SYNTHESIS OF (±)-(2*R**, 11b*S**)-3'-ARYL-9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROSPIRO-[BENZO[*a*]QUINOLIZIN-2,5'-OXAZOLIDINE]-2',4'-DIONES.

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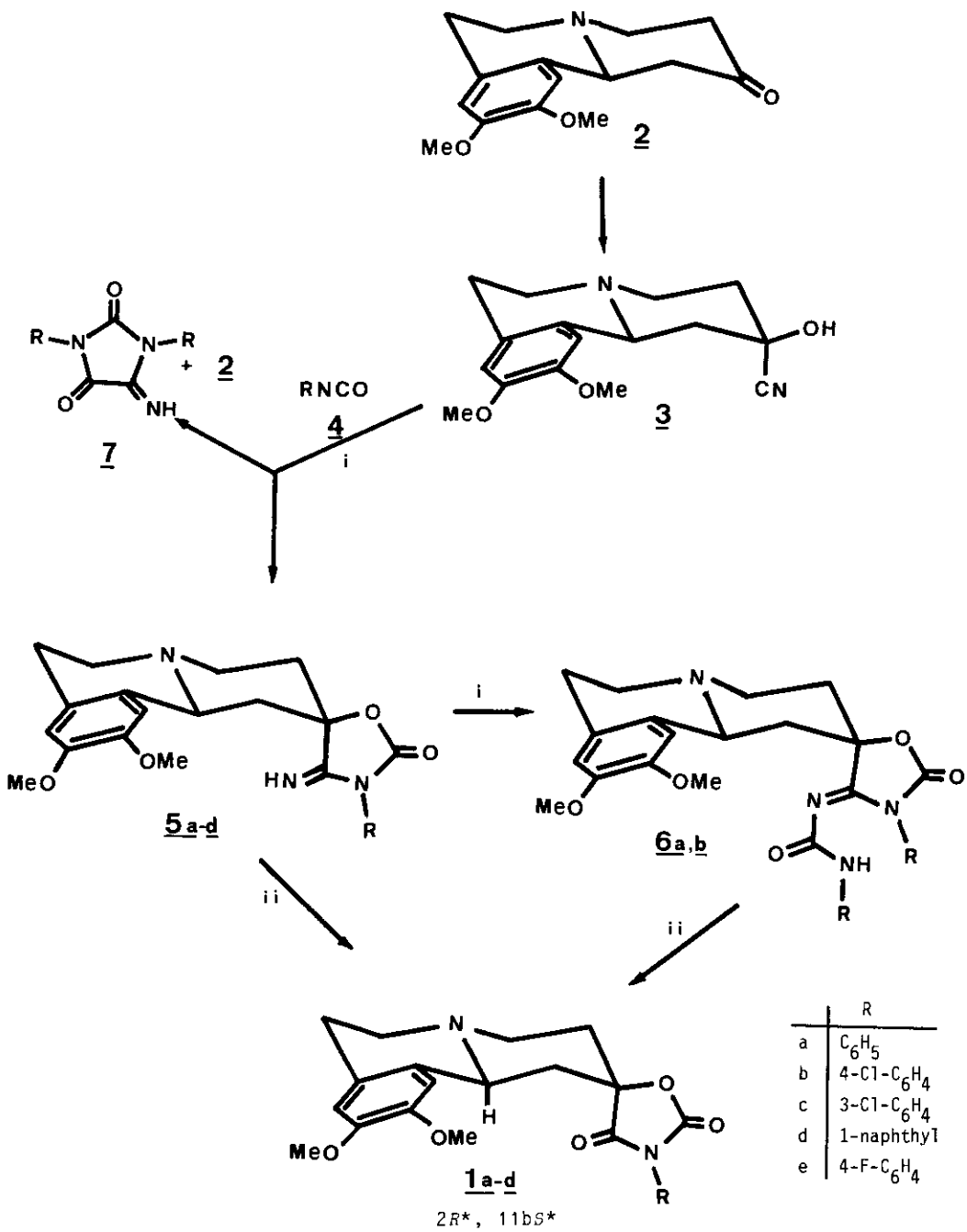
Abstract —— The synthesis of (±)-(2*R**, 11b*S**)-3'-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidine]-2',4'-diones (1) was achieved by two alternative routes involving the treatment of cyanohydrin 3 with aryl isocyanates via 4-imino derivatives 5 and 6 or the cyclization of the hydroxy ester 9 with aryl isocyanates. Compounds 1 present a *trans* conformation in the quinolizidine system and exist in a (2*R**, 11b*S**) configuration.

The discovery of α_2-adrenoceptor antagonism for several 2-substituted benzo[*a*]quinolizidines[1,2] may provide a basis on which to explain the antihypertensive[3] activity described for some of these derivatives, while, at the same time, it allows the prediction of additional pharmacological properties, like antidepressant[4] and hipoglycemic[5] activities, among others.

Within the scope of our current research on spiro derivatives with structural and electronic characteristics similar to those of 2β-substituted benzo[*a*]quinolizidinic α_2-adrenoceptor antagonists[6], we considered of special interest the synthesis of the (±)-(2*R**, 11b*S**) diastereomers of 3'-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizidin-2,5'-oxazolidine]-2',4'-diones (1).

A suitable route for the synthesis of diastereomers 1 would be the transformation of the 9,10-dimethoxybenzo[*a*]quinolizidin-2-one (2)[7] into the 2,4-oxazolidinedione system 1 via its cyanohydrin 3, followed by treatment with aryl isocyanates and hydrolysis[8] (Scheme 1). This approach is based on the stereoselective cyanation of substituted cyclohexanones through an axial attack of the cyanide ion on the most stable conformation.[9]

Thus, the treatment of the cyanohydrin 3[6] with two equivalents of aryl isocyanate always led to 4'-imino-2-oxazolidinones 5 and, in some cases, also to their 4'-carbamoylimino derivatives 6.



	R
a	C_6H_5
b	4-Cl-C_6H_4
c	3-Cl-C_6H_4
d	1-naphthyl
e	4-F-C_6H_4

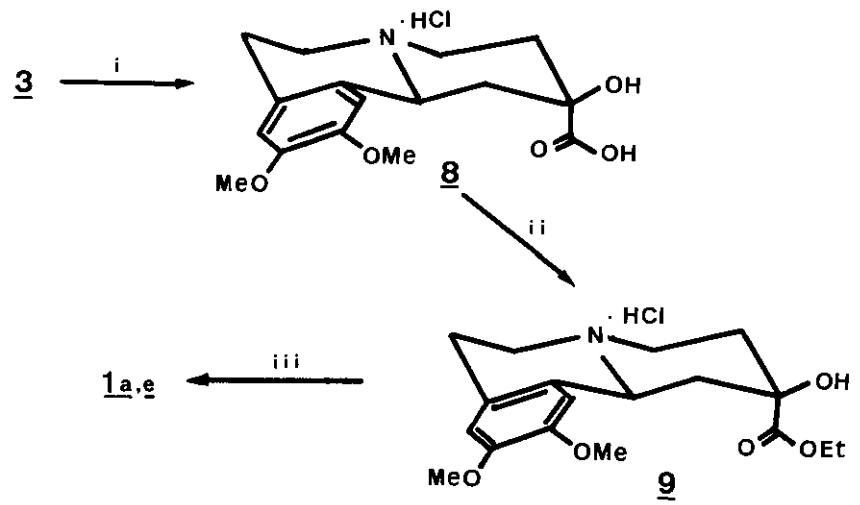
i CH_2Cl_2-DMF, Et_3N or DABCO, Reflux or ultrasound.

ii 35 % HCl, EtOH, Reflux, 1 h.

Scheme 1

As it has been previously reported,[8] the moderate yields of iminooxazolidinones 5 are mainly due to formation of the 5-imino-2,4-imidazolidinediones 7 as secondary products, which arise from the reaction between two molecules of isocyanate 4 and one molecule of hydrogen cyanide formed in dissociation of cyanohydrin 3 to 2. Changes in the basic catalyzer using triethylamine or 1,4-azabicyclo[2.2.2]octane did not avoid the formation of 7. Acid hydrolysis of 5 or 6 gave the expected 2,4-oxazolidinediones in good yields.

In an attempt to improve the above-described method, an alternative procedure, shown in Scheme 2 was also assayed. Acid hydrolysis of cyanohydrin 3 to the α-hydroxy acid 8, followed by esterification in ethanol employing dry hydrogen chloride or boron trifluoride etherate as a catalyst, led to 9 in high yield. When 9 was heated in the absence of solvent with aryl isocyanates 4 at 60 ºC for 16 h, the desired 2,4-oxazolidinediones were obtained in one step. The *O*-carbamoyl derivatives described in the literature for analogous reactions[10] were not isolated in this case.



i 35% HCl, reflux, 2 h

ii EtOH, HCl (g) or BF_3-Et_2O, reflux

iii R-NCO, Δ

Scheme 2

In the stereochemical analysis of compounds 1, the conformation of the quinolizidine ring system and the relative configurations of the chiral atoms are to be considered. A predominant *trans* conformation can be proposed on the basis of ir[11,12] and ^{13}C-nmr[13,14] data. Thus, compound 1a shows a coupling constant $^{1}J(^{13}C\text{-}H)$ of 133 Hz for C_{11b} and chemical shifts of 51.40 and 29.61 ppm for C_6 and C_7, respectively.

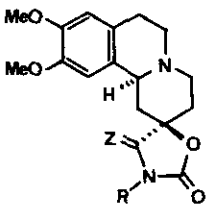
The assigment of the (2*R**, 11b*S**) configuration to compounds 1 was based upon two independent criteria: the high value found for the half-width of the C_4, signal ($W_{1/2} \simeq 18$ Hz) in the ^{13}C coupled spectrum of 1a, which is in agreement with the vicinal coupling between C_4, and the two *anti* C_1-H and C_3-H hydrogen atoms;[14] and the found deshielding effect of the C_4, carbonyl group on the C_{11b} proton[15] in the ^{1}H-nmr spectrum (signal al ca. 4.2 ppm for 1a).

EXPERIMENTAL

Melting points are uncorrected and were determined in a Büchi apparatus. Spectral data were recorded on the following instruments: ir — Perkin Elmer 577; ^{1}H-nmr — Hitachi-Perkin Elmer R-24 (60 MHz) and Brucker WM-200-SY (200.16 MHz); ^{13}C-nmr — Brucker WM-200-SY (50.32 MHz). All chemical shifts are referred to TMS. Elemental analyses were determined using a Carlo Erba Elemental Analyser model 1104.

(±)-(2*R**, 11b*S**)-3'-Aryl-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidin]-2'-ones (5) and (±)-(2*R**, 11b*S**)-3'-aryl-4'-arylcarbamoylimino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidin]-2'-ones (6). A mixture of 3.5 mmol of cyanohydrin 3, the suitable isocyanate 4 (7 mmol), and triethylamine (0.2 g) or 1,4-diazabiciclo-[2.2.2]octane (0.2 g) in 35 ml of dry CH_2Cl_2-dimethylformamide (6:1) was irradiated with ultrasound at room temperature for 2-3 h. The reaction mixture was evaporated *in vacuo* and the residue obtained was extracted with hot EtOH, from which were successively precipitated crops of *N*,*N*'-diarylurea and 1,3-diaryl-4-imino-2,5-imidazolidinediones 7, followed by compounds 5 and 6, which were collected by filtration (Table 1).

(±)-(2*R**, 11b*S**)-2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carboxylic acid Hydrochloride (8). A mixture of 5 g (17.4 mmol) of 3 and 10 ml of 35% aqueous HCl was heated in a 120 °C bath for 2 h. The reaction mixture was kept at 0 °C for 24 h and the inorganic solid formed was filtered off. The addition of 10 ml of EtOH allowed crystallization of 4.8 g (80 %) of 8; mp 255-258 °C (EtOH). Anal. Calcd for $C_{16}H_{22}NO_5Cl$: C, 55.89; H, 6.40; N. 4.08. Found: C, 55.61; H, 6.40; N, 3.95. Ir (KBr): 1700 cm^{-1} (C=O). ^{1}H-Nmr (60 MHz, d_6-DMSO) δ : 6.80 and 6.60 (2 s, 2H, 8-H and 11-H), 5.20 (s, 1H, OH), 4.35 (d, J = 11 Hz, 1H, 11b-H), 3.70 (s, 6H, 2 OMe), 3.60-1.60 (m, 10H).



5 Z = NH

6 Z = NCONHR

Table 1 : Main experimental data for compounds 5 and 6

Compd. no.	Yield/%	mp /°C (recryst.)	Ir(KBr)/cm^{-1} Z	C-H[a]	C_2,=O	C_4,=N	^{1}H-Nmr (d_6-DMSO, 60 MHz) [b] δ NH (s,1H)	8-H and 11-H (2 s, 2H)	11b-H (m,1H)	OMe (s,6H)	R (m)	Elemental analysis Calculated / Found C	H	N
5a	23	206-207	3420	2800	1800	1680	[c]	6.80, 6.70	4.05	3.65	7.50	67.81	6.14	10.32
		(EtOH)		2760								67.59	6.03	10.12
5b	20	111-113	3290	2800	1795	1680	9.00	6.70, 6.65	4.00	3.70	7.60-7.20	62.51	5.44	9.51
		(EtOH)		2755								62.37	5.31	9.37
5c	40	119-121	3460	2800	1800	1680	7.95	6.80, 6.70	4.15	3.75	7.80-7.50	62.51	5.44	9.51
		(iC_3H_7OH)		2765								62.28	5.29	9.23
5d	35	237-238	3440	2800	1790	1670	8.60	6.78, 6.67	4.00	3.72	8.20-8.10	70.90	5.91	9.19
		(iC_3H_7OH)		2760						3.71	7.80-7.60	70.67	5.63	8.91
6a	20	193-195	3300	2805	1800	1680	8.75	6.80, 6.70	3.90	3.70	7.80-6.90	68.44	5.70	10.65
		(EtOH)	1715	2760								68.44	5.70	10.43
6b	25	132-133	3250	2800	1795	1680	7.90	6.73, 6.66	3.98	3.72	7.67-7.48	60.50	4.70	9.41
		(EtOH)	1750	2760								60.31	4.59	9.28

[a] Bohlmann bands. [b] Except 5d (d_5-pyridine, 200.16 MHz) and 6b (d_6-DMSO, 200.16 MHz).

[c] Not detected.

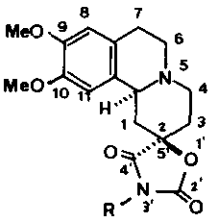


Table 2 : Main experimental data for compounds 1

Compd. no.	Method	Yield/%	mp /°C (recryst.)	Ir: C=O[a] $C_{2'}$=O	Ir: C=O[a] $C_{4'}$=O	^{1}H-Nmr(d_6-DMSO, 60 MHz)[b] δ H-8 and H-11 (2 s, 2H)	H-11b (m,1H)	OMe (s)	R(m)	Elemental analysis Calculated / Found C	H	N
1a	C	40	205-207	1820	1750	6.95, 6.74	4.25	3.76	7.50-7.30	70.58	5.88	6.86
1a · HCl	A	73	(EtOH)					3.65		70.32	5.61	6.71
	B	61	218-220							62.09	5.62	6.30
			(EtOH-Et_2O)							61.87	5.52	6.14
1b · HCl	A	80	233-235	1815	1740	6.80	4.00	3.70	7.70-7.10	57.62	5.01	5.84
	B	65	(EtOH)							57.41	4.83	5.61
1c · HCl	A	85	227-229	1815	1740	6.85, 6.80	4.75	3.75	7.75-7.35	57.62	5.01	5.84
			(EtOH)							57.32	4.79	5.73
1d · HCl	A	85	254-255	1825	1735	6.80, 6.70	4.80	3.80	8.30-7.40	65.52	5.46	5.66
			(iC_3H_7OH)							65.39	5.38	5.41
1e	C	42	169-171	1815	1740	6.85, 6.70	[c]	3.75	7.70-7.00	64.79	5.40	6.57
			(EtOH)							64.51	5.23	6.41

[a] All compounds studied as free bases showed Bohlmann bands at ca. 2760 and 2800 cm^{-1}.

[b] Except 1a (d_5-pyridine, 200.16 MHz). [c] Signal not detected.

(±)-(2*R**, 11b*S**)-Ethyl 2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carboxylate Hydrochloride (9). Method A: A suspension of 8 (3.45 g, 10 mmol) in 100 ml of EtOH was saturated with dry HCl and refluxed for 2 h under continuous stream of dry HCl, then cooled and filtered. The filtrate obtained was evaporated to dryness and the residue was recrystallized from 2-propanol. Yield, 3.2 g (86 %); mp 212-214 °C (2-propanol). Anal. Calcd for $C_{18}H_{26}NO_5Cl$: C, 58.41; H, 6.99; N, 3.77. Found: C, 57.98; H, 6.81; N, 3.43. Ir (KBr): 3520, 3300 (O-H), 1730 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, d_6-DMSO) δ : 6.90 and 6.70 (2 s, 2H, 8-H and 11-H), 4.30 (m, 1H, C_{11b}-H), 4.25 (q, J = 7 Hz, 2H, CH_2-CH_3), 3.75 (s, 6H, 2 OMe), 3.60-1.60 (m, 10H), 1.30 (t, J = 7 Hz, 3H, CH_2-CH_3). Method B: A mixture of 0.3 g (0.87 mmol) of 8, 5 ml of anhidrous EtOH, and 0.15 ml of freshly distilled BF_3-Et_2O complex was refluxed for 20 h in a 110 °C bath, then cooled and filtered. The filtrate was diluted with 5 ml of water, basified with NaOH pellets and extracted with $CHCl_3$ (3 x 25 ml). The combined chloroform extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in 3 ml of 2-propanol and treated with dry HCl to precipitate 0.3 g (92 %) of 9.

(±)-(2*R**, 11b*S**)-3'-Aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidine]-2',4'-diones (1). Method A: A solution of 1.5 mmol of the adequate derivative of 5 in EtOH (5 ml) and 35 % hydrochloric acid (1 ml) was refluxed for 1 h. The cooled reaction mixture was evaporated to dryness and the residue was recrystallized as hydrochloride. Method B: A mixture of 1.5 mmol of 6, 5 ml EtOH and 1 ml of concentrated hydrochloric acid was refluxed for 1 h. The cooled reaction mixture was poured on ice (25 g), the *N*-arylurea thus precipitated was filtered off and the filtrate was evaporated and the residue was recrystallized as hydrochloride. Method C: A mixture of 0.8 g (2.4 mmol) of 9 (base) and 24 mmol of the adequate isocyanate 4 was heated at 60 °C for 16 h. The excess of 4 was distilled off and the residue was taken up with EtOH. After filtration of small amounts of *N*,*N*'-diarylurea, the expected oxazolidinediones 1 precipitated. Data for compounds 1 can be found in Table 2. Compound 1a, ^{13}C-nmr (50.32 MHz, d_5-pyridine) δ : 174.60 ($C_{4'}$, s, $W_{1/2} \simeq 18$ Hz), 153.82 ($C_{2'}$, s), 148.59* and 148.30* (C_{10} and C_9, 2 s), 131.88 ($C_{1''}$, s), 129.29 ($C_{3''}$ and $C_{5''}$, d, J = 160 Hz), 129.10 ($C_{4''}$, d, J = 160 Hz), 128.89 (C_{11a}, s), 127.32 (C_{7a}, s), 126.64 ($C_{2''}$ and $C_{6''}$, d, J = 160 Hz), 112.69 (C_8, d, J = 154 Hz), 109.61 (C_{11}, d, J = 154 Hz), 83.46 (C_2, s), 57.90 (C_{11b}, d, J = 133 Hz), 55.99** and 55.80** (C_{13} and C_{12}, 2 q, J = 145 Hz), 51.43$^+$ and 51.11$^+$ (C_6 and C_4, 2 t; J = 133 Hz), 32.59 (C_3, t, J = 132 Hz), 29.61 (C_7, t, J = 127 Hz). The signals marked with *,**, and $^+$ could not be asigned with certainty.

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