Synthesis and Reactions of some 5,6,7,8-Tetrahydroquinoxaline Derivatives

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5,6,7,8-Tetrahydroquinoxaline derivatives containing an oxygen functionality in the 6-position were prepared by ring closure of suitable 2,3-disubstituted pyrazines such as **6** and **12**. The chemistry of these novel 5,6,7,8-tetrahydroquinoxalines is discussed.

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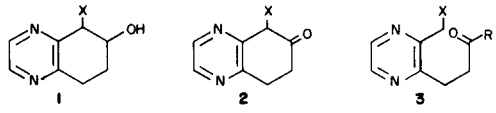
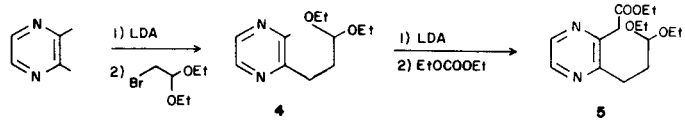
Our interest in the chemistry of 5,6,7,8-tetrahydroquinoxaline, led us to explore new synthetic methods enabling the introduction of an oxygen functionality in the 6-position of this molecule. In particular we were interested in the preparation of compounds such as **1** and **2** where X is an electron withdrawing group such as an ester.

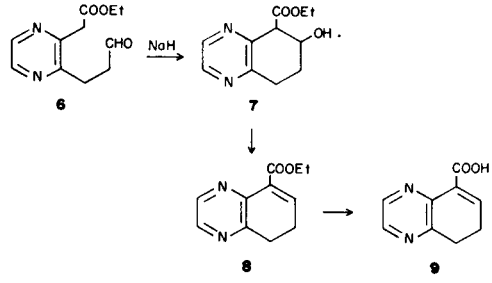


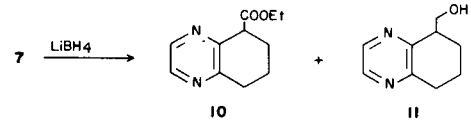
5,6,7,8-Tetrahydroquinoxalines are easily obtained by reacting 1,2-ethylenediamines with 1,2-cyclohexanediones followed by oxidation (1). Similarly, 1,2-diketones can be condensed with 1,2-diaminocyclohexanes (1). Neither of these condensations however, is suitable for the synthesis of compounds such as **1** and **2** since the necessary 1,2-diaminocyclohexanes or 1,2-cyclohexandiones are either not available or very difficult to synthesize. Reduction of quinoxaline itself or its derivatives is another method for obtaining tetrahydroquinoxalines. However, the required ring selectivity in these reductions has not yet been reported. In fact, in all cases studied, including a variety of reducing agents, reduction proceeded exclusively on the heteroaromatic ring (2,3). We have therefore decided to approach the synthesis of the above target molecules by attempting ring closure of suitable 2,3-disubstituted pyrazines such as **3** where R = H, or OR.

Treatment of 2,3-dimethylpyrazine with lithium diisopropylamide (LDA) followed by bromoacetaldehyde diethylacetal gave **4**. The latter was further reacted with LDA followed by diethylcarbonate to give the ester-acetal **5**. It is interesting to note that anion formation in **4**



proceeded exclusively at the 3-methyl group, most probably because of the greater steric hinderance at the 2-methylene group. Mild acid hydrolysis of **5** gave the ester-aldehyde **6** in quantitative yield. It was found that **6** is unstable on storage at room temperature. Nevertheless, a freshly prepared sample of **6** upon treatment with sodium hydride in ether underwent smooth ring closure to form **7**. Two other products, one (**8**) resulting from dehydration of **7** and another (**9**) from hydrolysis of **8** were also isolated in the reaction. Careful examination of this reaction by tlc indicated that the transformations **7** → **8** → **9** occur only after the addition of water, during work up. The hydroxy-ester **7** was found to be very sensitive to both acids and bases. Attempted acidic or basic hydrolysis of the ester group in **7** resulting in either case in a very rapid dehydration-hydrolysis to form a mixture of **8** and **9**. Dehydration was found also to be catalysed by silica-gel. Nevertheless, a sample of **7** slightly contaminated with **8** could be obtained by preparative tlc. Treatment of **7** with lithium borohydride in ether gave a mixture of **10** and **11**. Careful examination of this reaction by tlc indicated the following transformation sequence: **7** → **8** → **10** → **11**. When excess of lithium borohydride was used the only detected product was **11**. Here again, dehydration turned out to be much faster than reduction. The observation that in **8** the carbon-carbon double bond is reduced prior to the ester group is not unusual. It is known that double bonds activated by electron withdrawing groups are easily reduced by a variety of metal hydrides. For example, alkylidenecyanoacetic esters are reduced with sodium borohydride to the corresponding alkylcyanoacetic esters (4).





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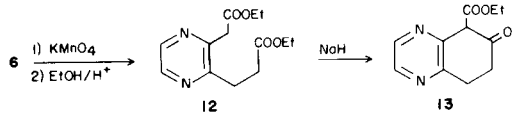
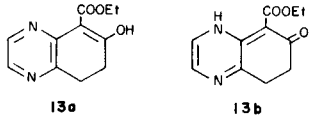
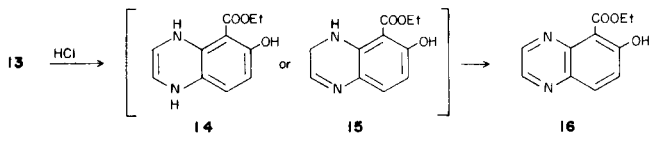
The preparation of compounds such as **2** was examined by attempted ring closure of **3** where R = OEt. Oxidation of the aldehyde-ester **6** with potassium permanganate



followed by esterification gave the diester **12**. Treatment of the latter with sodium hydride in ether resulted in a smooth ring closure to form **13**. The nmr spectrum of **13** in deuteriochloroform shows two AB quartets for the pyrazine-ring protons: one sharp centered at δ 8.24 (J = 2.7 Hz) and one broad centered at δ 7.45 (J = 3.9 Hz), which together integrate as 2H. Two other peaks at δ 13.62 (sharp singlet) and δ 14.42 (very broad) which together integrate as 1H and which are exchangable with deuterium oxide also appear in the spectrum. The δ 7.45 quartet is strongly sharpened after the deuterium oxide exchange. The rest of the nmr spectrum accounts for the ethoxy and CH_2CH_2 groups. The integration ratios of the δ 7.45 to the δ 14.42 peaks as well as the ratio of the δ 8.24 to the δ 13.62 peaks were found to be in both cases 2:1. The ir of **13** in chloroform shows a weak broad peak at 3250 cm^{-1} and three peaks in the carbonyl-double bond region at 1640, 1595 and 1570 cm^{-1}. The above data suggest that **13** consists of two isomers, **13a** and **13b**, which exist in equilibrium in solution. The equilibrium ratio of **13a** to **13b** in deuteriochloroform was found to be 12:5. In deuterium oxide one sharp AB quartet, centered at 7.88 (J = 5.0 Hz), appears in the nmr spectrum. This may indicate either the presence of only one isomer of **13**, or more likely the two isomers rapidly equilibrating in that solvent.



Another quite interesting property of **13** is observed in an attempted acid hydrolysis of its ester group. Treatment of **13** with dilute hydrochloric acid resulted in the formation of the quinoxaline derivative **16** instead of the expected 5,6,7,8-tetrahydroquinoxalin-6-one resulting from hydrolysis-decarboxylation. Since the reaction was carried out under nitrogen it is very unlikely that oxidation took place during the acid treatment. We believe that the acid catalyzes isomerization of **13** to the dihydroquinoxaline **14** or **15** which in turn is rapidly oxidized to **16** during workup. Indeed 1,2- or 1,4-dihydroquinoxalines are known to be readily oxidized by molecular oxygen to the corresponding quinoxalines (5).



EXPERIMENTAL

All reactions involving organometallic reagents were carried out under a nitrogen atmosphere. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 621 spectrophotometer. Nmr spectra were recorded with a Brucker WP80 spectrometer and the chemical shifts are given in δ units downfield from internal TMS. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee. Tlc was carried out on silica gel GF plates, using hexane containing 15-30% acetone as the eluent.

2-(1,1-Diethoxy-3-propyl)-3-methylpyrazine (**4**).

To a solution of diisopropylamine (20.2 g., 0.2 mole) in ether (300 ml.) at 0°, was added with stirring *n*-butyllithium (0.2 mole in 100 ml. of hexane). The mixture was stirred at 0° for 15 minutes. A solution of 2,3-dimethylpyrazine (21.6 g., 0.2 mole) in ether (50 ml.) was slowly added and the resulting red suspension was stirred at 0° for 20 minutes. Bromoacetaldehyde diethyl acetal (39.4 g., 0.2 mole) in ether (50 ml.) was added and the solution was left stirring at room temperature for 4 hours. Water was added and the ether layer was separated, washed with water and dried (magnesium sulfate). The solution was evaporated under reduced pressure to give an oil. Pure **4** (13.5 g., 30%) was obtained by distillation, b.p. 86-92° at 0.5 mm Hg; ir (neat): 1445, 1410, 1375, 1125, 1065 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (t, 6H, $2CH_3$), 1.95-2.30 (m, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.75-3.05 (m, 2H, CH_2), 3.60 (m, 4H, $2CH_2$), 4.60 (t, J = 6 Hz, CH), 8.32 (ABq, J = 4.5 Hz, 2H, pyrazine).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.32; H, 8.88; N, 12.75.

Ethyl 2-(1,1-Diethoxy-3-propyl)-3-pyrazineacetate (**5**).

To a solution of lithium diisopropylamide (0.05 mole) in ether (100 ml.) and hexane (20 ml.), at 0° was added with stirring a solution of **4** (11.2 g., 0.05 mole) in ether (50 ml.). The resulting red solution was stirred at 0° for 15 minutes. A slight excess of diethylcarbonate (7 g.) in ether (40 ml.) was added and the mixture stirred at 0° for 30 minutes. Water was added and the ether layer separated. The aqueous layer was extracted with methylene chloride and the two organic layers were combined, dried (magnesium sulfate), and the solvents removed under reduced pressure to give an oil (16.5 g.). Distillation gave pure **5** (6.6 g., 44.6%); b.p. 128-134° at 0.3 mm Hg; ir (neat): 1740, 1410, 1370, 1250, 1175, 1120, 1060 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.18 (t, 6H, $2CH_3$), 1.25 (t, 3H, CH_3), 1.90-2.25 (m, 2H, CH_2), 2.75-3.02 (m, 2H, CH_2), 3.58 (two q, 4H, $2CH_2$), 3.94 (s, 2H, 3-CH_2), 4.19 (q, 2H, CH_2), 8.45 (ABq, J = 3.5 Hz, 2H, pyrazine).

Anal. Calcd. for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.96; H, 8.31; N, 9.26.

Ring Closure of **6**.

A solution of the ester-acetal **5** (3 g., 0.01 mole), in ethanol (125 ml.) and water (25 ml.) containing 1 ml. of concentrated hydrochloric acid was heated at 30-40° for 2 hours. Water was added (100 ml.) and the solution adjusted to *p*H 5 with dilute sodium carbonate. Most of the ethanol was removed under reduced pressure and the remaining aqueous solution was extracted with methylene chloride. The organic layer was dried (magnesium sulfate) and evaporated under reduced pressure to yield 2.1 g. (93.3%) of almost pure **6** (by tlc); ir (neat): 1740 and 1735 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26 (t, 3H, CH_3), 2.86-3.25 (m, 4H, $2CH_2$), 3.96 (s, 2H, CH_2), 4.17 (q, 2H, CH_2), 8.35 (m, 2H, pyrazine), 9.86 (t, J = 1 Hz, CHO).

To a suspension of sodium hydride (0.168 g., 0.007 mole) in ether (150

ml.) was added, with stirring at 0°, a solution of **6** (1.1 g., 0.005 mole) in ether (25 ml.). The resulting mixture was stirred at 0° for 2 hours. Water was added and the ether layer was separated. The aqueous layer was adjusted to *p*H 5 with dilute hydrochloric acid and extracted with methylene chloride. The combined organic layers were evaporated under reduced pressure to give an oil. Preparative tlc afforded 170 mg. (15.5%) of almost pure 5-carbethoxy-6-hydroxy-5,6,7,8-tetrahydroquinoxaline (**7**) as an oil; ^{1}H nmr (deuteriochloroform): δ 1.27 (t, 3H, CH_3), 1.80-2.35 (m, 2H, 7-CH_2), 3.10 (m, 2H, 8-CH_2), 4.02 (d, J = 6.4 Hz, 5-CH), 4.24 (q, 2H, CH_2), 4.50 (m, 1H, 6-CH), 8.39 (s, 2H, pyrazine). Also isolated was 380 mg. (37.5%) of pure 5-carbethoxy-7,8-dihydroquinoxaline (**8**) as an oil; ir (neat): 1670, 1625 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.36 (t, 3H, CH_3), 2.47-2.80 (m, 2H, 7-CH_2), 2.95-3.29 (m, 2H, 8-CH_2), 4.36 (q, 2H, CH_2), 7.15 (t, J = 5.5 Hz, 1H, vinylic), 8.36 (ABq, J = 3.5 Hz, 2H, pyrazine). Also obtained was 7,8-dihydro-5-quinoxalinecarboxylic acid (**9**) (410 mg., 47.0%), m.p. 121-123° (needles from hexane-acetone, 4:1); ir (nujol): about 2600 (very br), 1720, 1625, 1495, 1430, 1420, 1260; ^{1}H nmr (deuteriochloroform): δ 2.60-3.43 (m, 4H, $2CH_2$), 7.83 (t, J = 5 Hz, 1H, vinylic), 8.41 (ABq, J = 3.5 Hz, 2H, pyrazine), 14.00 (broad, COOH).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.08; H, 4.69; N, 15.90.

When the above work up procedure was carried out at 0°, the major product isolated was **7**, slightly contaminated with **8**.

Acidic and Basic Hydrolysis of **7**.

A solution of the hydroxy-ester **7** (30 mg.) in water (5 ml.) containing one drop of concentrated hydrochloric acid was left at room temperature for 10 minutes. Tlc indicated quantitative formation of **8**. When one drop of 50% sodium hydroxide was used instead of hydrochloric acid a mixture of **8** and **9** could be detected by tlc.

Lithium Borohydride Reduction of **7**.

To a solution of **7** (1.1 g., 0.005 mole) in ether (150 ml.) was added lithium borohydride (109 mg., 0.005 mole) and the resulting mixture was stirred at room temperature for 4 hours. Water was added and the ether layer separated. The aqueous layer was extracted with methylene chloride and the combined organic layers dried (magnesium sulfate) and evaporated under reduced pressure. Preparative tlc gave 5-carbethoxy-5,6,7,8-tetrahydroquinoxaline (**10**) (110 mg., 10.8%) as an oil; ir (neat): 1730, 1405, 1175, 1160 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.26 (t, 3H, CH_3), 1.79-2.40 (m, 4H, $2CH_2$), 2.95-3.14 (m, 2H, CH_2), 4.00 (t, J = 6 Hz, 1H, CH), 4.22 (q, 2H, CH_2), 8.39 (s, 2H, pyrazine).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.84; H, 6.93; N, 13.48.

Also separated by tlc was 5-hydroxymethyl-5,6,7,8-tetrahydroquinoxaline (**11**) (560 mg., 68.9%) as an oil; ir (neat): 3325, 1400, 1160, 1050 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.12-2.40 (m, 4H, $2CH_2$), 2.80-3.31 (m, 3H, CH_2 + CH), 3.89 (d, J = 6 Hz, 2H, CH_2), 8.40 (ABq, J = 3.5 Hz, 2H, pyrazine). An analytical sample was obtained by gc.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.69; H, 7.49; N, 16.93.

When a large excess of lithium borohydride was used the only detected product was **11**.

Ethyl 2-(Ethyl-3-propionate)-3-pyrazineacetate (**12**).

To a solution of **6** (1 g., 0.0045 mole) in water (50 ml.) was added slowly at room temperature a solution of potassium permanganate (0.6 g.) in water (20 ml.). The resulting mixture was stirred at room temperature for 1 hour and then left in the refrigerator for 3 hours. The solution was filtered and acidified to *p*H 3 with dilute hydrochloric acid. The product was extracted with methylene chloride, the solution dried (magnesium sulfate) and evaporated under reduced pressure. The oil so obtained was dissolved in absolute ethanol (80 ml.) containing three drops of concentrated sulphoric acid. The resulting mixture was left at room temperature for 2 days. Water was added and the solution adjusted to *p*H 3 with dilute sodium carbonate. Most of the ethanol was removed under reduced pressure and the remaining solution was extracted with methylene chloride. The solution was dried (magnesium sulfate) and evaporated under reduced pressure to give an oil (1.1 g.). Preparative tlc afforded pure **12** (0.92 g., 76.8%); ir (neat): 1730-1740 cm^{-1} (br); ^{1}H nmr (deuteriochloroform): δ 1.19 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 2.55-3.14 (m, 4H, $2CH_2$), 3.83 (s, 2H, CH_2), 3.97 (q, 2H, CH_2), 4.05 (q, 2H, CH_2), 8.04 (ABq, J = 3 Hz, 2H, pyrazine).

5-Carbethoxy-5,6,7,8-tetrahydroquinoxalin-6-one (**13**).

To a solution of **12** (266 mg., 0.001 mole) in ether (180 ml.) was added a slight excess of sodium hydride (30 mg.) and the mixture was stirred at room temperature for 36 hours. Water was added and the ether layer was separated. The aqueous layer was acidified to *p*H 3 with dilute hydrochloric acid and extracted with methylene chloride. The combined organic layers were dried (magnesium sulfate) and evaporated under reduced pressure. Preparative tlc afforded pure **13** (45 mg., 20.5%). The rest of the material was mainly unreacted **12**. Recrystallization from acetone gave yellow needles, m.p. 145-147°; ir (nujol): 3125, 1660, 1565 (br) cm^{-1}; ir (chloroform): 3250, 1640, 1595, 1570 cm^{-1}; ^{1}H nmr (deuteriowater): δ 1.35 (t, 3H, CH_3), 2.52-3.28 (m, 4H, $2CH_2$), 4.34 (q, 2H, CH_2), 7.88 (ABq, J = 5.0 Hz, 2H, pyrazine); ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3H, CH_3), 2.53-3.30 (m, 4H, $2CH_2$), 4.44 (q, 2H, CH_2), 8.24 and 7.45 (two ABq, J = 2.7 Hz and 3.9 Hz, 2H, pyrazine) 13.62 and 14.42 (1H).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.38; N, 12.64.

5-Carbethoxy-6-hydroxyquinoxaline (**16**).

A solution of **13** (30 mg.) in 5% hydrochloric acid (30 ml.) was refluxed under nitrogen for 1.5 hours. The solution was cooled and adjustes to *p*H 5 with aqueous sodium carbonate. The product was extracted with methylene chloride, the solution dried (magnesium sulfate) and concentrated under reduced pressure. Preparative tlc gave pure **16** (18 mg., 60.6%). Recrystallization from hexane gave needles: m.p. 133-134°; ^{1}H nmr (deuteriochloroform): δ 1.52 (t, 3H, CH_3), 4.63 (q, 2H, CH_2), 7.80 (ABq, J = 11.5 Hz, 2H, aromatic), 8.79 (ABq, J = 2.5 Hz, 2H, heteroaromatic), 12.39 (s, 1H, OH).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.39; H, 4.42; N, 12.62.

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