HETEROCYCLIC SPIRO COMPOUNDS. II. SYNTHESIS OF 1'-SUBSTITUTED 1,3,4,6,7,11b-HEXAHYDRO-SPIRO[BENZO[a]QUINOLIZINE-2,3'-PYRROLIDINE]-2',5'-DIONES

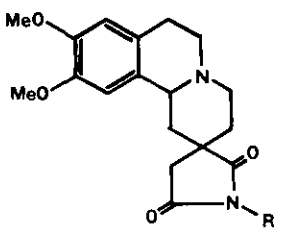
J. Carlos Menéndez, Gregorio G. Trigo, and Mónica M. Söllhuber*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

Abstract ——*The synthesis of 1'-substituted derivatives of 1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizine-2,3'-pyrrolidine]-2',5'-dione is achieved starting from a suitable cyanohydrin 4 and ethyl sodiocyanoacetate, according to reaction Scheme 1. The structure of the intermediate of the cyclization reaction that leads to the target compounds 2 is described.*

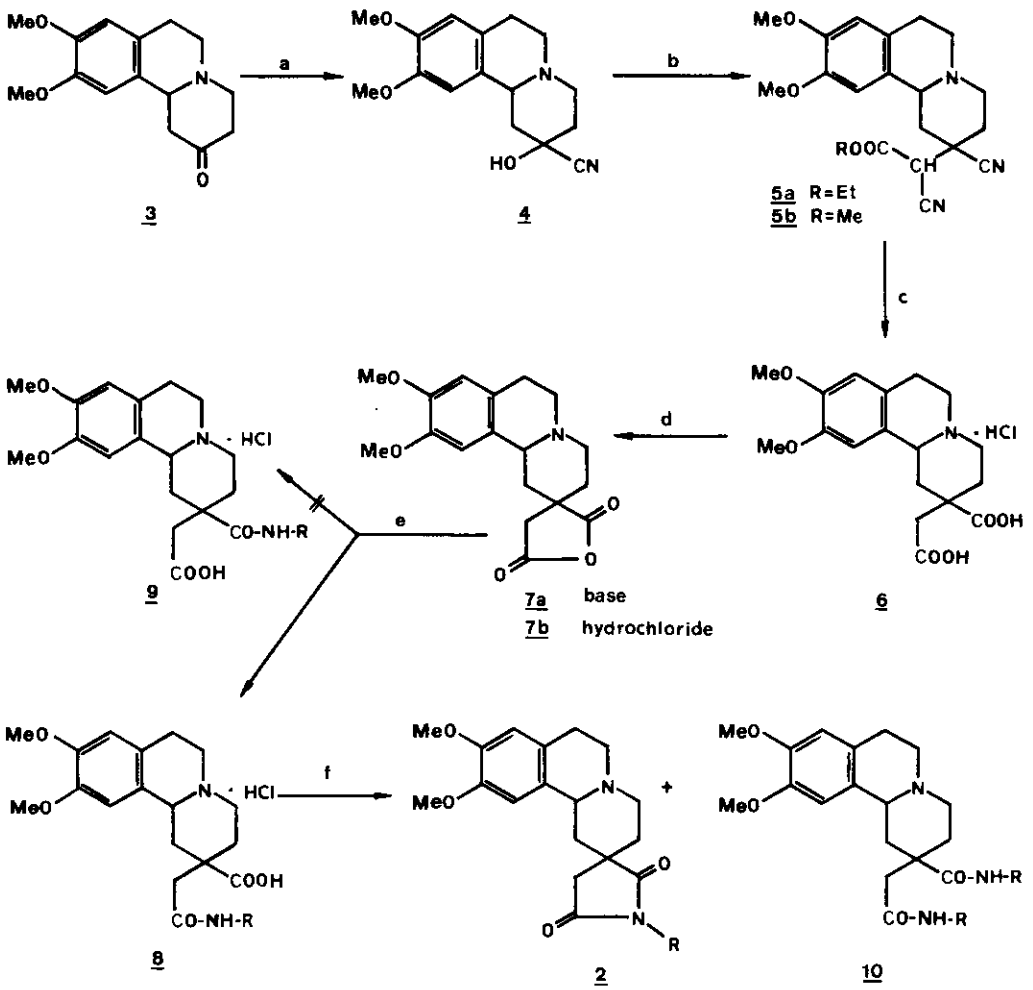
A wide variety of alkaloids such as emetine and tubulosine present a benzo[a]quinolizine ring system. Certain benzo[a]quinolizines have been reported to possess useful pharmacological properties, such as reserpine-like and antineoplastic activities[1]. In the last few years additional antihypertensive[2], antiinflamatory[3] and anticonvulsant[4] properties were reported for 2-substituted derivatives. The pharmacological interest of these compounds induced us to include some 2-spiro derivatives of benzo[a]quinolizine in our studies on heterocyclic spirans with the purpose of exploring their possible chemotherapeutic and cardiovascular activity.

In a previous paper[5] we reported the synthesis of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro [benzo[a]quinolizine-2,3'-pyrrolidine]-2',5'-dione 1. We want now to extend this work to various alkyl, aryl and alkylamino substituted derivatives of this parent ring. The reaction scheme used is shown in Scheme 1.



	R
1	H
2a	$CH(CH_3)_2$
2b	nC_4H_9
2c	C_6H_5
2d	$CH_2C_6H_5$
2e	$CH_2CH_2C_6H_5$

	R
2f	$C_2H_4C_6H_3$ (3,4-OCH_3)
2g	NHC_6H_5
2h	piperidino
2i	1-pyrrolidinyle
2j	morpholino



3 4 5a R=Et 5b R=Me 6 9 7a base 7b hydrochloride 8 2 10

a KCN, HCl, 0-4°C

b $(NC\text{-}CH\text{-}COOEt)^- Na^+$, R-OH, r.t.

c 35 % HCl, reflux[5]

d Ac_2O[5]

e,f $R\text{-}NH_2$, 4 Å molecular sieve

SCHEME 1

In our previously reported synthesis[5], a Cope-condensation product of aminoketone 3 proved to be an adequate starting material for two convenient reaction schemes that ended in dicarboxylic acid 6. In an attempt to increase the yield of 6, an alternative procedure based on an early, seldom used reaction[6] was examined. Thus, cyanohydrin 4 was obtained in quantitative yield treating 3 with potassium cyanide and hydrochloric acid; a substantial improvement of the results previously described[4] for an analogous compound was achieved. Reaction of 4 with ethyl sodiocyanoacetate in absolute R-OH at room temperature led to 5a (65.2 %, R = Et) or 5b (78.1 % , R = Me), which on acid hydrolysis afforded 6 quantitatively[5]. The overall yield for this route is as high as that previously reported by us (ca. 78 % in the case 5b), with the advantage of a shorter and easier handling.

The transformation of anhydride 7 into succinimides 2 was attempted in several different experimental conditions. Thus, heating 7 as a free base (7a) or as a hydrochloride (7b) with amines at 220-225°C in an inert atmosphere, as described by Lundahl et al.[8], yielded the expected succinimides 2 as impure, hardly recrystallizable products. The results did not improve when 7a was treated in milder conditions, such as described by Scott et al.[9] However, when a suspension of 7b in xylene was treated with amines or hydrazines followed by refluxing for 5-12 h in the presence of molecular sieve, the desired N-substituted spiro succinimides 2 were obtained with reasonable purity, along with small amounts of diamides 10[12] as secondary products in several cases. The diamides were distilled "in vacuo" from the residue left by the evaporation of the xylene phase.

A reduction of the refluxing time of 7b to 1-2 h or a stirring at room temperature for 2 h allowed the isolation and study of the intermediate of the cyclization reaction leading to 2, for which the structures 8 and 9 might be proposed. Treatment of 7b with aniline or benzylamine gave respectively 8c and 8d as only products. The structural assignment of 8 was accomplished by comparison of the ^{13}C-nmr spectra of the dicarboxylic acid 6 and the carbamoyl acids 8c and 8d, with reference to the studies of Stanetty[10] on 1-carboxycyclohexaneacetic acids and esters. Only the carboxylic group of the acetic acid moiety presents a displacement of chemical shift from 171.30 ppm (6) to 168.67 ppm (8d) and 167.77 ppm (8c). The carboxylic group directly linked to the heterocycle does not show any noteworthy shift, appearing at 174.98 (6) and 175.11 (8c and 8d). When 8c was heated for 1 h at 220 °C in nitrogen atmosphere, the corresponding imide 2c was obtained (90.2 %).

EXPERIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following spectrometers : IR—Perkin Elmer 577; ^{1}H-nmr—Hitachi-Perkin Elmer R-24 (60 MHz) and Varian EM 390 (90 MHz) (reference, tetramethylsilane); ^{13}C-nmr—Brucker WM-200-SY (reference and solvent, dimethylsulfoxide); mass—Hitachi-Perkin Elmer RMU-6M. Elemental analyses were determined using a Carlo Erba Elemental Analyzer model 1104.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-hydroxybenzo[a]quinolizine-2-carbonitrile 4.

To a stirred, ice-cooled suspension of 3 (10 g, 38 mmole), H_2O (15 ml) and 35 % HCl (3.9 ml, 38 mmole) a solution of KCN (2.49 g, 38 mmole) in H_2O (10 ml) was dropwise added. Stirring was maintained for additional 15 min and the reaction was completed by leaving it for 3 h in a refrigerator at 4°C. The white solid formed was filtered off, washed with a small amount of cold H_2O and dried "in vacuo" over P_2O_5 at room temperature. Yield 10.7 g (98.0 %). Mp 126-127°C (CH_2Cl_2-Et_2O). IR (KBr) : 3510 (O-H), 3200 (O-H), 2220 (C≡N) cm^{-1}. ^{1}H-nmr (d_6-DMSO) δ : 6.80 (2H, s, 11-H and 8-H) , 3.70 (6H, s, 2 OMe) , 3.50-2.40 (12H, m)

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-hydroxybenzo[a]quinolizine-2-carbonitrile Hydrochloride.

Dry, gaseous HCl was bubbled during 10 min through a methanolic solution of 4 (1 g) placed in a -10°C bath. The white precipitate formed (0.95 g) was filtered off and washed with cold MeOH. Mp 143-146°C (MeOH). Anal. Calcd. for $C_{16}H_{21}N_2O_3Cl$: C, 59.35 ; N, 8.65 ; H, 6.49. Found : C, 59.17 ; N, 8.44 ; H, 6.27.

Ethyl 2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-cyanoacetate 5a.

A well cooled suspension of ethyl sodiocyanoacetate prepared from ethyl cyanoacetate (2.35 g, 20.7 mmole) and sodium (0.45 g, 19.56 mmole) in 10 ml of absolute EtOH was gradually added to an ice-cooled suspension of 4 (6 g, 20.8 mmole) in EtOH (120 ml). The reaction mixture was allowed to stand for 48 h at room temperature. The solution was filtered off from a small amount of a solid product identified as ketone 3 and neutralized to pH 7 with 15 % HCl. The precipitate formed was filtered off and washed with EtOH. Yield 5.2 g (65.2 %). Mp 157-158°C (d) (2-propanol). Mixed mp[5] 157-158°C (d). IR (KBr) : 2250 (C≡N), 1755 (C=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ : 6.60 (2H, s, 11-H and 8-H) , 4.40 (2H, q, J=7 Hz) , 3.88 (6H, s, 2 OMe) , 3.85 (1H, s, 2'-H) , 3.65 (1H, m, 11b-H) , 3.10-1.60 (10H, m) , 1.38 (3H,t). Anal. Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.79 ; H, 6.53 ; N, 10.96. Found : C, 65.57 ; H, 6.28 ; N, 10.66

Methyl 2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-cyanoacetate 5b.

To a well cooled suspension of ethyl sodiocyanoacetate, prepared from ethyl cyanoacetate (0.19 g, 1.74 mmole) and sodium (40 mg, 1.74 mmole) in 5 ml of absolute MeOH, a solution of 4 (0.5 g, 1.74 mmole) in absolute MeOH (10 ml) was dropwise added. The reaction mixture was allowed to stand for 40 h at room temperature. The solution was concentrated "in vacuo" to half its volume and the precipitated solid was filtered off. Yield 0.5 g (78.1 %). Mp 166-167°C (d) (2-propanol). IR (KBr) : 2220 (C≡N), 1755 (C=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ : 6.60 (2H, s, 11-H and 8-H) , 3.80 (3H, s, OMe), 3.75 (6H, s, 2 OMe) , 3.62 (1H, s, 2'-H) , 3.45 (1H, m, 11b-H) , 3.30-1.50 (10H, m). Anal. Calcd. for $C_{20}H_{23}N_3O_2$: C, 65.04 ; N, 11.38 ; H, 6.23. Found : C, 64.92 ; N, 11.21 ; H, 6.12.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-[(N-phenylcarbamoyl)methyl]-benzo[a]quinolizine-2-carboxylic Acid Hydrochloride 8c. A suspension of analytically pure anhydride 7b (1.4 g, 3.8 mmole), aniline (0.35 g, 3.8 mmole) and dry xylene (15 ml) was stirred in the presence of 4 Å molecular sieve (0.2 g) for 2 h in an oil bath at 155-160°C. The solid product (1.5 g, 85.5 %) was filtered off. Mp 222-223°C. IR (KBr) : 3225 (NH), 3100-2220 (OH and R_3NH^+), 1730 (COOH), 1650 (CONH) cm^{-1}. ^{1}H-nmr (d_6-DMSO) δ : 10.30 (1H, s, COOH) , 7.90-7.00 (5H, m, C_6H_5) , 6.90,6.75 (2H, 2 s, 11-H and 8-H) , 4.40 (1H, m, 11b-H) , 3.80 (6H, s, 2 OMe) , 2.80 (2H, s, 2'-H). Anal. Calcd. for $C_{24}H_{29}N_2O_5Cl$: C, 62.54 ; N, 6.08 ; H, 6.29. Found : C, 62.23 ; N, 5.87 ; H, 6.04.

2-[(N-Benzylcarbamoyl)methyl]-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizine-2-carboxylic Acid Hydrochloride 8d. A solution of analytically pure anhydride 7b (0.2 g, 0.54 mmole) and benzylamine (58 mg, 0.54 mmole) in acetonitrile (6 ml) was magnetically stirred for 2 h at room temperature. The white precipitate formed was filtered off. Yield 0.2 g (77.4 %). Mp 201-202°C acetonitrile). IR (KBr) : 3315 (NH), 3100-2290 (OH and R_3NH^+), 1725 (COOH), 1645 (CONH) cm^{-1}. ^{1}H-nmr(d_6-DMSO) δ: 10.35 (1H, broad s, COOH) , 7.30 (5H, s, C_6H_5) , 6.80, 6.70 (2H, 2 s, 11-H and 8-H) , 4.35 (1H, m, 11b-H) , 4.25 (2H, s, CH_2) , 3.80 (6H, s, 2 OMe) , 2.60 (2H, s, 2'-H). Anal. Calcd. for $C_{25}H_{31}N_2O_5Cl$: C, 63.22 ; N, 5.90 ; H, 6.53. Found : C, 62.98 ; N, 5.61 ; H, 6.31.

Table I : Elemental analyses for spiro compounds 2.HCl

	Calculated			Found		
Cmpd. no.	C	H	N	C	H	N
2a	61.89	7.09	6.85	61.95	7.29	6.68
2b	62.78	6.90	6.66	62.62	7.06	6.45
2c	65.08	6.10	6.32	64.80	5.86	6.07
2d	65.72	6.35	6.13	65.99	6.44	5.90
2e	66.31	6.58	5.95	66.27	6.36	5.77
2f	63.33	6.59	5.28	63.07	6.37	5.06
2g	62.95	6.12	9.18	62.75	6.35	8.95
2h	61.40	7.12	9.34	61.27	6.94	9.13
2i	60.62	6.89	9.64	60.59	6.65	9.45
2j	58.47	6.64	9.30	58.25	6.41	9.04

General Procedure for the Synthesis of 2 a-b. Anhydride 7b (1 g, 2.7 mmole), the suitable primary amine (5.4 mmole), 4 Å molecular sieve (0.2 g) and dry xylene (30 ml) were stirred together at 40 °C for 1 h and then at 155-160°C for 5 h.

General Procedure for the Synthesis of 2 c-j. Anhydride 7b (1 g, 2.7 mmole), the suitable primary amine or hydrazine (5.4 mmole), 4 Å molecular sieve (0.2 g) and dry xylene (30 ml) were stirred together for 6 h (12 h for 2c and 2g) while heated in an oil bath at 155-160°C.

General Procedure for the Isolation of 2. a) Compounds 2a and 2d-f : the filtered xylene layer was evaporated to dryness. Secondary[12] products 10 were distilled off in Kugelrohr under reduced pressure, the residue dissolved in absolute isopropyl alcohol and treated with dry HCl. The solid formed was filtered off and recrystallized from an appropriate solvent. b) Compounds 2e and 2h-j : the solid formed was filtered off and recrystallized from an appropriate solvent. c) Compounds 2b and 2g : the solid formed was filtered off and the xylene layer was treated as described in a) giving an additional amount of 2b or 2g.

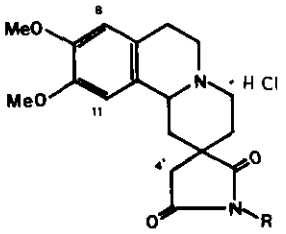


Table 2

Physical and Spectral Properties of Spiro Compounds[a]

Cmpd. no.	Yield %	Mp/°C	Recryst.	IR: C=O ν_{as}	IR: C=O ν_{s}	^{1}H-nmr (60 MHz)[b] δ R	4'-H	11-H,8-H	OMe
2a	35.1	194-6	2-C_3H_7OH	1695	1770	1.25(6H,d,J=7)	2.60(2H,s)	6.60(2H,s)	3.85(6H,s)
2b[11]	52.7	248-9	2-C_3H_7OH	1700	1770	0.7-3.7(9H,m)	2.55(2H,s)	6.70(2H,s)	3.85(6H,s)[c]
2c	90.8	247-8(d)	MeOH-Et_2O	1705	1780	7.50(5H,s)	2.75(2H,s)	6.40(1H,s)	3.80(6H,s)*
								6.30(1H,s)	
2d	60.3	259-61	EtOH	1695	1775	7.35(5H,s)	2.98(2H,s)	6.80(1H,s)	3.90(3H,s)[d]
						4.78(2H,s)		6.65(1H,s)	3.85(3H,s)
2e[11]	64.3	247-8	2-C_3H_7OH	1695	1760	7.30(5H,s)	2.85(2H,s)	6.86(1H,s)	3.80(6H,s)
								6.75(1H,s)	
2f	64.5	228-9	2-C_3H_7OH	1695	1775	6.80(3H,s)	2.85(2H,s)	6.62(1H,s)	3.85(6H,s)
						3.85(3H,s)		6.55(1H,s)	
2g	65.0	218-20	MeOH-Et_2O	1720	1790	6.95-7.6(5H,m)	3.00(2H,s)	6.75(2H,s)	3.85(6H,s)
2h	81.9	230-2(d)	MeOH-Et_2O	1720	1760	1.80-3.6(5H,m)	3.10(2H,s)	6.90(2H,s)	4.00(6H,s)
2i	89.3	268-9(d)	MeOH-Et_2O	1720	1760	2.20-3.7(8H,m)	3.05(2H,s)	6.85(2H,s)	3.95(6H,s)
2j	60.9	222-4	MeOH-Et_2O	1720	1785	2.20-3.6(8H,m)	3.00(2H,s)	6.90(2H,s)	3.95(6H,s)

[a]Satisfactory elementary analyses were obtained in all cases ; [b]Solvent for hydrochlorides CF_3COOH except *(d_6-DMSO) ; [c]Used as free base ($CDCl_3$) ; [d]90 MHz

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11. Mass spectra : 2b 386 (M^+), 219, 218, 205, 192, 191, 190 ; 2e 434 (M^+), 259, 245, 219, 218, 205, 192, 191, 190.
12. Data for compounds 10 :

10b : bp 125-130°C (0.1 mm) ; IR (NaCl) : 3295 (N-H), 1665 (C=O) cm^{-1}. 10c : bp 140-145°C (0.4 mm) ; IR (NaCl) : 3330 (N-H), 1670 (C=O) cm^{-1}. 10d : bp 150-155°C (0.6 mm) ; IR (NaCl) : 3380 (NH), 1675 (C=O). 10e : bp 140-145°C (0.5 mm) ; IR (NaCl) : 3350 (N-H), 1675 (C=O) cm^{-1}. 10f : bp 125-130°C (0.2 mm) ; IR (NaCl) : 3350 (N-H), 1670 (C=O) cm^{-1} ; ^{1}H-nmr (d_6-DMSO) δ : 7.80 (2H, broad s, NH) , 6.75 (8H, s, Ar-H), 3.70 (18H, s, 6 OMe), 3.50-1.80 (13H, m). 10g : bp 160-165°C (0.4 mm) ; IR (NaCl) : 3300 (N-H), 1680 (C=O).

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