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Functional Derivatives of Sterically Hindered Amines: Piperazine Diesters

František Vašš

Bratislava (Slovakia), VASACHEM Co.

Jozef Lustoň

Bratislava (Slovakia), Polymer Institute, Slovak Academy of Sciences

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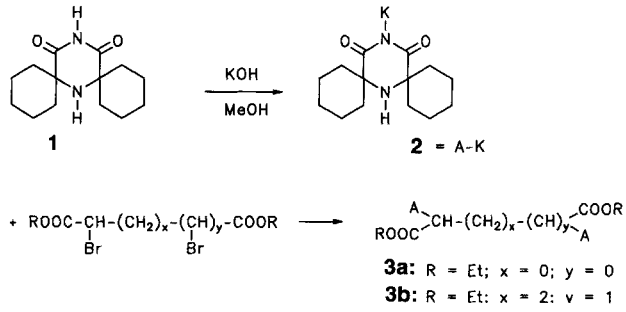
Abstract. Several diesters of dicarboxylic acids with pendant sterically hindered amines of the piperazine type were prepared from α-bromo- and α,α'-dibromosubstituted dicarboxylic acid esters by reactions with 14,16-dioxo-7,15-diaza-dispiro[5,1,5,3]hexadecane and 7,15-diazadispiro [5,1,5,3] hexadecane.

Sterically hindered amines represent an interesting group of chemical compounds which have found a broad application in organic, physical and polymer chemistry, and in biochemistry. Known are their applications as non-nucleophilic bases [1–4], pharmaceutically active compounds [5–8], however, their most important commercial application is in the field of polymer chemistry. Sterically hindered amines are powerful light stabilizers for the most of commodity polymers, particularly for polyolefins [9–11].

However, the drawback of low molecular weight derivatives of this family is their high volatility and easy extractibility from polymer substrates. These properties impair long-term effectiveness of these stabilizers [12–14]. Therefore, there appeared attempts to prepare polymeric stabilizers on the basis of sterically hindered amines [15–19], some of them were commercialized. Sterically hindered amines are known also as precursors of stable nitroxyl radicals which are useful as spin labels, spin probes, and radical scavengers in various biochemical and physical studies [20–24].

Recently we have reported the synthesis of glycidyl derivatives of sterically hindered amines including a stable nitroxyl radical [25], and the synthesis of polyalkylpiperidine diesters [26]. In this paper the preparation of diesters based on sterically hindered piperazines is reported.

The synthesis of the diethylester of 2-(14,16-dioxo-7,15-diazadispiro[5,1,5,3]hexadecan-15-yl)propanedioic acid (**3a**) and the diethylester of 2,5-bis(14,16-dioxo-7,15-diazadispiro[5,1,5,3]hexadecan-15-yl)hexanedioic acid (**3b**) was performed in a way similar to Gabriel synthesis (Scheme 1).



Scheme 1

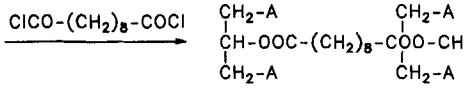
The weak acidity of the imidic amino group in 15-position was exploited for the preparation of the potassium salt **2** from **1** and methanolic KOH. The next step included a nucleophilic substitution reaction of **2** with the α-bromo or the α,α'-dibromo dicarboxylic acid ester in dry DMF. Under mild conditions excellent yields of pure products were achieved. Good yields can also be predicted for the same reaction performed under PTC conditions [33].

The potassium salt **2** was also used for the preparation of 2-hydroxy-1,3-bis(14,16-dioxo-7,15-diazadispiro[5,1,5,3]hexadecan-15-yl)propane (**4**) which is an

intermediate for the synthesis of bulky diester of decanedioic acid (**5**) (Scheme 2).

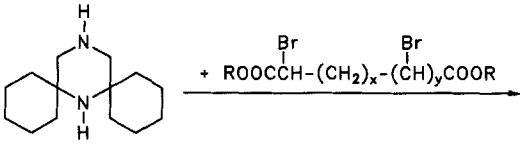
4 was prepared in high yield by the reaction of **2** with 1,3-dichloro-2-propanol in dry DMF at 80 °C. The synthesis of the bulky diester **5** was carried out at low temperature by condensation of **4** with the dichloride of decanedioic acid in anhydrous toluene in the presence of triethylamine. The formation of solid triethylamine hydrochloride enabled visual detection of the course of reaction. A high yield of **5** was obtained after standard purification procedures. The measured molecular weight 1230 (VPO) was in excellent agreement with the calculated value 1280, and the IR and ^{1}H NMR spectra are in accordance with the proposed structure.

4

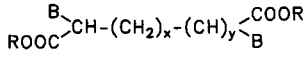


5

Scheme 2



6 = B-H



7a: R = Et; x = 0; y = 0
7b: R = Et; x = 2 y = 1

Scheme 3

The synthesis of the diethylester of (7,15-diazadispiro-[5,1,5,3]hexadecan-15-yl)propanedioic acid (**7a**) and the similar compound (**7b**) was accomplished by nucleophilic replacement of 7,15-diazadispiro [5,1,5,3] hexadecane **6** with the corresponding α-bromo- or α,α'-dibromosubstituted aliphatic dicarboxylic acid esters (Scheme 3).

The compound **6** contains two secondary amino groups which differ in reactivity due to sterical hindrance of the 7-amino group. As the result, in the replacement reaction only the 15-amino group is involved. Two procedures were used. In procedure A, the reaction was performed in dry DMF, while procedure B is performed in dry benzene in the presence of triethylamine. In general, procedure A gave excellent yields, about 20% higher than procedure B, possibly due to the increase in polarity of the solvent. Both procedures are very sensitive to the presence of moisture in the system.

The prepared compounds **3a**, **3b**, **7a** and **7b** can be used as monomers or comonomers for polycondensation reactions, for preparation of polyesters with light stabilizing structures. The compound **5** represents a bulky compound containing stabilizing structures with reduced volatility and extractibility from a polymer matrix.

Experimental

Infrared spectra were recorded on a Specord IR-75 spectrometer (Carl Zeiss Jena, Germany) in chloroform. ^{1}H NMR spectra were measured on a BS-467 (60 MHz, Tesla, Czecho-Slovakia) and FT JNM FX 100 (JEOL, Japan) spectrometers in deuterochloroform using TMS as internal standard. Melting points were measured on a Kofler melting point apparatus (VEB Analytik, Germany), and are uncorrected. VPO measurements were done in $CHCl_3$ (Knauer, Germany). Microanalyses were done in the Microanalytical Laboratory of the Chemical Institute of the Slovak Academy of Sciences (Bratislava, Slovakia).

14,16-Dioxo-7,15-diazaspiro[5,1,5,3]hexadecane (**1**)

was prepared by condensation of cyclohexanone with potassium cyanide, ammonia, and ammonium chloride, followed by cyclization of the formed di(1-cyanocyclohexyl)amine in concentrated sulfuric acid according to literature [27]. After recrystallization from ethanol, the product with m.p. 159–161 °C was obtained (lit. [27] 155–160 °C).

7,15-Diazadispiro[5,1,5,3]hexadecane (**6**) was prepared by reduction of **1** with $LiAlH_4$ in ether according to literature [27, 28]. After recrystallization from *n*-heptane, the product with m.p. 88–90 °C was obtained (lit. [27] 89–90 °C , [28] 87–89 °C).

The diethylester of 2-bromopropanedioic acid and the diethylester of 2,5-dibromohexanedioic acid were prepared according to literature [29, 30]. The dichloride of decanedioic acid was prepared according to literature [31]. 1,3-Dichloro-2-propanol (Aldrich) was used as received. Triethylamine (Lachema, Czecho-Slovakia) was distilled after refluxing for 5 hours over potassium hydroxide pellets. Other solvents (Lachema, Czecho-Slovakia) were purified by standard methods [32].

Diethylester of 2-(14,16-dioxo-7,15-diazadispiro[5,1,5,3] hexadecan-15-yl)propanedioic acid (**3a**)

The potassium salt of 14,16-dioxo-7,15-diazadispiro [5,1,5,3] hexadecane **2** was prepared from **1** (2.50 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) by gentle heating in 25 ml of dry methanol for 0.5 hour, followed by evaporation of the solvent and reaction water, and drying on a vacuum line.

Potassium salt **2** was dispersed in dry DMF (30 ml), and diethylester of 2-bromopropanedioic acid (2.39 g, 0.01 mol) in dry DMF (10 ml) was added dropwise at 80 °C during 1 hour. The reaction mixture was stirred at 80 °C for 3 hours. After cooling, the reaction mixture was three times extracted with diethyl ether. The combined extracts were washed with water and brine, and dried over sodium sulfate. Ether was distilled off and after recrystallization from ethanol white crystals of **3a** (3.41 g, 83.5%) were obtained, m.p. 82–85 °C.

$C_{21}H_{32}N_2O_6$ (408.50): calcd. 61.75% C, 7.90% H, 6.86% N; found, 62.04% C, 7.91% H, 6.58% N.

IR ($CHCl_3$): 3370 (N–H), 2930 and 2855 (CH), 1750, 1725 and 1680 (C=O), 1445 (CH), 1295 (C–N).

^{1}H NMR ($CDCl_3$) δ: 1.11 (s, 1H, NH), 1.27 (t, 6H, CH_3), 1.74 (br. s, 20H, ring CH_2), 4.28 (q, 4H, CH_2), 5.67 (s, 1H, CH).

Diethylester of 2,5-bis(14,16-dioxo-7,15-diazadispiro [5,1,5,3]hexadecan-15-yl)hexanedioic acid (3b)

The compound **3b** was prepared in the same way as **3a** from **2** (2.88 g, 0.01 mol) and diethylester of 2,5-dibromohexanedioic acid (1.80 g, 0.005 mol). After recrystallization from ethanol, white crystals of **3b** were obtained (2.99 g, 85.5%), m.p. 197–200 °C.

$C_{38}H_{58}N_4O_8$ (698.91): calcd. 65.31% C, 8.36% H, 8.02% N; found, 66.40% C, 8.50% H, 8.05% N.

IR ($CHCl_3$): 3370 (N–H), 2940 and 2870 (CH), 1740 and 1680 (C=O), 1450 (CH), 1270 (C–N).

^{1}H NMR ($CDCl_3$) δ: 1.03 (s, 2H, NH), 1.17 (t, 6H, CH_3), 1.70 (br. s, 40H, ring CH_2), 2.01 (s, 4H, CH_2), 4.11 (q, 4H, CH_2), 5.07 (m, 2H, CH).

2-Hydroxy-1,3-bis(14,16-dioxo-7,15-diazadispiro [5,1,5,3] hexadecan-15-yl)propane (**4**)

The compound **4** was prepared in the same manner as **3a** from **2** (2.88 g, 0.01 mol) and 1,3-dichloro-2-propanol (0.645 g, 0.005 mol). Crude product (2.58 g, 92.8%) after recrystallization from ethanol yielded white crystals, m.p. 144–147 °C.

$C_{31}H_{48}N_4O_5$ (556.75): calcd. 66.88% C, 8.69% H, 10.06% N; found, 66.65% C, 8.74% H, 10.12% N.

IR ($CHCl_3$): 3500 (OH), 3360 (NH), 2940 and 2860 (CH), 1715 and 1665 (C=O), 1450 (CH), 1335 (C–N), 1015 (COH).

^{1}H NMR ($CDCl_3$) δ: 1.25 (s, 2H, NH), 1.65 (br. s, 40H, ring CH_2), 3.05 (s, 1H, OH), 3.30 (m, 1H, CH), 3.80 (s, 4H, CH_2).

Di-{1,3-bis(14,16-dioxo-7,15-diazadispiro[5,1,5,3] hexadecan-15-yl)prop-2-yl}ester of decanedioate (**5**)

A solution of dichloride of decanedioic acid (0.179 g, 0.75 mmol) in dry toluene (10 ml) was added dropwise during 1 hour at room temperature to a solution of **4** (0.835 g, 1.5 mmol) and triethylamine (1 ml) in dry toluene (15 ml). The reaction mixture was stirred for 5 hours. The formed precipitate of triethylamine hydrochloride was filtered off, the toluene solution was washed 3 times with distilled water and brine, and dried over sodium sulfate. The solvent was evaporated, and the residue treated in a vacuum oven at 50 °C and 13 Pa for 6 hours. A pale yellow, glassy, easily powderable solid was obtained (0.86 g, 89.6%), m.p. 44–46 °C, MW = 1230 (VPO).

$C_{72}H_{110}N_8O_{12}$ (1278.73): calcd. 67.58% C, 8.66% H, 8.76% N; found, 66.92% C, 8.57% H, 8.70% N.

IR ($CHCl_3$): 3360 (NH), 2960 and 2870 (CH), 1730 and 1680 (C=O), 1465 (CH), 1350 (C–N).

^{1}H NMR ($CDCl_3$) δ: 1.25 (s, 4H, NH), 1.65 (br. s, 80H, ring CH_2), 2.25 (br. band, 16H, CH_2), 3.45 (m, 2H, CH), 3.90 (m, 8H, CH_2).

Diethylester of (7,15-Diazadispiro[5,1,5,3]hexadecan-15-yl)propanedioic acid (**7a**)

Procedure A: A solution of diethylester of 2-bromopropanedioic acid (2.39 g, 0.01 mol) in dry DMF (10 ml) was added dropwise during 1 hour to a solution of **6** (2.22 g, 0.01 mol) in dry DMF (20 ml). The reaction mixture was stirred at room temperature for 5 hours, then poured into distilled water (60 ml) and alkalized with 40% NaOH solution. The reaction mixture was thoroughly extracted with chloroform. The combined extracts were washed with distilled water and brine, and dried over sodium sulfate. The crude product (3.09 g, 83.9%) which was obtained after evaporation of the solvent, after recrystallization from ethanol afforded white crystals, m.p. 163–165 °C.

Procedure B: A solution of the diethylester of 2-bromopropanedioic acid (7.17 g, 0.03 mol) in dry benzene (20 ml) was added dropwise during 1 hour at room temperature to a solution of **6** (6.66 g, 0.03 mol) and triethylamine (3.64 g, 0.036 mol) in benzene (120 ml). The reaction mixture was stirred for 24 hours. The precipitated triethylamine hydrochloride was filtered off, dissolved in saturated potassium carbonate solution, and extracted thoroughly with ether. The ether extracts were combined with the benzene solution, and dried over sodium sulfate. The crude product (6.67 g, 60.4%) which was obtained after evaporation of solvents, after recrystallization from ethanol yielded white crystals, m.p. 164–167 °C.

$C_{21}H_{36}N_2O_4$ (380.52): calcd. 66.28% C, 9.54% H, 7.36% N; found, A: 66.53% C, 9.79% H, 7.49% N; B: 66,98% C, 9.61% H, 7.52% N.

IR ($CHCl_3$): 3370 (NH), 2930 and 2860 (CH), 1720 (C=O), 1450 (CH), 1360 (C–N).

^{1}H NMR ($CDCl_3$) δ: 1.01 (s, 1H, NH), 1.31 (t, 6H, CH_3), 1.51 (br. s, 20H, ring CH_2), 2.33 (s, 4H, CH_2N), 4.26 (q, 4H, CH_2), 7.30 (s, 1H, CH).

Diethylester of 2,5-Bis(7,15-diazadispiro[5,1,5,3]hexadecan-15-yl)hexanedioic acid (**7b**)

The compound **7b** was prepared in the same way as **7a** from **6** (2.22 g, 0.01 mol) and diethylester of 2,5-dibromohexanedioic acid (1.80 g, 0.005 mol). Procedure A yielded 2.52 g (78.4%) crude product while procedure B gave 2.00 g (62.4%). After recrystallization from ethanol white crystals were

obtained, m.p. 155–158 °C.
$C_{38}H_{66}N_4O_4$ (642.97): calcd. 70.94% C, 10.35% H, 8.71% N; found, 70.93% C, 10.40% N, 8.80% N.
IR ($CHCl_3$): 3360 (NH), 2940 and 2860 (CH), 1720 (C=O), 1450 (CH), 1340 (C–N).
^1H NMR ($CDCl_3$) δ: 1.00 (s, 2H, NH), 1.28 (t, 6H, CH_3), 1.50 (br. s, 40H, ring CH_2), 2.23 (m, 4H, CH_2), 2.83 (m, 4H, CH_2), 3.43 (m, 2H, CH), 4.18 (q, 4H, CH_2).

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Address for correspondence:
Dr. J. Luston
Polymer Institute
Slovak Academy of Sciences
84236 Bratislava, Slovakia