

PREPARATION OF DEUTERATED NAPHTHALENES, ANILINES,
m-TOLUIDINES, AND ANISOLES BY REDUCTIVE DEHALOGENATION OF THE
CORRESPONDING HALOGENATED DERIVATIVES WITH RANEY CU-AL ALLOY
IN AN ALKALINE DEUTERIUM OXIDE SOLUTION

Masashi Tashiro,* Hirohisa Tsuzuki,^a Takehito Tsukinoki,^b
Shuntaro Mataka,^a Kouji Nakayama,^c and Tadashi Yonemitsu^d

^aInstitute of Advanced Material Study, Kyushu University, and

^bDepartment of Molecular Science and Technology, Graduate
School of Engineering Sciences, Kyushu University, 6-1,
Kasuga-koh-en, Kasuga-shi, Fukuoka, 816, Japan.

^cFaculty of Pharmaceutical Science, Jousai University, 1-1,
Keyakidai, Sakado-shi, Saitama, 350-02, Japan.

^dDepartment of Industrial Chemistry, Faculty of Engineering,
Kyushu Sangyo University, 2-327, Matsukadai, Kashi-i,
Higashi-ku, Fukuoka-shi, Fukuoka, 813, Japan.

SUMMARY

Four deuterated naphthalenes, ten deuterated anilines,
three deuterated m-toluidines, and five deuterated anisoles
were prepared in high isotopic purities from the corresponding
halo-substituted derivatives by the reductive dehalogenation
with Raney Cu-Al alloy in an alkaline deuterium oxide solution.

Key Words: Deuterium Labelling, Reductive Dehalogenation,
Synthesis, Raney Cu-Al Alloy, NaOD-D₂O

INTRODUCTION

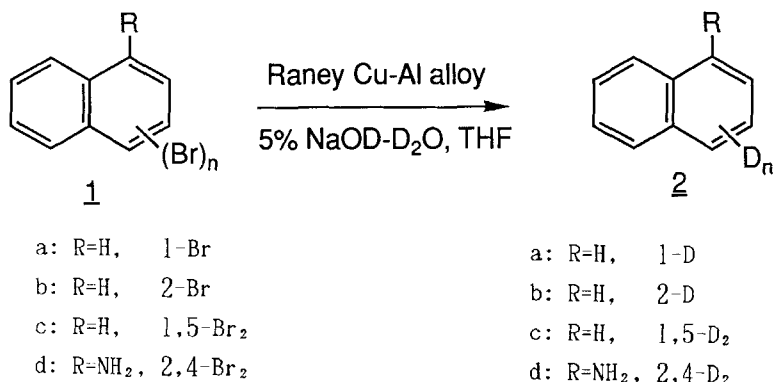
It has been previously reported that deuterated phenols¹, benzoic
acids², 1-phenylethanols³, thiophen-2-, furan-2-, and pyrrole-2-
carboxylic acids⁴, and salicylic acids⁵ were prepared in high yields
and in high isotopic purities from the corresponding halogenated
derivatives by the reductive dehalogenation with Raney alloys in an
alkaline deuterium oxide solution. The deuterated naphthalenes,
anilines, m-toluidines, and anisoles might be useful for the
preparative intermediates of various deuterated aromatic compounds.

In order to determine the scope and limitation of the reductive method using Raney alloys in an alkaline solution, preparations of the titled deuterated compounds from the corresponding halogenated derivatives were carried out in this study.

RESULTS AND DISCUSSION

Preparation of Deuterated Naphthalenes.

Bromonaphthalenes such as 1-bromo- (1a), 2-bromo- (1b), 1,5-di-bromo- (1c), and 1-amino-2,4-dibromo-naphthalene (1d) were treated with Raney Cu-Al alloy in 5% NaOD-D₂O and THF solution to afford the expected 1-deutero- (2a), 2-deutero- (2b), 1,5-dideutero- (2c), and 1-amino-2,4-dideutero-naphthalene (2d) in low yield but in high isotopic purity, respectively (Scheme 1 and Table 1).



Scheme 1

Table 1 Preparation of deuterated naphthalenes (2a-d) from the corresponding bromo derivatives (1a-d) by reduction with Raney Cu-Al alloy in a mixture of 5% NaOD-D₂O and THF.*

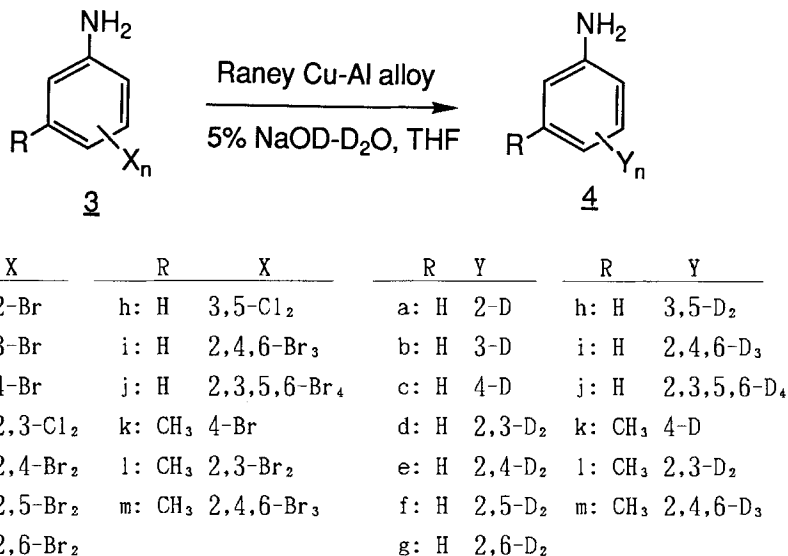
Run	Substrate	Product Yield(%) ^b	Composition of (2) (%) ^c				
			D ₀	D ₁	D ₂	D ₃	D ₄
1	(<u>1a</u>)	(<u>2a</u>) 37	1	99	0	0	0
2	(<u>1b</u>)	(<u>2b</u>) 28	5	95	0	0	0
3	(<u>1c</u>)	(<u>2c</u>) 43	7	5	84	4	0
4	(<u>1d</u>)	(<u>2d</u>) 78	0	6	94	0	0

a) (1) (15 mmol)/ alloy (3.75 g)/ 5% NaOD-D₂O (40 ml)/ THF (5 ml).

b) Isolated yields are shown. c) Compositions were obtained from mass spectral data.

Preparation of Deuterated Anilines and *m*-Toluidines.

Monobromo- (3a-c), dibromo- (3e-g), tribromo- (3i), and tetra-bromo-aniline (3j) were reductively debrominated by the treatment with Cu-Al alloy in 5% NaOD-D₂O and THF, giving the corresponding deuterated anilines, (4a-c), (4e-g), (4i), and (4j) in high isotopic purities (Scheme 2 and Table 2).



Scheme 2

Table 2 Preparation of deuterated anilines (4a-j) and *m*-toluidines (4k-m) from the corresponding haloanilines (3a-j) and halotoluidines (3k-m) by the reduction with Raney Cu-Al alloy in 5% NaOD-D₂O and THF.^a

Run	Substrate	Alloy(g)	Product		Composition of (<u>4</u>) (%) ^c					
			Yield (%) ^b		D ₀	D ₁	D ₂	D ₃	D ₄	D ₅
1	(<u>3a</u>)	3.75	(<u>4a</u>) 75		1	97	2	0	0	0
2	(<u>3b</u>)	3.75	(<u>4b</u>) 74		6	92	2	0	0	0
3	(<u>3c</u>)	3.75	(<u>4c</u>) 76		7	89	3	1	0	0
4	(<u>3d</u>)	7.50	(<u>4d</u>) 82		0	5	88	4	3	0
5	(<u>3e</u>)	7.50	(<u>4e</u>) 65		2	11	83	4	0	0
6	(<u>3f</u>)	7.50	(<u>4f</u>) 81		0	15	75	10	0	0
7	(<u>3g</u>)	7.50	(<u>4g</u>) 82		0	13	83	4	0	0
8	(<u>3h</u>)	7.50	(<u>4h</u>) 76		3	12	73	9	2	1
9	(<u>3i</u>)	11.25	(<u>4i</u>) 69		0	0	13	83	4	0

10	(3j)	15.00	(4j)	45	2	1	3	15	77	2
11	(3k)	3.75	(4k)	78	11	89	0	0	0	0
12	(3l)	7.50	(4l)	55	0	14	79	7	0	0
13	(3m)	11.25	(4m)	71	0	0	20	77	3	0

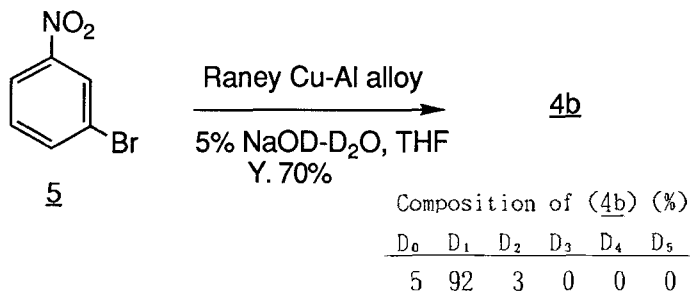
a) (3) (15 mmol)/ 5% NaOD-D₂O (40 ml)/ THF (2.5 ml).

b) Isolated yields are shown. c) Compositions were obtained from mass spectral data.

Interestingly, chloroanilines such as (3d) and (3h) could be reduced under ultrasonic irradiation with Cu-Al alloy, which did not reduce chloro-phenols and -benzoic acids, to give the corresponding deuterated anilines, (4d) and (4h), in high isotopic purities.

Deutero-m-toluidines (4k-m) in high isotopic purities were similarly prepared from bromo-m-toluidines (3k-m).

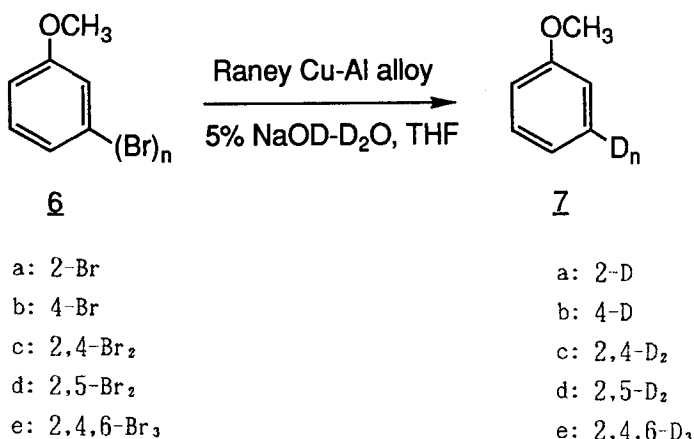
m-Bromonitrobenzene (5) was reduced in a similar manner to give (4b) in high yield and in high isotopic purity (Scheme 3).



Scheme 3

Preparation of Deuterated Anisoles.

It was previously found⁶ that ultrasonic irradiation accelerated the reductive debromination of 2,6-dibromoanisole with Raney Cu-Al alloy in 5% NaOH and THF. Therefore, when 2-bromo- (6a), 4-bromo- (6b), 2,4-dibromo- (6c), 2,5-dibromo- (6d), and 2,4,6-tribromo-anisole (6e) were treated with Cu-Al alloy in 5% NaOD-D₂O and THF with ultrasonic irradiation, the desired deuterated anisoles (7a-e) were obtained in high yield and in high isotopic purity, respectively (Scheme 4 and Table 3).



Scheme 4

Table 3 Preparation of deuterated anisoles (7a-e) from the corresponding bromoanisoles (6a-e) by reduction with Raney Cu-Al alloy in a mixture of 5% NaOD-D₂O and THF under ultrasonic irradiation.^a

Run	Substrate	Alloy(g)	Product Yield (%) ^b	Composition of (<u>7</u>) (%) ^c					
				D ₀	D ₁	D ₂	D ₃	D ₄	D ₅
1	(<u>6a</u>)	3.75	(<u>7a</u>) 63	0	99	1	0	0	0
2	(<u>6b</u>)	3.75	(<u>7b</u>) 53	2	95	2	1	0	0
3	(<u>6c</u>)	7.50	(<u>7c</u>) 56	0	4	95	1	0	0
4	(<u>6d</u>)	7.50	(<u>7d</u>) 42	0	8	91	1	0	0
5	(<u>6e</u>)	11.25	(<u>7e</u>) 85	0	0	0	94	6	0

a) (6) (15 mmol)/5% NaOD-D₂O (40 ml)/THF (2.5 ml).

b) Isolated yields are shown. c) Compositions were obtained from mass spectral data.

It was also found that the similar reduction of bromotoluenes with Cu-Al alloy in an alkaline solution did not proceed. This result and the results described above mean that the polar groups such as amino and methoxy group accelerate the reduction of haloarenes with Cu-Al alloy in an alkaline solution.

The position of deuterium labelling of deuterated naphthalenes, anilines, m-toluidines was confirmed from their ¹³C n.m.r. spectra. The representative ¹³C spectra is shown in Figure 1 and 2.

¹³C{¹H} spectrum of 1-amino-2,4-dideuteronaphthalene (2d) showed the signal of the deuterium-bounded carbon atom as a triplet with J=24.5 Hz (Figure 1).

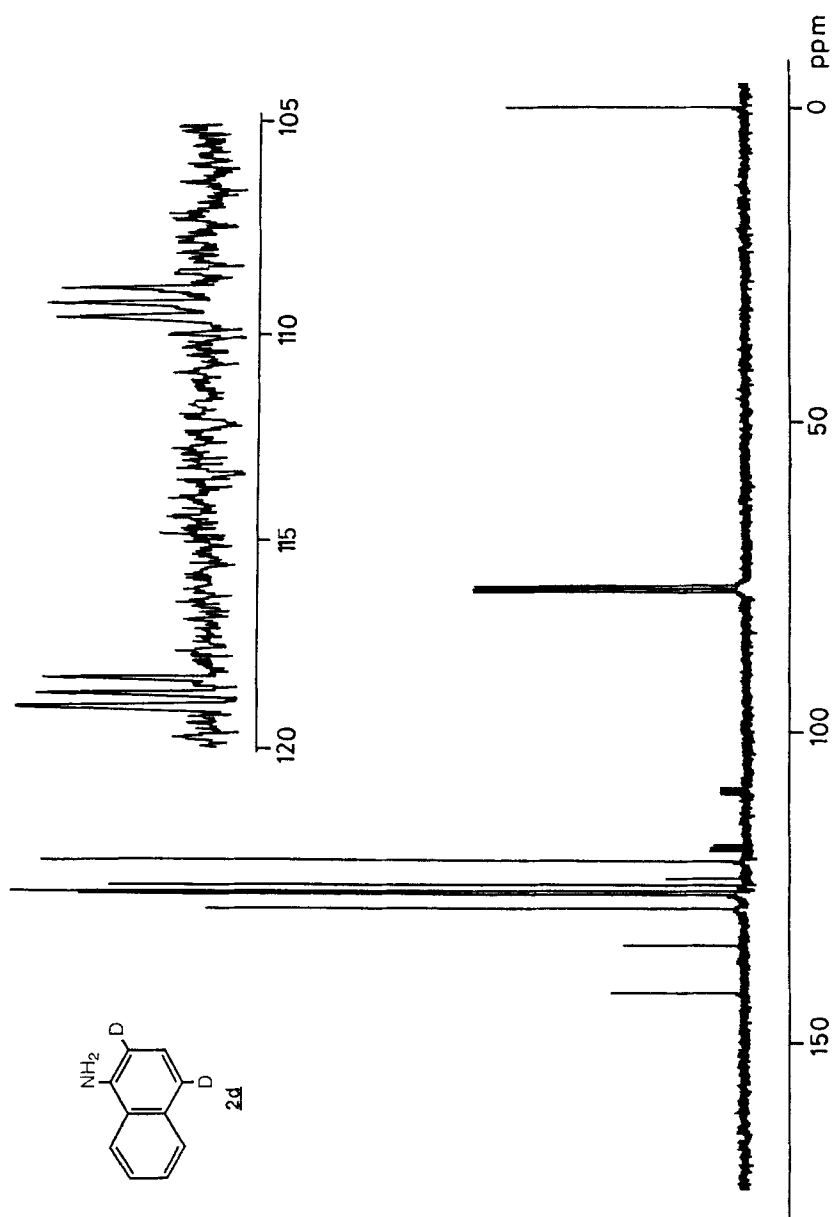


Figure 1. ^{13}C n.m.r. spectra of (**2d**) at 67.94 MHz in CDCl_3 .

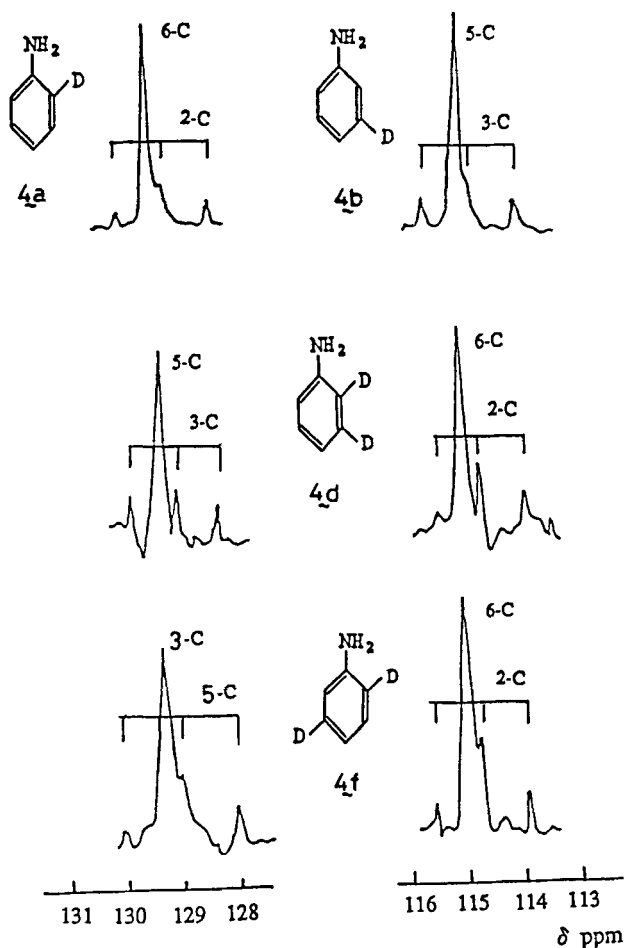


Figure 2. ^{13}C n.m.r. spectra of deuterated anilines (4a), (4b), (4d) and (4f).

In the ^{13}C spectra of 2-deutero (4a), 3-deutero (4b), 2,3-dideutero (4d), and 2,5-dideutero-aniline (4f) (Figure 2), the deuterium-bounded carbon atoms appeared as a triplet with $J = \text{ca. } 24 \text{ Hz}$ at the slightly up-fielded position.

The ^1H spectra of 2,4-dideutero- (7c), 2,5-dideutero- (7d), and 2,4,6-trideutero-anisole (7e) are sufficiently simple and deuterated positions were confirmed by 1-st order analyses of the spectra. The spectra of 2-deutero- (7a) and 4-deutero-anisole (7b) were simulated⁷ to confirm the deuterated positions. The observed and calculated ^1H spectra of (7a) are shown (Figure 3).

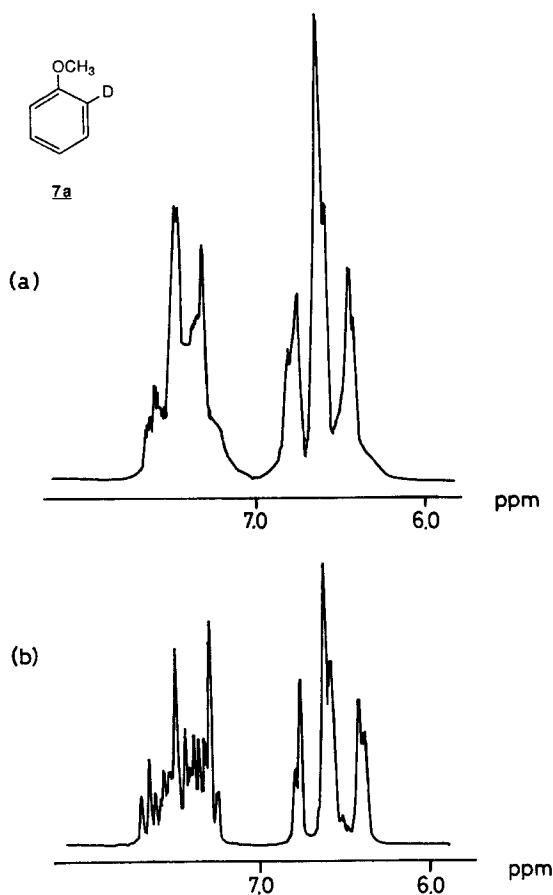


Figure 3. ^1H n.m.r. spectra of 2-deuteratedanisole (7a).
; (a) Observed. (b) Calculated.

In summary, the deuterated naphthalenes (2a-d), anilines (4a-j), m-toluidines (4k-m), and anisoles (7a-e) were prepared from the corresponding halo-substituted compounds in 73-99% isotopic purities with Cu-Al alloy in 5% NaOD- D_2O and THF solution. The positions of deuterium labelling were identified by ^1H and ^{13}C spectra and simulation calculation.

EXPERIMENTAL

The boiling points of the deuterated compounds which obtained in this study were almost the same with those of the corresponding parent compounds. ^1H n.m.r. spectra were recorded on a Hitachi R-90 H FT n.m.r. spectrometer and $^{13}\text{C}\{^1\text{H}\}$ n.m.r. spectra were taken on a JEOL GSX-270 (67.94 MHz) n.m.r. spectrometer in CDCl_3 with Me_4Si as an

internal reference. In simulation of ¹H n.m.r. spectra of the deuterated naphthalenes, anilines, and anisoles, was used a programme developed for the personal computer, NEC PC-9801 (16 K) and Apple Computer Macintosh II (M5333JA). A Branson model ATH1012-12 (40 kHz, 50 Hz) ultrasound laboratory cleaner was used for sonication.

Materials.

Compounds (1a), (1b), (3a-d), (3g-h), and (6a-b) were commercially available, and compounds (1c)⁸, (1d)⁹, (3e)¹⁰, (3f)¹¹, (3i)¹², (3j)¹³, (3k)¹⁴, (3l)¹⁵, (3m)¹⁶, (6c)¹⁷, (6d)¹⁸, and (6e)¹⁹ were prepared according to reported methods.

Preparation of Deuterated Naphthalenes. Typical Procedure. To a vigorously stirred mixture of 1.56 g (7.5 mmol) of (1a) in 20 ml of 5% NaOD-D₂O and 2.5 ml of THF was added at 60 °C under a nitrogen atmosphere 125 mg of Raney Cu-Al alloy over a period of 10 min in 15 times (total amount of the alloy was 1.875 g) and the reaction mixture had been stirred at 60 °C for 2 h. After it had been cooled to room temperature, the formed Cu and unreacted alloy were filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane and the extracts and the dichloromethane washing were combined. The combined dichloromethane solution was washed with water, dried (MgSO₄), and evaporated in vacuo to leave a residue which was sublimed at 80 °C under a reduced pressure to afford 350 mg (37%) of (2a). In the case of (2d), it was obtained as a colorless oil (b.p. 140 °C/ 1.8 Torr) by vacuum distillation under a reduced pressure but not sublimation.

Preparation of Deuterated Anisoles. Typical Procedure. To a vigorously stirred mixture of 2.81 g (15 mmol) of (5a) in 40 ml of 5% NaOD-D₂O and 2.5 ml of THF was gradually added 0.25 g of Cu-Al alloy under ultrasonic irradiation at 60 °C over a period of 10 min in 15 times (total amount of the alloy was 3.75 g). The reaction mixture was treated and worked up as described above to afford 1.04 g (63%) of (6a) as a colorless oil (b.p. 75 °C/ 30 Torr).

Preparation of Deuterated Anilines. Typical Procedure. To a vigorously stirred mixture of 2.66 g (15 mmol) of (7a) in 40 ml of 5% NaOD-D₂O and 2.5 ml of THF was gradually added 0.25 g of Cu-Al alloy at 60 °C over a period of 10 min (total amount of the alloy was 3.75 g). The reaction mixture was treated and worked up as described above to give 1.09 g (75%) of (8a) as a colorless oil (b.p. 90 °C/ 15 Torr).

REFERENCES

- 1) Tashiro, M., Iwasaki, A., and Fukata, G. - J. Org. Chem., 43: 136 (1978).
- 2) Tashiro, M., Nakayama, K., and Fukata, G. - J. Chem. Soc., Perkin Trans. 1, 1983, 2315.
- 3) Tashiro, M., Mataka, S., Nakamura, H., and Nakayama, K. - J. Chem. Soc., Perkin Trans. 1, 1988, 173.
- 4) Tashiro, M., Mataka, S., Nakayama, K., Tsuzuki, H., and Yonemitsu, T. - J. Chem. Res., (S), 1988, 176.
- 5) Tashiro, M., Tsuzuki, H., Matsumoto, J., Mataka, S., Nakayama, K., Tsuruta, Y., and Yonemitsu, T. - J. Chem. Res., (S), (M), (1989) in press.
- 6) Tashiro, M., Mataka, S., Nakayama, K., and Tsukinoki, T. - Rep. Res. Inst. Ind. Sci. (Kyushu Daigaku Seisan Kagaku Kenkyusho Houkoku), 82: 117 (1987).
- 7) Brugel, W. - 'Handbook of NMR Spectral Parameters', Heydon, London, 1979, p. 35.
- 8) Chatelain, G. - Comm. Energie At. (France) Rappt., 1965, 67; Chem. Abstr., 65: 13626 (1966).
- 9) Consden, R. and Kenyon, J. - J. Chem. Soc., 1935, 1594.
- 10) Wurster, C. - Ber., 6: 1486 (1873).
- 11) Meter, V. and Stuber, O. - Justus Liebigs Ann. Chem., 231: 169 (1885).
- 12) Colman, H. and Falbot, W. F. - Org. Syn. Coll. Vol. 2, 592 (1943).
- 13) Claus, A. - J. Prakt. Chem., 51: 399 (1895).
- 14) Bamberger, E. - Ber., 57: 2082 (1924).
- 15) Nevile, R. H. C. and Winter, A. - Ber., 13: 962 (1880).
- 16) Qvist, W. - Acta Acad. Aboensis, Math. et Phys., 12: 17 (1947); Chem. Abstr., 41: 2397 (1947).
- 17) Wood, A.S. and Pope, E.G. - J. Chem. Soc., 1912, 1823.
- 18) Mayer, V. and Stuber, O. - Justus Liebigs Ann. Chem., 165, 161 (1873).
- 19) Aroney, M. J., Corfield, M. G., and Le Fevre, R. J. W. - J. Chem. Soc., 1964, 2954.