Two Anomalous Cyclizations in the Dibenz[b,f][1,4]oxazepine Series

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The cyclization of 3,5′-dichloro-2′-phenoxypropionanilide (**2**) to a trimeric cyclohexane **4** and of 4-bromo-5′-chloro-2′-phenoxybutyranilide (**1**) to a tetracyclic pyrrolooxazepine **5** is reported.

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A number of dibenz[*b,f*][1,4]oxazepines have been prepared in these laboratories in order to evaluate their activity as antipsychotic agents (1). In the course of this effort, the two haloanilides **1** and **2** were subjected to Bischler-Napieralski cyclization conditions (2). The initially formed oxazepines reacted further to form additional carbon-carbon bonds and to give more highly cyclized products.

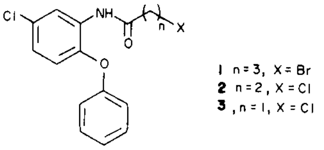

Figure 1

The chloropropionanilide **2** gave the trimer **4** as a high melting, nearly insoluble compound in 70% yield. The structure assignment is largely based on the ^{13}C nmr spectrum which shows three distinct imino carbon atom singlets. The spectrum also shows three aromatic C-10a carbon singlets, three alicyclic methylene triplets and a plethora of overlapping aromatic carbon signals. There are two aromatic singlets in a 2:1 ratio of peak heights that have been assigned to the three carbons 4a with the assumption that two of the lines are coincident. A similar 2:1 pair of alicyclic doublets has been assigned to the three benzylic methine carbon atoms. The empirical formula, $C_{45}H_{30}Cl_3N_3O_3$, of the trimer **4** was confirmed by high resolution mass spectroscopy. The ^1H nmr spectrum also confirms the structure assignment with three broad alicyclic signals in the ratio of 3:4:2.

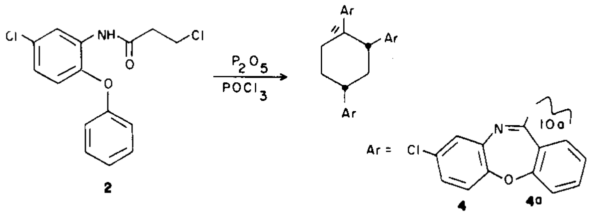

Figure 2

The trimer **4** is shown as a 1,2,4-trisubstituted cyclohexane. The 1,2,3 arrangement is less likely because this would require carbon-carbon bond breakage as well as bond formation to give **4** from **2**. The 1,3,5 arrangement is eliminated on symmetry grounds.

The stereochemistry of **4** is shown as the all equatorial *trans-syn* configuration rather than as one of the three alternatives which has an axial aromatic group. Whereas this assignment has not been rigorously established, it is supported by the ^1H nmr spectrum. The benzylic methine hydrogen atoms show a broad band 25 Hz in width at half-height. One would expect chemical shift differences of greater than 48 Hz at 80 MHz if one of the protons was geminally and axially disposed to an aromatic ring (3). No mechanism is presented for the formation of **4**.

When bromo amide **1** was subjected to the Bischler-Napieralski cyclization, a product was obtained in high yield which, high resolution mass spectroscopy revealed, had lost the elements of both water and hydrogen bromide. The structure of this product, **5**, was deduced from its ^1H nmr spectrum which shows a one-proton triplet at δ 5.28 assigned to the vinyl hyrogen, a two-proton doublet of triplets at 2.70 assigned to the allylic methylene hydrogens, and a two-proton triplet at 3.82 assigned to the methylene hydrogens adjacent to nitrogen. The chemical shift of the last triplet and the absence of a N-H stretching band in the ir spectrum rule out the alternative structure **6**.

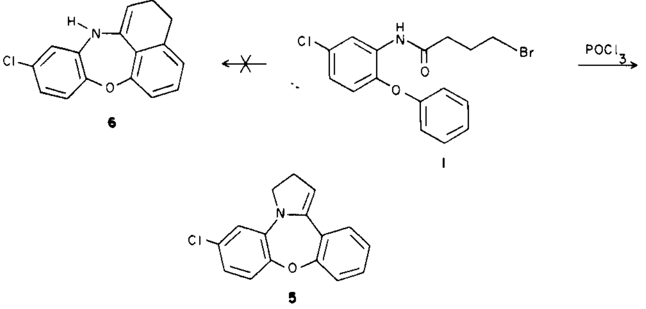

Figure 3

Compound **5** rapidly darkened upon exposure to air. It was also oxidized with dichlorodicyanobenzoquinone or mercuric acetate to give a dark oil that was devoid of alicyclic signals in the ^1H nmr. We were unable to characterize any of the oxidation products. Catalytic hydrogenation of **5** gave a white, crystalline, air-stable tetrahydropyrrole **7**, which has been completely characterized.

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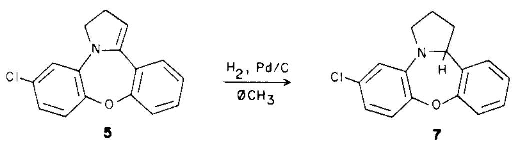

Figure 4

The normal Bischler-Napieralski cyclization of **1** must be followed by alkylation on nitrogen by the side chain with concurrent double bond migration.

Cyclization of the chloroacetanilide **3** has been reported by Nagarajan and co-workers to proceed normally to the 11-chloromethyl dibenz[*b,f*][1,4]oxazepine (4). Hunziker has reported an anomalous cyclization of a 4-amino 2′-phenoxy-butyranilide which did not give a dibenz[*b,f*]-[1,4]oxazepine (5).

EXPERIMENTAL

Infrared, uv, ^{13}C nmr, and mass spectra were run on a Perkin-Elmer 21, Cary 14, Varian FT-80 and AEI MS9 spectrometer, respectively. The ^{1}H nmr were obtained on Varian EM-360, FT-80, and HA-100 spectrometers.

The microanalyses were performed by the Lederle Scientific Services Department. Melting points were obtained on a Thomas-Hoover Unimelt in unsealed capillaries and are not corrected. Pyridine was dried by distillation from calcium hydride and THF by distillation from lithium aluminum hydride. All reactions were carried out in an argon atmosphere, and organic extracts were dried over anhydrous magnesium sulfate.

4-Bromo-5′-chloro-2′-phenoxybutyranilide (**1**). General Procedure.

A mixture of 31.66 g. (144.1 mmoles) of 5-chloro-2-phenoxyaniline (6) and 12.6 ml. (156 mmoles) of dry pyridine was dissolved in 300 ml. of dry THF. The solution was cooled in an ice-bath and 29.0 g. (156 mmoles) of freshly distilled 4-bromobutyryl chloride was added dropwise over a period of 1 hour. The resulting slurry was stirred overnight as it warmed to room temperature. The reaction mixture was diluted with 200 ml. of ether and the resulting slurry filtered. The filtrate was washed with 10% sodium bicarbonate (1 × 100 ml.), dried and evaporated to give 48.91 g. of a red oil that solidified upon standing. Recrystallization from isopropyl ether/hexane gave a first crop of 34.08 g. of a white solid, m.p. 86-88°; ir (potassium bromide): 1667 (amide I), 1597 (aromatic), 1524 (amide II), 1414 cm^{-1}; nmr (deuteriochloroform): δ 8.48 (d, J = 4, 1H, *o*-N), 7.83 (b, 1H, NH), 6.86-7.54 (m, 6H, aromatic), 6.75 (d, J = 9, 1H, *m*-N), 3.47 (t, J = 6, 2H, Br-CH_2), 2.52 (t, J = 6, 2H, $CH_2C{=}O$), 2.21 (q, J = 6, 2H, C-CH_2-C); ms (70 eV): m/e 367 (9.8%, M+), 287 (11.8, M-HBr), 274 (3.9, M-O∅), 219 (100, M-C_4H_5BrO). Concentration of the mother liquor, gave a second crop of 1.67 g., m.p. 79-84° (Σ = 35.75 g., 67.3 % yield).

Anal. Calcd. for $C_{16}H_{15}BrClNO_2$: C, 52.13; H, 4.10; N, 3.80. Found: C, 52.13; H, 4.17; N, 3.82.

3,5′-Dichloro-2′-phenoxypropionalilide (**2**).

This compound was obtained as a white solid, m.p. 102.5-104.5° in 70.7% yield; ir (chloroform): 1698, 1600, 1520 cm^{-1}; nmr (deuteriochloroform): δ 8.47 (d, J = 4, 1H), 7.91 (b, 1H), 6.82-7.50 (m, 6H), 6.71 (d, J = 9, 1H), 3.79 (t, J = 6, 2H), 2.78 (t, J = 6, 2H); ms (70 eV): m/e (23.2%, M+), 273 (3.2), 219 (100).

Anal. Calcd. for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; Cl, 22.86; N, 4.52. Found: C, 58.25; H, 4.22; Cl, 23.16; N, 4.62.

11,11′,11″-(Cyclohexane-1,2,4-triyl)tris[8-chlorodibenz[*b,f*][1,4]oxazepine] (**4**).

A mixture of 7.00 g. (22.6 mmoles) of **2** 9.65 g. of phosphorus pentoxide, and 75 ml. of phosphorus oxychloride was heated at reflux for 3 hours. The cooled reaction mixture was evaporated at reduced pressure and the residue poured onto 300 ml. of ice and 100 ml. of concentrated ammonium hydroxide. Filtration and drying gave 6.72 g. of a yellow solid. The solid was digested with hot methanol and filtered to give 4.20 g. (72.2% yield) of a yellow powder, m.p. 205° dec. The powder was recrystallized from pyridine/isopropyl ether to give the analytical sample, 1.55 g. (26.6% yield) of a white solid, m.p. 289-292°; ir (potassium bromide): 2920 (w, CH), 1615, 1490 (aromatic) cm^{-1}; nmr (pyridine-d_5): δ 7.00-7.88 (m, 21H, aromatic), 3.54-4.02 (b, 3H, Ar-CH), 2.36-2.83 (m, 4H, CH_2-CH_2), 1.86-2.26 (b, 2H, ArC-CH_2-CAr); ^{13}C nmr (pyridine-d_5): 175.2 (27), 174.6 (25), and 174.0 (16, s, N=C), 162.2 (14) and 161.7 (24, s, aromatic C-4a), 142.5 (18), 142.3 (13), and 142.2 (17, s, aromatic C-10a), 46.6 (54, d, C-4), 41.9 (95, d, C-1 and 2), 36.7 (34, t, C-3), 34.7 (27) and 34.4 (41, t, C-5 and 6) ppm; ms (70 eV): m/e 765.1290 (9.7%, M+, calcd. for $C_{45}H_{30}Cl_3N_3O_3$: 765.1253), 547 (12), 537 (17.9, M-Ar), 522.0882 (14.8, M-HArCH_2, calcd. for $C_{31}H_{20}Cl_2N_2O_2$: 522.0902), 509 (36.4 M-ArCHCH_2), 243 (100, HArCH_2).

Anal. Calcd. for $C_{45}H_{30}Cl_3N_3O_3$: C, 70.46; H, 3.94; Cl, 13.86; H, 5.48. Found: C, 70.21; H, 4.24; Cl, 13.53; N, 5.64.

6-Chloro-2,3-dihydrodibenz[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine (**5**).

A mixture of 5.01 g. (13.6 mmoles) of **1**, 5.8 g. phosphorus pentoxide, and 27 ml. of phosphorus oxychloride was heated at reflux for 6 hours. The cooled reaction mixture was evaporated at reduced pressure and the residue poured onto 50 ml. of concentrated ammonium hydroxide and 100 g. of ice. Extraction with methylene chloride (3 × 50 ml.), drying, and evaporation, gave 3.67 g. of dark red solid (100% yield), m.p. 111-115°, which was not sufficiently stable for elemental analysis; ir (chloroform): 2837 (w), 1595, 1498 cm^{-1}; nmr (deuterochloroform): δ 6.60-7.67 (m, 7H, aromatic), 5.28 (t, J = 3.5, 1H, =CH), 3.82 (t, J = 9.5, 2H, N-CH_2), 2.70 (t of d, J = 9.5 and 3.5, 2H, =C-CH_2); ms (70 eV): Calcd. for $C_{16}H_{12}ClNO$, m/e 269.0607; found, 269.0597.

6-Chloro-1,2,3,13b-tetrahydrodibenz[*b,f*]pyrrolo[1,2-*d*]oxazepine (**7**).

A mixture of 3.52 g. (13.0 mmoles) of **5** and 250 mg. of 10% palladium on carbon in 50 ml. of toluene was hydrogenated over the weekend at 48 psi in a Parr Shaker. The mixture was filtered with the aid of Celite and evaporated to give 3.31 g. of black oil. The oil was chromatographed on a Waters Prep LC-500 employing a 30:1 mixture of hexane:ethyl acetate. A flow rate of 250 ml./minute was used and one major peak with a retention time of 3.6 minutes was obtained. Removal of the solvent at reduced pressure left 1.28 g. (36% yield) of an orange solid, m.p. 130-136°. The analytical sample was recrystallized from isopropyl ether-ethyl acetate, m.p. 140-141.5°; ir (potassium bromide): 1591, 1496, 1200 cm^{-1}; nmr (deuterochloroform): δ 7.16 (b, 4H), 6.96 (d, J = 10, 1H, H-8), 6.49 (d of d, J = 10 and 2, 1H, H-7), 6.37 (d, J = 2, 1H, H-5), 5.50 (t, J = 8, 1H, ∅-CH), 3.32 (m, 2H, NCH_2), 1.78-2.52 (b, 4H); uv (methanol): λ max 215 mμ (log ϵ = 4.51), 268 (4.02), 313 (3.69); ms (70 eV): m/e 271 (100%, M+), 254 (1.), 242 (7.), 217 (17); ^{13}C nmr (deuterochloroform): see figure 5.

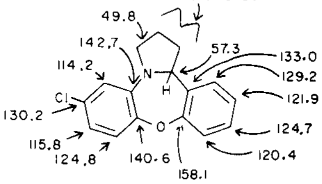

Figure 5

Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; Cl, 13.05; N, 5.15. Found: C, 70.89; H, 5.30; Cl, 12.78; N, 5.16.

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