HETEROCYCLIC SPIRO COMPOUNDS. III. SYNTHESIS OF [2R*, 11bR*]-9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROBENZO[a]QUINOLIZINE-2-SPIRO-3'-PYRROLIDINES AND [2R*, 11bR*]-9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROBENZO[a]QUINOLIZINE-2-SPIRO-3'-PYRROLIDIN-2'-ONES.

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Abstract —— The stereochemistry of succinimides 1, pyrrolidines 2 and pyrrolidinones 3 is reported on the basis of spectroscopic data. The results of the reduction of 1 with lithium aluminum hydride and diborane are described.

The benzo[a]quinolizidine system has been linked with a broad spectrum of biological properties. Besides the classical chemotherapeutic actions of the ipecac alkaloids emetine and tubulosine,[1] neuroleptic,[2] antihypertensive,[3] antiinflamatory,[4] and anticonvulsant activities[5] have been described. Recently, several 2-substituted benzo[a]quinolizidine derivatives have been shown to antagonize α_2 adrenoceptors. This effect might account for the antihypertensive action mentioned above, as well as for other interesting properties, like antidepressant and hypoglycemic activities.[6]

Our interest in heterocyclic 2-spirobenzo[a]quinolizidine systems led us to the synthesis of *N*-substituted 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-spiro-3'-pyrrolidine-2',5'-diones[7] 1, which are currently under pharmacological assay. In order to complete this study, we now wish to report the stereochemistry of compounds 1 and their reduction to 2-spiro-3'-pyrrolidines 2 and 2-spiro-3'-pyrrolidin-2'-ones 3 (Scheme 1).

The succinimide derivatives 1 were synthesized [7] from 2-carboxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-acetic anhydride 5 via 2-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a] quinolizine-2-carbonitrile 4. The assignment of the relative configuration of succinimides 1 as the [2R*, 11bR*] diastereomeres, with the benzo[a]quinolizine system adopting a *trans* conformation, is based on spectral data, employing the *N*-benzylsuccinimide 1b as the model compound.

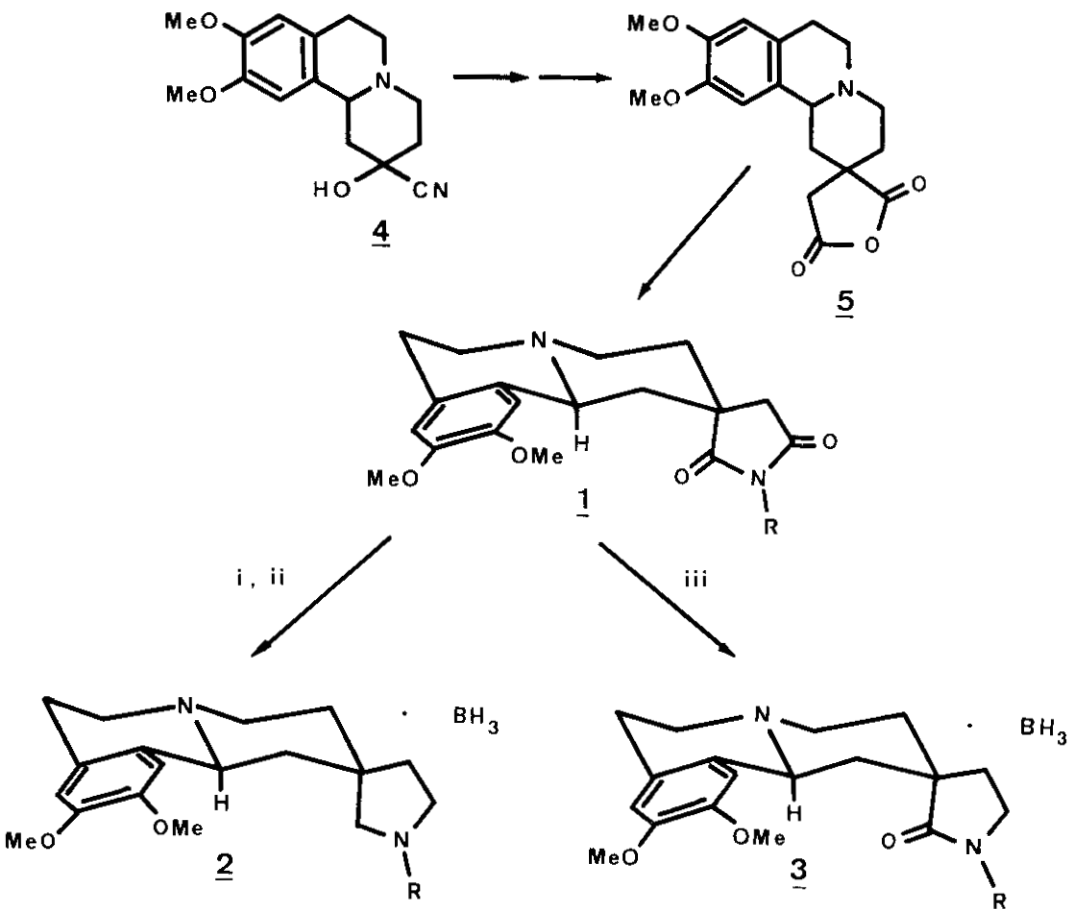
^{13}C-Nmr can be considered as the more reliable spectroscopic tool for conformational studies of benzo[a]quinolizidine systems, as shown by the work of van Binst and Tourwe[8] and Sugiura *et al.* [9]

As a result of the partial delocalization of the nitrogen lone pair electrons into the antiparallel C-H-bonds, the coupling constant $^1J(^{13}C\text{-}H)$ for a *cis* conformation of the 11b proton and the nitrogen lone pair is 6-12 Hz larger than that for a *trans* conformation.[8] C_{11b} shows a coupling constant $^1J(^{13}C\text{-}H) = 133$ Hz, which is within the range of 126-133 Hz described for *trans* benzo[*a*]-quinolizidines,[8] while the *cis* conformers have coupling constants of 139-143 Hz. These data are confirmed by the observed values of 51.8 and 28.9 ppm for C_6 and C_7, respectively, which are in the range of 50.8-53.4 ppm and 28.6-30.2 ppm reported[9,10b] for several *trans* benzo[*a*]quinolizidines. The presence of Bohlmann bands at *ca.* 2755 and 2800 cm^{-1} can be considered as additional confirmation of the *trans* orientation.[10]

The assignment of the relative configuration of the [2R*-11bR*] diastereomer 1 is based on the localization of the 2' carbon atom. While in the [2R*- 11bR*] isomer the $C_{2'}$ is *anti* with respect to two hydrogen atoms at C_1 and C_3, in a [2R*- 11bS*] diastereomer it would be *gauche* with respect to all of them. The *anti* disposition in the [2R*- 11bR*] isomer leads to a higher value for the vicinal coupling constant $^3J(^{13}C\text{-}H)$ and, therefore, to a broader peak. The halfwidth value found for $C_{2'}$ atom (*ca.* 19 Hz) in the proton-coupled spectrum is in good agreement with that described for related spiro compounds in which the carbonyl group directly attached to the benzo[*a*]quinolizidine system is axial.[11] The anomalous chemical shift of the 11b proton in the ^{1}H-Nmr spectrum (4.25 ppm), which is displaced downfield from the expected value for a *trans* conformer,[12] can be attributed to the deshielding effect of the $C_{2'}$ carbonyl group, which in the [2R*- 11bR*] isomer is placed near the C_{11b} proton. This provides further evidence for the proposed structure.

The reduction of succinimides 1 with lithium aluminum hydride in refluxing THF for 72 h led to only moderate yields of the expected pyrrolidines 2. Diborane, generated *in situ* from sodium borohydride and boron trifluoride, is an efficient reagent for the reduction of amides.[14] However, few examples are known of its use for the reduction of succinimides.[15] The application of the reaction conditions described in the literature[15] for the reduction of sterically hindered succinimide systems to the corresponding pyrrolidines (*i.e.*, stirring at room temperature for 24 h), only allowed the recovery of the starting material as a borane complex. When the reaction was carried out at 100°C for 24 h in an open system, the γ-butyrolactams 3 were obtained and isolated as borane complexes. A single carbonyl absorption at 1670 cm^{-1} and the disappearance of the singlet at $\delta \simeq 2.6$ ppm ($C_{4'}$ protons in 1) in the ^{1}H-Nmr spectra confirm this structure. Additionally, the chemical shift of the C_{11b} proton of *ca.* 4.2 ppm is indicative of the presence of a carbonyl group in an axial disposition at a *trans* benzo[*a*]quinolizidine 2-carbon atom, as indicated above.

Finally, the reduction of succinimides 1 with boron trifluoride etherate complex and sodium borohydride in diglyme at 45-60 °C for 24-28 h in a sealed flask allowed the synthesis of pyrrolidines 2 in a higher yield than the reduction with lithium aluminum hydride, with the additional advantages of a purer product and a more convenient experimental procedure.



	R
a	C_6H_5
b	CH_2-C_6H_5
c	CH_2-CH_2-C_6H_5
d	CH_2-CH_2-C_6H_3(3,4-MeO)
e	n-C_4H_9

i - $LiAlH_4$, THF, reflux, 72 h. ii - $NaBH_4$, BF_3-Et_2O, 45-60 °C; 24-48 h, sealed flask.
iii - $NaBH_4$, BF_3-Et_2O, 100 °C, 6 h, open system.

Scheme 1

EXPERIMENTAL

Melting points were obtained in a Büchi apparatus and are uncorrected. Spectral data were recorded on the following spectrometers: (Ir—Perkin Elmer 577; ^{1}H-Nmr—Hitachi-Perkin Elmer R-24B (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. All coupling constants are given in Hz and correspond to the first order analysis of the spectra. Elemental analyses were obtained using a Carlo Erba Elemental Analyzer equipped with a digital integrator model C SI 38.

1'-Benzyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizidine-2-spiro-3'-pyrrolidine-2',5'-dione (free base) (1b). A solution of 300 mg of the hydrochloride of 1b[7] in water (10 ml) was basified to pH 12 with 30% aqueous NaOH and extracted with $CHCl_3$ (5 x 25 ml). The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. Yield, 250 mg (90%). Mp 160-162 °C (2-propanol). Ir (KBr) cm^{-1}: 2795, 2760 (C-H, Bohlmann bands), 1755, 1700 (C=O). ^{1}H-Nmr (d_6-DMSO, 200.16 MHz) δ : 7.40-7.20 (m, 5H, $CH_2C_6H_5$), 6.63 and 6.60 (2s, 2H, C_8-H and C_{11}-H), 4.57 (s, 2H, $CH_2C_6H_5$), 4.24 (d, 1H, J≈10 Hz, C_{11b}-H), 2.63 (s, 2H, $C_{4'}$-H), 3.35-1.80 (m, 10H). ^{13}C-Nmr ($CDCl_3$, 50.32 MHz) δ : 28.94 (t, J = 129 Hz, C_7), 33.50 (t, J = 130 Hz, C_3), 41.99 (s, C_2), 41.99 (t, J = 133 Hz, C_3'), 51.64* (t, J = 132 Hz, C_4), 51.81* (t, J = 132 Hz, C_6), 55.72** (c, J = 144 Hz, C_9-OMe), 55.93** (c, J = 144 Hz, C_{10}-OMe), 57.51 (d, J = 133 Hz, C_{11b}), 107.72 (d, J = 153 Hz, C_{11}), 111.51 (d, J = 155 Hz, C_8) 126.62 (s, C_{7a}), 128.80 (s, C_{11a}), 147.12^{+} (s, C_9), 147.48^{+} (s, C_{10}), 174.85 (s, $C_{2'}$, $W_{1/2}\cong$9.5 Hz), 181.08 (s, $C_{5'}$, $W_{1/2}\cong$19 Hz), 44.25 (t, J = 131 Hz, $CH_2C_6H_5$), 127.80 (d(t), J = 7 Hz, $C_{4''}$), 128.57 (d(d), J = 161 Hz (8 Hz), $C_{3''}$), 128.57 (d(dd), J = 163 Hz (7.5 Hz), $C_{2''}$), 135.93 (s, $C_{1''}$). The signals marked with *, ** and $^{+}$ could not be assigned with certainty.

General Procedure for the Synthesis of N-Substituted 9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine -2-spiro-3'-pyrrolidines (2). Method A. To a stirred suspension of lithium aluminum hydride (4.8-8 mmol) in anhydrous THF (100-150 ml) was added the suitable succinimide 1 (1.2-2 mmol) dissolved in ether (25-30 ml). The resulting mixture was refluxed for 72 h, after which it was cooled, decomposed in the usual way, and filtered off from the inorganic solid which developed. This was extracted with ethyl ether in a Soxhlet apparatus for 24 h. The combined ethereal extracts, together with the THF layer, were dried (Na_2SO_4) and evaporated. The residue was dissolved in 5% aqueous HCl (15 ml), washed with Et_2O, basified with 30% aqueous NaOH, and extracted with Et_2O (5 x 25 ml). Evaporation of the solvent and crystallization from petroleum ether afforded 2a (R=C_6H_5) (35%). Analytical samples of 2c and 2d were obtained by column chromatography (silica gel) using 7:3 toluene-2-propanol as eluant. 2b was dissolved in 2-propanol, treated with dry hydrogen chloride and recrystallized from 2-propanol. (Table 1).

Table 1. Physical properties of compounds 2

Comp. No.	Yield/% Met. A / Met. B	mp/°C[b] (recryst.)	R_f[a]	Elemental analysis Calculated N	C	H	Found N	C	H
2a	35	134-135	0.65	7.41	76.19	7.93	7.22	75.99	7.88
	45	(pet. ether)		7.14	73.47	8.42	6.91	73.31	8.35
2b	53	227-230[c]	--	6.03	64.65	7.33	5.81	64.37	7.21[c]
	68	(2-propanol)							
2c	38	--	0.65	6.89	76.85	8.37	6.61	76.55	8.21
	--								
2d	35	--	0.67	6.01	72.10	8.15	5.75	71.92	8.05
	55								

[a]In toluene-2-propanol (7:3) [b]mp of borane complex : 2a, 242-244 (EtOH); 2b, 210-212 (EtOH); 2d, 233-236 (EtOH) [c]As dihydrochloride

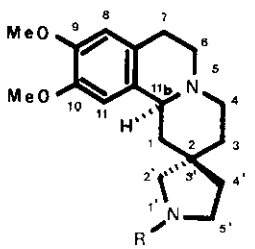


Table 2. Spectroscopic properties of compounds 2

Comp. No.	Ir/cm^{-1}	^{1}H-nmr(60 MHz, $CDCl_3$)[a] δ C_8-H,C_{11}-H	OMe	$C_{2'}$-H	R
2a	2840,2760,	6.75(s,1H)[b]	3.75(s,6H)	3.30(s,2H)	7.35-7.10(m,2H,3'-H,5'-H)
	1615	6.65(s,1H)[b]			6.80-6.50(m,3H,2',4',6'-H)
2b	2920,2580,	6.65(s,1H)	3.85(s,3H)	2.50(s,2H)	7.30(s,5H,$CH_2C_6H_5$)
	1620	6.50(s,1H)	3.80(s,3H)		3.65(s,2H,$CH_2C_6H_5$)
2c	2800,2760,	6.70(s,1H)	3.85(s,6H)	2.80(s,2H)	7.25(s,5H)
	1615	6.60(s,1H)			
2d	2790,2750,	6.65(s,1H)	3.80(s,6H)	2.75(s,2H)	6.80-6.60(m,3H)
	1615	6.55(s,1H)			3.80(s,6H)

[a]As free bases [b]Overlapped with phenyl signals

Method B. To a stirred solution of succinimide 1 (1.5 mmol) in diglyme (25 ml) was added dropwise 0.5 ml (3.62 mmol) of freshly distilled BF_3-Et_2O in diglyme (15 ml). To the resulting cooled (0 °C) mixture was added 0.11 g (3.62 mmol) of $NaBH_4$ in diglyme (15 ml). The flask containing the reaction mixture was sealed, heated at 45 °C (1a) or 60 °C (1b, 1d) for 24 h (1a) or 48 h (1b, 1d) and poured on ice water (250 ml). The solid formed was filtered off and recrystallized. General Procedure for the Synthesis of N-Substituted 9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-spiro-3'-pyrrolidin-2'-ones 3b and 3e. To a well cooled solution of succinimide 1b or 1e (3.62 mmol) in diglyme (25 ml) were succesively added dropwise 0.5 ml (3.62 mmol) of freshly distilled BF_3-Et_2O complex and a solution of $NaBH_4$ (0.11 g, 3.62 mmol) in diglyme (15 ml). The reaction mixture was heated in a 100 °C bath for 5-6 h and, once cooled, poured on ice water (150 ml). The solid obtained, identified as one of the boranes 3, was filtered off and recrystallized. 3b : Yield, 45%. Mp 268-270 °C (EtOH). Ir (KBr) cm^{-1}: 2330 (BH_3), 1675 (C=O). ^{1}H-Nmr (d_6-DMSO, 200.16 MHz) δ : 6.68 and 6.47 (2 s, 2H, C_8-H and C_{11}-H), 4.15 (m, 1H, C_{11b}-H); 3.70 (s, 6H, 2 OMe), 3.45 (m, 2H, $C_{5'}$-H), 7.40-7.20 (m, 5H, $CH_2C_6H_5$), 4.39 (s, 2H, $CH_2C_6H_5$), 3.30-1.60 (m, 12H). Anal. Calcd for $C_{25}H_{36}N_2O_3B$: C, 70.92; H, 8.51; N, 6.62. Found : C, 70.68; H, 8.42; N, 6.50. 3e : Yield, 55%. Mp 183-185 °C (EtOH). Ir (KBr) cm^{-1} : 2340 (BH_3), 1675 (C=O) cm^{-1}. ^{1}H-Nmr (d_6-DMSO, 200.16 MHz) δ : 6.90 (s, 2H, C_8-H and C_{11}-H) 4.19 (d, 2H, C_{11b}-H), 3.98 (s, 6H, 2 OMe), 3.50 (m, 2H, $C_{5'}$-H), 3.00-2.30 (m, 10 H), 1.90-1.20 (m, 8H), 0.90 (t, 3H). Anal. Calcd for $C_{22}H_{37}N_2O_3B$: C, 70.92; H, 8.51; N, 7.22. Found : C, 67.81; H, 9.32; N, 7.15.

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REFERENCES

1. R. S. Gupta, "Emetine, Cryptopleurine, Tylocrebrine and other Functionally Related Alkaloids," in "Antibiotics", ed. by F. E. Hahn, Springer Verlag, 1983, p. 46.
2. C. Kaiser and P. E. Setler, "Antipsychotic Agents" in "Burger's Medicinal Chemistry", ed. by M. E. Wolff, John Wiley, and Sons, 1981, 859.
3. (a) J. W. Van Dyke, H. J. Havera, R. D. Johnson, H. Vidrio, and A. Viveros, J. Med. Chem. 1972, 15, 91; (b) H. Vidrio, A. Viveros and R. Vargas, Arzneim.-Forsch. (Drug Res.), 1971,

21, 941; (c) J. M. Caroon, R. D. Clark, A. F. Kluge, C. H. Lee, and A. M. Strosberg, J. Med. Chem., 1983, 26, 1426; (d) J. L. Archibald, R. Beardsley, T. J. Ward, and J. F. White, J. Med. Chem., 1983, 26, 416.

4. C. Szántay, L. Szabó, L. Toeke, I. Toth, S. Virag, E. Kanyó, and A. David, U. S. Patent 4,342,871 (1982); Chem. Abstr., 1982, 97 216035r.
5. F. D. Popp and R. F. Watts, J. Pharm. Sci., 1978, 67, 871.
6. R. D. Clark, A. D. Michel, and R. L. Whiting, Progress Med. Chem., 1986, 23, 1.
7. J. C. Menéndez, G. G. Trigo, and M. M. Söllhuber, Heterocycles, 1986, 24, 1393.
8. G. Van Binst and D. Tourwé, Heterocycles, 1973, 1, 257.
9. (a) M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, Chem. Pharm. Bull., 1979, 27, 3144; Chem. Pharm. Bull., 1978, 26, 1168.
10. (a) F. Bohlmann, Chem. Ber., 1958, 91, 2157; (b) M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, Chem. Pharm. Bull., 1978, 26, 1901.
11. J. C. Menéndez and M. M. Söllhuber, Heterocycles, 1987, 26, 3203.
12. M. Uskokovic, H. Bruderer, C. Von Planta, T. Williams, and A. Brossi, J. Am. Chem. Soc., 1964, 86, 3364.
13. C. F. Lane, "Diborane", in "Synthetic Reagents", vol. 3, ed. by J. S. Pizey, Ellis Horwood Limited, 1977, p. 1.
14. J. March, "Advanced Organic Chemistry, 3rd. ed.", John Wiley and Sons, 1985, p. 1099 and references cited therein.
15. W. Merkel, D. Bormann, D. Mania, H. Muschawerk, and H. Hropt, Eur. J. Med. Chem., 1976, 11, 399.

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