1H, br, NH), 2.32 (3H, s, Me), and 2.13 (3H, s, Me); Found: M^+, 330.1359. Calcd for $C_{21}H_{18}N_2O_2$: M, 330.1367.

7) T. Nozoe and T. Someya, Bull. Chem. Soc. Jpn., 51, 3316 (1978).

8) Reaction indexes (f_r^N) for nucleophilic reactions of parent compound of 11 by the HMO method: C-1 (0.001), C-2 (0.005), C-3 (0.000), C-4 (0.004), C-4a (0.002), C-5 (0.029), C-5a (0.558), C-6 (0.046), C-7 (0.414), C-8 (0.276), C-9 (0.151), C-10 (0.509), C-10a (0.002), C-11 (0.000), and C-11a (0.003).

9) 10a: Brown needles (from benzene); mp 76-77 °C; UV λ max (MeOH) 261, 269, 300,^{sh} 396, 415, 443,^{sh} and 490 nm (log ε 4.33, 4.33, 4.29, 3.85, 3.98, 3.77, and 3.14); (MeOH + 3 M HCl) 224, 260,^{sh} 268, 288, 323, 438, and 460 nm (log ε 4.33, 4.21, 4.25, 4.08, 3.90, 3.89, and 3.84); IR(KBr) 1622 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ =7.17 (1H, dd, J=8.8 and 1.1 Hz, H-9), 6.43-7.05 (4H, m, H-1,2,3,4), 6.11 (1H, ddd, J=10.8, 9.3, and 1.0 Hz, H-7), 5.62 (1H, ddd, J=10.8, 8.8, and 1.0 Hz, H-8), and 5.53 (1H, dd, J=9.3 and 1.0 Hz, H-6); ($CDCl_3$ + CF_3COOD) δ =8.15 (1H, dd, J=10.3 and 1.5 Hz, H-9), 7.46 (1H, ddd, J=10.7, 9.7, and 1.5 Hz, H-7), and 6.66-7.07 (6H, m, others); Found: M^+, 272.9784 and 274.9779 (1:1). Calcd for $C_{13}H_8NOBr$: M, 272.9789 and 274.9769.

10) 14: yellow needles (from MeOH); mp 186-187 °C (decomp.); UV λ max (MeOH) 228, 236,^{sh} 276, 313, and 416 nm (log ε 4.53, 4.44, 3.90, 3.81, and 3.43); IR(KBr) 3260 (NH), 2880, 2780, 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 6.45 (1H, dd, J=8 and 2 Hz, H-6); Found: M^+, 211.0658. Calcd for $C_{13}H_9NO_2$: M, 211.0633.

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