BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (7), 2185—2186 (1978)

Reactive Troponoids and *o*-Aminophenol. I. Synthesis of Cyclohepta[*b*][1,4]benzoxazine[1)]

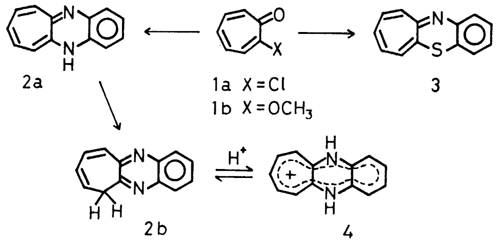
Tetsuo Nozoe,* Harue Okai, and Taichi Someya†
Tokyo Reseach Laboratory of Kao Soap Co., Ltd., Bunka, Sumida-ku, Tokyo 131
† *Central Reseach Laboratory of Takasago Perfumery Co., Ltd., Kamata, Ohta-ku, Tokyo 144*

(Received December 15, 1977)

Synopsis. Cyclohepta[*b*][1,4]benzoxazine and 2-(*o*-hydroxyanilino)tropone were obtained by the reactions of 2-chloro- and 2-methoxytropone with *o*-aminophenol. A similar reaction with *o*-methoxylaniline gave 2-(*o*-methoxyanilino)tropone and 1-(*o*-methoxyanilino)-7-(*o*-methoxyphenylimino)-1,3,5-cycloheptatriene. The chemical and physical properties of cyclohepta[*b*][1,4]benzoxazine were discussed.

Benzotropazine (**2a**)[2)] and cyclohepta[*b*][1,4]benzothiazine (**3**),[3)] which are heterocyclic compounds containing two hetero atoms, with a 6,6,7-ring system, were obtained by the reactions of 2-chloro- (**1a**) or 2-methoxytropone (**1b**) with *o*-phenylenediamine and with *o*-aminobenzenethiol, respectively.

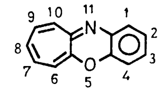
The correct structure of 6*H*-cyclohepta[*b*]quinoxaline (**2b**) was proposed for **2a** by means of NMR.[4,5)] We wish to report on the reaction of **1a, b** with *o*-aminophenol giving cyclohepta[*b*][1,4]benzoxazine (**5**), which is a heterocyclic compound with a 6,6,7-ring system containing an oxazine ring, and its chemical and physical properties.



Results and Discussion

Heating of **1a** with *o*-aminophenol in acetic acid under reflux yielded two condensation products **5** and **6** in 48 and 40% yields, respectively. In a similar manner, the reaction of **1b** with *o*-aminophenol also gave **5** and **6** in 16 and 70% yields, respectively. When these reactions were carried out in ethanol, the product was almost solely **6**. This indicates that **5** is formed from **6** in acidic medium. In fact, heating of **6** in acetic acid, in the presence of concd sulfuric acid, afforded **5** in a quantitative yield. Heating of **5** in ethanol with dilute alkali gave **6** quantitatively. However, longer heating with excess alkali resulted in its decomposition into tropolone and *o*-aminophenol. The results reveal that **6** is 2-(*o*-hydroxyanilino)tropone and **5** is cyclohepta[*b*][1,4]benzoxazine. The structures were also supported by elemental analyses and mass and IR spectra.

The reactions of **1a** and **1b** with *o*-methoxyaniline chiefly gave **7**, with 1—3% of **8**. Since **7** was also obtained by the methylation of **6**, **7** was identified as 2-(*o*-methoxyanilino)tropone, and **8** was identified as 1-(*o*-methoxyanilino)-7-(*o*-methoxyphenylimino)-1,3,5-cycloheptatriene by elemental analysis and spectral data. Moreover, **8** gave a copper(II) chelate as brown crystals, mp 234—236 °C, by the known method for 2-aminotropone imines.[6)] Formation of **8** suggests that, in the reaction of **1** with *o*-aminophenol in acidic conditions, the amino group of the reagent reacts not only at the carbon atom with leaving group but also at the carbonyl group of **1**.



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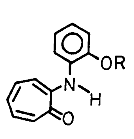
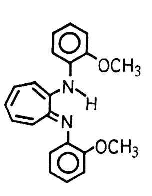


6 R=H
7 R=CH$_3$



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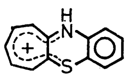
Fukunaga reported that tetrafluoroborate (**4**) of **2b** is a resonance stabilized (aromatic) 4*nπ* system by comparison of the NMR spectrum of **4** in acetonitrile-d_3 with the related compounds.[4)] On the other hand, measurement of the NMR spectra of **3** in trifluoroacetic acid and chloroform-*d*, shows that the seven-membered ring protons of the cation (**9**) derived from **3** shift about 1.0 ppm towards lower magnetic field, while the benzene ring protons hardly shows any shift. Thus the positive charge of the cation (**9**) is not thought to be delocalized over the benzene ring.[7)]

The NMR data of **5** measured in trifluoroacetic acid and chloroform-*d*, show shift of the seven-membered ring protons by 1.22—1.40 ppm and that of the benzene ring protons by 0.10—0.22 ppm towards lower magnetic field. This indicates that the positive charge of the cation (**10**) derived from **5** is also delocalized over both the seven-membered ring and the heterocyclic part as in the case of **9**.



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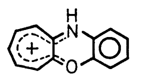

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Experimental

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, spots being detected with a UV lamp. IR and UV spectra were taken on Hitachi EPI-G2 and Hitachi 124 spectrometers, respectively. UV spectra of acidic or basic medium were measured by adding three drops of 1 M HCl or 1 M NaOH to the sample solution. NMR spectra were recorded on 60 MHz Hitachi R-24A and 100 MHz Varian HA-100 spectrometers with TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-6M mass spectrometer operating at 75 eV.

2-(o-Hydroxyanilino)tropone (6). A mixture of **1a** (1.0 g, 7.1 mmol), *o*-aminophenol (1.0 g, 9.2 mmol), and acetic acid (15 ml) was refluxed for 75 min. After removal of acetic acid under reduced pressure, water (30 ml) was added to the residue and precipitate A was separated from filtrate B. Recrystallization of A from benzene gave 0.16 g (40%) of **6** as yellow needles: mp 163 °C; $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 205 (4.40), 231 (4.40), 342 (4.00), and 404 (4.18); $\lambda_{\max}^{\text{MeOH+HCl}}$ nm (log ε): 239 (4.36) and 382 (4.03); $\lambda_{\max}^{\text{MeOH+NaOH}}$ nm (log ε): 231 (4.48), 340 (3.95), and 411 (4.06); IR (KBr): 3260 (NH), 3100 (OH), and 1610 cm^{-1} (C=O); NMR ($CDCl_3$, 60 MHz); δ 9.50 (br s, 1H, OH), 8.70 (br s, 1H, NH), and 6.50—7.40 ppm (m, 9H). Found: C, 72.95; H, 5.19; N, 6.51%; M$^+$, 213. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57%; M, 213.

Cyclohepta[b][1,4]benzoxazine (5). Filtrate B was extracted with chloroform. After removal of the solvent, the residue was dissolved in ethanol and treated with picric acid to precipitate the picrate. The picrate was washed with ether, and decomposed with 2 M NaOH in ethanol. The solution was extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 0.66 g (48%) of **5** as dark brown needles. Recrystallization from hexane gave an analytical sample: mp 93 °C; $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 215 (4.33), 262 (4.38), 270$^{\text{sh}}$ (4.35), and 410 (4.05); $\lambda_{\max}^{\text{MeOH+HCl}}$ nm (log ε): 225 (4.34), 265$^{\text{sh}}$ (4.35), 273 (4.38), 320 (3.87), and 435 (3.93); NMR ($CDCl_3$, 100 MHz): δ 6.73 (m, 3H, $C_{1,2,3}$-H), 6.36 (m, 1H, C_4-H), 6.03 (m, 2H, $C_{6,7}$-H), 5.92 (d d, 1H, J=11.0 and 9.0 Hz, C_9-H), 5.77 (m, 1H, C_8-H), and 5.36 ppm (d d, 1H, J=9.0 and 1.0 Hz, C_{10}-H); NMR (CF_3COOH, 100 MHz): δ 6.83 ($C_{1,2,3}$-H), 6.58(C_4-H), 7.35 ($C_{6,7}$-H), 7.17 (C_9-H), 7.00 (C_8-H), and 6.76 ppm (C_{10}-H). Found: C, 80.13; H, 4.80; N, 7.14%; M$^+$, 195. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.11%; M, 195. Picrate: dark red needles (from EtOH), mp 203.5—204 °C (dec); Found: C, 53.88; H, 3.09; N, 13.34%. Calcd for $C_{19}H_{12}N_4O_8$ C, 53.78; H, 2.85; N, 13.21%.

Reaction of 2-Methoxytropone (1b) with o-Aminophenol. A mixture of **1b** (1.0 g, 7.3 mmol), *o*-aminophenol (1.0 g, 9.2 mmol), and acetic acid (15 ml) was refluxed for 2 h. After the same treatment as described above, 1.1 g (70%) of **6** and 0.23 g (16%) of **5** were obtained.

Reactions of 1a and 1b with o-Aminophenol in Ethanol. A mixture of **1a** or **1b** and *o*-aminophenol was refluxed in ethanol for 3 h. The reaction mixture was found to be a mixture of **6** and *o*-aminophenol by TLC.

Conversion of 6 into 5. A solution of **6** (200 mg) in 5 ml of acetic acid and one drop of concd H_2SO_4 was refluxed for 30 min. After removal of acetic acid, the residue was dissolved in benzene, washed with aq $NaHCO_3$ and water, dried and evaporated. Recrystallization of the residue from hexane gave 175 mg (95%) of **5**.

Conversion of 5 into 6. A solution of **5** (150 mg) in 8 ml of ethanol and 1 M NaOH (4 ml) was refluxed for 30 min. After removal of ethanol, the residue was dissolved in water (10 ml) and neutralized with 1 M HCl. The resulting precipitate was filtered and dried in a desicater. Recrystallization from benzene gave 155 mg (95%) of **6**. A solution of **6** in ethanol and large excess 1 M NaOH was refluxed for 2 h. The neutralized solution was found to be a mixture of tropolone and *o*-aminophenol by TLC.

2-(o-Methoxyanilino)tropone (7). A mixture of **1a** (1.5 g, 10.7 mmol), *o*-methoxyaniline (2.5 g, 20.3 mmol), and acetic acid (6 ml) was refluxed for 1.5 h. The solution was concentrated to dryness and the residue was recrystallized from benzene to yield 2.2 g (91%) of **7** as yellow prisms, mp 117 °C; $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 205 (4.70), 231 (4.69), 344 (4.38), and 404 (4.56); $\lambda_{\max}^{\text{MeOH+HCl}}$ nm (log ε): 205 (4.70), 240 (4.71), and 382 (4.47); IR (KBr): 3270 (NH), 1610 (C=O), 2850, 1240, and 1025 cm^{-1} (OMe); NMR ($CDCl_3$, 60 MHz): δ 8.75 (br s, 1H, NH), 6.50—7.45 (m, 9H), and 3.78 ppm (s, 3H, OMe). Found: C, 73.99; H, 5.86; N, 6.11%; M$^+$, 227. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%; M, 227.

1-(o-Methoxyanilino)-7-(o-methoxyphenylimino)-1,3,5-cycloheptatriene (8). From the mother liquor of the recrystallization of **7**, 35 mg (1%) of **8** was obtained by preparative TLC as orange red oil; $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 213 (4.89), 236 (4.89), 285 (4.54), 370 (3.60), and 415 (3.68); $\lambda_{\max}^{\text{MeOH+HCl}}$ nm (log ε): 215 (4.89), 252 (4.88), and 415 (3.75); IR (neat): 3230 (NH), 2850, 1250 and 1025 cm^{-1} (OMe); NMR ($CDCl_3$, 60 MHz): δ 9.20 (br s, 1H, NH), 6.85—7.30 (m, 8H, brezene ring protons), 6.05—6.75 (m, 5H, cycloheptatriene ring protons), and 3.76 ppm (s, 6H, OMe); MS *m/e* (rel intensity): 332 (M$^+$, 10), 224 (36), 181 (37), 167 (46), 155 (38), 92 (58), 77 (100), 65 (70), and 51 (80). Picrate: yellow prisms, mp 193 °C (dec). Found: C, 57.48; H, 3.94; N, 12.21%. Calcd for $C_{27}H_{23}N_5O_9$: C, 57.75; H, 4.12; N, 12.47%.

Reaction of 1b with o-Methoxyaniline. A mixture of **1b** (1.5 g, 11.0 mmol), *o*-methoxyaniline (2.0 g, 16.2 mmol), and acetic acid (6 ml) was refluxed for 1.5 h. By the same procedure as described above, **7** (2.1 g, 85%) and **8** (0.1 g, 3%) were obtained.

The authors wish to express their thanks to Dr. Tadamichi Fukunaga, E. I. Du Pont de Nemours & Co. U.S.A. and Dr. Kazuko Takahashi, Tohoku University for their kind communications. Thanks are also due to Dr. Masao Sugimura and Sankyo Co., Ltd. for the measurements of mass spectra, 100 MHz NMR spectra and elemental analyses.

References

1) A part of this work was presented at the 34th National Meeting of the Chemical Society of Japan, Kanagawa, April 1976, II, p. 738.

2) T. Nozoe, Y. Kitahara, K. Takase, and T. Sasaki, *Proc. Jpn. Acad.*, **32**, 349 (1956).

3) T. Nozoe, T. Asao, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **34**, 146 (1961).

4) a) T. Fukunaga, XXIII IUPAC Congress, Boston (July 1971), Abstracts p. 102; b) T. Fukunaga, private communication.

5) Fukunaga considered that the earlier reported benzotropazine[2] was in fact a dimer of **2a**.[4]

6) W. R. Brasen, H. E. Holmquist, and R. E. Benson, *J. Am. Chem. Soc.*, **83**, 3125 (1961).

7) Kindly measured by Dr. K. Takahashi (Tohoku University).