Reactive Troponoids and *o*-Aminophenol. III. The Reaction of 2-Bromo-7-methoxytropone[1]

Tetsuo NOZOE, Taichi SOMEYA,* and Harue OKAI†

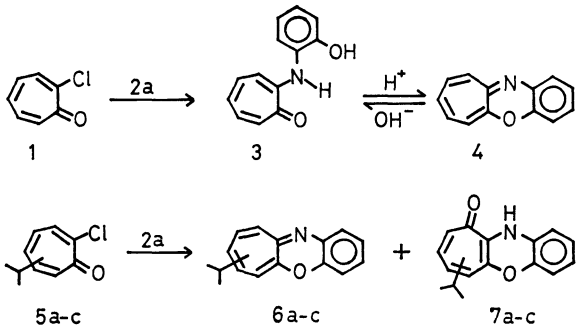
Central Research Laboratory of Takasago Perfumery Co., Ltd., Kamata, Ohta-ku, Tokyo 144

† *Tokyo Research Laboratory of Kao Soap Co., Ltd., Bunka, Sumida-ku, Tokyo 131*

(Received September 9, 1978)

The reaction of 2-bromo-7-methoxytropone with *o*-aminophenol gave 2-bromo-7-(*o*-hydroxyanilino)tropone (**9**), besides small amounts of cyclohepta[*b*][1,4]benzoxazin-6(11*H*)-one (**10**) and 15*H*-[1,4]benzoxazino[3′,2′: 3,4]-cyclohepta[2,1-*b*][1,4]benzoxazine (**11**). The heating of **9** with a strong acid afforded 6-bromocyclohepta[*b*][1,4]-benzoxazine (**13**) quantitatively. On the other hand, the heating of **13** with *o*-aminophenol in ethanol gave **10**, while in acetic acid a mixture of **10** and **11** was obtained. The mechanism of the formation of these products is discussed.

We have previously reported that the reaction of 2-chlorotropone (**1**) with *o*-aminophenol (**2a**) afforded 2-(*o*-hydroxyanilino)tropone (**3**) and cyclohepta[*b*][1,4]-benzoxazine (**4**).[2] The reactions of 4-, 5-, and 6-isopropyl-2-chlorotropones (**5a—c**) with *o*-aminophenol gave isopropylcyclohepta[*b*][1,4]benzoxazines (**6a—c**), besides a small amount of cyclohepta[*b*][1,4]benzoxazin-10(11*H*)-ones (**7a—c**). We also found that, in these reactions, the amino group of *o*-aminophenol attacked the 1- and 2-positions of the tropone ring equally.[3]

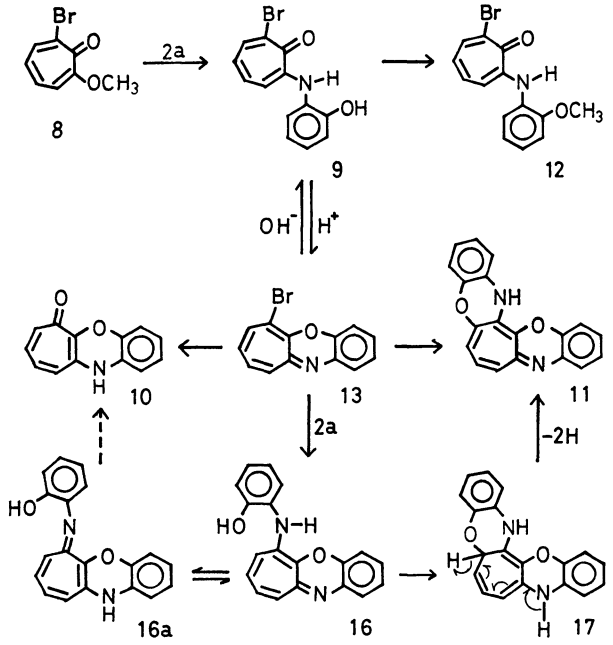


In the present investigation, the reaction of *o*-aminophenol with 2-bromo-7-methoxytropone (**8**), which has two leaving groups, was carried out to find which of two groups, bromo or methoxyl, reacted preferentially and to see if the use of an excess of *o*-aminophenol would give a seven-membered tropylium compound with two oxazine rings.

Results and Discussion

The refluxing of **8** with *o*-aminophenol (**2a**) in acetic acid for 2 h gave yellow prisms (**9**, 82%), orange yellow needles (**10**, 4.7%), and dark violet needles (**11**, 0.5%). The methylation of **9** with diazomethane gave a product which agreed with the 2-bromo-7-(*o*-methoxyanilino)-tropone (**12**) obtained by the reaction of **8** with *o*-methoxyaniline (**2b**) (Scheme 1).

The heating of **9** in acetic acid, in the presence of concd sulfuric acid, resulted in the quantitative formation of **13**, which then easily reverted to **9** on being heated in dilute ethanolic alkali. The catalytic reduction of **13** gave cyclohepta[*b*][1,4]benzoxazine (**4**).[2] These pieces of evidence indicate that **9** is 7-bromo-2-(*o*-hydroxyanilino)tropone and that **13** is 6-bromocyclo-



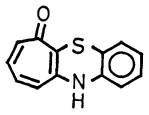
Scheme 1.

hepta[*b*][1,4]benzoxazine. These structures were also supported by the results of the elemental analyses and by the spectral data.

The electronic spectrum of **10** (M^+, 211; $C_{13}H_9NO_2$) is very similar to that of cyclohepta[*b*][1,4]benzothiazin-6(11*H*)-one (**14**).[4] The IR spectrum of **10** shows absorptions at 3300 (NH) and at 1650 cm^{-1} (C=O), which correspond well with those at 3280 (NH) and at 1633 cm^{-1} (C=O) in the IR spectrum of **14**.[4] Consequently, **10** was determined to be cyclohepta[*b*][1,4]-benzoxazin-6(11*H*)-one.

The IR spectrum of **11** (M^+, 300; $C_{19}H_{12}N_2O_2$) shows an absorption at 3250 cm^{-1} (NH). Since the further heating of **13** with **2a** in acetic acid afforded **11** besides **10**, **11** was assumed to be 15*H*-[1,4]benzoxazino[3′,2′: 3,4]cyclohepta[2,1-*b*][1,4]benzoxazine. The visible absorption maximum at 500 nm in **11** corresponds well with that at 490—500 nm in **15**, a tropylium compound with two condensed thiazine rings, which was obtained by the reaction of 3,5-dibromotropolone with *o*-amino-benzenethiol.[4]

The bromo compound **13** was fairly stable on heating in strong acids and did not undergo any change, but the



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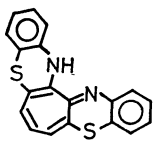

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refluxing of **13** with **2a** in acetic acid resulted in the formation of **10** and **11**, although it should be noted that the refluxing of **13** with **2a** in ethanol gave mainly **10**, and no **11**. It is interesting to note that, although **13** does not change in strong acids, **13** loses bromine by the reaction with almost neutral **2a** even in ethanol and that the bromine atom is replaced with an oxygen atom. The experiments mentioned above suggest that the saponification of the bromine atom in **13** should be preceded by substitution with **2a**, giving the 6-(*o*-hydroxyanilino) compound (**16**). The Schiff base **16a**, a tautomeric form of **16**, could be saponified under dilute acidic conditions to give the ketone (**10**).

However, since the ketone (**10**) was not obtained by the reaction of **13** with aniline under the same reaction conditions, the hydroxyl group in the substituent at C-6 in **16** seems to participate in the formation of **10**. A study of the mechanism of the ketone (**10**) is now under investigation.

Compound **16** would also be cyclized at the 7-position to form **17**, which then undergoes dehydrogenation to form the more stable **11**.

It is quite notable that the hydroxyanilino group bonded to the seven-membered ring undergoes cyclization on the seven-membered ring not containing a functional group.[3]

Experimental

If not otherwise stated, the instruments and methods are as previously described.[2]

Reaction of 2-Bromo-7-methoxytropone (8) with 2a. A mixture of **8** (1.5 g, 7.0 mmol), **2a** (0.9 g, 8.4 mmol), and acetic acid (4.5 ml) was refluxed for 2 h. After the removal of the acetic acid under reduced pressure, a small amount of ethanol was added to the residue and the precipitate was filtered. The recrystallization of the crude crystals from ethanol gave 1.23 g of **9**. The filtrate and the mother liquor of the recrystallization were chromatographed on a silica gel column. Then, **11** (10 mg, 0.5%), **10** (70 mg, 4.7%), and **9** (370 mg) were obtained from the benzene, benzene–ether (1: 1), and ether fractions respectively.

2-Bromo-7-(o-hydroxyanilino)tropone (9): Yellow prisms; mp 202 °C; λ_{max}^{MeOH} nm (log ε): 205 (4.52), 250 (4.38)^{sh}, 260 (4.39), 346 (3.98), and 418 (4.20); $\lambda_{max}^{MeOH+NaOH}$ nm (log ε): 240 (4.72), 346 (3.98), and 423 (4.20); IR (KBr): 3280 (NH), 3200 (OH), and 1585 cm^{-1} (C=O); NMR (60 MHz in DMSO-d_6): δ 10.0 (s, 1H, OH), 9.25 (s, 1H, NH), 8.24 (dd, 1H, J=10 and 1 Hz, C_3–H), 7.15—7.55 (m, 2H, $C_{5,6}$–H), 6.80—7.15 (m, 4H, benzene ring), and 6.55 ppm (t, 1H, J=10 and 10 Hz, C_4–H). Found: C, 53.40; H, 3.54; N, 4.62%; M$^+$, 293. Calcd for $C_{13}H_{10}NO_2Br$: C, 53.44; H, 3.45; N, 4.80%; M, 293.

Cyclohepta[b][*1,4*]*benzoxazin-6(11H)-one (10)*: Orange yellow needles; mp 115 °C (from hexane); λ_{max}^{MeOH} nm (log ε): 207 (4.28), 227 (4.43), 275 (3.88), 310 (3.48), and 435 (3.74); IR (KBr): 3300 (NH) and 1650 cm^{-1} (C=O); NMR (60 MHz in $CDCl_3$): δ 9.10 (s, 1H, NH) and 6.30—7.05 ppm (m, 8H). Found: C, 73.64; H, 4.27; N, 6.70%; M$^+$, 211. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63%; M, 211.

15H-[*1,4*]*Benzoxazino*[*3',2': 3,4*]*cyclohepta*[*2,1-*b][*1,4*]*benzoxazine (11)*: Dark violet needles; mp 245 °C (from hexane); λ_{max}^{MeOH} nm (log ε): 207 (4.10), 254 (3.99), 350—360 (3.43), and 500 (3.68); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 207 (4.08), 223 (4.02), 275 (4.00), 325 (3.57)^{sh}, 410 (3.68), and 535 (3.54); IR (KBr): 3250 cm^{-1} (NH); NMR (60 MHz in DMSO-d_6): δ 6.70—6.45 (m, 8H, benzene ring) and 5.72 ppm (m, 3H, cycloheptatriene ring). Found: C, 76.25; H, 4.09; N, 9.38%; M$^+$, 300. Calcd for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03; N, 9.33%; M, 300.

2-Bromo-7-(o-methoxyanilino)tropone (12). a) An ether solution of diazomethane (0.51 mmol) was added to a solution of **9** (0.1 g, 0.34 mmol) in ether (20 ml), and the mixture was stirred for 5 min at room temp. After the removal of the ether, the recrystallization of the residue from benzene gave 0.1 g (95%) of **12**.

b) A mixture of **8** (0.1 g, 0.45 mmol), **2b** (66 mg, 0.54 mmol), and acetic acid (1 ml) was refluxed for 5 h. After the removal of the acetic acid under reduced pressure, the residue was dissolved in benzene. The benzene solution was washed with aq $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column; then **12** (61 mg, 91%) and **9** (53 mg) were obtained from the benzene–ether (3: 1) and ether fractions respectively. **12**: Yellow needles; mp 132 °C; λ_{max}^{MeOH} nm (log ε): 205 (4.46), 244 (4.33), 260 (4.34), 348 (4.10), and 420 (4.31); IR (KBr): 3260 (NH) and 1680 cm^{-1} (C=O); NMR (60 MHz in DMSO-d_6): δ 9.25 (s, 1H, NH), 8.20 (d, 1H, J= 10 Hz, C_3–H), 7.20—7.52 (m, 2H, $C_{5,6}$–H), 6.85—7.20 (m, 4H, benzene ring), and 6.57 ppm (m, 1H, C_4–H). Found: C, 55.17; H, 4.07; N, 4.40; Br, 26.16%; M$^+$, 307. Calcd for $C_{14}H_{12}NO_2Br$: C, 54.92; H, 3.95; N, 4.58; Br, 26.10%; M, 307.

6-Bromocyclohepta[b][*1,4*]*benzoxazine (13).* A solution of **9** (0.7 g, 2.4 mmol), acetic acid (5 ml), and a small amount of concd H_2SO_4 was refluxed for 1 h. After the removal of the acetic acid under reduced pressure, the residue was dissolved in benzene. The benzene solution was washed with aq $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. The recrystallization of the residue from hexane gave 0.65 g (98%) of **13** as brown needles; mp 119 °C; λ_{max}^{MeOH} nm (log ε): 208 (4.30), 227 (4.31), 262 (4.43), 268 (4.42), and 410 (4.08); NMR (60 MHz in CCl_4): δ 6.40—6.75 (m, 4H, benzene ring) and 5.30—6.55 ppm (m, 4H, cycloheptatriene ring); NMR (in CF_3COOH): δ 7.75 (d, 1H, J=11 Hz, C_7–H) and 6.45—7.40 ppm (m, 7H). Found: C, 57.08; H, 2.84; N, 5.06; Br, 29.27%; M$^+$, 275. Calcd for $C_{13}H_8NOBr$: C, 56.96; H, 2.94; N, 5.11; Br, 29.15%; M, 275.

The hydrogenation of **13** in ethyl acetate and a small amount of pyridine with palladium carbon (5%) as a catalyst under normal pressure at room temp gave cyclohepta[*b*][1,4]benzoxazine[2] as brown needles; mp 93 °C.

Conversion of 13 into 9. A solution of **13** (50 mg) in EtOH (1 ml) and 1 M NaOH (1 ml) was refluxed for 1 h. After the removal of the ethanol, water (2 ml) was added to the residue, and the mixture was washed with benzene. The water layer was neutralized with 1 M HCl and extracted with benzene. The extract was washed with water, dried, and evaporated to dryness. Recrystallization from hexane gave 45 mg (84%) of **9**.

Reaction of 13 with 2a. A mixture of **13** (55 mg, 0.2 mmol), **2a** (26 mg, 0.24 mmol), and acetic acid (5 ml) was

refluxed for 4 h. After the removal of the acetic acid under reduced pressure, the residue was extracted with benzene. From the extract, 10 mg (17%) of **11** and 15 mg (36%) of **10** were obtained by preparative TLC developed with benzene. On the other hand, a mixture of **13** (85 mg), **2a** (45 mg), and EtOH (5 ml) was refluxed for 3 h. By the method described above, a 50-mg portion (76%) of **10** was obtained.

The authors wish to express their thanks to Dr. Isao Kawamoto and the Sankyo Co., Ltd., for measuring some of the mass spectra and for their elemental analyses.

References

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