Tetrahedron. Vol. 30, pp. 3933 to 3934. Pergamon Press 1974. Printed in Great Britain

PREPARATION OF ^{3}H-LABELLED ALCOHOLS BY REDUCTION OF CARBONYL COMPOUNDS WITH LITHIUM BOROHYDRIDE PARTIALLY HYDROLYSED WITH TRITIATED WATER

R. H. CORNFORTH

Shell Research Ltd., Milstead Laboratory of Chemical Enzymology, Sittingbourne Research Centre,
Sittingbourne, Kent, England

(*Received in the UK 13 June 1974; Accepted for publication 25 June 1974*)

Abstract—$LiBH_4$ partially hydrolysed with tritiated water in THF solution reduces carbonyl compounds to ^{3}H-labelled alcohols with a negligible amount of exchange of hydrogen in the α-position provided there is no additional activation of this position. The labile methylene H atoms of phenylacetaldehyde suffer about 2% exchange during reduction.

In a previous paper[1] concerned with the exchange of hydrogen attached to boron when $LiBH_4$ in THF solution reacts with hydroxylic compounds it was reported that partial hydrolysis of the $LiBH_4$ with tritiated water provided a convenient and cheap alternative to tritiated alumino- and boro- hydrides for the preparation of tritiated alcohols by reduction of carbonyl compounds. Only two such reductions were performed at the time, on benzophenone and ethyl phenylacetate; in the former case there are no exchangeable hydrogen atoms adjacent to the carbonyl group and in the latter the resulting phenylethanol would be expected to contain about 10% of the label in the 2-position, as indicated by mass spectrometry of the product from a parallel experiment using D_2O. The opinion was expressed that there should be no such exchange of α-hydrogens during the extremely rapid reduction of aldehydes and ketones and that probably exchange would not occur during reduction of an aliphatic ester, despite the much more vigorous conditions necessary for such reductions.

However, Caspi *et al.*[2] have found quite extensive (9%) incorporation of tritium on the 2-carbon atom during reduction of octanal with $LiBH_4$ partially hydrolysed with tritiated water. The experimental conditions differed considerably from those recommended[1]; in particular a suspension, rather than a solution, of $LiBH_4$ was employed. The author nevertheless thought it advisable to investigate a little further the extent of labelling in the 2-position when carbonyl compounds are reduced by the recommended procedure.

It was found that octanol from reduction of octanal contained only 0·05% of the total radioactivity in the 2-position, and octanol from methyl octanoate 0·14%. When phenylacetaldehyde, with its much more labile methylene hydrogen atoms, was reduced in the same way as octanal the resulting 2-phenylethanol contained 1·9% of the total label in the 2-position. For determination of the amount of label in the 2-position the alcohols were oxidised to the corresponding carboxylic acids with $Zn(MnO_4)_2 . 6H_2O$ in acetone; it has been shown in this laboratory[3] that there is no exchange of α-hydrogens during oxidation of aliphatic alcohols by this method.

Thus the usefulness of the method is confirmed for the reduction of carbonyl compounds not possessing additional activation of hydrogens on their α-carbon atoms.

EXPERIMENTAL

M.ps were taken on a microscope hot stage and are uncorrected. Samples were counted for radioactivity on a Packard Tri-carb Model 3775 liquid scintillation counter.

Solutions of $LiBH_4$ are made by refluxing, with magnetic stirring, suspensions in anhyd THF (freshly distilled from LAH) for 2·5 to 4 h, decanting the cooled soln from the residue into a dried measuring cylinder and allowing the suspended sediment to settle. The clear supernatant soln is estimated iodometrically by the method of Lyttle *et al.*[4] In a particular instance $LiBH_4$ (820 mg), refluxed for 2·5 h with anhyd THF (25 ml), gave an 0·62M soln. For estimation of solns up to 0·75M 1 ml of the soln is added to 0·5N NaOH (25 ml) and 0·25N KIO_3 (25 ml); KI (2g) and 4N H_2SO_4 (20 ml) are added and the liberated iodine is titrated with 0·1N $Na_2S_2O_3$. The molarity of the $LiBH_4$ is then

$$\frac{6{\cdot}25-0{\cdot}1\times \text{ml of }0{\cdot}1\text{ N } Na_2S_2O_3}{8}.$$

These solns can be kept for prolonged periods with little loss of titre if the stopper of the cylinder is greased and sealed externally with tape.

Preparation of tritiated borohydride reducing medium. An aliquot of a standardised soln (usually

0·5 – 0·7M) of $LiBH_4$ in anhyd. THF containing n mmoles of $LiBH_4$ was stirred magnetically during addition of n mmoles of tritiated water (specific activity 72 mCi mmole). The soln was refluxed for 1 h during which time a white solid precipitated; the mixture was then cooled and used for the reduction.

Reduction of octanal. A reducing mixture prepared from 1 mmole of $LiBH_4$ was cooled and well stirred during gradual addition of freshly distilled octanal (160 mg; 1·25 mmole) in dry Et_2O (1 ml), a further 1 ml Et_2O being used for washing in; the reducing power employed here was about 66% excess over the theoretical. After 30 min at room temperature the solvents were removed on a rotary evaporator; N HCl (1 ml) was added to the residue which was then heated at 80° for 5 min, cooled and treated with N NaOH (1 ml). The product was extracted with pentane; the pentane soln was washed with saturated NaCl soln, dried and evaporated to yield 155 mg of crude 1-^3H-octanol.

In an unlabelled experiment octanal (5 mmoles) was reduced in the same manner and gave a 95% yield of distilled octanol containing no trace of octanal (by IR or GLC on a 5' 10% Carbowax column).

A portion of the octanol (54 mg) was converted into the 3,5-dinitrobenzoate by the action of 3,5-dinitrobenzoyl chloride (100 mg) and pyridine (0·05 ml) in benzene (0·2 ml). The product was recrystallised twice from 60–80° petrol (1 ml) to give 104 mg m.p. 59·5–60·5°, specific radioactivity 4·61 mCi/mmole.

A soln of the remaining octanol (102 mg) in AR acetone (6 ml) was cooled in ice-water and stirred during addition of $Zn(MnO_4)_2 \cdot 6H_2O$ (264 mg) over 5 min. Stirring was continued for 1·5 h; H_2O (1·6 ml) and 5N H_2SO_4 (0·8 ml) were then added followed by 30% H_2O_2 (0·16 ml); the mixture was stirred until the MnO_2 had dissolved. The acetone was evaporated, water was added to the residue and the product was extracted with pentane; the pentane soln was washed twice with H_2O, then extracted with 2 ml N NaOH. The alkaline layer was acidified and the octanoic acid isolated by pentane extraction. The dried octanoic acid (75 mg) was dissolved in warm CH_2Cl_2 (1 ml) and added to a warm solution of dicyclohexylcarbodiimide* (110 mg) and *p*-toluidine (56 mg) in CH_2Cl_2 (2 ml). After 3 h the mixture was filtered from dicyclohexyl urea; the residue from evaporation of the filtrate was dissolved in Et_2O, washed with N NaOH, H_2O, N H_2SO_4 and H_2O. Evaporation of the dried ethereal soln left 150 mg which was dissolved in hot 60–80° petrol; the soln was filtered from insoluble material, concentrated to 1 ml and allowed to crystallise overnight. The crystals (75 mg, m.p. 62–5°) were recrystallised 3 times from 60–80° petrol to give 61 mg m.p. 66–7°, undepressed with an authentic sample of octanoic *p*-toluidide, m.p. 68°, prepared via the acid chloride. The specific activity was 0·0023 mCi/mmole, 0·05% of that of the octyl 3,5-dinitrobenzoate.

Reduction of methyl octanoate. A soln of methyl octanoate (158 mg; 1 mmole) in dry Et_2O (0·5 ml + 0·5 ml for washing in) was added to a reducing mixture prepared from 2 mmoles of $LiBH_4$ (100% excess reducing power) and the mixture was refluxed for 4 h; it had previously been determined, by GLC on a 5 ft. 10% Carbowax column of the product from an unlabelled experiment, that reduction was complete under these conditions. The reaction mixture was worked up as described above, yielding 119 mg of 1-$^3H_2$-octanol. A sample (20 mg) of the octanol was converted into the 3,5-dinitrobenzoate and the remainder was oxidised as described above to octanoic acid, which was then converted by the DCC method into the *p*-toluidide. Both derivatives were recrystallised 4 times from 60–80° petrol. The octyl 3,5-dinitrobenzoate had m.p. 59·5–60·5° and specific activity 10·42 mCi/mmole and the octanoic *p*-toluidide had m.p. 66–67° and specific activity 0·014 mCi/mmole. Thus 0·14% of the total radioactivity of the octanol was in the 2-position.

Reduction of phenylacetaldehyde. Freshly distilled phenylacetaldehyde (300 mg; 2·5 mmoles) in dry Et_2O (1 ml) was added gradually to a cooled, well stirred reducing mixture prepared from 2 mmoles $LiBH_4$ (giving 66% excess reducing power); a further 1 ml Et_2O was used for washing in. After 30 min at room temp N HCl (2 ml) was added slowly to the resulting slurry, the solvents were evaporated and the residue was heated at 80° for 5 min. The mixture was cooled, treated with N NaOH (2 ml) and extracted with Et_2O. The ethereal solution was washed with H_2O, dried and evaporated to yield 295 mg 1-^3H-2-phenylethanol.

A portion (27·6 mg) of the product was converted into the 3,5-dinitrobenzoate, which was recrystallised 4 times from EtOH to give 50 mg, m.p. 106–107°; sometimes a dimorphic crystalline form, m.p. 94–95°, not previously recorded, separated. The specific activity was 4·31 mCi/mmole.

The remainder of the phenylethanol (267·4 mg) in AR acetone (17·5 ml) was cooled in ice and stirred during addition of $Zn(MnO_4)_2 \cdot 6H_2O$ (737 mg) over 12 min. After a further 45 min H_2O (4·4 ml) and 5N H_2SO_4 (2·2 ml) were added, followed, gradually, by 30% H_2O_2 (0·44 ml). When the MnO_2 had dissolved the acetone was evaporated; water was added to the residue and the product was extracted with Et_2O. The ethereal soln was washed twice with water and then extracted with N NaOH (2 ml). The alkaline aqueous layer was acidified and extracted with Et_2O. Evaporation of the dried ethereal soln left 166 mg m.p. 44–46°; the methyl ester prepared from a representative sample with CH_2N_2 was shown by GLC on a 5 ft. 10% Carbowax column to be 75% methyl phenylacetate and 25% methyl benzoate. Three crystallisations of the mixture of acids from 60–80° petrol (0·8 ml, 1·5 ml, 0·5 ml) gave a pure sample (36 mg) of phenylacetic acid, m.p. 74–76°, giving only one peak on GLC of the methyl ester. The specific activity was 0·081 mCi/mmole, indicating that 1·9% of the radioactivity of the 2-phenylethanol was in the 2-position.

Acknowledgments—I thank Miss L. Bowen for skilled technical assistance and Miss J. C. M. Seton for the radioactivity measurements.

REFERENCES

[1] R. H. Cornforth, *Tetrahedron* **26**, 4635 (1970)

[2] B. Yagen, J. S. O'Grodnick, C. Tamm and E. Caspi; personal communication from E. Caspi prior to publication

[3] J. A. Schofield and J. C. Brown, unpublished work.

[4] D. A. Lyttle, E. H. Jensen and W. A. Struck, *Analyt. Chem.* **24**, 1843 (1952)

---

*Although the yield of *p*-toluidide obtained by this method is inferior to that via the acid chloride, it was used to avoid the remotest possibility of exchange of the α-hydrogen atoms.