SYNTHESIS OF 1-PYRENYLOXIRANE-3,6,8-$^3H_1$

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SUMMARY

The syntheses of 1-pyrenyloxirane-3,6,8-$^3H_1$, 7, and its precursor, pyrene-1,3,6,8-$^3H_1$, 4, are described. The synthesis pathway includes a novel preparation of 4 from 1-pyrenyllithium and tritiated water in theoretical yield.

Key Words: Tritium, 1-Pyrenyloxirane-3,6,8-$^3H_1$, Pyrene-1,3,6,8-$^3H_1$, Labeled aryloxiranes

INTRODUCTION

Polynuclear aromatic hydrocarbons (PAH) are metabolically converted into oxirane derivatives which have been implicated as the ultimate carcinogens in chemical carcinogenesis [1,2]. Tritium-labeled 1-pyrenyloxirane was required as a model compound in order to facilitate the studies of the structure-activity relationships in chemical mutagenesis and carcinogenesis for selected PAH. The details of the synthesis of this compound and of the parent ^3H-labeled hydrocarbon are reported herein.

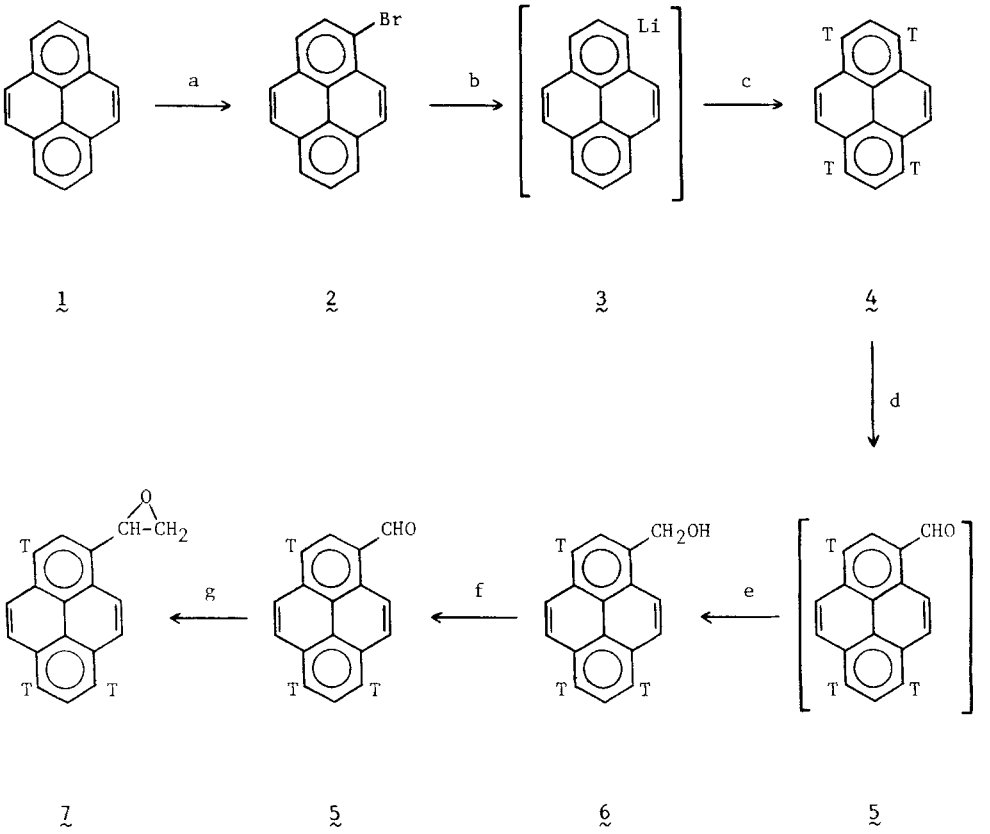
DISCUSSION

The pathway used for the preparation of 1-pyrenyloxirane-3,6,8-$^3H_1$ is depicted in Scheme I. The sequence consists of an efficient synthesis of ^3H-labeled pyrene via THO quenching of 1-pyrenyllithium followed by conversion of 4 to 7 by a previously reported procedure [2] which was modified for radiosynthesis.

Direct tritiations of 5 and the corresponding carbinol 6 were unsuccessful using procedures previously utilized for the tritiation of other PAH, such as direct exchange with CF_3COOT [3] or the ethylaluminum dichloride-catalyzed THO exchange technique [4,5]. Accordingly, pyrene was brominated [6] to 2 and the resulting pure 1-bromopyrene was converted to 3 using n-butyllithium [7].

0362-4803/81/101465-06$01.00
 Received October 20, 1980

Scheme I



1 2 3 4 5 6 5 7

[a] $CuBr_2$, chlorobenzene. [b] n-BuLi, dry benzene. [c] THO. [d] N-methylformanilide, $POCl_3$. [e] $NaBH_4$, EtOH. [f] MnO_2. [g] DMSO, NaH, trimethylsulfonium iodide, THF.

Treatment of 3 with tritiated water gave 4 in quantitative yield and without the occurrence of a possible isotope effect. It should also be noted that this method is more convenient for the preparation of larger amounts of 4 than any of the standard isotope exchange tritiation procedures. Catalytic replacement of halogen by tritium using tritium gas (T_2), although more economical, was not considered due to the necessity of handling T_2 gas.

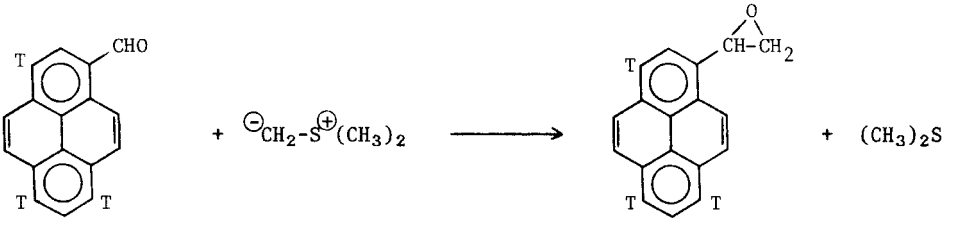
The epoxy vinylation of 4 (specific activity 496 mCi/mmole) to 7 (specific activity 421 mCi/mmole) occurred with a 15.2% loss of tritium instead of the

expected 25%, which is indicative of a possible positive isotope effect in the formylation reaction step. The resulting tritiated 1-pyrenecarboxaldehyde 5 was then purified by reduction to the corresponding carbinol 6 followed by reoxidation to 5 by treatment with MnO_2. The synthesis of the desired aryloxirane 7 was then achieved by the reaction of the purified aldehyde 5 with a solution of dimethylsulfonium methylide prepared in situ [8] as shown below in Scheme II.

Scheme II

$$(CH_3)_2SO + NaH \longrightarrow Na^{\oplus}{}^{\ominus}CH_2SOCH_3 + H_2$$

$$Na^{\oplus}{}^{\ominus}CH_2SOCH_3 + (CH_3)_3S^{\oplus}I^{\ominus} \longrightarrow {}^{\ominus}CH_2\text{-}S^{\oplus}(CH_3)_2 + NaI + (CH_3)_2SO$$



5 7

EXPERIMENTAL

Tritiated water was purchased from Amersham Corporation. Radioactivity was determined by means of a Packard Model 2425 liquid scintillation spectrometer using Liquifluor (New England Nuclear). Radiochemical purity was determined by autoradiography and radiochromatogram scanning of TLC plates. Radiochromatogram scans were obtained with a Packard Model 7201 radiochromatogram scanner, and high speed LKB Ultrofilm ^3H was used for the autoradiographic registration. Silica gel plates (precoated with fluorescent silica gel, 5 x 20 cm, Brinkman 60F-254) were used for TLC, utilizing one of the following systems as the developing solvent: (A) benzene; (B) benzene:cyclohexane (9:1); (C) cyclohexane:THF (3:2).

Known standards were used on TLC for visual comparison with the radiolabeled samples. The specific activity of the intermediates and of the final product was determined by assaying the radioactivity of a solution of a known concentration determined directly by UV. The sample concentrations were determined from the UV spectra (Varian Superscan III), and the standard extinction coefficient was determined from quantitative UV spectra using authentic standards of ≧ 98% purity.

1-Bromopyrene, 2

A solution of 15.3 g (0.075 mmole) of pyrene in 250 ml chlorobenzene was brought to reflux under an argon atmosphere, and 33.8 g (0.151 mmole) cupric bromide was added with caution (foaming) to the solution. The reaction mixture was kept under reflux for 2 hr, then filtered through Celite and concentrated in vacuo. The residue was then flushed through a short column of alumina (20 mm x 100 mm) and eluted with benzene. The resulting crude 2 was then recrystallized three times from benzene:hexane, yielding 14 g (75%) of pure pyrene bromide; TLC (SiO_2, solvent system A), R_f = 0.68.

Pyrene-1,3,6,8-$^3H_1$, 4

To a solution of 1-bromopyrene (1.055 g, 3.73 mmoles) in 15 ml benzene (dried over molecular sieves), 7 ml (14 mmoles) of a 2 molar solution of n-BuLi in hexane was added all at once. The reaction mixture was then stirred for 72 hr at room temperature in a stoppered flask filled with argon. Centrifugation at 2,000 rpm followed by washing with 2 x 5 ml dry benzene and 10 ml dry hexane gave fine white crystals of 1-pyrenyllithium. The lithium salt 3 was suspended immediately in 4 ml absolute THF (dried over molecular sieves) and THO (3.6 Ci, 75 µl, approximately 450 mCi/mAt) was added all at once. The reaction mixture was then stirred under argon overnight and, after addition of 10 ml water, the resulting tritiated pyrene was extracted into 25 ml benzene. Removal of labile tritium was achieved by washing the benzene solution with 4 x 15 ml water. After drying over anhydrous Na_2SO_4, the crude pyrene-1,3,6,8-$^3H_1$ 4 was purified by chromatography on a silica gel column (Woehlm, 70-250 mesh, 40 mm x 200 mm) eluted with benzene. Yield, 548 mg (2.7 mmoles) (72%) of pyrene-1,3,6,8-$^3H_1$ at a specific

activity of 496 mCi/mmole. The radiochemical purity (≧ 98%) was determined by TLC: solvent system B, R_f = 0.7.

1-Pyrenecarboxaldehyde-3,6,8-$^3H_1$, 5

A mixture of 4 (202 mg, 1.0 mmole, 497 mCi), N-methylformanilide (0.27 ml, 2.2 mmoles) and $POCl_3$ (0.17 ml, 1.8 mmoles) was heated on a steam bath for 2 hr, then stirred with 10 ml of 10% aqueous NaOAc. The precipitated crude aldehyde 5, which was removed by filtration, was taken up in 10 ml of ethanol and converted to the corresponding carbinol 6 by addition of 1 g $NaBH_4$ and heating at 75° for 5 min. The crude carbinol was precipitated by addition of water followed by filtration. The solid 6 was then dissolved in benzene and, after drying over K_2CO_3, was purified by chromatography on a Florisil column (12 mm x 120 mm) packed in benzene. Elution with benzene afforded unreacted pyrene (approximately 20 mg, 10% recovery) and the desired pure carbinol 6 which was eluted with a solution of 5% acetone in benzene and, after removing the solvents in vacuo, was reoxidized to 5 by treatment with MnO_2 (500 mg) in refluxing benzene (10 ml) for 5 min. Purification of this crude 5 via passage through a short silica gel column packed with benzene followed by removal of the solvent in vacuo gave 111 mg (54%) of 1-pyrenecarboxaldehyde-3,6,8-$^3H_1$. The radiochemical purity (≧ 98%) was determined by TLC: solvent system A, R_f = 0.5.

1-Pyrenyloxirane-3,6,8-$^3H_1$, 7

A solution of dimsyl anion was prepared as follows: sodium hydride, 50% suspension in mineral oil (1.0 g, 20 mmoles), was washed three times with hexane by decantation to remove the mineral oil, followed by drying in a stream of argon. DMSO (15 ml) was added and the mixture was stirred under argon at 60° for 1 hr. The resulting clear solution was cooled to room temperature and diluted with 15 ml dry THF. A 3-ml (2.0 mmoles) aliquot of this solution was withdrawn, cooled to -5°, and a solution of 410 mg (2 mmoles) trimethylsulfonium iodide in 2 ml DMSO added. To this mixture cooled at 0°, a solution of 6 (111 mg, 0.48 mmole) dissolved in 1-2 ml THF was added while maintaining the temperature at 0° for 5 min. The above reaction mixture was added to 50 ml of cyclohexane:ether

(1:1) followed by washing with 5 x 50 ml water and drying over K_2CO_3. Removal of the solvent in vacuo, treatment of the resulting oil with 0.5 ml methanol followed by chilling at 0°, afforded 99.7 mg (95%) 1-pyrenyloxirane-3',6',8'-$^3H_1$, 7, as off-white needles with a specific activity of 421 mCi/mmole. The radiochemical purity (≧ 98%) was determined by TLC: solvent system C, R_f = 0.7.

ACKNOWLEDGMENT

We gratefully acknowledge the support of this work by the National Cancer Institute, Contract No. NO1-CP-33387.

REFERENCES

1. Jerina D.M. - in Origin of Human Cancer, H.H. Hiatt, J.D. Watson and J.D. Winstein (Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1977, Book B, pp. 639-659; Levin W. et al. - ibid., pp. 659-689.

2. Yang N.C., Chiang W., Leonow D., Leonow E., Bilyk I. and Kim B. - J. Org. Chem., 43(17): 3425 (1978).

3. Breeman G.E.M., Kaspersen F.M. and Westra J.G. - J. Labelled Compd. and Radiopharm., XIV(5): 741 (1978).

4. Duncan W.P., Ogilvie, II, E.J. and Engel J.F. - J. Labelled Compd. and Radiopharm., XI: 461 (1975).

5. Susàn A.B., Kwoka W., Wiley, Jr., J.C. and Duncan W.P. - Chem. and Ind., 285 (1980).

6. Mosnaim A.D., Wolf M.E., Saavedra I., Amaro A.M. and Cordano G. - Tetrahedron Lett., 17: 1491 (1973).

7. Stüdt P. - Liebigs Ann. Chem., 528 (1978).

8. Covey E.J. and Chaykovsky M. - J. Amer. Chem. Soc., 87: 1353 (1965).