

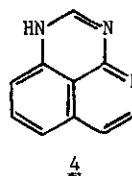
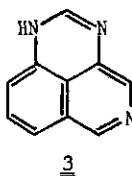
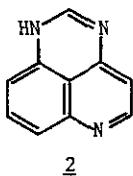
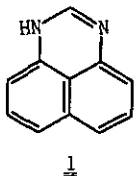
THE PREPARATION OF PYRIDO[4,3,2-de]QUINAZOLINE AND PYRIDO[3,4,5-de]QUINAZOLINEPaul D. Woodgate,^{a*} John M. Herbert,^a and William A. Denny^b

a. Department of Chemistry, University of Auckland, New Zealand

b. Cancer Research Laboratory, University of Auckland, New Zealand

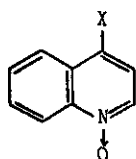
Abstract - The preparation of the novel ring systems, pyrido[4,3,2-de]quinazoline and pyrido[3,4,5-de]quinazoline, from quinoline and isoquinoline respectively, is described.

The condensed heterocycle perimidine (1) has unusual properties, being one of the few azines in which the lone pair of a pyrrole-like nitrogen participates in the π -electron system of the molecule. Perimidine is therefore a 14π electron system, isoelectronic with the phenalenyl anion. An important consequence of this interaction is a transfer of electron density from the heterocyclic ring into the naphthalene moiety, so that perimidine exhibits simultaneously the characteristics of both π -deficient and π -excessive systems.¹ As part of an investigation into the development of potential DNA-intercalating antitumour drugs,² attempts were made to modify perimidine in such a way as to make the system more electron-deficient. One way to achieve this is to replace one CH unit of the naphthalene moiety with a nitrogen atom, thus forming an isoelectronic pyrido[de]quinazoline (or "azaperimidine"). There are three such ring systems, represented by the parent compounds 2, 3, and 4. We now report syntheses of two of these; pyrido[4,3,2-de]quinazoline (2) and pyrido[3,4,5-de]quinazoline (3).

(i) PYRIDO[4,3,2-de]QUINAZOLINE

Pyrido[4,3,2-de]quinazoline (2) was prepared in six steps from quinoline. Thus, quinoline was treated with hydrogen peroxide in acetic acid to give quinoline-1-oxide (5a, 93%), which was nitrated with nitric acid in sulphuric acid at 70°C to afford 4-nitroquinoline-1-oxide (5b, 66%).³

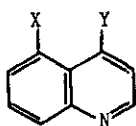
The next step was the deoxygenation of 5b to give 4-nitroquinoline (6a), and to this end three different procedures were investigated, although none was found to be entirely satisfactory. On occasion excellent yields of 4-nitroquinoline (6a) could be obtained by treatment of the N-oxide 5b with phosphorus tribromide in chloroform below 30°C,⁴ but more often the desired product was accompanied by a larger quantity of a mixture of two products which were identified as 2-bromo-4-nitroquinoline (7a) and 2,4-dibromoquinoline (7b).⁵



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a: X = H

b: X = NO₂

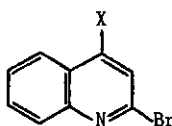


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a: X = H; Y = NO₂

b: X = Y = NO₂

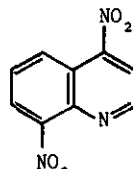
c: X = Y = NH₂



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a: X = NO₂

b: X = Br



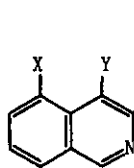
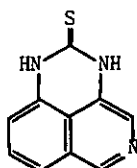
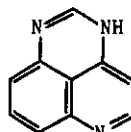
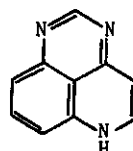
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With the aim of avoiding the formation of the undesired halides 7a and 7b, 4-nitroquinoline-1-oxide (5b) was treated with phosphorus tribromide in chloroform at -23°C. Although no brominated side-products were isolated in this instance, the yield of 4-nitroquinoline (6a) was never better than 59%. A recent report by Kaneko and co-workers recommends the use of trimethyl phosphite under photolytic conditions as a reagent for the deoxygenation of heteroaromatic N-oxides.⁶ Indeed, extended photolysis of a dichloromethane solution of 4-nitroquinoline-1-oxide (5b) and trimethyl phosphite with a 1kW sun-lamp on one occasion returned an 86% yield of the desired product, but the reaction proved to be somewhat capricious and more commonly only starting material was recovered.

Nitration⁷ of 4-nitroquinoline (6a) with potassium nitrate in 98.5% sulphuric acid at 65-75°C gave a mixture of 4,5-dinitroquinoline (6b, 44%) and 4,8-dinitroquinoline (8, 16%). Hydrogenation of 6b in glacial acetic acid in the presence of palladium-charcoal catalyst proceeded readily to give 4,5-quinolinediamine (6c), previously isolated only as the acetate.⁸ The diamine could be sublimed without difficulty but appeared to be susceptible to aerial oxidation, darkening appreciably on standing for a period of hours. Conversion into pyrido[4,3,2-de]quinazoline (2) was accomplished by heating 6c with formic acid, furnishing the new heterocycle in a yield of 89%.

(ii) PYRIDO[3,4,5-de]QUINAZOLINE

Pyrido[3,4,5-de]quinazoline (3) was prepared in four steps from isoquinoline. The key intermediate, 4,5-dinitroisoquinoline (9a), was obtained by nitration of 4-nitroisoquinoline (9b), and independently by nitration of 5-nitroisoquinoline (9c). Thus, treatment of isoquinoline with nitric acid in acetic anhydride at 80°C gave 4-nitroisoquinoline (9b, 11%),⁹ accompanied by a considerable quantity of dark, oily material. Nevertheless, this procedure has one advantage over other approaches to 9b in that it provides the desired isomer in a single step, whereas far more circuitous routes are required otherwise.⁹ Further nitration of 4-nitroisoquinoline with potassium nitrate in sulphuric acid at 75°C then furnished the desired intermediate (9a, 73%). Alternatively, 9a was formed in a 26% yield by nitration of 5-nitroisoquinoline (9c) with nitric acid in acetic anhydride at 120°C. Using either of these two routes, 4,5-dinitroisoquinoline was obtained in only a low yield, largely as a consequence of the difficulty in introduction of a nitro group at C4 (cf. ref. 9). The latter sequence gives a better overall yield of the desired material, but the former is more economical, as most of the isoquinoline does not react with nitric acid in acetic anhydride and can be recovered from the reaction mixture, whereas under the conditions required for the further nitration of 5-nitroisoquinoline, much of the substrate is converted into a complex mixture of unidentified by-products.

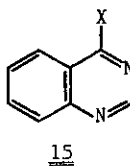
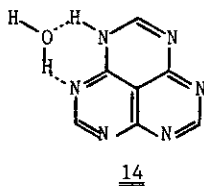
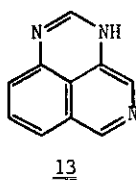
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- a: X = Y = NO₂
 b: X = H; Y = NO₂
 c: X = NO₂; Y = H
 d: X = Y = NH₂

4,5-Dinitroisoquinoline was hydrogenated in glacial acetic acid in the presence of palladium-charcoal to give 4,5-isoquinolinediamine (9d, 94%). This intermediate was far more stable than the isomeric quinolinediamine 6c, and showed no sign of decomposition even after standing for several months. Subsequently, 9d was heated with refluxing formic acid to give pyrido[3,4,5-de]quinazoline (3, 73%). Treatment of 9d with carbon disulphide in ethanol at room temperature, in the presence of a catalytic quantity of potassium hydroxide, gave

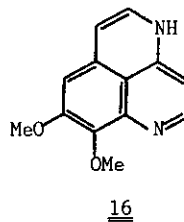
pyrido[3,4,5-de]quinazoline-2-thione (10, 95%).

Both pyrido[4,3,2-de]quinazoline (2) and pyrido[3,4,5-de]quinazoline (3) displayed spectroscopic properties comparable to those of perimidine. However, in the infrared spectra (KBr disc) of both 2 and 3, the NH stretching band is very much broader than the corresponding band in the infrared spectrum of perimidine. A likely explanation of this phenomenon is that the azaperimidines 2 and 3 are both able to exist in more than one nondegenerate tautomeric form, represented by structures 11, 12, and 13. The simultaneous presence of more than one tautomer in the solid state results in broadening of the NH stretching band. In tetradeuteriomethanol solution however, tautomerism is faster than the proton nmr timescale, and no broadening of proton resonances when compared to those of perimidine was observed. Interestingly, pyrido[3,4,5-de]quinazoline (3) crystallised from methanol as a partial (1/3) hydrate, and therefore occupies a position intermediate between perimidine (1), which does not form a hydrate, and 1,3,4,6,7,9-hexaazaphenalene, which exists preferentially as the stable monohydrate (14).¹⁰



a: X = NHCH₂CH(OEt)₂

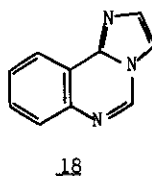
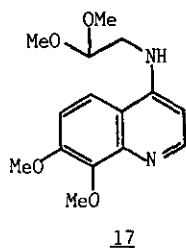
b: X = Cl



(iii) ATTEMPTED SYNTHESIS OF PYRIDO[2,3,4-de]QUINAZOLINE

A direct approach to the third azaperimidine, pyrido[2,3,4-de]quinazoline (4), envisaged cyclisation of the acetal 15a. A similar methodology was used recently by Kelly¹¹ in a total synthesis of the marine alkaloid aaptamine (16) via the acetal 17. The acetal 15a was prepared by treatment of 4-chloroquinazoline (15h)¹² with aminoacetaldehyde diethyl acetal in benzene at room temperature. However, when 15a was treated with boron trifluoride etherate at room temperature for an extended period, only the starting material was recovered. When 15a was treated with Eaton's reagent (10% phosphorus pentoxide-methanesulphonic acid),¹³ or with trifluoromethanesulphonic acid, the recovery of material was consistently poor, and the products were complex mixtures. When a solution of the acetal 15a in acetic anhydride was heated under reflux, a trace of a product was isolated from the resulting mixture, whose mass spectrum contained a molecular ion in the correct

position (m/z 169) for 4. However, this compound was not obtained sufficiently pure to enable full characterisation; it is possible that this product could instead be the imidazo[1,2-*c*]quinazoline derivative 18, as products of this type have been isolated in the past from related starting materials.¹⁴ A significant factor militating against the desired cyclisation is the tendency of quinazoline to undergo [intermolecular] electrophilic substitution at C6,¹⁵ rather than at C5 as is the case with the majority of azanaphthalenes. Moreover, the successful cyclisation of acetal 17 reported by Kelly almost certainly reflects the enhanced rate of electrophilic attack on the activated dimethoxybenzo ring.



EXPERIMENTAL

4,5-Quinolinediamine (6c)

A suspension of 4,5-dinitroquinoline (62 mg, 0.28 mmol) and 10% palladium-charcoal (10 mg) in glacial acetic acid (10 ml) was shaken under an atmosphere of hydrogen (50 psi) for 1 h at room temperature. The mixture was filtered, and the filtrate was diluted with water (20 ml) and neutralised with aqueous ammonia. The resulting solution was saturated with sodium chloride and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried (MgSO_4) and evaporated under reduced pressure to give 6c (45 mg, 100%) as a yellow oil which crystallised on standing. Sublimation (98°C/0.06 mmHg) gave pale yellow crystals, mp 134-139°C, which darkened on standing in air. HRMS Calcd. for $\text{C}_9\text{H}_9\text{N}_3$: M^+ 159.0796. Found: M^+ , 159.0801. ν_{max} (KBr) 3400 (br, NH_2), 1660-1580 cm^{-1} (br, NH_2 , C=N, C=C). δ_{H} (CDCl_3) ca. 4.5 (br s, 4H, 2NH_2), 6.41 (d, J 5.5 Hz, 1H, H3), 6.69 (dd, J_{O} 7 Hz, J_{m} 1 Hz, 1H, H6), 7.18-7.65 (m, 2H, H7, H8; partially obscured by solvent peak), 8.37 (d, J 5.5 Hz, 1H, H2). m/z 159 (M, 100%), 132 (M-HCN, 30), 131 (132-H, 26), 115 (132-HCN, 9).

1H-Pyrido[4,3-d]quinazoline (2)

A solution of 4,5-quinolinediamine (45 mg, 0.28 mmol) in formic acid (1 ml) was heated under reflux for 1 h, cooled, and then added to water (10 ml) and neutralised with aqueous ammonia. The mixture was extracted with ethyl acetate (3 x 20 ml), and the combined extracts were dried (MgSO_4) and evaporated under reduced pressure to give 2 (42 mg, 89%), which was sublimed at $120^\circ/0.05$ mmHg to give bright yellow needles, mp $241\text{--}244^\circ\text{C}$ (decomp). HRMS Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3$: M^+ , 169.0640. Found: M^+ , 169.0640. ν_{max} (KBr) 3450 (br, NH), 1650, 1620 (C=N), 1595 cm^{-1} (C=C). δ_{H} (CD_3OD) 6.23 (d, J 6.5 Hz, 1H, H4), 6.91 (dd, J_{O} 8 Hz, J_{m} 1 Hz, 1H, H9), 7.05 (dd, J_{O} 8 Hz, J_{m} 1 Hz, 1H, H7), 7.58 (t, J 8 Hz, 1H, H8), 7.81 (d, J 6.5 Hz, 1H, H5), 7.94 (s, 1H, H2). m/z 169 (M, 100%), 142 (M-HCN, 34), 115 (142-HCN, 21), 114 (115-H, 19).

4,5-Dinitroisoquinoline (9a)

(A) Fuming nitric acid (12 ml, 0.29 mol) was added dropwise to a stirred solution of 5-nitroisoquinoline (10.0 g, 0.057 mol) in acetic anhydride (100 ml) to give a white suspension which was heated to 120°C , clarifying after ca. 1 min to give an orange-yellow solution. The solution was heated for 60 min at 120°C , then added to water (1 L), and the mixture was left overnight to allow the acetic anhydride to hydrolyse. The supernatant liquid was decanted and the residue was taken up in ethyl acetate (250 ml). The resulting solution was washed with water (250 ml), dried (MgSO_4), and evaporated to give a yellow solid which was washed with dichloromethane to leave 9a (2.9 g, 23%). Recrystallisation from acetone gave broad white needles, mp $215\text{--}215.5^\circ\text{C}$, s.p. $144^\circ\text{C}/0.2$ mmHg. Anal. Calcd. for $\text{C}_9\text{H}_5\text{N}_3\text{O}_4$: C, 49.3; H, 2.3; N, 19.2. Found: C, 49.1; H, 2.2; N, 18.9%. ν_{max} (KBr) 1630 (C=N), 1530, 1350 cm^{-1} (NO_2). δ_{H} (CD_3SOCD_3) 8.13 (t, J 8 Hz, 1H, H7), 8.70–8.93 (m, 2H, H6, H8), 9.38 (s, 1H, H3), 9.92 (s, 1H, H1). m/z 219 (M, 15 %), 173 (M- NO_2 , 43), 145 (173-CO, 40), 115 (145-NO, 100), 88 (115-HCN, 55).

(B) Potassium nitrate (1.62 g, 16 mmol) was added during 5 min to a stirred solution of 4-nitroisoquinoline (1.00 g, 5.5 mmol) in concentrated sulphuric acid (25 ml) at 75°C , and the resulting solution was heated at the same temperature for a further 2.5 h. The hot solution was added to ice and the resulting suspension was filtered to give 9a (0.88 g, 73 %).

4,5-Isoquinolinediamine (9d)

A suspension of 4,5-dinitroisoquinoline (0.97 g, 4.6 mmol) and 10% palladium-charcoal (100 mg) in glacial acetic acid (25 ml) was shaken under an atmosphere of hydrogen (40 psi) for 1 h at room temperature. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the brown residue was treated with dilute aqueous ammonia (40 ml) and chloroform (40 ml). The organic layer was separated, dried (CaCl_2), and evaporated to leave 9d (0.68 g, 94 %) as a light brown solid which was sublimed ($84^\circ\text{C}/0.04 \text{ mmHg}$) to give pale yellow needles, mp $151.5\text{--}153^\circ\text{C}$. *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{N}_2$: C, 67.9; H, 5.7; N, 26.4. Found: C, 68.1; H, 5.7; N, 26.3%. ν_{max} (KBr) 3400 (NH_2), 1620 ($\text{C}=\text{N}$), 1585 cm^{-1} ($\text{C}=\text{C}$). δ_{H} (CDCl_3) 4.50 (br s, 4H, 2NH_2), 6.82 (dd, J_{O} 9 Hz, J_{m} 4.5 Hz, 1H, H6), 7.23–7.45 (m, 2H, H7, H8) 7.84 (s, 1H, H3), 8.63 (s, 1H, H1). m/z 159 (M, 100 %), 132 (M–HCN, 24), 131 (132–H, 20), 115 (132– NH_2 , 8), 104 (131–HCN, 14), 77 (104–HCN, 11).

1H-Pyrido[3,4,5-de]quinazoline (3)

A solution of 4,5-isoquinolinediamine (23 mg, 0.15 mmol) in formic acid (1 ml) was heated under reflux for 30 min in a nitrogen atmosphere, then diluted with water (10 ml), neutralised with aqueous ammonia, and extracted with ethyl acetate (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 3 (18 mg, 73%) as a yellow solid, which was recrystallised from aqueous methanol to give yellow crystals, mp $246\text{--}249^\circ\text{C}$. *Anal.* Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3 \cdot 1/3\text{H}_2\text{O}$: C, 68.6; H, 4.4; N, 24.0. Found: C, 68.4; H, 4.4; N, 24.0%. ν_{max} (KBr) 3450 (NH), 1620 ($\text{C}=\text{N}$), 1590 cm^{-1} ($\text{C}=\text{C}$). δ_{H} (CD_3OD) 6.74 (dd, J_{O} 6 Hz, J_{m} 3 Hz, 1H, H9), 7.13–7.46 (m, 3H, H2, H7, H8), 7.63 (s, 1H, H4), 8.47 (s, 1H, H6). m/z 169 (M, 100%), 142 (M–HCN, 20), 141 (M–HCNH, 10), 115 (142–HCN, 21), 114 (141–HCN, 17), 88 (115–HCN, 12).

Pyrido[3,4,5-de]quinazoline-2-thione (10)

Carbon disulphide (0.10 ml) was added to a solution of 4,5-isoquinolinediamine (50 mg, 0.34 mmol) and potassium hydroxide (ca. 10 mg) in ethanol (50 ml). After 1 h, filtration gave 10 (65 mg, 95 %) as a pale yellow solid. Sublimation at $170^\circ\text{C}/0.04 \text{ mmHg}$ gave pale yellow crystals, mp $> 300^\circ\text{C}$. *Anal.* Calcd. for $\text{C}_{11}\text{H}_7\text{N}_2\text{S}$: C, 59.7; H, 3.5; N, 20.9. Found: C, 59.6; H, 3.7; N, 20.7%. ν_{max} (KBr) 3150 (NH), 1615 cm^{-1} ($\text{C}=\text{S}$). δ_{H} (CD_3SOCD_3) 6.90 (dd, J_{O} 6 Hz, J_{m} 3 Hz, 1H, H9), 7.38–7.54 (m, 2H, H7, H8), 7.83 (s, 1H, H4), 8.64 (s, 1H, H6). m/z 201 (M, 100 %), 167 (M– H_2S , 91), 140 (167–HCN, 30).

4-(2,2-Diethoxyethylamino)quinazoline (15a)

A solution of 4-chloroquinazoline (0.82 g, 5 mmol) and aminoacetaldehyde diethyl acetal (1.45 ml, 10 mmol) in dry benzene (10 ml) was left to stand for 1 h, then filtered to remove the precipitate of aminoacetaldehyde diethyl acetal hydrochloride. Evaporation of the filtrate gave a pale yellow oil which was crystallised from benzene to give 15a (0.54 g, 42 %) as white needles, mp 130°C.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.3; H, 7.3, N, 16.1. Found: C, 64.1; H, 7.6 %; N, 16.1%. $\nu_{\max}(\text{KBr})$ 3275 (NH), 1620 (C=N), 1590, 1575 cm^{-1} (C=C). $\delta_{\text{H}}(\text{CDCl}_3)$ 1.27 (t, J 7 Hz, 6H, 2CH_3) 3.46-4.02 (m, 6H, 3CH_2), 4.75 (t, J 5 Hz, 1H, $\text{CH}[\text{OEt}]_2$), 6.13 (br s, 1H, NH), 7.37-7.97 (m, 4H, H5, H6, H7, H8), 8.7 (s, 1H, H2). m/z 261 (M, 4 %), 158 (M- $\text{CH}[\text{OEt}]_2$, 14), 129 (158- $\text{CH}_2=\text{NH}$, 14), 103 (129-CN, 100), 75 (C_6H_5 , 59), 47 ($\text{C}_2\text{H}_5\text{N}$, 92).

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