HYDROXYALKYL DERIVATIVES OF 5,5-DIETHYLBARBITURIC ACID

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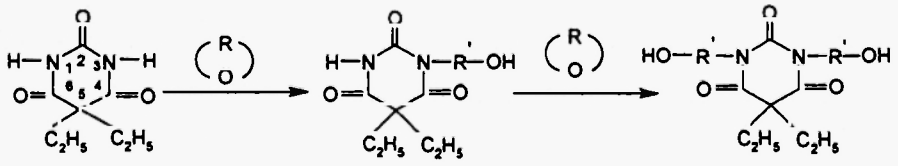
Abstract : The reaction of 5,5-diethylbarbituric acid with formaldehyde or oxiranes (ethylene oxide, EO and propylene oxide, PO) towards hydroxyalkyl derivatives in presence of triethylamine catalyst was described. The alternative synthetic route with ethylene and propylene carbonates (EC and PC, respectively) was also explored. The products of hydroxyalkylation were isolated at high yields and identified based on elemental analysis, IR and ^{1}H NMR spectra.

Introduction

Polyetherols and diols synthesized from azacyclic compounds like isocyanuric, uric, or parabanic acids and excess of oxiranes like EO and PO, or, alternatively, alkylene carbonates are useful substrates for preparation of polymers of high thermal stability [1-4]. The thermal stability of appropriate polyesters of polyurethanes is consistent with the presence of azacyclic rings in those macromolecules. Among those azacyclic precursors the 5,5-diethylbarbituric acid (DEBA) is promising candidate due to its high melting point (190^{0}C [5]) and high temperature of decomposition (>200^{0}C). The compound itself was reported mostly in the context of its medical application as neurodrug (veronal) [6] and no data are available on its use as substrate for polymer chemistry. The data on hydroxyalkylation of DEBA with PO and glycerol epichlorhydrin (ECH) were the matter of three patents [7-9]. The advantageous property of this substrate is a good solubility of DEBA in organic solvents like dioxane, dimethylformamide (DMF) or dimethylsulfoxide (DMSO), the convenient solvents for hydroxyalkylation. We have used DEBA for hydroxyalkylation with oxiranes and alkylene carbonates and the results of our studies are describes here. The mono- and bis-hydroxyalkyl derivatives in reactions of DEBA with oxiranes, alkylene carbonates and formaldehyde are formed according to the scheme:



(1) (2)

where: R - $-CH_2-$ and R' = $-CH_2-$

$-CH_2-CH_2-$ or $-CH_2-CH_2-O-C(=O)-$ and R' = $-CH_2-CH_2-$

$-CH_2-CH(CH_3)-$ or $-CH(CH_3)-CH_2-O-C(=O)-$ and R' = $-CH_2-CH(CH_3)-$

$-CH_2-CH(CH_2Cl)-$ and R' = $-CH_2-CH(CH_2Cl)-$

Experimental

Reaction of DEBA with formaldehyde

18.4 g DEBA (0.1 mole) and variable amounts of 33.5% formaline (9.0 g, 0.1 mole; 18.0, 0.2 mole; or 36.0 g, 0.4 mole) were placed in three-necked 100 cm^3 flask equipped with mechanical stirrer, reflux condenser and thermometer. In case of the 1:1 molar mixture additionally 2 g of water were introduced in order to homogenize the reaction mixture. The mixtures were heated at 92°C for 0.5 hr and afterwards cooled to room temperature. Upon cooling of the 1:1 reaction mixture the formation of white precipitate was observed, which was filtered off, washed with water and dried at 40°C under reduced pressure to constant mass. The reaction mixtures containing the reagents at 1:2 and 1:4 molar ratio were worked up by removal of water on rotary evaporator at 80° and later at temperature below 40° under reduced pressure. The products were resins. The product of reaction from DEBA:CH_2O 1:2 reaction system solidified after one month upon standing at room temperature.

Reaction of DEBA with EO and PO

9.2 g DEBA (0.05 mole), 20 g DMF, 0.5 g TEA and 2.2 g (0.05 mole) or 4.4 g (0.1 mole) EO or 2.9 g (0.05 mo-le) or 5.8 g (0.1 mole) PO were placed in high pressure 100 cm^3 reactor equipped with cooling coat and mechanical stirrer. The mixtures were heated at 55-60 or 65 -70° C for 23 hours (for mixtures containing 0.05 moles of EO or PO) or 34 hours (in case of 0.1 mole of EO was used) or 50 hours (in case of 0.1 mole of PO was used). The progress of reaction was monitored by determination of epoxide number. After reaction was completed the DMF was distilled off under reduced pressure (12 hPa, temperature of distillation was gradually increased from 35 to 135°C, while the temperature of condensation was maintained at 32-50°C). The products of reaction with EO were resins, which solidified after one month. They were further purified by reprecipitation from benzene. With mixtures obtained from PO, the herbal smell resins were obtained.

Reaction of DEBA with ECH

9.2 g DEBA (0.05 mole) and 9.25 g of ECH (0.1 mole) were placed in a three-necked 100 cm^3 flask equipped with mechanical stirrer, reflux condenser and thermometer. The reaction mixture was stirred and heated at 128-130°C for 12 hours. The progress of reaction was monitored by determination of epoxide number. The process of accompanied by strong exothermic effect at 100°C, upon which the temperature of reaction mixture was increased to 180°C. The DEBA gradually dissolved upon heating the mixture. The product was light-brown resin.

Synthesis of 1,3-bis(2-hydroxyethyl) 5,5-diethylbarbiturate (BHEDEB) in the reaction between 1 equivalent of DEBA with 2 equivalents of EC

36.8 g (0.2 mole) of DEBA, 36 g (0.41 mole) EC and 0.4 g K_2CO_3 as catalyst were placed in a three-necked 100 cm^3 flask equipped with mechanical stirrer, reflux condenser and thermometer. The reaction mixture was stirred and heated at 135°C for 2.5 hours, while the foaming due to carbon dioxide formation was observed, which eventually ceased after the reaction mixture was heated to 150°C. The heating was stopped after the determination of unreacted EC indicated the absence of the reagent and mass balance reached the appropriate value. The raw product was purified by precipitation from benzene.

Synthesis of 1,3-bis(2-hydroxypropyl) 5,5-diethylbarbiturate (BHPDEB) in the reaction between 1 equivalent of DEBA with 2 equivalents of PC

36.8 g (0.2 mole) DEBA, 40.8 g (0.4 mole) PC and 0.6 g K_2CO_3 as catalyst were placed in a three-necked 100 cm^3 flask equipped with mechanical stirrer, reflux condenser and thermometer. The reaction mixture was heated at 150°C until PC was reacted and mass balance indicated the formation of product containing two equivalents of converted PC per one equivalent of DEBA. During the reaction PC reagent partially decomposes to PO and CO_2, therefore the PC was added in portions into the reaction mixture during the synthesis.

Analyses

The progress of reactions between DEBA and oxiranes was estimated by determination of epoxide number using the hydrochloric acid in dioxane [10], while in case of alkylene carbonates it was estimated based upon carbonate determination using titration with barium hydroxide [11]. The percentage of weakly-bound formaldehyde in hydroxymethyl derivatives of DEBA was determined by iodometric method [12], while in monohydroxyalkyl derivatives it was determined by determination of acidic number (AN). The ^{1}H-NMR were recorded at Bruker Avance 500 MHz instrument in DMSO-d_6 and HMDS as internal standard. IR spectra were obtained at Perkin Elmer PARAGON 1000 FT spectrophotometer. Elemental analyses were performed with EA 1108, Carlo-Erba analyzer.

Analytical data

N-hydroxymethyl 5,5-diethylbarbiturate (1, R = -CH_2-), $C_9H_{14}O_4N_2$; Yield - 80 %; m.p. 81-83^{0}C; AN [mg KOH/g], Calcd.: 262, Found: 240; %CH_2O, Calcd.: 14.0, Found: 13.6; elemental analysis - % Calcd.: C 50.47; H 6.54; N 13.08; % Found: C 50.33; H 6.69; N 13.13; IR (KBr), [cm^{-1}]: 3453 (OH), 3082 (NH), 2853-2970 (CH_2, CH_3), 1765, 1718, 1679

(C=O), 1464, 1380 (CH_2), 1416, 1244 (NH), 1075 (OH); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, CH_3), 1.8 (4H, q, C-CH_2), 5.1 (2H, d, N-CH_2), 6.4 (H, s, OH,), 11.5 (H, s, NH).

The product of reaction between 1 eq. of DEBA with 2 eq. CH_2O (3), $C_{10}H_{16}O_5N_2$; Yield - 95 %; AN [mg KOH/g], Calcd.: 230, Found: 220; %CH_2O, Calcd.: 24.6 Found: 23.3; elemental analysis - % Calcd.: C 49.18; H 6.56; N 11.48; % Found: C 49.00; H 6.73; N 11.39; IR (KBr), [cm^{-1}]: 3445 (OH), 2853-2970 (CH_2, CH_3), 1755, 1675 (C=O), 1457 (CH_2), 1364 (CH_3), 1277, 1052 (OH), 1021(C-O-C); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, CH_3), 1.8 (4H, q, C-CH_2), 4.6 (1.2H, m,-$(CH_2\text{-}O)_{0,6}$-, 5.2 (2H, m, N-CH_2), 6.4 (H, s, OH,), 11.5 (0.4H, s, -$(NH)_{0,4}$-).

The product of reaction between 1 eq. of DEBA with 4 eq. CH_2O (2, R = -CH_2-O-CH_2-), $C_{12}H_{20}O_7N_2$; Yield -100 %; %CH_2O,Calcd.: 39.5 Found: 40.2; elemental analysis - % Calcd.: C 47.37; H 6.58; N 9.21; % Found: C 47.52; H 6,42; N 9.25; IR (capillary film), [cm^{-1}]: 3439 (OH), 2853-2970 (CH_2, CH_3), 1676 (C=O), 1457 (CH_2), 1367 (CH_3), 1277 (OH), 1277 (OH), 970 (C-O-C); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, CH_3), 1.8 (4H, q, C-CH_2), 4.6 (2H,m,-CH_2-O-), 5.2 (2H, m, N-CH_2), 6.4 (H, m, OH).

N-hydroxyethyl 5,5-diethylbarbiturate (1, R = -CH_2-CH_2-), $C_{10}H_{16}O_4N_2$; Yield after precipitation from benzene - 80%; m.p. 182-183^{0}C; elemental analysis - % Calcd.: C 52.63; H 7.01; N 12.28; % Found: C 52.58; H 7.37; N 12.12; IR (KBr), [cm^{-1}]: 3373-3256 (OH), 3082 (NH), 2853-2970 (CH_2, CH_3), 1766, 1766, 1707, 1683 (C=O), 1463 (CH_2), 1378 (CH_3), 1415, 1244 (NH), 1075 (OH); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, CH_3), 1.8 (4H, q, C-CH_2), 3.4 (2H,t,CH_2-O-), 3.8 (2H, t, N-CH_2), 4.7 (H, s, OH), 11.5 (H, s, NH).

N,N'-bis(2-hydroxyethyl) 5,5-diethylbarbiturate (2, R = -CH_2-CH_2-), $C_{12}H_{20}O_5N_2$ (BHEDEB); Yield after pre-cipitation from benzene - 85%; m.p. 59-62^{0}C; elemental analysis - % Calcd.: C 53.00; H 7.42; N 10.04; % Found: C 52.94; H 7.35; N 10.29; IR (KBr), [cm^{-1}]: 3268 (OH), 2853-2970 (CH_2, CH_3), 1688 (C=O), 1438 (CH_2), 1398 (CH_3), 1291,1062 (OH);^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.6 (6H, t, CH_3), 1.8 (4H, q, C-CH_2), 3.45 (4H, t,-CH_2-O-), 3.85 (4H, t, N-CH_2), 4.7 (2H, t, CH_2-OH).

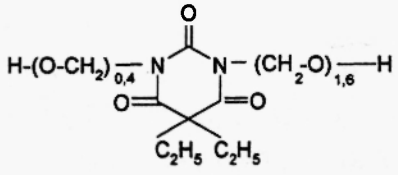
N-(2-hydroxypropyl) 5,5-diethylbarbiturate (1, R = -CH_2-$CH(CH_3)$-), $C_{11}H_{18}O_4N_2$; Yield – 100%, elemental analysis - % Calcd.: C 54.55; H 7.44; N 11.57; % Found: C 54.78; H 7.53; N 11.45; IR (capillary film), [cm^{-1}]: 3473-3227 (OH), 3102 (NH), 2853-2970 (CH_2, CH_3), 1674 (C=O), 1436 (CH_2), 1368 (CH_3), 1400, 1309 (NH), 1074 (OH); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, C_5-CH_2-$\underline{CH_3}$). 1.0 (3H, d, CH-$\underline{CH_3}$), 1.8 (4H, q., C_5-CH_2), 3.1-3.5 (H, m, CH), 3.8 (2H, m, N-CH_2), 8 (2H, s, NH, OH).

N,N'-bis(2-hydroxypropyl) 5,5-diethylbarbiturate (2, R = -CH_2-$CH(CH_3)$-), $C_{14}H_{24}O_5N_2$ (BHPDEB) ; Yield – 100%, ele-mental analysis - % Calcd.: C 56.00; H 8.00; N 9.33; % Found: C 55.82; H 8.29; N 9.04; IR (capillary film) [cm^{-1}]: 3394 (OH), 2880-2970 (CH_2, CH_3), 1675 (C=O), 1436 (CH_2), 1397 (CH_3), 1280, 1078 (OH); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, C_5-CH_2-$\underline{CH_3}$), 1.05 (6H, d, CH-$C\underline{H_3}$), 1.8 (4H, q, C_5-CH_2), 3.25 (2H, m, CH), 3.8 (4H, m, N-CH_2), 4.7 (2H, s, OH).

N,N'-bis(3-chloro-2-hydroxypropyl) 5,5-diethylbarbiturate(2, R = -CH_2-$CH(CH_2Cl)$-), $C_{11}H_{17}O_4N_2Cl$; Yield - 100 %; elemental analysis - % Calcd.: C 45.53; H 5.96; N 7.79; % Found: C 45.23; H 6.19; N 7.53; IR (capillary film), [cm^{-1}]: 3457 (OH), 2970-2880 (CH_2, CH), 1668 (C=O), 1436 (CH_2), 1397 (CH_3), 1285, 1080 (OH), 750 (C-Cl); ^{1}H-NMR (d_6-DMSO), δ [ppm]; 0.7 (6H, t, CH_3), 1.8 (4H, q, C_5-CH_2), 3.5 (10H, m, $C\underline{H_2}$-$C\underline{H}$-$C\underline{H_2}$Cl), 3.8 (4H, m, N-CH_2), 5.3-5.6 (2H, d, OH).

Results and Discussion

Hydroxyalkylation of DEBA with formaldehyde is facile in formaline. The N-hydroxymethyl 5,5-diethylbarbiturate precipitates from the DEBA : CH_2O 1:1 reaction mixture upon cooling. When 2-fold excess of formaldehyde is applied, the bis-hydroxymethyl derivative is not obtained due to facile addition of formaldehyde to N-hydroxymethyl groups formed instead of its addition to imide groups. In the ^{1}H-NMR spectra of reaction mixture we have observed the resonance at 4.6 ppm attributed to –O-CH_2-O of the product:



(3)

Upon long standing of the resin post-reaction mixture slow solidification of mono- and bis-derivatives takes place. These can also be obtained by heating the reaction mixture in benzene; the mixture of mono- and bis-hydroxymethyl derivatives of DEBA precipitate from cold benzene. The resonance at 4.6 ppm is not present in the spectrum of the reaction mixture and the product of consecutive addition of formaldehyde to N-hydroxymethyl groups remains in the solution. The integration of the corresponding resonances in the ^{1}H NMR spectrum indicates that mono- and bis- derivatives are present at 0.4 : 0.6 molar ratio. Total blocking of imide groups occurs upon addition of four moles of formaldehyde to DEBA. Obtained hydroxymethyl derivatives are well soluble in acetone, tetrahydrofuran and dioxane, and

slightly in dichloromethane. The product obtained from DEBA : CH_2O 1:4 reaction mixture is soluble in oxiranes like EO or PO already at room temperature. Thus, it can used for further conversion into oligoetherols with pyrimidine ring.

2-Hydroxyethyl and 2-hydroxypropyl derivatives of DEBA can also be obtained by hydroxyalkylation of DEBA with corresponding oxiranes (EO or PO) or with alkylene carbonates (EC or PC). Hydroxyalkylation with oxiranes is facile in DMF at temperature ranging between 50 and 70°C. Depending on the initial excess of oxirane, the mono- or bis-derivatives can be obtained. The reactions with the glycerol epichlorohydrin can be performed in neat ECH. It seemed that the more convenient procedure of synthesis of hydroalkyl derivatives of DEBA were the reaction in dioxane due to its lower boiling point in comparison with that of DMF. However, we have noticed that in dioxane the precipitation of white compound occurred after 15 minutes; the analytical data indicated that the it was DEBA, which precipitated from the reaction mixture. Its melting point was 183 to 185°C corresponding to one of its reported polymorphic form [13]. Thus, during the reaction DEBA converts into this form in reaction conditions. Therefore, we have applied the synthetic protocol towards N,N'-bis(hydroxyalkyl) derivatives of DEBA in neat alkylene carbonates. Mono-hydroxyalkyl derivatives were not isolated in these conditions due to inhomogenicity of reaction mixture.

The obtained products are new type of diols; the convenient precursors for synthesis of polyurethanes and polyesters with thermal stability pyrimidine ring.

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