

HETEROCYCLIC SPIRO COMPOUNDS. I. SYNTHESIS OF 9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDRO-SPIRO[BENZO[a]QUINOLIZINE-2,3'-PYRROLIDINE]-2',5'-DIONE

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**Abstract** —The synthesis of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)-quinolizine-2,3'-pyrrolidine]-2',5'-dione (9) was achieved from the corresponding 2-benzo(a)quinolizidinone (2) by two different routes.

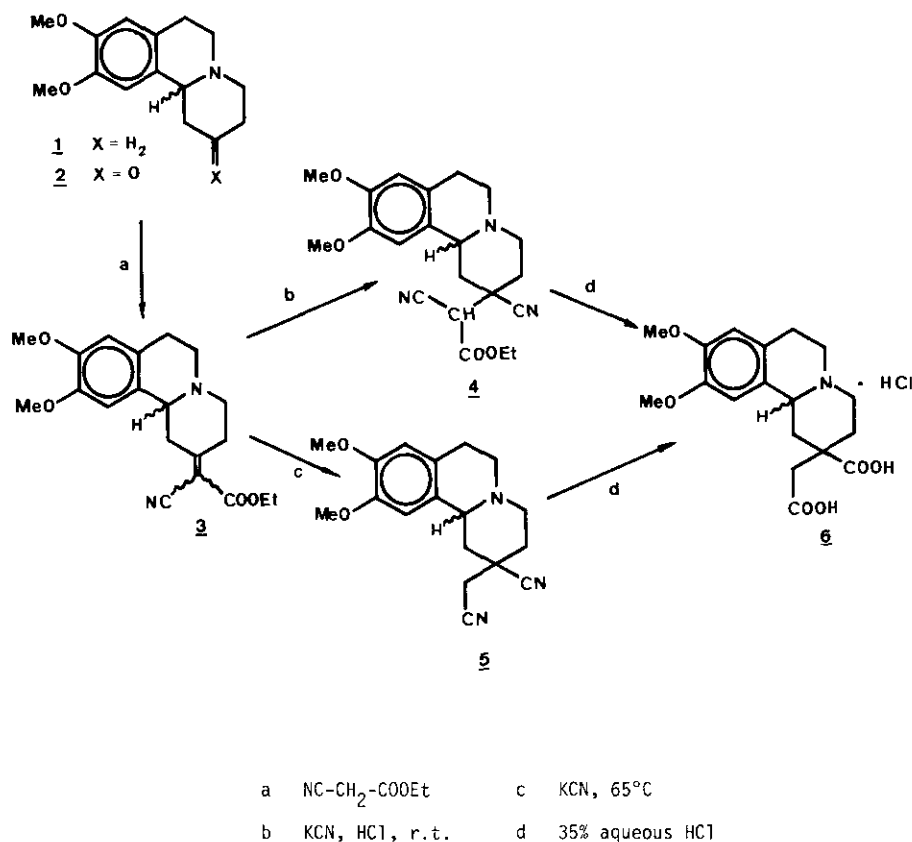
The 1,3,4,6,7,11b-hexahydro-2H-benzo(a)quinolizine system 1 is present in several ipecac alkaloids of well-known amoebicidal properties as well as in some antipsychotic drugs, such as tetrabenazine and benzquinamide<sup>1</sup>. Recent pharmacological studies have shown antihypertensive<sup>2-5</sup>, antiinflammatory<sup>6</sup> and anticonvulsant<sup>7</sup> properties for several benzo(a)quinolizidine derivatives.

Within the scope of our studies on the synthesis of heterocyclic spirans from aminoketones, we considered of interest the preparation of spiro[benzo(a)quinolizidin-2,3'-pyrrolidine]-2',5'-dione 9. The transformation of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizidin-2-one<sup>8</sup> 2 into 9 was initially carried out using 2-carboxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizidine-2-acetic acid hydrochloride (6) as a synthetic intermediate. The synthesis of 6 was accomplished by two different routes, as shown in Scheme 1.

The Cope condensation<sup>9</sup> between benzo(a)quinolizidin-2-one 2 and cyanoacetic ester in the presence of triethylamine gave 3 in good yield. Addition of hydrogen cyanide to 3 was attempted in a variety of experimental conditions<sup>10-12</sup>, among which only the reaction of 3 with two equivalents of hydrogen cyanide in aqueous alcoholic solution at room temperature for 5 days afforded 4 in a sufficiently high yield. Hydrolysis of 4 with concentrated hydrochloric acid gave the dicarboxylic acid 6 in quantitative yield.

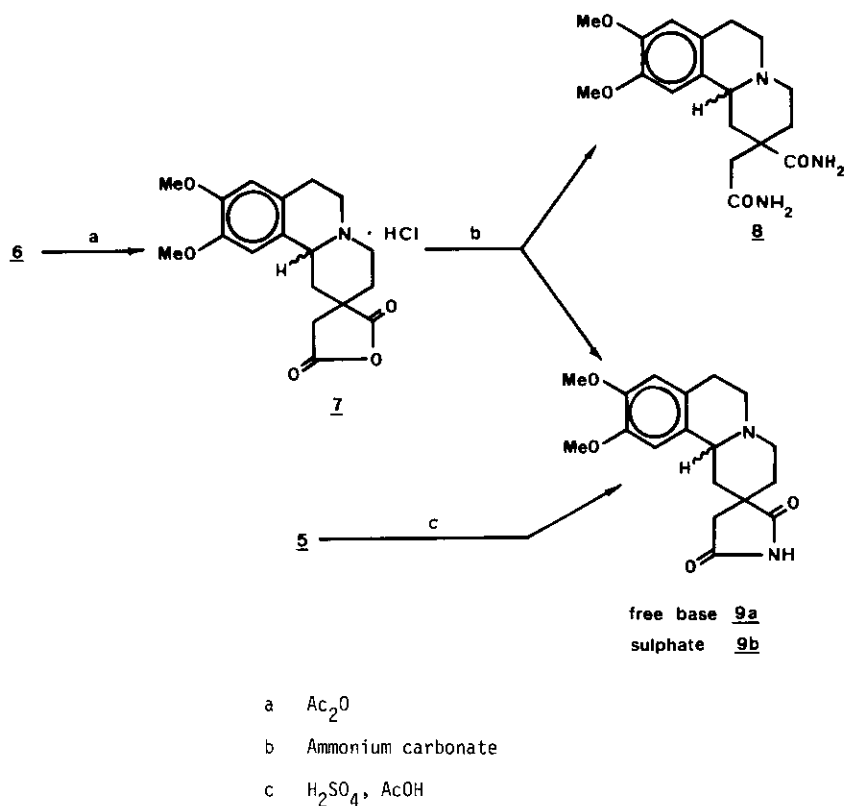
An alternative method was found during the studies on cyanide addition to 3, which on treatment with potassium cyanide in aqueous 2-propanol at 65°C for 16 h yielded dinitrile 5 (88.9%). Compound 5 was identified by spectroscopic methods and assumed to have come probably from the hydrolysis and decarboxylation of the intermediate product 4. Lundahl et al.<sup>12</sup> reported analogous results for

a similar reaction of an adamantan-2-one derivative employing a strongly alkaline medium. Finally, acid hydrolysis of 5 quantitatively yielded 6.



SCHEME 1

The synthesis of the target compound 9 is depicted in scheme 2, both from 5 and 6 as starting materials. Heating 6 with acetic anhydride afforded 7 in quantitative yield. When anhydride 7 was fused with ammonium carbonate, an acceptable yield (30.2%) of spiro compound 9a was obtained, together with some diamide 8 (19.5%). Their different solubilities in acetone allowed an easy separation of 9a. On the other hand, hydrolytic cyclization of dinitrile 5 with a mixture of sulphuric and acetic acids at  $120^\circ\text{C}$  during 1 h equally afforded compound 9a as the hydrogen sulphate salt in acceptable yield (40.0%).



SCHEME 2

The quinolizidine system presents a trans conformation in all compounds synthesized, as shown by the ir Bohlmann bands<sup>13</sup> and by the chemical shift of the C-11b proton in the  $^1\text{H}$ -nmr spectra<sup>14</sup>. Compounds 2, 3, 4, 5, 8 and 9a display a multiplet at a field higher than  $\delta$  3.8. The displacement of the signal to a lower field (about  $\delta$  4.2) observed for the salts 6, 7 and 9b is probably due to the deshielding effect of the positive charge placed on the quaternary nitrogen.

## EXPERIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following spectrometers : ir—Perkin Elmer 577 ;  $^1\text{H}$ -nmr—Hitachi-Perkin Elmer R-24 (60 MHz) (reference, tetramethylsilane) ; ms—Hitachi-Perkin Elmer RMU-6M. Elemental analyses were determined using a Carlo Erba Elemental Analyzer model J104 equipped with a digital integrator C SI 38.

Ethyl (9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-benzo(a)quinolizinylidene)cynoacetate (3).

A solution of ketone 2 (3 g, 11.49 mmole)<sup>8</sup>, ethyl cyanoacetate (1.3 g, 13.80 mmole), glacial acetic acid (0.3 ml), and Et<sub>3</sub>N (0.1 ml) in 25 ml of dry benzene was refluxed for 2 h in an oil bath at 120-125°C, using a Dean-Stark water separator. The cooled reaction mixture was washed with 3 x 15 ml of saturated aqueous NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure, leaving 4.2 g of an orange oil which yielded 3.6 g (87.4 %) of crystals on addition of 5 ml of ethyl ether. Mp 127-128°C (petroleum ether). Ir (KBr) cm<sup>-1</sup> : 2790, 2760, 2220 (C≡N), 1730 (C=O), 1600. <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ : 6.65 (1H,s,11-H) , 6.55 (1H,s,8-H) , 4.40 (2H,q,J=7 Hz) , 3.85 (3H,s,OMe), 3.82 (3H,s,OMe) , 3.65 (1H,m,11b-H) , 3.60-2.20 (10 H,m) , 1.40 (3H,t,J=7 Hz). Anal. Calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> : C, 67.42 ; H, 6.74 ; N, 7.86. Found : C, 67.64 ; H, 6.71 ; N, 7.71.

Ethyl (2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2-benzo(a)quinoliziny)cyanoacetate (4).

To an ice-cooled solution of 3 (0.3 g, 0.94 mmole) in a mixture of 2-propanol (15 ml) and 35% aqueous HCl (0.17 ml, 1.68 mmole) was added a solution of KCN (0.11 g, 1.68 mmole) in H<sub>2</sub>O (3 ml). The mixture was left at room temperature for 5 days. The yellow needles of 4 that precipitated were filtered off and washed with a small amount of 2-propanol, yielding 0.25 g (76.1 %) of 4. Mp 157-158°C (2-propanol). Ir (KBr) cm<sup>-1</sup> : 2800, 2765, 2250 (C≡N), 1755 (C=O). <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ : 6.60 (2H,broad 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<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> : C, 65.79 ; H, 6.53 ; N, 10.96. Found : C, 65.57 ; H, 6.18 ; N, 10.66.

2-Cyano-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetonitrile (5).

A solution of KCN (1.65 g, 25.32 mmole) in H<sub>2</sub>O (5 ml) was added to a solution of 3 (3.6 g, 10.06 mmole) in 2-propanol (40 ml). The mixture was heated at 65°C for 16 h and then cooled to precipitate 2.75 g (88.9 %) of 5. Mp 144-145°C (2-propanol). Ir (KBr) cm<sup>-1</sup> : 2800, 2760, 2260 (C≡N), 2240 (C≡N). <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ : 6.65 (1H,s,11-H) , 6.60 (1 H,s,8-H) , 3.85 (3 H,s,OMe) , 3.80 (3 H,s,OMe) , 3.50 (1 H,broad d,J~12 Hz,11b-H) , 2.75 (2 H,s,2'-H) , 3.20-1.60 (10 H,m). Anal. Calcd. for C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> : C, 69.45 ; H, 6.75 ; N, 13.50. Found : C, 69.69 ; H, 6.69 ; N, 13.44. Ms m/e : 311 (M<sup>+</sup>), 310, 271, 218, 205, 192, 191.

2-Carboxy-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrobenzo(a)quinolizine-2-acetic Acid Hydrochloride (6).

a) 6.15 g (15.95 mmole) of 4 was refluxed with 15 ml of 35% aqueous HCl in an oil bath at 120-125 °C for 4 h. The white precipitate formed after cooling was filtered off to yield 4.65 g (76.1 %) of 6. A second crop (1.4 g) was obtained by concentration to dryness of the mother liquors and recrystallization from H<sub>2</sub>O. Total yield, 6.05 g (99.0 %). Mp 245-246°C (H<sub>2</sub>O). Ir (KBr) cm<sup>-1</sup> : 3300-2300 (OH, R<sub>3</sub>NH<sup>+</sup>), 1730 (C=O), 1700 (C=O). <sup>1</sup>H-nmr (d<sub>6</sub>-DMSO) δ : 6.77 (1 H,s,11-H) , 6.62 (1 H,s,8-H) , 4.38 (1 H,broad d,J~11 Hz) , 3.76 (6 H,s,2 OMe) , 2.58 (2 H,s,2'-H) , 3.80-2.00 (10 H,m). Anal. Calcd. for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Cl : C, 56.03 ; H, 6.22 ; N, 3.63. Found : C, 55.83 ; H, 5.97 ;

N, 3.88.

b) 0.5 g (1.61 mmole) of 5 was treated in the same manner as described above to give 6 in 98.9 % yield. Mixed mp 245-246°C. Ir and  $^1\text{H}$ -nmr, the same as above.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-furan]-2',5'-(4'H)-dione hydrochloride (7).

The above acid 6 (3 g, 8.16 mmole) was refluxed with acetic anhydride (60 ml) for 6 h. The white solid formed during the reaction was filtered off, yielding 1.5 g (52.4 %) of 7. Additional 1.35 g of 7 was obtained by elimination of the acetic anhydride under reduced pressure, addition of 5 ml of dry toluene, and evaporation to dryness. Total yield, 2.85 g (99.6 %). Mp 249-251°C (decomp.) (acetic anhydride). Ir (KBr)  $\text{cm}^{-1}$ : 2780-2100 ( $\text{R}_3\text{NH}^+$ ), 1855 ( $-\text{CO}-\text{O}-\text{CO}-$ ,  $\nu_s$ ), 1760 ( $-\text{CO}-\text{O}-\text{CO}-$ ,  $\nu_{\text{as}}$ ), 940.  $^1\text{H}$ -nmr ( $d_6$ -DMSO)  $\delta$ : 6.90 (1 H,s,11-H), 6.82 (1 H,s,8-H), 4.70 (1 H,m,11b-H), 3.75 (6 H,s,2 OMe), 3.10 (2 H,s,4'-H), 3.70-2.10 (10 H,m). Anal. Calcd. for  $\text{C}_{18}\text{H}_{22}\text{NO}_5\text{Cl}$ : C, 58.77; H, 5.99; N, 3.81. Found: C, 58.41; H, 5.75; N, 3.62.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-pyrrolidine]-2',5'-dione (9a).

A magnetically stirred mixture of 7 (1.5 g, 4.08 mmole) and ammonium carbonate (3 g) was melted at 180°C during 2 h under nitrogen atmosphere. After cooling, the solid was crystallized from ethanol and charcoal. The white solid obtained was dissolved in ca. 5 ml of  $\text{H}_2\text{O}$  and precipitated with an equimolecular amount of 15% aqueous NaOH. The first crop obtained was identified as pure 9a; the successive crops consisted of a mixture of 9a and a secondary product 8. Treatment of this mixture with boiling acetone dissolved 9a and left pure 8 undissolved, which was identified from its spectral and analytical data as 2-carbamoyl-9,10-dimethoxy-1,3,4,5,7,11b-hexahydrobenzo(a)quinolizine-2-acetamide (8). The acetone solution of 9a was evaporated under reduced pressure and the residue recrystallized from  $\text{H}_2\text{O}$ . Total yield of 9a, 0.4 g (30.2 %). Mp 230-233°C (decomp.) ( $\text{H}_2\text{O}$ ). Ir (KBr)  $\text{cm}^{-1}$ : 3450 (N-H), 2800, 2750, 1760 ( $-\text{CO}-\text{NH}-\text{CO}-$ ,  $\nu_s$ ), 1710 ( $-\text{CO}-\text{NH}-\text{CO}-$ ,  $\nu_{\text{as}}$ ).  $^1\text{H}$ -nmr ( $d_6$ -DMSO)  $\delta$ : 6.65 (1 H,s,11-H), 6.55 (1 H,s,8-H), 3.70 (6 H,s,2 OMe), 2.52 (2 H,s,2'-H), 3.60-1.00 (11 H,m). Anal. Calcd. for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 65.48; H, 6.66; N, 8.48. Found: C, 65.23; H, 6.39; N, 8.23. Yield of 8, 0.25 g (19.5 %). Mp 235-237°C (EtOH). Ir (KBr)  $\text{cm}^{-1}$ : 3480 (N-H), 1680 ( $\text{C}=\text{O}$ ).  $^1\text{H}$ -nmr ( $d_6$ -DMSO)  $\delta$ : 6.80 (1 H,s,11-H), 6.70 (1 H,s,8-H), 4.70 (4 H,s,2  $\text{CONH}_2$ ), 3.80 (6 H,s,2 OMe), 3.52 (1 H,m,11b-H), 2.40 (2 H,s,2'-H), 3.30-1.35 (10 H,m). Ms m/e: 347 ( $\text{M}^+$ ), 331, 330, 288, 191, 190. Anal. Calcd. for  $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_4$ : C, 62.25; H, 7.20; N, 12.10. Found: C, 61.97; H, 7.05; N, 12.02.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo(a)quinolizine-2,3'-pyrrolidine]-2',5'-dione hydrogen sulphate (9b).

A mixture of the acetonitrile 5 (2.15 g, 6.91 mmole), glacial acetic acid (8 ml), and 75% aqueous  $\text{H}_2\text{SO}_4$  (2.80 g) was heated at 120-125°C for 1 h. The acetic acid was distilled off under reduced

pressure and the residue was treated with hot ethyl acetate. The insoluble fraction was crystallized from 2-propanol. Yield, 0.75 g (40.0 %). Mp 259-261°C (2-propanol). Ir (KBr)  $\text{cm}^{-1}$  : 3450 (N-H), 1760 (-CO-NH-CO-,  $\nu_s$ ), 1710 (-CO-NH-CO-,  $\nu_{as}$ ).  $^1\text{H}$ -nmr ( $\text{CF}_3\text{COOH}$ )  $\delta$  : 6.80 (2 H, broad s, 11-H and 8-H), 3.75 (6 H, s, 2 OMe), 4.90 (1 H, m, 11b-H), 2.65 (2 H, s, 4'-H), 3.65-1.50 (10 H, m). Anal. Calcd. for  $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_8\text{S}$  : C, 50.94 ; H, 5.66 ; N, 6.60. Found : C, 50.70 ; H, 5.43 ; N, 6.75.

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