Reactions of 3-Acetyltropolone and Its Methyl Ethers with *o*-Aminophenol

Kimiaki IMAFUKU,* Akihiro SHIGENOBU, and Makoto OGURA
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860
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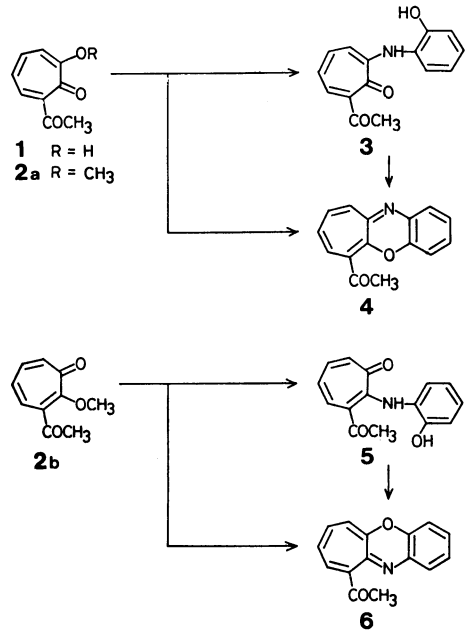
Synopsis. 3-Acetyltropolone (**1**) and 2-acetyl-7-methoxytropone (**2a**) reacted with *o*-aminophenol in ethanol to afford 2-acetyl-7-(*o*-hydroxyanilino)tropone (**3**). The reaction of 3-acetyl-2-methoxytropone (**2b**) gave 3-acetyl-2-(*o*-hydroxyanilino)tropone (**5**). The compounds **3** and **5** were cyclized to 6-acetyl- and 10-acetylcyclohepta[*b*][1,4]benzoxazines (**4** and **6**), respectively, by heating their acetic acid solutions in the presence of a trace amount of concentrated sulfuric acid. The compounds **4** and **6** were also obtained directly from **1** (or **2a**) and **2b**, respectively, by the reaction with *o*-aminophenol in acetic acid. The compound **5** exists as a tautomeric mixture with **5′**.

It is well known that the reactions of so-called ractive troponoids——2-methoxytropones or 2-chlorotropones ——with *o*-phenylenediamine,[1,2] *o*-aminophenol,[3] and *o*-aminobenzenethiol[4] afford 6*H*-cyclohepta[*b*]quinoxaline, cyclohepta[*b*][1,4]benzoxazine, and cyclohepta[*b*][1,4]benzothiazine, respectively. These products are heterocyclic compounds containing two hetero-atoms with a 6,6,7-ring system. Previously, in a series of chemistry of 3-acetyltropolone, we reported the formation of a benzodiazaheptalene derivative with a 6,7,7-ring system, besides 5*H*- and 6*H*-cyclohepta[*b*]quinoxalines with a 6,6,7-ring system, by the reactions of 3-acetyltropolone methyl ethers with *o*-phenylenediamine.[5]

In the present work, the reactions of 3-acetyltropolone (**1**) and its methyl ethers (**2a** and **2b**) with *o*-aminophenol were carried out in expectation of the formation of an oxazepine ring—a 6,7,7-ring system. However, the reactions gave no oxazepine ring but gave acetyl-substituted (*o*-hydroxyanilino)tropones (**3** and **5**) and cyclohepta[*b*][1,4]benzoxazines (**4** and **6**).



Scheme 1.

Results and Discussion

In general, tropolones do not show any indication to react with nucleophilic reagents as well as phenols. However, tropolones bearing a strong electron-withdrawing group, such as nitro or nitroso group, react with nucleophiles to give 2-substituted tropones.[6] Recently, we found that 3-acetyltropolone (**1**) reacts with amines to afford 2-acetyl-7-aminotropones.[7] The refluxing of 3-acetyltropolone (**1**) with *o*-aminophenol in ethanol gave 2-acetyl-7-(*o*-hydroxyanilino)tropone (**3**) in 15% yield. The reactivity of **1** would be based on the electron-withdrawing effect of the acetyl group. The same reaction was carried out in acetic acid containing a trace amount of concentrated sulfuric acid to afford a cyclized product——6-acetylcyclohepta[*b*][1,4]benzoxazine (**4**)——in 3% yield. The compound (**3**) in acetic acid was refluxed in the presence of concentrated sulfuric acid to cyclize to **4**.

The refluxing of 2-acetyl-7-methoxytropone (**2a**) with *o*-aminophenol in ethanol gave **3** in 44% yield, the same reaction in acetic acid giving **4** in 33% yield. Similarly, the reaction of 3-acetyl-2-methoxytropone (**2b**) with *o*-aminophenol in ethanol gave 3-acetyl-2-(*o*-hydroxyanilino)tropone (**5**) in 31% yield, the reaction in acetic acid giving 10-acetylcyclohepta[*b*][1,4]benzoxazine (**6**) in 27% yield. The compound (**5**) was also converted to **6** in 55% yield by heating its acetic acid solution. The structures of all the products were determined by their elemental analyses and spectral data (see: Experimental part).

As shown in Fig. 1, the ^{1}H NMR spectrum of **5** in chloroform-d_1 shows two singlet peaks at δ 2.03 and 2.50 for =C(OH)–CH_3 and –C(=O)–CH_3 protons, respectively. These two singlet peaks indicate that **5** exists as a tautomeric mixture with **5′**. The spectrum in more polar solvent—methanol-d_4—shows only one singlet peak at δ 2.02 and the signal near δ 2.50, which

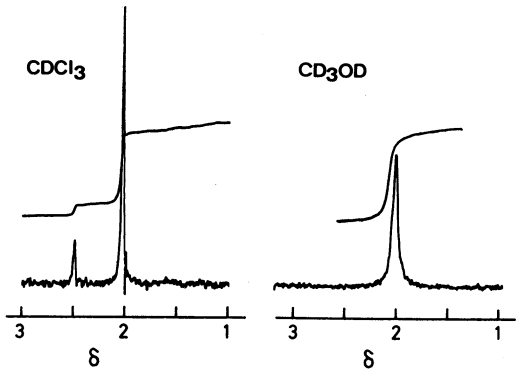
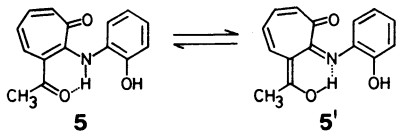


Fig. 1. The ^{1}H NMR spectra of **5** in chloroform-d_1 and methanol-d_4.



Scheme 2.

appeared in chloroform-d_1, is not observed. A similar keto-enol tautomerism of the acetyl group was observed in the spectrum of 6-acetyl-5*H*-cyclohepta[*b*]quinoxaline.[5]

The ^{1}H NMR spectrum of **4** measured in trifluoroacetic acid shows shift of the seven-membered ring protons by *ca.* 1.0 ppm and that of the benzene ring protons by *ca.* 0.1 ppm towards lower magnetic field than those in chloroform-d_1. Similar phenomena were observed in a parent compound——cyclohepta[*b*][1,4]benzoxazine,[3] and 6*H*-cyclohepta[*b*]quinoxaline.[2] These observations indicate that the positive charge is delocalized over both the seven-membered ring and the heterocycle but little over t he benzene ring. The spectrum of **6** also shows a similar tendency.

In this work, the expected 6,7,7-ring system, which is produced by the reaction at the acetyl group, was not isolated. This might be due to the instability of the oxazepine ring.

Experimental

The melting points were determined with a Yanagimoto MP-S2 melting-point measuring apparatus and are uncorrected. The IR spectra were taken on a JASCO IRA-1 spectrophotometer, and the UV spectra on a Hitachi EPS-3T spectrophotometer. The spectra in acidic medium were measured by adding three drops of 1M hydrochloric acid to the sample solution. The ^{1}H NMR spectra were recorded with a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz).

*Reaction of 3-Acetyltropolone (**1**) with o-Aminophenol. a)*: A mixture of 3-acetyltropolone (**1**) (200 mg, 1.2 mmol) and *o*-aminophenol (250 mg, 2.3 mmol) in absolute ethanol (15 ml) was refluxed for 6 h. After removal of the solvent, the residue was twice chromatographed on a Wakogel B-10 plate (30×30 cm^2) with chloroform to afford 47 mg (15%) of 2-acetyl-7-(*o*-hydroxyanilino)tropone (**3**) as reddish orange plates (from benzene–hexane); mp 109—110 °C; IR ($CHCl_3$) 3380, 3260 1700, 1595 cm^{-1}; UV (CH_3OH) 232 (log ε 4.36), 360 (3.90), 433 nm (4.33); UV (CH_3OH+HCl) 236 (log ε 4.36), 359 (3.89), 433 nm (4.31); NMR ($CDCl_3$) δ=2.50 (s, 3H,$COCH_3$), 6.5—7.6 (m, 9H), 8.85 (br, 1H). Found: C, 70.45; H, 5.14; N, 5.44%. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49%.

b): Concentrated sulfuric acid (3 drops) was added to a solution of **1** (216 mg, 1.3 mmol) and *o*-aminophenol (287 mg, 2.6 mmol) in acetic acid (5 ml). The mixture was refluxed for 3 h. After removal of the acetic acid under reduced pressure, the residue was dissolved in chloroform, washed with saturated sodium hydrogencarbonate solution and twice with water, and dried over anhydrous sodium sulfate. The chloroform was evaporated off and the residue was chromatographed on two Wakogel B-10 plates (30×30 cm^2) with chloroform to afford 10 mg (3%) of 6-acetylcyclohepta[*b*][1,4]benzoxazine (**4**) as dark brown plates (from benzene–hexane); mp 97—99 °C; IR ($CHCl_3$) 1705 cm^{-1}; UV (CH_3OH) 265 (log ε 4.38), 432 nm (4.31); UV (CH_3OH+HCl) 229 (log ε 4.39), 274 (4.36), 325 (3.85), 461 nm (3.92); NMR ($CDCl_3$) δ=2.38 (s, 3H, $COCH_3$), 5.7—6.2 (m, 4H, H-7,8,9,10), 6.4—7.3 (m, 4H, H-1,2,3,4). Found: C, 75.90; H, 4.77; N, 5.92%. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90%.

*Cyclization of 2-Acetyl-7-(o-hydroxyanilino)tropone (**3**).* A solution of **3** (178 mg) in acetic acid (5 ml) containing concentrated sulfuric acid (3 drops) was refluxed for 2 h. The reaction mixture was worked up, as mentioned above, to give 87 mg (53%) of **4**.

*Reaction of 2-Acetyl-7-methoxytropone (**2a**) with o-Aminophenol. a)*: A mixture of 2-acetyl-7-methoxytropone (**2a**) (206 mg, 1.2 mmol) and *o*-aminophenol (234 mg, 2.1 mmol) in absolute ethanol (15 ml) was refluxed for 4 h. The reaction mixture was worked up, as mentioned above, to give 135 mg (44%) of **3**.

b): A solution of **2a** (181 mg, 1.1 mmol) and *o*-aminophenol (217 mg, 1.9 mmol) in acetic acid (5 ml) containing concentrated sulfuric acid (3 drops) was refluxed for 4 h. The reaction mixture was worked up, as mentioned above, to give 79 mg (33%) of **4**.

*Reaction of 3-Acetyl-2-methoxytropone (**2b**) with o-Aminophenol. a)*: A mixture of 3-acetyl-2-methoxytropone (**2b**) (275 mg, 1.5 mmol) and *o*-aminophenol (328 mg, 3.0 mmol) in absolute ethanol (15 ml) was refluxed for 5 h. After removal of the solvent, the residue was twice chromatographed on two Wakogel B-10 plates (30×30 cm^2) with chloroform to afford 122 mg (31%) of 3-acetyl-2-(*o*-hydroxyanilino)tropone (**5**) as reddish brown needles (from benzene–hexane); mp 149—150 °C; IR ($CHCl_3$) 3370, 3200, 1720, 1600 cm^{-1}; UV (CH_3OH) 252 (log ε 4.30), 425 nm (4.18); UV (CH_3OH+HCl) 396 nm (log ε 3.96); NMR ($CDCl_3$) δ=2.03 (s, =C(OH)–CH_3), 2.50 (s, –C(=O)–CH_3), 6.5—7.5 (m, 9H), 9.62 (br, 1H); NMR (CD_3OD) δ=2.02 (s, 3H, =C(OH)–CH_3), 6.5—7.5 (m, 9H). Found: C, 70.56; H, 5.22; N, 5.27%. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49%.

b): A solution of **2b** (178 mg, 1.0 mmol) and *o*-aminophenol (217 mg, 2.0 mmol) in acetic acid (5 ml) containing concentrated sulfuric acid (3 drops) was refluxed for 5 h. The acetic acid was evaporated off under reduced pressure and the residue was worked up, as mentioned above, to give 65 mg (27%) of 10-acetylcyclohepta[*b*][1,4]benzoxazine (**6**) as dark brown plates; mp 124—125 °C; IR ($CHCl_3$) 1700 cm^{-1}; UV (CH_3OH) 263 (log ε 4.28), 425 nm (3.95); UV (CH_3OH+HCl) 236 (log ε 4.27), 267 (4.15), 275 (4.13), 336 (3.80), 406 (3.78), 452 nm (sh, 3.73); NMR ($CDCl_3$) δ=2.40 (s, 3H, $COCH_3$), 5.5—6.5 (m, 4H, H-6,7,8,9), 6.6—7.0 (m, 4H, H-1,2,3,4). Found: C, 75.92; H, 4.83; N, 5.74%. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90%.

*Cyclization of 3-Acetyl-2-(o-hydroxyanilino)tropone (**5**).* A solution of **5** (106 mg) in acetic acid (5 ml) containing concentrated sulfuric acid (3 drops) was refluxed for 1.5 h. The reaction mixture was worked up, as mentioned above, to give 54 mg (55%) of **6**.

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