SYNTHESIS OF PYRILAMINE-d_6

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SUMMARY

Pyrilamine-d_6 (N-[(4-methoxyphenyl)methyl]-N',N'-di[$^2H_3$]methyl-N-2-pyridinyl-1,2-ethanediamine) was synthesised from N-2-[(4-methoxyphenyl)methyl]-aminopyridine and 2-(N,N-di[$^2H_3$]methylamino)ethyl chloride in 83% yield. The alkyl chloride was prepared in 37% overall yield in a three step reaction from toluene-4-sulphondi[$^2H_3$]methylamide.

Key words: Deuterated, Pyrilamine, Synthesis.

A number of drugs, containing the dimethylamino group, have been shown to produce the carcinogen dimethylnitrosamine (DMN) upon treatment with nitrosating agents (1). DMN is known to be metabolised in vivo to an active alkylating agent resulting in the methylation of macromolecules, particularly DNA (2). Some years ago Lijinsky and co-workers (3) showed that fully deuterated DMN (d_6-DMN) also gave rise to methylation of DNA where the trideuteromethyl group was transferred intact allowing this metabolic process to be distinguished from either the production of diazomethane (where one deuterium atom would be lost) or one-carbon metabolic incorporation (where the deuterium atoms would by lost by exchange).

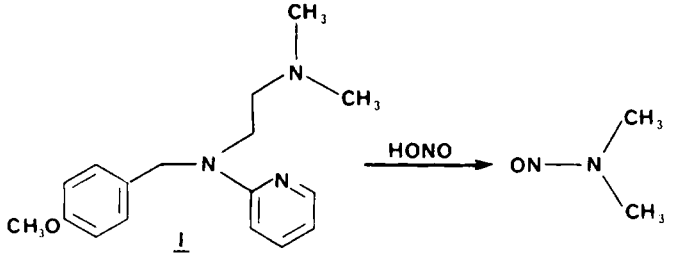
As part of our work on the development of methods to monitor exposure to alkylating agents we require alkylating agents

0362-4803/85/020109–07$01.00

Received July 18, 1984

or precursors which contain the trideutero methyl group so that the de novo methylation of macromolecules can be measured in the presence of comparatively high background levels of naturally occurring methylated residues (4).

Pyrilamine (1, N-[(4-methoxyphenyl)methyl]-N',N',-dimethyl-N-2-pyridinyl-1,2-ethanediamine, CAS Reg No. 91-84-9) is an anti-histamine drug which contains a dimethylamino moiety (Scheme 1) and is structurally similar to methapyrilene, a drug which is known to give rise to dimethylnitrosamine on treatment with acidified nitrite (5).



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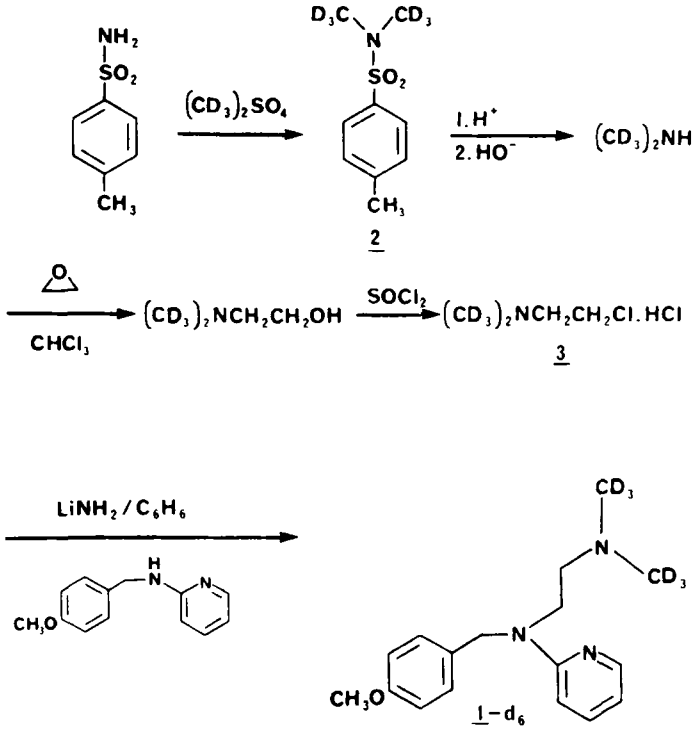
Scheme 1. Postulated production of dimethylnitrosamine from pyrilamine.

Pyrilamine which has a fully deuterated (d_6) dimethylamino moiety is neither commercially available nor has its synthesis been reported in the literature.

1 is prepared from commercially available 2-(4-methoxybenzylamino)pyridine and 2-(N,N-dimethylamino)ethylchloride under basic conditions (6). Our synthesis of 1-d_6 therefore required the preparation of 2-(N,N-di[$^2H_3$]methylamino)ethyl chloride (3).

The synthesis of 1-d_6 is summarised in Scheme 2.



Scheme 2. Synthesis of pyrilamine d_6.

Di[$^2H_3$]methylamine was prepared by a method similar to that reported for the unlabelled compound (7) and condensed with ethylene oxide in chloroform. After removal of the excess reagents the resulting crude 2-(N,N-di[$^2H_3$]methylamino)ethanol was converted to 3 in excess refluxing thionyl chloride (8) in 37% overall yield from the sulphonamide (2). The nmr (D_2O) spectrum of 3 was identical in every respect with that of non deuterated material except that the signal at δ 2.95 ppm due to the dimethyl amino group was absent.

Condensation of 3 with 2-(4-methoxybenzylamino)pyridine

followed by work up and chromatography on octadecylsilane modified silica gel (9) afforded 1-d_6 in 83% yield as the free base. The nmr spectrum ($CDCl_3$) of 1-d_6 was identical to 1 prepared from the commercially available maleate salt (97%, obtained from Sigma Chemical Company) except that the signal at δ 2.25 ppm was absent. The electron impact mass spectrum of 1-d_6 showed a weak molecular ion (m/z 291) confirming the presence of 6 deuterium atoms in the molecule. The chemical ionisation mass spectrum showed an intense protonated molecular ion (MH^+ m/z 292). 1-d_6 was converted to the crystalline maleate salt for use in our experiments which will be described elsewhere.

EXPERIMENTAL

Di[$^2H_3$]methyl sulphate (99+%) was obtained from Aldrich Chemical Co Ltd and used as supplied. Thin layer chromatography (TLC) was carried out on aluminium backed silica gel plates (Merck Silica Gel 60F_{254} No. 5554) or silanised silica gel glass plates (Merck Silanised Silica 60F_{254} No. 5747). Compounds were purified by column chromatography using silica gel (Merck Silica gel G, No. 7734) or silanised silica gel (9). Nmr spectra were recorded at 60 MHz on a Perkin Elmer R12B instrument. Mass spectra (70 eV) were recorded on a VG7070 double focussing mass spectrometer.

Toluene-4-sulphondi[$^2H_3$]methylamide (2)

Di[$^2H_3$]methyl sulphate (2.5 mL, 30 mmoles) was added to a solution of toluene-4-sulphonamide (2 g, 12 mmoles) in 2.5 M NaOH (12 mL) and water (10 mL) which was then stirred vigorously at room temperature (1 h). Crystalline 2 was filtered off and washed with 5% NaOH (50 mL) then with water until the washings were neutral. Occasionally 2 separated as an oil which crystallised on cooling in ice. The colourless crystalline product was dried *in vacuo* over P_2O_5/KOH. TLC (toluene/acetone, 3:1 v/v) indicated the presence of a minor product which was

removed by column chromatography on silica gel. Yield 1.9 g (80%) mp 78-79.5°C nmr ($CDCl_3$) δ 2.42 (3H,s,CH_3) 2.2-2.8 (4H, m, arom) m/z 205 (M^+).

Di[$^2H_3$]methylamine

2 (1.7 g, 8.3 mmoles) in 70% H_2SO_4 (7 mL) was boiled under reflux (30 min). After cooling on ice 40% NaOH (20 mL) was cautiously added and di[$^2H_3$]methylamine released by flushing the warmed solution with a slow stream of nitrogen. The amine was dried by passage through a column of crushed KOH pellets and condensed (ethanol/dry ice bath) into a weighed screw-top test tube. Yield, 365 mg (75%). This material was used without further purification in the next step.

2-(N,N-Di[$^2H_3$]methylamino)ethylchloride hydrochloride (3)

Dry chloroform (7 mL), cooled on ice, was added to the product from the previous step and the resulting solution was treated with ethylene oxide (0.36 mL, 7.3 mmoles). The capped tube was heated to 80°C (5 hrs). After cooling insoluble material was removed by filtration and the filtrate concentrated on a rotary evaporator. The residue was dissolved in dry chloroform (85 mL), thionyl chloride (0.8 mL) added and the solution heated under reflux (2 hrs). After cooling, ethanol (5 mL) was added and the solution heated under reflux (2 hrs). Removal of solvent and reagents on a rotary evaporator gave a crystalline residue which was washed with ether and dried *in vacuo* over P_2O_5/KOH to give 460 mg (42%) of 3 mp 184-204°C (decomp) nmr (D_2O)δ3.75 (m,-CH_2CH_2-).

Pyrilamine-d_6 (1-d_6)

A mixture of 3 (250 mg, 1.7 mmoles), 2-(4-methoxybenzyl amino)pyridine (355 mg, 1.7 mmoles, Aldrich Chemical Co Ltd) and lithium amide (81 mg, 3.5 mmoles, Aldrich Chemical Co Ltd) in benzene (7.5 mL) was heated under reflux for 24 hours at which time the reaction was complete as judged by TLC (reversed phase, methanol/water, 5:1 v/v). After cooling, the reaction mixture was

filtered, concentrated in vacuo, dissolved in the minimum volume of methanol and applied to a column of silanised silica gel (9). The eluting solvent was gradually changed from methanol/water (1:1 v/v) to methanol/water (5:1 v/v). Fractions containing a single product were combined and concentrated in vacuo (<40°C) to give a pale yellow oil (400 mg, 83%) nmr ($CDCl_3$)δ 2.5 (2H, tr,-$C\underline{H}_2$-) 3.65 (2H, tr,-$C\underline{H}_2$-) 3.75 (3H,s, -$OC\underline{H}_3$) 4.71 (2H,s,Ø-$C\underline{H}_2$-) 6.3-7.6 (7H,m,arom) 8.15 (1H,arom) m/z (EI) 291 (M^+, 0.8%), 214 (M^+-CH_2=CH-$N(CD_3)_2$, 12%), 121 ($CH_3OC_6H_4CH_2^+$, 100%), 78 ($[CH_2CH_2N(CD_3)_2]^+$, 18.7%), 64 ($[CH_2N(CD_3)_2]^+$, 66.6%) (CI, isobutane) 292 (MH^+).

The free base was quantitatively converted to the maleate salt in the following manner. 1-d_6 (200 mg, 0.7 mmoles) in acetone (5 mL) was treated with maleic acid (81 mg, 0.7 mmoles) and evaporated to give a residue which spontaneously crystallised. The crystals were washed with ether (2 x 20 mL) to remove excess maleic acid and dried in vacuo over P_2O_5/KOH to give the maleate salt of 1-d_6 mp 98-99°C.

ACKNOWLEDGEMENT

We thank Dr Peter Farmer for helpful discussions and suggestions. John Lamb is thanked for obtaining the mass spectra.

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