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# Synthesis and stereochemistry of 8,13-diaza-2,3-dimethoxygona-1,3,5(10),9(11)-tetraen-12-one and D-homo derivatives

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*From the condensation reaction of* O-*methylbutyrolactim (**2**),* O-*methylvalerolactim (**3**),* O-*methylcaprolactim (**4**) and* O-*methyl-4-*t*-butylcaprolactim (**5**) with ethyl 6,7-dimethoxy-α-[1-(1,2,3,4-tetrahydro-isoquinolyl)]acetate (**1**), 8,13-diaza-2,3-dimethoxygona-1,3,5(10),9(11)-tetraen-12-one (**6**)* D*-homo-derivatives (**7–9**), and medium-sized ring cyclic diamides (**10,11**) were obtained. The stereoselective reduction of compounds **6–9** by Adam's platinum catalyst afforded 8,13-diaza-2,3-dimethoxygona-1,3,5(10)-trien-12-one (**12**) and its* D*-homo derivatives (**13–15**). The structures of the compounds obtained were established by NMR and X-ray crystallographic analyses.* (*Steroids* **63**:375–382, 1998) © *1998 by Elsevier Science Inc.*

**Keywords:** 8,13-diazasteroids; stereochemistry; X-ray structure analysis

## Introduction

Azasteroids were first synthesized some time ago[1–5] and have been shown recently to have significant biological activity.[6–9] The synthesis of diazasteroids[1] has also been accomplished, including some containing bridgehead nitrogens. The first synthesis of the 8,13-diazasteroid system was accomplished by Burckhalter et al.,[10] and the structures were confirmed by X-ray[11] analysis. It has been found that the hydrogens at positions H-9 and H-14 are both α in orientation. Later, Redeuilh and Viel[12] studied 8,13-diazaestrone derivatives by IR and NMR methods. The structures of these compounds have been defined, particularly the *trans* configurations of the B/C and C/D ring junctions. The position of the hydrogens when compared to H-9 to H-14, were *cis* and α, the same configuration found in the natural estrone. This finding was supported by investigations[13] with $^{13}C$ NMR. A general conclusion that can be drawn from the spectroscopic data of the 8,13-diazasteroids is that the compounds are stereochemically homogeneous both in crystalline form and in solution, despite the fact that there are nitrogen atoms at both bridgehead positions.[1]

A new method for the synthesis of 8,13-diazasteroids worked out by Yamazaki et al[14] is both stereochemically specific and pharmacologically useful. In this method, the ethyl 6,7-dimethoxy-α-[1-(1,2,3,4,-tetrahydroisoquinolyl)]-acetate (**1**) is reacted with two molar equivalents of the lactim ether [e.g., (**2**)] without solvent, and the tetracyclic immonium salt is obtained as an intermediate. Reduction of the intermediate with sodium borohydride or Adam's platinum catalyst gives the 8,13-diaza-2,3-dimethoxygona-1,3,5(10)-triene-12-one. These compounds and their salts possess analgesic and antiinflammatory[15] activity.

Two products are usually obtained from the condensation reactions of β-aminoesters (**1**) with lactim ethers.[16–19] This could be attributed to the presence of both tautomeric forms (imine and enamine)[18] of the lactim ethers. However, only a single product was formed from the reaction of β-aminoester (**1**) and methyl-butyrolactime (**2**), the imine-type product. Although the reported[14] synthesis of 8,13-diazasteroids is very attractive method, unfortunately under the same reaction conditions the expected D-homo-derivatives of 8,13-diazasteroids were not formed.

In the present, work we report a more convenient and

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Received July 2, 1997; accepted January 20, 1998.



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0039-128X/98/$19.00
PII S0039-128X(98)00011-7

more highly selective method for synthesis of the 8,13-diazasteroid system than previously[14] described. Condensation of the ethyl 6,7-dimethoxy-α-[1-(1,2,3,4-tetrahydroisoquinolyl)]acetate (**1**) with different ring-sized lactim ether (**2–5**) led to the formation of 8,13-diazasteroid systems. Herein, we discuss the stereochemistry of the products on the basis of spectroscopic and X-ray data.

## Experimental

### *General methods*

$^1$H NMR spectra were obtained on Brucker AC-250 and JEOL FX-100 spectrometers at room temperature. Chemical shifts were given on the (Δ)-scale. In the ID, measurements 32 K data points were used for FID. For homonuclear $^1$H NOE experiments, a delay time of 3 s was applied. $^1$H NOE difference assessments and two-dimensional carbon-proton correlated experiments were performed using the Brucker DISNMR software package. In the $^2$H experimental, 1KX1K data matrices were transformed. Mass spectra were recorded on a Finningan-MAT 8230 mass spectrometer. X-Ray crystallographic data were collected on a Rigaku AFC6S diffractometer with a graphite monochromator and with Mo-$K_\alpha$ ($\lambda$ = 0.710 69 A) radiation. Elemental analyses were obtained with a KOVO (Czechoslovakia) CHN automatic analyzer.

Thin-layer chromatography (TLC) was performed with glass plates (0.25 mm) precoated with silica gel G, which were purchased form Merck (Darmstadt). Spots were visible under short-wavelength UV light or made visible by spraying with EtOH-$H_2SO_4$ (1:1) and heating the plates to 100°C. Reaction components were visualized under UV light, in an iodine chamber, or by spraying with Dragendorff's reagent. Lactim ethers (**2–5**) were prepared by the method of Peterson and Titze.[20]

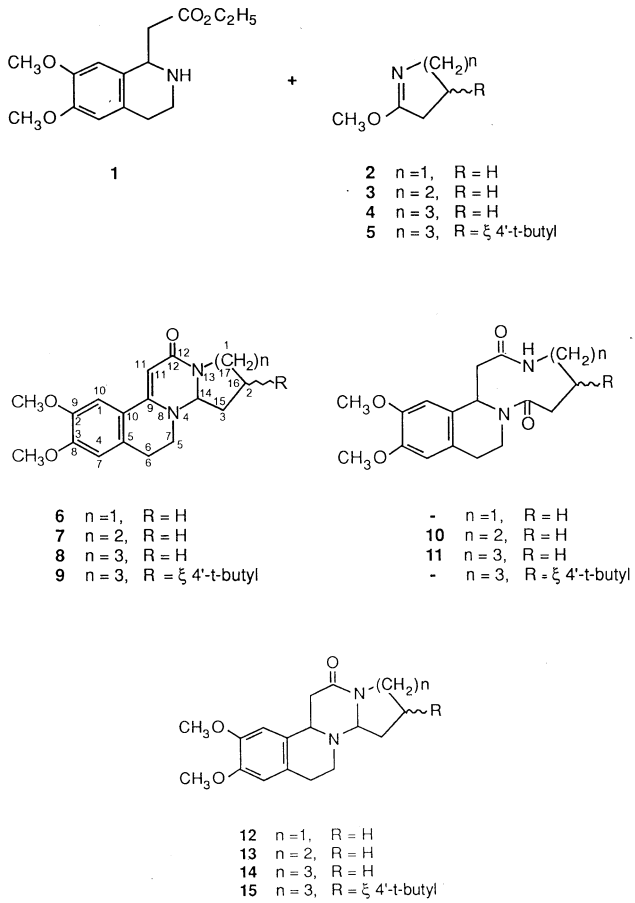
### *General procedure for the preparation of 8,13-diaza-2,3-dimethoxygona-1,3,5(10)9(11)-tetraen-12-one and D-homo derivatives (**6–9**) as well as medium ring-size diamides (**10–11**) and compound (**17**)*

Lactim ether (**2–5**) (11 mmol) was added to a stirred suspension of ethyl 6,7-dimethoxy-α-[1-(1,2,3,4-tetrahydroisoquinolyl)]acetate (**1**) (2.8 g 10 mmol) in xylene (25 mL). The mixtures were allowed to warm to reflux and were kept there for 80–140 h. Subsequently, they were concentrated in vacuo to give dark brown oil products. The residues were purified by column chromatography on silica gel (EtOAc:$CHCl_3$ = 2:1 and/or benzene:EtOH = 4:1). Eluting with EtOAc:$CHCl_3$ initially afforded the **6–9** 8,13-diazagona compounds, then the **10,11** cyclic diamides, and finally compound **17** (2,3,15b,15c-tetramethoxy-15,16-benzo-8,13-diaza-D-homogona-1,3,5(10)trien-12-one). The greatest amount of compound **17** precipitated from the solution of xylene during the reaction.

The chromatographic fractions were analyzed by TLC (benzene:EtOH = 4:1). The **6–9** diazasteroids showed higher $R_f$ values than the **10–11** cyclic diamides. Compounds **6–9** became visible as dark brown spots in an iodine chamber much faster than compounds **10–11**, which appeared later as pale yellow spots. The $R_f$ values of the compounds will be published in a separate paper. The obtained diazasteroids **6–9** had a yellow color, and the cyclic diamides **10,11** were white crystalline compounds. The physical, $^1$H NMR, and MS data are summarized in Table 1; $^{13}$C NMR data are summarized in Table 2.

### *8,13-Diaza-2,3-dimethoxygona-1,3,5(10)-9(11)-tetraen-12-one (**6**)*

Analysis calculated for $C_{17}H_{20}N_2O_3$: C, 67.97; H, 6.71; N, 9.33. Found: C, 67.74; H, 6.59; N, 9.18.




**Scheme 1** Synthesis and reduction products of 8,13 diazasteroid and D-homo-derivatives with cyclic diamides (Numbers inside the rings corresponds to the steroid; numbers outside the rings indicate the heterocyclic numbering conventions. Numbering in Tables 1 through 6 and compounds **6** and **12** follow the steroid convention, while in the Experimental section, for **7–11** and **13–15** the heterocyclic numbering convention was followed).

### *9,10-Dimethoxy-1,2,3,4,4a,6,7,13-octahydroisoquino[1,2-f]pyrido[2,1-b]pyrimidin-13-one (**7**)*

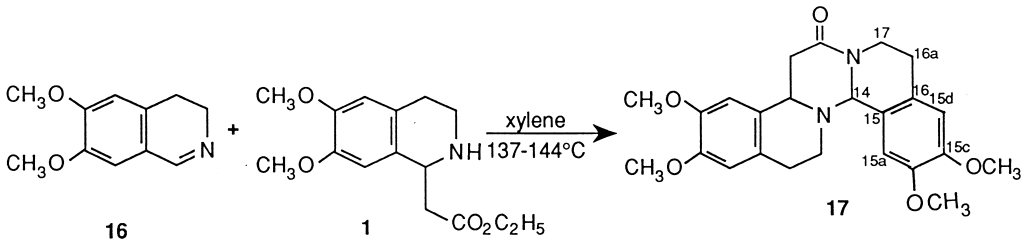
Ratio of products: 21% (**7**), 34% (**10**), and 8% (**17**), remainder was unchanged compound (**1**). Analysis calculated for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91. Found: C, 68.64; H, 6.93; N, 8.78.

### *10,11-Dimethoxy-1,2,3,4,5,5a,7,8-octahydro-14H-isoquino[1,2-f]azepino[2,1-b]pyrimidin-14-one (**8**)*

Ratio of products: 17% (**8**), 43% (**11**), and 10% (**17**); the remainder was unchanged compound (**1**). Analysis calculated for $C_{19}H_{24}N_2O_3$: C, 69.48; H, 7.36; N, 8.53. Found: C, 69.34; H, 7.22; N, 8.47.

### *10,11-Dimethoxy-1,2,3,4,5,5a,7,8-octahydro-14H-3-tert-butyl-isoquino[1,2-f]azepino[2,1-b]pyrimidin-14-one (**9**)*

Ratio of products: 14% (**9**), the corresponding cyclic diamide was not isolated, 11% (**17**), the remainder was unchanged compound (**1**). Analysis calculated for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.28. Found: C, 71.73; H, 8.22; N, 7.18.




**Scheme 2** Synthesis of 2,3,15b,15c-tetramethoxy-15,16-benzo-8,13-diaza-D-homogona-1,3,5(10)-trien-12-one.

### *1-(1,5-Diaza-2,6-dioxocyclodecanyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10**)*

Analysis calculated for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.92; H, 7.11; N, 8.32.

### *1-(1,5-Diaza-2,6-dioxocycloundecanyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**)*

Analysis calculated for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.08. Found: C, 65.91; H, 7.44; N, 8.11.

### *Reduction of the 8,13-diaza-2,3-dimethoxygona-1,3,5(10)-9(11)-tetraen-12-one and D-homo derivatives (**6–9**): General procedure*

A stirring suspension of Adam's $PtO_2$ catalyst (0.1 g) in EtOH (15 mL) at room temperature was prehydrogenated for 2 h under an atmosphere of hydrogen, and then a solution of the 8,13-diazasteroids (**6–9**) in 50–130 mL of EtOH was added to the suspension. The reaction mixtures were hydrogenated at 1 atm for 6 h, subsequently filtered, and the solvents were evaporated from the filtrate. Removal of the solvent gave solid residues, which were recrystallized from the proper solvents (see Table 1) to give the pure products **12–15**. The yields and physical data of compounds **12–15** are summarized in Table 1.

### *8,13-Diaza-2,3-dimethoxygona-1,3,5(10)-trien-12-one (**12**)[14]*

Analysis calculated for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.26. Found: C, 67.63; H, 7.38; N, 9.30.

### *9,10-Dimethoxy-1,2,3,4,4a,6,7,11b,12,13,-decahydroisoquino[1,2-f]pyrido[2,1-b]pyrimidin-13-one (**13**)*

Analysis calculated for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.24; H, 7.49; N, 8.58.

### *10,11-Dimethoxy-1,2,3,4,5,5a,7,8,12b,13,14-undecahydroisoquino[1,2-f]azepino[2,1-]pyrimidin-14-one (**14**)*

Analysis calculated for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.92; H, 8.02; N, 8.27.

### *10,11-Dimethoxy-1,2,3,4,5,5a,7,8,12b,13,14-undecahydro-3-tert-butyl-isoquino[1,2f]azepino[2,1-b]pyrimidin-14-one (**15**)*

Analysis calculated for $C_{23}H_{34}N_2O_3$: C, 71.46; H, 8.86; N, 7.25. Found: C, 71.32; H, 8.72; N, 7.12.

### *Conversion of compound **10** to compound **7***

A solution of compound **10** (0.33 g, 1 mmol) in 50 mL of xylene and a solution of methylvalerolactim (**3**) (0.11 g, 1 mmol) dissolved in 5 mL of xylene were mixed and placed in a 100-mL round-bottomed flask. The mixture was heated under reflux for 48 h. Evaporation of the solvent and purification of the residue by chromatography on silica gel (EtOH:$CHCl_3$ = 3:1) provided 0.27 g (87%) of **7** as a pale yellow crystalline solid: m.p. 216–218°C. The $^1$H NMR and $^{13}$C NMR data were the same as the compound obtained by another procedure.

### *Preparation of compound **17***

A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (**16**) (0.36 g, 1.8 mmol) in 25 mL xylene and a solution of **1** (0.53 g, 1.8 mmol) in 20 mL xylene were combined, and the resulting mixture was heated under reflux for 54 h. The conversion of starting material was followed by TLC (benzene:EtOH = 4:1; under UV light or an iodine chamber) and resulted in **17** with $R_f$ 0.61. The reaction mixture was cooled, and compound **17** was precipitated as a pale yellow crystalline product (0,12 g, 16%): m.p. 247–50°C. Recrystallization of the product from xylene gave a solid, m.p. 251–252°C. Analysis calculated for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found C, 67.78; H, 6.61; N, 6.38. MS $^1$H NMR, and $^{13}$C NMR data (see Tables 1 and 2).

### *X-ray diffraction*

Crystal and molecular structures of the azasteroids **6** and **8** were determined by direct methods using diffractometer data. Both compounds crystallized in a monoclinic system with space group $P2_1/c$. Crystal data and experimental details are listed in Table 3. Intensity data were collected at 298–299(1) K with a Rigaku AFC6S diffractometer using graphite monochromated Mo K$\alpha$ radiation and a 2kW sealed tube generator. Lattice parameters were refined by least squares fit of 21/23 reflections in a $2\theta$ range of 35.03–40.66° for **6** and 20.19–33.52° for **8**. For both crystals, three standard reflections were measured after every 150 reflections. They remained constant throughout data collection, indicating crystal and electronic stability. Thus, no decay correction was applied in either case. Data were then corrected against Lorentz and polarization effects. An empirical absorption correction based on azimuthal scans of several reflections was applied for **6**, which resulted in the transmission factors ranging from 0.98 to 1.00. No need for absorption correction was indicated by a similar azimuthal scan for **8**. A total of 3003 and 3281 reflections were collected from the thin crystal plates of **6** and **8**, respectively. 2853 reflections were unique and nonzero ($R_{int}$ = 0.234) for **6** and 3103 ($R_{int}$ = 0.037) for **8**. Intensities with $I \geq 2\sigma$ (I) were used to solve the structures by direct methods (using programs MITHRIL[21] and DIRDIF[22]) and to refine the structures by using full-matrices least-squares to minimize the function $\Sigma w(F_o\text{-}k|F_c|)^2$. Weights

**Table 1** Physical and Spectral Data of Compounds[a] **6–15** and **17**

| Compound | Yield (%) | m.p. (°C)/(cryst solvent) | $^1$H NMR and MS spectral data |
|---|---|---|---|
| **6** | 81 | 264–268, (DMF) | NMR ($CDCl_3$), 100 MHz; 7.12 (s, 1, H-1), 6.62 (s, 1H, H4), 2.70–3.05 (m, 3H, $H_2$-6, $H_{eq}$-15), (2H, $H_2$-17), 1.80–2.50 (m, 5H, $H_{ax}$-15, $H_2$-16, $H_2$-16a), 3.86 (s, 3H, MeO), 3.88 (s, 3H, MeO); MS (FAB) m/z 299 $[M-H]^-$ |
| **7** | 21 | 218–219, (EtOH) | NMR ($CDCl_3$), 250 MHz; 7.08 (s, 1H, H-1), 6.61 (s, 1H, H-1), 2.75–3.00 (m, 2H, $H_2$-6), 3.25 (t, 2H, $H_2$-7), 5.18 (s, 1H, H-1), 4.68 (dd, 1H, $J$ = 10.0 Hz, 3 Hz, $H_{ax}$-14), 1.80–2.15 (m, 2H, H-15), 1.40–1.80 (m, 4H, $H_2$-16, $H_2$-16a), 2.55 (m, 1H, $H_{ax}$-17), 4.58 (dt, 1H, $J$ = 12.0 Hz, 2.5 Hz, $H_{eq}$-17), 3.84 (s, 3H, MeO), 3.87 (s, 3H, MeO); MS (FAB) m/z 313 $[M-H]^-$ |
| **8** | 17 | 165–167, (Aceton/Ether) | NMR ($CDCl_3$), 100 MHz; 7.07 (s, 1H, H-1), 6.63 (s, 1H, H-4), 2.88 (m, 2H, $H_2$-7), 5.30 (s, 1H, H-11), 4.60 (dd, 1H, $J$ = 10.8 Hz, 2.8 Hz, H-14), 1.90–2.30 (m, 2H, $H_2$-15), 1.40–1.90 (m, 4H, $H_2$-16, $H_2$-16a), 2.75 (m, 1H, $H_{ax}$-17), 4.43 (ddd, 1H, $J$ = 13.5 Hz, 7 Hz, 5 Hz, $H_{eq}$-17), 3.86 (s, 3H, MeO), 3.88 (s, 3H, MeO); MS (FAB) m/z 327 $[M-H]^-$ |
| **9** | 14 | 225–228, (EtOH) | NMR ($CDCl_3$), 100 MHz; 7.09 (s, 1H, H-1), 6.61 (s, 1H, H-4), 2.87 (m, 2H, $H_2$-6), 3.31 (t, 2H, $H_2$-7), 5.28 (s, 1H, H-11), 4.57 (dd, 1H, $J$ = 11.0 Hz, 3 Hz, H-14), 1.00–2.60 (m, 6H, $H_2$-15, $H_2$-16, $H_2$-16a), 2.75 (m, 1H, $H_{ax}$-17), 4.40 (m, 1H, $H_{eq}$-17), 3.86 (s, 3H, MeO), 3.88 (s, 3H, MeO, 0.85 (s, 9H, $Me_3C$); MS (FAB) m/z 383 $[M-H]^-$ |
| **10** | 34 | 202–205, (EtOH) | NMR ($CDCl_3$), 250 MHz; 6.73 (s, 1H, H-1), 6.61 (s, 1H, H-4), 5.23 (dd, 1H, $J$ = 9.5 Hz, 3 Hz, $H_{ax}$-9), 2.60 (m, 2H from decoupling experiment $H_2$-11), 3.86 (s, 3H, MeO), 3.88 (s, 3H, MeO), 4.92 (m, 1H, $H_{eq}$-7), 3.85 (m, 1H from decoupling experiment, H-17), 5.47 (dd, 1H, $J$ = 9 Hz, 2 Hz, NH), 1.5–31 (m, 13 H, other skeleton protons); MS (FAB) m/z 331 $[M-H]^-$ |
| **11** | 43 | 262–265, (EtOH) | NMR ($CDCl_3$), 100 MHz; 6.72 (s, 1H, H-1), 6.57 (s, 1H, H-4), 5.26 (dd, 1H, $J$ = 9 Hz, 4.5 Hz, $H_{ax}$-9) 2.60 (m, 2H, from decoupling experiment, $H_2$-11), 3.83 (s, 3H, MeO) 3.85 (s, 3H, MeO, 4.87 (m, 1H, $H_{eq}$-7) 3.65 (m, 1H, H-17), 6.24 (t, 1H, $J$ = 6 Hz, NH); MS (FAB) m/z 345 $[M-H]^-$ |
| **12** | 98 | 212–214, (EtOH/ether)[b] | NMR ($CDCl_3$), 250 MHz; 6.56 (s, 1H, H-1), 6.60 (s, 1H, H-4), 3.76 (dd, 1H, $J$ = 11.5 Hz, 5 Hz, $H_{ax}$-9), 2.48 (dd, 1h, $J$ = 17.5 Hz, 11.5 Hz, $H_{ax}$-11), 3.04 (dd, 1H, $J$ = 17.5 Hz, 5.0 Hz, $H_{eq}$-11), 3.98 (dd, 1H, $J$ = 9.0 Hz, 5.0 Hz, $H_{ax}$-14), 3.82 (s, 3H, MeO), 3.84 (s, 3H, MeO), 1.75–2.04 (m, 4H, $H_2$-15, $H_2$-16), (1.85 m, from decoupling experiment, $H_{ax}$-15), 2.54 ddd (1H, $J$ = 11.0 Hz, 9.0 Hz, 5.0 Hz, $H_{ax}$-17), 2.70–3.80 (m, 5H, $H_2$-6, $H_2$-7, $H_{eq}$-17); MS (FAB) m/z 301 $[M-H]^-$ |
| **13** | 99 | 193–194, (EtOH) | NMR ($CDCl_3$), 100 MHz; 6.55 (s, 1H, H-1), 6.58 (s, 1H, H-4), 3.78 (dd, 1H, $J$ = 10.5 Hz, 5 Hz, $H_{ax}$-9), 2.48 (dd, 1H, $J$ = 17.5 Hz, 10.5 Hz, $H_{ax}$-11), 2.92 (dd, 1H, $J$ = 17.5 Hz, 5 Hz, $H_{eq}$-11), 3.7–3.9 (m, 1H, in overlapping H-14) 3.80 (s, 3H, MeO), 3.83 (s, 3H, MeO), 1.20–3.40 (m, 11H, other skeleton protons, 2.48 m, from decoupling experiment, $H_{ax}$-17), 4.82 (ddd, 1H, $J$ = 12.0 Hz, 3.5 Hz, 2.0 Hz, $H_{eq}$-17); MS (FAB) m/z 315 $[M-H]^-$ |
| **14** | 97 | 162–165, (ether/hexane) | NMR ($CDCl_3$), 100 MHz; 6.55 (s, 1H, H-1), 6.60 (s, 1H, H-4), 3.97 (dd, 1H, $J$ = 11.0 Hz, 4.0 Hz, $H_{ax}$-9), 2.55 (dd, 1H, $J$ = 17.5 Hz, 11.0 Hz, $H_{ax}$-11), 2.85 (dd, 1H, $J$ = 17.5 Hz, 4.0 Hz), 4.29 (t, 1H, $J$ = 4 Hz, $H_{eq}$-14), 3.82 (s, 3H, MeO), 1.40–3.40 (m, 13H, other skeleton protons), 3.70–4.10 (m, 1H, $H_{eq}$-17); MS (FAB) m/z 329 $[M-H]^-$ |
| **15** | 99 | 183–184 (MeOH/ether) | NMR ($CDCl_3$), 10 MHz; 6.52 (s, 1H, H-1), 6.61 (S, 1H, H-4), 3 (dd, 1H, $J$ = 11.0 Hz, 5.0 Hz, $H_{ax}$-9), 2.70 (m, 1H, from decoupling experiments, $H_{ax}$-11), 2.95, (1H, from decoupling experiments, $H_{eq}$-11), 4.24, (dd, 1H, $J$ = 9.5 Hz, 2.5 Hz, $H_{ax}$-14), 3.84 (s, 3H, MeO), 1.00–3.50, (m, 12H, other skeleton protons), 3.9–4.3 (m, 1H, Heq-17), 0.87 (s, 9H, $Me_3C$); MS (FAB) m/z 385 $[M-H]^-$ |
| **17** | 8 | 251–253 (EtOH) | NMR ($CDCl_3$), 250 MHz; 6.58 (s, 2H, 4, -15d), 6.50 (s, 1H, H-1), 6.98 (s 1H broad, H-15a), 5.75 (s, 1H, $H_{ax}$-14, 4.86 (m, 1H, $H_{eq}$-17), 4.45 (t, 1H, $J$ = 8.5 Hz, H-9, 2.45–2.90 (m, 9H other skeleton protons, from decoupling experiment and C/H correlation 2.68 $H_{ax}$-7, 2.85 $H_{ax}$-17), 3.85 (s, 3H, MeO), 3.82 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.97 (s, 3H, MeO); MS (FAB) m/z 423 $[M-H]^-$ |

[a]The steroid skeleton numbering convention was followed in compounds (**6–15**) and (**17**).
[b]Lit m.p. 219–240°C.

assigned to individual observations were $w = 4F_o^2/\sigma^2(F_o^2)$, where $\sigma^2(F_o^2) = [S^2(C + R^2B) + (pF_o^2)]/L_p^2$ with the parameters: S, scan rate; C, total integrated peak count; R, ratio of scan time to background counting time; B, total background count; and $L_p$, Lorentz polarization factors. For both data sets, the fudge factor was $p = 0.01$. For each hydrogen, positions were generated from assumed geometry but were not refined. They were only included in the final rounds of least squares with isotropic displacement parameters set to 20% greater than the bonded partner. The final R values together with maximum and minimum peaks in the final difference Fourier maps are given in Table 3. Neutral atomic scattering factors were taken from Cromer and Waber.[23] All calculations were performed using the TEXSAN[24] crystallographic software package (Molecular Structure Corporation). The sample of **6** was poorly crystalline; its peaks were wide and, in some cases, rather unsymmetrical. This resulted in a limited data set of low intensities (Table 3). Although the data/parameter ratio is lower than

**Table 2** $^{13}C$ NMR Chemical Shifts of Products **6–15** and **17** (δppm; $CDCl_3$/TMS)

| Compound | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | $C_7$ | $C_9$ | $C_{10}$ | $C_{11}$ | $C_{12}$ | $C_{14}$ | $C_{15}$ | $C_{16}$ | $C_{16a}$ | $C_{16b}$ | $C_{17}$ | $CH_3O$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | 107.4 | 147.9 | 150.2 | 110.2 | 128.5 | 28.3 | 43.9[a] | 153.1 | 119.9 | 91.4 | 164.8 | 74.9 | 32.8 | 21.5 | — | — | 43.4[a] | — |
| | | | | | | | | | | | | | | | | | | — |
| 7 | 108.2 | 148.2 | 149.1 | 110.5 | 128.1 | 28.8 | 44.3 | 151.1 | 121.0 | 85.7 | 166.2 | 77.9 | 24.5 | 25.8 | 24.1 | — | 44.0 | 56.0 |
| | | | | | | | | | | | | | | | | | | 56.0 |
| 8 | 107.7 | 147.9 | 148.6 | 110.3 | 128.0 | 28.9 | 45.3 | 150.7 | 121.0 | 87.1 | 165.0 | 78.6 | 28.7[a] | 25.1[b] | 25.3[b] | 28.2[b] | 43.6 | 55.9 |
| | | | | | | | | | | | | | | | | | | 55.9 |
| 9 | 107.7 | 147.9 | 148.7 | 110.3 | 128.0 | 28.2 | 45.2 | 150.7 | 121.0 | 86.6 | 165.2 | 78.5 | 28.9 | 26.3 | 46.6 | 28.9 | 43.0 | 55.9 |
| | | | | | | | | | | | | | | | | | | 55.9 |
| 10 | 109.7 | 148.0[a] | 148.2[a] | 111.2 | 126.7[b] | 28.3 | 39.5 | 54.5 | 126.9[b] | 35.2 | 172.5 | 170.5 | 28.6 | 23.9 | — | — | 25.6 | 55.9 |
| | | | | | | | | | | | | | | | | | | 55.9 |
| 11 | 109.7 | 147.9 | 147.9 | 111.1 | 126.4[a] | 28.6 | 41.7 | 54.3 | 127.8[a] | 35.1 | 171.9 | 170.9 | 28.0 | 22.7 | 24.3 | — | 25.1 | 55.9 |
| | | | | | | | | | | | | | | | | | | 56.2 |
| 12 | 107.9 | 147.5 | 147.5 | 111.0 | 125.6 | 28.3 | 46.3 | 58.8 | 128.0 | 31.9 | 166.6 | 79.0 | 24.2 | 20.7 | — | — | 44.6 | 55.7 |
| | | | | | | | | | | | | | | | | | | 55.7 |
| 13 | 108.3 | 147.6 | 147.7 | 111.2 | 126.0 | 29.1 | 44.8 | 55.7 | 128.2 | 39.6 | 167.3 | 77.1 | 31.2 | 23.5[a] | 24.0[a] | — | 41.7 | 55.7 |
| | | | | | | | | | | | | | | | | | | 55.7 |
| 14 | 108.1 | 147.6 | 147.7 | 111.2 | 125.7 | 28.9 | 43.5 | 56.4 | 128.7 | 37.9 | 168.1 | 77.9 | 33.3 | 23.5 | 27.3[a] | 28.9[a] | 43.2 | 55.8 |
| | | | | | | | | | | | | | | | | | | 55.8 |
| 15 | 108.6 | 147.6 | 147.6 | 111.6 | 125.6 | 29.0 | 42.6 | 56.0 | 129.2 | 37.6 | 168.4 | 79.0 | 34.1 | 27.2[a] | 49.6 | 27.3[a] | 41.4 | 56.0 |
| | | | | | | | | | | | | | | | | | | 56.0 |
| 17 | 108.9 | 147.2 | 147.7 | 111.7 | 125.3 | 28.6 | 35.3 | 55.3 | 129.7 | 35.2 | 167.9 | 74.4 | 124.3[c] | 128.9 | 28.0 | — | 37.7 | 55.7 |
| | | | | | | | | | | | | | | | | | | 55.8 |

[a,b]Tentative assignment; [c]$C_{15a}$ 109.4; $C_{15b}$ 148.1; $C_{15c}$ 148.3; $C_{15d}$ 110.6.

ideal, the refinement proceeded well resulting in a structure comparable to that of **8**. At any rate, the ring puckering and general conformation of the diazasteroid skeletons in the solid state could be characterized and compared.

**Table 3** Crystal Data and Experimental Details

| | Compound **6** | Compound **8** |
|---|---|---|
| Molecular formula | $C_{17}H_{20}N_2O_3$ | $C_{19}H_{24}N_2O_3$ |
| M | 300.36 | 328.41 |
| Crystal system | Monoclinic | Monoclinic |
| Space group | $P2_1/c$ | $P2_1/c$ |
| a (Å) | 11.427 (3) | 10.921 (2) |
| b (Å) | 6.905 (3) | 15.282 (3) |
| c (Å) | 19.192 (3) | 10.239 (2) |
| b (deg) | 101.92 (2) | 99.06 (2) |
| V (Å$^3$) | 1481.6 (7) | 1687 (1) |
| Z | 4 | 4 |
| $D_c$ (g.cm$^{-3}$) | 1.346 | 1.293 |
| $\mu$(mm$^{-1}$) | 0.87 | 0.82 |
| F(000) | 640 | 704 |
| Crystal dimensions (mm) | 0.40 × 0.30 × 0.08 | 0.40 × 0.15 × 0.10 |
| Maximum $2\theta$ (deg) | 50.1 | 50.0 |
| Radiation (Å) | Mo K$\alpha$, 0.71069 | Mo K$\alpha$, 0.71069 |
| Scan mode | $\omega/2\theta$ | $\omega/2\theta$ |
| Scan width (deg) | 1.84 + 0.30tan$\theta$ | 1.00 + 0.30tan$\theta$ |
| Temperature (K) | 298 (1) | 299 (1) |
| Number of reflections: unique | 2853 | 3103 |
| With $I \geq 2\sigma(I)$ | 919 | 1320 |
| No. of parameters refined | 199 | 218 |
| Goodness-of-fit on F | 2.03 | 1.65 |
| R | 0.061 | 0.052 |
| $R_w$ | 0.046 | 0.039 |
| $\rho$max in ΔF map (eÅ$^{-3}$) | 0.24 | 0.20 |
| $\rho$min in ΔF map (eÅ$^{-3}$) | −0.25 | −0.18 |

## Results and discussion

### *Synthesis*

The reaction of a 1.1 molar equivalent of methyl butyrolactim (**2**) with **1** in xylene at 137–144°C for 80 h gave only the imine-type product 8,13-diaza-2,3-dimethoxygona-1,3,5(10),9(11)-tetraen-12-one (**6**) in 81% yield (Table 1). This product, when reduced with Adam's catalyst in ethanol, furnished a pale yellow crystalline compound (**12**, m.p. 212–214°C, Table 1). This differed from the m.p. reported in the literature (219–240°C).[14] The previously reported product was obtained by reduction of the quaternary immonium iodide of 8,13-diazasteroid with Adam's catalyst in acetic acid. Presumably, the latter compound was a mixture of configurational isomers. The basis of this conclusion is the observed broad range of the melting point; our product seems to be stereohomogeneous, as judged by $^1H$ NMR and $^{13}C$ NMR data.

Similar reaction of lactim ethers **3–5** with **1** gave the imine-type D-homo-8,13-diazagonane derivatives **7–9** and provided the medium-sized ring cyclic diamides **10,11**. The same diamide formation was not observed when lactim ether **2** was reacted with **1**. The probable reason is that the nine-membered ring diamide was very strained. The ratio of the two kinds of products strongly depends on the ring size of the lactim ethers, as shown in Table 1. The major products were cyclic diamides; **10,11** and the D-homo-8,13-diazagona derivatives **7–9** were the minor products when lactim ethers **3** and **4** were used in the annelation reactions. The corresponding cyclic diamides were not isolated from the reaction of lactim ether **5** with β-aminoester **1**. The physical and $^1H$ NMR data are shown in Table 1, and the $^{13}C$ NMR data are summarized in Table 2.

When the β-aminoester **1** was reacted with lactim ether **3**, the imine-type product **7** and the cyclic diamide **10** were

accompanied by an unexpected pentacyclic compound: 2,3,15b,15c-tetramethoxy-15,16-benzo-8,13-diaza-D-homogona-1,3,5(10)trien-12-one (**17**). The structure of this compound was determined by MS, $^1$H NMR (Table 1), and $^{13}$C NMR (Table 2). Results of COLOC[25] analysis are shown in Table 4, and one-dimensional $^1$H NOE difference measurements are given in Table 5. Evaluations of the spectroscopic data are presented in the section titled "Assignment of Structure". The spectral studies were in complete accordance with the structure of **17**.

In the present studies, we proposed to form the compound **17**. Under basic conditions, the β-aminoester **1** underwent a *retro*-Mannich reaction to form 6,7-dimethoxy-3,4-dihydroisoquinoline (**16**). The opposite reaction was observed by Pelletier and Cava.[26] When **16** was condensed with diethyl malonate to form β-aminoester **1**, we presume compound **16** reacted with β-aminoester **1** to afford **17** in a slow reaction. When compound **16** reacted with β-aminoester **1** in xylene at 75°C for 54 h, compound **17** was formed in 8% yield. At higher temperature (138°C) in xylene for 54 h, the yield of compound **17** was 16%. In both cases after removal of the precipitated compound **17** by filtration, the reactions were continued. Compound **17** was detected in the reaction of the β-aminoester **1** with lactim ethers **4** and **5**, but was not observed in the reaction with lactim ether **2**. The lack of formation of compound **17** can be explained by the fact that the reaction with lactim ether **2** was much faster than that with lactim ethers, **3–5** and the 8,13-diazasteroid (**6**) was formed in good yield (81%), with no starting material from the *retro*-Mannich reaction remaining. It was observed that subjecting the cyclic diamide **10** to the same reaction conditions under which 8,13-diazasteroids were formed, produced the diazasteroid **7**.

The lactam **11** did not convert to the 8,13-diazasteroid homolog **8**. As we proposed on the basis of the stereochemical model of **11**, in this structure, it is impossible for the N-C═O and -NH-C═O groups to approach close enough for ring closure to occur.

The hydrogenation of compounds **7–9** was carried out as for compound **6**, giving **13–15**. The conformation of the B/C ring was similar to that of compound **12**. The catalytic hydrogenation carried out by the stereospecific pathway does not depend on the ring-member of ring D. The $^1$H NMR and $^{13}$C NMR data of compounds **13–15** are summarized in Tables 1 and 2.

**Table 4** Determination of Carbon–Proton Connectivity over Two and Three Bonds for Compound **17** by the COLOC Method ($J_{opt}$ = 7 Hz)

| Proton | Carbon |
|---|---|
| H-1 | C(3), C(5), C(9) |
| H-4/H-15d | C(2), C(10), C(15, C(15b) |
| H-9 | C(1), C(10) |
| H-14 | C(7), C(9), C(15), C(15h), C(16) |
| H-15a | C(15c), C(16) |
| H-eq-17 | C(12), C(16), C(16a) |

**Table 5** Results of the $^1$H NOE Difference Measurements of Compound **17**

| Irradiate | Observe | % NOE |
|---|---|---|
| H-1 | H-9 | 8.1 |
| | $H_2$-11 | 3.2 |
| | MeO-2 | 15.7 |
| H-9 | H-1 | 8.4 |
| | $H_{eq}$-11/$H_{ax}$-7 | 4.7 |
| | H-14 | 17.2 |
| H-14 | $H_2$-7 | 3.2 |
| | H-9 | 15.2 |
| | H-15a | 5.5 |
| H-15a | H-14 | 4.8 |
| | MeO-15b | 10.2 |

### *Assignment of structures of compounds 6–15 and 17 by NMR spectroscopy*

The dd multiplicity of the H-9 signal and its couplings (9.5 Hz/3.0 Hz and 9.0 Hz/4.5 Hz) indicate that, in the case of the ten- and eleven-membered ring compounds (**10** and **11**), a conformer is predominant in which the dihedral angles of H-9 and protons of H-11 are approximately 180° and 60°.

It is well known that in solution a *trans* ⇌ *cis*-1 ⇌ *cis*-2 equilibrium can be formed in isoquinoline-type nitrogen bridgehead compounds.[27] In compounds **6–9**, the bridgehead N-8 atom is part of an enamine moiety and has a planar or nearly planar geometry; consequently, in this peculiar case, the formation of the above mentioned conformational equilibrium does not take place. The dd multiplicity of the H-14 signal and the couplings of 10 Hz and 3 Hz support the axial position of this proton. The triplet multiplicity of the signal of the H-7 methylene protons is indicative of the fast interconversion of the two possible half-chair conformers of the flexible B ring.

In the reduced 8,13-diazasteroids (**12–15**), the proton at H-9 is *axial*, as follows from the bond coupling constants of 11 Hz and 5 Hz between the H-9 and H-11 methylene proton measurements. Similar multiplicity of the H-14 proton and the coupling constants of 9.5 Hz and 4.0 Hz in compounds **12**, **13** and **15** indicate that the H-14 proton is also *axial*. The stereochemistry of these compounds was also supported by NOE measurements. Significant NOE was detected between H-14 and H-9 protons, which indicates a *cis-diaxial* position for the two hydrogens; in other words, the ring junctions of B/C and C/D are *trans* as in the natural steroids. This finding was consistent with the $^{13}$C NMR chemical shifts measured for these compounds. A noteworthy change was observed in the conformation of the seven-membered ring by the introduction of a *tert*-butyl group. In compound **14**, the triplet multiplicity of the H-14 proton and coupling constants of 4 Hz indicated that in this compound, H-14 is equatorial. However, the same compound with a bulky *tert*-butyl group in ring-D (**15**), resulted in an axial H-14 proton, which exhibited a doublet of doublets resonance with J = 9.5 and 2.5 Hz.

In compound **17**, the elucidation of the relative stereochemistries of protons H-9 and H-14 required a more detailed examination. However, the signal of H-9 appeared separately in the $^1$H NMR spectrum of the vicinal H-11 protons, which

**Table 6** Relevant Torsion Angles for **6** and **8**

| | **6** | **8** |
|---|---|---|
| Ring B | | |
| C5-C6-C7-N8 | 45 (1) | −54.8 (5) |
| C6-C7-N8-C9 | −48 (1) | 46.1 (5) |
| C7-N8-C9-C10 | 24.4 (9) | −11.4 (6) |
| N8-C9-C10-C5 | 1.9 (9) | −14.0 (6) |
| C9-C10-C5-C6 | −3 (1) | 1.2 (6) |
| C10-C5-C6-C7 | −20 (1) | 33.3 (6) |
| Ring C | | |
| N8-C9-C11-C12 | 0 (1) | 7.4 (6) |
| C9-C11-C12-N13 | 3 (1) | −14.6 (6) |
| C11-C12-N13-C14 | 16 (1) | −11.7 (5) |
| C12-N13-C14-N8 | −36 (1) | 40.7 (5) |
| N13-C14-N8-C9 | 36 (1) | −47.3 (5) |
| C14-N8-C9-C11 | −20 (1) | 25.2 (6) |
| Ring D | | |
| C17-N13-C14-C15 | 24.9 (9) | — |
| C19-N13-C14-C15 | — | 87.6 (4) |
| N13-C14-C15-C16 | −28.7 (9) | −70.7 (5) |
| C14-C15-C16-C17 | 22.5 (9) | 51.3 (7) |
| C15-C16-C17-N13 | −8.8 (9) | — |
| C15-C16-C17-C18 | — | −62.5 (8) |
| C16-C17-N13-C14 | −9.5 (9) | — |
| C16-C17-C18-C19 | — | 74.9 (8) |
| C17-C18-C19-N13 | — | −33.8 (7) |
| C18-C19-N13-C14 | — | −40.6 (6) |
| Exocyclic torsion angles | | |
| C9-C11-C12-O12 | −173.2 (8) | 161.2 (4) |
| C14-N13-C12-O12 | −167.8 (8) | 172.5 (4) |
| C1-C2-O2-C2′ | −1 (1) | 4.0 (7) |
| C4-C3-O2-C3′ | 1 (1) | 0.2 (6) |
| C7-N8-C14-N13 | 178.1 (7) | 163.0 (3) |
| N8-C14-N13-C19 | — | −147.1 (4) |
| N8-C14-N13-C17 | 160.0 (6) | — |

were strongly coupled, and their signals were overlapped, prohibiting an adequate spectral analysis. The H-14 signal appeared as a singlet; thus, from the coupling constants, the stereochemistry of compound **17** could not be concluded. The 1,3-diaxial position of H-9 and H-14 was confirmed by $^1$H NOE difference spectroscopy. The results of the $^1$H NOE difference measurements of compound **17** (summarized in Table 5) contributed to the assignment of other proton signals.

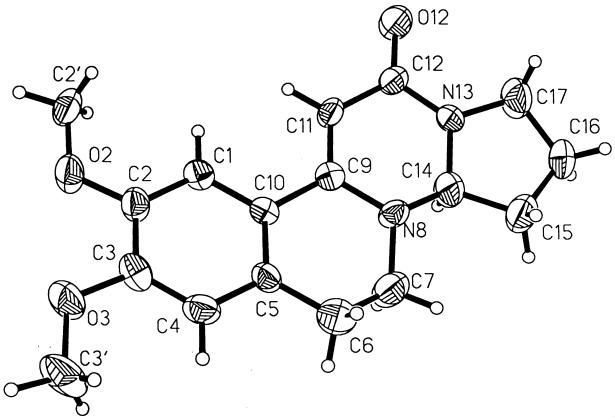



**Figure 1** Molecular structure of compound **6**. ORTEP diagram with atomic labeling and thermal ellipsoids with 50% probability level. The hydrogen atoms are shown but not labeled.

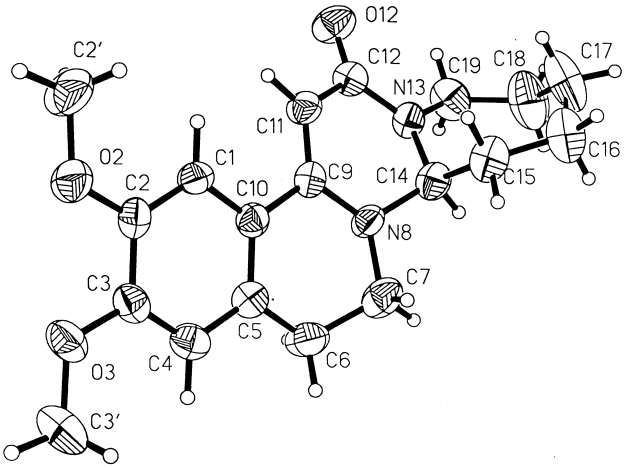



**Figure 2** Molecular structure of compound **8**. ORTEP diagram with atomic labeling and thermal ellipsoids with 50% probability level. The hydrogen atoms are shown but not labeled.

For a complete assignment of $^{13}$C NMR signals, the two-dimensional C/H correlation measurement was used, while for the assignment of quaternary carbon atoms, especially in the cases where the *CH*-signals were overlapped, the COLOC[25] method was used. This measurement was optimized for $J$(C,H) = 7 Hz long-range couplings. The detected proton-carbon connectivities over two and three bonds, for compound **17** are summarized in Table 4.

### *X-ray diffraction*

Crystallographic data and experimental details for **6** and **8** are listed in Table 3. Selected torsion angles are given in Table 6. Racemates of the diazasteroids crystallized in the monoclinic space group $P2_1/c$. Due to the aromatic ring A, the double bond between C9–C11, and the N-8 and N-13 atoms sitting in the B/C and C/D ring junctions, only one chiral center, C-14, was retained. Figures 1 and 2 show the C-14(**S**) enantiomers for both structures with thermal ellipsoidal plots and numbering schemes. The stereoscopic representation of molecule **6** (Figure 3) revealed a practically coplanar skeleton; only C-7 and C-14 were visibly out of the least squares plane in the $\alpha$-position at a distance of −0.576(6) and −0.385(7)Å, respectively. Both B/C and C/D rings junctions are *trans* like. The puckering parameters[28] [Q = 0.387(8), 0.285(9)Å, $\varphi$ = 121(1), 113(2)°, $\theta$ = 123(1), 123(2)°] showed that the B and C heterorings equally assume envelope conformation with C-7 and C-14 on the flaps (the corresponding asymmetry factors[29] $fC_s$ = 0.9 pm and 2.9 pm), while the five membered hetero ring is in half-chair [Q = 0.268(9)Å, $\varphi$ = 235(2°)] conformation

**Figure 3** Stereoscopic view of molecule **6** showing its basically flattened comformation. To fix the enantiomer with the chirality of C-14(**S**), the C-14 hydrogen atom is also presented.

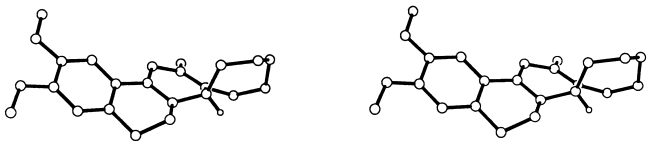


**Figure 4** Stereoscopic view of molecule **8** showing its twisted conformation. To fix the enantiomer with the chirality of C-14(**S**), the C-14 hydrogen atom is also presented.

with a twofold axis [$fC_2$ = 0.4 pm] bisecting atom C-17. The pyramidality of the nitrogen atoms result from their distance from the plane of the three atoms bonded by N-C multiple bonds: ΔN-8 = 0.288(8) and ΔN-13 = 0.117(7)Å. (An alternative measurement of pyramidality is suggested by Dunitz and Winkler[30] calculated from properly chosen pairs of endo- and exocyclic torsion angles (cf Table 6) pertaining to the nitrogen atoms: $\chi_{N8}$ = 0.21, $\chi_{N13}$ = 0.09 rad). In contrast, molecule **8**, as depicted in Figure 4, is twisted approximately around the axis defined by atoms C-10 and C-18. The seven-membered ring exhibits distorted twist-chair (TC) conformation with endocyclic torsion angles close to those of the canonical form.[31] Their discrepancies were measured by the asymmetry factor of $fC_2$ = 6.2 pm calculated[24] for the twofold axis, which bisects atom C-19 and bond C15–C16. Ring D is *cis*-like and fused to ring C which, instead of the envelope shape found in **6**, has a skewed form [Q = 0.481(5)Å, $\varphi$ = 280(1)°, $\theta$ = 63(1)°].

The twist of ring C is propagated further onto ring B, which also assumes a skewed form [Q = 0.409(5)Å, $\varphi$ = 287(1)°, $\theta$ = 66(1)°]. But, similarly to **6**, the out-of-plane atoms are again C-7 and C-14. These features of the molecule and, in particular the *cis*-C/D junction, give rise to the very low pyramidality of N-13 [ΔN-13 = −0.056(4)Å, $\chi_{N13}$ = 0.04 rad]. Similarly, the out-of-plane amplitude of N-8 is less [ΔN-8 = −0.231(5).Å, $\chi_{N8}$ = 0.17 rad] than that of compound **6**. Finally, it is worth noting that the enantiomers assigned C-14(S) chirality exhibit torsion angles with opposite signs for rings B and C, which is due to the difference in their C/D ring junctions (*trans* versus *cis*).

## Acknowledgments

Financial support from the Ministry of Education, Hungary (Grant No. MKM-224) and from the Hungarian National Science Foundation (Grant No. OTKA-T 014978) is gratefully acknowledged.

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