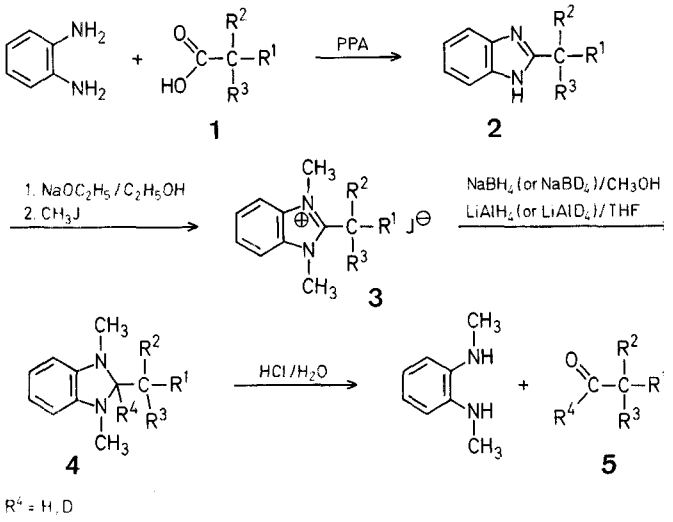

Conversion of Carboxylic Acids into Aldehydes and their C-1 or C-2 Deuteriated Derivatives

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Methods for converting acids into aldehydes generally make use of the controlled partial reduction of secondary or tertiary amides derived from carbazole, *N*-methylaniline, imidazole, or *N,N'*-carbonyldiimidazole with lithium aluminum hydride, partial reduction of esters or cyanides using diisobutylaluminum hydride, or partial reduction of acid chlorides with lithium tri-*t*-butoxyaluminum hydride[1,2].

The need for an efficient preparation of aldehydes deuteriated at C-1 or C-2 for biochemical mechanistic studies prompted us to develop the following method. Conversion of a carboxylic acid (**1**), acid chloride, anhydride, amide, ester, or nitrile into the 2-substituted benzimidazole **2** is easily achieved[3] in high yield by reaction with 1,2-diaminobenzene (*o*-phenylenediamine) in the presence of hydrochloric[4] or polyphosphoric acid[5]. The products are readily purified by crystallization (benzene/chloroform) or vacuum sublimation. A one-step quaternization of **2** to the quaternary 1,3-dimethylbenzimidazolium salts **3** is readily accomplished with iodomethane and sodium methoxide in refluxing methanol (sealed vessel, 3 h), or in refluxing benzene (18 h), or with dimethyl sulfate and aqueous sodium hydrogen carbonate at room temperature (18 h)[6]. While the free benzimidazoles (**2**) are not readily reduced, the benzimidazolium salts **3** are rapidly reduced in high yield with sodium borohydride at room temperature to the corresponding 2,3-dihydrobenzimidazoles (**4**) (R^4 = H) which show a signal in the ^{1}H-N.M.R. spectrum at δ = 4.9 ppm due to the new proton at C-2. A similar reduction carried out with sodium borodeuteride gives the corresponding 1,3-dimethyl-2,3-dihydrobenzimidazole-2-*d* (**4**, R^4 = D), the N.M.R. spectrum of which displays no signal at δ = 4.9 ppm. The desired aldehydes **5** are readily obtained in high purity from these *gem*-diamines by brief shaking of a hexane solution of **4** with 4% hydrochloric acid at room temperature. The corresponding 2-deuterio compounds (**4**, R^4 = D) afford the pure 1-deuterioaldehydes (**5**, R^4 = D), the ^{1}H-N.M.R. spectrum showing 98–99% incorporation of D at C-1.

When the reduction of 1,3-dimethyl-2-phenylbenzimidazolium iodide is carried out in methanol, subsequent hydrolysis affords benzaldehyde containing 93% deuterium at the aldehydic C-atom. When methanol-O-*d* is used as solvent for the reduction, the aldehyde contains >99% deuterium. A similar finding is made for the reduction of the 2-furyl analogue, but not for the 2-methyl- or 2-hexyl derivatives of **3**. The explanation must therefore be loss of isotope by exchange in the intermediate benzimidazolidine **4**, where the H-atom at C-2 is sufficiently acidic, when R^1 = phenyl or 2-furyl, to undergo deprotonation by the alkaline borohydride reagent, and re-protonation then occurs from solvent methanol. This problem can be easily overcome by using methanol-O-*d* when required.

Instead of sodium borohydride, lithium aluminum hydride (or deuteride) in tetrahydrofuran at room temperature can be employed for the reduction of **3**→**4**, and gives the aldehydes in comparable yields and isotopic purity. The 2-deuteriated aldehydes (**5**, $R^2 = R^3$ = D) cannot be obtained by direct exchange of the aldehyde under either acidic or alkaline conditions; extensive decomposition results. Attempted preparation of the 2-deuteriated acid (**1**, $R^2 = R^3$ = D) by direct base-catalyzed exchange (sodium deuteroxide in refluxing deuterium oxide) is very slow (10% exchange in 18 h), as is acid-catalyzed exchange[7]. However, the required acid (**1**, $R^2 = R^3$ = D) may be obtained from the corresponding malonic acid[8] (**1**, R^2 = —COOH) by exchange of the 2-H atom at room temperature, followed by decarboxylation at 140 °C to give a quantitative yield of the acid **1** ($R^2 = R^3$ = D). Conversion of this acid into the benzimidazole (**2**, $R^2 = R^3$ = D) is accompanied by the loss of some deuterium (25–30%), which is however readily replaced by acid-catalyzed exchange with deuterium oxide. Since base-catalyzed exchange cannot be used for this reaction, the methylation of **2** ($R^2 = R^3$ = D) to **3** ($R^2 = R^3$ = D) and its reduction to **4** ($R^2 = R^3$ = D) can be achieved in normal solvents without loss of isotope. The hydrolysis of **4** ($R^2 = R^3$ = D) to the aldehyde **5** ($R^2 = R^3$ = D), however, requires the use of deuterium chloride in deuterium oxide to give a product fully deuteriated at C-2; using non-deuterated acid results in substantial loss of isotope in the aldehyde formed.

2-Hexylbenzimidazole (2, $R^2 = R^3$ = H, $R^1 = n$-C_5H_{11}); Typical Procedure:

A mixture of heptanoic acid (6.5 g), *o*-phenylenediamine (5.4 g), and polyphosphoric acid (20 g, 85%) is heated with stirring at 175 °C for 4 h and then poured into excess dilute ammonium hydroxide. The solid is filtered off, dried, and sublimed (140 °C/0.01 torr) to give the pure product; yield: 8.8 g (87%); m.p. 137–137.5 °C (Ref.[9], m.p. 136–136.5 °C).

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Table 1. 1,3-Dimethylbenzimidazolium Iodides (**3**, $R^2 = R^3 = H$)

R^1	Yield [%]	m.p. [°C] found	m.p. [°C] reported or Molecular formula	^{1}H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
CH_3	77	256°	255°[11]	
	76	278–280°	280°[11]	3.98 [s, $N(CH_3)_2$]; 7.95 (br, H_{arom})
	70	246–247°	$C_{13}H_{13}JN_2O$ (340.2)[a]	4.28 [s, $N(CH_3)_2$]; 5.29 (q, J=4 Hz, 4′-H); 6.2–6.35 (br, 5H, 5′-H and H_{arom}); 6.84 (br, 3′-H)

[a] calc. C 45.92 H 3.85 N 8.24
found 45.92 3.88 8.10

Table 2. 1,3-Dimethyl-2,3-dihydrobenzimidazoles (**4**, $R^2 = R^3 = H$)

R^1	R^4	Yield [%]	m.p. [°C] found	m.p. [°C] reported or Molecular formula	^{1}H-N.M.R. δ [ppm]
CH_3	H	81	23–24° (b.p. 57°/ 0.025 torr)	25–26°[11]	($CDCl_3$/TMS): 2.6 [s, $N(CH_3)_2$]; 1.4 (d, J=6 Hz, CH_3); 3.9 (q, J=6 Hz, 2-H)
	H	82	92–94°	93–94°[11]	($CDCl_3$/TMS): 4.89 (s, 1H, 2-H)
	D	82	92–94°	[a]	($CDCl_3$/TMS): 2.55 [s, $N(CH_3)_2$]; 6.6 (m, 6H); 7.48 (m, 5H, C_6H_5)
	H	89	101–103°	$C_{13}H_{14}N_2O$[b] (214.3)	(DMSO-d_6/TMS): 5.1 (s, 1H, 2-H)
	D	89	101–103°	[c]	(DMSO-d_6/TMS): 2.68 [s, $N(CH_3)_2$]; 6.6 (m, 6H_{arom})

[a] >99% D by ^{1}H-N.M.R. analysis. Mixture m.p. with protio compound is undepressed. I.R. (KBr): ν=2060, 2020 cm^{-1} (C-D stretch).
[b] calc. C 72.96 H 6.59 N 13.09
found 72.69 6.57 12.96
[c] 98% D by ^{1}H-N.M.R. analysis. Mixture m.p. with protio compound is undepressed. I.R. (KBr): ν=2060, 2020 cm^{-1} (C-D stretch).

Table 3. Aldehydes **5** ($R^2 = R^3 = H$)

R^1	R^4	Yield of free Aldehyde **5** [%]	m.p. of 2,4-Dinitrophenyl Hydrazone [°C] found	m.p. of 2,4-Dinitrophenyl Hydrazone [°C] reported
CH_3	H	72[a]	145–147°[b]	147°[10]
	H	76[a]	235–237°[b]	237°[10]
	D	73[c]	235–237°[b]	
	H	66[a]	228°[b]	229°[10]
	D	66[d]	226–228°[b]	

[a] I.R. and N.M.R. spectra identical with those of an authentic sample.
[b] Mixture m.p. with authentic material undepressed.
[c] >99% D by ^{1}H-N.M.R. analysis.
I.R. (neat): ν=2100, 2075, 2050 cm^{-1} (C-D stretch).
[d] 98% D by ^{1}H-N.M.R. analysis.
I.R. (neat): ν=2120, 2080 cm^{-1} (C-D stretch).

^{1}H-N.M.R. ($CDCl_3$): δ=0.8 (m, CH_3); 1.2 [m, $(CH_2)_3$]; 1.9 (m, CH_2); 3.07 [t, (=C—CH_2—)]; 7.4 ppm (m, H_{arom}).

2-Hexylbenzimidazole-1′,1′-d_2 (1, $R^2 = R^3 = D$, $R^1 = n$-C_5H_{11}):
A solution of pentylmalonic acid (20.2 g) in deuterium oxide (9 ml) is allowed to equilibrate at 50–55 °C for 4 h before the solvent is removed in vacuo. Three further equilibrations give the acid (20.2 g) showing no detectable acid proton and >99% deuterium in the α-position by ^{1}H-N.M.R. spectroscopy. Heating the acid at 140 °C until no further carbon dioxide is evolved affords heptanoic acid-2,2-d_2 (15.4 g, 99%), shown (^{1}H-N.M.R.) to contain >98% deuterium in the α-position. Reaction of the labelled heptanoic acid with *o*-phenylenediamine as above gives 2-hexylbenzimidazole-1′,1′-d_2 (85% yield) containing 71% deuterium in the 1′,1′-positions (^{1}H-N.M.R.). The product is heated at 120 °C in deuterium oxide (30 ml) with 10 normal deuterium chloride in deuterium oxide (1 ml) for 24 h and the solvent removed in vacuo. After 3 such exchanges, the residue is neutralized with sodium deuteroxide in deuterium oxide, filtered, and the product crystallized from acetone/hexane as colorless plates; m.p. 135.5–136 °C. ^{1}H-N.M.R. analysis shows >99% deuterium in the 1′,1′-positions.

1,3-Dimethyl-2-hexylbenzimidazolium Iodide (3, $R^2 = R^3 = H$, $R^1 = n$-C_5H_{11}); Typical Procedure:
A solution of sodium (0.46 g, 0.02 mol) in methanol (8 ml) is treated with 2-hexylbenzimidazole (4.04 g, 0.02 mol) and iodomethane (4 ml) and the mixture heated in a sealed container (glass or stainless steel) for 3 h at 100 °C. The cooled product is recrystallized from acetone to give colorless needles; yield: 5.16 g (72%), m.p. 182–184 °C.

$C_{15}H_{23}N_2J$	calc.	C 50.29	H 6.42	N 7.82
(357.9)	found	50.14	6.40	7.87

^{1}H-N.M.R. ($CDCl_3$): δ=0.9 (m, CH_3); 1.4 [m, $(CH_2)_3$]; 3.50 [t (—C—CH_2)]; 4.16 (s, 2 N—CH_3); 7.8 ppm (m, H_{arom}).

1,3-Dimethyl-2-hexyl-2,3-dihydrobenzimidazole (4, $R^2=R^3=R^4=H$, $R^1=n\text{-}C_5H_{11}$); Typical Procedure:

A solution of 1,3-dimethyl-2-hexylbenzimidazolium iodide (3 g) in methanol (30 ml) is treated with sodium borohydride (0.4 g) portionwise over 15 min. The solvent is removed and the residue extracted with hexane (3 × 40 ml) under nitrogen. The hexane extract is dried with magnesium sulfate and evaporated to give the product as a colorless oil; yield: 1.89 g (97%); b.p. 90–93 °C/0.024 torr.

$C_{15}H_{24}N_2$	calc.	C 77.58	H 10.34	N 12.07
(232.4)	found	77.35	10.44	12.13

^{1}H-N.M.R. ($CDCl_3$): $\delta=2.61$ (s, 2 N—CH_3); 4.15 (t, $J=2.5$ Hz, 2-$H_{imidazole}$); 6.5 ppm (m, H_{arom}).

1,3-Dimethyl-2-hexyl-2,3-dihydrobenzimidazole-2-d_1 (4, $R^2=R^3=H$, $R^4=D$, $R^1=n\text{-}C_5H_{11}$):

Obtained by the above procedure using sodium borodeuteride; yield: 90%.

I.R. (film): $\nu=1975$, 1025 cm^{-1} (C-D stretching).

^{1}H-N.M.R. ($CDCl_3$): No signal at 4.15 ppm; >99% deuterated at 2-position.

Heptanal; Typical Procedure:

A solution of 1,3-dimethyl-2-hexyl-2,3-dihydrobenzimidazole (1.74 g) in pentane (75 ml) is shaken with 4% hydrochloric acid (35 ml) in a separatory funnel for 5 min. The aqueous layer is separated, extracted with pentane, and the combined pentane layers are washed with sodium chloride solution, dried with magnesium sulfate, and evaporated to give heptanal as a colorless oil; yield: 0.64 g (75%); G.L.C.: single peak; retention time identical with that of an authentic sample.

I.R. and ^{1}H-N.M.R. spectra are identical with those of an authentic sample.

2,4-Dinitrophenylhydrazone: m.p. 106–108 °C, undepressed on admixture with an authentic sample (Ref.[10], m.p. 108 °C).

Heptanal-1-d_1:

Obtained by hydrolysis of 1,3-dimethyl-2-hexyl-2,3-dihydrobenzimidazole-2-d_1 (0.466 g) as described above; yield: 0.17 g (75%), colorless oil; m.p. of 2,4-dinitrophenylhydrazone: 106–108 °C.

I.R. (film): $\nu=2070$ cm^{-1} (C-D stretching).

^{1}H-N.M.R. ($CDCl_3$): No signal at $\delta=9.78$ ppm; >99% deuterated at C-1.

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