Syntheses and NMR, MS and X-ray Investigations of Homoadamantane-fused Pyridopyrimidinones

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The reactions of ethyl 5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate (**2**) with methyl-substituted 2-aminopyridines in polyphosphoric acid (PPA) gave two products, linearly-condensed pyridopyrimidinones **4a–c** and 2-pyridylcarboxamides **5a–c**, whereas the reactions with amino, hydroxy and nitro derivatives of 2-aminopyridine furnished only linearly-condensed pyridopyrimidinones (**4g–j**). Use of a mixture of PPA and phosphorus oxychloride as solvent afforded both linearly- (**4a–c**,**e**,**f**) and angularly-condensed (**6a–c**,**e**,**f**) pyridopyrimidinones. In toluene, with *p*-toluenesulfonic acid as catalyst, 2-pyridylcarboxamides **5a–f** were obtained. In a mixture of PPA and phosphorus oxychloride at 80–120 °C, **5a–f** yielded angularly-condensed pyridopyrimidinones **6a–f**. All the products exhibited characteristic features, as determined by NMR and electron ionization mass spectrometry and X-ray crystallography.

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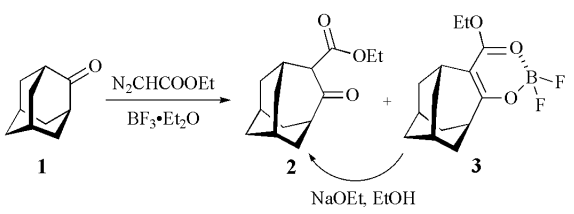
Introduction.

Pyridopyrimidinones are of pharmaceutical importance: they possess analgesic, antipyretic, antiarteriosclerotic, antibiotic, *etc*. effects [1,2]. The syntheses and chemical reactivities of a great number of bicyclic and tricyclic pyridopyrimidinones we reported earlier [3–6]. Tricyclic pyridopyrimidinones were prepared *via* the reactions of 2-oxocycloalkanecarboxylic acid esters and 2-aminopyridines. Merely linearly-condensed products were observed [7]. In the course of the present work, both linearly and angularly homoadamantane-fused pyridopyrimidinones were synthesized. The structures were proved by NMR, MS and X-ray methods.

Results and Discussion.

The starting material (**2**) for the preparation of homoadamantane-fused pyridopyrimidinones was obtained by the reaction between adamantan-2-one (**1**) and ethyl diazoacetate in the presence of boron trifluoride diethyl etherate [8–10] (Scheme 1).

Scheme 1



The main product (**2**) was always accompanied by a high yield of the difluoroborate complex of its enol form (**3**). This complex seemed to be more stable than the analogous complexes of other β-ketocarboxylates. In earlier papers [9,10], such boron complexes were decomposed by treating the reaction mixture with aqueous sodium bicarbonate or dilute aqueous ammonia solution. However, these methods were not applicable for the decomposition of complex **3**: a stronger nucleophile, ethanolic sodium ethoxide, was required. In fact, NMR analyses revealed that **2** consisted of the oxo and enol forms in almost equal amounts (51:49). However, the various reactions can still proceed unaffected since the forms are in equilibrium with each other in solution.

The reactions of **2** with methyl-substituted 2-aminopyridines in polyphosphoric acid (PPA) gave both linearly-condensed pyridopyrimidinones (**4a–c**) and 2-pyridylcarboxamides (**5a–c**) (Scheme 2).

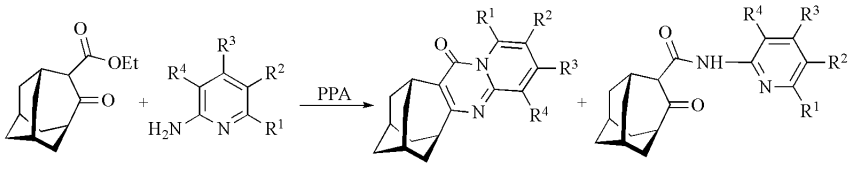
Carboxamides **5a–c** were expected to undergo cyclization in PPA to furnish the angularly-condensed pyridopyrimidinones, but even at elevated temperatures the yields were low and finally almost complete decomposition occurred.

Use of a mixture of PPA and phosphorus oxychloride (Scheme 3) instead of PPA alone (Scheme 2) afforded both linearly-condensed (**4a–c**,**e**,**f**) and angularly-condensed (**6a–c**,**e**,**f**) pyridopyrimidinones.

Angularly-condensed pyridopyrimidinones were formed only when some formation of the carboxamide from the corresponding β-oxoester and 2-aminopyridine was observed in the course of the reaction. Accordingly, these carboxamides were synthesized and their reactivities under different conditions were studied.

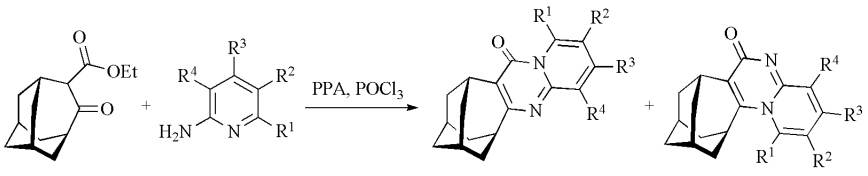
Carboxamides **5a–f** were prepared by the reactions of β-oxoester **2** with 2-aminopyridines in toluene with *p*-toluenesulfonic acid as catalyst at reflux temperature. In a mixture of PPA and phosphorus oxychloride, **5a–f** yielded angularly-condensed pyridopyrimidinones **6a–f** (Scheme 4) as the only products at 80–120 °C, while the cyclization of carboxamides in PPA alone failed.

Scheme 2



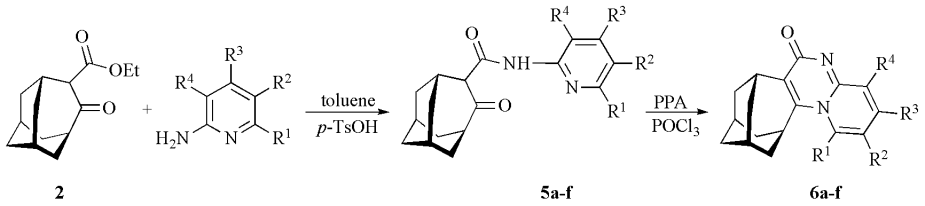
4	5	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H

Scheme 3



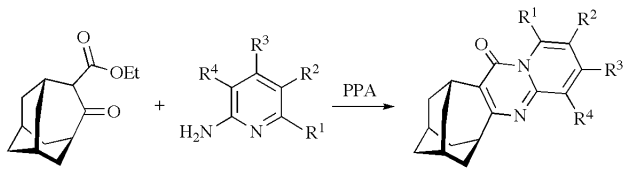
4	6	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H
e	**e**	H	Br	H	H
f	**f**	H	Cl	H	H

Scheme 4



5	6	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H
d	**d**	H	H	H	H
e	**e**	H	Br	H	H
f	**f**	H	Cl	H	H

Scheme 5



4	R^1	R^2	R^3	R^4
g	NH_2	H	H	H
h	H	H	H	OH
i	OH	H	H	H
j	H	NO_2	H	H

In fact, we first studied the reactions of **2** with amino, hydroxy and nitro derivatives of 2-aminopyridine in PPA. It was found that, in agreement with the literature data [7], these reactions gave a single product, the linearly-condensed pyridopyrimidinones, **4g–j** (Scheme 5).

Structure Elucidation.

^{1}H and ^{13}C NMR Spectra.

The proton and carbon chemical shifts for compounds **4** and **6** are given in Tables 1 and 2, respectively, and those for compounds **2**, **3** and **5** in the experimental. The atom numbering is presented in Figure 1.

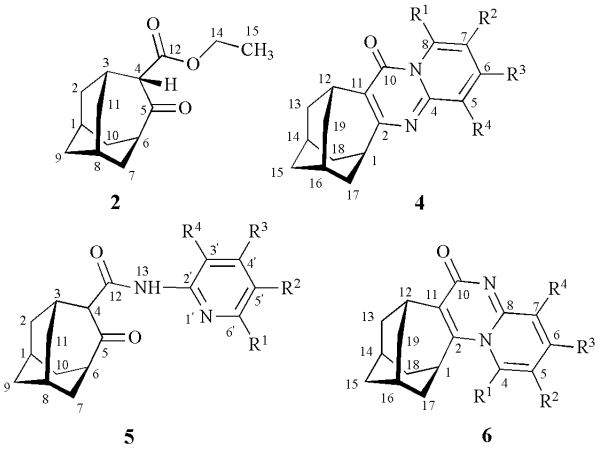


Figure 1. Atom numbering for the compounds studied.

The molecules in sub-series **4** and **6** have a plane of symmetry, in which the pyridopyrimidinone moiety lies. This is evident from the chemical equivalence of the protons and carbons at positions 13/19, 17/18 and 14/16. In series **6**, the irradiation of H1 resulted in a strong NOE in H4 (or Me in the case of **6c**), thereby proving the angular fusion. For series **4**, a similar enhancement was not observed, which confirmed the linear condensation. As a whole, comparison of the chemical shifts in Tables 1 and 2 reveals the differences expected on the basis of the linear and angular structures, respectively. Some special features deserve mention. In general, H1 and C1 resonate at clearly higher or lower field, respectively, in linear compounds **4** than in angular compounds **6**. Compound **4h** with a hydroxy substituent at C5, and compound **6c** with a methyl substituent at C4, show distinct H1 and C1 chemical shifts due to the effects caused by the substituents mentioned. In compounds **4**, in consequence of the coplanarity with the carbonyl groups, H8 resonates at exceptionally low field (Table 1a,b). It is therefore relatively easy to distinguish linearly- (**4**) and angularly- condensed (**6**) compounds from each other on the basis of their ^{1}H and ^{13}C NMR spectra. In fact the vicinal H,H-coupling constants in the aromatic N-CH-CH-C segments are clearly smaller (by *ca.* 1.5 Hz) than in the C-CH-CH-C segments (Table 3). The coupling constants were extracted by PERCH [11].

Carboxamides **5** have an additional chiral carbon (C4) in the homoadamantane moiety, and consequently, they have no plane of symmetry. All the protons and carbons in the carbocyclic moiety are therefore chemically inequivalent. The irradiation of H4 demonstrated an NOE enhancement in H11eq (for **5f**), allowing the correct assignment of the signals within the pairs 2/11, 1/8 and 7/10. All of compounds **5** exhibited the presence of small amounts of the enol form of the homoadamantone moiety. The carbon signals corresponding to this minor form could not be resolved because of its small concentration. In the ^{1}H spectra, however, some of the signals of the enol forms were resolved as follows: 2.51–2.53 ppm (H6), 2.62–2.66 ppm (H3) and 14.46–14.64 ppm (5-OH). The tautomeric ratios (keto/enol) were in all cases ≥ 20.

The ^{1}H spin sub-system of the homoadamantane moiety is relatively complex as a result of the overlapping strongly coupled signals, and the reported chemical shift values of these signals may be inaccurate.

X-ray Structures.

During crystallization **4c** undergoes spontaneous resolution, which results in an enantiomeric space group $P4_12_12$. Additionally, it contains linear ring junctions, lying on the twofold axes that are the plane diagonals of the tetragonal unit cell. Since the overall C_2 molecular symmetry is violated by the three heteroatoms N3, N9 and O10 and the

Table 1a
^{1}H NMR Chemical Shifts of Compounds **4a–f** in $CDCl_3$ at 25 °C

Compd	**4a**	**4b**	**4c**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**
R^1	H	H	Me	H	H	NH_2	H	OH	H
R^2	H	Me	H	Br	Cl	H	H	H	NO_2
R^3	Me	H	H	H	H	H	H	H	H
R^4	H	H	H	H	H	H	OH	H	H
H1	3.03	3.05	2.95	3.05	3.05	2.91	4.04	3.01	3.08
H5	7.31	7.47	7.28	7.41	7.48	6.72	–	6.92	7.55
H6	–	7.49	7.32	7.64	7.55	7.30	8.05	7.56	8.23
H7	6.91	–	6.59	–	–	5.89	7.46	6.23	–
H8	8.91	8.83	–	9.13	9.03	–	8.77	–	9.96
H12	3.77	3.80	3.63	3.77	3.77	3.58	3.71	3.56	3.75
H13*ax*,H19*ax*	2.05	2.07	2.05	2.05	2.05	2.02	2.08	2.07	2.06
H13*eq*,H19*eq*	1.78	1.78	1.77	1.77	1.77	1.74	1.80	1.73	1.78
H14, H16	2.15	2.16	2.14	2.16	2.16	2.12	2.23	2.15	2.19
H15x, H15y	1.84; 1.86	1.86	1.84	1.85; 1.87	1.85; 1.87	1.82	1.89	1.84	1.87; 1.89
H17*ax*,H18*ax*	2.03	2.04	2.01	2.03	2.04	2.01	2.16	2.04	2.06
H17*eq*,H18*eq*	1.96	1.96	1.95	1.95	1.95	1.93	2.04	1.92	1.96
R	2.45	2.41	3.03	–	–	7.51	n.d.	1.60	–

Table 1b

^{13}C NMR Chemical Shifts of Compounds **4a–f** in $CDCl_3$ at 25 °C

Compd	**4a**	**4b**	**4c**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**
R^1	H	H	Me	H	H	NH_2	H	OH	H
R^2	H	Me	H	Br	Cl	H	H	H	NO_2
R^3	Me	H	H	H	H	H	H	H	H
R^4	H	H	H	H	H	H	OH	H	H
C1	43.83	43.76	43.07	43.74	43.72	43.36	36.99	43.98	43.68
C2	172.66	171.91	170.36	172.34	172.30	172.09	162.65	175.35	173.32
C4	148.56	147.46	150.89	146.82	146.76	151.41	138.20	160.82	147.82
C5	124.14	125.51	125.09	127.13	127.10	111.79	147.49	112.61	127.18
C6	146.45	137.57	133.74	137.87	135.80	136.93	119.74	139.24	127.23
C7	117.65	125.09	117.87	110.21	123.61	97.77	125.45	100.07	138.21
C8	127.02	125.08	143.54	127.79	125.43	150.65	119.67	149.30	128.28
C10	157.74	157.56	161.92	156.81	156.91	163.50	154.94	164.64	157.48
C11	120.74	121.53	123.55	122.74	122.66	119.65	121.07	118.38	124.13
C12	27.96	28.04	27.75	28.12	28.12	27.35	28.75	26.63	28.12
C13,C19	34.58	34.55	34.56	34.32	34.32	34.87	33.49	34.69	33.99
C14,C16	28.35	28.35	28.36	28.27	28.27	28.15	27.75	28.01	28.19
C15	35.76	35.75	35.78	35.63	35.63	35.66	34.98	35.43	35.49
C17,C18	33.08	33.11	33.07	32.92	32.93	33.15	32.26	33.00	32.67
Me	21.31	18.37	24.71	–	–	–	–	–	–

Table 2a

^1H NMR Chemical Shifts of Compounds **6a–f** in $CDCl_3$ at 25 °C

Compd	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**
R^1	H	H	Me	H	H	H
R^2	H	Me	H	H	Br	Cl
R^3	Me	H	H	H	H	H
R^4	H	H	H	H	H	H
H1	3.49	3.55	3.02	3.52	3.45	3.47
H4	7.92	7.80	–	8.04	8.15	8.09
H5	6.59	–	6.57	6.76	–	–
H6	–	7.30	7.28	7.43	7.47	7.39
H7	7.09	7.26	7.07	7.31	7.21	7.27
H12	3.96	3.99	3.83	3.96	3.95	3.95
H13*ax*,H19*ax*	1.98	1.99	1.96	1.97	2.00	2.00
H13*eq*,H19*eq*	1.80	1.82	1.82	1.80	1.80	1.80
H14,H16	2.19	2.21	2.18	2.19	2.22	2.22
H15x,H15y	1.85	1.85; 1.92	1.76; 1.85	1.84; 1.90	1.87; 1.94	1.86; 1.92
H17*ax*,H18*ax*	2.06	2.09	1.98	2.07	2.11	2.12
H17*eq*,H18*eq*	1.90	1.91	1.91	1.91	1.92	1.92
Me	2.34	2.31	2.56	–	–	–

Table 3

Selected aromatic $^1H,^1H$ coupling constants [Hz] for compounds **4a**-**c**, and **6a**-**d** in $CDCl_3$ at 25°C

Compound	**4a**	**4b**	**4c**	**6a**	**6b**	**6c**	**6d**
R^1	H	H	Me	H	H	Me	H
R^2	H	Me	H	H	Me	H	H
R^3	Me	H	H	Me	H	H	H
R^4	H	H	H	H	H	H	H
H4,H5	-	-	-	7.51	-	-	7.42
H4,H6	-	-	-	-	1.94	-	1.36
H5,H6	-	9.07	8,85	-	-	6.71	6.55
H5,H7	1.90	-	2.32	2.15	-	1.48	1.62
H6,H7	-	-	7.07	-	9.09	8.93	9.03
H6,H8	-	2.06	-	-	-	-	-
H7,H8	7.32	-	-	-	-	-	-

Table 2b

^{13}C NMR Chemical Shifts of Compounds **6a–f** in $CDCl_3$ at 25 °C

Compd	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**
R^1	H	H	Me	H	H	H
R^2	H	Me	H	H	Br	Cl
R^3	Me	H	H	H	H	H
R^4	H	H	H	H	H	H
C1	31.19	31.21	36.96	31.21	31.49	31.49
C2	152.08	152.31	153.39	152.49	149.81	149.77
C4	126.38	124.51	140.49	127.19	127.15	125.09
C5	115.41	122.39	116.46	112.76	106.91	120.54
C6	145.69	136.89	133.79	133.95	137.31	135.31
C7	123.70	125.49	122.47	125.83	126.79	126.70
C8	151.45	150.46	153.42	151.37	152.79	152.31
C10	167.72	167.60	167.80	167.47	167.18	167.21
C11	133.45	133.91	136.03	134.07	134.35	134.36
C12	27.90	28.00	28.92	27.95	28.04	28.05
C13,C19	32.74	32.80	32.68	32.67	32.63	32.63
C14,C16	27.80	27.84	28.05	27.73	27.71	27.71
C15	35.21	35.25	35.29	35.12	35.07	35.07
C17,C18	32.32	32.38	33.44	32.25	32.26	32.25
Me	20.85	18.36	24.12	–	–	–

methyl group, the crystallographic twofold symmetry can be maintained by rotational disorder of the planar pyridopyrimidinone tail. While the homoadamantyl moiety is located on the twofold axis, the aromatic rings are significantly displaced from it (Figure 2). The twofold axis is defined by the positions of C15 and C7. Along the twofold rotor, N9 displaced.

Compounds **6e** and **6f** differ only in their halogen (bromine versus chlorine) substituent, and their monoclinic crystals therefore exhibit a rather high degree of isostructurality [11,12]. Their intramolecular bonding and conformation hardly differ. In both structures (Figure 3a and 3b), the angular ring junctions give rise to a rather short H···H contact between the sp^3-C1 and the aromatic C4. The planarity of the pyridopyrimidinone moieties [the torsion angles C1–C2–N3–C4 are 4.4(2)° (Cl) and 5.4(4)° (Br)] do not allow a greater separation of H1 and H4 than 1.84 Å (Cl) and 1.89 Å (Br).

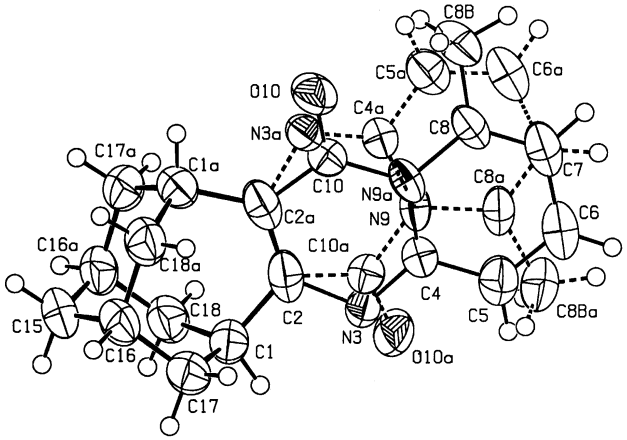


Figure 2. Perspective molecular view of **4c**, showing heavy atoms with their vibrational ellipsoids at 50% probability level. The rotational disorder of the pyridopyrimidinone moiety is distinguished by solid and dashed lines. The crystallograpic twofold axis is defined by C7 and C15, while the symmetry-equivalent atoms are differentiated by the suffix "a".

Mass Spectra.

Carboxamides **5**.

The fragments corresponding to the base peaks in the spectra of **5a**–**f** are always the protonated 2-aminopyridine derivative. This reaction possibly occurs predominantly through the enol form, either because of its enhanced stability in the gas phase or because of the easier access of the hydroxy proton of the enol. The counterion of the protonated 2-aminopyridines, $C_{12}H_{14}O_2^{+\bullet}$, *m/z* 190, which is equal to the ion $[M–EtOH]^{+\bullet}$ released from the enol form of compound **2**, is also present in most of the spectra, the relative abundance depending on the stabilizing/destabilizing effect of the R^1–R^3 substitution.

Linearly- (4) and Angularly-condensed (6) Pyridopyrimidinones.

Although the same peaks can be found in the low-resolution spectra of correspondingly substituted linearly- and angularly- condensed homoadamantane pyridopyrimidinones (Table 4), the two isomers can be readily identified on the basis of their respective mass spectra, as seen from Figure 4. The main features of the fragmentations of series 4 and 6 are summarized in Scheme 6. The main differences in the mass spectra of compounds 4 and 6 are as follows:

1. The relative abundance (RA) of the $[M–H]^+$ peak in series **4** is only 3–7% whereas in series **6** it is 70–92%, with the exception of **6c** (11%). Table 5 lists the ratios

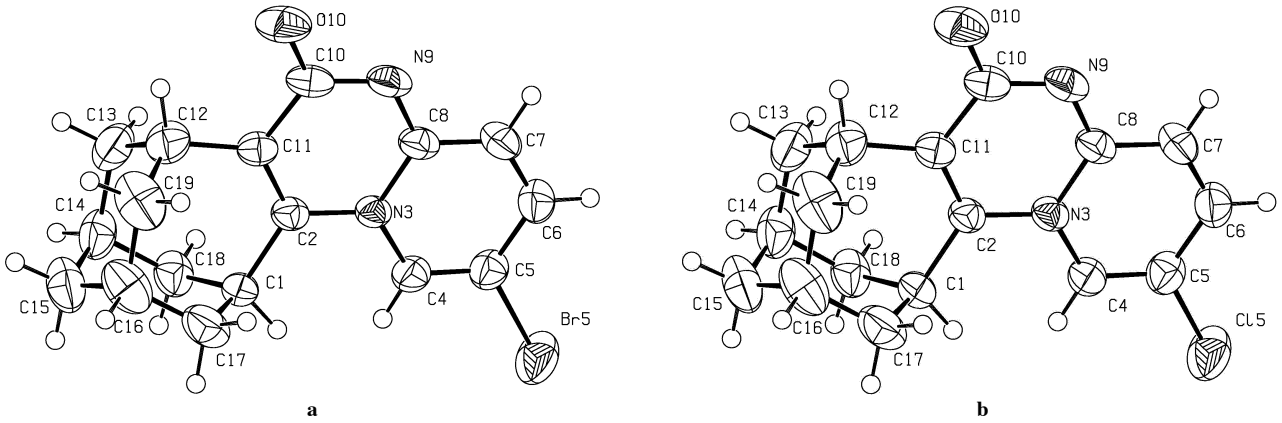


Figure 3. Perspective molecular views of **6e** (a) and **6f** (b), showing heavy atoms with their vibrational ellipsoids at the 50% probability level. The overall geometries of these compounds are rather similar.

Table 4

Mass Spectral Fragments (mostly with relative abundance (RA) ≥ 5%) for Studied Compounds. Peaks below m/z 50 are not listed

Compd	*m/z* (RA, %)
4a	280($M^{+\bullet}$,100), 279(8), 265(13), 252(4), 251(6), 239(20), 238(8), 237(15), 225(10), 224(10), 223(11), 212(5), 211(18), 210(5), 209(5), 195(6), 91(17), 65(11)
4b	280($M^{+\bullet}$,100), 279(7), 265(15), 252(5), 251(7), 239(21), 238(9), 237(15), 225(10), 224(10), 223(10), 212(5), 211(17), 210(6), 209(6), 195(6), 92(13), 65(10)
4c	280($M^{+\bullet}$,100), 279(7), 265(7), 252(23), 251(10), 239(9), 238(5), 237(16), 225(5), 224(6), 223(8), 211(12), 210(6), 209(10), 197(6), 196(5), 195(9), 183(7), 93(5), 92(18), 65(12)
4e	346($M^{+\bullet}$,100), 345(25), 344($M^{+\bullet}$,100), 343(5), 331(11), 329(11), 318(5), 317(7), 316(5), 315(6), 305(15), 304(9), 303(26), 302(7), 301(11), 291(7), 290(9), 289(14), 288(8), 287(8), 277(13), 276(7), 275(16), 261(7), 158(11), 156(11), 77(8), 76(7)
4f	302($M^{+\bullet}$,35), 301(22), 300($M^{+\bullet}$,100), 299(5), 285(13), 272(6), 271(6), 261(6), 260(5), 259(21), 258(7), 257(13), 245(10), 244(9), 243(8), 233(6), 232(5), 231(15), 229(5), 217(5), 215(5), 112(12), 76(5)
4g	281($M^{+\bullet}$,100), 280(13), 266(9), 253(8), 252(9), 240(8), 239(6), 238(16), 226(7), 225(10), 224(14), 213(5), 212(15), 211(5), 210(8), 198(6), 196(6), 184(5), 94(6), 93(16), 66(10)
4h	282($M^{+\bullet}$,100), 281(4), 267(11), 254(4), 253(6), 241(16), 240(6), 239(11), 227(7), 226(8), 225(8), 213(12)
4i	282($M^{+\bullet}$,100), 281(3), 267(3), 254(32), 253(5), 239(7), 225(5), 213(10), 199(5), 185(7), 94(5), 85(13), 83(21), 66(6)
4j	311($M^{+\bullet}$,100), 310(4), 296(11), 283(6), 282(5), 270(12), 269(7), 268(9), 256(7), 255(8), 254(6), 242(12), 76(8)
6a	280($M^{+\bullet}$,100), 279(70), 278(8), 265(5), 252(3), 251(6), 239(26), 238(6), 237(10), 225(9), 213(7), 212(8), 211(35), 199(11), 112(5), 92(9), 91(6), 77(7), 65(9)
6b	280($M^{+\bullet}$,100), 279(77), 278(8), 265(5), 252(2), 251(5), 239(24), 238(6), 237(10), 225(8), 213(7), 212(8), 211(34), 199(11), 112(5), 105(5), 92(8), 91(6), 77(7), 65(10)
6c	280($M^{+\bullet}$,87), 279(11), 265(100), 252(11), 251(8), 239(19), 238(5), 237(10), 225(6), 224(7), 223(7), 213(5), 212(8), 211(26), 209(7), 199(7), 197(5), 195(7), 183(5), 135(9), 105(7), 92(13), 91(12), 79(7), 78(5), 77(10), 66(5), 65(17), 53(5)
6d	266($M^{+\bullet}$,100), 265(71), 264(9), 251(4), 238(2), 237(6), 225(25), 224(6), 223(10), 211(9), 199(7), 198(8), 197(35), 185(11), 105(8), 91(8), 79(6), 78(15), 77(8), 65(5), 51(6)
6e	346($M^{+\bullet}$,93), 345(100), 344($M^{+\bullet}$,93), 343(86), 329(4), 317(6), 316(2), 315(6), 305(22), 304(11), 303(33), 302(8), 301(12), 291(8), 290(5), 289(10), 279(6), 278(8), 277(35), 276(8), 275(32), 265(12), 264(7), 263(13), 262(5), 168(5), 158(5), 156(5), 131(6), 128(5), 121(5), 115(6), 104(5), 103(8), 91(15), 79(9), 78(8), 77(18), 76(7), 65(9), 53(5), 51(6)
6f	302($M^{+\bullet}$,33), 301(40), 300($M^{+\bullet}$,100), 299(71), 298(9), 285(4), 272(3), 271(6), 261(8), 260(6), 259(29), 258(7), 257(11), 245(9), 233(17), 232(9), 231(34), 221(5), 220(5), 219(11), 155(5), 129(5), 128(6), 105(6), 103(5), 91(10), 78(7), 77(14), 76(7), 65(7), 53(6), 51(8)

$M^{+\bullet}/[M-H]^+$ for compounds **4** and **6**. They demonstrate even better the great difference for the hydrogen loss in these compounds since the ratio varies from 12 to 23 for **4a–4h**, and is even somewhat larger for **4i** and **4j**, whereas in series **6** it is much smaller and practically constant, at about 1.3. However, for **6c** this ratio is *ca*. 8, which supports the postulation that in this series it is H4 which is lost most easily, because of its steric crowding as compared with any of the respective protons in series **4**. The NH_2 substituent on C8 also seems to facilitate the loss of hydrogen ($M^{+\bullet}/[M-H]^+$ ~8).

2. The ratios $M^{+\bullet}/[M-CH_3]^+$ for **4** are in most cases roughly between 7 and 9, except for compounds **4c**, **4g** and **4i**. In all of these exceptions, there is a substituent at C8 (Me, NH_2 or OH), which apparently interacts with the parallel C=O in such a way that reactions other than methyl loss from the homoadamantanone moiety are relatively more favoured. This is in line

with what is said below, except that the NH_2 in **4g** seems to depress the loss of CO, obviously as a consequence of relatively strong hydrogen bonding. In series **6**, the relative loss of methyl is less abundant resembling that in **4c**, **4g** and **4i**, an exception is **6c**, where steric factors clearly enhance the presence of the ion $[M–CH_3]^+$, which is even slightly more abundant than $M^{+\bullet}$.

3. In series **4**, the ratio $M^{+\bullet}/[M–CO]^{+\bullet}$ varies from 19 to 41 (Table 5) with the exceptions of compounds **4c**, **4g**, and **4i** again where C8 has either a methyl (ratio 4.4), an NH_2 (ratio 14) or a hydroxy substituent (ratio 3.1), which obviously facilitates the loss of CO because of steric crowding. In series **6**, the above ratio is always clearly higher (from 65 to 100), except for compound **6c** (8.1), where the R^1 = Me substitution seems (again for steric reasons), to affect the whole primary fragmentation pattern of this compound, the lower loss of hydrogen being accompanied by an increased loss of the methyl substituent, together with an enhanced loss of the carbonyl. The loss of HCO exhibits already much less stereospecificity.
4. Compounds **6** lose significantly more of the fragments $C_5H_9^{\bullet}$ and $C_6H_9^{\bullet}$, whereas the series **4** compounds tend to lose more $C_4H_9^{\bullet}$. In fact, the alkyl loss patterns are typically different for series **4** and **6** (Figure 4). Otherwise, the formation of the fragments $[M–Alk]^+$ resembles that of the adamantane derivatives [13–15].

Table 5

Relative Abundances of loss of $H^{\bullet}$, $CH_3^{\bullet}$, CO and $HCO^{\bullet}$ from Compounds **4** and **6** as Compared with that of $M^{+\bullet}$. The Numbers in Parentheses are the Relative Contributions of CO/C_2H_4 and HCO/C_2H_5

Compd	$M^{+\bullet}/[M–H]^+$	$M^{+\bullet}/[M–CH_3]^+$	$M^{+\bullet}/[M–CO]^{+\bullet}$	$M^{+\bullet}/[M–HCO]^+$
4a	12	7.7	41 (2:1)	31 (1:1)
4b	13	6.8	29 (2:1)	29 (1:1)
4c	15	14	4.4 (only CO)	12 (8:1)
4e	22	8.7	19 (only CO)	16 (only HCO)
4f	20	7.8	21 (5:1)	26 (3:2)
4g	7.8	12	14 (6:1)	14 (5:1)
4h	23	9.1	32 (3:1)	30 (3:2)
4I	39	33	3.2 (only CO)	24 (7:1)
4j	28	8.8	20 (6:1)	39 (1:1)
6a	1.4	22	77 (1:1)	48 (1:2)
6b	1.3	21	88 (1:1)	75 (1:3)
6c	7.9	0.9	8.1 (only CO)	41 (1:3)
6d	1.4	24	100 (3:4)	53 (1:2)
6e	1.1	23	80 (1:1)	∞ (only C_2H_5)
6f	1.4	27	65 (1:1)	69 (1:3)

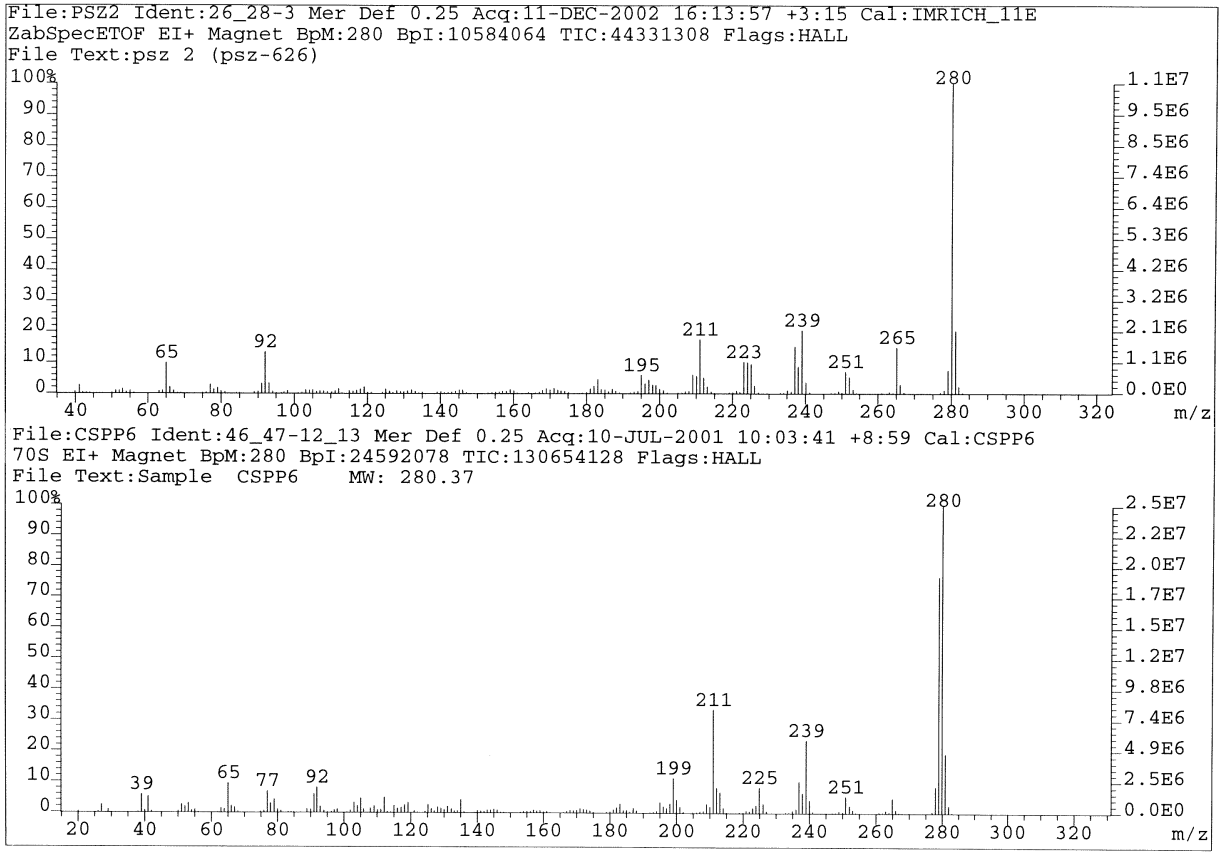


Figure 4. Low-resolution mass spectra of compounds **4b** (top) and **6b** (bottom).

Conclusion.

In contrast with earlier data [7], which indicated only the formation of the linearly-condensed pyridopyrimidinones, the present paper describes the syntheses of both linearly and angularly homoadamantane-fused pyridopyrimidinones. The structures were proved by ^{1}H and ^{13}C NMR, mass spectrometric fragmentation and X-ray structure studies.

EXPERIMENTAL

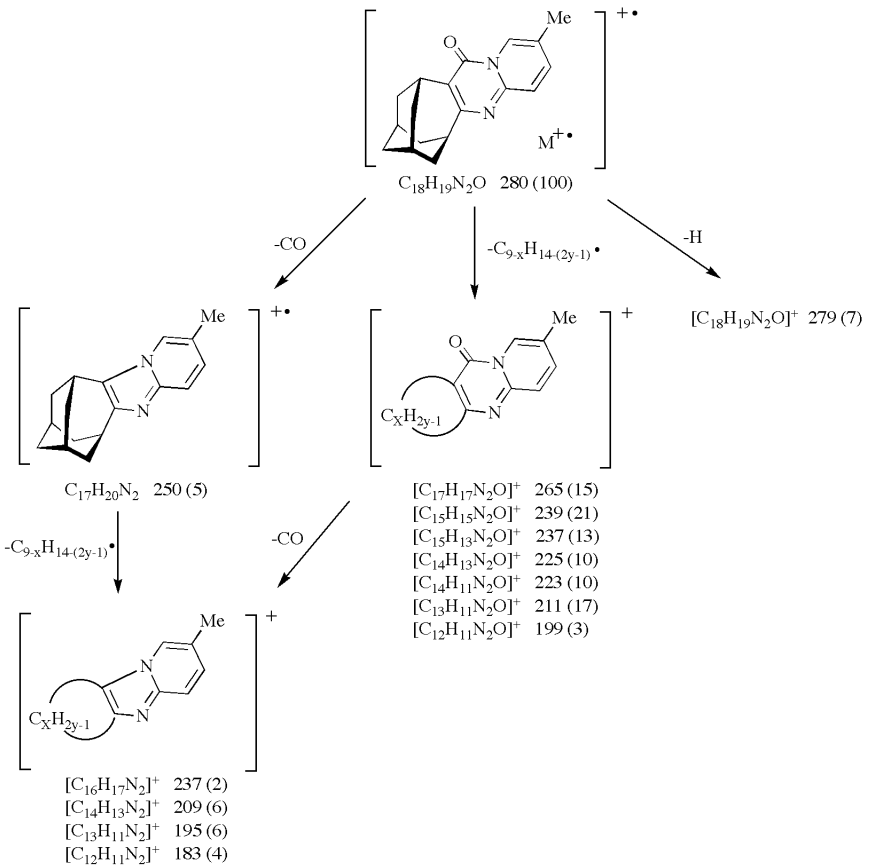
NMR.

The ^{1}H and ^{13}C NMR spectra were acquired with JEOL JNM-LA400 (^{1}H: 399.78 MHz, ^{13}C: 100.54 MHz) and JEOL JNM-A500 (^{1}H: 500.16 MHz, ^{13}C: 125.78 MHz) NMR spectrometers in $CDCl_3$ at 25 °C, with tetramethylsilane (TMS) as an internal reference (δ = 0.00 ppm for both ^{1}H and ^{13}C). 1D Proton spectra were acquired by applying normal 450° single-pulse excitation, with spectral widths of 8 kHz, consisting of 32 k data points, using 16–64 scans. ^{13}C spectra with broad-band proton decoupling consisted of 65 k data points within a 30 kHz frequency range, and were accumulated by using 45° single-pulse excitations until a sufficient S/N ratio was achieved (100–3000 scans). 0.3 Hz exponential weighting was applied prior to Fourier transformation. In homonuclear NOE difference experiments, the ^{1}H spectra had 8 k data points in an 8 kHz spectral range, and irradiation times of 7–10 s were employed. The percentage NOE enhancement for the proton signals was estimated by giving a reference value of –100% to the integral of the irradiated signal. DEPT 135° experiments were optimized for 145 Hz J_{CH} couplings, other parameters being similar to those in the basic carbon measurement. In 2D correlation spectra, spectral widths were optimized by using the corresponding 1D spectra. 2D FIDs were zero-filled (t_2: × 1 or × 2, t_1: × 2 or × 4) and weighted (0.3 Hz exponential decay together with a shifted sine bell) prior to FT. 2D experiments consisted of phase-sensitive DQF-COSY, f_1-decoupled CH shift correlation (optimized for 145 Hz $^1J_{CH}$) and COLOC (optimized for 8 Hz $^nJ_{CH}$). NOE difference and COLOC were employed for at least one compound in each sub-series (**4**, **5** and **6**) in order to confirm the chemical shift assignments. The other compounds were then assigned by analogy.

X-ray Crystallography of **4c, 6e** and **6f**.

Details of the cell data, data collection and refinement are provided in Table 5. Each data set was collected on CAD-4 diffractometer *via* either graphite- monochromated Cu-K_α (**4c** and **6f)** or Mo-K_α radiation (**6e**). The data sets were corrected against absorption by the use of a psi-scan. The space groups were determined from the unit cell symmetry and systematic absences. The crystallographic phase problems were solved by direct methods,

Scheme 6



using the program *SHELXS*97 [16]. The atomic positions for each structure were refined with anisotropic displacement parameters in the F^2 mode, using the program *SHELXL*97 [17]. The hydrogen atoms were placed in calculated ideal positions on their respective heavy atoms and were refined in the riding mode. The absolute structure of **4c**, in the polar space group $P4_12_12$, was determined by refining the Flack parameter [18]. The rotational disorder shown by the aromatic part of **4c** was refined with occupancy factors of 0.5.

Mass Spectra.

The 70 eV mass spectra were recorded on a VG ZabSpec oaTOF instrument or a VG Analytical 7070E instrument, both equipped with an Opus data system. Low-resolution spectra were measured either on the VG Analytical 7070E (**5b**,**c**,**e**,**f**,**6a–d** and **6f**), for which the acceleration voltage was 6 kV, the ionization current was 100 μA and the temperature of the ion source was ~450 K, or on the VG ZabSpec oaTOF (**4a–c**,**e–j**,**5a**,**5d**, and **6e**), for which the acceleration voltage was 8 kV, the ionization current was 200 μA and the source temperature was ~430 K.

With only a few exceptions accurate mass measurements by peak matching (10% valley) and metastable measurements (1st FFR) were carried out on the VG ZabSpec oaTOF instrument. The samples were introduced into the mass spectrometer *via* the solid inlet system. The probe tip was heated only when necessary. The resolution used was ~1000 (VG Analytical 7070E) or 2000–3000 (VG ZabSpec oaTOF) for low-resolution and metastable measurements, and 4000–5000 (VG Analytical 7070E) or 9000–12000 (VG ZabSpec oaTOF) for high-resolution measurements.

Adamantan-2-one, ethyl diazoacetate, boron trifluoride diethyl etherate, 2-aminopyridines and solvents were products of Aldrich, Fluka or Merck with 95–99% purity. All solvents were purified and dried by standard methods. Preparative chromatographic separations were performed by means of column chromatography on Merck Kieselgel 60 (0.040–0.063 μm). Melting points were determined by the hot-plate method and are uncorrected. Elemental analyses were carried out with a Perkin–Elmer 2400 CHNS instrument.

Ethyl 5-Oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate and Ethyl 5-Oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate difluoroborate (**2** and **3**).

To a solution of adamantan-2-one (**1**) (10 g, 0.067 mol) in dichloromethane (70 mL), boron trifluoride diethyl etherate (10.8 g, 0.072 mol) was added at 0 °C. To this reaction mixture, ethyl diazoacetate (12.2 mL, 0.116 mol) was added dropwise and the solution was stirred under a nitrogen atmosphere at 0 °C for 6–8 hours. The resulting mixture was neutralized with saturated aqueous sodium bicarbonate solution (300 mL). The organic layer was separated off and dried over magnesium sulfate. After filtration, the solvent was evaporated. From the resulting mixture, **3** was collected by filtration (7.4 g, 39%) and washed with diisopropyl ether (3 × 10 mL). The combined filtrate was subjected to evaporation and the resulting crude **2** was purified by vacuum distillation (6 mmHg, 5.8 g, 37%).

Table 6

Crystal data and details of data collection and final refinement calculations for the compounds studied

	4c	**6e**	**6f**
CCDC deposition number	CCDC 205382	CCDC 205383	CCDC 205384
Chemical formula	$C_{18}H_{20}N_2O$	$C_{17}H_{17}BrN_2O$	$C_{17}H_{17}ClN_2O$
Formula weight	280.36	345.24	300.78
Crystal system,	tetragonal $P4_12_12$	monoclinic $P2_1/n$	monoclinic $P2_1/n$
Space group	(No. 92)	(No. 14)	(No. 14)
a, *b*, *c* [Å]	10.548(1), 10.548(1), 13.283(1)	11.131(1), 11.346(2), 12.700(1)	11.096(1), 11.358(1), 12.570(1)
Alpha, beta, gamma [deg]	90, 90, 90	90, 111.10(1), 90	90, 111.10(1), 90
V [Å^3]	1477.9(2)	1496.4(3)	1478.0(2)
Z	4	4	4
D(calc) [g/cm^3]	1.26	1.53	1.35
μ [/mm]	0.62	2.75	2.28
F(000)	600	704	632
Crystal size [mm]	0.25x0.30x0.45	0.30x0.40x0.50	0.20x0.30x0.35
Temperature (K)	293	293	293
Radiation λ [Å]	Cu-*K*α 1.54180	Mo-*K*α 0.71070	Cu-*K*α 1.54180
Theta min-max [deg]	5.3, 74.9	2.5, 28.0	4.6, 75.0
Dataset	−13:13; −13:13; −16:16	−14:13; −14:0 ; 0:16	−12:13; −14:0; −15:0
Tot., uniq. data, *R*(int)	12718, 1522, 0.045	3861, 3593, 0.043	3275, 3033, 0.032
Observed data [$I > 2.0\ \sigma(I)$]	1461	2124	2684
*N*ref, *N*par	1522, 139	3593, 190	3033, 191
R, *wR*2, *S*	0.0388, 0.1467, 1.29	0.0518, 0.1573, 1.00	0.0515, 0.1838, 1.59
$w =$ where $P=(Fo^2+2Fc^2)/3$	$1/[\sigma^2(Fo^2)+(0.1000P)^2]$	$1/[\sigma^2(Fo^2)+(0.1000P)^2]$	$1/[\sigma^2(Fo^2)+(0.1000P)^2]$
Flack *x*	0.1(5)	–	–
Max. and av. Shift/error	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min. and max. resd. dens. [e/Å^3]	−0.10, 0.12	−0.79, 0.88	−0.55, 0.32

Ethyl 5-Oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate (**2**) from the Difluoroborate Complex (**3**).

To the solution of sodium ethylate in ethanol [sodium (0.5 g, 1.3 eq.) in ethanol (100 mL)], difluoroborate complex **3** (5 g, 0.018 mol) was added. After **3** had completely dissolved, the reaction mixture was stirred for 2 hours at room temperature. The solution was then neutralized with ethanolic hydrochloric acid (20%), and the solvent was evaporated off *in vacuo*. The residue was dissolved in water (5 mL) and extracted with diethyl ether (3 × 10 mL), after which the organic layer was dried over sodium sulfate, filtered and evaporated. The crude product was purified by vacuum distillation (6 mmHg, 2.1 g, 50%).

Ethyl 5-Oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate (**2**).

This compound has bp 128–131 °C (6 mmHg); LRMS: *m/z* (%) = 236 (100, $M^{+\bullet}$), 190 (83, $[M–EtOH]^{+\bullet}$), 179 (34.5), 162 (14), 148 (14), 134 (36.5), 119 (14), 107 (8), 105 (9.5), 93 (20), 92 (25), 91 (27), 67 (17), 55 (18), 53 (10), 41 (24); δ_H (500.16 MHz, $CDCl_3$, 25 °C; keto/enol form) 1.28/1.30 (H15), 1.64/~1.74 (H9x), 1.70/~1.68 (H11eq), 1.71/~1.74 (H9y), 1.77/~1.84 (H7eq), ~1.85/~1.84 (H10eq), ~1.90/~1.68 (H2eq), ~1.93/1.85 (H2ax), 1.94/~1.91 (H7ax), ~1.95/~1.91 (H10ax), 2.00/2.05 (H1), 2.04/2.05 (H8), 2.16/1.85 (H11ax), 2.38/3.05 (H3), 2.83/2.48 (H6), 3.52/- (H4), ~4.18/4.20 (H14x), ~4.22/4.20 (H14y), -/12.81 (5-OH); δ_C (125.78 MHz, $CDCl_3$, 25 °C, keto/enol form) 14.17/14.33 (C15), 26.73/28.09 (C1), 26.73/28.09 (C8), 29.91/26.81 (C3), 31.81/32.04 (C10), 32.20/32.04 (C7), 32.83/34.81 (C2), 35.20/35.75 (C9), 38.31/34.81 (C11), 48.91/39.76 (C6), 61.01/60.39 (C14), 64.23/106.16 (C4), 171.34/173.23 (C12), 212.44/184.06 (C5).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.52.

Ethyl 5-Oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate difluoroborate (**3**).

This compound has mp 135–137 °C; LRMS: *m/z* (%) = 284 (100, $M^{+\bullet}$), 265 (7), 256 (6), 236 (11), 227 (5), 190 (87, $[M–EtOH]^{+\bullet}$), 180 (6.5), 162 (17), 135 (8), 134 (43), 133 (9), 121 (7), 120 (6), 119 (10), 107 (6), 106 (8), 105 (15), 94 (6), 92 (28), 91 (24), 81 (7), 80 (9), 79 (24), 77 (16), 67 (11), 65 (7), 55 (16), 53 (9), 41 (19); δ_H (500.16 MHz, $CDCl_3$, 25 °C) 1.42 (3 H, H15), 1.66 (2 H, H2eq/H11eq), 1.76 (1 H, H9x), 1.78 (1 H, H9y), 1.90 (2 H, H7eq/H10eq), 1.91 (2 H, H2ax/H11ax), 1.94 (2 H, H7ax/H10ax), 2.10 (2 H, H1/H8), 2.69 (1 H, H6), 2.98 (1 H, H3), 4.49 (2 H, H14); δ_C (125.78 MHz, $CDCl_3$, 25 °C) 14.10 (1 C, C15), 25.76 (1 C, C3), 27.57 (2 C, C1/C8), 31.36 (2 C, C7/C10), 34.65 (2 C, C2/C11), 35.13 (1 C, C9), 41.77 (1 C, C6), 65.95 (1 C, C14), 103.61 (1 C, C4), 173.13 (1 C, C12), 194.36 (1 C, C5).

Anal. Calcd. for $C_{14}H_{19}BF_2O_3$: C, 59.19; H, 6.74. Found: C, 59.06; H, 6.72.

General Reaction in PPA.

A mixture of β-oxoester **2** (0.2 g, 0.85 mmol) and 2-aminopyridine (0.7 mmol) in PPA (2.5 g) was stirred at 100 °C for 2 hours. After cooling, water (2–5 mL) was added to the reaction mixture and the pH was corrected to 8–9 with sodium hydroxide solution (10%, w/w). The mixture was extracted with chloroform (3 × 25 mL) and the organic layer was dried over sodium sulfate and concentrated *in vacuo*, yielding the crude products, which were separated by column chromatography (petroleum ether (bp 40–60 °C)/ethyl acetate 1/1).

General Reaction in a Mixture of PPA and Phosphorus Oxychloride.

A mixture of β-oxoester **2** (0.2 g, 0.85 mmol) and 2-aminopyridine (0.7 mmol) in PPA (2.6 g) was stirred at 100 °C for 2 hours. Phosphorus oxychloride (0.5 mL) was then added and the reaction was allowed to proceed for 1 hour at the same temperature. The work-up of the reaction mixture was performed as described previously. The crude products were separated by column chromatography on silica gel (petroleum ether (bp 40–60 °C)/ethyl acetate 2/1).

General Reaction in Toluene in the Presence of *p*-Toluenesulfonic Acid.

To a solution of β-oxoester **2** (2.0 g, 8.5 mmol) and 2-aminopyridine (7.0 mmol) in toluene (80 mL), a catalytic amount of *p*-toluenesulfonic acid (5 μg) was added. The reaction mixture was refluxed until the water formed had been quantitatively separated by azeotropic distillation. After cooling, the reaction mixture was washed with saturated sodium carbonate solution (5%, w/w), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by recrystallization from ethyl acetate:ethanol.

Cyclization of Carboxamides **5a**–**f** in a Mixture of PPA and Phosphorus Oxychloride.

A mixture of carboxamide (1 mmol), PPA (0.1 g) and phosphorus oxychloride (0.3 mL) was stirred at 100 °C. After 1 hour, further phosphorus oxychloride (0.15 mL) was added to the reaction mixture. The reaction was allowed to proceed for 30 minutes. After cooling, water (2–5 mL) was added to the reaction mixture and the pH was corrected to 8 with sodium hydroxide solution (10%, w/w). The mixture was extracted with chloroform (3 × 30 mL), and the organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (chloroform/methanol 9/1).

6-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4a**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 40%; mp 207–209 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.98; H, 7.18; N, 9.97.

7-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4b**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 43%; mp 200–203 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.01; H, 7.18; N, 10.00.

8-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4c**)

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 37%; mp 232–233 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.18; H, 7.20; N, 10.01.

7-Bromo-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4e**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 28%; mp 215–218 °C.

Anal. Calcd. for $C_{17}H_{17}BrN_2O$: C, 59.14; H, 4.96; N, 8.11. Found: C, 59.35; H, 4.97; N, 8.08.

7-Chloro-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4f**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 27%; mp 206–209 °C.

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 68.01; H, 5.71; N, 9.36.

8-Amino-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4g**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 38%; mp 362–364 °C.

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.37; H, 6.75; N, 15.08.

5-Hydroxy-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4h**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 42%; mp 209–212 °C.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.53; H, 6.50; N, 9.95.

8-Hydroxy-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4i**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 35%; mp 290–295 °C.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.48; H, 6.49; N, 9.88.

7-Nitro-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{4,9}]-nonadeca-2(11),3,5,7-tetraene (**4j**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 39%; mp 253–255 °C.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.75; H, 6.47; N, 13.48.

N-(4'-Methylpyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5a**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 44%; mp 145–148 °C; LRMS *m/z* (%): 298 (34, $M^{+\bullet}$), 270 (8, $[M-CO]^{+\bullet}$), 191 (6), 190 (36), 177 (8), 135 (24), 134 (23), 119 (9), 109 (20), 108 (100), 107 (6), 106 (5), 105 (10), 94 (5), 93 (16), 92 (34), 91 (23), 81 (25), 80 (45), 79 (25), 78 (9), 77 (15), 68 (7), 67 (10), 66 (9), 65 (11), 55 (8), 53 (16), 52 (6), 51 (7); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.67 (1 H, H9x), 1.68 (1 H, H11eq), 1.71 (1 H, H9y), 1.80 (1 H, H7eq), ~1.88 (2 H, H10ax & H10eq), 1.97 (1 H, H7ax), ~2.00 (2 H, H1 & H2ax), ~2.01 (1 H, H2eq), 2.06 (1 H, H8), 2.24 (1 H, H11ax), 2.35 (3 H, CH_3), 2.73 (1 H, H3), 2.93 (1 H, H6), 3.44 (1 H, H4), 6.86 (1 H, H5'), 8.04 (1 H, H3'), 8.14 (1 H, H6'), 9.22 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 21.36 (1 C, CH_3), 26.55 (1 C, C8), 26.59 (1 C, C1), 28.78 (1 C, C3), 31.92 (1 C, C10), 31.93 (1 C, C7), 33.21 (1 C, C2), 34.83 (1 C, C9), 38.24 (1 C, C11), 49.72 (1 C, C6), 64.28 (1 C, C4), 114.69 (1 C, C3'), 121.01 (1 C, C5'), 147.57 (1 C, C6'), 149.72 (1 C, C4'), 151.28 (1 C, C2'), 167.57 (1 C, C12), 214.95 (1 C, C5).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.29; H, 7.44; N, 9.41.

N-(5'-Methylpyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5b**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 39%; mp 148–150 °C; LRMS *m/z* (%): 298 (37, $M^{+\bullet}$), 270 (6, $[M-CO]^{+\bullet}$), 190 (2), 177 (7), 135 (31), 134 (2), 119 (2), 109 (19), 108 (100), 107 (9), 93 (5), 92 (9), 91 (5), 81 (7), 80 (5), 79 (7), 67 (6), 65 (5), 55 (5), 53 (5); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.64 (1 H, H9x), 1.67 (1 H, H11eq), 1.73 (1 H, H9y), 1.78 (1 H, H7eq), ~1.88 (2 H, H10ax & H10eq), 1.99 (1 H, H7ax), ~2.00 (3 H, H1 & H2ax & H2eq), 2.05 (1 H, H8), 2.23 (1 H, H11ax), 2.29 (3 H, CH_3), 2.72 (1 H, H3), 2.92 (1 H, H6), 3.44 (1 H, H4), 7.50 (1 H, H4'), 8.07 (1 H, H3'), 8.10 (1 H, H6'), 9.28 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 17.83 (1 C, CH_3), 26.55 (1 C, C8), 26.59 (1 C, C1), 28.79 (1 C, C3), 31.93 (1 C, C10), 31.94 (1 C, C7), 33.19 (1 C, C2), 34.84 (1 C, C9), 38.24 (1 C, C11), 49.72 (1 C, C6), 64.21 (1 C, C4), 113.69 (1 C, C3'), 129.12 (1 C, C5'), 138.77 (1 C, C4'), 147.82 (1 C, C6'), 149.17 (1 C, C2'), 167.40 (1 C, C12), 215.07 (1 C, C5).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.54; H, 7.44; N, 9.38.

N-(6'-Methylpyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5c**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 42%; mp 145–148 °C; LRMS *m/z* (%): 298 (44, $M^{+\bullet}$), 270 (8, $[M-CO]^{+\bullet}$), 190 (2), 177 (10), 135 (33), 134 (2), 119 (2), 109 (23), 108 (100), 93 (6), 92 (10), 91 (6), 81 (11), 80 (5), 79 (7), 67 (7), 65 (6), 55 (6); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.66 (1 H, H9x), 1.68 (1 H, H11eq), 1.73 (1 H, H9y), 1.78 (1 H, H7eq), ~1.89 (2 H, H10ax & H10eq), ~1.98 (2 H, H2ax & H2eq), 1.99 (2 H, H1 & H7ax), 2.06 (1 H, H8), 2.24 (1 H, H11ax), 2.45 (3 H, CH_3), 2.72 (1 H, H3), 2.92 (1 H, H6), 3.43 (1 H, H4), 6.88 (1 H, H5'), 7.56 (1 H, H4'), 7.97 (1 H, H3'), 9.05 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 24.09 (1 C, CH_3), 26.56 (1 C, C8), 26.59 (1 C, C1), 28.83 (1 C, C3), 31.91 (1 C, C10), 31.96 (1 C, C7), 33.17 (1 C, C2), 34.85 (1 C, C9), 38.26 (1 C, C11), 49.71 (1 C, C6), 64.36 (1 C, C4), 110.83 (1 C, C3'), 119.25 (1 C, C5'), 138.46 (1 C, C4'), 150.53 (1 C, C2'), 156.97 (1 C, C6'), 167.47 (1 C, C12), 214.92 (1 C, C5).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.50; H, 7.42; N, 9.41.

N-(Pyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5d**).

This compound was obtained in 55% yield, mp 161–163 °C (from ethyl acetate:ethanol); LRMS *m/z* (%): 284 (44, $M^{+\bullet}$), 256 (13), 191 (7), 190 (32), 163 (12), 162 (5), 136 (5), 135 (8), 134 (22), 121 (28), 119 (10), 107 (6), 106 (5), 105 (9), 95 (27), 94 (100), 93 (18), 92 (26), 91 (23), 81 (8), 80 (10), 79 (28), 78 (20), 77 (17), 68 (6), 67 (43), 66 (10), 65 (8), 55 (10), 53 (11), 52 (5), 51 (8); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.66 (1 H, H11eq), 1.68 (1 H, H9x), 1.73 (1 H, H9y), 1.80 (1 H, H7eq), ~1.88 (2 H, H10ax & H10eq), 1.95 (1 H, H7ax), ~2.00 (3 H, H1 & H2ax & H2eq), 2.05 (1 H, H8), 2.22 (1 H, H11ax), 2.71 (1 H, H3), 2.92 (1 H, H6), 3.47 (1 H, H4), 7.03 (1 H, H5'), 7.69 (1 H, H4'), 8.19 (1 H, H3'), 8.29 (1 H, H6'), 9.46 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 26.54 (1 C, C8), 26.58 (1 C, C1), 28.80 (1 C, C3), 31.87 (1 C, C10), 31.96 (1 C, C7), 33.15 (1 C, C2), 34.83 (1 C, C9), 38.27 (1 C, C11), 49.69 (1 C, C6), 64.27 (1 C, C4), 114.25 (1 C, C3'), 119.79 (1 C, C5'), 138.26 (1 C, C4'), 147.90 (1 C, C6'), 151.39 (1 C, C2'), 167.74 (1 C, C12), 214.95 (1 C, C5).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.99; H, 7.10; N, 9.87.

N(5'-Bromopyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5e**).

This compound was obtained in 57% yield, mp 163–165 °C (from ethyl acetate:ethanol); LRMS *m/z* (%): 364 (44, $M^{+\bullet}$), 362 (44, $M^{+\bullet}$), 336 (8), 334 (8), 243 (7), 241 (7.5), 201 (14), 199 (15), 191 (11), 190 (10), 175 (16), 174 (97), 173 (17), 172 (100), 164 (9), 162 (5.5), 158 (7), 156 (7), 147 (9), 145 (9), 135 (23), 134 (7), 121 (6), 119 (11), 117 (5), 107 (9), 105 (7), 95 (7), 94 (7), 93 (29), 92 (19), 91 (25), 81 (21), 80 (9), 79 (39), 78 (10), 77 (26), 75 (6), 69 (10), 68 (11), 67 (33), 66 (19), 65 (15), 64 (9), 55 (28), 54 (6), 53 (21), 52 (6), 51 (10), 50 (7), 41 (44), 39 (34); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.66 (1 H, H9x), 1.69 (1 H, H11eq), 1.74 (1 H, H9y), 1.82 (1 H, H7eq), 1.83 (1 H, H10eq), 1.92 (1 H, H10ax), ~1.96 (1 H, H2eq), 1.99 (1 H, H7ax), ~2.02 (2 H, H1 & H2ax), 2.07 (1 H, H8), 2.24 (1 H, H11ax), 2.76 (1 H, H3), 2.94 (1 H, H6), 3.44 (1 H, H4), 7.78 (1 H, H4'), 8.13 (1 H, H3'), 8.33 (1 H, H6'), 9.45 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 26.47 (1 C, C8), 26.53 (1 C, C1), 28.45 (1 C, C3), 31.74 (1 C, C7), 32.10 (1 C, C10), 33.21 (1 C, C2), 34.73 (1 C, C9), 38.28 (1 C, C11), 49.75 (1 C, C6), 63.97 (1 C, C4), 114.61 (1 C, C5'), 115.33 (1 C, C3'), 140.58 (1 C, C4'), 148.83 (1 C, C6'), 149.99 (1 C, C2'), 167.34 (1 C, C12), 215.17 (1 C, C5).

Anal. Calcd. for $C_{17}H_{19}BrN_2O_2$: C, 56.21; H, 5.27; N, 7.71. Found: C, 56.30; H, 5.26; N, 7.72.

N(5'-Chloropyridin-2'-yl)-5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide (**5f**).

This compound was obtained in 53% yield, mp 164–165 °C (from ethyl acetate:ethanol); LRMS *m/z* (%): 320 (13, $M^{+\bullet}$), 318 (38, $M^{+\bullet}$), 290 (7), 197 (7), 191 (8), 190 (6.5), 164 (6), 157 (4.5), 155 (14), 135 (16), 134 (5), 131 (6), 130 (32), 129 (18), 128 (100), 119 (6), 112 (10), 107 (6), 105 (5), 103 (4.5), 101 (11), 93 (19), 92 (11), 91 (17), 81 (13.5), 80 (6), 79 (27), 77 (17), 76 (6), 69 (7), 68 (7), 67 (22), 66 (9), 65 (9), 64 (5), 55 (20), 53 (15), 51 (7), 41 (33), 39 (24); δ_H (399.78 MHz, $CDCl_3$, 25 °C) 1.67 (1 H, H9x), 1.69 (1 H, H11eq), 1.74 (1 H, H9y), 1.81 (1 H, H7eq), 1.82 (1 H, H10eq), 1.92 (1 H, H10ax), 1.94 (1 H, H2eq), 1.99 (1 H, H7ax), 2.02 (2 H, H1 & H2ax), 2.07 (1 H, H8), 2.25 (1 H, H11ax), 2.77 (1 H, H3), 2.94 (1 H, H6), 3.45 (1 H, H4), 7.65 (1 H, H4'), 8.17 (1 H, H3'), 8.24 (1 H, H6'), 9.45 (1 H, H13); δ_C (100.54 MHz, $CDCl_3$, 25 °C) 26.48 (1 C, C8), 26.53 (1 C, C1), 28.45 (1 C, C3), 31.74 (1 C, C7), 32.10 (1 C, C10), 33.22 (1 C, C2), 34.73 (1 C, C9), 38.27 (1 C, C11), 49.75 (1 C, C6), 63.93 (1 C, C4), 114.78 (1 C, C3'), 126.70 (1 C, C5'), 137.81 (1 C, C4'), 146.59 (1 C, C6'), 149.61 (1 C, C2'), 167.28 (1 C, C12), 215.21 (1 C, C5).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79. Found: C, 63.96; H, 6.00; N, 8.81.

6-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]-nonadeca-2(11),4,6,8-tetraene (**6a**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 45%; mp 247–250 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.24; H, 7.18; N, 9.98.

5-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]-nonadeca-2(11),4,6,8-tetraene (**6b**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 47%; mp 302–304 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.11; H, 7.19; N, 9.99.

4-Methyl-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]-nonadeca-2(11),4,6,8-tetraene (**6c**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 51%; mp 253–256 °C.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.99; H, 7.20; N, 10.01.

10-Oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]nonadeca-2(11),4,6,8-tetraene (**6d**).

Eluent for column chromatography: petroleum ether/ethyl acetate 2/1; yield: 43%; mp 226–229 °C.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.45; H, 6.83; N, 10.55.

5-Bromo-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]-nonadeca-2(11),4,6,8-tetraene (**6e**).

Eluent for column chromatography: chloroform/methanol 9/1; yield: 58%; mp 340–343 °C.

Anal. Calcd. for $C_{17}H_{17}BrN_2O$: C, 59.14; H, 4.96; N, 8.11. Found: C, 59.14; H, 4.96; N, 8.11.

5-Chloro-10-oxo-3,9-diazapentacyclo[12.3.1.1^{12,16}.0^{2,11}.0^{3,8}]-nonadeca-2(11),4,6,8-tetraene (**6f**).

Eluent for column chromatography: chloroform/methanol 9/1; yield: 53%; mp 335–338 °C.

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 67.92; H, 5.70; N, 9.32.

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