Synthesis and Reactivity of Some Imidazo-, Triazolo- and Tetrazolo-Isoquinoline Derivatives

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1-Acetylimino-3-methyl-1*H*-isochromene-4-carbonitrile, **1**, reacts with glycine ethyl ester under basic conditions to give an imidazo[2,1-*a*]isoquinoline derivative, while reaction with hydrazine hydrate in 1,4-dioxane, with further chemistry, provides access to [1,2,4]triazolo[5,1-*a*]isoquinoline, [1,2,4]triazolo[3,4-*a*]isoquinoline and tetrazolo[5,1-*a*]isoquinoline analogs. Benzene ring nitration and radical bromination of substituent methyl groups were investigated in the four tricycles, with some different positional reactivities being found. Two bromomethyl derivatives so produced were oxidised; ethyl 2-bromomethyl-6-cyano-5-methylimidazo[2,1-*a*]isoquinoline-3-carboxylate gave the anticipated ethyl 6-cyano-2-formyl-5-methylimidazo[2,1-*a*]isoquinoline-3-carboxylate (which reacted further with hydrazine to form a new system, 8,9-dihydro-6-methyl-8-oxopyridazino[4',5':4,5]imidazo[2,1-*a*]isoquinoline-5-carbonitrile), while 5-bromomethyl-2-methyl[1,2,4]triazolo[5,1-*a*]isoquinoline-6-carbonitrile unexpectedly gave directly another new system, 5,6-dihydro-5-hydroxy-2-methyl-7*H*-pyrrolo[3,4-*c*][1,2,4]triazolo[5,1-*a*]isoquinolin-7-one.

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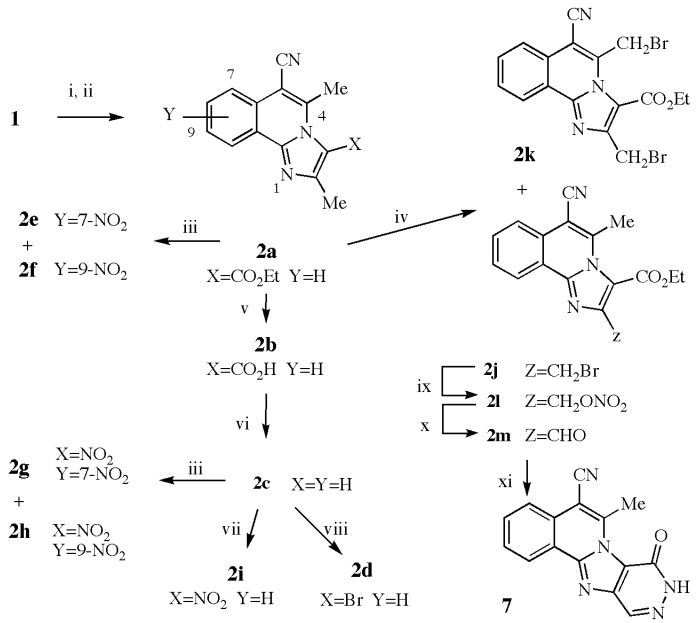
This is part of a program to investigate the chemistry of some polycyclic ring systems, with the ultimate aim of preparing suitably substituted derivatives for biological testing. We report here on the use of a readily accessible starting material **1** [1] for the synthesis of systems containing imidazo- triazolo- and tetrazolo- rings fused to the *a* face of isoquinoline (Figure 1), and on some potentially useful functional group manipulations.

The basic ring systems are all known and diverse biological properties of derivatives have been reported, including antitumour (imidazo) [4], antiviral (triazolo[3,4-*a*]) [5], animal pregnancy-terminating (triazolo[5,1-*a*]) [6] and monoamine oxidase inhibiting (tetrazolo) [7] agents. It is therefore of interest to explore the synthetic possibilities provided by **1** to access new routes and derivatives.

Synthesis of the Ring Systems.

We previously reported that reaction of **1** with amine nucleophiles produced a ring opening-ring closing sequence to form the isoquinoline ring [8] and, with glycine ethyl ester under basic conditions, further cyclization gave the fused imidazole **2a** (Scheme 1). Minor modi-

Scheme 1



(i) $NH_2CH_2CO_2Et$.HCl/NEt_3/dioxane/20°/2 h. (ii) NaOEt/EtOH-dioxane/20°/2 h. (iii) 3 mol KNO_3/c.H_2SO_4/20°/4 h. (iv) NBS/$(BzO)_2$/C_6H_6/reflux/6 h. (v) 0.77% NaOH in EtOH-H_2O/50°/6 h. (vi) 120°/5 mmHg/6 h. (vii) 1 mol KNO_3/c.H_2SO_4/20°/4 h. (viii) Br_2/$CHCl_3$/20°/1 min. (ix) $Hg_2(NO_3)_2$.$2H_2O$/$(MeOCH_2)_2$/reflux/6 h. (x) NEt_3/$(MeOCH_2)_2$/reflux/1 h. (xi) N_2H_4.H_2O/dioxane/reflux/2 h.

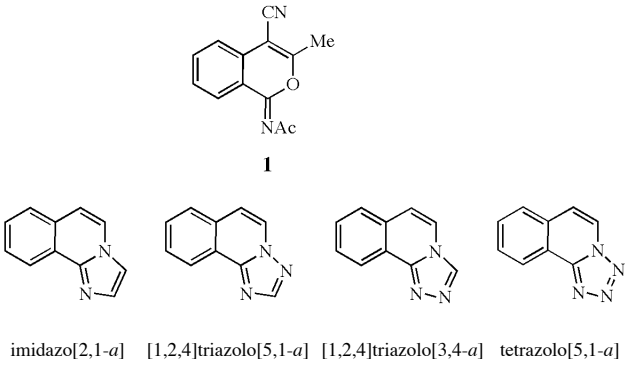


Figure 1. Fused isoquinoline ring systems accessible from **1**.

fication to this synthesis has now been made and 2D nmr experiments allowed full assignment of ^{13}C and ^{1}H spectra. Further, the ester function is readily hydrolysed in basic conditions and the product acid **2b** was found to undergo ready thermal decarboxylation to afford **2c**.

Our previous paper also contained the synthesis of the triazolo compound **3a**, by reaction of **1** with hydrazine hydrate in 1,4-dioxane, where the isoquinoline nitrogen comes from the hydrazine. It transpires that another product **4a** is also formed in this reaction by a competing pathway, where the isoquinoline nitrogen comes from **1**; reaction conditions have now been found which allow the ready isolation of both **3a** and **4a** (Scheme 2).

The structure of **4a** was assigned from mass spectral, microanalytical and nmr data, and from further reactions. This compound was a useful intermediate since (a) it was cyclized with hot phosphoryl chloride [9] to **5a**, isomeric with **3a**, and (b) deacetylation to **4b** followed by reaction with nitrous acid [10] also brought about cyclization, to the fused tetrazolo compound **6a**.

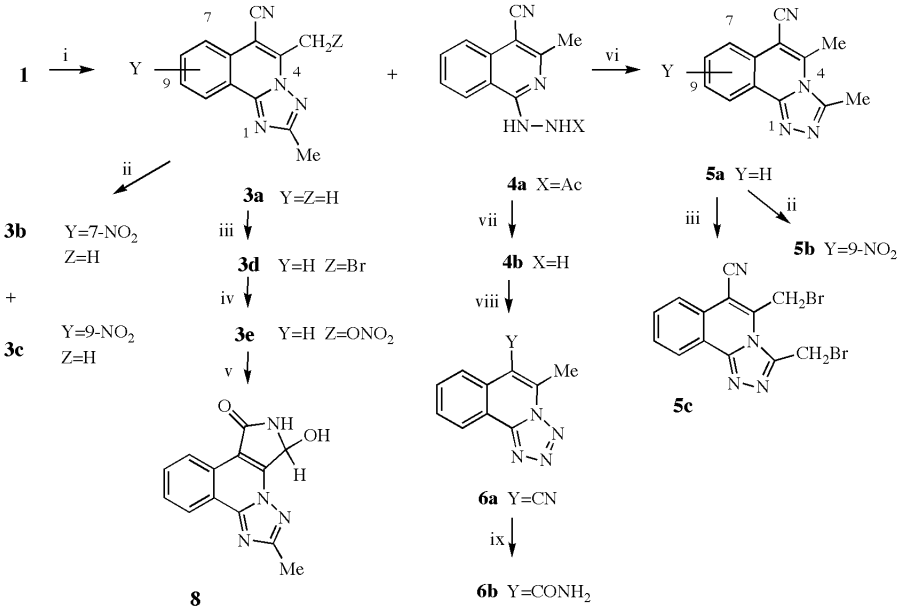
Thus, tricyclic compounds **2a**, **2c**, **3a**, **5a** and **6a** were available for a study of their comparative chemistries.

Nitration.

Since ring substituted analogs of the starting material for synthesis of **1** are not readily accessible, it would be advantageous if electrophilic substitution in the benzo ring of the tricyclic compounds could produce useable derivatives. Nitration was chosen to investigate product orientation and common conditions of 3 mol equivalents of potassium nitrate in concentrated sulfuric acid at room temperature for 4 hours were used.

The isomeric triazoles showed quite unexpectedly different behaviour. Compound **3a** gave a 2:1 mixture of two isomers in 75% yield. Repeated recrystallization allowed the major isomer to be purified and this was assigned as the 7-nitro compound **3b**; the absence of any $^{3}J_{CH}$ coupling to the characteristic C-6 (δ 92.1 ppm) in the HMBC nmr spectrum was a key piece of evidence. The minor isomer was not separated, but the ^{1}H nmr signals of the mixture were sufficiently separated that it could be identified

Scheme 2



(i) $N_2H_4.H_2O$/NEt_3/dioxane/20°/1 h. Filter **4a**, filtrate→**3a**. (ii) KNO_3/c.H_2SO_4/20°/4 h. (iii) NBS/$(BzO)_2$/CCl_4/reflux/6 h. (iv) $Hg_2(NO_3)_2.2H_2O$/MeCN/reflux/6 h. (v) NEt_3/MeCN/20°/5 min. (vi) $POCl_3$/reflux/5 h. (vii) dioxane-c.HCl (1:1)/reflux/1.5 h. (viii) $NaNO_2$/c.HCl/0°, then 20°/1 h. (ix) KNO_3/c.H_2SO_4/100°/2 h.

as the 9-nitro compound **3c**. Conversely, the same reaction of **5a** also gave a 75% yield but the product was >95% of the 9-isomer and recrystallization gave the pure compound **5b**. An HMBC nmr experiment showed $^{3}J_{CH}$ coupling between C-6 (δ 97.9 ppm) and a doublet at δ 8.09 in the ^{1}H spectrum, consistent only with this being H-7 of the 9-nitro isomer. The reason for the marked difference in preferred nitration site in the two isomers is not apparent.

Benzene ring nitration in the diazolo compounds **2a** and **2c** gave the same 2:1 distribution of 7- and 9-nitro isomers as did **3a**. However, the 3-position was in fact the most reactive one in **2c** (the characteristic singlet for H-3 in the ^{1}H nmr spectrum of **2c** was absent in the products). Standard nitration conditions therefore gave a mixture of 3,7- (**2g**) and 3,9-dinitro (**2h**) compounds, from which the former was isolated by recrystallization. When one equivalent of nitrating agent was used, the mono nitrated product **2i** was isolated in 91% yield.

The result for the tetrazolo compound **6a** was anomalous in that nitration did not occur. The starting material was recovered unchanged from the standard conditions, while hydrolysis of the nitrile to give carboxamide **6b** was the sole reaction when the nitration mixture was heated at 100° for 2 hours.

N-Bromosuccinimide Bromination

Aromatic methyl groups are, through oxidation, potential sources of useful functionality. Our experience is that, in polycyclic systems, direct oxidation with classic strong oxidants such as chromic acid commonly results in breakdown of the ring system, and indirect methods are required. Specifically, the bromomethyl group can be oxidised in various ways [11] and so, in the present investigation, we have looked at *N*-bromosuccinimide (NBS) bromination of methyl groups in **2a**, **2c**, **3a** and **5a**. All brominations were carried out in refluxing benzene or carbon tetrachloride and catalyzed with benzoyl peroxide.

In each substrate, the two methyl groups provided potentially competing sites and so it was especially of interest to probe any reactivity differences. HMBC nmr experiments allowed each methyl group to be unequivocally identified. As recorded above, C-6 (δ *ca* 98 ppm) was characteristic and $^{3}J_{CH}$ coupling to protons of the 5-methyl group was definitive.

As seen for nitration, the triazolo isomers again showed different behaviour. Reaction of compound **3a** with 1.1 equivalents of NBS for 6 hours gave bromination only at CH_3-5, and **3d** was isolated in 84% yield; the 2-methyl group was not affected. By contrast, in the isomeric **5a** under the same conditions, both methyl groups reacted at comparable rates and the bis(bromomethyl) compound **5c** was formed.

Interestingly, in the diazolo compound **2a**, there was again (some) discrimination between the two methyl groups, but here the 2-methyl was more reactive. Careful control of conditions was required for a preparatively useful outcome. Thus, reaction with 1.5 equivalents of NBS under reflux for 6 hours gave a mixture of starting compound **2a**, bis bromomethyl product **2k** and 2-bromomethyl product **2j** in an approximately 1:1:4 ratio. Recrystallization from acetonitrile gave **2j** in 69% yield, sufficiently pure for further reaction; further recrystallizations gave an analytically pure sample.

Reaction of **2c** with NBS gave complex mixtures, but the highly reactive nature of position-3 was again illustrated by reaction with bromine in chloroform. The 3-bromo product **2d** precipitated out within 1 minute at room temperature.

Reaction of Bromomethyl Compounds.

Further chemistry of diazolo (**2j**) and triazolo (**3d**) compounds was then studied. Of the oxidation methods referred to above, we have had success [12] with a modification of a method [13] that gives an aldehyde by way of base treatment of an intermediate nitrate ester. In the case of **2j**, the nitrate ester **2l** was formed and reaction with triethylamine gave the expected outcome, formation of aldehyde **2m**. A known [14] reaction with hydrazine proceeded readily to couple the adjacent aldehyde and ester groups to give the new ring system **7**.

With **3d**, however, the reaction took a different course. The nitrate ester **3e**, when reacted with triethylamine in acetonitrile gave the tetracycle **8** in 81% yield. The target aldehyde may have been formed as an intermediate species but further intramolecular reaction with the adjacent nitrile group occurred. The structure was assigned from spectroscopic evidence and by analogy with this type of structure reported as arising from reaction of *o*-cyanobenzaldehyde with triethylamine in aqueous acetonitrile [15].

EXPERIMENTAL

^{1}H Nuclear Magnetic Resonance (nmr) spectra and ^{13}C nmr spectra were recorded at 300.13 MHz and 75.47 MHz, respectively, on a Bruker AM 300 or Bruker Avance 300 spectrometer. Chemical shifts are reported as delta values (δ) in parts per million relative to tetramethylsilane. Various standard 2D experiments were used to make proton and carbon assignments. Melting points are uncorrected. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

1-Acetylimino-3-methyl-1*H*-isochromene-4-carbonitrile (**1**) [2].

A mixture of α-cyano-*o*-tolunitrile (Aldrich) (10.0 g) and anhydrous sodium acetate (5.0 g) in distilled acetic anhydride (35 mL) was heated under reflux for 2 hours. The resulting mixture was poured onto ice and stirred for 0.25 hour. The solid which separated was collected by filtration, washed with water and dried, to give **1** (14.5 g, 91%) as a light brown solid, sufficiently pure for further reactions; ^{1}H nmr (deuteriochloroform): δ 2.29 (s, 3H, $COCH_3$), 2.48 (s, 3H, CCH_3), 7.50 (t, 1H, J = 8.0 Hz, H-6(7)), 7.57 (d, 1H, J = 7.7 Hz, H-5), 7.70 (t, 1H, J = 7.4 Hz, H-7(6)), 8.10 (d, 1H, J = 7.8 Hz, H-8).

Ethyl 6-Cyano-2,5-dimethylimidazo[2,1-*a*]isoquinoline-3-carboxylate (**2a**).

Glycine ethyl ester hydrochloride (4.75 g, 34.1 mmol) was added to a solution of triethylamine (4.91 g, 48.7 mmol) in 1,4-dioxane (10 mL), and this was in turn added to a solution of **1** (7.33 g, 32.4 mmol) in 1,4-dioxane (50 mL). The resultant mixture was then stirred for 2 hours, after which time the solvents were evaporated at reduced pressure. The residue was extracted with dichloromethane (175 mL). The extract was washed twice with water (150 mL), dried over magnesium sulfate and the solvent was evaporated to give the intermediate, ethyl (1-acetylimino-4-cyano-3-methyl-1,2-dihydroisoquinolin-2-yl)acetate (9.11 g, 29.3 mmol). This was dissolved in 1,4-dioxane (60 mL) and a solution of sodium (0.71 g, 30.8 mmol) in ethanol (20 mL) was added. The solution was stirred for 2 hours and then evaporated to dryness at reduced pressure. The residue was extracted with dichloromethane and the extract was washed twice with water, dried over magnesium sulfate and the solvent was evaporated at reduced pressure to give ester **2a** (4.81 g, 50% from **1**), sufficiently pure for further reaction; mp 126-128° (ethanol) (lit. [8] mp 126-128°); ^{1}H nmr (deuteriochloroform): δ 1.44 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.66 (s, 3H, 2-CH_3), 2.95 (s, 3H, 5-CH_3), 4.45 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.66–7.77 (m, 2H, H-8,9), 8.02 (d, 1H, J = 7.9 Hz, H-7), 8.65 (d, 1H, J = 7.7 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_2CH_3), 15.4 (CH_3-2), 20.7 (CH_3-5), 61.2 (CH_2CH_3), 99.0 (C-6), 115.5 (CN), 117.3 (C-3), 120.5 (C-10a), 123.8 (C-7), 124.1 (C-10), 127.6 (C-6a), 128.6 (C-9), 130.2 (C-8), 143.1 (C-5), 145.2 (C-10b), 151.0 (C-2), 160.7 (CO).

2,5-Dimethylimidazo[2,1-*a*]isoquinoline-6-carbonitrile (**2c**).

To ester **2a** (1.0 g, 3.4 mmol) dissolved in hot ethanol (60 mL) was added water (60 mL) and 10% sodium hydroxide solution (10 mL). The mixture was then stirred at 50° for 6 hours during which time a solution was formed. This was cooled to 25° and acidified to pH 5 with concentrated hydrochloric acid. The precipitate that formed was filtered to afford 6-cyano-2,5-dimethylimidazo[2,1-*a*]isoquinoline-3-carboxylic acid (**2b**) (0.65 g, 72%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.54 (s, 3H, CH_3-2), 2.85 (s, 3H, CH_3-5), 7.57–7.85 (m, 3H, H-7,8,9), 8.45 (d, 1H, J = 7.7 Hz, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 15.3 (2-CH_3), 20.6 (5-CH_3), 97.9 (C-6), 111.2 (CN), 115.9 (C-5), 118.8 (C-3), 120.5 (C-10a), 123.6 (C-10), 124.0 (C-7), 127.4 (C-6a), 129.0 (C-9), 130.8 (C-8), 144.2 (C-10b), 149.6 (C-2), 161.9 (CO).

This acid (0.50 g, 1.89 mmol) was heated at 120° for 6 hours at 5 mm Hg. The crude decarboxylated compound was then recrystallized from light petroleum (bp 90–120°) to give **2c** as a pale orange solid (0.39 g, 94%), mp 168–171°; ^{1}H nmr (deuteriochloroform): δ 2.51 (s, 3H, 2-CH_3), 2.86 (s, 3H, 5-CH_3), 7.32 (s, 1H, H-3), 7.64–7.67 (m, 2H, H-8,9), 7.96–7.98 (m, 1H, H-7), 8.57–8.60 (m, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_3-2), 17.9 (CH_3-5), 96.1 (C-6), 109.1 (C-3), 115.7 (CN), 120.9 (C-10a), 123.1 (C-7), 124.1 (C-10), 126.5 (C-6a), 128.3 (C-9), 129.0 (C-8), 140.1 (C-5), 142.2 (C-10b), 143.0 (C-2).

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.44; H, 4.95; N, 19.10.

3-Bromo-2,5-dimethylimidazo[2,1-*a*]isoquinoline-6-carbonitrile (**2d**).

Bromine (0.25 mL) was added dropwise, with stirring, to a solution of **2c** (0.05 g, 0.23 mmol) in chloroform (10 mL) at room temperature. A yellow hydrobromide salt of the product precipitated during 1 minute, which was collected by filtration (0.065 g) and dissolved in warm acetonitrile. A little 5% sodium carbonate was added, then more water to afford **2d** as a white solid (0.05 g, 74%), mp 172–174° (acetonitrile); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.33 (s, 3H, CH_3-2), 3.20 (s, 3H, CH_3-5), 7.67–7.80 (m, 3H, H-7,8,9), 8.39 (d, 1H, J = 7.5 Hz, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ_13.5 (CH_3-2), 20.1 (CH_3-5), 96.3 (C-3), 98.0 (C-6), 115.7 (CN), 120.7 (C-10a), 122.9 (C-10), 123.7 (C-7), 126.2 (C-6a), 129.2 (C-9), 130.3 (C-8), 141.9 (C-2), 142.6 (C-10b), 143.6 (C-5).

Anal. Calcd. for $C_{14}H_{10}BrN_3$: C, 56.02; H, 3.36; N, 14.00. Found: C, 56.22; H, 3.33; N, 13.85.

Ethyl 6-Cyano-2,5-dimethyl-7-nitroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**2e**) and Ethyl 6-Cyano-2,5-dimethyl-9-nitroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**2f**).

To a stirred solution of potassium nitrate (0.10 g, 1.02 mmol) in concentrated sulfuric acid (2 mL) was added ester **2a** (0.10 g, 0.34 mmol), and the whole was stirred for 4 hours. The solution was then poured onto ice/water and the precipitate that formed was collected by filtration to give a mixture of isomeric nitro products **2e** and **2f** (0.08 g, 69%) in a ratio of 2:1, respectively. Repeated recrystallization from acetonitrile gave a sample of **2e** sufficiently pure to record the ^{13}C nmr spectrum; ^{1}H nmr **2e** (deuteriochloroform): δ 1.45 (t, 3H, J = 6.9 Hz, CH_2CH_3), 2.69 (s, 3H, CH_3-2), 3.01 (s, 3H, CH_3-5), 4.48 (t, 2H, J = 6.8 Hz, CH_2CH_3), 7.76 (t, 1H, J = 8.0 Hz, H-9), 8.05 (d, 1H, J = 8.9 Hz, H-8), 8.94 (d, 1H, J = 8.2 Hz, H-10); ^{13}C nmr **2e** (deuteriochloroform): δ 14.2 (CH_2CH_3), 15.4 (CH_3-2), 21.2 (CH_3-5), 61.8 (CH_2CH_3), 93.0 (C-6), 114.1 (CN), 118.3 (C-6a), 122.2 (C-3,10a), 126.5 (C-8), 128.4 (C-10), 129.3 (C-9), 143.7 (C-10b), 145.9 (C-7), 148.5 (C-5), 151.3 (C-2), 160.1 (CO); ^{1}H nmr **2f** (deuteriochloroform): δ 1.45 (t, 3H, J = 6.9 Hz, CH_2CH_3), 2.69 (s, 3H, CH_3-2), 3.04 (s, 3H, CH_3-5), 4.48 (t, 2H, J = 6.8 Hz, CH_2CH_3), 8.20 (d, 1H, J = 9.1 Hz, H-7), 8.52 (dd, 1H, J = 8.9, 2.4 Hz, H-8), 9.55 (d, 1H, J = 2.7 Hz, H-10).

Anal. (Isomeric mixture) Calcd. for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found C, 60.44; H, 4.55; N, 16.73.

2,5-Dimethyl-3,7-dinitroimidazo[2,1-*a*]isoquinoline-6-carbonitrile (**2g**) and 2,5-Dimethyl-3,9-dinitroimidazo[2,1-*a*]-isoquinoline-6-carbonitrile (**2h**).

To a stirred solution of potassium nitrate (0.37 g, 3.67 mmol) in concentrated sulfuric acid (4 mL) was added imidazole **2c** (0.27 g, 1.22 mmol), and the whole was stirred for 4 hours at room temperature. The solution was then poured onto ice/water and the precipitate that formed was collected by filtration to give a mixture of isomeric dinitro products **2g** (3,7-) and **2h** (3,9-) in a ratio of 2:1 (0.30 g, 81%). Two recrystallizations from ethanol gave the 3,7-dinitro isomer **2g**, mp 247–250°; ^{1}H nmr **2g** (deuteriochloroform): δ 2.70 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 8.01 (t, 1H, J = 8.0 Hz, H-9), 8.45 (d, 1H, J = 7.8 Hz, H-8), 8.93 (d, 1H, J = 8.1 Hz, H-10); ^{1}H nmr **2h** (deuteriochloroform): δ 2.67 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 8.26 (d, 1H, J = 8.9 Hz, H-7), 8.65 (d, 1H, J = 8.4 Hz, H-8), 9.26 (d, 1H, J = 1.9 Hz, H-10).

Anal. (Isomeric mixture) Calcd. for $C_{14}H_9N_5O_4$: C, 54.02; H, 2.91; N, 22.50. Found: C, 54.31; H, 2.70; N, 22.46.

2,5-Dimethyl-3-nitroimidazo[2,1-*a*]isoquinoline-6-carbonitrile (**2i**).

To a stirred solution of potassium nitrate (0.09 g, 0.90 mmol) in concentrated sulfuric acid (4 mL) was added imidazole **2c** (0.2

g, 0.90 mmol). The whole was stirred for 4 hours, then poured onto ice/water and the precipitate that formed was collected by filtration to give **2i** as a brown solid (0.22 g, 91%), mp 188–191° (acetonitrile); ^{1}H nmr (deuteriochloroform): δ 2.66 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 7.86 (t, 1H, J = 7.1 Hz), 7.94–8.02 (m, 2H), 8.62 (d, 1H, J =8.0 Hz, H-10).

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found C, 63.07; H, 3.67; N, 21.13.

Ethyl 2-Bromomethyl-6-cyano-5-methylimidazo[2,1-*a*]isoquinoline-3-carboxylate (**2j**).

To a solution of **2a** (1.39 g, 4.74 mmol) in benzene (100 mL), was added *N*-bromosuccinimide (1.27 g, 7.12 mmol) and benzoyl peroxide (0.11 g, 0.47 mmol), and the whole was heated under reflux for 6 hours. The solution was then washed twice with 10% sodium carbonate, the organic layer was dried over magnesium sulfate and the solvent was evaporated to give a mixture of starting material **2a**, bisbromo **2k** and monobromo **2j** (*ca* 1:1:4) (1.98 g). This orange solid was recrystallized from acetonitrile to give **2j** (1.21 g, 69%), mp 182–184°, as a white solid containing only trace amounts of the impurities. It was used in this state in further reaction, while a sample for microanalysis was recrystallized a further 3 times from acetonitrile; ^{1}H nmr (deuteriochloroform): δ 1.50 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.98 (s, 3H, CH_3), 4.50 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.83 (s, 2H, CH_2Br), 7.67–7.79 (m, 2H, H-8,9), 8.01 (d, 1H, J = 7.6 Hz, H-7), 8.67 (dd, 1H, J = 7.9, 0.9 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 13.9 (CH_2CH_3), 20.7 (CH_3), 24.3 (CH_2Br), 62.0 (CH_2CH_3), 100.2 (C-6), 115.2 (CN), 117.9 (C-3), 120.7 (C-10a), 123.9 (C-7), 124.4 (C-10), 127.5 (C-6a), 128.9 (C-9), 130.7 (C-8), 142.9 (C-5), 145.3 (C-10b), 149.0 (C-2), 159.5 (CO).

Anal. Calcd. for $C_{17}H_{14}BrN_3O_2$: C, 54.86; H, 3.79; N, 11.29. Found: C, 55.43; H, 4.14; N, 11.35.

2,5-Dimethyl[1,2,4]triazolo[5,1-*a*]isoquinoline-6-carbonitrile (**3a**) and 1-Acetylhydrazino-3-methylisoquinoline-4-carbonitrile (**4a**).

A hot solution of the nitrile **1** (5.0 g, 22.1 mmol) in 1,4-dioxane (5 mL) and triethylamine (5 mL) was added dropwise and with stirring to a warm solution of hydrazine monohydrate (1.38 g, 27.7 mmol) in 1,4-dioxane (5 mL). Stirring was continued for 1 hour, after which time the yellow solid which separated was collected by filtration and washed with a little dichloromethane to give the acetylhydrazine **4a** as a white solid (1.52 g, 29%), mp 208-210° (ethanol). Unrecrystallized material was routinely used in further reactions; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.96 (s, 3H, $COCH_3$), 2.55 (s, 3H, CH_3), 7.58 (t, 1H, J = 7.3 Hz, H-7), 7.76–7.84 (m, 2H, H-5,6), 8.33 (d, 1H, J = 8.3 Hz, H-8), 10.04–10.07 (m, 2H, NHNH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.8 ($COCH_3$), 23.9 (CH_3), 92.2 (C-4), 114.1 (C-8a), 117.8 (CN), 123.2 (C-5), 123.7 (C-8), 126.9 (C-7), 132.6 (C-6), 135.5 (C-4a), 156.2 (C-1), 158.5 (C-3), 169.0 (CO).

Anal. Calcd. for $C_{13}H_{12}N_4O\bullet0.5H_2O$: C, 62.64; H, 5.27; N, 22.48. Found: C, 62.31; H, 5.39; N, 22.49.

The filtrate was evaporated to dryness and the residue was crystallized from a small volume of acetonitrile to give the triazole **3a** as a white solid (2.76 g, 56%), mp 137–139° (lit [8] 138-140°); nmr data were as previously reported [8].

2,5-Dimethyl-7-nitro[1,2,4]triazolo[5,1-*a*]isoquinoline-6-carbonitrile (**3b**) and 2,5-Dimethyl-9-nitro[1,2,4]triazolo[5,1-*a*]isoquinoline-6-carbonitrile (**3c**).

To a stirring solution of potassium nitrate (0.14 g, 1.35 mmol) in concentrated sulfuric acid (2 mL), was added the triazole **3a** (0.1 g, 0.45 mmol) in one portion. Stirring was continued for 4 hours and the red solution was then poured onto water (50 mL). The cream solid that precipitated was collected by filtration and washed with water to give a 2:1 mixture of 7-nitro **3b** and 9-nitro **3c** compounds (0.09 g, 75%). Two recrystallizations from ethanol gave **3b**, mp 225–228°; ^{1}H nmr **3b** (deuteriochloroform): δ 2.69 (s, 3H, CH_3-2), 3.13 (s, 3H, CH_3-5), 7.81 (t, 1H, J = 7.9 Hz, H-9), 8.05 (d, 1H, J = 7.7 Hz, H-8), 8.82 (d, 1H, J = 8.1 Hz, H-10); ^{13}C nmr **3b** (deuteriochloroform): δ 14.1 (CH_3-2), 17.2 (CH_3-5), 92.1 (C-6), 112.6 (CN), 119.3 (C-6a), 121.1 (C-10a), 126.2 (C-8), 128.1 (C-9, C-10), 146.5 (C-7), 146.9 (C-5), 148.8 (C-10b), 164.9 (C-2); ^{1}H nmr **3c** (deuteriochloroform): δ 2.71 (s, 3H, CH_3-2), 3.15 (s, 3H, CH_3-5), 8.29 (d, 1H, J = 8.9 Hz, H-7), 8.61 (dd, 1H, J = 9.1, 2.1 Hz, H-8), 9.49 (d, 1H, J = 2.2 Hz, H-10).

Anal. (Isomeric mixture) Calcd. for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.39; N, 26.21. Found: C, 58.28; H, 3.22; N, 26.28.

5-Bromomethyl-2-methyl[1,2,4]triazolo[5,1-*a*]isoquinoline-6-carbonitrile (**3d**).

To a warm, stirring solution of the triazole **3a** (1.30 g, 5.86 mmol) in carbon tetrachloride (50 mL), was added *N*-bromosuccinimide (1.15 g, 6.44 mmol) and benzoyl peroxide (0.14 g, 0.59 mmol), and the mixture was then heated under reflux for 6 hours. It was then filtered and the orange filtrate was washed with 10% sodium carbonate (2 × 30 mL). The carbon tetrachloride fraction was dried over magnesium sulfate and solvent was removed at reduced pressure to give an orange solid, which was recrystallized from acetonitrile to give the bromomethyl triazole **3d** as a white solid (1.48 g, 84%), mp 200–202°; ^{1}H nmr (deuteriochloroform): δ 2.68 (s, 3H, CH_3), 5.11 (s, 2H, CH_2Br), 7.75–7.85 (m, 2H, H-8,9), 8.11 (d, 1H, J = 7.7 Hz, H-7), 8.55 (d, 1H, J = 7.6 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3), 21.9 (CH_2Br), 97.9 (C-6), 113.5 (CN), 120.4 (C-10a), 124.4 (C-7), 125.1 (C-10), 128.2 (C-6a), 129.9 (C-9), 131.2 (C-8), 140.4 (C-5), 150.1 (C-10b), 164.4 (C-2).

Anal. Calcd. for $C_{13}H_9BrN_4O_2$: C, 51.85; H, 3.01; N, 18.60. Found: C, 52.17; H, 2.77; N, 18.48.

3,5-Dimethyl[1,2,4]triazolo[3,4-*a*]isoquinoline-6-carbonitrile (**5a**).

A solution of the acetylhydrazine **4a** (0.4 g, 1.67 mmol) in phosphoryl chloride (5 mL) was heated under reflux for 5 hours with constant stirring. The yellow solution was then poured onto ice/water (50 mL) and the white solid which separated was collected by filtration and washed with water to give the triazole **5a** (0.27 g, 73%), mp 234-236° (ethanol). ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.95 (s, 3H, CH_3-3), 3.05 (s, 3H, CH_3-5), 7.69–7.79 (m, 3H, H-7,8,9), 8.47 (d, 1H, J = 7.8 Hz, H-10). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.5 (CH_3-3), 18.8 (CH_3-5), 99.1 (C-6), 115.0 (CN), 119.2 (C-10a), 123.6 (C-10), 124.1 (C-7), 127.1 (C-6a), 129.7 (C-9), 131.6 (C-8), 143.2 (C-5), 147.7 (C-10b), 148.1 (C-3).

Anal. Calcd. for $C_{13}H_{10}N_4\bullet2H_2O$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.87; H, 4.46; N, 21.94.

3,5-Dimethyl-9-nitro[1,2,4]triazolo[3,4-*a*]isoquinoline-6-carbonitrile (**5b**).

Triazole **5a** (0.27 g, 1.22 mmol) was added to a stirring solution of potassium nitrate (0.37 g, 3.65 mmol) in concentrated sulfuric acid (2.5 mL) and stirring was continued for 4 hours. The

red solution was poured onto ice/water (50 mL) and the solid that separated was collected by filtration to afford the 9-nitro isomer **5b** (0.24 g, 74%), as a brown solid which contained <5% of the 7-nitro isomer. Recrystallization from acetonitrile gave **5b**, mp 283–286°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.97 (s, 3H, CH_3-3), 3.13 (s, 3H, CH_3-5), 8.09 (d, 1H, J = 8.8 Hz, H-7), 8.57 (dd, 1H, J = 8.8, 2.0 Hz, H-8), 9.12 (d, 1H, J = 2.0 Hz, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.6 (CH_3-3), 19.1 (CH_3-5), 97.9 (C-6), 114.7 (CN), 118.5 (C-10), 120.1 (C-9), 125.0 (C-8), 126.2 (C-7), 131.4 (C-6a), 147.2 (C-10a(10b)), 147.3 (C-10b(10a)), 147.5 (C-5), 148.8 (C-3).

Anal. Calcd. for $C_{13}H_9N_5O_2$•0.25H_2O: C, 57.46; H, 3.52; N, 25.77. Found: C, 57.42; H, 3.25; N, 25.93.

Bromination of Triazole **5a**.

Triazole **5a** (0.1 g, 0.45 mmol) was reacted with NBS (0.09 g, 0.51 mmol) as for the preparation of **3d**. The red, oily crude product (0.1 g) was primarily 3,5-bis(bromomethyl)[1,2,4]triazolo[3,4-*a*]isoquinoline-6-carbonitrile **5c** from nmr analysis. ^{1}H nmr (deuteriochloroform): δ 5.33 (s, 2H, CH_2Br), 5.36 (s, 2H, CH_2Br), 7.24–7.57 (m, 1H), 7.86–7.89 (m, 1H), 8.06–8.16 (m, 1H), 8.81–8.84 (m, 1H).

5-Methyltetrazolo[5,1-*a*]isoquinoline-6-carbonitrile (**6a**).

The acetylhydrazine **4a** (2.9 g, 12.1 mmol) was heated under reflux in 1:1 1,4-dioxane/concentrated hydrochloric acid (50 mL) for 1.5 hours. The mixture was then poured onto ice and neutralised with 10% sodium hydroxide. The solid that formed was collected by filtration and washed with water to give the intermediate 1-hydrazino-3-methylisoquinoline-4-carbonitrile **4b** as a brown solid (1.72 g, 8.69 mmol, 72%), mp 204–206° (decomp.). This was dissolved in concentrated hydrochloric acid (15 mL) and sodium nitrite (0.90 g, 13.03 mmol) was added in portions, with stirring, at 0°. The mixture was then stirred for 1 hour at room temperature and poured onto ice/water. The resultant precipitate was collected by filtration and washed with water to afford tetrazole **6a** as an orange solid (1.25 g, 69%), mp 197–199° (ethanol); ^{1}H nmr (deuteriochloroform): δ 3.21 (s, 3H, CH_3), 7.85 (t, 1H, J = 7.6 Hz, H-9), 7.94 (t, 1H, J = 6.8 Hz, H-8), 8.14 (d, 1H, J = 8.1 Hz, H-7), 8.70 (d, 1H, J = 7.8 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 16.7 (CH_3), 101.3 (C-6), 113.5 (CN), 117.6 (C-10a), 124.8 (C-7), 125.2 (C-10), 129.1 (C-6a), 130.1 (C-9), 132.7 (C-8), 140.4 (C-5), 147.5 (C-10b).

Anal. Calcd. for $C_{11}H_7N_5$: C, 63.15; H, 3.37. Found: C, 63.23; H, 3.05.

5-Methyltetrazolo[5,1-*a*]isoquinoline-6-carboxamide (**6b**).

To a stirring solution of potassium nitrate (0.29 g, 2.87 mmol) in concentrated sulfuric acid (3 mL) was added tetrazole **6a** (0.2 g, 0.96 mmol), and the whole was heated at 100° for 2 hours. The solution was then poured onto ice/water and the precipitate that formed was collected by filtration, washed with water and recrystallized from ethanol to give carboxamide **6b** as a light brown solid (0.19 g, 87%), mp 284–287°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.85 (s, 3H, CH_3), 7.84–7.98 (m, 3H, H-7,8,9), 8.15 (br s, 1H, NH), 8.23 (br s, 1H, NH), 8.64 (d, 1H, J = 7.8 Hz, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 15.2 (CH_3), 117.8 (C-6), 124.6 (C-10), 124.7 (C-10a), 125.5 (C-7), 128.7 (C-5), 129.4 (C-9), 129.7 (C-6a), 132.3 (C-8), 146.7 (C-10b), 166.4 (CO).

Anal. Calcd. for $C_{11}H_9N_5O$•0.25H_2O: C, 57.01; H, 4.13; N, 30.22. Found: C, 56.70; H, 3.80; N, 29.85.

8,9-Dihydro-6-methyl-8-oxopyridazino[4',5':4,5]imidazo[2,1-*a*]isoquinoline-5-carbonitrile (**7**).

To a solution of bromomethyl compound **2j** (0.20 g, 0.54 mmol) in 1,2-dimethoxyethane (20 mL) was added mercurous nitrate dihydrate (0.46 g, 1.62 mmol nitrate equivalents), and the whole was heated under reflux for 6 hours, then filtered to remove mercury salts, and the filtrate was evaporated at reduced pressure. The crude residue was extracted with dichloromethane (40 mL) and washed with water (2 × 20 mL). The organic extract was dried over magnesium sulfate and evaporated under reduced pressure to give ethyl 6-cyano-2-nitrooxymethyl-5-methylimidazo[2,1-*a*]isoquinoline-3-carboxylate **2l** (0.10 g, 52%) as a pale orange solid; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, 3H, J = 7.1 Hz, CH_2CH_3), 3.00 (s, 3H, CH_3), 4.49 (q, 2H, J = 7.2 Hz, CH_2CH_3), 5.82 (s, 2H, CH_2ONO_2), 7.72–7.86 (m, 2H, H-8,9), 8.06 (d, 1H, J = 7.6 Hz, H-7), 8.69 (dd, 1H, J = 7.5, 1.5 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 13.8 (CH_2CH_3), 20.7 (CH_3), 62.2 (CH_2CH_3), 67.3 (CH_2ONO_2), 100.7 (C-6), 115.0 (CN), 119.3 (C-3), 120.7 (C-10a), 124.0 (C-7), 124.7 (C-10), 127.6 (C-6a), 129.2 (C-9), 131.0 (C-8), 142.8 (C-5), 144.0 (C-2), 145.7 (C-10b), 159.2 (CO).

To a solution of methanol nitrate ester **2l** (0.10 g, 0.28 mmol) in 1,2-dimethoxyethane (10 mL) was added triethylamine (0.28 g, 2.82 mmol), and the solution was heated under reflux for 1 hour, then evaporated at reduced pressure. The residue was extracted with dichloromethane (20 mL) and washed with water (2 × 10 mL). The organic extract was dried over magnesium sulfate and evaporated under reduced pressure to give ethyl 6-cyano-2-formyl-5-methylimidazo[2,1-*a*]isoquinoline-3-carboxylate **2m** (0.12 g, 80%) as a brown solid; ^{1}H nmr (deuteriochloroform): δ 1.49 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.98 (s, 3H, CH_3), 4.58 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.77–7.86 (m, 2H, H-8,9), 8.07 (d, 1H, J = 7.5 Hz, H-7), 8.79 (d, 1H, J = 7.6 Hz, H-10).

To a stirring solution of aldehyde **2m** (0.11 g, 0.36 mmol) in 1,4-dioxane (4 mL) was added, dropwise, hydrazine monohydrate (0.02 g, 0.36 mmol) in 1,4-dioxane (1 mL). After 10 minutes, the mixture was heated under reflux for 2 h, then cooled to room temperature. The white precipitate which separated was collected by filtration to give pyridazine **7** (0.04 g, 41%), mp >300° (1,4-dioxane); ^{1}H nmr (dimethyl sulfoxide-d_6, 100°): δ 3.51 (s, 3H, CH_3), 7.80–7.86 (m, 1H), 7.91–7.99 (m, 2H), 8.55 (s, 1H, H-11), 8.71 (d, 1H, J = 8.1 Hz, H-1), 12.77 (br s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6, 100°): δ 21.8 (CH_3), 98.9 (C), 115.5 (CN), 120.8 (C), 123.9 (CH), 125.3 (CH), 128.8 (C), 129.4 (CH), 132.5 (CH), 133.4 (CH), 144.9 (C), 146.0 (C), 149.1 (C), 154.5 (CO).

Anal. Calcd. for $C_{15}H_9N_5O$•0.25H_2O: C, 64.40; H, 3.42; N, 25.03. Found: C, 64.36; H, 3.16; N, 25.01.

5,6-Dihydro-5-hydroxy-2-methyl-7*H*-pyrrolo[3,4-*c*][1,2,4]triazolo[5,1-*a*]isoquinolin-7-one (**8**).

To a solution of bromomethyl compound **3d** (0.51 g, 1.69 mmol) in warm acetonitrile (50 mL), was added mercurous nitrate dihydrate (1.43 g, 5.08 mmol nitrate equivalents) and the whole was heated under reflux for 6 hours. The yellow mixture was then filtered and the filtrate was poured onto ice/water (150 mL). The cream solid which separated was collected by filtration and recrystallized from acetonitrile to afford 6-cyano-2-methyl[1,2,4]triazolo[5,1-*a*]isoquinoline-5-methanol nitrate **3e** (0.34 g, 71%), mp 165–168°; ^{1}H nmr (deuteriochloroform): δ

2.67 (s, 3H, CH_3), 6.18 (s, 2H, CH_2ONO_2), 7.84–7.92 (m, 2H, H-8,9), 8.20 (d, 1H, J = 7.4 Hz, H-7); 8.62 (dd, 1H, J = 6.5, 1.6 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 14.2 (CH_3), 66.2 (CH_2ONO_2), 100.7 (C-6), 113.1 (CN), 120.9 (C-10a), 124.4 (C-7), 125.4 (C-10), 127.9 (C-6a), 130.5 (C-9), 131.4 (C-8), 134.7 (C-5), 150.2 (C-10b), 164.8 (C-2).

To a solution of **3e** (0.10 g, 0.34 mmol) in warm acetonitrile (3 mL) was added triethylamine (3 mL), with constant stirring. After 5 minutes, a red precipitate formed and was collected by filtration to give the tetracycle **8** (0.07 g, 81%), mp >300° (dimethylformamide); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.57 (s, 3H, CH_3), 6.21 (d, 1H, J = 8.1 Hz, H-5) [16], 6.85 (d, 1H, J = 8.8 Hz, OH) [17], 7.78–7.86 (m, 2H, H-9,10), 8.49 (d, 1H, J = 7.8 Hz, H-11), 8.82 (d, 1H, J = 7.8 Hz, H-8), 9.06 (br s, 1H, NH) [17]; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.3 (CH_3), 75.2 (C-5), 112.3 (C-7a), 121.1 (C-11a), 123.5 (C-8), 124.4 (C-11), 126.8 (C-7b), 128.9 (C-10), 131.0 (C-9), 144.6 (C-4a), 151.5 (C-11b), 163.7 (C-2), 167.9 (C-7).

Anal. Calcd. for $C_{13}H_{10}N_4O_2 \bullet 0.4H_2O$: C, 59.72; H, 4.16; N, 21.43. Found: C, 59.75; H, 3.72; N, 21.36.

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[1] The synthesis was first recorded in ref. 2 while the correct structure was reported in ref. 3.

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