Preparation of 9-Amino-1,9-diazatricyclo[6.4.0.0^{4,8}]dodecane-2,10-dione by a Retro-Diels−Alder Reaction

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Dedicated to Professor K. Pihlaja on the occasion of his 60th birthday

Keywords: Cycloreversions / Polycycles / Nitrogen heterocycles / Retro reactions

Treatment of di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazides (**1a** and **1b**) with ethyl 2-(2-oxocyclopentyl)acetate (**2**) yields norbornene-condensed 9-amino-1,9-diazatricyclo[6.4.0.0^{4,8}]dodecane-2,10-diones **3a** and **3b**, the condensed bis(lactams) **4a** and **4b** and (from **1b** and **2**) the cyclopenta[*c*]pyridazinone **5**. After separation, **3a** and **3b** both decompose on heating by loss of cyclopentadiene to give 9-amino-1,9-diazatricyclo[6.4.0.0^{4,8}]dodecane-2,10-dione (**6**).

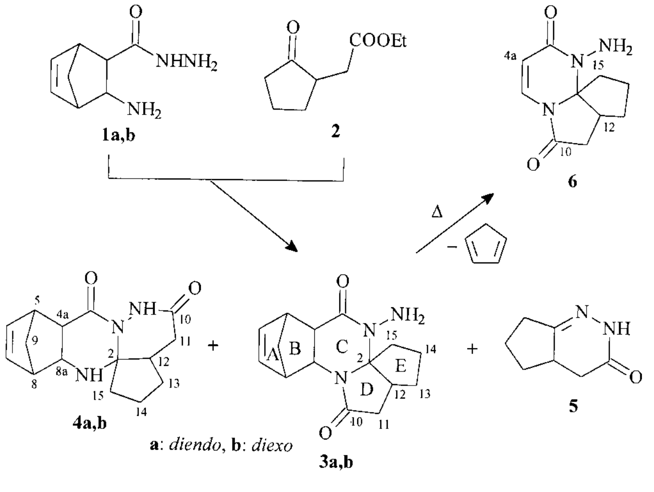
Introduction

The retro-Diels−Alder reaction (RDAR) is an efficient technique for the introduction of a double bond into a heterocyclic skeleton.[1] Our aim is to synthesize heterocycles that are new or substituted in a new manner. Accordingly, we have developed a method by which di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids or their derivatives are applied to form heterocyclic compounds, and the carrier cyclopentadiene is then cleaved off by heating of the parent molecule in the final step. By this route, numerous new and already known heteromonocycles, pyrimidinones and 1,3-oxazinones[2a,2b] have been prepared, even in condensed heterocyclic systems.[2c] Double RDAR was recently applied for the preparation of a pyrimidopyridazine,[2d] and the method has also been used for the synthesis of pyrimidophthalazines and isoindoles.[2e]

This work deals with an extension of this process to a tricyclic system. The aim is to find new fused heterocyclic compounds that can be produced by application of the developed method and to widen the scope of the RDAR concerning polycyclic derivatives.

Results and Discussion

Refluxing of di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazides (**1a**/**1b**) with ethyl 2-(2-oxocyclopentyl)acetate (**2**) in toluene and in the presence of PTSA as catalyst yields a mixture of norbornene-condensed 1,5-diazatricyclododecanediones **3a** and **3b**, together with the pentacyclic bis(lactams) **4a** and **4b** and (a product of **1b** and **2**) the cyclopentane-fused bicyclic pyridazinone **5** (Scheme 1). The latter compound had previously been prepared from **2** with hydrazine,[3] formed here by reaction of **2** with the primary amino group of hydrazide **1b** and subsequent intramolecular transacylation of the intermediate.[4,5] This mechanism operates only in the case of **1b**; the di-*endo* compound **1a** does not give **5** for steric reasons. The compounds were isolated by column chromatography, and their structures were established by means of NMR measurements and, for **3a** and **3b**, also by X-ray analysis (Figure 1). When heated to the melting point, **3a** and **3b** decomposed by splitting off of cyclopentadiene; this thermal cleavage yielded 9-amino-1,9-diazatricyclo[6.4.0.0^{4,8}]-dodecane-2,10-dione (**6**) in 85% yield.



Scheme 1. The labelling corresponds with that in Figure 1 and in Tables 1 and 2 and is not based on the nomenclature

The IR and ^{1}H and ^{13}C NMR spectroscopic data proving the structures are given in Tables 1 and 2. The unexpected

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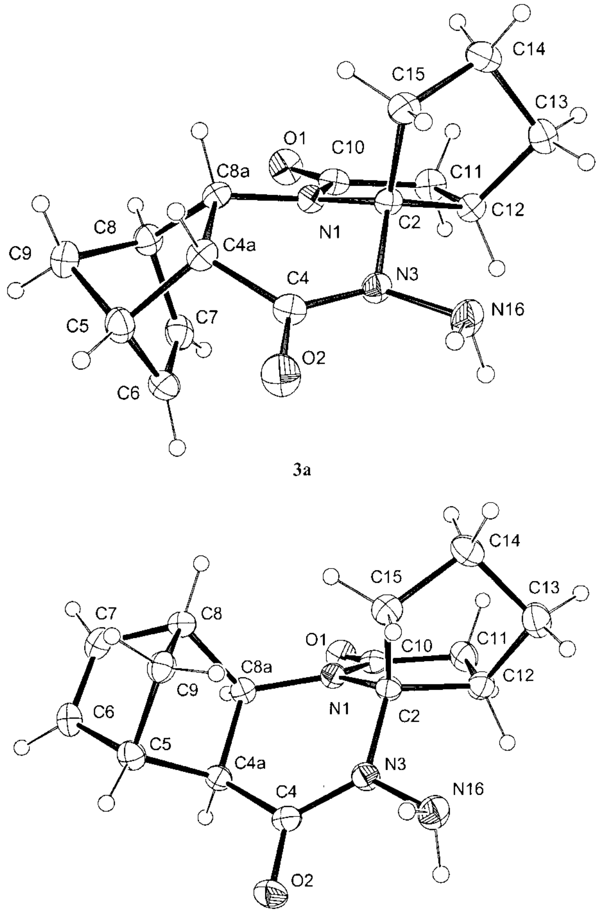

3a

3b

Figure 1. ORTEP-3 perspective views of **3a** and **3b**, showing the labelling system; thermal ellipsoids are drawn at a probability level of 30%

formation of **3a** and **3b** instead of the linearly condensed systems **4a** and **4b** was confirmed unambiguously by the appearance of NH_2 spectral signals and the lack of two NH groups. Hence, the first step in the ring closure is probably the formation of a cyclic diazaketal by condensation of the ketone with the primary amino group and the amide NH. In the second step, S_N acylation of the ester group either by the amino group or by the primary hydrazine group affords compounds of type **3** or **4**.

The constitutions of **3a** and **3b** and **4a** and **4b** follow from the spectroscopic data, and only the stereostructures remain to be determined.

As far as the annulation of the norbornene moiety to the heterocycle is concerned, the vicinal couplings of 4a-,5-H and 8-,8a-H (for the numbering, see Scheme 1) are determinant, in line with the splitting rule described earlier;[6,7] as usual, this annulation remains unaltered in the reaction products. Because of the dihedral angles of ca. 30° between the interacting hydrogen atoms[8a,8b] the corresponding splittings in the di-*endo* compounds **3a** and **4a** are about 4.0 and 3.2 Hz, but less than 1.5 Hz in their di-*exo* counterparts **3b** and **4b**, in which the dihedral angles are ca. 90°.

For determination of the configurations at C-2 and C-12, DNOE experiments were applied. On saturation of the 8a-H signal (at $\delta = 4.07$) of **3a**, one of the 15-H signals (at $\delta = 2.09$) responded, confirming their proximity; 8a-H and the 15-CH_2 group are thus on the same side of the molecular skeleton. If the more favourable *cis* annulation of the strained five-membered rings D and E is presumed, the full stereostructure of **3a** can be regarded as proved. X-ray measurements confirmed these postulated structures. Compound **3a** crystallizes with one molecule in the asymmetric unit, with one of its NH hydrogen atoms involved in a hydrogen bond, while **3b** crystallizes with two molecules in the asymmetric unit, with all four NH hydrogen atoms involved in hydrogen bonds.

The 2D-NOESY spectrum of **3b** displays a cross-peak, suggesting an interaction between 5-H and one of the methylene hydrogen atoms in the cyclopentane ring. If *cis*-D/E fusion is presumed, 12-H and 4a-,8a-H, and, similarly, ring E and the bridging methylene group, respectively, are (*S*)-*cis*-oriented, which is in accordance with the X-ray results.

DNOE measurements on **4b** indicate the steric closeness of 8a-H and the 15-H_2 group. If *cis* fusion of the cyclopentane ring is presumed, the stereostructure with (2*R**,4a*S**,5*S**,8*R**,8a*R**,12*R**) configuration can be considered as proved.

Assuming *cis*-fused rings D/E also in **4a**, the identical type of NOE observed between 8a-H and the 15-H_2 group demands an (*S*)-*cis* arrangement of ring E and 4a-H and 8a-H. Thus, a (2*S**,4a*R**,5*S**,8*R**,8a*S**,12*S**) relative configuration follows for **4a**.

A similar structure of the spirotricyclic moiety C−D−E is supported by the chemical shifts of C-2 and C-12 in **4a** and **4b**. Similarly, the identical C-2 and hardly different C-12 shifts in **3a** and **6** suggest analogous stereostructures, i.e., *cis*-annulated five-membered rings and a *cis* orientation of the amide N-3 and the methylene C-12[(2*S**,12*R**) configuration] in **6**.

The above method provides a good means of preparing the tricyclic system **6**, which contains a free amino group, even though it is attached to a ring nitrogen atom. A similarly substituted pyrimidoisoindole has been prepared by RDAR from one reaction product of **1b** with aroylcyclohexanecarboxylic acid.[2e] We earlier found that cycloreversion takes place easily on heating to the melting point, or even on boiling in a solvent, when the target molecule containing an oxo- or thioxo-substituted heteroaromatic system is formed. For condensed cycles, only the ring containing the new double bond needs to be electron-rich; the amino group provides sufficient electron density in the present case. It is noteworthy that **4a** and **4b** do not undergo decomposition under the conditions applied. The reason for this may be the presence of two vicinal lactam moieties, as observed in another case.[2e]

Although **3a** or **3b** are isolated chromatographically before the thermal decomposition, the RDA method is advantageous because **6** can be obtained on a preparative scale. Another procedure frequently applied is flash vacuum pyrolysis,[9] although simple melting is sufficient here. The

Table 1. ^{1}H NMR spectroscopic data and characteristic IR frequencies of compounds **3a**, **3b**, **4a**, **4b**, and **6**

Assignment	Compound									
	3a		**3b**		**4a**		**4b**		**6**	
^{1}H NMR data[a][b]										
4a-H, d or dd[c](1 H)	2.94		2.53		2.68		2.15		5.49	
5-H, "s" (1 H)	3.18		3.25		3.47		3.43		–	
6-H, dd[d] (1 H)	6.01		6.18		6.45		6.33		–	
7-H, d[d] (1 H)	5.85		6.38		6.22		6.16		–	
8-H, "s" (1 H)	3.93		ca. 2.8[e]		3.15		2.83		–	
8a-H, d or dd[f] (1 H)	4.07		4.33		3.98		3.32		7.30	
9-H, 2 × d (2 × 1 H)[g]	1.32	1.35	1.56	1.70[e]	1.49	1.68	1.55	1.68	–	
11-H, 2 × dd (2 × 1 H)[h]	1.88	2.57	2.14	2.70	2.30	2.41	2.38	2.55	2.17	2.90
12-H, m (1 H)	2.83		ca. 2.8[e]		ca. 2.3[e]		2.35		3.06	
13-H, 2 × m (2 × 1 H)	ca. 1.42[e]	ca. 1.77	1.55	ca. 2.1[e]	1.44	1.93	1.47[e]	1.97	1.61	2.01
14-H, 2 × m (2 × 1 H)	ca. 1.42[e]	ca. 1.67	ca. 1.65[e]	ca. 1.90	ca. 1.6	ca. 1.8	1.62	1.83	1.52	1.82
15-H, 2 × m (2 × 1 H)	1.61	2.09	ca. 2.1[e]		ca. 1.7	ca. 2.3[e]	1.72	2.30	1.74	2.14
NH_2 or 2 × NH, br. (2 H or 2 × 1 H)	4.70		4.15		1.25[i]	8.75[j]	ca. 1.5[e] [i]	8.66[j]	4.04	
Characteristic IR frequencies[k]										
$\nu_{as}NH_2$ and ν_sNH_2 or 2 νNH bands	3327	3282	3310	3206	3235[i] 3250−2750[j]		3244[i] 3250−2750[j]		3348	3210
Amide-I IR band[l]	1694	1650	1684	1626	1696	1641	1694	1631	1710	1660

[a] Chemical shifts (in ppm, $\delta_{TMS} = 0$) and coupling constants (in Hz) at 500 MHz in $CDCl_3$ solution. – [b] The assignments were supported by 2D-HSC (HMQC), and for **3a**, **3b**, **4a**, and **4b** also by DNOE or 2D-NOESY measurements. – [c] d, $J = 8.5$ (**3b**), 7.1 (**4b**), 7.5 (**6**), dd, $J = 8.6$ and 4.0 (**3a**, **4a**). – [d] $J = 5.6$ and 3.0 ± 0.1. – [e] Coalesced signals. – [f] d, $J = 7.1$ (**4b**), 7.5 (**6**), dd, $J = 8.6$ and 3.2 (**3a**, **4a**), 8.6 and 1.4 (**3b**). – [g] d, $J = 8.9$ (**3a**, **4a**), 9.6 (**3b**), 9.9 (**4b**). – [h] $J = 17.7$, 4.5 and 11.2 (**3a**), 17.7, 6.6 and 11.0 (**3b**), 15.2, 1.9 and 5.8 (**4a**, **4b**), 18.6, 6.0 and 11.1 (**6**). – [i] Amine group, hidden by the methylene multiplets in the ^{1}H NMR spectrum of **4b**. – [j] Amide NH. – [k] In KBr discs (in cm^{-1}). – [l] The high frequencies originate from the γ-lactam group (**3a**, **3b**, **6**) or secondary CONH group (**4a**, **4b**).

Table 2. ^{13}C NMR chemical shifts of compounds **3a**, **3b**, **4a**, **4b**, and **6**

Assignment[a]	Compound				
	3a	**3b**	**4a**	**4b**	**6**
C-2	90.1	90.1	84.9	84.3	90.2
C-4	170.6	169.8	165.3	165.5	165.3
C-4a	45.0	42.1[b]	44.1	44.1	106.6
C-5	46.1	48.0	47.07	46.4	–
C-6	137.1	137.2	140.1	139.4	–
C-7	135.8	139.8	133.6	135.6	–
C-8	46.5	47.7	47.14	48.5	–
C-8a	53.9	51.9	55.3	54.0	132.6
C-9	46.2	45.5	48.5	44.4	–
C-10	172.5	174.5	171.6	171.6	172.3
C-11	37.9	36.6	34.9	35.0	37.1
C-12	38.2	42.6[b]	48.7	48.9	39.6
C-13	34.2	32.6	32.1	32.1	32.8
C-14	24.3	25.0	25.0	25.0	23.3
C-15	35.9	38.9	36.7	35.8	34.0

[a] In ppm ($\delta_{TMS} = 0$), in $CDCl_3$ solution at 125.7 MHz. The assignments were supported by DEPT, 2D-HSC (HMQC) and for **3a**, **4a**, **4b**, and **6** also by 2D-COLOC (HMBC) measurements. – [b] Interchangeable assignments.

reactions proceed as if the heterotricycle is built up on the cyclopentadiene, which is then removed in the final step.

Experimental Section

General: IR spectra were measured as KBr discs with a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. – ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temp. with a Bruker DRX 500 FT spectrometer at 500.13 (^{1}H) or at 125.76 (^{13}C) MHz, respectively, using the deuterium signal of the solvent as lock and TMS as internal standard. DEPT spectra[10] were run in a standard way,[11] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. For DNOE measurements[12,13] the standard Bruker microprogram DNOEMULT was used to generate NOEs. 2D-COSY[14] and 2D-HSC spectra[14] were obtained by using the standard Bruker pulse programs COSY-45 and HXCOU, respectively.

X-ray Crystal Structure Dterminations: Crystallographic data were collected at room temperature with a Rigaku AFC5S diffractometer with graphite-monochromated Mo-K_α ($\lambda = 0.71069$ Å) radiation. To collect intensity data, an ω-2θ scan mode at an ω-scan speed of 4.0°/min was applied. Weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. For **3a**, 2418 reflections were collected ($2\theta_{max} = 50°$), and for **3b**, 4868. All data were corrected for Lorentz polarization effects. The intensities of three check reflections showed only statistical fluctuations. The structures were solved by direct methods (SIR92)[15] and refined by full-matrix, least-squares techniques (SHELXL-97)[16] to an $R1$ value of 0.039 ($wR2 = 0.062$) for **3a** and of 0.045 ($wR2 = 0.086$) for **3b**; these final R values are based on the reflections with $I > 2\sigma(I)$. The heavy atoms were refined anisotropically. The CH hydrogen atoms were included in calculated positions with fixed isotropic temperature factors (1.2 U_{eq} of the carrying atom) and the NH hydrogen atoms were refined with isotropic temperature factors. Calculations were performed with teXsan for Windows[17] crystallographic software. The figures were drawn with ORTEP-3 for Windows.[18] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151736 (**3a**) and -151737 (**3b**). Copies of

Table 3. Physical and analytical data on compounds **3**, **4**, and **6**

Compound	M.p. [°C]	Formula	Calcd.			Found		
			C	H	N	C	H	N
3a	240−241[a]	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37	65.85	7.04	15.30
3b	256−257[b]	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37	65.81	7.12	15.48
4a	245−247[a]	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37	65.71	7.00	15.42
4b	227−228[a]	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37	65.98	6.92	15.30
6	110−111.5[c]	$C_{10}H_{13}N_3O_2$	57.96	6.32	20.28	57.82	6.35	20.21

[a] Crystallization solvent: EtOAc. − [b] EtOH. − [c] Et_2O.

the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Crystal Data for 3a: Colourless prism, crystal dimensions 0.22 × 0.22 × 0.24 mm, $C_{15}H_{19}N_3O_2$, M_r = 273.33, triclinic, space group $P\bar{1}$ (no. 2), lattice parameters: a = 9.3236(7), b = 10.9107(11), c = 7.0517(7) Å, α = 106.352(8), β = 108.014(7), γ = 75.915(7)°, Z = 2, V = 644.92(10) Å^3, D_c = 1.408 g/cm^3, μ(Mo-K_α) = 0.096 mm^{-1}, F(000) = 292, T = 294 K.

Crystal Data for 3b: Colourless plate, crystal dimensions 0.22 × 0.30 × 0.32 mm, $C_{15}H_{19}N_3O_2$, M_r = 273.33, triclinic, space group $P\bar{1}$ (no. 2), lattice parameters: a = 11.475(3), b = 12.929(5), c = 10.087(2) Å, α = 103.78(2), β = 113.222(17), γ = 74.38(2)°, Z = 4, V = 1309.7(6) Å^3, D_c = 1.386 g/cm^3, μ(Mo-K_α) = 0.094 mm^{-1}, F(000) = 584, T = 294 K.

Di-*endo*- and Di-*exo*-norbornene-Condensed 9-Amino-1,9-diazatricyclo[6.4.0.0^{4,8}]dodecane-2,10-diones 3a and 3b: A mixture of di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (**1a** or **1b**) [2d] (3.0 g, 18 mmol), ethyl 2-(2-oxocyclopentyl)acetate (**2**) (3.06 g, 18 mmol), and PTSA (0.05 g) in toluene (50 mL) was refluxed for 12 h, with a Dean−Stark apparatus being applied. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (20 mL), transferred to a silica gel column (Merck 60 silica gel, 230−400 mesh ASTM) and eluted with EtOAc/*n*-hexane (2:1) and then with EtOAc. In the case of **1a**, the first eluates contained **3a** (yield 0.73 g, 15%), while the later ones contained **4a** (yield 1.9 g, 39%); the first eluates from **1b** contained **5** [yield 0.72 g, 29% (ref.[3] m.p. 144−146 °C)] and the later ones **3b** together with **4b**. On crystallization of the residues of the eluates from EtOH, **3b** separated first (yield 0.6 g, 12%); **4b** (yield 1.23 g, 25%) mostly remained in the mother liquor and could be crystallized from EtOAc. Physical and analytical data on **3a**, **3b**, **4a**, and **4b** are listed in Table 3.

9-Amino-1,9-diazatricyclo[6.4.0.0^{4,8}]dodec-11-ene-2,10-dione (6): Compound **3a** or **3b** (0.27 g, 1 mmol) was heated in a bath of Wood alloy at 250−260 °C (**3a**) for 5 min or at 270−275 °C (**3b**) for 10 min. The products were dissolved in $CHCl_3$ (5 mL) and chromatographed on a silica gel column, using EtOAc/*n*-hexane (2:1) as eluent. After concentration, **6** could be crystallized; yield 0.17 g, (83%).

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