Reactive Troponoids and *o*-Aminophenol. II. The Formation of Cyclohepta[*b*][1,4]benzoxazine and 11*H*-Cyclohepta[*b*][1,4]benzoxazin-10-one Derivatives from Isomeric Isopropyl-2-chlorotropones

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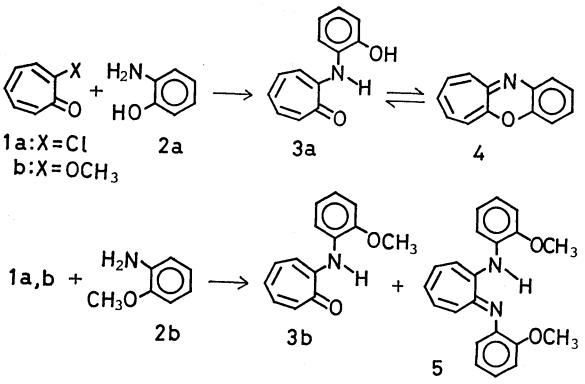
The reactions of three isomeric isopropyl-2-chlorotropones with *o*-aminophenol were investigated. 8-Isopropylcyclohepta[*b*][1,4]benzoxazine was obtained from 5-isopropyl-2-chlorotropone, while 4- and 6-isopropyl-derivatives gave the same mixture of 7- and 9-isopropylcyclohepta[*b*][1,4]benzoxazine. These facts showed that the amino group of *o*-aminophenol attacked both the C-1 and C-2 positions of 2-chlorotropones. Also 6-, 7-, and 8-isopropyl-11*H*-cyclohepta[*b*][1,4]benzoxazin-10-ones were obtained as the minor products of these reactions.

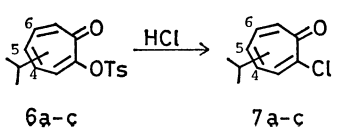
In the preceding paper,[1] we reported the formation of 2-(*o*-hydroxyanilino)tropone (**3a**) and cyclohepta[*b*]-[1,4]benzoxazine (**4**) by the reaction of 2-chloro- (**1a**) or 2-methoxytropone (**1b**) with *o*-aminophenol (**2a**). Since the reaction of **1a, b** with *o*-methoxyaniline (**2b**) resulted in the formation of a small amount of 1-(*o*-methoxyanilino)-7-(*o*-methoxyphenylimino)-1,3,5-cycloheptatriene (**5**), besides the corresponding aminotropone (**3b**), it has been shown that the amino group of *o*-aminophenol reacted not only with C-2 (or C-7), but also with the carbonyl group (C-1).[2]



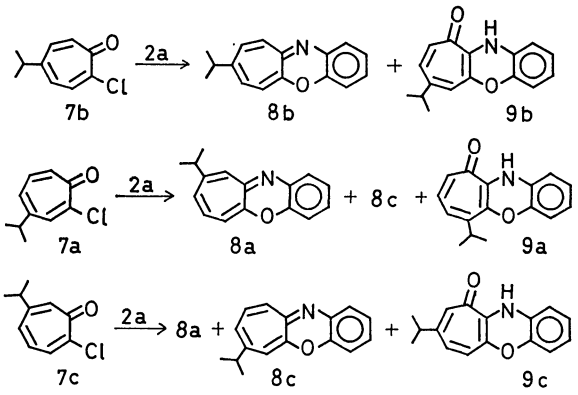
In order to confirm the position attacked by the amino group of the reagent on the seven-membered ring, we investigated the reactions of three isomeric isopropyl-2-chlorotropones (**7a—c**) with *o*-aminophenol. From the kinds of products obtained and their ratio, the amino group of the reagent was found to attack both the C-1 and C-2 positions of 2-chlorotropones approximately equally.

Results and Discussion

The most popular method of the synthesis of 2-chlorotropone is to treat tropolone with thionyl chloride,[3] but this method is not convenient when using alkyltropolones. We found the reaction of 2-tosyloxytropone with dry hydrogen chloride in dioxane[4] is most advantageous in such a case. By the use of this method, three isomeric isopropyl-2-chlorotropones (**7a—c**) were obtained in about a 90% yield from the corresponding tosylates (**6a—c**),[5] which indicated that normal replacement has taken place in these reactions.



The reaction of 2-chloro-5-isopropyltropone (**7b**) with *o*-aminophenol in acetic acid afforded **8b** (78%) and **9b** (0.5%). The heating of **8b** with 2 eq. of ethanolic alkali resulted in the quantitative formation of **10b**, along with a minute amount of **9b**, and **10b** reverted to **8b** quantitatively when heated in acetic



Scheme 1.

TABLE 1. NMR SPECTRAL DATA OF ISOPROPYLCYCLOHEPTA-[*b*][1,4]BENZOXAZINES (100 MHz in $CDCl_3$)

Proton	Chemical shift δ in ppm		
	7-*i*-Pr (**8c**)	8-*i*-Pr (**8b**)	9-*i*-Pr (**8a**)
6	5.40(d)[a]	5.37(d)[c] (6.74)[h]	5.37(d d)[e]
7		5.79(d)[d] (7.10)[h]	5.90(d d)[f]
8	5.66(d)[b]		5.68(br d)[g]
9	6.02(m, 2H)	6.07(d, 2H) (7.32)[h]	
10			6.04(br s)
4	6.37(m)	6.34(m) (6.54)[h]	6.37(m)
1—3	6.71(m)	6.70(m) (6.81)[h]	6.72(m)

a) J=1.1 Hz. b) J=7.0 Hz. c) J=9.7 Hz. d) J=9.7 Hz. e) J=9.0 and 1.1 Hz. f) J=11.3 and 9.0 Hz. g) J=11.3 Hz. h) In CF_3COOD.

acid in the presence of concd sulfuric acid. From these results, and from their elemental analytical and spectral data, **8b** was determined to be 8-isopropylcyclohepta[*b*][1,4]benzoxazine and **10b** as 5-isopropyl-2-(*o*-hydroxyanilino)tropone.

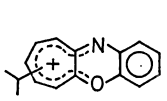
The reaction of 2-chloro-4-isopropyltropone (**7a**) with *o*-aminophenol afforded **8a** (40%) and **8c** (38%), besides **9a** (0.5%). In the same reaction, 2-chloro-6-isopropyltropone (**7c**) also gave **8a** (36%) and **8c** (42%), besides **9c** (0.5%). The structures of **8a** and **8c** were determined to be 9-isopropyl- (**8a**) and 7-isopropylcyclohepta[*b*][1,4]benzoxazine (**8c**) from their NMR spectra, shown in Table 1.

When **8a** was heated with 2 eq. of ethanolic alkali, **10a** was obtained quantitatively, along with traces of **9a**. In the same manner, **10c** and traces of **9c** were obtained from **8c**. **10a** and **10c** were reverted to **8a** and **8c** respectively by heating in acetic acid in the presence of concd sulfuric acid. From these results, **10a** and **10c** were determined to be 4-isopropyl- and 6-isopropyl-2-(*o*-hydroxyanilino)tropone, respectively (Scheme 2).

The NMR spectral measurement of **8b** in trifluoroacetic acid, which exists as a cation, **11**, shows, as in the case of the parent **4**,[1] shifts of the seven-membered ring protons by 1.22—1.37 ppm and those of the benzene-ring protons by 0.11—0.20 ppm to a lower magnetic field (Table 1).

It should be noted in these reactions that the same mixture of **8a** and **8c** was obtained from both **7a** and **7c**, indicating that the amino group of *o*-aminophenol attacked both C-2 and C-1 positions to the same extent. It is clear from the formation of these products that the so-called cine-reaction[6] (abnormal substitution at C-7 instead of C-2) has not taken place. Tropones act as tropylium ions in an acidic medium, so C-1 positions also seem liable to be attacked by nucleophiles.

The three products (**9a—c**) obtained in small amounts were found to be isomers with the same formula of $C_{16}H_{15}NO_2$, and their IR absorptions at 3200—3250 cm^{-1} (NH) and 1607—1610 cm^{-1} (C=O) agree with those at 3218 cm^{-1} (NH) and at 1607 cm^{-1} (C=O) in the 11*H*-cyclohepta[*b*][1,4]benzothiazin-10-one (**12a**) obtained earlier.[7]



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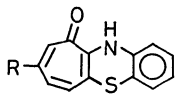
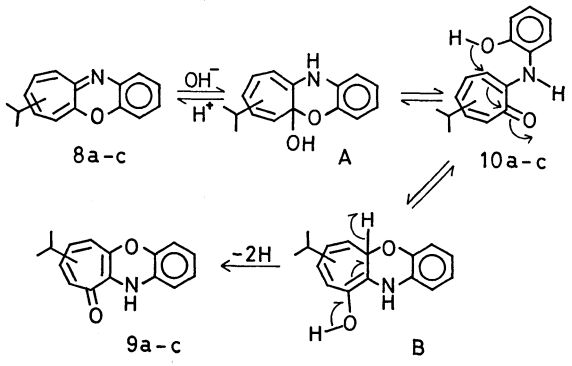


12 a: R = H
b: R = iPr

In the NMR spectrum of **9c**, the broad singlet at δ 6.98 ppm was considered to be the proton on C-9, next to the carbonyl group in the seven-membered ring; this agrees well with the absorption at δ 7.05 ppm (br s, C_9–H) in the NMR spectrum of 11*H*-8-isopropylcyclohepta[*b*][1,4]benzothiazin-10-one (**12b**).[8] From this evidence, **9c** was determined to be 11*H*-8-isopropylcyclohepta[*b*][1,4]benzoxazin-10-one. It was considered that **9c** was formed by the dehydrogenation of the intermediate B, derived from the cyclization of **10c** at the C-3 position. A similar explanation can be put forward for the formation of 11*H*-6-isopropyl- (**9a**) and 11*H*-7-isopropylcyclohepta[*b*][1,4]benzoxazin-10-one (**9b**) from **10a** and **10b** respectively. Interconversion between **8** and **10** obviously proceeds *via* the hydrated intermediate, A (Scheme 2).



Scheme 2.

Experimental

All the melting points are uncorrected. TLC and preparative TLC were carried out on Kiesel gel 60 F_{254} (Merck) and Wakogel BF-5 (Wako) respectively, developed with benzene, and spots were detected with an UV lamp. The IR and UV spectra were taken on a Hitachi EPI-G2 and a Hitachi 124 spectrophotometer respectively. The UV spectra in an acidic or basic medium were measured by adding three drops of 1 M HCl or 1 M NaOH to the sample solution. The NMR spectra were recorded on a 60 MHz Hitachi-R-24A and a 100 MHz Varian HA-100 spectrometer, with TMS as the internal standard. The mass spectra were recorded on a Hitachi RMU-6M mass spectrometer operating at 75 eV.

2-Chloro-5-isopropyltropone (7b). A solution of 5-isopropyl-2-tosyloxytropone (**6b**)[5] (1.6 g, 5.0 mmol) in dry dioxane (30 ml) was refluxed by passing dry hydrogen chloride through for 20 min. After the dioxane has been removed under reduced pressure, the residue was dissolved in ether. The ether solution was passed through an alumina column to give 0.9 g (97%) of **7b** as a pale yellow oil.

By the same procedure, 2-chlorotropone was obtained from 2-tosyloxytropone in a 96% yield.

2-Chloro-4-isopropyltropone (7a) and 2-Chloro-6-isopropyltropone (7c). 4-Isopropyl- (**6a**) and 6-isopropyl-2-tosyloxytropone (**6c**) were prepared from β-thujaplicin by the reported method.[5] By the method described above, from **6a** (2.1 g, 6.6 mmol) 1.1 g (90%) of **7a** were obtained as a pale yellow oil. Similarly, 3.3 g (94%) of **7c** were obtained from **6c** (6.2 g, 19.5 mmol); subsequent recrystallization from hexane afforded pale yellow needles; mp 48 °C. (Lit,[5] 46.5—48.5 °C)

8-Isopropylcyclohepta[b][*1,4*]*benzoxazine (8b).* A mixture of **7b** (0.8 g, 4.4 mmol), **2a** (0.8 g, 7.3 mmol), and acetic acid (4 ml) was refluxed for 2 h. After the removal of the acetic acid under reduced pressure, 30 ml of water was added to the residue, and it was extracted with $CHCl_3$. The extract was evaporated, the residue of dark brown oil was dissolved in EtOH, and an EtOH solution of picric acid was added. When the resulting picrate was filtered and washed with ether, 1.46 g were obtained; mp 193—196 °C. The picrate was stirred with EtOH (5 ml) and 1M NaOH (25 ml) for 20 min at room temp. The mixture was then extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated. The recrystallization of the residue from hexane gave 0.76 g (78%) of **8b** as dark

brown plates; mp 105 °C; λ_{max}^{MeOH} nm (log ε): 214 (4.24), 263 (4.31), 270 (4.27), and 418 (3.99); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 221 (4.27), 265 (4.32), 273 (4.46), 320 (3.80), and 436 (3.82); NMR (see Table 1). Found: C, 81.00; H, 6.41; N, 6.07%; M+, 237. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%; M, 237. Picrate: brown needles (from EtOH); mp 198 °C (dec).

11H-7-Isopropylcyclohepta[b][*1,4*]*benzoxazin-10-one* (**9b**). From the filtrate of the preparation of the picrate, 50 mg of **7b** and 6 mg (0.5%) of **9b** were obtained by preparative TLC. Recrystallization from ethyl acetate gave red needles; mp 114 °C; λ_{max}^{MeOH} nm (log ε): 208 (4.39), 228 (4.45), 257 (4.35), 268 (4.34), 285 (4.25), 420 (3.79)^{sh}, and 480 (3.97); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 208 (4.37), 228 (4.48), 260 (4.28), 270 (4.29), 286 (4.36), 325 (3.85), and 470—490 (3.93); IR (KBr): 3240 (NH) and 1610 cm^{-1} (C=O). Found: C, 75.65; H, 6.01; N, 5.58%; M+, 253. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%; M, 253.

Reaction of **7a** *with* **2a**. A mixture of **7a** (1.0 g, 5.5 mmol), **2a** (1.0 g, 9.2 mmol), and acetic acid (4 ml) was refluxed for 2 h. By a method similar to the reaction of **7b** with **2a**, 3g of dark brown crystals were obtained. These crystals were shown by TLC to be a mixture of two components. Then **8a** (0.52 g, 40%) and **8c** (0.49 g, 38%) were obtained by preparative TLC. From the filtrate which the picrate was separated, 7 mg (0.5%) of **9a** were obtained by preparative TLC.

9-Isopropylcyclohepta[b][*1,4*]*benzoxazine* (**8a**): Dark brown needles (from hexane); mp 63 °C; λ_{max}^{MeOH} nm (log ε): 207 (4.17), 215 (4.17), 263 (4.31), 270 (4.29), and 414 (3.95); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 205 (4.13), 227 (4.20), 265 (4.24)^{sh}, 275 (4.28), 316 (3.83), and 435—450 (3.82); NMR (see Table 1). Found: C, 80.77; H, 6.27; N, 6.13%; M+, 237. Picrate: brown needles (from EtOH); mp 221—222 °C (dec).

7-Isopropylcyclohepta[b][*1,4*]*benzoxazine* (**8c**): Dark brown needles (from hexane); mp 109 °C; λ_{max}^{MeOH} nm (log ε): 207 (4.23), 215 (4.24), 263 (4.31), 270 (4.29), and 415 (3.96); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 206 (4.22), 226 (4.33), 265 (4.25)^{sh}, 275 (4,28), 317 (3.84), and 435—450 (3.84); NMR (see Table 1). Found: C, 80.73; H, 6.23; N, 5.90%; M+, 237. Picrate: brown needles (from EtOH), mp 201—202 °C (dec).

11H-6-Isopropylcyclohepta[b][*1,4*]*benzoxazin-10-one* (**9a**): Orange red needles (from EtOAc); mp 141 °C; λ_{max}^{MeOH} nm (log ε): 207 (4.36), 230 (4.45), 257 (4.34), 269 (4.33), 286 (4.28), 410 (3.76)^{sh}, and 470 (3.98); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 207 (4.34), 228 (4.49), 260 (4.28), 270 (4.31), 288 (4.37), 325 (3.82)^{sh}, and 450—470 (3.93); IR (KBr): 3200 (NH) and 1610 cm^{-1} (C=O); NMR (100 MHz in $CDCl_3$): δ 6.90 (m, 1H, C_9-H), 6.38—6.78 (m, 6H), 3.24 (m, 1H, CH), and 1.19 ppm (d, 6H, J=7.0 Hz, CH_3). Found: C, 75.75; H, 6.03; N, 5.57%; M+, 253.

Reaction of **7c** *with* **2a**. A mixture of **7c** (3.0 g, 16.4 mmol), **2a** (3.0 g, 27.5 mmol), and acetic acid (20 ml) was refluxed for 2 h. After the treatment described above, **8a** (1.3 g, 36%), **8c** (1.5 g, 42%), **9c** (19 mg, 0.5%), and **7c** (0.25 g) were obtained.

11H-8-Isopropylcyclohepta[b][*1,4*]*benzoxazin-10-one* (**9c**): Red needles (from EtOAc); mp 172 °C; λ_{max}^{MeOH} nm (log ε): 205 (4.34), 233 (4.45), 258 (4.35), 270 (4.35), 283 (4.22) 415 (3.76)^{sh}, and 480 (3.97); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 205 (4.34), 230 (4.46), 260 (4.32)^{sh}, 270 (4.35), 285 (4.36), 322 (3.80)^{sh}, and 450—485 (3.94); IR (KBr): 3250 (NH), and 1607 cm^{-1} (C=O); NMR (100 MHz in $CDCl_3$): δ 6.98 (br s, 1H, C_9-H), 6.28—6.68 (m, 6H), 2.60 (m, 1H, CH), and 1.13 ppm (d, 6H, J=7.0 Hz, CH_3). Found: C, 75,73; H, 5.92; N, 5.54%; M+, 253.

4-Isopropyl-2-(o-hydroxyanilino)tropone (**10a**). A solution of **8a** (0.5 g, 2.1 mmol) in ethanol (10 ml) and 1M NaOH (5 ml) was refluxed for 1 h. After the subsequent removal of the ethanol, the residue was dissolved in water (5 ml) and adjusted to make it slightly acidic with 1M HCl. The resulting precipitate was filtered and dried in a desiccator. Recrystallization from hexane afforded 0.47 g (88%) of **10a** as yellow needles; mp 170 °C. From the mother liquor, 2 mg of **9a** was obtained by preparative TLC. **10a**: λ_{max}^{MeOH} nm (log ε): 208 (4.45), 235(4.28), 255 (4.18), 343 (3.88), and 400 (4.07); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 208 (4.25), 245 (4.32), 257 (4.30), and 378 (3.92); $\lambda_{max}^{MeOH+NaOH}$ nm (log ε): 235 (4.85), 340 (3.62)^{sh}, and 410 (4.00); IR (KBr): 3300 (NH), 3050 (OH), and 1590 cm^{-1} (C=O); NMR (60 MHz in $CDCl_3$): δ 9.70 (br s, 1H, OH), 8.75 (br s, 1H, NH), 6.50—7.30 (m, 8H), 2.72 (m, 1H, CH), and 1.15 ppm (d, 6H, J=7.0 Hz, CH_3). Found: C, 75.23; H, 6.73; N, 5.55%; M+, 255. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%; M, 255.

5-Isopropyl-2-(o-hydroxyanilino)tropone (**10b**). By the method described above, 0.48 g (89%) of **10b** and 2 mg of **9b** were obtained from 0.5 g of **8b**. **10b**: Orange yellow needles (from hexane); mp 181 °C; λ_{max}^{MeOH} nm (log ε): 208 (4.38), 236 (4.42), 346 (3.96), and 409 (4.07); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 241 (4.41) and 382 (3.96); $\lambda_{max}^{MeOH+NaOH}$ nm (log ε): 236 (4.64), 346 (3.65), and 418 (4.00); IR (KBr): 3250 (NH), 3050 (OH), and 1600 cm^{-1} (C=O); NMR (60 MHz in $CDCl_3$): δ 9.60 (br s, 1H, OH), 8.60 (br s, 1H, NH), 6.70—7.25 (m, 8H), 2.75 (m, 1H, CH), and 1.16 ppm (d, 6H, J=8.0 Hz, CH_3). Found: C, 75.05; H, 6.74; N, 5.41%; M+, 255.

6-Isopropyl-2-(o-hydroxyanilino)tropone (**10c**). By the method described above, 0.48 g (89%) of **10c** and 2 mg of **9c** were obtained from 0.5 g of **8c**. **10c**: Orange yellow needles (from hexane); mp 181 °C; λ_{max}^{MeOH} nm (log ε): 236 (4.28), 250 (4.28), 345 (3.87), and 400 (4.08); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 245 (4.20), 255 (4.19), and 383 (3.88); $\lambda_{max}^{MeOH+NaOH}$ nm (log ε): 235 (4.27) and 410 (3.88); IR (KBr): 3300 (NH), 3000 (OH), and 1590 cm^{-1} (C=O); NMR (60 MHz in $CDCl_3$): δ 9.30 (br s, 1H, OH), 8.50 (br s, 1H, NH), 6.45—7.20 (m, 8H), 2.70 (m, 1H, CH), and 1.10 ppm (d, 6H, J=7.0 Hz, CH_3). Found: C, 75.16; H, 6.58; N, 5.53%; M+, 255.

Conversion of **10a—c** *into* **8a—c**. A solution of **10** (0.2 g) in acetic acid (2 ml) and one drop of concd H_2SO_4 was refluxed for 15 min. The solution turned dark brown. After the removal of the acetic acid, the residue was extracted with benzene. The extract was washed with aq $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. The recrystallization of the residue from hexane gave **8**. The yields were **8a** (90%), **8b** (89%), and **8c** (90%) respectively.

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References

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2) It has been known that, in the reactions of reactive troponoids (**1**) with amines, usually the amino group of

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8) Kindly measured by Dr. Kazuko Takahashi (Tohoku University).