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LIPOPHILIC COMPLEXONES. PART 2[1]

SYNTHESIS OF POLYETHERS DERIVED FROM 2-ALKYL-1, 3-PROPANEDIOLS AND 2, 2-BIS (HYDROXYMETHYL) DECANOL

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Abstract—Tripodand, dipodands, and crown ethers were synthesized in reasonable yields from 2-alkyl-1, 3-propanediols and 2, 2-bis(hydroxymethyl) decanol. These alcohols were alkylated with chloroacetic acid, reduced, and then the oxyethylenated derivatives were converted into the desired lipophilic complexones via a simple nucleophilic substitution.

In our research on the oxidation of aromatics with metal ion oxidants we needed the complexones which could bring these ions into an organic phase.[2] In order to avoid substantial decrease of redox potential we designed, in accordance with the general rules,[3] the ligands which, we hoped, should complex Ce(IV) oxidant ions not too strongly but simultaneously bring them into the organic phase. Our attention was drawn to lipophilic podands[4] which could be prepared from long-chain polyalcohols.

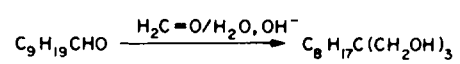
In this paper we report the synthesis of such new compounds starting from the easily accessible 2-alkyl-1, 3-propanediols **1** and 2, 2-bis(hydroxymethyl) decanol **2**, prepared as shown in Scheme 1. An attempt to attach two oxyethylene chains directly to diol **1** failed and only the mono-oxyethylene derivatives **3** and **5** were obtained. We overcame this difficulty by alkylation of alcohols **1** and **2** with chloroacetic acid and then reduction of products **6–8** with lithium aluminium hydride to the corresponding alcohols **9** and **10**. In the case of liquid acids, they were converted into methyl esters, distilled, and then reduced. Obtained alcohols **9** and **10** gave sulphonates which afforded the desired podands **12** and **14**. This route gave reasonable yields and can be considered as a general approach to various lipophilic complexones.

The synthesis of **14** described above offers an improvement as compared with the tedious synthesis of the analogous podand derived from pentaerythritol monoether.[5] Diols **9** could be utilized for the efficient synthesis of lipophilic crowns **15**.

The preliminary results of our study on the application of **12** and **14** as catalysts in the two-phase oxidation with Ce(IV) ions demonstrated that these complexones act as inhibitors, probably modifying the interface, thus hindering contact of the reagents. Further research on these complexones and on the synthesis of new ones is underway in our laboratory.

1

R = C_4H_9 **1a** ; $C_{10}H_{21}$ **1b** ; $C_{18}H_{37}$ **1c**



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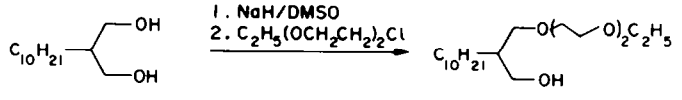

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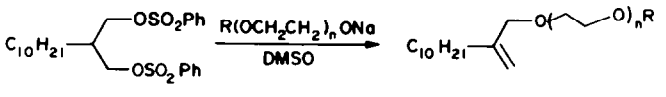
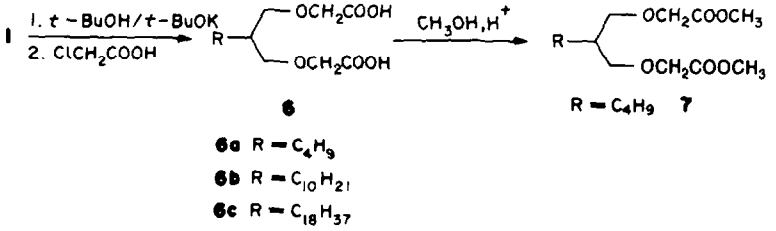


4

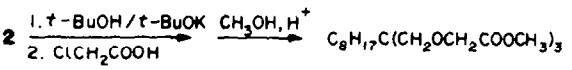
5a n = 2, R = C_2H_5
5b n = 3, R = CH_3



6

6a R = C_4H_9
6b R = $C_{10}H_{21}$
6c R = $C_{18}H_{37}$

R = C_4H_9 **7**



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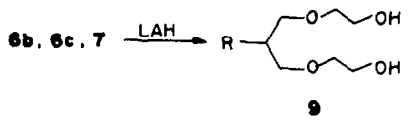
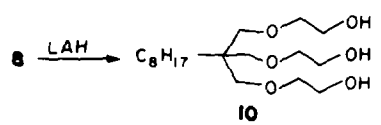


9

R = C_4H_9 **9a** $C_{10}H_{21}$ **9b**; $C_{18}H_{37}$ **9c**



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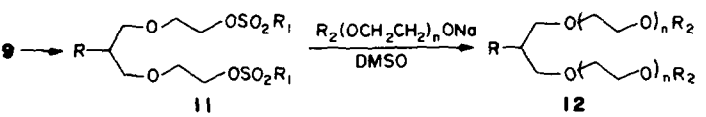
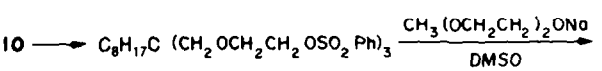


11 **12**

R = $C_{10}H_{21}$, R_1 = Ph **11a**
R = $C_{18}H_{37}$, R_1 = CH_3 **11b**

R = $C_{10}H_{21}$, R_2 = C_2H_5, n = 3, **12a**
R = $C_{18}H_{37}$, R_2 = C_2H_5, n = 3, **12b**
R = $C_{18}H_{37}$, R_2 = CH_3, n = 4, **12c**



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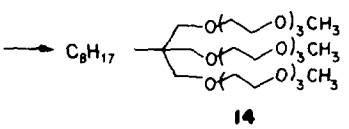
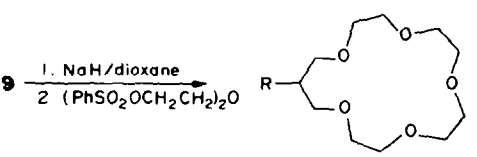


14



15

R = C_4H_9 **15a**; $C_{10}H_{21}$ **15b**

TLC plates prepared with silica gel on glass were purchased from Merck.

2-alkylpropanediols-1,3 **1**. Corresponding alkylmalonate diethyl esters were reduced with LAH in the usual manner, as described for **1a**.[6]

1b M.p. 60°, IR (KBr) ν_{C-O} 1035, ν_{C-H} 2875, 2940, ν_{O-H} 3320 br.; NMR ($CDCl_3$) 1.24 (3H, t, 6 Hz, $-CH_3$), 1.61 (18H, m, $-CH_2-$), 2.00 (1H, m, -CH=), 3.80–4.12 (4H, m, $-CH_2O-$), 4.58 (2H, s, OH). **1c** M.p. 86–89°, IR (KBr) ν_{C-O} 1060, ν_{C-H} 2870, 2935, ν_{O-H} 3310 br.; NMR ($CDCl_3$) 1.25 (3H, t, 7 Hz, $-CH_3$), 1.65 (34H, s, $-CH_2-$), 2.10 (1H, m, -CH=), 3.94–4.10 (4H, m, $-CH_2-$), 4.23 (2H, s, OH).

2,2-bis(hydroxymethyl)decanol **2**. n-Decanal was hydroxymethylated as described in literature.[7] M.p. 72–75° (lit.[7] 72–73°, lit.[8] 73–75°).

Di(benzenesulphonate) of 2-decylpropanediol-1,3 **4**. To a soln of **1b** in dry pyridine, an excess of benzenesulphonyl chloride was added dropwise at 0°. The mixture was stirred for 3 h at room temp, poured into ice-water and extracted with methylene dichloride. The extract was washed with hydrochloric acid solution, then with water, and dried over $MgSO_4$. The solvent was evaporated and crystallization from light petroleum yielded the product. m.p. 34°, IR (KBr) ν_{C-O} 1095, ν_{SO_3} 1185, 1365, ν_{C-H} 2875, 2940, 3070; NMR ($CDCl_3$) 1.21 (3H, t, 6 Hz, $-CH_3$), 1.44–1.58 (18H, m, $-CH_2-$), 2.30 (1H, m, -CH=), 4.30 (4H, m, $-CH_2O-$), 7.84–8.24 (10H, m, aromatic).

Mono-oxyethylene derivative **3**. Sodium hydride (0.48 g, 50% in oil, 10 mmol), washed twice with dry pentane, reacted with **1b** (1.0 g, 5 mmol) in dry DMSO under nitrogen. To this mixture a soln of 1-chloro-3, 6-dioxaoctane (1.6 ml, 10.5 mmol) in DMSO (5 ml) was injected and the mixture was stirred at 60° for 10 h. Then mixture was poured into water, extracted with methylene dichloride; the extract was washed with water and dried over anh. $CaSO_4$. After evaporation the residue was chromatographed on silica gel and gave 0.505 g (31%) of **3** as the sole product; R_f 0.23, chloroform-ethyl acetate 2 : 1; IR (film) ν_{C-O}, 1110, ν_{C-H} 2870, 2935, ν_{O-H} 3370 br.; NMR ($CDCl_3$) 1.20 (3H, t, 6 Hz, $CH_2CH_2CH_3$), 1.53 (3H, t, 7 Hz, OCH_2CH_3), 1.59 (18H, s, CCH_2C), 2.08 (1H, m, =CH-), 3.17 (1H, s, OH), 3.80–3.97 (14H, m, OCH_2-).

Mono-oxyethylene derivatives **5**. Sodium hydride (1.01 g, 50% in oil, 21 mmol), washed with dry pentane, reacted with the monoethyl ether of diethylene glycol (2.8 ml, 21 mmol) in THF (10 ml) for 20 min. To this soln **4** (4.9 g 10 mmol in THF (25 ml was added under nitrogen and the mixture was stirred at 50° for 14 h. After cooling cyclohexane (50 ml) was added, the mixture was left for 2 h, then filtered through Cellite and evaporated. Column chromatography on silica gel gave 1.20 g (38%) of **5a**; R_f 0.53, chloroform–ethyl acetate 2 : 1; IR (film) ν_{C-O} 1117, $\delta_{=CH_2}$ 900, $\nu_{C=C}$ 1645, ν_{C-H} 2875, 2945, 3095; NMR ($CDCl_3$) 1.23 (3H, t, 6 Hz, $-CH_2CH_2CH_3$), 1.54 (3H, t, 7 Hz, $-OCH_2CH_3$), 1.60 (16H, s, $CH_3(CH_2)_8CH_2$), 2.40 (2H, t, 7 Hz, $CH_3(CH_2)_8CH_2-$), 3.83–4.06 (10H, m, $-CH_2CH_2O-$), 4.31 (2H, s, $\diagdown\!\!\diagup C-CH_2O-$), 5.23 and 5.33 (2H, ds, $=CH_2$).

Analogously, using monomethyl ether of triethylene glycol, corresponding **5b** was obtained in 54% yield: R_f 0.39, chloroform–ethyl acetate 2 : 1; IR (film) ν_{C-O} 1110, $\delta_{=CH_2}$ 900, $\nu_{C=C}$ 1645, ν_{C-H} 2875, 2940, 3095; NMR ($CDCl_3$) 1.23 (3H, t, 6 Hz, $-CH_2CH_3$), 1.64 (16H, s, $CH_3(CH_2)_8CH_2-$), 2.40 (2H, t, 7 Hz, $CH_3(CH_2)_8CH_2-$), 3.75 (3H, s, $-OCH_3$) 3.90–4.04 (12H, m, $-OCH_2CH_2-$), 4.31 (2H, s, $C-CH_2O-$), 5.24 and 5.35 (2H, ds, $=CH_2$).

Dicarboxylic acids **6** *and ester* **7**. 2-alkylpropanediol-1,3 **1** (40 mmol) was dissolved in t-BuOH (150 ml) and reacted with potassium (200 mmol) under N_2. To the soln of alkoxide, chloroacetic acid (100 mmol) soln in t-BuOH was added slowly and the mixture was stirred under reflux for 4 h. After cooling *ca* 4 ml of conc. HCl soln was added and the solvent was removed on a rotatory evaporator. The residue was diluted with benzene and dried by azeotropic distillation. After filtering off KCl, the benzene soln was left overnight, and crystallized acid was collected. Recrystallization from the benzene-cyclohexane mixture gave:

6b, 66% yield, m.p. 71–73°; IR (KBr) $\nu_{C=O}$ 1720, ν_{C-H} 2875, 2940, ν_{O-H} 3000 br.; NMR ($CDCl_3$) 1.24 (3H, t, 6 Hz, CH_3-), 1.64 (18H, s, $-CH_2-$), 2.26 (1H, m, -CH=), 3.96 (4H, d, 6 Hz, $-CH_2O-$), 4.50 (4H, s, $-CH_2CO_2H$), 10.75 (2H, s, $-CO_2H$),

6c, 79% yield, m.p. 92–93°, IR (KBr) $\nu_{C=O}$ 1720, 1740, ν_{C-H} 2875, 2935, ν_{O-H} 3000 br.; NMR ($CDCl_3$) 1.24 (3H, t, 6 Hz, CH_3-), 1.66 (34H, s, $-CH_2-$), 2.30 (1H, m, -CH=), 3.96 (4H, m, $-CH_2O-$), 4.50 (4H, s, $-CH_2CO_2H$), 6.30 (2H, s, $-CO_2H$).

In the case of **6a**, benzene was evaporated and an oily residue was refluxed with methanol and a trace of *p*-toluenesulphonic acid for 24 h. Methanol was evaporated, the resulting ester taken into carbon tetrachloride, washed with aqueous $NaHCO_3$ and water, and dried over $MgSO_4$. Solvent was evaporated and obtained ester **7** was distilled *in vacuo*; 53% yield, $b.p._{0.5}$ 132–134°, R_f 0.53, ethyl acetate with 1% of methanol; IR (film) ν_{C-O} 1130, 1220, $\nu_{C=O}$ 1760, ν_{C-H} 2880, 2940, NMR ($CDCl_3$) 1.22 (3H, t, 7 Hz, CH_3), 1.62 (6H, m, $-CH_2-$), 2.26 (1H, m, -CH=), 3.86 (4H, d, 6 Hz, $-CH_2O-$), 4.07 (6H, s, $-OCH_3$), 4.11 (4H, s, $-OCH_2CO_2$).

Triester **8**. For the preparation of **8**, the above procedure was applied using 0.3 g-at. of potassium and 150 mmol of chloroacetic acid. The ester was obtained in 46% yield. $B.p._{0.5}$ 200°; R_f 0.61, ethyl acetate with 1% of methanol; IR (CCl_4 soln) ν_{C-O} 1130, 1220, $\nu_{C=O}$ 1755, ν_{C-H} 2870, 2935; NMR ($CDCl_3$) 1.20 (3H, t, 6 Hz, CH_3-), 1.60 (14H, m, $-CH_2-$), 3.79 (6H, s, $-CH_2O-$), 4.05 (9H, s, $-OCH_3$), 4.40 (6H, s, $-OCH_2CO_2$).

Glycols **9** *and* **10**. All the reductions were performed with LAH in THF, under reflux for 1 h. After the usual work up with aqueous NaOH, precipitated salts were filtered off through Celite and THF was evaporated. The residue was dried azeotropically with benzene and then crystallized (**9c**), distilled (**9a**) and (**9b**) or submitted directly to the following reaction (**10**). **9c**, 82% yield, m.p. 54–56° (acetone), IR (KBr) ν_{C-O} 1075, 1135, ν_{C-H} 2885, 2935, ν_{O-H} 3340 br.; NMR ($CDCl_3$) 1.22 (3H, t, 7 Hz, CH_3-), 1.62 (34H, m, $-CH_2-$), 2.22 (1H, m, -CH=), 3.37 (2H, s, OH), 3.87 (8H, t, 6 Hz, $-OCH_2CH_2O-$), 4.02 (4H, d, 5.5 Hz, $-CH_2O-$); **9b**, 70% yield, $b.p._{0.5}$ 172–174°, R_f 0.31, ethyl acetate with 1% of methanol; IR (film) ν_{C-O} 1060, 1120, ν_{C-H} 2870, 2935, ν_{O-H} 3390 br.; NMR ($CDCl_3$) 1.23 (3H, t, 6 Hz, CH_3-), 1.63 (18H, m, $-CH_2-$), 2.22 (1H, m, -CH=), 3.74 (2H, s, -OH), 3.85 (8H, t, 6 Hz, $-OCH_2CH_2O-$), 4.02 (4H, m, $-CH_2O-$); **9a**, 75% yield, $b.p._{0.4}$ 120° R_f 0.25, ethyl acetate with 1% of MeOH; IR (film) ν_{C-O} 1060, 1120, ν_{C-H} 2870, 2935, ν_{O-H} 3380 br.; NMR ($CDCl_3$) 1.24 (3H, t, 6 Hz, CH_3-), 1.65 (6H, m, $-CH_2-$), 2.20 (1H, m, -CH=), 3.86 (8H, t, 6 Hz, $-OCH_2CH_2O-$), 4.03 (4H, m, $-CH_2O-$), 4.07 (2H, s, OH). In the case of **10**, the crude product (R_f 0.23, ethyl acetate with 1% of methanol) was directly converted into benzenesulphonate.

Sulphonates **11** *and* **13**. The esters were obtained from **9** and **10** with sulphonyl chloride in dry pyridine, as described above for **4**. **11a**, 98% yield, oil, IR (film) ν_{C-O} 1020, 1130, ν_{SO_3} 1185, 1365, ν_{C-H} 2870, 2940, 3085, NMR ($CDCl_3$) 1.18 (3H, t, 6 Hz, CH_3-), 1.55 (18H, m, $-CH_2-$), 1.88 (1H, m, -CH=), 3.55 (4H, d, 5.5 Hz, $-CH_2O-$), 3.81 (4H, d, 5 Hz, $-CH_2O-$)[9], 4.38 (4H, t, 5 Hz, $-CH_2OSO_2-$), 7.76–8.18 (10H, m, aromatic); **11b**, 80% yield, m.p. 53–54° (pentane), IR (KBr) ν_{C-O} 1020, 1115, ν_{SO_3} 1160, 1370, ν_{C-H} 2880, 2960; NMR (CCl_4) 1.20 (3H, t, 6 Hz, CH_3), 1.60 (34H, s, $-CH_2-$), 1.92 (1H, m, -CH=), 3.29 (9H, s, CH_3SO_2), 3.77 (4H, d, 6 Hz, $-CH_2O-$), 3.98 (4H, m, $-OCH_2CH_2OSO_2-$), 4.59 (4H, m, $-OCH_2CH_2OSO_2-$). **13**, 57% yield for two steps, oil, purified by flash chromatography on silica gel; IR (film) ν_{C-O} 1015, 1130, ν_{SO_3} 1190, 1360, ν_{C-H} 2870, 2940, 3080; NMR ($CDCl_3$) 1.15 (3H, t, 6 Hz, CH_3-), 1.57 (14H, m, $-CH_2-$), 3.53 (6H, s, $-CH_2O-$), 3.91 (6H, t, 5 Hz, $-OCH_2CH_2OSO_2-$), 4.50 (6H, t, 5 Hz, $-OCH_2CH_2OSO_2-$), 7.90–8.32 (10H, m, aromatic).

Dipodands **12**. To a soln of NaH (0.528 g, 50% in oil, without washing, 11 mmol) in DMSO (20 ml) and monoethyl ether of diethylene glycol (1.480 g, 11 mmol), **11a** (2.92 g, 5 mmol) in DMSO (5 ml) was added. The mixture was stirred under nitrogen at room temperature for 20 h. After work up with water and extraction with methylene dichloride, the crude product was obtained. Column chromatography on silica gel gave 1.0 g (37%) of **12a**. R_f 0.64, ethyl acetate, oil; IR (film) ν_{C-O} 1125vs, ν_{C-H} 2870, 2940; NMR ($CDCl_3$) 1.20 (3H, t, 5 Hz, CH_3-) 1.53 (6H, t, 7 Hz, $-OCH_2CH_3$), 1.60 (18H, m, $-CH_2-$), 2.05 (1H, m, -CH=), 3.75–3.96 (32H, m, $-OCH_2-$). The reactions were run in the same manner for **11b** with the monoethyl ether of diethylene glycol

and monomethyl ether of triethylene glycol, respectively. After column chromatography on silica gel following products were obtained: **12b**, 78% yield, oil, IR (film) ν_{C-O} 1120vs, ν_{C-H} 2870, 2940; NMR ($CDCl_3$) 1.23 (3H, t, 6 Hz, CH_3-), 1.52 (6H, t, 6 Hz, $-OCH_2CH_3$), 1.57 (34H, s, $-CH_2-$), 3.68–4.00 (32H, m, $-CH_2O-$); **12c**, 44% yield, oil, IR (film) ν_{C-O} 1120 vs, ν_{C-H} 2875, 2950; NMR (CCl_4) 1.17 (3H, t, 5.5 Hz, CH_3-), 1.55 (34H, s, $-CH_2-$), 2.04 (1H, m, –CH=), 3.57 (6H, s, $-OCH_3$), 3.74–3.84 (36H, m, $-OCH_2-$).

Tripoland **14**. Sodium hydride (0.794 g, 50% in oil, 16 mmol) was reacted under nitrogen with a soln of monomethyl ether of diethylene glycol (2.6 g, 22 mmol) in THF (10 ml) and DMSO (3 ml) mixture. After stirring at 50° for 1 h and cooling to room temp, a soln of **13** (2.57 g, 3.33 mmol) in THF–DMSO (1:1 v/v) mixture (10 ml) was injected with a syringe and the reaction mixture was stirred for 38 h at 68°. After cooling, the mixture was worked up with methylene dichloride and the saturated soln of sodium chloride. The organic layer was dried over anh. $CaSO_4$ and evaporated. An oily residue (1.2 g) was chromatographed on silica gel. Tripodand **14** was obtained as an oil (0.5 g, 23%); R_f 0.20, ethyl acetate; IR (film) ν_{C-O} 1120, ν_{C-H} 2880, 2930; NMR ($CDCl_3$) 1.23 (3H, t, 5 Hz, CH_3CH_2-), 1.62 (14H, s, $-CH_2-$), 3.68 (6H, s, $-C(CH_2O)-$) 3.76 (9H, m, CH_3O-), 3.90–4.03 (36H, m, $-OCH_2CH_2O-$).

Crown ether **15b**. To a soln of diol **9b** (1.913 g, 6.3 mmol) in dioxane (40 ml), NaH (0.620 g, 50% in oil, 13 mmol) was added under nitrogen, and then a solution of the benzenesulphonate of diethylene glycol (2.55 g, 6.6 mmol) in dioxane (20 ml) was injected. This mixture was refluxed under nitrogen for 24 h, then water (2 ml) was added and the mixture was additionally refluxed for 48 h. After cooling, a few drops of concd. HCl were added, dioxan was removed by evaporation under reduced pressure, and the remaining oil was worked up with water and methylene dichloride. The organic phase was washed with water, dried over $MgSO_4$, and evaporated. Column chromatography on basic alumina gave crown ether **15b** (1.2 g, 50%), oil, IR (CCl_4) ν_{C-O} 1120, ν_{C-H} 2870, 2940; NMR (CCl_4) 1.19 (3H, t, 6.5 Hz, CH_3-), 1.58 (18H, s, $-CH_2-$), 1.92 (1H, m, –CH=), 3.71 (4H, d, 5.5 Hz, $=CHCH_2O-$), 3.85 (16H, m, $-OCH_2CH_2O-$).

Crown ether **15a**. This compound was prepared in the same way using diol **9a**. The crude product, after being evaporated (100°/12 mm Hg), was distilled at 170–175° (bath)/0.1 mm Hg and gave 78% yield of **15a**. Oil, IR (CCl_4 soln.) ν_{C-O} 1125, ν_{C-H} 2875, 2940, 2970; NMR (CCl_4) 1.20 (3H, t, 7 Hz, CH_3-), 1.57 (6H, m, $-CH_2-$), 1.95 (1H, m, –CH=), 3.70 (4H, d, 5.5 Hz, $=CHCH_2O-$), 3.85 (16H, m, $-OCH_2CH_2O-$).

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[9]Both $-CH_2O-$ groups are non-equivalent.
[10]All new products gave satisfactory microanalyses C, ±0.5%; H, ±0.3%.