The Synthesis of Perdeuterated Azone (d_{35}-1-Dodecylhexahydro-2*H*-azepin-2-one)

Paul W. Groundwater*[a], Jonathan Hadgraft[b], Julian E. Harrison[b], and Adam C. Watkinson[c].

a Department of Chemistry, University of Wales Cardiff, P. O. Box 912, Cardiff CF1 3TB.

b The Welsh School of Pharmacy, University of Wales Cardiff, Redwood Building, King Edward VII Avenue, Cathays, Cardiff, CF1 3XF.

c An-eX, Redwood Building, King Edward VII Avenue, Cathays, Cardiff, CF1 3XF.

Summary

Perdeuteroazone (**3**) has been synthesised *via* the base-catalysed coupling of d_{11}-hexahydro-2*H*-azepin-2-one (**2**) with d_{25}-1-chlorododecane.

Keywords

Perdeuteroazone, mass spectrometry, ^{2}H NMR, Beckmann rearrangement

Introduction

Azone (1-dodecylhexahydro-2*H*-azepin-2-one) (**1**) is a well established dermal penetration enhancer[1] that is known to increase

CCC 0362–4803/94/111047–07

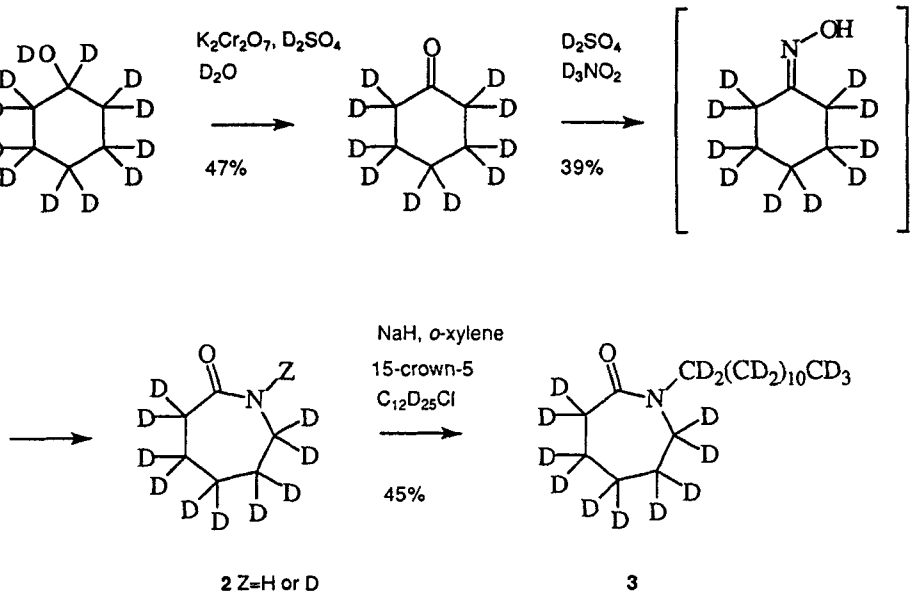
Received 18 May, 1994
Revised 27 June, 1994

the passage of a wide range of molecules through the skin. The precise mechanism by which this is achieved is, however, still unknown. The synthesis of the fully deuterated azone (**3**) would provide a useful tool with which to further investigate the mechanism of action of azone by the use of fourier transform infrared spectroscopy[2,3] and neutron reflectometry[4,5].

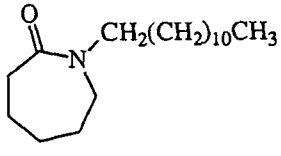
Results and Discussion

The synthesis of perdeuterated azone (d_{35}-1-dodecylhexahydro-2*H*-azepin-2-one) (**3**) was achieved *via* the base-catalysed coupling of d_{11}-hexahydro-2*H*-azepin-2-one (**2**) with d_{25}-1-chlorododecane. d_{11}-Hexahydro-2*H*-azepin-2-one (**2**) was prepared as shown in Scheme 1. d_{12}-Cyclohexanol, which is commercially available from Aldrich, was oxidised to d_{10}-cyclohexanone using a standard procedure. This oxidation was performed in fully deuterated solvents and with deuterated reagents to prevent the loss of deuterium experienced by Farmer *et al.*[6] Upon oxidation of d_{12}-cyclohexanol with chromic acid in protiated media, these workers obtained d_{10}-cyclohexanone with a d_{10}:d_9 ratio of 100:45, which they attributed to the loss of deuterium *via* exchange at the 2- or 6-positions. This loss could be reversed by treating the product with boiling DCl-D_2O to give d_{10}-cyclohexanone with a d_{10}:d_9 ratio of 100:9. These workers also observed a gradual deuterium loss on storage of the d_{10}-cyclohexanone. Comparison of the mass spectra of d_{10}-cyclohexanone and cyclohexanone shows that oxidation under fully deuterated conditions has maintained the d_{10}:d_9 ratio at 100:11. Analysis using an isotopic abundance calculation programme[7] indicates that this represents greater than 98 atom % D.

d_{11}-Hexahydro-2*H*-azepin-2-one was then prepared from d_{10}-cyclohexanone by the one-step Beckmann rearrangement procedure of Novotny.[7] This one-step method obviates the need for the



Scheme 1



1

isolation and purification of the intermediate cyclohexanone oxime and thus results in a higher yield since oximes are notoriously difficult to purify. Once again, the reaction was performed with the deuterated reagents to ensure no loss of deuterium. Calculations of the % D are complicated in this case by the ready exchange of the *N*-D.

The optimum conditions for the base-catalysed coupling of d_{11}-hexahydro-2*H*-azepin-2-one (**2**) and d_{25}-1-chlorododecane involved the use of sodium hydride as base in *o*-xylene with the addition of 15-crown-5, Scheme 1. The d_{25}-1-chlorododecane was prepared by

the chlorination of d_{25}-1-dodecanol, available commercially from Cambridge Isotopes, U.K., with thionyl chloride. Comparison of the mass spectra of d_{35}-1-dodecylhexahydro-2*H*-azepin-2-one (**3**) and 1-dodecylhexahydro-2*H*-azepin-2-one (**2**) and use of the mass calculation programme indicates that (**3**) contains greater than 98 atom % D.

Experimental

All experiments were initially tested on the corresponding protiated materials and the base-catalysed coupling of the protiated species was also attempted, with D_2O quenching, to ensure that no exchange occurred under the conditions used. Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer using sodium chloride plates. Solid samples were run as nujol mulls and liquid samples as thin films. The ^2H NMR spectrum of (**3**) was acquired on a Bruker WM360 spectrometer at 55.3 MHz. ^2H NMR chemical shifts are relative to an internal standard of $CDCl_3$. Low resolution electron impact mass spectra were obtained on a Varian CH5-D spectrometer (Cardiff) and high resolution spectra on a VG ZAB-E spectrometer (S.E.R.C. Mass Spectrometry Service Centre, Swansea). The extent of isotopic labelling was determined by comparison of the mass spectra of the perdeuterated species with those of the corresponding protiated compounds. Repeated scans were taken at an ionising voltage of 70eV and a source temperature of 140°C.

d_{10}-Cyclohexanone

A chromic acid solution was prepared by dissolving potassium dichromate (11.65g, 0.04 mol) in deuterium oxide (36mL). d_2-Sulphuric acid (16.21g, 0.16 mol) was then added slowly. The solution was cooled in ice with vigorous stirring, made up to 60mL using deuterium oxide and then stored under nitrogen until ready for use.

A solution of d_{12}-cyclohexanol (3g, 0.027 mol) in ether (15mL) was cooled to below 0°C under nitrogen. The chromic acid solution (15mL) was added slowly to the vigorously stirred d_{12}-cyclohexanol solution over a period of 15 minutes whilst ensuring that the temperature remained below 5°C. This procedure was repeated for another 15 mL of the chromic acid solution and then the mixture was stirred for a further 15 minutes at 0°C. The ether layer was separated and the aqueous layer was washed with ether (2x25mL). The ether layers were combined and washed with 5% w/v sodium carbonate in deuterium oxide (30mL) followed by deuterium oxide (3x25mL). The ether solution was dried over anhydrous magnesium sulphide and the ether was then removed by distillation at atmospheric pressure. Fractional distillation of the residue gave d_{10}-cyclohexanone; yield; 1.38g (47%); b.p. 50°C/10mm Hg (lit.[6] b.p. 153-155°C); ν_{max} (film)/cm^{-1} 2210, 2108 (C-D), and 1710 (C=O); m/z 109 (3%), 108 (M^+, 36), 107 (4), 106 (2), 76 (21), 74 (29), 63 (17), and 59 (100).

[Cyclohexanone; m/z 99 (5%), 98 (M^+, 37), 97 (3), 70 (21), 69 (30), and 55 (100).]

d_{11}-Hexahydro-2*H*-azepin-2-one (2)

This was prepared using an adaptation of the method of Novotny.[8] To well stirred d_2-sulphuric acid (1.57g, 0.0157 mol), heated to 125°C under nitrogen, was added d_3-nitromethane (1g, 0.0157 mol), dropwise, with external cooling when necessary to maintain the temperature at 125-130°C. When the addition was complete the mixture was stirred for a further 5 minutes at that temperature. d_{10}-Cyclohexanone (1.38g, 0.013 mol) was added slowly to the mixture, which was heated, if necessary, to hold the temperature at 120-125°C. After 5 minutes stirring at that temperature the reaction was cooled to below 36°C and slowly neutralised with 28% ammonia solution. The mixture was then filtered under vacuum and the

filtrate extracted with chloroform (3x25mL). The combined chloroform extracts were dried over magnesium sulphate and the solvent removed by distillation at atmospheric pressure. Fractional distillation of the residue gave (**2**) as a straw coloured waxy solid; yield: 0.61g (39%); b.p. 155°C/10mm Hg (lit.[9] hexahydro-2H-azepin-2-one b.p. 139°C/12mm Hg); ν_{max} (film)/cm^{-1} 3420 (N-H), 2209, 2108 (C-D), and 1648 (C=O); m/z 125 (2%), 124 (22), 123 (100), 122 (12), 121 (2), 108 (44), 93 (18), 92 (26), 85 (24), and 83 (42). [Hexahydro-2*H*-azepin-2-one; MS: m/z 115 (1%), 114 (7), 113 (M^+, 100), 85 (55), 84 (53), 83 (23), 57 (54), and 55 (93).]

d_{25}-1-Chlorododecane

To freshly distilled thionyl chloride (4.52g, 0.038 mol) was added d_{25}-1-dodecanol (2g, 0.095 mol), with vigorous stirring under nitrogen, over a period of 2 hours. The mixture was then heated under reflux with continued stirring for 24 hours. The excess thionyl chloride was removed by distillation and the crude product purified by distillation to give d_{25}-1-chlorododecane; yield: 1.92g (88%), b.p. 120°C/10mm Hg; m/z 231 (0.8%), 230 (0.5), 229 (0.5), 228 (0.4), 115 (33), 101 (41), 99 (100), 67 (85), 63 (57), and 49 (93).

d_{35}-1-Dodecylhexahydro-2*H*-azepin-2-one (3)

This was prepared using an adaptation of the method of Marvel and Mayer.[10] To d_{11}-hexahydro-2*H*-azepinone (0.54g, 0.0044 mol) and sodium hydride (60% dispersion in oil, 0.176g, 0.44 mol) in *o*-xylene (20mL) under nitrogen was added 15-crown-5 (10 drops) and the mixture was refluxed with stirring for 10 hours. The mixture was then cooled and d_{25}-1-chlorododecane (1g, 0.0044 mol) dissolved in *o*-xylene (5mL) was added. The reaction mixture was refluxed for a further 6 hours and filtered hot. The solid obtained was washed with toluene (50mL) and the filtrate and washings were combined. The solvents were removed by distillation at 10 mmHg and the

product was isolated by fractional distillation to give (**3**) as a straw coloured liquid; yield: 0.63g (45%), b.p. 170°C/0.06 mmHg (lit.[1] 1-dodecylhexahydro-2*H*-azepin-2-one b.p. 160°C/0.1 mmHg). (Found: M^+, 316.4916, $C_{18}D_{35}NO$ requires M, 316.4916); ^2H NMR ($CHCl_3$) δ_D 0.82 (3D, s), 1.14 (18D, s), 1.5 (8D, m), 2.46 (2D, s), and 3.28 (4D, s); ν_{max} (film)/cm^{-1} 2197, 2099 (C-D), and 1639 (C=O); m/z 317 (4%), 316 (M^+, 33), 315 (14), 314 (7), 138 (100), and 89 (52). [1-Dodecylhexahydro-2*H*-azepin-2-one; MS: m/z 283 (1%), 282 (7), 281 (M^+, 33), 280 (2), 127 (54), 126 (100), and 98 (39).]

We are grateful to Dr. D.R. Kelly for help with the analysis of the mass spectra.

1. Hadgraft, J.; Williams, D.G.; Allen, G. In *Pharmaceutical Skin Penetration Enhancement*; Walters, K.A.; Hadgraft, J., Eds.; Marcel Dekker Inc., New York, 1993.
2. Ongpipattanakul, B.; Burnette, R.R.; Potts, R.O.; Francoeur, M.L. *Pharm. Res.* **1991**, 8, 350.
3. Casal, H.L.; Mantsch, H.H. *Biochem. Biophys. Acta* **1984**, 779, 381.
4. Watkinson, A.C.; Hadgraft, J. In *Mechanisms of Transdermal Drug Delievery*; Potts, R.O.; Guy, R.H., Eds.; Marcel Dekker Inc., New Yor, (in press).
5. Street, P.R. PhD Thesis, University of Wales College of Cardiff, 1993.
6. Farmer, P.B.; Foster, A.B.; Jarman, M.; Oddy, M.R.; Reed, D.J. *J. Med. Chem.* **1978**, 21, 514.
7. Himass. 15, copyright Dr. D.R. Kelly (Univ. of Wales, Cardiff), 1987-1994.
8. Novotny, A. 1951, U.S. Pat. 2,569,114; *Chem. Abs.* **1952**, 46, 5078).
9. Dictionary of Organic Chemistry, Eyre and Spottiswoode Ltd., London.
10. Marvel, C.S.; Mayer Jnr, W.W. *J. Org. Chem.* **1957**, 22, 1065.