2,6-Dihydroxy-4*H*-pyridazino[3,4,5-*de*]quinazoline: A New Ring System

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The synthesis and spectral properties of 2,6-dihydroxy-4*H*-pyridazino[3,4,5-*de*]quinazoline **1** are described. This compound represents the first member of a new tetraazatricyclic ring system and exhibits biological activity.

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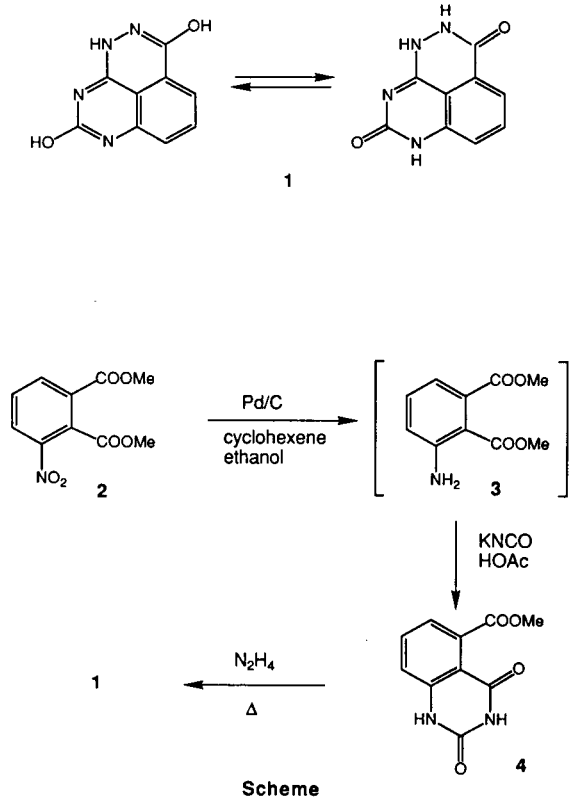
Introduction.

Our work with heterocycles having biological activity has led us to investigate quinazolinones and quinazolinediones with effects on the cardiovascular system [1,2]. Related to these compounds are a large number of possible isomeric tetraazaphenylenes. Taking, as a small subset, those isomers in which one of the fused rings is carbocyclic and in addition that there are no nitrogen atoms at a bridgehead position, there are nine possibilities. We report here the synthesis of one such compound, the pyridazino[3,4,5-*de*]quinazoline variation. Compound **1** is the first example of this ring system, which can be represented in several tautomeric forms due to the enol-lactam nature of the 2,6-dihydroxy substitution pattern.

Chemistry.

Readily available dimethyl 3-nitrophthalate **2** [3] was reduced by catalytic transfer hydrogenation using cyclohexene as the hydrogen doner and 10% palladium on carbon as the catalyst [4]. The aniline **3** was isolated as an oil and converted directly to the 5-carbomethoxyquinazolindione **4** [5] in quantitative yield with potassium cyanate. This three step procedure can be performed in nearly quantitative yield and can be run on a multi-gram scale. The methyl ester could be saponified to the corresponding acid with aqueous sodium hydroxide, but failed to yield an amide with a number of primary and secondary amines. Compound **4** did react, however, with neat hydrazine hydrate to give the title compound, as a high melting insoluble white solid, with loss of a molecule of methanol and one of water. The structure was verified by its mass spectrum as well as ir, ^{1}H and ^{13}C nmr spectra.



Scheme

Discussion.

Compound **4** and its alkylation have been described by several workers [5,6], although the method of synthesis presented here appears to be the most efficient. The steric and electronic factors contributing to the lack of reactivity of the ester function led us to react compound **4** with a stronger nucleophilic reagent (*eg.* hydrazine). The highly insoluble product of this reaction displayed a FAB (fast atom bombardment) molecular ion at [M+H] = 203 and contained nine distinct carbon resonances, all in the aromatic region of the ^{13}C nmr spectrum. The proton nmr spectrum displayed a well defined ABC pattern of peaks between 7.2 and 7.8 ppm indicitive of a 1,2,3-trisubstituted benzene ring. Exchangeable protons represented by a broad peak at 10.75 ppm and a sharper peak at 11.7 ppm were also observed. The ir spectrum supports assignment of the keto tautomer of the molecule with peaks at 1606 and 1700 cm^{-1}.

Compound **1** exhibited positive inotropic activity similar to other quinazoline-containing cardiotonic compounds such as bemarinone [1].

In an attempt to make derivatives of the new heterocycle, **1** was heated in acetic anhydride to afford a monoacetylated analog with a molecular ion at 244 and base peak at 202 representing loss of ketene. Due to the poor solubility of **1** in common organic solvents, other derivatizing reactions failed to give pure isolatable products.

Conclusion.

The synthesis and spectral characterization of a new heterocycle from 5-carbomethoxy-2,4-dihydroxyquinazoline and hydrazine in 87% yield have been described. 2,6-Dihydroxy-4*H*-pyridazino[3,4,5-*de*]quinazoline is the first member of this series.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. The ^1H and ^{13}C nmr spectra were recorded relative to TMS in dimethyl sulfoxide-d_6 solution at 300 MHz on a General Electric QE-300 NMR spectrometer or in trifluoroacetic acid solution at 90 MHz on a Varian EM-390 instrument. Microanalyses were performed on a Perkin Elmer model 240c elemental analyzer and mass spectra were obtained at 70 eV by direct insertion on a Finnigan 1015c ms instrument.

2,6-Dihydroxy-4*H*-pyridazino[3,4,5-*de*]quinazoline **1**.

5-Carbomethoxy-2,4-dihydroxyquinazoline **4** (5 g, 23 mmoles) was heated at reflux for 3 hours in anhydrous hydrazine (20 ml). The white solid was collected by filtration and washed with water then methanol and air dried to give 4.0 g (87%) of white fluffy solid with mp >300°; ir (potassium bromide): cm^{-1} 1606 (C=O), 1700 (C=O), 3000-3200 broad (NH); ^1H nmr: 11.77 (s, 1H, NH), 10.75 (bs, 2H, OH), 7.74 (t, 1H, H8, J = 2.6 Hz), 7.58 (d, 1, H7, J = 2.6 Hz), 7.21 (d, 1, H9, J = 2.7 Hz). ^{13}C nmr: 157.7, 149.7, 140.7, 137.6, 133.8, 127.4, 116.7, 115.3, 110.4; ms: M+ = 202.

Anal. Calcd. for $C_9H_6N_4O_2$: C, 53.45; H, 2.99; N, 27.71. Found: C, 53.35; H, 3.03; N, 28.18.

5-Carbomethoxy-2,4-dihydroxyquinazoline **4**.

Dimethyl 3-nitrophthalate **2** (15 g, 63 mmoles) was heated at reflux in ethanol (200 ml) containing cyclohexene (25 g) and 10% palladium on carbon (0.5 g) for 3 hours. The solution was filtered through Celite and the filtrate evaporated to give dimethyl 3-aminophthalate **3** as an oil which was used without further purification.

Compound **3** was dissolved in acetic acid (100 ml) and potassium cyanate (10 g) added. The mixture was heated on a steam bath for 30 minutes then cooled and basified by addition of concentrated ammonium hydroxide. The precipitate was collected by filtration and washed with water. The solid was dried in vacuum desiccator for two days yielding 14.0 g (100% for two steps) of white powder with mp >310°; ^1H nmr (TFA): 7.9 (t, 1H, aromatic, J = 8 Hz), 7.5 (d, 1H, aromatic, J = 5 Hz), 7.4 (d, 1H, aromatic, J = 5 Hz), 4.1 (s, 3H, COOMe).

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.67; N, 12.72. Found: C, 54.51; H, 3.63; N, 12.71.

Dimethyl 3-Nitrophthalate **2**.

3-Nitrophthalic acid (15 g) was slurried in ethyl ether and diazomethane (6 g) in ether solution added in small portions. When addition was complete acetic acid (1 ml) was added to destroy excess diazomethane and the solution filtered by gravity. The filtrate afforded 17 g of diester (100%) upon evaporation of the solvent.

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