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A NOVEL SYNTHESIS OF CYCLOHEPTA[2,1-b:2,3-b']DI[1,4]BENZOXAZINES AND 14H[1,4]BENZOXAZINO[3',2':3,4]CYCLOHEPTA[1,2-b][1,4]BENZOXAZINES[1)]

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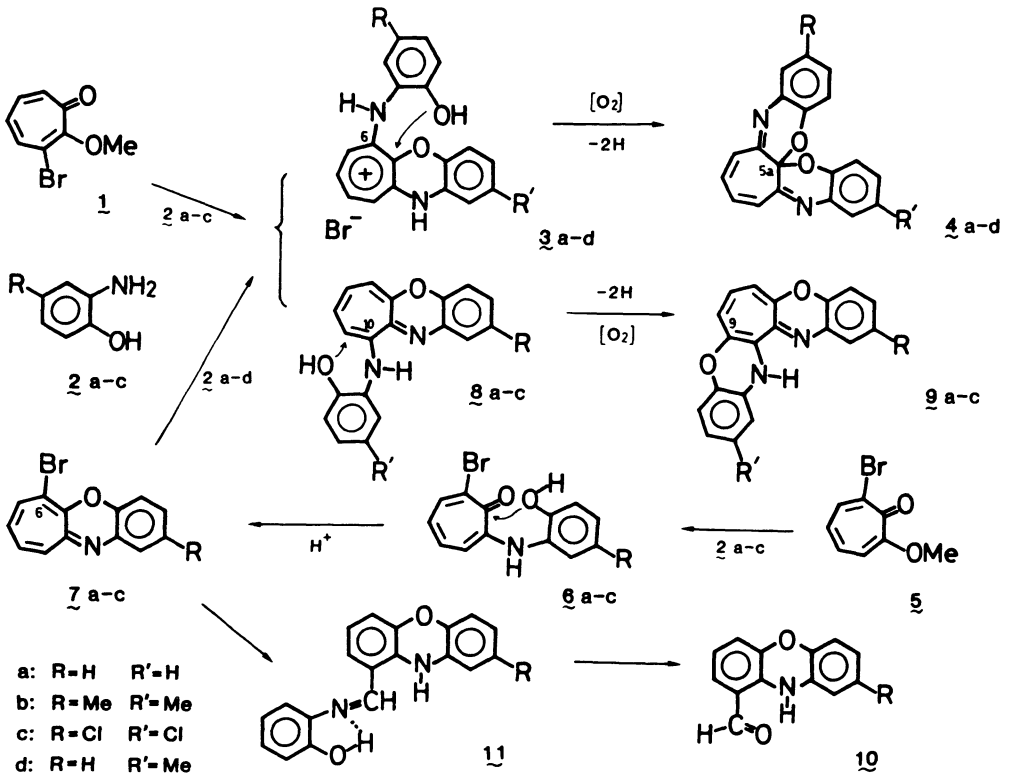
The title compounds, namely, the chiral acetals and their positional isomers were efficiently prepared by heating 6-bromocyclohepta-[b][1,4]benzoxazines and the substituted o-aminophenols at 120 °C in acetic acid.

We recently reported[2)] that the condensation of 3-bromo-2-methoxytropone (1) and o-aminophenol (2a) in refluxing acetic acid gave, besides many kinds of other interesting products, a small amount of 6-(o-hydroxyanilino)cyclohepta[b][1,4]-benzoxazine hydrobromide (3a), which, on exposure to air under weakly basic conditions, yielded a trace amount of an acetal 4a having a spirane-ring. Our keen interest in investigating the chirality of this unique tropoquinonoid compound necessitated to establish a more efficient route for the preparation of 4a and its derivatives, which we now wish to describe in this letter; the results of the studies on the optical resolution, the photochemical racemization of 4a-d, and the determination of the absolute configuration of the dichloro acetals 4c by X-ray diffraction will be reported in the following paper.[3)]

Although the condensation of isomeric 2-bromo-7-methoxytropone (5) with 2a in hot acetic acid had been found to afford a high yield of 2-bromo-7-(o-hydroxyanilino)tropone (6a), which in turn had cyclized to 6-bromocyclohepta[b][1,4]-benzoxazine (7a) in refluxing acetic acid containing a trace of concd sulfuric acid,[4)] it became evident by our recent systematic study that this type of troponoid compounds were extremely sensitive towards the reaction conditions employed, such as kinds of solvent, concentration of reactants, and the temperature of reaction, thus giving rise to a wide variety of different kinds of products with fluctuating yields.[5)] For example, it was found for the above reaction that the use of a larger amount of concd sulfuric acid or prolonged heating caused a disproportionation reaction of 6a to give cyclohepta[b][1,4]benzoxazine (12) and its 6,8-dibromo derivative, and the former (12) gradually decomposed by autoxidation at elevated temperatures, resulting in a lower yield of 7a.[6)]

Thus, when 398 mg of 6a was dissolved in 4 ml of acetic acid containing a trace of concd sulfuric acid and heated under nitrogen at 120 °C for 1.5 h, compound 7a became available constantly in ≈60% yield. Two other derivatives 7b and

7c were likewise prepared as follows: the condensation products 6b[7] and 6c,[8] readily obtained from 5 with the methyl- and chloro-derivatives (2b and 2c) in 90 and 51% yield, respectively, were similarly treated under nitrogen with refluxing acetic acid containing a trace of concd sulfuric acid, giving 7b (61% yield)[9] and 7c (54% yield).[10]

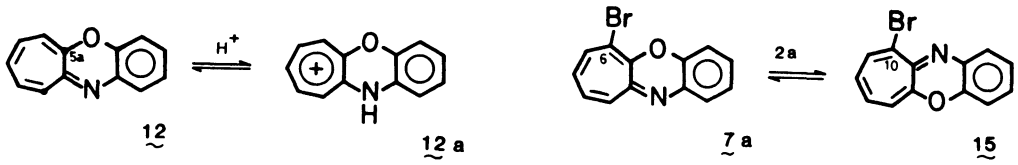


Scheme 1.

Compound 7a was then heated with 2 equiv. of 2a in acetic acid at 120 °C for 2 h. The resultant precipitate was filtered off, slightly basified with sodium hydrogen carbonate in methanol, subjected to air-oxidation by allowing to stand overnight at room temperature, and then purified by silica gel column chromatography with benzene-hexane (20:1) as the eluant. The fastest-eluting fraction afforded 9a (20-30% derived via oxidation of the intermediate 8a),[11] then a mixture of 10[4] and its Schiff base 11 (≈10% combined yield),[11] and finally 4a (48% yield)[4] (with methanol-benzene, 1:20). Similarly, the dimethyl and dichloro derivatives, 4b (56% yield)[12] and 4c (36% yield),[13] were obtained from 7b and 7c, respectively; compounds 9b (30% yield)[14] and 9c (36% yield)[15] were also isolated as side products by these reactions. A combination of 7a and 2b in this condensation reaction caused an exchange of heterocycles,[1] giving rise to a separable mixture of 4a (15% yield), 4b (15% yield), and the monomethyl derivative 4d (35% yield).[16]

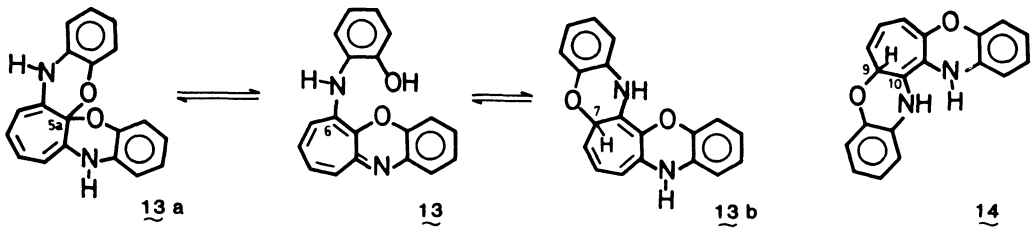
Compound 4a, which can be regarded as an acetal of a 1,2,3-tropoquinonoid derivative,[17] was stable in cold ethanolic 1 M sulfuric acid or 2 M sodium hydroxide but gradually decomposed on standing at ≈20 °C for several days or more rapidly on heating.[6] Our attempts to isolate the free base 13 have failed, becuase of the formation of a mixture of the reversible tautomers 13a,b, which were gradually

oxidized on exposure to air to produce 4a.[1)]



12 12a 7a 15

The other substitution product 8a, which is also unstable on exposure to air to yield 9a via cyclic tautomer 14 (or its isomer), is considered to be formed by the normal substitution of the 10-bromo analogs 15 derived from 7a by the hetero-ring exchange, because an equilibrium between 7a and 15 was found to exist in methanolic acetic acid in the presence of o-aminophenol and the latter (15) was more liable to nucleophilic substitution reaction.[1)]



13a 13 13b 14

The facile cyclization of these intermediates 8 and 13 is apparently owing to a large contribution of the polarized tropylium form 12a to the structure of cyclohepta[b][1,4]benzoxazine (12).

We thank Professor H. Yamamoto (Okayama Univ.) for his helpful discussions.

References

1) T.Nozoe, H.Okai, S.Ishikawa, K.Shindo, and H.Wakabayashi, Presented at 15th Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, Kyoto, 1982 October, Abstr., No. C1-17.

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4) T.Nozoe, T.Someya, and H.Okai, Bull. Chem. Soc. Jpn., 52, 1156 (1979).

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6) H.Wakabayashi, S.Ishikawa, H.Okai, and T.Nozoe, to be published.

7) 6b: Yellow needles; mp 217-218 °C; UV λmax (MeOH) 258, 346, and 418 nm (log ε 4.30, 4.03, and 4.18);(MeOH+ 3 M-NaOH) 238, 346, and 423 nm; IR (KBr) 3260 (NH) and 1590cm^{-1}(C=O); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 8.14 (1H, dd, J=1.0 and 10.3 Hz, H-3), 7.20 (1H, ddd, J=1.0, 9.7,and 10.0 Hz, H-5), 6.78 (1H, d, J=10.0 Hz, H-6), 6.60 (1H, dd, J=9.7 and 10.3 Hz, H-4), 6.9-7.2 (3H, m, H-3',4',6'), 2.31 (3H, s, Me), 8.61 (1H, bs, NH), and 6.22 (1H, s, OH); Found: C, 54.01; H, 3.92; N, 4.44%; M$^+$, 307. Calcd for $C_{14}H_{12}NO_2Br$: C, 54.92; H, 3.95; N, 4.56%; M, 307.

8) 6c: Yellow needles; mp 119-201 °C; UV λmax (MeOH) 257, 346, and 418 nm (log ε 4.26, 3.97, and 4.19);(MeOH+ 3 M-NaOH) 243, 265, 345, 425, and 460 nm (log ε 4.33, 4.21, 3.84, 4.11, and 4.02); IR (KBr) 3260 (NH) and 1580cm^{-1}(C=O); ^{1}H-NMR (270 MHz, DMSO-d_6) δ 8.24 (1H, d, J=10.2 Hz, H-3), 7.37 (1H, dd, J=10.3 and

9.5 Hz, H-5), 6.82 (1H, d, J=10.3 Hz, H-6), 6.67 (1H, dd, J=10.2 and 9.5 Hz, H-4), 10.3 (1H, brs, NH), and 9.28 (1H, s, OH); Found: C, 47.74; H, 2.70; N, 4.27%; M^+, 329. Calcd for $C_{13}H_9NO_2BrCl$: C, 47.81; H, 2.78; N, 4.29%; M, 329.

9) 7b: Brown needles; mp 98-99 °C; UV λmax (MeOH) 228, 264, 272, 306, and 415 nm (log ε 4.30, 4.35, 4.31, 3.84, and 4.02); (MeOH+ 3 M-HCl) 230, 272, 276, 332, and 447 nm (log ε 4.30, 4.31, 4.30, 3.92, and 3.91); IR (KBr) 1630cm^{-1} (C=N); ^{1}H-NMR (100 MHz, CDCl) δ 6.35 (1H, td, J=12.0 and 1.0 Hz, H-7), 6.0 (2H, m, H-9,10), 5.51 (1H, ddd, J=3.7, 5.1,and 12.0 Hz, H-8), 6.4-6.7 (3H, m, H-1,3,4), and 2.15 (3H, s, Me).

10) 7c: Brown needles; mp 139-140 °C; UV λmax (MeOH) 229, 264, 274, 310, and 415 nm (log ε 4.26, 4.38, 4.35, 3.81, and 3.99); (MeOH+ 3 M-HCl) 233, 274, 325, and 440 nm (log ε 4.32, 4.36, 3.90, and 3.91); IR (KBr) 1625cm^{-1} (C=N); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.42 (1H, d, J=11.7 Hz, H-7), 6.1 (2H, m, J=3.0 and 6.0 Hz H-9,10), 5.61 (1H, ddd, J=3.6 and 11.7 Hz, H-8), 6.83 (1H, d, J=3.0 Hz, H-1), 6.78 (1H, dd, J=3.0 and 8.8 Hz, H-3), and 6.50 (1H, d, J=8.8 Hz, H-4); Found: C, 50.71; H, 2.39; N, 4.40%; M^+, 311. Calcd for $C_{13}H_7NOBrCl$: C, 50.60; H,2.29; N, 4.54%; M, 311.

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12) 4b: Yellow needles; mp 225-227 °C; UV λmax (MeOH) 237, 286, and 375 nm (log ε 4.28, 4.28, and 3.86); M^+, 328; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.45 (2H, d, J=2.0 Hz, H-4,11), 6.97 (4H, m, H-2,6,9,13), 6.61 (2H, d, J=8.0 Hz, H-1,14), 6.54 (2H, dd, J=3.5 and 9.5 Hz, H-7,8), and 2.37 (6H, s, Me).

13) 4c: Yellow needles; mp 209-210 °C; UV λmax (MeOH) 237, 279, and 375 nm (log ε 4.33, 4.29, and 3.85); M^+, 372; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.66 (2H, d, J=2.2 Hz, H-4,11), 7.14 (2H, dd, J=2.2 and 8.8 Hz, H-2,13), 6.67 (2H, d, J=8.8 Hz, H-1,14), 6.98 (2H, dd, J=3.7 and 9.5 Hz, H-6,9), and 6.61 (2H, dd, J=3.7 and 9.5 Hz, H-7,8).

14) 9b: Dark violet needles; mp 210-213 °C; UV λmax (MeOH) 265, 277, 320, 365, 400, 425, and 505 nm; (MeOH+ 3 M-HCl) 282, 328, 418, and 545 nm; IR (KBr) 3280 (NH) and 1622cm^{-1} (C=N); M^+, 328; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.14 (6H, s, Me), 6.46 (2H, dd, J=2.0 and 8.0 Hz, H-3,11), 6.45 (2H, d, J=2.0 Hz, H-1.13), 6.34 (2H, d, J=8.0 Hz, H-4,10), 5.82 (1H, dd, J=9.5 and 11.7 Hz, H-7), and 5.65 (2H, m, J=9.5 and 11.7 Hz, H-6,8).

15) 9c: Dark violet needles; mp 274-276 °C; UV λmax (MeOH) 257, 280, 319, 365, 400, 424, and 515 nm (log ε 4.36, 4.27, 3.85, 3.75, 3.75, 3.50, and 3.95); (MeOH + 3 M-HCl) 282, 319, 410, and 534 nm (log ε 4.41, 3.85, 3.99, and 3.84); IR (KBr) 3250 (NH) and 1618cm^{-1} (C=N); M^+, 372; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.69 (2H, d, J=2.1 Hz, H-1,13), 6.61 (2H, dd, J=2.1 and 8.1 Hz, H-3,11), 6.38 (2H, d, J=8.1 Hz, H-4,10), 5.95 (1H, dd, J=9.5 and 10.9 Hz, H-7), and 5.72 (2H, m, J=9.5 and 10.9 Hz, H-6,8).

16) 4d: Yellow solid; UV λmax (MeOH) 234, 285, and 375 nm; M^+, 314.

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