

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

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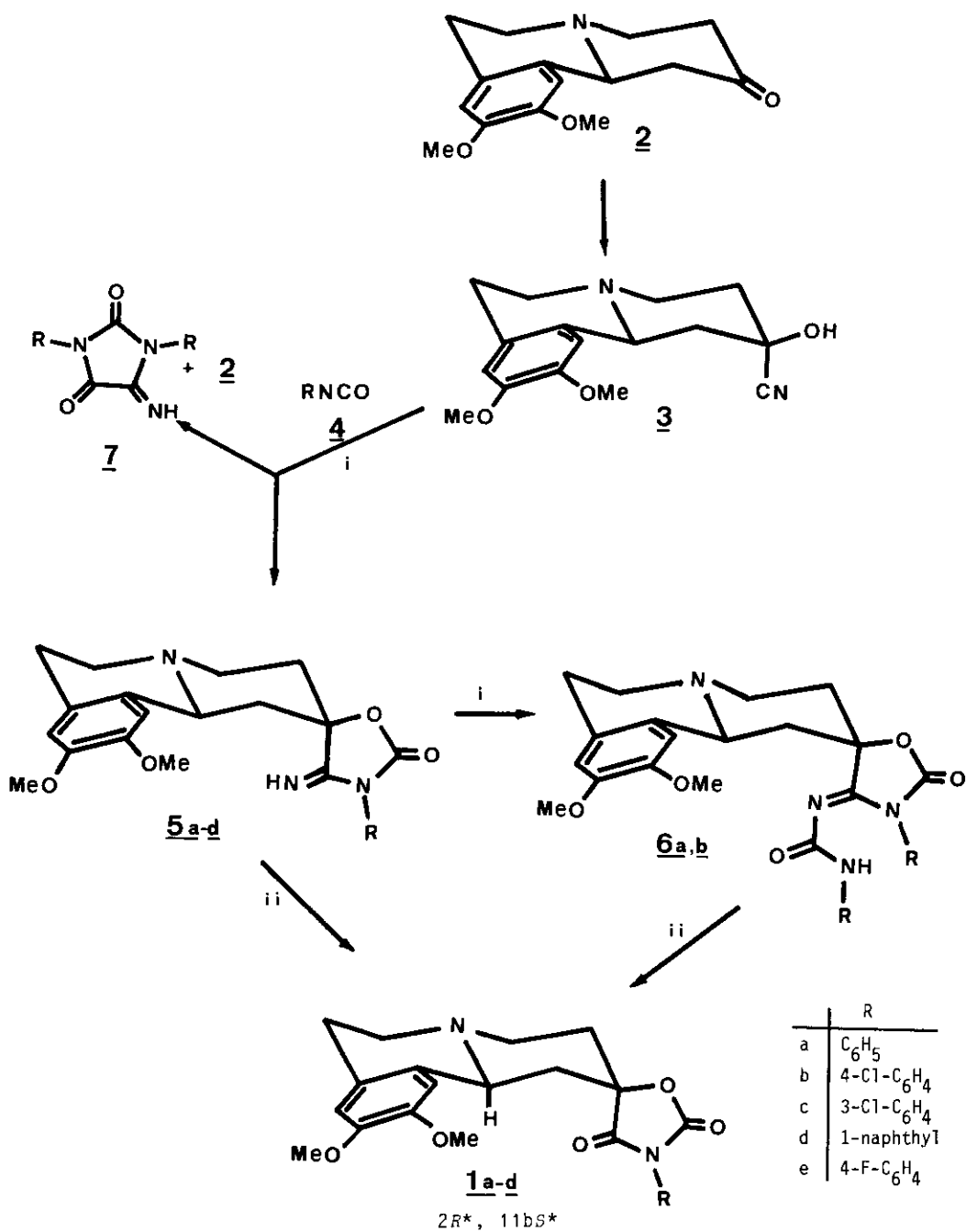
Abstract — The synthesis of (\pm)-(2*R**, 11*bS**)-3'-aryl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrospiro[benzo[*a*]quinolizidin-2,5'-oxazolidine]-2',4'-diones (**1**) was achieved by two alternative routes involving the treatment of cyanohydrin **3** with aryl isocyanates via 4-imino derivatives **5** 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**, 11*bS**) 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 antihypertensive³ activity described for some of these derivatives, while, at the same time, it allows the prediction of additional pharmacological properties, like antidepressant⁴ and hipoglycemic⁵ activities, among others.

Within the scope of our current research on spiro derivatives with structural and electronic characteristics similar to those of 2 β -substituted benzo[*a*]quinolizidinic α_2 -adrenoceptor antagonists⁶, we considered of special interest the synthesis of the (\pm)-(2*R**, 11*bS**) diastereomers of 3'-aryl-9,10-dimethoxy-1,3,4,6,7,11*b*-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 hydrolysis⁸ (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**.



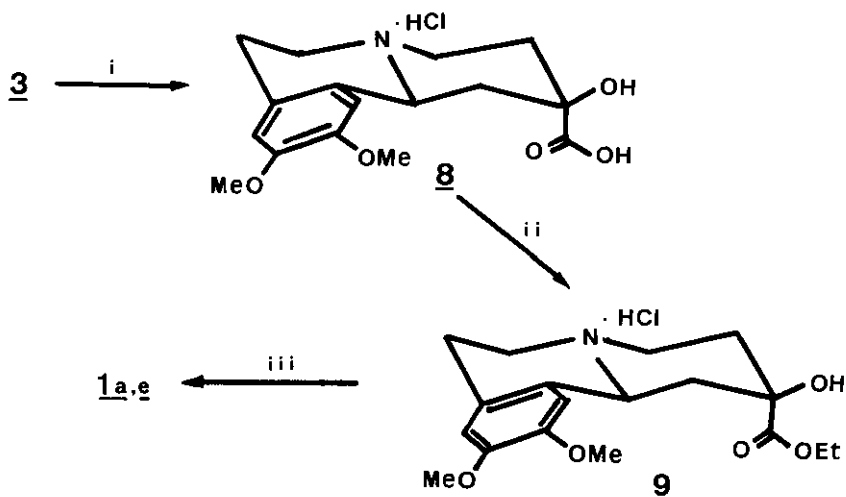
i CH₂Cl₂-DMF, Et₃N or DABCO, Reflux or ultrasound.

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

Scheme 1

As it has been previously reported,⁸ the moderate yields of imino-oxazolidinones 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 °C for 16 h, the desired 2,4-oxazolidinediones were obtained in one step. The *O*-carbamoyl derivatives described in the literature for analogous reactions¹⁰ were not isolated in this case.



i 35% HCl, reflux, 2 h

ii EtOH, HCl (g) or $\text{BF}_3\text{-Et}_2\text{O}$, 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 ¹³C-nmr^{13,14} data. Thus, compound 1a shows a coupling constant $^1J(^{13}\text{C-H})$ of 133 Hz for C_{11b} and chemical shifts of 51.40 and 29.61 ppm for C₆ and C₇, respectively.

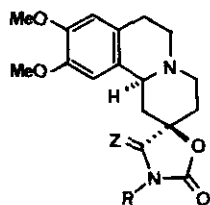
The assignment of the (2*R**, 11*bS**) configuration to compounds 1 was based upon two independent criteria: the high value found for the half-width of the C₄ signal ($W_{1/2} \approx 18$ Hz) in the ¹³C coupled spectrum of 1a, which is in agreement with the vicinal coupling between C₄ and the two *anti* C₁-H and C₃-H hydrogen atoms;¹⁴ and the found deshielding effect of the C₄ carbonyl group on the C_{11b} proton¹⁵ in the ¹H-nmr spectrum (signal at 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; ¹H-nmr — Hitachi-Perkin Elmer R-24 (60 MHz) and Bruker WM-200-SY (200.16 MHz); ¹³C-nmr — Bruker 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**, 11*bS**)-3'-Aryl-4'-imino-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrospiro[benzo[α]quinolizin-2,5'-oxazolidin]-2'-ones (5) and (±)-(2*R**, 11*bS**)-3'-aryl-4'-arylcabamoylimino-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrospiro[benzo[α]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-diazabicyclo-[2.2.2]octane (0.2 g) in 35 ml of dry CH₂Cl₂-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'*-diaryurea 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**, 11*bS**)-2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrobenzo[α]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 C₁₆H₂₂NO₅Cl: 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). ¹H-Nmr (60 MHz, d₆-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, 11*b*-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				¹ H-Nmr (d ₆ -DMSO, 60 MHz) ^b δ					Elemental analysis		
			Z	C-H ^z	C ₂ '=O	C ₄ '=N	NH (s, 1H)	8-H and 11-H (2 s, 2H)	11b-H (m, 1H)	OMe (s, 6H)	R (m)	Calculated		
												C	H	N
<u>5a</u>	23	206-207	3420	2800	1800	1680	^a	6.80, 6.70	4.05	3.65	7.50	67.81	6.14	10.32
		(EtOH)		2760								67.59	6.03	10.12
<u>5b</u>	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
<u>5c</u>	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 ₃ H ₇ OH)		2765								62.28	5.29	9.23
<u>5d</u>	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 ₃ H ₇ OH)		2760						3.71	7.80-7.60	70.67	5.63	8.91
<u>6a</u>	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
<u>6b</u>	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

^aBohlmann bands. ^bExcept 5d (d₅-pyridine, 200.16 MHz) and 6b (d₆-DMSO, 200.16 MHz).

^aNot detected.

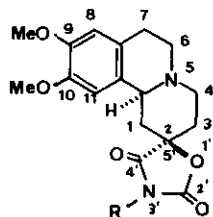


Table 2 : Main experimental
data for compounds 1

Compd. no.	Method	Yield/%	mp /°C (recryst.)	Ir: C=O ^a		¹ H-Nmr(d ₆ -DMSO, 60 MHz) ^b δ				Elemental analysis		
				C ₂ ,=O	C ₄ ,=O	H-8 and H-11 (2 s, 2H)	H-11b (m, 1H)	OMe (s)	R(m)	Calculated Found		
										C	H	N
<u>1a</u>	C	40	205-207	1820	1750	6.95, 6.74	4.25	3.76	7.50-7.30	70.58	5.88	6.86
<u>1a</u> · HCl	A	73	(EtOH)					3.65		70.32	5.61	6.71
	B	61	218-220 (EtOH-Et ₂ O)							62.09	5.62	6.30
<u>1b</u> · 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
<u>1c</u> · HCl	A	85	227-229 (EtOH)	1815	1740	6.85, 6.80	4.75	3.75	7.75-7.35	57.62	5.01	5.84
										57.32	4.79	5.73
<u>1d</u> · HCl	A	85	254-255 (iC ₃ H ₇ OH)	1825	1735	6.80, 6.70	4.80	3.80	8.30-7.40	65.52	5.46	5.66
										65.39	5.38	5.41
<u>1e</u>	C	42	169-171 (EtOH)	1815	1740	6.85, 6.70	^c	3.75	7.70-7.00	64.79	5.40	6.57
										64.51	5.23	6.41

^aAll compounds studied as free bases showed Bohlmann bands at ca. 2760 and 2800 cm⁻¹.

^bExcept 1a (d₅-pyridine, 200.16 MHz).

^cSignal not detected.

(\pm)-(2*R**, 11*bS**)-Ethyl 2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrobenzo[α]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 C₁₈H₂₆N₂O₅Cl: 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. ¹H-Nmr (60 MHz, d₆-DMSO) δ : 6.90 and 6.70 (2 s, 2H, 8-H and 11-H), 4.30 (m, 1H, C_{11*b*}-H), 4.25 (q, ν = 7 Hz, 2H, CH₂-CH₃), 3.75 (s, 6H, 2 OMe), 3.60-1.60 (m, 10H), 1.30 (t, ν = 7 Hz, 3H, CH₂-CH₃). Method B: A mixture of 0.3 g (0.87 mmol) of 8, 5 ml of anhydrous EtOH, and 0.15 ml of freshly distilled BF₃-Et₂O 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 CHCl₃ (3 x 25 ml). The combined chloroform extracts were dried (Na₂SO₄) 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.

(\pm)-(2*R**, 11*bS**)-3'-Aryl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydrospiro[benzo[α]quinolizine-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,N'*-diarylurea 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, ¹³C-nmr (50.32 MHz, d₅-pyridine) δ : 174.60 (C_{4'}, s, $W_{1/2} \approx 18$ Hz), 153.82 (C_{2'}, s), 148.59* and 148.30* (C₁₀ and C₉, 2 s), 131.88 (C_{1''}, s), 129.29 (C_{3''} and C_{5''}, d, ν = 160 Hz), 129.10 (C_{4''}, d, ν = 160 Hz), 128.89 (C_{11*a*}, s), 127.32 (C_{7*a*}, s), 126.64 (C_{2''} and C_{6''}, d, ν = 160 Hz), 112.69 (C₈, d, ν = 154 Hz), 109.61 (C₁₁, d, ν = 154 Hz), 83.46 (C₂, s), 57.90 (C_{11*b*}, d, ν = 133 Hz), 55.99** and 55.80** (C₁₃ and C₁₂, 2 q, ν = 145 Hz), 51.43⁺ and 51.11⁺ (C₆ and C₄, 2 t; ν = 133 Hz), 32.59 (C₃, t, ν = 132 Hz), 29.61 (C₇, t, ν = 127 Hz). The signals marked with *,**, and ⁺ could not be assigned with certainty.

ACKNOWLEDGEMENTS

We thank Prof. M. Martínez Moreno for providing the elemental analyses. Grateful acknowledgements

are made to the Dirección General de Investigación Científica y Técnica (project PA86-0317) and to Universidad Complutense (project UCP 025/87) for financial support. A research grant to JCM from the Plan Nacional de Formación de Personal Investigador is also appreciated.

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Received, 26th September, 1988