

PREPARATION OF BIPHENYL-2,2',3,3',5,5',6,6'-²H₈

Alice M. Clark, Patrick J. Davis, and Robert V. Smith*
Drug Dynamics Institute, College of Pharmacy
The University of Texas at Austin
Austin, Texas 78712 (U.S.A.)

SUMMARY

Biphenyl-2,2',3,3',5,5',6,6'-²H₈ was prepared from biphenyl-d₁₀. Initial bromination of biphenyl-d₁₀ followed by hydrogenolysis of the 4,4'-dibromobiphenyl-d₈ with lithium aluminum hydride gave the desired product in 40% overall yield.

Key Words: Biphenyl, deuterium

INTRODUCTION

As part of ongoing studies of the use of microorganisms as models for mammalian metabolism¹⁻³, hydroxylations of biphenyl by three fungi have been studied⁴. Aspergillus parasiticus, Cunninghamella echinulata, and Helicostylum piriforme convert biphenyl (1) to 4,4'-dihydroxybiphenyl (2), 4-hydroxybiphenyl (3), and 2-hydroxybiphenyl (4), respectively. The regiospecific hydroxylation of biphenyl by these fungi parallel the hydroxylation activities found in mammals⁵⁻⁷. The preparation of specifically deuterated biphenyl derivatives was desired for studies of the mechanism(s) of hydroxylation. Of particular interest are determinations of whether hydroxylations proceed through arene oxide intermediates which should undergo NIH-shifts.

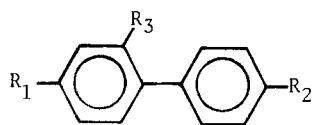
RESULTS AND DISCUSSION

Initially, attempts were made to prepared biphenyl-4,4'-²H₂ (5) for the proposed NIH-shift studies. All of these efforts were unsuccessful including lithium aluminum deuteride (LAD) reduction⁸ of 4,4'-dibromobiphenyl (6) in tetrahydrofuran (THF), deuterolysis (²H₂, 10% Pd/C) of 6, Grignard reaction of

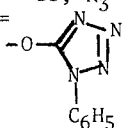
*To whom reprint requests should be addressed.

6 (followed by work up with $^2\text{H}_2\text{O}$), and deuterolysis ($^2\text{H}_2$, 10% Pd/C) of the di(1-phenyltetrazole)ether of 4,4'-dihydroxybiphenyl (7). In both the case of the LAD reduction and the deuterolysis of 6, the major product appeared to be biphenyl-4- ^2H (8). Incomplete deuterium exchange with LAD may be due to the presence of moisture in the solvent used for the reaction or workup. The cost of preparing LAD-treated solvents was deemed to be prohibitive. Even though 4,4'-dideuterobiphenyl can theoretically be obtained from each reaction, it was never produced free of the monodeutero (8) product as indicated by mass spectral analyses. The major product obtained with the Grignard reaction of 6 and the deuterolysis of 7 appeared to be (by mass spectral analysis) biphenyl itself (m/e 154, 100%).

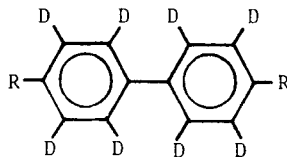
Due to the difficulties encountered in attempts to prepare pure biphenyl-4,4'- $^2\text{H}_2$ (5), an alternative method was pursued for preparing a suitably labelled biphenyl for use in mechanistic studies. Commercially available biphenyl- $^2\text{H}_{10}$ was brominated to yield 4,4'-dibromobiphenyl- $^2\text{H}_8$ (9). Mass spectral analysis of the product showed the characteristic pattern for the molecular ion of dibrominated compounds. The melting point of the dibrominated product is close to the literature value for 6⁹ and its ^{13}C -nmr spectrum is consistent with the structure for 9. Reduction of the dibromide 9 with lithium aluminum hydride (LAH) afforded biphenyl-2,2',3,3',5,5',6,6'- $^2\text{H}_8$ (10). Compound 10 possessed a m.p., MS and ^{13}C NMR data consistent with its proposed structure.



- $\frac{1}{2}$ $R_1 = R_2 = R_3 = -\text{H}$
 $\frac{2}{3}$ $R_1 = R_2 = -\text{OH}; R_3 = -\text{H}$
 $\frac{3}{4}$ $R_1 = -\text{OH}; R_2 = R_3 = -\text{H}$
 $\frac{4}{5}$ $R_1 = R_2 = -\text{H}; R_3 = -\text{OH}$
 $\frac{5}{6}$ $R_1 = R_2 = -\text{D}; R_3 = -\text{H}$
 $\frac{6}{7}$ $R_1 = R_2 = -\text{Br}; R_3 = -\text{H}$
 $\frac{7}{8}$ $R_1 = R_2 =$



- $\frac{8}{9}$ $R_1 = -\text{D}; R_2 = R_3 = -\text{H}$



- $\frac{9}{10}$ $R = -\text{Br}$
 $\frac{10}{11}$ $R = -\text{H}$

The preparation of the octadeuterobiphenyl 10 affords a product which can be used for the determination of the occurrence of an NIH-shift during the biological hydroxylation of biphenyl. Compound 10 is being used as a substrate, to study the migration and retention of hydrogen in the phenolic metabolites obtained from A. parasiticus and C. echinulata.

EXPERIMENTAL

Biphenyl-²H₁₀ was obtained from ICN Life Sciences or Stohler Isotopes and was shown to be pure by mass spectral analysis. Lithium aluminum hydride and lithium aluminum deuteride were obtained from Aldrich Chemical Co. All other solvents and reagents were analytical reagent grade. ¹³C NMR spectra were recorded on a Jeol-FX60 Fourier Transform NMR spectrometer using tetramethylsilane as internal standard. Mass spectral analyses were obtained with a DuPont 491-Mass Spectrometer.

Bromination of biphenyl

Biphenyl (154 g, 1 mmol) was brominated using 1.2 ml Br₂, according to the published procedure⁹. Crystallization of the resulting crude product from benzene, followed by thermal gradient sublimation gave white needles, m.p. 160-162°C (lit.⁹, m.p. 162-164°C); MS, m/e (rel. abund.): 314 (52%), 312 (100%), 310 (53%), 152 (93%); ¹³C NMR (CDCl₃): δ139.0 (C-1,1'), 132.1 and 128.6 (C-2,2', 3,3',5,5',6,6'), 122.1 (C-4,4').

4,4'-Dibromobiphenyl-²H₈

Biphenyl-d₁₀ (500 mg, 3 mmol) was dissolved in 2 ml of Br₂ and the solution was allowed to stand at room temperature for 15 min, then diluted with 50 ml of CHCl₃. The CHCl₃ solution was washed carefully with saturated NaHSO₃ to remove excess Br₂. The CHCl₃ layer was dried with anhydrous Na₂SO₄ and evaporated in vacuo to give a white crystalline residue (910 mg, 97%), m.p. 145-150°C. The crude product was crystallized from benzene as white needles, m.p. 159-161°C (427 mg, 43%); MS, m/e (rel. abund.): 322 (51%), 320 (100%), 318 (42%), 160 (47%); ¹³C NMR (CDCl₃): δ138.8 (C-1,1'), 131.7 (t, J_{C-D} = 25.4 Hz), 128.1 (t, J_{C-D} = 24.4 Hz) (C-2,2',3,3',5,5',6,6'), and 121.8 (C-4,4').

Lithium Aluminum Deuteride Reduction of 4,4'-Dibromobiphenyl

To a refluxing solution of LAD (100 mg, 2.4 mmol) in THF (distilled from LAH) under N₂ atmosphere was added 100 mg of 6. The solution was refluxed under N₂ atmosphere for 17 hr. After destruction of the excess LAD with ethyl acetate, the reaction mixture was evaporated in vacuo to give a white solid residue. The residue was triturated with Et₂O and filtered. The clear filtrate was evaporated in vacuo and the resulting residue was sublimed at 1 mm Hg, 70°C to give white crystals (48 mg, 28%), m.p. 66-68°C (biphenyl, m.p. 69-71°C); MS, m/e (rel. abund.): 156 (100%), 155 (84%), 154 (56%).

Lithium Aluminum Hydride Reduction of 4,4'-Dibromobiphenyl-²H₈

The reduction of 9 (344 mg, 1.7 mmol) with LAH (700 mg, 18 mmol) in THF was carried out as described above. Sublimation of the product gave white crystals (131 mg, 48%), m.p. 68-70°C (biphenyl, m.p. 69-71°C); MS, m/e (rel. abund.) 162 (100%, M⁺); ¹³C NMR (CDCl₃) δ140.3 (C-1,1') and 127.0 (C-4,4').

ACKNOWLEDGEMENTS

This work was supported by grant F-690 from the Robert A. Welch Foundation. The authors gratefully acknowledge Dr. C.D. Hufford, School of Pharmacy, The University of Mississippi, for recording the ¹³C NMR spectra.

REFERENCES

- 1) Smith, R.V. and Rosazza, J.P.- Arch. Biochem. Biophys. 161: 551 (1974).
- 2) Smith, R.V. and Rosazza, J.P.- J. Pharm. Sci. 64: 1737 (1975).
- 3) Smith, R.V., Humphrey, D.W., Engel, K.O. and Rosazza, J.P.- Appl. Environ. Microbiol. 31: 448 (1976).
- 4) Smith, R.V., Davis, P.J., Clark, A.M. and Glover-Milton, S., to be published.
- 5) Meyer, T. and Scheline, R.R.- Acta Pharmacol. Toxicol. 39: 419 (1976).
- 6) Meyer, T., Larsen, J.C., Hansen, E.V. and Scheline, R.R.- Acta Pharmacol. Toxicol. 39: 433 (1976).
- 7) Meyer, T.- Acta Pharmacol. Toxicol. 40: 193 (1977).
- 8) Karabatsos, G.J., Shone, R.L. and Scheppele, S.E.- Tetrahedron Letters: 2113 (1964).
- 9) Buckles, R.E. and Wheeler, N.G.- Organic Synthesis, 4: 256 (1963).