# Tricyclic Heteroaromatic Systems. 1,2,4-Triazolo[1,5-*a*]quinoxaline



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The parent 1,2,4-triazolo[1,5-*a*]quinoxaline was prepared by a few-step reaction from ethyl $N^1$-(2-nitrophenyl)-$N^3$-ethoxalyloxamidrazonate, which afforded the key intermediate diethyl 1-(2-nitrophenyl)-1,2,4-triazole-3,5-dicarboxylate in satisfactory yield. The latter was cyclized, hydrolyzed, decarboxylated, reduced and dehydrogenated to yield the title compound.

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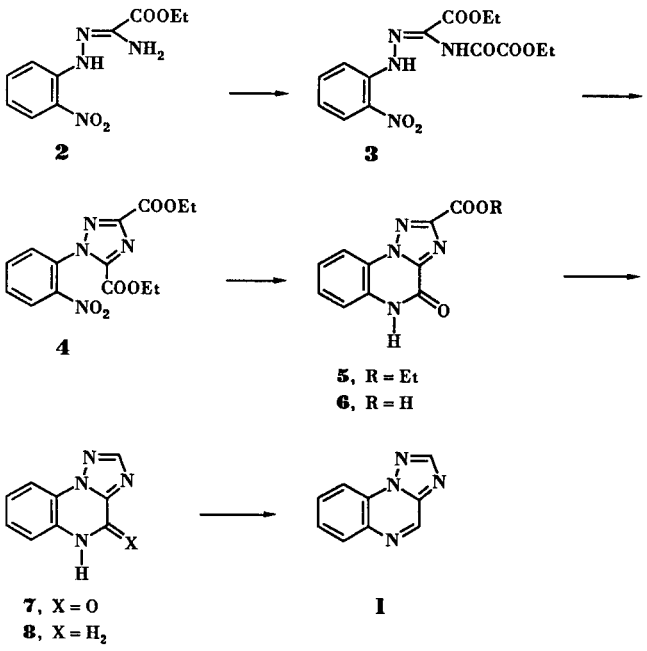
Rationalization of the structural requirements for the binding of 6,6,5-tricyclic heteroaromatic systems to the benzodiazepine receptors has led us to the synthesis of more than a hundred compounds of similar size and shape [1]. More recently our interest has been focused on the synthesis of 1,2,4-triazolo[1,5-*a*]quinoxaline derivatives as potential benzodiazepine receptor ligands. Although some 1,2,4-triazolo[1,5-*a*]quinoxaline derivatives are reported in the literature [2-6], the synthesis of the parent tricyclic ring system has however never been reported. In this paper we therefore describe the synthesis of the new tricyclic ring system 1,2,4-triazolo[1,5-*a*]quinoxaline **1**.

The synthetic pathway shown in Scheme 1 was followed.

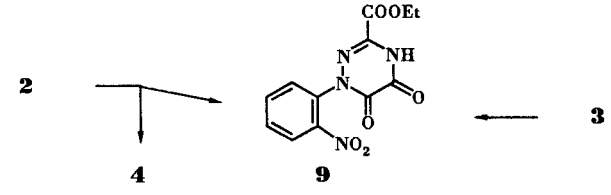
Scheme 1




By heating the ethoxalyl derivative **3** of the amidrazone **2** [7] above its melting point, the diethyl 1-(2-nitrophenyl)-1,2,4-triazole-3,5-dicarboxylate **4** was isolated. Reduction of the nitro group with iron in glacial acetic acid yielded the tricyclic ester **5**, which was hydrolyzed to the acid **6**. The latter was decarboxylated to the cyclic amido derivative **7** which was reduced with lithium aluminium hydride to the 4,5-dihydro-derivative **8**. Dehydrogenation of the latter gave the parent compound **1**.

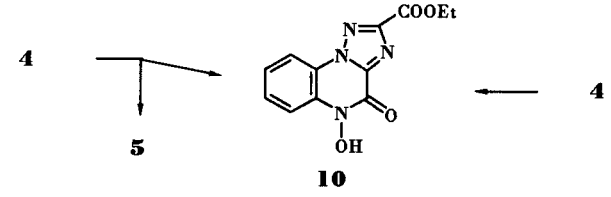
The synthetic pathway described has two crucial steps: the preparation of the triazole **4** and its reduction. It was reported [8] that the ethyl 1,3-diphenyl-1,2,4-triazole-5-carboxylate could be prepared by allowing **2** to react with ethyl oxalyl chloride in the presence of triethylamine. However following this method for the preparation of **4**, the main product isolated was the triazine derivative **9**, while **4** was recovered in low yield. Compound **9** was the sole product isolated when **3** was heated with triethylamine in dimethylformamide (see Scheme 2). It should be noted that compound **4** was easily obtained with a two-step reaction *via* the ethoxalyl amididrazone **3** (see Scheme 1).

Scheme 2




The reduction of **4** may lead to different products, depending on the reaction conditions (see Scheme 3). Compound **5** ensued by reduction of **4** with iron in glacial acetic acid, while the hydrogenation of the same starting ma-

Scheme 3



terial catalyzed by Pd/C gave a mixture of **5** and ethyl 4-oxo-5-hydroxy-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**10**). The latter was the only product of the reduction of **4** catalyzed by platinum dioxide.

All the structures of the reported compounds were attributed by spectroscopic means.

## EXPERIMENTAL

Silica gel plates (Merck $F_{254}$) and silica gel 60 (Merck, 70-230 mesh) were used for analytical and column chromatography, respectively. All melting points were determined on a Gallenkamp capillary melting point apparatus. Microanalyses were performed with a Perkin-Elmer 260 elemental analyzer. Mass spectra were obtained using a Carlo-Erba QMD 1000 mass spectrometer and samples were introduced by direct inlet probe (DIE). The ir spectra were recorded with a Perkin-Elmer 1420 spectrometer in nujol mulls. The $^1$H nmr spectra were obtained with a Varian Gemini 200 instrument in the Fourier transform mode at 200 MHz using an acquisition time of 1.5 seconds, a flip angle of 42° and a spectral width of 3000 Hz. The deuterium signal provided the field frequency lock. Chemical shifts are reported in $\delta$ (ppm) and measured relatively to the central peak of the solvent (deuteriochloroform = 1385 Hz, dimethyl sulfoxide-$d_6$ = 792 Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Ethyl $N^1$-(2-Nitrophenyl)-$N^3$-ethoxalyloxamidrazonate (**3**).

Ethyl oxalyl chloride (4.76 mmoles) was diluted with diethyl ether (2 ml) and added dropwise at room temperature to a stirred suspension of **2** [7] (2.38 mmoles) in anhydrous diethyl ether (2 ml). The red starting suspension turned yellow. Anhydrous toluene (6 ml) was added. The mixture was heated at reflux until a clear solution was obtained (about 15 minutes). The solution was cooled and the orange solid collected and recrystallized from toluene, mp 140-142°, 79% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 1.27-1.34 (m, 6H, $2CH_3$), 4.25-4.42 (m, 4H, $2CH_2$), 7.1-7.2 (m, 1H, benzene proton), 7.7-7.8 (m, 2H, benzene protons), 8.2-8.3 (m, 1H, benzene proton), 10.90 (s, 1H, NH hydrazide), 13.17 (s, 1H, NH amide) the latter signals exchange with deuterium oxide; ir: ($cm^{-1}$) 3360, 3320, 1745, 1720; ms: m/z 352 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{16}N_4O_7$ (352.34): C, 47.72; H, 4.59; N, 15.91. Found: C, 47.81; H, 4.49; N, 16.10.

Diethyl 1-(2-Nitrophenyl)-1,2,4-triazole-3,5-dicarboxylate (**4**).

Compound **3** (7.1 mmoles) was heated at 180-190° under nitrogen flow for 30 minutes. The cooled mass was dissolved in chloroform (100 ml). The organic solvent was washed three times with a diluted (0.5 *N*) solution of potassium hydroxide (50 ml each time) and then with water (50 ml). Evaporation at the rotavapor of the dried (anhydrous sodium sulfate) organic solvent afforded a residue which was recrystallized from cyclohexane/ethyl acetate: mp 115-116°, 66% yield; $^1$H nmr (deuteriochloroform): 1.34 (t, 3H, $CH_3$), 1.47 (t, 3H, $CH_3$), 4.37 (q, 2H, $CH_2$), 4.54 (q, 2H, $CH_2$), 7.5-7.6 (m, 1H, benzene proton), 7.7-7.9 (m, 2H, benzene protons), 8.3-8.4 (m, 1H, benzene proton); ir: ($cm^{-1}$) 1745.

*Anal.* Calcd. for $C_{14}H_{14}N_4O_6$ (334.32): C, 50.29; H, 4.23; N, 16.76. Found: C, 50.41; H, 4.09; N, 16.65.

Diethyl 1-(2-Nitrophenyl)-1,2,4-triazole-3,5-dicarboxylate (**4**) and Ethyl 1,4,5,6-Tetrahydro-1-(2-nitrophenyl)-5,6-dioxo-1,2,4-triazine-3-carboxylate (**9**).

Ethyl oxalyl chloride (17.8 mmoles) was diluted in anhydrous benzene (5 ml) and added dropwise and at room temperature to a stirred suspension of **2** [7] (5.95 mmoles) and triethylamine (35.7 mmoles) in anhydrous benzene (20 ml). The mixture was heated at reflux for 8 hours. The solid (triethylamine hydrochloride) was filtered off and the solvent was evaporated at the rotavapor. The residue was dissolved in chloroform (50 ml). The solvent was washed four times with a diluted (0.5 *N*) solution of hydrochloric acid (50 ml each time) and then with water (50 ml). The dried (anhydrous sodium sulfate) organic solvent was evaporated at the rotavapor to give an oily residue containing the title compounds, which were separated by column chromatography, eluting system chloroform/methanol, 9:1.

Compound **4** was obtained in the first running eluates, 12% yield.

Compound **9** was obtained in the second running eluates, mp 177-180° (ethyl acetate), 63% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 1.26 (t, 3H, $CH_3$), 4.34 (q, 2H, $CH_2$), 7.7-7.8 (m, 2H, benzene protons), 7.9-8.0 (m, 1H, benzene proton), 8.1-8.2 (m, 1H, benzene proton), 12.6 (br s, 1H, NH); ir: ($cm^{-1}$) 3120, 1735, 1690; ms: m/z 306 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{10}N_4O_6$ (306.26): C, 47.06; H, 3.30; N, 18.30. Found: C, 46.92; H, 3.18; N, 18.47.

Ethyl 1,4,5,6-Tetrahydro-1-(2-nitrophenyl)-5,6-dioxo-1,2,4-triazine-3-carboxylate (**9**).

Triethylamine (1.62 mmoles) dissolved in dimethylformamide (1 ml) was added dropwise and at room temperature to a solution of **3** (0.54 mmoles) in anhydrous dimethylformamide (2 ml). The mixture was heated at 80° for 24 hours. Evaporation at reduced pressure of the solvent afforded a residue which was recrystallized from ethyl acetate, yield 52%.

Ethyl 4,5-Dihydro-4-oxo-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**5**).

Iron powder (3.65 g) was added to a solution of **4** (3.65 mmoles) in glacial acetic acid. The mixture was heated at 90° for 1 hour. Evaporation of the solvent at reduced pressure afforded a residue which was suspended in water (120 ml). The mixture was bleached with hydrochloric acid (6 *N*). The solid was collected, washed with water, dried and extracted in a Soxhlet extraction apparatus with acetone (250 ml). Evaporation at the rotavapor of the solvent afforded a residue which was recrystallized from acetone, mp 289-290°, 70% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 1.40 (t, 3H, $CH_3$), 4.47 (q, 2H, $CH_2$), 7.4-7.6 (m, 3H, benzene protons), 8.1-8.2 (m, 1H, benzene proton), 12.5 (br s, 1H, NH); ir: ($cm^{-1}$) 1745, 1695.

*Anal.* Calcd. for $C_{12}H_{10}N_4O_5$ (258.26): C, 55.80; H, 3.91; N, 21.70. Found: C, 55.98; H, 3.82; N, 21.59.

Ethyl 4,5-Dihydro-4-oxo-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**5**) and Ethyl 4,5-Dihydro-4-oxo-5-hydroxy-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**10**).

Pd/C (10%, 0.11 g) was added to a solution of **4** (1.2 mmoles) in ethyl acetate (50 ml) and the mixture was hydrogenated in a Parr apparatus at 1.5 atmospheres for 1 hour. The solid was collected and washed three times with boiling acetone (25 ml each time). The catalyst was filtered off and **10** precipitated from the cooled solution. The ethyl acetate solution contained compound **5** which was recovered by evaporation at the rotavapor of the organic solvent.

Compound **10** had mp 250-252° (acetone), 35% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 1.41 (t, 3H, $CH_3$), 4.48 (q, 2H, $CH_2$), 7.5-7.6 (m, 1H, benzene proton), 7.7-7.9 (m, 2H, benzene protons), 8.2-8.3 (m, 1H, benzene proton), 12.1 (br s, 1H, NOH); ir: ($cm^{-1}$) 1740, 1690.

*Anal.* Calcd. for $C_{12}H_{10}N_4O_4$ (274.26): C, 52.55; H, 3.68; N, 20.43. Found: C, 52.27; H, 3.81; N, 20.62.

Compound **5**, yield 34%.

Ethyl 4,5-Dihydro-4-oxo-5-hydroxy-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**10**).

Platinum dioxide (0.03 g) was added to a solution of **4** (0.9 mmoles) in absolute ethanol (50 ml) containing 13% (w/v) of hydrogen chloride. The mixture was hydrogenated in a Parr apparatus at 1.8 atmospheres for 2 hours. The solid was collected and washed with boiling acetone (80 ml). Evaporation at the rotavapor of the acetone afforded a residue. Another small amount of title compound was recovered by evaporating the ethanolic solution. The combined residues were recrystallized, 65% overall yield.

4,5-Dihydro-4-oxo-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylic Acid (**6**).

A suspension of **5** (3.08 mmoles) in a 0.6 *M* solution of sodium hydroxide in ethanol/water (1:1, 100 ml) was heated at reflux for 3 hours. The sodium salt was collected, dissolved in water and the solution acidified with 6 *N* hydrochloric acid. The resulting precipitate was collected, washed with cold water and recrystallized from water, mp >300°, 90% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 7.4-7.6 (m, 3H, benzene protons), 8.1-8.2 (m, 1H, benzene proton), 12.4 (br s, 1H, NH); ir: ($cm^{-1}$) 1715, 1700.

*Anal.* Calcd. for $C_{10}H_6N_4O_3$ (230.20): C, 52.17; H, 2.63; N, 24.34. Found: C, 51.99; H, 2.59; N, 24.45.

4,5-Dihydro-1,2,4-triazolo[1,5-*a*]quinoxalin-4-one (**7**).

A catalytic amount of cuprous oxide (0.02 g) was added under nitrogen flow to a stirred hot (120°) suspension of **6** (5.2 mmoles) in diethylene glycol (14 ml). The mixture was heated at 135° for 13 hours. The solid was collected, washed with a 0.5 *M* solution of sodium hydrogen carbonate (10 ml) and then with a few drops of a buffer solution of ammonia/ammonium chloride (*p*H 9), mp >300° (glacial acetic acid/water), 75% yield; $^1$H nmr (dimethyl sulfoxide-$d_6$): 7.4-7.6 (m, 3H, benzene protons), 8.1-8.2 (m, 1H, benzene proton), 8.63 (s, 1H, triazole proton), 12.4 (br s, 1H, NH); ir: ($cm^{-1}$) 1710.

*Anal.* Calcd. for $C_9H_6N_4O$ (186.19): C, 58.05; H, 3.25; N, 30.10. Found: C, 57.89; H, 3.32; N, 30.21.

4,5-Dihydro-1,2,4-triazolo[1,5-*a*]quinoxaline (**8**).

Lithium aluminium hydride (17.6 mmoles) was added to a boiling solution of **7** (1.76 mmoles) in anhydrous tetrahydrofuran (250 ml). The mixture was heated at reflux for 15 minutes. The excess of lithium aluminium hydride was quenched with ice. After the addition of ethyl acetate (150 ml) the solid was filtered off and the solution was dried over anhydrous sodium sulfate. Evaporation of the solvents at reduced pressure afforded a residue which was recrystallized from diethyl ether, mp 174-175°, 66% yield; $^1$H nmr (deuteriochloroform): 4.0 (br s, 1H, NH), 4.79 (d, 2H, $CH_2$, J = 1.8 Hz), 6.7-6.9 (m, 2H, benzene protons), 7.0-7.1 (m, 1H, benzene proton), 7.7-7.8 (m, 1H, benzene proton), 8.02 (s, 1H, triazole proton); ir: ($cm^{-1}$) 3360, 3120.

*Anal.* Calcd. for $C_9H_8N_4$ (172.21): C, 62.77; H, 4.69; N, 32.54. Found: C, 62.90; H, 4.55; N, 32.41.

1,2,4-Triazolo[1,5-*a*]quinoxaline (**1**).

An excess of Pd/C (10%, 0.87 g) was added to a solution of **8** (1.16 mmoles) in toluene (10 ml). The mixture was heated at reflux for 1 hour. Elimination of the catalyst and evaporation at reduced pressure of the solvent afforded an oily residue which was recrystallized from petroleum ether (bp 40-70°), 58% yield; $^1$H nmr (deuteriochloroform): 7.7-7.9 (m, 2H, benzene protons), 8.2-8.3 (m, 1H, benzene proton), 8.5-8.6 (m, 2H, 1 benzene proton + triazole proton), 9.34 (s, 1H, H-4); ir: ($cm^{-1}$) 3110; ms: m/z 170 ($M^+$).

*Anal.* Calcd. for $C_9H_6N_4$ (170.29): C, 63.51; H, 3.56; N, 32.93. Found: C, 63.39; H, 3.35; N, 33.04.

## REFERENCES AND NOTES

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