ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 9, pp. 1812–1818. © Pleiades Publishing, Ltd., 2010.
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The β-Cyclodextrin Cationic Derivatives Containing Residues of Some Pharmacologically Important Acids

M. K. Grachev, A. A. Charaev, G. I. Kurochkina, L. K. Vasyanina, V. N. Shmelev, and E. E. Nifant'ev

Moscow State Pedagogical University, Nesvizhskii per. 3, Moscow, 119021 Russia
e-mail: chemdept@mtu-net.ru

Received October 1, 2009

Abstract—The cationic derivatives of β-cyclodextrin containing residues of covalently bound pharmacologically important acids were obtained by alkylation of nucleophilic reagents with 6-halo-6-deoxy-β-cyclodextrin.

DOI: 10.1134/S1070363210090161

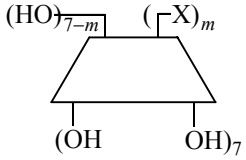
Among the numerous β-cyclodextrin compounds, its cationic derivatives with increased water solubility and other practically important properties inherent to alkylammonium ("charged") amphiphilic cyclodextrins attract special attention [1]. For the preparation of appropriate cationic derivatives the respective derivatives of 6-azido-6-dezoxy derivatives of cyclodextrins were often used, whose treating with triphenylphosphine in aqueous ammonia gave ammonium derivatives [2]. However, this method is suitable for primary alkylammonium cyclodextrin derivatives. Previously we have shown to be promising the direct synthesis of cationic derivatives by alkylation of a suitable amine by either cyclodextrin per-6-deoxy-per-6-bromo- [3] or deoxy-derivatives bearing a smaller number of bromine atoms [4]. In the latter case, the difficulty lies in the fact that although the preparation of per-6-deoxy-6-halocyclodextrins can be reached well using Reiden [5] or Vilsmeier–Haack [6] reagents, the synthesis of cyclodextrins containing fewer halogen atoms requires another approach, for example, the application of tosyl and silyl derivatives [7]. It is important that, in contrast to the classical alkylation of amines by alkyl halides, the hydrophobic cavity of cyclodextrin exerts a specific (supramolecular) influence on the course of the alkylation [4] and an individual approach to the development of the methods for the alkylation by 6-halodeoxycyclodextrins is required.

In this paper, we set a target to examine the preparation of cationic derivatives of cyclodextrins **I**–**III** containing residues of some pharmacologically important acids: 1-(4-isobutylphenyl)propionic acid (**IV**, H-*Y*) (the pharmaceutical in "Ibuprofen" drug), acetylsalicylic acid (**V**, H-*W*) (medicinal drug "Aspirin"), benzoic acid (**VI**, H-*Z*) and *p*-aminobenzoic acid (**VII**), on the basis of cyclodextrin 6-halo derivatives. Previously we have obtained conjugates with some of these compounds, that is, the covalently bound residues of acids (**IV**) and (**V**) to the cyclodextrin skeleton [8], and showed their potential for further pharmacological studies [9]. In continuation of this trend is of interest to join the drug residue to the cationic fragment of the cyclodextrin core using so-called spacers (*legs* or *hands*), among which were selected 1,2-*N*,*N*-dimethylaminoethanol (**VIII**) and 1,3-*N*,*N*-dimethylaminopropanol (**IX**). It is assumed that by changing length (*n*) and the nature of the *legs* a better embedding of the drug carrier in the lipid matrix can be achieved and can facilitate the overcoming the biological barriers [10]. Note also that the benefits of our proposed direction of synthesis is the lack of necessity to protect the secondary hydroxy groups and the subsequent removing the protection, so that the *broad* part cyclodextrin skeleton remains free for the inclusion of various *guests*, for example of those possessing other pharmacological action, that extends medical application of the studied structures.

For the synthesis of halo-derivatives **I**–**III**, we used different approaches: per-6-bromo-per-6-deoxy-β-cyclodextrin (**I**) was obtained using Vilsmeier–Haack reagent [6], tetra-6-bromo-tetra-6-deoxy-β-cyclo-dextrin (**II**) was prepared through β-cyclodextrin silyl derivative [7],

and tri-6-iodine-tri-6-deoxy-β-cyclo-dextrin (**III**) was obtained using the β-cyclodextrin tosyl derivative (see Experimental).

Nucleophilic reagents **X**–**XV** for the alkylation, containing terminal dimethylamino group and the residues of drugs **IV**–**VI** we obtained through processing aminoalcohol **VIII** or **IX** with the corresponding acid chloride in benzene in the presence of sodium hydrogen carbonate. Compounds **X**–**XV** were isolated in the individual state and characterized by ^{1}H NMR spectroscopic data, TLC, and elemental analysis.



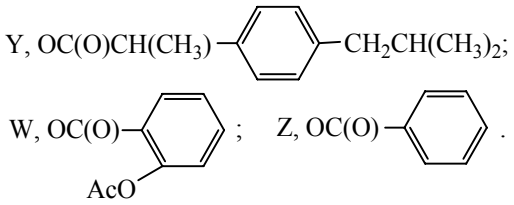
I–III

$Me_2N–(CH_2)_n–Y(W,Z)$

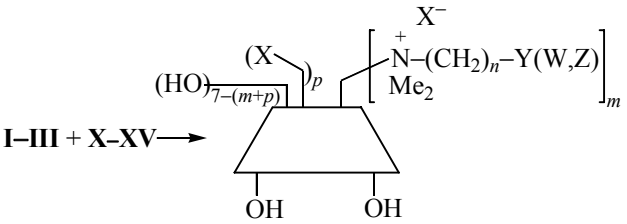
X–XV

I, X = Br, m = 7; **II**, X = Br, m = 4; **III**, X = I, m = 3; **X**, n = 2, Y; **XI**, n = 2, W; **XII**, n = 2, Z; **XIII**, n = 3, Y; **XIV**, n = 3, W; **XV**, n = 3, Z.

The central point of the investigation is selecting the conditions for the alkylation of the terminal amino group of compound **X**–**XV** or acid **VII** by the cyclodextrin halo derivative **I**–**III**. The reaction was carried out in DMF (in other solvents the halo derivatives **I**–**III** are poorly soluble) at 135°C (80°C), using a large excess of amine **X**–**XV**. The product of alkylation was precipitated by adding diethyl ether, washed with acetone, dried in a vacuum[1] and its individuality was analyzed by methods of ^{1}H NMR spectroscopy, TLC, and elemental analysis.

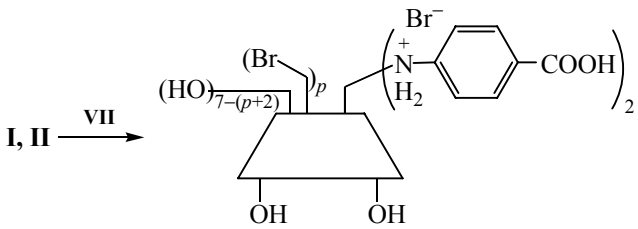


The *average* degree of alkylation (m) was estimated from the data of ^{1}H NMR spectroscopy by comparing integral intensities of the signals of cyclodextrin skeleton protons at 3.22–3.90 ppm with the integral intensity of N-methyl protons at 2.81 ppm. It turned out that the average degree of alkylation m = 1 is reached only in the reaction of β-cyclodextrin bromo- (**I**) and iodo-derivatives (**III**) with amino derivatives **X** and **XII** at 80°C for 6 hours with the yield of the product **XVI**–**XVIII** of 76–81%. At the shorter reaction duration (3 h) a significant amount of the non-reacted cyclodextrin halo derivative remains in the reaction mass. The longer exposure of the reaction mixture to 80°C does not lead to a substantial increase in conversion. Therefore, further syntheses of compounds **XIX**–**XVIII** we carried out at a higher temperature (135°C) and at the reaction duration 39 h. Under these conditions the alkylation by the cyclodextrin derivatives **I**–**III** of the amino derivatives **X**–**XV** proceeds with an average degree m = 2 (compounds **XIX**–**XXVIII**). Longer heating at this temperature does not lead to a significant increase in the degree of alkylation.



XVI, X = Br, n = 2, m = 1, p = 6, Y; **XVII**, X = Br, n = 3, m = 1, p = 6, Y; **XVIII**, X = I, n = 3, m = 1, p = 2, Y; **XIX**, X = Br, n = 2, m = 2, p = 5, Y; **XX**, X = Br, n = 3, m = 2, p = 5, Y; **XXI**, X = Br, n = 2, m = 2, p = 5, W; **XXII,** X = Br, n = 3, m = 2, p = 5, W; **XXIII,** X = Br, n = 2, m = 2, p = 2, Y; **XXIV**, X = Br, n = 3, m = 2, p = 2, Y; **XXV**, X = Br, n = 2, m = 2, p = 2, W; **XXVI**, X = Br, n = 3, m = 2, p = 2, W; **XXVII**, X = Br, n = 2, m = 2, p = 2, Z; **XXVIII**, X = Br, n = = 3, m = 2, p = 2, Z.

Processing amino acids **VII** with per- (**I**) and tetrabromo- (**II**) cyclodextrin derivatives also resulted in the degree of alkylation m = 2, with the formation of the corresponding ammonium derivatives **XXIX** and **XXX**.



XXIX, XXX

XXIX, p = 5; **XXX**, p = 2.

[1] Another possibility of amine alkylation by per-6-bromo-per-6-deoxy-β-cyclodextrin was described in the literature, but for simpler amines and under the other conditions [11].

Analyzing the results, we have to note that under these conditions of synthesis of compounds **XIX**–**XXX** the found average degree of alkylation (m = 2) corresponds to the maximum, despite the presence of a large excess of amine. Use of iodine derivative **III** instead of bromo compound did not lead to a higher degree of alkylation. Apparently, this is a result of the complex competitive, including supramolecular, interacttions of the solvent (DMF), reagents, reaction products with the cyclodextrin cavity. For example, it was also noted in [11] that the alkylation of amines by per-6-bromo-per-6-deoxycyclodextrin in DMF medium is incomplete.

Thus, we investigated new possibilities of alkylation of nucleophilic reagents bearing terminal dimethylamino group by 6-halo-6-deoxy-β-cyclodextrin, and on this basis proposed practical ways of synthesis of β-cyclodextrin cationic derivatives of different structures, containing residues of covalently bound pharmacologically important acids that are interesting for biomedical research in various aspects.

EXPERIMENTAL

All experiments were carried out in anhydrous solvents purified by standard methods.

^{1}H NMR spectra were recorded on a spectrometer JNM-ECX400 (400 MHz), external reference TMS.

For thin layer chromatography aluminum plates were used with fixed layer of silica gel (Silufol UV-254), eluents methanol–chloroform 3:1 (A), benzene–dioxane 3:1 (B), benzene–dioxane–water 1:10:1 (C).

We used β-cyclodextrin from "Wacker" (USA) subjected to thorough dehydration.

Tri-6-iodo-tri-6-deoxy-β-cyclodextrin (III). To a solution of 0.51 g of tri-6-*O*-tosyl-tri-6-deoxy-β-cyclodextrin [7] in 15 ml of DMF was added at stirring 0.32 g of potassium iodide, and the mixture was maintained at 55ºC for 48 h. The reaction mixture was evaporated to syrupy state and poured at stirring in 50 ml of acetone. The precipitate formed was separated, washed with water (2×5 ml), stirred, and ground with 4 ml of chloroform. The solvent was removed, and the residue was dried at 60ºC for 3 h in a vacuum (1 mm Hg). Yield of compound **III** 0.34 g (71%), mp 192–194ºC (decomp.), R_f 0.65 (A). The ^{1}H NMR spectrum, DMSO-d_6, δ, ppm: 3.08–3.96 m (42H; C^2H–C^5H, C^6H_2), 4.79–5.20 m (11H; C^6OH, C^1H), 5.62–6.20 m (14H; C^2OH, C^3OH). Found, %: C 34.12; H 4.95. $C_{42}H_{67}I_3O_{32}$. Calculated, %: C 34.44; H 4.61.

2-*N*,*N*-Dimethylaminoethyl 1-(4-isobutylphenyl)-propionate (X). To a solution of 5.00 g of acid chloride **IV** in 10 ml of benzene was added dropwise at stirring 2.00 g of amino derivative **VIII** in 25 ml of benzene. The stirring was continued at 20ºC for 3 h, 30 ml of benzene was added and the stirring was continued at 20ºC for 24 h. To the reaction mixture was added 10 ml of saturated solution of $NaHCO_3$, the mixture was stirred, then the benzene layer was separated, dried over $CaCl_2$, the solvent was then removed and the residue was maintained at 60ºC for 5 h in a vacuum (1 mm Hg). Yield of compound **X**[2] 5.20 g (84%), R_f 0.45 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 0.84 d [6H, HC(CH_3)$_2$, $^3J_{HH}$ 6.4], 1.36 d [3H, (O)CCHCH_3, $^3J_{HH}$ 7.0], 1.73–1.86 m (1H, CH_2CH), 2.07 s [6H, N(CH_3)$_2$], 2.34–2.43 m (4H; $C_6H_4CH_2$, NCH_2), 3.72 q [1H, (O)CCHCH$_3$, $^3J_{HH}$ 7.1], 4.07 t (2H, CH_2O, $^3J_{HH}$ 5.6), 7.09 d (2H, $C_6H_{ortho}CH_2$, $^3J_{HH}$ 7.8), 7.18 d (2H, $C_6H_{meta}CH_2$, $^3J_{HH}$ 8.0). Found, %: C 74.02; H 9.56. $C_{17}H_{27}NO_2$. Calculated, %: C 73.61; H 9.81.

2-*N*,*N*-Dimethylaminoethyl acetylsalicylate (XI) was synthesized by analogy to compound **X** from 5.00 g of acid chloride **V** and 2.24 g of amino derivative **VIII**. Yield of compound **XI** 5.26 g (83%), R_f 0.57 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.16 s [6H, N(CH_3)$_2$], 2.26 s [3H, C(O)CH_3], 2.54 t (2H, NCH_2, $^3J_{HH}$ 6.0), 4.27 t (2H, CH_2O, $^3J_{HH}$ 5.8), 7.19 d [1H, $C_6H_{ortho}C(O)$, $^3J_{HH}$ 7.8], 7.37 t [1H, $C_6H_{para}C(O)$, $^3J_{HH}$ 6.4], 7.62 t [1H, $C_6H_{meta}C(O)$, $^3J_{HH}$ 6.8], 7.91 d [1H, $C_6H_{ortho}OC(O)$, $^3J_{HH}$ 6.4]. Found, %: C 61.81; H 7.13. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.82.

2-*N*,*N*-Dimethylaminoethyl benzoate (XII) was synthesized by analogy to compound **X** from 5.00 g of acid chloride **VI** and 3.17 g of amino derivative **VIII**. Yield of compound **XII** 5.75 g (84%), R_f 0.49 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.10 s [6H, N(CH_3)$_2$], 2.30 t (2H, NCH_2, $^3J_{HH}$ 6.9), 4.29 t (2H, CH_2O, $^3J_{HH}$ 6.5), 7.50 t [2H, $C_6H_{meta}C(O)$, $^3J_{HH}$ 7.4], 7.65 t [1H, $C_6H_{para}C(O)$, $^3J_{HH}$ 6.4], 7.95 d [2H, $C_6H_{ortho}C(O)$, $^3J_{HH}$ 7.4]. Found, %: C 68.07; H 8.03. $C_{11}H_{15}NO_2$. Calculated, %: C 68.37; H 7.82.

3-*N*,*N*-Dimethylaminopropyl 1-(4-isobutylphenyl)-propionate (XIII) was synthesized by analogy to compound **X** from 5.00 g of acid chloride **IV** and 2.30 g of amino derivative **IX**. Yield of compound **XIII** 5.54 g (85%), R_f 0.40 (B). The ^{1}H NMR spectrum

[2] Compounds **X**–**XV** are viscous light yellow oily liquids.

(DMSO-d_6), δ, ppm (*J*, Hz): 0.89 d [6H, HC(CH_3)$_2$, $^3J_{HH}$ 6.5], 1.48 d [3H, (O)CCHCH_3, $^3J_{HH}$ 7.1], 1.64–1.91 m (3H; CH_2CH, $CH_2CH_2CH_2$), 2.08–2.32 m [8H; N(CH_3)$_2$, NCH_2], 2.44 d (2H, $C_6H_4CH_2$, $^3J_{HH}$ 7.1), 3.67 q [1H, (O)CC*H*CH$_3$, $^3J_{HH}$ 7.1], 4.12 t (2H, CH_2O, $^3J_{HH}$ 5.7), 7.08 d (2H, $C_6H_{ortho}CH_2$, $^3J_{HH}$ 7.9), 7.20 d (2H, $C_6H_{meta}CH_2$, $^3J_{HH}$ 7.9). Found, %: C 74.53; H 6.86. $C_{18}H_{29}NO_2$. Calculated, %: C 74.18; H 7.03.

3-*N*,*N*-dimethylaminopropyl acetylsalicylate (XIV) was synthesized by analogy to compound **X** from 5.00 g of acid chloride **V** and 2.60 g of amino derivative **IX**. Yield of compound (**XIV**) 5.65 g (85%), R_f 0.51 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.81 m (2H, $CH_2CH_2CH_2$), 2.16 s [6H, N(CH_3)$_2$], 2.28 s [3H, C(O)CH_3], 2.35 t (2H, NCH_2, $^3J_{HH}$ 7.1), 4.25 t (2H, CH_2O, $^3J_{HH}$ 6.5), 7.23 d [1H, $C_6H_{ortho}C(O)$, $^3J_{HH}$ 8.1], 7.40 t [1H, $C_6H_{para}C(O)$, $^3J_{HH}$ 7.6], 7.67 t [1H, $C_6H_{ortho}OC(O)$, $^3J_{HH}$ 7.7], 7.94 d [1H, $C_6H_{meta}C(O)$, $^3J_{HH}$ 7.8]. Found, %: C 62.99; H 7.50. $C_{14}H_{19}NO_4$. Calculated, %: C 63.38; H 7.22.

3-*N*,*N*-dimethylaminopropyl benzoate (XV) was synthesized by analogy to compound **X** from 5.00 g of acid chloride **VI** and 3.67 g of amino derivative **IX**. Yield of compound **XV** 6.17 g (84%), R_f 0.57 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.83 m (2H, $CH_2CH_2CH_2$), 2.12 s [6H, N(CH_3)$_2$], 2.32 t (2H, NCH_2, $^3J_{HH}$ 7.0), 4.28 t (2H, CH_2O, $^3J_{HH}$ 6.5), 7.52 t [2H, $C_6H_{meta}C(O)$, $^3J_{HH}$ 7.5], 7.64 t [1H, $C_6H_{para}C(O)$, $^3J_{HH}$ 6.4], 7.95 d (2H, $C_6H_{ortho}C(O)$, $^3J_{HH}$ 7.6). Found, %: C 69.13; H 8.46. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27.

Mono-6-({3-*O*-[1-(4-isobutylphenyl)propanoyl]-ethyleneoxy-1-yl}dimethylammonium bromide)hexa-6-bromohepta-6-deoxy-β-cyclodextrin (XVI). To a solution of 0.20 g of cyclodextrin halo derivative **I** in 3 ml of DMF was added 1.50 g of nucleophilic reagent **X**, and the mixture was maintained at 80ºC for 6 h. To the reaction mixture was added 5 ml of acetone, the mixture was stirred, then filtered, the precipitate was washed with diethyl ether (2×3 ml), and the solvent was removed in a vacuum. The residue was dried at 50ºC for 5 h in a vacuum (1 mm Hg). Yield of compound **XVI** 0.18 g (76%), mp 184–186ºC (decomp.)[3], R_f 0.79 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.84 d [6H, CH(CH_3)$_2$, $^3J_{HH}$ 6.6], 1.37 d [3H, (O)CCHCH_3, $^3J_{HH}$ 7.2], 1.72–1.88 m [1H, C*H*(CH$_3$)$_2$], 2.70–2.76 m (4H; NCH_2, $CHCH_2$), 3.32 s [6H, N(CH_3)$_2$], 3.47–4.16 m [45H; C^2H–C^5H, C^6H_2, (O)CC*H*CH$_3$, CH_2O], 4.82–5.00 br.s (7H, C^1H), 5.62–6.08 m (14H; C^2OH, C^3OH), 7.08–7.43 m (4H, CH_{arom}). Found, %: C 38.54; H 4.68. $C_{59}H_{90}Br_7NO_{30}$. Calculated, %: C 38.25; H 4.90.

Mono-6-({3-*O*-[1-(4-isobutylphenyl)propanoyl]-propyleneoxy-1-yl}dimethylammonium bromide)hexa-6-bromo-hepta-6-deoxy-β-cyclodextrin (XVII) was synthesized by analogy to compound **XVI** from 0.20 g of the cyclodextrin halo derivative (**I**) and 0.55 g of the nucleophilic reagent **XIII**. Yield of compound **XVII** 0.19 g (81%), mp 179–180ºC (decomp.), R_f 0.73 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.84 d [6H, CH(CH_3)$_2$, $^3J_{HH}$ 6.5], 1.38 d [3H, (O) CCHCH_3, $^3J_{HH}$ 7.1], 1.71–2.15 m [3H; $CH_2CH_2CH_2$, C*H*(CH$_3$)$_2$], 2.73–2.87 m (4H; NCH_2, $CHCH_2$), 3.36 s [6H, N(CH_3)$_2$], 3.39–3.95 m [43H; C^2H–C^5H, C^6H_2, (O)CC*H*CH$_3$], 4.05 t (2H, CH_2O, $^3J_{HH}$ 6.0), 4.78–5.40 m (21H; C^1H, C^2OH, C^3OH), 7.10 d (2H, $C_6H_{ortho}CH_2$, $^3J_{HH}$8.2), 7.19 d (2H, $C_6H_{meta}CH_2$, $^3J_{HH}$ 8.0). Found, %: C 38.23; H 5.19. $C_{60}H_{92}Br_7NO_{30}$. Calculated, %: C 38.61; H 4.97.

Mono-6-({3-*O*-[1-(4-isobutylphenyl)propanoyl]-propyleneoxy-1-yl}dimethylammonium iodide)di-6-iodo-tri-6-deoxy-β-cyclodextrin (XVIII) was synthesized by analogy to compound **XVI**, from 0.20 g of the cyclodextrin halo derivative **III** and 0.27 g of the nucleophilic reagent **XIII**. Yield of compound (**XVIII**) 0.18 g (77%), mp 195–197ºC (decomp.), R_f 0.60 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.83 d [6H, CH(CH_3)$_2$, $^3J_{HH}$ 6.5], 1.37 d [3H, (O)CCHCH_3, $^3J_{HH}$ 6.9], 2.03–2.28 m [3H; $CH_2CH_2CH_2$, C*H*(CH$_3$)$_2$,], 2.60–2.88 m (4H; NCH_2, $CHCH_2$), 3.32 s [6H, N(CH_3)$_2$], 3.39–3.80 m [43H; C^2H–C^5H, C^6H_2, (O)CC*H*CH$_3$, CH_2O], 4.12–4.21 m (2H, CH_2O), 4.45–4.62 br.s (4H, C^6OH), 4.70–4.85 m (7H, C^1H), 5.63–6.95 br.s (14H; C^2OH, C^3OH), 7.10 d (2H, $C_6H_{ortho}CH_2$, $^3J_{HH}$ 7.7), 7.44 d (2H, $C_6H_{meta}CH_2$, $^3J_{HH}$ 7.9). Found, %: C 40.67; H 5.79. $C_{60}H_{96}I_3NO_{34}$. Calculated, %: C 41.04; H 5.51.

Bis-6-({2-*O*-[1-(4-isobutylphenyl)propanoyl]ethyl-eneoxy-1-yl}dimethylammonium bromide)penta-6-bromohepta-6-deoxy-β-cyclodextrin (XIX). To a solution of 0.20 g of cyclodextrin halo derivative **I** in 3 ml of DMF was added 0.53 g of nucleophilic reagent **X** and the mixture was maintained at 135ºC for 39 h. To the reaction mixture was added 5 ml of acetone, the mixture was stirred, then filtered, the precipitate was washed with diethyl ether (2×3 ml) and the solvent was removed in a vacuum. The residue was dried at

[3] Compounds **XVI–XXX** are light-brown solid amorphous substances.

50°C for 5 h in a vacuum (1 mm Hg). Yield of compound **XIX** 0.20 g (75%), mp 158–160°C (decomp.), R_f 0.70 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.86 d [12H, CH(CH_3)$_2$, $^3J_{HH}$ 6.9], 1.45 d [6H, (O)CCHCH_3, $^3J_{HH}$ 7.4], 1.70–1.89 m [2H, CH(CH$_3$)$_2$], 2.65–2.80 m (8H; NCH$_2$, CHCH_2), 3.29 s [12H, N(CH$_3$)$_2$], 3.37–4.21 m [48H; C^{2}H–C^{5}H, C^{6}H$_2$, (O)CCHCH$_3$, CH$_2$O], 4.78–5.11 br.s (7H, C^{1}H), 5.53–6.02 m (14H; C^{2}OH, C^{3}OH), 7.06–7.28 m (8H, CH$_{arom}$). Found, %: C 43.15; H 5.22. $C_{76}H_{117}Br_7NO_{32}$. Calculated, %: C 42.85; H 5.54.

Bis-6-({3-*O*-[1-(4-isobutylphenyl)propanoyl]propyleneoxy-1-yl}dimethylammonium bromide)-penta-6-bromohepta-6-deoxy-β-cyclodextrin (XX) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **I** and 0.55 g of nucleophilic reagent **XIII**. Yield of compound **XX** 0.21 g (76%), mp 155–157°C (decomp.), R_f 0.58 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.87 d [12H, CH(CH_3)$_2$, $^3J_{HH}$ 7.2], 1.42 d [6H, (O)CCHCH_3, $^3J_{HH}$ 7.3], 1.70–2.17 m [6H; CH$_2$CH_2CH$_2$, CH(CH$_3$)$_2$], 2.70–2.86 m (8H; NCH$_2$, CHCH_2), 3.21 s [12H, N(CH$_3$)$_2$], 3.35–3.91 m [44H; C^{2}H–C^{5}H, C^{6}H$_2$, (O)CCHCH$_3$], 4.09 t (4H, CH$_2$O, $^3J_{HH}$ 6.4), 4.73–5.48 m (21H; C^{1}H, C^{2}OH, C^{3}OH), 7.11 d (4H, C$_6H_{ortho}$CH$_2$, $^3J_{HH}$ 7.3), 7.20 d (4H, C$_6H_{meta}$CH$_2$, $^3J_{HH}$ 7.5). Found, %: C 43.89; H 5.47. $C_{78}H_{121}Br_7N_2O_{32}$. Calculated, %: C 43.41; H 5.65.

Bis-6-{[2-*O*-acetylsalicyl)ethyleneoxy-1-yl]dimethylammonium bromide}-penta-6-bromohepta-6-deoxy-β-cyclodextrin (XXI) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **I** and 0.22 g of nucleophilic reagent **XI**. Yield of compound **XXI** 0.19 g (73%), mp 152–154°C (decomp.), R_f 0.69 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.25 s [6H, C(O)CH$_3$], 2.56–2.67 m (4H, NCH$_2$), 3.09 s [12H, N(CH$_3$)$_2$], 3.21–3.96 m (46 H; C^{2}H–C^{5}H, C^{6}H$_2$, CH$_2$O), 4.82–5.21 m (7H; C^{1}H), 5.62–6.08 br.s (14H; C^{2}OH, C^{3}OH), 6.54–7.68 m (8H, CH$_{arom}$). Found, %: C 39.56; H 4.52. $C_{68}H_{97}Br_7N_2O_{36}$. Calculated, %: C 39.31; H 4.71.

Bis-6-{[3-*O*-(acetylsalicyl)propyleneoxy-1-yl]dimethylammonium bromide}-penta-6-bromohepta-6-deoxy-β-cyclodextrin (XXII) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **I** and 0.51 g of nucleophilic reagent **XIV**. Yield of compound **XXII** 0.21 g (78%), mp 167–169°C (decomp.), R_f 0.65 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06–2.14 m (4H, CH$_2$CH_2CH$_2$), 2.29 s [6H, C(O)CH$_3$], 2.73–2.87 m (4H, NCH$_2$), 3.13–3.85 m [54H; C^{2}H–C^{5}H, C^{6}H$_2$, N(CH$_3$)$_2$], 4.38–4.45 m (4H, CH$_2$O), 4.86–5.29 m (7H, C^{1}H), 5.61–6.03 br.s (14H; C^{2}OH, C^{3}OH), 6.89–7.95 m (8H, CH$_{arom}$). Found, %: C 40.23; H 4.51. $C_{70}H_{101}Br_7N_2O_{36}$. Calculated, %: C 39.92; H 4.83.

Bis-6-*(*{2-*O*-[1-(4-isobutylphenyl)propanoyl]ethyleneoxy-1-yl}dimethylammonium bromide)di-6-bromotetra-6-deoxy-β-cyclodextrin (XXIII) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.28 g of nucleophilic reagent **X**. Yield of compound **XXIII** 0.21 g (75%), mp 173–175°C (decomp.), R_f 0.71 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.81 d [12H, CH(CH_3)$_2$, $^3J_{HH}$ 6.8], 1.38 d [6H, (O)CCHCH_3, $^3J_{HH}$ 7.0], 1.68–1.79 m (2H, CHCH$_2$), 2.38 d (4H, CHCH_2, $^3J_{HH}$ 6.5) 2.67 t (4H, NCH$_2$, $^3J_{HH}$ 6.8), 2.96 s [12H, N(CH$_3$)$_2$], 3.37–3.70 m (46H; C^{2}H–C^{5}H, C^{6}H$_2$, CH$_2$O), 3.76 q [2H, (O)CCHCH$_3$, $^3J_{HH}$ 7.2], 4.35–4.51 br.s (3H, C^{6}OH), 4.78–5.11 br.s (7H, C^{1}H), 5.53–6.02 br.s (14H; C^{2}OH, C^{3}OH), 7.08 d (4H, C$_6H_{ortho}$CH$_2$, $^3J_{HH}$ 7.9), 7.19 d (4H, C$_6H_{meta}$CH$_2$, $^3J_{HH}$ 8.1). Found, %: C 47.24; H 6.02. $C_{76}H_{120}Br_4N_2O_{35}$. Calculated, %: C 46.99; H 6.28.

Bis-6-*(*{3-*O*-[1-(4-isobutylphenyl)propanoyl]-propyleneoxy-1-yl}dimethylammonium bromide*)*-di-6-bromotetra-6-deoxy-β-cyclodextrin (XXIV) was synthesized by analogy to compound (**XIX**) from 0.20 g of the cyclodextrin halo derivative **II** and 0.30 g of nucleophilic reagent **XIII**. Yield of compound **XXIV** 0.22 g (76%), mp 162–164°C (decomp.), R_f 0.63 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.80 d [12H, CH(CH_3)$_2$, $^3J_{HH}$ 6.9], 1.39 d [6H, (O)CCHCH_3, $^3J_{HH}$ 7.3], 1.69–1.81 m (4H, CH$_2$CH_2CH$_2$), 1.83–2.04 m (2H, CHCH$_2$), 2.37 d (4H, CHCH_2, $^3J_{HH}$ 6.8), 2.69 t (4H, NCH$_2$, $^3J_{HH}$ 7.3), 2.97 s [12H, N(CH$_3$)$_2$], 3.25–3.68 m (42H; C^{2}H–C^{5}H, C^{6}H$_2$), 3.72 q [2H, (O)CCHCH$_3$, $^3J_{HH}$ 6.7], 3.95–4.15 m (4H, CH$_2$O) 4.37–4.52 br.s (3H, C^{6}OH), 4.76–5.09 br.s (7H, C^{1}H), 5.55–6.08 br.s (14H; C^{2}OH, C^{3}OH), 7.10 d (4H, C$_6H_{ortho}$CH$_2$, $^3J_{HH}$ 8.1), 7.18 d (4H, C$_6H_{meta}$CH$_2$, $^3J_{HH}$ 7.7). Found, %: C 47.82; H 6.04. $C_{78}H_{124}Br_4N_2O_{35}$. Calculated, %: C 47.57; H 6.35.

Bis-6-{[2-*O*-(acetylsalisyl)ethyleneoxy-1-yl]dimethylammonium bromide}-di-6-bromotetra-6-deoxy-β-cyclodextrin (XXV) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.25 g of nucleophilic reagent **XI**. Yield of compound **XXV** 0.21 g (75%), mp 148–150°C (decomp.), R_f 0.76 (C).

The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.26 s [6H, C(O)CH_3], 2.60–2.69 m (4H, NCH_2), 3.10 s [12H, $N(CH_3)_2$], 3.26–3.89 m (46H; C^2H–C^5H, C^6H_2, CH_2O), 4.35–4.48 br.s (3H, C^6OH), 4.73–5.15 br.s (7H, C^1H), 5.50–6.01 br.s (14H; C^2OH, C^3OH), 6.43–7.68 m (8H, CH_{arom}). Found, %: C 42.95; H 5.72. $C_{68}H_{100}Br_4N_2O_{39}$. Calculated, %: C 43.23; H 5.34.

Bis-6-{[3-*O*-(acetylsalicyl)propyleneoxy-1-yl]dimethylammonium bromide}-di-6-bromotetra-6-deoxy-β-cyclodextrin (XXVI) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.27 g of nucleophilic reagent **XIV**. Yield of compound **XXVI** 0.20 g (71%), mp 145–147ºC (decomp.), R_f 0.68 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00–2.18 m (4H, $CH_2CH_2CH_2$), 2.27 s [6H, C(O)CH_3], 2.68–2.75 m (4H, NCH_2), 3.11 s [12H, $N(CH_3)_2$], 3.15–3.87 m (42 H; C^2H–C^5H, C^6H_2), 4.36 t (4H, CH_2O, $^3J_{HH}$ 6.7), 4.42–4.73 br.s (3H, C^6OH), 4.85–5.27 m (7H; C^1H), 5.62–6.05 br.s (14H; C^2OH, C^3OH), 6.73–7.93 m (8H, CH_{arom}). Found, %: C 43.58; H 5.86. $C_{70}H_{104}Br_4N_2O_{39}$. Calculated, %: C 43.85; H 5.47.

Bis-6-{[2-*O*-(benzoyl)ethyleneoxy-1-yl]dimethylammonium bromide}-di-6-bromotetra-6-deoxy-β-cyclodextrin (XXVII) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.20 g of nucleophilic reagent **XII**. Yield of compound **XXVII** 0.19 g (74%), mp 175–177ºC (decomp.), R_f 0.56 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.37–2.45 m (4H, NCH_2), 3.16 s [12H, $N(CH_3)_2$], 3.25–4.14 m (46H; C^2H–C^5H, C^6H_2, CH_2O), 4.36–4.66 br.s (3H, C^6OH), 4.92–5.21 m (7H; C^1H), 5.63–6.05 br.s (14H; C^2OH, C^3OH), 7.36–8.10 m (10H, CH_{arom}). Found, %: C 43.39; H 5.17. $C_{64}H_{96}Br_4N_2O_{35}$. Calculated, %: C 43.15; H 5.46.

Bis-6-{[3-*O*-(benzoyl)propyleneoxy-1-yl]dimethylammonium bromide}-di-6-bromotetra-6-deoxy-β-cyclodextrin (XXVIII) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.21 g of nucleophilic reagent **XV**. Yield of compound **XXVIII** 0.19 g (72%), mp 170–172ºC (decomp.), R_f 0.51 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.04–2.18 m (4H, $CH_2CH_2CH_2$), 2.34–2.41 m (4H, NCH_2), 3.09 s [12H, $N(CH_3)_2$], 3.25–3.80 m (42H; C^2H–C^5H, C^6H_2), 4.31 t (4H, CH_2O, $^3J_{HH}$ 6.8), 4.37–4.62 br.s (3H, C^6OH), 4.90–5.23 m (7H; C^1H), 5.65–6.12 br.s (14H; C^2OH, C^3OH), 7.51 t [4H, $C_6H_{meta}C(O)$, $^3J_{HH}$ 7.2], 7.64 t [2H, $C_6H_{para}C(O)$, $^3J_{HH}$ 6.8], 7.97 d (4H, $C_6H_{ortho}C(O)$, $^3J_{HH}$ 7.4). Found, %: C 44.38; H 5.32. $C_{66}H_{100}Br_4N_2O_{35}$. Calculated, %: C 44.01; H 5.60.

Bis-6-(*p*-carboxyphenylammonium bromide)penta-6-bromo-hepta-6-deoxy-β-cyclodextrin (XXIX) was synthesized by analogy to compound **XIX**, from 0.20 g of the cyclodextrin halo derivative **I** and 0.35 g of nucleophilic reagent **VII**. Yield of compound **XXIX** 0.16 g (70%), mp 225–227ºC (decomp.), R_f 0.67(C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.22–3.88 m (42 H; C^2H–C^5H, C^6H_2), 4.77–5.12 m (7H, C^1H), 5.50–6.06 br.s (14H; C^2OH, C^3OH), 6.49–6.51 br.s (4H, NH_2), 7.56–7.95 m (8H, CH_{arom}), 8.29 s [2H, C(O)OH]. Found, %: C 36.68; H 3.88. $C_{56}H_{77}Br_7N_2O_{32}$. Calculated, %: C 36.37; H 4.20.

Bis-6-(*p*-carboxyphenylammonium bromide)di-6-bromotetra-6-deoxy-β-cyclodextrin (XXX) was synthesized by analogy to compound **XIX** from 0.20 g of the cyclodextrin halo derivative **II** and 0.40 g of nucleophilic reagent **VII**. Yield of compound **XXX** 0.17 g (72%), mp 184–186ºC (decomp.), R_f 0.45 (C). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.11–4.15 m (42 H; C^2H–C^5H, C^6H_2), 4.35–4.63 br.s (3H, C^6OH), 4.75–5.11 m (7H, C^1H), 5.52–6.05 br.s (14H; C^2OH, C^3OH), 6.47–6.54 br.s (4H, NH_2), 7.58–7.96 m (8H, CH_{arom}), 8.23 s [2H, C(O)OH]. Found, %: C 40.85; H 4.63. $C_{56}H_{80}Br_4N_2O_{35}$. Calculated, %: C 40.50; H 4. 86.

ACKNOWLEDGMENTS

This work was financially supported by Russian Foundation for Basic Research (grant no. 08-03-00374a) and Grant of the President of Russian Federation for support of leading scientific schools (project no. NSh-582.2008.3).

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