^{13}C LABELED BENZO[a]PYRENES AND DERIVATIVES. 2. THE SYNTHESIS OF BENZO[a]PYRENE-6-^{13}C.

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SUMMARY

The synthesis of benzo[a]pyrene-6-^{13}C is described. Perinaphthane was converted to 6-benzoyl-carbonyl-^{13}C-perinaphthane which was cyclized to 2,3-dihydrobenzo[a]pyren-6(1H)-one-6-^{13}C. Subsequent reduction of the ketone followed by dehydration and dehydrogenation gave benzo[a]pyrene-6-^{13}C in 29% overall yield.

Key Words: Benzo[a]pyrene, Carbon-13, Carcinogenic Hydrocarbons.

INTRODUCTION

We have been carrying out the synthesis of benzo[a]pyrenes labeled with ^{13}C (90%) at each of the peripheral carbon atoms of the ring system for use in metabolism studies and evaluation of the application of ^{13}C nmr in such studies. The synthesis of benzo[a]pyrene-6-^{13}C is described herewith.

DISCUSSION

The synthesis of benzo[a]pyrene-6-^{13}C (1) was accomplished by a modification of the procedure originally described by Fieser and Hershberg (1) and subsequently used by Heidelberger (2) in the synthesis of benzo[a]pyrene-6-^{14}C as shown in Scheme I.

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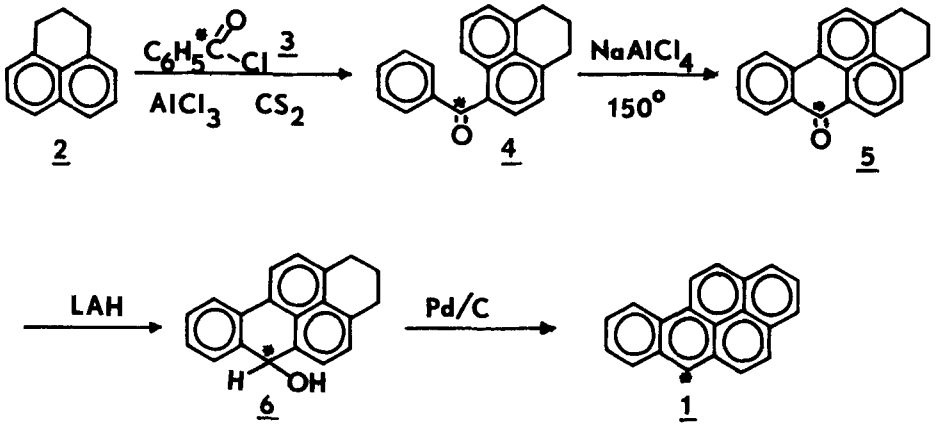

Scheme I

Perinaphthane (2)(3) was allowed to react with benzoyl-carbonyl-^{13}C chloride (3) in the presence of aluminum chloride in carbon disulfide affording 6-benzoyl-carbonyl-^{13}C-perinaphthane (4) in 79% yield. Cyclization of 4 to 2,3-dihydrobenzo[a]pyren-6(1H)-one-6-^{13}C (5) was accomplished by heating for five hours with sodium aluminum chloride (1) at 130-150°C. The crude ketone 5 was reduced with lithium aluminum hydride in refluxing ether-benzene solution to give 1,2,3,6-tetrahydrobenzo[a]pyren-6-ol-6-^{13}C which was directly dehydrated and dehydrogenated over Pd/C at 250°C to benzo[a]pyrene-6-^{13}C (1). The overall yield of 1 from benzoic-carboxyl-^{13}C acid was 29%.

The ^{13}C NMR spectrum of 1 showed that the correct chemical shift for C_6 of BaP is 124.59 (δ_C from TMS) and not 125.38 as assigned by Buchanan and Ozubko (4).

EXPERIMENTAL

Materials and Methods -- Benzoic-carboxyl-^{13}C acid was supplied by the Stable Isotopes Resource (LASL/NIH/ERDA) through Group H-11, Los Alamos Scientific Laboratory. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{13}C NMR spectra were obtained in $CDCl_3$ on a pulse Fourier transform Varian CFT-20 or FT-80A spectrometer. Peaks

were referenced to $CDCl_3$ (76.9 ppm) and are reported relative to TMS. Product purity and reaction progress were detected with analytical thin-layer chromatography using 2.5 x 10 cm Analtech plates coated with silica gel GF.

Benzoyl-carbonyl-^{13}C Chloride (3). A 50 ml round-bottom flask equipped with a reflux condenser and $CaCl_2$ drying tube was charged with 3.07 g (24.9 mmol) of benzoic carboxyl-^{13}C acid, 5.0 g $SOCl_2$, and 3 drops of anhydrous DMF (5). The mixture was refluxed for 2 h, after which time the evolution of HCl had ceased. The solution was diluted with anhydrous benzene and the benzene and excess $SOCl_2$ removed on a rotary evaporator. Distillation (Kugel-Rohr) of the residue at reduced pressure afforded 3.39 g (96%) of benzoyl-carbonyl-^{13}C chloride (3), fraction collected from 72-83°C at 10 torr. This was used immediately in the next step.

6-Benzoyl-carbonyl-^{13}C-perinaphthane (4). A 250 ml Erlenmeyer flask fitted with a reflux condenser, addition funnel, $CaCl_2$ drying tube, and magnetic stirrer was charged with 3.23 g (24.2 mmol) of anhydrous $AlCl_3$ and 75 ml of anhydrous CS_2. A solution of freshly prepared benzoyl-carbonyl-^{13}C chloride (3) (3.39 g, 24.0 mmol) and perinaphthane (2)(3)(4.0 g, 23.8 mmol) in 30 ml of anhydrous CS_2 was added dropwise over 15 min. The reaction mixture warmed to gentle reflux during the addition and turned blood red. It darkened somewhat while being heated at reflux for an additional 30 min, after which it was poured over 200 g of ice and 25 ml of 5% HCl. The reaction flask was rinsed with CS_2 and H_2O. After standing overnight, the CS_2 was removed by gentle boiling to give a dark brown oil. This was extracted into ether (2 x 75 ml) and the combined ether extracts were washed once with 5% Na_2CO_3 (50 ml) and once with H_2O (75 ml). The ether layer was dried over anhydrous $MgSO_4$, and the ether was removed on a rotary evaporator to give 6.21 g of a brown oil (major spot on TLC in benzene gave R_f = 0.43). Distillation of the oil in a Kugel-Rohr gave as the major fraction 5.1 g (79%) of 4 as a viscous light orange oil at 160-205°C at 0.05 torr, reported, bp 160-180°C at 0.01 torr (2). ^{13}CNMR ($CDCl_3$): 197.88 (C=O). This was used in the next step without further purification.

Benzo[a]pyrene-6-^{13}C (1). A 125 ml Erlenmeyer flask was charged with 7.6 g (130 mmol) of anhydrous NaCl and 26.4 g (198 mmol) of anhydrous $AlCl_3$. This mixture was heated with a Bunsen burner until a melt was produced (1,2). The flask was immediately placed in an oil bath at 135-140°C, and 4.80 g (17.6 mmol) of 4 prewarmed to 110°C was added. The reaction flask was loosely stoppered with a plug of glass wool and stirred with a glass rod every 10-15 min while heating at 135°C for 3 h. During this time the reaction mixture darkened and became more viscous. Heating was continued for an additional 2 h at 145°C. At the end of this time crushed ice was added to the flask to bring the contents to a volume of 100 ml. The flask was then placed in a sonicator bath for 1 h during which time the stirring rod was used to help break up the very viscous complex. The contents of the flask were poured into a beaker and fresh portions of water were added to the flask to complete the hydrolysis. A water layer of 250 ml containing a brown mushy product was finally obtained. The aqueous slurry was extracted three times with 135 ml portions of benzene, and the combined benzene layers were washed once with water. The dark brown benzene layer was dried over anhydrous $MgSO_4$ for 4 h before it was filtered and was used immediately in the next step. TLC (benzene) showed at least 7 spots with major spots at R_f 0.18 and 0.68. Comparison of the chemical shift for the ^{13}C label(183.69 ppm, $CDCl_3$) in the crude product with that for the carbonyl group (183.57 ppm, $CDCl_3$) in benzanthrone established the fact that this crude product contained 2,3-dihydrobenzo[a]pyren-6(1H)-one-6-^{13}C (5) as the major component.

A one liter Erlenmeyer flask equipped with a reflux condenser, addition funnel, and magnetic stirrer was charged with 3.7 g (98 mmol) of $LiAlH_4$ and 200 ml of anhydrous ether under N_2. The dried benzene solution of the ketone 5 was added dropwise over a period of 40 min, and the mixture was heated at reflux with stirring for 12 h. The reaction mixture was cooled (ice bath), and 20 ml of ethanol was added slowly to decompose the excess $LiAlH_4$. The reaction mixture was poured into 350 ml of 2% HCl, the organic layer was separated, and the aqueous layer was washed with 150 ml of benzene. The organic layers were com-

bined and washed twice with 50 ml portions of sat'd salt solution and once with 50 ml of water. The orange organic layer was dried over $MgSO_4$, and the solvents were evaporated under reduced pressure to give 4.25 g (89% recovery of organic material) of orange oil. This material contained 6 and/or its dehydration product. TLC (benzene) showed a major spot at R_f 0.69 plus 4-5 minor spots. This material was directly dehydrogenated by heating with 0.45 g of 10% Pd/C, 6.30 g (34.9 mmol) of 1,1-diphenylethene, and 45 ml of 1-methylnaphthalene at 245-255°C for 7 h under a slow stream of N_2. The reaction mixture was cooled and diluted with 50 ml of benzene. The calalyst was removed by filtration, and the benzene was removed on a rotary evaporator. The 1-methylnaphthalene, 1,1-diphenylethane, and unreacted 1,1-diphenylethene were removed in a Kugel-Rohr at 40-80°C and 0.05-0.1 torr. The resulting dark residue (4.38 g) dissolved slowly in 20 ml of benzene with warming on a steam bath. The dark red solution was applied to a 36 x 290 mm column of neutral Woelm alumina, and the column was eluted with benzene. The first 100 ml of eluant contained 0.9 g of material which did not contain any 1 (TLC). The next 350-450 ml afforded 2.1 g of solid, mp 145-175°C, which was shown by TLC to contain considerable amounts of 1. This solid was dissolved in benzene and added to 1.9 g of picric acid dissolved in 42 ml of benzene. The resulting dark solution was concentrated to 40 ml and allowed to cool to room temperature. The picrate was isolated (41% overall from 4) and converted to 1 by chromatography on Woelm neutral alumina. Elution with benzene followed by concentration and addition of methanol gave a total of 1.55 g of benzo[a]pyrene-6-^{13}C (1) in three crops: 1.2 g, mp 175.5-177°C, yellow needles: 0.25 g, mp 175-178°C, yellow needles; 0.1 g, mp 172-176.5°C, yellow powder; reported (6), mp 176-177°C. ^{13}C NMR ($CDCl_3$) gave the chemical shift for C_6 of 1 as 124.59 ppm in disagreement with the value assigned by Buchanan and Ozubko (4) and corresponds to their assignment for C_1. Based on 3.07 g of benzoic-carboxyl-^{13}C acid used, the overall yield was 29%.

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