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The Preparation of Deuterated Organic Compounds from Activated Organic Halides by Reduction with Zinc–Deuterium Oxide[1]

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Reductive elimination of halogen from α-halo esters with zinc and deuterium oxide in polar aprotic solvents provides a convenient method for the preparation of the corresponding α-deuterated substances. The procedures developed for carrying out these transformations can be applied to the synthesis of large quantities of either mono- or dideuterated esters with good isotopic purity. Several isolated experiments suggest that this method should also be applicable to the conversion of α-halogenated nitriles and amides to the corresponding α-deuterated materials; when applied to the reductive deuteration of α-halogenated ketones and acid chlorides, the isotopic purities of the deuterated products are lower. This technique for the synthesis of α-deuterated esters is superior to the base-catalyzed exchange techniques in general use when the prerequisite α-halogenated analogs are available, both in its economical use of deuterium oxide and in its ability to introduce a single deuterium atom into a methyl or methylene group containing multiple equivalent exchangeable protons.

The acid- or base-catalyzed exchange of enolizable protons for deuterons is a widely used technique in isotopic synthesis.[3] Despite its simplicity and convenience, this technique suffers from two important disadvantages. First, the achievement of high isotopic purity by exchange requires multiple treatments of the substrate with deuterium oxide, itself of high isotopic purity, and is accordingly intrinsically wasteful of deuterium. Second, it is not suitable for the introduction of a specified number of deuterium atoms into a position containing a larger number of equivalent exchangeable hydrogens.[4]

In the course of other work, we required quantities of mono- and dideuterated alkyl halides having high isotopic purity. In an effort to circumvent exchange procedures for the preparation of these materials, we investigated the utility of synthetic methods for introducing deuterium based on the reductive elimination of halogen from α-halo carbonyl and nitrile derivatives with metallic zinc in the presence of deuterium oxide.[5] Here we report that this procedure provides a useful method for the preparation of esters, and probably of amides and nitriles, containing deuterium next to the unsaturated group; when applied to ketones the isotopic purity of the product is lower, and other procedures for the introduction of deuterium are presumably preferable to that described here.[3,6]

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(3) A Murray, III, and D. L. Williams, "Organic Syntheses with Isotopes, Part II," Interscience, New York, N. Y., 1958; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry, Alkaloids," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 2; M. Fetizon and J. Gramain, *Bull. Soc. Chim. Fr.*, 651 (1969); F. Asinger and H. H. Vogel, in "Methoden der Organischen Chemie," 4th ed, Vol 5/1a, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1970, pp 598–626; A. F. Thomas, "Deuterium Labeling in Organic Chemistry," Appleton-Century-Crofts, New York, N. Y., 1971.

(4) For a kinetic treatment of sequential exchange, see C. Rappe, *Acta Chem. Scand.*, **20**, 2236 (1966).

(5) Dehalogenation of α-halo ketones with zinc–acetic acid-*O-d* has been used previously to prepare α-deuterio ketones; *cf.*, for example, E. J. Corey and G. A. Gregoriou, *J. Amer. Chem. Soc.*, **81**, 3127 (1959); E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956); R. R. Sauers and C. K. Hu, *J. Org. Chem.*, **36**, 1153 (1971).

(6) J. Hooz and D. M. Gunn, *J. Amer. Chem. Soc.*, **91**, 6195 (1969); J. P. Schaefer and D. S. Weinberg, *Tetrahedron Lett.*, 1801 (1965); J. Deutsch and A. Mandelbaum, *ibid.*, 1351 (1969); K. Kuhlein, W. P. Neumann, and H. Mohring, *Angew. Chem., Int. Ed. Engl.*, **7**, 455 (1968) [for a more detailed description of the procedure for preparation of $(C_4H_9)_3SnD$ than that given in this paper, see G. M. Whitesides and J. San Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 6611 (1970)]; M. Wahren, P. Hädge, H. Hubner, and M. Mühlstadt, *Isotopenpraxis*, **1**, 65 (1965); N. P. Buu-Hoi, N. Dat Xuong, and N. van Bac, *Bull. Chim. Soc. Fr.*, 2442 (1963); M. F. Semmelhack, R. J. DeFranco, and J. Stock, *Tetrahedron Lett.*, 1371 (1972).

Results and Discussion

Reductions were carried out by adding the organic halide (1 equiv) and deuterium oxide (~2–4 equiv) to zinc powder (~2 equiv) at 80° in diglyme or dimethoxyethane. Traces of exchangeable protons present in the reaction apparatus or on the zinc powder were exchanged for deuterium before addition of the organic halide by addition of deuterium oxide to the reaction flask containing the zinc and azeotropic distillation of this small initial charge of deuterium oxide from the reaction flask with benzene. The surface of the zinc was cleaned before this exchange by a brief washing with 5% hydrochloric acid; it was sometimes activated immediately before addition of the organic halide by reaction with iodine or 1,2-dibromoethane. The reductions frequently showed an induction period, particularly with less reactive organic chlorides; in certain instances, particularly those involving nitriles, these induction periods were capable of contributing to a significant decrease in the isotopic purity of the products if sufficiently prolonged, presumably by permitting isotopic exchange in the starting materials; further, accumulation of an excessive quantity of unreacted halide in the reaction flask during a lengthy induction period occasionally led to embarassingly exothermic reactions when initiation finally did take place. Thus, cleaning and activating the zinc surface, and checking to make certain that the reaction was initiated early in the addition of the organic halide (with appropriate use of 1,2-dibromoethane or iodine as initiating agents if necessary), were important in achieving high yields and isotopic purities.

Representative yields and isotopic purities obtained following this procedure are listed in Table I. To avoid obtaining inaccurate mass spectroscopic isotopic compositions as a result of exchange of deuterium for hydrogen in the mass spectrometer inlet system, the substances isolated directly from the reductions were converted to nonexchangeable derivatives more suitable for isotopic analysis (and for several types of further synthetic manipulation). These derivatives are also listed in Table I, and appropriate details of their preparation are described in the Experimental Section.

The significant conclusion to be drawn from the data of Table I is that the reductive dehalogenation of activated organic halides provides an attractive synthetic route to deuterated organic compounds. The

TABLE I

YIELDS AND ISOTOPIC PURITIES OF PRODUCTS OBTAINED ON DEHALOGENATION OF ACTIVATED ORGANIC HALIDES USING ZINC–DEUTERIUM OXIDE

Starting material	Yield,[a] %	Substrate[b]	Isotopic compn, % d_0	d_1	d_2	d_3
$ClCH_2CO_2$-*n*-C_3H_7	17	DCH_2CH_2I	2.5	96.0	1.5	
$Cl_3CCO_2CH_3$	63	$D_3CCH_2CH_2CH_2Br$		1.5	6.5	92.0
$BrCH_2CO_2$-*n*-C_3H_7	52	DCH_2CH_2I	2.0	98.0		
$CH_3CH_2CHBrCO_2C_2H_5$	50	$CH_3CH_2CHDCH_2Br$	1.4	98.6		
$CH_3CH_2CCl_2CO_2C_2H_5$	73	$CH_3CH_2CD_2CH_2Br$		2.4	97.6	
$C_2H_5OCO(CH_2)_3CHBrCO_2C_2H_5$	58	$Br(CH_2)_4CHDCH_2Br$	2.1	97.9		
$ClCH_2CN$	47	$DCH_2CH_2NH_2$	2.0	94.0	4.0	
$CH_3CH_2CCl_2CN$	76	$CH_3CH_2CD_2CH_2NH_2$		1.0	99.0	
$BrCH_2CON(C_6H_5)C_2H_5$	36	$DCH_2CH_2N(C_6H_5)C_2H_5$	7.0	93.0		
$ClCH_2COCl$	51[c]	DCH_2CH_2I	2.0	82.0	15.0	1.0
$ClCH_2COCH_3$	61	$DCH_2CHBrCH_3$	9.0	50.0	34.0	7.0

[a] Isolated yields of the products obtained by zinc–deuterium oxide reduction of the starting materials. [b] Substances on which the mass spectroscopic isotopic composition measurements were performed. [c] Acetic acid-d_2 was the isolated product.

procedure works best for esters,[7] and less well for the more acidic (and more rapidly exchangeable) ketones and nitriles. Since α-halogenated esters are relatively readily available using a number of synthetic techniques,[8] this procedure seems to provide the method of choice for preparation of specifically α-deuterated esters and derivatives.

Experimental Section

General Methods.—Nmr spectra were recorded using a Varian T-60 spectrometer in carbon tetrachloride solutions; chemical shifts are reported in parts per million (δ) from tetramethylsilane. Mass spectra were determined on a Hitachi Perkin–Elmer model RMU 6 spectrometer. Preparative glpc analyses were performed on a Hewlett–Packard Model 700 chromatograph with a thermal conductivity detector using the following columns: column A, 8-ft, 0.25-in. 10% DEGS on 60–80 mesh Chromosorb W; column B, 10-ft, 0.25-in. 10% Carbowax 20M on 60–80 mesh Chromosorb P; column C, 8-ft, 0.25-in. 5% SE-30 on 60–80 Chromosorb P; column D, 8-ft, 0.25-in. 10% XF-1150 on 60–80 mesh Chromosorb P.

Diglyme was distilled from calcium hydride, and degassed before use by bubbling a slow stream of nitrogen through it for 20 min. Dimethoxyethane (DME) was purified by distillation from a deep purple solution of sodium benzophenone dianion. The 2,2-dichlorobutyronitrile used was a gift of the Dow Chemical Co. Other halogenated ketones, esters, nitriles, and acid halides were obtained from Eastman Organic Chemicals, and were used without further purification. Reagent grade zinc dust (Mallinkrodt) was generally used without further purification, although activation with 10% hydrochloric acid is advisable for zinc dust which has been opened to air for considerable lengths of time.[9]

Isotopic compositions were determined mass spectrometrically on samples purified by preparative glpc. All spectra for isotopic analysis were obtained using ionizing voltages as close as possible to the appearance potential of the compound under examination. Isotopic compositions were normally obtained from peak area data; however, indistinguishable data resulted from analysis of peak heights. During collection of compounds from the glpc care was taken to collect all of the peak of interest, to avoid isotopic fractionation.[10]

Ethyl Butyrate-2-d_1.—Reagent zinc dust (130 g, 2 g-atoms), diglyme (300 ml) freshly distilled from calcium hydride, and benzene (200 ml) were placed in a 1-l., three-necked flask fitted with a Dean-Stark trap and a mechanical stirrer. One neck of the flask was sealed with a No-Air stopper. The mixture was heated to reflux and 15 ml of deuterium oxide was added dropwise over the course of 2 hr to exchange possible sources of protons. Recovery of water (15 ml) from the Dean-Stark trap was complete. The Dean-Stark trap was removed, benzene was separated from the reaction mixture by simple distillation, a reflux condenser was fitted to the apparatus, and 10 ml of deuterium oxide was added. The reaction mixture was heated to 80° and ethyl 2-bromobutyrate (2 ml) was added. An immediate 5–10° temperature rise indicated initiation of the reaction. The reaction flask was immersed in a large ice bath. The internal temperature of the reaction flask was maintained at 50–60° by cautious alternate addition of aliquots of ethyl 2-bromobutyrate (226 g, 1.16 mol) and deuterium oxide (80 g, 4.0 mol); each reagent was added in 12 equal portions.

Glpc analysis using column A at 100° showed that ethyl 2-bromobutyrate was reduced as rapidly as it was added to the reaction mixture. At the conclusion of the reaction, excess zinc and insoluble zinc salts were filtered from the reaction mixture and washed with two 100-ml portions of ether. The ether washes and diglyme solution were combined, and the product was isolated by a preliminary distillation. Material boiling between 50 and 160° was dried ($MgSO_4$) and carefully redistilled, yielding ethyl butyrate-2-d_1 (67 g, 0.58 mol, 50%) having bp 120–121°. The nmr spectrum was consistent with the proposed deuterium substitution.

1-Butanol-2-d_1 was prepared from ethyl butyrate-2-d_1 (67 g, 0.58 mol) dissolved in ether (50 ml) by dropwise addition to a solution of lithium aluminum hydride (25 g, 0.62 mol) in 300 ml of ether at 0°. The mixture was refluxed for 30 min, quenched with ethyl acetate (50 g, 0.56 mol), water (25 ml), 15% (w:w) aqueous sodium hydroxide (25 ml), and additional water (75 ml). The ether was decanted and the residual aluminum salts were refluxed with two 100-ml portions of ether. The ethereal solutions were combined, and distilled through a 120-cm platinum spinning band column to yield 1-butanol-2-d_1 (24 g, 0.32 mol, 55%) having bp 116–118°.

1-Butanol-2,2-d_2 was prepared from ethyl 2,2-dichlorobutyrate (145 g, 0.81 mol) and deuterium oxide (80 g, 4 mol) by zinc reduction and subsequent treatment with lithium aluminum hydride as described previously.[11]

Ethanol-2,2,2-d_3 was prepared from methyl trichloroacetate (176 g, 1.0 mol) and deuterium oxide (88 g, 4.4 mol) by zinc re-

(7) Side products formed in the reaction were not investigated; however, they are probably similar to those formed in the Reformatsky reaction. *Cf.* W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965); T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967); R. L. Shriner, *Org. React.*, **1**, 4 (1942); M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).

(8) For representative references, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 155–156; A. Markovac and S. F. MacDonald, *Can. J. Chem.*, **43**, 3364 (1965); H. Reinheckel, *Chem. Ber.*, **93**, 2222 (1960); B. Castro, J. Villieras, and N. Ferracutti, *Bull. Soc. Chim. Fr.*, 3521 (1969); H. J. Ziegler, L. Walgraeve, and F. Binon, *Syn.*, **1**, 39 (1969); H. Reinheckel, *J. Prakt. Chem.*, **15**, 260 (1962); H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Amer. Chem. Soc.*, **90**, 1911 (1968); E. E. Smissman, *ibid.*, **76**, 5805 (1954); J. G. Gleason and D. N. Harpp, *Tetrahedron Lett.*, 3431 (1970); H. Staudinger, E. Anthes, and H. Schneider, *Chem. Ber.*, **46**, 3539 (1939); A. Roedig, N. Kreutzkamp, H. Meerwein, and R. Stroh, in "Methoden der Organischen Chemie," 4th ed, Vol. V/4, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1960, pp 197–212.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1276.

(10) For a discussion of the calculation of isotopic compositions by mass spectroscopy, see K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962.

(11) G. M. Whitesides, J. F. Gaasch, and E. R. Stedronsky, *J. Amer. Chem. Soc.*, **94**, 5258 (1972).

duction followed by lithium aluminum hydride reduction as described previously.[12]

1-Bromoethane-*2,2,2-d*$_3$, **1-bromobutane-*2,2-d*$_2$**, and **1-bromobutane-*2-d*$_1$** were prepared from the analogous alcohols using a procedure similar to that described by Marvel and Kamm.[13] Thus, ethanol-*2,2,2-d*$_3$ (18 g, 0.36 mol) was added to a cooled mixture of 48% hydrobromic acid (82 g) and concentrated sulfuric acid (24 g) in a 250-ml single-necked flask. Concentrated sulfuric acid (40 g) was added, and the stirred mixture was warmed gently to distill the product as it formed into a trap cooled in a Dry Ice–acetone bath. The trap and its contents were warmed to 0° and the aqueous layer was removed using a Pasteur pipet. The organic layer was washed with two 10-ml portions of water and several 10-ml portions of concentrated sulfuric acid until the sulfuric acid layer remained clear and water white. Most of the sulfuric acid was removed using a Pasteur pipet, and the 1-bromoethane-*2,2,2-d*$_3$ (37 g, 0.33 mol, 91%) was separated from the residual concentrated sulfuric acid by bulb-to-bulb distillation at reduced pressure. The nmr of the distilled material consisted of a broadened singlet at δ 3.4.

1-Butanol-*4,4,4-d*$_3$ was prepared in 52% yield by reaction of ethyl-*2,2,2-d*$_3$-magnesium bromide with ethylene oxide, using a procedure analogous to that described by Huston and Langham.[14]

***n*-Propyl 2-Chloroacetate.**—*n*-Propyl alcohol (60 g, 1 mol) was placed in a 250-ml, three-necked, round-bottomed flask equipped with a dropping funnel, Teflon-coated magnetic stirring bar, and adaptor leading to a bubbler. The apparatus was flushed with nitrogen, and cooled to −15° in a Dry Ice–isopropyl alcohol bath. Chloroacetyl chloride (38 ml, 57 g, 0.5 mol) was added to the stirred reaction mixture over a period of 2 hr. The cooling bath was maintained at −20 to −10° by the occasional addition of Dry Ice. The mixture was allowed to warm to room temperature, then distilled through a 6-in. Vigreux column to yield *n*-propyl 2-chloroacetate (57.4 g, 0.42 mol, 84%): bp 75° (22 Torr) [lit.[15] bp 52.6–52.8° (10 Torr)]; nmr (CCl_4) δ 0.92 (t, 3, J = 6 Hz), 1.58 (m, 2, J = 6 Hz), 4.17 (m, 4, J = 6 Hz).

***n*-Propyl 2-bromoacetate** was prepared by a procedure analogous to that used in the synthesis of *n*-propyl 2-chloroacetate. From bromoacetyl bromide (100 g, 0.5 mol) and *n*-propyl alcohol (60 g, 1.0 mol), 67.8 g of *n*-propyl 2-bromoacetate (0.38 mol, 75%) was obtained: bp 79° (19 Torr) [lit.[16] bp 175–177° (762 Torr)]; nmr (CCl_4) δ 0.95 (t, 3, J = 6 Hz), 1.60 (m, 2, J = 6 Hz), 3.90 (s, 2), 4.07 (t, 2, J = 6 Hz).

***n*-Propyl Acetate-*2-d*$_1$.**—The experimental apparatus and procedure were similar to those described for ethyl butyrate-*2-d*$_1$. Zinc dust (32.7 g, 0.5 g-atom) was treated with 5 ml of deuterium oxide in a mixture of 60 ml of benzene and 100 ml of diglyme. After removal of the benzene and deuterium oxide, the reaction mixture was heated to 80°, and 5 ml of deuterium oxide, a crystal of iodine, and 2 ml of 1,2-dibromoethane were added. *n*-Propyl 2-chloroacetate (34.4 g, 0.25 mol) diluted with *ca.* 4 ml of 1,2-dibromoethane and additional deuterium oxide were added in 10 portions over 1 hr by syringe, *ca.* 1 ml of deuterium oxide being added after each 3.3-ml aliquot of ester; the total quantity of deuterium oxide used by the end of the reaction was 16.5 ml (15 g, 0.75 mol). The mixture was stirred and heated an additional 15 min. The apparatus was arranged for distillation and the first 35 ml of material distilling under an aspirator vacuum (∼22 Torr) was collected. The distillate consisted of two phases; the aqueous phase was saturated with sodium chloride and extracted three times with 30-ml portions of ether. The organic phases were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column, yielding *n*-propyl acetate-*2-d*$_1$ (4.3 g, 0.042 mol, 17%): bp 100–102°; nmr (CCl_4) δ 0.92 (t, 3, J = 6 Hz), 1.52 (m, 2, J = 6 Hz), 1.92 (t, 2, J = 2 Hz), 3.95 (t, 2, J = 6 Hz).

n-Propyl acetate-*2-d*$_1$ (13.3 g, 0.13 mol, 52%) was also prepared from *n*-propyl 2-bromoacetate (45 g, 0.25 mol) using an analogous procedure.

Ethanol-*2-d*$_1$.—Lithium aluminum hydride (1.5 g, 0.04 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, reflux condenser, and Teflon-coated magnetic stirring bar. To the stirred mixture was added dropwise through a syringe *n*-propyl acetate-*2-d*$_1$ (3.9 g, 0.038 mol) diluted with ether (15 ml). The mixture was refluxed an additional 2 hr, and water (1.5 ml), 15% (w:w) aqueous sodium hydroxide (1.5 ml), and additional water (4.5 ml) were cautiously added dropwise by syringe to the well-stirred slurry. The white aluminum salts were separated by suction filtration and washed with ether. The aluminum salts were then extracted overnight with an additional 50 ml of ether in a Soxhlet extractor. The ether portions were combined, dried ($MgSO_4$), and distilled to yield ethanol-*2-d*$_1$, (0.8 g, 0.017 mol, 45%), bp 78–79°.

1-Iodoethane-*2-d*$_1$ was prepared from ethanol-*2-d*$_1$ using a procedure based on that of Stone and Shechter,[17] and purified for isotopic analysis by preparative glpc using column C.

Diethyl 2-bromoadipate was synthesized in 77% yield using a literature procedure.[18] Its conversion to **diethyl adipate-*2-d*$_1$** was accomplished on a 30-g scale (58% yield) using a procedure analogous to that described for *n*-propyl acetate-*2-d*$_1$. **1,6-Hexanediol-*2-d*$_1$** and **1,6-dibromohexane-*2-d*$_1$** were obtained by procedures analogous to those described above for other alcohols and bromides.

Acetonitrile-*d*$_1$.—Zinc dust (43.5 g, 0.66 g-atom) was treated with 8 ml of deuterium oxide in a mixture of 100 ml of diglyme and 60 ml of benzene. After removal of the benzene and deuterium oxide by azeotropic distillation, 5 ml of deuterium oxide was added, the mixture was heated to 80°, and a crystal of iodine and 3 ml of 1,2-dibromoethane[19] were added. Chloroacetonitrile (18.8 g, 0.24 mol) and additional deuterium oxide (13 ml; the total quantity added was 18 ml, 20 g, 1 mol) were added in successive portions of 1 ml and 1.2 ml, respectively. The mixture was stirred and heated for an additional 15 min. The apparatus was arranged for distillation and the first 25 ml of material distilling under an aspirator vacuum (∼22 Torr) was collected. Ether (20 ml) was added to this distillate, the organic layer was separated, and the aqueous layer was saturated with sodium chloride and extracted twice with 20-ml portions of ether. The organic fractions were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column to yield acetonitrile-*d*$_1$ (4.7 g, 0.11 mol, 47%), bp 81–82°, nmr δ 1.98 (t, J = 2 Hz).

Ethylamine-*2-d*$_1$.—Lithium aluminum hydride (4.5 g, 0.12 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a reflux condenser and Teflon-coated magnetic stirring bar. One neck of the flask was fitted with a No-Air stopper. Acetonitrile-*d*$_1$ (4.6 g, 0.11 mol) diluted with ether (20 ml) was added dropwise from a syringe to the stirred mixture. After the mixture had refluxed an additional hour, the condenser top was fitted with an adaptor leading to a receiver cooled to −78°. Cautious addition of water (4.5 ml), 15% (w:w) aqueous sodium hydroxide solution (4.5 ml), and additional water (13.5 ml) resulted in the liberation of ethylamine-*d*$_1$, bp 17°, which condensed in the cold trap. Significant amounts of ether were also swept over. The cold ether solution of ethylamine-*d*$_1$ was treated with dry gaseous hydrogen chloride. Ethylamine hydrochloride, which precipitated as a fine white solid, was separated by filtration and dissolved in water (20 ml). The aqueous solution of the amine hydrochloride was transferred to a three-necked, 50-ml, round-bottomed flask equipped with a distillation take-off, and a Teflon coated magnetic stirring bar. One neck of the flask was fitted with a No-Air stopper. Addition of concentrated aqueous sodium hydroxide resulted in the liberation of ethylamine-*d*$_1$, which was swept into a receiver cooled with liquid nitrogen with a stream of nitrogen. The solid material in the receiver was contaminated with small amounts of water, but this impurity did not affect the mass spectral determination of the isotopic purity of the labeled ethylamine. Approximately 2.2 g (45%) of ethylamine-*2-d*$_1$ was obtained by this procedure.

Butyronitrile-*2,2-d*$_2$.—Zinc dust (65.4 g, 1 g-atom) suspended in a mixture of 125 ml of diglyme and 75 ml of benzene was treated with 8 ml of deuterium oxide using procedures described previously. After removing the initial charge of deuterium oxide and the benzene by azeotropic distillation, a Claissen adaptor and two 60-ml addition funnels were added to the apparatus. One funnel was charged with 36 ml of deuterium oxide (40 g, 2.0 mol), the other with 34.5 g (0.25 mol) of 2,2-

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(13) C. S. Marvel and O. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 25.

(14) R. C. Huston and C. C. Langham, *J. Org. Chem.*, **12**, 90 (1947).

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(16) A. I. Vogel, *J. Chem. Soc.*, 644 (1948).

(17) H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

(18) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

(19) The elimination of the induction period by activation of the zinc is extremely important in obtaining satisfactory isotopic purities with nitriles.

dichlorobutyronitrile. Deuterium oxide (*ca.* 5 ml) was added, the mixture was heated to reflux, and 2 ml of 1,2-dibromoethane was added through the reflux condenser. Deuterium oxide and 2,2-dichlorobutyronitrile were added to the stirred mixture simultaneously at the rate of *ca.* 1 drop/sec, although the addition was stopped if the reaction became too vigorous. After addition was complete, the mixture was maintained at reflux for an additional 4 hr, cooled, and distilled at aspirator vacuum (~22 Torr). The first 60 ml of crude distillate was collected. The organic layer was separated from the aqueous layer, which was saturated with sodium chloride and extracted twice with 35-ml portions of ether. The organic fractions were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column to yield 13.5 g of butyronitrile-*2,2-d*$_2$ (0.19 mol, 76%): bp 116–118°; nmr δ 0.97 (t, 3, J = 6 Hz), 1.41 (q, 2, J = 6 Hz).

Buylamine-*2,2-d*$_2$.—Lithium aluminum hydride (2.85 g, 0.075 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, reflux condenser, and Teflon-coated magnetic stirring bar. To the stirred mixture was added dropwise with a syringe 5.2 g (0.073 mol) of butyronitrile-*2,2-d*$_2$ diluted with ether (20 ml). The mixture was refluxed for an additional 2 hr and cooled, and water (2.8 ml), 15% (w:w) aqueous sodium hydroxide (2.8 ml), and additional water (8.4 ml) were cautiously added by syringe to the well-stirred slurry. The white aluminum salts were removed by suction filtration and washed with ether. The ether solution was dried ($MgSO_4$) and concentrated by rotary evaporation. A sample of the remaining yellow oil (~3.8 g, 70%) was purified by glpc on column C to yield a sample of butyronitrile-*2,2-d*$_2$ sufficiently pure for analysis by mass spectrometry.

***N*-Ethyl-*N*-phenyl-2-bromoacetamide** was prepared by a method analogous to that of Weaver and Whaley.[20] In a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and dropping funnel were placed 100 g of *N*-ethylaniline (0.84 mol) and 250 ml of 1,2-dichloroethane. The reaction vessel was cooled in a Dry Ice–isopropyl alcohol bath maintained between −20° and −30° and swept with nitrogen. Bromoacetyl bromide (85 g, 0.42 mol) was added from the dropping funnel to the well-stirred reaction mixture over a 4-hr period. At the conclusion of the reaction, the amine hydrochloride salts were separated by suction filtration and washed with 1,2-dichloroethane (50 ml). The filtrate was distilled at 22 mm to remove most of the 1,2-dichloroethane. The red liquid remaining was analyzed by glpc (column C) and nmr, and was found to contain a maximum of 80% (by weight) of *N*-ethyl-*N*-phenyl-2-bromoacetamide; almost all of the remaining 20% consisted of 1,2-dichloroethane. This crude material was used in the following step without further purification.

***N*-Ethyl-*N*-phenylacetamide-*2-d*$_1$** was prepared following procedures outlined above by reaction between zinc dust (32.7 g, 0.50 g-atom), *N*-ethyl-*N*-phenyl-2-bromoacetamide (~60 g of crude material, ~0.25 mol), and deuterium oxide (20 g, 1.0 mol) in 100 ml of diglyme. Following conventional work-up of the reaction mixture, the crude product was distilled through a 10-cm Vigreux column as an oily liquid, bp 82° (0.09 Torr), which solidified in the receiver. Recrystallization from warm ether yielded 14.8 g of *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$ (0.09 mol, 36%): nmr δ 1.03 (t, 3, J = 6 Hz), 1.73 (*t*, 2, J = 2 Hz), 3.63 (q, 2, J = 6 Hz), 7.37 (m, 5).

***N*,*N*-Diethylaniline-*d*$_1$** was prepared by the reduction of *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$ with lithium aluminum hydride using standard procedures.

(20) W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.*, **69**, 515 (1947).

Acetic acid-*d*$_n$ was prepared by reaction of zinc dust (32.7 g, 0.5 g-atom) suspended in 100 ml of diglyme with chloroacetyl chloride (28.2 g, 0.25 mol) and deuterium oxide (15.4 g, 0.75 mol) at 60°. The general procedure was that described previously; the chloroacetyl chloride and 9 ml of the deuterium oxide were added in nine portions during ~45 min to the reaction mixture. The apparatus was arranged for distillation and the first 40 ml of material distilling under an aspirator vacuum was collected. This crude distillate was carefully redistilled through a 20-cm Nester-Faust Teflon spinning band column, yielding a fraction boiling between 97 and 105°, as well as acetic acid-*d*$_n$ (5.4 g, 0.087 mol, 35%), bp 117–119°, nmr δ 1.98 (t, J = 2 Hz). The lower boiling fraction was saturated with sodium chloride and extracted three times with 30-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and distilled through the spinning band column to yield an additional 2.5 g of acetic acid-*d*$_n$ (7.9-g total, 0.127 mol, 51%).[21]

Ethanol-*d*$_n$.—Sodium borohydride (3.65 g, 0.096 mol) and diglyme (20 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, Teflon-coated magnetic stirring bar, dropping funnel, and reflux condenser, with an adaptor leading to a mercury–acetone bubbler. The mixture was stirred for *ca.* 5 min, and a solution of acetic acid-*d*$_n$ (7.9 g, 0.127 mol) in diglyme (15 ml) was added slowly with a syringe. Frothing of the reaction mixture was evident during the addition. The reaction vessel was flushed with nitrogen, and boron trifluoride etherate (17.7 g, 0.125 mol) diluted with diglyme (20 ml) was added to the stirred reaction mixture from the dropping funnel over the course of 2 hr. The mixture was stirred an additional 0.5 hr and quenched with octyl alcohol (3 ml) and water (10 ml). The residual inorganic salts were removed by suction filtration and washed with ether (*ca.* 50 ml). The organic layer was separated and dried ($MgSO_4$), and the residue distilled through a 20-cm Nester-Faust Teflon spinning band column to yield ethanol-*d*$_n$ (4.2 g, 0.09 mol, 71%), bp 76–78°.

Acetone-*d*$_n$ was prepared by reduction of chloroacetone (21.6 g, 0.23 mol) with zinc powder (43.5 g, 0.67 g-atom) in diglyme using a procedure similar to that described previously. After removing the initial charge of deuterium oxide and benzene, the chloroacetone was added to the reaction flask, and the reaction mixture maintained at reflux temperature for 1 hr. After this time deuterium oxide (20 g, 1 mol) was added. The apparatus was arranged for distillation, and all material boiling below 150° was rapidly collected. This crude distillate was dried and redistilled to yield acetone-*d*$_n$ (8.4 g, 0.14 mol, 61%), having bp 56–57°.

This material was converted to isopropyl bromide for isotopic analysis by reduction to 2-propanol with lithium aluminum hydride, conversion to isopropyl tosylate, and treatment with calcium bromide in DMF.[22]

Registry No.—Ethylbutyrate-*2-d*$_1$, 13224-13-0; 1-butanol-*2-d*$_1$, 35223-78-0; 1-bromoethane-*2,2,2-d*$_3$, 7439-86-3; *n*-propyl 2-chloroacetate, 5396-24-7; *n*-propyl 2-bromoacetate, 35223-80-4; *n*-propyl acetate-*2-d*$_1$, 35223-81-5; ethanol-*2-d*$_1$, 1624-36-8; acetonitrile-*d*$_1$, 26456-53-1; ethylamine-*2-d*$_1$, 35223-83-7; butyronitrile-*2,2-d*$_2$, 35223-84-8; butylamine-*2,2-d*$_2$, 27847-12-7; *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$, 35223-86-0; acetic acid-*2-d*$_1$, 35223-87-1; ethanol-*2-d*$_1$, 6181-08-4; acetone-*d*$_1$, 4468-52-4.

(21) A more efficient procedure for the synthesis of acetic acid-*d*$_2$ consists of the reaction of ketene with deuterium oxide: H. L. Mitchell, unpublished work.

(22) G. L. Jenkins and J. C. Kellett, *J. Org. Chem.*, **27**, 624 (1962).