SYNTHESIS AND STEREOCHEMICAL STUDY OF (±)-(2*R**, 11b*S**)-9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROSPIRO[BENZO[*a*]QUINOLIZINE-2, 5'-OXAZOLIDINE]-2', 4'-DIONE

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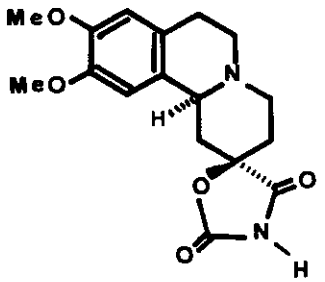
Abstract —The synthesis of (±)-(2*R**, 11b*S**)-9,10-dimethoxy-1,3,4,6,7,11b-*hexahydrospiro*[*benzo*[*a*]*quinolizine*-2, 5'-*oxazolidine*]-2',4'-dione (1) was achieved by two alternative routes, involving the cyclization of α-hydroxy amide (5) with ethyl carbonate in the presence of sodium hydride or treatment of cyanohydrin (3) with chlorosulfonyl isocyanate followed by acid hydrolysis. The stereochemistry of 1 was established on the basis of a spectroscopic study of its precursor (6).

The characterization of some 2β-(alkylsulfonylamino)areno[*a*]quinolizidines as stereoselective α_2-adrenoceptor antagonists[1] by analogy with rauwolscine and yohimbine provides support to the hypothesis that the sulfonamido group can act as a surrogate of the rauwolscine ester moiety.[2] Further research proved that this bioisosteric role can also be played by suitable heterocyclic rings linked to the C-2 atom of areno[*a*]quinolizidines,[1] provided the heterocycle bears an electronic and steric resemblance to the bioisosteric ester or sulfonamido groups.

Within the scope of our research into spiro derivatives of benzo[*a*]quinolizidine, we considered of interest the preparation of the (±)-(2*R**, 11b*S**)-*oxazolidinedione* (1), *due* to its potential as an α_2-adrenergic antagonist, in view of the close relationship of cyclic ureides and related heterocycles and sulfonamides. In connection with this, it must be mentioned that structurally similar compounds (2) have been shown to behave as potent antihypertensives and α_2-adrenergic antagonists,[3] although no effort has been

made to determine their α_2/α_1 selectivity.



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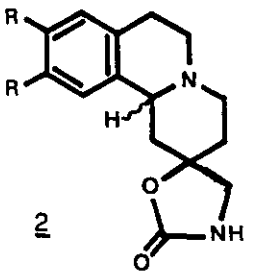
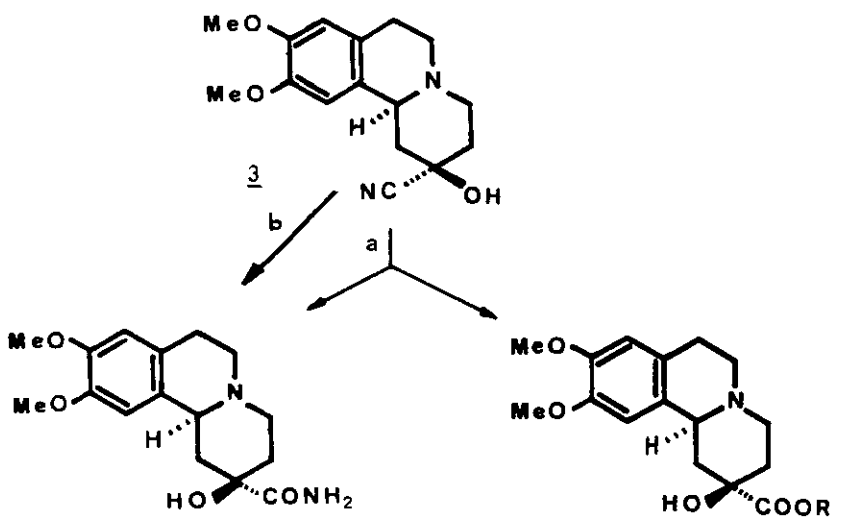


2

The fact that substituted cyclohexanones generally give stereoselective cyanation, corresponding to an axial attack of cyanide anion on the most stable conformation,[4] made cyanohydrin 3[5,6] a suitable starting material for the preparation of the desired oxazolidinedione (1). The methods classically employed for the synthesis of 2,4-oxazolidinedione derivatives[7,8] usually involve the cyclization of an α-hydroxy ester or



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5

4

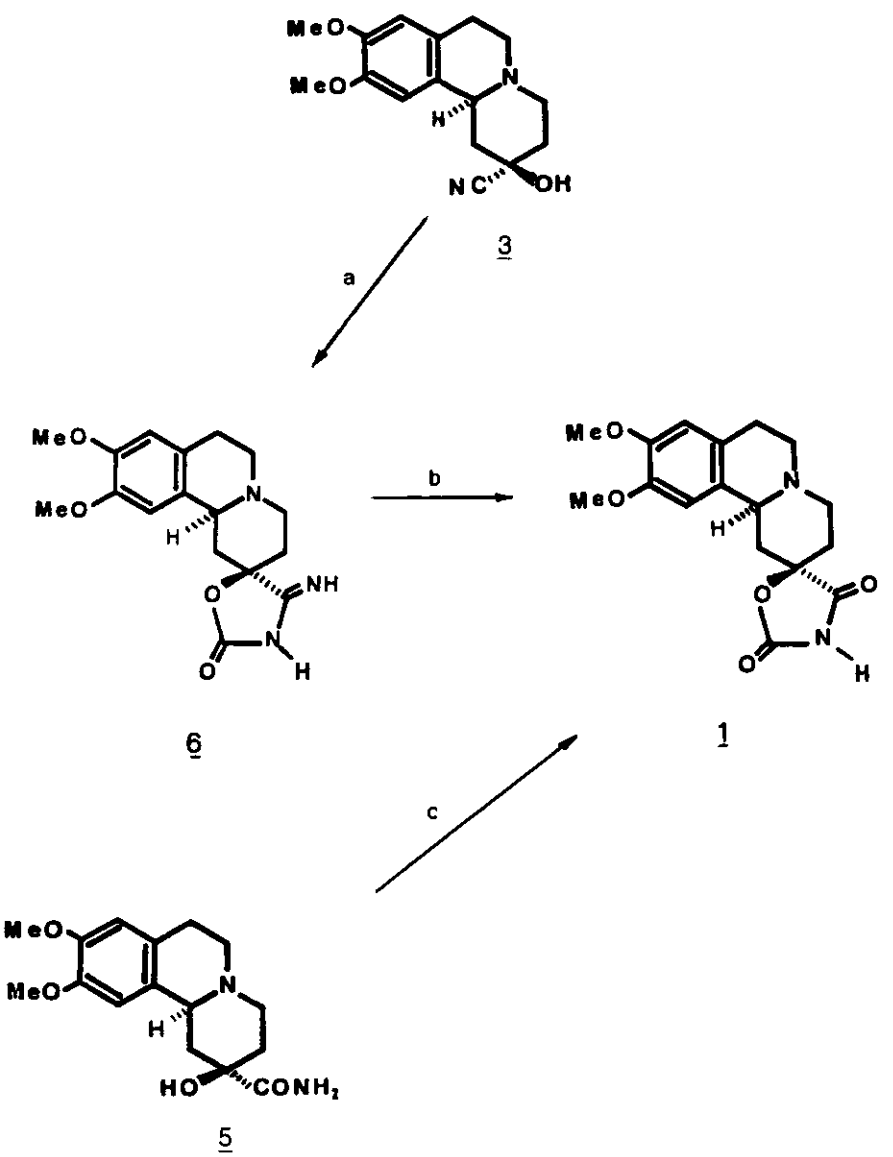
a. i) EtOH, HCl (g), -30 °C; ii) H_2O, H^+, room temperature
b. HCl (g), Et_2O-H_2O, 0 °C-room temperature

Scheme 1

an α-hydroxy amide. Ethanolysis of cyanohydrin (3) with dry hydrogen chloride at -30 °C followed by hydrolysis at room temperature did not afford the expected α-hydroxy ester (4) as the only product, but a mixture of 4 and α-hydroxy amide (5) in a 2:1 ratio. On the other hand, stirring a suspension of 3 in moist ether saturated with gaseous hydrogen chloride for 48 h at room temperature afforded the hydroxy amide (5) in good yield (Scheme 1).

All attempts to cyclize the hydroxy ester (4) into the target oxazolidinedione (1) under different literature conditions[7-11] led only to recovery of the starting material. The hydroxy amide (5), however, could be transformed into 1 by treatment with ethyl carbonate in the presence of sodium hydride. The modest yield obtained led us to attempt an alternative route (Scheme 2), which allowed the efficient praparation of 1 without the need of first transforming 3 into the corresponding hydroxy ester or hydroxy amide. Thus, treatment of 3 with chlorosulfonyl isocyanate followed by acid hydrolysis gave the desired oxazolidinedione (1) in good overall yield. Although this reaction sequence could be performed in one pot, it has been possible to isolate and fully characterize the 4-imino-2-oxazolidinone (6) as an intermediate of the process. This is in agreement with previous observations of other workers[12] for the related reaction between α-amino nitriles and chlorosulfonyl isocyanate.

The stereochemical study of the compounds described in this paper was carried out using 6 as a model structure, using spectroscopic criteria based upon those employed for the study of related benzo[*a*]quinolizidine derivatives.[13] Thus, the presence of Bohlmann bands[14,15] at 2800 and 2760 cm^{-1} in the ir spectrum of 6, together with the chemical shifts found for C-6 and C-7 in the ^{13}C-nmr spectrum[16] (δ = 53.19 and 27.90 ppm, respectively), suggests a *trans* structure for the quinolizidine ring junction. The downfield displacement of the C_{11b}-H signal in the ^{1}H-nmr spectrum of 6 (*ca.* 0.5 ppm from the expected value for the expected value[17] for a *trans*-benzo[*a*]quinolizidine) can only be attributed to the deshielding effect of the imino group at C-4', and is therefore compatible only with the (2*R**, 11b*S**) structure depicted in Schemes 1 and 2 for the compounds described here.



a. $ClSO_2NCO$, -30 °C–80 °C b. H_2O, H^+ c. $(EtO)_2CO$, NaH

Scheme 2

EXPERIMENTAL

Melting points are uncorrected and were measured in open capillary tubes, using a Büchi immersion apparatus. Elemental analyses were determined on a Carlo Erba Elemental Analyzer model 1104. Spectral data were obtained on the following instruments: Ir, Perkin Elmer 577; ^{1}H-nmr, Hitachi-Perkin Elmer R-24 B (60 MHz) and Brucker WM-200-SY (200 MHz); ^{13}C-

nmr, Brucker WM-200-SY (50.3 MHz).

(±)-(2*R**, 11b*S**)-2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carboxylic acid ethyl ester (4). A solution of (±)-(2*R**, 11b*S**)-2-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carbonitrile[5] (1 g, 3.37 mmol) in anhydrous ethanol (15 ml) was cooled to -30 °C and saturated with dry hydrogen chloride. The solvent was then removed at 0 °C and 0.5 torr, and the solid residue was added to a stirred biphasic system of 10 % hydrochloric acid (15 ml) and chloroform (25 ml). The aqueous phase was extracted with additional 3 x 25 ml of chloroform, and the combined organic layers were dried over anhydrous sodium sulphate and evaporated to yield a solid residue of crude 4·HCl, which was recrystallized from ethanol, giving 0.45 g (40 %) of a compound whose chromatographic and spectral properties were identical to those of a sample prepared by an alternative, two-step method.[18]

Free base. A solution of the hydrochloride (0.45 g, 1.21 mmol) in ethanol (10 ml) was treated with an ethanolic solution of sodium ethoxide, prepared by adding sodium (31 mg, 1.35 mg-atom) to absolute ethanol (5 ml). The solvent was evaporated *in vacuo* and the residue was extracted with boiling acetone (4 x 50 ml). Evaporation of this solvent left 0.39 g (96 %) of the desired free base, which was employed without further purification.

(±)-(2*R**, 11b*S**)-2-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carboxamide (5). Method A. The aqueous phase from the synthesis of 4 was basified with 30 % aqueous sodium hydroxide and extracted with chloroform (4 x 25 ml). After drying with anhydrous sodium sulphate and evaporating the solvent, the residue obtained was recrystallized from ethanol to yield 0.2 g (20 %) of 5.

Method B. A suspension of 2-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carbonitrile (3) (1 g, 3.5 mmol) in ether (40 ml) and 35 % aqueous hydrogen chloride (0.1 ml) was placed in a 0 °C bath and treated with dry, gaseous hydrogen chloride while magnetically stirred. The flask was then sealed and stirring was continued for 48 h at room temperature. The precipitated solid was filtered and recrystallized from ethanol-ether to yield 0.9 g (76 %) of 5·HCl.mp, 170-173 °C. Anal. Calcd for $C_{16}H_{23}N_2O_4Cl$: C, 56.06; H, 6.72; N, 8.18. Found: C, 55.89; H, 6.65; N, 7.95. Ir (KBr): 3480, 3405, 3280 (OH and NH), 2800-2300 (OH and NH), 2800-2300 (N^+-H), 1670 (C=)) cm^{-1}. ^{1}H-Nmr (60 MHz, DMSO-d_6) : 6.80 (s, 2H, C_8-H and C_{11}-H), 5.20 (br s, 1H, OH), 4.50 (m, 1H, C_{11b}-H), 3.95 (s, 6H, 2 x OMe), 3.70-2.00 (m, 10H). This hydrochloride was transformed into the corres-

ponding base using the same procedure described above for compound (4).

(±)-(2*R**, 11b*S**)-4'-Imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidin]-2'-one (6). To a solution of (±)-(2*R**, 11b*S**)-2-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carbonitrile (3) (1 g, 3.5 mmol) in a dry mixture of dichloromethane (30 ml) and dimethylformamide (4 ml), placed in a -30 °C bath, was added dropwise over 5 min a cooled solution of chlorosulfonyl isocyanate (0.6 g, 4.3 mmol) in dry dichloromethane (5 ml). The reaction mixture was allowed to warm to room temperature in 3 h and was then heated for 6 h in an oil bath at 80 °C. The inorganic precipitate formed during the reaction was filtered off and the filtrate was evaporated *in vacuo* and the residue was dissolved in water and basified to pH 6.5-7.0 to precipitate 0.45 g of 6. After readjusting the pH of the aqueous solution to 7.0, 0.3 g of the starting compound (3) was recovered. Yield, 56 % (based on the unrecovered 3). mp, 174-176 °C (2-propanol). Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.63; H, 6.34; N, 12.69. Found: C, 61.31; H, 6.34; N, 12.47. Ir (KBr): 3440, 3370 (NH), 1735 (C=O), 1620 (C=N) cm^{-1}. ^{1}H-Nmr (200 MHz, pyridine-d_5) : 8.20 (s, 1H, $N_{3'}$-H), 7.38 (s, 1H, $C_{4'}$=NH), 6.91 (s, 1H) and 6.73 (s, 1H) (C_8-H and C_{11}-H), 3.76 and 3.71 (2 s, 6H, 2 x OMe), 3.75 (m, 1H, C_{11b}-H), 3.30-1.90 (m, 10H). ^{13}C-nmr (50.3 MHz, pyridine-d_5) : 157.50 ($C_{2'}$), 129.11 (C_{11a})*, 127.63 (C_{7a})*,112.96 $(C_8)^+$, 109.68 $(C_{11})^+$, 69.74 (C_2), 59.99 (C_{11a}), 56.30 and 56.00 (2 x OMe), 53.19 (C_4), 51.68 (C_4), *38.32* (C_3), *27.90* (C_7). *Assignments marked with * and $^+$ can be interchanged.*

(±)-(2*R**, 11b*S**)-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizin-2,5'-oxazolidine]-2',4'-dione hydrochloride (1·HCl). Method A. A solution of the 4-imino-2-oxazolidinone (6) (0.2 g, 0.60 mmol) in methanol (5 ml) and 35 % aqueous hydrochloric acid (0.5 ml) was refluxed for 6 h. The solvent was evaporated *in vacuo* and the residue was recrystallized from 2-propanol to give 0.17 g (76 %) of (1)·HCl. mp, 225-227 °C. Anal. Calcd for $C_{17}H_{21}N_2O_5Cl$: C, 62.64; H, 5.70; N, 7.60. Found: C, 62.41; H, 5.63; N, 7.48. Ir (KBr): 3400 (N-H), 2800-2280 (N^+-H), 1825, 1750 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, DMSO-d_6) : 6.70 (s, 2H, C_8-H and C_{11}-H), 4.40 (m, 1H, C_{11b}-H), 3.65 (s, 6H, 2 x OMe), 3.50-2.00 (m, 10H).

Method B. An 80 % solution of sodium hydride in paraffin (0.6 g, 20 mmol) was washed with dry pentane (2 x 15 ml), and a solution of (±)-(2*R**, 11b*S**)-2-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine-2-carboxamide (5) (1.5 g, 5 mmol) in a dry 3:1 dichloromethane-dimethylformamide mixture (80 ml) was added. The stirred suspension was

treated dropwise with diethyl carbonate (1.2 ml, 10 mmol) in the same solvent mixture (40 ml). The resulting mixture was heated in an oil bath at 100 °C for 24 h, or irradiated with ultrasound at room temperature for the same period, filtered, and evaporated, and the residue was washed with brine (25 ml) and water (2 x 25 ml). The insoluble fraction was triturated with ether, yielding a precipitate that was recrystallized from ethanol. Yield, 0.15 g (10 %) of 1. Addition and subsequent evaporation of ethanol (5 ml) and 35 % aqueous hydrochloric acid (1 ml), followed by recrystallization from 2-propanol, afforded the hydrochloride (0.15 g, 95 %), identical to the compound obtained by the alternative procedure.

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