Use of Debenzylation of Quaternary Benzylammonium Salts in the Synthesis of α-Deuteriated Tertiary Amines

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Simple syntheses are described of two deuteriated tertiary amines, namely *NN*-dimethyl-*p*-nitro[α-$^2H_2$]benzylamine and tri([1-$^2H_2$]ethyl)amine. The deuteriation step in the preparation of the former amine involves a selective exchange of the benzyl protons in dimethylbis-(*p*-nitrobenzyl)ammonium bromide by treatment with alkaline deuterium oxide. The second preparation requires [1-$^2H_2$]ethyl iodide, which is converted into benzyltri([1-$^2H_2$]-ethyl)ammonium iodide. The final, key step common to both syntheses is the debenzylation of the quaternary ammonium ion.

An α-deuteriated amine can often be synthesised by a reductive procedure, for example the reduction of an amide,[1] carbamate,[2] nitro-compound,[3] or nitrile[4] by lithium aluminium deuteride. Other methods include the conversion of an α-deuteriated carboxylic acid into the α-deuteriated primary amine *via* a Curtius rearrangement of the azide,[4] or the reaction of an amine or ammonia with labelled alkyl halide.[5] However, the utility of the latter reaction is frequently severely limited by the occurrence of quaternisation.

During our investigations into the mechanisms of oxidation of tertiary amines,[6] we have needed to synthesise a variety of deuteriated amines. However, the foregoing methods are unsuitable for the synthesis of either α-deuteriated tertiary amines with substituents which are reduced by hydride reducing agents, or tertiary amines of the type $(RCD_2)_3N$. We describe here the use of debenzylation of quaternary benzylammonium salts in the synthesis of two such α-deuteriated amines, namely *NN*-dimethyl-*p*-nitro[α-$^2H_2$]benzylamine (4) and tri([1-$^2H_2$]ethyl)amine (12).

In exploratory experiments two reactions that might have served as routes to *NN*-dimethyl-*p*-nitro[α-$^2H_2$]-benzylamine (4) were examined. The first involved the attempted selective reduction of the amide function of *NN*-dimethyl-*p*-nitrobenzamide by sodium borohydride and aluminium trichloride in bis-(2-methoxyethyl) ether. Brown and Subba Rao[7] report that this reducing system reacts readily with *NN*-dimethylbenzamide, but is unreactive towards nitrobenzene; however with the

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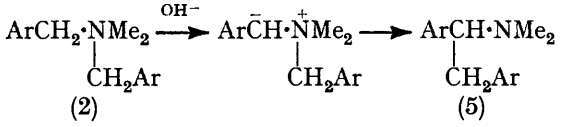
[6] D. H. Rosenblatt, M. M. Demek, and G. T. Davis, *J. Org. Chem.*, 1973, **37**, 4148; J. R. Lindsay Smith, R. O. C. Norman, and A. G. Rowley, *J.C.S. Perkin I*, 1973, 566; and previous papers in these series.
[7] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1956, **78**, 2582.

nitrobenzamide none of the desired *NN*-dimethyl-*p*-nitrobenzylamine (1) was obtained.

In the second procedure a suspension of *NN*-dimethyl-*p*-nitrobenzylamine (1) in alkaline deuterium oxide was heated to reflux under nitrogen in an attempt to exchange the benzyl protons for deuterons from the solvent. The mixture became homogeneous and changed colour from yellow to deep red; work-up showed that all the amine (1) had been consumed. When this reaction was repeated at room temperature the substrate was recovered unchanged.

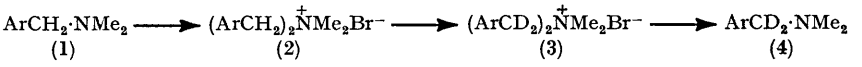
Aśperger and his co-workers [8] have shown that the protons α to the nitrogen atom in trimethyl(phenethyl)-ammonium salts do not exchange in basic deuterium oxide or in ethan[^{2}H]ol in the presence of ethoxide. Thus, we argued that in the trimethyl-(*p*-nitrobenzyl)-ammonium ion the methyl protons would be inactive to



exchange whereas the benzyl protons, being activated by the positive nitrogen atom and the *p*-nitrophenyl group, might be selectively exchanged for deuterium. A solution of trimethyl-(*p*-nitrobenzyl)ammonium iodide in basic deuterium oxide was heated to reflux; the ammonium salt was then recovered and found to be >95% deuteriated in the benzylic position. Attempted dealkylation by sodium benzenethiolate [9] gave no *NN*-dimethyl-*p*-nitro[α-^{2}H$_2$]benzylamine (4), presumably because the nucleophilic displacement occurs preferentially at the benzyl and not the methyl carbon atom.

These experiments showed the way to the successful synthetic route outlined in Scheme 1. Dimethylbis-(*p*-nitrobenzyl)ammonium bromide (2) was prepared from *NN*-dimethyl-*p*-nitrobenzylamine and *p*-nitrobenzyl bromide.

An investigation of the best conditions for deuterium exchange showed that in deuterium oxide no exchange occurs in the absence of base. Some deuterium is incorporated from hot basic deuterium oxide but another product is also formed. The latter was not fully characterised, but the n.m.r. and mass spectra of the protio-analogue obtained by heating dimethylbis-(*p*-nitrobenzyl)ammonium bromide (2) in aqueous sodium hydroxide show that it is probably deuteriated *NN*-dimethyl-4,4′-dinitrobibenzyl-α-ylamine (5), the product from a Stevens rearrangement. An attempt to repeat the exchange at room temperature proved unsuccessful, probably because the substrate is less soluble in cold water. However, by use of a mixed solvent system (deuterium oxide with dimethyl sulphoxide or dimethylformamide) the solubility problem was overcome and the required exchange occurred at room temperature in the presence of base. The dimethylformamide system was the more successful; the reaction in



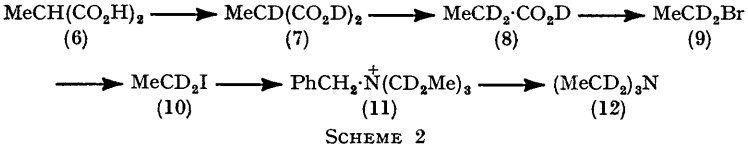
SCHEME 1

deuterium oxide–dimethyl sulphoxide produced significant amounts of an unknown product. After two exchanges the quaternary salt (3) was obtained in 79% yield with a deuterium incorporation of >95% in the benzylic positions.

The de-*p*-nitrobenzylation of the deuteriated quaternary salt (3) by sodium benzenethiolate in diethylene glycol [9] gave *NN*-dimethyl-*p*-nitro[α-^{2}H$_2$]benzylamine (4) in 47% yield with >95% benzylic deuteriation. In a small-scale experiment replacing the glycol with dimethylformamide improved the yield to *ca.* 80% without affecting the deuterium content of the amine (4).

The difference in behaviour of the two anions deuteri-oxide and benzenethiolate with dimethylbis-(*p*-nitrobenzyl)ammonium bromide is noteworthy. The former acts solely as a base, inducing exchange and the Stevens rearrangement *via* an ylide, whereas with the latter it is unlikely that the ylide is formed and the predominant reaction is a nucleophilic displacement.

In the synthesis of the tri([^{2}H$_2$]ethyl)amine the aim was to find a simple route utilising deuterium oxide as the source of deuterium. The initial steps involve the preparation of [1-^{2}H$_2$]ethyl iodide from methylmalonic acid; alternatively the deuteriated iodide is available commercially. The route chosen for the conversion of the iodide into the tertiary amine (12) involves formation of the benzyltriethylammonium salt followed by debenzylation. The advantages of the final steps of this route (over one involving the direct conversion of the iodide into the tertiary amine) are that they avoid the



SCHEME 2

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[9] J. McKenna, B. G. Hutley, and J. White, *J. Chem. Soc.*, 1965, 1729.

problem of quaternisation as a side reaction, they occur in high yield, and the intermediate ammonium salt can be readily purified by recrystallisation.

The methyl[$^2H_3$]malonic acid (7) was readily obtained from the protio-analogue (6) by exchange with deuterium oxide, and without purification was decarboxylated to [2-$^2H_2$]propionic [^{2}H]acid (8). The [$^2H_2$]ethyl bromide (9) (97·3% 1-deuteriation) was obtained from the propionic acid by the Hunsdieker procedure.[10] The ethyl iodide (10) was generated *in situ* and treated with benzylamine. In initial experiments potassium carbonate was used to neutralise the acid formed; however, improved yields (89·5%) were obtained when this was replaced by an excess of *N*-ethyldi-isopropylamine. In the final step sodium benzenethiolate was again used as the nucleophile in the debenzylation, and satisfactory yields were obtained by use of deuterium oxide as solvent. Methylmalonic acid (>98·5% α-^{2}H,*O*-$^2H_2$) gave triethylamine hydrochloride (>79% α-$^2H_6$) in an overall yield based on [1-$^2H_2$]ethyl bromide of over 50%.

EXPERIMENTAL

Analytical Methods.—^{1}H N.m.r. spectra were measured on a Perkin-Elmer R10 60 MHz and Varian A60A and A60D 60 MHz spectrometers. Mass spectrometry was carried out with an A.E.I. MS 12 spectrometer. I.r. spectra were recorded with a Unicam SP 200 spectrophotometer. A Pye series 104 chromatograph with glass columns (1·6 m × 4·0 mm) and a flame ionisation detector coupled to an RE 511 Goerz Servoscribe recorder was used for analytical g.l.c.

Attempted Reduction of NN-*Dimethyl*-p-*nitrobenzamide.*—*NN*-Dimethyl-*p*-nitrobenzamide, prepared by the method of Hallmann [11] from *p*-nitrobenzoyl chloride, had m.p. 95—96° (from water) (lit.,[12] 97°). Treatment of a solution of the amide in bis-(2-methoxyethyl) ether with sodium borohydride in the presence of aluminium chloride gave no *NN*-dimethyl-*p*-nitrobenzylamine.

Attempted Deuterium Exchange with NN-*Dimethyl*-p-*nitrobenzylamine* (1).—The amine (1) (0·5 g), prepared by the method of Craig *et al.*,[13] was heated to reflux in alkaline deuterium oxide (Ryvan Chemical Co. Ltd., 99·8%). On cooling no amine was recovered.

Trimethyl-(p-*nitro*[α-$^2H_2$]*benzyl*)*ammonium Iodide.*—Trimethyl-(*p*-nitrobenzyl)ammonium iodide, prepared by the method of Stedman,[14] had m.p. 204—206° (lit.,[14] 198°), τ [$(CD_3)_2SO$] 1·6 (2H, d), 2·05 (2H, d), 5·15 (2H, s), and 6·85 (9H, s). The ammonium iodide (0·53 g) with sodium hydroxide (0·21 g) was heated to reflux in deuterium oxide (5 ml). On cooling orange crystals (0·26 g) of the [$^2H_2$]-benzylammonium iodide (deuterium content >95%) were obtained. Recrystallisation failed to remove the coloured impurity.

Dimethylbis-(p-*nitrobenzyl*)*ammonium Bromide* (2).—*NN*-Dimethyl-*p*-nitrobenzylamine (1) (18 g) and *p*-nitrobenzyl bromide (21·6 g) were dissolved in methanol (150 ml) and refluxed for 3 h. On cooling, off-white crystals of the ***ammonium bromide*** (2) were obtained (36·0 g, 91%); m.p. (from methanol) 222—224°, τ [$(CD_3)_2SO$] 1·6 (4H, d), 2·0 (4H, d), 5·0 (4H, s), and 6·95 (6H, s) (Found: C, 48·7; H, 4·6; Br, 20·7; N, 10·6. $C_{16}H_{18}BrN_3O_4$ requires C, 48·5; H, 4·6; Br, 20·2; N, 10·6%).

Dimethylbis-(p-*nitro*[α-$^2H_2$]*benzyl*)*ammonium Bromide* (3).—After preliminary experiments using deuterium oxide with dimethylformamide the following large-scale procedure was adopted. The bromide (2) (24 g) was dissolved with warming in dimethylformamide (192 ml), deuterium oxide (144 ml) was added, and the solution was cooled. Concentrated potassium hydroxide (5 ml) was added slowly with cooling and the mixture was kept for 24 h at 0°. The green crystals that formed were removed and dried (14·2 g). Cooling the filtrate with ice gave a further batch of crystals (1·1 g). The remaining filtrate was made slightly acidic with concentrated hydrochloric acid and concentrated. Cooling gave a third batch of crystals (6·7 g). These materials (22 g, 93%), which contained a small amount of deuteriated *NN*-dimethyl-4,4′-dinitrobibenzyl-α-ylamine, had 90—96% deuterium incorporation in the benzylic position. After a second exchange, the product (3) was obtained with a deuterium content of 95—98% in an overall yield of 79%.

Stevens Rearrangement of Dimethylbis-(p-*nitrobenzyl*)-*ammonium Bromide* (2).—The ammonium salt (2) (1 g) was dissolved in boiling water (25 ml) containing concentrated potassium hydroxide (0·25 ml) and the mixture was maintained at 100° for 0·5 h. The red-brown solid that formed on cooling was collected and dissolved in methanol; the solution was filtered and evaporated to give a slightly impure product, m.p. 179—187°; τ 1·90 (4H, m), 2·78 (4H, m), 6·3—7·3 (3H, m), and 7·74 (6H, s); *m/e* 315 (M^+).

NN-*Dimethyl*-p-*nitro*[α-$^2H_2$]*benzylamine* (4).—(*a*) The ammonium bromide (3) (16 g) was dissolved in diethylene glycol (150 ml) and a solution of sodium benzenethiolate (26·6 g) in diethylene glycol (95 ml) was added. The mixture was heated to 100° and allowed to cool before water (250 ml) was added followed by 6M-hydrochloric acid (600 ml). The acidic solution was extracted with ether, then made strongly alkaline, and the organic bases were extracted into ether. This second extract was dried ($MgSO_4$) and evaporated and the residue was distilled to give the product (4·9 g; b.p. 120—135° at 15 mmHg). G.l.c. showed the distillate to contain some diethylene glycol, which was removed by dissolving all the material in acid and repeating the extraction procedure. A second distillation gave *NN*-dimethyl-*p*-nitro[α-$^2H_2$]benzylamine (4) (3·4 g, 47%) with >95% deuteriation at the benzylic positions; b.p. 133—135° at 13 mmHg.

(*b*) Sodium benzenethiolate (0·28 g) was added to the ammonium bromide (3) (0·2 g) dissolved in dimethylformamide (5 ml). The purple solution was kept at room temperature for 15 min and then poured into 2M-hydrochloric acid to give a pale yellow emulsion. The acidic solution was extracted with ether, made strongly alkaline, and re-extracted with ether. The latter extract was dried and concentrated; analysis by g.l.c. and g.l.c.–mass spectrometry showed that it contained *NN*-dimethyl-*p*-nitro-[α-$^2H_2$]phenylamine (4) (0·073 g, 80%) with 97% deuteriation in the benzylic positions.

Methyl[$^2H_3$]*malonic Acid* (7).—Methylmalonic acid (59 g) in deuterium oxide (60 ml) (Diaprep Incorporated; 99·8%) was heated at 55° for 18 h. The deuterium oxide was

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[11] F. Hallmann, *Ber.*, 1876, **9**, 846.
[12] H. Wenker, *J. Amer. Chem. Soc.*, 1938, **60**, 1081.
[13] J. C. Craig, N. Y. Mary, and L. Wolf, *J. Org. Chem.*, 1964, **29**, 2868.
[14] E. Stedman, *J. Chem. Soc.*, 1927, 1902.

recovered by vacuum distillation and this exchange procedure was repeated three times to give methyl[$^2H_3$]malonic acid (7), which was shown by n.m.r. spectroscopy to have a deuterium content of >98·5%.

[2-$^2H_2$]*Propionic* [^{2}H]*Acid* (8).—The crude deuteriated acid (7) from the previous stage was heated in an oil-bath at 140—180° in a flask set up for distillation with a Vigreux column and a drying tube ($CaCl_2$) attached to the receiver. The product, which contained some water, was taken up in ether; the solution was dried (Na_2SO_4) and the ether was removed by flash distillation over a steam-bath. The residue was distilled through a spinning-band column to give the [$^2H_3$]propionic acid (8) (29·0 g, 78%).

[1-$^2H_2$]*Ethyl Bromide* (9).—The procedure used was a modification of that of Meek and Osuga [10] for the synthesis of cyclopropyl bromide. A solution of the [$^2H_3$]propionic acid (8) (29 g) and bromine (22 ml) in tetrachloroethane (100 ml) was added dropwise over 1·5 h with stirring to a suspension of mercury(II) oxide (52 g) in tetrachloroethane (120 ml) heated to 50—70°. The mixture was connected *via* a reflux condenser to a trap cooled in solid CO_2–acetone. Heating was continued for a further 0·5 h before the contents of the trap were added to the reaction mixture, and the combined mixture was chilled and filtered through a sintered glass funnel into a chilled flask. The precipitate was washed with a few ml of tetrachloroethane and the combined filtrate and washings were treated with water and small portions of sodium disulphite until they were colourless. The organic layer was then washed with aqueous sodium hydrogen carbonate and water and dried ($CaCl_2$) before distillation through a short Vigreux column. All material of b.p. <120° was collected and redistilled through a spinning-band column to give [1-$^2H_2$]ethyl bromide (9) (21·07 g, 50%), b.p. 35—37° (lit. for protio-analogue,[15] 38°). Analysis by n.m.r. spectroscopy showed the product to be 97·3% α-deuteriated.

Benzyltri([1-$^2H_2$]*ethyl*)*ammonium Iodide* (11).—The [$^2H_2$]-ethyl bromide (9) (19·5 g) was stirred for 15 h with sodium iodide (36 g) in acetonitrile (250 ml). The precipitate was filtered off and washed with a little acetonitrile, and the washings with the filtrate were added to benzylamine (4·2 g) and *N*-ethyldi-isopropylamine (12·3 g) and refluxed for 23 h. The acetonitrile was removed under vacuum and the residue was taken up in water (50 ml). After addition of potassium carbonate (14 g) the solution was first extracted with ether (3 × 50 ml) and then treated with sodium iodide (14 g) and extracted with methylene chloride (3 × 50 ml). The combined methylene chloride solutions were washed with water (25 ml), dried (Na_2SO_4), and evaporated to give the crude ammonium iodide (11), which after recrystallisation from propan-2-ol (yield 10·8 g, 85%) had m.p. 140—158°.

The impure salt was redissolved in water, treated with potassium carbonate (5 g), and extracted with ether (3 × 50 ml). The aqueous layer, after addition of sodium iodide (10 g), was extracted with methylene chloride (3 × 50 ml) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was recrystallised to give benzyltri([1-$^2H_2$]ethyl)ammonium iodide (11) (8·58 g, 67%), m.p. 165—168° (from propan-2-ol). N.m.r. spectroscopy showed this material to be 96·8% α-deuteriated in the ethyl groups.

Repetition of this procedure with commercial [1-$^2H_2$]-ethyl iodide (50·65 g) (Stohler Isotope Chemicals Inc.; 99·8%) gave the ammonium iodide (11) (25·92 g, 89·5%), m.p. 163—167° (lit. for protio-analogue,[16] 170°).

Tri([1-$^2H_2$]*ethyl*)*amine Hydrochloride*.—The ammonium salt (11) (25·92 g) was added to a solution of sodium hydroxide (10·8 g) and benzenethiol (33 ml) in deuterium oxide (105 ml), and the mixture was refluxed for 20 h. After cooling, the solution was acidified with concentrated hydrochloric acid (45 ml) and extracted with ether (3 × 100 ml). The aqueous layer together with a back-washing of the combined ethereal extracts (50 ml) was basified with sodium hydroxide (75 g) in water (50 ml) and the amine was distilled into a chilled receiver. The chilled distillate was treated with concentrated hydrochloric acid (30 ml) and evaporated to dryness. The residue was recrystallised to give tri([1-$^2H_2$]ethyl)amine hydrochloride (12) (8·37 g, 73·0%), m.p. 256—259° [lit. for protio-analogue,[17] 246—251°, and [18] 260° (decomp.)].

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