Synthesis of Perimidine and Fused Perimidine Derivatives from Reaction of 1,8-Naphthalenediamine with an Iminoisocoumarin

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The isocoumarin derivative 1*H*-1-acetylimino-3-methylbenzo[*c*]pyran-4-carbonitrile reacts with 1,8-naphthalenediamine under basic conditions to give, primarily, 12-acetylisoquino[2,1-*a*]perimidin-13-amine. This undergoes a variety of reactions to give other isoquino[2,1-*a*]perimidine derivatives, ring opening to 2-(1*H*-perimidin-2-yl)phenylacetic acid derivatives and, in polyphosphoric acid, a new hexacyclic system, 6-methyl-7,13,13d-triazadibenzo[*def,qr*]chrysene.

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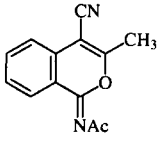
We recently discovered that the isocoumarin derivative **1**, the product from reaction of α-cyano-*o*-tolunitrile with acetic anhydride, reacts readily with nitrogen nucleophiles to give polycyclic systems [1]. Included was the reaction with *o*-phenylenediamine under mild base conditions to give the little studied benzimidazo[2,1-*a*]isoquinoline system **2**. As derivatives of such polycyclic systems are of current interest as antitumor compounds [2,3], we are investigating extensions to this synthesis and report here on the more complex reaction with 1,8-naphthalenediamine which has led to various derivatives of the perimidine system.

The details of reactions of diamines with **1** have not been fully elucidated but there are clearly parallels with the Gabriel isoquinolone synthesis in which an isocoumarin is reacted with ammonia [4]. This has been extended to arylamines to form the relevant *N*-arylisoquinolones [5,6] but, until our work, not to o-diamines.



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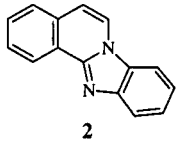

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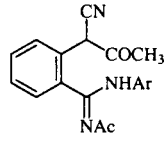

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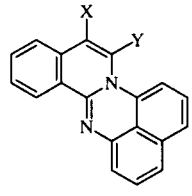
The isocoumarin ring in **1** is cleaved during the amine attack; the essentials of a possible intermediate are shown in **3**. When cyclization recurs, both the acetyl and cyano functions are potential sites for reaction. In the previous study, only products of the former were isolated. The present 1,8-naphthalenediamine reaction is different in that products from both paths were obtained. Surprisingly, the one obtained under the triethylamine/dioxan conditions used before was **4a** through ring closure onto the cyano group. Key pointers to the structure were the existence of a broad two-proton singlet, exchangeable in deuterium oxide, in the ^{1}H nmr spectrum, and a signal at 195 ppm in the ^{13}C nmr spectrum for the ketone carbon. Other conditions were also investigated, with generally more complex results. For example, reaction in hot pyridine gave a mixture containing the originally expected compound **4b** (isolated), **4a** and a compound later identified as a ring-opened product, **5a**.

The pyrido ring of **4** appears to lack much aromatic stability (it has features of an enamine system); quite ready ring-opening appears to be a feature of these fused perimidine structures and governs much of the chemistry observed. Thus **4a**, the kinetically favoured cyclization product, gave an unexpectedly diverse range of products under various solvolytic conditions, all of which seem to require opening of the pyrido ring at some stage. As an example, an attempted acetylation of **4a** with acetic anhydride under the same solvent conditions which first led to **4a**, instead gave a smooth conversion to **4b**, apparently the thermodynamic product. This is a better preparation of **4b** than the pyridine reaction above, and the structure was assigned from microanalytical data and electrospray mass spectrum, together with the presence of methyl (nmr) and cyano (ir) groups. The ring-opened product seen in the pyridine reaction described above, **5a**, was also produced in good yield from **4a** by reaction with ammonium hydroxide.



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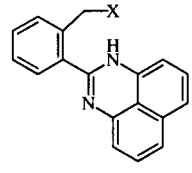
a X = Ac, Y = NH_2
b X = CN, Y = CH_3
c X = H, Y = OH
d X = Ac, Y = OH



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a X = CN
b X = CO_2H

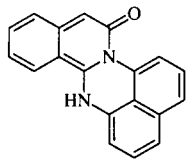
Acidic conditions resulted in a different set of products. Thus, hydrolysis of **4a** with aqueous acetic acid gave a main product which was apparently an isoquino[2,1-*a*]perimidine derivative without a 12-substituent (from the characteristic singlet at 5.86 ppm in the ^{1}H nmr spectrum). This was assigned structure **6** rather than the alternative hydroxy form **4c**, from the occurrence of a peak at 1680 cm^{-1} in the infrared spectrum, though the nmr spectra were equivocal.

Both lactam and lactim tautomers have been identified in isoquinolin-3(2*H*)-ones [7]. When recrystallization of this compound was attempted in acetic acid, an insoluble, high melting green solid was formed, with very similar ^{1}H nmr spectrum but in which the peak for H-12 in **6** had disappeared. We suspect that an oxidative dimerization has occurred through this position, analogous to that observed through the *ortho* position in some substituted phenols. The reactivity of this position was demonstrated when reaction of **6** with acetyl chloride in pyridine gave a product with spectral features consistent with the *C*-acylated product **4d**. Here, the hydroxy form is favored by hydrogen bonding to the adjacent acetyl function.

When a little sulfuric acid was added to the acetic acid medium and heated with **4a**, a different pathway occurred; the pyrido ring was cleaved and the acid **5b** was isolated. This, however, appears not to be an intermediate in the aqueous acetic acid formation of **6** described above as compound **5b** was unchanged under these conditions. It did undergo this dehydrative cyclization to **6**, however, in hot polyphosphoric acid.

The most unexpected reaction of all was in fact one with polyphosphoric acid. When **4a** was heated with polyphosphoric acid, a compound assigned structure **7** was isolated in >90% yield. Apart from electrospray and microanalytical data, 9 aromatic protons (apart from the high field singlet for H-8) and the methyl group were key nmr features and the absence of an oxygen is accommodated. The mechanism for the formation of this compound is not known though an acetylamino substituted precursor would seem logical.

The chemistry described above reveals a complex set of products arising from, basically, one reaction and a number of possibilities exist for further derivatization of some of these for biological testing.



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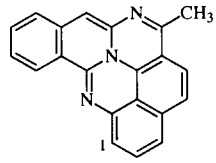

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EXPERIMENTAL

The nmr spectra were recorded, in dimethyl-d_6 sulfoxide unless stated otherwise, on a Bruker AM-300 spectrometer operating at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C). The ^{1}H nmr multiplicities alone are quoted for aromatic signals and refer to single protons unless stated otherwise. *Ortho* couplings were typically ≈ 8 Hz; significant differences are noted. Various standard techniques were used to identify proton-bound carbons in ^{13}C nmr spectra. The ir spectra were recorded on a Perkin-Elmer 1720X FTIR spectrometer, using a diffuse reflectance accessory with potassium bromide background, or on a Bruker Vector 22 Fourier-transform spectrometer with nujol background. The electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer using a water/methanol/acetic acid (50:50:1) mobile phase. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

12-Acetylisoquino[2,1-*a*]perimidin-13-amine (**4a**).

A hot solution of **1** [8] (4.0 g) in dioxan (40 ml) was added to a refluxing solution of 1,8-diaminonaphthalene (3.2 g) in a mixture of dioxan (40 ml) and triethylamine (40 ml). After being heated under reflux for 2 hours, the mixture was poured onto ice and the solution taken to *p*H 9-10 with concentrated hydrochloric acid. The solid which formed was filtered, washed with water and recrystallized from ethanol to give the product as orange needles (3.90 g, 68%), mp 213-214°; ^{1}H nmr: δ 2.41 (s, 3, CH_3), 7.12 (dd, 1, J = 6.6, 1.4 Hz), 7.25 (t), 7.39- 7.61 (m, 7), 8.16 (d), 9.11 (br s, 2, NH_2); ^{13}C nmr: δ 30.6 (CH_3), 96.0 (C), 114.9 (CH), 117.9 (CH), 122.0 (CH), 122.7 (CH), 123.1 (C), 123.9 (CH), 124.5 (C), 125.5 (CH), 125.8 (CH), 127.3 (CH), 128.5 (CH), 131.3 (CH), 131.9 (C), 134.3 (C), 134.6 (C), 139.8 (C), 147.9 (C), 151.6 (C), 195.2 (CO); ir (potassium bromide): ν_{max} 3420, 1620 cm^{-1}; esms: m/z 326 (M+1).

Anal. Calcd. for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.42; H, 4.40; N, 13.09.

13-Methylisoquino[2,1-*a*]perimidine-12-carbonitrile (**4b**).

(a) A mixture of **4a** (0.50 g) in dioxan (20 ml), triethylamine (10 ml) and acetic anhydride (10 ml) was heated under reflux for 4 hours. The solution was poured onto ice, and the solid which separated was filtered off and washed with water to give the product as an orange-brown solid (0.45 g, 95%), mp 236-237° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 2.68 (s, 3, CH_3), 6.71 (d), 7.19-7.49 (m, 6), 7.60-7.66 (m, 2), 8.41 (d); ^{13}C nmr (deuteriochloroform): δ 20.1 (CH_3), 97.0 (C), 114.7 (CH), 116.5 (C), 118.2 (CH), 121.6 (CH), 123.1 (CH), 123.5 (CH), 123.9 (C), 126.1 (CH), 126.3 (C), 126.6 (CH), 128.4 (CH), 128.6 (CH), 130.4 (C), 132.4 (CH), 133.2 (C), 134.3 (C), 140.0 (C), 146.7 (C), 147.9 (C); ir (nujol): ν_{max} 2211 cm^{-1}; esms: m/z 308 (M+1).

Anal. Calcd. for $C_{21}H_{13}N_3 \cdot 0.25H_2O$: C, 80.88; H, 4.36; N, 13.47. Found: C, 81.00; H, 4.07; N, 13.61.

(b) A hot solution of **1** (0.20 g) in pyridine (4.5 ml) was added to a refluxing solution of 1,8-diaminonaphthalene (0.16 g) in pyridine (4.5 ml). After being heated under reflux for 75 hours, the solution was poured onto ice and taken to *p*H 6 with concentrated hydrochloric acid. The solid which separated was filtered, washed with water and recrystallized from ethanol to give the product as a brown solid (0.04 g, 21%), identical with that from (a).

2-(1*H*-Perimidin-2-yl)phenylacetonitrile (**5a**).

A solution containing **4a** was generated from **1** (0.2 g) as described above. To this was added concentrated ammonium hydroxide (2 ml) and heating under reflux was continued for a further 6 hours. The mixture was poured onto ice and allowed to stand at 4° overnight. The solid which formed was filtered off and washed with water to give the product as a brown solid (0.21 g, 84%), mp 199- 201° [from methanol/water (2:1)]; ^{1}H nmr: δ 4.30 (s, 2, CH_2), 6.40 (d), 6.63 (d), 7.01-7.21 (m, 4), 7.51-7.57 (m, 3), 7.67 (d), 10.61 (s, 1, NH); ^{13}C nmr: δ 21.4 (CH_2), 102.7 (CH), 113.9 (CH), 117.9 (CH), 119.1 (C), 119.6 (CH), 121.6 (C),

128.1 (CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 129.9 (C), 130.1 (CH), 130.7 (CH), 133.9 (C), 135.2 (C), 138.6 (C), 144.8 (C), 153.5 (C); ir (nujol): ν_{max} 2210 cm^{-1}; esms: m/z 284 (M+1).

Anal. Calcd. for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.21; H, 4.59; N, 14.67.

6-Methyl-7,13,13d-triazadibenzo[*def,qr*]chrysene (**7**).

A mixture of **4a** (1.0 g) in polyphosphoric acid (75 g) was heated, with stirring, at 120° for 7.5 hours. On being cooled, the solution was taken to *p*H 8 with sodium hydroxide (10%). The solid which formed was filtered and washed with water to give the product as a dark brown solid (0.91 g, 96%), mp 222-224° (from ethanol); ^{1}H nmr (75°): [9] δ 2.13 (s, 3, CH_3), 5.81 (s, H-8), 6.33 (d, H-3(1)), 6.74 (d, H-1(3)), 6.92 (d, H-4(5)), 7.00 (d, H-5(4)), 7.06 (t, H-2), 7.12 (t, H-11), 7.13 (d, H-9), 7.37 (t, H-10), 7.90 (d, H-12); ^{13}C nmr (deuteriochloroform): δ 21.8 (CH_3), 101.3 (CH), 109.5 (C), 116.4 (CH), 119.2 (CH), 121.4 (C), 121.7 (CH), 122.1 (CH), 123.4 (C), 125.5 (CH), 126.0 (CH), 126.6 (CH), 132.3 (CH), 133.3 (CH), 137.1 (C), 137.8 (C), 140.9 (C), 144.1 (C), 147.2 (C), 149.8 (C), 163.3 (C); esms: m/z 308 (M+1).

Anal. Calcd. for $C_{21}H_{13}N_3$: C, 82.06; H, 4.26; N, 13.67. Found: C, 81.57; H, 4.18; N, 13.57.

2-(1*H*-Perimidin-2-yl)phenylacetic Acid (**5b**).

A mixture of **4a** (0.20 g), glacial acetic acid (10 ml) and concentrated sulfuric acid (200 µl) was heated under reflux for 16 hours, then poured onto ice. The solid which formed was filtered and washed with water to give the product as a brown solid (0.10 g, 54%), mp >240° dec (from ethanol); ^{1}H nmr: δ 3.90 (s, 2, CH_2), 6.52 (d, 2, J = 7.1 Hz), 7.05-7.18 (m, 4), 7.39-7.51 (m, 3), 7.64 (d); ^{13}C nmr: δ 40.0 (CH_2), 119.4 (CH), 121.4 (CH), 127.3 (CH), 128.6 (CH), 128.8 (CH), 130.9 (CH), 131.7 (CH), 133.0 (C), 134.1 (C), 135.0 (C), 155.3 (C), 172.0 (C); esms: m/z 303 (M+1).

Anal. Calcd. for $C_{19}H_{14}N_2O_2 \cdot 0.5H_2O$: C, 73.30; H, 4.86; N, 9.00. Found: C, 73.43; H, 4.54; N, 9.13.

Isoquino[2,1-*a*]perimidin-13(7*H*)-one (**6**).

(a) Compound **4a** (0.50 g) was heated under reflux in acetic acid/water (9:1, 10 ml) for 16 hours. The solution was poured onto ice and the solid which formed was filtered, washed with water and recrystallized from ethanol to give the product as a green-yellow solid (0.25 g, 57%), mp 264° (rapid heating); ^{1}H nmr: δ 5.86 (s), 6.64 (d), 7.14 (t), 7.21 (d), 7.28-7.35 (m, 2), 7.42-7.56 (m, 2), 7.58 (d), 8.07 (d), 8.91 (d), 10.41 (s, NH); ^{13}C nmr: δ 84.1 (CH), 104.3 (CH), 114.8 (C), 115.4 (CH), 117.2 (CH), 121.2 (C), 122.8 (CH), 123.6 (CH), 124.0 (CH), 127.1 (CH), 127.6 (CH), 128.2 (CH), 131.8 (C), 133.3 (CH), 133.6 (C), 133.9 (C), 138.1 (C), 139.2 (C), 162.6 (C); ir (nujol): ν_{max} 3277, 1680 cm^{-1}.

Anal. Calcd. for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85. Found: C, 80.30; H, 4.07; N, 10.09.

(b) A mixture of **5b** (0.02 g) in polyphosphoric acid (3 g) was heated, with stirring, at 100° for 2 hours. On being cooled, the solution was taken to *p*H 8 with sodium hydroxide (10%), and the solid which formed was filtered off and washed with water to give the product as a green solid (0.01 g, 53%), identical with that from (a).

Dimer of **6**.

A mixture of **6** (0.10 g) in acetic acid (2 ml) was heated under vigorous reflux for 1 hour. On being cooled, the solid was removed by filtration and washed with water to give the product as a green solid (0.07 g, 70%), mp >300°; ^{1}H nmr: δ 6.79 (dd, J = 6.1, 2.2 Hz), 6.94 (d), 7.18-7.22 (m, 3), 7.39 (t), 7.51-7.62 (m, 2), 8.26 (d), 8.86 (d), 9.06 (s, 1, NH).

Alternatively, when **6** was slowly heated to 300°, the same compound was formed (in this case a dark brown solid), in quantitative yield.

Anal. Calcd. for $C_{38}H_{22}N_4O_2 \cdot 0.5H_2O$: C, 79.29; H, 4.03; N, 9.73. Found: C, 79.17; H, 3.96; N, 9.72.

12-Acetyl-13-hydroxyisoquino[2,1-*a*]perimidine (**4d**).

Acetyl chloride (0.04 g) was added over 15 minutes, with stirring, to a solution of **6** (0.10 g) in pyridine (20 ml) and the whole was stirred for a further 3 hours. Water was added, and the solid which formed was filtered off and washed with water to give the product as a brown solid (0.07 g, 61%), mp 167-169° (from ethanol); ^{1}H nmr: δ 2.58 (s, 3, CH_3), 6.91 (d), 7.34-7.43 (m, 2), 7.50 (t), 7.62 (d), 7.68 (t), 7.75 (d), 8.14 (d), 8.22 (d), 14.28 (s, 1, OH); ^{13}C nmr: δ 31.3 (CH_3), 95.1 (C), 107.7 (CH), 116.4 (CH), 117.7 (C), 120.3 (CH), 122.8 (C), 123.9 (CH), 124.3 (CH), 125.0 (CH), 127.3 (CH), 127.6 (CH), 128.4 (CH), 130.3 (C), 130.9 (C), 133.3 (CH), 133.5 (C), 135.4 (C), 146.6 (C), 162.0 (C), 196.5 (C).

Anal. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.32; N, 8.58. Found: C, 77.21; H, 4.19; N, 8.75.

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[9] Partial assignments are based on decoupling experiments.