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SYNTHESIS OF SIX SPECIFICALLY DEUTERATED ANALOGS OF 1,2-DIBROMO-3-CHLOROPROPANE

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SUMMARY

The convenient preparation of six selectively deuterated analogs of 1,2-dibromo-3-chloropropane have been described. The compounds were prepared by direct chlorination of the correspondingly deuterated 2,3-dibromopropanol derivatives using N-chlorosuccinimide and triphenylphospine. Spectral analysis revealed that the isotope incorporation was high and specific in all cases.

Key Words: Deuterated 2,3-Dibromopropanol, Deuterated 1,2-Dibromo-3-chloropropane, N-chlorosuccinimide chlorination.

INTRODUCTION

Because of its ease of preparation, low cost, and broad range of effectiveness, 1,2-dibromo-3-chloropropane (DBCP) was a widely used nematocide from 1956-1977 (1,2). The commercial production of DBCP was suspended in 1977 following a report that it was carcinogenic (3). Subsequent toxicity studies revealed that DBCP was also a mutagenic agent, an acute nephrotoxicant, and an acute gonadal toxicant (4,5). The reports indicate that DBCP

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is not directly harmful, but that metabolic activation is required to produce the observed toxicities (6,7). However, the exact chemical mechanisms of DBCP metabolism to toxic agents are not known.

The use of specifically deuterated analogs of parent compounds has become an important tool in toxicity studies involving xenobiotic metabolism. When a metabolic event is involved, the deuterated analog may be less toxic than the parent toxicant if all or even part of an isotope effect is expressed in the bioactivation process. It was felt that specifically deuterated analogs would be a valuable contribution to the ongoing toxicity studies with DBCP. In this paper, convenient preparations for six selectively deuterated DBCP analogs are described.

RESULTS AND DISCUSSION

The syntheses of specifically deuterated analogs of DBCP were greatly simplified by avoiding the preparation of the highly volatile allyl chloride. Instead, a series of deuterated 2,3-dibromopropanol (DBP) analogs (Figure 1, A-F) were prepared and then chlorinated to yield the specifically deuterated DBCP analogs (Figure 2, A-F). The incorporation of DBP as an intermediate in the synthetic scheme of DBCP offered several important advantages over the commercial preparation via allyl chloride (8). The first advantage was that DBP is a stable compound which does not undergo 1,3-transposition like allyl chloride. Thus, it was possible to prepare DBCP analogs with deuterium in specific positions. The second advantage of DBP was its high boiling point. This enables one to easily separate DBP from low boiling solvents. This property of DBP became very important in the preparation of the tetra-and pentadeuterated DBCP analogs (2E and 2F). The final advantage in using DBP as an intermediate was the fact that three

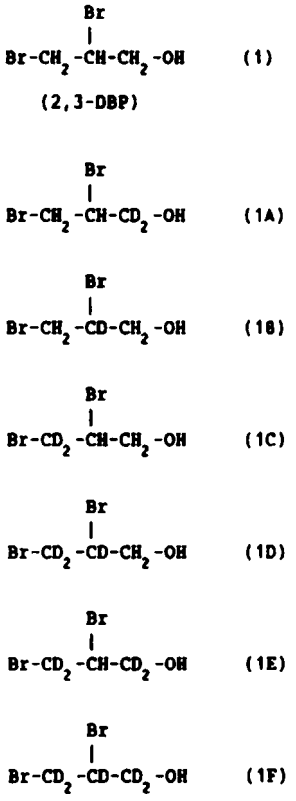

Figure 1. Structures of the deuterated analogs of dibromopropanol (DRP).

deuterated analogs of this compound had been previously prepared for our toxicity studies with the flame retardant tris(2,3-dibromopropyl)phosphate (Tris-BP) (9).

The first steps towards synthesis of the specifically deuterated DBCP analogs involved preparation of the correspondingly deuterated DBP analogs. The [1,1 - $^2H_2$], [2 - ^2H] and [3,3 - $^2H_2$] analogs of DBP (1A - 1C, respectively in Figure 1) were prepared using previously published methods (9). In all three synthetic schemes, the appropriate allyl alcohol analog was prepared and brominated using bromine in carbon tetrachloride. The [2,3,3 - $^2H_3$] analog of DBP (1D) was synthesized using procedures similar to those developed in the preparation of the [2-$^2H_1$] and [3,3- $^2H_2$] DBP analogs (10). In this procedure, [3 - $^2H_1$] - propargyl

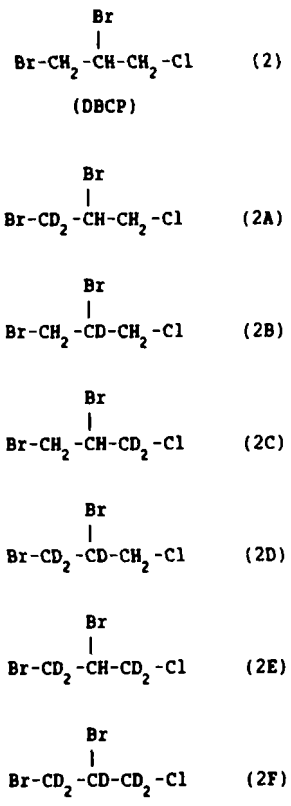

Figure 2. Structures of the deuterated analogues of 1,2-dibromo-3-chloropropane (DBCP).

alcohol was reduced with lithium aluminum deuteride followed by hydrolysis of the lithio salt with deuterium oxide to afford [2,3,3 - $^{2}H_{3}$]-allyl alcohol. The DBP was obtained by bromination as previously described above. The synthesis of [1,1,2,2 - $^{2}H_{4}$] and [1,1,2,3,3 - $^{1}H_{5}$] analogs of DBP (1E and 1F, respectively), required the preparation of [3,3 - $^{2}H_{2}$]-2,3-dibromopropionic acid and [2,3,3 - $^{2}H_{3}$]-2,3-dibromo-propionicacid. The acids were obtained by oxidation of the corresponding DBP analogs using Jones Reagent (11). The 2,3,-dibromopropionic acids were then converted to the acid chlorides with thionyl chloride. The acid chlorides were reduced with sodium borodeuteride to yield the [1,1,2,2, - $^{2}H_{4}$] and [1,1,2,3,3 - $^{2}H_{5}$] DBP analogs (see Figure 3).

The preparation of the specifically deuterated DBCP analogs

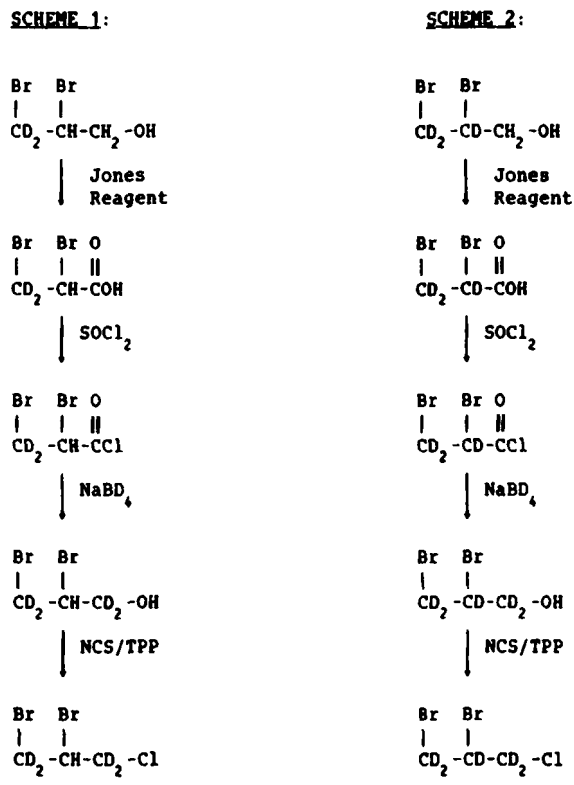

Figure 3. Schemes for the synthesis of the tetradeutered and pentadeuterated analogs of DBCP.

was accomplished by direct chlorination of the correspondingly deuterated DBP analogs. The chlorination procedure employed N-chlorosuccinimide (NCS) and triphenylphosphine (TPP) in tetrahydrofuran (THF) (12). This procedure required extremely mild reaction conditions and eliminates any possibility of halogen scrambling. The DBCP analogs that were produced were minimally 98% chemically pure as judged by GC analysis and all of the analogs had low residual protium content. Both of these factors are important for accurate interpretation of toxicity studies. The overall yield for the synthesis of the [1,1, - $^{2}H_{2}$], [2 - $^{2}H_{1}$], [3,3 - $^{2}H_{2}$], and [1,1,2 - $^{1}H_{3}$] DBCP analogs (2A - 2D, respectively, Figure 2) from propargyl alcohol was approximately 30%. The yields for the syntheses of the [1,1,2,2 - $^{2}H_{4}$] and

[1,1,2,3,3 - $^{2}H_{5}$] DBCP analogs (2E and 2F, respectively) from deuterated dibromopropanols was approximately 25%.

The physical characteristics and NMR spectra of the deuterated DBCP analogs were indistinguishable from those of the nondeuterated standards except for the spectral features attributable to isotopes enrichment.

EXPERIMENTAL

Instrumentation. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM360A spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as the internal standard. Boiling points are uncorrected. Mass spectra were recorded in the electron impact mode (EIMS) on a VG 7070H double-focusing instrument using an accelerating voltage of 4kV and an electron energy of 70eV at a nominal mass resolution of $M/\Delta M$ = 1000 (10% valley). Gas chromatography (GC) was performed on a Hewlett Packard Model 5840 gas chromatograph.

Conditions for GC Analysis. The purity of DBCP and its deuterated analogs was analyzed using a 30m by 0.32mm id fused silica column coated with Carbowax (CBWAX) as a stationary phase (J and W Scientific). Analyses were performed using the following GC conditions: carrier gas, helium (head pressure, 15 psi); injector temperature 250°C; temperature program, spitless injection at oven temperature of 60°C then raised after five min by 10°/min to 200°C. The retention time of DBCP and its analogs was approximately 8.95 min or 16.6 methylene units (MU) when measured relative to a homologous series of N-alkanes.

The lithium aluminum hydride reduction reactions were monitored using a 6 foot glass column packed with GP 60/80 Carbopack B/5% Carbowax 20m (Supelco). Analyses were performed using the following GC conditions: carrier gas, helium (column flow 20ml/min); injector temperature 150°C; temperature program,

on column injection at oven temperature of 80°C then raised after 6 min by 5°/min to 100°C. The retention times were: N-propanol, 5.4 min; allyl alcohol, 6.3 min; propargyl alcohol, 10.7 min.

Chemicals. Lithium aluminum hydride, N-chlorosuccinimide, triphenylphosphine, propargyl alcohol, bromine, thionyl chloride, tetramethylsilane, sodium borodeuteride (98 atom % D), lithium aluminum deuteride (98 atom % D), deuterated chloroform (99.8 atom % D) and acryloyl chloride were obtained from Aldrich Chemical Co., Milwaukee, WI. Deuterium oxide was obtained from Stohler Stable Isotopes, Cambridge, MA. Sodium bisulfite, chromium trioxide, potassium mercuric iodide and barium oxide were purchased from J. T. Baker Chemical Co., Phillipsburg, N.J. All other solvents and chemicals were of reagent grade from commercial suppliers.

Syntheses:

2,3-Dibromo-[1,1,- $^{2}H_{2}$]-propanol (1A), 2,3-Dibromo-[2-$^{2}H_{1}$]-propanol (1B)and 2,3-Dibromo-[3,3- $^{2}H_{2}$]-propanol(1C).

These compounds were prepared by a previously published method (9).

2,3-Dibromo-[2,3,3-$^{2}H_{3}$]-propanol (1D).

[3-$^{2}H_{1}$]-propargyl alcohol (8.0 g, 0.14 mol) dissolved in 100 ml dry ethyl ether was added dropwise under argon to a slurry of lithium aluminum deuteride (6.3 g, 0.15 mol) in 200 ml of ether maintained at 4-6°C in an ice bath. After the addition was complete (90 min), the reaction mixture was stirred at room temperature for 8h at which time GC analysis showed that about 11% of the starting material remained. Deuterium oxide (20 ml) was cautiously added at 0°C and the mixture then stirred vigorously at room temperature for 16h. The precipitated inorganic solids were removed and washed well with ether. The combined filtrates were

stirred with K_2HgI_4 (6.0 g, 7.5 mmol) in a 15% aqueous potassium hydroxide solution (15 ml) to remove the unreacted propargyl alcohol as verified by GC analysis. The remaining crude material was distilled under vacuum to give a colorless liquid (14.5 g, 47.7%) b.p. 54-57°C/ 0.5 mm; lit. (13) b.p. 109°C/20mm. NMR ($CDCl_3$); δ 4.02 (s, 2H, C-1 methylene), 2.64 (s, 1H, -OH).

2,3-Dibromo-[1,1,3,3-$^2H_4$]-propanol (1E).

Jones reagent (135 ml, 0.25 mol) was added dropwise to a solution of 2,3-dibromo-[3,3- $^2H_2$]-propanol (8.0g, 37.0 mmol) in 135 ml of acetone at 4-6°C in an ice bath (11). After the addition was complete (45 min) the reaction mixture was stirred at room temperature for 72 h. The solution was then extracted with methylene chloride (3 x 200 ml) and the resultant methylene chloride layer was washed in succession with aqueous 10% (w/v) HCl and water (250 ml). The methylene chloride layer was dried over anhydrous sodium sulfate and evaporated to a light blue oil. The crude product was then refluxed for 6 h in thionyl chloride (10 ml) under an argon atmosphere and then distilled under reduced pressure. The fraction from 45-55°C/ 0.5 mm (3.1g, 35.2%) was collected and immediately used in the next reaction.

The acid chloride (3.2g, 13.0 mmol) was dissolved in 25 ml glyme and was added dropwise under argon to a slurry of sodium borodeuteride (1.05 g, 26.0 mmol) in 50ml of glyme maintained at 4-6°C in an ice bath. After the addition was complete (30 min), the reaction mixture was stirred at room temperature for 14 h and the mixture was concentrated under reduced pressure. The residue was then taken up slowly in 10 ml of methanol followed by 40 ml of aqueous 10% w/v HCl. The reaction mixture was left stirring for 4h, then extracted with methylene chloride (3 x 50 ml). The methylene chloride extract was washed in succession with aqueous 5% (w/v) $NaHCO_3$ and water (75 ml). The extract was then dried over anhydrous sodium sulfate and concentrated to a pale yellow

oil (2.7 g, 34.0%).

2,3-Dibromo-[1,1,2,3,3-$^2H_5$]-propanol (1F).

Jones reagent (135 ml, 0.25 mol) was added dropwise to a solution of 2,3-dibromo-[2,3,3-$^2H_3$]-propanol 37.0 mmol) in 135 ml of acetone at 4-6°C in an ice bath. The solution was stirred at room temperature for 72 h. The crude product was refluxed for 6 h in thionyl chloride (10 ml) distilled under reduced pressure. This fraction from 45-55°C/ 0.5 mm (3.7 g, 39.6%) was collected for immediate use in the next reaction.

The acid chloride (3.7 g, 16.0 mmol) was dissolved in 25 ml glyme and was added to a slurry of sodium borodeuteride (1.20 g, 32.0 mmol) in 50 ml glyme maintained at 4-6°C in an ice bath. The slurry was stirred 14 h at room temperature. Completion of the procedure yielded a pale yellow oil (3.3 g, 41%). NMR ($CDCl_3$): no peaks observed; mass spectrum, m/z 222 (M+H), 204 (M-OH). The deuterium content was < 0.1% $^2H_3$, 10.1% $^2H_4$ and 89.9% $^2H_5$ based on the (M-OH) ions at m/z 199-209.

1,2-Dibromo-3-chloro-[1,1- $^2H_2$]-propane (2A).

This analog was synthesized by chlorination of the corresponding DBP using the procedure described by Bose and Lai (12). A solution of triphenylphosphine (TPP) (6.3 g, 24.0 mmol) in 75 ml of tetrahydrofuran (THF) was added to a solution of N-chlorosuccinimide (NCA) (3.5 g, 26.2 mmol) in 75 ml of THF over a period of 15 min at room temperature. Once the addition was complete, a solution of 2,3-dibromo-[3,3- $^2H_2$]-propanol 93.0 g, 13.8 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the THF was removed by rotoevaporation and the resulting residue partitioned between diethyl ether and water, 100 ml each. The ether layer was dried over sodium sulfate and evaporated to an oily residue. The oily residue was then stirred in hexane (100 ml) for 2 h, at which time any undissolved material was removed by filtration. The hexane extract was then evaporated

to give a light yellow oily product. This crude oil was distilled under vacuum to give a colorless liquid (2.05 g, 62.9%) b.p. 34-35°C/ 0.4 mm, lit. (14) b.p. 78°C/ 16mm; NMR ($CDCl_3$); δ 4.35 (t, 1H, J = 5.8 Hz, C-2H), 3.96 (d, 2H, J = 5.8Hz, C-3 methylene). EI direct probe mass spectrum, m/z no ($M^{+\cdot}$), 157 (M-Br). The deuterium content was < 0.1% $^2H_0$, 3.3% $^2H_1$ and 96.7% $^2H_2$ based on the M-Br ions at m/z 155-162. The sample was 98% pure by GC analysis.

1,2-Dibromo-3-chloro-[2-$^2H_1$]-propane (2B).

TPP (6.3 g, 24.0 mmol) in 75 ml of THF was added to a solution of NCS (3.5 g, 26.2 mmol) in 75 ml of THF over a period of 15 min at room temperature. Once the addition was complete, a solution of 2,3-dibromo-[2-$^2H_1$]-propanol (3.0 g, 13.8 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the procedure was completed and the crude oil was distilled under vacuum to give a colorless liquid (1.7 g, 52.1%) b.p. 32-33°C/ 0.3 mm, lit. (14) b.p. 78°C/ 16mm); NMR ($CDCL_3$); δ 3.97 (s, 2H, C-3 methylene), 3.84 (s, 2H, C-1 methylene). EI direct probed mass spectrum m/z no ($M^{+\cdot}$), 156 (M-Br). The deuterium content was 1.8% $^2H_0$ and 98.2% $^2H_1$ based on the (M-Br) ions at m/z 155-159. The sample was > 98% pure by GC analysis.

1,2-Dibromo-3-chloro-[3,3-$^2H_2$]-propane (2C).

TPP (6.3 g, 24.0 mmol) in 75 ml of THF was added to a solution of NCS (3.5 g, 26.2 mmol) in 75 ml of THF over a period of 15 min at room temperature. Once the addition was complete, a solution of 2,3-dibromo-[1,1-$^2H_2$]-propanol (3.0 g, 13.8 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the procedure was completed and the crude oil was distilled under vacuum to give a colorless liquid (2.2 g, 67.5%) b.p. 32-33°C/ 0.3 mm, lit. (14) b.p. 78°C/ 16mm); NMR ($CDCl_3$); δ 4.35 (t, 1H, J = 5.8 Hz, C-2H), 3.84 (d, 2H, J = 5.8Hz, C-1 methylene), EI direct probe m/z no ($M^{+\cdot}$), 157 (M-Br). The deuterium content was

< 0.1% $^2H_0$, 1.9% $^2H_1$, and 98.1% $^2H_2$ based on the (M-Br) ions at m/z 155-162. The sample was >98% pure by GC analysis.

1,2-Dibromo-3-chloro-[1,1,2-$^2H_3$]-propane (2D).

TPP (6.3g, 24.0 mmol) in 75 ml of THF was added to a solution of NCS (3.5 g, 26.2 mmol) in 75 ml of THF over a period for 15 min at room temperature. Once the addition was complete, a solution of 2,3-dibromo-[2,3,3-$^2H_3$]-propanol (3.0g, 13.8 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the procedure was completed and the crude oil was distilled under vacuum to give a colorless liquid (2.1 g, 64.4%) b.p. 32-33°C/0.3mm, lit. (14) b.p. 78°C/16mm); NMR ($CDCl_3$) 3.97 (s, assumed 2H, C-3 methylene). EI direct probe mass spectrum m/z no ($M^{+\cdot}$), 158 (M-Br). The deuterium content was <0.1% $^2H_0$, <0.1% $^2H_1$, 3.9% $^2H_2$, 96.1% $^2H_3$ based on the (M-Br) ions at m/z 155-160. The sample was >98% pure by GC analysis.

1,2-Dibromo-3-chloro-[1,1,3,3-$^2H_4$]-propane (2E).

TPP (4.8 gm, 18.4 mmol) in 75 ml THF was added to a solution of NCS (2.7 g, 20.1 mmol) in 75 ml of THF over a period of 15 min at room temperature. Once the addition was complete, a solution of 2,3-dibromo-[1,1,3,3-$^2H_4$]-propanol (2.3 g, 10.6 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the procedure was completed and the crude oil distilled under vacuum to give a colorless liquid (1.2 g, 48%) b.p. 41-42°C/0.6 mm, lit. (14) b.p. 78°C/ 78mm); NMR ($CDCl_3$); δ 4.35 (s, 1H, C-2H). EI direct probe mass spectrum, m/z no ($M^{+\cdot}$), 159 (M-Br). The deuterium content was <1.0% $^2H_2$, 9.4% $^2H_3$ and 90.6% $^2H_4$ based on the (M-Br) ions at m/z 155-164. The sample was 98% pure by GC analysis.

1,2-Dibromo-3-chloro-[1,1,2,3,3-$^2H_5$)-propane (2F).

TPP (4.2 g, 16.1 mmol) in 50 ml of THF was added to a solution of NCS (2.3 g, 17.2 mmol) in 50 ml of THF over a period of 15 min at room temperature. Once the addition was complete, a

solution of 2,3-dibromo-[1,1,2,3,3-$^2H_5$]-propanol (1.9 g, 8.5 mmol) in 10 ml of THF was rapidly added to the NCS-TPP mixture. After 12 h, the procedure was completed and the crude oil distilled under vacuum to give a colorless liquid (1.05 g, 52.5%) b.p. 33-34°C/ 0.4 mm, lit. (14) b.p. 78°C/ 16mm; NMR ($CDCl_3$), no peaks. EI direct probe mass spectrum, m/z no ($M^{+\cdot}$) 160 (M-Br). The deuterium content was 0.1% $^2H_3$, 10.1% $^2H_4$ and 89.9% $^2H_5$ based on the (M-Br) ions at m/z 155-165. The sample was 98% pure by GC analysis.

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