Synthesis of 1′-Substituted and 1′,3′-Disubstituted (±)-2R^*,11bS^*-9,10-Dimethoxy-1,3,4,6,7,11b-Hexahydrospiro-[benzo[*a*]quinolizin-2,5′-imidazolidine]-2′,4′-diones

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The results of the reaction between (±)-2R^*,11bS^*-2-alkyl(aryl)amino-1,3,4,6,7,11b-hexahydrobenzo[*a*]-quinolizine-2-carbonitriles **2** and isocyanates under a variety of experimental conditions are discussed. The ureides **3** and iminohydantoins **4** thus obtained were used to prepare N_3-monosubstituted and N_1,N_3-disubstituted derivatives of the (±)-2R^*,11bS^*-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5′-imidazolidine]-2′,4′-dione system **1**. The stereochemistry of these compounds is discussed, on the basis of spectroscopic evidence and study of their chemical reactivity.

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Introduction.

Several types of benzo[*a*]quinolizidine derivatives, specially 2β-alkylsulfonylaminobenzo[*a*]quinolizidines, have recently been characterised as potent and selective α_2-adrenergic antagonists [1-4]. This observation may account for the antihypertensive activity observed in many benzo[*a*]quinolizidines [1,5-8] and allows the prediction of other potentially interesting properties, such as antidepressant and hypoglycemic activities [9,10]. The pharmacological relevance of benzo[*a*]quinolizidine systems led to our research into its 2-spiro derivatives, a class of compounds on which hardly any information is available in spite of their interest. Within the scope of this research, we wish to report here the synthesis of (±)-2R^*,11bS^*-9,-10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizidin-2,5′-imidazolidin]-2′,4′-dione derivatives **1**, which bear a close structural and electronic resemblance to the sulphonamide-based class of α_2-antagonistic benzo[*a*]-quinolizidines.

Results and Discussion.

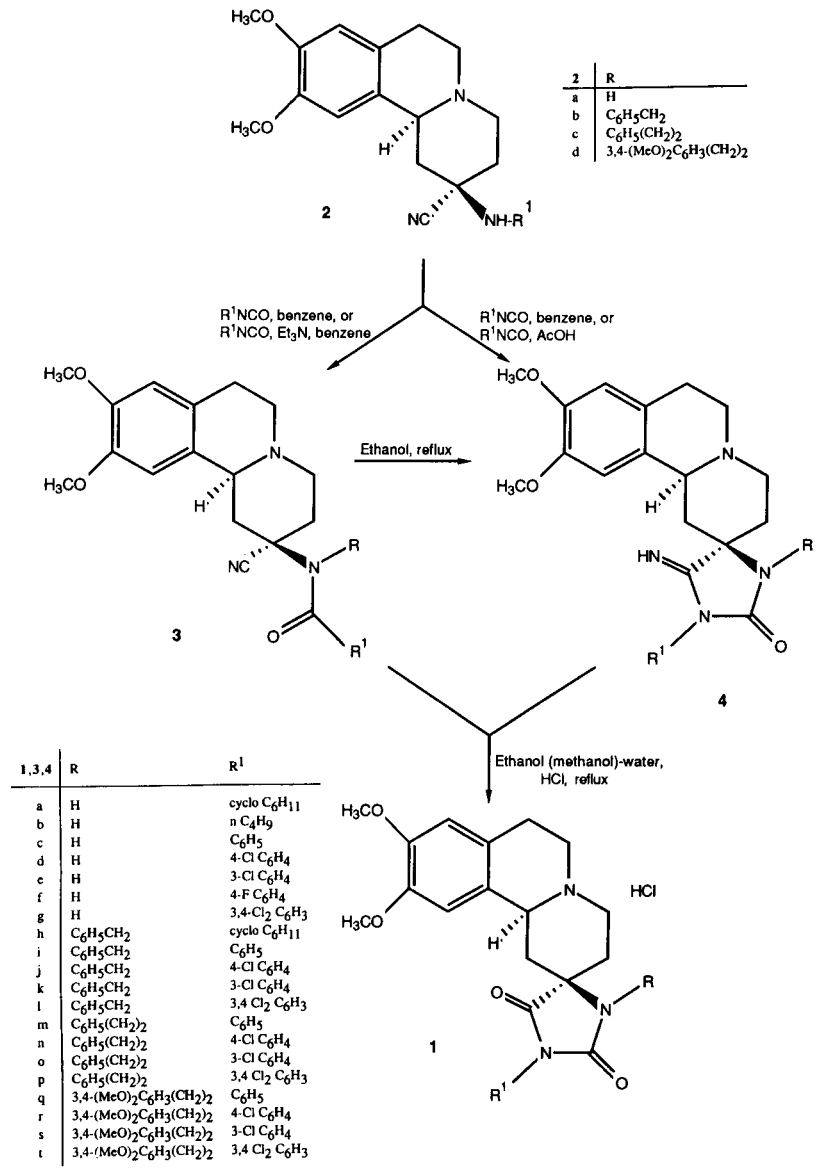
Synthesis.

Aminonitriles **2** [11] can be transformed into compounds **1** as outlined in Scheme 1. Treatment of **2a** (R = H) with isocyanates in benzene solution gave ureides **3** in all cases. While aryl isocyanates, and specially those bearing an electron-withdrawing group, react at room temperature, alkyl isocyanates require a six hour reflux for the reaction to achieve completion. This behaviour changed when the reaction was carried out in acetic acid solution; under these conditions, iminohydantoins **4** were the only products isolated. Aryl derivatives of **4** could also be obtained by refluxing the corresponding ureides **3** in ethanol for 1 hour. Finally, reaction of **2a** with isocyanates in the presence of triethylamine led to mixtures of **3** and **4**; no special operations were required for their separation, as the ureides precipitated from the benzene reaction media, while iminohydantoins remained dissolved. The higher lipophillicity of disubstituted derivatives of **3** prevented their precipitation and therefore favoured their cyclization to iminohydantoins **4**, which were the only products isolated in these cases. *N*-Aryl aminonitriles **2** (R = C_6H_5, 4-MeC_6H_4) failed to react with isocyanates under any of the conditions described above.

Finally, acid hydrolysis of either **3** or **4** led to the desired hydantoins **1** in excellent yields.

The fact that treatment of **2a** with isocyanates yields the same iminohydantoin derivative **4** irrespectively of the presence of acid, basic or no catalysis is worth a brief commentary, It is a well-known fact that, while 2-aminonitriles preserve their thermodynamically more stable β configuration in acidic solution, they have the capability to isomerize to the α structure in a basic medium. This has been used to explain the fact that the Bucherer-Bergs and Read hydantoin syntheses, which are carried out in basic and acid solution, respectively, yield compounds with opposing stereochemistries (α and β, respectively) in spite of having the same β-aminonitrile as a common intermediate [12-14]. The ability of **2a** to undergo epimerization in a basic medium was proved by the observation that it led exclusively to a β-hydantoin when submitted to Read synthesis, but yielded a product mixture consisting mainly of the α-hydantoin under Bucherer-Bergs conditions [15,16]. Therefore, it might have been expected that its reaction with isocyanates would have led to different stereoisomers of **3** or **4** in acid and basic conditions. The β-stereochemistry found in both cases suggests that **2a** does not have the chance to isomerize during the base-catalyzed reaction with isocyanates, probably because nucleophillic attack on the isocyanate carbon is more rapid than the establishment of the $\beta \rightleftharpoons \alpha$ equilibrium, a complex process that requires the formation of an intermediate imine. Once an alkyl- or aryl- carbonylamino group is built into the 2β position, its steric bulk makes the isomerization to an α structure less probable.

Scheme 1



2	R
a	H
b	$C_6H_5CH_2$
c	$C_6H_5(CH_2)_2$
d	3,4-$(MeO)_2C_6H_3(CH_2)_2$

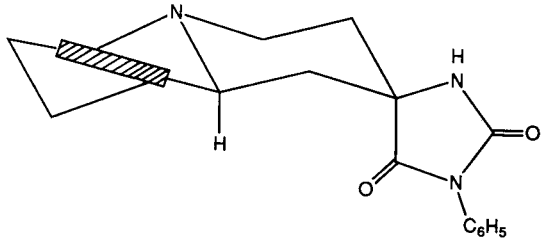
1,3,4	R	R^1
a	H	cyclo C_6H_{11}
b	H	n C_4H_9
c	H	C_6H_5
d	H	4-Cl C_6H_4
e	H	3-Cl C_6H_4
f	H	4-F C_6H_4
g	H	3,4-Cl_2 C_6H_3
h	$C_6H_5CH_2$	cyclo C_6H_{11}
i	$C_6H_5CH_2$	C_6H_5
j	$C_6H_5CH_2$	4-Cl C_6H_4
k	$C_6H_5CH_2$	3-Cl C_6H_4
l	$C_6H_5CH_2$	3,4 Cl_2 C_6H_3
m	$C_6H_5(CH_2)_2$	C_6H_5
n	$C_6H_5(CH_2)_2$	4-Cl C_6H_4
o	$C_6H_5(CH_2)_2$	3-Cl C_6H_4
p	$C_6H_5(CH_2)_2$	3,4 Cl_2 C_6H_3
q	3,4-$(MeO)_2C_6H_3(CH_2)_2$	C_6H_5
r	3,4-$(MeO)_2C_6H_3(CH_2)_2$	4-Cl C_6H_4
s	3,4-$(MeO)_2C_6H_3(CH_2)_2$	3-Cl C_6H_4
t	3,4-$(MeO)_2C_6H_3(CH_2)_2$	3,4 Cl_2 C_6H_3

Stereochemistry.

The stereochemistry of compounds **1** was analyzed using **1c** (R = H, R^1 = C_6H_5) as a model system, with the aid of previously established criteria [16]. Spectral data suggest the *trans*-2*R**,11b*S** structure depicted in Scheme 2. A *trans*-conformation can be proposed for the quinolizidine ring junction on the basis of ir data (Bohlmann bands [17,18] at 2760 and 2805 cm^{-1}), and also of ^{13}C-nmr data, such as the 132 Hz coupling constant for C_{11b}-H, well within the range usually accepted for *trans*-benzo[*a*]quinolizidines [19], and chemical shifts for C_6 (51.81 ppm) and C_7 (29.71 ppm) [20,21]. The assignment of the 2*R**,11b*S**-configuration was based upon three independent criteria. One of them is the high value (*ca.* 18.5 Hz) found for the half-width of the $C_{4'}$ signal in the proton-coupled ^{13}C-nmr spectrum of **1c**, which can be attributed to vicinal couplings between $C_{4'}$ and the two *anti* hydrogens in C_1 and C_3 of the quinolizidine system [12,13], consistent only with the 2*R**,11b*S** (β) structure. Additional support for the proposed isomer can be found in the downfield shift found for the C_{11b} proton (δ = 4.41 ppm) with respect to the value expected for a *trans*-benzo[*a*]quinolizidine [22], attributed to the deshielding effect of the $C_{4'}$ carbonyl and consistent only with the β structure. Finally, the fact that **1c** could be acetylated at $N_{3'}$ by reflux in acetic anhydride for 9 hours also supports the proposed structure, since it

has been previously shown for related compounds [16] that the $N_{3'}$ atom of the α isomer experiences a severe steric hindrance and cannot be acetylated, even after 17 hours of reflux in acetic anhydride.

Scheme 2



EXPERIMENTAL

All melting points are uncorrected and were determined in open capillary tubes using a Büchi immersion apparatus. Spectral data were recorded on the following instruments: ir, Perkin Elmer 577, with all samples compressed into potassium bromide pellets; ^{1}H-nmr, Hitachi Perkin-Elmer R-24B (60 MHz) and Brucker WM-200-SY (200 MHz). ^{13}C-nmr, Brucker WM-200-SY (50.3 MHz). All chemical shifts are referred to TMS and given in the δ scale. Mass spectra were obtained on a Hewlett-Packard 5995 CG-MS, using the DIP mode for the introduction of the samples; data are reported as m/z (intensity relative to the base peak = 100%). Elemental analyses were determined using Carlo Erba 1104 and Perkin Elmer 2400 CHN Elemental Analyzers. All reagents were employed as received from commercial suppliers. Solvents were purified and dried using standard methods; the expression "petroleum ether" refers to the fraction with boiling point 40-60°.

General Procedure for the Synthesis of *N*-(Alkyl or aryl)-*N'*-(2-cyano-9,10-dimethoxy-1,3,4,6,7,1b-hexahydrobenzo[*a*]quinolizin-2-yl)ureas **3** from **2a** (R = H) in the Absence of Catalysts.

A solution of 0.4 g (14.0 mmoles) of analytically pure 2-amino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carbonitrile (compound **2a**, R = H [11]) in dry benzene (14 ml) was treated with a suitable isocyanate (14 mmoles), added in small portions over a period of one minute. The reaction mixture was stirred at room temperature for 2 hours which, in some cases (4-chlorophenyl, 3-chlorophenyl, 4-fluorophenyl and 3, 4-dichlorophenyl isocyanates), led to the formation of a white precipitate of the corresponding urea derivatives (compounds **3d**, **3e**, **3f** and **3g**, respectively). Other reaction mixtures were refluxed for six hours and evaporated *in vacuo* to give a foamy residue. The residue was recrystallized from 2-propanol to yield compounds **3a**, **3b** and **3c** as white crystals.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-cyclohexylurea (**3a**).

This compound was obtained in 85% yield as white crystals (2-propanol), mp 161-163°; ir: ν NH 3330, CH (Bohlmann bands) 2805, 2760, C≡N 2215, C=O 1650 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 6.75 and 6.65 (2 s, 2H, C$_8$-H and C$_{11}$-H), 5.80 (br s, 1H, NH), 5.30 (br s, 1H, N'-H), 3.80 (s, 6H, 2 OMe), 3.60-0.90 (m, 22H).

Anal. Calcd. for $C_{23}H_{32}N_4O_3$: C, 66.99; H, 7.77; N, 13.59. Found: C, 66.75; H, 7.49; N, 13.37.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-butylurea (**3b**).

This compound was obtained in 85% yield as white crystals (2-propanol), mp 176-178°; ir: ν NH 3340, CH (Bohlmann bands) 2810, 2765, C≡N 2210, C=O 1655 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 6.70 (s, 2H, C$_8$-H and C$_{11}$-H), 6.05 (br s, 1H, NH), 5.40 (br s, 1H, NH), 3.70 (s, 6H, 2 OMe), 3.60-0.50 (m, 20H).

Anal. Calcd. for $C_{21}H_{30}N_4O_3$: C, 65.28; H, 7.77; N, 14.51. Found: C, 65.05; H, 7.54; N, 14.31.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-phenylurea (**3c**).

This compound was obtained in 90% yield, as white crystals (2-propanol), mp 170-172°; ir: ν NH 3360, 3320, CH (Bohlmann bands) 2800, 2760, C≡N 2210, C=O 1690 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 8.65 (br s, 1H, N'H), 7.60 (br s, 1H, NH), 7.60-6.75 (m, 5H, C$_6$H$_5$), 6.70 and 6.65 (2 s, 2H, C$_8$-H and C$_{11}$-H), 3.70 (s, 6H, 2 OMe), 3.55-2.00 (m, 11H).

Anal. Calcd. for $C_{23}H_{26}N_4O_3$: C, 67.98; H, 6.40; N, 13.79. Found: C, 67.75; H, 6.29; N, 13.57.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-(4''-chlorophenyl)urea (**3d**).

This compound was obtained in 95% yield, as white crystals (2-propanol) mp 168-169°; ir: ν NH 3360, 3330, CH (Bohlmann bands) 2800, 2760, C≡N 2210, C=O 1695 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 8.75 (s, 1H, N'H), 7.35 (s, 4H, 4-Cl C$_6$H$_4$), 7.05 (s, 1H, NH), 6.80 and 6.70 (2 s, 2H, C$_8$-H and C$_{11}$-H), 3.75 (s, 6H, 2 OMe), 3.50-2.00 (m, 11H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3Cl$: C, 62.66; H, 5.67; N, 12.71. Found: C, 62.51; H, 5.58; N, 12.58.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-(3''-chlorophenyl)urea (**3e**).

This compound was obtained in 95% yield, as white crystals (2-propanol) mp 175-176°; ir: ν NH 3370, 3320; CH (Bohlmann bands) 2805, 2760; C≡N 2215; C=O 1695 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 8.75 (br s, 1H, N'H), 7.65 (s, 1H, NH), 7.40-7.00 (m, 4H, 3-Cl C$_6$H$_4$), 6.70 and 6.60 (2 s, 2H, C$_8$-H and C$_{11}$-H), 3.75 (s, 6H, 2 OMe), 3.60-1.90 (m, 11H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3Cl$: C, 62.66; H, 5.67; N, 12.71. Found: C, 62.49; H, 5.60; N, 12.63.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-(4''-fluorophenyl)urea (**3f**).

This compound was obtained in 90% yield, as white crystals (2-propanol) mp 154-155°; ir: ν NH 3360, 3320; CH (Bohlmann bands) 2800, 2760, C≡N 2215, C=O 1690 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d$_6$): δ 8.60 (br s, 1H, N'H), 7.60-7.20 (m, 4H, 4-F C$_6$H$_4$), 6.95 (s, 1H, NH), 6.75 and 6.65 (2 s, 2H, C$_8$-H and C$_{11}$-H), 3.70 (s, 6H, 2 OMe), 3.65-1.90 (m, 11H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3F$: C, 65.09; H, 5.89; N, 13.21. Found: C, 64.79; H, 5.71; N, 13.09.

(±)-2*R**,11b*S**-*N*-(2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-2-yl)-*N'*-(3'',4''-dichlorophenyl)urea (**3g**).

This compound was obtained in 95% yield, as white crystals (2-propanol) mp 158-159°; ir: ν NH 3360; CH (Bohlmann bands)

2805, 2760, C≡N 2220, C=O 1700 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.85 (s, 1H, N'H), 7.40-7.10 (m, 3H, 3,4-Cl_2 C_6H_3), 7.10 (s, 1H, NH), 6.70 and 6.60 (2 s, 2H, C_8-H and C_{11}-H), 3.70 (s, 6H, 2 OMe), 3.60-2.00 (m, 11H).

Anal. Calcd. for $C_{23}H_{24}N_4O_3Cl_2$: C, 58.10; H, 5.05; N, 11.79. Found: C, 57.90; H, 4.95; N, 11.61.

(±)-2*R**,11b*S**-4'-Imino-9,10-dimethoxy-1,3,4,6,7-11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one Derivatives **4**. General Procedures.

Method A. Reaction Between **2a** (R = H) and Isocyanates in Acetic Acid.

A solution of **2a** (R = H) (0.7 g, 2.44 mmoles) and the adequate isocyanate (2.44 mmoles) in glacial acetic acid (10 ml) was heated for 6 hours in a bath at 100°. The cooled reaction mixture was basified with 20% aqueous ammonium hydroxide and extracted with chloroform (3 x 25 ml). Organic extracts were joined, washed with water (2 x 30 ml), dried over sodium sulphate and evaporated *in vacuo*. The residue was crystallized by addition of ethanol or 2-propanol, filtered and recrystallized in the solvent indicated in each case.

Method B. Thermal Cyclization of Ureides **3**.

A solution of the suitable ureide **3** (1.5-2.5 mmoles) in ethanol (30 ml) was refluxed for 1 hour. After cooling, the corresponding iminohydantoin **4** precipitated and was filtered. Compounds **3a** and **3b** led to a mixture of the expected **4** derivative and starting material, even after 8 hours of reaction.

(±)-2*R**,11b*S**-3'-Cyclohexyl-4'-imino-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4a**).

This compound was obtained in 45% yield (method A) as white crystals (petroleum ether) mp 221-223°; ir: ν NH 3265, CH (Bohlmann bands) 2805, 2755, C=O 1745, C=N 1670 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.20 (s, 1H, N_1-H), 6.80 (s, 1H, C_4'=NH), 6.65 (s, 2H, C_8-H and C_{11}-H), 4.15 (m, 1H, C_{11b}-H), 3.70 (s, 6H, 2 OMe), 3.60-2.40 (m, 10H), 2.60-1.50 (m, 11H).

Anal. Calcd. for $C_{23}H_{32}N_4O_3$: C, 66.99; H, 7.77; N, 13.59. Found: C, 66.71; H, 7.58; N, 13.45.

(±)-2*R**,11b*S**-3'-Butyl-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4b**).

This compound was obtained in 40% yield (method B), after purification of the crude reaction product by flash chromatography on silica gel, eluting with dichloromethane-methanol (9:1), as white crystals (ethanol) mp 215-216°; ir: ν NH 3250, 3200, CH (Bohlmann bands) 2805, 2755, C=O 1745, C=N 1670 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.10 (s, 1H, N_1-H), 6.90 (s, 1H, C_4'=NH), 6.65 (s, 2H, C_8-H and C_{11}-H), 4.15 (m, 1H, C_{11b}-H), 3.85 (s, 6H, 2 OMe), 3.60-0.90 (m, 19H).

Anal. Calcd. for $C_{21}H_{30}N_4O_3$: C, 65.28; H, 7.77; N, 14.51. Found: C, 65.41; H, 7.45; N, 14.37.

(±)-2*R**,11b*S**-4'-Imino-9,10-dimethoxy-3'-phenyl-1,3,4,6,7,-11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4c**).

This compound was obtained in 60% yield (method B) as white crystals (ethanol) mp 212-214°; ir: ν NH 3260, 3210, CH (Bohlmann bands) 2805, 2755, C=O 1740, C=N 1670 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.00 (s, 1H, N_1-H), 7.60-7.20 (m, 5H, C_6H_5), 7.10 (s, 1H, C_4'=NH), 6.60 (s, 2H, C_8-H and C_{11}-H), 4.10 (m, 1H, C_{11b}-H), 3.85 (s, 6H, 2 OMe), 3.60-2.00 (m, 10H); ms: (m/z) 406 (M^+), 391, 218, 205, 191, 190, 177.

Anal. Calcd. for $C_{23}H_{26}N_4O_3$: C, 67.98; H, 6.40; N, 13.79. Found: C, 67.61; H, 6.25; N, 13.52.

(±)-2*R**,11b*S**-3'-(4''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1,-3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4d**).

This compound was obtained in 95% yield (method B) as white crystals (ethanol) mp 127-128°; ir: ν NH 3245, 3130, CH (Bohlmann bands) 2800, 2755, C=O 1740, C=N 1655 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.05 (s, 1H, N_1-H), 7.50-7.20 (m, 4H, 4-Cl C_6H_4), 6.80 and 6.65 (2 s, 2H, C_8-H and C_{11}-H), 4.05 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.60-2.00 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3Cl$; C, 62.66; H, 5.67; N, 12.71. Found: C, 62.47; H, 5.61; N, 12.51.

(±)-2*R**,11b*S**-3'-(3''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4e**).

This compound was obtained in 95% yield (method B) as white crystals (ethanol) mp 134-135°; ir: ν NH 3200, 3130, CH (Bohlmann bands) 2800, 2755, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.10 (s, 1H, N_1-H), 7.60-7.30 (m, 4H, 3-Cl C_6H_4), 6.80 and 6.70 (2 s, 2H, C_8-H and C_{11}-H), 4.00 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.60-1.90 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3Cl$: C, 62.66; H, 5.67; N, 12.71. Found: C, 62.49; H, 5.78; N, 12.45.

(±)-2*R**,11b*S**-3'-(4''-Fluorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4f**).

This compound was obtained in 90% yield (method B) as white crystals (2-propanol) mp 144-146°; ir: ν NH 3260, 3130, CH (Bohlmann bands) 2800, 2755, C=O 1745, C=N 1670 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.00 (s, 1H, N_1-H), 7.45 (s, 2H, 4-FC_6H_4), 7.30 (s, 2H, 4-F C_6H_4), 7.30 (s, 1H, C_4'=NH), 6.75 and 6.65 (2 s, 2H, C_8-H and C_{11}-H), 4.05 (m, 1H, C_{11b}-H), 3.70 (s, 6H, 2 OMe), 3.65-2.00 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_4O_3F$: C, 65.09; H, 5.89; N, 13.21. Found: C, 64.92; H, 5.86; N, 12.98.

(±)-2*R**,11b*S**-3'-(3'',4''-Dichlorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4g**).

This compound was obtained in 56% yield (method A) or 95% yield (method B) as white crystals (2-propanol) mp 128-130°; ir: ν NH 3260, 3140, CH (Bohlmann bands) 2800, 2755, C=O 1750, C=N 1665 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.60-7.00 (m, 3H, 3,4-Cl_2 C_6H_3), 6.80 (s, 1H, C_4'=NH), 6.55 (s, 2H, C_8-H and C_{11}-H), 4.10 (m, 1H, C_{11b}-H), 3.80 (s, 6H, 2 OMe), 3.60-1.90 (m, 10H).

Anal. Calcd. for $C_{23}H_{24}N_4O_3Cl_2$: C, 58.11; H, 5.05; N, 11.79. Found: C, 57.89; H, 4.98; N, 11.58.

Base-catalyzed Reaction Between 2-Amino(2-alkyl or arylalkylamino)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carbonitriles **2** and Isocyanates. General Procedures.

Triethylamine (0.2 ml) and the suitable isocyanate (2.44 mmoles) were added to a solution of **2a** (R = H) (0.7 g, 2.44 mmoles) in warm, dry benzene (15 ml). The reaction was refluxed for 8 hours (method A) or irradiated with ultrasound at room temperature for 3 hours (method B). Reaction products were

isolated as follows:

a) Substitution pattern **a**: The cooled reaction mixture from methods A or B was evaporated under reduced pressure. The residue was washed with boiling petroleum ether (3 x 40 ml) and treated with a small amount of ethanol at room temperature, which caused the precipitation of iminohydantoin **4a** (5%). Evaporation of the ethanol yielded ureide **3a** (90%).

b) Substitution patterns **c-g**: After using method B, the crystalline compound precipitated during the reactions **d** and **f** was filtered and identified, respectively, as the ureides **3d** (69% yield) and **3f** (85% yield). Mother liquors were evaporated *in vacuo* and the residue was washed with boiling petroleum ether (3 x 40 ml). The remaining thick syrup was crystallized from the appropriate solvent (see individual compounds in the sections above), yielding the iminohydantoins **4c** (88% yield), **4d** (10% yield), **4e** (75% yield) and **4g** (95% yield).

c) Substitution patterns **h-t**: the cooled reaction mixture was evaporated *in vacuo*. The residue was washed with boiling petroleum ether (3 x 40 ml) and, after being identified as one of the iminohydantoins **4h-4t** by spectral means, was used for the next reaction without further purification. Analytical samples were obtained by flash column chromatography, using the eluants indicated in each case.

(±)-2R*,11bS*-1'-Benzyl-3'-cyclohexyl-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4h**).

This compound was obtained in 84% yield (method A). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3360, C=O 1725, C=N 1650 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.40 (s, 5H, $CH_2C_6H_5$), 6.80 (s, 2H, C_8-H and C_{11}-H), 6.60 (s, 1H, NH), 4.55 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.65-1.30 (m, 22H).

Anal. Calcd. for $C_{30}H_{38}N_4O_3$: C, 71.71; H, 7.57; N, 11.16. Found: C, 71.58; H, 7.45; N, 11.09.

(±)-2R*,11bS*-1'-Benzyl-4'-imino-3'-phenyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4i**).

This compound was obtained in 78% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3360, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.60-7.20 (m, 5H, C_6H_5), 7.45 (s, 5H, $CH_2C_6H_5$), 7.40 (s, 1H, NH), 6.85 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.60 (s, 2H, $CH_2C_6H_5$), 3.75 (s, 6H, 2 OMe), 3.70-1.90 (m, 11H).

Anal. Calcd. for $C_{30}H_{32}N_4O_3$: C, 72.58; H, 6.45; N, 11.29. Found: C, 72.29; H, 6.53; N, 11.25.

(±)-2R*,11bS*-1'-Benzyl-3'-(4''-chlorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,-5'-imidazolidin)-2'-one (**4j**).

This compound was obtained in 81% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with dichloromethane-methanol (95:5); ir: ν NH 3300, C=O 1735, C=N 1655 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.80-7.20 (m, 4H, 4-Cl C_6H_4), 7.55 (s, 1H, NH), 7.30 (s, 5H, $CH_2C_6H_5$), 6.75 (s, 2H, C_8-H and C_{11}-H), 4.55 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.65-2.10 (m, 11H).

Anal. Calcd. for $C_{30}H_{31}N_4O_3Cl$: C, 67.86; H, 5.84; N, 10.56. Found: C, 67.54; H, 5.75; N, 10.41.

(±)-2R*,11bS*-1'-Benzyl-3'-(3''-chlorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4k**).

This compound was obtained in 85% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3290, C=O 1740, C=N 1655 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.80-7.30 (m, 4H, 3-Cl C_6H_4), 7.50 (s, 1H, NH), 7.40 (s, 5H, $CH_2C_6H_5$), 6.75 (s, 2H, C_8-H and C_{11}-H), 4.50 (s, 2H, $CH_2C_6H_5$), 3.75 (s, 6H, 2 OMe), 3.70-2.00 (m, 11H).

Anal. Calcd. for $C_{30}H_{31}N_4O_3Cl$: C, 67.86; H, 5.84; N, 10.56. Found: C, 67.73; H, 5.72; N, 10.41.

(±)-2R*,11bS*-1'-Benzyl-3'-(3'',4''-dichlorophenyl)-4'-imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4l**).

This compound was obtained in 90% yield (method A). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (95:5); ir: ν NH 3300, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.90-7.30 (m, 3H, 3,4-Cl_2 C_6H_3), 7.40 (s, 1H, NH), 7.30 (s, 5H, $CH_2C_6H_5$), 6.65 (s, 2H, C_8-H and C_{11}-H), 4.60 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.65-2.10 (m, 11H).

Anal. Calcd. for $C_{30}H_{30}N_4O_3Cl_2$: C, 63.72; H, 5.31; N, 9.91. Found: C, 63.45; H, 5.23; N, 9.78.

(±)-2R*,11bS*-4'-Imino-9,10-dimethoxy-3'-phenyl-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4m**).

This compound was obtained in 95% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with dichloromethane-methanol (98:2); ir: ν NH 3320, C=O 1735, C=N 1665 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.40 (m, 5H, C_6H_5), 7.30 (s, 6H, NH and $CH_2CH_2C_6H_5$), 6.70 (s, 2H, C_8-H and C_{11}-H), 3.75 (s, 6H, 2 OMe), 3.70-1.60 (m, 15H); ms: (m/z) 510 (M^+), 483, 219, 218, 205, 176, 105, 91, 77.

Anal. Calcd. for $C_{31}H_{34}N_4O_3$: C, 72.94; H, 6.66; H, 10.98. Found: C, 72.69; H, 6.53; N, 10.86.

(±)-2R*,11bS*-3'-(4''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4n**).

This compound was obtained in 87% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3250, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.60-7.20 (m, 4H, 4-Cl C_6H_4), 7.20 (s, 6H, NH and $CH_2CH_2C_6H_5$), 6.65 (s, 2H, C_8-H and C_{11}-H), 3.70 (s, 6H, 2 OMe), 3.60-1.80 (m, 15H).

Anal. Calcd. for $C_{31}H_{33}N_4O_3Cl$: C, 68.32; H, 6.06; N, 10.28. Found: C, 68.05; H, 6.15; N, 10.39.

(±)-2R*,11bS-3'-(3''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidin]-2'-one (**4o**).

This compound was obtained in 79% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with dichloromethane-methanol (98:2); ir: ν NH 3340, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.80-7.20 (m, 4H, 3-Cl C_6H_4), 7.20 (s, 6H, NH and $CH_2CH_2C_6H_5$), 6.70 (s, 2H, C_8-H and C_{11}-H), 3.70 (s, 6H, 2 OMe), 3.70-1.90 (m, 15H).

Anal. Calcd. for $C_{31}H_{33}N_4O_3Cl$: C, 68.32; H, 6.06; N, 10.28. Found: C, 68.15; H, 5.97; N, 10.04.

(±)-2*R**,11b*S**-3'-(3'',4''-Dichlorophenyl)-4'-imino-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4p**).

This compound was obtained in 83% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3340, C=O 1740, C=N 1655 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.00-7.30 (m, 3H, 3,4-Cl_2 C_6H_3), 7.30 (s, 6H, NH and $CH_2CH_2C_6H_5$), 6.70 (s, 2H, C_8-H and C_{11}-H), 3.80 (s, 6H, 2 OMe), 3.70-1.80 (m, 15H).

Anal. Calcd. for $C_{31}H_{32}N_4O_3Cl_2$: C, 64.25; H, 5.53; N, 9.67. Found: C, 64.09; H, 5.38; N, 9.86.

(±)-2*R**,11b*S**-4'-Imino-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-3'-phenyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4q**).

This compound was obtained in 75% yield (methods B). The analytical sample was obtained by flash chromatography on silica gel, eluting with dichloromethane-methanol (95:5); ir: ν NH 3340, C=O 1740, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.40-7.10 (m, 5H, C_6H_5), 7.30 (s, 1H, NH), 6.90-6.50 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.55 (s, 2H, C_8-H and C_{11}-H), 3.80 (s, 12H, 4 OMe), 3.70-1.80 (m, 15H).

Anal. Calcd. for $C_{33}H_{38}N_4O_5$: C, 69.47; H, 6.66; N, 9.82. Found: C, 69.56; H, 6.79; N, 9.99.

(±)-2*R**,11b*S**-3'-(4''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4r**).

This compound was obtained in 85% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (98:2); ir: ν NH 3335, C=O 1730, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.60-7.20 (m, 4H, 4-Cl C_6H_4), 7.30 (s, 1H, NH), 7.00-6.60 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.70 (s, 2H, C_8-H and C_{11}-H), 3.70 (s, 12H, 4 OMe), 3.70-1.80 (m, 15H).

Anal. Calcd. for $C_{33}H_{37}N_4O_5Cl$: C, 65.51; H, 6.12; N, 9.26. Found: C, 65.32; H, 5.98; N, 9.12.

(±)-2*R**,11b*S**-3'-(3''-Chlorophenyl)-4'-imino-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-1,3,4,6,7,11b-hexahydrospiro-[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4s**).

This compound was obtained in 80% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with dichloromethane-methanol (95:5); ir: ν NH 3335, C=O 1720, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.80-7.20 (m, 4H, 3-Cl C_6H_4), 7.30 (s, 1H, NH), 6.90-6.60 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.65 (s, 2H, C_8-H and C_{11}-H), 3.70 (s, 12H, 4 OMe), 3.60-1.90 (m, 15H).

Anal. Calcd. for $C_{33}H_{36}N_4O_5Cl_2$: C, 65.51; H, 6.12; N, 9.26. Found: C, 65.32; H, 6.09; N, 9.37.

(±)-2*R**,11b*S**-3'-(3'',4''-Dichlorophenyl)-4'-imino-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidin]-2'-one (**4t**).

This compound was obtained in 90% yield (method B). The analytical sample was obtained by flash chromatography on silica gel, eluting with ethyl acetate-methanol (95:5); ir: ν NH 3330, C=O 1720, C=N 1660 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.90-7.20 (m, 3H, 3,4-Cl_2 C_6H_3), 7.40 (s, 1H, NH), 6.90-6.60 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.70 (s, 2H, C_8-H and C_{11}-H), 3.70 (s, 12H, 4 OMe), 3.60-1.95 (m, 15H).

Anal. Calcd. for $C_{33}H_{36}N_4O_5Cl_2$: C, 61.97; H, 5.63; N, 8.76. Found: C, 61.75; H, 5.51; N, 8.52.

(±)-2*R**,11b*S**-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro-[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-diones **1**. General Procedure.

A solution of the suitable ureide **3** (method **A**) or iminohydantoin **4** (method B) (1.2 mmoles) in ethanol or methanol (5 ml) and 35% aqueous hydrochloric acid (0.5 ml) was refluxed for 9 hours. The solid hydantoin **1** (hydrochloride) that precipitated during the reaction was filtered and recrystallized from the appropriate solvent, or the reaction mixture was evaporated and the residue was recrystallized. Both types of starting compounds gave identical products, with the same yields in the cases where a comparison was established.

(±)-2*R**,11b*S**-3'-Cyclohexyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1a**).

This compound was obtained in 85% yield (method A) as white crystals (ethanol) mp 281-282°; ir: ν C=O 1770, 1700 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 8.30 (br s, 1H, N_5 $^+$-H), 7.60 (s, 1H, $N_{1'}$-H), 6.80 (s, 2H, C_8-H and C_{11}-H), 5.30 (m, 1H, C_{11b}-H), 3.90 (s, 6H, 2 OMe), 3.60-1.10 (m, 21H).

Anal. Calcd. for $C_{23}H_{32}N_3O_4Cl$: C, 61.40; H, 7.12; N, 9.34. Found: C, 61.12; H, 7.06; N, 9.13.

(±)-2*R**,11b*S**-3'-Butyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1b**).

This compound was obtained in 80% yield (method A) as white crystals (ethanol) mp 242-244°; ir: ν C=O 1770, 1700 cm^{-1}; ^{1}H-nmr (60 MHz, CF_3CO_2H): δ 8.40 (br s, 1H, $N_5$$^+$-H), 7.40 (s, 1H, $N_{1'}$-H), 6.90 (s, 2H, C_8-H and C_{11}-H), 5.40 (m, 1H, C_{11b}-H), 3.95 (s, 6H, 2 OMe), 3.60-1.00 (m, 19H).

Anal. Calcd. for $C_{21}H_{30}N_3O_4Cl$: C, 59.50; H, 7.02; N, 9.92. Found: C, 59.22; H, 7.01; N, 9.69.

(±)-2*R**,11b*S**-9,10-dimethoxy-3'-phenyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1c**).

This compound was obtained in 100% yield (method B) as white crystals (ethanol) mp 258-260°; ir: ν C=O 1780, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6, trifluoroacetic acid, 3:1): δ 11.20 (br s, 1H, $N_5$$^+$-H), 8.75 (s, 1H, $N_{1'}$-H), 7.60 (s, 5H, C_6H_5) 6.80 and 6.60 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.90 (s, 6H, 2 OMe), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{23}H_{26}N_3O_4Cl$: C, 62.23; H, 5.86; N, 6.22. Found: C, 61.98; H, 5.69; N, 6.39.

Free Base.

A solution of the hydrochloride in boiling water was basified, while still warm, with solid sodium hydroxide. The precipitated free base was collected by filtration and recrystallized from ethanol to give 95% yield of the free base, as white crystals; ir: ν CH (Bohlmann bands) 2800, 2755, C=O 1780, 1720 cm^{-1}; ^{1}H-nmr (200 MHz, pyridine-d_5): δ 9.94 (s, 1H, $N_{1'}$-H), 7.66 (d, 2H, J = 8 Hz, $C_{2''(4'')}$-H), 7.41 (t, 2H, J = 8 Hz, $C_{3''(5'')}$-H), 7.09 (t, 1H, J = 8 Hz, $C_{4''}$-H), 7.07 and 6.71 (2 s, 2H, C_8-H and C_{11}-H), 4.41 (br d, 1H,

C_{11b}-H), 3.74 and 3.66 (2 s, 6H, 2 OMe), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_3O_4$: C, 67.81; H, 6.14; N, 10.32. Found: C, 67.59; H, 6.06; N, 10.43.

(±)-2R*,11bS*-3'-(4''-Chlorophenyl)-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1d**).

This compound was obtained in 95% yield (methods A and B) as white crystals (ethanol) mp 234-236°; ir: ν C=O 1780, 1715 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 11.70 (br s, 1H, N_5-H), 8.30 (s, 1H, N_1-H), 7.60 (s, 4H, 4-Cl C_6H_4), 6.95 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.60-2.00 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_3O_4Cl_2$: C, 57.74; H, 5.23; N, 8.79. Found: C, 57.58; H, 5.13; N, 8.62.

(±)-2R*,11bS*-3'-(3''-Chlorophenyl)-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1e**).

This compound was obtained in 100% yield (methods A) or 95% yield (method B) as white crystals (ethanol) mp 268-270°; ir: ν C=O 1780, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 11.90 (br s, 1H, N_5-H), 8.45 (s, 1H, N_1-H), 7.70-7.50 (m, 4H, 3-Cl C_6H_4), 7.00 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.80 (s, 6H, 2 OMe), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_3O_4Cl_2$: C, 57.74; H, 5.23; N, 8.79. Found: C, 57.56; H, 5.09; N, 8.55.

(±)-2R*,11bS*-3'-(4''-Fluorophenyl)-9,10-dimethoxy-1,3,4,6,-7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]--2',4'-dione Hydrochloride (**1f**).

This compound was obtained in 90% yield (method A) or 95% yield (method B) as white crystals (2-propanol) mp 296-297°; ir: ν C=O 1780, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 11.80 (br s, 1H, N_5-H), 8.30 (s, 1H, N_1-H), 7.70-7.30 (m, 4H, 4-F C_6H_4), 6.90 and 6.70 (2 s, 2H, C_8-H and C_{11}-H), 4.85 (m, 1H, C_{11b}-H), 3.80 (s, 6H, 2 OMe), 3.60-2.00 (m, 10H).

Anal. Calcd. for $C_{23}H_{25}N_3O_4FCl$: C, 59.80; H, 5.42; N, 9.10. Found: C, 59.61; H, 5.35; N, 8.97.

(±)-2R*,11bS*-3'-(3'',4''-Dichlorophenyl)-9,10-dimethoxy-1,3,4,-6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',-4'-dione Hydrochloride (**1g**).

This compound was obtained in 95% yield (methods A and B) as white crystals (ethanol) mp 245-247°; ir: ν C=O 1785, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.00 (br s, 1H, N_5-H), 8.40 (s, 1H, N_1-H), 7.60-7.50 (m, 3H, 3,4-Cl_2 C_6H_4), 6.90 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.55-2.10 (m, 10H).

Anal. Calcd. for $C_{23}H_{24}N_3O_4Cl_3$: C, 53.85; H, 4.68; N, 8.19. Found: C, 53.62; H, 4.54; N, 8.01.

Free Base.

Obtained as in **1c** in 93% yield; ir: ν CH (Bohlmann bands) 2800, 2755, C=O 1780, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, deuteriochloroform): δ 8.70 (s, 1H, N_1-H), 8.00-7.40 (m, 3H, 3,4-Cl_2 C_6H_3), 6.85 and 6.70 (2 s, 2H, C_8-H and C_{11}-H), 4.40 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{23}H_{23}N_3O_4Cl_2$: C, 57.98; H, 4.83; N, 8.82. Found: C, 58.07; H, 4.75; N, 8.76.

(±)-2R*,11bS*-1'-Benzyl-3'-cyclohexyl-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1h**).

This compound was obtained in 75% yield (method B) as white crystals (ethanol) mp 239-240°; ir: ν C=O 1765, 1695 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.40 (br s, 1H, N_5-H), 7.35 (m, 5H, CH_2- C_6H_5), 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.85 (m, 1H, C_{11b}-H), 4.55 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.60-0.80 (m, 21H).

Anal. Calcd. for $C_{30}H_{38}N_3O_4Cl$: C, 66.72; H, 7.09; N, 7.78. Found: C, 66.49; H, 7.05; N, 7.62.

(±)-2R*,11bS*-1'-Benzyl-9,10-dimethoxy-3'-phenyl-1,3,4,6,7,-11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1i**).

This compound was obtained in 85% yield (method B) as white crystals (ethanol) mp 263-265°; ir: ν C=O 1770, 1710 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.10 (br s, 1H, N_5-H), 7.60 (m, 5H, C_6H_5), 7.40 (m, 5H, $CH_2C_6H_5$), 6.80 and 6.70 (2 s, 2H, C_8-H and C_{11}-H), 4.80 (m, 1H, C_{11b}-H), 4.60 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.60-2.20 (m, 10H).

Anal. Calcd. for $C_{30}H_{32}N_3O_3Cl$: C, 67.47; H, 6.04; N, 7.87. Found: C, 67.59; H, 5.85; N, 7.65.

(±)-2R*,11bS*-1'-Benzyl-3'-(4''-chlorophenyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1j**).

This compound was obtained in 80% yield (method B) as white crystals (2-propanol) mp 224-226°; ir: ν C=O 1770, 1715 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.15 (br s, 1H, N_5-H), 7.60 (s, 4H, 4-Cl C_6H_4), 7.40 (m, 5H, $CH_2C_6H_5$), 6.90 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 4.65 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.55-2.00 (m, 10H).

Anal. Calcd. for $C_{30}H_{31}N_3O_4Cl_2$: C, 63.38; H, 5.46; N, 7.39. Found: C, 63.17; H, 5.27; N, 7.18.

(±)-2R*,11bS*-1'-Benzyl-3'-(3''-chlorophenyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1k**).

This compound was obtained in 70% yield (method B) as white crystals (ethanol) mp 187-189°; ir: ν C=O 1770, 1710 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.15 (br s, 1H, N_5-H), 7.70-7.20 (m, 4H, 3-Cl C_6H_4), 7.30 (m, 5H, $CH_2C_6H_5$), 6.80 (s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 4.65 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{30}H_{31}N_3O_4Cl_2$: C, 63.38; H, 5.46; N, 7.39. Found: C, 63.14; H, 5.29; N, 7.15.

(±)-2R*,11bS*-1'-Benzyl-3'-(3'',4''-dichlorophenyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1l**).

This compound was obtained in 85% yield (method B) as white crystals (ethanol) mp 245-247°; ir: ν C=O 1775, 1715 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.15 (br s, 1H, N_5-H), 7.90-7.50 (m, 3H, 3,4-Cl_2 C_6H_3), 7.35 (m, 5H, $CH_2C_6H_5$), 6.80 (s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 4.65 (s, 2H, $CH_2C_6H_5$), 3.70 (s, 6H, 2 OMe), 3.60-2.00 (m, 10H).

Anal. Calcd. for $C_{30}H_{30}N_3O_4Cl_3$: C, 59.85; H, 4.99; N, 6.98. Found: C, 59.53; H, 4.97; N, 7.12.

(±)-2*R**,11b*S**-9,10-dimethoxy-3'-phenyl-1'-phenylethyl-1,3,4,6,-7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1m**).

This compound was obtained in 85% yield (method B) as white crystals (ethanol) mp 203-204°; ir: ν C=O 1770, 1710 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.10 (br s, 1H, N_5^+-H), 7.60 (s, 5H, C_6H_5), 7.30 (s, 5H, $CH_2CH_2C_6H_5$), 6.85 and 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.70-1.40 (m, 14H).

Anal. Calcd. for $C_{31}H_{34}N_3O_4Cl$: C, 67.94; H, 6.25; N, 7.67. Found: C, 68.07; H, 6.17; N, 7.51.

(±)-2*R**,11b*S**-3'-(4''-Chlorophenyl)-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1n**).

This compound was obtained in 65% yield (method B) as white crystals (ethanol) mp 253-254°; ir: ν C=O 1765, 1710 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.15 (br s, 1H, N_5^+-H), 7.60 (s, 4H, 4-Cl C_6H_4), 7.30 (s, 5H, $CH_2CH_2C_6H_5$), 6.80 (2 s, 2H, C_8-H and C_{11}-H), 4.85 (m, 1H, C_{11b}-H), 3.75 (s, 6H, 2 OMe), 3.70-1.60 (m, 14H).

Anal. Calcd. for $C_{31}H_{33}N_3O_4Cl_2$: C, 63.92; H, 5.71; N, 7.21. Found: C, 63.78; H, 5.65; N, 7.34.

(±)-2*R**,11b*S**-3'-(3''-Chlorophenyl)-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1o**).

This compound was obtained in 65% yield (method B) as white crystals (2-propanol) mp 193-194°; ir: ν C=O 1770, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.25 (br s, 1H, N_5^+-H), 8.00-7.60 (m, 4H, 3-Cl C_6H_4), 7.30 (s, 5H, $CH_2CH_2C_6H_5$), 6.85 (s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.80 (s, 6H, 2 OMe), 3.70-1.50 (m, 14H).

Anal. Calcd. for $C_{31}H_{33}N_3O_4Cl_2$: C, 63.92; H, 5.71; N, 7.21. Found: C, 63.82; H, 5.67; N, 7.14.

(±)-2*R**,11b*S**-3'-(3'',4''-Dichlorophenyl)-9,10-dimethoxy-1'-phenylethyl-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione hydrochloride (**1p**).

This compound was obtained in 70% yield (method B) as white crystals (ethanol) mp 248-250°; ir: ν C=O 1775, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.25 (br s, 1H, N_5^+-H), 8.00-7.40 (m, 3H, 3,4-Cl_2 C_6H_3), 7.30 (s, 5H, $CH_2CH_2C_6H_5$), 6.85 (s, 2H, C_8-H and C_{11}-H), 4.90 (m, 1H, C_{11b}-H), 3.80 (s, 6H, 2 OMe), 3.70-1.50 (m, 14H).

Anal. Calcd. for $C_{31}H_{32}N_3O_4Cl_3$: C, 60.34; H, 5.19; N, 6.81. Found: C, 60.06; H, 5.30; N, 6.92.

(±)-2*R**,11b*S**-3'-(4''-Chlorophenyl)-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]-quinolizin-2,5'-imidazolidine]-2',4'-dione hydrochloride (**1q**).

This compound was obtained in 65% yield (method B) as white crystals (ethanol) mp 180-182°; ir: ν C=O 1770, 1720 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.15 (br s, 1H, N_5^+-H), 7.65 (s, 4H, 4-Cl C_6H_4), 7.10-6.90 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.90 (s, 2H, C_8-H and C_{11}-H), 4.85 (m, 1H, C_{11b}-H), 3.80 (s, 12H, 4 OMe), 3.70-1.50 (m, 14H).

Anal. Calcd. for $C_{33}H_{37}N_3O_6Cl_2$: C, 61.68; H, 5.76; N, 6.54. Found: C, 61.45; H, 5.70; N, 6.69.

(±)-2*R**,11b*S**-3'-(3'',4''-Dichlorophenyl)-9,10-dimethoxy-1'-(3''',4'''-dimethoxyphenylethyl)-1,3,4,6,7,11b-hexahydrospiro-[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione Hydrochloride (**1r**).

This compound was obtained in 80% yield (method B) as white crystals (ethanol) mp 190-191°; ir: ν C=O 1770, 1715 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 12.20 (br s, 1H, N_5^+-H), 7.90-7.40 (m, 3H, 3,4-$Cl_2C_6H_3$), 7.00-6.70 (m, 3H, 3,4-$(MeO)_2C_6H_3$), 6.70 (s, 2H, C_8-H and C_{11}-H), 4.80 (m, 1H, C_{11b}-H), 3.80 (s, 12H, 4 OMe), 3.60-1.40 (m, 14H).

Anal. Calcd. for $C_{33}H_{36}N_3O_6Cl_3$: C, 58.54; H, 5.32; N, 6.21. Found: C, 58.39; H, 5.25; N, 6.19.

(±)-2*R**-11b*S**-1'-Acetyl-3'-phenyl-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione.

A solution of **1c** (100 mg, 0.25 mmole) in acetic acid anhydride (5 ml) was heated for 9 hours in an oil bath at 150°. The excess acetic anhydride was evaporated under reduced pressure and the residue was recrystallized from 2-propanol-charcoal to give 95 mg (86%) of the acetylated compound as white crystals (2-propanol); ir: ν CH (Bohlmann bands) 2800, 2755, C=O 1795, 1730, 1700 cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 7.55 (s, 5H, C_6H_5), 6.75 (s, 2H, C_8-H and C_{11}-H), 4.20 (m, 1H, C_{11b}-H), 3.70 (s, 6H, 2 OMe), 2.50 (s, 3H, $COCH_3$), 3.60-2.10 (m, 10H).

Anal. Calcd. for $C_{26}H_{27}N_3O_5$: C, 67.88; H, 5.86; N, 9.11. Found: C, 67.44; H, 5.71; N, 8.98.

Bucherer-Bergs Reaction of 2-Amino-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrobenzo[*a*]quinolizine-2-carbonitrile (**2**, R = H).

A mixture of **2** (R = H) (100 mg, 0.35 mmole), potassium cyanide (34 g, 0.52 mmole) and ammonium carbonate (250 mg) was dissolved in a mixture of water (3 ml) and ethanol (2 ml) and heated in a sealed flask at 60° for 48 hours. The precipitate formed after cooling the reaction mixture was filtered and purified by column chromatography on silica gel, eluting with acetone, to yield 91 mg (78%) of (±) 2*S**,11b*S**-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-imidazolidine]-2',4'-dione and 10.5 mg (9%) of its (±)-2*R**,11b*S**-isomer (**1**, R = R^1 = H); both compounds showed analytical and spectral data identical to those previously described [16].

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