SYNTHESIS OF DEUTERATED 1,2,3,4-TETRAHYDROISOQUINOLINES

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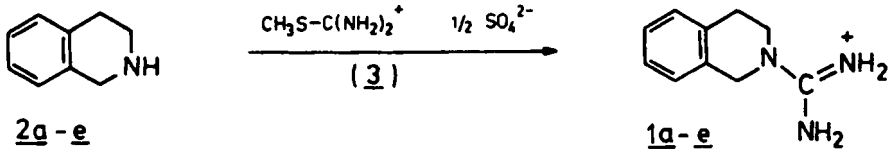
SUMMARY

The synthesis of five 1,2,3,4-tetrahydroisoquinolines (2), which were either randomly labelled (1,1,3,3,4,4-$^2H_6$,2b) or regioselectively labelled (1,1-$^2H_2$,2c; 3,3-$^2H_2$, 2d; 4,4-$^2H_2$, 2e) from isoquinoline (4), indan-2-one (7), and phenylacetonitrile (11) is described. These deuterated bases were used in the preparation of labelled analogues of the antihypertensive agent debrisoquine.

Key words: deuteration; 1,2,3,4-tetrahydroisoquinolines, debrisoquine

INTRODUCTION

As part of our studies on the molecular mechanisms of polymorphic drug oxidation of the sparteine/debrisoquine type (1) we required deuterated analogues of the antihypertensive test agent debrisoquine (1) which were labelled at the heterocyclic moiety of the molecule. Because 1 is readily prepared by guanidination of 1,2,3,4-tetrahydroisoquinoline (2) using S-methylisothiouronium sulphate (3) (2), the synthetic programme was focussed on the synthesis of deuterated analogues of 2 which were labelled at carbon atoms 1,3 or 4 (Scheme 1).



2a - e

1a - e

Scheme 1

d : $^2H_6$; b : 1,1,3,3,4,4-$^2H_6$; c : 1,1-$^2H_2$; d : 3,3-$^2H_2$; e : 4,4-$^2H_2$

So far only one example of the preparation of decadeuterated 1,2,3,4-tetrahydroisoquinoline and debrisoquine from isoquinoline, with a yield of about 16% and 5% respectively, has been reported in the literature (3). Regioselective and more efficient routes of synthesis of the title compounds are therefore required.

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RESULTS AND DISCUSSION

The first and most convenient approach is based on the observation that the heterocyclic moiety of isoquinoline (4) is selectively saturated with hydrogen gas in the presence of Adam's catalyst and weak acids (4). However, use of deuterium gas and deuterated solvents cleanly afforded a randomly labelled 1,2,3,4-tetrahydroisoquinoline (2b) which contained more than the expected three deuterium atoms (Scheme 2). Analysis of the ^{1}H- and ^{13}C-NMR spectra indicated that the deuterium is predominantly localized in the heterocyclic ring and that the carbon atoms 1,3, and 4 had been labelled to a different degree (see Experimental). These results can be explained in part by a nobel metal catalyzed deuterium exchange in the hydroaromatic 2 (see e.g. Ref. (5)).

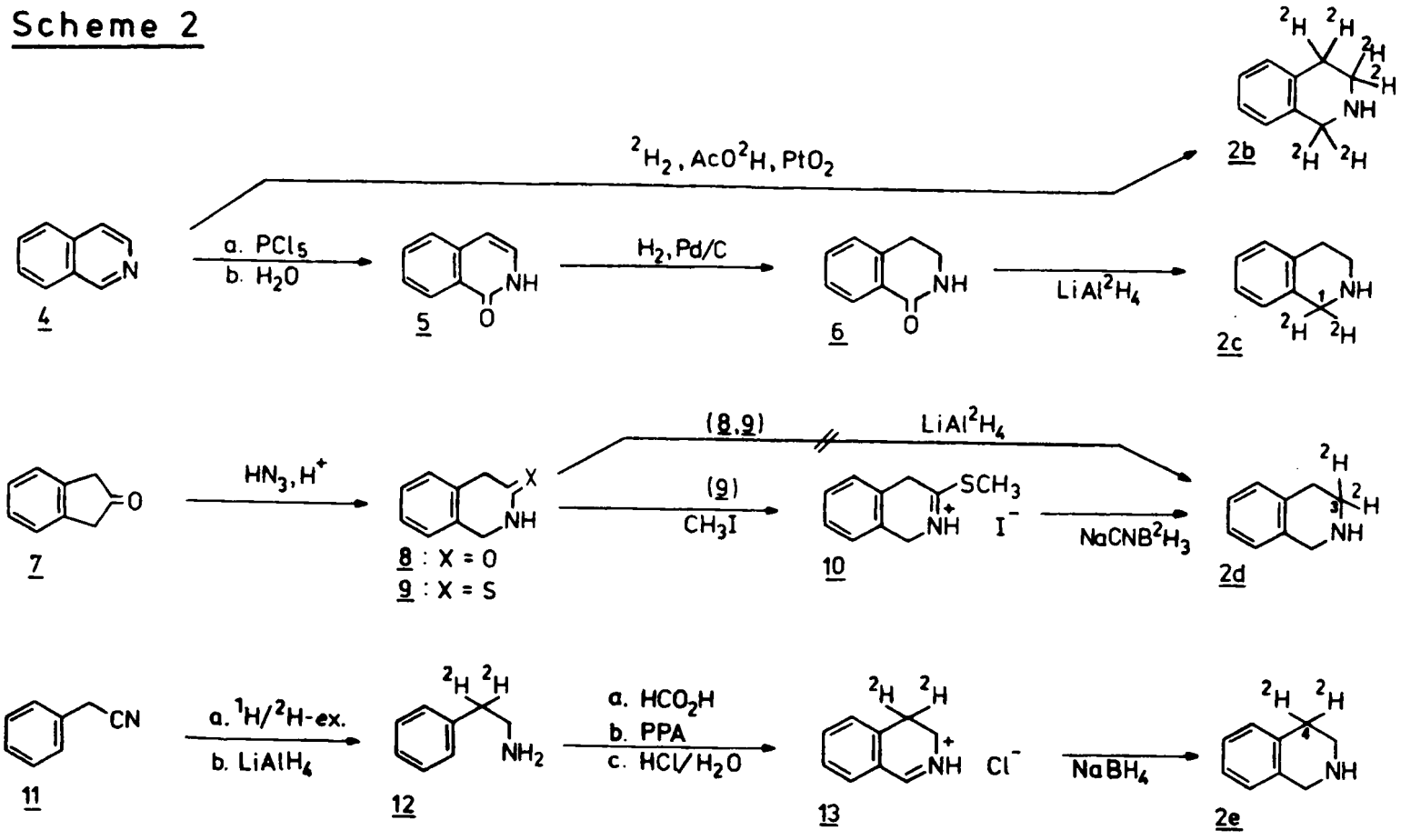
Isoquinoline (4) also served as starting material for the synthesis of 2c. One-pot chlorination followed by hydrolysis (6) yielded 1,2-dihydro-1-oxo-isoquinoline (5, 1-hydroxyisoquinoline, isocarbostyril) (7) which, in contrast to a previous report (8), was readily hydrogenated over palladium on carbon to give 6 (8). Reductive deoxygenation by use of lithium aluminium deuteride, as described for the 4-hydroxy analogue (9), yielded highly and regioselectively labelled 2c.

For the synthesis of 3,3-($^{2}H_2$)-1,2,3,4-tetrahydroisoquinoline (2d) a different route was explored. Because the Beckmann rearrangement of the oxime of 7 was of low yield, the lactame 8 (10) was prepared by the Schmidt reaction (11). However, deoxygenation and deuteration of 8 using lithium aluminium deuteride gave only a poor yield of 2d although no problems had been encountered in this step in the case of structurally related alkaloids (12). Unsatisfactory results were also obtained when 9, prepared from 8 and Lawesson' Reagent (13), was used in place of 8. Thus, the thioamide 9 was alkylated according to the general procedure published in Ref. (14) and the resultant methyl thioimidate 10 was subsequently desulphurized and reduced to give 2d using sodium cyanoborodeuteride, as described for other substrates (15).

Regioselective introduction of deuterium into position 1 or 4 of the tetrahydroisoquinoline skeleton was accomplished in the following manner. Preparative (16) base catalyzed $^{1}H/^{2}H$ exchange of the benzylic hydrogen atoms of phenylacetonitrile 11 followed by nitrile reduction by use of $LiAlH_4$ gave 2,2-($^{2}H_2$)-phenylethylamine 12 which was converted into its intermediate formamide by heating with concentrated formic acid. In contrast to a previous report on a related compound (17), polyphosphoric acid (PPA) catalyzed cyclization of the formamide did not yield the saturated 1,2,3,4-tetrahydroisoquinoline directly. Instead, 3,4-dihydroisoquinoline was formed and converted into its hydrochloride 3, which was smoothly reduced to give 2e using sodium borohydride in methanol, as described for other substrates (18).

The new deuterated analogues of 1,2,3,4-tetrahydroisoquinoline were fully characterized either as free bases, their hydrochlorides or pyrimidine derivatives (19) of 1 (see Experimental). Because of the drastic reaction conditions employed, unevitable loss of label was observed in 2e ($^{2}H_1$:16%, $^{2}H_2$:76%) whereas 2c and 2d exhibit rather high isotopic purities (98% and 89% $^{2}H_2$, respectively). Virtually no incorporation of deuterium atoms at the other aromatic or aliphatic positions was observed. The synthetic routes outlined in Scheme 2 should also allow further selective deuterium incorporation via either reduction of 5 with molecular deuterium gas, reduction of 5 and 11 with lithium aluminium deuteride or, reduction of 13 with sodium

Scheme 2


$^2H_2$, AcO^2H, PtO_2
2b
a. PCl_5
b. H_2O
H_2, Pd/C
$LiAl^2H_4$
4
5
6
2c
(8,9)
$LiAl^2H_4$
HN_3, H^+
(9)
CH_3I
$NaCNB^2H_3$
7
8 : X = O
9 : X = S
10
2d
a. $^1H/^2H$-ex.
b. $LiAlH_4$
a. HCO_2H
b. PPA
c. HCl/H_2O
$NaBH_4$
11
12
13
2e

borodeuteride. Conversion of the deuterated bases 2b - 2e into the corresponding labelled analogues of debrisoquine (1) by use of S-methylisothiouronium sulphate completed the synthetic programme.

Because many naturally occuring alkaloids also contain the 1,2,3,4-tetrahydroisoquinoline structure, it is expected that the methodology described in this paper could be useful in the synthesis of deuterated analogues of natural products.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

TLC: SiO_2 60 F_{254} (E.Merck); solvent systems used: (I),EtOAc; (II),$CHCl_3$/ MeOH/AcOH(90:5:5); (III),EtOAc/n-hexane(1:5).- Melting points(m.p.), uncorrected(Electrothermal).- MS: Hewlett-Packard 5985A.- NMR(80 MHz/ ^1H, 20 MHz/^{13}C-proton-decoupled): Bruker WP 80; int. std. TMS($CDCl_3$), 3-(trimethylsilyl)propanoic acid-$^2H_4$ sodium salt (D_2O) or acetonitrile (D_2O,^{13}C:δ (CH_3)= 1.30 ppm). Chemical shifts are reported in ppm (δ - scale).

1,1,3,3,4,4-($^2H_6$)-1,2,3,4-Tetrahydroisoquinoline, 2b.

A mixture of isoquinoline (1.0 g, 7.7 mmol; TLC: R_f 0.71(I)), EtO^2H (3 ml), AcO^2H(480 mg, 15.6 mmol) and 25 mol% of Adam's catalyst (PtO_2,435 mg, 1.9 mmol) was stirred at room temperature under an atmosphere of deuterium gas (99.7% ^2H) for 6 h. The apparatus was then flushed with argon and excess aqueous 5 N HCl was added. The mixture was filtered, evaporated, and excess aqueous NaOH was added. The product was isolated by extraction with CH_2Cl_2 to give 700 mg(66%) of essentially pure 2b,TLC:R_f 0.35(I). An analytical sample was distilled (b.p.42°C/0.01 mm; n_D^{23} = 1.5661), converted into its hydrochloride and recrystallized from boiling EtOH,m.p.196.5-198°C (1a:m.p. 196°C, (20)). Found C 61.89%, ^1H+^2H 9.61%, Cl 20.30%, N 7.89%; calc. for $C_9{}^1H_7{}^2H_5ClN$ (174.7) C 61.88%, ^1H+^2H 9.80%, Cl 20.30%, N 8.02%.- ^1H-NMR spectrometry showed about 70% $^2H_2$ at C-1 and C-3 and 85% $^2H_2$ at C-4. Mass spectrometric analysis exhibited an isotopic maximum (29.3%) at $^2H_5$ (see 1b).

Deuteration of 4 (12 g) over 2.8 mol% of PtO_2(0.6 g) in AcO^2H(14 ml) for 24 h gave a product with an isotopic maximum at $^2H_4$ (29.2%).

1,2-Dihydroisoquinolin-1-one, 5, was prepared as described (6) from isoquinoline with about 10% yield. It is also commercially available (Aldrich), m.p.205-208°C)(EtOAc/n-hexane)(Ref.21:m.p.207-208°C). TLC: R_f 0.34(II).

1,2,3,4-Tetrahydroisoquinolin-1-one, 6.

A rapidly stirred solution of 5 (2.4 g, 16 mmol) in 240 ml of EtOH was hydrogenated for 18 h in the presence of 10% Pd/C(3.0 g). The mixture was filtered, evaporated, redissolved in a minimum of EtOAc, and filtered through about 10 g of resin Dowex AG 50W-X8 (H^+- form) to remove traces of 2a. Evaporation gave an oil which gradually solidified, 2.3 g (95%), m.p.69-70°C (from EtOAc/n-hexane) (Ref.8:m.p.70-71°C). TLC: R_f 0.25(II).

1,1-($^2H_2$)-1,2,3,4-Tetrahydroisoquinoline, 2c.

To a stirred suspension of lithium aluminium deuteride (2.0 g, 48 mmol, 98% ($^2H_2$), Aldrich) in

40 ml of dry tetrahydrofuran was added dry lactam 6 under an argon atmosphere. After 1 h reflux, the mixture was cooled (0°C) and excess reagent was destroyed by slow addition of 12 ml MeOH followed by 10 ml of water. The product was isolated by extraction with diethyl ether (8x50 ml) and purified by distillation (b.p.100°C/17 mm) to yield pure 2c as an oil, 1.1g (62%); n_D^{25}=1.5644. Found C 79.81%, $^1H+^2H$ 9.95%, N 10.29%; calc. for $C_9{}^1H_9{}^2H_2N$ (135.2) C 79.95%, $^1H+^2H$ 9.69%, N 10.36%.-

Hydrochloride of 2c: m.p.197-199°C. Found C 63.01%, $^1H+^2H$ 8.22%, N 8.06%; calc. for $C_9{}^1H_{10}{}^2H_2$ ClN(171.7) C 62.99%, $^1H+^2H$ 8.20%, N 8.16%.-

1,2,3,4-Tetrahydroisoquinolin-3-one, 8, was prepared essentially as dexcribed previously (11) by Schmidt reaction of indan-2-one with hydrazoic acid giving a yield of 23%, m.p. 148-149°C (Ref.10: m.p.150°C). TLC R_f 0.18 (II).

1,2,3,4-Tetrahydroisoquinolin-3-thione, 9.

To a solution of 8 (11.6 g, 79 mmol) in 150 ml of dry toluene was added 19.4 g (47 mmol) Lawesson's reagent (2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane) under an argon atmosphere. After stirring at 100°C for 1 h the solvent was distilled off and the product was extracted with CH_2Cl_2. The combined extracts were filtered through silica gel and evaporated. The residue was recrystallised twice from toluene to yield colourless needles of 9,11.2 g(87%),m.p. 155°C(dec.). TLC: R_f 0.82.

Found C 66.36%, H 5.62%, N 8.57%, S 19.93%; calc. for C_9H_9NS(163.2) C 66.22%, H 5.56%, N 8.58%, S 19.64%.- ^{1}H-NMR ($CDCl_3$):4.08(t, J=1.7 Hz, 2H,H-4), 4.51(dt,J=2.9/1.7 Hz, 2H,H-1), 7.23(m,4H, aryl-H), 9.22(broad s, 1H,NH).- ^{13}C-NMR($CDCl_3$):45.5,47.9(CH_2); 125.4,127.2,127.3, 128.3,129.6,131.5(aryl-C),201.1(C=S).-

3-Methylthio-1,4-dihydroisoquinolinium iodide, 10.

A mixture of 9 (3.4 g,21 mmol), acetonitrile (100 ml) and methyl iodide (14 ml) was refluxed for 1h. Solvent and excess reagent were then removed under vacuum and the crystalline residue was washed with dry diethyl ether. After drying (P_2O_5), 6.2 g (97%) of essentially pure salt 10 was obtained; m.p.185°C. Found C 39.48%, H 4.01%, I 41.58%, N 4.63%, S 10.69%; calc. for $C_{10}H_{12}INS$(305.1) C 39.36%, H 3.96%, I 41.58%, N 4.59%, S 10.51%.- ^{1}H-NMR($CDCl_3$): 3.17(s, 3 H,SCH_3), 4.03(t,J=2.2Hz,2H,H-4),5.09(t,J=2.2 Hz,2H, H-1),7.38(m,4H,aryl-H).-

3,3-($^2H_2$)-1,2,3,4-Tetrahydroisoquinoline, 2d.

Bromocresol green was added (22) to a mixture of methanol (10 ml), sodium cyanoborodeuteride (1.0 g,16 mmol), and 10 (1.6 g, 5.3 mmol) and the pH maintained at about 4 by addition of a few drops of acetic acid during 2.5 h of reflux. The reaction was quenched with excess aqueous HCl, concentrated to dryness and treated with excess aqueous KOH. The free base 2d was extracted with 30 ml portions (4x) of n-hexane and the combined extracts were dried (Na_2SO_4) and evaporated to give 600 mg (84%) of a light yellow oil. Because of trace impurities the crude product turned blue on exposure to air. An analytical sample was distilled and converted into its hydrochloride, m.p. 198-199°C. Found C 62.80%, H 8.16%, N 8.19%; calc. for $C_9{}^1H_{10}{}^2H_2$ClN (171.7) C 62.99, $^1H+^2H$ 8.20, N 8.16.-

2,2-($^2H_2$)-2-Phenylethylamine, 12.

A mixture of phenylacetonitrile (25.4 g,0.22 mol), CH_3O^2H(40 ml, 0.98 mol; 99.5% ^2H), and 40% $NaO^2H/^2H_2O$ (1 ml) was stirred at room temperature under an atmosphere of argon. After 18 h ^{1}H-NMR analysis indicated approximately 50% $^1H/^2H$ exchange. The solvent was distilled off

and replaced by ^2H_2O (5 ml), CH_3O^2H (30 ml) and 40% $NaO^2H/^2H_2O$. After 18 h the exchange was repeated a third time. The base was neutralized by dropwise addition of 20% $^2HCl/^2H_2O$ and the deuterated nitrile was isolated by extraction with diethyl ether. Evaporation gave 24.2 g (91%) of product which was used in the next step without further purification.

The nitrile was dissolved in 100 ml of dry diethyl ether and added slowly to a stirred suspension of lithium aluminium hydride (11 g, 0.29 mol) under an argon atmosphere. After 30 min the reaction was quenched by dropwise addition of water (10 ml), 8 ml of 20% aqueous NaOH, and 50 ml of water. The organic phase was separated and the aqueous phase and precipitate were extracted with diethyl ether (10x50 ml). The combined organic phases were evaporated and the residual amine was distilled under vacuum (b.p.89-91°C/17mm) to yield 12.0 g(45%) of pure 12.

The isotopic purity of 12 was determined from the mass spectra (EI/SIM) of the N-(dimethyl-tert.-butylsilyl) derivatives of the unlabelled amine (M=235) and 12 (M=237), using the abundant M^+-56 fragment: $^2H_0$ 1.3%,$^2H_1$ 18.0%, $^2H_2$ 80.7%.

An analytical sample was converted into its hydrochloride, m.p.219-221°C. Found C 60.09%, $^1H+^2H$ 8.99%, N 8.69%; Calc. for $C_8{}^1H_{10}{}^2H_2ClN$(159.6) C 60.19%, $^1H+^2H$ 8.83%,N 8.77%.

4,4 -($^2H_2$)-1,2,3,4-Tetrahydroisoquinoline, 2e.

For the preparation of 13 the method of Bailey et al. (17) was used. Briefly, amine 12 was converted into its formamide (93%) which subsequently was heated at 170-180°C in the presence of polyphosphoric acid to give essentially pure 13 with a yield of 85-95%. -^{13}C-NMR($CDCl_3$): 24.9(weak m,C-4),47.3(C-3),127.1,127.5,128.7,130.9,136.2(aryl-C),159.9(C-1). The air-sensitive base of 13 was converted into the hydrochloride 13 using an equivalent amount of aqueous hydrochloric acid at 0°C followed by evaporation.

14.1 g(83 mmol) of dried (P_2O_5) solid hydrochloride 13 was dissolved in 20 ml of dry methanol and treated with small portions (in total 1.7 g, 46 mmol) of sodium borohydride under argon at 0°C. After 3 h the mixture was diluted with water (100 ml), saturated with solid NaCl and then extracted with diethyl ether (7x30 ml). The combined ethereal extracts were dried (Mg_2SO_4) and evaporated to give 9.9 g (88%) of essentially pure 2e. An analytical sample was distilled under vacuum and converted into its hydrochloride, m.p.198 - 199°C(from EtOH). Found C 63.10%, $^1H+^2H$ 7.98%, N 8.21%; calc. for $C_9{}^1H_{10}{}^2H_2ClN$ (171.7) C 62.99%, $^1H+^2H$ 8.20%, N 8.16%.

Guanidination of 2-General procedure

1,2,3,4-Tetrahydroisoquinoline 2 (7 mmol) was added to a suspension of S-methylisothiouronium hemisulphate (974 mg, 3.5 mmol) in water (1.0 ml), and the resultant clear solution was stirred in a well ventilated hood at 40-50°C. After 18 h the mixture was heated to reflux and the precipitate was dissolved by addition of water. On cooling (0°C) for 8-12 h the crystalline sulphates were obtained in 70-80% yield. Analytical samples were recrystallised twice from boiling water (1 ml/0.34 g), m.p.270-272°C (dec.). The following salts 1 were prepared:

1,2,3,4-Tetrahydroisoquinoline-2-carboxamidinium sulphate, 1a (2).

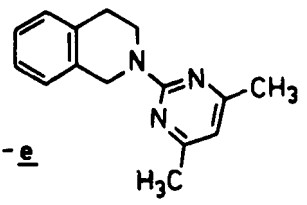
1,1,3,3,4,4-($^2H_6$)- 1,2,3,4-Tetrahydroisoquinoline-2-carboxamidiniumsulphate, 1b, found C 52.46%, $^1H+^2H$ 8.24%, N 18.38%; calc. for $C_{10}{}^1H_9{}^2H_5N_3 \times 0.5\ SO_4$ (229.3) C 52.38%, $^1H+^2H$ 8.35%, N 18.33%.-

1,1-($^2H_2$)- 1,2,3,4-Tetrahydroisoquinoline-2-carboxamidinium sulphate, 1c, found C 53.02%, $^1H+^2H$ 6.87%, N 18.85%, S 6.82%; calc. for $C_{10}{}^1H_{12}{}^2H_2N_3$ x 0.5 SO_4 (226.3) C 53.07%,$^1H+^2H$ 7.13%, N 18.57%, S 7.09%.-

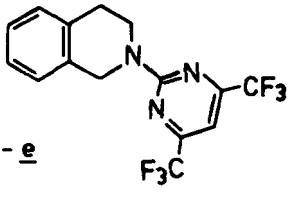
3,3-($^2H_2$)-1,2,3,4-Tetrahydroisoquinoline-2-carboxamidinium sulphate, 1d, found C 53.24%,$^1H+^2H$ 7.26%, N 18.76%, S 6.88%.-

4,4-($^2H_2$)-1,2,3,4-Tetrahydroisoquinoline-2-carboxamidinium sulphate, 1e, found C 53.04%, $^1H+^2H$ 7.09%, N 18.63%, S 6.93%.-

In order to determine the isotopic composition (see below) the pyrimidine derivatives 14 and 15 (index a-e;see Scheme 1,2) were prepared either in analytical (19) or preparative scale.



14a - e



15a - e

Synthesis of pyrimidine derivatives of 1 - General procedure

A mixture of 2.0 mmol of hemisulphate 1, sodium hydrogencarbonate (300 mg), water (3 ml), toluene (10 ml), and 1.5 ml of either 2,4-pentandione (acetylacetone, for the preparation of 14) or 1,1,1,5,5,5-hexafluoro-2,4-pentandione (hexafluoroacetylacetone, for the preparation of 15) was refluxed for 18 h. After cooling to room temperature, 20 ml of n-hexane was added and the organic phase was separated, dried (Na_2SO_4) and evaporated to give essentially pure product in 70-80% yield which was recrystallised from hot methanol by the addition of water; 14: m.p. 83°C,R_f 0.56(III), 15: m.p. 90°C, R_f 0.78(III).

2-(4',6'-Dimethyl-2'-pyrimidinyl)-1,2,3,4-tetrahydroisoquinoline, 14a,
found C 75.36%, H 7.15%, N 17.53%; calc. for $C_{15}H_{17}N_3$ (239.3) C 75.28%, H 7.16%,N 17.56%.-
1,1,3,3,4,4-($^2H_6$)-2-(4',6'-Dimethyl-2'-pyrimidinly)-1,2,3,4-tetrahydroisoquinoline, 14b, found C 73.71%, $^1H+^2H$ 9.02%, N 17.20%; calc. for $C_{15}{}^1H_{12}{}^2H_5N_3$ (244.3) C 73.73%, $^1H+^2H$ 9.07%,N 17.20%.-
4,4-($^2H_2$)-2-(4',6'-Dimethyl-2'-pyrimidinyl)-1,2,3,4-tetrahydroisoquinoline, 14e, found C 74.84%, $^1H+^2H$ 8.03%, N 17.52%; calc. for $C_{15}{}^1H_{15}{}^2H_2N_3$ (241.3) C 74.65%, $^1H+^2H$ 7.94%, N 17.41%.-
2-(4',6'-Bis(trifluoromethyl)-2'-pyrimidinyl)-1,2,3,4-tetrahydroisoquinoline, 15a, found C 51.94%, H 3.21%, N 12.19%; calc. for $C_{15}H_{11}F_6N_3$ (347.3) C 51.88%, H 3.19%, N 12.10%.-

The isotopic composition of 1 was determined by gas chromatography/mass spectrometry of the pyrimidine derivatives 14b-e (PI/CI-NH_3) and 15b-e (NI/CI-CH_4) by comparison with the mass spectra of the unlabelled pyrimidine derivatives 14a and 15a using selected ion monitoring (SIM) of the molecular cluster ions $[M+1]^+$ and $[M]^{-\cdot}$ respectively.

1b(prepared by use of 25 mol% Adam's catalyst), NI/CI ionisation: $^2H_1$ 0.5%,$^2H_2$ 2.6%, $^2H_3$ 11.3%, $^2H_4$ 21.8%, $^2H_5$ 29.3%, $^2H_6$ 25.2%,$^2H_7$ 7.5%, $^2H_8$ 1.6%, $^2H_9$ 0.2%; ^2H_o (referred to $^2H_5$) $\leq$0.2%.

1b (prepared by use of 2.8 mol% Adam's catalyst),NI/CI ionisation: $^2H_0$ 1.0%, $^2H_1$ 5.8%, $^2H_2$ 18.4%, $^2H_3$ 29.1%, $^2H_4$ 29.2%, $^2H_5$ 12.7%, $^2H_6$ 3.3%.-

1c, NI/CI ionisation: $^2H_1$ 1.3%, $^2H_2$ 97.8%, $^2H_3$ 0.9%; $^2H_0$(referred to $^2H_2$) $\leq$ 0.5%.-

1d, NI/CI ionisation: $^2H_0$ 1.4%, $^2H_1$ 9.3%,$2H_2$ 89.3%.-

1e, NI/CI ionisation: $^2H_0$ 7.4%, $^2H_1$ 16.4%, $^2H_2$ 76.2%.-
PI/CI ionisation: $^2H_0$ 7.5%, $^2H_1$ 16.5%, $^2H_2$ 76.0%.-

^{1}H-NMR data

1a (D_2O): 2.96(t,J=5.8 Hz,2H,H-4),3.59(t,J=5.8 Hz,2H,H-3),4.55(s,2H, H-1),7.3(broad s,4H,aryl-H).-

2a, base($CDCl_3$):1.66(s,1H,NH),2.78(t,J~6 Hz,2H,H-4),3.14(t,J~6 Hz,2H,H-3),4.01(s,2H,H-1),6.9-7.3(m,4H,aryl-H).-

2a, hydrochloride(D_2O): 3.15 (t,J= 6Hz, 2H, H-4), 3.55 (t,J= 6Hz, 2H, H-3), 4.41 (s, 2H, H-1), 7.2-7.5 (m, 4H, aryl-H).-

14a ($CDCl_3$):2.31(s,6H,CH_3),2.91(t,J~6 Hz,2H,H-4),4.09(t,J~6 Hz, 2H, H-3),4.94(s,2H,H-1),6.28(s,1H,H-5'),7.1-7.3(m,4H,H-5,6,7,8).-

15a ($CDCl_3$):2.97(t,J~6 Hz,2H,H-4),4.13(t,J~6 Hz,2H,H-3),4.97(s,2H, H-1),7.04(s,1H,H-5'),7.1-7.3(m,4H,H-5,6,7,8).-

^{13}C-NMR data

1a (D_2O):28.1(C-4),43.8(C-3),46.9(C-1);127.0,127.5,128.2,128.7,132.0,135.4,(aryl-C);156.7(C=N).-

2a, base($CDCl_3$)(23):29.2(C-4),43.9(C-3),48.4(C-1),125.8(C-6),126.1(C-7), 126.3(C-8),129.3(C-5),134.9(C-9),136.2(C-10).-

2a, hydrochloride(D_2O):24.9(C-4),42.2(C-3),44.9(C-1),127.4,127.7,128.2, 128.7, 129.2, 132.1.-

14a ($CDCl_3$):24.2(CH_3),29.1(C-4),41.4(C-3),46.3(C-1),108.9(C-5'),126.2,126.7, 128.8,135.0,135.7(aryl C-5,6,7,8,9,10),162.0(C-2'),167.2(C-4',6').-

The NMR spectra of the corresponding deuterated analogues (not shown) exhibited the expected loss of signal resonance intensities (^{1}H,^{13}C) or couplings (^{1}H) which, in turn, confirmed the signal assignments presented above.

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