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# Lipophilic Complexones, Part 3[1]. Synthesis of Polyamines Derived from 2-Alkyl-1,3-propanediols and 2,2-Bis(hydroxymethyl)alkanols

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Lipophilic di-, tri-, tetra-, and hexaamines were synthesized from 2-alkyl-1,3-propanediols and 2,2-bis(hydroxymethyl)alkanols. The alcohols were converted into the sulfonate esters which were substituted with ethylenediamine or sodium azide. The azides were directly reduced to give amines. Also di-oxyethylenated 2-octadecyl-1,3-propanediol yielded the corresponding amine. Some amines were converted into the salicylidene derivatives.

*(Keywords: Complexone; Polyamines)*

*Lipophile Komplexone, 3. Mitt.*[1]:
*Synthesen von Polyamin-Derivativen von 2-Alkyl-1,3-propandiolen und 2,2-Bis(hydroxymethyl)-alkanolen*

Lipophile Di-, Tri-, Tetra- und Hexamine wurden aus 2-Alkyl-1,3-Propandiolen und 2,2-Bis(Hydroxymethyl)-alkanolen dargestellt. Die Alkohole wurden in die Sulfonestern übergeführt, welche weiter durch Ethylendiamine oder Natriumazid substituiert wurden. Die Azide wurden direkt zu Aminen reduziert. Aus Di-oxyethylenierten 2-Oktadeka-1,3-propandiolen wurden entsprechende Amine gewonnen. Aus einigen Aminen wurden Salizylidenederivative dargestellt.

## Introduction

A key problem of catalysis of the metal ion redox reactions with lipophilic organic substrates is bringing both reacting species together, thus bridging a gap of hydrophobic repulsions between the reagents. In our approach to this problem[2] we used various lipophilic complexones[1] and now we turn to polyamines. Such compounds are well known as

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strongly complexing agents toward the most transition metals. Introduction of a lipophilic function into these molecules should produce interesting catalysts. Recently a ligand of this kind has been synthesized and was successfully used in an oxygen carrier system[3].

## Results and Discussion

This paper describes the synthesis of new lipophilic derivatives of 1,3-propanediamine (**4**), *N*,*N*-bis(2-aminoethyl)-1,3-propanediamine (**5**), 2,2-bis(aminoethyl)alkaneamine (**8**) and *N*,*N*,*N*-tris(aminoethyl)-alkaneamine (**9**). The complexing *Schiff* bases were prepared from some amines and salicylaldehyde as well. The starting polyalcohols were prepared by an improved malonate synthesis[4] followed by reduction by *LAH* (**2**) and by *Tollens* reaction (**6**). The alcohols were converted into the corresponding sulfonate esters which underwent nucleophilic substitution to give aminoethylamines or azides. The last compounds were reduced with *LAH* and gave the desired amines. This route from alcohol to primary polyamine has already been described[5], but in the case of long-chain diols and triols it required different conditions of nucleophilic substitution (*DMF* or *HMPA*-$Bu_4NCl$ instead of ethylene glycol).

$$R\text{—Br} + H_2C(CO_2Et)_2 \xrightarrow{K_2CO_3/Bu_4NBr} R\text{—}HC(CO_2Et)_2$$

$R$: $C_4H_9$, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{18}H_{37}$ **1**

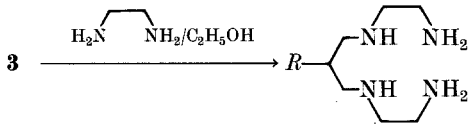
$$\mathbf{1} \xrightarrow{LAH/\text{ether}} R\text{—}CH(OH)_2 \xrightarrow{R^1SO_2Cl/C_5H_5N} R\text{—}CH(OSO_2R^1)_2$$

**2**

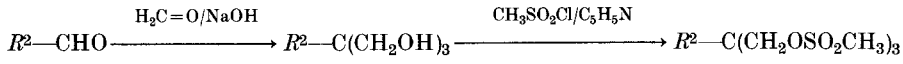
**3** **a**, $R$: $C_4H_9$, $R^1$: Ph
**b**, $R$: $C_{10}H_{21}$, $R^1$: Ph
**c**, $R$: $C_{12}H_{25}$, $R^1$: $CH_3$
**d**, $R$: $C_{18}H_{37}$, $R^1$: $CH_3$

$$\mathbf{3} \xrightarrow{NaN_3/DMF} R\text{—}CH(N_3)_2 \xrightarrow{LAH/THF} R\text{—}CH(NH_2)_2$$

**4** **a**, $R$: $C_4H_9$
**b**, $R$: $C_{10}H_{21}$
**c**, $R$: $C_{18}H_{37}$

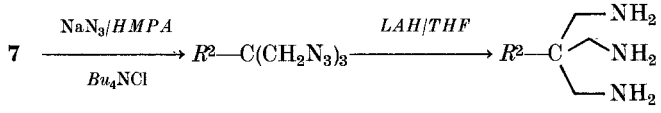


**5** **a**, $R$: $C_{10}H_{21}$
**b**, $R$: $C_{12}H_{25}$
**c**, $R$: $C_{18}H_{37}$

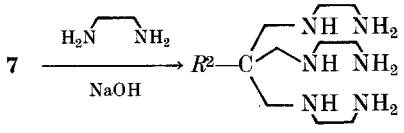


**6** **a**, $R^2$: $C_8H_{17}$
**b**, $R^2$: $C_{12}H_{25}$

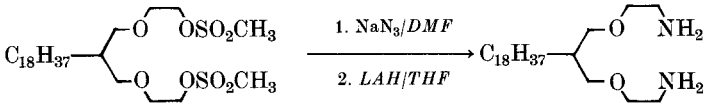
**7** **a, b**



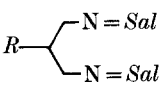
**8** **a**, $R^2$: $C_8H_{17}$
**b**, $R^2$: $C_{12}H_{25}$

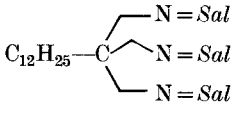


**9** **a**, $R^2$: $C_8H_{17}$
$R^2$: $C_{12}H_{25}$



**10** **11**





**12** **a**, $R$: $C_4H_9$
**b**, $R$: $C_{10}H_{21}$

**13**

A successful direct substitution of both di- and trisulfonates with ethylenediamine demonstrates the wider scope of this method as compared with the reported one[3]. The products were distilled (**5a, b**), crystallized (**5c**), chromatographed (**9a**) or crystallized as the hydrochloride (**9b**). Amines obtained by reduction of azides were essentially pure (over 98% by g.l.c.) and could be additionally purified by distillation, recrystallization or crystallization of hydrochlorides. The oxyethylenated sulfonate **10** gave also the corresponding amine **11**. The amines obtained could be converted into other interesting complexones, and namely salicylidene derivatives **12** and **13** were obtained.

## Acknowledgement

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## Experimental

Melting points and boiling points are uncorrected. IR spectra were recorded with a Perkin-Elmer 621 spectrophotometer. $^1$H NMR spectra were obtained on a Tesla 100 MHz apparatus using *HMDS* as external standard, δ-scale. TLC plates (glass) coated with silica gel and with cellulose were purchased from Merck. All new products gave satisfactory microanalyses (C ± 0.5%, H ± 0.3%).

*Alkyl malonates* (**1**) were obtained in 70–80% yield by alkylation of ethyl malonate with equimolar amount of alkyl bromide in the presence of 2.5 mol% of $Bu_4NBr$ and excess of anh. $K_2CO_3$ at 110° for 2.5 h[4].

*2-Alkyl-1,3-propanediols* (**2**) were prepared as described elsewhere, **2a**[6], **2b**[1b], **2c**[7], and **2d**[1b].

*2,2-Bis(hydroxymethyl)alkanols* (**6**) were obtained by the *Tollens* reaction, **6a**[8], **6b**[9].

*Sulfonate esters* **3** *and* **7**. Corresponding alcohols were dissolved in dry pyridine and reacted with benzenesulfonyl chloride or methanesulfonyl chloride at 0–10° for 2 h, then poured into ice-water and extracted with dichloromethane. The extracts were washed with hydrochloric acid solution, then with water and sodium bicarbonate solution and dried over $MgSO_4$. The solvent was evaporated and crystallization gave the products in over 90% yield.

**3a**: M.p. 75–76°; IR (KBr): $\nu_{SO_3}$ 1183, 1360, $\nu_{C-H}$ 2890, 2980, 3080; NMR ($CDCl_3$): 1.11 (t, 3H, 6 Hz, $-CH_3$), 1.49 [m, 6H, $-(CH_2)_3-$], 2.31 (m, 1H, $-CH=$), 4.33 (m, 4H, $-CH_2O-$), 8.07 (m, 10H, aromatic).

**3b**: M.p. 34°, reported earlier[1b].

**3c**: M.p. 62–64°; IR (KBr): $\nu_{SO_3}$ 1170, 1350, $\nu_{C-H}$ 2860, 2930, 3025; NMR ($CDCl_3$): 1.23 (t, 3H, 6 Hz, $-CH_3$), 1.62 [m, 22H, $-(CH_2)_{11}-$], 2.50 (m, 1H, $-CH=$), 3.40 (s, 6H, $CH_3SO_2-$), 4.58 (m, 4H, $-CH_2O-$).

**3d**: M.p. 76–78°; IR (KBr): $\nu_{SO_3}$ 1170, 1352, $\nu_{C-H}$ 2860, 2930, 3025; NMR ($CDCl_3$): 1.23 (t, 3H, 6 Hz, $-CH_3$), 1.62 [s, 35H, $=CH(CH_2)_{17}-$], 3.38 (s, 6H, $CH_3SO_2-$), 4.58 (m, 4H, $-CH_2O-$).

**7a:** Oil, $R_f$ 0.47 (silica gel, isopropyl ether—ethyl acetate 1:1 *v/v*); IR (film): $\nu_{SO_2}$ 1175, 1350, $\nu_{C-H}$ 2860, 2930, 3020; NMR ($CDCl_3$): 1.26 (t, 3H, 6Hz, $-CH_3$), 1.66 [s, 14H, $-(CH_2)_7-$], 3.45 (s, 9H, $CH_3SO_2-$), 4.54 (s, 6H, $-CH_2O-$).

**7b:** M.p. 56–57.5°; IR (KBr): $\nu_{SO_2}$ 1175, 1345, $\nu_{C-H}$ 2860, 2930, 3025; NMR ($CDCl_3$): 1.26 (t, 3H, 6Hz, $-CH_3$), 1.64 [s, 22H, $-(CH_2)_{11}-$], 3.46 (s, 9H, $CH_3SO_2-$), 4.55 (s, 6H, $-CH_2O-$).

*Sulfonate diester* **10** was described earlier[1b].

*2-Alkyl-1,3-propanediamines* (**4**). Sulfonate ester **3** (10 mmol) dissolved in dry *DMF* (50 ml) was stirred with sodium azide (3.9 g, 60 mmol) at 60° overnight. After cooling the reaction mixture was diluted with the same volume of water and extracted with *n*-hexane (3 × 40 ml). The combined extracts were washed with water and dried over $MgSO_4$, then over molecular sives 4 Å. *n*-Hexane was evaporated and the residue [homogeneous by TLC; IR (film): $\nu_{N_3}$ 1265, 2150; NMR ($CCl_4$): 3.50 $-CH_2N_3$] was dissolved in dry *THF* (10 ml). This solution was added drop by drop to the stirred slurry of *LAH* (1.12 g, 30 mmol) in *THF* (50 ml) under nitrogen. The mixture was stirred at 60° overnight and then treated slowly with 15% NaOH till a white, granular precipitate was formed. After filtration through Cellite *THF* was distilled off, the oil left dried azeotropically with benzene and finally evaporated. The products (over 98% pure by g.l.c.) were additionally purified as follows.

**4a:** Dist., b.p. 70–75°/15 mm Hg, 69% yield; IR (film): $\delta_{CH_2}$ 1460, $\delta_{NH_2}$ 1590, $\nu_{C-H}$ 2870, 2930, $\nu_{N-H}$ 3260, 3360; NMR ($CCl_4$): 1.19 (s, 4H, $-NH_2$), 1.28 (t, 3H, 6Hz, $-CH_3$), 1.56 [m, 7H, $=CH(CH_2)_3-$], 2.94 (d, 4H, 5Hz, $-CH_2N$); hydrochloride, m.p. 185—188°.

**4b:** Dist., b.p. 165—168°/15 mm Hg, 72% yield; IR (film): $\delta_{CH_2}$ 1460, $\delta_{NH_2}$ 1585, $\nu_{C-H}$ 2860, 2930, $\nu_{N-H}$ 3290 br, 3360 br; NMR ($CCl_4$): 1.20 (t, 3H, 6Hz, $-CH_3$), 1.35 (s, 4H, $-NH_2$), 1.57 [m, 19H, $=CH(CH_2)_9-$], 2.93 (d, 4H, 4.5Hz, $-CH_2N$); ($CF_3COOH$): 0.83 (t, 3H, 5.5Hz, $-CH_3$), 1.26 [m, 19H, $=CH(CH_2)_9-$], 3.36 (m, 4H, $-CH_2N^+$), 7.10 (br s, $NH^+$); hydrochloride, m.p. 298–300° (dec.).

**4c:** Cryst. (*n*-hexane), m.p. 49–50°, 67% yield; IR (KBr): $\delta_{CH_2}$ 1470, $\delta_{NH_2}$ 1585, $\nu_{C-H}$ 2870, 2930, $\nu_{N-H}$ 3260 br, 3360 br; NMR ($CF_3COOH$): 0.76 (t, 3H, 5.5Hz, $-CH_3$), 1.22 [m, 35H, $=CH(CH_2)_{17}-$], 3.30 (m, 4H, $-CH_2N^+$), 7.00 (br s, $NH^+$); hydrochloride, m.p. 130° (dec.).

*Diamine* **11** was obtained in the same way from disulfonate **10**, m.p. 47–50° (pentane), 75% yield; NMR ($CDCl_3$—$CD_3OD$): 1.24 (t, 3H, 7Hz, $-CH_3$), 1.64 [m, 35H, $=CH(CH_2)_{17}-$], 2.68 (m, 4H, $-CH_2NH_2$), 3.20 (m, 4H, $-CH_2CH_2O-$), 3.76 (m, 4H, $=CH-CH_2O-$); diacetamide of **11**, m.p. 94–95°; IR (KBr): $\nu_{C-O}$ 1130, $\nu_{C=O}$ 1640, $\nu_{C-H}$ 2860, 2930, $\nu_{N-H}$ 3290; NMR ($CDCl_3$): 1.25 (s, 3H, 6Hz, $-CH_3$), 1.62 [s, 35H, $=CH(CH_2)_{17}-$], 2.32 (s, 6H, $-COCH_3$), 3.23–3.36 (m, 12H, $-CH_2OCH_2CH_2N=$), 6.37 (s, 2H, NH); after Eu(*DPM*)$_3$ was added: 1.20–2.50 (m, 37H, $C_{18}H_{37}-$), 3.04 [m, 1H, $-CH(CH_2O-)_2$], 4.20 [d, 4H, 6Hz, $-CH(CH_2O-)_2$], 4.73 (t, 4H, 5Hz, $-OCH_2CH_2N$), 4.94 (s, 6H, $CH_3CO-$), 6.32 (br s, 4H, $-CH_2N$), 8.64 (br s, 2H, NH).

*2,2-Bis(aminomethyl)alkaneamines* **8** were prepared in the reaction of mesylates **7** (16 mmol) with sodium azide (8 g, 120 mmol) and 0.2 g of $Bu_4NCl$ stirred in dry *HMPA* (25 ml) at 110–115° for 5 h and the azides were isolated and subsequently reduced as described above for diamines **4**, using 1.7 fold larger amounts of *LAH*.

**8a:** Dist., b.p. 168–170° bath/0.05 mm Hg, 75% yield; IR (5% soln in $CCl_4$): $\delta_{CH_2}$ 1450, $\delta_{NH_2}$ 1570, $\nu_{C-H}$ 2860, 2920, $\nu_{N-H}$ 3290 br, 3380 br; NMR ($CCl_4$): 1.20 (t, 3H, 6 Hz, $-CH_3$), 1.46, 1.93 (d s, 6H, $-NH_2$), 1.58 [m, 14H, $-(CH_2)_7-$], 2.81 (s, 6H, $-CH_2NH_2$); hydrochloride, m.p. 260–263° (dec.).

**8b:** Dist., b.p. 200–210° bath/0.05 mm Hg, 77% yield; NMR($CCl_4$): 1.18 (t, 3H, 6 Hz, $-CH_3$), 1.55 [m, 22H, $-(CH_2)_{11}-$], 2.66 (s, 6H, $-NH_2$), 2.80 (s, 6H, $-CH_2NH_2$); hydrochloride, m.p. 295° (dec.); IR (KBr): $\delta_{CH_2}$ 1460, $\delta_{NH_3^+}$ 1500, 1595, $\nu_{C-H}$ 2860, 2930, $\nu_{N-H}$ 2950 v br; NMR ($D_2O$): 1.17 (t, 3H, 5 Hz, $-CH_3$), 1.58 [s, 22H, $-(CH_2)_{11}-$], 3.58 (s, 6H, $-CH_2N^+$).

*Tetraamines* **5.** Sulfonate ester **3** (17.5 mmol) dissolved in absol. ethanol (10 ml) was added gradually to ethylenediamine (9 ml, 135 mmol) under nitrogen and refluxed for 1 h, then powdered KOH (8 g) was added and the mixture was additionally refluxed for 0.5 h. After cooling 50 ml of ether were added, the mixture was filtered through Cellite, washed with ether and evaporated. The remaining oil was dried azeotropically with benzene and distilled in vacuo (**5a** and **5b**) or crystallized (**5c**).

**5a:** B.p. 126–130°/0.05 mm Hg, 53% yield; IR (film): $\delta_{CH_2}$ 1465, $\delta_{NH_2}$ 1570, $\nu_{C-H}$ 2820, 2930, $\nu_{N-H}$ 3300 br; NMR ($CCl_4$) 1.18 (t, 3H, 7 Hz, $-CH_3$), 1.54 [s, 19H, $-(CH_2)_9CH=$], 1.59 (m, 6H, NH), 2.54–3.00 (m, 12H, $-CH_2N$).

**5b:** B.p. 135–140°/0.05 mm Hg, m.p. 25–26°, Lit.[3] b.p. 140°/0.03 mm Hg, 41% yield; IR (film): $\delta_{CH_2}$ 1460, $\nu_{C-H}$ 2860, 2930, $\nu_{N-H}$ 3370 br; NMR ($CCl_4$): 1.18 (t, 3H, 6 Hz, $-CH_3$), 1.57 [m, 23H, $=CH(CH_2)_{11}-$], 1.59 (m, 6H, NH), 2.40–3.00 (m, 12H, $-CH_2N$).

**5c:** M.p. 53–55° (pentane), 59% yield; NMR ($CDCl_3$): 1.21 (t, 3H, 7 Hz, $-CH_3$), 1.57 [s, 35H, $=CH(CH_2)_{17}-$], 2.54 (s, 6H, NH), 2.70–3.10 (m, 12H, $-CH_2N$); hydrochloride, m.p. 120° (dec.) (ethanol); IR (KBr): $\delta_{CH_2}$ 1460, $\delta_{NH_3^+}$ 1590, $\nu_{C-H}$ 2860, 2940, $\nu_{N-H}$ 2950 v br, 3380 br; NMR ($D_2O$, 70 °C): 1.21 (t, 3H, 5 Hz, $-CH_3$), 1.66 [s, 35H, $=CH(CH_2)_{17}-$], 3.20–4.70 (m, 12H, $-CH_2N^+$).

*Hexaamines* **9.** Mesylate **7** (3.3 mmol) was refluxed in ethylenediamine (20 ml, ca. 300 mmol) under nitrogen for 72 h, powdered NaOH (3 g) was added and the mixture was additionally refluxed for 7 h. After cooling 50 ml of benzene was added, the mixture was filtered off and evaporated (100°/15 mm Hg). The remaining oil was subjected to the column chromatography on cellulose (Wathman CF 11, *n*-butanol saturated with aqueous acetic acid 5:5:1 *v/v*) (**9a**) or dissolved in ethanol and treated with concd. HCl solution to give a crystalline hydrochloride (**9b**).

**9a:** Oil, $R_f$ 0.50 (cellulose, *n*-butanol, water, acetic acid 5:5:1 *v/v/v*), 60% yield; NMR ($CCl_4$): 1.20 (t, 3H, 6 Hz, $-CH_3$), 1.35 (m, 6H, NH), 1.61 [m, 14H, $-(CH_2)_7-$], 2.78–3.28 (m, 18H, $-CH_2N$); hydrochloride (glass), NMR ($D_2O$): 1.20 (t, 3H, 4 Hz, $-CH_3$), 1.65 [s, 14H, $-(CH_2)_7-$], 3.60–4.64 (m, 18H, $-CH_2N^+$).

**9b:** Oil, 50% yield; NMR ($CCl_4$): 1.20 (t, 3H, 6 Hz, $-CH_3$), 1.40 (m, 6H, —NH), 1.58 [m, 22H, $-(CH_2)_{11}-$], 2.77–3.36 (m, 18H, $-CH_2N$); hydrochloride, m.p. 228° (dec.) (ethanol); IR (KBr): $\delta_{CH_2}$ 1460, $\delta_{NH_3^+}$ 1590, $\nu_{C-H}$ 2930, $\nu_{N-H}$ 2900 v br, 3380 br; NMR ($D_2O$): 1.21 (t, 3H, 5 Hz, $-CH_3$), 1.61 [s, 22H, $-(CH_2)_{11}-$], 3.70–4.64 (m, 18H, $-CH_2N^+$).

*Salicylidene derivatives* **12** *and* **13.** The corresponding amine (2 mmol) dissolved in benzene (5 ml) was refluxed with salicylaldehyde (4 mmol for **4a, b** or 6 mmol for **8b**) in the presence of anh. $K_2CO_3$ (0.5 g) and molecular sives 3 Å

for 30 min, then filtered off and evaporated. The crude products were purified by chromatography on Florisil eluted with an ether—petroleum ether mixture.

**12 a:** Oil, 56% yield; IR (film): $\nu_{C-O}$ 1275, $\nu_{C=N}$ 1630, $\nu_{C-H}$ 2870, 2930, 2960, 3060; NMR ($CCl_4$): 1.18 (t, 3 H, 7 Hz, $-CH_3$), 1.63 [s, 6 H, $-(CH_2)_3-$], 2.30 [m, 1 H, $-CH(CH_2NSal)_2$], 3.78 (d, 4 H, 6 Hz, $-CH_2N=$), 6.96-7.54 (m, 8 H, aromatic), 8.46 (s, 2 H, *Ar*—CH=N—), 13.18 (s, 2 H, OH).

**12 b:** Oil, 34% yield; IR (film): $\nu_{C-O}$ 1280, $\nu_{C=N}$ 1630, $\nu_{C-H}$ 2870, 2935, 3060; NMR ($CCl_4$): 1.16 (t, 3 H, 6 Hz, $-CH_3$), 1.58 [m, 18 H, $-(CH_2)_9-$], 2.30 [m, 1 H, $-CH(CH_2NSal)_2$], 3.85 (d, 4 H, 4.5 Hz, $-CH_2N=$), 6.96-7.57 (m, 8 H, aromatic), 8.53 (s, 2 H, *Ar*—CH=N—), 13.18 (s, 2 H, OH).

**13:** Oil, 38% yield; IR (film): $\nu_{C-O}$ 1280, $\nu_{C=N}$ 1630, $\nu_{C-H}$ 2860, 2935, 3070; NMR ($CDCl_3$): 1.22 (t, 3 H, 7 Hz, $-CH_3$), 1.60-1.80 [m, 22 H, $-(CH_2)_{11}-$], 3.98 (s, 6 H, $-CH_2N=$), 7.12-7.65 (m, 12 H, aromatic), 8.50 (s, 3 H, *Ar*—CH=N—), 13.56 (br s, 3 H, OH).

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