SYNTHESIS AND STEREOCHEMISTRY OF TROPANE 6-SPIRO-HYDANTOINS

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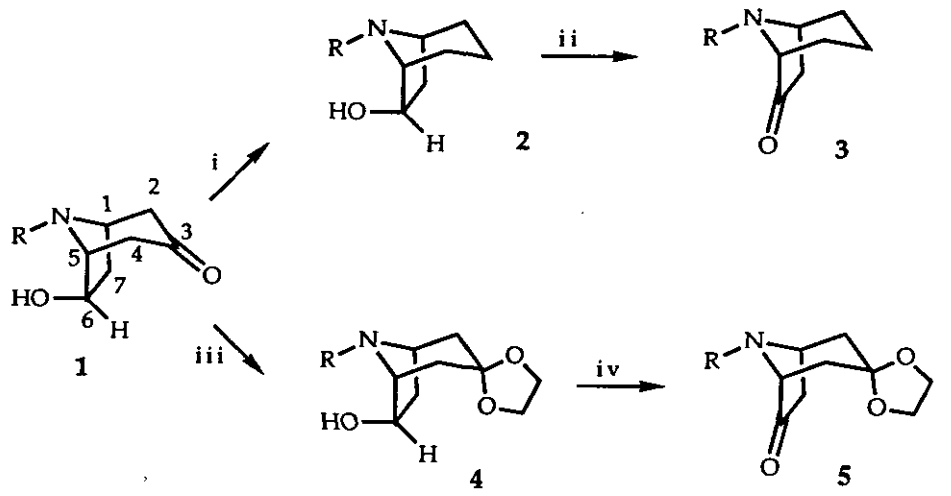
Abstract - The synthesis of several representatives of the previously unknown N-alkyl-nortropane-6-spirohydantoin ring system by Bucherer-Bergs reaction of 8-alkyl-8-azabicyclo[3.2.1]octan-6-ones is described. 3-Oxo derivatives of the parent structure were also prepared. The stereochemical outcome of the Bucherer-Bergs reaction is discussed on the basis of ^{1}H-nmr and ^{13}C-nmr data.

The good analgesic, antiinflamatory, anticonvulsant, antiarrhytmic and anticholinergic activities[1-3] found in several tropane-3-spiro-5'-hydantoin derivatives[4] prompted our interest in the preparation of their positional isomers. In this paper we describe the synthesis of several derivatives of a new ring system, namely the tropane-6-spiro-5'-hydantoin structure (compounds **7-10**).

Target compounds were prepared by Bucherer-Bergs reaction of the corresponding 8-alkyl-8-azabicyclo[3.2.1]octan-6-ones, whose synthesis is depicted in Scheme 1. Compounds (**1a**)[5] and (**1b**) were reduced under Wolff-Kishner conditions to derivatives (**2a**)[5] and (**2b**). Oxidation of **2** with two equivalents of chromium (VI) oxide in acetic acid at 70-80 °C for 16 h afforded the desired tropan-6-ones (**3a**)[5] and (**3b**). Preparation of 3-oxohydantoins (**7**) and (**8**) required the previous synthesis of ketones (**5**), which was achieved by protection of the carbonyl group of **1a, b** with 1, 2-ethanediol to yield **4a**[6] and **4b**, followed by dimethyl sulfoxide-dicyclohexylcarbodiimide oxidation[7] to the corresponding ketones (**5a**)[6] and (**5b**).



a R = CH_3
b R = $CH(CH_3)_2$

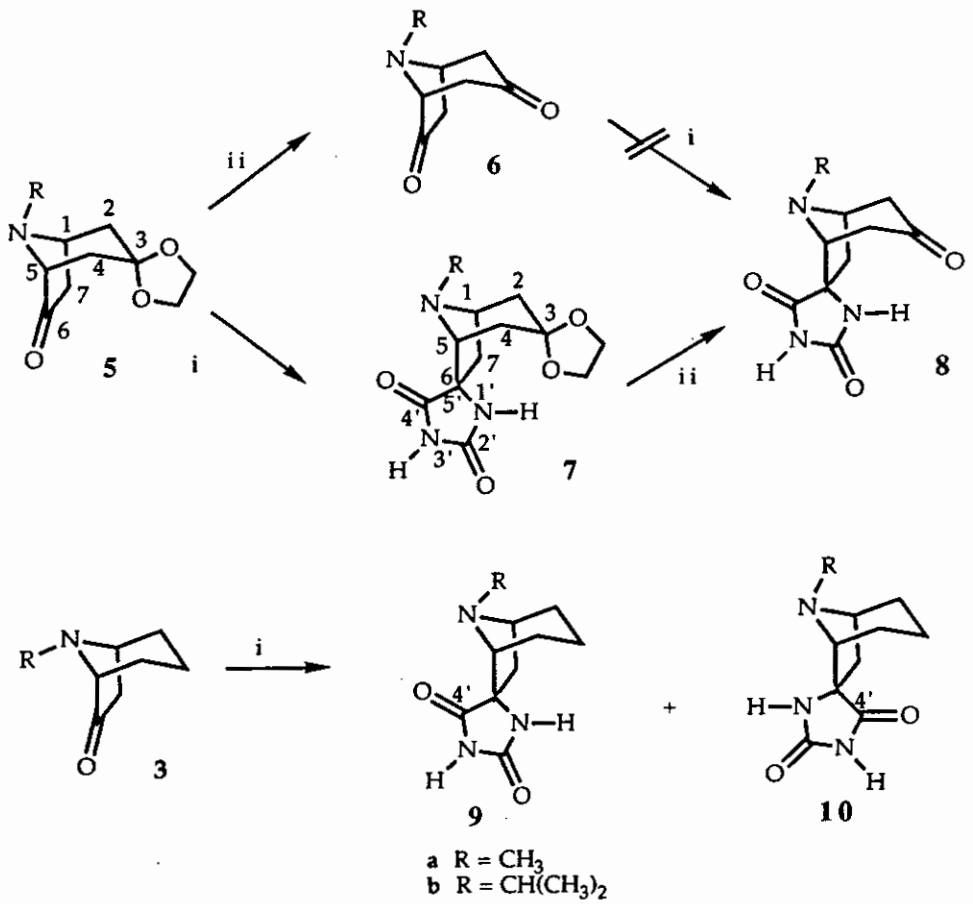
Reagents and conditions: i a) NH_2-NH_2, 120 °C, 3 h; b) KOH, 130-190 °C, 4.5 h
ii b) CrO_3, CH_3CO_2H, 70-100 °C, 18 h
iii c) $HOCH_2CH_2OH$, TsOH, benzene, reflux (Dean-Stark), 6 h
iv d) DMSO, DCC, H_3PO_4, room temperature, 6 h

Scheme 1

Preparation of compounds (**8**) through Bucherer-Bergs reaction of diketone (**6**) was one of our initial aims. After several unsuccessful attempts at the synthesis of **6** by oxidation of **1** with chromic acid and Collins' reagent, this compound could be prepared by acid hydrolysis of **5**. Due to its low stability, no attempt was made to isolate **6**; instead, the crude hydrolysis product was treated under Bucherer-Bergs conditions to give a complex mixture. Therefore, an alternative route was devised, where Bucherer-Bergs reaction of compounds (**5**) to give hydantoins (**7**), followed by deprotection of the carbonyl group at C_3 gave the desired compounds (**8**). The reaction was stereoselective, yielding the isomer with an *exo* orientation for C_4, as the only product (Scheme 2). An attempt to prepare the tropane-3,6-bis-spirohydantoin system by Bucherer-Bergs reaction of compounds (**8**) led only to recovery of the starting material. Previous efforts by other authors[8] to transform diketones into dihydantoins were unsuccessful, and monohydantoins were the only products isolated; this was attributed to precipitation

of these compounds from the reaction medium. However, compounds (**8**) were freely soluble in the 1:1 ethanol-water mixture employed by us, and therefore the failure of the reaction must be due to steric hindrance on C_3 to axial attack of cyanide, due to the presence of the hydantoin ring in C_6.

On the other hand, Bucherer-Bergs reaction of ketones (**3**) yielded a 9:1 mixture of the hydantoins (**9a**) and (**10a**), and a 5.5:1 mixture of **9b** and **10b**; this is in contrast with the behaviour observed for tropan-3-ones, which afforded exclusively the product with an equatorial stereochemistry for the $C_{4'}$ atom of the hydantoin system.[9]



Reagents and conditions: i KCN, $(NH_4)_2CO_3$, C_2H_5OH-H_2O, 60 °C, 2-15 days
ii 6N HCl, CH_3CO_2H, room temperature, 60 h

Scheme 2

The main stereochemical features to be established in the structural study of compounds (**7-10**) are the stereochemistry of the *N*-alkyl chain and of the spiro atom, together with the conformation of the piperidine moiety. They were determined by examination of the ^{1}H-nmr and ^{13}C-nmr data found on Tables 1 and 2.

Chemical shifts for C_2 and C_4 are *ca.* 7 ppm lower than expected;[10,11] thus, C_2 and C_4 signals of 8-methyl-8-azabicyclo[3.2.1]octan-3-one appear at 47.1 ppm, while the corresponding signals of compound (**8a**) can be found at 40.77 (C_2) and 40.59 (C_4). This can be attributed to an axial orientation of the *N*-alkyl chain, the shifts arising from steric polarization effects on the C_2-H and C_4-H bonds and attendant expansion about the nucleus.[12]

Comparison of molecular models of the two isomers of the tropane-6-spirohydantoin system reveals that, in the isomer with an *exo* orientation for the $C_{4'}$ = O group, the C_6-$C_{4'}$ bond is *syn* with respect to two of the C-H bonds of the neighbouring C_5 and C_7 atoms and *gauche* with respect to the third, while in the *endo* isomer there are one *syn* and two *gauche* relationships. Therefore, the signal for $C_{4'}$ in the carbon-proton coupled spectrum should be wider for the *exo* than for the *endo* orientation of $C_{4'}$ = O. Since the half-height widths of these signals in compounds (**9b**) and (**10b**) are 16 Hz and 7.4 Hz, respectively, the *exo* stereochemistry for $C_{4'}$ = O must be attributed to **9**, thus supporting the structures depicted in Scheme 2. The stereochemistry found for the major product of the Bucherer-Bergs reaction is consistent with the results described by Tager and Christensen[13] for norbornene.

^{1}H-Nmr data also support the proposed structures. Thus, comparison of the ^{1}H-nmr spectra of compounds (**9b**) and (**10b**) shows an upfield shift of 0.6 ppm for the C_3-H_{ax} proton of **10b** with respect to the corresponding atom of **9b**, attributed to the anisotropic effect of the $C_{4'}$ = O group. When $N_{1'}$ occupies the *exo* position (compounds **10**), it exerts similar effects on C_7-H_{exo} and C_7-H_{endo}, and the chemical shifts of these protons are very similar. In compounds (**9**), instead, the C_6-$N_{1'}$ bond is *syn* with respect to the C_7-H_{endo} bond, and *anti* with respect to the C_7-H_{exo} bond; this explains the fact that the chemical shifts of these protons differ in *ca.* 1 ppm, providing additional evidence in favour of the structures (**9b**) and (**10b**).

Finally, the conformation of the piperidine ring can be established as a flattened chair. The chair conformation is supported by the chemical shifts of C_2 and C_4, which would be displaced to higher

Compd.	N_1-H	N_3-H	C_1-H	C_5-H	C_7-H_{exo}[§]	C_7-H_{endo}	C_3-H_{ax}	C_3-H_{eq}	$C_{(2)4}$-H_{ax}	$C_{(2)4}$-H_{eq}	R[§§]	OCH_2CH_2O
7a**	6.60(s)	10.50(s)	3.24(m)	3.21(m)	2.38(dd)	1.92(d)	---	---	2.08(dd, *J*=-14.1 and 3.0)	1.76(d)	2.37(s)	4.06-3.62
							---	---	2.02(dd, *J*=-14.8 and 4.0)	1.59(d)		(m,4H)
7b*	6.79(s)	8.33(s)	3.66(m)	3.58(m)	2.59(dd)	2.06(d)	---	---	2.21(dd, *J*=-14.4 and 3.2)	1.60(d)	3.02(m)	4.08-3.91
							---	---	2.09(dd, *J*=-15.1 and 4.2)	1.81(d)	1.11(d)	(m,4H)
							---	---			1.07(d)	
8a**	7.76(s)	10.69(s)	3.45(m)	3.45(m)	2.57(dd)	1.74(d)	---	---	2.62(dd, *J*=-17.8 and 6.0)	2.20(d)	2.49(s)	
							---	---	2.69(dd, *J*=-17.8 and 6.0)	2.39(d)		
8b**	7.72(s)	10.61(s)	3.72(m)	2.69(m)	2.48(dd)	1.68(d)	---	---	2.58(dd, *J*=-17.7 and 6.0)	2.16(d)	3.00(m)	
							---	---	2.61(dd, *J*=-17.7 and 6.0)	2.36(d)	1.05(d)	
							---	---			1.03(d)	
9a*	6.01(s)	7.65(s)	3.36(m)	3.20(s)	2.82(dd)	1.78(d)	1.73(m)	1.23(m)	2.05(m)	1.51(m)	2.56(s)	
										1.38(m)		
9b*	6.08(s)	7.69(s)	3.57(m)	3.45(s)	2.71(dd)	1.75(m)	1.76(m)	1.20(m)	1.96(m)	1.50(m)	3.17(m)	
										1.37(m)	1.09(d)	
											1.05(d)	
10b*	6.04(s)	8.25(s)	3.57(m)	3.24(s)	2.30(dd)	2.43(d)	2.37(m)	1.09(m)	1.91(m)	1.54(m)	3.19(m)	
									1.78(m)	1.38(m)	1.06, 1.03(2 d)	

Notes: * $CDCl_3$ ** DMSO-d_6 § $J_{1,7exo}$ = 7.0 and J_{gem} = -13.0 Hz §§ J = 6.1 Hz

Table 1. ^{1}H-Nmr spectra of compounds **7-10** (300 MHz).

	Compound **8a**		Compound **9a**	Compound **9b**		Compound **10b**	
Position	δ, ppm	^1J (^{13}C-H), Hz	δ, ppm	δ, ppm	^1J (^{13}C-H), Hz	δ, ppm	^1J (^{13}C-H), Hz
C_1	57.90 (d)	141.9	57.41	53.45 (d)	141.7	52.78 (d)	142.6
C_2	40.77 (t)*	131.2	22.03	22.12 (t)	125.4	20.90 (t)	125.2
C_3	207.00 (s)	---	15.92	15.87 (t)	126.4	15.62 (t)	126.4
C_4	40.59 (t)*	131.2	19.19	17.45 (t)	125.8	17.44 (t)	125.3
C_5	65.24 (d)	145.3	64.31	60.33 (d)	143.0	65.05 (d)	143.11
C_6	68.79 (s)	---	67.66	67.20 (s)	---	69.54 (s)	---
C_7	43.79 (t)	131.2	39.26	38.92 (t)	132.1	40.81 (t)	132.7
$C_{2'}$	156.99	8.3§	157.80	157.48	4.4§	156.27	---
$C_{4'}$	178.16	17.3§	178.79	178.81	16.0§	176.33	7.4§
R	36.28 (q)	134.0	34.54	43.63 (d, CH)	130.4	43.22 (d, CH)	130.4
				21.17 (q, CH_3)	125.4	21.35 (q, CH_3)	125.4
				21.92 (q, CH_3)	125.4	21.99 (q, CH_3)	125.4

Notes: * Interchangeable assignments. § Half-height width values (Hz)

Table 2. ^{13}C-Nmr data for compounds **8a**, **9a**, **9b** and **10b** (75.4 MHz, DMSO-d_6).

fields in boat structures.[10] Coupling constants $J_{1,2ax}$ and $J_{4ax,5}$, had values of 3-6 Hz in those compounds where they could be accurately measured (**7** and **8**), and were different from $J_{1,2eq}$ and $J_{4eq,5}$, each < 1 Hz. Therefore, the dihedral angle $H_{2,4\ eq}$-C-C-$H_{1,5}$ is larger than $H_{2,4\ ax}$-C-C-$H_{1,5}$, and the chair must be flattened.

Spectral data for compounds (**7**) and (**8**) (Tables 1 and 2) are also in agreement with the structures depicted in Scheme 2.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 577 spectrophotometer, with all compounds compressed into KBr pellets. ^{1}H-Nmr spectra were obtained on the following instruments: Hitachi Perkin-Elmer R-24B (60 MHz) and Varian VXR-300 (300 MHz). ^{13}C-Nmr spectra (75.4 MHz) were run on the latter instrument. $CDCl_3$ or DMSO-d_6 were used as solvents, and tetramethylsilane was added in all cases as an internal standard. All chemical shifts are referred to tetramethylsilane (TMS) and are given in the δ scale, and all *J* values are given in Hz; only those *J* values that could be accurately measured are given. Elemental analyses were determined on a Carlo Erba 1104 microanalyzer. Melting points were measured in open capillary tubes, using a Büchi inmersion apparatus, and are uncorrected. All reagents were employed as received from commercial suppliers (Aldrich, Fluka, Merk, Carlo Erba, Scharlau, Probus, Panreac).

8-Isopropyl-8-azabicyclo[3.2.1]octan-6β-ol (**2b**). A solution of 6β-hydroxytropinone (**1a**)(3 g, 16 mmol) and 98 % hydrazine hydrate (7.65 g, 150 mmol) in ethanol (30 ml) was heated at 120 °C for 3 h, with distillation of the solvent during the last hour. Powdered solid potassium hydroxide (8 g, 142 mmol) was added and the reaction mixture was heated at 130 ° C (1 h), 160 °C (2 h) and 190 °C (1.5 h). The solid product thus obtained was dissolved in water (90 ml), and the solution was extracted with ether (3 x 90 ml). The extracts were dried (sodium sulfate) and evaporated to yield a yellow oil, which was crystallized from acetone. Yield, 2.4 g (87 %). mp 96-98 °C (acetone). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.31; N, 8.27. Found: C, 70.74; H, 11.46; N, 8.10. Ir (NaCl, film): 3400 (O-H) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 4.20 (dd, *J* = 7 and 3 Hz, 1H, C_6-H), 3.60 (s, 1H, exch. D_2O, OH), 3.50 (m, 1H, C_1-H), 3.20 (s, 1H, C_5-H), 3.15 (m, 1H, $CH(CH_3)_2$), 2.55 (dd, $J_{1,7}$=6 Hz, J_{gem}=-17 Hz, 1H, C_7-H_{exo}), 1.90 (d, J_{gem}=-17 Hz, 1H, C_7-H_{endo}), 1.80-0.90 (m, 6H, $C_{2,3,4}$-H), 1.05 (d, *J*=7 Hz, 6H, $CH(CH_3)_2$).

8-Isopropyl-8-azabicyclo[3.2.1]octan-6-one (**3b**). A solution of chromium (VI) oxide (2.8 g, 28 mmol) in glacial acetic acid (10 ml) was dropwise added to a cooled solution of compound (**2b**) (2.4 g, 14 mmol) in glacial acetic acid (20 ml). The solution was heated at 70-80 °C for 16 h and at 100 °C for 2 h, and then cooled and evaporated *in vacuo*. The residue was dissolved in an aqueous saturated solution of potassium carbonate (20 ml), which was extracted with ether (3 x 20 ml). The extracts were dried (sodium sulfate) and evaporated, and the residue was distilled in a Kugelrohr apparatus to yield 1.42 g (60 %) of compound (**3b**), as a colorless oil. bp 95-105 °C (0.25 torr, Kugelrohr). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.63; H, 10.03; N, 8.47. Ir (NaCl, film), 1750 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 3.70 (m, 1H, C_1-H), 3.15 (s, 1H, C_5-H), 2.95 (m, 1H, $CH(CH_3)_2$), 2.50 (dd, $J_{1,7}$=6 Hz, J_{gem}=-18 Hz, 1H, C_7-H_{exo}), 1.95 (d, J_{gem}=-18 Hz, 1H, C_7-H_{endo}), 1.90-1.00 (m, 6H, $C_{2,3,4}$-H), 1.00 (d, J=7 Hz, 6H, $CH(CH_3)_2$).

3,3-Ethylenedioxy-8-isopropyl-8-azabicyclo[3.2.1]octan-6β-ol (**4b**). A solution of compound (**3b**) (4.55 g, 25 mmol), ethylene glycol (8.6 g, 57.6 mmol) and *p*-toluenesulfonic acid (8.6 g, 57.6 mmol) in dry benzene (200 ml) was refluxed for 6 h in a Dean-Stark apparatus. The cooled reaction mixture was treated with sodium carbonate (13.2 g) and brine (300 ml), and extracted with chloroform (6 x 200 ml). The combined extracts were dried (sodium sulfate) and condensed, and the residue was crystallized from acetone. Yield, 4.0 g (72 %). mp 95-96 °C (acetone). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.71; H, 9.61; N, 6.14. Ir (KBr): 3300 (O-H), 1290, 1270 (C-O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 4.35 (dd, $J_{6,7\ endo}$=7 Hz, $J_{6,7\ exo}$=3 Hz, 1H, C_6-H), 3.85 (m, 4H, OCH_2CH_2O), 3.50 (m, 1H, C_1-H), 3.30 (m, 1H, C_5-H), 3.00 (m, 1H, $CH(CH_3)_2$), 2.55 (dd, J_{gem}=-14 Hz, $J_{6,7}$=7 Hz, 1H, C_7-H_{exo}), 2.10 (m, 1H, C_7-H_{endo}), 1.90-1.30 (m, 4H, $C_{2,4}$-H), 1.00 (d, J=7 Hz, 6H, $CH(CH_3)_2$).

3,3-Ethylenedioxy-8-isopropyl-8-azabicyclo[3.2.1]octan-6β-one (**5b**). A stream of dry nitrogen was passed through a solution of compound (**4a**) (2.5 g, 10.9 mmol) and dicyclohexylcarbodiimide (6.88 g, 32.3 mmol) in dry dimethyl sulfoxide (40 ml). A solution of anhydrous phosphoric acid (1.59 g, 16.2 mmol) in dry dimethyl sulfoxide (10 ml) was slowly added. The reaction mixture was stirred at room temperature in a nitrogen atmosphere. After filtering dicyclohexylurea, dimethyl sulfoxide was distilled off and the residue was dissolved in 5 % aqueous ammonium hidroxide (100 ml). The solution was extracted with chloroform (4 x 100 ml), which was dried (sodium sulfate) and condensed, leaving

a residue that was distilled in Kugelrohr. Yield, 2.6 g (64 %). bp 130-135 °C (0.5 torr, Kugelrohr). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.00; H, 8.44; N, 6.22. Found: C, 63.85; H, 8.31; N, 6.13. Ir (NaCl, film): 1750 (C=O), 1290 (C-O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 3.80 (br s, 4H, OCH_2CH_2O), 3.30 (m, 2H, $C_{1,5}$-H), 2.90 (m, 1H, $CH(CH_3)_2$), 2.50-1.50 (m, 6H, $C_{2,4,7}$-H), 1.05 (d, *J*=7 Hz, 6H, $CH(CH_3)_2$).

8-Methyl-8-azabicyclo[3.2.1]octane-3,6-dione (**6**). A solution of compound (**5a**) (2.47 g, 12.5 mmol) in 6N hydrochloric acid (110 ml) and acetic acid (110 ml) was stirred at room temperature for 60 h, and evaporated. The residue was dissolved in a 20% aqueous solution of potassium carbonate (30 ml), which was extracted with ether (3 x 30 ml). The extracts were dried (sodium sulfate) and condensed, and the residue was distilled in a Kugelrohr apparatus to yield 1.4 g (74 %) of **6**, as a slightly impure oil that was used for an attempted Bucherer-Bergs reaction without further purification. Ir (NaCl, film): 1750, 1710 cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 3.80 (s, 1H, C_4-H), 3.30 (m, 3H, C_1-H and C_7-H), 2.55 (s, 3H, CH_3), 2.10 (m, 4H, $C_{2,4}$-H).

General Procedure for the Bucherer-Bergs Reactions of N-Alkylnortropan-6-ones A solution of the suitable ketone (15 mmol) in ethanol (8 ml) was mixed with another solution of potassium cyanide (1.4 g, 21.6 mmol) and ammonium carbonate (4.5 g) in water (24 ml). The flask was sealed and heated for 3-15 days in an oven at 60 °C. The reaction mixture was cooled and condensed to half-volume, and an inorganic solid was filtered off. The filtrate was evaporated to dryness and the residue was extracted with boiling ethanol or ethyl ether. The extracts were condensed and recrystallized from an appropriate solvent, or purified by column chromatography.

(±)-(1*R**, 5*S**, 6*R**)-3,3-Ethylenedioxy-8-methyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione (**7a**). Yield, 66 %, after 7 days of reaction and recrystallization from ethyl acetate. mp 192-194 °C (ethyl acetate). Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 54.09; H, 6.61; N, 15.60. Ir (KBr): 3420 (N-H), 1780, 1730 (C=O) cm^{-1}.

(±)-(1*R**, 5*S**, 6*R**)-3,3-Ethylenedioxy-8-isopropyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione (**7b**). Yield, 62 %, after 7 days of reaction and recrystallization from ethanol. mp 217-219 °C (ethanol). Anal. Calcd for $C_{14}H_{21}N_3O_4$: C, 56.93; H, 7.16; N, 14.22. Found: C, 57.05; H, 7.38; N, 14.17. Ir (KBr): 3380 (N-H), 1775, 1725 (C=O) cm^{-1}.

(±)-(1*S**, 5*R**, 6*R**)-8-Methyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione (**9a**) and (±)-(1*S**, 5*R**, 6*S**)-8-methyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione

(10a) Yield, 30 % (**9a**:**10a** = 9:1, by ^{1}H-nmr), after 15 days of reaction and column chromatography (silica gel), eluting with 9:1 chloroform-ethanol. An analytical sample of **9a** was obtained by recrystallization from ethanol. Compound (**10a**) could not be purified. Data for compound (**9a**): mp 241-242 °C (ethanol). Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.30; H, 7.42; N, 20.04. Ir (KBr): 3420, 3320 (N-H), 1770, 1730 (C=O) cm^{-1}.

(±)-(1*S**, 5*R**, 6*R**)-8-Isopropyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione (9b) Yield, 28 %, after 2 days of reaction and separation from **10b** by column chromatography (alumina), eluting with 95:5 chloroform-ethanol. mp 172-174 °C (ethanol). Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.06; N, 17.70. Found: C, 60.49; H, 7.98; N, 17.63. Ir (KBr): 3280-3160 (N-H), 1760, 1720 (C=O) cm^{-1}.

(±)-(1*S**, 5*R**, 6*S**)-8-Isopropyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-2',4'-dione (10b) Yield, 5 %, after 2 days of reaction and separation from **9b** by column chromatography (alumina), eluting with 95:5 chloroform-ethanol. mp 239-240 °C (ethanol). Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.06; N, 17.70. Found: C, 60.33; H, 8.00; N, 17.59. Ir (KBr): 3280-3160 (N-H), 1770, 1720 (C=O) cm^{-1}.

General Procedure for the Deprotection of Compounds 7. A solution of the suitable compound (**7**) (11.2 mmol) in 6 N hydrochloric acid (10 ml) and acetic acid (10 ml) was stirred at room temperature for 60 h, and evaporated to dryness. The residue was dissolved in water (5 ml), basified with 6 N aqueous sodium hydroxide and extracted with chloroform (3 x 10 ml), which was evaporated, leaving a residue that was crystallized from ethanol.

(±)-(1*R**, 5*S**, 6*R**)-8-Methyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-3,2',4'-trione (8a). Yield, 68 %. mp 216-218 °C (ethanol). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.73; H, 5.92; N, 18.64. Ir (KBr): 3340, 3150 (NH), 1780, 1730, 1690 (C=O) cm^{-1}.

(±)-(1*R**, 5*S**, 6*R**)-8-Isopropyl-8-azabicyclo[3.2.1]octane-6-spiro-5'-imidazolidine-3,2',4'-trione (8b). Yield, 65 %. mp 221-222 °C (ethanol). Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.81; N, 16.72. Found: C, 57.35; H, 6.91; N, 16.51. Ir (KBr): 3240-3360, 3140 (NH), 1775, 1725, 1700 (C=O) cm^{-1}.

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