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SYNTHESIS OF 5-,6-, AND 7-DEUTERO SPARTEINES

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SUMMARY

Kinetically controlled $^{1}H/^{2}H$ exchange at carbon atom 5 of (-)-1,6-dehydrosparteinium monoperchlorate (3a) followed by sodium borohydride or sodium borodeuteride reduction of the iminium double bond gave optically active 5,5-($^{2}H_{2}$)-sparteine (1b) and 5,5,6-($^{2}H_{3}$)-sparteine (1c), respectively. Under thermodynamic control a third deuterium atom was incorporated into 3 at carbon atom 7. Borohydride reduction or rapid re-exchange followed by reduction lead to the novel sparteine analogues 5,5,7-($^{2}H_{3}$)-sparteine (1d) and 7-(^{2}H)-sparteine (1e). The title compounds have been prepared in 76 to 83 % yield and 89 to 97 % isotopic purity.

Key words: deuteration, sparteine, ^{13}C nuclear magnetic resonance

INTRODUCTION

Deuterated analogues of the quinolizidine alkaloid sparteine (1a) are useful research tools in studies concerning mass spectrometric fragmentation processes (1) or configuration elucidation by use of infra red (2,3) or ^{1}H-,^{2}H-,^{13}C-NMR spectroscopy (4-8). Kinetic deuterium isotope effects after administration of regioselectively deuterated drug to humans (9,10), in addition to loss or retention of label can contribute to a better understanding of the mechanism and site of the metabolic attack which is catalyzed by a hepatic cytochrome P-450 isozyme. Although a variety of deuterated sparteines (labelled at the positions 2,6,10,15 or 17 of the carbon skeleton or combinations thereof) have been prepared for these purposes (1-4,7-11), no synthesis of a deuterated sparteine which carries the label at carbon atoms 5 or 7 has been described. In this contribution an efficient and novel route to the title compounds will be presented.

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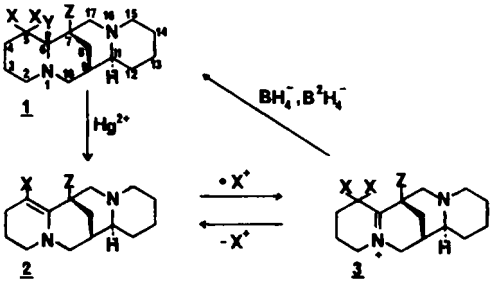
RESULTS AND DISCUSSION

Most deuterated sparteines have been either prepared by reductive deoxygenation of the corresponding lactams or by reduction of the CN-double bonds around N-1 or N-16 of appropriate dehydro-imonium salts (10-13). However, these methods are not applicable in the synthesis of 5-(^{2}H)- or 7-(^{2}H)-sparteines. Our approach is based on the observation that 2,3-enamines were protonated at the ß-carbon to give iminium salts (14,15). Thus, unlabelled 5,6-dehydro-sparteine (2a), which is readily available from sparteine (1a) (13,16), was converted into its perchlorate salt 3a and then dissolved in CH_3O^2H in the presence of catalytic amounts of enamine 2a (Scheme 1).

Scheme 1

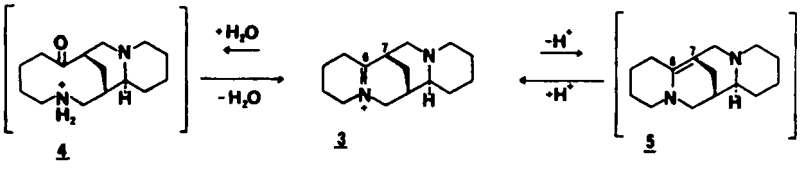


a: X = Y = Z = ^{1}H
b: X = ^{2}H; Y = Z = ^{1}H
c: X = Y = ^{2}H; Z = ^{1}H
d: X = Z = ^{2}H; Y = ^{1}H
e: X = Y = ^{1}H; Z = ^{2}H

After completion of the kinetically controlled ^{1}H/^{2}H-exchange the intermediate salt 3b was reduced with sodium borohydride or sodium borodeuteride to give pure 1b and 1c, respectively, in 76-77% yield.

In the course of these experiments we observed that prolonged exchange time and the presence of larger amounts of base and water lead to the incorporation of a third deuterium atom into 3b. It is well known that in 5-oxo-amines a pH dependent ring-chain equilibrium exists which in general is almost completely shifted towards the cyclic piperideine (17). In like manner it is possible that under thermodynamic control 3b is hydrolyzed to give intermediate 4 which could form an 6,7-enol and thus exchange hydrogen at carbon 7.

Scheme 2



However, no oxime of 4 could be isolated when 3 was treated with hydroxylamine under the usual exchange reaction conditions. Although such a transannular interaction (18) cannot be ruled out completely, the slow deuterium incorporation at carbon atom 7 could also be explained by a minor contribution of the strained 6,7-enamine 5 upon deprotonation of the conjugate acid 3 (Scheme 2). The assumed Bredt-type (19,20) intermediate 5 resembles one of the enolates of bicyclo [3,3,1]nonan-2-one, in which

base-catalyzed deuterium exchange led to incorporation of three deuterium atoms (21). As expected, borohydride reduction of 3d yielded 1d.

The large differences in the rate of $^{1}H/^{2}H$-exchange between the positions C-5 and C-7 can further be utilized to prepare regioselectively labelled 7-(^{2}H)-sparteine. Rapid re-exchange ($^{2}H/^{1}H$) of 3d in aqueous buffer (pH 7) followed by borohydride reduction of intermediate 3e lead to the deuterated analogue 7-(^{2}H)-sparteine (1e). Quantitative mass spectrometric analysis of the isotopic composition of all labelled analogues indicated a high degree of deuterium content (89-97 % ^{2}H at the isotopic maximum) whereas the site of labelling is more favourably monitored by ^{13}C-NMR spectrometry on the basis of previous signal resonance assignments (5) (Fig.1).

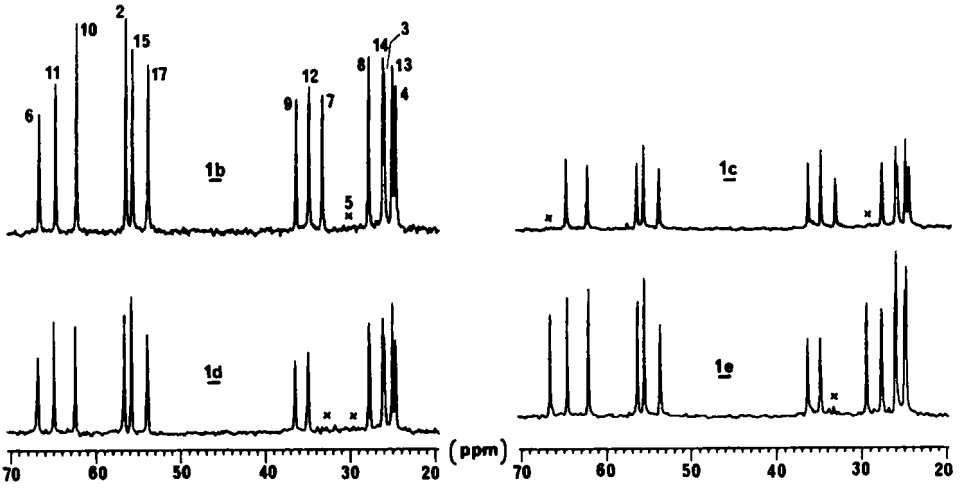


Figure 1. ^{13}C-NMR spectra (c=200 mg/3.5 ml) of 1b - 1e and signal resonance assignment (according to Ref. (5), shown in the spectrum of 1b). Unlabelled sparteine (1a) exhibits carbon resonances at (δ): 24.8 (C-4), 24.9 (C-13), 25.9 (C-3), 26.0 (C-14), 27.7 (C-8), 29.4 (C-5), 33.2 (C-7), 34.8 (C-12), 36.3 (C-9), 53.7 (C-17), 55.5 (C-15), 56.3 (C-2), 62.1 (C-10), 64.6 (C-11) and 66.6 (C-6) ppm.

As demonstrated with the synthesis of some novel deuterated sparteine analogues, selective ß-deuteration of iminium salts is simple and effective. This labelling technique is expected to be useful in the preparation of other deuterated alkaloids.

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EXPERIMENTAL

TLC: Reversed phase plates Nanosil C-18 100 F_{254} (Macherey/Nagel, FRG); solvent system used: acetone/H_2O/Et_3N(70:24:6;v/v,%). The sparteines 1 (R_f=0.30) and 2 (R_f=0.18) were

visualized on the plates either by spraying with ninhydrin (0.1% in EtOH) followed by heating at 140°C to give brown spots, or with iodine vapour (5 min) followed by heating at 140°C for 15 min to yield a violet flourescence upon irradiation with UV light (366 nm).- Melting points (m.p.): Electrothermal (uncorrected).- Optical rotations: Jasco DIP Model 360.- ^{13}C-NMR: 20 MHz, proton-decoupled, Bruker WP 80; int.std. TMS, solvent $CDCl_3$, shifts in ppm(δ scale).- MS: Hewlett-Packard 5985 A, PI/CI(NH_3,72 eV) ionization.- All work undertaken with 2 or 3 was carried out under argon atmosphere.

(-)-5,6-Dehydrosparteine, 2a, was prepared from 1 as described (13,16). It was in part converted into its monoperchlorate 3a (13) as described below.

(-)-5,5-($^2H_2$)-Sparteine, 1b.

A solution of 12.0 g (36 mmol) 1,6-dehydrosparteinium monoperchlorate (3a) and 0.97 g (4.1 mmol) 5,6-dehydrosparteine (2a) in a mixture of CH_3O^2H (100 ml, 99.5% ^2H) and ^2H_2O (30 ml, 99.8%) was left at room temperature under an atmosphere of argon. After 48h the methanol was distilled off and the exchange was repeated for 92h by use of 100 ml of CH_3O^2H. Excess base 2 was neutralized by dropwise addition of $^2HClO_4$/ ^2H_2O(68%,w/w; 99% ^2H) and solid sodium borohydride (11.4g, 0.3 mol) was added at 0°C in small portions. After a further 30 min at the same temperature the mixture was warmed at 50°C for 1 h. After cooling to room temperature, excess 1 N KOH was added and the free base 1b was isolated by repeated extraction with diethyl ether (4x100 ml). The combined extracts were dried ($MgSO_4$), concentrated on a rotary evaporator and then distilled in vacuum to give 6.5 g (77%) of pure (-)-5,5-($^2H_2$)-sparteine, b.p.98°C/0.05 mm, $[\alpha]_D^{21}$ -16.7 (c=1.0,EtOH), n_D^{20} 1.5271. The monohydrogensulphate of 1b was prepared as described below, m.p.134-138°C (dec.), $[\alpha]_D^{21}$ -21.4(c=5.0,H_2O). Calc.for $C_{15}{}^1H_{24}{}^2H_2N_2xH_2SO_4x5\ H_2O$ (424.5) C 42.44%, $^1H+^2H$ 9.50 %, N 6.59 %, S 7.55 %; found C 42.50 %, $^1H+^2H$ 9.23%, N 6.56 %, S 7.69 %.

5,5,6-($^2H_3$)-Sparteine, 1c.

The $^1H/^2H$ exchange described in the synthesis of 1b was repeated in the 10 mmol scale and the intermediate salt 3b was reduced by use of sodium borodeuteride (4.2 g, 0.1 mol) to give 1.8 g (76 %) of (-)-1c after distillation; sulphate: m.p. 139°C (dec.), $[\alpha]_D^{21}$ -21.2(c=3.7, H_2O). Calc. for $C_{15}{}^1H_{23}{}^2H_3N_2xH_2SO_4x5H_2O$ (425.5) C 42.34%, $^1H+^2H$ 9.71%, N 6.58%, S 7.53%; found C 42.35 %, ^1H + ^2H 9.56% N 6.47% S 7.61%.

(-)-5,5,7-($^2H_3$)-Sparteine, 1d.

A mixture of 3a (2.0 g, 6.0 mmol), 2a (271 mg, 1.2 mmol) ^2H_2O (1 ml) and CH_3O^2H (25 ml) was refluxed for 5 h and then left at room temperature for 12 h. The solvent was distilled off and replaced by 25 ml of CH_3O^2H. The mixture was again refluxed for 2 h and then left at room temperature for 56 h. Work-up (addition of acid followed by reduction) as described above afforded 1.4 g (83%) 1d after distillation, n_D^{24} 1.5269. The monoperchlorate of 1d was prepared as described below, m.p. 170-171°C, $[\alpha]_D^{21}$ -18.2(c=2.3, acetonitrile). Calc. for $C_{15}{}^1H_{23}{}^2H_3N_2xHClO_4$ (337.8) C 53.33%, ^1H + ^2H 8.95%, N 8.29%, Cl 10.49%; found C 53.49 %, ^1H + ^2H 9.16%, N 8.30%, Cl 10.67%.

(-)-7-(^2H)-Sparteine, 1e.

A solution of 3d (4.6 mmol) was prepared as described in the synthesis of 1d and 130 ml of 0.2 M phosphate buffer (pH 7) was added at room temperature. After 10 min the

mixture was cooled (0°C) and sodium borohydride (1.7 g, 44 mmol) was added in portions. Work-up as described for 1b yielded 900 mg (83%) essentially pure 1e, n_D^{24} 1.5270. Monoperchlorate of 1e:m.p. 170°C, $[\alpha]_D^{21}$ -18.5 (c=2.5, acetonitrile). Calc. for $C_{15}{}^1H_{25}{}^2HN_2xHClO_4$(335.8) C 53.64%, ^1H+2H 8.40%, N 8.34%, Cl 10.56%; found C 53.88%, ^1H+^2H 8.59%, N 8.35%, Cl 10.70%.

General procedures

Preparation of monohydrogensulphates of 1

To a stirred solution of 4 mmol of freshly distilled free base 1 in a cooled (0°C) mixture of 2-propanol (28.5 ml) and water (1.5 ml) was slowly added 4 mmol of concentrated sulphuric acid. The precipitated crystals were redissolved by gentle warming and the mixture was then left at -20°C. After 18h the precipitated crystals were collected, washed with a minimum of cold solvent mixture, and recrystallized a second time from 2-propanol/water to give analytically pure sulphates in about 75-90% yield. Drying in air provided pentahydrates while drying over P_2O_5 led to complete loss of crystal water. However, anhydrous sulphates of 1 are rather hygroscopic and thus less conveniently handled.

Preparation of monoperchlorates of 1

To a cooled (0°C) solution of the free base 1 (0.85 mmol) in ethanol (10 ml) was added perchloric acid (0.85 mmol; 60% aqueous solution). The mixture was then left at -20°C for 18h. The collected crystals were washed with a small quantity of ethanol and recrystallized from the same solvent. After drying (P_2O_5) colourless needles were obtained in nearly quantitative yield.

The isotopic composition of the free bases 1b - 1e was estimated by gas chromatography/mass spectrometry using selected ion monitoring of the molecular cluster ion $[M + 1]^+$ and chemical ionization (reactant gas NH_3) by comparison with the mass spectrum of unlabelled 1a ($[M + 1]^+$: m/z 235).

1b: 97%$^2H_2$, 3% $^2H_1$; 1c: 1% $^2H_1$, 4% $^2H_2$, 92% $^2H_3$, 3% $^2H_4$; 1d: 2% $^2H_1$, 9% $^2H_2$, 89% $^2H_3$; 1e: 9% $^2H_0$, 91% $^2H_1$.

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