SYNTHESIS OF SIX SPECIFICALLY DEUTERATED INDOLES OF BIOLOGICAL INTEREST

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SUMMARY

Procedures for the preparation of N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptamine, 5-methoxy-N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptamine, 5-hydroxy-N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptamine, ($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptophol, 5-methoxy-($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptophol and 5-hydroxy-($\alpha,\alpha,\beta,\beta$-$^2H_4$)tryptophol are described. Deuterium was introduced by treatment with lithium aluminium deuteride of the appropriate indole-3-(N-methylglyoxylamide) or ethyl indole-3-glyoxalate. The isotopic purity of the products was greater than 97.3%.

INTRODUCTION

Indoleamines have gained in interest during recent years with regard to their possible involvement in mental disorders[1]. According to the transmethylation hypothesis, tryptamines are N-methylated to form psychoactive N,N-dimethylated tryptamines. The N-monomethylated tryptamines are intermediates in this transformation. Tryptophols (indole-3-ethanols) are reductive metabolites of the tryptamines.

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Gas chromatography - mass spectrometry (GCMS) is a specific and sensitive analytical technique which can be used for analysis of biogenic amines and their metabolites[2]. The use of GCMS offers the possibility of using stable isotope labelled analogues as internal standards.

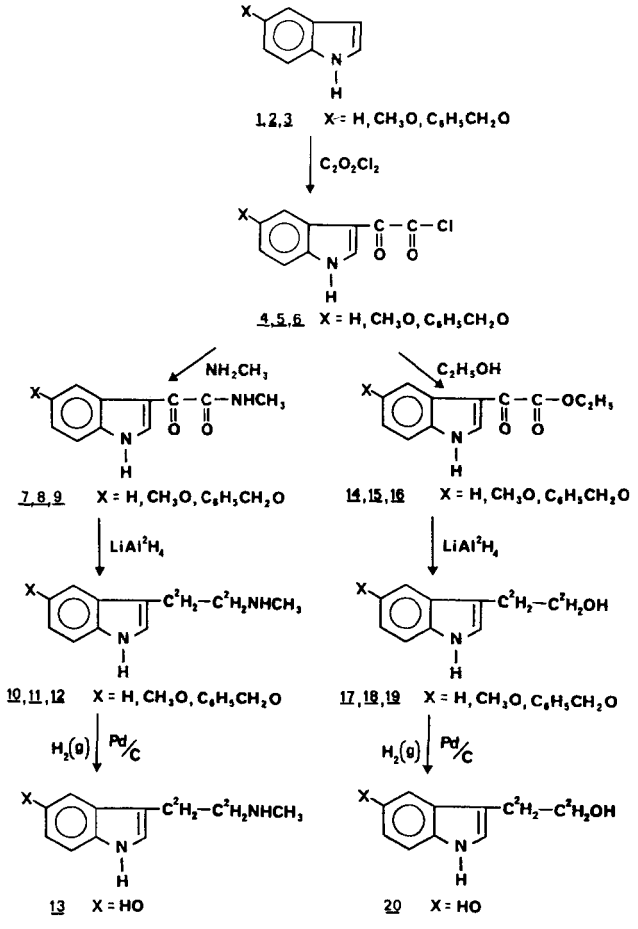


Figure 1. Scheme of the syntheses.

In this paper, procedures for the preparation of six deuterium labelled N-methyl-tryptamines and tryptophols are described.

DISCUSSION

The syntheses are shown schematically in fig. 1. The syntheses of the various indole-3-glyoxyloyl chlorides (4,5,6) were carried out according to Nogrady[3], by acylation of the appropriate indole (1, 2, 3) with oxalyl chloride in yields exceeding 87%.

The indole-3-(N-methylglyoxylamides) (7,8,9) were prepared in yields exceeding 89%, according to the procedure of Shaw, Wright and Milne[4] for the synthesis of 5-benzyloxy-indole-3-(glyoxylamide). Reduction of the indole-3-(N-methylglyoxylamides) with lithium aluminium deuteride gave the tetradeuterated N-methyltryptamines (10,11,12). Use of tetrahydrofuran as a solvent and a reaction time of 2 to 23 h. after final addition of substrate was sufficient to give yields from 31 to 41% for this step.

The various tryptophols were prepared according to the procedure of Nogrady and Doyle[5] for the synthesis of tryptophol. The ethyl indole-3-glyoxalates (14,15,16) were prepared from the corresponding glyoxyloyl chlorides (4,5,6) by treatment with ethanol, in the presence of triethylamine. The crude esters, obtained in 95% yields, were reacted with lithium aluminium deuteride in tetrahydrofuran to give the tetradeuterated tryptophols (17,18,19) in yields exceeding 81%.

Hydrogenolysis of 12 and 19 gave the corresponding 5-hydroxyindoles (13,20).

The mass spectra of the final products showed the isotopic purity to be greater than 97.3% and the ratio $^{2}H_{0}/^{2}H_{4}$ to be less than 0.2%. This purity is sufficient for use as internal standards in quantitative GCMS.

EXPERIMENTAL

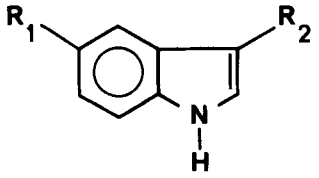
The melting points were determined on an electrothermal melting point apparatus and are uncorrected. Electron impact (70eV) mass spectra were recorded on an LKB 2091 gas chromatograph mass spectrometer. Precise isotope enrichments were calculated from the mass spectra by the method of Biemann[6].

Indole-3-glyoxyloyl chloride (4) - Oxalyl chloride (5,0 g, 39,6 mmol) was added dropwise to a stirred solution of indole (1, 4,0 g, 34,2 mmol) in dry diethyl ether (100 ml) at 5°C. The resulting mixture was stirred for an additional 15 minutes at room temperature. The solid product was collected by filtration (table 1).

5-Methoxyindole-3-glyoxyloyl chloride (5) and 5-benzyloxyindole-3-glyoxyloyl chloride (6) - These compounds were prepared as 4 from 5-methoxyindole (2) and 5-benzyloxyindole (3) (table 1).

Indole-3-(N-methylglyoxylamide) (7) - Dry methylamine gas was passed through a suspension of 4 (7,0 g, 33,8 mmol) in dry benzene (50 ml) until the colour changed from orange to light yellow. The solid product was collected by filtration (table 1).

Table 1.



Compound No.	R_1	R_2	Yield(%)	m.p.°C	m.p.°C lit.	ref.
4	H	COCOCl	87	137-9	136-8	3
5	CH_3O	COCOCl	95	129-30	127-8	7
6	$ArCH_2O$	COCOCl	89	148-50	143-7	4
7	H	$COCONHCH_3$	95	227-30	223-4	8
8	CH_3O	$COCONHCH_3$	89	208-10	203-4	9
9	$ArCH_2O$	$COCONHCH_3$	90	235-6	247-9	10
10	H	$C^2H_2C^2H_2NHCH_3$	31	178-9(a)	175-7(a)	8
11	CH_3O	$C^2H_2C^2H_2NHCH_3$	31	102-4(b)	102-2.5	9
12	$ArCH_2O$	$C^2H_2C^2H_2NHCH_3$	43	205-7(a)		
13	OH	$C^2H_2C^2H_2NHCH_3$	43	172-4(c)		
14	H	$COCOOC_2H_5$	95	187-90	184-6	5
15	CH_3O	$COCOOC_2H_5$	96	218-9	214-5	9
16	$ArCH_2O$	$COCOOC_2H_5$	97	215-7		
17	H	$C^2H_2C^2H_2OH$	81	54-5	54-5	5
18	CH_3O	$C^2H_2C^2H_2OH$	93	41-2		
19	$ArCH_2O$	$C^2H_2C^2H_2OH$	94	97-8	93-5	11
20	OH	$C^2H_2C^2H_2OH$	79	108-9	105-7	11

(a) as hydrochloride
(b) recrystallized from n-hexane
(c) as picrate

5-Methoxyindole-3-(N-methylglyoxylamide) (8) and 5-benzyloxy--indole-3-(N-methylglyoxylamide) (9) - These compounds were prepared as 7 from 5 and 6 (table 1).

N-Methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptamine hydrochloride (10) - The glyoxylamide (7) (2,40 g, 11,9 mmol) was added to a stirred suspension of $LiAl^2H_4$ (5,0 g, 119 mmol) in dry tetrahydrofuran (400 ml). The mixture was refluxed for 2 hours before adding excess wet tetrahydrofuran. The resulting mixture was further refluxed for 15 minutes before filtration. The filtrate was concentrated in vacuo and the resulting oil was taken up in chloroform, washed successively with NaOH solutions and water, and dried (Na_2SO_4). The solvent was evaporated, final traces of water were removed from the light brown oil by azeotropic distillation with benzene and the oil was then taken up in chloroform. Ethanol saturated with hydrogen chloride gas was added to neutrality. The solvent was evaporated giving an oily residue which was taken up in tetrahydrofuran, whereby white crystals were formed. The solid product was collected by filtration (table 1). Mole percent deuterated species: ($^2H_4$) = 96.4%, ($^2H_3$) = 2.8%, ($^2H_2$) = 0.8%. Mass spectrum: 178 (M^+)(3), 134(9), 133(70), 132(40), 131(9), 105(4), 78(5), 47(5), 46(100) and 45(5).

5-Methoxy-N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptamine (11) - This compound was prepared as 10 from 8 (0.89 g, 3.84 mmol) using 0.89 g. (21.2 mmol) $LiAl^2H_4$. The refluxing time was 23 h. and the crude product was isolated by vacuum distillation (table 1). Mole percent deuterated species: ($^2H_4$) = 92.8%, ($^2H_3$) = 6.2%, ($^2H_1$) = 1.0%. Mass

spectrum: 208 (M^+)(5), 164(10), 163(74), 162(36), 148(11), 147(10), 91(3), 47(4), 46(100) and 45(4).

5-Benzyloxy-N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptamine hydrochloride (12) - This compound was prepared as 10 from 9 (1.0 g, 3.24 mmol) using 1.36 g (32.4 mmol) $LiAl^2H_4$. The refluxing time was 20 h. (table 1).

5-Hydroxy-N-methyl-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptamine (13) picrate - A solution of 12 in ethanol (100 ml) was hydrogenated at atmospheric pressure overnight with Pd/C (10%, 0.20 g) as a catalyst. The catalyst was filtered off, the solvent evaporated and the oily residue was dissolved in a small amount of water. A solution of water saturated with picric acid was added and the mixture was kept refrigerated (4°C) for several days. The red-brown crystals were collected by filtration (table 1). Mole percent deuterated species: ($^2H_4$) = 95.7%, ($^2H_3$) = 1.0%, ($^2H_2$) = 0.7%, ($^2H_1$) = 2.6%. Mass spectrum: 194 (M^+)(4), 150(12), 149(70), 148(41), 147(10), 93(5), 91(5), 47(6), 46(100) and 45(5).

Ethyl indole-3-glyoxalate (14) - A mixture of 4 (10,35 g, 50,0 mmol) in ethanol (60 ml) and triethylamine (7 ml) was refluxed for 30 minutes. After cooling, the crystals were filtered off and washed with ethanol. The filtrate was concentrated *in vacuo* and the residue was triturated with water giving additional crystalline product which was collected by filtration (table 1).

Ethyl 5-methoxy-indole-3-glyoxalate (15) and ethyl 5-benzyloxy-indole-3-glyoxalate (16) - These compounds were prepared as 14 from 5 and 6 (table 1).

($\alpha,\alpha,\beta,\beta$-$^2H_4$) Tryptophol (17) - The ethyl glyoxalate 14 (0,74 g, 3,40 mmol) was added to a suspension of $LiAl^2H_4$ (0.50 g, 11.90 mmol) in dry tetrahydrofuran (50 ml). After refluxing for 2 h. an excess of wet tetrahydrofuran was added. The solid material was filtered off and washed with tetrahydrofuran. The filtrate was dried over sodium sulphate and the solvent was evaporated to give a white crystalline residue (table 1). Mole percent deuterated species: ($^2H_4$) = 94.0%, ($^2H_3$) 5.4%, ($^2H_2$) 0.4%, ($^2H_1$) = 0.2%. Mass spectrum: 165 (M^+)(23), 133(10), 132(100), 131(6), 105(6), 104 (5), 79(4), 78(6), 77(4) and 52(3).

5-Methoxy-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptophol (18) and 5-benzyloxy ($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptophol (19) - These compounds were prepared as 17 from 15 and 16 (table 1). Mole percent deuterated species of 18: ($^2H_4$) = 93.7%, ($^2H_3$) = 5.6%, ($^2H_2$) = 0.1%, ($^2H_1$) = 0.6%. Mass spectrum: 195 (M^+)(26), 163(12), 162(100), 161(5), 147(15), 146(2), 109(8), 108(2), 92(2) and 91(2).

5-Hydroxy-($\alpha,\alpha,\beta,\beta$-$^2H_4$) tryptophol (20) - A solution of 19 (0,40 g, 1,48 mmol) in ethyl acetate (10 ml) was hydrogenated at atmospheric pressure overnight with Pd/C (10%, 0,20 g) as a catalyst. After filtering off the catalyst the solvent was evaporated to give a crystalline residue (table 1). Mole percent deuterated species: ($^2H_4$) = 91.6%, ($^2H_3$) = 6.9%, ($^2H_2$) = 0.8%, ($^2H_1$) = 0.6%, ($^2H_0$) = 0.1%. Mass spectrum: 181 (M^+)(24), 149(11), 148(100), 147(7), 120(3), 119(5), 93(4), 92(3), 91(2) and 66(2).

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