SYNTHESIS OF CLONIDINE AND 1,3-DIMETHYLCLONIDINE LABELLED AT SPECIFIC POSITIONS WITH DEUTERIUM AND CARBON-13

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SUMMARY

The synthesis is reported of a number of analogues of clonidine and 1,3-dimethylclonidine labelled specifically and in high isotopic purity with deuterium and carbon-13. 2,6-Dichloro[4-$^{2}H_{1}$]aniline and 2,6-dichloro-[3,4,5-$^{2}H_{3}$]aniline were employed to prepare compounds substituted in the aromatic ring with one and three atoms of deuterium, respectively, while the use of appropriate derivatives of ethylenediamine led to products in which the imidazolidine ring was labelled with carbon-13 or deuterium.

Key words: Clonidine, deuterium, carbon-13, synthesis, mass spectra

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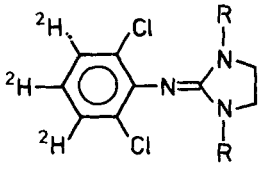
INTRODUCTION

Clonidine, 2-(2,6-dichlorophenylimino)imidazolidine is a potent antihypertensive agent which is widely used clinically for the treatment of high blood pressure. Whereas the pharmacokinetics of clonidine in both human subjects and experimental animals have been studied extensively, little detailed information is available on its metabolism, although conversion of the drug into 2,6-dichlorophenylguanidine, a product of imidazolidine ring cleavage, has been reported to occur in rat and dog (1). In order to define the mechanism of this unusual ring cleavage reaction and to assess the quantitative importance of this pathway relative to the other known route of clonidine metabolism, namely aromatic hydroxylation at the para position (2), a preliminary in vitro study using rat liver preparations was undertaken in which metabolites of clonidine and a structurally-related imidazolidine, 1,3-dimethylclonidine, were investigated using gas chromatography-mass spectrometry (GC-MS). This work led to a requirement for deuterium-labelled analogues of the compounds in question for use either as internal standards in stable isotope dilution GC-MS assay procedures or as substrates in metabolic experiments when information on the site(s) of biotransformation may be obtained through loss or retention of labelled hydrogen atoms located at specific positions. In the present communication, we report on the synthesis of five substituted 2-arylimino-imidazolidines, labelled specifically and in high isotopic purity with deuterium, together with an analogue of clonidine labelled with ^{13}C at the metabolically labile positions (C-4 and C-5) of the heterocyclic ring (Fig. 1).



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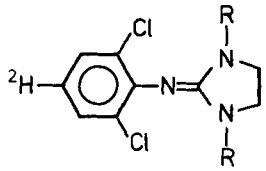

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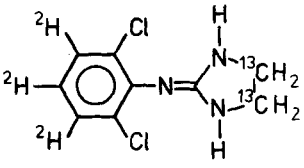

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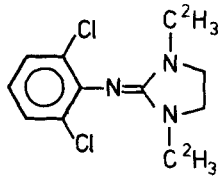

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Fig. 1 Analogues of clonidine and 1,3-dimethylclonidine labelled with deuterium and carbon-13

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on glass plates (5 x 20 cm), precoated with 0.25 mm layers of silica gel 60 F_{254} (Merck AG, Darmstadt, Germany). Three solvent systems were used: (A) chloroform/ethyl acetate/ 15M NH_4OH (10:30:0.5 by vol.), (B) chloroform/methanol/15M NH_4OH (40:15:0.5 by vol.), (C) n-butanol/acetic acid/water (12:30:50 by vol.) and spots were visualized either by viewing under UV light (λ = 254 nm) or by spraying with ninhydrin reagent and heating. Preparative TLC was carried out on glass plates (20 x 20 cm), precoated with 2 mm layers of silica gel 60 F_{254} (Merck AG). Bands were scraped off and compounds were eluted with ethyl acetate.

Nuclear magnetic resonance (NMR) spectrometry was performed at 60 MHz on a Hitachi Perkin-Elmer R-24 instrument. Chemical shifts are reported relative to tetramethylsilane.

Mass spectrometry (MS). Mass spectra (25 eV) were recorded with a Finnigan 3200 instrument, equipped with a Finnigan 6000 series interactive data system. Samples were introduced either via the direct insertion probe or via the gas chromatographic inlet. A U-shaped glass column (5ft x 2 mm i.d.) was used for GC-MS analyses, packed with 3% OV-1 on Gas Chrom Q (100-120 mesh) and operated at temperatures of between 100° and 200° with He (30 ml min^{-1}) as carrier gas. Determination of the deuterium content of synthetic intermediates and products was based on measurements of the relative intensities within respective molecular ion clusters and is expressed as atoms % excess. Unless otherwise noted, determinations were performed on underivatized samples.

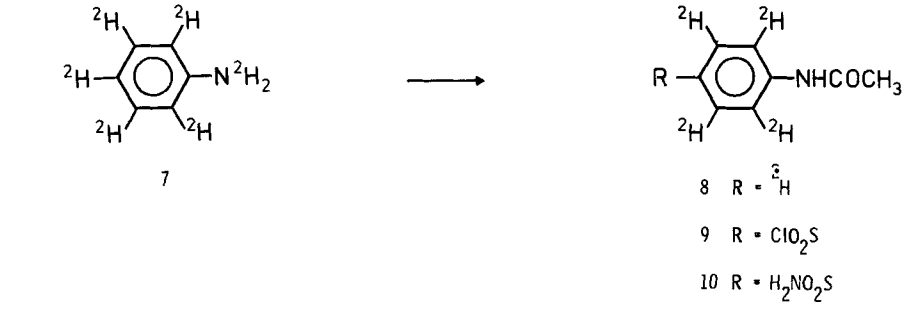
Reagents

$[^{2}H_{7}]$Aniline (98 atom % excess), dibromo$[^{13}C_{2}]$ethane (90 atom % excess), $[^{2}H_{3}]$methyl iodide (99.5 atom % excess) and $[^{2}H_{2}]$sulphuric acid (> 99 atom % excess) were purchased from Merck Sharp and Dohme Canada Ltd (Montreal, Canada). Deuterium oxide (99.7 atom % excess) was obtained from BDH Chemicals Ltd (Enfield, Middx). Ethylenediamine and N,N'-dimethylethylenediamine were purchased from the Aldrich Chemical Co. Ltd (Gillingham, Dorset) and trimethylanilinium hydroxide (TMAnH) from Pierce and Warriner (UK) Ltd (Chester). Other reagents were purchased from either BDH Chemicals Ltd or the Aldrich Chemical Co.

SYNTHESIS

2-(2,6-Dichloro[3,4,5-$^2H_3$]phenylimino)imidazolidine ([$^2H_3$]clonidine; 1)

[$^2H_7$]Aniline (7; 10.0 g, 100 mmole) was acetylated at room temperature using acetic anhydride (12.5 ml, 135 mmole) to yield acet[$^2H_5$]anilide (8; 11.5 g, 82 mmole) (Scheme 1). TLC (solvent system A): R_f = 0.50. MS (direct inlet): m/e 140 (M^+), 98 (base peak), 71 and 43. Deuterium content: 1% $^2H_3$, 4% $^2H_4$ and 95% $^2H_5$.



Scheme 1

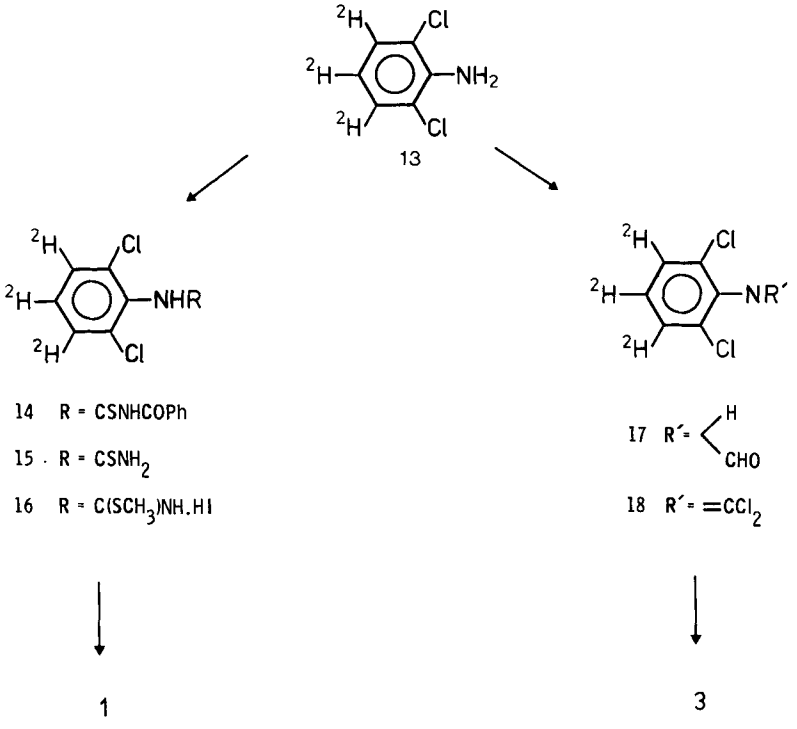
The deuterated acetanilide 8 (11.5 g, 82 mmole) was heated with chlorosulphonic acid (29 ml, 4.40 mmole) for 1 h at 90°. The reaction mixture was poured into ice, stirred for several minutes and the product was isolated by filtration. The 4-acetamido[2,3,5,6-$^2H_4$]benzenesulphonyl chloride (9) thus obtained was immediately treated with aqueous ammonia (7.5M) and heated just below boiling point for 15 min. The resulting suspension was cooled in ice, acidified (9M H_2SO_4) and filtered to give an amorphus white solid, 4-acetamido[2,3,5,6-$^2H_4$]benzenesulphonamide (10; 11.5 g, 53 mmole). TLC (solvent system A): R_f = 0.11. MS (direct inlet): m/e 218 (M^+), 176 (base peak), 160, 112, 96 and 43.

The [$^2H_4$] sulphonamide 10 (11.5 g, 53 mmole) was refluxed for 40 min in 4M HCl. The resulting yellow solution was cooled, treated with decolourising charcoal and filtered to give an almost colourless filtrate. This solution was neutralised by the addition of solid sodium bicarbonate and the sulphanilimide 11 was isolated by filtration (yield 7.8 g, 44 mmole). TLC (solvent system A): R_f = 0.20. MS (direct inlet): m/e 174-176 (M^+), 158-160, 110-112, 94-96 and 67-69. Deuterium content: 23% $^2H_2$, 48% $^2H_3$ and 29% $^2H_4$.

The labelled sulphanilimide 11 (7.8 g, 44 mmole) was converted to its 2,6-dichloro derivative 12 using hydrochloric acid and hydrogen peroxide as described by Sieket (3). The yield of [2,6-$^2H_2$]3,5-dichlorosulphanilamide (12) was 6.4 g (26 mmole). TLC (solvent system A): R_f = 0.50. MS (direct inlet): m/e 242 (M^+), 226, 178 (base peak), 162 and 126. Deuterium content: 4% $^2H_1$ and 96% $^2H_3$.

The sulphonamide group was hydrolyzed using 70% (by wt.) $^2H_2SO_4$ in ^2H_2O (32 ml). After heating on an oil bath at 190° for 2 h, water (200 ml) was added and the product, 2,6-dichloro[3,4,5-$^2H_3$]aniline (13) was

purified by steam distillation (yield 3.5 g, 21 mmole). TLC (solvent system A): R_f = 0.68. NMR (C^2HCl_3): no aromatic proton, δ 4.35 (broad s, NH_2). MS (GC inlet): m/e 164 (M^+ and base peak), 137, 129, 102 and 93. Deuterium content: 13% $^2H_2$ and 87% $^2H_3$.



Scheme 2

The labelled 2,6-dichloroaniline 13 was converted to [$^2H_3$ clonidine (1) via the S-methylisothiuronium iodide 16 (Scheme 2) (4). Thus, 2,6-dichloro[3,4,5-$^2H_3$ aniline (13; 1.4 g, 8.5 mmole) was heated with benzoyl-chloride (1.3 g, 9.0 mmole) and ammonium thiocyanate (0.68 g, 9.0 mmole) in dry acetone (30 ml). After 1 h half the acetone was distilled off and the product poured into water (100 ml) to precipitate N-benzoyl-N'-2,6-dichloro[3,4,5,-$^2H_3$]phenylthiourea (14, 2.6 g, 8.0 mmole). This was subjected to alkaline hydrolysis to yield the pale yellow solid 2,6-dichloro[3,4,5-$^2H_3$]phenylthiourea (15; 1.3 g, 5.8 mmole) (5). TLC (solvent system A): R_f = 0.44. MS (direct inlet): m/e 223 (M^+), 206, 188 (base peak), 164, 153, 125, 93 and 60.

The thiourea 15 (1.3 g, 5.8 mmole) was methylated using methyl iodide (0.36 ml, 5.8 mmole) to afford N-2,6-dichloro[3,4,5-$^2H_3$]phenyl-S-methylisothiuronium iodide (16; 1.75 g, 5.4 mmole). TLC (solvent system A): R_f = 0.60. MS (direct inlet): m/e 237 (M^+ of free base), 202, 190 (base peak), 163 and 127.

The isothiuronium salt 16 (0.4 g, 1.2 mmole) underwent condensation with anhydrous ethylenediamine (0.20 ml, 3.0 mmole) by heating at 150° for 1 hr (4,6). The [$^2H_3$]clonidine produced was purified by preparative TLC (solvent system B; R_f = 0.65), and was converted to the hydrochloride salt (yield 85 mg, 0.32 mmole). NMR ([$^2H_6$]DMSO/ ^2H_2O): no aromatic protons, δ 3.82 (S, CH_2-CH_2). MS (direct inlet): m/e 232 (M^+ and base peak), 197, 175 and 162. Deuterium content (as determined by GC-MS analysis of the N,N'-dimethyl derivative): 13% $^2H_2$ and 87% $^2H_3$.

1,3-Dimethyl-2-(2,6-dichloro[3,4,5-$^2H_3$]phenylimino)imidazolidine (1,3-dimethyl[$^2H_3$]clonidine; 3)

1,3-Dimethyl[$^2H_3$]clonidine (3) was prepared from 2,6-dichloro[3,4,5-$^2H_3$]aniline (13) via N-2,6-dichloro[3,4,5-$^2H_3$]phenyldichloroimine (18), as outlined in Scheme 2 (7). Thus, 2,6-dichloro[3,4,5-$^2H_3$]aniline (13; 1.0 g, 6.0 mmole) was converted to 2,6-dichloroform[3,4,5-$^2H_3$] anilide, (1.1 g, 5.7 mmole) using formic acid and acetic anhydride as described by Timmermans et al (6). The product gave: TLC (solvent system B): R_f = 0.72. MS (direct inlet): m/e 192 (M^+), 164, 157 (base peak) 102 and 93.

The formanilide 17 (1.1 g, 5.7 mmole) was stirred with sulphuryl chloride (0.46 ml, 5.7 mmole) in thionyl chloride (3 ml) for 16 h at 50° to yield the pale yellow oil 2,6-dichloro[3,4,5-$^2H_3$]phenyldichloroimine (18;

1.0 g 4.1 mmole). TLC (solvent system B): R_f = 0.79. MS (GC inlet): m/e 244 (M^+), 209 (base peak), 174, 148 and 111.

To a mixture of triethylamine (0.8 ml, 5.7 mmole) in ethyl acetate (0.8 ml), solutions of the dichloroimine 18 (0.25 g, 1.0 mmole) in ethyl acetate (0.5 ml) and N,N'-dimethylethylenediamine (0.22 ml, 2.0 mmole) in ethyl acetate (0.5 ml) were added simultaneously and the resulting mixture was stirred for 2 h at room temperature. Water was then added, the aqueous solution was extracted twice with ethyl acetate, and the organic extracts were evaporated to dryness. The residue was dissolved in dilute HCl and the resulting solution was extracted with ether. The ether extract was discarded while the aqueous phase was made alkaline (conc. NH_3) and extracted twice with chloroform. The chloroform extracts were combined and dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. The product, 1,3-dimethyl[$^2H_3$]clonidine (3), was converted to its hydrochloride salt (yield 0.16 g, 0.54 mmole). TLC (solvent system B): R_f = 0.80. NMR ($C^2H_3O^2H$): no aromatic protons, δ 3.88 (s, 4H, CH_2-CH_2), δ 2.89 (s, 6H $2NCH_3$). MS (direct inlet) is illustrated in Fig. 3. Deuterium content: 13% $^2H_2$ and 87% $^2H_3$.

2-(2,6-Dichloro[4-$^2H_1$]phenylimino)imidazolidine ([$^2H_1$]clonidine: 2)

Using the procedures described above, and unlabelled sulphanilamide (11a) as starting material, 2,6-dichloro[4-$^2H_1$]aniline (13a) was prepared as shown in Scheme 2. This material was then used to synthesize [$^2H_1$]clonidine (2), which had the following properties: TLC (solvent system B): R_f = 0.65. NMR ([$^2H_6$]DMSO/^2H_2O): δ 7.60 (s, 2H, Aryl-H), δ 3.75 (s, 4H, CH_2-CH_2). MS (direct inlet) is illustrated in Fig. 2. Deuterium content: 7% $^2H_0$, 76% $^2H_1$ and 17% $^2H_2$.

1,3-Dimethyl-2-(2,6 dichloro[4-$^{2}H_{1}$]phenylimino)imidazolidine (1,3-dimethyl[$^{2}H_{1}$]clonidine; 4)

Using 2,6-dichloro[4-$^{2}H_{1}$]aniline, (13a), and the "dichloroimine" pathway (Scheme 2), 1,3-dimethyl[$^{2}H_{1}$]clonidine (4) was prepared in a similar fashion to the trideuterated species, 3. TLC (solvent system B): R_f = 0.80. NMR ($C^{2}H_{3}O^{2}H$): δ 7.68 (s, 2H, Aryl-H), δ 3.86 (s, 4H, CH_2-CH_2), δ 2.88 (s, 6H, $2NCH_3$). MS (direct inlet) is illustrated in Fig. 3. Deuterium content: 8% $^{2}H_{0}$, 75% $^{2}H_{1}$ and 17% $^{2}H_{2}$.

2-(2,6-Dichloro[3,4,5-$^{2}H_{3}$]phenylimino)[4,5-$^{13}C_{2}$]imidazolidine ([$^{13}C_{2}$, $^{2}H_{3}$]clonidine; 5)

[$^{13}C_{2}$, $^{2}H_{3}$]Clonidine was prepared by condensation of the [$^{2}H_{3}$]isothiuronium salt (16) with [$^{13}C_{2}$]ethylenediamine prepared from dibromo[$^{13}C_{2}$]ethane by a modification of the Gabriel phthalimide synthesis (8). Thus, potassium phthalimide (10.5 g, 57 mmole) and dibromo[$^{13}C_{2}$]ethane (5.0 g, 26 mmole) were heated with stirring in dimethylformamide (35 ml). After 2 h at 90°, the mixture was allowed to cool and water (100 ml) was added. The resulting diphthalimino[$^{13}C_{2}$]ethane was extracted with chloroform (250 ml), which was dried ($MgSO_4$) and evaporated under reduced pressure (yield 8.4 g, 26 mmole). TLC (solvent system B): R_f = 0.83. MS (direct inlet): m/e 322 (M^+), 175 (base peak) and 161. Carbon-13 content (as determined by MS (direct inlet) using the fragment at m/e 175) was found to be as follows (atoms % excess): 1% $^{13}C_{o}$, 17% $^{13}C_{1}$, 82% $^{13}C_{2}$. The diphthaliminoethane (8.4 g, 26 mmole) was hydrolyzed at room temperature with aqueous KOH (5.75 M, 40 ml) (9). When all the solid had dissolved (~ 48 h), the solution was distilled to dryness. Water (60 ml) was added to the residue and the resulting mixture was again distilled to dryness. In order to isolate the labelled [$^{13}C_{2}$] ethylenediamine in pure form, the distillate was acidified with HCl and

evaporated almost to dryness; the [$^{13}C_2$]ethylenediamine hydrochloride was then precipitated with ethanol and collected by filtration (yield 2.7 g, 20 mmole). TLC (solvent system C): R_f = 0.43.

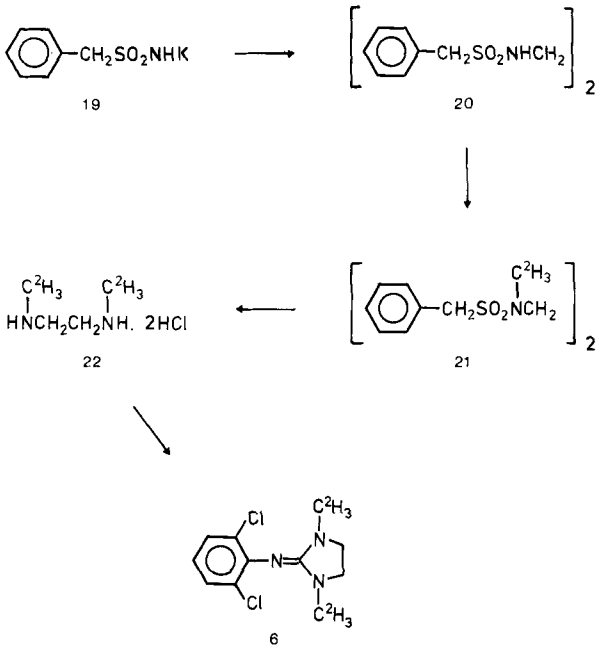
To obtain [$^{13}C_2$]ethylenediamine as the free base, the hydrochloride salt (2.7 g, 20 mmole) was mixed with an equal weight of calcium oxide and the solid mixture distilled over a free flame. The oily distillate was dried by first distilling over potassium hydroxide pellets and then several times over sodium metal to give the anhydrous [$^{13}C_2$]ethylenediamine as a colourless oil (0.5 ml, 7.5 mmole). TLC (solvent system C): R_f = 0.43. NMR (CCl_4): δ 2.68 (d, $J_{^{13}C-H}$ = 131 Hz, 4H, $^{13}CH_2$-$^{13}CH_2$), δ 1.00 (s, 4H, $2NH_2$).

The anhydrous [$^{13}C_2$]ethylenediamine (0.2 ml, 3.0 mmole) was condensed with the [$^2H_3$]isothiuronium salt (16; 0.4 g, 1.2 mmole) as described above to give [$^{13}C_2$,$^2H_3$]clonidine (5; 61 mg, 0.22 mmole). TLC (solvent system B): R_f = 0.65. NMR ($C^2H_3O^2H$): no aromatic protons, δ 3.83 (d, $J_{^{13}C-H}$ = 145 Hz, 4H, $^{13}CH_2$-$^{13}CH_2$). MS (direct inlet) is illustrated in Fig. 2. The mass spectrum of this multiply-labelled analogue of clonidine indicated that no loss of deuterium or ^{13}C had occurred from 2,6-dichloro [3,4,5-$^2H_3$]aniline and [$^{13}C_2$]ethylenediamine, respectively, during the synthetic sequence. The product had a $^{13}C_2$ content of 82 atoms % excess and a $^2H_3$ content of 87 atoms % excess.

1,3-Di[$^2H_3$]methyl-2-(2,6-dichlorophenylimino)-imidazolidine (1,3-di[$^2H_3$]methylclonidine; 6)

1,3-Di[$^2H_3$]methylclonidine was prepared by condensation of unlabelled 2,6-dichlorophenyldichloroimine with N,N'-di[$^2H_3$]methylethylenediamine hydrochloride which was prepared by deuteromethylation of dibenzyl-sulphonethylenediamine (20) as shown in Scheme 3 (10).

α-Toluenesulphonamide was prepared from α-toluenesulphonylchloride by heating in aqueous ammonia (7.5M) for 15 min. The resulting suspension was cooled in ice, acidified with H_2SO_4 (9M) and filtered. The precipitate



Scheme 3

was dissolved in aqueous potassium hydroxide to give the potassium salt of α-toluenesulphonamide (19). TLC (solvent system A): R_f = 0.35. MS (direct inlet) m/e 171, 107, 91 (base peak) and 65. Potassium α-toluenesulphonamide (19; 32 g, 153 mmole) was heated with dibromoethane (6.5 ml, 75 mmole) for 16 h at 110°. The product was washed with water and ether to give a white amorphus solid, dibenzylsulphonethylenediamine (20; 9.7 g, 26 mmole). MS (direct inlet): m/e 368 (M^+), 304, 213, 184, 120 and 91 (base peak). The dibenzylsulphonethylenediamine (20; 9.0 g, 24 mmole) was refluxed in an aqueous solution of potassium hydroxide

(2.8 g, 50 mmole) for 1 h. The mixture was then filtered and the filtrate evaporated to dryness. The residue was then dissolved in aqueous ethanol (50%) and heated under reflux for 5 h with $[^2H_3]$ methyl iodide (4 ml, 65 mmole). The precipitate was collected by filtration, washed with 20% NaOH and water to give dibenzylsulphondi $[^2H_3]$methylethylenediamine (21; 4.1 g, 10 mmole). MS (direct inlet): m/e 402 (M^+), 247, 201, 137 and 91 (base peak).

To obtain N,N'-di$[^2H_3]$methylethylenediamine, the crude sulphonamide 21 (1.5 g, 3.7 mmole) was hydrolysed with H_2SO_4 (80% w/w, 5 ml), by heating at 150° for 5 min. This mixture was allowed to cool, diluted with water (25 ml) and made alkaline with aqueous ammonia (15M). The resulting alkaline solution was filtered and the filtrate distilled. The distillate was acidified with HCl and evaporated to dryness to give the white solid N,N'-di$[^2H_3]$methylethylenediamine hydrochloride (22; 0.3 g, 1.8 mmole). TLC (solvent system C): R_f = 0.33. MS (direct inlet): m/e 94 (M^+ free base), 61 and 47.

To a mixture of 2,6-dichlorophenyldichloroimine (0.5 g, 2.1 mmole) in isopropanol (10 ml) and N,N'-di$[^2H_3]$methylethylenediamine hydrochloride 22 (0.135 g, 8.0 mmole) in isopropanol (10 ml), sodium hydroxide (0.4 g, 10 mmole) in water (1.5 ml) was added. The resulting solution was stirred at 40° for 2 h, and then evaporated to dryness. Water (20 ml) was added and extracted twice with chloroform. The organic extracts were combined and evaporated to dryness. The neutral products were removed by extraction from acidic solution as described for 1,3-dimethyl $[^2H_3]$ clonidine. The product, 1,3-di$[^2H_3]$methylclonidine (6) was converted

to its hydrochloride salt (yield 0.22 g, 0.73 mmole). TLC (solvent system B): R_f = 0.80. NMR (^2H_2O): δ 7.65 (M, 3H, aryl), δ 3.82 (s, 4H, CH_2-CH_2). MS (GC inlet) is illustrated in Fig. 3. Deuterium content: 7% $^2H_0$ and 93% $^2H_6$.

RESULTS AND DISCUSSION

In the present work, established procedures for the synthesis of clonidine and 1,3-dimethylclonidine were modified for the preparation of analogues labelled specifically with either deuterium alone or with a combination of deuterium with carbon-13. Of the two preferred synthetic routes leading to compounds with the basic clonidine structure, each of which utilizes 2,6-dichloroaniline as starting material, the "dichloroimine" pathway (7) was employed to synthesize deuterated derivatives of 1,3-dimethylclonidine, while labelled analogues of clonidine itself were obtained *via* the "isothiouronium iodide" route (4) (Scheme 2). The isotopic purities of synthetic intermediates and products are given in the Experimental section, while representative mass spectra are illustrated in Figs. 2 and 3.

The preparation of clonidine and 1,3-dimethylclonidine labelled with deuterium in the aromatic ring was achieved by use of appropriately deuterated 2,6-dichloroanilines (13 and 13a) which were synthesized, in turn, as outlined in Scheme 1. Thus, [$^2H_7$]aniline (7) was first converted, using standard procedures, into the tetradeutero sulphonamide derivative. Subsequent acid-catalyzed hydrolysis of the acetamido

function to give 11 was found to be accompanied by considerable back-exchange of deuterium from the positions ortho to the primary amine group, to afford a product comprising mainly trideuterated molecules. Subsequent introduction of chlorine at the ortho positions, followed by treatment with $^2H_2SO_4$, gave 2,6-dichloro[3,4,5-$^2H_3$]aniline (13) with an isotopic purity of 87 atom % excess. Similarly, when unlabelled sulphonilamide (11a) was subjected to the two terminal steps of the above sequence, 2,6-dichloro[4-$^2H_1$]aniline (13a) was obtained, although the presence in the reaction product of approximately 17% of dideuterated molecules indicated that appreciable acid-catalyzed exchange of protons at the meta positions of the aniline ring had accompanied introduction of the deuterium at C-4. Conversion of the labelled 2,6-dichloroanilines into [$^2H_3$]clonidine (1), [$^2H_1$]clonidine (2), 1,3-dimethyl[$^2H_3$]clonidine (3), 1,3-dimethyl[$^2H_1$]clonidine (4) and [$^{13}C_2$, $^2H_3$]clonidine (5) was accomplished without any significant loss of label from the aromatic ring.

In conclusion, a variety of stable-isotope-labelled analogues of clonidine and 1,3-dimethylclonidine have been prepared by appropriate modifications of existing synthetic routes, to afford products of high isotopic purity. The use in metabolic studies of these compounds, together with suitable ^{14}C-labelled radiotracers (11,12) has furnished valuable information on qualitative, quantitative and mechanistic aspects of clonidine metabolism. The results from these studies will be published elsewhere (13).

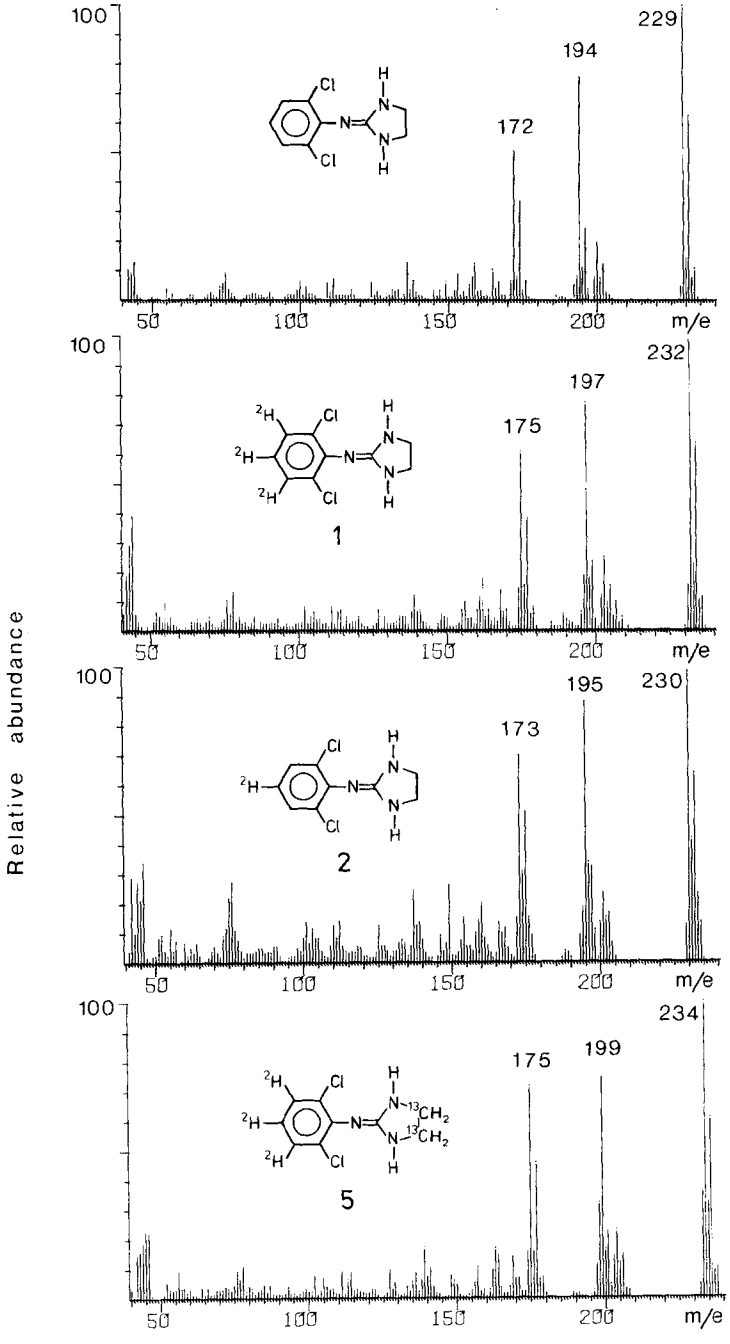


Figure 2 Mass spectra (25 eV) of clonidine and isotopically labelled analogues of clonidine

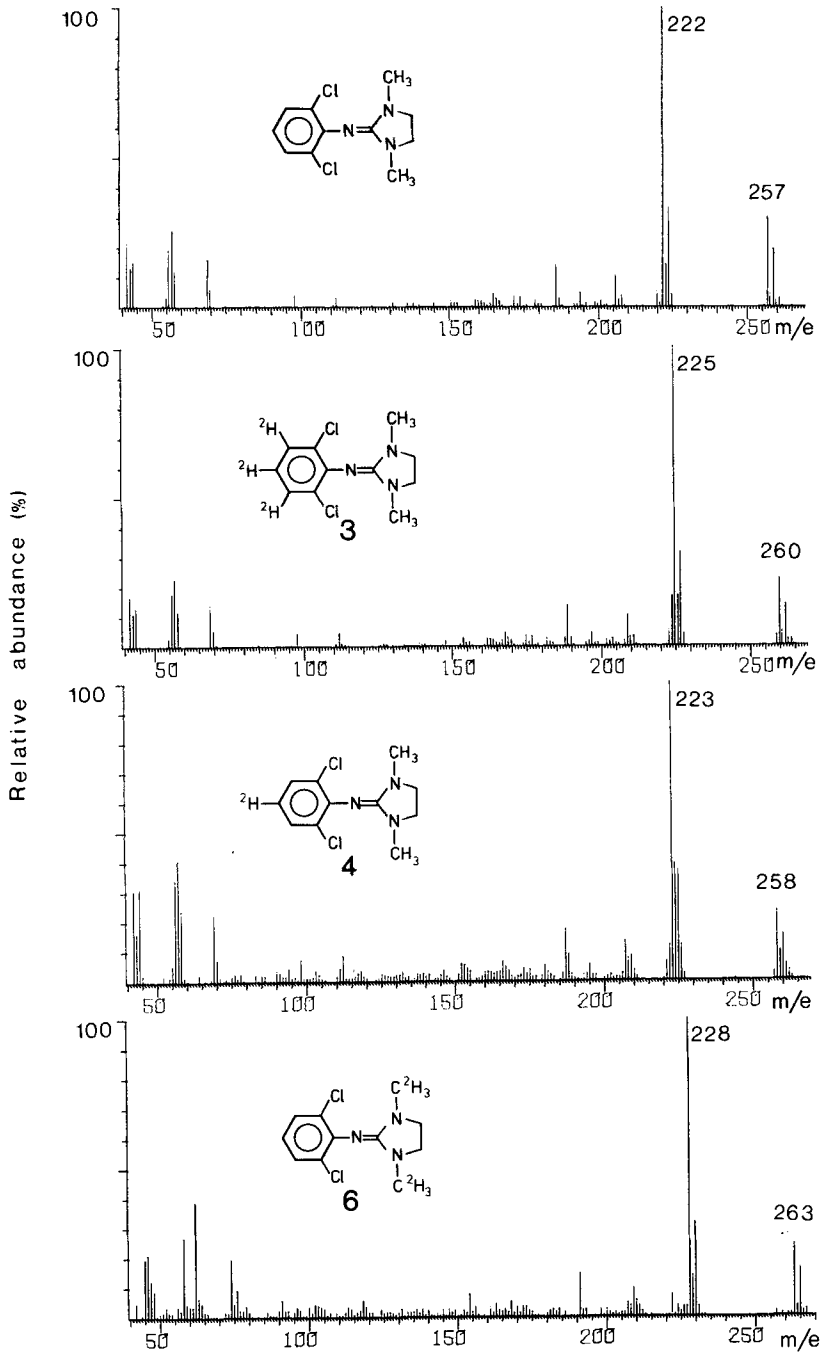


Figure 3. Mass spectra (25 eV) of 1,3-dimethylclonidine and isotopically labelled analogues of 1,3-dimethylclonidine

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