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Synthesis of Furan Derivatives. LIX.[1] Synthesis of 5-Substituted-2-(2-furyl)-1,3,4-oxadiazoles from 1-Furoyl-2-arylidene-hydrazine with Lead Tetraacetate

HARUO SAIKACHI, NOBUHIRO SHIMOJO and YASUJIRO UEHARA

Faculty of Pharmaceutical Sciences, Kyushu University[2]

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It was found out that N-(2-furoyl)-N′-aryl aldehyde hydrazones (Schiff's base) were even more available as starting material for the formation of the corresponding 2-(2-furyl)-5-aryl-1,3,4-oxadiazole rings by the oxidative cyclization of lead tetraacetate.

2,5-Diaryl substituted-1,3,4-oxadiazoles have usually been prepared by the oxidative cyclization of 1-aroyl-2-arylidene-hydrazine with sodium ferrocyanide or sodium nitrite[3] as oxidizing reagent.

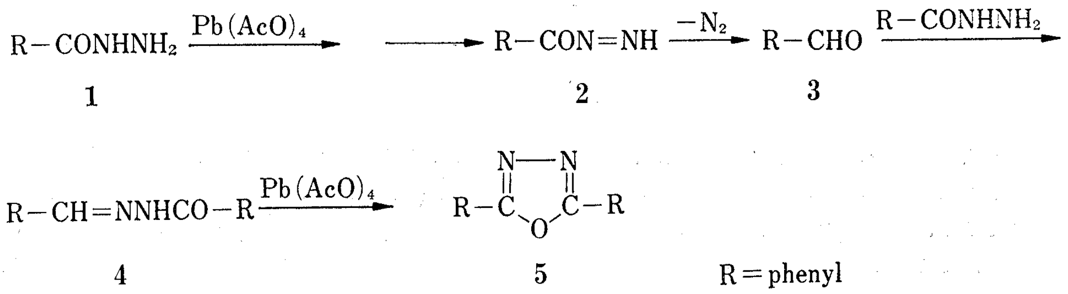

Chart 1

In several recent papers,[4] the formation of 2,5-diphenyl-1,3,4-oxadiazole has been succeeded by the oxidative cyclization of benzhydrazide with lead tetraacetate (Chart 1). Judging from the reaction mechanism,[4] it is essential that over-all two equivalents of lead tetraacetate are required at least. In detail, it is most likely that at the first step one equivalent of lead tetraacetate may bring about oxidation to the acyldi-imide (**2**), and at the second step **2** may be cleaved to the corresponding benzaldehyde (**3**) with elimination of nitrogen molecule, which may condense successively with an excess of one mole of benzhydrazide to isolable 1-benzoyl-2-benzylidenehydrazine (Schiff's base).[4] Therefore, it has been suggested that **4** can safely be available for the formation of 2,5-diphenyl-1,3,4-oxadiazole (**5**) by the oxidative cyclization with lead tetraacetate.

On the another method,[5] 2,5-difuryl-1,3,4-oxadiazole, an analogue of **5**, has been synthesized by oxidation of 1,2-difuroylhydrazine (**9**) with sulfur trioxide-DMF complex in very poor yield.

In this paper, our interest was focused on the scrutiny of the selective oxidation with lead tetraacetate for the ring-formation of 2-furyl-5-aryl-1,3,4-oxadiazoles from 1-furoyl-2-arylidene-hydrazine (Schiff's base) (Chart 3).

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[1] H. Saikachi and H. Muto, *Chem. Pharm. Bull.* **19**, 2262 (1971).

[2] Location: *Katakasu, Fukuoka.*

[3] R. Stlle and E. Munch, *J. Prakt. Chem.*, **70**, 416 (1904).

[4] J.B. Aylward and R.O.C. Norman, *J. Chem. Soc.*, C **1968**, 2399; T. Sasaki and T. Yoshioka, *Bull. Chem. Soc.* (Japan), **43**, 2989 (1970).

[5] E. Baltazzi and A.J. Wysochi, *Chem. Ind.* (London), **1963**, 1080.

In the case of the oxidation of furoylhydrazide (**6**) with lead tetraacetate, the solvent effect was respectively tested in the three different solvents (methanol, anisole and dichloromethane) by a modification of Aylward's method[4] (see experimental). In this case at least, however, no desired oxadiazole (**23**) was obtained, and incidentally the following each different product was isolated from the each reaction mixture using the following different solvents: in methanol (methyl furoate (**7**)[6]), in anisole (*p*-methoxy-2-furyl ketone (**8**)[7]) and in dichloromethane or in acetic acid (both 1,2-difuroylhydrazine (**9**)[8] and furoic acid (**10**)) (Chart 2). From the above results, it was suggested that the solvent effect is responsible for the possibility of these reactions.

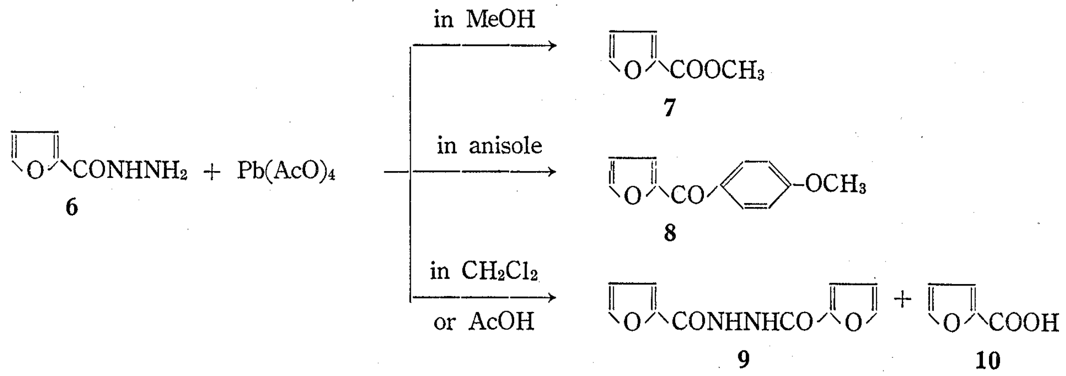

Chart 2

Precisely, for example, the oxidation of **6** in methanol gave an unexpected **7** in 41% yield, and **7** was proved to be identical with infrared (IR) data of an authentic sample[6] (bp 64—65°/35 mm). The result showed that furoyl cation ($C_4H_3OCO^+$) liberated from **6** in the course of this treatment must be strictly reactive enough to form the corresponding methyl ester in methanol solution. Similarly the compound **8** was obtained in anisole (Chart 2). The formation of **8** may be considered to be due to an attack of the furoyl cation against 4-position of anisole ring. NMR spectrum (in $CDCl_3$) of **8** showed a sharp singlet peak at 3.87 ppm (CH_3O-), 1,4-disubstituted phenyl protons at 7.48 ppm (two doublet, $J=9$ Hz), 2-substituted furan protons at 6.55 ppm, 7.19 ppm and 7.64 ppm (quartet). IR spectrum (KBr) of **8** exhibited the presence of carbonyl (1635 cm^{-1}).

In the same way, the oxidation of **6** in dichloromethane (or acetic acid) at room temperature gave unexpectedly both 1,2-difuroylhydrazine (**9**) and furoic acid (**10**) instead of a desired 2,5-difuryloxadiazole (Chart 2). In addition, it was recognized that a yield of **9** in dichloromethane is about three times higher than that in acetic acid as solvent.

On the above unexpected experimental situation, it seemed to be the most useful approach of this work that on the path-way A[4] (Chart 3), 1-(2-furoyl)-2-arylidene-hydrazines, very stable intermediates, can preferably be used as starting material in the oxidative cyclization. Emphatically, these 1-(2-furoyl)-2-arylidene-hydrazines (Schiff's bases) as handy starting material in this cyclization can be readily prepared from furoyl hydrazide in ethanol with some aryl aldehydes (furfural, thenaldehyde, benzaldehyde, 5-methylfurfural, 5-bromofurfural, anisaldehyde, 5-nitrofurfural, 5-nitrothenaldehyde, *p*-nitrobenzaldehyde, *m*-nitrobenzaldehyde and *o*-nitrobenzaldehyde) in good yield. The IR spectral bands (KBr) to be attributable to the characteristic carbonylamide group of the compound were newly observed at 1645 cm^{-1} (**11**—**16**), 1663 cm^{-1} (**18**—**22**) and especially absorption band of -CON= of **17** shifted to higher field by about 40 cm^{-1}. Thus, twelve hydrazones obtained above were fol-

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[6] R. R. Burtner, *J. Amer. Chem. Soc.*, **56**, 666 (1934).
[7] W. Boreche and H. Leditschke, *Ann.*, **529**, 108 (1937).
[8] Th. Curtius and R. Leimbach, *J. Prakt. Chem.*, **65**, 20 (1902).

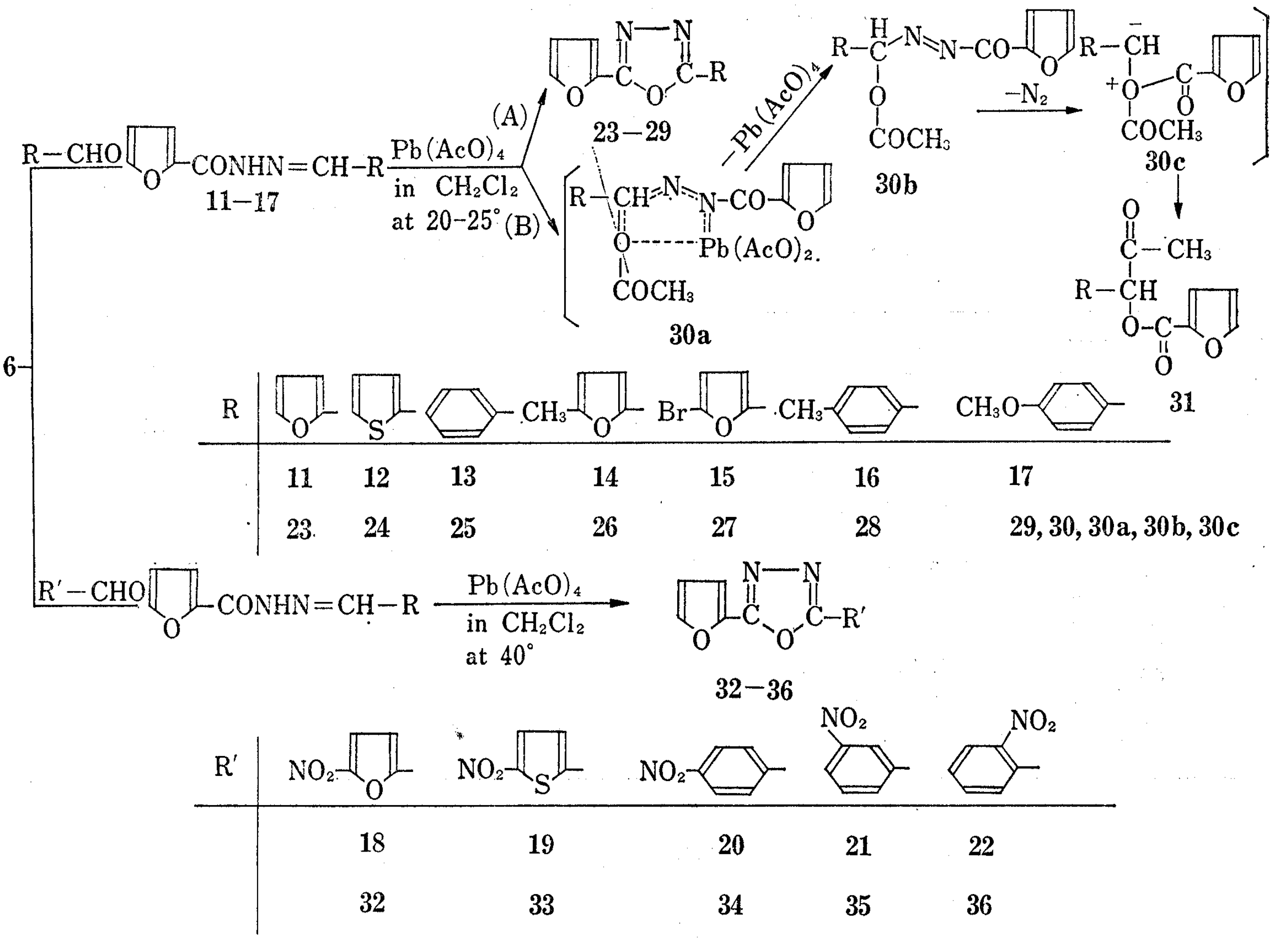

Chart 3

lowed by the oxidative cyclization with lead tetraacetate in dichloromethane to obtain twelve corresponding 2-(2-furyl)-5-substituted-1,3,4-oxadiazoles (**23**—**29** and **32**—**36**) in good yield, respectively (Chart 3, Table I and II).

Next, one equivalent of lead tetraacetate was added to dichloromethane solution of 1-(2-furoyl)-2-arylidene-hydrazines (**11**—**16**) at room temperature to obtain the corresponding 2-furyl-5-substituted-1,3,4-oxadiazoles in high yield, respectively (Table I). The IR spectra (KBr) of these products (**23**—**28**) lacked a characteristic band of amide, but showed a medium band at 1630 cm^{-1}, presumably due to -C=N- group instead of strong amide. Analytical data of **23**—**28** supported each chemical formula. In the compounds (**23**—**28**), nuclear magnetic resonance (NMR) spectra of the three protons of the 2-substituted furan ring exhibited respectively quartet, that is, 6.59—6.61 ppm attributable to proton at 4-position, 7.17—7.22 ppm at 3-position and 7.63—7.65 ppm at 5-position (Table I).

However, the oxidation of 1-(2-furoyl)-2-(*p*-methoxy-benzylidene)hydrazine (**17**) with lead tetraacetate in dichloromethane at room temperature gave both 5-(*p*-methoxyphenyl)-2-furyl-1,3,4-oxadiazole (**29**), mp 134° and α-acetyl-(*p*-methoxyphenyl)furoate (**31**), mp 122° (Chart 3). The IR spectrum (KBr) of **29** showed an absorption of 1623 cm^{-1}, characteristic of -C=N- in the ring of oxadiazole. The NMR spectrum ($CDCl_3$) of **29** showed 3H singlet assigned to methoxy protons, two doublets to the 1,4-disubstituted phenyl protons each centered at 6.97 ppm and 8.00 ppm with J=8.75 (Hz) and quartet to the furan protons each centered at 6.59 ppm, 7.17 ppm and 7.63 ppm. It is conceivable that the formation[9]

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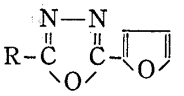
[9] D.C. Iffland and T.M. Davies, *J. Am. Chem. Soc.*, **85**, 2182 (1963).

Table I. 2-(-2-Furyl)-5-aryl-1,3,4-oxadiazole Compounds



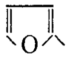
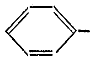
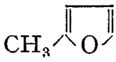
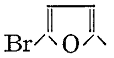
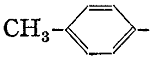
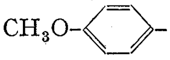
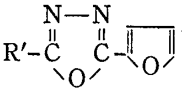
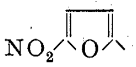
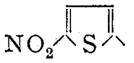
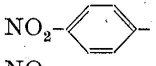
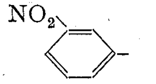
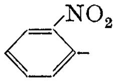
Compd. No.	R	Appearance (recryst. solvt.)	mp (°C)	yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (>C=N-)
23		colorless needles (EtOH)	140	81	59.41	2.99	13.86	59.49	3.03	13.87	1632
24		colorless prisms (pet-benzine)	110	46	55.04	2.77	12.84	54.92	2.96	12.76	1638
25		colorless plates (EtOH)	106—107	78	67.92	3.80	13.20	67.92	3.84	13.15	1637
26		pale yellow needles (EtOH)	121	82	61.11	3.73	12.96	61.22	3.69	12.99	1630
27		colorless needles (EtOH)	153	80	42.73	1.79	9.97	42.94	1.77	9.92	1632
28		cololress needles (*n*-hexane)	134—136	84	69.01	4.46	12.38	69.15	4.47	12.35	1635
29		colorless needles (EtOH)	134	18.5	64.46	4.16	11.57	64.15	3.91	11.94	1622

Table II. 2-(-2-Furyl)-5-aryl-1,3,4-oxadiazole Compounds



Compd. No.	R′	Appearance (recryst. solvt.)	mp (°C)	yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (>C=N-)
32		yellow needles (THF)	260—261	27.7	48.59	2.04	17.00	48.95	2.23	16.95	1628
33		yellow plates (THF)	215	80.5	45.64	1.92	15.97	45.40	2.01	15.94	1630
34		pale yellow plates (THF)	256	80.8	56.03	2.74	16.34	56.04	2.84	16.25	1637
35		pale yellow needles (THF)	178	90	56.03	2.74	16.34	56.22	2.89	16.38	1630
36		pale yellow needles (THF)	143	95	56.03	2.74	16.34	55.77	2.87	16.31	1623

of **31** from **17** may be brought about with elimination of one nitrogen molecule from **17** through intermediates (**30a,b,c**) in the sequences of this reaction pathway (B) (Chart 3). More precisely, the reaction may be interpreted as the formation of **30b** *via* a tetravalent lead ester (**30a**). Elimination of elemental nitrogen from azo group (**30b**) gives the ionic species (**30c**), which rearranges by a 1,2-shift[9] to **31**, finally. **31** was colorless needles, mp 122—123° (from ethanol); the IR spectrum (KBr) of **31** is 1675 cm^{-1} (C=O, carbonyl), 1745 cm^{-1} (C=O, ketone); NMR spectrum (CDCl$_3$) shows the 3H singlet signal due to CH$_3$CO protons, two doublets due to

1,4-disubstituted phenyl protons centered at 6.86 ppm and 7.44 ppm with J=8.75 (Hz) and quartet due to the furan protons at 6.45 ppm, 7.22 ppm and 7.51 ppm.

The successful synthesis of 2-furyl-5-(nitro substituted aryl)-1,3,4-oxadiazoles (**32**—**36**) promoted us to undertake oxidation of 1-(2-furoyl)-2-arylidene-hydrazines (**18**—**22**) with lead tetraacetate in dichloromethane at 40° (Chart 3 and Table II). The IR spectra (KBr) of those nitro products (**32**—**36**) lacked absorption due to amide, but showed a medium 1623—1637 cm^{-1}, presumably due to -C=N-, instead of the strong amide (1663—1680 cm^{-1}). In NMR spectra of the nitro compounds (**32**—**36**) obtained from 1-(2-furoyl)-2-(nitro-arylidene)-hydrazines (**18**—**22**), each proton at 3,4 and 5 position of furan ring show quartet at 7.41—7.51 ppm, 6.83—6.85 ppm and 8.06—8.10 ppm and also signals of proton in -NH- and -N=CH- of the hydrazones (**18**—**22**) lack. Strong support of the formation of the expected structure of 2,5-disubstituted-1,3,4-oxadiazoles comes from the both above NMR results and elemental analytical data.

Experimental

Materials——Lead tetraacetate was dried in a vacuum desiccator containing sodium hydroxide. The infrared spectra were recorded on a Koken DA-301 model grating spectrometer and the NMR spectra on a Nihondenshi Model C-60H NMR Spectrometer (60 MHz, TMS as the internal reference). All melting points and boiling point are uncorrected.

2-Methyl Furoate (**7**)——Furoyl hydrazide (**6**) (5 g, 0.039 mole) was added at 25° for 1 hr, with stirring, to a solution of lead tetraacetate (43.5 g, 0.098 mole) in methanol (130 ml). Effervescence began at once and ceased within *ca.* one min of the final addition. After removal of the solvent the residue was extracted with ethylacetate. The yellow layer was washed with water. Drying and evaporation left a yellow oil which was distilled at 64—65° (3.5 mm) to give colorless oil of **7** (2 g, 41%). The products were identified in comparison of the IR spectrum with the authentic sample. *Anal.* Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.34; H, 5.17.

***p*-Methox-yphenyl 2-Furyl Ketone** (**8**)——**6** (5 g, 0.039 mole) was added at 25° in 1 hr, with stirring, to a solution of lead tetraacetate (43.5 g, 0.098 mole) in anisole (130 ml). When effervescence had ceased, solvent were distilled off under reduced pressure. And the resulting residue was chromatographed on silica gel (CC-7, Mallinckrodt) using ethylacetate as the solvent. The pale yellow band was eluted and recrystallized from petroleum ether to give colorless needles of **8** (0.15 g, 2.4%), mp 61—62.5°. *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28, H, 4.99. Found: C, 71.00; H, 5.09. The NMR spectrum ($CDCl_3$) of **8** showed a singlet peak at 3.87 ppm (CH_3O–), 1,4-disubstituted phenyl protons at 6.94 ppm and 8.00 ppm as each two doublets, J=9 (Hz), 2-substituted furan protons at 6.55 ppm, 7.19 ppm and 7.64 ppm (quartet). Its IR spectrum (KBr) showed the presence of carbonyl (1635 cm^{-1}).

1,2-Difuroylhydrazine (**9**) **and 2-furoic acid** (**10**)——**6** (4 g, 0.032 mole) was added at 25° in 1 hr with stirring to a suspended solution of lead tetraacetate (17.5 g, 0.04 mole) in acetic acid (50 ml). When effervescence had ceased, acetic acid was distilled off under reduced pressure. And the resulting mixture was washed with water. 1,2-Difuroylhydrazine (**9**) was isolated by sublimation on a cold surface; colorless needles, yield, 0.3 g (4.3%), mp 248—250°. *Anal.* Calcd. for $C_{10}H_8N_2O_4$; C, 54.55; H, 3.66; N, 12.72. Found: C, 54.64; H, 3.72; N, 12.68. IR spectrum (Nujol) of the compound showed the presence of amide (1635 cm^{-1}). Furoic acid (**10**) was separated from concentrated water phase; colorless needles, yield, 1.58 g (43%), mp 130—132°. This product was identified with the authentic sample of **9** (was prepared from hydrazine hydrate with furoyl chloride) by a mixed fusion (the mixed mp 131—132°) and comparison of IR spectra. The product of **10** was identified comparison of the IR spectrum with authentic material.

General Procedure for the Preparation of 2-Furyl-1,3,4-oxadiazoles (23—29 **and** 32—36)——A) 2,5-Difuryl-1,3,4-oxadiazole (23) : Lead tetraacetate (4.43 g, 0.01 mole) in dichloromethane (100 ml) was added for 1 hr, with vigorous stirring, to a dichloromethane (200 ml) solution of 1-(2-furoyl)-2-furfurylidenehydrazine (**11**) (2.04 g, 0.01 mole), and furthermore, the mixture was washed with water, dried over fused Na_2SO_4, and evaporated to leave crude **11**. The residue was recrystallized from ethanol to afford 1.65 g (81%) of **11**, mp 140°. IR spectrum (KBr) of the product lacked an absorption due to –C=N–. NMR spectrum showed quartet at 6.61 ppm, 7.21 ppm and 7.65 ppm correspondeing the 2-substituted furan ring protons of 1,3,4-oxadiazole. In the same manner, those compounds (**24**—**29**) were each prepared from the compounds (**12**—**17**) with lead tetraacetate. Appearance and analytical data are listed in Table I.

B) 2-Furyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazole (32) : Lead tetraacetate (2.57 g, 0.058 mole) in dichloromethane (100 ml) was added at 40° for 4 hr, with vigorous stirring, to a suspension of 1-(2-furoyl)-2-(5-nitro-2-furfurylidene)hydrazine (1 g, 0.039 mole) in dichloromethane (300 ml). The mixture was allowed to stand at room temperature overnight, washed with water, dried (Na_2SO_4), evaporated under reduced pressure, to leave crude **32**, which was recrystallized from tetrahydrofuran to afford 0.8 g of pure **32**, pale yellow plates, mp 256°. In the same manner, those compounds (**33**—**36**) were each prepared from **19**—**22** with lead tetraacetate, respectively. Appearance and analytical data were listed in Table II.

Acknowledgement The authors are indebted to Dr. S. Shimoyama, Department of Development, Mitsubishi Chemical Works, Kurosaki and Dr. W. Kashiwara for their contribution of many important chemicals for this work. The micro analytical data were obtained through the courtesy of the staffs in the analytical research section of Kyushu University.