Synthesis and structure of cycloalkane- and norbornane-condensed 6-aryl-1,2,4,5-tetrahydropyridazinones

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Dedicated to Prof. Sándor Antus on the occasion of his 60th birthday.

The C=N double bond of certain *cis*- or *trans*-cycloalkane and *diexo*- or *diendo*-norbornane-condensed pyridazinones was reduced with $NaBH_3CN$. The *cis*- or *trans* nature of the starting cycloalkane derivatives was always retained in the saturated products, with a high degree of diastereoselectivity: the hydrogen on the new stereocenter and the annelational hydrogen next to the carbonyl always exhibited the same steric orientation. The stereostructures were determined by means of nmr measurements and confirmed by molecular modelling.

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Numerous cycloalkane-condensed 4,5-dihydropyridazin-3(2*H*)-ones have recently been prepared [1-3] and dehydrogenated with $SOCl_2$ in benzene and with $CuCl_2$ in CH_3CN [4,5] or reacted with Zn/HCl, which leads to a diastereoselective reductive ring contraction [6]. The selective reduction and ring transformation of pyridazinones and phthalazinones are carried out under similar conditions [7,8]. By cleavage of the N-N bond, the reduction of phthalazinones with BH_3/THF affords α-substituted 1,2-benzenedimethanamines [9]. The hydrogenation of pyridazinones with $LiAlH_4$ furnishes the partially reduced 1,4,5,6-tetrahydropyridazinones [10], which behave as nonsteroidal progesterone receptor ligands [11]. For saturation of the C=N bond in pyridazinones, sodium cyanoborohydride ($NaBH_3CN$) was found to be a mild, simple and regioselective reducing agent; its application has been well documented and reviewed in detail [12]. In this way, the macrocyclic dilactam skeleton of peptidal antibiotics (*e.g.* glidobactin A) [13] and 1,2-diazetid-3-ones has been prepared [14].

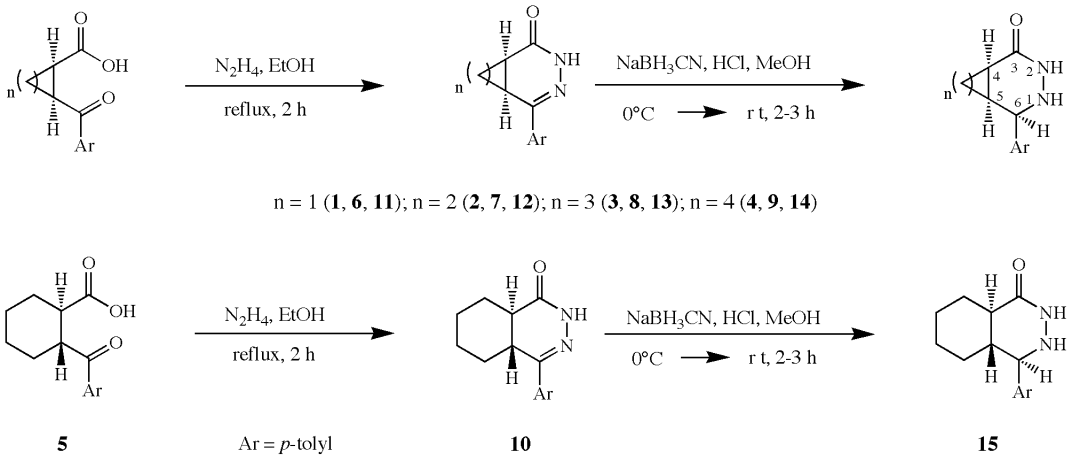
Our present investigation was focused on the saturation of cycloalkane-condensed pyridazinones by the application of $NaBH_3CN$ in an effort to attain diastereoselectivity.

Results.

For saturation of the double bond in the bicyclic *cis*- or *trans*-cyclohexane- and tricyclic, norbornane-condensed dihydropyridazinones **6-10**, **16** and **17**, which are easily accessible *via* the reactions of *cis*- or *trans*-2-*p*-toluoylcycloalkane- or *diexo*- and *diendo*-norbornanecarboxylic acids [15] with hydrazine [1], $NaBH_3CN$ in MeOH solution was added in portions at 0 °C, followed by hydrochloric acid dropwise (Schemes 1 and 2). The mixtures were made slightly alkaline and extracted with CH_2Cl_2 and the products were purified by column chromatography. In all cases, only a single diastereomer could be isolated. The *trans* dihydropyridazine **10** gave the saturated *trans* product **15**.

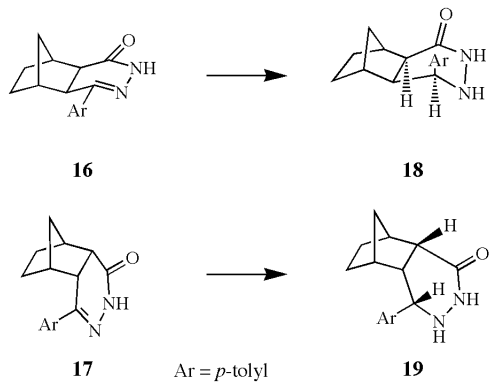
For the *diendo*-norbornane-fused derivative **19**, only a markedly poor (28%) yield was obtained, whereas all the other reactions resulted in the saturated derivatives in good to excellent yields (75-94%). The reason for this poor yield of **19** might be that the *diendo* position is sterically hindered as concerns nucleophilic attack by cyanoboro-

Scheme 1



hydride on the polar C=N bond. The unreacted **17** could be recovered after chromatographic purification.

Scheme 2



16 **18**

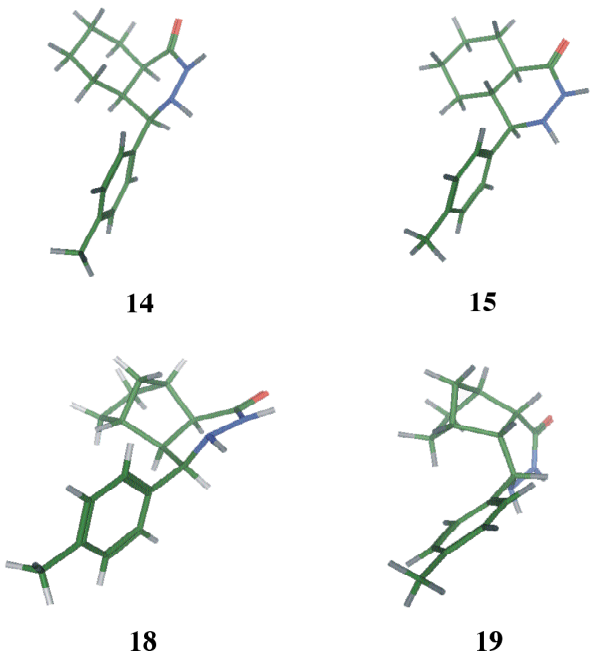
17 Ar = *p*-tolyl **19**

Structure.

In the ^{1}H nmr spectra of the products **11**-**15**, **18** and **19**, the signals of the annelational hydrogens appear in the region 4.36-4.43 ppm and the COSY connectivities confirm most of the assignments. The protons and carbons chemical shifts can be assigned *via* HSQC and HMBC experiments [16,17]. The relative positions of the annelational hydrogens were deduced from the J-couplings and the NOESY spectra. *J* of H-6 shows ~ 3 Hz for **13**-**14** *cis*- and 8.6 Hz for **15** *trans* arrangement between H-6 and H-5. *J* of H-4 is 8.6 Hz for **18,** which is a typical value for *diexo* compound. The NOE cross-peak for the protons at positions 4 and 5 shows that the arrangement is *cis* for compounds **11**-**14**, *diexo* for **18**, *trans* for **15**, and *diendo* for **19**. The configurations of the aryl-substituted carbon in **11-15**, **18**, **19**, *i.e.* the stereoposition of the hydrogen on this carbon, were determined by means of NOE, where the cross-peak of H-4 and H-6 proves their *cis* arrangement.

The structures were confirmed by molecular modelling. The conformational protocol comprised a stochastic search, using the Merck Molecular Force Field (MMFF94) [18]. Figure 1 depicts a stereoview of the typical minimum-energy molecular structures for pyridazines **14, 15, 18** and **19**.

It was concluded that cyanoborohydride successfully reduced these (bi)cycloalkane-condensed pyridazinones with a high degree of diastereoselectivity: in the saturated products, the hydrogen atom on the new stereocentre and the annelational hydrogen next to the carbonyl are always *cis*.



14 **15**

18 **19**

Figure 1. Stereoview of typical minimum-energy structures for **14, 15, 18** and **19**.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H nmr, NOESY, COSY, HSQC and HMBC spectra were recorded on a Bruker *Avance* DRX 400 MHz spectrometer (mixing time for the NOESY spectrum = 0.4 s). $CDCl_3$ was used as solvent; the concentration of the samples was 20 mg/mL. Chemical shifts: δ, in ppm, TMS as an internal standard, coupling constants (J values) in Hz. The conformational search protocol comprised a stochastic search using MMFF94 implemented in the Chemical Computing Group's MOE software.

General Procedure for the Preparation of **11-15** and **18**, **19**.

To a solution of the pyridazinone (**6**: 4.00 g, **7**: 4.28 g, **8**: 4.56 g, **9**: 4.84 g, **10**: 4.84 g, **16**: 5.08 g, **17**: 5.08 g, 20 mmol) in MeOH (100 mL), $NaBH_3CN$ (2.51 g, 40 mmol) was added in portions at 0 °C, and HCl (36% 4 mL) was then added dropwise. The mixture was stirred at room temperature for 2-3 h. After the dropwise addition of NaOH (N) until the solid has dissolved (pH ~7.5-8.0), the solution was evaporated down and the residue was dissolved in CH_2Cl_2 20 mL) and purified by column chromatography (silica gel, CH_2Cl_2 and then EtOAc). The eluates were evaporated down and the residue was crystallized from EtOAc.

6-(*p*-Tolyl)-*cis*-4,5-cyclopropa-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**11**).

This compound was obtained in 88% yield (3.56 g), mp 182-184 °C. ^{1}H nmr: 1.36 (ddd, 1H, H-7, J = 6.3, 7.6, 13.6 Hz), 1.65 (q, 1H, H-7, J = 5.3 Hz), 1.87 (ddd, 1H, H-4, J = 4.5, 9.3 Hz), 1.98-2.06 (m, 1H, H-5), 2.35 (s, 3H, CH_3), 4.36 (s, 1H, H-6), 7.18 (d, 2H, H-3', H-5', J = 7.8 Hz), 7.37 (d, 2H, H-2', H-6', J = 7.8 Hz); ^{13}C nmr: 6.9 (CH_2), 16.8 (C-4), 21.4 (CH_3), 22.0 (C-5), 55.7 (C-6), 128.1 (C-2', C-6'), 129.6 (C-3', C-5'), 135.2 (C-1'), 138.5 (C-4'), 172.7 (C-3).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found. C, 71.35; H, 7.04; N, 13.89.

6-(*p*-Tolyl)-*cis*-4,5-cyclobuta-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**12**).

This compound was obtained in 91% yield (3.94 g), mp 185-187 °C. ^{1}H nmr: 1.90-2.03 (m, 1H, H-8), 2.04-2.27 (m, 2H, H-8 and

H-7), 2.33 (s, 3H, CH_3), 2.53-2.70 (m, 1H, H-8), 3.25-3.45 (m, 2H, H-5 and H-4), 4.16 (d, 1H, H-6, J = 3.3 Hz), 7.09-7.21 (m, 4H, H-2', H-3', H-5', H-6'), 7.72 (bs, 1H, NH); ^{13}C nmr: 19.1 (C-8), 21.5 (CH_3), 23.8 (C-7), 37.2 (C-5), 37.5 (C-4), 59.0 (C-6), 127.1 (C-2', C-6'), 129.6 (C-3', C-5'), 134.2 (C-1'), 137.6 (C-4'), 176.0 (C-3).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found. C, 72.31; H, 7.52; N, 13.03.

6-(*p*-Tolyl)-*cis*-4,5-cyclopenta-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**13**).

This compound was obtained in 95% yield (4.37 g), mp 179-180 °C. ^{1}H nmr: 1.15-1.29 (m, 1H, H-9), 1.39-1.54 (m, 2H, H-8 and H-7), 1.63-1.80 (m, 2H, H-9 and H-8), 2.15-2.26 (m, 1H, H-9), 2.30 (s, 3H, CH_3), 2.75-2.87 (m, 1H, H-5), 2.97 (dd, 1H, H-4, J = 9.1, 16.4 Hz), 4.36 (d, 1H, H-6, J = 2.8 Hz), 7.10-7.15 (m, 4H, H-2', H-3', H-5', H-6'), 8.60 (bs, 1H, NH); ^{13}C nmr: 21.4 (CH_3), 26.4 (C-8), 27.1 (C-9), 32.9 (C-7), 43.8 (H-4), 44.1 (H-5), 60.2 (H-6), 126.3 (C-2', C-6'), 129.4 (C-3', C-5'), 136.5 (C-1'), 136.8 (C-4'), 176.7 (C-3).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found. C, 73.23; H, 7.96; N, 12.21.

6-(*p*-Tolyl)-*cis*-4,5-cyclohexa-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**14**).

This compound was obtained in 72% yield (3.52 g), mp 170-172 °C. ^{1}H nmr: 1.04-1.28 (m, 3H, H-10, H-8, H-9), 1.34-1.48 (m, 2H, H-10, H-7), 1.54-1.64 (m, 1H, H-8), 1.71-1.79 (m, 1H, H-9), 2.18-2.27 (m, 1H, H-5), 2.34 (s, 3H, CH_3), 2.57 (dt, 1H, H-7, J = 1.7, 13.6 Hz), 2.85 (t, 1H, H-4, J = 5.4 Hz), 4.35 (d, 1H, H-6, J = 2.3 Hz), 7.16 (s, 4H, H-2', H-3', H-5', H-6'), 8.16 (bs, 1H, NH); ^{13}C nmr: 21.4 (CH_3), 22.3 (C-10), 23.3 (C-8), 25.4 (C-9), 26.5 (C-7), 38.9 (C-5), 42.0 (C-4), 61.2 (C-6), 126.2 (C-2', C-6'), 129.5 (C-3', C-5'), 135.4 (C-1'), 137.3 (C-4'), 172.7 (C-3).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found. C, 73.87; H, 8.30; N, 11.51.

6-(*p*-Tolyl)-*trans*-4,5-cyclohexa-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**15**).

This compound was obtained in 80% yield (3.91 g), mp 198-200 °C. ^{1}H nmr: 1.10-1.59 (m, 4H, H-10, H-9, H-8, H-7), 1.74-1.99 (m, 4H, H-5, H-10, H-9, H-8), 2.19-2.40 (m, 2H, H-4, H-7), 2.42 (s, 3H, CH_3), 3.76 (d, 1H, H-6, J = 8.6 Hz), 7.20-7.25 (m, 2H, H-3', H-5'), 7.25-7.30 (m, 2H, H-2', H-6'); ^{13}C nmr: 21.5 (CH_3), 25.9 (C-9, C-8), 26.2 (C-7), 31.5 (C-10), 44.4 (C-4), 46.2 (C-5), 65.0 (C-6), 127.4 (C-2', C-6'), 129.8 (C-3', C-5'), 138.0 (C-4'), 138.3 (C-1'), 176.2 (C-3).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found. C, 73.79; H, 8.33; N, 11.40.

6-(*p*-Tolyl)-4,5-*diexo*-norborna-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**18**).

This compound was obtained in 67% yield 3.43 g, mp 227-229 °C. ^{1}H nmr: 1.23-1.36 (m, 2H, H-11, H-8), 1.40-1.55 (m, 2H, H-8, H-9), 1.58-1.64 (m, 1H, H-11), 1.70-1.80 (m, 1H, H-9), 2.13 (s, 1H, H-10), 2.41 (s, 4H, H-5, CH_3), 2.75 (d, 1H, H-4, J = 8.6 Hz), 2.83 (d, 1H, H-7, J = 3.8 Hz), 4.30 (d, 1H, H-6, J = 3.8 Hz), 7.22-7.27 (m, 4H, H-2', H-3', H-5', H-6'), 7.75 (bs, 1H, NH); ^{13}C nmr: 21.1 (CH_3), 28.5 (C-9), 31.7 (C-8), 36.8 (C-10), 37.2 (C-11), 44.0 (C-7), 47.2 (C-5), 50.2 (C-4), 60.1 (C-6), 126.2 (C-2', C-6'), 129.4 (C-3', C-5'), 136.3 (C-4'), 136.9 (C-1'), 174.6 (C-3).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found. C, 75.12; H, 7.81; N, 10.85.

6-(*p*-Tolyl)-4,5-*diendo*-norborna-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (**19**).

This compound was obtained in 28% yield (1.43 g), mp 212-214 °C. ^{1}H nmr: 1.12-1.65 (m, 7H, 2 x H-9, 2 x H-8, H-7, 2 x H-11), 2.20 (t, 1H, H-10, J = 3.7 Hz), 2.28 (s, 3H, CH_3), 2.62-2.71 (m, 1H, H-5), 2.87-2.95 (m, 1H, H-4), 4.43 (d, 1H, H-6, J = 5.6 Hz), 7.06-7.14 (m, 4H, H-2', H-3', H-5', H-6'); ^{13}C nmr: 21.4 (CH_3), 24.3 (C-9), 26.2 (C-8), 40.6 (C-10), 41.4 (C-11), 42.1 (C-7), 42.9 (C-5), 45.6 (C-4), 60.6 (C-6), 126.0 (C-2', C-6'), 129.6 (C-3', C-5'), 136.1 (C-1'), 136.9 (C-4'), 174.5 (C-3).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found. C, 75.08; H, 7.93; N, 11.04

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