Reissert Compound Studies. XLI. Synthesis and Reactions of the Pyrrolo[1,2-*a*]quinoxaline Reissert Compound and its Analogs

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Reaction of pyrrolo[1,2-*a*]quinoxaline, either by the phase-transfer catalyst method or by the trimethylsilyl cyanide method, yielded the Reissert compound, 5-benzoyl-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline. This Reissert compound rearranged to 4-benzoylpyrrolo[1,2-*a*]quinoxaline upon sodium hydride treatment. It also underwent methylation with methyl iodide and sodium hydride. A few Reissert analogs of the pyrroloquinoxaline were also prepared and their reactions studied.

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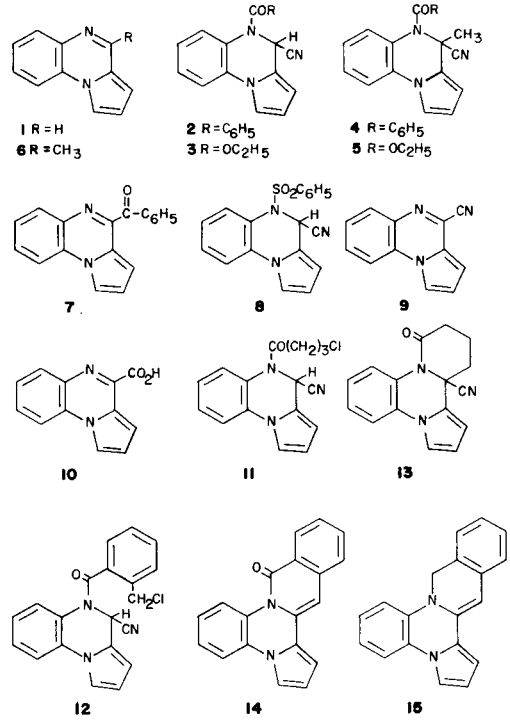
In connection with our study of the application of Reissert compound chemistry (1) to diazaaromatic systems (2) we have reported that, although phthalazine gives a normal Reissert compound (3) and quinazoline (4) and cinnoline (4) give compounds related to Reissert compounds, quinoxaline and 2-methylquinoxaline undergo ring-opening to give rise to *o*-phenylenediaminedibenzamide (4). We now report on the behavior of another quinoxaline derivative, pyrrolo[1,2-*a*]quinoxaline (**1**) towards Reissert compound formation.

Unlike quinoxaline, pyrrolo[1,2-*a*]quinoxaline (**1**) gave the Reissert compound (**2**) by either the phase-transfer catalyst method (5) or by the trimethylsilyl cyanide method (6). The use of ethyl chloroformate in place of benzoyl chloride in the trimethylsilyl cyanide procedure led to the formation of the carbethoxy Reissert analog **3**. Both **2** and **3** reacted with methyl iodide and sodium hydride at 0-10° in anhydrous dimethylformamide under an atmosphere of nitrogen to give 61% of **4** and a quantitative yield of **5**, respectively. Alkaline hydrolysis of **4** resulted in the formation of **6**. 4-Methylpyrrolo[1,2,-*a*]quinoxaline (**6**) had previously (7) been prepared by cyclization of the acetyl derivative of *N*-(2-aminophenyl)pyrrole. Hydrolysis of the Reissert analog **5** also gave rise to **6**. As observed in the quinoline and isoquinoline series (1), Reissert compound **2** rearranged to **7** upon treatment with sodium hydride.

The benzenesulfonyl Reissert analog **8**, which was obtained by a procedure similar to that described for the preparation of **2**, was quite susceptible to treatment with sodium hydroxide. Thus, a mixture of the Reissert analog **8** and the cyano compound **9** was obtained when the final alkaline wash step was included in the usual work-up, while almost pure **8** was obtained in the absence of that step. The cyano compound **9**, which was obtained from **8** was converted to the carboxylic acid **10** by refluxing with ethanolic potassium hydroxide.

As expected (8,9), both the 4-chlorobutanoyl Reissert compound **11** and the 2-chloromethylbenzoyl Reissert compound **12** underwent intramolecular alkylation in the presence of sodium hydride to afford the novel piperidino-pyrrolo-quinoxaline **13** and the pentacyclic derivative **14**, respectively. The base-induced loss of hydrogen cyanide accompanying the cyclization of **12** is to be expected as it leads to a 4 n + 2 (n = 5) π-electron system. Such a driving force is absent in the cyclization of **11**. Reduction of **14** with lithium tetrahydridoaluminate gave **15**.



The reactions described in this article seem to suggest that the chemistry of the pyrrolo[1,2-*a*]quinoxaline Reissert compound parallels that of the quinoline Reissert compound. The [1,2-*a*] fusion of pyrrole to quinoxaline apparently makes the N-1 of quinoxaline sufficiently inert so as to prevent the ring opening observed (4) with quinoxaline and 2-methylquinoxaline.

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EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 710-B spectrometer. Proton magnetic resonance spectra were determined with a Hitachi Perkin-Elmer R24B spectrometer using tetramethylsilane as an internal standard. Microanalyses were performed by Spang Microanalytical Laboratory and mass spectra were obtained from the Midwest Center for Mass Spectrometry at the University of Nebraska (Supported under the N.S.F. Regional Instrumentation Facilities Program). Pyrrolo[1,2-*a*]quinoxaline was purchased from Aldrich and recrystallized from *n*-heptane before use.

5-Benzoyl-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**2**).
Method A.

To a well-stirred mixture of 1.0 g (5.945 mmoles) of pyrrolo[1,2-*a*]-quinoxaline (**1**), 1.18 g (11.89 mmoles) of trimethylsilyl cyanide, and 0.05 g of aluminum chloride in 30 ml of anhydrous dichloromethane was added 1.63 g (11.95 mmoles) of benzoyl chloride. The mixture was stirred for 28 hours and the dichloromethane was washed successively with water (3 x 30 ml), 5% hydrochloric acid (3 x 40 ml), water (40 ml), 10% sodium hydroxide (3 x 40 ml) and water (40 ml). Removal of the solvent from the dried (magnesium sulfate) organic layer, followed by trituration with ethanol afforded 1.41 g (79%) of **2**, mp 171-172° (from ethanol); ir (potassium bromide): 3140, 2950, 1650, 1595, 1500, 1185, 1140, 1120, 910 cm^{-1}; pmr (deuteriochloroform): δ 7.34 (m, 8H), 6.78 (m, 3H), 6.38 (m, 2H).

Anal. Calcd. for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.32; H, 4.47; N, 14.15.

Method B.

The procedure of Bhattacharjee and Popp (5a), and Uff and Budhram (5b) was used to obtain **2** (28%) from pyrrolo[1,2-*a*]quinoxaline (1), benzoyl chloride, aqueous potassium cyanide, benzyltriethylammonium chloride (5% by weight of potassium cyanide) and dichloromethane.

5-Carbethoxy-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**3**).

Using the procedure described for the preparation of **2**, 1.0 g (5.945 mmoles) of **1**, 1.18 g (11.89 mmoles) of trimethylsilyl cyanide, 0.05 g of aluminum chloride, and 1.29 g (11.89 mmol) of ethyl chloroformate gave a 69% yield of **3**, mp 113-115° (from ethanol); ir (potassium bromide): 3130, 2985, 1720, 1600, 1510, 1300, 1145, 1060, 920 cm^{-1}; pmr (deuteriochloroform): δ7.72 (m, 1H), 7.30 (m, 4H), 6.76 (s, 1H), 6.32 (m, 2H), 4.31 (q, J = 7 Hz, 2H) and 1.30 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.51; H, 4.93; N, 15.75.

5-Benzoyl-4-cyano-4-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**4**).

To a well-stirred solution of 0.5 g (1.67 mmoles) of **2** and 1 ml of methyl iodide in 5 ml of anhydrous dimethylformamide at 0-5° under an atmosphere of nitrogen was added 0.12 g (2.50 mmoles) of 50% sodium hydride in oil. After stirring for 2.5 hours, the contents were poured onto ice and the product filtered. Recrystallization from ethanol gave 0.32 g (61%) of **4**, mp 169-171°; ir (potassium bromide): 3050, 1660, 1590, 1505, 1260, 1165, 910, 845, 805 cm^{-1}.

Anal. Calcd. for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.83; N, 13.41. Found: C, 76.81; H, 4.84; N, 13.49.

5-Carbethoxy-4-cyano-4-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**5**).

By a procedure identical to that described for the preparation of **4**, 0.32 g (1.197 mmoles) of **3** gave 0.34 g (100%) of **5**, mp 93-94° (from *n*-hexane); ir (potassium bromide): 3140, 3000, 1720, 1590, 1510, 1375, 1300, 1130, 1050, 800 cm^{-1}; pmr (deuteriochloroform): δ 7.27 (m, 5H), 6.36 (m, 2H), 4.30 (q, J = 7 Hz, 2H) 1.99 (s, 3H) and 1.33 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.30; H, 5.38; N, 15.00.

4-Methylpyrrolo[1,2-*a*]quinoxaline (**6**).
Method A.

A mixture of 0.36 g (1.149 mmoles) of **4**, 0.5 g of potassium hydroxide in 1 ml of water, and 10 ml of ethanol was refluxed for 1.25 hours. Most of the ethanol was then removed *in vacuo*, the contents diluted with water and extracted with dichloromethane. Evaporation of the dried (magnesium sulfate) dichloromethane extract gave a crude compound which was chromatographed on a column of silica gel using chloroform as eluant. Removal of chloroform from the eluate gave 0.16 g (77%) of **6**, mp 134-136° (from *n*-hexane), reported (7) mp 135.5-138°; pmr (deuteriochloroform): δ 7.86 (m, 3H), 7.38 (m, 2H), 6.84 (m, 2H) and 2.71 (s, 3H).

Method B.

A mixture of 70 mg of **5** and 2 ml of 10% aqueous sodium hydroxide in 4 ml of ethanol was heated on a steam-bath for 0.5 hours. The ethanol was removed, the contents diluted with water, and extracted with dichloromethane (2 × 25 ml). Evaporation of the dried (magnesium sulfate) organic extract gave 21 mg (47%) of **6** identical in all respects (mp, ir and tlc) with a sample prepared by Method A.

4-Benzoylpyrrolo[1,2-*a*]quinoxaline (**7**).

Compound **2** (0.2 g, 0.668 mmoles) and 0.064 g (1.333 mmoles) of 50% sodium hydride were reacted in 5 ml of anhydrous dimethylformamide under conditions identical to those described for the preparation of **4** to afford 0.11 g (60%) of **7**, mp 170-171° (from ethanol); ir (potassium bromide): 3130, 1660, 1595, 1460, 1380, 1315, 1260, 1210, 1045, 885 cm^{-1}; ms: m/e 273.0984 ($^{13}CC_{17}H_{12}N_2O$, 18.32%), 272.0946 ($C_{18}H_{12}N_2O$, 100%), 271.0872 (72.97%), 245.0203 (5.01%), 218.0834 (12.31%), 140.0495 (9.32%), 105.0342 (50.91%), 77.0405 (90.04%).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.27; H, 4.58; N, 10.28.

5-Benzenesulfonyl-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**8**).

A mixture of 1.0 g (5.945 mmoles) of **1**, 1.18 g (11.89 mmoles) of trimethylsilyl cyanide, 0.05 g of aluminum chloride, and 2.1 g (11.89 mmoles) of benzenesulfonyl chloride in 30 ml of anhydrous dichloromethane was stirred for 29 hours. The dichloromethane was then washed with water (3 x 35 ml), 5% hydrochloric acid (3 x 35 ml) and water (40 ml). Evaporation of the dried (magnesium sulfate) dichloromethane extract gave 0.67 g (34%) of **8**, mp 142-143° (from *n*-heptane/dichloromethane); ir (potassium bromide): 3050, 2975, 1600, 1495, 1360, 1180, 1170, 1060, 960, 920, 815 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H. 3.91; N, 12.53. Found: C, 64.57; H, 3.89; N, 12.48.

4-Cyanopyrrolo[1,2-*a*]quinoxaline (**9**).

A mixture of 0.42 g (1.252 mmoles) of **8** and 0.07 g (1.458 mmoles) of 50% sodium hydride in 5 ml of anhydrous dimethylformamide was stirred for 1.75 hour and poured onto ice. The yellow solid was filtered and crystallized from ethanol to obtain 0.22 g (91%) of **9**, mp 205-207°; ir (potassium bromide): 3100, 1605, 1540, 1420, 1380, 1260, 1110, 1050, 865 cm^{-1}.

Anal. Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.44; H, 3.75; N, 21.61.

Pyrrolo[1,2-*a*]quinoxaline-4-carboxylic Acid (**10**).

A mixture of 0.34 g (1.76 mmoles) of **9** and 0.9 g (16.04 mmoles) of potassium hydroxide in 12 ml of ethanol was refluxed for 6.5 hours. Most of the ethanol was then removed and the contents carefully acidified with concentrated hydrochloric acid to get 0.25 g (67%) of **10**, mp 149-151° dec (from ethanol); ir (potassium bromide): 3075-2700 (b), 1660, 1600, 1530, 1440, 1400, 1350, 1300, 1160, 1030, 940 cm^{-1}.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.89; H, 3.89; N, 13.14.

5-(4-Chlorobutanoyl)-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**11**).

Using the procedure described for the preparation of **2**, 1.0 g (5.945

mmoles) of **1**, 1.18 g (11.89 mmoles) of trimethylsilyl cyanide, 0.05 g of aluminum chloride, and 1.68 g (11.91 mmoles) of 4-chlorobutyryl chloride gave 1.14 g (64%) of **11**, mp 87-89° (from ethanol); ir (potassium bromide): 3130, 2960, 1665, 1590, 1500, 1380, 1340, 1240, 985, 875 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.02; H, 4.68; N, 14.02.

4a-Cyano-1-oxo-2,3,4,4a tetrahydro-1H-pyrido[1,2-*a*]pyrrolo[2,1-*c*]quinoxaline (**13**).

A mixture of 0.53 g (1.768 mmoles) of **11** and 0.125 g (2.604 mmoles) of 50% sodium hydride in 4 ml of anhydrous dimethylformamide was stirred at 0-10° for 1.5 hours and poured onto ice to obtain 0.36 g (77%) of **13**, mp 135-137° (from ethanol); ir (potassium bromide): 2955, 1660, 1600, 1505, 1475, 1360, 1340, 1280, 1190, 1150, 1095, 950, 850 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.91; H, 5.00: N, 15.87.

5-(2-Chloromethylbenzoyl)-4-cyano-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**12**).

Using the procedure described for the preparation of **2**, 0.5 g (2.973 mmoles) of *1*, 0.02 g of aluminum chloride, 0.59 g (5.947 mmoles) of trimethylsilyl cyanide and 1.13 g (5.978 mmoles) of 2-chloromethylbenzoyl chloride gave 0.61 g (59%) of **12**, mp 157-159° (from ethanol); ir (potassium bromide): 2975, 1660, 1590, 1505, 1480, 1430, 1350, 1275, 1190, 1160, 1100, 960, 800 cm^{-1}; pmr (deuteriochloroform): δ 7.36 (m, 5H), 6.89 (m, 5H), 6.37 (m, 2H), 5.08, 4.43 (dd, J = 12 Hz, 2H).

Anal. Calcd. for $C_{20}H_{14}ClN_3O$: C, 69.06; H, 4.06; N, 12.08. Found: C, 69.22; H, 4.03; N, 12.13.

14-Oxo-14H-isoquinolino[2,3-*a*]pyrollo[2,1-*c*]quinoxaline (**14**).

Using the procedure described for the preparation of **13**, 0.30 g (0.863) mmole) of **12**, and 0.09 g (1.875 mmoles) of 50% sodium hydride in 4 ml of anhydrous dimethylformamide gave 0.19 g (78%) of **14**, mp 201-203° (from ethanol); ir (potassium bromide): 3145, 1660, 1620, 1600, 1560, 1510, 1450, 1380, 1340, 1200, 1140, 1030, 840, 760 cm^{-1}; ms: m/e 284.0945 ($C_{19}H_{12}N_2O$, 100%), 228.0796 (7.45%), 127.0446 (8.35%).

Anal. Calcd. for $C_{19}H_{12}N_2O$: C, 80.26; H, 4.25; N, 9.86. Found: C, 80.67; H, 4.34; N, 9.86.

Reduction of **14**.

To a solution of 0.27 g (0.95 mmole) of **14** in 20 ml of tetrahydrofuran (distilled from lithium tetrahydridoaluminate) was added 0.2 g (5.27 mmoles) of lithium tetrahydridoaluminate. The contents were refluxed for 13 hours, cooled, diluted with 150 ml of water, and extracted with chloroform (3 x 100 ml). Evaporation of the dried (magnesium sulfate) chloroform extract gave a dark solid which was taken up in anhydrous benzene (50 ml) and treated with activated charcoal. Removal of the charcoal and the benzene afforded 0.16 g (62%) of **15**, mp 134-143° (maroon needles from *n*-heptane/benzene); ir (potassium bromide) 1615, 1560, 1460, 1355, 1230, 1200, 1105, 1025, 790, 750 cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.31; H, 5.38; N, 10.27.

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