Synthesis of 6-Hydroxy-12-methyl-7,12-dihydrobenzo[6,7]-cyclohept[1,2-*b*]indol-7-one

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(Received April 26, 1978)

5,6,7,12-Tetrahydrobenzo[6,7]cyclohept[1,2-*b*]indol-7-ones were obtained by the oxidation of 5,6,7,12-tetrahydrobenzo[6,7]cyclohept[1,2-*b*]indoles with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in wet dioxane. The α,α-dibromo compound, obtained by bromination of 12-methyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohept-[1,2-*b*]indol-7-one with phenyltrimethylammonium tribromide (PTAB), was hydrolyzed to give the diketone (**5**). By treatment with alkali, compound **5** was converted to 6-hydroxy-12-methyl-7,12-dihydrobenzo[6,7]cyclohept-[1,2-*b*]indol-7-one.

Many troponoid compounds which contain a tropone ring fused with a heterocyclic ring have been found. In a previous paper,[1,2] the preparation of fused tropones containing indole ring was reported. We now report the synthesis of 7,12-dihydrobenzo[6,7]cyclohept[1,2-*b*]-indol-7-ones.

Results and Discussion

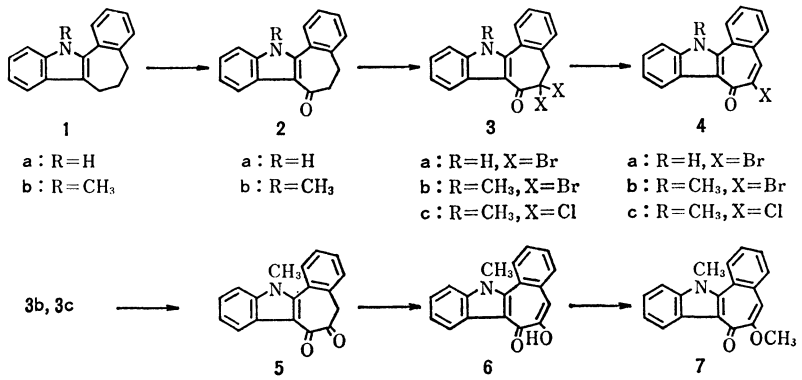
5,6,7,12-Tetrahydrobenzo[6,7]cyclohept[1,2-*b*]indole (**1a**) and its 12-methyl derivative (**1b**) obtained from the reaction of benzosuberone (5*H*-6,7,8,9-tetrahydrobenzocyclohepten-5-one) with phenylhydrazine or *N*-methylphenylhydrazine underwent oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[3,4] (DDQ) in wet dioxane to give 5,6,7,12-tetrahydrobenzo[6,7]cyclohept-[1,2-*b*]indol-7-one (**2a**) and its 12-methyl derivative (**2b**) respectively. The IR and PMR spectra of compounds **2a** and **2b** supported the structure described above (Experimental section). Compound **2b** was also obtained by the treatment of **2a** with dimethyl sulfate.

Compounds **2a** and **2b** were brominated with phenyltrimethylammonium tribromide (PTAB) in dry tetrahydrofuran to give their 6,6-dibromo derivatives (**3a** and **3b**). Dichloro derivative (**3c**) was obtained by the treatment of **2b** with copper(I) chloride in 50% dioxane–water. The dehydrobromination of compounds **3a**—**c** with lithium chloride in boiling *N*,*N*-dimethylformamide (DMF) gave 6-halo-7,12-dihydrobenzo[6,7]cyclohept-[1,2-*b*]indol-7-ones (**4a**—**c**). Compound **3a** also gave **4a** when refluxed in ethanol with 2 M sodium hydroxide.

Compounds **3b** and **3c**, on the other hand, gave yellow prisms (mp 182—184 °C) upon being heated with dilute sodium hydroxide in ethanol. The analytical data revealed a composition with the formula $C_{18}H_{13}O_2N$. The mass spectrum showed a parent peak at *m/e* 275. On the basis of the spectral data (IR, PMR, and CMR: experimental section), the compound may be considered to have the structure of 12-methyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohept[1,2-*b*]indole-6,7-dione (**5**).

Furthermore, compound **5**, when treated with 2 M sodium hydroxide and ethanol (1 : 2 vol%), was converted into yellow plates (mp 235—237 °C). The analytical data revealed a composition with the formula of $C_{18}H_{13}O_2N$, which is the same as that of **5**. The mass spectrum showed a parent peak at *m/e* 275. The IR and PMR spectral data support the assertion that the compound has the structure of 6-hydroxy-12-methyl-7,12-dihydrobenzo[6,7]cyclohept[1,2-*b*]indol-7-one (**6**). These spectral data are shown in the experimental section. Compound **5** was also converted into **6** in trifluoroacetic acid. Compound **6** produced a brown color with iron(III) chloride reagent and gave a complex by the treatment with copper(II) sulfate. The reaction of **6** with dimethyl sulfate gave the methyl ether of **6** as pale yellow plates.

The structure of **5** corresponds to a diketo form of **6**. But its enolization was not as easy as that described above. The unexpected stability of **5** is thought to be due to the steric interaction between the fused benzene and the indole ring, which are prevented from arranging in the same plane on enolization. However, no attempts to achieve the reverse change, from **6** to **5**, were successful. It has been reported[5] that the diketone type tautomer was isolated on monocyclic tropolone.



Experimental

All the melting points are uncorrected.

5,6,7,12-Tetrahydrobenzo[6,7]cyclohept[1,2-b]indol-7-one (2a). To a solution of 5,6,7,12-tetrahydrobenzo[6,7]cyclohept-[1,2-*b*]indole (2.0 g) obtained by the reaction of 5*H*-6,7,8,9-tetrahydrobenzocyclohepten-5-one with phenylhydrazine in dioxane (100 ml) and water (10 ml), we added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (3.88 g) at 5 °C. The mixture was stirred for 10 min, the resulting precipitate was filtered off, and the filtrate was concentrated. The residue was extracted with chloroform. The organic layer was washed with 2 M sodium hydroxide, dried on anhydrous sodium sulfate, and concentrated. The residue was recrystallized from benzene–ethanol to give colorless plates (1.5 g, 71%); mp 246—246.5 °C. IR(KBr): ν_{NH} 3210; $\nu_{C=O}$ 1610 cm^{-1}. Found: C, 82.44; H, 5.37; N, 5.29%. Calcd for $C_{17}H_{13}ON$: C, 82.57; H, 5.30; N, 5.66%.

12-Methyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohept[1,2-b]indol-7-one (2b). *(a)*: Into a solution of **1b** (2.0 g) in dioxane (100 ml) and water (10 ml), we added DDQ (3.6 g). The reaction mixture was treated by a method similar to that used for the preparation of **2a**. Colorless plates (1.4 g, 66%); mp 214–216 °C. PMR (100 MHz, $CDCl_3$): δ 8.62 (1H, m, H-8), 7.3—7.6 (7H, m, benzenoid), 3.89 (3H, s, N–CH_3), and 2.7—3.2 (4H, m, 2×CH_2). The H-8 signal can be compared with that of **1b** (δ 7.73). IR(KBr): $\nu_{C=O}$ 1628 cm^{-1}. Found: C, 82.66; H, 5.61; N, 5.48%. Calcd for $C_{18}H_{15}ON$: C, 82.73; H, 5.79; N, 5.36%.

(b): A mixture of **2a** (3.0 g), dimethyl sulfate (5.0 g), and 2 M sodium hydroxide (25 ml) in acetone (150 ml) was refluxed for 2 h. The reaction mixture was concentrated and diluted with water, followed by extraction with chloroform. The extract was dried with anhydrous sodium sulfate and the solvent was removed. The residue was recrystallized from acetonitrile to give colorless plates (2.8 g, 89%); mp 214—216 °C. The IR spectrum was identical with that of the sample prepared by means of Method (a) and the mixed melting point with the sample was not depressed.

Dibromo Compound (3a) of 2a. To a solution of **2a** (1.43 g) in dry tetrahydrofuran (60 ml), we added phenyltrimethylammonium tribromide (PTAB) (4.35 g) at room temperature. The mixture was stirred for 4 h. The resulting precipitate was filtered off, the filtrate was evaporated, and the residue was recrystallized from methanol to give **3a** as yellowish green micro needles (1.87 g, 80%); mp 204—205 °C (dec). IR(KBr): ν_{NH} 3255, $\nu_{conjugated\ C=O}$ 1606 cm^{-1}. Found: C, 49.97; H, 2.90; N, 3.63; Br, 39.46%. Calcd for $C_{17}H_{11}ONBr_2$: C, 50.41; H, 2.74; N, 3.46; Br, 39.32%.

Dibromo Compound (3b) of 2b. To a solution of **2b** (1.28 g) in dry tetrahydrofuran (90 ml), we added PTAB (3.68 g). The mixture was then treated by a method similar to that used for the preparation of **3a**. Yellow micro needles (from methanol) (1.64 g, 80%); mp 183—184 °C. IR(KBr): $\nu_{C=O}$ 1649 cm^{-1}. Found: C, 51.29; H, 3.48; N, 3.77; Br, 38.34%. Calcd for $C_{18}H_{13}ONBr_2$: C, 51.58; H, 3.13; N, 3.34; Br, 38.14%.

Dichloro Compound (3c) of 2b. A mixture of **2b** (0.2 g) and copper(I) chloride dihydrate (2.61 g) in dioxane (35 ml) and water (35 ml) was refluxed for 24 h on the oil bath. The reaction mixture was concentrated and extracted with chloroform. The extract was dried with anhydrous sodium sulfate and the solvent was removed. The oily residue was recrystallized from cyclohexane to give pale yellow needles (0.15 g, 59%); mp 167—168 °C. IR(KBr): $\nu_{C=O}$ 1621 cm^{-1}. PMR (100 MHz, in $CDCl_3$): δ 8.40 (1H, m, H-8), 7.2—7.7 (7H, m, benzenoid), 3.97 (2H, s, methylene), and 3.90 (3H, s, N–CH_3). Found: C, 65.50; H, 3.91; N, 4.15; Cl, 21.31%. Calcd for $C_{18}H_{13}ONCl_2$: C, 65.47; H, 3.97; N, 4.24; Cl, 21.48%.

6-Bromo-7,12-dihydrobenzo[6,7]cyclohept[1,2-b]indol-7-one (4a). *(a)*: A mixture of dibromo compound (**3a**) (0.6 g) and lithium chloride (0.13 g) in *N,N*-dimethylformamide (20 ml) was refluxed under nitrogen for 4 h. The solvent was removed under reduced pressure, after which the residue was diluted with water. The resulting precipitate was collected, dried under reduced pressure, and chromatographed on a silica gel. The product obtained from the acetone effluent was recrystallized from acetone to give pale yellow micro needles (0.45 g; 94%); mp>290 °C. IR(KBr): $\nu_{conjugated\ C=O}$ 1597 cm^{-1}. Found: C, 62.80; H, 3.02; N, 4.32; Br, 24.70%. Calcd for $C_{17}H_{10}ONBr$: C, 62.97; H, 3.11; N, 4.32; Br, 24.65%.

(b): A mixture of **3a** (0.27 g) and 2 M sodium hydroxide (2 ml) in ethanol (10 ml) was refluxed for 30 min. The reaction mixture was concentrated and made slightly acid with 6 M sulfuric acid. The resulting precipitate was treated by a method similar to that used for Method (a). Pale yellow micro needles (0.2 g, 93%); mp>290 °C. The IR spectrum was identical with that of the sample prepared by means of Method (a).

6-Bromo-12-methyl-7,12-dihydrobenzo[6,7]cyclohept[1,2-b]indol-7-one (4b). A mixture of dibromo compound (**3a**) (0.6 g) and lithium chloride (0.12 g) in *N,N*-dimethylformamide (20 ml) was refluxed under nitrogen atmosphere for 4 h. The reaction mixture was treated by a method similar to that used for the preparation of **4a**. Yellow prisms (0.48 g, *ca.* 100%); mp 195—196 °C. IR(KBr): $\nu_{conjugated\ C=O}$ 1591 cm^{-1}. Found: C; 63.93; H, 3.52; N, 4.33%. Calcd for $C_{18}H_{21}ONBr$: C, 63.99; H, 3.58; N, 4.15%.

6-Chloro-12-methyl-7,12-dihydrobenzo[6,7]cyclohept[1,2-b]indol-7-one (4c). A mixture of dichloro compound (**3c**) (0.5 g) and lithium chloride (0.1 g) in *N,N*-dimethylformamide (20 ml) was refluxed under nitrogen atmosphere. The reaction mixture was treated by a method similar to that used for the preparation of **4a**. Yellow micro needles (0.38 g, 85%); mp 163—164 °C. IR(KBr): $\nu_{conjugated\ C=O}$ 1601 cm^{-1}. Found: C, 73.58; H, 4.01; N, 4.92; Cl, 12.07%. Calcd for $C_{18}H_{12}ONCl$: C, 73.59; H, 4.12; N, 4.77; Cl, 12.07%.

12-Methyl-5,6,7,12-tetrahydrobenzo[6,7]cyclohept[1,2-b]indole-6,7-dione (5). *(a)*: A mixture of dibromo compound (**3b**) (1.43 g) and 2 M sodium hydroxide (5 ml) in ethanol (50 ml) was refluxed for 30 min on the water bath. The mixture was concentrated, diluted with water, and made acid by adding 2 M sulfuric acid. The resulting precipitate was collected and dried under reduced pressure. It was chromatographed on silica gel. From the benzene effluent, **5** was obtained as pale yellow needles (0.55 g, 59%); mp 182—184 °C. IR(KBr): $\nu_{C=O}$ 1641 cm^{-1}. UV: λ_{max}^{MeOH} 244 (log ε=4.40), 250 (4.45), 269 (4.51), 291 (4.37), 363 (4.12), and 379 (4.18) nm. Found: C, 78.62; H, 4.63; N, 5.01%. Calcd for $C_{18}H_{13}O_2N$: C, 78.53; H, 4.76; N, 5.09%. MS: *m/e* 275 (M^+), 247 (M^+-CO), and 218 (M^+-2CO, base). PMR (100 MHz, in $CDCl_3$): δ 8.17 (1H, m, H-8), 7.2—7.8 (7H, m, benzenoid), 4.47 (1H, d, J=4.5 Hz, C_5-methylene Ha), 4.19 (1H, d, J=4.5 Hz, C_5-methylene Hb), and 3.96 (3H, s, N–CH_3). ^{13}C NMR (DMSO-d_6): δ 61.3 (N–$\underline{C}H_3$), 67.6 (C-5), 111.0, 119.9, 122.6, 123.9, 125.1, 127.1, 128.9, 131.4, 132.9, 138.5, and 192.1 (C=O). These signals at δ 67.6 and 61.3 were assigned to C-5 and N–$\underline{C}H_3$ respectively, using the off-resonance coherent proton spin-decoupling technique.

From the chloroform effluent, trace amounts of reddish brown micro needles was obtained; mp 278 °C (dec). The structure of this material has not been clarified yet. IR(KBr): 1634, 1592, and 1489 cm^{-1}.

(b): A mixture of dichloro compound (**3c**) (0.2 g) a 2 M sodium hydroxide (1 ml) in ethanol (20 ml) was refluxed for 1 h. The reaction mixture was treated by a method similar to that used for Method (a). Yellow needles (0.12 g, 72%); mp 182—184 °C. The IR spectrum was identical with that of a sample prepared by Method (a) and the mixed melting point was not depressed.

*6-Hydroxy-12-methyl-7,12-dihydrobenzo[6,7]cyclohept[1,2-*b*]indol-7-one (**6**).* *(a)*: A mixture of **5** (0.3 g) and 2 M sodium hydroxide (30 ml) in ethanol (60 ml) was refluxed for 1 h. The reaction mixture was concentrated and diluted with water. It was made slightly acid by adding 2 M sulfuric acid, and then extracted with chloroform. The solvent was removed and the residue was chromatographed on silica gel. From benzene effluent, **6** was obtained as yellow plates (0.14 g, 47%); mp 235—237 °C. IR(KBr): ν_{OH} 3272 and $\nu_{conjugated\ C=O}$ 1636 cm^{-1}. PMR (100 MHz, in DMSO) δ 7.3—9.1 (m) and 4.18 (s, N-CH_3). UV: λ_{max}^{MeOH} 233 (log ε=4.34); 312 (4.67); and 422 (3.86) nm. Found: C, 78.64; H, 4.70; N, 5.38%. Calcd for $C_{18}H_{13}O_2N$: C, 78.53; H, 4.76; N, 5.09%. MS: *m/e* 275 (M^+); 247 (M^+-CO, base), and 218 (M^+-2CO).

(b): Compound **5** was dissolved in trifluoroacetic acid, followed by dilution with water to give **6**.

*6-Methoxy-12-methyl-7,12-dihydrobenzo[6,7]cyclohept[1,2-*b*]indol-7-one (**7**).* A mixture of **6** (0.2 g); dimethyl sulfate (0.48 g); and 2 M sodium hydroxide (2.4 ml) in acetone (20 ml) was refluxed for 2 h. The reaction mixture was poured into water and extracted with chloroform. The extract was dried and the solvent was removed. The residue was chromatographed on silica gel. The product obtained from the benzene effluent was recrystallized from ethanol to give yellow needles (0.13 g, 62%); mp 211—213 °C. IR(KBr): 1593, 1581, and 1130 cm^{-1}. UV: λ_{max}^{MeOH} 244 (log ε=4.30); 266 (4.12), and 295 (4.72) nm. PMR (100 MHz, in $CDCl_3$): δ 8.74 (1H; m, H-8), 7.2—7.9 (7H, m, benzenoid), 6.80 (1H, s, H-5), 3.97 (3H, s, N-CH_3 or O-CH_3), and 3.93 (3H, s, C-CH_3 or O-CH_3). Found: C, 78.79; H, 5.19; N, 4.83%. Calcd for $C_{19}H_{15}O_2N$: C, 78.87; H, 5.23; N, 4.84%.

The authors wish to express their thanks to Dr. Masafumi Yasunami and Professor Kahei Takase of Tohoku University for their helpful suggestions and for obtaining the ^{13}C NMR spectrum. We also would like to thank Professor Yasuo Iwanami of Keio University and Dr. Takeshi Inagaki of Nitto Chemical Industry Co., Ltd, for measurements and analyses of the mass spectra. The authors are grateful to the Sankyo Co., Ltd., for doing a part of the elemental analyses.

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