Reaction of 2-Chlorocyclohepta[*b*]pyrrole-3-carbaldehyde with *o*-Phenylenediamine

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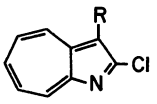
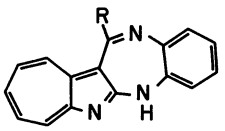
Synopsis. Reaction of 2-chlorocyclohepta[*b*]pyrrole-3-carbaldehyde with *o*-phenylenediamine gave 1*H*-2-(2-chlorocyclohepta[*b*]pyrrol-3-yl) benzimidazole (**3a**) and 5*H*-12,13-dihydrocyclohepta[1′,2′:4,5]pyrrolo[2,3-*b*][1,5]benzodiazepine (**4a**). Some reactions of **3a** and **4a** were also described.

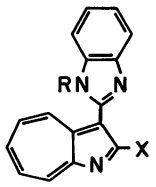
Heterocycles used on azaazulene skeleton are interesting not only to investigate their chemical properties, but also to study their physiological properties.[1–3] Although several papers have appeared on the syntheses of cyclohepta[*b*]pyrrole (1-azaazulene) derivatives fused with heterocycles, little is known regarding the azepine or diazepine rings fused on the cyclohepta[*b*]pyrrole skeleton.[4] Recently, we reported the synthesis of 5*H*-12-methoxycyclohepta[1′,2′:4,5]pyrrolo[2,3-*b*][1,5]benzodiazepine (**2a**) by the treatment of ethyl 2-chlorocyclohepta[*b*]pyrrole-3-carboxylate (**1a**) with *o*-phenylenediamine and subsequent reactions.[4] To obtain the fused diazepine **2b**, itself, it was considered that 2-chlorocyclohepta[*b*]pyrrole-3-carbaldehyde[5] (**1b**) would be an efficient substance. We therefore treated **1b** with *o*-phenylenediamine; however, the expected fused diazepine (**2b**) was not obtained. Instead, 1*H*-2-(2-chlorocyclohepta[*b*]pyrrol-3-yl)benzimidazole (**3a**) and fused dihydrodiazepine (**4a**) were obtained. Here we describe the syntheses and some reactions of **3a** and **4a**.



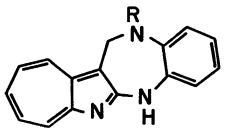
1a: R = CO_2Et
1b: R = CHO



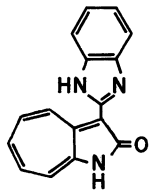
2a: R = OMe
2b: R = H



3a: R = H, X = Cl
3b: R = Ac, X = Cl
3c: R = H, X = OC_4H_9



4a: R = H
4b: R = Ac



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Treatment of **1b** with *o*-phenylenediamine in ethanol under reflux for 2 h gave **3a** and **4a** in 63 and 29% yield, respectively. When the same reaction was carried out for 30 h in dichloromethane in the presence of acetic acid at room temperature, **3a** (60%) and **4a** (12%) were obtained. These structures were deduced by means of their spectroscopic data and elemental analyses as well as some chemical reactions. In the mass spectrum of **3a**, the molecular ion peak was seen at *m/z* 279 (for ^{35}Cl) and 281 (for ^{37}Cl), and no carbonyl signal was seen in its IR spectrum. This shows that *o*-phenylenediamine reacts with the formyl group and not with the chloro substituent on the cyclohepta[*b*]-pyrrole nucleus. The result is appreciated from the reports that formyl group at C-3 is more reactive than chloro group at C-2 on cyclohepta[b]pyrrole nucleus toward hydroxylamine and phenylhydrazine,[5] and that the reactions of aldehydes with *o*-phenylenediamine are well known methods leading to 2-substituted benzimidazoles.[6] In the ^1H NMR spectrum of **3a**, signals of H-4 of cyclohepta[*b*]pyrrole nucleus appeared at δ=10.27, which would be deshielded by a benzimidazole ring having a co-planarity with the 1-azaazulene ring. Acetylation of **3a** with acetic anhydride gave the acetate **3b** in excellent yield. In the ^1H NMR spectra of **3b**, the signals of H-4 were observed at δ=8.78; this is a higher field resonation than that of **3a**. This would be attributed to a shielding effect of benzimidazole ring, which may deviate from a co-plane of cyclohepta[*b*]pyrrole ring. Compound **4a** was acetylated with acetic anhydride to give **4b** in excellent yield. In the mass spectra of **4a** and **4b**, molecular ion peaks were seen at *m/z* 247 and 289, respectively. In the ^1H NMR spectrum of **4a**, the 2H siglet of methylene protons at C-12 was observed at δ=4.51, whereas a coupled pair of 2H doublets were seen at δ=4.12 and 6.23 with 15.0 Hz in the ^1H NMR spectrum of **4b**. This is resonably considered to be an anisotropic effect of the acetyl group. Other signals of the spectra accord with the proposed structures.

It is considered that compound **4a** was produced reductively; thus, an increased yield of **4a** was expected under the reductive conditions. Therefore, the reaction was carried out in the presence of zinc powder and trifluoroacetic acid but gave only a complex mixture, from which no distinct product was obtained. Although the mechanisms of the formations of **3a** and **4a** are not known so far, it is suggested that the

formations of **3a** and **4a** may partly involve the oxidation–reduction stage of both the precursors each other to remove mutual instabilities.

It is considered that preferred cyclization of a five-membered ring rather than a seven-membered ring causes a supperior formation of the precursor of **3a**, which would partly undergo autoxidation to give **3a**.

In the mass spectrum of **4a**, a peak of ($M^+ -2$) is seen at *m/z* 245 with 20% of the relative intensity. Therefore, the formation of **2b** was expected to be achieved by dehydration of **4a**. Treatment of **4a** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, nevertheless, afforded a sparingly soluble dark red powder; no **2b** was detected.

Next, to synthesize **2b**, the bromination of **4a** and successive hydrobromination was attempted. However, the bromination of **4a** with *N*-bromosuccinimide gave a complex mixture and no identified product was obtained.

Expecting intramolecular cyclization, **3a** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing 1-butanol but afforded the ether **3c** and cyclohepta[*b*]pyrrol-2(1*H*)-one derivative **5** in 60% and 6% yield, respectively. Compound **3c** is converted to **5** in excellent yield by treatment with 48% HBr.

Experimental

The melting points were uncorrected. The ^{1}H NMR spectra (250 MHz) and the ^{13}C NMR spectra (62.87 MHz) were taken on a Hitachi R-250H spectrometer using $CDCl_3$ as a solvent (TMS as an internal standard) unless otherwise stated. The IR spectra were recorded for Nujol mulls with a Hitachi 270-50 infrared spectrophotometer. The mass spectra were determined with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. Column chromatography was performed on Kieselgel 60.

Reaction of 1*b* with *o*-Phenylenediamine. a) A mixture of **1b**[5] (0.383 g, 2 mmol) and *o*-phenylenediamine (0.216 g, 2 mmol) in ethanol (30 ml) was refluxed for 2 h and evaporated; the residue was chromatographed. Elution with chloroform gave recovered **1b** (0.010 g, 3%). Further elution gave **3a** (0.350 g, 63%), which was recrystallized from cyclohexane–dichloromethane to give red scales, mp 221—223 °C; ^{1}H NMR δ=7.30—7.40 (2H, m, H-5′ and 6′), 7.60—7.85 (2H, m, H-4′ and 7′), 7.95 (1H, dd, *J*=11.0 and 9.8 Hz, H-7), 8.01 (1H, dd, *J*=11.0 and 9.2 Hz, H-5), 8.09 (1H, dd, 11.0 and 9.2 Hz, H-6), 8.71 (1H, d, *J*=9.8 Hz, H-8), 10.20 (1H, brs, NH), and 10.27 (1H, d, *J*=11.0 Hz, H-4); IR 3000—2600 cm^{-1} (NH); MS *m/z* (rel intensity) 281 (3, M^+ +2), 280 (36, M^+ +1), 279 (36, M^+), 278 (85), 277 (53), and 244 (100, M^+ −Cl). Found: C, 68.62; H, 3.67; N, 15.06%. Calcd for $C_{16}H_{10}N_3Cl$: C, 68.70; H, 3.60; N, 15.02%. Elution with ethyl acetate gave **4a** (0.144 g, 29%), which was recrystallized from ethanol to give orange scales, mp 236—237 °C; ^{1}H NMR δ=4.25—4.40 (2H, brs, exchangeable, NH), 4.51 (2H, s, H-12), 6.85—7.02 (4H, m, H-1, 2, 3, and 4), 7.31 (1H, dd, *J*=9.8 and 9.2 Hz, H-8), 7.39 (1H, dd, *J*=10.4 and 9.2 Hz, H-10), 7.48 (1H, dd, *J*=9.8 and 9.2 Hz, H-9), 7.69 (1H, d, *J*=10.4 Hz, H-11), and 7.95 (1H, d, *J*=9.2 Hz, H-7); δ (CF_3CO_2D)=5.31 (2H, s, H-12), 7.48 (1H, dd, *J*=8.5 and 7.3 Hz, H-2), 7.56 (1H, dd, *J*=8.5 and 7.9 Hz, H-3), 7.70 (1H, d, *J*=7.3 Hz, H-1), 7.73 (1H, d, *J*=7.9 Hz, H-4), 8.17—8.25 (3H, m, H-8, 9, and 10), 8.42—8.50 (1H, m, H-11), and 8.55—8.62 (1H, m, H-7); IR 3260 and 3195 cm^{-1} (NH); MS *m/z* (rel intensity) 247 (85%, M^+), 246 (100), 245 (20), and 219 (17). Found: C, 76.21; H, 5.30; N, 16.59%. Calcd for $C_{16}H_{13}N_3 \cdot 1/4\ H_2O$: C, 76.31; H, 5.40; N, 16.69%.

b) A mixture of **1b** (0.958 g, 5.00 mmol), *o*-phenylenediamine (0.541 g, 5.00 mmol), and acetic acid (1 ml) in dichloromethane (50 ml) was stirred for 30 h at room temperature and then poured into water. The mixture was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue gave **3a** (0.833 g, 60%) and **4a** (0.154 g, 12%), successively.

c) To a mixture of **1b** (0.060 g, 0.31 mmol), *o*-phenylenediamine (0.034 g, 0.31 mmol), and zinc powder (0.030 g) in dichloromethane (20 ml) trifluoroacetic acid (1 ml) was added. The solution was immediately discolored and then changed to a brown color. After the mixture was stirred for 20 h at room temperature, water was added; the mixture was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was evaporated to dryness; the chromatography of the residue gave no distinct product.

Acetylation of 3a. A mixture of **3a** (0.230 g, 0.94 mmol), acetic anhydride (3 ml), and pyridine (1 ml) was stirred for 7 d at room temperature. To the mixture water was added; the mixture was neutralized with $NaHCO_3$ and then extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated to give **3b** (0.261 g, 99%) as red crystals, which was recrystallized from cyclohexane to give orange needles, mp 175—176 °C; ^{1}H NMR δ=2.28 (3H, s, CH_3), 7.45—7.55 (2H, m, H-5′ and 6′), 7.87 (1H, dm, *J*=6.1 Hz, H-4′), 7.88 (1H, dd, *J*=10.4 and 9.8 Hz, H-5), 7.99 (1H, dd, *J*=10.1 and 10.0 Hz, H-7), 8.08 (1H, dd, 10.0 and 9.8 Hz, H-6), 8.25 (1H, dm, *J*=7.3 Hz, H-7′), 8.77 (1H, d, *J*=10.1 Hz, H-8), and 8.78 (1H, d, *J*=10.4 Hz, H-4); IR 1716 cm^{-1} (C=O); MS *m/z* (rel intensity) 323 (8, M^+ +2), 322 (5, M^+ +1), 321 (19, M^+), 286 (34), 281 (22), 280 (31), 279 (59), 278 (64), 244 (100), 243 (44), 113 (20), and 90 (25). Found: C, 67.23; H, 3.62; N, 13.08%. Calcd for $C_{18}H_{12}N_3ClO$: C, 67.19; H, 3.76; N, 13.06%.

Acetylation of 4a. A mixture of **4a** (0.130 g, 0.53 mmol), acetic anhydride (10 ml) and 2 drops of concd H_2SO_4 was warmed for 30 min at 70 °C and poured into water. The mixture was neutralized with $NaHCO_3$ and extracted with dichloromethane. The extract was dried (Na_2SO_4) and evaporated to give **4b** (0.144 g, 95%) as orange crystals, which was recrystallized from cyclohexane–dichloromethane to give orange needles, mp 225—226 °C; ^{1}H NMR δ=1.92 (3H, s, CH_3), 4.12 (1H, d, *J*=15.0 Hz, H-12), 6.23 (1H, d, *J*=15.0 Hz, H-12), 7.05—7.20 (3H, m, H-2, 3, and 4), 7.24—7.31 (2H, m, H-9 and NH), 7.45—7.52 (3H, m, H-1, 8, and 10), 8.01 (1H, d, *J*=9.8 Hz, H-7), 8.02 (1H, *J*=11.0 Hz, H-11); IR 3256 (NH) and 1662 cm^{-1} (C=O); MS *m/z* (rel intensity) 289 (20, M^+), 247 (18), 246 (41), 231 (22), 169 (17), 77 (11), and 43 (100). Found: C, 73.81; H, 5.26; N, 14.48%. Calcd for $C_{18}H_{15}N_3O \cdot 1/4\ H_2O$: C, 73.58; H, 5.32; N, 14.30%.

Reaction of 3a with 1-Butanol. A mixture of **3a** (0.200 g, 0.71 mmol) and DBU (0.3 ml) in 1-butanol (20 ml) was refluxed for 4 d and evaporated. The residue was chromatographed. Elution with chloroform gave **3c** (0.136 g, 60%) as orange crystals, which was recrystallized from cyclohexane–dichloromethane to give orange needles, mp 190—191 °C; ^{1}H NMR δ=1.08 (3H, t, *J*=7.3 Hz, CH_3), 1.64 (2H, qt, *J*=7.3 and 7.0 Hz, CH_2), 2.06 (2H, quint., *J*=7.0 Hz, CH_2), 4.89 (2H, t, *J*=7.0 Hz, CH_2), 7.24—7.34 (2H, m, H-5′ and 6′), 7.40—7.65 (2H, m, H-4′ and 7′), 7.65—7.90 (3H, m, H-5, 6, and 7), 8.32—8.40 (1H, m, H-8), 9.99 (1H, d, *J*=9.8 Hz, H-4), and 10.2 brs, NH); IR 3150 cm^{-1} (NH). Found: C, 75.52; H, 5.93; N, 13.36%. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24%. Elution with ethyl acetate gave **5** (0.015 g, 6%) as orange crystals, which was recrystallized from ethanol to

give red needles, mp>300 °C; ^{1}H NMR δ (CF_3CO_2D)=7.65—7.72 (2H, m, H-5′ and 6′), 7.80—7.87 (2H, m, H-4′ and 7′), 8.07 (1H, dd, J=10.4 and 9.2 Hz, H-6), 8.17 (1H, dd, J=10.4 and 9.2 Hz H-7), 8.24 (1H, dd, J=10.4 and 9.2 Hz, H-5), 8.42 (1H, d, J=9.2 Hz, H-8), and 8.85 (1H, d, J=10.4 Hz, H-4); IR 3348 and 2900—2700 (NH), and 1646 cm^{-1} (C=O); MS m/z (rel intensity) 261 (100, M^+), 260 (92), 232 (10), 205 (11), 169 (18), 125 (15), 112 (21), 97 (29), 83 (26), 71 (32), 69 (30), and 58 (50). Found: C, 73.51; H, 4.39; N, 16.00%. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08%.

Reaction of 3c with Hydrobromic Acid. A mixture of **3c** (0.050 g, 0.16 mmol) and 48% hydrobromic acid (20 ml) was refluxed for 3 h and poured into water. The mixture was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give **5** (0.040 g, 97%) as red crystals.

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