8-Hydroxylated Derivatives of Diazabicyclo[4.3.0]nonanes, 2,5-Dioxodiazabicyclo[4.3.0]nonanes and Some Related Esters

Lahcen Diafi, Jacques Couquelet and Pierre Tronche*

Groupe de Recherches de Pharmacochimie, Faculté de Pharmacie,
28, place Henri Dunant, 63001 Clermont-Ferrand Cedex, France

Daniel Gardette and Jean-Claude Gramain

Laboratoire de Chimie et Biochimie des Substances Naturelles,
URA n °485 CNRS, Université Blaise Pascal,
63177 Aubière Cédex, France

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Pharmacological considerations prompted the authors to synthesize a series of 8-hydroxylated optically active derivatives of diazabicyclo[4.3.0]nonanes and of their 2,5-dioxo analogs from *trans*-4-hydroxy-L-proline. Esterification with appropriate anhydrides led to the corresponding esters with 6*S*,8*R* configuration. Inversion of configuration at C-8 was performed using Mitsunobu method and led to the diastereoisomeric series of 6*S*,8*S* esters. A tentative pharmacological evaluation was carried out in the area of sedative and spasmolytic activities.

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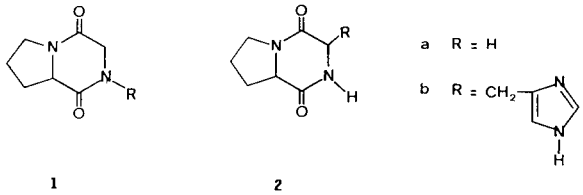
The formation of diketopiperazine ring system may occur by an intramolecular cyclisation process between two close amino acids during the synthesis or the degradation of peptides, mainly when they incorporate a proline moiety [1,2]. But diketopiperazine ring may be also encountered as bicyclic or polycyclic systems in a number of natural products, such as fermentation broth of *Aspergillus ustus* [3], austamides and brevomides [4], *Streptomyces*



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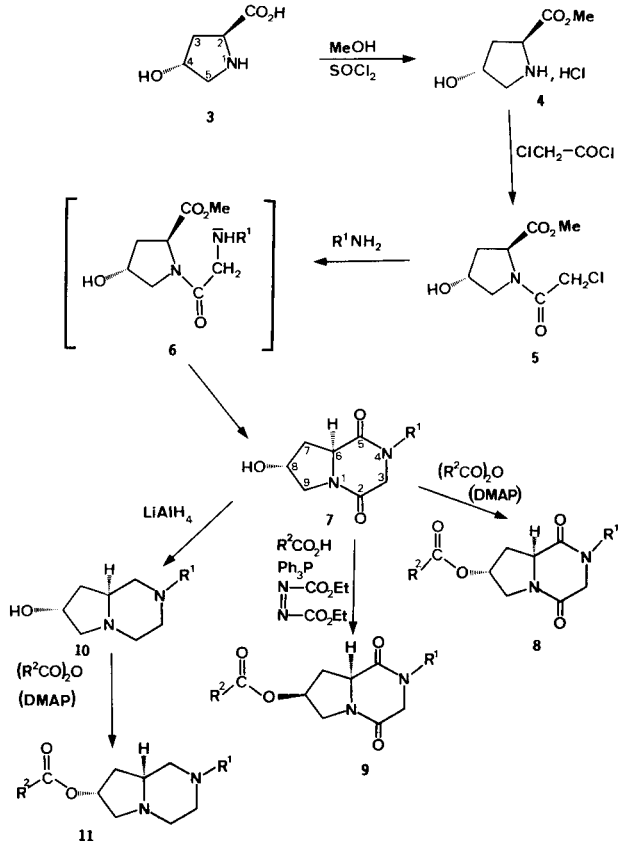
K73 [5], marine organisms such as sea stars [6], sponges *Tediana ignis* [7] and *Geodia Boretti* [8]. Previously we prepared various thiaza and thiadiazabicycloalkanes which exhibited potential psychotropic activities [9,10]. So we thought it was of interest to investigate more extensively the properties of some alcohols and esters including a diaza and dioxodiazabicyclo[4.3.0]nonane cyclic system, potential analogues respectively of sedative aminoalcohols and antispasmodic bicyclic aminoesters. There are several methods in the literature describing the synthesis of pyrrolodioxopyrazine derivatives **1** and **2**; most of them refer to a cyclisation process of various esters of proline containing dipeptides [11-14].

We prepared a series of new fused 2,5-dioxopiperazines in three steps using as starting material the natural *trans*-4-hydroxy-L-proline, the absolute configuration of which is 2*S*,4*R* (Scheme). First the methyl ester of 4-hydroxy-L-proline (**4**) was obtained in good yield as the hydrochloride by reacting the amino acid at low temperature with an excess of methanol and thionyl chloride [15]. The infrared spectrum exhibited a strong absorption band at 1740 cm^{-1}, assigned to a carbonyl ester functional group. The proton nmr spectrum exhibited a singlet at 3.8 ppm for the protons of the methyl group and an exchangeable multiplet at 10.3 ppm assigned to the NH proton. Acylation of **4** with an equivalent of chloroacetyl chloride [16] afforded the *N*-acetylated derivative **5**. If the reaction was per-

Scheme

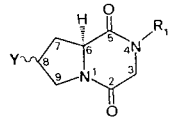


formed with an excess of acyl chloride, it gave rise to a mixture of *N*- and *O*-acylated derivatives which may be separated by column chromatography. The infrared spectrum exhibited two absorption bands at 1650 cm^{-1} (amidic carbonyl) and 1750 cm^{-1} (ester carbonyl). The proton nmr spectrum possessed signals at 3.75 ppm (singlet) for the methyl group, at 4.4 ppm (singlet) for the methylene group in the *alpha* position of the amidic function, and between 4.5 and 5.5 ppm (broad absorption) for the hydroxylic proton, exchangeable with deuterium oxide. The ^{13}C nmr spectrum, recorded at 20° and at 80°, allowed us to postulate the existence of two rotamers.

Refluxing *N*-acyl derivatives **5** with an aliphatic or aryl-aliphatic primary amine in 2-ethoxyethanol in the presence of triethylamine afforded (6*S*,8*R*)-2,5-dioxo-8-hydroxy-1,4-diazabicyclo[4.3.0]nonanes **7b-f**. Volatile

Table I

2,5-Dioxo-1,4-diazabicyclo[4.3.0]nonaes



No.	Y	C-8	R_1	Yield %	mp °C	$[\alpha]_J^{25}$	Formula	Analysis % Calcd/Found C	H	N
7a	OH	(R)	CH_3	80	110-112	-127°	$C_8H_{12}N_2O_3$	52.17 51.97	6.52 6.58	15.21 15.11
7b	OH	(R)	$CH(CH_3)_2$	30	132-134	-112°	$C_{10}H_{16}N_2O_3$	56.60 56.52	7.54 7.64	13.20 13.13
7c	OH	(R)	cyclopentyl	26	178	- 98°	$C_{12}H_{18}N_2O_3$	60.50 60.26	7.56 7.50	11.76 11.84
7d	OH	(R)	cyclohexyl	43	184	-110°	$C_{13}H_{20}N_2O_3$	62.00 61.87	7.93 8.03	11.11 11.07
7e	OH	(R)	$CH_2C_6H_5$	63	146-147	-119°	$C_{14}H_{16}N_2O_3$	64.61 64.72	6.15 6.20	10.77 10.82
7f	OH	(R)	$(CH_2)_2C_6H_5$	42	79-80	-101°	$C_{15}H_{20}N_2O_4$ [a]	61.64 61.59	6.84 6.79	9.59 9.60
8a	$OCOCH_3$	(R)	$CH_2C_6H_5$	80	195	- 60°	$C_{16}H_{18}N_2O_4$	63.60 63.56	6.00 6.03	9.27 9.25
8b	$OCOC_6H_5$	(R)	$CH_2C_6H_5$	66	130	-100°	$C_{21}H_{20}N_2O_4$	69.23 68.97	5.49 5.54	7.69 7.73
8c	$OCOCH_2C_6H_6$	(R)	CH_3	60	liq.	- 90°	$C_{16}H_{18}N_2O_4$	63.57 63.45	5.96 5.98	9.27 9.23
8d	$OCOCH_2C_6H_6$	(R)	$CH_2C_6H_5$	76	128-130	- 76°	$C_{22}H_{22}N_2O_4$	69.84 69.67	5.82 5.88	7.40 7.34
8e	$OCOCH_2C_6H_6$	(R)	$(CH_2)_2C_6H_5$	62	100	- 70°	$C_{23}H_{24}N_2O_4$	70.40 70.54	6.12 6.24	7.14 7.06
8f	$OCOCH(C_6H_5)_2$	(R)	CH_3	71	119-120	- 80°	$C_{22}H_{22}N_2O_4$	69.84 69.68	5.82 5.87	7.40 7.31
8g	$OCOCH(C_6H_5)_2$	(R)	$CH_2C_6H_5$	75	79	- 51°	$C_{28}H_{26}N_2O_4$	74.00 73.59	5.73 5.85	6.17 6.08
8h	$OCOCH(C_6H_5)_2$	(R)	$(CH_2)_2C_6H_5$	60	122	- 32°	$C_{29}H_{28}N_2O_4$	74.35 74.15	5.98 6.02	5.98 6.08
9a	$OCOC_6H_5$	(S)	$CH_2C_6H_5$	63	104-106	+ 25°	$C_{21}H_{20}N_2O_4$	69.23 69.41	5.49 5.44	7.69 7.65
9b	$OCOCH_2C_6H_5$	(S)	CH_3	86	98-100	+ 21°	$C_{16}H_{18}N_2O_4$	63.57 63.47	5.96 5.99	9.27 9.23
9c	$OCOCH_2C_6H_5$	(S)	$CH_2C_6H_5$	70	132-134	+ 27°	$C_{22}H_{22}N_2O_4$	69.84 69.78	5.82 5.77	7.40 7.46
9d	$OCOCH(C_6H_5)_2$	(S)	CH_3	54	liq.	+ 38°	$C_{22}H_{22}N_2O_4$	69.84 69.69	5.82 5.85	7.40 7.33
9e	$OCOCH(C_6H_5)_2$	(S)	$CH_2C_6H_5$	55	114-115	+ 29°	$C_{28}H_{26}N_2O_4$	74.00 73.93	5.73 5.69	6.16 6.08

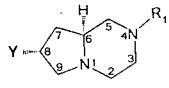
[a] Monohydratee.

methylamine was reacted in ethanolic solution by autoclaving to afford **7a**. Moreover when using an aromatic amine the cyclisation did not proceed, owing to the low nucleophilic character of the intermediate amine **6**. In any case only the 6*S*,8*R* diastereoisomer was obtained. No trace of the 6*R*,8*R* isomer, which could result from epimerisation at C-6 during cyclisation, was detected even by ^{13}C nmr spectroscopy. Esterification of 6*S*,8*R* bicyclic alcohols **7** was performed at room temperature with the appropriate anhydrides in presence of triethylamine and dimethylaminopyridine as catalysts [17], providing esters **8** with the same configuration. Further evidence for 6*S*,8*R* configuration was provided by proton nmr spectra at 300 MHz of **7a** and of its diphenylacetic ester **8f**. The six coupling protons system of the hydroxyproline nucleus was analysed according to Abraham-McLaughlan procedure [18]. It presents an ABMX system for H-7α and H-7β (AB part), H-6 (M), H-8 (X). Furthermore the H-8 proton is a part of an A'B'X system including H-9α and H-9β. The protons in 3 position give an AB system (see Experimental). Moreover we have improved our analysis by the interpretation of a COSY spectrum of compound **7a**.

Esterification with inversion of configuration at C-8 was performed from alcohols **7a** and **7e** through a nucleophilic substitution reaction described by Mitsunobu [19], using triphenylphosphine, diethylazodicarboxylate and a suitable carboxylic acid. A mechanism of this reaction was suggested by Loibner and Zbiral [20]. According to this procedure the 6*S*,8*S* bicyclic esters **9** were obtained. Yields are ranging from 54 to 86% and the inversion of the configuration at C-8 is complete: no trace of the 6*S*,8*R* epimers **8** could be detected. Furthermore it can be noted that esters **9** were dextrarotatory whereas esters **8** were levorotatory.

Recently the 1,4-diazabicyclo[4.3.0]nonane moiety was incorporated in various chemical structures of pharmacological interest to afford potent drugs such as neuroleptic phenothiazines [21], anxiolytic benzodiazepines [22] antibacterial quinolones [23] antiarrhythmic benzamides [24]. Therefore we were prompted to prepare the 6*S*,8*R* reduced derivatives **10** of the 2,5-dioxo-8-hydroxy-1,4-diazabicyclo[4.3.0]nonanes **7**, and some of their esters **11**. We performed the reduction of the amido groups using lithium and aluminium hydride in dry tetrahydrofuran [25]. The

Table II
1,4-Diazabicyclo[4.3.0]nonanes



No.	Y	R_1	Yield %	mp °C	$[\alpha]_J^{25}$	Formula	Analysis % Calcd/Found C	H	N	Cl
10a	OH	CH_3	60	215-216	-31°	$C_8H_{18}Cl_2N_2O$	41.92	7.86	12.22	31.01
							42.02	7.77	12.11	30.97
10b	OH	$CH_2C_6H_5$	73	105	-20°	$C_{14}H_{20}N_2O$	72.41	8.62	12.07	
							72.29	8.57	12.12	
10c	OH	$(CH_2)_2C_6H_5$	51	75-76	-4,5°	$C_{15}H_{22}N_2O$	73.17	8.94	11.38	
							73.16	9.02	11.42	
11a	$OCOCH_2C_6H_5$	CH_3	72	164-166	-5°	$C_{16}H_{24}Cl_2N_2O_2$ [b]	55.33	6.91	8.07	20.46
							55.28	7.03	7.99	20.39
11b	$OCOCH_2C_6H_5$	$CH_2C_6H_5$	72	210-212	-8°	$C_{22}H_{28}Cl_2N_2O_2$ [b]	62.41	6.62	6.62	16.78
							62.49	6.65	6.66	16.74
11c	$OCOCH_2C_6H_5$	$(CH_2)_2C_6H_5$	75	liq.	-11°	$C_{23}H_{27}N_2O_2$	76.04	7.44	7.72	
							75.92	7.46	7.68	
11d	$OCOCH(C_6H_5)_2$	CH_3	85	168-170	-4°	$C_{22}H_{30}Cl_2N_2O_3$ [c]	59.86	6.80	6.35	16.09
							59.75	6.78	6.26	16.19
11e	$OCOCH(C_6H_5)_2$	$CH_2C_6H_5$	70	102	-7,1°	$C_{28}H_{32}N_2O_3$ [a]	75.67	7.20	6.30	
							75.54	7.09	6.20	
11f	$OCOCH(C_6H_5)_2$	$(CH_2)_2C_6H_5$	73	89-90	-18°	$C_{29}H_{32}N_2O_2$	79.09	7.27	6.36	
							79.19	7.34	6.29	
11g	$OCOC(OH)(C_6H_5)_2$	$CH_2C_6H_5$	22	119-120	-18°	$C_{28}H_{30}N_2O_3$	76.02	6.79	6.33	
							76.14	6.82	6.29	

[a] Monohydrate. [b] Dihydrochloride. [c] Dihydrochloride monohydrate.

crude hydroxydiamines **10a-c** were purified by column chromatography on alumina. The spectral data comply with the proposed structures: disappearance of carbonyl bands on infrared spectra, signal of the methylenic protons in 2 and 5 positions included in a broad multiplet which resonates between 1.5 and 3.0 ppm on ^1H nmr spectra. From the ^{13}C spectral data it can be postulated that only one diastereoisomer was obtained and that no epimerisation occurred at C-6.

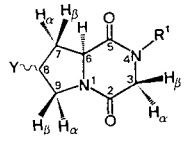
The phenylacetic and diphenylacetic esters **11a-f** were obtained from 8-hydroxy-1,4-diazabicyclo[4.3.0]nonanes **10a-c** through a conventional procedure with the corresponding anhydrides. 4-Benzyl-8-benzyloyloxy-1,4-diazabicyclo[4.3.0]nonane (**11g**) was obtained by a transesterification procedure between ethyl benzilate and 4-benzyl-8-hydroxy-1,4-diazabicyclo[4.3.0]nonane (**10b**).

Pharmacological Assay.

The 2,5-dioxo-8-hydroxy derivatives **7a-e** were assayed for their potential sedative activity in the photoelectric actimeter test on albinos mice [26] using chlorpromazine as reference. Compounds **7a**, **7b**, **7d**, **7e** were inactive. Only **7c** was poorly but not significantly active, except at high doses. The analgesic activity was investigated by preventing painful crisis in mice after phenylbenzoquinone intraperitoneal injection [27] using noramidopyrine as reference. The tested compounds **10b**, **10c** failed to protect the animals even at 100 mg/kg. The esters **11a**, **11b**, **11d**, as water soluble hydrochlorides, were selected for testing their spasmolytic activity on the isolated rat ileus [28] us-

Table III

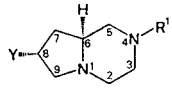
IR and ^1H NMR Spectroscopic Data of 2.5-Dioxo-1,4-diazabicyclo[4.3.0]nonanes



No.	IR (KBr)(cm^{-1})	^1H NMR (δ ppm) (deuteriochloroform)
7a	3310, 1650	Spectrum at 300 MHz (see Experimental)
7b	3340, 1650	1.2 (d, 6H, $2CH_3$), 2.0-2.7 (m, 2H, 2H-7), 3.4-5.1 (m, 8H, 2H-3, H-6, H-8, 2H-9, isopropylic C*H*,OH)
7c	3330, 1660	1.1-2.7 (m, 10H, 2H-7, $4CH_2$, cyclopentyl), 3.25-5.3 (m, 8H, 2H-3, H-6, H-8, 2H-9, C*H* cyclopentyl, OH)
7d	3340, 1650	1.0-2.4 (m, 12H, 2H-7, $5CH_2$ cyclohexyl), 3.2-4.1 (m, 5H, 2H-3, 2H-9, C*H* cyclohexyl), 4.3-4.7 (m, 2H, H-6, H-8), 5.2 (m, 2H, H-6, H-8), 5.2 (m, 1H, OH)
7e	3330, 1630	2.0-2.6 (m, 2H, H-7), 3.4-4.8 (m, 9H, 2H-3, H-5, H-8, 2H-9, CH_2-Ar, OH), 7.3 (s, 5H, Ar)
7f	3340, 1640	1.7-2.5 (m, 2H, 2H-7), 2.9 (t, 2H, CH_2Ar), 3.2-4.0 (m, 7H, 2H-3, 2H-9, CH_2-CH_2-Ar, OH), 4.2-4.8 (m, 2H, H-6, H-8), 7.3 (s, 5H, Ar)
8a	1740, 1650	2.0 (s, 3H, CH_3), 2.1-2.7 (m, 2H, 2H-7), 3.2-4.9 (m, 7H, 2H-3, H-6, 2H-9, CH_2Ar), 5.3 (m, 1H, H-8), 7.4 (s, 5H, Ar)
8b	1730, 1670	2.0-3.1 (m, 2H, 2H-7), 3.5-5.1 (m, 7H, 2H-3, H-6, 2H-9, CH_2Ar), 5.5-5.8 (m, 1H, H8), 7.0-8.3 (m, 10H, Ar)
8c	1740, 1680	1.8-2.6 (m, 2H, 2H-7), 3.0 (s, 3H, CH_3), 3.7 (s, 2H, CH_2Ar), 3.1-4.6 (m, 5H, 2H-3, H-6, 2H-9), 5.4 (m, 1H, H-8), 7.4 (s, 5H, Ar)
8d	1745, 1675	2.2-2.7 (m, 2H, 2H-7), 3.7 (s, 2H, OCOCH_2Ar), 3.8-4.9 (m, 7H, 2H-3, H-6, 2H-9, N-CH_2Ar), 5.4 (m, 1H, H-8), 7.3(br s, 10H, Ar)
8e	1740, 1665	2.0-2.6 (m, 2H, 2H-7), 2.7-4.5 (m, 9H, 2H-3, H-6, 2H-9, CH_2-CH_2Ar), 3.7 (s, 2H, OCO-CH_2Ar), 5.3-5.6 (m, 1H, H-8), 7.3 (br s, 10H, Ar)
8f	1745, 1675	Spectrum at 300 MHz (see Experimental)
8g	1740, 1670	2.1-2.6 (m, 2H, 2H-7), 3.3-4.7 (m, 7H, 2H-3, H-6, 2H-9, NCH_2Ar), 5.0 (s, 1H, C*H*Ar_2), 5.1-5.3 (m, 1H, H-8), 7.3 (br s, 15H, Ar)
8h	1730, 1660	2.0-2.6 (m, 2H, 2H-7), 2.7-4.3 (m, 9H, 2H-3, H-6, 2H-9, CH_2-CH_2Ar), 5.1 (s, 1H, C*H*Ar_2), 5.5 (m, 1H, H-8), 7.4 (br s, 15H, Ar)
9a	1720, 1670	2.6-3.1 (m, 2H, 2H-7), 3.4-4.6 (m, 5H, H-6, 2H-3, 2H-9), 4.7 (s, 2H, CH_2Ar), 5.5-5.8 (m, 1H, H-8), 7.1-8.2 (m, 10H, Ar)
9b	1745, 1660	2.5-2.8 (m, 2H, 2H-7), 3.1 (s, 3H, CH_3), 3.6 (s, 2H, CH_2Ar), 3.3-4.4 (m, 5H, H-6, 2H-3, 2H-9), 5.2-5.6 (m, 1H, H-8), 7.4 (s, 5H, Ar)
9c	1730, 1670	2.4-2.8 (m, 2H, 2H-7), 3.3-4.5 (m, 7H, H-6, 2H-3, 2H-9, OCO-CH_2Ar), 4.6 (s, 2H, N-CH_2Ar), 5.1-5.4 (m, 1H, H-8), 7.3 (br s, 10H, Ar)
9d	1740, 1670	2.4-2.8 (m, 2H, 2H-7), 2.9 (s, 3H, CH_3), 3.3-4.4 (m, 5H, H-6, 2H-3, 2H-9), 5.0 (s, 1H, C*H*Ar_2), 5.1-5.6 (m, 1H, H-8), 7.3 (br s, 10H, Ar)
9e	1740, 1680	2.5-2.9 (m, 2H, 2H-7), 3.3-4.9 (m, 7H,H-6, 2H-3, 2H-9, N-CH_2Ar), 5.0 (s, 1H, C*H*Ar_2), 5.2-5.6 (m, 1H, H-8), 7.3 (br s, 15H, Ar)

Table IV

IR and ^{1}H-NMR Spectroscopic Data of 1,4-Diazabicyclo[4.3.0]nonanes



No.	IR ($CHCl_3$)(cm^{-1})	$^{-1}$H NMR (δ ppm) (deuteriochloroform)
10a	3600, 3340, 2950, 2800	1.5-3.1 (m, 10H, 5C*H*$_2$), 2.3 (s, 3H, C*H*$_3$), 3.3-3.7 (m, 1H, H-6), 4.1-4.6 (m, 1H, H-8), 4.8 (s, 1H, OH, deuterium oxide exchangeable)
10b	3600, 3350, 2800	1.5-3.0 (m, 10H, 5C*H*$_2$), 3.1 (s, 1H, OH), 3.2-3.5 (m, 1H, H-6), 3.6 (s, 2H, C*H*$_2$-Ar), 4.2-4.6 (m, 1H, H-8), 7.3 (s, 5H, Ar)
10c	3600, 3310, 2925, 2800	1.2-3.0 (m, 14H, 7C*H*$_2$), 3.2-3.6 (m, 1H, H-6), 4.2-4.7 (m, 2H, H-8, OH), 7.2 (s, 5H, Ar)
11a	2800, 1735	1.6-3.1 (m, 10H, 5C*H*$_2$), 2.3 (s, 3H, C*H*$_3$), 3.3-3.8 (m, 1H, H-6), 3.6 (s, 2H, C*H*$_2$-Ar), 5.0-5.4 (m, 1H, H-8), 7.4 (s, 5H, Ar)
11b	2800, 1735	[a] 1.9-2.3 (m, 2H, 2H-7), 2.8-4.8 (m, 13H, H-6, 6C*H*$_2$), 5.1-5.5 (m, 1H, H-8), 7.0-7.6 (m, 10H, Ar)
11c	2800, 1730	1.7-3.2 (m, 14*H*, 7C*H*$_2$), 3.3-3.8 (m, 3H, H-6, N-C*H*$_2$-CH$_2$-Ar), 5.0-5.4 (m, 1H, H-8), 7.3 (m, 10H, Ar)
11d	2800, 1720	[a] 2.4-2.8 (m, 2H, 2H-7), 3.2 (s, 3H, C*H*$_3$), 3.1-4.4 (m, 9H, 4C*H*$_2$, H-6), 5.5 (s, 1H, C*H*-Ar$_2$), 5.6-6.0 (m, 1H, H-8), 7.4 (s, 10H, Ar)
11e	2800, 1735	1.6-3.0 (m, 10H, 5C*H*$_2$), 3.2-3.6 (m, 3H, H-6, C*H*$_2$-Ar), 5.0 (s, 1H, C*H*-Ar$_2$), 5.3 (m, 1H, H-8), 7.3 (br s, 15H, Ar)
11f	2800, 1730	1.5-3.2 (m, 14H, 7C*H*$_2$), 3.3-3.8 (m, 1H, H-6), 5.0 (s, 1H, C*H*-Ar$_2$), 5.1-5.4 (m, 1H, H-8), 7.2-7.6 (m, 15H, Ar)
11g	3530, 2800, 1730	1.6-3.2 (m, 10H, 5C*H*$_2$), 3.3-3.8 (m, 3H, H-6, C*H*$_2$-Ar), 3.8-4.4 (m, 1H, OH, deuterium oxide exchangeable), 5.0-5.6 (m, 1H, H-8), 7.1-7.7 (m, 15H, Ar)

[a] Deuterium oxide.

Table V

^{13}C NMR Selected Data (δ ppm) for 2,5-Dioxo-1,4-diazobicyclo[4.3.0]-nonanes and 1,4-Diazabicyclo[4.3.0]nonanes (deuteriochloroform)

No.	C-2	C-3	C-5	C-6	C-7	C-8	C9
7a	163.0	53.3	167.6	54.0	33.3	67.6	40.1
7b	163.6	53.8	167.0	57.4	37.5	67.7	45.0
7c	163.6	53.5	167.5	57.3	37.5	67.7	46.2
7e	163.4	50.9	167.5	54.0	37.9	67.7	49.3
7f	163.6	52.3	167.5	54.2	37.8	67.9	48.0
8b	162.7	50.9	165.3	51.7	35.5	71.2	49.2
8d	162.7	51.6	166.4	50.7	44.0	71.0	49.2
8f	162.6	53.4	166.4	56.9	35.5	71.5	51.7
8g	162.8	51.5	166.4	57.1	49.3	71.4	50.7
9a	163.6	49.5	165.7	50.8	33.9	71.4	51.2
9b	162.9	50.6	166.1	53.1	33.8	70.8	40.8
9c	163.4	50.9	166.4	53.1	40.8	71.0	49.6
9d	162.9	53.1	166.0	56.5	33.8	71.3	50.5
9e	163.3	50.8	166.3	56.7	49.8	71.5	50.7
10a	62.4	50.5	60.0	53.9	38.8	68.3	45.5
10b	62.7	52.0	62.6	56.9	39.1	68.9	50.9
11a	59.9	51.0	59.4	53.9	40.9	72.4	45.6
11b	61.4	47.1	59.0	50.4	34.3	71.4	46.1
11c	49.7	56.0	51.5	42.8	32.4	72.5	41.3
11d	60.5	51.0	58.6	54.0	45.3	73.1	47.9
11e	60.3	56.9	62.7	56.9	50.9	73.2	52.3
11f	57.1	52.3	59.8	56.9	36.1	73.2	50.9
11g	52.3	57.0	50.9	62.8	35.8	75.0	60.3

ing atropine sulfate as reference. None of them prevents spasms induced by acetylcholine or baryum chloride.

EXPERIMENTAL

Melting points were determined on a Reichert micro-hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer spectrophotometer either as potassium bromide pellets or in chloroform or carbon tetrachloride solution. Proton magnetic resonance spectra at 60 MHz were determined with a Jeol C 60 H or a Varian EM 360 A instrument, using tetramethylsilane as an internal standard. The ^{13}C magnetic resonance spectra were determined on a Jeol FX60 spectrometer. The high field ^{1}H (300 MHz) and ^{13}C nmr spectra were recorded on a Brücker MSL 300 spectrophotometer. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hz. The ^{1}H nmr spectral data of the final products at 60 MHz are reported in Tables III and IV, and ^{13}C nmr selected spectral data in Table V. The nmr signals were designated as follows: s, singlet, br s, broad singlet, d, doublet, t, triplet, q, quadruplet, m, multiplet. Rotatory powers were determined at 578 nm wavelength on a Perkin Elmer 241 polarimeter in chloroform or in water for hydrochlorides. Microanalysis for C, H, Cl, N were performed by the Service Central d'Analyse du CNRS (Thiais, France).

Silica gel (200-400 mesh) from Amicon and neutral alumina from Merck were used for column chromatographic separations. Usual treatment of the final organic solutions consisted in drying over anhydrous magnesium sulfate and removing the solvent to afford the purified compound.

(2*S*,4*R*)-4-Hydroxy-2-methoxycarbonylpyrrolidine Hydrochloride (**4**).

A suspension of 30 g (0.228 mole) of *trans*-4-hydroxy-L-proline

in 250 ml of anhydrous methanol was cooled between 0 and 5°, then 54.5 g (0.457 mole) of thionyl chloride were added dropwise while stirring. At the end of the addition the reaction mixture was kept for 4 hours at room temperature. The solvent was evaporated; the crude solid was recrystallized from a mixture ethanol-ether (80:20) to afford 40 g (95%) of **4** as a white powder, mp 170-172°, lit 171-172° [15]; $[\alpha]_D^{25}$ (water) −25°; ir (potassium bromide): ν 3340, 1735 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.9-2.6 (m, 2H, H-3), 2.7-4.6 (m, 4H, H-2, H-4, H-5), 3.8 (s, 3H, CH_3), 4.8-5.2 (m, 1H, OH), 9.2-10.2 (m, 2H, $^+NH_2$); ^{13}C nmr (DMSO-d_6): δ 37.1 (C-2), 42.4 (C-3), 53.4 (C-7), 57.8 (C-5), 68.6 (C-4), 169.2 (C-6).

Anal. Calcd. for $C_6H_{12}ClNO_3$: C, 39.67; H, 6.61; Cl, 19.56; N, 7.72. Found: C, 39.65; H, 6.68; Cl, 19.63; N, 7.74.

(2*S*,4*R*)-1-Chloroacetyl-4-hydroxy-2-methoxycarbonylpyrrolidine (**5**).

Chloroacetyl chloride (11.3 g, 0.1 mole) was added dropwise while stirring to a suspension of **4** (18.15 g, 0.1 mole) in 500 ml of anhydrous benzene at room temperature. The reaction mixture was refluxed for 2 hours. The hot organic solution was filtered on charcoal and evaporated to give 19.3 g (87%) of a crystallized residue which was washed with ether, mp 109-110°; $[\alpha]_D^{25}$ (water) −18°; ir (potassium bromide); ν 3350, 1735, 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.1 (m, 2H, H-3), 3.6 (s, 3H, CH_3), 3.2-4.6 (m, 4H, H-2, H-4, H-5), 4.4 (s, 2H, CH_2Cl), 5.2 (m, 1H, exchangeable OH); ^{13}C nmr (DMSO-d_6): δ 39.8 (C-3), 42.6 (C-7), 51.7 (C-5), 54.7 (CH_2Cl), 57.9 (C-2), 69.0 (C-4), 164.9 (C-8), 171.9 (C-6).

Anal. Calcd. for $C_8C_{12}ClNO_4$: C, 43.34; H, 5.42; Cl, 16.03; N, 6.32. Found: C, 43.45; H, 5.40; Cl, 16.05; N, 6.28.

(6*S*,8*R*)-2,5-Dioxo-8-hydroxy-4-methyl-1,4-diazabicyclo[4.3.0]-nonane (**7a**).

To a solution of 9 g (40 mmoles) of **5** in 90 ml of absolute methanol, an excess (18 ml) of a 33% methanolic solution of methylamine was added and the mixture was autoclaved at 60° for 12 hours and then allowed to stand at room temperature for 8 hours. The solvent was removed, the residue dissolved in chloroform and the filtered solution dried over anhydrous magnesium sulfate. The crude product was purified on neutral alumina column using ethyl acetate-methanol (90:10) as eluent. The yield, formula, elemental analysis and spectral data of the pure compound are listed on Tables I and III; ^1H nmr (deuteriochloroform): 300 MHz δ 2.0-2.1 (m, 1H, H-7β, $J_{7\beta\text{-}7\alpha}$ = 13 Hz, $J_{7\beta\text{-}6}$ = 11.5 Hz, $J_{7\beta\text{-}8}$ = 4.5 Hz), 2.4 (m, 1H, H-7α, $J_{7\alpha\text{-}7\beta}$ = 13 Hz, $J_{7\alpha\text{-}6}$ = 6 Hz), 3.0 (s, 3H, CH_3), 3.5 (d, 1H, H-9α, $J_{9\alpha\text{-}9\beta}$ = 13 Hz), 3.7-3.8 [m, 3H, H-9β ($J_{9\beta\text{-}9\alpha}$ = 13 Hz, $J_{9\beta\text{-}8}$ = 4.5 Hz), H-3β ($J_{3\beta\text{-}3\alpha}$ = 17.5 Hz), OH (deuterium oxide exchangeable)], 4.2 (d, 1H, H-3α, $J_{3\alpha\text{-}3\beta}$ = 17.5 Hz), 4.4-4.5 (dd, 1H, H-6, $J_{6\text{-}7\alpha}$ = 6 Hz, $J_{6\text{-}7\beta}$ = 11.5 Hz), 4.53 (t, 1H, H-8, $J_{8\text{-}7\beta}$ = $J_{8\text{-}9\beta}$ = 4.5 Hz).

(6*S*,8*R*)-4-Substituted 2,5-Dioxo-8-hydroxy-1,4-diazabicyclo[4.3.0]-nonanes **7b-f**.

General Procedure.

A mixture of 15.5 g (0.07 mole) of **5**, a primary amine (0.085 mole) and triethylamine (9.10 g, 0.09 mole) was refluxed in 2-ethoxyethanol (250 ml) for 48 hours. The solvent was removed and the residue treated with a mixture of methylene chloride and benzene. The precipitate was filtered off and the clear solution was evaporated under reduced pressure; the crude residue was purified on a silica gel column using ethyl acetate-methanol (95:5) as eluent. The yields, formula, elemental analysis and spectral data are listed on Tables I and III.

(6*S*,8*R*)-8-acyloxy-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonanes **8a-h**.

General Procedure.

To a solution of **7a**, **7e** or **7f** (6 mmoles) in anhydrous benzene were added a stoichiometric amount of a suitable anhydride and 50 mg of dimethylaminopyridine (DMAP). The mixture was stirred at room temperature for 12 hours, then washed with a 5% aqueous solution of hydrochloric acid. Usual treatment of organic phase afforded a crude residue which was purified on silica gel column using ethyl acetate-hexane (8:2) as eluent. The yields, formula, elemental analysis and spectral data are listed on Tables I and III. ^1H nmr of **8f** at 300 MHz (deuteriochloroform): δ 2.1-2.2 (m, 1H, H-7β, $J_{7\beta\text{-}7\alpha}$ = 14 Hz, $J_{7\beta\text{-}6}$ = 11.5 Hz, $J_{7\beta\text{-}8}$ = 5 Hz), 2.4-2.5 (q, 1H, H-7α, $J_{7\alpha\text{-}6}$ = 6 Hz), 2.95 (s, 3H, CH_3), 3.55 (d, 1H, H-9α, $J_{9\alpha\text{-}9\beta}$ = 14 Hz), 3.75 (d, 1H, H-3β, $J_{3\beta\text{-}3\alpha}$ = 16 Hz), 3.9 (dd, 1H, H-9β, $J_{9\beta\text{-}9\alpha}$ = 14 Hz, $J_{9\beta\text{-}8}$ = 5 Hz), 4.15 [m, 2H, H-3α ($J_{3\alpha\text{-}3\beta}$ = 16 Hz), H-6 ($J_{6\text{-}7\beta}$ = 11 Hz, $J_{6\text{-}7\alpha}$ = 6 Hz)], 5.0 [s, 1H, N-CH(C_6H_5)$_2$], 5.55 (t, 1H, H-8, $J_{8\text{-}7\beta}$ = $J_{8\text{-}9\beta}$ = 5 Hz), 7.3 (s, 10H, Ar).

(6*S*,8*S*)-8-acyloxy-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonanes **9a-e**.

General Procedure.

To a solution of **7a** or **7e** (5 mmoles) in anhydrous tetrahydrofuran (50 ml) were added 2.62 g (10 mmoles) of triphenylphosphine and an excess (10 mmoles) of the suitable acid. The mixture was stirred at room temperature. When dissolution was achieved a solution of 1.74 g (10 mmoles) of diethyl azodicarboxylate (DEAD) in tetrahydrofuran was added dropwise while an exothermic reaction occurred. The mixture was stirred for 16 hours, then the solvent removed; the crude residue purified by flash chromatography (ethyl acetate) afforded the expected (6*S*,8*S*) esters. The yields, formula, elemental analysis and spectral data are listed in Tables I and III.

(6*S*,8*R*)-8-Hydroxy-1,4-diazabicyclo[4.3.0]nonanes **10a-c**.

General Procedure.

A solution of **7a**, **7e** or **7f** (27 mmoles) in 75 ml of anhydrous tetrahydrofuran was added dropwise to a suspension of lithium aluminium hydride (3 g, 81 mmoles) in 100 ml of cooled anhydrous tetrahydrofuran and the mixture was treated successively with 20 ml of water and 5 ml of 15% aqueous sodium hydroxide solution. After stirring for 10 minutes, filtration and washing with ether, the organic phase was dried on magnesium sulfate. The crude residue was purified on alumina column using ethyl acetate-methanol (85:15) as eluent. The yields, formula, elemental analysis and spectral data are listed in Tables II and IV.

(6*S*,8*R*)-8-Acyloxy-1,4-diazabicyclo[4.3.0]nonanes (**11a-f**).

General Procedure.

These compounds were prepared from **10a**, **10b** or **10c** using the procedure described for esters **8a-h**.

(6*S*,8*R*)-4-Benzyl-8-benziloyloxy-1,4-diazabicyclo[4.3.0]nonane (**11g**).

To a solution of 0.77 g (3.3 mmoles) of **10b** in 40 ml of anhydrous toluene, 100 mg of sodium were added and the suspension refluxed for 30 minutes. Separately a solution of 0.85 g (3.3 mmoles) of ethyl benzilate in 40 ml of toluene was prepared. The

solutions were mixed together in a distillation apparatus and refluxed until the azeotropic mixture was separated, then the reflux was maintained for 24 hours. After removing the solvent, the crude residue was purified by flash chromatography (ethyl acetate) to afford 290 mg (22%) of pure ester. Elemental analysis, formula and spectral data are recorded in Tables II and IV.

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