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Synthesis of novel intranuclear diazasteroids

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By use of the aza Diels-Alder reaction a series of aminoisoquinolines and aminoquinolines have been elaborated to provide an effective synthesis of diverse diazasteroids. In particular, representative 1,11-diaza-, 3,11-diaza-, and 4,11-diazasteroids have been synthesized from cyclopentadiene. From dihydropyran a 4,11-diaza-15-oxa-D-homosteroid has been obtained. (*Steroids* **60**:693–698, 1995)

Keywords: diazasteroid; diazaoxasteroid; Diels-Alder; aminoquinoline; aminoisoquinoline

Introduction

Although both extranuclear monoazasteroids, where the nitrogen functionality is in the form of a group attached to the steroid skeleton, and intranuclear monoazasteroids, where the nitrogen functionality is an integral part of the steroid skeleton, occur naturally, there are few naturally occurring diazasteroids. There are no intranuclear diazasteroids. The recent chemistry of monoazasteroids has demonstrated the importance of synthetic programs generating monoazasteroids of non-natural origin. In particular, 15-azasteroids having high anti-fungal activity show promise in combatting Candida infections, which are associated with AIDS and immunocompromised patients.[1] 4-Azasteroids, prepared by synthesis,[2] offer a non-surgical remedy for treatment of benign prostatic hypertrophy. The syntheses of many other categories of monoazasteroid have been developed.[3–6] However, many fewer strategies have been developed for the synthesis of diazasteroids. Although certain categories of biological activity have been associated with diazasteroids,[7,8] an impediment to thorough biological studies has been the lack of a developed synthetic chemistry. Earlier routes were described for the preparation of a number of categories of diazasteroid, notably 1,11-diazasteroids,[9] 4,6-diazasteroids and other diazasteroids,[10] 6,7-diazasteroids,[11] 13,14-diazasteroids,[11] and 15,16-diazasteroids.[7] We have recently exploited[12,13] the discovery of Grieco and Bahsas[14] that tetrahydroquinolines can be easily synthesized by reaction of cyclopentadiene with iminium ions derived from anilines and aldehydes. This reaction is formally a Diels-Alder addition (see Scheme 1) in which the cyclopentadiene acts as a dienophile. We have been able, however, to show that these syntheses with a variety of alkene dienophiles take place via multi-step sequences. In this paper we describe the reaction of formaldehyde and cyclopentadiene with a variety of bicyclic heteroaromatic amines, in order to establish whether this methodology might lead to new routes to diazasteroids. We illustrate the methodology by an extension to the synthesis of heterosteroids from dihydropyran, an electron-rich alkene.

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Experimental

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 360 MHz on a Bruker WH-360 spectrometer or at 60 MHz on a Hitachi-Perkin-Elmer R-24B spectrometer. ^{13}C NMR spectra were recorded at 68 MHz on a Jeol JNM-GX270 spectrometer or at 90 MHz on a Bruker WH-360 spectrometer. In describing the ^{1}H and ^{13}C NMR spectra, the numbering of the carbon atoms of the assigned signals is based on the numbering system of the starting aromatic amine. Thus for the 11-azasteroid (**7**), C-8 (steroid numbering) becomes C-6 (amine numbering). Infrared spectra were recorded on a Perkin Elmer 298 spectrometer as chloroform solutions. Mass spectra (EI) were obtained using a VG Analytical 70-250-SE spectrometer. Analytical thin-layer chromatography was carried out using precoated silica gel plates (SIL G 25 UV_{254}, 0.25 mm, Macherey-Nagel) or precoated basic aluminum oxide plates (ALOX-25 UV_{254}, 0.25 mm, Macherey-Nagel). Flash chromatography was carried out using silica gel (C60 Sorbsil, May and Baker) or deactivated (3% by weight of water) basic aluminium oxide (pH 9.3–9.7, type 5016A, Fluka). Ether refers to diethyl ether and petrol refers to petroleum ether (b.p. 40–60°C). All solvents were dried and freshly distilled before use. Cyclopentadiene was obtained by freshly cracking dicyclopentadiene.

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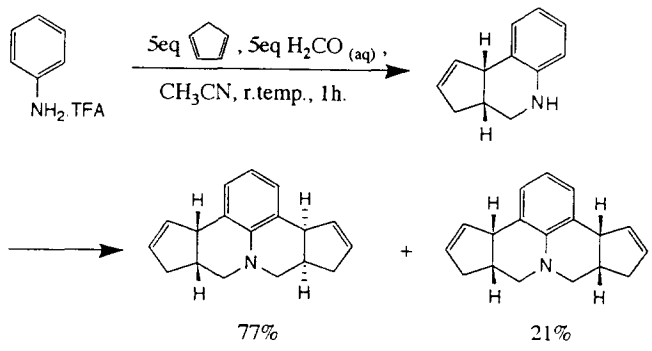


Scheme 1

Synthesis of starting materials

5-Aminoquinoline (**1;** m.p. 108–110°C; lit.[15] 108–109°C) was prepared in 96% yield by reduction of 5-nitroquinoline with iron powder in glacial acetic acid (Figure 1). 7-Aminoquinoline (**2;** m.p. 95–97°C; lit.[16] 94°C) and 8-aminoquinoline (**3;** m.p. 64.5–66.5°C; lit.[17] 63–64°C) was similarly obtained from 7-nitroquinoline (90% yield) and 8-nitroquinoline (90% yield), respectively. 5-Aminoisoquinoline (**4;** m.p. 127.5–129.5°C; lit.[18] 128°C) was obtained in 81% yield by reduction of 5-nitroisoquinoline with iron powder in glacial acetic acid.

Cyclocondensation of 5-aminoquinoline (1) with formaldehyde and cyclopentadiene

5-Aminoquinoline (**1;** 0.72 g, 5 mmol) was dissolved in acetonitrile (7.1 mL) containing 1 Eq of trifluoroacetic acid (0.57 g, 5 mmol) to give a 0.7 M solution of the amine. This orange solution was added with stirring to a heterogeneous mixture at 0°C of cyclopentadiene (0.66 g, 10 mmol) and 37% formalin solution (0.41 mL, 5 mmol) to give a deep-red solution which was stirred at room temperature under nitrogen for 45 min. The reaction mixture was added to saturated aqueous sodium bicarbonate solution (50 mL) and then extracted with dichloromethane (5 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product. Flash chromatography on deactivated basic alumina onto which the products had been preadsorbed afforded the amine (**5**) as a yellow solid (0.97 g, 87%, eluant 4/1 ether/petrol, v/v, R_f = 0.25) along with a mixture of diastereoisomers (**9**) and (**10**) of its para-coupled dimer as a yellow oil (0.14 g, 12%, eluant 1/1 ether/ethyl acetate, v/v, R_f = 0.06). R_f of 5-amino-quinoline = 0.11. R_f values for basic alumina, 4/1 ether/petrol, v/v.

Recrystallization of (**5**) from absolute alcohol gave yellow crystals (m.p. 167–169°C). δ*H* (360 MHz) 8.81 (1 H, dd, *J* = 4.2, 1.6 Hz, ArC_2-*H*); 8.06 (1 H, dd, *J* = 8.5, 1.6 Hz, ArC_4-*H*); 7.53 (1 H, d, *J* = 8.7 Hz, ArC_7-*H*); 7.50 (1 H, d, *J* = 8.7 Hz, ArC_8-*H*); 7.27 (1 H, dd, *J* = 8.5, 4.2 Hz, ArC_3-*H*); 5.93 (1 H, m, =C*H*); 5.72 (1 H, m, =C*H'*); 4.55 (1 H, vbr. s, N*H*); 3.99 (1 H, m, C*H*); 3.28 (1 H, dd, *J* = 11.1, 4.5 Hz, CH_2-N); 2.95 (1 H, dd, *J* = 11.1, 9.6 Hz, CH_2-N); 2.75 (2 H, m, CH_2-C=, C*H*); 2.21 (1 H, m, CH_2-C=). δC (90 MHz) 149.35 (ArC_2-H); 147.76 (ArC_{8a}); 140.39 (ArC_5-N); 135.69 (=*C*H); 131.89 (ArC_7-H); 128.81 (=*C*H'); 128.38 (ArC_4-H); 119.48 (ArC_6-C); 119.47 (ArC_3-H); 118.99 (ArC_8-H); 118.49 (ArC_{4a}); 46.71 (*C*H); 44.52 (CH_2-N); 37.21 (CH_2-C=); 35.66 (*C*H). The structure and assignments were confirmed by ^{13}C-^1H coupled, ^1H-^1H COSY, ^1H-^{13}C COSY, and NOE spectra. ν_{max} ($CHCl_3$): 3300 (br. w, N-H); 3075 (w), 2960 (br. m), 2865 (m) (C-H); 1625 (w, C=C); 1593 (m), 1583 (s), 1484 cm^{-1} (s) (C-Car). *m/z* found: 222.1149 (M^+ 100%); 207 (17); 193 (26); 181 (35); 168 (12); 157 (11). $C_{15}H_{14}N_2$ requires 222.1157. *Elemental analysis* found: *C* 80.6, *H* 6.4, *N* 12.3. $C_{15}H_{14}N_2$ requires *C* 81.0, *H* 6.35, *N* 12.6%.

The minor fraction from the chromatography was a mixture of the diastereomers (**9**) and (**10**). ν_{max} ($CHCl_3$): 3420 (br. w, N-H); 3065 (w), 2955 (br. m), 2855 (m) (C-H); 1617 (w, C=C); 1592 (s), 1483 cm^{-1} (s) (C-CAr). *m/z* found: 456 (M^+ 100%); 389 (18); 235 ($(M\text{-}C_{15}H_{13}N_2)^+$ 39); 221 ($(M\text{-}C_{16}H_{15}N_2)^+$ 49); 207 (15); 193 (21). $C_{31}H_{28}N_4$ requires 456. It was found that the yield of the cycloadduct (**5**) was decreased in favor of the para-coupled dimers (**9**) and (**10**) if the number of equivalents of formaldehyde and cyclopentadiene in the reaction was increased or if a longer reaction time was used. Reaction under the following conditions afforded the diastereoisomers (**9**) and (**10**) as the major products.

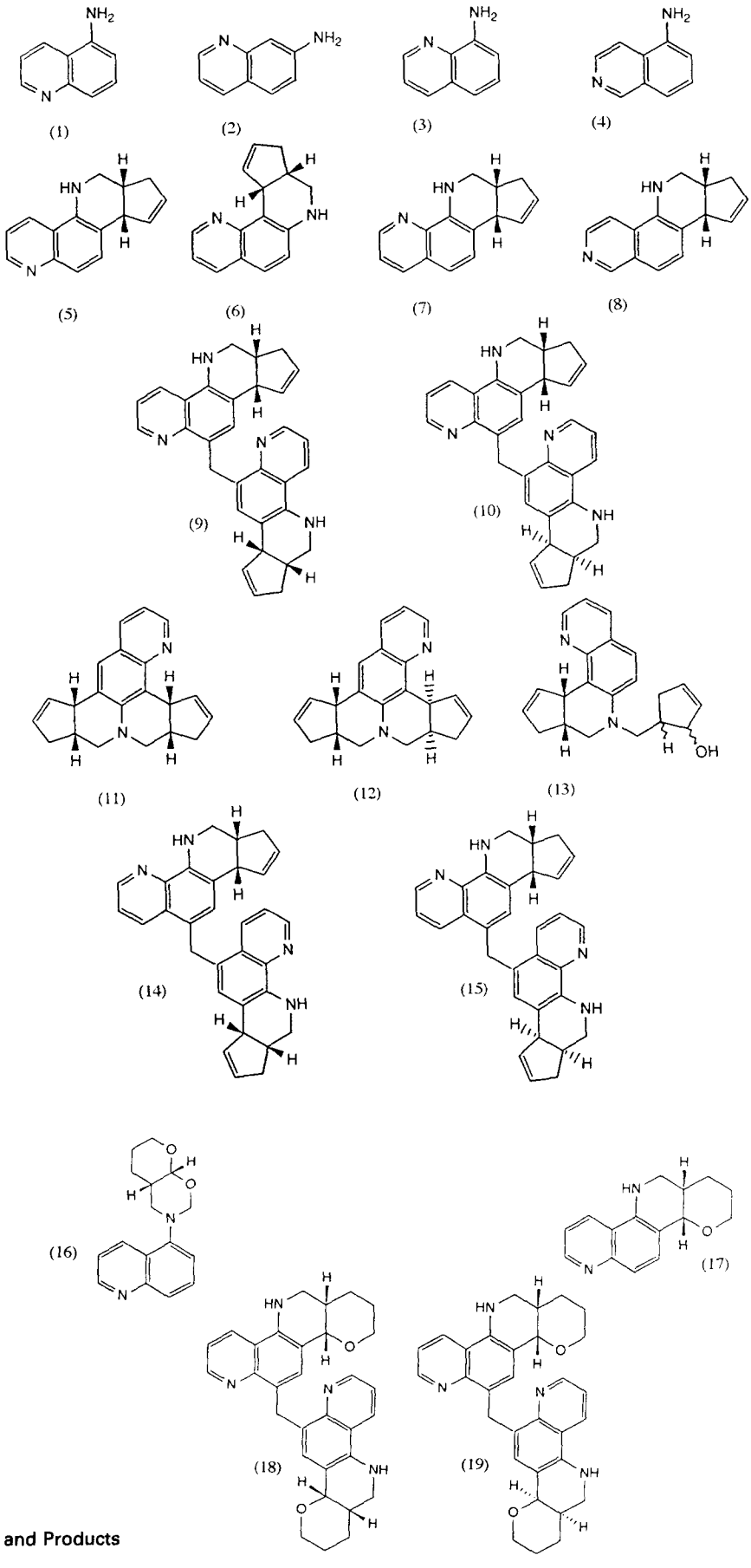
5-Aminoquinoline (**1;** 0.38 g, 2.64 mmol) was dissolved in acetonitrile (3.8 mL) containing 1 equivalent of trifluoroacetic acid (0.30 g, 2.63 mmol) to give a 0.7 M solution of the amine. This orange solution was added with stirring to a heterogeneous mixture at 0°C of cyclopentadiene (0.35 g, 5.30 mmol) and 37% formalin solution (0.43 mL, 5.30 mmol) to give a deep red solution which was stirred at room temperature under nitrogen for 6 h. Work-up afforded a red solid (0.85 g) which was purified as above to give the title adduct (**5**) as a yellow solid (0.18 g, 31%) along with a mixture of diastereoisomers (**9**) and (**10**) of its para-coupled dimer as a yellow oil (0.35 g, 58%).

Cyclocondensation of 7-aminoquinoline (2) with formaldehyde and cyclopentadiene

7-Aminoquinoline (**2;** 0.12 g, 0.83 mmol) was dissolved in acetonitrile (1.2 mL) containing 1 Eq of trifluoroacetic acid (0.10 g, 0.87 mmol) to give a 0.7 M solution of the amine. This orange solution was added with stirring to a heterogeneous mixture at 0°C of cyclopentadiene (0.28 g, 4.24 mmol) and 37% formalin solution (0.34 mL, 4.19 mmol) and the mixture was stirred at room temperature under nitrogen for 3.5 h. Workup afforded a yellow/green solid (0.34 g) which was purified as above to give a mixture of the diastereoisomeric adducts (**11**) and (**12**) as a yellow oil (0.06 g, 24%, eluant 4/1 petrol/ethyl acetate, v/v. R_f = 0.83); the amine (**6**) as a yellow oil (0.05 g, 27%, eluant 7/3 petrol/ethyl acetate, v/v. R_f = 0.73) and a mixture of isomers of the intermediate alcohol (**13**) as a yellow oil (0.12 g, 45%, eluant 1/4 petrol/ethyl acetate, v/v. R_f = 0.39–0.51). R_f of 7-aminoquinoline = 0.05. R_f values for basic alumina, 1/4 petrol/ethyl acetate, v/v. All products of this reaction were unstable, as they rapidly turned dark green on exposure to air. The mixture of diastereoisomers (**11**) and (**12**) was characterized by δ*H* (60 MHz) 8.64 (1 H, dd, *J* = 4.2 Hz, ArC_2-*H*); 7.79 (1 H, dd, *J* = 8.2 Hz, ArC_4-*H*); 7.28 (1 H, s, ArC_5-*H*); 7.01 (1 H, dd, *J* = 8.4 Hz, ArC_3-*H*); 6.20 (1 H, m, =C*H*); 5.67 (3 H, m, =C*H*); 4.65 (1 H, m, C*H*); 4.00 (1 H, m, C*H*); 2.10–3.10 (10 H, m, CH_2-N, CH_2-C=, C*H*). ν_{max} ($CHCl_3$) 3068 (w), 2940 (m), 2860 (m) (C-H); 1617 (br. m, C=C, C-CAr); 1585 (w), 1495 cm^{-1} (m) (C-CAr). m/z found: 300.1161 (M^+ 100%); 285 (22); 271 (10); 259 (24); 243 (22); 219 (10). $C_{21}H_{20}N_2$ requires 300.1626.

The desired amine (**6**) was characterized by δH (60 MHz) 8.80 (1 H, dd, *J* = 4.2 Hz, ArC_2-*H*); 7.89 (1 H, dd, *J* = 8.2 Hz, ArC_4-*H*); 7.40 (1 H, d, *J* = 9 Hz, ArC_5-*H*); 7.08 (1 H, dd, *J* = 8.4 Hz, ArC_3-*H*); 6.79 (1 H, d, *J* = 9 Hz, ArC_6-*H*); 6.30 (1 H, m, =C*H*); 5.77 (1 H, m, =C*H'*); 4.62 (1 H, m, C*H*); 4.02 (1 H, br. s, N*H*); 3.82 (1 H, m, CH_2-N); 2.55–3.23 (3 H, m, CH_2-N, CH_2-C=, C*H*); 2.17 (1 H, br. d, *J* = 14 Hz, CH_2-C=). ν_{max} ($CHCl_3$): −3435 (br. w, N-H); 3062 (w), 2937 (s), 2855 (s) (C-H); 1622 (br. s, C=C, C-CAr); 1581 (w), 1512 cm^{-1} (s) (C-CAr). *m/z* found: 222 (M^+ 100%); 207 (33); 193 (19); 181 (23); 168 (17); 110 (18). $C_{15}H_{14}N_2$ requires 222.

A third fraction of alcohols (**13**) was characterized by: δ*H* (60



Scheme 2 Reactants and Products

MHz) 8.66 (1 H, dd, J = 4.2 Hz, ArC_2-*H*); 7.78 (1 H, dd, J = 8.2 Hz, ArC_4-*H*); 7.41 (1 H, d, J = 9 Hz, ArC_5-*H*); 7.00 (2 H, m, ArC_3-*H*, ArC_6-*H*); 6.26 (1 H, m, =C*H*); 5.72 (3 H, m, =C*H*); 4.64 (2 H, m, C*H*, C*H*OH); 1.70–3.60 (11 H, m, CH_2-N, CH_2-C=, C*H*, O*H*). ν_{max} ($CHCl_3$): 3600 (w), 3370 (br. w) (O-H); 3060 (w), 3008 (m), 2937 (br. s), 2858 (m) (C-H); 1614 (s, C=C, C-CAr); 1570 (s), 1436 cm^{-1} (s) (C-CAr). *m/z* found: 318 (M^+ 10%); 300 ($(M-H_2O)^+$ 7); 235 ($(M-C_5H_7O)^+$ 100); 221 (15); 205 (7); 193 (5); 181 (4). $C_{21}H_{22}N_2O$ requires 318.

Cyclocondensation of 8-aminoquinoline (3) with formaldehyde and cyclopentadiene

8-Aminoquinoline (**3;** 0.54 g, 3.75 mmol) was dissolved in acetonitrile (5.4 mL) containing 2 Eq of trifluoroacetic acid (0.86 g, 7.54 mmol) to give a 0.7 M solution of the amine. This orange solution was added with stirring to a heterogeneous mixture at 0°C for cyclopentadiene (0.50 g, 7.58 mmol) and 37% formalin solution (0.31 mL, 3.82 mmol) to give a deep-red solution which was stirred at room temperature under nitrogen for 45 min. Workup afforded a yellow/brown oil (0.97 g) which was purified as above to give the title adduct (**7**) as a yellow solid (0.62 g, 74%, eluant 3/7 ether/petrol, v/v. R_f = 0.55) along with a mixture of diastereoisomers (**14**) and (**15**) of its para-coupled dimer as a yellow solid (0.14 g, 16%, eluant 4/1 ether/petrol, v/v. R_f = 0.28). (R_f of 8-aminoquinoline = 0.25. R_f values for basic alumina, 1/1 ether/petrol, v/v).

Recrystallization of amine (**7**) from absolute alcohol gave yellow crystals (m.p. 67–69°C). δ*H* (270 MHz) 8.70 (1 H, dd, J = 4.2, 1.6 Hz, ArC_2-*H*); 8.02 (1 H, dd, J = 8.3, 1.6 Hz, ArC_4-*H*); 7.34 (1 H, d, J = 8.4 Hz, ArC_6-*H*); 7.30 (1 H, dd, J = 8.3, 4.2 Hz, ArC_3-*H*); 7.10 (1 H, d, J = 8.4 Hz, ArC_5-*H*); 5.92 (2 H, m, =C*H*, N*H*); 5.72 (1 H, m, =C*H*′); 4.02 (1 H, m, C*H*); 3.35 (1 H, dd, J = 10.7, 4.7 Hz, CH_2-N); 2.99 (1 H, dd, 10.7, 9.3 Hz, CH_2-N); 2.70–2.90 (2 H, m, CH_2-C=, C*H*); 2.24 (1 H, m, CH_2-C=). δ*C* (68 MHz) 147.43 (ArC_2-H); 142.21 (ArC_8-N); 138.41 (ArC_{8a}); 136.00 (ArC_4-H); 135.82 (=*C*H); 129.55 (ArC_7-C); 129.01 (ArC_6-H); 128.82 (=*C*H′); 127.11 (ArC_{4a}); 120.87 (ArC_3-H); 114.94 (ArC_5-H); 46.62 (*C*H); 43.97 (CH_2-N); 37.33 (CH_2-C=); 36.11 (*C*H). ν_{max} ($CHCl_3$): 3410 (w, N-H); 3065 (w), 3005 (w), 2945 (m), 2855 (m) (C-H); 1623 (w, C=C); 1575 (m), 1514 (s), 1485 cm^{-1} (s) (C-CAr). *m/z* found: 222.1139 (M^+ 100%); 207 (20); 194 (21); 181 (29); 168 (9); 157 (8). $C_{15}H_{14}N_2$ requires 222.1157.

Elemental analysis. Found: *C* 81.0, *H* 6.2, *N* 12.5. $C_{15}H_{14}N_2$ requires *C* 81.05, *H* 6.35, *N* 12.6%].

Recrystallization of the diastereomers (**14**) and (**15**) from absolute alcohol gave a yellow crystalline solid (m.p. 190–192°C). This material was still a mixture of two diastereoisomers (**14**) and (**15**), as evidenced by the doubling up of certain signals in the ^{13}C spectrum: δ*H* (270 MHz) 8.73 (2 H, d, J = 4.2 Hz, ArC_2-*H*); 8.20 (2 H, br. d, J = 8.5 Hz, ArC_4-*H*); 7.30 (2 H, dd, J = 8.4, 4.1 Hz, ArC_3-*H*); 6.94 and 6.96 (2 H, s, ArC_6-*H*); 5.93 (2 H, br. s, N*H*); 5.65 (4 H, m, =C*H*); 4.57 (2 H, m, Ar-CH_2-Ar); 3.85 (2 H, m, C*H*); 3.33 (2 H, dd, J = 10.7, 4.7 Hz, CH_2-N); 2.98 (2 H, m, CH_2-N); 2.60–2.90 (4 H, m, CH_2-C=, C*H*); 2.21 (2 H, br. d, J = 16.4 Hz, CH_2-C=). δ*C* (68 MHz) 147.13 (ArC_2-H); 141.00 (ArC_8-N); 138.94 (ArC_{8a}); 135.70 and 135.73 (=*C*H); 132.55 (ArC_4-H); 129.48 (ArC_6-H); 128.83 and 128.86 (=*C*H′); 125.97 (ArC_{4a}); 123.36 (ArC_7-C); 120.73 and 120.75 (ArC_5-CH_2-Ar); 120.65 (ArC_3-H); 46.45 (*C*H); 44.10 (CH_2-N); 37.30 (CH_2-C=); 36.11 (*C*H); 33.75 and 33.85 (Ar-CH_2-Ar). ν_{max} ($CHCl_3$): 3400 (br. w, N-H); 3065 (w), 3002 (m), 2950 (br. m), 2855 (m) (C-H); 1623 (w, C=C); 1577 (m), 1510 (s), 1486 cm^{-1} (s) (C-CAr). *m/z* found: 456.2300 (M^+ 100%); 390 (17); 235 ($(M-C_{15}H_{13}N_2)^+$ 27); 221 ($(M-C_{16}H_{15}N_2)^+$ 11); 207 (9); 195 (19). $C_{31}H_{28}N_4$ requires 456.2314. *Elemental analysis*. Found: *C* 80.4, *H* 6.0, *N* 12.0. $C_{31}H_{28}N_4$ requires *C* 81.55, *H* 6.2, *N* 12.3%.

Cyclocondensation of 5-aminoisoquinoline (4) with formaldehyde and cyclopentadiene

5-Aminoisoquinoline (**4;** 0.36 g, 2.5 mmol) was dissolved in acetonitrile (3.6 mL) containing 2 Eq of trifluoroacetic acid (0.57 g, 5 mmol) to give a 0.7 M solution of the amine. This yellow solution was added with stirring to a heterogeneous mixture at 0°C of cyclopentadiene (0.33 g, 5 mmol) and 37% formalin solution (0.21 mL, 2.6 mmol) to give an orange solution which yielded an orange precipitate after 5 min. The mixture was stirred at room temperature under nitrogen for a further 10 min and then worked up to give a yellow/brown oil (0.61 g) which was purified as above to give the amine (**8**) as a yellow/orange oil (0.53 g, 95%, eluant 4/1 ether/ethyl acetate, v/v. R_f = 0.31). (R_f of 5-aminoisoquinoline = 0.24. R_f values for basic alumina, ether). δ*H* (270 MHz) 9.11 (1 H, s, ArC_1-*H*); 8.44 (1 H, d, J = 6.0 Hz, ArC_3-*H*); 7.47 (1 H, d, J = 6.0 Hz, ArC_4-*H*); 7.42 (1 H, d, J = 8.3 Hz, ArC_7-*H*); 7.33 (1 H, d, J = 8.3 Hz, ArC_8-*H*); 5.92 (1 H, m, =C*H*); 5.74 (1 H, m, =C*H*′); 4.52 (1 H, br. s, N*H*); 4.01 (1 H, br. s, C*H*); 3.31 (1 H, dd, J = 10.7, 4.2 Hz, CH_2-N); 2.97 (1 H, dd, 10.7, 9.7 Hz, CH_2-N); 2.78 (2 H, m, CH_2-C=, C*H*); 2.22 (1 H, br. d, J = 15.7 Hz, CH_2-C=). δ*C* (68 MHz) 152.79 (ArC_1-H); 142.29 (ArC_3-H); 139.63 (ArC_5-N); 135.43 (=*C*H); 129.58 (ArC_7-H); 129.16 (=*C*H′); 127.91 (ArC_{8a}); 126.10 (ArC_{4a}); 128.07 (ArC_6-C); 116.90 (ArC_8-H); 113.27 (ArC_4-H); 47.06 (*C*H); 44.46 (CH_2-N); 37.30 (CH_2-C=); 35.69 (*C*H). The structure was confirmed by an NOE spectrum. ν_{max} ($CHCl_3$): 3290 (br. w, N-H); 3075 (w), 2975 (br. s), 2865 (m) (C-H); 1628 (m, C=C); 1580 (br. s), 1504 cm^{-1} (br. s) (C-CAr). *m/z* found: 222.1146 (M^+ 100%); 207 (17); 193 (24); 181 (29); 168 (12); 157 (9). $C_{15}H_{14}N_2$ requires 222.1157.

Reaction of 5-aminoquinoline with formaldehyde and 3,4-dihydro-2H-pyran

5-Aminoquinoline (0.36 g, 2.5 mmol) was dissolved in acetonitrile (3.6 mL) containing 1 Eq of trifluoroacetic acid (0.29 g, 2.5 mmol) to give a 0.7 M solution of the amine. This orange solution was added with stirring to a heterogeneous mixture at 0°C of 3,4-dihydro-2*H*-pyran (0.42 g, 5 mmol) and 37% formalin solution (0.41 mL, 5 mmol). The mixture was stirred at room temperature under nitrogen for 30 min and then worked up to give a deep-red oil (0.79 g) which was purified by chromatography on alumina to give the adduct (**16**) as a yellow oil (0.22 g, 33%, eluant 7/3 ether/petrol, v/v. R_f = 0.69); the diazaoxasteroid (**17**) as a yellow/brown solid (0.11 g, 18%, eluant 3/2 ether/ethyl acetate, v/v. R_f = 0.50); a mixture of the diastereoisomers (**18**) and (**19**) of the para-coupled dimer of the diazaoxasteroid (**17**) as a yellow/brown oil (0.07 g, 11%, eluant 1/2 ether/ethyl acetate, v/v. R_f = 0.35) and recovered 5-aminoquinoline (**1**) as a yellow/orange solid (0.08 g, 22%, eluant 4/1 ether/ethyl acetate, v/v. R_f = 0.56). (R_f values for basic alumina, 1/2 ether/ethyl acetate, v/v). The adduct (**16**) was characterized by δ*H* (360 MHz) 8.87 (1 H, dd, J = 4.2, 1.8 Hz, ArC_2-*H*); 8.44 (1 H, br. d, J = 8.2 Hz, ArC_4-*H*); 7.82 (1 H, d, J = 8.4 Hz, ArC_8-*H*); 7.59 (1 H, m, ArC_7-*H*); 7.54 (1 H, br. d, J = 7.7 Hz, ArC_6-*H*); 7.37 (1 H, dd, J = 8.4, 4.2 Hz, ArC_3-*H*); 5.23 (1 H, d, J = 10.2 Hz, N-CH_2-O); 5.01 (1 H, d, J = 2.7 Hz, O-C*H*-O); 4.70 (1 H, d, J = 10.2 Hz, N-CH_2-O); 4.08 (1 H, m, CH_2-O); 3.73 (1 H, m, CH_2-N); 3.63 (1 H, m, CH_2-O); 3.27 (1 H, m, CH_2-N); 2.03 (1 H, br. m, C*H*); 1.37–1.80 (4 H, m, CH_2). δ*C* (68 MHz) 150.37 (ArC_2-H); 149.58 (ArC_{8a}); 146.79 (ArC_5-N); 132.46 (ArC_4-H); 129.45 (ArC_7-H); 125.26 (ArC_8-H); 123.89 (ArC_{4a}); 120.54 (ArC_3-H); 118.09 (ArC_6-H); 97.82 (O-*C*H-O); 79.45 (N-CH_2-O)*; 65.29 (CH_2-O)*;

52.31 (CH_2-N)*; 32.52 (*CH*)*; 24.70 (CH_2); 22.54 (CH_2). (Note that signals marked with an asterisk (*) were broad and of weak intensity). The structure and assignments were confirmed by a ^{1}H-^{13}C COSY spectrum. ν_{max} ($CHCl_3$): 2950 (br. s), 2870 (m) (C-H); 1614 (w), 1595 (s), 1578 (m), 1472 cm^{-1} (m) (C-CAr). m/z found: 270.1372 (M^+ 36%); 240 ((M-CH_2O)$^+$ 7); 171 (2); 156 (M-$C_6H_{10}O_2$)$^+$ 100); 128 (13); 116 (2); 101 (6). $C_{16}H_{18}N_2O_2$ requires 270.1368.

Recrystallization of **(17)** from methanol gave a yellow crystalline solid (m.p. 185.5–187.5°C). δ*H* (270 MHz) 8.82 (1 H, br. d, *J* = 3.4 Hz, ArC$_2$-*H*); 8.08 (1 H, br. d, *J* = 8.5 Hz, ArC$_4$-*H*); 7.54 (1 H, d, *J* = 8.6 Hz, ArC$_7$-*H*); 7.43 (1 H, d, *J* = 8.6 Hz, ArC$_8$-*H*); 7.26 (1 H, dd, *J* = 8.8, 4.3 Hz, ArC$_3$-*H*); 4.74 (1 H, vbr. s, N*H*); 4.55 (1 H, d, *J* = 2.4 Hz, C*H*O); 3.97 (1 H, m, CH_2-O); 3.60–3.78 (2 H, m, CH_2-O, CH_2-N); 3.23 (1 H, dd, *J* = 11.2, 3.4 Hz, CH_2-N); 2.12 (1 H, m, C*H*); 1.67–2.02 (3 H, m, CH_2); 1.49 (1 H, m, CH_2). δ*C* (68 MHz) 150.07 (ArC$_2$-H); 149.19 (ArC$_{8a}$); 140.42 (ArC$_5$-N); 132.49 (ArC$_7$-H); 129.03 (ArC$_4$-H); 119.36 (ArC$_3$-H); 118.13 (ArC$_8$-H); 118.06 (ArC$_{4a}$); 115.30 (ArC$_6$-C); 73.64 (*C*HO); 67.70 (*C*H_2-O); 41.90 (*C*H_2-N); 32.05 (*C*H); 25.41 (CH_2); 22.72 (CH_2). ν_{max} ($CHCl_3$): 3455 (br. w, N-H); 2952 (br. s), 2858 (m) (C-H); 1619 (w), 1585 (s), 1521 (w), 1486 cm^{-1} (m) (C-CAr). m/z found: 240.1258 (M^+ 82%); 211 (7); 195 (11); 181 ((M-C_3H_7O)$^+$100); 169 (6); 157 (5); 128 (5). $C_{15}H_{16}N_2O$ requires 240.1263. Elemental analysis. Found: *C* 73.6, *H* 6.9, *N* 11.1. $C_{15}H_{16}N_2O$ requires *C* 75.0, *H* 6.7, *N* 11.7%].

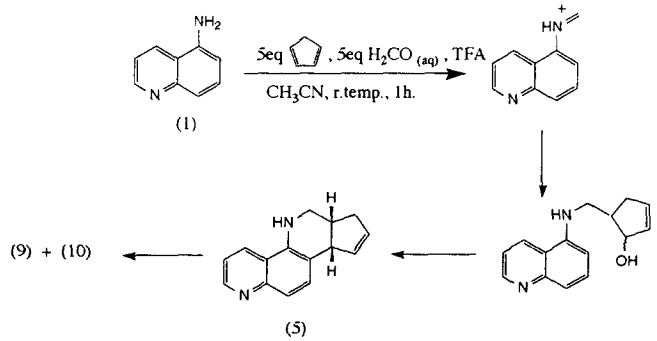
An impure mixture of two diastereoisomers **(18)** and **(19)** was evidenced by the doubling up of most signals in the ^{13}C spectrum: δ*H* (270 MHz) 8.82 (2 H, m, ArC$_2$-*H*); 7.98 (2 H, br. d, *J* = 8.7 Hz, ArC$_4$-*H*); 7.27 and 7.32 (2 H, s, ArC$_7$-*H*); 7.16 (2 H, dd, *J* = 8.4, 4.2 Hz, ArC$_3$-*H*); 5.01 (2 H, m, Ar-CH_2-Ar); 4.35 and 4.39 (2 H, br. s, C*H*O); 3.83 (2 H, br. m, CH_2-O); 3.40–3.65 (4 H, br. m, CH_2-O, CH_2-N); 3.13 (2 H, br. m, CH_2-N); 2.60–4.80 (2 H, vbr. s, N*H*); 2.00 (2 H, br. m, C*H*); 1.60–1.90 (6 H, br. m, CH_2); 1.42 (2 H, br. m, CH_2). δ*C* (68 MHz) 148.98 and 149.02 (ArC$_2$-H); 147.67 (ArC$_{8a}$); 138.77 (ArC$_5$-N); 132.55 and 132.68 (ArC$_7$-H); 129.14 (ArC$_4$-H); 128.79 and 128.83 (ArC$_8$-CH_2-Ar); 119.01 (ArC$_3$-H); 118.49 (ArC$_{4a}$); 115.23 and 115.34 (ArC$_6$-C); 73.53 and 73.60 (*C*HO); 67.14 and 67.50 (*C*H_2-O); 41.92 and 42.13 (*C*H_2-N); 32.06 and 32.13 (*C*H); 31.37 and 31.49 (Ar-*C*H_2-Ar); 25.37 and 25.50 (CH_2); 22.70 and 22.86 (CH_2). m/z found: 492 (M^+ 100%); 462 (13); 433 ((M-C_3H_7O)$^+$ 17); 311 (9); 253 ((M-$C_{15}H_{15}N_2O$)$^+$8); 239 ((M-$C_{16}H_{17}N_2O$)$^+$ 4); 187 (10). $C_{31}H_{32}N_4O_2$ requires 492.

Further experiments carried out at reflux and using fewer equivalents of formaldehyde and 3,4-dihydro-2*H*-pyran favored the production of the cycloadduct **(17)** and its para-coupled dimers **(18)** and **(19)** as products.

Results and discussion

The chosen amines were 5-aminoquinoline **(1)**, 7-aminoquinoline **(2)**, 8-aminoquinoline **(3)**, and 5-aminoisoquinoline **(4)**. They were selected because of their ready availability by reduction from commercially available nitroquinolines, and the opportunity that these amines presented to test the efficiency of generation of diazasteroids. In each case the amines were prepared by reduction using iron powder in acetic acid. The aminoheterocycles were reacted with formaldehyde and cyclopentadiene in the presence of trifluoroacetic acid in acetonitrile. In all cases mixtures of products were obtained. Amines **(5–8)** were isolated by flash chromatography of crude reaction products and could thus be separated from the variety of side products **(9–15)**. The reaction with 5-aminoquinoline was the most studied in order to investigate the effect of reaction conditions upon the relative yield of the desired diazasteroid **(5)** and the side products **(9)** and **(10)**. The optimum yield of amine **(5;** 87%) was obtained following reaction at 0°C for 45 min. An increase in reaction time resulted in an increased yield of the diastereoisomeric products **(9)** and **(10)**, which are clearly formed by reaction of excess formaldehyde with the desired amine **(5)**. Similarly, reaction in presence of additional formaldehyde resulted in the formation of the diastereoisomers **(9)** and **(10)**. In the case of reaction of 5-aminoquinoline **(1)**, the imine resulting from condensation with formaldehyde will be protonated in the presence of trifluoroacetic acid. Subsequent reaction between this iminium ion and cyclopentadiene (see Scheme 2) is likely to afford a tricyclic intermediate capable of cyclization to give the desired tetracyclic amine **(5)**. In this example, cyclization cannot afford an alternative regioisomer. The structure of the isolated major product **(5)** was established by a combination of microanalysis, high resolution MS and detailed ^{1}H and ^{13}C NMR analysis. The only possible structural ambiguity, the stereochemistry of the newly formed ring junction, was resolved by NOE analysis. A *cis*-stereochemistry was established and could be further supported by other observations recently reported, e.g., Grieco and Bahsas[14] consistently observe the creation of a *cis*-stereochemistry in related cyclisations. In the creation of tricyclic systems[19] the NMR data of cyclopentadiene adducts, having a *cis* ring fusion, are very similar to our observations. The nature of the minor products **(9)** and **(10)**, which are obtained as a single fraction, is less securely established. The mass spectral data indicates as the parent ions (m/z 456) products formed from two equivalents of the amine **(5)** reacting with formaldehyde, and the observation of additional ions of mass 221 and 235 supports the structural assignment. Further confirmation is obtained by observation of a product evolution as a function of reactant concentrations and reaction times. It is likely that the pair of diasteroisomers **(9)** and **(10)** will be formed in similar amounts. The site of reaction of formaldehyde with the amine **(5)** is clarified by observation of the NH stretching band in the IR spectrum of **(9)** and **(10)**. Overreaction of formaldehyde at carbon centers of relatively nucleophilic aromatic compounds is well precedented.

The reaction of 7-aminoquinoline **(2)** was more complex than expected. Under the reaction conditions, a relatively



Scheme 2

modest yield (27%) of the tetracyclic amine **(6)** was isolated. Three further products, all rather unstable, were isolated. The isolation of the adducts **(11)** and **(12)**, products of further reaction of the desired adduct **(6)** with formaldehyde and cyclopentadiene, is well precedented from the work of Grieco and Bahsas.[14] Again, as anticipated, a mixture of steroisomers was obtained. In this case the products **(11)** and **(12)** are related, respectively, as *cis* and *trans* isomers. The third side-product was less expected. Analysis showed formation of the mixture of stereoisomeric alcohols **(13)**. The extent of formation of this fraction depended on the period of reaction. The alcohol is isolated on work-up and shows the multi-step nature of the cyclizations leading to the adducts of a Diels-Alder type cyclization.

The cyclization of 8-aminoquinoline **(3)** followed a very similar path to that of 5-aminoquinoline **(1)**. The major product was the desired diazasteroid **(7)**, but minor quantities of the diastereoisomeric products **(14)** and **(15)** were observed. In this case the products of further reaction could be recrystallized to give a sharp melting crystalline product. However, ^{13}C NMR analysis established that the crystals represented two very closely related structures, and the individual isomers **(14)** and **(15)** could not be separated by fractional crystallization.

Interestingly, 5-aminoisoquinoline afforded a single product, the desired diazasteroid **(8)**, in 95% yield. In this case, no evidence of formation of products of further reaction was found. Our observations suggest that the aminoquinolines tend to overreact more easily than 5-aminoisoquinoline **(4)**.

Finally, the reaction of dihydropyran with formaldehyde and 5-aminoquinoline was studied. This permitted the generation of diazaoxasteroids by using a vinyl ether in the cyclocondensation reaction. The desired diazaoxasteroid **(17)**, a novel 4,11-diaza-15-oxa-D-homosteroid was obtained and readily characterized. However, there were side-products. The adduct **(16)** is again easily identified from spectroscopic data. Observation of the ArC_6-H proton of the quinoline system at 7.54 ppm (d, J = 7.7 Hz) indicates that no cyclization to give a steroid skeleton has occurred. The N-CH_2O group was observed at 5.23 and 4.70 ppm (J = 10 Hz), suggesting the incorporation of an extra molecule of formaldehyde. The OCHO acetal proton was observed as a doublet at 5.01 ppm (J = 2.7 Hz). This information confirms the formation of the tetracycle **(16)** and indicates a *cis* ring fusion. The origin of the tetracycle **(16)** is supported by the observation that the other products **(17–19)** are preferentially formed, when the reaction is conducted with a lower proportion of formaldehyde. A further fraction, the diastereoisomers **(18)** and **(19)**, was isolated but again the two isomers could not be separated chromatographically. However this cyclocondensation shows that novel diazaoxasteroids can be isolated from a single-step procedure from readily available starting materials.

These results establish that access to 4,11-diaza-15-oxa-, 4,11-diaza-, 1,11-diaza-, and 3,11-diazasteroids using the aza-Diels-Alder reaction is easy. With the anticipation that other aminoquinolines and aminoisoquinolines might similarly react, and the recognition that cyclopentadiene can be replaced in these reactions by other dienophiles, it appears that a wide range of diazasteroids are now available through this strategy. An unexpected bonus is isolation of the 2:1 steroid:formaldehyde products such as **(14)** and **(15)**. Models suggest that the four nitrogen atoms are situated so that they might interact in formation of metal-ion complexes. No such complexes based on diazasteroids have been previously prepared.

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