

Ozone-mediated Nitration of Benzoic Acid, its Alkali and Alkaline-earth Metal Salts, Ester, Acid Chloride, Nitrile and Amide with Nitrogen Dioxide

Hitomi Suzuki,^a Jun-ichiro Tomaru^b and Takashi Murashima^a

^a Department of Chemistry, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606-01, Japan

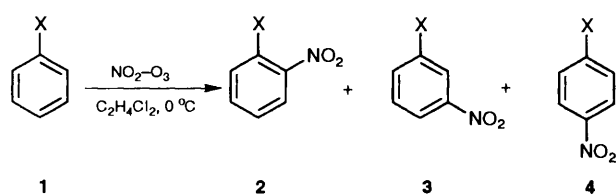
^b Chemical Research Laboratories, Nippon Kayaku Co. Ltd., Simo 3-chome, Kita-ku, Tokyo 115, Japan

The title compounds except for the amide are smoothly nitrated with nitrogen dioxide at low temperatures in the presence of ozone, giving a mixture of the corresponding nitro derivatives mainly composed of the *meta* isomer in high yield. The nitration products are generally rich in the *ortho* isomer compared with those obtained by the conventional procedures based on the use of nitric acid or mixed acid. Under similar conditions, benzamide readily loses nitrogen to afford benzoic acid and its nitro derivatives, while *N,N*-diethylbenzamide is converted into a mixture of three isomeric nitro derivatives with an approximate ratio *ortho* : *meta* : *para* = 3 : 3 : 4.

Nitrogen dioxide has proved itself to be a good nitrating agent for aromatic systems in the presence of ozone. It smoothly converts nonactivated and even deactivated arenes into the corresponding mononitro or polynitro derivatives in good to excellent yields.¹ As part of our continuing efforts to define the scope and elucidate the mechanism of this novel nitration (referred to as kyodai-nitration), we describe in this article the ozone-mediated reaction of benzoic acid **1a** and some of its derivatives **1b–1g** with nitrogen dioxide. Nitrobenzoic acids and derivatives are important as intermediates in the manufacture of dyestuffs, drugs, agrochemicals, resins and other chemical commodities.

Results and Discussion

The nitration of benzoic acid **1a** has been studied using nitric acid,^{2–4} mixed acid,² nitrosylsulfuric acid,⁵ dinitrogen pentoxide³ and ammonium nitrate–trifluoroacetic anhydride.⁶ The isomer compositions of the nitration products are in the ranges *ortho* 17–22%, *meta* 76–82% and *para* 1–5%. Compound **1a** was easily nitrated with nitrogen dioxide in the presence of ozone to give a mixture of three isomeric nitrobenzoic acids **2a**, **3a** and **4a** in excellent yield (Scheme 1). The isomer composition



- a X = CO₂H
 b X = CO₂⁻M⁺
 (M = Li, Na, K, Ca and Ba)
 c X = CO₂Me
 d X = COCl
 e X = CN
 f X = CONH₂
 g X = CONEt₂

Scheme 1

of the product was rich in the *ortho* isomer compared with those obtained by conventional procedures based on the use of nitric acid or mixed acid (Table 1). The preferred explanation for this difference is that the nitration of compound **1a** under

strong acid conditions proceeds in part in the form of the conjugate acid, while kyodai-nitration occurs mainly on the unprotonated substrate. Changing the solvent from 1,2-dichloroethane to the more polar nitromethane led to an appreciable increase of the *meta* isomer. No dinitration products could be detected in the product mixture.

As has recently been demonstrated,⁷ one of the remarkable features of kyodai-nitration is that acid-sensitive compounds such as acetals and acylals can be nitrated successfully under neutral conditions. We provide herein an additional example of such a case. When alkali metal salts **1b** of benzoic acid were subjected to kyodai-nitration as a suspension in an inert organic solvent at low temperature, they were smoothly nitrated to give a mixture of isomeric nitrobenzoic acids **2a**, **3a** and **4a** in good yield. The proportion of the *meta* isomer was appreciably higher compared with that of the nitration product of free acid **1a** (Table 1). This trend was more prominent with the alkaline-earth metal salts than the alkali metal salts, and it was further enhanced in a polar solvent such as nitromethane. To the best of our knowledge, there are no reports in the literature on the direct nitration of benzoic acid salts. Isomer control in the nitration of arenecarboxylic acids based on this methodology will be a subject of forthcoming publication.

Dinitrogen pentoxide generated *in situ* from nitrogen dioxide and ozone is probably the reagent for the present nitration. The assumption that the nitration of alkali metal salts **1b** occurs *via* the initial formation of benzoyl nitrate **5** followed by its reversible conversion into benzoic anhydride **6** and dinitrogen pentoxide (path *b*) as depicted in Scheme 2,⁸ is incompatible with the observed remarkable influence of the alkali metal cation on the isomer distribution. The kyodai-nitration of anhydride **6** proceeded more slowly under the same conditions and produced a mixture of benzoic nitrobenzoic anhydride **7** and nitrobenzoic anhydride **8**. At present, we favour the view that compound **1a** and salt **1b** compete for the active nitrating species, the contribution of the former substrate becoming increasingly important as the reaction proceeds (*i.e.* as the amount of nitric acid formed increases) (path *a*). In support of this, the *ortho*–*meta* isomer ratio of the nitration products was found to increase gradually as the reaction went on further (Table 1). The greater influence of the alkaline-earth salt compared with the alkali salt over the isomer distribution of the nitration product may be due to the divalent cation more effectively promoting the heterolytic cleavage of the dinitrogen pentoxide molecule through coordination to the terminal oxygen atom.

Table 1 Nitration of benzoic acid **1a** and its metal salts **1b** to give nitrobenzoic acids

Compound	Reagent system	Reaction time (h), temperature (°C)	Yield (%)	Isomer proportion (%)			Ratio <i>ortho/meta</i>
				<i>ortho</i>	<i>meta</i>	<i>para</i>	
1a	NO ₂ -O ₃	2, 0	94	27	72	1 ^a	0.38
		1.5, 0 ^b	98	29	69	2 ^a	0.42
		2, 0 ^c	95	23	75	2 ^a	0.31
	HNO ₃ (99%) HNO ₃ (<i>d</i> 1.5) HNO ₃ (<i>d</i> 1.52) HNO ₃ (61%)–H ₂ SO ₄ (97%) HNO ₃ (98%)–H ₂ SO ₄ O ₂ NSO ₃ H (50%)–HNO ₃ (<i>d</i> 1.5) NH ₄ NO ₃ –(CF ₃ CO) ₂ O, CHCl ₃ N ₂ O ₅ –P ₂ O ₅ , CCl ₄	—, 30	—	22	77	1	0.29 ^d
		—, –10	—	—	82	—	— ^e
		—, 0	88	17	82	1	0.21 ^f
		—, 0	99	11	88	1	0.13 ^g
		—, 30	—	20	75	5	0.27 ^d
		—, —	86 ⁱ	—	—	—	— ^h
		2, 25	98 ⁱ	—	—	—	— ^j
1b M = Li	NO ₂ -O ₃	2, 0 ^b	96	21	78	1 ^a	0.27
		3, 0 ^c	96	16	83	1 ^a	0.19
M = Na	NO ₂ -O ₃ , MgO ^k	2, 0 ^b	96	14	85	1 ^a	0.17
		0.5, 0 ^b	5	13	85	2 ^a	0.15
M = K	NO ₂ -O ₃	2, 0 ^b	96	20	78	2 ^a	0.26
		3, 0 ^c	95	16	83	1 ^a	0.19
		2, 0 ^b	94	26	73	1 ^a	0.36
M = 1/2Ca	NO ₂ -O ₃	4, 0 ^c	45	14	84	2 ^a	0.17
M = 1/2Ba		1, 0 ^b	97	9	89	2 ^a	0.10
		1, 0 ^b	96	10	88	2 ^a	0.11

^a Product composition was determined on a Hitachi L-6000 liquid chromatograph using a Hitachi Inertsil ODS-2 column. ^b 1,2-Dichloroethane was employed as the solvent. ^c Nitromethane was employed as the solvent. ^d Ref. 2. ^e Ref. 3. ^f Ref. 4. ^g Present work. ^h Ref. 5. ⁱ Yield of *meta*-nitro derivative. ^j Ref. 6. ^k The reaction was carried out in the presence of MgO (6 mmol).

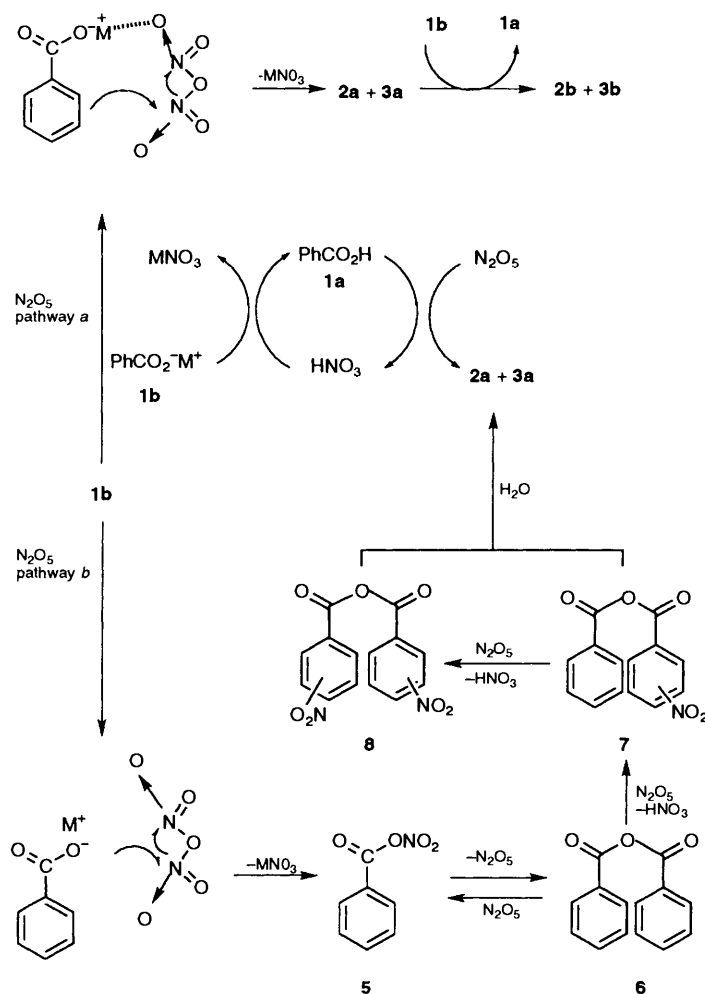
**Scheme 2**

Table 2 Nitration of methyl benzoate **1c**, benzoyl chloride **1d**, benzonitrile **1e** and *N,N*-diethylbenzamide **1g**

Compound	Reagent system	Reaction time (h), temperature (°C)	Yield (%)	Isomer proportion (%)			Ratio <i>ortho/meta</i>
				<i>ortho</i>	<i>meta</i>	<i>para</i>	
1c	NO ₂ -O ₃	3, 0 ^b	88	31	66	3 ^a	0.47
		2.5, 0 ^c	91	27	69	4 ^a	0.39
	HNO ₃ (<i>d</i> 1.52)	—, 0	—	21	73	6	0.29 ^d
		—, 0	—	—	73	—	— ^e
1d	HNO ₃ (<i>d</i> 1.42)-H ₂ SO ₄	1.3, 5-15	81-85 ^g	—	—	—	— ^f
		0.3, 30	88 ^g	—	—	—	— ^h
	NO ₂ BF ₄ , sulfolane	3, -10	99	1	99	— ^{a,i}	0.01
		2, -10	—	—	91	2	— ^j
1e	NO ₂ BF ₄ , sulfolane	0.5, 20-35	85 ^{g,j}	—	—	—	— ^k
		4, 0 ^b	93	22	72	6 ^{a,l}	0.31
	NO ₂ -O ₃	6, 0 ^c	85	15	80	5 ^{a,l}	0.19
		3, 0	100	17	81	2	0.21 ^m
	HNO ₃ (100%)	fuming HNO ₃	2.5, 0	—	—	81	— ⁿ
		HNO ₃ (<i>d</i> 1.52)	1.5, -10	—	—	89	— ^o
	HNO ₃ (100%)-H ₂ SO ₄	0.8, 0	100	15	84	2	0.18 ^m
		fuming-HNO ₃ -HClO ₄ (72%)	8, 25	—	14	82	4
	fuming-HNO ₃ -(CF ₃ CO) ₂ O	1.5, 55	85 ^g	—	—	—	— ^q
		—, 10	89 ^g	—	—	—	— ^r
	KNO ₃ -H ₂ SO ₄	—, 20-35	85 ^g	—	—	—	— ^h
		NO ₂ BF ₄ , sulfolane	—, 20-35	85 ^g	—	—	—
1f	HNO ₃ (<i>d</i> 1.5)	6, -15	—	27	70	3	— ^j
1g	NO ₂ -O ₃	7, 0 ^b	72	29	28	43 ^{a,s}	1.0
		5.5, 0 ^c	57	21	33	46 ^{a,s}	0.64
	HNO ₃ (61%)-H ₂ SO ₄ (97%)	1, 0	75	1	96	3	0.01 ^t
		14, r.t.	84	8	58	34	0.14 ^t
fuming-HNO ₃	—, -10	85	—	30	—	— ^u	

^a Product composition was determined on a Hitachi L-6000 liquid chromatograph using a Hitachi Intersil ODS-2 column, unless otherwise indicated.

^b 1,2-Dichloroethane was employed as the solvent. ^c Nitromethane was employed as the solvent. ^d Ref. 11. ^e Ref. 12. ^f Ref. 9. ^g Yield of *meta*-nitro derivative. ^h Ref. 13. ⁱ Determined as the methyl esters. ^j Ref. 3. ^k Halogen exchange to acid fluoride took place. ^l Determined on a Shimadzu GC-14A gas chromatograph using a Shimadzu CBP-1 M25-025 capillary column. ^m Ref. 15. ⁿ Ref. 16. ^o Ref. 14. ^p Ref. 18. ^q Ref. 19. ^r Ref. 20. ^s Determined on a Hitachi D-3000 gas chromatograph using a Kagakuin Kensa Kyokai G-100 capillary column. ^t Present work. ^u Ref. 21.

The *kyodai*-nitration of methyl benzoate **1c** similarly proceeded with ease, giving a mixture of three isomeric methyl nitrobenzoates **2c**, **3c** and **4c** in high yield. Compared with the isomer composition (*meta* = 81–85%) of the nitration product obtained by the classical procedure,⁹ the enhancement of the *ortho*-substitution (*o*:*m*:*p* = 27–31:66–69:3–4) was noticeable. Such a pronounced trend towards *ortho*-substitution is in line with observations in the nitration of aromatic carbonyl compounds¹⁰ and acylals.⁷ The nitration of ester **1c** has been studied using nitric acid,^{11,12} mixed acid⁹ and nitronium tetrafluoroborate.¹³ The isomer distribution reported is *ortho* 21%, *meta* 73% and *para* 6%.¹¹

Benzoyl chloride **1d** and benzonitrile **1e** were quite slow to react with the present nitrating system, but they were easily nitrated in the presence of methanesulfonic acid as catalyst. Although these compounds are subject to extensive hydrolysis under the conditions of ordinary nitration, no products arising from hydrolysis accompanied our reaction. In the methanesulfonic acid system the isomer distribution was again rich in the *ortho* isomer, however, this trend became less prominent in a polar solvent such as nitromethane (Table 2). The nitration of compound **1d** with dinitrogen pentoxide in carbon tetrachloride has been reported to give nitro derivatives **3d** and **4d** in 90–91% and 2% yields, respectively.³ Compound **1e** has been nitrated using nitric acid alone,^{14–16} nitric acid–sulfuric acid,^{15,17} nitric acid–perchloric acid,¹⁸ trifluoroacetyl nitrate,¹⁹ potassium nitrate–sulfuric acid²⁰ and nitronium tetrafluoroborate.¹³ The isomer compositions of the nitration products are in the ranges *ortho* 14–17%, *meta* 81–89% and *para* 2–4%.

The nitration of benzamide **1f** with fuming nitric acid has been reported to give a mixture of the corresponding nitro derivatives with an isomeric composition *ortho* 27%, *meta* 70% and *para* 3%.³ However, this compound readily lost nitrogen under our conditions to yield the parent acid **1a** and its nitration products with *N*-nitrosoamide as an intermediate. In contrast,

N,N-diethylbenzamide **1g** underwent smooth nuclear nitration to afford a mixture of three isomeric nitro derivatives **2g**, **3g** and **4g** in an approximate ratio of 3:3:4. Neither the addition of an acid catalyst nor the change of the solvent system had much influence on the product composition. As far as can be judged from the isomer distribution, the diethylcarbamoyl group may be better classified as *ortho-para* directing contrary to the general acceptance that the amide group directs an electrophile preferentially at the *meta* position. This finding also substantiates the important role of the conjugate acid as substrate under strong acid conditions.²²

In conclusion, benzoic acid and derivatives were smoothly nitrated with nitrogen dioxide in the presence of ozone at low temperatures, giving a mixture of the corresponding nitro derivatives in high yields. The isomer compositions were generally rich in the *ortho* isomer compared with those from the classical nitrations.

Experimental

General experimental details were given in a previous paper of this series.²³ All reagents except for compound **1g** were obtained from commercial sources. 1,2-Dichloroethane was dried by distillation from calcium hydride and nitromethane from molecular sieves. Nitrogen dioxide (99% pure) was obtained in a cylinder from Sumitomo Seika Co. Ltd. and used after transfer distillation. A Nippon Ozone Co. Ltd., type ON-1-2 apparatus was used for the generation of ozone. The machine produced ozone at a rate of 10 mmol h⁻¹, and its efficiency was calibrated by iodometric titration. All products except for nitroamide **2g** were known and identified by IR, ¹H NMR and GC-MS or by direct comparison with authentic samples.

Kyodai-nitration of Alkali Metal Salts of Benzoic Acid. Typical Procedure.—A suspension of lithium benzoate **1b** (M =

Li) (10 mmol) in freshly distilled 1,2-dichloroethane (50 cm³) was placed in a three-necked 50 cm³ flask fitted with two gas inlet tubes and a vent, and cooled to -10 °C by an external ice-salt bath, while a stream of ozonized oxygen was introduced through one of the gas inlet tubes, which was submerged below the surface of the liquid. A stream of nitrogen dioxide was slowly introduced through the other inlet tube, which opened just above the surface of the liquid. Throughout the reaction, both ozonized oxygen and nitrogen dioxide were fed continuously at a low flow rate. It was necessary to carry out the reaction in the presence of an excess of nitrogen dioxide. Although the chalky appearance of the reaction mixture remained unchanged, the nitration was almost complete after 2 h. The reaction was quenched by the addition of dilute hydrochloric acid, and the organic phase was separated, washed with water, dried, and then evaporated under reduced pressure to leave a mixture of nitrobenzoic acids.

Kyodai-nitration of N,N-Diethylbenzamide 1g.—Into a solution of benzamide **1g** (20 mmol) in dry 1,2-dichloroethane (50 cm³) kept at 0 °C was slowly introduced streams of ozonized oxygen and nitrogen dioxide in a manner described above. The progress of the reaction was monitored by TLC. After 7 h the reaction was complete and the usual work-up gave a mixture of isomeric nitrobenzamides **2g**, **3g** and **4g** as a solid.

N,N-Diethyl-2-nitrobenzamide 2g. M.p. 44.5–45.5 °C; ν_{\max} (KBr)/cm⁻¹ 1638, 1530, 1348, 1289, 1221, 1107, 1071 and 853; δ_{H} (200 MHz; CDCl₃) 1.07 (3 H, t, *J* 7.2), 1.31 (3 H, t, *J* 7.2), 3.11–3.14 (2 H, m), 3.59 (2 H, br s), 7.39 (1 H, dd, *J* 1.5 and 7.6), 7.54–7.58 (1 H, m), 7.69–7.72 (1 H, m) and 8.19 (1 H, dd, *J* 0.9 and 8.2); *m/z* 222 (M⁺, 1.2), 150 (94.3) and 72 (100) (Found: C, 59.3; H, 6.4, N, 12.7. C₁₁H₁₄N₂O₃ requires C, 59.4; H, 6.4, N, 12.6%).

N,N-Diethyl-3-nitrobenzamide 3g. M.p. 73–74 °C (lit.,²⁴ 75–76 °C); ν_{\max} (KBr)/cm⁻¹ 1625, 1536, 1355, 1310, 1105, 1072, 838 and 725; δ_{H} (200 MHz; CDCl₃) 1.16 (3 H, br s), 1.27 (3 H, br s), 3.27 (2 H, br s), 3.58 (2 H, br s), 7.62 (1 H, t, *J* 8.3), 7.74 (1 H, d, *J* 7.7), 8.26 (1 H, s) and 8.27 (1 H, d, *J* 7.7); *m/z* 222 (M⁺, 13.8), 150 (100), 104 (45.1) and 76 (44.4).

N,N-Diethyl-4-nitrobenzamide 4g. M.p. 64–65 °C (lit.,²⁵ 64–65 °C); ν_{\max} (KBr)/cm⁻¹ 1627, 1533, 1350, 1297, 1095, 850 and 725; δ_{H} (200 MHz; CDCl₃) 1.13 (3 H, t, *J* 7.0), 1.28 (3 H, t, *J* 7.0), 3.23 (2 H, q, *J* 7.0), 3.58 (2 H, q, *J* 7.0), 7.56 (2 H, d, *J* 8.1) and 8.28 (2 H, d, *J* 8.1); *m/z* 222 (M⁺, 17.2), 150 (100), 104 (43.9) and 76 (36.7).

Acknowledgements

We acknowledge support of this work by a Grant-in-Aid for Scientific Research No. 05554023 from the Ministry of Education, Science and Culture. T. M. thanks the Japan Society for the Promotion of Science for the Fellowship (No. 2178).

References

- H. Suzuki, T. Murashima, K. Shimizu and K. Tsukamoto, *Chem. Lett.*, 1991, 817; *J. Chem. Soc., Chem. Commun.*, 1991, 1049; H. Suzuki, T. Ishibashi, T. Murashima and K. Tsukamoto, *Tetrahedron Lett.*, 1991, 32, 6591.
- A. F. Holleman, *Ber. Dtsch. Chem. Ges.*, 1906, 39, 1715.
- K. E. Cooper and C. K. Ingold, *J. Chem. Soc.*, 1927, 836.
- B. Aliprandi, F. Cacace and G. Ciranni, *Anal. Chem.*, 1964, 36, 2445.
- P. S. Varma and D. A. Kulkarni, *J. Am. Chem. Soc.*, 1925, 47, 143.
- J. V. Crivello, *J. Org. Chem.*, 1981, 46, 3056.
- H. Suzuki, S. Yonezawa, T. Mori and K. Maeda, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1367.
- V. Gold, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1950, 2452.
- O. Kamm and J. B. Segur, *Org. Synth.*, Coll. Vol. I, 1941, 372.
- H. Suzuki, T. Murashima, A. Tatsumi and I. Kozai, *Chem. Lett.*, 1993, 1421; H. Suzuki and T. Murashima, *J. Chem. Soc., Perkin Trans. 1*, 1994, 903.
- A. F. Holleman, *Recl. Trav. Chim. Pays-Bas*, 1899, 18, 267.
- A. Zaki, *J. Chem. Soc.*, 1928, 983.
- S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.*, 1961, 83, 4564.
- B. Flürscheim and E. L. Holmes, *J. Chem. Soc.*, 1928, 2230.
- J. P. Wibaut and R. van Strik, *Recl. Trav. Chim. Pays-Bas*, 1958, 77, 316.
- J. W. Baker, K. E. Cooper and C. K. Ingold, *J. Chem. Soc.*, 1928, 426.
- M. Schopff, *Ber. Dtsch. Chem. Ges.*, 1885, 18, 1063.
- G. S. Hammond and K. J. Douglas, *J. Am. Chem. Soc.*, 1959, 81, 1184.
- E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 1952, 1695.
- M. T. Bogert and H. T. Beans, *J. Am. Chem. Soc.*, 1904, 26, 464.
- A. Zaki, *J. Chem. Soc.*, 1932, 1184.
- R. B. Moodie, J. R. Penton and K. Schofield, *J. Chem. Soc. B*, 1969, 578.
- H. Suzuki, T. Murashima, I. Kozai and T. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1591.
- H. Erlenmeyer, J. P. Jung and E. Sorkin, *Helv. Chim. Acta*, 1946, 29, 1960.
- H. Baganz and H. Keßlar, *Chem. Ber.*, 1955, 88, 1995.

Paper 4/01903B

Received 30th March 1994

Accepted 13th May 1994