NOTE

SYNTHESES OF |6-^{2}H|-INDOLE, |6-^{2}H|-GRAMINE AND |6-^{3}H|-GRAMINE

A. A. Ghini, G. Burton and E. G. Gros

Departamento de Química Orgánica y UMYMFOR, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

SUMMARY

The title compounds were obtained from the corresponding 6-bromo derivatives by conversion to the 1,6-dilithio-compounds followed by treatment with deuteriated or tritiated water and exchange of the 1-deuterium or tritium with water.

Key Words: |6-^{2}H|-Indole, |6-^{2}H|-Gramine, |6-^{3}H|-Gramine, Synthesis

As part of our studies on the biodegradation of gramine in *Hordeum vulgare* plants (1) we required this alkaloid labelled with tritium at position 6. Lautié has reported the preparation of several specifically deuterated indoles (2) but not at the 6-position. We now describe an efficient method for the preparation of gramine and indole specifically deuterated or tritiated at C-6. The labelled indole can be easily converted into other simple indole derivatives involved in the catabolism of gramine (3).

6-Bromoindole (1a) was obtained from p-toluidine (4) and was converted to 6-bromogramine (1b) by treatment with formaldehyde-dimethylamine. Sequential treatment of either 1a or 1b with one equivalent of n-butyllithium and two equivalents of t-butyllithium in diethyl ether-THF (3:1) afforded the corresponding 1,6-dilithio-derivative (2a, 2b). Quenching of the reaction with deuterium oxide (2 equivalents) followed by dilution with water and extractive work-up rendered the 6-deuterio-compounds (3a, 3b; X=^{2}H), the deuterium at position 1 being exchanged during the water treatment. When tritiated water was used on 2b, |6-^{3}H|-gramine (3b, X=^{3}H) was obtained. The specificity of the deuterium labelling was ascertained by ^{1}H- and ^{2}H-NMR spectroscopy and the degree of labelling was shown to be *ca.* 100% monodeuteration based on analysis of the mass spectra. This highly efficient preparation should be specially adequate for the synthesis of tritium labelled indoles with high specific activity.

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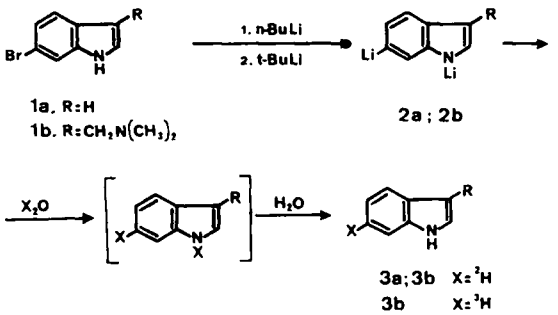
EXPERIMENTAL

Melting points are uncorrected. ^{1}H- and ^{2}H-NMR spectra were measured at 100.1 and 15.36 MHz respectively in a modified Varian XL-100-15 FT-NMR spectrometer. Mass spectra were determined at 70 eV (direct inlet) with a Varian-MAT CH7-A mass spectrometer. Deuterium oxide was purchase from Merck,Sharp and Dohme and tritiated water was provided by the Comisión Nacional de Energía Atómica of



Argentina.

6-Bromogramine (1b). 6-Bromoindole (1a, 50 mg) was dissolved in glacial acetic acid (0.1 ml) and treated with 36% formaldehyde (0.02 ml) and dimethylamine 28% (0.04 ml). The reaction mixture was heated at 105°C for 10 min, left 1 hr at room temp and poured into water. The suspension was made basic with 2N NaOH solution and extracted with CH_2Cl_2-MeOH (4:1). Evaporation of the solvent rendered 1b (61 mg) of m.p. 130-131°C. ^{1}H-NMR ($CDCl_3$-TMS): δ 2.30 (6H, s, N-Me_2), 3.63 (2H, s, CH_2-N), 7.04 (1H, b.s., H-2), 7.21 (1H, dd, J=8 and 2 Hz, H-5), 7.45 (1H, d, J=2 Hz, H-7), 7.55 (1H, d, J=8 Hz, H-4), 8.82 (1H, b.s., N-H). MS (m/z, %): 252-254 (M^+, 65), 208-210 (M - N-Me_2, 100), 129 (208 - Br, 66).

|6-^{2}H|-Indole (3a). 6-Bromoindole (1a, 24.3 mg) was dissolved in Et_2O (3 ml) and THF (1 ml) in a nitrogen atmosphere and cooled to -78°C. *n*-Butyllithium 1.55 M in hexane (0.09 ml) was added and the reaction mixture was warmed to 0°C and kept at that temperature for 30 min with stirring. The stirred solution was again cooled to -78°C and *t*-butyllithium 2.6 M in pentane (0.11 ml) was rapidly added and the yellow-green solution was warmed to -30°C and stirred at that temperature for 1 hr. ^2H_2O (0.006 ml) was added and the resulting colourless solution was poured into water and extracted with CH_2Cl_2. Evaporation of the solvent followed by separation of unreacted 6-bromoindole by RP-HPLC on an Altex Ultrasphere ODS 5 μm column (250 x 10 mm) using MeOH-water 9:1 as eluent, afforded |6-^{2}H|-indole (12 mg). ^{1}H-NMR ($CDCl_3$-TMS): δ 6.55 (1H, b.s., H-3), 7.16 (2H, m, H-2 and H-5), 7.38 (1H, s, H-7), 7.65 (1H, d, J=8 Hz, H-4), 8.08 (1H, b.s., N-H). MS (m/z, %): 118 (M^+, 100), 91 (M - HCN, 27), 90 (M - HCNH, 18).

|6-^{2}H|-Gramine (3b). 6-Bromogramine (1b, 48 mg) was suspended in Et_2O (3 ml)

and THF (1 ml) in a nitrogen atmosphere and cooled to -78°C. *n*-Butyllithium 1.55 M in hexane (0.15 ml) was added and the reaction mixture was warmed to 0°C. The resulting purple red solution was again cooled to -78°C and treated with *t*-butyl lithium 2.6 M in pentane (0.18 ml); after stirring for 1 hr at -30°C, ^2H_2O (0.01 ml) was added followed by extractive work-up as above, yielding 6-^{2}H-gramine (30 mg). ^{1}H-NMR ($CDCl_3$-TMS): δ 2.30 (6H, s, NMe_2), 3.65 (2H, s, CH_2-N), 7.04 (1H, b.s., H-2), 7.11 (1H, d, J=8 Hz, H-5), 7.30 (1H, s, H-7), 7.69 (1H, d, J=8 Hz, H-4), 8.80 (1H, b.s., NH). ^{2}H-NMR (CH_2Cl_2): 7.15 ppm (6-^{2}H). MS (m/z, %): 175 (M^+, 28), 131 (M - NMe_2, 100).

|6-^{3}H|-Gramine (3b, X=^{3}H). 6-Bromogramine (1b, 48 mg) was made to react as above, and the reaction was quenched by addition of ^3H_2O (30 mCi/ml, 0.008 ml) affording 6-^{3}H-gramine (29 mg, 0.42 mCi/mmol) with spectroscopic properties identical to those from an authentic sample.

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