Notes

An Unusual Rearrangement of a Benzoxazepinone to an Indoline

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In the course of a synthetic effort on one of our favorite templates, namely, the benzoxazepine ring system, we had occasion to prepare the benzoxazepinone **4** by a sequence of three steps starting with the known aminobenzhydrol derivative **1**, as depicted in Scheme I. When compound **4** was subjected to LAH reduction, an unusual transformation took place to produce the indoline aldehyde derivative **5**. The structure was established by single-crystal X-ray analysis and was also confirmed by ^{1}H NMR spectrum (see Experimental Section).

Furthermore, reaction of **5** with $NaBH_4$ gave carbinol **6**. The analytical and spectral results for **6** were consistent with the proposed structure.

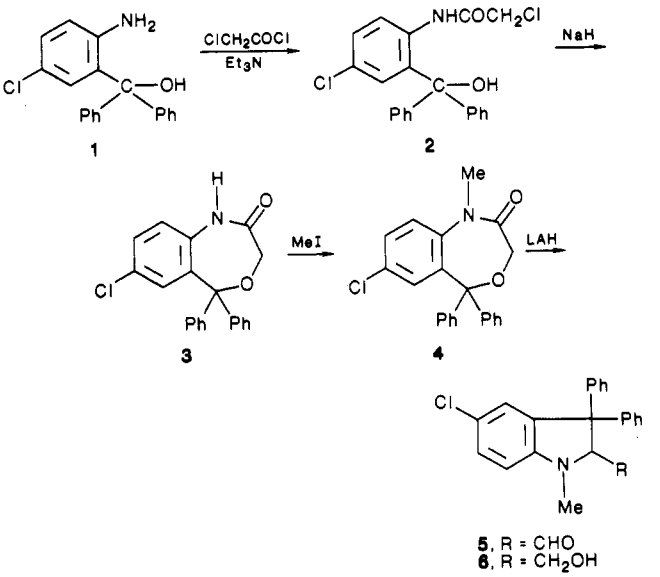
We propose two mechanisms, A and B (Schemes II and IV), to account for the transformation **4** → **5**. In mechanism A (Scheme II) two steps are considered. As to the first step, several precedents for the formation of an enamine as a result of the reduction of a tertiary amide with a hydride reagent (as in **4** → a) are found in the literature.[3] In step 2, we propose that the generation of the anion from the enol ether system (as shown in structure a) takes precedence over the enamine system (see structure b in Scheme III), to produce the observed product **5** after workup of the LAH reaction. During reduction the integrity of the C=O bond must be protected as an aluminum complex. An enamine-type mechanism (b → c, Scheme III) would have led to the amino ketone c, but it does not take place since the aniline nitrogen is only weakly nucleophilic being a part of the *p*-Cl-substituted aniline system. In mechanism B, step 2, d → e (Scheme IV), a C–O cleavage reaction to form an extended conjugated system is depicted. Step 3 represents a Mannich-type cyclization and leads after workup to the final product, aldehyde **5**.

Experimental Section

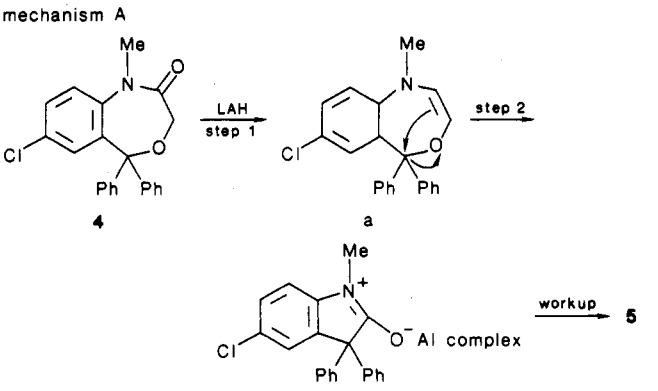
Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, IR spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, and NMR spectra on a Varian Model XL-100 spectrometer. NMR peaks are recorded in parts per million downfield from tetramethylsilane.

***N*-(2-Chloroacetyl)-4-chloro-α-hydroxy-α,α-diphenyl-*o*-toluidine (2).** Triethylamine (10.1 g; 0.1 mol) was added to a solution of compound 1[1] (15.49 g; 0.05 mol) in 290 mL of ether, and the solution was cooled to 5 °C and treated dropwise during 1 h with a solution of chloroacetyl chloride (5.65 g; 0.05 mol) in 145 mL of ether keeping the temperature at 5 °C. The mixture was then stirred at 5 °C for 1 h at room temperature for 18 h. It was cooled in ice, 290 mL of H_2O was added, and the mixture was stirred at room temperature for 30 min. The suspension was

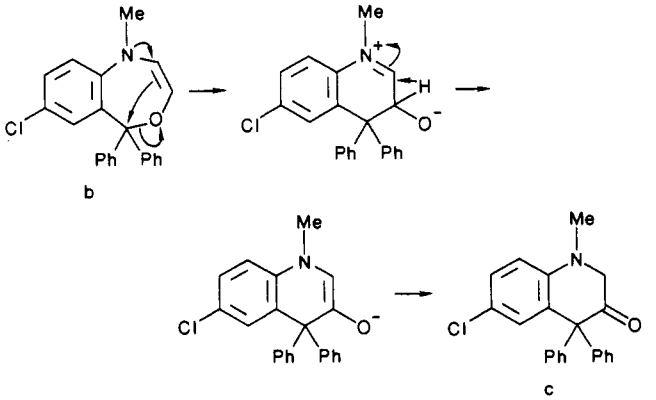
Scheme I



Scheme II



Scheme III



(1) Petyunin, P. A.; Konshin, M. E. *J. Gen. Chem. USSR (Engl. Transl.)* **1957**, *27*, 539.
(2) To be submitted to *Acta Crystalogr. Sec. C: Chem. Struct. Commun.*
(3) See, for example: Nagata, W.; Hirai, S.; Kawata, K; Okumura, T. *J. Am. Chem. Soc.* **1967**, *89*, 5046; **1968**, *90*, 1650. Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *Chem. Commun.* **1969**, 877.
(4) We gratefully acknowledge the discussion with Dr. E. Jon Jacobsen.

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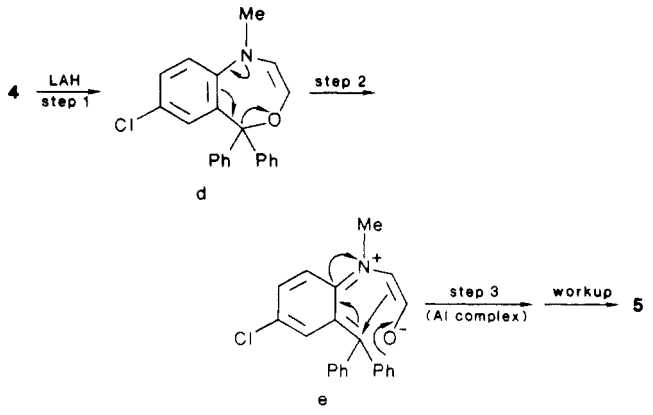
Scheme IV

mechanism B



filtered, and the solid washed with H_2O and ether to give 8.15 g of compound **2**, mp 185–186.5 °C. The filtrate was separated into layers, and the aqueous layer was extracted once with ether. The combined ether extract was washed with cold solvents as follows: H_2O (100 mL), 10% HCl (3 × 50 mL), H_2O, $NaHCO_3$ solution (3 × 50 mL), and saturated salt solution. It was dried ($MgSO_4$) and evaporated. Crystallization from ether gave 5.05 of **2**, g mp 184–185 °C. Yield: 68%. The analytical sample melted at 186–187 °C (from ether): UV (EtOH) λ_{max} 252 nm (ϵ 14 450), 289 sh (1050); IR 3410, 3280 (NH/OH), 3060 (=CH), 1650 (C=O), 1600, 1585, 1495 (C=C), 1535 (amide H), 1445, 1395, 1270 (CH/C-N), 835, 765, 750, 700, 655 (Ar/ether) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.92 (C(=O)CH_2Cl, A_2, s), 6.5 (H_3, d, $J_{3,4}$ = 3 Hz), 7.4 (H_5, d of d, $J_{5,6}$ = 8 Hz), 8.18 (H_6, d), 7.35 (Ph's), 10.4 (NH-C=O); mass spectrum, *m/e* 385.

Anal. Calcd for $C_{21}H_{17}Cl_2NO_2$: C, 65.29; H, 4.44; Cl, 18.36; N, 3.63. Found: C, 65.24; H, 4.61; Cl, 18.46; N, 3.60.

7-Chloro-1,5-dihydro-5,5-diphenyl-4,1-benzoxazepin-2-(3*H*)-one (3). A solution of **2** (88.84 g; 0.230 mol) in 460 mL of THF was added during 15 min to a suspension of NaH (19.36 g; 0.46 mol of 57% dispersion in mineral oil, washed with ether) in 2300 mL of THF. The mixture was stirred at room temperature for 20 h and then refluxed for 1.75 h. It was evaporated, and the residue was cooled in ice and stirred with 2 L of H_2O for 30 min (200 mL of ether was added to aid solidification). The suspension was filtered and the solid washed with H_2O and ether. Crystallization from MeOH gave 48.53 g of compound **3** as prisms, mp 211.5–212.5 °C. Second crop, 11.1 g, mp 197–198 °C. Yield: 74%. Both crops were identical by NMR, TLC and mixed mp with the polymorph obtained from a previous run which melted at 197–198 °C (from MeOH) and was analyzed: UV (EtOH) λ_{max} 254 nm (ϵ 15 950), 287 sh (2200), 294 sh (1600); IR 3210, 3120, 3080 (NH/=CH), 1690, 1675 (C=O), 1600, 1575, 1685 (C=C), 1415, 1400 (CH), 1220, 1110 (C-N/C-O), 885, 835, 760, 700 (Ar) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.28 (H_3, s), 6.48 (H_6, d, J = 2.5 Hz), 7.45 (H_8, d of d), 7.0–7.5 (H_9), 7.0–7.5 (Ph's), 10.1 (NHC=O); mass spectrum, *m/e* 349.

Anal. Calcd for $C_{21}H_{16}ClNO_2$: C, 72.10; H, 4.61; Cl, 10.13; N, 4.01. Found: C, 71.95; H, 4.48; Cl, 10.22; N, 4.02.

7-Chloro-1,5-dihydro-1-methyl-5,5-diphenyl-4,1-benzoxazepin-2(3*H*)-one (4). Sodium hydride (0.421 g; 0.01 mol of 57% dispersion in mineral oil) was added to a solution of **3** (3.49 g; 0.01 mol) in 100 mL of DMF, and the mixture was stirred for 2.25 h. The resulting solution was treated with methyl iodide (2.84 g; 0.02 mol) during 2 min and then stirred for 24 h (allowed to stand 48 h). It was evaporated, the residue was taken up in CH_2Cl_2–H_2O, and the organic layer was washed with H_2O and saturated salt solution, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether–petroleum ether (30–60 °C) to give 2.60 g of compound **4**, mp 163.5–164.5 °C. Second crop: 0.261 g, mp 164–165 °C. Yield: 79%.

The analytical sample melted at 164–165 °C: UV (EtOH) λ_{max} 253 nm (ϵ 12 900), 258 sh (11 450), 264 sh (8350), 271 sh (4900), 287 sh (1050), 291 sh (800); IR (C=O), 1685, 1640, 1590, 1565, 1475 (C=C), 1445, 1410 (CH), 1095, 1075 (C-O), 835, 770, 755, 700 (Ar) cm^{-1}; NMR ($CDCl_3$) δ 2.59 (CH_3NC=O), 4.3 (H_3, s), 6.65 (H_6, d, J = 2.5 Hz), 7.1 (H_9, d, J = 9 Hz), 7.3 (Ph's), 7.4 (H_8, dd, J = 2.5, 9 Hz); mass spectrum, *m/e* 363.

Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; Cl, 9.74; N, 3.85. Found: C, 72,57; H, 5.22; Cl, 9.63; N, 3.92.

5-Chloro-1-methyl-3,3-diphenyl-2-indolinecarboxaldehyde (5). A solution of **4** (4.57 g; 0.0126 mol) in 100 mL of THF was added to a solution of LAH (4.57 g) in 250 mL of THF during 10 min, and the mixture was stirred at room temperature for 19.5 h. It was cooled in ice and decomposed in succession with 4.6 mL of H_2O, 4.6 mL of 15% aqueous NaOH, and 13.8 mL of H_2O. The suspension was then stirred for 1 h and filtered and the cake washed with THF. The filtrate was dried ($MgSO_4$) and evaporated to give 4.6 g of an amorphous yellow solid. Crystallization from MeOH at −70 °C gave a solid which showed two spots on TLC (silica gel, 50% ethyl acetate–cyclohexane). The total product was therefore chromatographed on 450 g of silica gel by using 10% ethyl acetate–cyclohexane. Fractions 1–5 (625 mL) gave no material. Fractions 6–124 (25 mL each) gave 3.0 g of compound **5** (pure by TLC and identical by TLC and MNR with the crystallized sample below). Crystallization from MeOH at −70 °C gave 1.5 g of **5**: mp 111–117 °C; UV (EtOH) λ_{max} 258 nm (ϵ 9250), 319 (2850); IR (C=O), 1720 1600, 1480 (C=C), (C-N), 1300, 1210, 1100, 820, 700 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (NCH_3), 4.55 (H_2, d, J = 4.0 Hz), 6.5 (H_7, $J_{6,7}$ = 9 Hz), 7.0–7.6 (H_4, H_6, Ph's, m), 9.1 (CHO, d, J = 4.0 Hz); mass spectrum, *m/e* 347.

Anal. Calcd for $C_{22}H_{18}ClNO$: C, 75.96; H, 5.22; Cl, 10.19; N, 4.03. Found: C, 76.24; H, 5.34; Cl, 10.26; N, 4.13.

Better crystals were obtained for X-ray by crystallization from ethyl acetate–petroleum ether (30–60 °C), mp 126–127 °C.

5-Chloro-1-methyl-3,3-diphenyl-2-indolinemethanol (6). Sodium borohydride (0.3 g) was added to a solution of **5** (0.3 g) in 10 mL of EtOH and stirred for 21 h. EtOH was evaporated at 35 °C in vacuo, 10 mL of H_2O and 25 mL of ether were added, and the aqueous layer was extracted once more with ether. The combined ether extract was washed once with H_2O and saturated salt solution, dried ($MgSO_4$), and evaporated to give 0.286 g of an oily solid. The product (0.256 g) was chromatographed on 25.6 g of silica gel using 10% ethyl acetate–cyclohexane. Fractions 1–3 (220 mL) gave no material. Fractions 4–7 (10 mL each) gave a trace. Fractions 8–18 (10 mL each) gave no material. Fractions 19–39 (10 mL each) gave 0.195 g of compound **6** (single spot on TLC). Crystallization from petroleum ether (30–60 °C) gave 0.113 g: mp 58 °C (effervesces); UV (EtOH) λ_{max} 262 nm (ϵ 9600), 266 sh (9300), 272 sh (7760), 318 (2660); IR 3370 (OH), 1595, 1490, 1480 (C=C), 1045, 1035 (C-O), 815, 700 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (OH, exchangeable), 2.95 (NCH_3, 3.6 (CH_2O, m), 4.27 (H_2, t), 6.45 (H_7, d, $J_{6,7}$ = 9 Hz), 7.0–7.5 (H_4, H_6, Ph's, m); mass spectrum, *m/e* 349.

Anal. Calcd for $C_{22}H_{20}ClNO$: C, 75.52; H, 5.76; Cl, 10.13; N, 4.00. Found: C, 75.49; H, 5.98; Cl, 10.02; N, 4.00.

In another experiment the product was obtained after chromatography without crystallization as a polymorph melting at 104–107 °C. It was identical with the above crystallized sample as shown by IR, UV, and TLC.

Registry No. 1, 21741-00-4; **2**, 98414-59-6; **3**, 98414-60-9; **4**, 105104-37-8; **5**, 105104-38-9; **6**, 105104-39-0.

An Unusual Isomerization of a Furan-Containing Compound

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In connection with our interest in tazadolene succinate, a structurally novel nonopioid analgesic with antidepressant properties[1] (1), we became interested in compound

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