

Preparation of All the Possible Ring-deuteriated Benzoic Acids by Reductive Dehalogenation of the Corresponding Halogenobenzoic Acids with Raney Alloys in an Alkaline Deuterium Oxide Solution¹

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All the possible undeuteriated benzoic acids were prepared mainly by treatment of the corresponding bromobenzoic acid with Raney Cu–Al alloy in 10% NaOD–D₂O solution. [2,3,4,5,6-²H₅]Benzoic acid was obtained from pentafluorobenzoic acid by a similar reaction. However, only [2,3,4,5-²H₄]benzoic acid was prepared by decarboxylation of [2,3,4,5-²H₄]phthalic acid.

It has been previously reported that reduction of bromophenols with Raney Cu–Al alloy in 10% NaOD–D₂O solution afforded the corresponding deuteriated phenols in high yield and in high isotopic purity, equation (1), and that treatment of 2-bromophenoxyacetic acid with Raney Ni–Al alloy in 10% NaOD–D₂O solution gave [2-²H]phenoxyacetic acid in good yield, equation (2).²

The latter result suggests that this reductive method for the introduction of deuterium atoms at the desired positions of the aromatic ring might be applied to carboxylic compounds such as benzoic acid.

We now report the use of Raney alloys for the reduction of halogenobenzoic acids (1a–s) in 10% NaOD–D₂O solution.

Results and Discussion

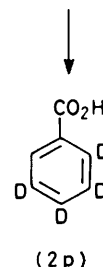
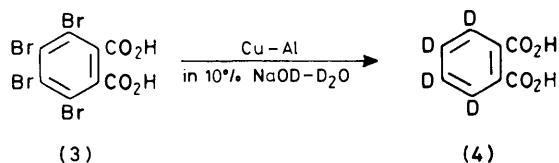
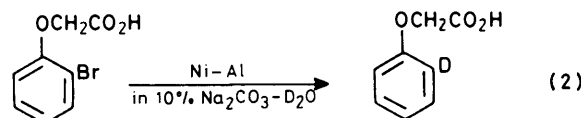
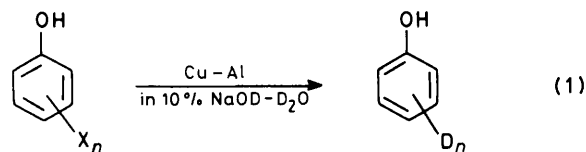
There are 19 possible ring-deuteriated benzoic acids (2a–s). In order to obtain all the deuteriated benzoic acids, the corresponding halogenobenzoic acids were reduced with Raney alloys such as Ni–Al and Cu–Al † in 10% NaOD–D₂O solution. The results are summarized in the Table. The data in the Table show that the expected deuteriated benzoic acids (2a–o) and (2q–s) were formed in high yield and in high purity from the corresponding halogenobenzoic acids with Raney Cu–Al or Ni–Al alloy, and that (2a) was obtained in low purity from (1a) and (1b) with Raney Ni–Al alloy. The Cu–Al alloy was less active than the Ni–Al alloy, so it could not reduce (1a) containing a chlorine atom. Treatment of (1a) with Ni–Al alloy at room temperature did not give the corresponding pentadeuteriated benzoic acid (2s). However, reduction at higher temperature did afford (2s) in high purity.

It should be noted that use of Raney Ni–Al alloy leads to the introduction of more than the expected number of deuterium atoms.

The isomer (2p) was obtained from tetrabromophthalic acid *via* tetradeuteriophthalic acid as shown in Scheme 1.

The ¹H n.m.r. spectra of (2a–s) shown in Figure 1 indicate that the desired number of deuterium atoms were introduced at the desired positions of the ring of the starting materials (1) in the reductive system with the Cu–Al alloy.

It was also found that treatment of benzoic acid (5) itself with Raney Ni–Al alloy in NaOD–D₂O solution afforded the



(Composition: D₂, 1.4;
D₃, 11.0; D₄, 87.6%)

Scheme 1.

mixture of deuteriated benzoic acids, (2') (composition: D₁, 10.2; D₂, 30.9; D₃, 33.2; D₄, 10.4; D₅, 4.3%) (Scheme 2). On the other hand, the Raney Cu–Al alloy did not give the deuteriated benzoic acids, and the starting compound (5) was recovered in almost quantitative yield.

For this reason, use of Raney Ni–Al alloy should be avoided since more than the expected number of deuterium atoms may be introduced in the aromatic ring during the reduction of

† Devarda's alloy (Cu–Zn–Al) could be also used in place of Raney Cu–Al alloy.

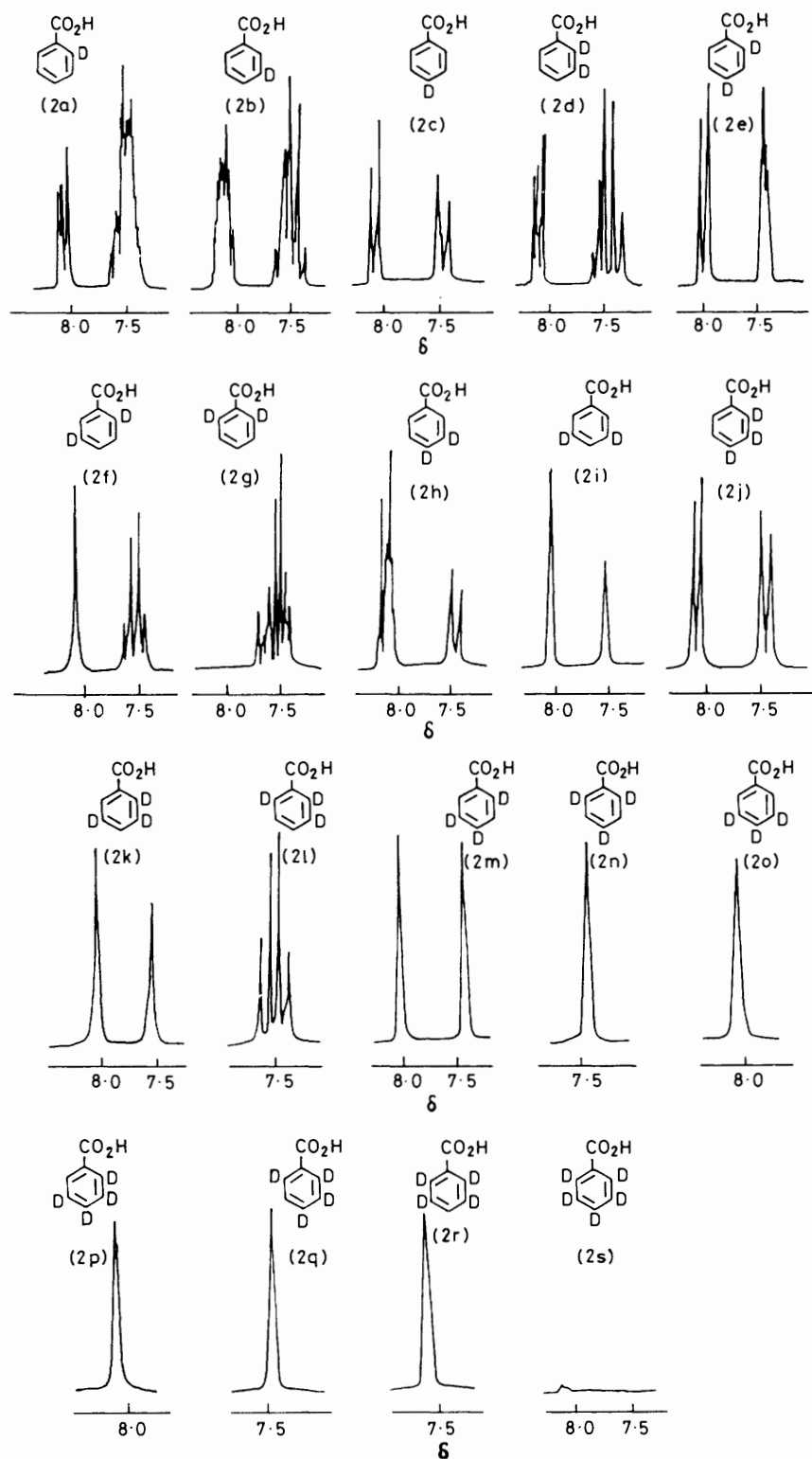


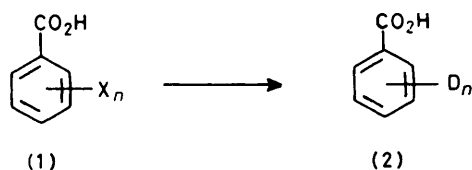
Figure 1. ¹H N.m.r. spectra of deuterated benzoic acids (2a–s)

halogenobenzoic acids as mentioned above. Such an exchange reaction was also observed in the treatment of (2s) with Raney Ni–Al alloy in 10% NaOH–H₂O solution which gave a mixture (2''), equation (3).

The ¹H n.m.r. spectra of both (2') and (2'') are shown in Figure 2. The data of Figures 1 and 2 indicate that (2') might

contain mainly (2h) and 2(o) and that (2'') might include mainly (2g) and (2l). This means that the hydrogen–deuterium and deuterium–hydrogen exchange reactions might occur fairly well at the *para* and *meta* positions, but not at the *ortho* position, of (5) and (2s), respectively.

Treatment of (1h) with Raney Ni–Al alloy in 10% NaOD–

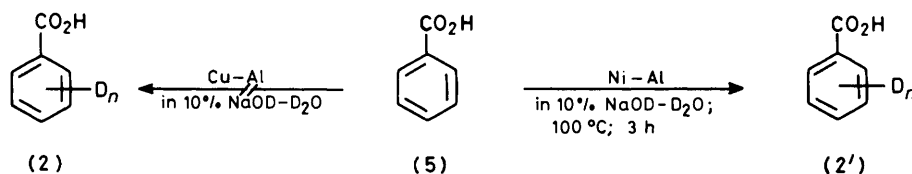


a; 2-Cl	k; 2,3,4-Br ₃	a; 2-D	j; 2,3,4-D ₃
b; 2-Br	l; 2,3,5-Br ₃	b; 3-D	k; 2,3,5-D ₃
c; 3-Br	m; 2,3,6-Br ₃	c; 4-D	l; 2,3,6-D ₃
d; 4-Br	n; 2,4,5-Br ₃	d; 2,3-D ₂	m; 2,4,5-D ₃
e; 2,3-Br ₂	o; 2,4,6-Br ₃	e; 2,4-D ₂	n; 2,4,6-D ₃
f; 2,4-Br ₂	p; 3,4,5-Br ₃	f; 2,5-D ₂	o; 3,4,5-D ₃
g; 2,5-Br ₂	q; 2,3,4,6-Br ₄	g; 2,6-D ₂	q; 2,3,4,6-D ₄
h; 2,6-Br ₂	r; 2,3,5,6-Br ₄	h; 3,4-D ₂	r; 2,3,5,6-D ₄
i; 3,4-Br ₂	s; 2,3,4,5,6-Br ₅	i; 3,5-D ₂	s; 2,3,4,5,6-D ₅
j; 3,5-Br ₂			

Table. Reduction of halogenobenzoic acids (1) with Raney alloys in 10% NaOD-D₂O solution ^a

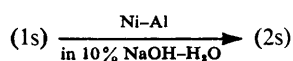
Run	Substrate	Alloy	Time (min.)	Temp. (°C) ^b	Product (Yield %) ^c	Composition of (2) (%) ^d					
						D ₀	D ₁	D ₂	D ₃	D ₄	D ₅
1	(1a)	Ni-Al	40	80	(2a) 84	13.0	51.7	19.7	9.0	5.3	1.3
2	(1a)	Cu-Al	40	80	no reaction						
3	(1b)	Cu-Al	30	40	(2a) 88	1.6	95.8	2.6	0	0	0
4	(1c)	Cu-Al	40	40	(2b) 83	2.8	95.0	1.2	1.0	0	0
5	(1d)	Ni-Al	40	40	(2c) 80	3.7	29.8	34.7	28.1	3.3	0.4
6	(1d)	Cu-Al	30	40	(2c) 86	2.4	94.9	1.4	1.3	0	0
7	(1e)	Cu-Al	30	40	(2d) 84	0	2.4	93.3	2.6	1.7	0
8	(1f)	Cu-Al	30	40	(2e) 83	0	3.3	88.9	4.3	3.5	0
9	(1g)	Cu-Al	30	40	(2f) 81	0.6	2.6	90.2	4.3	1.9	0.4
10	(1h)	Cu-Al	30	40	(2g) 82	0	2.4	95.8	1.8	0	0
11	(1i)	Cu-Al	30	40	(2h) 83	1.6	3.8	89.4	4.4	0.8	0
12	(1j)	Cu-Al	30	40	(2i) 80	0.5	2.5	91.7	4.0	1.0	0.3
13	(1k)	Cu-Al	30	40	(2j) 80	0	0	2.7	91.8	4.2	1.3
14	(1l)	Cu-Al	30	40	(2k) 74	0	0	3.8	92.6	2.5	1.1
15	(1m)	Cu-Al	30	40	(2l) 83	0	0	1.8	94.7	2.4	1.1
16	(1n)	Cu-Al	30	40	(2m) 81	0	0	4.3	93.7	2.0	0
17	(1o)	Cu-Al	30	40	(2n) 83	0.1	0.5	6.2	89.2	2.5	1.5
18	(1p)	Cu-Al	30	40	(2o) 75	0	0	8.5	91.1	0.4	0
19	(1q)	Cu-Al	30	40	(2q) 82	0	0	0.9	6.9	87.2	5.0
20	(1r)	Cu-Al	30	40	(2r) 78	0	0	0	0	96.7	3.3
21	(1s)	Ni-Al	60	40	no reaction						
22	(1s)	Ni-Al	60	100	(2s) 81	0	0	0	0	9.0	91.0

^a To a solution of (1) in 10% NaOD-D₂O was added slowly Raney alloy at room temperature and the mixture was stirred at constant temperature for the specified time shown. ^b Temperature of the oil bath. ^c Isolated yields are shown. The yields determined by g.c. analyses were almost quantitative. ^d The compositions were obtained by mass spectroscopy.



Scheme 2.

D₂O afforded (2s), which was also obtained from (1s) as described above, in good yield and isotopic high purity. Its ¹H n.m.r. spectrum agreed with that of the sample obtained from (1s). This result strongly supports the assumption described above.



The detailed mechanism of the exchange reaction is still obscure; however, we tentatively propose the substrate-catalyst binding shown in Figure 3.

The distances from the surface of the Ni catalyst generated *in situ* to each position might decrease in the order *ortho* > *meta* > *para*. So, the hydrogen and deuterium atoms of the *ortho* positions of aromatic rings might resist such exchange reactions.

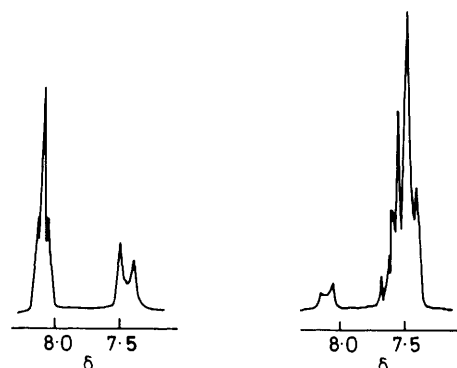
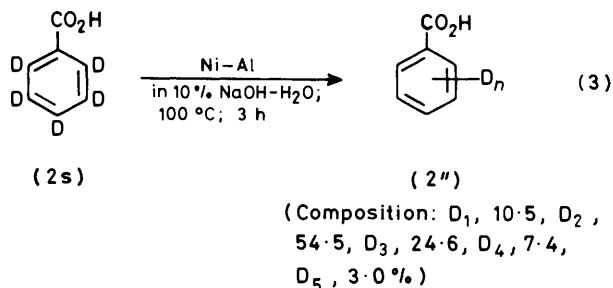
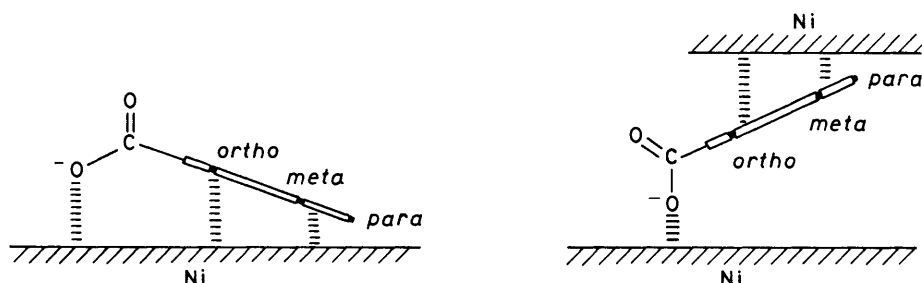
Figure 2. ¹H N.m.r. spectra of (2') and (2'')

Figure 3.

Experimental

N.m.r. spectra were determined at 100 MHz with a Nippon Denshi JEOL FT-100 NMR spectrometer with Me₄Si as internal reference, and mass spectra were obtained on a Nippon Denshi JMS-01-SA-2 spectrometer at 75 eV by using a direct-inlet system.

Halogenobenzoic Acids.—Compounds (1a), (1b), (1c), (1d), and (1s) were commercially available and (1g),³ (1i),⁴ and (1o)⁵ were prepared according to the reported methods. The preparation of (1d), (1e), (1f), (1h), (1j), (1k), (1l), (1m), (1n) (1p), (1q), and (1r) was previously described.⁶

Typical Procedure for Reduction of Halogeno Acids (1).—To a solution of the acid (1b) (402 mg, 2 mmol) in D₂O–NaOD (10 ml), prepared from 40% NaOD–D₂O (2.5 ml) and D₂O (7.5 ml), was gradually added Cu–Al alloy (50 : 50) (0.2 g) at room temperature during 15 min.

After addition of the alloy, the reaction mixture was stirred and heated at 40 °C for 30 min, and then insoluble materials were filtered off. The filtrate was acidified with concentrated hydrochloric acid and extracted with dichloromethane. The extract was dried over sodium sulphate and evaporated under reduced pressure to afford the deuteriated acid (2a) (206 mg, 84%).

The deuteriobenzoic acids (2c), (2d), and (2s) were commercially available.

Treatment of Tetrabromophthalic Acid (3) with Raney Cu–Al Alloy in 10% NaOD–D₂O Solution.—To a suspension of the acid (3) (726 mg, 1.5 mmol) in 10% NaOD–D₂O (20 ml) was added Raney Cu–Al alloy (1.0 g). After the reaction mixture had been heated at 60 °C for 1 h it was worked up and treated as described above to give the tetradeuteriated phthalic acid (4) (204 mg, 80%).

Preparation of 2,3,4,5-Tetradeuteriobenzoic Acid (2p) from (4).—To a solution of compound (4) (107 mg, 1 mmol) in 0.4M NaOH (5 ml) was added a solution of mercury(II) acetate (319 mg, 1 mmol) in water (5 ml) and acetic acid (0.2 ml). The colourless precipitate which formed was collected, washed with ethanol (10 ml), dried, and then suspended in hexamethylphosphonic triamide (5 ml) with powdered soft glass (330 mg). After the suspension had been heated at 175 °C for 1 h it was diluted with water (20 ml) and filtered to leave a solid. To a suspension of this solid in ethanol (15 ml) was added sodium borohydride (100 mg, 0.26 mmol). After the reaction mixture had been stirred for 15 min it was acidified with conc. hydrochloric acid (3 ml), diluted with acetone (5 ml), and filtered through Celite. The filtrate was evaporated under reduced pressure to afford the acid (2p) (106 mg, 80%).

Proton–Deuterium or Deuterium–Proton Exchange Reaction of (5) or (2s).—The reaction was carried out at 100 °C (bath temperature) for 3 h and the reaction mixture was treated and worked up as described above.

References

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