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A FACILE SYNTHESIS OF THE 3-AMINO-5,6,7,8-TETRAHYDRO[1,6]NAPHTHYRIDINE SYSTEM AND SOME ALKYLATED AND POLYCYCLIC HOMOLOGUES

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ABSTRACT

A facile, two step synthesis of the 3-amino-5,6,7,8-tetrahydro[1,6]naphthyridine system **1** and its more substituted homologues **2–5** via the condensation of mono- and bicyclic-4-piperidinones **11a–c**, **12–14** with 3,5-dinitro-1-methyl-2-pyridone **6** in the presence of ammonia is described.

During the course of our research on potential anticonvulsants[1] we required the synthesis of 3-amino-6-methyl-5,6,7,8-tetrahydro[1,6]-naphthyridine **1d**, hopefully utilising methodology that would also allow for the rapid synthesis of a number of homologues **2b–5b**. Although much is known about the synthesis and chemistry of the fully aromatic 1,6-naphthyridine system,[2,3] much less is known[4–11] about the corresponding, partially reduced system **1**. The 8,8-disubstituted **2** and tricyclic systems **3–5** have not previously been reported. (The only reported synthesis of

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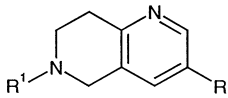
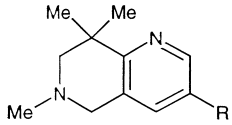
3-amino-6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine **1d** promising any degree of versatility was published by Marcelis and Van der Plas.[11]

The authors described the condensation of enamines with 5-nitropyrimidine to give fused nitropyridines, of which **1a** and **1b** are illustrated examples. However, the yield of **1a** was a disappointing 16% and the utility of the reaction was not exhaustively investigated.)

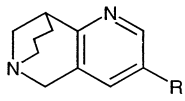
Furthermore, apart from this one exception, the published syntheses



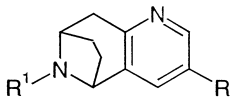
1a R = NO_2, R^1 = Me
b R = NO_2, R^1 = Bn
c R = NO_2, R^1 = CO_2CMe_3
d R = NH_2, R^1 = Me
e R = NH_2, R^1 = Bn
f R = NH_2, R^1 = CO_2CMe_3
g R = NHOH, R^1 = Bn



2a R = NO_2
b R = NH_2



3a R = NO_2
b R = NH_2

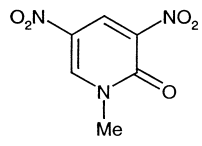


4a R = NO_2, R^1 = Me
b R = NH_2, R^1 = Me
5a R = NO_2, R^1 = CO_2CMe_3
b R = NH_2, R^1 = CO_2CMe_3

of 5,6,7,8-tetrahydro[1,6]naphthyridines containing a nitrogen functionality at C(3) are highly convoluted, universally low yielding and not amenable to the rapid synthesis of analogues containing further substituents in the partially saturated ring. Moreover, 3-nitropyridines are notoriously difficult molecules to synthesize by simple nitration.[12] Tohda *et al.*[13–15] later described the condensation of 3,5-dinitro-1-methyl-2-pyridone **6** with cyclic ketones **7** and ammonia to give 3-nitro-5,6,7,8-tetrahydroquinolines **8** as shown in Scheme 1.

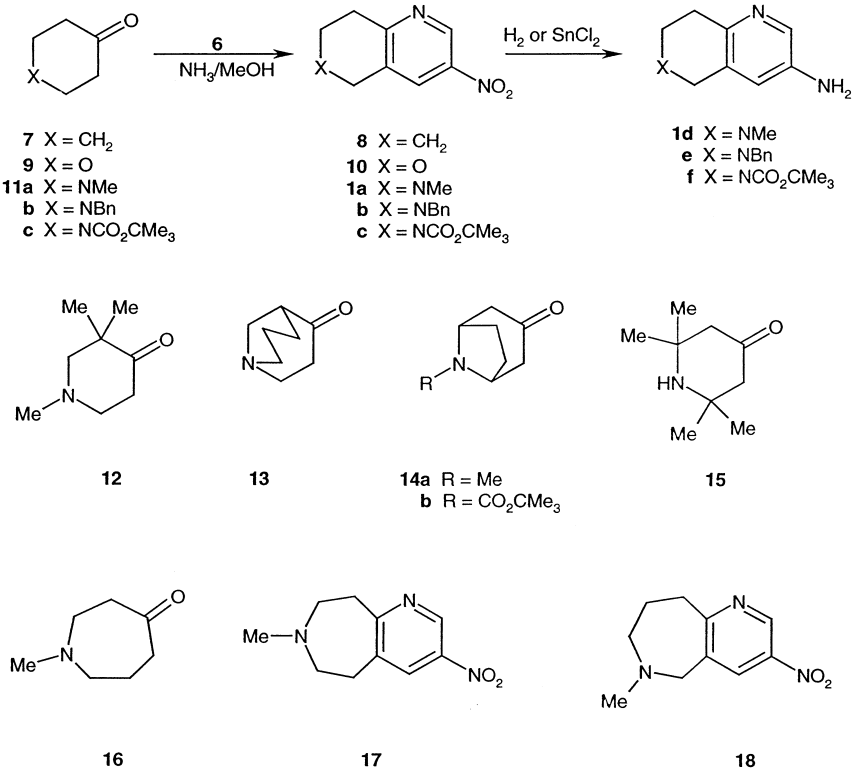
Subsequently, Takada *et al.*[16] demonstrated that pyranones **9** would also participate in the reaction giving rise to 3-nitro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine containing a second heterocyclic ring **10**.

No literature reports have appeared to date, however, describing the use of 4-piperidinones **11a–c**, **12–15** in this reaction, which would be expected to give 3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridines **1a–c**, **2a–5a**. We now wish to report the results of our work in this area and to describe the preparation of a number of hitherto, unknown and rather inaccessible



6

Scheme 1.



3-nitro- and 3-aminoheterocycles **1–5**, which are readily available using this chemistry.

The condensation of a small range of N(1)-substituted-4-piperidinones **11a–c** with dinitropyridone **6** demonstrated that the bulk of the substituent at N(1) has no detrimental effect on the outcome of the reaction. Indeed, the smaller N-methyl-4-piperidinone **11a** gave the bicycle **1a** in 59% yield, whereas, the bulkier N-benzyl **11b** and N t-butoxycarbonyl **11c** 4-piperidinones gave naphthyridines **1b** and **1c** in 93% and 84% yields respectively.

Substitution at the C3 position of the 4-piperidinone ring, as in **12**, also had little or no effect, the bicycle **2a** being isolated in 57% yield. The azabicyclic ketones **13** and **14a** also participated in the reaction, giving **3a** and **4a** in 52% and 50% yields respectively; **14b**, however, only gave bicycle **5a** in a disappointing 40% yield. Interestingly, we were unable to find any trace of product when the tetramethyl-4-piperidinone **15** was used in the reaction and the azepan-4-one **16** only gave trace amounts of the expected bicyclic products **17** and **18**.[17]

Catalytic reduction of the nitro derivatives was facile and no evidence of 5,6 cleavage was ever seen. In the case of the N-benzyl derivative **1b**, the nitro group was smoothly reduced to the amine **1e** with tin(II) chloride and conc. hydrochloric acid in hot ethanol, although the corresponding, partially reduced hydroxylamine **1g** was also obtained in 9% yield.

In conclusion, we have demonstrated a rapid and versatile method by which to access the 3-amino-5,6,7,8-tetrahydro[1,6]naphthyridine system. This methodology was also shown to be applicable to the assembly of more substituted or polycyclic homologues.

EXPERIMENTAL

Chromatography refers to flash chromatography through Merck Silica Gel 60 (less than 0.063 mm) and the solvent is stated. Infra red spectra were recorded for dichloromethane solutions on a Perkin–Elmer 1600 FTIR. ^{1}H NMR spectra were obtained using a Brucker AC250 and the solvent is stated. Accurate mass measurements were recorded by Analytical Sciences, SB, on a Jeol JMS DX303/DA 5000 at 70 eV. Melting points were taken on a Galen III Kofler hotstage and are uncorrected.

6-Methyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine 1a

Pyridone **6**[18] (5.97 g, 30 mmol) was treated with a solution of ammonia in methanol (1.22 M, 300 ml, 366 mmol) followed by **11a** (3.73 g, 33 mmol) and the resulting mixture heated at an oil bath temperature of 60°C for 5 h. The mixture was allowed to stand at ambient temperature for 72 h before being evaporated to dryness under reduced pressure. The residual orange/red solid was digested with dichloromethane (2×100 ml) and the dichloromethane extracts combined and evaporated to dryness under reduced pressure. The red residue was subjected to chromatography, eluting with ethyl acetate, and the title compound (3.14 g, 59%) isolated as a red solid; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1530 and 1351; δ_H ($CDCl_3$) 2.53 (3H, s, NMe), 2.85

(2H, t, J = 6 Hz, 8-CH_2), 3.18 (2H, t, J = 6 Hz, 7-CH_2), 3.69 (2H, s, 5-CH_2), 8.14 (1H, d, J = 2 Hz, 4-H), 9.23 (1H, s, J = 2 Hz, 2-H); Found: 193.0832. $C_9H_{11}N_3O_2$ requires: 193.0851.

3-Amino-6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine 1d

A solution of **1a** (2.72 g, 1.41 mmol) in methanol (100 ml) was hydrogenated over 10% palladium on charcoal (1.0 g). The catalyst was removed by filtration through Celite and the combined filtrate and washings evaporated to dryness under reduced pressure. The residue was triturated under diethyl ether and the product (1.89 g, 83%) collected by filtration, washed with diethyl ether and dried under reduced pressure. Recrystallization from dichloromethane – 60–80° petroleum ether gave the title compound as white crystals, mp. 153–154°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 3377; δ_H($CDCl_3$) 2.46 (3H, s, NMe), 2.75 (2H, t, J = 6 Hz, 8-CH_2), 2.95 (2H, t, J = 6 Hz, **7**-CH_2), 3.50 (2H, s, 5-CH_2), 3.56 (2H, brs, exchangeable, NH_2), 6.65 (1H, d, J = 2 Hz, 4-H), 7.92 (1H, d, J = 2 Hz, 2-H). Found: 163.1106. $C_9H_{13}N_3$ requires: 163.1106.

6-Benzyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine 1b

6 (1.99 g, 10 mmol) was added to methanolic ammonia (1.1 M, 100 ml, 110 mmol) and the resulting mixture treated with **11b** (2.27 g, 12 mmol). The mixture was heated in an oil bath at 60°C for 5 h. Evaporation to dryness under reduced pressure gave a red solid, which was triturated under dichloromethane and the insolubles removed by filtration. The filtrate and washings were combined and evaporated to dryness under reduced pressure. The residue was triturated under ethyl acetate and the insolubles again removed by filtration. The filtrate and washings were combined, evaporated to dryness under reduced pressure then chromatographed, eluting with 50% ethyl acetate in 60–80° petroleum ether, to give the title compound (2.5 g, 93%). A sample was recrystallized from ethyl acetate – 60–80° petroleum ether as a pale orange, microcrystalline solid, mp. 108°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1523 and 1351; δ_H($CDCl_3$) 3.03 (2H, t, J = 6 Hz, 8-CH_2), 3.28 (2H, t, J = 6 Hz, 7-CH_2), 3.83 and 3.87 (2s, each 2H, 5-CH_2 and NCH_2Ph), 7.38–7.49 (5H, m, C_6H_5), 8.21 (1H, d, J = 2 Hz, 4-H), 9.33 (1H, d, J = 2 Hz, 2-H); Found: C, 66.75, H, 5.48, N, 15.61%. $C_{15}H_{15}N_3O_2$ requires: C, 66.84, H, 5.56, N, 15.60%.

3-Amino-6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine 1e and 6-Benzyl-3-hydroxyamino-5,6,7,8-tetrahydro[1,6]naphthyridine 1g

1b (790 mg, 2.93 mmol) was dissolved in ethanol (100 ml) and the resulting solution heated to 50°C and treated with a solution of tin(II) chloride dihydrate (2.65 g, 11.73 mmol) in conc. hydrochloric acid (10 ml). After 10 min, the reaction mixture was concentrated to low volume under reduced pressure, basified to pH 10 with 2 M aq. sodium hydroxide solution and extracted with dichloromethane (2×50 ml). The extracts were combined, washed with water, saturated brine, dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography, eluting with ethanol in ethyl acetate (0 to 20% ethanol gradient), to give **1g** (143 mg, 19%) as a yellow foam; δ_H [$(CD_3)_2SO$] 2.72–2.76 (4H, brm, $(CH_2)_2$), 3.52 and 3.66 (each 2H, 2brs, 5-CH_2 and NCH_2Ph), 6.85 (1H, brs, 4-H), 7.27–7.37 (5H, m, C_6H_5), 7.94 (1H, brs, 2-H), 8.34 and 8.42 (each 1H, 2brs, exchangeable, *NH* and *OH*); Found: 256.1450. $C_{15}H_{18}N_3O$ requires: 256.1431.

Furhter elution gave **1e** (275 mg, 39%) as a white powder; δ_H [$(CD_3)_2SO$] 2.51 (4H, br, 7 and 8 CH_2's), 3.25 and 3.45 (each 2H, 2brs, 5-CH_2 and NCH_2Ph), 4.84 (2H, brs, exchangeable, NH_2), 6.37 (1H, brs, 4-H), 7.11–7.22 (5H, m, C_6H_5), 7.56 (1H, brs, 2-H); Found: 240.1501. $C_5H_{18}N_3$ requires: 240.1584.

6-t-Butoxycarbonyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine 1c

11c (l0.14 g, 50.9 mmol) and **6** (9.12 g. 45.8 mmol) were suspended in methanol (250 ml) and the resulting mixture treated with 0.88 aq. ammonia solution (20 ml). The resulting mixture was heated at 70°C for 5 h then left to stand at ambient temperature for 18 h. Volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane and water. The phases were separated and the organic phase washed with water (×2), saturated brine, dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography, eluting with 50% ethyl acetate in 60–80° petroleum ether, to give **1c** (10.75 g, 84%) as a fawn powder. **1c** was recrystallized as white needles from ethanol-water, mp. 143–144°C; $\nu_{max/cm^{-1}}$ (CH_2C1_2) 1692, 1529 and 1353; $\delta_H(CDCl_3)$ 1.51 (9H, s, CMe_3), 3.12 (2H, t, J = 6 Hz, 8-CH_2), 3.81 (2H, t, J = 6 Hz, 7-CH_2), 4.72 (2H, s, 5-CH_2), 8.23 (1H, d, J = 2 Hz, 4-H), 9.25 (1H, d, J = 2 Hz, 2-H); Found: 279.1224. $C_{13}H_{17}N_3O_4$ requires: 279.1900.

3-Amino-6-t-butoxycarbonyl-5,6,7,8-tetrahydro[1,6]naphthyridine 1f

1c (1.62 g, 5.80 mmol) was dissolved in methanol (50 ml) and the mixture hydrogenated at STP over 10% palladium on carbon (200 mg) until hydrogen uptake ceased. Catalyst was removed by filtration through Celite, the filter bed washed well with methanol and the filtrate and washings combined and evaporated to dryness under reduced pressure. The residue was crystallized from dichloromethane – 60–80° petroleum ether to give **1f** as brown, microcrystalline plates (1.22 g, 84%), mp. 117–119°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1684, 1422 and 1250; $\delta_H(CDCl_3)$ 1.49 (9H, s, CMe_3), 2.88 (2H, t, J = 6 Hz, 8-CH_2), 3.64 (2H, br, exchangeable, NH_2), 3.71 (2H, t, J = 6 Hz, 7-CH_2), 4.50 (2H, s, 5-CH_2), 6.73 (1H, d, J = 2 Hz, 4-H), 7.94 (1H, d, J = 2 Hz, 2-H); Found: 249.1476. $C_{13}H_{19}N_3O_2$ requires: 249.1477.

3-Nitro-6,8,8-trimethyl-5,6,7,8-tetrahydro[1,6]naphthyridine 2a

12[19] (1.69 g, 12 mmol) and **6** (l.99 g, 10 mmol) were mixed together in methanol (50 ml) containing 0.88 aq. ammonia solutions. The resulting mixture was heated at 70°C for 5 h. After cooling to room temperature, the volatiles were removed under reduced pressure. The residue was digested with dichloromethane (2 × 50 ml) and the combined extracts were evaporated to dryness under reduced pressure. Chromatography of the residue, eluting with 50% ethyl acetate in 60–80° petroleum ether, gave the title compound as a yellow oil, which crystallized on standing (1.26 g, 57%). Recrystallization from acetone-water gave **2a** as yellow needles, mp. 54–56°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1525 and 1349; δ_H ($CDCl_3$) 1.38 (6H, s, CMe_2), 2.47 (3H, s, NMe), 2.55 (2H, s, 7-CH_2), 3.64 (2H, s, 5-CH_2), 8.09 (1H, d, J = 3 Hz, 4-H), 9.25(1H, d, J = 3 Hz, 2-H); Found: 221.1164. $C_{11}H_{15}N_3O_2$ requires: 221.1164.

3-Amino-6,8,8-trimethyl-5,6,7,8-tetrahydro[1,6]naphthyridine 2b

2a (1.0 g, 4.5 mmol) was dissolved in methanol (30 ml) and hydrogenated at STP over 10% palladium on charcoal (100 mg) until hydrogen uptake had ceased. Catalyst was removed by filtration through Celite and the combined filtrate and washings evaporated to dryness under reduced pressure to give **2b** as a white powder (864 mg, 100%). Recrystallization from dichloromethane – 60–80° petroleum ether gave white needles, mp. 121–122°C; $\delta_H(CDCl_3)$ 1.31 (6H, s, CMe_2), 2.41 (3H, s, NMe), 2.46 (2H, s, 7-CH_2), 3.45 (2H, s, 5-CH_2), 3.43 (2H, brs, NH_2, exchangeable),

6.61 (1H, d, J = 3 Hz, 4-H), 7.97 (1H, d, J = 3 Hz, 2-H); Found: 191.1420. $C_{11}H_{17}N_3$ requires: 191.1422.

5-Nitro-3,9-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene 3a

13 (1.93 g, 12 mmol)[20] and **6** (1.99 g, 10 mmol) were mixed together in methanolic ammonia (2 M, 100 ml, 200 mmol) and the resulting mixture heated at 60°C for 5 h. Evaporation to dryness under reduced pressure followed by chromatography, eluting with methanol in dichloromethane gradient, gave the product (1.13 g, 52%). A sample was recrystallized from 60–80° petroleum ether as yellow plates, mp. 125–127°C, $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1528 and 1348; δ_H($CDCl_3$)[21] 1.14–1.20 and 1.31–1.34 (each 1H, 2m, 11-CH_2), 1.94–1.96 and 2.01–2.06 (each 1H, 2m, 12-CH_2), 3.07–3.16 (4H, m, 1-H, 10-CH_2 and 13-H), 3.34 (1H, d, J = 12 Hz, 13-H), 3.95 and 4.43 (each 1H, 2d, J = 18 Hz, 8-CH_2), 8.17 (1H, d, J = 2 Hz, 6-H), 8.24 (1H, d, J = 2 Hz, 4-H). Found: 219.1006. $C_{11}H_{13}N_3O_2$ requires: 219.1008.

5-Amino-3,9-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene 3b

3a (1.1 g, 5 mmol) was dissolved in methanol (50 ml) and hydrogenated at STP over 10% palladium on charcoal (100 mg) until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate and washings evaporated to dryness under reduced pressure. Trituration under diethyl ether gave **3b** (795 mg, 84%). Recrystallization from dichloromethane gave off-white, microcrystalline colonies, mp. 181–182°C; δ_H (CD_3OD) 1.00–1.40 (2H, m, 11-CH_2), 1.60–1.90 (2H, m, 12-CH_2), 2.60–3.25 (5H, m, 10-CH_2, 13-CH_2 and CH), 3.68 and 4.10 (2H, ABq, J = 18 Hz, 8-CH_2), 6.74 (1H, br, 6-H), 7.71 (1H, d, J = 2 HZ, 4-H); Found: 189.1265. $C_{11}H_{15}N_3$ requires: 189.1266.

12-Methyl-4-nitro-6,12-diazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene 4a

14a (1.67 g, 12 mmol) and **6** (1.99 g, 10 mmol) were mixed together in methanol (100 ml). 0.88 aq. Ammonia solution (10 ml) was added and the resulting mixture heated at 60°C for 5 h then left at ambient temperature for 18 h. The volatiles were removed by evaporation to dryness under reduced pressure and the residue digested with dichloromethane (2×50 ml). Filtration and evaporation of the filtration to dryness under reduced

pressure gave a red semi-solid residue, which was purified by chromatography, eluting with dichloromethane then 2% methanol in dichloromethane. The appropriate fractions were combined and evaporated to dryness under reduced pressue. Extraction of the residue with hot 60–80° petroleum ether gave, after evaporation, **4a** (1.1 g, 50%). Recrystallization from 60–80° petroleum ether gave chunky, yellow needles, mp. 93–94°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1526 and 1348; δ_H (CD_3OD) 1.78–2.62 (7H, 3m, 10-CH_2, 11-CH_2 and NMe), 2.92 (1H, d, J = 19 Hz, 8-H), 3.49 and 3.56 (1H, dd, J = 19 and 5 Hz, 8-H), 3.75–3.80 (1H, m, 9-H), 4.32 (1H, d, J = 6 Hz, 1-H), 8.48 (1H, d, J = 2 Hz, 3-H), 9.31 (1H, d, J = 2 Hz, 5-H); Found: 219.1017. $C_{11}H_{13}N_3O_2$ requires: 219.1008.

4-Amino-12-methyl-6,12-diazatricyclo[7. 2.1.0^{2,7}]dodeca-2,4,6-triene 4b

4a (1.1 g, 5 mmol) was dissolved in methanol (50 ml) and hydrogenated at STP over 10% palladium on carbon (100 mg) until hydrogen uptake ceased. The catalyst was removed by filtration through Celite, the filter bed washed well with methanol and the filtrate and washings combined. Evaporation to dryness under reduced pressure, followed by trituration under diethyl ether and collection by filtration, gave **4b** (795 mg, 84%) as a grey powder; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 3628 and 3420; δ_H (CD_3OD) 1.73–2.55 (7H, 3m, 10-CH_2, 11-CH_2 and NMe), 2.63 (1H, d, J = 17 Hz, 8-H), 3.29 and 3.36 (1H, dd, J = 17 and 5 Hz, 8-H), 3.66–3.71 (1H, m, 9-H), 3.99 (1H, d, J = 6 Hz, 1-H), 6.95 (1H, d, J = 3 Hz, 3-H), 7.95 (1H, d, J = 3 Hz, 5-H); Found: 181.1273. $C_{11}H_{15}N_3$ requires: 181.1266.

12-t-Butoxycarbonyl-4-nitro-6,12-diazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene 5a

14b (5.0 g, 22.2 mmol) and **6** (4.42 g, 22.2 mmol) were mixed together in methanol (100 ml) containing 0.88 aq. ammonia solution (25 ml) and the resulting mixture heated at 70°C for 5 h. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic phase was washed with water (2×50 ml), saturated brine, dried and evaporated to dryness under reduced pressure. Chromatography, eluting with 25% ethyl acetate in 60–80° petroleum ether, gave the product as a yellow oil, which crystallized on standing (2.73 g, 40%). Recrystallization from ethyl acetate – 60–80° petroleum ether gave **5a** as needles, mp. 97–100°C; $\nu_{max/cm^{-1}}$ (CH_2Cl_2) 1690, 1528, 1349 and 1274;

δ_H ($CDCl_3$) 1.42 and 1.50 (each 9H, 2s, CMe_3, rotamers), 1.60–2.45 (4H, 3m, 10-CH_2 and 11-CH_2), 2.89 (1H, d, J = 18 Hz, 8-H), 3.40–3.60 (1H, brm, 8-H, rotamers), 4.65 (1H, brm, 9-H, rotamers), 5.08 (1H, brm, 1-H), 8.18 (1H, d, J = 2 Hz, 3-H), 9.24 (1H, d, J = 2 Hz, 5-H); Found: 305.1380. $C_{15}H_{19}N_3O_4$ requires: 305.1376.

4-Amino-12-t-butoxycarbonyl-6,12-diazatricyclo [7.2.1.$0^{2,7}$]dodeca-2,4,6-triene 5b

5a (2.66 g, 8.7 mmol) was dissolved in methanol (50 ml) and hydrogenated at STP over 10% palladium on charcoal (300 mg) until hydrogen uptake had ceased. The catalyst was removed by filtration through Celite and the combined filtrate and washings were evaporated to dryness under reduced pressure to give a white solid (2.18 g, 91%). A small sample of **5b** was recrystallized from dichloromethane – 60–80° petroleum ether as a white, microcrystalline solid, mp. 141–142°C; δ_H ($CDCl_3$)[22] 1.42 and 1.50 (2s, each 9H, CMe_3, rotamers). 1.60–2.40 (4H, 3m, 10-CH_2 and 11-CH_2), 2.62 (1H, d, J = 17 Hz, 8-H), 3.20–3.45 (1H, brm, 8-H, rotamers), 4.40–4.65 (1H, brm, 9-H, rotamers), 4.70–4.90 (1H, brm, 1-H, rotamers), 6.70 (1H, brd, 3-H, rotamers), 7.92 (1H, d, J = 2 Hz, 5-H); Found: 275.1635. $C_{15}H_{21}N_3O_2$ requires: 275.1634.

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17. Both **16** and **17** were isolated in single figure yields and possessed satisfactory ^{1}H NMR, infra red and mass spectral data.
18. The authors would like to point out that preparation of **6**[13] proceeds with a large exotherm and recommend great care be taken when adding 1-methyl-2-pyridone to fuming nitric acid.
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21. 400 MHz ^{1}H NMR COSY experiments were performed on **3a** to confirm the structure.
22. Further ^{1}NMR studies at 400 MHz, i.e. COSY, NOESY, TOCSY and variable temperature, we used to confirm the structure of **5b**. The rotamers coalesced at 353°K.

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